



News Release

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Phase 3 SHINE Results Show IMBRUVICA® (ibrutinib)-Based Combination Regimen Significantly Reduced the Risk of Disease Progression or Death in Older Patients with Newly Diagnosed Mantle Cell Lymphoma

Primary results from the first frontline Phase 3 study of a Bruton's tyrosine kinase inhibitor in MCL to be presented as late-breaking data at the 2022 ASCO Annual Meeting and also published in The New England Journal of Medicine

June 3, 2022 (CHICAGO) – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced primary results from the Phase 3 SHINE study ([Abstract #7502](#)), which demonstrated that the combination of once-daily oral IMBRUVICA® (ibrutinib) plus bendamustine-rituximab (BR) and rituximab maintenance significantly reduced the risk of disease progression or death by 25 percent compared to patients who received placebo plus BR and rituximab maintenance in patients aged 65 years or older with newly diagnosed mantle cell lymphoma (MCL).¹ This study is one of the largest clinical trials ever conducted in first-line MCL and the first for a Bruton's tyrosine kinase inhibitor (BTKi).¹ The data are being presented in an oral session and featured in a press briefing during the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting, and were published in [The New England Journal of Medicine](#) today. The data will also be presented as an oral presentation at the 2022 European Hematology Association (EHA) Annual Congress.

MCL is a type of aggressive, rare non-Hodgkin lymphoma (NHL) that is incurable and difficult to treat.² It commonly affects people over the age of 65, who typically cannot tolerate intensive chemoimmunotherapy and stem cell transplantation, resulting in poor clinical outcomes and contributing to the need to develop additional treatment options for these patients.²

“There is an urgent need to improve outcomes for older patients with MCL,” said Michael L. Wang, M.D., Professor, Department of Lymphoma & Myeloma, The University of Texas MD Anderson Cancer Center and principal study investigator.[‡] “Given the median progression-free survival of 6.7 years, the ibrutinib combination demonstrated the potential to be a first-line treatment in this population.”

The Phase 3 SHINE (MCL3002) study ([NCT01776840](https://clinicaltrials.gov/ct2/show/study/NCT01776840)) – sponsored by Janssen Biotech, Inc., in collaboration with Pharmacyclics LLC, an AbbVie Company – enrolled 523 patients aged 65 years or older with newly diagnosed MCL.¹ All participants were randomly assigned to receive IMBRUVICA[®] (560 mg orally daily until progression or unacceptable toxicities) or placebo plus BR for a maximum of six 28-day cycles; participants with a complete response (CR) or partial response (PR) continued to receive maintenance therapy with rituximab every second cycle for a maximum of 12 additional doses.¹ IMBRUVICA[®] or placebo was administered daily until progressive disease or unacceptable toxicity.¹

The SHINE study met its primary endpoint of progression-free survival (PFS). Key findings from the Phase 3 SHINE study include:

- With a median follow-up of 84.7 months, the IMBRUVICA[®] plus BR and rituximab maintenance combination showed a statistically significant and clinically meaningful 2.3-year improvement in median PFS.¹ Median PFS in the IMBRUVICA[®] plus BR arm was 6.7 years compared to 4.4 years in the placebo plus BR arm (stratified hazard ratio [HR]: 0.75, 95 percent confidence interval [CI], 0.59-0.96; $p = 0.011$).¹
- Key secondary endpoints included: CR, time-to-next treatment (TTNT), overall survival (OS), and overall response rate (ORR).¹
 - A CR was achieved in 171 patients (65.5 percent) in the IMBRUVICA[®] plus BR arm and 151 patients (57.6 percent) in the placebo plus BR arm ($p = 0.057$).¹ The rates of objective response were similar between the two arms (IMBRUVICA[®] plus BR: 89.7 percent; placebo plus BR: 88.5 percent).¹

- Median TTNT was not reached in the IMBRUVICA® plus BR arm.¹ The median TTNT was 92 months in the placebo plus BR arm (HR: 0.48, 95 percent CI, 0.34-0.66).¹
- OS was similar between treatment arms and median OS was not reached in either treatment arm (HR: 1.07, 95 percent CI, 0.81-1.40).¹

“More than eight years since its first FDA approval, IMBRUVICA has treated over 250,000 patients globally, fundamentally changing the treatment paradigm for complex B-cell malignancies,” said Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs, Janssen Research & Development, LLC. “The Phase 3 SHINE study reinforces our continued commitment to the development of IMBRUVICA to provide meaningful differences and change outcomes for patients with B-cell malignancies where high unmet medical needs still remain.”

The safety profile of the IMBRUVICA® plus BR regimen was consistent with known safety profiles of IMBRUVICA® as well as BR.¹ Across all treated patients, the most common Grade 3/4 Adverse Events (AEs) ≥5 percent were neutropenia (IMBRUVICA® plus BR: 47.1 percent; BR: 48.1 percent), pneumonia (IMBRUVICA® plus BR: 20.1 percent; BR: 14.2 percent), anemia (IMBRUVICA® plus BR: 15.4 percent; BR: 8.8 percent), thrombocytopenia (IMBRUVICA® plus BR: 12.7 percent; BR: 13.1 percent), rash (IMBRUVICA® plus BR: 12 percent; BR: 1.9 percent), and diarrhea (IMBRUVICA® plus BR: 6.9 percent; BR: 3.8 percent).¹ Treatment-emergent AEs of clinical interest with BTKis included atrial fibrillation (AF) which was reported in 13.9 percent of patients in the IMBRUVICA® plus BR arm and 6.5 percent in the placebo arm; hypertension in 13.5 percent and 11.2 percent; major bleeding in 5.8 percent and 4.2 percent; any bleeding 42.9 percent and 21.5 percent; and arthralgia in 17.4 percent and 16.9 percent, respectively.¹

IMBRUVICA® is currently approved globally for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.³ Within the U.S., this indication is approved under accelerated approval based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

About IMBRUVICA®

IMBRUVICA® (ibrutinib) is a once-daily oral medication that is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacylics LLC, an AbbVie company.

IMBRUVICA® blocks the Bruton's tyrosine kinase (BTK) protein, which is needed by normal and abnormal B cells, including specific cancer cells, to multiply and spread. By blocking BTK, IMBRUVICA® may help move abnormal B cells out of their nourishing environments and inhibits their proliferation.^{4,5,6}

IMBRUVICA® is approved in more than 100 countries for at least one indication and has been used to treat more than 250,000 patients worldwide. There are more than 50 company-sponsored clinical trials, including 18 Phase 3 studies, with over 11 years evaluating the efficacy and safety of IMBRUVICA®.

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. These include indications to treat adults with CLL/SLL with or without 17p deletion (del17p), and adults with Waldenström's macroglobulinemia (WM), and adult patients with previously treated mantle cell lymphoma (MCL)*, as well as to treat 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.³

[†]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.

The National Comprehensive Cancer Network® (NCCN®), recommends ibrutinib (IMBRUVICA®) as a preferred regimen for the initial treatment of CLL/SLL and has Category 1 treatment status for treatment-naïve patients without deletion 17p/TP53 mutation and as a preferred treatment for treatment-naïve patients with deletion 17p/TP53 mutation. The NCCN Guidelines also recommend IMBRUVICA®, with or without rituximab, as a preferred regimen for the treatment of relapsed/refractory MCL, as a Category 1 preferred regimen for both untreated and previously treated WM patients, and as a preferred regimen for relapsed/refractory MZL.⁷

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 post procedural hemorrhage) occurred in 4.2% 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.

Cardiac Arrhythmias, Cardiac Failure and Sudden Death: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Deaths due to cardiac causes or sudden deaths occurred in 1% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy

or combination regimens. These adverse reactions occurred in patients with and without preexisting hypertension or cardiac comorbidities. Patients with cardiac comorbidities may be at greater risk of these events.

Grade 3 or greater ventricular tachyarrhythmias were reported in 0.2%, Grade 3 or greater atrial fibrillation and atrial flutter were reported in 3.7%, and Grade 3 or greater cardiac failure was reported in 1.3% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These events have occurred particularly in patients with cardiac risk factors including hypertension and diabetes mellitus, a previous history of cardiac arrhythmias, and in patients with acute infections.

Evaluate cardiac history and function at baseline, and monitor patients for cardiac arrhythmias and cardiac function. Obtain further evaluation (e.g., ECG, echocardiogram) as indicated for patients who develop symptoms of arrhythmia (e.g., palpitations, lightheadedness, syncope, chest pain), new onset dyspnea, or other cardiovascular concerns. Manage cardiac arrhythmias and cardiac failure appropriately, follow dose modification guidelines, and consider the risks and benefits of continued IMBRUVICA® treatment.

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®, initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate, and follow dosage modification guidelines for Grade 3 or higher hypertension.

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 2.8%, based on laboratory measurements. Monitor complete blood counts monthly.

Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (3.9%), 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. Increased ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of IMBRUVICA® are 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). Avoid grapefruit and Seville oranges during IMBRUVICA® treatment, as these contain strong or moderate inhibitors of CYP3A. 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, & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at [@JanssenGlobal](https://twitter.com/JanssenGlobal) and [@JanssenUS](https://twitter.com/JanssenUS). Janssen Research & Development, LLC and Janssen Biotech, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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‡Dr. Wang, M.D. 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 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 2, 2022, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other 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 Wang M., et al. Primary results from the double-blind, placebo-controlled, phase III SHINE study of ibrutinib in combination with bendamustine-rituximab (BR) and R maintenance as a first-line treatment for older patients with mantle cell lymphoma (MCL). 2021 American Society of Clinical Oncology Annual Meeting. June 3-7, 2022.
- ² Lymphoma.org. Mantle Cell Lymphoma. <https://lymphoma.org/aboutlymphoma/nhl/mcl/>. Accessed June 2022.
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- ⁴ Genetics Home Reference. Isolated growth hormone deficiency. <http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency>. Accessed June 2022.
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- 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 NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V2.2022. National Comprehensive Cancer Network. Accessed June 2022.