

**A PHASE II TRIAL OF IBRUTINIB IN
COMBINATION WITH EGFR INHIBITION IN
PATIENTS WITH RECURRENT/METASTATIC
HEAD AND NECK SQUAMOUS CELL
CARCINOMA**

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IST PROTOCOL

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WITH EGFR INHIBITION IN PATIENTS WITH
RECURRENT/METASTATIC HEAD AND NECK
SQUAMOUS CELL CARCINOMA

PROTOCOL NUMBER: Version 3

STUDY DRUG: Ibrutinib (PCI-32765)

INVESTIGATOR
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SYNOPSIS

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| Study Title: | A PHASE II TRIAL OF IBRUTINIB IN COMBINATION WITH EGFR INHIBITION IN PATIENTS WITH RECURRENT/METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA |
| Protocol Number: | TBD |
| Study Phase: | 2 |
| Study Duration: | 12 months |
| Sample Size | 18 patients will be enrolled to ibrutinib/cetuximab; before modification to the protocol, 2 patients were treated with ibrutinib/nivolumab |
| Investigational Product and Reference Therapy: | Ibrutinib will be supplied by Pharmacyclics as 140 mg hard gelatin capsules for oral (PO) administration. Cetuximab will be supplied as a clear, colorless liquid formulated for intravenous administration. Commercial supply will be used. |
| Objectives: | <p>Primary Objective: To determine the clinical efficacy of ibrutinib in combination with cetuximab in patients with R/M HNSCC.</p> <p>Secondary Objectives: Secondary objectives are to evaluate:</p> <ul style="list-style-type: none"> • Overall frequency and severity of adverse events • Progression-free survival • Overall survival • Duration of response of both combinatorial treatment regimens <p>Exploratory Objectives: To prospectively collect blood and tumor tissue specimens to determine biomarkers of response to treatment with ibrutinib in combination with cetuximab. Evaluations to include measurement of biomarkers of ibrutinib and cetuximab response, including BCR and TCR sequencing, immune checkpoint expression, cytokine profiling, gene expression profiling, tumor whole exome sequencing and neoantigen discovery, and to correlate biomarkers to clinical responses</p> |
| Study Design: | A single-arm, phase II, Simon's two-stage clinical trial. |
| Population: | The study will enroll patients who develop R/M HNSCC have not yet been treated with EGFR inhibitors in the recurrent/metastatic setting. All patients being considered for the study must be ≥ 18 years of age and will receive ibrutinib + cetuximab. |
| Centers: | Emory University, Oregon Health & Science University |

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| <p>Inclusion Criteria:</p> <p><i>Refer to Section 4.0 for the complete and detailed list of inclusion/exclusion criteria.</i></p> | <p><i>Disease Related</i></p> <ul style="list-style-type: none"> • Histologically or cytologically proven squamous cell carcinoma of the head and neck not amenable to curative intent therapy. • Presence of measurable tumor lesions per RECIST criteria v1.1 by investigator review. • Life expectancy greater than 12 weeks. • Previously archived or newly obtained tumor specimens for correlative analysis. <p><i>Laboratory</i></p> <ul style="list-style-type: none"> • Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening and randomization, with the exception of pegylated G-CSF (pegfilgrastim) and darbepoetin which require at least 14 days prior to screening and randomization defined as: <ul style="list-style-type: none"> Absolute neutrophil count >750 cells/mm³ (0.75×10^9/L). Platelet count $>50,000$ cells/mm³ (50×10^9/L). Hemoglobin >8.0 g/dL. • Adequate hepatic and renal function defined as: <ul style="list-style-type: none"> Serum aspartate transaminase (AST) or alanine transaminase (ALT) $\leq 3.0 \times$ upper limit of normal (ULN). Estimated Creatinine Clearance ≥ 30 ml/min (Cockcroft-Gault) Bilirubin $\leq 1.5 \times$ ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) • PT/INR $<1.5 \times$ ULN and PTT (aPTT) $<1.5 \times$ ULN <p><i>Demographic</i></p> <ul style="list-style-type: none"> • Men and women ≥ 18 years of age. • Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. |
| <p>Exclusion Criteria:</p> | <p><i>Disease-Related</i></p> <ul style="list-style-type: none"> • Prior therapy with an EGFR inhibitor in the recurrent or metastatic setting • Nasopharyngeal carcinoma histology • Known, clinically active central nervous system metastases (stable metastases permitted) |

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| | <p><i>Concurrent Conditions</i></p> <ul style="list-style-type: none">• Chemotherapy ≤ 28 days prior to first administration of study treatment and/or monoclonal antibody ≤ 16 weeks prior to first administration of study treatment.• Prior exposure to BTK inhibitor• History of other malignancies, except:<ul style="list-style-type: none">Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.Adequately treated carcinoma in situ without evidence of disease.• Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.• Recent infection requiring systemic treatment that was completed ≤ 14 days before the first dose of study drug.• Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.• Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.• History of stroke or intracranial hemorrhage within 6 months prior to enrollment.• Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.• Any uncontrolled active systemic infection.• Any history of interstitial lung disease.• Major surgery within 4 weeks of first dose of study drug.• Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.• Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional |
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| | <p>Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.</p> <ul style="list-style-type: none"> • Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. • Concomitant use of warfarin or other Vitamin K antagonists. • Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subject who requires continuous treatment with a strong CYP3A inhibitor (see Appendix 3). • Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C according to the Child Pugh classification • Female subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days of last dose of study drug. Male subjects who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug. • Unwilling or unable to participate in all required study evaluations and procedures. • Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations) |
| Study Treatment: | In this study, ibrutinib administration will begin 7 days prior to the start of the second agent (cetuximab) as supported by preclinical studies. |
| Concomitant Therapy: | <i>Refer to Section 6 for information on concomitant therapy.</i> |
| Safety Plan: | Data safety and toxicity will be continuously monitored in the study under the guidance from the Data Safety Monitoring Committee. The study will be suspended if there are 1 or more treatment-related deaths within the first 6 patients enrolled to ibrutinib/cetuximab during the initial safety assessment which indicates the treatment-related mortality is > 5%. These treatment-related deaths must be attributable to direct organ toxicity by study treatment agents with the exception of deaths attributable to immunosuppression (i.e. infections). |
| Statistical Methods and Data Analysis: | <p>All efficacy and safety analyses will be performed among all patients who received at least one dose of study medication.</p> <p><u>Primary Efficacy Analysis:</u></p> <p>Demographic and clinical characteristics of the patients will be summarized using frequency counts and percentages, means and standard deviations or medians and interquartile ranges, as appropriate. Best overall response will be summarized as proportion with 95% confidence intervals.</p> |

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| | <p><u>Secondary Efficacy Analysis:</u></p> <p>Progression-free survival, overall survival, and duration of response will be described by Kaplan-Meier models to plot these endpoints and estimate median times with a 95% confidence interval.</p> <p><u>Exploratory Efficacy Analysis:</u></p> <p>Serial estimate of biomarker expression will be plotted and summarized over time using means and standard deviations, possibly on a log scale.</p> <p><u>Safety Analysis:</u></p> <p>Adverse events will be summarized by grade, type and patient.</p> <p>The initial protocol had an ibrutinib/nivolumab arm; this was closed due to emerging scientific data. Several patients were treated on this arm prior to closure; results from the patients treated with this combination will be described by descriptive statistics.</p> |
| Interim Analysis | <p>The interim analysis will be conducted when the 12th patient has been on study for 8 weeks. 12 patients will be accrued to receive ibrutinib and cetuximab and enrollment will suspend pending outcome of the interim analysis. If there are 1 or fewer responses observed in these 12 patients at the interim analysis, this study will be discontinued. If the null hypothesis is true and the true response rate is 10% or less, the probability of stopping the trial early will be 66%.</p> <p>Safety will be continuously monitored.</p> |
| Sample Size Determination | <p>Based on Simon's two stage minmax design, 18 patients treated with ibrutinib/cetuximab will yield a study with 84% power at one-sided type I error rate of 0.05 to detect a true response rate of greater than 40% , versus a null hypothesis of 10%. These power estimates adjust for potential censoring of observations at the end of Stage 1 (at the interim analysis; please see statistical section for explanation). The initial protocol had an ibrutinib/nivolumab arm; this was closed due to emerging scientific data.</p> |

Abbreviations

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| CRF | case report form |
| DCF | data clarification form |
| DMC | Data Monitoring Committee |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders (4th edition) |
| ECG | Electrocardiogram |
| eDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| GCP | Good Clinical Practice |
| HBsAg | hepatitis B surface antigen |
| HIV | human immunodeficiency virus |
| HNSCC | head and neck squamous cell carcinoma |
| HPV | human papillomavirus |
| HRQOL | health-related quality of life |
| IAC | Interim Analysis Committee |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IRB | Institutional Review Board |
| IVRS | interactive voice response system |
| IWRS | interactive web response system |
| LC-MS/MS | liquid chromatography/mass spectrometry/mass spectrometry |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRU | medical resource utilization |
| PD | Pharmacodynamic |
| PD-1 | programmed death-1 receptor |
| PD-L1 | programmed death ligand-1 |
| PFS | progression-free survival |
| PK | Pharmacokinetic |
| PQC | Product Quality Complaint |
| PRO | patient-reported outcome(s) |
| R/M | recurrent or metastatic |
| TIL | tumor infiltrating lymphocyte |
| USP | United States Pharmacopeia |

1. BACKGROUND

1.1.Disease/Histology

Head and neck cancer is the sixth most common cancer worldwide with the predominant histology involving squamous cell carcinoma (HNSCC). Within the United States, HNSCC accounts for 3% of all cancers diagnosed annually and 2% of cancer-related deaths. The 2015 estimates for new incidences and anticipated deaths in the United States are approximately 60,000 and 12,000, respectively (American Cancer Society 2015). The majority of patients with HNSCC initially present with advanced stage disease (Stage III to IV) (Argiris 2008, Seiwert 2005). Despite aggressive, combined modality treatment, a significant proportion of patients will develop recurrent or metastatic (R/M) disease that is no longer amenable to curative therapy. Few treatment options exist for these patients who progress after first-line platinum-based therapy. Survival outcomes remain poor in this population with median survival approaching two months with best supportive care. (Leon 2005).

1.1.1. Treatment Options

There is no accepted standard treatment approach for patients with R/M HNSCC. Methotrexate, taxanes, and fluorouracil are often used alone or in combination as second-line therapy after platinum failure (Colevas 2006). Unfortunately, these therapies only confer a modest improvement in response rates and no improvement in survival.

1.1.2. Role of Epidermal Growth Factor Receptor Inhibition in Disease/Histology

The epidermal growth factor receptor (EGFR) is overexpressed in more than 90% of HNSCC and plays a central role in the pathogenesis of HNSCC, thus making it an attractive drug target in recent years (Santini 2006, Grandis 1993). Cetuximab, an IgG1 chimeric (human-murine) monoclonal antibody that competitively binds to EGFR with high affinity, is the only approved targeted therapy that has been shown to improve survival in the R/M setting. The drug currently has two FDA-approved indications in the R/M setting: in combination with platinum-based therapy and as monotherapy for patients who have progressed after platinum-based therapy. The Phase III EXTREME trial confirmed the benefit of adding cetuximab to first-line platinum-based therapy with 5-fluorouracil, resulting in an improvement of median overall survival to 10.1 months from 7.4 months for patients treated with combined platinum and 5-fluorouracil alone (Vermorken 2008). Regardless, prognosis still remains poor in this population with active cytotoxic regimens portending observed response rates of 36% and median progression-free survival (PFS) of 5.6 months. For patients who are platinum-refractory or platinum-ineligible, cetuximab monotherapy provides modest activity with response rates on the order of 10-20% and median PFS averaging 2.4 months or less (Vermorken 2007, Seiwert 2014). Limited treatment options for this patient population emphasize the need for novel therapeutic approaches that offer better clinical outcomes and quality of life.

1.1.3. Role of BTK in Disease/Histology

Recent research surrounding the biology of squamous cell carcinomas by Affara et al has led to a strong body of preclinical evidence that supports therapeutic strategies aimed at B-cell depletion to alter the tumor microenvironment and thus augment the anti-tumor response. Tumor screening for B-cell infiltration using CD20 and/or Ig mRNA expression revealed that HNSCC exhibited significant increases as compared to corresponding normal mucosa. Phosphorylated BTK was also more prominent in HNSCC tissue sections in both CD20⁺ B-cells and infiltrating myeloid cells (Affara 2014). Treatment with B-cell depleting agents demonstrated improved chemo-responsiveness by inhibiting tumor angiogenesis and facilitating CD8⁺ T cell infiltration (Affara 2014).

Moreover, in mouse models of pancreas cancer, Dr. Varner and Dr. Coussens have recently shown that inhibition of BTK with ibrutinib relieves immune suppressive programs in myeloid cells resulting in mobilization of functional cytotoxic T cell responses (manuscript submitted for publication). These findings support B-cell depleting treatment approaches for HNSCC.

Additionally, ibrutinib also inhibits interleukin-2 inducible T-cell kinase, an essential enzyme in some Th2 T cells. In doing so, interleukin-2 inducible T-cell kinase inhibition can shift the balance between Th1 and Th2 T cells, potentially enhancing anti-tumor immune responses (Sagiv-Barfi 2015).

1.1.4. Rationale for Combination Therapy

Cetuximab is an EGFR inhibitor that is currently approved for the treatment of HNSCC. Based on promising trial results, and with the recent early closure of the CheckMate-141 study, PD-1 inhibition with nivolumab is also likely to receive approval in the near future. The study treatments for this trial would then combine BTK inhibition with standard of care treatments for R/M HNSCC.

In addition to inhibition of the EGFR and its downstream pathways, the effects of cetuximab therapy may also be mediated by antibody-dependent, cell-mediated cytotoxicity as well as stimulation of innate immunity. PD-1 targeting leads to released inhibition of the adaptive response. Preclinical data from Sagiv-Barfi et al demonstrated that the enhanced therapeutic activity of PD-L1 inhibition by ibrutinib was accompanied by enhanced anti-tumor T-cell immune responses in lymphoma, triple negative breast cancer, and colon cancer. Interestingly, preclinical models of ibrutinib in EGFR-mutant non-small cell lung cancer show that ibrutinib may also function as an EGFR inhibitor, thus further supporting its use in HNSCC.

BTK inhibition targets protumoral B cells and humoral immune-activated pathways, thus favoring an antineoplastic effect. This effect would likely be augmented by combining BTK inhibition with agents that stimulate anti-tumor immunity and immunogenic cell death.

1.2. Investigational Product Name and Description

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC for the treatment of B-cell malignancies.

Ibrutinib has been approved in over 80 countries, including the US and EU, for indications covering the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), including CLL/SLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's macroglobulinemia, patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy, and adult patients with cGVHD after failure of 1 or more lines of systemic therapy. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

For the most up to date and comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, in vitro and in vivo preclinical activity, and toxicology of ibrutinib, always refer to the latest version of the ibrutinib Investigator's Brochure and/or the applicable regional labeling information.

1.3. Summary of Nonclinical Data

1.3.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the BTK (Pan 2007). In vitro, ibrutinib is a potent inhibitor of BTK activity ($IC_{50} = 0.39$ nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation ($IC_{50} = 80$ nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

For more detailed and comprehensive information regarding nonclinical pharmacology, refer to the current Investigator's Brochure.

1.3.2. Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. In vivo safety pharmacology assessments performed in a cardiovascular study in telemetry-monitored dogs showed PR interval prolongation, lowered heart rate and shortening of QT interval corrected for heart rate (QTc).

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 20 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily and 420 mg, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals.

For the most comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current IB.

1.3.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

1.4. Summary of Ibrutinib Clinical Data

For the most comprehensive clinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

1.4.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging of 420 to 840 mg/day, exposure to ibrutinib increased proportionally with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib ranged from 4 to 6 hours, with a median time to maximum plasma concentration (T_{max}) 1 to 2 hours. Despite the doubling in mean systemic exposure when dosed with food, the favorable safety profile of ibrutinib allows dosing with or without food. Ibrutinib is extensively metabolized primarily by CYP 3A-mediated metabolic pathways. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure implying non-clinically

relevant accumulation. About 8% of ibrutinib is excreted in the urine. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

For the most up to date and comprehensive pharmacokinetics (PK) and product metabolism information regarding ibrutinib, please refer to the current IB.

1.5.Summary of Ibrutinib Clinical Safety

A brief summary of safety data from combination therapy studies is provided below. For the most up to date and most comprehensive safety information regarding ibrutinib, please refer to the current IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (e.g., USPI, SmPC).

Integrated safety data for a total of 422 with B-cell malignancies from 4 combination therapy studies that have completed primary analysis or final analysis included in the CSR as of 31 July 2017 are briefly summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=422):

| Most frequently reported TEAEs > 10% ^a | Most frequently reported Grade 3 or 4 TEAEs > 5% ^a | Most frequently reported Serious TEAEs > 2% ^a |
|---|---|--|
| Neutropenia | Neutropenia | Neutropenia |
| Diarrhea | Diarrhea | Diarrhea |
| Nausea | Nausea | Thrombocytopenia |
| Thrombocytopenia | Thrombocytopenia | Fatigue |
| Fatigue | Fatigue | Anemia |
| Anemia | Anemia | Pyrexia |
| Pyrexia | Pyrexia | Pneumonia |
| Infusion related reaction | Upper respiratory tract infection | Febrile neutropenia |
| Upper respiratory tract infection | Constipation | Atrial fibrillation |
| Constipation | Vomiting | Cellulitis |
| Vomiting | Rash | Hypertension |
| Rash | Headache | Hyperuricaemia |
| Headache | Pneumonia | Leukopenia |
| Cough | Decreased appetite | Neutrophil count decreased |
| Muscle spasms | Contusion | Tumor lysis syndrome |
| Pneumonia | Febrile neutropenia | Urinary tract infection |
| Oedema peripheral | | White blood cell count decreased |
| Arthralgia | | |
| Decreased appetite | | |
| Contusion | | |
| Insomnia | | |
| Chills | | |
| Peripheral sensory neuropathy | | |
| Stomatitis | | |
| Febrile neutropenia | | |
| Abdominal pain | | |
| Back pain | | |
| Bronchitis | | |

^a Source is Table 7 of [IB \(v11\)](#)

For more detailed information refer to the current version of the IB.

1.5.1. Risks

1.5.1.1. Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed, refer to Section 6.2.4. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures. Patients with congenital bleeding diathesis have not been studied.

1.5.1.2. Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section 6.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

1.5.1.3. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding. Monitor complete blood counts monthly.

1.5.1.4. Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.5.1.5. Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

1.5.1.6. Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

1.5.1.7. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.5.1.8. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

For subject and ibrutinib management guidance, refer to Section 5.3.1.5

1.5.1.9. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see [Section 5.3.1.4](#)).

1.5.2. Summary of Cetuximab Clinical Data

Please see cetuximab package insert for full data.

1.5.3. Clinical Trial Data

Cetuximab as a single agent has been approved for R/M HNSCC based on data from a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN. All patients had documented disease progression within 30 days of a platinum-based chemotherapy regimen. Patients received a 20-mg test dose of Erbitux on Day 1, followed by a 400 mg/m² initial dose, and 250 mg/m² weekly until disease progression or unacceptable toxicity. The objective response rate was 13% (95% confidence interval 7%–21%). Median duration of response was 5.8 months (range 1.2–5.8 months). (ERBITUX package insert). A prospective phase II trial also studied cetuximab administered on a Q2 week schedule and found similar efficacy (Fury et al, 2012)

1.5.3.1. Infusion reactions

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of cetuximab included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in Studies 1, 3, 5, and 6 receiving cetuximab, with fatal outcome in 1 patient. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Recommendations are to monitor patients for 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

Immediately and permanently discontinue cetuximab in patients with serious infusion reactions (ERBITUX package insert).

1.5.3.2. Cardiopulmonary arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation

therapy alone in a study in locally advanced HNSCC. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab. In a study in R/M HNSCC, fatal cardiac disorders and/or sudden death occurred in 7 (3%) of 219 patients treated with EU-approved cetuximab and platinum-based therapy with 5-FU as compared to 4 (2%) of 133 patients treated with chemotherapy alone. Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin(ERBITUX package insert).

1.5.3.3. Pulmonary Toxicity

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving cetuximab in trials in colorectal cancer and head and neck cancer. Interrupt cetuximab for acute onset or worsening of pulmonary symptoms. Recommendations are to permanently discontinue cetuximab for confirmed ILD (ERBITUX package insert).

1.5.3.4. Dermatologic Toxicity

Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis occurred in patients receiving cetuximab therapy. Acneiform rash occurred in 76–88% of 1373 patients receiving cetuximab in clinical trials. Severe acneiform rash occurred in 1–17% of patients. Acneiform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days (ERBITUX package insert).

1.5.3.5. Hypomagnesemia and Electrolyte Abnormalities

In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of 365 patients receiving cetuximab in clinical trials in colorectal cancer and head and neck cancer and was severe (NCI CTC Grades 3 and 4) in 6–17%.

1.6.Study Rationale

As discussed above, standard treatment approaches for patients with R/M HNSCC are not curative, do not produce a remission in the majority of patients, and survival for patients who fail or progress while on therapy is poor. Clearly, there is an urgent need for more effective treatments for patients with R/M HNSCC. Given that ibrutinib has demonstrated enhanced antitumor activity in combination with conventional chemotherapy or checkpoint blockade in murine models of HPV16-induced squamous cell carcinoma and BTK-independent tumors,

respectively (Affara 2014, Sagiv-Barfi 2015), investigation of the activity of ibrutinib in R/M HNSCC is warranted. The purpose of this Phase II multi-institutional study is to evaluate the safety and efficacy of ibrutinib administered in combination with cetuximab or nivolumab. Cetuximab is currently FDA-approved for use as a single agent in R/M HNSCC and has been shown to partially mediate its therapeutic effects through immunogenic mechanisms. Checkpoint inhibitor nivolumab that targets the PD-1 molecule on immune effector cells have recently gained FDA approval for the treatment of metastatic melanoma and metastatic non-small cell lung cancer, and based on positive results from the CheckMate-141 study, is likely to gain an indication in R/M HNSCC soon. Recent work has demonstrated the ability of ibrutinib to alter T-cell immune responses by dampening humoral immunity (Sagiv-Barfi 2015), thus introducing a strong rationale for combining this drug with other immune modulating therapies. We hypothesize that the combination of immunomodulatory agents such as cetuximab or nivolumab with ibrutinib, a covalent inhibitor of BTK that causes B-cell depletion, will lead to enhanced antitumor activity by regulating Th1-type T-cell recruitment. Although its clinical experience in HNSCC is lacking, ibrutinib has been shown to be well-tolerated in many B-cell malignancies. The addition of ibrutinib to a regimen of either cetuximab or nivolumab with previously established efficacy and tolerability will allow us to evaluate the hypothesis that these agents may act together to improve efficacy, with acceptable toxicity.

1.7.Dosing Rationale

Ibrutinib has been studied in a number of combination studies and overall has been well tolerated. In an ongoing phase I trial in GI/GU tumors (NCT02599324), 8 patients have been treated with cetuximab and ibrutinib in the doses used in this trial. No DLTs were noted in these patients, and currently patients are being treated with a higher dose of ibrutinib (840 mg PO daily) (personal communication). Ibrutinib has also been studied in combination with checkpoint inhibitors. Ibrutinib 420 mg PO daily has been combined with nivolumab in CLL and has been well tolerated (Jain, 2016). Ibrutinib 560 mg PO daily has been combined with PD-L1 inhibitor durvalumab in an ongoing phase I/II study in solid tumors (NCT02403271) and thus far has been well tolerated with no unexpected adverse events (personal communication)

2. STUDY OBJECTIVE

2.1.Primary Objective

- 2.1.1.** To determine the clinical efficacy of ibrutinib in combination with cetuximab in patients with R/M HNSCC as defined by overall response rate

2.2.Secondary Objective(s)

- 2.2.1.** To determine overall frequency and severity of adverse events
- 2.2.2.** To determine progression-free survival

2.2.3. To determine overall survival

2.2.4. To determine the duration of response of these two treatment regimens

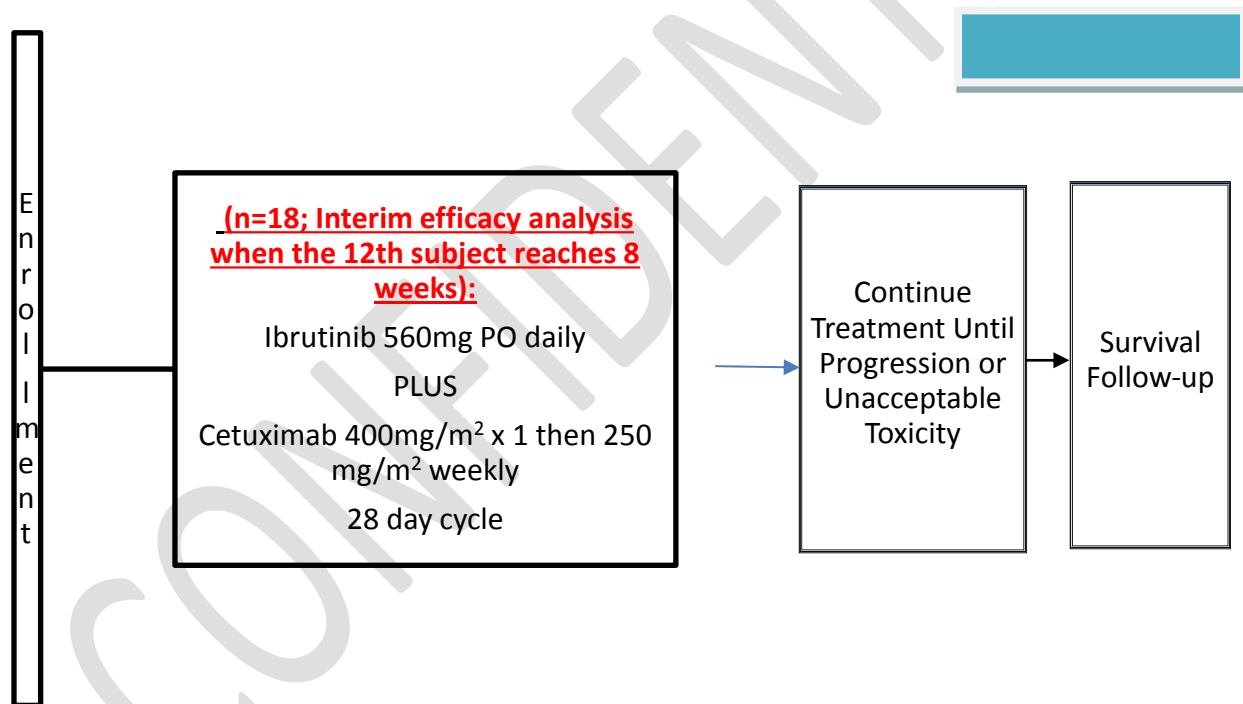
2.3.Exploratory Objective(s)

2.3.1. To prospectively collect blood and tumor tissue specimens to determine biomarkers of response to treatment with ibrutinib in combination with cetuximab

3. STUDY DESIGN

3.1.Overview of Study Design

3.1.1. Study Schema



Primary endpoint: Clinical efficacy as defined by overall response rate

3.2. Study Design Rationale

3.2.1. Study Population And Treatment

The study will enroll 18 patients who develop R/M HNSCC who have not yet been treated with EGFR inhibitors for recurrent or metastatic disease to be treated with ibrutinib/cetuximab. The initial version of this protocol had an arm with ibrutinib/nivolumab; this arm was closed based on emerging science. Patients treated on this arm will not count towards the total sample size of 18 patients. All patients being considered for the study must be ≥ 18 years of age and will receive ibrutinib + cetuximab.

Approximately four study centers will participate in this study

3.2.2. Dose Selection

The dose and schedule for ibrutinib will be 560mg taken orally once daily.

The dose and schedule for cetuximab will be $400\text{mg}/\text{m}^2 \times 1$ as a loading dose, then $250\text{ mg}/\text{m}^2$ weekly given intravenously.

All drugs will be continued until progression, intolerable toxicity, or withdrawal of consent.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria.

Disease Related

1. Histologically or cytologically proven squamous cell carcinoma of the head and neck not amenable to curative intent therapy. P16 or HPV status must be known on all patients with oropharyngeal primaries or unknown primaries.
2. Known p16 and/or HPV status by institutional standard.
3. Presence of measurable tumor lesions per RECIST criteria v1.1 by investigator review
4. Life expectancy greater than 12 weeks
5. Previously archived or newly obtained tumor specimens for correlative analysis

Laboratory

1. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening and randomization, with the exception of pegylated G-CSF (pegfilgrastim) and darbepoetin which require at least 14 days prior to screening defined as:
 - Absolute neutrophil count >750 cells/mm³ (0.75×10^9 /L).
 - Platelet count $>50,000$ cells/mm³ (50×10^9 /L).
 - Hemoglobin >8.0 g/dL.
2. Adequate hepatic and renal function defined as:
 - Serum aspartate transaminase (AST) or alanine transaminase (ALT) $\leq 3.0 \times$ upper limit of normal (ULN).
 - Estimated Creatinine Clearance ≥ 30 ml/min (Cockcroft-Gault)
 - Bilirubin $\leq 1.5 \times$ ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
3. PT/INR $<1.5 \times$ ULN and PTT (aPTT) $<1.5 \times$ ULN

Demographic

4. Men and women ≥ 18 years of age.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

Ethical/Other

6. Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥ 1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.
7. Male and female subjects of reproductive potential who agree to use both highly effective methods of birth control (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence, or sterilized partner) and a barrier method (e.g., condoms, vaginal ring, sponge, etc.) during the period of therapy and for 30 days after the last dose of study drug for females and 90 days for males. Ability and willingness to provide written informed consent

4.2.Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

Disease-Related

1. Prior therapy with an EGFR inhibitor in the recurrent or metastatic setting

2. Nasopharyngeal carcinoma histology
3. Known, clinically active central nervous system metastases (stable metastases permitted)

Concurrent Conditions

1. Chemotherapy ≤ 28 days prior to first administration of study treatment and/or monoclonal antibody (including immunotherapy) ≤ 28 days prior to first administration of study treatment.
2. Prior exposure to BTK inhibitor
3. History of other malignancies, except:
 - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
 - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
 - Adequately treated carcinoma in situ without evidence of disease.
4. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
5. Recent infection requiring systemic treatment that was completed ≤ 14 days before the first dose of study drug.
6. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE v4.03), Grade ≤ 1 , or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
7. Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.
8. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
9. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). *Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.*
10. Any uncontrolled active systemic infection.
11. Any history of interstitial lung disease.
12. Major surgery within 4 weeks of first dose of study drug.
13. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.

14. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
15. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
16. Concomitant use of warfarin or other Vitamin K antagonists.
17. Subject who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subject who requires continuous treatment with a strong CYP3A inhibitor (see [Appendix 3](#)).
18. Subjects with chronic liver disease with hepatic impairment Child-Pugh Class B or C according to the Child-Pugh Classification (see [Appendix 4](#)).
19. Female subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days of last dose of study drug. Male subjects who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug.
20. Unwilling or unable to participate in all required study evaluations and procedures.
21. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

5. TREATMENT OF SUBJECTS

5.1. Study treatment

Treatment of this study will consist of a combination of ibrutinib and cetuximab.

5.1.1. Route and schedule

In this study, ibrutinib administration will begin 7 days prior to the start of the second agent as supported by preclinical studies.

Ibrutinib will be administered continuously at 560mg given as 4 capsules on a daily basis of each 28 day cycle. On days where patients receive both ibrutinib and the second agent (cetuximab), ibrutinib will be given first. Ibrutinib will be administered per institutional guidelines.

Cetuximab will be administered at 400mg/m² x 1 as a loading dose given as a 120 minute IV infusion, following by 250 mg/m² weekly. Subsequent infusions may be given over 60 minutes. Cetuximab will be administered per institutional guidelines.

5.2.Dose Modifications

Please see sections 5.4.1.4, 5.4.2.2, and 5.4.3.2 for discussion of dose modifications for ibrutinib and cetuximab for toxicities. If one drug is held, the other drug may be continued. For example, if a patient develops neutropenia thought to be related to ibrutinib or cetuximab may be continued. If cetuximab is held for toxicities clearly related to those drugs, ibrutinib treatment may continue. When there are toxicities that may be attributed to either agent (e.g., diarrhea), a discussion will occur between the treating physician and the study principal investigator to determine whether one drug or both should be held.

5.3.Study Medication

5.3.1. Ibrutinib

5.3.1.1. Formulation/Packaging/Storage

Ibrutinib will be supplied by Pharmacyclics.

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.1.2. Dose and Administration

Ibrutinib 560 mg (4 x 140-mg capsules) is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Refer to Section 6.2 and Appendix 3).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

Dosing will be on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Study drug may not be shipped to the subject without approval from PCYC and may not be dispensed to anyone other than the subject. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be redispensed to anyone.

5.3.1.3. Overdose

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.4 for further information regarding AE reporting.

5.3.1.4. Dose Modification for Adverse Reactions

The dose of ibrutinib should be modified according to the dose modification guidelines in Table 1 if any of the following toxicities occur:

- Grade 4 ANC ($<500/\mu\text{L}$) for more than 7 days. See Section 6.1 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia ($<50,000/\mu\text{L}$) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia ($<25,000/\mu\text{L}$).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (See Section 6.2.4).

If the dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

Table 1. Ibrutinib Dose Modifications

| Occurrence | Action to be Taken |
|------------|---|
| First | Withhold study drug until recovery to Grade \leq 1 or baseline; may restart at original dose level |
| Second | Withhold study drug until recovery to Grade \leq 1 or baseline; may restart at 1 dose level lower (i.e., 280 mg/day for 420 mg/day dose; 420 mg/day for 560 mg /day dose) |
| Third | Withhold study drug until recovery to Grade \leq 1 or baseline; may restart at 1 dose level lower (i.e., 140 mg/day for 420 mg/day dose; 280 mg/day for 560 mg /day dose) |
| Fourth | Discontinue study drug |

Table 2. Ibrutinib Dose Reduction Levels

| Starting Dose Level | 560 mg |
|------------------------|-------------|
| Dose Reduction Level 1 | 420 mg |
| Dose Reduction Level 2 | 280 mg |
| Dose Reduction Level 3 | Discontinue |
| Dose Reduction Level 4 | NA |
| Dose Reduction Level 5 | NA |

5.3.1.5. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child-Pugh class B or C) are excluded from study participation. Refer to Appendix 4 for Child-Pugh classification. For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) at enrollment, the starting dose has to be adjusted to a level of 280 mg daily (two capsules). For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules) unless lower doses had already been implemented. For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better and could be re-treated according to resolved hepatic conditions (i.e., 140 mg or 280 mg for moderate or mild impairment, respectively). Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in Section 5.3.1.4.

5.3.2. Cetuximab

5.3.2.1. Formulation/Packaging/Storage

Commercial supply of cetuximab will be used.

Cetuximab is supplied for intravenous administration at a concentration of 2mg/ml as a 100mg/50ml, single-use vial or as a 200mg/100ml, single-use vial as a sterile, clear, colorless, injectable liquid containing no preservatives. Single-use vials are individually packaged in cartons.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.2.2. Dose and Administration

Cetuximab is administered intravenously weekly via infusion pump or syringe pump with infusion rate not to exceed 10 mg/min. Patients will be monitored during and after each cetuximab infusion with assessment of vital signs per standard procedure. Premedications will be used as per institutional protocols.

Patients will be monitored for the presence of infusion-related reactions. Dose modification and toxicity management for infusion-related reactions are outlined in the dose modification section (Section 5.3.2.3).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

5.3.2.3. Dose Modification for Adverse Reactions

Tables 3 and 4 should be used as guidelines for cetuximab dose modifications. Please refer to the cetuximab label for additional information.

Table 3. Cetuximab Dose Modifications for Infusion Reactions

| NCI-CTCAE Grade | Dose Modification |
|---|---|
| 1 | Reduce infusion rate by 50% |
| 2 | |
| Non-serious grade 3 | |
| Serious grade 3 (e.g. requiring hospitalization) or any grade 4 | Immediately and permanently discontinue cetuximab |

Table 4. Cetuximab Dose Modifications for Dermatologic Toxicity

| Severe Acneiform Rash | Cetuximab Delay/Discontinuation | Outcome | Dose Modification |
|----------------------------|---------------------------------|----------------|--------------------------------------|
| 1 st Occurrence | Delay infusion by 1-2 weeks | Improvement | Continue at 250mg/m ² |
| | | No improvement | Discontinue cetuximab |
| 2 nd Occurrence | Delay infusion by 1-2 weeks | Improvement | Reduce dose to 200 mg/m ² |
| | | No improvement | Discontinue cetuximab |
| 3 rd Occurrence | Delay infusion by 1-2 weeks | Improvement | Reduce dose to 150 mg/m ² |
| | | No improvement | Discontinue cetuximab |
| 4 th Occurrence | Discontinue cetuximab | | |

5.4. Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. For a complete list of criteria for permanent discontinuation of study treatment, refer to Section 9.2.

An End-of-Treatment Visit (Section 8.3) is required for all subjects except for those subjects who have withdrawn full consent.

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be recorded from the time of ICF signing until 30 days after the last dose of study drug.

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Short courses (≤ 14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted. Steroids for management of immune-related adverse events are allowed.

After consultation with the investigator the following may be considered; localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

6.2. Medications to be Used with Caution

6.2.1. CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and therefore strong CYP3A inhibitors should be avoided. If a strong CYP3A inhibitor (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, cobicistat, and posaconazole) must be used, either reduce ibrutinib dose to 140 mg for the duration of inhibitor use or withhold treatment temporarily (for 7 days or less). Subjects should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor (e.g., fluconazole, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, and dronedarone) must be used, reduce ibrutinib to 140mg (for 840 mg/day dose, reduce to 280 mg) for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).

Avoid concomitant use of systemic strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix 3. A comprehensive list of inhibitors, inducers, and substrates may be found at <http://medicine.iupui.edu/clinpharm/ddis/main-table/>. This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

6.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC₅₀ of 2.15 µg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There is no clinical data available; therefore,

to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin or methotrexate, should be taken at least 6 hours before or after ibrutinib.

6.2.3. QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic electrocardiogram (ECG) and electrolyte monitoring should be considered.

6.2.4. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.4). Subjects with congenital bleeding diathesis have not been studied.

Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.3. Prohibited Concomitant Medications

Any non-study protocol related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of the underlying malignancy is prohibited (Refer to Section 6.1 for further guidance).

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedure

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, skin or needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the

procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

6.4.2. Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention (except for emergency procedures) and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

7. STUDY EVALUATIONS

7.1. Description of Procedures

7.1.1. Assessments

1. Informed consent
2. Medical history – Complete medical, surgical, and oncologic history. Changes from screening [e.g., worsening severity or abnormal findings) are considered to be adverse events (AEs)].
3. Demographics – Profile will include date of birth, gender, race, and ethnicity.
4. Review patient eligibility criteria – Review eligibility criteria as described in Section 4 to ensure patient qualification for study entry.
5. Review previous and concomitant medications – All prior medication taken by the patient within 4 weeks before starting the study is to be recoded. Concomitant medications taken by the patient during the study are to be recorded up until 30 days after last study dose. If a reportable AE (see Section 11.4) occurs within 30 days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.
6. Physical exam including vital signs, height, body weight, and pulse oximetry. Physical exam to include thorough examination of the oral cavity and neck.
7. ECOG performance status evaluated at screening and monthly intervals.
8. Adverse event assessment – Baseline assessment of patient status for determining adverse events, that is, change from

baseline. See Section 11.4 for Adverse Event monitoring and reporting.

9. Twelve lead ECG at baseline and when clinically indicated

7.1.2. Laboratory

1. Hematology – Complete blood count with differential
2. Screening coagulation studies – International normalized ratio (INR), protime (PT), activated partial thromboplastin time (aPTT)
3. Serum chemistries – Electrolytes (sodium, potassium, chloride, bicarbonate), BUN, creatinine, random glucose, calcium, magnesium, albumin, ALT/SGPT, AST/SGOT, total bilirubin, total protein, magnesium
4. Hepatitis B and C serologies – Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody total, hepatitis C antibody
5. HIV serology – HIV 1/2 antibody
6. Pregnancy test for females of child bearing potential – Serum beta-hCG.
7. Blood draw for correlative testing – 30 mL of peripheral blood will be collected prior to initiation of study treatment and on cycle 2 day 1 (+/- 7 days)

7.1.3. Diagnostics/Procedures

1. CT scan of the soft tissue neck and thorax with intravenous contrast for baseline disease assessment. Additional scans (e.g., abdomen/pelvis etc.) may be conducted as needed per each patient's disease burden.
2. Tumor biopsy for correlative testing – A tumor biopsy sample will be collected prior to initiation of study treatment (unless previously archived but new sample preferred) and on cycle 2 day 1 (+/- 7 days)

7.1.4. Pharmacokinetics/Biomarkers (as applicable)

1. Blood and tumor tissue specimens prior to initiation of study treatment and on cycle 2 day 1 (+/- 7 days) to measure potential biomarkers that can be used to predict response to therapy for an individual patient in future trials.

7.2.Efficacy Evaluations

1. Restaging CT scans will be performed after every 2 cycles and compared to baseline to assess clinical response to study treatment. Response will be determined based on RECIST 1.1 criteria (see section 10).

7.3.Sample Collection and Handling

Blood and tumor tissue specimens will be collected prior to initiation of study treatment and on cycle 2 day 1 (+/- 7 days). These specimens will be collected as part of this protocol and stored in the tissue bank.

Additional peripheral blood and tumor tissue samples may be collected on patients who relapse/progress while in follow-up as part of this protocol. The samples in follow-up are optional.

These samples will be delivered to the tissue procurement core facility at each designated cancer center and processed according to institutional standard operating procedures and frozen.

8. STUDY PROCEDURES

8.1.Screening Phase

The following screening procedures listed will be conducted within 4 weeks prior to initiation and pick-up of ibrutinib. Routine tests or evaluations taken prior to patient consent may be used to satisfy entry criteria.

1. Obtain signed, written informed consent – consent must be obtained prior to initiation of ibrutinib in order to obtain appropriate study lab samples
2. Demography
3. Medical history
4. Concomitant medications, including parenteral nutrition: record all medications from the start of ibrutinib
5. Physical examination, including vital signs, height, body weight, and pulse oximetry
6. Documented confirmation of disease and staging
7. ECOG performance status assessment (see Appendix 2)
8. Baseline CT imaging to quantify disease burden per RECIST criteria v1.1
9. Clinical laboratory testing: CBC and differential, comprehensive metabolic panel (CMP), screening coagulation studies, pregnancy test for women of child bearing potential (within 72 hours of starting ibrutinib), HIV serology, hepatitis B and C serologies with confirmatory negative PCR testing if serologies are positive
10. Tumor biopsy for specimen analysis and correlative testing or confirmation of previously archived specimen
11. HPV and/or p16 tumor status by institutional standard procedures

12. Verify that patient meets all entry criteria
13. ECG

8.2.Treatment Phase

For this study, the following assessments will be performed on Cycle 1, Day 8 (+/- 3 days) of the second agent of each study treatment:

1. Brief update of medical history
2. Physical exam with vital signs, height, body weight, and pulse oximetry
3. Document concomitant medications
4. Collect adverse events
5. Labs: CBC with differential, CMP, magnesium
6. ECOG performance assessment

The following assessments will be performed on a monthly basis, coinciding with Day 1 of each subsequent cycle (+/- 3 days).

1. Brief update of medical history
2. Physical exam with vital signs, height, body weight, and pulse oximetry
3. Document concomitant medications
4. Collect adverse events
5. Labs: CBC with differential, CMP, magnesium
6. ECOG performance status assessment
7. Tumor tissue biopsy for specimen analysis and correlative testing and blood draw for correlative studies around Day 28 of cycle 1 only (+/- 7 days)

The following assessments will be performed on day 15 of each cycle (+/- 3 days), prior to cetuximab infusion:

1. Labs: CMP, magnesium

8.3.Follow-up Phase

Patients will be followed for 5 years from study entry, or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients taken off study to undergo non-study treatment will be censored as progressive disease as of the date they begin non-protocol therapy. Patients refusing protocol-defined follow-up will be censored as to their status on the day of last contact.

Patients will be seen within 28 days of the last treatment dose. At this visit, the following assessments will be conducted:

1. Brief update of medical history
2. Physical exam with vital signs, height, body weight, and pulse oximetry
3. Labs: CBC with differential, basic metabolic panel, hepatic function panel
4. ECOG performance status assessment

5. Collect adverse events

9. SUBJECT WITHDRAWAL

9.1. Withdrawal from Study Treatment

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

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Patient demonstrates disease progression (unless continued treatment with study regimen is deemed appropriate at the discretion of the investigator);
- Patient experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Lost to follow-up. If a research patient cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the patient during the two years must be documented and approved by the Data Monitoring Committee.

9.2. Withdrawal from Study

Within the provisions of informed consent and good clinical judgement with respect to safety, every attempt should be made to have patients complete the study. The following are reasons to terminate the participation of any patient in the study:

- Intolerable adverse effects
- Gross non-compliance with the protocol
- The patient wishes to withdraw for whatever reason
- Investigator judgement
- The Sponsor elects to end the study, or any portion thereof, for any reason

Although a patient is not obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. All patients who are enrolled and treated (i.e., receive any amount of study product) will

be included in the safety analyses. Thus, every effort will be made to contact a patient who fails to appear for any follow-up appointments/contacts, in order to ensure that he/she is in satisfactory health.

10. **MEASUREMENT OF EFFECT**

10.1. **Antitumor Effect**

Tumor measurements will be performed on scans. Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1.1. **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from time of signed consent until 30 days following last dose of study drug.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 2 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.1.2. **Disease Parameters**

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

Note: Tumor lesions that are situated in a previously irradiated area can be considered measurable if there has been documented progression in these lesions following the completion of radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.1.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over

time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.1.4. Response Criteria

10.1.4.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.1.4.2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.1.4.3. Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required* |
|----------------|--------------------|-------------|------------------|--|
| CR | CR | No | CR | ≥4 wks. Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. Confirmation** |
| CR | Not evaluated | No | PR | |

| | | | | |
|---|-----------------------------|-----------|----|--|
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥ 4 wks. from baseline** |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |
| <p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>.” Every effort should be made to document the objective progression even after discontinuation of treatment.</p> | | | | |

11. CORRELATIVES AND BIOMARKER STUDIES

We will prospectively collect blood and tumor tissue specimens to determine biomarkers of response to treatment with ibrutinib in combination with cetuximab. Depending on tissue availability, not all studies may be able to be performed on every specimen.

Planned analyses include:

- Investigate ITK/BTK occupancy in tumor tissue to demonstrate potential therapeutic mechanisms of the combination therapy.
- Multiplex IHC to study the immune microenvironment
- BCR and TCR deep sequencing to identify dominant clone in peripheral blood. This work will be performed by Adaptive Biotechnologies
- Whole exome sequencing, RNAseq/gene expression profiling on baseline tissue to study quantitative evaluation of gene expression patterns and genomic alterations to demonstrate immune checkpoint targets, functional T cell responses, candidate tumor antigens

Analysis will be performed at University of California San Diego. Specimens should be sent to:

Sharmeela Kaushal, Ph.D.

Biorepository Manager,

University of California San Diego, Moores Cancer Center

3855 Health Sciences Dr
RM 3345/3G, GG
La Jolla, CA 92093-0819
Office: 858-822-7661
Cell: 858-348-7180

Please refer to standard operating procedures for details on assays.

12. STATISTICAL METHODS AND ANALYSIS

12.1. Subject Information

Demographic data (age, sex, ethnicity, height, body weight) and baseline disease characteristics will be tabulated and summarized and presented in data listings.

12.2. Endpoints

12.2.1. Primary Endpoints

The primary endpoint is the clinical efficacy as defined by the overall response rate (proportion of patients with a partial or complete response in tumor burden based on best overall response) using RECIST v1.1.

12.2.2. Secondary Endpoints

Progression-free survival (PFS), defined as the interval from the date of first dose of study drug (ibrutinib or cetuximab whichever occurs first) to disease progression or death from any cause, whichever occurs first.

Overall survival (OS), defined as the date of first dose of ibrutinib or cetuximab, whichever given first, to the date of death from any cause.

Duration of response is measured from the time measurement criteria are met for complete response or partial response (whichever is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or death of any cause.

Overall frequency and severity of adverse events per CTCAE v4.0.

12.2.3. Exploratory Endpoints

Measurement of biomarkers of ibrutinib and cetuximab response, including BCR and TCR sequencing, immune checkpoint expression, cytokine profiling, gene expression profiling, tumor whole exome sequencing and neoantigen discovery, and to correlate biomarkers to clinical responses

12.3. Sample Size Determination and Primary Analysis

The primary analysis will use Simon's two stage minimax design. The one-sided overall Type I error rate will be 5%. The analysis population will be all subjects who have received at least one dose of study drug.

For the study treatment of ibrutinib plus cetuximab, the null hypothesis that the true response rate is 10% will be tested against a one-sided alternative of greater than 10%. 10% is chosen as the appropriate null response rate because based on historical data for single agent cetuximab in this population (Seiwert TY et al, 2014). In the first stage, 12 patients will be accrued, and enrollment will suspend pending outcome of the interim analysis. If there are 1 or fewer responses observed in these 12 patients at the interim analysis, this study will be discontinued for lack of efficacy. Otherwise, 6 additional patients will be accrued for a total of 18 patients. The null hypothesis will be rejected if 5 or more responses are observed among these 18 patients at the final analysis. The conclusion will be that the response rate is significantly greater than 10%. This study yields a one-sided Type I error rate of 5%, and under the assumption that all patients are followed until progression so that all best responses are observed, a power of 90% when the observed response is 40%. Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 66%. Modification of these operating characteristics because of potential censoring of observations at the interim analysis is discussed below. We anticipate that one-sided Type I error will remain at 5% or less, and that true power will be between 80% and 90%, and that the probability of early stopping under the null will be at least 66%.

An initial version of this protocol included an ibrutinib plus nivolumab arm; based on emerging data, enrollment to that arm was halted. Patients treated with the ibrutinib/nivolumab combination will not count towards the 18 patients in the final analysis of the ibrutinib/cetuximab arm; results for patients treated with ibrutinib/nivolumab will be based on descriptive statistics only.

The Final efficacy analyses will calculate the uniformly minimum variance unbiased estimator (UMVUE), p-value and 95% CI for the response rates (Jung 2004, Koyama 2008). The calculation will be performed using R *clinfun* package (www.r-project.org).

12.4. Interim Analysis and Futility Stopping Rules

Enrollment will suspend after stage 1 enrollment is complete, until the results of the interim analysis are known. The interim analysis will be conducted when 12th subject has reached the 8 week restaging visit. As described above, if there are 1 or fewer responses observed among the first 12 patients, this study will be discontinued for lack of efficacy. Note that at this time point, some subjects may not yet have attained their best response. This will reduce the chance of observing a response, and the power will be decreased by an amount which is estimated below. The final power is estimated at 80% for this study. If the null hypothesis is true and the true response rate is 10% or less, the probability of stopping the trial early will be 66%.

Brahmer reports single agent use of nivolumab in squamous cell lung cancer, which is biologically very similar to HNSCC. In this paper, time to first response is given in Figure 2, panel A, (Brahmer J et al, 2015). We use these data to estimate the operating characteristics of the Simon design, adjusting for potential censoring of response at the interim analysis. In Table 1 below, column 2 shows the time on study for each subject at the interim analysis, assuming accrual of 2 subjects per month. Column 3 shows the proportion of responses which were observed by that time in Brahmer 2015.

| Table 1. Time on study for the first 12 patients at the interim analysis, given accrual of 2 subjects per month. | | |
|--|---|--|
| Patient start month | Time on study, when the last enrolled patient has been observed for 8 weeks | Proportion of responses observed by this time. (Figure 2, panel A, Brahmer 2015) |
| Patient 1 & 2 start at month 1 | 28w | 89% |
| Patient 3 & 4 start at month 2 | 24w | 89% |
| Patient 5 & 6 start at month 3 | 20w | 85% |
| Patient 7 & 8 start at month 4 | 16w | 63% |
| Patient 9 & 10 start at month 5 | 12w | 59% |
| Patient 11 & 12 start at month 6 | 8w | 59% |

From the average of the third column of the above table, we obtain a mean observed response rate of 74% of the true response rate, where the true response rate assumes we observed all these subjects to progression. Then, for this study, using a true response rate of 10% as the original null hypothesis, the observed null response rate will be 74%*10%, which is 7.4%. This adjustment accounts for the censoring from assessing response at an early time point. Similarly, the unadjusted alternative hypothesis is that the response rate equals 40%, and the adjusted

alternative hypothesis is the response rate equals $74\% \times 40\%$, which is 30%. The probability of early stopping ($p(x \leq 1), x \sim \text{Bin}(n=12, p=0.30)$) under the adjusted alternative hypothesis is 9%. The probability of stopping early ($p(x \leq 1), x \sim \text{Bin}(n=12, p=0.4)$) under the original alternative hypothesis is 2%. To compute the power under the adjusted alternative hypothesis, note that the probability that we reject the null is $p(\text{reject at stage II} \mid \text{continue at stage I}) \times p(\text{continue at stage I})$. We can adjust the second factor, $p(\text{continue at stage I})$, by multiplying the power computed with the unadjusted alternative by the ratio: probability of continuing under adjusted alternative hypothesis ($1 - 9\% = 91\%$) divided by probability of continuing under unadjusted alternative hypothesis ($1 - 2\% = 98\%$), which is 0.93. Thus, this design using an interim analysis at week 8 for subject 12 will actually yield a power of 0.9×0.93 , which is 0.84, when the true response rate is 0.4 and the adjusted response rate is 0.4×0.74 .

12.5. Secondary Efficacy Analysis

Demographic and clinical characteristics of the patients will be summarized using frequency counts and percentages, means and standard deviations or medians and interquartile ranges, as appropriate. Best overall response will be summarized as proportion with 95% confidence intervals. Progression-free survival, overall survival, and duration of response will be described by Kaplan-Meier models to plot these endpoints and estimate median times with a 95% confidence interval. Associations of treatment satisfaction and tolerability with HRQOL will be assessed.

12.6. Safety Analysis

Safety will be evaluated according to the CTCAE v4.0. Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests throughout the conduct of the study. Laboratory test abnormalities will be reviewed for clinical significance and only those deemed clinically significant will be reported as adverse events. The MedDRA medical dictionary will be used to map the AE/SAE verbatim terms to specific system organ classes and preferred terms. Frequencies and incidence rates of AEs and SAEs will be tabulated and presented in by-subject listings by system organ classes and preferred term. Summary tables of AEs by grade and body system will be presented.

All adverse events of any grade occurring in the first 48 hours following combinatorial treatment administration will also be assessed as potential infusion reactions. The number and percent of subjects who develop any adverse event consistent with an infusion reaction will be summarized by overall grade.

Early stopping for safety: Data safety and toxicity will be continuously monitored in the study under the guidance from the Data Safety Monitoring Committee. The study will be suspended if there are 1 or more treatment-related deaths within the first 6 patients enrolled during the initial safety assessment, which indicates the treatment-related mortality is $> 5\%$. These treatment-

related deaths must be attributable to direct organ toxicity by study treatment agents with the exception of deaths attributable to immunosuppression (i.e. infections).

12.7. Biomarker Analyses

Serial estimate of biomarker expression will be plotted and summarized over time using means and standard deviations, possibly on a log scale.

12.8. Interim Analysis

As described above, when 12 patients have been treated in the study, an interim analysis for efficacy will be conducted. This analysis will be completed once the 12th patient has completed their first restaging (after 8 weeks of therapy). It will include any assessments of response performed on patients prior to that time. If there are 1 or fewer responses observed among the first 12 patients at the time of the interim analysis, this study will be discontinued for lack of efficacy. If the null hypothesis is true and the true response rate is 10% or less, the probability of stopping the trial early will be 66%.

13. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and are mandated by regulatory agencies worldwide.

13.1.1. Definitions

13.1.2. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug.

(<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073087.pdf>)

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an adverse event term. As an example, “worsening of underlying disease” or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

13.1.3. Serious Adverse Events

A serious adverse event based on International Conference on Harmonisation (ICH) and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (i.e., the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the IND Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.

- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

13.1.4. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of *nonhematologic* AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

13.1.5. Causality (Attribution)

The investigator is to assess the causal relation (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

| | |
|--------------------------|---|
| Not Related: | Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible. |
| Unlikely: | The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely. |
| Possibly Related: | There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes. |
| Related: | The AE is clearly related to use of the investigational product. |

13.2. Unexpected Adverse Events

An “unexpected” AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. “Unexpected” also refers to AEs that are mentioned in the Investigator's 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 study drug under investigation.

13.3. Special Reporting Situations

Special reporting situation on a study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject exposure to the study drug, e.g., name confusion)

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an AE, it should be recorded on the AEs eCRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious and should be reported on the Serious Adverse Event Report Form. We will be applying for IND exemption for this

study. If IND exempt, The Serious Adverse Event Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness. If not IND exempt, forms will be sent to Pharmacyclics Drug Safety within 15 days of awareness.

13.4. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

13.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the AEs CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded adverse event or serious adverse event will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

13.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported. (See Section 11.1.1)

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

13.4.3. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 90 days after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a female subject or male subject's partner from the time of first dose up until 90 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

13.4.4. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

13.4.5. Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or Designee, within 24 hours of awareness.

13.4.5.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*.
- Any treatment-emergent serious adverse events of bleeding of any grade

- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 13.4.5 above.

13.4.6. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakeCT@pcyc.com) or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee, within 24 hours of knowledge of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

Reporting to Regulatory Agencies:

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the Investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

14. STUDY MANAGEMENT

14.1. Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

14.2. Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

14.3. Required Documentation For Multi-site Studies

Before the study can be initiated at any site, the following documentation must be provided to the UCSD Moores Cancer Center Clinical Trials Office:

- A copy of the official IRB approval letter for the protocol and informed consent.
- A copy of the IRB-approved consent form
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation. (NOTE: this is required if UCSD holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values.
- Executed clinical research contract.

14.4. Patient Registration

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to the study. Prior to registration, eligibility criteria must be confirmed with the UCSD Study Coordinator. To register a patient, call (858)-xxx-xxx Monday through Friday,

8:00am-4:30pm Pacific Time. Study sites other than UCSD must fax informed consent documentation, completed eligibility checklist, and all source documentation for eligibility confirmation to the UCSD Clinical Trials Office (Fax: 858-822-5380).

Patients will be given a unique sequential study number at the time of enrollment. UCSD will fax the outside study site for confirmation of patient registration, the patient's study number, and ability to start study treatment.

14.5. Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

14.6. Data and Safety Monitoring/Auditing

In addition to adverse event monitoring and clinical oversight by the Study Chair, site principal investigator and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon risk-based assessments.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported annually and will include:

- 1) the protocol title, IRB protocol number, and the activation date of the study.
- 2) the number of patients enrolled to date.
- 3) the date and site of patients' enrollment.
- 4) a summary of all adverse events regardless of grade and attribution.
- 5) a response evaluation for evaluable patients when available.
- 6) a summary of any recent literature that may affect the ethics of the study.

14.7. Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

14.7.1. Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB along the lines of a protocol deviation or violation, depending on the nature of the modification.

14.7.2. Protocol Violations

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion. For the UCSD IRB:

- A. Major violations must be reported to the IRB within 10 working days of awareness of the violation.

Major violations include:

- Instances that have harmed or increased the risk of harm to one or more research participants.
- Instances that have damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

- B. Minor violations may be reported to the IRB at the time of the continuing review.

Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

14.8. Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB.

The written amendment, and if required the amended consent form, must be sent to the IRBs at each site and submitted to the FDA by the Study Chair for approval prior to implementation.

14.9. Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB 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.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

14.10. Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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16. APPENDICES

CONFIDENTIAL

Appendix 1. Schedule of Assessments

SCHEDULE OF ASSESSMENTS

| Procedure | Screen/ Baseline (≤ 28 days, unless otherwise noted) | Treatment Cycles (4-week cycles) | | | | | | | | | | | | | | | | | | | | End of Treatment (within 28 days after last dose) | Follow-up (q2 months (± 14 days) from EOT) | |
|---------------------------------------|---|----------------------------------|---|---|----|----|-----------------------|---|----|----|-----------------------|---|----|----|-----------------------|---|----|----|--|---|----|---|---|----|
| | | Cycle 1 (± 3 days) | | | | | Cycle 2 (± 3 days) | | | | Cycle 3 (± 3 days) | | | | Cycle 4 (± 3 days) | | | | Each Additional Cycle (± 3 days) | | | | | |
| | | -7 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | | | 22 |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Eligibility | X | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | | | |
| HPV or p16 status ¹ | | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant Medications Assessment | X | | | X | | | X | | | | X | | | | X | | | | X | | | | X | |
| Adverse Event Assessment | X | | | X | | | X | | | | X | | | | X | | | | X | | | | X | |
| Physical Exam ² | X | | | X | | | X | | | | X | | | | X | | | | X | | | | X | |
| Vital Signs & Height | X | | | X | | | X | | | | X | | | | X | | | | X | | | | X | |
| ECOG | X | | | X | | | X | | | | X | | | | X | | | | X | | | | X | |
| CBC with Diff ³ | X | X | | X | | | X | | | | X | | | | X | | | | X | | | | X | |
| CMP and magnesium ⁴ | X | X | | X | x | | X | | x | | X | | x | | X | | x | | X | | x | | X | |
| PT/INR, aPTT | X | X | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test ⁵ | Within 72 hours | | | | | | | | | | | | | | | | | | | | | | | |
| HIV | X | | | | | | | | | | | | | | | | | | | | | | | |
| HEP B & C | X | | | | | | | | | | | | | | | | | | | | | | | |
| T4 and TSH | X | | | | | | X | | | | X | | | | X | | | | X | | | | | |
| ECG | X | | | | | | | | | | | | | | | | | | | | | | | |
| Tumor tissue collection ⁶ | Within 42 days | | | | | | X ¹ 0 | | | | | | | | | | | | | | | | | |

[illegible]

Cycles are 28 days in length, with the exception of cycle 1, which is 35 days long due to start of ibrutinib 7 days prior to second drug.

1. By standard institutional practices. Required only for oropharyngeal and unknown primary tumors
2. Full physical exam at baseline; targeted physical exam at other time points.
3. CBC with Diff: Complete blood count with differential.
4. CMP: Comprehensive metabolic panel (bicarbonate, calcium, chloride, creatinine, glucose, potassium, sodium BUN, albumin, bilirubin total, alkaline phosphatase, total protein, ALT, AST).
5. Pregnancy test for females of child-bearing potential only. Should be obtained with 72 hours of starting therapy and again as indicated
6. Newly obtained tumor tissue collection should be performed when feasible. Otherwise, an archived tumor specimen is adequate.
7. Blood for correlative studies should be collected at the same time blood is drawn for CBC and CMP if possible. 30 ml blood to be collected prior to initiation of study treatment and on cycle 2 day 1 (± 7 days).
8. Imaging for radiographic disease assessment will be performed every 8 weeks (every 2 cycles) following treatment initiation (± 7 days). The same imaging modality should be used throughout the study when feasible. For patients who are clinically stable, a repeat scan will be required 4 weeks (± 7 days) after initial radiographic findings of disease progression as a confirmatory assessment. For CT or MRI, neck and chest should be evaluated; abdomen/pelvis as indicated. If a PET/CT is utilized, CT must be diagnostic quality.
9. Ibrutinib administration will begin 7 days before the start of the second agent and is taken orally on a daily basis.
10. +/- 7 days

Appendix 2. ECOG Status Scores

| Status | Eastern Cooperative Oncology Group (ECOG) Performance Status** |
|--------|---|
| 0 | Fully active, able to carry on all predisease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. |
| 2 | Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

**Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Available at: http://www.ecog.org/general/perf_stat.html. Accessed January 4, 2008.

Appendix 3. Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to [Section 6.2.1](#) on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

Source: <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>.

| Inhibitors of CYP3A | Inducers of CYP3A |
|-------------------------------------|--------------------------|
| <u>Strong inhibitors:</u> | carbamazepine |
| indinavir | efavirenz |
| nelfinavir | nevirapine |
| ritonavir | barbiturates |
| clarithromycin | glucocorticoids |
| itraconazole | modafinil |
| ketoconazole | oxcarbazepine |
| nefazodone | phenobarbital |
| saquinavir | phenytoin |
| suboxone | pioglitazone |
| telithromycin | rifabutin |
| cobicistat | rifampin |
| boceprevir | St. John's Wort |
| mibefradil | troglitazone |
| telaprevir | |
| troleandomycin | |
| posaconazole | |
| <u>Moderate inhibitors:</u> | |
| aprepitant | |
| amprenavir | |
| amiodarone | |
| atazanavir | |
| ciprofloxacin | |
| crizotinib | |
| darunavir/ritonavir | |
| dronedarone | |
| erythromycin | |
| diltiazem | |
| fluconazole | |
| fosamprenavir | |
| grapefruit juice | |
| Seville orange juice | |
| verapamil | |
| voriconazole | |
| imatinib | |
| <u>Weak inhibitors:</u> | |
| cimetidine | |
| fluvoxamine | |
| <u>All other inhibitors:</u> | |
| chloramphenicol | |
| delaviridine | |
| diethyl-dithiocarbamate | |
| gestodene | |
| mifepristone | |

| | |
|---------------|--|
| norfloxacin | |
| norfluoxetine | |
| star fruit | |

Appendix 4. Child-Pugh Score

| Measure | 1 point | 2 points | 3 points |
|--|------------|--|------------------------------|
| Total bilirubin, $\mu\text{mol/L}$ (mg/dL) | <34 (<2) | 34-50 (2-3) | >50 (>3) |
| Serum albumin, g/L (g/dL) | >35 (>3.5) | 28-35 (2.8-3.5) | <28 (<2.8) |
| PT INR | <1.7 | 1.71-2.30 | >2.30 |
| Ascites | None | Mild | Moderate to Severe |
| Hepatic encephalopathy | None | Grade I-II (or suppressed with medication) | Grade III-IV (or refractory) |

| Points | Class |
|--------|-------|
| 5-6 | A |
| 7-9 | B |
| 10-15 | C |

Source:

1. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. *The liver and portal hypertension*. Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R. "Transection of the oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60: 646-9.


Appendix 5. Patient Pill Diaries

Participant Dosing Diary and Instructions

Study IRB #161755 **Study site and ID # _____**
Cycle #: _____

Site Staff Instructions:

Please enter below the dates (mm/dd/yyyy) for the current cycle for Day 1-28.

| | Study Medication | | Daily Dose | Source |
|---|---|--|-----------------------|---------------|
| Day 1 - 28 Medications From: -- / / -- (MM / DD / YYYY) To: -- / / -- (MM / DD / YYYY) |  | 140 mg Ibrutinib x 4 capsules = 560 mg daily | 4 capsules | 140 mg bottle |

Participant Instructions:

- Swallow study drug whole and do not to chew or open them prior to swallowing.
- Take medication four capsules per day WITH 8 OZ OF WATER, at approximately the same time daily.
- If you miss a day's dose at the scheduled time, it can be taken as soon as possible on same day with a return to the normal schedule the following day.
- If you miss a day's dose entirely, you should NOT make it up the next day.
- If you vomit after taking a dose you should NOT make it up and should resume treatment the next day.
- If you inadvertently take 1 extra dose during a day, you should NOT take the next day's dose.
- Keep the medication in the bottles provided and do not transfer it to any other container.
- Record each dose of study medication in the diary section below. To prevent any dosage error, the participant diary should be completed every day.
- UNUSED DRUG and bottles should be RETURNED to the site at the next study visit.
- ALWAYS BRING your completed participant diary to the clinic at EACH study visit.
- Please avoid grapefruit and Seville oranges for the duration of the study.
- Please avoid using CYP3A inhibitors/inducers (e.g. indinavir, nefazodone)
- In case of any question, problem, or if you are not feeling well, please contact your study doctor.

| DAY | DATE (mm/dd/yy) | TIME Hour/Min (24:00 clock) | Number of Capsules TAKEN (Daily dose is 4 capsules, please add to the appropriate columns below; "4" if 4 pills were taken or "0" if no pills were taken) | COMMENT (e.g., Please use this section to write down any side effects you are experiencing on a given day, explanation for any extra doses taken or missed doses, etc.) |
|---|--------------------|-----------------------------------|---|---|
| | | | 140 mg = each pill | |
| 1 | | | | |
| The dose of Day 1 should be taken in the clinic according to site staff's instructions. Take Ibrutinib before Cetuximab infusion. | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | | | | |
| Take Ibrutinib before Cetuximab infusion. | | | | |
| 9 | | | | |
| 10 | | | | |
| 11 | | | | |
| 12 | | | | |
| 13 | | | | |
| 14 | | | | |
| 15 | | | | |
| Take Ibrutinib before Cetuximab infusion. | | | | |
| 16 | | | | |
| 17 | | | | |
| 18 | | | | |
| 19 | | | | |
| 20 | | | | |
| 21 | | | | |
| 22 | | | | |
| Take Ibrutinib before Cetuximab infusion. | | | | |
| 23 | | | | |
| 24 | | | | |
| 25 | | | | |

| | | | | |
|----|--|--|--|--|
| 26 | | | | |
| 27 | | | | |
| 28 | | | | |

Other Medications Taken

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the “Dates Taken”

| Drug Name | Dose and Schedule | Dates Taken | Reasons Taken |
|-----------|-------------------|-------------|---------------|
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