Protocol I1D-MC-JIAE(c)

A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Study of LY2228820, a p38 MAPK Inhibitor, plus Gemcitabine and Carboplatin versus Gemcitabine and Carboplatin for Women with Platinum-Sensitive Ovarian Cancer

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Approval date: 16-Mar-2017

1. Protocol I1D-MC-JIAE(c)

A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Study of LY2228820, a p38 MAPK Inhibitor, plus Gemcitabine and Carboplatin versus Gemcitabine and Carboplatin for Women with Platinum-Sensitive Ovarian Cancer

p38 Mitogen-Activated Protein Kinase (MAPK) Inhibitor (LY2228820)

This trial is a Phase Ib dose escalation study followed by a randomized, double-blind, placebo-controlled Phase 2 study of a p38 MAPK inhibitor administered in combination with gemcitabine and carboplatin to patients with platinum-sensitive ovarian cancer.

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Protocol Electronically Signed and Approved by Lilly on 11 January 2012
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Amendment (b) Electronically Signed and Approved by Lilly 08 January 2014
Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 16-Mar-2015 GMT

2. Synopsis

Study Rationale

p38 mitogen-activated protein kinase (MAPK) is a signaling protein activated by cancer cells to enable survival after exposure to either radiation or chemotherapy. p38 MAPK phosphorylates a number of substrates, including MAPK-activated protein kinase 2 (MAPKAP-K2), and also regulates the tumor microenvironment's production of such key cytokines as tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8). These cytokines are upregulated in many human malignancies, including ovarian cancer. In addition to promoting survival, these cytokines also enhance growth, invasion, angiogenesis, and metastasis. Thus, pharmacologic inhibition of p38 MAPK in both the cancer cell and its supportive microenvironment represents a novel therapeutic strategy for improving outcomes for patients with ovarian cancer.

Study I1D-MC-JIAE will evaluate efficacy of the p38 MAPK inhibitor, LY2228820, in combination with gemcitabine and carboplatin for patients with platinum-sensitive ovarian cancer.

Clinical Protocol Synopsis: Study I1D-MC-JIAE(c)

Name of Investigational Product: LY2228820

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Study of LY2228820, a p38 MAPK Inhibitor, plus Gemcitabine and Carboplatin versus Gemcitabine and Carboplatin for Women with Platinum-Sensitive Ovarian Cancer

Number of Planned Patients:	**Phase of Development:** 1b/2
Entered: ~130 Enrolled/Randomized: ~120/110 Completed: ~110	

Length of Study: 40 months
Planned first patient visit: April 2012
Planned last patient visit: August 2015
Planned interim analyses:

1. All patients in Phase 1b have received at least 1 cycle: safety and pharmacokinetics (PK)
2. Approximately 30 patients in Phase 2 have received at least 1 cycle: safety and PK
3. Approximately 60 patients in Phase 2 have received at least 2 cycles: safety, and PK

For the purposes of database lock and completion of the study report, this study will be considered complete following the analysis of PFS (primary Phase 2 objective). After the study is considered complete, patients and investigators will remain blinded and survival data will continue to be collected. The analysis of overall survival (OS) will be performed after all patients in the Phase 2 portion of the study have been followed for at least 2 years.

Objectives:

The primary objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose of LY2228820 that can be safely administered in combination with gemcitabine and carboplatin.

The primary objective of the Phase 2 portion of this study is to compare progression-free survival in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin.

The secondary objectives of the study are to evaluate:

- Change in tumor size, CA125 (serum biomarker for ovarian cancer), overall response rate, and overall survival
- Safety and tolerability of the combination: LY2228820 plus gemcitabine and carboplatin
- Pharmacokinetics (PK) of LY2228820 and evaluation for effect of LY2228820 on the PK of gemcitabine, its metabolite (dFdU), and carboplatin
- Biomarkers related to p38 MAPK pathway activity and the pathogenesis of ovarian cancer
- Patient-reported outcomes for patients enrolled in the Phase 2 portion of the study

Study Design:

This trial is a Phase 1b dose escalation followed by a randomized, double-blind, placebo-controlled Phase 2 study of LY2228820 plus gemcitabine and carboplatin versus gemcitabine and carboplatin for women with platinum-sensitive ovarian cancer.

In the Phase 1b portion of the trial, approximately 2 cohorts will be needed to determine the maximum tolerated dose of LY2228820 in combination with gemcitabine and carboplatin.

Once the maximum tolerated dose for LY2228820 in combination with gemcitabine and carboplatin is defined, approximately 110 patients will be randomized 1:1 to the LY2228820 or placebo arm. All patients will receive gemcitabine and carboplatin. After completion of 6 cycles of combination therapy, patients with stable disease or evidence of biomarker and/or tumor response will receive maintenance therapy with LY2228820 or placebo until disease progression. Maintenance therapy will be administered based on original 1:1 randomization.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Main inclusion criteria for study entry are:

- Women at least 18 years of age at the time of randomization who have cytologically or histologically proven epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with evidence of recurrence or progression, which is advanced and not amenable to curative surgery or radiotherapy
- Have recurrence of cancer at least 6 months after completion of first-line platinum-based therapy
- For Phase 1b, have either measurable or non-measurable disease; for Phase 2, must have at least 1 measurable lesion assessable using standard techniques according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines (Eisenhauer et al. 2009)
- Have a performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale
- Have adequate hematologic, hepatic, and renal function

Main exclusion criteria for study entry are:

- Are currently enrolled in, or discontinued <14 days from, a clinical trial involving an investigational drug or device
- Have previously completed or withdrawn from this study or any other study investigating LY2228820
- Have previously been treated with gemcitabine for epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
- Receiving concomitant cytotoxic or other antineoplastic treatment
- Have had, in the judgment of the investigator, a major bowel resection that would alter oral drug absorption
- Are receiving, in the judgment of the investigator, concurrent administration of immunosuppressive therapy
- Have, in the judgment of the investigator, serious concomitant systemic disorders (e.g., acute myocardial infarction within 6 months of study entry, uncontrolled hypertension) incompatible with the study
- Have received more than 1 previous chemotherapy regimen for ovarian cancer, fallopian tube cancer or primary peritoneal cancer

Test Product, Dose, and Mode of Administration:

Study drugs are administered on a 21-day cycle during induction therapy (Cycles 1 through 6) and on a 28-day cycle during maintenance therapy (Cycle 7 and beyond). LY2228820 is administered orally every 12 hours on Days 1 through 10 of a 21-day cycle during induction therapy and on Days 1 through 14 of a 28-day cycle during maintenance therapy. Gemcitabine (1000 mg/m^2) is administered intravenously (IV) over 30 minutes (+15 min) on Days 3 and 10 of induction therapy only. Carboplatin (area under the plasma concentration–time curve [AUC] 4 with maximum dose of 600 mg) is administered IV over 30 minutes (+15 min) on Day 3 of induction therapy only.

Planned Duration of Treatment:

Induction therapy (Cycles 1 through 6): six 21-day cycles or until discontinuation criteria are fulfilled

Maintenance therapy (Cycle 7 and beyond): until discontinuation criteria are fulfilled

Short-term post-discontinuation period: approximately 30 days

Long-term post-discontinuation period: until death or lost to follow-up (for a maximum of 2 years after enrollment in study)

Reference Therapy, Dose, and Mode of Administration:

Study drugs are administered on a 21-day cycle during induction therapy (Cycles 1-6) and on a 28-day cycle during maintenance therapy (Cycle 7 and beyond). Placebo is administered orally every 12 hours on Days 1 through 10 of a 21-day cycle during induction therapy and on Days 1 through 14 of a 28-day cycle during maintenance therapy. Gemcitabine (1000 mg/m^2) is administered IV over 30 (+15) minutes on Days 3 and 10 of induction therapy only. Carboplatin (AUC4 with maximum dose of 600 mg) is administered IV over 30 (+15) minutes on Day 3 of induction therapy only.

Criteria for Evaluation:

Efficacy: Progression-free survival, change in tumor size, CA-125, overall response rate, and overall survival

Safety: Adverse events, safety laboratories, and electrocardiograms

Health outcomes: FACT-Ovarian (FACT-O) instrument

Pharmacokinetic: PK parameters, such as C_{max}, $t_{max,}$ AUC, V_d/F, CL/F, and $t_{½}$, and other relevant parameters for LY2228820, gemcitabine and its metabolite (dFdU), and carboplatin; population PK parameters for LY2228820

Statistical Methods:

Efficacy: Although an efficacy analysis is not appropriate for the Phase Ib portion of this trial, any tumor response data will be tabulated. In the Phase 2 portion of the study, PFS is the primary endpoint; the hazard ratio will be estimated from survival data on all randomized patients using a Cox proportional hazard model with appropriate covariates. The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curve as well as survival rates at various time points for each treatment group. The following secondary endpoints will be summarized for each treatment group:

- Change in tumor size
- CA-125
- Overall response rate
- Overall survival

Safety: During the study, interim analyses will be performed to evaluate safety, PK, futility, and efficacy. Interim analyses for the Phase 2 portion of the study will be performed under the guidance of an internal assessment committee.

Health outcomes: Patient-reported outcomes will be evaluated only during the Phase 2 portion of the study. Time to worsening of symptoms and changes in symptoms from baseline will be measured using the FACT-O instrument.

Pharmacokinetic: For all patients in Phase 1b and a subset of patients (10 patients/arm) in Phase 2, the 90% confidence interval for the difference of means will be used to estimate potential for drug interactions among patients who are treated with LY2228820 plus gemcitabine and carboplatin compared with those treated with placebo plus gemcitabine and carboplatin. Log-transformed PK parameters will be used to assess such interactions with back transformation to the original scale.

3. Table of Contents

A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Study of LY2228820, a p38 MAPK Inhibitor, plus Gemcitabine and Carboplatin versus Gemcitabine and Carboplatin for Women with Platinum-Sensitive Ovarian Cancer

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4. Abbreviations and Definitions

Term	Definition
AC	assessment committee
adverse event (AE)	any untoward medical occurrence in a patient or clinical investigation subject 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
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
assent	agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs])
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
audit	a systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s)
blinding/masking	a procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s); unless otherwise specified, blinding will remain in effect until final database lock; a single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not; a double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received
BMI	body mass index
case report form (CRF) and electronic case report form (eCRF)	sometimes referred to as clinical report form; printed or electronic form for recording study participants' data during a clinical study, as required by the protocol
clinical research physician (CRP)	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
CI	confidence interval

CNS	central nervous system
complaint	any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system
compliance	adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Change in tumor size (CTS)	a measure of tumor dynamics from which tumor response is derived; tumor size is the sum of tumor measurements across all target tumors at a given evaluation (RECIST criteria version 1.1)
DLT	dose-limiting toxicity
DMC	data monitoring committee
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
end of study (trial)	the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study
enroll/randomize	the 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/consent	the act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial; patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives
ePRO/PRO	(electronic) patient-reported outcome
ESAs	erythropoiesis-stimulating agents
evaluable patient (for Phase 1b)	any patient who experiences a DLT or receives at least 75% of planned doses of LY2228820 in Cycle 1
evaluable patient (for Phase 2)	any randomized patient
FSH	follicle-stimulating hormone
GCP	good clinical practice
GFR	glomerular filtration rate

GnRH	gonadotropin-releasing hormone
H_0	null hypothesis
H_a	alternative hypothesis
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMS	Isotope Dilution Mass Spectrometry
IND	Investigational New Drug application
institutional review board/ethical review board (IRB/ERB)	a board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected
intention-to-treat (ITT)	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
interim analysis	an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked
investigator	a person responsible for the conduct of the clinical trial at a trial site; if a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator
IV	intravenous
IVRS	interactive voice-response system
legal representative	an individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study
LLT	Lower Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
OUS	outside the United States
patient	a study participant who has the disease or condition for which the investigational product is targeted
PD	pharmacodynamic
PDA	personal data assistant
per protocol set (PPS)	the set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model
PET	positron emission tomography
PFS	progression-free survival
PO	oral
PK	Pharmacokinetic
PR	partial response
PS	performance status
PT	Preferred Term
QTc	corrected QT interval
Q12H	every 12 hours
RECIST Version 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	Recommended Phase 2 dose (in combination with gemcitabine and carboplatin)
SAE	serious adverse event
Screen	The act of determining if an individual meets minimum requirements for participation in a clinical study.
SD	stable disease
SOC	System Organ Class
suspected unexpected serious adverse	serious events that are not listed in the Investigator's Brochure (IB) and that the investigator identifies as related to investigational product or procedure

reactions	
TPO	third-party organization
treatment-emergent adverse event (TEAE)	any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment
TTTF	time to treatment failure
UGT	UDP-glucuronosyltransferase
US	United States

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5. Introduction

5.1. Rationale and Justification for the Study

p38 mitogen-activated protein kinase (MAPK) is a signaling protein activated by cancer cells to enable survival after exposure to either radiation or chemotherapy. p38 MAPK phosphorylates a number of substrates, including MAPK-activated protein kinase 2 (MAPKAP-K2), and also regulates the tumor microenvironment's production of such key cytokines as tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8). These cytokines are upregulated in many human malignancies, including ovarian cancer. In addition to promoting survival, these cytokines also enhance growth, invasion, angiogenesis, and metastasis (Balkwill and Mantovani 2001; Lewis et al. 2006). Thus, pharmacologic inhibition of p38 MAPK in both the cancer cell and its supportive microenvironment represents a novel therapeutic strategy for improving outcomes for patients with ovarian cancer.

Study I1D-MC-JIAE will evaluate efficacy of the p38 MAPK inhibitor, LY2228820, in combination with gemcitabine and carboplatin for patients with platinum-sensitive ovarian cancer.

5.2. Ovarian Cancer

Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies. It is the fifth most frequent cause of cancer death in women after cancers of the lung, breast, colon/rectum, and pancreas (Howlader 2011). Seventy percent of patients present with advanced disease (Fleming et al, 2009). In 2010, an estimated 21,900 new cases were diagnosed, and an estimated 13,900 deaths were due to this cancer in the United States alone (Jemal 2010). The 5-year survival rate of women with diagnosed ovarian cancer is approximately 40% (Jemal 2009). However, for women with platinum-sensitive recurrent ovarian cancer, the median progression-free survival (PFS) is only 8.6 months (Pfisterer et al. 2006), indicating the importance of improving therapeutic outcomes for these women.

5.3. General Introduction to LY2228820

LY2228820 dimesylate (hereafter referred to as LY2228820) is a potent and selective inhibitor of p38 MAPK that binds competitively to the ATP binding site of the kinase to impair phosphorylation of its substrates. In multiple ovarian cancer xenograft studies, LY2228820 has demonstrated in vivo antineoplastic activity. LY2228820 has been evaluated previously for safety and tolerability in a Phase 1 study (I1D-MC-JIAD, hereafter referred to as Study JIAD)

for patients with advanced cancer. Detailed information about LY2228820 is provided in the Investigator's Brochure (IB).

5.4. Mechanism of Action and In Vitro/In Vivo Activity

LY2228820 inhibits phosphorylation of p38 MAPK substrates and abrogates signaling events critical not only to cancer cell survival but also to production of key cytokines by the tumor microenvironment. LY2228820 exhibits inhibitory activity against p38 MAPK with more than 1000-fold selectivity towards the alpha isoform of p38 MAPK (IC_{50} = 5.3 nM) compared with a panel of 179 representative kinases. Furthermore, LY2228820 strongly inhibits the p38 MAPK pathway as indicated by reduction in phosphorylation of MAPKAP-K2 and TNFα production. Specifically, LY2228820 inhibits anisomycin-induced MAPKAP-K2 phosphorylation in mouse RAW264.7 cells (IC_{50} = 35.3 nM) and lipopolysaccharide (LPS)-induced TNFα secretion by mouse macrophages (IC_{50} = 6.3 nM). Finally, a single 10-mg/kg oral dose of LY2228820 achieves more than 40% inhibition of phosphorylated MAPKAP-K2 in murine B16-F10 melanoma xenografts for approximately 4 to 8 hours after the dose. Most importantly, LY2228820 demonstrates in vivo antineoplastic activity in xenograft models of human glioblastoma, multiple myeloma, lung cancer, and ovarian cancer.

5.5. Biomarkers

In this study, a number of biomarkers related to p38 MAPK pathway activity and the pathogenesis of ovarian cancer will be assayed in either blood or archived tumor samples for correlation with safety and efficacy outcomes associated with LY2228820 therapy. These evaluations will help to determine the potential usefulness of the selected biomarkers for patient tailoring in future clinical studies.

Circulating plasma proteins regulated by p38 MAPK (such as TNFα, IL-1β, IL-6, and IL-8) will be measured. The tumor suppressor p53 will be evaluated for gene expression and mutation as well as for protein expression in archived tumors. The tumor suppressor PTEN will be evaluated for gene mutation and protein expression in archived tumors. For p53 and PTEN, a whole blood sample will also be obtained for the isolation and mutational analysis of germline deoxyribonucleic acid (DNA) from peripheral blood mononuclear cells (PBMCs). Additional biomarkers related to the pathogenesis of ovarian cancer and to the p38 MAPK pathway (such as p-MAPKAP-K2) may be assessed in either blood or archived samples.

5.6. Nonclinical Pharmacokinetics

Plasma pharmacokinetics of [^{14}C] LY2228820 were evaluated after a single dose in male Fischer 344 rats and cynomolgus monkeys. Based on AUC, LY2228820 accounted for 56% and 3% of the plasma radioactivity in rats and monkeys, respectively. The half-life of LY2228820 was similar in both species (approximately 10 hours), whereas the half-life of radioactivity was longer (104 hours in monkeys and 32 hours in rats), indicating that some metabolite(s) are cleared more slowly than parent.

In multiple-dose pharmacokinetic studies in Fischer 344 rats for 7 cycles (14 consecutive dosing days followed by 14 days of a washout period between each cycle), exposure to LY2228820, as

determined by AUC and C_{max}, increased over the dose range from 25 mg/kg to 150 mg/kg, but the increase was not consistently dose proportional. The exposures were slightly higher in females than in males, but the differences in general were not over 2-fold. No accumulation of LY2228820 was observed in rat plasma after multiple dosing. In similar studies in monkeys, systemic exposure to LY2228820, although highly variable, increased with increasing dose from 15 mg/kg to 60 mg/kg. Exposures generally appeared to be lower after multiple dosing when compared to a single dose and the toxicokinetics of LY2228820 were similar in both male and female monkeys.

The nonclinical tumor growth delay models from 2 studies in mice indicated efficacy in the 10-mg/kg groups corresponding to an $AUC_{(0\text{-}24hr)}$ of 13.4 μg*hr/mL. The preclinical pharmacokinetic/pharmacodynamic (PK/PD) model in mouse was developed to characterize the relationship between drug concentrations and phosphorylated MAPKAP-K2 levels. This PK/PD model integrated the time course of the pharmacokinetics of the compound and the inhibition of phosphorylated MAPKAP-K2 in PBMCs. Allometric scaling was performed using data from 4 preclinical species: mouse, rat, dog, and monkey. The initial (pre-FHD) human PK predictions assumed linear pharmacokinetics at therapeutic doses and employed a 2-compartment PK model. The human PK/PD simulations (based on allometric prediction of PK and the murine xenograft model) predicted that a range of 40 to 120 mg administered orally every 12 hours would achieve the required 80% maximal inhibition of phosphorylated MAPKAP-K2 associated with tumor growth delay in preclinical efficacy studies. However, interim human PK data from the first 7 cohorts in Study JIAD indicated that the predicted efficacious dose range required to achieve this threshold may be higher than the initial preclinical PK/PD model predictions.

5.7. Nonclinical Toxicology

The toxicity of LY2228820 has been characterized in a broad range of nonclinical safety studies. In monkeys, repeat-dose studies of 1 month's duration with daily dosing, and of 3 and 6 months' duration using an intermittent dosing schedule of 2 weeks on treatment and 2 weeks off treatment have been conducted. In rats, repeat-dose studies of 1 month's duration (daily dosing) and 6 months' duration (intermittent dosing schedule) have been conducted. Other nonclinical studies include a single-dose study in rat; a battery of safety pharmacology studies (assessing the central nervous, cardiovascular, respiratory and gastrointestinal systems), a battery of genetic toxicity studies, an embryo-fetal development study in rats, and a phototoxicity assessment. Collectively, these studies have adequately characterized the toxicology profile to support clinical testing with LY2228820.

Gastrointestinal tract, liver and skin have been identified as the primary target organs toxicity in nonclinical species. In addition, hypercellular bone marrow and peripheral leukocytosis have been observed in both rat and monkey. Intermittent dosing generally ameliorated the toxicities observed with daily dosing, or resulted in similar toxicity despite longer durations of dosing (three to six months). With daily dosing for 1 month in monkeys, the no observed adverse effect level (NOAEL) was not identified (<3 mg/kg), and the maximum tolerated dose (MTD) was 15 mg/kg; however, in a 6-month intermittent dosing study, the NOAEL was 15 mg/kg and the MTD was 30 mg/kg. In rats, a NOAEL for daily dosing for 1 month was not identified (<25

mg/kg), and the MTD was 150 mg/kg. When the duration was extended to 6 months with intermittent dosing, the NOAEL and the MTD were 25 mg/kg due to a small number of deaths at 75 mg/kg; however, most rats tolerated 75 mg/kg, and most male rats tolerated 150 mg/kg for the duration of the study. Decreased fetal weight, increased skeletal developmental variations, increased postimplantation loss, malformed fetuses, and decreased numbers of viable fetuses were observed in pregnant rats treated with LY22288200 during the period of organogenesis. In safety pharmacology studies, monitorable and manageable increases in blood pressure, decreases in tidal volume, and central nervous system effects were observed.

5.8. Interaction with Cytochrome P450 (CYP) Enzymes and Enzymes Responsible for the Metabolism of LY2228820

The effect of LY2228820 on drug-metabolizing enzymes has been studied in vitro using human liver microsomes. LY2228820 was found to competitively inhibit the biotransformation of midazolam to 1′-hydroxy-midazolam with an estimated Ki of 1.2 μM (0.5 μg/mL). LY2228820 was also shown to inhibit CYP3A in a time-dependent manner with a k_{inact} of 0.069 min^{-1} and K_I of 9.5 μM (3.99 μg/mL). These data suggested the possibility that LY2228820 might modulate clearance of drugs that are metabolized by CYP3A in vivo.

The ability of LY2228820 to induce catalytic activities associated with CYP1A2, CYP2B6, and CYP3A was examined in primary cultures of fresh human hepatocytes. LY2228820 was found unlikely to cause in vivo induction of the above CYP isoforms within the concentration range examined (0.01 to 10 μM).

The effect of LY2228820 on the activity of CYP3A in vivo has been evaluated in the dose confirmation phase of Study JIAD (Part B) in which patients were administered a 2-mg oral dose of midazolam in the absence or presence of 420 mg LY2228820 administered every 12 hours (after fourteen doses). Results showed that mean PK parameters (C_{max} and AUC) of midazolam administered with LY2228820 were no higher than those of midazolam administered alone, indicating that LY2228820 may not inhibit the CYP3A activity up to the dose level investigated (18 patients at 420 mg given every 12 hours).

In vitro studies using human liver microsomes indicated that the metabolic clearance of LY2228820 is primarily mediated by the UDP-glucuronosyltransferase (UGT) pathway (87%), with CYP-mediated pathway contributing to only 13%. Further CYP phenotyping studies using recombinant human CYPs indicated that CYP3A contributed to 72% of the CYP-mediated metabolic clearance of LY2228820. Taken together, the contribution of CYP3A to the total metabolic clearance of LY2228820 is estimated to be less than 10%. The regulatory guidance suggests that any enzyme contributing <25% to the systemic clearance of the drug is not clinically significant (FDA 2012).

Collectively, the above in vitro and in vivo data suggest that clinical interactions are unlikely when LY2228820 is coadministered with substrates, inhibitors and or inducers of CYP3A. When coadministered, inhibitors of UGT may increase the plasma concentrations of LY2228820 and inducers of UGT may decrease the plasma concentrations of LY2228820.

Refer to Section 9.8, Concomitant Therapy, for more information regarding inhibitors and inducers of UGT.

5.9. Rationale for Selection of Dose Range

The dose range of LY2228820 for the Phase 1b component of this study consists of doses previously explored in the first-in-human Phase 1 Study JIAD, wherein the single-agent MTD was identified at a dose level of 420 mg administered every 12 hours on Days 1 through 14 of a 28-day cycle. However, a relatively high frequency of Grade 1/Grade 2 dizziness and tremor and Grade 3 rash were observed in a subsequent dose-confirmation cohort, and led to a decision to further explore the 300-mg every 12 hours (Q12H) dose. Of the 11 patients in Study JIAD who received LY2228820 at 300 mg Q12H, 2 patients (18%) experienced a possibly related Grade 3 rash dose-limiting toxicity (DLT)-equivalent event and only 1 patient (9.1%) each experienced a possibly related Grade 1 dizziness event and possibly related Grade 1 tremor event. Therefore, the 300-mg Q12H dose was recommended as the Phase 2 dose for monotherapy, and will be the maximum dose of LY2228820 administered for this Phase 1b/2 study (JIAE).

The Phase 1b portion of JIAE will include 2 cohorts at LY2228820 doses of 200 mg and 300 mg every 12 hours and the Phase 2 portion of JIAE will be conducted at a single recommended LY2228820 dose not exceeding 300 mg every 12 hours. In JIAE, LY2228820 (or placebo) is administered on a 21-day cycle (every 12 hours on Days 1 through 10) in combination with gemcitabine (Days 3 and 10) and carboplatin (Day 3) during induction therapy (Cycles 1 through 6) and on a 28-day cycle (every 12 hours on Days 1 through 14) as a single agent during maintenance therapy (Cycle 7 and beyond).

The dose of LY2228820 for the Phase 2 component of this study will be a single-dose level identified during the Phase 1b portion of the study as the MTD when LY2228820 is administered in combination with gemcitabine and carboplatin.

Throughout induction therapy (Cycles 1 through 6), the dose for gemcitabine will start at 1000 mg/m^2 on Days 3 and 10 and the dose for carboplatin will start at AUC 4 (with a maximum dose of 600 mg) on Day 3 of a 21-day cycle.

5.10. Rationale for Amendment (a)

In April 2012, Study JIAE was amended to address a number of protocol issues noted since the start of enrollment. The most significant changes included the following: revisions to allow measurement of serum creatinine by the Isotope Dilution Mass Spectrometry (IDMS) method; changes to a secondary objective to clarify rationale for measuring plasma concentrations of gemcitabine, its metabolite (dFdU), and carboplatin; inclusion of a 600-mg maximum dose for carboplatin; decrease in the fasting period around the LY2228820 dose; and addition of a Day 10 electrocardiogram (ECG) during Cycles 1 and 2.

5.11. Rationale for Amendment (b)

After 2 reported DLTs of Grade 4 thrombocytopenia occurred in patients enrolled in the Phase 1b portion of Study JIAE, the Phase 2 portion of the study was opened on 21 May 2013, utilizing a dose of 200 mg of LY2228820 in combination with gemcitabine and carboplatin as the recommended Phase 2 dose for induction therapy.

Lilly then conducted a thorough review of the Phase 1b data and blinded adverse event data from patients enrolling concurrently in the Phase 2 portion, noting the following:

1. Thirty-three percent of Phase 1b patients (2/6) experienced Grade 4 transient thrombocytopenia (lasting 1 and 4 days or less). The expected incidence of Grade 3/4 thrombocytopenia for the gemcitabine/carboplatin combination is approximately 35% (Pfisterer et al. 2006). Lilly, in collaboration with study investigators, concluded that the protocol hematologic DLT criteria did not take into account the known toxicities of the gemcitabine/carboplatin combination, and thus limited the use of those criteria (alone) for the identification of maximum tolerated dose of LY2228820 to be administered with the standard-of-care combination.

2. Drug-related adverse events that characterized the DLTs of LY2228820 administered as a single agent (Study JIAD), such as ataxia, dizziness, and rash, were infrequent and low grade in Study JIAE to that point (no dermatological toxicities were reported; 2 of 6 patients experienced Grade 3 syncope judged by the investigators to be unrelated to study therapy).

3. PK analyses from Studies JIAD and JIAE and preclinical modeling studies suggest that a 300-mg dose of LY2228820 administered every 12 hours provides a greater chance to achieve potentially efficacious exposures.

4. Blinded adverse event data from 9 patients in the Phase 2 portion of Study JIAE (200-mg dose LY2228820) showed a relatively low rate of DLT-level toxicity. Neurological and dermatological toxicities included Grade 1 dizziness, Grade 1 rash, Grade 2 rash, and Grade 3 rash (1 patient each). Hematological toxicities reported were Grade 2 neutropenia (2 patients) and Grade 3 neutropenia (2 patients), with no Grade 3/4 thrombocytopenia reported. These findings supported further exploration of the 300-mg dose of LY2228820.

Therefore, as of 25 September 2013, enrollment in the Phase 2 portion of Study JIAE was temporarily halted. The protocol is amended here to reflect revised DLT criteria to better account for expected toxicities from the gemcitabine/carboplatin combination and to resume the Phase 1b investigation of the 300-mg LY2228820 dose in combination with gemcitabine and carboplatin in an additional cohort of 3 patients.

5.12. Rationale for Amendment (c)

Metabolic clearance analysis has recently been completed which revealed that CYP3A mediated metabolism is not the primary clearance pathway of LY2228820. This allows for the restriction of the CYP3A inhibitors, inducers, or substrates to be removed and for the use of dexamethasone and other anti-emetics during treatment with LY2228820.

Based on the available preclinical data, there is a possible risk of clinical drug–drug interaction when LY2228820 is administered with inhibitors or inducers of UGT enzymes. In the absence of clinical data to refine the risk of interaction, caution is warranted in the concomitant use of UGT enzyme inhibitors such as valproic acid and probenecid and inducers such as carbamazepine, phenytoin and rifampin. When, in the clinical investigator's opinion, concomitant use of valproic acid or probenecid is indicated, LY2228820-related DLTs of ataxia, dizziness and rash should be carefully monitored.

The ovarian cancer landscape has changed during the course of this study. Maintenance therapy as a part of or after a first line platinum regimen has become more prevalent. Several studies are examining the effect of maintenance after patients achieve a CR with the first line platinum regimen. In order to balance these patients between the placebo and LY2228820 arms, prior maintenance therapy has been added as a randomization factor.

The original sample size calculation for the Phase 2 portion of the study included a censoring rate assumption of 6% with 103 PFS events needed from 110 patients. Upon reflection, Lilly considers that this assumed censoring rate is too low. If just 8 or more patients are lost to follow up, the actual censoring rate would be higher. With this protocol amendment, the censoring rate estimate has been increased to 28% resulting in a reduction in the number of PFS events needed to 79. The hazard ratio of 0.7 has been maintained but the power has been reduced to 77% from 83%. These assumptions are consistent with enrollment and censoring experience in this phase of development.

In addition, the interim analyses for the study have been updated as follows:

- The third interim analysis will be performed when approximately 60 patients in the Phase 2 portion of the study have completed 2 cycles of treatment, and will examine safety and PK only. Futility has been eliminated as Lilly does not expect that enough PFS events will have been observed to allow a futility analysis to occur at that time.
- The fourth interim analysis has been removed as all patients will have been enrolled and the PFS data will be immature. This interim would not be informative for futility or efficacy. Trial level safety will continue to be monitored throughout the study.

6. Objectives

6.1. Primary Objective

The primary objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose of LY2228820 that can be safely administered in combination with gemcitabine and carboplatin.

The primary objective of the Phase 2 portion of this study is to compare the progression-free survival in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin.

6.2. Secondary Objectives

The secondary objectives of the study are to evaluate:

- Change in tumor size, CA125 (serum biomarker for ovarian cancer), overall response rate, and overall survival (OS)
- Safety and tolerability of the combination: LY2228820 plus gemcitabine and carboplatin
- Pharmacokinetics (PK) of LY2228820 and evaluation for effect of LY2228820 on the PK of gemcitabine, its metabolite (dFdU), and carboplatin
- Biomarkers related to p38 MAPK pathway activity and the pathogenesis of ovarian cancer
- Patient-reported outcomes for patients enrolled in the Phase 2 portion of the study

7. Study Population

7.1. Inclusion Criteria

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

[1] Women ≥18 years of age who have a cytologically or histologically proven epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with evidence of recurrence or progression, which is advanced and not amenable to curative surgery or radiotherapy. See Attachment 4 (International Federation of Gynecology and Obstetrics [FIGO] Staging) (Odicino et al. 2008).

[2] Have recurrence of cancer at least 6 months after completion of first-line platinum-based therapy.

[3] For Phase 1b, have either measurable or non-measurable disease. For Phase 2, must have at least 1 measurable lesion assessable using standard techniques according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines (Eisenhauer et al. 2009).

[4] Have a performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale. See Attachment 5.

[5] Have discontinued all previous therapies for cancer (including chemotherapy, investigational therapy) for at least 14 days prior to study enrollment and recovered from the acute effects of therapy. Previous radiotherapy must be terminated at least 21 days before study drug administration.

[6] Have adequate organ function, including:

- Hematologic: absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin until 1 day after the erythrocyte transfusion.
- Hepatic: bilirubin ≤1.5 times upper limits of normal and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times upper limits of normal.
- Renal: creatinine clearance ≥50 ml/min calculated using the Cockcroft and Gault formula (Attachment 6).

[7] For women of child-bearing potential, must have a negative serum pregnancy test within 7 days prior to the first dose of LY2228820 and agree to use a reliable method of birth control during the study and for 3 months following the last dose of LY2228820. All women are deemed to be of child-bearing potential unless they fulfill one or both of the following criteria: 1) ≥50 years of age with no menstrual period for at least 24 months or 2) prior surgical castration.

[8] Have given written informed consent/assent prior to any study-specific procedures.

[9] Are able to swallow tablets.

7.2. Exclusion Criteria

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

[10] Are currently enrolled in, or discontinued <14 days from, a clinical trial involving an investigational drug or device.

[11] Have previously completed or withdrawn from this study or any other study investigating LY2228820.

[12] Have previously been treated with gemcitabine for epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

[13] Receiving concomitant cytotoxic or other antineoplastic treatment. Hormone replacement therapy is allowed.

[14] Have had, in the judgment of the investigator, a major bowel resection that would alter oral drug absorption.

[15] Have a diagnosis of inflammatory bowel disease (Crohn's disease or ulcerative colitis).

[16] Exclusion criterion [16] has been deleted

[17] Require concurrent administration of immunosuppressive therapy such as corticosteroids (prednisone >10 mg/day, or equivalent). Intermittent corticosteroids used as part of an antiemetic regimen are permitted.

[18] Have known central nervous system malignancy or metastasis.

[19] Have a concurrent or previous malignancy (other than epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer), unless that prior malignancy was treated with definitive therapy at least 5 years previously with no evidence of recurrence. However, cervical carcinoma (in situ) or localized non-melanoma skin cancer treated with definitive therapy with no evidence of recurrence are not subject to this 5-year requirement.

[20] Have serious concomitant systemic disorders (e.g., acute myocardial infarction within 6 months of study entry, uncontrolled hypertension) incompatible with the study.

[21] Have received more than 1 previous chemotherapy regimen for ovarian cancer.

[22] Have any diagnosis of ovarian borderline tumor.

[23] Exclusion Criterion [23] has been deleted.

[24] Are pregnant or lactating women.

7.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [10] eliminates drugs that cannot be mapped to a standard drug dictionary, or for which little data are known to analyze the potential relationship of adverse events (AEs) or drug interactions. Exclusion Criteria [11], [12], [13], [17], [20], [21], [23], and [24] exclude patients with confounding therapy, conditions, or circumstances. Exclusion Criteria [14], [15], and [16] exclude patients receiving medications that may alter absorption or metabolism of LY2228820. Exclusion Criteria [18], [19], and [22] exclude patients with conditions that have a distinct prognosis.

7.3. Discontinuations

7.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, Lilly or its designee must be contacted. In these cases, the investigator must obtain documented approval from Lilly to allow the patient to continue to receive study drug.

In addition, patients will be discontinued from the study treatment and/or study in the following circumstances.

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/physician decision
    - The investigator/physician decides that the patient should be withdrawn from the study treatment and/or study. If this decision is made because of toxicity, a serious AE, or a clinically significant laboratory value, the study drug(s) should be discontinued and appropriate measures taken.
    - If 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 the study treatment occurs prior to introduction of the new agent.
- Patient decision
    - The patient, or the patient's designated representative, requests that the patient be withdrawn from the study treatment and/or study.
- Sponsor decision
    - The investigator or Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.
- The patient is noncompliant with study treatment and/or procedures.
- Evidence of progressive disease as defined by RECIST 1.1.
- Unacceptable toxicity.
- It is necessary to delay a patient's treatment more than 21 days due to toxicity.

- A patient's calculated creatinine clearance has not returned to ≥50 mL/min at the beginning of an induction cycle (see Section 9.1.1.1).
- The patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).

Exceptions may be granted in rare circumstances in which the patient has a serious or life-threatening condition for which there is no effective alternative therapy and, in the judgment of the investigator, is receiving benefit from study treatment. In these rare cases, the investigator must obtain documented approval from Lilly to allow the patient to continue to receive study treatment.

The reason and date for discontinuation will be collected for all patients. All patients who discontinue but receive at least one dose of study treatment will have procedures performed as shown in the Study Schedule (Attachment 1).

For Phase 1b, any patient who experiences a dose-limiting toxicity or receives at least 75% of planned doses of LY2228820 in Cycle 1 will be deemed evaluable for safety assessment at that dose level. Non-evaluable patients may be replaced to ensure at least 3 evaluable patients at each dose level, unless accrual to that cohort has stopped because 2 or more patients at that dose level have experienced a DLT. In no case should patients be replaced if they were discontinued from the study due to toxicity. Patients who are evaluable for safety assessment at a dose level but have insufficient PK sampling may be replaced upon consultation with the investigator(s) and the Lilly Clinical Research Physician (CRP) to ensure adequate PK data, unless accrual to that cohort has stopped because 2 or more patients at that dose level have experienced a DLT.

7.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

7.3.3. Discontinuation of the Study

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

8. Investigational Plan

8.1. Summary of Study Design

Study JIAE consists of Phase 1b dose escalation followed by a Phase 2 randomized, double-blind, placebo-controlled trial in women with advanced epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have relapsed at least 6 months after first-line platinum-based therapy (refer to Figure JIAE.1).

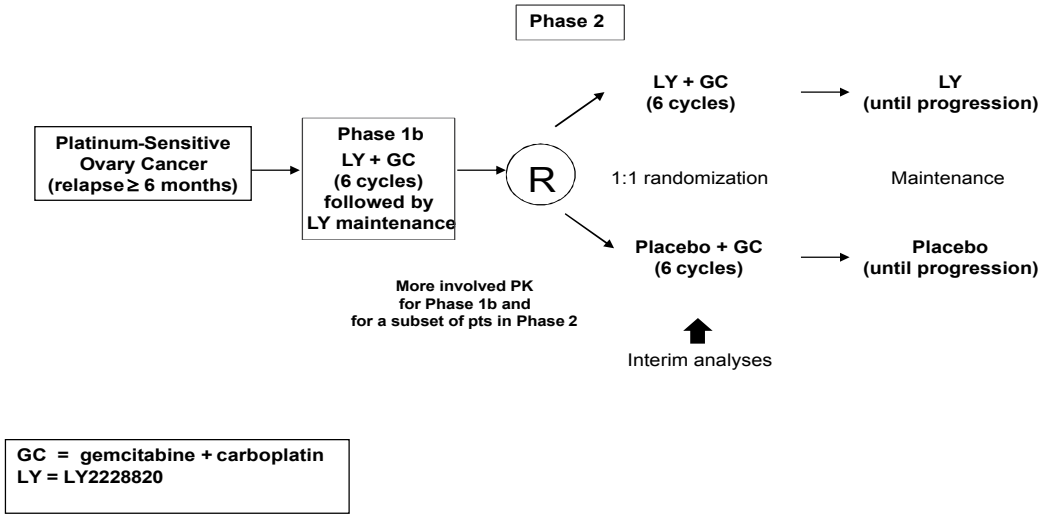

Figure JIAE.1. Study design for Protocol 1ID-MC-JIAE.

Throughout the study, LY2228820 (or placebo) will be administered orally on an intermittent schedule (every 12 hours on Days 1 through 10 of a 21-day cycle during induction therapy and every 12 hours on Days 1 through 14 of a 28-day cycle during maintenance therapy).

During induction therapy, gemcitabine will be administered IV over approximately 30 (+15) minutes on Days 3 and 10 of the 21-day cycle and carboplatin will be administered IV 30 minutes after gemcitabine over approximately 30 (+15) minutes on Day 3 of the 21-day cycle.

8.1.1. Phase 1b

An unblinded, Phase 1b dose escalation of LY2228820 in combination with standard doses of gemcitabine and carboplatin will be completed prior to opening the randomized, double-blind, placebo-controlled Phase 2 portion of this study. Using a "3+3" dose escalation method, cohorts of 3 patients will be treated with induction therapy at escalating doses of LY2228820, orally

administered every 12 hours on Days 1 through 10 of a 21-day cycle, in combination with gemcitabine (1000 mg/m^2 on Days 3 and 10) and carboplatin (AUC 4 on Day 3). Patients will receive 6 cycles of induction therapy unless the discontinuation criteria are fulfilled. All patients in the Phase 1b portion of the study that achieve stable disease or better will also receive maintenance therapy consisting of LY2228820 as a single agent at a dose of 300 mg every 12 hours on Days 1 through 14 of a 28-day cycle. Patients will continue maintenance therapy until the discontinuation criteria are fulfilled.

8.1.2. Phase 2

After the optimal dose of LY2228820 in combination with gemcitabine and carboplatin has been determined from the Phase 1b portion and discussed with study investigators, the Phase 2 portion of the study will open to enrollment. The recommended Phase 2 dose of LY2228820 in combination with gemcitabine and carboplatin will not exceed the single-agent LY2228820 dose of 300 mg every 12 hours. In the Phase 2 portion, approximately 110 patients will be randomized 1:1 to receive either LY2228820 plus gemcitabine and carboplatin (Arm A) or placebo plus gemcitabine and carboplatin (Arm B). Patients will receive 6 cycles of induction therapy unless the discontinuation criteria are fulfilled. All patients in the Phase 2 portion of the study that achieve stable disease or better will also receive maintenance therapy consisting of LY2228820 as a single agent at a dose of 300 mg every 12 hours on Days 1 through 14 of a 28-day cycle. Patients will continue maintenance therapy until the discontinuation criteria are fulfilled.

Approximately 110 patients will be randomized 1:1 to provide 83% power for identifying a hazard ratio of 0.7 (LY2228820 arm to placebo arm) with a false-positive rate of 0.2 (one-sided) (refer to Section 12 for additional details regarding the sample size description). Patients will be randomized with a minimization method (Pocock and Simon 1975) using the following factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months) and ECOG performance status (0 and 1 versus 2).

Starting from protocol (c), randomization scheme is updated by adding another randomization factor. Patients who consent to protocol (c) will be randomized using following factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no).

8.1.3. Maintenance Therapy

After completion of 6 cycles of combination therapy, patients with stable disease or better will receive maintenance therapy with either LY2228820 or placebo according to the original randomization until the discontinuation criteria are fulfilled (refer to Section 7.3.1). After discontinuation from study treatment, patients will have a short-term follow-up period of approximately 30 days with a long-term follow-up period until death or until the patient is lost to follow-up. Patients who benefit may continue to receive study treatment for long-term durations even after the study has met its primary objective.

This study will be considered complete following the analysis of PFS. The database will be locked, and the Clinical Study Report will be completed after at least 103 PFS events have been observed. After the study is considered complete, patients and investigators will remain blinded and survival data will continue to be collected. The analysis of OS will be performed after all patients in the Phase 2 portion of the study have been followed for at least 2 years. After the analysis of OS, both patients and investigators will be unblinded; patients receiving maintenance therapy with placebo will discontinue study treatment, whereas patients receiving maintenance therapy with LY2228820 may continue study treatment on the extension phase of the study until the discontinuation criteria are fulfilled.

8.1.4. Interim Analyses

The first interim analysis will be conducted to assess safety and PK; it will be performed when all evaluable patients in the Phase 1b portion of the study have received at least 1 cycle of study treatment.

The second interim analysis will be conducted to assess safety and PK; it will be performed when approximately 30 patients in the Phase 2 portion of the study have received at least 1 cycle of study treatment.

The third interim analysis will be conducted to assess safety, and PK; it will be performed when approximately 60 patients in the Phase 2 portion of the study have received at least 2 cycles of study treatment.

Interim analyses for the Phase 2 portion of the study will be performed under the guidance of an internal assessment committee. See Section 12.2.11 for further details regarding interim analyses.

8.1.5. Study Period Definitions

Terms used to describe the study periods are defined below:

- **Baseline:** from the time of screening to first study treatment (or discontinuation, if no treatment is given)
- **Study Treatment Period:** time from treatment start to discontinuation from study treatment
- **Post-discontinuation Follow-Up:** begins the day after the patient discontinues study treatment.
    - The ***short-term follow-up period*** begins 1 day after the patient discontinues study treatment and lasts approximately 30 days.
    - The ***long-term follow-up period*** begins 1 day after the short-term follow-up period is completed and continues until death or until the patient is lost to follow-up. During the long-term follow-up period, patients should be assessed for survival every 84 ±14 days.

Patients will receive study treatment until the discontinuation criteria are fulfilled (refer to Section 7.3.1).

All patients in the Phase Ib portion of the study will have intensive PK sampling. Approximately 20 patients (10 patients/arm) in the Phase 2 portion of the study will also have intensive PK sampling; all other patients in the Phase 2 portion will have standard PK sampling at regularly scheduled clinic visits as outlined in the study schedule.

8.1.6. Baseline and Study Treatment Period Assessments

The Study Schedule (Attachment 1) describes the timing of baseline and study treatment period assessments for both phases. All patients who receive at least one dose of study treatment will have procedures performed as shown in the Study Schedule (Attachment 1).

Written informed consent must be obtained prior to any study-specific pretreatment evaluations. At baseline and/or during the study treatment period, the following assessments will be completed: medical history, physical examination, tumor assessment, radiologic imaging, clinical laboratory tests, ECG, stored sample for pharmacogenomics (where local regulations allow), samples for PK, circulating plasma proteins, Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O) instrument, and archived tumor sample.

Tumor measurements will be performed by radiologic imaging every 2 cycles according to the study schedule until evidence of progressive disease as defined by RECIST 1.1 is observed (refer to Section 10.1). Tumor responses will be confirmed. Imaging methods used at baseline must be consistently used during study. For patients continuing on study treatment after the analysis of PFS and secondary objective are complete (see Section 8.1.3), efficacy assessments will be done at the investigator's discretion based on the standard of care.

All enrolled patients will be assessed for toxicity using Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Adverse event reporting will be done as specified in Table JIAE.10.1 (Section 10.3).

8.1.7. Post-discontinuation Follow-Up Period Assessments

All patients should be followed and AEs reported for a minimum of 30 days after the patient discontinues study treatment. Other follow-up assessments will be conducted according to the Study Schedule (Attachment 1).

8.1.8. Study Extension

The analysis of OS will be performed after all patients in the Phase 2 portion of the study have been followed for at least 2 years. After the final analysis of OS, both patients and investigators will be unblinded; patients receiving maintenance therapy with placebo will discontinue study treatment, whereas patients receiving maintenance therapy with LY2228820 may continue study treatment on the extension phase of the study until the discontinuation criteria are fulfilled.

Serious AEs will be collected and reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE.

Adverse events leading to discontinuation and dose reduction of treatment will also be collected.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, the results of all these assessments may not be routinely collected by the sponsor.

The patient's participation in the study extension will be completed after discontinuation of study treatment. There will be no post-discontinuation follow-up period in the extension phase of the study.

8.2. Discussion of Design and Control

The Phase 1b portion of this study utilizes a standard 3+3 design involving 2 sequential cohorts of at least 3 patients treated during induction therapy with gemcitabine and carboplatin plus escalating LY2228820 doses (200 mg and 300 mg every 12 hours on Days 1 through 10 of a 21-day cycle, respectively).

The Phase 2 portion of this study utilizes a randomized, controlled design. Randomization minimizes systematic bias in the selection and assignment of patients to study treatment and provides justification for inferential statistical methods applied to data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study treatment and minimizes bias in the assessment and interpretation of observed treatment effects.

Investigational treatment administration in this study is double-blind. Patients, study personnel at investigational sites, and study personnel at the sponsor do not have immediate access to treatment assignments for any patients. This design feature minimizes potential bias due to knowledge of treatment assignments during the study.

9. Treatment

9.1. Treatments Administered

Study treatments will be administered as summarized in Table JIAE.9.1.

Table JIAE.9.1. Treatment Regimens/Dosing Schedule

Treatment	Cycle Duration	Regimen
Phase 1b (Cohort 1)	21 days (Cycles 1-6) (Induction)	LY2228820 **200** mg PO Q12H on Days 1-10 Gemcitabine 1000 mg/m^2 IV over 30 minutes on Days 3 and 10[a] Carboplatin AUC 4 [max dose 600 mg] IV over 30 minutes on Day 3[a, b]
	28 days (Cycles 7+) (Maintenance)	LY 2228820 **300** mg PO Q12H on Days 1-14
Phase 1b (Cohort 2)	21 days (Cycles 1-6) (Induction)	LY2228820 **300** mg PO Q12H on Days 1-10 Gemcitabine 1000 mg/m^2 IV over 30 minutes on Days 3 and 10[a] Carboplatin AUC 4 [max dose 600 mg] IV over 30 minutes on Day 3[a, b]
	28 days (Cycles 7+) (Maintenance)	LY2228820 **300** mg PO Q12H on Days 1-14
Phase 2 (Arm A)	21 days (Cycles 1-6) (Induction)	LY2228820 RP2D PO Q12H on Days 1-10[c] Gemcitabine 1000 mg/m^2 IV over 30 minutes (+15 minutes) on Days 3 and 10[a] Carboplatin AUC 4 [max dose 600 mg] IV over 30 minutes (+15 minutes) on Day 3[a, b]
	28 days (Cycles 7+) (Maintenance)	LY2228820 **300** mg PO Q12H on Days 1-14
Phase 2 (Arm B)	21 days (Cycles 1-6) (Induction)	Placebo RP2D PO Q12H on Days 1-10[c] Gemcitabine 1000 mg/m^2 IV over 30 minutes (+15 minutes) on Days 3 and 10a Carboplatin AUC 4 [max dose 600 mg] IV over 30 minutes (+15 minutes) on Day 3[a, b]
	28 days (Cycles 7+) (Maintenance)	Placebo **300** mg PO Q12H on Days 1-14

Abbreviations: PO = oral; IV = intravenous; Q12H = every 12 hours; max = maximum; RP2D = recommended phase 2 dose (in combination with gemcitabine and carboplatin).

[a] An extension of the gemcitabine and/or carboplatin infusion times to 45 minutes is permissible; however, every effort should be made to adhere to a 30-minute infusion time. The total infusion time should be recorded in the case report form.

[b] The carboplatin dosage will be calculated as follows: Dose (mg)= target (AUC)[4] x (GFR +25). For a target AUC=4, the maximum dose is 600 mg.

[c] The recommended Phase 2 dose will be communicated to investigative sites by a formal study communication.

Any measurements used to determine dose should be taken at each cycle, and dose should be re-calculated for each cycle. Patients must meet the criteria to receive all 3 drugs on Day 1 in order to start the next cycle.

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

- Explaining the correct use of the drug(s) and planned duration of each individual's treatment to the patient and site personnel
- Verifying that instructions are followed properly
- Maintaining accurate records of study drug dispensing and collection
- Returning all unused medication to Lilly or its designee at the end of the study

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug(s) so that the situation can be assessed.

9.1.1. Carboplatin Dosing

Carboplatin dosing, using the Calvert formula, is often based upon a calculated creatinine clearance using serum creatinine as a surrogate for renal function. Several assays are available to measure serum creatinine. In the United States and many parts of the world, most laboratories use methods that are standardized against reference material in which the creatinine value has been assigned by IDMS. After 31 December 2010, all clinical laboratories in the United States, and some laboratories in countries outside the US (OUS), will use creatinine methods standardized relative to the IDMS reference material.

The recalibration of serum creatinine measurements against the IDMS reference material may result in slight differences in reported serum creatinine levels in the low range of normal. Consequently, measurement of serum creatinine relative to the IDMS standard could result in an overestimation of glomerular filtration rate (GFR) in some patients with normal renal function. If the total carboplatin dose is calculated based on an estimated GFR using an IDMS-standardized serum creatinine and the Calvert formula, carboplatin dosing could be higher than if the GFR had been directly measured, and could result in increased toxicity.

At sites where creatinine is determined by a method standardized to the IDMS reference material, the estimated GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min for patients who have not begun therapy. After 31 December 2010, all US sites and any other OUS site where the IDMS method is available should calculate carboplatin doses based upon serum creatinine values that were measured by the IDMS method. At sites where the IDMS method is not available, for the estimated GFR used to calculate the Calvert formula, all sites will follow the dosing guidelines outlined below and cap the GFR at 125 mL/min.

The site is responsible to consult the local lab to determine what method of serum creatinine measurement is used by that laboratory.

For this study, the carboplatin dose must be calculated using the Calvert formula (Attachment 7).

9.1.1.1. Calculated Creatinine Clearance

Creatinine clearance will be calculated using the Cockcroft and Gault formula (Attachment 6). This formula should be used to calculate a patient's creatinine clearance at baseline and for all subsequent cycles of induction therapy. If a patient's calculated creatinine clearance has not returned to ≥50 mL/min at the beginning of a cycle during induction therapy, the patient must not receive further carboplatin unless approved by the Lilly CRP. Alternative formulas, such as Modification of Diet in Renal Disease (MDRD) Study Group formula, may not be used to calculate the creatinine clearance.

9.2. Materials and Supplies

LY2228820 will be provided by Lilly. Gemcitabine, carboplatin, and other standard of care drugs will be provided according to local requirements. Clinical trial materials will be labeled according to the country's regulatory requirements. All study drugs should be stored within the temperature range stated on the label.

9.2.1. LY2228820

LY2228820 will be supplied as tablets for oral administration. LY2228820 tablets should be stored within the temperature range stated on the label. Investigators should instruct patients to store the tablets at home in the original package and to keep out of the reach of children. Tablets should not be split, crushed, or dissolved.

9.2.2. Gemcitabine

Gemcitabine is supplied as a lyophilized powder in sterile vials containing either 200 mg or 1 g of gemcitabine as the hydrochloride salt with mannitol and sodium acetate. The lyophilized product should be stored at room temperature. Drug will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL (not to exceed 40 mg/mL). Once the drug has been reconstituted it should be stored at room temperature and used within 24 hours. Any unused portion of a vial must not be stored for future use and must be discarded.

9.2.3. Carboplatin

Carboplatin is supplied as a sterile, pyrogen-free solution available in 10 mg/mL multiple-dose vials containing 50 mg, 150 mg, 450 mg, or 600 mg of carboplatin for administration by intravenous infusion.

Note: Aluminum reacts with carboplatin, causing precipitate formation and loss of potency; therefore, needles or IV sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

9.2.4. Placebo

Placebo will be supplied as tablets (consisting of inactive ingredients) for oral administration.

9.3. Method of Assignment to Treatment

In the Phase 1b portion of the study, patients will be assigned to a specific dose level in cohorts of 3 patients as described in Section 9.5.

In the Phase 2 portion of the study, approximately 110 patients will be randomized 1:1 in a double-blind manner by an interactive voice-response system (IVRS) to either Arm A (LY2228820 plus gemcitabine and carboplatin) or Arm B (placebo plus gemcitabine and carboplatin). Randomization will minimize imbalance between treatment arms according to the following factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months) and ECOG performance status (0 and 1 versus 2).

Starting from protocol (c), the randomization scheme is updated by adding another randomization factor. Patients who consent to protocol (c) will be randomized using following the factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no).

This procedure is based on a well-defined algorithm (Pocock and Simon 1975). The randomization probability factor will be set at 0.75.

The IVRS will be used to assign blisterpacks containing double-blind study drug to each patient. Site personnel will confirm that they have located the correct blisterpacks by entering a confirmation number found on the blisterpacks into the IVRS.

9.4. Selection and Timing of Doses

As described in Table JIAE.9.1, Phase 1b is the dose escalation phase of the study and Phase 2 is the randomized phase of the study.

Patients will receive LY2228820 (or placebo) in combination with gemcitabine and carboplatin for 6 cycles as induction therapy. LY2228820 (or placebo) will be administered every 12 hours on Days 1 to 10 of a 21-day cycle. Gemcitabine 1000 mg will be administered on Days 3 and 10 and carboplatin AUC 4 will be administered on Day 3. After the completion of induction therapy, LY2228820 (or placebo) will be taken on Days 1 to 14 of a 28-day cycle for maintenance therapy. .

LY2228820 is administered prior to chemotherapy to allow LY2228820 to reach steady state and achieve maximal p38 MAPK inhibition, blocking a potential survival mechanism by which tumor cells evade gemcitabine- and carboplatin-induced DNA damage. The study drug administration schedule is intended to mimic the 50% on/off schedule of single-agent usage of LY2228820 within the 21-day schedule required for the gemcitabine /carboplatin combination.

9.4.1. Phase 1b

9.4.1.1. Induction Therapy

LY2228820 will be administered orally every 12 hours (±3 hours) on Days 1 through 10 of a 21-day cycle. Patients should not consume food beginning 1 hour before and ending 1 hour after taking the study drug. LY2228820 should be taken at the same time of the day (for example, 0800 hours and 2000 hours) with a full glass of water. If a patient misses or vomits a dose, that dose should be omitted. Patients must record the time and amount of each dose taken (or alternatively, the time and amount of the dose missed or vomited) in a daily diary.

Gemcitabine, 1000 mg/m^2, will be administered IV over approximately 30 (+15) minutes on Days 3 and 10 of a 21-day cycle. The gemcitabine infusion will be started following the morning dose of LY2228820.

Carboplatin, AUC 4 (maximum dose, 600 mg), will be administered IV over approximately 30 (+15) minutes on Day 3 of a 21-day cycle. The carboplatin infusion will follow the gemcitabine infusion. Antiemetics should be administered according to institutional standard procedures.

9.4.1.2. Maintenance Therapy

After completion of 6 cycles of induction therapy, patients with stable disease or better will receive maintenance therapy with LY2228820 until the discontinuation criteria are fulfilled (refer to Section 7.3.1). After discontinuation from study treatment, patients will have a short-term follow-up period of approximately 30 days with a long-term follow-up period until death or until the patient is lost to follow-up. Patients who benefit may continue to receive study treatment even after the study has met its primary and secondary objectives.

9.4.2. Phase 2

9.4.2.1. Induction Therapy

LY2228820 or placebo will be administered orally every 12 hours (±3 hours) on Days 1 through 10 of a 21-day cycle. Patients should not consume food beginning 1 hour before and ending 1 hour after taking the study drug. LY2228820 or placebo should be taken at the same time of the day (for example, 0800 hours and 2000 hours) with a full glass of water. If a patient misses or vomits a dose, that dose should be omitted. Patients must record the time and amount of each dose taken (or alternatively, the time and amount of the dose missed or vomited) in a daily diary.

Gemcitabine, 1000 mg/m^2, will be administered IV over approximately 30 (+15) minutes on Days 3 and 10 of a 21-day cycle. The gemcitabine infusion will be started following the morning dose of LY2228820.

Carboplatin, AUC 4 (maximum dose, 600 mg), will be administered IV over approximately 30 (+15) minutes on Day 3 of a 21-day cycle. The carboplatin infusion will follow the gemcitabine infusion.

9.4.2.2. Maintenance Therapy

After completion of 6 cycles of induction therapy, patients with stable disease or better will receive maintenance therapy with LY2228820 or placebo according to their original treatment assignment until the discontinuation criteria are fulfilled (refer to Section 7.3.1). After discontinuation from study treatment, patients will have a short-term follow-up period of approximately 30 days followed by a long-term follow-up period until death or until the patient is lost to follow-up. Patients who benefit may continue to receive study treatment even after the study has met its primary objective.

9.4.3. Dose Adjustments

9.4.3.1. Treatment Delays between Cycles

A cycle may be delayed to allow a patient sufficient time for recovery from toxicity related to study treatment. Before the start of each cycle, hematologic toxicities must resolve according to the guidelines in Table JIAE.9.3. Nonhematologic toxicities must resolve to the patient's baseline CTCAE grade or lower. If a delay in the start of treatment is necessary, all 3 study drugs (LY2228828 or placebo, gemcitabine, and carboplatin) should be held. A cycle may be delayed by 7 days to accommodate a patient's schedule or for other unforeseen circumstances. Treatment delays between cycles that fulfill these criteria do not constitute a protocol violation. Patients who require a delay in treatment of more than 21 days for toxicity will be required to discontinue study treatment and enter the Post-Discontinuation Follow-up Period (Attachment 1).

9.4.3.1.1. LY2228820 Dose Adjustments

Dose adjustments for LY2228820/placebo should be managed according to Table JIAE.2. Please note these toxicities apply to those attributed to LY2228820/placebo and not necessarily those expected from gemcitabine and carboplatin.

Table JIAE.9.2. Intercycle Dose Adjustments for LY2228820 or Placebo

If		Then
Patient experiences a Grade 3 or Grade 4 toxicity **related to LY2228820/placebo**…	During induction therapy	Decrease dose (between cycles) by a 100 mg decrement (required). Continue gemcitabine and carboplatin according to the Study Schedule (Attachment 1).
	During maintenance therapy	Decrease dose (between cycles) by a 100 mg decrement (required).
Patient experiences a Grade 1 or Grade 2 toxicity **related to LY2228820/placebo**…	During induction therapy	Dose may be decreased (between cycles) by a 100 mg decrement at the discretion of the investigator. Continue gemcitabine and carboplatin according to the Study Schedule (Attachment 1).
	During maintenance therapy	Dose may be decreased (between cycles) by a 100 mg decrement at the discretion of the investigator.

Any patient who requires a dose reduction in LY2228820/placebo will continue to receive the reduced dose for the remainder of the study.

Any patient who experiences a Grade 3 or Grade 4 toxicity related to LY2228820/placebo at a dose of 100 mg every 12 hours (during either induction or maintenance therapy) must be discontinued from LY2228820/placebo; however, gemcitabine and carboplatin should be continued during induction therapy according to the Study Schedule (Attachment 1). If LY2228820/placebo was discontinued during induction therapy due to a Grade 3 or 4 toxicity related to LY2228820/placebo, it may not be re-started in maintenance therapy.

9.4.3.1.2. Gemcitabine Dose Adjustments

Gemcitabine dosage adjustment for hematologic toxicity within a cycle of treatment or between cycles of treatment is based on the absolute neutrophil count ANC and platelet count. These dose modifications are based on hematologic labs obtained on Day 1 and Day 10 of a cycle. If marrow suppression is detected, gemcitabine dosage should be modified according to guidelines in Table JIAE.9.3.

Table JIAE.9.3. Dosage Reduction Guidelines for Gemcitabine for Myelosuppression on Day of Treatment

Treatment Day	Absolute Neutrophil Count		Platelets	% of Full Dose
Day 1 (for gemcitabine dosing on Day 3)	≥1500/mm^3	and	≥100,000/mm^3	100
	≤1500/mm^3	or	≤100,000/mm^3	Delay treatment cycle
Day 10	≥1500/mm^3	and	≥100,000/mm^3	100
	1000–1499/mm^3	or	75,000–99,999/mm^3	50
	≤1000/mm^3	or	<75,000/mm^3	Hold gemcitabine

Dose adjustments for gemcitabine in combination with carboplatin for subsequent cycles are based upon observed toxicity and should be managed according to the guidelines in Table JIAE.9.4.

Table JIAE.9.4. Gemcitabine Dose Modification for Myelosuppression in Previous Cycle

Occurrence	Myelosuppression During Previous Treatment Cycle	Dose Modification
Initial Occurrence	Absolute granulocyte count less than 500 x 10^6/L for more than 5 days Absolute granulocyte count less than 100 x 10^6/L for more than 3 days Febrile neutropenia Platelets less than 25,000 x10^6/L Cycle delay of more than one week due to toxicity	Permanently reduce gemcitabine to 800 mg/m^2 on Days 3 and 10.
Subsequent Occurrence	If any of the above toxicities occur after the initial dose reduction	Permanently reduce gemcitabine to 800 mg/m^2 and administer on Day 3 only (Day 10 dose omitted).

Withhold gemcitabine or reduce dose by 50% for other severe (Grade 3 or 4) nonhematologic toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

Gemcitabine therapy should be permanently discontinued for any of the following:

- Unexplained dyspnea deemed related to study drug, or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic Uremic Syndrome
- Capillary Leak Syndrome

9.4.3.1.3. Carboplatin Dose Adjustments

There will be no dose adjustment for carboplatin in this study. For patients with a calculated creatinine clearance <50 mL/min, refer to Section 9.1.1.1 for additional guidance.

9.4.3.1.4. Clinically Significant Effusions

For patients who have a clinically significant pleural or peritoneal effusion (on the basis of symptoms or clinical examination), consideration should be given to draining the effusion prior to study treatment.

9.5. Dose Escalation (Phase Ib)

The dose will be escalated following assessment of toxicity using the standard scoring system, Common Terminology Criteria for Adverse Events (CTCAE Version 4.0), established by the National Cancer Institute (NCI).

During Phase 1b, dose escalation of LY2228820 will occur in cohorts of 3 patients treated at the dose levels outlined in Table JIAE.9.1. The LY2228820 starting dose of 200 mg every 12 hours in Study JIAE has been explored previously in Study JIAD and is 1 dose level lower than the

single-agent recommended Phase 2 dose of 300 mg every 12 hours. All patients in Study JIAE will receive gemcitabine and carboplatin during induction therapy, as outlined in Section 9.4.

Dose escalation will proceed cohort by cohort until 1 patient at a given dose level experiences a DLT, as defined in Section 9.5.1. In the event a DLT occurs in 1 of 3 patients at a given dose level, the cohort will be expanded up to a total of 6 patients. If no further DLTs are observed at that dose level, the dose escalation can resume. If a DLT occurs in 2 or more of 6 patients or 33.3% of patients at a given dose level, then the combination MTD has been identified or exceeded and dose escalation will cease. However, following discussions between the investigators and the sponsor, additional patients may be treated at intermediate doses to define the combination MTD more precisely. During Phase 1b, intrapatient dose escalation is not permitted, and dose escalation to the next cohort cannot occur without prior discussion and agreement between the investigator and the responsible Lilly CRP.

9.5.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

A DLT is defined as an AE likely related to LY2228820 that occurs during Cycle 1 in Phase 1b and fulfills any one of the following criteria:

- Grade 3 or 4 nonhematologic toxicity except for nausea/vomiting, diarrhea, or electrolyte disturbances
- Grade 3 or 4 nausea/vomiting or diarrhea that persists $\geq$2 days despite the use of adequate or maximal medical intervention
- Grade 3 or 4 electrolyte disturbances that persist $\geq$ 5 days despite maximal supportive treatment
- Grade 4 hematologic toxicity that persists more than 5 days
- Grade 3 or 4 thrombocytopenia with bleeding
- Febrile neutropenia

All toxicities should be graded according to CTCAE Version 4.0.

Investigators, in consultation with the Lilly CRP, can declare a DLT if a patient has increasing toxicity and therapy cannot be continued without exposing the patient to excessive risk.

The MTD is defined as the highest dose level at which no more than 33% of patients experience a DLT during Cycle 1 that does not exceed the single-agent MTD for LY2228820 (300 mg Q12H).

9.6. Continued Access to Study Drug

Study drug may be made available after conclusion of the study to patients who are still receiving and benefitting from study treatment in countries where the drug cannot be lawfully prescribed.

9.7. Blinding

The Phase 1b portion of this study is open-label whereas the Phase 2 portion of this study is double-blind.

To preserve blinding of the study, a minimum number of sponsor personnel will see the randomization table and treatment assignments before PFS and OS analyses are completed.

Emergency unblinding for AEs may be performed through an IVRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used only if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IVRS.

The investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone.

Every effort will be made to blind both the patient and the investigator to the treatment assignment, but the inadvertent unblinding of a patient may occur. A double-blind study design is known to be imperfect because the potential for individual unblinding exists due to treatment-related signs and symptoms. If a patient or investigator is unblinded, the unblinding will not alone be sufficient cause for that patient to be discontinued from study treatment or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

Patients and investigators will remain blinded to study treatment with no sharing of efficacy information among sites until both PFS and OS analyses are completed. Treatment assignment will be blinded in the reporting database except for a minimum number of sponsor personnel required to perform the interim and final analyses. This will ensure unblinded aggregate efficacy results are not available outside of the Assessment Committee until the time of final data analysis. Patients and investigators may be unblinded after both PFS and OS analyses are completed.

For this study, there are 4 planned interim analyses (1 for Phase 1b and 3 for Phase 2). During Phase 2, blinding of the study requires that interim analyses be conducted under the guidance of an Assessment Committee. See Section 12.2.11 for further details.

9.8. Concomitant Therapy

With the exceptions listed in the following sections, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment. The need for any form of radiotherapy (including palliative) will be cause for early discontinuation from study treatment. In addition any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from study treatment.

Appropriate documentation of all forms of premedication's, supportive care, and concomitant medications must be captured at each visit in the case report form (CRF). Concomitant medications and supportive care therapies must be documented at the time of discontinuation and also at the 30-day follow-up visit.

Based on the available preclinical data, there is a possible risk of clinical drug–drug interaction when LY2228820 is administered with inhibitors or inducers of UGT enzymes. In the absence of clinical data to refine the risk of interaction, caution is warranted in the concomitant use of UGT enzyme inhibitors such as valproic acid and probenecid and inducers such as carbamazepine, phenytoin and rifampin. When, in the clinical investigator's opinion, concomitant use of valproic acid or probenecid is indicated, LY2228820-related DLTs of ataxia, dizziness and rash should be carefully monitored.

It is recommended that patients minimize alcohol use during the study and, if clinically feasible, avoid medications acting as depressants of the central nervous system.

9.8.1. Supportive Care

Patients should receive full supportive care if necessary. Supportive care is defined as a treatment that lacks antineoplastic activity and is given specifically with the intent to maximize quality of life. Those therapies considered acceptable include, but are not limited to, transfusions of red blood cells and platelets as well as medications that are not excluded as "concomitant therapy." Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. Use of any supportive care therapy should be reported on the case report forms.

9.8.2. Carboplatin Infusion Reactions

Patients who experience a hypersensitivity reaction to carboplatin should receive epinephrine, corticosteroid, and antihistamine therapy according to institutional standards. If the institutional standards differ from this regimen, the Lilly CRP should be consulted.

9.8.3. Colony-Stimulating Factors

The protocol permits the routine use of granulocyte colony-stimulating factors and erythropoiesis-stimulating agents (ESAs) as supportive care agents according to ASCO guidelines (Rizzo et al. 2010). Granulocyte colony-stimulating factors should not be used prophylactically unless previously discussed with the Lilly CRP. The protocol does not allow the use of products that stimulate thrombopoiesis.

Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia for patients with hemoglobin <10 g/dL after the patients has been counseled about the risks and benefits of ESA use (Rizzo et al. 2008; Smith et al. 2006). Because recommendations on the use of ESAs are rapidly evolving, investigators should refer to the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and/or Centers for Medicare and Medicaid Services web sites for the latest guidelines.

9.9. Treatment Compliance

Patient compliance with LY2228820 will be assessed at each visit. Compliance will be assessed by patient diary entries, direct questioning, and counting returned tablets. Patients must take ≥75% of the scheduled doses of LY2228820 in a cycle to be judged compliant with oral study drug administration. Similarly, a patient will be considered significantly noncompliant if judged by the investigator to have intentionally or repeatedly taken ≥125% of the scheduled doses of LY2228820. Any missed doses will be omitted and not replaced during the treatment period. In the event of a missed dose, patients should resume and continue the dosing schedule beginning with the next scheduled dose.

Discontinuation of a patient due to oral study drug noncompliance will be discussed between the investigator and the Lilly CRP before making the final determination for discontinuation. If a patient is discontinued due to noncompliance, the patient may be replaced.

Gemcitabine and carboplatin will be administered only at the investigational sites by the authorized study personnel. As a result, treatment compliance is ensured.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

Each patient will be assessed by one or more of the following radiologic tests for tumor measurement at the time specified in the Study Schedule:

- Computerized tomography (CT) scan
- Magnetic resonance imaging (MRI)

Each patient's extent of disease will also be assessed with the following procedures:

- Tumor measurement of palpable or visible lesions (refer to Modified Response Evaluation Criteria in Solid Tumors [RECIST] Guidelines Version 1.1, Attachment 8)
- CA125
- Evaluation of performance status (refer to the ECOG Scale, Attachment 5)

10.1.1. Efficacy Assessments at Baseline and during Study

Within 28 days before the first dose of study drug, baseline tumor measurement(s) will be performed on each patient. Computed tomography, including spiral CT scans, and MRI are the preferred methods of measurement.

The method of assessment used at baseline must be used consistently for tumor assessment and will be repeated every other cycle.

10.1.2. Efficacy Assessments during the Post-discontinuation Period

For those patients who discontinue study treatment without progressive disease, the investigative sites will continue to monitor patients and periodically evaluate tumor response according to the institutional standard of care frequency by the same method used at baseline and throughout the study until the discontinuation criteria are fulfilled. After the patient has confirmed progressive disease, radiologic tests are no longer required and the patient will be followed every 84 days (±14 days) until death or until the patient is lost to follow up.

After patients have discontinued study treatment, they may receive additional anticancer therapy at the discretion of the investigator. The additional treatments should be documented on the CRF.

10.1.3. Primary Efficacy Measure

In the Phase 2 portion of the study, the primary efficacy measure is PFS. This measure is calculated from the date of randomization to the date of objective progression or death due to any cause, whichever occurs first. Section 12.1 describes the method used for censoring PFS.

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1).

10.1.4.1. Overall Response Rate

Overall response rate is the percentage of patients who achieved a best response of either complete response (CR) or partial response (PR), as determined by RECIST 1.1.

Best response is determined from a sequence of responses assessed. For CR or PR, best response must be confirmed with a second assessment that is performed ≥28 days after the first evidence of response. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Best response of stable disease (SD) is defined as disease that does not meet the criteria for CR, PR, or progressive disease and has been evaluated at least 1 time, at least 6 weeks after the start of study treatment. All lesions must be assessed by the same method as at baseline to qualify for response confirmation. The date of first documented objective disease progression will be recorded on the CRF.

10.1.4.2. Change in Tumor Size

Change in tumor size will be assessed in each patient using radiographic imaging. This endpoint will be based on tumor measurements collected by the centers according to RECIST (version 1.1). Tumor size is the sum of the tumor measurements for target tumors at each tumor evaluation. Change in tumor size is defined as the ratio of tumor size from the evaluation at the end of Cycle 2 to the baseline evaluation.

10.1.4.3. Overall Survival

Overall survival is defined as the time from date of randomization to the date of death due to any cause. For patients who are not known to have died as of the data inclusion cut-off date, OS will be censored at the date that the patient was last known to be alive.

10.2. Health Outcome/Quality of Life Measures

The multiple burdens of cancer and the effects of anticancer treatment can have a profound impact on patients' health-related quality of life (HRQoL). A diminished HRQoL can have detrimental effects on the efficacy of cancer treatment and may affect treatment outcomes. The FACT-O will be used in this study to assess and compare changes in HRQoL between the 2 treatment arms. Health outcome measures will only be collected during the Phase 2 part of this study.

10.2.1. Patient-Reported Outcomes

The FACT-O instrument (refer to Attachment 10) is a reliable and valid instrument to measure HRQoL in patients with ovarian cancer (Basen-Engquist 2001). The instrument consists of 38 items with 5-point rating scales in which 0 equals "not at all" and 4 equals "very much." The questionnaire is organized into 5 sections with physical, social/family, emotional, functional well-being and ovarian subscales.

The validated FACT-O instrument will be used in the Phase 2 portion of the study to help better understand the properties of the instrument in this specific patient population and to generate hypotheses for subsequent studies. Patient-reported outcome data will be analyzed for statistically significant, clinically important, and favorable differences in assessments associated with abdominal pain and gastrointestinal symptoms as measured by the FACT-O items O3 (cramps in stomach), GP2 (nausea), O2 (vomiting), and C6 (good appetite), as well as by assessments associated with treatment-related AEs/intolerance as measured by the FACT item GP5 (bothered by side effects of treatment). The FACT-O scores will be calculated using scoring criteria proposed by the developer (Cella 2004). Results of the FACT-O can be reported as the scores for 5 individual subscales, a FACT-General total score (sum of physical, social/family, emotional, and functional well-being subscales), a Trial Outcome Index (TOI) (sum of physical well-being, functional well-being, and ovarian subscale), and a FACT-O total score (sum of the FACT-General total score and the ovarian subscale). For all reports, a higher score represents a better quality of life.

Both, time to worsening (TTW) and changes from baseline in dimensions of HRQoL using FACT-O will be compared between treatment arms. Minimally important difference (MID) for change in scores will be used to determine meaningful differences in patients' FACT-O scores (Yost and Eton 2005).

The TOI is considered to be a valuable summary measure of physical well-being, functional well-being, and disease-specific symptoms (Yost and Eton 2005). In patients with ovarian cancer, the patients' well-being (including functional/physical abilities and disease-specific symptoms) will generally continue to worsen as disease progresses. The TTW is defined as a decrease in the TOI score that is considered at least a MID, as compared with the patient's baseline score. The upper range of MID points (Yost and Eton 2005) will be used as a guide to determine the meaningful decrease for individual patient's score. The TTW is measured from the date of randomization to the first date of a worsening in the TOI (as defined by a decrease from baseline in TOI that is at least the MID) or of death from any cause. For patients who receive any subsequent systemic anticancer therapy prior to an observation of worsening, TTW will be censored at the date of the last worsening-free assessment prior to the subsequent systemic anticancer therapy. For patients not known to have died or with an observation of worsening as of the data cut-off date, TTW will be censored at the date of the last worsening-free assessment. Time to worsening in other dimensions of FACT-O will be measured in a similar fashion. The looser range of MID (Yost and Eton 2005) will be used for interpreting the group mean change, and the upper limit will be used for interpreting the change in an individual patient's score.

The FACT-O is to be completed at baseline, on Day 3 of Cycles 1 through 6 (induction therapy), and at the 30-day post-study follow-up visit as shown in the Study Schedule (Attachment 1).

The FACT-O should be completed at the beginning of office visits, before extensive contact and consultation with the clinician/study investigator. Consultation with the clinician may bias perceptions about HRQoL and symptoms and thus affect assessments. Patients will complete the questionnaire prior to administration of subsequent cycles of study drug.

The FACT-O will be completed by the patient. Only patients with adequate literacy and for whom there is a validated translation in the language in which the patient is fluent will be asked to complete any self-administered questionnaires.

10.2.2. Resource Utilization

Investigators will be asked to document the use of best supportive care measures, concomitant medications, transfusions, and treatment-related hospitalization days. Such assessments are to be taken throughout the study through the 30-day post-discontinuation visit and will largely be derived from clinical data routinely collected through the CRFs. Medical resource utilization data will be analyzed for exploratory purposes.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered 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 investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JIAE.10.1 describes AE and SAE collection with regard to the type of events to be collected in each study period.

Table JIAE.10.1. Adverse Event and Serious Adverse Reporting Guidelines for Study JIAE

Treatment Period	Types of AEs/SAEs Collected/Reported
Baseline (pretreatment)	Pre-existing conditions Procedure-related AEs/SAEs
Study treatment period (on therapy)	All AEs/SAEs
30-day post-discontinuation follow-up visit after the last dose	All AEs/SAEs
Subsequent post-discontinuation follow-up visits, if necessary	SAEs are required to be reported only if the investigator feels the events were related to either study drug or a protocol procedure

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

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from ECGs, laboratory assessments, vital sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal exposures to study drug or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

In addition, all AEs occurring after the patient receives the first dose of study drug must be reported to Lilly or its designee via CRF/electronic data entry.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, study drug, and/or drug delivery system via CRF/electronic data entry.

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug or procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause-and-effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Does not know:** the investigator cannot determine
- **Not related**: without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The National Cancer Institute (NCI)-CTCAE version 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE version 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing

severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the CRF. This collection is in addition to verbatim text used to describe the AE.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via CRF/electronic data entry the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent but prior to receiving study drug, the event will not be collected unless the investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert Lilly or its designee of any serious adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone 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. An SAE is any adverse event from this study that results in one of the following outcomes:

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- 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 adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

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

Serious adverse events occurring after a patient has taken the last dose of study drug will be collected in the pharmacovigilance system and clinical data collection database for 30 days after discontinuation from study treatment, regardless of the investigator's opinion of causation.

Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB. Adverse events reasonably anticipated in the ovarian cancer population include fatigue, anorexia, constipation, anemia, venous thrombosis/embolism, pain, confusion, liver dysfunction, hypercalcemia, hyperuricemia, major cardiovascular events (such as myocardial infarction and stroke), and infections.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions are serious events that are not listed in the Development Core Safety Information (DCSI) in the IB and that the investigator identifies as related to the study drug or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of suspected unexpected serious adverse reactions that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Collection of Electrocardiograms

For each subject, 12-lead ECGs will be collected according to the Study Schedule (Attachment 1) as a single ECG. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms 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 subject is still present, to determine whether the subject meets entry criteria and for immediate subject management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, syncope) and to determine if the subject 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.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- AEs

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring board (an advisory group for this study formed to protect the integrity of data; refer to the Interim Analysis Section that follows) can conduct additional analyses of the safety data.

For the purpose of this study, in which survival is a primary endpoint, all deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to ensure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or clinical AE is deemed serious, unexpected, and possibly related to study drug, only Lilly Global Patient Safety will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

10.3.4. Complaint Handling

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

Complaints related to unblinded comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 9 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. Although fewer invasive samples may actually occur, this will not require a protocol amendment.

10.4.1. Samples for Standard Efficacy, Safety Laboratory Testing

Blood samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry and hematology panels will be performed. A pregnancy test will be performed (if applicable). Other clinical laboratory tests will be analyzed by a central and/or local laboratory. Attachment 2 lists the specific tests that will be performed for this study.

Enrollment and treatment decisions may be based upon results of tests performed locally. If local lab tests are used for this purpose, then a duplicate specimen must be sent to the central laboratory for use in the safety analysis. Discrepancies between local and central laboratory results that may have an impact on eligibility or treatment decisions will not be considered protocol violations. When both a local and a central laboratory result are obtained and there is a discrepancy in the laboratory values, the local laboratory values will be used for determining patient eligibility and this data will be recorded in the study case report forms.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant; however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Archival Tumor Tissue Sample

A small amount of preserved tissue previously taken to diagnose the patient's disease will be obtained for biomarker research related to the p38 MAPK pathway in ovary cancer. The tumor suppressor p53 will be evaluated for gene expression, mutation, and protein expression in archived tumors. Additionally, the tumor suppressor PTEN will be evaluated for mutation and protein expression in archived tumors.

Pretreatment formalin-fixed, paraffin-embedded tumor tissue obtained at the time of original diagnosis should be in a whole block, partial block, or unstained slides. Stored samples will retain the patient identifier and therefore, will not be stored indefinitely. Any blocks or slides submitted will either be returned to the site or discarded within 15 years after last patient visit for the trial. If archival tissue is not available for a specific patient, it will not constitute a protocol violation.

For p53 and PTEN mutation analyses comparing tumor to germline DNA, a single whole-blood sample will be collected one time to isolate DNA from PBMCs. Samples will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at

a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator site personnel.

Supplies required for the collection and shipment of the patients stored samples will be supplied by the sponsor. Sample handling and shipment to the central laboratory will occur according to instructions given to the study sites.

10.4.3. Pharmacogenetic Samples

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow, a blood sample will be collected for pharmacogenetic analysis. It is a one-time collection, as noted in the Study Schedule (Attachment 1).

Samples will be stored, and analysis may be performed on genetic variants thought to play a role in metabolism of LY2228820 and gemcitabine and carboplatin, including but not limited to CYP3A, correlations among genotype, and pharmacokinetics to evaluate their association with observed clinical outcomes to LY2228820.

In the event of an unexpected AE or the observation of unusual response, the samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY2228820. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Samples will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator site personnel.

10.4.4. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 2 years following the last patient visit for the study.

Pharmacokinetic (PK) sampling in Phase 1b will be intensive, with samples collected to measure LY2228820 at the times and visits indicated in the Pharmacokinetic Sampling Schedule (Attachment 1 and Attachment 3). Another intensive PK sampling schedule will also be used for approximately 20 patients (10 patients/arm) in the Phase 2 portion of the study. The remainder of the patients in the Phase 2 portion of the study will have PK samples drawn during regularly

scheduled clinic visits. On these days, the dose of LY (or placebo) should be held until after the pre-dose PK sample has been taken. The actual date/time of dosing on the day of sampling and the actual date/time of collection for each of the samples must be recorded. In the Phase 2 portion of the study, dose information (date, time, and dosing amount for LY2228820/placebo, gemcitabine, and carboplatin) must be collected for the last and next-to-last dose taken prior to the sampling.

At the visits and times specified in the Study Schedule (Attachment 1) and PK/PD Sampling Schedule (Attachment 3), venous blood samples will be collected. Blood samples will be used to determine the plasma concentrations of LY2228820, gemcitabine and its metabolite (dFdU), and carboplatin. For carboplatin, both total and free platinum drug concentrations will be measured. The actual date and time (24-hour clock time) of each sampling will be recorded.

For measurement of LY2228820 and carboplatin, approximately 4 mL of whole blood will be collected in a sodium heparin tubes. For measurement of gemcitabine and its deaminated metabolite deoxydifluorouridine (dFdU), approximately 4 mL of whole blood will be collected in a sodium heparin tube containing tetrahydrouridine (THU). Sites will be supplied by the central laboratory with THU and instructions for the addition of THU to collection tubes.

A maximum of 5 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

Pharmacodynamic samples will be collected as specified in the PK and PD Sampling Schedule (Attachment 3). Circulating plasma proteins regulated by p38 MAPK (such as such as TNF, IL-1, IL-6, and IL-8) will be measured. Supplies required for the collection and shipment of the patients stored samples will be supplied by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study sites. Pharmacodynamic samples collected to measure circulating plasma proteins will be retained for a maximum of 15 years after the last patient visit for the study.

10.5. Appropriateness of Measurements

Progression-free survival, change in tumor size, overall response rate, OS, and patient-reported outcomes are acceptable endpoints that are clinically relevant for patients with platinum-sensitive ovarian cancer. The FACT-O is a reliable and valid instrument used to assess quality of life in patients with cancer (Basen-Engquist 2001).

11. 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 a start-up training session 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 may 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.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

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

Case report form data collected by the third-party organization (TPO) will be encoded and stored electronically in the TPO's database system. Validated data will subsequently be transferred to the sponsor's data warehouse, using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor according to the contract.

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 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.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose of LY2228820 that can be safely administered in combination with gemcitabine and carboplatin. The sample size for this part of the study is customary and not subject to statistical calculations.

The primary objective of the Phase 2 portion of this study is to compare the progression-free survival in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin. A group sequential design will be used to control type 1 error across the interim analyses and the final PFS analysis in Phase 2 (see Section 12.2.11 for details). The primary analysis will be performed after 79 PFS events have occurred. Assuming a hazard ratio (HR) of 0.7, this sample size yield at least 77% power with a false-positive rate of 0.2 (1-sided) using a log-rank test. This assumes exponentially distributed PFS times, median PFS of 8.6 months for the control arm, enrollment duration of 12 months, and follow-up time of 18 months after the last patient is enrolled. Assuming 28% censoring rate of the PFS, a total of 110 patients will be randomized (55 patients in each arm) to achieve 79 PFS events at the primary analysis.

12.2. Statistical and Analytical Plans

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designated TPO.

No formal statistical analysis will be performed on the Phase 1b portion of the study in which the primary objective is to assess safety and tolerability of LY2228820 plus gemcitabine and carboplatin. Efficacy analyses for the Phase 2 portion of the study will be conducted on the full analysis set. This set includes all data from all patients receiving at least 1 dose of LY2228820/placebo. All patients who receive at least 1 dose of the LY2228820/placebo will be subject to safety evaluation.

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.2 unless otherwise stated. All CIs will be given at a 2-sided 90% level unless otherwise stated.

Starting from protocol (c), an additional factor is included during patient enrollment as randomization factor (see Section 8.1.2). For patients who randomized to phase 2 before the approval of protocol (c), the value of maintenance therapy as a part of or after a first line platinum regimen for these patients will be imputed as “not collected”.

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.

Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan. Any other

change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

This study will be considered complete following final validation and authorization to "lock" the database after the protocol-specified primary objective has been met. The Lilly CRP will notify investigators in the event of study closure.

12.2.1. Patient Disposition

A detailed description of patient disposition will be provided. It will include 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, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol violations will be provided.

12.2.2. Patient Characteristics

Patient demographics including age, gender, screening height and weight will be summarized using descriptive statistics. Other baseline disease characteristics that need to be summarized include:

- Time from completion of first-line platinum-based therapy to relapse
- Pathologic diagnosis
- Disease stage at the time of initial diagnosis
- Pre-existing conditions
- Prior cancer therapies
- Concomitant drugs
- ECOG performance status

12.2.3. Concomitant Therapy

Concomitant medications will be listed and summarized for the safety population.

12.2.4. Treatment Compliance

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

12.2.5. Primary Outcome and Methodology

The primary objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose of LY2228820 that can be safely administered in combination with gemcitabine and carboplatin.

The primary objective of the Phase 2 portion of this study is to compare the progression-free survival in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin.

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 enrollment 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

For the primary endpoint of PFS, the HR will be estimated from survival data on all randomized patients using a Cox proportional hazards model with assigned study treatment arm as fixed effect along with cofactors for time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected).

The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curve as well as survival rates at various time points for each treatment group. The log-rank test will be used to compare PFS distributions between treatment groups in phase 2.

12.2.6. Efficacy Analyses

The primary objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose of LY2228820 that can be safely administered in combination with gemcitabine and carboplatin. Thus, no formal efficacy analysis is planned for this part of the trial. Any antitumor activity observed will be reported.

The primary objective of the Phase 2 portion of this study is to compare the progression-free survival in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin. To support the primary efficacy analysis, additional efficacy analysis will be performed on change in tumor size, CA125 (serum biomarker for ovarian cancer), overall response rate, and OS.

CA125 data will be log-transformed first and analyzed using a mixed-effect model repeated measures analysis with treatment, time, and treatment by time interaction as fixed effect, along with cofactors for time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected).

The log ratio of tumor size at the end of Cycle 2 to tumor size at baseline will be calculated for each patient. This measure follows a normal distribution and will be compared between treatment groups using a t-test. Analysis of variance will be used to assess the effect of baseline factors on the change in tumor size.

The overall response rate is estimated as the total number of CRs and PRs, based on RECIST version 1.1, divided by the total number of randomized patients. The efficacy endpoint of overall response rate and its exact 90% confidence interval will be estimated for each treatment arm. The proportion in each treatment arm will be compared using the Chi-square test.

The efficacy analysis on OS will be conducted after all the patients have been followed for at least 2 years. The HR will be estimated from survival data on all randomized patients using a Cox proportional hazards model using assigned study treatment arm as fixed effect with time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected).

Additional exploratory analyses may be performed as deemed appropriate.

12.2.7. Pharmacokinetic/Pharmacodynamic Analyses

12.2.7.1. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on data from patients who have received at least 1 dose of the study drug and have had sufficient post-dose samples collected to allow estimation of the PK parameters.

The PK parameters for LY2228820 will be computed by standard noncompartmental methods. The C_{max}, AUC, half-life, apparent volume of distribution (V_d/F), apparent clearance (CL/F), and other relevant parameters (such as intercycle accumulation) that can be calculated from the data will be reported. Parameters will be calculated following administration on Day 1 and on Day 10 of Cycle 1 as well as on Day 10 of Cycle 2 for the Phase 1b portion; on Day 3 and on Day 10 of Cycle 1 for the induction part of the Phase 2 portion, and on Day 3 of Cycle 7 for the maintenance part of the Phase 2 portion.

The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be used if appropriate, warranted, and approved by Global Pharmacokinetic management.

Providing that data allow in the Phase 1b portion, the pharmacokinetic parameter estimates (C_{max} and AUC) for LY2228820 will be evaluated statistically to delineate the effects of dose proportionality using the methods described previously (Smith et al. 2000). Least-square estimates of geometric means and their corresponding 90% confidence intervals will be provided by dose and with the dose-normalized ratio of geometric means and confidence interval.

The primary PK parameters for gemcitabine, its metabolite (dFdU), and carboplatin that will be used to detect potential drug–drug interaction are the maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from zero to the last measurable time [$AUC_{(0-tlast)}$], area under the plasma concentration-time curve from 0 to 24 hours [$AUC_{(0-24hr)}$], and area under the plasma concentration-time curve from time 0 to infinity [$AUC(0-\infty)$]. The AUC values will be calculated by the linear/log trapezoidal method, in which the linear trapezoidal

method will be employed up to the t_{max}, and the log trapezoidal rule will be used for concentrations beyond t_{max}. Descriptive statistics will be reported for other secondary PK parameters (for example, t_{max}, CL/F, Vd/F, and terminal elimination half-life).

The 90% confidence interval for the AUC and C_{max} ratios will be computed to assess the potential effect of LY2228820 on gemcitabine and carboplatin. The ratios will be calculated for the Phase 2 portion for gemcitabine, its metabolite (dFdU), and carboplatin on Day 3 of Cycle 1 in the LY2228820 arm versus the placebo arms.

The 90% confidence interval for the AUC and C_{max} ratios will be computed to assess the potential effect of gemcitabine and carboplatin on LY2228820. The ratios will be calculated for the Phase 2 portion for LY2228820 on Day 3 of Cycle 1 versus Day 3 of Cycle 7.

In addition to a standard noncompartmental assessment, the plasma LY2228820 data will also be analyzed using nonlinear mixed effect modeling (as implemented in NONMEM).

All available plasma data from all patients may be analyzed to determine the compartmental pharmacokinetics parameters and between and within patient variability. The drug–drug interaction may also be assessed using this approach using the typical covariates approach.

12.2.7.2. Pharmacodynamic Analysis

Pharmacodynamic data from all patients undergoing PD assessments will be analyzed. Pharmacodynamic data will be documented in the study report by dose. Absolute and percentage change from baseline for PD markers may be summarized by providing the mean, standard deviation, median, minimum, and maximum for each cohort. Data may be log-transformed prior to summarizing if necessary. The interpatient variability in human PD response may also be assessed where appropriate.

12.2.8. Health Outcome/Quality of Life Analyses: FACT-O

Findings of the FACT-O and compliance with completing the questionnaire will be summarized for all treated patients for the given time points: baseline, each treatment cycle, and discontinuation visit. Frequency distributions, including measures of central tendency and variability, will be calculated for individual items and for the total scale. The time-to-worsening variables, including TTW in TOI, will be analyzed using the same methods utilized for other time-to-event variables. All randomized patients with a baseline assessment will be included in the TTW analysis. Clinically important difference thresholds will be used to define the proportion of patients that improve, remain stable, or worsen. The FACT-O scores will be summed at baseline and for each visit in order to calculate changes from baseline mean scores. These data will be compared between the 2 treatment arms. The scores will include the FACT-O total and subscale scores and TOI-O. All randomized patients with baseline and at least 1 post-baseline measure will be included in the change from baseline analysis. Other exploratory analyses may be performed, including longitudinal modeling (for example, repeated measures models and the impact of covariates) and subgroup analysis (for example, age $\leq$70 versus >70 years, and subgroups based on ECOG performance status, tumor response status, PFS, and OS). Individual responses, using an a priori responder definition (that is, the individual patient PRO

score change over a predetermined time period that should be interpreted as a treatment benefit) will be displayed using the cumulative distribution function of responses between treatment groups.

Exploratory analysis may be performed to assess potential relationships between patient reported symptoms and endpoints of interest such as OS and PFS. Compliance with completing the FACT-O will be summarized.

12.2.9. Safety Analyses

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study medication, and repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Fisher's exact test.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline.

The number of patients who experienced a TEAE, SAE, or AE related to study drug, as well as those who died or discontinued from the study due to an AE will be summarized by treatment.

Common Terminology Criteria for Adverse Events version 4.0 will be used to report AEs by CTCAE terms.

Laboratory and nonlaboratory CTCAEs will be summarized by CTCAE term and maximum CTCAE grade, including the total for maximum Grade 3 and 4. These summaries will be provided for events regardless of study drug causality, and repeated for events deemed by the investigator to be possibly related to study medication.

Reasons for death will be summarized separately for on-therapy and within 30 days of last dose of study drug/last visit. All SAEs will be summarized by preferred term.

Hospitalizations and transfusions during the study treatment period or during the 30-day post-discontinuation follow-up period will be summarized by treatment group.

12.2.10. Subgroup Analyses

There are no planned subgroup analyses. However, exploratory analyses may be performed to generate hypotheses about the efficacy of study therapy in certain subgroups for evaluation in future clinical studies.

12.2.11. Interim Analyses

All interim analyses will be conducted under the guidance of an internal assessment committee (AC).

12.2.11.1. Interim Analysis for Phase 1b

Safety data for all patients will be reviewed continuously throughout this component of the study. One interim analysis is planned for the Phase 1b portion of the study and will be conducted for safety and pharmacokinetics after all patients in Phase 1b have completed at least 1 cycle of study treatment. If the combination MTD has been identified prior to completion of the interim analysis and patients are available for Phase 2, with investigator and Lilly CRP approval, those patients will be randomized into the Phase 2 component of the study without delay.

12.2.11.2. Interim Analyses for Phase 2

Two interim analyses are planned for the Phase 2 portion of the study. The first analysis will be conducted for safety and pharmacokinetics when approximately 30 patients in Phase 2 have completed at least 1 cycle of study treatment. The second interim analysis will be conducted for safety and PK when approximately 60 patients in Phase 2 have completed at least 2 cycles of study treatment. Patient enrollment will continue along with the interim analyses. The Phase 2 interim analyses will be conducted using unblinded data under the guidance of an internal assessment committee.

Unblinding procedures are specified in the Statistical Analysis Plan.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including 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.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for 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 protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly must agree with all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s).

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

The study site's ERB(s) should be provided with the following:

- The current IB or package labeling and updates during the course of the study
- ICF
- Relevant curricula vitae

13.3. 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
- The International Conference on Harmonization Good Clinical Practices Guideline [E6]
- Applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

All or some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

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

13.3.2. Protocol Signatures

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.

13.3.3. 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 investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The sponsor's responsible medical officer and responsible 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.

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Attachment 1. Protocol JIAE Study Schedule

Study Schedule, Baseline Assessments, Protocol I1D-MC-JIAE(c)

Study Period	Baseline		
Cycle	BL		
Visit	0		
Duration	28 days		
Relative day within a cycle	28	14	7

Procedure Category	Procedure				Comments
Study Entry/ Enrollment	Informed Consent Form signed		X		Prior to performance of any protocol-specific tests / procedures.
	Inclusion/Exclusion evaluation		X		
Medical History	Initial history/preexisting conditions		X		
	Historical illnesses		X		
	Habits assessment		X		
Physical Examination	Height		X		
	Weight		X		
	Blood pressure/pulse/ respiration rate/temperature		X		
	ECOG performance status		X		
	Calculated creatinine clearance		X		Calculate using the Cockcroft and Gault formula (Attachment 6).
Tumor Assessment	Tumor measurement (palpable or visible)		X		Must be completed at least 24 hours prior to Cycle 1 Day 1.
	Radiologic imaging according to RECIST		X		Baseline radiological tumor assessment per RECIST version 1.1 should be done during screening. Radiologic assessments obtained previously as part of routine clinical care may be used as the baseline assessment if performed within 28 days of receiving the first dose of study drug on Day 1of Cycle 1. Baseline radiologic assessments must be completed at least 24 hours prior to Cycle 1 Day 1.

Study Schedule, Baseline Assessments, Protocol I1D-MC-JIAE(c), continued

Study Period	Baseline		
Cycle	BL		
Visit	0		
Duration	≤28 days		
Relative Day	≤28	≤14	≤7

Procedure Category	Procedure				Comments
Adverse Events	Adverse Events Collection/CTCAE Grading	X			Must be completed at least 24 hours prior to Cycle 1 Day 1.
Concomitant Meds	Concomitant Medication Notation	X			Must be completed at least 24 hours prior to Cycle 1 Day 1.
Lab/ Diagnostic Tests	Local hematology		X		Must be completed at least 24 hours prior to Cycle 1 Day 1.
	Central chemistry		X		At the discretion of the investigator, local chemistry may be collected for safety and dosing calculations. This central chemistry collection is distinct from the Cycle 1 Day 1 collection and must be completed at least 24 hours prior to Cycle 1 Day1.
	Local serum pregnancy test			X	Must be completed at least 24 hours prior to Cycle 1 Day 1.
	Local ECG		X		Must be completed at least 24 hours prior to Cycle 1 Day 1.
	Stored samples for pharmacogenomics	X			One-time only sample collection. Must be completed at least 24 hours prior to Cycle 1 Day 1. Sample may be sent to Sponsor at any time during study once patient has signed informed consent document.
	CA-125		X		Must be completed at least 24 hours prior to Cycle 1 Day 1.
	Circulating plasma proteins		X		This sample is distinct from the predose sample on Day 1 of Cycle 1 and must be completed at least 24 hours prior to Cycle 1 Day 1.
	FACT-O		X		Protocol Attachment 10. Must be completed at least 24 hours prior to Cycle 1 Day 1.
	Archived tumor sample	X			Must be completed at least 24 hours prior to Cycle 1 Day 1.
	Stored sample for germline DNA	X			Must be completed at least 24 hours prior to Cycle 1 Day 1.

Study Schedule, Treatment Period, Protocol I1D-MC-JIAE(c)

	Study Period	Study Treatment Period														Comments
	Cycle	1					2-6					7 and Beyond				
	Visit	1					2-6					7-X				
	Duration	21					21					28				
	Relative day within a cycle	1	3	10	11	12-21	1	3	10	11	12-21	1	3	4-14	15-28	
Procedure Category	Procedure															
Physical Examination	Weight		X	X				X	X			X				Obtain prior to infusion on-therapy cycles. May be obtained on Day 1 if necessary.
	Blood pressure/pulse/ respiratory rate/temperature		X	X				X	X			X				Obtain prior to infusion on-therapy cycles. May be obtained on Day 1 if necessary.
	ECOG performance status		X					X				X				Obtain prior to infusion on-therapy cycles. May be obtained on Day 1 if necessary.
	Calculated creatinine clearance		X					X								Obtain prior to infusion on-therapy cycles. Calculate using the Cockcroft and Gault formula (Attachment 6).
Tumor Assessment	Tumor measurement (palpable or visible)									X					X	Perform at the same time as radiologic imaging.
	Radiologic imaging according to RECIST									X					X	Perform between Days 11 through 21 (during induction therapy) and Days 15 through 28 (during maintenance therapy) of every even cycle. Radiologic assessment can be performed at any time if there is evidence of disease progression. Radiological exams should be performed using the same imaging method for each assessment whenever possible.
Adverse Events	Adverse event collection/CTCAE grading	X					X					X				
Concomitant Medications	Concomitant medication notation	X					X					X				

Study Schedule, Treatment Period, Protocol I1D-MC-JIAE(c), continued

	Study Period	Study Treatment Period														Comments
	Cycle	1					2-6					7 and Beyond				
	Visit	1					2-6					7-X				
	Duration	21					21					28				
	Relative day within a cycle	1	3	10	11	12-21	1	3	10	11	12-21	1	3	4-14	15-28	
	Procedure															
Lab/Diagnostic Tests	Local hematology	X		X			X		X			X				May be performed ≤24 hours in advance of Day 1 of each cycle.
	Central chemistry	X		X			X		X			X				May be performed ≤24 hours in advance of Day 1 of each cycle.
	Local ECG			X					X							Obtain on Day10 of Cycle 1 and Cycle 2 only.
	Phase 1b (Intensive) PK sampling	X		X	X		X		X	X			X			Refer to PK and PD Sampling Schedule (Attachment 3) for detailed instructions about collection of these samples.
	Phase 2 (Intensive) PK sampling		X	X	X		X						X			Refer to PK and PD Sampling Schedule (Attachment 3) for detailed instructions about collection of these samples.
	Phase 2 (Standard) PK sampling		X					X								PK samples to be collected pre-dose on Day 3 for Cycles 1, 2 and 3 only when in clinic for gemcitabine/carboplatin IV treatment. Refer to PK and PD Sampling Schedule (Attachment 3) for detailed instructions about collection of these samples.
	Circulating plasma proteins	X		X					X							Refer to PK and PD Sampling Schedule (Attachment 3) for detailed instructions about collection of these samples.
	CA-125						X					X				

Study Schedule, Treatment Period, Protocol I1D-MC-JIAE(c), continued

	Study Period	Study Treatment Period														Comments
	Cycle	1					2-6					7 and Beyond				
	Visit	1					2-6					7-X				
	Duration	21					21					28				
	Relative day within a cycle	1	3	10	11	12-21	1	3	10	11	12-21	1	3	4-14	15-28	
	Procedure															
PRO	FACT-O		X					X								Protocol Attachment 10.
Study Therapy	LY2228820 or Placebo	X Days 1 to 10					X Days 1 to 10					X Days 1 to 14				Patients should not consume food beginning 1 hour before and ending 1 hour after taking LY2228820 (or placebo). Doses of LY2228820 (or placebo) should be taken at the same time of the day with a full glass of water, 12 ± 3 hours apart.
	Gemcitabine		X	X				X	X							Administer IV over 30 (+15) minutes.
	Carboplatin		X					X								Administer IV over 30 (+15) minutes. Carboplatin should be administered after gemcitabine.

Abbreviations: AE = adverse events; Con Meds = Concomitant Medications; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetics; PRO = patient-reported outcomes; IV = intravenously; RECIST = Response Evaluation Criteria in Solid Tumors.

Study Schedule, Follow-Up Period, Protocol I1D-MC-JIAE(c)

		Study Period	Post-Discontinuation Follow-Up		Comments
		Cycle	Short Term Follow-Up	Long Term Follow-Up	
		Visit	801	802-XXX	
		Duration	Approximately 30 days	84 days (±14 days)	
		Relative day within a cycle	Period begins the day after stopping of study treatment and lasts approximately 30 days	Period begins 1 day after short-term follow-up period is completed and continues until death or until the patient is lost to follow-up	
Procedure category	**Procedure**				
Physical Examination	Blood pressure/pulse/respiratory rate/temperature		X		
	ECOG performance status		X		
Adverse Events	Adverse events collection/CTCAE grading		X	X	
Con Meds	Concomitant medication notation		X		
Lab	Local hematology		X		
	Local chemistry		X		
	CA-125		X		
PRO	FACT-O		X		
Tumor Assessment	Radiologic imaging according to RECIST		X	X	Radiologic assessments during the follow-up phase of the trial should be done according to the institutional standard of care frequency and by the same method used at baseline and throughout the study.
Follow-Up	Survival assessment			X	Approximately every 84 (±14) days (telephone assessment is acceptable).

Abbreviations: Con Meds = Concomitant Medications; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; PRO = patient-reported outcomes; RECIST = Response Evaluation Criteria in Solid Tumors.

Attachment 2. Protocol JIAE Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[b]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
	Potassium
Erythrocyte count (RBC)	Magnesium
Mean cell volume (MCV)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented and bands	Alanine aminotransferase (ALT/SGPT)
	Aspartate Aminotransferase (AST/SGOT)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine[c]
Eosinophils	Uric acid
Basophils	Calcium
Platelets	Glucose, random
	Albumin
	Cholesterol
Tumor Marker[a]	Creatine kinase (CK)
CA125	
	Serum Pregnancy Test[b]

Abbreviations: RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated central laboratory. At the discretion of the investigator, local chemistry may be collected for safety and dosing calculations.

[b] Local or investigator-designated laboratory.

[c] IDMS for US sites. OUS sites should use IDMS if available. If IDMS not available OUS, the site should continue to utilize the method that has been used historically at the site and should follow the guidance in Section 9.1.1 about capping the dose.

Attachment 3. PK and PD Sampling Schedule

Intensive PK sampling will be performed during Phase 1b induction therapy (Cycles 1-3 only) and maintenance therapy (Cycle 7 only) for all patients. On PK sampling days, the dose of LY2228820 should be held until after the pre-dose PK sample has been drawn.

Phase 1b Intensive PK Sampling: Induction Therapy (Cycles 1-3 only) and Maintenance Therapy (Cycle 7 only)

Cycle	Day	Dosing Schedule	Sampling Time for PK (LY2228820)	Sampling Time for PD
Induction Therapy				
1	Baseline			At baseline (≤14 days)
1	1	**LY** q 12 hr for 10 days between Day1 and Day10	Predose	Predose on Day 1 of Cycle 1
1	1		0.5 hr +/-5 min post LY dose	
1	1		1 hr +/-15 min post LY dose	
1	1		2 hr +/-15 min post LY dose	
1	1		4 hr +/-15 min post LY dose	
1	1		6 hr +/-15 min post LY dose	
1	1		8 hr +/-15 min post LY dose	
1	10	LY q 12 hr	Predose	Predose
1	10	**Gemcitabine**: 1000 mg/m^2, IV over 30 (+15) min		
1	10	(Sample collected at the end of the gemcitabine infusion)	0.5 hr +/-5 min post LY dose	
1	10	(30 min after the end of the gemcitabine infusion)	1 hr +/-15 min post LY dose	
1	10		2 hr +/-15 min post LY dose	

Phase 1b Intensive PK Sampling: Induction Therapy (Cycles 1-3 only) and Maintenance Therapy (Cycle 7 only)

Cycle	Day	Dosing Schedule	Sampling Time for PK (LY2228820)	Sampling Time for PD
1	10		8 hr +/-15 min post LY dose	
1	11	No drug	12 hr ±2 hr after Day 10 evening LYdose	
2	1	**LY** q 12 hr	**Predose** (276 hr ±2 hr after Day 10 evening LY dose	
2	10	**LY~~2228820~~** morning dose	Predose	Predose
2	10	**Gemcitabine** 1000 mg/m^2 over 30 (+15) min		
2	10	(Sample collected at the end of the gemcitabine infusion)	0.5 hr +/-5 min post LY dose	
2	10	(30 mins after the end of the gemcitabine infusion)	1 hr +/-15 min post LY dose	
2	10		2 hr +/-15 min post LY dose	
2	10		4 hr +/-15 min post LY dose	4hr +/-15 min post LY dose
2	10		6 hr +/-15 min post LY dose	
2	10		8 hr +/-15 min post LY dose	
2	11	No drug	12 hr (±2 hr) after Day 10 evening LYdose	
3	1	**LY** q 12 hr	**Predose** (276 hr ±2 hr after Day 10 evening LY dose	

Phase 1b Intensive PK Sampling: Induction Therapy (Cycles 1-3 only) and Maintenance Therapy (Cycle 7 only)

Maintenance Therapy				
Cycle	**Day**	**Dosing Schedule**	**Sampling Time for PK (LY2228820)**	**Sampling Time for PD**
7	3	**LY or placebo** q 12 hr for 10 days between Day1 and Day10		
7	3		Predose	
7	3		0.5 hr +/-5 min post LY dose	
7	3		1 hr +/-15 min post LY dose	
7	3		2 hr+/-15 min post LY dose	
7	3		4 hr +/-15min post LY dose	
7	3		6 hr +/-15min post LY dose	

Abbreviations: hr = hour, LY = LY2228820, min(s) = minute(s), q = every, PD = pharmacodynamics; PK = pharmacokinetics.

Intensive PK sampling will be performed during Phase 2 induction therapy (Cycles 1-2 only) and maintenance therapy (Cycle 7 only) for approximately 20 patients (10 patients/arm). On PK sampling days, the dose of LY2228820 (or placebo) should be held until after the pre-dose PK sample has been drawn.

Phase 2 Intensive PK Sampling: Induction Therapy (Cycles 1-2 only) and Maintenance Therapy (Cycle 7 only)

Cycle	Day	Dosing Schedule	PK Sampling Time for LY2228820	PK Sampling Time for Gemcitabine and dFdU	PK Sampling Time for Carboplatin	PD Sampling Time
Induction Therapy						
1	Baseline					At baseline (≤14 days)
1	1	**LY or placebo** q 12 hr for 10 days between Day 1 and Day 10				Predose on Day 1 of Cycle 1
1	3		Predose			
1	3	**Gemcitabine** 1000 mg/m^2 over 30 (+15) min				
1	3	(Collected at end of Gem infusion)	0.5 hr +/-5 min post LY dose	Immediately prior to end of infusion (<5 min)		
1	3		1 hr +/-15 min post LY dose	1 hr after start of infusion (±5 min)		
1	3	**Carboplatin** AUC4 over 30 (+15) min (1hr after start of				

		gemcitabine infusion)				

Phase 2 Intensive PK Sampling: Induction Therapy (Cycles 1-2 only) and Maintenance Therapy (Cycle 7 only)

Cycle	Day	Dosing Schedule	PK Sampling Time for LY2228820	PK Sampling Time for Gemcitabine and dFdU	PK Sampling Time for Carboplatin	PD Sampling Time
1	3				Immediately prior to end of infusion (<5 min)	
1	3		2 hr +/-15 min post LY dose	2 hr after start of infusion (±10 min)	1 hr after start of infusion (±5 min)	
1	3				1.5 hr after start of infusion (±10 min)	
1	3		4 hr +/-15 min post LY dose	4 hr after start of infusion (±15 min)	3 hr after start of infusion (±15 min)	
1	3		6 hr +/-15 min post LY dose	6 hr after start of infusion (±15 min)	5 hr after start of infusion (±15 min)	
1	3		8 hr +/-15 min post LY dose	8 hr after start of infusion (±15 min)		
1	10		Predose			Predose
1	10	**Gemcitabine** 1000 mg/m^2 over 30 (+15) min				
1	10	(Sample collected at the end of the gemcitabine infusion)	0.5 hr +/-5 min post LY dose	Immediately prior to end of infusion (<5 min)		

Phase 2 Intensive PK Sampling: Induction Therapy (Cycles 1-2 only) and Maintenance Therapy (Cycle 7 only)

Cycle	Day	Dosing Schedule	PK Sampling Time for LY2228820	PK Sampling Time for Gemcitabine and dFdU	PK Sampling Time for Carboplatin	PD Sampling Time
1	10	(30 min after the end of the gemcitabine infusion)	1 hr +/-15 min post LY dose	1hr after start of infusion (±5 min)		
1	10		2 hr +/-15min post LY dose	2 hr after start of infusion (±10 min)		
1	10		4 hr +/-15 min post LY dose	4 hr after start of infusion (±15 min)		4hr +/-15 min post LY dose
1	10		6 hr +/-15 mi post LY dose	6 hr after start of infusion (±15 min)		
1	10		8 hr +/-15 min post LY dose	8 hr after start of infusion (±15 min)		
1	11	No drug	12 hr (± 2 hr) after Day 10 evening dose of LY			
2	1	**LY or placebo** - morning dose	Predose			
Maintenance Therapy						
7	3	**LY or placebo** q 12 hr for 10 days between Day1 and Day10				
7	3		Predose			
7	3		0.5 hr +/-5 min post LY dose			

Phase 2 Intensive PK Sampling: Induction Therapy (Cycles 1-2 only) and Maintenance Therapy (Cycle 7 only)

Cycle	Day	Dosing Schedule	PK Sampling Time for LY2228820	PK Sampling Time for Gemcitabine and dFdU	PK Sampling Time for Carboplatin	PD Sampling Time
7	3		1 hr +/-15 min post LY dose			
7	3		2 hr+/-15 min post LY dose			
7	3		4 hr +/-15min post LY dose			
7	3		6 hr +/-15min post LY dose			
7	3		8 hr +/-15min post LY dose			

Abbreviations: hr = hour, LY = LY2228820, min = minute, q = every, PD = pharmacodynamics; PK = pharmacokinetics.

Standard PK sampling will be performed during Phase 2 induction therapy for all patients who do not have intensive PK sampling.

On PK sampling days, the dose of LY2228820 (or placebo) should be held until after the pre-dose PK sample has been drawn.

Phase 2 Standard PK Sampling: Induction Therapy (Cycles 1-3 only)

Cycle	Day	Dosing Schedule	PK Sampling Time for LY2228820	PD Sampling Time for LY2228820
		LY2228820 or placebo po q 12 hr for 10 days between Day 1 and Day 10		
1	1			Pre-dose
1	3		Pre-dose	
1	10			Pre-dose
1	10			4hr +/-15 min post LY dose
2	3		Pre-dose	
3	3		Pre-dose	

Abbreviations: hr = hours; PD = pharmacodynamics; PK = pharmacokinetics; po = by mouth; q = every

Attachment 4. International Federation of Gynecology and Obstetrics (FIGO) Staging

STAGES

I	Tumour confined to ovaries
IA	Tumour limited to one ovary, capsule intact No tumour on ovarian surface No malignant cells in the ascites or peritoneal washings
IB	Tumour limited to both ovaries, capsules intact No tumour on ovarian surface No malignant cells in the ascites or peritoneal washings
IC	Tumour limited to one or both ovaries, with any of the following: Capsule ruptured, tumour on ovarian surface, positive malignant Cells in the ascites or positive peritoneal washings
II	Tumour involves one or both ovaries with pelvic extension
IIA	Extension and/or implants in uterus and/or tubes No malignant cells in the ascites or peritoneal washings
IIB	Extensions to other pelvic organ No malignant cells in the ascites or peritoneal washings
IIC	IIA/B with positive malignant cells in the ascites or positive peritoneal washings
III	Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph nodes metastasis
IIIA	Microscopic peritoneal metastasis beyond the pelvis
IIIB	Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension
IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph nodes metastasis
IV	Distant metastasis beyond the peritoneal cavity

Attachment 5. ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

Attachment 6. Formula for Calculating Creatinine Clearance

Note: This formula should be used to calculate creatinine clearance (CrCl) during screening and for all subsequent cycles of induction therapy. Only **local** laboratory values should be used in the calculation.

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

Attachment 7. Formula for Calculating Carboplatin Dose

The Calvert formula **must** be used for the calculation of the carboplatin dose in this study.

Calvert Formula:

Total Dose (mg) = (target AUC) × (GFR + 25)

Maximum carboplatin dose (mg) = target AUC 4 (mg•min/mL) × (125 + 25) = 4 × 150 mL/min = 600 mg.

Reference: Calvert et al. 1989.

Attachment 8. RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as one liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response

(in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease.

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

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

Progressive Disease: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-progressive disease: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-progressive disease	No	PR
CR	Not evaluated	No	PR
PR	Non-progressive disease or not all evaluated	No	PR
SD	Non-progressive disease or not all evaluated	No	SD
Not all evaluated	Non-progressive disease	No	NE
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; NE = not evaluable.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-progressive disease	No	Non-CR/non-progressive disease[a]
Not all evaluated	No	NE
Unequivocal progressive disease	Yes or No	Progressive disease
Any	Yes	Progressive disease

Abbreviations: CR = complete response; NE = not evaluable.

[a] non-CR/non-progressive disease is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor-evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of progressive disease).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 9. Protocol JIAE Sampling Summary

This table summarizes the maximum number of samples and volumes for all sampling and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

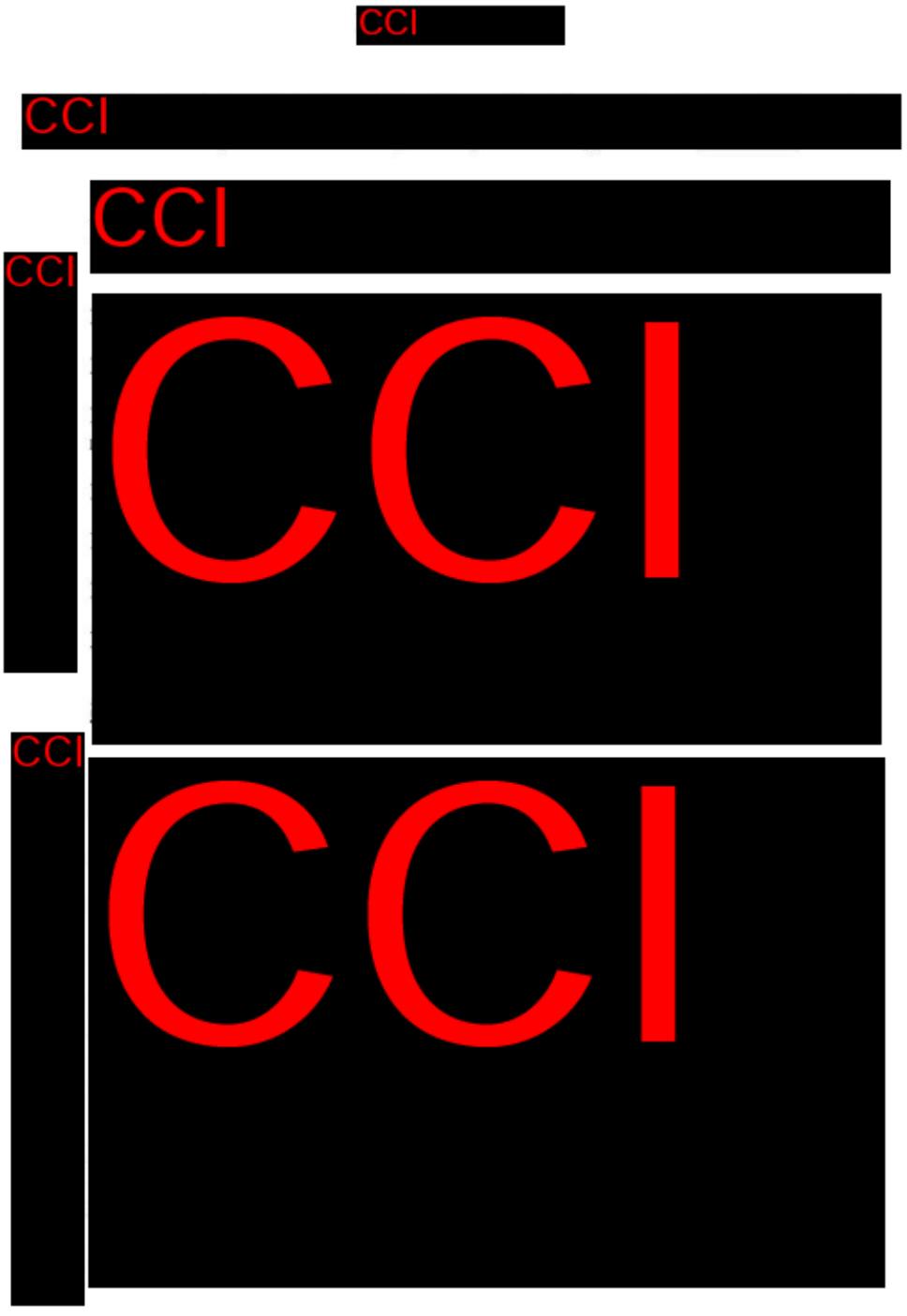
Protocol I1D-MC-JIAE(c) Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Screening tests[a]	Blood	9 mL	1	9 mL
Standard laboratory tests[a]				
Chemistry	Blood	5 mL	8	40 mL
Hematology	Blood	4 mL	10	40 mL
CA125	Blood	5 ml		
Circulating plasma proteins	Blood	5 ml		
Drug concentration	Blood	6 mL	24	144 mL
Pharmacogenetic samples	Blood	10 mL	1	10 mL
Stored sample for germline DNA	Blood	10 mL	1	10 mL
Other exploratory samples archival tissue	Block or Slides			
Total blood		54 mL	45	253 mL

Abbreviations: mL = milliliters.

[a] Additional samples may be drawn if needed for safety purposes.

Attachment 10. FACT-Ovarian (FACT-O) Instrument



English (United States)
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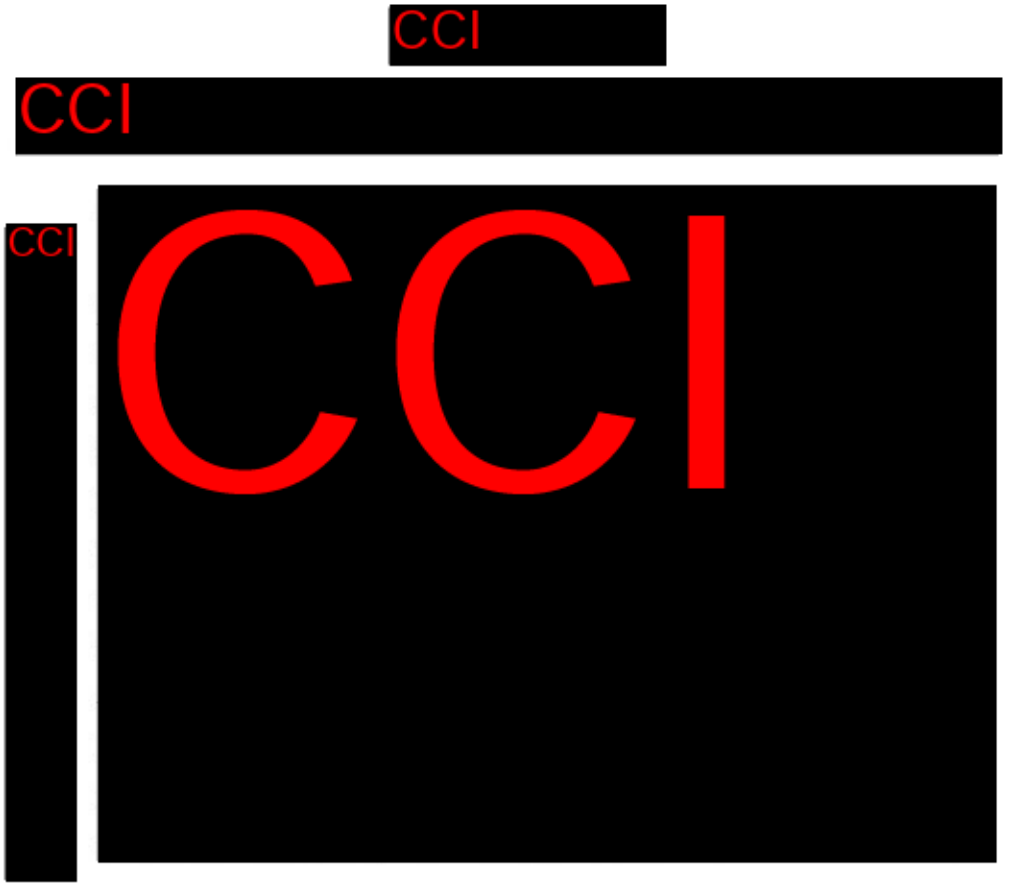
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Attachment 11. Protocol JIAE Amendment (c) Summary

Overview

Protocol I1D-MC-JIAE, A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Study of LY2228820, a p38 MAPK Inhibitor, plus Gemcitabine and Carboplatin versus Gemcitabine and Carboplatin for Women with Platinum-Sensitive Ovarian 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 rationale for the amendment was as follows:

Metabolic clearance analysis has recently been completed which revealed that CYP3A mediated metabolism is not the primary clearance pathway of LY2228820. This allows for the restriction of the CYP3A inhibitors, inducers, or substrates to be removed and for the use of dexamethasone and other anti-emetics during treatment with LY2228820.

Based on the available preclinical data, there is a possible risk of clinical drug–drug interaction when LY2228820 is administered with inhibitors or inducers of UGT enzymes. In the absence of clinical data to refine the risk of interaction, caution is warranted in the concomitant use of UGT enzyme inhibitors such as valproic acid and probenecid and inducers such as carbamazepine, phenytoin and rifampin. When, in the clinical investigator's opinion, concomitant use of valproic acid or probenecid is indicated, LY2228820-related DLTs of ataxia, dizziness and rash should be carefully monitored.

The ovarian cancer landscape has changed during the course of this study. Maintenance therapy as a part of or after a first line platinum regimen has become more prevalent. Several studies are examining the effect of maintenance after patients achieve a CR with the first line platinum regimen. In order to balance these patients between the placebo and LY2228820 arms, prior maintenance therapy has been added as a randomization factor.

The original sample size calculation for the Phase 2 portion of the study included a censoring rate assumption of 6% with 103 PFS events needed from 110 patients. Upon reflection, Lilly considers that this assumed censoring rate is too low. If just 8 or more patients are lost to follow up, the actual censoring rate would be higher. With this protocol amendment, the censoring rate estimate has been increased to 28% resulting in a reduction in the number of PFS events needed to 79. The hazard ratio of 0.7 has been maintained but the power has been reduced to 77% from 83%. These assumptions are consistent with enrollment and censoring experience in this phase of development.

In addition, the interim analyses for the study have been updated as follows:

- The third interim analysis will be performed when approximately 60 patients in the Phase 2 portion of the study have completed 2 cycles of treatment, and will examine safety and

PK only. Futility has been eliminated as Lilly does not expect that enough PFS events will have been observed to allow a futility analysis to occur at that time.

- The fourth interim analysis has been removed as all patients will have been enrolled and the PFS data will be immature. This interim would not be informative for futility or efficacy. Trial level safety will continue to be monitored throughout the study.

The overall changes made to this protocol are as follows:

Revised Protocol Sections

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

Global changes:

Protocol ID: I1D-MC-JIAE(~~b~~**c**)

2. Synopsis

Length of Study: 40 months
Planned first patient visit: April 2012
Planned last patient visit: August 2015
Planned interim analyses:

1. All patients in Phase 1b have received at least 1 cycle: safety and pharmacokinetics (PK)
2. Approximately 30 patients in Phase 2 have received at least 1 cycle: safety and PK
3. Approximately 60 patients in Phase 2 have received at least 2 cycles: safety, ~~PK,~~ and **PK**~~futility~~
4. ~~All patients in Phase 2 have received at least 2 cycles: safety, PK, futility, and efficacy~~

Diagnosis and Main Criteria for Inclusion and Exclusions:

Main exclusion criteria for study entry are:

- Are currently enrolled in, or discontinued <14 days from, a clinical trial involving an investigational drug or device
- Have previously completed or withdrawn from this study or any other study investigating LY2228820
- Have previously been treated with gemcitabine for epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
- Receiving concomitant cytotoxic or other antineoplastic treatment
- Have had, in the judgment of the investigator, a major bowel resection that would alter oral drug absorption
- ~~Have received, within 7 days of the initial dose of study drug, either grapefruit juice or treatment with a drug that is a known inducer or moderate/strong inhibitor of CYP3A4~~
- Are receiving, in the judgment of the investigator, concurrent administration of immunosuppressive therapy
- Have, in the judgment of the investigator, serious concomitant systemic disorders (e.g., acute myocardial infarction within 6 months of study entry, uncontrolled hypertension) incompatible with the study

Test Product, Dose, and Mode of Administration:

Study drugs are administered on a 21-day cycle during induction therapy (Cycles 1 through 6) and on a 28-day cycle during maintenance therapy (Cycle 7 and beyond). LY2228820 is administered orally every 12 hours on Days 1 through 10 of a 21-day cycle during induction therapy and on Days 1 through 14 of a 28-day cycle during maintenance therapy. Gemcitabine (1000 mg/m^2) is administered intravenously (IV) over 30 minutes **(+15 min)** on Days 3 and 10 of induction therapy only. Carboplatin (area under the plasma concentration–time curve [AUC] 4 with maximum dose of 600 mg) is administered IV over 30 minutes **(+15 min)** on Day 3 of induction therapy only.

Reference Therapy, Dose, and Mode of Administration:

Study drugs are administered on a 21-day cycle during induction therapy (Cycles 1-6) and on a 28-day cycle during maintenance therapy (Cycle 7 and beyond). Placebo is administered orally every 12 hours on Days 1 through 10 of a 21-day cycle during induction therapy and on Days 1

through 14 of a 28-day cycle during maintenance therapy. Gemcitabine (1000 mg/m^2) is administered IV over 30 **(+15)** minutes on Days 3 and 10 of induction therapy only. Carboplatin (AUC4 with maximum dose of 600 mg) is administered IV over 30 **(+15)** minutes on Day 3 of induction therapy only.

4. Abbreviations and Definitions

evaluable patient (for Phase 2)	any randomized patient ~~who receives at least one dose of study treatment~~

5. Introduction

5.8. Interaction with Cytochrome P450 (CYP) Enzymes and Enzymes Responsible for the Metabolism of LY2228820

The effect of LY2228820 on drug-metabolizing enzymes has been studied in vitro using human liver microsomes. LY2228820 was found to competitively inhibit the biotransformation of midazolam to 1′-hydroxy-midazolam with an estimated Ki of 1.2 μM (0.5 μg/mL). LY2228820 was also shown to inhibit CYP3A in a time-dependent manner with a k_{inact} of 0.069 min^{-1} and K_I of 9.5 μM (3.99 μg/mL). These data suggested the possibility that LY2228820 might modulate clearance of drugs that are metabolized by CYP3A **in vivo**.

The ability of LY2228820 to induce catalytic activities associated with CYP1A2, CYP2B6, and CYP3A was examined in primary cultures of fresh human hepatocytes**.** ~~, prepared from three separate donors.~~ LY2228820 was found unlikely to cause in vivo induction of the above CYP isoforms within the concentration range examined (0.01 to 10 μM).

The effect of LY2228820 on the activity of CYP3A in vivo **has been**~~is being~~ evaluated in the dose confirmation phase of Study JIAD (Part B) in which patients **were**~~are~~ administered a 2-mg oral dose of midazolam in the absence or presence of 420 mg LY2228820 administered every 12 hours (after fourteen doses). **Results showed**~~Preliminary results from 9 patients indicate~~ that mean PK parameters (C_{max} and AUC) of midazolam administered with LY2228820 were no higher than those of midazolam administered alone**, indicating**~~. These data indicate~~ that LY2228820 may not inhibit the CYP3A activity up to the dose level investigated (**18 patients at** 420 mg given every 12 hours).

In vitro studies using human liver microsomes indicated that the metabolic clearance of LY2228820 is primarily mediated by the UDP-glucuronosyltransferase (UGT) pathway (87%), with CYP-mediated pathway contributing to only 13%. Further CYP phenotyping studies using recombinant human CYPs indicated that CYP3A contributed to 72% of the CYP-mediated metabolic clearance of LY2228820. Taken together, the contribution of CYP3A to the total metabolic clearance of LY2228820 is estimated to be less than 10%. The regulatory guidance suggests that any enzyme contributing <25% to the systemic clearance of the drug is not clinically significant (FDA 2012).

Collectively, the above in vitro and in vivo data suggest that clinical interactions are unlikely when LY2228820 is coadministered with substrates, inhibitors and or inducers of CYP3A. When coadministered, inhibitors of UGT may increase the plasma concentrations of LY2228820 and inducers of UGT may decrease the plasma concentrations of LY2228820.

Refer to Section 9.8, Concomitant Therapy, for more information regarding ~~inducers and moderate/strong~~ inhibitors **and inducers** of **UGT**~~CYP3A4~~.

5.12. Rationale for Amendment (c)

Metabolic clearance analysis has recently been completed which revealed that CYP3A mediated metabolism is not the primary clearance pathway of LY2228820. This allows for the restriction of the CYP3A inhibitors, inducers, or substrates to be removed and for the use of dexamethasone and other anti-emetics during treatment with LY2228820.

Based on the available preclinical data, there is a possible risk of clinical drug–drug interaction when LY2228820 is administered with inhibitors or inducers of UGT enzymes. In the absence of clinical data to refine the risk of interaction, caution is warranted in the concomitant use of UGT enzyme inhibitors such as valproic acid and probenecid and inducers such as carbamazepine, phenytoin and rifampin. When, in the clinical investigator's opinion, concomitant use of valproic acid or probenecid is indicated, LY2228820-related DLTs of ataxia, dizziness and rash should be carefully monitored.

The ovarian cancer landscape has changed during the course of this study. Maintenance therapy as a part of or after a first line platinum regimen has become more prevalent. Several studies are examining the effect of maintenance after patients achieve a CR with the first line platinum regimen. In order to balance these patients between the placebo and LY2228820 arms, prior maintenance therapy has been added as a randomization factor.

The original sample size calculation for the Phase 2 portion of the study included a censoring rate assumption of 6% with 103 PFS events needed from 110 patients. Upon reflection, Lilly considers that this assumed censoring rate is too low. If just 8 or more patients are lost to follow up, the actual censoring rate would be higher. With this protocol amendment, the censoring rate estimate has been increased to 28% resulting in a reduction in the number of PFS events needed to 79. The hazard ratio of 0.7 has been maintained but the power has been reduced to 77% from 83%. These assumptions are consistent with enrollment and censoring experience in this phase of development.

In addition, the interim analyses for the study have been updated as follows:

- **The third interim analysis will be performed when approximately 60 patients in the Phase 2 portion of the study have completed 2 cycles of treatment, and will examine safety and PK only. Futility has been eliminated as Lilly does not expect that enough PFS events will have been observed to allow a futility analysis to occur at that time.**

- **The fourth interim analysis has been removed as all patients will have been enrolled and the PFS data will be immature. This interim would not be informative for futility or efficacy. Trial level safety will continue to be monitored throughout the study.**

7. Study Population

7.1. Inclusion Criteria

[6] Have adequate organ function, including:

- Hematologic: absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin until 1 day after the erythrocyte transfusion.
- Hepatic: bilirubin ≤1.5 times upper limits of normal and alanine aminotransferase **(ALT) and aspartate aminotransferase (AST)**~~and~~ ≤2.5 times upper limits of normal.

7.2. Exclusion Criteria

[15] Have a diagnosis of inflammatory bowel disease (Crohn's disease or ulcerative colitis).

[16] Exclusion criterion [16] has been deleted

~~[16] Have received, within 7 days of the initial dose of study drug, either grapefruit juice or treatment with a drug that is a known inducer or moderate/strong inhibitor of CYP3A4 (refer to Attachment 10). In addition, patients should not receive grapefruit juice or treatment with a known inducer or moderate/strong inhibitor of CYP3A4 during the study.~~

[17] Require concurrent administration of immunosuppressive therapy such as corticosteroids (prednisone >10 mg/day, or equivalent). **Intermittent corticosteroids used**~~For corticosteroid use~~ as **part of an** antiemetic **regimen are permitted.**~~agents, see Section 9.8.~~

7.3.1. Discontinuation of Patients

The reason and date for discontinuation will be collected for all patients. All patients who discontinue but receive at least one dose of study treatment will have procedures performed as shown in the Study Schedule (Attachment 1).

~~Patients who withdraw from the study before receiving study treatment will be replaced and will not be included in the safety or efficacy assessments.~~

For Phase 1b, any patient who experiences a dose-limiting toxicity or receives at least 75% of planned doses of LY2228820 in Cycle 1 will be deemed evaluable for safety assessment at that dose level. **Non-evaluable**~~Nonevaluable~~ patients may be replaced to ensure at least 3 evaluable patients at each dose level, unless accrual to that cohort has stopped because 2 or more patients at that dose level have experienced a DLT. In no case should patients be replaced if they were discontinued from the study due to toxicity. Patients who are evaluable for safety assessment at a dose level but have insufficient PK sampling may be replaced upon consultation with the investigator(s) and the Lilly Clinical Research Physician (CRP) to ensure adequate PK data, unless accrual to that cohort has stopped because 2 or more patients at that dose level have experienced a DLT.

~~For Phase 2, any randomized patient who receives at least one dose of study treatment will be deemed evaluable for efficacy assessment. Nonevaluable patients may be replaced. Patients who are evaluable for efficacy assessment but have insufficient PK sampling may be replaced upon consultation with the investigator(s) and the Lilly CRP to ensure adequate PK data.~~

8. Investigational Plan

8.1.2. Phase 2

Approximately 110 patients will be randomized 1:1 to provide 83% power for identifying a hazard ratio of 0.7 (LY2228820 arm to placebo arm) with a false-positive rate of 0.2 (one-sided) (refer to Section 12 for additional details regarding the sample size description). Patients will be randomized with a minimization method (Pocock and Simon 1975) using the following factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months) and ECOG performance status (0 and 1 versus 2).

Starting from protocol (c), randomization scheme is updated by adding another randomization factor. Patients who consent to protocol (c) will be randomized using following factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no).

8.1.4. Interim Analyses

The first interim analysis will be conducted to assess safety and PK; it will be performed when all evaluable patients in the Phase 1b portion of the study have received at least 1 cycle of study treatment.

The second interim analysis will be conducted to assess safety and PK; it will be performed when approximately 30 patients in the Phase 2 portion of the study have received at least 1 cycle of study treatment.

The third interim analysis will be conducted to assess safety, ~~PK,~~ and **PK**~~futility~~; it will be performed when approximately 60 patients in the Phase 2 portion of the study have received at least 2 cycles of study treatment.

~~The fourth interim analysis will be conducted to assess safety, PK, futility, and efficacy; it will be performed when enrollment in the study is complete and all evaluable patients in the Phase 2 portion of the study have received at least 2 cycles of study treatment.~~

9. Treatment

9.3. Method of Assignment to Treatment

In the Phase 2 portion of the study, approximately 110 patients will be randomized 1:1 in a double-blind manner by an interactive voice-response system (IVRS) to either Arm A (LY2228820 plus gemcitabine and carboplatin) or Arm B (placebo plus gemcitabine and carboplatin). Randomization will minimize imbalance between treatment arms according to the following factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months) and ECOG performance status (0 and 1 versus 2).

Starting from protocol (c), the randomization scheme is updated by adding another randomization factor. Patients who consent to protocol (c) will be randomized using following the factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no).

-This procedure is based on a well-defined algorithm (Pocock and Simon 1975). The randomization probability factor will be set at 0.75.

9.4.2.1. Induction Therapy

Gemcitabine, 1000 mg/m^2, will be administered IV over approximately 30 (+15) minutes on Days 3 and 10 of a 21-day cycle. The gemcitabine infusion will be started following the morning dose of LY2228820.

Carboplatin, AUC 4 (maximum dose, 600 mg), will be administered IV over approximately 30 (+15) minutes on Day 3 of a 21-day cycle. The carboplatin infusion will follow the gemcitabine infusion. ~~Antiemetics should be administered according to institutional standard procedures. Patients may receive a single dose of dexamethasone as part of the antiemetic regimen prior to administration of intravenous chemotherapy (refer to Section 9.8).~~

9.4.3.1.1. LY2228820 Dose Adjustments

Table JIAE.9.2. Intercycle~~Intracycle~~ Dose Adjustments for LY2228820 or Placebo

9.5.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

All toxicities should be graded according to CTCAE Version 4.0.

~~Nausea/vomiting should be treated promptly with antiemetics (for example, prochlorperazine, and metoclopramide). Diarrhea should be treated with antidiarrheals (for example, loperamide). Supportive interventions should not involve treatment with medications that are inducers or moderate/strong inhibitors of CYP3A4 (refer to Attachment 10).~~

9.8. Concomitant Therapy

With the exceptions listed in the following sections, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment. The need for any form of radiotherapy (including palliative) will be cause for early discontinuation from study treatment. In addition any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from study treatment. Appropriate documentation of all forms of premedication's, supportive care, and concomitant medications must be captured at each visit in the case report form (CRF). Concomitant medications and supportive care therapies must be documented at the time of discontinuation and also at the 30-day follow-up visit.

Based on the available preclinical data, there is a possible risk of clinical drug–drug interaction when LY2228820 is administered with inhibitors or inducers of UGT enzymes. In the absence of clinical data to refine the risk of interaction, caution is warranted in the concomitant use of UGT enzyme inhibitors such as valproic acid and probenecid and inducers such as carbamazepine, phenytoin and rifampin. When, in the clinical investigator's opinion, concomitant use of valproic acid or probenecid is indicated, LY2228820-related DLTs of ataxia, dizziness and rash should be carefully monitored.

~~Patients are not allowed to consume grapefruit juice and/or drugs that are inducers or moderate/strong inhibitors of CYP3A4 (see Attachment 10). Patients will have to discontinue these medications or will be discontinued from study treatment if unwilling to stop drugs that are inducers or moderate/strong inhibitors of CYP3A4. The only exception to this requirement is that patients may receive a single dose of dexamethasone (an inducer of CYP3A4) as part of the antiemetic regimen prior to administration of intravenous chemotherapy.~~

~~To avoid potential drug-drug interactions with LY2228820, antiemetics that are not CYP3A4-inducers or inhibitors should be used, such as prochlorperazine or metoclopramide.~~

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

10.3.1.1. Serious Adverse Events

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Serious adverse events~~Death~~ due to disease progression**, including death,** should not be reported ~~as an SAE~~ unless the investigator ~~also~~ deems **them**~~there~~ to be **possibly**~~a possible contribution~~ related to ~~the~~ study drug.

10.4.2. Archival Tumor Tissue Sample

Pretreatment formalin-fixed, paraffin-embedded tumor tissue obtained at the time of original diagnosis should be in a whole block, partial block, or unstained slides. Stored samples will retain the patient identifier and therefore, will not be stored indefinitely. Any **blocks or slides**~~whole block~~ submitted will **either** be returned to the site **or discarded within 15 years after last patient visit for the trial**. If archival tissue is not available for a specific patient, it will not constitute a protocol violation.

For p53 and PTEN mutation analyses comparing tumor to germline DNA, a single whole-blood sample will be collected one time to isolate DNA from PBMCs. **Samples will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator site personnel.**

Supplies required for the collection and shipment of the patients stored samples will be supplied by the sponsor. Sample handling and shipment to the central laboratory will occur according to instructions given to the study sites.

10.4.4. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

Pharmacodynamic samples will be collected as specified in the PK and PD Sampling Schedule (Attachment 3). Circulating plasma proteins regulated by p38 MAPK (such as such as TNF, IL-1, IL-6, and IL-8) will be measured. Supplies required for the collection and shipment of the patients stored samples will be supplied by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study sites. **Pharmacodynamic samples collected to measure circulating plasma proteins will be retained for a maximum of 15 years after the last patient visit for the study.**

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of the Phase 2 portion of this study is to compare the progression-free survival in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin. A **group sequential design will be used to control type 1 error across the interim analyses and the final PFS analysis in Phase 2 (see Section 12.2.11 for details). The primary analysis will be performed after 79**~~total of 103~~ PFS events **have occurred. Assuming**~~provide 83% power for identifying~~ a hazard ratio (HR) of 0.7**, this sample size yield at least 77% power** ~~-~~with **a** false-positive rate of 0.2 (1-sided) using a log-rank test. This assumes exponentially distributed PFS times, median PFS of 8.6 months for the control arm, enrollment duration of 12 months, and follow-up time of 18 months after the last patient is enrolled. Assuming **28**~~6~~% censoring rate of the PFS, a total of 110 patients will be randomized (55 patients in each arm) to achieve **79**~~103~~ PFS events at the primary analysis.

12.2. Statistical and Analytical Plans

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.2 unless otherwise stated. All CIs will be given at a 2-sided 90% level unless otherwise stated.

Starting from protocol (c), an additional factor is included during patient enrollment as randomization factor (see Section 8.1.2). For patients who randomized to phase 2 before the approval of protocol (c), the value of maintenance therapy as a part of or after a first line platinum regimen for these patients will be imputed as "not collected".

12.2.5. Primary Outcome and Methodology

For the primary endpoint of PFS, the HR will be estimated from survival data on all randomized patients using a Cox proportional hazards model with assigned study treatment arm as fixed effect **along with cofactors for**~~and~~ time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months**),**~~) and~~ ECOG performance status (0 and 1 versus 2) **and maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected).**~~as covariates.~~

The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curve as well as survival rates at various time points for each treatment group. **The log-rank test will be used to compare PFS distributions between treatment groups in phase 2.**

12.2.6. Efficacy Analyses

CA125 data will be log-transformed first and analyzed using a mixed-effect model repeated measures **analysis** with treatment, time, **and** treatment **by**~~and~~ time interaction as fixed effect, **along** with **cofactors for** time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months**),**~~) and~~ ECOG performance status (0 and 1 versus 2) **and**

maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected).~~as covariates.~~

The log ratio of tumor size at the end of Cycle 2 to tumor size at baseline will be calculated for each patient. This measure follows a normal distribution and will be compared between treatment groups using a t-test. Analysis of variance will be used to assess the effect of baseline factors on the change in tumor size.

The overall response rate is estimated as the total number of CRs and PRs, based on RECIST version 1.1, divided by the total number of **randomized** patients. The efficacy endpoint of overall response rate and its exact 90% confidence interval will be estimated for each treatment arm. The proportion in each treatment arm will be compared using the Chi-square test.

The efficacy analysis on OS will be conducted after all the patients have been followed for at least 2 years. The HR will be estimated from survival data on all randomized patients using a Cox proportional hazards model using assigned study treatment arm as fixed effect with time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months**),**~~) and~~ ECOG performance status (0 and 1 versus 2) **and maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected).**~~as covariates.~~

Additional exploratory analyses may be performed as deemed appropriate.

12.2.11.2. Interim Analyses for Phase 2

Two~~Three~~ interim analyses are planned for the Phase 2 portion of the study. The first analysis will be conducted for safety and pharmacokinetics when approximately 30 patients in Phase 2 have completed at least 1 cycle of study treatment. The second interim analysis will be conducted for safety **and PK when approximately 60**~~, PK, and futility when approximately 60 patients in Phase 2 have completed at least 2 cycles of study treatment. The third interim analysis will be conducted for safety, PK, futility, and efficacy when all~~ patients in Phase 2 have completed at least 2 cycles of study treatment. Patient enrollment will continue along with the interim analyses. The Phase 2 interim analyses will be conducted using unblinded data under the guidance of an internal assessment committee.

~~Futility analyses using PFS will be performed at interim analyses 2 and 3 in the Phase 2 portion of the study. The study could be terminated if the posterior probability of the HR less than 0.7 is less than 15%.~~

Unblinding procedures are specified in the Statistical Analysis Plan.

14. References

Food and Drug Administration. 2012. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf (Last accessed: 20 January 2015)

Attachment 3. PK and PD Sampling Schedule

Phase 2 Standard PK Sampling: Induction Therapy (Cycles 1-3 only)

Cycle	Day	Dosing Schedule	PK Sampling Time for LY2228820	PD Sampling Time for LY2228820
		LY2228820 or placebo po q 12 hr for 10 days between Day 1 and Day 10		
1	1			Pre-dose
1	3		Pre-dose	
1	10			Pre-dose
1	10			**4hr +/-15 min post LY** ~~Post-~~dose
2	3		Pre-dose	
3	3		Pre-dose	

Abbreviations: hr = hours; PD = pharmacodynamics; PK = pharmacokinetics; po = by mouth; q = every

Attachment 10. Inducers and Moderate/Strong Inhibitors of CYP3A4

Inducers of CYP3A4

Carbamazepine
Dexamethasone*
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

Strong inhibitors of CYP3A4

All HIV protease inhibitors
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone

Moderate inhibitors of CYP3A4

Aprepitant
Diltiazem
Erythromycin
Fluconazole
Fluvoxamine
Fosamprenavir
Grapefruit juice
Mibefradil
Verapamil

*Important exception: Patients may receive a single dose of dexamethasone as part of the antiemetic regimen prior to administration of intravenous chemotherapy.