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IMBRUVICA® (ibrutinib) Plus Obinutuzumab Showed Significant Improvement in Progression-Free Survival Compared to Chlorambucil Plus Obinutuzumab in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- *Phase 3 iLLUMINATE results featured as oral presentation at ASH 2018 (abstract #691) and simultaneously published in The Lancet Oncology*
- *Data served as the basis for a recent sNDA to the U.S. FDA, which received Priority Review designation*
- *Also presented at ASH were study results from up to seven years of follow-up of IMBRUVICA monotherapy in CLL/SLL, the longest follow-up study for a BTK inhibitor in CLL/SLL (abstract #3133)*

SAN DIEGO, December 3, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced results from the Phase 3 iLLUMINATE (PCYC-1130) study, which showed the combination of IMBRUVICA® (ibrutinib) plus obinutuzumab significantly improved progression-free survival (PFS) versus chlorambucil plus obinutuzumab in patients

with newly diagnosed chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), the most common form of leukemia in adults.[1,2] In addition, IMBRUVICA data from the Phase 1b/2 study and its extension study (PCYC-1102, PCYC-1103) with up to seven years of follow-up in patients with newly diagnosed and relapsed/refractory (R/R) CLL/SLL, demonstrated durable, long-term survival benefits as a monotherapy, representing the longest follow-up for a Bruton's tyrosine kinase (BTK) inhibitor in CLL/SLL. IMBRUVICA, a BTK inhibitor studied in patients with CLL for up to seven years, is jointly developed and commercialized by Janssen Biotech, Inc., and Pharmacyclics LLC, an AbbVie company.[3]

"These long-term results suggest that 80 percent of newly diagnosed patients with chronic lymphocytic leukemia receiving IMBRUVICA monotherapy sustained remission through seven years without chemotherapy. Together with the iLLUMINATE study findings, these data provide compelling evidence to consider IMBRUVICA as a single agent or combination option for appropriate newly diagnosed patients with CLL," said Craig Tendler, M.D., Vice President, Clinical Development and Global Medical Affairs, Janssen Research & Development, LLC. "Since its first approval more than five years ago, IMBRUVICA has been regarded as an important treatment in CLL, and we continue to study and pursue its full potential across the spectrum of blood cancers through our comprehensive clinical development programs."

The iLLUMINATE data were presented today in an oral session at the 2018 American Society of Hematology (ASH) Annual Meeting and simultaneously published in *The Lancet Oncology*. On October 16, the U.S. Food and Drug Administration (FDA) granted Priority Review for a supplemental New Drug Application (sNDA) seeking to expand the use of IMBRUVICA to include combination with obinutuzumab in CLL/SLL.

Phase 3 data supporting IMBRUVICA plus obinutuzumab in CLL/SLL featured as oral presentation at ASH 2018 (Abstract #691)

At a median follow-up of 31.3 months, IMBRUVICA plus obinutuzumab significantly prolonged the Independent Review Committee (IRC)-assessed PFS compared with chlorambucil plus obinutuzumab (median not reached [NR] vs. 19.0 months; HR 0.23; 95 percent confidence interval [CI]: 0.15-0.37; P<0.0001), with a 77 percent reduction in risk of progression or death.

Superior PFS in the IMBRUVICA plus obinutuzumab arm compared to the chlorambucil plus obinutuzumab arm was also seen in the high-risk population, including those with unmutated IGHV, del11q, del17p and/or TP53 mutation, with an 85 percent reduction in risk of progression or death (median NR vs. 14.7 months; HR 0.15; 95 percent CI: 0.09-0.27; P<0.0001). In addition, IRC-assessed overall response rate (ORR) was higher in the IMBRUVICA plus obinutuzumab arm versus the chlorambucil plus obinutuzumab arm (88 percent vs. 73 percent); complete response (CR)/complete response with incomplete blood recovery (CRi) rates were also higher with 19 percent versus 8 percent, respectively. Minimal residual disease (MRD) was undetectable in blood and/or bone marrow ($<10^{-4}$ by flow cytometry) for 35 percent of patients treated with IMBRUVICA plus obinutuzumab, compared to 25 percent of patients treated with chlorambucil plus obinutuzumab. Overall survival (OS) rates at 31 months were 86 percent for the IMBRUVICA plus obinutuzumab arm compared to 85 percent for the chlorambucil plus obinutuzumab arm.

The most common Grade 3 or higher adverse events (AEs) in the IMBRUVICA plus obinutuzumab arm versus chlorambucil plus obinutuzumab arm were neutropenia (43 percent vs. 63 percent), thrombocytopenia (35 percent vs. 25 percent), diarrhea (34 percent vs. 10 percent), cough (27 percent vs. 12 percent), infusion-related reactions (IRRs; 25 percent vs. 58 percent), arthralgia (22 percent vs. 10 percent), pyrexia (19 percent vs. 26 percent), anemia (17 percent vs. 25 percent), and nausea (12 percent vs. 30 percent). No patients discontinued obinutuzumab due to IRRs in the IMBRUVICA plus obinutuzumab arm compared to the chlorambucil plus obinutuzumab arm (6 percent). AEs led to the discontinuation of IMBRUVICA in 16 percent of patients and led to the discontinuation of chlorambucil in 9 percent of patients. AEs led to the discontinuation of obinutuzumab in the IMBRUVICA plus obinutuzumab arm (9 percent) and chlorambucil plus obinutuzumab arm (13 percent). With about three years of follow-up, 70 percent of patients in the IMBRUVICA plus obinutuzumab arm remain on IMBRUVICA monotherapy.

"With 2.5 years of follow-up, results from the iLLUMINATE study showed significantly prolonged progression-free survival of IMBRUVICA plus obinutuzumab versus a commonly used chemoimmunotherapy regimen in chronic lymphocytic leukemia," said Carol Moreno, M.D., Ph.D., Consultant Hematologist, Hospital de la Santa Creu Sant Pau, Autonomous University of Barcelona, Barcelona, Spain, and lead investigator of the iLLUMINATE study. "IMBRUVICA plus obinutuzumab represents an important advance and a welcome potential new combination regimen for patients living with CLL."

iLLUMINATE (PCYC-1130) evaluated newly diagnosed patients with CLL/SLL who were randomized to receive IMBRUVICA 420 mg once-daily continuously until disease progression or unacceptable toxicity in combination with obinutuzumab 1000 mg intravenously over 6 cycles (n=113), or chlorambucil on Days 1 and 15 of each cycle plus obinutuzumab 1000 mg intravenously over 6 cycles (n=116). Median age of the patients was 71 years and 65 percent of the patients had high-risk genomic features.

Up to seven years of follow-up showed durable, long-term survival benefits of IMBRUVICA monotherapy for patients with newly diagnosed and R/R CLL/SLL (Abstract #3133)

With up to seven years of follow-up, the studies (Phase 1b/2, PCYC-1102 and its extension, PCYC-1103) evaluated newly diagnosed and R/R patients with CLL/SLL (n=132; newly diagnosed=31, R/R=101), including those with high-risk features who received 420 mg or 840 mg once-daily IMBRUVICA until disease progression or unacceptable toxicity. As of the cutoff, 55 percent of newly diagnosed and 21 percent of R/R patients continued IMBRUVICA with median follow-up of 67 months.

Results from these studies showed durable efficacy of IMBRUVICA in newly diagnosed and R/R patients with CLL/SLL. These long-term data showed sustained PFS and OS rates. The estimated seven-year PFS rates were 80 percent for patients with newly diagnosed disease and 32 percent for patients with R/R disease. Notably, administering IMBRUVICA in earlier lines of therapy resulted in improved PFS outcomes for R/R patients.

ORR was 89 percent for all patients (CR, 15 percent) with similar rates in newly diagnosed (87 percent [CR, 32 percent]) and R/R CLL/SLL patients (89 percent [CR, 10 percent]). Median duration of response (DOR) was NR (95 percent CI: 0+-85+) for newly diagnosed CLL/SLL patients and was 57 months (95 percent CI: 0+-85+) for R/R CLL/SLL patients. Median PFS was NR (95 percent CI: NE, NE) for newly diagnosed CLL/SLL patients and was 51 months (95 percent CI: 37-70) for R/R CLL/SLL patients. The median OS was NR in newly diagnosed (95 percent CI: 80-NE) or R/R CLL/SLL patients (95 percent CI: 63-NE) with estimated 7-year OS rates of 75 percent and 52 percent, respectively.

Grade 3 or higher AEs were reported in 74 percent of newly diagnosed and 89 percent of R/R patients with CLL/SLL. Hypertension (newly diagnosed, 32 percent; R/R, 26 percent), diarrhea (newly diagnosed, 16 percent; R/R, 4 percent), and hyponatremia (newly diagnosed, 10 percent; R/R, 0 percent) were among the most common Grade 3 or higher treatment-emergent AEs. Major hemorrhage and Grade 3 or higher atrial fibrillation, thrombocytopenia, anemia, and arthralgia were observed in 11 percent or less of newly diagnosed and R/R patients. In addition, infection (newly diagnosed, 23 percent; R/R, 55 percent) was more common in R/R CLL/SLL patients. No new or unexpected AEs were observed, and the occurrence of most Grade 3 or higher AEs and serious AEs decreased over time, with the exception of hypertension.

About IMBRUVICA

IMBRUVICA (ibrutinib) is a first-in-class, once-daily oral medicine that works differently than chemotherapy as it blocks the Bruton's tyrosine kinase (BTK) protein. The BTK protein sends important signals that tell B cells to mature and produce antibodies; BTK signaling is needed by specific cancer cells to multiply and spread.[4,5] By blocking BTK, IMBRUVICA may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs.[6,7]

IMBRUVICA is approved in more than 90 countries, and, to date, has been used to treat more than 135,000 patients worldwide across approved indications. It was first approved by the U.S. Food and Drug Administration in 2013, and today is indicated in six disease areas, including five hematologic cancers – chronic lymphocytic leukemia (CLL) with or without 17p deletion (del17p), small lymphocytic lymphoma (SLL) with or without del17p, Waldenström's macroglobulinemia (WM), previously-treated patients with mantle cell lymphoma (MCL)*, previously-treated patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy* – and previously-treated patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.[7]

IMBRUVICA is the first and only FDA-approved medicine in WM, MZL* and cGVHD. IMBRUVICA has been granted four Breakthrough Therapy Designations by the FDA, and it was one of the first medicines to receive U.S. approval through the Breakthrough Therapy Designation.

IMBRUVICA is a comprehensively studied molecule in the oncology industry. The robust clinical oncology development program includes more than 150 active clinical trials studying IMBRUVICA alone and in combination with other medicines in several blood cancers and other serious diseases. For more information, visit www.IMBRUVICA.com.

** Accelerated approval was granted for MCL and MZL based on overall response rate. Continued approval for MCL and MZL may be contingent upon verification and description of clinical benefit in confirmatory trials.*

Additional Information about IMBRUVICA®

INDICATIONS

IMBRUVICA is indicated to treat adults with[3]

- 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 3%

of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to IMBRUVICA® in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% 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 24% of 1,011 patients exposed to IMBRUVICA® in clinical trials. 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 (23%), thrombocytopenia (8%), and anemia (3%) 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 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to IMBRUVICA® in clinical trials. 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 has occurred in 12% of 1,011 patients treated with IMBRUVICA® in clinical trials with a median time to onset of 5 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 (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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 (58%)*, neutropenia (58%)*, diarrhea (42%), anemia (39%)*, rash (31%), musculoskeletal pain (31%), bruising (31%), nausea (28%), fatigue (27%), hemorrhage (23%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (36%)*, thrombocytopenia (15%)*, and pneumonia (10%).

Approximately 6% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] 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 adjustments 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 click here for full 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 @JanssenGlobal and @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 a new improved indication for 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 Research & Development, LLC, 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," in the company's most recent Quarterly Report on Form 10-Q and the company's 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. Neither 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.

# # #

[1] Moreno C., et al. Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab As First-Line Treatment in Patients with Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL): Results from Phase 3 iLLUMINATE. ASH 2018. Abstract #691.
[2] American Cancer Society. What Is Chronic Lymphocytic Leukemia? https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html. Accessed December 2018.
[3] Byrd, et al. ASH 2018 Abstract #3133.
[4] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed December 2018.
[5] Turetsky, et al. Single cell imaging of Bruton's Tyrosine Kinase using an irreversible inhibitor. Scientific Reports. volume 4, Article number: 4782 (2014)
[6] e Rooij MF, Kuil A, Geest CR, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood. 2012;119(11):2590-2594.
[7] IMBRUVICA U.S. Prescribing Information, August 2018.