Roche provides update on FDA application for T-DM1

Basel, 27 August 2010

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Roche expects a global regulatory submission mid 2012

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the U.S. Food and Drug Administration (FDA) issued a Refuse to File letter for accelerated approval for the companyÃ¢â‚¬™s trastuzumab-DM1 (T-DM1) Biologics License Application (BLA). As planned Roche will continue with its ongoing Phase III EMILIA registration study. Roche will continue to work with the FDA and expects a global regulatory submission of T-DM1 mid 2012.

The BLA submitted in July 2010 requested accelerated approval for T-DM1 based on the results of a single-arm Phase II study, which showed T-DM1 shrank tumors in one-third of women with advanced HER2 positive breast cancer, who had received on average seven prior medicines, including two HER2 targeted agents.

Consideration by the FDA for accelerated approval requires recognition of a defined patient population of unmet need (a life-threatening disease with limited treatment choices), for whom a medicineÃ¢â‚¬™s early safety and efficacy data are reasonably likely to predict clinical benefit. Following the pre-submission meeting with the FDA in March 2010, Roche concluded it was appropriate to submit a BLA for accelerated approval. In their review of the BLA, FDA stated the T-DM1 trials did not meet the standard for accelerated approval because all available treatment choices approved for metastatic breast cancer, regardless of HER2 status, had not been exhausted in the study population.

Ã¢â‚¬Å“We firmly believe in the potential of T-DM1 as a novel HER2 targeted option and remain fully committed to its ongoing development,Ã¢â‚¬ said Hal Barron, M.D., Head of Global Development and Chief Medical Officer for Roche.

Roche will submit the data from the amended Phase III randomized EMILIA study to support a global regulatory submission in mid 2012. The EMILIA study compares T-DM1 to lapatinib in combination with capecitabine in people with advanced HER2 positive breast cancer whose disease has worsened after receiving initial treatment.

About T-DM1

T-DM1 is an antibody-drug conjugate (ADC), also known as an armed antibody,

being studied for advanced HER2 positive breast cancer. T-DM1 attaches trastuzumab and the chemotherapy DM1 together using a stable linker, which is designed to keep T-DM1 in one piece until it reaches specific 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 bodyÃ¢â‚¬™s immune system to attack the cells. Then, once T-DM1 is absorbed into those cancer cells, it is designed to destroy them by releasing the DM1. Genentech licenses technology for T-DM1 under an agreement with ImmunoGen, Inc.

About studies with T-DM1 and other HER2 targeted agents

The FDA submission was based on a Phase II study known as TDM4374g, a single-arm, multi-center trial designed to assess single-agent T-DM1 in 110 women with HER2 positive advanced breast cancer whose disease had worsened after receiving at least two prior HER2 targeted treatments (Herceptin and lapatinib) in the metastatic setting, as well as an anthracycline, a taxane and capecitabine. The primary endpoint of the study was objective response rate (a complete or partial tumor shrinkage of at least 30 percent, determined by two tumor assessments at least 28 days apart), as measured by an independent review facility.

Results from the study were presented at the 2009 San Antonio Breast Cancer Symposium and demonstrated that T-DM1 shrank tumors in 33 percent of women with advanced HER2 positive breast cancer that had worsened following treatment with an average of seven prior medicines for metastatic disease. In the study, most side effects were mild (Grade 1-2) and similar to those observed in previous clinical trials of T-DM1. The most common adverse events of any grade were fatigue (62 percent) and nausea (37 percent). The most common severe adverse events (Grade 3 or higher) were a low level of platelets in the blood (7 percent), fatigue (5 percent) and cellulitis (4 percent). No severe cardiac-specific side effects were observed. One patient with pre-existing, non-alcoholic fatty liver disease died with liver failure. The safety results were consistent with data from earlier studies, including a proof-of-concept Phase II study (TDM4258g), which also was included in the submission to the FDA.

Several other Phase II and III trials of T-DM1, and other HER2 targeted medicines are ongoing:

- Preliminary results from a randomized Phase II study (TDM4450g) comparing T-DM1 to Herceptin (trastuzumab) in combination with docetaxel chemotherapy in people who have not been previously treated for their advanced HER2 positive breast cancer have been accepted for presentation at the European Society of Medical Oncology (ESMO) congress in Milan (Italy) in October.
- An ongoing Phase III study, MARIANNE, will compare both T-DM1 alone and T-DM1 in combination with pertuzumab to Herceptin in combination with a taxane chemotherapy in people with advanced HER2 positive breast cancer

who have not been previously treated for advanced disease.
- CLEOPATRA is the pivotal registration trial with pertuzumab in combination with Herceptin and docetaxel in first-line HER2 positive metastatic breast cancer. Filing timelines remain unchanged; Roche expects a global regulatory filing of pertuzumab based on the CLEOPATRA study at the end of 2011.

About pertuzumab

Pertuzumab is a new type of targeted anti-tumor agent called a HER2 dimerisation inhibitor (HDI), which inhibits the pairing (or dimerisation) of the HER2 protein with other HER-family receptors. This pairing is responsible for initiating intracellular HER signaling. HER-signaling pathways are believed to play an important role in the growth and survival of several different cancer types. The modes of action of Herceptin and pertuzumab are believed to be synergistic. Herceptin also binds to HER2, but in a different place.

About Herceptin

Herceptin is a humanized 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 bodyÃ¢â‚¬™s immune system and suppresses HER2 to target and destroy the tumor. Herceptin has demonstrated unprecedented efficacy in treating both early and advanced (metastatic) HER2 positive breast cancer. Given on its own as monotherapy as well as in combination with or following standard chemotherapy, Herceptin has been shown to improve response rates, disease-free survival and overall survival while maintaining quality of life in women with HER2 positive breast 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 more than 740,000 patients with HER2 positive breast cancer worldwide.

About breast cancer

Breast cancer is the most common cancer among women worldwide [1)] . Each year more than one million new cases of breast cancer are diagnosed worldwide, and nearly 400,000 people will die of the disease annually [2)] .

In HER2 positive breast cancer, increased quantities of the HER2 protein are present on the surface of the tumor cells. This is known as Ã¢â‚¬ËœHER2 positivityÃ¢â‚¬™ and affects approximately 20-25% of women with breast cancer. When HER2 positive breast cancer is advanced, the disease has spread to other parts of the body, most commonly to the lungs, bones, liver and brain.

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