

**News Release**

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**IMBRUVICA® (ibrutinib)-Based Combination Regimen as a Fixed-Duration, First-Line Treatment for Chronic Lymphocytic Leukemia Demonstrates High Rates of Disease Control**

*Janssen presents new data at ASCO showing efficacy of IMBRUVICA® plus venetoclax (CAPTIVATE study) in previously untreated patients with chronic lymphocytic leukemia, and up to seven-year follow-up results (RESONATE-2 study) on progression-free and overall survival benefits with single-agent IMBRUVICA®*

**May 19, 2021 (RARITAN, N.J.)** – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced new data from the fixed-duration cohort of the investigational Phase 2 CAPTIVATE study, showing that 95 percent of patients treated with combined IMBRUVICA® plus venetoclax were alive and progression-free at two years.<sup>1</sup> Deep remissions were seen across all subgroups, including patients with high-risk chronic lymphocytic leukemia (CLL).<sup>1</sup> In addition, long-term data from the RESONATE-2 ([PCYC-1115/1116](#)) study will be presented, providing the longest follow-up Phase 3 data for any BTK inhibitor to date. These data reinforce the long-term survival benefits and well-established safety profile of single-agent IMBRUVICA® for patients with CLL.<sup>2</sup> The data will be presented during the 2021 American Society of Clinical Oncology (ASCO) Annual

Meeting, June 4-8.

**First Data from the Fixed-Duration Cohort of the Phase 2 CAPTIVATE (PCYC-1142) Study of IMBRUVICA®-Based Combination Regimen in Previously Untreated CLL Patients ([Abstract #7501](#))<sup>1</sup>**

The CAPTIVATE study evaluated previously untreated CLL/small lymphocytic lymphoma (SLL) patients 70 years or younger, including patients with high-risk disease.<sup>1</sup> In the fixed-duration cohort (N=159; median age, 60 years), all patients received three months of IMBRUVICA® lead-in therapy followed by 12 months of combination IMBRUVICA® plus venetoclax therapy and then stopped therapy regardless of minimal residual disease (MRD) status.<sup>1</sup> More than 90 percent of patients completed 12 cycles of IMBRUVICA® plus venetoclax treatment.<sup>1</sup>

At a median follow-up of 27.9 months, the complete response (CR) rate in the overall population was 56 percent (n=88; 95 percent Confidence Interval [CI], 48–64) and was consistent across high-risk subgroups.<sup>1</sup> Of the patients who achieved a CR, 89 percent had a durable CR of at least one year.<sup>1</sup> Among the remaining 11 percent, one patient had progressive disease; the remaining patients with response follow-up of less than one year were not evaluable.<sup>1</sup> The overall response rate (ORR) was 96 percent.<sup>1</sup> Estimated 24-month progression-free survival (PFS) with IMBRUVICA® plus venetoclax was 93 percent for patients with unmutated IGHV and 97 percent for patients with mutated IGHV (unmutated IGHV 95 percent CI, 85–97; mutated IGHV 95 percent CI, 88–99) and overall survival (OS) was 98 percent (95 percent CI, 94–99) for all treated patients.<sup>1</sup> Seventy-seven and 60 percent of patients achieved undetectable minimal residual disease (uMRD) at any time in the peripheral blood and bone marrow, respectively.<sup>1</sup>

“The use of continuous treatment with IMBRUVICA in CLL has well been established as the standard-of-care for patients, including those with high-risk disease,” said Paolo Ghia<sup>†</sup>, M.D., Ph.D., Professor of Medical Oncology, Università Vita-Salute San Raffaele, Italy and principal study investigator. “The latest data from the CAPTIVATE study underscore that IMBRUVICA in an all-oral fixed-duration combination with venetoclax also delivers a high rate of progression-free survival at two years while enabling treatment-free remission for patients.”

Of note, 94 percent of patients with high baseline tumor lysis syndrome (TLS) risk based on tumor burden shifted to medium- or low-risk after IMBRUVICA® lead-in therapy, and no TLS events occurred.<sup>1</sup> Adverse events (AEs) were primarily Grade 1/2.<sup>1</sup> The most common Grade 3/4 AEs were neutropenia (33 percent), infections (eight percent), hypertension (six percent), and neutrophil count decrease (five percent).<sup>1</sup> Discontinuations due to AEs were infrequent (three percent for IMBRUVICA®).<sup>1</sup>

Findings from the uMRD-guided cohort of the CAPTIVATE study were [presented](#) at the 2020 American Society of Hematology (ASH) Annual Meeting. The Phase 3 GLOW study ([NCT03462719](#)) is also evaluating fixed-duration IMBRUVICA® plus venetoclax, with a comparison to chlorambucil plus obinutuzumab, for first-line treatment of elderly or younger unfit patients with CLL or SLL. These studies are part of a comprehensive development program exploring the potential of IMBRUVICA®-based fixed-duration therapy.

**Long-Term Data from the Phase 3 RESONATE-2 Study Demonstrate Efficacy and Safety of Single-Agent IMBRUVICA® in Previously Untreated CLL Patients ([Abstract #7523](#))<sup>2</sup>**

The RESONATE-2 study evaluated 269 previously untreated patients with CLL ages 65 years or older, without del(17p), who were randomly assigned to receive continuous IMBRUVICA® or chlorambucil up to 12 cycles.<sup>2</sup> With up to seven years of follow-up, PFS benefit with single-agent IMBRUVICA® was sustained (PFS Hazard Ratio [HR] 0.160 [95 percent CI, 0.111–0.230]).<sup>2</sup> At 6.5 years, the median PFS with IMBRUVICA® has not been reached; 61 percent of patients treated with single-agent IMBRUVICA® were alive and progression-free compared with nine percent of patients treated with chlorambucil.<sup>2</sup> The PFS benefit for patients treated with IMBRUVICA® was seen in all subgroups, including those with high-risk genomic features of *TP53* mutation, unmutated IGHV or 11q deletion (HR 0.091 [95 percent CI, 0.054–0.152]).<sup>2</sup> Additionally, 78 percent of patients in the IMBRUVICA® treatment arm were alive at 6.5 years.<sup>2</sup> The CR rate with IMBRUVICA® treatment has increased over time to 34 percent.<sup>2</sup> Nearly half of patients continue to receive IMBRUVICA® treatment with up to seven years of follow-up.<sup>2</sup>

“The positive results from the CAPTIVATE study demonstrate the potential of IMBRUVICA and venetoclax, with complementary mechanisms of action, to provide deep responses with a once-daily, fixed-duration combination that can be administered in the outpatient setting for younger, fit patients,” said Craig Tendler, M.D., Vice President, Clinical Development and

Global Medical Affairs, Oncology, Janssen Research & Development, LLC. "The results from RESONATE-2 further support the long-term benefit of IMBRUVICA monotherapy in front line CLL for which the breadth and maturity of data continue to grow in support of this standard-of-care treatment and its impact on progression-free and overall survival."

Single-agent IMBRUVICA® was well-tolerated as a long-term treatment with no new safety signals.<sup>2</sup> Ongoing rates of Grade 3 or higher AEs of interest remained low for hypertension (five-to-six-year interval: n=20; six-to-seven-year interval: n=15) and atrial fibrillation (five-to-six-year interval: n=7; six-to-seven-year interval: n=5).<sup>2</sup> Additionally, no Grade 3 or higher major hemorrhage occurred in the five-to-seven-year interval.<sup>2</sup> Any-grade AEs leading to discontinuations were seen in three percent (n=2) of patients from year five to year six and no patients discontinued treatment in the IMBRUVICA® arm due to AEs from year six to year seven.<sup>2</sup>

### **About IMBRUVICA®**

IMBRUVICA® (ibrutinib) is a once-daily oral medication that is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company. IMBRUVICA® blocks the Bruton's tyrosine kinase (BTK) protein, which is needed by specific cancer cells to survive.<sup>3,4</sup> IMBRUVICA® helps to force cancerous B cells out of environments in which they thrive and multiply, like the lymph nodes, and prevents them from returning. This action of IMBRUVICA, along with other effects of blocking BTK, reduces the ability of cancerous B cells to survive.<sup>5</sup>

IMBRUVICA® is approved in more than 100 countries, and, to date, has been used to treat more than 230,000 patients worldwide. IMBRUVICA® is the only BTKi that has demonstrated overall survival benefits in three CLL clinical trials, with response durability persisting up to eight years,<sup>6,7,8</sup> and seven out of 10 patients alive and without disease progression after five years.<sup>7</sup> IMBRUVICA® is the only BTKi that has been shown to mediate short- and long-term immune restoration.<sup>9</sup>

IMBRUVICA® 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) /small lymphocytic lymphoma (SLL) with or without 17p deletion (del17p), Waldenström's macroglobulinemia (WM), patients with previously treated mantle cell lymphoma (MCL)\*, patients with previously treated marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior

anti-CD20-based therapy\* – and patients with previously treated chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.<sup>10</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.*

IMBRUVICA® is the most comprehensively studied BTKi, with more than 150 active clinical trials in several blood cancers and other serious diseases. 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 postprocedural 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 of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively.

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 and Cardiac Failure:** Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% 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.

At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure 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<sup>®</sup> 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<sup>®</sup> with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA<sup>®</sup> may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA<sup>®</sup> 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<sup>®</sup> in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA<sup>®</sup> dose and monitor more frequently for adverse reactions of IMBRUVICA<sup>®</sup>.

Please [click here](#) to see the 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](https://twitter.com/JanssenUS) and [@JanssenGlobal](https://twitter.com/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 January 3, 2021, 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.*

†Dr. Paolo Ghia has served as a consultant to Janssen; he has not been paid for any media work.

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<sup>1</sup> Ghia P., et al. Fixed-Duration (FD) First-Line Treatment (tx) with Ibrutinib (I) Plus Venetoclax (V) For Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Primary Analysis of the FD Cohort of the Phase 2 CAPTIVATE Study. 2021 American Society of Clinical Oncology Annual Meeting. June 4-8, 2021.

<sup>2</sup> Barr P., et al. Up to 7 Years of Follow-up in the RESONATE-2 Study of First-Line Ibrutinib Treatment for Patients With Chronic Lymphocytic Leukemia. 2021 American Society of Clinical Oncology Annual Meeting. June 4-8, 2021.

<sup>3</sup> Genetics Home Reference. Isolated growth hormone deficiency. <http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency>. Accessed June 2021.

<sup>4</sup> Turetsky A, et al. Single cell imaging of Bruton's tyrosine kinase using an irreversible inhibitor. *Scientific Reports*. 2014;6:4782.

<sup>5</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>6</sup> Shanafelt TD et al. *N Engl J Med*. 2019;381:432-443.

<sup>7</sup> Burger JA et al. *Leukemia*. 2020;34:787-798.

<sup>8</sup> Byrd JC et al. *N Engl J Med*. 2014;371(3):213-223.

<sup>9</sup> Solman IG et al. *Leuk Res*. 2020;97:106432.

<sup>10</sup> IMBRUVICA U.S. Prescribing Information, December 2020.