

Brand Name: Imbruvica

Generic Name: ibrutinib

Manufacturer¹: Pharmacyclics, Inc.

Drug Class: Antineoplastic agent^{2,3,4}, Biologic Response Modifier², Signal Transduction Inhibitor², Tyrosine Kinase Inhibitor^{3,4}

Uses:

Labeled Uses^{1,2,3,4,5}: Chronic lymphocytic leukemia (CLL) in patients who received at least one prior therapy, Mantle cell lymphoma (MCL) in patients who received at least one prior therapy

Unlabeled Uses^{1,2,3,4,5}: None

Mechanism of Action^{1,2,3,4,5}: Inhibits Bruton's tyrosine kinase (BTK), an enzyme responsible for proliferation, differentiation, apoptosis, and cell migration of B-cells. Because constitutive activation of B-cell receptor signaling is important for survival of malignant B-cells, BTK inhibition results in decreased malignant B-cell proliferation and survival. Nonclinical studies show that ibrutinib also inhibits B-cell migration and substrate adhesion in vitro.

Pharmacokinetics^{1,2,3,4,5}:

T_{max}	1-2 hours
V_d	10,000 L
t_{1/2}	4-6 hours
Clearance	1000 L/h
Protein Binding	97%
Bioavailability	Administration with food increased exposure ~2-fold (compared to overnight fasting)

Metabolism: Ibrutinib is metabolized primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Metabolism is the main route of elimination for ibrutinib. *In vitro* studies indicate that ibrutinib and PCI-45227 are not likely to inhibit any major CYP450 isoenzymes at clinical doses. Ibrutinib is not a substrate of p-glycoprotein (P-gp) nor a P-gp inhibitor, but P-gp substrates in the gastrointestinal tract may be affected due to higher local concentrations of ibrutinib.

Elimination: Ibrutinib, mainly if the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [¹⁴C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces.

Efficacy:

Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2013; 369(6): 507-16.

Study Design: Multicenter, international, open-label, non-randomized phase 2 study

Description of Study: *Methods:* One hundred and eleven patients diagnosed with mantle-cell lymphoma were enrolled without randomization and were classified as having either received treatment with bortezomib (≥ 2 cycles) or not having received such treatment (< 2 complete cycles or no prior bortezomib therapy). Patients included in the study had received at least one but no more than five previous lines of treatment, with no partial or better response to the most recent treatment regimen or with disease progression after the most recent regimen. Enrolled patients received single-agent ibrutinib administered orally at a daily dose of 560 mg until progression of disease or until unacceptable levels of adverse events occurred. The primary outcome was overall response rate. *Outcome Results:* A response rate of 68% (75 patients) was observed, with a complete response rate of 21% and a partial response rate of 47%. Prior treatment with bortezomib had no effect on the response rate. The most common treatment-related adverse events were mild or moderate diarrhea, fatigue, and nausea. Grade 3 or higher hematologic events included neutropenia (16%), thrombocytopenia (11%), and anemia (10%). With an estimated median follow-up of 15.3 months (range 1.9 to 22.3), the estimated median response duration was 17.5 months (95% CI, 15.8 to not reached), and the estimated median progression-free survival was 13.9 months (95% CI 7.0 to not reached). The median time to a complete response was 5.5 months (range, 1.7 to 11.5), and the median time to a response was 1.9 months (range, 1.4 to 13.7). The median overall survival was not reached. The estimated rate of overall survival was 58% at 18 months.

Limitations: The study was funded by Pharmacyclics, the manufacturer of ibrutinib. There were seven authors employed by Pharmacyclics and several others with varying affiliations with the company. This involvement introduces a potential conflict of interest. The differences between the groups at baseline were recorded, but the significance of these were not expressed (no p-values). Likewise, adverse events during treatment were reported, but no p-values were given to express the significance of these. The study was also open-label and non-randomized.

Conclusion: Single-agent ibrutinib produced a high response rate in patients with relapsed or refractory mantle-cell lymphoma, including patients with high-risk features. Previous data show that such a high response rate in this patient population has only occurred with highly myelosuppressive chemotherapy regimens. The response rate of ibrutinib was high during the short period of follow-up (estimated median duration of response, 17.5 months), but long-term studies are required to investigate the durability of these responses. Because this study provided the data for ibrutinib to receive accelerated approval, more studies are needed to provide long-term safety and efficacy data.

Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med. 2013; 369(1): 32-42.

Study Design: Phase 1b-2, open-label, multicenter study

Description of Study: *Methods:* A total of 85 patients were enrolled at eight sites and divided into three cohorts. Patients included had a diagnosis of relapsed or refractory chronic

lymphocytic leukemia (CLL) or small lymphocytic lymphoma, a need for treatment, adequate renal and hepatic function, and an absence of active infection. Cohort 1 (n=27) and cohort 3 (n=24) were assigned to receive a fixed daily dose of 420 mg of ibrutinib. Cohort 2 (n=34) was assigned to receive a daily dose of 840 mg. Cohort 3 was added to study the effect of 420 mg in patients with high-risk disease. All cohorts took doses orally on a continuous schedule until the onset of disease progression or unacceptable toxicity. The primary end point was the safety of the two fixed-dose regimens, while secondary end points included overall response rate, progression-free survival, pharmacodynamics, and pharmacokinetics. *Outcome Results:* Out of the 85 patients, 65% had advanced-stage disease, 33% had 17p13.1 deletions, and 36% had 11q22.3 deletions. The most common adverse events were diarrhea, fatigue, and upper respiratory tract infection, and most resolved without the need for treatment suspension. The most common adverse events of grade 3 or higher were pneumonia (12%) and dehydration (6%). The overall response rate was 71% (2 complete responses and 34 partial responses) in the 420-mg cohort and 71% (24 partial responses) in the 840-mg cohort. Ten patients in the 420-mg cohort (20%) and 5 patients in the 840-mg cohort (15%) had a partial response with persistent lymphocytosis. Treatment-related lymphocytosis developed at similar frequencies in patients with unmutated and those with mutated immunoglobulin variable-region heavy chain genes. However, in patients with unmutated genes, lymphocyte counts normalized more rapidly (median, 6.4 vs 14.8 months) and more frequently (85% vs 50% of patients). The response to ibrutinib did not appear to vary according to traditional high-risk prognostic features. The only factor associated with a response was the mutation status of the immunoglobulin variable-region heavy-chain gene. The 26-month estimated rate of progression-free survival was 75%, and the rate of overall survival was 83%. Disease progression developed in 11 patients (13%) during follow-up, and 7 of those patients had progression by biologic transformation. Among the 11 patients with progressive disease, 10 had a 17p13.1 or 11q22.3 deletion. Among the 28 patients with a 17p13.1 deletion (a poor prognostic feature), the 26-month estimated rate of progression-free survival was 57% and the rate of overall survival was 70%.

Limitations: The study was funded by Pharmacyclics, the manufacturer of ibrutinib, and was sponsored by both Pharmacyclics and Janssen. It is stated that the sponsors confirmed the accuracy of the data and compiled it for summation and analysis, but it is unclear if an outside party also analyzed the data. Several of the authors report being employees of or having affiliations with Pharmacyclics and/or Janssen, introducing a potential conflict of interest. The differences between the groups at baseline were documented, but their significance is unknown as no p-values were reported. Also, the adverse events that were reported were not divided by cohort, and no p-values were reported. There seems to be some bias in the discussion. Also, the analysis of immunoglobulin levels was limited to patients with relatively preserved levels, since those who received intravenous immune globulin were excluded. Lastly, the authors do not specify if and how patients were randomized into treatment groups, and this was an open-label study.

Conclusion: Both the 420 mg and the 840 mg doses produced similar responses, providing support for the use of the 420 mg dose in patients with relapsed CLL. Single-agent ibrutinib produced a high response rate (71%) in both cohorts. This response was also durable, including those patients with high-risk features such as the 17p13.1 deletion. Although the authors concluded that the response to ibrutinib was not influenced by factors such as high-risk

features, the majority of patients with progressive disease did possess high-risk features such as the 17p13.1 deletion. Therefore, further studies are needed to investigate the long-term response and durability of the response, especially in patients with poor prognostic features.

Advani RH, Buggy JL, Sharman JP, Smith SM, Boyd TE, Grant B, et al. Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients with Relapsed/Refractory B-Cell Malignancies. J Clin Oncol 2012; 31: 88-94.

Study Design: Phase I, open-label, dose-escalation trial

Description of Study: The purpose of this study was to evaluate ibrutinib in a phase I trial to determine the dose, safety profile, pharmacokinetics, pharmacodynamics, and tumor response in patients with relapsed or refractory B-cell non-Hodgkin lymphoma (NHL) and B-cell chronic lymphocytic leukemia (CLL). *Methods:* Fifty six patients were enrolled and received one or more doses of ibrutinib. Patients were divided into seven cohorts; five cohorts were treated with 28 days on, 7 days off schedule at 1.25, 2.5, 5, 8.3, or 12.5 mg/kg once daily. The other two cohorts were treated on the continuous dosing at 8.3 mg/kg once daily or a fixed dose of 560 mg once daily. Patients were to continue therapy until disease progression, unacceptable toxicity, or patient or investigator decision to end therapy. Computed tomography (CT) or positron emission tomography (PET) and bone marrow/aspirate were required to confirm complete response. *Outcome Results:* Fifty patients were determined to be evaluable for tumor response if they received at least two cycles of therapy. Of these patients, 60% achieved an objective response (complete or partial response), with an overall response rate of 54% in the intent-to-treat population. Although a dose-response curve was not provided, data was provided concerning best clinical response by dose-level cohort. Patients receiving 560 mg/day continuously had the highest percentage of partial responses (67%), although the rate of complete responses in this group were not higher than other dosing regimens. Responses were observed across all histologies. Responses were durable, with median progression-free survival of 13.6 months at the time of data cutoff. The maximum tolerated dose (MTD) was not achieved. Only two dose-limiting toxicities occurred: one grade 3 allergic hypersensitivity and one dose interruption for more than 7 days because of transient grade 2 neutropenia. The most common adverse events were typically grade 1 or 2. Grade 3 or 4 events were infrequent and independent of dose. Grade 3 to 4 hematologic toxicities included neutropenia (12.5%), thrombocytopenia (7.2%), and anemia (7.1%). The highest response rate was observed in patients with mantle-cell lymphoma (78%) and CLL/small lymphocytic lymphoma (79%).

Limitations: The study was sponsored by Pharmacyclics, the manufacturer of ibrutinib. Also, many authors were employed by or had affiliations with Pharmacyclics. These factors introduce a potential conflict of interest. Also, it is unclear as to why five cohorts were treated with the 28 day on, 7 day off schedule while only two cohorts were assigned to continuous dosing. The authors used intent-to-treat to include all patients who received any amount of study drug. Potentially, this could decrease the perceived efficacy of the study drug. This was an open-label study, introducing the potential for bias. Also, the study excluded patients with CNS involvement by lymphoma and those with significant comorbidities.

Conclusion: Although this was a phase I study to determine optimal dosing, pharmacokinetics, and pharmacodynamics, there were fifty patients evaluated for tumor response. The majority

of these patients achieved either a partial or complete response which was also durable. A majority of patients with an objective response maintained their response for at least 10 months. The study drug was well tolerated, as most of the adverse events were grade 1 or 2 and easily managed. The high response rate in patients with mantle-cell lymphoma is noteworthy because of the poor response of patients with relapsed disease treated with bortezomib. Also, the intermittent and continuous dosing schedules had similar occupancy on Bruton's tyrosine kinase and equivalent toxicity and kinetic profiles. However, the intermittent dosing schedule was associated with transient reversal of treatment-related lymphocytosis during the 7 days off period, suggesting a reversal of the biologic effect. Because of this and the tolerability of the daily 560 mg dose, the continuous dose of 560 mg was selected for phase II studies.

Contraindications^{1,2,3,4,5}: None

Precautions^{1,2,3,4,5}:

Hemorrhage: Five percent of patients with MCL and 6% of patients with CLL had Grade 3 or higher bleeding events (subdural hematoma, ecchymoses, gastrointestinal bleeding, and hematuria). Bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily and 63% of patients with CLL treated at 420 mg daily. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre- and post-surgery depending upon type of surgery and risk of bleeding.

Infections: Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of patients with MCL and 35% of patients with CLL had infections Grade 3 or greater. Monitor patients for fever and infections and evaluate promptly.

Myelosuppression: Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients with MCL and 35% of patients with CLL. These included neutropenia (29%), thrombocytopenia (17%), and anemia (9%) in patients with MCL and neutropenia (27%) and thrombocytopenia (10%) in patients with CLL. Monitor complete blood counts monthly.

Renal Toxicity: Fatal and serious cases of renal failure have occurred with ibrutinib therapy. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients with MCL and 23% of patients with CLL. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients with MCL and 4% of patients with CLL. Periodically monitor creatinine levels. Maintain hydration.

Second Primary Malignancies: Other malignancies have occurred in 5% of patients with MCL and 10% of patients with CLL who have been treated with ibrutinib. Four percent of patients with MCL had skin cancers and 1% had other carcinomas. Eight percent of patients with CLL had skin cancers and 2% had other carcinomas.

Hyperuricemia: Increased uric acid levels have been observed, including Grade 4 elevations.

Embryo-Fetal Toxicity: Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL,

receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patients should be apprised of the potential hazard to a fetus.

Lactation: It is not known if ibrutinib is secreted in human milk in a woman who is breast-feeding. Because of the potential of serious adverse reactions in nursing infants, women should be advised against breast-feeding their infants while taking ibrutinib.

Pediatrics Use: The safety and effectiveness of ibrutinib have not been established in children.

Geriatrics Use: Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonitis and cellulitis), and gastrointestinal events (diarrhea and dehydration) occurred more frequently with geriatric patients than younger patients. Monitor closely for adverse effects.

Hepatic Impairment: Ibrutinib is metabolized in the liver and significant increases in exposure are expected in patients with hepatic impairment. Ibrutinib has not been studied in patients with serum transaminases (ALT/SGPT or AST/SGOT) ≥ 3 times the upper limit of normal, although preliminary pharmacokinetic data from an ongoing trial suggests that ibrutinib exposure is increased 6-fold in patients with moderate hepatic impairment (Child-Pugh B, n = 3). Avoid use of ibrutinib in patients with baseline hepatic impairment.

Renal Impairment: Ibrutinib is mainly excreted by the kidney and exposure is not affected in patients with mild to moderate impairment, but renal failure has been observed in studies (see above). Use with caution in patients with pre-existing renal impairment. Ibrutinib has not been studied in those with severe impairment or in patients on dialysis.

Adverse Effects^{1,2,3,4,5}:

>10%:

Cardiovascular: Peripheral edema (MCL: 35%, CLL: 23%), hypertension (CLL: 17%)

Central nervous system: Fatigue (MCL: 41%, CLL: 31%), dizziness (14% to 21%), headache (13% to 19%), chills (CLL: 13%)

Dermatologic: Skin rash (25% to 27%), skin infection (14% to 17%)

Endocrine & metabolic: Increased uric acid (38% to 40%; hyperuricemia >10 mg/dL: MCL 13%, CLL 4%), dehydration (MCL: 12%)

Gastrointestinal: Diarrhea (CLL: 63%, MCL: 51%), nausea (MCL: 31%, CLL: 21%), constipation (23% to 25%), abdominal pain (MCL: 24%, CLL: 15%), vomiting (19% to 23%), decreased appetite (17% to 21%), stomatitis (17% to 21%), dyspepsia (11% to 13%)

Genitourinary: Urinary tract infection (10% to 14%)

Hematologic & oncologic: Decreased platelet count (CLL: 71%, MCL: 57%; grades 3/4: 10% to 17%), bruise (CLL: 54% to 63%, MCL: 30% to 48%), neutropenia (47% to 54%; grades 3/4: 27% to 29%), decreased hemoglobin (41% to 44%; grades 3/4 MCL: 9%), petechia (11% to 17%)

Infection: Infection (grades 3/4: CLL 35%, MCL \geq 25%)

Neuromuscular & skeletal: Musculoskeletal pain (MCL: 37%, CLL: 27%), arthralgia (CLL: 23%, MCL: 11%), muscle spasm (14% to 19%), weakness (13% to 14%)

Renal: Increased serum creatinine (\leq 1.5 x ULN: MCL 67%, CLL 23%; 1.5 to 3 x ULN: 4% to 9%)

Respiratory: Upper respiratory tract infection (CLL: 48%, MCL: 34%), dyspnea (MCL: 27%, CLL: 10%), sinusitis (13% to 21%), cough (19%), oropharyngeal pain (CLL: 15%), pneumonia (10% to 14%), epistaxis (MCL: 11%)

Miscellaneous: Fever (18% to 25%)

1% to 10%:

Cardiovascular: Atrial fibrillation (\geq 5%)

Central nervous system (CLL): Anxiety (10%), insomnia (10%), peripheral neuropathy (10%)

Hematologic & oncologic: Malignant neoplasm (secondary; 5% to 10%; includes one death due to histiocytic sarcoma), anemia (MCL; grades 3/4: 9%), malignant neoplasm of skin (4% to 8%), hemorrhage (5% to 6%; grade 3 or higher bleeding events including subdural hematoma, ecchymosis, gastrointestinal bleeding, and hematuria), other carcinomas (1% to 2%)

Miscellaneous: Laceration (CLL: 10%)

Frequency not defined: Renal failure

Drug Interactions:

CYP3A Inhibitors: Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Concomitant use of strong CYP3A inhibitors which would be taken chronically is not recommended.

Dosing Adjustments with CYP3A Inhibitors: For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g. antifungals and antibiotics), consider interrupting ibrutinib therapy until the CYP3A inhibitor is no longer needed. Reduce ibrutinib dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g. fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products, and ciprofloxacin).

CYP3A Inducers: Administration of ibrutinib with strong inducers of CYP3A decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (e.g. carbamazepine, rifampin, phenytoin, and St. John's Wort).

Dosing/Administration: Administer ibrutinib orally once daily at approximately the same time each day. Swallow the capsules whole with water. Do not open, break, or chew the capsules.

Adult Dosing:

Mantle Cell Lymphoma: 560 mg (four 140 mg capsules) orally once daily

Chronic Lymphocytic Leukemia: 420 mg (three 140 mg capsules) orally once daily

Renal Impairment Dosing:

Mild to moderate impairment (CrCl \geq 25 mL/min): No dosage adjustment

Severe impairment (CrCl < 25 mL/min) or ESRD requiring dialysis: Not studied

Hepatic Impairment Dosing: No dosage adjustment provided, but significant increases in drug exposure are expected in patients with hepatic impairment. Avoid use of ibrutinib in patients with baseline hepatic impairment.

Dose Modifications for Adverse Reactions: Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg/day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur after two dose reductions, discontinue ibrutinib.

Toxicity Occurrence	MCL Dose Modification After Recovery Starting Dose = 560 mg	CLL Dose Modification After Recovery Starting Dose = 420 mg
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

Use in Special Circumstances:

Pregnancy: Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patients should be apprised of the potential hazard to a fetus.

Lactation: It is not known if ibrutinib is secreted in human milk in a woman who is breast-feeding. Because of the potential of serious adverse reactions in nursing infants, women should be advised against breast-feeding their infants while taking ibrutinib.

Conclusion: Ibrutinib is an effective single-agent therapy for patients with relapsed or refractory mantle cell lymphoma or chronic lymphocytic leukemia. It is only approved for use in patients who have received at least one prior therapy, limiting its use as a potential frontline therapy. Although there are significant adverse events reported with the use of ibrutinib, the manufacturer has provided a detailed dose modification schedule in the event of toxicity. Caution must be used when using ibrutinib with a

strong CYP3A4 inhibitor or inducer. Given the high response rate and durability of responses in studies and the convenience of a once daily oral treatment, ibrutinib appears to be a clinically useful option for relapsed or refractory mantle cell lymphoma or chronic lymphocytic leukemia. Because ibrutinib received accelerated approval from the FDA for these indications, more studies will be needed to investigate long-term adverse events and efficacy.

Recommended References:

1. Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics, Inc.: 2014.
2. Ibrutinib. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2014. Available at: <http://www.clinicalpharmacology.com> Accessed: March 28, 2014.
3. Ibrutinib. Lexi-Drugs [database online]. Lexi-Comp, Inc; March 28, 2014
4. Ibrutinib. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed March 28, 2014.
5. Ibrutinib Oral. Facts and Comparisons 4.0 Online [Internet database]. Wolters Kluwer. Available at: <http://online.factsandcomparisons.com>. Accessed March 28, 2014.
6. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med*. 2013; 369(6): 507-16.
7. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med*. 2013; 369(1): 32-42.
8. Advani RH, Buggy JL, Sharman JP, Smith SM, Boyd TE, Grant B, et al. Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients with Relapsed/Refractory B-Cell Malignancies. *J Clin Oncol* 2012; 31: 88-94.

Prepared by: Kristen Thomas, Doctor of Pharmacy Candidate