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Phase 3 Study Evaluating IMBRUVICA® (ibrutinib) in Combination with Rituximab in Waldenström's Macroglobulinemia Met Primary Endpoint

Study will be unblinded based on positive pre-specified interim analysis

RARITAN, NJ, December 5, 2017 – Janssen Research & Development, LLC (Janssen) announced that the Phase 3 iNNOVATE (PCYC-1127) study evaluating IMBRUVICA® (ibrutinib) in combination with rituximab (RITUXAN®) in relapsed/refractory and treatment-naïve patients with Waldenström's macroglobulinemia (WM) successfully met its primary endpoint of progression-free survival (PFS). An Independent Data Monitoring Committee (IDMC) recommended unblinding iNNOVATE based on efficacy results observed in the pre-specified interim analysis. IMBRUVICA is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor jointly developed and commercialized by Janssen Biotech, Inc., and Pharmacyclics LLC, an AbbVie company.

"It is gratifying to see that patients with Waldenström's macroglobulinemia – a rare, difficult-to-treat form of blood cancer – have achieved this magnitude of benefit with the IMBRUVICA combination with rituximab as compared to rituximab alone in either the relapsed/refractory or newly diagnosed setting," said Craig Tendler, M.D., Vice President, Late-Stage Development and Global Medical Affairs, Janssen Oncology. "Since the approval of IMBRUVICA in 2013 for Waldenström's, we have added to the body of evidence and patient experience, by conducting this randomized Phase 3 trial and confirming IMBRUVICA's clinical benefit first seen in the relapsed/refractory setting and now demonstrated with earlier use in the treatment journey for the WM patient."

Janssen and Pharmacyclics will share and discuss the unblinded data from the study with health authorities around the world. IMBRUVICA received FDA approval in WM in January 2015.

About iNNOVATE

iNNOVATE is a Pharmacyclics-sponsored, randomized, placebo-controlled, double-blind, Phase 3 study, which is evaluating IMBRUVICA (ibrutinib) in combination with rituximab, and placebo in combination with rituximab in 150 patients with relapsed/refractory and treatment-naïve Waldenström's macroglobulinemia (WM). In the study, patients were randomized to receive intravenous rituximab 375 mg/m^2 once weekly for four consecutive weeks, followed by a second four-weekly rituximab course following a three-month interval. All patients received either IMBRUVICA 420 mg or placebo once daily continuously until criteria for permanent discontinuation were met. The primary endpoint is progression-free survival, with secondary objectives including overall response rate, hematological improvement measured by hemoglobin, time-to-next treatment, overall survival, and number of participants with adverse events as a measure of safety and tolerability within each treatment arm. WM is a form of non-Hodgkin's lymphoma and is a rare disease, with an incidence rate of about three cases per million per year in the U.S. Roughly 1,000 to 1,500 people are diagnosed with WM each year in the U.S.[1]

About IMBRUVICA

IMBRUVICA (ibrutinib) was one of the first therapies to receive U.S. approval after having received the FDA's Breakthrough Therapy Designation.[2] 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.[3] IMBRUVICA targets and blocks BTK, inhibiting the survival and spread of cancer cells, and impacting signaling associated with other serious conditions. Worldwide, IMBRUVICA was used to treat more than 90,000 patients to date. For more information, visit www.IMBRUVICA.com.

Additional Information about IMBRUVICA®

INDICATIONS

IMBRUVICA® is indicated to treat adults with[2]

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Mantle cell lymphoma (MCL) patients 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 and description of clinical benefit in a confirmatory trial.

- Marginal zone lymphoma (MZL) patients who require systemic therapy and have received at least one prior anti-CD20-based therapy
    - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic Graft-Versus-Host Disease (cGVHD) patients who failed one or more lines of systemic therapy

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 post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) 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®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and 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 with B-cell malignancies 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 (e.g., 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 anti-hypertensive medications and/or initiate anti-hypertensive 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 (e.g., 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

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

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%), thrombocytopenia (16%), and pneumonia (10%).

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.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%), muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%), and pneumonia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) reported in patients with cGVHD were fatigue (12%), diarrhea (10%), neutropenia (10%), pneumonia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

DRUG INTERACTIONS

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

CYP3A Inhibitors: Dose adjustment may be recommended.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® 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 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 www.janssenrnd.com for more information.

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.

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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[1] American Cancer Society. What Is Waldenstrom Macroglobulinemia? Available from: https://www.cancer.org/cancer/waldenstrom-macroglobulinemia/about/what-is-wm.html. Accessed October 2017.

[2] IMBRUVICA U.S. Prescribing Information, August 2017

[3] Genetics Home Reference. Isolated growth hormone deficiency. Available from: http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed October 2017.