

Preliminary Report Project Topic I

A Phase III Randomized, Controlled Trial of Myocet, Trastuzumab and Paclitaxel versus Trastuzumab and Paclitaxel for first line therapy of Metastatic Breast Cancer.

Francesco Atzori

Overview of Activities

The primary objectives of my fellowship period at Vall d'Hebron University hospital was to run two clinical trials: the first one (the main project for which I have received financial support from ESMO) is a Phase III clinical trial comparing the standard regimen of paclitaxel/trastuzumab to a novel triplet of paclitaxel/trastuzumab/lyposomal-doxorubicin in patients with HER2-positive metastatic breast cancer and assess response rate, survival and safety of the triplet. In addition, under the supervision of Dr Baselga and Dr Taberero, I am carrying out a Phase I trial to test a new monoclonal antibody, MK-0466 directed against the IGF1 receptor in patients with advanced tumors and multiple myeloma. This is a first-in-human trial with this compound that requires a complete pharmacodynamic evaluation, including sequential skin and tumor samples. Moreover, I am involved in clinical activities within the Breast Unit team.

Introduction

The combination of two or more agents is an established approach in cancer therapy and has the potential to further improve response rates and increase survival. Doxorubicin and paclitaxel are considered the most active agents and are widely used in the treatment of breast cancer producing high response rates when used in combination. The use of these drugs in combination is associated with higher response rates and improved Time to Treatment Failure (TTF) compared with the use of either agent alone¹

In preclinical experiments trastuzumab has additive and synergistic activity when combined with cytotoxic agents including taxanes and anthracyclines. In clinical studies,

there is an improved survival rate for trastuzumab combinations (doublets) with doxorubicin or paclitaxel. It is reasonable to hypothesize that trastuzumab triplets would show even greater activity in MBC. This is indeed the case in HER2+ breast cancer cell lines and therefore several triplets are being investigated in clinical studies². Combination therapy of trastuzumab with both a taxane and a less cardiotoxic anthracycline would offer the opportunity to deliver the most effective breast cancer chemotherapeutic agents with trastuzumab for metastatic breast cancer patients with the HER2 over expressed disease, while minimizing the cardiotoxicity risk. However, there is data from large, international, randomized trials, showing that trastuzumab plus doxorubicin, or another anthracycline, is associated with a three fold increase in cardiac toxicity when compared to that expected with AC or trastuzumab alone (Herceptin Package Insert June 2004). We hypothesize that Myocet has the potential to overcome this cardiac liability and allow the safe development of highly active triplets that contain trastuzumab, taxanes, and doxorubicin.

In this regard the preliminary data of Cortes, Baselga et al. are encouraging and provide the background for this pivotal trial. These authors investigated the triple combination of Myocet, Herceptin and paclitaxel in a Phase II study of first-line treatment of locally advanced and metastatic breast cancer. At the 2004 San Antonio Breast Cancer Symposium the updated results for the Phase II Study M77035 (Myocet combined with Weekly Herceptin and Paclitaxel in Patients with HER2-Positive Locally Advanced or Metastatic Breast Cancer (LABC/MBC)) were presented.³

This study demonstrated that the triple combination is highly active with an ORR of 92.6% (LABC 93.3% and MBC 91.7%) in 54 valuable patients. Median follow-up for TTP was reported to be 24.8 months. Of the 51 patients valuable for TTP seven had progressed with a median TTP of 28.5 months. Of particular note, no patient experienced symptomatic cardiac disease while receiving this combination. Encouragingly LVEF was generally maintained over time. The investigators additionally reported that only nine patients with LVEF decreases to below 50% discontinued treatment.

In addition to the experience in Study M77035, other clinical experience has shown that the combinations of Myocet with Paclitaxel or docetaxel do not result in the appearance of additional or unexpected or synergistic toxicities. While these latter studies were

designed to establish the Maximum Tolerated Dose for each combination, the results do indicate that the combinations are well tolerated with high levels of clinical activity.

Based on the abovementioned data. The proposed Phase III clinical trial will compare the standard regimen of paclitaxel/trastuzumab to a novel triplet of paclitaxel/trastuzumab/Myocet in patients with HER2-positive metastatic breast cancer and assess response rate, survival and safety of the triplet.

Objective

The primary objective is to demonstrate the efficacy and cardiac safety of Myocet when given in combination with trastuzumab and paclitaxel in patients with HER2+ metastatic breast cancer.

Secondary objectives are to assess the overall response rate and the overall survival.

Material and Methods

Leveraging 105 global centers we anticipate a target accrual of 600 randomized patients (300 in each arm) with an estimated recruitment period of 18 months. Accrual in Europe with the exception of Russia started on August 2006.

From August 2006-to date, our center has enrolled four patients in this study. Two were assigned to the protocol arm containing the standard regimen and two patients to the arm containing the novel triplet.

Preliminary Report Project Topic II

Title of the Study

An open-labeled, dose escalation Phase I of MK-0646 given as a once weekly infusion in patients with advanced solid tumors and multiple myeloma.

Introduction

One successful therapeutic approach in the treatment of cancer has been to develop monoclonal antibodies against receptor tyrosine kinases. Two such drugs in clinical use are: trastuzumab for breast cancer patients whose tumor over express Human Epidermal Growth Factor Receptor 2 (HER2) and cetuximab for colon cancer patients whose tumors express the Epidermal Growth Factor (EGF) receptor⁴⁻⁵

Insulin-like growth factor receptor type 1 (IGF-1R) is a receptor tyrosine kinase. Activation and over expression of this receptor tyrosine kinase induces mitosis, is required to establish and maintain a transformed phenotype, and protects cells against apoptosis. Prospective epidemiological studies show a modest association between IGF-1 ligand levels and increased risk for breast, prostate and colon cancer⁶. IGF-1R signaling pathways overlap significantly with those of EGF/HER2 receptors⁷

IGF-1R is expressed on most human cells and has 70% homology to the insulin receptor (IR)⁸. In preclinical studies, immunohistochemical staining on paraffin embedded tissues using a commercial monoclonal antibody to IGF-1R demonstrated widespread over expression of IGF-1R on several tumor types including breast, colon, lung and prostate tumors. Thus multiple cancer types are potential indications for treatment with an IGF-1R antibody.

MK-0646 is a humanized IgG1 monoclonal antibody that binds to the IGF-1R with a Kd of approximately 1nM. Assays have demonstrated that MK-0646 reduces tyrosine kinase signaling through IGF-1R⁹.

Objective

The primary objective of our study is to evaluate the safety and tolerability of MK0646 and also to establish its pharmacokinetic parameters. The secondary objectives include the following: to determine the dose level where systemic clearance of MK0646 becomes constant; to evaluate pharmacodynamic effects following treatment with MK-0646; to test for the occurrence of human-anti-humanized-antibody (HAHA) response to MK-0646 and to obtain preliminary data on its antitumor activity.

Metabolic study

In addition, an exploratory investigation is being conducted to determine the potential effects of MK0646 on glucose metabolism (such as perturbation of the IGF1 and growth hormone axis). Therefore, serum levels of diverse parameters involved in glucose metabolism (IGF1, GH, Fructosamine, Insulin and HbA1c) are being analyzed prior, during and after administration of MK0646.

Material and Methods

The study was launched on February 2006. To date, 25 patients with advanced tumors, who have already exhausted standard treatments or for which standard treatment does not exist, entered into this study. Patients received MK-0646 as a weekly intravenous infusion at a starting dose of 1.25 mg/kg. The dose escalation scheme includes six dose levels. To date, we have completed patient accrual of four out of the six levels. Patient enrollment at dose level 5 (15 mg/kg) is still ongoing.

Moreover, we anticipate gathering preliminary results of Pharmacokinetic and Pharmacodynamic parameters which could facilitate with the achievement of our overall goals.

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