14 November 2019
EMA/652550/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kadcyla

International non-proprietary name: trastuzumab emtansine

Procedure No. EMEA/H/C/002389/II/0045

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Background information on the procedure 6
1.1. Type II variation 6
1.2. Steps taken for the assessment of the product 7
2. Scientific discussion 7
2.1. Introduction 7
2.1.1. About the product 10
2.2. Non-clinical aspects 11
2.2.1. Ecotoxicity/environmental risk assessment 11
2.2.2. Discussion on non-clinical aspects 11
2.2.3. Conclusion on the non-clinical aspects 11
2.3. Clinical aspects 11
2.3.1. Introduction 11
2.3.2. Pharmacokinetics 12
2.3.3. Discussion on clinical pharmacology 12
2.3.4. Conclusions on clinical pharmacology 12
2.4. Clinical efficacy 13
2.4.1. Dose response study 13
2.4.2. Main study 13
2.4.3. Discussion on clinical efficacy 57
2.4.4. Conclusions on the clinical efficacy 62
2.5. Clinical safety 62
2.5.1. Discussion on clinical safety 91
2.5.2. Conclusions on clinical safety 94
2.5.3. PSUR cycle 94
2.6. Risk management plan 95
2.7. Update of the Product information 112
2.7.1. User consultation 112
3. Benefit-Risk Balance 113
3.1. Therapeutic Context 113
3.1.1. Disease or condition 113
3.1.2. Available therapies and unmet medical need 113
3.1.3. Main clinical studies 113
3.2. Favourable effects 113
3.3. Uncertainties and limitations about favourable effects 114
3.4. Unfavourable effects 114
3.5. Uncertainties and limitations about unfavourable effects 115
3.6. Effects Table 115
3.7. Benefit-risk assessment and discussion 116
3.7.1. Importance of favourable and unfavourable effects 116
3.7.2. Balance of benefits and risks 116
3.8. Conclusions 116

4. Recommendations..... 117

List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AEGT	adverse event group term
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CCoD	clinical cut-off date
CEC	Clinical Events Committee
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DM1	a derivative of maytansine
DFS	disease-free survival
DRFI	distant recurrence-free interval
E-R	exposure-response
EBC	early breast cancer
eCRF	electronic case report form
EF	ejection fraction
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
E.U.	European Union
FDA	Food and Drug Administration
FEC	5-fluorouracil, epirubicin, and cyclophosphamide
GCP	Good Clinical Practice
GHS	global health status
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
iDCC	independent Data Coordinator Center
IDFS	invasive disease-free survival
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
ISH	in situ hybridization
ITT	intent-to-treat
IV	Intravenous
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-BR23	Quality of Life Questionnaire-Breast Cancer 23
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MAH	Marketing Authorisation Holder
MBC	metastatic breast cancer
NAbs	neutralizing antibodies
NCI	National Cancer Institute
NRH	nodular regenerative hyperplasia
NSABP	National Surgical Adjuvant Breast and Bowel Project
NYHA	New York Heart Association
OS	overall survival
pCR	pathologic complete response
PD	pharmacodynamic
PgR	progesterone receptor
PK	pharmacokinetic
PopPK	population pharmacokinetics
PT	preferred term
PRO	patient-reported outcomes
q3w	every 3 weeks
QLQ	Quality of Life Questionnaire
RT	radiotherapy

SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SPA	special protocol assessment
SPNBC	second primary non-breast cancer
T-DM1	Trastuzumab emtansine, Kadcyla
TNBC	triple-negative breast cancer
TTZ	Trastuzumab
ypTN	Post-neoadjuvant treatment pathological stage of the tumour and lymph nodes

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 4 February 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the adjuvant treatment of adult patients with HER2-positive early breast cancer for Kadcyla; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce editorial changes. An updated RMP version 9.0 has been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 17 November 2011 (EMEA/H/SA/1401/4/2011/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac

Timetable	Actual dates
Submission date	4 February 2019
Start of procedure:	1 March 2019
CHMP Rapporteur Assessment Report	25 April 2019
PRAC Rapporteur Assessment Report	2 May 2019
PRAC members comments	7 May 2019
Updated PRAC Rapporteur Assessment Report	9 May 2019
PRAC Outcome	16 May 2019
CHMP members comments	20 May 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2019
Request for supplementary information (RSI)	29 May 2019
CHMP Rapporteur Assessment Report	20 August 2019
PRAC Rapporteur Assessment Report	23 August 2019
PRAC members comments	28 August 2019
PRAC Outcome	5 September 2019
CHMP members comments	09 September 2019
Updated CHMP Rapporteur Assessment Report	12 September 2019
2nd Request for supplementary information (RSI)	19 September 2019
CHMP Rapporteur Assessment Report	30 October 2019
PRAC Outcome	31 October 2019
CHMP members comments	04 November 2019
Updated CHMP Rapporteur Assessment Report	8 November 2019
Opinion	14 November 2019

2. Scientific discussion

2.1. Introduction

Disease or condition

A new indication is proposed for Kadcyla, as a single agent, for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have invasive residual disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

The amount of residual disease is an important prognosis factor assessed after neoadjuvant systemic treatment. Patients with early breast cancer with residual invasive tumour are patients who had not achieved pathological complete response (pCR) in the breast and/or axillary lymph nodes following

completion of preoperative systemic therapy. Pathologic complete response is defined by the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of the neoadjuvant systemic therapy (ypT0/cis ypN0). According to the ESMO Clinical practice guideline, the Residual Cancer Burden (RCB) is the preferred method for quantifying residual disease in clinical trials although other methods can be used according to regional preference.

Epidemiology and risk factors, screening tools/prevention

Breast cancer was the second most commonly diagnosed cancer in the world and the most commonly diagnosed cancer among women with 2.09 million new cases and approximately 627,000 deaths in 2018 (IARC Breast Cancer 2018). This is a disease affecting 10%–12% of women worldwide (Benson et al. 2009). In 2018, the estimate of breast cancer incidence was 522,513 and the estimate of breast cancer mortality was 137,707 in Europe (GLOBOCAN, Breast cancer 2018).

The main screening tool consists in mammography sometimes combined with magnetic resonance imaging (MRI) (e.g. in women with familial history of breast cancer). Its introduction together with the ageing of the population has made the incidence of breast cancer increase.

Genetic predisposition, exposure to oestrogens, ionising radiation, low parity, high breast density and a history of atypical hyperplasia are important risk factors to develop breast cancer in women. In men, breast cancer is rare (1% of cases) and important risk factors consist in clinical disorders carrying hormonal imbalances (especially gynaecomastia and cirrhosis), radiation exposure, a positive family history and genetic predisposition (ESMO guideline).

Biologic features

Approximately 15%–20% of human breast cancers overexpress the human epidermal growth (HER) factor–2, a transmembrane receptor tyrosine kinase, because of an amplification event in the gene encoding HER2 on chromosome 17. HER2-positive breast cancer is a heterogeneous disease. There is concurrent expression of oestrogen receptor (ER) or progesterone receptor (PgR) in nearly 50% of patients.

The vast majority of breast cancer cases in male patients are ductal invasive carcinomas of the luminal-like type.

Clinical presentation, diagnosis and stage/prognosis

Clinical examination, imaging and pathological assessment are combined for diagnosis. Staging is based on the AJCC TNM staging system. The expression of ER/PgR, HER2 and proliferation markers (e.g. Ki67), the number of involved regional lymph nodes, tumour histology, the size, grade and the presence of peritumoral vascular invasion are important prognosis factors in early breast cancer. The ipsilateral breast recurrence risk is also related to the status of the surgical margins and the presence of ductal carcinoma in situ (DCIS) for patients undergoing breast-conserving therapy (BCT) (ESMO Guideline, 2019).

Without treatment, HER2 overexpression is associated with aggressive tumour growth and poor clinical outcomes (Slamon et al. 1987; Slamon et al 1989; Wolff et al. 2007; Chia et al. 2008; Ross et al. 2009). Ten-year survival of breast cancer exceeds 70% in most European regions (Allemani C et al. 2013). Despite the use of trastuzumab-based therapy in the EBC setting, approximately 15% to 25% of HER2-positive patients will eventually have breast cancer recurrence.

Management

Loco-regional surgery, radiotherapy (RT) and systemic anti-cancer treatment (chemotherapy, endocrine therapy, targeted therapy) combined with supportive measures are part of the treatment algorithm for early breast cancer. Tumour biology, tumour burden, patient characteristics and preferences, and predicted sensitivity to treatment(s) are factors to be considered when deciding on the use of (neo)adjuvant therapies.

Between 60% and 80% of newly diagnosed cancers are amenable to breast conservation (wide local excision and RT) at diagnosis or after primary systemic therapy.

Endocrine therapies are used in all luminal-like cancer. The use of chemotherapy depends on several factors as mentioned above and sensitivity to chemotherapy has been shown to depend on intrinsic phenotype such as HER2-positive (when combined with anti-HER2 therapy) and TNBC.

The use of adjuvant trastuzumab in HER2-positive (HER2+) early-stage breast cancer (EBC) improves patient outcomes as shown in several large, randomized trials. The 3-year disease-free survival (DFS) rate for patients receiving trastuzumab in these studies, all of whom had operable disease, was approximately 85% to 90% (Romond et al. 2005; Piccart-Gebhart 2005; Slamon et al. 2011). The most frequently used regimens contain anthracyclines and/or taxanes, although in selected patients cyclophosphamide/ methotrexate/5-fluorouracil (CMF) may still be used (ESMO Guideline).

A variety of trastuzumab-based chemotherapy regimens are considered effective for the treatment of non-metastatic HER2+ breast cancer. These include doxorubicin and cyclophosphamide followed by a taxane (docetaxel or paclitaxel) plus trastuzumab (AC-TH); docetaxel, carboplatin, and trastuzumab (TCbH); and 5-fluorouracil, epirubicin, and cyclophosphamide in sequence with docetaxel plus trastuzumab (FEC-TH or THFEC). Additionally, pertuzumab, another anti-HER2 monoclonal antibody, has been approved in combination with trastuzumab and chemotherapy for the neoadjuvant (NEOSPHERE and TRYPHAENA trials) and adjuvant (APHINITY trial) of patients with "high-risk" early HER2+ breast cancer (EPAR Perjeta).

For patients with operable EBC, it has been shown in several randomized trials that neoadjuvant treatment results in survival outcomes similar to adjuvant therapy, with the added benefit of improving breast conservation rates. The ESMO guideline recommends a neoadjuvant approach in subtypes highly sensitive to ChT, such as triple-negative and HER2-positive, in tumours >2 cm.

It has also been shown that patients who achieve a pathological complete response (pCR) (defined as no invasive disease both in the breast and axilla), after neoadjuvant treatment have an improved prognosis compared with those who have residual invasive disease present in the surgical specimen (non-pCR) (Rastogi et al. 2008). Although there are only limited data for neoadjuvant therapy conducted exclusively in patients with HER2-positive breast cancer, in general, pCR rates of approximately 40%–60% have been observed, and patients who attain a pCR have a more favourable prognosis than those who have residual invasive disease (Buzdar et al. 2005; Gianni et al. 2010; von Minckwitz et al. 2012; Cortazar et al. 2014).

A meta-analysis of neoadjuvant studies by Loibl et al. evaluated the prognostic value of pCR in 662 HER2-positive patients who had received trastuzumab. With pCR defined as no invasive or non-invasive residual disease in the breast or lymph nodes, there was a significant benefit in OS for attainment of pCR ($p < 0.0001$). Therefore, the absence of pCR after appropriate neoadjuvant therapy allows identification of a patient population at higher risk of disease recurrence. This is a clinical setting where the application of more effective therapies would have a potentially large absolute impact on patient outcomes and can be considered an area of unmet medical need.

It is recognized that HER2-positive patients without pCR after neoadjuvant treatment are at increased risk of recurrence. Until recently these patients were recommended to receive the same adjuvant therapies as would be used for any patient with HER2-positive breast cancer, regardless of surgical findings, that is, to complete 12 months of treatment with trastuzumab (SmPC Herceptin).

Furthermore, neratinib has recently been approved for the treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy and is recommended for use in clinical guideline albeit at the cost of significant toxicity mostly diarrhoea (EPAR Nerlynx).

For male patient, tamoxifen is the standard adjuvant systemic therapy when of luminal-like type while chemotherapy and anti-HER2 therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients (ESMO Guideline).

2.1.1. About the product

Trastuzumab emtansine (also known as ado-trastuzumab emtansine, T-DM1, Kadcyla) is an antibody-drug conjugate (ADC), specifically designed for the treatment of HER2+ breast cancer. It is composed of the following components: trastuzumab, a humanized antibody directed against the extracellular region of HER2; DM1, an anti-microtubule agent derived from maytansine; and a thioether linker molecule used to conjugate DM1 to trastuzumab. Trastuzumab emtansine (from now on Kadcyla) binds to HER2 with an affinity similar to that of unconjugated trastuzumab. It is hypothesized that after binding to HER2, Kadcyla undergoes receptor-mediated internalization, resulting in intracellular release of DM1 and subsequent cell death. DM1 is an inhibitor of tubulin polymerization; it binds to tubulin competitively with vinca alkaloids.

Kadcyla as monotherapy was approved in November 2013 for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who had previously received trastuzumab and a taxane, separately or in combination.

Because Kadcyla has shown activity in patients who have previously progressed after chemotherapy and HER2-directed therapy in the metastatic setting, there was a rationale to explore whether there may be a benefit of administering Kadcyla to patients with HER2-positive EBC who have not had an optimal response to standard neoadjuvant treatment regimens.

The present application is to extend the indication of Kadcyla to the adjuvant treatment of HER2+ early breast cancer patients based on the primary analysis of efficacy and safety data from the pivotal study KATHERINE, a phase III, two-arm, randomised, multicentre, open label trial comparing Kadcyla versus trastuzumab as adjuvant therapy in patients with HER2+ EBC who have received preoperative chemotherapy and HER2-targeted therapy including trastuzumab followed by surgery, with a finding of residual invasive disease in the breast or axillary lymph nodes.

In addition, supportive safety data from the Phase II study TDM4874g/BO22857 (designed primarily to assess safety, with a focus on cardiac events) are provided. Study TDM4874g/BO22857 was a Phase II, multicentre, multinational, single arm, open label trial to assess the clinical safety and feasibility of Kadcyla given sequentially after anthracycline-based chemotherapy, as adjuvant or neoadjuvant therapy for patients with early stage HER2-positive breast cancer.

The claimed indication was as follows: Kadcyla, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual disease, in the breast and/or lymph nodes, after pre-operative systemic treatment that included HER2-targeted therapy.

The recommended indication is as follows: Kadcyla, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy (see SmPC section 4.1).

The recommended dose of trastuzumab emtansine is 3.6 mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle).

Patients should receive treatment for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

Patients treated with trastuzumab emtansine should have HER2 positive tumour status, defined as a score of 3 + by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) assessed by a CE-marked In Vitro Diagnostic (IVD) medical device. If a CE-marked

IVD is not available, the HER2-status should be assessed by an alternate validated test (see SmPC section 4.2).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP (see discussion on non-clinical aspects).

2.2.1. Ecotoxicity/environmental risk assessment

The predicted use of trastuzumab emtansine is not expected to increase due to the present type II variation, as this particular patient group is already included in the original refined Fpen, and will lead to worst-case PECs in surface waters and sewage treatment that are far below regulatory thresholds and levels of potential risk. As the PECsurfacewater for both T-DM1 and MCC-DM1 have been determined to be smaller than the 0.01 µg/L threshold as well as the logKow for MCC-DM1 was smaller than the 4.5 limit, there is no need for any further studies on environmental safety.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application.

This new indication does not lead to a significant increase in environmental exposure further to the use of trastuzumab emtansine.

2.2.3. Conclusion on the non-clinical aspects

Considering the above data, trastuzumab emtansine is not expected to pose a risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see SmPC section 6.6).

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Protocol Location	Study Design	Diagnosis, Inclusion Criteria	No. of Pts*	Criteria for Evaluation	Dose, Duration	Study Status
Pivotal study						
BO27938 KATHERINE Global	Two-arm, Phase III, randomized, multicenter, multinational, open-label study of trastuzumab emtansine versus trastuzumab as adjuvant therapy	HER2-positive primary breast cancer: patients who received neoadjuvant chemotherapy and HER2-directed therapy including trastuzumab followed by surgery, with a finding of residual invasive disease in the breast or axillary lymph nodes	1486	Efficacy (IDFS, DFS, OS, and DRFI) PRO Safety, incl. cardiac safety	T-DM1: 3.6 mg/kg IV q3w Trastuzumab: Loading dose of 8 mg/kg, then 6 mg/kg IV q3w. for 14 cycles	Ongoing: Primary CSR planned for inclusion in submission Q1 2019
Supportive safety study						
TDM4874g/ BO22857 Global	Open-label, single-arm, Phase II study of T-DM1 administered sequentially with anthracycline-based chemotherapy, as adjuvant or neoadjuvant therapy	Early stage HER2-positive breast cancer	153	Safety, incl. cardiac safety	T-DM1: 3.6 mg/kg IV q3w, for 17 cycles	Study Completed Final CSR January 2014

2.3.2. Pharmacokinetics

During the course of Study BO29738, one or more PK samples were collected from 428 patients in the trastuzumab emtansine arm and 405 patients in the trastuzumab arm. Patients who received 3.6 mg/kg of trastuzumab emtansine intravenously every 3 weeks had a mean Cycle 1 maximum serum concentration (Cmax) of trastuzumab emtansine of 72.6 (± 24.3) µg/mL, respectively.

2.3.3. Discussion on clinical pharmacology

Following trastuzumab emtansine administration, Cmax and Cmin of trastuzumab emtansine conjugate in Study BO27938 were comparable to PK data from Study TDM4370g/BO21977 (EMILIA) at Cycle 1 and at steady state. Consistent with PK data from Study TDM4370g/BO21977, repeated dosing of trastuzumab emtansine on a q3w regimen did not result in any noticeable accumulation of trastuzumab emtansine conjugate. Similarly, no difference in serum total trastuzumab and plasma DM1 Cmax or Cmin was observed between Study BO27938 and Study TDM4370g/BO21977. There is no evidence of plasma DM1 accumulation following repeat dosing of trastuzumab emtansine.

2.3.4. Conclusions on clinical pharmacology

The population pharmacokinetic analysis suggested no difference in trastuzumab emtansine exposure based on disease status (adjuvant vs. metastatic setting).

2.4. Clinical efficacy

2.4.1. Dose response study

No new dose-response study was submitted (see discussion on clinical aspects).

2.4.2. Main study

Study KATHERINE (Study BO27938)

KATHERINE (Study BO27938) is a Phase III, two-arm, randomised, multicentre, multinational, open label study in patients with HER2-positive primary breast cancer who have received neoadjuvant chemotherapy and HER2-targeted therapy, including trastuzumab, followed by surgery, with a finding of pathologically documented residual invasive disease in the breast or axillary lymph nodes.

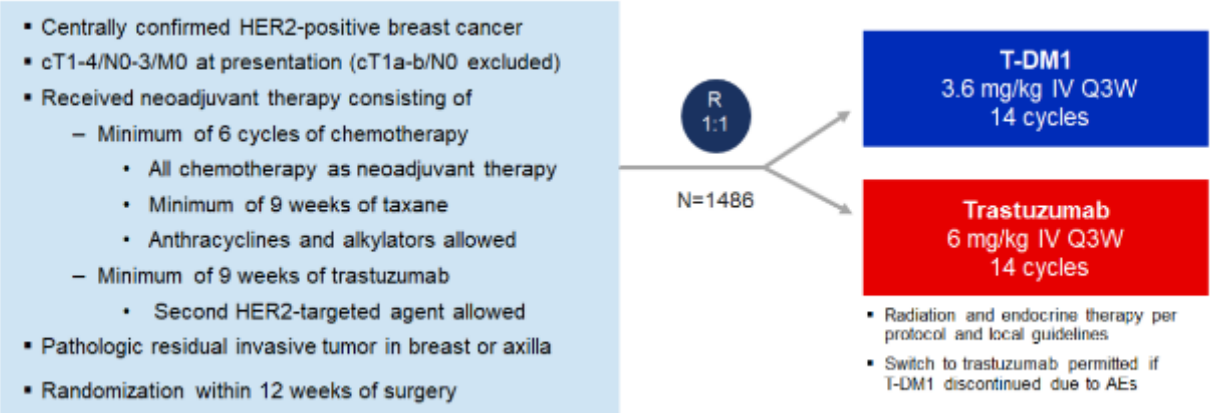


Figure 1: Overview of Study Design for Study KATHERINE

Methods

Study participants

Inclusion criteria:

- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Life expectancy ≥ 6 months
- Adequate hematologic , renal and liver function
- For women who were not postmenopausal (≥12 months of non-therapy induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of study
- Negative serum pregnancy test for premenopausal women including women who have had a tubal ligation and for women less than 12 months after the onset of menopause. For women who were not postmenopausal (≥ 12 months of non-therapy induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods. Male patients whose partners were pregnant must have used condoms or truly refrain from sexual activity for the duration of the pregnancy.

- Documentation of hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies.
- HER2+ breast cancer:
    - HER2-positive status was defined as an immunohistochemistry (IHC) score of 3+ and/or positive by in situ hybridization (ISH) prospectively and centrally confirmed on pretreatment biopsy material. ISH positivity was defined as a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of signals for chromosome 17 copies. A central laboratory performed both IHC and ISH assays; however, only one positive result was required for eligibility into the study. In the event that sufficient material from the pretreatment biopsy was not available, central HER2 determination for eligibility on residual tumor tissue from the time of definitive surgery was allowed. Patients with synchronous bilateral invasive disease were eligible provided both lesions were HER2-positive.
    - The tumor had to be histologically confirmed invasive breast carcinoma
    - Clinical stage at presentation of T1–4, N0–3, M0 (Note: Patients with T1a/bN0 tumors were not eligible).
    - Prior to enrollment, patients had to have completed preoperative systemic chemotherapy and HER2-directed treatment (patients may have received more than one HER2-directed therapy). Systemic therapy must have been completed preoperatively and consist of at least 6 cycles of chemotherapy, with a total duration at least 16 weeks, including at least 9 weeks of trastuzumab and at least 9 weeks of taxane based chemotherapy. Within these criteria:
        - Patients may have received an anthracycline as part of preoperative therapy in addition to taxane chemotherapy. Patients with cumulative doses of anthracyclines exceeding pre-specified levels were not eligible: Doxorubicin > 240 mg/m^2; Epirubicin or Liposomal Doxorubicin-Hydrochloride (Myocet) > 480 mg/m^2; For other anthracyclines, exposure equivalent to doxorubicin > 240 mg/m^2.
        - Patients receiving dose-dense chemotherapy regimens were eligible, provided at least 8 weeks of taxane-based therapy and at least 8 weeks of trastuzumab were given. A dose-escalated (225 mg/m^2 once every 2 weeks [q2w]) dose-dense regimen of paclitaxel over 6 weeks is allowed.
    - Patients had to have undergone surgery resulting in removal of all clinically evident disease in the breast and lymph nodes. This entailed either a total mastectomy with no gross residual disease at the margin of resection, or breast-conserving surgery with margins of excision being histologically free of invasive tumor and ductal carcinoma in situ (DCIS). If pathologic examination demonstrated tumor at the line of resection, additional operative procedures could be performed to obtain clear margins. If this did not result in complete removal, the patient must undergo total mastectomy to be eligible. Patients with margins positive for LCIS were eligible without additional resection.
    - In case of positive results from biopsies of axillary lymph node(s) performed prior to preoperative therapy, additional surgical evaluation of the axilla following preoperative therapy was required, unless only micrometastases were present in sentinel nodes preoperatively (i.e., if the greatest diameter of the nodal metastasis in a sentinel node is 0.2 mm or less), then no additional surgical evaluation of the axilla is required.
    - If sentinel node biopsy performed either before or after preoperative therapy was negative, no additional surgery evaluation of the axilla was required. If the only sentinel node identified by isotope scan was in the internal mammary chain, surgical evaluation of the axilla was recommended. If sentinel node biopsy performed after preoperative therapy was positive, additional surgical evaluation of the axilla was also recommended. Lastly, axillary dissection in the absence of sentinel node evaluation was permitted after preoperative therapy.

- The patient had to have pathologic evidence of residual invasive carcinoma in the breast or axillary lymph nodes following completion of preoperative therapy. If invasive disease was present in both breasts, residual invasive carcinoma had to be present in at least 1 breast or axillary lymph node postoperatively.
- The patient's hormone receptor positivity status must have been determined, by either known positive ER or known positive PgR status; hormone receptor-negative status must be determined by both known negative ER and known negative PgR.
- Eligible patients had to be enrolled with no more than 12 weeks between the date of primary surgery and the date of randomization.

Exclusion criteria:

- Stage IV (metastatic) breast cancer.
- History of any prior (ipsi- or contralateral) breast cancer except lobular CIS.
- Evidence of clinically evident gross residual or recurrent disease following preoperative therapy and surgery.
- An overall response of PD according to the investigator at the conclusion of preoperative systemic therapy.
- Treatment with any anti-cancer investigational drug within 28 days prior to commencing study treatment.
- History of other malignancy within the last 5 years except for appropriately treated CIS of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other non-breast malignancies with an outcome similar to those mentioned above.
- Patients for whom radiotherapy would be recommended for breast cancer treatment but for whom it was contraindicated because of medical reasons (e.g., connective tissue disorder or prior ipsilateral breast radiation).
- Current NCI CTCAE (Version 4.0) Grade ≥ 2 peripheral neuropathy.
- Cardiopulmonary dysfunction as defined by any of the following:
    - History of NCI CTCAE (Version 4.0) Grade ≥ 3 symptomatic CHF or NYHA criteria Class ≥ II
    - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
    - High-risk uncontrolled arrhythmias.
    - Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia while or since receiving preoperative therapy.
    - History of a decrease in LVEF to < 40% with prior trastuzumab treatment (e.g., during preoperative therapy)
    - Uncontrolled hypertension.
    - Evidence of transmural infarction on ECG.
    - Requirement for continuous oxygen therapy.
- Prior treatment with Kadcyla.

- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders; ulcers).
- For female patients, current pregnancy and/or lactation.
- Major surgical procedure unrelated to breast cancer or significant traumatic injury within approximately 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment.
- Any known active liver disease, for example, disease due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis.
- Concurrent, serious, uncontrolled infections or known infection with HIV.
- History of intolerance, including Grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins or any components of the product.
- Active, unresolved infections at screening requiring treatment.
- Assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol.

Treatments

Patients should have received their first dose of study treatment the day of randomization if possible, but no later than five business days after randomization.

Kadcyla arm: Kadcyla was administered on Day 1 of a 3-week cycle at the approved dose of 3.6 mg/kg IV. The total dose was calculated based on the patient's weight on Day 1 of (or up to 3 days before) each cycle with no upper limit. Changes in weight of <10% from baseline did not require dose recalculation.

Trastuzumab arm: Trastuzumab was administered on Day 1 of a 3-week cycle at a maintenance dose of 6 mg/kg IV. A loading dose of 8 mg/kg was required if > 6 weeks had elapsed since the prior dose of trastuzumab.

Patients received study treatment for a total of 14 cycles; treatment was discontinued prior to 14 cycles in the event of disease recurrence, unacceptable toxicity, or study termination by the Sponsor. Patients who discontinued Kadcyla could have completed the duration of their study therapy with trastuzumab if appropriate based on toxicity considerations.

Concomitant therapy

Although one inclusion criterion stated the requirement of an International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN, patients under anticoagulant or antiplatelet therapy were allowed to participate. Patients on anti-coagulant treatment should have had their platelet count monitored closely during treatment with trastuzumab emtansine.

Radiotherapy and/or hormonal therapy (for patients with hormone receptor-positive tumours) concurrent with study treatment was administered if indicated.

Criteria for dose modification or withdrawal from treatment:

Kadcyla could be reduced by a maximum of 2 dose levels, to 2.4 mg/kg, according to the dose-modification guidelines.

Table 2: Dose reduction for trastuzumab emtansine - Study KATHERINE

Dose Level	Dose
0	3.6 mg/kg
-1	3.0 mg/kg
-2	2.4 mg/kg
Indication for further dose reduction	Off study treatment

Dose delays of up to 42 days from the last administered dose were permitted. After appropriate recovery from an adverse event, Kadcyla could have been resumed with one dose level reduction (e.g., Kadcyla reduced from 3.6 mg/kg to 3 mg/kg or from 3 mg/kg to 2.4 mg/kg). For patients who had an event while being treated with Kadcyla 2.4 mg/kg, study treatment was discontinued. The dose of Kadcyla, once reduced, could not be re-escalated.

There were no dose reductions permitted for trastuzumab.

Prior treatment:

Patients must have completed neoadjuvant systemic treatment consisting of at least 6 cycles with a total duration of at least 16 weeks, including at least 9 weeks of trastuzumab and at least 9 weeks of taxane-based chemotherapy (or, if receiving dose-dense chemotherapy regimens, at least 6-8 weeks of taxane-based therapy and at least 8 weeks of trastuzumab). HER2-directed therapy and chemotherapy could be given concurrently. Patients could have received more than one HER2-directed therapy. Patients could have received an anthracycline as part of neoadjuvant therapy (see also inclusion criteria).

Objectives

Primary efficacy objective: To compare invasive disease-free survival (IDFS) in patients with residual invasive breast cancer after treatment with preoperative chemotherapy and HER2-directed therapy including trastuzumab followed by surgery between the two treatment arms.

Secondary efficacy objectives: To compare IDFS including second non-breast cancers, DFS, OS, and distant recurrence-free interval (DRFI) between the two treatment arms.

Safety objectives: To compare cardiac safety and overall safety between the two treatment arms according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

PRO objectives: To compare Patient Reported Outcomes (PROs) between the two treatment arms using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) questionnaire and Quality of Life Questionnaire – Breast Cancer (QLQ-BR23) module.

PK objectives: To characterize the PK of Kadcyla (including total trastuzumab and DM1) in Kadcyla treated patients; To characterize the PK of trastuzumab in trastuzumab-treated patients and permit an intra-study comparison of trastuzumab exposure in the two treatment arms; To investigate exposure–effect (efficacy and safety) relationships in this patient population.

Exploratory objectives: To assess correlations between biomarker status and efficacy and/or safety; To assess the incidence of anti-therapeutic antibodies (ATAs) and the effect of ATAs on PK, safety, and efficacy.

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint of the study was invasive disease free survival (IDFS) defined as the time between randomization and date of first occurrence of any one of the following IDFS event:

- Ipsilateral invasive breast tumour recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)

- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast)

- Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)

- Contralateral invasive breast cancer

- Death attributable to any cause including breast cancer, non-breast cancer or unknown cause (but cause of death should be specified if at all possible).

Key secondary endpoints:

- IDFS including second primary non-breast cancer (IDFS-SPNBC): defined the same way as IDFS for the primary endpoint but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and carcinoma in situ [CIS] of any site)
- Disease-free survival: defined as the time between randomization and the date of the first occurrence of an invasive disease-free survival event including second primary non-breast cancer event or contralateral or ipsilateral DCIS
- Overall survival (OS): defined as the time from randomization to death due to any cause
- Distant recurrence-free interval (DRFI): defined as the time between randomization and the date of distant breast cancer recurrence

Patient-Reported Outcome analyses:

HRQOL data were captured using the following questionnaires: the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), Quality of Life Questionnaire-Breast Cancer 23 (QLQ-BR23), and the EuroQoL EQ-5D-3L.

Safety reporting and analysis:

Safety analyses were performed on the safety-evaluable population. The safety of trastuzumab emtansine was assessed through treatment exposure, summaries of AEs, SAEs, cardiac-specific AEs, LVEF measurements, and laboratory test results (including thrombocytopenia and transaminases). The specific safety outcome measures assessed, as specified in the protocol, included:

- Incidence, type and severity of all AEs based on NCI CTCAE Version 4.0 (including incidence and type of Grade≥3 AEs)
- Incidence, type, and severity of SAEs
- Incidence and type of AEs leading to dose discontinuation, modification, or delay
- Cause of death on study
- Abnormal laboratory values
- LVEF decreases
- Cardiac events, defined as death from cardiac cause or severe CHF (NYHA Class III or IV) with a decrease in LVEF of ≥10 percentage points from baseline to an LVEF of <50%.

For classification purposes, lower level terms were assigned by the Sponsor to the original terms entered on the CRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA 21.0) terminology for adverse events and diseases and the [Roche INN (International Non-proprietary Name) Drug Terms and Procedures Dictionary for medications and treatments.

Biomarkers assessment:

Mandatory tumor tissue samples were collected for biomarker analysis after central HER2 testing for eligibility. HER2-positive BC was defined in the study by an IHC score of 3 + or gene amplified by ISH as defined by a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of chromosome 17 copies. In addition, tumor tissue samples were used in the analysis of phosphatidylinositol-3-kinase catalytic subunit alpha isoform (PIK3CA) mutation status.

The analysis methods for these biomarkers were performed according to manufacturer's instructions as follows:

- HER2 IHC was measured using Pathway HER2 (4B5) IHC assay (Ventana).
- HER2 ISH was measured using INFORM Dual ISH DNA Probe Cocktail (Ventana).
- PIK3CA mutations in exons 1, 4, 7, 9 and 20 in DNA were analyzed using the commercially available cobas PIK3CA Mutation Test (Roche Molecular Diagnostics) and the cobas z 480 analyzer (Roche Molecular Systems Inc.).

Sample size

The sample size of the study was primarily driven by the analysis of IDFS. To detect a hazard ratio (HR) of 0.75 in IDFS (a 6.5% improvement in 3-year IDFS from 70% in the control arm to 76.5% in the Kadcyla arm), approximately 384 IDFS events were required to achieve 80% power at a 2-sided significance level of 5%. Approximately 1484 patients were planned to be enrolled in the study.

The study was expected to be fully enrolled around 35 months after the first patient enrolled in the study (FPI). The final IDFS analysis will be performed after approximately 384 events have occurred, which is projected to be approximately 64 months from FPI.

With the study sample size of 1484 patients and approximately 10 years of follow up from the date of randomization of the first patient, this study had approximately 56% power to detect a HR of 0.8 in OS (a 2.8% improvement in 3-year OS from 85% in the control arm to 87.8% in the Kadcyla arm) at a two sided significance level of 5%.

Randomisation

Patients were randomized in a 1:1 ratio by a permuted block randomization scheme to one of the two treatment arms (trastuzumab or Kadcyla) through use of the IVRS/IWRS. Randomization was stratified by the following stratification factors:

- Clinical stage at presentation: inoperable (Stage T4NxM0 or TxN2–3M0) versus operable (Stages T1-3 N0 to 1 M0)
- Hormone receptor status: ER or PgR positive versus ER and PgR negative/unknown
- Preoperative HER2-directed therapy: trastuzumab versus trastuzumab plus additional HER2-directed agent(s)
- Pathologic nodal status evaluated after preoperative therapy: node positive versus node negative/not done.

Blinding (masking)

This was an open-label study.

Statistical methods

Analysis populations:

Two analysis populations were used for the analysis of data from this study:

- The randomized patient population included all patients who were randomized to the study, regardless of whether they received any study treatment.
- The safety-evaluable population included all randomized patients who received any amount of study treatment.

Analyses of demographics and other baseline information were based on the randomized patient population, and per treatment assigned by the IVRS/IWRS.

The randomized patient population was to form the basis for all efficacy analyses. In all efficacy analyses, following the intent-to-treat principle, patients were to be included in the treatment group to which they were randomized by the IVRS/IWRS.

All safety analyses were performed on the safety-evaluable population and were based on actual treatment received. Specifically, a patient was included in the Kadcyla arm in safety analyses if the patient received any treatment with Kadcyla, regardless of the initial treatment assignment by IVRS/IWRS.

Efficacy analyses/endpoints:

Primary endpoint, IDFS:

The log-rank test, stratified by the protocol-defined stratification factors, was planned to compare IDFS between the two treatment arms. The unstratified log-rank test results were also planned as a sensitivity analysis. If, at the time of analysis, the smallest stratum was < 5 patients in either arm and it was considered that robust stratified analyses cannot be conducted, the unstratified analysis was to be used as the primary analysis. The Cox proportional hazards model was used to estimate the HR between the 2 treatment arms and its 95% CI, and the unstratified analysis was considered the primary result. The Kaplan-Meier approach was used to estimate 3-year IDFS rates and corresponding 95% CIs for each treatment arm.

IDFS-SPNBC and DFS were secondary endpoints and served as the sensitivity analyses for the primary analysis of IDFS. Additional sensitivity analyses to assess the robustness of the primary endpoint IDFS included the following:

- Censoring patients at the time they started a new anti-cancer therapy before experiencing an IDFS event. This included patients who continued on trastuzumab after discontinuation of Kadcyla before 14 cycles without experiencing an IDFS event. For these patients, data were censored at the time of initiation of trastuzumab treatment.
- Censoring patients at the time they discontinued study treatment due to any reason before experiencing an IDFS event. This included patients who continued on trastuzumab after discontinuation of Kadcyla before 14 cycles without experiencing an IDFS event. For these patients, data were censored at the time of last Kadcyla treatment.

Secondary endpoints:

Secondary endpoints were analyzed in a similar manner as the primary endpoint to estimate 3-year event rates (and 5-year survival rate for OS) for each treatment arm and the HR between the two treatment arms

with 95% CI. A testing hierarchy was used to control the overall type I error rate at 5%. The formal hypothesis testing of OS was planned to be performed when the primary endpoint IDFS reached statistical significance.

Censoring:

For the analyses of IDFS, IDFS including second primary non-breast cancer, DFS and DRFI, data for patients who do not experience an event will be censored at the date they are last known to be alive and event free. Data for patients who are randomized without any post-baseline assessments will be censored at the date of randomization plus 1 day.

For the analysis of OS, data for patients who are alive at the time of the data cutoff will be censored at the last date they were known to be alive. Data for patients who are randomized without any post-baseline information will be censored at the date of randomization plus 1 day.

Efficacy analyses timings:

One interim analysis and one final analysis of IDFS were planned. The interim efficacy analysis of IDFS was planned after 257 (67%) of the targeted 384 IDFS events had occurred. At this interim analysis, IDFS was tested at the significance level determined using the Lan-DeMets alpha spending function with an O'Brien-Fleming stopping boundary ($p < 0.0124$ or observed $HR < 0.732$) so that the overall 2-sided type I error rate would be maintained at the 5% level for the IDFS primary endpoint if needed.

Table 3: Summary of planned analyses of invasive disease-free survival - Study KATHERINE

Analysis of IDFS	No. of events	Efficacy Stopping Boundary [a]	Estimated Timing [b]
Interim	257	$p < 0.0124$ or observed $HR < 0.732$	48 months
Final	384	$p < 0.0462$ or observed $HR < 0.816$	64 months

HR = hazard ratio; IDFS = invasive disease-free survival.

[a] p-value will be based on 2-sided stratified log-rank test.

[b] Time from the enrollment of first patient to data cutoff.

The interim analysis was to be performed by the iDCC statistician and the results were to be presented to the iDMC by the iDCC statistician. The purpose of the interim analysis was to evaluate whether there was an overwhelming difference in the efficacy observed in the Kadcyla arm compared with the trastuzumab arm in terms of IDFS. The study was to continue until 10 years of follow-up and IDFS analysis to be updated when 384 IDFS events have occurred.

Three formal interim OS analyses and one final OS analysis were planned as shown in the table below. The first OS interim analysis was to be performed at the time of the interim IDFS analysis. The second interim OS analysis was to be performed at the time of the final IDFS analysis (when 384 IDFS events have occurred), followed by the third OS interim analysis at approximately 2 years (88 months from FPI) after the second OS interim analysis. The final OS analysis was to be performed at the end of 10 years of follow-up.

Table 4: Summary of planned analyses of overall survival - Study KATHERINE

Analysis Of OS	No. of Events	Efficacy Stopping Boundary [a]	Estimated Timing [b]
Interim 1 (at interim IDFS)	150	p < 0.0009 or observed HR < 0.5826	48 months
Interim 2 (at final IDFS)	206	p < 0.0053 or observed HR < 0.6785	64 months
Interim 3	279	p < 0.0184 or observed HR < 0.754	88 months
Final	367	p < 0.0435 or observed HR < 0.8099	119 months

HR = hazard ratio; IDFS = invasive disease-free survival; OS = overall survival.

[a] p-value will be based on 2-sided stratified log-rank test.

[b] Time from the enrollment of first patient to data cutoff.

The overall type I error was controlled at 0.05 for the formal OS interim analyses and final OS analysis using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary. The boundaries used at each interim and final OS analysis depend on the timing of the analyses and the number of death events actually included in the analyses.

Subgroup analyses:

Subgroup analyses of IDFS and OS were to be performed based on age, race, stratification factors, and other potential baseline prognostic factors as appropriate.

PRO:

Summaries of the compliance rates by treatment arm were provided at each assessment time point as specified in the protocol. Compliance rate was defined as the number of patients who completed each assessment (i.e., at least 1 item has been answered on the EORTC QLQ-C30 and BR23) divided by the total number of eligible patients at that time point according to protocol specified assessment schedule.

For scoring of the QLQ-C30 and QLQ-BR23 questionnaires, if more than 50% of the constituent items were completed, a pro-rated score was computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale was considered to be missing. Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of absolute scores and change from baseline scores of the QLQ-C30 and QLQ-BR23 subscales were summarized at each assessment time point for the two treatment arms. Only patients with a baseline assessment and at least one post-baseline assessment were included in this analysis.

The proportion of patients that experienced a clinically meaningful deterioration (or worsening) in symptoms, in their function, or in GHS/HRQoL were summarized, and the difference in proportions between treatment arms was evaluated with chi-squared statistical analysis.

Assessment of clinically meaningful deterioration in symptoms (score decrease) and functions (score increase) was based on the published thresholds reported by Cocks et al. 2012 for each applicable subscale. Specifically, the score increase for each symptom scale reported and used was ≥15 points in constipation or diarrhea, ≥14 points in appetite loss, ≥11 points in dyspnea, nausea/vomiting, or pain, ≥10 points in fatigue, any hair loss, or systemic therapy side effects, ≥9 points increase in insomnia. The score decrease for each function scale reported and used was ≥10 points in physical functioning, ≥7 points in cognitive functioning, and ≥14 points in role functioning. For the rest of the function and symptom scales, a ≥10 points change was considered clinically meaningful.

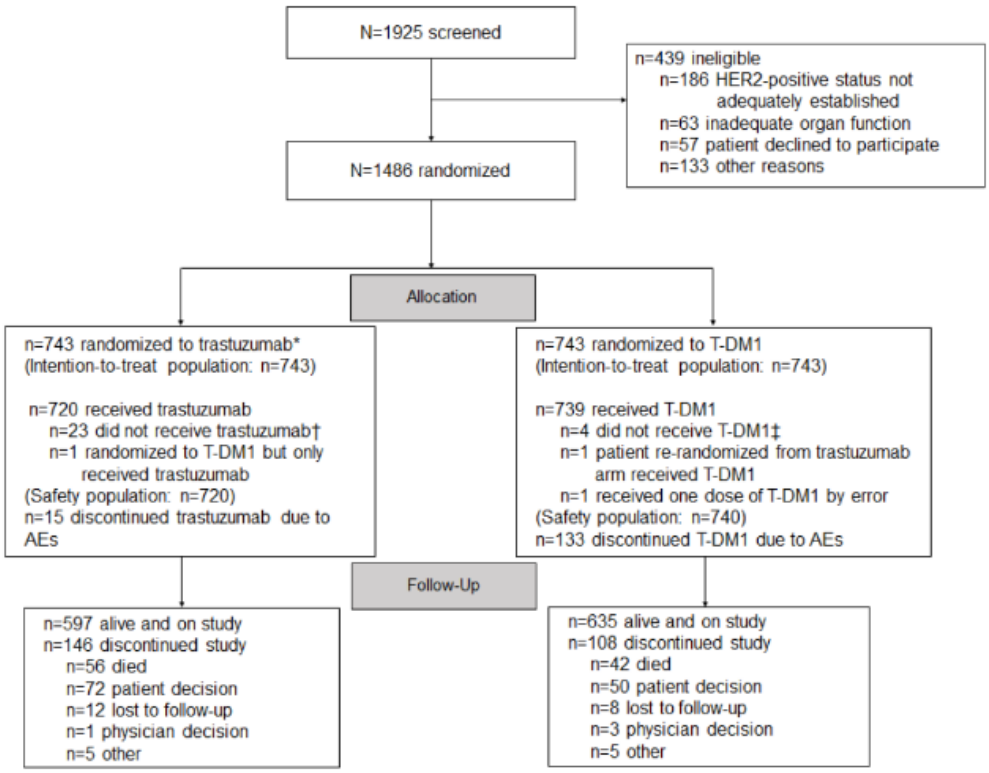
A clinically meaningful deterioration in GHS/HRQoL was defined as a score decrease of ≥10 points, based on the thresholds reported by both Cocks et al. 2012 and Osoba et al, 1998.

Repeated measures mixed-effects models were performed on the function scales and the GHS/HRQoL scale of the EORTC QLQ-C30 and QLQ-BR23. Each model had a variable for time, a variable for treatment group, and a variable for treatment-by-time interaction. Covariates were added as appropriate.

Results

Since the pre-specified efficacy boundaries were crossed, the Independent Data Monitoring Committee (iDMC) recommended an early release of study data the results from the interim analysis are now designated as the primary analysis of IDFS and presented below.

Participant flow



*One patient was randomized twice in error. The patient was first randomized to the trastuzumab arm but did not receive treatment. The patient was included in the trastuzumab intention-to-treat population. The patient was then randomized to the Kadcyla arm and treated with Kadcyla. The patient was thus included in the Kadcyla safety population (n=740) based on treatment actually received. This patient's data has been analysed as follows, to ensure adherence to the principles of analysis populations and non-duplication of data: Data for the first assigned randomized treatment to trastuzumab is included in any randomized population numbers and ITT efficacy analyses, but does not contribute to any safety analyses; data from the same patient under their second randomization ID does not contribute to any randomized population numbers or ITT efficacy analyses, but are included in all safety analyses, under the Kadcyla arm.
One patient was randomized to trastuzumab but was administered 13 cycles of trastuzumab and one cycle of Kadcyla in error so was included in the Kadcyla safety population.
One patient was randomized to Kadcyla but was administered 9 cycles of trastuzumab in error and was thus included in the trastuzumab safety population.
†Three of these patients are being followed for disease recurrence and survival.
‡Two of these patients are being followed for disease recurrence and survival.

Figure 2: Participant flow (clinical cut-off date: 25 July 2018) - Study KATHERINE

At the CCOD of 25 July 2018, all patients had completed treatment and the majority of patients were alive and ongoing in the study (80.3% in the trastuzumab arm, 85.5% in the Kadcyla arm). Of those patients in follow-up, most patients had not yet had an IDFS reported. A total of 98 patients had died (56 [7.5%] in the trastuzumab arm and 42 [5.7%] in the Kadcyla arm).

Table 5: Patient disposition during study - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Alive and ongoing in study	597 (80.3%)	635 (85.5%)
Completed Study	0	0
Discontinued from study without further follow-up	146 (19.7%)	108 (14.5%)
Discontinued with IDFS event reported		
DEATH due to		
Adverse event	1 (0.1%)	1 (0.1%)
Breast cancer	52 (7.0%)	39 (5.2%)
Other	3 (0.4%)	2 (0.3%)
Underlying Cancer a Contributing Factor in Death	3 (0.4%)	2 (0.3%)
Yes	1 (0.1%)	0
No	0	0
Unknown	2 (0.3%)	2 (0.3%)
ENTIRE WITHDRAWAL BY SUBJECT	12 (1.6%)	4 (0.5%)
LOST TO FOLLOW-UP	2 (0.3%)	0
OTHER	1 (0.1%)	1 (0.1%)
PHYSICIAN DECISION	1 (0.1%)	1 (0.1%)
Discontinued without prior IDFS event reported		
ENTIRE WITHDRAWAL BY SUBJECT	60 (8.1%)	46 (6.2%)
LOST TO FOLLOW-UP	10 (1.3%)	8 (1.1%)
OTHER	4 (0.5%)	4 (0.5%)
PHYSICIAN DECISION	0	2 (0.3%)

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ds_stud.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ds_stud_IT.out
08NOV2018 12:53 Page 1 of 1

Table 6: Duration of follow-up - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Duration of Follow-up (months)		
Median	40.94	41.43
95% CI for Median	(39.98, 41.69)	(40.84, 42.84)
25% and 75%-ile	33.91, 48.39	34.99, 49.18
Min to Max	0.1 to 62.6	0.1 to 62.7

Duration of Follow-up is calculated as time from randomization to clinical cut-off date or the last date the patient was known to be alive. Median duration of Follow-up estimated with Kaplan-Meier method. The confidence interval (CI) for the median was computed using the method of Brookmeyer and Crowley.

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ef_fu.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ef_fu_IT.out
23NOV2018 17:12 Page 1 of 1

Table 7: Patient disposition during treatment period - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Status	Trastuzumab * (N=743)	Trastuzumab Emtansine ** (N=743)
Patients who received no study treatment	23 (3.1%)	4 (0.5%)
Completed planned study treatment (total 14 cycles)	585 (78.7%)	527 (70.9%)
Discontinued planned study treatment due to	135 (18.2%)	212 (28.5%)
Recurrence Of Disease	39 (5.2%)	16 (2.2%)
Adverse Event	15 (2.0%)	133 (17.9%)
Other	2 (0.3%)	1 (0.1%)
Withdrawal By Subject	57 (7.7%)	49 (6.6%)
Physician Decision	15 (2.0%)	11 (1.5%)
Lost To Follow-Up	3 (0.4%)	0
Pregnancy	1 (0.1%)	0
Protocol Violation	0	2 (0.3%)
Non-Compliance	3 (0.4%)	0

*Reasons for "other" discontinuation from trastuzumab: did not complete 14 total cycles by misunderstanding
**Reasons for "other" discontinuation from T-DM1: delay in treatment >42 days due to scheduling difficulties

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ds_trt.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ds_trt_IT.out
16NOV2018 11:24 Page 1 of 1

Table 8: Patient disposition during treatment period: patients who received trastuzumab as study treatment after discontinuing trastuzumab emtansine - Study KATHERINE

Patient Disposition during Treatment Period : Patients who received trastuzumab as study treatment after discontinuing
trastuzumab emtansine, Switch Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Status	Trastuzumab (N=71)
Completed 14 cycles (trastuzumab emtansine + trastuzumab)	63 (88.7%)
After switch, discontinued trastuzumab treatment due to	8 (11.3%)
Adverse Event	2 (2.8%)
Physician Decision	2 (2.8%)
Withdrawal By Subject	4 (5.6%)

"Completed trastuzumab treatment" marked as "completed" on trastuzumab treatment discontinuation form. Patient was
randomised to trastuzumab emtanise and switched to trastuzumab.

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ds_trt.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ds_trt_CR.out
08NOV2018 12:53 Page 1 of 1

Recruitment

A total of 1925 patients with HER2-positive EBC were screened, of whom 1486 patients were randomized from 268 centres across 28 countries: Argentina (3 centres), Austria (4), Belgium (4), Brazil (10), Canada (12), China (7), Columbia (3), Czech Republic (3), France (16), Germany (47), Greece (2), Guatemala (1), Hong Kong (3), Ireland (6), Israel (6), Italy (19), Mexico (5), Panama (2), Peru (5), Serbia (2), South Africa (6), Spain (13), Sweden (3), Switzerland (2), Taiwan (5), Turkey (5), UK (14), US (60).

First patient was randomised on 03 April 2013; last patient was randomised on 31 December-2015. Clinical data cut-off was on 25 July 2018.

Conduct of the study

Protocol amendments:

The first version of the protocol was issued on 19 October 2012. Five amendments to the protocol have been made. The key changes are summarized below.

Version 2 of the protocol (dated April 2013) made the following changes:

- Clarification and details of IHC and ISH assays used for determining HER2 status.
- Inclusion of patients who had received dose-dense chemotherapy regimens, provided at least 8 weeks of taxane-based therapy and at least 8 weeks of trastuzumab had been given.
- Revision of language to differentiate radiotherapy for T3 disease with and without lymph node involvement.
- Recommendations for hormonal therapy were revised to allow 5 to 10 years, rather than only 5 years, of tamoxifen therapy as a result of changing practice guidelines.
- Guidelines for managing the specific adverse events of nodular regenerative hyperplasia and interstitial lung disease were added. For nodular regenerative hyperplasia, a new appendix for guidelines for liver biopsy was added.
- Radiotherapy-related toxicity was split into interstitial lung disease and skin toxicity, in order to differentiate between radiation-induced and drug-induced toxicities.
- Text on use of strong/potent CYP3A4/5 inhibitors was revised to provide further instruction to investigators, and remove erythromycin from the list of examples as it is only a moderate CYP3A4/5 inhibitor, not a potent inhibitor.
- Suspected transmission of an infection agent by the study drug was added as an adverse event of special interest.

Version 3 of the protocol (dated September 2013) made the following key updates:

- The duration of patient monitoring following first dose of Kadcyla was changed from 60 minutes to 90 minutes.
- Assessment of total protein at baseline was added to the list of assessments because it was inadvertently omitted.
- Requirements for long-term reporting of concomitant medication, adverse events and serious adverse events were clarified.
- Detail on severe/fatal haemorrhage was added under the identified risk of hematologic toxicity.

Protocol Version 4 (dated March 2014) introduced the following key changes:

- Addition of language to allow shorter duration of an escalated dose-dense administration of paclitaxel.
- Inclusion criteria were revised to clarify that if pre-chemotherapy LVEF assessments were not conducted, the screening LVEF assessment must be at least 55% in order for the patient to be eligible.
- Dose modifications related to increases in AST and for thrombocytopenia were revised. Guidelines for Grade 1-2 pneumonitis were updated such that to require diagnosis of drug-related ILD/pneumonitis should lead to permanent discontinuation of Kadcyla treatment.

Protocol Version 5 (dated July 2014) was issued rapidly after Version 4, to correct a small but significant error in language in the general inclusion critieria, and indicate that left ventricular ejection fraction (LVEF) should be ≥50% prior to receiving neoadjuvant chemotherapy instead of after receiving neoadjuvant chemotherapy.

A local version of the protocol was created for Argentina at Version 5, to allow for the following specific local requirements:

- Per local regulations, pregnancy testing had to be conducted at each cycle and then at each month in the follow up period for 7 months.
- Since HIV testing was not part of standard of care, the exclusion criteria for Argentina were amended to include the documentation of negative HIV status prior to study entry.

Version 6 of the protocol (dated October 2015) made the following key changes:

- Data that became available from the Phase III study TDM4788g/BO22589 was included.
- The reporting of LVSD events as SAEs was clarified.
- Pregnancy reporting requirements were updated, in line with the Global Enhancement Pharmacovigilance Pregnancy Program.
- The changes in the local Argentinian version of Protocol Version 6 mirrored the changes in the global version.

<u>Changes to planned analyses:</u>

The primary analysis to compare IDFS between the two treatment arms was planned to be a log-rank test, stratified by the protocol-defined stratification factors per IxRS, with the unstratified log-rank test results to be provided as a sensitivity analysis. However, per the SAP specifications, since the smallest stratum was found to have < 5 patients in either arm, it was deemed that robust stratified analyses could not be conducted, and thus the unstratified analysis is used as the primary analysis. In light of this, the pre-planned sensitivity analysis to evaluate use of stratification factors per eCRF was no longer relevant and thus was not performed.

Protocol deviations:

Table 9: Major protocol deviations - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Protocol Deviations of Interest	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
No. Of Patients With At Least One		
Protocol Deviation	93 (12.5%)	156 (21.0%)
Major Exclusion Criteria Deviation	12 (1.6%)	6 (0.8%)
Major Inclusion Criteria Deviation	72 (9.7%)	79 (10.6%)
Major On-Study Protocol Deviation	9 (1.2%)	83 (11.2%)
Major Exclusion Criteria Deviation		
Patients With At Least One Exclusion Criteria Deviation	12 (1.6%)	6 (0.8%)
Active Liver Disease: 15	0	2 (0.3%)
Active, Unres Infections Requiring Treatment: 18	4 (0.5%)	0
Exceed Cumulative Dose Of Anthracyclines: 9	1 (0.1%)	0
Hbv/Hcv But Liver Tests Not Repeated In Scr: 15	6 (0.8%)	1 (0.1%)
History Of Other Malignancy In Last 5 Years: 6	0	1 (0.1%)
Pd By Inv At End Of Preoperative Systemic Chemo: 4	1 (0.1%)	0
Prohibited Cardiopulmonary Dysfunction: 10	0	2 (0.3%)
Major Inclusion Criteria Deviation		
Patients With At Least One Inclusion Criteria Deviation	72 (9.7%)	79 (10.6%)
<=12 Wks From Primary Surgery To Randomization: 7	6 (0.8%)	6 (0.8%)
Adequate Anc, Platelets, Hemoglobin: 13a-C	1 (0.1%)	2 (0.3%)
Adequate Ast, Alt, Bilirubin, Alk: 13f-H	4 (0.5%)	10 (1.3%)
Adequate Coagulation Labs: 13e	8 (1.1%)	7 (0.9%)
Adequate Contraception Methods: 14	0	3 (0.4%)
Adequate Creatinine: 13d	0	2 (0.3%)
Adequate Excision Of Breast And Lymph Disease: 5	7 (0.9%)	6 (0.8%)
Adequate Organ Function Missing Required Labs: 13	10 (1.3%)	7 (0.9%)
Adequate Systemic Chemo And Tras Prior To Sx: 4	7 (0.9%)	6 (0.8%)
Confirmed Her2-Positive Bc By Central Lab: 1	5 (0.7%)	6 (0.8%)
Documented Hbv And Hcv Status Per Protocol: 16	10 (1.3%)	9 (1.2%)
Inadequate Baseline Lvef: 13.I	3 (0.4%)	7 (0.9%)
Negative Pregnancy Test Per Protocol: 15	3 (0.4%)	0
No Icf/Signed Icf Approved By Irb/Ec: 9	13 (1.7%)	15 (2.0%)
Pathologic Evidence Of Residual Inv Disease: 6	1 (0.1%)	0
Major On-Study Protocol Deviation		
Patients With At Least One Major On-Study Protocol Deviation	9 (1.2%)	83 (11.2%)
Dose Delay > 42 Days For Toxicity	0	1 (0.1%)
Dose Deviating >20% Of Planned Dose	1 (0.1%)	0
Dose Not Reduced/Held Per Protocol	4 (0.5%)	78 (10.5%)
Drug Not Discontinued Despite Meeting Criteria	1 (0.1%)	0
Received Incorrect Study Medication	1 (0.1%)	2 (0.3%)
Received Prohibited Concomitant Medication	1 (0.1%)	0
Sae Not Reported Within The Expected Timelines	1 (0.1%)	3 (0.4%)

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_dv.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_dv_IT.out
23NOV2018 16:56

Baseline data

Table 10: Demographic and baseline characteristics - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Age (yr)		
n	743	743
Mean (SD)	49.2 (10.9)	49.0 (10.4)
Median	49.0	49.0
Range	23 - 80	24 - 79
Age (yr)		
n	743	743
<40	153 (20.6%)	143 (19.2%)
40-64	522 (70.3%)	542 (72.9%)
65-74	61 (8.2%)	56 (7.5%)
>=75	7 (0.9%)	2 (0.3%)
Sex		
n	743	743
Male	3 (0.4%)	2 (0.3%)
Female	740 (99.6%)	741 (99.7%)
Ethnicity		
n	743	743
Hispanic or Latino	107 (14.4%)	91 (12.2%)
Not Hispanic or Latino	543 (73.1%)	579 (77.9%)
Not Stated	49 (6.6%)	35 (4.7%)
Unknown	44 (5.9%)	38 (5.1%)
Race		
n	743	743
American Indian or Alaska Native	50 (6.7%)	36 (4.8%)
Asian	64 (8.6%)	65 (8.7%)
Black or African American	19 (2.6%)	21 (2.8%)
Native Hawaiian or other Pacific Islander	1 (0.1%)	0
White	531 (71.5%)	551 (74.2%)
Multiple	1 (0.1%)	1 (0.1%)
Unknown	77 (10.4%)	69 (9.3%)
Region		
n	743	743
North America	164 (22.1%)	170 (22.9%)
Western Europe	403 (54.2%)	403 (54.2%)
Rest of the World	176 (23.7%)	170 (22.9%)
Weight (kg) at baseline		
n	732	738
Mean (SD)	71.19 (15.67)	70.64 (14.64)
Median	68.95	68.45
Range	43.0 - 145.5	40.0 - 169.0
Height (cm) at baseline		
n	732	738
Mean (SD)	163.02 (7.25)	163.17 (7.10)
Median	163.00	163.00
Range	142.0 - 188.0	137.0 - 186.0
BMI (WHO Classification)		
n	743	743
Underweight	17 (2.3%)	21 (2.8%)
Normal	306 (41.2%)	306 (41.2%)
Overweight	225 (30.3%)	245 (33.0%)
Obese	184 (24.8%)	166 (22.3%)
Unknown	11 (1.5%)	5 (0.7%)

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Hormone receptor status (IxRS)		
n	743	743
Negative (ER negative and PgR negative/unknown)	210 (28.3%)	213 (28.7%)
Positive (ER and/or PgR positive)	533 (71.7%)	530 (71.3%)
Hormone receptor status (eCRF)		
n	743	743
Negative (ER negative and PgR negative/unknown)	203 (27.3%)	209 (28.1%)
Positive (ER and/or PgR positive)	540 (72.7%)	534 (71.9%)
Preoperative HER2-directed therapy (IxRS)		
n	743	743
Trastuzumab only	600 (80.8%)	601 (80.9%)
Trastuzumab plus additional HER2	143 (19.2%)	142 (19.1%)
Preoperative HER2-directed therapy (eCRF)		
n	743	743
Trastuzumab only	596 (80.2%)	600 (80.8%)
Trastuzumab plus additional HER2	147 (19.8%)	143 (19.2%)
Preoperative Pertuzumab (eCRF)		
n	743	743
Received pertuzumab	139 (18.7%)	133 (17.9%)
Did not receive pertuzumab	604 (81.3%)	610 (82.1%)
Prior Anthracycline received		
n	743	743
Received prior anthracycline	564 (75.9%)	579 (77.9%)
Did not receive prior anthracycline	179 (24.1%)	164 (22.1%)
Menopausal Status at screening		
n	743	743
Pre menopausal	413 (55.6%)	399 (53.7%)
Post menopausal	330 (44.4%)	344 (46.3%)
ECOG Performance Status		
n	743	743
0	613 (82.5%)	597 (80.3%)
1	130 (17.5%)	146 (19.7%)
LVEF pre-chemotherapy		
n	573	597
Mean (SD)	64.31 (6.22)	63.93 (6.19)
Median	65.00	64.00
Quartiles	60.00 - 69.00	60.00 - 67.60
Range	46.0 - 85.0	46.0 - 86.0
LVEF at screening		
n	743	743
Mean (SD)	62.66 (6.02)	62.66 (5.85)
Median	62.00	62.00
Quartiles	59.00 - 66.57	59.00 - 66.00
Range	50.0 - 90.0	50.0 - 80.0
ECG at screening		
n	739	741
Normal	633 (85.7%)	619 (83.5%)
Abnormal, not clinically significant	105 (14.2%)	122 (16.5%)
Abnormal, clincally significant	1 (0.1%)	0

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_dm.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_dm_IT.out
09NOV2018 17:27
Page 2 of 2
Abridged from t_dm_IT

Tumor prognostic characteristics including hormone receptor status (positive: 72.3%, negative: 27.7%), clinical stage at presentation (inoperable: 25.3%, operable: 74.8%) and pathological nodal status after preoperative therapy (node positive: 46.4%, node negative or not evaluated: 53.6%) were similar in the study arms.

The majority of the patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. 19.5% percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 93.8% of these patients received pertuzumab. All of the patients had received taxanes as part of neoadjuvant chemotherapy.

Table 11: Breast cancer characteristics - Study KATHERINE

Breast Cancer Characteristics, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Site of Primary Tumor		
n	743	743
left	388 (52.2%)	371 (49.9%)
right	352 (47.4%)	366 (49.3%)
bilateral	3 (0.4%)	6 (0.8%)
Time since initial diagnosis (in months from randomization)		
n	731	734
Mean (SD)	8.34 (1.79)	8.42 (1.73)
Median	8.25	8.25
Range	0.5 - 20.6	0.0 - 22.1
Histological subtype		
n	743	743
Ductal	679 (91.4%)	688 (92.6%)
Lobular	38 (5.1%)	21 (2.8%)
NOS	17 (2.3%)	16 (2.2%)
Other	9 (1.2%)	18 (2.4%)
Histological grade		
n	743	743
Well-differentiated	56 (7.5%)	57 (7.7%)
Moderately differentiated	263 (35.4%)	276 (37.1%)
Poorly differentiated	283 (38.1%)	282 (38.0%)
Unknown	141 (19.0%)	128 (17.2%)
Primary Tumor Estrogen Receptor (ER) status (local)		
n	743	743
Negative	219 (29.5%)	223 (30.0%)
Positive	524 (70.5%)	520 (70.0%)
Primary Tumor Progesterone Receptor(PR) status (local)		
n	743	743
Negative	316 (42.5%)	322 (43.3%)
Positive	416 (56.0%)	410 (55.2%)
Unknown	11 (1.5%)	11 (1.5%)
Primary Tumor ER/PR status (local)		
n	743	743
Negative/Unknown	203 (27.3%)	209 (28.1%)
Positive	540 (72.7%)	534 (71.9%)
Primary Tumour Stage (at initial diagnosis)		
n	743	743
cT1	81 (10.9%)	99 (13.3%)
cT2	389 (52.4%)	365 (49.1%)
cT3	185 (24.9%)	177 (23.8%)
cT4,cT4a,cT4b,cT4c	54 (7.3%)	59 (7.9%)
cT4d	34 (4.6%)	43 (5.8%)
cTX	0	0
Regional Lymph Node Stage (at initial diagnosis)		
n	743	743
cN0	239 (32.2%)	237 (31.9%)
cN1	370 (49.8%)	385 (51.8%)
cN2	99 (13.3%)	75 (10.1%)
cN3	33 (4.4%)	43 (5.8%)
cNX	2 (0.3%)	3 (0.4%)
Were Lymph Nodes pathologically assessed at initial diagnosis (prior to Neoadjuvant Chemotherapy)?		
n	743	743
Yes	319 (42.9%)	309 (41.6%)
No	424 (57.1%)	434 (58.4%)
Number of Positive Lymph Nodes (at initial diagnosis)		
n	319	309
Mean (SD)	1.07 (2.78)	1.07 (1.87)
Median	1.00	1.00
Interquartile Range	0.00 - 1.00	0.00 - 1.00
Range	0.0 - 45.0	0.0 - 25.0
Primary Tumour Stage (at definitive surgery)		
n	743	743
ypT0	39 (5.2%)	38 (5.1%)
ypTis	13 (1.7%)	20 (2.7%)
ypT1mic	33 (4.4%)	31 (4.2%)
ypT1a	135 (18.2%)	138 (18.6%)
ypT1b	86 (11.6%)	104 (14.0%)
ypT1c	184 (24.8%)	172 (23.1%)
ypT1	0	3 (0.4%)
ypT2	185 (24.9%)	174 (23.4%)
ypT3	57 (7.7%)	51 (6.9%)
ypT4	10 (1.3%)	12 (1.6%)
ypTX	1 (0.1%)	0

Regional Lymph Node Stage (at definitive surgery)		
n	743	743
ypN0	335 (45.1%)	344 (46.3%)
ypN1	213 (28.7%)	220 (29.6%)
ypN2	103 (13.9%)	86 (11.6%)
ypN3	30 (4.0%)	37 (5.0%)
ypNX	62 (8.3%)	56 (7.5%)
Were Lymph Nodes pathologically assessed at definitive surgery following Neoadjuvant Therapy?		
n	743	743
Yes	676 (91.0%)	679 (91.4%)
No	67 (9.0%)	64 (8.6%)
Number of Positive Lymph Nodes (at definitive surgery)		
n	676	679
Mean (SD)	1.99 (3.37)	1.83 (3.22)
Median	1.00	1.00
Interquartile Range	0.00 - 3.00	0.00 - 2.00
Range	0.0 - 22.0	0.0 - 23.0

Note: Staging at initial diagnosis refers to clinical staging, staging at definitive surgery refers to pathologic staging.
Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/program/PR6551_t_dm_bc.sas

Two thirds (996 out of 1486, 67%) of patients had 'small' post-neoadjuvant tumour sizes (ypT0, ypTis, ypTmic, ypT1a, ypT1b, ypT1c). All but two of the patients with ypN0 staging had residual invasive disease at primary tumour. These two patients did not fill the inclusion criteria and constitute a major protocol violation.

Table 12: Central HER2 Status as used for eligibility - Study KATHERINE

Central HER2 Status as used for eligibility, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)	Total (N=1486)
Pre-surgical (601) sample used for eligibility	603 (81.2%)	592 (79.7%)	1195 (80.4%)
Surgical (701) sample used for eligibility	138 (18.6%)	151 (20.3%)	289 (19.4%)
Central HER2 status* by ISH			
n	743	743	1486
Negative	4 (0.5%)	7 (0.9%)	11 (0.7%)
Positive	722 (97.2%)	707 (95.2%)	1429 (96.2%)
Unknown	17 (2.3%)	29 (3.9%)	46 (3.1%)
Central HER2 status* by IHC			
n	743	743	1486
IHC0/1+	13 (1.7%)	12 (1.6%)	25 (1.7%)
IHC2+	168 (22.6%)	158 (21.3%)	326 (21.9%)
IHC3+	559 (75.2%)	573 (77.1%)	1132 (76.2%)
Unknown	3 (0.4%)	0	3 (0.2%)
Central combined IHC/ISH status*			
n	743	743	1486
ISH+/IHC3+	540 (72.7%)	537 (72.3%)	1077 (72.5%)
ISH+/IHC2+	168 (22.6%)	158 (21.3%)	326 (21.9%)
ISH+/IHC0 or ISH+/IHC1+	13 (1.7%)	12 (1.6%)	25 (1.7%)
ISH+/IHC unknown	1 (0.1%)	0	1 (<0.1%)
ISH-/IHC3+	4 (0.5%)	7 (0.9%)	11 (0.7%)
IHC Unknown/ISH Unknown	2 (0.3%)	0	2 (0.1%)
ISH Unknown/IHC3+	15 (2.0%)	29 (3.9%)	44 (3.0%)

* HER2-status derived from the pre-treatment or surgical specimen. Two patients [redacted] in the IHC2+/ISH+ subgroup are positive based on the DAKO IQFISH pharmDx test and have an unknown Ventana DDISH test result. A missing HER2 status is presented for [redacted] due to protocol violation, but the sample of this patent was HER2-positive (rerandomized as [redacted]).

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_dm_her2.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_dm_her2_IT.out
06NOV2018 13:29 Page 1 of 1

Regarding HER-2 status, three samples were retested for HER2 positivity using IQFISH Dako PharmDx since DDISH HER2 testing from Ventana gave invalid results. Two patients were enrolled based on the Dako FISH results.

Table 13: Summary of PIK3CA mutation status - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
PIK3CA mutation status Staining score		
n	743	743
Mutated	174 (23.4%)	176 (23.7%)
Non-mutated	503 (67.7%)	510 (68.6%)
Unknown/missing	66 (8.9%)	57 (7.7%)

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_dm_pikmut.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_dm_pikmut_IT.out
23NOV2018 17:29 Page 1 of 1

Table 14: Cardiac history by treatment regimen - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Total number of patients with at least one condition	63 (8.5%)	67 (9.0%)
Overall total number of conditions	69	74
Previous Cardiac History		
Total number of patients with at least one condition	6 (0.8%)	4 (0.5%)
Total number of conditions	6	4
Angina Pectoris	0	0
Arterial Hypertension	1 (0.1%)	1 (0.1%)
Cardiac Arrhythmias That Required Treatment	1 (0.1%)	1 (0.1%)
Heart Failure	0	0
Myocardial Infarction	0	1 (0.1%)
Other	4 (0.5%)	1 (0.1%)
Current Cardiac History		
Total number of patients with at least one condition	57 (7.7%)	64 (8.6%)
Total number of conditions	63	70
Angina Pectoris	0	1 (0.1%)
Arterial Hypertension	29 (3.9%)	33 (4.4%)
Cardiac Arrhythmias That Required Treatment	3 (0.4%)	5 (0.7%)
Heart Failure	1 (0.1%)	0
Myocardial Infarction	2 (0.3%)	0
Other	28 (3.8%)	31 (4.2%)

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ch.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ch_IT.out
09NOV2018 11:39 Page 1 of 1
spacing modified from t_ch_IT

Table 15: Prior breast cancer therapy - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Cumulative Dose of Prior Anthracyclines [mg/m2] (for Patients with known dose)		
n	522	525
Mean (SD)	268.7 (98.03)	263.9 (100.77)
Median	282.0	295.0
Min - Max	9 - 600	2 - 488
Prior Therapy Type		
Chemo (Anthracycline)	564 (75.9%)	579 (77.9%)
Chemo (Non-Anthracycline)	743 (100.0%)	743 (100.0%)
Hormonal	524 (70.5%)	528 (71.1%)
Trastuzumab	743 (100.0%)	743 (100.0%)
HER2-directed therapy other than trastuzumab	147 (19.8%)	143 (19.2%)
Other	1 (0.1%)	2 (0.3%)
Overall Clinical Response after Neoadjuvant Therapy		
Complete response	82 (11.0%)	74 (10.0%)
Partial response	501 (67.4%)	499 (67.2%)
Stable disease	72 (9.7%)	59 (7.9%)
Unknown but no progression	86 (11.6%)	110 (14.8%)
Not applicable	2 (0.3%)	1 (0.1%)
Prior Therapy Administered		
Trastuzumab		
n	743	743
Trastuzumab overall	743 (100.0%)	743 (100.0%)
Other HER2-targeted agents		
n	147	143
Afatinib	2 (0.3%)	4 (0.5%)
Lapatinib	5 (0.7%)	6 (0.8%)
Neratinib	1 (0.1%)	1 (0.1%)
Pertuzumab	139 (18.7%)	133 (17.9%)
Taxanes overall		
n	743	743
Docetaxel	424 (57.1%)	407 (54.8%)
Nanoparticle Paclitaxel	6 (0.8%)	6 (0.8%)
Paclitaxel	331 (44.5%)	350 (47.1%)
Other agents		
*cisplatin/*cyclophosphamide/*epirubicin/*etoposide/ Fluorouracil	0	3 (0.4%)
Bevacizumab	1 (0.1%)	1 (0.1%)
Bkm120	0	1 (0.1%)
Blinded Bkm120	0	1 (0.1%)
Capecitabine	1 (0.1%)	0
Carboplatin	147 (19.8%)	138 (18.6%)
Cisplatin	6 (0.8%)	4 (0.5%)
Cyclophosphamide	426 (57.3%)	440 (59.2%)
Cyclophosphamide/Fluorouracil	1 (0.1%)	1 (0.1%)
Cyclophosphamide/Fluorouracil/Methotrexate	1 (0.1%)	0
Doxorubicin	199 (26.8%)	194 (26.1%)
Epirubicin	366 (49.3%)	389 (52.4%)
Fluorouracil	140 (18.8%)	142 (19.1%)
Methotrexate	4 (0.5%)	3 (0.4%)
Pirarubicin	2 (0.3%)	0
Tegafur	1 (0.1%)	0
Vinorelbine	1 (0.1%)	0

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_dm_trt.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_dm_trt_IT.out
27DEC2018 18:05

*Note that due to a transcriptional error the regimen *cisplatin + epirubicin +fluorouracil (FEC) is showing as *cisplatin/*cyclophosphamide/*epirubicin/*etoposide/Fluorouracil in this table; patients received the standard FEC combination and did not receive either cyclophosphamide or etoposide.

Table 16: Breast cancer surgery - Study KATHERINE

Breast Cancer Surgery, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Time to definitive surgery (in months from randomization)		
n	743	743
Mean (SD)	-1.85 (1.41)	-1.92 (2.32)
Median	-1.61	-1.64
Range	-14.2 - 9.3	-49.3 - 10.8
Patients with any type of definitive breast cancer surgery	743 (100.0%)	743 (100.0%)
Lumpectomy/partial mastectomy	297 (40.0%)	295 (39.7%)
Simple/radical/modified radical mastectomy	446 (60.0%)	448 (60.3%)
Other surgeries and biopsies	663 (89.2%)	665 (89.5%)
Reconstructive surgery	57 (7.7%)	68 (9.2%)
Re-excision of surgical margins	24 (3.2%)	30 (4.0%)
Sentinel node biopsy/axillary sampling	270 (36.3%)	263 (35.4%)
Axillary dissection	360 (48.5%)	367 (49.4%)
Biopsy	552 (74.3%)	557 (75.0%)

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_dm_surg.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_dm_surg_IT.out
21NOV2018 11:08 Page 1 of 1

Numbers analysed

Table 17: Analysis Populations by Treatment Regimen - Study KATHERINE

Randomized Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab	Trastuzumab Emtansine
Patients randomised - ITT population	743	743
Safety Population	720	740
Randomized to Trastuzumab	719	1
Randomized to Trastuzumab emtansine	1	739

Patients who received no Study Treatment are excluded from the Safety Analysis Population.

Outcomes and estimation

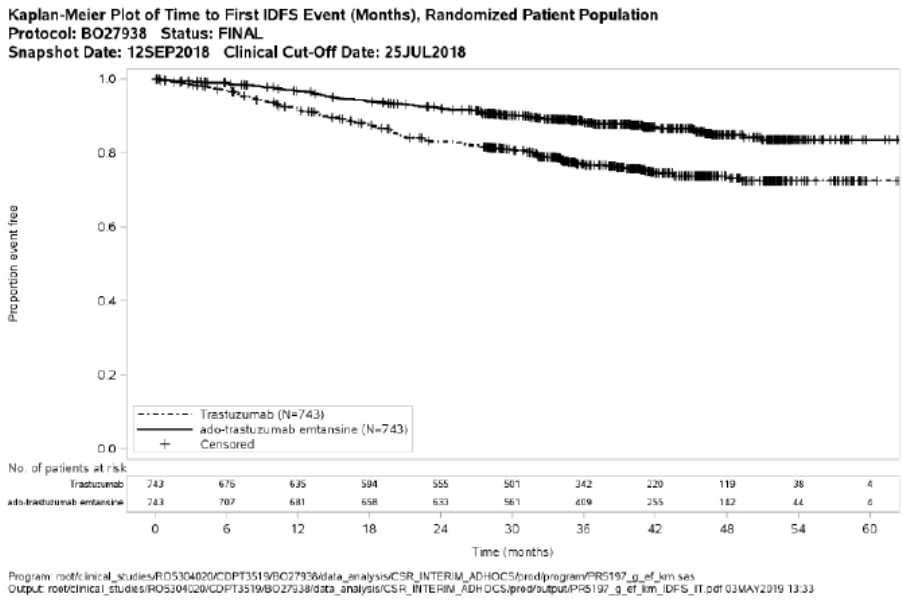
Primary efficacy endpoint: IDFS (ITT)

Table 18: Summary of time to first IDFS event - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Patients with event (%)	165 (22.2%)	91 (12.2%)
Earliest contributing event		
Distant recurrence - non CNS	79	32
Distant recurrence - CNS	30	43
Locoregional recurrence	43	11
Contralateral breast cancer	10	3
Death without prior event	3	2
Patients without event (%)	578 (77.8%)	652 (87.8%)
Time to event (months)		
Median	NE	NE
95% CI for Median	NE	NE
25% and 75%-ile	41.59, NE	NE
Range	0.1* to 62.6*	0.1* to 62.7*
Stratified Analysis		
p-value (log-rank)	<.0001	
Hazard Ratio	0.48	
95% CI	(0.37, 0.62)	
Unstratified Analysis		
p-value (log-rank)	<.0001	
Hazard Ratio	0.50	
95% CI	(0.39, 0.64)	
3-years Duration		
Patients remaining at risk	342	409
Event Free Rate (%)	77.02	88.27
95% CI	(73.78, 80.26)	(85.81, 90.72)

Due to stratum with <5 patients, the unstratified analysis figures are to be used for the primary analysis. Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value have been adjusted for the randomization stratification variables as recorded in the IXRS: clinical stage at presentation , hormone receptor status, preoperative HER2-directed therapy, and pathologic nodal status evaluated after preoperative therapy.
Patients who experience >1 IDFS event are reported in the category associated with their earliest IDFS event. If >1 event is reported on the same date, patients are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event. CNS metastases is a subset of Distant recurrence.



Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/program/PR5197_g_ef_km.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/output/PR5197_g_ef_km_IDFS_IT.pdf 03MAY2019 13:33

Figure 3: Kaplan-Meier Plot of Time to First IDFS Event (Months), Randomized Patient Population - Study KATHERINE

Table 19: Summary of IDFS reasons for censoring- Study KATHERINE

Summary of IDFS reasons for censoring of patients by Treatment Regimen, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Patients with event (%)	165 (22.2%)	91 (12.2%)
Patients without event (%)	578 (77.8%)	652 (87.8%)
Censoring status*		
No-post baseline assessments	31 (4.2%)	13 (1.7%)
Event-free and on treatment	0	0
Event-free in follow-up	504 (67.8%)	591 (79.5%)
Event-free discontinued study	43 (5.8%)	48 (6.5%)
Lost to follow-up	10 (1.3%)	8 (1.1%)
Withdrawal by patient	31 (4.2%)	36 (4.8%)
Other	2 (0.3%)	4 (0.5%)

*categories are exclusive. Patients with no-post baseline assessments, i.e. censored at randomization + 1 day, are not counted in any of the other categories

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/program/PR5197_t_ef_rea_cens.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/output/PR5197_t_ef_rea_cens_IDFS_IT.out
14JUN2019 15:20 Page 1 of 1

The diverse categories of recurrence that fulfilled the definition of IDFS event were provided (see **Table 18**). In this case the *earliest* event was considered. The different numbers presented in **Table 20** imply that some patients might have *ascended* in category because they experienced an *additional* IDFS event, one with a higher hierarchy, within 61 days of the first one. CNS recurrence was prioritised in the hierarchy above non-CNS recurrence in cases where the patient had both types of relapse at the same IDFS event defining date.

The percentages presented in the **Table 20** are calculated using the N of each arm (i.e. 743) as a denominator. Taking into account the possibility of additional IDFS events in the following assessment, the numbers of patients categorised as "contralateral breast cancer" and "death without prior event" were stable whereas a few patients with "locoregional recurrence" were moved to the distant recurrence categories. The high proportion of patients with CNS recurrence in the Kadcyla arm was maintained.

Table 20: Summary of first occurrence of an IDFS event applying hierarchy and time window by treatment regimen: randomized patient population- Study KATHERINE

Summary of First Occurrence of an IDFS Event Applying Hierarchy and Time Window by Treatment Regimen, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Total Patients with IDFS Event: n (%)	165 (22.2%)	91 (12.2%)
Category of IDFS Event: n (%)		
Distant recurrence - non CNS	86 (11.6%)	34 (4.6%)
Distant recurrence - CNS	32 (4.3%)	44 (5.9%)
Locoregional recurrence	34 (4.6%)	8 (1.1%)
Contralateral breast cancer	10 (1.3%)	3 (0.4%)
Death without prior event	3 (0.4%)	2 (0.3%)

Patients who experience additional IDFS event(s) within 61 days of their 1st IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ef_sum_window.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ef_sum_window_IDFS_IT.out
15NOV2018 14:04
Page 1 of 1

*The denominator for the all the proportions in this table is the population for each arm, i.e. 743.

Table 21: Summary of first occurrence of an IDFS event applying no hierarchy - Study KATHERINE

Summary of First Occurrence of an IDFS Event Applying no Hierarchy by Treatment Regiment, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Total Patients with IDFS Event: n (%)	165 (22.2%)	91 (12.2%)
Category of IDFS Event: n (%)		
Distant recurrence - CNS	30 (18.2%)	43 (47.3%)
Distant recurrence - non CNS	86 (52.1%)	38 (41.8%)
Locoregional Event	52 (31.5%)	14 (15.4%)
Contralateral Event	10 (6.1%)	3 (3.3%)
Death	3 (1.8%)	2 (2.2%)

Patients with multiple events recorded as their first event will be counted in all respective categories.

Program:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/program/PR5409_t_ef_sum.sas
Output:
root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/output/PR5409_t_ef_sum_IDFS_IT.out
26JUN2019 15:22
Page 1 of 1

Note: the 61-day time window was not applied.

*The denominator for the proportions in the category of IDFS events in this table is the total of patients with IDFS event in each arms, i.e. 165 in trastuzumab and 91 in Kadcyla

Table 22: Summary of CNS recurrence - Study KATHERINE

Summary of CNS recurrence, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Total number of patients with CNS recurrence*	40	45
CNS recurrence as earliest IDFS event	30	43
CNS recurrence as first IDFS event, including patients with additional IDFS events within 61 days of their first IDFS event*	32	44
CNS recurrence after first IDFS event*	8	1
Total number of patients with CNS as only event^	21	36

*Patients who experience a CNS recurrence within 61 days of their 1st IDFS event are reported in the category 'CNS recurrence as first IDFS event'. CNS recurrence occurring more than 61 days after the first IDFS event are reported in the category 'CNS recurrence after first IDFS event'.
^No time window applied.

Program:
root/clinical studies/RO5304020/CDPT3519/BO27938/data analysis/CSR INTERIM ADHOCS/prod/program/PR5409 t ef cns time.sas
Output:
root/clinical studies/RO5304020/CDPT3519/BO27938/data analysis/CSR INTERIM ADHOCS/prod/output/PR5409 t ef cns time IT.out
26JUN2019 15:23
Page 1 of 1

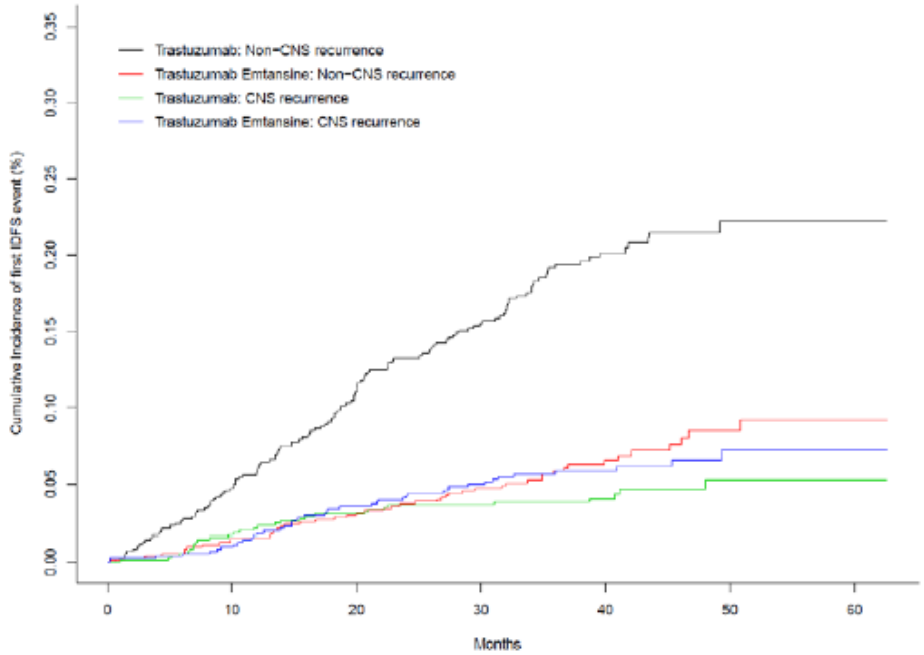


Table 23: Competing risk analysis of incidence of first IDFS events for 1486 patients - Study KATHERINE

Secondary efficacy endpoints

IDFS including Second Primary Non-breast Cancer (IDFS-SPNBC)

Table 24: Summary of Time to First IDFS Including SNPBC - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)		Trastuzumab Emtansine (N=743)
Patients with event (%)	167 (22.5%)		95 (12.8%)
Patients without event (%)	576 (77.5%)		648 (87.2%)
Time to event (months)			
Median	NE		NE
95% CI for Median	NE		NE
25% and 75%-ile	41.17, NE		NE
Range	0.1* to 62.6*		0.1* to 62.7*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.50	
95% CI		(0.38, 0.64)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.51	
95% CI		(0.40, 0.66)	
3-years Duration			
Patients remaining at risk	341		408
Event Free Rate (%)	76.89		87.68
95% CI	(73.65, 80.14)		(85.18, 90.18)

* Censored value.Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value have been adjusted for the randomization stratification variables as recorded by IxRS: clinical stage at presentation , hormone receptor status, preoperative HER2-directed therapy, and pathologic nodal status evaluated after preoperative therapy. Patients who experience >1 IDFS event are reported in the category associated with their earliest IDFS event. If >1 event is reported on the same date, patients are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Second primary non-breast invasive cancer [5] Death without prior event. CNS metastases is a subset of Distant recurrence.

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ef_tte.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t ef tte SPNBC IT.out

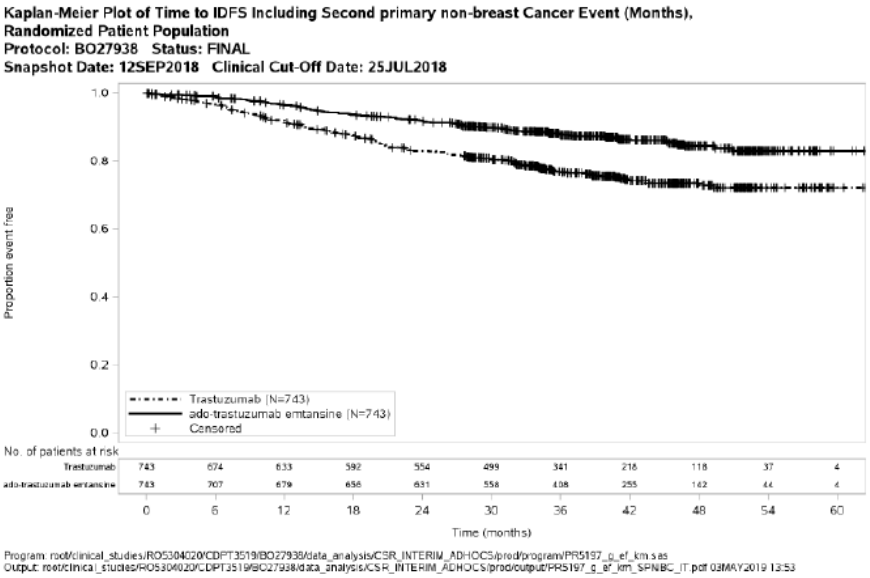


Figure 4: Kaplan-Meier curve of time to IDFS including second primary non-breast cancer - Study KATHERINE

Disease Free Interval (DFS)

Table 25: Summary of Time to First DFS Event - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)		Trastuzumab Emtansine (N=743)
Patients with event (%)	167 (22.5%)		98 (13.2%)
Patients without event (%)	576 (77.5%)		645 (86.8%)
Time to event (months)			
Median	NE		NE
95% CI for Median	NE		NE
25% and 75%-ile	41.17, NE		NE
Range	0.1* to 62.6*		0.1* to 62.7*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.51	
95% CI		(0.40, 0.66)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.53	
95% CI		(0.41, 0.68)	
3-years Duration			
Patients remaining at risk	341		408
Event Free Rate (%)	76.89		87.41
95% CI	(73.65, 80.14)		(84.88, 89.93)

* Censored value.Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value have been adjusted for the randomization stratification variables as recorded in the IXRS: clinical stage at presentation , hormone receptor status, preoperative HER2-directed therapy, and pathologic nodal status evaluated after preoperative therapy. Patients who experience >1 IDFS event are reported in the category associated with their earliest IDFS event. If >1 event is reported on the same date, patients are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event. CNS metastases is a subset of Distant recurrence.

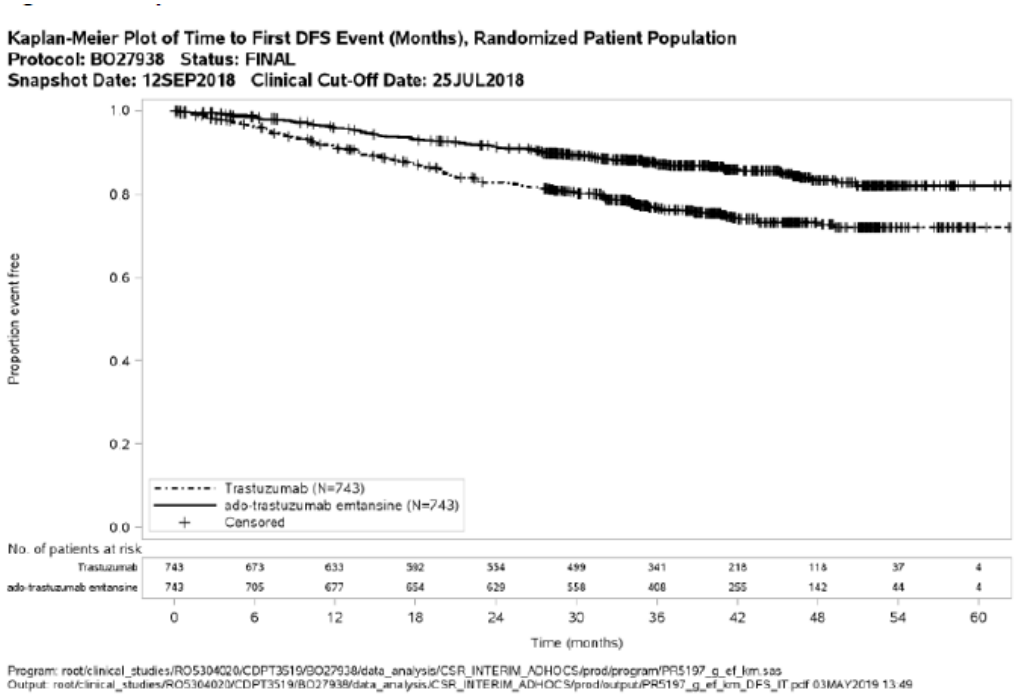


Figure 5: Kaplan-Meier Plot of Time to First DFS Event (Months), Randomized Patient Population - Study KATHERINE

Overall Survival (OS)

Table 26: Summary of Overall Survival - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Patients with event (%)	56 (7.5%)	42 (5.7%)
Patients without event (%)	687 (92.5%)	701 (94.3%)
Time to event (months)		
Median	NE	NE
95% CI for Median	NE	NE
25% and 75%-ile	NE	NE
Range	0.1* to 62.6*	0.1* to 62.7*
Stratified Analysis		
p-value (log-rank)	0.0561	
Hazard Ratio	0.68	
95% CI	(0.45, 1.01)	
Unstratified Analysis		
p-value (log-rank)	0.0848	
Hazard Ratio	0.70	
95% CI	(0.47, 1.05)	
5-years Duration		
Patients remaining at risk	8	12
Event Free Rate (%)	86.79	92.09
95% CI	(80.95, 92.63)	(89.44, 94.74)

Time to OS event (months) - Censoring: OS (1=censored, 0=event)* Censored value
Summaries of Event-Free Survival (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy and apthologic nodal status evaluated after preoperative therapy. Hazard ratios were estimated by Cox regression.

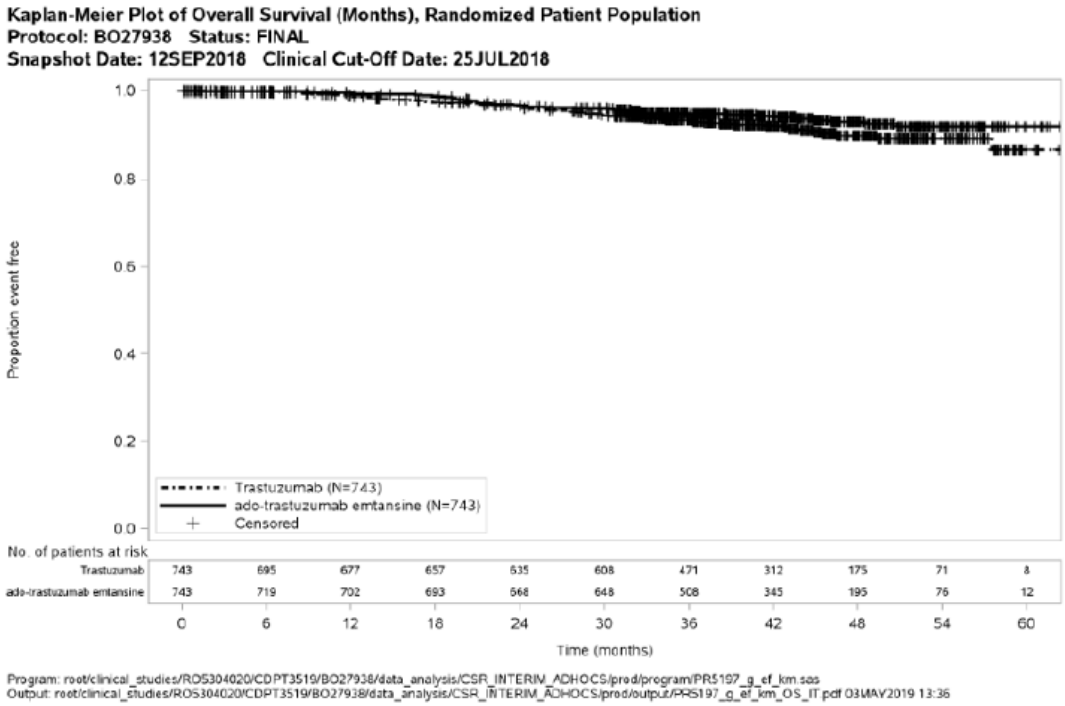


Figure 6: Kaplan-Meier Plot of Overall Survival - Study KATHERINE

Distant recurrence free interval (DRFI)

Table 27: Summary of Distant Recurrence-Free Interval (DRFI) - Study KATHERINE

Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=743)		Trastuzumab Emtansine (N=743)
Patients with event (%)	121 (16.3%)		78 (10.5%)
Patients without event (%)	622 (83.7%)		665 (89.5%)
Time to event (months)			
Median	NE		NE
95% CI for Median	NE		NE
25% and 75%-ile	NE		NE
Range	0.1* to 62.6*		0.1* to 62.7*
Stratified Analysis			
p-value (log-rank)		0.0001	
Hazard Ratio		0.58	
95% CI		(0.43, 0.77)	
Unstratified Analysis			
p-value (log-rank)		0.0003	
Hazard Ratio		0.60	
95% CI		(0.45, 0.79)	
3-years Duration			
Patients remaining at risk	359		412
Event Free Rate (%)	83.01		89.69
95% CI	(80.10, 85.92)		(87.37, 92.01)

* Censored value.Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value have been adjusted for the randomization stratification variables as recorded in the IXRS: clinical stage at presentation , hormone receptor status, preoperative HER2-directed therapy, and pathologic nodal status evaluated after preoperative therapy.

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ef_tte.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ef_tte_DRFI_IT.out

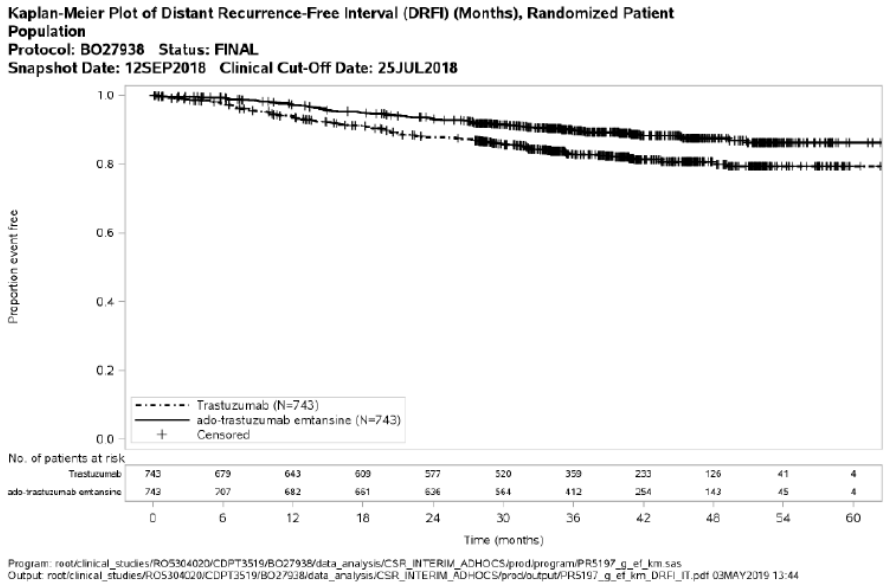


Figure 7: Kaplan-Meier Plot of Distant Recurrence-Free Interval (DRFI) - Study KATHERINE

Patient reported outcomes (PRO)

Table 28: Summary of Completion Rates by Visit and Treatment Regimen for EORTC-QLQ-C30 and EORTC-QLQ-BR23 Questionnaires (ITT Population) - Study KATHERINE

Visit	EORTC QLQ-C30		EORTC QLQ-BR23	
	Trastuzumab (N = 743)	Trastuzumab Emtansine (N = 743)	Trastuzumab (N = 743)	Trastuzumab Emtansine (N = 743)
Screening				
Evaluable patients [a]	743	743	743	743
Completed ≥ 1 question [b]	632 (85.1%)	655 (88.2%)	630 (84.8%)	655 (88.2%)
Cycle 5				
Evaluable patients [a]	674	684	674	684
Completed ≥ 1 question [b]	592 (87.8%)	610 (89.2%)	591 (87.7%)	610 (89.2%)
Cycle 11				
Evaluable patients [a]	613	636	613	636
Completed ≥ 1 question [b]	528 (86.1%)	529 (83.2%)	527 (86.0%)	528 (83.0%)
Trastuzumab Completion/Early Discontinuation				
Evaluable patients [a]	743	73	743	73
Completed ≥ 1 question [b]	584 (78.6%)	58 (79.5%)	584 (78.6%)	58 (79.5%)
Trastuzumab Emtansine Completion/Early Discontinuation				
Evaluable patients [a]	0	743	0	743
Completed ≥ 1 question [b]	0	526 (70.8%)	0	526 (70.8%)
FU Month 6				
Evaluable patients [a]	621	667	621	667
Completed ≥ 1 question [b]	446 (71.8%)	496 (74.4%)	446 (71.8%)	496 (74.4%)
FU Month 12				
Evaluable patients [a]	568	628	568	628
Completed ≥ 1 question [b]	414 (72.9%)	458 (72.9%)	414 (72.9%)	456 (72.6%)

Note: Percentages are based on the number of ITT population.

[a] Evaluable patients as defined by the protocol and, for cycle 5, cycle 11, follow-up Month 6, and follow-up Month 12, additionally including all patients who completed the measure at this time point even if not mandated by the protocol. Evaluable patients in the trastuzumab emtansine arm at the trastuzumab completion/early discontinuation visit reflected the number of patients randomized to the trastuzumab emtansine arm but received at least one dose of trastuzumab .

[b] Measure completion is defined as the completion of at least 1 question on the respective questionnaire (EORTC QLQ-C30/EORTC QLQ-BR23).

Sources: EORTC QLQ-C30 completion rates , EORTC QLQ-BR23 completion rates

Table 29: Clinically Meaningful Deterioration in Functions (Cognitive, Physical, Role) and GHS/HRQoL by Visit – EORTC QLQ-C30 - Study KATHERINE

Clinically Meaningful Deterioration in functions - EORTC QLQ-C30 and QLQ-BR23, by Visit, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Parameter Timepoint	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Cognitive Functioning		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	177 (28.9%)	187 (29.2%)
Cycle 11	182 (29.7%)	181 (28.3%)
Trastuzumab completion/early discontinuation	190 (31.0%)	19 (3.0%)
Trastuzumab emtansine completion/early discontinuation	0	183 (28.6%)
Follow-up Month 6	147 (24.0%)	182 (28.4%)
Follow-up Month 12	127 (20.8%)	173 (27.0%)
Physical Functioning		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	98 (16.0%)	119 (18.6%)
Cycle 11	73 (11.9%)	106 (16.6%)
Trastuzumab completion/early discontinuation	91 (14.9%)	8 (1.3%)
Trastuzumab emtansine completion/early discontinuation	0	112 (17.5%)
Follow-up Month 6	61 (10.0%)	78 (12.2%)
Follow-up Month 12	59 (9.6%)	81 (12.7%)
Global Health Status / QoL		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	116 (19.0%)	140 (21.9%)
Cycle 11	91 (14.9%)	132 (20.6%)
Trastuzumab completion/early discontinuation	112 (18.3%)	9 (1.4%)
Trastuzumab emtansine completion/early discontinuation	0	114 (17.8%)
Follow-up Month 6	82 (13.4%)	93 (14.5%)
Follow-up Month 12	60 (9.8%)	82 (12.8%)
Role Functioning		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	133 (21.7%)	169 (26.4%)
Cycle 11	110 (18.0%)	140 (21.9%)
Trastuzumab completion/early discontinuation	122 (19.9%)	13 (2.0%)
Trastuzumab emtansine completion/early discontinuation	0	129 (20.2%)
Follow-up Month 6	67 (10.9%)	107 (16.7%)
Follow-up Month 12	70 (11.4%)	93 (14.5%)

*n = number of patients with baseline and at least one post-baseline assessment in the respective subscale.
Clinically meaningful deterioration is defined as a decrease in score of 10 points in Physical function and HRQoL; decrease of 7 points in Cognitive function and decrease of 14 points in Role function.

Table 30: Clinically Meaningful Deterioration in Certain Symptoms by Visit – EORTC QLQ-C30 and EORTC QLQ-BR23 - Study KATHERINE

Clinically Meaningful Increase in symptoms - EORTC QLQ-C30 and QLQ-BR23, by Visit, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Parameter Timepoint	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Appetite Loss		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	65 (10.6%)	134 (20.9%)
Cycle 11	53 (8.7%)	84 (13.1%)
Trastuzumab completion/early discontinuation	58 (9.5%)	5 (0.8%)
Trastuzumab emtansine completion/early discontinuation	0	96 (15.0%)
Follow-up Month 6	34 (5.6%)	45 (7.0%)
Follow-up Month 12	44 (7.2%)	39 (6.1%)
Any Hair Loss		
n*	44 (100.0%)	43 (100.0%)
Cycle 5	3 (6.8%)	3 (7.0%)
Cycle 11	2 (4.5%)	2 (4.7%)
Trastuzumab completion/early discontinuation	4 (9.1%)	0
Trastuzumab emtansine completion/early discontinuation	0	4 (9.3%)
Follow-up Month 6	7 (15.9%)	4 (9.3%)
Follow-up Month 12	8 (18.2%)	5 (11.6%)
Systemic Therapy Side Effects		
n*	610 (100.0%)	638 (100.0%)
Cycle 5	82 (13.4%)	166 (26.0%)
Cycle 11	78 (12.8%)	153 (24.0%)
Trastuzumab completion/early discontinuation	94 (15.4%)	6 (0.9%)
Trastuzumab emtansine completion/early discontinuation	0	139 (21.8%)
Follow-up Month 6	82 (13.4%)	88 (13.8%)
Follow-up Month 12	75 (12.3%)	91 (14.3%)
Diarrhoea		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	63 (10.3%)	53 (8.3%)
Cycle 11	69 (11.3%)	35 (5.5%)
Trastuzumab completion/early discontinuation	56 (9.2%)	9 (1.4%)
Trastuzumab emtansine completion/early discontinuation	0	31 (4.8%)
Follow-up Month 6	35 (5.7%)	42 (6.6%)
Follow-up Month 12	37 (6.0%)	42 (6.6%)
Dyspnea		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	112 (18.3%)	132 (20.6%)
Cycle 11	102 (16.7%)	96 (15.0%)
Trastuzumab completion/early discontinuation	111 (18.1%)	13 (2.0%)
Trastuzumab emtansine completion/early discontinuation	0	98 (15.3%)
Follow-up Month 6	83 (13.6%)	103 (16.1%)
Follow-up Month 12	101 (16.5%)	110 (17.2%)

Fatigue		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	204 (33.3%)	267 (41.7%)
Cycle 11	171 (27.9%)	210 (32.8%)
Trastuzumab completion/early discontinuation	175 (28.6%)	15 (2.3%)
Trastuzumab emtansine completion/early discontinuation	0	197 (30.8%)
Follow-up Month 6	129 (21.1%)	157 (24.5%)
Follow-up Month 12	135 (22.1%)	145 (22.7%)
Nausea / Vomiting		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	82 (13.4%)	114 (17.8%)
Cycle 11	73 (11.9%)	102 (15.9%)
Trastuzumab completion/early discontinuation	63 (10.3%)	8 (1.3%)
Trastuzumab emtansine completion/early discontinuation	0	81 (12.7%)
Follow-up Month 6	50 (8.2%)	54 (8.4%)
Follow-up Month 12	45 (7.4%)	56 (8.8%)
Insomnia		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	141 (23.0%)	146 (22.8%)
Cycle 11	144 (23.5%)	136 (21.3%)
Trastuzumab completion/early discontinuation	142 (23.2%)	15 (2.3%)
Trastuzumab emtansine completion/early discontinuation	0	125 (19.5%)
Follow-up Month 6	116 (19.0%)	114 (17.8%)
Follow-up Month 12	97 (15.8%)	111 (17.3%)
Pain		
n*	612 (100.0%)	640 (100.0%)
Cycle 5	163 (26.6%)	184 (28.8%)
Cycle 11	147 (24.0%)	175 (27.3%)
Trastuzumab completion/early discontinuation	146 (23.9%)	14 (2.2%)
Trastuzumab emtansine completion/early discontinuation	0	164 (25.6%)
Follow-up Month 6	126 (20.6%)	148 (23.1%)
Follow-up Month 12	107 (17.5%)	129 (20.2%)

*n=number of patients with baseline and at least one post-baseline assessment in the respective subscale.
Clinically meaningful increase in symptoms is defined as an increase in score (deterioration) of 11 points in Nausea and vomiting, Pain, Dyspnoea; increase of 9 points in Insomnia; increase of 14 points in Appetite loss; increase of 15 points in Diarrhoea, Constipation; increase of 10 points in Fatigue, Systemic therapy side effects, Hair loss.

Table 31: Summary of Clinically Meaningful Deterioration in Certain QLQ-C30 and QLQ-BR23 Subscales (ITT Population) - Study KATHERINE

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)	p-value (Chi-square)[d]
Patients with a valid baseline and valid post baseline assessment	612	640	
EORTC QLQ–C30	No. patients with a clinically meaningful deterioration (%)[c]		
Global health status/QoL	255 (41.7%)	290 (45.3%)	0.1934
Function subscales			
Cognitive	346 (56.5%)	386 (60.3%)	0.1753
Physical	206 (33.7%)	247 (38.6%)	0.0694
Role	253 (41.3%)	315 (49.2%)	0.0051
EORTC QLQ-C30	No. patients with a clinically meaningful increase (%)[c]		
Symptom subscales			
Appetite loss	169 (27.6%)	244 (38.1%)	<0.0001
Constipation	233 (38.1%)	300 (46.9%)	0.0016
Diarrhea	166 (27.1%)	139 (21.7%)	0.0259
Dyspnea	249 (40.7%)	286 (44.7%)	0.1525
Fatigue	370 (60.5%)	423 (66.1%)	0.0386
Nausea/Vomiting	181 (29.6%)	247 (38.6%)	0.0008
Insomnia	297 (48.5%)	313 (48.9%)	0.8939
Pain	327 (53.4%)	372 (58.1%)	0.0946
EORTC QLQ-BR23	No. patients with a clinically meaningful increase (%)[c]		
Symptom subscales			
Any hair loss[a]	15 (34.1%)	12 (27.9%)	0.5331
Systemic therapy side effects[b]	217 (35.6%)	310 (48.6%)	<0.0001

Ancillary analyses

Sensitivity analyses

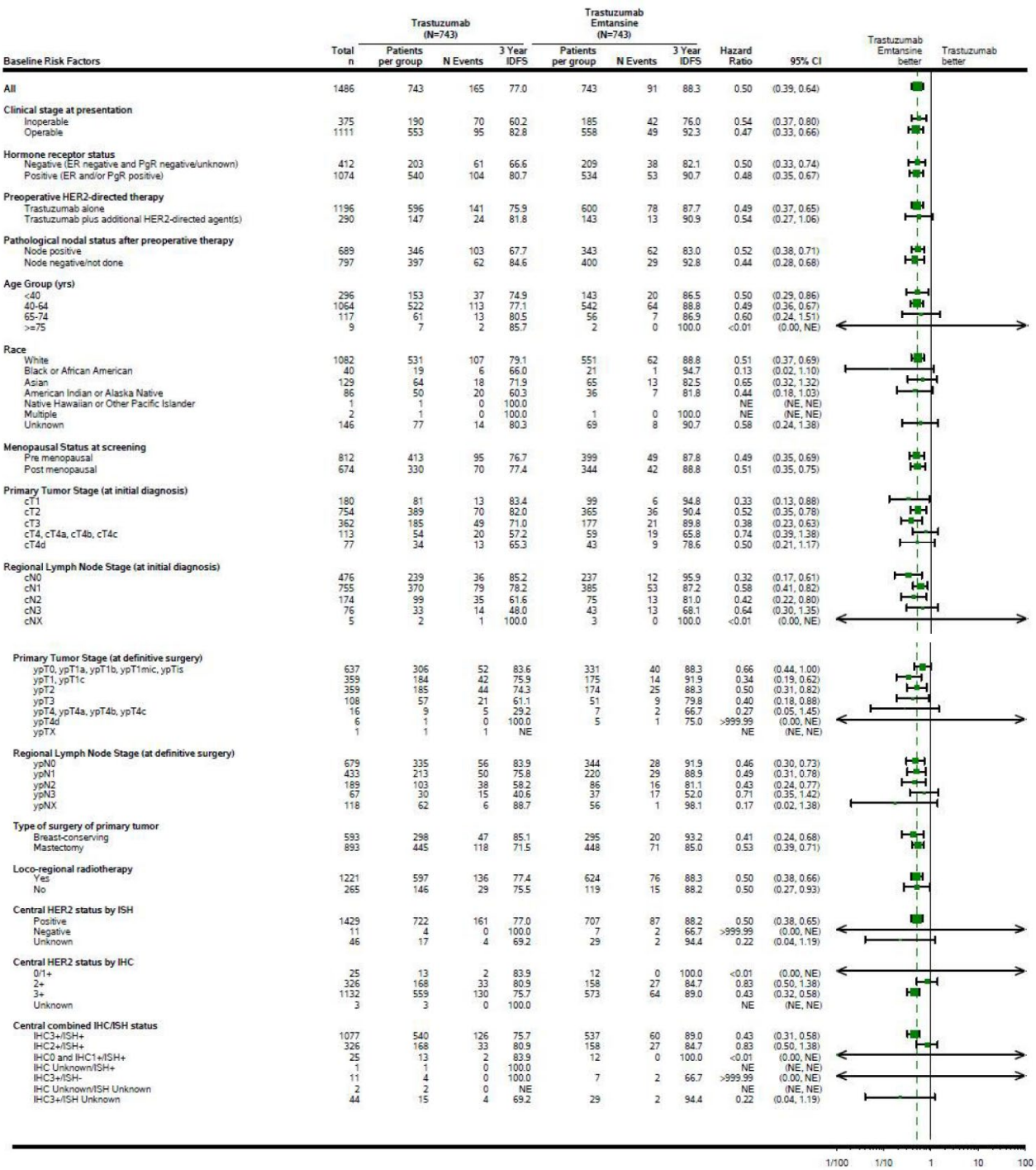
Table 32: Overview of Sensitivity Analysis Results for IDFS (ITT Population) - Study KATHERINE

Analysis	3-year IDFS event-free rates (95% CI)		HR for IDFS	95% CI
	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)		
Assessment of Robustness				
Censoring for new anti-cancer Therapy	77.4% (74.2, 80.7)	88.1% (85.5, 90.7)	0.51	0.39, 0.66
Censoring for Discontinuation of Study Treatment	81.6% (78.3, 84.8)	90.2% (87.6, 92.8)	0.54	0.39, 0.74

Source: t_ef_tte_nact_IT, t_ef_tte_disc_IT

Subgroup analyses

IDFS Forest Plot by Subgroups, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018



Baseline Risk Factors	Total n	Trastuzumab (N=743) Patients per group	N Events	3 Year IDFS	Trastuzumab Emtansine (N=743) Patients per group	N Events	3 Year IDFS	Hazard Ratio	95% CI
All	1486	743	165	77.0	743	91	88.3	0.50	(0.39, 0.64)
Clinical stage at presentation									
Inoperable	375	190	70	60.2	185	42	76.0	0.54	(0.37, 0.80)
Operable	1111	553	95	82.8	558	49	92.3	0.47	(0.33, 0.66)
Hormone receptor status									
Negative (ER negative and PgR negative/unknown)	412	203	61	66.6	209	38	82.1	0.50	(0.33, 0.74)
Positive (ER and/or PgR positive)	1074	540	104	80.7	534	53	90.7	0.48	(0.35, 0.67)
Preoperative HER2-directed therapy									
Trastuzumab alone	1196	596	141	75.9	600	78	87.7	0.49	(0.37, 0.65)
Trastuzumab plus additional HER2-directed agent(s)	290	147	24	81.8	143	13	90.9	0.54	(0.27, 1.06)
Pathological nodal status after preoperative therapy									
Node positive	689	346	103	67.7	343	62	83.0	0.52	(0.38, 0.71)
Node negative/not done	797	397	62	84.6	400	29	92.8	0.44	(0.28, 0.68)
Age Group (yrs)									
<40	296	153	37	74.9	143	20	86.5	0.50	(0.29, 0.86)
40-64	1064	522	113	77.1	542	64	88.8	0.49	(0.36, 0.67)
65-74	117	61	13	80.5	56	7	86.9	0.60	(0.24, 1.51)
>=75	9	7	2	85.7	2	0	100.0	<0.01	(0.00, NE)
Race									
White	1082	531	107	79.1	551	62	88.8	0.51	(0.37, 0.69)
Black or African American	40	19	6	66.0	21	1	94.7	0.13	(0.02, 1.10)
Asian	129	64	18	71.9	65	13	82.5	0.65	(0.32, 1.32)
American Indian or Alaska Native	86	50	20	60.3	36	7	81.8	0.44	(0.18, 1.03)
Native Hawaiian or Other Pacific Islander	1	1	0	100.0				NE	(NE, NE)
Multiple	2	1	0	100.0	1	0	100.0	NE	(NE, NE)
Unknown	146	77	14	80.3	69	8	90.7	0.58	(0.24, 1.38)
Menopausal Status at screening									
Pre menopausal	812	413	95	76.7	399	49	87.8	0.49	(0.35, 0.69)
Post menopausal	674	330	70	77.4	344	42	88.8	0.51	(0.35, 0.75)
Primary Tumor Stage (at initial diagnosis)									
cT1	180	81	13	83.4	99	6	94.8	0.33	(0.13, 0.88)
cT2	754	389	70	82.0	365	36	90.4	0.52	(0.35, 0.78)
cT3	362	185	49	71.0	177	21	89.8	0.38	(0.23, 0.63)
cT4, cT4a, cT4b, cT4c	113	54	20	57.2	59	19	65.8	0.74	(0.39, 1.38)
cT4d	77	34	13	65.3	43	9	78.6	0.50	(0.21, 1.17)
Regional Lymph Node Stage (at initial diagnosis)									
cN0	476	239	36	85.2	237	12	95.9	0.32	(0.17, 0.61)
cN1	755	370	79	78.2	385	53	87.2	0.58	(0.41, 0.82)
cN2	174	99	35	61.6	75	13	81.0	0.42	(0.22, 0.80)
cN3	76	33	14	48.0	43	13	68.1	0.64	(0.30, 1.35)
cNX	5	2	1	100.0	3	0	100.0	<0.01	(0.00, NE)
Primary Tumor Stage (at definitive surgery)									
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	306	52	83.6	331	40	88.3	0.66	(0.44, 1.00)
ypT1, ypT1c	359	184	42	75.9	175	14	91.9	0.34	(0.19, 0.62)
ypT2	359	185	44	74.3	174	25	88.3	0.50	(0.31, 0.82)
ypT3	108	57	21	61.1	51	9	79.8	0.40	(0.18, 0.88)
ypT4, ypT4a, ypT4b, ypT4c	16	9	5	29.2	7	2	66.7	0.27	(0.05, 1.45)
ypT4d	6	1	0	100.0	5	1	75.0	>999.99	(0.00, NE)
ypTX	1	1	1	NE				NE	(NE, NE)
Regional Lymph Node Stage (at definitive surgery)									
ypN0	679	335	56	83.9	344	28	91.9	0.46	(0.30, 0.73)
ypN1	433	213	50	75.8	220	29	88.9	0.49	(0.31, 0.78)
ypN2	189	103	38	58.2	86	16	81.1	0.43	(0.24, 0.77)
ypN3	67	30	15	40.6	37	17	52.0	0.71	(0.35, 1.42)
ypNX	118	62	6	88.7	56	1	98.1	0.17	(0.02, 1.38)
Type of surgery of primary tumor									
Breast-conserving	593	298	47	85.1	295	20	93.2	0.41	(0.24, 0.68)
Mastectomy	893	445	118	71.5	448	71	85.0	0.53	(0.39, 0.71)
Loco-regional radiotherapy									
Yes	1221	597	136	77.4	624	76	88.3	0.50	(0.38, 0.66)
No	265	146	29	75.5	119	15	88.2	0.50	(0.27, 0.93)
Central HER2 status by ISH									
Positive	1429	722	161	77.0	707	87	88.2	0.50	(0.38, 0.65)
Negative	11	4	0	100.0	7	2	66.7	>999.99	(0.00, NE)
Unknown	46	17	4	69.2	29	2	94.4	0.22	(0.04, 1.19)
Central HER2 status by IHC									
0/1+	25	13	2	83.9	12	0	100.0	<0.01	(0.00, NE)
2+	326	168	33	80.9	158	27	84.7	0.83	(0.50, 1.38)
3+	1132	559	130	75.7	573	64	89.0	0.43	(0.32, 0.58)
Unknown	3	3	0	100.0				NE	(NE, NE)
Central combined IHC/ISH status									
IHC3+/ISH+	1077	540	126	75.7	537	60	89.0	0.43	(0.31, 0.58)
IHC2+/ISH+	326	168	33	80.9	158	27	84.7	0.83	(0.50, 1.38)
IHC0 and IHC1+/ISH+	25	13	2	83.9	12	0	100.0	<0.01	(0.00, NE)
IHC Unknown/ISH+	1	1	0	100.0				NE	(NE, NE)
IHC3+/ISH-	11	4	0	100.0	7	2	66.7	>999.99	(0.00, NE)
IHC Unknown/ISH Unknown	2	2	0	NE				NE	(NE, NE)
IHC3+/ISH Unknown	44	15	4	69.2	29	2	94.4	0.22	(0.04, 1.19)

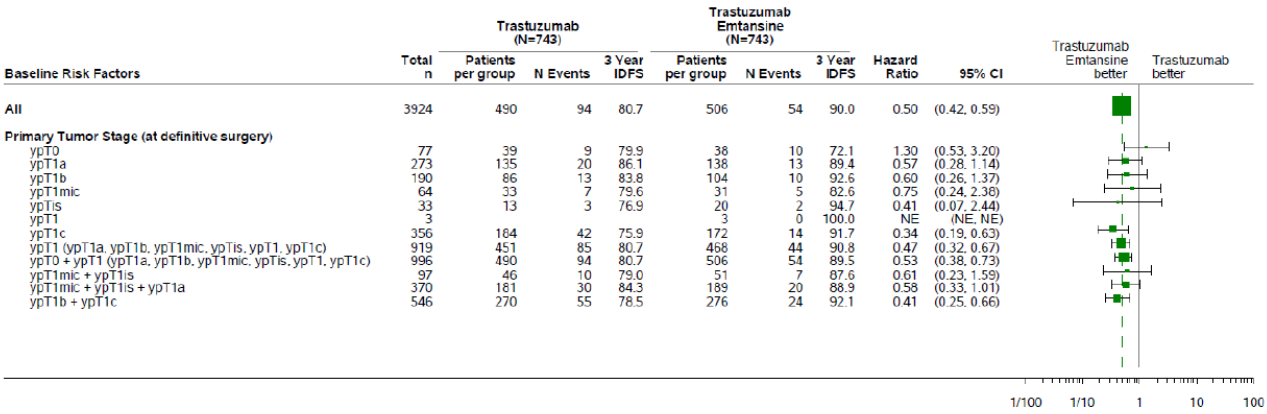
3 year KM represents the Kaplan-Meier estimate for IDFS at 3 years. Hazard ratio represents the hazard for patients randomized to trastuzumab emtansine vs. patients randomized to trastuzumab.

Note: Staging at initial diagnosis refers to clinical staging, staging at definitive surgery refers to pathologic staging.
Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/g_ef_fp.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/g_ef_fp_IDFS_IT.pdf 23NOV2018 17:19

Figure 8: IDFS Forest Plot by Subgroups, Randomized Patient Population - Study KATHERINE

Forest plot focusing on small primary tumours and multiples sub-categorisation

IDFS Forest Plot by Primary Tumor Stage, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

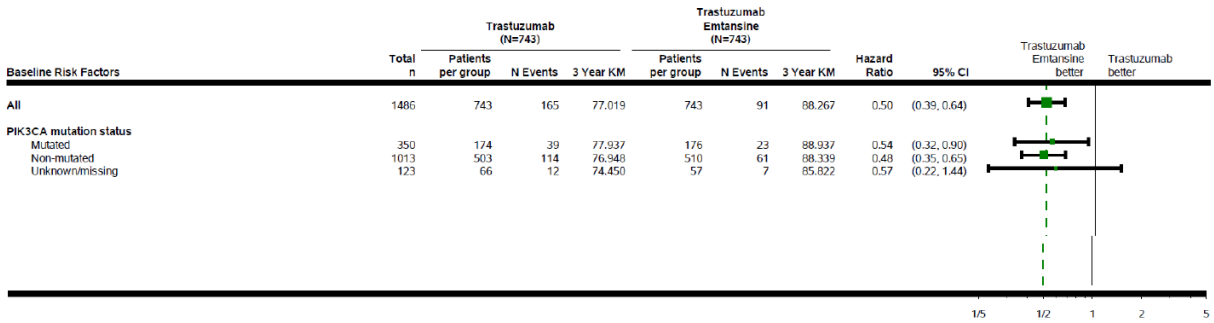


Baseline Risk Factors	Total n	Trastuzumab (N=743) Patients per group	N Events	3 Year IDFS	Trastuzumab Emtansine (N=743) Patients per group	N Events	3 Year IDFS	Hazard Ratio	95% CI
All	3924	490	94	80.7	506	54	90.0	0.50	(0.42, 0.59)
Primary Tumor Stage (at definitive surgery)									
ypT0	77	39	9	79.9	38	10	72.1	1.30	(0.53, 3.20)
ypT1a	273	135	20	86.1	138	13	89.4	0.57	(0.28, 1.14)
ypT1b	190	86	13	83.8	104	10	92.6	0.60	(0.26, 1.37)
ypT1mic	64	33	7	79.6	31	5	82.6	0.75	(0.24, 2.36)
ypTis	33	13	3	76.9	20	2	94.7	0.41	(0.07, 2.44)
ypT1	3				3	0	100.0	NE	(NE, NE)
ypT1c	356	184	42	75.9	172	14	91.7	0.34	(0.19, 0.63)
ypT1 (ypT1a, ypT1b, ypT1mic, ypTis, ypT1, ypT1c)	919	451	85	80.7	468	44	90.8	0.47	(0.32, 0.67)
ypT0 + ypT1 (ypT1a, ypT1b, ypT1mic, ypTis, ypT1, ypT1c)	996	490	94	80.7	506	54	89.5	0.53	(0.38, 0.73)
ypT1mic + ypT1is	97	46	10	79.0	51	7	87.6	0.61	(0.23, 1.59)
ypT1mic + ypT1is + ypT1a	370	181	30	84.3	189	20	88.9	0.58	(0.33, 1.01)
ypT1b + ypT1c	546	270	55	78.5	276	24	92.1	0.41	(0.25, 0.66)

Staging at definitive surgery refers to pathologic staging.The total n appears higher due to patients counted in multiple tumor stage categories.
Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/program/PR5652_g_ef_fp.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/output/PR5652_g_ef_fp_IDFS_IT.pdf 19JUN2019 8:09

Figure 9: IDFS Forest Plot by primary tumor stage, Randomization Patient Population - Study KATHERINE

IDFS Forest Plot by PIK3CA mutation status, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

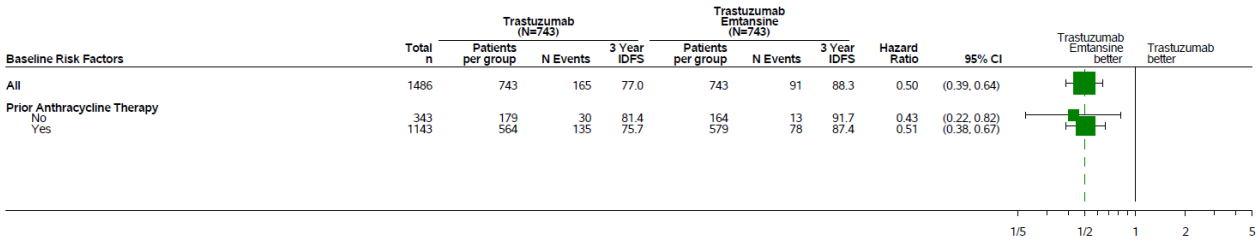


Baseline Risk Factors	Total n	Trastuzumab (N=743) Patients per group	N Events	3 Year KM	Trastuzumab Emtansine (N=743) Patients per group	N Events	3 Year KM	Hazard Ratio	95% CI
All	1486	743	165	77.019	743	91	88.267	0.50	(0.39, 0.64)
PIK3CA mutation status									
Mutated	350	174	39	77.937	176	23	88.937	0.54	(0.32, 0.90)
Non-mutated	1013	503	114	76.948	510	61	88.339	0.48	(0.35, 0.65)
Unknown/missing	123	66	12	74.450	57	7	85.822	0.57	(0.22, 1.44)

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/g_ef_fp_biom3.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/g_ef_fp_biom3_IDFS_IT.pdf 07DEC2018 17:40

Figure 10: IDFS Forest Plot by PIK3CA mutation status, Randomization Patient Population - Study KATHERINE

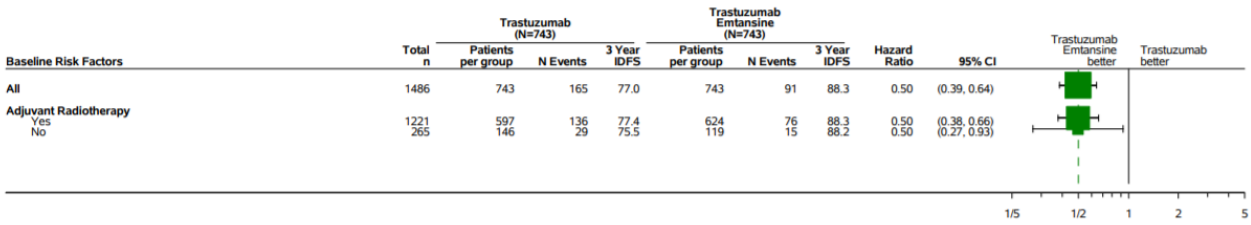
IDFS Forest Plot by Subgroups, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018



3 year KM represents the Kaplan-Meier estimate for IDFS at 3 years. Hazard ratio represents the hazard for patients randomized to trastuzumab emtansine vs. patients randomized to trastuzumab.
Note: Staging at initial diagnosis refers to clinical staging, staging at definitive surgery refers to pathologic staging.
Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/g_ef_fp3.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/g_ef_fp3_IDFS_IT_NonCSR.pdf 15NOV2018 17:47

Figure 11: IDFS Forest Plot by prior anthracycline therapy, Randomization Patient Population - Study KATHERINE

Forest plot of Time to First IDFS Event (Months) for adjuvant radiotherapy (yes vs no), Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018



3 year KM represents the Kaplan-Meier estimate for IDFS at 3 years.
Hazard ratio represents the hazard for patients randomized to trastuzumab emtansine vs. patients randomized to trastuzumab.
Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/program/PR5198_g_ef_fp.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM_ADHOCS/prod/output/PR5198_g_ef_fp_IDFS_IT.pdf 06MAY2019 15:01

Figure 12: IDFS Forest Plot by adjuvant radiotherapy, Randomization Patient Population - Study KATHERINE

Concomitant therapies

Table 33: Summary of anti-estrogens and aromatase inhibitors therapy by treatment regimen, Safety - Study KATHERINE

Summary of Anti-Estrogens and Aromatase Inhibitors Therapy By Treatment Regimen:, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one treatment	512 (71.1%)	525 (70.9%)
Overall total number of treatments	652	633
ANTI-ESTROGENS		
Total number of patients with at least one treatment	322 (44.7%)	347 (46.9%)
Total number of treatments	348	361
TAMOXIFEN	321 (44.6%)	345 (46.6%)
FULVESTRANT	4 (0.6%)	2 (0.3%)
TOREMIFENE CITRATE	1 (0.1%)	1 (0.1%)
AROMATASE INHIBITORS		
Total number of patients with at least one treatment	261 (36.3%)	235 (31.8%)
Total number of treatments	304	272
LETROZOLE	158 (21.9%)	125 (16.9%)
ANASTROZOLE	100 (13.9%)	95 (12.8%)
EXEMESTANE	41 (5.7%)	42 (5.7%)

Multiple uses of a specific medication for a patient were counted once in the frequency for the medication. Likewise, multiple uses within a specific medication class for a patient were counted once in the frequency for the medication class.Includes medications recorded on the 'Adjuvant hormone therapy' eCRF page.
All patients received these agents in the adjuvant setting with the following exceptions:
Tamoxifen: 2 patients trastuzumab arm and , T-DM1 arm); Fulvestrant: all patients;
Letrozole: (and , both in the trastuzumab arm); Exemestane (T-DM1 arm).
Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_dm_horm2.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_dm_horm2_SE.out
14NOV2018 10:11 Page 1 of 1

Table 34: Summary of adjuvant radiotherapy by treatment regimen - Study KATHERINE

Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with adjuvant radiotherapy	590 (81.9%)	623 (84.2%)
Site		
n	590	623
R Chest Wall	149 (20.7%)	147 (19.9%)
L Chest Wall	151 (21.0%)	152 (20.5%)
R breast	141 (19.6%)	172 (23.2%)
L breast	164 (22.8%)	169 (22.8%)
R axilla/Super Clavicular	162 (22.5%)	150 (20.3%)
L axilla/Super Clavicular	177 (24.6%)	165 (22.3%)
Internal Mammary	56 (7.8%)	61 (8.2%)
Tumor Bed	123 (17.1%)	122 (16.5%)
Other	89 (12.4%)	92 (12.4%)

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_adjrad.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_adjrad_SE.out
13NOV2018 15:24 Page 1 of 1

Follow-up treatments

Table 35: Follow-up Medications by Treatment Regimen, Safety Evaluable Patients - Study KATHERINE

Follow-up Medications by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Class Standardized Medication Name	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one treatment	131 (18.2%)	72 (9.7%)
Overall total number of treatments	442	177
5-HT3 ANTAGONISTS		
Total number of patients with at least one treatment	0	1 (0.1%)
Total number of treatments	0	1
ONDANSETRON	0	1 (0.1%)
ALKYLATING AGENTS		
Total number of patients with at least one treatment	7 (1.0%)	2 (0.3%)
Total number of treatments	7	2
CYCLOPHOSPHAMIDE	6 (0.8%)	2 (0.3%)
TEMOZOLOMIDE	1 (0.1%)	0
ANGIOGENESIS INHIBITORS		
Total number of patients with at least one treatment	1 (0.1%)	1 (0.1%)
Total number of treatments	1	1
BEVACIZUMAB	1 (0.1%)	1 (0.1%)
ANTI-ESTROGENS		
Total number of patients with at least one treatment	1 (0.1%)	0
Total number of treatments	1	0
FULVESTRANT	1 (0.1%)	0
ANTICONVULSANTS		
Total number of patients with at least one treatment	0	1 (0.1%)
Total number of treatments	0	1
LEVETIRACETAM	0	1 (0.1%)
ANTIFUNGAL AGENTS		
Total number of patients with at least one treatment	0	1 (0.1%)
Total number of treatments	0	1
NYSTATIN	0	1 (0.1%)
ANTIMETABOLITES		
Total number of patients with at least one treatment	38 (5.3%)	27 (3.6%)
Total number of treatments	56	31
CAPECITABINE	35 (4.9%)	24 (3.2%)
GEMCITABINE	9 (1.3%)	3 (0.4%)
METHOTREXATE	4 (0.6%)	2 (0.3%)
FLUOROURACIL	3 (0.4%)	2 (0.3%)
GEMCITABINE HYDROCHLORIDE	2 (0.3%)	0
ANTINEOPLASTIC AGENTS		
Total number of patients with at least one treatment	12 (1.7%)	9 (1.2%)
Total number of treatments	18	10
PALBOCICLIB	5 (0.7%)	3 (0.4%)
ERIBULIN	5 (0.7%)	2 (0.3%)
ABEMACICLIB	1 (0.1%)	1 (0.1%)
ALPELISIB	1 (0.1%)	0
ANTINEOPLASTIC AGENT NOS	0	1 (0.1%)
BLINDED ARRY-380	1 (0.1%)	0
CAPECITABINE/PERTUZUMAB/TRASTUZUMAB	1 (0.1%)	0
EVEROLIMUS/EXEMESTANE	0	1 (0.1%)
GOSERELIN/LETROZOLE	0	1 (0.1%)
IXABEPILONE	1 (0.1%)	0
LENVATINIB	1 (0.1%)	0
MM-302	1 (0.1%)	0
TRASTUZUMAB/VINORELBINE	0	1 (0.1%)
ANTIPSYCHOTIC AND ANTIMANIC AGENTS		
Total number of patients with at least one treatment	0	1 (0.1%)
Total number of treatments	0	1
HALOPERIDOL	0	1 (0.1%)
AROMATASE INHIBITORS		
Total number of patients with at least one treatment	3 (0.4%)	2 (0.3%)
Total number of treatments	4	2
ANASTROZOLE	2 (0.3%)	1 (0.1%)
LETROZOLE	1 (0.1%)	1 (0.1%)
EXEMESTANE	1 (0.1%)	0
BENZODIAZEPINES		
Total number of patients with at least one treatment	1 (0.1%)	0
Total number of treatments	1	0
CLONAZEPAM	1 (0.1%)	0
BISPHOSPHONATES		
Total number of patients with at least one treatment	13 (1.8%)	11 (1.5%)
Total number of treatments	13	11
ZOLEDRONIC ACID	12 (1.7%)	7 (0.9%)
IBANDRONIC ACID	0	3 (0.4%)
ALENDRONIC ACID	1 (0.1%)	1 (0.1%)
BONE MODULATING AGENTS		
Total number of patients with at least one treatment	2 (0.3%)	0
Total number of treatments	2	0
ALENDRONIC ACID/COLECALCIFEROL	2 (0.3%)	0
CALCIUM COMPOUNDS AND REGULATORS		
Total number of patients with at least one treatment	0	1 (0.1%)
Total number of treatments	0	1
CALCIUM CARBONATE/COLECALCIFEROL	0	1 (0.1%)

CORTICOSTEROIDS		
Total number of patients with at least one treatment	5 (0.7%)	2 (0.3%)
Total number of treatments	5	2
DEXAMETHASONE	4 (0.6%)	2 (0.3%)
PREDNISOLONE	1 (0.1%)	0
CYTOTOXIC ANTIBIOTICS		
Total number of patients with at least one treatment	6 (0.8%)	1 (0.1%)
Total number of treatments	7	1
DOXORUBICIN	3 (0.4%)	1 (0.1%)
BLEOMYCIN	1 (0.1%)	0
EPIRUBICIN	1 (0.1%)	0
MITOMYCIN	1 (0.1%)	0
MITOXANTRONE	1 (0.1%)	0
GONADOTROPIN AND ANALOGUES		
Total number of patients with at least one treatment	1 (0.1%)	0
Total number of treatments	1	0
GOSERELIN	1 (0.1%)	0
IMMUNOSUPPRESSANTS		
Total number of patients with at least one treatment	1 (0.1%)	0
Total number of treatments	1	0
EVEROLIMUS	1 (0.1%)	0
MONOCLONAL ANTIBODIES		
Total number of patients with at least one treatment	99 (13.8%)	41 (5.5%)
Total number of treatments	190	60
TRASTUZUMAB	83 (11.5%)	35 (4.7%)
PERTUZUMAB	48 (6.7%)	11 (1.5%)
TRASTUZUMAB EMTANSINE	33 (4.6%)	4 (0.5%)
DENOSUMAB	8 (1.1%)	7 (0.9%)
MARGETUXIMAB	1 (0.1%)	0
TRASTUZUMAB DERUXTECAN	0	1 (0.1%)
NON-STEROIDAL ANTI-INFLAMMATORIES		
Total number of patients with at least one treatment	2 (0.3%)	0
Total number of treatments	2	0
DIPYRONE	1 (0.1%)	0
ESOMEPRAZOLE/NAPROXEN	1 (0.1%)	0
OPIOID ANALGESICS		
Total number of patients with at least one treatment	0	1 (0.1%)
Total number of treatments	0	1
CODEINE	0	1 (0.1%)
OSMOTIC DIURETICS		
Total number of patients with at least one treatment	0	1 (0.1%)
Total number of treatments	0	1
MANNITOL	0	1 (0.1%)
PHARMACOTHERAPEUTIC CLASS NOT KNOWN		
Total number of patients with at least one treatment	0	1 (0.1%)
Total number of treatments	0	1
INVESTIGATIONAL DRUG NOS	0	1 (0.1%)
PLATINUM COMPOUNDS		
Total number of patients with at least one treatment	13 (1.8%)	3 (0.4%)
Total number of treatments	14	3
CARBOPLATIN	10 (1.4%)	2 (0.3%)
CISPLATIN	3 (0.4%)	1 (0.1%)
SURGICAL & MEDICAL PROCEDURES		
Total number of patients with at least one treatment	3 (0.4%)	3 (0.4%)
Total number of treatments	4	4
RADIOTHERAPY	1 (0.1%)	2 (0.3%)
ELECTROCHEMOTHERAPY	1 (0.1%)	0
RADIOTHERAPY TO BONE	1 (0.1%)	0
RADIOTHERAPY TO BRAIN	0	1 (0.1%)
TAXANES		
Total number of patients with at least one treatment	71 (9.9%)	17 (2.3%)
Total number of treatments	77	17
PACLITAXEL	38 (5.3%)	9 (1.2%)
DOCETAXEL	34 (4.7%)	8 (1.1%)
NANOPARTICLE PACLITAXEL	2 (0.3%)	0
TYROSINE KINASE INHIBITORS		
Total number of patients with at least one treatment	24 (3.3%)	19 (2.6%)
Total number of treatments	24	20
LAPATINIB	20 (2.8%)	19 (2.6%)
NERATINIB	2 (0.3%)	0
LAPATINIB TOSILATE	1 (0.1%)	0
PAZOPANIB	1 (0.1%)	0
VINCA ALKALOIDS		
Total number of patients with at least one treatment	14 (1.9%)	5 (0.7%)
Total number of treatments	14	5
VINORELBINE	14 (1.9%)	5 (0.7%)

Multiple uses of a specific medication for a patient were counted once in the frequency for the medication. Likewise, multiple uses within a specific medication class for a patient were counted once in the frequency for the medication class.Includes medications recorded on the Follow-up medications eCRF page.

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_cm.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_cm_FUM_SE.out
23NOV2018 17:23 Page 4 of 4

Exploratory analyses

Immunogenicity – Anti-drug antibodies

Table 36: Baseline Prevalence and Post-Baseline Incidence of Anti-Drug Antibodies (ADAs) Safety Evaluable Patients - Study KATHERINE

Baseline Prevalence and Post-Baseline Incidence of Anti-Drug Antibodies (ADAs)
Safety Evaluable Patients
Protocol: BO27938

	Trastuzumab Emtansine (N=740)
Baseline Prevalence of ADAs	
Baseline evaluable patients	410
Patients with a positive sample at baseline	17 (4.1%)
Patients with no positive samples at baseline	393
Incidence of Treatment Emergent ADAs	
Post-baseline evaluable patients	401
Patients positive for Treatment Emergent ADA	15 (3.7%)
Treatment-induced ADA	14
Treatment-enhanced ADA	1
Patients negative for Treatment Emergent ADA	386
Treatment unaffected	15

Table 37: Baseline Prevalence and Post-Baseline Incidence of Anti-Drug RO0452317 Antibodies (ADAs), Safety Evaluable Patients - Study KATHERINE

Baseline Prevalence and Post-Baseline Incidence of Anti-Drug RO0452317 Antibodies (ADAs)
Safety Evaluable Patients
Protocol: BO27938

	Trastuzumab (N=720)
Baseline Prevalence of ADAs	
Baseline evaluable patients	386
Patients with a positive sample at baseline	11 (2.8%)
Patients with no positive samples at baseline	375
Incidence of Treatment Emergent ADAs	
Post-baseline evaluable patients	392
Patients positive for Treatment Emergent ADA	15 (3.8%)
Treatment-induced ADA	13
Treatment-enhanced ADA	2
Patients negative for Treatment Emergent ADA	377
Treatment unaffected	9

Table 38: Baseline Prevalence and Incidence of Neutralizing Antibodies (NAbs) to Serum RO5304020, Safety Evaluable Patients - Study KATHERINE

Baseline Prevalence and Incidence of Neutralizing Antibodies (NAbs) to Serum RO5304020
Safety Evaluable Patients
Protocol: BO27938

	Trastuzumab Emtansine (N=740)
Post-baseline evaluable patients for ADA	401
Patients positive for ADA	15
Patients positive for NAb	5
Patients negative for NAb	11

Table 39: IDFS by ADA Status - Study KATHERINE

IDFS by ADA Status, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	TDM1 ADA+ (N=15)			TDM1 ADA- (N=385)		
Subgroup	Patients per group	N Events	3 Year KM	Patients per group	N Events	3 Year KM
All	15	1	92.857	385	50	89.770

Table 40: IDFS by NAb status - Study KATHERINE

IDFS by NAB Status, Randomized Patient Population
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	TDM1 NAB+ (N=5)			TDM1 NAB- (N=10)		
Subgroup	Patients per group	N Events	3 Year KM	Patients per group	N Events	3 Year KM
All	5	0	100.000	10	1	88.889

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 41: Summary of Efficacy for trial KATHERINE

BO27938 (KATHERINE): A randomised, multicenter, open-label Phase III Study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor present pathologically in the breast or axillary lymph nodes following preoperative therapy.			
Study identifier	BO27938, NCT01772472		
Design	Phase III, multicentre, multinational, randomised, open-label, two-arm		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable, event-driven Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Trastuzumab		Trastuzumab 6 mg/Kg IV q3w for 14 cycles, n=743
	Kadcyla		Kadcyla 3.6 mg mg/Kg IV q3w for 14 cycles, n=743
Endpoints and definitions	Primary endpoint	IDFS	Invasive disease-free survival
	Secondary endpoint	IDFS-SPNBC	Invasive disease-free survival including second primary non-breast cancer
	Secondary endpoint	DFS	Disease-free survival
	Secondary endpoint	OS	Overall survival

	Secondary endpoint	DRFI	Distant recurrence-free interval
Database lock	25 July 2018		
Results and Analysis			
Analysis description	**Primary Analysis (Interim analysis results crossed the efficacy stopping boundary)**		
Analysis population and time point description	Intent to treat=1486, when 257 (67%) of the targeted 384 IDFS events had occurred		

	Treatment group	Trastuzumab	Kadcyla
	Number of subjects	743	743
	IDFS, patients with event (%)	165 (22.2%)	91 (12.2%)
	IDFS, 3-year event-free rate	77.02	88.27
	95% CI	73.78, 80.26	85.81, 90.7
	OS, patients with event (%)	56 (7.5%)	42 (5.7%)
	OS, 3-year event-free rate	93.59	95.18
	95% CI	91.71, 95.47	93.58, 96.79

Effect estimate per comparison	Time to first IDFS event	Comparison groups	Kadcyla vs. Trastuzumab
		Unstratified Hazard Ratio	0.50
		95% CI	0.39, 0.64
		P-value	<0.0001
	Overall survival	Comparison groups	Kadcyla vs. Trastuzumab
		Unstratified Hazard Ratio	0.70
		95% CI	0.47, 1.05
		P-value	0.0848

Notes	Due to stratum with <5 patients, unstratified analyses were done for all endpoints 3-year event-free rates derived from Kaplan-Meier estimates

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

KATHERINE is a phase III, two-arm, randomised, multicentre, open label trial comparing Kadcyla versus trastuzumab as adjuvant therapy in patients with HER2+ EBC who have received preoperative chemotherapy and trastuzumab (with or without other anti-HER2 agents such as pertuzumab) followed by surgery, with a finding of residual invasive disease in the breast or axillary lymph nodes. Achieving pCR following neoadjuvant therapy has been reported as being associated with significantly improved disease recurrence and survival, particularly for triple negative and HER2+ breast cancer patients (Spring et al. SABCS 2018; GS2-03). The defined population of the trial is supported.

Currently, most patients with HER2+ EBC are treated with neoadjuvant chemotherapy + trastuzumab +/- pertuzumab and after surgery, they complete one year (often 14 remaining cycles) of trastuzumab +/- pertuzumab. The decision to add pertuzumab in the neoadjuvant or adjuvant setting often rests on a situation of 'high risk of recurrence', which has a rather broad definition, but it often encompasses either lymph node-positive or hormone receptor-negative disease (ESMO guideline). To date, no studies had addressed the particular issue of 'high-risk' conferred by invasive residual disease in the breast and/or lymph nodes.

No new dose-response study was submitted which is considered acceptable. The dose used in study KATHERINE is the approved dose of Kadcyla is 3.6 mg/kg bodyweight administered as an intravenous

infusion every 3 weeks (21-day cycle). This dose showed favourable benefit-risk profiles when administered as monotherapy in advanced HER2+ BC across Phase II and III clinical studies (see EPAR Kadcyla).

The overall design of the trial is generally in line with the scientific advice that was given in 2011 and supported. The definitions of HER2 status, neoadjuvant chemotherapy + HER2-directed treatment, breast and lymph node surgery requirements and exclusion criteria are acceptable. However, the key inclusion criterion required *pathologic evidence of residual invasive carcinoma in the breast or lymph nodes after completion of neoadjuvant therapy,* entailing that patients with residual *in situ* disease (e.g. ypTis ypN0) were considered 'low-risk' and hence not allowed to participate. The indication wording has been revised accordingly.

Although, the adjuvant scene for HER2+ EBC patients has considerably changed in the last few years, the control arm (trastuzumab at the approved dose every 3 weeks for 14 cycles) was deemed appropriate at the time when the study was designed. Permitting patients who discontinued Kadcyla because of toxicity issues to complete treatment with trastuzumab is endorsed.

The primary efficacy endpoint of the trial, invasive disease free survival (IDFS) is acceptable for the intended adjuvant setting of EBC. It implies the decreased likelihood of local or distant relapse and has been used in the past to define benefit in the adjuvant setting of EBC. According to the study protocol, the definition of IDFS does not follow the standardized definitions for breast cancer clinical trial endpoints in the adjuvant setting from the STEEP system (Hudis et al, JCO 2007). However, the possible occurrence of second primary non-breast cancer events was assessed both as a secondary endpoint and as a sensitivity analysis for the primary endpoint. The remaining exploratory, PRO, safety and secondary efficacy endpoints are considered acceptable.

According to the SAP, a testing hierarchy was used to control the overall type I error, and OS would only be tested if IDFS were statistically significant. The MAH clarified that the formal hierarchical testing of endpoints refers to IDFS and OS. IDFS including second primary non-breast cancer, DFS, and DRFI were also secondary endpoints, but they were not analysed under a testing hierarchy and therefore did not have allocated alpha spending.

The planning of the interim analysis is adequate. The type I error control for multiple looks for IDFS and OS using the Lan-DeMets alpha spending function with an O'Brien-Fleming stopping boundary is acceptable.

The sample size (~1484 subjects) was primarily driven by the analysis of IDFS. The study had approximately 80% power to detect a HR of 0.75 in IDFS by observing 384 IDFS events. This is considered adequate. However, the study only has 56% power to detect a HR of 0.80 in OS after 10 years of follow-up from the date of randomization of the first patient. It is acknowledged that a study adequately powered to show differences in OS may not have been feasible. To assess whether the current sample size is sufficient to detect an overall detrimental OS effect, various OS HR scenarios were examined. The different scenarios indicate that a detrimental effect in OS could be detected with the current sample size. The Applicant also presented an updated 5-years OS rate: 88.1% (95%CI: 85.1%, 91.1%) in the trastuzumab arm and 91.1% (95%CI: 88.5%, 93.7%) in the Kadcyla arm, which supports the positive trend in OS observed in the primary analysis.

The permuted block randomisation method is endorsed and the stratification factors used are all clinically relevant and hence acceptable. However, it is noticed that around 24% of patients where incorrectly classified in the IxRS system. Nevertheless, the sensitivity analysis on IDFS using the eCRF stratification factors (instead of IxRS) was consistent with the primary analysis (data not shown).

The study was open-label but given the significantly different toxicity profile between both drugs, the arguments for not performing a double-blind study were accepted by the CHMP at the time of study planning.

With regards to statistical methods, the use of the Cox model and the Kaplan-Meier approach to analyse the time to event endpoints is agreed. The fact that unstratified log-rank test was performed as part of the primary analysis because the smallest stratum had less than five patients is understood. However, the stratification factors were chosen by the Applicant for a reason and if any stratum had a different HR, this would not be observed in the current analysis. In this regard, it is reassuring that departures for the proportional hazards assumption are not observed in the survival curves.

Regarding the censoring rules for IDFS, data for those patients who do not experience an event were censored at the date they are last known to be alive and event-free. Data for patients who are randomized without any post-baseline assessments were censored at the date of randomization plus 1 day. All patients must be followed for approximately 10 years, regardless of treatment discontinuation. Several sensitivity analyses for IDFS where the censoring rules were modified were performed (data not shown). The results of the sensitivity analyses were concordant with those presented for the primary analysis, indicating that changes in the censoring rules are negligible on the results.

The censoring rules for OS are endorsed. The MAH also clarified the censoring rules for the secondary endpoints and performed several sensitivity analyses for OS and DRFI to assess the impact of the censoring rules (data not shown). The results of the sensitivity analyses were consistent with those presented for the primary analysis, indicating that changes in the censoring rules were negligible on the results. No sensitivity analyses were presented for other secondary endpoints since there were only 12 patients with a different result between IDFS, IDFS including second primary non-breast cancer and DFS.

1486 out of 1925 screened patients were enrolled into the study. The screen failure rate (23%) is acceptable and suggests that the recruited patients represent the target population. The reasons for screen failure were disclosed and considered pertinent. In the light of an open-label trial, the unbalance in the number of patients who were randomised but then did not receive treatment (23 patients in the trastuzumab arm and 4 patients in the Kadcyla arm) is important. However the numbers are considered too small to have a relevant impact on the results. The planned 14 cycles of therapy were received by 79% of patients in the trastuzumab arm versus 71% in the Kadcyla arm. This difference is likely driven by the significant amount of patients withdrawn from treatment because of AEs: 133 (18%) in the Kadcyla arm vs. 15 (2%) in the trastuzumab arm. As permitted by protocol, 71 out of 212 patients who prematurely discontinued Kadcyla were switched to trastuzumab. Most of the switched-patients (61 out of 71, 86%) had discontinued Kadcyla because of AEs.

The overall distribution of baseline characteristics is balanced between both arms of the trial and corresponds to what is expected from HER2+ EBC.

Two thirds (996 out of 1486, 67%) of patients had 'small' post-neoadjuvant tumour sizes (ypT0, ypTis, ypTmic, ypT1a, ypT1b, ypT1c). All but two of the patients with ypN0 staging had residual invasive disease at primary tumour. These two patients did not fill the inclusion criteria and constitute a major protocol violation. The MAH has provided the numbers and proportions of the subcategories from 'small' post-neoadjuvant tumour sizes. Nearly half of the patients from the ITT were free of nodal disease (ypN0: 679/1486, 45.7%). However, most of those ypN0 patients were also in the subcategories with 'less' primary tumour. In fact, the proportion of ypN0 decreases as the ypT category increases: ypT1mic + ypN0: 41/64, 64.1%, ypT1a + ypN0: 169/273, 61.9%, ypT1b + ypN0: 121/190, 63.4%, ypT1c + ypN0: 184/356, 51.7%, ypT2 + ypN0: 127/359, 35.4%, ypT3 + ypN0: 29/108, 26.9%, ypT4 + ypN0: 1/21, 4.8%.

The details of the treatment the patients have received before the HER2-directed adjuvant scheme (neoadjuvant chemotherapy + HER2-directed treatment, type of surgery, response after neoadjuvant treatment, concomitant hormone therapy, adjuvant radiotherapy, etc.) were also well balanced between arms. Only 272 patients (18.3%) from the ITT population of the KATHERINE study received trastuzumab + pertuzumab + chemotherapy as neoadjuvant treatment. Although such combination was not approved at

the time, it currently constitutes the preferred regimen for patients with HER2+ EBC that are to receive neoadjuvant therapy.

The wording of the indication has also been amended to clearly reflect the studied population, i.e. clarifying the fact that both taxanes and trastuzumab were part of the neoadjuvant scheme.

Acknowledging the participation of 5 male patients in the study and the targeted nature of the agent, extrapolation to male patients is supported.

The protocol amendments were acceptable and none of them are considered to influence directly the efficacy endpoints. There was a considerable imbalance of major protocol deviations between both arms (21% in the Kadcyla arm vs. 12.5% in the trastuzumab arm) driven by on-study protocol deviations (11.2% in the Kadcyla arm vs. 1.2% in the trastuzumab arm). Almost all the incidences (78 out of 83) regarding this issue concern "dose not reduced/held per protocol", which can be explained as dose reductions were only allowed in the Kadcyla arm.

Efficacy data and additional analyses

Median follow up for both arms (40.9 months in the trastuzumab arm and 41.4 months in the Kadcyla arm) is similar and reasonable for the targeted event rate estimated for IDFS interim analysis, which had been planned to take place when ~67% (approximately 257 out of 384) of IDFS events had occurred, with an established efficacy-stopping boundary of $p<0.0124$ or $HR<0.732$. Of note, 230 (31.0%) alive patients in the trastuzumab arm and 202 (27.2%) patients in the Kadcyla arm from the ITT population had $\leq$3 years of follow-up on study.

After 256 IDFS events at data cut-off 25 July 2018, the study has met its primary efficacy endpoint by achieving a statistically significant improvement in IDFS for Kadcyla (91 events, estimated 3-year event-free rate 88.3%) over trastuzumab (165 events, estimated 3-year event-free rate 77.0%), with an unstratified HR of 0.50 (95% CI 0.39, 0.64) and $p<0.0001$. Since results from this interim analysis have crossed the O'Brien-Fleming stopping boundary, they are now considered the primary analysis of IDFS and formal OS testing has been performed.

Data from the stratified analysis (HR 0.48, 95% CI 0.37, 0.62; $p<0.0001$) are not used because one of the strata had less than 5 patients. The Kaplan-Meier curves separate from the beginning and remain divergent for the duration of follow-up but a heavy degree of censoring is obvious as of approximately 27 months of follow-up. As expected, most of this censoring comes from patients who were event-free and in follow-up.

As expected, distant recurrence was the most frequent IDFS event in both arms (66.1% of cases in the trastuzumab arm and 82.4% in the Kadcyla arm). Although 43 out of all 91 recurring patients in the Kadcyla arm (47%) vs. 30 out of 165 in the trastuzumab arm (18%) presented CNS recurrence as the earliest contributing IDFS event, the total number of patients with CNS recurrence across follow up does not differ significantly between arms (45 in the Kadcyla arm and 40 in the trastuzumab arm). One possible explanation behind this difference of particular events along time is the competing risks hypothesis, by which Kadcyla would exhibit higher effectiveness at preventing recurrences outside of sanctuary sites (distant non-CNS, locoregional and/or contralateral).

Median time to CNS recurrences on the Kadcyla arm was 17.5 months, as compared to 11.9 months in the trastuzumab arm. Furthermore, median time to OS event in patients with CNS-recurrence does not differ significantly between arms: 14.3 months in trastuzumab (21 out of 40 patients) vs. 12.5 months in Kadcyla (26 out of 45 patients).

The MAH also performed a sensitivity analysis that assigns alive-patients with CNS recurrence as death events on the date of the recurrence (worst-case scenario)(data not shown), that is consistent with the first interim OS analysis.

The IDFS advantage from Kadcyla over trastuzumab is maintained across all the subgroups analysed, in particular those concerning the stratification factors. Nevertheless, the degree of benefit from Kadcyla vs. trastuzumab in patients with small tumours (ypTmic, ypT1a, ypT1b, ypT1c) without nodal disease or with little nodal disease (e.g. one or two positive lymph nodes) cannot be established due to the possible heterogeneity of patients, which leads to low numbers and non-interpretable results.
The "trastuzumab plus additional HER2-directed agents" subgroup included 290 patients, out of which 272 (94%) had received pertuzumab + trastuzumab + chemotherapy, the currently preferred neoadjuvant regimen for HER2+ EBC. It is unlikely that the HR of that subgroup analysis would be altered if the 18 patients who received anti-HER2 agents other than pertuzumab were excluded.

Censoring the patients who began a new anti-cancer therapy or those who discontinued study treatment for any reason, as means of sensitivity analyses, did not alter the results from the primary IDFS analysis.

Albeit not corrected for multiplicity, secondary endpoints that included other clinical situations as events (secondary non breast cancer for IDFS-SPNBC and DCIS for DFS) are in line with the clinical advantage from Kadcyla over trastuzumab.

At clinical cut-off, only 98 OS events (6.6%) had occurred compared to 150 deaths estimated to have occurred at the first interim OS analysis. The 95% confidence intervals of the 3-year OS event-free rate are overlapping: 95.18% (93.58, 96.79) for Kadcyla and 93.59% (91.71, 95.47) for trastuzumab. Although a trend for improved outcome from Kadcyla over trastuzumab is maintained (unstratified HR 0.70; 95% CI 0.47, 1.05; p=0.0848), immaturity of the data prevent a firm conclusion regarding a non-detrimental OS effect from Kadcyla. It is nonetheless reassuring that departures for the proportional hazards assumption are not observed in any of the Kaplan-Meier plots for the primary or secondary endpoints. In order to confirm a non-detrimental effect on OS from Kadcyla in the targeted population, the MAH will ensure adequate post-approval follow-up of OS data from patients from the KATHERINE trial. The MAH will provide the final analysis post-approval as an Annex II condition (see PI, Annex II).

Data on follow-up treatment were presented. More patients from the trastuzumab arm experienced a distant recurrence event (121 vs. 78 in the Kadcyla arm). Consequently, it was expected that more patients in this arm would receive follow-up systemic treatments (131 vs. 72 patients in the Kadcyla arm). Most patients in both arms went on to receive anti-HER2 antibodies [trastuzumab (63% and 49%, respectively), pertuzumab (36% and 15%, respectively) and Kadcyla (25% and 5%, respectively)], and other anti-HER2 drugs, such as lapatinib (15% and 26%, respectively).

The study included Patient-Reported Outcome analyses. Although the instruments (EORTC QLQ-C30 and QLQ-BR23 selected for evaluating PROs are considered appropriate for the target population and the completion rates are adequate, the clinical relevance of such data from an open-label study are limited. The MAH stated that mean scores of HRQoL, physical function and role function were comparable between arms *throughout the course of treatment.* Although the differences are slight, the proportion of patients who declared deterioration of functions (cognitive, physical and role) and global health status throughout the study was numerically higher in the Kadcyla arm. Moreover, when the percentage of patients with clinically meaningful deterioration is examined, differences clearly disfavor the Kadcyla arm in all subscales. When the number/percentage of patients with deterioration of specific symptoms is examined, appetite loss, fatigue, nausea/vomiting and systemic therapy side effects affect a considerably higher proportion of patients in the Kadcyla arm. This, in fact, corresponds to the striking differences seen in the incidence of chemotherapy-related symptoms (nausea, fatigue, dry mouth/stomatitis/dysgeusia, constipation, peripheral neuropathy and decreased appetite) (see safety section). Furthermore, results from a series of specific items from the QLQ-BR23 scale have not been interpreted by the MAH: breast symptoms, upset by hair loss, body image, future perspectives, sexual enjoyment and sexual functioning. Overall, the inclusion of the PROs results in the SmPC is not supported.

Exploratory analyses included immunogenicity assessment. With regards to ADAs, out of 720 patients included in the safety population of trastuzumab, only 386 were evaluable for ADAs to trastuzumab *at baseline*, with 11 positive results (2.8%). 392 patients had at least one *post-dose* sample available for ADA analysis, with 15 positive results. From these 15 patients, 13 (3.3%) were treatment-emergent (negative at baseline) and 2 were "treatment-enhanced" (positive at baseline, but with a ≥4-fold increase in titres).

Out of 740 patients included in the safety population of Kadcyla, 410 patients had *baseline* samples, with 17 patients who tested positive (4.1%). 401 patients gave at least one *post-dose sample* for ADA analysis, with 15 positive results (14 treatment-emergent and 1 treatment-enhanced). From these 15 patients, 5 tested positive for neutralising antibodies (NAbs) to Kadcyla. Only 1 IDFS event has occurred in the 15 patients from the Kadcyla arm with ADA+ status (and none in the 5 patients with NAbs), which does not allow for any conclusion regarding the impact of such antibodies in efficacy. The same is true for safety: only 1 patient who was ADA+ and NAb+ presented a SAE of hypersensitivity (Grade 3) (see discussion on clinical safety).

2.4.4. Conclusions on the clinical efficacy

Across subgroups and diverse time-to-relapse endpoints, the overall risk of recurrence in patients with HER2+ EBC and residual disease after neoadjuvant treatment and surgery is significantly reduced with adjuvant Kadcyla as compared to trastuzumab. This beneficial effect primarily concerns the risk of recurrence outside of sanctuary sites (distant non-CNS, locoregional and/or contralateral), since no differences between arms were seen for overall CNS-recurrence event rates. Given immature OS data, appropriate follow-up is ensured to confirm a non-detrimental effect on OS from Kadcyla in the targeted population.

The CHMP considers the following measures necessary to address issues related to efficacy:

PAES: In order to further investigate the efficacy of trastuzumab emtansine in the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy, the MAH should submit the final analysis of OS from the phase 3, randomised, open-label study KATHERINE (BO27938). Due date: 30 June 2024.

2.5. Clinical safety

Introduction

The safety of Kadcyla had been evaluated in 884 metastatic breast cancer patients in clinical studies before its approval in the EU. In this patient population:

- The most common adverse drug reactions (ADRs) (≥25%) with Kadcyla were haemorrhage (including epistaxis), increased transaminases, fatigue, musculoskeletal pain, and headache. The majority of ADRs reported were of Grade 1 or 2 severity.
- The most common serious ADRs were pyrexia, thrombocytopenia, vomiting, abdominal pain, nausea, constipation, diarrhoea, dyspnoea and pneumonitis.
- The most common National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or 4 ADRs (> 2%) were thrombocytopenia, fatigue, increased transaminases, anaemia, hypokalaemia, musculoskeletal pain and neutropenia.
- Thrombocytopenia, or decreased platelet counts, was commonly reported with Kadcyla and was the most common adverse reaction leading to treatment discontinuation.

- Cases of bleeding events with a fatal outcome have been observed. Severe cases of haemorrhagic events, including central nervous system haemorrhage, have been reported in clinical studies.

To support the proposed indication of Kadcyla for the adjuvant treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC) with residual invasive disease following completion of neoadjuvant therapy, safety data from the ongoing pivotal Phase III study KATHERINE (BO27938) and supplementary safety data from completed Phase II study TDM4874g/BO22857 have been provided (see Table 1).

Patient exposure

A total of 1460 patients who received at least one dose of study drug (Kadcyla or trastuzumab) were included in the safety analysis population (720 patients in the trastuzumab arm, 740 patients in the Kadcyla arm). At the CCoD of 25 July 2018, all patients had completed or discontinued treatment.

Table 42: Exposure to trastuzumab (safety evaluable patients) - Study KATHERINE

Exposure to Trastuzumab, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=720)
Total Treatment Duration (months)	
n	720
Median	10
Range	1 - 13
No. of cycles of Trastuzumab treatment	
n	720
Median	14
Range	1 - 14
Number (%) of patients completing at least a total of X cycles of Trastuzumab treatment:	
1 cycle	720 (100.0%)
4 cycles	683 (94.9%)
7 cycles	664 (92.2%)
11 cycles	618 (85.8%)
14 cycles	583 (81.0%)

Table 43: Exposure to Trastuzumab Emtansine (Safety Evaluable Patients) - Study KATHERINE

Exposure to Trastuzumab Emtansine, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab Emtansine (N=740)
Total Treatment Duration (months)	
n	740
Median	10
Range	1 - 12
No. of cycles of Trastuzumab Emtansine treatment	
n	740
Median	14
Range	1 - 14
Number of Cycles completed of any study treatment~ including switch therapy	
n	740
Median	14
Range	1 - 14
Number (%) of patients completing at least a total of X cycles of Trastuzumab Emtansine treatment:	
1 cycle	740 (100.0%)
4 cycles	677 (91.5%)
7 cycles	637 (86.1%)
11 cycles	579 (78.2%)
14 cycles	528 (71.4%)
Number (%) of patients completing at least a total of X cycles of all study treatment:	
1 cycle	740 (100.0%)
4 cycles	698 (94.3%)
7 cycles	673 (90.9%)
11 cycles	639 (86.4%)
14 cycles	593 (80.1%)

Number of patients who had at least one dose reduction*	
n	740
No dose reduction	634 (85.7%)
Dose reduction by one level (3.0 mg/kg)	77 (10.4%)
Dose reduction by 2 levels (2.4 mg/kg)	29 (3.9%)
Cycle of first dose reduction being	
Cycle 1	0
Cycle 2	9 (1.2%)
Cycle 3	11 (1.5%)
Cycle 4 to 7	35 (4.7%)
Cycle 8 to 11	34 (4.6%)
Cycle 12 to later	17 (2.3%)

*Patients were counted once at the lowest dose level received. Infusion modification is ticked "yes" if there was an interruption or a flow rate change during the infusion. ~ "All treatment" refers to any study treatment including the switch therapy

Table 44: Exposure to Trastuzumab (Switch Patients after Discontinuation from Trastuzumab Emtansine) - Study KATHERINE

Exposure to Trastuzumab : Switch Patients (after discontinuation from trastuzumab emtansine)
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=71)
After switch, trastuzumab treatment duration (months)	
n	71
Median	5
Range	1 - 10
After switch, Number (%) of patients completing at least a total of:	
1 cycle	71 (100.0%)
4 cycles	60 (84.5%)
7 cycles	38 (53.5%)
11 cycles	17 (23.9%)
14 cycles	0
Total number of cycles of either study treatment (trastuzumab emtansine + trastuzumab)	
1	0
2	0
3	0
4	0
5	0
6	0
7	1 (1.4%)
8	0
9	2 (2.8%)
10	1 (1.4%)
11	1 (1.4%)
12	2 (2.8%)
13	1 (1.4%)
14	63 (88.7%)
Primary reason for discontinuation from trastuzumab (after discontinuation of trastuzumab emtansine)	
Adverse Event	2 (2.8%)
Physician Decision	2 (2.8%)
Withdrawal By Subject	4 (5.6%)

Table 45: Summary of trastuzumab emtansine exposure (treated patients) across studies

	TDM4370g/ BO21977 (T-DM1 arm) N = 490	**TDM4450g/ BO21976[c] (T-DM1 arm) N = 69**	**Pooled T-DM1[a] N = 288**	**Total T-DM1-exposed[b] N = 882**
Number of doses received				
n	490	69	288	882
Mean (SD)	11.7 (8.4)	17.4 (12.2)	12.1 (13.5)	12.2 (10.8)
Median	9.0	16.0	7.0	9.0
Range	1.0 – 41.0	1.0 – 41.0	1.0 – 69.0	1.0 – 69.0
Average dose received (mg/kg)				
n	490	69	287	881
Mean (SD)	3.49 (0.20)	3.5 (0.5)	3.51 (0.20)	3.50 (0.24)
Median	3.50	3.60	3.57	3.56
Range	2.70 – 4.00	3.00 – 6.00	2.50 – 4.19	2.50 – 6.00
Dose Intensity (%)[d]				
n	490	68	288	882
Mean (SD)	97.85 (10.92)	95.0 (11.9)	95.69 (8.38)	96.90 (10.58)
Median	99.92	99.30	99.49	99.70
Range	54.67 – 200.72	61 – 158	55.17 – 107.52	54.67 – 200.72
Treatment Duration (months)				
n	490	69	288	882
Mean (SD)	7.7 (6.1)	11.9 (8.8)	8.2 (10.1)	8.2 (7.9)
Median	5.7	10.4	4.2	5.6
Range	0.0 – 28.4	0 – 29	0.0 – 47.1	0.0 – 47.1

Concomitant therapies

Table 46: Concomitant medications by treatment regimen, safety evaluable patients - Study KATHERINE

Concomitant Medications by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Class Standardized Medication Name	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
ANTICOAGULANTS		
Total number of patients with at least one treatment	60 (8.3%)	44 (5.9%)
Total number of treatments	80	50
ENOXAPARIN SODIUM	25 (3.5%)	23 (3.1%)
HEPARIN SODIUM	13 (1.8%)	8 (1.1%)
RIVAROXABAN	6 (0.8%)	4 (0.5%)
TINZAPARIN SODIUM	4 (0.6%)	3 (0.4%)
NADROPARIN CALCIUM	3 (0.4%)	3 (0.4%)
FONDAPARINUX SODIUM	4 (0.6%)	0
WARFARIN SODIUM	3 (0.4%)	1 (0.1%)
DALTEPARIN SODIUM	3 (0.4%)	0
CERTOPARIN SODIUM	2 (0.3%)	0
LOW MOLECULAR WEIGHT HEPARINS	1 (0.1%)	1 (0.1%)
PHENPROCOUMON	2 (0.3%)	0
DABIGATRAN ETEXILATE	0	1 (0.1%)
HEPARINOIDS	1 (0.1%)	0
HIRUDIN	0	1 (0.1%)
PENTOSAN POLYSULFATE SODIUM	1 (0.1%)	0
PLATELET AGGREGATION INHIBITORS		
Total number of patients with at least one treatment	11 (1.5%)	3 (0.4%)
Total number of treatments	11	5
ASPIRIN	2 (0.3%)	2 (0.3%)
ASPIRIN/DIPYRIDAMOLE	3 (0.4%)	1 (0.1%)
CLOPIDOGREL	4 (0.6%)	0
ASPIRIN DL-LYSINE	2 (0.3%)	0

Adverse events

Verbatim descriptions of AEs were mapped to Medical Dictionary for Regulatory Activities (MedDRA) (Version 21.0) thesaurus terms and graded according to the NCI CTCAE, Version 4.0. All AEs, including SAEs, AEs leading to death, and AEs leading to study treatment discontinuation, occurring on or after the first dose of study treatment (i.e., treatment-emergent AEs), were summarized by NCI CTCAE grade. For repeated events of varying severity in an individual patient, the highest grade was used in the summaries.

Cardiac assessments: LVEF assessment was by ECHO/MUGA, and was performed prior to anthracycline treatment, at the end of anthracycline (chemotherapy period 1) treatment, after Cycles 2 and 4 of Kadcyla, and every 4 cycles of Kadcyla thereafter. Any time a new treatment period was started (e.g., optional docetaxel or radiotherapy), an ECHO/MUGA was obtained before and after the new treatment. In the follow-up phase, ECHO/MUGA was obtained every 3 months for 6 months.

Table 47: Overview of Safety Summary by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Safety Summary by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one adverse event	672 (93.3%)	731 (98.8%)
Total number of adverse events	5317	8429
Total number of patients with at least one		
AE with fatal outcome	0	1 (0.1%)
Serious AE	58 (8.1%)	94 (12.7%)
Serious Related AE	8 (1.1%)	39 (5.3%)
Grade >=3 AEs	111 (15.4%)	190 (25.7%)
AE leading to withdrawal from Trastuzumab/Trastuzumab Emtansine excluding switched treatment*	15 (2.1%)	133 (18.0%)
AE leading to dose reduction of Trastuzumab Emtansine	0	90 (12.2%)
AE leading to dose interruption of Trastuzumab/ Trastuzumab Emtansine excluding switched treatment*	37 (5.1%)	106 (14.3%)
AE related to Trastuzumab/Trastuzumab Emtansine*	326 (45.3%)	641 (86.6%)
Selected AEs for trastuzumab emtansine: patients with		
Hepatotoxicity (all grades)	76 (10.6%)	276 (37.3%)
NCI-CTCAE Grade >=3	3 (0.4%)	12 (1.6%)
Cardiac dysfunction	40 (5.6%)	23 (3.1%)
NCI-CTCAE Grade >=3	9 (1.3%)	4 (0.5%)
Thrombocytopenia	17 (2.4%)	211 (28.5%)
NCI-CTCAE Grade >=3	2 (0.3%)	42 (5.7%)
Peripheral Neuropathy	122 (16.9%)	239 (32.3%)
NCI-CTCAE Grade >=3	1 (0.1%)	12 (1.6%)
Hemorrhage	69 (9.6%)	216 (29.2%)
NCI-CTCAE Grade >=3	2 (0.3%)	3 (0.4%)
IRR/hypersensitivity (type 1)	19 (2.6%)	57 (7.7%)
NCI-CTCAE Grade >=3	0	1 (0.1%)
IRR/hypersensitivity symptoms	9 (1.3%)	42 (5.7%)
NCI-CTCAE Grade >=3	0	0
Pulmonary toxicity	6 (0.8%)	21 (2.8%)
NCI-CTCAE Grade >=3	0	3 (0.4%)

Table 48: Most Common (≥ 5%) Adverse Events by Treatment Regimen in either Arm (Safety Evaluable Patients) - Study KATHERINE

Most Common (>=5%) Adverse Events by Treatment Regimen in either arm, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA Preferred Term	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one adverse event	634 (88.1%)	719 (97.2%)
Total number of events	3339	5976
FATIGUE	243 (33.8%)	366 (49.5%)
NAUSEA	94 (13.1%)	308 (41.6%)
RADIATION SKIN INJURY	199 (27.6%)	188 (25.4%)
ARTHRALGIA	148 (20.6%)	192 (25.9%)
HEADACHE	122 (16.9%)	210 (28.4%)
ASPARTATE AMINOTRANSFERASE INCREASED	40 (5.6%)	210 (28.4%)
HOT FLUSH	146 (20.3%)	95 (12.8%)
PLATELET COUNT DECREASED	17 (2.4%)	211 (28.5%)
ALANINE AMINOTRANSFERASE INCREASED	41 (5.7%)	171 (23.1%)
MYALGIA	80 (11.1%)	114 (15.4%)
PERIPHERAL SENSORY NEUROPATHY	50 (6.9%)	138 (18.6%)
INFLUENZA LIKE ILLNESS	87 (12.1%)	100 (13.5%)
INSOMNIA	86 (11.9%)	101 (13.6%)
COUGH	86 (11.9%)	100 (13.5%)
CONSTIPATION	59 (8.2%)	126 (17.0%)
PAIN	92 (12.8%)	93 (12.6%)
EPISTAXIS	25 (3.5%)	159 (21.5%)
DIARRHOEA	90 (12.5%)	91 (12.3%)
PAIN IN EXTREMITY	70 (9.7%)	86 (11.6%)
VOMITING	37 (5.1%)	108 (14.6%)
ANAEMIA	60 (8.3%)	74 (10.0%)
DIZZINESS	57 (7.9%)	70 (9.5%)
BACK PAIN	66 (9.2%)	53 (7.2%)
DYSPNOEA	53 (7.4%)	62 (8.4%)
UPPER RESPIRATORY TRACT INFECTION	53 (7.4%)	58 (7.8%)
DRY MOUTH	9 (1.3%)	100 (13.5%)
STOMATITIS	27 (3.8%)	80 (10.8%)
PYREXIA	29 (4.0%)	77 (10.4%)
URINARY TRACT INFECTION	39 (5.4%)	65 (8.8%)

WHITE BLOOD CELL COUNT DECREASED	42 (5.8%)	61 (8.2%)
PARAESTHESIA	41 (5.7%)	60 (8.1%)
ABDOMINAL PAIN	42 (5.8%)	58 (7.8%)
NEUTROPHIL COUNT DECREASED	36 (5.0%)	61 (8.2%)
BREAST PAIN	42 (5.8%)	53 (7.2%)
PRURITUS	42 (5.8%)	51 (6.9%)
BONE PAIN	35 (4.9%)	52 (7.0%)
DEPRESSION	44 (6.1%)	41 (5.5%)
LYMPHOEDEMA	48 (6.7%)	37 (5.0%)
DRY SKIN	36 (5.0%)	48 (6.5%)
OEDEMA PERIPHERAL	52 (7.2%)	29 (3.9%)
DECREASED APPETITE	16 (2.2%)	62 (8.4%)
MUSCLE SPASMS	45 (6.3%)	33 (4.5%)
HYPERTENSION	35 (4.9%)	42 (5.7%)
BLOOD ALKALINE PHOSPHATASE INCREASED	13 (1.8%)	61 (8.2%)
DYSGEUSIA	11 (1.5%)	60 (8.1%)
ANXIETY	42 (5.8%)	28 (3.8%)
OROPHARYNGEAL PAIN	33 (4.6%)	37 (5.0%)
RASH MACULO-PAPULAR	26 (3.6%)	42 (5.7%)
HYPOKALAEMIA	14 (1.9%)	48 (6.5%)
DERMATITIS ACNEIFORM	21 (2.9%)	39 (5.3%)
LACRIMATION INCREASED	13 (1.8%)	41 (5.5%)
CHILLS	14 (1.9%)	39 (5.3%)
BLOOD BILIRUBIN INCREASED	2 (0.3%)	49 (6.6%)

Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once Table includes all AEs during treatment period to 30 days post last dose and AEs related to study treatment or study procedures in the follow up period.

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ae_inc.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ae_inc_5PER_SE.out
06NOV2018 16:23

Table 49: Adverse Events (any Grade) with a Difference of at least 5% between Treatment Arms by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Adverse Events (any grade) with a difference of at least 5% between treatment arms by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class MedDRA Preferred Term	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one adverse event	486 (67.5%)	672 (90.8%)
Overall Total number of events	1279	3473
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	259 (36.0%)	394 (53.2%)
FATIGUE	243 (33.8%)	366 (49.5%)
PYREXIA	29 (4.0%)	77 (10.4%)
Total number of events	308	555
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	175 (24.3%)	429 (58.0%)
NAUSEA	94 (13.1%)	308 (41.6%)
CONSTIPATION	59 (8.2%)	126 (17.0%)
VOMITING	37 (5.1%)	108 (14.6%)
DRY MOUTH	9 (1.3%)	100 (13.5%)
STOMATITIS	27 (3.8%)	80 (10.8%)
Total number of events	265	939
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	169 (23.5%)	337 (45.5%)
HEADACHE	122 (16.9%)	210 (28.4%)
PERIPHERAL SENSORY NEUROPATHY	50 (6.9%)	138 (18.6%)
DYSGEUSIA	11 (1.5%)	60 (8.1%)
Total number of events	209	497
INVESTIGATIONS		
Total number of patients with at least one adverse event	78 (10.8%)	360 (48.6%)
ASPARTATE AMINOTRANSFERASE INCREASED	40 (5.6%)	210 (28.4%)
PLATELET COUNT DECREASED	17 (2.4%)	211 (28.5%)
ALANINE AMINOTRANSFERASE INCREASED	41 (5.7%)	171 (23.1%)
BLOOD ALKALINE PHOSPHATASE INCREASED	13 (1.8%)	61 (8.2%)
BLOOD BILIRUBIN INCREASED	2 (0.3%)	49 (6.6%)
Total number of events	132	870
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	148 (20.6%)	192 (25.9%)
ARTHRALGIA	148 (20.6%)	192 (25.9%)
Total number of events	162	221
VASCULAR DISORDERS		
Total number of patients with at least one adverse event	146 (20.3%)	95 (12.8%)
HOT FLUSH	146 (20.3%)	95 (12.8%)
Total number of events	154	99
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	25 (3.5%)	159 (21.5%)
EPISTAXIS	25 (3.5%)	159 (21.5%)
Total number of events	30	222
METABOLISM AND NUTRITION DISORDERS		
Total number of patients with at least one adverse event	16 (2.2%)	62 (8.4%)
DECREASED APPETITE	16 (2.2%)	62 (8.4%)
Total number of events	19	70

Grade 3-4 AEs

Table 50: NCI-CTCAE Grade ≥ 3 AEs with at least 1% Incidence in either arm by PT and by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

NCI-CTCAE Grade >=3 Adverse Events by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class MedDRA Preferred Term	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
INVESTIGATIONS		
PLATELET COUNT DECREASED	2 (0.3%)	42 (5.7%)
NEUTROPHIL COUNT DECREASED	5 (0.7%)	9 (1.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
RADIATION SKIN INJURY	7 (1.0%)	10 (1.4%)
VASCULAR DISORDERS		
HYPERTENSION	9 (1.3%)	15 (2.0%)
NERVOUS SYSTEM DISORDERS		
PERIPHERAL SENSORY NEUROPATHY	0	10 (1.4%)
METABOLISM AND NUTRITION DISORDERS		
HYPOKALAEMIA	1 (0.1%)	9 (1.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	1 (0.1%)	8 (1.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
ANAEMIA	1 (0.1%)	8 (1.1%)

Adverse drug reactions

The safety of trastuzumab emtansine has been evaluated in 2,611 breast cancer patients in clinical studies. In this patient population:

- the most common serious ADRs (> 0.5% of patients) were haemorrhage, pyrexia, thrombocytopenia, dyspnoea, abdominal pain, musculoskeletal pain, and vomiting.
- the most common adverse drug reactions (ADRs) (≥25%) with trastuzumab emtansine were nausea, fatigue, musculoskeletal pain, haemorrhage, headache, transaminases increased, thrombocytopenia, and peripheral neuropathy. The majority of ADRs reported were of Grade 1 or 2 severity.
- the most common National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade ≥ 3 ADRs (> 2%) were thrombocytopenia, increased transaminases, anaemia, neutropenia, fatigue and hypokalaemia.

The table below presents pooled data from the overall treatment period in the MBC studies (N= 1871; median number of cycles of trastuzumab emtansine was 10) and in KATHERINE (N=740; median number of cycles was 14).

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia, Anaemia	Neutropenia, Leucopoenia	
Immune system disorders		Drug hypersensitivity	
Metabolism and nutrition disorders		Hypokalaemia	
Psychiatric disorders	Insomnia		
Nervous system disorders	Neuropathy peripheral, Headache	Dizziness, Dysgeusia, Memory impairment	
Eye disorders		Dry eye, Conjunctivitis, Vision blurred, Lacrimation increased	
Cardiac disorders		Left ventricular dysfunction	
Vascular disorders	Haemorrhage	Hypertension	
Respiratory, thoracic and mediastinal disorders	Epistaxis, Cough, Dyspnoea		Pneumonitis (ILD)
Gastrointestinal disorders	Stomatitis, Diarrhoea, Vomiting, Nausea, Constipation, Dry mouth, Abdominal pain	Dyspepsia, Gingival bleeding	
Hepatobiliary disorders	Transaminases increased	Blood alkaline phosphatase increased, blood bilirubin increased	Hepatotoxicity, Hepatic failure, Nodular regenerative hyperplasia, Portal hypertension
Skin and subcutaneous tissue disorders		Rash, Pruritus, Alopecia, Nail disorder, Palmar-plantar erythrodysaesthesia syndrome, Urticaria	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, Arthralgia, Myalgia		
General disorders and administration site conditions	Fatigue, Pyrexia, Asthenia	Peripheral oedema, Chills	Injection site extravasation
Injury, poisoning and procedural complications		Infusion-related reactions	Radiation pneumonitis

Serious adverse event/deaths/other significant events

Serious AEs

Table 51: Summary of Serious Adverse Events by Treatment Regimen Occurring in at least 2 Patients in either Treatment Arm (Safety Evaluable Patients) - Study KATHERINE

Serious Adverse Events by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class MedDRA Preferred Term	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one adverse event	58 (8.1%)	94 (12.7%)
Overall Total number of events	70	114
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	21 (2.9%)	37 (5.0%)
MASTITIS	6 (0.8%)	8 (1.1%)
DEVICE RELATED INFECTION	0	6 (0.8%)
BRONCHITIS	1 (0.1%)	3 (0.4%)
PNEUMONIA	1 (0.1%)	3 (0.4%)
SKIN INFECTION	2 (0.3%)	2 (0.3%)
LUNG INFECTION	1 (0.1%)	2 (0.3%)
URINARY TRACT INFECTION	2 (0.3%)	1 (0.1%)
WOUND INFECTION	2 (0.3%)	1 (0.1%)
APPENDICITIS	0	2 (0.3%)
GASTROENTERITIS	0	2 (0.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total number of patients with at least one adverse event	8 (1.1%)	8 (1.1%)
WOUND DEHISCENCE	1 (0.1%)	3 (0.4%)
RADIATION PNEUMONITIS	0	2 (0.3%)
TIBIA FRACTURE	0	2 (0.3%)
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	5 (0.7%)	10 (1.4%)
VOMITING	2 (0.3%)	3 (0.4%)
ABDOMINAL PAIN	1 (0.1%)	3 (0.4%)
INVESTIGATIONS		
Total number of patients with at least one adverse event	1 (0.1%)	12 (1.6%)
PLATELET COUNT DECREASED	0	10 (1.4%)
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	1 (0.1%)	8 (1.1%)
PERIPHERAL SENSORY NEUROPATHY	0	3 (0.4%)
PERIPHERAL MOTOR NEUROPATHY	0	2 (0.3%)
SYNCOPE	0	2 (0.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	1 (0.1%)	8 (1.1%)
EPISTAXIS	0	2 (0.3%)
PNEUMONITIS	0	2 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	4 (0.6%)	4 (0.5%)
NON-CARDIAC CHEST PAIN	2 (0.3%)	3 (0.4%)
HEPATOBILIARY DISORDERS		
Total number of patients with at least one adverse event	2 (0.3%)	5 (0.7%)
NODULAR REGENERATIVE HYPERPLASIA	0	2 (0.3%)
VASCULAR DISORDERS		
Total number of patients with at least one adverse event	5 (0.7%)	2 (0.3%)
EMBOLISM	3 (0.4%)	1 (0.1%)
CARDIAC DISORDERS		
Total number of patients with at least one adverse event	4 (0.6%)	2 (0.3%)
CARDIAC FAILURE	2 (0.3%)	2 (0.3%)
IMMUNE SYSTEM DISORDERS		
Total number of patients with at least one adverse event	0	4 (0.5%)
HYPERSENSITIVITY	0	4 (0.5%)

Deaths and primary cause of deaths

Table 52: Summary of Deaths by Reason for Death by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Summary of Deaths by Reason for Death by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Cause of Death	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total No. of Deaths	56 (7.8%)	42 (5.7%)
Cause of Death		
Breast cancer	52 (7.2%)	39 (5.3%)
Adverse event	1 (0.1%)	1 (0.1%)
Other	3 (0.4%)	2 (0.3%)

Adverse events leading to death included intracranial hemorrhage and encephalitis. Other causes of death were pneumonia (n=2), cerebrovascular event with renal insufficiency (n=1), death after osteosynthesis (n=1), and cerebrovascular event (n=1). These were non-reportable adverse events because they occurred >30 days after last study treatment and were not related to study treatment or study procedures .One patient in the Trastuzumab arm died due to encephalitis infection, this was not related to study treatment and outside the protocol-specified reporting period for adverse events.

Five patients died with reason reported as "other" (terms reported were pneumonia [n=2], and cerebrovascular event [n=1] in the trastuzumab arm; cerebrovascular event with renal insufficiency [n=1] and death after osteosynthesis [n=1] in the Kadcyla arm). Per protocol, these were non-reportable adverse events because they occurred >30 days after last study treatment and were not related to study treatment or study procedures.

There was one fatal AE during the protocol-defined AE reporting period: intracranial haemorrhage in a patient receiving Kadcyla. The patient received the first cycle of Kadcyla on Study Day 1 and died on Day 32 due to intracranial haemorrhage. The investigator assessed the fatal intracranial haemorrhage to be related to Kadcyla.

In addition, one patient in the trastuzumab arm died due to encephalitis infection. This event occurred outside the protocol-specified reporting period for adverse events of 30 days (the patient had discontinued from study treatment on Study Day 212 and had subsequently received one dose of trastuzumab as non-study treatment on Study Day 239), was not related to study treatment or study procedure. Therefore this was not reportable as an AE, but was erroneously marked as a death due to an AE on the eCRF instead of under “other”, and therefore appears in Table 52 under the AE category.

This patient had neurological symptoms (disorientation and incoherent speech on Study Day 252; CT scan of the brain showed decrease in size, oedema of brain, and metastases (previously reported). No bleeding or new lesions were found. The cerebrospinal fluid was positive for herpes virus type 1 and the patient was diagnosed with encephalitis. On Study Day 257, the patient died due to encephalitis and secondary neurological deterioration. No autopsy was performed. The physician assessed encephalitis infection to be not related to trastuzumab, but related to disease under study and concomitant medication (dexamethasone) that may have increased her susceptibility to infection.

Selected AEs

Thrombocytopenia

Thrombocytopenia was reported in 28.5% of patients in EBC clinical studies with trastuzumab emtansine and was the most common reported adverse reaction for all grades and grades ≥ 3, as well as the most common adverse reaction leading to treatment discontinuation (4.2%), dose interruptions, and dose reductions.

Independent of race, the incidence of Grade 3 or 4 events (< 50,000/mm^3) was 5.7% in patients with EBC.

Table 53: Summary of Selected AEs of Thrombocytopenia by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Selected Adverse Events by Highest NCI CTCAE Grade, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class Preferred Term	Grade	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Thrombocytopenia			
- Overall -	- Any Grade -	17 (2.4%)	211 (28.5%)
	1	14 (1.9%)	105 (14.2%)
	2	1 (0.1%)	64 (8.6%)
	3	1 (0.1%)	27 (3.6%)
	4	1 (0.1%)	15 (2.0%)
	5	0	0
PLATELET COUNT DECREASED	- Any Grade -	17 (2.4%)	211 (28.5%)
	1	14 (1.9%)	105 (14.2%)
	2	1 (0.1%)	64 (8.6%)
	3	1 (0.1%)	27 (3.6%)
	4	1 (0.1%)	15 (2.0%)
	5	0	0

Investigator text for AEs encoded using MedDRA version 21.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Percentages are based on N in the column headings. Table includes all AEs during treatment period to 30 days post last dose and AEs related to study treatment or study procedures in the follow up period.

Table 54: Summary of Reversibility/Resolution of Grade ≥ 3 Selected AEs of Thrombocytopenia (Safety Evaluable Patients) - Study KATHERINE

Reversibility/Resolution of Grade >=3 Selected Adverse Events, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Selected AEs : Thrombocytopenia

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
No. pts with Grade >=3 AE	2	42
Pts with resolved AEs	2 (100.0%)	40 (95.2%)
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	2 (4.8%)
No. pts with T-DM1 discontinuation due to Grade >= 3 event	0	12
Pts with resolved AEs	0	10 (83.3%)
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	2 (16.7%)
No. pts with T-DM1 dose reductions due to Grade >= 3 event	0	9
Pts with resolved AEs	0	9 (100.0%)
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	0
No. pts with T-DM1 dose delays due to Grade >= 3 event	0	0
Pts with resolved AEs	0	0
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	0

Only the worst outcome of adverse events is summarised in the categroies of drug discontinuation, reductions and delays. For example, if an adverse event led to dose delay, then dose reduction and finally dose discontinuation, it would only appear under study drug discontinuations. A patient who dies prior to resolution of AE (due to AE or other reasons) will show up under "Pts with unresolved AEs". AE resolution date may be after data cut-off as this is not subject to the data cut.

Haemorrhage

More patients in the trastuzumab emtansine arm (216 patients [29.2%]) had at least one AE in the hemorrhage category than in the trastuzumab arm (69 patients [9.6%]). The most commonly reported AEs (in at least 1% patients in either arm) were: epistaxis (3.5% for trastuzumab vs. 21.5% for trastuzumab emtansine), contusion (1.1% vs. 1.8%), vaginal haemorrhage (0.8% vs. 1.6%), haematoma (0.8% vs. 1.4%), rectal haemorrhage (0.7% vs. 1.4%), menorrhagia (0.3% vs. 1.5%), mouth haemorrhage (0.1% vs. 1.6%), and gingival bleeding (0.1% vs. 1.2%). No patient had an AE of Grade 4 intensity in either arm.

Two patients (0.3%) in the trastuzumab arm and three patients (0.4%) in the trastuzumab emtansine arm had at least one Grade ≥3 AE. A total of 4 patients (2 patients in each arm) were reported to have AEs resolved at CCoD. In the trastuzumab emtansine arm, one patient had a Grade 5 event (haemorrhage intracranial). No other events of CNS haemorrhage were reported.

In some of the observed cases the patients had thrombocytopenia, or were also receiving anti-coagulant therapy or antiplatelet therapy; in others there were no known additional risk factors.

Cardiac safety

Table 55: Summary of Selected AE of Cardiotoxicity by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Selected Adverse Events by Highest NCI CTCAE Grade, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class Preferred Term	Grade	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Cardiac dysfunction			
- Overall -	- Any Grade -	40 (5.6%)	23 (3.1%)
	1	2 (0.3%)	2 (0.3%)
	2	29 (4.0%)	17 (2.3%)
	3	9 (1.3%)	4 (0.5%)
	4	0	0
	5	0	0
EJECTION FRACTION DECREASED	- Any Grade -	31 (4.3%)	19 (2.6%)
	1	0	0
	2	28 (3.9%)	16 (2.2%)
	3	3 (0.4%)	3 (0.4%)
	4	0	0
	5	0	0
LEFT VENTRICULAR DYSFUNCTION	- Any Grade -	4 (0.6%)	3 (0.4%)
	1	0	2 (0.3%)
	2	0	0
	3	4 (0.6%)	1 (0.1%)
	4	0	0
	5	0	0
CARDIAC FAILURE	- Any Grade -	4 (0.6%)	2 (0.3%)
	1	0	0
	2	2 (0.3%)	1 (0.1%)
	3	2 (0.3%)	1 (0.1%)
	4	0	0
	5	0	0
DIASTOLIC DYSFUNCTION	- Any Grade -	2 (0.3%)	0
	1	2 (0.3%)	0
	2	0	0
	3	0	0
	4	0	0
	5	0	0

Table 56: Summary of Reversibility/Resolution of Grade ≥ 3 Selected AE of Cardiotoxicity (Safety Evaluable Patients) - Study KATHERINE

Reversibility/Resolution of Grade >=3 Selected Adverse Events, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Selected AEs : Cardiac dysfunction

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
No. pts with Grade >=3 AE	9	4
Pts with resolved AEs	9 (100.0%)	4 (100.0%)
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	0
No. pts with T-DM1 discontinuation due to Grade >= 3 event	0	3
Pts with resolved AEs	0	3 (100.0%)
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	0
No. pts with T-DM1 dose reductions due to Grade >= 3 event	0	0
Pts with resolved AEs	0	0
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	0
No. pts with T-DM1 dose delays due to Grade >= 3 event	0	0
Pts with resolved AEs	0	0
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	0

Only the worst outcome of adverse events is summarised in the categroies of drug discontinuation, reductions and delays. For example, if an adverse event led to dose delay, then dose reduction and finally dose discontinuation, it would only appear under study drug discontinuations. A patient who dies prior to resolution of AE (due to AE or other reasons) will show up under "Pts with unresolved AEs". AE resolution date may be after data cut-off as this is not subject to the data cut.

Table 57: Cardiac Events as Adjudicated Positively by the Cardiac Review Committee by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Cardiac Events as adjudicated positively by the Cardiac Review Committee by Treatment Regimen , Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Any cardiac event	27 (3.8%)	19 (2.6%)
Treatment difference (trastuzumab emtansine - trastuzumab) 95% CI*		-1.2 (-3.0, 0.7)
Definite cardiac death	0	0
Probable cardiac death	1 (0.1%)	0
Symptomatic		
NYHA Class III or IV with a decrease in LVEF of >=10 percentage points from baseline to an LVEF <50%	3 (0.4%)	1 (0.1%)
Symptomatic LVSD not meeting protocol specified cardiac event criteria (NYHA Class II)	9 (1.3%)	6 (0.8%)
Asymptomatic		
Asymptomatic confirmed decrease in LVEF of >=10 percentage points from baseline to an LVEF <50%	6 (0.8%)	4 (0.5%)
Asymptomatic unconfirmed decrease in LVEF of >=10 percentage points from baseline to an LVEF <50%	10 (1.4%)	8 (1.1%)
Other	0	0
Non-evaluable	1 (0.1%)	0

Percentages are based on N in the column headings. * 95% confidence interval with Hauck-Anderson correction

Table 58: Recovery from Cardiac Events as Adjudicated Positively by the Cardiac Review Committee by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Recovery from Cardiac Events as adjudicated positively by the Cardiac Review Committee by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Number of patients with any non-fatal cardiac event#	26 (3.6%)	19 (2.6%)
LVEF recovery achieved*		
n	26	19
Yes	22 (84.6%)	14 (73.7%)
No	4 (15.4%)	5 (26.3%)
Time to recovery (weeks)		
n	22	14
Median	7.5	9.7
Range	3.0 - 52.6	3.0 - 87.0
Number of patients with symptomatic left ventricular dysfunction (NYHA class III or IV) with confirmed LVEF decrease#	0	0
LVEF recovery achieved*		
n	0	0
Yes	0	0
No	0	0
Time to recovery (weeks)		
n	0	0
Median	NE	NE
Range	NE - NE	NE - NE
Number of patients with asymptomatic left ventricular dysfunction with confirmed LVEF decrease#	6 (0.8%)	4 (0.5%)
LVEF recovery achieved*		
n	6	4
Yes	4 (66.7%)	2 (50.0%)
No	2 (33.3%)	2 (50.0%)
Time to recovery (weeks)		
n	4	2
Median	12.3	57.6
Range	7.3 - 20.4	28.3 - 87.0

*Recovery defined as at least 2 consecutive LVEF assessments >=50% after the date of the cardiac event.
#Excluding patients with later cardiac death.

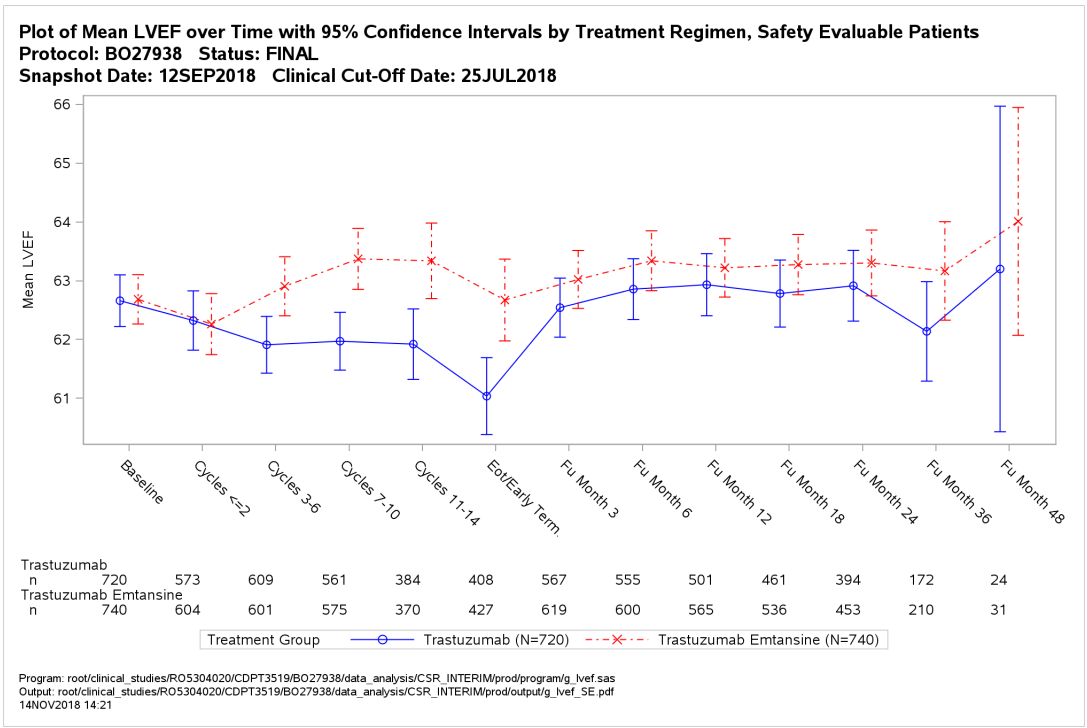


Figure 13: Plot of Mean LVEF over Time with 95%CI by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Left ventricular dysfunction occurred in 3.0% of patients with EBC, with Grade 3 or 4 in 0.5% of patients.

28 patients (vs. 24 in the Kadcyla arm) presented a significant change from basal LVEF (defined as an absolute value <50% and decrease ≥10 points from baseline). 4 patients in the trastuzumab arm and 2 in the Kadcyla arm reached LVEF values <40%, all 6 of them previously treated with anthracyclines.

Table 59: Summary of Maximum Decrease in LVEF Measures by Treatment Regimen (Absolute Value < 50% and Decrease from Baseline ≥ 10 or ≥ 15 EF Points) (Safety Evaluable Patients) - Study KATHERINE

Summary of Maximum Decrease in LVEF Measures by Treatment Regimen, absolute value <50% and decrease from baseline >=10 or >=15 EF points, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=720)		Trastuzumab Emtansine (N=740)
Absolute value <50% and decrease from baseline >= 10 EF points	28		23
Change from Baseline to Worst Value			
n	28		23
Mean (SD)	-16.4 (7.0)		-15.8 (4.7)
Median	-15.0		-15.0
Range	-43 - -10		-25 - -10
Treatment difference*		0.6	
95% C.I.		(-2.8, 4.0)	
Worst value <40%			
Yes	2 (7.1%)		4 (17.4%)
No	26 (92.9%)		19 (82.6%)
Absolute value <50% and decrease from baseline >= 15 EF points	16		14
Change from Baseline to Worst Value			
n	16		14
Mean (SD)	-20.0 (7.4)		-18.6 (3.7)
Median	-18.0		-18.0
Range	-43 - -15		-25 - -15
Treatment difference*		1.4	
95% C.I.		(-3.0, 5.7)	
Worst value <40%			
Yes	2 (12.5%)		4 (28.6%)
No	14 (87.5%)		10 (71.4%)

Treatment difference defined as trastzumab emtansine - trastuzumab

Hepatotoxicity

Increased transaminases (AST/ALT) were reported in 32.4% of patients with EBC. Grade 3 and 4 increased transaminases were reported in 1.5% of patients with EBC.

Table 60: Summary of Selected AE of Hepatotoxicity by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Selected Adverse Events by Highest NCI CTCAE Grade, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class / Preferred Term	Grade	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Hepatotoxicity			
- Overall -	- Any Grade -	76 (10.6%)	276 (37.3%)
	1	65 (9.0%)	191 (25.8%)
	2	8 (1.1%)	73 (9.9%)
	3	3 (0.4%)	12 (1.6%)
	4	0	0
	5	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	- Any Grade -	40 (5.6%)	210 (28.4%)
	1	36 (5.0%)	171 (23.1%)
	2	2 (0.3%)	35 (4.7%)
	3	2 (0.3%)	4 (0.5%)
	4	0	0
	5	0	0
ALANINE AMINOTRANSFERASE INCREASED	- Any Grade -	41 (5.7%)	171 (23.1%)
	1	35 (4.9%)	136 (18.4%)
	2	4 (0.6%)	32 (4.3%)
	3	2 (0.3%)	3 (0.4%)
	4	0	0
	5	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED	- Any Grade -	13 (1.8%)	61 (8.2%)
	1	13 (1.8%)	52 (7.0%)
	2	0	8 (1.1%)
	3	0	1 (0.1%)
	4	0	0

	5	0	0
BLOOD BILIRUBIN INCREASED	- Any Grade -	2 (0.3%)	49 (6.6%)
	1	1 (0.1%)	36 (4.9%)
	2	1 (0.1%)	13 (1.8%)
	3	0	0
	4	0	0
	5	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	- Any Grade -	4 (0.6%)	27 (3.6%)
	1	2 (0.3%)	10 (1.4%)
	2	2 (0.3%)	13 (1.8%)
	3	0	4 (0.5%)
	4	0	0
	5	0	0
HYPOALBUMINAEMIA	- Any Grade -	7 (1.0%)	8 (1.1%)
	1	7 (1.0%)	8 (1.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
HEPATIC STEATOSIS	- Any Grade -	5 (0.7%)	6 (0.8%)
	1	5 (0.7%)	6 (0.8%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
SPIDER NAEVUS	- Any Grade -	1 (0.1%)	6 (0.8%)
	1	1 (0.1%)	6 (0.8%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
HEPATIC PAIN	- Any Grade -	2 (0.3%)	1 (0.1%)
	1	2 (0.3%)	1 (0.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
NODULAR REGENERATIVE HYPERPLASIA	- Any Grade -	0	2 (0.3%)
	1	0	0
	2	0	0
	3	0	2 (0.3%)
	4	0	0
	5	0	0
ASCITES	- Any Grade -	0	1 (0.1%)
	1	0	1 (0.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
HEPATITIS	- Any Grade -	0	1 (0.1%)
	1	0	0
	2	0	1 (0.1%)
	3	0	0
	4	0	0
	5	0	0
HEPATOCELLULAR INJURY	- Any Grade -	0	1 (0.1%)
	1	0	0
	2	0	1 (0.1%)
	3	0	0
	4	0	0
	5	0	0
TRANSAMINASES INCREASED	- Any Grade -	0	1 (0.1%)
	1	0	1 (0.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0

Table 61: Summary of Reversibility/Resolution of Grade ≥ 3 Selected AE of Hepatotoxicity (Safety Evaluable Patients) - Study KATHERINE

Reversibility/Resolution of Grade >=3 Selected Adverse Events, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Selected AEs : Hepatotoxicity

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
No. pts with Grade >=3 AE	3	12
Pts with resolved AEs	1 (33.3%)	7 (58.3%)
Pts with unresolved AEs	2 (66.7%)	2 (16.7%)
Pts with recovering/resolving AEs	0	3 (25.0%)
No. pts with T-DM1 discontinuation due to Grade >= 3 event	0	2
Pts with resolved AEs	0	1 (50.0%)
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	1 (50.0%)
No. pts with T-DM1 dose reductions due to Grade >= 3 event	0	2
Pts with resolved AEs	0	2 (100.0%)
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	0
No. pts with T-DM1 dose delays due to Grade >= 3 event	0	0
Pts with resolved AEs	0	0
Pts with unresolved AEs	0	0
Pts with recovering/resolving AEs	0	0

Only the worst outcome of adverse events is summarised in the categroies of drug discontinuation, reductions and delays. For example, if an adverse event led to dose delay, then dose reduction and finally dose discontinuation, it would only appear under study drug discontinuations. A patient who dies prior to resolution of AE (due to AE or other reasons) will show up under "Pts with unresolved AEs". AE resolution date may be after data cut-off as this is not subject to the data cut.

Peripheral neuropathy

The overall incidence was 32.3% and 10.3% for Grade ≥2.

Table 62: Summary of selected AE of peripheral neuropathy by treatment regimen (safety evaluable patients)

Selected Adverse Events by Highest NCI CTCAE Grade, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class Preferred Term	Grade	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Peripheral Neuropathy			
- Overall -	- Any Grade -	122 (16.9%)	239 (32.3%)
	1	100 (13.9%)	163 (22.0%)
	2	21 (2.9%)	64 (8.6%)
	3	1 (0.1%)	12 (1.6%)
	4	0	0
	5	0	0
PERIPHERAL SENSORY NEUROPATHY	- Any Grade -	50 (6.9%)	138 (18.6%)
	1	39 (5.4%)	90 (12.2%)
	2	11 (1.5%)	38 (5.1%)
	3	0	10 (1.4%)
	4	0	0
	5	0	0
PARAESTHESIA	- Any Grade -	41 (5.7%)	60 (8.1%)
	1	38 (5.3%)	49 (6.6%)
	2	2 (0.3%)	10 (1.4%)
	3	1 (0.1%)	1 (0.1%)
	4	0	0
	5	0	0
MUSCULAR WEAKNESS	- Any Grade -	12 (1.7%)	15 (2.0%)
	1	9 (1.3%)	13 (1.8%)
	2	2 (0.3%)	2 (0.3%)
	3	1 (0.1%)	0
	4	0	0
	5	0	0
PERIPHERAL MOTOR NEUROPATHY	- Any Grade -	8 (1.1%)	16 (2.2%)
	1	8 (1.1%)	8 (1.1%)
	2	0	5 (0.7%)
	3	0	3 (0.4%)
	4	0	0
	5	0	0
DYSAESTHESIA	- Any Grade -	7 (1.0%)	7 (0.9%)
	1	6 (0.8%)	7 (0.9%)
	2	1 (0.1%)	0
	3	0	0
	4	0	0
	5	0	0
NEURALGIA	- Any Grade -	5 (0.7%)	9 (1.2%)
	1	2 (0.3%)	2 (0.3%)
	2	3 (0.4%)	7 (0.9%)
	3	0	0
	4	0	0
	5	0	0
NEUROPATHY PERIPHERAL	- Any Grade -	7 (1.0%)	6 (0.8%)
	1	5 (0.7%)	3 (0.4%)
	2	2 (0.3%)	3 (0.4%)
	3	0	0
	4	0	0
	5	0	0

HYPOAESTHESIA	- Any Grade -	6 (0.8%)	5 (0.7%)
	1	6 (0.8%)	5 (0.7%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
SKIN BURNING SENSATION	- Any Grade -	0	3 (0.4%)
	1	0	3 (0.4%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
GAIT DISTURBANCE	- Any Grade -	0	2 (0.3%)
	1	0	2 (0.3%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
NEUROTOXICITY	- Any Grade -	1 (0.1%)	1 (0.1%)
	1	1 (0.1%)	1 (0.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
POLYNEUROPATHY	- Any Grade -	1 (0.1%)	1 (0.1%)
	1	1 (0.1%)	1 (0.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
BURNING SENSATION	- Any Grade -	0	1 (0.1%)
	1	0	1 (0.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
MYELOPATHY	- Any Grade -	1 (0.1%)	0
	1	1 (0.1%)	0
	2	0	0
	3	0	0
	4	0	0
	5	0	0
NEURITIS	- Any Grade -	0	1 (0.1%)
	1	0	1 (0.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0
PERONEAL NERVE PALSY	- Any Grade -	0	1 (0.1%)
	1	0	1 (0.1%)
	2	0	0
	3	0	0
	4	0	0
	5	0	0

Other events

Infusion-related reactions were reported in 1.6% of patients with EBC, with no Grade 3 or 4 events reported.

Hypersensitivity was reported in 2.7% of patients with EBC, with Grade 3 or 4 in 0.4% of patients.

Laboratory findings

Table 63: Laboratory abnormalities observed in patients treated with trastuzumab emtansine in study BO27938/KATHERINE

Parameter	Trastuzumab emtansine (N=740)		
	All Grade %	Grade 3 (%)	Grade 4 (%)
Hepatic			
Increased bilirubin	11	0	0
Increased AST	79	<1	0
Increased ALT	55	<1	0
Haematologic			
Decreased platelet count	51	4	2
Decreased haemoglobin	31	1	0
Decreased neutrophils	24	1	0
Potassium			
Decreased potassium	26	2	<1

Table 64: Laboratory Test Results Shift Table for Hematology: Highest NCI CTACE Grade Post Baseline by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Laboratory Test Results Shift Table: Highest NCI CTCAE Grade Post-Baseline by Treatment Regimen,
Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Laboratory Category: Hematology
Parameter: Platelet (Low)

Treatment Group / Post-Baseline NCI-CTCAE Grade	Baseline NCI-CTCAE Grade: Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Trastuzumab (N=720)						
Grade 0	595 (86.7%)	2 (9.1%)	0	0	0	1 (50.0%)
Grade 1	90 (13.1%)	19 (86.4%)	0	0	0	1 (50.0%)
Grade 2	0	0	0	0	0	0
Grade 3	1 (0.1%)	0	0	0	0	0
Grade 4	0	1 (4.5%)	0	0	0	0
Trastuzumab Emtansine (N=740)						
Grade 0	332 (47.8%)	4 (12.1%)	0	0	0	2 (100.0%)
Grade 1	276 (39.7%)	18 (54.5%)	0	0	0	0
Grade 2	45 (6.5%)	8 (24.2%)	0	0	0	0
Grade 3	28 (4.0%)	1 (3.0%)	0	0	0	0
Grade 4	14 (2.0%)	2 (6.1%)	0	0	0	0

Table entries provide the number of patients with the highest post-baseline NCI-CTCAE grade, that is, post-baseline values during study treatment and up to 30 days after last dose. Baseline is the patient's last observation prior to initiation of study drug.

Table 65: Laboratory Test Results–Shift Table for Hepatic Chemistry: Highest NCI CTACE Grade Post Baseline by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Laboratory Test Results Shift Table: Highest NCI CTCAE Grade Post-Baseline by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

Laboratory Category: Chemistry
Parameter: Alkaline Phosphatase (High)

Treatment Group / Post-Baseline NCI-CTCAE Grade	Baseline NCI-CTCAE Grade: Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Trastuzumab (N=720)						
Grade 0	553 (83.5%)	5 (11.9%)	0	0	0	3 (60.0%)
Grade 1	108 (16.3%)	37 (88.1%)	0	0	0	2 (40.0%)
Grade 2	1 (0.2%)	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Trastuzumab Emtansine (N=740)						
Grade 0	444 (65.4%)	4 (8.3%)	0	0	0	3 (75.0%)
Grade 1	227 (33.4%)	37 (77.1%)	0	0	0	1 (25.0%)
Grade 2	8 (1.2%)	7 (14.6%)	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0

Laboratory Category: Chemistry
Parameter: SGPT/ALT (High)

Treatment Group / Post-Baseline NCI-CTCAE Grade	Baseline NCI-CTCAE Grade: Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Trastuzumab (N=720)						
Grade 0	467 (76.7%)	16 (23.2%)	0	0	0	4 (80.0%)
Grade 1	139 (21.9%)	51 (73.9%)	0	0	0	1 (20.0%)
Grade 2	8 (1.3%)	2 (2.9%)	0	0	0	0
Grade 3	1 (0.2%)	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Trastuzumab Emtansine (N=740)						
Grade 0	266 (39.8%)	3 (4.8%)	0	0	0	0
Grade 1	380 (56.8%)	53 (85.5%)	0	0	0	1 (100.0%)
Grade 2	18 (2.7%)	6 (9.7%)	0	0	0	0
Grade 3	5 (0.7%)	0	0	0	0	0
Grade 4	0	0	0	0	0	0

Laboratory Category: Chemistry
Parameter: SGOT/AST (High)

Treatment Group / Post-Baseline NCI-CTCAE Grade	Baseline NCI-CTCAE Grade: Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Trastuzumab (N=720)						
Grade 0	513 (77.3%)	8 (21.1%)	0	0	0	4 (57.1%)
Grade 1	145 (21.8%)	28 (73.7%)	0	0	0	3 (42.9%)
Grade 2	5 (0.8%)	2 (5.3%)	0	0	0	0
Grade 3	1 (0.2%)	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Trastuzumab Emtansine (N=740)						
Grade 0	112 (16.4%)	1 (2.3%)	0	0	0	1 (33.3%)
Grade 1	545 (79.6%)	32 (74.4%)	0	0	0	1 (33.3%)
Grade 2	25 (3.6%)	7 (16.3%)	0	0	0	1 (33.3%)
Grade 3	3 (0.4%)	3 (7.0%)	0	0	0	0
Grade 4	0	0	0	0	0	0

Laboratory Category: Chemistry
Parameter: Bilirubin (High)

Treatment Group / Post-Baseline NCI-CTCAE Grade	Baseline NCI-CTCAE Grade: Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Trastuzumab (N=720)						
Grade 0	674 (96.4%)	0	0	0	0	4 (100.0%)
Grade 1	17 (2.4%)	3 (75.0%)	0	0	0	0
Grade 2	3 (0.4%)	1 (25.0%)	1 (100.0%)	0	0	0
Grade 3	5 (0.7%)	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Trastuzumab Emtansine (N=740)						
Grade 0	645 (88.5%)	0	0	0	0	2 (100.0%)
Grade 1	65 (8.9%)	0	0	0	0	0
Grade 2	19 (2.6%)	1 (100.0%)	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0

With regards to platelet count shifts, 87% of patients with normal baseline platelet count remained with normal count in the trastuzumab arm. Conversely, 52% of patients from the Kadcyla arm with normal baseline platelet count underwent platelet count decreases that re-classified them as *platelet count decreased.* 45 patients from the Kadcyla arm (6.1%) experienced clinically relevant shifts (baseline G0-1 to post-baseline G3-4) as compared to only 2 patients in the trastuzumab arm (0.3%).

In terms of liver enzyme shifts, adjuvant treatment with trastuzumab had minimal impact in liver enzymes. On the contrary, treatment with Kadcyla adversely affected their values, particularly ASAT (38 patients with baseline G0-1 to post-baseline G2-3) and ALAT (29 patients). Of note, 5 patients treated with Kadcyla suffered bilirubin shifts from baseline G0 to post-baseline G3.

Safety in special populations

AEs by age

The vast majority of patients (90.8%-92.2%) were below 65 years old, with a median age of 49.0 years in both arms. No notable clinically meaningful differences were observed and there were no major additional safety concerns associated with Kadcyla in patients aged 65-74.

The number of patients ≥75 years old (N=9 total) was small. In the trastuzumab arm, 2 out of 7 patients ≥75 years old experienced at least one SAE. In the Kadcyla arm, no patient was reported to have experienced any SAE in this age group.

The incidence of Grade ≥3 AEs was similar across the treatment arms for patients between 65-74 years old. Further, no notable difference was observed between the age group of 40-64 years versus 65-74 years in terms of incidence of Grade ≥3 AEs. However, the older patients (65-74 years) in the trastuzumab arm tended to have numerically higher incidence of Grade ≥3 AEs than the younger patients in that treatment arm.

AEs by race

The majority of patients in this study were white (71.5% patients in the trastuzumab armand 74.2% patients in the trastuzumab emtansine arm, per randomized population). Overall, 8.6% of the randomized population was Asian. In the trastuzumab emtansine arm, the incidence of Grade ≥ 3 AEs and SAEs was higher in Asian patients than in White patients: this difference was not seen in the trastuzumab arm. In the trastuzumab emtansine arm, the difference between the Asian and White patients in terms of SAEs and Grade ≥ 3 AEs was mainly due to the event of platelet count decreased (SAE: 7.8% in Asian patients vs. 0.4% in White patients; Grade ≥ 3 AEs: 18.8% in Asian patients vs.3.1% in White patients).

In the trastuzumab emtansine arm, a higher incidence of all Grade and Grade ≥ 3 thrombocytopenia was reported among Asian patients compared with other subgroups (All Grade: White [135 patients, 24.5%] vs. Asian [32 patients, 50.0%] vs. Black [5 patients, 25.0%] vs. Other [39 patients, 36.8%]); Grade ≥ 3AEs: White [17 patients, 3.1%] vs. Asian [12 patients, 18.8%] vs. Black [2 patients, 10.0%] vs. Other [11 patients, 10.4%]) which is consistent with previous findings.

In the trastuzumab emtansine arm, overall there was a higher incidence of patients with at least one AE leading to withdrawal from the study treatment among Asian compared with other races (White [90 patients, 16.4%] vs. Asian [20 patients, 31.3%] vs. Black [3 patients, 15.0%] vs. Other [20 patients, 18.9%]). Similarly, a higher incidence of AEs leading to dose reduction and interruption of trastuzumab emtansine was reported among Asian patients compared with patients from other races.

Table 66: Safety Summary by Treatment Regimen and Race, Safety Evaluable Patients - Study KATHERINE

Safety Summary by Treatment Regimen and Race, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

	Trastuzumab (N=720)				Trastuzumab Emtansine (N=740)			
	White (N=510)	Asian (N=62)	Black (N=20)	Other (N=128)	White (N=550)	Asian (N=64)	Black (N=20)	Other (N=106)
Total number of patients with at least one adverse event	473 (92.7%)	57 (91.9%)	20 (100.0%)	122 (95.3%)	543 (98.7%)	64 (100.0%)	20 (100.0%)	104 (98.1%)
Total number of adverse events	3565	343	177	1232	6016	664	294	1455
Total number of patients with at least one								
AE with fatal outcome	0	0	0	0	0	1 (1.6%)	0	0
Serious AE	39 (7.6%)	1 (1.6%)	2 (10.0%)	16 (12.5%)	66 (12.0%)	14 (21.9%)	3 (15.0%)	11 (10.4%)
Serious Related AE	5 (1.0%)	0	0	3 (2.3%)	23 (4.2%)	9 (14.1%)	1 (5.0%)	6 (5.7%)
Grade >=3 AEs	75 (14.7%)	5 (8.1%)	5 (25.0%)	26 (20.3%)	131 (23.8%)	26 (40.6%)	9 (45.0%)	24 (22.6%)
AE leading to withdrawal from Trastuzumab/Trastuzumab Emtansine excluding switched treatment*	14 (2.7%)	0	0	1 (0.8%)	90 (16.4%)	20 (31.3%)	3 (15.0%)	20 (18.9%)
AE leading to dose reduction of Trastuzumab Emtansine	0	0	0	0	66 (12.0%)	13 (20.3%)	1 (5.0%)	10 (9.4%)
AE leading to dose interruption of Trastuzumab/Trastuzumab Emtansine excluding switched treatment*	21 (4.1%)	2 (3.2%)	2 (10.0%)	12 (9.4%)	70 (12.7%)	16 (25.0%)	2 (10.0%)	18 (17.0%)
AE related to Trastuzumab/Trastuzumab Emtansine*	222 (43.5%)	25 (40.3%)	13 (65.0%)	66 (51.6%)	465 (84.5%)	61 (95.3%)	18 (90.0%)	97 (91.5%)
Selected AEs for trastuzumab emtansine: patients with								
Hepatotoxicity (all grades)	48 (9.4%)	7 (11.3%)	1 (5.0%)	20 (15.6%)	191 (34.7%)	26 (40.6%)	8 (40.0%)	51 (48.1%)
NCI-CTCAE Grade >=3	1 (0.2%)	1 (1.6%)	0	1 (0.8%)	6 (1.1%)	2 (3.1%)	1 (5.0%)	3 (2.8%)
Cardiac dysfunction	28 (5.5%)	3 (4.8%)	2 (10.0%)	7 (5.5%)	15 (2.7%)	2 (3.1%)	2 (10.0%)	4 (3.8%)
NCI-CTCAE Grade >=3	8 (1.6%)	0	0	1 (0.8%)	2 (0.4%)	0	1 (5.0%)	1 (0.9%)
Thrombocytopenia	11 (2.2%)	3 (4.8%)	0	3 (2.3%)	135 (24.5%)	32 (50.0%)	5 (25.0%)	39 (36.8%)
NCI-CTCAE Grade >=3	2 (0.4%)	0	0	0	17 (3.1%)	12 (18.8%)	2 (10.0%)	11 (10.4%)
Peripheral Neuropathy	83 (16.3%)	8 (12.9%)	3 (15.0%)	28 (21.9%)	186 (33.8%)	16 (25.0%)	7 (35.0%)	30 (28.3%)
NCI-CTCAE Grade >=3	0	0	0	1 (0.8%)	10 (1.8%)	2 (3.1%)	0	0
Hemorrhage	43 (8.4%)	5 (8.1%)	1 (5.0%)	20 (15.6%)	147 (26.7%)	24 (37.5%)	7 (35.0%)	38 (35.8%)
NCI-CTCAE Grade >=3	1 (0.2%)	0	0	1 (0.8%)	1 (0.2%)	1 (1.6%)	1 (5.0%)	0
IRR/hypersensitivity (type 1)	9 (1.8%)	2 (3.2%)	1 (5.0%)	7 (5.5%)	42 (7.6%)	3 (4.7%)	1 (5.0%)	11 (10.4%)
NCI-CTCAE Grade >=3	0	0	0	0	1 (0.2%)	0	0	0
IRR/hypersensitivity symptoms	4 (0.8%)	2 (3.2%)	1 (5.0%)	2 (1.6%)	33 (6.0%)	2 (3.1%)	1 (5.0%)	6 (5.7%)
Pulmonary toxicity	6 (1.2%)	0	0	0	12 (2.2%)	4 (6.3%)	0	5 (4.7%)
NCI-CTCAE Grade >=3	0	0	0	0	1 (0.2%)	1 (1.6%)	0	1 (0.9%)

Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Table includes all AEs during treatment period to 30 days post last dose and AEs related to study treatment or study procedures in the follow up period. Total number of deaths are counted over the whole study period ,including post-treatment follow- up. * In the Trastuzumab emtansine arm, only adverse events related to Trastuzumab emtansine are evaluated.
White = white . Black = Black or African American , Asian = Asian: Indian subcontinent or Asian: Other than Indian subcontinent , Other = American Indian or Alaska Native , Native Hawaiian or Pacific Islander or Other or U nknown or multiple .

Program: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_saf_sum_race.sas
Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_saf_sum_race_SE.out
16NOV2018 17:27

Page 1 of 1

Safety related to drug-drug interactions and other interactions

No new study was submitted to assess safety related to drug-drug interactions.

Immunogenicity

A total of 1243 patients from seven clinical studies were tested at multiple time points for anti-drug antibody (ADA) responses to trastuzumab emtansine.

Table 67: Anti-drug Antibody Responses to Trastuzumab Emtansine

Study Number	Study Phase	No. of ADA Evaluable Patients [a]	No. of Patients Determined to be Positive for ADA [b]
TDM3569	I	48	1
TDM4258g	II	108	8
TDM4374g	II	108	6
TDM4688g	II	47	0
TDM4450g/BO21976	II	65	9
TDM4370g/BO21977	III	466	24
BO27938	III	401	15
Total		1243	63
Overall Kadcyla ADA Incidence		5.1% (63/1243)	

Source: 2.7.2 Summary of Clinical Pharmacology Studies
[a] Patients with at least one evaluable post-treatment ADA time point were considered evaluable for an ADA response to trastuzumab emtansine.
[b] Except for study BO27938, patients with at least one positive post-dose ADA response were considered to be ADA positive, irrespective of baseline status. For study BO27938, patients with treatment-emergent responses were considered to be ADA positive.

Following trastuzumab emtansine dosing, 5.1% (63/1243) of patients tested positive for anti-trastuzumab emtansine antibodies at one or more post-dose time points. In the Phase I and Phase II studies, 6.4% (24/376) of patients tested positive for anti- trastuzumab emtansine antibodies. In the EMILIA study (TDM4370g/BO21977), 5.2% (24/466) of patients tested positive for anti-trastuzumab emtansine

antibodies, of which 13 were also positive for neutralizing antibodies. In the KATHERINE (BO27938) study, 3.7% (15/401) of patients tested positive for anti-trastuzumab emtansine antibodies, of which 5 were also positive for neutralizing antibodies.

Discontinuation due to adverse events

Table 68: AEs Leading to Study Treatment Discontinuation Occurring in at Least 2 Patients in either Treatment Arm (Safety Evaluable Patients) - Study KATHERINE

Adverse Events Leading to Discontinuation of Trastuzumab /Trastuzumab emtansine by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class MedDRA Preferred Term	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one adverse event	15 (2.1%)	133 (18.0%)
Overall Total number of events	17	198
INVESTIGATIONS		
Total number of patients with at least one adverse event	10 (1.4%)	74 (10.0%)
PLATELET COUNT DECREASED	0	31 (4.2%)
BLOOD BILIRUBIN INCREASED	0	19 (2.6%)
EJECTION FRACTION DECREASED	10 (1.4%)	9 (1.2%)
ASPARTATE AMINOTRANSFERASE INCREASED	0	12 (1.6%)
ALANINE AMINOTRANSFERASE INCREASED	0	11 (1.5%)
NEUTROPHIL COUNT DECREASED	0	3 (0.4%)
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	0	22 (3.0%)
PERIPHERAL SENSORY NEUROPATHY	0	11 (1.5%)
HEADACHE	0	4 (0.5%)
PERIPHERAL MOTOR NEUROPATHY	0	4 (0.5%)
DIZZINESS	0	2 (0.3%)
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	1 (0.1%)	13 (1.8%)
NAUSEA	0	7 (0.9%)
ABDOMINAL PAIN	0	3 (0.4%)
DIARRHOEA	0	3 (0.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	1 (0.1%)	12 (1.6%)
PNEUMONITIS	0	7 (0.9%)
EPISTAXIS	0	2 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	0	11 (1.5%)
FATIGUE	0	3 (0.4%)
INFLUENZA LIKE ILLNESS	0	3 (0.4%)
PYREXIA	0	3 (0.4%)
PAIN	0	2 (0.3%)
CARDIAC DISORDERS		
Total number of patients with at least one adverse event	3 (0.4%)	5 (0.7%)
CARDIAC FAILURE	1 (0.1%)	2 (0.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	0	7 (0.9%)
ARTHRALGIA	0	2 (0.3%)
MYALGIA	0	2 (0.3%)
PAIN IN EXTREMITY	0	2 (0.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total number of patients with at least one adverse event	0	5 (0.7%)
RADIATION PNEUMONITIS	0	3 (0.4%)
PSYCHIATRIC DISORDERS		
Total number of patients with at least one adverse event	1 (0.1%)	4 (0.5%)
DEPRESSION	1 (0.1%)	2 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	0	2 (0.3%)
ANAEMIA	0	2 (0.3%)

Note: In the trastuzumab emtansine arm, only adverse events leading to discontinuation of trastuzumab emtansine are evaluated.Investigator text for AEs encoded using MedDRA version 21.0.

Table 69: AEs Leading to Dose Reduction of Study Drug by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Adverse Events Leading to Dose Reduction of Trastuzumab/Trastuzumab emtansine by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class MedDRA Preferred Term	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one adverse event	0	90 (12.2%)
Overall Total number of events	0	128
INVESTIGATIONS		
Total number of patients with at least one adverse event	0	65 (8.8%)
PLATELET COUNT DECREASED	0	23 (3.1%)
BLOOD BILIRUBIN INCREASED	0	20 (2.7%)
ALANINE AMINOTRANSFERASE INCREASED	0	14 (1.9%)
ASPARTATE AMINOTRANSFERASE INCREASED	0	11 (1.5%)
WEIGHT DECREASED	0	2 (0.3%)
WHITE BLOOD CELL COUNT DECREASED	0	2 (0.3%)
BLOOD ALKALINE PHOSPHATASE INCREASED	0	1 (0.1%)
NEUTROPHIL COUNT DECREASED	0	1 (0.1%)
Total number of events	0	81
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	0	9 (1.2%)
FATIGUE	0	8 (1.1%)
PAIN	0	1 (0.1%)
PYREXIA	0	1 (0.1%)
Total number of events	0	10
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	0	8 (1.1%)
PERIPHERAL SENSORY NEUROPATHY	0	4 (0.5%)
HEADACHE	0	1 (0.1%)
NERVE COMPRESSION	0	1 (0.1%)
PARAESTHESIA	0	1 (0.1%)
SYNCOPE	0	1 (0.1%)
Total number of events	0	8
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	0	6 (0.8%)
NAUSEA	0	4 (0.5%)
DIARRHOEA	0	2 (0.3%)
ABDOMINAL PAIN	0	1 (0.1%)
ABDOMINAL PAIN UPPER	0	1 (0.1%)
CONSTIPATION	0	1 (0.1%)
DRY MOUTH	0	1 (0.1%)
DYSPHAGIA	0	1 (0.1%)
MOUTH HAEMORRHAGE	0	1 (0.1%)
VOMITING	0	1 (0.1%)
Total number of events	0	14
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	0	3 (0.4%)
DEVICE RELATED INFECTION	0	1 (0.1%)
MASTITIS	0	1 (0.1%)
UPPER RESPIRATORY TRACT INFECTION	0	1 (0.1%)
Total number of events	0	3

METABOLISM AND NUTRITION DISORDERS		
Total number of patients with at least one adverse event	0	3 (0.4%)
DECREASED APPETITE	0	2 (0.3%)
HYPOKALAEMIA	0	1 (0.1%)
Total number of events	0	3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	0	3 (0.4%)
ARTHRALGIA	0	1 (0.1%)
MUSCULOSKELETAL PAIN	0	1 (0.1%)
MYALGIA	0	1 (0.1%)
Total number of events	0	3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	0	2 (0.3%)
EPISTAXIS	0	2 (0.3%)
Total number of events	0	2
EYE DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.1%)
VISION BLURRED	0	1 (0.1%)
Total number of events	0	1
HEPATOBILIARY DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.1%)
CHOLECYSTITIS	0	1 (0.1%)
Total number of events	0	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total number of patients with at least one adverse event	0	1 (0.1%)
SEROMA	0	1 (0.1%)
Total number of events	0	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.1%)
RASH MACULO-PAPULAR	0	1 (0.1%)
Total number of events	0	1

Table 70: AEs Leading to Drug Interruption by Treatment Regimen (Safety Evaluable Patients) - Study KATHERINE

Adverse Events Leading to Drug Interruption of Trastuzumab/Trastuzumab emtansine by Treatment Regimen, Safety Evaluable Patients
Protocol: BO27938 Status: FINAL
Snapshot Date: 12SEP2018 Clinical Cut-Off Date: 25JUL2018

MedDRA System Organ Class MedDRA Preferred Term	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one adverse event	37 (5.1%)	106 (14.3%)
Overall Total number of events	45	158
INVESTIGATIONS		
Total number of patients with at least one adverse event	13 (1.8%)	46 (6.2%)
EJECTION FRACTION DECREASED	11 (1.5%)	7 (0.9%)
PLATELET COUNT DECREASED	1 (0.1%)	14 (1.9%)
ASPARTATE AMINOTRANSFERASE INCREASED	0	12 (1.6%)
NEUTROPHIL COUNT DECREASED	0	9 (1.2%)
BLOOD BILIRUBIN INCREASED	0	4 (0.5%)
WHITE BLOOD CELL COUNT DECREASED	0	4 (0.5%)
ALANINE AMINOTRANSFERASE INCREASED	0	3 (0.4%)
LYMPHOCYTE COUNT DECREASED	1 (0.1%)	1 (0.1%)
TROPONIN T INCREASED	0	1 (0.1%)
Total number of events	13	60
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	8 (1.1%)	18 (2.4%)
BRONCHITIS	2 (0.3%)	2 (0.3%)
MASTITIS	2 (0.3%)	2 (0.3%)
HERPES ZOSTER	1 (0.1%)	2 (0.3%)
GASTROENTERITIS	0	2 (0.3%)
LUNG INFECTION	1 (0.1%)	1 (0.1%)
PNEUMONIA	0	2 (0.3%)
UPPER RESPIRATORY TRACT INFECTION	0	2 (0.3%)
DIVERTICULITIS	0	1 (0.1%)
FOLLICULITIS	0	1 (0.1%)
HERPES SIMPLEX	0	1 (0.1%)
INFLUENZA	0	1 (0.1%)
NAIL INFECTION	1 (0.1%)	0
TONSILLITIS	0	1 (0.1%)
VIRAL INFECTION	0	1 (0.1%)
WOUND INFECTION	1 (0.1%)	0
Total number of events	8	20
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	4 (0.6%)	14 (1.9%)
INFLUENZA LIKE ILLNESS	1 (0.1%)	6 (0.8%)
PYREXIA	2 (0.3%)	4 (0.5%)
FATIGUE	0	2 (0.3%)
NON-CARDIAC CHEST PAIN	1 (0.1%)	1 (0.1%)
CHILLS	0	1 (0.1%)
Total number of events	4	15
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	3 (0.4%)	10 (1.4%)
COUGH	1 (0.1%)	3 (0.4%)
EPISTAXIS	0	3 (0.4%)
DYSPNOEA	1 (0.1%)	1 (0.1%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	1 (0.1%)
NASAL CONGESTION	0	1 (0.1%)
OROPHARYNGEAL PAIN	1 (0.1%)	0
PLEURAL EFFUSION	0	1 (0.1%)
Total number of events	3	10

GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	3 (0.4%)	9 (1.2%)
DIARRHOEA	3 (0.4%)	0
NAUSEA	0	2 (0.3%)
STOMATITIS	0	2 (0.3%)
ABDOMINAL PAIN	0	1 (0.1%)
DRY MOUTH	0	1 (0.1%)
MOUTH HAEMORRHAGE	0	1 (0.1%)
RECTAL HAEMORRHAGE	0	1 (0.1%)
VOMITING	0	1 (0.1%)
Total number of events	3	9
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total number of patients with at least one adverse event	2 (0.3%)	10 (1.4%)
INFUSION RELATED REACTION	1 (0.1%)	6 (0.8%)
RADIATION PNEUMONITIS	0	1 (0.1%)
RADIATION SKIN INJURY	0	1 (0.1%)
RECALL PHENOMENON	0	1 (0.1%)
SKIN WOUND	0	1 (0.1%)
WRIST FRACTURE	1 (0.1%)	0
Total number of events	2	10
CARDIAC DISORDERS		
Total number of patients with at least one adverse event	4 (0.6%)	3 (0.4%)
CARDIAC FAILURE	2 (0.3%)	0
PALPITATIONS	0	2 (0.3%)
ANGINA PECTORIS	0	1 (0.1%)
ATRIAL FIBRILLATION	1 (0.1%)	0
CONDUCTION DISORDER	1 (0.1%)	0
Total number of events	4	3
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	1 (0.1%)	6 (0.8%)
PARAESTHESIA	1 (0.1%)	1 (0.1%)
PERIPHERAL SENSORY NEUROPATHY	0	2 (0.3%)
DYSAESTHESIA	0	1 (0.1%)
HEADACHE	0	1 (0.1%)
NYSTAGMUS	0	1 (0.1%)
Total number of events	1	7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	1 (0.1%)	5 (0.7%)
RASH MACULO-PAPULAR	0	2 (0.3%)
DERMATITIS BULLOUS	0	1 (0.1%)
PRURITUS	0	1 (0.1%)
SKIN REACTION	0	1 (0.1%)
URTICARIA	1 (0.1%)	0
Total number of events	1	5
VASCULAR DISORDERS		
Total number of patients with at least one adverse event	1 (0.1%)	3 (0.4%)
HYPERTENSION	1 (0.1%)	2 (0.3%)
PHLEBITIS	0	1 (0.1%)
Total number of events	1	3
IMMUNE SYSTEM DISORDERS		
Total number of patients with at least one adverse event	2 (0.3%)	1 (0.1%)
HYPERSENSITIVITY	2 (0.3%)	1 (0.1%)
Total number of events	2	8
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	0	2 (0.3%)
ANAEMIA	0	2 (0.3%)
Total number of events	0	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	0	2 (0.3%)
MYALGIA	0	2 (0.3%)
ARTHRALGIA	0	1 (0.1%)
Total number of events	0	3
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Total number of patients with at least one adverse event	2 (0.3%)	0
UTERINE HAEMORRHAGE	1 (0.1%)	0
UTERINE PROLAPSE	1 (0.1%)	0
Total number of events	2	0
EAR AND LABYRINTH DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.1%)
EAR PAIN	0	1 (0.1%)
Total number of events	0	1
EYE DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.1%)
STRABISMUS	0	1 (0.1%)
Total number of events	0	1
PSYCHIATRIC DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.1%)
SUICIDAL IDEATION	0	1 (0.1%)
Total number of events	0	1
SURGICAL AND MEDICAL PROCEDURES		
Total number of patients with at least one adverse event	1 (0.1%)	0
MENINGIOMA SURGERY	1 (0.1%)	0
Total number of events	1	0

Post marketing experience

As of 21 February 2018 (the Data Lock Point for the Kadcyla annual Periodic Benefit Risk Evaluation Report [PBRER]), an estimated cumulative total of 75,448 patients have received Kadcyla in the marketed setting.

The cumulative post-marketing data is consistent with the data submitted in previous PBRERs. No new safety concerns were identified.

2.5.1. Discussion on clinical safety

To support the proposed indication safety data from the ongoing pivotal Phase III study KATHERINE (BO27938) and supplementary safety data from completed Phase II study TDM4874g/BO22857 have been provided (data not shown). The safety data of the two studies were not pooled because of significant differences between the studies, primarily in treatment modalities with respect to chemotherapy and/or radiotherapy given as part of the study treatment.

Post-marketing signal evaluation from the global safety database has confirmed thrombocytopenia, hepatotoxicity and haemorrhage as Kadcyla's major safety risks. It must be emphasised that, to date, Kadcyla has mainly been used in patients with metastatic incurable disease, i.e. in a palliative setting. The toxicity threshold tolerated in the palliative setting is very different from that in the adjuvant one.

Kadcyla as a single agent in early breast cancer was first evaluated in the phase II study TDM4874g/BO22857, designed primarily to assess safety, with a focus on cardiac events. There were no symptomatic cardiac events and the incidence and severity of thrombocytopenia and hepatotoxicity were similar to that from MBC studies, but haemorrhages (43.9%) and peripheral neuropathy (33%) were more frequent than expected (data not shown). It was nevertheless concluded that such safety results indicated that Kadcyla was well tolerated in the EBC setting.

The target population of the KATHERINE trial was constituted by patients already exposed to cytotoxic chemotherapy in the neoadjuvant setting, nearly all suffering alopecia, fatigue and a degree of peripheral neuropathy, and after surgery, most of them will still face the unpleasant effects from radiotherapy and endocrine treatment. Safety population was constituted by 720 patients in the trastuzumab arm and 740 patients from the Kadcyla arm. The majority of patients in the trastuzumab arm (81.0%) completed all 14 cycles of treatment compared to the Kadcyla arm (71.4%). This considerable difference matters because most of the patients who prematurely discontinued Kadcyla did so because of toxic AEs: 133 (18%) in the Kadcyla arm vs. 15 (2%) in the trastuzumab arm. AEs from Kadcyla also led to one-level dose reductions in 77 (10.4%) patients and two-level dose reductions in 29 (3.9%). Furthermore, 71 (9.6%) patients from the Kadcyla arm ended up being switched to trastuzumab.

Overall exposure to Kadcyla in the KATHERINE trial (median number of cycles = 14) considerably exceeds that from the pivotal EMILIA trial (median number of cycles = 9).

In general, in safety terms, adjuvant Kadcyla compares quite unsatisfactorily to trastuzumab. Although most patients in both arms from the KATHERINE study experienced at least one AE, the amount and proportion of ≥ G3 AEs (26% vs. 15%), serious AEs (5% vs. 1%) and AEs leading to treatment withdrawal (18% vs. 2%) in the Kadcyla arm is significantly higher than those at the trastuzumab arm.

Likewise, the higher incidence of those AEs that particularly concern Kadcyla as compared to trastuzumab is notorious: any-grade hepatotoxicity (38% vs. 11%), thrombocytopenia (29% vs. 2%), peripheral neuropathy (32% vs. 17%), haemorrhage (29% vs. 10%), infusion-related reactions (8% vs. 3%) and pulmonary toxicity (3% vs. 1%). Furthermore, Kadcyla is more often associated to the occurrence of typically chemotherapy-related symptoms such as nausea, fatigue, dry mouth/stomatitis/dysgeusia, constipation, peripheral neuropathy and decreased appetite.

For the management of ADRs, adequate dose modification guidelines for patients with early breast cancer have been included in section 4.2 of the SmPC.

The incidence of baseline peripheral neuropathy was similar in both arms (22.7% in the Kadcyla arm vs 21.4% patients in the trastuzumab arm). In most cases, this neuropathy was attributable to neoadjuvant taxanes, although of course, there might be other causalities. The fact that the overall incidence of peripheral neuropathy is 16.9% in the adjuvant trastuzumab arm supports the hypothesis that in clinical practice, peripheral neuropathy symptoms tend to reduce over the course of months after chemotherapy (at least in a group of patients). In patients who received Kadcyla, nevertheless, the post-adjuvant incidence of peripheral neuropathy affects one third of the patients. Sensory/motor neuropathy is a disabling AE with likely chronic consequences and a detrimental impact in quality of life. Considering its overall incidence (29.0% in MBC and 32.3% in EBC), peripheral neuropathy has been added in the listing of 'most common ADRs' in Section 4.8 of the SmPC. Mainly Grade 1 and predominantly sensory, has been reported in clinical studies with trastuzumab emtansine. MBC patients with ≥ Grade 3 and EBC patients with ≥ Grade 2 peripheral neuropathy at baseline were excluded from clinical studies. Furthermore a warning has been included in section 4.4 of the SmPC to reflect that treatment with trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to ≤ Grade 2. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

There were 4 cases of serious hypersensitivity in the Kadcyla arm and none in the trastuzumab arm. However, in 3 of these patients the event was deemed unrelated to Kadcyla and more likely a consequence from antihypertensive medication.

In study KATHERINE, 211 patients from the Kadcyla arm (28.5%) experienced any-grade thrombocytopenia. Half of the patients experienced G1 thrombocytopenia, while the remaining half had ≥G2 events. 20% of patients experienced high-grade (≥G3) events. Most of the high-grade events (40, 95.2%) had resolved by the CCOD. In comparison, only 17 patients (2.4%) from the trastuzumab arm presented this AE. The proportion of thrombocytopenia in the supportive study was similar.

Overall, thrombocytopenia is Kadcyla's most common drug-specific AE (any-grade), high-grade (≥G3) AE, AE leading to treatment reduction and AE leading to treatment discontinuation. A significant number of haemorrhagic events (with or without relationship to thrombocytopenia) have been reported in patients treated with Kadcyla. A few of these bleeding events have had fatal outcomes, both in clinical trials and in the post-marketing routine signal detection activity. Considering thrombocytopenia and haemorrhage as Kadcyla's most important adverse drug reactions, the existing warning in section 4.4 of the SmPC has been updated to reflect that thrombocytopenia was the most common adverse reaction leading to treatment discontinuation, dose reduction, and dose interruption.

A significant number of haemorrhagic events (with or without relationship to thrombocytopenia) have been reported in patients treated with Kadcyla in study KATHERINE. 216 patients (29.2%) from the Kadcyla arm and 69 patients (9.6%) from the trastuzumab arm experienced haemorrhage of diverse categories. Most of these AEs were low-grade and with minor clinical implications, but 5 patients from both arms suffered high-grade bleeding AEs. The proportion of haemorrhage AEs in the supportive study TDM4874g/BO22857 was even higher: 43.9% of any-grade events. Most of the events were G1 and G2, but there were 2 patients with G3 epistaxis.

It is noted that 71 patients from the trastuzumab arm and 47 from the Kadcyla arm were taking anticoagulant or antiplatelet therapy in Study KATHERINE. The SmPC already includes a warning about the added risk of anticoagulant and antiplatelet agents (see section 4.4 of SmPC).

Regarding cardiac toxicity, it has to be recalled that patients from the KATHERINE study were highly selected (see inclusion/exclusion criteria). The incidence of overall cardiac dysfunction was higher in the trastuzumab

arm. All 14 Grade 3 events (9 in the trastuzumab arm and 4 in the Kadcyla arm) were however resolved at the time of the clinical cut-off date. Symptomatic cardiac failure (NYHA III/IV) or asymptomatic decrease in LVEF ≥10% from baseline, as adjudicated by the Cardiac Review Committee, was also more frequent in the trastuzumab arm as compared with the Kadcyla arm. When these cardiac events were separated based on the prior use of anthracyclines, their proportion was slightly higher in patients from both arms who have received these cytotoxics as expected (3.5% vs. 2.1% in patients who have not). The differences between arms were not significant in either group (data not shown).

As anticipated, a considerable proportion of these cardiac events occurred in the first 6 months of the study (63%), i.e. while the patients were still on treatment; 6 out of 46 events happened after the IDFS events and could have been confounded by ulterior treatments. Recovery of the LVEF occurred in 80% of the patients, without considerable differences between arms. Looking at the mean LVEF over time, the very subtle decline in LVEF occurs only in the trastuzumab arm and peaks towards end of treatment.

The co-primary endpoint of the supportive study TDM4874g/BO22857 (N=148) was the rate of cardiac events within the first 12 weeks of Kadcyla treatment, but there were none observed (data not shown). However, there were 5 patients who presented asymptomatic cardiac dysfunction events (ejection fraction decreased) at any time during the study: 4 patients experienced a G2 event (3 of them recovered) and 1 patient had a G1 event.

Overall, existing risk minimisation activities are adequate to address cardiac toxicity. A warning on left ventricular dysfunction is already included in section 4.4 of the SmPC.

The rate of hepatotoxic events in the Kadcyla arm tripled that from the trastuzumab arm: 37.3% vs. 10.6%. G1 events were the most prevalent, but G2-3 events occurred in 85 patients (11.5%) from the Kadcyla arm and 12 patients (1.7%) from the control arm. The most common any-grade hepatotoxic events in the Kadcyla arm were increases of ASAT (28.4%), ALAT (23.1%), alkaline phosphatase (8.2%), bilirubin (6.6%) and GGT (3.6%). At least for the first three events, their incidences were considerably higher than those reported previously for Kadcyla (N=882): 23%, 15% and 6%, respectively (EPAR). 12 patients from the Kadcyla arm experienced G3 hepatotoxicity events (vs. 3 in the trastuzumab arm). These AEs had resolved in 7 patients and were resolving in 3 at the CCOD. The other 2 patients had unresolved events, one had nodular regenerative hyperplasia (NRH) and the other had GGT increased). The narratives from both patients who developed NRH suggest the AE was related to the Kadcyla. No patient fulfilled Hy's Law laboratory criteria. It is considered that the risk of hepatotoxicity is adequately covered in section 4.4 of the SmPC and in the RMP.

In relation to pulmonary toxicity, the existing warning has been amended to cover radiation pneumonitis. Treatment with trastuzumab emtansine is to be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥ Grade 3 or for Grade 2 not responding to standard treatment (see SmPC sections 4.2 and 4.4). Patients with dyspnoea at rest due to complications of advanced malignancy, co morbidities, and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary events.

Most of the deaths in the study were associated to progression of the underlying breast cancer (91 out of 98, 93%). The narratives of the 5 patients who died for reasons other than breast cancer or AEs are concise and render unlikely the participation of trastuzumab or Kadcyla in the final cause of death. However, one patient died from intracranial haemorrhage after the first dose of Kadcyla.

Regarding special populations, only 126 patients from the ITT (8.5%) were ≥65 years old, limiting a specific safety analysis in this age subgroup. However, the incidence of serious or ≥G3 AEs in both arms arm does not seem to vary significantly across age subgroups.

Regarding race, 129 patients (8.7%) from the ITT of the KATHERINE trial were Asian. 32 out of 64 (50%) patients in the Kadcyla arm experienced any-grade thrombocytopenia (compared to 25% of white or black patients). The incidence of ≥G3 thrombocytopenia was also higher in Asian patients: 18.8% (vs. 3.1% of white patients and 10.0% of black patients). Alarmingly, 5 out of all 10 patients (50%) who experienced serious thrombocytopenia were Asian. The SmPC from Kadcyla already states that the incidence and severity of thrombocytopenia were higher in Asian patients (see SmPC section 4.4).

Based on the review of the data, section 4.7 of the SmPC has also been updated to reflect that trastuzumab emtansine has minor influence on the ability to drive and use machines. The significance of reported adverse reactions such as fatigue, headache, dizziness and blurred vision on the ability to drive or use machines is unknown. Patients experiencing infusion related reactions (flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia) should be advised not to drive and use machines until symptoms abate.

No new study of drug-drug interaction was provided which is considered acceptable. Available information on drug-drug interactions is reflected in the current SmPC.

Section 4.8 of the SmPC has been updated to reflect updated safety information. Pulmonary toxicity and hepatotoxicity are known risks for trastuzumab emtansine, two new adverse drug reactions (ADRs: radiation pneumonitis and blood bilirubin increased) were added to section 4.8 of the SmPC to fully characterize the safety profile in the adjuvant EBC setting. For the majority of the ADRs, the frequency categories were consistent between the MBC and EBC settings. The following ADRs are now listed in a lower frequency category based on updated safety data: Hypokalaemia (from very common to common), Rash (from very common to common), Chills (from very common to common). Furthermore, a sub-section has been added to present information on peripheral neuropathy.

As with all therapeutic proteins, there is the potential for an immune response to trastuzumab emtansine. Due to the low incidence of ADA, conclusions cannot be made on the impact of anti- trastuzumab emtansine antibodies on the pharmacokinetics, safety, and efficacy of trastuzumab emtansine.

Overall, the safety profile of trastuzumab emtansine in the proposed indication of early breast cancer is currently not expected to be different from the known safety profile in terms of type of adverse drug reactions reported. However, the frequency and severity of Kadcyla-specific AEs are increased in EBC. The SmPC has been updated to reflect the safety information available in EBC and update existing warnings as appropriate. No additional pharmacovigilance activities were considered needed as a result of the present procedure (see RMP).

2.5.2. Conclusions on clinical safety

The frequency and severity of Kadcyla-specific AEs is increased in the EBC setting. The product information has been updated to inform healthcare professionals about the major safety risks derived from thrombocytopenia, haemorrhage and hepatotoxicity when considering adjuvant Kadcyla in patients with HER2+ EBC and residual invasive disease. Peripheral neuropathy is not a life-threatening symptom, but its much higher incidence from Kadcyla must be considered, since this disabling adverse effect can worsen quality of life for prolonged periods.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 9.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• ILD / ARDS • Hepatic toxicity • Nodular regenerative hyperplasia • Infusion related reactions • Hypersensitivity • Left ventricular dysfunction • Thrombocytopenia • Peripheral neuropathy
Important potential risks	• Foetal harm • Medication error
Missing information	• Use in patients with hepatic impairment • Use in patients with LVEF < 50% • Use in elderly patients (> 75 years) • Use in pregnant women • Use in lactation women • Clinical impact of anti-therapeutic antibodies • Use of non-validated HER2 tests

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA	NA	NA	NA	
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	
Category 3 - Required additional pharmacovigilance activities				
MO28231 (KAMILLA) A multicenter, single arm study of trastuzumab emtansine (T-DM1) in HER2 positive locally advanced or metastatic breast cancer patients who have received	Primary objective: To evaluate the safety and tolerability of trastuzumab emtansine. Secondary Objectives: • Progression Free Survival (PFS) • Overall survival (OS) • Overall response	• Left Ventricular Dysfunction • Safety in Elderly Patients • Use of a non-validated HER2 test	Primary Analysis Primary CSR Final Analysis Final CSR	Q4 2016 Q4 2017 (Complete) Q4 2020 Q4 2021

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
prior anti-HER2 and chemotherapy-based treatment	rate (ORR) • Clinical Benefit Rate (CBR) • Duration of Response (DoR) • Time to Response (TTR) Pharmacoeconomics Outcome Objective: • Health Resource Utilization			
BO27938 (KATHERINE) A randomized, multicenter, open label Phase III study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor present pathologically in the breast or axillary lymph nodes following preoperative therapy.	Objectives • To compare invasive disease free survival in patients with residual invasive breast cancer after treatment with preoperative chemotherapy and HER2-directed therapy including trastuzumab followed by surgery between the 2 treatment arms The secondary efficacy objective for this study is as follows: • To compare cardiac safety and overall safety between the 2 treatment arms	• Left Ventricular Dysfunction • Safety in Elderly Patients • Anti-therapeutic antibodies	Study start Primary Analysis Primary CSR Final Analysis Final CSR	April 2013 Q4 2018 Q1 2019 (Complete) Q2 2023 Q2 2024
BO28407 (KAITLIN) A randomized, multicenter, openlabel, Phase III trial comparing trastuzumab plus pertuzumab plus a taxane following anthracyclines versus trastuzumab emtansine plus pertuzumab following anthracyclines as adjuvant therapy in patients with operable HER2-positive primary breast cancer	EBC - Adjuvant Efficacy Objectives: The co-primary efficacy objectives for this study are as follows: • To compare invasive diseasefree survival (IDFS) (1) in the node−positive subpopulation and (2) in the overall protocol– defined population of patients with HER2-positive breast cancer randomized to either receive a taxane and 1 year of trastuzumab plus pertuzumab	• Left Ventricular Dysfunction • Safety in Elderly Patients • Anti-therapeutic antibodies	Study start Primary Analysis Primary CSR Final Analysis Final CSR	31 January 2014 Q3 2019 Q3 2020 Q1 2024 Q1 2025

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	following anthracycline-based chemotherapy or 1 year of trastuzumab emtansine plus pertuzumab following anthracycline-based chemotherapy. The secondary efficacy objectives for this study are as follows: • To compare IDFS plus second non-breast primary cancers, disease-free survival (DFS), and distance recurrence-free interval (DRFI) (1) in the node−positive subpopulation and (2) in the overall protocol defined population between the two treatment arms • To compare overall survival (OS) (1) in the node−positive subpopulation and (2) in the overall protocol-defined population between the two treatment arms Safety Objectives: • To compare overall safety, cardiac safety, hepatic, and pulmonary safety in the overall protocol defined population between the two treatment arms.			
BO28408 (KRISTINE) A randomized, multicenter, openlabel,two-arm, Phase III neoadjuvant study evaluating trastuzumab emtansine plus pertuzumab compared with	EBC – Neoadjuvant Efficacy Objectives: • To compare the pathological complete response (pCR) rate (ypT0/is, ypN0) between chemotherapy, trastuzumab plus pertuzumab (Arm	• Left Ventricular Dysfunction • Safety in Elderly Patients • Anti-therapeutic antibodies	Study start Primary Analysis Primary CSR Final Analysis Final CSR	25 June 2014 25 February 2016 Q2 2017 (Complete) Q3 2018 (Complete)

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
chemotherapy plus trastuzumab and pertuzumab for patients with HER2-positive breast cancer.	A) and trastuzumab emtansine plus pertuzumab (Arm B) using local evaluation The secondary efficacy objectives for this study are: • To evaluate event-free survival EFS), invasive disease-free survival (IDFS), overall survival (OS) and rate of breast conserving surgery across treatment arms Safety Objectives: • To evaluate cardiac, hepatic, and overall safety in each treatment arm			Q2 2019
BO39807 A retrospective cohort study based on the secondary use of Flatiron's US electronic health records database (Flatiron Health, Inc. New York, NY, USA)	Objective of PV activity: • To evaluate the risk for patients who have a LVEF between 40 - 49% prior to initiating treatment with trastuzumab emtansine. Objectives of this study are: • To describe the characteristics of the patients in this cohort prior to or at trastuzumab emtansine initiation in terms of demographics, disease characteristics and risk factors for cardiac events. • To describe the evolution of LVEF as recorded over time from the latest LVEF measurement recorded within the 60 days prior to treatment with trastuzumab emtansine (baseline) to the 84th day following	Patients who have a LVEF between 40 – 49% prior to initiating treatment with trastuzumab emtansine	Study Start Interim Study Report Final Report	2017 2018 (Complete) 2019

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	treatment discontinuation (absolute value and incidence of LVEF decrease > 10% from baseline). • To describe the event rate, incidence rate and cumulative incidence of the following cardiac events in this cohort from the initiation of treatment with trastuzumab emtansine (index date) to the 84th day following treatment discontinuation: – congestive heart failure – 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).			

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Interstitial lung disease/Acute Respiratory Distress Syndrome	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety concern	Risk minimization measures	Pharmacovigilance activities
(ILD/ARDS)	precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥Grade 3 or for Grade 2 not responding to standard treatment. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristic (EU SmPC). **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**signal detection** None **Additional pharmacovigilance activities:** None
Hepatic Toxicity	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** Guided questionnaires

Safety concern	Risk minimization measures	Pharmacovigilance activities
	precautions for use) Section 4.8 (Undesirable effects) Section 5.2 (Pharmacokinetic properties) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × upper limit of normal (ULN) and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** None
Nodular regenerative hyperplasia (NRH)	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Guided questionnaires **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	specific clinical measures to address the risk: Diagnosis of NRH can be confirmed only by histopathology. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued. This has been adequately captured in EU SmPC Section 4.4 **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	None
Infusion-related reaction	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.7 Effects on ability to drive and use machines Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8 of EU SmPC). Trastuzumab emtansine should be discontinued in case of	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Hypersensitivity	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8 of EU SmPC). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Left ventricular dysfunction	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** Collection and separate analysis of cardiological safety data in the following studies: – MO28231 (KAMILLA) – BO27938 (KATHERINE) – BO28407 (KAITLIN) – BO28408 (KRISTINE)
Thrombocytopenia	**Routine risk communication:** **SmPC:**	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. See Section 4.4 EU SmPC **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None
Peripheral neuropathy	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be clinically monitored on an ongoing basis for	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	signs/symptoms of neurotoxicity.This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Fetal harm	**Routine risk communication:** **SmPC:** Section 4.6 (Fertility, pregnancy and lactation) Section 5.3 (Preclinical safety data) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab emtansine and for at least 7 months after treatment has concluded. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** Global Enhanced Pharmacovigilance (PV) pregnancy program **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	
Medication error	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) **Routine risk minimization activities recommending specific clinical measures to address the risk:** In order to prevent medication errors it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not Herceptin (trastuzumab). **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** Educational materials for health care providers.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None
Use in patients with hepatic impairment	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance**

Safety concern	Risk minimization measures	Pharmacovigilance activities
		activities: None
	Routine risk minimization activities recommending specific clinical measures to address the risk: Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × ULN and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Use in patients with left ventricular ejection fraction (LVEF) <50%	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. The dose	**Routine pharmacovigilance activities beyond adverse \reactions reporting and** **signal detection** None **Additional pharmacovigilance activities:** – Study BO39807

Safety concern	Risk minimization measures	Pharmacovigilance activities
	should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see section 4.2). This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Use in elderly patients (>= 75 years)	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 5.1 Pharmacodynamic properties Section 5.2 Pharmacokinetic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** None **Additional pharmacovigilance activities:** Collection and separate analysis of safety data for elderly patients in the following studies: – MO28231 (KAMILLA) – BO27938 (KATHERINE) – BO28407 (KAITLIN) – BO28408 (KRISTINE)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	prescription. **Additional risk minimization measures:** None	
Use in pregnant women	**Routine risk communication:** **SmPC:** Section 4.6 (Fertility, pregnancy and lactation) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should be advised to use effective contraception during treatment with Trastuzumab emtansine and for at least 7 months after treatment has concluded. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Global Enhanced Pharmacovigilance (PV) pregnancy program **Additional pharmacovigilance activities:** None
Use in lactating women	**Routine risk communication:** **SmPC:** Section 4.6 (Fertility, pregnancy and lactation) **Routine risk minimization activities recommending**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	specific clinical measures to address the risk: Women should discontinue nursing prior to initiating treatment with trastuzumab emtansine. Women may begin nursing 7 months after concluding treatment. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** None
Clinical impact of anti-therapeutic antibodies	**Routine risk communication:** **SmPC:** Section 4.8 (Undesirable effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** – BO27938 (KATHERINE) – BO28407 (KAITLIN) – BO28408 (KRISTINE)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	
Use of non-validated HER2 tests	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients treated with trastuzumab emtansine should have HER2 positive tumour status, assessed by a CE-marked In Vitro Diagnostic (IVD) medical device. If a CE-marked IVD is not available, the HER2-status should be assessed by an alternate validated test. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** • MO28231 (KAMILLA)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The proposed Type II variation seeks to extend the Kadcyla Marketing Authorisation to include adjuvant treatment for patients with HER2- positive EBC. User consultation was conducted at the time of the initial marketing authorisation application for Kadcyla, approved in patients with MBC. It is reasonable not to conduct a User Consultation for the Package Leaflet for this variation because:

- No significant changes affecting the readability of the Package Leaflet have been made.
- The new additions follow the same structure and use similar descriptions and terminology as used in the approved Package Leaflet.
- The posology proposed in this application does not differ from that previously described; only the timing and duration of the treatment is different.
- The safety profile remaims consistent with the known profile for Kadcyla, with no new safety signals seen in the adjuvant setting.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH is currently seeking an extension of indication of Kadcyla for the adjuvant treatment of adult patients with HER2-positive early breast cancer (EBC) who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane and HER2 targeted therapy.

3.1.2. Available therapies and unmet medical need

Preoperative chemotherapy plus trastuzumab and pertuzumab attains high rates of pCR and constitutes the standard of care in the neoadjuvant setting of HER2+ EBC. To further minimise the risk of relapse, trastuzumab is often maintained for up to a year in the adjuvant setting. Despite this progress, however, approximately 15% to 25% of HER2-positive patients will eventually experience local or metastatic recurrence, which calls for the identification and investigation of newer and better therapies.

It has been reported that achieving pCR following neoadjuvant therapy is associated with significantly improved disease recurrence and survival, particularly for triple negative and HER2+ BC patients. To date, no specific adjuvant regiments are recommended for patients with HER2+ BC who did not achieve a complete response (i.e. those with residual disease) and are thus at higher risk of disease recurrence and decreased survival. Therefore, this population has a high level of unmet medical need.

3.1.3. Main clinical studies

The application is based on efficacy and safety data from KATHERINE (Study BO27938), a phase III, two-arm, randomised, open label trial in patients with HER2+ BC with residual invasive disease in the breast or lymph nodes after neoadjuvant chemotherapy and HER2-targeted agents, data cut-off 25 Jul 2018.

3.2. Favourable effects

After 256 IDFS events (predefined IA by protocol), the study has met its primary efficacy endpoint by achieving a statistically significant improvement in IDFS for Kadcyla with an unstratified HR of 0.50 (95% CI 0.39, 0.64) and $p<0.0001$. The efficacy-stopping boundary has been crossed and the results are now considered the primary analysis.

The IDFS benefit from Kadcyla is maintained across all the subgroups analysed, particularly those concerning the stratification factors.

The lowered risk of IDFS events from Kadcyla vs. trastuzumab seems limited to recurrence outside of sanctuary sites (distant non-CNS, locoregional and/or contralateral), since no differences between arms were seen for overall CNS-recurrence event rates.

Albeit not corrected for multiplicity, secondary endpoints that included other clinical situations as events (secondary non breast cancer for IDFS-SPNBC, DCIS for DFS, distant recurrence as or beyond the earliest IDFS event for DRFI) support the advantage from adjuvant Kadcyla over trastuzumab.

98 OS events (6.6%) had occurred to cut-off date. Although OS data are immature, a benefit trend of Kadcyla was observed.

Sensitivity analyses (censoring patients who began a new anti-cancer therapy or those who discontinued study treatment for any reason) were consistent with the primary analysis of IDFS.

3.3. Uncertainties and limitations about favourable effects

Albeit adjusted to the statistical plan of the trial, median follow-up (40.9 months in the trastuzumab arm and 41.4 months in the Kadcyla arm) is certainly limited for a study in the adjuvant setting of breast cancer. In fact, nearly one third of alive patients from the ITT had ≤3 years of follow-up on study.

Although the benefit trend of Kadcyla is observed in formal OS testing, the result is not statistically significant (unstratified HR 0.70; 95% CI 0.47, 1.05; p=0.0848). Hence, a long-term non-detrimental OS effect from Kadcyla cannot be yet established. To further investigate the efficacy of Kadcyla in the claimed indication, the MAH will provide the final analysis results by the second quarter of 2024 (see Annex II of the PI).

Although the IDFS forest plot suggests that the benefit from Kadcyla was seen across most stage and substage subgroups, the high variability of breast cancer according to specific staging creates too small fractions to determine the absolute benefit in patients with small residual tumours and none or little nodal disease, as compared to the more apparent benefit in patients with bigger tumours and/or N2/N3 stage.

Immaturity of the IDFS data prevents determining the potential effect of ADAs on efficacy. The clinical impact of anti-therapeutic antibodies will continue to be monitored (see RMP).

3.4. Unfavourable effects

The incidence of ≥G3 AEs (26% vs. 15%), serious AEs (5% vs. 1%) and AEs leading to treatment discontinuation (18% vs. 2%) in the Kadcyla arm was higher than in the trastuzumab arm.

Kadcyla-specific AEs were expectedly more frequent than the control arm: hepatotoxicity (38% vs. 11%), thrombocytopenia (29% vs. 2%), peripheral neuropathy (32% vs. 17%), haemorrhage (29% vs. 10%) and pulmonary toxicity (3% vs. 1%).

Certain symptoms typically related to chemotherapy (nausea, fatigue, dry mouth/stomatitis/dysgeusia, constipation, peripheral neuropathy and decreased appetite) were also more prevalent in the safety population of Kadcyla.

211 patients treated with Kadcyla (28.5%) experienced any-grade thrombocytopenia. Half of them (105 out of 211) experienced G1 thrombocytopenia, while the remaining 106 patients had ≥G2 events. High-grade (≥G3) thrombocytopenia occurred in 42 patients (5.7%) and serious events were reported in 10. Undoubtedly, thrombocytopenia was also the AE most frequently implied in dose interruptions (14 patients), dose reductions (23 patients) and permanent discontinuations (31 patients) from the Kadcyla arm. The incidence and severity of thrombocytopenia was higher in the Asian subgroup than in the other race subgroups.

There was one G5 AE related to Kadcyla in a patient with traumatic intracranial haemorrhage and G4 thrombocytopenia.

216 patients (29.2%) from the Kadcyla arm and 69 patients (9.6%) from the trastuzumab arm experienced haemorrhage of diverse categories. Most of these events were of low grade and with minor clinical consequences, but 5 patients from both arms suffered high-grade events.

The rate of hepatotoxic events in the Kadcyla arm tripled that from the trastuzumab arm: 37.3% vs. 10.6%. G2-3 events occurred in 85 patients (11.5%) treated with Kadcyla. The most common any-grade hepatotoxic events in the Kadcyla arm were increased ASAT (28.4%), ALAT (23.1%), alkaline phosphatase (8.2%), bilirubin (6.6%) and GGT (3.6%).

The incidence of peripheral neuropathy, a disabling AE with likely chronic consequences and a detrimental impact in quality of life, in the Kadcyla arm (32.3%) nearly doubles that of the trastuzumab arm (16.9%).

Cardiotoxicity from Kadcyla did not raise major concerns. The incidence of overall cardiac dysfunction events was higher in the trastuzumab arm (40 vs. 23 patients in the Kadcyla arm).

Nearly 1 out of each 5 patients withdrew from the Kadcyla arm because of intolerable toxicity. Almost one quarter of all discontinuations in the Kadcyla arm were a result of thrombocytopenia: 31 events in 133 patients (23.3%). Other AEs leading to permanent treatment withdrawal from Kadcyla were increased bilirubin, ASAT increased, ALAT increased, peripheral sensory neuropathy and ejection fraction decreased.

3.5. Uncertainties and limitations about unfavourable effects

Safety analysis in the ≥65-year-old age subgroup was limited and inconclusive by the low number of patients. The use of Kadcyla in elderly patients will continue to be closely monitored (see also RMP).

3.6. Effects Table

Table 71: Effects Table for Kadcyla vs. trastuzumab in the adjuvant treatment of patients with HER2+ EBC and residual invasive disease after neoadjuvant chemotherapy and HER2-targeted agents, data cut-off 25 Jul 2018.

Effect	Short description	Unit	Kadcyla (experimental)	Trastuzumab (control)	Uncertainties / Strength of evidence	References
Favourable Effects						
IDFS	Time between randomization and date of first occurrence of any one of the following IDFS event	Patients with event (%)	91 (12.2)	165 (22.2)	Unstratified HR 0.50 (0.39, 0.64) p < 0.0001 *CNS recurrence rates do not differ between Kadcyla and trastuzumab	
IDFS 3-year event-free rate	3-year IDFS event free rate	Rate (95% CI)	88.27 (85.81, 90.72)	77.02 (73.78, 80.26)		
OS	Time from randomization to death due to any cause	Patients with event (%)	42 (5.7)	56 (7.5)	Unstratified HR 0.70 (0.47, 1.05) p = 0.0848 *Immaturity of data (6.6% of events) does not establish non-detrimental OS effect from Kadcyla	
OS 3-year event-free rate	3-year OS event free rate	Rate (95% CI)	95.18 (93.58, 96.79)	93.59 (91.71, 95.47)		
Unfavourable Effects						
≥Grade 3 AEs		%	25.7	15.4		
AEs leading to treatment		%	18.0	2.1		

Effect	Short description	Unit	Kadcyla (experimental)	Trastuzumab (control)	Uncertainties / Strength of evidence	References
discontinuation						
Thrombocytopenia	Any grade Grade ≥ 3	%	28.5 5.7	2.4 0.3		
Haemorrhage	Any grade Grade ≥ 3	%	29.2 0.4	9.6 0.3		
Hepatotoxicity	Any grade Grade ≥ 3	%	37.3 1.6	10.6 0.4		
Peripheral neuropathy	Any Grade Grade ≥ 3	%	32.3 0	16.9 1.4		

Abbreviations: CI= confidence interval; IDFS= invasive disease free survival; OS= Overall Survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from the first interim analysis from the KATHERINE trial suggest that residual invasive disease can also be a predictive biomarker in HER2+ EBC: patients treated with Kadcyla presented an overall lower risk of invasive recurrence than those who received trastuzumab.

Recurrence in the CNS, often in the form of brain metastases, is a particularly dreadful event with higher incidence in HER2+ and triple negative breast cancer, entailing the worst survival prognosis from all types of recurrence events. However, the beneficial effect from adjuvant Kadcyla seems to be exerted outside of sanctuary sites such as the brain.

With this limitations and uncertainties in consideration, the overwhelming difference in acute and chronic toxicity between standard-of-care trastuzumab and Kadcyla must be considered. Undeniably, adjuvant Kadcyla was not well tolerated and compared quite unsatisfactorily to trastuzumab in safety terms, putting a considerable amount of patients at risk for unpleasant, disabling and even life-threatening adverse events.

3.7.2. Balance of benefits and risks

As compared to trastuzumab, Kadcyla demonstrated a clinically meaningful reduction in the overall recurrence rate in the targeted population of the KATHERINE trial. Significant toxicity and obvious safety risks are observed in patients treated with Kadcyla. Nonetheless, the magnitude of clinical benefit of Kadcyla in the proposed patient population outweighs the observed safety concerns. Furthermore, measures are in place to minimise the risks as reflected in the PI and RMP.

3.8. Conclusions

The overall B/R of Kadcyla as a single agent, for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have invasive residual disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy is positive.

The CHMP considers the following measures necessary to address issues related to efficacy:

PAES: In order to further investigate the efficacy of trastuzumab emtansine in the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy, the MAH should submit the final analysis of OS from the phase 3, randomised, open-label study KATHERINE (BO27938). Due date: 30 June 2024.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the use of Kadcyla as a single agent for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have invasive residual disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce editorial changes throughout the product information. An updated RMP version 9.2 has been agreed.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

This CHMP recommendation is subject to the following new condition:

Conditions and requirements of the marketing authorisation

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
PAES: In order to further investigate the efficacy of trastuzumab emtansine in the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy, the MAH should submit the final analysis of OS from the phase 3, randomised, open-label study KATHERINE (BO27938).	30 June 2024