Ibrutinib (IMBRUVICA®) Three Year Follow-up of Single-Agent and Combination Study Results in Chronic Lymphocytic Leukemia

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RARITAN, NJ, May 31, 2014 - Three year follow-up data from the Phase 1b/2 PCYC-1102 trial of single-agent ibrutinib (IMBRUVICA®) suggest continued durable responses in patients with treatment-naïve (TN) or relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), according to data from an analysis that will be discussed in an oral presentation on Tuesday, June 3 at the American Society of Clinical Oncology (ASCO) 50th annual meeting in Chicago, IL. Janssen Research & Development, LLC, announced the results today, which show ibrutinib continued to produce high overall response rates (ORR) (78 percent for all treated patients, with the median duration of response not achieved after almost 30 months). In addition, the rate of Grade 3 or higher adverse events (AEs) or those leading to hospitalization decreased after one year on treatment.

In a separate poster presentation to be discussed today, data suggest the combination of single-agent ibrutinib administered orally once-daily with ofatumumab, a CD20-directed cytolytic monoclonal antibody administered intravenously, is tolerable in patients with previously treated relapsed or refractory CLL/SLL.

"The data presented this week at ASCO will help us gain a more complete understanding of the utility of ibrutinib in CLL. The Phase 3 RESONATE data showed an improvement in overall survival with single-agent ibrutinib, the three year follow-up data showed the duration of response and reduction of adverse events over time and PCYC-1109 helps us to understand its potential in combination with other therapies, such as a CD20 monoclonal antibody," said Peter F. Lebowitz, M.D., Ph.D., Global Oncology Head, Janssen Research & Development, LLC.

In 2011, Janssen Biotech, Inc. and Pharmacyclics, Inc. entered into an agreement to jointly develop and commercialize ibrutinib.

Three Year Follow-up of Single Agent Ibrutinib in Phase 1b/2 Trial
Three year follow-up from the initial Phase 1b/2 PCYC-1102 trial of single-agent ibrutinib showed continued durable responses in patients with treatment-naïve (n=31) or relapsed or refractory CLL or SLL (n=101). Ibrutinib was associated with a 78 percent ORR, with durable responses regardless of prior treatment history (83.9 percent in treatment-naïve patients, 76.2 percent in relapsed or refractory patients, 55.9 percent in relapsed or refractory patients with a deletion of the short arm of chromosome 17 [del 17p]). In addition, five patients with relapsed or refractory CLL and two with del 17p achieved a partial response (PR) with lymphocytosis as best response. Patients received single-agent ibrutinib once-daily at either 420 mg or 840 mg doses. ORR was assessed based on International Working Committee on Chronic Lymphocytic Leukemia (IWCLL) criteria. The median time on study was 29.4 months (range, 0.7-38.1 months).

"These results suggest significantly extended response to ibrutinib in patients with CLL three years after starting treatment," said Susan O'Brien, M.D., presenter of the analysis and professor in the Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX.† "We are especially encouraged to see that patients showed durable responses to treatment with ibrutinib monotherapy regardless of their treatment history."

The median duration of response was not reached for the full set of patients (n=132) evaluated for the analysis. For relapsed or refractory patients with del 17p, the median duration of response was 25 months (range 4.8 - 34.3 months).

Grade 3 or 4 AEs in the pooled analysis related to ibrutinib (investigator-assessed) decreased from 24 percent to four percent after three years of follow-up. Grade 3 or higher serious AEs (SAEs) related to ibrutinib also decreased over time from eight percent in the first year to one percent after three years of treatment. No new safety signals were observed in long-term follow-up and 64 percent of patients remain on treatment with ibrutinib. The rate of Grade 3 or higher adverse events or those leading to hospitalization decreased after one year on treatment with ibrutinib.

Combination Data
Separately, data from the Phase 1b/2 PCYC-1109 study, to be presented today at ASCO, showed treatment with single-agent ibrutinib administered once-daily in combination with ofatumumab administered intravenously is tolerated and highly active in patients with relapsed or refractory CLL/SLL (n=71). The combination produced an 83 percent ORR in patients across all three dosing regimens studied, including a 100 percent ORR (n=27) in patients who started with one cycle of ibrutinib therapy followed by ofatumumab; additionally, two patients in the study achieved a PR with lymphocytosis. Additionally, at 12 months, the average progression-free survival (PFS) across all patients was approximately 88 percent, with 64 percent of patients continuing on single-agent ibrutinib in a long-term extension study. Three patients with Richter's transformation receiving ibrutinib and ofatumumab achieved disease control followed by progression after Day 471, 168 and 137, respectively.

The most common Grade 3 or 4 AE in the study (occurring in 10 percent or more of patients) was neutropenia (17%). The most frequent AEs (occurring in 20 percent or more of patients) were diarrhea (68%), infusion-related reaction (45%), peripheral sensory neuropathy (nerve damage; 42%) and stomatitis (inflammation of the mouth and lips; 37%). Six patients (8%) experienced AEs leading to discontinuation of treatment with ibrutinib. Nine patients (12.7%) died within 30 days of the last dose and two died within the follow-up period.

Ibrutinib is marketed as IMBRUVICA in the U.S. for the treatment of patients with CLL who have received at least one prior therapy and the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.[1] These indications are both based on ORR. An improvement in survival or disease-related symptoms has not been established.[1]

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage - Five percent of patients with mantle cell lymphoma (MCL) and 6% of patients with CLL had Grade 3 or higher bleeding events (subdural hematoma, ecchymoses, gastrointestinal bleeding, and hematuria). Overall, 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.

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. At least 25% of patients with MCL and 35% of patients with CLL had infections Grade 3 or greater according to NCI Common Terminology Criteria for Adverse Events (CTCAE). 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 IMBRUVICA® 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 IMBRUVICA®. 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.

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
CLL: The most commonly occurring adverse reactions (≥ 20%) in the clinical trial were thrombocytopenia*, diarrhea (63%), bruising (54%), neutropenia*, anemia*, upper respiratory tract infection (48%), fatigue (31%), musculoskeletal pain (27%), rash (27%), pyrexia (25%), constipation (23%), peripheral edema (23%), arthralgia (23%), nausea (21%), stomatitis (21%), sinusitis (21%), and dizziness (21%).

*Treatment-emergent decreases (all grades) of platelets (71%), neutrophils (54%) and hemoglobin (44%) were based on laboratory measurements per IWCLL criteria and adverse reactions.

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia (8%), hypertension (8%), atrial fibrillation (6.0%), sinusitis (6%), skin infection (6%), dehydration (6.0%), and musculoskeletal pain (6%). Treatment-emergent Grade 3 or 4 cytopenias were reported in 35% of patients.

Five patients (10%) discontinued treatment due to adverse reactions in the trial (N=48). These included 3 patients (6%) with infections and 2 patients (4%) with subdural hematomas. Adverse reactions leading to dose reduction occurred in 13% of patients.

MCL: The most commonly occurring adverse reactions (≥ 20%) in the clinical trial were thrombocytopenia*, diarrhea (51%), neutropenia*, anemia*, fatigue (41%), musculoskeletal pain (37%), peripheral edema (35%), upper respiratory tract infection (34%), nausea (31%), bruising (30%), dyspnea (27%), constipation (25%), rash (25%), abdominal pain (24%), vomiting (23%), and decreased appetite (21%).

*Treatment-emergent decreases (all grades) of platelets (57%), neutrophils (47%) and hemoglobin (41%) were based on laboratory measurements and adverse reactions.

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5.4%), diarrhea (5%), fatigue (5%), and skin infections (5%). Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients.

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

DRUG INTERACTIONS
CYP3A Inhibitors - Avoid concomitant administration with strong or moderate inhibitors of CYP3A. 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 baseline hepatic impairment.

For the full prescribing information, visit http://www.IMBRUVICA.com/.

About Chronic Lymphocytic Leukemia
CLL is a slow-growing blood cancer of white blood cells called lymphocytes, most commonly B cells.[2] CLL is the most common adult leukemia in the Western world and predominantly a disease of the elderly with a median age of diagnosis of 72.[3] This orphan disease often eventually progresses; patients are faced with fewer treatment options and are often prescribed multiple lines of therapy as they relapse or become resistant to treatments.[4] SLL is a slow-growing lymphoma in which too many immature white blood cells cause lymph nodes to become larger than normal.[2]

About IMBRUVICA®
IMBRUVICA was one of the first therapies to receive U.S. approval via the FDA's Breakthrough Therapy Designation and was approved under the FDA's Subpart H regulation.[5] IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.[1] These indications are both based on an overall response rate (ORR). An improvement in survival or disease-related symptoms has not been established.[1]

IMBRUVICA works by blocking a specific protein called Bruton's tyrosine kinase (BTK).[1] 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.[1,6] IMBRUVICA targets and blocks BTK, inhibiting cancer cell survival and spread.[1]

About Janssen Research & Development, LLC
At Janssen, we are dedicated to addressing and solving some of the most important unmet medical needs of our time in oncology, immunology, neuroscience, infectious diseases and vaccines, and cardiovascular and metabolic diseases. Driven by our commitment to patients, we develop innovative products, services and healthcare solutions to help people throughout the world. Janssen Research & Development is part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Please visit www.janssenrnd.com for more information.

About Janssen Biotech, Inc.
Janssen Biotech, Inc. redefines the standard of care in immunology, oncology, urology and nephrology. Built upon a rich legacy of innovative firsts, Janssen Biotech has delivered on the promise of new treatments and ways to improve the health of individuals with serious disease. Beyond its innovative medicines, Janssen Biotech is at the forefront of developing education and public policy initiatives to ensure patients and their families, caregivers, advocates and health care professionals have access to the latest treatment information, support services and quality care. For more information on Janssen Biotech, Inc. or its products, visit www.janssenbiotech.com.

Janssen Biotech is one of the Janssen Pharmaceutical Companies of Johnson & Johnson, which are dedicated to addressing and solving some of the most important unmet medical needs in oncology, immunology, neuroscience, infectious diseases and vaccines, cardiovascular and metabolic diseases. Driven by our commitment to patients, we work together to bring innovative ideas, products, services and solutions to people throughout the world. Follow us on Twitter at www.twitter.com/JanssenUS.

Janssen in Oncology
In oncology, our goal is to fundamentally alter the way cancer is understood, diagnosed, and managed, reinforcing our commitment to the patients who inspire us. In looking to find innovative ways to address the cancer challenge, our primary efforts focus on several treatment and prevention solutions. These include a focus on hematologic malignancies, prostate cancer and lung cancer; cancer interception with the goal of developing products that interrupt the carcinogenic process; biomarkers that may help guide targeted, individualized use of our therapies; as well as safe and effective identification and treatment of early changes in the tumor microenvironment.

(This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding product development. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges inherent in new product development, including obtaining regulatory approvals; competition, including technological advances, new products and patents attained by competitors; challenges to patents; changes in behavior and spending patterns or financial distress of purchasers of health care products and services; changes to governmental laws and regulations and domestic and foreign health care reforms; general industry conditions including trends toward health care cost containment; and increased scrutiny of the health care industry by government agencies. A further list and description of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 29, 2013, including in Exhibit 99 thereto, and our subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical companies or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.)

†***Disclaimer****: Dr. O'Brien has served as an unpaid advisor to both Pharmacyclics and Janssen in developing the compound ibrutinib. Dr. O'Brien does not have a financial interest in either company.*

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[1]IMBRUVICA Prescribing Information, February 2014.

[2]American Cancer Society. Detailed guide: what is chronic lymphocytic leukemia. Available from: http://www.cancer.org/acs/groups/cid/documents/webcontent/003111-pdf.pdf Accessed April 2014.

[3]Decision Resources estimate 2013.

[4]Veliz M, Pinilla-Ibarz J. Treatment of relapsed or refractory chronic lymphocytic leukemia. *Cancer Control*. 2012 Jan;19(1):37-53.

[5]The U.S. Food and Drug Administration. CFR - Code of Federal Regulations Title 21. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8. Accessed April 2014.

[6]Genetics Home Reference. Isolated growth hormone deficiency. Available from: http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed April 2014.

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