Protocol: I4D-MC-JTJN(b)

A Phase 2 Study of Prexasertib in Platinum-Resistant or Refractory Recurrent Ovarian Cancer

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A Phase 2 Study of Prexasertib in Platinum-Resistant or Refractory Recurrent Ovarian Cancer

Prexasertib (LY2606368)

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1. Synopsis

Protocol Title:
A Phase 2 Study of Prexasertib in Platinum-Resistant or Refractory Recurrent Ovarian Cancer

Rationale:
Effective treatment options for patients with platinum-resistant or platinum-refractory high-grade serous ovarian (HGSOC), primary peritoneal, or fallopian tube cancer who have failed standard of care are limited. Over 75% of HGSOCs are associated with alterations in DNA damage response (DDR) pathways or increased replication stress. These alterations are predicted to increase sensitivity to a CHK1 inhibitor such as prexasertib. Study I4D-MC-JTJN (Study JTJN) will evaluate the efficacy of prexasertib in both platinum-resistant and platinum-refractory patients with HGSOC, primary peritoneal, or fallopian tube cancer.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To estimate the overall response rate (ORR) for each cohort	• ORR: proportion of all enrolled patients who achieve a best overall response of PR+CR as determined per RECIST version 1.1.
Secondary	
To characterize the safety and toxicity profile of prexasertib	• The safety endpoints evaluated will include but are not limited to the following: AEs, SAEs, clinical laboratory tests, ECGs, vital signs, and physical examinations
To characterize the PK of prexasertib	• Prexasertib concentrations in plasma
To estimate secondary efficacy measures including DCR, DoR, CA-125 response, PFS, OS	• DCR: proportion of patients who achieve a best overall response of CR, PR and SD (for at least 4 months) as determined per RECIST version 1.1. • DoR: time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date of documented PD, per RECIST 1.1, or the date of death from any cause in the absence of documented PD. • CA-125 response: at least a 50% reduction in CA-125 levels from a pretreatment sample that is at least twice the upper limit of the reference range and obtained within 2 weeks before starting the treatment, with confirmation after 4 weeks according to GCIG criteria. • PFS: time from enrollment until the first radiographic documentation (as assessed by the investigator) of progression or death from any cause in the absence of documented PD • OS: time from enrollment until death from any cause

Abbreviations: AEs = adverse events; CR = complete response; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; GCIG = Gynecologic Cancer Intergroup; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors version 1.1 (Eisenhauer et al. 2009); SAEs = serious adverse events; SD = stable disease.

Overall Design:
Study JTJN is a multicenter, nonrandomized, parallel cohort, Phase 2 study in patients with high-grade serous ovarian, primary peritoneal, or fallopian tube cancer.

Patients will be assigned to the following cohorts:

- Cohort 1: Platinum-resistant, *BRCA* negative, and received ≥3 lines of prior therapy
- Cohort 2: Platinum-resistant, *BRCA* negative, and received <3 lines of prior therapy
- Cohort 3: Platinum-resistant, *BRCA* positive, there is no restriction on number of lines of prior therapy, but patients must have received prior poly (ADP-ribose) polymerase (PARP) inhibitor
- Cohort 4: Platinum-refractory, *BRCA* positive or negative, no restriction on number of lines of prior therapy

Patients with *BRCA* test results positive for deleterious or suspected deleterious mutations are referred to as *BRCA* positive, and patients with *BRCA* test results negative for deleterious or suspected deleterious *BRCA* mutations are referred to as *BRCA* negative. Patients with variants of unknown significance should be considered *BRCA* negative.

Number of Patients:
The total sample size is estimated to be approximately up to 180 patients.

Treatment Arms and Duration:
Patients in all cohorts will receive 105 mg/m^2 prexasertib as an approximately 60 (+10) minute intravenous (IV) infusion on Day 1 and 15 of a 28-day cycle. Patients will be treated until radiographically documented disease progression, unacceptable toxicity, or another permitted reason for study discontinuation.

2. Schedule of Study Activities

Table JTJN.1. Schedule of Inclusion and Baseline Assessments

	Study Period	Baseline			
	Cycle	Baseline (Screening)			
	Visit	0			
	Duration	Up to 42 days			
	Relative Day C1D1	≤42	≤28	≤14	
Procedure Category	**Procedure**				**Comments**
Study Entry/ Enrollment	Informed Consent Form signed	X			Prior to conducting any protocol specific tests/procedures.
	Cohorts 1-3: Confirm availability of local *BRCA* result	X			Data from a blood or tissue based test are acceptable (i.e., either germline or somatic tests are acceptable). The test may have occurred prior to consent. If both somatic and germline status are known, the somatic status should be used for cohort assignment. Patients in Cohort 4 do not need to have local *BRCA* results.
	Inclusion/Exclusion evaluation		X		All criteria except the confirmation of availability of local *BRCA* test results must be assessed within 28 days from first dose.
Medical History	Initial history/ preexisting conditions		X		Including significant historical illnesses that resolved.
	Habits		X		Only smoking history.
Physical Examination	Physical examination			X	Includes height and weight.
	ECOG performance status			X	
	Vital signs			X	Temperature, blood pressure, pulse rate.
Tumor Assessment	Radiologic imaging according to RECIST version 1.1 and tumor measurement (palpable or visible)		X		Baseline radiological tumor assessment per RECIST version 1.1. Radiologic assessments obtained previously as part of routine clinical care may be used as baseline assessment provided they were done no more than 28 days before the first dose of study drug.
Adverse Events Collection/ CTCAE Grading			X		CTCAE version 4.0.
Concomitant Medication Notation			X		Includes information on over-the-counter and prescription analgesics
Laboratory/ Diagnostic Tests	Hematology			X	See Appendix 2
	Chemistry			X	See Appendix 2
	Urinalysis			X	See Appendix 2
	CA-125			X	Centrally assessed.
	Pregnancy test		X		Women of childbearing potential must have negative pregnancy test prior to biopsy (to confirm eligibility) and a negative pregnancy test within 24 hours prior to drug exposure. Either a urine or serum test is acceptable.
	ECG			X	Single local ECG.
	Pretreatment biopsy		X		May be performed at any time, but sample should be taken only after study eligibility is confirmed.

Schedule of Inclusion and Baseline Assessments

	Study Period	Baseline			
	Cycle	Baseline (Screening)			
	Visit	0			
	Duration	Up to 42 days			
	Relative Day C1D1	≤42	≤28	≤14	
Procedure Category	**Procedure**				**Comments**
Health Outcome Assessments	Worst Pain NRS		X		One question assessing worst pain will be administered by site personnel and completed by the patient prior to extensive interaction with site staff.
	NFOSI-18		X		NFOSI-18 will be administered by site personnel and completed by the patient prior to extensive interaction with site staff.

Abbreviations: C1D1 = Cycle 1 Day 1; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; IV = intravenous; NRS = numeric rating scale; NFOSI-18 = National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy – Ovarian Symptom Index-18; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1 (Eisenhauer et al. 2009).

Table JTJN.2. On-Study Treatment Schedule of Activities

Procedure Category	Procedure	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2-n Day 1	Cycle 2-n Day 15	Notes
	Study Period	**Cycle**				
	Cycle/Visit	**1**		**2-n**		
	Duration	**28 days**		**28 days**		
	Relative Day within Dosing Cycle	**1**	**15**	**1**	**15**	
Physical Examination	Physical examination	X		X		Includes weight and calculated BSA. May be completed up to 7 days prior to treatment infusion.
	Vital signs	X	X	X	X	Includes blood pressure, pulse, and temperature. Complete before each treatment infusion.
	ECOG performance status	X		X		Complete before treatment infusion on Day 1.
Laboratory/ Diagnostic Tests	Hematology	X	X	X	X	May be drawn up to 3 days before the day of dosing. Additional assessments may be obtained at the discretion of the investigator.
	Chemistry	X		X		May be drawn up to 3 days before the day of dosing. Additional assessments may be obtained at the discretion of the investigator.
	Pregnancy test	X		X		Applies only to women of childbearing potential. Where required by local law/ regulation or institutional guidelines, perform once every 28 days (±7 days). Either a urine or serum test is acceptable.
	CA-125	X		X		May be drawn up to 3 days before the day of dosing
	PK sampling	X		X		Sparse PK sampling will be conducted over multiple cycles of therapy (see Appendix 4 for additional details).
	Stored blood sample for pharmacogenetics	X				Collect once. Sample can be collected at any time if not collected on Day 1 of Cycle 1.
	Plasma biomarker sample	X		X		Collect only in Cycles 1 and 4. May be drawn up to 3 days before the day of dosing.
	ECG	X	X	X	X	Single local ECG collected at each time point only. Cycle 1 Day 1 and Cycle 2 Day 1: predose, within 15 min after EOI. Cycle 1 Day 15, Cycle 2 Day 15, and Cycle 3-n: Day 1 and 15 prior to each dose. Additional ECGs may be obtained at the discretion of the investigator. When ECGs and PK are required at the same time point, the ECG should be obtained prior to the PK draw.
	Optional tumor biopsy	X				Can occur at any time during patient's treatment. Patients should have adequate neutrophils and platelets prior to biopsy. See Section 9.8.1.

On-Study-Treatment Schedule of Activities

	Study Period	Cycle				
	Cycle/Visit	1		2-n		
	Duration	28 days		28 days		
	Relative Day within Dosing Cycle	1	15	1	15	
Procedure Category	**Procedure**					**Notes**
Tumor Assessment	Radiologic imaging according to RECIST version 1.1 and tumor measurement (palpable or visible)	X				Perform approximately every 8 weeks (±1 week) up to 1 year, thereafter every 12 weeks (±1 week). The first scan should be approximately 8 weeks (±1 week) from Cycle 1 Day 1. The 8-week/12-week scanning interval should be maintained even if cycles are delayed. As a result, the scans may not always occur at the end of a cycle. The same method of imaging used at baseline should be used for each subsequent assessment. Scans should also be obtained as clinically indicated. Scans to confirm responses may be performed sooner than 8 weeks, but should be at least 4 weeks following the initial observation of an objective response. The next scan should be 8 weeks (±1 week) following the confirmatory scan.
Adverse Events Collection/ CTCAE Grading		X				Collect throughout the study, CTCAE version 4.0; includes hospitalizations, emergency department visits, and/or occurrence of SBO.
Concomitant Medication Notation		X				Collect throughout the study; includes transfusions (platelets and RBC) and information on over-the-counter and prescription analgesics use.
Health Outcome Assessments	Worst Pain NRS	X				The patient will complete the single item worst pain NRS, at home immediately prior to bedtime every day. Collection of the Worst Pain NRS will be discontinued during study treatment at progression or Day 28 of Cycle 6, whichever comes first.
	NFOSI-18			X		The NFOSI-18 will be administered by site personnel prior to extensive interaction with site staff as well as administration of study drug on Day 1 of every cycle, beginning with Cycle 2.
Study Treatment	Prexasertib	X	X	X	X	Administer on Days 1 and 15 of every 28-day cycle, IV over approximately 60 (+10) minutes.

Note: Baseline/screening labs drawn within the indicated window of C1D1 may be used for both screening/baseline and C1D1 labs. Note that eligibility (including baseline/screening labs) must be confirmed prior to obtaining the biopsy and patient should fully recover from the acute effects of the biopsy prior to starting treatment.

Abbreviations: BSA = body surface area; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; IV = intravenous; NRS = numeric rating scale; NFOSI-18 = National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy – Ovarian Symptom Index-18, PK = pharmacokinetics; QTcF = corrected QT interval using Fridericia's formula; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1 (Eisenhauer et al. 2009); SBO = small bowel obstruction.

Table JTJN.3. Post-Study-Treatment Follow-Up Schedule of Activities

	Study Period	Post-Discontinuation Follow-Up		
		Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
	Duration	30 ± 5 days	60 ± 14 days	
	Visit	801	802-X	
Procedure Category	**Procedure**			**Comments**
Physical Examination	Physical examination (including weight)	X		
	Vital signs	X		Includes blood pressure, pulse, and temperature.
	ECOG performance status	X		
Tumor Assessment	Radiologic imaging according to RECIST version 1.1	X	X	Perform approximately every 8 weeks (±1 week) up to 1 year, thereafter every 12 weeks (±1 week) by the same method used at baseline and throughout the study, until the patient has documented disease progression, starts another therapy, or study completion. The same method of imaging used at baseline should be used for each subsequent assessment. Scans should also be obtained as clinically indicated.
	Tumor measurement (palpable or visible)	X		
Adverse Events Collection/ CTCAE Grading		X	X	CTCAE version 4.0; for visit 801: includes hospitalizations, emergency department visits, and/or occurrence of SBO. After Visit 801, only study treatment-related serious events are to be reported.
Concomitant Medication Notation		X		Includes transfusions (platelets and RBCs) and information on over-the-counter and prescription analgesics use.
Laboratory/ Diagnostic Tests	Hematology	X		See Appendix 2.
	Chemistry	X		See Appendix 2.
	CA-125	X	X	Collect approximately every 8 weeks (±1 week) up to 1 year, thereafter every 12 weeks (±1 week) at same time as radiologic imaging (+/- 3 days), until the patient has documented disease progression, starts another therapy, or study completion.
	ECG	X		
	Plasma biomarker sample	X		
	Optional post-treatment biopsy	X		Can be obtained any time prior to the start of next therapy

Post-Study-Treatment Follow-Up Schedule of Activities

	Study Period	Post-Discontinuation Follow-Up		
		Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
	Duration	30 ± 5 days	60 ± 14 days	
	Visit	801	802-X	
Procedure Category	Procedure			Comments
Health Outcome Assessments	Worst Pain NRS, NFOSI-18	X		PRO instrumentation will be administered during the short term follow-up visit prior to extensive interaction with site staff.
Follow-Up	Survival assessment		X	Approximately every 90 (±14) days (telephone assessment is acceptable)

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; NRS = numeric rating scale; NFOSI-18 = National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy – Ovarian Symptom Index-18; NRS = numeric rating scale; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1 (Eisenhauer et al. 2009); SBO =small bowel obstruction.

a Period begins the day after the decision that the patient will discontinue study treatment is made and lasts approximately 30 days.

b For patients who have discontinued without progression, follow-up should occur every 60 days. For patients with progression, the follow-up interval is 90 days for survival assessments. Period begins 1 day after short-term follow-up period is completed and continues until death, study withdrawal, or the patient is lost to follow-up.

Table JTJN.4. Continued Access Schedule of Activities

	Study Treatment	Follow-Up[a]	
Visit	501-5XX	901	
Procedure[b]			Comments
Adverse event collection	X	X	
Administer prexasertib	X		IV over approximately 60 (+10) minutes once every 14 days.

Abbreviations: IV = intravenously.

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

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

3. Introduction

3.1. Study Rationale

Ovarian cancer is the fifth leading cause of cancer deaths for women in the United States (Siegel et al. 2017). Approximately 80-85% of all carcinomas are serous tumors, the vast majority being high-grade serous ovarian cancer (HGSOC) (Soslow 2008). High-grade serous adenocarcinomas from the fallopian tube or peritoneal cavity are extrauterine adenocarcinomas of Müllerian epithelial origin and are staged and treated like HGSOC. As a result, they are commonly included in ovarian cancer clinical trials (Dubeau and Drapkin 2013). Frontline chemotherapy consists of a platinum and taxane doublet with or without bevacizumab (Ozols et al. 2003; Vasey et al. 2004; Katsumata et al. 2009; Burger et al. 2011; Perren et al. 2011). Although HGSOCs are initially chemo-sensitive, up to 80% of patients relapse leading to a disappointing 46.2% overall survivorship at 5 years from ovarian cancer diagnosis (Ozols et al. 2003; Rustin et al. 2010; SEER [WWW]). Therapy at the time of recurrence is determined largely by the time elapsed since completing initial platinum-based chemotherapy; patients with "platinum-sensitive" and "platinum-resistant" relapse have disease progressing >6 months or <6 months from the previous platinum-based treatment, respectively (Gore et al. 1990; Hoskins et al. 1991; Davis et al. 2014). Patients with platinum-refractory disease progress during or within 4 weeks of the last dose of the initial line of platinum-based chemotherapy for ovarian cancer. The standard of care for a woman with a platinum-sensitive recurrence is retreatment with a platinum doublet (Parmar et al. 2003).

Unlike platinum-sensitive disease, there is not a clear standard of care for platinum-resistant or platinum-refractory disease, and the agents used vary by center and geography. A variety of single-agent chemotherapies are used for platinum-resistant disease, including PEGylated liposomal doxorubicin (PLD), gemcitabine, paclitaxel, topotecan, docetaxel, and etoposide (National Comprehensive Cancer Network [NCCN] [WWW]). However, patients will ultimately relapse and new agents are needed for platinum-resistant patients who have failed or exhausted standard treatment options.

Poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib and rucaparib have been approved as monotherapy for patients with recurrent ovarian cancer, especially for patients with germline *BRCA1* or *BRCA2* mutations (Alsop et al. 2012; Pennington et al. 2014; NCCN [WWW]). Notably, a pooled subgroup analysis of the rucaparib studies ARIEL2 and Study 10 showed that in HGSOC patients who had received ≥2 prior therapies, rucaparib monotherapy had a higher overall response rate (95% confidence interval [CI]) in platinum-sensitive patients (65.8% [54.3-76.1]) compared with platinum-resistant (25.0% [8.7-49.1]) or platinum-refractory patients (0% [0.0-41.0]) (Oza et al. 2017).

3.2. Background

3.2.1. Description of CHK1 and Prexasertib

Checkpoint kinase 1 (CHK1) is a multifunctional protein kinase and regulator of the DNA damage response (Dai and Grant 2010). In response to exogenous DNA damage, CHK1 mediates cell-cycle arrest to allow time for DNA repair or if the damage is extensive, to trigger apoptosis. CHK1 is essential for homologous recombination repair (HRR) of double-strand DNA breaks. It also affects the initiation of DNA replication origin firing, stabilization of replication forks, resolution of replication stress, and coordination of mitosis, even in the absence of exogenous DNA damage (McNeely et al. 2014). Thus, the inhibition of CHK1 disrupts DNA replication, induces DNA damage, and subsequently prevents repair, leading eventually to death by replication or mitotic catastrophe due to the presence of unresolved DNA breaks (King et al. 2015). CHK1 inhibition also enhances the activity of DNA-damaging cytotoxic chemotherapeutics by interfering with cell-cycle control and DNA repair (McNeely et al. 2014). Tumors that have high levels of replication stress and/or defects in DNA damage repair pathways such as HGSOC are hypothesized to be susceptible to the effects of a CHK1 inhibitor (Lin et al. 2017; Murai 2017).

Prexasertib is an inhibitor of CHK1 which has been evaluated as a treatment for patients with advanced cancers and may have utility both as monotherapy and in combination with other DNA-damaging agents, targeted agents, or radiation (Zeng et al. 2017).

3.2.2. Rationale for Prexasertib in Ovarian Cancer

3.2.2.1. Role in DNA-Damage Repair and Replication Stress

Preclinical data suggest that tumors with high endogenous levels of replication stress are more sensitive to single-agent CHK1 inhibitors (Cole et al. 2011; Brooks et al. 2013; Lecona and Fernández-Capetillo 2014). *CCNE1* (cyclin E1) is amplified in 15-20% of HGSOCs (Etemadmoghadam et al. 2013; Konstantinopoulos et al. 2015), and overexpression of cyclin E induces replication stress and DNA damage that activates HRR (Jones et al. 2013). CHK1 inhibition by prexasertib in *CCNE1*-amplified ovarian cancers may diminish the ability of cells to tolerate high levels of replication stress induced by cyclin E overexpression by inhibiting CHK1-mediated replication fork stabilization and repair of collapsed forks through HRR as well as exacerbating replication stress by promoting late replication origin firing.

Defective DNA repair also results in increased sensitivity to single-agent CHK1 inhibitors (Rundle et al. 2017). Approximately half of HGSOCs harbor mutations in genes that modulate HRR (Konstantinopoulos et al. 2015; Lord and Ashworth 2016). Germline *BRCA1* and *BRCA2* mutations are present in about 15% of epithelial ovarian cancers and as many as 22.6% of HGSOCs, and somatic *BRCA1* and *BRCA2* mutations have been identified in about 7% of high-grade serous epithelial ovarian cancers (Konstantinopoulos et al. 2015). Furthermore, epigenetic silencing of *BRCA1* and *RAD51C* has been observed in 10-20% and 3% of HGSOCs, respectively (Konstantinopoulos et al. 2015; Lord and Ashworth 2016). HRR deficiency through inactivation of RAD51 confers hypersensitivity to CHK1 inhibition

(Krajewska et al. 2015); therefore, defects in HRR may confer an increased sensitivity to double-strand DNA breaks induced by prexasertib. Alterations in other DNA damage response and repair pathways may similarly contribute to CHK1 inhibitor sensitivity in ovarian cancer (Murai 2017) and include mutations in *ATM* or *ATR* observed in 2% of HGSOCs and mutations in genes of the Fanconi anemia DNA repair pathway observed in 5% of HGSOCs (Lord and Ashworth 2016).

The potential for synthetic lethality between HRR deficiencies or other DNA repair defects and prexasertib as well as the role of *CCNE1* in increasing replication stress make CHK1 an attractive target in this disease.

3.2.2.2. Nonclinical Data

Broad antiproliferative effects of prexasertib monotherapy were demonstrated in various tissue culture studies using growth inhibition or clonogenic survival in soft agar as a phenotypic endpoint. A panel of 621 genomically characterized tumor cell lines derived from multiple cancer types and various histologies were tested. Prexasertib showed widespread antiproliferative effects; growth of 66% of these lines was inhibited at half-maximal inhibitory concentration (IC_{50}) concentrations of ≤50 nM . Further, the antiproliferative activity of prexasertib in the subset of 23 cell lines derived from human ovarian cancers showed IC_{50} values that ranged between 2 and 320 nM; 70% (16 of 23) of these lines had IC_{50} values ≤50 nM.

Studies in xenograft tumors also demonstrated prexasertib to be a potent inhibitor of tumor cell growth. Studies in the orthotopically implanted intraperitoneal SKOV-3 model using a 3-days-on/4-days-off schedule showed prexasertib monotherapy resulted in a dose-dependent inhibition of tumor growth. At the end of the dosing period (Day 31), inhibition was 52.7% and 70.7% for groups treated with 4 and 12 mg/kg of prexasertib, respectively, compared with vehicle. Necropsy showed dose-dependent reductions in ascites fluid volume and number of tumor colonies (localized metastases) in the peritoneal cavity. These results are concordant with studies of subcutaneous-implanted xenograft such as the A-2780 model, in which tumor growth inhibition at the end of the active dosing period was 60.3%, 63.1%, and 93% after monotherapy with 1, 4, and 12 mg/kg of prexasertib, respectively (McNeely et al. 2011).

3.2.2.3. Clinical Data in Patients with High-Grade Serous Ovarian Cancer

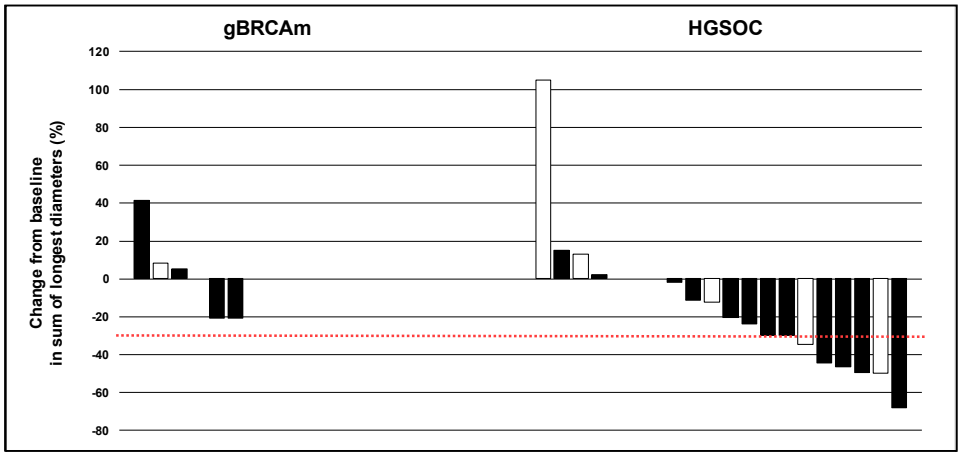
The safety profile of prexasertib is consistent with toxicities commonly observed with standard of care cytotoxic agents used to treat cancer. Hematologic toxicity is the most frequent and severe toxicity after treatment with 105 mg/m^2 prexasertib every 14 days. Nonhematologic toxicity occurs at a lower frequency than hematologic toxicity and has been predominantly Grade 1 or 2 in severity. Complications from hematologic toxicities such as febrile neutropenia, infections, and clinically significant bleeding events have also been observed, but can be mitigated by supportive care approaches such as granulocyte colony stimulating factor (G-CSF) and transfusions. Events with a fatal outcome have occurred following sepsis/infection and clinically significant bleeding. Patients should be closely monitored for signs of infections, sepsis, and bleeding complications. Clinical data from completed and ongoing studies across the

clinical program are summarized in the Investigator's Brochure (IB). Interim data available from 1 study in patients with ovarian cancer are summarized below.

The National Cancer Institute (NCI; principal investigator, Jung-min Lee, MD) is sponsoring a Phase 2 pilot study with a primary objective of determining the overall response rate (ORR) of prexasertib monotherapy in patients with breast cancer, ovarian cancer, or prostate cancer (NCT02203513, I4D-MC-E001[E001]). Patients receive prexasertib on Days 1 and 15 of a 28-day cycle at the recommended Phase 2 dose (RP2D) of 105 mg/m^2 (NCI 2017b). Preliminary results from 32 heavily pretreated female patients with HGSOC were presented at the meeting of the European Society for Medical Oncology (ESMO) in October 2016 (Lee et al. 2016). Interim data included 7 patients in Group 1 (with documented deleterious germline *BRCA1*/*BRCA2* mutation [g*BRCA1/2*m]) and 25 patients in Group 2 (with negative family history of hereditary breast ovarian cancer syndrome or negative g*BRCA1/2*m test) (Lee et al. 2016).

Grade 4 neutropenia was observed in 69% of patients and 75% of the Grade 3 and 4 neutropenia events resolved to Grade ≤2 within 8 days after onset; 2 patients (6%) had febrile neutropenia and 56% received G-CSF. Other toxicities included decreased white blood cell (WBC) count (78%), anemia (66%), and decreased platelet count (34%). Nonhematologic adverse events (AEs) included fatigue, nausea, vomiting, and diarrhea (9% each); all were generally mild (Lee et al. 2016). One patient had Grade 3 diarrhea and vomiting during infusion. Only 1 patient (3%) required a dose reduction (80 mg/m^2) (Lee et al. 2016).

Figure JTJN.3.1 presents a plot of best responses for target lesions by patient among patients treated with prexasertib. Of the 25 patients treated in Group 2, 20 were evaluable for tumor response. Seven (35%) evaluable patients achieved partial response (PR) (including 2 whose disease was platinum-sensitive and 5 whose disease was platinum-resistant or -refractory). The median duration of response was 6 months (range: 2-13 months), and 5 (25%) patients achieved stable disease (SD) lasting ≥4 months, for a DCR of 60%. Patients were heavily pretreated. Platinum-resistant patients had a median of 4 prior lines of therapy (range: 1-13). Of the 7 patients treated in Group 1, 6 were evaluated for tumor response. None of the evaluable patients in Group 1 achieved CR or PR, but 4 (67%) achieved SD lasting ≥4 months, for a DCR of 67%. As with Cohort 2, patients had received numerous prior treatments (median: 7, range: 3-12). These preliminary results suggest that prexasertib could be a novel approach to improve the outcomes of patients with HGSOC (Lee et al. 2016).



Abbreviations: *gBRCA*m = germline *BRCA* mutated; HGSOC = high-grade serous ovarian cancer. White bar = platinum-sensitive disease; black bar = platinum-resistant or –refractory disease.

Figure JTJN.3.1 Best response for target lesions, among patients with platinum-sensitive, -resistant, or -refractory disease treated with prexasertib.

3.2.2.4. Rationale for JTJN Cohorts

Patients enrolled in Study JTJN will be assigned to one of 4 cohorts:

- Cohort 1: Platinum-resistant, *BRCA* negative, and received ≥3 lines of prior therapy
- Cohort 2: Platinum-resistant, *BRCA* negative, and received <3 lines of prior therapy
- Cohort 3: Platinum-resistant, *BRCA* positive, there is no restrictions on number of lines of prior therapy, but patients must have received prior PARP inhibitor
- Cohort 4: Platinum-refractory, *BRCA* positive or negative, no restrictions on number of lines of prior therapy.

Patients with *BRCA* test results positive for deleterious or suspected deleterious mutations are referred to as *BRCA* positive, and patients with *BRCA* test results negative for deleterious or suspected deleterious *BRCA* mutations are referred to as *BRCA* negative. Patients with variants of unknown significance should be considered *BRCA* negative.

As described in Section 3.2.2.3, preliminary data from Study E001 suggest clinical benefit of prexasertib in heavily pretreated patients (Lee et al. 2016). To test this hypothesis, Cohort 1 and 2 will segregate patients based on the number of prior lines of therapy. Similarly, Study E001 suggests potential differences in activity in patients with and without *BRCA* mutation. Although data are limited, the cohort of patients without *BRCA* mutation had a higher response rate than those with *BRCA* mutation. The reason for this difference is not clear. Alternations in the HRR pathway, such as *BRCA* mutations, are reported to be mutually exclusive with *CCNE1* amplification (Kroeger and Drapkin 2017). As described in Section 3.2.2.1, *CCNE1* amplification may increase replication stress and result in sensitivity to a CHK1 inhibitor such as prexasertib. Notably, in Study E001 all patients with *BRCA* mutation had been treated with a PARP inhibitor (Lee et al. 2016). Mechanisms of PARP inhibitor resistance that restore HRR may lead to diminished sensitivity to prexasertib; prior treatment with PARP inhibitors could

confound results in *BRCA* mutant patients who are subsequently treated with prexasertib, as tumors in these patients may be proficient for HRR. Note that mechanisms of resistance to PARP inhibitors that do not involve restoration of HRR also have been characterized (Lord and Ashworth 2013; Rondinelli et al. 2017), some of which would not be implicated in cross-resistance to prexasertib. Cohort 3 of Study JTJN was designed to better characterize effects of prexasertib in patients with a *BRCA* mutation who had a prior PARP inhibitor. Study E001 enrolled a cohort of 7 patients with the germline *BRCA* mutation, of which 6 patients had platinum-resistant or –refractory disease (Lee et al. 2016). Cohort 4 in Study JTJN will include platinum-refractory patients to determine any prexasertib benefit in these high-unmet medical need patients.

As described in Section 3.1, gemcitabine, paclitaxel, and PLD are common standard of care agents for HGSOC recurrent disease. The present study, JTJN, could prompt the initiation of a randomized controlled trial that may include investigator's choice of these chemotherapy options as the control arm. Excluding patients (Cohorts 1-3) that have received more than two of these agents for platinum resistant disease is consistent with the entry criteria that are likely to be applied in future studies.

3.3. Benefit/Risk Assessment

Given the high unmet need for additional therapies to treat platinum-resistant or –refractory HGSOC, the mechanistic rationale supporting a role for CHK1 inhibition to improve outcomes for patients with HGSOC, nonclinical model data (including HGSOC) on prexasertib monotherapy, prexasertib clinical safety profile, and preliminary efficacy observed in patients with HGSOC, the risk/benefit assessment supports evaluation of prexasertib monotherapy in the proposed patient population. More information on known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of prexasertib are described in the IB.

4. Objectives and Endpoints

Table JTJN.5 shows the objectives and endpoints of the study.

Table JTJN.5. Objectives and Endpoints

Objectives	Endpoints
Primary	
To estimate the ORR for each cohort	• ORR: proportion of all enrolled patients who achieve a best overall response of PR+CR as determined per RECIST version 1.1.
Secondary	
To characterize the safety and toxicity profile of prexasertib	• The safety endpoints evaluated will include but are not limited to the following: AEs, SAEs, clinical laboratory tests, ECGs vital signs, and physical examinations
To characterize the PK of prexasertib	• Prexasertib concentrations in plasma
To estimate secondary efficacy measures including DCR, DoR, CA-125 response, PFS, OS	• DCR: proportion of patients who achieve a best overall response of CR, PR and SD (for at least 4 months) as determined per RECIST version 1.1. • DoR: time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date of documented PD, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented PD. • CA-125 response: at least a 50% reduction in CA-125 levels from a pretreatment sample that is at least twice the upper limit of the reference range and obtained within 2 weeks before starting the treatment, with confirmation after 4 weeks according to GCIG criteria. • PFS: time from enrollment until the first radiographic documentation (as assessed by the investigator) of progression or death from any cause in the absence of documented PD • OS: time from enrollment until death from any cause
Tertiary/Exploratory	
To assess the relationship between biomarkers, prexasertib exposure (PK), and clinical outcomes	• Biomarker research assessed from blood or tissue samples, unless precluded by local regulations • Plasma concentration of prexasertib • Clinical outcomes data
To evaluate patient-reported outcomes using NCCN-FACT-FOSI 18 and Worst Pain NRS	• Change from baseline • Time to progression • Association between time to pain progression and analgesic consumption • Association between time to progression and select efficacy outcomes

Abbreviations: AEs = adverse events; CR = complete response; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; GCIG =Gynecologic Cancer Intergroup; NFOSI-18 = National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy – Ovarian Symptom Index-18; NRS = numeric rating scale; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors version 1.1 (Eisenhauer et al. 2009); SAEs = serious adverse events; SD = stable disease.

5. Study Design

5.1. Overall Design

Study I4D-MC-JTJN is a multicenter, nonrandomized, parallel cohort, Phase 2 study in approximately up to 180 patients with high-grade serous ovarian, primary peritoneal, or fallopian tube cancer. Patients will be assigned to the following cohorts:

- Cohort 1: Platinum-resistant, *BRCA* negative, and received ≥3 lines of prior therapy
- Cohort 2: Platinum-resistant, *BRCA* negative, and received <3 lines of prior therapy
- Cohort 3: Platinum-resistant, *BRCA* positive, there is no restriction on number of lines of prior therapy, but must have received prior PARP inhibitor
- Cohort 4: Platinum-refractory, *BRCA* positive or negative, no restrictions on number of lines of prior therapy

Interim analyses will occur at specified intervals. Based on protocol-defined rules, enrollment to a cohort can stop due to lack of efficacy or continue at each interim analysis until the total sample size is reached. See Section 10.3.4 for further details regarding interim analyses.

5.2. Number of Patients

The maximum total sample size of this study is estimated to be approximately 180 patients. For each of the 4 cohorts, the minimum sample size is approximately 20 patients. The sample size for each cohort will be dependent on the outcomes of the interim analyses. As cohorts are halted, new eligible patients will be allocated to the enrolling cohorts. As a result, the maximum sample size of a single cohort is approximately 120 patients (e.g., if enrollment to all but one of the cohorts is stopped after the first interim analysis).

5.3. End of Study Definition

Study completion occurs after the clinical trial database is locked and final analysis of primary and secondary endpoints have been performed. End of the trial is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

An open-label, parallel cohort, nonrandomized Phase 2 study without concurrent controls is appropriate for patients with high-grade serous ovarian, primary peritoneal, or fallopian tube cancer. There is not a clear world-wide standard of care for HGSOC patients with platinum-resistant or platinum-refractory disease. Given the high unmet medical need, this nonrandomized design will enable all participants to receive study drug. The details of the study design are described in Section 5, and details of the sample size determination are provided in Section 10.1.

5.5. Justification for Dose

Based on the nonclinical prexasertib pharmacokinetic (PK)/pharmacodynamic model (inhibition of phosphorylated CHK1 and tumor growth response in Calu-6 xenografts) used to predict the

human efficacious exposure range, the population based PK analysis from the first-in-human dosing (FHD) study JTJA demonstrating that a body surface area (BSA)-based dose regimen is justified for prexasertib administration, the similar systemic exposure and similar safety profile between schedules of administration, as well as the increased patient convenience, 105 mg/m^2 of prexasertib on Day 1 of a 14-day schedule was selected as the RP2D.

The population PK predicted (from 1000 simulated individual PK profiles) median $AUC_{(0\text{-}72)}$ (2034 ng•hr/ml) following administration of 105 mg/m^2 every 14 days is greater than the median $AUC_{(0\text{-}72)}$ (1896 ng•hr/mL) predicted from a Calu-6 xenograft model before clinical investigation to achieve the maximal tumor response with prexasertib monotherapy. In addition, the average prexasertib plasma concentrations over the first 72 hours ($C_{av,72}$) predicted from the population PK model from Study JTJA after 105 g/m^2 (approximately 28 ng/mL) is greater than the IC_{50} (14.1 ng/mL) determined from the single-agent nonclinical Calu-6 xenograft PK/pharmacodynamic model, also demonstrating that the prexasertib systemic exposure at the R2PD is in a potentially efficacious range. Additional details are described in Sections 5.2.3 and 6 of the IB.

6. Study Population

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

6.1. Inclusion Criteria

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

[1] Women who have histologically or cytologically verified high-grade serous ovarian, primary peritoneal or fallopian tube cancer.

[2] Cohorts 1 to 3: Have platinum-resistant disease, which is defined as disease progression within 6 months of last dose of platinum-based chemotherapy. Progression due to rising CA125 only is not considered as platinum-resistant disease.

Cohort 4: Have primary platinum-refractory disease defined as disease progression during or within 4 weeks after the last dose of initial line of platinum-based chemotherapy.

Note: disease progression may be either radiographic progression or documented clinical progression. Residual disease is not considered progression.

[3] Cohort 1: Are *BRCA* negative and have received 3 or more prior lines of therapy for high-grade serous ovarian, primary peritoneal, or fallopian tube cancer (including immunotherapy, targeted therapies, or chemotherapy (systemic or intraperitoneal).

Cohort 2: Are *BRCA* negative and have received less than 3 prior lines of therapy for high-grade serous ovarian, primary peritoneal, or fallopian tube cancer (including immunotherapy, targeted therapies, or chemotherapy (systemic or intraperitoneal).

Note for Cohorts 1 and 2: Each line of therapy is preceded by evidence of clinical or radiographic disease progression (initial therapy is considered the first line). Switch of an agent within the same drug class (for example, cisplatin to carboplatin) within a regimen to manage toxicity does not define the start of a new line of therapy. Similarly, maintenance therapy (continuation maintenance or switch maintenance) will not be considered a new line of treatment. Hormonal therapy is not considered a line of therapy. All adjuvant therapy should be considered as a line of therapy.

Cohort 3: Are *BRCA* positive and have previously received a PARP inhibitor at any time following diagnosis. Note: there is no restriction on number of lines of prior therapy.

Cohort 4: Are *BRCA* positive or negative; no restriction on number of lines of prior therapy.

[4] Have a performance status (PS) of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982).

[5] Have discontinued all previous treatments for cancer and recovered from acute effects of therapy. Patients must be discontinued from previous treatments, as per below:

Previous Treatment	Length of Time Prior to First Dose of Prexasertib
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥21 days or ≥ 5 half-lives, whichever is shorter
Biologic agents that are large molecules including immunotherapy	≥28 days
Investigational agents	≥28 days. If the agent has a long half-life (e.g. >2 weeks), then 3 months or 5 half-lives (whichever is longer) should have passed
Radiotherapy	
Limited-field radiotherapy with palliative intent	≥14 days
Other radiotherapy	≥28 days
Major surgery, excluding biopsy	≥28 days

[6] Have at least 1 measurable lesion using standard techniques by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009).

[7] Have given written informed consent prior to any study-specific procedures and agree and are able to follow the requirements of the protocol.

[8] Are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age.

[9] Have adequate organ function, as defined below. These values must be met during the baseline visit (prior to biopsy) as well as predose Cycle 1 Day 1:

System	Laboratory Value
Hematologic	
ANC	≥1.5×10^9/L
Platelets	≥100×10^9/L
Hemoglobin	≥9 g/dL
Note: transfusions to increase a patient's hemoglobin level or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug. If a patient receives transfusions, erythropoietin, or G-CSF therapy ≥14 days prior to the first dose, the hematologic criteria listed above must be met following the 14 day window and prior to the first dose of study therapy.	
Hepatic	
Direct bilirubin	≤1.5×ULN
ALT and AST	≤3×ULN **OR** ≤5×ULN if the liver has tumor involvement
Renal	
Serum creatinine **OR** Measured creatinine clearance **OR** Calculated creatinine clearance	<1.5×ULN **OR** ≥40 mL/min/1.73 m^2
Albumin	
Albumin	>30 g/L **OR** 25-30 g/L and the value does not decrease across 2 readings separated by ≥14 days (without an intravenous albumin infusion)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; G-CSF = granulocyte colony stimulating factor; ULN = upper limit of normal.

[10] Women of child-bearing potential participating must agree to use one highly effective (less than 1% failure rate) method of contraception or use a combination of two effective methods of contraception during treatment with study drug and for at least 12 weeks following the last dose of study drug.

Note: Unless not allowed by local regulations, women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

[11] Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative pregnancy test at the screening visit (prior to biopsy) and within 24 hours prior of drug exposure.

[12] Cohorts 1-3: Have documented test results assessing alterations in the *BRCA1* and *BRCA2* genes by a local laboratory prior to receiving study treatment. Results from either a blood or tissue based test are acceptable.

[13] Must be able and willing to undergo mandatory tumor biopsy which will be collected following determination of eligibility and before treatment (≤28 days before C1D1). Note that the biopsy may be collected prior to the predose Cycle 1 Day 1 pregnancy test and labs. Tumor tissue obtained from a prior biopsy may be permitted for the pretreatment sample after discussion and agreement between Lilly clinical research physician (CRP) / clinical research scientist (CRS) and investigator if a patient has not received any therapies for the disease between the time biopsy was obtained to start of prexasertib treatment. The decision to use a tumor tissue sample from a prior biopsy will be documented in writing.

6.2. Exclusion Criteria

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

[14] Cohorts 1-3: Have previously received all of the following agents at any time in the platinum-resistant setting: gemcitabine, PEGylated liposomal doxorubicin, and paclitaxel. It is acceptable to have received 1 or 2 of these agents for platinum-resistant disease.

[15] Have non-epithelial or mixed epithelial/non-epithelial tumors (including malignant mixed Müllerian tumors), ovarian tumors with low malignant potential (borderline tumors), endometrioid, clear cell, mucinous or low-grade serous carcinomas or not otherwise specified (NOS) ovarian tumors.

[16] Have known central nervous system (CNS) malignancy or metastasis. Patients with treated brain metastases that have been CNS recurrence-free for 1 year prior to study treatment may be considered if approved by the Lilly CRP/CRS.

[17] Have prior malignancies unless approved by the Lilly CRP/CRS. For instance, patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low, as judged by the Lilly CRP/CRS, may be eligible for this study.

[18] Are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[19] Have previously completed or withdrawn from this study or any other study investigating prexasertib or a CHK1 inhibitor or have shown hypersensitivity to the study drug or excipients.

[20] Have a known serious medical condition (e.g., active infection, increased risk of bleeding events) that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol or tolerate the study treatment.

[21] Have at least one of the following:
- history of abdominal fistula or gastrointestinal (GI) perforation
- intra-abdominal abscess within last 3 months prior to the first dose of study drug
- a radiographically confirmed bowel obstruction (including sub-occlusive disease) within 3 months prior to the first dose of study drug.

[22] Have a symptomatic human immunodeficiency virus (HIV) infection or symptomatic activated/reactivated hepatitis A, B, or C (screening is not required).

[23] Have a serious cardiac condition, such as:
- symptomatic congestive heart failure or any uncontrolled cardiac disease
- New York Heart Association Class III/IV heart disease
- unstable angina pectoris
- symptomatic or poorly controlled cardiac arrhythmia
- myocardial infarction within the last 3 months
- have a QT interval using Fridericia's correction (QTcF) of >480 msec on more than one electrocardiogram (ECG) obtained during the baseline (screening) period
- family history of long-QT syndrome.

[24] Have a history of prior radiotherapy to the whole pelvis.

[25] Have chronic daily treatment with corticosteroids (dose >10 mg/day methyl-prednisolone equivalent), excluding inhaled and topical steroids.

[26] Have known factors that may increase the risk of infection while on study drug treatment. These may include, but are not limited to, an indwelling peritoneal catheter or open wounds. Catheters for vascular access are permitted.

6.3. Lifestyle Restrictions

There are no specific lifestyle restrictions for this protocol.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened a maximum of 2 times. The interval between rescreenings should be ≥2 weeks. Each time rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

7. Treatments

7.1. Treatments Administered

Patients in all cohorts will receive 105 mg/m^2 prexasertib as an approximately 60 (+10) minute intravenous (IV) infusion on Day 1 and 15 of a 28-day cycle.

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

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

7.1.1. Packaging and Labelling

The drug product, prexasertib (LY2606368) for injection, is supplied for clinical trial use as a lyophilized, yellow to white powder, in glass vials and is composed of prexasertib lactate monohydrate and the inactive ingredients trehalose, polysorbate 80 and mannitol. Clinical trial materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Upon obtaining informed consent, the site will register the patient via the interactive web response system (IWRS), which is accessible 24 hours a day, to assign a patient number. Patients who meet all criteria for enrollment will be assigned to a cohort based on *BRCA* status, platinum resistant vs refractory, and/or lines of prior therapy. The IWRS will be used to dispense study drug to and/or track the allocation of each patient.

7.2.1. Selection and Timing of Doses

A cycle is defined as an interval of 28 days.

The actual doses of study treatment to be administered will be determined by calculating the patient's BSA at the beginning of each cycle. Although it is acceptable to recalculate more frequently, if the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior cycle or from baseline, the BSA will not need to be recalculated. A ±10% variance in the calculated total dose will be allowed for ease of dose administration.

A patient may continue to receive study treatment until she meets 1 or more of the specified reasons for discontinuation.

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

The following rules should guide dosing:

- Before each dose:
  - Nonhematologic toxicities must resolve to Grade 0 or 1 or baseline, except AEs with no immediate medical consequence or those that can be controlled with adequate treatment (for example, pain, alopecia, fatigue, nausea, vomiting, or diarrhea)
  - Neutropenia and anemia must resolve to Grade ≤2, and thrombocytopenia to Grade ≤1, as shown in Table JTJN.6.

Table JTJN.6. Hematologic Parameters Required Prior to Each Dose

	Dose
Neutrophils	≥1000/mm^3
Platelets	≥75/mm^3
Hemoglobin	≥8 g/dL

- A delay of a dose due to holiday, weekend, inclement weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation.
  - Initiation of a dose may be delayed for a maximum of 14 days (28 days from prior dose) to allow a patient sufficient time for recovery from study treatment related toxicity (for example, a delay of 14 days from the planned Day 1 of the cycle). Note that if the Day 15 dose cannot be administered within 7 days of the planned Day 15 (e.g. 21 days from the prior dose (by Day 22), it should be omitted and the next dose administered 28 days of the prior dose as the start of a new cycle. In addition, if there is a persistent downward trend in the predose neutrophil/platelet counts a treatment delay may be considered.
- In exceptional circumstances, a longer delay is permitted upon agreement between the investigator and the Lilly CRP/CRS. Dosing delay of study drugs due to non-study drug related AEs may be permissible if deemed clinically necessary by the investigator and following discussion between the investigator and the CRP/CRS. The interval between prexasertib doses must not be less than 14 days. If a dose is delayed (for toxicity or other circumstances), the next dose should be adjusted so that there is a ≥14-day interval. If needed, the cycle length should be extended to accommodate the delay.
- Dose adjustments and delays on either Day 1 or 15 will be made based on the clinical assessment of hematologic and nonhematologic AEs as shown in Table JTJN.7. In addition, the dose can also be delayed or adjusted at the investigator's discretion as clinically indicated.

Table JTJN.7. Dose Adjustments and Delays

Toxicity	CTCAE Grade	Action	Dose Adjustments and Considerations
Neutropenia	Grade 3 or Grade 4	Delay treatment until ≤Grade 2 (≥1000/mm^3)	Recommend prophylactic G-CSF[a]
Thrombocytopenia	Grades 2, 3 or Grade 4	Delay treatment until ≤Grade 1 (≥75/mm^3)	Investigator discretion
Anemia	Grade 3 or Grade 4	Consider RBC transfusion or EPO (if consistent with institutional guidelines). Delay treatment until ≤Grade 2 (≥8 g/dL)	Investigator discretion
Febrile neutropenia (without prophylactic G-CSF)	Any Grade	Delay treatment until afebrile and neutrophils ≤Grade 2 (≥1000/mm^3)	Investigator discretion Recommend prophylactic G-CSF[a]
Febrile neutropenia (with prophylactic G-CSF)	Any Grade	Delay treatment until afebrile and neutrophils ≤Grade 2 (≥1000/mm^3)	Reduce to next lower dose level unless there is documented agreement between investigator and CRP/CRS.
Allergic/ hypersensitivity reaction[b]	Grade 1 or Grade 2	Administer treatment per institutional guidelines for allergic/hypersensitivity reactions. Monitor closely for any worsening symptoms. A reduced infusion rate can be used for subsequent infusions.	Investigator discretion
	≥Grade 3	Stop infusion immediately and disconnect infusion tubing from the patient. Administer treatment per institutional guidelines. Patient must not receive any further treatment with prexasertib.	
Other nonhematologic toxicity[c]	Grade 2	Delay treatment until ≤Grade 1 or baseline[d]	Investigator discretion
	Grade 3 or Grade 4	Delay treatment until ≤Grade 1 or baseline	Reduce to next lower dose level

Abbreviations: CRP = clinical research physician; CRS = clinical research scientist; CTCAE = Common Terminology Criteria for Adverse Events version 4.0; G-CSF = granulocyte colony stimulating factor; RBC = red blood cells

[a] Refer to Section 7.7.

[b] Please refer to the IB for the most recent guidance on allergic/hypersensitivity reactions

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

[d] Baseline is considered prior to dosing on Cycle 1 Day 1.

If a patient requires a dose reduction, prexasertib should be reduced as shown in Table JTJN.8. After a dose reduction, re-escalation is acceptable.

Table JTJN.8. Prexasertib Dose Reductions

Reduction	Dose
1st prexasertib dose reduction	80 mg/m2
2nd prexasertib dose reduction	60 mg/m2
3rd prexasertib dose reduction	Discontinue from prexasertib

7.5. Preparation/Handling/Storage/Accountability

All prexasertib should be refrigerated.

Prexasertib will be administered as an IV infusion using a central or peripheral IV line and will be filtered through an in-line filter. Prexasertib should be handled according to standard procedures and precautions consistent with a cytotoxic anticancer drug.

The dosage strength of 67-mg prexasertib lactate monohydrate drug product will be used in Study JTJN. The vial will contain a slight excess to facilitate the withdrawal of the labeled amount 67 mg/vial for use with an appropriate device, such as an infusion set. Reconstituting the vial contents with water for injection yields a clear yellow solution with a concentration of 3.3 mg/mL of prexasertib.

For the most current detailed formulation information and preparation instructions, refer to the IB and Pharmacy Binder.

7.6. Treatment Compliance

The study medication will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

7.7. Concomitant Therapy

Except as noted, no other chemotherapy, immunotherapy, cancer-related hormone therapy, herbal drugs, or experimental drugs will be permitted while the patients are on study treatment. Patients on stable doses of bisphosphonates or RANK-L targeted agents (for example, denosumab) are allowed to continue. These agents should not be initiated within the 2 weeks prior to study enrollment or at any point while on the study. Replacement hormonal therapy or tamoxifen or aromatase inhibitors initiated before study entry will be allowed.

Radiotherapy (including palliative radiotherapy) will only be permitted if it is agreed upon by both the investigator and the Lilly CRP/CRS. If the lesion that is to be treated is a target lesion, the lesion will be censored at the time of treatment. However, the patient may be eligible to remain on study drug treatment provided there are other lesions that can be followed for progression. Treatment delays of prexasertib may be required if radiotherapy is administered.

In addition, any disease progression requiring other forms of specific antitumor therapy will necessitate discontinuation from study treatment.

Patients should receive full supportive care during the trial. Guidelines from ASCO (Smith et al. 2015) should be followed for patients requiring support with G-CSF. Primary or secondary

prophylactic G-CSF support is permitted at the discretion of the investigator. Primary prophylaxis with G-CSF starting in the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia on the basis of patient-, disease-, and treatment-related factors. As outlined in the ASCO guidelines, the following factors may be relevant to the JTJN patient population and should be considered when estimating the patient's overall risk of febrile neutropenia: Age ≥65, advanced disease, previous chemotherapy or radiation therapy, poor nutritional status, cardiovascular disease, or multiple comorbid conditions. It is recommended that prophylactic short-acting G-CSF be initiated within 24-72 hours of study drug administration and continued through post-nadir recovery (Crawford et al. 2010). It is recommended that long-acting G-CSFs, such as pegfilgrastim, be administered the day after treatment (Crawford et al. 2017). Per NCCN guidelines, Phase 2 data support the use of pegfilgrastim in regimens with a 2-week cycle, with uniform consensus that this is appropriate (Category 2A) (Crawford et al. 2017). .

Prophylactic antibiotics may be considered for use in patients who have experienced neutropenic fever or patients deemed at higher risk for neutropenic fever by the investigators. The treatment should be consistent with ASCO guidelines (Flowers et al. 2013).

Erythropoietin and packed RBC transfusion may be used according to ASCO guidelines (Rizzo et al. 2008) if clinically indicated at any time during the study. Patients who are stable on erythropoietin for >1 month before study entry may continue their treatment.

On days when prexasertib is administered, patients should avoid taking multiple (>1) concomitant medications that are known or suspected to cause prolonged QTc or Torsades de Pointes and, if possible, alternative agents should be considered. In addition, at the start of the study and on days when prexasertib is administered, care should be taken to ensure that serum electrolyte levels are within the normal range.

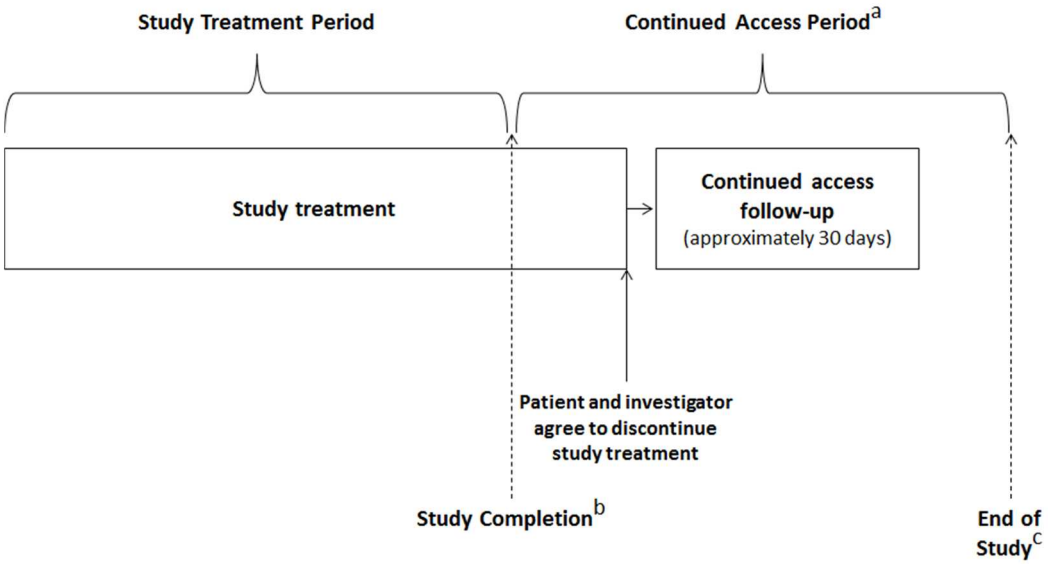
Strong P-gp and BRCP inhibitors (e.g., amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, propafenone, quinidine, ranolazine, verapamil, cyclosporine A, or eltrombopag) should be used with caution, as prexasertib is a substrate of both P-gp and BCRP.

7.8. Treatment after the End of the Study

Patients who are still on prexasertib at the time of study completion may continue to receive prexasertib if they are experiencing clinical benefit and no undue risks. The continued access period will apply to this study only if ≥1 patient is still on prexasertib when study completion occurs. Lilly will notify investigators when the continued access period begins. Lilly may allow patients to enroll in a "rollover" protocol to provide long-term continued access for patients enrolled in this study.

The continued access period will begin after study completion and ends at End of Trial (Figure JTJN.7.1). The patient's continued access to prexasertib will end when a criterion for discontinuation is met (Section 8). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue prexasertib and lasts approximately 30 (±7)

days. Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities Table JTJN.3.



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Study completion occurs after the clinical trial database is locked and the final analysis of the primary and secondary endpoints have been performed. Lilly will notify sites when study completion occurs.
[c] End of study occurs at the last visit or last scheduled procedure for the last patient.

Figure JTJN.7.1. Continued access diagram.

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

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

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

- the patient is enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment
- disease progression
- unacceptable toxicity
- 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 prexasertib will occur prior to introduction of the new agent
- the investigator decides that the patient should be discontinued from prexasertib
- the patient requests to be discontinued from prexasertib
- the patient's designee (legal representative) requests that the patient be discontinued from prexasertib.

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

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP/CRS and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study. Patients who are discontinued from prexasertib will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.2. Discontinuation from the Study

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

- the investigator or Lilly, for any reason, but considering the rights, safety and well-being of the patient(s) and in accordance with International Council for Harmonization (ICH)/Good Clinical Practice (GCP) Guidelines and local regulations, stops the study or stops the patient's participation in the study.
- the patient becomes pregnant during the study. See Section 9.2.1 regarding regulatory reporting requirements on fetal outcome.

- the investigator decides that the patient should be discontinued from the study:
- the patient requests to be discontinued from the study:
- the patient's designee (legal representative) requests that the patient be discontinued from the study.

The study will be discontinued if Lilly judges it is necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. Prior to discontinuation, the Ethical Review Board (ERB) (which approved the trial) will be notified according to local regulation.

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

8.3. Lost to Follow-Up

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

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

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

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 2 provides a list of the laboratory tests that will be performed for this study.

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

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

9.1. Efficacy Assessments

Tumor assessments, including tumor markers, will be performed for each patient at the times shown in the Schedule of Activities (Section 2).

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

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

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiologic scan of the thorax, abdomen, and pelvis is required. As an independent review of all or a subset of radiographic imaging scans may be conducted, copies of scans will be collected throughout the study and stored by a coordinating vendor designated by Lilly.

See Section 10.3.1 for definitions of the efficacy endpoints.

9.1.1. Appropriateness of Assessments

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

9.2. Adverse Events

The investigator should provide adverse event (AE) verbatim terms and then the terms will be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) Lower Level term (LLT) dictionary. The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to assign AE severity grades.

Investigators are responsible for:

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

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

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

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

Adverse event grading of toxicities related to estimated glomerular filtration rate (GFR) should be evaluated based on the Cockcroft-Gault method or measured GFR (Appendix 6).

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity

- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above.

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

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

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

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

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

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

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and Regulation (EU) No 536/2014 and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2.3. Complaint Handling

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

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

9.3. Treatment of Overdose

Refer to the IB for current guidance on overdose.

9.4. Safety

9.4.1. Safety Measures and Monitoring

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

Results from any clinical laboratory test analyzed by a central laboratory (refer to Appendix 2) will be provided to investigative sites by Lilly or its designee.

Refer to Section 9.2 for details on the recording of AEs.

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.1.1. Special Hepatic Safety Data Collection and Monitoring Criteria

Hepatic data should be collected on the appropriate CRF forms in the event that ≥1 of the following condition(s) are met for the patient during the course of the study:

- elevation of serum alanine aminotransferase (ALT) ≥10×upper limit of normal (ULN)
- without liver tumors or metastasis: ALT ≥5×ULN and total bilirubin ≥2×ULN
- with liver tumors or metastasis: ALT ≥8×ULN and total bilirubin ≥2×ULN
- discontinuation from study treatment due to hepatic event or liver test abnormality
- occurrence of a hepatic event considered to be an SAE.

Close hepatic monitoring as outlined below should be initiated if the following conditions are met by a patient:

- elevated ALT ≥5×ULN and elevated total bilirubin ≥2×ULN or ALT ≥8×ULN
- for patients entering the study with ALT ≥3×ULN, monitoring should be triggered at ALT ≥2×baseline and elevated total bilirubin ≥2×ULN.

Liver tests (Appendix 5), including ALT, aspartate aminotransferase (AST), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Appendix 5) and in

consultation with the Lilly CRS/CRP. Monitoring of ALT, AST, and total bilirubin should continue until levels normalize or return to approximate baseline levels.

9.5. Pharmacokinetics

The PK samples will be collected as specified in the PK Sampling Schedule (Appendix 4).

Sparse PK samples for prexasertib will be collected over multiple cycles of therapy to determine the plasma concentrations of prexasertib. The data from this study will be pooled with other PK data in a planned population based PK meta-analysis.

At the visits and times specified in the Study Schedule, venous blood samples will be collected to determine the plasma concentrations of prexasertib. A maximum of 5 samples may be added or removed during the study if warranted and agreed upon between both the investigator and Lilly. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

These samples will be analyzed at a laboratory designated by the sponsor by using a validated liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) method.

The PK samples will be stored at a facility designated by the sponsor. Bioanalytical samples collected to measure prexasertib concentrations will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

Pharmacodynamics samples will not be collected for this trial.

9.7. Pharmacogenomics

A whole blood sample will be collected for pharmacogenetic analysis as specified in Section 2, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable response to prexasertib and to investigate genetic variants thought to play a role in high-grade serous ovarian, primary peritoneal, or fallopian tube cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome

sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements. This study may analyze biomarkers relevant to prexasertib, the mechanism of action of prexasertib, the variable response to study drugs, immune function, tumor microenvironment, replication stress, angiogenesis, and pathways associated with high-grade serous ovarian, primary peritoneal, or fallopian tube cancer. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

The collection of a pretreatment tumor biopsy is required in Study JTJN for exploratory correlative biomarker research because archival tumor tissue obtained from biopsies collected years earlier might not accurately reflect the molecular alterations that may have occurred during the evolution of the disease (Olson et al. 2011). Both archived tissue and a pretreatment biopsy are collected in Study JTJN so that changes in potential markers that may be related to sensitivity to prexasertib can be assessed.

Testing to assess *BRCA* status will be completed at the Study JTJN central laboratory on newly obtained pretreatment biopsies or archival tissues accepted in place of newly obtained pretreatment biopsies (See Section 9.8.1). This testing is in addition to the local laboratory *BRCA* testing used to meet eligibility and for cohort assignment.

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.7, 9.8.1, and 9.8.2. The report containing the *BRCA* results from the local laboratory will be sent to the Study JTJN central laboratory.

9.8.1. Tissue Samples for Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 9.8. The following samples for biomarker research will be collected according to the sampling schedule in Section 2, where local regulations allow.

Collection of the following tumor tissue samples is **required** for all patients to participate in this study:

- a newly obtained biopsy specimen collected following determination of eligibility and before treatment (≤28 days before C1D1) (see Section 6.1, Inclusion Criterion [13]).

Note: a tumor tissue sample obtained from a prior biopsy may be permitted for the pretreatment sample after discussion and agreement between Lilly CRP / CRS and investigator if a patient has not received any therapies for the disease between the time biopsy was obtained to start of prexasertib treatment. This will be permitted only if a formalin-fixed paraffin-embedded (FFPE) tissue block is available (slides are not acceptable).

- an archived tumor sample collected at any time prior to discontinuation of last therapy for the disease, if available and not restricted by local regulations. Archived samples should be sent within 2 weeks of C1D1. It will not be considered a protocol deviation if this timeframe is not met, unless there are multiple occurrences at a single site.

Collection of the following tumor tissue sample(s) is **optional** for all patients participating in this study:

- additional optional biopsy samples may be requested at additional study time points, if warranted and agreed upon by the investigator and Lilly. If these additional samples are requested, they will be used to further investigate biomarkers that may help further characterize treatment response and resistance mechanisms, particularly in patients that have experienced clinical benefit from prexasertib.

The sponsor has a right to retain a portion of the submitted tissue, and archival blocks will be returned to the study site. Slides and tissue samples collected on study will not be returned.

Tumor tissue samples should be obtained using an excisional or core needle (minimum 18 gauge) biopsy. Cytological samples and fine-needle aspiration specimens are not acceptable.

Archival FFPE tumor tissue obtained from the primary tumor or metastatic site should be provided as a block or unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. The pathology report accompanying tissue may also be requested. The pathology report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit of the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables the use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of prexasertib or after prexasertib becomes commercially available.

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

9.8.2. Other Samples for Biomarker Research

The following samples for biomarker research will be collected according to the sampling schedule in Section 2, where local regulations allow:

- whole blood
- plasma.

A maximum of 5 samples may be collected at additional study time points, if warranted and agreed upon by the investigator and Lilly. All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of prexasertib or after prexasertib becomes commercially available. Technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, and/or multiplex assays may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

9.9. Health Economics

Health care resource use information related to the frequency of hospitalizations, emergency department (ED) visits, and small bowel obstruction (SBO) will be collected to support the safety assessment of prexasertib. Similarly, information on the following concomitant medications will also be collected: granulocyte or macrophage colony stimulating factor (G[M]-CSF), erythropoiesis stimulating agents (ESAs), transfusions (platelets and RBCs), antibiotics, antifungals, and analgesics (over-the-counter [OTC] and prescription).

9.10. Health Outcome Measures

Palliation and symptom control are central to the treatment of most patients with advanced ovarian cancer, given the limited opportunity for cure. The patient-reported outcome (PRO) assessments in this study will focus on two fundamental concepts: ovarian cancer-related symptoms and worst pain. These 2 focused dimensions are among the highest priority to advanced ovarian cancer patients, based on direct input from patients as well as gynecologic oncology specialists (Jensen et al. 2011 and Cella et al. 2003).

The impact of prexasertib on ovarian-cancer related symptoms will be measured via the National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy – Ovarian Symptom Index-18 (NFOSI-18) (Table JTJN.9). This instrument consists of 18 questions that comprise 3 domains: disease-related symptoms, treatment-related side effects, and functional well-being. It is a 5-level, Likert scale with the following response options: “not at all,” “a little bit,” “somewhat,” “quite a bit,” or “very much.” The recall period is 7 days. It was developed

based on input from patients with advanced ovarian cancer and gynecologic oncology experts in an effort to prioritize the most relevant symptoms experienced by patients (Jensen et al. 2011).

The impact of prexasertib on worst pain will be evaluated via the Worst Pain Numeric Rating Scale (NRS) (Table JTJN.9). The Worst Pain NRS was developed after similar principles seen within Effect of Cancer on Quality of Life (Cleeland 1991). The Worst Pain NRS is a single-item, subject-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "pain as bad as you can imagine."

Table JTJN.9. Instruments Used to Assess Patient-Reported Outcomes

Concept(s) of Interest	Instrument	Number of questions
Ovarian cancer-related symptoms	NCCN-FACT-FOSI-18	18
Worst pain	Worst Pain NRS	1

Abbreviations: NRS = numeric rating scale; NFOSI-18 = National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy-Ovarian Symptom Index-18.

Both instruments will be administered electronically via a handheld device. Only patients fluent in an available translation will complete the questionnaires. If a translation is not available, the patient is still permitted to enter the study; however, this scenario must first be communicated to the study team.

Data on OTC and prescription analgesic medications including dose, unit, frequency, and route of administration will be collected by site personnel at baseline and at every infusion day; it will be analyzed in conjunction with patient-reported data from the Worst Pain NRS. Any changes compared to the prior infusion will be recorded. Pain medication will be classified into medication categories, using the analgesic quantification algorithm (Chung et al. 2014).

10. Statistical Considerations

10.1. Sample Size Determination

The study employs a Bayesian adaptive design that may close enrollment in specific cohorts early based on the interim analysis results during the course of the trial. The study will initially enroll approximately 20 patients to each cohort and then a Bayesian model will be used to evaluate the posterior probability of activity for each cohort. A cohort will be closed if the posterior probability of activity is <20%. Subsequent interim analyses will be done to further evaluate the posterior probability of activity after additional patients are enrolled to each cohort.

The study will enroll up to approximately 180 patients in total. The sample size for each cohort will be dependent on the outcomes of the interim analyses. As cohorts are halted, new eligible patients will be allocated to the enrolling cohorts. As a result, the maximum sample size of a single cohort is approximately 120 patients (e.g., if enrollment to all but one of the cohorts is stopped after the first interim analysis). The posterior credible intervals of ORR when the observed ORR is in the range of 0-35% are summarized in Table JTJN.10. For illustrative purpose, the study drug will be considered active if ORR>25% and the uniform prior beta (1,1) is assumed in the Bayesian model. With the minimum sample size of N=20, the posterior probability of ORR exceeding 25% is <20% if the upper bound of 60% credible interval is <25%. With the maximum sample size of N=120, the posterior probability of ORR exceeding 25% is >80% if the lower bound of 60% credible interval is >25%.

The study efficacy may be monitored on an ongoing basis. The decision to close a cohort early may be made if results suggest the posterior probability of ORR exceeding the prespecified threshold of activity is well below 20%. For example, if the true response rate is 25%, the probability of observing 0 responses out of 6 patients is 17.8%. Under the uniform prior beta (1,1), the posterior probability that ORR is greater than 25% is only 13.3%. If the true response rate is 15%, the probability of observing 0 responses out of 10 patients is 19.7%. Under the same prior, the posterior probability that ORR is greater than 15% is only 16.7%.

Patients who have been assigned to a cohort but not treated may be replaced to ensure that a sufficient number of patients can be treated for each interim analysis.

Table JTJN.10. Observed ORR and 60% Credible Interval

N=20			N=120		
Number of Responders	Observed ORR	60% Credible Interval	Number of Responders	Observed ORR	60% Credible Interval
0	0%	1.1%-7.4%	0	0%	0.2%-1.3%
1	5%	3.9%-13.6%	6	5%	3.9%-7.4%
2	10%	7.4%-19.3%	12	10%	8.3%-12.9%
3	15%	11.1%-24.7%	18	15%	12.8%-18.3%
4	20%	15.1%-29.9%	24	20%	17.4%-23.5%
5	25%	19.1%-35.0%	30	25%	22.1-28.7%
6	30%	23.3%-40.0%	36	30%	26.8%-33.8%
7	35%	27.6%-44.9%	42	35%	31.6%-38.9%

Abbreviations: ORR=overall response rate.

10.2. Populations for Analyses

The following analysis sets will be defined for this study:

Intent-to-Treat (ITT) population: will include all enrolled patients (i.e., patients have been assigned to a cohort). The ITT population will be used for all baseline, efficacy and PRO analyses.

Per-Protocol population: will include all treated patients who do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be used for efficacy and PRO sensitivity analyses.

Safety population: will include all enrolled patients who have received ≥1 dose of prexasertib, regardless of their eligibility for the study. The safety population will be used for all dosing/exposure, and safety analyses.

Pharmacokinetic population: will include all enrolled patients who have received ≥1 full dose of prexasertib and have baseline and ≥1 postbaseline evaluable PK sample.

Biomarker population: will include all enrolled patients from whom a valid assay result has been obtained.

10.3. Statistical Analyses

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

The primary analysis will be conducted approximately 6 months after the last responder's first response date or approximately 1 year after the last patient has been enrolled, whichever occurs first. Additional updated analyses of efficacy and safety may be conducted at later times (approximately 6-12 months after the primary analysis) if deemed appropriate by the sponsor.

All CIs will be given at a 2-sided 95% level, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis

methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Efficacy Analyses

Overall response rate (ORR) is defined as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR) divided by the total number of enrolled patients per cohort. The ORR, with corresponding 95% exact CI, will be summarized for each cohort. The posterior estimates of ORR and posterior probability of ORR that is greater than the cutoff value will also be derived via a Bayesian model. See details in Section 10.3.4.

Disease control rate (DCR) is defined as the number of patients who achieve a best overall response of CR, PR or stable disease for ≥4 months divided by the total number of enrolled patients per cohort. The DCR, with corresponding 95% exact CI, will be summarized for each cohort.

CA-125 response is defined as ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for ≥28 days according to GCIG criteria. Patients must have a pretreatment sample that is ≥2 times the upper limit of the reference range and obtained within 2 weeks before starting the treatment. The response rate based on CA-125 will be summarized for each cohort.

Progression-free survival (PFS) is defined as the time from the first dose until the first occurrence of documented disease progression per RECIST 1.1, or death from any cause in the absence of progressive disease. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment (a detailed PFS event/censoring scheme is provided in SAP).

Duration of response (DoR) is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST 1.1, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. The DoR will be censored according to the same rules as PFS.

Overall survival (OS) is defined as the time from the first dose until death from any cause. If the patient is alive, lost to follow-up or withdrawn from study at the time of data analysis, OS data will be censored on the last date the patient is known to be alive.

For time-to-event variables, such as PFS, DoR and OS, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the curves, median time and 95% CI for each cohort.

10.3.2. Safety Analyses

All patients who receive ≥1 dose of prexasertib will be evaluated for safety and toxicity.

The Medical Dictionary for Regulatory Activities (MedDRA®) Version 20.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA LLT will be used in the treatment-

emergent computation. Adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within SOC. CTCAE version 4.0 will be used to report AE severity grades.

Safety analyses will include summaries of the following:

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

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as number and percentage of patients completing the study (patients who receive ≥1 dose of study drug and have ≥1 post-baseline tumor assessment), or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

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

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported by cohort using descriptive statistics. Other patient baseline characteristics will be summarized by cohort as deemed appropriate.

10.3.3.3. Treatment Compliance

Study treatment will be administered at the investigator site; therefore, treatment compliance is assured.

10.3.3.4. Extent of Exposure

The number of cycles received, cumulative dose, duration of therapy, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by cohort.

10.3.3.5. Concomitant Therapy

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

10.3.3.6. Post-Study-Treatment Therapy

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

10.3.3.7. Pharmacokinetic/Biomarker Analyses

A descriptive summary (for example, end of infusion, minimum plasma concentration [Cmin], and accumulation ratio) of the prexasertib PK data collected from all patients who receive ≥1 dose of prexasertib and have samples collected for analysis of prexasertib plasma concentration data will be provided across multiple cycles of treatment. The observed PK data will also be compared with the current prexasertib human population PK model (from Study JTJA) and included with the descriptive summary in the final clinical study report.

Mean population PK parameters for prexasertib in plasma (clearance, volume of distribution, and half-life) and inter-individual PK variability will also be computed for this study using nonlinear mixed-effect modelling implemented in NONMEM in order to describe the dose-concentration relationship in the target population. Covariate effects (such as age, BSA, prior therapies, hepatic/renal function, etc.) on the PK parameters of prexasertib will also be investigated.

Additional exploratory population based PK/pharmacodynamic analyses using nonlinear mixed effect modeling implemented in NONMEM may be performed (if the data warrant) that include the re-estimation of prexasertib PK parameters at the patient level to:

- evaluate the potential relationship between PK and biomarkers
- evaluate the relationship between exposure and response in terms of safety and efficacy (e.g., neutropenia, CA-125, change in tumor size, PFS, OS, etc.).

The population based PK and PK/ pharmacodynamic analyses will be reported in separate standalone reports for this study. The version of any software used for the analyses 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.

10.3.3.8. Biomarker Analyses

Summary statistics for biomarkers (e.g., *BRCA* status based on the central lab) will be reported. The association between biomarkers and clinical outcomes will be explored. Further exploratory analysis of biomarkers may be conducted if deemed necessary and a sufficient number of patients who express the biomarker(s) are available.

10.3.3.9. Health Outcome/Patient-Reported Outcomes

For each questionnaire, the compliance rate by cohort will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study). Compliance rates will be calculated for each questionnaire. Reasons for noncompliance will be collected only for assessments administered via the site-based device.

Home device:

For the worst pain NRS, missed assessments will not be considered a protocol deviation provided that in a given cycle all of the following criteria are met:

- ≥50% of the assessments are completed
- 4/7 assessments are completed in the 7 days preceding the first dose of each cycle, starting prior to cycle 2.

Collection of the Worst Pain NRS will be discontinued at progression, or after Day 28 of Cycle 6, whichever comes first.

Site-based device:

The target compliance threshold/completion rate for the NFOSI-18 and worst pain NRS is 100%; every missed assessment will be considered a protocol deviation.

Change from baseline for pre-specified concepts of interest (worst pain and ovarian cancer related symptoms) will be descriptively analyzed. Time to progression will be summarized for the pre-specified concepts of interest descriptively using the KM method. Data for cohorts that have stopped early may not be analyzed. Exploratory analyses may be conducted on other domains as well as individual items of the NFOSI-18. Data on analgesic consumption will be analyzed in conjunction with PRO data from the worst pain NRS. The association between PRO measures and efficacy outcomes will be evaluated. Further details will be defined in the SAP.

10.3.3.10. Healthcare Resource Utilization

Hospitalizations, transfusions, ED visits, SBO, and concomitant medications during study treatment will be summarized by cohort.

10.3.4. Interim Analyses

Interim analyses will be conducted regularly to evaluate closing enrollment early due to futility. For each cohort, the first futility interim analysis will be conducted after approximately 20 patients have been treated and completed ≥2 cycles or have discontinued before the first post-baseline tumor assessment. Although confirmation of response is not required to complete the interim analysis, the interim analysis may be potentially delayed to obtain confirmation of response. The futility rule is based on the posterior probability of activity via a Bayesian model. A cohort will be closed if the posterior probability is less than the prespecified futility threshold (e.g., 20% probability that ORR exceeds the prespecified threshold of activity). Borrowing of information across cohorts may be allowed, and the strength of borrowing may depend on the similarity among the cohorts. The prior distribution of response rate used in the model may be derived from the ongoing NCI-sponsored Phase 2 Study E001 (NCT02203513). The futility rules for each cohort are described as follows (ORR of 25% and 15% are considered the threshold of activity for Cohorts 1 – 3 and 4, respectively):

- Cohorts 1 to 3 (platinum-resistant): Pr (ORR>25%) <20%
- Cohort 4 (platinum-refractory): Pr (ORR>15%) <20%.

It is planned that enrollment can continue while interim analyses are conducted, but the sponsor may decide to pause the enrollment, if necessary. For the cohorts that can continue after the evaluation of the approximately first 20 patients, subsequent interim analyses will occur after approximately every 20 additional patients. The interval between interim analyses may be adjusted if deemed appropriate based on enrollment rates and available data. At each subsequent interim for each cohort, the posterior probability of response rate will be updated based on the available data and a higher futility threshold for the posterior probability may be adopted if deemed appropriate by the sponsor.

At each interim analysis, although the decision of whether to continue a cohort will be made primarily based on the futility rules, the totality of data (including safety, efficacy, PK, and biomarker data, if available) will also be reviewed and considered in the final decision made by the sponsor. The decision will be communicated to sites in writing if the sponsor determines a cohort is to be closed. The evaluation of efficacy may be based on all treated patients with centrally confirmed *BRCA* mutation status if available. Other interim analyses may be conducted if deemed appropriate by the sponsor. The interim analyses may be combined if they are expected to occur within a similar timeframe; interim analyses may also be combined with any prespecified safety review or annual reporting (such as an update to the IB or Development Safety Update Review, etc.).

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
***BRCA* negative**	refers to patients with *BRCA* test results negative for deleterious or suspected deleterious *BRCA* mutations.
***BRCA* positive**	refers to patients with *BRCA* test results positive for deleterious or suspected deleterious *BRCA* mutations
BUN	blood urea nitrogen
BSA	body surface area
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{min}	minimum plasma concentration
CNS	central nervous system
collection database	a computer database where clinical study data are entered and validated
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	clinical research scientist
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Term	Definition
DCR	disease control rate
DDR	DNA-damage response
DoR	duration of response
ECG	electrocardiogram
ED	emergency department
ECOG	Eastern Cooperative Oncology Group
Effective method of contraception	examples of effective methods of contraception include male or female condoms with spermicide, diaphragms with spermicide
end of study	date of the last visit or last scheduled procedure shown in the Schedule of Activities for the last patient
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported-outcome
ERB	ethical review board
EU	European Union
FFPE	formalin-fixed paraffin-embedded
FHD	first-in-human dosing
GCP	good clinical practice
G[M}-CSF	Granulocyte or macrophage colony stimulating factor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
Highly effective method of contraception	Contraception methods that have <1% failure rate. Examples include oral contraceptives implanted contraceptives or intrauterine devices
HGSOC	high-grade serous ovarian cancer
HIV	human immunodeficiency virus
HRR	homologous recombination repair
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form

Term	Definition
ICH	International Council for Harmonization (formerly the International Conference on Harmonization)
interim analysis	an analysis of clinical study data conducted before the final reporting database is created/locked
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ITT	intent-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive Web response system
LC-MS/MS	liquid chromatography–mass spectrometry/mass spectrometry
LLT	MedDRA Lower Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NFOSI-18	National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy-Ovarian Symptom Index-18
NRS	numeric rating scale
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PARP	Poly (ADP-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PLD	PEGylated liposomal doxorubicin
PR	partial response

Term	Definition
PS	performance status
PT	MedDRA Preferred Term
QTc	corrected QT interval
QTcF	QT interval using Fridericia's correction
randomize	the process of assigning patients to an experimental group on a random basis
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
rescreen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	statistical analysis plan
SBO	small bowel obstruction
SD	stable disease
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a study
SOC	MedDRA System Organ Class
study completion	Study completion occurs after the clinical trial database is locked and the final analysis of the primary and secondary endpoints have been performed., as determined by Lilly.
SUSARs	suspected unexpected serious adverse reactions
ULN	upper limit of normal
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,c]	**Clinical Chemistry**[a,b]
Leukocytes (WBC)	**Serum Concentrations of:**
Neutrophils[c]	Alanine aminotransferase (ALT)
Lymphocytes	Albumin
Monocytes	Alkaline phosphatase
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Bilirubin, direct
Erythrocytes (RBC)	Bilirubin, total
Hemoglobin (HGB)	Blood urea nitrogen (BUN) or blood urea
Hematocrit (HCT)	Calcium
Platelets (PLT)	Creatinine
	Glucose (random)
Urinalysis[c]	Potassium
Blood	Protein
Glucose	Sodium
	CA-125
Ketones	
pH	**Pregnancy Test**[c,d]
Protein	Urine pregnancy test
Specific gravity	Serum pregnancy test
Urine leukocyte esterase[e]	

Abbreviations: CRF = case report form; RBC = red blood cells; WBC = white blood cells.

[a] Treatment and enrollment decisions will be based on local laboratory results.
Note: Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[b] Central laboratory. In addition, local labs may be collected at investigator's discretion.

[c] Local or investigator-designated laboratory.

[d] For female patients of childbearing potential.

[e] Urine microscopy may be used in place of the urine leukocyte esterase assessment to test for the presence of WBC

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that the patient's participation is voluntary
- ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any study procedures and prior to the administration of prexasertib
- providing a copy of the signed ICF(s) to the patient and retaining a copy of the signed ICF in the site file
- 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 the patient's participation in the study.

Ethical Review

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

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

- protocol, protocol amendments, and relevant protocol addenda, and the current IB and updates during the course of the study
- ICFs
- other relevant documents (for example, curricula vitae advertisements).

Regulatory Considerations

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

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

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

Investigator Information

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct investigators and study coordinators. This session will give instruction on the protocol, completion of case report forms (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/evaluate CRF data using standard computer edits to detect errors in data collection
- conduct a quality review of the database.

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

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

Data Capture System

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

Electronic patient-reported outcome (ePRO) measures (for example, a rating scale) or other data reported directly by the patient (for example, daily dosing schedule, event diary) are entered into an ePRO instrument at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

If ePRO records are stored at a third-party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data collected via InForm, the clinical trial database, will be encoded by a third-party organization and stored electronically in the third-party organization's database system. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Validated data will be transferred from these systems to the Lilly data warehouse, using standard Lilly file transfer processes.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a daily dosing schedule, or an event diary.

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Sampling Schedule for Pharmacokinetics

Pharmacokinetic samples will be collected for prexasertib in this study. It is essential that the exact infusion start and stop times are recorded using actual clock readings. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. The PK blood samples should not be withdrawn from the same IV site as the drug infusion. Predose (that is, prior to infusion of prexasertib) sample should be taken as close as possible to the start of the infusion (<2 hours and ideally <10 minutes prior to start), and the exact clock reading should be recorded. Postdose (that is, end of infusion) PK samples should be drawn immediately after end of infusion (range = after end of infusion +15 minutes), and exact clock reading should be recorded. Although every effort to should be made to obtain the samples in the timeframes described above and noted below in the table, PK samples taken outside the specified windows will not be considered a protocol deviation. Similarly, a missed PK sample (i.e., not collected at all or collected improperly) will not be considered a protocol deviation.

Prexasertib Pharmacokinetic Sampling Schedule

Sample Series	Cycle	Day	Prexasertib PK Sampling Times[a]
1	1	1	End of prexasertib infusion (+15 min)[b]
2	1	1	1-2 hours following end of prexasertib infusion[b]
3	2	1	Prior to start of prexasertib infusion
4	2	1	End of prexasertib infusion (+15 min)[b]
5	2	1	1-2 hours following end of prexasertib infusion[b]
6	4	1	End of prexasertib infusion (+15 min)[b]
7	4	1	1-2 hours following end of prexasertib infusion[b]
8	6	1	End of prexasertib infusion (+15 min)[b]
9	6	1	1-2 hours following end of prexasertib infusion[b]

Abbreviations: min = minute; PK = pharmacokinetic.

[a] The sampling schedule is relative to the prexasertib infusion times as noted in the table. The actual timing of the samples may be adjusted at the discretion of Lilly and the investigators as PK data become available.

[b] PK samples that are collected after the start of the infusion will need to be drawn from a clean site, unless an adequately flushed vascular access catheter is the only option (record in CRF if the case).

Appendix 5. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]
- Hemoglobin (HGB)
- Hematocrit (HCT)
- Erythrocytes (RBC)
- Leukocytes (WBC)
- Neutrophils[b]
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets (PLT)

Hepatic Chemistry[a]
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma-glutamyl transferase (GGT)
- Creatine phosphokinase (CPK)

Haptoglobin[a]

Hepatic Coagulation[a]
- Prothrombin time (PT)
- Prothrombin time, INR

Hepatic Serologies[a,c]
- Hepatitis A antibody, total
- Hepatitis A antibody, IgM
- Hepatitis B surface antigen
- Hepatitis B surface antibody
- Hepatitis B Core antibody
- Hepatitis C antibody
- Hepatitis E antibody, IgG
- Hepatitis E antibody, IgM

Recommended Autoimmune Serology[a]
- Anti-nuclear antibody
- Anti-smooth muscle antibody
- Anti-actin antibody

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

[a] Assayed by Lilly-designated laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

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

Appendix 6. Creatinine Clearance Formula

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

Cockcroft-Gault prediction of creatinine clearance from serum creatinine (1976)

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Source: Cockcroft and Gault 1976.

Appendix 7. Protocol Amendment I4D-MC-JTJN(b) Summary
A Phase 2 Study of Prexasertib in Platinum-Resistant or Refractory Recurrent Ovarian Cancer

Overview

Protocol I4D-MC-JTJN (A Phase 2 Study of Prexasertib in Platinum-Resistant or Refractory Recurrent Ovarian Cancer) has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Section 2 Table JTJN.1. Schedule of Inclusion and Baseline Assessments: clarified that Cohort 4 does not need local *BRCA* results
- Section 2 Post-Study Treatment Follow-Up Schedule of Activities: differentiated follow-up intervals for patients who have discontinued without progression versus with progression
- Section 6.1 Inclusion Criteria: inclusion [3] clarifies what is considered as a line of therapy
- Section 7.4 Table JTJN.7: included Grade 2 for consideration in thrombocytopenia; specified when treatment should be delayed for anemia
- Section 10.2: included definition for per-protocol population
- Section 10.3: modified when to conduct primary analysis and additional updated analyses of efficacy and safety, based on a recommendation from the FDA
- Section 10.3.3.4 Extent of Exposure: clarified definition with additional criteria
- Section 10.3.4 Interim Analyses: defined threshold of activity for each cohort

Revised Protocol Sections

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

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

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

Table JTJN.11. Schedule of Inclusion and Baseline Assessments

Procedure Category	Procedure				Comments
Study Entry/ Enrollment	…				
	Cohorts 1-3: Confirm availability of local *BRCA* result		X		Data from a blood or tissue based test are acceptable (i.e., either germline or somatic tests are acceptable). The test may have occurred prior to consent. If both somatic and germline status are known, the somatic status should be used for cohort assignment. Patients in Cohort 4 do not need to have local *BRCA* results.

Post-Study-Treatment Follow-Up Schedule of Activities

…

[a] Period begins the day after the decision that the patient will discontinue study treatment is made and lasts approximately 30 days.

[b] For patients who have discontinued without progression, follow-up should occur every 60 days. For patients with progression, the follow-up interval is 90 days for survival assessments. Period begins 1 day after short-term follow-up period is completed and continues until death, study withdrawal, or the patient is lost to follow-up.

6.1 Inclusion Criteria

[3] …

Note for Cohorts 1 and 2: Each line of therapy is preceded by evidence of clinical or radiographic disease progression (initial therapy is considered the first line). Switch of an agent within the same drug class (for example, cisplatin to carboplatin) within a regimen to manage toxicity does not define the start of a new line of therapy. Similarly, maintenance therapy (continuation maintenance or switch maintenance) will not be considered a new line of treatment. ~~Neither adjuvant therapy nor hormonal therapy are considered lines of therapy.~~ Hormonal therapy is not considered a line of therapy. All adjuvant therapy should be considered as a line of therapy.

Table JTJN.12. Dose Adjustments and Delays

Toxicity	CTCAE Grade	Action	Dose Adjustments and Considerations
…			
Thrombocytopenia	Grades 2, 3 or Grade 4	Delay treatment until ≤Grade 1 (≥75/mm^3)	Investigator discretion
Anemia	Grade 3 or Grade 4	Consider RBC transfusion or EPO (if consistent with institutional guidelines). ~~Treatment may proceed or be delayed at the discretion of the investigator.~~ Delay treatment until ≤Grade 2 (≥8 g/dL)	Investigator discretion
…			

10.2. Populations for Analyses

The following analysis sets will be defined for this study:

…

Per-Protocol population: will include all treated patients who do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be used for efficacy and PRO sensitivity analyses.

10.3. Statistical Analyses

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

The primary analysis ~~of the primary endpoint of ORR will be performed when all enrolled patients have completed ≥2 months of follow-up and/or investigator-assessed best response assessments have been completed for all patients. All secondary endpoints will be evaluated at this time.~~ will be conducted approximately 6 months after the last responder's first response date or approximately 1 year after the last patient has been enrolled, whichever occurs first. Additional updated analyses of efficacy and safety may be conducted at later times (approximately ~~10-18~~ 6-12 months after ~~last patient is enrolled~~ the primary analysis) if deemed appropriate by the sponsor.

10.3.3.4 Extent of Exposure

The number of cycles received, cumulative dose, duration of therapy, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by cohort.

10.3.4 Interim Analyses

Interim analyses will be conducted regularly to evaluate closing enrollment early due to futility. For each cohort, the first futility interim analysis will be conducted after approximately 20 patients have been treated and completed ≥2 cycles or have discontinued before the first post-baseline tumor assessment. Although confirmation of response is not required to complete the interim analysis, the interim analysis may be potentially delayed to obtain confirmation of response. The futility rule is based on the posterior probability of activity via a Bayesian model. A cohort will be closed if the posterior probability is less than the prespecified futility threshold (e.g., 20% probability that ORR exceeds the prespecified threshold of activity). Borrowing of information across cohorts may be allowed, and the strength of borrowing may depend on the similarity among the cohorts. The prior distribution of response rate used in the model ~~will be~~ may be derived from the ongoing NCI-sponsored Phase 2 Study E001 (NCT02203513). The futility rules for each cohort are described as follows (ORR of 25% and 15% are considered the threshold of activity for Cohorts 1 – 3 and 4, respectively):

- Cohorts 1 to 3 (platinum-resistant): Pr (ORR>25%) <20%
- Cohort 4 (platinum-refractory): Pr (ORR>15%) <20%.

It is planned that enrollment can continue while interim analyses are conducted, but the sponsor may decide to pause the enrollment, if necessary. For the cohorts that can continue after the evaluation of the approximately first 20 patients, subsequent interim analyses will occur after approximately every 20 additional patients. The interval between interim analyses may be adjusted if deemed appropriate based on enrollment rates and available data. At each subsequent interim for each cohort, the posterior probability of response rate will be updated based on the available data and a higher futility threshold for the posterior probability may be adopted if deemed appropriate by the sponsor~~(e.g., 40% probability ORR exceeds the prespecified threshold of activity)~~.

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