1. SYNOPSIS/ABSTRACT

Title

AN OBSERVATIONAL STUDY OF CARDIAC EVENTS IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER WHO HAVE A LEFT VENTRICULAR EJECTION FRACTION (LVEF) BETWEEN 40%-49% PRIOR TO INITIATING TREATMENT WITH KADCYLA®

Keywords

Non-interventional study (NIS), left ventricular ejection fraction, HER2-positive metastatic breast cancer, Kadcyla (trastuzumab emtansine), cardiac events.

Rationale and Background

Kadcyla (trastuzumab emtansine) is a HER2-targeted therapy, approved for the treatment of patients with HER2-positive, unresectable locally advanced breast cancer (LABC) or metastatic breast cancer (MBC) who have received prior treatment with trastuzumab and a taxane. Patients treated with Kadcyla (which comprises trastuzumab conjugated to DM1 moieties via a stable linker) are at risk of developing cardiac events, including decreased left ventricular ejection fraction (LVEF) and congestive heart failure (CHF). Typically, patients with baseline LVEF measurement of below 50% have been excluded from Kadcyla clinical trials, as a precautionary measure, but for many of these patients Kadcyla may be the only treatment option. Therefore, the Pharmacovigilance Risk Assessment Committee (PRAC) requested an evaluation of the risk of cardiac events in patients with a LVEF between 40% and 49% prior to initiation of treatment with Kadcyla.

Research Question and Objectives

The research questions were:

1. What are the patient characteristics of the population of metastatic breast cancer patients with a LVEF between 40% and 49% prior to initiating treatment with Kadcyla?
2. What is the risk of a drop in LVEF of >10% points, congestive heart failure or other relevant cardiac events in this population during treatment with Kadcyla and the 84 days following treatment discontinuation?

The objectives of this observational study were:

1. To describe the characteristics of the patients in this cohort prior to or at Kadcyla initiation in terms of demographics, disease characteristics and risk factors for cardiac events.
2. To describe the evolution of LVEF as recorded over time from the latest LVEF measurement recorded within the 60 days prior to treatment with Kadcyla (baseline) to the 84th day following treatment discontinuation (absolute value and incidence of LVEF decrease $>$ 10% from baseline).
3. To describe the event rate, incidence rate and cumulative incidence of the following cardiac events in this cohort from the initiation of treatment with Kadcyla (index date) to the 84th day following treatment discontinuation:
    a. congestive heart failure
    b. other relevant cardiac events (active cardiac tachyarrhythmia, ventricular tachycardia or ventricular fibrillation, acute coronary syndrome, unstable angina or myocardial infarction, cardiac hospitalization, death attributed to a cardiac event and any event referred to as “treatment discontinuation due to cardiac toxicity” in the charts).

Amendment and Updates to Protocol

None.

Study Design

Secondary data use NIS using electronic health records following a single arm retrospective cohort design.

Setting

The source population was from U.S. academic or community oncology practices treating patients with MBC. The study population was the subgroup of patients with the most recent LVEF value between 40% and 49% up to 60 days prior to the index date.

Subject and study size (including dropouts)

Patients with a diagnosis of MBC with a documented latest LVEF reported between 40% and 49% within 60 days prior to Kadcyla initiation were identified and followed-up during routine clinical practice.

This final study report includes a primary cohort of 32 patients with LVEF values reported between 40% and 49% within 60 days prior to the initiation of Kadcyla (index date). An additional sensitivity analysis cohort of 67 patients (the expanded cohort) with LVEF value (or range of values) reported between 40% and 50% (inclusive) within 60 days prior to the index date is also described.

Variables and Data Sources

The key study variables collected as recorded prior to or on the index date were demographics, disease characteristics, and cardiac risk factors. Other variables such as antineoplastic treatments, LVEF measures, cardiac events, and death were defined as recorded at any time during the study period.

Primary Safety Variables

- LVEF values

Secondary Safety Variables

- Documented congestive heart failure
- Documented other relevant cardiac events (active cardiac tachyarrhythmia, ventricular tachycardia or ventricular fibrillation, acute coronary syndrome, unstable angina or myocardial infarction, cardiac hospitalization, cardiac death, and any event referred to as “treatment discontinuation due to cardiac toxicity”).

Patients’ clinical data were extracted from the Flatiron Health Analytic Database, which includes data from both structured and unstructured data (e.g., physician notes and scanned lab reports) within patients’ electronic health records.

In the main analysis, patients were followed for up to 84 days following discontinuation of Kadcyla treatment.

Results

Among almost 2,000 MBC patients initiating Kadcyla in the Flatiron Health network, 1.6% had a LVEF measurement between 40% and 49% in their latest test during the 60 days prior to Kadcyla initiation; 3.3% had an LVEF measurement between 40% and 50%. In this final analysis, a total of 32 patients were eligible for the primary cohort. These patients had a median age of 64.5 years, median body mass index (BMI) of 26.1 kg/m^2 and were predominantly white (65.6%). Cardiovascular risk factors were documented at baseline in this patient cohort as follows: hypertension 65.6%, CHF signs and symptoms 34.4%, CHF 28.1%, hypercholesterolaemia 28.1%, and diabetes 25.0%. The majority of patients (62.5%) had discontinued a previous breast cancer treatment due to cardiotoxicity Monitoring of LVEF was conducted during therapy for 17 of the 21 patients (81.0%) who continued Kadcyla therapy for longer than 2 months.

The main cardiac events of interest, LVEF drop of >10% experienced by 4 patients and CHF events (experienced by 5 patients) The event proportions were 12.5% and 15.6% respectively. These 9 events occurred in 7 unique patients, 6 of whom had cardiovascular risk factors recorded in their electronic health record (EHR) at baseline. The expanded cohort, which comprised an additional 35 patients (N=67) one additional CHF event was recorded; the event proportions were 6.0% and 9.2% for LVEF drop of >10% and CHF respectively. Two patients who had cardiovascular events of interest died during the follow-up period of what were potentially cardiovascular causes.

Discussion

This study describes the patient population with low LVEF who receive Kadycla for the treatment of MBC in clinical practice. The presence of cardiovascular risk factors for CHF documented in their health records at baseline is evidence of the existing cardiovascular morbidity in this patient population. A small number of events were observed in the primary cohort, with 5 of the 7 patients experiencing these events of LVEF drop>10% or CHF in less than 3 months following initiation of Kadcyla.

Patients with CHF prior to initiating Kadcyla are of interest as this is a recognized risk factor for LVEF drop and recurrent CHF. In analyses by subgroup, the patient numbers and numbers of events were too small to determine whether there was excess risk of these events, but numerically, more events occurred in those patients with no prior history of CHF.

The strengths of this study are that it has provided data on a patient subgroup where clinical trial data is lacking. These patients have a complex profile of risk factors in terms of cardiovascular morbidity and prior treatment of breast cancer which makes comparison with other populations difficult. As such, this is a single arm study. The inclusion of the additional patients in the expanded cohort gives more precision to the estimates.

Conclusion

The completion of this study constitutes the largest cohort of Kadcyla-treated patients with MBC and low LVEF. These results, describing the very small proportion of patients (1.6%) initiating Kadcyla with an LVEF greater or equal to 40% and lower than 50% at treatment initiation. A small number of these patients (N=7, 21.9%) experienced events of LVEF drop of $>$10% and/or CHF. Patients with low LVEF appear to be monitored for such events while being treated with Kadcyla in routine clinical practice in the United States.

These findings are consistent with both the feasibility and interim analyses, given the understanding of the benefits and risks of Kadcyla, these results do not constitute a new safety signal. In the context of the cardiovascular morbidity of these patients, initiation of Kadcyla does not constitute an unacceptable cardiac risk.

The decision for physicians to prescribe Kadcyla in patients with low LVEF should be considered in the context of the risk for cardiovascular events and availability of

alternative anticancer therapies, and cardiac function should be monitored at regular intervals during treatment.

Marketing Authorisation Holder(s)

Roche Registration GmbH
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

Names and affiliations of principal researchers

Role/Responsibility	Company/Organization
Dr. Thibaut Sanglier PharmD, MPH, PhD Senior Data Scientist, PDP, RWD Oncology, Office: +41 616 883 669 Mobile: [redacted] Email: thibaut.sanglier@roche.com	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124 CH-4058 BASEL
[redacted] MPharm, PhD Data Scientist, PDP, RWD Oncology, PHC Data Science Mobile: [redacted] Email: [redacted]	F. Hoffmann - La Roche Ltd. 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, UK
[redacted] MS Associate Data Scientist, PDP, Data Science Analytics Office: [redacted] Mobile: [redacted] Email: [redacted]	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124 CH-4058 BASEL