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**New Data Demonstrate Long-Term Benefit of IMBRUVICA® (ibrutinib)  
as First-Line Treatment for High-Risk Chronic Lymphocytic Leukemia**

*IMBRUVICA® pooled clinical trial analyses presented at ASH demonstrate sustained efficacy and safety in patients with historically poor outcomes*

*Data from real-world evidence studies featured as oral presentations highlight the benefit of IMBRUVICA®-based therapies in the first-line setting*

**December 6, 2020 (RARITAN, N.J.)** – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today results from pooled analyses of long-term follow-up from multiple clinical trials evaluating the use of IMBRUVICA® (ibrutinib) monotherapy and in combination as first-line treatment for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with high-risk features. The data were presented at the American Society of Hematology (ASH) Annual Meeting. Results from an integrated analysis of two clinical trials with up to 79 months of follow-up ([Abstract #2220](#))<sup>1</sup> demonstrated similar progression-free survival (PFS) and overall response rates (ORR) with IMBRUVICA® in patients with or without high-risk genomic features, and further showed significant PFS and ORR benefits with IMBRUVICA® compared with chlorambucil-based therapy regardless of genomic risk features.<sup>1</sup>

In addition, data with a median follow-up of more than four years were presented from a pooled analysis of 89 patients with high-risk CLL bearing TP53 aberrations from four clinical trials showing that first-line treatment with IMBRUVICA® resulted in sustained efficacy, including PFS, suggesting that IMBRUVICA® has meaningfully improved the poor prognosis in this high-risk population ([Abstract #2219](#)).<sup>2</sup>

“These large integrated data sets with follow-up up to six years, in addition to other data presented at the meeting in similar populations, contribute to the accumulating evidence supporting the clinically meaningful, long-term treatment benefit of IMBRUVICA as first-line therapy for patients with CLL,” said Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs, Oncology, Janssen Research & Development, LLC. “IMBRUVICA is an approved standard of care in first-line treatment of CLL, and the data presented at the ASH Annual Meeting further demonstrate the durability of responses in CLL patients with traditional high-risk features.”

Two additional studies will be presented in the oral sessions showing real-world treatment patterns or outcomes in patients with CLL treated outside of a clinical trial setting. The first study is a U.S. retrospective analysis describing treatment patterns and time to next treatment (TTNT) in patients with high-risk CLL treated with first-line IMBRUVICA® or chemoimmunotherapy (CIT) ([Abstract #372](#)).<sup>3</sup> In this U.S. retrospective study, the largest of its kind to date, patients with high-risk CLL treated with single-agent IMBRUVICA® had significantly longer TTNT compared with patients treated with first-line CIT.<sup>3</sup> In the second oral presentation, results from the U.S. informCLL™ registry ([Abstract #547](#)) highlighted infrequent prognostic biomarker testing rates prior to initiating CLL therapy, and limited use of such information to guide optimal treatment selection for many patients with high-risk CLL, suggesting an opportunity for additional education of healthcare providers.<sup>4</sup>

### **Integrated Analysis of the Phase 3 RESONATE-2 and iLLUMINATE Trials Evaluated Outcomes of First-Line IMBRUVICA® in Patients with CLL and High-Risk Genomic Features with up to 6.5 Years Follow-up ([Abstract #2220](#))**

Data were presented from a pooled analysis of two Phase 3 studies (RESONATE-2 and iLLUMINATE) with up to 79 months of follow-up evaluating IMBRUVICA®-based therapy in first-line treatment of CLL/SLL patients with various high-risk genomic features.<sup>1</sup>

#### **Key Study Findings:**

- In patients treated with IMBRUVICA<sup>®</sup>-based therapy, PFS was comparable between patients with versus without specified high-risk genomic features, including del(17p)/TP53 mutated/BIRC3 mutated, the highest risk category.<sup>1</sup>
- At 42 months, PFS rates were significantly higher across all high-risk genomic subgroups in previously untreated patients treated with IMBRUVICA<sup>®</sup>-based treatment (63 to 82 percent) compared with those receiving chlorambucil-based treatment (6 to 34 percent) with or without obinutuzumab, regardless of mutation.<sup>1</sup>
- At a median duration of IMBRUVICA<sup>®</sup> treatment of 35.7-43.8 months across high-risk subgroups, there were no meaningful differences in the rates of treatment-emergent adverse events (AEs) of any Grade, or Grade 3 or greater AEs compared to those of the overall population.<sup>1</sup>

“Certain genomic abnormalities and mutations are predictors of inferior outcomes with chemoimmunotherapy in patients with CLL,” said Jan A. Burger, M.D., Ph.D., Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, and principal study investigator. “Chemoimmunotherapy remains common in real-world practice despite evidence that shows small molecule inhibitor therapies like ibrutinib have demonstrated improved outcomes in high-risk patients compared to chemoimmunotherapy.”

**Large, Pooled, Multi-Study Dataset Assessed Long-Term Benefit of First-Line IMBRUVICA<sup>®</sup>-Based Treatment in Patients with TP53 Aberrations with up to Four Years Follow-up ([Abstract #2219](#))**

Data were presented from a pooled analysis of four clinical studies evaluating the long-term efficacy and safety of first-line IMBRUVICA<sup>®</sup>-based therapy in CLL patients with TP53 aberrations present.<sup>2</sup> The four studies are: RESONATE-2; iLLUMINATE; the E1912 study 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 (NIH); and the 1122e study sponsored by the National Heart, Lung, and Blood Institute (NHLBI).<sup>2</sup>

**Key Study Findings:**

- With a median follow-up of 50 months, median PFS was not reached (95% CI: 67 months to not estimable).<sup>2</sup> At 48 months, the PFS rate was 79 percent and the OS rate was 88 percent among high-risk patients treated with IMBRUVICA<sup>®</sup> monotherapy.<sup>2</sup>

- Additionally, 46 percent of patients with TP53 aberrations remained on IMBRUVICA® treatment and 39 percent had a complete response.<sup>2</sup>
- No new safety signals were identified in this analysis and in general the rates of Grade ≥3 AEs of clinical interest declined after the first year of ibrutinib treatment.<sup>2</sup>

**Clinical Outcomes Among Real-World Patients with CLL Initiating First-Line IMBRUVICA® or Chemoimmunotherapy Stratified by Risk Status: Results From a U.S. Retrospective Chart Review Study ([Abstract #372](#))**

Data were presented as an oral presentation from a large real-world study comparing clinical outcomes (TTNT) in high-risk and non-high-risk patients with CLL receiving IMBRUVICA® compared to CIT in the first-line setting.<sup>3</sup>

**Key Study Findings:**

- Data presented showed that high-risk patients receiving IMBRUVICA® significantly prolonged TTNT compared to those receiving CIT.<sup>3</sup>
- IMBRUVICA® also provided sustained clinical benefit regardless of risk status, which is consistent with clinical trial results.<sup>5,6,7</sup>
- This study highlighted the need for cytogenetic/molecular testing before CIT treatment, consistent with clinical treatment guidelines.<sup>8,9</sup>

**Real-World Prognostic Biomarker Testing, Treatment Patterns, And Dosing Among Patients With CLL/SLL From the informCLL™ Prospective Observational Registry ([Abstract #547](#))**

An oral presentation on Monday, December 7, will feature results from the informCLL™ real-world prospective observational registry assessing treatment patterns in the era of novel agents.<sup>4</sup>

**Key Study Findings:**

- The most common index treatment was IMBRUVICA®; the majority of patients treated with IMBRUVICA® remained on therapy at two-year follow-up; and CIT was also used for one-third of patients.<sup>4</sup>
- Data also demonstrated that prognostic biomarker testing rates were poor, especially for high-risk patients harboring TP53 and IGHV mutational status.<sup>4</sup>

- Data from informCLL™ also indicate a 'knowledge gap' in terms of prognostic marker testing, interpretation and selection of optimal therapies for patients with high-risk disease.

### **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.<sup>10,11</sup> By blocking BTK, IMBRUVICA® may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow and other organs.<sup>12</sup>

IMBRUVICA® is the most comprehensively studied BTK inhibitor, with more than 150 ongoing clinical trials and five Phase 3 studies supporting the U.S. label. Ongoing clinical trials for IMBRUVICA® include six pivotal Phase 3 trials in CLL, including more than five years of efficacy, safety and tolerability data. It is also the only BTK inhibitor with long-term data in the U.S. label demonstrating progression-free survival in large randomized clinical trials.

IMBRUVICA® is approved in more than 100 countries for at least one indication, and, to date, has been used to treat more than 200,000 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 del 17p, 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.<sup>13</sup>

*\*\* 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. The NCCN also updated its guidelines as of February 2020 to elevate IMBRUVICA® with or without rituximab from “other recommended regimens” to a “preferred regimen” for the treatment of relapsed/refractory MCL.

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](http://www.IMBRUVICA.com).

## **IMBRUVICA® IMPORTANT SAFETY INFORMATION**

### **WARNINGS AND PRECAUTIONS**

**Hemorrhage:** Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage ( $\geq$  Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events, including bruising and petechiae, occurred in 39% of patients who received 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. Across clinical trials, 3.1% of 2,838 patients who received 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 21% of 1,476 patients who received 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:** In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, Grade 3 or 4 neutropenia occurred in 23% of patients, Grade 3 or 4 thrombocytopenia in 8% and Grade 3 or 4 anemia in 3%, based on laboratory measurements.

Monitor complete blood counts monthly.

**Cardiac Arrhythmias:** Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA®. 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 1,476 patients who received 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 occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 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%), occurred among the 1,476 patients who received 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®. 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 pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

## **ADVERSE REACTIONS**

**B-cell malignancies:** The most common adverse reactions ( $\geq 30\%$ ) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)\*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)\*, rash (35.8%), anemia (35.0%)\*, and bruising (32.0%).

The most common Grade  $\geq 3$  adverse reactions ( $\geq 5\%$ ) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)\*, thrombocytopenia (13.6%)\*, pneumonia (8.2%), and hypertension (8.0%). Approximately 9% (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 ( $\geq 20\%$ ) 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 ( $\geq 5\%$ ) 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.

**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  $\leq 7$  days). See dose modification guidelines in USPI sections 2.3 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 recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

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.

Learn more at [www.janssen.com](http://www.janssen.com). Follow us at [@JanssenUS](#) and [@JanssenGlobal](#). Janssen Research & Development, LLC and Janssen Biotech, Inc. 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 product development and the potential benefits and treatment impact of 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 or 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 29, 2019, 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](http://www.sec.gov), [www.jnj.com](http://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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<sup>1</sup> Burger JA. et al. Outcomes of first-line ibrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and high-risk genomic features with up to 6.5 years follow-up: integrated analysis of two phase 3 studies (RESONATE-2 and iLLUMINATE). 2020 American Society of Hematology Annual Meeting. December 2020.

<sup>2</sup> Allan JN. et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukemia (CLL) with 4 years of follow-up in patients with TP53 aberrations (del(17p) or TP53 mutation): a pooled analysis from 4 clinical trials. 2020 American Society of Hematology Annual Meeting. December 2020.

<sup>3</sup> Lori LA. et al. Clinical outcomes among real-world patients with chronic lymphocytic leukemia (CLL) initiating first-line ibrutinib or chemoimmunotherapy stratified by risk status: results from a US retrospective chart review study. 2020 American Society of Hematology Annual Meeting. December 2020.

<sup>4</sup> Mato A. et al. Real-world prognostic biomarker testing, treatment patterns and dosing among 1461 patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) from the informCLL™ prospective observational registry. 2020 American Society of Hematology Annual Meeting. December 2020.

<sup>5</sup> Woyach JA. et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *The New England Journal of Medicine*. 2018; 379:2517-2528.

<sup>6</sup> Moreno C. et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncology*. 2019; 20:43-56.

<sup>7</sup> Shanafelt TD. et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. *The New England Journal of Medicine*. 2019; 381:432-443.

<sup>8</sup> Weirda WG. et al. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 4.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2020 Feb;18(2):185-217.

<sup>9</sup> Hallek M. et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018; 131:2745-2760.

<sup>10</sup> Genetics Home Reference. Isolated growth hormone deficiency. <http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency>. Accessed April 2020.

<sup>11</sup> Turetsky A, et al. Single cell imaging of Bruton's tyrosine kinase using an irreversible inhibitor. *Scientific Reports*. 2014;6:4782.

<sup>12</sup> 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.

<sup>13</sup> IMBRUVICA U.S. Prescribing Information, April 2020.