NI PASS PROTOCOL (SECONDARY DATA USE)

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®**
PROTOCOL NUMBER:	**BO39807**
VERSION NUMBER:	[redacted] 1.0
AUTHOR:	Dr. [redacted] PharmD, MPH, PhD | Scientist RWD-S Oncology F. Hoffmann-La Roche Ltd. | Grenzacherstrasse 124 | CH-4058 BASEL Office: [redacted] | Email: [redacted]
DATE FINAL:	See electronic date stamp below
EU PAS REGISTER NUMBER:	**"Study not registered yet"**
ACTIVE SUBSTANCE:	Trastuzumab emtansine
STUDIED MEDICINAL PRODUCT:	Trastuzumab emtansine (Kadcyla®)
PRODUCT REFERENCE NUMBER:	EU/1/13/885

FINAL PROTOCOL APPROVAL

PROCEDURE NUMBER{S}:	
JOINT PASS	NO
RESEARCH QUESTION AND OBJECTIVES:	The research questions are: 1. What are the patient characteristics of the population of metastatic breast cancer patients with a left ventricular ejection fraction (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 are: 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).
COUNTRY OF STUDY POPULATION:	United States of America
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
MAH CONTACT PERSON:	Dr. [redacted] PharmD, MPH, PhD epidemiology Scientist RWD-S Oncology F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124 | CH-4058 BASEL Office: [redacted] | Email: [redacted]

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1. LIST OF ABBREVIATIONS AND GLOSSARY

Abbreviation	Definition
CHF	Congestive Heart Failure
CRO	Contract research organization
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EHR	Electronic Health Records
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiological Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
LVEF	Left ventricular ejection fraction
MAH	Marketing Authorization Holder
mBC	Metastatic Breast Cancer
NIS	Non-interventional study
QPPV	Qualified Person for Pharmacovigilance

GLOSSARY

Index date: is the date the treatment with Kadcyla® is initiated for the first time in the electronic health records database.

Baseline: is the period of time starting from the date the first information is recorded in the electronic health records database to the index date. The baseline is defined for each patient.

Baseline LVEF: is the latest LVEF value recorded within the 60 days prior to index date.

Event rate: is a measure of occurrence of an event of interest that accounts for the length of time an individual was observed. The event rate is assumed to be constant over the interval it is defined on.

Group at risk: is defined as the group of patients who have not experienced the event of interest at the time the event of interest is assessed (e.g., free of the event prior to the initiation of treatment with Kadcyla®). By definition, the size of a group at risk is decreasing over time as patients are being observed with the event of interest.

Incidence rate: is defined similarly to the *event rate* but will only be estimated in the *patients at risk* of developing the condition. The incidence rate is closer to the true risk of developing a condition than the event rate as the incidence rate focusses on the first event ever. The incidence rate is assumed to be constant over the interval it is defined on.

Cumulative incidence: is the probability F(*t*) of observing an event of interest before time *t*. If the time to event was observed for everyone in the sample then the cumulative incidence would be equivalent to the relative frequency of observing the event before *t*. Of note, the estimation of the cumulative incidence will not be restricted to the group at risk.

Cumulative incidence function: function F(t) that estimates the cumulative incidence of observing an event of interest before time *t.*

2. RESPONSIBLE PARTIES

Protocol Development Responsible

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Complementary information is given in Appendix A.

3. ABSTRACT/SYNOPSIS

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®**
PROTOCOL NUMBER:	BO39807
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	February 2017
EU PAS REGISTER NUMBER:	Not registered
STUDIED MEDICINAL PRODUCT:	Trastuzumab emtansine (Kadcyla®)
SCIENTIFIC RESPONSIBLE	[redacted]
PHASE:	IV, non-interventional study
INDICATION:	In Europe, Kadcyla®, as a single agent, is indicated for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for locally advanced or metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy. In the U.S. KADCYLA®, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy
MARKETING AUTHORIZATION	Roche Registration Ltd 6 Falcon Way, Shire Park

HOLDER:	Welwyn Garden City AL7 1TW United Kingdom
RESEARCH QUESTION AND OBJECTIVES:	The research questions are: 1. What are the patient characteristics of the population of metastatic breast cancer patients with a left ventricular ejection fraction (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 are: 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).

STUDY DESIGN: NIS secondary data use based on electronic health records following a single retrospective cohort design.

POPULATION: The source population is from U.S. academic or community oncology practices treating patients with metastatic breast cancer. The study population will be the subgroup of patients with a most recent LVEF value between 40% and 49% up to 60 days prior to the index date.

VARIABLES: The key study variables collected as recorded prior to or on the index date are demographics, disease characteristics and cardiac risk factors. Other variable such as antineoplastic treatments, LVEF measures, cardiac events and death will be 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”).

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

STUDY SIZE: The study is anticipated to include approximately 35 patients by 2019.

DATA ANALYSIS: The cardiac risk will be described from the initiation of Kadcyla® treatment up until the 84th day following Kadcyla® treatment discontinuation in order to limit the capture of cardiac events related to subsequent treatment in the primary analysis. The cardiac risk will be characterized by evaluating LVEF values over time, as well as the incidence rates and the cumulative incidence of a LVEF drop >10% points from baseline, congestive heart failure, and other cardiac events

previously described as secondary safety variables.

MILESTONES: The study start date will be the date of the study dataset creation. The planned start date is Q4 2017. The estimated end of the study will be Q2 2019 when final analysis of data will be completed.

4. AMENDMENTS AND UPDATES

Substantial protocol amendments/updates so far: None.

5. MILESTONES

Milestone	Planned Date
Start of feasibility dataset creation	Q4 2016
End of feasibility dataset creation	Q1 2017
Feasibility status report	Q2 2017
Registration in the EU PASS register (after PRAC approval)	Q4 2017
Start of dataset creation (after registration in the EU PASS)	Q4 2017
Interim report	Q2 2018
End of dataset creation	Q4 2019
Final report of study results (CSR)	Q2 2019

6. RATIONALE AND BACKGROUND

Trastuzumab emtansine (hereafter referred to as Kadcyla®) is a HER2 targeted therapy approved for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer (mBC) who have received prior treatment with trastuzumab and a taxane (RocheProductsLtd.). Kadcyla® is the antibody drug conjugate of trastuzumab and a cytotoxic agent (DM1). EMA/PRAC requested the marketing authorization holder (MAH) to evaluate the risk of cardiac events in locally advanced or metastatic breast cancer (mBC) patients with a left ventricular ejection fraction (LVEF) between 40% and 49% prior to initiation of treatment with Kadcyla®, as this population is usually excluded from clinical trials and many of these patients may be in a situation where there is no alternative to Kadcyla®.

The MAH has initiated pharmacovigilance activities, including exploration of disease registries, to characterize the safety profile of different drugs in the HER2-positive mBC patient population. The approval dates of Kadcyla® (November, 2013 and February, 2013 in the EU and in the U.S. respectively) and the limited size of the HER2-positive mBC population with baseline LVEF ≤ 49% treated with Kadcyla® makes the identification and the recruitment of these patients challenging as this gave limited time for the drug to be widely used. As of February 2015, 1023 mBC patients have been recruited worldwide in disease registries initiated by the MAH. Of these patients, 221 patients received Kadcyla® treatment and 3 (1.4%) patients presented with a LVEF ≤ 49%

recorded within 60 days prior to the start of treatment with Kadcyla®. As a result of the low number of patients enrolled in the registries meeting the evaluation criteria, it is not currently possible to adequately assess risk using these registries.

6.1 CANCER TREATMENT AND CARDIAC TOXICITY

Cardiovascular morbidity and mortality in cancer survivors is of growing concern (Ewer & Ewer, 2010; Yeh & Bickford, 2009): a meta-analysis concluded that the use of trastuzumab is associated with an increased risk of cardiac toxicities, such as decline in LVEF and congestive heart failure (CHF) (Balduzzi et al., 2014). Patients treated with Kadcyla® can be at risk of developing cardiac events, including decreased LVEF and CHF (Chen et al., 2012; Pivot et al., 2015; Anthony F. Yu et al., 2015). The potential impact of pre-existing low LVEF on the cardiac risk in these patients is unknown. Studies on the use of trastuzumab therapy in the adjuvant breast cancer setting identified the following risk factors for CHF (Zamorano et al., 2016):

- low baseline LVEF values (< 55%)
- advancing age (> 65 years)
- low LVEF levels prior to or following the use of paclitaxel in the adjuvant setting
- prior or concomitant use of antihypertensive medicinal products
- previous therapy with an anthracycline

6.2 LVEF AND HEART FAILURE

There is no consensus on the normal value of LVEF. The 2016 position paper on cancer treatments and cardiovascular toxicity of the European Society of Cardiology lower limit of normal of LVEF in echocardiography is defined as 50% (Zamorano et al., 2016). However, both European and American Societies of Echocardiography have defined normal LVEF to range from 53% to 73%(Lang et al., 2015) In a U.S. community-based population the prevalence estimates of LVEF≤50%, LVEF≤40% and CHF were 6%, 2% and 2.6% respectively (Redfield et al., 2003). Tashakkor et al used the National Health and Nutrition Examination Survey (NHANES 2002–2008) to report a CHF prevalence estimate of 5% in U.S. breast cancer survivors (Tashakkor, Moghaddamjou, Chen, & Cheung, 2013).

Borderline or mildly depressed LVEF (45% to 54%) is associated with a higher risk of developing heart failure and greater mortality (Gottdiener et al., 2002; Pandhi, Gottdiener, Bartz, Kop, & Mehra, 2011; Tsao et al., 2016). However limited data exist on the incidence of CHF according to LVEF level (Roger, 2013).

Five randomized trials that recruited a total of approximately 3500 participants with left ventricular systolic dysfunction reported annual CHF rates ranging from 4.9% to 20.0% (Investigators, 1992; Kober et al., 2000; Kober et al., 1995; Pfeffer et al., 1992; Sharpe, Murphy, Smith, & Hannan, 1990; Thomas J. Wang et al., 2003). In retrospective cohorts of women diagnosed with incident, invasive breast cancer treated with trastuzumab, the estimated cumulative incidence of CHF and/or cardiomyopathy at one year was reported between 1.5% and 8.2% (Bowles et al., 2012) or between 15.7% and 22% (Chen et al., 2012). Chen et al used Surveillance, Epidemiology, and End Results-Medicare data, as such their population was older (67 to 94 years of age) and presented with more frequent comorbidity. The incidence of CHF according to LVEF level is unknown.

Many risk factors have been identified for CHF, the most important ones are hypertension (Jong, Yusuf, Rousseau, Ahn, & Bangdiwala, 2003; Sciarretta, Palano, Tocci, Baldini, & Volpe, 2011) and coronary artery disease (CAD) as they accounted for >80% of all CHF events in the 34-year follow-up of the Framingham Heart Study (Kannel & Belanger, 1991). These findings are consistent with other epidemiological reports.(He et al., 2001) Diabetes(Lind et al., 2011), obesity(Artham, Lavie, Patel, & Ventura, 2008; Bahrami et al., 2008; Kenchaiah et al., 2002; Kenchaiah, Gaziano, & Vasan, 2004; Loehr et al., 2010) and myocardial infarction(Wang, Levy, Benjamin, & Vasan, 2003) were also identified as important risk factors.

6.3 USE OF ELECTRONIC HEALTH RECORDS FOR RESEARCH PURPOSES

Electronic Health Record (EHR) use has largely increased over the last decade; up to 78% of office-based physicians in the US use EHR (Hsiao C-J, 2014). EHR data can be used to complement (Bickell & Chassin, 2000) or to estimate accuracy of the data present in tumor registries (Manasanch et al., 2011). EHRs are also used to examine potential safety concerns such as the toxicity of trastuzumab in the community (da Fonseca et al., 2014; A. F. Yu et al., 2015; Anthony F. Yu et al., 2015) and in the elderly (Adamo et al., 2014), to describe and monitor potential off-label use of drugs (Kahan, Waitman, Blackman, & Vardy, 2010), to improve cancer patient management (Murphy et al., 2015) or for long term safety follow-up in randomized controlled clinical trials (Ford, Murray, McCowan, & Packard, 2016).

The MAH proposes to complement current pharmacovigilance activities by identifying a sample of the population of interest using a large longitudinal EHR database compiling information from oncology practices in the U.S. (Flatiron Health, Inc. New York, NY, USA). This approach will retrospectively use information recorded during routine medical practice in 240 oncology practices. The study will identify mBC patients initiating Kadcyla® treatment with a latest

LVEF value ≤ 50% recorded prior to Kadcyla® initiation. This will allow the identification and the selection of the relevant study sample from an initial pool of over one million cancer patients. The study is retrospective by nature and the data will be updated annually until 2018 in order to maximize patient number and duration of follow-up.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

1. What are the patient characteristics of the population of metastatic breast cancer patients with a left ventricular ejection fraction (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?

7.2 OBJECTIVES

The objectives for this study are as follows:

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).

8. RESEARCH METHODS

8.1 STUDY DESIGN

This is a Non-Interventional Study (NIS) with secondary data use following a single retrospective cohort design. Flatiron (Flatiron Health, Inc. New York, NY,

USA) processes data from multiple EHRs, including oncology specific EHRs (e.g., OncoEMR) and general EHRs (e.g., Epic, Cerner). This processing includes both structured data (i.e., data points that are organized in a predefined manner, such as drop-down fields that reside in the EHR to capture a patient's gender or date of birth) and unstructured data (i.e., information that is not organized in a pre-existing data model, such as free text from a physician's note or lab report). Oncology nurses abstract information from patients' unstructured data such that the information can be stored in de-identified structured datasets transmitted to the study sponsor (i.e., the MAH) for analysis. Details on the nature of the data processing are provided in Appendix B.

The study population selection process is described below:

Table 1: Selection process in the source population.

Selection criteria	N
Any cancer	X'XXX'XXX
ICD-9/ICD-10 BC and two visits on or after 01/01/2011	XXX'XXX
ICD-9/ICD-10 BC and two visits on or after 01/01/2011+ Kadcyla®	X'XXX
mBC confirmed and Kadcyla® initiated post mBC* via manual abstraction	XXX
Latest LVEF at any time prior to Kadcyla® ≤50%	XX

*Details on the medical charts abstraction process are provided in Appendix C.

LVEF can be reported using an absolute value or a range. For instance a patient with a LVEF reported to be within the range [46%-50%]. Such a patient could not be classified as <50%. In order to be comprehensive and allow for sensitivity analyses, the charts of patients with a latest LVEF value reported as an absolute number ≤ 50% or a range of values overlapping with 50% at any time prior to Kadcyla initiation will be abstracted (see sections 8.3, 8.7.5 and Appendix C).

The primary source of information will consist of the physicians' assessment notes and diagnoses as recorded in patients' medical charts. They will be used to describe the evolution of LVEF over time (based on ECHO or MUGA reports where available or other sources such as physician notes if no report was available), to estimate the cumulative incidence of symptomatic CHF and other relevant cardiac events. The endpoints of the study are described in section 8.3.4.

The incident user design (patients selected at treatment initiation) and the definition of subgroups free of the event at index date (hereinafter referred as *subgroup at risk*) allows:

1. mitigation of the risk of depletion of susceptible patients observed in studies with a prevalent user design (Moride & Abenhaim, 1994),
2. estimation of the event rate to describe the risk of onset of any type of event (recurrent or not),
3. estimation of the incidence rate of a first event to describe the risk of onset of a first event (*incident event*).

8.2 SETTING

8.2.1 Source Population

The source population is the overall population reported in the EHR and managed in at least one of the U.S. oncology clinics taking part in the Flatiron health network from 01 January 2011 onwards. As of 2015 the network included 240 oncology clinics; the network is growing over time, and thus each annual report is expected to document the outcome for an increasing number of patients.

8.2.2 Cohort Definition

Patients with a diagnosis of mBC, with a documented latest LVEF between 40% and 49% and reported up to 60 days prior to Kadcyla® initiation will be selected and followed-up during routine clinical practice.

8.2.2.1 Inclusion Criteria

Patients are included if they fulfill each of the following inclusion criteria:

1. Diagnosis of breast cancer (ICD-9 174.x or ICD-10 C50.x) and pathology confirmed by medical chart review (see Appendix D). At least two visits in the EHR database on or after 01 January 2011 (in order to exclude patients not actually followed in clinical practice).
2. Initiating Kadcyla® treatment after the date of metastatic breast cancer diagnosis (confirmed by medical charts review).
3. Evidence of LVEF < 50% within 60 days prior to initiation of Kadcyla®.

8.2.2.2 Exclusion Criteria

Patients will be excluded from the selection if they fulfill either of the following:

1. Latest LVEF < 40% within 60 days prior to initiation of Kadcyla®.
2. No LVEF recorded within 60 days prior to initiation of Kadcyla®.

8.2.2.3 Index date

The *index date* will be defined as the date of first administration of Kadcyla®.

8.2.2.4 Baseline Period

The *baseline period* will cover the entire available patient medical history up to and including the index date.

8.2.2.5 Follow-up Period

In the main analysis, patients will be followed up to the 84th day following discontinuation of Kadcyla® treatment.

The definition of the follow-up until the 84th day post discontinuation of Kadcyla® treatment is considered conservative as the product's terminal elimination half-life is 3.94 days (Lu et al., 2014) and because cardiac events related to Kadcyla® should be reported closely to treatment discontinuation.

Kadcyla® was approved for commercial use in the US in February 2013 allowing for a study period duration of up to nearly 3.5 years for the first analysis and up to nearly 5.5 years for the final analysis. A schematic of the study design is provided in Figure 1.

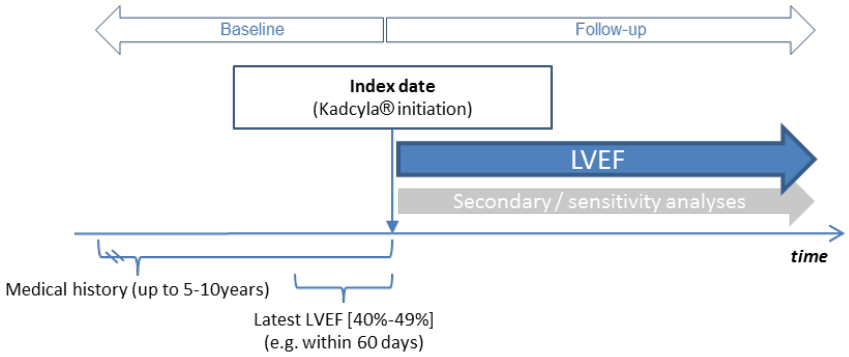

Figure 1: Study design.

8.2.2.6 Analyses groups

8.2.2.6.1 Main analysis

Patients who met all inclusion criteria, and did not meet any exclusion criteria will be used to describe study population characteristics at baseline. The longitudinal evolution of LVEF during follow-up and the onset of cardiac events will be described using graphics summarizing LVEF values over time and descriptive statistics.

8.2.2.6.2 Subgroups based on history of CHF at *index date*

As a LVEF below normal value is a selection criterion, the study sample is anticipated to be a mixture of prevalent cases of CHF and patients without history of CHF at index date. History of CHF (present or absent) will be used to split the study cohort in two subgroups that will be described separately. The *subgroup at risk* of incident CHF (i.e. free of CHF at index date) will be used to estimate the *incidence rate of a first CHF event* (see 8.7.4).

8.2.2.6.3 Subgroups based on history of other cardiac events at index date

The subgroups at risk of a new cardiac event (i.e., free of the event of interest at the index date) will allow estimating the *incidence rates* of *other first cardiac events of interest* (see 8.7.4).

8.2.2.7 Population Representativeness

The source population of this study is diverse, includes 17% of all cases of cancer in the U.S. and mainly includes community practices. The inclusion/exclusion criteria for the study were defined to provide a reasonable balance between sample size, data quality and representativeness of the U.S. population of patients with metastatic breast cancer with a LVEF between 40% and 49% recorded within 60 days prior to initiating treatment with Kadcyla®.

8.2.3 Comparison Group

This is a single arm retrospective study; no comparison group will be included a priori.

8.3 VARIABLES

8.3.1 Primary Safety Variables

LVEF values, dates and test used will be retrieved from the examination of cardiac monitoring reports. The latest LVEF measurement recorded within 60 days prior to *index date* will be considered as baseline LVEF value.

8.3.2 Secondary Safety Variables

8.3.2.1 Congestive heart failure

Diagnosis of CHF and date of onset will be searched in the electronic health records (including physician notes).

8.3.2.2 Other Cardiac Events of Interest

Other cardiac events of interest and date of onset will be searched and abstracted from the electronic health records (including physician notes) and will include:

1. cardiac tachyarrhythmia (atrial fibrillation, atrial flutter, atrial tachycardia, ventricular tachycardia or ventricular fibrillation)
2. acute coronary syndrome
3. unstable angina
4. myocardial infarction
5. Kadcyla® treatment discontinuation due to cardio-toxicity
6. abnormal results for biomarkers of cardiac distress (BNP, pro-BNP, troponin)
7. hospitalization for cardiac reason or admission to cardiology intensive care unit
8. death and death for cardiac reason[1]

8.3.3 Other Variables

8.3.3.1 Patient demographics and disease characteristics

Patient demographics will include variables such as gender and age. Breast cancer characteristics will include variables including but not limited to biomarker status (HER2 and hormone receptor status), staging at first diagnosis and prior cardio-toxic treatments (radiation exposure and previous therapy with an anthracycline or HER2 targeted therapies). More details provided in section 8.7.1.

8.3.3.2 Cardiac risks factors

Cardiac risk factors will include variables such as BMI, presence and date of onset of the following conditions: hypercholesterolemia, coronary artery disease, diabetes, and hypertension. Prior or concomitant use of antihypertensive medicinal products will also be collected.

8.3.3.3 Cardiac history

Cardiac history will include variables such as presence and date of onset of CHF and *other cardiac events* (as detailed previously) and previous treatment discontinuation due to cardiac toxicity. Furthermore, management by a cardiologist, signs and symptoms of CHF, cardiac procedures and devices will also be collected prior to and after Kadcyla® initiation.

8.3.3.4 Kadcyla® treatment discontinuation

Subsequent Kadcyla® administrations recorded within 84 days from each other will define an episode of treatment during which the exposure to Kadcyla is considered continuous. As such, Kadcyla® treatment will be considered

[1] Availability of this data element may be limited due to incomplete documentation of cause of death in the patient charts.

discontinued if the patient missed more than 4 consecutive infusions (4x21=84). Furthermore if a patient initiates a new antineoplastic treatment or is reported deceased within the 84 days of the last Kadcyla administration the treatment will also be considered discontinued. Loss to follow-up on treatment will define the instances where the treatment gap of 84 days cannot be observed (last patient visit or clinical cut of date within the 84 days following the last Kadcyla administration) and where no new antineoplastic treatment is initiated and no mortality is reported.

8.3.3.5 Death and cardiac death

Death events and their date will also be abstracted from the EHR, whether the death is attributed to cardiac cause or not. The study is not designed to estimate overall mortality or other effectiveness measures. This information will be collected to define patient-time at risk (see risk competition in section 8.7.3).

More details on collected variables are provided in Appendix E.

8.3.4 Endpoints

8.3.4.1 Primary Endpoint

The primary objective of this study is to characterize the patient profile and to document the cardiac safety of Kadcyla® in a low LVEF population. Hence the primary endpoints of this study are:

- LVEF values by time
- The incidence rate and the cumulative incidence of LVEF decrease greater than 10% points from baseline

The primary outcomes will be described in all patients as well as in the subgroups of patients with and without history of CHF at index date.

8.3.4.2 Secondary Endpoints

Date of onset for the event of interest (e.g. CHF) will be used to estimate secondary endpoints. Each secondary endpoint will be described for the whole study population (where *events* can be observed for the first time or not) and per relevant *subgroup at risk* to allow estimation of the incidence rate of a first event.

The secondary outcomes of this study are:

- CHF *event rate, incidence rate* and *cumulative incidence* of CHF event observed during the cohort's follow-up. The relevant *subgroup at risk* (patients without history of CHF at index date) will be analyzed separately allowing the estimation of the CHF *incidence rate* and the respective *cumulative incidence*.

- The *event rate*, the *incidence rate* and their respective *cumulative incidence* will also be estimated for each of the other cardiac events of interest.

8.4 DATA SOURCE(S)

Flatiron's cloud-based oncology EHR database will be used. Data analyzed in this study will include both the data automatically recorded by the patients' management software used by the oncologists during routine clinical practice (e.g. type of visit for a patient and date) and information abstracted manually from the patients' EHR (e.g. scanned laboratory reports, notes from the oncologist). Patients in the Flatiron EHR system represent ~17% of incident cancer cases in the United States, which makes it the largest available real-world oncology data source with integrated clinical data.

8.5 STUDY SIZE

This study is a single arm retrospective study. Analysis of study data will only be descriptive. Therefore no a priori hypothesis will be formally tested, and no comparison group will be used. Accordingly, no formal sample size calculation has been performed. The focus will be on estimation of event rates and incidence rates and their respective confidence intervals.

Based on the data extracted on July 31th 2016, the Flatiron EHR database at the time included 1049 Kadcyla® patients and it is anticipated that approximately 6% of the mBC population will present with LVEF ≤50% prior to initiation of treatment with Kadcyla® (Redfield et al., 2003). All the patients identified with LVEF ≤50% prior to Kadcyla® initiation in the EHR database will be considered for data extraction to allow for sensitivity analyses. The main analysis however will focus on the subset of patients with LVEF higher or equal to 40% and lower than 50%. The respective sample size for this main analysis as described in section 8.2.2 is anticipated to be up to 35 patients assuming a data cut-off date of July 2018.

8.6 DATA MANAGEMENT

Across the clinics in the Flatiron Provider Network, Flatiron has access to and securely maintains the entire patient chart, enabling a complete longitudinal data view of cancer patients with resolution at the disease and treatment level.

Each patient record will be abstracted by two independent oncology nurses. Any abstraction discrepancy will be reviewed and adjudicated by Flatiron's internal abstraction team, involving an external cardio-oncologist to assess relevant cases.

The following steps will be used for data management::

- The MAH will approve the eCRF specifications for this study

- Source data will be entered manually via EDC system.
- Flatiron Health will produce a Data Quality Review Plan that is approved by the MAH and describes the quality checking to be performed on the data.
- eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at Flatiron Health and records retention for the study data will be consistent with Flatiron Health standard procedures.
- Data will be transferred electronically from Flatiron Health to the MAH, and MAH standard procedures will be used to handle and process the electronic transfer of these data.

Flatiron Health will comply with the MAH procedures regarding content, archiving and records management of process documents defined in MAH reference model (RRM).

Data from Flatiron will be transferred to Roche via SFTP server along with documentation including the data dictionary and summary of any changes to data structures. Roche will move the files from SFTP Server to a Linux server (Landing Zone Server), where the data will be archived and unzipped. Extract, Transform and Load Informatica Mappings will be used for each Flatiron data file that is created in the above unzip process to load data from the source files to the staging tables and ultimately to the core tables in the Teradata database. Each of the 29 source files will go into a separate table in the Flatiron Database named RWD_VDM_FLATIRON_SE_KADCYLA. Examples of the naming convention for tables are RWD_VDM_FLATIRON_SE_KADCYLA.DEMOGRAPHICS, RWD_VDM_FLATIRON_SE_KADCYLA.DIAGNOSIS, RWD_VDM_FLATIRON_SE_KADCYLA.ECOG etc. This means that all CSV datasets, all observations, and all variables, will be loaded directly into the Teradata Flatiron Database. Roche will keep track of data appends to existing Flatiron tables through two columns in each table - Valid Start and Valid End. Based on these two columns the analyst will select specific data batches.

Flatiron provides information with regard to the number of observations per dataset; this information will be checked by Roche. At the end of the data upload, Roche will perform a full comparison between the original files delivered by Flatiron and the files that are loaded into Roche Flatiron Database, ensuring quality check for all observations, variables and their content. The checked files from the Roche Flatiron Database will be available in the form of Teradata views for study analysis.

8.7 DATA ANALYSIS

This is a secondary data use NIS. It is designed to describe LVEF values over time to describe the cardiac risk in patients with low LVEF when receiving treatment with Kadcyla® for mBC. Analyses will be performed two times including one interim analysis and one final analysis.

Categorical variables will be summarized using absolute frequencies and percentages, and continuous variables will be summarized using descriptive statistics (i.e., mean, median, standard deviation and range), separately for the whole study population and by relevant subgroups (e.g. patients with and without CHF at baseline).

A detailed statistical analysis plan will be developed. All statistical analyses will be performed in-house using Statistical Analysis System (SAS) 9.X or R.

8.7.1 Analysis of Demographics and Baseline Characteristics

Descriptive statistics will be used to characterize the distribution of patients at the index date.

Table 2: Patients demographics and baseline characteristics at index date.

Demographics	• age • gender • race • body mass index at the most recent examination prior to the index date • year of the index date • type of practice (community practice or academic center) • type of insurance plan
Breast cancer characteristics	• MBC diagnosis type (De Novo if BC diagnosis date is within the 90 days prior to MBC diagnosis date and recurrent otherwise) • duration (in months) from date of early breast cancer diagnosis to mBC diagnosis • duration (in months) from date of MBC diagnosis to date of *index date* (i,.e., Kadcyla® initiation) • most recent ECOG performance status prior to index date • biomarker status for HER2 and hormone receptors • group stage at initial breast cancer diagnosis.

	• site(s) of metastasis
Cardiac risk profile	• baseline LVEF value and measurement method, • presence of relevant comorbidities (e.g. hypertension, diabetes, hypercholesterolemia or metabolic syndrome) • cardiac history (congestive heart failure, cardiac tachyarrhythmia, atrial fibrillation, atrial flutter or atrial tachycardia, ventricular tachycardia or ventricular fibrillation, coronary artery disease (CAD), positive cardiac stress test, acute coronary syndrome (ACS), unstable angina, myocardial infarction (MI)) • cardiac procedures (e.g. coronary bypass surgery, cardiac catheterization, stent placement, valve replacement or repair, cardioversion, atrial flutter/fibrillation ablation, admission to the cardiology ICU, pacemaker, defibrillator) • cardiac medication
Antineoplastic treatment characteristics	• dose per kilogram used for the first infusion • prior exposure to anthracycline • endocrine treatment • HER2 targeted therapies • prior radiation therapy • previous treatment discontinuation due to cardio-toxicity

8.7.2 Safety Analyses

8.7.3 Primary Safety Analyses

LVEF values will be described over time using absolute values. In the case of multiple LVEF measurements per patient being reported on the same date during the follow-up period, the lowest value will be used. Conversely, the highest value will be used if reported on the same day on or prior to the index date. LVEF values and change from baseline of LVEF will be summarized by study follow-up duration using baseline and intervals of follow-up (e.g. day 1 to day 90 for the first quarter). In the instance where multiple values are observed on different days within the same interval for the same patient, the mean value will be used.

As per Kadcyla label, the study population is anticipated to start Kadcyla relatively late in the course of their mBC disease. In this instance, mortality from cancer is anticipated to potentially preclude the observation of a cardiac event of

interest. As such, the risk of non-cardiac mortality competes with the cardiac risk. When estimating the crude incidence of outcomes in a competing risk situation, the cumulative incidence function should be preferred over the Kaplan-Meier survival function (Fine & Gray, 1999). Indeed, estimating the risk of cardiac events ignoring the potential competition with the risk of non-cardiac death would lead to biased and inflated estimates (Satagopan et al., 2004). Furthermore, as the duration of treatment (and the duration of follow-up) is *a priori* unknown, the *cumulative incidence* will be estimated at any time of the follow-up through the *cumulative incidence function* and non-cardiac mortality will be considered as a competing event.

The risk of a first drop in LVEF >10% points will be described using *incidence rate*, the *cumulative incidence and respective 95% confidence interval will be computed*. The time to onset of a drop in LVEF >10% will be defined as the number of days between the index date and the first recorded date of the event. The study is non-interventional, as a consequence the date of a LVEF drop >10% will be conditional to cardiac monitoring and interpreted with caution.

8.7.4 Secondary Safety Analyses

It is anticipated that some patients will already have experienced one of the events of interest at the *index date (*i.e. prevalent case for CHF). As a consequence such patients cannot be considered at risk to develop the condition per se. However, it is still clinically relevant to describe any event a physician reported (whether it is first ever or not). As such, *event rates* and *cumulative incidence* will be estimated in the whole study population to describe the risk of occurrence of a *cardiac event of interest* after index date (whether it is a first event ever or a recurrence). Conversely, the incidence rate and *cumulative incidence* of a first event of interest and 95% confidence interval will be estimated within the *subgroup at risk* for the event only.

In the instance multiple events of interest are observed during the follow-up of a patient only the first event observed during the follow-up will be considered, and only the time to first event will be considered as *time at risk* to estimate the rates.

For patients who experience more than one event classified into different categories (e.g., a patient may have experienced both an acute myocardial infarction (MI) and angina), each event will be counted separately.

8.7.5 Sensitivity analyses

Sensitivity analyses replicating the main analysis will be conducted and will include (but will not be limited to) the following variations from the primary study design:

- Patients with a baseline LVEF value reported as an absolute value equal to 50% or reported as a range overlapping with 50% will be added to the study cohort to define an “expanded cohort”. This analysis will allow the estimation of the risk of cardiac dysfunction in patients for whom the latest LVEF value is possibly inferior or equal to 50%.
- The duration of follow-up will be extended (e.g. follow-up extended beyond 84 days). This analysis will capture events that are likely to be related to treatments initiated after Kadcyla but will allow to describe longer term outcomes.
- The potential misclassification of CHF will be mitigated by using signs and symptoms compatible with CHF.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

Flatiron will be responsible for data management of the data used in this study, including quality checking of the data. The Flatiron team will set up a Data Review strategy that describes the quality checking to be performed on the data. The MAH will perform oversight of the data management, including approval of the Flatiron data management plans and specifications. Data will be annually transferred electronically from Flatiron to the MAH, and the MAH standard procedures will be used to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored in the Flatiron EHR database and records retention for the study data will be consistent with the Flatiron standard procedures. The data sent by Flatiron will be scrutinized to ensure patient selection complies with the inclusion and exclusion criteria, and patient counts will be compared to those expected in feasibility counts. Output data will be sense-checked and compared with what is known from the current literature. Verification of the completeness of data will be performed variable by variable.

The data will then be analyzed by the MAH following the current protocol and corresponding statistical analysis plan.

The MAH must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, and documentation of IRB/EC and governmental notification (if required).

The Marketing Authorization Holder shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Data not held within MAH systems will be periodically transferred electronically from Flatiron Health to the MAH, and the MAH standard procedures will be used

to handle and process the electronic transfer of these data. Flatiron Heath will comply with the MAH procedures regarding content, archiving and records management of process documents.

Retention of Records

Records and documents pertaining to the conduct of this study must be retained for at least 15 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the marketing authorization holder. Written notification should be provided to the marketing authorization holder prior to transferring any records to another party or moving them to another location.

8.9 LIMITATIONS OF THE STUDY

8.9.1 Selection bias

This study will focus on patients initiating Kadcyla® treatment with a low LVEF. It is anticipated that the study sample size will be small, for two main reasons:

1. The prevalence of low LVEF or CHF in pre-treated HER2+ mBC is modest (below 3% and 9%, respectively, as per OHERA ASR 2015, a trastuzumab PASS study in early breast cancer).
2. Kadcyla® has not been studied in patients with LVEF < 50% prior to initiation of treatment (RocheProductsLtd.).

Furthermore it is acknowledged that patients with low LVEF may have limited treatment options, in such situations clinicians have to make the decision of initiating Kadcyla® on a case by case basis, assessing the relative risks of cardiac dysfunction versus disease progression.(Giordano et al., 2014) As a result the study population will be relatively selected compared with the general mBC population initiating Kadcyla®. However the study population selection criteria were defined to make the study population representative of the population initiating Kadcyla® with a LVEF ≥40% and ≤49%.

8.9.2 Misclassification

8.9.2.1 LVEF

Prior studies used look back periods of up to 84 days prior to the first dose of an investigational medical product to define patients' baseline LVEF value.(Tolaney et al., 2013) However, breast cancer patients with low LVEF value should have

their LVEF re-evaluated within 3 weeks giving rationale for using a shorter look back period (e.g. 60 days). Sensitivity analyses will be conducted using different look back periods (e.g. up to 180 days) to identify the baseline LVEF value.

8.9.2.2 CHF

Kadcyla® is indicated to treat mBC in a pre-treated population. In the later course of mBC, disease symptoms of breast cancer can overlap with CHF possibly hindering the timely identification of CHF events. There is a risk of underreporting or under identification of CHF potentially resulting in misclassifying prevalent cases (i.e., with CHF at baseline) as incident cases of symptomatic CHF. Furthermore, the assessment of free-text information in the EMRs can be challenging due to possible use of synonyms/alternative wording to document the same concept (such as CHF). Several measures were taken to mitigate such limitations. First, the study is based on secondary data analysis and is reliant on rigorous data abstraction from electronic medical records. Second, abstractors will be oncology nurses only and are anticipated to be used to identifying CHF signs and symptoms and other relevant conditions as well as cardiac toxicities. Third, information on every patient will be abstracted twice by independent oncology nurses and discrepancies will be adjudicated by an external third party involving a trained cardio-oncologist if needed. Finally, in order to identify potential missed case of CHF, sensitivity analyses using signs and symptoms of CHF as well as diagnosis of CHF will be conducted.

8.9.3 Missing data

The opportunity to observe a potential change in LVEF during the follow-up is conditioned on the frequency of LVEF monitoring conducted in routine clinical practice. In this light, the longitudinal description of the LVEF values during the follow-up as well as the incidence rate of LVEF drop in the observational setting will have to be interpreted with caution. Sensitivity analyses imputing LVEF values in between two intervals will be conducted to better describe the evolution of LVEF values over time. However, LVEF monitoring is part of the management of mBC patients and the cardiac toxicity of HER2 treatment is well known.(Curigliano et al., 2012; Eschenhagen et al., 2011; Giordano et al., 2014; Jones et al., 2009; Martin et al., 2009) As a consequence, EHRs from oncology practices should represent a valuable data source to describe the risk of interest.

Flatiron data are generated from real-world clinical practice, and are subject to miscoding and errors usually encountered in the oncology clinic.

CHF is a major cause of hospitalization.(Collins et al., 2013) Nonetheless, the majority of hospitalizations of heart failure patients are for reasons other than acute heart failure (Blecker et al., 2010; Dunlay et al., 2009) as a consequence

the risk of lost to follow-up due to CHF is not considered to threaten study validity. In this study the risk of missing a diagnosis of CHF due to lost to follow-up was mitigated by using synonyms of CHF as well as signs and symptoms of CHF that could appear before hospitalization.

In order to maximise the chance of capturing the relevant information, the abstractors will be provided with a list of words and concepts and also requested to collect data for generic terms (such as “discontinuation due to cardiotoxicity”) as well as precise concepts regarded as potential markers of CHF (such as initiation of treatments for CHF, abnormalities in cardiac biomarkers, hospital admission in intensive care unit for cardiac reasons).

8.9.4 Confounding

This observational study is not attempting to draw conclusions with regard to the causal relationship of exposures and outcomes. Analysis of confounding is outside the scope of the study.

8.9.5 Other limitations

The study is limited by the retrospective nature of collecting the available data. Although it is possible that cardiology consultations and medical therapies received outside the oncology practices can be missed, the chart will be extensively reviewed for any updated medications and referrals before, during, and after cancer therapy.

Patients with cancer typically receive multiple cancer drugs and sometimes radiation, with the potential for cardio toxic effects from interactions among the different therapeutic modalities.(Khouri et al., 2012) This will limit the ability of study to establish a causal relationship between the events observed and the use of Kadcyla®.

The small number of patients will limit interpretation of the findings and the ability to perform adjusted analyses in order to identify risk factors for worse outcome.

The potential selection bias toward patients without an alternate treatment option can also induce a shorter follow-up due to initiating Kadcyla® later in the course of mBC. In such instance, mortality may also compete with cardiac risk. Risk competition will be taken into account in the analyses by estimating the cumulative incidence functions of various cardiac events and non-cardiac death.

This study has several strengths. This study will be the first to describe an unknown risk in a poorly understood patient population. The study will make use

of the richness of the full EHR database by examining numerous aspects of cardiac risk.

The relatively recent approval of Kadcyla® and the rarity of the condition of interest are factors limiting the study population, making the research questions challenging to address.

The use of a large anonymized secondary data set that offers the ability to abstract data from electronic medical charts constitutes a unique opportunity to quickly aggregate and analyze data, describe, and monitor relevant risks in real life. Automated healthcare data sources (such as EMR or healthcare claims data that usually contain hundred thousands of patients) have been used to assess LVEF levels (Bovitz, Gilbertson, & Herzog, 2016; Li et al., 2011) but they do not allow rigorous patient selection and lack granular medical information, making the chart abstraction necessary. Flatiron's EHR offers good capture of clinical information and access to the full oncology EHR history has advantages over structured EHR fields and claims data for the identification and characterization of oncology patients.(Liede et al., 2015)

As the dataset used for this analysis is one of the largest oncology datasets worldwide it is believed that this study uses the most appropriate data source to describe what is performed in routine clinical practice. Indeed as disease registries tend to enroll patients from academic centers, representativeness can be an issue, especially when it comes to management of specific scenarios. As such the exclusive use of data recorded during routine clinical practice a priori and independently from the current protocol makes the nature of this secondary data use study purely observational and reflective of real world practice.

9. PROTECTION OF PATIENTS

9.1 INFORMED CONSENT

It will generally not be possible/practical to obtain informed consent for use of secondary data in a NIS; however certain other precautions must be taken, including:

- Ensuring data are anonymized / pseudonymized
- Ensuring final analysis data are anonymized / pseudonymized
- Ensuring possibility of linkage back to individual identified patients is impossible or tightly controlled
- Obtaining ethical committee approval for use of data as proposed (e.g., the review of and extraction of information from individual medical charts) records for the proposed use ahead of study initiation.

Individual patient-level EHR data were encrypted at rest and in transit so that all analyses will be de-identified to protect patient privacy consistent with the final Health Insurance Portability and Accountability Act (HIPAA) Security Rule from the US Department of Health and Human Services.

9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

9.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

Flatiron's full dataset from which the data for this study will be extracted is covered by Flatiron's Parent Protocol version 3.0 (21 Sep 2016) approved by the [redacted] under [redacted]. The current study and relevant supporting information was submitted to the [redacted] as an amendment to that parent protocol: [redacted] - Trastuzumab-Emtansine in Metastatic Breast Cancer Patients with Low LVEF [redacted]. Flatiron will notify the IRB of any unanticipated problems in accordance with IRB requirements.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a NI-PASS involving the use of secondary data and thus the reporting of adverse reactions in the form of ICSRs is not required.

It is assumed that safety reporting of data which are going to be extracted/analyzed as part of this study have been appropriately performed and documented at the time this data were collected through primary data collection mechanism.

10.1 ADVERSE EVENTS

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.2 SERIOUS ADVERSE EVENTS

A SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are <u>not</u> synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTC AE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

11. <u>PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RRESULTS</u>

Regardless of the outcome of NI-PASS, the marketing authorization holder is dedicated to openly providing information on the NI-PASS to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The marketing authorization holder will comply with all requirements for publication of study results.

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Appendix A Documents Not Included in the Protocol

Data Analysis Plan

Flatiron Analytic Guide

Flatiron QA/QC Documentation Kadcyla® LVEF

Flatiron Roche Kadcyla® LVEF Abstraction Form

IRB parent protocol

Notification of approval [redacted] IRB [redacted] COA)

Appendix B Data processing by Flatiron Health

Flatiron Health can process data from many source EHR, including oncology specific EHRs (e.g. OncoEMR) as well as general EHRs (e.g. Epic, Cerner). Flatiron processes both *structured data* (i.e. data points that are organized in a predefined manner, such as drop-down fields that reside in the EHR to capture a patient's gender or date of birth) and *unstructured data* (i.e. information that is not organized in a pre-existing data model, such as free text from a physician note or lab report) and stores the output in anonymized data sets.

The unstructured dataset relies on a chart abstraction process by which information is extracted from the hard-to-reach unstructured data within a patient chart (e.g., histology information from a pathology report, stage of disease captured in a clinical note). The unstructured data are abstracted by experienced oncology nurses, each case will be abstracted twice by independent abstractors. Operating procedures, documented best practice guidelines and continuous quality monitoring govern the process. Abstractor reliability scores, quantified as kappas and proportional agreement, are required to remain within a defined range (specific to the diagnosis and project data model) during both initial training and ongoing quality assurance (QA) checks. Oncologists are involved in each step, providing oversight, training support, adjudication, quality review and medical context. Previous research reports suggest that compared with usual EHR and claims database approaches technology-enabled abstraction of EHR can improve data completeness and accuracy (Liede et al., 2015)

Appendix C Technology-enabled chart abstraction

Flatiron developed a technology-enabled, modular approach to optimize both the accuracy and efficiency of data abstraction from unstructured sources in the EHR. This approach uses a software tool developed for the identification and targeted display of selected portions of the patient chart for abstraction. A team of clinically trained professionals (Flatiron Health oncology nurses and certified tumor registrars) access each chart within this software to collect only specific data elements across many patients' charts, rather than review the entirety of any individual patient chart.

This modular approach allows chart abstractors to focus their attention on specific data elements (e.g., dates of bone metastasis) and to collect these elements uniformly. The approach also enables iterative assessment and improvement of the quality of each data element separately. Quality is continuously assessed by computing inter-abstractor agreement (inter-rater reliability) after subsets of charts were shown to multiple abstractors.

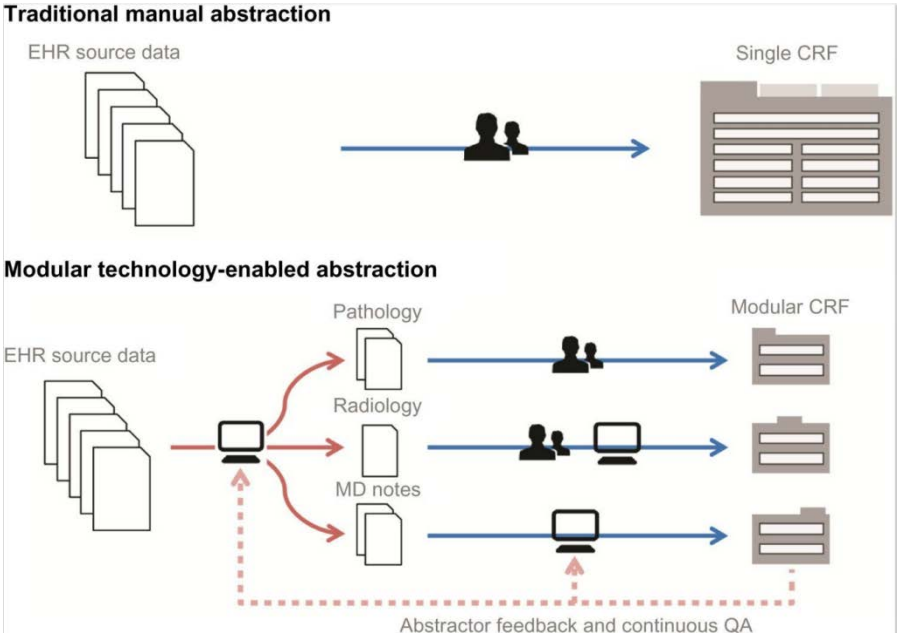

Figure 3: Traditional and modular technology-enabled chart abstraction process from HER.(Liede et al., 2015)

Notes: In traditional chart abstraction, the abstractor is presented with the entire chart and a single CRF. In a modular approach, the CRF is divided into thematically related modules and abstractors are presented with relevant data only. **Abbreviations:** EHR, electronic health records; CRF, case report form; MD, Medicine Doctor or physician; QA, quality assurance.

Appendix D Abstraction of breast cancer patients

For this project abstractors are nurses with experience in staging tumors and an oncology background. They have an expertise finding information in medical records. For edge cases or outliers that they are not confident in abstracting, abstractors are instructed to elevate the case to a Review Panel, where it is handled by flatiron senior clinical team of oncology nurse practitioners and oncologists.

Pathology consistent with breast cancer and evidence of stage IV or recurrent mBC refers to the following abstraction strategy:

Abstractors will be instructed to exclude patients with in situ carcinoma.

Abstractors will be first directed to search through pathology records for biopsy information that may have diagnosed the patient with breast cancer.

If the diagnosis information is not found in pathology records, abstractors will be then directed to look through the physician documentation to confirm the diagnosis.

Radiology records alone will not be relied upon for diagnosis information; the diagnosis will be confirmed from scan data.

Appendix E Summarized abstraction form

Terms and synonyms used to collect data using the abstraction form:

Atrial tachyarrhythmia also includes: atrial fibrillation, atrial flutter or atrial tachycardia.

Ventricular tachyarrhythmia also includes: ventricular tachycardia, ventricular fibrillation.

Congestive heart failure also includes: mention of “heart failure,” “systolic heart failure,” or “diastolic heart failure”

Coronary artery disease also includes, but was not limited to: non-obstructive coronary disease, any mention of coronary disease on a catheterization or coronary CT scan

Positive cardiac stress test: A “positive” test was defined as any test that did not fall within the institutional normal range, documentation of inducible ischemia was considered a positive cardiac stress test

Hypercholesterolemia also includes: “hyperlipidemia” or “high cholesterol”.

Hypertension also includes: Mention of “high blood pressure”

Myocardial infarction could also include, but was not limited to, any of the following terms: Acute myocardial infarction (AMI), Myocardial infarction (MI), Non ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), Myocardial infarction (within the past year) or metabolic syndrome.

(Abstraction form starts on the next page)

Questions / subquestions on abstraction form

LVEF Assessments (any point in time)
• Date of LVEF assessment.
• Imaging modality
• LVEF result
  ○ If modality = "ECHO" or "Other / Unknown", select the LVEF range
  ○ (If modality = "MUGA" or "Cardiac MRI", select the LVEF value

Cardiac History and Risk Factors (Prior to Kadcyla initiation)
• History of a cardiac tachyarrhythmia?
  ○ History of atrial fibrillation, atrial flutter or atrial tachycardia?
  ■ Date of onset
  ○ History of ventricular tachycardia or ventricular fibrillation?
  ■ Date of onset
• History of congestive heart failure (CHF)?
  ○ Date of onset
• History of coronary artery disease (CAD)?
  ○ Date of diagnosis
• Cardiac stress test result that did not fall in the institutional normal range?
  ○ Date of the test
• History of diabetes?
  ○ Date of diagnosis
• History of hypercholesterolemia?
  ○ Date of diagnosis
• History of hypertension?
  ○ Date of diagnosis
• History of acute coronary syndrome (ACS)?
  ○ Date of diagnosis
• History of unstable angina?
  ○ Date of diagnosis
• History of a myocardial infarction (MI)?
  ○ Did the patient have an MI in the last year prior to Kadycla initiation?
  ■ Date of the first known event within the last year
• History of metabolic syndrome?
  ○ Date of diagnosis

Cardiac History and Risk Factors (Following Kadcyla initiation)
• Active cardiac tachyarrhythmia?
  ○ Active atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia)?
  ■ Date of the event.
  ■ Treated for this event?
  ■ Did the diagnosis of atrial tachyarrhythmia precede the initiation of Kadcyla?
  ○ Active ventricular tachyarrhythmia (ventricular tachycardia or ventricular fibrillation)?
  ■ Date of the event.
  ■ Treated for this event?
  ■ Did the diagnosis of ventricular tachyarrhythmia precede the initiation of Kadcyla?
• Active CHF?
  ○ Date of the event
• Did the patient develop acute coronary syndrome?

(abstraction form continues on the next pages)

- Date of diagnosis
- Did the patient develop unstable angina?
  - Date of diagnosis
- Did the patient have a new MI?
  - Date of the event
- Is the patient deceased?
  - Was the patient's death attributed to a cardiac event reported in the record?

CHF Signs/Symptomatology (Prior to Kadcyla initiation)

- Shortness of breath with exertion that limited normal activity?
  - Date of documentation
- Orthopnea or paroxysmal nocturnal dyspnea (PND)?
  - Date of documentation
- Lower extremity edema with shortness of breath?
  - Date of documentation
- Weight gain and shortness of breath?
  - Date of documentation
- Shortness of breath and any of the following on a physical exam?: Jugular venous distention (JVD), Rales or crackles in the lungs, S3 on cardiac auscultation
  - Date of documentation
- BNP lab measurement?
  - Date of measurement
  - Result (free text)
  - What was the result relative to the institutional reference range?
- Pro-BNP lab measurement?
  - Date of measurement
  - Result (free text)
  - What was the result relative to the institutional reference range?
- Troponin lab measurement?
  - Date of measurement
  - Result (free text)
  - What was the result relative to the institutional reference range?

CHF Signs/Symptomatology (Following Kadcyla initiation)

- Shortness of breath with exertion that limited normal activity?
  - Date of documentation
- Orthopnea or paroxysmal nocturnal dyspnea (PND)?
  - Date of documentation
- Lower extremity edema with shortness of breath?
  - Date of documentation
- Weight gain and shortness of breath?
  - Date of documentation
- Shortness of breath and any of the following on a physical exam?: Jugular venous distention (JVD), Rales or crackles in the lungs, S3 on cardiac auscultation
  - Date of documentation
- BNP lab measurement?
  - Date of measurement
  - Result (free text)
  - What was the result relative to the institutional reference range?
- Pro-BNP lab measurement?
  - Date of measurement
  - Result (free text)
  - What was the result relative to the institutional reference range?
- Troponin lab measurement?
  - Date of measurement
  - Result (free text)
  - What was the result relative to the institutional reference range?

(abstraction form continues on the next pages)

Cardiac Medications at the time of Kadcyla initiation

- Did the patient take a cardiac medication?
  - Select the name(s) of the medication (If "Other", enter the name)

Cardiac Medications after Kadcyla initiation

- Did the patient take a cardiac medication?
  - Select the name(s) of the medication (If "Other", enter the name)
  - Enter the start date or dose change of the drug

Cardiac Procedures (Both prior to and following Kadcyla initiation)

- Had coronary bypass surgery?
  - Was the surgery after the initiation of Kadcyla?
    - Date of surgery
- Had a cardiac catheterization?
  - Was this procedure after initiation of Kadcyla?
    - Date of procedure
  - Stent placement?
- Had a valve replacement or repair?
  - Was this procedure after initiation of Kadcyla?
    - Date of procedure
- Had a cardioversion?
  - Was this procedure after initiation of Kadcyla?
    - Date of procedure
- Had an atrial flutter/fibrillation ablation?
  - Was this procedure after initiation of Kadcyla?
    - Date of procedure
- Did the patient require an admission to the cardiology ICU?
  - Was the admission after the initiation of Kadcyla?
    - Date of admission
- Pacemaker in place?
  - Date it was placed
- Defibrillator in place?
  - Date it was placed

(abstraction form continues on the next page)

Hormonal Therapies and cardio-toxic antineoplastics (Prior to Kadcyla initiation)

- Did the patient experience cardiac toxicity associated with a specific therapy prior to initiating treatment with Kadcyla?
  - Enter the date of documentation
- Treated with an anthracycline?
  - What was the patient's cumulative dose of anthracycline relative to the following thresholds: doxorubicin: 300mg/m2, epirubicin 600mg/m2
  - How many cycles of the anthracycline did the patient complete? (free text)
- Treated with an endocrine therapy?
- Treated with trastuzumab for early stage breast cancer?
  - Did patient discontinue treatment with trastuzumab due to cardiac toxicity?
- Treated with trastuzumab for metastatic breast cancer?
  - Did patient discontinue treatment with trastuzumab due to cardiac toxicity?
- Treated with pertuzumab for early stage breast cancer?
  - Did patient discontinue treatment with pertuzumab due to cardiac toxicity?
- Treated with pertuzumab for metastatic breast cancer?
  - Did patient discontinue treatment with pertuzumab due to cardiac toxicity?
- Did the patient receive radiation treatment to the chest?
  - Left chest?
  - Right chest?

Hospitalization (Allow multiples)

- Hospitalized at any point?
  - Date of admission
  - Date of documentation
  - Explicitly attributed to a cardiac reason?
    - Select the reason (drop-down)

Cardiology Care History

- Cardiologist care prior to initiating Kadcyla?
  - Did the patient first see a cardiologist >90 days before initiating Kadcyla?
- Cardiologist care after initiating Kadcyla?