The Use of Real-World Evidence in Drug Development

Amy Abernethy, MD, PhD
Chief Medical Officer/Chief Scientific Officer
Flatiron Health
Agenda

- Role of real-world evidence in oncology drug development
- Key steps in preparing EHR data to contribute to real-world evidence
- Case study: Trastuzumab emtansine (Kadcyla)
- Policy recommendations
Role of real-world evidence in oncology drug development
Real-world Evidence

Definition

- Information derived from healthcare delivered outside the traditional clinical trial setting
- Includes electronic health records (EHRs), claims/admin data, registries, and patient-generated health data
- Complements clinical trials ---> more generalizable knowledge
- Randomization may or may not be a feature of RWE studies

21st Century Cures Act
PDUFA VI
Real-world Data / Big Data / Real-world Evidence

Real-world data

- One dataset or many accumulated datasets can contribute to real-world data
- “Big data”
  - Amalgamation of data types to more clearly complete the picture of what is happening to patients in the real world
  - “Big” → velocity, volume, variety, veracity
- Real-world data analyzed in a consistent manner to generate clinically-meaningful generalizable evidence → RWE

- Example applications of RWE in oncology:
  - Confirming benefit for new indications → label expansion
  - Optimizing clinical use → label revisions
  - Post marketing requirements
  - Safety monitoring
RWE along the continuum

Clinical Practice → REAL WORLD DATA → Clinical Trial Dataset

- Retrospective RWE
  - Retrospective Capture with Longitudinal Follow-Up
  - Consent with or without randomization

- Prospective RWE
  - Prospective Capture
RWE along the continuum

Clinical Practice → REAL WORLD DATA → Clinical Trial Dataset

Retrospective RWE

Prospective RWE

Retrospective Capture with Longitudinal Follow-Up → Prospective Capture → Consent with or without randomization

Identification of rare patients
Observational data on off label use
Real-world follow-up on clinical outcomes
Pragmatic trial
Data Requirements for Real-world Evidence

<table>
<thead>
<tr>
<th>Data Requirements</th>
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<tbody>
<tr>
<td>● Drug development use cases (for the most part) require:</td>
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<tr>
<td>○ Aggregated, high quality, complete, longitudinal datasets</td>
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<tr>
<td>○ Reproducibility and provenance</td>
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<tr>
<td>○ Patient-level data linkage</td>
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<tr>
<td>○ Endpoints/outcomes</td>
</tr>
<tr>
<td>○ Study objectives and analysis plans</td>
</tr>
<tr>
<td>○ Careful cohort selection</td>
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<table>
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<tr>
<th>EHRs as a way forward</th>
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<tr>
<td>● EHR data can act at the backbone and organizing framework</td>
</tr>
<tr>
<td>○ &gt;90% of US oncologists use an EHR</td>
</tr>
<tr>
<td>○ Linkable</td>
</tr>
<tr>
<td>○ Quality can be documented and improved</td>
</tr>
<tr>
<td>○ Can use a registry analytic framework</td>
</tr>
</tbody>
</table>
Key steps in preparing EHR data to contribute to real-world evidence
Aggregate EHR data into single common dataset

- 258 Cancer Clinics
- 2,400 Clinicians
- 1.5M Active Cancer Patients in Network
Standardize EHR data to a common data model

Structured Data
- Demographics
- Diagnosis
- Visits
- Labs
- Therapies

Electronic Health Record

Unstructured Data
- Physician Notes
- Radiology Report
- Pathology Report
- Discharge Notes

Outside Practice
- Hospital
- Lab

Structured Data Processing

Unstructured Data Processing

Real World Database

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Standardize EHR data to a common data model

Standard EHR Data

Structured Data

- Demographics
- Diagnosis
- Visits
- Labs
- Therapies

Electronic Health Record

Structured Data Processing

Real World Database
Standardize EHR data to a common data model: Harmonization and normalization of structured data

- Certain structured data elements may be coded and collected in multiple ways in the EHR across practices (*example: albumin*)
- Combine and map datasets across sites to a single dataset
- Map all data elements to a single set of definitions (data model)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD25001600</td>
<td>ALBUMIN/GLOBULIN RATIO QD (calc)</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD25001400</td>
<td>ALBUMIN QD</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD50058600</td>
<td>ALBUMIN</td>
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<tr>
<td>QD50055700</td>
<td>ALBUMIN</td>
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</tr>
<tr>
<td>CL3215104</td>
<td>Albumin % (EPR)</td>
<td>%</td>
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<tr>
<td>LC001081</td>
<td>ALBUMIN, SERUM (001081)</td>
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<td>LC133751</td>
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<td>LC133686</td>
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<td>QD50060710</td>
<td>MICROALBUMIN</td>
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<td>QD85991610</td>
<td>ALBUMIN</td>
<td>relative %</td>
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<tr>
<td>50058600</td>
<td>ALBUMIN UPEP RAND</td>
<td>%</td>
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<td>CL3210074</td>
<td>ALBUMIN LEVEL</td>
<td>g/dL</td>
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<td>QD86008211</td>
<td>ALBUMIN/GLOBULIN RATIO (calc)</td>
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<td>LC149520</td>
<td>Albumin</td>
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<tr>
<td>QD45069600</td>
<td>PREALBUMIN</td>
<td>mg/dL</td>
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<tr>
<td>QD900415245</td>
<td>ALBUMIN, SERUM</td>
<td>mg/dL</td>
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<tr>
<td>QD900429745</td>
<td>ALBUMIN</td>
<td>g/dL</td>
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<td>CL3215124</td>
<td>Albumin Electrophoresis</td>
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<td>LC016931</td>
<td>Prealbumin</td>
<td>mg/dL</td>
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<tr>
<td>QD50060800</td>
<td>MICROALBUMIN, 24 HOUR UR</td>
<td>mg/24 h</td>
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<tr>
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<td>MICROALBUMIN, 24 HOUR UR</td>
<td>mcg/min</td>
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<tr>
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<td>CL3213320</td>
<td>PREALBUMIN</td>
<td>mg/dL</td>
</tr>
<tr>
<td>QD85995225</td>
<td>PROTEIN ELECTROPHORESIS ALBUMIN</td>
<td>g/dL</td>
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1751-7 Albumin [Mass/volume] in Serum or Plasma g/dL

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Standardize EHR data to a common data model

Electronic Health Record

- Physician Notes
- Discharge Notes
- Radiology Report
- Pathology Report

Unstructured Data

Real World Database

Outside Practice

- Hospital
- Lab

Unstructured Data Processing

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For every PD-1/PD-L1 test a patient receives, Flatiron biomarker Data Model captures:

- Test status
- Test result
- Date biopsy collected
- Date biopsy received by laboratory
- Date result received by provider
- Lab name
- Sample type
- Tissue collection site
- Type of test (e.g., FISH)
- Assay / kit (e.g., Dako 22C3)
- Percent staining & staining intensity
Abstraction of unstructured data through Patient Manager allows for comparability across patients as well as different oncology practices.
Standardize EHR data to a common data model: Centralized data processing and QA/QC

**Operational Controls**
- All abstracted data is collected through controlled forms
- All abstracted data is processed in accordance with approved procedures
- Structured clinical data is subject to medical informatics mapping
- Cross-functional oversight by oncology, statistical, technology, compliance teams
- Pre-specified protocol for IRB review and approval

**Quality Controls**
- Quantitative Scientists planning, oversight and final of data
  - Detailed analytic guide which pre-specified parameters
- Quality control and auditing of abstraction (unstructured data)
  - Edge cases escalated for review by oncologist for adjudication
- Agreement scores (e.g. kappas) and monitoring of abstracted data

**System Controls**
- Electronic Health Record (structured and unstructured data):
  - Full access to EHR data throughout the lifecycle of patient care
  - Updated in real time to allow for data recency
- Patient Manager Abstraction Software (unstructured data):
  - Audit trails, documentation and traceability of abstracted data
  - System does not allow for untrained staff to complete abstraction
### Standardize EHR data to a common data model: Centralized data processing and QA/QC

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Characterize data quality

Completeness of technology-enabled abstraction

**Example: Advanced NSCLC**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Structured data only</th>
<th>Flatiron data completeness</th>
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<tr>
<td>Metastatic diagnosis</td>
<td>26%</td>
<td>100%</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0%(^1)</td>
<td>94%</td>
</tr>
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<td>Histology</td>
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<td>Stage</td>
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1 58% are free text in dedicated field in EHR (requiring hand abstraction)
2 Including 8% of patients with results pending or unsuccessful test
3 Including 6% of patients with results pending or unsuccessful test

Accuracy of technology-enabled abstraction

**Example: Sites of metastases**

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<th>Kappa</th>
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### Completeness of technology-enabled abstraction

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Link processed EHR data to other datasets

- External mortality datasets
- Germline & somatic genomic data
- Claims data
- Prospective data capture
- Patient-reported outcomes
- Biosensors

Processed structured & unstructured EHR data
Incorporate endpoints / outcomes

5 key types of outcomes

- Mortality
- Tumor response / treatment change
- Toxicity
- Patient-generated health data
- Health resource utilization

Combining data sources enables development of a high-quality consensus date of death for patients across the database
Diagnosed with Stage II NSCLC

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR

Starts 2L therapy, deteriorates and is hospitalized

Death

Example: Non-small cell lung cancer
Diagnosed with Stage II NSCLC

Undergoes surgery for early-stage disease

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR

Starts 2L therapy, deteriorates and is hospitalized

Death

Example: Non-small cell lung cancer

Organize datasets for analysis
Diagnosed with Stage II NSCLC

Patient age
Gender
Race
Insurance

Develops metastatic disease

Tested for EGFR and ALK

Undergoes surgery for early-stage disease

Regimen name
Duration of therapy
Dosage
Concomitant meds

Starts 1L therapy

Starts 2L therapy, deteriorates and is hospitalized

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR

Death

Date of death

Datasets linked & organized
Structured EHR data
Diagnosed with Stage II NSCLC

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Starts 2L therapy, deteriorates and is hospitalized

Death

- Patient age
- Date of surgery
- Sites of metastases
- Biopsy date
- Type of test conducted
- Turnaround time for test
- Number of unsuccessful tests
- Test result, if successful
- Type of EGFR mutation
- Regimen name
- Duration of therapy
- Dosage
- Concomitant meds
- Response
- Biopsy date
- Lab name
- Test result
- T790M mutation
- Date of death

Datasets linked & organized

Structured EHR data

Unstructured EHR data

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Diagnosed with Stage II NSCLC

- Patient age
- Gender
- Race
- Insurance
- TNM staging

Undergoes surgery for early-stage disease

- Date of surgery

Develops metastatic disease

- Sites of metastases

Tested for EGFR and ALK

- Biopsy date
- Type of test conducted
- Turnaround time for test
- Number of unsuccessful tests
- Test result, if successful
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- Biopsy date
- Lab name
- Test result
- T790M mutation

Starts 2L therapy, deteriorates and is hospitalized

- Date of death
- Date of death

Death

Datasets linked & organized:

- Structured EHR data
- Unstructured EHR data
- External Mortality data

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Diagnosed with Stage II NSCLC

Undergoes surgery for early-stage disease

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR

Starts 2L therapy, deteriorates and is hospitalized

Death

- Patient age
- Gender
- Race
- Insurance
- TNM staging
- Comorbidities

- Date of surgery
- Sites of metastases
- Time to recurrence
- Biopsy date
- Type of test conducted
- Turnaround time for test
- Number of unsuccessful tests
- Test result, if successful
- Type of EGFR mutation
- Regimen name
- Duration of therapy
- Dosage
- Concomitant meds
- Response
- Reason for discontinuation
- Biopsy date
- Lab name
- Test result
- T790M mutation
- Date of death
- Date of death
- Consensus date of death

Datasets linked & organized:
- Structured EHR data
- Unstructured EHR data
- External Mortality data
- Combined/Derived data

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Diagnosed with Stage II NSCLC

Undergoes surgery for early-stage disease

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR

Starts 2L therapy, deteriorates and is hospitalized

Death

- Patient age
- Gender
- Race
- Insurance
- TNM staging
- Comorbidities

- Date of surgery
- Sites of metastases
- Time to recurrence

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- Reason for discontinuation

- Biopsy date
- Lab name
- Test result
- T790M mutation

- Date of death
- Date of death
- Consensus date of death

- Date of hospitalization
- Cost of care

Datasets linked & organized

Structured EHR data
Unstructured EHR data
External Mortality data
Combined/Derived data
Claims data

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Diagnosed with Stage II NSCLC
Undergoes surgery for early-stage disease
Develops metastatic disease
Tests for EGFR and ALK
Starts 1L therapy
Progresses on 1L, re-tested for EGFR
Starts 2L therapy, deteriorates and is hospitalized
Death

<table>
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<tr>
<th>Patient</th>
<th>Demographics</th>
<th>Stage</th>
<th>Diagnosis Date</th>
<th>Biomarkers</th>
<th>Treatment</th>
<th>Response</th>
<th>Hospital Admissions</th>
<th>Mortality</th>
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<tr>
<td>A</td>
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**Document source, quality and provenance**

- Abstracted by Sue Smith on 8/31/16 at 10:10am
- Biomarker documents were reviewed
- Medical record from West Florida Cancer Clinic
- Quality of EGFR abstraction
  - Completeness is 99%
  - Sue Smith is 96% accurate at last testing
  - Inter-abstractor agreement 97%
  - Kappa 0.93
- Audit trail for any changes
- Dataset freeze and storage

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<tr>
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</tbody>
</table>

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Explicit study objectives and analysis plan

Real-world Data

Study Dataset

- Excluded Patients
- Eligible Cohort

Group A
- Endpoints
- Results and QA

Group B
- Endpoints

Study Objectives
- Cohort Selection
- Analysis Plan
- Interpretation

RWE
Drug development use cases (for the most part) require:
- Aggregated, high quality, complete, longitudinal datasets
- Reproducibility and provenance
- Patient-level data linkage
- Endpoints/outcomes
- Study objectives and analysis plans
- Careful cohort selection

Example applications of RWE in oncology:
- Confirming benefit for new indications → label expansion
- Optimizing clinical use → label revisions
- Post marketing requirements
- Safety monitoring

Case study: traztuzumab emtansine (Kadcyla)
Case study: Trastuzumab emtansine (Kadcyla)
RWE along the continuum

Clinical Practice -> REAL WORLD DATA

Retrospective RWE

Retrospective Capture with Longitudinal Follow-Up

Prospective Capture

Consent with or without randomization

Real-world follow-up on clinical outcomes

Observational data on off label use

Identification of rare patients

Pragmatic trial
Anti-HER2 agents have known cardiotoxicity

Major Kadcyla clinical studies excluded patients at risk for cardiotoxicity:
- EF <50% or h/o CHF, serious cardiac arrhythmia requiring treatment, MI or unstable angina w/i 6 mo
Anti-HER2 agents have known cardiotoxicity.

Major Kadcyla clinical studies excluded patients at risk for cardiotoxicity.

1 patient in the EMILIA study developed grade 3 cardiotoxicity on Kadcyla.

FDA issued a boxed warning:

- Kadcyla not well studied when EF ≤ 50%
- If EF drops < 40% (or 10% below pretreatment), repeat LVEF assessment and if persists d/c Rx

**Left Ventricular Dysfunction (Boxed WARNING)**

Patients treated with KADCYLA are at increased risk of developing left ventricular dysfunction (LVD). A decrease of left ventricular ejection fraction (LVEF) to < 40% has been observed in patients treated with KADCYLA. In EMILIA, left ventricular dysfunction occurred in 1.6% of patients in the KADCYLA-treated group and 3.3% of patients in the comparator group.

Assess LVEF prior to initiation of KADCYLA and at regular intervals (e.g., every 3 months) during treatment. Treatment with KADCYLA has not been studied in patients with LVEF < 50% prior to treatment. 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.
RWE Case Study: Trastuzumab emtansine usage in low-LVEF patients

Context

- Anti-HER2 agents have known cardiotoxicity
- Major Kadcyla clinical studies excluded patients at risk for cardiotoxicity
- 1 patient in the EMILIA study developed grade 3 cardiotoxicity on Kadcyla
- FDA issued a boxed warning

- Meanwhile, clinically, some patients with EF ≤50% still receive Kadcyla
  - Since patients with LVEF ≤50% do receive Kadcyla outside of the clinical trial setting, real world evidence offers an opportunity to understand the experience of Kadcyla usage in these patients
RWE Case Study: Trastuzumab emtansine usage in low-LVEF patients

Objectives:
- To assess the rate and severity of cardiac events in patients with metastatic breast cancer treated with trastuzumab emtansine who have a LVEF $\leq 50\%$ at treatment initiation
- Characterize patient population
- Other outcomes (OS, PFS, resource utilization)

Eligibility criteria:
- Diagnosis of breast cancer (ICD-9 174.x or ICD-10 C50.x)
- At least two visits in the Flatiron Health database on or after 1/1/2013
- Pathology consistent with breast cancer
- Evidence of stage IV or recurrent metastatic breast cancer with a metastatic diagnosis date on or after 1/1/2013
- Treatment with trastuzumab-emtansine (structured med admin data and confirmed via unstructured data review)
- LVEF $\leq 50\%$ at the time of initiation of treatment with trastuzumab-emtansine
RWE Case Study: Cohort selection

- Maintain a growing curated dataset in mBC
- At time of cohort selection >8,000 cases
- Allowed for the identification of >60 patients who had LVEF ≤50%

From **structured data**, patients with:
- ICD 9/10 diagnosis codes for breast cancer
- Two visits on or after 1/1/2013
- Structured medication order or administration for trastuzumab-emtansine

N = 1,149

From **unstructured data** review, confirmation of diagnosis with metastatic breast cancer on or after 1/1/2013

N = 1,070

From **unstructured data** review, confirmation of treatment with trastuzumab-emtansine

N = 1,000

From **unstructured data** review, LVEF ≤50% at the time of trastuzumab-emtansine initiation, as defined by the most recent LVEF assessment prior to trastuzumab-emtansine initiation

N = 66
INTERPRETATION SUMMARY
The global left ventricular systolic function is low normal. LV EF is estimated at 50%
There is no evidence for regional wall motion abnormality.

**Indication:** Cardiomyopathy, assess LV function.

**Left Ventricle Ejection Fraction:** 46.9%

**Final Conclusions:**
1. Sinus rhythm.
2. This was a technically adequate study.
3. This was a limited exam for LV function assessment.
4. The left ventricular size is normal.
5. Left ventricular wall thickness is normal.
6. Overall left ventricular systolic function is mildly impaired with an EF between 45 - 50%. Stable from 2014. Okay for Kadalay.
7. Compared to prior study of , no change.

Important task was to assess data quality of cardiac information
- Complex information in chart
- Duplicate abstraction
- Clinical adjudication
- Claims data comparison
<table>
<thead>
<tr>
<th>characteristic</th>
<th>description</th>
<th>median</th>
<th>range</th>
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<td>Time from initial diagnosis to Kadcyla initiation</td>
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<td>Time from metastatic diagnosis to Kadcyla initiation</td>
<td>Median = 2.3 years</td>
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<td>Range 1.2-4.1</td>
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<tr>
<td>Median follow up from index date</td>
<td>Median = 0.8 years</td>
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<td>Range 0.5-1.5</td>
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### RWE Case Study: Baseline characteristics (N=66)

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RWE Case Study: LVEF Data (N=66)

Breakdown By LVEF Value

- 20-24%: 2 patients
- 25-29%: 2 patients
- 30-34%: 1 patient
- 35-39%: 3 patients
- 40-45%: 31 patients
- 45-49%: 27 patients
- 50%: 0 patients

LVEF Range

Breakdown By Time Before Baseline

- 0-30 days: 13 patients
- 31-60 days: 32 patients
- 61-90 days: 4 patients
- 91+ days: 17 patients

Days Before Baseline

Note: Baseline = date of Kadcyla initiation
RWE Case Study: LVEF Data (N=66)

Breakdown By LVEF Value

LVEF Range

Breakdown By Time Before Baseline

Days Before Baseline

Note: Baseline = date of Kadcyla initiation

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RWE Case Study: LVEF Data (N=66)

Breakdown By LVEF Value

Breakdown By Time Before Baseline

LVEF Range

Days Before Baseline

Note: Baseline = date of Kadcyla initiation
RWE Case Study: Patient Journey

Abraxane
RWE Case Study: Patient Journey

EF 45%

Kadcyla
RWE Case Study: Patient Journey

Monitor EF over time

Hospitalizations: Discern if cardiac or cancer related
Policy recommendations
Policy recommendations

- Clarify the role of RWE in oncology drug development

- FDA guidance on RWE
  - Drug development scenarios where most applicable
  - Data quality requirements
  - Data management and dataset production requirements
    - Retrospective
    - Prospective studies / pragmatic trials
  - Optimal analytic approaches

- Clarify how RWE will be represented in the label

- Develop an approach to real-world endpoints using a multi-stakeholder transparent process