

MSK PROTOCOL COVER SHEET

II T: Single Arm, Open-Label, Phase II Study of Fulvestrant in Combination with Abemaciclib in Hormone Receptor Positive Adenocarcinoma of Endometrium

**Principal Investigator/Department:
Angela Green, MD / Medicine**



Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Single Arm, Open-Label, Phase II Study of Fulvestrant in Combination with Abemaciclib in Hormone Receptor Positive Adenocarcinoma of Endometrium.

This is a prospective, single arm study of combination CDK4 and CDK6 dual inhibitor Abemaciclib and selective estrogen receptor degrader Fulvestrant in hormone receptor positive recurrent endometrial carcinomas. Patients with recurrent or persistent hormone receptor [estrogen receptor (ER) and or progesterone receptor (PR)] positive endometrial adenocarcinoma with the following histologic epithelial cell types will be eligible: endometrioid adenocarcinoma and any mixed cell type of epithelial endometrial carcinoma as long as the non-endometrioid component comprises less than 5% of the total tumor. Patients are not required to but may have received no more than two 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. Up to one prior hormonal therapy is also allowed and will not count towards prior regimen total. Patients must have measurable disease as defined by RECIST (version 1.1). Twenty-five patients will be enrolled.

Eligible patients will take Abemaciclib 150 milligrams mg orally once every 12 hours on days 1-28. Fulvestrant will be dosed 500mg intramuscularly (IM) on days 1 and 15 during cycle 1 and then on Day 1 during subsequent cycles. Each cycle will be 28 days in duration. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, or study termination. Efficacy assessments will be performed every 8 weeks from cycle 1 Day 1 until disease progression. Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events (AEs), graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.03).

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 PRIMARY OBJECTIVES:

The primary objective of this study is to assess the activity of Fulvestrant in Combination with Abemaciclib in patients with hormone receptor positive recurrent or persistent endometrial cancer, as measured by the objective response rate

[defined as the percentage of patients with complete response (CR) + partial response (PR)] after initiating therapy.

2.2 SECONDARY OBJECTIVES

1. To determine the clinical benefit rate (CBR) of Fulvestrant in Combination with Abemaciclib therapy, defined as the percentage of patients with complete response (CR) + partial response (PR) + stable disease (SD) ≥ 16 weeks from the date of enrollment.
2. To determine progression free survival (PFS), defined as the interval from the date of enrollment until the first date on which recurrence, progression, or death due to any cause.
3. To determine overall survival (OS), defined as the interval from the date of enrollment until the date of death due to any cause.
4. To determine the duration of response (DOR) of Fulvestrant in Combination with Abemaciclib 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 Fulvestrant in Combination with Abemaciclib therapy in patients with ER positive recurrent/persistent endometrial cancer.

2.3 EXPLORATORY OBJECTIVES

1. To assess mutational status and/or copy number variations of cancer-related genes including, but not limited to, CDK4/6, CCND1, HER2, CDKN2A, ER, PR, RB, CCNE, PIK3CA, PTEN, or RAS in responders compared to nonresponders
2. To correlate mutational status detected in tumor samples and circulating tumor DNA, as well as genetic variants in drug metabolism and transport, if deemed necessary by the sponsor.
3. To explore expression biomarkers in blood (and tumor samples, if available) related to CDK4/6 and PI3K/mTOR signaling, including, but not necessarily limited to protein, RNA, and micro RNA, and correlated with response, if deemed necessary by the PI.
4. To explore whether on serial pre-, on-and post treatment blood samples for cell-free tumor DNA results correlate with clinical outcome. To determine potential mechanism(s) of acquired resistance for patients who respond to therapy and then progress utilizing MSKCC IRB# 12-245 Part B.

3.0 BACKGROUND AND RATIONALE

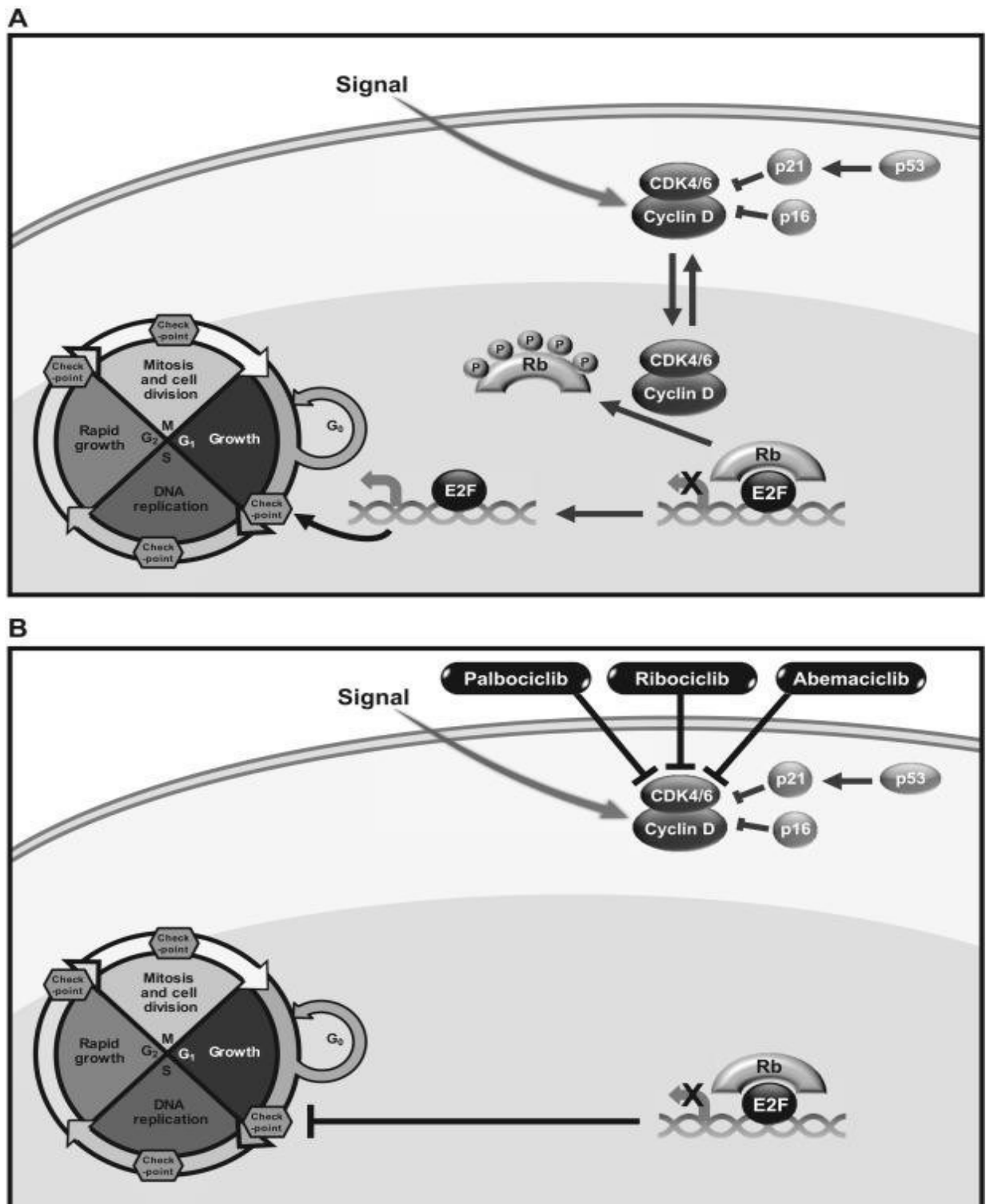
The CDK 4/6-inhibitor of CDK4 (INK4)-retinoblastoma (Rb) pathway controls cell cycle progression by regulating the G1-S checkpoint. Dysregulation of this pathway results in increased proliferation, and is frequently observed in many types of cancer. Due to the importance of CDK4/6 activity in cancer cells, CDK4/6 inhibitors have emerged as promising candidates for cancer treatment. The cell cycle is broadly divided into four sequential phases: G1 (pre-DNA synthesis), S (DNA synthesis), G2 (pre-division), and M (cell division). The key regulator of the G1-S transition is the cyclin D-CDK4/6-INK4-Rb pathway (Figure 1) [1]. CDK4 and CDK6 share 71% amino acid identity and have largely overlapping functions [4]. Both kinases are expressed in most cell types—albeit to different extents—and both can partner with all three D-type cyclins (D1, D2, and D3) [4]. Upon activation by mitogenic signaling pathways, D-type cyclins associate with CDK4 or CDK6. These active cyclin D-CDK4/6 complexes phosphorylate Rb, and thereby promote dissociation of the transcriptionally repressive Rb-E2F complex. The released E2F transcription factors are then free to activate genes required for entry into S phase and DNA replication [2].

CDK4/6 activity is regulated by the INK4 family of proteins (p16INK4A, p15INK4B, p18INK4C, and p19INK4D) and by the Cip and Kip family (particularly p21CIP1 and p27KIP1) [5]. The INK4 proteins inhibit cyclin D-CDK4/6 activity by directly binding to the CDK [2]. Of the four INK4 proteins, p16INK4A appears to be particularly important for tumor suppression [1]. p21CIP1 and p27KIP1 have context-dependent positive and negative effects on CDK4/6 activity; both can stabilize cyclin D-CDK4/6 complexes and both possess CDK4/6-inhibitory activity under certain conditions, creating a complex system of regulation [3].

While loss of Rb is responsible for G1-S transition in some cancer types, the vast majority of cancers retain wild-type Rb [1]. These Rb-positive (Rb+) cancers can instead be driven by overexpression or activation of cyclin D-CDK4/6, loss of cyclin D-CDK4/6 negative regulators, or by oncogenic signaling pathways that promote cyclin D-CDK4/6 activity, and are likely to be dependent on CDK4/6 activity for cell proliferation. Key oncogenic signaling pathways that promote cyclin D-CDK4/6 activity include phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), wnt/ β -catenin, janus kinase (JAK)-signal transducer and activator of transcription (STAT), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and steroid hormone signaling pathways (e.g. estrogen, progesterone, and androgen) [4]. These pathways converge at the point of cyclin D-CDK4/6 signaling (Figure 1) [4].

CDK4/6 mediates the transition from G1 to S phase by associating with D-type cyclins and regulating the phosphorylation state of Rb (Figure 1). Unphosphorylated Rb binds and represses the function of E2 family (E2F) transcription factors; upon phosphorylation, Rb dissociates from E2F transcription factors, freeing them to be able to participate in DNA replication and cell division. Increased cyclin D-CDK4/6 activity, which promotes phosphorylation of Rb, can occur through several mechanisms, including overexpression of D-type cyclins, mutation or amplification of CDK4/6, or loss of cyclin D-CDK4/6 negative regulators such as p16INK4A [1], and ultimately leads to cancer cell growth. Thus, the development of selective CDK4/6 inhibitors offers a novel therapeutic approach for patients with advanced cancer.

Figure 1.



Mechanisms of cyclin D-CDK4/6-INK4-Rb pathway activation

Amplification of the genes encoding cyclin D1 (CCND1), CDK4, or CDK6, or deletion of the locus encoding p16INK4A (cyclin-dependent kinase inhibitor 2A [CDKN2A]) are major mechanisms by which the cyclin D-CDK4/6-INK4-Rb pathway can be activated. For example, the ProfILER study characterized genomic alterations in advanced cancers (N = 105; breast, head and neck, and lung cancers accounted for >50% of cases) and identified amplifications in CCND1 (17% of cases), CDK4 (4%), and CDK6 (3%), as well as homozygous deletion of CDKN2A (21%) [5]. Other studies in breast cancer have reported CDK4 amplification in 16% of cases, CDK6 amplification in 17%, and loss of p16INK4A in 49% [6] and [7].

CCND1 amplification is seen in up to 35% of breast cancer cases, while the cyclin D protein is overexpressed in over 50% [7] and [8]. Amplification of CCND1 is also frequently observed in head and neck cancer (26–39% of cases), non-small cell lung cancer (NSCLC; 5–30%), endometrial carcinoma (26%), and pancreatic cancer (25%) [8]. Similarly, almost 50% of prostate cancers overexpress CDK6 [9], and overexpression or copy number variation of at least one cyclin D-CDK4/6-INK4-Rb pathway component occurs in most cases of melanoma (approximately 75%) [10], head and neck squamous cell carcinoma (loss of p16INK4A in approximately 80%) [11], and almost all cases of liposarcoma and neuroblastoma [12-15].

Similarly, specific mutations or translocations in the genes encoding cyclin D-CDK4/6-INK4-Rb pathway components can also result in aberrant pathway activation. For example, mutation of CDK4 at R24 prevents p16INK4A binding, resulting in enhanced kinase activity [2]. CDK4 R24 mutations were first characterized in familial melanoma [16], and were identified in 2.5% of melanoma cases in a whole-exome sequencing study [17]. This study also identified mutations in the p16INK4A transcript (21% of melanoma cases), CCND1 amplification (11%), and CDK4 amplification (3%) [17]. Mutation of the CDKN2A locus, encoding p16INK4A, is also associated with melanoma; at least 20% of familial melanoma cases are estimated to harbor mutations in this gene [18]. In a study of melanoma-prone families, the presence of a CDKN2A mutation in the family increased the prevalence of other cancers by 2–3-fold, including pancreatic, lung, and breast cancers [19]. Meanwhile, the hallmark of mantle cell lymphoma (MCL) is the t(11;14) translocation, which juxtaposes the CCND1 coding region to the IgH gene, resulting in constitutive overexpression of cyclin D1 and cell cycle dysregulation in virtually all cases [2]. Dysregulation of the cell cycle machinery in MCL is also often associated with CDK4 and CDK6 overexpression, or reduction in p16INK4A expression through deletion or transcriptional inhibition [20] and [21].

Multiple other mechanisms exist by which the cyclin D-CDK4/6-INK4-Rb pathway can be activated. Epigenetic alterations have been reported in ovarian cancer where repressive promoter methylation at the CDKN2A gene was higher than in corresponding benign ovarian tissue biopsies [22]. Mutations in upstream factors can also deregulate the cyclin D-CDK4/6-INK4-Rb pathway, as is the case in malignant rhabdoid tumors (MRTs) where the SMARCB1/INI1/SNF5 tumor suppressor gene is often inactivated [23]. A critical function of SMARCB1 is to restrict activity of cyclin D-CDK4/6 through direct transcriptional repression of CCND1 and increased expression of the negative regulators p21CIP1 and p16INK4A [24] and [25]. Downregulation of microRNAs (miRNAs) that target CDK4/6 has also been associated with cancer. For example, miRNAs that target CDK4 and CDK6 have been found to be downregulated in bladder cancer as compared with normal tissues [26] and [27]. Finally, dysregulation of upstream signaling pathways can also activate the cyclin D-CDK4/6-INK4-Rb pathway, as described earlier [4].

Pathway activation can occur through a variety of mechanisms, including gene amplification or rearrangement, loss of negative regulators, epigenetic alterations, and point mutations in key pathway components. Due to the importance of CDK4/6 activity in cancer cells, CDK4/6 inhibitors have emerged as promising candidates for cancer treatment. Moreover, combination of a CDK4/6 inhibitor with other targeted therapies may help overcome acquired or de novo treatment resistance. Ongoing studies include combinations of CDK4/6 inhibitors with endocrine therapy and phosphatidylinositol 3-kinase (PI3K) pathway inhibitors for hormone receptor-positive (HR+) breast cancers, and with selective RAF and MEK inhibitors for tumors with alterations in the mitogen activated protein kinase (MAPK) pathway such as melanoma. In particular, the combination of CDK4/6 inhibitors with endocrine therapy, such as palbociclib's recent first-line approval in combination with letrozole, is expected to transform the treatment of HR+ breast cancer. Currently, three selective CDK4/6 inhibitors have been approved or are in late-stage development: palbociclib, ribociclib, and Abemaciclib (LY2835219).

Endometrial Cancer Background:

Endometrial cancer (EC) is the 4th most common malignancy among women in the US. Carboplatin/paclitaxel is the standard first-line treatment regimen for advanced recurrent or persistent disease. In the setting of recurrent low grade, asymptomatic, or ER/PR positive endometrial cancer, hormone therapy alone is a recommended, guideline concordant treatment for patients with disseminated metastases per the National Comprehensive Cancer Center Network, even in the absence of prior systemic therapy. Despite the detailed genomic characterization of endometrial cancer, Megace is the only FDA approved "targeted" therapy or the palliative treatment of advanced EC. Response

rates for commonly used off label therapies including liposomal doxorubicin, topotecan, weekly paclitaxel, and bevacizumab range between approximately 0-10% (28-29). Response rates for hormonal therapy include range from 9-33% (30-32), and occur predominantly in ER +, FIGO G1-2 endometrioid adenocarcinomas.

CDK4/CDK6 inhibition in Endometrial Cancer:

Histologically, >80% of all endometrial cancer cases are diagnosed as endometrioid endometrial carcinoma (EEC) (33). Endometrioid EC is frequently associated with somatic mutations in genes involved in the RAS/PI3K pathway, such as KRAS, PIK3CA, PTEN, AKT1, CTNNB1, and CCND1 (33, 34). Cyclin D1 is upregulated by the RAS/PI3K/beta-catenins pathway and cooperates with cyclin-dependent kinase 4 and 6 (CDK4/6) to promote the cell cycle from the G1 to the S phase (34). Elevated CDK4 expression is observed in 34–77% of EEC cases and is considered to be an early event of neoplastic transformation in EEC (35, 36). Recently, it has been shown that in EC, CDK4/6-specific activity was significantly correlated with Ki-67 ($P=0.035$), but not with any other clinicopathological characteristics. CDK4/6SA was significantly higher ($P=0.002$) in pathologically low-risk patients (not receiving adjuvant chemotherapy, $n=74$) than in intermediate- or high-risk patients (receiving adjuvant chemotherapy, $n=35$). In addition, patients with high CDK4/6SA (>3.0) showed significantly ($P=0.024$) shorter progression-free survival (PFS) than those with low CDK4/6SA (<3.0). Although Ki-67 expression itself was not a marker for prognosis, the combination of high CDK4/6SA and high Ki-67 expression ($>15\%$) was robustly associated with shorter PFS ($P=0.015$), and this combination was an independent poor prognostic factor in the low-risk group.

Hormonal Blockade in Endometrial Cancer:

Progestogens have been used to treat patients with recurrent or metastatic endometrial cancers for almost 50 years, with variable response rates reported. The earliest studies, in the 1960s, reported response rates of over 50 % in patients treated with high-dose megestrol acetate. The response rates in later trials with more rigid, and standard criteria for response have been on the order of 15–25 % and usually of short duration, with a median time to progression of 2.5 months [37, 38]. It has been suggested that the short duration of response with progestogens may be due to the rapid downregulation of progesterone receptors. Two Gynecologic Oncology Group (GOG) trials (GOG 119 and GOG 153) studied alternating megestrol acetate and tamoxifen in an attempt to circumvent downregulation of progesterone receptors and potentially increase the activity of progestogens [39, 40,41]. However, progression-free survival and overall survival were

very similar to those in studies with progestogens alone. The response rate in a trial of tamoxifen administered daily in combination with intermittent weekly administration of medroxyprogesterone acetate (MPA) was 33 %, which was higher than in other trials. Only two phase II studies have assessed the activity of aromatase inhibitors in patients with advanced or recurrent endometrial carcinoma. They both showed low rates of response, 9.0 % and 9.4 %, to letrozole and anastrozole, respectively [42, 43]. These studies included unselected patients with ER- and PR-positive tumours as well as ER- and PR-negative tumours, and many patients had high-grade cancers, which may have contributed to the relatively low response rates.

Several studies have investigated the association between rates of response to hormonal agents and ER and PR positivity in endometrial cancers. In the GOG 119 trial of daily administration of tamoxifen and intermittent administration of MPA, a statistically significant relationship between clinical response and ER expression was observed [40]. PR staining, in contrast, was not associated with response. However, these findings have not been consistent in the existing trials, with some studies failing to find an association between receptor status and response. Also, in the previously mentioned study assessing letrozole in patients with advanced or recurrent endometrial cancer, no relations between ER or PR expression and response were observed [43]. These variable findings might be explained by differences in the criteria for hormone-receptor positivity and patient selection. They demonstrate the need for well-conducted larger prospective studies to demonstrate whether patient selection for hormonal treatment could be improved by using standardized methods to measure and quantify hormone receptor status as a predictive biomarker.

Fulvestrant:

Fulvestrant, is a 7a-alkylsulfinyl analog of 17b-estradiol with the molecular formula C₃₂H₄₇F₅O₃S. Fulvestrant functions as an ER antagonist by inhibiting activation-function 1 and activation-function 2 of ER and lacks any agonistic effects. Thereby, it is regarded as the first compound of a new class of selective ER down-regulator. Fulvestrant binds to ER in a dose-dependent manner and hinders essential receptor dimerization. [44] Thereby, the ubiquitin–proteasome complex degrades ER leading to an increased turnover and decreased half-life of ER. [45] Moreover, fulvestrant changes the conformation of ER and prevents it to shuttle toward the nucleus. [46] Fulvestrant disables activating function-1 and activating function-2 of ER, which leads to a nonfunctional fulvestrant– estrogen receptor complex and a suppressed gene transcription. [47] Furthermore, fulvestrant inhibits cell proliferation by the blockage of MAPK/ER/MDM2 signal pathway in EC cell lines.[48]

The most drug-related adverse events were mild or moderate in severity, and most commonly included nausea, fatigue, pain, and anemia. Adverse events grade 3, 4, and 5 were present in 30%, 12.2%, and 1.1%, respectively. According to the authors, the one reported grade 5 adverse event thrombosis/embolism was possibly related to fulvestrant. The reported grade 3 and 4 adverse events were anemia, fatigue, gastrointestinal, nausea, vomiting, diarrhea, anorexia, metabolic, neurologic, depression, pain, dyspnea, thrombosis/embolism, ascites, bone pain, vulvo-vaginal mycotic infection, edema, renal failure, hydronephrosis, ileus, hypertension, paresis, tachycardia, and aspiration.[49, 50] According to the results of one phase I trial in healthy volunteers, fulvestrant induced generalized pain, asthenia, vasodilatation, and an increased urinary frequency.[51]

Fulvestrant Experience in Endometrial Cancer:

Fulvestrant is a pure estrogen antagonist that has a high affinity for ER and has no agonist effects, contrary to tamoxifen. Two single arm phase II studies of fulvestrant 250 mg intramuscular every 4 weeks in RMEC were published in 2011 and 2013, respectively.[49, 50] Within the GOG trial, 67 patients were enrolled.[40] A number of 14 patients were excluded, 22 suffered from an ER negative, and 31 from an ER positive EC. As best response, 4 (18%) patients with ER negative disease showed a stable disease. One (3%), 4 (13%), and 9 (29%) patients with ER positive disease showed a complete response, partial response, and stable disease, respectively.[49] Within the AGO trial, 35 patients received at least once fulvestrant (intention to treat-population).[50] A number of 26 patients received the intended 3 applications of fulvestrant (per protocol population). Twenty eight out of 35 patients suffered from hormone receptor positive RMEC; for the remaining 7, the hormone receptor status was not available. No complete response was achieved. Four and 8 patients showed a partial response and a stable disease, respectively. Thereby, the RR was 11.4% in the intention to treat-population (4 out of 35) and 15.4% in the per protocol group (4 out of 26). Three out of 4 patients with partial response suffered from hormone receptor-positive RMEC. The median time to progression was 2.3 months and OS was 13.2 months in the intention-to treat population. [50](ITT). Both studies it is generally believed that a loading dose strategy and use to 500mg every 4 weeks would have favorably impacted efficacy of this treatment in both trials.

Abemaciclib:

The non-clinical and clinical experience with Abemaciclib is fully described in the current version of the Investigators Brochure. (IB)

Abemaciclib represents a selective and potent small molecule CDK4 and CDK6 dual inhibitor with a broad antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. This compound demonstrates significant inhibition of tumor growth as monotherapy in multiple human xenograft models including models for: breast cancer, colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, melanoma, mantle cell lymphoma (MCL), and non–small-cell lung cancer (NSCLC). Although characterized by a different constellation of genomic mutations, each of these human xenografts has an intact, functional Rb protein. Xenograft growth inhibition is generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 to 28 days. Additional nonclinical studies in xenograft models for human NSCLC and melanoma also show that abemaciclib may be used in combination with standard cytotoxic or targeted therapies to improve efficacy of these agents.

In nonclinical species, Abemaciclib distributes efficiently to the brain and potentially provides a unique opportunity to treat primary brain tumors as well as cancers that have metastasized to the brain. As a result of its brain exposure, treatment with Abemaciclib in a rat orthotopic brain tumor model produces statistically significant and dose-dependent improvement in survival.

Abemaciclib demonstrates moderate-to-high bioavailability in preclinical species. In repeat-dose toxicokinetic studies, Abemaciclib showed generally dose-dependent exposure with no gender differences. Abemaciclib is highly metabolized, and hepatic elimination plays a major role in the clearance of abemaciclib and its metabolites in rats, dogs, and humans. In humans, the terminal elimination half-life ($t_{1/2}$) in plasma ranges from approximately 17 to 38 hours across the dose range tested. At a single dose of 200 mg, the mean apparent oral clearance (CL/F) is 38.3 L/hour with a high interindividual variability (105% coefficient of variation [CV]) and the apparent volume of distribution is large at 1300 L (96% CV). In the xenograft models and skin biopsies from patients, Abemaciclib inhibited phosphorylated Rb (pRb) and topoisomerase II alpha (TopoII α) at clinically relevant doses and exposures.

In preclinical species, the primary target organs for toxicity (associated with up to 3 months of continuous daily dosing) are bone marrow (resulting in pancytopenia), gastrointestinal tract, lymphoid tissues, and male reproductive tract. All of these changes demonstrated complete or partial reversibility during the recovery period. In humans, the most common treatment-emergent adverse events (TEAEs) possibly related to the study drug for patients who received single agent abemaciclib include diarrhea, nausea, fatigue, neutropenia, vomiting, decreased appetite, leukopenia, thrombocytopenia, anemia, abdominal pain, and blood creatinine increased. Increased rates of skeletal and cardiac variations and

malformations, accompanied by decreased fetal weights, were observed in an embryo–fetal development study of abemaciclib in rats.

The first-in-human phase I trial of abemaciclib enrolled 75 patients with advanced solid tumors [54]. The dose escalation phase explored once-daily and twice-daily (every 12 h) dosing on a continuous schedule. Although the MTD for once-daily dosing was not reached, the MTD for twice-daily dosing was declared as 200 mg. The DLT was grade 3 fatigue in one of six patients at 200 mg and two of three patients at 275 mg. The most common all-grade treatment-related adverse events included diarrhea (52%), nausea (32%), fatigue, vomiting (21% each), and neutropenia (19%). The most common grade 3 treatment-related adverse events were diarrhea, neutropenia (7% each), fatigue, and nausea (5% each). At 200 mg, mean C_{max} at steady state was 291 ng/mL and AUC_{0–24h} was 5798 ng·h/mL. Pharmacodynamic evidence of targeted CDK4/6 inhibition was observed, as shown by a decrease in Rb phosphorylation in the skin. One patient with CDKN2A^{–/–}, NRAS-mutant melanoma had a confirmed PR, and prolonged SD or minor radiographic decreases were seen in patients with ovarian cancer, NSCLC, and breast cancer. One of the expansion cohorts from this study enrolled 57 patients with NSCLC. There were 2 PRs, and 12 patients (of which 8 had KRAS-mutant disease) received treatment for ≥6 months.

Another expansion cohort enrolled 47 patients with metastatic breast cancer [56] with a median of 7 prior systemic regimens received therapy with Abemaciclib. Among the 36 patients with hormone receptor positive metastatic breast cancer (HR+mBC), the median progression-free survival (PFS) was 8.8 months and there were 12 confirmed partial responses (PR) for an objective response rate of 33.3%. In the same study, the combination of Abemaciclib plus fulvestrant was also evaluated and demonstrated an acceptable safety profile in 19 women with HR+mBC. In addition, 4 confirmed partial responses were observed in these 19 patients. Based on these results, in October 2015 the Food and Drug Administration (FDA) granted abemaciclib a ‘Breakthrough Therapy’ designation with ‘Fast Track’ status for the treatment of advanced breast cancer.

The success of single-agent abemaciclib in HR+ metastatic breast cancer prompted expansion of the phase I study to evaluate abemaciclib (200 mg twice daily) in combination with the anti-estrogen fulvestrant (500 mg once monthly) in this patient population. In an interim analysis, 18 patients with a median of 4 prior systemic therapies had been treated; combination treatment had an acceptable safety profile and achieved a disease control rate of 72% [67]. Abemaciclib is also being investigated in combination with endocrine or HER2-targeted therapies in a phase Ib study in metastatic breast cancer. Phase III studies that are underway in

postmenopausal breast cancer include the MONARCH 2 study (NCT02107703) of abemaciclib plus fulvestrant in advanced HR+, HER2-negative breast cancer and the MONARCH 3 study (NCT02246621) of abemaciclib in combination with an NSAID (letrozole or anastrozole) in recurrent or metastatic HR+, HER2-negative breast cancer.

Abemaciclib Clinical Safety and Efficacy:

As of 22 September 2016, Abemaciclib has been administered to 2087 cancer patients. There are 16 ongoing and 5 completed clinical studies in cancer patients. Clinical study data are available for 870 patients from 5 completed studies

A total of 124 patient deaths have been reported, including 21 deaths while on therapy, 103 deaths during follow-up period. The majority of deaths (105) were due to study disease. Adverse event related deaths were attributed to included sepsis, lung infection, and pneumonitis.

Treatment emergent adverse events (TEAEs) Possibly Related to Abemaciclib Monotherapy In Study JPBA Part A (N = 33), included diarrhea (42.4%); fatigue, nausea, and neutrophil count decreased (21.2% each); vomiting (18.2%); creatinine increased (15.2%); and abdominal pain, anemia, and white blood cell (WBC) count decreased (12.1% each). Grade 3 TEAEs possibly related to abemaciclib for patients in Part A included fatigue (9.1%), neutrophil count decreased and WBC decreased (6.1% each) and anemia, creatinine increased, diarrhea, hypokalemia, lymphocyte count decreased, lung infection, and nausea (3.0% each). No Grade 4 or 5 TEAEs possibly related to abemaciclib treatment were reported in Part A.

In Study JPBA Parts B through F (N = 173), the most frequently reported TEAEs possibly related to abemaciclib (emaciclIn solid tumor patients who received single-agent abemaciclib during dose-expansion phase included diarrhea (63.0%), nausea (45.1%), fatigue (40.5%), vomiting (24.9%), WBC decreased (24.9%), platelet count decreased (23.1%), neutrophil count decreased (22.5%), anemia (19.7%), anorexia (17.3%), creatinine increased (11.0%), and weight loss (10.4%). Grade 3 TEAEs possibly related to study drug for patients in Parts B through F included WBC decreased (9.8%); neutrophil count decreased (9.2%); platelet count decreased (6.9%); diarrhea and lymphocyte count decreased (5.2% each); anemia (4.0%); fatigue (2.9%); nausea (2.3%); confusion, hypokalemia, hyponatremia, and vomiting (1.2% each); and ALT increased, colitis, dysphasia, febrile neutropenia, gait disturbance, hypotension, pneumonitis, and rash acneiform (0.6% each). Grade 4 TEAEs possibly related to study drug for patients in Parts B through F included neutrophil count decreased (1.2%) and

lymphocyte count decreased (0.6%). No patient had Grade 5 TEAEs possibly related to study drug.

In Study JPBA Parts A through F, there were no possibly related treatment-emergent CTCAE laboratory toxicities (any grade) that were reported. The most common TEAEs in patients who received single-agent abemaciclib included diarrhea (67.9%), thrombocytopenia (50.0%), neutropenia (39.3%), fatigue and vomiting (28.6% each), nausea (25.0%), anemia and blood creatinine increased (21.4% each), leukopenia (14.3%), and abdominal pain (10.7%). Grade 3 TEAEs possibly related to study drug included diarrhea (14.3%); thrombocytopenia (21.4%); leukopenia, nausea, and neutropenia (7.1% each); and blood creatinine increased, lung infection, lymphorrhea, pyrexia, and somnolence (3.6% each). Grade 4 TEAEs possibly related to study drug included neutropenia (25.0%) and thrombocytopenia (17.9%). One Grade 5 TEAE of sepsis that was possibly related to study drug was reported.

Possibly related treatment-emergent CTCAE laboratory toxicities (any grade) occurring in possibly related treatment-emergent CTCAE laboratory toxicities (any grade) neutropenia [39.3%]. In Study JPBC (N = 12), the most common TEAEs laboratory toxicities (any grade) occurring and hypokalemia, hyponatremia, and vomiting (1.2% each); and AL in Japanese patients with advanced cancer who received single-agent abemaciclib included blood creatinine increased and diarrhea (75.0% each); decreased appetite, neutropenia, vomiting, and WBC decreased (41.7% each); nausea (33.3%); dysgeusia, fatigue, leukopenia, thrombocytopenia, and weight decreased (25.0% each); anemia, malaise, neutrophil count decreased, platelet count decreased, and stomatitis (16.7%). Grade 3 TEAEs possibly related to study drug included WBC decreased (33.3%); and neutropenia, thrombocytopenia, diarrhea, neutrophil count decreased, hemoglobin decreased, and lymphocyte count decreased (8.3% each). No patient had Grade 4 or 5 TEAEs possibly related to study drug. All 12 patients experienced at least 1 CTCAE laboratory toxicity. Significant laboratory abnormalities were recorded as AEs.

In Study JPBE (N = 26), during drug-interaction phase, no TEAEs possibly related to abemaciclib were reported in drug-interaction phase, no TEAEs possibly abemaciclib-related TEAEs were Grade 1. During safety extension phase, the most common TEAEs (were Grade 1. During safety extension phase, the most were diarrhea (13 patients); fatigue (11 patients); neutrophil count decreased and anemia (9 patients each); vomiting and nausea (7 patients each); hypokalemia (6 patients); blood creatinine increased (5 patients); platelet count decreased, decreased appetite, and dysgeusia (3 patients each); dehydration, asthenia, headache, hypomagnesemia, hypotension, and stomatitis (2 patients each). Grade 3 TEAEs possibly related to study drug included neutrophil count decreased (6 patients); fatigue and anemia (4 patients each); diarrhea and nausea (2

patients each) and vomiting, WBC decreased, hyponatremia, hypokalemia, dehydration, and blood creatinine increased (1 patient each). One Grade 4 TEAE of anemia possibly related to study drug was reported. No patient had Grade 5 TEAEs possibly related to study drug. All clinically relevant clinical chemistry abnormalities were considered by the investigator to be unrelated to study drug, with the exception of an AE of hypoglycaemia (1 patient, related to clarithromycin) and an AE of increased AST (1 patient on Period 2, Day 5 following coadministration of LY2835219 and clarithromycin). There were no other clinically relevant abnormalities in liver parameters noted during the drug-interaction phase. The most frequently reported clinical chemistry abnormalities during the safety-extension phase, considered by the investigator to be related to study drug, included hypokalemia (6 patients), increased creatinine (5 patients), and hypomagnesemia (2 patients). Increased alanine transaminase, bilirubin, hypercalcemia, hyperglycemia, and hyponatremia were each reported for a single patient during the safety-extension phase.

In Study JPBN (N = 132), the most common TEAEs in the safety-extension phase drug in previously treated, hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2one receptor positive (HR+), human epidermal grow single-agent abemaciclib included diarrhea (88.6%); nausea (59.1%); fatigue (56.8%); decreased appetite (39.4%); neutropenia (36.4%); abdominal pain (30.3%); vomiting (29.5%); anemia (21.2%); thrombocytopenia (18.9%); leukopenia (17.4%); dry mouth and dysgeusia (12.1% each) and alopecia and stomatitis (10.6% each). Grade 3 TEAEs possibly related to study drug included neutropenia and diarrhea (18.9% each); fatigue (10.6%); leukopenia (5.3%); anemia (3.8%); thrombocytopenia, nausea, and decreased appetite (3.0% each); lymphopenia (2.3%); abdominal pain, AST increased, hypokalemia, and dyspnea (1.5% each); hematotoxicity, vomiting, pancreatitis, general physical health deterioration, skin infection, ALT increased, international normalized ratio increased, liver function test abnormal, muscular weakness, confusional state, chronic kidney disease, rash, embolism, and hypertension (0.8% each). Grade 4 TEAEs possibly related to study drug included neutropenia (5.3%); leukopenia, gammaglutamyltransferase increased, and hypertriglyceridemia (0.8% each). One Grade 5 TEAE of pneumonitis possibly related to study drug was reported. Six patients experienced a treatment-emergent Grade 3 ALT increased or AST increased; of these, 3 patients experienced progressive disease (PD) in their liver, 1 patient developed ascites, 1 patient had a single episode of Grade 3 ALT increased and AST increased that resolved without dose omission or reduction, and 1 patient experienced ALT increased 22 days after discontinuation of study medication for PD. One additional patient experienced a simultaneous rise in serum ALT and AST $>3 \times \text{ULN}$ with a rise in bilirubin $>2 \times \text{ULN}$. This patient experienced disease progression in the liver at the time of these events. Treatment-emergent CTCAE central laboratory abnormalities (any grade) that were

reported in urgent CTCAE central laboratory abnormalities (any grade) that w decreased (90.8%), neutrophil count decreased (87.7%), anemia (68.5%), lymphocyte count decreased (42.3%), platelet count decreased (41.4%), ALT increased (30.8%), AST increased (30.0%), and alkaline phosphatase increased and hypokalemia (26.2%). A review of the laboratory values shows the bulk of liver enzyme increases occurred during Cycle 2 and beyond. Three patients had the initial Grade 2 AST increased on Days 1, 93, and 99 of the study. Six patients had a maximum Grade 3 AST increased with the initial onset occurring between Days 1 and 382 after the start of abemaciclib. Similarly, 6 patients experienced Grade 2 ALT increased with the initial onset of the increase occurring on Days 15, 39, 57, 99 (2 patients), and 382. Four patients developed Grade 3 ALT increased that occurred on Days 29, 54, 93, and 344 of treatment.

TEAEs Possibly Related to Abemaciclib Combinations:

With fulvestrant: In Study JPBA Part G (N = 19), the most frequently reported TEAEs possibly related to study drug (Part G (N = 19), the most frequently reported TEAE abemaciclib with fulvestrant included diarrhea (78.9%); fatigue (68.4%); nausea (63.2%); neutrophil count decreased and vomiting (42.1% each); anorexia and WBC decreased (31.6% each); abdominal pain (21.1%); dehydration, hypokalemia, and watering eyes (15.8% each); and anemia, constipation, creatinine increased, dyspepsia, and platelet count decreased (10.5% each). Grade 3 TEAEs possibly related to study drug for patients in Part G included neutrophil count decreased (31.6%); WBC decreased (26.3%); abdominal pain and anemia (10.5% each); and diarrhea, fatigue, infection, syncope, and vomiting (5.3% each). No Grade 4 AEs possibly related to treatment were reported in Part G. No patient had Grade 5 TEAEs possibly related to study drug.

Two, unexpected hepatic SAEs (1 of liver failure and 1 of drug-induced liver injury) were identified in the open-label Phase 3 JUNIPER (I3Y-MC-JPBK) study comparing abemaciclib versus erlotinib in patients with Stage IV NSCLC. Both of these hepatic SAEs had confounding factors including prior treatment with nivolumab and baseline hepatic metastases. At this time and based on this review, there is a potential causal association of hepatic events, including ALT/AST elevation, with treatment with abemaciclib. Liver injury is considered an important potential risk with abemaciclib, and this risk will continue to be closely monitored in ongoing clinical program.

Three, fatal, unexpected SAEs of encephalopathy have been reported. One case from Study JPBB that was considered unrelated to abemaciclib treatment developed progressive multifocal leukoencephalopathy approximately 8 weeks after the start of abemaciclib treatment. The remaining 2 cases, both from Study JPBK, were considered possibly related to abemaciclib treatment by the investigator. In 1 patient, with CNS metastases, the onset of life-threatening encephalopathy occurred 13 days after the

initiation of abemaciclib. The patient presented with meaningless speech and agitation, a computed tomography showed ischemia cerebrovascular; despite medical management, the patient died the following day. No autopsy was performed. Confounding factors included central nervous system metastases, former alcohol use, and tobacco use. The second case presented with hepatic failure and also reported several other events including encephalopathy. The encephalopathy was diagnosed 9 weeks from the start of abemaciclib treatment. The patient's condition deteriorated with no improvement in the encephalopathy. There were multiple confounding factors. The patient died due to hepatic failure.

Teratogenic Effects:

Based on the findings in animals, Abemaciclib can cause fetal harm when administered to a pregnant woman. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on the area under the plasma concentration versus time curve (AUC) at the recommended human dose. Therefore, teratogenicity is considered an important potential risk for Abemaciclib. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

To minimize any potential risks, men and women with reproductive potential are either excluded from clinical studies, or instructed to use highly effective contraception during treatment and for 3 months following the last dose of abemaciclib. A negative serum pregnancy test is required for women of child-bearing potential prior to commencing abemaciclib therapy. There are no data on the presence of Abemaciclib in human milk, the effects of abemaciclib on the breastfed child, or the effects of abemaciclib on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from abemaciclib, advise a nursing woman to discontinue breastfeeding during treatment with abemaciclib.

Combined Fulvestrant and Abemaciclib in Endometrial Cancer :

Targeting the hormonal and CDK4/6 pathway represents an attractive strategy in patients with tumor types harboring an activating alteration of the ER/PR signaling pathway. To date, no hormonal/CDK4/6 inhibitor combination has been approved for endometrial cancer therapy, and hence this investigator initiated study represents a rational investigative and potentially promising treatment strategy for this specific cohort of advanced endometrial cancer. With the mechanistic and preclinical background provided above, we propose a single arm, open-label, phase II study of Fulvestrant in combination with Abemaciclib in hormone positive endometrioid adenocarcinoma of endometrium.

Currently, Phase I/II trials evaluating CDK4/6 inhibitors (Palbociclib and Ribociclib) in solid tumors including endometrial cancers are under way.

Dose Rationale:

Pharmacokinetic data obtained in the Study JPBA for abemaciclib from a total of 124 patients dosed repeatedly with Abemaciclib a 150mg and 200mg Q12 hours indicate that the range of study-state exposures achieved with 150mg Q12h is comparable to 200mg Q12h. In addition, in Study JPBA the steady-state exposure achieved with a 50mg unit dose, which is the lowest possible allowed dose in Study JPBL in the case of dose reduction when needed for AEs, are within the low end of the range of exposures achieved by the 150mg and 200mg dose levels. Skin biopsies collected in Study JPBA pre-dose and 4 hours post dose on Cycle 1Day15 show a decrease in the pRb and topolli α expression with increasing plasma concentration. Abemaciclib effectively inhibits CDK4/6, which results on cell cycle inhibition upstream of the G1 restriction point at both doses of 150mg and 200mg.

Tumor responses were observed in patients receiving both 150mg and 200mg Abemaciclib monotherapy. As of 20 August 2014, findings in the 47 patients with advanced or metastatic breast cancer who have been enrolled resulting in 12 confirmed PRs (including 8 responses at 150mg Q12 and 4 responses at 200mg Q12H) among 36 patients with HR+mBC, based on investigators assessment of response using RECIST v1.1. The objective response rate (ORR) for the 36 patients with HR+mBC was 33% and the disease control rate (DCR) was 80.6%, clinical benefit rate (CBR) was 61.1%, and the median PFS was 8.8 months.

In a subsequent cohort of 19 patients with HR+, advanced or metastatic breast cancer treated with fulvestrant plus 200mg abemaciclib Q12h, 17 patients abemaciclib dose reductions were observed. In addition, 4 confirmed PRs were observed for an ORR was 21.1% (36.4% in the 11 patients with measurable disease), the DCR was 78.9%, the CBR was 63.2%, and the median PFS was 10.3 months.

Although the Phase I experience demonstrated that the 200mg Q12H Abemaciclib dose was tolerable with administered in combination with fulvestrant, a substantial number of patients required abemaciclib dose suspension and/or reduction during the first 2 treatment cycles. Hence, based on this observation, initial dose of abemaciclib in combination with fulvestrant has been reduced to 150mg in MONARCH 2: A randomized, double-blind, placebo-controlled, phase III trial of fulvestrant with or without abemaciclib, a CDK4/6

inhibitor, for women with HR+, Her 2 negative locally advanced or metastatic breast cancer. And this dosing will be carried forth in our study.

Tumor Genetic Profiling at MSKCC

In January 2014 MSKCC received New York State CLIA-approval for a next generation Illumina HiSeq exon-capture based platform ("MSK-IMPACT") which offers complete coverage of nearly 500 cancers related genes and can identify base substitutions, indels, copy number alterations and select translocations. Importantly, MSK-IMPACT covers all genes relevant to the cyclin dependant kinase pathway, including CDK4, CDK6, CDKN2A, and RB1, as well as genomic alterations in the PI3K pathway including PTEN, PIK3CA, PIK3R1, PIK3R2, AKT1, mTOR, and the MAPK pathway (RAS, RAF, MAP2K), which may be involved in mechanisms of resistance. 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 molecular profiles associated with response and resistance to combination fulvestrant and Abemaciclib therapy.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

1.1 Design

This is an MSKCC investigator-initiated, single-center, non-randomized, open-label, phase II study to evaluate the activity of Abemaciclib dosed 150 mg orally once approximately every 12 hours on days 1-28 in combination with fulvestrant 500mg intramuscularly (IM) on days 1 and 15 during cycle 1 and then on Day 1 during subsequent cycles in patients with hormone positive recurrent or persistent endometrial cancer.

Each cycle will be 28 days in duration. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study, or study termination. Efficacy assessments will be performed every 8 weeks from cycle 1 Day 1 until disease progression. Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0).

Twenty-five patients will be enrolled over approximately 2 years.

1.2 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

Each dose of Abemaciclib should be taken with a minimum of 8 ounces of water. Patients should take the 150mg morning and evening doses of abemaciclib approximately 12 hours apart (preferably within a 10- to 14-hour range) on Days 1-28 of a 28-day cycle.

Patients should not consume food for approximately 1 hour before and 1 hour after taking the dose of Abemaciclib. Abemaciclib should be taken whole (not chewed or crushed). 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.

Fulvestrant will be administered as one 250 mg intramuscular injections (500 mg in total) slowly (approximately 1-2 minutes per injection), one in each buttock, on days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond.

Each cycle will be 28 days in duration. A cycle is defined as the planned treatment interval of 28 days plus any subsequent delay prior to start of the next cycle. A delay in the start of a cycle due to holidays, weekends, inclement weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation. For each 28 day cycle, a total of 56 doses of oral abemaciclib will be dispensed. In exceptional cases, for planned delays (including but not limited to vacation or holidays), additional oral drug may be dispensed.

On the days when both study drugs are administered, the morning dose of Abemaciclib should be administered first. Fulvestrant should be administered at the same time as (or within 20 minutes after) the morning dose of Abemaciclib, except if specified otherwise.

Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study or study termination.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Abemaciclib

Lilly compound number:	LY2835219
Chemical Name (CA Index Name):	2-Pyrimidinamine, N-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1Hbenzimidazol-6-yl]-N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1Hbenzo[d]imidazol-6-yl)pyrimidin-2-amine
Molecular weight:	506.60
Molecular/Empirical Formula:	C ₂₇ H ₃₂ F ₂ N ₈
Description:	Practically-white to yellow solid
pKa:	7.95, 4.48, 3.80
Stability:	Drug substance is stable at room temperature
Solubility:	0.001 mg/mL in water 22.313 mg/mL in ethanol

Drug Product Name, Unit Formula, and Strength(s)

Abemaciclib drug product is supplied for clinical trial use either as Abemaciclib with excipients in hypromellose capsules or as abemaciclib tablets.

The drug product is supplied as follows:

Abemaciclib will be provided as 50 mg tablets or capsules in bottles.

Abemaciclib must be stored at room temperature. For specific storage instructions refer to the product label.

Storage Conditions:

The drug products are stable when stored according to instructions on the label.

Labeling: Each bottle of Abemaciclib will be labeled in accordance with current FDA and specific national requirement. Fulvestrant will be locally sourced as 250mg prefilled syringes (25mg/5ml). Site will confirm fulvestrant source to ensure adequate supply. Fulvestrant should be stored according to the product label and administered according to the instructions in the protocol.

Drug Product Accountability: Study drug for the study is 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 before being returned. 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 is 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 signed an approved informed consent and authorization permitting release of personal information.
2. Age ≥ 18 years
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
4. Patients are not required to but may have received no more than two 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.
 - Chemotherapy administered in conjunction with primary radiation as a radiosensitizer **WILL** be counted as a systemic chemotherapy regimen.
5. Patients are not required to but may have received a single line of prior hormonal therapy with either an antiestrogen, anti-progesterone (or combination) or an aromatase inhibitor. Patients may not have received more than 1 line of endocrine therapy. This will not count toward prior therapy total.
6. Resolution of adverse effects of recent surgery, radiotherapy, chemotherapy, or hormonal therapy to Grade ≤ 1 prior to first study treatment with the exception of peripheral neuropathy and alopecia.
7. Postmenopausal status due to either surgical or natural menopause. Postmenopausal status due to surgical/natural menopause requires at least 1 of the following:
 - History of hysterectomy
 - Prior bilateral oophorectomy
 - Age ≥ 60
 - Age ≤ 60 and amenorrheic for at least 12 months (in the absence of chemotherapy, hormonal therapy or ovarian suppression) and FSH and estradiol levels in the postmenopausal range.
 - Have a negative serum pregnancy test at baseline (within 14 days prior to - initiation of treatment) and agree to use medically approved precautions to prevent pregnancy during the study and for 1 month following the last dose of Abemaciclib.

8. Disease that is measurable as per RECIST v1.1.
 - Tumors within a previously irradiated field will be designated as “non-target” lesions unless progression is documented, or a biopsy is obtained to confirm persistence of tumor $\geq$ 90 days following completion of radiation therapy.
9. No active infection requiring antibiotics (with the exception of uncomplicated urinary tract infection). Any hormonal therapy directed at the malignant tumor must be discontinued at least 2 weeks prior to the first study treatment.
10. Patients must meet all the following criteria to be eligible for study entry:
 - a) Patients must have recurrent or persistent endometrial carcinoma that is refractory to curative therapy or established treatments.
 - b) Histologic confirmation of the original primary tumor is required.
 - c) Histologic or cytologic confirmation of the recurrent/progressive disease is desired, but not required.
 - d) Patients with the following histologic epithelial cell types are eligible: endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, de-differentiated, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.), mucinous adenocarcinoma, squamous cell carcinoma, and transitional cell carcinoma.
 - For mixed epithelial cell type endometrial carcinomas, the endometrioid component should comprise at least 95% of the total tumor and the non-endometrioid component should comprise less than 5% of the total tumor.
 - e) Patient must have hormone receptor positive (HR+) endometrial cancer confirmed by MSK pathology:
 - To fulfill the requirement for HR+ disease, tumor must express by immunohistochemistry (IHC), at least 1 of the hormone receptors (estrogen receptor [ER] or progesterone receptor [PgR] as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Hammond et al, 2010)
11. Any prior therapy directed at the malignant tumor, including immunologic agents and radiotherapy, must be discontinued prior to first study treatment.
 - Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade $\leq$ 1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to randomization. A washout period of at least 21 days is required between last chemotherapy dose and randomization (provided the patient did not receive radiotherapy).

- Patients who received radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and randomization.
12. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first study treatment:
- Absolute neutrophil count (ANC) $\geq 1500/10^9\text{dL}$
 - Platelet count $\geq 100,000/10^9\text{dL}$
 - Hemoglobin $\geq 9.0\text{ g/dL}$
 - Albumin $\geq 3.0\text{ g/dL}$
 - Total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN)
 - AST and ALT $\leq 3.0 \times$ ULN
13. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN. For patients requiring therapeutic anticoagulation, a stable INR $\leq 3 \times$ ULN is required.
14. Are able to swallow capsules/tablets
15. Are willing to follow study procedures
16. 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 abemaciclib dose.

6.2 Subject Exclusion Criteria

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

1. Patient has received an experimental treatment in a clinical trial within the last 30 days or 5 half-lives, whichever is longer, prior to randomization, or is currently enrolled in any other type of medical research (for example: medical device) judged by the sponsor not to be scientifically or medically compatible with this study.
2. Patient who is experiencing a visceral crisis, lymphangitic disease spread, leptomeningeal carcinomatosis. Visceral crisis is not the mere presence of

visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of disease.

3. Patients who have received prior treatment with fulvestrant, everolimus, temsirolimus, ridaforolimus or another mTor inhibitor, or any CDK4 and CDK6 inhibitor
4. Patients who have received an autologous or allogenic stem-cell transplant
5. Clinically significant history of liver disease, including cirrhosis and current alcohol abuse.
6. Patients who have active systemic bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection.
7. Presence of positive test results for hepatitis B (hepatitis B surface antigen [HBsAGg] and/or total HB core antibody [anti-HBc]) or hepatitis C (hepatitis C virus [HCV] antibody serology testing)
8. Patients positive for anti-HBc are eligible only if also positive for HB surface antibody (anti-HBs) and polymerase chain reaction (PCR) assay is negative for HBV DNA.
 - Patients positive for HCV antibody are eligible only if testing for HCV RNA is negative.
9. Known HIV infection.
10. Active autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs.
11. Pregnancy, lactation, breastfeeding.
12. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
13. Major surgical procedure within 14 days prior to randomization, 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

14. Have initiated biphosphonate or RANKligand targeted agents (for example, denosumab) <7 days prior to Cycle 1 Day 1
15. Uncontrolled hypomagnesemia or hypokalemia, defined as values below the lower limit of normal despite optimal electrolyte supplementation or management
16. Leptomeningeal disease as a manifestation of cancer
17. Known untreated or active central nervous system (CNS) metastases (progression 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. Screening CNS radiographic study is ≤ 6 months after most recent intervention for CNS metastases (neurological resection, radiotherapy, or brain biopsy) and ≥ 4 months after the discontinuation of corticosteroids
18. Inability to comply with study and follow-up procedures
19. 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
20. Patients who have:
 - History of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest
 - New York Heart Association Class II or greater congestive heart failure (see Appendix A)
 - History of malabsorption syndrome or other condition that would interfere with enteral absorption

- Inability or unwillingness to swallow pills
- Serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).

7.0 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. Approximately 1 patient will accrue onto this study per month.

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.

Patients who respond to therapy and then progress will be offered a consent to MSKCC IRB# 06-107 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. Specifically, we will be looking for presence of genetic alterations which based on their understood biological mechanism may explain acquired resistance.

The goal is to establish xenografts utilizing IRB Protocol # 13-040 from patients whose tumors have been exposed to drug and demonstrated resistance. These tumors will then be genomically characterized to understand the possible basis for resistance and enable rational testing of drug strategies. Median Progression free survival with hormonal therapies is in the order of 2-4 months in advanced endometrial cancer, and while we hypothesize that the combination of Abemaciclib and Fulvestrant will result in improved efficacy, it is imperative that mechanisms of acquired resistance be explored so that further optimization of therapy for resistant patients can occur, and to that we can be better informed of next step combination

approaches to treat this disease, and in particular hormone receptor positive endometrial cancers, which comprise over 50% of recurrent disease cases.

8.0 PRETREATMENT EVALUATION

Within 28 days prior to treatment start:

- History and Physical
- Review of Medications
- Vital signs (blood pressure, heart rate and temperature), weight and height
- Performance status (ECOG)
- Toxicity assessment
- 12-lead ECG
- Radiographic tumor measurements (CT C/A/P)
- Hepatitis B and C screening (only if never done previously)

Within 14 days prior to treatment start:

- Complete Blood Count (CBC) with differential and platelets
- Comprehensive profile (BUN, sodium, potassium, chloride, CO₂, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT), CA125
- Body weight
- Urinalysis
- Blood glucose
- Pregnancy test (in women of child-bearing potential)

9.0 TREATMENT/INTERVENTION PLAN

Eligible patients will undergo screening and baseline procedures per the Study Schedule. Study inclusion and exclusion criteria will be applied per section 6.0

Each dose should be taken with a minimum of 8 ounces of water. Patients should take the 150mg morning and evening doses of Abemaciclib approximately 12 hours apart (preferably within a 10- to 14-hour range) on Days 1-28 of a 28-day cycle.

Patients should not consume food for approximately 1 hour before and 1 hour after taking the dose of Abemaciclib. Abemaciclib should be taken whole (not be chewed or crushed). 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.

Fulvestrant will be administered as one 250 mg intramuscular injections (500 mg in total) slowly (approximately 1-2 minutes per injection), one in each buttock, on days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond.

Each cycle will be 28 days in duration. A cycle is defined as the planned treatment interval of 28 days plus any subsequent delay prior to start of the next cycle. A delay in the start of a cycle due to holidays, weekends, inclement weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation. For each 28 day cycle, a total of 56 doses of oral abemaciclib will be dispensed. In exceptional cases, for planned delays (including but not limited to vacation or holidays), additional oral drug may be dispensed.

Fulvestrant should be administered at the same time as (or within 20 minutes of) the morning dose of Abemaciclib, except if specified otherwise.

Patients will receive study treatment until disease progression, intolerable toxicity elective withdrawal from the study or study termination.

If a patient withdraws from participant in the study prior to initiation of the study treatment, the withdrawn patients will be replaced. His or her enrollment number cannot be reused.

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.

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications will be captured at each visit in the eCRF and will be recorded throughout the patient's participation in the study. Concomitant medications and supportive care therapies will also be documented at the time of discontinuation and at the 30 day post treatment discontinuation visit.

With the exceptions listed in the sections below, therapies for cancer (including specifically aromatase inhibitors, anti-estrogens other than fulvestrant, chemotherapy, and immunotherapy) will not be permitted while patients are on study treatment. Use of megestrol acetate as an appetite stimulant is not permitted.

Results from the human disposition (I3Y-MC-JPBD) and in vitro human recombinant CYP phenotyping studies indicate that Abemaciclib is extensively metabolized primarily via CYP3A. based on these findings, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of CYP3A should be substituted or avoided if possible (Appendix B).

Additionally, invitro studies in cultured human hepatocytes indicate that abemaciclib and its major metabolites LSN2839567 and LSN3106726 downregulate mRNA of CYPs including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A at clinically relevant concentrations. The mechanism of down regulation and its clinical relevance are presently not understood. Therefore, care should be taken when coadministering substrate drugs of the above CYPs with narrow therapeutic margin (Attachment 8).

Radiotherapy is not permitted without permanent discontinuation from study treatment.

Supportive Care:

Patients should receive full supportive care to maximize quality of life. Patients may receive supportive care as decided by their treatment physician. Use of supportive care therapy should be reported in the eCRF.

Growth Factors:

Growth factors should not be administered to a patient to satisfy study inclusion criteria. Growth factors may be administered while on study treatment in accordance with ASCO guidelines (Smith et al. 2015). Dosing of study drug must

be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of study drug must be reduced by 1 dose level on recommencement.

Supportive Management for Diarrhea:

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

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patient should be encouraged to drink non-caffeinated fluids (e.g., 8-10 glasses per day)
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours at least Grade 1, study drug should be suspended until diarrhea is resolved to at least Grade 1.
- When Drug resumes, dosing should be adjusted as outlined in Section 11.
- In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.
- If diarrhea is severe (requiring IV rehydration) and/or associated with fever or neutropenia, broad spectrum antibiotics must be prescribed.
- Patients with severe diarrhea of any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid and electrolyte replacement.

Bisphosphonates and RANK-L Targeted Agents:

- Patients with bone metastases presents on baseline imaging may be appropriately treated with bisphosphate or RANK-L targeted agents, per approved labels. Initiation of bone-modifying agents must begin at least 7 days prior to initiation of study treatment. Patients receiving bisphosphate of RANK-L targeted agents should not switch treatments while on study treatment.

Treatment Compliance:

- Treatment compliance information will be collected through counts at each visit, and the number of abemaciclib capsules/tablets taken relative to the total number of expected to be taken will be summarized for each cycle. A patient must take $\geq 75\%$ of the planned doses for assigned study drug in a cycle to be deemed compliant. Similarly, a patient may be considered noncompliant if she is judged by the investigator to have intentionally or repeatedly taken $\geq 125\%$ of the planned doses of study drug in a cycle. Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the principal investigator before any determination is made to discontinue the patient.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

STUDY CALENDAR									
PARAMETER	Screening		Cycle 1			Cycle 2+	End of Treatment	30 Day Follow up	Follow-up
Day	28 Days before TX start date	14 Days before start TX start date	1	8 ± 3 Days	15 ± 3 Days	1 ± 3 Days	± 7 Days	± 14 Days	Every 3 months until death ±1 month
Medical History	X								
Physical Examination	X		X		X	X	X	X	
Performance Status	X		X	X	X	X	X	X	
Height	X								
Weight		X	X	X	X	X	X	X	
Vital Signs (blood pressure, heart rate and temperature)	X		X	X	X	X	X	X	
Adverse Event Assessment			X	X	X	X	X	X	
HBV/HCV/HIV ⁹	X								
CBC with differential		X	X ²	X	X	X	X	X	
Comprehensive Profile ¹⁰		X	X ²	X	X	X	X	X	
Magnesium		X	X ²	X	X	X	X	X	
Phosphorus		X	X ²	X	X	X	X		
PT, INR, PTT		X					X		
Pregnancy test		X ¹					X ¹		
CA125		X	X ²			X	X		
Urinalysis		X							
ECG	X			X		X	X		
CELL Free DNA ⁸			X ²	X		X (Day 1 of an Odd cycle)			
Radiographic disease assessment	X		X ³				X ³		X ⁴
Patient drug diary			X						
Survival Follow-up									X ⁵
Fulvestrant Administration			X ⁶		X ⁶	X ⁶			
Abemaciclib			X ⁷			X ⁷			

1. If the patient is of child-bearing potential per MSKCC guidelines a pregnancy test must be obtained as standard of care.
2. Test can be omitted on Cycle 1 Day 1 if screening labs were performed within 72 hours.
3. Perform every 8 weeks from cycle 1 Day 1 (window +/- 7 days) for the first 6 months, then every 12 weeks (+/- 7 days) until clinical progression. End of treatment radiographic disease assessment will be performed if due to toxicity.
4. Only if patient discontinues for reasons other than progression, repeat every 3 months (+/- 14 days) until disease progression or initiation of alternative anti-cancer therapy.
5. Phone call every 3 months.
6. Fulvestrant will be administered Days 1 and 15 of Cycle 1 and then Day 1 of Cycle 2 and Beyond
7. Abemaciclib will be taken orally every 12 hours on Days 1 through 28 of every cycle
8. CELL Free DNA: will be collected at the same time as routine blood collection at the specified time points. Processing will occur per MSKCC laboratory medicine procedures.
9. Those tests do not need to be repeated if results are available in EMR from prior testing.
10. ALT/AST will be monitored during screening/Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 15, Day 1 of Cycle 3 and beyond, and as clinically indicated.

11.0 TOXICITIES/SIDE EFFECTS

Dose Adjustments and Delays

Table 1: Toxicity Dose Adjustments and Delays for Abemaciclib

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 3	Dose MUST be suspended until toxicity resolves to at least Grade 2	Dose MAY be reduced by 1 dose level- investigator's discretion
Hematologic Toxicity	Recurrent Grade 3	Dose MUST be suspended until toxicity resolves to at least Grade 2	Dose MUST be reduced by 1 dose level
Hematologic Toxicity	Grade 4	Dose MUST be suspended until toxicity resolves to at least Grade 2	Dose MUST be reduced by 1 dose level
Hematologic Toxicity: Patient requires administration of blood cell growth factors	Regardless of severity (Growth factors Growth factor use according to ASCO Guidelines)	Dose MUST be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose MUST be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of the growth factor.
Nonhematologic Toxicity (Except Diarrhea, increased	Persistent of recurrent Grade 2 that does not resolve	Dose MUST be suspended until toxicity resolves to	Dose MUST be reduced by 1 dose level

ALT/AST, and ILD/Pneumonitis)	with maximal supportive measures within 7 days to baseline of Grade 1	either baseline or at least Grade 1	
Nonhematologic Toxicity (Except Diarrhea, increased ALT/AST, and ILD/Pneumonitis)	Grade 3 or 4	Dose MUST be suspended until toxicity resolves to either baseline or at least Grade 1	Dose MUST be reduced by 1 dose level
Diarrhea	Grade 2	Dose MUST be suspended until toxicity resolves to at least Grade 1, if toxicity does not resolve within 24 hours to at least Grade 1	Dose reduction is not required.
Diarrhea	Requires hospitalization or Grade 3 or 4	Dose MUST be suspended until toxicity resolves to at least Grade 1	Dose MUST be reduced by 1 dose level
Diarrhea	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 24 hours to at least Grade 1	Dose SHOULD be suspended until toxicity resolved to at least Grade 1	Dose MAY be reduced by 1 dose level- investigator's discretion
Diarrhea	Diarrhea recurs despite maximal supportive measures after resuming same dose level after initial Grade 2 diarrhea	Dose MUST be suspended until toxicity resolves to at least Grade 1	Dose MUST be reduced by 1 dose level
Increased ALT/AST	Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN), WITHOUT increase in total bilirubin above 2 X ULN	Dose MUST be suspended until toxicity resolves to baseline or Grade 1	Dose MUST be reduced by 1 dose level
Increased ALT/AST	Elevation in AST and/or ALT>3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue abemaciclib	
Increased ALT/AST	Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.	

Interstitial Lung Disease/Pneumonitis	Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose MUST be suspended until toxicity resolves to baseline or Grade 1	Dose MUST be reduced by 1 dose level
Interstitial Lung Disease/Pneumonitis	Grade 3 or 4	Discontinue abemaciclib	

Abbreviation: ASCO= American Society of Clinical Oncology

Note: May= per the investigator's clinical judgment; SHOULD=not mandatory but highly recommended; MUST=mandatory

Dose Adjustments:

Abemaciclib:

Abemaciclib dose adjustments are allowed both within a cycle and between cycles. For patients requiring dose reduction (s), re-escalation to a prior dose level is only permitted after consultation with the principal investigator.

Table 2: Dose Adjustments for Abemaciclib

Dose Adjustment	Oral Dose	Frequency
0	150mg	Q12
-1	100mg	Q12
-2	50mg	Q12

Abbreviation: Q12= every 12 hours

In the event that Abemaciclib must be completely discontinued, a patient may continue to receive fulvestrant.

Fulvestrant:

Dose adjustment for fulvestrant will be determined by the investigator in accordance with the label. For patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250mg injections. In the event that fulvestrant must be discontinued, a patient may continue to receive Abemaciclib.

Dose Suspension (within a cycle) and Cycle Delays:

Both dose suspension (within a cycle) and cycle delay are allowed up to 14 days to allow sufficient time for recovery from toxicity possibly related to a study drug. In the event of a dose suspension of abemaciclib during Cycle 1, fulvestrant may be administered as scheduled on Cycle 1 day 15. If a toxicity possibly related to abemaciclib occurs prior to initiating the next cycle, Fulvestrant may be administered and abemaciclib suspended until recovery from the toxicity. If fulvestrant is administered but the abemaciclib is suspended, the date of fulvestrant administration

shall constitute Day 1 of the next cycle. Patients not recovering from toxicity within 14 days of the last dose of drug(s) [Abemaciclib or Fulvestrant] should be considered for discontinuation of the relevant study (abemaciclib or fulvestrant) drug(s). In exceptional circumstances, a delay > 14 days is permitted upon agreement by the principal investigator.

In the event of a cycle delay due to logistical reasons (for example, due to patient availability), the patient should continue oral Abemaciclib if the patient has adequate drug supply. If a patient's Abemaciclib is interrupted as a result of not having sufficient drug supply, it may be delayed up to 7 days (not considered a protocol violation). In exceptional circumstances, a delay > 7 days is permitted upon discussion with the principal investigator.

General Guidance for Hepatic Monitoring

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation are considered as adverse drug reactions (ADR) with the use of abemaciclib.

Monitor ALT/AST prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.

Close Hepatic Monitoring and Evaluation:

Liver testing including ALT, AST, alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin (D. Bil), gamma-glutamyltransferase (GGT), and creatine kinase (CK), should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5×ULN	ALT or AST ≥5×ULN or ALT or AST ≥3×ULN concurrent with TBL ≥2×ULN
ALT or AST ≥1.5×ULN	ALT or AST ≥3× baseline or ALT or AST ≥2× baseline concurrent with TBL ≥2×ULN

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests, should be initiated by the investigator. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time (PT-INR); serological tests for viral hepatitis

A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the patient's history and initial evaluation results, further testing should be considered, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, and/or a liver biopsy.

General Guidance for Hematology Toxicity and Dose Modification

Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib. Patients should be monitored closely for signs of infection, anemia, and bleeding.

General Guidance for Diarrhea Management

Clinical trial data indicates the majority of patients who receive abemaciclib will develop diarrhea. Our experience indicates early identification and intervention for the management of diarrhea has been helpful to patients.

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

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- Refer to Table 1 for additional information for diarrhea management and dose modification.

General Guidance for Increases in Serum Creatinine and Assessment of Renal Insufficiency

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iothexol

clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

General Guidance for Interstitial Lung Disease (ILD)/Pneumonitis Events

Interstitial lung disease (ILD) /pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

Monitor for clinical symptoms such as hypoxia, dyspnea, cough, and fever, and or radiological changes indicative of ILD/pneumonitis and ask your patients to report any new or worsening pulmonary symptoms and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high resolution computed tomography, bronchoalveolar lavage, and biopsy as clinically indicated. Discontinue abemaciclib in cases of severe (Grade 3 or 4) ILD/pneumonitis.

General Guidance for Venous Thromboembolic Events

VTE has been identified as an ADR for abemaciclib in combination with endocrine therapy. VTEs were not considered to be risks in studies with single agent abemaciclib use in mBC, NSCLC, or other tumor types. No increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. Venous thromboembolic events have been reported with other CDK4 and 6 inhibitors, and ET is known to be associated with the occurrence of VTEs. Monitor patients for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

General Guidance for CYP3A Inhibitors and Inducers

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

CYP3A inducers

Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

Strong CYP3A inhibitors and/or inducers should not be used until the completion of the dose-limiting evaluation period.

General Guidance for Use of Radiotherapy in Combination With Abemaciclib

Limited data are available with abemaciclib and radiotherapy or alternate dosing schedules (e.g. induction phase). Thus, caution should be exercised with coadministering abemaciclib with radiotherapy.

General Guidance for Women of Child Bearing Potential and/or Use of Contraceptive Methods

Based on findings in animals, abemaciclib can cause fetal harm when administered to a pregnant woman. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on the area under the plasma concentration versus time curve (AUC) at the recommended human dose. Therefore, teratogenicity is considered an important potential risk for abemaciclib. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. Additionally, there are no available data on effects of breastfeeding. Advise a nursing woman to discontinue breastfeeding during treatment with abemaciclib.

- A female of childbearing potential must have a negative serum pregnancy test within the first 7 days of the first dose of abemaciclib and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib.
- Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Efficacy Assessments at Baseline and During Study Treatment

Computed tomography (CT), including spiral CT, scans and magnetic resonance imaging (MRI) are the preferred methods of measurement. In addition, bone scintigraphy will be performed for all patients with suspicious bony lesions. If no lesions are confirmed on scintigraphy, all such lesions will be evaluated at baseline with focused studies (X-ray, CT scan with bone windows or MRI) to enable serial assessment.

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 methods of assessment used at baseline must be used consistently for tumor assessment and will be repeated every 8 weeks (+/- 7 days) from Cycle 1 Day 1 for the first 6 months, then every 12 weeks (+/- 7 days) until clinical progression.

For those with bony lesions, the method of assessment used at baseline (X-ray, CT scan with bone windows, or MRI) must be used consistently for tumor assessment and will be repeated every 8 weeks until clinical progression.

Post discontinuation follow-up scans during the study will continue every 12 weeks (+/-14 days) for patients who discontinue treatment without progression of disease until progression of disease or until initiation of an alternative treatment.

After a patient has objective disease progression, radiological tests will no longer be required and the patient will be followed up approximately every 12 weeks ($\pm$ 14 days) until the patient's death or overall study completion.

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). 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.

Assessment of Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

Study Parameters

Definition of adverse events

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements subject data protection.

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP)E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action of intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE. Adverse events may be treatment emergent (i.e, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AE's.

Definition of a Serious Adverse Events (SAE's)

A serious adverse event is a AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the stud drugs that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Required inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject

- In an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAE's (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to Lilly.

Suspected Unexpected Serious Adverse Reactions

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

Any biopsy-related complications deemed grade 2 or higher via CTCAE version 4.0 will also be reported as an adverse event.

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 completed 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.) A cycle is considered complete if a patient received $\geq 75\%$ of planned doses.

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 follow-up. 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.

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).

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	
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. 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 "<i>symptomatic deterioration</i>." Every effort should be made to document the objective progression even after discontinuation of treatment.				

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.

Objective response rate is the percentage of patients with a best response of CR or PR.

Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of 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

13.0 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 on the appropriate eCRF.

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

- Disease progression, per investigator assessment
- Intolerable toxicity of abemaciclib and/or fulvestrant

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 than 2 dose reductions of Abemaciclib
- Treatment delay of more than 14 consecutive days or if patient requires more than 1 reduction (to 250mg) of fulvestrant

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.

* Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported to Lilly. If a patient is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.

14.0 BIOSTATISTICS

This study aims to assess the activity of abemaciclib in combination with fulvestrant in patients with hormone positive recurrent or persistent endometrial cancer as measured by the objective response rate as determined by RECIST 1.1. 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. 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 uses an exact, one-sample test for binomial proportion, with one sided Type I error=10%. 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, Covens 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%).

The overall response rate and its 90% one sided confidence interval will be reported. All patients with any post baseline assessment of efficacy response are evaluable for efficacy. Based on historical accrual rates in similar populations, we anticipate successful enrollment of 1 patient per month yielding a total accrual time of 25 months. Accrual will continue until we enroll 25 evaluable patients for efficacy.

In addition we will report the following statistics:

1. The clinical benefit rate (CBR) of abemaciclib and fulvestrant combination therapy, defined as the percentage of patients with complete response (CR) + partial response (PR) + stable disease (SD) ≥ 16 weeks from the date of enrollment will be reported and the 90% confidence interval will be estimated using exact binomial proportions. All patients will be followed up for 16 weeks
2. Progression free survival (PFS), defined as the interval from the date of enrollment until the first date on which recurrence, progression, or death due to any cause. 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 interval from the date of enrollment 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. The duration of response (DOR) of abemaciclib and fulvestrant combination 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 CTCAE v4.0 will be tabulated in order to assess the safety profile and tolerability of abemaciclib and fulvestrant combination therapy in patients with hormone positive recurrent/persistent endometrial cancer. All patients who receive at least one dose will be evaluable for toxicity.

In addition the study will analyze the following variables as part of assessing exploratory aims:

1. To have patient's tumors molecularly profiled using the MSK-IMPACT platform, pretreatment fresh tumor tissue will be obtained for this purpose. Genomic alterations defined by MSK-IMPACT testing performed on this pretreatment tumor tissue (looking for presence/absence of genes at baseline) will be correlated to objective responses outcomes (binary covariates of CR or PR versus not) in an exploratory manner. Chi square of Fishers' exact test will be used to test this association.
2. Consent for this testing, to be performed in the CLIA laboratory, will be obtained through a companion study MSKCC IRB# 12-245.
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 Rb, CD-K, PI3K- pathway alterations identified by pre-treatment archival tumor testing and descriptively correlated

to clinical outcome. Binary covariates (presence/absence) will be tested for association with response (binary: CR or PR vs not) using Chi square or Fishers' exact test

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.

A subset analysis of patients who respond and then 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 (at progression compared to baseline) which based on their understood biological mechanism may explain acquired resistance.

These analyses will be descriptive with the intention of understanding genetic alterations over time (at progression) and the types of mutation alterations among patients who respond and then progress. Patients will be followed up for a minimum of 12 months.

Most variables above are binary (presence/absence) or expressed (yes/no) and they will be tested for association with response (yes/no) using Chi square or Fishers' exact test. Circulating tumor DNA is a continuous variable and these will be assessed descriptively for changes over time as part of exploratory aims 2 and 4.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. 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.

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

N/A.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, extraction and data entry, data reporting, coordination of the activities of the protocol study team and, of the flow of regulatory compliance.

The data collected for the study will be entered into a secure database (MediData RAVE). All routine blood test results required per protocol will be captured in MediData RAVE in addition to the baseline medical conditions and disease information, response assessments, off-study

documentation, and toxicity grade and attribution. Source documentation will be available to support the electronic patient record.

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

Weekly registration reports will be generated by the CRC 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, prospective and retrospective deviations will be discussed with the study team and a corrective action plan will be generated and shared with the team. Accrual goals and factors impacting accrual goals will be discussed at the weekly GMO Protocol meetings.

If accrual proceeds more quickly than anticipated, it may be slowed or staggered at the discretion of the Principal Investigator, to account for safety concerns or data management resources.

16.1 Quality Assurance

Biweekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Enrollment logs will be sent to Lilly to facilitate drug inventory. These enrollment logs do not contain PHI.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at minimum of two times per year, and more frequently if indicated.

16.2 Data and Safety Monitoring

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/noticefiles/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](http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.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 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 MediData RAVE. 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.

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://smskpss9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20\(CRQA\)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf](http://smskpss9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf)

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSK'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). The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

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 participant 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 starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occurs after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event. The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
 - An explanation of how the AE was handled
 - A description of the participant's condition
 - Indication if the participant 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

For IND/IDE protocols:

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1 SAE Reporting to Eli Lilly

- To comply with applicable laws, regulations and standards regarding Investigator's and Institution's obligations, as the sponsor of the Study, to collect and report adverse events to regulatory authorities, IRBs, Ethics Committees or other third parties. In addition to the obligations set forth below, Investigator and Institution agree to provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly;
- To notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study patients and report new safety information to IRBs in accordance with applicable requirements;

To notify Lilly within fifteen (15) business days of Investigator and/or Institution receiving notification of any "serious" adverse event experienced by a patient participating in the Study and receiving Study Drug. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug.

17.2.2

Ethics and Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the Investigator's Brochure.

18.0 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.

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20.0 APPENDICES

Appendix A: Congestive Heart Failure New York Heart Association Criteria

Class	Definition
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even with rest. With any physical activity, increased discomfort is experienced.

Appendix B: Strong Inducers of CYP3A4 or Substrates of CYPs with Narrow Therapeutic Range

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

Inducers of CYP3A4

Carbamazepine

Dexamethasone

Phenobarbital/phenobarbitone

Phenytoin

Rifapentine

Rifampin

Rifabutin

St. John's wort

Strong inhibitors of CYP3A4

All HIV protease inhibitors

Clarithromycin

Itraconazole

Ketoconazole

Nefazodone

Cytochrome P450 Substrates with narrow Therapeutic Range

Cytochrome P450

Substrate

CYP1A2

Theophylline

Tizanidine

CYP2C8

Paclitaxel

CYP2C9

Warfarin

Phenytoin

CYP2D6

Thioridazine

Pimozide

CYP3A

Alfentanil

Astemizole

Cisapride

Cyclosporine

Dihydroergotamine

Ergotamine

Fentanyl

Pimozide

Quinidine

Sirolimus

Tacrolimus

Terfenadine