THE UNIVERSITY OF KANSAS

CANCER CENTER

Protocol: CBYL719XUS06T

Investigator Initiated Trial

Phase I/II Study of BYL719 and Nab-Paclitaxel in Subjects with Locally Recurrent or Metastatic HER-2 Negative Breast Cancer

PRINCIPAL INVESTIGATOR

Priyanka Sharma, MD
Associate Professor of Medicine
University of Kansas Medical Center
2330 Shawnee Mission Parkway, Suite 210, MS 5003
Westwood, KS 66205
[redacted]

Study Drug:	BYL719 (Alpelisib)
Drug Protocol Number:	CBYL719XUS06T
IND Number:	124440
Initial Version:	Version 3.0, November 10, 2014
Modification Date:	Version 4.0 - January 14, 2015 Version 5.0 - February 20, 2015 Version 6.0 - July 15, 2015 Version 7.0 - August 31, 2015 Version 8.0 - April 1, 2016 Version 9.0 - August 22, 2016

LIST OF KEY PERSONNEL

Project Collaborating Parties:	The University of Kansas Cancer Center Vanderbilt-Ingram Cancer Center
Coordinating Center	University of Kansas Medical Center (KUMC) / The University of Kansas Cancer Center (KUCC)
KUCC Principal Investigator:	Priyanka Sharma, M.D.
KUCC Sub-Investigators	[redacted]
Biostatistician	[redacted]
Vanderbilt Principal Investigator	Vandana Abramson, M.D. 2220 Pierce Ave, 777 PRB Nashville, TN 37232 [redacted]

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: CBYL719XUS06T

Protocol Title: Phase I/II Study of BYL719 and Nab-Paclitaxel in Subjects with Locally Recurrent or Metastatic HER-2 Negative Breast Cancer

Protocol Version and Date: Version 9 dated 08-22-2016

Principal Investigator Signature: _____ _____
Date

Print Name and Title: _____

Site Number: 001

Site Name: The University of Kansas Cancer Center / University of Kansas Medical Center

- - - - - - - - - - - - - - - - - -

Principal Investigator Signature: _____ _____
Date

Print Name and Title: _____

Site Number: 002

Site Name: Vanderbilt-Ingram Cancer Center

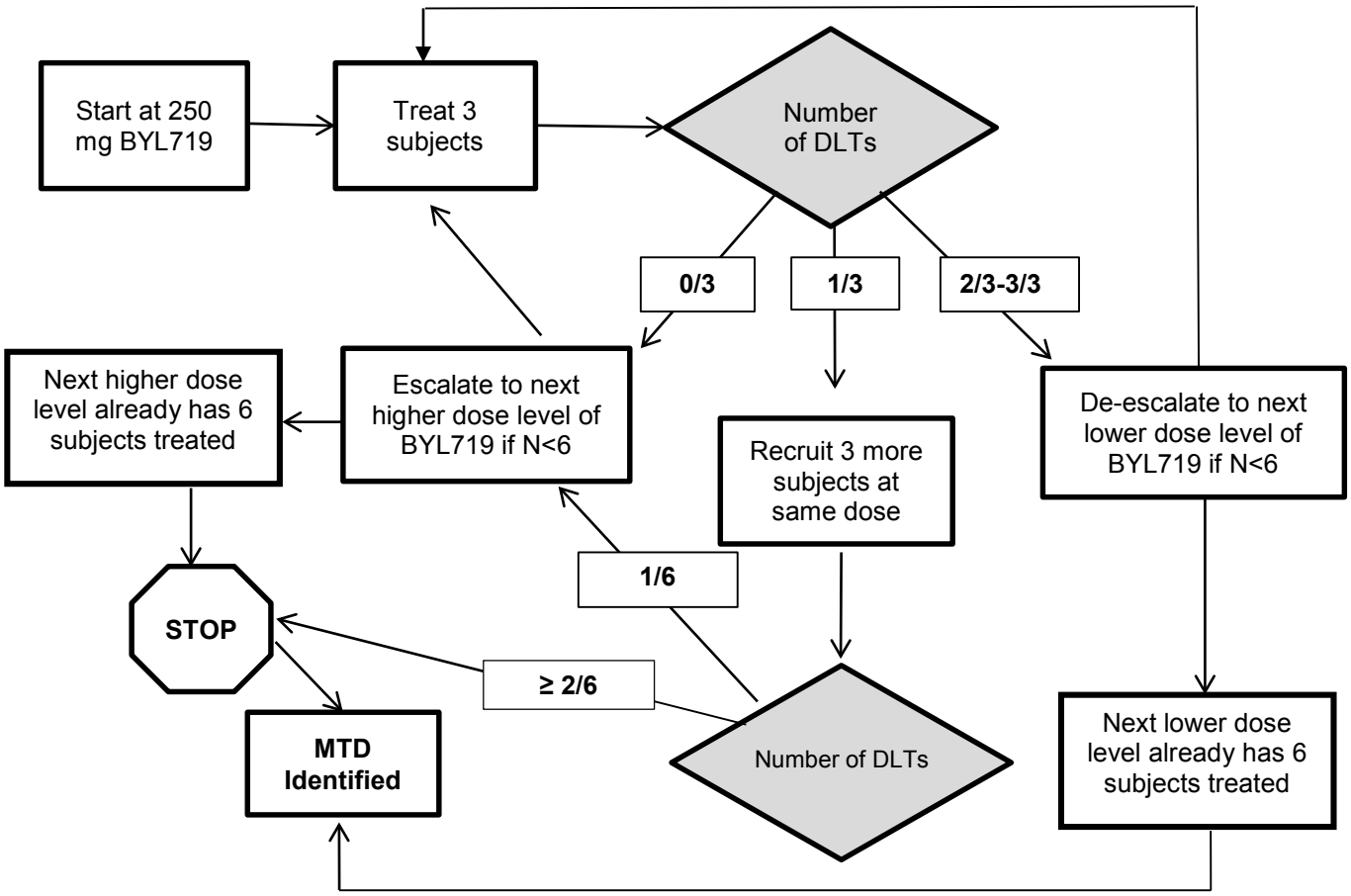
TABLE OF CONTENTS

ABBREVIATION LIST

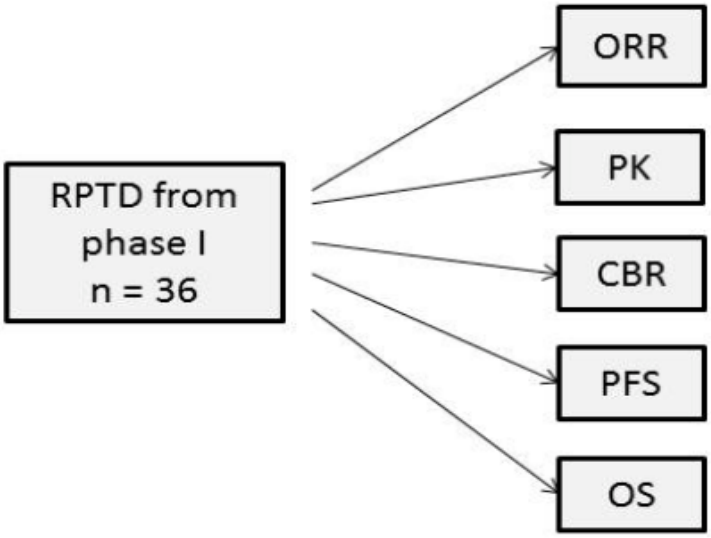
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCRP	Breast Cancer Reactive Protein
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen Receptor
FU	Follow-Up Visit
IULN	Institutional Upper Limit of Normal
HSC	Human Subjects Committee
ICF	Informed Consent Form
IRB	Institutional Review Board
KUMC	University of Kansas Medical Center
KUCC	The University of Kansas Cancer Center
LD	Longest Diameter
MBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease; Pharmacodynamics
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PI3K	Phosphatidylinositol-3-Kinase
PK	Pharmacokinetics
p.o.	Per Os/By Mouth/Orally
PR	Partial Response
PgR	Progesterone Receptor
QD	Daily
RECIST	Response Evaluation Criteria in Solid Tumors
RPTD	Recommended Phase II Dose
SAE	Serious Adverse Event
SD	Stable Disease
TNBC	Triple Negative Breast Cancer
WOCBP	Woman of Child Bearing Potential

STUDY SCHEMA

Phase I: Standard 3+3 dose escalation of BYL19 combined with 100 mg/m^2 Nab-Paclitaxel



Phase II: BYL719/alpelisib RPTD Used To Assess Endpoints



STUDY SUMMARY

Title	Phase I/II Study of BYL719 and Nab-Paclitaxel in Subjects With Locally Recurrent or Metastatic HER-2 Negative Breast Cancer
Short Title	Study of BYL719 and Nab-Paclitaxel in Locally Recurrent or Metastatic HER-2 Negative Breast Cancer
Phase	I/II
Methodology	Open-Label
Study Duration	3 years
Study Center(s)	The University of Kansas Cancer Center and Vanderbilt-Ingram Cancer Center
Objectives	Primary Objectives: • For Phase I, determine the recommended phase II dose (RPTD) of BYL719/alpelisib + Nab-Paclitaxel to be used in combination for treatment of advanced HER-2 negative breast cancer • For Phase II, assess ORR Secondary Objectives: • Assess pharmacokinetics of BYL719/alpelisib when administered with Nab-Paclitaxel • Assess pharmacokinetics of Nab-Paclitaxel when administered with BYL719/alpelisib • Determine the Clinical Benefit Rate (CBR) • Progression-Free Survival (PFS) and Overall Survival (OS) Exploratory Objective: • Investigate the correlation of PI3K aberration with response
Number of Subjects	Approximately 54 (18 in Phase I, 36 in Phase II)
Diagnosis and Main Inclusion Criteria	• Histologically-proven HER-2 negative breast cancer, which at the time of study is either stage III (locally advanced) disease not amenable to curative therapy or stage IV disease. • Demonstration of adequate bone marrow, kidney and hepatic function. Minimum criteria include: ANC > 1500/uL platelet count > 100,000/u/L, hemoglobin > 9 g/dL, serum creatinine < 1.5 mg/dL, transaminases < 2X IULN, total bilirubin < 1.5 mg/dL
Study Product(s), Dose, Route, Regimen	250-350 mg BYL719/alpelisib once daily on days 1-28 every 28 days plus 100 mg/m^2 Nab-Paclitaxel intravenous on days 1,8, and 15 of every 28 day cycle.
Duration of Administration	6, 28 day cycles of BYL719/alpelisib plus Nab-Paclitaxel after which Nab-Paclitaxel can be stopped and subjects will be allowed to take BYL719/alpelisib dosed continuously until disease progression/unacceptable toxicity.
Interim Monitoring	We will employ the following Bayesian sequential monitoring rule for toxicity during the Phase II portion of the study. We will stop the study if P (toxicity > 33% / data from the trial) > 0.95. This decision rule gives the following stopping rule. We assume a uniform prior distribution for the toxicity rate. Stop the study if [# of subjects with toxicity / # of subjects evaluated] ≥ 4/6, 5/7, 6/9, 7/11, 8/13, 9/16, 10/18, 11/20, 12/23, 13/25, 14/28, 15/30.
Statistical Methodology	Phase I: Standard 3+3 design for Phase I portion with three dose levels of BYL719/alpelisib (250 mg, 300 mg, 350 mg) and one level of Nab-Paclitaxel (100 mg/m^2), Phase II study is designed according to Simon's two stage Minimax design to detect an improvement in ORR from 20% to 40% (alpha 0.05 and power of 0.8).

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Breast cancer is the most common cancer and the second leading cause of cancer-related death in American women, with 232,340 new cases of breast cancer expected to be diagnosed in the year 2013[1]. Despite clinical advances in treatment of breast cancer over the last decade, up to 30% of women with early-stage, non-metastatic breast cancer at diagnosis will develop distant metastatic disease and 40,000 women still die as a result of breast cancer annually in the United States[1, 2]. The median survival for metastatic breast cancer (MBC) is 18-24 months though this varies widely based on tumor subtype, site(s) of metastatic involvement and burden of metastatic disease. Chemotherapy (usually a sequential single agent) remains the backbone of systemic treatment for subjects with HER-2 negative MBC. Although a majority of subjects with MBC respond to systemic chemotherapy, eventually all subjects will progress with a median time to progression of 3-7 months[3, 4]. While the exact mechanism for resistance or failure of systemic chemotherapy in MBC remain largely unclear, evidence suggests that the phosphatidylinositol-3-kinase (PI3K) pathway may play a role in primary and/or acquired resistance[5].

1.2 BYL719/Alpelisib Background and Associated Known Toxicities

The PI3K Pathway

PI3K signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration and angiogenesis[6]. Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors in many tumor types[7]. Resistance to a variety of therapeutic interventions including chemotherapy, hormonal therapy and anti-HER2 therapies can also be linked to constitutive activation of the PI3K pathway[8]. Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor or poor prognostic outcome in many cancers. The dysregulation of the PI3K signaling pathway is implicated in many human cancers[9-13] and includes the inactivation of the PTEN tumor suppressor gene[14], amplification/overexpression or activating mutations of some receptor tyrosine kinases (e.g., erbB3, erbB2, EGFR), and amplification of genomic regions containing *AKT* or *PIK3CA* genes[11, 15]. A schematic representation of these PI3K components is shown in Figure 1. Together these observations suggest that the PI3K pathway could be a critical therapeutic target for the treatment of subjects with advanced solid malignancies who often have limited therapeutic options beyond institutional standard of care.

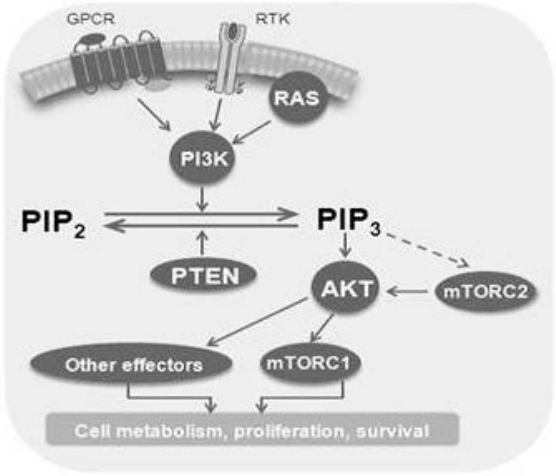


Figure 1: The PI3K pathway regulates numerous cellular activities and overexpression of these proteins has been associated with a variety of cancers.

PI3K Aberrations in Breast Cancer

Recent data shows that mutations/deregulations in the PI3K pathway are common in breast cancer. Gain-of-function mutations in oncogenes such as PIK3CA (encoding the catalytic subunit p110α have been observed in about 10% to 40% of BC subjects and are commonly observed in HR-positive (HR+) and triple-negative breast cancer (TNBC)[16, 17]. In activation of the tumor suppressor gene PTEN via loss-of-function mutations, gene deletion or transcriptional downregulation also leads to PI3K pathway activation and has been reported in 15-48% of BC subjects[18, 19]. Alternately, the PI3K pathway can be activated through various receptor classes or cross-talk with other pathways. For example, in HER-2 negative BC, specifically TNBC, the PI3K pathway appears to be modulated by the human epidermal growth factor receptor (EGFR). Preclinical models have demonstrated that EGFR signaling through the PI3K pathway leads to a higher level of Akt phosphorylation in TNBC cell lines[20-22]. Profiling of residual tumor tissue after neoadjuvant chemotherapy in subjects with TNBC revealed that 40% of the residual tumors demonstrated an aberration in PI3K/mTOR pathway, making it the most targetable aberration in chemoresistant TNBC[23]. Interestingly, TNBC cell lines have also been associated with lower expression of PTEN which correlates with increased activation of AKT and portends a favorable response to PI3K inhibition. Indeed, cell lines which are wild type for PIK3CA but have lost PTEN expression can be sensitive to a PI3K inhibitor[24] (Novartis internal data). These agents, therefore, represent an intriguing class of targeted anti-cancer therapy for subjects with HER-2 negative BC. The epidemiology data reported so far presents modest variation, however, based on these numbers, approximately 40% of TNBC subjects and 40% of HER-2/HR+ BC subjects, respectively, should harbor a constitutively activated PI3K pathway (defined as mutation in the PIK3CA gene and/or PTEN gene and/or loss of PTEN expression by immunohistochemistry). The metastatic HER-2 negative population is likely to be enriched for subjects/tumors with PI3K pathway aberrations, making this an attractive target to test in the metastatic setting.

Overview of BYL719/Alpelisib

BYL719/Alpelisib is an oral, class I PI3Kα-specific inhibitor belonging to the 2-aminothiazole class of compounds. BYL719/alpelisib strongly inhibits the PI3Kα isoform (both the p110α wild type and p110α mutation+) and is significantly less active against the other class I isoforms β, δ, and γ. In addition, it is inactive against the majority of other kinases. Targeting the alpha isoform of PI3K is expected to reduce the potential for inducing treatment-related toxicity and improve the therapeutic window over inhibitors with less isoform specificity. *In vitro*, BYL719/alpelisib has been shown to inhibit the proliferation of cell lines harboring PIK3CA mutations.

BYL Preclinical Efficacy in Breast Cancer Cell Lines

Several preclinical studies have demonstrated activity of class I PI3K inhibitors in HR+/HER-2 negative and basal-like/TNBC cell lines[25-27]. In xenograft models, PI3K/AKT inhibitors demonstrated activity against basal-like cancers and luminal breast cancer[28].

Pharmacodynamics of BYL719/Alpelisib

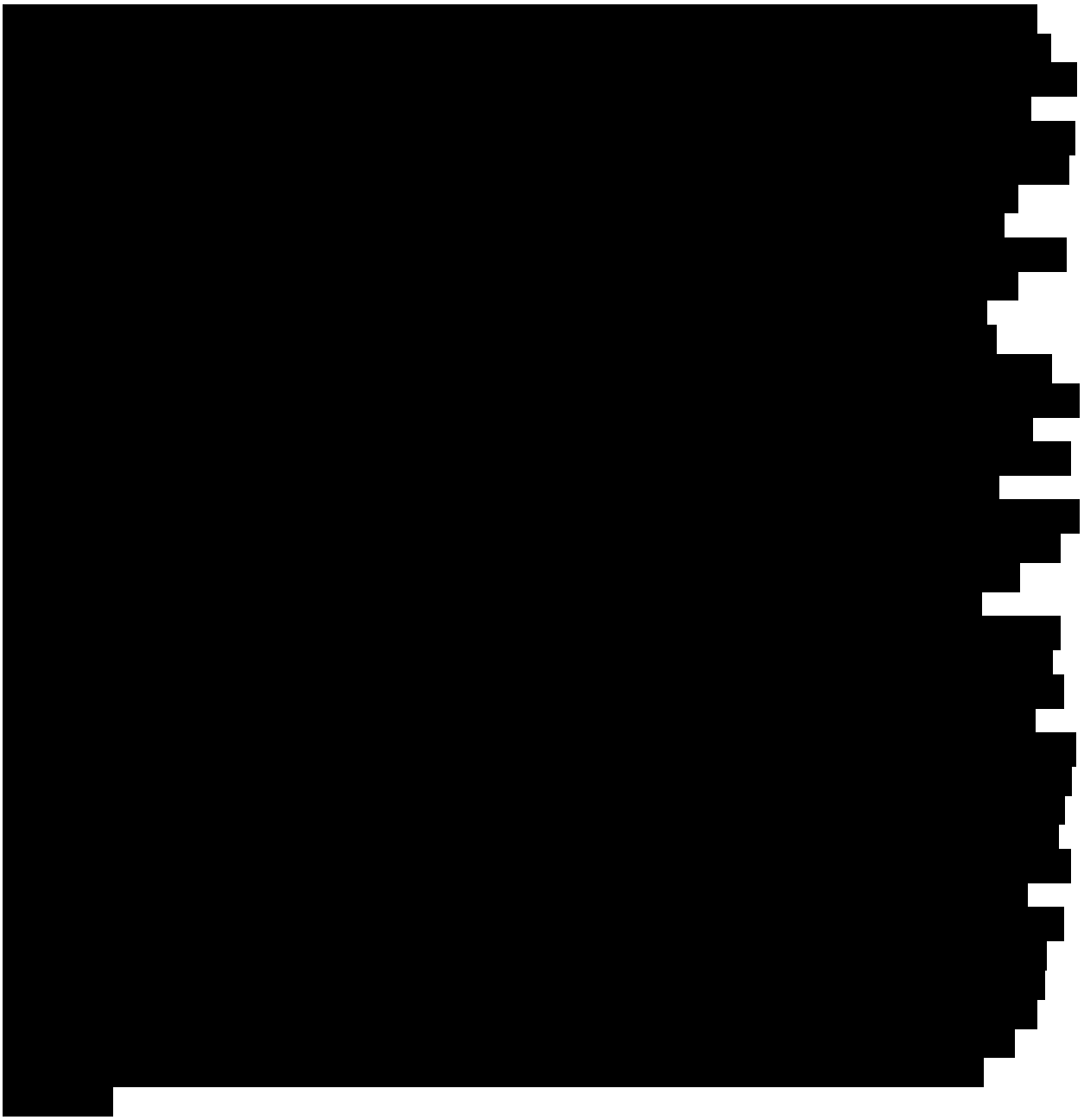
[redacted]

Nonclinical PK and Metabolism of BYL719/Alpelisib

[redacted]

Clinical Safety of BYL719/Alpelisib [CBYL719X2101]

[redacted]



1.3 Nab-Paclitaxel (Nab-Paclitaxel)

Taxanes are very active therapeutic agents in both early and advanced stage TNBC. Nab-Paclitaxel is a solvent-free, nanoparticle, albumin-based paclitaxel with activity in breast cancer. Nab-Paclitaxel was developed to take advantage of the antitumor activity of paclitaxel while decreasing or eliminating the toxicities typically associated with the solvent (Cremophor) used to administer the most common formulation of paclitaxel[29]. A phase III trial of Nab-Paclitaxel administered every three weeks in MBC showed improved response rates and time to progression (TTP) compared to solvent-based paclitaxel given every three weeks. Weekly Nab-Paclitaxel (150 mg/m^2) and every three-week Nab-Paclitaxel (300 mg/m^2) were found to have improved response rates and improved TTP compared to docetaxel in terms of efficacy. Nab-Paclitaxel is an approved chemotherapy for the treatment of advanced stage breast cancer and has demonstrated activity even in subjects with tumor progression on traditional paclitaxel[30].

Due to its formulation, Nab-Paclitaxel also does not require steroid premedication and has a short infusion time, which makes it easy to combine with other agents[31].

1.4 Rationale

Although taxanes are effective early on in advanced stage breast cancer, resistance often develops. While the exact mechanism(s) underlying the development of treatment resistance towards taxanes remain largely unknown, it has been demonstrated that activation of the PI3K/Akt pathway confers resistance to paclitaxel[32] and that increased Akt activity may be an early compensatory mechanism of resistance to chemotherapy[33]. Additionally, in preclinical models, concomitant inhibition of the PI3K pathway enhances the efficacy of taxanes as compared to each agent given separately[32]. This provides a rationale for studying a combination of a taxane with PI3K inhibitor in breast cancer. An ongoing randomized phase II study is evaluating a Class I PI3K inhibitor (BKM120) in combination with paclitaxel in the first line setting in HER-2 negative MBC (NCT01572727). However, taxanes are often used beyond first line setting in MBC, thus, providing a rationale for studying a combination of PI3K inhibitor and a taxane beyond the first line setting. We propose a phase Ib/II study of BYL719/alpelisib (PI3Kα-specific inhibitor) in combination with Nab-Paclitaxel.

1.5 Correlative Studies

[redacted]

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 For Phase I, determine the Recommended Phase II Dose (RPTD) of BYL719/alpelisib + Nab-Paclitaxel to be used in combination for treatment of advanced HER-2 negative breast cancer

2.1.2 For Phase II, assess Overall Response Rate (ORR) of subjects treated at the RPTD

2.2 Secondary Objectives

2.2.1 Determine Clinical Benefit Rate (CBR) at 16 weeks of study treatment for subjects treated at the RPTD

2.2.2 Assess PK of BYL719/alpelisib when administered with Nab-Paclitaxel

2.2.3 Assess the PK of Nab-Paclitaxel when administered with BYL719/alpelisib

2.2.4 Determine Progression-Free Survival (PFS) and Overall Survival (OS)

2.3 Exploratory Objectives

2.3.1 Investigate the correlation of PI3K aberrations with clinical response

2.4 Endpoints

Primary Endpoints: Recommended Phase II Dose of BYL719/alpelisib in combination with Nab-Paclitaxel (Phase I); Overall Response Rate of treated subjects (Phase II) according to RECIST v1.1 criteria

Secondary Endpoints: Phase II: Percentage of subjects that have achieved complete response, partial response or stable disease as a result of treatment (CBR), PK of BYL719/alpelisib and Nab-Paclitaxel individually when given in combination, average progression free survival (PFS) and overall survival (OS) time in days

Exploratory Endpoints: Assessment of molecular status of subject tumor tissue (archival primary tumor, metastatic tumor or new pre-treatment tumor biopsies), including PIK3CA, PTEN and KRAS mutations, PTEN protein expression by IHC, PI3K amplification and Akt phosphorylation

3.0 SUBJECT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

3.1.1 Ability to understand and the willingness to sign a written Informed Consent Form.

3.1.2 Age ≥ 18 years

3.1.3 Histologically proven HER-2 negative breast cancer (HER-2 negative defined as HER IHC 0 or 1+ and/or HER-2 FISH negative); HER-2 negative breast cancer includes hormone positive (ER and/or PR positive) breast cancer and TNBC

3.1.4 HER-2 negative breast cancer that at the time of study entry is either stage III (locally advanced) disease not amenable to curative therapy or stage IV disease. Histological confirmation of recurrent/metastatic disease is encouraged but not required if clinical evidence of stage IV disease is available

3.1.5 Have measurable (defined as at least one lesion that can be accurately measured in at least one dimension [longest diameter to be recorded] with minimum lesion size of ≥ 2 cm on conventional measurement techniques or ≥ 1 cm on spiral computed tomography (CT) scan

3.1.6 No limitations to number of prior chemotherapies for metastatic disease. Treatment with prior taxanes (except Nab-Paclitaxel) is allowed as long as it has been 6 months or more since exposure to prior taxane.

NOTE: For subjects who are, or who have previously received endocrine therapy for breast cancer, the treating investigator will decide how many days should pass between the last dose of endocrine therapy and the first dose of study treatment.

3.1.7 All patients should have received at least one line of chemotherapy in either the advanced or adjuvant setting and hormonal therapy (where appropriate)

3.1.8 Performance status of 2 or better as per ECOG criteria (See Appendix A for details)

3.1.9 Subject is able to swallow and retain oral medicines

3.1.10 Adequate marrow and organ function as defined below (labs must be performed within 14 days of subject registration)

- Absolute neutrophil count ≥ 1500/uL
- Platelets 100,000/uL (no transfusion allowed within 2 weeks)
- Hemoglobin > 9 g/dL (which may be reached by transfusion)
- Total bilirubin within normal range or ≤ 1.5X IULN if liver metastases are present or total bilirubin ≤ 3.0X IULN with direct bilirubin within normal range in subjects with well-documented Gilbert's Syndrome, which is defined as presence of unconjugated hyperbilirubinemia with normal results from CBC (including normal reticulocyte count and blood smear), normal liver function test results and absence of other contributing disease processes at the time of diagnosis
- AST(SGOT)/ALT(SPGT) ≤ 2.5X IULN or ≤ 5X IULN if liver metastases are present
- Serum creatinine ≤ 1.5X IULN
- INR ≤ 1.5
- Fasting plasma glucose ≤ 140 mg/dL or 7.8 mmol/L
  (NOTE: Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.)
- HBA1c ≤ 8%
- Potassium, calcium (corrected for serum albumin) and magnesium within IULN
- Serum Amylase $\underline{\leq}$ 2 x ULN and serum lipase within normal limits

3.1.11 IV bisphosphate and denosumab for bony metastatic disease will be allowed

3.1.12 Prior palliative radiation therapy to bony metastases is allowed. There should be a minimum of 14 days between the end of radiation treatment and start of study treatment

3.1.13 Subjects with previously treated brain metastases who are free of CNS symptoms and are > 3 months from treatment of brain metastases are eligible

Subjects should be > 2 weeks from prior systemic chemotherapy for breast cancer AND should have recovered to Grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy prior to study entry

NOTE: For subjects who are, or who have previously received endocrine therapy for breast cancer, the treating investigator will decide how many days should pass between the last dose of endocrine therapy and the first dose of study treatment.

3.1.14 Women of child bearing potential (WOCBP) and their partners must agree to use adequate contraception (barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. After confirmation of negative pregnancy test at screening, should a WOCBP become pregnant or suspect that she is pregnant while participating in

this study, she should inform her treating physician and the investigator immediately.

- WOCBP are defined as any females (regardless of sexual orientation, having undergone tubal ligation, or remaining celibate by choice) who meet the following criteria:
  - Have not undergone a hysterectomy or bilateral oophorectomy **OR**
  - Have not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months)

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

3.2.1 Subject has any other medical or psychiatric disorder that, in the opinion of the treating physician, would contraindicate the use of drugs in this protocol or place the subject at undue risk for treatment complications

3.2.2 Subject is pregnant or lactating

3.2.3 Subject has previously been treated with Nab-Paclitaxel

NOTE: Subjects who have had previous treatment with Nab-Paclitaxel will NOT be excluded if given in the adjuvant or neoadjuvant setting

Only in the metastatic setting, will subjects previously treated with Nab-Paclitaxel be excluded from this trial. Exceptions may be made for subjects who discontinued treatment with a previous Nab-Paclitaxel inhibitor for reasons other than progression and as long as it has been > 12 months since discontinuation of the previous Nab-Paclitaxel. This exception will require prior approval from the study PI at KUMC.

3.2.4 Subject has inflammatory breast cancer

3.2.5 Subject has a known hypersensitivity to any of the excipients of Nab-Paclitaxel or BYL719/alpelisib

3.2.6 Subject has a concurrent malignancy or malignancy within 3 years of study enrollment (with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer)

3.2.7 Subject has clinically manifest diabetes mellitus or documented steroid-induced diabetes mellitus

3.2.8 Subject has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection)

3.2.9 Subject is classified into Child-Pugh class C

3.2.10 Subject has a known history of HIV infection (testing not mandatory)

3.2.11 Subject has active, uncontrolled infection

3.2.12 Subject has symptomatic/untreated CNS disease

3.2.13 Subject has ≥ Grade 2 peripheral neuropathy

3.2.14 Subject has active cardiac disease or a history of cardiac dysfunction including any of the following:

- Unstable angina pectoris within 6 months prior to study entry
- Symptomatic peritonitis
- Documented myocardial infarction within 6 months prior to study entry
- History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Documented cardiomyopathy
- Subject has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO)
- Subject has any of the following cardiac conduction abnormalities
- Ventricular arrhythmias except for benign premature ventricular contractions
- Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medicine
- Conduction abnormality requiring a pacemaker
- Other cardiac arrhythmia not controlled with medication

3.2.15 Subject has a QTcF > 480 msec on the screening ECG (using the QTcF formula)

3.2.16 Subject is currently receiving treatment with a medication that has a known risk to prolong the QT interval or induce Torsades de Pointes and the treatment cannot be discontinued or switched to a different medication prior to randomization

3.2.17 Subject has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects

3.2.18 Subject is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug or who have not fully recovered from side effects of such treatment

3.2.19 Subject is currently receiving treatment with drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A. The subject must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the start of treatment

3.2.20 Subject is currently receiving warfarin or other coumarin-derived anti-coagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed

3.2.21 Subject has received previous treatment with a PI3K inhibitor. Exceptions may be made for subjects who discontinued treatment with a previous PI3K inhibitor for reasons other than toxicity or progression and as long as it has been > 12

months since discontinuation of the previous PI3K inhibitor. This exception will require prior approval from the study PI at KUMC.

3.2.22 Subjects who have received an investigational agent within 30 days OR within 5 half-lives of the investigational agent (whichever is shorter) prior to the possible enrollment date on this study.

3.2.23 Subject with history of acute within one year of study entry or past medical history of chronic pancreatitis.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

- Standard 3+3 design for Phase I portion with three dose levels of BYL719/alpelisib (250 mg, 300 mg, 350 mg PO Q day D1-28 every 28 days) and one dose level of Nab-Paclitaxel (100 mg/m^2 IV D1,8,15 +/- 1 day every 28 days)
- If starting dose of 250 mg of BYL719/alpelisib is not tolerated, it is permissible to lower the starting dose to 200 mg

Table 1: Dose Escalation Scheme

Dose Level	Dose of the Study Agent(s)*	Minimum Number of Subjects
Level -1	200 mg	3
Level 1	250 mg	3
Level 2	300 mg	3
Level 3	350 mg	3

- Required study treatment will continue for a minimum of 6 cycles in subjects with stable disease/PR/CR). In subjects with stable disease/PR/CR after 6 cycles of treatment, subjects can either continue both study drugs until disease progression/unacceptable toxicity or Nab-Paclitaxel can be stopped (at the discretion of the treating physician) but subjects will continue BYL719/alpelisib until disease progression/unacceptable toxicity. Potential dose modifications for Nab-Paclitaxel will be specified in more detail in section 5.5. Growth factor support will be allowed at the discretion of the treating physician.

Drug	Premedications	Dose	Route	Schedule	Cycle Length
BYL719/alpelisib	None	250 mg, 300 mg, or 350 mg	Oral	D1 to 28, every 28 days	4 weeks (28 days)
Nab-Paclitaxel	Benadryl 25 mg to 50 mg PO/IV; Tylenol 650 mg PO, Zofran 4 mg IV	100 mg/m^2	Benadryl can be PO/IV; Tylenol is PO, Zofran is IV	D1, 8, and 15 +/- 1 day every 28 days	4 weeks (28 days)

4.2 BYL719/Alpelisib Administration Instructions

BYL719/alpelisib tablets will be supplied by Novartis Pharmaceuticals. The tablets will be administered orally on a daily schedule (QD). At each visit, responsible site personnel will ensure that the appropriate dose of each study drug is administered at the clinic and will provide the subject with the correct amount of BYL719/alpelisib for subsequent dosing. Subjects will be instructed to return unused BYL719/alpelisib study drug to the site at each visit.

The following guidelines should be followed for BYL719/alpelisib administration:

- Subjects should be instructed to take one or more tablets of BYL719/alpelisib together with a glass of water (~250 ml or ~8 fluid ounces) daily in the morning approximately 1 hour after start of breakfast (not including grapefruit or grapefruit-based juice) at approximately the same time each day (recommended 8AM +/- 1 hour), except on days that blood collection is scheduled at the clinic; subjects will take their doses at clinic on those days. There are no restrictions on the composition or caloric intake of the breakfast meal.
- Subjects should not eat for 1 hour after the administration of BYL719/alpelisib.
- If by noon the subject forgets to take the study drug (BYL719/alpelisib), 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 subject should still take the scheduled morning dose of study drug with a glass of water. If this happens on days of PK sampling, it should be documented in the eCRF.
- Subjects should be instructed to swallow the tablets and not to chew or crush them.
- Subjects 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.
- Subjects should record if the dose was taken or not in the subject diary.
- If vomiting occurs during the course of treatment, no re-dosing of the subject is allowed before the next scheduled dose. The occurrence and frequency of any vomiting/diarrhea (or increase in stool frequency) within the 24 hours post-dosing on that day must be noted in a separate section of the eCRF.
- Subjects 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 the potential CYP3A interaction. Regular orange (Citrus X sinensis) juice is allowed.

On the days of Nab-Paclitaxel administration, BYL719/alpelisib should be taken 1 hour prior to the infusion of Nab-Paclitaxel.

- FPG Monitoring: On the days of FPG monitoring, subjects must be fasting overnight for at least 8 hours prior to the blood collection. Breakfast may be consumed after FPG draw. BYL719/alpelisib may be administered 1 hour after the start of breakfast. Subjects should continue to fast for 1 hour after the administration on the days of Nab-Paclitaxel administration.
    - **NOTE:** Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.
- PK Sampling: On the days of PK sampling, subjects must be fasting overnight for at least 8 hours prior to breakfast to achieve light fed conditions. Pre-dose PK sample should be collected just prior to BYL719/alpelisib intake. BYL719/alpelisib should be consumed/taken 1 hour prior to the Nab-Paclitaxel administration on the days of Nab-Paclitaxel administration.
- Any doses that are missed should be skipped and should not be replaced or made up during the next scheduled dosing or on a subsequent day, whichever applies
- Subjects must avoid consumption of grapefruit, grapefruit juice (Citrus paradise) and Seville orange juice (*Citrus aurantium*) during the entire study and preferably 7 days before the first dose of study medications due to potential CYP3A4 interaction with the study drug combination. Regular orange juice (*Citrus sinensis*) is allowed.
- Subjects should be instructed to swallow the tablets whole and not to chew or crush them.

- If vomiting occurs during the course of treatment, no re-dosing of the subject is allowed before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increase in stool frequency) should be noted. In addition, on the days of full PK sampling, the onset time of any episodes of vomiting and diarrhea (or increased stool frequency) within the first 4 hours post-dosing on that day should also be noted.

4.3 Nab-Paclitaxel Administration Instructions

Nab-Paclitaxel will be obtained from each center's commercial supply. Nab-Paclitaxel is supplied as a sterile lyophilized powder for reconstitution before use. Avoid errors, read entire preparation instructions prior to reconstitution.

1. Aseptically, reconstitute each vial by injecting 20 ml of 0.9% sodium chloride injection, USP.

2. Slowly inject the 20 ml of 0.9% sodium chloride injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the inside wall of the vial.

3. DO NOT INJECT the 0.9% sodium chloride injection, USP, directly onto the lyophilized cake as this will result in foaming.

4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.

5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.

6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides. Each mL of the reconstituted formulation will contain 5 mg/mL Nab-Paclitaxel. Calculate the exact total dosing volume of 5 mg/mL suspension required for the subject: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted Nab-Paclitaxel into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer Nab-Paclitaxel infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

<u>Dose-Limiting Toxicity (DLT) AND Maximally Tolerated Dose (MTD)</u>

Toxicity will be assessed using the NCI CTCAE, version 4.03 unless otherwise specified. A DLT is defined as an AE or abnormal laboratory value assessed as at least possibly related to the study medication, which occurs ≤ 28 days following the first dose of BYL719/alpelisib (Cycle 1) and meets any of the criteria listed in Table 3. Whenever a subject experiences toxicity that

fulfills the criteria for a DLT, treatment with the study drug will be stopped and the toxicity will be followed. For the purposes of dose escalation and determination of the MTD, the evaluation period for DLTs will be during the first cycle. Toxicity monitoring in the Phase I will follow the stopping rules in the 3+3 design. Toxicity monitoring in the Phase II will follow the Bayesian Sequential Monitoring design as described in section 13.3.

Recommended Phase 2 dose (RP2D)
The Recommended Phase 2 dose (RP2D) is defined as the next lower dose level below MTD (dose at which patients experienced a DLT).

Table 3: Criteria For Determining Dose-Limiting Toxicities

Toxicity	DLT criteria
Blood and lymphatic system disorders	Grade 4 neutropenia lasting for > 7 days or CTCAE Grade 4 neutropenia associated with fever (> 38.5^{o}C)
Cardiac disorders	Cardiac toxicity CTCAE Grade $\geq$ 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 $\geq$ 3
Vascular disorders/Hypertension	Persistent hypertension CTCAE Grade $\geq$ 3 requiring more than one drug or more intensive therapy than previously
General disorders and administration	Fatigue CTCAE Grade 3 for > 7 consecutive days
Skin and subcutaneous tissue disorders; Rash and Photosensitivity	Rash or photosensitivity CTCAE Grade 3 for > 7 consecutive days despite skin toxicity treatment Rash or photosensitivity CTCAE Grade 4
Metabolism and nutrition disorders: Hyperglycemia[b]	Hyperglycemia Grade 2 (FPG 200-250 mg/dL) [11.2-13.8 mmol/L] confirmed with a repeat FPG within 24 hrs that does not resolve to Grade 0 (FPG < 160 mg/dL) [< 7.8mmol/L] within 14 consecutive days after initiation of oral anti-diabetic treatment. Hyperglycemia Grade 3 (FPG 250-399 mg/dL)[13.9-22.2 mmol/L] confirmed with a repeat FPG within 24 hrs (whether related to use of steroid therapy or not); lasting > 72 hrs despite adequate antidiabetic therapy. Hyperglycemia Grade 4 (FPG $\geq$ 400 mg/dL) [$\geq$ 22.3 mmol/L] Hyperglycemia leading to diabetic keto-acidosis, hospitalization for IV insulin infusion, or non-ketotic coma **NOTE:** Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.
GI disorders[a]	Diarrhea CTCAE Grade $\geq$ 3 for $\geq$ 48 hrs despite the use of anti-diarrhea therapy Nausea/vomiting CTCAE Grade $\geq$ 3 for $\geq$ 48hrs despite the use of anti-emetic therapy Pancreatitis CTCAE Grade $\geq$ 3
Eye disorders	CTCAE Grade $\geq$ 3

Investigations[c]	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 ≥ 3 Platelet count CTCAE Grade 3 for > 7 consecutive days and/or signs of bleeding Platelet count CTCAE Grade 4 Hypomagnesemia CTCAE Grade 3 for > 3 consecutive days and not correctable with supplements or symptomatic Hypomagnesemia CTCAE Grade 4
Other hematologic and non-hematologic toxicities	≥ Grade 3 mood alteration[e] Any other CTCAE ≥ Grade 3 toxicity except lymphocyte count decrease (lymphocytopenia) CTCAE Grade ≥ 3 unless clinically significant

[a] Subjects will not initially receive prophylactic treatment for skin toxicity or nausea/vomiting for BYL719/alpelisib during Cycle 1. However, prophylactic treatment may be initiated in all subjects at the dose level where these toxicities have been observed and in all further subjects if at least 1 (one) subject has experienced skin toxicity or nausea/vomiting CTCAE Grade ≥ 3 or if at least 2 (two) subjects experienced skin toxicity or nausea/vomiting CTCAE Grade ≥ 2. However anti-emetics may be applied for treatment if the subject has experienced nausea/vomiting CTCAE Grade ≥ 1 at the discretion of the physician.

[b] Not according to CTCAE v4.03. Of note: Hyperglycemia occurring during corticosteroids administration will be only considered a DLT if not resolved within 2 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. If baseline laboratory value is elevated (or decreased) prior to drug therapy, an increase (or decrease) will not be considered a DLT unless there is a worsening by at least 2 toxicity grades.

[d] Refers to total bilirubin

[e] To be assessed for DLT status by physical examination and subject history

NOTE: Apart from criteria listed above, if a lower grade AE leads to a dose interruption of more than 7 consecutive days of BYL719/alpelisib, this AE may be considered as a DLT.

Follow up for toxicity

Subjects whose treatment is delayed or permanently discontinued due to an AE or clinically significant laboratory value must be followed up with at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4 week intervals until resolution or stabilization of the event, whichever comes first. All subjects must be followed for AEs and SAEs for 30 days following the last doses of BYL719/alpelisib. Subjects exhibiting hypomagnesaemia, hypocalcaemia, and/or hypokalemia should receive electrolyte replacement as indicated by national and institutional guidelines and must be followed until laboratory values have normalized or as clinically indicated.

4.4 Dose Modifications

4.4.1 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the subject to continue the study treatment. All dose modifications should be based on the worst preceding toxicity

(CTCAE version 4.03). If a subject experiences a DLT, study treatment should be interrupted and the toxicity should be followed.

4.4.2 Treatment Interruption and Treatment Discontinuation

At the discretion of the investigator, a one week delay prior to starting a new cycle maybe requested to accommodate patient travel or schedule burdens.

The criteria for dose modifications of BYL719/alpelisib for toxicities considered at least "possibly-related" to the study medication treatment are outlined in Table 4. If a subject requires a dose delay of > 28 consecutive days of BYL719/alpelisib, then the subject should be discontinued from the study treatment. In exceptional situations, if the subject is clearly benefitting 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 subject may remain on the study treatment. Subjects who discontinue from the study for a study-related AE or an abnormal laboratory value must be followed.

For each subject, a maximum of two (2) dose reductions will be allowed after which the subject will be discontinued from the study treatment. In addition, a subject 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 4 and the same toxicity reoccurs with the same severity, next treatment re-initiation must resume at the next lower dose level irrespective of duration.

For each subject, once a dose level reduction of BYL719/alpelisib has occurred, the dose level may not be re-escalated during subsequent treatment cycles with the study drugs. Dose reduction for BYL719/alpelisib means treatment at the next lower, previously tested respective dose level of BYL719/alpelisib.

4.5 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each subject will be assessed for the development of toxicity according to the Schedule of Events table contained within Section 6.4. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTACAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Table 4: Dose Adjustment and Management Recommendations: BYL719/alpelisib

Adverse Drug Reaction	Severity	Dose Adjustment and Management Recommendations
Hematology	ANC < 500/uL without fever and/or platelets < 75000/uL	Hold BYL719/alpelisib until ANC is ≥ 500/uL and platelet count is ≥ 75,000/uL. If treatment delay is ≤ 7 days, restart at same dose. If treatment delay is ≥ 7 days drop 1 dose level.
	ANC < 1000/uL with fever (> 38.3°C) or sustained fever ≥ 38 °C for more than 1 hour	Hold BYL719/alpelisib until ANC is ≥ 1000/uL. If treatment delay is ≤ 7 days, restart at same dose. If treatment delay is > 7 days, drop 1 dose level.
Cardiac – QTc prolongation	QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs.	**First Occurrence**: Omit BYL719/alpelisib Perform a repeat ECG within one hour of the first QTcF of > 500 ms or > 60 ms from baseline. If QTcF remains > 500 ms or > 60 ms from baseline, repeat ECG as clinically indicated, but at least once a day 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/alpelisib may be restarted at the next lowest dose. **Second Occurrence**: Permanently discontinue subject from BYL719/alpelisib
Cardiac – Left Ventricular systolic dysfunction	Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level and continue BYL719/alpelisib with caution; Repeat LVEF within 4 weeks or as clinically appropriate
	Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	Omit BYL719/alpelisib until resolved (subject is asymptomatic, has a resting ejection fraction ≥ 40% and ≤ 20 % decrease from baseline), then drop 1 (one) dose level
	Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue subject from BYL719/alpelisib
Cardiac Events (other than QTc prolongation or left ventricular systolic dysfunction)	Grade 1 or 2	Maintain dose level
	Grade 3	Omit dose until resolved to ≤ Grade 1, then lower 1 (one) dose level
	Grade 4	Permanently discontinue subject from BYL719/alpelisib
Diarrhea Please see Appendix G for guidelines for study drug-induced diarrhea management	Grade 1	Maintain dose level
	Grade 2	Omit dose until resolved to ≤ Grade 1, then restart at same dose.
	≥ Grade 3	Omit dose until resolved to ≤ Grade 1, then drop 1 (one) dose level.
Eye disorders	≥ 3 ocular/vision symptoms interfering with activities of daily life or requiring medication intervention	Discontinue subject from BYL719/alpelisib

Hepatic – bilirubin (*For subjects with Gilbert Syndrome; these dose modifications apply to changes in direct bilirubin only)	Grade 1 (>IULN – 1.5 x IULN)	Maintain dose level with LFTs* monitored as per protocol
	Grade 2 (> 1.5 – 3.0 x IULN) with ALT or AST ≤ 3.0 x IULN)	Omit dose until resolved to ≤ Grade 1, then: if treatment delay is ≤ 7 days, restart at same dose. If resolved in > 7 days, drop 1 (one) dose level.
	Grade 3 (> 3.0 - 10.0 x IULN) with ALT or AST ≤ 3.0 x IULN)	Omit dose until resolved to < Grade 1, then: if treatment delay is ≤ 7 days, restart at same dose. If resolved in > 7 days, discontinue subject from BYL719/alpelisib
	Grade 4 (>10.0 x IULN)	Permanently discontinue BYL719/alpelisib
Hepatic – AST or ALT	Grade 1 (> IULN – 3.0 x IULN)	Maintain dose level with LFTs monitored per protocol
	Grade 2 (>3.0 – 5.0 x IULN) without total bilirubin elevation to > 2.0 X IULN	Omit dose until resolved to ≤ Grade 1. If treatment delay is ≤ 7 days, restart at same dose. If resolved in > 7 days, drop 1 (one) dose level. In subjects with pre-existent AST/ALT elevation (>3.0 – 5.0 x IULN) due to metastatic disease to liver, maintain dose level with LFTs monitored per protocol.
	Grade 3 (> 5.0 – 20.0 x IULN) without bilirubin elevation to > 2.0 x IULN	Omit dose until resolved to < Grade 1 then drop 1 (one) dose level.
Hepatic - AST or ALT and concurrent Bilirubin **Note**: *LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 X ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. Hepatic toxicity monitoring (*for subjects with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 X ULN), alkaline phosphatase (fractionated if alkaline phosphatase is Grade 2 or higher) and GGT): In case of any occurrence of ALT/AST/bilirubin* increase > Grade 2, the LFTs must be monitored weekly or more frequently if clinically indicated until resolved to < Grade 1. In case of any occurrence of ALT/AST/bilirubin* increase > Grade 3, the LFTs must be monitored weekly or more frequently if clinically indicated until resolved to < Grade 1;	AST or ALT > 3.0 x IULN and total bilirubin > 2.0 x IULN	Permanently discontinue BYL719/alpelisib

hereafter the monitoring should be continued every other week or more frequently if clinically indicated until the end of treatment with study medication. Subjects who discontinued study treatment should be monitored weekly, including LFTs* or more frequently if clinically indicated until resolved to < Grade 1 or stabilization (no CTCAE grade change over 4 weeks).		
Hyperglycemia - Fasting Plasma Glucose (FPG) **NOTE**: A diabetologist consultation should always be considered. Based on current experience, hyperglycemia usually resolves within a few days after BYL719/alpelisib omission. Temporary omission of BYL719/alpelisib may be considered as clinically indicated to improve control of hyperglycemia. Special attention should be paid to the risk of hypoglycemia in subjects' interruption BYL719/alpelisib treatment and receiving insulin or sulfonylurea. **NOTE:** Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.	Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] confirmed within 24 hours	Continue BYL719/alpelisib 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 FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every 2 weeks.
	Asymptomatic Grade 2 (> 160 - 250 mg/dl) [> 8.9 - 13.9 mmol/L]	Maintain dose level and recheck within 24 hours. If grade worsens or improves, follow specific recommendations. If grading is confirmed, continue BYL719/alpelisib 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 FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1. If FPG does not resolve to ≤ Grade 1 within 14 days after institution of appropriate anti-diabetic treatment, reduce BYL719/alpelisib by 1 (one) dose level. Continue with anti-diabetic treatment and check FPG 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/alpelisib and recheck within 24 hours. If grade worsens or improves, follow specific recommendation. If grading is confirmed, omit BYL719/alpelisib 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 FPG as clinically indicated and at least twice weekly until FPG resolves to < Grade 1. If FPG resolves to Grade 1 within 14 days, then restart BYL719/alpelisib and reduce 1 (one) dose level. If FPG doesn't resolve to Grade 1 within 14 days, then discontinue subject from BYL719/alpelisib. Continue with anti-diabetic treatment and check FPG at least weekly for 8 wks; then continue checking at least every 2 wks.
	Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L] OR Grade 3 with signs or symptoms of	Omit BYL719/alpelisib, initiate or intensify medication with appropriate anti-diabetic treatment (consider adding insulin), recheck within 24 hours. If grade improves, then

	hyperglycemia (i.e. mental status changes, excessive thirst, polyuria)	follow specific grade recommendations. If FPG is confirmed at Grade 4, discontinue subject from BYL719/alpelisib.
Pancreatitis	Grade ≥ 3	Discontinue subject from BYL 719
Photosensitivity	Grade 1	Maintain dose level
	Grade 2	Omit dose until resolved to ≤ Grade 1. If not resolved in ≤ 7 days, reduce 1 (one) dose level. If resolved in > 7 days discontinue BYL719/alpelisib.
	Grade ≥ 3	Discontinue subject from BYL 719
Serum Creatinine	< 2 X IULN	Maintain dose level
	2- 3 X IULN	Omit dose until resolved to ≤ Grade 1. If treatment delay is ≤ 7 days, restart at same dose. If not resolved in > 7 days, then reduce 1 (one) dose level.
	Grade 3 (>3.0 - 6.0) X IULN	Permanently discontinue subject from BYL719/alpelisib
	Grade 4 (>6.0 X IULN)	Permanently discontinue subject from BYL719/alpelisib
Stomatitis/Oral Mucositis	Grade 1/Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash
	Intolerable Grade 2 or Grade 3	First occurrence hold until ≤ Grade 1 and reduce 1 (one) dose level. (If stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator).
	Grade 4	Permanently discontinue subject from BYL 719
All other adverse events (except pneumonitis, see pneumonitis management guidelines below)	Grade 1 or 2	Maintain dose level
	Grade 3	Omit dose until resolved to ≤ Grade 1; then reduce 1 (one) dose level.
	Grade 4	Permanently discontinue subject from BYL719/alpelisib. ***Note***: Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled.

Management Guidelines for Macropapular Rash

Grade (CTCAE v4.03)	**Actions and recommended concomitant medications**
Grade 1	Maintain BYL719/alpelisib dosing.
	Initiate antihistamine dosing. Recommend non-sedating regimen (e.g. hydroxyzine 25 mg bid) for at least 28 days
	Topical corticosteroid preparation**BID for affected areas for at least 28 days.
Grade 2	Maintain BYL719/alpelisib dosing.
	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 0.5-0.75 mg per kg QD or equivalent 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 in 14 days, continue or re-administer oral corticosteroid (recommend prednisone 0.5-0.75mg/kg QD or equivalent for 10 days; longer periods of dosing require tapered dosing).
	If hyperglycemia has been noted previous to initiating corticosteroid dosing, continue daily finger stick and change FPG monitoring to twice weekly and adjust oral anti-glycemic regimen according to hyperglycemia management guidance as needed with corticosteroid dosing (per study protocol).
Grade 3 and intolerable Grade 2	• Hold BYL719/alpelisib 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 0.5-0.75mg/kg QD or equivalent 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 (recommend prednisone 0.5-0.75mg/kg QD or equivalent) until resolved and BYL719/alpelisib is restarted. • If hyperglycemia has been noted previous to initiating corticosteroid dosing, continue daily fingerstick and change FPG monitoring to twice weekly and adjust oral antiglycemic regimen according to hyperglycemia management guidance as needed with corticosteroid dosing (per study protocol). • 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/alpelisib (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 for a minimum of 28 days after rechallenge with BYL719/alpelisib.
Grade 4	Permanently discontinue BYL719/alpelisib 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/alpelisib should be permanently discontinued.)

**Topical corticosteroid preparation recommended regimens

- For face and/or intertriginous areas (including genitalia) recommend alclometasone 0.05% of hydrocortisone 2.5% creams
- For other body areas (i.e. trunk and extremities), recommend clobetasol or betamethasone 0.05% creams. Consider a spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation.

Management of pneumonitis

1. Document review of baseline CT to confirm no relevant pulmonary complications are present
2. 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). Specific questions should be asked regarding the occurrence of: cough, dyspnoea, shortness of breath, fatigue, and/or fever.
3. Patients who are suspected to have developed pneumonitis [as evidenced by CXR findings or symptoms present] should undergo further appropriate imaging (high resolution CT scan) and consider a broncho-alveolar lavage for biopsy. Early consultation with a pulmonologist is mandatory.
4. Patients with suspected pneumonitis should stop all study medications immediately. BLY719 must not be restarted in patients with a confirmed diagnosis of pneumonitis.
5. Infectious causes of interstitial lung disease should be ruled out.
6. Investigators should follow institutional practice for management of pneumonitis which generally include treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes have not been ruled out.
7. The study drugs should be permanently discontinued and the risk of the occurrence of pneumonitis with other agents should be considered.

Table 5: Dose Adjustment and Management Recommendations: Nab-Paclitaxel. The following guidelines should be considered for dose modifications for AEs that are suspected to be caused by Nab-Paclitaxel

Toxicity	Treatment Modification
ANC < 1,000/µl on Day 1,8,15 of a treatment cycle	Hold Nab-Paclitaxel until ANC ≥ 1,000µl. Repeat counts at least weekly. Resume when counts have recovered, according to the following guidelines: IF ANC recovers to ≥ 1,000/µl in ≤ 1 week, retreat at current dose. IF ANC recovers to ≥ 1,000/µl after 1-3 weeks, the dose should be reduced by 20% for subsequent cycles. IF ANC < 1,000/µl after the 3-week delay, remove subject from Nab-Paclitaxel treatment.
Platelets < 75,000/µl on Day 1, 8, 15 of a treatment cycle	Hold Nab-Paclitaxel until platelets are ≥ 75,000/µl. IF platelets recover to ≥ 75,000/µl in ≤ 1 week, retreat at the current dose. IF platelets recover to ≥ 75,000 /µl after 1-3 weeks, Nab-Paclitaxel should be given at 20% dose reduction for subsequent cycles. IF the platelet count fails to recover to ≥ 75,000/ µl within 3 weeks, remove the subject from Nab-Paclitaxel treatment but continue to follow the subject on study. (NOTE: See below for dose modifications for Grade 3-4 thrombocytopenia).
Febrile Neutropenia* Grade 3 Day 1, 8, 15 of a treatment cycle	At the discretion of the investigator, subsequent cycles may be given at either: 1) full doses, but with prophylactic ciprofloxacin 500 mg PO BID or an alternative prophylactic antibiotic regimen of the investigator's choice, or 2) a 20% dose reduction of Nab-Paclitaxel (either with or without prophylactic antibiotics). IF a second episode occurs, Nab-Paclitaxel will be reduced by 20% (based on the current dose) when chemotherapy is resumed in all subsequent cycles. IF a third episode occurs, remove the subject from Nab-Paclitaxel therapy and continue to follow the subject on study.
Grade 3-4 Thrombocytopenia Day 8, 15 of a treatment cycle	Appropriate supportive care will be instituted. The dose of Nab-Paclitaxel will be reduced by 20% (based on the current dose) for subsequent cycles.

*Febrile neutropenia is defined as: ANC < 1000/uL and a single temperature of > 38.3ºC (101ºF) or a sustained temperature of > 38ºC (100.4º F) for more than one hour..
1. There will be no dose modifications for lymphopenia.
2. There will be no dose modifications for Grade 2-4 anemia. Transfusions will be given as clinically indicated.

Other Toxicities	Treatment Modification
In cases of Grade 2 non-hematologic AE (except alopecia) that are persistent despite medical management.	Consider holding Nab-Paclitaxel until event resolves to Grade 1 or better, then re-introduce at a 20% reduced dose.
Other toxicities Grade 3	Hold therapy until recovery to ≤ Grade 1. At the discretion of the investigator, dose of Nab-Paclitaxel will either be resumed at full dose or reduced by 20%. If the Grade 3 toxicity occurred or recurred despite appropriate supportive measures, reduce the dose of Nab-Paclitaxel by 20% for subsequent cycles. If more than 3 weeks is required for recovery, remove the subject from the Nab-Paclitaxel portion of the protocol therapy, but continue to follow the subject on study.
Other toxicities Grade 4	Discontinue Nab-Paclitaxel treatment. (If the investigator wishes to continue therapy, treatment may continue with a 20% dose reduction and institution of appropriate supportive measures with the consent of the KUCC Principal Investigator). Subjects will continue to be followed on study.
Patients with dose limiting cardiac events such as MI or unstable angina or dose-limiting neurological events such as stroke > Grade 3 should not be retreated.	

4.6 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 those physician-prescribed medications, but also all over-the-counter medications, herbal medications, and nutritional or vitamin supplements. Subjects will be instructed to notify the study site about any new medications he/she takes after starting study drug. Subjects taking medicine chronically should be maintained on the same dose and schedule throughout the sample period, as medically feasible. The days of full PK 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 PK sampling if medically feasible.

Permitted Concomitant Therapy: In general, the use of any concomitant medication/therapies deemed necessary for the care of the subject is permitted, except as specifically prohibited in Section 4.6.2.

Anti-emetics

Use of anti-emetics is allowed. It is recommended that subjects use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for TdP and are prohibited (refer to Appendix B, Table 2)

Bisphosphonates and Denosumab

The use of bisphosphonates and denosumab regardless of indication is allowed provided subjects have been on stable doses for at least two weeks prior to study entry. Stable dose should be maintained during the treatment period. Subjects 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 subjects' source documentation.

Oral anti-diabetics

Subjects who develop diabetes mellitus during the study should be treated according to the ADA (American Diabetes Association) guidance. It is recommended to start treatment with glimepiride, glibenclamide, or metformin. Subjects receiving oral anti-diabetics 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/alpelisib was found to be a moderate reversible inhibitor of these enzymes.

4.6.1 Permitted Concomitant Therapy Requiring Caution and/or Action

Hematopoietic Growth Factors

Hematopoietic growth factors (e.g. erythropoietins, G-colony stimulating factor (G-CSF) and GM-CSF) are not to be used prophylactically in cycle one. Use of erythropoietins should be reserved to subjects with severe anemia as per the labeling of these agents or as dictated by local practice. Prophylactic use of G-CSF will be allowed after cycle one at the discretion of the treating physician.

Anticoagulants

Anticoagulants other than warfarin/coumarin derivates (for this, refer to Section 4.6.3) or anti-aggregation agents may be administered under the discretion of the investigator. However, caution is advised when BYL719/alpelisib is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4, CYP2C9 and CYP2C19. BYL719/alpelisib has the potential to inhibit these enzymes and may therefore decrease the metabolic activation and clinical efficacy of these pro-drugs. Subjects using anti-platelet/pro-drugs should be carefully monitored.

Contraceptives

Hormonal contraceptives may be affected by cytochrome P450 interactions and are therefore not considered effective for this study. For allowed contraceptive methods, refer to section 3.1.15. Highly effective contraception should be maintained throughout the study and for 90 days after study drug discontinuation.

CYP450 Substrates

In vitro studies demonstrate that BYL719/alpelisib may be a strong inhibitor of CYP3A4. BYL719/alpelisib may increase exposure to drugs metabolized by CYP3A4 by more than 5-fold. BYL719/alpelisib may also inhibit the metabolic clearance of co-medications metabolized by CYP2C8, CYP2C9, and CYP2C19, if sufficiently high BYL719/alpelisib 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 B, Table 1). Subjects receiving such medications must be carefully monitored for potential toxicity due to any individual concomitant medications. Particularly, caution is advised when BYL719/alpelisib is co-administered

with drugs that are sensitive substrates for CYP3A4, CYP2C8, CYP2C9 or CYP2C19 and which have a narrow therapeutic index. Caution is advised when BYL719/alpelisib is coadministered 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. Subjects receiving BYL719/alpelisib and opioid analgesics should be carefully monitored. Synthetic opioids with clinically relevant interactions with CYP3A4 inhibitors include, but are not limited to, propoxyphene, fentanyl, alfentanyl and sufentanil. Use of alfentanyl, a sensitive CYP3A4 substrate with narrow therapeutic window, should be fully avoided whenever possible. The use of methadone and levomethadyl is prohibited (refer to Appendix B, Table 2).

Drugs With a Conditional or Possible Risk to Induce Torsade de Pointes/QT Prolongation

If a subject enrolled in the study requires the concomitant use of any medication with a possible or conditional risk for TdP (see Appendix B, Table 3 for a list of such medications), then investigators, at their discretion, may co-administer such medications. Subjects receiving such medications must however be monitored. Note: please refer also to Appendix B, Table 3 for a list if prohibited QT prolonging medication.

Gastric Protection Agents

BYL719/alpelisib and buparlisib are characterized by a pH-dependent solubility. Medicinal products that alter the pH of the upper gastrointestinal tract may alter the solubility of BYL719/alpelisib and hence, its bioavailability. These agents include, but are not limited to, proton-pump inhibitors (PPI) (e.g. omeprazole, H2-antagonists (e.g. ranitidine) and antacids. Due to long PD effect of PPIs, i.e. long-lasting reduction of gastric acid production over 36 hours, H2-antagonists and antacids are recommended to be used over PPIs whenever possible. Note that some proton pump inhibitors may possibly also inhibit BCRP (refer to Appendix B, Table 4). BYL719/alpelisib 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.

BCPR Inhibitors

BYL719/alpelisib was identified as a substrate for human BCRP. Coadministration of BYL719/alpelisib with BCRP inhibitors may possibly increase systemic exposure and/or alter tissue uptake of oral BYL719/alpelisib. The treatment with BCRP inhibitors should be kept as short as possible or if possible, fully avoided. See Appendix B, Table 4 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 subjects 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 PD, subjects should discontinue treatment. No dose modification of study treatment is needed during radiotherapy.

4.6.2 Prohibited Concomitant Therapy

Other Investigational and Antineoplastic Therapies

Other investigational therapies must not be used while the subject is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy and surgery) other than the study treatments must not be given to subjects while the subject is on the study medication. If such agents are required for a subject, then the subject must be discontinued from the study.

Drugs With a Known Risk for Torsades de Pointes/QT Prolongation

If a subject enrolled in the study requires the concomitant use of any medication included in Appendix B, Table 2, 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/alpelisib administration must be interrupted as long as the subject requires therapy with the QT prolonging agent. Note that Appendix B, Table 2 also prohibits drugs that are substrates for CYP3A and CYP2C with a possible or conditional risk for TdP. If the subject requires long-term therapy with such a QT prolonging agent, leading to study treatment interruption of > 21 days, the subject must be permanently discontinued from BYL719/alpelisib.

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. Subjects should stop using these herbal medications 7 days prior to first dose of study drug.

Warfarin and Coumarin Derivatives

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

4.7 Duration of Therapy

Subjects will be treated for 6 cycles, a complete treatment cycle being defined as 28 days during which BYL719/alpelisib is taken daily on days 1-28 and Nab-Paclitaxel is administered on days 1, 8, and 15 +/- 1 day. In subjects with stable disease/PR/CR after 6 cycles of treatment, subjects can either continue both study drugs until disease progression/unacceptable toxicity or, Nab-Paclitaxel can be stopped (at the discretion of the treating physician) but subjects will continue BYL719/alpelisib until disease progression/unacceptable toxicity.

Treatment may be stopped at any time during the schedule if any of the following occur:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Death
- Subject decision to withdraw from the study, **OR**
- General or specific changes in the subject's condition which render the subject unacceptable for further treatment in the judgment of the investigator

4.8 Duration of Follow-Up

Subjects will be followed for 30 days after removal from treatment or until death, whichever occurs first. A follow-up visit will be scheduled 30 (+/-) days post-end of treatment. Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.9 Removal of Subjects From Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.4 apply. Notification will be sent to the Principal Investigator and documentation of the reason for study removal and the date the subject was removed will be reported in the Case Report Form within 5 days of removal. The subject should be followed per protocol. Subjects who are removed from protocol therapy due to disease progression or toxicity will be counted as a treatment failure in the efficacy analysis.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline and All Study Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining Informed Consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before Informed Consent was obtained.

All lab screening procedures must be performed within 14 days prior to registration unless otherwise stated. All other screening procedures must take place within 30 days. The screening procedures include:

5.1.1 Informed Consent

5.1.2 Medical history

Complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

5.1.3 Demographics

Demographic profile will include date of birth, gender, race, ethnicity and zip code.

5.1.4 Review subject eligibility criteria

Review of eligibility criteria as described in Section 3.0 to ensure subject qualification for study entry.

5.1.5 Review previous and concomitant medications

All prior medication taken by the subject within 30 days before starting the study is to be recorded. At minimum, the start year of the medication should also be recorded. Concomitant medications taken by the subject during the study are to be recorded up until 30 days after last study dose. If a reportable adverse event (see Section 6.0) occurs within 30 days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.

5.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight, and assessment of all major body systems

5.1.7 Performance status

Subject performance status based on ECOG criteria (Zubrod scale) will be evaluated prior to study entry and possibly during study. Specific criteria for assessing performance status can be found in Appendix A.

5.1.8 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 6.0 for Adverse Event monitoring and reporting.

5.1.9 Hematology

Hematology to include hemoglobin (Hgb), platelets, red blood cells, white blood cells and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)

5.1.10 Serum chemistries

Serum chemistry to include: albumin, alkaline phosphatase, ALT, AST, GGT, bicarbonate, calcium, chloride, creatinine, potassium, sodium, calcium, magnesium, total bilirubin (direct must be collected only in case total bilirubin is elevated > IULN, total protein, BUN or urea.

5.1.11 Fasting Plasma Glucose (FPG)

FPG will be assessed at screening and on days 8, 15, 22 for cycle 1 and 2, then day 1 for each subsequent cycle and at EOT. Subjects must be fasting overnight for at least 8 hours prior to the blood draw. The study personnel will ask the subject whether he or she has been fasting, which will be recorded in the eCRF.

NOTE: Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.

5.1.12 Hemoglobin A1C

Hemoglobin A1C will be measured at screening, then on day 1 of every three cycles starting on Day 1 Cycle 3 and then again at the end of treatment

5.1.13 Coagulation

International normalized INR will be measured at screening and then as clinically indicated

5.1.14 C-Peptide

C-Peptide will be measured on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, and then again at the end of treatment

5.1.15 Insulin (IRI)

Insulin (IRI) will be measured on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, and then again at the end of treatment

5.1.16 Blood draw for correlative studies

See Section 8.1.1 for details.

5.1.17 Pregnancy test (for women of child bearing potential)

See Section 3.1.15 for definition.

5.1.18 ECG

Must be performed D-30 to D-1, D1 for cycles 2 – 6 and at end of treatment only.

5.1.19 MUGA/ECHO

Subjects must have a Left Ventricular Ejection Fraction (LVEF) of > 50% as determined by MUGA scan or ECHO.

5.1.20 Ophthalmologic Evaluation

A slit lamp exam must be performed at screening for all subjects and then as clinically indicated.

5.2 Procedures During Treatment

5.2.1 Screening/Enrollment

No more than 30 days prior to treatment start date:

- Signing of Informed Consent Form
- Medical History/Current Medical Conditions
- Demographics
- Inclusion/Exclusion Criteria Screening
- Concomitant Medications
- Physical Exam
- Performance Status
- Pregnancy Test
- ECHO
- ECG
- Tumor assessment by RECIST v1.1 criteria
- Ophthalmologic examination including a slit lamp examination

No more than 14 days prior to treatment start date:

- Hematology and Chemistry Labs
- Fasting Plasma Glucose
- Hemoglobin A1C
- Coagulation Status (INR)
- Pregnancy Test

Note: For Cycle 1, all labs, procedures and exams from screening (as long as done within the specific time frame) are sufficient, with the exception of the physical exam, hematology/chemistry labs which must be done with 7 days of Day 1 Cycle 1. When subject starts subsequent cycles, labs, procedures and exams must be done at the start of the cycle +/- 3 days. A window of + / - 3 days for protocol requirements on Days 8, 15, and 22 (if applicable, is allowed if needed).

5.2.2 Day 1, Cycle 1

- BYL719/alpelisib Dispensing
- BYL719/alpelisib Dosing
- Nab-Paclitaxel Administration
- PK Sampling (only for Phase I subjects)
- Study Labs (C-peptide and insulin)

NOTE: ECG done during screening will be used for Cycle 1.

5.2.3 Days 2-7, Cycle 1

- BYL Dosing

5.2.4 Day 8, Cycle 1

- Hematology and Chemistry Labs
- Fasting Plasma Glucose (Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.)
- BYL719/alpelisib Dosing
- Nab-Paclitaxel Administration
- Study Drug Compliance

NOTE: Laboratory assessments scheduled AFTER Cycle 1 Day 1 may be performed up to 24 hours BEFORE each visit, in order to facilitate subject fasting + eating breakfast at home before BYL dosing.

5.2.5 Days 9-14, Cycle 1

- BYL719/alpelisib Dosing

5.2.6 Day 15, Cycle 1

- Hematology and Chemistry Labs
- Fasting Plasma Glucose (Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.)
- BYL719/alpelisib Dosing
- Nab-Paclitaxel Administration
- Study Drug Compliance

5.2.7 Days 16-21, Cycle 1

- BYL719/alpelisib Dosing

5.2.8 Day 22, Cycle 1

- Hematology and Chemistry Labs
- Fasting Plasma Glucose (Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.)
- BYL719/alpelisib Dosing
- Study Drug Compliance

5.2.9 Days 23-28, Cycle 1

- BYL719/alpelisib Dosing

5.2.10 Repeat Cycle 1 for a total of 6 cycles, after which Nab-Paclitaxel may be stopped, but BYL719/alpelisib will continue until disease progression/unacceptable toxicity. (**NOTE: Please refer to Schedule of Events/footnotes for exceptions.)**

5.2.11 Safety follow-up phone call 30 days after treatment termination

5.2.12 Survival follow-up by phone, e-mail, etc. every 3 months for 36 months.

5.3 Schedule of Events

	Screening/Enrollment		Cycle 1 and 2 (28 days each)							
	D-30 to D1	D-14 to D1	D1	D2-D7	D8	D9-D14	D15	D16-D21	D22	D23-D28
Informed Consent	X									
Medical History/Current Medical Conditions	X									
Demographics	X									
Inclusion/Exclusion	X									
Concomitant Medications	X		Ongoing							
Physical Exam	X		X							
Performance Status	X		X							
Hematology[m]		X	X[g]		X		X		X	
Chemistry[m]		X	X[g]		X		X		X	
Fasting Plasma Glucose[m]		X	X		X		X		X	
Hemoglobin A1C[m]		X[c]								
Coagulation (INR) [m]		X[f]								
C-Peptide[n,m]			X[n]							
Insulin (IRI)[n,m]			X[n]							
Pregnancy Test		X[h]								
Correlative Blood Draw		X	X[j]							
Archived Tissue Collection	X[i]		X[i]							
PK Samples			X[k]							
MUGA/ECHO	X									
ECG	X[l]		X[l]							
Ophthalmologic Evolution	X									
BYL719/alpelisib Dispensing			X[d]							
BYL719/alpelisib Dosing			X	X	X	X	X	X	X	X
Abraxane Administration			X		X		X			
Subject Drug Compliance			X		X		X		X	
Tumor Assessment	X		X[e]							
Adverse Events			Ongoing							

	Cycle 3 – 6[a] (28 days each)								Cycle 7+	EOT	Safety FU	Survival FU
	D1	D2 to D7	D8	D9-D14	D15	D16-D21	D22	D23-D28	D1		30 days post-EOT	Every 3 mos for 36 months
Concomitant Medications	Ongoing											
Physical Exam	X											
Performance Status	X											
Hematology [m]	X		X		X				X	X		
Chemistry[m]	X								X	X		
Fasting Plasma Glucose[m]	X								X	X		
Hemoglobin A1C[m]	X[c]									X		
C-Peptide	X[n]									X[n]		
Insulin (IRI)	X[n]									X[n]		
Pregnancy Test	X											
ECG	X[l]									X[l]		
Correlative Blood Draw [m]	X[j]								X	X[j]		
BYL719/alpelisib Dispensing	X[d]								X			
BYL719/alpelisib Dosing	X	X	X	X	X	X	X	X	X			
Abraxane Administration	X		X		X				X[b]			
Subject Drug Compliance	X		X		X		X		X			
Tumor Assessment	X[e]								X[e]	X		
Adverse Events	Ongoing											
Safety Follow-Up via Phone Call											X	
Survival Follow-Up via Phone Call												X

Calendar Legend

a) Study treatment will continue for a minimum of 6 cycles in subjects with stable disease/PR/CR.

b) After 6 cycles, Nab-Paclitaxel treatment can end, but BYL719/alpelisib will be continued until disease progression/unacceptable toxicity. If subject continues on both Nab-Paclitaxel and BYL719/alpelisib, the hematology, chemistry and FPG monitoring for 7+ cycles will be similar to Cycles 3-6.

c) After measurement at screening, Hemoglobin A1C will be measured every third cycle, starting Day 1 Cycle 3 and then again at end of treatment.

d) BYL719/alpelisib will be dispersed for each cycle on Day 1.

e) Tumor assessment per RECIST v1.1 after every even # cycle. See section 9 for details. **NOTE:** For subjects who are on metformin and have been asked to hold metformin for full body scans, the treating physician may withhold the study drug (BYL719/alpelisib) on the days that metformin is withheld.

f) International normalized INR will be measured at screening and then on Day 1 of each treatment cycle as clinically indicated.

g) These assessments are done in screening for Cycle 1, but should be performed on Day 1 Cycle 2.

h) All female subjects of child bearing potential must undergo a serum pregnancy test at screening. Women of child-bearing potential must additionally undergo a urine or serum pregnancy test on Day 1 of each cycle.

i) Archived tumor block/20 unstained slides either from the primary or metastatic site will be collected. Subject can start study treatment even if the tumor tissue has not been collected.

j) Blood samples will be collected at time of enrollment, prior to each treatment cycle starting from Cycle 2 and at the time of disease progression; see section 8.1.1 for further details.

k) Only for Cycle 1 Day 1 for subjects in phase I portion of the study. See section 8.2.

l) Occurs during Day -30 to 1 and then on Day 1 of cycles 2, 3, 4, 5, 6, and at end of treatment only.
NOTE: ECG done during screening will be used for Cycle 1.

m) All laboratory assessments scheduled AFTER Cycle 1 Day 1 may be performed up to 24 hours BEFORE each visit, in order to facilitate subject fasting + eating breakfast at home before BYL dosing. **NOTE:** Fasting whole blood glucose testing is acceptable if fasting plasma glucose is not feasible.

n) C-Peptide and Insulin (IRI) will be measured on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, and then again at the end of treatment.

5.4 Removal of Subjects from Study Treatment and Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.4.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.4.2 Subject withdraws consent (termination of treatment and follow-up);

5.4.3 Subject is unable to comply with protocol requirements;

5.4.4 Subject demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.4.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.4.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.4.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event; see Section 6.0);

5.4.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.4.9 Lost to follow-up.

If a research subject cannot be located to document survival after 3 attempts by mail and/or telephone, the subject may be considered "lost to follow-up" All attempts to contact the subject must be documented.

6.0 ADVERSE EVENTS

Text below in italics is verbatim from "Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies", issued December 2012 by U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. The guidance may be retrieved from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf?source=govdelivery.

6.1 Definitions

6.1.1 Adverse Event [21 CFR 312.32(a)]

An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

This study will use the descriptions and grading scales from Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.03) for hematologic and non-hematologic toxicities. Detailed information may be found on the Cancer Therapy Evaluation Program (CTEP) website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Information for adverse events, whether reported by the subject, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the CRF as described in the following sections.

Adverse events experienced by subjects will be collected and reported from administration of the first dose of protocol therapy, throughout the study, and within 30 days of the last dose of protocol therapy. Subjects who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the principal investigator. Study subjects should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

Medical conditions/diseases, or cancer related symptoms present before starting study treatment are considered adverse events only if they worsen after initial screening. Adverse clinical events occurring before starting study drug but after signing the Informed Consent form are to be recorded on the Medical History/Current Medical Conditions CRF. All cancer-related symptoms that have occurred in the last 30 days prior to start of study drug must also be recorded on this CRF.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy. In this case they will be recorded on the Adverse Events CRF, along with the associated signs, symptoms or diagnosis. As far as possible, each adverse event will also be described by:

- its duration (start and end dates),
- grading of severity,
- its relationship to the study drug,
- the action(s) taken,
- outcome.

6.1.2 Suspected Adverse Reaction [21 CFR 312.32(a)]

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subject's response after study drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Unrelated - The AE is clearly **NOT** related to the study treatment.
- Unlikely - The AE is **doubtfully related** to the study treatment.
- Possible - The AE **may be related** to the study treatment.
- Probable - The AE is **likely related** to the study treatment.
- Definite - The AE is **clearly related** to the study treatment.

6.1.3 Unexpected [21 CFR 312.32(a)]

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application… "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the Particular drug under investigation.

This definition relies entirely on a listing of the adverse events or suspected adverse reactions in the investigator brochure…as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is unexpected. This means that events not listed for the Particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for safety reporting purposes.

6.1.4 Serious [21 CFR 312.32(a)]

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.5 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

6.2 Reporting Requirements for Adverse Events

6.2.1 Submitting Serious Adverse Events Reports to IRB

For serious adverse events, the clinical research site will follow local IRB policies and procedures.

6.2.2 Study Investigator Notification of Adverse Events

All **expected** and **unexpected** serious adverse events occurring after the subject has signed the Informed Consent and has started protocol treatment must be reported to the study principal investigator within 24 hours of becoming aware of the event:

Priyanka Sharma, M.D.
[redacted]

6.2.3 DSMC Notification of SAEs

All **expected** and **unexpected** serious adverse events occurring after the subject has signed the Informed Consent and has started protocol treatment must be reported by phone or email to the KUCC DSMC within 24 hours of becoming aware of the event to:

KUCC DSMC

[redacted]

A follow-up written report in the form of a MEDWATCH Form FDA 3500A is required within 5 days.

6.2.4 Reporting to Novartis:

[redacted]

6.2.5 Pregnancies

[redacted]

6.2.6 Submitting IND Safety Reports to FDA

The investigator-sponsor must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction
- Serious
- Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The following reports require expedited reporting.

- unexpected fatal or life-threatening adverse experiences associated with the use of the drug are to be reported by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- any adverse experience associated with the use of the drug that is both serious and unexpected is to be reported in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]

6.2.7 Recording Adverse Events and Documentation in VELOS

All **expected** and **unexpected** adverse events and serious adverse events occurring after the patient has signed the Informed Consent and has started protocol treatment must be fully recorded in the subject's case record form.

All AEs and SAEs regardless of causality must be entered in the KU implementation of eVELOS, called the Comprehensive Research Information System (CRIS). All SAEs regardless of causality must be entered into CRIS within 24 hours. Unexpected and expected adverse events must be entered within 5 days and include: new unexpected adverse events; worsening baseline conditions; clinically significant laboratory findings; disease-related signs and symptoms that were not present at baseline, and any event of findings that the Investigator feels is clinically significant.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

6.2.8 Reporting of Unexpected, Related SAEs for Concomitant Medications

For concomitant medications, all unexpected, related serious adverse experiences will be forwarded to the product manufacturer by the investigator using the Voluntary MEDWATCH Form FDA 3500.

6.2.9 Summary of Expedited Serious Adverse Event Reporting

	Relationship to Study Drug	**KUCC DSMC & Novartis**	**IRB**	**PI**	**VELOS**
Unexpected SAE	Related	24 hrs	Follow local IRB reporting requirements	24 hrs	24 hrs
Unexpected SAE	Not-related	24 hrs		24 hrs	24 hrs
Expected SAE	Related	24 hrs		24 hrs	24 hrs
Expected SAE	Not-related	24 hrs		24 hrs	24 hrs

7.0 DRUG INFORMATION

7.1 BYL719/Alpelisib

Please refer to the current Investigator's Brochure for more comprehensive information.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.2 Nab-Paclitaxel

7.2.1 Description

Nab-Paclitaxel is a novel biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intratumoral concentration of the drug by a receptor-

mediated transport process allowing transcytosis across the endothelial cell wall, thereby breaching the blood/tumor interface. This albumin-specific receptor-mediated process involves the binding of a specific receptor (gp60) on the endothelial cell wall, resulting in activation of a protein caveolin-1, which initiates an opening in the endothelial wall with formation of little caves or caveolae, with transport of the albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium. A protein specifically secreted by the tumor (SPARC) binds and entraps the albumin, allowing release of the hydrophobic drug to the tumor cell membrane. Nab-Paclitaxel is the first biologically interactive nanoparticle leveraging this gp-60/caveolin-1/SPARC pathway to increase intratumoral concentration of the drug and reducing toxic drug in normal tissue. Nab-Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for interphase and mitotic cellular function.

7.2.2 Drug Interactions

The metabolism of Nab-Paclitaxel is catalyzed by CYP2C8 and CYP3A4. Thus, Nab-Paclitaxel metabolism may be modified by drugs that induce, inhibit or are metabolized by cytochromes P2C8 and P3A4

7.2.3 Toxicity/Side Effects

- Neutropenia is the dose-limiting hematologic toxicity
- During organogenesis, Nab-Paclitaxel is embryotoxic and fetotoxic
- Hypersensitivity reactions are rare, but can occur
- Neurotoxicity (parasthesias, dysthesias, pain)
- Thrombocytopenia and anemia
- Infections and febrile neutropenia
- Bradycardia and hypotension
- Abnormal ECG changes
- Nausea/Vomiting/Diarrhea
- Mucositis
- Alopecia
- Transaminase or bilirubin elevation
- Arthralgias/myalgias

7.3 Drug Accountability/Subject Compliance

Records of study medications used, dosages administered, and intervals between visits will be kept during the study. Subjects will be asked to fill out a pill diary and bring with them for review after each cycle of study treatment. Drug accountability will be noted at the completion of the trial. Subjects will be asked to return all unused medication at the end of the study. Drug compliance will be calculated based on documentation of study drug dispensed vs. study drug returned.

7.4 Return and Retention of Study Drug

[redacted]

8.0 CORRELATIVES/SPECIAL STUDIES

[redacted]

8.2 Pharmacokinetic Sampling and Analysis

Samples for PK will be obtained through an intravenous line (IV line/port used for delivery of chemotherapy can be used for PK samples after adequate flushing) on Day 1 Cycle 1 only for subjects participating in the Phase I portion of the study. Blood samples will be collected in K3EDTA heparin tubes. A baseline blood sample will be obtained prior to BYL719/alpelisib and Nab-Paclitaxel administration. Oral dosing with BYL719/alpelisib will occur one hour prior to the start of Nab-Paclitaxel administration. Subjects will receive 100 mg/m2 Nab-Paclitaxel as a 30 minute infusion. Blood samples

for bioanalysis for both Nab-Paclitaxel and BYL719/alpelisib will be obtained at the end of infusion, at 30 minutes and at 1, 1.5, 2, 4, and 6 hours after the end of infusion.

Window for PK draw times will be as follows:

- +/- 5 min windows for the 0.5 and 1 hour draws
- +/- 10 min for 1.5 – 4 hour draws
- +/- 20 for the 6 hour draws

Plasma preparation of Samples will be processed according to the KU Cancer Center Correlative Laboratory Standard Operating Procedures (See Appendix C).

[redacted]

9.0 MEASUREMENT OF EFFECT

9.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) committee[34]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

9.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study drug.

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

9.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray, PET scan) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

The following radiologic and clinical assessments will be performed

- Chest, abdomen and pelvic CT at screening and at each subsequent tumor assessment. The preferred radiologic technique is CT with intravenous (IV). If a subject is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- A full body scan at screening for bone lesions according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI or positron emission tomography (PET)). If such a scan was already done during the regular work up of the subject within 6 weeks prior to the start of treatment, this scan can be considered as the screening scan for this study. After screening, scans need not be repeated, unless clinically indicated. If indicated, the same methodology as at screening should be used.

- If brain metastases are suspected, brain CT or MRI scan at screening. Brain CT or MRI will be continued at subsequent tumor assessments if brain lesions are identified at screening.

Clinical assessment of any existing superficial lesions (skin nodules and palpable lymph nodes) at screening and at each subsequent tumor assessment. CT or MRI of any other lesion not captured by any of the above listed images (e.g. neck) at screening and at each subsequent tumor assessment as clinically indicated.

9.2 Response Criteria

9.2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

9.2.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

9.2.3 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Note: If subjects respond to treatment and are able to have their disease resected, the subject's response will be assessed prior to the surgery.

9.3 Duration of Response

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

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

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

9.3.1 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment until objective tumor progression or death. Subjects who do not experience objective tumor progression or death during the evaluation period, or are lost to follow-up, will be censored on the date they were last known to be alive and without objective tumor progression.

9.3.2 Time to Progression

Time to progression is defined as the duration of time from start of treatment until objective tumor progression. Subjects who do not experience objective tumor

progression during the evaluation period will be censored on the date of death, lost to follow-up, or were last known to be without objective tumor progression.

9.3.3 Overall Survival

Overall survival is defined as the duration of time from start of treatment to death. Subjects who do not experience death during the evaluation period, or are lost to follow-up, will be censored on the date they were last known to be alive.

9.3.4 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events. Interim assessments for safety and associated early stopping criteria are detailed below.

10.0 DATA AND SAFETY MONITORING

10.1 Oversight and Monitoring Plan

The DSMC of the KUCC is responsible for monitoring subject safety for this trial. The DSMC is responsible for:

- Review of all clinical trials conducted by the KUCC for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Submission of recommendations for corrective action to the PI and the Deputy Director of the KUCC or designee
- Notification of external sites participating in multi-institution clinical trials coordinated by the KUCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications.

10.2 Review and Oversight Requirements

a) Serious Adverse Event
Serious adverse events that require expedited reporting will be reviewed by the DSMC Chair or designee who will determine if immediate action is required. If determined to be necessary by the DSMC, all participating sites will be notified of the event and of any resulting action within one working day of this determination.

b) Review of Adverse Event Rates
Once per month, adverse event rates will be monitored by the DSMC Coordinator. If any study has had 2 or more of the same SAE reported within one month, or more than 6 of the same SAE in 6 months, the DSMC will review summaries of SAEs, and discuss events in detail with the PI. The DSMC chair or designee determines whether further action is required. The DSMC Coordinator ensures that collaborating investigators and IRBs for all participating sites are notified of any resulting action.

c) Study Safety and Progress – Semi-Annual Review
An overall assessment of toxicities as described in the protocol is reviewed at quarterly DSMC meetings, but due to the expected slow accrual rate of this study, it is appropriate to review it on a semi-annual basis. This review enables DSMC members to assess whether significant risks are occurring that would warrant study suspension/closure or protocol amendment.

[redacted]

11.0 REGULATORY CONSIDERATIONS

11.1 Protocol Review and Amendments

This protocol, the proposed Informed Consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators. All decisions of the IRB concerning the conduct of the study must be made in writing.

11.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

11.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

1. ICH Consolidated Good Clinical Practice: Guidelines (E6)
   www.fda.gov/cder/guidance/iche6.htm

2. US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
   - Title 21 Part 11 – Electronic Records; Electronic Signatures
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
   - Title 21 Part 50 – Protection of Human Patients
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

3. State laws
4. Institutional research policies and procedures [redacted]

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

12.0 REGISTRATION PROCEDURES

12.1 General Guidelines for KUCC AND Other Participating Organizations

[redacted]

12.2 Registration Process for KUCC and Other Participating Centers

[redacted]

[redacted]

13.0 STUDY MANAGEMENT

13.1 Investigator Files and Retention of Documents

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, subject diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.2 Case Report Forms

Case report forms (CRFs) will be completed for each subject enrolled in a timely fashion to ensure accurate interim analyses. All CRFs will be complete and accurate. The medical chart and any other clinical worksheets, procedural reports, etc. are the source of verification of the data captured into the study database.

13.3 Study Monitoring

The study will be monitored at appropriate intervals to assure compliance to GCP and to assess the data quality and study integrity. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The Study Monitoring plan will describe monitoring activities to be conducted.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data.

We will employ the following Bayesian sequential monitoring rule for toxicity in the Phase II: We will stop the study if P(toxicity > 33% I data from the trial) > 0.95. That is, given the outcomes from the subjects who have already been evaluated, if we determine that there is more than a 95% chance that the toxicity/DLT rate is more than 33%, we will stop enrollment.

This decision rule gives the following stopping rule. We assume a uniform prior distribution for the toxicity rate. Stop the study if: [# of subjects with toxicity / # subjects evaluated] ≥4/6, 5/7, 6/9, 7/11, 8/13, 9/16, 10/18, 11/20, 12/23, 13/25, 14/28, 15/30.

The operating characteristics of this study design are shown in the following table:

Operating Characteristics of Safety Monitoring Rule – Maximum 33 Subjects				
Rate of Toxicity	Probability of Stopping	Sample Size		
0.10	0.002	33	33	33
0.20	0.025	33	33	33
0.30	0.143	33	33	33
0.40	0.456	10	33	33
0.50	0.810	6	12	27
0.60	0.972	6	6	12

Once we have completed the study, we will estimate the toxicity rate with a 90% credible interval (Thall, et al, 1995).

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design/Sample Size and Accrual

We will employ the 3+3 design to find the MTD of BYL719/alpelisib when given in combination with Nab-Paclitaxel. We will enroll a maximum of 18 subjects in cohorts of size 3 in each subject group. We will start by enrolling 3 subjects at the dose level 1 from the table below. After 3 subjects have been accrued to a dose level, that dose level will be closed to accrual until safety assessment of all the 3 patients is performed at the end of Cycle 1. If the dose level is well tolerated during these 4 weeks, then dose escalation will be performed at the next cohort.

Dose Level	BYL719/alpelisib	Nab-Paclitaxel
-1	200 mg	100 mg/m^2
1	250 mg	100 mg/m^2
2	300 mg	100 mg/m^2
3	350 mg	100 mg/m^2

We will then follow the algorithm described below:

- Enroll 3 subjects at the next highest dose until at least 1 subject experiences a DLT
- If 1 of 3 subjects experiences a DLT, then enroll a second cohort of 3 subjects at the current dose
- If only 1 of 6 subjects experience a DLT, then enroll 3 subjects at the next highest dose
- If 2 or more of 6 subjects experience a DLT at the current dose level, then the MTD has been determined and escalation will stop.
- Once the MTD has been determined, treat another 3 subjects at the previous dose level if there were only 3 subjects treated at that dose level
- The MTD is the highest dose level at which 6 subjects were treated and at most 2 subjects experienced a DLT. Recommended phase 2 dose (RPTD) will be the previous dose at which $\leq$ 1/6 subjects experienced a DLT.

- We do not plan to go beyond the 350 mg dose even if it is not the MTD

- The -1 dose level of 200 mg is to be used in the event that the 250 mg dose is not tolerated. Based on the availability of further data from ongoing studies with BYL719/alpelisib the dosing schedule at each dose level may be modified in the future (five days on, two days off every 7 days)

Since there are only three doses to be considered, and since we will have only a maximum of 6 subjects at each MTD, the maximum number of subjects enrolled in the phase I portion of the trial will be 18.

Once the MTD has been determined, we will evaluate the PK/PD data and the AE data at each of the three dose levels and determine the recommended phase II dose (RPTD). The RP2D is defined as the next lower dose level below MTD (dose at which $\leq$ 1/6 subjects experienced a DLT). The Phase II portion of the study follows a Simon's two stage Minimax design to detect an improvement in ORR from 20% to 40% (alpha 0.05 and power of 0.8). In the first stage, 18 subjects treated at the RPTD will be assessed with the study proceeding to the second stage if there are at least 5 responses. Enrollment into the second stage will not start until at least 5 responses in the first stage have been observed. In the second stage, an additional 15 subjects will be enrolled. If 11 or more subjects have an objective response among all 33 eligible subjects, the regimen would be considered promising. Assuming 10% of subjects are non-evaluable/ineligible, up to 36 subjects may be accrued at the RPTD.

14.2 Data Analyses Plans

Subject demographics and clinical characteristics will be summarized and reported for each dose level in the Phase I. Adverse events will be summarized and presented for each dose level in the Phase I. All analyses used to determine the RPTD will be reported.

Subject demographics and clinical characteristics will be summarized and reported for subjects enrolled in the Phase II portion of the study. ORR will be reported for both stages of the Simon's two-stage design.

At the conclusion of the study, the objective response, complete response, partial response, and stable disease rates will be estimated and 95% confidence intervals will be calculated. Progression free survival (PFS) and overall survival (OS) time in days will be assessed using Kaplan-Meier. Median PFS and OS times will be estimated.

15.0 REFERENCES

1. 2013, C.F.a.F.
2. Early Breast Cancer Trialists' Collaborative, G., *Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials.* Lancet, 2005. **365**(9472): p. 1687-717.
3. Miller, K., et al., *Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.* N Engl J Med, 2007. **357**(26): p. 2666-76.
4. Cortes, J., et al., *Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study.* Lancet, 2011. **377**(9769): p. 914-23.
5. West, K.A., S.S. Castillo, and P.A. Dennis, *Activation of the PI3K/Akt pathway and chemotherapeutic resistance.* Drug Resist Updat, 2002. **5**(6): p. 234-48.
6. Katso, R., et al., *Cellular function of phosphoinositide 3-kinases: implications for development, homeostasis, and cancer.* Annu Rev Cell Dev Biol, 2001. **17**: p. 615-75.
7. Liu, P., et al., *Targeting the phosphoinositide 3-kinase pathway in cancer.* Nat Rev Drug Discov, 2009. **8**(8): p. 627-44.
8. McCubrey, J.A., et al., *Roles of the RAF/MEK/ERK and PI3K/PTEN/AKT pathways in malignant transformation and drug resistance.* Adv Enzyme Regul, 2006. **46**: p. 249-79.
9. Samuels, Y. and V.E. Velculescu, *Oncogenic mutations of PIK3CA in human cancers.* Cell Cycle, 2004. **3**(10): p. 1221-4.
10. Hennessy, B.T., et al., *Exploiting the PI3K/AKT pathway for cancer drug discovery.* Nat Rev Drug Discov, 2005. **4**(12): p. 988-1004.
11. Markman, B., et al., *Status of PI3K inhibition and biomarker development in cancer therapeutics.* Ann Oncol, 2010. **21**(4): p. 683-91.
12. Wong, K.K., J.A. Engelman, and L.C. Cantley, *Targeting the PI3K signaling pathway in cancer.* Curr Opin Genet Dev, 2010. **20**(1): p. 87-90.
13. Yuan, T.L. and L.C. Cantley, *PI3K pathway alterations in cancer: variations on a theme.* Oncogene, 2008. **27**(41): p. 5497-510.
14. Sansal, I. and W.R. Sellers, *The biology and clinical relevance of the PTEN tumor suppressor pathway.* J Clin Oncol, 2004. **22**(14): p. 2954-63.
15. Shayesteh, L., et al., *PIK3CA is implicated as an oncogene in ovarian cancer.* Nat Genet, 1999. **21**(1): p. 99-102.
16. Kalinsky, K., et al., *PIK3CA mutation associates with improved outcome in breast cancer.* Clin Cancer Res, 2009. **15**(16): p. 5049-59.
17. Stemke-Hale, K., et al., *An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer.* Cancer Res, 2008. **68**(15): p. 6084-91.
18. Depowski, P.L., S.I. Rosenthal, and J.S. Ross, *Loss of expression of the PTEN gene protein product is associated with poor outcome in breast cancer.* Mod Pathol, 2001. **14**(7): p. 672-6.
19. Perez-Tenorio, G., et al., *PIK3CA mutations and PTEN loss correlate with similar prognostic factors and are not mutually exclusive in breast cancer.* Clin Cancer Res, 2007. **13**(12): p. 3577-84.
20. Umemura, S., et al., *Increased phosphorylation of Akt in triple-negative breast cancers.* Cancer Sci, 2007. **98**(12): p. 1889-92.
21. Marty, B., et al., *Frequent PTEN genomic alterations and activated phosphatidylinositol 3-kinase pathway in basal-like breast cancer cells.* Breast Cancer Res, 2008. **10**(6): p. R101.
22. Moulder, S.L., *Does the PI3K pathway play a role in basal breast cancer?* Clin Breast Cancer, 2010. **10 Suppl 3**: p. S66-71.

23. Balko, J.M., et al., *Profiling of residual breast cancers after neoadjuvant chemotherapy identifies DUSP4 deficiency as a mechanism of drug resistance.* Nat Med, 2012. **18**(7): p. 1052-9.
24. O'Brien, N.A., et al., *Activated phosphoinositide 3-kinase/AKT signaling confers resistance to trastuzumab but not lapatinib.* Mol Cancer Ther, 2010. **9**(6): p. 1489-502.
25. Ibrahim, Y.H., et al., *PI3K inhibition impairs BRCA1/2 expression and sensitizes BRCA-proficient triple-negative breast cancer to PARP inhibition.* Cancer Discov, 2012. **2**(11): p. 1036-47.
26. Hahne, J.C., et al., *Anti-tumour activity of phosphoinositide-3-kinase antagonist AEZS 126 in models of triple-negative breast cancer.* J Cancer Res Clin Oncol, 2013. **139**(6): p. 905-14.
27. O'Brien, C., et al., *Predictive biomarkers of sensitivity to the phosphatidylinositol 3' kinase inhibitor GDC-0941 in breast cancer preclinical models.* Clin Cancer Res, 2010. **16**(14): p. 3670-83.
28. Moestue, S.A., et al., *Metabolic biomarkers for response to PI3K inhibition in basal-like breast cancer.* Breast Cancer Res, 2013. **15**(1): p. R16.
29. Gradishar, W.J., et al., *Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.* J Clin Oncol, 2005. **23**(31): p. 7794-803.
30. Gradishar, W.J., et al., *Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer.* J Clin Oncol, 2009. **27**(22): p. 3611-9.
31. Gradishar, W.J., *Albumin-bound paclitaxel: a next-generation taxane.* Expert Opin Pharmacother, 2006. **7**(8): p. 1041-53.
32. Hu, L., et al., *Inhibition of phosphatidylinositol 3'-kinase increases efficacy of paclitaxel in in vitro and in vivo ovarian cancer models.* Cancer Res, 2002. **62**(4): p. 1087-92.
33. Clark, A.S., et al., *Constitutive and inducible Akt activity promotes resistance to chemotherapy, trastuzumab, or tamoxifen in breast cancer cells.* Mol Cancer Ther, 2002. **1**(9): p. 707-17.
34. Therasse, P., et al., *New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada.* J Natl Cancer Inst, 2000. **92**(3): p. 205-16.

16.0 APPENDICES

APPENDIX A. Performance Status

Zubrod (ECOG) Performance Scale

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

APPENDIX B: List of Concomitant Medications

Table 1: List of CYP450 substrates to be used with caution

CYP2C8	**CYP2C9**	**CYP2C19**	**CYP3A****	
Amodiaquine	Celecoxib	Clopidogrel	Alfentanil[1,2]	Ergotamine[2]
Cerivastatin	Diclofenac	Diazepam	Alphy-dihydroergocryptine[1]	Everolimus[1]
Repaglinide	Glipizide	Esoprazole	Alprazolam	Felodipine[1]
Rosiglitazone	Isbesartan	Lansoprazole	Amlopidine	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 GDA's "Guidance for Industry, Drug Interaction Studies" and the University of Washington's Drug Interaction Database.
[1]Sensitive substrates: Drugs whose plasma UAC 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).

All QT-prolonging drugs listed in Table 2 are prohibited for all subjects from screening through permanent discontinuation of study treatment

Table 2: List of prohibited QT prolonging drugs

Drug	QT risk*	Comment
Amiodarone	known risk	Female>Males, TdP risk regarded as low
Amitriptyline	conditional risk	Risk of TdP with overdose. 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 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.
Dronedatone	possible risk	Substrate for 3A4
Droperidol	known risk	
Erythromycin	known risk	Females > Males. Substrate 3A4
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 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 QT durgs.org Advisory Board of the Arizona CERT

Table 3: List of QT prolonging drugs to be used with caution

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 overdose
Diphenhydramine	conditional risk	Risk of QT increase/TdP in overdoses
Dolasetron	possible risk	
Doxepin	conditional risk	
Eribulin	possible risk	
Escitalopram	possible risk	
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 overdose
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		

Table 4: BCRP inhibitors to be used with caution

Drug	Comments
Diketopiperazines	P-glycoprotein inhibitors
Fumitremorgin C	Elacridar (GF-120918)
Tryprostatin A	Tariquidar (XR-9576)
Indolyldiketopiperazines	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

APPENDIX C: Specimen Collection for Correlative Studies

[redacted]

APPENDIX D: Guidelines for Management of Diarrhea

- Avoid milk, caffeinated beverages, alcohol, high-fat foods and high osmolar supplements
- Drink 8-10 glasses of clear liquids every day (water, Gatorade, broth)
- Eat frequent small meals and **BRAT** diet (**B**anana, **R**ice, **A**pplesauce, **T**oast, Pasta)
- Start Loperamide (Imodium) after you have the first loose stool/diarrhea
- Dosing of Imodium: Take 4 mg (2 tablets) after the first loose stool, followed by 2 mg every 4 hours or after every loose stool until free of diarrhea for 12 hours
- If diarrhea doesn't resolve in the next 12-24 hours, call your doctor
- You may need IV fluids or antibiotics
- If diarrhea resolves, you can gradually add solid foods to diet

Management of diarrhea

General Recommendations:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (e.g. Metamucil®) and stool softeners (e.g. docusate sodium, Colace®)
- Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)
- Drink 8-10 large glasses of clear fluids per day (e.g. water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g. bananas, rice, applesauce, toast)
- It is recommended that subjects are provided with loperamide tablets at the start of each cycle. Subjects should be instructed on the use of loperamide at Cycle 1 in order to manage signs and symptoms of diarrhea at home. Subjects should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day)) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the site should ensure that the subject understands the instruction. A the beginning of each cycle, each subject should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms, If symptoms were experienced, then the site should question the subject regarding the actions taken for these symptoms
- Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stool or overt diarrhea. Note that all concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications eCRF.
- Loperamide is the first-line treatment of diarrhea (any grade) in this recommended algorithm
- Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms. Another first-line treatment for diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide, however it is important to note that loperamide and diphenyloxylate hydrochloride/atropine sulfate must not be used in conjunction with one another due to the risk of developing paralytic ileus. Upon treatment with any antidiarrheal agents, the subject's response to treatment should be observed and appropriately documented in the source document and eCRF.

Treatment of diarrhea CTCAE Grade 1 or 2:
Diarrhea CTCAE Grade 1 or 2 will be treated with standard loperamide (initial at first administration 4mg, the 2 mg every 4 hrs (maximum of 16 mg/day) or after each unformed stool).

12-24 hrs later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12 hrs diarrhea-free interval

Diarrhea unresolved

- Persisting diarrhea CTCAE Grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of subjects condition to rule out dehydration, sepsis, ileus) medical check and selected workup if the subject does not need hospitalization (see section “Diarrhea Workup” and additional test in the particular trial protocol). Observe subject for response to antidiarrheal treatment.
- Persisting diarrhea CTCAE Grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, the 2 mg every 2 hours) and addition of opium tincture (DTO) or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of subjects condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing. Observe subject for response.

After 12-24 hrs:

Diarrhea resolved

- Continue instructions for dietary modifications
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12 hrs diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (CTCAE Grades 1 and 2) after 2x24 hrs with high dose loperamide and opiates then admit to hospital and employ measures as for CTCAE Grade 3 and 4 until diarrhea resolved
- If diarrhea still persisting and progressed to CTCAE Grades 3 and 4, employ measures described below

Treatment of diarrhea CTCAE Grade 3 or 4
Severe diarrhea CTCAE Grade 3 or 4 may be treated with hospitalization, high dose loperamide,(initial 4 mg, then 2 mg every 2 hrs and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of subject’s condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section “Diarrhea Workup” and additional test in the particular trial protocol). Observe subject for response.

After 12-24 hours:

- If diarrhea persisting, administer s.c. sandostatin/octreotide (100-500 μg TID)
- Continue IV fluids and antibiotics as needed
- If diarrhea CTCAE Grade 3 or 4 still persists, subjects should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea CTCAE Grade 3 or 4 is still persisting, s.c. sandostatin/octreotide (500-1000 μg TID) should be administered
- To controls and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea Workup

- Perform appropriate tests (Fine et al, 1999)

APPENDIX E: Summaries of Changes

[redacted]

[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]