Single-Arm, Open-Label, Phase II Study of LY3023414 for the Treatment of Recurrent or Persistent Endometrial Cancer

MSK PROTOCOL

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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	Zoe Goldberg, MD	Medicine
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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan, NY	All Protocol Activities
Basking Ridge, NJ	All Protocol Activities
Commack, NY	All Protocol Activities
Monmouth, NJ	All Protocol Activities
Nassau, NY	All Protocol Activities
Westchester, NY	All Protocol Activities

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1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Patients with recurrent or persistent endometrial adenocarcinoma with the following histologic epithelial cell types are eligible: endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.), mucinous adenocarcinoma, squamous cell carcinoma, transitional cell carcinoma, and carcinosarcoma.

Patients must have had at least one but no more than four prior chemotherapeutic regimens for management of endometrial carcinoma (including adjuvant chemotherapy). Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy, and chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen.

Patients must have PI3K pathway activation defined as EITHER of the following:

1. Genomic alteration resulting in loss of PTEN function including a) whole or partial gene deletion, frame shift mutations, or non-sense mutations. Missense mutations in PTEN will not be considered qualifying.
2. A previously characterized activating mutation in any component of the pathway including: PIK3CA, AKT1, PIK3R1, PIK3R2, mTOR

Patients must also not have a known concurrent activating RAS/RAF mutation or loss of function alternation in NF1 of NF2 resulting in MAP kinase pathway activation. Any mutational profiling performed in a CLIA laboratory either as routine standard of care or as part of a dedicating genomic profiling study such as MSKCC IRB# 12-245 will be accepted.

LY3023414 will be administered orally at the Recommended Phase 2 Dose (RP2D) of 200mg BID on a continuous basis. One cycle equals 3 weeks. Treatment will continue until progression, intolerance, or withdrawal, study completion, or study termination. Tumor evaluations will occur every 2 cycles.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 PRIMARY OBJECTIVES

To assess the activity of LY3023414 in patients with PI3K pathway activated recurrent or persistent endometrial cancer as measured by the best overall response rate as determined by RECIST 1.1.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:

1. To determine the clinical benefit rate (CBR) of LY3023414 therapy, defined as the percentage of patients with complete response (CR) + partial response (PR) + stable disease (SD) ≥12 weeks from the start of treatment.
2. To determine progression free survival (PFS), defined as the duration of time from start of treatment to time of recurrence, progression, or death due to any cause, whichever occurs first. .
3. To determine overall survival (OS), defined as the duration of time from start of treatment until the date of death due to any cause.
4. To determine the duration of response (DOR) of LY3023414 therapy, defined as the time from which measurement criteria are met for CR or PR (whichever status is recorded first) until the first date of documented disease progression.
5. To assess the safety profile and tolerability of LY3023414 therapy in patients with PI3K activated recurrent/persistent endometrial cancer.

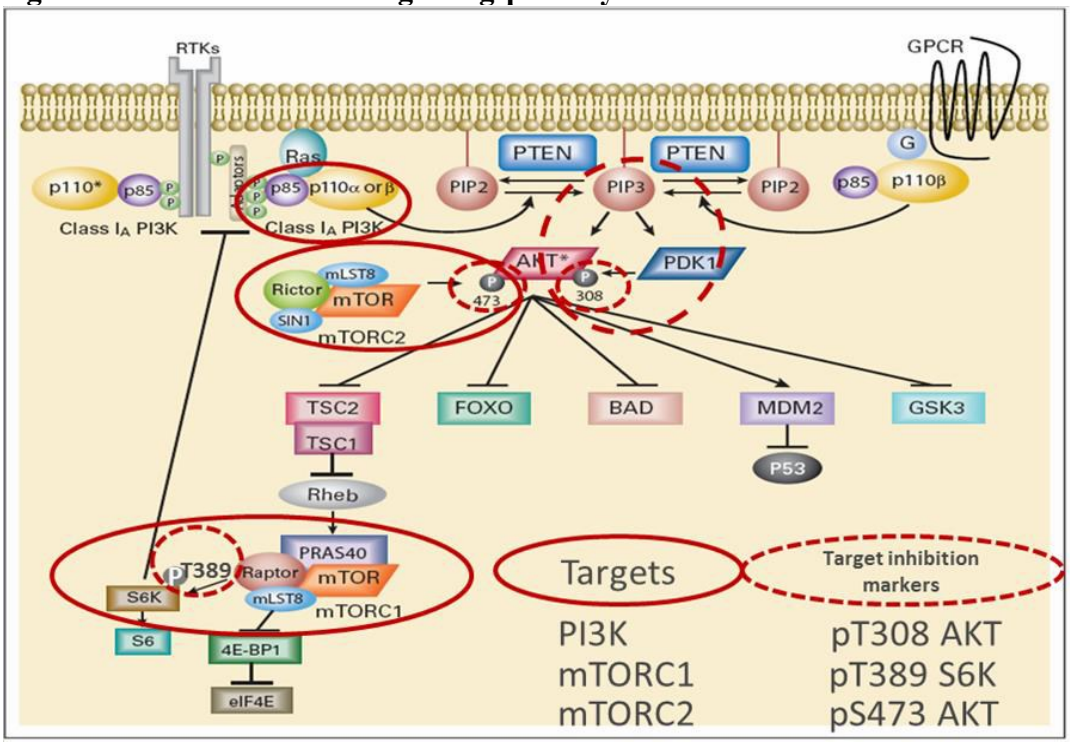
2.3 EXPLORATORY OBJECTIVES

1. For patients who have not already had their tumors molecularly profiled using the MSK-IMPACT platform, pretreatment archival tumor tissue will be obtained for this purpose. Consent for this testing, to be performed in the CLIA laboratory, will be obtained through a companion study MSKCC IRB# 12-245.
2. Serial pre-, on- and post-treatment blood samples will be collected for cell-free tumor DNA analysis and the results descriptively correlated to clinical outcome.
3. Patients who respond to therapy and then progress will be offered consent to MSKCC IRB# 12-245 Part B in order to obtain post-progression material for molecular profiling in order to determine the mechanism(s) underlying acquired resistance.

3.0 BACKGROUND AND RATIONALE

The phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway has been reported as activated in >70% of human cancers and has emerged as a promising target for anticancer therapies. PI3K/mTOR signaling plays a central role in regulating physiological processes such as growth, survival, proliferation, and metabolism, and in the development of malignant disease (Bjornsti and Houghton 2004; Samuels and Ericson 2006).

Figure 1. PI3K/mTOR signaling pathway in cancer.



Source: Adapted from Courtney et al 2010.

PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3, 4, 5-trisphosphate, a lipid second messenger, which binds the serine/threonine kinase AKT, and its activating kinase, 3-phosphoinositide-dependent kinase 1 (PDK-1) (Corvera and Czech 1998), which partially activates AKT. AKT controls cell survival, proliferation, and invasion via numerous downstream targets, including mTOR (Stahl et al. 2004; Cheng et al. 2005; Meier et al. 2005). The mTOR kinase exists in 2 complexes, mTORC1 and mTORC2. The mTORC1 complex is activated downstream of PI3K/AKT signaling, stimulates protein translation by activating p70S6 kinase and eIF4E, and is disrupted by rapamycin and analogues (rapalogs). The mTORC2 complex completes the activation of AKT by phosphorylating AKT at the critical serine-473 residue. Pharmacological inhibition of PI3K/mTOR blocks tumor growth and survival signaling in a variety of different tumor xenograft models (Courtney et al. 2010). Inhibition of PI3K/mTOR also blocks the metabolic actions of insulin, including glucose transport and glycogen synthesis, resulting in increased blood glucose and compensatory release of insulin (and C-peptide) from pancreatic cells (Katso et al. 2001). Hence, it is important to evaluate in the clinic the adverse events (AEs) on such metabolic pathways when novel PI3K/mTOR inhibitors are being investigated.

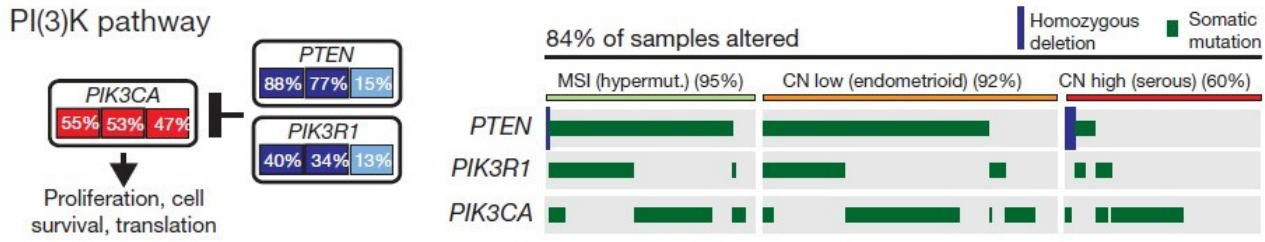
Targeting the PI3K/mTOR pathway represents an attractive strategy in patients with tumor types harboring an activating alteration of the PI3K/mTOR signaling pathway. There are several mechanisms that lead to aberrant activation of this pathway including mutations of growth factor receptors, PIK3CA, or loss of the tumor suppressor, PTEN (Stambolic et al. 1998; Courtney et al. 2010). In addition, PI3K amplification and activating mutations in AKT, PDK1, RAS, tuberous sclerosis protein 1 and 2 (TSC1/2), and mTOR have been identified as mechanisms of PI3K/mTOR pathway activation (Samuels and Ericson 2006). Frequent activating aberrations of PI3K/mTOR signaling have been reported amongst others for breast cancer, mesothelioma, non-

small cell lung cancer (NSCLC), and endometrial cancers (Opitz et al. 2008; Courtney et al. 2010; Miller et al. 2011; Varghese et al. 2011). To date, no dual PI3K/mTOR inhibitor has been approved for therapy. However, several molecules are currently under investigation in Phase 1 and 2 clinical trials as monotherapy or in combination with standard of care therapies. Monotherapy with PI3K/mTOR inhibitors is of interest in tumor types with a particular high incidence of aberrant PI3K pathway activation.

Endometrial Carcinoma Background

Endometrial cancer is the second leading cause of death from gynecologic cancer with an estimated 8,590 women dying in the United Stated annually (Siegel et al. 2014)). Carboplatin and paclitaxel is the standard first-line treatment regimen (Miller et al. 2012) for advanced recurrent or persistent disease. There are no FDA approved treatments for patients who progress on first line therapy. Response rates for commonly used off label therapies including liposomal doxorubicin, topotecan, weekly paclitaxel, and bevacizumab range between approximately 0-10% (Muggia et al. 2002; Miller et al. 2002; Lincoln et al. 2003; Aghajanian et al. 2011). As a result, there is tremendous opportunity for the development of rationally therapeutic agents in the recurrent/persistent endometrial cancer space. Detailed genomic characterization of endometrial cancer has identified the phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway as central to endometrial cancer pathogenesis. The TCGA found the PI3K pathway to be activated in 84% of primary surgical endometrial cancer specimens (Figure 2, Cancer Genome Atlas Research Network, 2013).

Figure 2: PI3K Pathway Activation in Endometrial Cancer



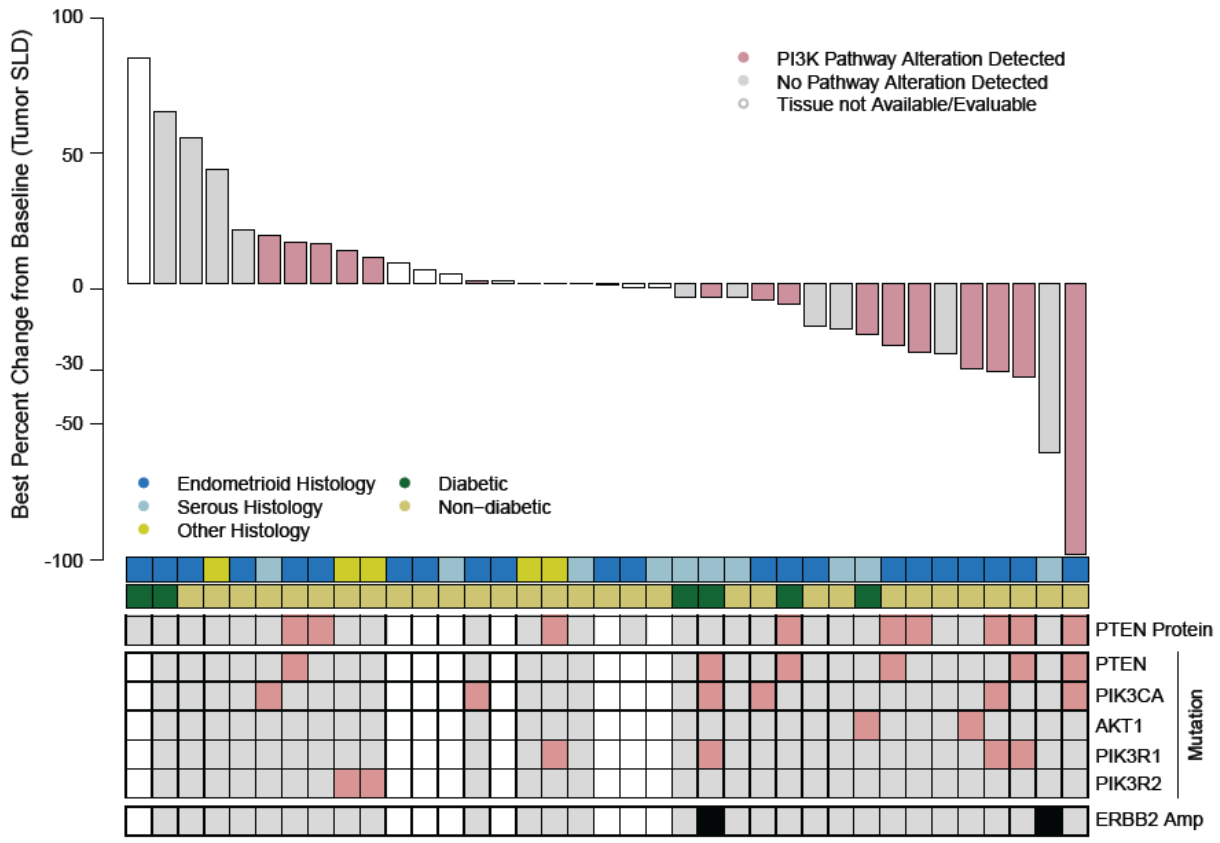
Source: Cancer Genome Atlas Research Network, Nature 2013

Inactivation of the PTEN tumor-suppressor gene is the most common genetic defect in endometrial cancers and is present in 30−83% of tumors (Mutter et al. 2000; Oda et al. 2005). Mutations in the catalytic p110α subunit of PI3K are found in approximately 30-40% of endometrial cancers, and these mutations are most frequent in tumors that also bear phosphatase and tensin homolog (PTEN) mutations (Hayes et al. 2006; Salvesen et al. 2009). With regard to endometrial cancer subtypes, PIK3CA mutations are found in 15% of serous cancers (Hayes et al. 2009). Somatic mutations in the PIK3R1 have been found in 43% of endometrioid (Type I) endometrial cancer and 12% of non-endometrioid (Type II) endometrial cancer (Cheung et al. 2011; Urick et al. 2011). The PIK3R2 (p85α is also frequently mutated (Cheung et al. 2011). Mutant p85 α proteins are believed to activate the PI3K pathway as five of seven different p85 α mutants expressed in cell lines were associated with increased p-AKT levels compared to cells expressing wild- type p85α (Urick et al. 2011).

Dual PI3K/mTOR Inhibition Endometrial Cancer:

The results of a single arm phase II study of GDC-0980 were presented at the ASCO 2014 Annual Meeting (Makker et al. 2014, Abstract 5513). MSKCC lead enrollment to this multicenter study. Anti-tumor activity was observed in a high proportion of evaluation subjects with the majority of subjects with tumor regression harboring an identifiable mutation in PTEN, PIK3CA, AKT1, PIK3R1, or PIK3R (Figure 3).

Figure 3: Waterfall Plot and Biomarker Correlates of GDC-0980 in Endometrial Cancer



Source: ASCO 2014 Annual Meeting, Makker V, Abstract 5513

The rate of PI3K pathway activation among all enrolled subjects was 67%, approximately 20% lower than the rate reported by the TCGA series that includes a high proportion of patients who are likely to be surgically cured. Moreover, 7/56 (12.5%) of patients harbored concurrent KRAS mutations which would be predicted to confer resistance to dual PI3K/mTOR inhibition. The observations of a lower rate of PI3K pathway activation in recurrent endometrial cancer patients as well as concurrent KRAS mutations support the need to prospectively screen patients with a comprehensive genomic assay prior to clinical trial enrollment. Despite a high proportion of objective responses in evaluable patients, clinical benefit to GDC-0980 in this study was limited by poor tolerability. Rates of Grade ≥3 hyperglycemia were 9/13 (69%) and 15/43 (35%) in

diabetics and non-diabetics, respectively. As a result, the median duration of treatment for diabetics on study was only 36 days. Poorly crafted eligibility criteria likely played an important role in this outcome as diabetics with an HgA1c $\leq$ 8.5 g/dL were permitted to enroll. Of note, the frequency of severe hyperglycemia observed to date in the first-in-human Phase I study of LY3023414 has been much lower than GDC-0980 (see Investigational Brochure), suggesting LY3023414 will be better tolerated in this patient population.

Tumor Genetic Profiling at MSKCC

In January 2014 MSKCC received New York State CLIA-approval for a next generation Ilumina HiSeq exon-capture based platform ("MSK-IMPACT") which offers complete coverage of 341 cancers related genes and can identify base substitutions, indels, copy number alterations and select translocations (see gene list in supplied Appendix for IRB 12-245). Importantly, MSK-IMPACT covers all genes relevant to the PI3K pathway including PTEN, PIK3CA, PIK3R1, PIK3R2, AKT1, and mTOR as well as genomic alterations which would be expected to confirm resistance to PIK3CA/mTOR inhibitors including those in the MAPK pathway (RAS, RAF, MAP2K, NF1, NF2). All metastatic endometrial cancers are consented to an IRB-approved center wide genomic profiling protocol and screened via the CLIA-approved MSK-IMPACT and the results entered into the medical record. As a result, MSKCC is uniquely positioned to prospectively identify PI3K pathway activated endometrial cancer patients early in their disease course.

LY3023414 Summary

LY3023414 is an orally available, potent selective inhibitor of the class I PI3K isoforms, mTOR, and DNA-PK. LY3023414 binds the adenosine triphosphate (ATP) active site of PI3K to competitively inhibit phosphorylation of phosphatidylinositol-4, 5-bisphosphate at low nanomolar concentrations. LY3023414 has demonstrated inhibitory activity against PI3K and mTOR, antiproliferative activity, and cell-cycle effects in cultured cancer cells. LY3023414 achieves good oral exposure and displayed in vivo target inhibition in xenograft tumors, as well as efficacy in 3 tumor xenograft models, a transgenic mutant PI3Kα-driven leukemia model, and multiple patient derived xenografts, including mesothelioma and squamous non-small cell lung cancer (NSCLC). In the transgenic mutant PI3Kα-driven leukemia model, combination studies with LY3023414 and standard of care agents, demonstrated synergy with LY3023414 plus gemcitabine or paclitaxel. Combinations of LY3023414 with rapamycin were synergistic in U87MG and NCI-H1975 xenograft models.

Safety Pharmacology

Nonclinical Toxicology

LY3023414 was evaluated in nonclinical toxicology studies up to 1 month in duration using daily oral dosing in rats and dogs to characterize the toxicity. Based on results from nonclinical studies in the rat and the dog, toxicities patients may experience include (but are not limited to) gastrointestinal toxicity, bone marrow and lymphoid organ toxicity (decreases in lymphocytes), and sores/scabbing of the skin. Pharmacologic effects of PI3K/mTOR inhibition related to glucose metabolism have also been observed, including hyperinsulinemia, hyperglycemia, and QT interval prolongation in nonclinical studies. In a rat embryo-fetal developmental pilot study of

LY3023414, embryo-fetal lethality was seen along with an increase in fetal and litter incidence of external, visceral, and skeletal malformations.

For additional details on nonclinical toxicology data, see Section 5.2.1 of the Investigator's Brochure (IB).

Nonclinical Efficacy Pharmacology Summary

LY3023414 is a potent selective inhibitor of the class I PI3K isoforms mTOR and DNA-PK, with selectivity in kinase enzyme assays as an ATP competitive inhibitor of PI3Kα (Ki 8.5nM). LY3023414 demonstrated inhibitory activity against PI3K/mTOR pathway targets *in vitro* and *in vivo* as measured by phosphoprotein levels from cultured cells and tumor xenografts. LY3023414 showed antiproliferative and cell-cycle arresting effects in cultured cancer cells, and anti-angiogenesis activity via inhibition of in vitro vascular cord formation. LY3023414 has excellent solubility and oral bioavailability across a wide pH range, allowing for simple suspension formulations to be used for oral administration in nude mice. In xenograft tumor models, LY3023414 demonstrated dose- and time-dependent target inhibition, as well as antitumor efficacy in a wide range of tumor models (including renal cancer and non-small cell lung carcinoma [NSCLC]). The mouse pharmacokinetic (PK)/pharmacodynamics (PDx) model indicates a direct inhibition of downstream target phosphoproteins (such as, phospho Akt [pAkt], phospho 70S6K [p70S6K]). LY3023414 has potential for combination with standard of care agents to produce synergistic effects in cell culture and *in vivo* xenograft models.

Nonclinical Pharmacokinetics/Pharmacodynamics

The nonclinical PK profile of LY3023414 was characterized in mice, rats, and dogs. Data from these studies were used to predict human PK via allometric scaling. The predicted mean human clearance (CL) is 16.3 L/h (90% CI: 13.5 to 19.9) and the predicted central and peripheral volumes of distribution (V) are 61 L (90% CI: 53 to 70) and 1200 L (90% CI: 0 to 12,000), respectively. The predicted effective half-life ($t_{1/2}$) in humans is 2.6 hours with a terminal elimination $t_{1/2}$ of 600 hours, reflecting <8% of the dose. The predicted bioavailability (74%) allows for once daily (QD) or twice daily (BID) oral dosing. Bioavailability was constant across preclinical species tested, and the predicted efficacious doses in humans are below the predicted maximum absorbable dose.

The *in vitro* metabolism of LY3023414 was evaluated in rat, mouse, dog, and human liver microsomes and in cryopreserved hepatocytes. LY3023414 was the major *in vitro* component observed in each species, based on the mass spectrometry (MS) signal. Metabolism was primarily oxidative (O-desmethyl, N-desmethyl, and parent + O) in both animals and humans. No Phase II conjugates were identified.

Preliminary studies were conducted to evaluate *in vivo* metabolism of LY3023414 in rat plasma, bile, urine, and feces and in dog plasma. *In vivo* LY3023414 appears to be predominantly cleared by oxidative metabolism as determined by the major metabolites detected in rat bile, urine, and feces. LY3023414 was the largest circulating entity in both rat and dog plasma along with oxidative and conjugative metabolites. The *in vivo* results qualitatively correlated well with the *in vitro* results.

Ongoing Studies and Clinical Safety

One Phase I study I6A-MC-CBBA (Study CBBA) of LY3023414 is ongoing. Study CBBA is a multicenter, nonrandomized, open-label, First-in-Human dose escalation study followed by cohort expansion of oral LY3023414 in patients with advanced and/or metastatic cancer. Study CBBA was designed to evaluate the safety and tolerability of LY3023414 administered orally over 21 days (one cycle).

As of 26 September 2014, a total of 47 patients have received LY3023414 in the first-human-dose Study CBBA. Of these patients, a total of 40 patients (83%) experienced at least 1 possibly study drug-related, treatment-emergent adverse event (TEAE). The most common possibly LY3023414-related AEs reported in at least 10% of patients included nausea (37.5%), fatigue (31.3%), vomiting (27.1%), diarrhea (16.7%), decreased appetite (14.6%), anemia (14.6%), stomatitis (12.5%), and asthenia 10.4%). Most of these events were graded as mild or moderate by the investigators.

Dose-limiting toxicities for LY3023414 QD dosing have been reported at 450 mg LY3023414 in 3 out of 3 patients, including 1 case each of thrombocytopenia (Grade 4), hypotension (Grade 3), and hyperkalemia (Grade 3). Therefore, a dose of 325 mg LY3023414 was defined as the maximum tolerated dose (MTD) for QD dosing. For BID dosing, Dose-limiting toxicities (DLTs) were observed in 3 out of 4 patients at the 250 mg BID LY3023414 dose in the form of hypophosphatemia (Grade 4), fatigue, and mucositis (Grade 3; all n = 1). At the next lower dose level of 200 mg BID, 1 out of 6 patients experienced a DLT in the form of nausea (Grade 2; n = 1). Therefore, a dose of 200 mg LY3023414 was defined as the MTD for BID dosing.

At doses up to and including the MTD for QD and BID dosing (n = 31 patients), no study drug related Grade 4 AEs have been reported. Six possibly related Grade 3 AEs have been observed in those patients, including 1 case each of fatigue, hyperglycemia, hypokalemia, neutropenia, hypomagnesemia, and anemia (anemia occurred in a patient entering the study with Grade 2 anemia).

Initial clinical LY3023414 pharmacokinetic/pharmacodynamic (PK/PD) data showed that LY3023414 maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{∞}) increased approximately dose-proportionally from 20 to 325 mg QD (that is within the QD dose range determined to be safe). However, the C_{max} and AUC_{∞} increase was greater than dose proportional at 450 mg QD (i.e., that is at the dose exceeding the MTD). LY3023414 PK data following repeated BID dosing (dose range of 150 to 250 mg BID) were consistent with PK data following 20 to 325 mg QD. The oral clearance (CL/F) ranged from approximately 77 to 130 L/hour across the 20 to 325 mg dose range associated with an oral volume of distribution (V/F) ranging from 185 to 315 L in that same dose range. This clearance and volume lead to mean half-life ($t_{1/2}$) of 2.07 hours (coefficient of variation [CV] = 45%, n = 35), consistent with the prediction.

The relative contribution of microsomal CYP-mediated clearance of LY3023414 was studied in vitro using human liver microsomes. Based on a substrate depletion approach, CYP 3A4 and CYP1A2 are responsible for 82% and 18% of hepatic CYP-mediated clearance of LY3023414, respectively. No in-vivo data are yet available.

The recent data from study CBBA indicate that LY3023414 is a weak inhibitor of CYP3A4. Concomitant administration of LY3023414 and midazolam lead to increase in midazolam exposure (fold increase: mean 1.459 [CV 30.5 %] [90% CI 1.21 – 1.76]). Hence LY3023414 may lead to increase in exposure of CYP3A4 substrate. Considering that CYP2C8, not CYP3A4, is the most relevant and major enzyme responsible for enzalutamide clearance and that the inhibitory effect of LY3023414 on CYP3A4 is weak, it is not anticipated that enzalutamide exposure will be significantly increased (i.e. > 1.5 fold change) after coadministration with LY3023414.

Biomarker assessment demonstrated target inhibition as measured by p4EBP1 inhibition in peripheral blood mononuclear cells (PBMC) at LY3023414 dose levels greater or equal to 150 mg QD in a dose related manner. With respect to anti-tumor activity, clinical benefit was observed in patients treated on both schedules of LY3023414, including 1 patient with a confirmed partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) and 10 additional patients (26.3%) who demonstrated a decrease in their tumor target lesion as best response to LY3023414 monotherapy in the dose-escalation part of Study CBBA.

Based on the safety and tolerability, pharmacokinetic/pharmacodynamic (PK/PD), and preliminary activity data outlined above, the recommended dose for LY3023414 is 200 mg BID.

Based on results from this study, the safety data for this protocol has been updated. One patient was treated until Cycle 2 Day 10 when she presented with coronavirus, unrelated to protocol treatment. Following this, on Cycle 2 Day 16, the patient was admitted with grade 4 fever, grade 3 hypokalemia and acute decline in mental status – treatment with intravenous Vancomycin, Zosyn, and Acyclovir was started. Grade 3 hypokalemia was attributed to drug versus secondary to malignancy. Throughout the hospitalization, patient was continuously febrile (grade 1-2) for 7 days, intermittently febrile for 2 days, and afebrile for the remaining 12 days until discharge. Treatment included intravenous Vancomycin, Ceftriaxone, Ampicillin, Acyclovir, and Doxycycline. Infectious disease workup, urine and blood cultures, and cerebrospinal fluid were all negative.

During the hospitalization, CPK increased to Grade 4 and normalized within a week. While the exact source was not clear, it was felt to possibly be secondary to the persistent fevers. Patient subsequently developed grade 4 hyponatremia was felt to be secondary to SIADH versus cerebral salt wasting, and unlikely secondary to trial drug. Throughout the hospitalization, platelets count continued to decline and on the last day in the hospital, thrombocytopenia was grade 4. Hemolytic Uremic Syndrome /TTP and hemolysis were ruled out. Etiology was felt secondary to infection, cancer or possibly trial drug related.
New onset of grade 3 hypertension occurred while hospitalized as well and was felt to be possibly related to her illness syndrome.

Etiology of mental status change remained unclear. The neurology team was consulted. EEG was negative for seizure. MRI of the brain was positive for white matter changes raising concerning for

a demyelinating process such as Multiple Sclerosis, but overall this did not explain patient's clinical presentation. EMG and Anti N-methyl-D-aspartate were negative and no evidence of neuroleptic malignant syndrome was found. Patient was treated with empiric thymine course and finally with 3 doses of Methylprednisolone, which ultimately led to resolution of the fevers and improvement in mental status. Based on all tests and results, the source of fevers and altered mental status was felt to be paraneoplastic versus virus-mediated versus possibly related to trial drug.

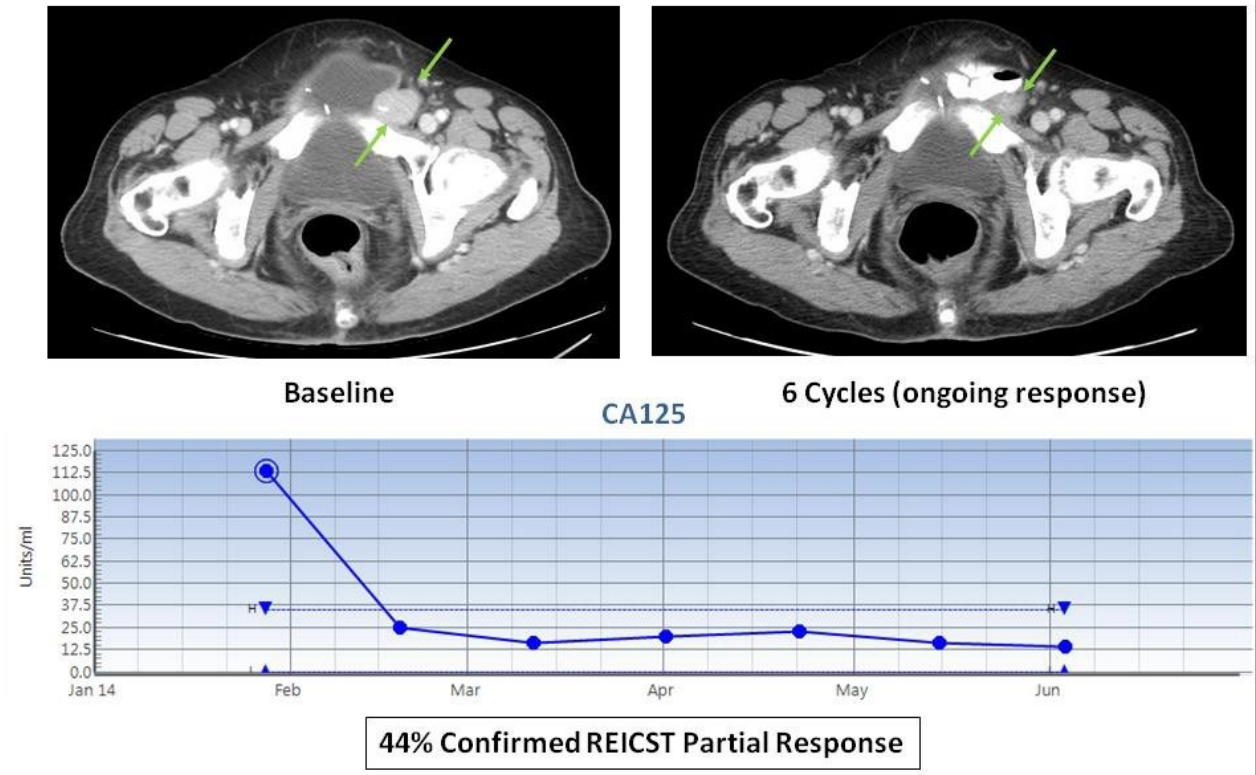
Patient was discharged to an inpatient rehabilitation center on 12/4/15 in stable condition.

Additional data are available in the latest Investigator's Brochure (IB).

Rationale for LY3023414 in PI3K-Activated Endometrial Cancer

MSKCC has been instrumental in the early phase development of this molecule and was one of only 3 sites to participate in the first-in-human Phase I study. During the dose escalation portion of this study 2/4 endometrial cancer patients treated at ≥50% of the MTD experienced RECIST tumor regressions of ≥20% (personal communication, V. Wacheck, Lilly). Representative images and tumor marker trends for one patient are shown in **Figure 4**. This patient has both PTEN loss and PIK3R1 mutation and remains on therapy after 7 cycles. MSKCC's early experience with LY3023414 will also help ensure that this early phase asset is managed safely in the context of an investigator initiated trial

Figure 4:



4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is an MSKCC investigator-initiated, single-center, non-randomized, open-label, phase II study to evaluate the activity of LY3023414 dosed at the RP2D of 200 mg orally twice daily in patients with recurrent or persistent endometrial cancer. The safety and tolerability of LY3023414 will also be evaluated.

Each cycle will be 21 days in duration. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination.

Efficacy assessments will be performed every 2 cycles from initiation of study treatment until disease progression.

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, graded according to the current version National Cancer Institute Common Terminology Criteria for Adverse Events

4.2 Intervention

Eligible patients will undergo screening and baseline procedures per the Study Schedule. Study inclusion and exclusion criteria will be applied per section 6.0. Enrolled patients will take LY3023414 200 mg orally twice a day. Each cycle will be 21 days in duration. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination

Efficacy assessments will be performed every 2 cycles from initiation of study treatment until disease progression. Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events.

Each dose should be taken with a minimum of 8 ounces of water. Patients should take the morning and evening doses of LY3023414 approximately 12 hours apart (preferably within a 10- to 14-hour range).

Patients should not consume food for approximately 1 hour before taking the dose of LY3023414. If a dose is vomited within one hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose and will not be replaced. If a patient misses a dose, the patient should skip that dose and resume dosing with the next scheduled dose.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

LY3023414 will be supplied as 25-, 100-, or 200- mg capsules/tablets for oral consumption. LY3023414 capsules/tablets should be stored within the temperature range stated on the label. Investigators should instruct patients to store the capsules/tablets at home in the provided container and to keep out of the reach of children. Capsules/tablets should not be opened, crushed, or dissolved. LY3023414 will be labeled according to local regulatory requirements and supplied by the sponsor.

Lilly compound number: Chemical Name (CA Index Name):	LY3023414 2*H*-Imidazo[4,5-*c*]quinolin-2-one, 8- [5-(1-hydroxy-1-methylethyl)-3-pyridinyl]-1- [(2*S*)-2-methoxypropyl]-3-methyl-
Other Names:	(*S*)-8-(5-(2-hydroxypropan-2-yl)pyridin-3- yl)-1-(2-methoxypropyl)-3-methyl-1H-imidazo[4,5-*c*]quinolin-2(3*H*)-one
Molecular weight:	406.48
Molecular/Empirical Formula:	$C_{23}H_{26}N_4O_3$
Description:	Practically white to light yellow solid
pKa:	4.92 and 3.75

pH:	5.79 (10 mg/mL suspension in water)
Specific Rotation	$[\alpha]_{436}$ – 42.09°; $[\alpha]_{589}$ 17.51°
Stability:	The drug substance is stable when stored at room temperature.
Solubility:	Water – Very slightly soluble Ethanol – Slightly soluble

Formulation: The drug product LY3023414 is supplied for clinical trial use as either 25-mg, 100-mg, or 200-mg capsules/tablets. The 25-mg capsules/tablets are an opaque white on the body and cap. The 100-mg capsules/tablets are an opaque blue on the body and cap. The 200-mg capsules/tablets are an opaque orangish-red color on the body and cap. Each capsule/tablet contains only LY3023414, with no inactive ingredients. The drug product is packaged in bottles and is stable when stored at room temperature conditions according to the label.

Labeling: Each bottle of LY3023414 will be labeled in accordance with current FDA and specific national requirements.

Storage condition for LY3022414 is 10-30°C (50-86°F).

LY3023414 Dosing Information: After the initial screening visit and registration in the study, patients will receive LY3023414 twice daily orally at a starting dose of 200mg.

Drug Product Accountability: Study drug for the study are provided by Eli Lilly and Company, Inc. and will be labeled as per the applicable regulations. Sites must request study drug by submitting an order form directly to the drug depot in order for the study drug to be shipped to the site pharmacy. The Investigator (or designee) will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

All clinical drug supplies must be kept in an appropriate, limited access, secure place until used Drug supplies will be counted and reconciled at the site. The study site will be required to maintain a log of the temperature where the study medication is stored.

All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

The Investigational medicinal product should not be used for any purpose outside the scope of this protocol, nor can Investigational medicinal product be transferred or licensed to any party not participating in the clinical study. Data for Investigational medicinal product are confidential and proprietary and shall be maintained as such by the Investigators.

The Principal Investigator (or an authorized designee) must maintain a careful record of the inventory of the Investigational medicinal product received using the Drug Accountability Form. The study drug will be destroyed as per MSKCC policy.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Patients must have recurrent or persistent endometrial carcinoma. Patients with the following histologic epithelial cell types are eligible: endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.), mucinous adenocarcinoma, squamous cell carcinoma, transitional cell carcinoma, and carcinosarcoma.
2. Age ≥ 18 years
3. Patients must have had at least one but no more than four prior chemotherapeutic regimens for management of endometrial carcinoma (including neo-adjuvant and/or adjuvant chemotherapy). Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen.
4. Patients tumors must have known PI3K pathway activation defined as EITHER of the following on a CLIA-approved molecular diagnostics test:
   a. Genomic alteration resulting in loss of PTEN function including a whole or partial gene deletion, frame shift mutations, or non-sense mutations. Missense mutations in PTEN will not be considered qualifying.
   b. A previously characterized activating mutation in any component of the pathway including: PIK3CA, AKT1, PIK3R1, PIK3R2, mTOR
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. Resolution of adverse effects of recent surgery, radiotherapy, or chemotherapy to Grade ≤1 prior to first study treatment (with the exception of alopecia or neuropathy).
7. Patients must have measurable disease. Measurable disease is defined by RECIST (version 1.1). Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.
8. No active infection requiring antibiotics (with the exception of uncomplicated urinary tract infection).
9. Any other prior therapy directed at the malignant tumor, including immunologic agents and radiotherapy, must be discontinued at least 2 weeks prior to first study treatment.
10. Adequate hematologic defined by the following laboratory results obtained within 14 days prior to first study treatment:
    a. Absolute neutrophil count (ANC) ≥1500/10^9dL
    b. Platelet count ≥ 100,000/10^9dL

c. Hemoglobin $\geq$ 9.0 g/dL

11. Adequate hepatic function defined by the following laboratory results obtained within 14 days prior to first study treatment:
    a. Total bilirubin$\leq$1.5x the upper limit of normal (ULN)
    b. AST and ALT $\leq$3.0x ULN (unless the patient has Gilbert's Syndrome, in which case AST and ALT $\leq$5.0x ULN is permitted
    c. Albumin $\geq$ 3.5 g/dL
12. Adequate renal function defined by the following laboratory results obtained within 14 days prior to first study treatment:
    a. Serum creatinine$\leq$1.5x ULN OR creatinine clearance $\geq$50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation
13. For all patients (regardless of known diabetes) the following is required at screening: Fasting blood glucose $\leq$135 mg/dL (7.49 mmol/L) and HbA_{1c} $\leq$7.0%
14. For patients of childbearing potential, agreement to use two effective forms of contraception (e.g., surgical sterilization, a reliable barrier method, birth control pills, or contraceptive hormone implants) and to continue its use for the duration of the study and for 30 days after the last LY3023414 dose.
15. Patients must have been enrolled, or agree to consent to the companion genomic profiling study MSKCC IRB# 12-245.
16. Willingness to sign written informed consent to this study.

6.2 Subject Exclusion Criteria

1. Patients with known concurrent activating RAS/RAF mutation or loss of function mutation or deletion in NF1 of NF2 resulting in MAP kinase pathway activation. Patients are not required to be evaluated for these alterations if not already performed.
2. Patients with diabetes requiring insulin or requiring more than one non-insulin hypoglycemia agents.
3. Patients previously treated with an mTOR, AKT, or PI3K inhibitor (including but not limited to GDC-0941, GDC-0980, BEZ235, BKM120, LY294002, PIK-75, TGX-221, XL147, XL765, SF1126, PX-866, D-87503, D-106669, GSK615, CAL101, everolimus, temsirolimus, and ridaforolimus). For agents not listed, the Study PI or Co-PI will make a determination.
4. History of myocardial infarction or unstable angina within 6 months prior to first study treatment.
5. New York Heart Association Class II or greater congestive heart failure.
6. Patients with a QTcF interval of >450 msec on screening electrocardiogram (ECG)
   Note: If >450 msec on the first ECG, 2 additional ECGs can be ordered same day and then the average may be used to determine eligibility.
7. History of malabsorption syndrome or other condition that would interfere with enteral absorption.
8. Inability or unwillingness to swallow pills
9. Clinically significant history of liver disease, including cirrhosis and current alcohol abuse.

10. Active hepatitis B or hepatitis C infection. Patients with previously resolved hepatitis B infection are eligible. Presence of positive test results for hepatitis B infection who have resolved the infection (defined by being positive for HB surface antibody (anti-HBs) and polymerase chain reaction (PCR) assay is negative for HBV DNA) are eligible. Patients positive for HCV antibody are eligible only if testing for HCV RNA is negative.
11. Known HIV infection.
12. Need for current chronic corticosteroid therapy (≥10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)
13. Pregnancy, lactation, or breastfeeding
14. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
15. Major surgical procedure or significant traumatic injury within 28 days prior to Day 1 or anticipation of the need for major surgery during the course of study treatment.
16. Known untreated or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Patients with a history of treated CNS metastases are eligible, provided that they meet all of the following criteria:
    a. Presence of measurable disease outside the CNS
    b. No radiographic evidence of worsening upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
    c. No history of intracranial hemorrhage or spinal cord hemorrhage
    d. No ongoing requirement for dexamethasone as therapy for CNS disease (anticonvulsants at a stable dose are allowed)
    e. Absence of leptomeningeal disease
17. Inability to comply with study and follow-up procedures.
18. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

7.1 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator or research team within the Gynecologic Medical Oncology Group at Memorial Sloan-Kettering Cancer Center (MSKCC). Patient recruitment will occur in the Gynecologic Medical Oncology clinics at MSKCC. The investigator will discuss the study with suitable participants, and should the patient consent to proceed with protocol therapy, will enroll their patient's in the research study. Based on historical accrual rates in similar populations, we anticipated successful enrollment of 2 patients per month yielding a total accrual time of 12 months. However, due to a slower than expected accrual rate, we have expanded the eligibility to allow patients who have received up to 4 prior lines of therapy to be eligible. We believe that with this modification, we will be able to accrue approximately 2 patients per month onto this study.

Patients must have PI3K pathway activation defined as EITHER of the following:

1. Genomic alteration resulting in loss of PTEN function including a) whole or partial gene deletion, frame shift mutations, or non-sense mutations. Missence mutations in PTEN will not be considered qualifying.
2. A previously characterized activating mutation in any component of the pathway including: PIK3CA, AKT1, PIK3R1, PIK3R2, mTOR

Patients must also not have a known concurrent activating RAS/RAF mutation or loss of function alternation in NF1 of NF2 resulting in MAP kinase pathway activation.

Any mutational profiling performed in a CLIA laboratory either as routine standard of care or as part of a dedicated genomic profiling study such as MSKCC IRB# 12-245 will be accepted. For patients who have not had mutational profiling performed in a CLIA laboratory or as part of a prior genomic profiling study, formally consenting to MSKCC IRB# 12-245 Part A will be required before consenting to the current study to ensure that the consenting patient has a PI3K pathway activating mutation as detailed above.

Patients who respond to therapy and then progress will be offered a consent to MSKCC IRB# 12-245 Part B in order to obtain post-progression material for molecular profiling in order to determine the mechanism(s) underlying acquired resistance. Participation in this companion study is optional for enrolled patients. IRB# 12-245 Part B is a separate consent, but it is similar to IRB# 12-245 Part A. IRB# 12-245 Part B consent is specifically utilized in cases where patients have received experimental targeted therapy and are undergoing repeat mutation profiling of post-treatment malignancy in an effort to determine the mechanism(s) underlying acquired resistance. Specifically, we will be looking for presence of genetic alterations which based on their understood biological mechanism may explain acquired resistance (for example, second "hits" on the PI3K pathway).

8.1 PRETREATMENT EVALUATION

Within 28 days prior to treatment start:

- History and Physical examination
- Review of concomitant medications
- Vital signs (blood pressure, heart rate and temperature), weight and height
- Performance status
- Toxicity assessment
- 12-lead ECG
- Radiographic tumor measurements (CT C/A/P, MRI, Chest X-ray)
- Hepatitis B and C screening
- Request archival tumor tissue (if required and done through IRB 12-245)

Within 7 days prior to treatment start:

- Complete Blood Count (CBC) with differential and platelets

- Comprehensive profile (BUN, creatinine (or creatinine clearance), sodium, potassium, chloride, CO2, calcium, toral bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)
- Phosphorus
- Magnesium
- PT/PTT
- CA125
- Hemoglobin A1c
- Insulin Level
- Fasting blood glucose
- Body weight
- Urinalysis
- Pregnancy test (in women of child bearing potential)

9.1 TREATMENT/INTERVENTION PLAN

9.2 Treatment

LY3023414 200 mg will be dosed orally twice a day. Each cycle will be 21 days in duration. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination. In limited circumstances patients may be treated beyond progression if, in the opinion of the Principal Investigator, the patient is benefiting from treatment. Approval from Eli Lilly will be required in these circumstances.

LY3023414 should be taken approximately 12 hours apart. Patients should not consume food for approximately 1 hour before taking the dose of LY3023414. If a dose is vomited within one hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose and will not be replaced.

Concomitant medication and treatment

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients may continue their baseline medication(s). All concomitant medication(s) must be recorded. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded, including dates, description of the procedure(s) and any clinical findings.

LY3023414 is a weak inhibitor of cytochrome P450 3A4 (CYP3A4) in patients and thereby impacts (decreases) the metabolic clearance of drugs that are metabolized through CYP3A4 (See also IB Section 6.1.2). The clinical implications of this risk have yet to be determined. Patients should avoid taking concomitant medications that are CYP3A4 substrates (for example, midazolam).

Investigators should monitor patients for unexpected clinical adverse effects as a result of unexpected high exposure to LY3023414 due to any potential interaction of concomitant medications with LY3023414.

9.3 Correlative Studies

Cell Free DNA: 2 extra Streck BCT tubes will be collected at the time of routine blood collection at the specified time points in the calendar in Section 10.0. Processing will occur per MSKCC laboratory medicine procedures.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

PARAMETER	Screening		Cycle 1			Cycle 2+	End of Treatment	Follow-up
Day	28 days before start	7 Days before start	1	8 ±3 days	15 ±3 days	1 ±4 days	30 days ±14 days	Every 3 months until death ±1 month
Medical History	X							
Physician Examination	X		X	X	X	X	X	
Performance Status	X		X	X	X	X	X	
Height	X							
Weight		X	X	X	X	X	X	
Vital Signs (blood pressure, heart rate and temperature)	X		X	X	X	X	X	
Adverse Event Assessment			X	X	X	X	X	
CBC, differential, hemoglobin, platelets, Electrolytes, BUN, Creatinine, Ca, Mg, Phosphorus, Bilirubin, AST/SGOT, ALT/SGPT, Alkaline Phosphatase		X	X[2]	X	X	X	X	
Fasting (≥8 hours) Blood Glucose		X	X[2]	X	X	X	X	
Insulin Level		X	X[2]	X	X	X	X	
Hemoglobin A1c		X	X[2]			X	X	

PARAMETER	Screening		Cycle 1			Cycle 2+	End of Treatment	Follow-up
Day	28 days before start	7 Days before start	1	8 ±3 days	15 ±3 days	1 ±4 days	30 days ±14 days	Every 3 months until death ±1 month
PT, INR, PTT		X					X	
Pregnancy test		X[1]					X	
CA125		X	X[2]			X	X	
Electrocardiogram	X			X		X	X	
CELL-Free DNA			X	X		X (Odd cycles Day1 only)		
Radiographic disease assessment	X					X[3]	X[4]	X[4]
Patient drug diary			X					
Survival Follow-up								X[5]

1. If the patient is of child-bearing potential per MSKCC guidelines. Must be obtained within 72 hours prior to initiating protocoltherapy.
2. Study can be omitted on Cycle 1 Day 1 with screen labs performed within 72 hours.
3. Performed during week 3 of each even numbered cycle (Days 15-21).
4. Only if patient discontinues for reasons other than progression, repeated every 3 months +/-2 weeks until disease progression or initiation of alternative anti-cancer therapy.
5. Phone call every 3 months.

11.1 TOXICITIES/SIDE EFFECTS

The dose delay and reduction instructions provided in Tables 11A and 11B are intended to serve as guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while ensuring patient safety. Patients may temporarily suspend dosing of LY3023414 for up to 14 days if they experience toxicity that is considered related to LY3023414 and requires that a dose be held. Patients who miss ≥ 14 consecutive days of scheduled LY3023414 treatment because of LY3023414 related AEs will be discontinued from the study. LY3023414 dosing delay beyond 2 weeks and up to 28 days may be permissible, if AEs are not considered to be primarily related to LY3023414 and the investigator deems continuation to have clinical benefit for the patient. Exceptions may be made after discussion with the approval by the Principal Investigator. Patients may suspend dosing of study drug for radiation therapy or surgery that is considered by the treating physicians to be of clinical benefit for the patient. After completion of the intervention, patients may restart the study drug as long as all criteria for dosing are met and there is no evidence of disease progression (unless approved by PI and sponsor as noted previously).

Dose modifications for LY3023414 for select AEs, should follow the guidance provided in Table 11A, and required dose reductions should follow the dose levels outlined in Table 11B. No dose re-escalation will be allowed.

Table 11A: Dose Delay Guidelines for LY3023414-Related Adverse Events

Event Type	Grade and Frequency	Dosing
Hyperkalemia	Grade 2 (baseline potassium ≤ULN)	• Hold until Grade ≤1 • Restart at same dose if recovery to Grade ≤1 is ≤7 days. • Restart at next lower dose if recovery to Grade ≤1 is ≥7 days
	Grade 2 (baseline potassium Grade 1)	• Consider holding until Grade ≤1 taking into account change from baseline. • Otherwise, follow directions above
	Grade 3: first and second event	• Hold until Grade ≤1 • Restart at next lower dose
	Grade 3: third event	• Discontinue
	Grade 4	• Discontinue
Hyperglycemia	Grade 3, asymptomatic [a]	• Begin home monitoring and check at next visit; if persistent pre-dose values of Grade 3, start or adjust oral anti-hyperglycemic agent or reduce by one dose level.
	Grade 3, with symptoms [a]	• Hold until resolution of symptoms and Grade ≤2. • Consider starting or adjusting oral anti-hyperglycemic agent or restarting at next lower dose level.
	Grade 3, with severe symptoms [b], or requiring hospitalization, or Grade 4 (non-life-threatening)	• Hold until resolution of symptoms and Grade ≤2. • Start or adjust oral anti-hyperglycemic agent. Restart at next lower dose level.
	Grade 4, life-threatening	• Discontinue
Anemia	Grade 1-2	• Maintain dose level and initiative standard supportive care
	Grade 3: first event	• Hold until Grade ≤1 • Consider restarting at next lower dose
	Grade 3 (second event) or Grade 4 (non-life-threatening)	• Hold until Grade ≤1 • Restart at next lower dose
	Grade 4 (life threatening)	• Discontinue

Thrombocytopenia	Grade 1 Grade 2-3 Grade 4	• Maintain dose level and initiative standard supportive care • Hold until Grade ≤1 • Restart at next lower dose • Discontinue
Other Clinically Significant Drug-Related AE	Grade 1 Grade 2 (intolerable) Grade 3-4 Grade 4 (life-threatening)	• Maintain dose level and initiative standard supportive care • Consider holding until Grade ≤1 and restarting at next lower dose • Hold until Grade ≤1 • Restart at next lower dose • Discontinue
Rash	Grade 1-2 Grade 3: First Event Grade 3: Recurrent	• Maintain dose level and initiative standard supportive care • Hold Until ≤ Grade 1 and restart at same dose. • Initiative standard supportive care an • Dermatology Consultation • Hold Until ≤ Grade 1 and restart at next lower dose. • Initiative standard supportive care an • Dermatology Consultation

ULN = upper limit of normal. Adverse event grading is based on the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Symptoms of hyperglycemia include blurry vision, polydipsia, and polyuria.

[b] Severe symptoms of hyperglycemia include neurological symptoms (lethargy, focal signs, or obtundation), hyperventilation, abdominal pain, and hypotension.

Table 11B: LY3023414 Dose Reduction Schedule

Starting Dose	200mg twice daily
Dose Level -1	150mg twice daily
Dose Level -2	100mg twice daily
Dose Level -3	Discontinue

It is expected that patients with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, patients with

persistent (≥ 24 hours) Grade≥3 toxicity in spite of optimal medical management require reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1.

Other non-hematologic toxicities with an impact on organ function of Grade ≥ 2 require reduction of one dose level and delay in subsequent therapy for a maximum of 28 days until recovered to Grade 1, or pre-therapy baseline

Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, romiplostim and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Antitumor Effect – Solid Tumors
Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [22]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease reevaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during followup. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. For these reasons, the GOG will not allow PET-CT use for RECIST 1.1 response criteria.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one

assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRIs advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

CA125 (Ovarian, fallopian tube and primary peritoneal cancer trials): CA125 alone cannot be used to assess response. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published (23) In addition; the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer (24).

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.4 Response Criteria

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of CA125 level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase
.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Progression Based on Serum CA-125 (for randomized phase 3 trials of initial therapy of ovarian, fallopian tube and primary peritoneal cancer ONLY):

Progression can be based upon serum CA-125, only during the period following completion of cytotoxic chemotherapy, if one of the three conditions is met:

1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

OR

2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

OR

3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be

accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response
Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival
Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of recurrence, progression, or death, whichever occurs first.

Survival
Survival is defined as the duration of time from start of treatment to time of death or the date of last contact

13.1 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. Any patient who withdraws will be encouraged to return to the study center for a treatment completion visit. Patients who

discontinue early should return within 30 days following the final dose of study treatment. The primary reason for discontinuation must be recorded in the medical record.

Patients may be withdrawn from the study if they experience any of the following:

- Disease progression, per investigator assessment
- Intolerable toxicity of LY3023414

Other reasons for patient discontinuation may include, but are not limited to, the following:

- Change in patient eligibility
- Non-compliance
- Patient decision
- If the patient becomes pregnant
- If patient requires more then 2 dose reductions of LY3023414
- If treatment is delayed for more than 28 consecutive days

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study; for reasons of noncompliance (e.g., missed doses, visits); or if the investigator determines it is in the best interest of the patient.

14.1 BIOSTATISTICS

This study aims to assess the activity of LY3023414 in patients with PI3K-pathway activated recurrent or persistent endometrial cancer as measured by the best overall response rate as determined by RECIST 1.1. Assuming we use a binary endpoint of response, defined as best overall response of CR or PR versus not, a sample size of 25 patients provides 90% power to test the hypothesis that the response rate is promising (defined as 30% or higher) against a non-promising rate of 10% or lower. This calculation is based on historical data from studies with ineffective agents in a similar patient population, which have ORR < 10% and PFS rate at 6 months < 20% (Fracasso et al, 2006, Schilder et al. 2004, Garcia et al. 2008 Aghajanian et al, 2011), and uses an exact, one-sample test for binomial proportion, with Type I error=10%. At the end of the study, if at least 5/25 responses are observed then this will be considered a positive study (i.e. conclude that RR is >10%).

Based on historical accrual rates in similar populations, and with the increased prior lines of therapy that will not be allowed for eligibility, we anticipate successful enrollment of 2 patients per month yielding a total accrual time of 12 months. Accrual will continue until 25 evaluable for response patients are treated (evaluable patients are defined in section 12.1)

In addition we will report the following statistics:

1. The clinical benefit rate (CBR) of LY3023414 therapy, defined as the percentage of patients with complete response (CR) + partial response (PR) + stable disease (SD) ≥12

weeks from the start of treatment will be reported and the 90% confidence interval will be estimated using exact binomial proportions

2. Progression free survival (PFS), defined as the duration of time from start of treatment to time of recurrence, progression, or death due to any cause, whichever occurs first. Patients will be censored at last follow up date. The Kaplan Meier estimate of median PFS will be reported.
3. Overall survival (OS), defined as the duration of time from start of treatment until the date of death due to any cause. Patients will be censored at last follow up date. The Kaplan Meier estimate of median OS will be reported.
4. Tthe duration of response (DOR) of LY3023414 therapy, defined as the time from which measurement criteria are met for CR or PR (whichever status is recorded first) until the first date of documented disease progression, will be estimated using the Kaplan Meier method. Patients without documented progression will be censored at last follow up.
5. Adverse events by the current version of Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0) will be tabulated in order to assess the safety profile and tolerability of LY3023414 therapy in patients with PI3K activated recurrent/persistent endometrial cancer.

In addition the study will analyze the following variables as part of assessing exploratory aims in a subset of patients who consent to 12-245:

1. For patients who have not already had their tumors molecularly profiled using the MSK-IMPACT platform, pretreatment archival tumor tissue will be obtained for this purpose. Genomic alterations defined by MSK-IMPACT testing performed on this pretreatment archival tumor tissue will be correlated to objective responses outcomes in an exploratory manner. Consent for this testing, to be performed in the CLIA laboratory, will be obtained through a companion study MSKCC IRB# 12-245. Genomic alterations will be binary and Fisher's exact test will be used to assess the correlation between genomic alterations and response (binary).

2. Serial pre-, on- and post-treatment blood samples will be collected for cell-free tumor DNA analysis and sequenced using continuous quantitative methods (digital droplet PCR or hybridization capture next-generation sequencing) for the PI3K- pathway alterations identified by pre-treatment archival tumor testing and descriptively correlated to clinical outcome. Pre and post treatment samples will be assessed graphically and pre treatment archival tumor testing will be assessed graphically with clinical outcome.

3. Patients who respond to therapy and then progress will be offered optional consent to MSKCC IRB# 12-245 Part B in order to obtain post-progression material for molecular profiling in order to determine the mechanism(s) underlying acquired resistance. A subset analysis of patients who progress and have post progression material for molecular profiling will be performed in order to determine the mechanism(s) underlying acquired resistance. Specifically, we will be looking for presence of genetic alterations which based on their understood biological mechanism may explain acquired resistance (for example, second “hits” on the PI3K pathway).

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

NA

16.0 DATA MANAGEMENT ISSUES

A research study assistant (RSA) will be assigned to study. The responsibilities of the RSA include project compliance, data collection, extraction and data entry, data reporting, coordination of the activities of the protocol study team and, and of the flow of regulatory paperwork.

The data collected for the study will be entered into a secure database (CRDB). All routine blood test results required per the protocol will be captured in CRDB in addition to baseline medical conditions and disease information, response assessments, off-study documentation, and toxicity grade and attribution. Source documentation will be available to support the computerized patient record.

MSKCC will hold the IND and will be responsible for all safety monitoring. All SAEs will be reported to the MSKCC IRB. The safety of the study will be monitored by the MSKCC Data and Safety Monitoring Committee.

Weekly registration reports will be generated by the RSA and reviewed by the PI to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies.

Accrual rates and extent and accuracy of evaluations and follow up will be monitored periodically throughout the study. Recurrent lapses in data collection, deviations or

violations will be discussed with the study team and a corrective plan will be generated. Accrual goals and factors impacting accrual goals will be discussed at the weekly New Patient/Protocol meetings.

16.1 Quality Assurance

The data and safety monitoring plan at Memorial Sloan-Kettering Cancer Center was approved by the National Cancer Institute in September 2001. The plan addressed the new policies set forth by the NCI and the document entitled "Policy of the National Cancer Institute for data and safety monitoring of clinical trials" which can be found at http://grants.nih.gov/grants/guide/notice-files/not98-084.html. The DSM plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC data and safety monitoring plan can be found on the MSKCC Internet at http://inside2/clinresearch/Documents/MSKCC Data and Safety Monitoring Plans.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. Memorial Sloan-Kettering Cancer Center has set up three distinct monitoring processes for our clinical trials program. There are two sub-committees that have the responsibility of data and safety monitoring. These are joint sub-committees with dual-reporting responsibilities. The Data and Safety Monitoring Committee (DSMC) is the sub-committee responsible for monitoring all Phase 1, 2, 1/2, pilot and non-phase clinical trials. The Data and Safety Monitoring Board (DSMB) is the sub-committee responsible for monitoring Phase 3 randomized clinical trials. The Therapeutic Response Review Committee (TRRC) is the sub- committee of Research Council responsible for the independent therapeutic response review for participants in IRB/PB approved clinical trials where therapeutic efficacy is a stated primary objective; typically phase 2 and 3 trials. Formal monitoring of such studies is designed to ensure that the interests of the participants are being scrutinized on a regular basis, and that the trial is progressing in a satisfactory manner.

The Data and Safety Monitoring Committee (DSMC) convenes once per quarter and monitors the risk participants are exposed to, the progress of the study, the adequacy of the data storage and whether sufficient data are being entered into the CRDB. The DSMC monitors phase 1, 2, 1/2, pilot and non-phase trials that are not being monitored by an industrial sponsor, and which meet the NCI definition of a Clinical Trial. This trial will qualify for monitoring by the DSMC.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required, and the monitoring procedures will be

established at the time of protocol activation. A detailed description of the data to be collected, process of data collection (i.e., data manager and/or data management office), database that will be utilized for data collection and storage (e.g., Clinical Research Database (CRDB), user-supported software), reporting requirements of the data to the institution (IRB), the sponsor and/or governing agency.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf*

17.1 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event(SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1

Any additional SAE reporting information required by the sponsor or drug supplier should be included in this section.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

None