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IMBRUVICA® (ibrutinib) Combination Therapy Data From Two Studies and Long-Term Integrated Analysis Presented at ASH 2019 Show Efficacy and Safety in First-Line Treatment of Chronic Lymphocytic Leukemia

- *Follow-up data from Phase 3 E1912 study (Abstract #33) evaluating the investigational use of IMBRUVICA® in combination with rituximab versus fludarabine, cyclophosphamide and rituximab showed statistically significant difference in progression-free survival (PFS) and overall survival (OS) were maintained in previously untreated patients (ages 70 or younger) with chronic lymphocytic leukemia (CLL)*
- *Integrated analysis from RESONATE™ and RESONATE™-2 studies in CLL (Abstract #3054) reported long-term PFS, OS and response rates with earlier treatment with IMBRUVICA®*
- *IMBRUVICA® plus venetoclax data from Phase 2 CAPTIVATE study (Abstract #35) showed high rates of undetectable minimal residual disease (uMRD) in peripheral blood (75 percent of patients) and in bone marrow (72 percent of patients) in previously untreated patients with CLL for time-limited, MRD-guided combination regimen*

ORLANDO, Fla., December 7, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced combination data from two studies and a long-term integrated analysis evaluating the use of IMBRUVICA® (ibrutinib) for the treatment of previously untreated patients with CLL or small lymphocytic lymphoma (SLL). Results from a 48-month follow-up analysis of the Phase 3 E1912 clinical study reported a statistically significant difference in PFS and OS for IMBRUVICA® plus rituximab compared to a standard chemoimmunotherapy regimen of fludarabine, cyclophosphamide and rituximab (FCR). Further, the latest integrated analysis from the Phase 3 RESONATE™ (PCYC-1112) and RESONATE™-2 (PCYC-1115/1116) studies investigating the use of single-agent IMBRUVICA® in CLL, reported that at up to six years of follow-up, PFS, OS and response rates improved when IMBRUVICA® was used in earlier lines of therapy. During this extended follow-up, IMBRUVICA® was tolerated across all lines of therapy with 19 percent of patients discontinuing due to adverse events.

In addition, results presented from the Phase 2 CAPTIVATE study suggest that patients who received IMBRUVICA® plus venetoclax as a time-limited treatment achieved high rates of uMRD in peripheral blood (75 percent of patients) and bone marrow (72 percent of patients).

These new findings from the E1912, RESONATE™/RESONATE™-2 and CAPTIVATE studies were presented at the 2019 American Society of Hematology (ASH) Annual Meeting.

"We're pleased to see follow-up results from the Phase 3 E1912 trial, where the investigational use of IMBRUVICA plus rituximab is shown to extend OS for previously untreated patients with CLL. In addition, with the integrated analysis of the Phase 3 RESONATE and RESONATE-2 studies, IMBRUVICA demonstrated an OS benefit in untreated and relapsed patients with improved outcomes in early lines of therapy," said Craig Tendler, M.D., Vice President, Clinical Development and Global Medical Affairs, Oncology, Janssen Research & Development, LLC. "We are also excited to see the first MRD data from the fixed-duration regimen of IMBRUVICA plus venetoclax in the Phase 2 CAPTIVATE trial, reporting a high rate of undetectable MRD at 15 months both in the peripheral blood and bone marrow."

E1912 extended follow-up of investigational use of IMBRUVICA® plus rituximab compared to FCR in patients with CLL/SLL ages 70 or younger (Abstract #33)

Longer-term outcomes data from the Phase 3 E1912 clinical trial – designed and conducted by the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) and sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health – were also presented. As previously reported in earlier data readouts, the study evaluated 354 previously untreated patients with CLL ages 70 years or younger who were randomly assigned to receive IMBRUVICA® and rituximab or six courses of intravenous FCR every 28 days.

At a median follow-up of 48 months, 73 percent of patients in the IMBRUVICA® plus rituximab treatment arm remained on IMBRUVICA® with median time on treatment of 43 months. PFS benefits were observed for the IMBRUVICA® plus rituximab arm as compared to the FCR treatment arm (hazard ratio [HR], 0.39; 95 percent confidence interval [CI], 0.26-0.57; p<0.0001). OS benefit also continued to favor the IMBRUVICA® plus rituximab arm (HR, 0.34; 95 percent CI, 0.15-0.79; p=0.009).

Grade 3 and above treatment-related adverse events (AEs) were observed in 70 percent of patients in the IMBRUVICA® plus rituximab arm versus 80 percent in the FCR arm (odds ratio [OR], 0.56; 95 percent CI, 0.34-0.90; p=0.013).

The E1912 study served as the basis of the recent supplemental New Drug Application to the U.S. Food and Drug Administration (FDA) to expand the IMBRUVICA® label to include the combination with rituximab for the first-line treatment of patients with CLL or SLL. The submission is being reviewed by the FDA under the Real-Time Oncology Review (RTOR) pilot program.

MRD cohort of the Phase 2 CAPTIVATE study on IMBRUVICA® plus venetoclax combination in patients with previously untreated CLL/SLL (Abstract #35)

The Phase 2 CAPTIVATE (PCYC-1142) clinical trial evaluated 164 patients younger than 70 years (median age of 58 years) with previously untreated CLL/SLL. Patients received IMBRUVICA® monotherapy as lead-in treatment for three cycles, followed by 12 cycles of IMBRUVICA® plus venetoclax combination therapy. MRD status was evaluated in peripheral blood (PB) after six, nine, and 12 cycles and in bone marrow (BM) after 12 cycles of IMBRUVICA® plus venetoclax.

"The new results from the CAPTIVATE study demonstrated the all-oral regimen of ibrutinib monotherapy followed by combined ibrutinib and venetoclax achieved promising rates of

undetectable minimal residual disease, an important indicator of deep response, in previously untreated patients with CLL," said Constantine Tam, M.D., Hematologist and Disease Group Lead, Low Grade Lymphoma and CLL, Peter MacCallum Cancer Centre, Victoria, Australia, and principal study investigator. "We look forward to continuing to explore the efficacy and safety profile of this regimen and its potential to provide a limited-duration option in first-line treatment of CLL."

Results showed undetectable MRD (uMRD) – defined as less than one CLL cell per 10,000 leukocytes (MRD<0.01 percent) by flow cytometry– was achieved at any time after baseline in PB for 75 percent of patients (122 of 163 patients) and in BM for 72 percent (111 of 155 patients). The high rates of uMRD in BM were consistent across high-risk subgroups, including in patients with del(17p); del(17p) or TP53 mutation; del(11q); complex karyotype; and unmutated IGHV status. In patients with uMRD in PB with matched BM samples, 93 percent of patients had uMRD in both PB and BM. With median follow-up of 14.7 months, three patients (2 percent) experienced disease progression.

The most common AEs of any grade (in 20 percent of patients or greater) were diarrhea (31 percent) and arthralgia (22 percent) during treatment with IMBRUVICA® alone; and diarrhea (60 percent), neutropenia (40 percent), nausea (34 percent), upper respiratory tract infection (24 percent), and fatigue (20 percent) during treatment with IMBRUVICA® plus venetoclax. AEs leading to dose reductions occurred in 20 percent of patients overall. AEs leading to discontinuation were infrequent, occurring in 7 percent of patients overall (IMBRUVICA®: 5 percent; venetoclax: 4 percent).

Results from the MRD-guided, randomized treatment discontinuation cohort and fixed-duration cohort of the CAPTIVATE clinical trial are being further evaluated and will be presented at a future medical meeting.

About IMBRUVICA®

IMBRUVICA® is a once-daily, first-in-class Bruton's tyrosine kinase (BTK) inhibitor that is administered orally, and is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company. IMBRUVICA® blocks the 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.[1,2] By blocking BTK,

IMBRUVICA® may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs.[3]

IMBRUVICA® is the most comprehensively studied molecule in the class with more than 150 ongoing clinical trials and four Phase 3 studies supporting the U.S. label. It is approved in more than 95 countries for at least one indication, and to date, has been used to treat more than 170,000 patients worldwide across approved indications. It was first approved by the U.S. Food and Drug Administration (FDA) in November 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.[4]

** 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.*

As of early 2019, the National Comprehensive Cancer Network® (NCCN®), a not-for-profit alliance of 28 leading cancer centers devoted to patient care, research, and education, recommends ibrutinib (IMBRUVICA®) as a preferred regimen for the initial treatment of CLL/SLL, and it is the only Category 1 single-agent regimen for treatment-naïve patients without deletion 17p. IMBRUVICA® is the only FDA-approved medicine in WM 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 with the Breakthrough Therapy Designation.

For more information, visit www.IMBRUVICA.com.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA® in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. In IMBRUVICA® clinical trials, 3.1% of patients taking IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms 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 1,124 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 1,124 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 of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 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%)*, diarrhea (41%), anemia (38%)*, neutropenia (35%)*, musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), 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 (18%)*, thrombocytopenia (16%)*, and pneumonia (14%).

Approximately 7% (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%)*, muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%)*, and pneumonia (21%).

The most common Grade 3 or higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (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.

DRUG INTERACTIONS

CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.4 and 7.1.

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 Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

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Cautions Concerning Forward-Looking Statements
This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding IMBRUVICA® (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 other Janssen Pharmaceutical Companies 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 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed 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. 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] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed December 2019.
[2] Turetsky, A, et al. Single cell imaging of Bruton's tyrosine kinase using an irreversible inhibitor. *Scientific Reports*. 2014;6:4782.
[3] de 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.
[4] IMBRUVICA U.S. Prescribing Information, September 2019.