THE UNIVERSITY OF ARIZONA Cancer Center

# Biomarker Modulation by Alpelisib (BYL719) in Transorally Resectable, HPV-Associated HNSCC: A Phase II Window Trial

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**SPONSOR-INVESTIGATOR:** Ricklie Julian, MD
University of Arizona Cancer Center
1515 N. Campbell Ave.
Tucson, AZ 85724
Phone: 520-694-2873
Email: rickliej@arizona.edu



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| Title | Biomarker Modulation by BYL719 in Transorally Resectable, HPV-Associated HNSCC: A Window Trial |
| Patient population | Patients with de novo stage I-IVa HPV associated, resectable, oropharyngeal head and neck squamous cell carcinoma (HNSCC) who are planned for definitive surgery. |
| Rationale for Study | Head and neck squamous cell carcinoma (HNSCC) is the sixth leading incident cancer worldwide with 600,000 incident cases in 2012. Five-year overall survival (OS) has increased incrementally in the past two decades. Improved prognosis is largely attributable to changing epidemiology; an increasing proportion of oropharyngeal HNSCC is infected with high-risk human papillomavirus (HPV), thought to confer sensitivity to conventional treatments. The PI3K/Akt/mTOR signaling network, a mitogenic pathway regulating cellular metabolism, proliferation and survival, plays a major role in HPV biology. Activation of the pathway is a nearly universal aspect of mammalian viral infection, and is of particular importance for dsDNA viruses such as HPV relying upon cap-dependent protein translation. The oncoproteins E5, E6 and E7 have direct roles in pathway activation: E5 upregulates PI3K; E6 binds tuberin, a component of the TSC which negatively regulates mTORC1; and E7 prevents de-phosphorylation of Akt following activation by PI3K. We would like to determine if PIK3CA mutations and/or gene amplification serve as predictive biomarkers for clinical responses to PI3K pathway inhibition in patients with transorally resectable HPV(+) HNSCC treated with the PI3K p110α-selective inhibitor BYL719. |
| Primary Objective | • To assess the preliminary efficacy of neoadjuvant BYL719 in patients with transorally-resectable, HPV+ HNSCC, as measured by quantitative change in tumor size (ΔT) following 10-21 days of treatment.<br>• To evaluate the relationship between genomic *PIK3CA* activation to ΔT |
| Secondary Objectives | • To describe the tolerability of brief neoadjuvant exposure to BYL719<br>• To assess the effect of BYL719 on the tumoral Ki-67 proliferation index<br>• To evaluate viral and molecular mediators of response and resistance to BYL719, including viral mRNA, E6 and E7 oncoproteins, and pHER3 |

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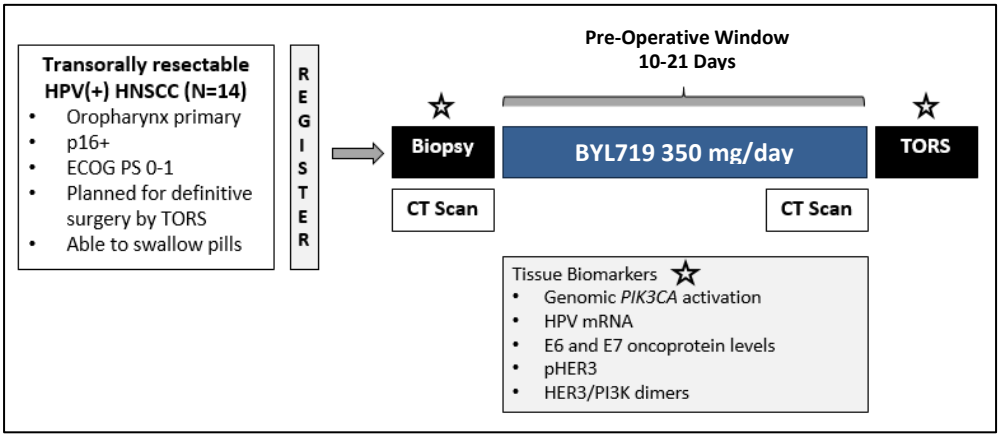
| Study Design | This is a study designed to assess the effect of the PI3K inhibitor BYL719 on tumor proliferation, size, and biomarker expression.<br>  |
| Number of patients | Projected accrual is 20 patients for this study, for a total of 14 biomarker-evaluable patients. |
| Duration of Therapy | Treatment will be during the pre-operative window of 10-21 days or up to 28 days for delays in planned surgery. |
| Duration of Follow up | 12-weeks post-operation, as deemed clinically necessary. |
| Duration of study | The study will complete accrual 24 months from the time the study opens and will close 36 months after the study opens.<br><br>*Note: Accrual to this study was significantly affected by the COVID-19 pandemic. Thus, the accrual time will be extended to 64 months from the time study opened and will close 84 months after the study opens.* |
| Study Drugs | BYL719/Alpelisib 350 mg PO daily as a pill |
| Safety Assessments | The safety of this window intervention will be reported descriptively, including tabulation of toxicities according to NCI CTCAE v.4, surgical complications, and length of hospital stay. |
| Efficacy Assessments | Preliminary efficacy of neoadjuvant BYL719 in patients with operable HPV+ HNSCC will determined by quantitative ΔTumor size. ΔTumor size will be measured using established RECIST v1.1 metrics for index lesions, however treated as a continuous variable. |

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| Biomarker Assessments | 1) *PIK3CA* genomic alteration (gene mutation or amplification in tumor)<br>2) Pre- and post-treatment tumor levels of:<br>• HPV mRNA (qPCR)<br>• E6, E7 protein<br>• Phospho-HER2<br>• HER3/PI3K dimers (monogram) |

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# 1 Introduction

## 1.1 Background on Indication

### Head and Neck Cancer

Head and neck squamous cell carcinoma (HNSCC) is the most common cancer arising in the upper aerodigestive tract. HNSCC is the sixth leading incident cancer worldwide with 600,000 incident cases in 2012.(1) Despite advances in multimodality therapy, 5-year overall survival (OS) is 40-60%, and has increased only incrementally in the past two decades.(2) The current standard of care for primary nonsurgical management of previously untreated, locally advanced (PULA) HNSCC is concurrent cisplatin-radiotheray (RT), which significantly improved overall survival (OS), progression-free survival (PFS), and locoregional control (LRC) compared with radiotherapy alone or the sequential administration of chemotherapy and RT. (3, 4) A developing standard is definitive radiotherapy with concurrent cetuximab, a chimeric monoclonal antibody against the epidermal growth factor receptor (EGFR), which improved survival relative to radiotherapy alone in patients with oropharyngeal, laryngeal, and hypopharyngeal HNSCC.(5)

## 1.2 Background on BYL719

Alpelasib or BYL719 (NVP-BYL719) is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds.

BYL719 inhibits p110α, in its wild-type form as well as when constitutively activated by somatic mutations, and is much less potent against the β, δ, and γ isoforms of PI3K, as well as Vps34 and mTOR. BYL719 shows significant antitumor activity and is well tolerated in relevant animal models. It also has good physico-chemical and pharmacological properties well-suited for drug development.

Most of the current oncology drug discovery and development work has shifted towards molecularly targeted therapies. A key focus has been on identifying inhibitors against components of pathways that drive tumor cell proliferation, survival, and metastasis such as the PI3K/mTOR pathway. PI3Ks are lipid kinases that are important in controlling signaling pathways involved in cell proliferation, motility, cell death and cell invasion. Class I PI3K contains four isoforms, p110α, p110β, p110δ and p110γ which carry out non-redundant signaling functions. The α and β isoforms are ubiquitously expressed, α is linked upstream mainly to receptor tyrosine kinases, whereas β can mediate signals from both G-protein-coupled receptors and from receptor tyrosine kinases. The γ and δ isoforms are expressed primarily in lymphocytes and play important roles in the regulation of immune responses.

A gain of function in PI3K signaling is common in many types of human cancer and include inactivation of the phosphatase and tensin homologue (PTEN) tumor suppressor gene, amplification/overexpression or activating mutations of some receptor tyrosine kinases (e.g.

ERBB3, ERBB2, epidermal growth factor receptor [EGFR]), amplification of genomic regions containing Akt, amplification of *PIK3CA* (the gene encoding p110α) and mutations in *PIK3CA*. More than 30% of various solid tumor types were recently found to contain mutations of *PIK3CA*. From these mutation frequencies, *PIK3CA* is one of the most commonly mutated genes identified in human cancers. As these mutations constitutively activate p110α kinase activity, the cancer-specific mutants of p110α appear to be ideal targets for drug development. p110α isoform-specific small molecular mass inhibitors, such as BYL719, could then have potential anti-cancer activity without causing the potential side effects that could be expected from interference with other isoforms or other members of the PI3K-related kinase (PIKK) family.

**Preclinical studies and pharmacodynamics**

In biochemical assays, BYL719 inhibits p110α (inhibitor concentration causing half maximal inhibition [IC50]=10 nM) much more potently than the p110δ and γ isoforms and PIK4β and has weak or no activity against p110β, Vps34 and mTOR. BYL719 is equipotent against the most common somatic mutations of p110α (H1047R, E545K) compared to wild type p110α, and is selective against a wide range of protein kinases with at least a 50-fold selectivity window compared to p110α. The potency and selectivity of BYL719 is confirmed at the cellular level in mechanistic and relevant tumor cell lines. BYL719 potently inhibits p110α cellular activity (IC50=74 nM) and shows significant selectivity against the p110β and p110δ isoforms (above 15-fold). BYL719 has no activity against mTOR (IC50> 10mM), and is not interfering with phospho-inositol 3 kinase-related kinases (PIKKs) involved in DNA-damage repair processes (IC50> 30mM on S15P-p53 and IC50> 10mM on S1981P-ataxia-telangiectasia mutation [ATM]). Its biological activity correlates with inhibition of various PI3K/Akt downstream signaling pathway components. *In vitro*, BYL719 inhibits the proliferation of cancer cell lines harboring gene alterations in *PIK3CA.*

*In vivo*, BYL719 shows dose and time-dependent inhibition of the PI3K/Akt pathway in relevant tumor xenograft models (p110α-mechanistic model and p110α-mutant xenograft models) in nude mice. *In vivo* analyses of tumor tissues, upon acute dose or after multiple treatments, show a good correlation between compound exposure and PI3K pathway blockade. BYL719 shows good tolerability and statistically significant dose-dependent antitumor efficacy in *PIK3CA* mutant and/or *ERBB2* amplified tumor xenograft models in mice. Moreover, in nude mice, after *in vivo* efficacy studies, blood glucose levels remained normal at all tested doses and time points. Plasma insulin levels were significantly increased at all tested doses to maintain glucose homeostasis, indicating on-target effects of BYL719 on the regulation of metabolism.

The combination of BYL719 with cetuximab was tested *in vitro* and *in vivo*. Superior anti-tumor effects were observed when BYL719 was combined with cetuximab compared to either agent alone. Combination of BYL719 and cetuximab led to tumor regression in two different xenograft models (FaDu and *PIK3CA* mutant HSC2 models), supporting the hypothesis of testing the combination of BYL719 with cetuximab in HNSCC cancer patients. In a phase II

clinical trial, BYL719 alone (n=32) or the combination of cetuximab plus BYL719 (n=5) was investigated in 37 patients with cetuximab-resistant, recurrent/metastatic HNSCC. With a confirmed response rate of 11% and a disease control rate of 51%, BYL719 was considered promising for further investigation, with or without cetuximab, in the cetuximab-resistant population(6).

**Preclinical Pharmacokinetics**

BYL719 had a low clearance (CL), a moderate volume of distribution at steady state (Vss) and a good absolute oral bioavailability in all preclinical species tests (Wistar rats, Beagle dogs, mice). The compound is moderately bound to plasma proteins independent of its concentration. BYL719 showed a rapid distribution to almost all rat tissues, except the brain (radiolabeled 14C-BYL719 study). BYL719 was found to be preferentially present in melanin containing tissues such as the choroid and ciliary body of the eye but declined with time. The highest tissue exposures after dosing were found in the liver, bile, harderian gland, hair follicles, tactile hair and in the preputial gland.

The overall metabolic turnover was very low in dog and human hepatocytes followed by the rat. Cytochrome P450 CYP3A4 was found to be the major P450 enzyme involved in hepatic oxidative metabolism *in vitro* with small contribution by other enzymes. While UGT phenotyping showed that UGT1A9 enzyme could be involved in the glucuronidation of BYL719 in human liver microsomes, the turnover rate of phase II metabolism *in vitro* was low. The main biotransformation pathway that was observed consistently *in vitro* and *in vivo* across species was amide hydrolysis to BZG791. No covalent drug protein adduct formation was noted in human microsomes or hepatocytes.

BYL719 is a substrate of breast cancer resistance protein (BCRP) and multidrug resistance (MDR)-1 protein (low affinity). It also showed little to no inhibition of the major uptake and efflux transporters (liver, kidney, and intestine). Uptake of BYL719 in human hepatocytes was found to be concentration-independent and was not influenced by inhibitors of the major transporter families OCT (organic cation transporters), OAT (organic anion transporters), OATP (organic anion transporting polypeptides) and NTCP (sodium/taurocholate cotransporting polypeptide). Assessment of the hepatobiliary disposition mechanisms of BYL719 in sandwich-cultured rat and human hepatocytes showed that it is actively transported into bile pockets.

Reversible weak inhibition of CYP2C8, CYP2C9 and CYP2C19 was observed *in vitro* with unlikely clinical relevance. The compound is also both a time-dependent inhibitor of CYP3A4 and inducer of CYP3A4 *in vitro.* Based on the current assessment both opposing effects seem to counterbalance each other. Refer to the IB, Sections 5.1.5 and 7.3 for a discussion of the transporter-based and metabolic drug-drug interaction potential. Results from 4-week and 13-week Good Laboratory Practice (GLP)-toxicology studies in dog showed a roughly dose-proportional increase in exposure. The rat exposure (in the GLP toxicology studies) increased until 30 mg/kg beyond which no further increase in exposure was noted following single dose administration. Increase in exposure up to doses of 50 mg/kg in rat was observed in a different

non-GLP rat toxicology study. The toxicology studies provided no clear evidence of increased exposures following multiple dosing (<2-3-fold). No gender differences were observed in rat or dog.

**Clinical Pharmacokinetics**

Currently, BYL719 pharmacokinetics as single agent was evaluated in the [CBYL719X2101] trial. The MTD was declared at 400 mg QD in escalating dose of single or repeated daily dosing regimens. Median Tmax at C1D8 ranged from 1.8 to 6.0 hours using QD dosing, and from 1.5 to 2.3 hours using BID dosing regimens. At clinically relevant doses (270-400 mg) between subject variability in the maximum plasma concentration (Cmax) at steady-state was moderate to high with 40-60% at C1D8. Plasma concentrations of BYL719 generally declined in a mono exponential manner, suggesting limited distribution towards the peripheral tissues. At steady state, the median terminal half-life generally appeared to be independent of dose and time and ranged between 6.8 and 9.4 hours. After dosing at 400 mg QD (MTD), the half life was approximately 7 to 8 hours. Steady state BYL719 plasma levels after daily dosing can be expected to be reached at 2 to 3 days following onset of therapy in most patients. Similar results are observed in the human ADME trial [CBYL719X2107]. Further description of the metabolism and excretion of BYL719 is described respectively in the IB, Section 5.1.3 and Section 5.1.4. In addition to these single-agent studies, preliminary pharmacokinetic results are presented for several studies using BYL719 in combination with fulvestrant, cetuximab, MEK162 and LGX818. The small size in these studies prevents making a conclusion at this time regarding potential interaction between BYL719 and these compounds.

The ADME characteristics of BYL719 in-vivo were tested in healthy volunteers in a hADME trial [CBYL719X2107] where 4 subjects received a single 400 mg oral dose of radiolabeled BYL719. After this single dose, the total recovery of radioactivity was almost complete, between 92.3 and 95.1, excretion was mainly via feces with approximately 77% recovery of radioactivity when only 9.9 to 18.8% of total radioactivity was recovered in feces. The absorption of BYL719 was estimated around 59%. The elimination of radioactivity followed a similar decline than BYL719 with an estimated terminal half-life of 18.0 hours No specific affinity for blood cells was observed. In plasma, BYL719 represented approximately 60% of the total radioactivity. The exposure in plasma of BZG719, major metabolite, represented about 27% of the total radioactivity, no other major metabolite was observed.

## 1.3 Rationale for Proposed Study

**Human Papillomavirus (HPV) in HNSCC**

Converging clinical, molecular and epidemiologic evidence now confirm that human papillomavirus (HPV) status is a critical determinant of prognosis in oropharyngeal HNSCC (OPSCC). HPV is an epitheliotropic, double-stranded DNA (dsDNA) virus with >100 characterized genotypes; HPV genotype 16 has predilection for oropharyngeal mucosa representing >90% of isolated DNA in OPSCC.(7) HPV underlies the epidemiologic

observation that both incidence and survival of OPSCC are increasing, in contrast to cancer associated with tobacco and alcohol.(8) In the U.S., population registry data confirmed epidemic rise in the proportion of OPSCC cases infected with high risk HPV from 1984 to 2004, from 16% to 72%.(9) Similar prevalence rates have been observed in Western Europe and Australia, although large regional, racial and ethnic variations are reflected by low reported rates in Central Europe, Latin America, and U.S. blacks.(10-13) In the U.S., approximately two-thirds of patients with oropharynx cancer have HPV-associated tumors. Hence, in 2012 approximately 4200 cases of OPSCC caused by tobacco and alcohol and 8400 cases of new HPV-associated OPSCC presented for treatment. The incidence of HPV-associated OPSCC in the U.S. is expected to surpass that of cervical cancer, universally associated with HPV, in 2020 – thus representing a major public health threat. Unlike cervical cancer, there is no established precursor lesion for OPSCC, and consequently no screening program for early detection or secondary prevention.

Emerging evidence indicates that both HPV status and tobacco use are the major independent prognostic factors for patients with HNSCC. Ang and colleagues presented a retrospective analysis of HPV status and tobacco use in RTOG 0129, a randomized phase III trial originally designed to compare accelerated-fractionation to standard-fractionation radiotherapy when delivered with concurrent cisplatin.(14) In multivariate analysis, patients with HPV positive tumors had a 58% reduction in risk of death compared with patients with HPV-negative tumors (hazard ratio 0.42; 95% CI 0.27-0.66). Of note, analysis of tumoral p16 protein expression by immunohistochemistry performed numerically better than detection of HPV DNA in identifying the good prognostic group (hazard ratio 0.33; 95% CI 0.21-0.53). Expression of p16 is upregulated when HPV E7 oncoprotein degrades Retinoblastoma, whereas p16 expression in HPV-negative tumors is usually silenced by epigenetic promoter methylation or genetic mutation.(15) Thus, tumoral expression of p16 protein reflects biologically relevant HPV infection, is not genotype-specific, and represents an accepted surrogate for HPV status in current clinical trial design (RTOG 1016, ECOG 1308).

The emerging understanding of the HPV epidemic in OPSCC, including a favorable prognosis when treated with conventional chemoradiotherapy (CRT), has framed the national clinical trial framework in PULA HNSCC.(13) Specifically, deintensification strategies are being investigated in patients with HPV-associated HNSCC, where current paradigms are thought to represent overtreatment – creating unnecessary and significant late toxicities from radiotherapy including dysphagia, aspiration, feeding tube dependence, neck contractures, facial lymphedema, voice changes, osteonecrosis, dental decay, chronic pain syndromes and secondary malignancies. In Eastern Cooperative Oncology Group (ECOG) 1308, the first cooperative group de-intensification trial, 80 patients with HPV-associated OPSCC were treated with induction cisplatin, paclitaxel and cetuximab.(16) Patients who experienced a clinical complete response at the primary site then underwent de-intensified radiation therapy (55 Gy). RTOG 1016 is comparing concurrent cisplatin to concurrent cetuximab with accelerated fractionation radiotherapy. This de-intensification model seeks to establish the non-inferiority of bioradiotherapy with cetuximab, given

cetuximab's favorable toxicity profile, however preserves the model of full dose, accelerated fractionation radiotherapy. Finally, the development of transoral surgical resection techniques for OPSCC, which demonstrate comparable oncologic outcomes yet reduced morbidity compared to historical open procedures, has resulted in surging interest in minimally-invasive surgery as a primary modality.(17-19) This has resulted in the design of ECOG 3311, a randomized trial evaluating radiation de-intensification after primary transoral resection for HPV-associated OPSCC. To date, de-intensification trial models in HPV-associated OPSCC have used available, U.S. FDA-approved agents initially developed in the era of HPV-negative HNSCC. As the biology of HPV-associated OPSCC is understood, investigators now have the opportunity to design trials exploiting targets unique to HPV biology.

**HPV and EGFR signaling**

Carcinogenesis by oncogenic HPVs is initiated predominantly *via* the two main oncoproteins, E6 and E7, with E5 also inducing proliferative activities. HPV-induced cancers of the cervix, oropharynx, anus, penis and vulva lack many of the activating mutations in cellular oncogenes, or in tumor suppressors *TP53* and *RB1***,** that non-viral cancers typically possess.(20-22) Rather, HPV transformation begins as E6 and E7 functionally inactivate tumor suppressor proteins, including, but not limited to, p53.(23-26) We recently showed that upon exposure of human keratinocytes to oncogenic HPV virus particles, signaling ensues from growth factor receptors (e.g., epidermal GFR, EGFR).(27) Subsequently, HPV induced signaling engages the downstream pathways of PI3K and MAPK that promote cell proliferation and survival.(28,29) Importantly, both of these cascades are activators of cellular AP1 transcription factors that stimulate HPV oncogene expression from four highly conserved AP1 binding sites in the HPV viral regulatory region.(30,31) In persistently HPV infected (non-cancerous) cells that resemble preneoplasias, stimulating EGFR signaling results in enhanced transcription of HPV oncogenes, and inhibiting MEK1/2 signals impedes oncogene transcription and viral genome levels (Fig. 1). This suggests that crosstalk between HPV and the EGFR pathway benefits the persistence of HPV infections. Additionally, E5 increases EGFR signaling in a ligand-independent manner(31-34) leading to higher levels of AP1 transcription factors and increased HPV transcription.(35) E6 and E7 proteins have multiple functions shown to positively interface with PI3K and MAPK signaling.(36-45) These observations prompt us to hypothesize that the initiation and maintenance of oncogenic HPV infections establishes a feed-forward regulatory loop with the PI3K and MAPK pathways to promote proliferation and survival. We further theorize that activating mutations or amplification of *PIK3CA* plays an essential role in driving progression of HPV-initiated lesions to malignancies. Extensive cross talk between PI3K and MAPK pathways and their common involvement in supports these ideas.(46, 47)

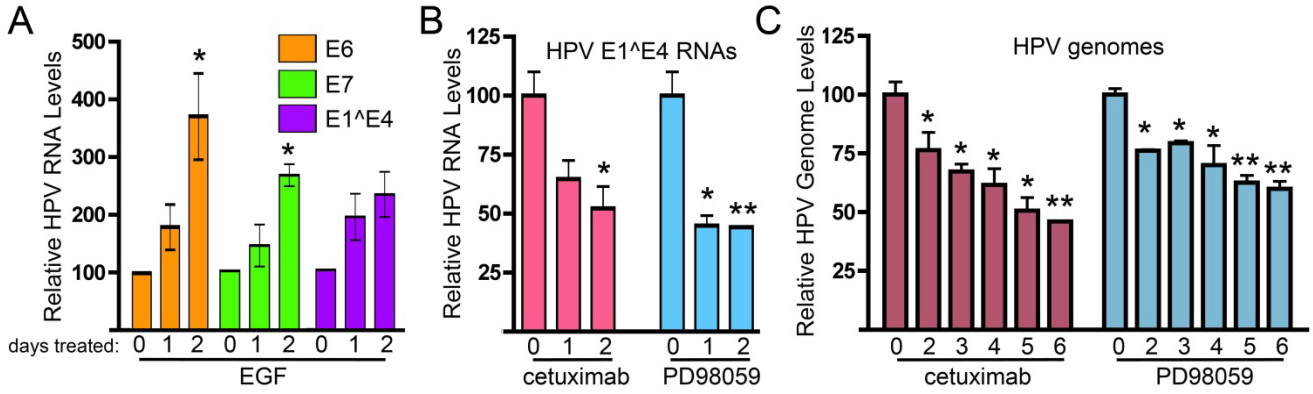



Figure 1. The EGFR signaling pathway regulates viral gene expression and replication in HPV16-infected cells. (A) NIKS-HPV16+ cells were exposed to 10 ng/ml EGF for 0h (mock), 1 or 2 days, then analyzed for HPV 16 early RNA levels normalized to β-actin RNA. (B,C) NIKS-HPV16+ cells were incubated in growth media with 100 μg/mL anti-EGFR antibody (cetuximab), 25 μM MEK1/2 inhibitor (PD98059) for the number of days indiated; 0 = vehicle-treated. (B) mRNA was harvested at indicated time points; RT-qPCR targeting HPV 16 E1^RNA normalized to β-actin RNAs. (C). Total cellular DNA was harvested at indicated time points and qPCR performed to quantify HPV16 genome levels. Error bars – SEM (n=2). Student's t-test: $p<0.05$(*), $p<0.001$ (**). Mock/vehicle treated cells were normalized to 100%.

**HPV and the PI3-Kinase (PI3K) Pathway**

The PI3K/Akt/mTOR signaling network, a mitogenic pathway regulating cellular metabolism, proliferation and survival, plays a major role in HPV biology. Starting with early infection, activation of PI3K suppresses autophagy and induces functional protein translational machinery.(28) Activation of the pathway is a nearly universal aspect of mammalian viral infection, and is of particular importance for dsDNA viruses such as HPV relying upon cap-dependent protein translation.(48) The oncoproteins E5, E6 and E7 have direct roles in pathway activation: E5 upregulates PI3K; E6 binds tuberin, a component of the TSC which negatively regulates mTORC1; and E7 prevents de-phosphorylation of Akt following activation by PI3K.(49-51)

Human cells contain three genes encoding the catalytic subunits of class IA PI3K enzymes: *PIK3CA* (encoding the p110α subunit, expressed in most tissues); *PIK3CB* (encoding p110β, expressed in most tissues); and *PIK3CD* (encoding p110δ, expressed primarily in leukocytes). Mutation in *PIK3CA* is the most common gain-of-function mutation in HNSCC, whereas mutations in *PIK3CB* and *PIK3CD* have not been observed.(21,22) Transformed, HPV-associated OPSCC demonstrates a strikingly high prevalence of genomic PI3K pathway activation, including activating *PIK3CA* mutations (27-31%), *PIK3CA* amplification (20%), and loss of *PTEN* (30%), the negative regulator of PI3K.(21, 22, 52) *Overall genomic events hypothesized to result in PI3K pathway activation are present in approximately 45-60% of HPV-transformed OPSCC(53,54)*, making this a naturally enriched population for the development of PI3K inhibitors. Moreover, HPV-associated OPSCC patient tumorgrafts bearing activating *PIK3CA* mutations are exquisitely sensitive to PI3K inhibitors, including

BYL719.(52)[unpublished data] BYL719 is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. BYL719 is a particularly attractive molecule to develop in HPV-associated OPSCC. Due to its PI3K p110α isoform specificity, it may be particularly effective in *PIK3CA* mutant/amplified cancer and has demonstrated fewer toxicities as compared to pan-isoform inhibition during Phase I development.

**Preclinical Data, Grandis and Ozbun Laboratories**

**PIK3CA genetic alterations enhance PI3K signaling and HPV(+) HNSCC growth.**

Activation of the PI3K signaling pathway by *PIK3CA* mutation or amplification drives tumor growth in many cancers.(55, 56) We showed that genes in the PI3K signaling pathway are frequently mutated in HNC. Although the majority of *PIK3CA* mutations (≈60%) occur at the known canonical hotspot loci (E542K, E545K, H1047R), about one-third arise elsewhere in p110α.(51) We developed an HPV(+) HNC cell model harboring unamplified WT *PIK3CA* to identify "driver" mutations. We employed this HPV(+) HNC platform to functionally screen PIK3CA mutations detected in human HPV(+) HNC tumors. Using this model, we have reported that a subset of novel *PIK3CA* mutations activate PI3K signaling.(51)

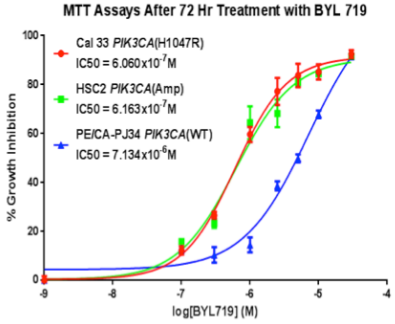



**Figure 2. *PIK3CA* alterations confer sensitivity to the p110α inhibitor BYL719.** HNSCC cell lines were treated with BYL719 at concentrations from 0-30 μM for 72 hours and then assessed by MTT assay (repeated 2x, n=8).

**_PIK3CA_ mutations confer sensitivity to PI3K inhibition in HPV(+) HNSCC**.

*PI3K* pathway inhibitors are more efficacious in patients with breast and gynecologic malignancies whose tumors harbor *PIK3CA* mutations.(57) Thus, we hypothesized that activation of PI3K signaling through gain-of-function mutations in *PIK3CA* would increase PI3K activation and serve as biomarkers for treatment with a PI3K inhibitor in HPV(+) HNC models. Indeed, we found that an HPV(+) HNC cell line harboring mutant H1047R *PIK3CA* was more sensitive to two separate PI3K inhibitors compared to an HNC cell line with WT *PIK3CA* and no gene amplification. In addition, the PI3K inhibitor decreased proliferation of HPV(+) HNC cells engineered to express E542K mutant *PIK3CA* to a greater degree than its WT counterpart.(51) The p110α-selective PI3K inhibitor BYL719 would be predicted to be most effective in cells with p110α mutations. To test this hypothesis, we compared BYL719 effects in *PIK3CA* mutant (Cal33), amplified (HSC2) or WT (PE/ CA-PJ34) HNC cells and found enhanced growth in HNC cells harboring mutant or amplified *PIK3CA* compared to those with unamplified, WT *PIK3CA* (Fig. 2). These findings support our hypothesis that *PIK3CA* mutations or amplification enhance sensitivity to PI3K pathway blockade. Prospective identification of patients whose tumors harbor these mutations will determine the biomarkers for treatment with agents that inhibit this pathway.

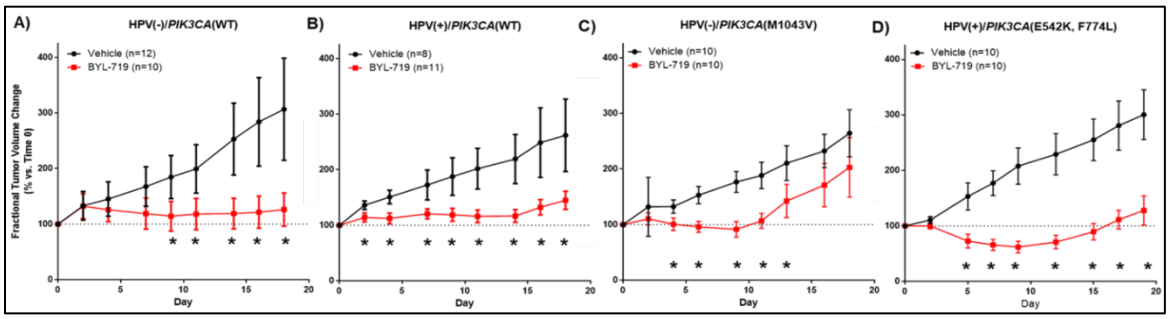
**Generation of heterotopic HPV(+) HNC tumor models**. *In vivo* studies generally rely on

xenograft tumors derived from inoculation of HNSCC cell lines into immunocompromised mice. In an attempt to generate a more clinically relevant *in vivo* platform to assess the antitumor effects of candidate therapies, we implant human HNC tumors directly into NOD/SCID gamma (NSG) mice. To date, we have successfully implanted tumors obtained from 53 HNSCC patients,(58) yielding tumors in mice at a median time of 16 weeks (range 6-26 weeks). This model allows passage and tumor expansion to facilitate therapeutic studies (i.e., 20-40 tumors generated from one primary tumor implant). Treatment of tumorgrafts derived from a HPV(+) tumor harboring an E542K *PIK3CA* mutation with a PI3K/mTOR inhibitor (BEZ-235), revealed significant antitumor effects.(51) These results suggest that PIK3CA mutation may serve as a biomarker of enhanced sensitivity to PI3K pathway inhibition in HPV(+) HNSCC.

**PI3K inhibition and HER3 activation**.

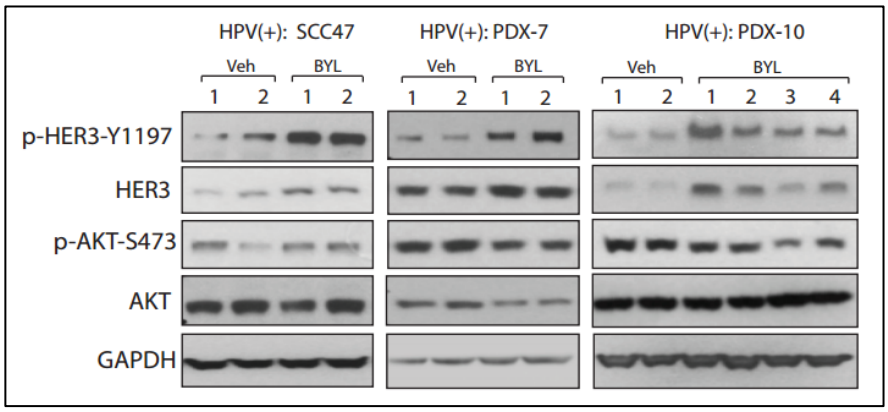
We next evaluated the p110 alpha-specific PI3K inhibitor, BYL719, against a panel of 8 HNSCC cell lines characterized by HPV status and *PIK3CA* mutation and found that endogenously mutated cells demonstrated the greatest sensitivity (data not shown). We next assessed the efficacy of BYL719 *in vivo* using 4 PDX models: 1 HPV(+) with WT *PIK3CA*; 1 HPV(+)with $PIK3CA^{E542K}$; 1 HPV(-) with WT *PIK3CA*; 1 HPV(-) with $PIK3CA^{M1043V}$. In all 4 PDX models, BYL719 demonstrated measureable anti-tumor effects, with greatest efficacy in

**Figure 3. BYL-719 Inhibits Patient-Derived HNSCC Xenografts (PDX)**



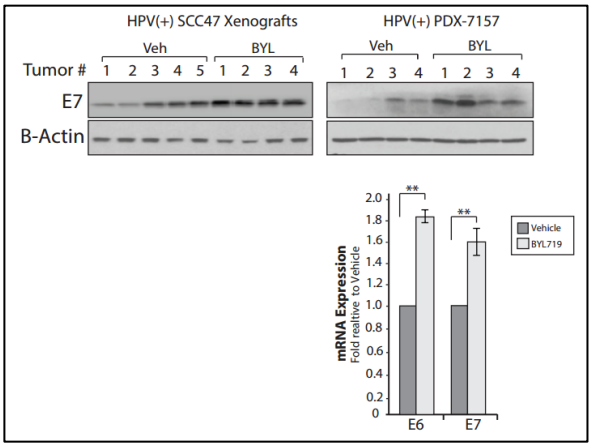

the HPV(+)$PIK3CA^{E542K}$ model (**Figure 3**). We also observed emergence of resistance after 2-3 weeks in both HPV(+) models. We characterized the proteomic response by reverse phase protein array (RPPA), observing that HER3 was upregulated coincident with the emergence of *in vivo* resistance.

**Figure 4. BYL719 Upregulates HER3 in *PIK3CA* Wild-type HPV(+) HNSCC**




To better characterize HER3 as a resistance mechanism to PI3K inhibition, and identify potential interactions between viral oncoproteins and resistance to BYL719, we first investigated cellular feedback mechanisms to BYL719 in three *PIK3CA*-WT HPV(+) in vivo models: SCC47 xenograft; PDX-7; PDX-10. BYL719 upregulated HER3 and pHER3 in all models (**Figure 4**). Upregulation of HER3 was coincident with upregulation of the E6 and E7 oncoproteins (**Figure 5**). In a subsequent series of cell line models, we observed: 1) *PIK3CA*-WT HPV(+) cell lines demonstrate greater endogenous resistance to BYL719 than their HPV(-) counterparts; 2) *PIK3CA*-WT HPV(+) cell lines were sensitized to BYL719 upon knockdown of the E6/E7 oncoproteins. We are currently studying this resistance mechanism in *PIK3CA*-mutant models.

**Figure 5. BYL719 Upregulates E6 and E7 Expression in *PIK3CA*-WT HPV(+) HNSCC**



# 2 Objectives of the Study

## 2.1 Primary Objective

- To assess the preliminary efficacy of neoadjuvant BYL719 in patients with transorally-resectable, HPV+ HNSCC, as measured by quantitative change in tumor size (ΔT) following 10-21 days of treatment.
- To evaluate the relationship between genomic *PIK3CA* activation to ΔT

## 2.2 Secondary Objectives

- To describe the tolerability of brief neoadjuvant exposure to BYL719
- To assess the effect of BYL719 on the tumoral Ki-67 proliferation index
- To evaluate viral and molecular mediators of response and resistance to BYL719, including viral mRNA, E6 and E7 oncoproteins, and pHER3

## 2.3 Endpoints

### 2.3.1 Primary Endpoint

- Quantitative change in the sum of RECIST-measurable index lesions on paired, pre- and post-treatment tumor measurement (ΔT) with size treated as a continuous variable.
- The difference in ΔT in patients with genomic *PIK3CA* pathway alteration (*PIK3CA* mutation, amplification, and FISH for PTEN loss) vs. no genomic activation

### 2.3.2 Secondary Endpoints

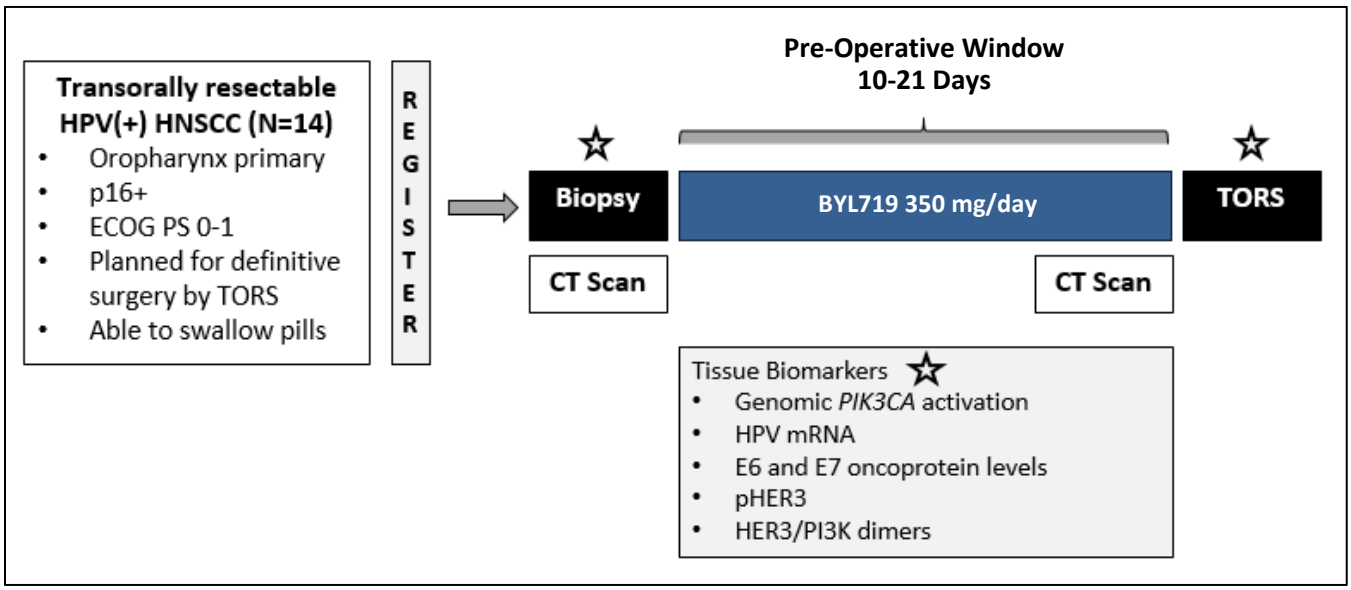
- Safety. The safety of this window intervention will be reported descriptively, including tabulation of toxicities according to NCI CTCAE v.4.03, surgical complications, and length of hospital stay.
- Mechanistic biomarker endpoints. Changes in pre- and post-treatment tumor levels of:
    - HPV mRNA (qPCR) – laboratory of Michelle Ozbun, PhD (UNM). We hypothesize that BYL719 will reduce HPV mRNA, and this will correlate with decrease in tumor size.
    - E6 and E7 oncoproteins – laboratory of Michelle Ozbun, PhD (UNM). We hypothesize that BYL719 will decrease tumoral E6 and E7 oncoprotein levels, and this will correlate with decrease in tumor size
    - Phospho-HER3 – laboratory of Jennifer Grandis, MD (UCSF). We hypothesize that pHER3 is a resistance mechanism for BYL719, and that pHER3 will be upregulated in non-responders.
    - HER3/PI3K dimers (Monogram). We hypothesize that HER3/PI3K dimerization is a resistance mechanism for BYL719, and that dimers will be upregulated in non-responders.

# 3 Study Design

## 3.1 Characteristics

This is a single-arm, open label phase II window trial to assess the effect of the PI3K inhibitor, BYL719 on tumor proliferation, size, and biomarker expression following 10-21 days (max 28 days for unexpected delays in planned surgery) of BYL719 monotherapy in patients with operable, HPV-associated oropharyngeal squamous cell carcinoma.

The study design involves baseline tumor biopsy, collection of peripheral blood, and tumor size assessment via CT scan or MRI. After 10-21 days, CT scan or MRI and peripheral blood collection will be repeated, followed by planned oncologic surgery with collection of post-treatment tumor specimen.




## 3.2 Number of Subjects

20 patients will be accrued to achieve the target of 14 evaluable patients.

## 3.3 Eligibility Criteria

### 3.3.1 Inclusion Criteria

1) Cytologic or histologic diagnosis of p16+ squamous cell carcinoma of oropharyngeal or unknown primary metastatic to the cervical met.

2) p16 positivity is defined as ≥70% of tumor cells demonstrating diffuse cytoplasmic and nuclear staining for p16 by immunohistochemistry in a CLIA certified pathology lab.

3) Clinical stage I-IVa p16+ oropharyngeal squamous cell carcinoma, based upon the AJCC staging manual, 7th edition.

4) No evidence of distant metastatic disease.

5) Appropriate candidate and planned for primary transoral resection and/or neck dissection.

6) ECOG performance status 0-1 at time of consent.

7) Clinically or radiologically measurable disease; the primary tumor and/or neck nodes may be measurable according to RECIST 1.1(tumor diameter ≥ 1 cm; short-axis lymph node diameter ≥ 1.5 cm) OR by caliper measurement (tumor diameter ≥ 1 cm).

8) Adequate hematologic, renal and hepatic function within 4 weeks of registration, as defined by:
   a) Absolute neutrophil count (ANC) ≥ 1,500/ul
   b) Creatinine ≤ 1.5 x institutional upper limit of normal (ULN).
   c) Bilirubin ≤ 1.5 x ULN,
   d) AST or ALT ≤ 2.5 x ULN.
   e) Fasting Serum amylase ≤ 2 × ULN
   f) Fasting Serum lipase ≤ ULN

   Note: A redraw is permitted within the 4 weeks for screening purposes.

9) Ability to swallow and retain oral study medication as a whole tablet (see Section 4.1.1).

10) Have signed the written informed consent

### 3.3.2 Exclusion Criteria

1. Prior therapy for head and neck cancer is not allowed.
2. Established diagnosis of diabetes mellitus type I or not controlled type II.
3. Known hypersensitivity to alpelisib, or to any of the excipients of alpelisib.

4. Currently documented pneumonitis (Note: The chest CT scan performed at baseline for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).

5. Any of the following cardiac abnormalities:
   a. Symptomatic congestive heart failure within 12 months prior to the start of study treatment
   b. History of documented congestive heart failure (New York Heart Association functional classification III-IV), documented cardiomyopathy
   c. Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO).
   d. Myocardial infarction ≤ 6 months prior to start of study treatment
   e. Unstable angina pectoris
   f. Serious uncontrolled cardiac arrhythmia
   g. History of angina pectoris, coronary artery bypass graft (CABG), symptomatic pericarditis prior to the start of study treatment
   h. Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. (Initiation or adjustment of antihypertensive medication(s) is allowed during screening; hypertension must be controlled prior to administering the study drug.)

   QTcF > 480 msec on the screening ECG (using the QTcF formula)

6. 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.

7. Currently receiving any of the following medications and cannot be discontinued at least 7 days prior to the start of the treatment:
   a. Medications that have a known risk to prolong the QT interval or induce Torsade de Pointes (TdP) and the treatment cannot be discontinued or switched to a different medication prior to starting treatment with BYL719 (refer to list of prohibited QT prolonging drugs provided in in Appendix 3)
   b. Herbal preparations/medications

8. Currently receiving treatment with drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A. The patient must have discontinued strong inducers for at least one week prior to the start of study treatment and must have discontinued strong inhibitors before the start of treatment. Switching to a different medication prior to randomization is allowed; (Refer to Appendix 2 and 3, Tables 1 and 2) for permitted and non-permitted medications).

9. History of acute pancreatitis within1 year of screening or past medical history of chronic pancreatitis

10. 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)

11. History of Stevens-Johnson-Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN).

12. Known positive serology for human immunodeficiency virus (HIV)

13. Any other condition, including severe and/or uncontrolled medical conditions, 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 study medication as a whole tablet, social/psychological complications

14. Currently taking herbal preparations/medications and dietary supplements (except for vitamins) and unwilling to stop.

15. 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)

16. 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 must use a condom during intercourse while taking BYL719 and for 1 week after the final dose of BYL719, and should not father a child in this period, but may be recommended to seek advice on conservation of sperm. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
    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 at least 1 week after the final dose of BYL719. 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 1+2):

1. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
2. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
3. Note: Hormonal contraception methods (e.g. oral, injected, and implanted) are not allowed as BYL719 may decrease the effectiveness of hormonal contraceptives.

NOTE: 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.

17. Active systemic infection requiring systemic antibiotics or anti-fungals within 7 days prior to first dose of study drug.

    **Note:** Active topical infections (for example oral thrush) do not exclude a subject even if treated with systemic antibiotics or systemic antifungals.

18. Chronic hepatitis

19. Severely impaired lung function

20. Unresolved osteonecrosis of the jaw

21. Prisoners or individuals who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious) illness.

### 3.4 Duration of Therapy

Treatment will occur during the pre-operative window of 10-21 days or up to 28 days for delays in planned surgery or until:

- Progressive disease at any time
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Excessive toxicity
- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Pregnancy
    - All women of child-bearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The Investigator must immediately notify Novartis in the event of a confirmed pregnancy in a patient participating in the study.
- Study Closure or termination
- Subject noncompliance with study procedures

### 3.5 Duration of Follow Up

Patients will be followed for up to 12 weeks post-operation. Patients removed from treatment for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events.

#### 3.5.1 Procedures for discontinuation

Subjects who discontinue prior to the end of treatment should, if possible, be seen and assessed by an investigator(s). The reason for withdrawal and the date of withdrawal must be documented. If possible, any diary cards and investigational products should be returned by the subject as soon as possible after study discontinuation.

### 3.6 Study Timeline

#### 3.6.1 Primary Completion

The study will reach primary completion 24 months from the time the study opens to accrual.

*Note: Accrual to this study was significantly affected by the COVID-19 pandemic. Thus, the accrual time will be extended to 64 months from the time study opened.*

#### 3.6.2 Study Completion

The study will reach completion 36 months from the time the study opens to accrual.

*Note: Accrual to this study was significantly affected by the COVID-19 pandemic. Thus, the accrual time will be extended to 64 months from the time study opened and will close 84 months after the study opens.*

## 4 Study Drugs – BYL719 Description, Supply, and Storage

### 4.1 BYL719 (Alpelisib) Description

Note: See the Investigator's Brochure for detailed information.

Classification

BYL719 is an oral inhibitor that selectively targets the α-isoform of Class I PI3K, with in vitro $IC_{50}$ values of 4.6, 1156, 250, and 290 nM for p110α, β, γ, and δ, respectively, as well as 4.0 and 4.8 nM for the *PIK3CA* mutants E545K and H1047R.

Mechanism of Action

BYL719 (alpelisib) is a selective PI3Kα inhibitor equipotent against the wild-type and the most common somatic mutations of PI3Kα (inhibition concentration 50% [IC50]= 5 nM).

Metabolism

BYL719 was eliminated predominantly by hepatobiliary excretion into feces and, to a lesser extent, via urine. Compounds identified in excreta mainly comprised of M4 and parent compound. Of the remaining metabolites, the most abundant are M3, M9, and M12. In vitro experiments suggested that M3 is formed by oxidation (Phase I, CYP3A4), and M12 is formed by glucuronidation (Phase II, UGT1A9). The primary metabolite M4 is pharmacologically inactive and not genotoxic.

Contraindications

In the absence of significant amounts of oxidation or glucuronidation, BYL719 is considered to have a low potential for interaction with other drugs—this is supported by clinical observations that inhibitors/inducers of CYP3A4 have a limited effect on the clearance of BYL719 in patients

### 4.2 BYL719 dosing

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 in a 21-28 day cycle. The recommended starting dose for single agent BYL719 studies is 350 mg/day.

The investigator or responsible site personnel should instruct the patient to take BYL719 as per protocol (promote compliance).

The following general guidelines should be followed for BYL719 administration:

- Patients should be instructed to take the dose of BYL719 once daily at approximately the same time each day after a meal (preferably in the morning after breakfast) except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic at any later point of time.
- BYL719 must be taken within 1 hour after a meal or snack. 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 at any later point in time.
- During treatment phase, the patient should record if the dose was taken or not in the alpelisib patient diary.
- BYL719 should be taken with a glass of water. Patients should swallow the tablets as a whole and not chew them.
- 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 during a treatment cycle must be noted in the adverse events section of the CRF.
- 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 must avoid concomitant intake of strong CYP3A inhibitors and inducers.

**NOTE**: for current information, please see the most recent version of the Investigator Brochure

### 4.3 Supply, receipt, and storage

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

Patients will be provided with a 21-day supply of BYL719 for self-administration at home until at least their next scheduled study visit.

#### 4.3.1 Drug compliance and accountability

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

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

The University of Arizona Investigational Drug Service (IDS) pharmacy uses the National Cancer Institute (NCI) drug accountability logs for all studies at this institution. Control logs will be used for inventory and patient dispensing at the University of Arizona Cancer Center.

#### 4.3.2 Disposal and destruction

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

### 4.4 Drug Accountability

The Investigational Pharmacist will manage drug accountability records. Damaged supplies will be destroyed at the study site and adequate records of the damaged supplies will be kept at the site. Study investigators will be responsible for drug accountability.

### 4.5 Drug Ordering

BYL719 will be supplied by Novartis Pharmaceuticals.

### 4.6 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per University of Arizona institutional standards, adhering to applicable local and federal laws.

# 5 Treatment Plan

## 5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

**Table 5.1 Regimen Description**

| Study Drug | Dose | Route | Schedule | Cycle Length |
|---|---|---|---|---|
| BYL719 | 350 mg | PO | daily | Pre-operative window (10-21 days) or up to 28 days for delayed surgery |

## 5.2 Dose Modification

A continuous monitoring rule for safety will be instituted, to guard against excess toxicity from pre-operative treatment with BYL719 at a starting dose of 350 mg daily.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. All dose modifications must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria ([NCI-CTCAE version 4.03]).

If the administration of BYL719 is interrupted for reasons other than toxicity, then treatment with BYL719 may be resumed at the same dose.

A maximum of 2 dose reductions of BYL719 from the recommended starting dose may be allowed before considering discontinuation of BYL719 treatment. Table 5.2 below describes the dose reduction steps for BYL719.

**Table 5. 2 Dose reduction steps for BYL719**

| **A single agent dose levels and dose reductions*** | |
|---|---|
| Starting dose level | 350 mg/day continuously |
| Dose level – 1 | 300 mg/day continuously |
| Dose level – 2 | 250 mg/ day continuously ** |

*Dose reduction should be based on the worst preceding toxicity.
** = If a dose reduction below dose level –2 is required, the patient must be permanently discontinued from BYL719

### 5.3 Treatment interruption and treatment discontinuation

All dose interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03).

Grade 4 adverse events will lead to permanent discontinuation, irrespective of recovery time, unless otherwise specified. Patients requiring > 2 dose reductions for BYL719 should be permanently discontinued.

Patients should have weekly follow-up for 30 days if they develop an AE after discontinuation of study treatment or resolution of the AE to ≤ grade 1, whichever occurs first, that includes all study assessments appropriate to monitor the event.

### 5.4 Procedures in case of Overdose

There are no known antidotes for BYL719. Additionally, the dose which constitutes an overdose has not been defined. Doses of study treatment in excess of that specified (350 mg daily) in the clinical study protocol are considered to be an overdose. Patients experiencing toxicity upon overdosing must be treated at the discretion of the treating physician with adequate supportive care as indicated by the symptoms observed in the patient. Patients will have to be followed until full recovery or confirmed stabilization of the events. There is no clinical experience regarding the effect of hemodialysis on decreasing the plasma levels of BYL719 elimination thus far. There have been four events of accidental overdose reported with BYL719 and these were all cases in combination studies. Adverse events associated with the overdose were those expected with the BYL719 known safety profile and included hyperglycemia, nausea, hyperuricemia, hyponatremia, asthenia and rash. Patients fully recovered after some days and supportive medication to treat the associated adverse events experienced with the overdose. Overdose, with or without associated symptoms, should be handled in the same way as a SAE. Signs or symptoms of an overdose that meet the criteria of SAE should be reported as a SAE in the appropriate manner and be documented as clinical sequelae to an overdose.

### 5.5 Procedures in Case of Pregnancy

To ensure patient safety, each pregnancy in a patient on study treatment must be reported 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 a Clinical Trial Pregnancy Form 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.

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.

### 5.6 Monitoring and Toxicity Management

Each patient receiving at least one dose of BYL719 will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.03. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

**Table 5. Dose Modifications - Criteria for Interruption and Re-initiation of BYL719**

| Worst toxicity CTCAE v.4.03 Grade | Dose Modifications for BYL719 |
|---|---|
| **Investigations (Fasting Plasma Glucose)** | |
| **Hyperglycemia**<br>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). | |
| Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]<br><br>For patients with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this apply only for values > 140 mg/dL (7.7 mmol/L) | **Maintain dose level** and remind patient on lifestyle changes*.<br>• If FPG < 140 mg/dl, consider adding metformin as per guidance below or in cooperation with diabetologist<br>• If FPG 140-160 mg/dl, start/intensify metformin as per guidance below or in cooperation with diabetologist<br><br>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.<br><br>Monitor FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every two weeks until FPG is within baseline values. |
| Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L] | **Maintain dose level** and remind patient on lifestyle changes*, 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.<br><br>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).<br>Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1<br>• If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce BYL719 by 1 dose level<br>• Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl |
| 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.<br>Exclude confounding factors like e.g. urinary tract infection and consider consultation with a diabetologist.<br><br>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.<br><br>Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1.<br><br>• 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, alert treating physician if FPG>250mg/dl<br>• 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 |
| Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L] | **Omit BYL719** confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.<br>Exclude confounding factors like e.g. urinary tract infection.<br>Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate.<br>Consider cooperation with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours.<br>• If grade improves then follow specific grade recommendations<br>• If FPG is confirmed at Grade 4 and confounding factors could be excluded, permanently discontinue patient from BYL719 |
| A diabetologist consultation should always be considered.<br>In case metformin is contraindicated or not tolerated even at low dose, another insulin-sensitizer (e.g., pioglitazone) may represent an alternative.<br>For all grades: 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 | |
| **Investigations (Hematologic)** | |
| **Neutropenia (ANC)** | |
| Grade 1 (ANC < LLN - 1.5 x $10^9$/L) Grade 2 (ANC < 1.5 - 1.0 x $10^9$/L) | Maintain dose level |
| Grade 3 (ANC < 1.0 - 0.5 x $10^9$/L) Grade 4 (ANC < 0.5 x $10^9$/L) | Omit dose until resolved to ≤ Grade 1, then:<br>• If resolved in ≤ 7 days, then maintain dose level |

| | |
|---|---|
| | ● If resolved in > 7 days, then ↓ 1 dose level |
| **Febrile neutropenia** | |
| (ANC < 1.0 x $10^9$/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥38 °C for more than one hour) | Omit dose until resolved, then ↓ 1 dose level |
| **Thrombocytopenia** | |
| Grade 1 (PLT < LLN - 75 x $10^9$/L) Grade 2 (PLT < 75 - 50 x $10^9$/L) | Maintain dose level |
| Grade 3 (PLT < 50-25 x $10^9$/L) | Omit dose until resolved to ≤ Grade 1, then:<br>● If resolved in ≤ 7 days, then maintain dose level<br>● If resolved in > 7 days, then ↓ 1 dose level |
| Grade 4 (PLT < 25 x $10^9$/L) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| **Investigations (Renal)** | |
| **Serum creatinine** | |
| < 2 x ULN | Maintain dose level |
| 2 – 3 x ULN | Omit dose until resolved to ≤ grade 1, then:<br>● If resolved in ≤ 7 days, then maintain dose level<br>● If resolved in > 7 days, then ↓ 1 dose level |
| Grade 3 (> 3.0 – 6.0 x ULN) | Permanently discontinue patient from BYL719 |
| Grade 4 (> 6.0 x ULN) | Permanently discontinue patient from BYL719 |
| | |
| **Investigations (Hepatic)** | |
| **Bilirubin**<br>**(*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:<br>● If resolved in ≤ 7 days, then maintain dose level<br>● 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:<br>● If resolved in ≤ 7 days, ↓ 1 dose level<br>● If resolved in > 7 days discontinue patient from BYL719 |
| Grade 4 (> 10.0 x ULN) | Permanently discontinue patient from BYL719 |
| **AST or ALT and concurrent Bilirubin** | |
| AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN | Permanently discontinue BYL719 |
| *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 | |

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| 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).<br>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). | |
| **Investigations (Cardiac)** | |
| **Cardiac – QTc prolongation** | |
| QTcF > 500 ms (≥ Grade 3, 4)<br>or > 60 ms change from baseline on at least two separate ECGs | First Occurrence:<br>● omit BYL719<br>● 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<br>● Perform a repeat ECG within one hour of the first QTcF of >500 ms or >60ms from baseline<br>● 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.<br>● Once QTcF prolongation has resolved, BYL719 may be restarted at a one lower dose level.<br>Second Occurrence: Permanently discontinue patient from BYL719 |
| **Isolated AST or ALT Elevation**<br>Confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorders, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction | |
| Grade 1 (> ULN – 3.0 x ULN) | Maintain dose level with LFTs[b] monitored per protocol |
| Grade 2 (> 3.0 - 5.0 x ULN)<br>• For patients with baseline value ≤ 3.0 x ULN<br>• For patients with baseline value > 3.0 -5.0 x ULN | • Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN<br>• Maintain dose level |

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| Grade 3 (> 5.0 - 20.0 x ULN)<br>**> 5.0 - 10.0 x ULN**<br>• For patients with baseline value ≤ 3.0 x ULN<br>• For patients with baseline value > 3.0 -5.0 x ULN | • Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTsb weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Then<br>If resolved in ≤ 14 days, maintain dose level<br>If resolved in > 14 days, ↓ 1 dose level<br>• Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b], weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN<br>If resolved in ≤ 21 days, maintain dose level<br>If resolved in > 21 days and confounding factors have been excluded, ↓ 1 dose level |
| **> 10.0 - 20.0 x ULN** | Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTsb weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then ↓ 1 dose level. |
| Grade 4 (> 20.0 x ULN)<br>• For patients deriving clinical benefit upon investigator's judgement<br>• For all other patients | • Omit dose. Repeat LFTsb as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTsb weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0 -5.0 x ULN), then resume treatment at □ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue patient from alpelisib.<br>• Discontinue patient from alpelisib<br>Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks |
| **Cardiac - Left Ventricular Systolic Dysfunction** | |
| Asymptomatic,<br>resting ejection fraction 40-50% or 10-20% drop from baseline | -Maintain dose level, and continue BYL719 with caution<br>-Repeat LVEF within 4 weeks or as clinically appropriate |
| Symptomatic,<br>responsive to intervention,<br>ejection fraction 20-39%<br>or > 20% drop from baseline | -Omit BYL719 until resolved* (as defined below), then ↓ 1 dose level<br>-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 | |

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| fraction ≥ 40% and ≤20% decrease from baseline. | |
| **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 patient from BYL719 |
| **Investigations (Gastrointestinal)** | |
| **Diarrhea** | |
| 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 ↓ 1 dose level |
| **Stomatitis/Oral mucositis** | |
| Grade 1/Tolerable Grade 2 | Maintain dose level.<br>Non-alcoholic or saltwater mouth wash. |
| Intolerable Grade 2 or Grade 3 | First occurrence: hold until ≤ Grade 1 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).<br>Second occurrence: hold until ≤ Grade 1 and ↓ 1 dose level. |
| Grade 4 | Permanently discontinue patient from BYL719 |
| **Skin and subcutaneous tissue disorders** | |
| Consultation with a dermatologist is highly recommended for better assessment and management of BYL719-induced skin toxicity. Dermatologist consult is mandated for serious cutaneous reactions (i.e., fulfilling seriousness criteria for AE Reporting) and for severe cutaneous reactions like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme. | |
| Grade 1 (<10% body surface area (BSA) with active skin toxicity*) | **Maintain dose level**<br>• 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<br><br>For patients with symptoms like burning and/or pruritus add non-sedating anti-histamine, consider adding a sedating anti-histamine at night<br>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**.<br>• Initiate topical corticosteroids 3-4x daily, preferred compounds to use are |

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| | Triamcinolone or Betamethasone as long as skin toxicity is active, during max. 28 days<br>• Consider adding systemic corticosteroids 20 40mg/d<br>If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued<br><br>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<br>• Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone for at least 28 days<br>• Add systemic corticosteroids 20-40mg/d<br>If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued<br>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<br>Re-start BYL719 dose once rash /skin toxicity is no longer active but fading (G1):<br>- at same dose in case of first occurrence, at reduced dose level in case of second occurrence<br>- 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<br>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, , ensure documentation by imaging like photographs, and obtain a skin biopsy. Treatment of rash may follow guidelines for Grade 3/ above with the exception of rechallenge. Additional measures may be taken as per local treatment guidance. |

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| **Any Grade of Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis or other SJS/TEN-like severe skin reactions** | • Permanently discontinue patient from alpelisib treatment<br>• Consult dermatologist, ensure documentation by imaging like photographs and obtain skin biopsy for central assessment<br>Follow local treatment guidelines for SJS/TEN |
| **Investigations (Pulmonary disorders)** | |
| **Pneumonitis** | • In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt PIQRAY immediately and evaluate the patient for pneumonitis.<br>• Permanently discontinue PIQRAY in all patients with confirmed pneumonitis. |
| **Investigations (any other)** | |
| **Other adverse events** | |
| Grade 1 or 2 | Maintain dose level |
| Grade 3 | Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level |
| Grade 4 | Omit dose and then discontinue from study drug treatment Omit dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic<br>(as per local practice) |

# 6 Study Procedures and Assessments

The study-specific assessments are detailed in this section. All on-study visit procedures are allowed **a window of ±5 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the Banner University Medical Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

## 6.1 Screening Period & Pre-treatment Procedures

### 6.1.1 Screening Evaluations

Screening assessments must be performed within 28 days prior to the first dose of investigational product, unless otherwise specified. Any results falling outside of the reference

ranges may be repeated at the discretion of the investigator.
Note that all these procedures, with the exception of MUGA, are standard of care procedures for a patient with HNSCC.

Required screening evaluations include:

- Medical history assessment within 8 weeks prior to study registration.
- Physical examination, to include surgical and medical evaluation, within 8 weeks prior to study registration.
    - This is to include a careful description of the location and extent of the primary lesion and nodal spread. Fiberoptic nasopharyngoscopy/laryngoscopy is recommended, unless fiberoptic exam is deemed unnecessary by the treating surgeon. Examination under anesthesia (EUA) is recommended, unless deemed unnecessary by the treating physician.
- Vital signs, weight, height within 8 weeks prior to study registration
- ECOG Performance Status within 8 weeks prior to study registration
- Documentation of concomitant medications within 4 weeks prior to first dose of drug.
    - Note: All medications taken within 28 days prior to first dose must be documented, including blood transfusions.
- Laboratory studies including the following:
    - CBC with differential (to include total white blood cell count, absolute neutrophil count, hemoglobin, hematocrit and platelets),
    - Serum chemistries (to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, fasting glucose, magnesium, and calcium),
    - Liver function tests (LFTs; to include total bilirubin, AST, ALT, total protein, albumin and alkaline phosphatase),
    - Fasting amylase and lipase,
    - Coagulation studies (PT/INR and PTT) and
    - HbA1c.
- Negative serum pregnancy test within 4 weeks of study registration in WOCBP.

  Note: the clinical research coordinator or treating investigator will document an additional negative serum or urine pregnancy test within 72 hours of starting BYL719 treatment.

- Cross-sectional radiologic evaluation within 6 weeks of study registration (within 4 weeks is preferred).
    - The minimum cross-sectional evaluation is a diagnostic, contrasted computed tomography (CT) scan of the neck.
    - PET/CT is the preferred modality, **provided it includes a diagnostic, contrasted CT scan of the neck** – however is not mandatory.
    - For patients with severe allergy to iodinated contrast dye despite premedication, or in the case of physician preference, neck MRI may be substituted.
- EKG. The standard of care EKG performed for pre-surgical evaluation should be used. EKGs performed within 12 weeks prior to study registration may be substituted, provided the patient has not experienced an interval cardiac event.
- Cardiac Multi Gated Acquisition (MUGA) or echocardiogram for determination of ejection fraction. MUGA or echocardiogram performed within 365 days prior to study registration may be substituted provided that the patient has not experienced an interval cardiac event.
- Confirmation of positive p16 status

### 6.1.2 Registration

- Questions regarding the eligibility of subjects must be directed to Ricklie Julian, MD.
- After eligibility has been confirmed, registration will be submitted to the University of Arizona Cancer Center using the eligibility checklist. The following source documents must be submitted with the eligibility checklist.
    - Signed consent page with subject ID added, and PHI redacted
- "Registration" is defined as the day Dr. Julian signs the Eligibility Checklist confirming that the subject is eligible to start the study drug.

### 6.1.3 **Mandatory Baseline** Procedures Occurring Day -21 to -1

These procedures must occur prior to the initial dose of study drug. They can occur any time after the subject signs informed consent.

**<u>These Procedures are Mandatory.</u>**

- **Baseline, pre-treatment tumor biopsy**
    - Note that a research biopsy of the primary tumor or malignant lymph node for biomarker studies is a condition for enrollment unless sufficient tissue is available to be repurposed for use in this trial.
    - The biopsy will be performed per standard-of-care procedure in the surgeon's outpatient office, or during the standard of care examination under anesthesia (EUA), as preferred by the surgeon.
    - The tissue can be obtained during the standard-of-care surgical/medical evaluation of the extent of primary lesion and nodal spread.
    - **NOTE**: Patients who have had research tissue procured under an omnibus tissue consent, who are determined to have sufficient fresh-frozen and paraffin tissue for biomarker analysis according to the PI, may substitute the archived tissue and do not need to undergo baseline research biopsy. Such tissue must have been obtained within 16 weeks prior to registration, provided no interval anti-neoplastic therapy was given.
    - Collection and preparation of tissue for biomarker analysis will be processed according to procedures described in in the Laboratory Manual.
- **Baseline research blood collection**
    - For logistical purposes, research labs may be drawn simultaneous with blood labs required for standard clinical management.
    - Blood for biomarker analysis will be collected and processed according to procedures described in the Laboratory Manual.

## 6.2 Treatment Period

### 6.2.1 Day 1 Study Visit

- BYL719 will be dispensed. The BYL719 tablets are provided in 200 mg and 50 mg tablets.
- Study diary will be provided and explained (see Appendix 6)
- Adverse event assessment (and reporting of SAEs) will begin upon the first dose of study drug.
    - Prior to the first dose, active diagnosis and conditions will be considered medical history
    - For all grade 2 adverse events, treating investigator's determination of tolerable or intolerable must be documented for determination of AEs to be entered into the AE CRF
- Concomitant medication assessment (medications, herbal medications, and food or vitamin supplements taken within 28 days prior to Day 1 must be documented)

### 6.2.2 Study Drug Treatment - Days 1-21 and 22 (+/- 3 days)

**NOTE:** BYL719 treatment is planned for 10-21 days, however, may be administered up to 28 days if required for logistical/scheduling purposes.

- BYL719 will be administered at 350 mg orally once daily. This is one 200 mg tablet and three 50 mg tablets.
- The last dose of BYL719 will be taken on the day prior to surgical resection. The interval between the last dose of BYL719 and surgery will be approximately 24 hours (+/- 8 hours).
- If surgery is delayed, BYL719 may be continued until the day prior to surgery, for a maximum of 28 days. If this is the case, additional drug may be dispensed at Day 22.
- Subjects will be asked to indicate on a drug diary (see Appendix 6) when doses of BYL719 are taken in order to monitor for compliance. Subjects may also use the drug diary for notations on side effects and other treatment related events.

### 6.2.3 Day 8, 15, and 22 (+/- 3 days) if patient is on BYL719 treatment

- Weekly fasting plasma glucose
- Adverse event assessment.
- Concomitant medication review.

### 6.2.4 Day 9-29 (inclusive of day of surgery)

**During treatment, pre-surgical**
Ideally, subjects will have the surgery on day 22 or later. All efforts should be made to schedule these evaluations on **the day prior to or the day of surgery**, however a 5-day window is provided for logistical purposes, except for subjects with surgery on day 11 through 14. Subjects with scheduled surgery on day 11 through 14 should not have these procedures earlier than day 9. Subjects will continue to take BYL719 until the day prior to planned surgery. The interval

between the last dose of BYL719 and surgery will be approximately 24 hours (+/- 8 hours).

Compliance as evidenced by pill count and patient drug diary will be assessed when the subjects return the bottles and any leftover pills. This may happen after their surgery at the first follow-up visit if they do not have a clinic visit the day before surgery.

- *History and Physical Examination (During treatment, Pre-operative):* Subjects will be evaluated by history and physical examination by the treating physician prior to planned surgery (including vital signs, weight, performance status). This visit will also include adverse event assessment and compliance assessment as evidenced by pill count and patient drug diary. For logistical convenience, this visit may be scheduled in conjunction with blood collection and imaging as specified below.

NOTE: If surgery is unexpectedly delayed, subjects will continue to take BYL719, and this pre-operative history and physical examination does not need to be repeated.

- *Clinical and Research Blood Collection:* Subjects will undergo clinical labs including
  - CBC with differential,
  - serum chemistries including fasting glucose,
  - LFTs, and
  - coagulation studies prior to planned surgery.

  Research blood will be drawn simultaneously with these standard pre-operative labs. NOTE: If surgery is delayed, subjects will continue to take BYL719 and the clinical blood tests do not need to be repeated, but the research blood may be redrawn if the delay causes the research blood draw to be outside of the 5-day window prior to surgery.

- *Cross-sectional Imaging for Tumor Measurements (Research)*: Subjects will undergo a repeat diagnostic CT scan of the neck with contrast prior to planned surgery as a part of the study. For patients with severe allergy to iodinated contrast dye despite premedication, or in the case of physician preference, neck MRI may be substituted. NOTE: If surgery is delayed, subjects will continue to take BYL719, and this pre-operative imaging does not need to be repeated.

  **NOTE**: in the event that a patient lacks a CT-measurable primary tumor or metastatic lymph node, measurable disease may be established by caliper measurement of an oropharyngeal tumor (≥ 1 centimeter). In this case, caliper measurement should be repeated and documented within 5 days prior to planned surgery, as a substitute for cross-sectional imaging.

### 6.3 Surgery and Post-treatment Tumor Tissue Collection

#### 6.3.1 Days 11-22 (window of +7 days up to day 29, inclusive of day of surgery)

- Oncologic head and neck cancer surgery
  - After 10-21 days of neoadjuvant treatment (+ 7 days if required for logistical and scheduling purposes), the patient will undergo the planned oncologic head and neck cancer surgery. The nature of complete resection of the primary head and neck

tumor, type of reconstruction, and levels of nodes to be dissected will be determined by the treating surgeon.
    - Prior to surgery, standard of care dental evaluation is recommended, to allow for any necessary dental extractions to be planned in conjunction with surgery. Consultations with a Nutritionist and Speech and Language Pathologist are strongly recommended prior to surgery and as ongoing support post-operatively. Placement of a nasogastric (eg. Dobhoff) or gastrostomy feeding tube is at the discretion of the subject and the study physicians.
- Intraoperative tumor tissue for biomarkers (post-treatment tumor tissue collection)
    - Part of the tumor and/or lymph node specimen will be sent to the research laboratory for mandatory biomarker analyses.
    - If surgery is unexpectedly cancelled and the primary tumor or lymph node is accessible for in-office biopsy in the judgment of the surgeon-investigator, a tumor biopsy may be substituted for the intraoperative specimen.

  Tissue collection procedures are described in Section 9.0.

**6.3.2** Post-operative therapy

After surgery, subjects may receive adjuvant radiation or radiation plus chemotherapy in accordance with appropriate standards, as determined by the subject's treating physicians.

## 6.4 End-of-Treatment/Follow-up/Final Study Visit Procedures

### 6.4.1 4 week (+/- 2 weeks) follow-up visit

- History and physical examination
- Blood tests as clinically indicated (CBC, chemistries, liver function tests in accordance with investigator judgment)
- If pill count and medication diary did not occur previously, it will be done at the 4-week follow-up visit
- Adverse event follow up:
    - Events considered related to the study drug will be followed until return to baseline or stabilization.
    - During the post-treatment follow-up, only AEs considered related to the study drug need to be documented.
    - If a subject's surgery is cancelled but they received study drug, they will be assessed for adverse events at the 4 weeks (+/- 2 week) follow-up visit.

**6.4.2** 12 week (+/- 4 weeks) Final Study Visit

- History and physical examination
- Blood tests as clinically indicated (CBC, chemistries, liver function tests in accordance with investigator judgment)

**6.4.3** Other visits

Additional non-protocol visits may occur during the 12-week post-operative period as deemed clinically necessary. Patients will be referred for adjuvant chemotherapy and radiation per standard of care, based upon pathologic findings.

Once the first 12 weeks of follow-up have been completed, study follow-up will be discontinued, and subjects will continue standard treatment and surveillance in accordance with national guidelines.

The standard post-operative visit which occurs 12 weeks post-op (+/- 4 weeks) will be considered the “final study visit.”

**Table 6.1 Schedule of Study Procedures and Assessments/Study Calendar**

| Study Procedures | Baseline | Days 1 through 21 | Days 22 through 28 (if surgery is delayed) [k] | Day of Surgery | 4-Week Post-op Visit | Final Study Visit (12-week post-op) [l] |
|---|---|---|---|---|---|---|
| Informed consent | X | | | | | |
| History & physical examination [a] | X | To be performed between days 9 through 21 | | | X | X |
| Vital signs, weight | X | To be performed between days 9 through 21 | | | X | X |
| ECOG-PS | X | To be performed between days 9 through 21 | | | X | X |
| Pregnancy test [b] | X | | | | | |
| EKG [c] | X | | | | | |
| Clinical blood tests [d] | X | To be performed between days 9 through 21 | | | X | X |
| Cross-sectional imaging study [e] | X | To be performed between days 9 through 21 | | | | |
| MUGA or echocardiogram [f] | X | | | | | |
| p16 status | X | | | | | |
| Adverse Event Assessment | | At each subject visit during treatment. | | | X | |
| Concomitant Medication Assessment | X | At each subject visit during treatment. | | | | |
| Fasting plasma glucose | X | Every 7 days (+/- 3 days) while on BYL719 | X | | | |
| Pill count/diary review | | Diary review to be done at each visit. Pill count to be done when subject returns bottles and any extra pills. | | | | |
| BYL719 [g] | | Take medication Days 1 through 21 | Continue BYL719 if surgery is delayed | | | |
| Surgery [h] | | Surgery is to be performed day 11 or later. | Surgery may be performed day 22 through day 29. | | | |
| Research blood collection [i] | X | Complete within 5 days prior to surgery | | | | |

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| Biopsy for Research [j] | X | | | X | | |

a. History and physical examination within 8 weeks prior to study entry. This should include surgical assessment of the primary tumor, including fiberoptic nasopharyngoscopy or examination under anesthesia as indicated per standard of care, and as determined by the treating surgeon.
b. Pre-menopausal women of child-bearing potential (WOCBP) must have a negative serum pregnancy test within 4 weeks of registration. A negative pregnancy test, serum or urine, must then be documented within 72 hours of Day 1 of BYL719 treatment.
c. The standard of care EKG performed for pre-surgical evaluation should be used. EKGs performed within 12 weeks prior to study entry may be substituted, provided the patient has experienced no interval cardiac event.
d. Clinical blood tests will be repeated once within 5 days prior to surgery, and at the 4 week and 12-week post-operative visits if clinically indicated according to the investigator. Blood tests include, CBC with differential, serum chemistries including fasting glucose, LFTs, coagulation studies, except **coagulation studies are not required at the 4 week or 12 week post-surgical visits.** Amylase, lipase, and HbA1c are done at baseline.
e. Within 6 weeks of study entry (within 4 weeks preferred), and again within 5 days prior to planned surgery, patients will undergo cross-sectional radiological evaluation using diagnostic contrasted CT, PET/CT (with diagnostic contrasted CT), or MRI of regions with radiologically or clinically identifiable tumor.
f. Cardiac imaging will be performed by Multiple Gated acquisition (MUGA) scan or Echocardiogram (ECHO) in order to assess the left ventricular ejection fraction (LVEF). MUGA or ECHO performed within 365 days prior to study entry may be substituted provided the patient has experienced no interval cardiac event.
g. The first day of BYL719 treatment will be considered Day 1. BYL719 will be administered at 350 mg daily, for 10-21 days, and will be discontinued on the day prior to surgical resection. If surgery is delayed, the study drug may be continued until surgery, for a maximum of 28 days.
h. Surgery will be scheduled during days 11-22 of BYL719 treatment. For logistical reasons, surgery may be delayed by up to 7 days (day 29). Postoperative complications, hospital days, and ICU days will be noted for each patient.
i. Research blood samples will be obtained at baseline (prior to study drug administration, within 3 weeks of registration) and within the 5 days prior to scheduled surgery.
j. Research biopsies will be obtained at baseline (prior to study drug administration, within 3 weeks of registration) and during planned surgery for resection of the tumor.
k. If surgery is delayed, subjects will continue to take BYL719 until the day prior to surgery (maximum 28 doses). The pre-operative history and physical examination, pre-operative clinical blood tests, vitals, assessment of ECOG status and pre-operative imaging do not need to be repeated. Research blood may be drawn again.
l. Patients will be seen for a standard 4 week post-operative visit (+/- 2 weeks), and again for a standard 12-week post-operative visit (+/- 4 weeks). Clinical blood tests will be obtained as deemed clinically necessary. Thereafter, patients will be followed off study per standard of care.

## 6.5 Usage of Concurrent/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.

Please refer to BYL719/alpelisib Investigator's Brochure.

All medications (excluding study treatment administered within 28 days prior to the administration of BYL) will be recorded in the Concomitant Medications log. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications (prohibited, see Section 6.5.3 below) and food or vitamin supplements. The investigator should instruct the patient to notify the investigational site about any new medications he/she takes after the start of the study drug.

### 6.5.1 Dietary Restrictions

Patients will be instructed to avoid grapefruit products/juice, or Seville (sour) oranges/juice due to its potential for CYP3A4/5 interaction.

### 6.5.2 Permitted Concomitant Therapy Medications

In vitro metabolism studies performed to examine the reversible and metabolism-dependent inhibition of CYPP450 enzymes showed that BYL719, apart from the time-dependent inhibition of CYP3A4, is a weak, reversible inhibitor of CYP2C8, CYP2C9 and CPY2C19. Note that with the data available, it is not possible to confirm whether such interactions will occur in patients. Thus, caution should in principle be used in administering concomitantly drugs whose disposition is mainly dependent on these cytochrome P450 isoenzymes and whose therapeutic index is narrow.

As it has been shown that BYL719 is a substrate of BCRP transporter in vitro and since the impact of this interaction has not been clinically investigated yet, BCRP inhibitors should also be used with caution to avoid a transport-related drug-drug-interaction.

Patients receiving such medications must be monitored for potentiation of toxicity due to any individual concomitant medications and may require dose titration or reduction of the drug substrate.

**Permitted medications to be used with caution during treatment with BYL719:**

**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. Please note that some anti-emetics have a known risk for TdP and are prohibited (refer to Appendix 3)

**Oral anti-diabetic Agents**

Patients who develop hyperglycemia during the study should be treated according to the ADA (American Diabetes Association) guidance. It is recommended to start treatment with metformin (or pioglitazone). 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 a moderate reversible inhibitor of these enzymes (refer to Table 1).

**Anticoagulation**

Anticoagulants other than warfarin/coumarin derivates 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 these enzymes and may therefore decrease the metabolic activation and clinical efficacy of these pro-drugs. Patients using anti-platelet pro-drugs should be carefully monitored (refer to Table 1).

**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 through at least 1 weeks after the final dose of BYL719.

**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 3).

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 3).

**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 Table 1). A drug-drug interaction study in human healthy volunteers confirmed that co-administration of alpelisib with the H2-antagonist ranitidine

after a meal lead to a decrease in exposure by only ~20%, considered to be not clinically relevant. Hence alpelisib can be co-administered with any ARAs.

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 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 for Table of Permitted Medications.

### 6.5.3 Prohibited concomitant therapy

The following medications are prohibited during treatment in this study (see Appendix 3, this list is not comprehensive and is only meant to be used as a guide. Please contact the PI with any questions):

- Medications with a known risk for TdP
- Other investigational and antineoplastic therapies

In addition, the use of herbal preparations/medications and dietary supplements (except for vitamins) are prohibited throughout the study, as a potential drug-drug interaction is possible. Herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

As far as possible avoid co-administering QT prolonging drugs (or any other drug with the potential to increase the risk of drug-related QT prolongation e.g. via a potential DDI increasing the exposure of the study drug or the exposure of the QT prolonging drug). If during the course of the study, concomitant administration of drugs with a known potential to cause Torsades de Pointe is required and cannot be avoided, study drug must be interrupted until an assessment of the potential safety risk has been performed. A definitive list of drugs associated with QT prolongation and/or TdP is available online at www.crediblemeds.org. If, based on the investigator assessment and clinical need study treatment is resumed, close ECG monitoring is advised.

Metabolism studies in both human and animal liver preparations (microsomes, hepatocytes) showed a low metabolism of BYL719 by phase I and phase II metabolic enzymes.

Phenotyping studies in human liver microsomes confirmed that biotransformation mainly takes place via CYP3A4 (minor involvement of CYP2J2) with no major participation of UGTs. In vitro metabolism studies performed to examine the reversible and metabolism-dependent inhibition of cytochrome P450 enzymes showed that BYL719 is a time-dependent inhibitor of CYP3A4.

The following medications are therefore prohibited during treatment with BYL719:

**Other anticancer therapy**

If a patient, enrolled in the study, requires the concomitant use of any medication included in Appendix 3 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 that Table2 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 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.

Radiation therapy must not be given with BYL719 to patients while the patient is treated. If radiation therapy is required for a patient then the patient must be discontinued.

## 7 Tumor Measurements

The primary objective of this study is to evaluate ΔTumor size, which will be measured using established RECIST v1.1 metrics for target lesions, however treated as a continuous variable as previously described (23). Target lesions will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter of metastatic lymph nodes are used in the RECIST v1.1 criteria.

**NOTE**: Because this is a pre-operative window study with only brief exposure to study drug, and RECIST responses are not anticipated, target lesions will be measured bi-dimensionally and recorded quantitatively. Quantitative change in the RECIST-defined baseline sum diameter (longest diameter of tumor + short axis diameter of up to three pathologic lymph nodes), expressed as a percent, will be the primary endpoint and will be correlated with biomarker modulation.

All tumor measurements pre- and post-treatment will be performed independently by a single neuroradiologist.

**Evaluable for quantitative change in tumor size**

Only those patients who have measurable disease present at baseline, have received at least 10 doses of BYL719, and have had their disease re-evaluated will be considered evaluable for change in tumor size.

## 7.1 Disease Parameter Definitions

**Measurable disease**

**Primary Tumors.** Measurable disease is defined as a primary tumor that can be accurately measured by one of the following techniques:

- Cross-sectional imaging (spiral CT or MRI): the primary tumor can be measured in at least one dimension (longest diameter to be recorded) and measures at least 10 mm, when using spiral CT or MRI with slice thickness no thicker than 5 mm.
- Caliper exam: the primary tumor measured at least 10mm in longest diameter by caliper measurement on clinical exam. Note: A photograph with superimposed caliper or ruler is strongly preferred for documentation of baseline and response.
- PET/CT

**Lymph Nodes.** Measurable disease is defined as a lymph node that can be accurately measured by cross-sectional imaging (spiral CT or MRI) and measures at least 15 mm in shortest diameter, when using spiral CT or MRI with slice thickness no thicker than 5 mm.

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters.

**Target lesions**

Only the following will be used as target lesions in this HNSCC window trial:

- Primary tumor (long axis)
- Up to two metastatic cervical lymph nodes (short axis)

**Non-target lesions**

All other lesions (or sites of disease) including any measurable lesions over and above the target lesions should be identified as non-target lesions and should also be recorded at baseline.

**Non-measurable disease (Tumor Markers)**

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable. (e.g., PSA, CA-125, CA19-9, CEA)

## 7.2 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers.

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

# 8 Documentation and Reporting of Adverse Events & Unanticipated Problems

All patients will be evaluable for toxicity from the time of their first treatment with the study drug. Analyses will be performed for all patients having received at least one dose of study drug using the CTCAE v4.03 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events.

## 8.1 Definitions of Adverse Events

### 8.1.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

### 8.1.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

#### 8.1.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

#### 8.1.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

#### 8.1.2.3 Serious

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:
    - Note that hospitalizations for the following reasons might not be reported as serious adverse events:
    - Routine treatment or monitoring of the patient's cancer indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the patient's cancer indication and has not worsened since the start of the treatment with alpelisib
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
    - 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 e.g. may require 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
    - Transmission of infectious agent via medicinal product

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.

In the event of a serious adverse event, the PI, the institutional review board (per institutional reporting requirements), and Novartis Corporation will be notified using the FDA Form 3500 MedWatch report.
All events meeting the definition of a serious adverse event should be recorded on a MedWatch 3500 Form (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf ) and submitted to:

1. DSMC
2. Local IRB per institutional reporting requirements
3. FDA
4. Novartis

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Event Description (section 5) of the MedWatch 3500 form:

- CTCAE term(s) and grade(s)
- Current status of study drug
- All interventions to address the AE (testing and result, treatment and response)
- Hospitalization and/or discharge dates
- Event relationship to study drug

#### 8.1.2.4 Life-threatening

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

### 8.2 Recording of an Adverse Event

Only AEs meeting one of the following criteria will be entered into the OnCore CRM study database, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

- Any AE that is Grade 3 or higher, regardless of relationship to the study drug
- Any intolerable Grade 2 AE
- Any Grade AE resulting in holding or dose-reducing BYL719
- Any Grade 2 laboratory or vital sign values that are deemed clinically significant by the treating investigator
- Any Grade AE in the following categories of interest:
    - Rash
    - Diarrhea
    - Pneumonitis
    - Hyperglycemia

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

| Relationship | Attribution | Description |
|---|---|---|
| Unrelated to investigational drug/intervention | Unrelated | The AE *is clearly NOT related* to the intervention |
| | Unlikely | The AE *is doubtfully related* to the intervention |
| Related to investigational drug/intervention | Possible | The AE *may be related* to the intervention |
| | Probable | The AE *is likely related* to the intervention |
| | Definite | The AE *is clearly related* to the intervention |

Grade 0: No AE (or within normal limits)

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE, the Investigator will grade as none, mild, moderate or severe according to the following grades and definitions.

### 8.3 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

Subjects who end treatment due to an AE determined to be at least possibly related to the study must have weekly follow up to assess the AE until the AE is resolved, returns to baseline grade, or stabilizes, whichever occurs first.

### 8.4 Adverse Event Monitoring

Adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the University of Arizona Data and Safety Monitoring Board (DSMB) and University of Arizona's Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the University of Arizona Comprehensive Cancer Center HNSCC Clinical Research Team (CRT) at minimum on a monthly basis. The CRT will review and discuss at each monthly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s), including all grade(s) 3-5 adverse events.

In addition, all grade(s) 3-5 adverse events and all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Board on an ongoing basis and discussed at DSMB meetings, which take place every four weeks.

8.5 Serious Adverse Event Reporting

In the event of a serious adverse event, the PI, the institutional review board (if applicable, per institutional reporting requirements), and Novartis will be notified using the FDA Form 3500 MedWatch report.

SAEs must be reported within 24 hours of learning of its occurrence. Additional information must be provided in a follow-up SAE report and also reported within 24 hours after receiving the information.

**ALL** events meeting the definition of a serious adverse event must be reported using the current FDA MedWatch 3500 Form and submitted to:

- UACC DSMB
- Novartis

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Event Description of the MedWatch 3500 form:

- CTCAE term(s) and grade(s)
- Current status of study drug
- All interventions to address the AE (testing and result, treatment and response)
- Hospitalization and/or discharge dates
- Event relationship to study drug

**Follow-up SAE Reports**

Additional information may be added to a previously submitted SAE report and submitted as follow-up SAE Report.

**Reporting to the UACC Data and Safety Monitoring Board**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has taken the first dose of study drug and through the end of the study follow-up period must be reported to the DSMB Chair (or qualified alternate) within 24 hours of learning of its occurrence.

If a death occurs during the treatment phase of the study or during the study follow-up period and it is determined to be related to the study drug or to a study procedure, the Investigator or his/her designee must notify the DSMB Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

**Reporting safety information to Novartis**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects 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 within 24 hours 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 Serious Adverse Event Report Form; all applicable sections of the form must 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 the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. 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.

### 8.6 Reporting Unanticipated Problems

Adverse events, serious adverse events, and deviations may be considered "unanticipated problems." Unanticipated problems, as defined below, will be reported to oversight entities including the IRB and FDA as required by regulation and/or policy.

Note: Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation/deviation.

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

## 9 Data and Safety Monitoring Plan:

### 9.1 Identification of the DSMB obligated for oversight responsibilities:

Dr. Julian at the University of Arizona Cancer Center (UACC) will assume the role of Sponsor. The UACC Data and Safety Monitoring Board (DSMB) will provide ongoing oversight of safety monitoring for this trial. Based on the UACC DSMB Charter, this is a high-risk study.

## 9.2 Identification of the entity obligated for routine monitoring duties:

This trial will undergo real-time monitoring by the PI and study team, including documentation of real-time monitoring of any new or ongoing safety issues.

The PI and study team will meet monthly to review the data and CRFs.

Routine monitoring will be provided monthly by the University of Arizona Cancer Center Compliance and Quality Assurance (CQA) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements. Affiliate sites that participate in this trial will choose, through a reciprocal agreement with UACC, either to:

1) Perform monitoring per the sites' Data and Safety Monitoring Plan, only if the site has fully approved NCI Data and Safety Monitoring Plan.
2) Allow UACC to conduct remote and on-site monitoring for this trial in accordance with the UACC's approved NCI Data and Safety Monitoring Charter/Monitoring Plan.
3) Perform monitoring per the UACC's Data and Safety Monitoring Charter/Plan.

If a site-specific monitoring plan will be used, the UACC DSMB must review the sites' Data and Safety Monitoring Plan and approve that the plan is acceptable. If the UACC DSMB finds that a plan is not acceptable, the UACC or the site's internal monitors will perform monitoring per the UACC Data and Safety Monitoring Plan.

Elements that are required to be included within each site-specific DSM plan are:

- A process to verify eligibility by the local monitoring team.
- Documented timelines in which serious adverse events are reported to the sponsor.
- Frequency and extent of monitoring activities for this trial at the site
- Monitoring reports will be provided to the PI, UACC DSMB, and UA IRB. The PI is responsible to follow up on any action items and/or findings in a timely manner.
- Monitoring reports will be provided to the PI, UACC DSMB, and UA IRB. The PI is responsible to follow up on any action items and/or findings in a timely manner.
- Monitoring reports will be provided to the PI, UACC DSMB, and UA IRB. The PI is responsible to follow up on any action items and/or findings in a timely manner.

## 9.3 Monitoring progress and data review process:

Routine monitoring of subject data will be conducted at least every month.
The first routine monitoring visit will include at a minimum:

- Informed consent – 100% of cases enrolled;
- Subject eligibility – 100% of cases, up to three subjects;
- Data review – 100% of cases, up to three subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based

on current enrollment and include continuing review of previously selected cases, as applicable.

Routine monitoring of regulatory documents and test article will be conducted every three months.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. The monitor will request additional source documentation, clarification, information, or corrections to the CRF and/or regulatory records from the Clinical Research Coordinator (CRC) or other applicable staff responsible for the study and resolution of queries/findings. Documentation of such a request will be maintained with a copy of the monitor's visit report for follow-up at the next monitoring visit. Electronic records will be available in the institutional database or provided by the CQA Program staff.

All monitoring reports must be completed and submitted to the local site PI, the Sponsor-Investigator, and UACC DSMB. All submitted serious adverse events will be submitted to the UACC DSMB Coordinator monthly and then reviewed by the DSMB Chair. Any identified SAE trends will be made available for review at the investigator teleconferences.

A teleconference will occur on a regular schedule to review study progress and any safety, or other, issues. Minutes of these teleconference meetings will be submitted to UACC DSMB for review.

At each site, the Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the OnCore electronic Case Report Form (eCRF), and other data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include adverse event forms, serious adverse event forms, and protocol or patient deviations must be completed via the RedCap database

### *9.4* Plan for assuring data accuracy and protocol compliance:

Any identified safety issue will be submitted to the UA IRB, DSMB or other oversight entity as applicable. Each month the DSMB will perform a review of study activity and safety information at each site. A summary of activity at all sites will be reviewed including the following:

- Study activity, cumulative and for the period under review;
- Safety information (non-serious and serious adverse events);
- Status of study in relationship to stopping rules;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Attachments (AE data reviewed by the PI to compile the report, SAE reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies. Data and Safety Monitoring Board determinations will be reported to the University of

Arizona IRB at least annually. DSMB determinations will be distributed to the sites contemporaneously.

Data, safety and study progress will be reported to:
- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least quarterly.

# 10 Statistical Considerations and Evaluation of Results

## 10.1 Study Endpoints

This is a phase II open label study to identify baseline and/or pharmacodynamics biomarkers of clinical response to BYL719 based on quantitative change in tumor size following 10-21 days of neoadjuvant BYL719 in patients with operable HNSCC. ΔTumor size will be treated as a continuous variable, based upon the percent change in RECIST-determined index lesions pre and post-treatment.

## 10.2 Determination of Sample Size and Accrual Rate

### 10.2.1 Sample Size and Power Estimate

The primary objective of the study is to identify baseline and/or pharmacodynamic biomarkers that might have predictive utility to determine the clinical response to BYL719. The overall sample size is 14 evaluable patients. Accrual will continue until 14 evaluable patients have enrolled If patient had baseline tissue samples obtained, has taken at least 10 doses of drug, and has undergone response assessment that is of sufficient quality to assess the primary clinical and biomarker endpoints, they are evaluable. Based upon prior window trials, up to 20 patients will be enrolled to meet these criteria. The sample size is based upon the following considerations: half of enrolled patients will demonstrate genomic PI3K pathway activation, defined as PIK3CA mutation or amplification, or PTEN deletion. We expect those with genomically activated PI3K to demonstrate a median ΔTumor size of (-)20%, whereas those with no genomic PI3K activation to demonstrate a median increase of (+)5%. Alpha is set to 0.03 and beta is set to 0.20.

As a biomarker study, the statistical design is to accrue a sufficient number of patients and provide 80% power to test one or any of 5 key hypotheses with individual alphas of 0.03: 1) relationship between ΔTumor size and baseline genomic *PIK3CA* activation; 2) relationship between ΔTumor size and change in expression of HPV mRNA (qPCR); 3) relationship between ΔTumor size and change in expression of E6, E7 oncoprotein (immunoblotting); 4) relationship between ΔTumor size and change in expression of phospho-HER3 (immunoblotting and RPPA); 5) relationship between ΔTumor size and change in expression of HER3/PI3K dimers (Monogram). 14 patients with complete biomarker data are needed to achieve 80% power for the 5 primary hypothesis and limit overall family wise error rate (FWER) to 15%. Based upon prior window trials, accounting for treatment compliance and quality paired tumor specimens, this will require enrollment of 20 patients.

As an example, to justify the sample size for the first key hypothesis (relationship between ΔTumor size and baseline genomic *PIK3CA* activation), the standard deviation of ΔTumor size

was estimated from the erlotinib arm of Dr. Bauman's previously completed study of erlotinib and dasatinib or both versus placebo (Bauman JE et al, JCI Insight 2017). In this study, the quantitative change in tumor size after 10-21 days of targeted therapy ranged from -30% to 55%. Assuming the same standard deviation for the change in tumor size after BYL719 treatment as observed for the erlotinib arm (sd = 8%), the study will have > 90% statistical power to detect the mean difference of -20% versus +5% in those with and without *PIK3CA* activation, assuming an alpha level of 0.03. The power was calculated based on a two-sample *t* test with equal variances, assuming an alpha level of 0.03 with $n$ = 7 per group.

### 10.2.2 Replacement Policy

Because this is an open label study with limited number of patients, 14 accrued eligible patients with clinical tumor assessments and biomarkers measurements at baseline and the end of study window are required for the study. Additional patients will be enrolled to replace patients without clinical tumor assessments and completed biomarker measurements for both timepoints and at least one of the five biomarkers of interest. However, all patients will be followed and included for safety assessments.

## 10.3 Protocol Early Stopping Rules

### 10.3.1 Toxicity

A continuous monitoring rule for safety will be instituted, to guard against excess toxicity from pre-operative treatment with BYL719 at 350 mg po daily, the RP2D for this agent. All patients will be treated at the dose of BYL719 350 mg po daily. After enrollment of the 6$^{th}$ patient, we will continuously monitor the number of patients who discontinue BYL719 and come off study for BYL719-attributable toxicity. A qualifying toxicity must be at least possibly related to BYL719, as judged by the treating investigator, and fulfill one of the following definitions:

- Grade ≥ 3 non-hematologic toxicity, with the exception of asymptomatic electrolyte abnormalities manageable with repletion.
- Intolerable non-hematologic toxicities of any grade, which persist despite optimal medical management.
- Grade ≥ 3 thrombocytopenia or neutropenia.
- Any grade toxicity that results in a significant delay of surgery, defined as more than 42 days from the start of BYL719 protocol treatment.

If the posterior probability of ≥ 33% toxicity rate exceeds 50% for patients having to discontinue window treatment due to qualifying toxicity, this would be considered unacceptable. The study would be placed on hold and would be referred to the UACC DSMB for evaluation of excess toxicity and recommendations for design change or study closure.

Table 8 below describes the number of toxicity events per number of treated patients required to trigger referral to the UACC DSMC. Table 8 also shows the posterior probability that the rate exceeds 33%, and the binomial probability associated with the decision for an assumed 33% discontinuation rate. The prior probability has a beta distributions with parameters a = 1 and b = 9, assumes a 10% mean with an approximate 80% mid-range of .0 to .22.

Table 8. Boundaries for the Excess Toxicity Rule

| Subjects | Treatment-Related Discontinuations | PP(π > 33%)* | Pr(X ≥ r\|p = .33) |
|---|---|---|---|
| 6 | 5 | .629 | .017 |
| 8 | 6 | .685 | .019 |
| 11 | 7 | .673 | .037 |
| 14 | 8 | .664 | .054 |
| 17 | 9 | .657 | .071 |
| 20 | 10 | .650 | .087 |

*π is the discontinuation rate. The minimum acceptable upper bound of a treatment-related discontinuation is 33%. PP(π > 33%) is the posterior probability that the discontinuation rate exceeds this 33% upper bound. This posterior probability of discontinuation is calculated from the prior distribution, the number of subjects treated and the observed number of treatment-related discontinuations.

### 10.3.2 Delay in Surgery

Because the protocol enrolls patients who will undergo potentially curative surgery, a conservative stopping rule is in place to guard against unacceptable delays in surgery. An unacceptable delay in surgery is defined as surgery occurring more than 42 days after the start of BYL719 protocol treatment, AND is due to a toxicity that is at least possibly related to BYL719 as judged by the treating investigator. Among the first 14 patients, if the number of patients with an unacceptable delay in surgery ever exceeds 3, then enrollment will be stopped and the study will be referred to the UACC DSMC for evaluation of unacceptable delays in surgery, and recommendations for study redesign or closure.

## 11 Study Management

### 11.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

### 11.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the UA CHR (UA Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the University of Arizona Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

### 11.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

### 11.4 Changes in the Protocol

Once the protocol has been approved by the IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UA study team will be responsible for updating any participating sites.

### 11.5 Deviations

A protocol deviation (noncompliance, unanticipated problem) may be either on the part of the participant, the investigator, or the study site staff. No changes from current IRB-approved research protocol are allowed except where a change may be necessary to eliminate an apparent immediate hazard to a human subject. Deviations may be identified by any study staff or monitoring/oversight entity. As a result of deviations, as applicable, corrective actions are to be developed by the site and implemented promptly.
Deviations will be documented in the CTMS and reported to oversight entities, as applicable.

### 11.6 Maintenance of Subject Specimens

Specimens collected as part of this study will be maintained for future use to learn about preventing or treating cancer. Subjects will be asked to consent to the future use during the informed consent process, and asked to positively indicate their consent to future use in writing within the informed consent document. Samples will be maintained in a secure location within the UACC.

### 11.7 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, study participants, investigator, Lilly, the FDA Investigational New Drug (IND and other regulatory authorities as applicable. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will

promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of the study meeting futility and/or stopping rules

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, and/or Food and Drug Administration (FDA).

### 11.8 Handling and Documentation of Clinical Supplies

The UA Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of the study drug. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the study drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the study drug to be used in any manner other than that specified in this protocol.

### 11.9 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UA personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UA DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only

be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

### 11.10 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, such as progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

### 11.11 Coordinating Center Documentation of Distribution [multi center studies]

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

## 12 Protection of Human Subjects

### 12.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject’s rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent

document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

### 12.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the PHI Authorization form (to authorize use and disclosure of PHI in compliance with HIPAA) form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

In the event that a subject revokes authorization to collect, use, and/or disclose PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

Only authorized individuals will have access to the identifiable study data. All records identifying subjects must be kept confidential per local and Federal policy. Minimum necessary standards must be followed. All subjects are assigned a study ID number. The study data to be used for purposes of analysis and reporting will be coded. Specimens will also be coded using the study ID number. Subject identities will not be used in any results that are published.

Study subjects and study data will be entered into the CTMS. The system is password protected and meets HIPAA requirements.

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## Appendices

### Appendix 1 Performance Status Criteria

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity<br>Fully active, able to carry on all pre-disease performance without restriction | 100 | Normal, no complaints, no evidence of disease |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 1 | Symptoms, but ambulatory<br>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work) | 80 | Normal activity with effort; some signs or symptoms of disease |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work |
| 2 | In bed < 50% of the time<br>Ambulatory and capable of all self-care, but unable to carry out any work activities<br>Up and about more than 50% of waking hours | 60 | Requires occasional assistance, but is able to care for most of his/her needs |
| | | 50 | Requires considerable assistance and frequent medical care |
| 3 | In bed > 50% of the time<br>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours | 40 | Disabled, requires special care and assistance |
| | | 30 | Severely disabled, hospitalization indicated<br>Death not imminent |
| 4 | 100% bedridden<br>Completely disabled<br>Cannot carry on any self-care<br>Totally confined to bed or chair | 20 | Very sick, hospitalization indicated<br>Death not imminent |
| | | 10 | Moribund, fatal processes progressing rapidly |
| 5 | Dead | 0 | Dead |

## Appendix 2 Permitted medications to be used with caution

**Table 1. List of medications to be used with caution during treatment with alpelisib**

| 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 |
| ModerateCYP3A 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 alpelisib 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 alpelisib 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 |

| Category | Drug Name |
|---|---|
| | dexamethasone and prednisone are known to induce CYP3A enzymes, thereby increasing the risk 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 alpelisib, 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 alpelisib is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which requirBYL719 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 2, Table 8.
[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 3 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, 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. |
| 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) |

| Category | Drug Name |
|---|---|
| [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)<br>[2]Herbal product<br>[3]P-gp inducer<br>[4]Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when<br>[5] Please also refer to http://crediblemeds.org/ for a comprehensive list of agents that prolong the QT interval. | |

## Appendix 4 Study Medication Instructions and Diary

### BYL719 Medication Instructions

Please complete the diary each day even if you miss your dose. If you do not take your medication on the day it is scheduled, please write in the reason. Also write in any side effects that you experience. Please also note if you lose any pills. *It is very important that you maintain this diary and bring it with you when you see your study doctor or nurse. Also bring all tablets and bottles with you.*

**Please remember: Do not take the dose on the day of clinic visits. Take the tablets with you to the clinic. They will be taken after the blood draw.**

The BYL719 tablets are provided in 200 mg tablets and 50 mg tablets. **The study dose is 350 mg/day, but if you experience side effects, you may be given a reduced dose.** Depending on your dose, you will take a different number of tablets. This table below provides details on how many tablets of each you will take depending on the dose.

| Dose | Number of 200 mg tablets to take | Number of 50 mg tablets to take |
|---|---|---|
| 350 mg/day | One 200mg tablet | Three 50 mg tablets |
| 300 mg/day | One 200mg tablet | Two 50 mg tablets |
| 250 mg/day | One 200mg tablet | One 50 mg tablet |

Instructions for taking the medication:

- The daily dose of BYL719 should be taken at approximately the same time each day, preferably in the morning, except on the days you will visit the clinic for a blood draw.
- The dose should be taken within 1 hour after a meal, and with a glass of water.
- The tablets must be swallowed whole; do not chew, crush, or break them.
- If vomiting occurs, do not take another dose that day.
  - Take the medication the following day, as usual.
  - Indicate the vomiting on the study diary.
- If you forget to take study treatment during the daytime, it should be taken in the evening at the latest within 1 hour after a meal, <u>but not later than 6 pm</u>.
  - If not taken by this time, the dose should be withheld that day.
  - Document the missed dose in the study diary
- Missed doses should not be made up the next day.
- <u>IMPORTANT</u>: Do not take a double dose to compensate for missed doses
- If you lose pills, make note on the diary.

- A pill count will be performed when medication is returned.

- There are medications you need to avoid while you are on the study medication. These are listed in the consent form. Before you begin any new medications, talk to the study doctor.

**If you have any questions or concerns, contact the study team.**

| | | |
|---|---|---|
| **Study Doctor:** | | |
| **Research Nurse:** | | |
| **Study Coordinator:** | | |

| THE UNIVERSITY OF ARIZONA Cancer Center | Initials | Year of Birth | Participant ID | Protocol # | BYL719 Trial Patient Diary |
|---|---|---|---|---|---|
| | | | | 1802258478 | |

| Day | Date | Dose time | Number of 200 mg Tablets Taken (If missed, mark 0) | Number of 50 mg Tablets Taken (If missed, mark 0) | Comments/Side Effects/Vomiting/Reason Missed |
|---|---|---|---|---|---|
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | | | | | |
| 8 | | | | | |
| 9 | | | | | |
| 10 | | | | | |
| 11 | | | | | |
| 12 | | | | | |
| 13 | | | | | |
| 14 | | | | | |

Other comments, including number of tablets lost, if any:

You will be asked to sign this document (both pages, if necessary) once complete to confirm that you or a caregiver completed the diary.

**Subject or Caregiver Signature: _____ Date: _____**

| THE UNIVERSITY OF ARIZONA Cancer Center | Initials | Year of Birth | Participant ID | Protocol # | BYL719 Trial Patient Diary |
|---|---|---|---|---|---|
| | | | | 1802258478 | |

| Day | Date | Dose time | Number of 200 mg Tablets Taken (If missed, mark 0) | Number of 50 mg Tablets Taken (If missed, mark 0) | Comments/Side Effects/Vomiting/Reason Missed |
|---|---|---|---|---|---|
| 15 | | | | | |
| 16 | | | | | |
| 17 | | | | | |
| 18 | | | | | |
| 19 | | | | | |
| 20 | | | | | |
| 21 | | | | | |
| 22 | | | | | |
| 23 | | | | | |
| 24 | | | | | |
| 25 | | | | | |
| 26 | | | | | |
| 27 | | | | | |
| 28 | | | | | |

Other comments, including number of tablets lost, if any:

You will be asked to sign this document (both pages, if necessary) once complete to confirm that you or a caregiver completed the diary.

**Subject or Caregiver Signature: _____ Date: _____**

## Appendix 5 Tumor Biomarkers

Tumor tissues obtained before treatment with BYL719 will be assessed for canonical *PIK3CA* mutations by SNaPshot PCR(60) and amplifications by FISH.(53) *PTEN* loss will be assessed by FISH.(53) In addition, we will assess *PIK3CA* mutations using a comprehensive full length sequencing approach covering 202 cancer associated genes to ultradeep depth developed as part of the SU2C PI3K in women project.(53) We will assess HPV viral load and levels of HPV E6 and E7 transcripts in paired, pre- and post-treatment tissues by RT-qPCR. We will assess HPV viral load by qPCR and levels of HPV E6 and E7 transcripts by RT-qPCR in paired, pre- and post-treatment tissues. We will also assess paired tumor cell lysates for expression of total and phosphorylated signaling proteins using reverse phase protein array (RPPA), a high-through-put quantitative proteomics platform to detect changes in signaling events.