CERTARA

Drug Safety for Targeted Cancer Treatment

Ensuring the safety of a combination treatment for breast cancer patients

Background

While increased screening and early treatment have led to a decrease in breast cancer mortality, metastatic breast cancer (MBC) remains incurable. However, new treatments—using combinations of drugs—have the potential to turn MBC into a manageable, chronic disease. This would enable patients to live longer and have a higher quality of life.

Human epidermal growth factor receptor 2 (HER2) is a cell surface receptor that controls cell growth, survival, and differentiation. It frequently becomes amplified and/or over expressed in a significant percentage of breast cancer patients.[1] Patients with HER+ tumors tend to experience increased tumor aggressiveness, higher rates of recurrence, and increased mortality. Thus, HER2 is an important target for managing HER2+ metastatic breast cancer (MBC).[2]

Challenge

The sponsor, a global pharmaceutical company, sought approval for pertuzumab, a targeted treatment that combined with trastuzumab and docetaxel gave patients with first-line MBC longer progression-free survival (PFS). Pertuzumab is a humanized monoclonal anti-HER2 antibody.[3] It blocks HER2 heterodimerization to inhibit ligand-activated downstream cell signaling.

A crucial step in gaining approval was demonstrating drug safety. Cardiotoxicity and drug-drug interactions (DDIs) are common concerns during the drug development. Cancer treatments often use regimens of multiple drugs being administered simultaneously, thus raising their potential for DDIs. Indeed, DDIs that cause unmanageable, severe adverse effects have led to restrictions in clinical use and even drug withdrawals from the market.

Likewise, adverse cardiac reactions have resulted in the withdrawal of more drugs from the market than any other adverse reaction in recent times. Therefore, all new drugs with systemic bioavailability must be assessed for their potential to delay cardiac repolarization as measured by the QT/QTc interval on the surface electrocardiogram (ECG).

Challenge

The sponsor sought to demonstrate the safety of a targeted treatment for breast cancer.

Solution

Certara Strategic Consulting scientists performed DDI analysis and concentration-QTc modeling.

Benefit

The pharmacometric analyses revealed no significant DDI between the novel drug and co-administered medications and no clinically relevant cardiac safety liability.

Solution

The sponsor conducted a pharmacokinetic (PK) and cardiac safety substudy to evaluate potential DDI of pertuzumab with trastuzumab and docetaxel. Certara Strategic Consulting scientists used PK modeling and simulations to assess potential DDI and address potential drug safety issues. Addition of trastuzumab and docetaxel did not significantly affect pertuzumab pharmacokinetics. Thus, based on PK modeling and simulations, no DDIs were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel.[4]

Likewise, Certara scientists performed linear mixed-effects modeling to evaluate potential exposure-response relationships between the concentration of pertuzumab and the magnitude of QTc prolongation. Cardiac monitoring and concentration-QTc modeling demonstrated that pertuzumab did not appear to cause clinically relevant effects on QTc or other ECG parameters.

Benefit

The sponsor gained robust evidence demonstrating the safety of pertuzumab in terms of cardiotoxicity and a low risk of DDIs with concurrent chemotherapy drugs.

Impact

The FDA approved Perjeta (pertuzumab injection) in combination with trastuzumab (Herceptin) and docetaxel as a first-line treatment for HER2+ metastatic breast cancer in June 2012.[5] On September 30, 2013, the FDA granted Perjeta accelerated approval for use in combination with Herceptin and docetaxel for neoadjuvant treatment of patients with HER2+ locally advanced, inflammatory, or early-stage breast cancer.[6]

References

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