TITLE PAGE

STUDY REPORT NO. ML29659

PASS INFORMATION

TITLE:	**UK – A DISEASE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
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STUDIED MEDICINAL PRODUCTS:	Ado-trastuzumab emtansine - Kadcyla, T-DM1
AUTHOR:	[redacted] Roche Products Ltd. Hexagon Place Shire Park 6 Falcon W ay AL7 1TW
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ACTIVE SUBSTANCES	L01FD03: trastuzumab-emtansine
PRODUCT REFERENCE NUMBER:	Kadcyla EMEA/H/C/002389
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JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	There are limited published data concerning treatment patterns for patients with HER2-positive unresectable locally advanced (LA)/mBC. However, clinicians and reimbursement agencies may require such information to inform decision-making regarding the best treatment strategies for patients throughout the course of their disease. This study will allow descriptive analyses to identify associations between patient characteristics,

	treatments, and outcomes. Additionally, as new information becomes available on potential risk factors and as new treatments become available, the study will provide an opportunity to gain an insight into the evolving treatment landscape. **Primary Objective** In patients with unresectable locally advanced (LA) or metastatic breast cancer (mBC), to observe the different anti-cancer treatment regimens and their sequencing throughout the course of the disease and to describe the clinical outcome for each treatment regimen measured as progression-free survival (PFS). **Secondary Objectives** The secondary objectives for this study are as follows: ***Safety objectives*** • To observe the safety of different anti-cancer treatment regimens through the reporting of serious adverse events (SAEs), specific adverse events relevant to HER2-targeted therapies, potential medicine-induced liver injury, suspected transmission of an infectious agent by study medicine, cardiac dysfunction and serious and non-serious pneumonitis; and AEs leading to discontinuation or dose modification of an anti-cancer therapy • To observe and describe the incidence of and reasons for anti-cancer treatment modifications • To observe and describe the treatment of populations of special interest by estimating the incidence and prevalence of cardiac events related to left ventricular dysfunction; pregnancy; and pregnancy outcomes. ***Effectiveness objectives*** • To observe regional differences in anti-cancer treatment regimens • To observe overall survival (OS) • To observe objective response rate (ORR) per anti-cancer treatment regimen • To observe duration of response (DoR) per anti-cancer treatment regimen • To evaluate time to treatment failure (to when treatment is stopped or switched or death)

	Other objectives • To observe patients' demographics and breast cancer histories for each anti-cancer treatment regimen • To document the incidence (during the observation period) of pregnancy and pregnancy outcomes • To examine utilisation or adherence to predefined clinical guidelines regarding anticancer treatment regimen decisions • To evaluate quality of life (QoL) using patient-reported outcomes (PROs), where collected as part of routine clinical practice • To evaluate CNS disease as related to: CNS as the site of first progression, and CNS-only disease progression • To observe patient characteristics, treatment patterns and outcomes in patients with oligometastatic disease
COUNTRY OF STUDY POPULATION:	United Kingdom

MARKETING AUTORISATION HOLDER(S)

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1. SYNOPSIS/ABSTRACT

TITLE

UK– A DISEASE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER

KEYWORDS

HER2, LA/mBC, non-interventional, Progression-free survival

RATIONALE AND BACKGROUND

There are limited published data concerning treatment patterns for patients with human epidermal growth factor receptor 2 (HER2) -positive unresectable locally advanced (LA)/metastatic breast cancer (mBC). However, clinicians and reimbursement agencies may require such information to inform decision-making regarding the best treatment strategies for patients throughout the course of their disease. This study allows descriptive analyses to identify associations between patient characteristics, treatments, and outcomes. Additionally, as new information becomes available on potential risk factors and as new treatments become available, the study provides an opportunity to gain an insight into the evolving treatment landscape.

RESEARCH QUESTION AND OBJECTIVES

This observational disease registry is a prospective, multicentre non-interventional study designed to observe clinical outcomes measured as progression-free survival (PFS), patient-reported outcomes (PROs) and QoL across anti-cancer treatment regimens and sequences during the course of HER2-positive unresectable LA/mBC.

AMENDMENT AND UPDATES TO PROTOCOL

Protocol V. 1.0, 15th September 2014: First internal version

Protocol V. 2.0, 13th November 2014: First official version

Protocol V. 3.0, 29th January 2015

Protocol V. 4.0, 16th May 2016

Protocol V. 4.1, 19th October 2018

Protocol V. 5.0, 3rd March 2022

STUDY DESIGN

This disease registry is a prospective, multicentre non-interventional study designed to observe anti-cancer treatment regimens and clinical outcomes with these regimens in patients with HER2-positive unresectable LA/mBC.

Patients were enrolled in 29 different sites, independently of the anti-cancer treatment regimen. The initial diagnosis of LA/mBC was made no more than 6 months prior to enrolment, without other pre-selection criteria. Enrolment was performed over 3 years with a further 5 years of follow-up after the last patient was enrolled.

Enrolled subjects received treatment and clinical assessments as determined by their treating physician, according to the standard of care and routine clinical practice at each site.

Follow-up visits were determined by the treating physician, but data were collected approximately every 3 months from subject charts, clinical notes, and diagnostic and laboratory test results. All anti-cancer treatment changes, clinical outcomes (including disease progression), adverse events (AEs) and survival status were collected.

Subjects were considered “on study” until death, withdrawal of consent, loss to follow-up, or end of study, whichever came first.

The end of study was defined as the date of the last follow-up visit of the last subject enrolled and occurred 5 years after the last subject was enrolled in the study.

SETTING

All eligible subjects were invited to participate in the study and enrolled sequentially. No other pre-selection criteria were applied.

Subjects met the following inclusion criteria for study entry:

- Males or females
- Initially diagnosed with HER2-positive unresectable LA/mBC no more than 6 months prior to enrolment, although they could have received anti-cancer treatment during that time
- Age ≥18 years
- Able and willing to provide written informed consent and to comply with the study protocol

No exclusion criteria were applied.

SUBJECT AND STUDY SIZE (INCLUDING DROPOUTS)

In total, 311 patients were enrolled in the study. Of these,104 permanently discontinued treatment in first line (9 withdrawals), 72 in second line (4 withdrawals), 25 in third line, 17 in fourth line and 4 in subsequent lines.

VARIABLES AND DATA SOURCES

Demographic and baseline characteristic data were transcribed from the medical records of the participating patients.

Primary Effectiveness Variable

The primary objective for this study was to observe treatment regimens and their sequencing, and to describe treatment outcomes in patients with HER2-positive unresectable LA/mBC in the setting of normal clinical practice.

The numbers and proportions of patients receiving each unique treatment regimen overall and as first line versus subsequent line therapy were summarised. First line treatment regimens were defined as therapies received after initial diagnosis of HER2-positive unresectable LA/mBC and before a patient experienced their first disease progression event.

For patients who received more than one treatment regimen while on study, the proportion of patients receiving each unique treatment regimen sequence was summarised. Temporal changes in treatment patterns were summarised across 6-month intervals.

Secondary Effectiveness Variables

Where available, the following efficacy parameters were documented:

- Patient characteristics associated with receipt of particular anti-cancer treatment regimens
- The sequencing of anti-cancer treatment regimens across the stages of unresectable LA/mBC
- OS for the overall population
- The number of treatment regimens received by patients
- The presence of CNS disease as the site of first progression.

Source data for patient data was taken from the patient's chart and other medical records and reported by means of a web-based electronic data collection system. Where PRO self-completed questionnaires were collected as part of routine clinical practice, these data were entered into the eCRF by site staff and analysed centrally by the Sponsor.

RESULTS

A broad range of treatment regimens are used for HER2-positive LA/mBC in the United Kingdom, with the most used first line treatment regimen being pertuzumab, trastuzumab and chemotherapy (67.8%), while trastuzumab-emtansine containing regimen was most frequently used in the second line (39.9%).

Out of 311 patients who started the first line of therapy for advanced breast cancer, 72 (23.1%) did not reach second line due to a fatal outcome and 59 patients (19%) did not reach third line of treatment, also due to fatal outcome.

The study's results highlight the potential benefits of regimen combination of pertuzumab, trastuzumab and chemotherapy, which exhibited the most promising median PFS in first line of treatment (35.9 months), the longest OS (67.0 months) and the highest objective response rate (33.2%).

Moreover, this regimen showed a favourable safety profile, with low percentages of AEs leading to treatment discontinuation (AEs: 17.1%; SAEs: 5.7%; Specific AEs relevant to HER2-targeted therapies: 2.8%) or dose modification (AEs: 18.5%; SAEs: 7.1%; Specific AEs relevant to HER2-targeted therapies: 0.5%) in first line of treatment.

Trastuzumab-emtansine regimen showed its potential benefit in second line of treatment with a PFS of 13.4 months and 44 patients (83.0%) achieving disease stability. A favourable safety profile was observed with low percentages of AEs leading to treatment discontinuation (AEs: 8.8%; SAEs: 7.0%; Specific AEs relevant to HER2-targeted

therapies: 0%) or dose modification (AEs: 19.3%; SAEs: 3.5%; Specific AEs relevant to HER2-targeted therapies: 0%).

Findings showed that efficacy of the treatments were not influenced by the age of the patients, as similar results between patients below and above 65 years were observed in PFS in first line (27.6 vs 23.3 months).

Also, the safety profile was not influenced by the age, as similar percentages of AEs were observed in patients below and above 65 years (AEs: 81.1% vs 86.4%; Specific AEs relevant to HER2-targeted therapies: 12.9% vs 11.8%; SAEs: 41.3% vs 41.8%).

The study also considered the evolution of CNS disease over time. 25.7% of patients had metastases at the first line treatment, with the majority being individuals experiencing a relapse (20.6%). A higher percentage of metastases were identified during first line (59 patients; 19%) than at baseline (21 patients; 6.8%). 33 patients (23.1%) had CNS metastases when entering second line treatment, 20 patients (35.1%) when entering third line, 9 patients (32.1%) when entering fourth line and 1 (25.0%) when entering subsequent lines.

60% of patients with CNS metastases received pertuzumab, trastuzumab, and chemotherapy regimen in the first line, showing a median OS of 47.4 months. An increasing trend in the number of patients developing CNS metastases over time was also observed, with more than 40% of patients having CNS metastases after approximately 70 months.

Cumulative rate of cardiac events was also analysed, showing an increase over time. The estimated cumulative incidence rate of cardiac events at 72 months was 22.6%. Cardiac AEs that necessitated discontinuation of therapy were observed in 1.9% of patients in first line of treatment, mostly due to a reduction in ejection fraction.

DISCUSSION

The results of this study offer valuable insights into the treatment regimens employed in the United Kingdom for HER2-positive locally advanced/metastatic breast cancer (LA/mBC) patients.

The potential benefits of regimen combination of pertuzumab, trastuzumab and chemotherapy in first line of treatment were observed, with a longer median PFS. In the second line of treatment, potential benefit on PFS was demonstrated by the standard of care (trastuzumab-emtansine regimen).

In the standard of care of both first and second line, few AEs relevant to HER2-targeted therapies were observed and even rarer were these AEs leading to dose modification or discontinuation of the anti-cancer treatment.

This finding is crucial, as it assures healthcare providers that these treatments are effective and safe across a broad age spectrum, which can guide treatment decisions for HER2-positive LA/mBC patients of varying ages.

This study had several limitations derived from its observational design. Moreover, some analyses could not be conducted due to missing data points, specifically in areas like ECOG performance status, quality of life assessments, and breast cancer assessments. Furthermore, the study faced challenges in drawing definitive conclusions due to the limited sample size in certain treatment groups.

CONCLUSION

This study highlights the combined pertuzumab, trastuzumab, and chemotherapy regimen as the standard of care in the first line treatment, with the trastuzumab emtansine regimen being recommended for second line treatment.

In routine clinical practice, as reflected by this registry, at least 40% of patients who initiate first line therapy for advanced breast cancer do not proceed to third line therapy, and brain metastases become increasingly common. These findings have implications for selection of optimal second and third line treatment.

This non-interventional study captured the heterogeneity of the patients enrolled, the treatments chosen by physicians, and the prior treatment history.

Observing patients in a real-world clinical setting allowed for the assessment of treatment effectiveness and tolerability outside the controlled environment of clinical trials. This, in turn, improved the relevance of the study's findings to everyday clinical practice.

ESTHER study fills the gap concerning the limited publication on treatment patterns for patients with HER2-positive unresectable (LA)/mBC, by identifying associations between patient characteristics, treatment and outcomes, and by giving clinicians and reimbursement agencies information for a more conscious decision-making process regarding the best treatment strategies for patients through the course of their disease.

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