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IMBRUVICA® (ibrutinib) in Combination with Rituximab Showed Greater Efficacy Compared to Placebo Plus Rituximab in Patients with Waldenström's Macroglobulinemia, a Rare and Incurable Form of Non-Hodgkin's Lymphoma

Phase 3 data featured as oral presentation (abstract #8003), selected for Best of ASCO 2018 Meetings, and simultaneously published in The New England Journal of Medicine

Study represents first randomized double-blind placebo-controlled trial evaluating treatment-naïve Waldenström's macroglobulinemia patients

A supplemental New Drug Application was submitted to the U.S. FDA based on this data

CHICAGO, June 1, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced results from a pre-planned interim analysis of the Phase 3 iNNOVATE (PCYC-1127) study evaluating the investigational use of IMBRUVICA® (ibrutinib) in combination with rituximab in relapsed/refractory and treatment-naïve patients with Waldenström's macroglobulinemia (WM). The study met its primary endpoint for a clinically and statistically significant difference in progression-free survival (PFS) for patients treated with IMBRUVICA plus rituximab versus those who received placebo plus rituximab. IMBRUVICA plus rituximab significantly reduced the risk of disease progression or death by 80 percent compared to placebo plus rituximab (hazard ratio, 0.20; confidence interval: 0.11-0.38, P <0.0001). Furthermore, secondary endpoints including the response rate, time to next treatment (TTnT), rate of sustained hemoglobin improvement and number of participants with adverse events (AEs) supported the primary endpoint. In late 2017, the Independent Data Monitoring Committee (IDMC) recommended unblinding iNNOVATE based on these results.

The data were presented today in an oral session at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting (abstract #8003) and simultaneously published in *The New England Journal of Medicine*. The presentation was selected for inclusion in the Best of ASCO 2018 Meetings. In addition, a supplemental New Drug Application (sNDA) was submitted to the U.S. Food and Drug Administration (FDA) based on this data to expand the use of IMBRUVICA as a combination therapy in WM. 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 important data demonstrate that ibrutinib plus rituximab resulted in marked improvement in progression-free survival across all lines of therapy in Waldenström’s macroglobulinemia regardless of patient subtypes, compared to placebo plus rituximab,” said Dr. Meletios A. Dimopoulos, Professor and Chairman of the Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens, Greece, and lead iNNOVATE study investigator. “Not only was there marked statistical and clinical difference in the efficacy compared to rituximab monotherapy, but the combination of ibrutinib and rituximab did not result in any unanticipated safety signals.”

“Waldenström’s macroglobulinemia remains a difficult-to-treat blood cancer, with nearly 3,000 new diagnoses in the U.S. each year,” said Dr. Lia Palomba, hematologist-oncologist at Memorial Sloan-Kettering Cancer Center, New York, and iNNOVATE study investigator. “The iNNOVATE study results make a compelling case for the potential use of ibrutinib in combination with rituximab for patients living with Waldenström’s macroglobulinemia.”

WM is a rare, slow-growing and incurable form of non-Hodgkin lymphoma (NHL) with limited treatment options. WM typically affects older adults and is primarily found in the bone marrow, although lymph nodes and the spleen also may be affected.[1] In January 2015, IMBRUVICA received FDA approval as monotherapy in WM and is the first and only FDA-approved therapy specifically indicated for this disease.

“The results from the iNNOVATE study provide physicians with compelling evidence to consider IMBRUVICA in combination with rituximab for the treatment of patients living with Waldenström’s macroglobulinemia, across all lines of treatment and patient subtypes, offering the potential for a chemotherapy-free option for these patients,” said Craig Tendler, M.D., Vice President, Clinical Development and Medical Affairs, Janssen Research & Development, LLC. “We look forward to working with the U.S. FDA to bring IMBRUVICA to additional patients living with Waldenström’s macroglobulinemia who may benefit from this treatment option.”

Abstract #8003: Randomized phase 3 trial of ibrutinib/rituximab vs placebo/rituximab in Waldenström's macroglobulinemia

Oral presentation: Friday, June 1, 3:45 p.m. CDT

The iNNOVATE study evaluated relapsed/refractory and treatment-naïve WM patients (N=150) who were randomized to receive intravenous rituximab 375 mg/m^2 once weekly for four consecutive weeks, followed by a second once-weekly for four consecutive weeks rituximab course after a three-month interval. All patients received either IMBRUVICA 420 mg or placebo once daily continuously until disease progression or unacceptable toxicity. The primary endpoint was PFS, as assessed by an independent review committee. Secondary objectives included overall response rate, hematological improvement measured by hemoglobin, median TTnT, overall survival (OS), and number of participants with AEs as a measure of safety and tolerability within each treatment arm.

With a median follow-up of 26.5 months, IMBRUVICA plus rituximab improved PFS compared with placebo plus rituximab (median PFS, not reached vs 20.3 months; HR, 0.20; CI: 0.11-0.38, *P* <0.0001), with PFS rates of 82% versus 28% at 30 months, respectively. Notably, IMBRUVICA plus rituximab prolonged PFS in all relevant subgroups, including treatment-naïve (HR, 0.34; CI: 0.12-0.95), relapsed (HR, 0.17; CI: 0.08-0.36), and in patients with MYD88^{L265P} and CXCR4^{WHIM} mutations (HR, 0.24; CI: 0.09-0.66) versus rituximab.

Overall response rates and major response rates were significantly higher for IMBRUVICA plus rituximab versus placebo plus rituximab (92% vs 47%; 72% vs 32% [both *P* <0.0001]). In addition, there was an improvement in hemoglobin seen in patients treated with the combination versus the placebo plus rituximab arm (73% vs 41%, *P* <0.0001).

Of the patients on IMBRUVICA plus rituximab, 75% continued on treatment at the time of analysis. TTnT was not reached for IMBRUVICA plus rituximab and 18 months for placebo plus rituximab (HR, 0.096; *P* <0.0001). The 30-month OS rates were 94% versus 92% in the two arms.

At the median time on treatment (IMBRUVICA plus rituximab, 25.8 months; rituximab plus placebo, 15.5 months), grade 3 or higher treatment-emergent AEs occurred in 60% of patients treated with IMBRUVICA plus rituxumab, versus 61% of patients treated with placebo plus rituxmab. Serious AEs occurred in 43% versus 33% of patients on IMBRUVICA plus ritxuimab compared to placebo plus rituximab. No fatal AEs occurred in the IMBRUVICA plus rituximab arm. Three fatal AEs occurred in the placebo plus rituximab arm. Meaningful reductions in any grade immunoglobin M flare (8% vs 47%) and grade 3 or higher infusion reactions were observed (1% vs 16%) with IMBRUVICA plus rituximab compared to placebo plus rituximab.

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 protein called Bruton's tyrosine kinase (BTK). The BTK protein transmits important signals that cause 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 has been used to treat more than 100,000 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.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0 to 1% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 0 to 6% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias 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%), bruising (30%), rash (30%), fatigue (29%), nausea (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%)*, stomatitis (29%), muscle spasms (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.
*Treatment-emergent decreases (all grades) were based on laboratory measurements and adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors: Dose adjustment may be recommended.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria)**:** Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose. **Please see Full Prescribing Information: https://www.imbruvica.com/prescribing-information.**

About the Janssen Pharmaceutical Companies of Johnson & Johnson

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/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Biotech, Inc. and Janssen Research & Development, LLC are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding ibrutinib. 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 known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Biotech, Inc., any of the Janssen Pharmaceutical Companies of Johnson & Johnson and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals;

uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions 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 31, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's subsequent Quarterly Reports on Form 10-Q and other 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 nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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[1] Lymphoma Research Foundation. Getting the facts: Waldenström macroglobulinemia. https://www.lymphoma.org/wp-content/uploads/2017/06/LRF_FACTSHEET_Waldenstro%CC%88m_Macroglobulinemia.pdf. Accessed June 2018.
[2] IMBRUVICA U.S. Prescribing Information, February 2018
[3] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed June 2018.