BYL719, Capecitabine and Radiation for Rectal Cancer: A Brown University Oncology Research Group Phase I Study.

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1.0 OBJECTIVES

1.1 Primary Objective

1.1.1. To determine the maximum tolerated dose of BYL719 with capecitabine and radiation for patients with newly diagnosed rectal cancer.

1.2 Secondary Objectives

1.2.1 To evaluate the safety of BYL719 with capecitabine and radiation for patients with rectal cancer.

1.2.2. To evaluate the pathologic complete response for patients with rectal cancer treated with BYL719, capecitabine and radiation.

1.2.3. To assess the surgical complication rate of patients receiving preoperative BYL179 capecitabine and radiation

1.2.4. To gather preliminary information as to whether mutations in KRAS, BRAF, or PIK3CA predict pathologic complete response to BYL719, capecitabine and radiation.

2.0 BACKGROUND

Rectal Cancer: There are approximately 41,000 new cases of rectal cancer diagnosed each year in the United States.[1] Stage-for-stage, recurrence rates are higher in rectal cancer in comparison to colon cancer.[2]

Preoperative Chemoradiation: Chemoradiation improves survival in patients with rectal cancer.[3-5] Preoperative fluoropyrimidine (fluorouracil or capecitabine) with concurrent radiation is a standard of care for stage II/III rectal cancer.[6] Preoperative chemoradiation improves local control and is associated with reduced toxicities as compared to postoperative chemoradiation.[6] Pathologic complete response rates for fluorouracil and radiation range are approximately 9-25%.[6-10] When added to fluoropyrimidine, no other agent (including oxaliplatin, irinotecan, EGFR inhibitors, or bevacizumab) increases pathologic complete response.[11-14]

The PI3K Pathway in Rectal Cancer: The phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling axis plays a critical role in the proliferation, resistance to apoptosis, angiogenesis and metastasis that is central to the development and maintenance of colorectal cancer.[15-18] The effects of PI3K on tumor growth and progression are thought to be mediated by Akt, a downstream effector of PI3K.[19-21] Inhibition of upstream PI3K/Akt pathway components decreases growth, increases apoptosis, increases sensitivity to chemotherapy and radiation and decreases the metastatic capability of CRCs.[22-29] PI3K mutations occur in approximately 12% of rectal cancers but PIK3 signaling, in the absence of mutation, is increased in the majority of rectal cancers. [21-24]

There are three classes of PI3Ks grouped according to structure and function. Class IA PI3K is the one most clearly implicated in human cancer.[30] Class IA PI3Ks consist of a regulatory subunit and a catalytic subunit. Three mammalian genes, PIK3R1, PIK3R2, and PIK3R3, encode p85α, p85β and p55γ regulatory subunits, respectively, which by convention are referred to collectively as p85.[31] The catalytic isoforms, p110 α , p110 β, and p110 γ, are the products of three genes, PIK3CA, PIK3CB, and PIK3CD.[25] Both PIK3CA and PIK3R1 can be somatically mutated in colorectal cancer, and these mutations promote activation of the PI3K pathway.[32]

BYL719: BYL719 is an oral small-molecule inhibitor of the p110α catalytic subunit of PI3K, which is encoded by the *PIK3CA* gene, one of the most commonly mutated genes in human cancers including rectal cancer. BYL719 inhibits proliferation of PI3Kα-driven cancer cell lines in vitro and causes regression of *PIK3CA*-mutant tumor models in vivo. A phase I study has been completed in patients with advanced solid tumors carrying a somatic mutation of *PIK3CA*.[33] Thirty-six patients received doses up to 450 mg/day. The maximum tolerated dose (MTD) for once-daily dosing was declared as 400 mg/day. Dose limiting toxicities (DLTs) were hyperglycemia, nausea, vomiting, and diarrhea. The most common BYL719-related adverse events were hyperglycemia (49%), nausea (45%), diarrhea (40%), decreased appetite (38%), vomiting (30%), and fatigue (27%). Partial responses were seen in 7 patients and seventeen patients stayed on study for >24 weeks demonstrated proof-of-concept of the importance of this pathway.

PI3K Inhibitors are Radiation Sensitizers: Resistance of tumors to radiation has been associated with the activation of intracellular signaling pathways, particularly the PI3K/AKT pathway.[24-29] Preclinical studies have shown the enhanced effect of radiation in combination with PI3K/AKT/mTOR in several cancer cell lines including colon cancer. [24-29] ***He et al reported that the local recurrence rate following preoperative chemoradiation for rectal cancer is three times higher in patients with PI3K mutations thanin patients without PI3K mutations.[24]***

Strategy to Develop BYL719 With Capecitabine and Radiation in Rectal Cancer: PIK3 signaling is increased in many rectal cancers. [24-29] Upregulation of PIK3 predicts radiation resistance.[21] PI3K inhibitors are radiation enhances. Thus the addition of BYL719 to capecitabine and radiation may improve pathologic complete response rates for rectal cancer. In this phase I study, any patient with rectal cancer needing preoperative radiation will be eligible since upregulation of PIK3 may occur in the absence of a mutation. This phase I study will provide the necessary preliminary data to study BYL719 within the developing framework of NRG where patients with rectal cancer will be treated with a targeted agent that correlates with the specific mutation detected in an individual tumor. It is anticipated that BYL719 will be dramatically effective as a radiation sensitizer in the 12% of patients with rectal cancer and PI3K mutations so phase II/III investigations of BYL719 within the cooperative group may focus on rectal cancers with PI3K mutations.

The Brown University Oncology Research Group is a national leader in the management of rectal cancer: Total Neoadjuvant Treatment (TNT): The Brown University Oncology Research Group has successfully piloted the concept of total neoadjuvant treatment for rectal cancer in a 39 patient study.[34,35] Patients with stage II and stage III rectal cancer received 8 cycles of FOLFOX, followed by capecitabine and concurrent radiation followed by surgery. Compliance to neoadjuvant FOLFOX was far superior to the traditional treatment paradigm when FOLFOX is administered after rectal surgery. NRG (the merger of the NSABP and the RTOG) has chosen the TNT approach to be the new standard treatment sequence for stage II-III rectal cancer. This approach is optimal for developing a targeted radiation sensitizer. During neoadjuvant FOLFOX, molecular testing can be performed. Based on the molecular profile of an individual tumor a specific radiation enhancer such as a PI3K inhibitor may be added when preoperative radiation is initiated based on the mutational status of the tumor.

Future Development of BYL719 in Rectal Cancer Following Demonstration of Safety in This Proposed Phase I Study: The current research focus of NRG is to develop a more promising regimen of radiation enhancement than capecitabine alone. Once safety of BYL719 with capecitabine/radiation is established, BYL719 can be definitively tested in NRG. It is envisioned that within the cooperative groups, new patients with rectal cancer will be treated within the TNT format with 8 cycles of FOLFOX followed by capecitabine and radiation. New patients with rectal cancer will be evaluated for specific molecular alterations. If a P13K mutation were detected, within this multi-institutional cooperative group framework, the effect of BYL719 on pathologic complete response could be definitively tested within the subgroup of patients with PI3K mutations. An agent that increases pathologic complete response would be a major advance in rectal cancer because it would decrease the number of patients with low rectal cancer requiring a permanent colostomy. The primary goal of this Brown University Oncology Research Group is to determine that a safe dose of BYL719 can be administered with capecitabine and radiation in patients with rectal cancer. *Therefore, the threshold of success for this phase I study is to establish safety.* In a subsequent NRG study, within the TNT framework, a randomized phase II study will be planned exclusively in patients with PIK3CA mutations to assess whether pathologic complete response is improved within this specific subgroup of patients.

3.0 PATIENT ELIGIBILITY

3.1 Conditions for Patient Eligibility

3.1.1 Patients must have histologically proven adenocarcinoma of the rectum with no evidence of distant metastases.

3.1.2 The tumor must be clinically Stage II (T3-4 N0) or stage III (N+). Stage of the tumor may be determined by CT scan, endorectal ultrasound or MRI. (For patients receiving chemotherapy prior to protocol chemoradiation, the initial clinical stage applies. CT/MRI/PET should be performed within 2 months of study entry to exclude disease progression.) For the MTD expansion phase only: patients who are stage IV, and in whom it is planned to administer capecitabine and radiation then have a resection of their rectal cancer, are also eligible. Submit documentation to BrUOG on location of metastatic disease sites with source confirmation (scan, pathology etc) and obtain confirmation that patients would meet this criterion.

3.1.3 Measurable disease not required at baseline. Patient's without measurable disease may be enrolled as long as they clinically meet stage II or III criteria or for MTD expansion phase: also stage IV.

3.1.4 Patients must not have received pelvic radiation for rectal cancer, or prior pelvic radiation for any other malignancy that would prevent the patient from receiving the required radiation treatments for this study. (Patients may receive neoadjuvant chemotherapy prior to study chemoradiation)

3.1.5 Patients must not have an active concurrent invasive malignancy. Patients with prior malignancies, , are eligible if they are deemed by their physician to be at low risk for recurrence. For example, patients with squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma of the cervix, early stage breast cancer, or carcinoma in situ of the colon that have been effectively treated are eligible, even if these conditions were diagnosed within 3 years prior to registration.

3.1.6 Patients must be $\geq$ 18 years of age,

3.1.7 ECOG performance status 0-1

3.1.8 ANC ≥1,000/µl, platelets ≥100,000/µl, total bilirubin ≤ ULN (except for patients with Gilbert's syndrome who may only be included if total bilirubin is ≤ 3xULN with direct bilirubin within normal range),

ALT ≤2.5xULN, AST ≤ 2.5xULN,

fasting plasma glucose ≤ 140 mg/dL and HbA1c ≤ 6.4% (both criteria have to be met),

HGB ≥ 9.0g/dL.

Serum creatinine ≤ 1.5xULN and/or creatinine clearance > 50% LLN
Potassium, Calcium and Magnesium (corrected for albumin) within normal range or ≤ grade 1 if determined not clinically significant by treating investigator (must send to BrUOG in writing)

INR ≤ 1.5

* For patients with FPG ≥ 100 mg/dL and/or HbA1c ≥5.7% (i.e. threshold for pre-diabetes) at screening, recommend lifestyle changes according to ADA guidelines, i.e. dietary advice (e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrate intake over the course of the day, three small meals and 2 small snacks rather than one large meal) and exercise. A consultation with a diabetologist is highly recommended

3.1.9 Patient is able to swallow and retain oral medication. Patients with feeding tubes are considered not able to retain oral medication, as this drug can not be suspended through a feeding tube.

3.1.10 LVEF within institutional normal limits (must submit what these are) or ≥50%

3.1.11 Signed informed consent and is able to comply with study and/or follow- up procedures.

3.1.12 QTcF <480 msec

3.1.13 Patients history of diarrhea has been review and patient has been informed of potential study drug induced diarrhea and management. This must be documented by treating MD. See section 5 for baseline assessments of patient history of diarrhea.

3.2 Exclusion Criteria

3.2.1 Patient has a known hypersensitivity to any of the excipients of BYL719 (alpelisib)

3.2.2 For stage II and III patients: Suspected or confirmed metastatic disease including CNS involvement. For stage IV patients: CNS involvement.

3.2.3 Patient with clinically manifest diabetes mellitus, or documented steroid induced diabetes mellitus

3.2.4 Patient with impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BYL719 (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with colostomies are allowed unless colostomy is for one of the precluded reason above.

3.2.5 Patient who has not recovered to grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy

3.2.6 Patient who has had systemic therapy within 4 weeks of starting study drug BYL719 (6 weeks for nitrosoureas or mitomycin C).

3.2.7 Patient who has undergone major surgery ≤ 4 weeks prior to starting study treatment or in the investigators opinion who has not recovered from side effects of such procedure

3.2.8 Patient has any of the following cardiac abnormalities:

A. symptomatic Congestive heart failure
    i. history of documented congestive heart failure (New York Heart Association functional classification III-IV), documented cardiomyopathy
    ii. Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
B. myocardial infarction ≤ 6 months prior to enrollment
C. unstable angina pectoris
D. serious uncontrolled cardiac arrhythmia
E. symptomatic pericarditis
F. QTcF > 480 msec on the screening ECG (using the QTcF formula)

3.2.9 Patient who is currently receiving medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes (TdP) and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug treatment. To be documented and submitted to BrUOG with registration. Please refer to appendices F and G.

3.2.10 Patient who has participated in a prior investigational cancer treatment study within 30 days prior to enrollment. This refers to treatment not follow-up.

3.2.11 Patient 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. To be documented and submitted to BrUOG with registration. Eliquis is allowed.

3.2.12 Patient is currently receiving treatment with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A. The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the start of treatment. Switching to a different medication prior to registration is allowed; (Refer to Section Concomitant Medication, Appendix F and G). To be documented and submitted to BrUOG with registration via conmed list. Patient must not be on any medications in Appendix G

3.2.13 Patient with known positive serology for human immunodeficiency virus (HIV)

3.2.14 Patient with any other condition that would, in the Investigator's judgment, preclude patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g. infection/inflammation, intestinal obstruction, unable to swallow oral medication, social/psychological complications, chronic active hepatitis, severe hepatic impairment etc

3.2.15 Patients who have other concurrent severe and/or uncontrolled medical conditions that would, in the Treating Physician's judgment, contraindicate patient participation in the individual patient program (eg. active or uncontrolled severe infection, chronic active hepatitis, immuno-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.)

3.2.16 Patient has a history of non-compliance to medical regimen or inability to grant consent

3.2.17 Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL). Pregnancy test not required for patients who are considered post-menopausal and not of childbearing potential as defined below.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate,

history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago.

For women with therapy-induced amenorrhea, oophorectomy or serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status.

3.2.18 Patient who does not apply highly effective contraception during the study and through the duration as defined below after the final dose of study treatment:

a. Sexually active males (unless surgically sterilized at least 6 months prior to screening which would mean no contraception is needed) should use a condom during intercourse while taking drug and for 6 months after the final dose of study treatment and should not father a child in this period, but may be recommended to seek advice on conservation of sperm. The use of spermicidal foam is also highly suggested to be used with a condom as another form of protection. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Males should be cautioned to not donate sperm while actively receiving treatment on study.

b. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through 6 months after the final dose of study treatment. Highly effective contraception is defined as either:

i. Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception].

ii. Female sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

iii. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female study subjects, the vasectomized male partner should be the sole partner for that patient]

iv. Use a combination of the following (both a+b):

a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Note: Hormonal contraception methods (e.g. oral, injected, and implanted) are not allowed as BYL719 may decrease the effectiveness of hormonal contraceptives.

c. Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago.

b. For women with therapy-induced amenorrhea, oophorectomy or serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status.

NOTE: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression.

* Please consult with local product labels should any combination agents or concomitant medications be used, as this period may be longer for other potentially genotoxic compounds.

A female is considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago before the treatment start.

For females with therapy-induced amenorrhea, oophorectomy or serial measurements of Follicle-Stimulating Hormone (FSH) and/or estradiol are needed to ensure postmenopausal status.

NOTE: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression.

3.2.19 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, Medical Marijuana and ginseng. Patients need to stop using these herbal medications 7 days prior to first dose of study drug.
3.2.20 Patient must not eat or drink 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
3.2.21 Patient is currently receiving or has received systemic corticosteroids $\leq$ 2 weeks prior to day 1 of study drug, or who has not fully recovered from side effects of treatment. The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
3.2.22 Patient is concurrently using other anti-cancer therapy

3.3 Re-Screening:
If a patient signs consent and then screen fails (does not meet the eligibility criteria) and the treating MD requests that the patient be re-screened outside of the 28 day screening window, sites are to contact BrUOG who will assess patients on a case by case basis. Depending on many diverse factors including the conditions that are being evaluated, the reasons why patient initially screen failed, and the nature of the initial results, re-screening may or may not be medically/scientifically appropriate. BrUOG should be made aware of such a situation with at least 72 hours and provided with information on screen-failure.

4.0 TREATMENT

4.1 Treatment:

This is a phase I dose escalation study adding BYL719 to standard capecitabine and radiation.

Capecitabine: 825mg/m^2/BID Sunday night through Friday morning on radiation days (See appendix H for capecitabine dosage per BSA)

Dosing: Sunday evening –Friday morning (the night before to the morning of each chemo treatment, not Monday AM-Friday PM): Dose 1 to be taken Sunday PM, then Monday –Thursday AM/PM dosing, then last dose Friday AM.

Radiation: 50.4 Gy, 180 cGY/fraction x 28 fractions:

BYL 719: BYL719 will be given once daily po, from Day 1 of radiation to the final treatment with radiation. BYL719 will be administered orally once daily on a continuous dosing schedule and dosed on a flat-fixed dose and not adjusted by body weight or body surface area.

Missed doses of BYL 719 are not made up and BYL719 will be stopped when radiation is completed.

IF RADIATION IS NOT GIVEN SECONDARY TO TOXICITY OR TOXICITY RECOVERY (OR PER PROTOCOL) ETC, THEN PATIENT IS TO BE INSTRUCTED TO NOT TAKE CAPECITABINE OR BYL719 DRUGS. IF RADIATION IS NOT GIVEN SECONDARY TO A HOLIDAY OR AN ADMINISTRATIVE REASON (MACHINE IS DOWN, SNOW STORM, SCHEDULING ETC) THEN CAPECITABINE IS TO BE HELD (ONCE IT IS KNOWN TREATMENT WON'T BE GIVEN, AS DRUG IS TO BE GIVEN WITH RADIATION). BYL719 HOWEVER, IS STILL TO BE GIVEN AS TREATMENT IS ON A CONTINUOUS BASIS AND REASON IS NOT FOR TOXICITY (BUT MUST BE STOPPED ONCE RADIATION ENDS).

Surgery will be performed approximately 6-10 weeks after the last treatment of BYL719/capecitabine + Radiation

No of pts	*Dose Level**	*Cohort Level**	*Capecitabine*	*Radiation.*
3-6	***1***	***BYL719 200 mg/day***	***Capecitabine, 825mg/m2 BID Sunday PM-Fri AM***	***50.4 GY RT***
3-6	***2***	***BYL 719 250 mg/day***	***Capecitabine, 825mg/m2 BID Sunday PM-Fri AM***	***50.4 GY RT***
3-6	***3***	***BYL 719 300 mg/day***	***Capecitabine, 825mg/m2 BID Sunday PM-Fri AM***	***50.4 GY RT***

(Dose Level -1: 150mg/day, to be used if dose level 1 is not tolerated based on DLTs or in the case when a dose reduction may be needed for a patient on dose level 1.

Only 1 dose reduction is permitted per patient for criteria noted in section 5)

Three patients will be accrued to level 1. If dose level 1 is not tolerated then dose level -1 will be investigated. If no dose limiting toxicities are observed following completion of BYL719, capecitabine and radiation, and after patients are observed for 2 weeks post completion, then accrual to level 2 will proceed. If a DLT is observed in one of the first 3 patients in a dose level, then accrual for that level will be expanded to 6 patients. Two or more instances of DLT in a cohort of 6 patients will result in the preceding dose level being defined as the MTD. After determination of the MTD, the final cohort will be expanded so that a total of 24 patients are treated on study. A patient will be considered inevaluable if they receive <67% of their total intended treatment (BYL719, Capecitabine or Radiation) for non-protocol required reasons.

During the MTD dose finding portion, patients who are removed from study for reasons other than a DLT, defined in section 5.2, will be replaced.

If a dose limiting toxicity occurs, BYL719 will be held until the toxicity reduces to ≤ grade 1 at which point patients will be permanently dose reduced by 1 dose level. Patients may continue to receive their capecitabine and radiation as per institutional standard of care when toxicities resolve to ≤ grade 2.

If treatment is held for more than 28 days, then patient should come off study.
Definition of Dose Limiting Toxicities

- Grade 4 neutropenia (ANC < 500/mm^3)
- ANC <1000/mm^3 with fever (temp > 101) or infection
- Grade 4 thrombocytopenia: Platelets <25,000/mm^3
- Platelets <50,000/mm^3 requiring transfusion
- Grade 3 or 4 treatment related non-hematologic toxicities excluding alopecia. Grade 3 nausea, vomiting or diarrhea will only be considered a dose limiting toxicity if it occurs for greater than 48 hours despite maximal medical support. Grade 3 electrolyte abnormalities will not be considered dose limiting toxicities if the electrolyte disorder can be corrected to grade 2 or less within 72 hours. A grade 4 electrolyte abnormality will be considered a DLT.
- Patients who receive < 67% of intended BYL719 or capecitabine secondary to treatment related toxicities will also be considered as having a DLT (patients will be considered inevaluable)

The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at the end. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

The following general guidelines should be followed for BYL719 administration:

- Patients should be instructed to take the dose (one or more tablets) of BYL719 with a glass of water (~250 ml or ~8 fluid ounces) daily in the morning and within approximately 1 hour after a meal (like breakfast) or snack
- Take BYL719 at approximately the same time each day after a meal or snack (preferable in the morning after breakfast) (recommended 8AM +/1 hour)
- If, for any reason, a breakfast (or other meal) was not consumed, then the patient should take study treatment with a glass of water within 1 hour after a snack that same day. If the patient forgets to take study treatment during the daytime it should be taken in the evening at the latest within 1 hour after a meal, **but not later than 6 pm.** If not taken by this time, the dose should be withheld that day. **Missed doses should not be made up the next day.**
- Patients should be instructed to swallow the tablets and not to chew or crush them. However for patients with swallowing dysfunction without G tube, BYL719 film-coated tablets can be administered as drinkable suspension by crushing the tablets and suspending them in water. The drinkable suspension prepared from the film-coated crushed tablets is not permitted for administration into feeding tubes.
- Patients should record if the dose was taken or not in the patient diary
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increase stool frequency) during the treatment must be noted in the adverse events section of the patient record.

- Patients must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, starfruits and cranberry juice from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A interaction. Regular orange (Citrus X sinensis) juice is allowed.
- Patients must avoid concomitant intake of strong CYP3A inhibitors and inducers.

4.2 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited below and in Appendix F and G and the Investigators Brochure (please know that medical marijuana is included in reference to herbal medications in Appendix G as a prohibited medication on study). All medications and significant non-drug therapies (including blood transfusions) patient is taking at baseline prior to the administration of BYL719 through 30 days after the last dose of BYL719 will be recorded on the Concomitant medications log.

The investigator should instruct the patient to notify the investigational site about any new medications she takes after the start of the study drug.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies section of the patient record, respectively.

4.2.1 Permitted concomitant therapy

Antiemetics

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the patient experiences nausea or vomiting, at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation (Appendix F). Please note that some anti-emetics have a known risk for TdP and are prohibited (refer to Appendix G)

Oral hypoglycemic anti-diabetic Agents

Patients 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. Patients receiving oral antidiabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, must be carefully monitored for hypoglycemia as BYL719 was found to be moderate reversible inhibitor of these enzymes (refer to Appendix F).

Anticoagulation

Anticoagulants other than warfarin/coumarin derivates may be administered under the discretion of the investigator. However, caution is advised when BYL719 is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4, CYP2C9 and CYP2C19. BYL719 has the potential to inhibit these enzymes and may therefore decrease the metabolic activation and clinical efficacy of these pro-

drugs. Patients using anti-platetet pro-drugs should be carefully monitored (refer to Appendix F).

Contraceptives

Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. For allowed contraception methods, refer to Exclusion Criteria. Highly effective contraception should be maintained throughout the study and for 6 months after study treatment discontinuation.

CYP450 substrates

In vitro studies demonstrate that BYL719 is a time dependent inhibitor of CYP3A4(Ki 5.6 μM, Kinact 0.011 min-1). Reversible inhibition of CYP2C8 (Ki 32 μM), CYP2C9 (Ki 22 μM) and CYP2C19 (IC50 75 μM) was also observed. BYL719 may inhibit metabolic clearance of co-medications metabolized by CYP3A4, CYP2C8, CYP2C9 and CYP2C19, if sufficiently high BYL719 concentrations are achieved in vivo. Investigators, at their discretion, may administer concomitant medications known to be metabolized by or are substrates for CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19. Patients receiving such medications and drugs which have a narrow therapeutic index must be carefully monitored for potential toxicity due to any individual concomitant medications. (refer to Appendix F).

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

Gastric protection agents

BYL719 is characterized by a pH-dependent solubility. Medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of BYL719 and hence its bioavailability. These agents include, but are not limited to, proton-pump inhibitors (PPI) (e.g., omeprazole), H_2-antagonists (e.g., ranitidine) and antacids. Due to long pharmacodynamic effect of PPIs, i.e. long-lasting reduction of gastric acid production over 36 hours, H_2-antagonists and antacids are recommend to be used over PPIs, whenever possible. Note that some proton pump inhibitors may possibly also inhibit BCRP (refer to Appendix F).

BYL719 should preferably be dosed in a staggered manner, i.e., at least 1 hour before or 10 hours after dosing with a gastric protection agent.

BCRP inhibitors

BYL719 was identified as a substrate for the human breast cancer related protein (BCRP). Co-administration of BYL719 with BCRP inhibitors may possibly increase systemic exposure and/or alter tissue uptake of oral BYL719.The treatment with BCRP inhibitors should be kept as short as possible or, if possible, fully avoided. See Appendix F for Table of Permitted Medications.

Corticosteroids

Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone may prolong or aggravate hyperglycemia (steroid-induced diabetes). Hyperglycemia is a common adverse event for Pi3K inhibitors like BYL719 and should therefore be used with caution and patients closely monitored.

The patient must be told to notify the investigational site about any new medications she/he takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications CRF pages.

4.2.2 Prohibited concomitant therapy

Other anticancer therapy

If a patient, enrolled in the study, requires the concomitant use of any medication included in Appendix G entitled "List of Prohibited Medications during BYL719 Treatment" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a **known** risk of causing TdP), BYL719 administration must be interrupted as long as the patient requires therapy with the QT prolonging agent. Note Appendix G also prohibits drugs that are substrates for CYP3A and CYP2C with a possible or conditional risk for TdP. If the patient requires long term therapy with such a QT prolonging agent, leading to study treatment interruption of > 28 days, the patient must be permanently discontinued from BYL719.

Herbal medications

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

Warfarin and coumarin derivates

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

4.3 Radiation Therapy

Note: Intensity modulated radiation therapy (IMRT) is mandatory for all patients for the initial pelvic field encompassing the gross tumor and at-risk lymph nodes in the pelvis.

Protocol treatment (chemotherapy and radiation therapy) should be initiated simultaneously on a Monday or Tuesday whenever possible

4.3.1 Dose Specifications

Treatment plans for patients on this protocol will consist of 2 phases: 1) the first phase will consist of inverse-planned IMRT-based treatment to the pelvis (rectum and draining lymphatics at risk) for a total of 45 Gy in 1.8 Gy daily fractions, and 2) the second phase will consist of a 3-dimensional conformal boost (a 3-field technique is suggested) to gross disease + a minimum 2 cm margin including all of the presacral space for an additional 5.4 Gy in 1.8 Gy daily fractions.

IMRT Dose Specifications

Inverse planning is required for the IMRT portion of treatment and planning constraints are provided in this section for both the planning target volume (PTV) as well as critical normal structures to be spared. Acceptable treatment plans will be established from a DVH-based analysis of the volumetric dose to both the PTV and critical normal structures to ensure that minimally acceptable constraints for each volume of interest have been met.

IMRT treatment to the pelvis will be planned to deliver a total of 45 Gy to the PTV in 25 fractions of 1.8 Gy over 5 consecutive weeks.

a. **Technical Factors**

i. Megavoltage equipment (minimum acceptable energy is 6 MV) capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required.

ii. Inverse-planning capable software is required.

b. **Localization, Simulation, and Immobilization**

i. A custom immobilization device (such as Alpha Cradle or vac-loc bag) for supine patients is suggested to minimize setup uncertainty.

ii. CT-based simulation (maximum 5 mm slice thickness) is required for this protocol and bowel exclusion techniques should be used when possible. Patients may be simulated supine or prone (if a belly board is utilized). Patients should be simulated in the "arms up" position whether prone or supine and with a full bladder.

c. **Treatment Planning/Target Volumes**

2. The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

i. *The Gross Tumor Volume (GTV)* is defined as all known gross disease as determined from a combination of physical exam, colonoscopy, ultrasound, CT (and MRI or PET-CT if performed).

ii. *The Clinical Target Volume (CTV)* is defined as the GTV plus areas considered at significant risk of harboring microscopic disease. The CTV for a T3 tumor should include all gross disease (rectal and nodal) as well as the internal iliac lymph nodes and the mesorectum (perirectal fat and the presacral space). The CTV for a T4 tumor will include the same structures as for a T3 tumor but will include the external iliac lymph nodes as well.

iii. *The Planning Target Volume (PTV)* will provide a margin around the CTV to compensate for the inter- and intra-fraction uncertainty consequent to daily setup uncertainty and to potential internal organ motion. By definition, the PTV will consist of a symmetrical 5 mm expansion around the CTV. In the event that PTVs extend outside of the skin surface, the clinician should manually trim the PTV contours to be 3-5 mm inside the outer skin (unless there is direct skin involvement).

1. The following are guidelines for generating CTV and a unified PTV.

a. Rectal GTV (+1.5 cm radially, +2.5 cm craniocaudally) = CTV

b. Nodal GTV + 1.5 cm symmetrical expansion = CTV

c. Uninvolved iliac vessels + 1.0 cm = CTV (include external iliac if T4)

d. Presacral lymphatic CTV is generated by contouring from mid S1-S5 and 8 mm tissue anterior to the anterior border of the sacral bone

e. The mesorectum and perirectal lymphatics CTV is generated by utilizing anatomic landmarks:

i. Posterior Border: anterior border of the sacrum and gluteus maximus

ii. Lateral Border: ileum, piriformis and obturator muscles

iii. Anterior Border: should overlap by 1 cm into the bladder, vagina or prostate

2. The PTV is generated by expanding all of the above structures by 0.5 cm symmetrically and unifying them into one 3-dimensional volume for planning purposes.

3. Examples of contoured patients are available for review on the RTOG website at http://www.rtog.org/CoreLab/ContouringAtlases/Anorectal.aspx. These examples are an excellent resource for the contouring of normal structures as well as GTV, CTV and PTV design.

4. PTV planning dose-volume constraints:

a. ≥ 98% of the PTV receives ≥ 93% of the prescribed dose

b. ≤ 10% of the PTV receives ≥ 105% of the prescribed dose

c. ≤ 5% of the PTV receives ≥ 110% of the prescribed dose

d. None of the PTV is to receive ≥ 115% of the prescribed dose

b. **Critical Structures (IMRT Planning Constraints)**

i. Small bowel:

1. No more than 180 cc above 35 Gy

2. No more than 100 cc above 40 Gy

3. No more than 65 cc above 45 Gy

4. No small bowel volume should receive 50 Gy

ii. Femoral heads:

1. No more than 40% volume above 40 Gy

3. No more than 25% volume above 45 Gy

4. No femoral head volume should receive 50 Gy

i. Bladder:

1. No more than 40% volume above 40 Gy

2. No more than 15% volume above 45 Gy

3. No bladder volume should receive 50 Gy

ii. Unspecified Tissue:

1. No specific constraints, however a DVH will be generated for "unspecified

tissue" which consists of any tissue within the skin but not contoured as a part of any of the normal structures above and/or the PTV

4.4 **Surgery:**
Surgery will be performed, according to standard institutional practices, 6-10 weeks after completion of radiation.

5.0 TOXICITIES, DOSE MODIFICATIONS, AND MANAGEMENT

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Toxicity Criteria (CTCAE) version 4.03 (Appendix C).

5.1 General Principles: This is a phase I study of 5 ½ weeks of treatment with BYL719 combined with standard capecitabine and radiation. If a dose limiting toxicity occurs, BYL719 will be held until the toxicity reduces to ≤ grade 1 at which point patients will be permanently dose reduced by 1 dose level. Patients may continue to receive their capecitabine and radiation as per institutional standard of care when toxicities resolve to ≤ grade 2.

IF RADIATION IS NOT GIVEN PATIENT IS TO BE INSTRUCTED TO NOT TAKE CAPECITABINE OR BYL719 DRUGS. See section 4.1 for more details on this.

If treatment is held for more than 28 days, then patient should come off study.

5.2 Definition of Dose Limiting Toxicities

- Grade 4 neutropenia (ANC < 500/mm^3)
- ANC <1000/mm^3 with fever (temp > 101) or infection
- Grade 4 thrombocytopenia: Platelets <25,000/mm^3
- Platelets <50,000/mm^3 requiring transfusion
- Grade 3 or 4 treatment related non-hematologic toxicities excluding alopecia. Grade 3 nausea, vomiting or diarrhea will only be considered a dose limiting toxicity if it occurs for greater than 48 hours despite maximal medical support. Grade 3 electrolyte abnormalities will not be considered dose limiting toxicities if the electrolyte disorder can be corrected to grade 2 or less within 72 hours. A grade 4 electrolyte abnormality will be considered a DLT.
- Patients who receive < 67% of intended BYL719 or capecitabine secondary to treatment related toxicities will also be considered as having a DLT

During the MTD dose finding portion, patients who are removed from study for reasons other than a DLT, defined in section 5.2, will be replaced.

5.3 Management of Specific Toxicities are outlined below for all patients: most conservative assessments must be used for management and modification:

If a dose limiting toxicity occurs, BYL719 will be held until the toxicity reduces to ≤ grade 1 at which point patients will be permanently dose reduced by 1 dose level. Patients may continue to receive their capecitabine and radiation as per institutional standard of care when toxicities resolve to ≤ grade 2.

If treatment is held for more than 28 days, then patient should come off study.

During the MTD dose finding portion, patients who are removed from study for reasons other than a DLT, defined in section 5.2, will be replaced.

For toxicities other than dose limiting toxicities, specific dose adjustments, based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria ([NCI-CTCAE version 4.03]), are described below. A maximum of 1 dose reduction of BYL719 from the starting dose may be allowed.

Missed doses of BYL 719 are not made up and BYL719 will be stopped when radiation is completed.

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
Worst toxicity (CTCAE 4.03 Grade)	**Dose Modifications for BYL719**
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 ANC <0.5 x 10^9/L without fever) * this is also a DLT*	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
ANC <1.0 x 10^9/L with fever (≥38.3°C or a sustained temperature of ≥ 38 °C for more than one hour)	(An ANC <1 with fever of >101 or infection is also considered a DLT) Hold BYL719 until resolved, then ↓ 1 dose level
Thrombocytopenia (PLT)	
Grade 3 (PLT < 50-25 x 10^9/L)	**Omit dose until resolved to ≤ Grade 1, then:** • **If resolved in ≤ 7 days, then maintain dose level** • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L) *this is also a DLT*	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
RENAL	
Serum creatinine	

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
< 2 x ULN	Maintain dose level
2 – 3 x ULN	Omit dose until resolved to ≤ grade 1, then: -- If resolved in ≤ 7 days, then maintain dose level -- If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue BYL719
Grade 4 (> 6.0 x ULN)	Permanently discontinue BYL719
HEPATIC	
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: -- If resolved in ≤ 7 days, then maintain dose level -- If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ● If resolved in ≤ 7 days, ↓ 1 dose level ● If resolved in > 7 days discontinue patient from BYL719
Grade 4 (> 10.0 x ULN)	Permanently discontinue BYL719
AST or ALT Confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorder, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction	

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
Grade 1 (> ULN – 3.0 x ULN)	Maintain dose level with LFTs* monitored per protocol
Grade 2 (> 3.0 - 5.0 x ULN) without total bilirubin elevation to >2xULN	Omit dose until resolved to ≦ baseline value If treatment delay is ≦ 7 days, restart at same dose If resolved in > 7 days, ↓ 1 dose level
Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≦ Baseline value, then If treatment delay is ≦ 7 days, restart at same dose **If resolved in > 7 days, ↓ 1 dose level**
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	**Omit dose until resolved to ≤ Grade 1, then ↓1 dose level**
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue patient from BYL719

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03) *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. For patients 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). Patients with grade 0 or 1 at screening experiencing ALT/AST/bilirubin increase ≥ grade 2 the liver function tests 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 liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1; hereafter the monitoring should be continued every other week or more frequently if clinically indicated until the end of treatment with study medication. Patients 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).
ENDOCRINE/METABOLIC
Fasting Plasma Glucose (FPG)
Always consider consultation with a diabetologist and recommend/reinforce on lifestyle changes as per ADA, i.e. exercise and dietary advice (e.g. small frequent meals, low carb, high fiber, balancing carbs over the course of the day. Three small meals and 2 small snacks rather than one large meal).

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]	Maintain dose level, remind patient on lifestyle changes, and re-check within 24 hours: *if patient has already had a confirmatory FPG check which confirmed grade 1 FPG then just continue to draw FPG weekly as noted in section 6 and at least weekly for 8 weeks then every 2 weeks until FPG resolves to baseline value or normal. Patient's must always have a 24 hour confirmatory FPG prior to moving to weekly FPG labs. if grade worsens, follow specific recommendations. *If on re-check FPG is within institutional normal range, no further assessment or any intervention is needed.*If grade 1 is confirmed: If FPG < 140mg/dl, consider adding metformin as per guidance below or in cooperation with a diabetologist. - If FPG 140-160 mg/dl, **start/intensify** metformin as per guidance below or in cooperation with diabetologist Metformin 500 mg once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg bid, with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. *Guidelines above are meant to be adjusted as per investigator's best clinical judgment. *If the treating physician, as per their clinical judgment, does not follow the above guidance to treat a FPG grade 1 by starting or intensifying metformin, documentation of this decision needs to be written and kept with the patient study information and submitted to BrUOG.* Check FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every 2 weeks. FPG to be checked until value resolves to baseline values. *be sure to send BrUOG all initial and re-check FPG testing*
Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	**Maintain dose level and remind patient on lifestyle changes,** confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
	*if patient has already had a confirmatory FPG check which confirmed grade 2 FPG then just continue to draw FPG weekly as noted in section 6 and at least weekly for 8 weeks then every 2 weeks until FPG resolves to baseline value or normal. Patient's must always have a 24 hour confirmatory FPG prior to moving to weekly FPG labs. Exclude confounding factors like e.g. urinary tract infection, consider consultation with a diabetologist and start oral-antidiabetic treatment, e.g. metformin 500 mg bid with breakfast and dinner. If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Titrate to the maximum tolerated dose over a period of 3 weeks. - if grade worsens or improves then follow specific grade recommendations. If FPG is still rising on maximum tolerated dose of metformin or persistently >160mg/dl (>8.9 mmol/L), add an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose). All confirmed grade 2: Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1 • If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce BYL719 by 1 dose level • Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks until resolves to grade ≤ 1. • Alert treating physician if FPG>250mg/dl *be sure to send BrUOG all initial and re-check FPG testing*
Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	Omit BYL719 and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors like e.g. urinary tract infection and consider consultation with a diabetologist.

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
Or Grade 2 with signs or symptoms of hyperglycemia (e.g., mental status changes, excessive thirst, polyuria)	Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate. Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of BYL719 -induced hyperglycemia given the short half-life of BYL719. • If FPG resolves to ≤ Grade1 within 3-5 days, while off study treatment and on metformin, re-start BYL719 and reduce 1 dose level, continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks until resolves to ≤ grade 1, alert treating physician if FPG>250mg/dl • If FPG does not resolve to Grade1 within 3-5 days while off study treatment and on metformin, consult a diabetologist for management of diabetes is strongly recommended. If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue patient from BYL719 treatment Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1. *be sure to send BrUOG all initial and re-check FPG testing*
Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L] Or Grade 3 with signs or symptoms of hyperglycemia (for ex., mental status changes, excessive thirst, polyuria)	Omit BYL719 confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors like e.g. urinary tract infection. Consider cooperation with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours. • If grade improves then follow specific grade recommendations • If FPG is confirmed at Grade 4 and confounding factors could be excluded, permanently discontinue patient from BYL719 *be sure to send BrUOG all initial and re-check FPG testing*

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
	A diabetologist consultation should always be considered. **<u>For all grades:</u> instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study** , e.g. .small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal **Guidelines above are meant to be adjusted as per investigator's best clinical judgment.** A diabetologist consultation should always be considered. Based on current experience, hyperglycemia usually resolves within a few days after BYL719 omission; temporary omission of BYL719 may be considered as clinically indicated to improve control of hyperglycemia. Special attention should be paid to the risk of hypoglycemias in patients interrupting BYL719 treatment and receiving insulin or sulfonylurea.
CARDIAC	
Cardiac - Left Ventricular systolic dysfunction	
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level, and continue BYL719 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 until resolved* (as defined below), then ↓ 1 dose level -LVEF measurement to be repeated, if not resolved* within 28 days permanently discontinue patient from BYL719 treatment
Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue patient from BYL719
*the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.	

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
Cardiac – QTc prolongation	
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	First Occurrence: Omit BYL719 Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed Perform a repeat ECG within one hour of the first QTcF of > 500ms or >60ms from baseline: if QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input Once QTcF prolongation has resolved, BYL719 may be restarted at one lower dose level **Second Occurrence:** Permanently discontinue patient from BYL719
Other Cardiac Events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue BYL719
Skin and subcutaneous tissue disorders	
Consultation with a dermatologist is highly recommended for better assessment and management of BYL719-induced skin toxicity.	
Grade 1(<10% body surface area (BSA) with active skin toxicity*)	Maintain dose level

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
	• Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are Triamcinolone, Betamethasone as long as skin toxicity is active, during maximum 28 days For patients with symptoms like burning and/or pruritus add non-sedating anti-histamine, consider adding a sedating anti-histamine at night If active rash is not resolved within 28 days of appropriate treatment, consider adding low dose systemic corticosteroid (20-40 mg/d)
Grade 2 (10-30% BSA with active skin toxicity*)	Maintain dose level. • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone as long as skin toxicity is active, during max. 28 days • Consider adding systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued For patients with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine, consider adding a sedating anti-histamine at night
Grade 3 (>30% BSA with active skin toxicity*)	Omit BYL719 dose until rash /skin toxicity is no longer active but fading (G1), consider exploratory skin biopsy for central assessment • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone for at least 28 days • Add systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued - If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with BYL719; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with BYL719, systemic corticosteroid may be discontinued

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
	For patients with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine during day time, consider adding a sedating anti-histamine at night Re-start BYL719dose once rash /skin toxicity is no longer active but fading (G1): - at same dose in case of first occurrence, at reduced dose level in case of second occurrence For patients with symptoms like burning, stinging and/or pruritus antihistamine regimen should be continued for a minimum of 28 days after re-challenge with BYL719.
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Permanently discontinue patient from BYL719 and consider a dermatology consult. . Treatment of rash should follow guidelines for Grade 3/ above with the exception of rechallenge and with any additional measures needed. • Consider exploratory skin biopsy
"Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.	
Diarrhea (also see below 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 reduce BYL719 by 1 dose level
Pneumonitis	please see Section below for information
Stomatitis/Oral Mucositis	

Dose Modifications for BYL719 (TREATMENT RELATED (BYL719)) : This table only applies once patient has begun treatment on study and it is only applicable while they are receiving treatment on study	
Grade 1 / Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash (see also Section Additional follow-up for selected toxicities)
Intolerable Grade 2 or Grade 3	First occurrence: hold until resolved to grade ≤ G1 and ↓ 1 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). Second occurrence: hold until resolved to grade ≤ G1 and ↓ 1 dose level.
Grade 4	Permanently discontinue BYL719
All other AEs not noted above (Treatment Related to BYL719):	
All other AEs (this pertains to non-lab AEs only)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then reduce BYL719 by 1 dose level Note: Omit dose for ≥ Grade 3 vomiting or ≥ Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic treatment as per local practice.
Grade 4	Permanently discontinue patient from BYL719 Note: Omit dose for ≥ Grade 3 vomiting or ≥ Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic treatment as per local practice.
** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03	

Management of Pneumonitis in patients receiving BYL719

All patients will be routinely asked about and observed for the occurrence of adverse events including new or changed pulmonary symptoms (consistent with lung abnormalities). Patients who are suspected to have

developed pneumonitis should suspend study treatment with BYL719 (alpelisib) immediately and undergo appropriate imaging (high resolution CT scan); and broncho-alveolar lavage and biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out. Investigators should follow institutional practice for management of pneumonitis which generally includes treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment. BYL719 (alpelisib), capecitabine and radiation (if suspected to be etiologically related to the AE of pneumonitis) should be permanently discontinued in all patients with confirmed pneumonitis.

Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment.

If the pneumonitis is confirmed to be study drug related, BYL719 must be discontinued.

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

Management of Pneumonitis

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

Guidelines for the treatment of BYL719 induced stomatitis/oral mucositis

General guidance and management include patient awareness and early intervention. Evaluation for herpes virus or fungal infection should be considered.

Patients should be informed about the possibility of developing mouth ulcers/ oral mucositis and instructed to report promptly any signs or symptoms to their Investigator,

Patients should be educated about good oral hygiene, instructed to avoid spicy/acidic/salty foods, and should follow the following guidelines:

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
- Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with BYL719 metabolism (see Section Concomitant Medications).

Although preclinical experiments demonstrated that alpelisib have no potential phototoxic effect, it is recommended to caution patients to avoid sun exposure during treatment with alpelisib, especially when they already have experienced rash or other skin toxicities. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts and long pants when outdoors.

Guidelines for the treatment of BYL719 induced skin toxicity

Skin toxicity is a class-effect adverse event observed with PI3Ki/mTORi agents.

Close monitoring of potential skin reactions should be performed at each planned visit and should be reported as adverse event. The most frequent skin adverse events reported are: maculopapular rash (only a minority present acneiform rash) pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate co-medication and treatment interruption if needed. Skin reactions may fade slowly over 10 days or more and may not require ongoing concomitant therapy. If there are no new lesions or new areas of involvement developing, and if the appearance is changing color from red to pale or light brown, it is likely the eruption has begun to fade, i.e. not considered active any longer. Consultation with a dermatologist is highly recommended for better assessment and management of BYL719-induced skin toxicity. Photographs of skin rashes events as well as skin biopsy, if possible, are recommended. According to the Investigator's discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) to further assess rash if clinically appropriate. At the Investigator's discretion, non-sedating antihistamines (e.g. cetirizine (Zyrtec©) once daily) may be used as prophylactic treatment to reduce severity of rash, especially for patients with a history of hypersensitivity reactions like seasonal allergies, hay fever, allergic asthma or drug induced exanthema.

Consultation with a dermatologist is highly recommended for better assessment and management of BYL719-induced skin toxicity.

Recommended therapies for skin toxicity events include:

- Topical steroids of Moderate Potency (face and folds): triamcinolone 0.025%; aclometasone 0.05% (<8 weeks continuously)
- Topical steroids of high potency (trunk/extremities): fluocinonide 0.05%; clobetasol 0.05% cream or spray (<8 weeks continuously)
- In case of burning, stinging, pruritus: oral antihistamines (sedating, evening): diphenhydramine 25-50mg tid; hydroxizine 25mg tid or q.i.d
- Oral antihistamines (non-sedating, day time): fexofenadine 180mg QD or 60mg TID (monitor the use of this class of drugs since skin toxicity has also been reported)
- Low dose oral corticosteroids, e.g. 20-40mg q.d: prednisone or equivalent up to 10 days of treatment
- If lesions are still not controlled with all of the above, consideration can be given to the use of:
    - Topical antibiotics: clindamycin 1 - 2%; erythromycin 1% -2% (gel or solution formulation can be used, ointments cannot be used); metronidazole 1%; silver sulphadiazine
    - Oral antibiotics: doxycycline 100mg bd; minocycline 100mg bd; oxytetracycline 500mg bd
    - Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
    - GABA Agonists: Gabapentin 300mg every 8 hours Pregabalin 50-75 mg every 8 hours (to adjust of renal impairment). Depending on patient's clinical condition be of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others AEs.

Dry skin has been reported, it is recommended that patients with dry skin use mild and fragrance free soaps and detergents. According to the severity and BSA extension patients may apply mild moisturizers, ammonium lactate cream 12% for example.

Although preclinical experiments demonstrated that BYL719 have no potential phototoxic effect, it is recommended to caution patients to avoid sun exposure during treatment with BYL719, especially when they already have experienced rash or other skin toxicities. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts and long pants when outdoors.

As outlined in Investigator Brochure version 10, dated July 12, 2017:

In combination studies, there have been two suspected cases of Stevens-Johnson-Syndrome (SJS) and two suspected cases of Erythema (EM) as of the cut-off date of the IB. All patients recovered from Stevens-Johnson-Syndrome/Erythema multiforme upon permanent discontinuation of BYL719.

As for other skin toxicities, a dermatologist consult is recommended. Any patent experiencing a severe cutaneous reaction should be permanently discontinued and not re-challenged with BYL719 treatment.

Guidelines for the treatment of BYL719 induced hyperglycemia

BYL719, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy 2012)[36]. BYL719 induced hyperglycemia is generally manageable with adequate antidiabetic treatment. BYL719 induced hyperglycemia typically occurs within the first month of treatment. Patients with pre-diabetes (i.e. FPG 100 – 125 mg/dl; 5.6 - 6.9 mmol/L) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in FPG while on BYL719treatment. However all patients, even those with FPG within normal limits at screening, may develop BYL719 induced hyperglycemia. Patients should always be instructed to follow dietary guidelines provided by the American Diabetes Association, e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal and exercise, as appropriate.

Detailed guidelines for management of BYL719 induced hyperglycemia include use of appropriate anti-diabetic treatment as is provided in the Table in section 5.3. following assessment by the treating physician. This includes early administration of metformin. Metformin may be titrated to a daily dose of 1000 mg BID. Local protocols per standard clinical practice may be followed. Fasting plasma glucose may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance. Special attention should be paid to the risk of hypoglycemia in patients interrupting alpelisib treatment and concomitantly receiving insulin and/or sulfonylureas.

These guidelines are meant to be adjusted as per investigator's best judgment and after consultation with Novartis medical team. A diabetologist consultation should always be considered.

Guidelines for the treatment of BYL719 induced diarrhea

Mild to moderate diarrhea has been reported within the ongoing studies of single-agent BYL719 and buparlisib. In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as well as proper management of diarrhea is mandatory. The following section outlines the recommended algorithm for management and treatment of BYL719 and buparlisib-induced diarrhea (Benson et al 2004; Kornblau et al 2000; Wadler et al 1998)[37-39].

The algorithm for treatment for diarrhea management is based on (Wadler et al 1998; Kornblau et al 2000)[38-39].

Patient history of diarrhea

At screening, the patient's history of diarrhea should be reviewed and the patient should be appropriately informed of potential study drug-induced diarrhea and its management:

- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;
- Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;

- Instruct patients regarding risk of developing diarrhea;
- Perform baseline clinical/laboratory studies according to the trial protocol (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients);
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading

First report of diarrhea

- Obtain history of onset and duration of diarrhea
- Description of number of stools and stool composition (e.g. watery, blood, mucus in stool)
- Assess patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)

Proactively look for occurrence of diarrhea. If no problems occur, instruct the patient to call when a problem does arise.

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 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g. bananas, rice, apple sauce, toast)

It is recommended that patients are provided with loperamide tablets at the start of each cycle. Patients should be instructed on the use of loperamide at first dose in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide at the first sign of loose stool or symptoms of abdominal pain. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the site should question the patient regarding the actions taken for these symptoms.

Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. Note that all concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications/Non-drug Therapies section of the patient record.

Loperamide should be 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 diphenoxylate 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 patient's response to treatment should be observed and appropriately documented in the source document and within the patient record.

Diarrhea grade 1 or 2

Diarrhea CTCAE grade 1 or 2 will be treated as per institutional standard of care taking into account the recommendations, which are with standard loperamide (initial at first administration 4 mg, then 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 grade 1 or 2 can be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of patients condition to rule out dehydration, sepsis, ileus) medical check and selected workup if patient does not need hospitalization (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response to antidiarrheal treatment.

After 12-24 hrs:

Diarrhea resolved

- Continue instructions for dietary modification
- 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 2x 24 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 or persisting 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 patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response.

- Grade 4 treatment related diarrhea is considered a DLT. Grade 3 diarrhea will only be considered a dose limiting toxicity if it occurs despite maximal medical support (See section 5.2)

After 12-24 hrs:

- 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 patients 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 control 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)[40].

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or
- Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations

Endoscopic examinations may be considered **only if absolutely necessary**. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR

Parameter	Pre-study, results and information to be sent with registration	Weekly during radiation (- 3 days prior to the first day of each week)[E]	2 & 4 weeks after radiation completed (+ 7 day window)	Surgery 6-10 weeks post end of radiation	FU
Informed Consent (within 30 days of day 1) *pts are to be re-consented if ICF will be outside 30 day window	X				
History	X				
Physical examination	X	X	X[G]		
Weight	X	X	X		
Vital signs	X	X	X		
Toxicity Assessment	X	X	X[F]		
Concomitant medications	X	X	X (2 weeks post)		
Performance Status	X	X	X		
Biopsy[H]	Anytime pre study				
Operative report and pathology report from rectal surgery				X[C]	
CBC, diff, platelet count	X (within 14 days)	X	X		
Na, K, BUN, Cr Ca, MG,	X (within 14 days)	X	X		
AST, ALT, TBili, albumin, Alk phos, fasting Glucose[I], HbA1C.[I]	X (within 14 days)	X	XI		
INR	X				
Serum Pregnancy[D]	X (within 14 days of drug)				
UA	X (within 14 days of drug)				
CT scan of Chest/abd/ Pelvis. MRI or PET may substitute [A]	X(within 56 days)		X[A]		X[A]
EKG[B]	X within 56 days	X[B]			
Echocardiogram or MUGA[B]	X within 56 days				
Survival and Disease status					Xj

[A]- CT Scan or MRI or PET scan for disease assessment to be performed within 56 days of study entry/registration. Report sent to BrUOG. A transrectal ultrasound may also be used for staging and if performed report sent to BrUOG. If this were performed at initial diagnosis it does not need to be repeated prior to study entry. Imaging post drug to be done approximately 4 weeks post radiation. +/- 2 week window provided. If Investigator orders imaging outside of this window rationale to be documented and submitted to BrUOG. Follow-up scans to be ordered as per institutional practice but are required to be sent to BrUOG with RECIST when completed. It is required that imaging that defined progression be sent to BrUOG as date of progression will be captured. Concern of pneumonitis or patients with respiratory changes, to be handled as per section 5.3 for chest imaging and monitoring. Chest imaging is not required to be done at end of treatment or follow up unless the patient symptoms of progression or toxicity such as pneumonitis. If however chest imaging is performed it must be submitted to BrUOG. Chest X-Ray may be used to substitute CT or MRI of chest.

[B]- EKG within 56 days of study entry. Report to be sent to BrUOG at registration.. ECHO or MUGA report with clear documentation of LVEF to be submitted. EKG also required to be done during week 3 of treatment and report to be sent to BrUOG. EKG, MUGA or ECHO to be ordered baseline and **then as clinically indicated should patient develop new cardiac symptoms or at discretion of treating MD(report submitted to BrUOG).**

[C]- The operative note and pathology note will be sent to BrUOG. Documentation of post op complications to be submitted to BrUOG as well.
[D] post-menopausal women (surgical menopause or lack of menses ≥12 months) do not need to have a pregnancy test, document status. If HCG is not drawn, sites are asked to document menopausal status on lab form.
[E] It is appropriate to use labs from screening for day 1, if labs are within 14 days. It is appropriate to use physical, weight, vitals, toxicity assessment, concomitant medication, performance status from screening for day 1 if within 14 days. Labs and assessments for all subsequent cycles are to occur within (-)3 days prior to day 1 of treatment of each week. This means that if RT and BYL719 begin on a Monday, the week of treatment is M-Sunday and therefore labs are to be done within (-) 3 days prior to dosing/treatment Monday. An additional day is provided for a holiday so that if there is a Monday holiday, assessments can be done on Friday to cover both BYL719 treatment Monday and Radiation Tuesday.
[F] Adverse event evaluation will be done 2 and 4 weeks (30 days post last dose) and SAEs will be captured for 30 days post last dose of study drug, capecitabine or last radiation treatment, whichever ends last. If AE evaluation cannot be done exactly 30 days post last treatment (radiation, capecitabine or study drug, whatever is the last date of treatment), a one week window is provided (+1 week). SAEs occurring outside this 30 day window must be reported if the event is considered to be possibly related to the drug. If a patient begins a new treatment, AE evaluation will be stopped unless the patient experiences an event (AE or SAE) that is thought to be possibly related to the study treatment. BrUOG must be made aware of new treatment with start date .
[G] Physical exam to be done in coordination with 30 day AE assessment only (+ 1 week window), No physical exams are required post 30 day post last dose of drug assessment.
[H] Biopsy for histologic confirmation of rectal cancer can be performed anytime pre-study (diagnostic biopsy).Assessment of PIK3CA status can be performed retrospectively, for example as part of the Lifespan pathology standard colorectal gene panel. PIK3CA or results of any mutation status not required at study enrollment unless already run. Once available, report of PIK3CA and tumor mutation status to be sent to BrUOG. While biopsy is required at registration, mutation result not required at baseline.
I Secondary to section 5.3 table and fasting labs , Friday lab draws/treatments should be avoided. HbA1c is required screening/baseline for registration then week 3 pre-drug and with EOT/2 week off labs.
J BrUOG will be notified every 6 months (+/- 2 months) for 2 years the disease-free and overall survival status.

7.0 RESPONSE ASSESSMENT:

Measurement of Response

Note: The primary endpoint of this study is safety. Measurable or assessable disease is not required in this study, but for patients who do have measurable disease, measurements must be submitted to BrUOG at baseline and RECIST to be used throughout to assess response. Radiographic response will be recorded when available but is not a primary endpoint.

Patient's without measurable disease at baseline: To be followed for survival. Progression and response can be defined as clinical progression, the appearance of one or more new lesions and tumor burden at baseline to be used for assessment and measurement for objective response by treating MD.

Response will be evaluated in this study using the international criteria proposed in the Revised Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 [*Eur J Cancer*. 2009;45:228-247.] See http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf? further details.

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

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis).

Response Criteria: Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions; Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

8.0 PATIENT REGISTRATION

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed / faxed to:

Kayla Rosati
Director, BrUOG
Brown University Oncology Research Group,
Brown University
Box G-R 001

Providence, RI 02912
Fax: 401-863-3820
Phone: 401-863-3000

All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form. Sites must confirm each element of inclusion and exclusion criteria and also provide support for all "pre-study" assessments on the schedule of evaluations table.

9.0 PHARMACEUTICAL INFORMATION

9.1 BYL719:

9.1.1 Drug Class: BYL719 is an oral small-molecule inhibitor of the p110α catalytic subunit of PI3K, which is encoded by the *PIK3CA* gene,

9.1.2 Supply: BYL719 (alpelisib) will be supplied by Novartis

9.1.3 Pharmaceutical Form: BYL719 (alpelisib) will be provided as film-coated tablets in 200mg and 50 mg strengths for once daily administration.

9.1.4 Storage: The storage conditions are provided on the label(s) of *the clinical supplies. Do not store above 25°C (77°F). Protect from moisture. Protect from light.* . Based on ongoing stability data, the storage conditions may be reconsidered, as appropriate.

9.1.5 Toxicities: Dose limiting toxicities (DLTs) of single agent studies with BYL719 were hyperglycemia, nausea, vomiting, and diarrhea. The most common BYL719-related adverse events **regardless of relationship** were nausea (64.2%), decreased appetite (59.7%), diarrhoea (58.2%), hyperglycaemia (56.7%), vomiting (49.3%), fatigue (46.3%), aneamia 29.1%), stomatitis (23.1%), weight decreased (22.4%) and asthenia, oedema peripheral and headache (20.9% each) and asthenia (20.1%).

A reported by Novartis in Investigator Brochure edition 10, overall 13 on-treatment deaths (9.7%) were reported (in the study CBYL719X2101 single agent trial), including nine deaths (13.8%) at the MTD dose level of 400mg, three deaths (37.5%) at 300mg and one death (6.7%) at 150mg b.i.d.. No deaths were reported in the 30 mg, 60 mg, 90 mg, 180 mg, 270 mg, 350 mg, 450 mg, 120 mg bid, and 200 mg bid treatment groups. Of these 13 deaths, 12 deaths were reported due to disease progression and one death due to hypoxia.
None of these deaths were suspected to be related to the study drug.

Hyperglycaemia appears early on, within the first two cycles of treatment with a peak around treatment day 8-10 and is well managed with oral anti-diabetic drugs like metformin or pioglitazones. Occasionally, insulin might also be needed for a short period of time to successfully control the hyperglycemia induced by BYL719. BYL719 induced hyperglycemia is usually reversible and may or may not be accompanied by clinical symptoms. The first manifestation of hyperglycaemia may be assessed by lab values only.

According to the Novartis safety database there has also been two hyperglycaemia-related events considered life-threatening and reported as hyperglycaemic hyperosmolar nonketotic syndrome (suspected to be drug-related), and one event reported as diabetic ketoacidosis (suspected to be drug-related). The one hyperglycaemic hyperosmolar nonketotic syndrome was reported in study CLEE011X2107 (phase Ib/II, combination of ribociclib and alpeslisib with letrozole) 265 days after

initiation of therapy, following episodes of elevated blood sugar level. Upon insulin therapy and interruption of BYL719, the patient fully recovered. The diabetic ketoacidosis event was also reported in the still blinded SOLAR-1 study fourteen days after initiation of therapy in the context of a urinary tract infection in a patient with an existing history of type 2 diabetes mellitus. Upon discontinuation with study medication, insulin therapy and other related measures, the patient fully recovered.

9.1.6 Drug Administration: See detailed information in section 4.1

9.1.7 Drug Interactions: See detailed information in section 4.2

9.2 Capecitabine

9.2.1 Mechanism of Action: Capecitabine is an oral prodrug of 5-fluorouracil. Metabolized in the liver to 5'-deoxy-fluorocytidine, subsequently converted to 5'-deoxy-5-fluorouridine which is then hydrolyzed to 5-fluorouracil (active). Peak plasma levels occur in 90 minutes, and elimination half-life is 45 minutes.

9.2.2 Supply: Capecitabine is commercially available.

9.2.3 Pharmaceutical Form: Capecitabine is supplied as a biconvex, oblong film-coated tablet for oral administration as 500 mg and 150 mg tablets.

9.2.4 Storage: Tablets should be stored at controlled room temperature (25°C) in tightly closed containers with excursions to 15-30°C permitted

9.2.5 Toxicities: Common side effects from capecitabine include diarrhea (which may be severe), dermatologic effects (hand-and-foot syndrome referred to as palmar-plantar erythrodysesthesia), hematologic effects (neutropenia, thrombocytopenia, anemia and lymphopenia), weight gain, gastrointestinal effects (diarrhea, nausea, vomiting stomatitis, abdominal pain and constipation). Uncommon side effects include hepatotoxicitiy (hyperbilirubinemia). Rare side effects may include cardiovascular effects (myocardial infarction, dysrhythmias, cardiomyopathy).

9.2.6 Administration: Food delays the time to peak plasma level by about 90 minutes, and reduces the peak plasma concentration about 60%. Despite the effects of food on capecitabine pharmacokinetics, the manufacturer recommends giving the drug at the end of a meal because established safety and efficacy data are based on administration with food. The capecitabine daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. The tablets should be taken with water.

9.2.7 Potential Drug Interactions:

Antacids

The administration of 20 mL of an antacid containing aluminum hydroxide and magnesium hydroxide may result in an increase in the area under the concentration-time curve (AUC) and maximum concentration (Cmax) of capecitabine of 16% and 35%, respectively. These changes were not considered clinically significant.

Oral Anticoagulants

Altered coagulation parameters and/or bleeding, including death, have been reported in patients receiving capecitabine and coumarin-derivative anticoagulants. Post marketing reports have revealed clinically significant increases in prothrombin time (PT) and INR in patients who were

stabilized on anticoagulants when capecitabine was initiated. These events occurred within several days to several months after concurrent therapy was initiated. Patients receiving capecitabine and an oral anticoagulant should be closely and regularly monitored.

Phenytoin

Some patients receiving capecitabine and phenytoin may experience phenytoin toxicity as a result of increased phenytoin plasma levels. Phenytoin levels should be closely monitored in patients taking concomitant phenytoin and capecitabine. The dose of phenytoin may need to be reduced.

CYP2C9 Substrate

Caution should be used when capecitabine is coadministered with drugs known to be CYP2C9 substrate.

10.0 AGENT ACCOUNTABILITY

Investigational Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all BYL719 using a Drug Accountability Record Form. Sites may utilize the NCI drug accountability form. Sites must track lot numbers, expiration dates and inventory. Sites must submit to BrUOG accountability logs during the study and prior to destruction. To be able to destroy drug, sites must contact BrUOG who will obtain approval from Novartis prior to destruction.

10.1 Treatment Compliance

Records of BYL719 and capecitabine used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted.

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

11.0 ADVERSE DRUG REACTION (ADR) REPORTING

BrUOG considers the SAE reporting period to begin when the subject signs the study specific informed consent.

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of BYL719 ® whether or not considered related to BYL719 ®. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

11.1 Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious adverse event (SAE)

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition **such as the need for inpatient radiation due to difficulties in transportation.**
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent **This must be documented and submitted to BrUOG**
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience**.**

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event. Sites to inform BrUOG of a visit with confirmation that treating MD or PI has confirmed that ER visit does not meet above criteria, including an important medical event.

Unexpected adverse event
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

11.2 Monitoring of Adverse Events and Period of Observation
Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

11.3 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS
Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 4.03. A copy of the CTCAE Version 4.03 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

11.3.1 Pregnancies
Pregnancies
To ensure patient safety, each pregnancy in a patient on study treatment must be reported to BrUOG by the site within 24 hours (1 business day) of learning of its occurrence and BrUOG will report to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on Medwatch 3500A and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Sites are also required to complete a MedWatch 3500 A SAE form as well.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

11.3.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study treatment (radiation, capecitabine or study drug, whatever is the last date of treatment), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first must be reported by BrUOG to Novartis within 24 hours (1 business day) of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported if the investigator suspects there may be a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode to BrUOG by the site, within 5 days of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the MedWatch 3500A. When BrUOG submits the Medwatch 3500A form to Novartis, the Novartis Serious Adverse Event Report Form will also be completed and sent, and all applicable sections of the form will be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete MedWatch 3500A form in English, within 5 days of being made aware of the event and BrUOG will then send the completed, signed Medwatch 3500A, and the Novartis SAE fax Report Form to the oncology Novartis Drug Safety and Epidemiology (DS&E) department within 24 hours (1 business day).

The telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E) are listed in the investigator folder provided to BrUOG. The original copy of the Novartis SAE fax Report Form, MedWatch 3500A and the fax confirmation sheet must be kept with the case report form documentation at BrUOG. The fax number is 1-877-778-9739.

Follow-up information is sent to the same contact(s) to whom the original/initial SAE was submitted. BrUOG again must send the Novartis SAE Report fax Form along with the site completed MedWatch 3500A. The Medwatch 3500A must state that this is a follow-up to the previously reported SAE. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator

Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Expedited Reporting by Investigator to Novartis
Serious adverse events (SAE) are defined above. All events must be reported, by FAX or email, to the Brown University Oncology Research Group who must inform Novartis in writing using a Medwatch 3500A form and Novartis Serious Adverse Event fax Report Form, of any SAE within 1 business day of being aware of the event via site submitted signed MedWatch 3500A. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE (such as discharge from hospital) is required. A copy of the fax transmission confirmation of the SAE report to Novartis should be attached to the SAE and retained with the study records at BrUOG.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy (radiation, capecitabine or study drug, whatever is the last date of treatment) must be reported to BrUOG within 5 days of the investigator being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks (30 days) after the patient has stopped study participation/treatment (radiation, capecitabine or study drug, whatever is the last date of treatment), or until the subject withdraws consent from study participation (declines participation) or at the time the patient becomes a screen failure, whichever occurs first, must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation (radiation, capecitabine or study drug, whatever is the last date of treatment) need only be reported if a relationship to the Novartis study drug (or therapy) is possibly suspected.
For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

11.4 Reporting requirements and procedures depend upon:

1. Whether investigational agents are suspected of causing toxicity;
2. Whether the possibility of such a toxicity was reported in the protocol, consent form, or manufacturer's literature (Expected toxicity); and
3. The severity of grade of the toxicity.

11.5 Assessing Causality:
Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used:

Yes: if the temporal relationship of the clinical event to treatment administration makes a

causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

11.6 Types of Report: For sites:
Telephone report: For SAE's contact BrUOG Central Office (401) 863-3000 (or via email), immediately upon learning of the event (within 24 hours) as a form of notification. For follow-up SAEs please inform BrUOG within 24 hours of sending in follow-up SAE reports.

Written report: Send the copy of the Medwatch 3500A form within 5 days of the investigator being made aware of the event to the BrUOG Central Office by email, scan or Fax:

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Emails: Kayla_rosati@brown.edu and Kristen_Mitchell@brown.edu

All deaths during treatment or within 30 days following completion of active protocol therapy (radiation, capecitabine or study drug, whatever is the last date of treatment) must be reported within 5 days of the investigator being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported to BrUOG via signed MedWatch 3500A **within 24 hours** of the investigator being made aware of the event.

MedWatch 3500A Reporting Guidelines:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Patient number, initials, age, sex, weight
- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned) * be sure to clearly document what serious events are versus what events may be non-serious.
- **Description of event, severity, treatment, and outcome, if known**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
- Expectedness of SAE
- Lot # of drug
- All SAE reports must be typed
- *It is required that the following are written on the Medwatch 3500A for tracking: BrUOG 302 & CBYL719XUS10T

A final report to document discharge from hospital is required.

Follow-up information:
Additional Info maybe added to a previously submitted report by any of the following methods.

- Adding to the original MedWatch 3500A report and submitting it as follow-up

- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

Summarize new information and fax it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted. (The subject identifiers are important so that the new information is added to the correct initial report).

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Novartis SAE form: For BrUOG
Information about all SAEs is collected and recorded on the Novartis Serious Adverse Event fax Report Form must have; all applicable sections of the form completed in order to provide a clinically thorough report. It is required that the following be listed on the Novartis fax cover sheet: BrUOG 302 & CBYL719XUS10T

11.7 BrUOG Responsibility Regarding Reporting:
The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 5 calendar days after initial receipt of the information. BrUOG will alert Novartis to an SAE within 24 hours,1 business day, of being made aware of the event and only when in receipt of the signed documentation. SAEs will be reported as an amendment to the IND (if applicable) within 5 calendar days of sponsor notification. They will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA(which will be sent to the Medwatch fax line for IND exemption or to the division fax if there is an IND). A copy of the form will be kept by the BrUOG Central Office.

Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND)

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well

All SAEs that are serious and reasonably or probably related to the use of BYL719 ® will be faxed to: Novartis

Novartis fax number for SAE reporting: 1-877-778-9739.

It is required that the following be listed on the Novartis fax cover sheet: BrUOG 302 & CBYL719XUS10T
11.8 Safety Reporting for IND Holders
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

a. Expedited IND Safety Reports:
BrUOG will fax reports to the FDA for IND Safety Reports: 1 (800) FDA – 0178, unless per the IND status BrUOG is to submit the SAEs to the Division Fax instead.

b. IND Annual Reports, for IND study only
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Novartis as a supporter of this study.

11.9 Adverse event updates/IND safety reports External
Novartis shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Extraordinary medical circumstances or withdrawal of consent by the patient: If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

1. **Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.**
2. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
3. The physician feels it is in the best interest of the patient to stop the treatment.
4. Inter current illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
5. Non protocol chemotherapy or immunotherapy is administered during the study
6. Noncompliance with protocol or treatment—major violation
7. Pregnancies or Suspected Pregnancies(including positive pregnancy test)
8. Patient is lost to follow-up
9. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
10. Death

In this event notify:

Brown University Oncology Research Group (BrUOG) Central Office,
Phone: (401) 863-3000
Fax: (401) 860-3820

The BrUOG Central Office will in turn notify the Principal Investigator.

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival with follow-up forms as dictated by the protocol**

13.0 FOLLOW-UP

All Subjects that discontinue treatment early for any reason (not including screen fails or patient with withdraw consent/decline study participation) as well as patients who complete therapy will be followed for survival (up to 5 years). At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 2 weeks and 30 days post the last treatment (radiation, capecitabine or study drug, whatever is the last date of treatment). In addition off study evaluations will be done when treatment is discontinued -Section 6.0.

14.0 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Howard Safran, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is supported by Novartis (the makers of BYL719).

14.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

14.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be provided to Brown University Oncology Research Group, and Novartis. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Novartis of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group, and Novartis. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

14.3 Protocol amendments or changes in study conduct:
Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed and approved and created by Brown University Oncology Research Group, who will obtain approval by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group, and Novartis.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group and Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology Research Group and Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

Examples of administrative changes not requiring formal protocol amendments include:

- Changes in the staff used to monitor trials (Novartis considers a change in Principal Investigator or the addition of sub-site(s) to be substantial and requires Novartis approval prior to implementation)
- Minor changes in the packaging or labeling of study drug.

15.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION
15.1 Good Clinical Practice: The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

15.2 Patient Confidentiality: In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Novartis or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.3 Protocol Compliance: The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Novartis and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to

patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Novartis and the regulatory authority (ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

15.4 On-site Audits: Regulatory authorities, the IEC/IRB and/or Novartis clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

15.5 Drug Accountability: Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to BrUOG prior to approval for disposal of the drug (if applicable and if approved by Novartis) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing BYL719 ® will be treated and disposed of as hazardous waste in accordance with governing regulations.

15.6 Premature Closure of the Study: This study may be prematurely terminated, if in the opinion of the investigator or Novartis, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Novartis by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to Novartis.

15.7 Record Retention:
The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principle Investigator (Howard Safran, M.D.) and Brown University Oncology Research Group Manager of Operations (Kayla Rosati) will monitor this study. The case report forms will be monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Amgen will notify the Principle Investigator if an application is filed.

16.0 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

17.0 STATISTICS

Sample Size Justification:

Three patients will be accrued to level 1. If no dose limiting toxicities are observed following completion of BYL719, capecitabine and radiation, and once the 2 week post treatment completion assessment is performed, then accrual to level 2 will proceed. If a DLT is observed in one of the first 3 patients in a dose level, then accrual for that level will be expanded to 6 patients. Two or more instances of DLT in a cohort of 6 patients will result in the preceding dose level being defined as the MTD. After determination of the MTD, the final cohort will be expanded to treat a total of 24 patients on the entire study. During the dose escalation phase, if 3 or more patients have a DLT or there is one grade 5 treatment-related serious adverse event that occurs, protocol accrual will be suspended. If this circumstance occurs, the Brown University Oncology Research Group data safety monitoring Chair will review the adverse event data and make

appropriate recommendations to the Brown University Oncology Research Group and the FDA about the study.Sample size: Approximately 24.

Threshold To Bring BYL719 Forward With Capecitabine and Radiation in Rectal Cancer: The primary goal of this Brown University Oncology Research Group is to determine that a safe dose of BYL719 can be administered with capecitabine and radiation in patients with rectal cancer. *Therefore, the threshold of success for this phase I study is to establish safety.* In a subsequent NRG study, within the TNT framework, a randomized phase II study will be planned exclusively in patients with PIK3CA mutations to assess whether pathologic complete response is improved within this specific subgroup of patients.

A patient will be considered inevaluable if they receive <67% of their total intended treatment (BYL719, Capecitabine or Radiation) for non-protocol required reasons.

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APPENDIX A

Agreement to Participate in a Research Study
And Authorization for Use and Disclosure of Information

BrUOG 302: BYL719, Capecitabine and Radiation for Rectal Cancer: A Brown University Oncology Research Group Phase I Study

You are being asked to take part in a research study. All research studies at <INSERT HOSPITAL NAME> hospitals follow the rules of the state of <INSERT STATE>, the United States government and <INSERT HOSPITAL NAME>. Before you decide whether to be in the study, you and the researcher will engage in the "informed consent" process. During this process, the researcher will explain the purpose of the study, how it will be carried out, and what you will be expected to do if you participate. The researcher will also explain the possible risks and benefits of being in the study, and will provide other information. You should feel free to ask any questions you might have. The purpose of these discussions is for you to decide whether participating in the study is the best decision for you.

If you decide to be in the study, you will be asked to sign and date this form in front of the person who explained the study to you. This form summarizes the information you discussed. You will be given a copy of this form to keep.

Nature and Purpose of the Study

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Howard Safran, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study, which is financially supported by Novartis, the makers of the drug BYL719.

You are being asked to take part in this study because you have rectal cancer. Prior to surgery to remove rectal cancer, the standard treatment is to first receive radiation therapy together with the chemotherapy pill capecitabine. Radiation is given once-a-day, Monday through Friday, for 28 treatments over approximately 6 weeks. Capecitabine is a type of chemotherapy pill that is given twice-a-day on the radiation treatment days and makes the radiation more effective. The study will evaluate adding a pill called BYL719 (alpelisib) with standard radiation and capecitabine. BYL719 blocks a cancer growth pathway called PI3K which may stimulate rectal cancers to grow. BYL719 may also make treatment with radiation more effective.

The purpose of this study is to determine the highest tolerable dose of BYL719 that can be given safely with radiation and capecitabine. We will also be studying the side effects of BYL719 in combination with radiation and capecitabine. BYL719 is an experimental drug which means it has not been approved by the United States Food and Drug Administration for the treatment of cancer.

We expect to enroll approximately 24 patients into this study. Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Howard Safran, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study, which is financially supported by Novartis, the makers of the drug BYL719.

Explanation of Procedures

What will happen if I take part in this research study?

If you take part in this study, you will have exams, tests and procedures to show if you can be in the study. If you choose to take part, then you will need the following tests and procedures, while on the study.

- Medical history
- Prior to entering this study you will have had a biopsy of your rectal cancer. If not previously performed, the pathology department at Rhode Island Hospital will perform a "molecular profile" of your cancer to evaluate standard genes that may be abnormal in your cancer. Genes may control how cells grow and react to chemotherapy.
- Physical examination, including weight, vitals, performance status (patient's level of functioning in terms of their ability to care for them self, daily activity, and physical ability), and toxicity assessment (a review of how you are handling the treatment) prior to starting Blood tests prior to starting treatment, approximately 3 tablespoons of blood. If you are a female of child-bearing potential you will also have a pregnancy test (via blood). All patients will also have a urinalysis
- CT scan (or MRI or PET scan) of the chest, abdomen and pelvis within 2 months of starting treatment. This will be repeated prior to starting the study treatment if you had one done a few months ago and have been receiving chemotherapy
- EKG prior to starting treatment.
- Echocardiogram or MUGA (A MUGA is a scan, which creates video images of the lower chambers of the heart that hold blood (called "ventricles") to check whether they are pumping blood properly. It shows any abnormalities in the size of the ventricles and in the movement of the blood through the heart) test prior to starting treatment.

On study/treatment:

- Physical examination, including weight, vitals, performance status, weekly for 6 weeks during radiation 4 weeks after radiation is completed. Toxicity assessment will be done weekly during treatment then at 2 and 4 weeks post completion of treatment.
- Blood tests, approximately 3 tablespoons of blood, weekly for 6 weeks during radiation then 2 and 4 weeks after radiation is completed.
- CT scan (or MRI or PET scan) of the chest, abdomen and pelvis approximately 4 weeks after completing treatment

Follow-up:
Once you complete the study treatment and surgery, you will see your study doctor as often as they normally see their patients who have been treated for rectal cancer for survival and disease status for approximately 2 years.

If you come off study early for any reason you will still be followed post your surgery and for survival and disease status for approximately 2 years.

You will receive radiation treatment for the rectal cancer, every day, Monday through Friday for 28 treatments. You will receive the chemotherapy pills capecitabine, twice a day, , starting Sunday evening thru Friday morning or until the morning you are due to receive your last radiation treatment, on the days

you receive radiation. Depending on your height and weight you will take approximately 4-6 pills of capecitabine per day. You will receive BYL719, to take approximately 3 pills per day, 7 days per week, beginning on the first day of radiation and ending on your final day of radiation. BYL719 will be administered orally, once daily on a continuous dosing schedule. BYL719 will be dosed on a flat-fixed dose and not adjusted by body weight or body surface area. Missed doses of BYL719 will not be made up and will be stopped when radiation is completed. If radiation is not given to you because it is held or missed, you may be instructed to NOT take the capecitabine or BYL719 drugs. The research staff will speak with you about any changes to your dosing schedule if radiation is not given.

All people on the trial will receive standard dosages of capecitabine and radiation. This study will determine the best dose of BYL719 to administer with capecitabine and radiation. Patients will be treated in groups of 3-6 patients to determine the highest safe dose of BYL719. Your doctor will discuss with you the dose of BYL719 that you will receive. The dose of BYL719 you receive depends on when you take part in the study and your dose will not be increased. Only after 3-6 patients have completed treatment at a dose level, and the dose level is determined to be safe, will 3-6 additional patients start a higher dose level of BYL719. Once the highest safe dose level is found more patients will be treated at the determined dose so that a total of 24 patients are treated on the study.

Approximately 6-10 weeks after you have finished radiation you will have standard surgery to remove your rectal cancer. You will be given a separate consent form for this surgery.

There are few instructions you have to follow with regards to taking the BYL719 drug:

- Take study drug BYL719 each morning with a glass of water (~250 ml or ~8 fluid ounces) daily approximately 1 hour after a light breakfast or a snack.
- Take study drug BYL719 at approximately the same time each day (recommended 8AM +/1 hour).
- If, for any reason, study drug BYL719 was not taken at the time you normally take it, then you should take study drug BYL719 within 1 hour after a meal or snack at any later point in time during the same day, but not later than 6 pm that day. If not taken by 6pm, do not take study drug BYL719 that day (skip that dose) and continue with your regular dosing on the next morning. **Do not ever** take a double dose to make up for the missed dose. Missed doses are not made up the next day.
- If you missed a dose please be sure to document it on the drug diary
- Swallow the tablets and not to chew or crush them.
- If vomiting occurs do not take another dose of medication until your next scheduled dosing. Please tell your Study Doctor if you experience any vomiting or diarrhea. Tell the research team when and how many times you may have experienced vomiting and diarrhea or about an increase in stool frequency.
- Avoid Seville or bitter oranges (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. These fruits are restricted because some can affect your metabolism with certain drugs. Regular orange (Citrus X sinensis) juice is allowed, such as Tropicana.
- Your study doctor will review the types of medications (called CYP3A inducers and inhibitors) that you will not be able to take while on this study.
- You will be asked to record when you take the study drug (and other study medication) on a drug diary, which the research staff will give to you each week.

How long will I be in the study?

You will receive BYL719 for approximately 6 weeks. Approximately 2 and 4 weeks post your last treatment you will be seen by your study doctor. You will then be followed by your doctors as they normally follow patients who received this type of treatment for rectal cancer for survival and disease status for approximately 2 years

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include the BYL719 drug, which will be provided at no charge by Novartis, the maker of the drug.

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. Examples are; all study doctor visits, blood tests, the capecitabine pills, radiation, drugs used to reduce side effects from chemotherapy, CT scans, EKG, echocardiogram/MUGA and the pathology department's genetic evaluation of your tumor tissue. These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

Contact Information: If you have any questions regarding this study, you may contact your site Principal Investigator, <INSERT CONTACT>, MD at <INSERT NUMBER>

Discomforts and Risks

You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or may never go away.

Taking part in this study may lead to time away from work.

BYL719:

The potential side effects described below for BYL719 are based on tests in animals and experience in cancer patients.

It is recommended that you avoid sun exposure and that you protect yourself from direct exposure to sunlight (by use of hats, wear of sunglasses, long-sleeve shirts and long pants and broad spectrum sunscreen) when outdoors due to potential skin reactions.

Most frequent events that may be caused by BYL719 in clinical studies (occurring in 10% or more of patients) observed in BYL719 clinical studies that may be caused by BYL719 include, but may not be limited to:

- Increase in blood sugar (hyperglycemia): increase in blood sugar usually appears within the first two cycles of treatment and may or may not be accompanied by clinical symptoms like excessive thirst, blurred vision, fatigue, headache, or frequent urination. In some instances, the first manifestation can be very high levels requiring hospitalization. Few patients have reported increased blood sugar levels considered life-threatening. Worsening of pre-existing diabetes leading to ketoacidosis (a serious diabetic complication when your body produces too much acid) has been reported in one patient. Increased blood sugar levels are closely monitored during the study and are generally well-managed with oral anti-diabetic drugs like metformin. Occasionally, insulin might also be needed for a short period of time to successfully control the increased blood sugar levels induced by BYL719. In order to ensure your safety your blood sugar levels will be closely monitored
- Nausea and/or vomiting
- Diarrhea
- Decreased appetite, decrease in weight
- Dyspepsia (stomach pain/upset)
- Inflammation and pain in the mouth
- Feeling tired/weak, fatigue
- Rash (eruption and/or redness of the skin with or without itchiness, which may be generalized). Please notify your doctor immediately if you notice any changes in your skin.
- Dry skin
- Dehydration
- Changes in taste sensation
- Decrease in blood cell counts (red cells)
- Swelling, particularly of the limbs
- Pain in the limbs
- Fever
- Insomnia (difficulty sleeping)
- Changes in blood tests results for kidney and liver - these may tell us if your kidney or liver are being irritated by the study medications or if they are working
- Low levels of certain minerals such as potassium and magnesium
- Headache
- Abdominal pain, constipation
- Shortness of breath

Common adverse events, occurring in more than or equal to 1% and less than 10% of patients, observed in BYL719 clinical studies that may be caused by BYL719, include but may not be limited to:

- Changes in blood tests results for pancreas - these may tell us if your pancreas is working
- Decrease in blood cell counts (platelets or lymphocytes)
- Inflammation (swelling and redness) of tissue that lines the body parts (mucosa)
- Swelling, particularly around eyes
- Increase in blood pressure
- Dry mouth, pain in the mouth
- Thirst
- Hair and/or finger nail loss
- Dry eyes, blurred vision
- Muscle spasms
- dizziness, forgetfulness
- Low blood levels of certain minerals, such as calcium or phosphate for which you may need to take supplements
- Increase in certain enzymes in the blood (such as alkaline phosphatase)
- Some changes in the electrical activity of the heart (ECG readings, such as prolongation of the QT interval) that may possibly be a sign of change in heart beat requiring further follow-up
- Cardiac events, not limited to hypertension, hypotension and arrhythmias (when your heart beats too fast or too slow)
- Anxiety and depression
- Hypersensitivity or allergic reactions
- Infection of the lung (pneumonia)
- Pneumonitis (inflammation of the lungs) Cases of pneumonitis with fatal outcome have been observed in patients receiving BYL719 in combination with other drugs. If you experience any new or changing respiratory symptoms such as new or worsening cough, wheezing, feeling short of breath or difficulty breathing, you should contact your doctor immediately. You will be monitored carefully to make sure you are not developing any pneumonitis related symptoms. If you develop any symptoms suggestive of pneumonitis during treatment with BYL719, you will have a chest CT scan to examine your lungs (you will generally have a chest x-ray or a CT scan to follow your disease at regular intervals even if you do not have pneumonitis). Your treating physician may also take a biopsy of your lung to collect lung tissue or may perform other procedures if considered appropriate (in your best interest).

Uncommon adverse events (occurring in less than 1% of patients) observed in BYL719 clinical studies that may be caused by BYL719 include, but may not be limited to:

- Sudden significant deterioration of kidney function known as acute kidney failure (decrease in how well your kidneys work)

Other serious or medically important conditions that may occur in some patients include, but are not limited to:

- An elevation of pancreas enzymes in the blood has occurred in patients receiving BYL719. Few patients have experienced an inflammation of the pancreas (pancreatitis) which may have led to

hospitalization and can be life-threatening. Tell your doctor if you have severe abdominal pain or vomiting. You will be monitored closely for any signs and symptoms related to the elevation of pancreas enzymes in the blood for your safety during the study.

- Anaphylactic reaction - a severe sudden allergic reaction soon after drug administration which can be life-threatening. If you experience difficulty breathing or tightness in the throat, you should contact your doctor immediately.
- Severe skin reactions including serious illness consisting of erythematous eruptions with or without shedding and blistering of the skin and involvement of the mucosal membranes (e.g.: mouth, eyes and genitals) have been reported with the use of BYL719. Two cases of Steven's Johnson Syndrome (SJS) were reported in combination with other drugs, which are not being used in this trial (One case using the additional drug: MEK162 was deemed by the treating physician to be related to the combination of BYL719 and MEK162 and one case using the additional drug: fulvestrant, was deemed by the treating physician to be suspected as related to BYL719). Steven's Johnson Syndrome is a rare but serious disorder, that can be fatal, that usually involves the skin and the mucous membranes. SJS usually begins with flu-like symptoms and then includes a painful red or purplish rash.
- A condition known as tumor lysis syndrome has been reported when BYL719 was given to patients with advanced colorectal cancer with a monoclonal antibody treatment known as cetuximab. Tumor lysis syndrome can occur when tumor cells die very quickly from anti-cancer medications and usually occurs in the first few weeks of treatment. When tumor cells die, they release substances in to the bloodstream that can be harmful to organs such as the kidneys and heart. Patients receiving this combination of anti-cancer drugs can be at risk for tumor lysis syndrome. Your doctor will monitor your blood to assess that your organs remain healthy whilst you are taking BYL719 treatment.

Toxicities caused by BYL719 might result in dose modification or delay with respect to the standard therapy you are receiving with capecitabine and radiation followed by surgery, which could increase your risk of your cancer recurring (coming back) after standard therapy. A recurrence after standard chemotherapy, radiation and surgery could require an extensive "salvage" surgery.

CAPECITABINE:

Risks and side effects related to the capecitabine include those which are :

Likely (>10%)

- Nausea
- Diarrhea
- Mouth sores
- Loss of appetite and weight loss
- Weakness
- Tiredness
- Redness and/or drying of the skin, especially the hands and feet.
- Skin or nail darkening
- Skin rash or peeling of skin on hands and feet
- Low blood counts which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Infection

Less Likely (1-10%)

- Vomiting
- Muscle aches
- Constipation
- Hair loss
- Change in liver function that could cause jaundice (yellowing of skin)
- Unsteadiness

Rare but serious (<1%)

- Chest pain or irregular heartbeat

Dangerous interaction between capecitabine and warfarin (Coumadin®): If you are taking warfarin or Coumadin® (medicine to prevent blood clotting), capecitabine may change the way your blood clots. The interaction between warfarin and capecitabine is very large and could result in severe bleeding. Because of this, if you were on warfarin (Coumadin) before starting study treatment, it was stopped and/or switched to a different type of blood thinner. Do not resume taking warfarin (Coumadin) until your study doctor tells you that it is safe to do so.

RADIATION:
Risks and side effects related to the radiation include those which are:

Likely (>10%)

- Stomach pain and intestinal discomfort, which usually occur during the last three weeks of radiation and generally go away within 2 months after the treatment is finished
- Nausea
- Diarrhea
- Fatigue
- Tanning, redness of skin, and hair loss within the radiation area, which is temporary
- Permanently dry skin in the radiation treatment area
- Low blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Loss of appetite and weight loss
- Mild muscle aches in the area treated

Less Likely (2-10%)

- Vomiting
- Infection

Rare but serious (<2%)

- Change in liver or kidney function, which is unlikely to cause symptoms.
- Bowel obstruction, which could result in abdominal pain, nausea and vomiting and may require surgery.
- Gastric, duodenal or small-bowel ulcer formation that can result in abdominal pain, nausea and vomiting, and bleeding, and may require surgery.

Risk of Secondary Cancers or Leukemia: Chemotherapy drugs (such as capecitabine and BYL719) and radiation may increase the risk of other cancers or leukemia (a blood cancer).

Reproductive Risks

Chemotherapy may decrease the sperm count. This is usually temporary but is infrequently permanent, which would result in sterility. Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through 6 months after the final dose of study treatment. Highly effective contraception is defined as either:

i. Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception].
ii. Female sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
iii. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female study subjects, the vasectomized male partner should be the sole partner for that patient]
iv. Use a combination of the following (both a+b):
    a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
    c. Note: Hormonal contraception methods (e.g. oral, injected, and implanted) are not allowed as BYL719 may decrease the effectiveness of hormonal contraceptives.

You should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

Sexually active males should use a condom during intercourse while taking drug and for 6 months after the final dose of study treatment and should not father a child in this period, but may be recommended to seek advice on conservation of sperm. It is also highly suggested that males use spermicidal foam with a condom as another precaution. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Males should avoid donating sperm while they are receiving treatment.

By signing this document you are acknowledging that you understand and agree to the information presented in this Reproductive Risk section.

Antiemetics (anti-nausea pre-medications): Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.

You will receive pre-medication to reduce the risk of infusion/injection reactions on your treatment days. Overall, the pre-medications you will be given are well tolerated.

Venipuncture (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

When you receive chemotherapy by vein, there is a slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.

In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests (blood tests, chest x-rays, or CT scans as needed) to determine the effects of your treatment and alter the drug dosages if necessary.

Risk of CT imaging: CT imaging uses x-rays. The radiation dose associated with this procedure is estimated to be a small fraction of the annual permissible dose to an x-ray technologist.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Benefits

The goal of this phase I study is to determine the best dose and side effects of the addition of BYL719 to standard capecitabine and radiation. The use of BYL719 in this study is unlikely to help you. We hope the information learned from this study will benefit other patients with cancer in the future.

Alternative Therapies

What other choices do I have if I do not take part in this study?

- Getting treatment for your rectal cancer with standard radiation and capecitabine.
- Getting radiation alone
- Having surgery.
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might

change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

Follow-up after Withdrawal of Consent

If you leave the study, it would still be useful for us to know how you do over the next 5 years. *We would appreciate if you would permit us to get follow-up information about your health from your doctor or your medical record.*

____ If I withdraw from the study, you have my permission to collect information about my health from my doctor or medical record.

_____ I do not give my permission for you to continue to collect information about me if I stop participating in the study.

_____ _____

Signature of study volunteer Date

You have the right to change your mind at any time regarding follow-up after withdrawal. If you decide to quit the study please tell your site Principal Investigator <INSERT NAME>, MD by calling <INSERT PHONE NUMBER>

Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Neither Dr. Howard Safran, the sponsor of the study, nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part

in research studies you may contact<INSERT NAME> in the <INSERT HOSPITAL NAME> Office of Research Administration, at <INSERT CONTACT>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies/ might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor Dr. Howard Safran, BrUOG, the group coordinating the study and their affiliates, and Novartis, the supplier of the drug, its authorized agents and financial supporter of this trial.
- Doctors, nurses, laboratories and others who provide services to you or the sponsor in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights; Governmental agencies in other countries where the study drug may be considered for approval
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.
- Accrediting Organizations

The results of this research study and any correlative studies, in which you agree to participate, will probably be shared with other people and may be published in scientific reports, but your name and the fact that you were in this study will be kept confidential. Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and

Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

Additionally, a description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

GINA STATEMENT This study involves 'genetic testing' as defined by the Genetic Information Nondiscrimination Act of 2008 (GINA). GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. There are some limitations to GINA's protections (it does not apply to all insurers or employers, nor does it apply to all genetic information, such as information related to a genetic disease that you already have). In addition to GINA's protections regarding the ultimate use to which your genetic information is put, <INSERT HOSPITAL NAME>'s privacy policies generally protect the privacy of such information and restrict its release outside of <INSERT HOSPITAL NAME>, unless you specifically authorize its disclosure or unless disclosure without your authorization is permitted under applicable privacy laws.

For more detail about your privacy rights see the <INSERT HOSPITAL NAME> Joint Privacy Notice which has or will be given to you.

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL NAME> Privacy Notice*

This informed consent document expires on _____.

The Researcher is required to provide a copy of this consent to you.

_____ _____ _____
Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____
Signature of witness (required if consent is presented orally or at the request of the IRB) Date

_____ _____
Signature of Translator Date

_____ _____ _____
Signature of researcher or designate Date and Time when signed

* If signed by agent other than study volunteer, please explain below.

_____

_____

APPENDIX B: Checklist

BYL719, Capecitabine and Radiation for Rectal Cancer:
A Brown University Oncology Research Group Phase I Study.

Inclusion Criteria

_____(y/n) Histologically proven adenocarcinoma of the rectum

_____(y/n) Voluntary, signed written informed consent, Date signed_____

_____(y/n) Age ≥18

_____(y/n) Must be willing to consent to use effective contraception while on treatment and for at least 6 months afterwards

_____(y/n) CT scan of chest/abdomen/pelvis prior to registration (PET or MRI can substitute)

_____(y/n) EKG within 8 weeks study entry

_____(y/n) Echocardiogram with within institutional normal limits or LVEF ≥50%

_____(y/n) No evidence of distant metastases

_____(y/n) The tumor must be clinically Stage II (T3-4 N0) or stage III (N+). Stage of the tumor may be determined by CT scan, endorectal ultrasound or MRI. For patients who are entering this study after first receiving chemotherapy, this stage may have been obtained at time of first diagnosis. For expansion phase: stage IV patients are allowable per 3.1.2

_____(y/n) No prior pelvic radiation or radiation for rectal cancer

_____(y/n) Able to swallow and retain oral medications.

_____(y/n) Absolute neutrophil count ≥ 1,000/ul, Date_____

_____(y/n) Platelet ≥ 100,000/uL, Date_____

_____(y/n) Total bilirubin ≤ ULN, Date_____ If patient has Gilbert's syndrome see inclusion criterion and submit documentation to BrUOG.

_____(y/n) AST≤ 2.5x ULN and ALT ≤ 2.5x ULN Institution

_____(y/n) Creatinine ≤1.5xULN and/or creatinine clearance > 50%LLN

_____(y/n) Fasting plasma glucose ≤ 140 mg/dL and HbA1c ≤ 6.4% (must meet both criteria), Date_____

_____(y/n) HGB ≥ 9.0g/dL

_____(y/n) Potassium, Calcium and Magnesium (corrected for albumin) within normal range or ≤ grade 1 if determined not clinically significant by treating investigator (must send to BrUOG in writing).

_____(y/n) INR ≤ 1.5

_____(y/n) ECOG 0-1

_____(y/n) Ability to comply with protocol and study follow-up procedures

_____(y/n) QTcF ≤480 msec

_____(y/n) Patients history of diarrhea has been review and patient has been informed of potential study drug induced diarrhea and management.

Exclusion Criteria:

_____(y/n) Patients must not have received pelvic radiation for rectal cancer, or prior pelvic radiation for any other malignancy that would prevent the patient from receiving the required radiation treatments for this study. (Patients may receive neoadjuvant chemotherapy prior to study chemoradiation)

_____(y/n) Patients must not have an active concurrent invasive malignancy. Patients with prior malignancies , are eligible if they are deemed by their physician to be at low risk for recurrence. For example, patients with squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma of the cervix, early stage breast cancer, or carcinoma in situ of the colon that have been effectively treated are eligible, even if these conditions were diagnosed within 3 years prior to registration.

_____(y/n) Patient with impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BYL719 (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with colostomies are allowed unless colostomy is for one of the precluded reason above.

_____(y/n) Suspected or confirmed metastatic disease including CNS involvement. See section 3.1.2 for stage IV patient eligibility.

_____(y/n) Prior hypersensitivity to any of the excipients of BYL719 (alpelisib)

_____(y/n) Patient who has undergone major surgery ≤ 4 weeks prior to starting study treatment or in the investigators opinion who has not recovered from side effects of such procedure

_____(y/n) Patient with clinically manifest diabetes mellitus, or documented steroid induced diabetes mellitus

_____(y/n) Patient who has not recovered to grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy

_____(y/n) Patient who has had systemic therapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to study treatment (BYL719 drug)

_____(y/n) Patient has a clinically significant cardiac disease or impaired cardiac function. See eligibility for more details)

_____(y/n) QTcF interval > 480 msec on screening ECG

_____(y/n) Patient who is currently receiving medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes (TdP) and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug treatment. To be documented and submitted to BrUOG with registration.

_____(y/n) Patient who has participated in a prior investigational cancer treatment study within 30 days prior to enrollment. This refers to treatment not follow-up.

_____(y/n) Patient with known positive serology for human immunodeficiency virus (HIV)

_____(y/n) Patients who have other concurrent severe and/or uncontrolled medical conditions that would, in the Treating Physician's judgment, contraindicate patient participation in the individual patient program (eg. active or uncontrolled severe infection, chronic active hepatitis, immuno-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.)

_____(y/n) Patient with any other condition that would, in the Investigator's judgment, preclude patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g. infection/inflammation, intestinal obstruction, unable to swallow oral medication, social/psychological complications, chronic active hepatitis, severe hepatic impairment etc

_____(y/n) Patient has a history of non-compliance to medical regimen or inability to grant consent

_____(y/n) Patient is currently receiving treatment with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A or that prolong QT interval (see eligibility for more details.

_____(y/n) Patient 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

_____(y/n) Pregnant or breastfeeding. Women of child bearing potential must have a negative serum or urine pregnancy test (<5mIU/mL) within 14 days prior to beginning of treatment. Post-menopausal women do not need to have a pregnancy test, please document status. See eligibility for more details. See exclusion for definition of post-menopausal.

_____(y/n) Patient who does not apply highly effective contraception during the study and through the duration as defined below after the final dose of study treatment as defined in eligibility

_____(y/n) 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, medical marijuana and ginseng. Patients need to stop using these herbal medications 7 days prior to first dose of study drug.

_____(y/n) Patient must not eat or drink 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

_____(y/n) Patient is currently receiving or has received systemic corticosteroids $\leq$ 2 weeks prior to day 1 of study drug, or who has not fully recovered from side effects of treatment. The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).

_____(y/n) Patient is concurrently using other anti-cancer therapy

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form Enclosed __Not Enclosed _____ Not Applicable __

2) Heme/Onc initial note Enclosed __Not Enclosed _____ Not Applicable __

3) Pathology Report(s) Enclosed __Not Enclosed _____ Not Applicable __

4) MRI/CT Report(s) Enclosed __Not Enclosed _____ Not Applicable __

5) Lab Source Document Enclosed __Not Enclosed _____ Not Applicable __

6) ICF signature page

7) Other documents, please list_____

IRB approval date of protocol: _____

Hospital where patient will be treated with Oncologist: _____

Location where radiation will be given:_____

Date patient will begin treatment Capecitabine: _____

Date patient will begin treatment BYL719: _____

Date patient will begin treatment Radiation: _____

Primary Physician: _____

Radiation Oncologist:_____

Your signature: _____

APPENDIX C

NCI CTC Version 4

Toxicity will be scored using NCI CTC Version 4 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4

APPENDIX D

ECOG PATIENT PERFORMANCE STATUS

STATUS	KARNOFSKY	ZUBROD-ECOG-WHO	Description
No complaints	100	0	Normal activity
Able to carry on normal activities	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed <50% of the day
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed >50% of the day, but not bedridden
Disabled, requires special care and assistance	40		

Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization Necessary. Active support treatment necessary	20		
Moribund	10		
Dead	0		

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536

APPENDIX E

CASE REPORT FORMS

Attached separately are the BrUOG Case Report Forms

Appendix F: Permitted medications to be used with caution

Table 7 List of medications to be used with caution during treatment with BYL719

Category	Drug Name
CYP2A6 substrates	Disulfiram, fadrozole, halothane, losigamone, methoxyflurane, nicotine, valproic acid
Sensitive CYP2C8 substrates[2]	Paclitaxel, repaglinide
Sensitive CYP2C9 substrates[2]	Phenytoin
Sensitive CYP2C19 substrates[2]	S-mephenytoin, R/S-lansoprazole, clobazam, omeprazole, tilidine
Moderate CYP3A Inhibitors	Amprenavir, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera[2], tofisopam, verapamil
Moderate CYP3A Inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Gastric protection agents	BYL719 is characterized by a pH-dependent solubility. Medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of BYL719 and hence its bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. BYL719 should preferably be dosed in a staggered manner, i.e., at least 1 hour before or 10 hours after dosing with a gastric protection agent. Note that some proton pump inhibitors may possibly inhibit BCRP (see below).
BCRP inhibitors	BYL719 was identified as a substrate for the human BCRP. Co-administration of BYL719 with BCRP inhibitors may possibly increase systemic exposure and/or alter tissue uptake of oral BYL719.The treatment with BCRP inhibitors should be kept as short as possible or, if possible, fully avoided.
Drugs with a possible risk for Torsades de Pointes / QT prolongation[4]	Alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, eribulin, escitalopram, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, levofloxacin, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, ondansetron, oxytocin, paliperidone, pasireotide, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tamoxifen, tizanidine, venlafaxine, voriconazole, ziprasidone
Hematopoietic growth factors	Hematopoietic growth factors (e.g. erythropoietins, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered prophylactically. Use of these drugs should be reserved to patients with severe neutropenia and anemia as per the labeling of these agents or as dictated by local practice (see also the guidelines established by the American Society of Clinical Oncology (ASCO)).
Corticosteroids	Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone are known to induce CYP3A enzymes, thereby increasing the risk

Category	Drug Name
	of reducing letrozole drug exposure to sub-therapeutic levels. Since corticosteroids may prolong or aggravate hyperglycemia (steroid-induced diabetes), which is a common adverse event for PI3K inhibitors such as BYL719, they should be additionally used with caution and closely monitored.
Anticoagulation	Anticoagulants other than warfarin/coumarin derivates (Appendix 2, Table 8) or antiaggregation agents may be administered under the discretion of the investigator. However, caution is advised when BYL719 is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4, CYP2C9 and CYP2C19. BYL719 has the potential to inhibit some of these enzymes and may therefore decrease the metabolic activation and clinical efficacy of these pro-drugs. Patients using anti-platetet pro-drugs should be carefully monitored.

[1]Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria, or as specified in Section Concomitant Medications of this guideline document or listed in Appendix G,

[2]Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.

[3]NTI = narrow therapeutic index 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., Torsades de Pointes).

[4] Please also refer to http://crediblemeds.org/ for a comprehensive list of agents that prolong the QT interval.

Appendix G: Prohibited medications

List of prohibited medications during BYL719 treatment

Category	Drug Name
Strong CYP3A Inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole
Strong CYP3A Inducers	Avasimibe[2,3], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]
CYP3A substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
Sensitive CYP3A Substrates[4]	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, indinavir, levomethadyl, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simvastatin, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc
Other investigational and antineoplastic therapies	Other investigational therapies should not be used while the patient is on the study. Anticancer therapy [chemotherapy, biologic or radiation therapy, and surgery (unless specified in protocol)] other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.
Herbal medications	Herbal preparations/medications are prohibited throughout the study, as a potential drug-drug-interaction is always possible. These herbal medications include, but are not limited to: St. John’s wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, medical marijuana, and ginseng. Patients 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 prohibited in this study. Warfarin has a narrow therapeutic range and BYL719 is a possible inhibitor of CYP2C8 and 2C9, the major metabolizing enzyme of warfarin. Therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

Category	Drug Name
Drugs with a known risk for Torsades de Pointes / QT prolongation[5]	Amiodarone, amitriptyline (2C19), arsenic trioxide, astemizole, cepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, clomipramine (2C19), disopyramide, dofetilide, domperidone, dronedarone (CYP3A4), droperidol, erythromycin, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quetiapine (3A4), quinidine, ritonavir (3A4), sotalol, sparfloxacin, tacrolimus (3A4), telithromycin (3A4), terfenadine, thioridazine, trazodone (3A4), vandetanib, vardenafil (3A4)

[1]NTI = narrow therapeutic index 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., Torsades de Pointes)
[2]Herbal product
[3]P-gp inducer
[4]Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when
[5] Please also refer to http://crediblemeds.org/ for a comprehensive list of agents that prolong the QT interval.

Appendix H: CAPECITABINE DOSING TABLE BASED UPON BODY SURFACE AREA CALCULATION

Dosing Table Based Upon Body Surface Area
Calculation: Capecitabine Starting Dose

Dose level 1650 mg/m^2/d		AM 150 mg	AM 500 mg	PM 150 mg	PM 500 mg
BSA (m^2)	Total Daily Dose (mg)				
<1.24	2000	0	2	0	2
1.25-1.36	2150	1	2	0	2
1.37-1.51	2300	1	2	1	2
1.52-1.64	2600	2	2	2	2
1.65-1.76	2800	1	3	1	2
1.77-1.91	3000	0	3	0	3
1.92-2.04	3150	1	3	0	3
2.05-2.17	3300	1	3	1	3
>2.18	3600	2	3	2	3