Media Release

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FDA approves Roche's Perjeta (pertuzumab) for adjuvant treatment of specific type of early breast cancer

- **Accelerated approval of Perjeta for neoadjuvant use also converted to full approval**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced the US Food and Drug Administration (FDA) has approved Perjeta® (pertuzumab), in combination with Herceptin® (trastuzumab) and chemotherapy (the Perjeta-based regimen), for adjuvant (after surgery) treatment of HER2-positive early breast cancer (eBC) at high risk of recurrence.[1] People should receive the adjuvant Perjeta-based regimen for one year (up to 18 cycles). The FDA has also converted the previously granted accelerated approval of the Perjeta-based regimen to full approval for neoadjuvant (before surgery) treatment of HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than two centimetres in diameter or node-positive). People receiving the neoadjuvant Perjeta-based regimen should continue Perjeta and Herceptin after surgery to complete one year of treatment.

"The goal of treating breast cancer early is to provide people with the best chance for a cure. While we come closer to this goal with each advance, many people still have a recurrence and progress to the metastatic stage," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "Today's approval of Perjeta means people with HER2-positive early breast cancer at high risk of recurrence have a new, clinically meaningful treatment option to reduce the chances of their disease returning."

The FDA-approved use of the Perjeta-based regimen for adjuvant treatment of HER2-positive eBC at high risk of recurrence is based on results of the phase III APHINITY study. At the time of the primary analysis with a median of 45.4 months follow-up:

- In the overall study population, Perjeta, Herceptin and chemotherapy significantly reduced the risk of invasive breast cancer recurrence or death by 18% compared to Herceptin and chemotherapy alone (HR=0.82, 95% CI 0.67-1.00, p=0.047).[1]

- High-risk patients included patients such as those with lymph node-positive or hormone receptor-negative breast cancer. The subgroup results were as follows:
    - Lymph node-positive subgroup (HR=0.77, 95% CI 0.62-0.96)
    - Hormone receptor-negative subgroup (HR=0.76, 95% CI 0.56-1.04)
    - Hormone receptor-positive subgroup (HR=0.86, 95% CI 0.66-1.13)
    - Lymph node-negative subgroup (HR=1.13, 95% CI 0.68-1.86)

The most common severe (Grade 3-4) side effects with the Perjeta-based regimen are low levels of white blood cells with or without a fever, diarrhoea, decrease in certain types of white blood cells, decrease in red blood cells, fatigue, nausea and mouth blisters or sores. The most common side effects are diarrhoea, nausea, hair loss, fatigue, nerve damage and vomiting.[1]

The supplemental Biologics License Application for the Perjeta-based regimen for adjuvant treatment of HER2-positive eBC was granted Priority Review,[2] a designation given to medicines the FDA has determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a disease.[3]

The combination of Perjeta, Herceptin and chemotherapy is licensed as a neoadjuvant treatment for people with HER2-positive eBC in more than 85 countries worldwide. Perjeta in combination with Herceptin and docetaxel chemotherapy is also approved in the US and the European Union for people with previously untreated HER2-positive metastatic breast cancer.

For more information about HER2-positive breast cancer and the goals of treatment, visit our Breast Cancer Hub on roche.com.

About APHINITY

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. The primary efficacy endpoint of the APHINITY study is invasive disease-free survival (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. The study will continue to follow participants for ten years.

The following table is a summary of APHINITY study results supporting this approval.

APHINITY Study Results[1] Median follow-up for intent-to-treat (ITT) population 45.4 months (381 events)		
Primary endpoint: invasive disease-free survival (iDFS) **HR=0.82, 95% CI 0.67-1.00, p=0.047***		
	Perjeta + Herceptin + chemotherapy n=2,400	**Placebo + Herceptin + chemotherapy** n=2,404
iDFS at 3 years		
ITT population n=4,804	94.1% 171 events	93.2% 210 events
	HR=0.82, 95% CI 0.67-1.00, p=0.047*	
Node-positive subgroup** n=3,005	92.0% 139 events n=1,503	90.2% 181 events n=1,502
	HR=0.77, 95% CI 0.62-0.96	
Node-negative subgroup** n=1,799	97.5% 32 events n=897	98.4% 29 events n=902
	HR=1.13, 95% CI 0.68-1.86	
Hormone receptor-positive subgroup** n=3,082	94.8% 100 events n=1,536	94.4% 119 events n=1,546
	HR=0.86, 95% CI 0.66-1.13	
Hormone receptor-negative subgroup** n=1,722	92.8% 71 events n=864	91.2% 91 events n=858
	HR=0.76, 95% CI 0.56-1.04	
Anthracycline chemotherapy subgroup** n=3,742	93.8% 139 events n=1,865	93.0% 171 events n=1,877
	HR=0.82, 95% CI 0.66-1.03	
Non-anthracycline chemotherapy subgroup** n=1,062	94.9% 32 events n=535	94.0% 39 events n=527
	HR=0.82, 95% CI 0.51-1.31	

Safety		
Heart failure* **	0.6%	0.2%
Most common (≥5%) severe (Grade 3-4) adverse events		
Neutropenia *Decrease in a certain type of white blood cell*	16%	16%
Febrile neutropenia *Fever associated with decrease in a certain type of white blood cell*	12%	11%
Diarrhoea	10%	4%
Neutrophil count decreased *Decrease in a certain type of white blood cell*	10%	10%
Anaemia *Decrease in red blood cells*	7%	5%

*Analysis stratified by nodal status, protocol version, central hormone receptor status and adjuvant chemotherapy regimen. Stratification factors are defined according to the randomisation data for iDFS.

**Exploratory analyses without adjusting for multiple comparisons. Results are considered descriptive.

***Symptomatic heart failure (New York Heart Association class III or IV) with left ventricular ejection fraction (LVEF) drop ≥10% from baseline and to below 50%.

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.[4,5] 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.[6,7]

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 15% to 20% of patients.[8] 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. 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. Roche has been recognised as the Group Leader in sustainability within the Pharmaceuticals, Biotechnology & Life Sciences Industry nine 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.

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