IMBRUVICA® (ibrutinib) Treatment Shows Efficacy and Tolerability in Heavily Treated Chronic Lymphocytic Leukemia Patients Following Allogeneic Stem Cell Transplant

SUNNYVALE, Calif., Feb. 17, 2015 /PRNewswire/ -- Pharmacyclics, Inc. (NASDAQ: [PCYC](http://studio-5.financialcontent.com/prnews?Page=Quote&Ticker=PCYC)) today announced that treatment with IMBRUVICA® (ibrutinib) was associated with an 88% overall response rate (ORR), with a median time on study of 23.3 months, in 16 patients with relapsed/refractory (R/R) high-risk chronic lymphocytic leukemia (CLL). These patients had a median of five prior therapies and 63% were high-risk del 17p CLL patients. The estimated median progression-free survival (PFS) at 24 months was 76.6%. All patients had previously undergone allogeneic stem cell transplant (allo-HCT), a procedure in which stem cells from one person (donor) are transplanted to another (recipient). These data were presented in an oral presentation by David B. Miklos, M.D., Ph.D., Medical Director of the Blood and Marrow Transplantation-Cellular Therapy Facility at the Stanford University Medical Center and Assistant Professor of Medicine at Stanford University at the American Society for Blood and Marrow Transplantation's 2015 BMT Tandem Meeting in San Diego, California. IMBRUVICA is jointly developed and commercialized by Pharmacyclics and Janssen Biotech, Inc.

A second presentation during the BMT Tandem meeting highlighted data from five patients with R/R CLL who had undergone allo-HCT. Of note, one patient achieved resolution of graft-versus-host disease (GVHD), a difficult-to-treat post-transplant complication, after six months of IMBRUVICA treatment. Christine E. Ryan of the Division of Blood and Marrow Transplantation-Cellular Therapy Facility at the Stanford University Medical Center and colleagues presented these findings in a poster.

The researchers concluded that these results support further study of IMBRUVICA in patients following allo-HCT, including those patients with chronic GVHD. Study PCYC 1129, a multicenter open--label Phase Ib/II study of IMBRUVICA in steroid--dependent or refractory chronic GVHD patients, has completed its Phase Ib without dose limiting toxicities and is now enrolling the Phase II portion at the recommended Phase II dose of 420 mg.

A stem cell transplant, or allo-HCT, is performed in high-risk CLL patients to restore healthy blood cells that have been damaged by disease or high doses of chemotherapy treatment. Patients who experience a relapse of CLL following allo-HCT often are difficult to treat with chemotherapy because they do not produce enough blood cells (hematopoietic reverse) or develop post-transplant complications, such as infections or GVHD, a life-threatening condition in which newly transplanted cells attack the patient's body.1

"These data support that IMBRUVICA may be an effective treatment option for relapsed post-transplant CLL patients, and are consistent with findings from clinical studies in the overall high-risk CLL population," said Danelle James, M.D., M.S., Head of Oncology, Pharmacyclics. "Moreover, these data provide supportive safety information as we evaluate IMBRUVICA in post allo-transplant patients who are suffering from chronic GVHD."

The data presented by Dr. Miklos were collected from four IMBRUVICA clinical trials in R/R CLL, ranging from Phases II to III, and included 16 patients who all had prior allo-HCT and had received IMBRUVICA as a single-agent or in combination with ofatumumab. Twelve (75%) patients received four or more prior therapies and 10 were high-risk CLL patients. The study endpoints were investigator-assessed ORR, duration of response (DOR), PFS, and overall survival (OS). Median DOR, PFS and OS were not reached at a median follow-up of 23 months. The median time on IMBRUVICA treatment was 18 months (range 0.4-38.8), with 69% (n=11) of patients continuing on study treatment.

Study investigators concluded IMBRUVICA was well tolerated in patients who had prior allo-HCT. Patients receiving IMBRUVICA showed a similar safety profile to that observed in the overall R/R CLL population. Five (31%) patients discontinued study treatment: two due to disease progression, two due to pneumonia and one voluntary patient withdrawal. The most frequently reported treatment-emergent serious adverse events (Grade 3 or 4) were infections observed in six patients.

The data presented by Ms. Ryan showed all five high-risk R/R CLL patients who had undergone prior allo-HCT showed sustained disease response and promising donor immune modulation. All patients received IMBRUVICA therapy following their prior relapse. Of note, four patients with abnormal lymph nodes prior to IMBRUVICA treatment experienced a dramatic reduction in size of their lymph nodes following therapy, with a 68% reduction after three months. Two patients receiving IMBRUVICA achieved undetectable CLL minimal residual disease (MRD) with single-agent IMBRUVICA treatment after 39 months and eight months, respectively. One of these patients achieved full donor CD3 chimerism (engraftment of donor cells) after one year of IMBRUVICA treatment and has maintained undetectable CLL MRD for more than 10 months after stopping therapy.

These data were previously presented in part at the 56th American Society of Hematology Annual Meeting in December 2014.

**About Chronic Lymphocytic Leukemia (CLL)**The prevalence of CLL is approximately 115,000 patients in the United States,2 with approximately 16,000 newly diagnosed patients every year.3 As this orphan disease frequently progresses following first-line therapy, patients are faced with fewer treatment options and often are prescribed multiple lines of therapy as they relapse or become resistant to treatments.4

In CLL, the genetic mutation del 17p occurs when part of chromosome 17 has been lost or deleted. CLL patients with del 17p have poor treatment outcomes.5 Del 17p is reported in approximately 7-10%% of treatment-naive CLL cases,6 and approximately 20% to 40% of relapsed/refractory patients harbor the mutation.7

**About IMBRUVICA**IMBRUVICA (ibrutinib) is a first-in-class, oral, once-daily therapy that inhibits a protein called Bruton's tyrosine kinase (BTK).8 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.8,9 IMBRUVICA blocks signals that tell malignant B cells to multiply and spread uncontrollably.8

IMBRUVICA is approved for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, CLL patients with del 17p,8 a genetic mutation that occurs when part of chromosome 17 has been lost, and patients with Waldenstrom's macroglobulinemia.8

IMBRUVICA is also approved for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Accelerated approval was granted for the MCL indication based on overall response rate (ORR). Continued approval for the MCL indication may be contingent upon verification of clinical benefit in confirmatory trials.8

IMBRUVICA is being studied alone and in combination with other treatments in several blood cancers. Over 5,100 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 58 trials are registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov/).

IMBRUVICA was one 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.

*To learn more about the medical terminology used in this news release, please visit*[*http://stedmansonline.com/*](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 (eg, 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 (greater than or equal to 25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash. Seven percent of patients receiving IMBRUVICA® discontinued treatment due to adverse events.

**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.

For additional important safety information, please see Full Prescribing Information at <http://www.imbruvica.com/downloads/Prescribing_Information.pdf>.

**About Pharmacyclics**Pharmacyclics, Inc. (NASDAQ: [PCYC](http://studio-5.financialcontent.com/prnews?Page=Quote&Ticker=PCYC)) is a biopharmaceutical company focused on developing and commercializing innovative small-molecule drugs for the treatment of cancer and immune mediated diseases. The company's mission is to build a viable biopharmaceutical company that designs, develops and commercializes novel therapies intended to improve quality of life, increase duration of life and resolve serious unmet medical needs. It will do so by identifying and controlling promising product candidates based on scientific development and administrative expertise, developing its products in a rapid, cost-efficient manner and, pursuing commercialization and/or development partners when and where appropriate.

Pharmacyclics markets IMBRUVICA and has three product candidates in clinical development and several preclinical molecules in lead optimization. The company is committed to high standards of ethics, scientific rigor and operational efficiency as it moves each of these programs to commercialization. Pharmacyclics is headquartered in Sunnyvale, CA. To learn more, please visit[www.pharmacyclics.com](http://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.*

*\*Disclaimer: Ms. Ryan does not have a financial interest in Pharmacyclics.*

IMBRUVICA is a registered trademark of Pharmacyclics, Inc.

|  |
| --- |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| [1] MedlinePlus, U.S. National Library of Medicine. Graft-versus-host-disease. <http://www.nlm.nih.gov/medlineplus/ency/article/001309.htm>.  Accessed February 2015. |
| [2] IMS Database [Data on File] |
| [3] American Cancer Society. What are the key statistics for chronic lymphocytic leukemia? Available from: <http://www.cancer.org/cancer/leukemia-chroniclymphocyticcll/detailedguide/leukemia-chronic-lymphocytic-key-statistics>. Accessed February 2015. |
| [4] Veliz M, Pinilla-Ibarz J. Cancer Control. Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia. January 2012, Vol. 19, No. 1. |
| [5] NCCN Clinical Practice Guidelines in Oncology. Non-Hodgkins Lymphomas. Version 1.2014. <http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf>.  Accessed February 2015. |
| [6] Schnaiter A, Stilgenbauer S. 17p deletion in chronic lymphocytic leukemia: risk stratification and therapeutic approach. Hematol Oncol Clin North Am. 2013; 27:289-301. |
| [7] Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010; 2010: 481-8. |
| [8] IMBRUVICA Prescribing Information, January 2015 |
| [9] Genetics Home Reference. Isolated growth hormone deficiency. Available at: <http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency>. Accessed February 2015. |

SOURCE Pharmacyclics, Inc.