Roche announces data at EHA2021 reinforcing efficacy of Venclexta/Venclyxto combinations in chronic lymphocytic leukaemia and acute myeloid leukaemia

- **Four-year follow-up analysis from the phase III CLL14 study showed progression-free survival rate of 74.0% in previously untreated patients with chronic lymphocytic leukaemia (CLL) three years after completion of a one-year fixed-duration treatment with Venclexta/Venclyxto plus Gazyva/Gazyvaro[1]**
- **New phase III MURANO study data suggested certain genetic risk factors may help tailor treatments for patients with previously treated CLL[2]**
- **A post-hoc analysis from the phase III VIALE-A study in newly diagnosed acute myeloid leukaemia indicated increased duration of response, event-free survival and overall survival in patients who achieved undetectable minimal residual disease[3]**

Basel, 11 June 2021 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced the latest data from three pivotal phase III studies of Venclexta®/Venclyxto® (venetoclax) – CLL14, MURANO and VIALE-A – to be presented at the European Hematology Association Virtual Congress, June 9-17 (EHA2021). Long-term follow-up data from the CLL14 and MURANO studies support the primary analysis of Venclexta/Venclyxto in chronic lymphocytic leukaemia (CLL) and the possibility of tailoring treatment approaches based on genetic risk factors. Furthermore, the latest research shows the potential of minimal residual disease (MRD) as a key measure of disease response in CLL and acute myeloid leukaemia (AML).

"The data from these Venclexta/Venclyxto combinations support our continued commitment to provide valuable therapeutic options for patients with hard-to-treat blood cancers," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "These data also advance our understanding of minimal residual disease, which we believe is a useful endpoint that may help identify patients more quickly who are in need of additional treatment."

Four-year follow-up analysis of the phase III CLL14 study

This four-year post-hoc analysis of investigator-assessed progression-free survival (PFS) had a median follow-up of 52.4 months (interquartile range: 49.5-56.2 months). The fixed treatment duration (12 months) study indicated that the chemotherapy-free Venclexta/Venclyxto plus Gazyva/Gazyvaro (obinutuzumab) regimen had an estimated PFS rate of 74.0% vs 35.4% for Gazyva/Gazyvaro plus chlorambucil. Importantly, the time to next treatment (TTNT) was significantly longer among patients treated with the Venclexta/Venclyxto plus Gazyva/Gazyvaro regimen versus the comparator (four-year TTNT 81.1% vs 59.9%; HR 0.46, 95% CI [0.32-0.65], p<0.0001).[1]

Furthermore, 30 months after the end of treatment, 26.9% of the Venclexta/Venclyxto-treated patients still had undetectable MRD (uMRD) compared with 3.2% of those treated with the comparator.[1] 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.[4] Undetectable MRD is emerging as a measure of disease response that may be useful to consider in treatment decision-making.

Common grade 3-4 adverse events with Venclexta/Venclyxto and Gazyva/Gazyvaro at 28 months follow-up were low white blood cell count and infections.[5]

Substudy from the phase III MURANO study
Results from this substudy suggested that increased prevalence of certain unfavourable genetic risk factors negatively impacted the MRD response of patients who were retreated with Venclexta/Venclyxto plus MabThera®/Rituxan® (rituximab) after progression on treatment with that regimen. These data indicate the potential to tailor treatment approaches for patients with previously treated CLL based on genetic risk factors.[2]

Post-hoc analysis of the phase III VIALE-A study
Additionally, a post-hoc analysis from the phase III VIALE-A study suggested the value of continued research to understand the role of MRD monitoring in AML. In the analysis, patients who achieved a composite complete remission and uMRD following treatment with Venclexta/Venclyxto and azacitidine, a hypomethylating agent, had improved survival outcomes compared with those who were MRD-positive following treatment. The 12-month estimates for duration of response, overall survival and event-free survival for both groups are listed below:

	Achieved composite complete remission and uMRD (MRD<10^{-3})	Did not achieve composite complete remission and uMRD (MRD≥10^{-3})
Duration of response	81.2% (95% CI 69.3-88.9)	46.6% (95% CI 35.6-56.8)
Overall survival	94.0% (95% CI 84.7-97.7)	67.9% (95% CI 57.6-76.2)
Event-free survival	83.2% (95% CI 71.6-90.3)	45.4% (95% CI 35.2-55.0)

Adverse events of grade ≥3 (MRD<10-3/MRD≥10-3) were febrile neutropenia (50%/43%), neutropenia (50%/35%), and thrombocytopenia (44%/44%), similar to the overall population.[3]

Roche is collaborating with regulatory authorities and others in the industry to advance understanding of MRD. The company continues to investigate Venclexta/Venclyxto in a robust clinical development programme, including in 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 is also approved in the US in combination with azacitidine, decitabine, or low dose cytarabine for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. In the EU, Venclyxto is approved in combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

About the CLL14 study

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. Four hundred and thirty-two 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 included PFS assessed by independent review committee, minimal residual disease status, overall response rate, complete response rate, and safety. The CLL14 study is being conducted in cooperation with the German CLL Study Group, headed by Michael Hallek, M.D., University of Cologne.

About the MURANO study

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. The study included 389 patients with chronic lymphocytic leukaemia (CLL), with or without 17p deletion, who had been previously treated with at least one line of therapy. A substudy from 2018 onward enrolled 34 relapsed or refractory CLL patients who progressed after initial treatment to receive

Venclexta/Venclyxto plus MabThera/Rituxan as retreatment (n=25) or who crossed over from the BR arm (n=9). 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 VIALE-A study
VIALE-A [NCT02993523] is a phase III, randomised, double-blind, placebo-controlled multicentre study evaluating the efficacy and safety of Venclexta®/Venclyxto® (venetoclax) plus azacitidine, a hypomethylating agent, compared to placebo with azacitidine, in 431 people with previously untreated acute myeloid leukaemia who are ineligible for intensive chemotherapy. Two-thirds of patients (n=286) received 400 mg Venclexta/Venclyxto daily, in combination with azacitidine, and the remaining patients (n=145) received placebo tablets in combination with azacitidine. Patients enrolled in the study had a range of mutational subtypes, including IDH1/2 and FLT3. VIALE-A met its primary and key secondary endpoints.

About Venclexta/Venclyxto
Venclexta®/Venclyxto® (venetoclax) 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/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 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 cancers.

In the US, Venclexta has been granted five Breakthrough Therapy Designations by the U.S. 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 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, as well as growing capabilities in the area of data-driven medical insights help Roche deliver truly personalised healthcare. Roche is working with partners across the healthcare sector to provide the best care for each person.

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. In recent years, Roche has invested in genomic profiling and real-world data partnerships and has become an industry-leading partner for medical insights.

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 2020 employed more than 100,000 people worldwide. In 2020, Roche invested CHF 12.2 billion in R&D and posted sales of CHF 58.3 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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