Roche & #039;s investigational medicine T-DM1 shows improvement in progression-free survival compared to standard of care in HER2-positive metastatic breast cancer

Roche

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Firstrandomised trial of an antibody-drug conjugate (ADC) for metastatic breast cancer highlights importance of personalised approach to cancer care

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced the results of the Phase II study TDM4450g in patients with previously untreated HER2-positive metastatic breast cancer (mBC). The study compared trastuzumab emtansine (also known as T-DM1) to standard treatment with Herceptin (trastuzumab) plus docetaxel chemotherapy. The results showed that people who received trastuzumab emtansine experienced a 41 percent reduction in the risk of their disease worsening or death (progression-free survival, PFS) and lived a median of five months longer without their disease worsening (HR=0.59, median PFS 14.2 months vs. 9.2 months). In addition, people who received trastuzumab emtansine experienced fewer common and severe adverse events compared to those who received Herceptin plus chemotherapy, with the rate of Grade 3 or higher adverse events reduced by nearly half (46.4 percent vs. 89.4 percent).

The data will be presented at the 2011 European Multidisciplinary Cancer Congress in Stockholm on September 25 and were featured in the official press program.

“The improvement in progression-free survival with fewer side effects seen with trastuzumab emtansine is very exciting,” said Hal Barron, M.D., Chief Medical Officer and Head, Global Product Development. “We believe this investigational antibody-drug conjugate approach, in which chemotherapy is attached to the antibody and selectively delivered to tumour cells, is an important potential weapon for fighting cancer and we look forward to the phase III study results with trastuzumab emtansine.”

Trastuzumab emtansine is an investigational medicine known as an antibody-drug conjugate (ADC) that attaches trastuzumab and the chemotherapy DM1 together using a stable linker. It is designed to target and inhibit HER2 signalling and deliver the chemotherapy directly inside HER2-positive cancer cells. Trastuzumab

emtansine reinforces Roche’s personalised healthcare approach of developing targeted medicines to fight cancer. Building on the results of trastuzumab emtansine studies to date, Roche/Genentech have approximately 30 ADCs in the pipeline.

About the TDM4450g study

TDM4450g is a Phase II, international, multicentre, two-arm, open-label study that enrolled 137 patients with previously untreated HER2-positive mBC from 108 sites worldwide. Patients were randomised 1-to-1 to either trastuzumab emtansine or Herceptin plus docetaxel chemotherapy. The primary endpoints of the study included PFS and safety profile. Secondary endpoints included overall survival (OS), one-year-survival rate, objective response rate (ORR), duration of objective response and clinical benefit rate (CBR). Patients in the Herceptin plus chemotherapy arm were allowed to receive trastuzumab emtansine upon disease progression.

Study Results

- There was a significant improvement in PFS for patients in the trastuzumab emtansine arm (N=67) compared to the Herceptin plus chemotherapy arm (N=70), (median PFS 14.2 vs. 9.2 months, HR=0.59, p= 0.035).
- ORR was greater in the trastuzumab emtansine arm compared to the Herceptin plus chemotherapy arm (64.2 percent compared to 58.0 percent).
- There was a significant reduction in common and severe (Grade 3 or higher) adverse events (AEs) in the trastuzumab emtansine arm compared to the Herceptin plus chemotherapy arm:
  The most common AEs in the trastuzumab emtansine arm were fatigue (49.3 percent), nausea (47.8 percent), increased levels of a specific enzyme released by the liver and other organs (aspartate aminotransferase or AST, 39.1 percent) and fever (39.1 percent). The most common adverse events in the Herceptin plus chemotherapy arm were hair loss (66.7 percent), a decreased number of a specific type of white blood cells (neutropenia, 63.6 percent), diarrhoea (45.5 percent), and fatigue (45.5 percent). Consistent with previously reported results, severe (Grade 3 or higher) AEs were reported less frequently in the trastuzumab emtansine arm than in the Herceptin plus chemotherapy arm (46.4 percent vs. 89.4 percent) as were treatment discontinuations due to AEs (7.2 percent vs. 28.8 percent). The most frequent severe AEs in the trastuzumab emtansine arm were increased levels of two different liver enzymes (ALT and AST) and low platelet count (all 8.7 percent). The most frequent severe AEs in the Herceptin plus chemotherapy arm were a decreased number of a specific type of white blood cell (neutropenia, 60.6 percent), a decrease in the overall number of white blood cells (leucopoenia, 25.8 percent) and fever associated with a decreased number of a specific type of white blood cell (febrile neutropenia, 13.6 percent).
- The overall survival data are not mature at this point in time. The number of deaths in each arm of the study was identical and no deaths were

considered by investigators to be related to treatment (trastuzumab emtansine or Herceptin plus chemotherapy).

About trastuzumab emtansine

Trastuzumab emtansine (the recommended International Non-proprietary Name for T-DM1) is an antibody-drug conjugate (ADC), being studied for HER2-positive mBC. It is designed to inhibit HER2 signalling and deliver the chemotherapy DM1 directly inside HER2-positive cancer cells. The antibody (trastuzumab) binds to the HER2-positive cancer cells, and is thought to block out-of-control signals that make the cancer grow while also calling on the body's immune system to attack the cancer cells. Once trastuzumab emtansine is absorbed into those cancer cells it is designed to destroy them by releasing the DM1. Trastuzumab emtansine attaches trastuzumab and DM1 together using a stable linker which is designed to keep trastuzumab emtansine in one piece until it reaches specific cancer cells.

About companion diagnostics for trastuzumab emtansine

Trastuzumab emtansine reinforces Roche's personalised healthcare approach of developing targeted medicines to fight cancer, in conjunction with a companion diagnostic test developed through Roche Tissue Diagnostics group (Ventana Medical Systems, Inc.). The phase III clinical trial programme includes the application of two companion diagnostic HER2 tests suitable for selecting patients for treatment with trastuzumab emtansine. Ventana Medical Systems, Inc. currently offers the PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody and INFORM HER2 Dual ISH DNA Probe Cocktail for determination of the HER2 protein expression and gene status respectively.

There are three ongoing Phase III studies of trastuzumab emtansine:

- MARIANNE is comparing three different treatment regimens (trastuzumab emtansine alone, trastuzumab emtansine in combination with pertuzumab, and Herceptin plus a taxane chemotherapy) in patients with HER2-positive mBC who have not been previously treated for their metastatic disease.
- EMILIA is comparing trastuzumab emtansine to lapatinib in combination with capecitabine in patients with HER2-positive mBC whose disease progressed after initial treatment. Roche plans to support a global regulatory submission for trastuzumab emtansine based on the results of the EMILIA trial in 2012.
- TH3RESA is comparing third-line trastuzumab emtansine to physician's choice of treatment in HER2-positive mBC.

In addition, a phase II study evaluating trastuzumab emtansine as neoadjuvant/adjuvant treatment for early breast cancer is currently ongoing.

Roche licenses technology for trastuzumab emtansine under an agreement with ImmunoGen, Inc.

About Herceptin

Herceptin is a humanised antibody designed to target and block the function of HER2, a protein produced by a specific gene with cancer-causing potential. The mode of action of Herceptin is unique in that it activates the body's immune system and suppresses HER2 to target and destroy the tumour. Herceptin has demonstrated unprecedented efficacy in treating both early and advanced (metastatic) HER2-positive breast cancer as well as HER2-positive advanced (metastatic) stomach cancer. Given on its own as monotherapy as well as in combination with or following standard chemotherapy, Herceptin has been shown to improve disease-free survival overall survival and response rates while maintaining quality of life in people with HER2-positive breast and stomach cancer. Herceptin is marketed in the United States by Genentech, in Japan by Chugai and internationally by Roche. Since 1998, Herceptin has been used to treat almost one million patients with HER2-positive breast and stomach cancer worldwide and is approved in more than 150 countries.

About Breast Cancer

Breast cancer is the most common cancer among women worldwide. Each year about 1.4 million new cases of breast cancer are diagnosed worldwide and over 450,000 people will die of the disease annually.[i]

In HER2-positive breast cancer, increased quantities of the HER2 receptor are present on the surface of the tumour cells. This is known as 'HER2 positivity' and affects approximately 15-20 percent of people with breast cancer.[ii]

SOURCE [1]

Links:
[1] http://www.roche.com/media/media_releases/med-cor-2011-09-25.htm