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Data Presented at ASH 2018 Provide Evidence of First-line Treatment Benefits with IMBRUVICA®▼ (ibrutinib)-Based Therapy Across All Patient Populations in CLL

Results from the interim analysis of the NCI-sponsored Phase 3 study led by the ECOG-ACRIN Cancer Research Group represent first head-to-head trial showing greater safety and efficacy of ibrutinib-based therapy versus FCR (abstract #LBA-4)

Phase 3 iLLUMINATE results featured as oral presentation (abstract #691) and simultaneously published in The Lancet Oncology

Also presented were results of up to seven years of follow-up of ibrutinib monotherapy in CLL, the longest follow-up study for a BTK inhibitor in CLL (abstract #3133)

BEERSE, BELGIUM, 5 December 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today new results from three key studies of IMBRUVICA® (ibrutinib) in chronic lymphocytic leukaemia (CLL), a difficult-to-treat form of blood cancer and the most common form of leukaemia in adults.[1] Findings were presented at the 60th American Society of Hematology (ASH) Annual Meeting, taking place in San Diego, CA.

Results from the National Cancer Institute (NCI)-sponsored Phase 3 study (E1912) led by the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) were presented during the Late-Breaker abstract oral session. The study evaluated ibrutinib plus rituximab compared to a chemotherapy regimen of fludarabine, cyclophosphamide, and rituximab (FCR) in previously untreated patients aged 70 years or younger with CLL. With nearly three years of follow-up, the data showed ibrutinib plus rituximab significantly prolonged progression-free survival (PFS) and overall survival (OS) versus FCR.[2]

Data from the Phase 3 iLLUMINATE (PCYC-1130) study were also presented in an oral session and simultaneously published in *The Lancet Oncology*. Findings showed the combination of ibrutinib plus obinutuzumab significantly improved PFS versus chlorambucil plus obinutuzumab in patients with newly diagnosed CLL.[3] These data recently supported the submission of a Type II variation application to the European Medicines Agency (EMA), seeking approval for the expanded use of ibrutinib in combination with obinutuzumab in previously untreated adults with CLL.

In addition, ibrutinib data from the Phase 1b/2 study and its extension study (PCYC-1102, PCYC-1103) with up to seven years of follow-up in patients with newly diagnosed and relapsed/refractory (R/R) CLL, demonstrated durable, long-term survival benefits as a

monotherapy, representing the longest follow-up for a Bruton's tyrosine kinase (BTK) inhibitor in CLL.[4]

"Findings from both iLLUMINATE and the ECOG-ACRIN study demonstrate impressive prolonged progression-free survival for the relevant ibrutinib-based combinations, versus commonly used chemo-immunotherapy regimens," said Dr Carol Moreno, Consultant Haematologist, Hospital de la Santa Creu Sant Pau, Autonomous University of Barcelona, Barcelona, Spain. "These non-chemotherapy regimens present an advance in how we might consider the management of patients, including younger patients and those with high risk CLL features with potential to address the trade-off between efficacy and toxicity for patients."

"The data presented at ASH provide further convincing evidence of the clinical benefit ibrutinib can offer to patients across the spectrum of CLL management. The long-term data also offer confidence of its sustained activity for patients," said Dr Catherine Taylor, Haematology Therapy Area Lead, Europe, Middle East and Africa (EMEA), Janssen-Cilag Limited. "We continue to explore the full potential of ibrutinib through a comprehensive clinical development programme, to improve outcomes and change what a blood cancer diagnosis means to patients."

Ibrutinib, a first-in-class BTK inhibitor, is jointly developed and commercialised by Janssen Biotech, Inc., and Pharmacyclics LLC, an AbbVie company.

Results From the Randomised Phase 3 Study of Ibrutinib (PCI-32765)-Based Therapy vs. FCR Chemoimmunotherapy in Untreated Younger Patients with CLL: A Study of the ECOG-ACRIN Cancer Research Group (E1912) (Abstract #LBA-4)

With a median follow-up of 33.4 months, the interim analysis observed 77 PFS events and 14 deaths. Ibrutinib plus rituximab significantly improved PFS compared to FCR (HR: 0.352; 95 percent confidence interval [CI]: 0.223-0.558; p<0.0001); the pre-specified boundary for PFS was crossed. The ibrutinib plus rituximab treatment arm also showed improved OS (HR: 0.168; 95 percent CI: 0.053-0.538; p=0.0003, pre-specified boundary for superiority p=0.0005).[2]

In a subgroup analysis for PFS, ibrutinib plus rituximab showed prolonged PFS independent of age, sex, performance status, disease stage, or the presence/absence of the cytogenetic abnormality, deletion 11q23. With current follow-up, ibrutinib plus rituximab was also superior to FCR for IGHV unmutated patients (HR: 0.262; 95 percent CI: 0.137-0.498; p<0.0001) but not IGHV mutated patients (HR: 0.435; 95 percent CI: 0.140-0.1350; p=0.07).[2]

Grade 3/4 treatment-related adverse events (AEs) were observed in 58 percent of ibrutinib plus rituximab treated patients and 72 percent of FCR treated patients (p=0.0042). FCR was more frequently associated with Grade 3 and 4 neutropenia (FCR: 44 percent vs. ibrutinib plus rituximab: 23 percent; p<0.0001) and infectious complications (FCR: 17.7 percent vs. ibrutinib plus rituximab: 7.1 percent; p<0.0001).[2]

Results from the Phase 3 iLLUMINATE study (Abstract #691)

At a median follow-up of 31.3 months, ibrutinib plus obinutuzumab significantly prolonged the Independent Review Committee (IRC)-assessed PFS compared with chlorambucil plus obinutuzumab (median not reached [NR] vs. 19.0 months; HR 0.231; 95 percent CI: 0.145-0.367; p<0.0001), with a 77 percent reduction in risk of progression or death.[3]

Superior PFS in the ibrutinib plus obinutuzumab arm compared to the chlorambucil plus obinutuzumab arm was also seen in the high-risk population, including those with unmutated IGHV, del11q, del17p and/or TP53 mutation, with an 85 percent reduction in risk of progression or death (median NR vs. 14.7 months; HR 0.154; 95 percent CI: 0.087-0.270; p<0.0001).[5] In addition, IRC-assessed overall response rate (ORR) was higher in the ibrutinib plus obinutuzumab arm versus the chlorambucil plus obinutuzumab arm (88 percent vs. 73 percent); complete response (CR)/complete response with incomplete blood recovery (CRi) rates were also higher with 19 percent versus eight percent, respectively. Minimal residual disease (MRD) was undetectable in blood and/or bone marrow ($<10^{-4}$ by flow cytometry) for 35 percent of patients treated with ibrutinib plus obinutuzumab, compared to 25 percent of patients treated with chlorambucil plus obinutuzumab. OS rates at 30 months were 86 percent for the ibrutinib plus obinutuzumab arm compared to 85 percent for the chlorambucil plus obinutuzumab arm.[3]

The most common Grade 3 or higher AEs in the ibrutinib plus obinutuzumab arm versus chlorambucil plus obinutuzumab arm were neutropenia (36 percent vs. 46 percent), thrombocytopenia (19 percent vs. 10 percent), pneumonia (7 percent vs. 4 percent), atrial fibrillation (5 percent vs. 0 percent), febrile neutropenia (4 percent vs. 6 percent), anaemia (4 percent vs. 8 percent) and infusion-related reactions (IRRs; 2 percent vs. 8 percent).[5] No patients discontinued obinutuzumab due to IRRs in the ibrutinib plus obinutuzumab arm compared to the chlorambucil plus obinutuzumab arm (6 percent). AEs led to the discontinuation of ibrutinib in 16 percent of patients and led to the discontinuation of chlorambucil in nine percent of patients. AEs led to the discontinuation of obinutuzumab in the ibrutinib plus obinutuzumab arm (9 percent) and chlorambucil plus obinutuzumab arm (13 percent). With about three years of follow-up, 70 percent of patients in the ibrutinib plus obinutuzumab arm remain on ibrutinib monotherapy.[3]

Results from up to seven years of follow-up in the Phase 1b/2 PCYC-1102 study and its extension, PCYC-1103 (Abstract #3133)

Results from these studies showed durable efficacy of ibrutinib in newly diagnosed and R/R CLL patients. These long-term data showed sustained PFS and OS rates. The estimated seven-year PFS rates were 80 percent for patients with newly diagnosed disease and 32 percent for patients with R/R disease. Notably, administering ibrutinib in earlier lines of therapy resulted in improved PFS outcomes for R/R patients.[4]

ORR was 89 percent for all patients (CR, 15 percent), with similar rates in newly diagnosed (87 percent [CR, 32 percent]) and R/R CLL patients (89 percent [CR, 10 percent]). Median duration of response (DOR) was NR (95 percent CI: 0+-85+) for newly diagnosed CLL patients and was 57 months (95 percent CI: 0+-85+) for R/R CLL patients.[6] Median PFS was NR (95 percent CI: not estimable [NE], NE) for newly diagnosed CLL patients and was 51 months (95 percent CI: 37-70) for R/R CLL patients.[4,6] The median OS was NR in newly diagnosed (95 percent CI: 80-NE) or R/R CLL patients (95 percent CI: 63-NE), with estimated seven-year OS rates of 75 percent and 52 percent, respectively.[4]

Grade 3 or higher AEs were reported in 74 percent of newly diagnosed and 89 percent of R/R patients with CLL. Hypertension (newly diagnosed, 32 percent; R/R, 26 percent), diarrhoea (newly diagnosed, 16 percent; R/R, 4 percent), and hyponatraemia (newly diagnosed, 10 percent; R/R, 0 percent) were among the most common Grade 3 or higher treatment-emergent AEs. Major haemorrhage and Grade 3 or higher atrial fibrillation, thrombocytopenia, anaemia, and arthralgia were observed in 11 percent or less of newly diagnosed and R/R patients. In addition, infection (newly diagnosed, 23 percent; R/R, 55 percent) was more common in R/R CLL patients.[6] No new or unexpected AEs were observed, and the occurrence of most Grade 3 or higher AEs and serious AEs decreased over time, with the exception of hypertension.[6]

#ENDS#

About the ECOG-ACRIN E1912 study

The Phase 3 study (E1912) evaluated previously untreated patients with CLL aged 70 years or younger, who were randomly assigned to receive ibrutinib (420 mg/day until disease progression) and rituximab (50 mg/m^2 on day 1 of cycle 2; 325 mg/m^2 on day 2 of cycle 2; 500 mg/m^2 on day 1 of cycles 3-7) (n=354) or six courses of intravenous fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) days 1-3 with rituximab (50 mg/m^2 on day 1 of cycle 1; 325 mg/m^2 on day 2 of cycle 1; 500 mg/m^2 on day 1 of cycles 2-6) every 28-days (n=175). The primary endpoint was PFS with a secondary endpoint of OS.[2]

The federally funded study was designed by researchers with ECOG-ACRIN. It was conducted through the NCI's National Clinical Trials Network. Pharmacyclics LLC provided ibrutinib under a cooperative research and development agreement with NCI and a separate agreement with ECOG-ACRIN.

About the iLLUMINATE study

iLLUMINATE (PCYC-1130) evaluated newly diagnosed CLL patients who were randomised to receive ibrutinib 420 mg once-daily continuously until disease progression or unacceptable toxicity in combination with obinutuzumab 1000 mg intravenously over six cycles (n=113); or chlorambucil on Days 1 and 15 of each cycle plus obinutuzumab 1000 mg intravenously over 6 cycles (n=116). Median age of the patients was 71 years and 65 percent of the patients had high-risk genomic features. The primary endpoint was PFS, as assessed by an Independent Review Committee. Secondary endpoints included PFS in a high-risk population, rate of undetectable MRD, ORR, OS, and safety.[3]

About PCYC-1102 and PCYC-1103

With up to seven years of follow-up, the studies (Phase 1b/2, PCYC-1102 and its extension, PCYC-1103) evaluated newly diagnosed and R/R CLL patients (n=132; newly diagnosed=31, R/R=101), including those with high-risk features, who received 420 mg or 840 mg once-daily ibrutinib until disease progression or unacceptable toxicity. As of the cutoff, 55 percent of newly diagnosed and 21 percent of R/R patients continued ibrutinib, with median follow-up of 67 months.[4]

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.

Ibrutinib is approved in more than 90 countries, and, to date, has been used to treat more than 135,000 patients worldwide across its approved indications.[10]

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 information on dosage and administration, contraindications and other precautions when using ibrutinib please refer to the Summary of Product Characteristics for further information.

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.

Janssen Biotech, Inc., Janssen-Cilag International NV and Janssen-Cilag Limited 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 a recommendation to broaden the existing marketing authorisation for 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 materialise, actual results could vary materially from the expectations and projections of Janssen-Cilag International NV, Janssen-Cilag Limited, Janssen Biotech, Inc., 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 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," in the company's most recently filed Quarterly Reports 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. Neither 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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