I3Y-MC-JPCJ(c) Clinical Protocol

An Adaptive, Open-Label, Randomized Phase 2 Study of Abemaciclib as a Monotherapy and in Combination with Other Agents Versus Choice of Standard of Care (Gemcitabine or Capecitabine) in Patients with Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma

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Abemaciclib (LY2835219)

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Amendment (c) Electronically Signed and Approved by Lilly on Date provided below.

Approval Date: 29-Jun-2017 GMT

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1. Synopsis

Protocol Title:

An adaptive, open-label, randomized Phase 2 study of abemaciclib as a monotherapy and in combination with other agents versus choice of standard of care (gemcitabine or capecitabine) in patients with previously treated metastatic pancreatic ductal adenocarcinoma

Rationale:

Cyclin-dependent kinase (CDK)4 and CDK6 pathway alterations, along with Kirsten rat sarcoma (KRAS) mutations, are key molecular signatures that occur in approximately 90% of pancreatic ductal adenocarcinoma (PDAC). Abemaciclib, a CDK4 and CDK6 inhibitor, has shown activity in *KRAS* mutant pancreatic cancer cell lines and has acceptable safety and tolerability in clinical studies. Given the relevance of the CDK4 and CDK6 pathway in PDAC, the activity of abemaciclib in KRAS mutant pancreatic cancer cell lines, acceptable safety and tolerability of abemaciclib in clinical studies, and the unmet medical need, this study aims to explore the safety and efficacy of abemaciclib in patients with PDAC.

This study also aims to explore the safety and efficacy of abemaciclib in combination with LY3023414, an orally available, potent selective inhibitor of the class I phosphatidylinositol 3-kinase (PI3K) isoforms, mammalian target of rapamycin (mTOR), and DNA-dependent protein kinase, in patients with PDAC. Upstream mitogenic growth factors, including PI3K, induce the expression of Cyclin D1, which further activates the Cyclin D1-CDK4 and CDK6 complex. Frequent activating aberrations of PI3K/mTOR signaling have been reported in several cancers. A potent impact of CDK4 and C.

DK6 inhibition in PDAC models has been observed; however, in the majority of models analyzed, acquired/intrinsic resistance has resulted through bypassing of this inhibition. PI3K/mTOR inhibitors demonstrated cooperative effects in combination with a CDK4 and CDK6 inhibitor in a pancreatic cancer tumor model. Synergistic activity of CDK4 and CDK6 and PI3K/mTOR blockade has been observed in other tumor models, and clinical trials are ongoing exploring this strategy.

Galunisertib (LY2157299) is a small molecule designed to selectively inhibit the serine/threonine kinase of the transforming growth factor beta (TGF-β) receptor type I (TGF-βRI). In PDAC, an increase in expression of epithelial-mesenchymal transition triggering factors, including TGF-β, has been observed and may contribute to the high metastatic potential. In pancreatic cancer cells, a CDK4 and CDK6 inhibitor exerted growth-inhibitory effects, although a TGF-βRI inhibitor alone was unable to suppress colony growth in 3-D culture. However, when the TGF-βRI inhibitor was combined with a CDK4 and CDK6 inhibitor, optimal growth inhibition was achieved. These preclinical data provide a basis for exploring the combination of abemaciclib and galunisertib in the current study, although with amendment (c) the assessment of this combination is being discontinued.

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.

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.

Overall Design:
Study I3Y-MC-JPCJ is a multicenter, randomized, open-label, Phase 2 trial in patients with metastatic pancreatic ductal adenocarcinoma who have been previously treated with at least one, but no more than 2, prior therapies for metastatic disease. At least one of the prior therapies must have been either gemcitabine-based or fluoropyrimidine-based therapy. The safety and efficacy of each investigational arm will be assessed versus the standard-of-care arm by implementing a 2-stage design. For Stage 1, the primary analyses of safety and efficacy will be evaluated for each of 2 investigational arms versus a standard-of-care arm approximately 16 weeks after the last planned Stage 1 patient enters treatment. The 2 investigational arms include abemaciclib monotherapy (Arm A) and abemaciclib plus LY3023414 (PI3K/mTOR dual inhibitor; Arm B). The comparator arm will be choice of standard-of-care (gemcitabine or capecitabine; Arm D). Following the completion of the Stage 1 assessment, any treatment arm(s) with a disease control rate (DCR) difference ≥ 0 as compared to the standard-of-care (Arm D) will be selected to advance to Stage 2. Enrollment in the nonadvancing arm(s) will be discontinued. For the treatment arms that advance to Stage 2, additional patients will be randomized equally among the treatment arms (Stage 2) for further evaluation of safety and efficacy.

Number of Patients:

Safety Lead-in:
According to the initial protocol, prior to initiating Stage 1 of the study, a safety lead-in period for abemaciclib plus galunisertib was to be conducted with up to 12 patients. At the time of amendment (c), Lilly determined no additional patients would be enrolled to the safety lead-in and that Arm C (abemaciclib plus galunisertib) would be removed from the study.

Stage 1:
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).

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

Treatment Arms and Duration:

Arm	Dose and Schedule
A	Abemaciclib (CDK4 and CDK6 inhibitor) 200 mg BID with or without food continuous dosing for 28-day cycles
B[a]	Abemaciclib 150 mg BID with or without food continuous dosing for 28-day cycles LY3023414 (PI3K/mTOR dual inhibitor) 150 mg BID with or without food continuous dosing for 28-day cycles
D	Standard-of-Care Choice of: Gemcitabine 1000 mg/m^2 over 30 minutes intravenously on the following days of a 28-day cycle. • Cycle 1: Days 1, 8, 15, and 22 • Cycle 2 and beyond: Days 1, 8, and 15 **OR** Capecitabine 1250 mg/m^2 administered orally BID within 30 minutes after a meal (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 21-day cycles

Abbreviations: BID = twice daily; CDK = cyclin-dependent kinase; PI3K = phosphatidylinositol 3-kinase

[a] Oral combination agents are to be taken at approximately the same time. There is no specific order of administration.

2. Schedule of Activities

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

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).

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.

	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).

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).

	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).

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**	
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.

	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.2.5. On-Study-Treatment Schedule of Activities—Standard of Care Capecitabine (Arm D)

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

	21-Day Cycles Cycle 1	21-Day Cycles Cycle 2- n	
Day within Cycle	**1**	**1**	
Procedure			**Instructions**
Physical examination	X	X	
Vital signs	X	X	Includes weight, temperature, blood pressure, pulse rate, and respiration rate.
Concomitant medication	X	X	
AE collection	X	X	CTCAE Version 4.0.
ECOG performance status	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	Performed by central laboratory ≤3 days prior Day 1 of each cycle (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	Performed by central laboratory ≤3 days prior to Day 1 of each cycle (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	≤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	Performed by central laboratory ≤3 days prior to Day 1 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).

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).

	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).

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.

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

[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

PDACs, $p16^{INK4A}$ is inactivated due to a genetic alteration in CDKN2A, which leads to excessive activation of Cyclin D-CDK4 and 6 signaling (Biankin et al. 2002; Jones et al 2008; Ryan et al 2014; Goel and Sun 2015). In addition, overexpression of Cyclin D1, due to amplification of CCND1, occurs in approximately 68% of pancreatic cancers and is associated with a poor prognosis (Biankin et al. 2002). Several preclinical reports have indicated that cell lines with loss or mutations of CDKN2A or loss of p16 protein expression are particularly sensitive to CDK4 and CDK6 inhibitors (Wiedemeyer et al. 2010; Konecny et al. 2011).

Abemaciclib (LY2835219) is a selective and potent small molecule inhibitor of CDK4 and CDK6. Abemaciclib prevents Rb phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumor growth in preclinical models following short-duration target inhibition. Abemaciclib has broad antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. In vitro, abemaciclib has demonstrated antiproliferative activity in some KRAS mutant pancreatic cancer cell lines (Lilly data on file). In addition, single-agent abemaciclib has demonstrated an acceptable toxicity profile and evidence of clinical activity in breast and non-small cell lung cancers (Dickler et al. 2016; Patnaik et al. 2016).

Given the relevance of the CDK4 and CDK6 pathway in PDAC, the activity of abemaciclib in *KRAS* mutant cancer cell lines, the acceptable toxicity profile of abemaciclib in clinical studies, and the unmet medical need, this study aims to explore the safety and efficacy of abemaciclib in patients with PDAC.

3.2.3. Phosphatidylinositol 3-Kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) Pathway and Role in Pancreatic Ductal Adenocarcinoma

The expression of Cyclin D1 is induced by mitogenic growth factors, acting through various upstream signaling pathways. These signaling pathways, including mitogen-activated protein kinase and PI3K, converge downstream at the Cyclin D1-CDK4 and CDK6 complex, leading to its activation. Frequent activating aberrations of PI3K/mTOR signaling have been reported for several cancers (Opitz et al. 2008; Courtney et al. 2010; Miller et al. 2011; Varghese et al. 2011). PI3K and mTOR signaling is stimulated by various growth factors and their receptors (including insulin) and regulates cell metabolism, growth, survival, proliferation, and motility. A potent impact of CDK4 and CDK6 inhibition in PDAC models has been observed; however, in the majority of models analyzed, acquired/intrinsic resistance has resulted in bypassing of this inhibition. As it is widely recognized that combination targeted therapies may be required for successful treatment of pancreatic cancer, a series of targeted agents were screened in conjunction with a CDK4 and CDK6 inhibitor in cell viability assays. Based upon this screening, PI3K/mTOR inhibitors demonstrated cooperative effects in combination with a CDK4 and CDK6 inhibitor in a pancreatic cancer tumor model (Franco et al. 2014). Synergistic activity of CDK4 and CDK6 and PI3K/mTOR blockade has been observed in other preclinical tumor

models (Gopalan et al. 2013; Ku et al. 2016), and clinical trials are ongoing exploring this strategy.

This study also aims to explore the safety and efficacy of LY3023414, an orally available, potent and selective inhibitor of the class I PI3K isoforms, mTOR, and deoxyribonucleic acid (DNA)-dependent protein kinase (DNA-PK), in combination with abemaciclib in patients with PDAC. LY3023414 has demonstrated an acceptable toxicity profile, and though limited efficacy data are available to date, preliminary evidence of single-agent activity was observed in the Phase 1 Study I6A-MC-CBBA (CBBA) in patients with solid tumors (Lilly data on file)

3.2.4. Transforming Growth Factor-Beta and Role in Pancreatic Ductal Adenocarcinoma

Transforming growth factor-beta (TGF-β) has been shown to be a tumor promoter in advanced, metastatic cancer (de Caestecker et al. 2000; Massagué et al. 2000; Wakefield and Roberts 2002; Derynck and Zhang 2003). In pancreatic cancer, TGF-β has been involved in tumor progression (Miyazono 2000), by activating matrix metalloproteinase-2 and the urokinase plasminogen pathway (Ellenrieder et al 2001). The TGF-β pathway is one of 12 core signaling pathways in pancreatic cancer, and mutations in the TGF-β receptors or the downstream transcription factors (SMAD) occur in 90% to 100% of tumors (Jones et al. 2008). In preclinical models of pancreatic cancer, TGF-β signaling induces Rb phosphorylation, and hence inactivation, leading to cellular proliferation (Biankin et al. 2002; Ouyang et al. 2014). Several mechanisms have been proposed to explain the tumor-promoting activity of TGF-β, such as increased tumor neovascularization, immunosuppression leading to the escape of tumor immune surveillance, and increased migration and invasion resulting in metastasis (Akhurst and Derynck 2001; Derynck et al. 2001; Siegel and Massagué 2003). Hence, recent studies have recognized that TGF-β plays an important role in the progression of pancreatic cancer (Truty and Urrutia 2007). These combined effects on the tumor microenvironment by TGF-β promote tumor progression and therefore, a TGFβ-RI kinase inhibitor is expected to cause arrest of tumor growth and metastasis in patients with PDAC.

Galunisertib (LY2157299) is a small molecule designed to selectively inhibit the serine/threonine kinase of TGF-βRI. Thus, the antitumor effect of galunisertib is expected to result in an increased tumor immune surveillance, reduced metastatic spread, and decreased tumor-associated neoangiogenesis. In a recent first-in-human dose study, Study H9H-MC-JBAH, single-agent administration of galunisertib was associated with partial tumor responses in patients with relapsed glioblastoma multiforme. In addition, galunisertib has shown a favorable toxicity profile and preliminary activity in pancreatic cancer in the clinic. In a randomized, double-blind, Phase 2 study (Study H9H-MC-JBAJ) in patients with PDAC comparing gemcitabine plus galunisertib versus gemcitabine plus placebo, higher PFS and OS were observed in the gemcitabine plus galunisertib arm (3.7 vs 2.8 months and 9.1 vs 7.6 months, respectively). The subgroup of patients with baseline TGFβ1 levels ≤4224 pg/mL had a median OS of 10.9 versus 7.2 months (hazard ratio [HR] = 0.68), respectively, and decreases in TGF-β1 occurred with treatment, correlating with improved OS (Melisi et al. 2016).

In PDAC, an overexpression of epithelial-mesenchymal transition triggering factors, including TGF-β, has been observed and may contribute to the high metastatic potential. In pancreatic cancer cells, a CDK4 and CDK6 inhibitor was found to exert growth-inhibitory effects, although a TGF-βRI inhibitor alone was unable to suppress colony growth in 3-dimensional culture. However, when the TGF-βRI inhibitor was combined with a CDK4 and CDK6 inhibitor, optimal growth inhibition was achieved (Liu and Korc 2012). These preclinical data provide a basis for exploring the combination of abemaciclib and galunisertib in the current study, although, with amendment (c) the assessment of this combination is being discontinued (see Section 5.4.3).

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of abemaciclib, galunisertib, and LY3023414 are to be found in their respective Investigator's Brochure (IB).

More detailed information about the known and expected benefits and risks of capecitabine and gemcitabine may be found in their respective product labels.

4. Objectives and Endpoints

Table JPCJ.4.1 shows the objectives and endpoints of Stage 1.

Table JPCJ.4.2 shows the objectives and endpoints of Stage 2.

Table JPCJ.4.1. Stage 1 Objectives and Endpoints

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

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.

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.

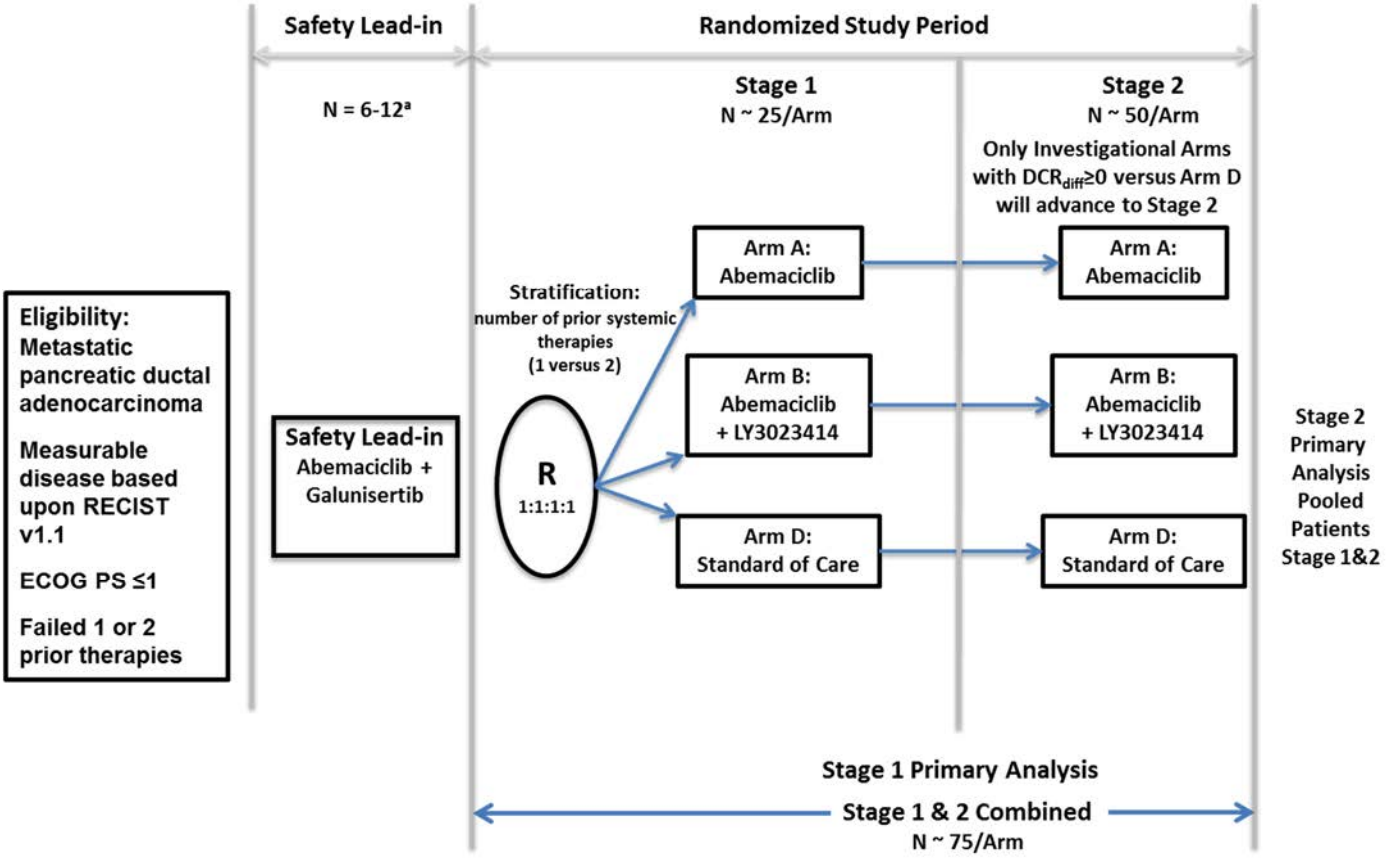
With amendment (c), Stage 1 of the study will randomize patients 1:1:1 into each of the following arms (25 patients per arm):

- 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.

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

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

- 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

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.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

[1] have cytologically or histologically confirmed diagnosis of ductal adenocarcinoma of the pancreas.

[2] have metastatic disease with documented disease progression following previous treatment with at least 1, but no more than 2 prior therapies for metastatic disease, with at least 1 of the prior therapies having been either gemcitabine-based or fluoropyrimidine-based therapy. Neoadjuvant and/or adjuvant therapies for localized resectable or unresectable PDAC each count as a line of therapy if multiagent chemotherapy regimens were administered (and neoadjuvant regimen was different than adjuvant regimen) and if the patient progressed with metastatic disease during treatment or within 6 months of completion of (neo)adjuvant therapy.

Note: Treatment with targeted therapies or immunotherapies for metastatic disease are counted toward the number of prior systemic therapies.

[3] have the presence of measurable disease as defined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009).

[4] have a performance status (PS) of 0 to 1 on the ECOG scale (Oken et al. 1982).

[5] is a patient for whom treatment with monotherapy chemotherapy such as gemcitabine or capecitabine is a reasonable choice.

[6] have discontinued all previous treatments for cancer (including cytotoxic chemotherapy, molecularly targeted therapy, radiotherapy, immunotherapy, and investigational therapy) for at least 14 days prior to receiving the initial dose of study treatment, and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia or peripheral neuropathy.

[7] have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
	Growth factors should not be administered to enable a patient to satisfy study inclusion criteria.
Platelets	≥100 × 10^9/ L
Hemoglobin	≥8 g/dL
	Transfusions to increase the patient's hemoglobin level to 5 mmol are permitted; however, study treatment must not begin until the day after the transfusion.
Hepatic	
Total bilirubin	≤1.5 × ULN
ALT and AST	≤2.5 × ULN **OR** ≤5 × ULN if the liver has tumor involvement
	Patients may have endoscopic or radiologic stenting to treat biliary obstructions. If so, then, bilirubin must return to ≤1.5 times ULN and AST and ALT to ≤5 times ULN prior to enrollment.
	Increased bilirubin up to 2.5 times ULN is acceptable if this elevation is not associated with other signs of liver toxicity or can be explained by mechanical obstruction. The investigator needs to obtain the approval from the Lilly clinical research physician prior to including such a patient.
Renal	
Serum creatinine	≤1.5 × ULN or calculated CrCl ≥50 mL/min by Cockcroft-Gault formula (Appendix 9).

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; CrCl = Creatinine Clearance; ULN = upper limit of normal.

[8] are at least 18 years old at the time of screening or of an age acceptable according to local regulations, whichever is older.

[9] men must be sterile or agree to use an *effective method of contraception* or a *highly effective method of contraception* during the study and for at least 6 months following the last dose of study drug.

Refer to Appendix 1 for definitions of *effective method of contraception* and *highly effective method of contraception*.

[10] women of child-bearing potential must:

a. have a negative serum pregnancy test within 7 days prior to study treatment initiation, and

b. agree to use a *highly effective method of contraception* during the study and for at least 6 months following the last dose of study drug.

Refer to Appendix 1 for the definition of *highly effective method of contraception*.

[11] have given written informed consent prior to any study-specific procedures.

[12] are able to swallow capsules and tablets.

[13] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

6.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[14] have a serious concomitant systemic disorder or preexisting condition (for example, active infection including human immunodeficiency virus, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis) that, in the opinion of the investigator, would compromise the patient's safety or ability to adhere to the protocol.

[15] have a personal history of any of the following conditions: syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.
Exception: Patients with controlled atrial fibrillation for ≥30 days prior to study treatment initiation are eligible.

[16] Deleted Criterion

[17] have insulin-dependent diabetes mellitus. Patients with type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetics as documented by hemoglobin A1c (HbA1c) <7%.

[18] have symptomatic central nervous system metastasis. Screening of asymptomatic patients is not required for enrollment.

[19] have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 2 years.

[20] have had major surgery within 7 days prior to initiation of study drug to allow for postoperative healing of the surgical wound and site(s).

[21] are currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving nonapproved use of a device, then agreement with the investigator and Lilly clinical research physician (CRP) is required to establish eligibility.

[22] have received treatment with a drug that has not received regulatory approval for any indication within 14 days prior to receiving the initial dose of study treatment.

[23] have previously received treatment with any CDK4 and 6 inhibitor or PI3K and/or mTOR inhibitor or have a known hypersensitivity to any component of the investigational products in this study.

[24] have a known hypersensitivity to investigator's choice of standard of care (gemcitabine or capecitabine) in anticipation that the patient may be randomized to Arm D.

[25] are pregnant or breastfeeding

6.3. Lifestyle Restrictions

Patients should avoid consuming grapefruit juice.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened no more than once (after signing a new informed consent form [ICF] and being assigned a new patient number), and only after discussion with and permission from the Lilly CRP or designee.

Repeating of laboratory tests during the screening period does not constitute re-screening. Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the screening period.

7. Treatments

7.1. Treatments Administered

Table JPCJ.7.1 shows the treatment regimens. Study treatment is defined as any of the individual study drugs (inclusive of standard of care) and/or the combination study drug.

Table JPCJ.7.1. Treatment Regimens

Arm	Dose and Schedule
A	Abemaciclib (CDK4 and CDK6 inhibitor) 200 mg BID with or without food continuous dosing for 28-day cycles
B[a]	Abemaciclib 150 mg BID with or without food continuous dosing for 28-day cycles LY3023414 (PI3K/mTOR dual inhibitor) 150 mg BID with or without food continuous dosing for 28-day cycles
D	Standard-of-Care Choice of: Gemcitabine 1000 mg/m^2 over 30 minutes intravenously on the following days of a 28-day cycle. • Cycle 1: Days 1, 8, 15, and 22 • Cycle 2 – n: Days 1, 8, and 15 **OR** Capecitabine 1250 mg/m^2 administered orally BID within 30 minutes after a meal (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 21-day cycles.

Abbreviations: BID = twice daily; CDK = cyclin-dependent kinase

[a] Oral combination agents are to be taken at approximately the same time. There is no specific order of administration.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the study treatments to the patient, study site personnel, and/or the patient's legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- at the end of the study, returning all unused study treatment to Lilly, or its designee, unless Lilly and sites have agreed all unused study treatment is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

All study treatments will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Safety Lead-in

Based on the original protocol, prior to the randomized portion of the study (Stage 1 and Stage 2) up to 12 patients who satisfied all inclusion criteria and none of the exclusion criteria were to be enrolled to a safety lead-in period. Initially, 6 patients were to be enrolled to receive abemaciclib plus galunisertib. If the combination of abemaciclib 150 mg BID and galunisertib 150 mg BID was not tolerated (that is, more than one patient experienced a DLT within the first 28-day cycle), then the dose of abemaciclib was to be reduced to 100 mg BID and an additional 6 patients enrolled at this dose. If the combination was not tolerated (that is, more than one patient experienced a DLT within the first 28-day cycle) at the reduced dose of abemaciclib, then patients were not to be enrolled to the abemaciclib plus galunisertib arm (Arm C).

For the safety lead-in, any patient who was discontinued from the study before receiving at least 75% of the planned doses of abemaciclib and galunisertib in Cycle 1 was deemed nonevaluable for assessment of that dose level and was replaced, unless that patient experienced a DLT before withdrawal. Nonevaluable patients were to be replaced to ensure that no fewer than 6 patients received at least 75% of the planned doses of abemaciclib and galunisertib in Cycle 1, unless enrollment to that cohort was stopped because more than one patient at that dose level experienced a DLT.

At the time of amendment (c), Lilly determined no additional patients would be enrolled to the safety lead-in and that Arm C would be removed from the study. A total of 7 patients had been enrolled in the safety lead-in and 2 were still on treatment. Ongoing patients enrolled to the safety lead-in may continue on study treatment if, at the discretion of the treating investigator, the patients are benefiting from therapy and not considered at risk from a safety standpoint.

Toxicities were graded according to Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0). If multiple toxicities were observed, the presence of DLTs was to be based on the most severe toxicity experienced. During the Safety Lead-in Period only, DLTs were defined as any of the following events that occurred during the first cycle of administration of the combination of abemaciclib and galunisertib and were considered by the investigator to be attributable to either study treatment alone or the combination of the two:

- Grade 3 or 4 nonhematologic toxicity (except for nausea, vomiting, diarrhea, or electrolyte disturbance)
- Grade 3 or 4 nausea or electrolyte disturbance that persisted more than 48 hours despite maximal supportive intervention
- Grade 3 vomiting or diarrhea that persisted more than 48 hours despite maximal supportive intervention
- Grade 4 vomiting or diarrhea of any duration
- Grade 4 hematologic toxicity that persisted more than 5 days
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia of any duration
- Grade 3 or 4 neutropenia with fever

As further enrollment to the Safety Lead-in will not occur and Arm C is removed with amendment (c), the randomized portion of the study will begin. Randomization will be stratified by number of prior systemic therapies (1 versus 2).

The period between randomization to study treatment and the first dose (Cycle 1, Day 1) should not exceed 7 days.

Stage 1

Patients will be randomized 1:1:1 among the investigational arms and the standard-of-care arm, to provide a total of 25 patients per arm. Patients assigned to the standard-of-care arm (Arm D) will be administered either gemcitabine or capecitabine, at the discretion of the investigator. In determining which standard-of-care therapy to administer, the investigator should take into consideration NCCN Guidelines, which indicate that patients previously treated with gemcitabine-based therapy should receive capecitabine and patients previously treated with fluoropyrimidine-based therapy should receive gemcitabine.

Stage 2

An additional 50 patients will be randomized to each investigational arm that passes Stage 1 as well as in the standard-of-care arm.

The interactive web-response system (IWRS) will be used to assign unique patient identification numbers and study treatment to each patient in the Safety Lead-In, Stages 1, and Stage 2.

7.2.1. Selection and Timing of Doses

A cycle is defined as an interval of 28 days for all study treatments except capecitabine (21-day cycle). During all cycles, oral study treatments should be taken with a glass of water at approximately the same time each day. Patients should not chew or crush these study treatments. If the patient misses or vomits a dose of oral study treatment, the patient should skip the dose and take the next dose as scheduled. For patients assigned to the safety lead-in or Arm B, combination agents are to be taken at approximately the same time, in no specific order of administration.

A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. A cycle delay due to toxicity is permitted up to 14 days (see Section 7.4). In the event only 1 of 2 study treatments for patients in the safety lead-in or Arm B is suspended or if each study treatment is reintroduced in a sequential manner, Day 1 of the next cycle is considered the date that the first of the individual study treatments is dispensed and administered to the patient.

The actual doses of gemcitabine and capecitabine to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the dose will not need to be recalculated. A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

A patient may continue to receive study treatment until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 8).

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

7.4.1. Dosage Modifications for Investigational Agents

Dose adjustments (suspensions and reductions) will be made based on the clinical assessment of hematologic and nonhematologic toxicities (defined as an AE possibly related to study treatment per investigator judgment). The CTCAE v 4.0 will be used to assess AEs. Treatment may be suspended for a maximum of 14 days to allow a patient sufficient time for recovery from study treatment-related toxicity. 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. Patients in the safety lead-in receiving galunisertib must receive a minimum of 10 days of dosing in a 28-day cycle.

This section is intended to be a guideline for the investigator and cannot fully replace the investigator's best judgment. The investigator should assess the contribution of each individual investigational agent to the AE and differentiate from disease-related signs and symptoms before deciding on a dose suspension or reduction. In assessing to which study treatment to assign a toxicity for the purposes of dose adjustments, the investigator may consult Table JPCJ.7.2, which includes the most common treatment-related AEs reported in the IB for each investigational agent. This listing of common treatment-related AEs is not exhaustive; investigators should consider all preclinical and clinical data provided in the respective IB (or product label in the case of Arm D) for each agent when determining whether to adjust a patient's study treatment. Additional dose modification guidance for patients experiencing events that are considered by the investigator to be related to at least 1 investigational agent can be found in Appendix 10.

Table JPCJ.7.2. Common Treatment-Related Adverse Events for Investigational Agents

Investigational Agents	Most Common Treatment-Related Adverse Events
Abemaciclib	diarrhea (63.0%), nausea (45.1%), fatigue (40.5%), vomiting (24.9%), white blood cell count decreased (24.9%), platelet count decreased (23.1%), neutrophil count decreased (22.5%), anemia (19.7%), anorexia (17.3%), creatinine increased (11.0%), and weight loss (10.4%)
LY3023414	nausea (36.1%), fatigue (34.0%), vomiting (29.7%), decreased appetite (23.4%), diarrhea (20.2%), rash (13.8%), and oral mucositis (11.7%)
Galunisertib	nausea (10.6%), fatigue (7.8%), diarrhea (7.2%), vomiting (7.2%), and pruritus (5.5%)

Dose reductions for investigational agents should be as shown in Table JPCJ.7.3. Study treatment must be reduced sequentially by one dose level unless an exception is granted in consultation with the Lilly CRP. Mid-cycle dose reductions for abemaciclib may be implemented by informing patients to reduce the number of 50-mg capsules taken for each dose (with dose reductions appropriately documented in the electronic case report form [eCRF]); however, mid-cycle dose reductions of LY3023414 and galunisertib will require patients to return to the clinic and the site to call the IWRS Help Desk to dispense new study treatment. If 1 study treatment (Safety Lead-in or Arm B) has been maximally dose-reduced due to toxicity and the toxicity has not resolved, patients may continue to receive the other study treatment at the current dose if it is apparent that the toxicity is not related to the other study treatment and the patient continues to receive clinical benefit.

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

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.

A new cycle of gemcitabine will not be given unless the ANC is $\geq 1.0 \times 10^9$/L and platelets are $\geq 100 \times 10^9$/L. All nonhematologic toxicities (excluding alopecia) should also return to CTCAE Grade ≤1 or baseline prior to reinitiating treatment. Treatment may be delayed up to 4 weeks after completion of the 28-day cycle to allow sufficient time for recovery.

For nonhematologic toxicities, gemcitabine should be permanently discontinued in the event any of the following occur: unexplained dyspnea or other evidence of severe pulmonary toxicity, severe hepatic toxicity, hemolytic-uremic syndrome, capillary leak syndrome, or posterior reversible encephalopathy syndrome. Gemcitabine should be suspended or the dose reduced by 50% for other severe (Grade 3 or 4) nonhematologic toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

For patients who have a gemcitabine dose reduction within a cycle, subsequent dose escalation to the original dose will be allowed, providing that the patient tolerates the cycle given at the reduced dose level.

If a patient requires a second reduction within a cycle and after a dose re-escalation, the dose should not be re-escalated to the higher level a second time. The patient should continue to receive the reduced dose for the remainder of the study. If a patient requires a second reduction after a cycle is completed, the dose should not be re-escalated to the higher level a second time unless, in the opinion of the investigator, this is likely not to result in additional toxicity.

Patients requiring more than 2 consecutive dose reductions (within a cycle or after a cycle is completed) for gemcitabine-related hematologic and/or nonhematologic toxicity, will be discontinued from the study unless there is clinical benefit for the patient.

7.4.3. Dosage Modifications for Capecitabine

The safety profile of capecitabine as monotherapy has been characterized for patients with colorectal and breast cancers. In the studies of patients with colorectal and breast cancers (Xeloda® capecitabine [tablets for oral use] prescribing instructions page [WWW]), patients received monotherapy with capecitabine 1250 mg/m^2 BID. For these patients, the incidence of Grade 3/4 hematologic abnormalities (neutropenia, thrombocytopenia, or decreases in hemoglobin) was low. Common nonhematologic Grade 3/4 toxicities include diarrhea, abdominal pain, hand-and-foot syndrome, and hyperbilirubinemia. Of note, elderly patients (≥65 years) may experience a higher incidence of Grade 3/4 toxicities and therefore therapy may be initiated at a lower dose per the discretion of the investigator and institutional guidelines.

The capecitabine dose can be adjusted following Table JPCJ.7.5, as this presents the in-label recommendations for dose reductions for capecitabine when used as monotherapy. Once the dose has been reduced, it should not be subsequently increased. Doses omitted for toxicity should not be replaced. Capecitabine will not be given unless the ANC is $\geq 1.5 \times 10^9$/L and platelets are $\geq 100 \times 10^9$/L. If Grade 3/4 neutropenia or thrombocytopenia occurs, stop therapy until condition resolves. If hand-and-foot syndrome occurs, stop treatment until event resolves or decreases in intensity. For management of diarrhea, see Section 7.7.2.

Table JPCJ.7.5. Capecitabine Dose Modifications

CTCAE Grade	During a Course of Therapy	Dose Adjustment for Next Treatment (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 0 to 1	100
2nd appearance		75
3rd appearance		50
4th appearance	Discontinue treatment permanently	-
Grade 3		
1st appearance	Interrupt until resolved to Grade 0 to 1	75
2nd appearance		50
3rd appearance	Discontinue treatment permanently	-
Grade 4	Discontinue permanently or if physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0 to 1	50

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009).

7.5. Preparation/Handling/Storage/Accountability

All study treatments will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements.

Abemaciclib will be supplied by Lilly as capsules for oral administration. Abemaciclib capsules should be stored according to the temperature range listed on the product label, and should not be opened, crushed, or chewed. Patients should store the abemaciclib capsules in the original package provided and be instructed to keep all medication out of reach of children.

LY3023414 will be supplied by Lilly as tablets for oral administration. LY3023414 should be stored according to the temperature range listed on the product label, and should not be crushed or dissolved.

Galunisertib will be supplied by Lilly as tablets in blister packs. Galunisertib should be stored according to the temperature range listed on the product label, and the tablet should remain in the blister pack until just prior to administration.

All commercial products will be supplied and labeled according to country regulation requirements. Products should be stored according to the label instructions.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by counting returned tablets/capsules. Deviations from the prescribed dosage regimen should be recorded in the case report form (CRF).

A patient will be considered significantly noncompliant if he or she misses more than 25% of the planned doses for study treatment in a cycle. A patient will also be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken

more than the prescribed amount of medication. As outlined in Section 7.4, dose suspensions due to treatment-related toxicities may occur and will not result in a patient being considered as noncompliant.

7.7. Concomitant Therapy

Patients should receive full supportive care therapies concomitantly during the study, including antiemetic treatment as per institutional guidelines.

The use of granulocyte-colony stimulating factor is permitted during investigational therapy at the discretion of the investigator as prescribed per American Society for Clinical Oncology guidelines (Smith et al. 2015). Growth factors should not be administered to enable a patient to satisfy study inclusion criteria. Dosing of study drug must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of study drug must be reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

Use of erythropoietin is allowed (Rizzo et al. 2008).

For patients assigned to abemaciclib treatment arms (safety lead-in as well as Arms A and B) or those assigned to Arm D who are receiving capecitabine, prothrombin time or international normalized ratio must be routinely monitored if patients are receiving concomitant oral coumarin-derivative anticoagulants.

For patients in Arm B requiring initiation of or changes to oral antidiabetic medications for blood glucose control, the first choice recommendation is sitagliptin because of low potential for drug interactions mediated via cytochrome P450 (CYP) 3A and renal transporters. Additional options may include repaglinide or low-dose sulfonylureas (with due precautions, including standard education of patients regarding the signs of hypoglycemia).

No other chemotherapy, immunotherapy, radiation therapy, hormonal cancer therapy, or experimental medications will be permitted while the patients are participating in this study. Any disease progression requiring anticancer therapy will be cause for early discontinuation from the study.

7.7.1. Surgery for Cancer

A patient may receive surgery (for example, metastasectomy) during the study treatment period if clinically indicated. Patients undergoing surgery should have study treatment suspended for at least 7 days prior to surgery, as well as 7 days postoperatively to allow for wound-healing. If a patient undergoes a surgical procedure that involves removal of tumor, then formalin-fixed paraffin-embedded (FFPE) tumor from that procedure may be requested.

7.7.2. Management of Diarrhea

Upon treatment initiation, patients assigned to abemaciclib treatment arms (Safety Lead-In as well as Arms A and B) or those assigned to Arm D who are receiving capecitabine should

receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to at least Grade 1, study treatment should be suspended until diarrhea is resolved to at least Grade 1.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring intravenous [IV] rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given IV fluid (IV hydration) and electrolyte replacement.

7.7.3. Management of Hyperglycemia

Hyperglycemia has been observed in patients treated with LY3023414. Patients who develop hyperglycemia during the study should be treated according to the American Diabetes Association and European Association for the Study of Diabetes consensus guidelines. It is recommended to start treatment with an oral antidiabetic medication, preferably sitagliptin. Additional options may include repaglinide or low-dose sulfonylureas (with due precautions, including standard education of patients regarding the signs of hypoglycemia) (see Section 7.7).

7.7.4. Supportive Management for Stomatitis/Mucositis

Stomatitis, including oral mucositis, has been observed in patients treated with LY3023414. Prophylactic treatment and early recognition of this AE is highly important. Early and active management includes the promotion of good oral hygiene. Topical treatments with corticosteroids and mouthwashes similar to those used for management of chemotherapy-induced stomatitis are recommended. However, mouthwashes containing alcohol, peroxide, iodine, and thyme derivatives should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed. Patients also should be advised to avoid acidic, spicy, and hard or crunchy foods, and to consume foods that are tepid rather than hot in temperature to prevent the potential for mechanical injury.

7.7.5. Concurrent Use of Inducers and Inhibitors of CYP3A4, Substrates of CYPS with Narrow Therapeutic Range, or Drugs Causing QTc Prolongation

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (area under the concentration-time curve) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE) and coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF). Based on these findings, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and inhibitors of CYP3A4 should be substituted or avoided if possible (Appendix 7).

In addition, *in vitro* studies in primary cultures of human hepatocytes indicate that abemaciclib and its active metabolites LSN2839567 and LSN3106726, down regulate messenger ribonucleic acid (mRNA) of CYPs including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A at clinically relevant concentrations. The mechanism of down regulation and its clinical relevance are presently not understood. Caution should be exercised when coadministering substrate drugs of CYPs with narrow therapeutic margin (Appendix 7).

Abemaciclib and its major metabolites inhibit the efflux transporters P-glycoprotein and breast cancer resistant protein and renal transporters organic cation transporter 2, multidrug and toxin extrusion protein 1 (MATE1) and MATE2-K at clinically relevant concentrations. Therefore, substrates of these transporters such as metformin and those with a narrow therapeutic index such as digoxin and dofetilide should be substituted or avoided if possible.

For LY3023414, preclinical data suggested potential inhibition of CYP3A4-mediated metabolism and potential corrected QT (QTc) interval prolongation likely secondary due to the sustained hyperglycemia induced by LY3023414 at plasma concentrations exceeding the ones observed in patients (for details, see the IB for LY3023414). Clinically, no obvious trend for QTc prolongation has been observed in patients receiving LY3023414. The clinical data from Study CBBA indicate LY3023414 is a weak inhibitor of CYP3A4, as concomitant administration of LY3023414 and midazolam leads to an increased exposure of midazolam (fold increase: mean 1.46). LY3023414 may lead to an increase in exposure to abemaciclib and other CYP3A4 substrates. Therefore, caution should be exercised when coadministering substrate drugs that are substrates of CYP3A4 with narrow therapeutic margin (Appendix 7) or drugs causing QTc interval prolongations (Appendix 8). As stated above, grapefruit juice as well as inducers and inhibitors of CYP3A4 should be substituted or avoided if possible (Appendix 7).

Galunisertib is cleared predominantly by oxidative metabolism, with identified (inactive) metabolites accounting for 76% of the recovered dose, compared to only 13% of the dose being excreted as intact parent drug in the urine and feces combined (Study H9H-MC-JBAM). An in vitro substrate depletion approach using recombinant human CYP enzymes showed that 99% of the in vitro hepatic CYP-mediated clearance of galunisertib was linked to CYP3A, with CYP2C19 accounting for the remaining 1%. As such, potent CYP3A inhibitors may have the

potential to increase exposures of galunisertib. There are no specific drug-drug interactive studies conducted to date.

7.8. Treatment after the Safety Lead-in, the End of Stage 1, and Study Completion

7.8.1. End of Safety Lead-in

Following the completion of the Safety Lead-in assessment, patients who are still on study treatment may continue to receive study treatment until discontinuation criteria have been met. Investigators will continue to follow the Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.2. End of Stage 1

Following the completion of the Stage 1 assessment, some treatment arms may not advance to Stage 2. Patients who are still on study treatment at the time of treatment arm discontinuation may continue to receive study treatment until discontinuation criteria have been met. Investigators will continue to follow the Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.3. Study Completion

Study completion will occur following the primary analysis of PFS after Stage 2, as determined by Lilly (that is, the scientific evaluation will be complete). Investigators will continue to follow the Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred. End of Study is defined in Section 5.3.

7.8.4. Continued Access

Patients (Safety Lead-in, Stage 1, and Stage 2) who are still on study treatment at the time of study completion may continue to receive study treatment until discontinuation criteria have been met (Figure JPCJ.7.1).

Continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.

The patient's continued access to study treatment will end when a criterion for discontinuation is met (Section 8). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue study treatment and lasts approximately 30 (±7) days. Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities (Table JPCJ.2.8).

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

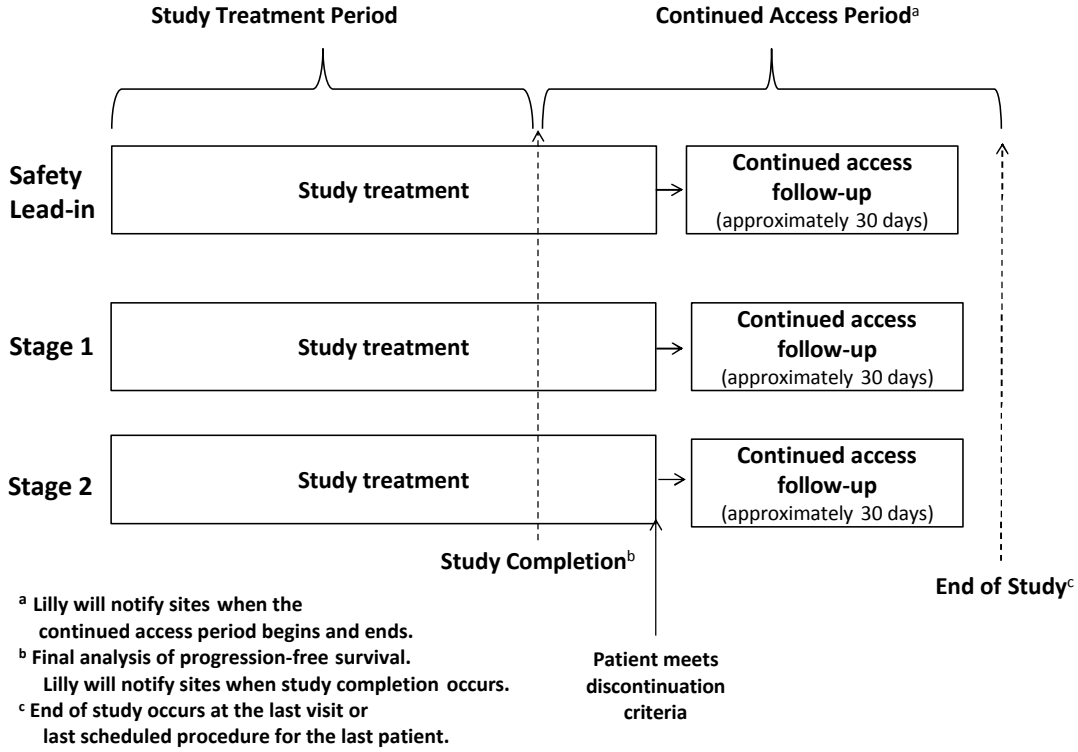


Figure JPCJ.7.1. Continued access diagram.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

For patients assigned to the Safety Lead-in or Arm B, if 1 study drug is discontinued due to toxicity, patients may continue to receive the other study drug until a discontinuation criterion has been met.

Patients will be discontinued from all study treatment in the following circumstances:

- the patient is enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- the patient becomes pregnant during the study. See Section 9.2 regarding regulatory reporting requirements on fetal outcome and breast-feeding.
- the patient is significantly noncompliant with study procedures and/or treatment
- disease progression
- unacceptable toxicity
- the patient has undergone the maximum allowable dose reductions and experiences an AE that would cause an additional dose reduction
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent.
- the investigator decides that the patient should be discontinued from study treatment
- the patient requests to be discontinued from study treatment
- the patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient be discontinued from study treatment

Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

8.2. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- the investigator decides that the patient should be discontinued from the study

- the patient requests to be discontinued from the study
- the patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient be discontinued from the study

Patients who discontinue from the study early will continue to be followed according to the Post-Treatment Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

Study site personnel, or an independent third party, will attempt to collect the survival status for all randomized patients who are lost to follow-up, including randomized patients who do not receive study treatment, within legal and ethical boundaries. Public sources may be searched for survival status information. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect survival status information.

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 3 provides a list of the laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Tumor assessments will be performed according to RECIST v.1.1 (Eisenhauer et al. 2009) for each patient at screening (within 28 days of randomization) and subsequently approximately every 8 weeks (±3 days). Upon initiation of Stage 2, Lilly or its designee will collect and store all tumor assessment images; retrospective collection of Stage 1 images will occur only for those arms that advance to Stage 2. An independent review of imaging scans may be performed by an independent panel of radiologists.

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, MRI is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous contrast is required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST v.1.1 (Eisenhauer et al. 2009).

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiological scan of the thorax, abdomen, and pelvis is required at screening; subsequently, scans of the thorax for tumor assessments (CT of the chest for safety is required per the Schedule of Activities for patients in the safety lead-in; see Section 9.4.1) are required only for those patients with evidence of disease on the baseline scan or if clinically indicated (that is, progressive disease is suspected).

Partial response or CR will not require confirmation to be considered a response. In the case of SD, postbaseline tumor assessments must have met the SD criteria at least once after randomization at a minimum interval of 6 weeks to assign a best response of SD.

See Section 10.3.1 for definitions of the efficacy endpoints.

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

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

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.

9.7. 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.

9.8.1. Blood Samples for Nonpharmacogenetic Biomarker Research

Plasma samples for nonpharmacogenetic biomarker research will be collected as specified in Appendix 4, where local regulations allow.

Samples will be examined for biomarkers related to variable responses in those treated with abemaciclib, galunisertib, LY3023414, gemcitabine, or capecitabine, including the mechanisms of action involving immune function, cell cycle regulation, and/or PDAC, and/or for related research methods or validation of diagnostic tools or assays.

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 ERBs/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, galunisertib, or LY3023414 or after these study treatments become commercially available.

9.8.2. Tissue Samples for Nonpharmacogenetic Biomarker Research

Tumor tissue samples will be examined for biomarkers related 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.

Collection of the following tumor tissue sample is **required** for all patients in order to participate in this study: FFPE tumor tissue obtained from the primary tumor or metastatic site as a block or unstained slides. However, if this sample is not available for a patient or provision of the sample is restricted by local regulations, a protocol deviation will not be incurred and the patient is eligible for the study. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. Pathology report accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned. 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.

Patients may be asked to undergo collection of an additional core needle biopsy specimen and blood sample after treatment with abemaciclib, LY3023414, gemcitabine, or capecitabine has been initiated or after disease progression. If requested, this biopsy specimen and blood sample will be used to further investigate molecular features that may explain treatment response and resistance mechanisms.

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 ERBs/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, galunisertib, or LY3023414 or after these study drugs become commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies, including mutation profiling, copy number variability, gene expression, multiplex assays, and/or immunohistochemistry, may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

9.9. Health Outcomes

The primary health outcomes research goal is to determine if abemaciclib therapy is able to palliate pain, as measured by the modified Brief Pain Inventory-short form (mBPI-sf) (Cleeland and Ryan 1994). Additionally, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (Aaronson et al. 1993) will assess the broader impact of abemaciclib therapy on symptoms, functioning and quality of life.

Patient-reported questionnaires should be completed by patients when a linguistically validated language translation is available in which the patient is fluent or literate.

At each time point identified in the Study Schedule (Section 2), a paper copy of the mBPI-sf and EORTC QLQ-C30 questionnaires should be administered to the patient prior to extensive interaction with site staff and study drug administration.

9.9.1. Pain Intensity

The mBPI-sf (Cleeland and Ryan 1994) is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for patients to record the presence of pain in general, pain relief, and pain interference with function (general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, and enjoyment of life).

Responses for the mBPI-sf items are captured through the use of 11-point numeric rating scales anchored at 0 (*no pain* or *does not interfere*) and ranged through 10 (*pain as bad as you can imagine* or *completely interferes*). The mBPI-sf recall period is 24 hours, and typical completion time for this instrument is less than 5 minutes. Focused analysis will be on “worst pain”.

Use of pain medication will be assessed in conjunction with the mBPI-sf assessment. Data on each individual prescription and over-the-counter analgesic medication will be recorded on the Concomitant Medications eCRF. The use of pain medications should be reviewed with the patient at each subsequent visit. Any changes to analgesic use (new or stopped analgesics) will be recorded on the eCRF. Pain medication will be classified into medication categories, using the World Health Organization analgesic ladder. A medication category will be assigned based on the maximum analgesic therapy administered for that cycle on a routine basis.

The BPI population will include all patients who completed at least 1 baseline followed by at least 1 BPI “worst pain” postbaseline assessment.

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.

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

which he or she was randomized. The safety population will be used for all dosing/exposure, safety, and resource utilization analyses.

Pharmacokinetic population: will include all randomized patients who received at least 1 dose of study treatment and have baseline and at least 1 postbaseline evaluable PK sample.

Biomarker population: will include the subset of patients from whom a valid assay result has been obtained.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Unless otherwise stated, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and all confidence intervals (CIs) will be given at a 2-sided 95% level.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Efficacy Analyses

Stage 1 analysis will be performed approximately 16 weeks after the last planned Stage 1 patient enters treatment. All tumor assessment data accumulated during this period (beyond 16 weeks for some patients, if available), will be included in the assessment of DCR. This analysis will compare DCR in the investigational arms (Arms A and B) to the standard-of-care arm (Arm D). Following the completion of the Stage 1 assessment, any treatment arm(s) with a DCR difference ≥ 0 as compared to the standard of care (Arm D) will be selected to advance to Stage 2. Enrollment may continue while Stage 1 analysis is ongoing. Any patients enrolled during the Stage 1 analysis will not be included in Stage 1 analysis but will be included in the analysis at the end of Stage 2.

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.

The stratification factors are captured in the IWRS and on eCRFs. Unless otherwise stated, all stratification analyses will be based on the stratification factors per CRF.

Key efficacy parameters are defined as follows:

ORR: The denominator of objective response rate (ORR) includes each randomized patient. The numerator includes those patients counted in the denominator with a best overall tumor response of PR or CR.

DCR: Using the same denominator as for ORR, the numerator of the DCR includes those patients counted in the denominator with a best tumor response of SD, PR, or CR.

DOR: The duration of response (DOR) is defined only for responders (patients with a CR or PR). It is measured from the date of first evidence of a CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date, DOR will be censored at the date of the last complete objective progression-free disease assessment.

PFS: The PFS time 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. The censoring is taken in the following order:

- if a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the randomization date, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,
- if a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last complete objective progression-free disease assessment date.

Additional sensitivity analysis using alternate censoring rules may be conducted. Additional details regarding these censoring rules will be defined in the SAP.

OS: OS duration is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cutoff date, OS will be censored at the last known alive date.

ORR, DCR, DOR, and PFS will be assessed based on RECIST 1.1.

For time-to-event parameters, such as PFS, OS, and DOR, the Kaplan-Meier method will be used to estimate parameters (for example, medians, quartiles, 3 months, and 6 month event rates) (Kaplan and Meier 1958). Comparison between abemaciclib-containing treatment arms and the standard-of-care arm will be done using the log-rank test stratified by randomization strata. An unstratified log-rank test will also be performed. The stratified and unstratified Cox proportional hazard model (Cox 1972) will be used to estimate the HR and corresponding 95% CI.

The ORR and DCR of each treatment arm will be calculated as defined by RECIST 1.1. All rates will be compared between abemaciclib-containing treatment arms and the standard-of-care arm based on a normal approximation for the difference between the rates.

Full details around analyses will be included in the SAP.

All rates will be compared between treatment arms based on a normal approximation for the difference between the rates.

10.3.2. Safety Analyses

All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

Adverse events will be reported using a unified CTCAE/Medical Dictionary for Regulatory Activities (MedDRA™) reporting process:

- The CTCAE v4.0 term reported by the investigator will be mapped to the MedDRA Preferred Term (PT) and System Organ Class (SOC) of the corresponding MedDRA Lower Level Term (LLT), unless the reported CTCAE term is 'Other – specify'.
- If the reported CTCAE term is 'Other – specify', the MedDRA LLT, PT, and SOC mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process.

Safety analyses will include summaries of the following:

- treatment-emergent AEs, including severity and possible relationship to study drug
- treatment-emergent SAEs, including possible relationship to study drug
- treatment-emergent AEs leading to dose adjustments
- discontinuations from study treatment due to treatment-emergent AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs.

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, as defined in the SAP, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population considered for regulatory approval.

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications by treatment arm will be reported.

10.3.3.4. Poststudy-Treatment-Discontinuation Therapy

The numbers and percentages of patients receiving poststudy-treatment-discontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy) and by drug class and/or name, overall and by line of therapy.

10.3.3.5. Treatment Compliance

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

Study treatment compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments.

10.3.3.6. Pharmacokinetic/Pharmacodynamic Analyses

PK analyses will be conducted on all patients who have received at least 1 dose of investigational agent and have evaluable PK samples and sufficient dosing information.

Mean population PK parameters for abemaciclib in plasma (for example, clearance, exposure, volume of distribution) and inter-individual PK variability will be computed using nonlinear mixed effect modelling (NONMEM).

Likewise, and if warranted by the data, mean population PK parameters for LY3023414 and galunisertib in plasma and interindividual variability estimates will also be computed using nonlinear mixed-effect modelling implemented in NONMEM.

The observed concentrations of abemaciclib and metabolites, LY3023414, and galunisertib, may be summarized by time and dose.

Pharmacodynamic samples will be collected as specified in the Study Schedule and PK and Pharmacodynamics (PD) Sampling Schedule (Appendix 4). Refer to these attachments (including footnotes) for important information about these samples and their collection.

Furthermore, PD data (such as neutrophil, lymphocyte, or platelet counts in blood) collected in this study may also be analyzed by means of NONMEM and connected to the population PK model in a PK/PD model.

Pharmacodynamic data from all patients undergoing PD assessments will be analyzed. The PD data will be combined and exploratory analyses will be conducted to determine if a relationship exists between plasma concentration and PD effect(s) in humans. Interpatient variability in human PD response may also be assessed.

10.3.3.7. Biomarker Analyses

Correlative analyses will be performed to investigate associations between biomarkers and clinical endpoints as deemed appropriate.

10.3.3.8. Health Outcome/Quality of Life Analyses

For each instrument, the compliance rate (overall, and by baseline [Screening, Cycle 1 Day 1], on-therapy [Cycle 2 Day 1 and later], and follow-up) by treatment arm will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study). Compliance rates, reasons for noncompliance, and data collected for each instrument will be summarized by treatment arm.

A multivariate mixed repeated model will be applied to compare the trend over time for a prespecified total score/domain score/item of interest between treatment arms and by response group (PR, SD, or progressive disease); the model will include time, treatment, and interaction of time and treatment, and may be adjusted for other covariates.

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.

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Appendix 1. Abbreviations and Definitions

Term	Definition
5-FU	5-fluorouracil
AC	assessment committee
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
CA	carbohydrate antigen
CDK	cyclin-dependent kinase
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
collection database	a computer database where clinical trial data are entered and validated.
CR	complete response
CRF/eCRF	case report form / electronic case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicities
DNA	deoxyribonucleic acid

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.

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

PK	pharmacokinetics
PR	partial response
PT	preferred term
PTT	partial prothrombin time
QTc	corrected QT interval
randomize	the process of assigning patients to an experimental group on a random basis
Rb	retinoblastoma
RECIST	Response Evaluation Criteria In Solid Tumors
reporting database	point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	statistical analysis plan
screen	act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TGF-β	transforming growth factor beta
TGF-βRI	TGF-β receptor type I
ULN	upper limit of normal

Appendix 2. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of study treatment.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

Ethical Review

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERBs/IRBs should be provided with the following:

- the current IBs, Package Inserts, and/or Summaries of Product Characteristics and updates during the course of the study
- the ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations.

Some obligations of Lilly may be assigned to a third-party organization.

Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The Lilly responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs/IRBs with direct access to original source documents.

Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into Lilly-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's

database system. All validated data will subsequently be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB/IRB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry[a]:**
Hemoglobin	Sodium
Hematocrit	Magnesium
Erythrocyte count (RBC)	Phosphorus
Mean cell volume (MCV)	Potassium
Mean cell hemoglobin concentration (MCHC)	Chloride
Leukocytes (WBC)	Calcium
Neutrophils (segmented and bands)	Albumin
Lymphocytes	Total protein
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Creatinine Clearance[f]
Platelets	Alkaline phosphatase
	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
	Total bilirubin and direct bilirubin
Renal Function[a,d]:	Glucose (fasting)[c]
Cystatin C	Lactate dehydrogenase
	Uric Acid
Coagulation[b,e]:	**HbA1c[a,c]**
Partial thromboplastin time (PTT) or	
International normalized ratio (INR)	**Serum pregnancy test** (women of childbearing potential only)[b]
Tumor Marker[a]:	**Urine pregnancy test** (women of childbearing potential only and only where required by local law or regulations)[b]
CA19-9	

Abbreviations: HbA1c = glycated hemoglobin; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated (central) laboratory.

[b] Assayed by investigator-designated (local) laboratory.

[c] Performed at screening for all patients, and subsequently only for patients receiving LY3023414 (PI3K/mTOR inhibitor; Arm B).

[d] Performed at screening for all patients, and subsequently as clinically indicated to assess renal function.

[e] Performed locally at screening for all patients receiving oral coumarin-derivative anticoagulants and subsequently except those patients participating in Arm D and receiving gemcitabine.

[f] Calculated by Lilly-designated (central) laboratory using Cockcroft-Gault formula only at the screening visit for eligibility purposes. If using local laboratories for eligibility purposes, please see Appendix 9 for calculation.

Appendix 4. Sampling Schedule for Pharmacokinetics and Biomarkers

It is essential that the exact date and time of dose administration for the 3 days prior to PK sampling is recorded in the patient diary and transcribed into the eCRF. The exact date and time of collection of each venous blood sample must also be recorded on the laboratory requisition.

Due to practical and logistical concerns, some deviation from the specified sampling time is normal and expected. Sites should keep in mind that drawing the sample and recording the actual time on the appropriate form are of principal importance. Differences from the time specified in the protocol are not considered protocol deviations as long as samples are collected and accurate dates and times are recorded in a timely manner on the appropriate forms.

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.

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.

Biomarker Sampling Schedule for All Patients

Sample Number	Cycle and Day	Plasma Sampling Time	Whole Blood Sample (Pharmaco-genetics)
1	C1D1	Predose	X
1b	C1D14	Predose[a]	
2	C2D1	Predose	
3	C3D1	Predose	
4-n	C4-n D1	X	
	30DFU	X	

Abbreviations: 30DFU = 30 day follow-up; C = cycle; D = day.

[a] For safety lead-in and Arms A, B, and C only.

Appendix 5. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Recommended Autoimmune Serology:**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	Anti actin antibody[a]

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated (central) laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 6. Echocardiographic Guidelines

Echocardiography

In this study, ECHO images were to be acquired with the purpose of ascertaining that patients enrolled in the Safety Lead-in have (and maintain during the study) baseline normal cardiac structure and function, normal pulmonary artery pressure, and absence of significant valvular disease (defined herein as no valvular regurgitation except for mild tricuspid, mild mitral, or mild aortic regurgitation, and no more than mild mitral or aortic valvular stenosis). Repeated ECHOs in each patient will be performed to establish the cardiac safety of galunisertib by comparison with the initial studies. Determination of normalcy status requires objective evaluation of cardiac chamber size and function and attention to the use of appropriate techniques in the performance of the ECHO examinations, in particular the use of standardized settings during the acquisitions of color flow Doppler imaging. Therefore, because quantitative ECHO is the goal, stringent criteria for image quality and reproducibility are essential.

In addition to qualitative assessment of valvular regurgitation when or if detected (trace, mild, moderate, or severe according to Singh et al. [1999] and Zoghbi et al. [2003; see below]) and qualitative/quantitative assessment of valvular stenosis when or if detected (mild, moderate, or severe, using mean and peak pressure gradient in mm Hg and orifice area in cm^2 as applicable), other ECHO parameters to be serially quantified are: LV cavity size (diameters, volumes), LV ejection fraction, LV mass and mass index, diastolic function based on mitral flow velocity, mitral deceleration time, pulmonary venous flow pattern, tissue Doppler, extrapolation of LV end-diastolic pressure by E/Em, left atrial volume index, and extrapolation of pulmonary artery systolic pressure when obtainable.

An ECHO with no clinically significant abnormalities is one defined specifically as: the LV (Schiller et al. 1989) internal dimension in diastole should be ≤ 2.8 cm/m^2, the left atrial (Tsang et al. 2002) end-systolic volume should be ≤ 36 mL/M^2, the left ventricular ejection fraction (Oh et al. 2006) should be $\geq 50\%$ without regional wall motion abnormalities, 2-dimensional ECHO-derived LV mass index (Schiller et al. 1989) should be ≤ 115 g/M^2 for males and ≤ 99 g/M^2 for females, the pulmonary artery pressure should be normal (tricuspid regurgitation jet velocity ≤ 2.5 m/s and/or pulmonary valve flow acceleration time ≥ 120 ms), the LV diastolic function (Khouri et al. 2004) should be normal (screening: mitral deceleration time ≥ 150 ms and ≤ 250 ms, mitral E/A ratio ≥ 0.75 and ≤ 1.5, mitral E velocity divided by Doppler mitral annular velocity [E/Em] <15), and there should be no evidence for pericardial or congenital or heart disease. In addition, there should be no evidence for more than mild mitral or aortic stenosis (mitral valve area should be >2.0 cm^2 and aortic valve area should be >1.5 cm^2) and no evidence of more than mild mitral or aortic regurgitation (Singh et al. 1999; Zoghbi et al. 2003). Patients enrolled in the study may have evidence for tricuspid (trace or mild), pulmonary, mitral (trace or mild), or aortic (trace or mild) regurgitation by Doppler techniques (Singh et al. 1999; Zoghbi et al. 2003).

References

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Appendix: Qualitative and Quantitative Parameters for Grading Valvular (Mitral and Aortic) Regurgitation Severity

Please refer to references below for information on qualitative and quantitative parameters for grading valvular (mitral and aortic) regurgitation severity.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol.* 1999;83(6):897-902.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16(7):777-802.

Appendix 7. Inducers and Inhibitors of CYP3A or Substrates of CYPS with Narrow Therapeutic Range

The information in this attachment is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Inhibitors of CYP3A
All HIV protease inhibitors
Aprepitant
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Verapamil

Cytochrome P450 Substrates with Narrow Therapeutic Range

Cytochrome P450	**Substrate**
CYP1A2	Theophylline
	Tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin
	Phenytoin
CYP2D6	Thioridazine
	Pimozide
CYP3A	Alfentanil
	Astemizole
	Cisapride
	Cyclosporine
	Dihydroergotamine
	Ergotamine
	Fentanyl
	Pimozide
	Quinidine
	Sirolimus
	Tacrolimus
	Terfenadine

Appendix 8. Drugs Associated with QT Interval Prolongation

Drugs with a Risk of Torsades de Pointes

amiodarone	clarithromycin	halofantrine	pentamidine	terfenadine
arsenic trioxide	disopyramide	haloperidol	pimozide	thioridazine
astemizole	dofetilide	ibutilide	probucol	vandetanib
bepridil	domperidone	levomethadyl	procainamide	
chlorpromazine	droperidol	mesoridazine	quinidine	
cisapride	erythromycin	methadone	sotalol	
citalopram	flecainide	moxifloxacin	sparfloxacin	

Drugs with a Possible Risk of Torsades de Pointes

alfuzosin	felbamate	lithium	ranolazine	voriconazole
amantadine	fingolimod	moexipril/HCTZ	risperidone	ziprasidone
atazanavir	foscarnet	nicardipine	roxithromycin	
azithromycin	fosphenytoin	nilotinib	sertindole	
chloral hydrate	gatifloxacin	octreotide	sunitinib	
clozapine	gemifloxacin	ofloxacin	tacrolimus	
dolasetron	granisetron	ondansetron	tamoxifen	
dronedarone	indapamide	oxytocin	telithromycin	
eribulin	isradipine	paliperidone	tizanidine	
escitalopram	lapatinib	perflutren lipid microspheres	vardenafil	
famotidine	levofloxacin	quetiapine	venlafaxine	

Drugs with a Conditional Risk of Torsades de Pointes

amitriptyline	doxepin	itraconazole	ritonavir	trimipramine
ciprofloxacin	fluconazole	ketoconazole	sertraline	
clomipramine	fluoxetine	nortriptyline	solifenacin	
desipramine	galantamine	paroxetine	trazodone	
diphenhydramine	imipramine	protriptyline	trimethoprim-Sulfa	

Source: Arizona Cert Center for Education and Research on Therapeutics page [WWW].

Appendix 9. Creatinine Clearance Formula

Note: This formula is to be used for calculating CrCl from **local laboratory results only**.

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85} \text{ (if female) or } \times \mathbf{1.0} \text{ (if male)}}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85} \text{ (if female) or } \times \mathbf{1.0} \text{ (if male)}}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ (\mu mol/L)}$$

[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Appendix 10. Dose Modification Recommendations for Study Treatment-Related Toxicities

Study JPCJ Dose Adjustment Guidance for Study Treatment-Related Toxicities – Arm A

Toxicity Type	Toxicity Severity	Suspend Abemaciclib	Dose-Reduce Abemaciclib
Hematologic (Neutropenia, thrombocytopenia, or anemia)	Grade 4	Yes	Yes
Hematologic (Neutropenia, thrombocytopenia, or anemia)	Grade 3	Yes	Investigator discretion
Hematologic	Recurrent Grade 3	Yes	Yes
Hematologic: Patient requires blood cell growth factors	Regardless of severity (Growth factors used according to ASCO Guidelines)	Yes (for at least 48 hours after last dose of blood cell growth factors)	Yes
Nonhematologic (except diarrhea)	Persistent or recurrent Grade 2 not resolving with maximal supportive measures within 7 days	Investigator discretion	Investigator discretion
Nonhematologic	Grade 3 or 4	Yes	Yes[a]
Diarrhea	Requires hospitalization or Grade 3 or 4	Yes	Yes
Diarrhea	Persistent or recurrent Grade 2 not resolving with maximal supportive measures within 24 hours	Recommended	Investigator discretion
Diarrhea	Recurrence despite maximal supportive measures after resuming same dose following initial Grade 2 diarrhea	Yes	Yes

Abbreviations: ASCO = American Society of Clinical Oncology.

[a] Except toxicities that can be controlled with adequate treatment such as asymptomatic electrolyte disturbances, hyperlipidemia, skin rash, nausea, or vomiting.

Study JPCJ Dose Adjustment Guidance for Study Treatment-Related Toxicities – Arm B

Toxicity Type	Toxicity Severity	Suspend Abemaciclib	Dose-Reduce Abemaciclib	Suspend LY3023414	Dose-Reduce LY3023414
Hematologic (Neutropenia)	Grade 4	Yes	Yes	Yes	Yes, if not resolved to ≤Grade 2 within 7 days; if re-occurring dose reduce
Hematologic (Thrombocytopenia or anemia)	Grade 4	Yes	Yes	Yes	Yes
Hematologic (Neutropenia, thrombocytopenia, or anemia)	Grade 3	Yes	Investigator discretion	Yes	Investigator discretion
Hematologic	Recurrent Grade 3	Yes	Yes	See adjustment for neutropenia, thrombocytopenia, and anemia	See adjustment for neutropenia, thrombocytopenia, and anemia
Hematologic: Patient requires blood cell growth factors	Regardless of severity (Growth factors used according to ASCO Guidelines)	Yes (for at least 48 hours after last dose of blood cell growth factors)	Yes	Yes (for at least 48 hours after last dose of blood cell growth factors)	Investigator discretion
Diarrhea	Requires hospitalization or Grade 3 or 4	Yes	Yes	Recommended	Investigator discretion
Diarrhea	Persistent or recurrent Grade 2 not resolving with maximal supportive measures within 24 hours	Recommended	Investigator discretion	Recommended	Investigator discretion
Diarrhea	Recurrence despite maximal supportive measures after resuming same dose following initial Grade 2 diarrhea	Yes	Yes	Investigator discretion	Investigator discretion
Stomatitis	Grade 4	Yes	Yes	Yes	Yes
Stomatitis	Grade 3	Yes	Yes	Yes	Yes, if not resolved despite supportive measures to ≤Grade 2 within 7 days; if re-occurring dose reduce
Stomatitis	Persistent or recurrent Grade 2 not resolving with maximal supportive measures	Investigator discretion	Investigator discretion	Investigator discretion	Investigator discretion

Toxicity Type	Toxicity Severity	Suspend Abemaciclib	Dose-Reduce Abemaciclib	Suspend LY3023414	Dose-Reduce LY3023414
Hyperglycemia	Grade 4	Investigator discretion	Investigator discretion	Yes	Yes if not resolved despite corrective treatment to ≤Grade 2 within 24 hours; if re-occurring dose reduce
Hyperglycemia	Grade 3	Investigator discretion	Investigator discretion	No – Initiate/intensify corrective treatment	Yes, if not resolved despite corrective treatment to ≤Grade 2 within 7 days; if re-occurring dose reduce
Hyperglycemia	Grade 2	No – Initiate/intensify corrective treatment	No	No – Initiate/intensify corrective treatment	No
Other nonhematologic	Grade 3 or 4	Yes	Yes [a]	Yes	Yes [a]

Abbreviations: ASCO = American Society of Clinical Oncology.

[a] Except toxicities that can be controlled with adequate treatment such as asymptomatic electrolyte disturbances, hyperlipidemia, skin rash, nausea, or vomiting.

Study JPCJ Dose Adjustment Guidance for Study Treatment-Related Toxicities – Safety Lead-in

Toxicity Type	Toxicity Severity	Suspend Abemaciclib	Dose-Reduce Abemaciclib	Suspend Galunisertib	Dose-Reduce Galunisertib
Cardiotoxicity (Moderate or severe heart valve toxicity, severe valvular regurgitation [as determined by ECHO], congestive heart failure, or aneurysm)	Grade 3 or 4	No	No	Yes – permanently	Not applicable
Hematologic (Neutropenia, thrombocytopenia, or anemia)	Grade 4	Yes	Yes	Yes	Yes
Hematologic (Neutropenia, thrombocytopenia, or anemia)	Grade 3	Yes	Investigator discretion	Yes	Investigator discretion
Hematologic	Recurrent Grade 3	Yes	Yes	Yes	Investigator discretion
Hematologic: Patient requires blood cell growth factors	Regardless of severity (Growth factors used according to ASCO Guidelines)	Yes (for at least 48 hours after last dose of blood cell growth factors)	Yes	Yes (for at least 48 hours after last dose of blood cell growth factors)	Investigator discretion
Diarrhea	Requires hospitalization or Grade 3 or 4	Yes	Yes	Recommended	Investigator discretion
Diarrhea	Persistent or recurrent Grade 2 not resolving with maximal supportive measures within 24 hours	Recommended	Investigator discretion	Recommended	Investigator discretion
Diarrhea	Recurrence despite maximal supportive measures after resuming same dose following initial Grade 2 diarrhea	Yes	Yes	Investigator discretion	Investigator discretion
Pruritus	Grade 3 or 4	Investigator discretion	Investigator discretion	Yes	Yes
Pruritus	Persistent or recurrent Grade 2 not resolving with maximal supportive measures	Investigator discretion	Investigator discretion	Yes	Investigator discretion
Other nonhematologic	Grade 3 or 4	Yes	Yes [a]	Yes	Yes [a]

Abbreviations: ASCO = American Society of Clinical Oncology; ECHO = echocardiogram.

[a] Except toxicities that can be controlled with adequate treatment such as asymptomatic electrolyte disturbances, nausea, or vomiting.

Appendix 11. Protocol Amendment I3Y-MC-JPCJ(c) Summary
An Adaptive, Open-Label, Randomized Phase 2 Study of Abemaciclib as a Monotherapy and in Combination with Other Agents Versus Choice of Standard of Care (Gemcitabine or Capecitabine) in Patients with Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma

Overview

Protocol I3Y-MC-JPCJ (A Phase 1 First-in-Human Dose Study of LY3023414 in Patients with Advanced Cancer) has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The major overall changes and rationale for the changes made to this protocol are as follows:

- Title page and document header were updated to reflect the approval date of the previous amendment and/or the current amendment status (c).
- The study design section was updated to reflect the removal of the abemaciclib plus galunisertib arm (Arm C) from Stages 1 and 2 and indicates that no additional patients would be enrolled to the safety lead-in based on Sponsor's decision.
- Appropriate modifications and adjustments were made in exclusion criteria and treatments to align with the modified study design.
- Other minor corrections and editorial changes were made throughout the protocol to improve clarity and to secure alignment with the intended study design. These changes are not documented below.

- **Revised Protocol Sections**

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

1. Synopsis

Galunisertib (LY2157299) is a small molecule designed to selectively inhibit the serine/threonine kinase of the transforming growth factor beta (TGF-β) receptor type I (TGF-βRI). In PDAC, an increase in expression of epithelial-mesenchymal transition triggering factors, including TGF-β, has been observed and may contribute to the high metastatic potential. In pancreatic cancer cells, a CDK4 and CDK6 inhibitor exerted growth-inhibitory effects, although a TGF-βRI inhibitor alone was unable to suppress colony growth in 3-D culture. However, when the TGF-βRI inhibitor was combined with a CDK4 and CDK6 inhibitor, optimal growth inhibition was achieved. These preclinical data provide a basis for exploring the combination of abemaciclib and galunisertib in the current study, although with amendment (c) the assessment of this combination is being discontinued.

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~~, and galunisertib~~

STAGE 2

• 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 ~~and galunisertib~~	• Exposure of abemaciclib~~,~~ and LY3023414~~ and galunisertib~~

• Exposure-response for abemaciclib and LY3023414~~and galunisertib~~	• Drug exposure and efficacy outcomes such as objective response rate or progression-free survival and safety outcomes such as neutropenia and diarrhea

Overall Design:

Study I3Y-MC-JPCJ is a multicenter, randomized, open-label, Phase 2 trial in patients with metastatic pancreatic ductal adenocarcinoma who have been previously treated with at least one, but no more than 2, prior therapies for metastatic disease. At least one of the prior therapies must have been either gemcitabine-based or fluoropyrimidine-based therapy. The safety and efficacy of each investigational arm will be assessed versus the standard-of-care arm by implementing a 2-stage design. For Stage 1, the primary analyses of safety and efficacy will be evaluated for each of ~~3~~ 2 investigational arms versus a standard-of-care arm approximately 16 weeks after the last planned Stage 1 patient enters treatment. The ~~3~~ 2 investigational arms include abemaciclib monotherapy (Arm A) and~~,~~ abemaciclib plus LY3023414 (PI3K/mTOR dual inhibitor; Arm B)~~, and abemaciclib plus galunisertib (Arm C)~~.

Number of Patients:

Safety Lead-in:

According to the initial protocol, p~~P~~rior to initiating Stage 1 of the study, a safety lead-in period for abemaciclib plus galunisertib ~~will~~was to be conducted with up to 12 patients. At the time of amendment (c), Lilly determined no additional patients would be enrolled to the safety lead-in and that Arm C (abemaciclib plus galunisertib) would be removed from the study.~~Initially, 6 patients will be enrolled to a safety lead-in period for abemaciclib plus galunisertib. Pending an assessment of safety after 1 cycle (28 days) of treatment, 6 additional patients may be enrolled to the safety lead-in.~~

Stage 1:

For Stage 1, a total of approximately ~~100~~ 75 patients (25 patients per arm) will be randomized in a 1:1:1~~:1~~ ratio to ~~4~~ 3 treatment arms. Randomization will be stratified by number of prior systemic therapies (1 versus 2).

Treatment Arms and Duration:

Arm	Dose and Schedule
A	Abemaciclib (CDK4 and CDK6 inhibitor) 200 mg BID with or without food continuous dosing for 28-day cycles
B[a]	Abemaciclib 150 mg BID with or without food continuous dosing for 28-day cycles LY3023414 (PI3K/mTOR dual inhibitor) 150 mg BID with or without food continuous dosing for 28-day cycles
~~C~~[~~a~~]	~~Abemaciclib 150 mg BID[b] with or without food continuous dosing for 28-day cycles~~ ~~Galunisertib (TGF βRI inhibitor) 150 mg BID with or without food dosed for 14 days followed by 14 days rest for 28-day cycles~~
D	Standard-of-Care Choice of: Gemcitabine 1000 mg/m^2 over 30 minutes intravenously on the following days of a 28-day cycle. • Cycle 1: Days 1, 8, 15, and 22 • Cycle 2 and beyond: Days 1, 8, and 15 **OR** Capecitabine 1250 mg/m^2 administered orally BID within 30 minutes after a meal (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 21-day cycles

Abbreviations: BID = twice daily; CDK = cyclin-dependent kinase; PI3K = phosphatidylinositol 3-kinase~~; TGFβ RI = transforming growth factor beta receptor type I.~~

[a] Oral combination agents are to be taken at approximately the same time. There is no specific order of administration.

~~[b] The dose of abemaciclib in combination with galunisertib may be reduced to 100 mg BID based on safety data from the Safety Lead-In Period~~

Table JPCJ.2.1. Baseline Schedule of Activities

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.
~~**Cardiac Assessments**~~				
~~ECG~~		~~X~~		~~To be performed and read locally~~
~~Echocardiogram~~	~~X~~			~~To be performed and read locally (see Appendix 6)~~
~~Chest CT scan with contrast or MRI (safety)~~	~~X~~			~~Performed locally for cardiac monitoring NOTE: At screening, if the MRI or CT scan with contrast done for tumor assessment has properly assessed the great vessels and the heart, this same scan may be used for safety screening.~~
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.

3.1. Study Rationale

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 ~~and a TGF-βRI inhibitor~~), versus choice of standard of care (gemcitabine or capecitabine) in patients with previously treated metastatic PDAC

3.2.4. Transforming Growth Factor-Beta and Role in Pancreatic Ductal Adenocarcinoma

In PDAC, an overexpression of epithelial-mesenchymal transition triggering factors, including TGF-β, has been observed and may contribute to the high metastatic potential. In pancreatic cancer cells, a CDK4 and CDK6 inhibitor was found to exert growth-inhibitory effects, although a TGF-βRI inhibitor alone was unable to suppress colony growth in 3-dimensional culture. However, when the TGF-βRI inhibitor was combined with a CDK4 and CDK6 inhibitor, optimal growth inhibition was achieved (Liu and Korc 2012). These preclinical data provide a basis for

exploring the combination of abemaciclib and galunisertib in the current study, although, with amendment (c) the assessment of this combination is being discontinued (see Section 5.4.3).

4. Objectives and Endpoints

Table JPCJ. 4.1. Stage 1 Objectives and Endpoints

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~~, and galunisertib~~	• Exposure of abemaciclib and LY3023414
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.

Table JPCJ. 4.2. Objectives and Endpoints Stage 2

Objectives	Endpoints
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~~, and galunisertib~~	• Exposure of abemaciclib and LY3023414~~, and galunisertib~~
• Exposure-response for abemaciclib and LY3023414~~, and galunisertib~~	• Drug exposure and efficacy outcomes such as objective response rate or progression-free survival and safety outcomes such as neutropenia and diarrhea

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.

~~Currently, n~~No safety data ~~have~~ had been generated for the combination of abemaciclib and galunisertib. Therefore, a Safety Lead-in Period was included in the original protocol~~prior to the randomization of patients to each of 4 study arms, a safety lead-in period will be conducted with up to 12 patients~~ (see Section7.2).

~~Following the safety lead-in~~With amendment (c), Stage 1 of the study will randomize patients 1:1:1~~: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 C: Abemaciclib plus galunisertib (LY2157299, TGF-βRI 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, and C~~) with the standard-of-care arm (Arm D), and will include assessment of disease control rate (DCR;

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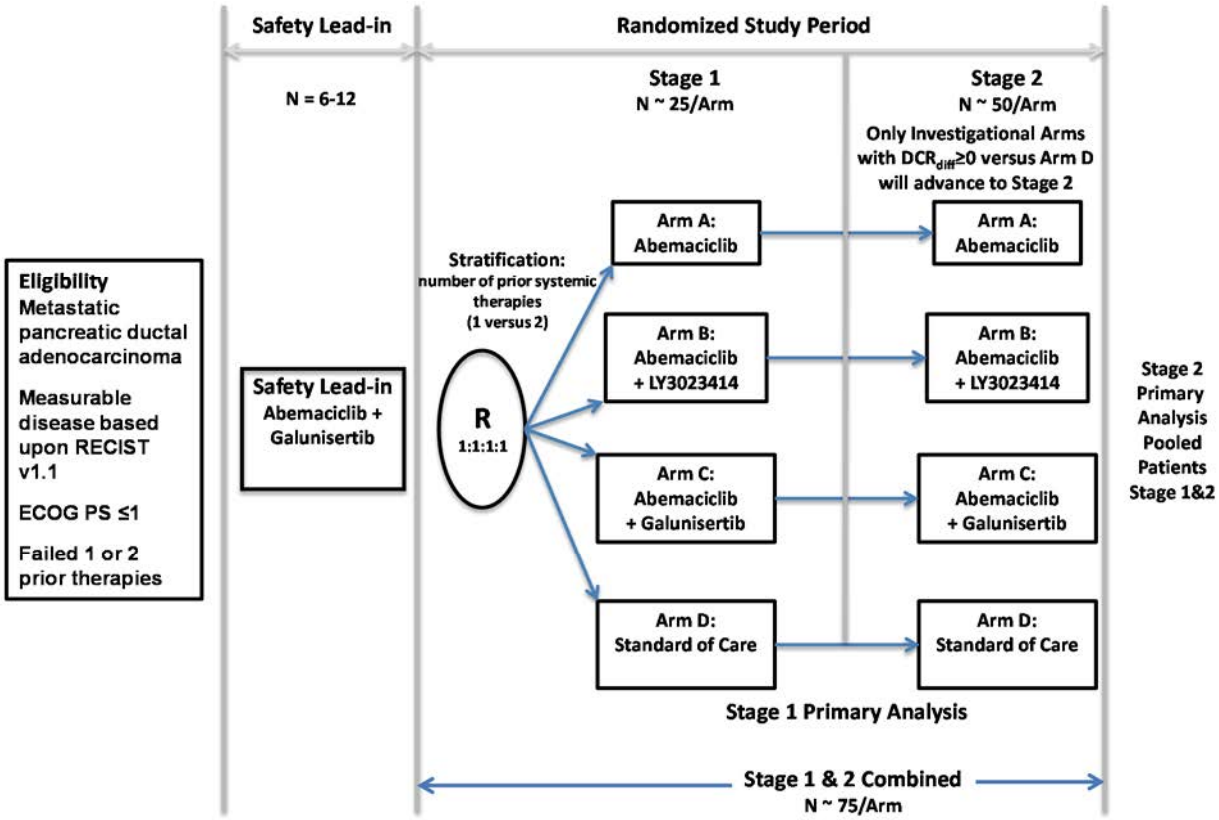

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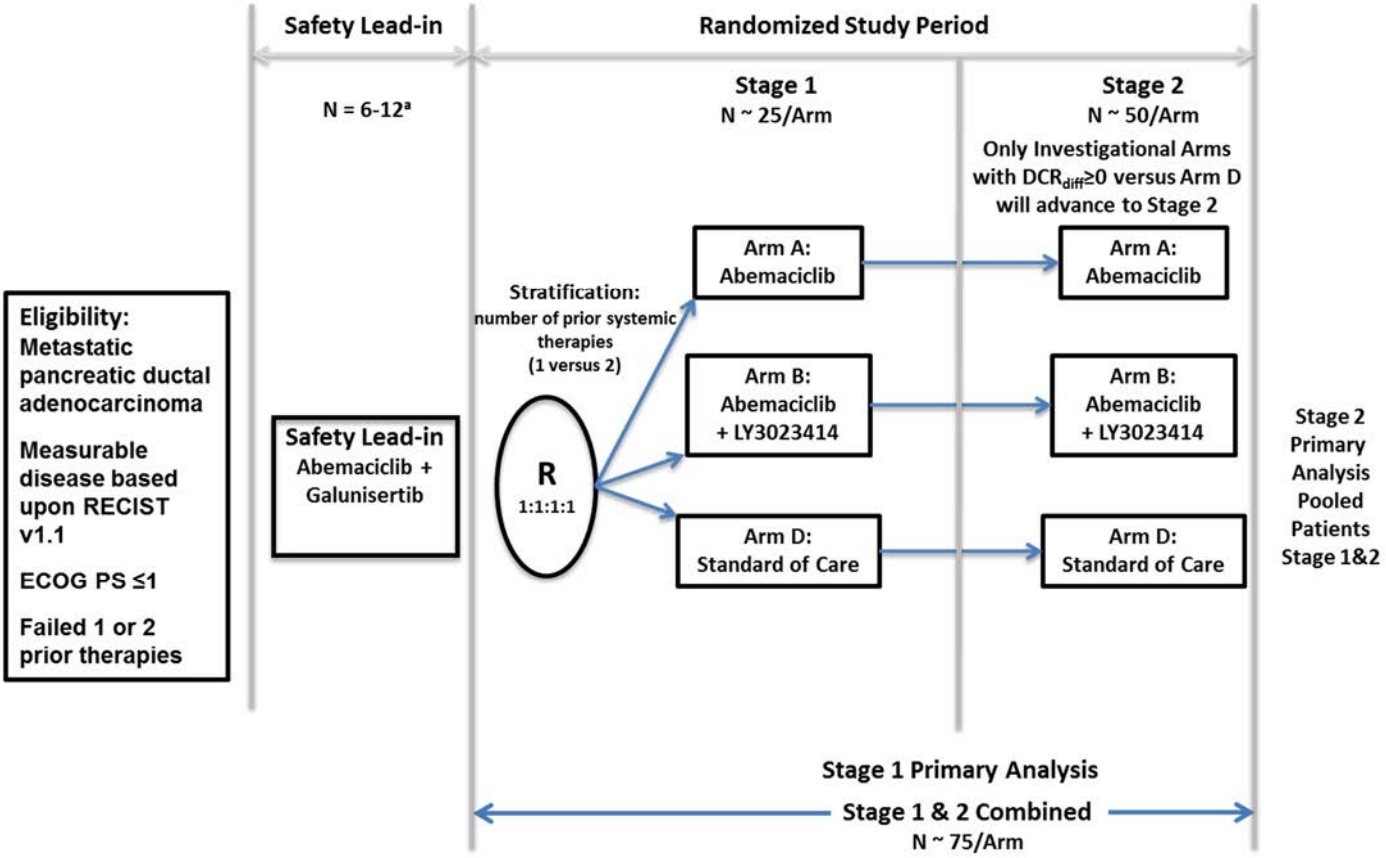

Abbreviations: ECOG = Eastern Cooperative Oncology Group; DCR_{diff} = disease control rate difference; N = number of patients; R = randomize; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; PS = performance status.

[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~~ill~~ to be conducted with up to 12 patients~~. Initially, 6 patients will be enrolled to receive abemaciclib plus galunisertib. Pending an assessment of safety after 1 cycle (28 days) of treatment, 6 additional patients may be enrolled to the safety lead-in at a reduced dose of abemaciclib~~ (see Section7.2), 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 ~~100~~ 75 patients (25 patients per arm) will be randomized in a 1:1:1~~:1~~ ratio to ~~4~~ 3 treatment arms.

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 ~~(following completion of the safety lead-in period)~~ 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.

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.

~~5.6~~.5.5. Justification for Doses of Investigational Treatments

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 th~~is study~~e 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 current study will assess the safety and pharmacokinetics (PK) of abemaciclib 150 mg BID plus galunisertib 150 mg BID ~~in~~ 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 ~~prior to initiation of Stage 1~~.

6.2. Exclusion Criteria

[15] have a personal history of any of the following conditions: syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.
Exception: Patients with controlled atrial fibrillation for ≥30 days prior to study treatment initiation are eligible.~~severe cardiac disease:~~

- ~~Myocardial infarction within 6 months prior to study screening, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension.~~
- ~~Documented major electrocardiogram (ECG) abnormalities, at the investigator's discretion (for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, bundle branch blocks,~~

~~ventricular hypertrophy, or recent myocardial infarction), not responding to medical treatments or not clinically stable for at least 6 months prior to study screening.~~

- ~~Major cardiac abnormalities documented by echocardiography (ECHO) with Doppler that are not clinically stable for at least 6 months prior to study screening (for example, severe heart valve function defect and/or left ventricular ejection fraction [LVEF] <50%, evaluation based on the institutional lower limit of normal). For additional details, refer to Echocardiography Protocol (Appendix 6).~~

[16] ~~Predisposing conditions that are consistent with development of aneurysms of the ascending aorta or aortic stress (for example, family history of aneurysms, Marfan Syndrome, bicuspid aortic valve, or evidence of damage to the large vessels of the heart documented by Computed Tomography [CT] scan or magnetic resonance imaging [MRI] with contrast).~~Deleted Criterion

[23] have previously received treatment with any CDK4 and 6 inhibitor, ~~TGF-β inhibitor,~~ or PI3K and/or mTOR inhibitor or have a known hypersensitivity to any component of the investigational products in this study.

Table JPCJ. 7.1. Treatment Regimens

Arm	Dose and Schedule
A	Abemaciclib (CDK4 and CDK6 inhibitor) 200 mg BID with or without food continuous dosing for 28-day cycles
B[a]	Abemaciclib 150 mg BID with or without food continuous dosing for 28-day cycles LY3023414 (PI3K/mTOR dual inhibitor) 150 mg BID with or without food continuous dosing for 28-day cycles
~~C~~[a]	~~Abemaciclib 150 mg BID[b] with or without food continuous dosing for 28-day cycles~~ ~~Galunisertib (TGF-βRI inhibitor) 150 mg BID with or without food dosed for 14 days followed by 14 days rest for 28-day cycles~~
D	Standard-of-Care Choice of: Gemcitabine 1000 mg/m^2 over 30 minutes intravenously on the following days of a 28-day cycle. • Cycle 1: Days 1, 8, 15, and 22 • Cycle 2 – n: Days 1, 8, and 15 **OR** Capecitabine 1250 mg/m^2 administered orally BID within 30 minutes after a meal (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 21-day cycles.

Abbreviations: BID = twice daily; CDK = cyclin-dependent kinase~~; TGF-βRI = transforming growth factor beta receptor type I.~~

[a] Oral combination agents are to be taken at approximately the same time. There is no specific order of administration.

~~[b] The dose of abemaciclib in combination with galunisertib may be reduced to 100 mg BID based on safety data from the Safety Lead-In Period~~.

7.2. Method of Treatment Assignment

Safety Lead-in

For the safety lead-in, any patient who was discontinued from the study before receiving at least 75% of the planned doses of abemaciclib and galunisertib in Cycle 1 was deemed nonevaluable for assessment of that dose level and was replaced, unless that patient experienced~~s~~ a DLT before withdrawal.

Based on the original protocol, p~~P~~rior to the randomized portion of the study (Stage 1 and Stage 2), up to 12 patients who satisfied~~y~~ all inclusion criteria and none of the exclusion criteria ~~will be~~were to be enrolled to a safety lead-in period. Initially, 6 patients ~~will~~were to be enrolled to receive abemaciclib plus galunisertib. If the combination of abemaciclib 150 mg BID and galunisertib 150 mg BID ~~is~~ was not tolerated (that is, more than one patient ~~experiences~~ experienced a DLT within the first 28-day cycle), then the dose of abemaciclib ~~will~~ was to be

reduced to 100 mg BID and an additional 6 patients enrolled at this dose. If the combination ~~is~~ was not tolerated (that is, more than one patient experienced~~s~~ a DLT within the first 28-day cycle) at the reduced dose of abemaciclib, then patients ~~will~~ were not to be enrolled to the abemaciclib plus galunisertib arm (Arm C).

For the safety lead-in, any patient who ~~is~~ was discontinued from the study before receiving at least 75% of the planned doses of abemaciclib and galunisertib in Cycle 1 was~~ill be~~ deemed nonevaluable for assessment of that dose level and ~~may be~~was replaced unless that patient experienced~~s~~ a DLT before withdrawal. Nonevaluable patients ~~may be~~were to be replaced to ensure that no fewer than 6 patients received at least 75% of the planned doses of abemaciclib and galunisertib in Cycle 1~~ at each dose level~~, unless enrollment to that cohort ~~h~~was stopped because more than one patient at that dose level ~~has~~ experienced a DLT.

At the time of amendment (c), Lilly determined no additional patients would be enrolled to the safety lead-in and that Arm C would be removed from the study. A total of 7 patients had been enrolled in the safety lead-in and 2 were still on treatment. Ongoing patients enrolled to the safety lead-in may continue on study treatment if, at the discretion of the treating investigator, the patients are benefiting from therapy and not considered at risk from a safety standpoint.

~~While it is not expected, it is possible that galunisertib will enhance the toxicity of abemaciclib or vice versa.~~ Toxicities were~~will be~~ graded according to Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0). If multiple toxicities were~~are~~ observed, the presence of DLTs was to~~should~~ be based on the most severe toxicity experienced. During the Safety Lead-in Period only, DLTs were~~will be~~ defined as any of the following events that occurred during the first cycle of administration of the combination of abemaciclib and galunisertib and ~~a~~were considered by the investigator to be attributable to either study treatment alone or the combination of the two:

- Grade 3 or 4 nausea or electrolyte disturbance that persist~~s~~ed more than 48 hours despite maximal supportive intervention
- Grade 3 vomiting or diarrhea that persist~~s~~ed more than 48 hours despite maximal supportive intervention
- Grade 4 vomiting or diarrhea of any duration
- Grade 4 hematologic toxicity that persisted~~s~~ more than 5 days
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia of any duration
- Grade 3 or 4 neutropenia with fever

~~After completion of~~ As further enrollment to the Safety Lead-in will not occur and Arm C is removed with amendment (c), the randomized portion of the study will begin. Randomization will be stratified by number of prior systemic therapies (1 versus 2).

Stage 1

Patients will be randomized 1:1:1~~:1~~ among the investigational arms and the standard-of-care arm, to provide a total of 25 patients per arm. Patients assigned to the standard-of-care arm (Arm D) will be administered either gemcitabine or capecitabine, at the discretion of the investigator. In determining which standard-of-care therapy to administer, the investigator should take into consideration NCCN Guidelines, which indicate that patients previously treated with gemcitabine-based therapy should receive capecitabine and patients previously treated with fluoropyrimidine-based therapy should receive gemcitabine.

7.2.1. Selection and Timing of Doses

Patients should not chew or crush these study treatments. If the patient misses or vomits a dose of oral study treatment, the patient should skip the dose and take the next dose as scheduled. For patients assigned to the safety lead-in or Arm B~~ or C~~, combination agents are to be taken at approximately the same time, in no specific order of administration.

A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. A cycle delay due to toxicity is permitted up to 14 days (see Section 7.4.4). In the event only 1 of 2 study treatments for patients in the safety lead-in or Arm~~s~~ B ~~or C~~ is suspended or if each study treatment is reintroduced in a sequential manner, Day 1 of the next cycle is considered the date that the first of the individual study treatments is dispensed and administered to the patient.

7.4.1. Dosage Modifications for Investigational Agents

Dose adjustments (suspensions and reductions) will be made based on the clinical assessment of hematologic and nonhematologic toxicities (defined as an AE possibly related to study treatment per investigator judgment). The CTCAE v 4.0 will be used to assess AEs. Treatment may be suspended for a maximum of 14 days to allow a patient sufficient time for recovery from study treatment-related toxicity. 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. Patients in the safety lead-in receiving galunisertib must receive a minimum of 10 days of dosing in a 28-day cycle.

Dose reductions for investigational agents should be as shown inTable JPCJ.7.3. Study treatment must be reduced sequentially by one dose level unless an exception is granted in consultation with the Lilly CRP. Mid-cycle dose reductions for abemaciclib may be implemented by informing patients to reduce the number of 50-mg capsules taken for each dose (with dose reductions appropriately documented in the electronic case report form [eCRF]); however, mid-cycle dose reductions of LY3023414 and galunisertib will require patients to return to the clinic and the site to call the IWRS Help Desk to dispense new study treatment. If 1 study treatment (Safety Lead-in or Arm B~~ or C~~) has been maximally dose-reduced due to toxicity and the toxicity has not resolved, patients may continue to receive the other study treatment at

the current dose if it is apparent that the toxicity is not related to the other study treatment and the patient continues to receive clinical benefit.

7.4.2. Dosage Modifications for Gemcitabine

A new cycle of g~~G~~emcitabine will not be given unless the ANC is $\geq 1.0 \times 10^9$/L and platelets are $\geq 100 \times 10^9$/L. All nonhematologic toxicities (excluding alopecia) should also return to CTCAE Grade ≤1 or baseline prior to reinitiating treatment. Treatment may be delayed up to 4 weeks after completion of the 28-day cycle to allow sufficient time for recovery.

7.7. Concomitant Therapy

For patients assigned to abemaciclib treatment arms (safety lead-in as well as Arms A and~~,~~ B~~, and C~~) or those assigned to Arm D who are receiving capecitabine, prothrombin time or international normalized ratio must be routinely monitored if patients are receiving concomitant oral coumarin-derivative anticoagulants

7.7.2. Management of Diarrhea

Upon treatment initiation, patients assigned to abemaciclib treatment arms (Safety Lead-In, as well as Arms A~~,~~and B~~, and C~~) or those assigned to Arm D who are receiving capecitabine should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

8.1. Discontinuation from Study Treatment

For patients assigned to the Safety Lead-in or Arm B~~ or Arm C~~, if 1 study drug is discontinued due to toxicity, patients may continue to receive the other study drug until a discontinuation criterion has been met.

Patients will be discontinued from all study treatment in the following circumstances:

8.2. Discontinuation from the Study

Patients who discontinue from the study early will continue to be followed according to the Post-Treatment ~~have end-of-study procedures performed as shown in the~~ Schedule of Activities (Section 2).

9.1. Efficacy Assessments

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiological scan of the thorax, abdomen, and pelvis is required at screening; subsequently, scans of the thorax for tumor assessments (CT of the chest for safety is required per the Schedule of Activities for patients in the safety lead-in ~~Arm C~~; see Section 9.4.1) are required only for those patients with evidence of disease on the baseline scan or if clinically indicated (that is, progressive disease is suspected).

9.4.1. Cardiac Monitoring

Hence, cardiotoxicity monitoring must be performed for patients participating in the Safety Lead-in ~~or Arm C~~ of this study, based on echocardiographs with Doppler and Chest CT/MRI (see Schedule of Activities [Section 2] andAppendix 6).

Chest CT Scan with Contrast or MRI (Safety Lead-in ~~and Arm C~~ Patients Only)

A chest CT scan with contrast or MRI ~~is~~ 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 ~~participating in the Safety Lead-in or Arm C~~. 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 ~~and Arm C~~ Patients Only)

Echocardiography with Doppler (ECHO/Doppler) ~~will~~ was ~~be~~ locally assessed at screening for all patients in the Safety Lead-in, and subsequently according to the Schedule of Activities (see Section 2) for these patients ~~participating in the Safety Lead-in or Arm C~~, 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 Saferty Lead-in site. The same person should be responsible for reading the ECHO on any individual study patient~~. Echocardiograms will be as performed as indicated in the Schedule of Activities (see Section 2) and according to Appendix 6 for all patients at screening, and subsequently for all patients participating in the Safety Lead-in or Arm C. The ECHO will be read locally~~

9.5. Pharmacokinetics

Pharmacokinetic (PK) samples will be collected as shown in Appendix 4. During the Safety Lead-in ~~as well as Stage 1~~, patients receiving the combination of abemaciclib and galunisertib will undergo intense PK sampling ~~until notified by Lilly that this intense sampling is no longer required. Subsequently, a sparse sampling schedule will be implemented.~~ For all patients participating in ~~any of the stages/arms~~ 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

9.7.1. Whole Blood Samples for Pharmacogenetic Research

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~~,~~ ~~galunisertib,~~ or LY3023414 or after these study treatments become commercially available

9.8.2. Tissue Samples for Nonpharmacogenetic Biomarker Research

Patients may be asked to undergo collection of an additional core needle biopsy specimen and blood sample after treatment with abemaciclib~~, galunisertib~~, LY3023414, gemcitabine, or capecitabine has been initiated or after disease progression. If requested, this biopsy specimen and blood sample will be used to further investigate molecular features that may explain treatment response and resistance mechanisms.

9.9. Health Outcomes

The primary health outcomes research goal is to determine if abemaciclib ~~combination~~ therapy is able to palliate pain, as measured by the modified Brief Pain Inventory-short form (mBPI-sf) (Cleeland and Ryan 1994). Additionally, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (Aaronson et al. 1993) will assess the broader impact of abemaciclib ~~combination~~ therapy on symptoms, functioning and quality of life.

10.1. Sample Size Determination

According to the original study protocol, p~~P~~rior to randomization for Stage 1, approximately 6 to 12 patients ~~will~~ 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.

10.3.1. Efficacy Analyses

Stage 1 analysis will be performed approximately 16 weeks after the last planned Stage 1 patient enters treatment. All tumor assessment data accumulated during this period (beyond 16 weeks for some patients, if available), will be included in the assessment of DCR. This analysis will compare DCR in the investigational arms (Arms A~~,~~ and B~~, and C~~) to the standard-of-care arm (Arm D).

10.3.5. Stage 1 Analyses

The Stage 1 analysis of efficacy will be conducted under the guidance of an ~~internal~~ 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.

Appendix 4. Sampling Schedule for Pharmacokinetics and Biomarkers

Intense Sampling Schedule for Pharmacokinetics of Abemaciclib + Galunisertib (Safety Lead-in ~~and Arm C~~)

~~Intense PK sampling will be performed until notified by Lilly that this intense sampling is no longer required. Subsequently, the sparse sampling schedule will be implemented~~

~~Sparse Sampling Schedule for Pharmacokinetics—Abemaciclib + Galunisertib (Safety Lead-in and Arm C)~~

~~Sparse PK sampling will be performed ONLY after notification by Lilly that intense sampling is no longer required.~~

~~PK Sample Number~~	~~Cycle and Day~~	~~PK Sampling Time[a]~~
~~1~~	~~C1D1~~	~~2 h after combination~~
~~2~~	~~C1D14[b]~~	~~Predose (0 h)~~
~~3~~	~~C2D1[c]~~	~~Predose (0 h)~~
~~4~~	~~C3D1[c]~~	~~Predose (0 h)~~
~~5~~	~~C4D1[c]~~	~~Predose (0 h)~~

~~Abbreviations: C = cycle; D = day; h = hour; 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.~~

~~[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.~~

Appendix 6. Echocardiographic Guidelines

Echocardiography

In this study, ECHO images ~~will~~ were ~~be~~ acquired with the purpose of ascertaining that patients enrolled in the Safety Lead-in ~~in the study~~ have (and maintain during the study) baseline normal cardiac structure and function, normal pulmonary artery pressure, and absence of significant valvular disease (defined herein as no valvular regurgitation except for mild tricuspid, mild mitral, or mild aortic regurgitation, and no more than mild mitral or aortic valvular stenosis).

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