News Release

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Real-World Study Shows Patients Treated with IMBRUVICA® (ibrutinib) Were Less Likely to Initiate a Next-Line Treatment than Patients on Acalabrutinib in First-line Chronic Lymphocytic Leukemia

More than two years of electronic medical records indicate patients were 89 percent more likely to start a next-line treatment when on acalabrutinib versus IMBRUVICA®

NEW ORLEANS, December 12, 2022 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced results of a real-world study showing that patients with chronic lymphocytic leukemia (CLL) treated with first-line acalabrutinib monotherapy were 89 percent more likely to start a next-line treatment than those treated with IMBRUVICA® (ibrutinib).[1] These data suggest the potential that first-line treatment with IMBRUVICA® in routine practice may provide patients with the ability to use once-daily, all-oral IMBRUVICA® as a monotherapy treatment for a longer period without the need to start the next line of therapy.[1] Data from the study were featured in an oral presentation during the 2022 American Society of Hematology (ASH) Annual Meeting (Abstract #797).

"There are currently no comparative clinical trials in first-line CLL among the BTKi class,[1] highlighting the critical need to leverage real-world experience to support optimized treatment selection," said Ryan Jacobs†, M.D., Clinical Director, Division of Lymphoma Therapy & Research, Department of Hematologic Oncology, Atrium Health Levine Cancer Institute and

principal study investigator. "These results demonstrate the possible impact of using ibrutinib versus acalabrutinib in the front-line setting and provide healthcare professionals with additional data showing differences in time to next treatment."

The study used Acentrus‡, de-identified academic electronic medical records (EMR) to identify patients initiating first-line treatment with IMBRUVICA® or acalabrutinib between November 21, 2019 and April 30, 2022 and examined time to next treatment (TTNT) as a clinically meaningful surrogate measure for disease progression.[1] TTNT was defined as the time from the index date to the initiation of a next or additional treatment.[1] Results showed the following:

- Among treatment-naïve patients with CLL/small lymphocytic leukemia (SLL), patients treated with first-line acalabrutinib (n=373) were 89 percent more likely to start a next treatment than those treated with first-line IMBRUVICA® (n=710) (adjusted hazard ratio [HR] [95 percent confidence interval]: 1.89 (1.12, 3.13); P=0.016).[1]
- A similar result was observed when censoring anti-CD20 add-on therapy any time after BTK inhibitor treatment (i.e., more than 180 days).[1]
- At 12 months, 95.3 percent of patients treated with IMBRUVICA® had not initiated a next treatment versus 91.2 percent of patients treated with acalabrutinib.[1]
- At 15 months, 94.6 percent of patients treated with IMBRUVICA® had not initiated next therapy versus 88.3 percent of patients treated with acalabrutinib.[1]

"Insights from real-world data are becoming more important to help physicians understand optimal treatments and sequencing, especially for patients living with chronic diseases like CLL," said Imran Khan, M.D., Ph. D., Vice President, Medical Affairs, Oncology, Janssen Biotech, Inc. "With nearly ten years of data since IMBRUVICA was first approved, we are sourcing real-world data to provide insights from large cohorts of patients further supporting IMBRUVICA as a first-line treatment option for CLL."

Additional Study Details

The Acentrus‡ database provides extensive information on medication orders, fills, and administrations. This enables the capture of oral medication use and is unique among available EMR datasets, including Flatiron.[1]

Patients were censored if another BTK inhibitor was initiated at any time, as this may be due to tolerability or non-medical switch rather than disease progression.[1] Other criteria for censored patients were initiation of a second anti-cancer agent in addition to the index BTK

inhibitor treatment within 180 days post-index, as this may indicate a first-line combination treatment strategy.[1] The addition of an anti-CD20 antibody or venetoclax after 180 days were considered next treatments.[1] Patients without a next or additional treatment were censored at death or end of data entries.[1]

The median age of patients treated with IMBRUVICA® and acalabrutinib were similar (IMBRUVICA® 73 years [n=710]; acalabrutinib 72 years [n=373]).[1]

Real-World Data Limitations

Real world data have the potential to supplement controlled trial data by providing additional information about how a medicine performs across clinical trials and in routine clinical practice. There are limitations, however, and these data cannot be used as stand-alone evidence to validate the efficacy or safety of a treatment.

Limitations exist based on EMR data, including potential omissions.[1] However, these would be at random and are expected to have minimal impact on results.[1] Further research is warranted with additional follow-up and larger sample size to inform the evidence gap on the comparative effectiveness of newer BTK inhibitors.[1]

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 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.[2,3,4]

IMBRUVICA® is approved in more than 100 countries and has been used to treat more than 270,000 patients worldwide. There are more than 50 company-sponsored clinical trials, including 18 Phase 3 studies, more than 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 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)*, 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 and pediatric patients aged one year and older with previously treated chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.[5]

**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.*

For more information, visit www.IMBRUVICA.com.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received 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) 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 percent, 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 (≥30%) in adult 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 (≥5%) in adult 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 adult 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 adult or pediatric patients with cGVHD were fatigue (57%), anemia (49%)*, bruising (40%), diarrhea (36%), thrombocytopenia (33%)*, musculoskeletal pain (30%), pyrexia (30%), muscle spasms (29%), stomatitis (29%), hemorrhage (26%), nausea (26%), abdominal pain (23%), pneumonia (23%), and headache (21%).

The most common Grade 3 or higher adverse reactions (≥5%) reported in adult or pediatric patients with cGVHD were pneumonia (14%), anemia (13%)*, fatigue (12%), pyrexia (11%), diarrhea (10%), neutropenia (10%)*, sepsis (10%), osteonecrosis (9%), stomatitis (9%), hypokalemia (7%), headache (5%), and musculoskeletal pain (5%).

Discontinuation of IMBRUVICA® treatment due to an adverse reaction occurred in 24% of adult patients and 23% of pediatric patients. Adverse reactions leading to dose reduction occurred in 26% of adult patients and 19% of pediatric 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

Pediatric Use: The safety and effectiveness of IMBRUVICA® have not been established for the treatment of cGVHD after failure of one or more lines of therapy in pediatric patients less than 1 year of age. The safety and effectiveness of IMBRUVICA® in pediatric patients have not been established in MCL, CLL/SLL, CLL/SLL with 17p deletion, WM, MZL or in patients with mature B-cell non-Hodgkin lymphoma.

In the randomized population from a study that included 35 patients (26 pediatric patients age 5 to less than 17 years) with previously treated mature B-cell non-Hodgkin lymphoma, major hemorrhage and discontinuation of chemoimmunotherapy due to adverse reactions occurred more frequently in the ibrutinib plus chemoimmunotherapy arm compared to the chemoimmunotherapy alone arm.

Hepatic Impairment:

Adult Patients with B-cell Malignancies: 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®.

Patients with cGVHD: Avoid use of IMBRUVICA® in patients with total bilirubin level > 3x upper limit of normal (ULN) (unless of non-hepatic origin or due to Gilbert's syndrome). Reduce recommended dose when administering IMBRUVICA® to patients with total bilirubin level > 1.5 to 3x ULN (unless of non-hepatic origin or due to Gilbert's syndrome).

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 and @JanssenUS. Janssen Biotech, Inc. is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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

‡ Acentrus is a health system solution utilized by 128,000 prescribers/physicians containing in-patient and out-patient data from 27 sites, including 10 NCI-designated sites and 6 NCCN network members, across 15 US states.

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 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] Jacobs R., et al. Real-World Comparison of Time to Next Treatment for Patients with CLL Initiated on First-line Treatment with Ibrutinib versus Acalabrutinib. 2022 American Society of Hematology Annual Meeting. December 12, 2022.
[2] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency.
[3] Turetsky A, et al. Single cell imaging of Bruton's tyrosine kinase using an irreversible inhibitor. *Scientific Reports.* 2014;6:4782.
[4] de Rooij MF, 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.
[5] IMBRUVICA® U.S. Prescribing Information, August 2022.