



News Release

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New Phase 3 Study Results Show IMBRUVICA® (ibrutinib)-Based Combination Regimen as an All-Oral Fixed-Duration Treatment Demonstrated Superior Progression-Free Survival in Adult Patients with Previously Untreated Chronic Lymphocytic Leukemia

GLOW study presented as a late-breaking abstract at the European Hematology Association (EHA) Virtual Congress

Raritan, N.J., June 12, 2021 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced primary results from the pivotal Phase 3 GLOW study ([NCT03462719](https://clinicaltrials.gov/ct2/show/study/NCT03462719)) evaluating fixed-duration IMBRUVICA® plus venetoclax (I+V) compared to chlorambucil plus obinutuzumab (Clb+O) for first-line treatment of elderly or unfit patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The study demonstrated superior progression-free survival (PFS) of a once-daily, all-oral, fixed-duration regimen of I+V versus Clb+O as first-line treatment of CLL; the study also showed improved duration of remission and significantly improved depth of remission.¹ With I+V, undetectable minimal residual disease (uMRD) in peripheral blood (PB) was sustained by 85 percent of patients one year after end of treatment.¹ The safety and tolerability profile of

I+V was consistent with CLL treatment in an older population with comorbidities.¹ These data were featured in the European Hematology Association (EHA) 2021 Virtual Press Briefing and will be presented as a late-breaking abstract during the EHA Virtual Congress ([Abstract #LB1902](#)).

“In the GLOW study, two very active blood cancer treatments are combined to create a complementary therapeutic regimen with the hope that deep responses might enable treatment-free remission for patients,” said Arnon Kater[†], M.D., Ph.D., deputy head of hematology, University of Amsterdam Faculty of Medicine, the Netherlands and principal study investigator. “The data from GLOW showed that IMBRUVICA in an oral, once-daily fixed-duration combination with venetoclax outperformed a standard chemoimmunotherapy regimen for older or unfit patients, providing the first comparative evidence that this approach has the potential to improve depth of response and, therefore, extends time to progression versus standard therapy.”

The GLOW study evaluated the efficacy and safety of first-line fixed-duration I+V versus Clb+O in elderly patients with CLL/SLL, or patients ages 18-64 with a cumulative illness rating scale (CIRS) score of greater than six or creatinine clearance less than 70 mL/min.¹ The CIRS score measures comorbidity, or concurrent non-CLL illness, in patients across multiple body systems.² GLOW excluded patients with del(17p) or known *TP53* mutations. Randomization to fixed-duration I+V or a standard six 28-day cycle of Clb+O was stratified by immunoglobulin heavy chain variable region gene (IgHV) mutational status and del(11q) status.¹ Patients in the I+V arm received three months of IMBRUVICA[®] lead-in therapy followed by 12 months of combination I+V therapy, and all patients stopped therapy regardless of MRD status.¹ In the study, 106 patients received I+V and 105 received Clb+O (n=211; median age, 71 years).¹

At a median follow-up of 27.7 months, independent review committee (IRC)-assessed PFS for fixed-duration I+V was superior to Clb+O [Hazard Ratio (HR) 0.216; 95 percent confidence interval [CI], 0.131-0.357; $p < 0.0001$] and the improvement in PFS favoring I+V was consistent across predefined subgroups, including older patients and patients with higher comorbidity scores.¹ Median PFS was not reached for I+V and 21.0 months for Clb+O (95 percent CI, 16.6-24.7).¹ At three months after the end of treatment (EOT+3), the rate of uMRD was significantly higher for I+V versus Clb+O in bone marrow (51.9 percent vs. 17.1 percent, respectively; $p < 0.0001$) and peripheral blood (54.7 percent vs. 39.0 percent, respectively; $p < 0.0001$).¹ Complete response (CR) rates (including CR with

incomplete hematologic recovery) by IRC assessment were also significantly higher for fixed-duration I+V versus Clb+O (38.7 percent vs. 11.4 percent; $p < 0.0001$).¹

Responses to fixed-duration I+V were sustained after EOT; 84.5 percent (49/58) of patients maintained peripheral blood uMRD from EOT+3 to the assessment 12 months after EOT (EOT+12).¹ Thereby, with a median follow-up of 27.7 months, time to next anti-cancer therapy was extended with I+V vs. Clb+O [HR, 0.143; 95 percent CI, 0.05-0.41].¹

The most common Grade 3 or higher treatment-emergent adverse events (TEAEs) for fixed-duration I+V were neutropenia/neutrophil count decrease (34.9 percent), infections (17 percent), and diarrhea (10.4 percent); and neutropenia/neutrophil count decrease (49.5 percent), thrombocytopenia (20 percent), and infections (11.4 percent) for Clb+O.¹ Deaths during treatment occurred in seven patients on fixed-duration I+V and two patients on Clb+O.¹ At time of analysis, overall survival was immature; there were eleven deaths in the fixed-duration I+V arm and twelve in the Clb+O arm.¹

Data from the Fixed-Duration Cohort of the Phase 2 CAPTIVATE (PCYC-1142) Study of IMBRUVICA®-Based Combination Regimen in Previously Untreated Patients with CLL ([Abstract #S147](#))

GLOW is part of a comprehensive development program exploring the potential of IMBRUVICA®-based fixed-duration therapy in previously untreated CLL. This includes the fixed-duration cohort from the [Phase 2 CAPTIVATE](#) study in young, fit patients that was recently presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting and will also be presented at EHA ([Abstract #S147](#)). The CAPTIVATE study evaluated previously untreated CLL/SLL patients 70 years or younger, including patients with high-risk disease.³ 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 MRD status.³ More than 90 percent of patients completed 12 cycles of IMBRUVICA® plus venetoclax treatment.³ At a median follow-up of 27.9 months, the CR rate in the overall population was 56 percent (n=88; 95 percent CI, 48–64) and was consistent across high-risk subgroups.³ Results also showed that 95 percent of patients treated with fixed-duration I+V were alive and progression-free at two years and deep remissions were seen across all subgroups, including patients with high-risk CLL.³

The safety profile of the I+V regimen in CAPTIVATE was consistent with known safety profiles of IMBRUVICA® and venetoclax.³ Of note, 21 percent of patients were at risk for tumor lysis syndrome (TLS) based on high tumor burden at baseline, and this was reduced to one percent after three cycles of IMBRUVICA® lead-in therapy.³ AEs were primarily Grade 1/2.³ The most common Grade 3/4 AEs were neutropenia (33 percent), infections (eight percent), hypertension (six percent), and neutrophil count decrease (five percent).³ Discontinuations due to AEs were infrequent (three percent for IMBRUVICA®).³

“IMBRUVICA and venetoclax have complementary mechanisms of action, and the promising results from the CAPTIVATE and GLOW studies show that this all-oral regimen that many patients can take at home may provide an effective, flexible treatment option for patients with CLL/SLL seeking a fixed-duration therapy,” said Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs, Oncology, Janssen Research & Development, LLC. “Between these two studies, more than 400 patients across the age and fitness spectrum of CLL patients requiring frontline therapy have been treated with IMBRUVICA in combination with venetoclax, further demonstrating the potential of IMBRUVICA in this regimen across multiple patient groups.”

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. 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. By blocking BTK, IMBRUVICA may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs.^{4,5,6}

IMBRUVICA® is approved in more than 100 countries, and, to date, is the only BTK inhibitor that has been used to treat more than 230,000 patients worldwide.

IMBRUVICA® was first approved by the U.S. Food and Drug Administration (FDA) in November 2013, and today is indicated for adult patients in six disease areas, including five hematologic cancers – adults with chronic lymphocytic leukemia (CLL) /small lymphocytic lymphoma (SLL) with or without 17p deletion (del17p), adults with Waldenström’s macroglobulinemia (WM), adult patients with previously treated mantle cell lymphoma (MCL)*, adult patients with previously treated marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy* – and

adult patients with previously treated chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

**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.

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 ≥ 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.

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 2.3 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 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](#) 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. 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.

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

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, Janssen Biotech, Inc., 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, 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 Kater P, et al. Fixed-Duration Ibrutinib Plus Venetoclax (I+V) Versus Chlorambucil Plus Obinutuzumab (Clb+O) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL): Primary Analysis of the Phase 3 GLOW Study. 2021 European Hematology Association 2021 Virtual Congress. June 9-17, 2021.

² Gribben JG. Chronic lymphocytic leukemia: planning for an aging population. *Expert Rev Anticancer Ther.* 2010;10(9):1389-1394. doi:10.1586/era.10.127

³ 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.

⁴ Genetics Home Reference. Isolated growth hormone deficiency. <http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency>. Accessed June 2021.

⁵ Turetsky A, et al. Single cell imaging of Bruton's tyrosine kinase using an irreversible inhibitor. *Scientific Reports.* 2014;6:4782.

⁶ 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.

⁷ IMBRUVICA U.S. Prescribing Information, December 2020.