Title: Leveraging Real World Data (RWD) to Assess Safety: Reasons for Treatment Discontinuation Among Patients with Breast Cancer Treated with Antibody Drug Conjugates (ADCs)

Short title: Common Data Model Harmonization (CDMH): Breast Cancer Use Case

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1. BACKGROUND

Breast cancer is the most common cancer in the world, with an estimated 2.3 million new cases of female BC in 2020 globally (11.7% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer globally, with an estimated 685,000 deaths.[1] In the United States, an estimated 313,510 new cases and 42,780 deaths are expected in 2024.[2]

Breast cancer is a heterogeneous disease with multiple subtypes. Classification of breast subtypes has evolved over the years; however, the most common and widely accepted classification is from an immunohistochemical perspective, based on the expression of hormone receptors, estrogen (ER) and progesterone (PR) receptors, and expression of human epidermal growth factor receptor 2 (HER2).[3] Breast cancers that do not express these receptors are largely classified as triple-negative breast cancer (TNBC).

Treatment, both in the early and advanced stage setting, is principally based on the breast cancer subtype. As such, the mainstay of treatment for breast cancers that are ER- and /or PR-positive (collectively referred to as HR-positive) is endocrine therapy, for HER2-positive is HER2-targeted therapy and for TNBC is chemotherapy with or without other agents (such as or immune checkpoint inhibitors [ICI] or PARP inhibitors for tumors with germline BRCA mutation).[4]

Targeted agents, such as small molecules and biologics (monoclonal antibodies [mAb] and antibody drug conjugates [ADCs]) are an essential part of the breast cancer treatment armamentarium. Trastuzumab, approved by the FDA in 1998, was the first mAb approved for the treatment of HER2-positive breast cancer. Subsequently other biologics (such as pertuzumab) and oral tyrosine kinase inhibitors (such as lapatinib, neratinib and tucatinib) were added to the breast cancer armamentarium.

Apart from trastuzumab emtansine (T-DM1), which has been FDA approved for the treatment of HER2-positive breast cancer since February 2013, ADCs represents an emerging treatment for breast cancer. Within the last 5 years or less, two other ADC's have been added to the breast cancer treatment armamentarium. Post-market data for these latter ADCs are still limited and our knowledge regarding safety and efficacy of these treatments are mainly confined to clinical trial data sources. In the real world, patients may carry an array of comorbidities and other conditions which may impact the safety and effectiveness of ADCs which may not be readily identified in clinical trials.

Randomized clinical trials (RCTs) provide the best evidence for drug approvals to date. Although RCTs are generally well-designed, confining our knowledge to clinical data may not provide the clearest or broadest picture of both safety and effectiveness of ADCs in the intended breast cancer population. Augmenting clinical trial data with information accumulated from patients in real world settings may

provide information related to important questions that may not have been addressed in the pivotal clinical trials leading to approval of ADCs. These include but not limited to questions pertinent to important consideration(s) when choosing ADC's as potential treatment as opposed to other treatment option such as in patients with comorbidities, specific end-organ dysfunction, or unusual concurrent medications.

Use of Real-World Data (RWD) to learn more about ADC's safety and tolerability profile broadens our knowledge about these agents which may in turn lead to greater awareness among regulators and health care providers and/or inform future investigations to better meet the clinical needs of patients. For instance, real-world data sources may offer information related to: (1) adverse events leading to treatment discontinuation highlighting specific safety and tolerability concerns for a particular ADC that either confirms, clarifies or perhaps even abrogates knowledge from clinical trials; (2) concomitant medications administered with ADCs augments our ability to monitor for possible emerging drug-drug interactions; (3) concomitant supportive care medications and the degree these are required to treat adverse drug reactions may address lingering question on mitigation strategies; (4) duration of therapy with an ADC may provide clues to effectiveness when an ADC use in the approved indication is generalized to the real world or provide hypothesis generating data on disease activity for non-approved indications; and (5) subsequent use of anticancer agent following use of ADCs may provide insight into appropriate sequencing of therapy in the setting of multiple alternative treatment options.

2. OBJECTIVES

The objective of this assessment is to facilitate the use of Real-World Data (RWD) (i.e., electronic health records data as data sources) to support evidence generation for regulatory and clinical decision making.

In this project, the team will focus on the safety of ADCs that have been FDA approved for the treatment of breast cancer, for the period of 2/1/2013 to 2/28/2023. The primary aim of this assessment would be safety, specifically on adverse events leading to treatment discontinuation of ADCs for the treatment of breast cancer, focusing on data elements representing the specific intended breast cancer population of each approved ADC.

Collaborating with two Health Information Exchanges (HIE): Indiana HIE (IHIE) and Nebraska HIE (CyncHealth), the specific objectives of this study are to:

a. Determine the frequency of use of FDA approved ADCs in breast cancer. For this demonstration project, extent of alignment with indicated approval will be exploratory.
b. Assess ADC treatment details including (if treated with more than 1 ADC, obtain information for each ADC used):
    i. Choice of a particular ADC and reason for the choice, if indicated
    ii. Duration of treatment.

iii. Reason for treatment discontinuation
iv. Subsequent therapy following ADC discontinuation.

c. (Exploratory) Explore the robustness/completeness to which EHRs as RWD sources capture the following data elements:
   i. Breast cancer diagnosis, staging and extent of subgroup identification (i.e., hormone receptors status and HER2 expression).
   ii. Alignment
   iii. Treatments other than ADC and disease setting of specific drug use, duration of treatment, reasons for treatment discontinuation and subsequent therapies.

The ultimate aim of this study is to have breast cancer use case to test Common Data Model Harmonization (CDMH) – the mappings among healthcare and clinical research standards, identify gaps in healthcare as well as existing clinical research standards, and to map the data elements to standard terminologies and convert the breast cancer clinical question of interest into a Health Level Seven (HL7) Clinical Quality Language (CQL), a standard-based query language.

3. COHORT IDENTIFICATION

a. Inclusion Criteria
   This assessment will utilize data spanning a decade, starting on 2/1/2013 through 2/28/2024 (starts on the month the first [trastuzumab emtansine] of the 3 ADCs of interest appears on the FDA approved list of drugs through at least 1 year after last approved indication of the 3rd ADC [Sacituzumab govitecan] on the list. Refer to Appendix A for listing of ADCs of interest:

   i. Adult patients with diagnosis of locally advanced or metastatic breast cancer and were treated with ADC(s) for their disease at any time point after 2/2013.
   ii. Only for T-DM1, patients treated in the early breast cancer setting are eligible.

b. Exclusion Criteria:
   i. Patients who were definitively treated with an ADC in a clinical trial.
   ii. Early-stage disease/no evidence of metastasis except those treated with T-DM1 in the adjuvant setting (n.b. although it may be useful to examine those patients that receive either T-DXd and/or SG in the early-stage setting, but this would be a small number and exploratory analysis since these drugs are not yet approved in the early breast cancer setting).

4. PARAMETERS OF INTEREST AND DESCRIPTION OF EACH PARAMETER

a. Breast cancer diagnosis and sub-type, stage at the time of ADC therapy (see Appendix B)

b. Treatment with ADC (see Appendix A), including line of therapy (i.e., first-line, 2nd-line, etc.). For T-DM1, include if treatment was in the early vs. advanced disease setting (or both).

c. Duration of ADC therapy
Duration is defined by the number of months/days between the beginning of the ADC treatment and end of the treatment. The assessment will be in terms of months/days between the first day of treatment and either:
- Last day of treatment (if the treatment ended prior to query), or
- Date of query (or time since ADC therapy initiation, in case of ongoing treatments)
- In case of lapse of treatment (i.e., patients who stopped and restarted the therapy)
  - days between end of an ADC therapy and resumption of the same ADC therapy
  - any gaps between infusions, which may be caused by adverse events/ toxicity
- Other measures of exposure, including total number of cycles, and/or cumulative dose, if available.

d. Reason for ADC treatment discontinuation
If the drug was discontinued, provide the reason for the discontinuation, if available. Describe whether the reason for discontinuation was:
- Progression of disease leading to alternative therapy
- Unacceptable toxicity
- Exacerbation of pre-existing comorbidity, if present.

Determine if reasons for ADC treatment discontinuation align with reasons for discontinuation identified in pivotal trials (See Appendix C).

e. Toxicity, including any attribution to the ADC if available.
Toxicity is defined by the adverse events (may also include laboratory data or imaging data) during ADC treatment (and up to 30 days after end of treatment or initiation of new anti-cancer therapy, whichever occurs first) (See Appendix D). Include the following, if available:
- Clinical toxicity grading (i.e., mild, moderate, severe, life-threatening) or other toxicity grading criteria (indicate which criteria used if available)
- Resolution of toxicity (resolved vs. ongoing) at the time of query.
- Recurrence of the same toxicity after initial resolution.
- Mitigation strategies to alleviate the identified toxicity, including dose modification and or supportive interventions.
- Sequelae from the toxicity, if any. Describe if sequelae is permanent, stable or ongoing at the time of query. Indicate if there was any improvement from initial severity/grade.

f. Temporal relationships of ADC use with the identified adverse events (AEs), if available

ADCs are related to specific AEs identified during drug development, confirmed in the pivotal clinical trial(s) leading to approval and identified in Section 5 (Warnings and Precautions) of the drug label (see Appendix D). There is also a population of patients that have been excluded from clinical trials with these agents due to safety as they may be particularly vulnerable to experiencing these listed toxicities. Even with careful patient selection in clinical trials, these AEs may still be important the reason for treatment discontinuation. Thus, when treatment is used in real-world setting, it is important to know if similar AEs remain as reasons for treatment discontinuation or if there are different or other AEs cited as reasons for treatment discontinuation.

g. Comorbid conditions
List diseases or illness that predates the use of ADC. Medications taken prior to initiation of ADC may also be informative of comorbidities that are not listed or readily apparent.

h. Concomitant medications
Concurrent medications vary based on underlying comorbidity or toxicities experienced with ADC treatment. Thus, it would be important to provide reasons for use of concurrent medications. If not readily apparent, temporal relationship or concurrency with an AE may be informative.

i. Imaging data
Although imaging data per se may not be readily available, imaging reports maybe available. These reports may help elucidate issues such as the presence of brain metastases, progression of disease or response to therapy. If imaging data/reports can be collected and analyzed efficiently, it may provide an opportunity to understand the reason for treatment discontinuation in the assessed cohorts.

j. Laboratory data
Laboratory data, collected and analyzed efficiently, may be another opportunity to understand the reason for treatment discontinuation (such as for hematologic toxicity, liver or kidney dysfunction). Analyze the following collected laboratory data:
    - Complete blood count including differential
    - Creatinine and/or creatinine clearance
    - Liver function test

k. Off-label use
Although exploratory, indicate any off-label use, defined by the use of the ADC in a specific patient for reasons other than the labeled indication as listed in Appendix A.

5. APPENDICES

a. **List of FDA approved ADCs for Breast Cancer Indication**
b. **List of Disease Characteristics of Interest (and Diagnostic Codes)**
c. **List of AEs Leading to Treatment Discontinuation from Pivotal Trials**
d. **List of Notable Adverse Reactions per ADC Label (USPI)**

APPENDIX A

List of FDA approved ADCs for Breast Cancer Indication

ADC	Approval Date	Approved Indication(s)	NDC Package Code	RxNorm
T-DM1 (Kadcyla)	2/2013	Treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination (Regular approval based on the EMILIA trial [NCT00829166])	50242-087-01 50242-088-01	**1371046** Or: **1658086**: trastuzumab Injection [KADCYLA] **1658087**: ado-trastuzumab emtansine 100 MG Injection [KADCYLA] **1658091**: ado-trastuzumab emtansine 160 MG Injection [KADCYLA]
	5/2019	Adjuvant treatment of patients with HER2-positive early breast cancer EBC) who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment (Regular approval based on the KATHERINE trial [NCT01772472])		**1371046**
T-DXd (Enhertu)	12/2019	Treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting (Accelerated approval based on DESTINY-Breast01 trial [NCT03248492]; regular approval based on DESTINY-Breast02 trial [NCT03523585])	65597-406-01	**2267577** Or: **2267581**: fam-trastuzumab deruxtecan-nxki 100 MG Injection [Enhertu]
	5/2022	Treatment of adult patients with unresectable or metastatic HER2-	65597-406-01	2267577

		positive breast cancer who have received a prior anti-HER2-based regimen either: in the metastatic setting, or in the neo-/adjuvant setting and have developed disease recurrence during or within six months of completing therapy (Regular approval based on DESTINY-Breast03 trial [NCT03529110])		
	8/2022	Treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (Regular approval based on DESTINY-Breast04 trial [NCT03734029])		2267577
SG (Trodelvy)	4/2020	Treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease (Accelerated approval based on IMMU-132-01 trial [NCT01631552])	55135-132-01	2360535 Or: 2360539: sacituzumab govitecan-hziy 180 MG Injection [Trodelvy]
	4/2021	Treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease (Regular approval based on the ASCENT trial [NCT02574455])	55135-132-01	2360535
	2/2023	Treatment of unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting (Regular approval based on the TROPiCS-02 trial [NCT03901339])	55135-132-01	2360535

APPENDIX B

Disease Characteristics of Interest (and Diagnostic Codes)

Breast cancer histology:	**ICD-10-CM 2025 Edition**	**SNOMED CT**
Invasive ductal carcinoma (Intraductal carcinoma)?		408643008
Intraductal carcinoma in situ of unspecified breast	D05.10	
Intraductal carcinoma in situ of right breast	D05.11	1306576000
Intraductal carcinoma in situ of left breast	D05.12	1306575001
Invasive lobular carcinoma in situ of unspecified breast	D05.0	Bilateral: 15952981000119103
Lobular carcinoma in situ of right breast	D05.01	354471000119108
Lobular carcinoma in situ of left breast	D05.02	354341000119108
Other histologies except metaplastic carcinoma	N/A	N/A
Receptor status		
Hormone receptor (HR) status		
Hormone receptor negative HR negative (ER and PR to <1% expression by IHC)	Z17.42	438628005
Hormone receptor positive HR positive: ER or PR >1% expression by IHC	Z17.41	417181009
HER2-receptor status		
Human epidermal growth factor receptor 2 negative status HER2 negative (IHC 0 or ISH-)	Z17.32	438628005
HER2 low (IHC 1+ or IHC 2+/ISH-)	N/A	N/A
Human epidermal growth factor receptor 2 positive status HER2 positive (IHC 3+ or ISH+/amplified)	Z17.31	417181009
Breast cancer sub-type:		
Hormone receptor negative with human epidermal growth factor receptor 2 negative status, Triple negative breast cancer Triple negative [TNBC] (ER-/PR- and HER2-)	Z17.421	706970001
Human epidermal growth factor receptor 2 positive status HER2-positive (HER2+, any HR status)	Z17.31 Z17.410	459391000124109

Hormone receptor positive with human epidermal growth factor receptor 2 positive status Hormone receptor negative with human epidermal growth factor receptor 2 positive status	Z17.420	
Hormone receptor positive with human epidermal growth factor receptor 2 negative status HR-positive, HER2-negative (HR+/HER2-)	Z17.411	431396003
Clinical Staging		
Metastatic disease or Stage IV (TxNxM1) De novo (TxNxM1 at initial diagnosis) Recurrent (initial diagnosis of TxNxM0 with subsequent TxNxM1) Metastatic breast cancer	C79.9 C79.81	254837009
Locally advanced, inoperable disease Inflammatory breast cancer [IBC] (T4d, any N, M0) Stage IIIc (Tx, N3, M0)	N61	254837009 266579006
Locally advanced, potentially curable disease Stage IIb (T2N1M0; T3N0M0) Stage IIIa (T0-1N2M0; T3N1M0; T2N1M0) Stage IIIb (T4N0-1M0; T4N2)	C50 C50.919	254837009 The SNOMED CT codes for Stage IIb, IIIa, IIIb and IIIc breast cancer are not explicitly defined.
Early stage disease Stage I (T1N0-1N1$_{mic}$M0) Stage IIa (T0-1N1M0; T2N0M0)	C50.919	254837009

Appendix C

List of AEs Leading to Treatment Discontinuation from Pivotal Trials

ADC	Clinical trial	AEs (in ~1% patients) leading to discontinuation
T-DM1 (Kadcyla)	EMILIA[6]	Thrombocytopenia Increased AST
	KATHERINE[7]	Decreased platelet count/thrombocytopenia Increased bilirubin Increased AST or ALT Decreased ejection fraction decreased Peripheral sensory neuropathy
T-DXd (Enhertu)	DESTINY-Breast01[8] DESTINY-Breast02[9]	ILD/pneumonitis
	DESTINY-Breast03[10]	ILD/pneumonitis Thrombocytopenia
	DESTINY-Breast04[11]	ILD/pneumonitis
SG (Trodelvy)	IMMU-132-01[12]	Anaphylaxis, Anorexia/fatigue Headache
	ASCENT[13]	Fatigue Pneumonia
	TROPiCS-02[14]	Asthenia General physical health deterioration Neutropenia

Abbreviations: AST-aspartate aminotransferase; ALT-alanine aminotransferase, ILD-Interstitial lung disease; SG-sacituzumab govitecan-hziy

Appendix D

List of Notable Adverse Reactions per ADC Label (USPI)

ADC	Label Section	
	Boxed Warning	**Adverse Reactions (related symptoms)**
T-DM1 (Kadcyla)	Hepatotoxicity/liver failure	• Hepatotoxicity
	Reduction in LVEF	• Left Ventricular Dysfunction
	Embryo-Fetal Toxicity	• Embryo-Fetal Toxicity (oligohydramnios, pulmonary hypoplasia, skeletal abnormalities and neonatal death)
		• Pulmonary Toxicity (ILD/pneumonitis) • Infusion-Related Reactions/Hypersensitivity Reactions (flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia) • Hemorrhage (CNS, respiratory and GI bleeding) • Thrombocytopenia/decreased platelet count • Neurotoxicity (peripheral neuropathy)
T-DXd (Enhertu)	ILD/pneumonitis	• ILD/pneumonitis
	Embryo-fetal harm	• Embryo-Fetal Toxicity (oligohydramnios, pulmonary hypoplasia, skeletal abnormalities and neonatal death)
		• Neutropenia (decreased neutrophil count, febrile neutropenia) • Left ventricular dysfunction (LVEF decrease
SG (Trodelvy)	Neutropenia	• Neutropenia
	Diarrhea	• Diarrhea
		• Hypersensitivity and Infusion Related Reactions (cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions) • Nausea and Vomiting

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