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Phase III HELIOS Study Results Show Ibrutinib (IMBRUVICA®) Combination Therapy Significantly Increased Progression-Free Survival in Previously-Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Patients

Data featured in today’s official press program at American Society of Clinical Oncology Annual Meeting - This release corresponds to abstract LBA7005

CHICAGO, May 30, 2015 /PRNewswire/ -- Today, Pharmacyclics LLC announced the results of the Phase III HELIOS trial (CLL3001), which found that patients with previously treated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who received ibrutinib (IMBRUVICA®) in combination with bendamustine and rituximab (BR) experienced an 80% reduction in the risk of progression or death compared to patients receiving placebo in combination with BR. Patients also experienced a higher overall response rate (ORR, a key secondary endpoint), including achieving a higher rate of complete responses (CR), after a median follow-up of 17 months.

These data will be presented in an oral, late-breaking abstract session by lead investigator Asher Chanan-Khan, M.D., Mayo Clinic, Jacksonville, FL during the Leukemia, Myelodysplasia, and Transplantation track at 2:27 p.m. CT today at the 51st American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL. IMBRUVICA is jointly developed and commercialized by Pharmacyclics and Janssen Biotech, Inc.

On March 16th, an independent data monitoring committee (IDMC) unanimously recommended that the HELIOS trial be unblinded based on clinically meaningful and statistically significant treatment benefit observed in the ibrutinib arm compared to placebo+BR.

"We knew ibrutinib was an effective single-agent treatment option with an established safety profile and we now have additional evidence suggesting that ibrutinib improves outcomes when combined with existing treatment regimens," said Simon Rule, M.D., Consultant Haematologist, Department of Haematology and Head of the Lymphoma Service, Derriford Hospital, Plymouth, UK and HELIOS study investigator. "The results from the HELIOS trial are very encouraging for previously-treated patients with CLL or SLL and suggest that the ibrutinib combination may be an option for these patients moving forward."

HELIOS is a Janssen-sponsored, randomized, double-blind, placebo-controlled, international, multicenter Phase III study conducted in 21 countries, which evaluated the safety and efficacy of ibrutinib+BR in 578 patients with relapsed/refractory CLL/SLL who had received at least one prior therapy. Patients were randomized to receive either the combination of oral, once-daily ibrutinib 420 mg and six cycles of BR, or a matching regimen of oral, once-daily placebo and six cycles of BR. Treatment with ibrutinib or placebo continued until disease progression or unacceptable toxicity.

PFS was the primary endpoint of the study, as assessed by an independent review committee (IRC). At 18 months, IRC-assessed PFS rates were 79% for patients in the ibrutinib+BR arm compared with 24% for patients in the placebo+BR arm. Key secondary endpoints included IRC-assessed ORR and overall survival (OS). At a median follow-up of 17 months, PFS was significantly longer with ibrutinib+BR versus placebo+BR (median not reached vs. 13.3 months; HR: 0.203, 95% CI: 0.150-0.276, P < 0.0001). Patients with the genetic mutation del 17p CLL were excluded from the study, but PFS rates were consistent across all other high-risk subgroups. Patients in the ibrutinib+BR arm experienced higher rates of ORR and CR/CRi (CR with incomplete hematopoietic recovery), 82.7% and 10.4%, respectively, compared to patients in the placebo+BR arm, 67.8% and 2.8%, respectively. The median OS has not yet been reached after a median follow up of 17 months.

Six cycles of BR were completed in the majority of patients in the ibrutinib and placebo arms (83% and 78%, respectively). The safety profile of ibrutinib+BR was consistent with the known individual safety profiles for the therapies. The addition of ibrutinib had no impact on the ability of BR to be administered in patients, with a similar number of BR cycles administered in both arms of the study.

"HELIOS demonstrated that when added, ibrutinib enhanced the treatment effect of standard bendamustine and rituximab treatment, resulting in a significant improvement in the outcomes for CLL and SLL patients, reducing the risk of progression or death by 80% compared to BR alone," said Danelle James, M.D., M.S., Head of Oncology at Pharmacyclics. "These findings support our belief that ibrutinib can become the backbone of CLL therapy."

The most common adverse events (AEs ≥20%) of all Grades in the HELIOS trial were neutropenia (58.2% in the ibrutinib+BR..."
arm vs. 54.7% in the placebo+BR arm); nausea (36.9% vs. 35.2%); diarrhea (35.5% vs. 23.7%); thrombocytopenia (30.7% vs. 24.4%); pyrexia (24.7% vs. 22%); anemia (22.6% vs. 28.9%); and fatigue (21.6% vs. 22.6%). The most common Grade 3/4 AEs (≥15%) were neutropenia (53.7% vs. 50.5%) and thrombocytopenia (15% in both arms). Higher rates of Grade 1/2 bleeding such as hematoma (8% vs. 1%), contusion (7.7% vs. 3.1%), epistaxis (5.9% vs. 3.1%), ecchymosis (3.1% vs. 0.7%) and petechiae (2.8% vs. 0.3%) were observed in patients taking ibrutinib+BR, compared with those in the placebo+BR arm. Rates of Grade 3 or greater hemorrhage were 3.8% vs. 1.7%, respectively. Rates of treatment-emergent Grade 3/4 atrial fibrillation and hemorrhage were 2.8% vs. 0.7% and 2.1% vs. 1.7%, respectively. The incidence of most AEs was similar between both arms.

Ninety patients (31%) in the placebo+BR arm with confirmed progressive disease crossed over to receive ibrutinib, as permitted in the protocol. AEs were the primary reason for discontinuation in patients taking ibrutinib+BR (14.2% vs. 11.8% in patients taking placebo+BR).

A full study report will be submitted to health authorities for future labeling considerations and will also be submitted to a peer-reviewed journal for potential publication.

**About Chronic Lymphocytic Leukemia (CLL)**

The prevalence of CLL/SLL is approximately 115,000 patients in the United States,[1] with approximately 16,000 newly diagnosed patients every year.[2] As this orphan disease frequently progresses following first-line therapy, patients are faced with fewer treatment options and are often prescribed multiple lines of therapy as they relapse or become resistant to treatments.[3]

In CLL/SLL, the genetic mutation del 17p occurs when part of chromosome 17 has been lost or deleted. CLL/SLL patients with del 17p have poor treatment outcomes.[4] Del 17p is reported in approximately 7% of treatment-naïve CLL/SLL cases,[5] and approximately 20% to 40% of relapsed/refractory patients harbor the mutation.[6]

**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-naïve) who have del 17p, a genetic mutation that occurs when part of chromosome 17 has been lost, and all patients (including treatment-naïve) with Waldenstrom’s macroglobulinemia. [7] 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.[7]

IMBRUVICA (ibrutinib) is a first-in-class, oral, once-daily therapy that inhibits a protein called Bruton's tyrosine kinase (BTK).[7] 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.[7],[8] IMBRUVICA blocks signals that tell malignant B cells to multiply and spread uncontrollably.[7]

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.


**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](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. Chanan-Khan served as the primary investigator of this Janssen-sponsored clinical study. He has served as an unpaid advisor to both Pharmacyclics and Janssen in developing the compound ibrutinib. Dr. Chanan-Khan does not have a financial interest in either company. Prof. Rule also served as an investigator of this study. He has served as an unpaid advisor to both Pharmacyclics and Janssen in developing the compound ibrutinib. Prof. Rule does not have a financial interest in either company.*


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