Roche announces new data reinforcing the long-term benefit of Venclexta/Venclyxto-based combination for people with relapsed or refractory chronic lymphocytic leukaemia

- **Long-term follow-up data from the phase III MURANO trial showed sustained progression-free survival with fixed-duration Venclexta/Venclyxto plus MabThera/Rituxan**
- **MURANO and phase III CLL14 trials confirm chronic lymphocytic leukaemia patients treated with Venclexta/Venclyxto-based regimens achieve higher rates of undetectable minimal residual disease*, which may be associated with a lower risk of future disease progression or death**

Basel, 5 December 2020 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that new data from the pivotal phase III MURANO and CLL14 studies support the efficacy of fixed-duration, chemotherapy-free Venclexta®/Venclyxto® (venetoclax)-based combinations in certain people with chronic lymphocytic leukaemia (CLL) and provide more evidence on the potential value of minimal residual disease (MRD). Data were presented at the all-virtual 62nd American Society of Hematology (ASH) Annual Meeting and Exposition on Saturday 5 December 2020.

"These results reinforce the long-term value of fixed-duration, chemotherapy-free Venclexta/Venclyxto-based combinations in CLL, potentially offering patients a significant period of time without treatment following initial therapy," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "These data also reflect our ongoing commitment to accelerating clinical advancements for patients by exploring the novel endpoint minimal residual disease as a potential predictor of patient outcomes."

Five-year data from the pivotal phase III MURANO trial continue to show sustained investigator-assessed progression-free survival (PFS) with Venclexta/Venclyxto plus MabThera*/Rituxan* (rituximab). Data, presented in an oral session, showed:

- Venclexta/Venclyxto plus MabThera/Rituxan reduced the risk of disease progression or death by 81% (HR= 0.19; 95% CI: 0.15, 0.26; p<0.0001) compared to bendamustine plus MabThera/Rituxan (BR) in people with relapsed or refractory (R/R) CLL.
- At the time of analysis, median overall survival (OS) had not been reached in either arm, however, five-year OS was 82.1% in the Venclexta/Venclyxto plus MabThera/Rituxan arm, compared to 62.2% in the BR arm (HR=0.40; 95% CI: 0.26, 0.62).
- In the Venclexta/Venclyxto arm, among the 130 patients who completed two years of treatment without progressive disease, 63.8% (n=83/130) had undetectable MRD (uMRD) levels at the end of treatment. In an analysis of this patient subgroup, uMRD was associated with improved progression-free survival. Undetectable MRD, sometimes referred to as MRD-negativity, means that no cancer cells could be detected using a specific and highly sensitive test, and is defined as less than one cancer cell in 10,000 leukocytes.

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- No new safety events were reported in the study.[1]

Data from the phase III CLL14 study contributes to growing evidence regarding the potential of MRD measurements to predict future outcomes for certain people with previously untreated CLL who were treated with fixed-duration Venclexta/Venclyxto plus Gazyva*/Gazyvaro* (obinutuzumab):

- Patients with uMRD and a partial response (PR) had longer PFS than patients with detectable MRD and a complete response (CR).[2]
- In collaboration with Adaptive Biotechnologies, clonal growth rate, a measure for how quickly cancer cells grow, was analysed using the next-generation sequencing Adaptive clonoSEQ* Assay and insights were used to better understand the potential role of MRD in predicting outcomes. In this analysis, after treatment with fixed-duration Venclexta/Venclyxto plus Gazyva/Gazyvaro, the estimated clonal growth rate was slower and lower, suggesting more effective MRD eradication in these patients compared to those treated with Gazyva/Gazyvaro plus chlorambucil. Early data suggest a correlation between MRD responses and PFS, which will be further evaluated by the study authors.[3]

Exploring novel endpoints, such as MRD, is an important area of development for Roche, which continues to investigate Venclexta/Venclyxto in a robust clinical development programme. This includes the phase III CRISTALLO trial in previously untreated CLL, which uses MRD as a primary endpoint.

Venclexta/Venclyxto is approved in the US and EU in combination with MabThera/Rituxan for the treatment of adult patients with CLL who have received at least one prior therapy; in combination with Gazyva/Gazyvaro for the treatment of adult patients with previously untreated CLL; and as a monotherapy for the treatment of CLL in the presence of 17p deletion or TP53 mutation in people who are unsuitable for or have failed a B-cell receptor pathway inhibitor.

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.

*Minimal residual disease (MRD) is a measure of the number of remaining cancer cells. Undetectable MRD (uMRD), sometimes referred to as MRD-negativity, means that no cancer cells could be detected using a specific and highly sensitive test, and is defined as less than one cancer cell in 10,000 leukocytes.

About the MURANO study [4]

MURANO [NCT02005471] is a phase III open-label, international, multicentre, randomised study evaluating the efficacy and safety of fixed-duration Venclexta*/Venclyxto* (venetoclax) in combination with MabThera*/Rituxan* (rituximab) compared to bendamustine in combination with MabThera/Rituxan (BR). All treatments were of fixed duration. Following a five-week dose ramp-up schedule for Venclexta/Venclyxto, patients on the Venclexta/Venclyxto plus MabThera/Rituxan arm received six cycles of Venclexta/Venclyxto plus MabThera/Rituxan followed by Venclexta/Venclyxto monotherapy for up to two years total. Patients on the BR arm received six cycles of BR. The study included 389 patients with chronic lymphocytic leukaemia, with or without 17p deletion, who had been previously treated with at least one line of therapy. Patients were randomly assigned in a 1:1 ratio to receive either Venclexta/Venclyxto plus MabThera/Rituxan or BR. The primary endpoint of the study was progression-free survival. Secondary endpoints included overall survival, overall response rate and complete response rate (with or without complete blood count recovery).

About the CLL14 study [5]

CLL14 [NCT02242942] is a randomised phase III study evaluating the combination of fixed-duration Venclexta*/Venclyxto* (venetoclax) plus Gazyva*/Gazyvaro* (obinutuzumab) compared to Gazyva/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 Venclexta/Venclyxto alongside six-month duration of Gazyva/Gazyvaro (Arm A) or six-month duration of Gazyva/Gazyvaro alongside 12-month duration of chlorambucil (Arm B). Arm A started with an initial dosing of Gazyva/Gazyvaro followed by a five-week Venclexta/Venclyxto dose ramp-up to help reduce the risk of tumour burden. The primary endpoint of the study is investigator-assessed progression-free survival (PFS). Secondary endpoints include PFS assessed by independent review committee, minimal residual disease (MRD) status, overall response rate, complete response rate (with or without complete blood count recovery), overall survival, duration of response, event-free survival, time to next CLL treatment, and safety. MRD-negativity, or undetectable MRD, means no cancer can be detected using a specific and 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.

About Venclexta/Venclyxto (venetoclax)

Venclexta*/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. Venclexta/Venclyxto blocks the BCL-2 protein and works to restore the process of apoptosis.

Venclexta is being developed by AbbVie and Roche. It is jointly commercialised by AbbVie and Genentech, a member of the Roche Group, in the US, and commercialised by AbbVie, under the brand name Venclyxto 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 Gazyva/Gazyvaro (obinutuzumab)
Gazyva®/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. Gazyva/Gazyvaro is designed to attack and destroy targeted B-cells both directly and together with the body's immune system.

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 Gazyva/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. [6] CLL mainly affects men and the median age at diagnosis is about 70 years.[7] Worldwide, the incidence of all leukaemias is estimated to be over 400,000, with an incidence of over 100,000 in Europe.[8] CLL is estimated to affect around one-third of all people newly diagnosed with leukaemia.[6]

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 T-cell engaging bispecific antibodies, glofitamab and mosunetuzumab, targeting both CD20 and CD3, and cevostamab, targeting FcRH5 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 twelfth 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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