Media Release

Eight-year data from APHINITY study show Roche's Perjeta-based regimen continues to reduce the risk of disease returning for people with HER2-positive early breast cancer

- **Greatest benefit continued to be seen in people who are at a high risk of recurrence (those with lymph node-positive disease)**
- **With longer follow-up, treatment effect continues to be seen regardless of hormone receptor status; however overall survival data remain immature**
- **The majority of HER2-positive breast cancer cases are diagnosed at an early stage, when the aim of treatment is cure [1,2]**

Basel, 14 July 2022 - Roche (SIX: RO, ROG; OTCQX: RHHBY), the Breast International Group (BIG), Institut Jules Bordet Clinical Trials Support Unit (IJB-CTSU) and Frontier Science Foundation (FS) today announced updated data from the phase III APHINITY study in HER2-positive early breast cancer. Results at 8.4 years median follow-up (101 months) showed the continued benefit of the combination of Perjeta® (pertuzumab), Herceptin® (trastuzumab) and chemotherapy (the Perjeta-based regimen), versus Herceptin, chemotherapy and placebo, when given as post-surgery (adjuvant) intravenous (IV) treatment for people with lymph node (LN)-positive, HER2-positive early breast cancer, who are at high risk of recurrence. For patients with lymph node (LN)-positive disease, results showed a 28% reduction in the risk of recurrence or death, corresponding to an absolute benefit at eight years of 4.9% (invasive disease-free survival [iDFS], hazard ratio [HR]=0.72, 95% confidence interval [CI] 0.60-0.87). The safety profile was consistent with previous studies. Full findings were presented today at the European Society for Medical Oncology (ESMO) Virtual Plenary (VP6-2022).[3]

"The eight-year APHINITY results show the great progress made in treating this aggressive form of early breast cancer," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "HER2-positive breast cancers are more likely than other subtypes to recur following surgery, so targeted treatment is critical to provide the best chance for a cure."

Prof. Sibylle Loibl, Chair of the German Breast Group (GBG) and the Chief Executive Officer of the GBG Forschungs GmbH, and APHINITY Study Chair, also commented: "These updated APHINITY data showed further reduction in the risk of cancer returning or death with a pertuzumab-based regimen in patients with LN-positive, HER2-positive early breast cancer, regardless of hormone receptor status. The trend towards a survival benefit was influenced by the LN-positive cohort and additional follow-up is very important to determine possible survival benefit and long-term safety of this regimen."

The third interim overall survival (OS) analysis of the APHINITY study was conducted after a median follow-up of 8.4 years (101 months), and also included updated results on iDFS and safety. The results showed remarkable outcomes consistent with prior analyses.[3,4,5]

After eight years, results showed: [3]

- Fewer deaths were observed with the Perjeta-based regimen (168 [7.0%] versus 202 [8.4%] [HR=0.83; 95% CI: 0.68-1.02]); however, OS data remain immature and statistical significance has not yet been reached.
- The Perjeta-based regimen continued to reduce the risk of breast cancer recurrence or death versus Herceptin, chemotherapy and placebo, by 23% in the overall study population (iDFS, HR=0.77, 95% CI 0.66-0.91).
- More people who received post-surgery treatment with the Perjeta-based regimen remained disease-free than those treated with Herceptin, chemotherapy and placebo (88.4% and 85.8% respectively, showing an absolute benefit of 2.6%).
- The greatest benefit continued to be observed in people at high risk of cancer recurrence, primarily those with LN-positive disease (when the cancer has spread from the breast to the lymph nodes), who are in highest need of more efficacious treatments. In these people there was a 28% reduction in the risk of recurrence or death with the Perjeta-based regimen (HR=0.72; 95% CI 0.60-0.87, showing an absolute benefit of 4.9%: 86.1% versus 81.2%).
- Consistent with the prior analysis, the effect of the Perjeta-based regimen was seen regardless of hormone receptor status. There was a 25% and 18% reduction in the risk of recurrence or death in people with hormone receptor-positive disease and those with hormone receptor-negative disease, respectively (hormone receptor-positive disease: HR=0.75; 95% CI 0.61-0.92 and hormone receptor-negative disease: HR=0.82; 95% CI 0.64-1.06).
- The safety profile, including cardiac safety, was consistent with previous studies and no new or unexpected safety signals were identified. [3,4,5]

Based on the primary analysis of the study in 2017, the clinical value of the Perjeta-based regimen has been recognised by health authorities worldwide. The regimen is approved for the treatment of people with early breast cancer who are at a high risk of recurrence in more than 100 countries, including the United States (US), the European Union (EU) and China. It has also been recognised in multiple international treatment guidelines, including those from the American Society of Clinical Oncology (ASCO), ESMO, the National Comprehensive Cancer Network (NCCN) and St Gallen International Breast Cancer Conference, which recommend it as a standard of care for the post-surgery treatment of people with HER2-positive early breast cancer at high risk of recurrence. [4,6,7,8,9,10]

More than 500,000 people worldwide who have HER2-positive breast cancer and are at high risk of recurrence have received the Perjeta-based regimen so far. [6]

Patients with either early or metastatic HER2-positive breast cancer may receive Perjeta and Herceptin at the same time in a single under-the-skin (subcutaneous) injection. Phesgo® is a fixed-dose combination of Perjeta and Herceptin with hyaluronidase, which offers faster administration under the skin in just minutes, compared to hours with standard IV administration. Phesgo, in combination with IV chemotherapy, has been approved in 73 countries, including the US and in the EU, for the treatment of people with HER2-positive early and metastatic breast cancer. [6,11,12]

Breast cancer is the most frequently diagnosed type of cancer, with major societal impact. HER2-positive breast cancer is a particularly aggressive form of the disease that affects approximately 15-20% of people with the condition. [13,14]

APHINITY iDFS results overview

Hazard Ratio (95% CI) iDFS in the intention to treat (ITT) population and in subgroups based on lymph node and hormone receptor status				**iDFS at eight years from randomisation (median follow-up of 8.4 years)**		
Population	**Primary Analysis 2017 [4]** (median follow-up 45.4 months)	**Updated Analysis 2019 [5]** (median follow-up 74.1 months)	**Updated Analysis 2022 [3]** (median follow-up 101 months)	**Perjeta + Herceptin + chemo [3]** (Perjeta-based regimen)	**Herceptin + chemo + placebo [3]**	**Absolute benefit [3]**
ITT	0.81 (0.66-1.00)	0.76 (0.64-0.91)	0.77 (0.66-0.91)	88.4%	85.8%	2.6%
LN-positive	0.77 (0.62-0.96)	0.72 (0.59-0.87)	0.72 (0.60-0.87)	86.1%	81.2%	4.9%
LN-negative	1.13 (0.68-1.86)	1.02 (0.69-1.53)	1.01 (0.72-1.42)	92.3%	93.3%	-1.0%
HR-positive	0.86 (0.66-1.13)	0.73 (0.59-0.92)	0.75 (0.61-0.92)	88.9%	86.1%	2.8%
HR-negative	0.76 (0.56-1.04)	0.83 (0.63-1.10)	0.82 (0.64-1.06)	87.5%	85.2%	2.3%

About the APHINITY breast cancer study [15]

APHINITY (Adjuvant Pertuzumab and Herceptin IN Initial TherapY in Breast Cancer, NCT01358877/ BO25126/ BIG 4-11) is a global, phase III, randomised, double-blind, placebo-controlled, two-arm study evaluating the efficacy and safety of Perjeta plus Herceptin and chemotherapy, compared to Herceptin and chemotherapy, as post-surgery (adjuvant) treatment in 4,804 people with operable HER2-positive early breast cancer.

The primary endpoint is invasive disease-free survival, which in this study is defined as the time a patient lives without recurrence of invasive breast cancer (when the cancer returns locally or spreads into the surrounding breast tissue and/or beyond) or death from any cause after post-surgery treatment. Secondary endpoints include cardiac and overall safety, overall survival and health-related quality of life. The study will continue to follow each participant for fifteen years from when the last patient was enrolled in the study.

About Perjeta [14,16,17]

Perjeta is a medicine that targets the HER2 receptor, a protein found on the outside of many normal cells and in high quantities on the outside of cancer cells in HER2-positive cancers. Perjeta is designed specifically to prevent the HER2 receptor from pairing (or 'dimerising') with other HER receptors (EGFR/HER1, HER3 and HER4) on the surface of cells, a process that is believed to play a role in tumour growth and survival. Binding of Perjeta to HER2 may also signal the body's immune system to destroy the cancer cells. The mechanisms of action of Perjeta and Herceptin are believed to complement each other, as both bind to the HER2 receptor, but to different locations. The combination of Perjeta and Herceptin is thought to provide a more comprehensive, dual blockade of HER signalling pathways, thus preventing tumour cell growth and survival.

About Phesgo [11,14,16,18]

Phesgo combines the same monoclonal antibodies as Perjeta and Herceptin with Halozyme Therapeutics' Enhanze® drug delivery technology in a novel formulation for subcutaneous (SC) use. This is the first time that Roche has combined two monoclonal antibodies that can be administered by a single SC injection.

Halozyme's Enhanze drug delivery technology may enable and optimise SC drug delivery for appropriate co-administered therapeutics. The technology is based on a proprietary recombinant human hyaluronidase PH20 (rHuPH20), an enzyme that temporarily degrades hyaluronan – a glycosaminoglycan or chain of natural sugars in the body – to aid in the dispersion and absorption of other injected therapeutic drugs.

Pertuzumab in Phesgo is the same monoclonal antibody as in intravenous (IV) Perjeta, and trastuzumab in Phesgo is the same monoclonal antibody as in IV Herceptin. The mechanisms of action of Perjeta and Herceptin are believed to complement each other as both bind to the HER2 receptor, but in different locations. The combination of Perjeta and Herceptin is thought to provide a more comprehensive, dual blockade of the HER signalling pathways.

Phesgo, in combination with IV chemotherapy, has been approved in 73 countries, including the US and in the EU, for the treatment of people with HER2-positive early and metastatic breast cancer.

About Roche's medicines for HER2-positive breast cancer

Roche has been leading research into the HER2 pathway for more than 30 years and is committed to improving the health, quality of life and survival of people with both early and metastatic HER2-positive disease. Roche has developed four innovative medicines that have helped transform the treatment of HER2-positive breast cancer: Herceptin, Perjeta, Phesgo and Kadcyla® (trastuzumab emtansine). Eligibility for treatment with Roche's HER2-targeted medicines is determined via a diagnostic test which identifies people who will likely benefit from these medicines at the onset of their disease.

About Roche

Founded in 1896 in Basel, Switzerland, as one of the first industrial manufacturers of branded medicines, Roche has grown into the world's largest biotechnology company and the global leader in in-vitro diagnostics. The company pursues scientific excellence to discover and develop medicines and diagnostics for improving and saving the lives of people around the world. We are a pioneer in personalised healthcare and want to further transform how healthcare is delivered to have an even greater impact. To provide the best care for each person we partner with many stakeholders and combine our strengths in Diagnostics and Pharma with data insights from the clinical practice.
In recognising our endeavour to pursue a long-term perspective in all we do, Roche has been named one of the most sustainable companies in the pharmaceuticals industry by the Dow Jones Sustainability Indices for the thirteenth consecutive year. This distinction also reflects our efforts to improve access to healthcare together with local partners in every country we work.
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.

About Breast International Group

The Breast International Group (BIG) is an international not-for-profit organisation for academic breast cancer research groups from around the world, based in Brussels, Belgium. Global collaboration is crucial to make significant advances in breast cancer research, reduce unnecessary duplication of effort, share data, contribute to the faster development of better treatments, and increase the likelihood of cures for patients. Therefore, BIG facilitates breast cancer research at international level, by stimulating cooperation between its members and other academic networks, and collaborating with, but working independently from, the pharmaceutical industry.
In 1999, BIG was founded by Dr Martine Piccart and Dr Aron Goldhirsch with the aim to address fragmentation in European breast cancer research. Research groups from other parts of the world rapidly expressed interest in joining BIG and, two decades later, BIG represents a network of over 50 like-minded research groups from around the world. These entities are tied to several thousand specialised hospitals, research centres and world-class breast cancer experts across approximately 70 countries on 6 continents. More than 30 clinical trials are run or are under development under the BIG umbrella at any one time. BIG

also works closely with the US National Cancer Institute (NCI) and the National Clinical Trials Network (NCTN), so that together they act as a strong integrating force in the breast cancer research arena.

BIG's research is supported in part by its philanthropy unit, known as BIG against breast cancer. This denomination is used to interact with the general public and donors, and to raise funds for BIG's purely academic breast cancer trials and research programmes.

For more information, visit www.BIGagainstbreastcancer.org.

About Frontier Science Foundation

Frontier Science & Technology Research Foundation (FSTRF) is a non-profit, research organisation which supports research networks, pharmaceutical companies and investigators to conduct scientifically meaningful high-quality clinical trials. The Aphinity trial involved research staff in the US and in the Affiliate office in Scotland.

FSTRF works with scientists and technicians in more than 800 laboratories, universities and medical centres around the world to provide a comprehensive range of research services throughout the clinical trial process including design, analysis and reporting.

Through its work, FSTRF aims to advance the application of statistical science and practice and data management techniques in science, healthcare and education.

For more information, visit www.frontierscience.org.

About Institut Jules Bordet Clinical Trials Support Unit

The Clinical Trials Support Unit (CTSU) of the comprehensive cancer centre Institut Jules Bordet (IJB) is a department of the Institut Jules Bordet. The hospital, which is an academic non-profit organisation, is fighting cancer through the design, set-up and conduct of innovative clinical trials that matter to patients. The Institut Jules Bordet is an integrated multi-disciplinary centre, unique in Belgium and with an international reputation. It strongly believes that its work contributes to improve the understanding of the disease and to improve diagnosis, care and cancer treatments.

Since 2013, the IJB-CTSU has also been assisting researchers to develop and run investigator-initiated trials (phases I, II and III) for all cancer types, as well as for all treatment and diagnostic modalities. The strength of the IJB-CTSU team lies in its proximity to and interactions with the "real-world" of cancer care.

The IJB-CTSU proposes a wide range of services in clinical study management, from scientific support to operational activities. We promote an academic research while encouraging collaboration with other academic partners and pharmaceutical companies. The Institut learns from every success as well as from every setback, yet ultimately it remains motivated to take up new challenges to help cancer patients by promoting quality cancer research.

For more information, please visit https://ctsu.bordet.be.

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