

European Commission approves Venclxyto plus Gazyvaro for adults with previously untreated chronic lymphocytic leukaemia

- **Combination regimen offers a new 12-month, fixed-duration, chemotherapy-free treatment option for adult patients with chronic lymphocytic leukaemia**
- **Results of the phase III CLL14 study add to the growing body of evidence supporting the potential of Venclxyto-based combinations across multiple lines**
- **Data showed that a fixed duration of treatment with Venclxyto plus Gazyvaro reduced the risk of disease progression or death by 65% compared to a current standard-of-care**

Basel, 12 March 2020 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the European Commission has approved Venclxyto® (venetoclax) in combination with Gazyvaro® (obinutuzumab) for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

“Venclxyto plus Gazyvaro is the first fixed-duration, chemotherapy-free treatment option that has been shown to help patients with untreated chronic lymphocytic leukaemia live longer without their disease progressing,” said Levi Garraway, M.D., Ph.D., Roche’s Chief Medical Officer and Head of Global Product Development. “This is an important step forward for adults with this disease in the EU, who will now have an effective treatment option that enables them to end treatment after one year.”

The approval is based on results from the primary analysis of the pivotal phase III CLL14 study, which evaluated the combination of 12-month, fixed-duration Venclxyto plus Gazyvaro compared to Gazyvaro plus chlorambucil in adults with previously untreated CLL who had co-existing medical conditions. Results from the primary analysis showed that the combination of Venclxyto plus Gazyvaro led to a 65% reduction in the risk of disease worsening or death (progression-free survival [PFS], as assessed by investigators) compared to Gazyvaro plus chlorambucil, a current standard-of-care for CLL (HR=0.35; 95% CI 0.23-0.53; p<0.0001). When PFS was assessed by an independent review committee, this finding was confirmed. Venclxyto plus Gazyvaro also showed higher response rates (ORR), doubled the complete response rates (CR/CRi) and demonstrated higher rates of minimal residual disease (MRD)-negativity, meaning that no cancer can be detected using a specific and highly sensitive test. In peripheral blood, MRD-negativity rates were 76% for Venclxyto plus Gazyvaro versus 35% for Gazyvaro plus chlorambucil, and in bone marrow MRD-negativity rates were 57% versus 17%, respectively. Results from an updated efficacy analysis (with a median follow-up of 40 months) were consistent with the primary data, and showed that the combination reduced the risk of disease worsening or death by 69% compared to Gazyvaro plus chlorambucil (HR=0.31; 95% CI 0.22-0.44). Safety for Venclxyto plus Gazyvaro appeared consistent with the known safety profile of the individual medicines, and no new safety signals were identified with the combination. The most commonly reported adverse events in people treated with Venclxyto plus Gazyvaro were low white blood cell count (neutropenia), diarrhoea and upper respiratory tract infection.

Results from the CLL14 study further demonstrate Venclyxto's potential across multiple lines (in the R/R and the frontline settings) in CLL. Previously, the European Commission has approved Venclyxto in combination with MabThera® (rituximab) for the treatment of adults with CLL who have received at least one prior therapy, and as a monotherapy for the treatment of CLL in the presence or absence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor. The US Food and Drug Administration (FDA) approved Venclexta® in combination with Gazyva® for the treatment of people with previously untreated CLL with co-existing medical conditions in May 2019. This followed rapid review and approval of the supplemental New Drug Application under the FDA's Real-Time Oncology Review (RTOR) and Assessment Aid pilot programmes. Additional submissions of the data to health authorities around the world are still ongoing, with the goal of bringing this new treatment option to more patients as soon as possible.

Venclexta/Venclyxto is being developed by AbbVie and Roche. It is jointly commercialised by AbbVie and Genentech, a member of the Roche Group, in the US, under the brand name Venclexta, and commercialised by AbbVie outside of the US.

About the CLL14 study¹

CLL14 (NCT02242942) is a randomised phase III study evaluating the combination of fixed-duration Venclyxto plus Gazyvaro compared to Gazyvaro plus chlorambucil in adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and co-existing medical conditions. 432 patients with previously untreated CLL were randomly assigned to receive either a 12-month duration of Venclyxto alongside six-month duration of Gazyvaro (Arm A) or six-month duration of Gazyvaro alongside 12-month duration of chlorambucil (Arm B). Arm A started with an initial dosing of Gazyvaro followed by a five-week Venclyxto dose ramp-up to help reduce the risk of tumour lysis syndrome. The primary endpoint of the study is investigator-assessed (INV) progression-free survival (PFS). Secondary endpoints include PFS assessed by independent review committee (IRC), minimal residual disease (MRD) status, overall response rate (ORR), complete response rate (CR, with or without complete blood count recovery), overall survival, duration of response, event-free survival, time to next CLL treatment, and safety. MRD-negativity means no cancer can be detected using a specific, highly sensitive test, and was defined as less than one cancer cell in 10,000 leukocytes. The CLL14 study is being conducted in cooperation with the German CLL Study Group, headed by Michael Hallek, MD, University of Cologne.

CLL14 study primary analysis results²		
Treatment arm	Venclyxto + Gazyvaro (n=216)	Gazyvaro + chlorambucil (n=216)
INV-assessed PFS (primary endpoint)		
Median PFS	Not reached	Not reached
Hazard ratio	0.35 (95% CI 0.23-0.53), p<0.0001	
Additional efficacy results (secondary endpoints)		
IRC-assessed PFS^a		
Median PFS	Not reached	Not reached
Hazard ratio	0.33 (95% CI 0.22-0.51), p<0.0001	
Response rates		
ORR	85%	71%
CR + complete remission with incomplete bone marrow recovery (CRi)	50%	23%
MRD^b		
MRD-negative, bone marrow,	57%	17%
p-value	p<0.0001	
MRD-negative, peripheral blood,	76%	35%
p-value	p<0.0001	
Safety		
Adverse events	The most common adverse reactions (≥20%) with Venclyxto plus Gazyvaro were low white blood cell count (neutropenia), diarrhoea and upper respiratory tract infection. The most common serious adverse events in people treated with Venclyxto plus Gazyvaro were febrile neutropenia, pneumonia, infusion-related infection and pyrexia.	

^a Data at median follow-up of 28 months

^b Data at three months following end of combination treatment, in the intention-to-treat population

About Venclyxto (venetoclax)

Venclyxto is a first-in-class targeted medicine designed to selectively bind and inhibit the B-cell lymphoma-2 (BCL-2) protein. In some blood cancers and other tumours, BCL-2 builds up and prevents cancer cells from dying or self-destructing, a process called apoptosis. Venclyxto blocks the BCL-2 protein and works to restore the process of apoptosis.

Venclexta/Venclyxto is being developed by AbbVie and Roche. It is jointly commercialised by AbbVie and Genentech, a member of the Roche Group, in the US, under the brand name Venclexta, and commercialised by AbbVie outside of the US. Together, the companies are committed to research with Venclexta/Venclyxto, which is currently being studied in clinical trials across several types of blood and other cancers.

In the US, Venclexta has been granted five Breakthrough Therapy Designations by the US Food and Drug Administration: one for previously untreated chronic lymphocytic leukaemia (CLL), two for relapsed or refractory CLL and two for previously untreated acute myeloid leukaemia.

About Gazyvaro (obinutuzumab)

Gazyvaro is an engineered monoclonal antibody designed to attach to CD20, a protein expressed on certain B-cells, but not on stem cells or plasma cells. Gazyvaro is designed to attack and destroy targeted B-cells both directly and together with the body's immune system. Gazyvaro is marketed as Gazyva in the US.

Gazyva/Gazyvaro is currently approved in more than 90 countries in combination with chlorambucil for people with previously untreated chronic lymphocytic leukaemia, in more than 80 countries in combination with bendamustine for people with certain types of previously treated follicular lymphoma and in more than 70 countries in combination with chemotherapy for previously untreated follicular lymphoma.

Additional combination studies investigating Gazyvaro with other approved or investigational medicines, including cancer immunotherapies and small molecule inhibitors, are underway across a range of blood cancers.

About chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia in the Western world.³ CLL mainly affects men and the median age at diagnosis is about 70 years.⁴ Worldwide, the incidence of all leukaemias is estimated to be over 400,000, with an incidence of over 100,000 in Europe.⁵ CLL is estimated to affect around one-third of all people newly diagnosed with leukaemia.³

About Roche in haematology

Roche has been developing medicines for people with malignant and non-malignant blood diseases for over 20 years; our experience and knowledge in this therapeutic area runs deep. Today, we are investing more than ever in our effort to bring innovative treatment options to patients across a wide range of haematologic diseases. Our approved medicines include MabThera®/Rituxan® (rituximab), Gazyva®/Gazyvaro® (obinutuzumab), Polivy® (polatuzumab vedotin), Venclexta®/Venclyxto® (venetoclax) in collaboration with AbbVie, and Hemlibra® (emicizumab). Our pipeline of investigational haematology medicines includes idasanutlin, a small molecule which inhibits the interaction of MDM2 with p53; T-cell engaging bispecific antibodies targeting both CD20 and CD3, Tecentriq® (atezolizumab), a monoclonal antibody designed to bind with PD-L1; and crovalimab, an anti-C5 antibody engineered to optimise complement inhibition. Our scientific expertise, combined with the breadth of our portfolio and pipeline, also provides a unique opportunity to develop combination regimens that aim to improve the lives of patients even further.

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management.

Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. More than thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Moreover, for the eleventh consecutive year, Roche has been recognised as one of the most sustainable companies in the Pharmaceuticals Industry by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2019 employed about 98,000 people worldwide. In 2019, Roche invested CHF 11.7 billion in R&D and posted sales of CHF 61.5 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

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References

- [1] Fischer K, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. *N Engl J Med*. 2019;380:2225-2236.
- [2] Venclyxto Summary of Product Characteristics 2020.
- [3] Wendtner CM, et al. Chronic lymphocytic leukemia. *Onkopedia guidelines 2012* [Internet; cited February 2020]. Available from: <https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/chronic-lymphocytic-leukemia-ctl/@guideline/html/index.html>.
- [4] SEER Stat Fact Sheets: Chronic Lymphocytic Leukemia (CLL). [Internet; cited February 2020]. Available from: <http://seer.cancer.gov/statfacts/html/clyl.html>.
- [5] Calculation for Worldwide and European incidence: GLOBOCAN 2018. World Fact Sheet. [Internet; cited February 2020]. Available from: <http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf>.

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