IMBRUVICA® (ibrutinib) Shows Sustained Progression-Free Survival in Patients with High-Risk Chronic Lymphocytic Leukemia with Genetic Mutation

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- ***Note: This press release corresponds to ASH abstracts 327, 3331 and 4696***

SAN FRANCISCO, CA and RARITAN, NJ, December 8, 2014 - Results from the Phase 2 RESONATE™-17 (PCYC-1117) study show IMBRUVICA® (ibrutinib) was associated with an 82.6 percent investigator-assessed overall response rate (ORR; the primary endpoint) and a 79 percent progression-free survival (PFS) rate at 12 months in people living with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have a genetic mutation known as deletion 17p (del 17p). These data were presented today by Susan O'Brien, M.D., professor in the Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, at the American Society of Hematology (ASH) Annual Meeting in San Francisco, CA, Janssen Research & Development, LLC (Janssen) announced today. Del 17p occurs when a portion of chromosome 17 has been lost. People with the del 17p mutation are considered to have high-risk disease, which is associated with poor prognosis.[1]

IMBRUVICA is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics, Inc.

"RESONATE-17 is the largest prospective trial dedicated solely to the study of patients with CLL and SLL who have the del 17p mutation. This subset of patients typically do not respond well to chemotherapies," said O'Brien.† "What was compelling about this study was not only the overall response rates seen with IMBRUVICA, but also the duration of these responses. In fact, after thirteen-months of follow-up, investigators determined duration of response had not yet been reached."

"The benefits of IMBRUVICA are evidenced by its robust clinical activity in patients with CLL, even in those with high-risk disease, chromosomal abnormalities or who have already been treated with a number of prior therapies," said Peter F. Lebowitz, M.D., Ph.D., Global Oncology Head, Janssen.

In RESONATE-17, 144 previously treated patients with del 17p (137 with CLL, seven with SLL) received single-agent IMBRUVICA once daily until progression. The primary endpoint of the open-label, single-arm, multicenter RESONATE-17 trial was ORR, as measured by an independent review committee (IRC). Duration of response (DOR), PFS and safety were key secondary endpoints. Investigator-assessed ORR was 82.6 percent and a complete response (CR) or CR with incomplete bone marrow recovery (CRi) occurred in three patients. IRC-assessed ORR was 65 percent. After a median follow-up of 13 months (range 0.5-16.7 months), the median PFS and DOR as assessed by the investigator had not been reached. At 12 months, 79.3 percent of patients were alive and progression-free, with an overall survival (OS) of 88.3 percent.

These data are consistent with the results seen in the pivotal Phase 3 RESONATE ™trial, which served as the basis for the July 28, 2014 U.S. Food and Drug Administration (FDA) approval of IMBRUVICA in patients with CLL who have received at least one prior therapy and in CLL patients with del 17p.

The most common Grade 3 or 4 adverse events (AEs) in the RESONATE-17 trial (occurring in five percent or more of IMBRUVICA patients) were neutropenia (low neutrophil count; 14 percent), anemia (8 percent), pneumonia (8 percent) and hypertension (8 percent). The most frequently reported AEs of any grade were diarrhea (36 percent), fatigue (30 percent), cough (24 percent) and arthralgia (joint pain; 22 percent). Atrial fibrillation of any grade was reported in 11 people (7.6 percent). Seven people reported basal or squamous cell skin cancer and one person had plasma cell myeloma. Major hemorrhage was reported in seven people (4.9 percent).

At the time of the data assessment, the median treatment duration was 11.1 months, and 70 percent of people continued treatment with IMBRUVICA.

Abstract #3331: Phase 3 RESONATE Follow-up
A poster presentation by Jennifer Brown, M.D., Ph.D., on Sunday, December 7, provided 16-month follow-up data from the randomized, multicenter, open-label Phase 3 RESONATE trial (N=391), showing an investigator-assessed PFS after 12 months of 84 percent, representing an 89.4 percent reduction in the risk of progression or death versus ofatumumab. After a median follow-up of 16 months, the investigator-assessed PFS was significantly longer in patients taking IMBRUVICA versus ofatumumab (not reached vs. 8.1 months). The median OS in patients receiving IMBRUVICA has not yet been reached, with 18-month survival rates of 85 percent versus 78 percent. The overall investigator-assessed response rate was 90 percent in patients taking IMBRUVICA (versus 25 percent in ofatumumab patients; $P<0.0001$), including eight percent of patients who achieved a partial response with lymphocytosis.

In an exploratory analysis, Brown showed that patients who had received only one versus two or more prior therapies before IMBRUVICA had a higher PFS (94 percent at 12 months versus 82 percent; $P=0.01$). An additional analysis also showed the rates of ORR and PFS were similar in patients with or without del 17p, indicating that the high risk del 17p mutation did not confer a worse outcome for patients receiving IMBRUVICA.

Overall, at a median follow-up of 16 months, seventy-six percent of people randomized to IMBRUVICA continued on treatment in the study. In total, 62 percent of patients randomized to receive ofatumumab have crossed over to receive IMBRUVICA, following the recommendation of the Independent Data Monitoring Committee to stop the study early due to a positive interim analysis.[2]

The most common Grade 3 or 4 AEs in the RESONATE trial analysis (occurring in five percent or more of IMBRUVICA patients) were neutropenia (18 percent), pneumonia (9 percent), thrombocytopenia (low platelets in the blood; 6 percent), anemia (6 percent) and hypertension (6 percent). The most frequently reported AEs of any grade were diarrhea (37 percent), nausea (24 percent), fatigue (18 percent) and atrial fibrillation (7 percent).

Forty-seven people (24 percent) discontinued IMBRUVICA: 17 due to progressive disease (9 percent), 13 due to AEs (7 percent) and 10 (5 percent) due to death.

Abstract #4696: Phase 3 RESONATE Hematologic and Immunologic Function
A poster presentation by Jacqueline Barrientos, M.D., on Monday, December 8, reported on patient well-being, including hematologic, immunologic and quality of life parameters from the Phase 3 RESONATE trial (N=391). Compared to ofatumumab, IMBRUVICA led to significant improvements in hematologic function and improvements in patient reported outcomes. New episodes of diarrhea were also shown to decline over time along with Grade 3 or higher hematologic AEs and pneumonia.

About Chronic Lymphocytic Leukemia
Chronic Lymphocytic Leukemia (CLL) is a slow-growing blood cancer that most commonly arises from B cells, a type of white blood cell (lymphocyte) that originates in the bone marrow.[3,4] CLL is predominantly a disease of the elderly, with a median age of 72 at diagnosis.[3] In CLL, the genetic mutation del 17p occurs when part of chromosome 17 has been lost. CLL patients with del 17p have poor treatment outcomes.[1] Del 17p is reported in seven percent of treatment-naïve CLL cases,[5] with approximately 20 to 40 percent of relapsed/refractory patients harboring the mutation.[6]

About IMBRUVICA
IMBRUVICA is 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).[2] 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.[2,7] IMBRUVICA targets and blocks BTK, inhibiting cancer cell survival and spread.[2] For more information, visit www.IMBRUVICA.com.

Additional Information about IMBRUVICA®
INDICATIONS

- IMBRUVICA is indicated to treat people with:
- Mantle cell lymphoma (MCL) who have received at least one prior therapy
  - Accelerated approval was granted for this indication based on overall response rate. Improvements in survival or disease-related symptoms have not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- Chronic lymphocytic leukemia (CLL) with 17p deletion

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - 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 anti-platelet or anti-coagulant 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. Twenty-five percent of patients with MCL and 26% of patients with CLL had Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 23 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 10%) including 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 8%).

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
MCL: The most common 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%), 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.

Fatal and serious cases of renal failure have occurred. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

CLL: The most common adverse reactions (≥20%) in the clinical trials were thrombocytopenia (56%), neutropenia (51%), diarrhea (51%), anemia (37%), fatigue (28%), musculoskeletal pain (28%), upper respiratory tract infection (28%), rash (26%), nausea (25%), and pyrexia (24%). Approximately 5% of patients receiving IMBRUVICA® discontinued treatment due to adverse events. These included infections, subdural hematomas, and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% 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.

Please see full prescribing information: http://www.imbruvica.com/downloads/Prescribing_Information.pdf

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, LLC and Janssen Biotech, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Please visit http://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. 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. Please visit oncology.janssenrnd.com.

† *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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