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Kadcyla (T-DM1) in HER2+ mBC
Label Update on LVEF following a post approval commitment – based on RWD

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BreastGyn Franchise

Disclaimer

- I am a full time Roche employee
- This presentation shares my views and not necessarily those of F.Hoffmann-La Roche

Agenda

- **Context**

RWD addressed EU Commitment leading to a CDS update & label changes in EU, U.S. and Canada (process ongoing for other countries)

- **Why RWD with secondary data use?**
- **What is the study about?**
- **What are the learnings?**

CDS: Core Data Sheet

Clinical context

- In the metastatic setting, Kadcyla is indicated in patients previously treated with HER2 targeted therapy*
- Kadcyla clinical development program generally excluded patients with LVEF<50%
  - No cardiac safety data on the use Kadcyla in patients with low LVEF
  - Patients treated with HER2 targeted therapy are at increased risk of developing left ventricular dysfunction
  - *Clinical guidelines (Giordano 2014): "clinicians treat patients with clinical congestive heart failure or compromised LVEF on a case-by-case basis, assessing the relative risks of cardiac dysfunction versus disease progression"*

Situation

Commitment: Evaluate cardiac safety outcomes in pts. with low LVEF treated with Kadcyla

Rare population

* Full indication in approved EU Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/kadcyla-epar-product-information_en.pdf (Accessed 21 October 2020)

**Giordano S.H., Temin S., Kirshner J.J. et al. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2– Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. JCO 2014

Timeline & regulatory context

Category 3 commitment in the RMP addressing cardiac safety

It was considered to be **of clinical value to evaluate the risk** for patients with a cardiac output between 40-50% in the post-marketing situation, as many of these patients may be in a situation where there are no alternatives to Kadcyla.

Very few patients with low LVEF were enrolled in the disease registries.
Roche **proposed to assess the feasibility** of using **Flatiron** EHR database to address the question.

2013	2014	2015	2016
Kadcyla MA			

Roche proposed to evaluate cardiac risk in the post-marketing setting using data from observational mBC **disease registries**. Rarity of pts. with low LVEF was an identified challenge.

Scope of Work signed in Jan.

Feasibility to be conducted within a year

Solution

Propose use of secondary data (**Flatiron EHR**) to identify the relevant patients

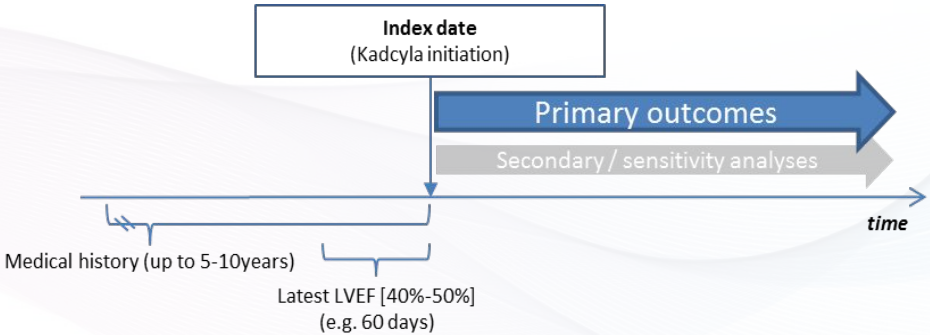
Describe patients <u>characteristics</u> and cardiac outcomes

Conduct feasibility study and assess HA interest

PRAC: The Pharmacovigilance Risk Assessment Committee is the European Medicines Agency's (EMA) committee responsible for assessing and monitoring the safety of human medicines.

Study design

- Retrospective cohort drawn from the medical charts of 240+ oncology practices
- **Population selection**
  - Study sample 40%≤ latest LVEF ≤ 50% (within 60 days prior index) from 1st Jan 2013 to 31st July 2018



- **Measures at baseline**
  - Population characteristics at index (age, setting, treatment history, selected morbidities…)
  - Cardiac status/condition at initiation

- **Definition of the outcomes over the risk period for <u>treatment emergent*</u> adverse event**
  - LVEF values + incidence of LVEF drop >10% points from baseline (Primary)
  - Incidence of CHF from index date
  - Incidence of <u>other cardiac event and CHF symptoms</u>

*from index date to the 84th days following Kadcyla last administration before discontinuation

Study challenges and design considerations

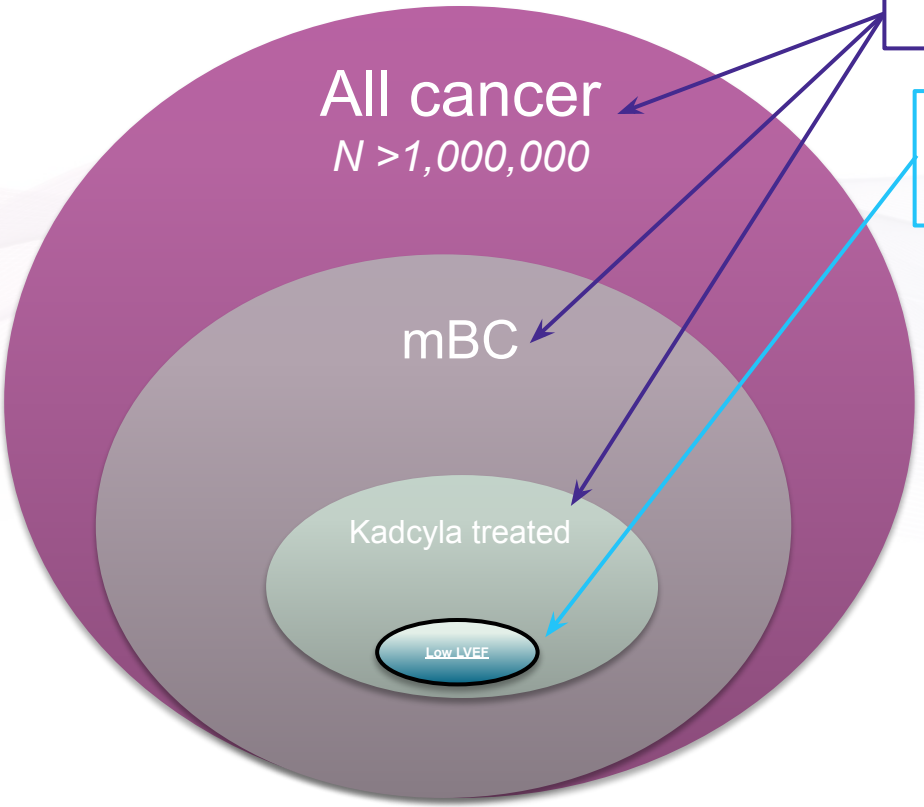
- Limitations
  - No background rate available in such a selected population
    - Risk of protopathic bias
    - Technically at a mix of incident and prevalent condition/events

  } Importance of accessing very granular baseline information

  - Risk period linked to treatment duration (range of **sensitivity analyses** was conducted)
  - Competing risk situation (risk of death vs. risk of cardiac events)
  - **Misclassification** and **under reporting** (signs and symptoms were used as sensitivity analyses)
  - **Informative censoring** (literature review, attempt to link with claims data*)
  - **Missing data** (multiple imputation*, composite endpoint)

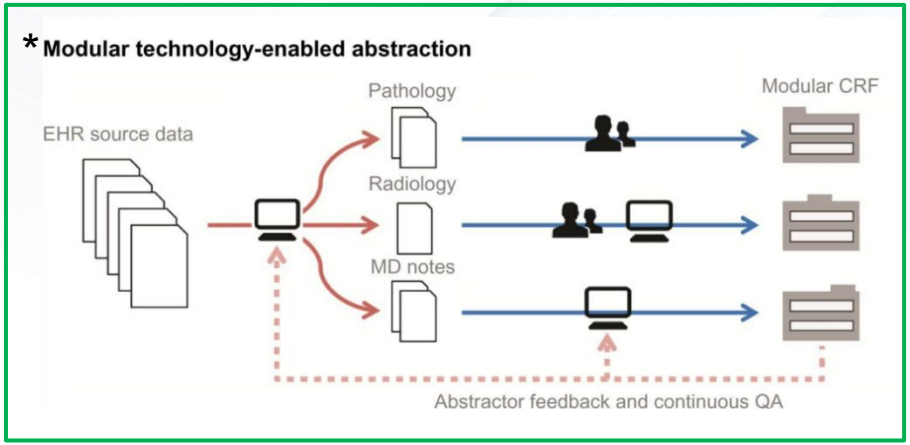
- *analyses were not implemented due to sample size or contractual reasons

Fulfilling post-approval commitment for Kadcyla



Screening using algorithms on structured data

mBC+Kadcyla abstracted*
N =[25-40] as of July 2016



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Patients selection

Flatiron Health database; May 31, 2018 (N >17 000)

Patients with ICD 9/10 breast cancer diagnosis and two visits on or after Jan 1, 2011 and a record of T-DM1 order or administration in structured data
(n = 2187)

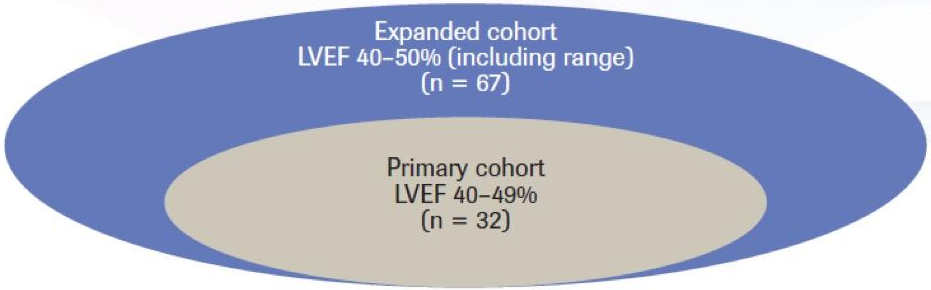
Patients with stage IV or recurrent MBC treated with T-DM1 and confirmed through unstructured data
(n = 1985*)

Patients with an LVEF of ≤50% prior to treatment initiation
(n = 137)

Exclusion of patients missing metastatic diagnosis dates (n = 2), or discrepancies between MBC diagnosis and index date (n = 0)
(n = 135)

Study cohorts

Patients with evidence of latest LVEF[†] recorded 60 days prior to initiation of T-DM1



* 1,833 (92.3%) had an LVEF assessment prior to the start of T-DM1.
[†] Latest LVEF value could be reported as an absolute value or range overlapping with 50%.
ICD, International Classification of Diseases; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; T-DM1, ado-trastuzumab emtansine

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Results

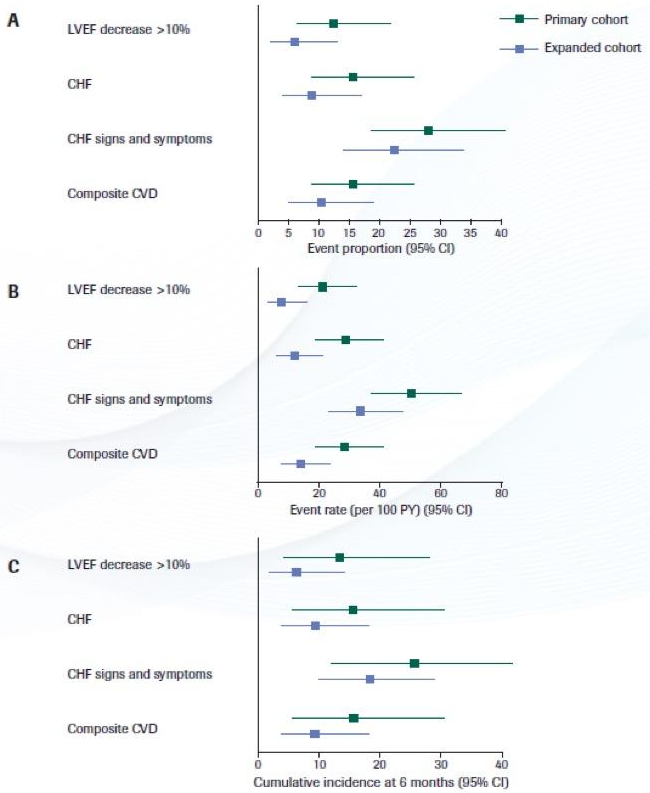
Baseline Characteristics

Risk factors in patients, n (%)	Primary cohort (n = 32)	Expanded cohort (n = 67)
Cardiac medication prescribed	27 (84.4)	53 (79.1)
Hypertension	21 (65.6)	39 (58.2)
Discontinuation of prior BC treatment due to cardiotoxicity	20 (62.5)	28 (41.8)
CHF signs and symptoms	11 (34.4)	19 (28.4)
Hypercholesterolemia	9 (28.1)	17 (25.4)
CHF	9 (28.1)	12 (17.9)
Diabetes	8 (25.0)	17 (25.4)
Coronary artery disease	5 (15.6)	8 (11.9)
Atrial tachyarrhythmia	4 (12.5)	8 (11.9)
Hospitalization due to CHF	<4 (<12.5)	<4 (<5.9)
Myocardial infarction	<4 (<12.5)	5 (7.5)

BC, breast cancer; CHF, congestive heart failure.

Outcomes in the primary cohort

- LVEF drop >10% points was observed in 4 patients
- CHF was observed in 5 patients
- 7 patients out of 32 (22%) had LVEF drop >10% or CHF



Includes patients who had already experienced an event prior to T-DM1 initiation.
Composite CVD is defined as the incidence of any events such as active CHF, active cardiac tachyarrhythmia, ventricular tachyarrhythmia, acute coronary syndrome, unstable angina, myocardial infarction, and cardiac death (only CHF and cardiac arrhythmia were identified in follow-up).
CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction; PY, person-years.; T-DM1, ado-trastuzumab emtansine

Sanglier, T., Shim, J., Liu, H., Song, C., Smitt, M., & Flahavan, E. M. (2020b). *Cardiac events in patients with HER2-positive metastatic breast cancer who have low left ventricular ejection fraction prior to initiating treatment with ado-trastuzumab emtansine: A retrospective cohort study using electronic health record data.* Presented at SABCS 2019.

Overall study conclusions

- Limited size of the population of interest (<5% of the Kadcyla population had prior LVEF [40-49%])
- Most of the cases already experienced cardiac events prior to Kadcyla initiation
- No “flare up” of the cardiac risk was observed in MBC patients (wide CIs reported)

- Individual B/R to be assessed on a case by case basis
- LVEF must be monitored

Timeline & Outcome

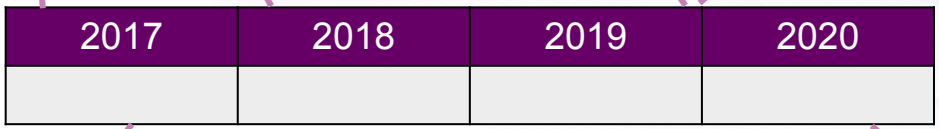
BO39807 listed as a category 3 study in the RMP addressing cardiac safety. LVEF study was accepted as commitment in lieu of registries in RMP

Following **promising feasibility results**, Roche proposed to update the EHR data annually and provide interim report in 2018 PBRER and final report in 2019 PBRER (Study BO39807)

Interim analysis conducted and report (N=31-57) submitted PRAC Assessment agreed with the discussion and conclusion

Publication SABCS 2019

CHMP positive opinion for text in **SmPC** with results from Study BO39807.



Challenges in finding patients in the disease registries

Study registration on **ENCePP**

Results did not constitute a new signal. **Final report** (N=32 to 67) submitted and proposal to add text based on results from Study BO39807 to SmPC

Approval for additional label text from FDA & Health Canada following CDS update

Key Insights

PRAC **acknowledges the difficulties** surrounding patient recruitment

PRAC was **receptive to using EHR data** to address PV

Secondary data was used instead of initially proposed registries

Change of RWD strategy

PBRER: periodic benefit-risk evaluation report is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions.

Regulatory - FDA Approved Wording

5 WARNINGS AND PRECAUTIONS

5.2 Left Ventricular Dysfunction

Patients treated with KADCYLA are at increased risk of developing left ventricular dysfunction. A decrease of LVEF to < 40% has been observed in patients treated with KADCYLA. Serious cases of heart failure, with no fatal cases, have been observed in clinical trials with KADCYLA. In EMILIA, left ventricular dysfunction occurred in 1.8% of patients in the KADCYLA-treated group and 3.3% of patients in the lapatinib plus capecitabine-treated group. In KATHERINE, left ventricular dysfunction occurred in 0.4% of patients in the KADCYLA-treated group and 0.6% of patients in the trastuzumab-treated group *[see Adverse Reactions (6.1)]*.

Based on limited data from a retrospective observational study, 22% (7 of 32) of patients with HER2-positive metastatic breast cancer (MBC) with a baseline LVEF of 40-49% treated with KADCYLA developed a congestive heart failure (CHF) or a > 10% reduction in LVEF [see Adverse Reactions (6.3)].

Assess LVEF prior to initiation of KADCYLA and at regular intervals (e.g. every three months) during treatment to ensure the LVEF is within the institution's normal limits. **KADCYLA has not been studied in an adequately controlled study in patients with LVEF<50%**

For patients with MBC, if, at routine monitoring, LVEF is < 40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold KADCYLA and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue KADCYLA if the LVEF has not improved or has declined further.

For patients with EBC, if, at routine monitoring, LVEF is < 45%, or is 45% to 49% with a 10% or greater absolute decrease below the pretreatment value, withhold KADCYLA and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue KADCYLA if the LVEF has not improved or has declined further *[see Dosage and Administration (2.2)]*.

Patients with a history of symptomatic CHF, serious cardiac arrhythmia, or history of myocardial infarction or unstable angina within 6 months were excluded from the EMILIA and KATHERINE studies *[see Clinical Studies (14.1)]*.

6 Post Marketing Experience:

6.3 Post-Marketing Experience:

The following adverse reactions have been identified during post-approval use of KADCYLA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse Reactions from Observational Studies

• CHF and > 10% reduction in LVEF in patients with HER2-positive metastatic breast cancer with a baseline LVEF of 40-49% treated with KADCYLA [see Warnings and Precautions (5.2)].

Adverse Reactions from Post-marketing Spontaneous Reports

• Tumor lysis syndrome (TLS): Cases of possible TLS have been reported in patients treated with KADCYLA. Patients with significant tumor burden (e.g., bulky metastases) may be at a higher risk. Patients could present with hyperuricemia, hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated.

Approved US Prescribing Information:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125427s108lbl.pdf (Accessed 23 October 2020)"

Key points

- **Why RWD with secondary data use?**
  - The research question is about routine clinical practice
  - Using disease registries approaches for studying this Kadcyla subpopulation was impractical (actually even more than we thought)

- **What is the study about?**
  - Closing the gap on missing safety information in population not studied in clinical studies

- **What are the learnings?**
  - Frequent updates on study status and transparency with regards to challenges
  - Bring sound feasibility
  - Study addressed EU Commitment leading to a CDS update & label changes in EU, U.S. and Canada (process ongoing for other countries)

CDS: Core Data Sheet

References

- Lynce, F., Barac, A., Geng, X., Dang, C., Yu, A. F., Smith, K. L., . . . Swain, S. M. (2019). Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function: the SAFE-HEaRt study. *Breast Cancer Res Treat, 175*(3), 595-603. doi:10.1007/s10549-019-05191-2

- https://www.ema.europa.eu/en/documents/product-information/kadcyla-epar-product-information_en.pdf

- ENCEPP registration: http://www.encepp.eu/encepp/viewResource.htm?id=22158

- Study results: Sanglier, T., Shim, J., Liu, H., Song, C., Smitt, M., & Flahavan, E. M. (2020b). Cardiac events in patients with HER2-positive metastatic breast cancer who have low left ventricular ejection fraction prior to initiating treatment with ado-trastuzumab emtansine: A retrospective cohort study using electronic health record data. Presented at SABCS 2019.

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Thank you!

Doing now what patients need next