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Data at ASCO Show Consistent Progression-Free Survival Benefit in Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Patients Treated with Ibrutinib, Including Those with High-Risk Disease, with Up to Four Years of Follow-Up

Additional follow-up data from the Phase 3 RESONATE™ trial showed a 59 percent progression-free survival at three years

Overall response rate was 91 percent, with complete response rates increasing with longer follow-up

This release corresponds to abstract #7510

CHICAGO and RARITAN, NJ, June 5, 2017 – Janssen Research & Development, LLC (Janssen) today announced longer follow-up of up to four years from the pivotal Phase 3 RESONATE™ trial (PCYC-1112) of IMBRUVICA® (ibrutinib) vs. ofatumumab in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). At a median follow-up of 44 months, the results demonstrated a three-year progression-free survival (PFS) rate of 59 percent vs. 3 percent with ibrutinib vs. ofatumumab, respectively. A consistent PFS benefit with ibrutinib was observed across all baseline disease and patient characteristics, particularly among patients with genetic mutation deletion 11q (del 11q), which is a prognostic feature usually conferring an increased risk for poor outcomes. With longer follow-up, the overall response rate (ORR) has now reached 91 percent, with a complete response (CR) of 9 percent (abstract #7510).

These results will be presented today at the 53rd Annual American Society of Clinical Oncology (ASCO) Meeting in Chicago (poster session: 8:00 – 11:30 a.m. CDT; poster discussion: 1:15 – 2:30 p.m. CDT). IMBRUVICA, a first-in-

class Bruton's tyrosine kinase (BTK) inhibitor, is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company.

"These findings demonstrated the continued benefit of ibrutinib in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma," said John C. Byrd, M.D., Distinguished University Professor at the Ohio State University Comprehensive Cancer Center and lead investigator of the study.* "Importantly, with long-term follow up, many patients receiving ibrutinib had a deepening of responses and continued improvement in progression-free survival. This study confirms ibrutinib as a major therapeutic option for chronic lymphocytic leukemia/small lymphocytic lymphoma patients."

CLL, a subtype of non-Hodgkin Lymphoma (NHL), is one of the most common forms of leukemia in adults.[1] CLL commonly arises from B cells, a type of white blood cell (lymphocyte) that originates in the bone marrow. CLL mainly affects older adults with a slightly higher risk in men than in women.[2] There are approximately 115,000 patients in the U.S. with CLL, [3] with more than 20,000 estimated new cases each year.[2] SLL is similar to CLL and affects the same lymphocytes; the only difference between the two is the location where the cancer primarily occurs.[4]

"The Phase 3 RESONATE trial served as a pivotal study supporting the FDA approval of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia in 2014. With more than four years of follow-up, we continue to be impressed with the durability and control by ibrutinib for patients with relapsed or refractory chronic lymphocytic leukemia," said Peter F. Lebowitz, M.D., Ph.D., Global Oncology Head, Janssen. "It is exciting to see how ibrutinib continues to provide clinical utility in these patients. Each year of additional follow-up adds to the clinical experience and knowledge about this medication and its use in patients with chronic lymphocytic leukemia."

Abstract #7510: Long-Term Efficacy and Safety with Ibrutinib (ibr) In Previously Treated Chronic Lymphocytic Leukemia: Up to Four Years Follow-Up of The RESONATE Study (Poster Board: #272)

- **Poster session: Monday, June 5, 8:00 - 11:30 a.m. CDT**
- **Poster discussion session: Monday, June 5, 1:15 - 2:30 p.m. CDT**

At up to four years of follow-up (median, 44 months and max 53 months), ibrutinib continued to show efficacy in CLL/SLL patients (n=391), with PFS significantly longer with ibrutinib compared to ofatumumab (median not reached vs. 8.1 months, respectively; Hazard Ratio [HR] 0.133; p<0.0001; three-year PFS 59 percent vs. 3 percent). Ibrutinib also demonstrated benefit in high-risk patient subgroups, i.e., deletion 17p (del 17p) and del 11q, with PFS in the del 11q subgroup showing the most favorable outcome, which was non-inferior to patients without these cytogenetic abnormalities. At time of analysis, with a majority of patients in the ofatumumab (68 percent) arm crossing over to the ibrutinib arm, three-year overall survival (OS) was longer for ibrutinib vs. ofatumumab (median OS was not reached for either arm). The OS rate for single agent ibrutinib at three years was 74 percent and the

ORR was 91 percent with CR/CRi (incomplete bone marrow recovery) increasing over time to 9 percent. Baseline cytopenias improved with extended ibrutinib therapy for hemoglobin (85 percent), platelet (95 percent) and absolute neutrophil counts (95 percent).

The adverse event (AE) profile of ibrutinib included major hemorrhage, Grade ≥3 atrial fibrillation and Grade ≥3 hypertension occurring in 6 percent, 6 percent, and 8 percent of patients, respectively, over a follow-up period of up to four years. Incidence of most Grade ≥3 AEs decreased from year one vs. year two to three: neutropenia (18 percent vs. 8 percent); pneumonia (11 percent vs. 4 percent); atrial fibrillation (4 percent vs. 2 percent), respectively. Discontinuations were most frequently caused by progressive disease (27 percent) and AEs (12 percent). At analysis, 90 ibrutinib patients (46 percent) continued the therapy in the study.

The risks associated with ibrutinib as listed in the Warnings and Precautions section of the prescribing information are hemorrhage, infections, cytopenias, atrial fibrillation, hypertension, secondary primary malignancies, tumor lysis syndrome and embryo fetal toxicities.[5]

RESONATE™, a Pharmacyclics-sponsored Phase 3 randomized, multi-center, open-label, international study, enrolled 391 patients with R/R CLL/SLL, who had received at least one prior therapy and were not considered appropriate candidates for treatment with a purine analog (median age 67). Study participants were treated with either 420 mg oral ibrutinib (n=195) once-daily until progression or unacceptable toxicity or intravenous ofatumumab for up to 24 weeks (n=196, initial dose of 300 mg followed by 11 doses at 2,000 mg per dose and schedule consistent with local labeling). The results showed significant improvements in PFS vs. ofatumumab, meeting the study's primary endpoint, and in OS and ORR, meeting the study's key secondary endpoints. Primary results from this trial were featured in the official press program at ASCO 2014, with a simultaneous publication in the *New England Journal of Medicine* in July 2014. The results were also the basis for the full approval of ibrutinib in R/R CLL in July 2014.

About IMBRUVICA

IMBRUVICA was one of the first therapies to receive U.S. approval after having received the FDA's Breakthrough Therapy Designation. IMBRUVICA works by blocking a specific protein called Bruton's tyrosine kinase (BTK). The BTK protein transmits important signals that tell B cells to mature and produce antibodies and is needed by specific cancer cells to multiply and spread. IMBRUVICA targets and blocks BTK, inhibiting cancer cell survival and spread. For more information, visit www.IMBRUVICA.com.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including 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 and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 13%) based on laboratory measurements occurred in patients treated with single agent 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, hypertension, 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. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 3% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2% to 13%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (eg, high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

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® and for 1 month after cessation of therapy. 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. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia** (61%), thrombocytopenia** (62%), diarrhea (43%), anemia** (41%), musculoskeletal pain (30%), rash (30%), nausea (29%), bruising (30%), fatigue (29%), hemorrhage (22%), and pyrexia (21%).

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

The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).
The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MZL patients were pneumonia (10%), fatigue (6%), diarrhea (5%), rash (5%), and hypertension (5%).

Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9% (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions. Most common adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each) in CLL/SLL patients and subdural hematoma (1.8%) in MCL patients. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea, and rash (1.6% each) in WM and MZL patients.

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid coadministration 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: https://www.imbruvica.com/prescribing-information.

About the Janssen Pharmaceutical Companies

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenUS and www.twitter.com/JanssenGlobal.

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

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[4] Lymphoma Research Foundation. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL). Available from: http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300147. Accessed May 2017.
[5] IMBRUVICA U.S. Prescribing Information, April 2017.
[6] Genetics Home Reference. Isolated growth hormone deficiency. Available from: http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed March 2017