Media Release

Basel, 05 June 2017

APHINITY study shows Roche's Perjeta®-based regimen reduced the risk of invasive cancer returning compared to Herceptin® and chemotherapy in HER2-positive early breast cancer

- **Phase III study confirms benefit of the Perjeta-based regimen over the current standard of care**
- **The study was positive in the overall population, with greatest risk reduction in patients with node-positive or hormone receptor-negative disease**
- **Data will be submitted to global health authorities**

Roche (SIX: RO, ROG; OTCQX: RHHBY), the Breast International Group (BIG), Breast European Adjuvant Study Team (BrEAST) and Frontier Science Foundation (FS) today announced the Phase III APHINITY study showed adjuvant (after surgery) treatment with the combination of Perjeta® (pertuzumab), Herceptin® (trastuzumab) and chemotherapy (the Perjeta-based regimen) significantly reduced the risk of breast cancer recurrence or death (invasive disease-free survival; iDFS) by 19% in people with HER2-positive early breast cancer (eBC) compared to Herceptin and chemotherapy alone (HR=0.81; 95% CI 0.66-1.00, p=0.045).[1] At three years, 94.1% of people treated with the Perjeta-based regimen did not have their breast cancer return compared to 93.2% treated with Herceptin and chemotherapy.[1] The safety profile of the Perjeta-based regimen was consistent with that seen in previous studies, with a low incidence of cardiac events and no new safety signals.[1,2]

Based on data available at the time of the primary analysis, an estimate of iDFS at four years showed that 92.3% of people treated with the Perjeta-based regimen did not have their breast cancer return compared to 90.6% treated with Herceptin and chemotherapy, suggesting that further analyses with longer follow-up will be important to provide additional insights on these treatments.[1]

"The goal of adjuvant treatment is to help each person with cancer have the best chance of a cure, and we come closer to this goal with each advance," said Sandra Horning, M.D., Chief Medical Officer and Head of Global Product Development. "In the APHINITY study, the Perjeta-based regimen improved upon the high bar set by Herceptin in people with HER2-positive early breast cancer. We look forward

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to working with global health authorities to bring this treatment option to patients."

Gunter von Minckwitz, M.D., study coordinator from the BIG and academic study partners, President of the German Breast Group, added, "APHINITY provides yet another example of the importance of industry-academic collaborations and their value in advancing cancer care for people affected by this challenging disease. The median follow-up at the primary analysis was 45.4 months, and these early data are very encouraging. As we continue to follow patients up to 10 years, we hope that future analyses will provide additional insights on the role of a pertuzumab-based regimen in HER2-positive early breast cancer."

At the time of the primary analysis, with median follow-up of 45.4 months, the reduction in risk of invasive breast cancer recurrence with the Perjeta-based regimen was greatest in people with lymph node-positive (HR=0.77; 95% CI 0.62-0.96, p=0.019) or hormone receptor-negative disease (HR=0.76; 95% CI 0.56-1.04, p=0.085).[1] At three years, among people with node-positive disease, 92.0% of people treated with the Perjeta-based regimen did not have their breast cancer return compared to 90.2% treated with Herceptin and chemotherapy, and iDFS rates in the hormone receptor-negative disease subgroup were 92.8% in the Perjeta-based arm and 91.2% in the Herceptin and chemotherapy arm.[1] The number of events in both treatment arms was low in people with node-negative disease, where no benefit with the Perjeta-based regimen was detected at this time.[1]

HER2-positive breast cancer is an aggressive form of the disease that affects approximately one in five people with breast cancer.[3] Despite advancements in the treatment of HER2-positive eBC, one in four people treated with Herceptin and chemotherapy will eventually see their cancer return in the long-term.[4,5] Treating breast cancer early, before it has spread, may help prevent the disease from returning and potentially reaching an incurable stage.[6] Adjuvant therapy is given after surgery and is aimed at killing any remaining cancer cells to help reduce the risk of the cancer returning.[6]

Full results of the primary analysis will be presented in an oral session today at the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago by Gunter von Minckwitz, M.D., study coordinator from the BIG and academic study partners (Abstract #LBA500), and will be featured in ASCO's official press programme. Results from the APHINITY trial will also be published today in the *New England Journal of Medicine.*

About APHINITY[7]

APHINITY (**A**djuvant **P**ertuzumab and **H**erceptin **IN I**nitial **T**herap**Y** in Breast Cancer, NCT01358877/ BO25126/ BIG 4-11) is an international, 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 adjuvant therapy in 4,805 people with operable HER2-positive eBC.

People enrolled in the study underwent surgery and were randomised to one of two arms (1:1) to receive either:

- Six to eight cycles of chemotherapy (anthracycline or non-anthracycline-containing regimen) with Perjeta and Herceptin, followed by Perjeta and Herceptin every three weeks for a total of one year (52 weeks) of treatment.
- Six to eight cycles of chemotherapy (anthracycline or non-anthracycline-containing regimen) with placebo and Herceptin, followed by placebo and Herceptin every three weeks for a total of one year (52 weeks) of treatment.

Radiotherapy and/or endocrine therapy could be initiated at the end of adjuvant chemotherapy. For people with hormone receptor-positive disease enrolled in the APHINITY trial, it was recommended that endocrine therapy be administered for at least five years after completing adjuvant chemotherapy. The APHINITY study allowed for a range of standard chemotherapy regimens to be used and participants with both node-positive and node-negative disease were eligible for enrolment. The primary efficacy endpoint of the APHINITY study is iDFS, which in this study is defined as the time a patient lives without return of invasive breast cancer at any site or death from any cause after adjuvant treatment. Secondary endpoints include cardiac and overall safety, overall survival, disease-free survival and health-related quality of life.

Median follow-up for ITT population 45.4 months[1]		
	Perjeta + Herceptin + chemotherapy n=2,400	**Placebo + Herceptin + chemotherapy** n=2,404
Invasive disease-free survival (iDFS) at 3 years		

Intent-to-treat population (ITT) n=4,804	94.1% 171 events	93.2% 210 events
	HR=0.81; 95% CI, 0.66-1.00, p=0.045	
Node-positive subgroup n=3,005	92.0% 139 events	90.2% 181 events
	HR=0.77; 95% CI, 0.62-0.96, p=0.019	
Node-negative subgroup n=1,799	97.5% 32 events	98.4% 29 events
	HR=1.13; 95% CI, 0.68-1.86, p=0.644	
Hormone receptor-positive subgroup n=3,082	94.8% 100 events	94.4% 119 events
	HR=0.86; 95% CI, 0.66-1.13, p=0.277	
Hormone receptor-negative subgroup n=1,722	92.8% 71 events	91.2% 91 events
	HR=0.76; 95% CI, 0.56-1.04, p=0.085	
Estimate of invasive disease-free survival (iDFS) at 4 years*		
Intent-to-treat population n=4,804	92.3%	90.6%
Node-positive subgroup n=3,005	89.9%	86.7%
Node-negative subgroup n=1,799	96.2%	96.7%
Hormone receptor-positive subgroup n=3,082	93.0%	91.6%
Hormone receptor-negative subgroup n=1,722	91.0%	88.7%
Safety		
Grade 3 or higher adverse event (AE)	64.2%	57.3%
Fatal AE	0.8%	0.8%
Primary cardiac event**	0.7%	0.3%
	Difference 0.4%; 95% CI, 0.0-0.8%	
Most common (≥5%) severe (Grade 3 or higher) AEs		
Neutropenia *Decrease in a certain type of white blood cell*	16.3%	15.7%

Febrile neutropenia *Fever associated with decrease in a certain type of white blood cell*	12.1%	11.1%
Diarrhoea	9.8%	3.7%
Diarrhoea *Onset after chemotherapy, during targeted therapy*	0.5%	0.2%
Neutrophil count decreased *Decrease in a certain type of white blood cell*	9.6%	9.6%
Anaemia *Decrease in red blood cells or haemoglobin*	6.9%	4.7%

** iDFS at four years was calculated based on data available at the time of primary analysis with median follow-up of 45.4 months*

*** Primary cardiac events included heart failure New York Heart Association (NYHA) class III or IV with left ventricular ejection fraction (LVEF) drop ≥10 points from baseline and to below 50%, and cardiac death*

About Perjeta

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.[8,9] 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 places. 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.[10,11]

About Roche's medicines for HER2-positive breast cancer

Roche has been leading research into the HER2 pathway for over 30 years and is committed to improving the health, quality of life and survival of people with both early and advanced HER2-positive disease. HER2-positive breast cancer is a particularly aggressive form of the disease that affects approximately 20% of patients.[3] Roche has developed three innovative medicines that have helped transform the treatment of HER2-positive breast cancer: Herceptin, Perjeta 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

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. Twenty-nine 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. Roche has been recognised as the Group Leader in sustainability within the Pharmaceuticals, Biotechnology & Life Sciences Industry eight years in a row by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2016 employed more than 94,000 people worldwide. In 2016, Roche invested CHF 9.9 billion in R&D and posted sales of CHF 50.6 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.

About the Breast International Group (BIG)

The Breast International Group (BIG) is a 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 an international level, by stimulating cooperation between its members and other academic networks, and collaborating with, but working independently from, the pharmaceutical industry.

Founded by leading European opinion leaders in 1999, BIG now constitutes a network of 56 collaborative groups from Europe, Canada, Latin America, Asia and Australasia. These entities are tied to several thousand specialised hospitals and research centres worldwide. 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 North American Breast Cancer Groups (NABCG), so that together they act as a strong integrating force in the breast cancer research arena.
www.BIGagainstbreastcancer.org

About the Breast European Adjuvant Studies Team (BrEAST)

The Breast European Adjuvant Studies Team (BrEAST) is a specialised clinical trials unit (data centre) located at the Institut Jules Bordet, Brussels, Belgium. It was created in 1997 in order to conduct large, international phase III studies in breast cancer aiming to register new drugs. The unit is responsible for setting up, coordinating and managing the data collected in these trials, which are run in collaboration with pharmaceutical companies and the Breast International Group (BIG). BrEAST manages complex trials involving more than 20,000 patients in over 40 countries.

About Frontier Science Foundation (FS)

Frontier Science Foundation (FS) is a not-for-profit corporation that has gained an international reputation as a highly capable data management and statistical organisation, collaborating with research networks, pharmaceutical companies and others in the design, conduct and execution of clinical trials and long-term observation studies.
Founded in 1975, Frontier Science provides innovative data management and analysis for clinical trials in a variety of disease settings throughout the world. Some of the significant advancements in the treatment of AIDS and cancer have resulted from studies in which Frontier Science played a major role.
Frontier Science has biostatistics, IT, data management and support staff in five locations in the United States, Greece and Scotland.

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