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Imbruvica®▼ (ibrutinib) in Combination with Rituximab Showed Greater Efficacy Compared to Placebo Plus Rituximab in Patients with Waldenström's Macroglobulinemia, a Rare and Incurable Form of Non-Hodgkin's Lymphoma

Phase 3 data featured as an oral presentation (Abstract #8003), selected for the Best of ASCO 2018 Meetings, and simultaneously published in the New England Journal of Medicine

BEERSE, BELGIUM, June 1, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced results from a pre-planned interim analysis of the Phase 3 iNNOVATE (PCYC-1127) study evaluating Imbruvica® (ibrutinib) in combination with rituximab in relapsed/refractory and treatment-naïve patients with Waldenström's macroglobulinemia (WM). The study met its primary endpoint for a clinically and statistically significant difference in progression-free survival (PFS) for patients treated with ibrutinib plus rituximab versus those who received placebo plus rituximab. Ibrutinib plus rituximab significantly reduced the risk of disease progression or death by 80 percent compared to placebo plus rituximab (hazard ratio [HR], 0.20; confidence interval [CI]: 0.11-0.38, *P* <0.0001). Furthermore, secondary endpoints including the response rate, time to next treatment (TTnT), rate of sustained haemoglobin improvement and number of participants with adverse events (AEs) supported the primary endpoint.[1,2] In late 2017, the Independent Data Monitoring Committee (IDMC) recommended unblinding iNNOVATE based on these results.

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The data were presented today in an oral session at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract #8003) and simultaneously published in the *New England Journal of Medicine*.[3] The presentation was also selected for inclusion in the Best of ASCO 2018 Meetings. Ibrutinib, a first-in-class Bruton's tyrosine kinase (BTK) inhibitor, is jointly developed and commercialised by Janssen Biotech, Inc., and Pharmacyclics LLC, an AbbVie company.

"These important data demonstrate ibrutinib plus rituximab resulted in marked improvement in progression-free survival across all lines of therapy in Waldenström's macroglobulinemia regardless of patient subtypes, compared to placebo plus rituximab," said Dr. Meletios A. Dimopoulos, Professor and Chairman of the Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens, Greece, and lead iNNOVATE study investigator. "Not only was there marked statistical and clinical difference in the efficacy compared to rituximab monotherapy, but the combination of ibrutinib and rituximab did not result in any unanticipated safety signals."

WM is a rare form of non-Hodgkin's lymphoma (NHL).[4] Incidence rates among men and women in Europe are approximately 7.3 and 4.2 per million persons, respectively.[5] The causes of WM are unknown with it typically affecting older adults and slightly more common in men than women.[4] In July 2015, ibrutinib received European Commission (EC) approval as a treatment option for adult patients with WM who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy, becoming the first EC-approved treatment for this rare B-cell lymphoma.[6]

Abstract #8003: Randomised phase 3 trial of ibrutinib/rituximab vs placebo/rituximab in Waldenström's macroglobulinemia*
Oral presentation: Friday, June 1, 3:45 p.m. CDT

With a median follow-up of 26.5 months, ibrutinib plus rituximab improved PFS compared with placebo plus rituximab (median PFS, not reached vs 20.3 months; HR, 0.20; CI: 0.11-0.38, *P* <0.0001), with PFS rates of 82% versus 28% at 30 months, respectively. Notably, ibrutinib plus rituximab prolonged PFS in all relevant subgroups, including treatment-naïve (HR, 0.34; CI: 0.12-0.95), relapsed (HR, 0.17; CI: 0.08-0.36), and in patients with $MYD88^{L265P}$ and $CXCR4^{WHIM}$ mutations (HR, 0.24; CI: 0.09-0.66) versus rituximab.[1]

Overall response rates and major response rates were significantly higher for ibrutinib plus rituximab versus placebo plus rituximab (92% vs 47%; 72% vs 32% [both *P* <0.0001]). In addition, there was an improvement in haemoglobin seen in patients treated with the combination versus the placebo plus rituximab arm (73% vs 41%, *P* <0.0001).[1,2]

Of the patients on ibrutinib plus rituximab, 75% continued on treatment at the time of analysis. TTnT was not reached for ibrutinib plus rituximab and 18 months for placebo plus rituximab (HR, 0.096; *P* <0.0001). The 30-month overall survival (OS) rates were 94% versus 92% in the two arms.[1,2]

At the median time on treatment (ibrutinib plus rituximab, 25.8 months; rituximab plus placebo, 15.5 months), grade 3 or higher treatment-emergent AEs occurred in 60% of patients treated with ibrutinib plus rituxumab, versus 61% of patients treated with placebo plus rituxmab. Serious AEs occurred in 43% versus 33% of patients on ibrutinib plus ritxuimab compared to placebo plus rituximab. No fatal AEs occurred in the ibrutinib plus rituximab arm. Three fatal AEs occurred in the placebo plus rituximab arm. Meaningful reductions in any grade immunoglobin M flare (8% vs 47%) and grade 3 or higher infusion reactions were observed (1% vs 16%) with ibrutnib plus rituximab compared to placebo plus rituximab.[1,2]

"The results from the iNNOVATE study add to the growing body of evidence demonstrating the efficacy and safety of ibrutinib, alone and in combination, in the treatment of rare B-cell malignancies such as Waldenström's macroglobulinemia," said Dr Catherine Taylor, Europe, Middle East and Africa (EMEA) Haematology Therapeutic Area Lead, Janssen. "Janssen Oncology's commitment to addressing unmet needs drives us to continue delivering treatment to those blood cancer patients with limited options and poor prognosis."

**Abstract submitted by ibrutinib co-developer partner, Pharmacyclics, an AbbVie company.*

#ENDS#

About iNNOVATE

The iNNOVATE study evaluated relapsed/refractory and treatment-naïve Waldenström's macroglobulinemia patients (N=150) who were randomised to receive intravenous rituximab 375 mg/m^2 once weekly for four consecutive weeks, followed by a second once weekly for

four consecutive weeks rituximab course after a three-month interval. All patients received either ibrutinib 420 mg or placebo once daily continuously until disease progression or unacceptable toxicity. The primary endpoint was PFS, as assessed by an independent review committee. Secondary objectives included overall response rate, haematological improvement measured by haemoglobin, median time-to-next treatment (TTnT), overall survival (OS), and number of participants with adverse events (AEs) as a measure of safety and tolerability within each treatment arm.[1,2]

For more information on the abstracts presented by Janssen, please click here.

About ibrutinib

Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor, which works by forming a strong covalent bond with BTK to block the transmission of cell survival signals within the malignant B-cells.[7] By blocking this BTK protein, ibrutinib helps kill and reduce the number of cancer cells, thereby delaying progression of the cancer.[8]

Ibrutinib is currently approved in Europe for the following uses:[9]

- Chronic lymphocytic leukaemia (CLL): As a single agent for the treatment of adult patients with previously untreated CLL, and as a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy.
- Mantle cell lymphoma (MCL): Adult patients with relapsed or refractory mantle cell MCL.
- Waldenström's macroglobulinemia (WM): Adult patients who have received at least one prior therapy or in first-line treatment for patients unsuitable for chemo-immunotherapy.

The most common adverse reactions seen with ibrutinib include diarrhoea, neutropenia, haemorrhage (e.g., bruising), musculoskeletal pain, nausea, rash, and pyrexia.[9]

For a full list of side effects and for further information on dosage and administration, contraindications and other precautions when using ibrutinib please refer to the Summary of Product Characteristics for further information.[9]

About Waldenström's macroglobulinemia

Waldenström's macroglobulinemia (WM) is a slow-growing cancer of the blood that is also known as lymphoplasmacytoid lymphoma.[10] WM causes overproduction of a protein, called monoclonal immunoglobulin M (IgM) antibody.[10] Excess IgM in the blood causes thickening of the blood which can be the cause of various symptoms.[10]

About the Janssen Pharmaceutical Companies

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com/emea. Follow us at www.twitter.com/janssenEMEA for our latest news.

Cilag GmbH International; Janssen Biotech, Inc.; Janssen Oncology, Inc. and Janssen-Cilag International NV 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 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-Cilag International NV, the Janssen Pharmaceutical Companies of Johnson & Johnson 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 behaviour 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 31, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking

Statements" and "Item 1A. Risk Factors," and in the company'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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