**Ibrutinib (IMBRUVICA®) Phase Ib/II Data Show Promise in Patients with Chronic Graft-Versus-Host-Disease**

**Data presented today at the American Society of Clinical Oncology Annual Meeting**
- This release corresponds to abstract #7024

SUNNYVALE, Calif., May 31, 2015 /PRNewswire/ -- Pharmacyclics LLC today announced interim results from the ongoing Phase Ib/II PCYC-1129 study suggesting that ibrutinib (IMBRUVICA®) may be a safe and effective treatment for patients with chronic graft-versus-host disease (cGVHD) who were either refractory to steroid treatment or were steroid-dependent. The data will be presented today at the 51st American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL at 8:00 a.m. CT. IMBRUVICA is jointly developed and commercialized by Pharmacyclics and Janssen Biotech, Inc.

Lead investigator David Miklos,* M.D., Ph.D., Stanford University, Stanford, CA, presented the data in full in a poster session.

cGVHD is a life-threatening condition in which newly transplanted cells attack the patient's body.¹ Patients may develop this common complication after undergoing allogenic stem cell or bone marrow transplantation.¹ There are currently no therapies specifically approved for this condition.

The ongoing Phase Ib/II study evaluated the safety and efficacy of ibrutinib for the treatment of patients with steroid-dependent or refractory cGVHD. The Phase Ib portion of the study was open-label and designed to determine the recommended Phase II dose of ibrutinib, starting at 420 mg. Six patients (median age 56 years, median Karnofsky score 85**) were enrolled in the Phase Ib portion. The median time from transplant was 23 months and the median time on ibrutinib was 19.3 weeks. The Phase II study is currently ongoing.

"Patients and physicians alike have long been searching for safe and effective non-steroidal options to treat this condition," said Danelle James, M.D., M.S., Head of Oncology at Pharmacyclics. "The initial data presented today provide compelling results that support the potential of ibrutinib as a promising therapy for chronic GVHD."

In a preliminary analysis, data show all five evaluable patients who had received at least three months of ibrutinib achieved a partial response (PR), and two patients who were evaluable at six months maintained a PR. Improvements in clinician-assessed GVHD-score, skin erythema (4 PRs at three months and one complete response [CR]) and mouth score (4 PRs at three months and 1 case of stable disease) were observed in patients during the initial analysis. Early pharmacokinetic data in the patients were within range with exposure in indications currently included in the IMBRUVICA product label. Overall, ibrutinib showed early clinical activity in the reduction of cGVHD based on the NIH consensus cGVHD Activity Assessment. As a result of the preliminary evaluation of the available data, researchers determined the Phase II dose of ibrutinib to be 420 mg.

The most common treatment-emergent adverse events (AEs) in this study included fatigue (n=5), diarrhea (n=4), ecchymosis or bruising (n=3) and stomatitis (n=2), all of which were Grade 1 or 2. Serious AEs (SAEs) occurred in two patients and included Grade 3 pneumonia, as well as pyrexia and fungal brain abscess; the latter was the only event leading to ibrutinib discontinuation, which occurred at 10.9 weeks. No dose-limiting toxicities were reported in Phase Ib.

**About IMBRUVICA**

IMBRUVICA is currently approved for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, all CLL patients (including treatment-naive) who have del 17p, a genetic mutation that occurs when part of chromosome 17 has been lost, and all patients (including treatment-naive) with Waldenstrom's macroglobulinemia.² IMBRUVICA is also approved under accelerated approval for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.² Accelerated approval was granted for the MCL indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.²

IMBRUVICA (ibrutinib) is a first-in-class, oral, once-daily therapy that inhibits a protein called Bruton's tyrosine kinase (BTK).² IMBRUVICA was one of the first medicines to receive U.S. FDA approval via the new Breakthrough Therapy Designation pathway, and is the only product to have received three Breakthrough Therapy Designations.
BTK is a key signaling molecule in the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B cells. IMBRUVICA blocks signals that tell malignant B cells to multiply and spread uncontrollably.

IMBRUVICA is being studied alone and in combination with other treatments in several blood cancers. Over 6,100 patients have been treated in clinical trials of IMBRUVICA conducted in 35 countries by more than 800 investigators. Currently, 13 Phase III trials have been initiated with IMBRUVICA and 67 trials are registered on www.clinicaltrials.gov.

To learn more about the medical terminology used in this news release, please visit http://stedmansonline.com/.

INDICATIONS

IMBRUVICA is indicated to treat people with:

- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- Chronic lymphocytic leukemia (CLL) with 17p deletion
- Waldenstrom's macroglobulinemia
- Mantle cell lymphoma (MCL) who have received at least one prior therapy - accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Patients taking IMBRUVICA for CLL or WM should take 420 mg taken orally once daily (or three 140 mg capsules once daily).

Patients taking IMBRUVICA for MCL should take 560 mg taken orally once daily (or four 140 mg capsules once daily).

Capsules should be taken orally with a glass of water. Capsules should be taken whole. Do not open, break, split or chew the capsules.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®. The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and non-fatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Monitor patients for fever and infections and evaluate promptly.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA® treatment and dose modification.

Second Primary Malignancies - Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11%).
**Tumor Lysis Syndrome** - Tumor lysis syndrome has been reported with IMBRUVICA® therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g., high tumor burden).

**Embryo-Fetal Toxicity** - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA®. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

**ADVERSE REACTIONS**

The most common adverse reactions (≥25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia+ (57%, 52%, 43%), neutropenia+ (47%, 51%, 44%), diarrhea (51%, 48%, 37%), anemia+ (41%, 36%, 13%), fatigue (41%, 28%, 21%), musculoskeletal pain (37%, 28%++, NA++), bruising (30%, 12%++, 16%++), nausea (31%, 26%, 21%), upper respiratory tract infection (34%, 16%, 19%), and rash (25%, 24%++, 22%+).

+Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

++Includes multiple ADR terms.

+++Not applicable; no associated ADRs.

The most common Grade 3 or 4 non-hematological adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).

Approximately 6% (CLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse events.

Approximately 5% (CLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse events. Most frequent adverse events leading to discontinuation were infections, subdural hematomas, and diarrhea in CLL patients and subdural hematoma (1.8%) in MCL patients.

**DRUG INTERACTIONS**

**CYP3A Inhibitors** - Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

**CYP3A Inducers** - Avoid co-administration with strong CYP3A inducers.

**SPECIFIC POPULATIONS**

**Hepatic Impairment** - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

**Please see full Prescribing Information:**

**About Pharmacyclics, An AbbVie Company**

Pharmacyclics, a wholly-owned subsidiary of AbbVie (NYSE: ABBV), is focused on developing and commercializing innovative small-molecule drugs for the treatment of cancer and immune-mediated diseases. Pharmacyclics' mission is to develop and commercialize novel therapies intended to improve quality of life, increase duration of life and resolve serious unmet medical needs.

Pharmacyclics markets IMBRUVICA and has three product candidates in clinical development and several preclinical molecules in lead optimization. Pharmacyclics is committed to high standards of ethics, scientific rigor and operational efficiency as it moves each of these programs toward commercialization. To learn more, please visit www.pharmacyclics.com.

**NOTE:** This announcement may contain forward-looking statements made in reliance upon the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements, among others, relating to our future capital requirements, including our expected liquidity position and
timing of the receipt of certain milestone payments, and the sufficiency of our current assets to meet these requirements, our future results of operations, our expectations for and timing of ongoing or future clinical trials and regulatory approvals for any of our product candidates, and our plans, objectives, expectations and intentions. Because these statements apply to future events, they are subject to risks and uncertainties. When used in this announcement, the words "anticipate", "believe", "estimate", "expect", "expectation", "goal", "should", "would", "project", "plan", "predict", "intend", "target" and similar expressions are intended to identify such forward-looking statements. These forward-looking statements are based on information currently available to us and are subject to a number of risks, uncertainties and other factors that could cause our actual results, performance, expected liquidity or achievements to differ materially from those projected in, or implied by, these forward-looking statements. Factors that may cause such a difference include, without limitation, our need for substantial additional financing and the availability and terms of any such financing, the safety and/or efficacy results of clinical trials of our product candidates, our failure to obtain regulatory approvals or comply with ongoing governmental regulation, our ability to commercialize, manufacture and achieve market acceptance of any of our product candidates, for which we rely heavily on collaboration with third parties, and our ability to protect and enforce our intellectual property rights and to operate without infringing upon the proprietary rights of third parties. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, performance or achievements and no assurance can be given that the actual results will be consistent with these forward-looking statements. For more information about the risks and uncertainties that may affect our results, please see the Risk Factors section of our filings with the Securities and Exchange Commission, including our Form 10-K for the year ended December 31, 2013 and quarterly reports on Form 10-Q. We do not intend to update any of the forward-looking statements after the date of this announcement to conform these statements to actual results, to changes in management's expectations or otherwise, except as may be required by law.

* Disclaimer: Dr. Miklos served as an investigator of this Pharmacyclics-sponsored clinical study. Dr. Miklos does not have a financial interest in the company. This study was sponsored by Pharmacyclics.

** The Karnofsky Performance Scale Index allows patients to be classified by functional impairment. This can be used to assess the efficacy of therapies and/or patients' prognosis. A lower Karnofsky score indicates worsening survival rates for most serious illnesses. More information is available here.

IMBRUVICA is a registered trademark of Pharmacyclics LLC


2 IMBRUVICA Prescribing Information, January 2015


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