A Phase I Trial of BYL719 plus Letrozole or Exemestane for Patients with Hormone-Receptor Positive Locally-Advanced Unresectable or Metastatic Breast Cancer

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

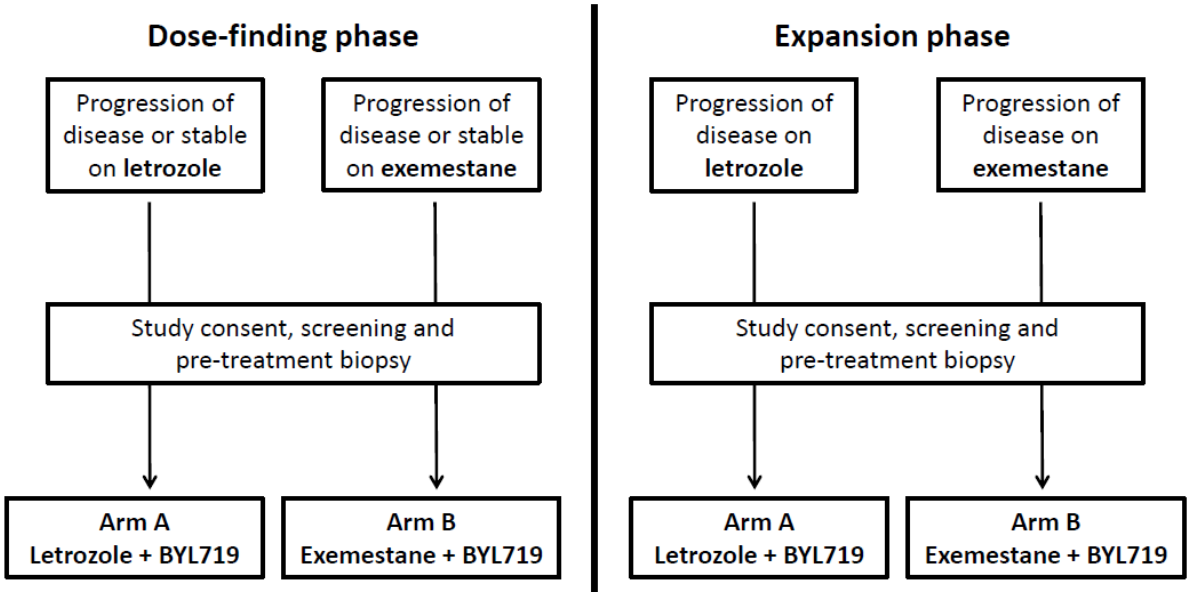
This is a phase I study of BYL719 in combination with letrozole or exemestane for the treatment of patients with locally-advanced unresectable or metastatic hormone-receptor positive (HR+) breast cancer. BYL719 is an oral PI3K inhibitor which selectively inhibits the class IA p110α isoform of PI3K.

The primary objective is to determine the recommended phase II dose of BYL719 when administered in combination with either letrozole or exemestane. We are interested in this combination because we hypothesize that PI3Kα inhibition will be less toxic than pan-PI3K or mTOR inhibition, tolerable in combination with an aromatase inhibitor (AI), and effective in combination with an AI, even after progression on the same AI. As of January 2014, this trial is being amended such that an additional primary objective is to determine the recommended phase II dose of BYL719 administered in a 7 day on, 7 day off schedule, in combination with letrozole, and the recommended phase II dose of BYL719 administered on a 5 day on, 2 day off schedule, in combination with exemestane.

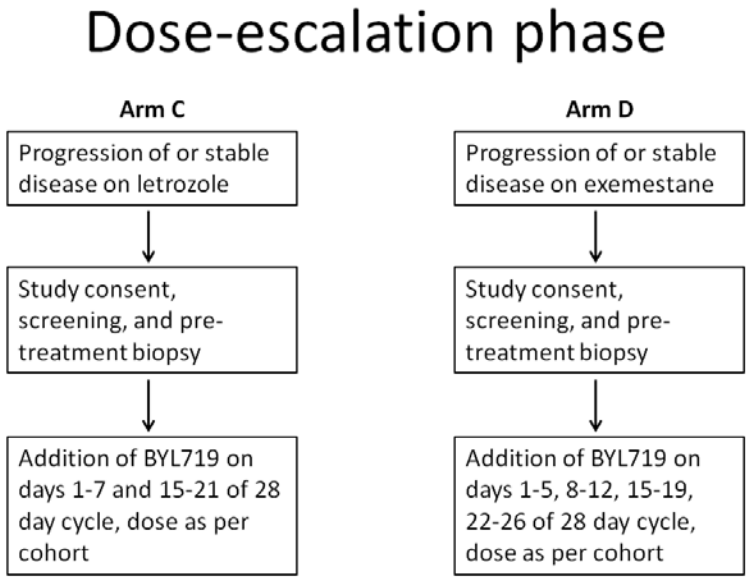
This clinical trial was initially comprised of two arms, one for BYL719 in combination with letrozole (Arm A) and another for BYL719 in combination with exemestane (Arm B). As of January 2014, Arms A and B will no longer accrue patients and the study will be amended to include Arms C and D. Arm C will involve letrozole with BYL719 given on days 1-7 and 15-21 of a 28 day cycle. Arm D will involve exemestane with BYL719 given on days 1-5, 8-12, 15-19, 22-26 of a 28 day cycle. Anastrozole will not be evaluated in this study because anastrozole is a non-steroidal AI similar to letrozole. Arms C and D employ distinct aromatase inhibitors for clarity throughout clinical care. However, given the similar toxicity profile seen with both aromatase inhibitors with continuously dosed BYL719 (Arms A and B), results from either arm are felt to be generalizable to either aromatase inhibitor.

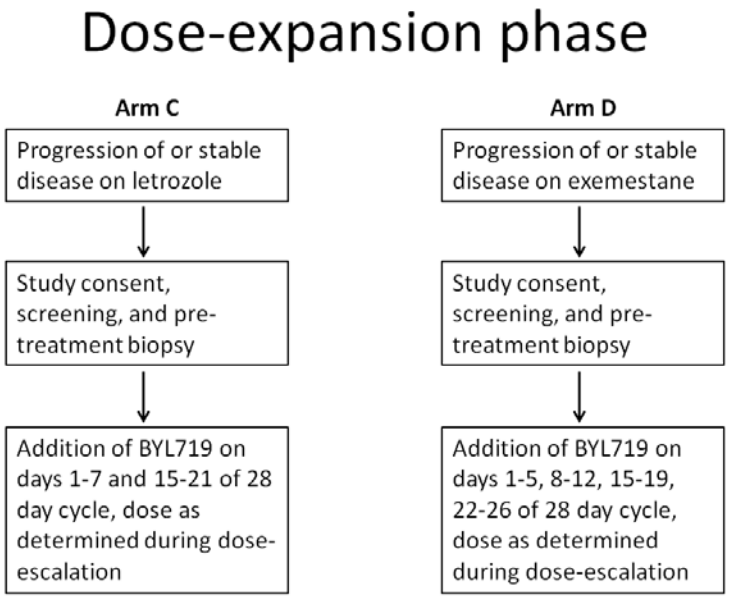
Subjects currently enrolled onto Arms A and B will continue on Arms A and B. They will be re-consented with the revised Arm A and B consents which will reflect our updated toxicity profile. In addition, planned secondary objectives for Arms A and B (evaluation of safety and toxicity, estimation of efficacy, pharmacokinetic studies) will continue, though the analyses will only be performed based on those subjects enrolled onto Arms A and B (dose-escalation) as no subjects will be enrolled onto Arms A and B dose-expansion.

As of January 2017, this trial is being amended to revise the restaging scans and clinic visit requirements for patients who have been receiving protocol therapy for greater than 75 weeks. At the time of this amendment (Amendment 13) this study has closed to patient accrual after enrolling a total of 51 patients.



The original study schema (for Arms A and B) is shown above, and the schema for Arms C and D is shown below. Rather than proceed further with the dose-finding phase or continue to the expansion phase for Arms A and B, we will proceed directly to the dose-finding phase for Arms C and D given toxicity concerns discussed below. For Arm C and Arm D, there will be a dose-finding phase and an expansion phase. When the recommended phase II dose of intermittent BYL719 in combination with letrozole or exemestane has been determined in the dose-finding phase, an additional 10 patients will be enrolled onto Arm C and Arm D in an expansion phase of the study. The purpose of the expansion phase is to further define the safety and feasibility of BYL719 in combination with letrozole or exemestane given on two intermittent schedules, at the recommended phase II dose, and to estimate efficacy.





Patients will be eligible for either Arm C or Arm D depending on which AI they were taking before study enrollment. For both the dose-finding phase and the expansion phase, patients may have stable or progressive disease on letrozole or exemestane, and BYL719 will be added.

A treatment cycle will consist of 28 days. The regimen will consist of BYL719 in combination with letrozole or exemestane administered orally each day. Patients will be on treatment until unacceptable toxicity or progression of disease. Treatment doses and schedule are shown below:

Arm	**AI dose**	**BYL719 schedule (dose per cohort)**
A	Letrozole 2.5mg orally once daily	Days 1-28 of 28 day cycle
B	Exemestane 25mg orally once daily	Days 1-28 of 28 day cycle
C	Letrozole 2.5mg orally once daily	Days 1-7, 15-21 of 28 day cycle
D	Exemestane 25mg orally once daily	Days 1-5, 8-12, 15-19, 22-26 of 28 day cycle

The dose-finding phase will follow a standard 3 + 3 design, according to the cohorts in the tables below. The starting dose of BYL719 in Arms A and B will be 300mg daily, which is 75% of the MTD from the single agent phase I study. The starting dose of BYL719 in Arms C and D will be 250mg daily.

Arms A and B

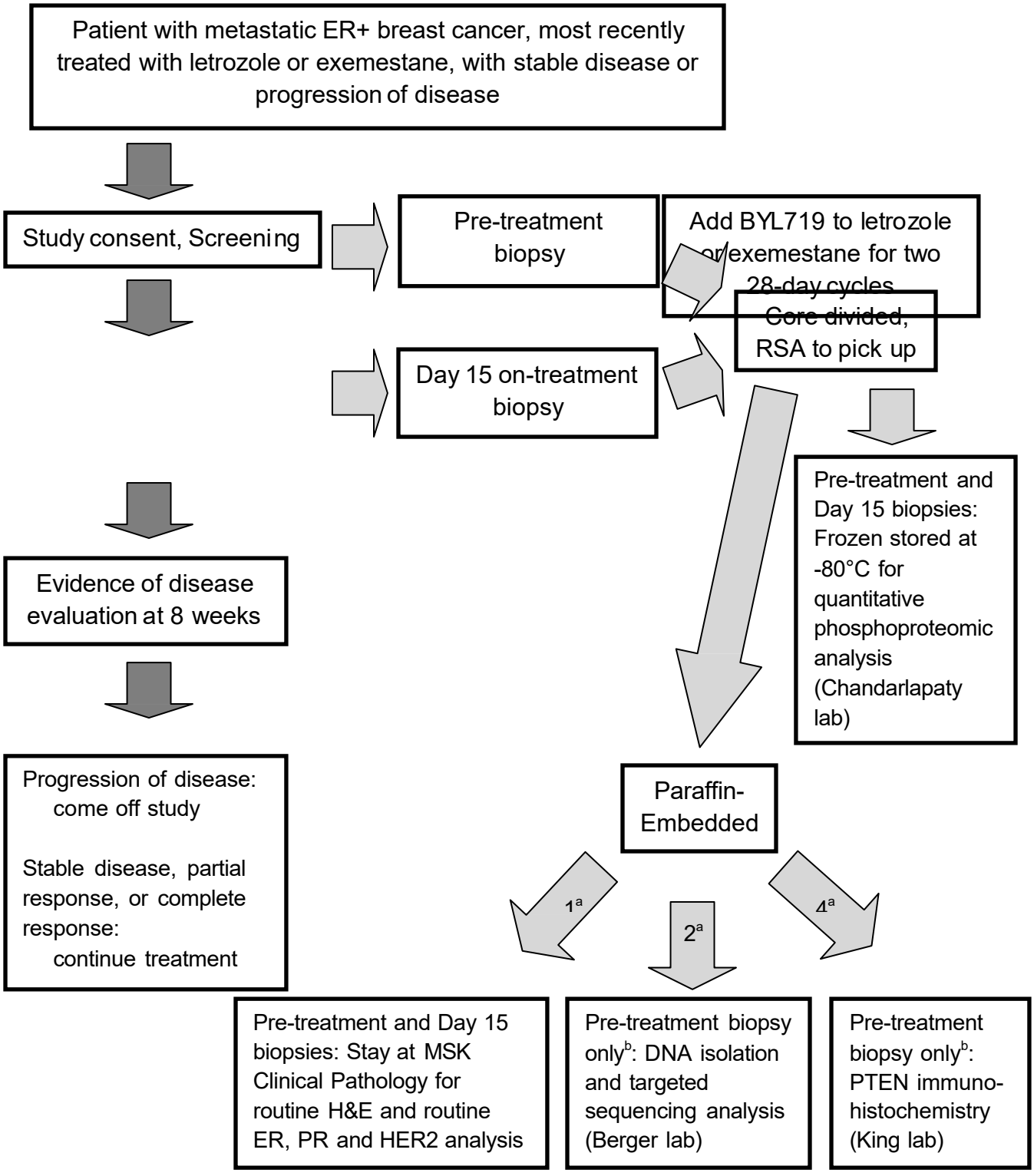
COHORT	BYL719 dose
+2	400mg orally once daily (100% of MTD for single agent BYL719)
+1	350mg orally once daily (87.5% of MTD for single agent BYL719)
0 (starting dose)	300mg orally once daily (75% of MTD for single agent BYL719)
-1	250mg orally once daily (62.5% of MTD for single agent BYL719)
-2	200mg orally once daily (50% of MTD for single agent BYL719)

Arms C and D

COHORT	BYL719 dose
+2	350mg
+1	300mg
0 (starting dose)	250mg
-1	200mg

Tumor tissue biopsies will be obtained to further define the biology of AI-resistance in metastatic ER+ breast cancer, and to evaluate predictive and pharmacodynamic biomarkers of treatment with BYL719 (see schema on following page).

We will no longer accrue to Arm A or Arm B. For Arm C and Arm D, we anticipate 4-18 patients per arm for the dose-finding phase of the trial, and we estimate an accrual rate of 2 patients per month, with a total time of 1 year to complete. We anticipate 20 patients for the expansion phase of the trial (10 patients in each arm), which will require an additional 1 year to complete.



[a]Numbers represent priority order if insufficient tumor tissue is present in the biopsy for all correlatives

[b]Pre-treatment biopsy is preferred for the exploratory objectives being studied. We anticipate that tumor tissue may be insufficient in up to 3 biopsies, in which case these analyses may be performed on an archival primary or metastatic tumor specimen.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective

- Arm A and Arm B: To determine the recommended phase II dose of BYL719 when administered in combination with either letrozole or exemestane to patients with HR+ locally-advanced or metastatic breast cancer
- Arm C and Arm D: To determine the recommended phase II dose of BYL719 when administered in combination with letrozole in a 1 week on, 1 week off schedule, or with exemestane in a 5 of 7 days weekly schedule, to patients with HR+ locally-advanced or metastatic breast cancer

2.2 Secondary Objectives

- Arms A, B, C and D: To describe the safety and tolerability of BYL719 when administered in combination with either letrozole or exemestane to patients with HR+ locally-advanced or metastatic breast cancer

- Arm A and Arm B: To estimate the efficacy of BYL719 plus letrozole or exemestane in patients with HR+ locally-advanced or metastatic breast cancer, by calculation of the following in an expansion cohort:
    - Progression-free survival
    - Overall response rate (complete response + partial response)
    - Clinical benefit rate at 16 weeks (complete response + partial response + stable disease)
    - Time to treatment failure

- Arm C and Arm D: To estimate the efficacy of BYL719 in two distinct schedules, plus letrozole or exemestane, in patients with HR+ locally-advanced or metastatic breast cancer, by calculation of the following in an expansion cohort:
    - Progression-free survival
    - Overall response rate (complete response + partial response)
    - Clinical benefit rate at 16 weeks (complete response + partial response + stable disease)
    - Time to treatment failure

- Arm A and Arm B: To describe the pharmacokinetics of daily BYL719 when given in combination with letrozole or exemestane

- Arm C and Arm D: To describe the pharmacokinetics of BYL719 on two distinct administration schedules when given in combination with letrozole or exemestane

2.3 Exploratory Objectives

- Arms A, B, C and D: To evaluate mechanisms of AI resistance and predictors of BYL719 sensitivity through next generation sequencing and fine copy number analysis of a pre-treatment biopsy

- Arms A, B, C and D: To evaluate predictive and pharmacodynamic markers of PI3K pathway inhibition with BYL719 through proteomic analysis of pre-treatment and on-treatment biopsies

- Arms A, B, C and D: To evaluate cell free DNA (cfDNA) as a predictive biomarker of PI3K pathway inhibition with BYL719 through the sequential quantification of *PIK3CA* mutant alleles by digital PCR (dPCR) on serial plasma collections.

- Arms A, B, C and D: To evaluate mechanisms of acquired resistance with correlative studies of on-treatment and optional post-progression tumor biopsies

3.0 BACKGROUND AND RATIONALE

3.1 Hormone-Receptor Positive (HR+) Metastatic Breast Cancer

Despite advances in treatment, breast cancer remains the second highest cause of cancer deaths in women. Over two thirds of breast tumors are found to be positive for the estrogen receptor (ER) and/or progesterone receptor (PR). Growth of these HR+ tumors is often estrogen-dependent, and therefore, endocrine therapy plays an important role in the treatment of HR+ metastatic breast cancer.

3.2 Endocrine Therapy for HR+ Metastatic Breast Cancer

Endocrine therapy is generally better tolerated than standard cytotoxic chemotherapy and often the first line treatment for HR+ metastatic breast cancer[1]. Several endocrine agents are FDA-approved for treatment of HR+ metastatic breast cancer. Tamoxifen is a selective ER modulator which antagonizes ER in breast tissue. Aromatase inhibitors (AIs) block the conversion of androgens to estrogens and include the non-steroidal AIs, letrozole and anastrozole, and the steroidal AI, exemestane[1]. Fulvestrant is an ER antagonist which binds to and downregulates ER.

For patients with HR+ metastatic breast cancer, the development of resistance to endocrine therapy is a major cause of disease progression and mortality. Delaying resistance to endocrine therapy may significantly impact management of this large group of patients.

3.3 Role of PI3K in Resistance to Anti-Estrogen Therapy

Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases that are important in controlling signaling pathways involved in cell proliferation, motility, cell death and cell invasion. There is substantial evidence that, in many tumors, the PI3K signaling pathway is constitutively activated. This is thought to be a critical step in mediating the transforming potential and growth stimulating activity of various oncogenes (i.e., HER2, EGFR, IGF1R). When activated, PI3K catalyzes the phosphorylation of the cell membrane-embedded phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-triphosphate (PIP_3). In turn, PIP_3 acts as a docking site for signaling proteins, most notably PDK1, where activation can take place, effecting downstream cellular pathways critical for cell growth and

survival, including the AKT and mTOR pathway. Whereas normal cells rely on these pathways for regulatory functions, such as insulin signaling, cancer cells exploit these pathways for tumorigenesis.

Class I PI3K contains four isoforms, p110α, p110β, p110δ and p110γ, which carry out non-redundant signaling functions. Mutations in *PIK3CA*, the gene encoding p110α, are found in multiple human tumor types, suggesting that p110α is a key isoform for promoting tumor growth. The *PIK3CA* gene is frequently mutated in human breast cancers, and more commonly in HR+ disease. In our clinical database of tumor tissue genotyped for *PIK3CA* mutations, from 590 patients who underwent resection of primary breast tumors at Memorial Sloan-Kettering Cancer Center (MSKCC), 480 had HR+ breast tumors; of these, 182 (37.9%) were found to harbor *PIK3CA* mutations.[2]

Laboratory studies have demonstrated that hormonal and PI3K signaling cooperate in breast cancer pathogenesis. Crowder et al demonstrated that the combination of estrogen deprivation and knockdown of the PI3Kα catalytic subunit promoted cell death in multiple HR+ breast cancer cell lines.[3] Miller et al showed that PI3K pathway hyperactivation was associated with endocrine resistance and that PI3K pathway inhibition suppressed hormone-independent cell growth in long-term estrogen-deprived HR+ breast cancer cell lines.[4]

The cross-talk of the PI3K pathway with ER transcriptional activity is summarized in Figure 3-1 below, adapted from Miller et al.[4] PI3K pathway activation contributes to ligand-independent phosphorylation of ER and activation of associated transcription cofactors. In turn, ER promotes gene transcription of ligands and growth factor receptors upstream of the PI3K pathway.[5]

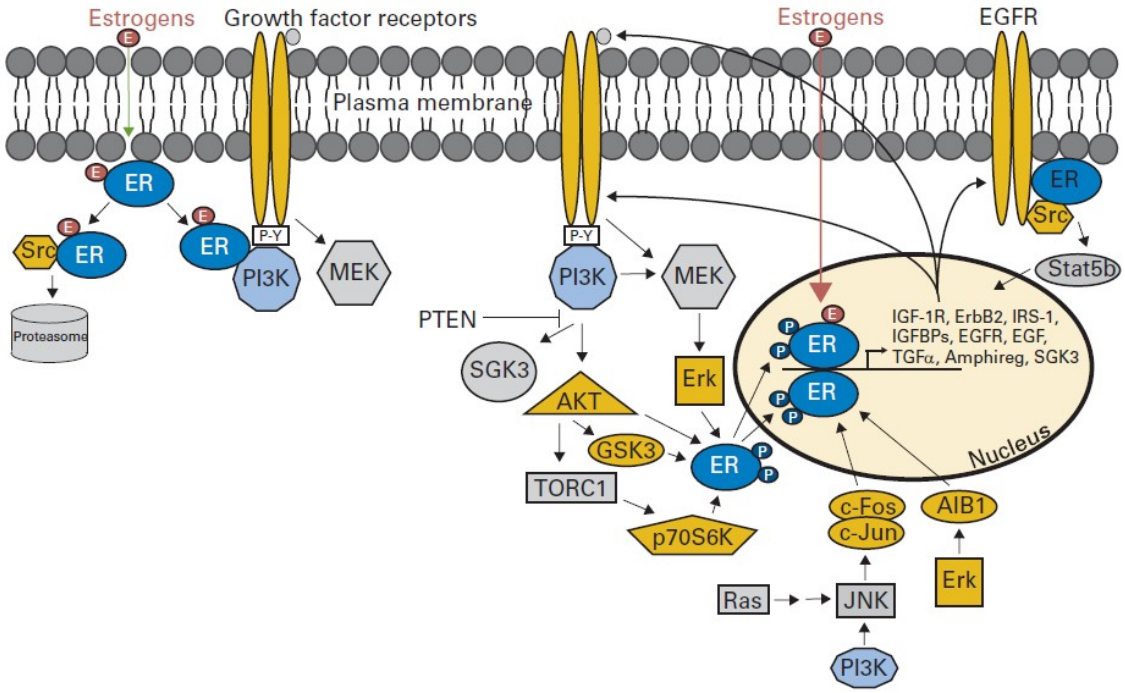


Figure 3-1, from Miller T et al[5]

3.4 Activity of mTOR Inhibition in Breast Cancer

The mTOR protein is activated downstream of PI3K/AKT, and forms the TORC1 complex (see Figure 3-1), which is involved in cell growth and survival signaling.

Two recent clinical trials have evaluated the role of everolimus, an mTOR inhibitor, in combination with endocrine therapy for the treatment of HR+ metastatic breast cancer after progression on treatment with an AI. In the phase II TAMRAD study, 111 patients with metastatic HR+ breast cancer who progressed on prior AI therapy were randomized to everolimus in combination with tamoxifen versus tamoxifen alone.[6] The 6 month clinical benefit rate was 61% for the combination and 42% for tamoxifen alone, suggesting increased activity in the combination arm.[6]

The recent phase III BOLERO-2 study demonstrated that the addition of everolimus to exemestane in patients with metastatic breast cancer who developed resistance to a non-steroidal AI (letrozole or anastrozole) resulted in improved progressive-free survival.[7] Median progression-free survival for patients receiving everolimus in combination with exemestane was 6.9 months, compared to 2.8 months in the group receiving placebo plus exemestane (HR 0.43, 95% CI 0.35-0.45, $p<0.001$).[7] This was an unselected population in regards to *PIK3CA* mutation status, and biomarker data is not available.

Notably, mTOR inhibition with rapalogs has had virtually no efficacy in breast cancer as a single agent, further suggesting synergy between the PI3K-mTOR pathway and ER activation. A phase II study of temsirolimus as a single agent for the treatment of 31 unselected patients with metastatic breast cancer did not result in any objective responses.[8]

Adverse effects related to mTOR inhibition were seen in both the TAMRAD and BOLERO-2 studies. These included stomatitis, rash, fatigue, diarrhea, decreased appetite, hyperglycemia and pneumonitis.[6,7] Although perhaps considered acceptable in the context of metastatic disease, there is notable toxicity associated with mTOR inhibition, which may conceivably be improved with more direct inhibition of the mutant oncoprotein. The preclinical work described in Section 3.3 (and also in Section 3.6 below) suggests that targeting PI3K may be optimal in the setting of HR+ breast cancer which has developed resistance to endocrine therapy.

3.5 PI3Kα Inhibition with BYL719

Class I PI3K contains four isoforms, p110α, p110β, p110δ and p110γ, which carry out non-redundant signaling functions. Mutations in *PIK3CA*, the gene encoding p110α, are found in multiple human tumor types, suggesting that p110α is the main PI3K isoform which drives tumor growth. Therefore, the development of a p110α specific PI3K inhibitor is expected to reduce the potential for inducing treatment-related toxicity, resulting in an improved therapeutic window.

NVP-BYL719 (BYL719) is an oral class I α-specific PI3K inhibitor belonging to the 2-aminothiazole class of compounds. It strongly inhibits the PI3Kα isoform (wild-type and mutant) and much less strongly the β, δ and γ isoforms. BYL719 has demonstrated anti-tumor activity in preclinical in vitro and in vivo tumor models. In vivo, BYL719 has demonstrated dose dependent tumor growth inhibition in various subcutaneous tumor

transplant models. BYL719 is currently being investigated in a Phase I dose escalation trial and the maximum tolerated dose (MTD) was declared at 400 mg once daily.

For further details on preclinical and clinical experience, please refer to Section 3.5.1 and Section 3.5.2 and the current BYL719 Investigator's Brochure (IB).

3.5.1 Preclinical Experience with BYL719

In biochemical assays, BYL719 inhibits p110α (IC_{50} = 5 nM) much more potently than the p110δ and γ isoforms and PI4Kβ and has weak or no activity against p110β, Vps34 and mTOR. BYL719 is equipotent against the most common somatic mutations of p110α (H1047R, E545K) compared to wild type p110α, and is selective against a wide range of protein kinases with at least a 50-fold selectivity window compared to p110α.

In vitro, BYL719 was found to inhibit proliferation of cancer cell lines, regardless of their *PIK3CA* mutation status. BYL719 inhibited *PIK3CA*-mutated breast cancer cell lines, and this activity correlated with inhibition of downstream targets of the PI3K-AKT-mTOR pathway. In *PIK3CA*-mutant mice xenograft models, BYL719 demonstrated statistically significant dose-dependent anti-tumor activity.

BYL719 demonstrates low plasma clearance (CL), a moderate volume of distribution at steady state (Vss) and a good absolute oral bioavailability in all preclinical species tested (Wistar rats, Beagle dogs, mice). The compound is moderately bound to plasma proteins and showed a rapid distribution to almost all rat tissues, except the brain.

BYL719 is a substrate of breast cancer resistant protein (BCRP) and has low affinity for Permeability glycoprotein (P-gp). BYL719 does not inhibit BCRP or multidrug resistance-associated protein 2 (MRP2), but showed very weak inhibition of P-gp (IC50 97 µM). As the maximal inhibition of P-gp was only about 32% with respect to positive control, the overall interaction potential is expected to be low.

BYL719 was found to be a time dependent inhibitor of cytochrome P450 3A4 (CYP3A4). Reversible inhibition of CYP2C8, CYP2C9 and CYP2C19 was also observed. BYL719 may inhibit metabolic clearance of co-medications metabolized by CYP3A4 and, to a lesser extent, CYP2C8, CYP2C9 and CYP2C19, if sufficiently high concentrations are achieved in vivo. Results from 4-week GLP toxicology studies in dog showed a roughly dose-proportional increase in exposure, while in rat the exposure increased up to a dose of 30 mg/kg beyond which no further increase was noted following single dose administration. The toxicology studies provided no clear evidence of increase in exposure following multiple dosing. No gender differences in exposure were observed in rat or dog.

The overall biotransformation of BYL719 in hepatocytes was low. The main biotransformation pathway that was observed was hydrolysis. CYP450 dependent oxidative metabolism is expected to be minor. No covalent drug protein adduct formation was noted in human microsomes or hepatocytes. Please refer to the BYL719 IB for further details.

Routine safety pharmacology and toxicology studies were conducted in rats and dogs. In addition, for exploratory studies, such as insulin/glucose tolerance tests, mice were also used. BYL719 was relatively well tolerated in the repeated-dose toxicity studies (daily dosing of up to 4 weeks of duration) at dosages at which tumor growth control was achieved. BYL719 affected rapidly dividing tissues, which resulted only in pharmacological relevant observation in the animals exposed to a BYL719 dose close to or at MTD. The most frequently affected organs were the bone marrow, lymphoid tissue (spleen, thymus), and the epithelia of the alimentary tract, while other tissues like the vagina and uterus in rats, or prostate in dogs were also affected at higher doses. Bone/cartilage and tooth-forming structures were only affected in rats. In dogs, epithelial effects were seen in the cornea; however, the dose-dependency of this cornea observation was not evident. No other ophthalmologic abnormalities, associated with BYL719 treatment, were observed in rats or in dogs. Abnormal clinical chemistry and histopathology (pancreatic islets) findings indicated an altered glucose metabolism, correlating with a clear effect towards insulin insensitivity. In both rats and dogs, histopathology and clinical pathology findings were generally observed at higher doses which were also associated with reduced body weight development (in the growing animals) and reduced food intake. All toxic events were reversible or showed a tendency to reversibility after a 4-week treatment-free recovery period.

Cardiac safety studies, conducted in vitro and in vivo, did not indicate an electrophysiological risk. Furthermore, BYL719 in the rat safety pharmacology studies showed no effect on neuronal or pulmonary function, and no evidence of a phototoxic potential was found in a 3T3 neutral red uptake test in vitro.

In conclusion, the majority of the observed toxicological effects of BYL719 were related to the pharmacological activity of BYL719 as a p110α specific inhibitor of PI3K pathway, such as an influence on insulin (and potentially glucose) homeostasis and the risk of increased blood pressure. The pharmacologically relevant toxicity was mainly observed at dosages close to or at MTD with the bone marrow and lymphoid tissue, pancreas, and some reproductive organs of both genders being the main target organs of the toxic effects. Please refer to the BYL719 IB for further details.

BYL719 is not genotoxic in vitro, based on the results of an Ames test and a chromosome aberration test.

3.5.2 Clinical Experience with BYL719

BYL719 is currently tested in 3 clinical studies. CBYL719X2101 is a first-in-human phase IA, multicenter, open-label dose escalation study of oral BYL719, in adult patients with advanced solid malignancies, whose tumors have an alteration of the *PIK3CA* gene. CBYL719X1101 is a phase I study of BYL719, in adult Japanese patients with advanced solid malignancies. CMEK162X2109 is a phase Ib, open-label, multi-center, dose escalation and expansion study of an orally administered combination of BYL719 plus MEK162 in adult patients with selected advanced solid tumors.

In CBYL719X2101 dose escalation phase, 7 dose levels have been tested from 30 mg QD to 450 mg daily. The maximum tolerated dose (MTD) was declared at 400 mg daily. A safety

expansion cohort at 400 mg daily is currently being tested, and an additional cohort of BID dosing is also under testing.

As of 20 Apr 2012, a total of 50 patients with advanced cancer have received at least one dose of BYL719 and have been evaluated for safety.

Overall, 43 (86%) patients experienced AEs which were suspected to be related to BYL719. The most frequently reported treatment-related AEs, regardless of CTCAE Grade and dose were hyperglycemia 23/50 (46%), decreased appetite 17/50 (34%), nausea 17/50 (34%), diarrhea 16/50 (32%), fatigue (12/50; 24%) and vomiting (12/50; 24%). Among these, 16 (32%) patients experienced at least one CTCAE Grade 3/4 AE suspected to be treatment-related. The most common treatment-related CTCAE Grade 3/4 AEs were hyperglycemia and nausea.

Six DLTs were reported by the cut-off date, all from the CBYL719X2101 study. There were 4 cases in 450 mg daily cohort (2 x CTCAE Grade 3 hyperglycemia, CTCAE Grade 3 nausea, and intractable nausea), one case in 400 mg daily expansion cohort (Grade 3 nausea and Grade 3 vomiting), and one case in 200 mg BID cohort (CTCAE Grade 3 hyperglycemia).

In summary, the current data indicate a favorable clinical safety profile of BYL719.

Signs of single-agent clinical efficacy were also reported. There were 3 partial tumor responses per RECIST, including a partial response in a patient with ER+ breast cancer treated at 270mg daily.[10]

Preliminary clinical pharmacokinetic data of BYL719 after single and multiple daily dosing is available from the first-in-human trial CBYL719X2101. BYL719 was administered orally as a tablet (doses ranging between 30 and 450 mg) and full pharmacokinetic profiles were collected on Day 1 and Day 8 of Cycle 1 and on Day 1 of Cycle 2.

Following administration of the first dose, BYL719 was well absorbed, with median time to reach peak plasma concentration (Tmax) ranging from 1.5 to 7.1 hours across cohorts. Median Tmax appeared to be independent of dose and was unchanged after multiple oral doses. Maximum Tmax spanned a wide range across cohorts (2.15-22.4 hours), indicating slow absorption in some subjects. Geometrical mean plasma peak drug concentration (Cmax) and drug exposure (AUCinf) after single oral dose of BYL719 increased in an approximate dose-proportional manner. At the MTD (400 mg daily), the Cmax and AUCinf were ~2617 ng/ml and ~36858 ng.hr/ml (geometrical mean), and showed moderate inter-individual variability (41% and 49% in CV% for Cmax and AUCinf).

Plasma concentrations of BYL719 generally declined in a mono-exponential manner, suggesting rapid distribution towards the peripheral tissues. Mean terminal half-life was approximately 10 hours, and generally appeared to be independent of dose and time.

At lower daily doses (30 mg-180 mg), oral drug clearance appeared to be independent of both dose and time, and an approximate dose-proportional increase in drug exposure (Cmax and AUC) was observed after one week and one month of daily dosing. Apparent total body clearance (CL/F) calculated from exposure data after 1 month of dosing ranged between 9.40 and 10.8 L/hr across the lower dose cohorts (30 – 180 mg), indicating that BYL719 is a

low clearance drug. Similar oral clearance values were obtained from total drug exposure (AUCinf) after single dose administration.

At higher daily doses (> 180 mg), oral drug clearance within the first week of dosing (C1D8) ranged between 9.48 and 11.3 L/hr, which is in close agreement with the CL/F observed after single dose administration. However, after one month of dosing at 270 mg and 400 mg, a tendency towards an increase in drug exposure (AUC0-24h) and Cmax with time was observed. At 400 mg daily, the geomean drug accumulation ratio (Racc) was ~3 fold (range 1.91 and 4.42).

3.6 Role of mTOR in Negative Feedback

Chandarlapaty and colleagues have investigated the consequences of PI3K pathway inhibition and found that targeting mTOR almost invariably leads to activation of receptor tyrosine kinases and PI3K through a loss-of-feedback mechanism[9] (see Figure 3-2). So, mTOR inhibition may lead to activation of the upstream PI3K pathway. Therefore, we hypothesize that patients who experience progression on an mTOR inhibitor, such as everolimus, may still obtain benefit from subsequent treatment with a PI3Kα inhibitor.

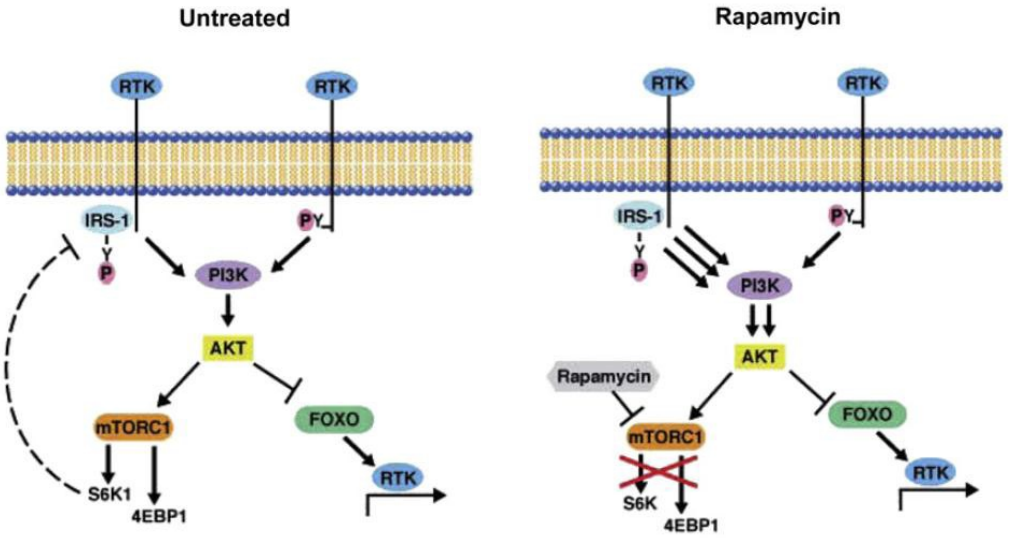


Figure 3-2, adapted from Chandarlapaty et al[9]

3.7 Rationale for evaluating non-daily dosing schedules

As discussed above, there is a strong rationale for the therapeutic combination of BYL719 with endocrine therapy in hormone receptor-positive breast cancer. However, clinical experience at our institution and elsewhere suggests that escalation to potentially efficacious doses of BYL719 may be hindered by the development of dose-limiting toxicity (DLT), and in

particular, skin toxicity. Maculopapular rash is being seen with increasing frequency when BYL719, and to a lesser extent, other PI3K inhibitors, are administered in conjunction with endocrine therapy **(Figure 3-3)**.

Thus far, in the dose-escalation phase of the current phase I trial, BYL719 was administered daily in conjunction with either letrozole (Arm A) or exemestane (Arm B). In both arms, dose-limiting toxicity required dose-reductions from BYL719 300mg orally daily to BYL719 250mg, as compared with the single-agent maximally tolerated dose of 400mg orally daily. Three of four dose-limiting toxicities were grade 3 maculopapular rash. Our data (discussed below and displayed in **Tables 3-1 and 3-2**) and clinical experience suggest that this rash generally occurs between days 10-14 of treatment. Typically, patients report a burning, prickly skin sensation followed by the relatively rapid eruption of erythematous macules and papules that encompass the majority of patients' body surface area. Upon withholding therapy and initiating timely referral to dermatology, in addition to oral corticosteroids, topical corticosteroids, and oral antihistamine therapy, the rash generally resolves quickly without long-term sequelae. However, it is bothersome to patients and conceivably may affect adherence to this oral medication. Furthermore, the rash is generally grade 3 in extent and therefore necessitates treatment interruptions for patients who are on clinical trial with this therapeutic combination.

In Arm A, the overall incidence of rash (any grade) that was possibly, probably, or definitely related to BYL719 is 57% (4 of 7 patients), with 3 of 4 patients having grade 3 rash. Furthermore, one of these patients with grade 3 rash was on treatment with BYL719 at dosing cohort -1 (250mg). In Arm B, the overall incidence of rash that was possibly, probably, or definitely related to BYL719 is also 57% (4 of 7 patients), and all affected patients had grade 3 rash. Of all 8 patients across arms who developed maculopapular rash that was possibly, probably or definitely related to BYL719, 75% developed rash between days 10-14 of treatment. One of 7 patients on the letrozole arm and 1 of 7 patients on the exemestane arm discontinued therapy on study due to rash. Complete data is displayed in **Table 3-1** and **Table 3-2** below.

Despite this rash, preliminary signals of efficacy are encouraging and support the use of alternate dosing schedules to mitigate the need for dose de-escalation of this potentially efficacious therapy. In Arm A, 2 of 2 patients who have undergone evaluation of disease assessments continue on study. One patient who previously had progression of disease on letrozole achieved stable disease with addition of BYL719, most recently on cycle 5 day 1 scan, and a second patient had a 43% reduction of disease from baseline per RECIST criteria. On Arm B, 2 of 5 patients who have undergone imaging assessments continue had minor responses at first EOD imaging, yielding a preliminary clinical benefit rate at 8 weeks of 40%.

Table 3-1: Skin toxicity and patient responses from continuously dosed BYL, Arm A - Letrozole + BYL719

Patient	BYL719 dose	*PIK3CA* mutation status	On-study status	Worst skin toxicity*	Timing of skin toxicity onset	Patient's response to BYL719 + AI**

003	300mg	Unknown	Off study due to DLT (rash)	Grade 3 rash	C1d11	n/a
004	300mg	Positive	On study	none	n/a	Stable disease, most recently on C5d1 imaging
005	300mg	Unknown	Off study due to nonadherence	Grade 3 rash	C1d14	n/a
009	300mg	Positive	On study Required dose reduction due to DLT (grade 3 abd pain, hyperglycemia)	none	n/a	Partial response at C3d1 with 43% decrease fro baseline
013	250mg	Positive	On study	Grade 1 rash	C1d22	n/a
016	250mg	Negative	On study	Grade 3 rash	C1d12	n/a
017	250mg	Positive	On study	None	n/a	n/a

Table 3-2: Skin toxicity and patient responses from continuously dosed BYL, Arm B – Exemestane + BYL719

Patient	**BYL719 dose**	***PIK3CA* mutation status**	**On-study status**	**Worst skin toxicity***	**Timing of skin toxicity onset**	**Patient's response to BYL719 + AI****
001	300mg	Negative	Off study due to DLT (rash)	Grade 3 rash	C1d13	n/a
002	300mg	Positive	Off study due to POD (C4d1)	none	n/a	Minor response at C3d1 with 24% decrease from baseline, then POD
006	300mg	Negative	Off study due to POD (C3d1)	Grade 3 rash	C1d13	POD at C3d1

007	300mg	Positive	On study	Grade 3 rash	C1d27	SD at C3d1
008	300mg	Positive	Off study due to POD (C3d1)	none	n/a	POD at C3d1
012	300mg	Positive	Off study due to rapid POD (C1d7)	None	n/a	n/a
014	300mg	Negative	Off study due to POD (C3d1) Required dose reduction	Grade 3 rash	C1d10	POD at C3d1

*Only skin toxicity that is possibly, probably, or definitely related to BYL719 is noted
**N/a refers to patients who are off study prior to first EOD assessment, or who have not yet undergone EOD assessment

Colleagues at the Washington University School of Medicine recently presented data from their Phase I trial involving fulvestrant with BKM120, a pan-PI3K inhibitor, dosed daily or dosed 5 of 7 days weekly, with findings that further support the exploration of alternate, non-daily dosing schedules. Grade 3 rash was seen in 2 of 7 patients treated with daily BKM120, while only 1 of 11 patients treated during 5 of 7 days developed grade 3 rash. The incidences of other adverse events, including transaminase elevation, hyperglycemia, and diarrhea were also lower with intermittent dosing. No DLTs were seen in either group. Stable disease or better at 6 months was seen in 57% (4 of 7) patients receiving daily BKM120 and 45% (5 of 11) patients receiving BKM120 on 5 of 7 days. It should be noted that one patient who achieved a partial response with daily dosing withdrew from study participation in the setting of grade 3 rash. Furthermore, the longest sustained responses were seen on the intermittent dosing arm, with 2 patients achieving disease stability and continuing on treatment for 15 and 17 months at the time of data presentation in December 2013. These data demonstrate that toxicity is not infrequently seen with daily dosing of PI3K inhibitors, that alternate dosing schedules may reduce rate of toxicity, and that alternate dosing schedules may still allow for significant and prolonged therapeutic responses. Increasing recognition of this dose-limiting toxicity seen with daily PI3K inhibitor dosing has lead to efforts by Dr. Sarat Chandarlapaty of the Memorial Sloan Kettering Human Oncology and Pathogenesis Program to pursue preclinical modeling of alternate dosing schedules. Preliminary findings further suggest that alternate dosing schedules warrant further clinical exploration.

Given the above, we propose an amendment to include two additional study arms, Arm C and Arm D, to examine intermittent dosing of BYL719. As further discussed in Section 4.0,

Overview of Study Design/Intervention, and Section 9.2, BYL719 administration, patients on Arm C will receive BYL719 daily during days 1-7 and days 15-21 of a 28 day cycle, representing a 1 week on, 1 week off schedule. Patients on Arm D will receive BYL719 daily during days 1-5, 8- 12, 15-19, and 22-26 of a 28 day cycle, representing a 5 days on, 2 days off schedule. The starting dose of BYL719 in both arms will be 250mg orally daily. Dose and daily administration of aromatase inhibitors will remain unchanged.

The rationale for the current amendment is founded on our experiences to date, as well as the experiences of others as discussed above. The incidence of rash with BYL719 when used with an aromatase inhibitor is prohibitive, both in the setting of clinical trial dose escalation, as well as conceivably in clinical practice. The general timing of rash onset on days 10-14, and its prompt reversal with interventions including withholding therapy, argue for intermittent dosing.

Given the similar toxicity rates of the two arms seen during daily continuous BYL719 dosing, findings from both arms are felt to be applicable to either aromatase inhibitor.

3.8 Hypothesis

We therefore propose a clinical trial of BYL719 in combination with an AI. We hypothesize that the combination of BYL719 with an AI will represent a highly potent, non-chemotherapy combination that safely, effectively and durably treats HR+ breast cancers. We additionally hypothesize that intermittent dosing of BYL719 will allow for dose escalation and treatment with less toxicity than daily BYL719.

Hyperglycemia is the most common side effect of BYL719, and may even represent a pharmacodynamic marker of clinical efficacy. Significant overlapping toxicity between BYL719 and either letrozole or exemestane is not anticipated. However, these drugs have not been tested together in humans. Therefore, we propose a phase I trial of this combination to evaluate the safety and tolerability of this regimen. The starting dose of BYL719 on Arms A and B of this study (300mg daily) will be 75% of the single-agent MTD (400mg daily). As of January 2014, we are closing accrual to Arms A and B and amending the study to allow for examination of intermittent dosing through the addition of Arms C and D to the trial. The starting dose of BYL719 on Arms C and D of this study will be 250mg, with intermittent dosing schedules as outlined above. Once a safe dose of BYL719 in the combination has been established for Arms C and D, we propose an expansion phase for these arms to further evaluate safety, and to estimate the efficacy of this combination.

We propose testing BYL719 in an unselected population in regards to *PIK3CA* genotype. Preclinical data suggest that subsets of tumors with alterations in the PI3K pathway may be particularly sensitive (e.g., *PIK3CA* mutation) or resistant (e.g., PTEN loss) to this combination. This has yet to be evaluated clinically. It is not clear that the presence or absence of a *PIK3CA* mutation restricts the efficacy of BYL719 in patients with HR+ breast cancer which has progressed on endocrine therapy. The BOLERO-2 study showed efficacy of mTOR inhibition in an unselected population in regards to *PIK3CA* genotype, and no biomarker data is available.[7] We therefore propose testing BYL719 in an unselected population in regards to *PIK3CA* genotype, and a detailed molecular analysis of tumor biopsies of patients on this trial, looking at next generation sequencing and fine copy number

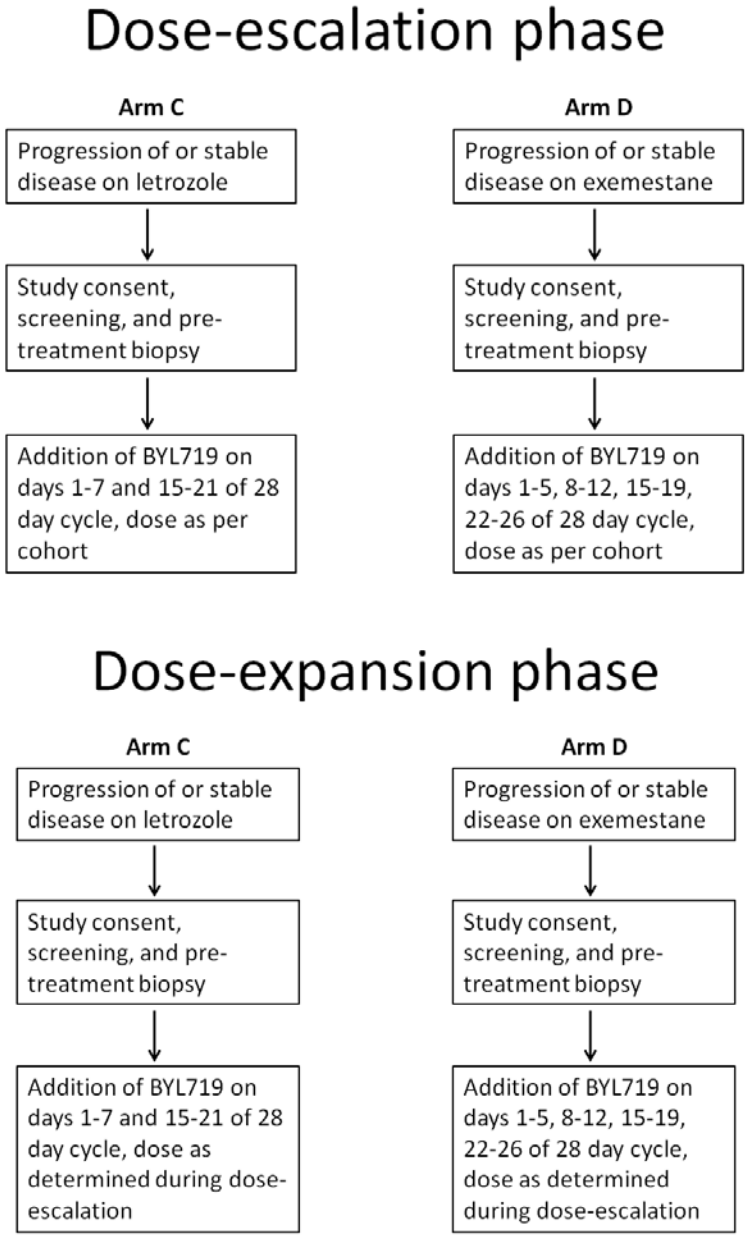
analysis to identify determinants of sensitivity. In order to understand the action of BYL719 on HR+ breast cancer treated with an AI, we will also evaluate a Day 15 on-treatment biopsy for pharmacodynamic markers of pathway inhibition which correlate with improved PFS.

If this study is successful, these results may lead to further study of this non-chemotherapy combination, supported by science from MSKCC labs and Novartis, ultimately moving towards our goal of delaying or preventing resistance to endocrine therapy in the treatment of HR+ breast cancer.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

This is a single institution phase I dose-finding study with an expansion cohort. The primary objective is to determine the recommended phase II dose of BYL719 when administered in combination with either letrozole or exemestane to patients with HR+ locally-advanced or metastatic breast cancer. As of January 2014, this trial is being amended such that an additional primary objective is to determine the recommended phase II dose of BYL719 administered in a 7 day on, 7 day off schedule, in combination with daily letrozole, and the recommended phase II dose of BYL719 administered on a 5 day on, 2 day off schedule, in combination with daily exemestane. An expansion cohort for Arms C and D will be treated at the final dose level to further define the safety and feasibility of each combination, and to estimate efficacy.

This clinical trial was initially comprised of two arms, one for daily BYL719 in combination with letrozole (Arm A) and another for BYL719 in combination with exemestane (Arm B). As of January 2014, Arms A and B will no longer accrue patients and the study will be amended to include Arms C and D. Arm C will involve letrozole with BYL719 given on days 1-7 and 15-21 of a 28 day cycle. Arm D will involve exemestane with BYL719 given on days 1-5, 8-12, 15-19, 22-26 of a 28 day cycle. The figure below shows the overall study scheme for Arms C and D. Patients will be eligible for only one of the two arms depending on which AI (letrozole or exemestane) they were taking before study enrollment. Patients will not be randomized to one of the two arms.



For both the dose-finding and expansion phases of Arms C and D, patients may have stable or progressive disease on letrozole or exemestane, and BYL719 will be added. We anticipate 12-30 patients for the dose-finding phase of the trial (6-15 patients in Arm C, and 6-15 patients in Arm D), and 20 patients for the expansion phase of the trial (10 patients in Arm C, and 10 patients in Arm D).

As of June 2015, the recommended phase II dose of BYL719 has been determined to be 350mg for Arm D and we are currently enrolling 10 patients to the corresponding arm in the expansion phase of the study. Dose Expansion to Arm C is currently on hold.

A treatment cycle will consist of 28 days. Treatment doses for each AI will be fixed at the established dose (see Section 9.1) and treatment doses for BYL719 will be determined based on patient cohort. Treatment schedule of BYL719 is as above. The dose-finding phase will follow a standard 3+3 design (see Section 9.4).

Subjects currently enrolled onto Arms A and B will continue on Arms A and B. They will be re-consented with the revised Arm A and B consents which will reflect our updated toxicity profile. In addition, planned secondary objectives for Arms A and B (evaluation of safety and toxicity, estimation of efficacy, pharmacokinetic studies) will continue, though the analyses will only be performed based on those subjects enrolled onto Arms A and B (dose-escalation) as no subjects will be enrolled onto Arms A and B dose-expansion.

Patients will continue on treatment until progression of disease or unacceptable toxicity. The initial scan interval to assess disease status will be every two cycles (8 weeks) for the first four cycles (16 weeks), and then every 3rd cycle (12 weeks) thereafter (see Section 10.10). For patients who are on study under Amendment 13, the scan interval will become every 4th cycle (16 weeks ±4 weeks) from their last scan. Toxicity will be tabulated using the NCI Common Toxicity Criteria (CTCAE), version 4.0, and data will be entered into the MSKCC Clinical Research Data Base (CRDB).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 BYL719 Mode of Action

BYL719 is an oral PI3K inhibitor which selectively inhibits the class IA p110α isoform of PI3K. BYL719 will be considered the investigational treatment or the “study drug” for this study. See Section 3.5 for an overview of the pre-clinical and clinical experience with BYL719.

5.2 BYL719 Availability and Storage

BYL719 will be supplied by Novartis as tablets for oral use of 50mg and 200mg dosage strength. The tablets will be differentiated through different tablet sizes and/or colors. BYL719 will be dosed on a flat scale and not individually adjusted by weight or body surface area.

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, BYL719 should be stored according to the instructions specified on the drug labels. Study medication will be dispensed by an authorized person at MSKCC.

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

The drug supply will be destroyed at a Novartis facility, or Novartis will provide guidelines for destruction, if investigational site is approved to destroy drug per prior agreement with Novartis.

5.3 BYL719 Administration

Please refer to Section 9.2 for BYL719 administration guidelines.

5.4 BYL719 Toxicity

Please refer to Section 11.0 for BYL719 Toxicity.

5.5 BYL719 Pharmacology

For details on preclinical and clinical experience, please refer to Section 3.5.1 and Section 3.5.2 and the current BYL719 Investigator's Brochure (IB).

5.6 BYL719 Drug Interactions

Please refer to Section 9.6 entitled "Concomitant medications" for information regarding BYL719 drug interactions.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

6.2.1 Women age ≥ 18 years

6.2.2 Willing and able to comply with scheduled visits, treatment plan and laboratory tests

6.2.3 Willing and able to consent for biopsy of locally-advanced or metastatic breast cancer prior to treatment

6.2.4 Metastatic or locally-advanced unresectable breast cancer (includes metastatic or locally-advanced unresectable breast cancer which is diagnosed while on adjuvant letrozole or exemestane)

6.2.5 Histologically documented HR+ breast cancer in either the primary or metastatic setting, as defined by ER+ or PR+; results from the local lab are acceptable. Eligibility will not be affected by HER2 status.

6.2.6 The most recent treatment prior to enrollment must be one of the following (duration of treatment ≥2 weeks), and must have been adequately tolerated according the treating physician's judgment:

- Letrozole
- Exemestane
- Exemestane + everolimus (everolimus must be discontinued for ≥ 3 weeks prior to starting study treatment)

- Letrozole or exemestane in combination with an experimental agent(s) on a clinical trial, provided that the experimental agent(s) is not a PI3K inhibitor or AKT inhibitor (see Section 6.2.3) (experimental agent(s) must be discontinued for ≥ 3 weeks prior to starting study treatment)

6.2.7 Any number of prior endocrine therapies (including tamoxifen, fulvestrant and/or aromatase inhibitors in either the adjuvant or metastatic setting) and any number of prior chemotherapy regimens. Anti-cancer systemic therapy, such as chemotherapy or biologics or endocrine therapy, other than the AI, must be discontinued for ≥ 3 weeks prior to starting study treatment.

6.2.8 For the dose-finding phase, patients may have stable disease OR progression of disease on the most recent treatment. For the expansion phase, patients must also have stable disease OR progression of disease on the most recent treatment. Progression of disease is defined as new or worsening disease on objective imaging. Progression of disease includes recurrence diagnosed while on adjuvant letrozole or exemestane.

6.2.9 Postmenopausal women, as defined by one of the following (estradiol assay cutoff takes into account that the patient is on aromatase inhibitor therapy):

- Age ≥ 55 years and one year or more of amenorrhea
- Age < 55 years and one year or more of amenorrhea, with an estradiol assay within the post-menopausal range
- Age < 55 years with prior hysterectomy but intact ovaries, with an estradiol assay within the post-menopausal range
- Surgical menopause with bilateral oophorectomy
- Ovarian suppression with a LH-RH agonist, with an estradiol assay within the post-menopausal range at baseline and periodically on-study

6.2.10 Measurable or non-measurable disease per RECIST criteria v1.1

6.2.11 ECOG performance status 0-1

6.2.12 Adequate organ function, as defined by all of the following:

- Hematologic parameters:
  - Absolute neutrophil count (ANC) ≥ 1500/µl (without growth factor support)
  - Platelets ≥ 100,000/µl (no transfusion allowed within 2 weeks)
  - Hemoglobin ≥ 9.0 g/dl (may be reached by transfusion)
- Liver function:
  - Serum bilirubin ≤ 1.5 x upper limit of normal (ULN) unless attributable to Gilbert's syndrome
  - AST ≤ 2.5 x ULN, or ≤ 5 x ULN if liver metastases are present
  - ALT ≤ 2.5 x ULN, or ≤ 5 x ULN if liver metastases are present
- Kidney function:
  - Creatinine ≤ 1.5 ULN

- Endocrine function:
    - Fasting plasma glucose <140 mg/dl (may be on antiglycemic agents other than insulin). Fasting glucose measurement must be obtained at least 8 hours after the most recent caloric intake.

6.2.13 Ability to swallow oral medication

6.2.14 Willing to discontinue all herbal preparations / medications at least 7 days prior to the first dose of study drug and throughout the study. These include, but not limited to, St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

6.3 Subject Exclusion Criteria

Patients eligible for this study must not meet **any** of the following criteria:

6.3.1 Pregnant patients or women who are breast-feeding (patients must be postmenopausal, see Section 6.1.9)

6.3.2 Patients with central nervous system (CNS) involvement may participate if:

- Clinically stable with respect to the CNS tumor at the time of screening and >4 weeks from prior therapy completion (including radiation and/or surgery) to the start of study treatment
- Not receiving steroid therapy
- Not receiving enzyme inducing anti-epileptic medications that were started for brain metastases (these include carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, topiramate, and vigabatrin)

6.3.3 Prior PI3K inhibitor or AKT inhibitor (patients previously treated with everolimus are eligible, see rationale in Section 3.6)

6.3.4 History of toxicity to the most recent AI (letrozole or exemestane) that warrants cessation of the AI

6.3.5 Patients who have received radiotherapy ≤ 2 weeks prior to starting study treatment

6.3.6 Patients who have undergone major surgery ≤ 4 weeks prior to starting study treatment, who have not recovered from side effects of such procedure

6.3.7 Uncontrolled diabetes (as defined by fasting glucose ≥ 140mg/dL) and/or insulin-dependent diabetes. Fasting glucose measurement must be obtained at least 8 hours after the most recent caloric intake. Patients currently requiring the use of antiglycemic agents (other than insulin) may be enrolled if fasting glucose <140mg/dL.

6.3.8 Current need for chronic corticosteroid therapy (≥10mg of prednisone daily or an equivalent dose of other corticosteroid), or patients who have received systemic corticosteroids ≤ 2 weeks prior to starting study drug

6.3.9 Current therapeutic anticoagulation with warfarin (or coumarin derivatives)

6.3.10 Active infection or serious underlying medical condition that would impair the patient's ability to receive protocol treatment

6.3.11 Clinically significant cardiac disease or impaired cardiac function, such as:

- Congestive heart failure requiring treatment (e.g., New York Heart Association Class II, III or IV)
- Acute coronary syndromes < 3 months prior to screening (including myocardial infarction, unstable angina, coronary artery bypass graft, coronary angioplasty, or stenting)
- Uncontrolled arterial hypertension defined by blood pressure > 140/100 mm Hg at rest (average of 3 consecutive readings)
- History or current evidence of unstable, clinically significant cardiac arrhythmias or patients that require medications with a narrow therapeutic window, atrial fibrillation and/or conduction abnormality, e.g. congenital long QT syndrome, high-Grade/complete AV-blockage
- Corrected QT interval (QTc) > 480 msec on screening ECG

6.3.12 Patients who are currently receiving medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes (TdP) and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug treatment (see Section 9.6.3 and Appendix F)

6.3.13 Impaired gastrointestinal function or poorly controlled gastrointestinal disease that may significantly alter the absorption of oral BYL719 (e.g. Crohn's disease, ulcerative colitis, malabsorption syndrome, small bowel resection, uncontrolled nausea or vomiting, or grade ≥ 3 diarrhea of any etiology) based on treating physician assessment

6.3.14 Patients may not have a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse.

6.3.15 Patients with rapidly progressive or extensive symptomatic visceral metastatic disease

7.0 RECRUITMENT PLAN

The study is open to eligible patients at Memorial Sloan Kettering Cancer Center (MSKCC) main campus only. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigators, or research team at MSKCC.

Patients who are potentially eligible will be evaluated at the Breast Cancer Center at MSKCC main campus. This encounter will include a discussion of the proposed treatment, the rationale for its use, potential risks, and alternatives. Eligible patients who are interested in participating will be required to review and sign an informed consent.

8.0 PRETREATMENT EVALUATION

8.1 Physical examination within **4 weeks** prior to starting treatment (including ECOG performance status, height, weight, temperature, blood pressure, pulse)

8.2 Medical history within **4 weeks** prior to starting treatment (including documentation of all prior therapies for breast cancer and complete medication list for any medications taken within 4 weeks prior to starting treatment, see Section 9.3 for prohibited concomitant medications)

8.3 Evidence of disease (EOD) evaluation within **4 weeks** prior to starting treatment

- CT of chest/abdomen +/- pelvis, with oral and IV contrast unless contraindicated (will be a baseline measure for the study)
- Bone scan
- For patients with locally-advanced unresectable breast cancer, radiographic assessment using MRI is acceptable (may be used as a baseline measure for the study instead of CT, although a pretreatment CT of chest/abdomen is also required)

8.4 Pre-treatment biopsy is required within **4 weeks** prior to starting treatment, unless felt to put the patient at unacceptable risk. After obtaining separate informed consent, a core biopsy will be obtained and processed for both targeted gene sequencing and proteomic analyses (Section 10.12)

8.5 EKG within **2 weeks** prior to starting treatment.

8.6 Bloodwork within **2 weeks** prior to starting treatment:

- Complete blood count (CBC) including WBC (absolute neutrophil count required, remainder of differential not required), Hgb and platelet count
- Comprehensive profile (CMP), including BUN, creatinine and liver function tests
- PT/INR and PTT
- Magnesium, amylase and lipase
- Fasting glucose (8 hours after the most recent caloric intake)
- Companion normal DNA for targeted gene sequencing analysis (1ml whole blood for correlative science, Section 10.12).
- Plasma collection from 10 ml blood for cfDNA extraction and analysis

9.1 TREATMENT/INTERVENTION PLAN

9.2 Aromatase Inhibitor Administration

This clinical trial was initially comprised of two arms, one for BYL719 in combination with letrozole (Arm A), and another for BYL719 in combination with exemestane (Arm B). As of January 2014, the study is being amended to include two additional arms, and patients will no longer be enrolled onto Arms A or B. On Arm C, patients will receive intermittent BYL719 (7 days on, 7 days off) in combination with daily letrozole, and on Arm D, patients will receive intermittent BYL719 (5 days on, 2 days off) in combination with daily exemestane. Patients will be eligible for only one of the two arms, Arm C or Arm D, depending on which AI

(letrozole or exemestane) they were taking before study enrollment (i.e., a patient who was taking letrozole will continue to take letrozole, and a patient who was taking exemestane will continue to take exemestane). Patients will not be randomized to one of the two arms.

Letrozole or exemestane will be self-administered by the study patients orally once daily. . On days that patients are taking BYL719, aromatase inhibitor should be swallowed concomitantly with BYL719, or less than 5 minutes apart, at approximately the same time every day. The recommended time of administration is approximately 9 am (+/- 2 hrs). On a day of PK bloodwork, patients will take the scheduled dose in clinic. Treatment doses for each AI will be fixed at the established dose (see Table 9-1 below). There will be no dose escalation or dose reduction for letrozole or exemestane.

Table 9-1

Arm	**AI dose**	**BYL719 schedule (dose per cohort)**
A	Letrozole 2.5mg orally once daily	Days 1-28 of 28 day cycle
B	Exemestane 25mg orally once daily	Days 1-28 of 28 day cycle
C	Letrozole 2.5mg orally once daily	Days 1-7, 15-21 of 28 day cycle
D	Exemestane 25mg orally once daily	Days 1-5, 8-12, 15-19, 22-26 of 28 day cycle

9.3 BYL719 Administration

BYL719 will be taken orally (see Table 9-1, Table 9-2, and Section 9.4 for dose-finding schema). A new bottle of medication at the appropriate dose level will be dispensed on Day 1 of each 28-day cycle, regardless of the number of tablets remaining in the bottle from the previous cycle. For patients receving treatment under Amendment 13; medication bottles will be dispensed on Day 1 of every other 28 day cycle such that each dispensation will provide enough tablets for two cycles. Patients will be provided with an adequate supply of BYL719 for self-administration at home until at least their next scheduled study visit. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded appropriately.

Arms C and D

COHORT	BYL719 dose
+2	350mg
+1	300mg
0 (starting dose)	250mg
-1	200mg

Patients may be seen up to 7 days prior to or following the planned cycle start for the purpose of scheduling/conflicts. This window is also applicable to patients who are being seen in clinic every two cycles under Amendment 13.In the case of such changes for

scheduling/conflicts, BYL719 should continue to be self-administered. Day 1 of each cycle will remain as every 28 days.

Patients will be instructed to take BYL719 as per protocol.

The following general guidelines should be followed for BYL administration:

- Patients should be instructed to take one or more tablets of BYL719 together with a glass of water (~250 ml or ~8 fluid ounces) daily in the morning approximately 1 hour after start of a light breakfast (e.g., consisting of non-grapefruit based juice, toast and jam) at approximately the same time each day (recommended 8AM +/1 hour), except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic. A light breakfast is defined as approximately 500 calories, with approximately 75% from carbohydrates and approximately 25% from protein and/or fat.
- Patients should not eat for 1 hour after the administration of BYL719.
- If by noon the patient forgets to take the study drug (BYL719), then the dose should be withheld that day. Missed doses should not be made up. If, for any reason, a breakfast was not consumed, then the patient should still take the scheduled morning dose of study drug with a glass of water.
- Patients should be instructed to swallow the tablets and not to chew or crush them.
- Patients should be dosed in a staggered manner at least 1 hour before or 10 hours after dosing with medicinal products that may alter the pH of the upper GI tract.
- Patients should record if the dose was taken or not in the patient diary.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increase stool frequency) during the treatment must be noted in the adverse events section of the eCRF.
- Patients must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, starfruits and cranberry juice from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A interaction. Regular orange (Citrus X sinensis) juice is allowed.

On a day of scheduled fasting glucose testing, patients must be fasting overnight for at least 8 hours prior to the blood collection. A light breakfast should be consumed after fasting glucose blood draw. BYL719 will be taken in clinic approximately 1 hour after the start of breakfast. Patients should then fast for 1 hour after the administration of BYL719.

Fasting glucose testing and PK sampling may be performed on the same day: fasting overnight for at least 8 hours → fasting blood collection and pre-dose PK sample → light breakfast → 1 hour wait → BYL719 oral administration → post-dose PK sample at the appropriate time intervals (see Section 10.11).

Patients will be given a medication diary to record the date and time of their BYL719 dose each day (Appendix H and Appendix I).

9.4 Dose-Limiting Toxicity (DLT) Definition

Toxicity will be tabulated using the NCI Common Toxicity Criteria (CTCAE), version 4.0. A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as at least possibly related to the study medication, meeting any of the criteria listed in the table below, and occurring during Cycle 1 (≤ 28 days following the first dose of BYL719, including those in which the event started in Cycle 1 and the confirmation of the DLT occurs in a subsequent cycle). Whenever a patient experiences toxicity that fulfills the criteria for a DLT, treatment with the study drug will be interrupted and the toxicity will be followed up (see toxicity management guidelines in Section 10).

As an additional safety measure to assess for late-appearing toxicity, a confirmatory safety assessment will be performed at the end of Cycle 2. If dose-limiting toxicity is observed between 28 days and 56 days, then safety data will be reviewed by the Principle Investigator and Novartis, and this information will inform the dose-finding cohorts.

Table 9-2 Dose-Limiting Toxicity Criteria

Toxicity	DLT criteria
Blood and lymphatic system disorders	Anemia CTCAE Grade 3 for > 14 consecutive days
	Anemia CTCAE Grade 4
	Febrile neutropenia CTCAE Grade ≥ 3
	Neutropenia CTCAE Grade 3 for > 7 consecutive days
	Neutropenia CTCAE Grade 4
	Thrombocytopenia CTCAE Grade 3 for > 7 consecutive days and/or with signs of clinically significant bleeding
	Thrombocytopenia CTCAE Grade 4
Cardiac disorders	Cardiac toxicity CTCAE Grade ≥ 3 or cardiac event that is symptomatic or requires medical intervention
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin CTCAE Grade 3 (confirmed with a repeat Troponin within 24 hrs)
	ECG QTc interval prolonged CTCAE Grade ≥ 3
Vascular disorders/ Hypertension	Persistent hypertension CTCAE Grade ≥ 3 requiring more than one drug or more intensive therapy than previously
General disorders and administration site conditions	Fatigue CTCAE Grade 3 for > 7 consecutive days
Skin and subcutaneous tissue disorders [a]: Rash and/or photosensitivity	Rash or photosensitivity CTCAE Grade 3 for >7 consecutive days despite skin toxicity treatment, or any second or third occurrence of CTCAE Grade 3 rash regardless of duration
	Rash or photosensitivity CTCAE Grade 4
Metabolism and nutrition disorders: Hyperglycemia [b]	Hyperglycemia Grade 3(fasting plasma glucose 250 – 500mg/dL) (confirmed with a repeat fasting plasma glucose test within 48 hours) that does not resolve to grade 0 within 14 consecutive days (after initiation of oral anti-diabetic treatment)
	Hyperglycemia Grade 4
	Hyperglycemia leading to diabetic keto-acidosis, hospitalization for IV insulin infusion, or non-ketotic coma
GI disorders [a]	Diarrhea CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-diarrhea therapy
	Nausea/vomiting CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-emetic therapy
	Pancreatitis CTCAE Grade ≥ 3
Eye disorder	CTCAE Grade ≥ 3

Toxicity	DLT criteria
Blood chemistries [c]	Blood bilirubin [d] CTCAE Grade 2 for > 7 consecutive days
	Blood bilirubin [d] CTCAE Grade ≥ 3
	AST or ALT CTCAE Grade ≥ 3 in conjunction with blood bilirubin [d] CTCAE Grade ≥ 2 of any duration
	AST or ALT CTCAE Grade 3 for > 7 consecutive days
	AST or ALT CTCAE Grade 4
	Serum alkaline phosphatase CTCAE Grade 4
	Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 3 for > 7 consecutive days
	Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 4
	Serum creatinine CTCAE Grade 2 for > 7 consecutive days
	Serum creatinine CTCAE Grade ≥ 3
Other hematologic and non-hematologic toxicities	Any other **clinically significant** CTCAE ≥ Grade 3 toxicity
	Any intolerable CTCAE Grade 2 toxicity
	Apart from the criteria listed above, if a lower grade AE leads to a dose interruption of more than 7 consecutive days of BYL719, this AE will be considered as DLT

[a] Patients will receive prophylactic treatment for rash with an antihistamine beginning on cycle 1 day 1. Patients will not initially receive prophylactic treatment for nausea/vomiting during Cycle 1. However, prophylactic treatment may be initiated in all patients at the dose level where these toxicities have been observed and in all further patients if at least 1 patient has experienced nausea/vomiting CTCAE Grade ≥ 3 or if at least 2 patients experienced skin toxicity or nausea/vomiting CTCAE Grade ≥ 2 (see Section 11.2 and Table 10-2 for further details). Anti-emetics may be applied for treatment if the patient has experienced nausea/vomiting CTCAE Grade ≥ 1, at the discretion of the physician.

[b] Hyperglycemia occurring during corticosteroids administration will be only be considered DLT if not resolved within 5 days after the end of corticosteroid treatment.

[c] For any hepatic toxicity CTCAE Grade 4, or CTCAE Grade 3 that does not resolve within 7 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan should be performed to assess if it is related to disease progression.

[d] Refers to total bilirubin.

9.5 Dose-Finding Phase

The dose-finding phase will follow a standard 3 + 3 design. A treatment cycle will consist of 28 days. Patients will continue on treatment until progression of disease or unacceptable toxicity.

For Arms A and B, the starting dose of BYL719 for the first cohort (Cohort 0) will be 300mg daily, which is 75% of the MTD from the phase I study. Treatment doses for BYL719 for each cohort are presented below:

Table 9-3 Dose-Finding Cohorts for Arms A and B

COHORT	BYL719 dose
+2	400mg orally once daily (100% of MTD for single agent BYL719)
+1	350mg orally once daily (87.5% of MTD for single agent BYL719)
0 (starting dose)	300mg orally once daily (75% of MTD for single agent BYL719)
-1	250mg orally once daily (62.5% of MTD for single agent BYL719)
-2	200mg orally once daily (50% of MTD for single agent BYL719)

For Arms C and D, the starting dose of BYL719 for the first cohort (Cohort 0) will be 250mg daily. Treatment doses for BYL719 for each cohort on Arms C and D are shown below:

Table 9-4 Dose-Finding Cohorts for Arms C and D

COHORT	BYL719 dose
+2	350mg
+1	300mg
0 (starting dose)	250mg
-1	200mg

During the dose-finding phase, a periodic teleconference will be held at least monthly with the primary investigator and Novartis to review toxicity data and ensure patient safety moving forward.

Dose escalation or de-escalation schema:
On each arm, three patients will be enrolled onto Cohort 0 at the starting BYL719 dose. All patients within a cohort will be observed for toxicity for one cycle (28 days) prior to entering additional patients. If a patient discontinues study participation during the first cycle (within 28 days of starting study treatment) for reasons unrelated to an adverse event, an additional patient may be enrolled to replace that subject. Between 6 and 15 patients in each arm will be necessary to determine the recommended phase II dose of BYL719 in combination with letrozole or exemestane.

There will be no intrapatient dose escalation. Intrapatient dose reductions of BYL719 will not be allowed during Cycle 1 (within 28 days of starting study treatment), unless a DLT has occurred and been counted towards informing enrollment of future cohorts of patients. This is in order to accurately determine the safe and tolerable dose of BYL719 when used in combination with letrozole or exemestane.

Schema for Cohort 0:
If none of the initial three patients in Cohort 0 experience dose-limited toxicity (DLT), as defined above, then three new patients will be enrolled in Cohort +1 (dose escalation).

If one of the initial three patients in Cohort 0 experiences DLT, then up to three additional patients will be treated at the same dose level. If no more than one of six patients in Cohort 0 experiences DLT, then three new patients will be enrolled in Cohort +1 (dose escalation).

If two or more patients in Cohort 0 experience DLT, then three new patients will be enrolled in Cohort -1 (dose de-escalation).

Schema for Cohort +1:
If none of the initial three patients in Cohort +1 experience dose-limited toxicity (DLT), as defined above, then three new patients will be enrolled in Cohort +2 (dose escalation).

If one of the initial three patients in Cohort +1 experiences DLT, then up to three additional patients will be treated at the same dose level. If no more than one of six patients in Cohort +1 experiences DLT, then three new patients will be enrolled in Cohort +2 (dose escalation).

If two or more patients in Cohort +1 experience DLT, then the dose level in Cohort 0 will be re-considered as the recommended phase II dose. If only three patients were treated in Cohort 0, then up to three additional patients will be accrued to that dose level. If no more than one of six patients in Cohort 0 experiences DLT, then that dose level will be confirmed as the recommended phase II dose of BYL719 in this combination.

Schema for Cohort +2:
If none or one of the initial three patients in Cohort +2 experience DLT, then up to three additional patients will be treated at the same dose level. If no more than one of six patients in Cohort +2 experiences DLT, then that dose level will be the recommended phase II dose of BYL719 in this combination.

If two or more patients in Cohort +2 experience DLT, then the dose studied in Cohort +1 will be re-considered. If only three patients were treated in Cohort +1, then up to three additional patients will be accrued to that dose level. If no more than one of six patients in Cohort +1 experiences DLT, then that dose level will be confirmed as the recommended phase II dose of BYL719 in this combination.

Schema for Cohort -1:
If none or one of the initial three patients in Cohort -1 experience DLT, then up to three additional patients will be treated at the same dose level. If no more than one of six patients in Cohort -1 experiences DLT, then that dose level will be confirmed as the recommended phase II dose of BYL719 in this combination. If two or more patients in Cohort -1 experience DLT, then three new patients will be enrolled in Cohort -2.

Schema for Cohort -2:
If none or one of the initial three patients in Cohort -2 experience DLT, then up to three additional patients will be treated at the same dose level. If no more than one of six patients in Cohort -2 experiences DLT, then that dose level will be confirmed as the recommended phase II dose of BYL719 in this combination. If two or more patients in Cohort -2 experience DLT, then we will conclude that the combination is not feasible and will discontinue the affected arm of the trial. If this occurs, accrual onto the unaffected arm will be halted until safety data is reviewed by the primary investigator and Novartis to determine whether to continue or close the unaffected arm of the trial.

9.6 Expansion Phase

As of June 2015, the recommended phase II dose of BYL719 has been determined to be 350mg for Arm D and we are currently enrolling 10 patients to the corresponding arm in the expansion phase of the study. The purpose of the expansion phase is to further define the safety and feasibility of BYL719 daily or intermittently in combination with letrozole or exemestane, and to estimate efficacy.

Patients will be eligible for only one of the four arms depending on which AI (letrozole or exemestane) they were taking immediately prior to study enrollment. Patients will not be randomized to one of the four arms.

In the expansion phase, BYL719 will be administered orally on the same administration schedule for that arm as for the dose-finding phase and at the dose established in the dose-finding phase of the trial. For Arm D, the established dose is 350mg for BYL719. Patients will continue on treatment until progression of disease or unacceptable toxicity.

In order to help ensure that the DLT rate observed among the additional 10 patients in each arm is consistent with the DLT rate observed at the established dose from the dose-finding portion, the following decision rule will be implemented for each of the two study arms. If ≥ 4 DLTs are seen at any time in any one expansion arm, then it is likely that the safe and tolerable dose determined during the dose-finding portion of the trial is too toxic. The safety data will then be reviewed with the primary investigator and Novartis to determine how to move forward. Depending on the circumstances, we may consider de-escalating the dose of BYL719 to the next lower dose level and accruing 10 additional patients at that level. The probability of observing at least 4 patients with a DLT in the 10 additional patients is .28 if 1 of 6 patients were seen with a DLT in the dose-finding phase of the study. The probability of observing at least 4 patients with a DLT in the 10 additional patients is .09 if 0 of 6 patients were seen with a DLT in the dose-finding phase of the study.[11]

The two arms of the study will be monitored in tandem, and we have added an overall sequential global stopping rule to be applied as both expansion cohorts are accruing. We include this early stopping rule across both arms because the mechanism and toxicities of both AIs are known to be very similar. Our global stopping rule is based on repeated significance testing and serves as a global safety measure. We assume a grade 4 toxicity rate of 10% as acceptable and 35% as unacceptable. With these assumptions, if 2 of the first 5 patients, 3 of the first 10 patients, 4 of the first fifteen or 5 of 20 patients accrued experience a grade 4 toxicity, we will discontinue the entire study. With this rule, the probability of discontinuing the study if the true toxicity rate is 35% is .92. If the true toxicity rate is 10%, this probability is .10.
Likewise, if two different recommended phase II doses are determined in the separate arms, safety data will be reviewed with the primary investigator and Novartis, and we will determine how to move forward. Depending on the circumstances, we will consider reducing the dose of BYL719 in the unaffected arm of the trial, if felt to be appropriate to ensure patient safety.

9.7 Concomitant Medications

All medications (other than the study drugs) taken within 4 weeks of study treatment initiation and all concomitant therapy and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study, with reasons for use, should be recorded. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications and nutritional or vitamin supplements.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after starting study drug. Upon enrollment, patients should be given the handout titled "Patient Information for BYL719 Drug and Food Interactions" (Appendix C), and this information should be reviewed with the patient.

Patients taking medication chronically should be maintained on the same dose and schedule throughout the study period, as medically feasible. The days of full pharmacokinetic blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of full pharmacokinetic sampling, if medically feasible.

9.6.1 Permitted concomitant therapy

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited in Section 9.6.3.

Antiemetics: Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the patient experienced nausea or vomiting at the discretion of the investigator (refer to Table 10-2 for toxicity management guidelines). It is recommended that patients use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for Torsades de Pointes (e.g.,chlorpromazine, droperidol, haloperidol) and are prohibited (refer to Section 9.6.3 and Appendix F). Some other anti-emetics (e.g., ondansetron) are to be used with caution (refer to Appendix G).

Bisphosphonates: The use of bisphosphonates regardless of indication is allowed provided patients have been on stable doses for at least 2 weeks prior to study entry. Stable dose should be maintained during the treatment period. Patients requiring initiation of bisphosphonates during the course of the study should be discontinued due to progressive disease unless disease progression can be completely ruled out and this is clearly documented in the patients' source documentation.

Oral anti-diabetics: Patients who develop diabetes mellitus during the study should be treated according to the ADA (American Diabetes Association) guidance (refer to Section 10.10.3). Patients receiving oral antidiabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, must be carefully monitored for hypoglycemia as BYL719 was found to be moderate reversible inhibitor of these enzymes (refer to Appendix D).

9.6.2 Permitted concomitant therapy requiring caution and/or action

Hematopoietic growth factors: Hematopoietic growth factors (e.g. erythropoietins, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered prophylactically. Use of these drugs should be reserved to patients with severe neutropenia and anemia as per the labeling of these agents or as dictated by local practice (see also the guidelines established by the American Society of Clinical Oncology).

Anticoagulation: Anticoagulants other than warfarin/coumarin derivates or antiaggregation agents may be administered under the discretion of the investigator (refer to Section 9.6.3). However, caution is advised when BYL719 is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4, CYP2C9 and CYP2C19. BYL719 has the potential to inhibit these enzymes and may therefore decrease the metabolic activation and clinical efficacy of these pro-drugs. Patients using anti-platelet pro-drugs should be carefully monitored.

CYP450 substrates: In vitro studies demonstrate that BYL719 is a mechanism based inhibitor of CYP3A4. BYL719 may increase exposure to drugs metabolized by CYP3A4 by more than 5-fold. BYL719 may also inhibit the metabolic clearance of co-medications metabolized by CYP2C8, CYP2C9, CYP2C19, if sufficiently high BYL719 concentrations are achieved in vivo. Investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19 (refer to Appendix D). Patients receiving such medications must be carefully monitored for potential toxicity due to any individual concomitant medications. Particularly, caution is advised when BYL719 is co-administered with drugs that are sensitive substrates for CYP3A4, CYP2C8, CYP2C9 or CYP2C19 and which have a narrow therapeutic index (Appendix D, footnote 2).

Opioid analgesics: Caution is advised when BYL719 is co-administered with opioid analgesics. Inhibition of opioid metabolism by CYP3A4 can lead to opioid toxicity, including fatal respiratory depression, or an enhanced risk for QTc prolongation. Patients receiving BYL719 and opioid analgesics should be carefully monitored. Synthetic opioids with clinically relevant interactions with CYP3A4 inhibitors include, but are not limited to, propoxyphene, fentanyl, alfentanil and sufentanil. Use of alfentanil, a sensitive CYP3A4 substrate with narrow therapeutic window, should be fully avoided whenever possible. The use of methadone or levomethadyl is prohibited (refer to Appendix F).

Drugs with a conditional or possible risk to induce Torsade de Pointes (TdP): Please refer to Section 9.3.3 and Appendix F for a list of prohibited QT prolonging medication. If a patient, enrolled in the study, requires the concomitant use of any medication with a possible or conditional risk for TdP (see Appendix G for a list of such medications), then investigators, at their discretion, may co-administer such medications. Patients receiving such medications must however be monitored.

Gastric protection agents: BYL719 is characterized by a pH-dependent solubility. Medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of BYL719 and hence its bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. BYL719 should preferably be dosed in a staggered manner, i.e., at least 1 hour before or 10 hours after dosing with a gastric protection agent. Note that some proton pump inhibitors may possibly inhibit BCRP (refer to Appendix E). The treatment with BCRP inhibitors should be kept as short as possible or, if possible, fully avoided.

BCRP Inhibitors: BYL719 was identified as a substrate for the human BCRP. Co-administration of BYL719 with BCRP inhibitors may possibly increase systemic exposure

and/or alter tissue uptake of oral BYL719. The treatment with BCRP inhibitors should be kept as short as possible or, if possible, fully avoided. See Appendix E for a list of BCRP inhibitors.

Palliative radiotherapy: Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. Whenever possible, these patients should have a tumor assessment of the lesion(s) before they actually receive the radiotherapy in order to rule out progression of disease. In case of disease progression, patients should discontinue treatment and be removed from the study. No dose modification of study treatment is needed during radiotherapy.

Steroids: Chronic administration of corticosteroids (> 5 days) can induce CYP3A4. Due to this and concern for hyperglycemia, steroids should be used briefly and with caution. Patients who have a current need for chronic corticosteroid therapy at the time of screening (≥10mg of prednisone daily or an equivalent dose of other corticosteroid) are not eligible to enroll.

9.6.3 Prohibited concomitant therapy

Other investigational and antineoplastic therapies: Other investigational therapies must not be used while the patient is on the study. Systemic anticancer therapy (chemotherapy, biologic) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.

Drugs with a known risk for Torsades de Pointes (TdP): If a patient, enrolled in the study, requires the concomitant use of any medication included in Appendix F entitled “List of Prohibited QT prolonging drugs” (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a known risk of causing TdP), BYL719 administration must be interrupted as long as the patient requires therapy with the QT prolonging agent. Note that Appendix D also includes drugs that are substrates for CYP3A and CYP2C with a possible or conditional risk for TdP. If the patient requires long term therapy with such a QT prolonging agent, leading to study treatment interruption of > 21 days, the patient must be permanently discontinued from BYL719.

Herbal medications: Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John’s wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

Warfarin and coumarin derivates: Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants are not permitted. Warfarin has a narrow therapeutic range and BYL719 is a possible inhibitor of CYP2C8 and 2C9, the major metabolizing enzyme of warfarin. Therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

Opioid analgesics: See Section 9.3.2 for opioid analgesics to be used with caution. Use of alfentanil, a sensitive CYP3A4 substrate with narrow therapeutic window, should be fully avoided whenever possible. The use of methadone or levomethadyl is prohibited.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Evaluation Summary

Table 10-1 Evaluation Summary Chart

	Pre-Rx[a]	Cycle 1 Day 1	Cycle 1 Day 8 (+/- 3 days)	Cycle 1 Day 15 (+/- 3 days)	Cycle 2 Day 1 (+/- 3 days)	Cycle 2 Day 15 (+/- 3 days)	Cycle 3+ Day 1 (+/- 7 days)[h]	End of Rx (within 28 days)[b]
Letrozole or Exemestane	Continuous daily dosing, Days 1-28							
BYL719, Arm A/B	Continuous daily dosing, Days 1-28							
BYL719, Arm C	Days 1-7, 15-21 of 28 day cycle							
BYL719, Arm D	Days 1-5, 8-12, 15-19, 22-26 of 28 day cycle							
Tumor biopsy	X			X				X
History and physical	X	X	X	X	X	X	X	X
Toxicity assessment		X	X	X	X	X	X	X
Assessment of Concomitant Medications	X	X	X	X	X	X	X	X
Complete blood count (CBC)	X	X		X	X	X	X	X
Comprehensive metabolic panel (CMP)	X	X		X	X	X	X	X
Magnesium, amylase, lipase	X	X		X	X	X	X	X
PT/INR and PTT	X							
Fasting glucose	X	X		X	X	X	X	X
Tumor markers (CA15-3 and CEA)		X			X		X	X
Blood draw for companion normal DNA[c]	X							
Blood draw for plasma collection (cfDNA)	X	X	X	X	X		X	X
EKG[j]	X	X		X	X	X	X[d]	X
EOD evaluation	X						X[d]	X[e]
Research PK		X		X	X	X	X[f]	
Estradiol[g]	X						X[d]	

[a] See Section 8 for required time frames for pre-treatment studies

[b] Pre-treatment and Day 15 on-treatment biopsies will be required, unless felt to put the patient at unacceptable risk (note: patients with bone-only metastases will have a pre-treatment biopsy only). See Section 10.12 for processing. The tumor biopsy is not required to be scheduled on the same day as the MD visit. While every attempt will be made to schedule the on-treatment tumor biopsy on Day 15, the exact timing of the research biopsy will be at the discretion of the investigators. All patients may be asked to undergo an optional tumor biopsy at progression, with the exact timing to be at the discretion of the investigator and patient (not necessarily within 28

	days of last dose of BYL719), although a 2 week window is allowed. **c** Companion normal DNA for targeted gene sequencing analysis (1ml whole blood for correlative science, Section 10.12) **d** Day 1 +/- 7 days of Cycle 3, Cycle 5, and then every 3rd cycle (Cycle 8, Cycle 11, etc) **e** If EOD not already performed in the last 28 days **f** Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 8 and Cycle 10 for letrozole arm (Arm A) and Cycle 3 only for exemestane arm (Arm B) **g** Estradiol to be tested only on women who are receiving pharmacologic ovarian suppression **h** Patients on study under Amendment 13 will have relevant blood and cfDNA collection every other cycle (+/- 7 days). **i** Patients on study under Amendment 13 will have EOD evaluations will be preformed every 16 weeks +/- 4 weeks from their last scan. **j** Patients on study under Amendment 13 will have EKG evaluations every 4 cycles. EKG evaluations may be preformed more frequently at the discretion of the MD.

10.2 Cycle 1 Day 1

10.2.1 MD visit, with history and physical examination, including weight, blood pressure, pulse, ECOG performance status, and updated medication list. Concurrent medications will be reviewed for potential drug-drug interactions with study medication (see Section 9.6).

10.2.2 Toxicity will be assessed and the type, severity, timing, and relationship of each adverse event to therapy will be determined as per the NCI Common Toxicity Criteria, version 4.0.

10.2.3 Fasting bloodwork prior to taking BYL719 in clinic on this day (if screening bloodwork was not performed within 72 hours of dosing). A light breakfast may be consumed after fasting plasma glucose draw. BYL719 may be administered 1 hour after breakfast. Patients should fast for 1 hour after the administration of BYL719. Bloodwork results do not need to be resulted prior to dosing on this day; however, all bloodwork must be reviewed and the patient contacted within 24 hours (excluding weekends and holidays) if an abnormality is detected which would affect dosing. If a patient is being screened and starting treatment on the same day, then results of CBC, CMP and fasting glucose must be reviewed prior to enrollment and initiation of treatment.

- CBC, including WBC (differential not required), Hgb and platelet count
- CMP, including BUN, creatinine and liver function tests
- Magnesium, amylase and lipase
- Fasting glucose
- PT/INR and PTT
- Tumor markers (CA 15-3 and CEA)
- Plasma collection from 10 ml blood for cfDNA extraction analysis

10.2.4 EKG will be performed (if screening EKG was not performed within 72 hours of dosing). EKG must be reviewed prior to dosing.

10.2.5 PK bloodwork for research purposes (see schedule in Section 10.11).

10.2.6 Patients will be prescribed or advised to take an over the counter antihistamine daily, unless contraindicated for that specific patient. Initiation of anti-histamine therapy is recommended but not required at the start of BYL719 therapy.

10.3 Cycle 1 Day 8 (+/- 3 days)

10.3.1 MD visit, with history and physical examination, including weight, blood pressure, pulse, ECOG performance status, and updated medication list. Concurrent medications will be reviewed for potential drug-drug interactions with study medication (see Section 9.6).

10.3.2 Research blood draw for plasma collection from 10ml blood for cfDNA extraction and analysis

10.4 Cycle 1 Day 15 (+/- 3 days)

10.4.1 MD visit, with history and physical examination, including weight, blood pressure, pulse, ECOG performance status, and patient drug diary review.

10.4.2 Toxicity will be assessed and the type, severity, timing, and relationship of each adverse event to therapy will be determined as per the NCI Common Toxicity Criteria, version 4.0.

10.4.3 Fasting bloodwork prior to taking BYL719 in clinic on this day. A light breakfast may be consumed after fasting plasma glucose draw. BYL719 may be administered 1 hour after breakfast. Patients should fast for 1 hour after the administration of BYL719. Bloodwork results do not need to be resulted prior to dosing on this day (because BYL719 dosing is continuous); however, all bloodwork must be reviewed and the patient contacted within 24 hours (excluding weekends and holidays) if an abnormality is detected which would affect dosing.

- CBC, including WBC (differential not required), Hgb and platelet count
- CMP, including BUN, creatinine and liver function tests
- Magnesium, amylase and lipase
- Fasting glucose
- Plasma collection from 10 ml blood for cfDNA extraction and analysis

10.4.4 EKG will be performed and reviewed prior to dosing.

10.4.5 PK bloodwork for research purposes (see schedule in Section 10.11).

10.4.6 Day 15 on-treatment tumor biopsy will be required, unless felt to put the patient at unacceptable risk (note: patients with bone-only metastases will have a pre-treatment biopsy only). This biopsy is for research purposes. After obtaining separate informed consent, a core biopsy will be obtained and processed for proteomic analysis (Section 10.12). The tumor biopsy should be taken 2-8 hours after the BYL719 dose on that day. The tumor biopsy is not required to be scheduled on the same day as

the MD visit. While every attempt will be made to schedule the tumor biopsy on Day 15, the exact timing of the research biopsy will be at the discretion of the investigators.

10.5 Cycle 2 Day 1 (+/- 3 days)

10.5.1 MD visit, with history and physical examination, including weight, blood pressure, pulse, ECOG performance status, patient drug diary review, and updated medication list. Concurrent medications will be reviewed for potential drug-drug interactions with study medication (see Section 9.6).

10.5.2 Toxicity will be assessed and the type, severity, timing, and relationship of each adverse event to therapy will be determined as per the NCI Common Toxicity Criteria, version 4.0.

10.5.3 Fasting bloodwork prior to taking BYL719 in clinic on this day. A light breakfast may be consumed after fasting plasma glucose draw. BYL719 may be administered 1 hour after breakfast. Patients should fast for 1 hour after the administration of BYL719. Bloodwork results do not need to be resulted prior to dosing on this day (because BYL719 dosing is continuous); however, all bloodwork must be reviewed and the patient contacted within 24 hours (excluding weekends and holidays) if an abnormality is detected which would affect dosing.

- CBC, including WBC (differential not required), Hgb and platelet count
- CMP, including BUN, creatinine and liver function tests
- Magnesium, amylase and lipase
- Fasting glucose
- Tumor markers (CA 15-3 and CEA)
- Plasma collection from 10 ml blood for cfDNA extraction and analysis

10.5.4 EKG will be performed and reviewed prior to dosing.

10.5.5 PK bloodwork for research purposes (see schedule in Section 10.11).

10.6 Cycle 2 Day 15 (+/- 3 days)

10.6.1 MD visit, with history and physical examination, including weight, blood pressure, pulse, ECOG performance status, and patient drug diary review.

10.6.2 Toxicity will be assessed and the type, severity, timing, and relationship of each adverse event to therapy will be determined as per the NCI Common Toxicity Criteria, version 4.0.

10.6.3 Fasting bloodwork prior to taking BYL719 in clinic on this day. A light breakfast may be consumed after fasting plasma glucose draw. BYL719 may be administered 1 hour after breakfast. Patients should fast for 1 hour after the administration of BYL719. Bloodwork results do not need to be resulted prior to dosing on this day

(because BYL719 dosing is continuous); however, all bloodwork must be reviewed and the patient contacted within 24 hours (excluding weekends and holidays) if an abnormality is detected which would affect dosing.

- CBC, including WBC (differential not required), Hgb and platelet count
- CMP, including BUN, creatinine and liver function tests
- Magnesium, amylase and lipase
- Fasting glucose

10.6.4 EKG will be performed and reviewed prior to dosing.

10.6.5 PK bloodwork for research purposes (see schedule in Section 10.11).

10.7 Subsequent Cycles (Cycle 3+) Day 1 (+/- 7 days)

10.7.1 One MD clinic visit per cycle, with history and physical examination, including weight, blood pressure, pulse, ECOG performance status, patient drug diary review, and updated medication list. Concurrent medications will be reviewed for potential drug-drug interactions with study medication (see Section 9.6).

10.7.2 Toxicity will be assessed and the type, severity, timing, and relationship of each adverse event to therapy will be determined as per the NCI Common Toxicity Criteria, version 4.0.

10.7.3 Fasting bloodwork prior to taking BYL719 in clinic on this day. A light breakfast may be consumed after fasting plasma glucose draw. BYL719 may be administered 1 hour after breakfast. Patients should fast for 1 hour after the administration of BYL719. Bloodwork results do not need to be resulted prior to dosing on this day (because BYL719 dosing is continuous); however, all bloodwork must be reviewed and the patient contacted within 24 hours (excluding weekends and holidays) if an abnormality is detected which would affect dosing.

- CBC, including WBC (differential not required), Hgb and platelet count
- CMP, including BUN, creatinine and liver function tests
- Magnesium, amylase and lipase
- Fasting glucose
- Tumor markers (CA 15-3 and CEA)
- Plasma collection from 10 ml blood for cfDNA extraction and analysis

10.7.4 EKG will be performed and reviewed on Day 1 +/- 7 days of Cycle 3, Cycle 5, and then every 3rd cycle (Cycle 8, Cycle 11, etc).

10.7.5 PK bloodwork for research purposes (for specified cycles only, see schedule in Section 10.11).

10.7.6 Estradiol will be performed Day 1 +/- 7 days of Cycle 3, Cycle 5, and then every 3rd cycle (Cycle 8, Cycle 11, etc) thereafter, for patients who are receiving pharmacologic ovarian suppression

10.7.7 Patients who are on study under Amendment 13 will present for one MD visit every other cycle. Patient's will complete all assessments per Section 10.1.

10.8 End of Treatment (within 28 days of last dose of BYL719)

10.8.1 MD visit, with history and physical examination, including weight, blood pressure, pulse, ECOG performance status, and final patient drug diary review.

10.8.2 Toxicity will be assessed and the type, severity, timing, and relationship of each adverse event to therapy will be determined as per the NCI Common Toxicity Criteria, version 4.0.

10.8.3 Fasting bloodwork (if not already performed in the last 28 days).

- CBC, including WBC (differential not required), Hgb and platelet count
- CMP, including BUN, creatinine and liver function tests
- Magnesium, amylase and lipase
- Fasting glucose
- Tumor markers (CA 15-3 and CEA)
- Plasma collection from 10 ml blood for cfDNA extraction and analysis

10.8.4 EKG will be performed (if not already performed in the last 28 days).

10.8.5 All patients may be asked to undergo an optional tumor biopsy at progression, with the exact timing to be at the discretion of the investigator and patient (not necessarily within 28 days of last dose of BYL719), although a 2 week window is allowed.

10.9 Evidence of Disease (EOD) Evaluation

Patients on all study arms will have an evidence of disease (EOD) evaluation at baseline, consisting of CT of chest/abdomen +/- pelvis (with oral and IV contrast unless contraindicated) and a bone scan. Patients will then have EOD evaluation with CT of chest/abdomen +/- pelvis every two cycles (8 weeks) for the first four cycles (16 weeks) of study treatment (Day 1 +/- 7 days of Cycle 3 and Cycle 5), and then every 3rd cycle (12 weeks) thereafter (Day 1 +/- 7 days of Cycle 8, Cycle 11, etc). EOD evaluation will occur every 16 weeks +/- 4 weeks from the last evaluation for patients who are on study under Amendment 13. EOD evaluation will also be performed at the end of study treatment, if not already performed in the last 28 days. A bone scan may also be performed per investigator discretion. In patients without bone-only disease, bone scans may be repeated in the event of clinical suspicion of progression of existing bone lesions, the development of new bone lesions, and in the assessment of a complete response, if any disease was evident at screening. For patients with locally-advanced unresectable breast cancer, radiographic assessments using MRI scans are acceptable to evaluate response, and a CT scan of chest/abdomen is not required.

It remains to be determined whether FDG-PET response accurately predicts tumor response to PI3K/AKT pathway inhibitors. Glucose metabolism is regulated through PI3K/AKT signaling. Inhibition of the PI3K/AKT pathway therefore inhibits glucose uptake on FDG-PET. Although FDG-PET may be a pharmacodynamic marker of pathway inhibition, clinical correlation with tumor response has not been confirmed. Therefore, CT imaging (+/- bone scan) is the preferred approach at this time.

RECIST criteria version 1.1 will be used to evaluate therapeutic response. With the development of progressive disease, patients will be removed from the study. For equivocal findings of progression (e.g., very small and uncertain new lesions, cystic changes or necrosis in existing lesions, or other such equivocal findings), treatment may continue until the next scheduled assessment at the discretion of the treating physician. If, at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

10.10 Toxicity Management

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All AEs and SAEs whether volunteered by the patient, discovered by the study personnel during questioning, or detected through physical examination, laboratory test, or other means will be recorded in the patient's medical history and on the appropriate AE or SAE CRDB page. Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, and suspected relationship to the protocol treatment. Since this trial's primary outcome is to measure safety and feasibility of the intervention by assessing toxicity to determine the MTD by measuring experiences of DLT, suspected relationships or attributions of adverse events will only be collected if assessed as grade ≥2. Additionally all laboratory toxicities will be collected for assessment if the results are considered grades ≥2.

Toxicity will be assessed using the NCI Common Toxicity Criteria, version 4.0, unless otherwise specified. The type, severity, timing and relationship of each adverse event will be documented. Criteria for defining dose-limiting toxicities (DLTs) are defined in Section 9.3. Criteria for defining serious adverse events (SAEs) are defined in Section 17.2.

10.10.1 Toxicity Follow-up

Whenever a patient experiences toxicity that fulfills the criteria for a dose limiting toxicity (DLT) or serious adverse event (SAE), treatment with the study drug will be interrupted and the toxicity will be followed up. Patients whose treatment is interrupted or permanently discontinued due to a DLT, other adverse event, or clinically significant laboratory value, must be followed up at least once a week (or more frequently if clinically indicated) for 4 weeks, and subsequently at approximately 4 week intervals, until resolution or stabilization of the event, whichever comes first. Clinic visits may include physical examination, assessment of residual toxicity, and blood tests (including CBC and CMP). Appropriate clinical experts (such as cardiologists or dermatologists, etc) should be consulted as deemed necessary.

10.10.2 Dose Reductions and Dose Delays

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. All dose modifications should be based on the worst preceding toxicity (NCI Common Toxicity Criteria, version 4.0).

Prior to completion of Cycle 1, treatment (either BYL719 or AI or both) can be held for up to 7 days for any reason, and then resumed at the same dose. After completion of Cycle 1,

treatment (either BYL719 or AI or both) can be held for up to 3 weeks for any reason, and then resumed at the same dose. The investigator may remove any patient from study for any toxicity if he/she believes that it is in the best interest of the patient to discontinue study treatment.

Intrapatient dose reductions of BYL719 will not be allowed during Cycle 1 (within 28 days of starting study treatment), unless a DLT has occurred and been counted. This is in order to accurately determine the safe and tolerable dose of BYL719 when used in combination with letrozole or exemestane.

BYL719 dose modification guidelines for toxicities considered at least possibly related to the study treatment are outlined in Table 10-2 below. If a patient experiences unacceptable toxicity that fails to resolve after a maximum BYL719 dose delay of 21 consecutive days, then the patient should be discontinued from the study treatment. In exceptional situations, if the patient is clearly benefiting from the study treatment (i.e., stable disease, partial response, complete response), and in the opinion of the investigator no safety concerns are present, the patient may remain on the study treatment. Patients who discontinue from the study for a study-related adverse event or an abnormal laboratory value must be followed as described in Section 10.10.1.

For each patient, a maximum of two dose reductions (minimum dose of BYL719 for this study is 200mg daily on Arm A and Arm B, and 150mg intermittently on Arm C and Arm D) will be allowed after which the patient will be discontinued from the study treatment. Dose reduction for BYL719 means treatment at the next lower dose level of BYL719 (e.g., 300mg daily if the prior dose was 350mg daily, and 250mg daily if the prior dose was 300mg daily). In addition, a patient must discontinue treatment if, after treatment is resumed at a lower dose, the same toxicity reoccurs with the same or worse severity. If, after interruption of treatment and resolution, treatment is resumed at the same dose following the criteria in Table 10-2, and the same toxicity reoccurs with the same severity, next treatment re-initiation must resume at the next lower dose level irrespective of duration.

There will be no intrapatient dose escalation for BYL719. For each patient, once a dose level reduction of BYL719 has occurred, the dose level may not be re-escalated during subsequent treatment cycles with the study drug.

There will be no dose escalation or dose reduction for letrozole or exemestane.

For specific guidelines related to hyperglycemia, see Section 10.10.3.

Table 10-2 Criteria for interruption and re-initiation BYL719 treatment

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
BLOOD AND LYMPHATIC SYSTEM DISORDER	
Anemia	
Grade 1 (Hgb < LLN-10.0 g/dL)	Maintain dose level of BYL719.
Grade 2 (Hgb < 10.0 g/dL - 8.0 g/dL)	Maintain dose level of BYL719.

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
Grade 3 (Hgb < 8.0 g/dL); transfusion indicated	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1 or baseline - If resolved in ≤ 14 days, then maintain dose level of BYL719. - If resolved in > 14 days, then ↓ 1 dose level [a] of BYL719.
Grade 4 (Life threatening consequences; urgent intervention indicated)	Discontinue study treatment.
ANC decreased (Neutropenia)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	Maintain dose level of BYL719.
Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level of BYL719.
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level of BYL719. - If resolved in > 7 days, then ↓ 1 dose level [a] of BYL719.
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose of BYL719 until resolved to CTCAE ≤ Grade 1, then ↓ 1 dose level [a] of BYL719.
Febrile neutropenia	
Grade 3 (ANC < 1.0 x 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C)	Omit dose of BYL719, then - If resolved by ≤ 7 days, then ↓ 1 dose level [a] of BYL719. - If not resolved within 7 days discontinue patient from study treatment.
Grade 4	Discontinue study treatment.
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75 x 10^9/L)	Maintain dose level of BYL719.
Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level of BYL719.
Grade 3 (PLT < 50 - 25 x 10^9/L)	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level of BYL719. - If resolved in > 7 days, then ↓ 1 dose level [a] of BYL719.
Grade 4 (PLT < 25 x 10^9/L)	Discontinue study treatment.
Bleeding	
Any bleeding (related to BYL719) resulting in platelet transfusion	Omit dose of BYL719 until no further bleeding has been observed. Continuation of study treatment may be considered.
CARDIAC DISORDERS	
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	**First Occurrence**: -Interrupt BYL719 -Perform a repeat ECG within one hour of the first QTcF of > 500 ms or >60ms from baseline - If QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated until the QTcF returns to < 480 ms. -Seek cardiologist input; address electrolytes, calcium and magnesium abnormalities; concomitant medication must be reviewed. Once QTcF prolongation has resolved, BYL719 may be restarted at a one lower dose level **Second Occurrence:** Permanently discontinue BYL719 treatment
Cardiac disorders - others Grade 1 and 2	Maintain dose level of BYL719.

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
Grade ≥ 3	Discontinue study treatment.
VASCULAR DISORDERS	
Hypertension	
Persistent hypertension CTCAE Grade 3 requiring more than one drug or more intensive therapy than previously	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level [a] of BYL719.
Persistent hypertension CTCAE Grade 4 requiring more than one drug or more intensive therapy than previously	Discontinue study treatment.
INVESTIGATIONS – RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level of BYL719.
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1 or baseline, then - If resolved in ≤ 7 days, then maintain dose level of BYL719. - If resolved in > 7 days, then ↓ 1 dose level [a] of BYL719.
Grade ≥ 3 (> 3.0 x ULN)	Discontinue study treatment.
INVESTIGATIONS – HEPATIC	
Blood Bilirubin [b] (for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level of BYL719.
Grade 2 (>1.5 – 3.0 x ULN)	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level of BYL719. - If resolved in > 7 days, then ↓ 1 dose level [a] of BYL719.
Grade ≥ 3 (> 3.0 x ULN)	Discontinue study treatment. **Note:** If CTCAE Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level [a] of BYL719 and continue treatment at the discretion of the Investigator.
AST or ALT	
Grade 1 (> ULN - 3 x ULN)	Maintain dose level of BYL719.
Grade 2 (> 3 - 5.0 x ULN)	Maintain dose level of BYL719.
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 in case of liver metastasis), then - If resolved in ≤ 7 days, then maintain dose level of BYL719. - If resolved in > 7 days, then ↓ 1 dose level [a] of BYL719. **Note:** If BYL719 is held for hepatic toxicity, then letrozole or exemestane should be also held until hepatic toxicity resolves to CTCAE ≤ Grade 1 (or CTCAE Grade ≤ 2 in case of liver metastasis).
Grade 4 (> 20.0 x ULN)	Discontinue study treatment.
METABOLISM AND NUTRITION DISORDERS	
Fasting Plasma Glucose	Please refer to the guidelines for study drug-induced hyperglycemia provided in Section 10.10.3

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
Amylase and/or lipase elevation	
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level of BYL719.
Grade 3 (> 2.0 - 5.0 x ULN)	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 2, then - If resolved in ≤ 7 days, maintain dose level of BYL719. - If resolved in > 7 days, then ↓ 1 dose level [a] of BYL719.
Grade 4 (> 5.0 x ULN)	Discontinue study treatment. **Note:** A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any CTCAE ≥ Grade 3 of amylase and/or lipase. If asymptomatic CTCAE Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.
NERVOUS SYSTEM DISORDERS	
Neurotoxicity	
Grade 1	Maintain dose level of BYL719.
Grade 2	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, then resume treatment at the same dose level.
Grade ≥ 3 or second occurrence of Grade 2	Discontinue study treatment.
GI DISORDERS	
Pancreatitis	
Grade ≥ 3	Discontinue study treatment.
Diarrhea	
Grade 1	Maintain dose level of BYL719, but initiate anti-diarrhea treatment.
Grade 2	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, initiate anti-diarrhea treatment, then maintain dose level of BYL719.
Grade 3	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, initiate anti-diarrhea treatment, then - If resolved in ≤ 48 hours, maintain dose level of BYL719. - If resolved in > 48 hours, then ↓ 1 dose level [a] of BYL719. For 2nd occurrence of diarrhea CTCAE Grade 3 for > 48 hours despite the use of anti-diarrhea treatment, discontinue study treatment.
Grade 4	Discontinue study treatment. **Note:** Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.
Nausea/Vomiting	
Grade 1	Maintain dose level of BYL719, but initiate anti-emetic treatment (see Section 9.6.1).
Grade 2	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment (see Section 9.6.1), then maintain dose level of BYL719.
Grade 3	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment (see Section 9.6.1), then - If resolved in ≤ 48 hours, maintain dose level of BYL719. - If resolved in > 48 hours, then ↓ 1 dose level [a] of BYL719.
Grade 4	Discontinue study treatment.
SKIN and SUBCUTANEOUS DISORDERS	

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
Rash/ photosensitivity	Please refer to the guidelines for study drug-induced hyperglycemia provided in Section 10.10.4

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
GENERAL DISORDERS	
Fatigue	
Grade 1 or 2	Maintain dose level of BYL719.
Grade 3	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, maintain dose level of BYL719. - If resolved in > 7 days, discontinue patient from study treatment.
OTHER ADVERSE EVENTS	
Grade 1 or 2	Maintain dose level of BYL719. For intolerable grade 2 toxicity, may omit dose of BYL719 until resolved.
Grade 3	Omit dose of BYL719 until resolved to CTCAE Grade ≤ 1, then ↓ dose level of BYL719.
Grade 4	Discontinue study treatment. **Note:** These are general guidelines. The investigator may omit dose of BYL719, ↓ dose level of BYL719 or remove any patient from study for any toxicity, if he/she believes that it is in the best interest of the patient.

- All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require more than two dose reductions of BYL719 will be discontinued from study drug treatment.
- If a patient requires a dose delay of > 21 consecutive days of BYL719 then the patient must be discontinued from the study treatment. Patients who discontinue from the study for a study-related adverse event or an abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first, except specifically mentioned.
- For patients on either Arm C, receiving BYL719 on days 1-7 and 15-21 of a 28 day cycle, or arm D, receiving BYL719 on days 1-5, 8-12, 15-19, 22-26, omitted days will be counted from the date of decision to omit therapy. For example, for a patient on Arm C whose BYL719 is omitted at cycle 2 day 20, but whose toxicity resolves at cycle 2 day 27, therapy will be resumed at Cycle 3 day 1. That is, the study treatment calendar will continue unchanged irregardless of treatment omissions. For a patient on Arm D whose BYL719 is omitted beginning cycle 2 day 15, but whose toxicity resolves at cycle 2 day 20, the patient will still not receive treatment on days 20 and 21 as per the unchanged study treatment calendar. Any issues arising in the setting of therapy held for toxicity will be discussed between the Principal Investigator and Novartis.

[a] Dose reduction for BYL719 means treatment at the next lower dose level of BYL719 (e.g., 250mg daily if the prior dose was 300mg daily, and 200mg daily if the prior dose was 250mg daily).
[b] Refers to total bilirubin
[c] Refer to the guidelines for study drug-induced hyperglycemia provided in Section 10.10.3.

10.10.3 Hyperglycemia Management

PI3K is a key component of the insulin signaling pathway. Therefore, hyperglycemia may be a marker of BYL719 activity on its intended target.

In the BYL719 single agent first-in-human study, hyperglycemia occurred in 24/50 patients (48%), in a dose-related fashion. At a dose of 270 mg daily, one patient experienced hyperglycemia CTCAE Grade 1, but no Grade 3/4 hyperglycemia was reported. At the MTD of 400mg daily, 10/16 (62%) of patients experienced hyperglycemia, among them 4 (25%) with Grade 3/4 hyperglycemia. In the majority of patients, hyperglycemia could be managed by administration of oral anti-diabetic drugs such as metformin or glimepiride. Occasionally treatment with insulin was required.

No hyperglycemia or related metabolic abnormalities have been noted in a large phase III studies of letrozole and exemestane.

Patients with controlled, non-insulin-dependent diabetes may be enrolled if fasting glucose <140mg/dL, even if currently requiring the use of anti-hyperglycemic agents (other than insulin). We are including these patients with well-controlled diabetes because we anticipate that they will be familiar with glucose management, and thus able to manage hyperglycemia associated with BYL719 potentially better than those patients without a prior diagnosis of diabetes.

Fasting glucose levels will be obtained at selected study visits during each cycle as shown in Table 10-1. For the purposes of dose delay decisions, glucose measurements should be in a fasted state, defined as a level obtained at least 8 hours after the most recent caloric intake.

Any patient experiencing hyperglycemia will be managed per the guidelines in the table below, and per standard medical practice for sequelae of hyperglycemia such as dehydration and acidosis.

Grade 4 hyperglycemia must be reported to the MSKCC IRB and Novartis. See Section 17.2 for reporting requirements.

Table 10.3 Hyperglycemia Management

- The below are guidelines that may be modified at the discretion of the Principal Investigator.
- Management of steroid-induced hyperglycemia and resultant decisions regarding dose-reduction are also at the discretion of the Principal Investigator.
- For any hyperglycemia ≥ grade 1, if, upon recheck of the fasting plasma glucose, hyperglycemia is not present or is of a lower grade than the initial value, the patient should be managed as per guidelines for the more severe toxicity. For example, if a patient has a fasting glucose in the grade 2 range, and on recheck is grade 1, the patient should be managed as if she has a grade 2 toxicity. However, if the initial value would result in a DLT, and the repeat value is in a lower-grade range, determination of DLT is at the discretion of the Principal Investigator.
- Should a patient experience toxicity during the resolution of a prior, higher-grade toxicity, the patient should continue to be managed as per the guidelines for the higher-grade toxicity. For example, if the patient experiences grade 3 hyperglycemia on day 1, and this improves to a value within grade 2 hyperglycemia on day 5, the patient should continue being management as for grade 3 hyperglycemia rather than switch to management for grade 2 hyperglycemia.

Severity	**Dose adjustment and management recommendations**
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] confirmed within 48 hours	Continue BYL719 dosing and maintain the current dose level As per investigator's discretion, initiate or intensify medication with appropriate anti-diabetic treatment such as oral anti-hyperglycemic therapy (e.g. metformin) Check fasting glucose as clinically indicated and at least weekly for 8 weeks
Asymptomatic grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	Maintain dose level and re-check within 24 hours: if grade worsens or improves, follow specific recommendations; if grading is confirmed: Continue BYL719 dosing. Initiate or intensify medication with appropriate anti-diabetic treatment such as oral anti-hyperglycemic therapy (e.g. metformin) as per investigator's discretion; consider adding a second oral agent if no improvement after several days Monitor fasting glucose as clinically indicated and at least weekly until fasting glucose resolves to ≤ Grade 1 If fasting glucose does not resolve to ≤ Grade 1 within 14 days after institution of appropriate anti-diabetic treatment, reduce BYL719 by 1 dose level Continue with anti-diabetic treatment and check fasting glucose at least weekly for 8 weeks, then continue checking at least every 2 weeks
Asymptomatic grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L] Or Grade 2 with signs or symptoms of hyperglycemia (e.g., mental status changes, excessive thirst, polyuria)	Omit BYL719 and re-check within 24 hours: if grade worsens or improves, follow specific recommendations. If grading is confirmed: Omit BYL719 dosing. Consider administering intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate Initiate or intensify medication with appropriate anti-diabetic treatment (consider adding insulin) as per investigator's discretion. Monitor fasting glucose as clinically indicated and at least twice weekly until fasting glucose resolves to ≤ Grade 1 If fasting glucose resolves to Grade1 within 14 days, then re-start BYL719 and reduce 1 dose level If fasting glucose doesn't resolve to Grade1 within 14 days, then discontinue patient from BYL719 Continue with anti-diabetic treatment and check fasting glucose at least weekly for 8 weeks, then continue checking at least every 2 weeks

Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L] Or Grade 3 with signs or symptoms of hyperglycemia (for ex., mental status changes, excessive thirst, polyuria)	Omit BYL719, initiate or intensify medication with appropriate anti-diabetic treatment (consider adding insulin), re-check within 24 hours. If grade improves then follow specific grade recommendations. If fasting glucoses confirmed at Grade 4: Discontinue patient from BYL719
A diabetologist consultation should always be considered. Based on current experience, hyperglycemia usually resolves within a few days after BYL719 omission; temporary omission of BYL719 may be considered as clinically indicated to improve control of hyperglycemia. Special attention should be paid to the risk of hypoglycemia in patients interrupting BYL719 treatment and receiving insulin or sulfonylurea. For all grades : instruct patient to follow dietary guidelines according to local and/or institutional st andards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study	

10.10.4 Rash Management Guidelines

- BYL719 can be associated with maculopapular rash, as discussed in Section 3.7 above. The below are recommendations that have been developed to guide meticulous management of this toxicity and may be modified at the discretion of the Principal Investigator. Discussion or formal consultation with dermatology is recommended with rash of any grade.

Grade (CTCAE v4.0)	**Dose adjustment and management recommendations**
Grade 1	• Maintain BYL719 dosing. • Augment antihistamine dosing or consider alternate/additional agent(s) (e.g. hydroxyzine 25 mg bid, non-sedating regimen) for at least 28 days • Consider topical corticosteroid preparation bid for affected areas for at least 28 days.
Grade 2	• Maintain BYL719 dosing. • Consider augmenting antihistamine dosing or consider alternate/additional agent(s) (e.g. non-sedating regimen during the daytime and sedating at QHS such as hydroxyzine 25 mg AM and noon followed by diphenhydramine 25-50 mg QHS) for at least 28 days. • Consider topical corticosteroid preparation bid for affected areas for at least 28 days. • Oral corticosteroid (recommend prednisone 10mg PO TID for 10 days). If rash resolves to Grade 0-1 within 10 days, oral corticosteroid may be discontinued, tapered dosing not needed. If oral prednisone administered continuously for >10 days, tapered dosing is indicated. Intravenous steroid administration can be substituted for oral administration. • If rash is not grade ≤1 within 14 days of optimal medical management, consider increasing steroid duration, with taper)

Grade 3/intolerable Grade 2	• Hold BYL719 dosing until rash resolved to Grade 0-1 and consider dermatology consult for skin biopsy and photographs. • Initiate antihistamine dosing. Recommend non-sedating regimen during the daytime and sedating at QHS (e.g. hydroxyzine 25 mg AM and noon followed by diphenhydramine 25-50 mg QHS) for at least 28 days. • Topical corticosteroid preparation bid for affected areas for at least 28 days. • Oral corticosteroid (recommend prednisone 10mg PO TID for 10 days). If rash resolves to Grade 0-1 within 10 days (and does not recur with redosing; see below for guideline on rechallenge), oral corticosteroid may be discontinued, tapered dosing not needed. If oral prednisone administered continuously for >10 days, tapered dosing is indicated. Intravenous steroid administration can be substituted for oral administration. • If rash is not grade ≤1 in 14 days, continue or readminister oral corticosteroid until resolved and BYL719 is restarted. • A dose reduction of one dose level is recommended if this is a second occurrence. Dose reduction is not necessary following the first occurrence of Gr 3 or intolerable Gr 2 rash. • Upon **rechallenge** with BYL719 (once rash Grade ≤1), continue oral corticosteroid for at least 48 hours. If rash and/or pruritus do not recur in 48 hours, discontinue corticosteroid dosing. Antihistamine regimen should be continued.
Grade 4	• Permanently discontinue BYL719 and consider a dermatology consult. • Treatment of rash should follow guidelines for Grade 3/intolerable Grade 2 rash above with the exception of rechallenge and with any additional measures needed. (BYL719 should be permanently discontinued.)

10.10.5 Pneumonitis Management Guidelines

If the pneumonitis is confirmed to be study drug related (BYL719 + Exemestane or Letrozole), BYL719 must be discontinued as well as the combination drug if the relationship is suspected, regardless of the grade.

As per the new guidance, the table can be summarized as hereafter:

Pneumonitis	Required Investigations	Management of Pneumonitis	Study Treatment Modification
Any Grade	• Obtain appropriate imaging (e.g. high resolution CT scan) • Consider broncho-alveolar lavage (BAL) and biopsy if clinically appropriate • Infectious causes of interstitial lung disease should be ruled out	• Follow institutional practice for management of pneumonitis (e.g. treatment with high dose corticosteroids; concurrent antibiotic therapy if infectious causes are suspected). • Consultation with a pulmonologist is highly recommended	• Immediately interrupt both BYL719 and Exemestane or Letrozole for any case of suspected pneumonitis. • For all patients with confirmed pneumonitis • BYL719 should be permanently discontinued • Exemestane or Letrozole should be permanently discontinued if suspected to be etiologically related to the pneumonitis

Additional follow-up for selected toxicities

Management of pneumonitis in patients receiving BYL719

All patients will be routinely asked about and observed for the occurrence of adverse events including new or changed pulmonary symptoms (consistent with lung abnormalities). Patients who are suspected to have developed pneumonitis should suspend study treatment (BYL719 and Exemestane or Letrozole) immediately and undergo appropriate imaging (high resolution CT scan); and broncho-alveolar lavage and biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out. Investigators should follow institutional practice for management of pneumonitis which generally includes treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment. BYL719 and any other drug (if suspected to be etiologically related to the AE of pneumonitis) should be permanently discontinued in all patients with confirmed pneumonitis.

10.11 Pharmacokinetics

Pharmacokinetic (PK) sampling will be more intensive for the letrozole arm. Letrozole is considered to be a sensitive substrate for CYP3A4. BYL719 is likely to decrease letrozole clearance via its potent irreversible inhibition of CYP3A4, with a potential considerable increase in both letrozole systemic drug exposure and its elimination half-life. The increase in the elimination half-life is expected to delay the attainment of steady-state, which may only be reached after several weeks. Although letrozole is not known to have serious toxicities

(potential toxicities include hot flashes, arthralgias, fatigue, and bone density loss over time), pharmacokinetic sampling has been designed to carefully evaluate the potential drug-drug interaction with BYL719.

In contrast, the risk for drug-drug interaction in the exemestane arm is considerably lower. In a clinical pharmacokinetic study, the specific inhibition of CYP 3A4 by ketoconazole showed no significant effects on the pharmacokinetics of exemestane. This data suggest that the fractional clearance of exemestane via CYP3A4 is not significant and therefore the impact of BYL719, a potent CYP3A4 inhibitor, on the oral drug clearance of exemestane can be considered low. Also, in vitro evidence showed that exemestane is metabolized not only through CYP3A4 but that alternative metabolic pathways such as aldoketoreductases exist. Exemestane does not inhibit any of the major CYP isoenzymes, indicating a low risk to affect BYL719 clearance. In addition, the available preclinical metabolism data of BYL79 indicate that CYP450 enzymes are unlikely to play a major role in BYL719 metabolism.

PK blood samples will be collected from all patients in the study. The sampling regimen assumes that both BYL719 and letrozole will be swallowed concomitantly, or less than 5 minutes apart; and both drugs will be taken at the same time every day.

The exact clock time of dosing as well as actual sample collection date and time and any sampling problems must be noted on appropriate source documentation. When patients come for the pre-dose PK (except for Cycle 1, Day 1) it should be noted when BYL719 and letrozole were taken the day before.

At the specified time points, 2.0 mL of blood will be collected in tubes containing EDTA. Plasma sample will be collected for BYL719 concentration measurement. Refer to the Laboratory Manual for detailed instructions for the collection, handling, and shipping of PK samples. Plasma concentrations of BYL719 will be measured by a laboratory designated by Novartis using a validated high-performance liquid chromatography (HPLC) method with tandem mass spectrometry (LC/MS/MS). Samples will be shipped for analysis to Novartis, Basel.

1. Please see laboratory manual for details regarding collection, shipping, and processing of PK samples.
2. Samples are to be stored at a minimum –70° Celsius until ready for shipment/analysis.

Pharmacokinetic (PK) sampling will be performed according to the table below for all study Arms. Also, if a patient experiences an adverse event that is related to BYL719, it is recommended to collect a blood sample for BYL719 PK.

Table 10-4 Pharmacokinetic sampling

	Arms A and C (Letrozole + BYL719)	Arm A Sample Number	Arms B and D (Exemestane + BYL719)	Arm B Sample Number
Cycle 1 Day 1	Predose	US101A	Predose	US130B

	30 min ± 6 min post dose 1 hr ± 15 min post dose 2 hr ± 15 min post dose 3 hr ± 15 min post dose 4 hr ± 15 min post dose 8 hr ± 1 hr post dose	US102A US103A US104A US105A US106A US107A	1 hr ± 15 min post dose 6 hr ± 30 min post dose	US131B US132B
Cycle 1 Day 15	Predose	US108A	Predose	US133B
Cycle 2 Day 1	Predose 30 min ± 6 min post dose 1 hr ± 15 min post dose 2 hr ± 15 min post dose 3 hr ± 15 min post dose 4 hr ± 15 min post dose 8 hr ± 1 hr post dose	US109A US110A US111A US112A US113A US114A US115A	Predose 1 hr ± 15 min post dose	US134B US135B
Cycle 2 Day 15	Predose	US116A	Predose 1 hr ± 15 min post dose	US136B US137B
Cycle 3 Day 1	Predose	US117A	Predose 1 hr ± 15 min post dose	US138B US139B
Cycle 4 Day 1	Predose	US118A	Predose	US140B
Cycle 5 Day 1	Predose	US119A	No PK	
Cycle 6 Day 1	Predose	US120A	No PK	
Cycle 8 Day 1	Predose	US121A	No PK	
Cycle 10 Day 1	Predose	US122A	No PK	
	Unscheduled	US1000A+	Unscheduled	US1000B+

10.12 Biopsy Specimen Processing and Analysis and Cell-free DNA (cfDNA) Studies

Pre-treatment, Day 15 on-treatment, and optional at-progression biopsies will be obtained to further define the biology of AI-resistance in metastatic ER+ breast cancer, and to evaluate predictive and pharmacodynamic biomarkers of treatment with BYL719. Pre-treatment and Day 15 on-treatment biopsies will be required, unless felt to put the patient at unacceptable risk (note: patients with bone-only metastases will have a pre-treatment biopsy only). Patients will also be asked for their permission to store tissue for future use. All patients may be asked to undergo an optional tumor biopsy at progression, with the exact timing to be at the discretion of the investigator and patient (not necessarily within 28 days of last dose of BYL719), although a 2 week window is allowed

For retrospective feasibility and observational studies, tissue use at MSKCC is governed by the Human Biospecimen Utilization Committee (HBUC). The HBUC has trans-departmental and multidisciplinary representation. The HBUC reviews tissue-related applications for Exemptions for Existing Data (formerly Waiver of Authorization).The applicant will be asked to include information on the availability of the specific material that is being requested in the bank and its heritage, including information on the curation, the consent linked to the specimen (if any), and rarity of the resource including frequency of available and quantity of material.

Certain archived specimens have been obtained for specific purposes – for example, to determine protocol eligibility based on expression of a biologic determinant, or for pharmacodynamic assessments in association with a clinical trial. In the frozen specimen archive these purposes have been appropriately flagged in the specimen annotations, so that review committees and bank curators do not mistakenly authorize the use of such specimens for other than the purposes for which they were acquired.

Specimens will not be released if there is a concern with respect to amount of tumor available (i.e. a small tumor embedded in a single block); or if the request would deplete the MSKCC archive, unless MSKCC is specifically requested to do so by the patient. The HBUC will give special consideration to tissues requested for correlative analysis as part of a clinical trial, or to develop a tissue bank at an academic institution, cooperative group or corporate entity. In cases where specimens reside in local repositories curated by PI's of specific procurement protocols, the PI's are under the same obligation to seek HBUC (and other necessary) approval for use of the resource in their own studies as other investigators in the Center. This is so, because specimen resources are ultimately institutional resources, wherever they are stored and by whatever means they are ascertained. Approval of such studies by the HBUC will be by the same criteria as noted above. Special care should attend review of requests where approval would exhaust the resource.

In cases where specimens are needed fresh and will be used prospectively, the individual investigator needs to write an IRB biospecimen protocol. This protocol is fast-tracked through departmental and Research Council review and is reviewed at IRB by the expedited review process. This protocol is only for research that will be done on biospecimens obtained under specifically identified banking protocols and their informed consent and research authorization. The consent and research authorization for the use of the biospecimens will be waived as per 45 CFR 46.116(d) and 45 CFR 164.512(i)(2)(ii).

Pre-treatment biopsy will be performed within 4 weeks prior to starting treatment. A metastatic site is preferred to a primary breast tumor site, when safely accessible. When multiple sites of metastatic disease are safely accessible, a biopsy of a bone metastasis is **not** preferred, because processing may interfere with the proteomic analysis. In patients with bone-only metastases, a pre-treatment biopsy of a bone metastasis will still be informative for targeted sequencing analysis and immunohistochemistry for PTEN loss (however, patients with bone-only metastases will not undergo a Day 15 on-treatment biopsy, because processing may interfere with the proteomic analysis). After obtaining separate informed consent, a core biopsy will be obtained by surgery or interventional radiology and processed for both targeted gene sequencing and proteomic analyses. The

core will be divided into a frozen sample and paraffin blocks. For gene sequencing, we will also obtain a blood sample for a normal tissue comparison.

The following information must be provided in the IR referral at the time of a biopsy request:

1. Protocol number
2. Target of biopsy: Is there a specific target to be biopsied, or is decision left to the IR attending to choose? (highly recommended if possible)
3. Specimen required: FNA, core biopsy, or IR attending decides (example: "at least five 18-20 gauge cores")
4. Specimen handling information
5. Time frame : First available date, within a time period, or a fixed date
6. Is this a single biopsy or will a second "post treatment" biopsy be needed. If a second biopsy is needed, then IR needs to know the date range of the second biopsy for scheduling.
7. Name and pager number of the specimen contact person

An appropriate example of a request is; "Protocol xx-xxx, Right adrenal mass, 4 cores in formalin to go to surgical pathology, 1 core to be flash frozen by RSA Joe XX b1234, pretreatment biopsy requested for first week of August. Post treatment biopsy to be done one week after the first biopsy"

At-progression biopsy may be performed on patients, with tissue preferably obtained from the same site as prior pre-treatment and/or on-treatment biopsy. At progression biopsy will be sent for genomic sequencing and/or proteomic evaluation, with utilization of tissue to be at the discretion of the investigators.

In collaboration with Dr. Michael Berger (Department of Pathology), as we plan to perform massively parallel sequencing[12] of all exons corresponding to 230 cancer genes, including all currently druggable or "actionable" somatic mutations as well as additional oncogenes and tumor suppressor genes shown to have strong associations with cancer genesis and progression. The technique used to sequence exons of genes of interest[13] and the technical implementation of an oncogene screening profile[14] have been described previously. A small amount of tumor tissue is required for this sequencing platform (25ug of gross tissue, minimum 500ng DNA). Exonic DNA will be captured via solution-based hybrid selection[12] and sequenced on the Illumina HiSeq platform. The sequencing data will be analyzed for base mutations, insertions, deletions, copy number alterations and genomic rearrangements in all target genes, with germ-line DNA (whole blood) serving as a reference. Corroborating studies in cell lines will be performed in the lab of Dr. Sarat Chandarlapaty (HOPP) in order to evaluate the biological plausibility of potential hits.

This approach has recently been used with success to identify genomic alterations underlying both drug sensitivity and resistance. In breast cancer, we have piloted this approach on a panel of 22 prospectively collected HER2 amplified metastatic tumors (MSKCC IRB # 06-163, Chandarlapaty - PI) and have identified several mutations which may confer resistance to HER2-targeted therapy. Also using this platform, a TSC2 mutation was identified in a patient at MSKCC with advanced bladder cancer who had an uniquely favorable response to treatment with rapamycin on a clinical trial (personal communication, David Solit). In a patient with *BRAF*-mutated melanoma who developed acquired resistance

to vemurafenib, a *MEK1* mutation was identified in the post-treatment sample that proved to confer resistance to RAF inhibition with further corroborating studies.[14] These results highlight the ability of a targeted, next generation sequencing approach to identify mechanisms of drug sensitivity and resistance.

In order to determine if pharmacodynamic markers of PI3K pathway hyperactivation and inhibition (e.g. P-AKT, P-S6, P-4EBP) predict for PFS, we will also perform proteomic analysis of pre-treatment and on-treatment biopsies. When possible, Day 15 on-treatment biopsies should be performed from the same tumor site as the pre-treatment biopsies. The levels of pathway protein expression and their activation will be determined by Collaborative Enzyme Enhanced Reactive-immunoassay (CEER, Promethius Biosciences). CEER can be performed in a multiplexed fashion directly on clinical samples that may be available in limited amounts. This phosphoproteomic assay utilizes the formation of unique immuno-complexes between capture antibodies (Abs) printed on a nitrocellulose microarray surface, the target molecule (in cell lysate reacted with the slide), and two independent detector-Abs. One of the detector-Abs is conjugated to glucose oxidase (GO), and the other is conjugated to Horse Radish Peroxidase (HRP). Target detection requires the presence of both detector-Abs and the enzyme channeling event between GO and HRP will not occur unless both Abs are in close proximity. Using this assay, receptor tyrosine kinases and downstream pathway proteins can be detected at the single cell level (sensitivity of about 100 zeptomoles). Intrapatient percent change in quantitative PI3K pathway activation signature will be scored and compared to percent tumor volume change at 8 week CT scan. The Spearman's rank correlation of intrapatient percent change in PI3K pathway activation signature (measured as a continuous variable) with percent tumor volume change at 8 week CT scan (measured as a continuous variable) will be calculated to evaluate whether pharmacodynamic markers of PI3K pathway inhibition are predictive of response to therapy.We will also perform immunohistochemistry on a paraffin block to evaluate for PTEN loss. This may be performed on archival primary tumor block or archival metastatic tumor if not enough tumor is available from the pre-treatment metastatic biopsy. PTEN will be scored as 0 (PTEN loss), 1 or 2, as previously described for breast cancer tissue by Dr. Tari King at MSKCC[14]. Specifically, the cytoplasmic and/or nuclear immunoreaction will be scored based on intensity whereby a score of 2 = positive (equal in intensity to normal epithelial cells), a score of 1 = weak (reduced intensity as compared with normal epithelial cells), and a score of 0 = negative (no immunoreaction).[15]

Sequencing data will be analyzed for base mutations, insertions, deletions, and copy number alterations. Corroborating studies in cell lines will be performed in the lab in order to evaluate the biological plausibility of potential hits. Results of correlative studies will be primarily descriptive and provide the preliminary evidence necessary to recommend specific biomarkers for future clinical study or new drug development.

Tumor specimen macrodissection will be performed in the MSK clinical pathology department. Immunohistochemistry for PTEN will be performed in the lab of Dr. Tari King (Department of Surgery, Breast Service). DNA isolation and targeted sequencing analysis will be performed in the lab of Dr. Michael Berger (Department of Pathology). Proteomic analyses and corroborating studies in cell lines will be performed in the lab of Dr. Sarat Chandarlapaty (Department of Medicine, HOPP).

The detection of tumor derived fragments of DNA in a blood sample provides the opportunity for relatively non-invasive serial assessment of the genetic alterations harbored in the tumor. Optimally the analysis of cfDNA will be used to determine tumor mutation status for patients in whom a biopsy is not feasible and serial assessment for new genetic alterations that occur during tumor progression and therapeutic resistance (Forshew, Murtaza et al. 2012; Misale, Yaeger et al. 2012; Murtaza, Dawson et al. 2013). Small studies have begun to examine the clinical utility of cfDNA; quantitatively as a prognostic biomarker and specifically as a surrogate for tumor burden and response to treatment by quantifying known somatic mutations identified in the tumor (Spindler, Pallisgaard et al. 2012; Dawson, Tsui et al. 2013). Incorporation of formal testing for its predictive utility in prospective studies examining pathway inhibition with targeted therapy is currently under investigation.

cfDNA will be extracted and quantified by qPCR under the direction of Dr. Mary Ellen Moynahan (Department of Medicine, Jasin Lab) at intervals designated in Table 10-1. Known *PIK3CA* mutations will be serially quantified by dPCR in the Genomic Core Facility. Additional mutations identified by targeted exome sequencing will undergo dPCR assay design and validation.

11.0 TOXICITIES/SIDE EFFECTS

Potential BYL719 toxicities are listed below. Definitions of dose limiting toxicities (DLTs) are provided in Section 9.3. Toxicity management guidelines are provided in Section 10.10. Definitions of serious adverse events, and reporting requirements are provided in Section 17.2.

Percentages below refer to adverse events reported to date in the ongoing phase I single-agent study (n=50). For details on preclinical and clinical experience, please refer to Section 3.5.1 and Section 3.5.2 of this protocol and the current BYL719 Investigator's Brochure (IB).

Cardiovascular: hypertension (2%)

Endocrine: hyperglycemia (46%)

Gastrointestinal: nausea (34%), decreased appetite (34%), diarrhea (32%), vomiting (24%), dyspepsia (14%), dysgeusia (12%)

Hepatic: ALT increase (4%), AST increase (4%), alkaline phosphatase increase (2%)

Skin: skin toxicity including rash (28%)

Miscellaneous: fatigue (24%), weight decrease (14%), asthenia (10%)

There is also noted to be a rare but serious risk of hypersensitivity. One patient with colon cancer on the ongoing single-agent phase I study experienced hypersensitivity which was considered possibly drug related. The patient was hospitalized 12 days after start of treatment with 400 mg BYL719 daily, with generalized rash, pyrexia and prickly sensation. The study medication was temporarily interrupted and the patient received treatment with hydrocortisone and piriton. When treatment was restarted 2 days later, the allergic reaction (which included reddening of skin, pyrexia, and prickling sensation) reoccurred on the same

day and resolved again following treatment with hydrocortisone and piriton. This event was considered serious and unexpected, and an investigator notification was issued.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary objective of this study is to determine the recommended phase II dose of BYL719 when administered in combination with either letrozole or exemestane. As of January 2014, this trial is being amended such that an additional primary objective is to determine the recommended phase II dose of BYL719 administered in a 7 day on, 7 day off schedule, in combination with letrozole, and the recommended phase II dose of BYL719 administered on a 5 day on, 2 day off schedule, in combination with exemestane. All patients who receive at least one dose of BYL719 will be evaluable for toxicity assessment. See Section 9.3 for the definitions of dose limiting toxicities and Section 9.4 for the dose-finding schema.

In order to estimate the efficacy of BYL719 plus letrozole or exemestane (a secondary endpoint), we will calculate the following for each arm separately in the expansion cohort only:

a. Progression-free survival (PFS) will be examined using Kaplan-Meier methods.
b. Overall response rate (ORR = complete response (CR) plus partial response (PR)) will be calculated with an exact confidence interval.
c. Clinical benefit rate at 16 weeks (CBR = CR + PR + stable disease) will be calculated with an exact confidence interval.
d. Time to treatment failure (TTF) will be examined using Kaplan-Meier methods.

The RECIST criteria version 1.1 will be used to evaluate therapeutic response. All patients who receive at least one week of BYL719 in combination with letrozole or exemestane will be evaluable for response. Patients with measurable or non-measurable lesions are included in this study. Measurable lesions are defined as those that can be measured accurately in at least one diameter, that is ≥ 20mm using conventional imaging techniques (including incremental CT) or ≥ 10mm using spiral CT equipment. Non-measurable lesions include bony metastases, leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast cancer, lymphangitic carcinomatosis, and heavily calcified and cystic/necrotic lesions.

Patients will have an evidence of disease (EOD) evaluation at baseline, consisting of CT of chest/abdomen +/- pelvis (with oral and IV contrast unless contraindicated) and a bone scan. Patients will then have EOD evaluation with CT of chest/abdomen +/- pelvis every two cycles (8 weeks) for the first four cycles (16 weeks) of study treatment (Day 1 +/- 7 days of Cycle 3 and Cycle 5), and then every 3rd cycle (12 weeks) thereafter (Day 1 +/- 7 days of Cycle 8, Cycle 11, etc). EOD evaluation will occur every 4th cycle (16 weeks) +/- 4 weeks from the last evaluation for patients who are on study under Amendment 13. A bone scan will also be performed if the baseline bone scan showed evidence of osseous metastatic disease (otherwise, a bone scan is not required, but may be obtained at the investigator's discretion if clinically indicated). For patients with locally-advanced unresectable breast cancer, radiographic assessments using MRI scans are acceptable to evaluate response, and a CT scan of chest/abdomen is not required.

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

13.1 CRITERIA FOR REMOVAL FROM STUDY

Criteria for removal from the study are:

- Progressive disease
- Unacceptable toxicity
- Three or more consecutive weeks of a delay in treatment due to toxicities
- Intercurrent, non-cancer related illness that prevents continuation of protocol therapy or follow-up
- Major protocol violation that would render the patient inevaluable for safety/toxicity
- Repeated non-compliance by the patient with protocol requirements
- Changes in the patient's condition or study drug related toxicity such that, in the opinion of the investigator, continued participation in the protocol would compromise the patient's well-being
- Withdrawal of the patient's consent for any reason
- Termination of the clinical trial by the investigator or Novartis, the drug manufacturer

14.1 BIOSTATISTICS

This is a single institution phase I study of BYL719 in combination with letrozole or exemestane, with a dose-finding phase and an expansion phase. The primary objective is to determine the recommended phase II dose of BYL719 when administered in combination with either letrozole or exemestane to patients with HR+ locally-advanced or metastatic breast cancer. As of January 2014, this trial is being amended such that an additional primary objective is to determine the recommended phase II dose of BYL719 administered in a 7 day on, 7 day off schedule, in combination with letrozole, and the recommended phase II dose of BYL719 administered on a 5 day on, 2 day off schedule, in combination with exemestane.

This clinical trial was initially comprised of two arms, one for BYL719 in combination with letrozole (Arm A) and another for BYL719 in combination with exemestane (Arm B). As of January 2014, Arms A and B will no longer accrue patients and the study will be amended to include Arms C and D. Arm C will involve letrozole with BYL719 given on days 1-7 and 15-21 of a 28 day cycle. Arm D will involve exemestane with BYL719 given on days 1-5, 8-12, 15-19, 22-26 of a 28 day cycle. Anastrozole will not be evaluated in this study because anastrozole is a non-steroidal AI similar to letrozole. Arms C and D employ distinct aromatase inhibitors for clarity throughout clinical care. However, given the similar toxicity profile seen with both aromatase inhibitors with continuously dosed BYL719 (Arms A and B), results from either arm are felt to be generalizable to either aromatase inhibitor.

The dose-finding phase will require 4 to 24 patients for each arm that will accrue patients (Arm C and Arm D), and the expansion phase will require 10 patients for each arm. We anticipate ~38 patients total across both arms, and we estimate an accrual rate of at least 2 patients per month, with a total time of two years to complete the study.

14.2 Dose-Finding Phase

The purpose of the dose-finding portion of the study is to determine the recommended phase II dose of BYL719 in combination with a fixed dose of either letrozole or exemestane. For Arm A and Arm B, the five proposed doses of BYL719 are 200mg, 250mg, 300mg, 350mg or 400mg. For Arms C and D, the five proposed doses of BYL719 are 150mg, 200mg, 250mg, 300mg, and 350mg.

The plans for dose escalation or de-escalation consist of entering patients in cohorts of three. The specific details are given in Section 9.4. Dose-limiting toxicities are defined in Section 9.3. All patients within a cohort will be observed for toxicity for one cycle (28 days) prior to entering patients at the next dose level. If a patient discontinues study participation during the first cycle (within 28 days of starting study treatment) for reasons unrelated to an adverse event or disease progression, an additional patient may be enrolled to replace that subject. We expect this early dropout to be a rare event, occurring 5% of the time, and will be examined closely as a source for potential bias. Otherwise, all patients who receive at least one dose of BYL719 in combination with letrozole or exemestane will be evaluable for toxicity. All patients who receive at least one week of BYL719 in combination with letrozole or exemestane will be evaluable for response.

The probability that dose escalation or de-escalation will occur at any stage during this portion of the study is a function of the underlying DLT rate at the current dose level. This probability can be calculated as the sum of the binomial probabilities of the following two outcomes that would permit escalation to occur:

1. No DLT observed in the first three patients.
2. One DLT is observed in the first three patients followed by no DLT observed in three additional patients at the same dose level.

The true risk of toxicity is expected to be in the range of 10%-40%. The following table shows the corresponding probabilities of dose escalation:

True Risk of Toxicity	.10	.20	.30	.40
Probability of Escalation	.91	.71	.49	.31

These numbers show that the probability of escalating to the next dose level is large when the underlying true toxicity rate is small and the probability of escalating decreases appropriately as the true toxicity rate increases.

Between 2-6 patients will be treated at each dose level. Assuming 4 dose levels, this portion of the trial will require a minimum of 4 and a maximum of 24 patients for each arm. If 2 or more patients in the lowest dose cohort (Cohort -2 for Arms A and B, and Cohort -1 for Arms C and D) for either arm experience DLT, then we will conclude that the combination is not

feasible and will discontinue the affected arm of the trial. If this occurs, accrual onto the unaffected arm will be halted until safety data is reviewed by the primary investigator and Novartis to determine whether to continue or close the unaffected arm of the trial.

We expect both arms (Arm C and Arm D) to accrue simultaneously, as letrozole is typically given first-line for HR+ metastatic breast cancer, while exemestane is more often used in the second-line setting. With an expected accrual rate of at least 2 patients per month, it is expected that the dose-finding portion of the trial will take less than 1 year. This allows each 3-patient cohort to be observed for 28 days, the length of time for treatment with one cycle of therapy, prior to additional patients being accrued.

14.3 Expansion Phase

In the expansion portion of the study, 10 additional patients will be enrolled in each arm, Arm C and Arm D, in order to further define the safety and feasibility of BYL719 in combination with letrozole or exemestane at the established dose from the dose-finding phase, and to estimate the efficacy of this combination.

In order to help ensure that the DLT rate observed among the additional 10 patients in each arm is consistent with the DLT rate observed at the established dose from the dose-finding portion, the following decision rule will be implemented for each of the two study arms. If ≥ 4 DLTs are seen at any time in any one expansion arm, then it is likely that the safe and tolerable dose determined during the first portion of the trial is too toxic. The safety data will then be reviewed with the primary investigator and Novartis to determine how to move forward. Depending on the circumstances, we may consider de-escalating the dose of BYL719 to the next lower dose level and accruing 10 additional patients at that level. The probability of observing at least 4 patients with a DLT in the 10 additional patients is .28 if 1 of 6 patients were seen with a DLT in the dose-finding phase of the study. The probability of observing at least 4 patients with a DLT in the 10 additional patients is .09 if 0 of 6 patients were seen with a DLT in the dose-finding phase of the study.[11] The below table provides additional details on the probability of observing at least 1 to 9 patients with DLTs in the expansion cohort of 10 patients given that 0 or 1 patient in the initial dose-finding cohort of 6 patients had a DLT.[11]

	DLTs in expansion cohort								
DLTs in dose-finding cohort	1 DLT (of 10)	2 DLTs	3 DLTs	4 DLTs	5 DLTs	6 DLTs	7 DLTs	8 DLTs	9 DLTs
0 (of 6)	0.59	0.33	0.18	0.09	0.04	0.02	0.01	<0.01	<0.01
1(of 6)	0.85	0.64	0.44	0.28	0.16	0.08	0.04	0.01	0.01

The two arms of the study will be monitored in tandem, and we have added an overall sequential global stopping rule to be applied as both expansion cohorts are accruing. We include this early stopping rule across both arms because the mechanism and toxicities of both AIs are known to be very similar. Our global stopping rule is based on repeated significance testing and serves as a global safety measure. We assume a grade 4 toxicity rate of 10% as acceptable and 35% as unacceptable. With these assumptions, if 2 of the

first 5 patients, 3 of the first 10 patients, 4 of the first fifteen or 5 of 20 patients accrued experience a grade 4 toxicity, we will discontinue the entire study. With this rule, the probability of discontinuing the study if the true toxicity rate is 35% is .92. If the true toxicity rate is 10%, this probability is .10.

14.4 Secondary Objectives

There are several planned secondary analyses. Selected non-hematologic and hematologic toxicities will be described, as measured by the NCI Common Toxicity Criteria, version 4.0, with the maximum grade over all cycles used as the summary measure per patient.

In order to estimate the efficacy of BYL719 plus letrozole or exemestane, we will calculate the following for each arm, Arm C and Arm D separately in the expansion cohort only:

a. Progression-free survival (PFS) will be examined using Kaplan-Meier methods.
b. Overall response rate (ORR = complete response (CR) plus partial response (PR)) will be calculated with an exact confidence interval.
c. Clinical benefit rate (CBR = CR + PR + stable disease at 16 weeks) will be calculated with an exact confidence interval.
d. Time to treatment failure (TTF) will be examined using Kaplan-Meier methods.

Pharmacokinetic parameters such as AUC and Cmax of daily BYL719 will be calculated.

14.5 Exploratory Objectives

Correlative studies examining patient and clinical factors correlated with BYL719 sensitivity will be done using next generation sequencing and fine copy number analysis of pre-treatment biopsies, as well as proteomic analysis of pre-treatment and on-treatment biopsies. cfDNA analysis in plasma obtained at baseline, Cycle 1 day 1, Cycle 1 day 8, Cycle 1 day 15 and at each subsequent treatment cycle will be performed to assess for a correlation between mutant allele quantification and response to BYL719.We feel that combining the letrozole and exemestane arms for these exploratory analyses is reasonable given their similar mechanisms of action at the level of the breast cancer cell. The correlative studies will be primarily descriptive and provide the preliminary evidence necessary to recommend BYL719 and specific biomarkers for future clinical study.

cfDNA extraction from 2-6 ml plasma obtained at the time of routine blood draws has been feasible in patients with metastatic breast cancer according to ongoing study, MSKCC IRB #13-050, Moynahan – PI. DNA quantity and integrity is assessed by qPCR and uniformly has yielded amplifiable fragments suitable for dPCR and small amplicon library construction. We anticipate that this approach will be informative for patients with tumors harboring a *PIK3CA* mutation and exploratory for patients whose tumors harbor potential driver mutations for which additional dPCR assays will be designed (Dawson, Tsui et al. 2013).

The protocol consent form asks participants for permission to discuss their research findings if their samples are used in an HBUC or Biospecimen project and an incidental finding is made that may be critical to their preventative care. If a participant agrees to be contacted, the participant will not be told the specific results of the research test, but will be informed that their samples were used in a project and a potential risk was uncovered. If the participant is interested in further discussion of the research findings, the participant will be

asked to come into MSKCC Clinical Genetics Service for counseling and specific genetic testing.

Based on our ongoing experience with our tumor biopsy study to evaluate molecular mechanisms of resistance in patients with HER2+ disease (MSKCC IRB # 06-163, Chandarlapaty - PI), we anticipate that it will be feasible to obtain a pre-treatment biopsy in at least 80% of patients (~30 patients assuming total accrual of 38 patients). Due to logistical issues, such as lack of sufficient viable cells in the biopsy sample, it is possible that a viable pre-treatment biopsy sample may not be obtained in several patients.

In order to determine if pharmacodynamic markers of PI3K pathway hyperactivation and inhibition predict for PFS, proteomic analysis of pre-treatment and Day 15 on-treatment biopsies will be performed. The Spearman's rank correlation of intrapatient percent change in PI3K pathway activation signature (measured as a continuous variable) with percent tumor volume change at 8 week CT scan (measured as a continuous variable) will be calculated to evaluate whether pharmacodynamic markers of PI3K pathway inhibition are predictive of response to therapy.

We anticipate that it will be feasible to obtain a Day 15 on-treatment biopsy in at least 50% of patients (~19 patients assuming total accrual of 38 patients).

To evaluate mechanisms of AI resistance, the analysis will include pre-treatment tumor biopsies obtained in patients who had POD on an AI at the time of study consent, on-treatment biopsies, as well as optional post-progression biopsies. We estimate that this will include about half of patients in the dose-finding phase (because those with stable disease will be excluded), and all patients in the expansion phase who have a viable pre-treatment biopsy sample.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

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

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

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

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

15.3 Randomization

Randomization will not be necessary for this study. Patients will be eligible for only one of the two arms depending on which AI (letrozole or exemestane) they were taking before study enrollment. Patients will not be randomized to one of the two arms.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the study team.

The Clinical Research Database (CRDB) will be used for data collection. The data will be reported to the institution (IRB) and the drug manufacturer (Novartis) as appropriate.

Tumor slides will be stored in the breast surgery laboratory. Results from laboratory studies will include photomicrographs of IHC studies, computer files of sequencing data, and computer files from microarray analyses. These files will be stores on the Department of Medicine server. Documentation linking patient identifiers and patient samples and results will be securely maintained in the CRDB with access limited to study investigators.

It is estimated that 2 patients will be accrued per month and it will take up to two years to accrue.

16.2 Quality Assurance

Routine 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. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

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

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://www.cancer.gov/clinicaltrials/learningabout/patientsafety/dsm-guidelines/page1. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://smskpsps9/dept/ocr/OCR%20W ebsite%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.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. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and *the Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative treatment options, including non-protocol treatment options, will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits approximately every 4 weeks and approximately every 8 weeks at minimum for patients on study under Amendment 13 of the protocol. Every effort will be made to keep study records private. Neither the patient's name nor anything else that could identify the patient will be used in any reports or publications that result from this study. Trained staff at Memorial Sloan-Kettering Cancer Center, the Food and Drug Administration, or the drug manufacturer, Novartis, will be able to review the medical records if necessary. The financial costs of the study will be discussed with the patient; BYL719 will be provided free of charge. The cost of the pharmacokinetic studies and correlative research on tumor biopsies will be covered by RNB.

17.2 Privacy

Medical information is confidential. The participant's personal identity will not be used in reports that are written about the research. The MSKCC IRB/PB will review all requests for research performed involving biospecimens ascertained through this protocol. Blood and tissue samples will be stored with a code linked to the patient's medical record. With the permission of the IRB/PB, research studies on cellular, genetic, immunologic, or other features of tumor or normal samples may be performed with no names attached to the samples but linked by codes to personal identifiers. The results of any research using blood or tissues will not be placed in the medical record.

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

The consent also indicates that samples and genetic information collected may be shared with other qualified researchers. Such information will not include identifying information such as name. It is also stated in the consent and Research Authorization that research data (e.g. genomic sequence) may be placed into databases monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government.

The requirements for submission of genotype/phenotype data into the NIH GWAS Repository (or any other public database) will be outlined in the biospecimen analysis application, i.e. IRB Biospecimen Correlative Protocol.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (BYL719), even if the event is not considered to be related to study drug. Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded and followed as appropriate. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

A serious adverse event (SAE) is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening,
2. required or prolonged hospitalization,
3. results in persistent or significant disability/incapacity,
4. constitutes a congenital anomaly or a birth defect, or
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition,
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen,
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 30 daysafter the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

Hyperglycemia is an adverse event of interest. Grade 3 or 4 hyperglycemia must be reported to the IRB and Novartis.

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days.

The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

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

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

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

The principal investigator has the obligation to report all serious adverse events to the IRB, FDA (all correspondence with the FDA must go through the MSKCC IND Office), and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

SAEs will be reported to Novartis concurrent to MSKCC CRDB SAE Report Form using the MSKCC CRDB SAE Report Form.

The investigator must complete the SAE Report Form and Novartis SAE fax coversheet in English, assess the relationship to study treatment and send the initial completed SAE Report Form and Novartis SAE coversheet by fax 1.888.299.4565 within 24 hours of learning of its occurrence (excluding weekends and holidays) to the local Novartis DS&E Department. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis DS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious

adverse events. The original and the duplicate copies of the SAE Report Form, Novartis SAE coversheet, and the fax confirmation sheet must be kept at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The SAE Report Form, Novartis SAE coversheet, and fax confirmation sheet must be retained.

18.1 INFORMED CONSENT PROCEDURES

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

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

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

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

Subjects currently enrolled onto Arms A and B will continue on Arms A and B. They will be re-consented with the revised Arm A and B consents which will reflect our updated toxicity profile.

19.0 REFERENCES

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20.0 APPENDICES

Appendix A: Patient BYL719 Drug Diary (Letrozole) (attached separately)

Appendix B: Patient BYL719 Drug Diary (Exemestane) (attached separately)

Appendix C: Patient Information for BYL719 Drug and Food Interactions (attached separately)

Appendix D: List of CYP450 Substrates to Be Used With Caution*

CYP 2C8	CYP 2C9	CYP 2C19	CYP 3A**	
Amodiaquine	Acenocoumarol	Clopidogrel	Alfentanil [1,2]	Ergotamine [2]
Cerivastatin	Celecoxib	Diazepam	Alpha-dihydroergocryptine [1]	Everolimus [1]
Repaglinide	Diclofenac	Esoprazole	Alprazolam	Felodipine [1]
Rosiglitazone	Glipizide	Lansoprazole	Amlodipine	Fentanyl [2]
Torasemide	Irbesartan	Moclobemide	Aplaviroc	Fluticasone [1]
	Losartan	Omeprazole	Aprepitant [1]	Indinavir [1]
	Phenytoin [2]	Pantoprazole	Aripiprazole	Lopinavir [1]
	Piroxicam	Phenobarbitone	Atorvastatin	Lovastatin [1]
	S-ibuprofen	Phenytoin [2]	Boceprevir	Maraviroc [1]
	Sulfamethoxazole	Proguanil	Brecanavir	Midazolam [1]
	Tolbutamide	Rabeprazole	Brotizolam [1]	Nifedipine
	Torasemide	S-mephenytoin	Budesonide [1]	Nisoldipine
			Buspirone [1]	Nitrendipine
			capravirine	Perospirone [1]
			casopitant	Quinine
			Conivaptan [1]	Saquinavir [1]
			Cyclosporine [2]	Sildenafil [1]
			Darifenacin [1]	Simvastatin [1]
			Darunavir [1]	Sirolimus [1,2]
			Diazepam	Telaprevir
			Diergotamine [2]	Tipranavir [1]
			Diltiazem	Tolvaptan
			Ebastine [1]	Triazolam [1]
			Eletriptan [1]	Verapamil
			Eplerenone [1]	

* This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, and from (Zhou et al 2009)

** CYP3A substrates were compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented by the FDA's "Guidance for Industry, Drug Interaction Studies" and the University of Washington's Drug Interaction Database.

1. Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.
2. Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. TdP).

Appendix E: List of BRCP Inhibitors to Be Used With Caution

Diketopiperazines	P-glycoprotein inhibitors
Fumitremorgin C	Elacridar (GF-120918)
Tryprostatin A	Tariquidar (XR-9576)
Indolyl diketopiperazines	Biricodar
Steroid(-like) compounds	Flavonoids
Corticosterone	Chrysin
Digoxin	Biochanin A
Beclometasone	Benzoflavone
6 α-Methylprednisolone	6-Prenylchrysin
Dexamethasone	Tectochrysin
Triamcinolone	Naringenin
Mometasone	Quercetin
Ciclesonide	Acacetin
Antivirals	Kaempferol
Nelfinavir	Silymarin
Lopinavir	Hesperetin
Delavirudine	Daidzein
Efavirenz	Resveratrol
Saquinavir	Genistein
Atazanavir	Naringenin-7-glucoside
Immunosupressants	3´,4´,7-Trimethoxyflavone
Sirolimus	Eupatin
Ciclosprin A	Azoles:
(Dihydro)pyridines	Pantoprazole
Niguldipine	Omeprazole
Nicardipine	Oxfendazole
Nitrendipine	Ketoconazole
Dipyridamole	Itraconazole
Nimodipine	Estrogens, estrogen agonists, estrogen antagonists
Nifedipine	17-ß-estradiol
	Diethylstilbestrol
	Toremifene

List of moderate and strong CYP3A4 and CYP2C8 inducers and inhibitors

Category	Drug Name
Strong CYP3A Inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole
Strong CYP3A Inducers	Avasimibe[1,2], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[2], St. John's wort (hypericum perforatum)[2]
Moderate CYP3A Inhibitors	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera[1], tofisopam, verapamil
Moderate CYP3A Inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Strong and moderate CYP2C8 inhibitors	Gemfibrozil (strong), defasirox (moderate)
Strong and moderate CYP2C8 inducers	rifampin (rifampicin)[2]

1. Herbal product
2. P-gp inducer

All QT-prolonging drugs listed in Table 5 are prohibited for all patients from screening through permanent discontinuation of study treatment. Table 5 lists drugs with a known risk for TdP as well as CYP3A and CYP2C substrates (with a possible or conditional risk for TdP).

Appendix F: List of prohibited QT prolonging drugs

Drug	QT risk*	Comment
Amiodarone	known risk	Females>Males, TdP risk regarded as low
Amitriptyline	conditional risk	Risk of TdP with overdosage. Substrate of CYP2C19
Arsenic trioxide	known risk	
Astemizole	known risk	No Longer available in U.S. Substrate for 3A4
Bepridil	known risk	Females>Males
Chloroquine	known risk	
Chlorpromazine	known risk	
Cisapride	known risk	No longer available in the U.S.; available in Mexico. Substrate for 3A4
Citalopram	known risk	
Clarithromycin	known risk	Substrate for 3A4
Clomipramine	conditional risk	
Disopyramide	known risk	Females>Males
Dofetilide	known risk	
Domperidone	known risk	Not available in the U.S.
Dronedarone	possible risk	Substrate for 3A4
Droperidol	known risk	
Erythromycin	known risk	Females>Males. Substrate for 3A4
Drug	**QT risk***	**Comment**
Flecainide	known risk	
Halofantrine	known risk	Females>Males
Haloperidol	known risk	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases. Substrate for 3A4
Ibutilide	known risk	Females>Males
Levomethadyl	known risk	Not available in the U.S.
Mesoridazine	known risk	
Methadone	known risk	Females>Males. Substrate for 3A4
Moxifloxacin	known risk	
Pentamidine	known risk	Females>Males
Pimozide	known risk	Females>Males. Substrate for 3A4
Probucol	known risk	No longer available in U.S.
Procainamide	known risk	
Quetiapine	possible risk	Substrate for 3A4
Quinidine	known risk	Females>Males. Substrate for 3A4
Ritonavir	conditional risk	Substrate for 3A4
Sotalol	known risk	Females>Males
Sparfloxacin	known risk	
Tacrolimus	possible risk	Substrate for 3A4
Telithromycin	possible risk	Substrate for 3A4
Terfenadine	known risk	No longer available in U.S.Substrate for 3A4
Thioridazine	known risk	
Trazodone	conditional risk	Substrate for 3A4
Vandetanib	known risk	
Vardenafil	possible risk	Substrate for 3A4
* Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

Appendix G: List of QT prolonging drugs to be used with caution

Patients receiving any study treatment may use the following medications but should be monitored closely.

Drug	QT risk*	Comment
Alfuzosin	possible risk	
Amantadine	possible risk	
Atazanavir	possible risk	
Azithromycin	possible risk	Rare reports
Chloral hydrate	possible risk	
Ciprofloxacin	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Clozapine	possible risk	
Desipramine	conditional risk	Risk of TdP with overdosage
Diphenhydramine	conditional risk	Risk of QT increase/TdP in overdosages
Dolasetron	possible risk	
Doxepin	conditional risk	
Eribulin	possible risk	
Escitalopram	possible risk	
Drug	**QT risk***	**Comment**
Famotidine	possible risk	
Felbamate	possible risk	
Fingolimod	possible risk	
Fluconazole	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Fluoxetine	conditional risk	
Foscarnet	possible risk	
Fosphenytoin	possible risk	
Galantamine	conditional risk	
Gatifloxacin	possible risk	
Gemifloxacin	possible risk	
Granisetron	possible risk	
Imipramine	conditional risk	Risk of TdP in overdosage
Indapamide	possible risk	
Isradipine	possible risk	
Itraconazole	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Ketoconazole	conditional risk	Drug metabolism inhibitor
Levofloxacin	possible risk	
Lithium	possible risk	
Moexipril/HCTZ	possible risk	
Nicardipine	possible risk	
Nortriptyline	conditional risk	
Octreotide	possible risk	
Ofloxacin	possible risk	
Ondansetron	possible risk	
Oxytocin	possible risk	
Paliperidone	possible risk	
Paroxetine	conditional risk	

Perflutren lipid microspheres	possible risk	
Protriptyline	conditional risk	
Ranolazine	possible risk	
Risperidone	possible risk	
Roxithromycin*	possible risk	*not available in the United States
Sertindole	possible risk	
Sertraline	conditional risk	
Solifenacin	conditional risk	
Tizanidine	possible risk	
Trimethoprim-Sulfa	conditional risk	
Trimipramine	conditional risk	
Venlafaxine	possible risk	
Voriconazole	possible risk	
Ziprasidone	possible risk	
* Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

Appendix H: Patient BYL719 Drug Diary (Letrozole, Arm C) (attached separately)

Appendix I: Patient BYL719 Drug Diary (Exemestane, Arm D) (attached separately)