

**Emulation of the MONARCH-3 (NCT02246621) trial using specialty oncology  
electronic health records databases**

**NCT07225790**

**9<sup>th</sup> February 2026**

## 1. Title Page

|   |   |
|---|---|
| <b>Title</b>  | Emulation of the MONARCH-3 (NCT02246621) trial using specialty oncology electronic health records databases   |
| <b>Research question &amp; Objectives</b>   | Emulation of the MONARCH-3 (NCT02246621) trial, which compared abemaciclib–letrozole/anastrozole to letrozole/anastrozole alone with progression-free survival (PFS) as the primary endpoint and overall survival (OS) as a secondary endpoint in postmenopausal women with hormone receptor (HR)-positive [estrogen receptor (ER) and/or progesterone receptor (PR)], human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. |
| <b>Protocol version</b>   | V2.0  |
| <b>Last update date</b>   | February 9, 2026  |
| <b>Contributors</b>   | <b>Primary investigators:</b><br>Denys Shay, Shirley V. Wang  |
| <b>Study registration</b>   | <b>Site:</b> clinicaltrials.gov<br><b>Identifier:</b> NCT07225790   |
| <b>Sponsor</b>  | <b>Organization:</b> Food and Drug Administration<br><b>Contact:</b> n/a  |
| <b>Conflict of interest</b>   | SVW has been an ad hoc consultant to Exponent Inc, Cytel Inc, and MITRE a federally funded research and development center for the Centers for Medicare and Medicaid  |
| <b>Protocol repository</b>  | Clinicaltrials.gov  |
| <b>Analytic code repository</b>   | <a href="https://gitlab-scm.partners.org/drugapi/encore/monarch3-nct-02246621">https://gitlab-scm.partners.org/drugapi/encore/monarch3-nct-02246621</a><br>(access within Mass General Brigham network only)  |
| <b>Quarto study report<br/>(including annotated code and output)</b>  | <a href="https://gitlab-scm.partners.org/drugapi/encore/monarch3-nct-02246621/-/tree/main/public?ref_type=heads">https://gitlab-scm.partners.org/drugapi/encore/monarch3-nct-02246621/-/tree/main/public?ref_type=heads</a> (access within Mass General Brigham network only)   |
| <b>encore.io<sup>1</sup> version</b>  | 0.2.0 (see attached documentation <i>encore.io_0.2.0.pdf</i> )  |
| <b>encore.analytics<sup>1</sup> version</b>   | 0.2.0 ( <a href="https://janickweberpals.github.io/encore.analytics/">https://janickweberpals.github.io/encore.analytics/</a> )   |
| <sup>1</sup> Internally-developed R package to streamline analytics across all available databases and to enhance consistency, transparency and reproducibility in variable definitions and analytic workflows across trial emulations. |   |

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## 2. Abstract

This trial emulation study aims to emulate the MONARCH-3 trial (NCT02246621) using real-world specialty oncology electronic health records data and to investigate the concordance between the trial's original and the emulated treatment effect estimate on overall survival (OS). MONARCH 3 is a double-blind, randomized phase III study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor in 493 postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Patients received abemaciclib or placebo (150 mg twice daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole/anastrozole, daily.

## 3. Amendments and updates

| Version date      | Version number | Section of protocol           | Amendment or update   | Reason   |
|-------------------|----------------|-------------------------------|---|--|
| November 3, 2025  | V1.0           | NA                            | Initial version   | NA   |
| November 10, 2025 | V1.1           | - 10.2 and 10.3               | - Slightly different matched cohorts and power  | - Fixed minor error in the code  |
| November 14, 2025 | V1.2           | - 6.6, Table 5                | - Categorization of dem_race to nominal (White, Asian, Other), as in the original MONARCH-3 trial<br><br>- Socioeconomic status index and practice type are not available in EDB3 and EDB4<br><br>- Family history of cancer is not available in EDB1<br><br>- Change of unit of glucose to mg/dL<br><br>- Change of unit of urea nitrogen to mg/dL | - Fixed minor errors in the protocol   |
| February 9, 2026  | V2.0           | 6.1.1, Table 7, Table 8, 10.3 | - EDB4 was excluded from the primary analysis and included in sensitivity analysis #11 (meta-analysis)  | Because the study identification period (10/01/2018-09/30/2023) began after the 2017 approval of ribociclib, patients who initiated ribociclib before 10/01/2018 were only |

|  |  |  |  |   |
|--|--|--|--|---|
|  |  |  |  | included if they survived until the start of the study period, which may introduce immortal time and selection bias due to left truncation. |
|--|--|--|--|---|

#### 4. Rationale and background

Randomized controlled trials (RCTs) are generally regarded as the gold-standard of evidence for establishing efficacy of medical products. However, real-world data (RWD) are increasingly used to complement evidence from RCTs. Yet, to have confidence in the accuracy of non-interventional studies medical products and their outcomes in oncology, investigators need to know what questions can be validly answered, with which non-interventional study designs, and which analysis methods are appropriate, given the data that is available. Building on a process from the RCT DUPLICATE initiative<sup>1-4</sup> **Emulation of Comparative Oncology trials with Real-world Evidence (ENCORE)** is part of the expansion project specific to oncology and aims to emulate 12 randomized oncology RCTs using multiple EHR data sources.

The purpose of this protocol is to describe the emulation of the **MONARCH-3 trial**. MONARCH 3 is a double-blind, randomized phase III study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor in 493 postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Patients received abemaciclib or placebo (150 mg twice daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole/anastrozole, daily.

The **primary trial endpoint** was **progression-free survival (PFS)**, with a hazard ratio (HR) for progression or death of 0.54 (95% CI, 0.41 to 0.72; P = .000021). The **median follow-up was not reached** in the abemaciclib-plus-letrozole/anastrozole group compared with **14.7 months** in the letrozole/anastrozole-alone group. The FDA granted abemaciclib approval in [March 2017](#), in combination with letrozole/anastrozole for the treatment of ER-positive, HER2-negative advanced breast cancer as initial endocrine based therapy in postmenopausal women.

**Overall survival (OS)** was a **secondary endpoint**. At the final OS analysis, a non-significant overall survival benefit was observed, with a median overall survival of 66.8 months in the abemaciclib group and 53.7 months in the placebo group (**HR for death**, 0.804; 95% confidence interval 0.637-1.015; P = 0.0664).

The PFS endpoint was published in the *JCO* on October 2, 2017 ([PMID: 28968163](#)).<sup>5</sup>

Updated results were published in *npj breast cancer* on January 17, 2019 ([PMID: 30675515](#)).<sup>6</sup>

The final OS endpoint was published in the *Ann Oncol.* on May 8, 2024 ([PMID: 38729566](#)).<sup>7</sup>

## 5. Research question and objectives

The primary and secondary research question is summarized in Table 1.

### A. Primary research question and objective

**Table 1. Primary and secondary research questions and objective.**

|  |  |
|--|--|
| <b>Objective:</b>  | To compare the overall survival [OS] in patients who initiated abemaciclib plus letrozole/anastrozole versus patients who initiated letrozole/anastrozole alone.   |
| <b>Hypothesis:</b>   | Initiation of abemaciclib plus letrozole/anastrozole improves OS time as compared to initiation of letrozole/anastrozole alone.  |
| <b>Population (<i>mention key inclusion-exclusion criteria</i>):</b> | <ul style="list-style-type: none"><li>• Age <math>\geq 18</math> years</li><li>• Postmenopausal women with ER/PR-positive, HER2-negative locally advanced or metastatic breast cancer who receive treatment without curative intent<ul style="list-style-type: none"><li>○ The line of therapy for patients in EDB1 and EDB3 is implicitly advanced/metastatic because the line of therapy classification starts after their advanced/metastatic diagnosis in the respective database</li><li>○ In EDB4, patients must explicitly have any evidence of a metastasis prior initiating abemaciclib plus letrozole/anastrozole or letrozole/anastrozole alone</li></ul></li><li>• No prior systemic treatment for advanced/metastatic disease</li><li>• ECOG 0 or 1</li></ul> |
| <b>Exposure:</b>   | Initiation of abemaciclib plus letrozole/anastrozole   |
| <b>Comparator:</b>   | Initiation of letrozole/anastrozole  |
| <b>Outcome:</b>  | Primary: Time to all-cause mortality (OS)<br>Secondary: Time to next treatment (TTNT)  |
| <b>Time (<i>when follow up begins and ends</i>):</b>                 | One day after the end of the assessment window until outcome, death, last observed clinical activity/last sign of the patient being alive, or data cut-off, whichever occurred earliest  |
| <b>Setting:</b>  | 1L HR/PR-positive, HER2-negative locally advanced or metastatic breast cancer  |

|                         |                       |
|-------------------------|-----------------------|
| Main measure of effect: | Hazard ratio (95% CI) |
|-------------------------|-----------------------|

The emulation of the main protocol elements of the MONARCH-3 is illustrated side by side in **Table 2**.

**Table 2. Trial emulation table summarizing the main protocol elements of the MONARCH-3 trial and the planned emulation.**

| Protocol component          | MONARCH-3 RCT  | Emulation   | Comments  |
|-----------------------------|--|---|---|
| <b>Eligibility criteria</b> | <ul style="list-style-type: none"> <li>• Postmenopausal women aged <math>\geq 18</math> years with diagnosis of breast cancer</li> <li>• Locoregionally recurrent or metastatic disease not amenable to curative resection/radiotherapy</li> <li>• ER/PR-positive status</li> <li>• HER2-negative status</li> <li>No prior systemic therapy for advanced/metastatic disease</li> <li>• Measurable disease per RECIST v1.1 or bone-only disease confirmed by imaging</li> <li>• WHO/ECOG performance status 0 or 1</li> <li>• Inflammatory breast cancer</li> <li>• Current or prior chemotherapy or endocrine therapy (except letrozole/anastrozole) for locoregionally recurrent or metastatic breast cancer</li> </ul> | <ul style="list-style-type: none"> <li>• Female aged <math>\geq 18</math> years at treatment initiation with a diagnosis of breast cancer</li> <li>• Evidence of metastatic or recurrent disease</li> <li>• Documentation of ER/PR-positive (or -missing) status</li> <li>• Documentation of HER2-negative (or -missing) status</li> <li>• No systemic anti-cancer therapy<sup>a</sup> following initial record indicating metastatic disease and prior to index date</li> <li>• N/A</li> <li>• WHO/ECOG performance status of 0 or 1 within 90 days of index date</li> <li>• Record of inflammatory breast cancer</li> <li>• NA</li> </ul> | <ul style="list-style-type: none"> <li>• Although postmenopausal status is not directly captured in RWD, it is likely to be fulfilled given the alignment with the indication for the exposures of interest</li> <li>• If ER/PR is missing and a patient received the exposures of interest, then ER/PR is likely to be positive given the alignment with the indication for the exposures of interest</li> <li>• If HER2 is missing and a patient received the exposures of interest, then HER2 is likely to be negative given the alignment with the indication for the exposures of interest</li> <li>• It is reasonable to assume that all patients in RWD had measurable disease if they received treatment</li> <li>• Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole/anastrozole</li> </ul> |

|  |  |  |
|--|--|--|
| <ul style="list-style-type: none"> <li>• Prior (neo)adjuvant endocrine therapy (e.g., anti-estrogens or aromatase inhibitors) with a disease-free interval <math>\leq 12</math> months from completion of treatment</li> </ul> | <ul style="list-style-type: none"> <li>• Treatment with (neo)adjuvant endocrine therapy <math>\leq 12</math> months from MBC</li> </ul>  |  |
| <ul style="list-style-type: none"> <li>• No other malignancy within 3 years</li> </ul>   | <ul style="list-style-type: none"> <li>• No prior record of non-breast cancer malignancy within 3 years</li> </ul>   | <ul style="list-style-type: none"> <li>• Prior non-breast cancer malignancy within 3 years is approximated with advanced prior treatments based on recommendation by the data vendor for EDB4<sup>b</sup></li> </ul> |
| <ul style="list-style-type: none"> <li>• N/A</li> </ul>  | <ul style="list-style-type: none"> <li>• Restriction to the time period 2017-2023</li> </ul>   | <ul style="list-style-type: none"> <li>• 2017 was the approval year for abemaciclib, and 2023 is the end of the available data stream</li> </ul>   |
| <ul style="list-style-type: none"> <li>• N/A</li> </ul>  | <ul style="list-style-type: none"> <li>• Record of systemic anti-cancer therapy other than the trial treatments<sup>c</sup> during the exposure assessment window based on proprietary business rules</li> </ul> |  |

|                       |  |   |  |
|-----------------------|--|---|--|
| Treatment strategies  | Abemaciclib+ letrozole/anastrozole vs. placebo + letrozole/anastrozole                                   | Patients initiating abemaciclib+ letrozole/anastrozole vs. letrozole/anastrozole alone, using an exposure assessment window to capture combination treatments, based on each data vendor's proprietary business rules | Use treatment start dates to define exposure   |
| Assignment procedures | Randomized 1:1 to abemaciclib+ letrozole/anastrozole or placebo + letrozole/anastrozole                  | Propensity score-based matching or weighting to emulate randomization   | Balance baseline covariates to reduce confounding  |
| Follow-up period      | Time from randomization to death or censoring  | After exposure assessment window until death or censoring   | The purpose of an exposure assessment window is a rule-based identification of combination therapies                             |
| Outcome               | Primary: Progression-free survival (PFS) per investigator assessment<br>Secondary: Overall survival (OS) | Primary: OS<br>Secondary: Time-To-Next-Treatment (TTNT)   | Lack of good measurement of progression, so inferred by initiation of next treatment as a secondary endpoint rather than primary |
| Causal contrast       | Intent-to-treat effect   | Effect of initiating abemaciclib+ letrozole/anastrozole versus letrozole/anastrozole  | Analogous to ITT; emulates initiation rather than adherence  |

<sup>a</sup>Includes the following (same as antineoplastic drugs in 6.6.4) : abemaciclib, alpelisib, anastrozole, atezolizumab, bevacizumab, capecitabine, capivasertib, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, elacestrant, entrectinib, epirubicin, eribulin, etoposide, everolimus, exemestane, fluorouracil, fulvestrant, gemcitabine, goserelin, inavolisib, ixabepilone, larotrectinib, letrozole, methotrexate, nab-paclitaxel, olaparib, paclitaxel, palbociclib, pembrolizumab, pertuzumab, ribociclib, sacituzumab, talazoparib, tamoxifen, toremifene, trastuzumab, and vinorelbine.

**Includes the following:** adagrasib, afatinib, alectinib, amivantamab, atezolizumab, bevacizumab, belantamab mafodotin, bendamustine, binimetinib, bortezomib, brigatinib, cabozantinib, capmatinib, carfilzomib, cemiplimab, ceritinib, cetuximab, ciltacabtagene autoleucel, cisplatin, crizotinib, dabrafenib, dacomitinib, daratumumab, datopotomab, dexamethasone, dostarlimab, durvalumab, elotuzumab, elranatamab, encorafenib, ensartinib, entrectinib, erdafitinib, erlotinib, etoposide, fam-trastuzumab deruxtecan, fluorouracil, fruquintinib, gefitinib, gemcitabine, idecabtagene vicleucel, ipilimumab, irinotecan, isatuximab, ixazomib, lapatinib, larotrectinib, lazertinib, lenalidomide, leucovorin, levoleucovorin, linvoseltamab, lorlatinib, melphalan, mobocertinib, nivolumab, osimertinib, oxaliplatin, panitumumab, panobinostat, pembrolizumab, pemetrexed, pomalidomide, pralsetinib, ramucirumab, regorafenib, repotrectinib, retifanlimab, selinexor, selpercatinib, sotorasib, sunvozertinib, taletrectinib, talquetamab, teclistamab, telisotuzumab vedotin, tepotinib, thalidomide, tislelizumab, toripalimab, trametinib, tremelimumab, vandetanib, venetoclax, vemurafenib, vinorelbine, zenocutuzumab, ziv-aflibercept, zongertinib.

**Includes the following:** same as in a, except for abemaciclib, letrozole, and anastrozole.

## 6. Research methods

### 6.1. Data sources

#### 6.1.1. Context and rationale for data sources

The overall ENCORE project uses data from a total four different oncology-specific electronic health records (EHR)-derived data sources: ConcertAI, COTA, Flatiron Health, McKesson/Ontada. For ENCORE, not all databases are available for each cancer indication and the names of the databases will henceforth be blinded and referred to as ENCORE DataBase (EDB) 1, 2, 3 and 4 (the numbering does not coincide with the above order of mention of the databases).

For this trial emulation, breast cancer-specific data are available for EDB1, EDB3 and EDB4. The fitness-for-purpose of the data for the given trial emulation were assessed and considered for the final selection of the databases.

**Reason for selection:** All considered databases draw from a comprehensive national sample of patients with cancer in the US with detailed EHR-derived information on the information necessary to study medication effectiveness in oncology.

**Strengths of data source(s):** Size and detailed clinical information on oncology-specific variables and outcomes (validated composite all-cause mortality sourced from different data sources<sup>8,9</sup>).

**Limitations of data source(s):** General limitations across all data sources include missing data, potential lack of data continuity, heterogeneous data provenance, quality/heterogeneous ascertainment of mortality endpoint data and the variability in how line of treatment is captured and curated (a more comprehensive discussion of the data sources and approaches is provided in section 7. After a comprehensive assessment of all data sources regarding their fitness for the purpose of emulating the MONARCH-3 trial, EDB3 and EDB4 were found insufficient to be included in the main analysis for the following reasons:

- **Rationale for excluding of EDB3 from primary analysis:** After applying all I/E criteria, EDB3 results in a cohort with a very small sample size even before matching (Figure 6). The cohort in EDB3 did not show sufficient balance in measured covariates after matching (Figure 9).

- Rationale for excluding of EDB4 from primary analysis: Since the study identification period (10/01/2018-09/30/2023) began after the 2017 approval of abemaciclib, patients who initiated abemaciclib before 10/01/2018 were only included if they survived until the start of the study period, which may introduce selection bias due to left truncation.<sup>10</sup>

For these reasons, only EDB1 will be used for the main analysis. However, EDB3 and EDB4 will be considered as part of a sensitivity analysis in which all databases are individually analyzed (see sensitivity analysis #11 in Table 8).

**Data source provenance/curation:** In brief, all databases provide EHR-derived oncology-specific patient-level information which are either derived directly (e.g., through structured data fields and dropdown menu selections) from EHR and/or undergo semi-automated abstraction processes from unstructured reports. The detailed data provenance, abstraction processes and implemented business rules to curate and prioritize certain variables may vary by database and can be found in legacy publications by the data partners.

**Table 3. Metadata about data sources and software.**

|  | EDB1  | EDB3   | EDB4   |
|--|---|--|--|
| Data Source(s):                        | EHR-derived   | EHR-derived  | EHR-derived  |
| Study Period:                          | Patient identification period: 01/01/2011-04/30/2024 with follow-up information through data cut-off date on 04/30/2024   | Follow-up information through June 2023 (there is no specific time period restrictions for patient eligibility)  | Patient identification period: 10/01/2018-09/30/2023 with follow-up information through data cut-off date on 09/30/2023.   |
| Eligible Cohort Entry Period:          | Anytime at start of study drug initiation   | Anytime at start of study drug initiation  | Anytime at start of study drug initiation  |
| Data Version (or date of last update): | Delivery: Jul 11, 2024  | Delivery: Jun 16, 2023   | Delivery: Oct 24, 2023<br>Updated (demographics): Feb 29, 2024   |
| Data sampling/extraction criteria:     | Patients are sampled if they have a confirmed diagnosis of metastatic breast cancer via abstraction on or after 1 Jan 2011, and at least 2 EHR visits on or after 1 Jan 2011. Both ICD-9 (174.x) and ICD-10 (C50.x) codes are used for the initial selection, and advanced diagnosis are then confirmed via abstraction (since ICD codes do not specify advanced diseases). | EDB3 identifies patients for curation using a structured ICD-10 diagnosis code (ICD-10 C50*), corresponding to the indication of interest, along with at least the year of diagnosis. Once this initial screening list is generated, patients are randomly selected for further review. Curation begins with confirmation of the diagnosis and diagnosis date, primarily based on pathology reports and other unstructured data sources. All patients must be over 18 years of age at the time of their first diagnosis. Certain breast cancer cases are excluded from curation. Specifically, in-situ breast cancers such as ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) without an invasive component are not eligible. However, DCIS with microinvasion or DCIS associated with Paget's disease qualifies for curation. Additionally, in-situ breast cancers that later progress to invasive carcinoma are eligible; in these cases, the diagnosis date | Breast cancer patients with an office visit in the reporting period will be included in the report with full patient history. Patients are sampled if they were diagnosed with breast cancer and with a documented visit date, within the defined reporting period, to one of the facilities and were at least 20 years of age at the time of first diagnosis. Patients who were on a clinical trial at any point in their treatment history are excluded. |

|                                  |  |  |   |
|----------------------------------|--|--|---|
|                                  |  | <p>should reflect the date of the original in-situ diagnosis, not the later invasive diagnosis.</p> <p>Patients are ultimately selected for inclusion in data products through quality control processes that assess consistency and potential conflicts in their records. These evaluations may rely on structured data alone or a combination of structured and curated data, depending on the specific data product. Importantly, CAI does not exclude patients based on data completeness, in order to prevent the introduction of selection bias.</p> |   |
| Type(s) of data:                 | EHR-derived  | EHR-derived  | EHR-derived   |
| Data linkage <sup>1</sup> :      | Mortality/date of death is a composite endpoint of structured and unstructured data from the EHR, obituary data, and the social security death index | Mortality/date of death is a composite endpoint derived from structured EHR data, manual curation, and third-party sources including obituary data and the Social Security Death Index. De-identified tokens link patients across datasets using hashed PII. Curated data is prioritized, followed by EHR and then third-party sources. Reported death dates are shifted to the nearest Sunday within four days to enhance privacy. Curated death information follows a source hierarchy: death certificate, obituary, or provider-reported date.          | Mortality/date of death is a composite endpoint of structured and unstructured EHR data, supplemented with commercially available claims data, obituary data, and the Social Security Administration death master file. |
| Conversion to CDM <sup>2</sup> : | No   | Yes  | No  |
| Software for data management:    | R 4.3.2  | R 4.3.2  | R 4.3.2   |

<sup>1</sup> Mortality/date of death is a composite endpoint that is often derived from various linked sources including social security death index/ Social Security Administration death master file, obituary data and EHR records

<sup>2</sup> CDM = Common Data Model

## 6.2. Data management

Data is stored on secure Mass General Brigham corporate provisioned and backed up servers physically located in our Mass General Brigham corporate data centers. Mass General Brigham corporate data centers are designed to insure availability of the affiliated hospitals' and research applications and IT systems in the event of a disaster. The Division follows Mass General Brigham workstation requirements which include: encryption at rest, up-to-date malware protection including antivirus, spyware detection and removal tools, CrowdStrike End Point protection installed, devices enrolled in enterprise Mobile Device Management (MDM) solution as appropriate, any laptop/computer used for business purposes must not be shared with family, friends, or other unauthorized individuals, and compliance with enterprise Password Requirements. Only authorized personnel have read-only access to raw data files.

Cleaned and analysis-ready datasets, i.e., +/- imputed one-row-per-patient tables with all required exposure, outcome and covariate variables, are stored in separate sub-directories dedicated for the specific emulated trial.

## 6.3. Quality control

Upon delivery, data quality procedures included checks on delivered tables and variables, per table checks, descriptives on most important measures such as demographic and stage distributions by sex at time of initial diagnosis, regimen/exposure frequency counts and time-trends and overall survival benchmarks against literature and general cancer registry statistics. The R code to reproduce the quality assessments is deposited on the Mass General Brigham-provisioned GitLab server <https://gitlab.partners.org/drugapi/encore/quality> (repository is only accessible within the Mass General Brigham network and additionally only to authorized study personnel).

## 6.4. Study design

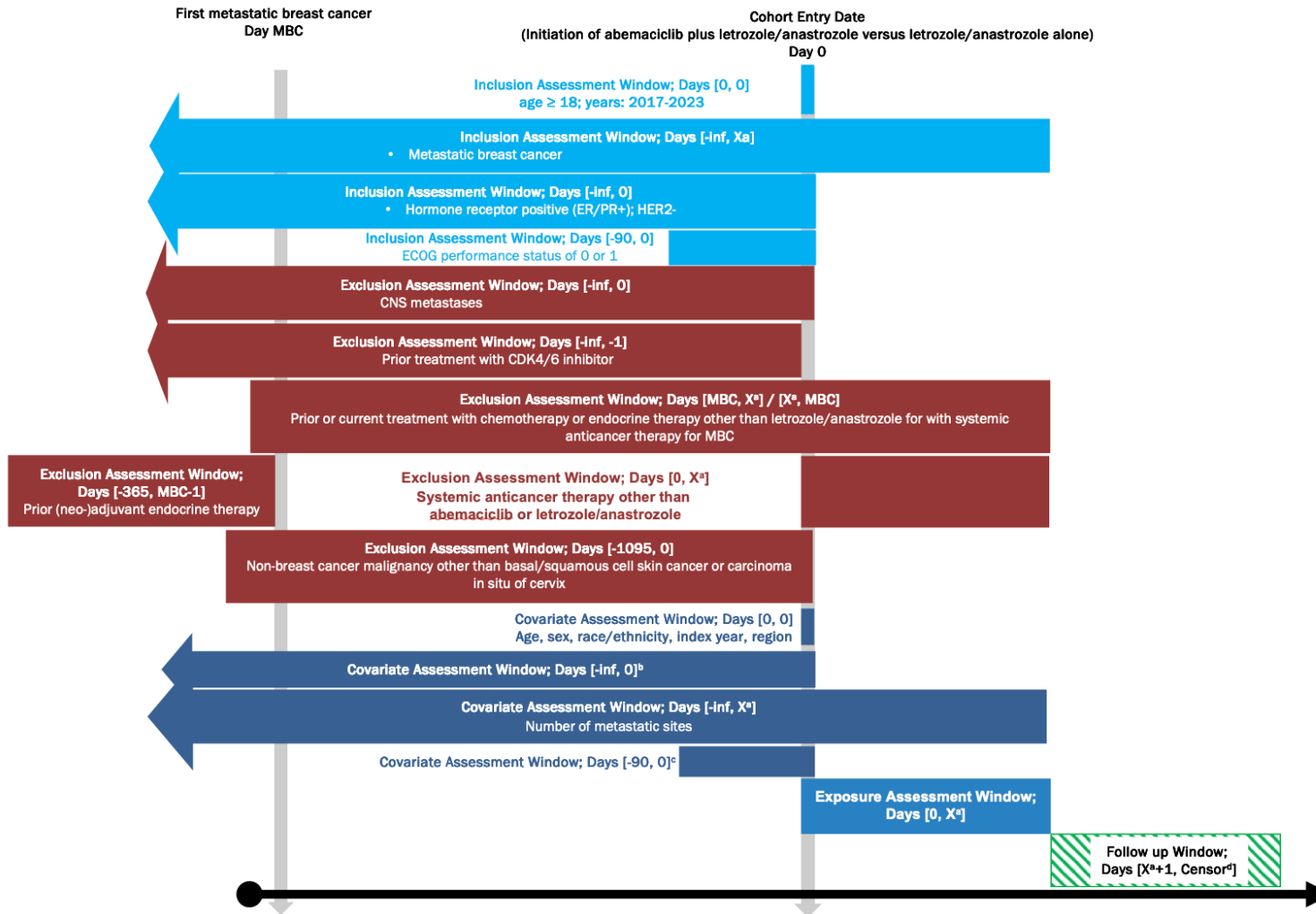
**Research design (e.g. cohort, case-control, etc.):** Cohort study

**Rationale for study design choice:** Resembles the principles of the (target) trial emulation framework.<sup>10</sup>

## 6.5. Study design diagram

Figure 1 depicts study design and variable measurement considerations for the emulation of the MONARCH-3 trial. The selection of key confounders/prognostic factors is driven by expert knowledge and additionally based on covariates included in the real-world prognostic score (ROPRO) which is a published and validated pan-tumor and cancer-specific prognostic score framework for overall survival.<sup>11-15</sup>

**Figure 1. Study design illustration for MONARCH-3 trial emulation.**



- Proprietary business rules to define initiation of the line of therapy (including exposure assessment window) cannot be shared.
- De novo metastatic status, time initial diagnosis to index date, time from first evidence of metastatic disease to index date, smoking, family history, race/ethnicity, etc.
- Labs (albumin, hemoglobin, etc.) and vitals (BMI, etc.) that are part of the ROPRO prognostic score<sup>8</sup>
- Intention-to-treat: death due to any reason or last observed clinical activity/sign of patient being alive or data cut-off date (whichever occurred earlier)

No observability criterion was applied because measures like continuous enrollment periods (claims data) are not available in electronic health records.

Abbreviations: MBC = Metastatic Breast Cancer; ER = Estrogen Receptor; PR = Progesterone Receptor; HER2 = Human Epidermal Growth factor Receptor 2; ECOG = Eastern Cooperative Oncology Group; CNS = Central Nervous System; CDK4/6 = Cyclin-Dependent Kinase 4/6; ROPRO = Real-wOrld PROgnostic score

## 6.6. Setting

### 6.6.1. Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

Time 0 in this database study is defined as the date a patient initiated abemaciclib plus letrozole/anastrozole (exposure) or letrozole/anastrozole alone (comparator) as part of their 1L systemic antineoplastic treatment for advanced/metastatic adenocarcinoma of the breast. This aims to emulate the date of randomization and cohort entry in the RCT (the time from randomization to first dose is not reported in the [clinicaltrials.gov study report](#) or the trial articles).

### 6.6.2. Context and rationale for study inclusion criteria

Study inclusion criteria were defined to emulate all key inclusion criteria for the trial that were deemed both clinically relevant and measurable in EHR data. See Excel appendix Table 1 (Table1\_I\_E) for a one-by-one evaluation. A summary of the operational definitions of the inclusion criteria that were applied for each database can be found in the Excel appendix Table 2 (Table2\_I\_E). In addition, the eligible time period (years) was based on the approval year of the trial's intervention drug as well as the numbers of treatment initiation. A flowchart of the study cohort assembly is provided in the appendix (10.1).

### 6.6.3. Context and rationale for study exclusion criteria

Study exclusion criteria were defined to emulate all key exclusion criteria for the trial that were deemed both clinically relevant and measurable in EHR data. See Excel appendix table 1 (Table1\_I\_E) for a one-by-one evaluation. A summary of the operational definitions of the exclusion criteria that were applied for each database can be found in the Excel appendix Table 2 (Table2\_I\_E). A flowchart of the study cohort assembly is provided in the appendix (10.1).

### 6.6.4. Context and rationale for exposure(s) of interest

The exposure and comparator were defined to emulate the agents compared for the trial, i.e., initiation of abemaciclib plus letrozole/anastrozole versus letrozole/anastrozole alone in a 1L metastatic setting.

- **EDB1:** Exposure is derived using a manually curated line of therapy (LOT) table provided by the data partner that programmatically categorizes treatment regimens into a coherent line of treatment, based on a proprietary business rule with an exposure assessment window. That is, each patient is represented with one row per curated line of therapy with corresponding information on line number, regimens as well start and end dates. Based on this table, patients are identified who received abemaciclib-plus-letrazole/anastrozole or letrozole/anastrozole-alone treatment regimen by their generic names (string match) in 1L, using the exposure assessment window; follow-up begins after the end of the exposure assessment window. The LOT implicitly only considers regimens that were given as part of a metastatic disease setting. More details and annotated code to identify initiators can be found in the 'Derive cohort EDB1' Quarto report (access within MGB network only).
- **EDB3:** Exposure is derived using a manually curated line of therapy (LOT) table provided by the data partner that programmatically categorizes treatment regimens into a coherent line of treatment, based on a proprietary business rule with an exposure assessment window. That is, each patient is represented with one row per curated line of therapy AND drug name with corresponding information online number, regimens as well start and end dates. Based on this table, patients are identified who received only abemaciclib and letrozole/anastrozole within the first line of therapy, and

letrozole/anastrozole alone within the first line of therapy by their generic names (string match), using the exposure assessment window; follow-up begins after the end of the exposure assessment window. The LOT implicitly only considers regimens that were given as part of a metastatic disease setting. More details and annotated code to identify initiators can be found in the 'Derive cohort EDB3' Quarto report' (access within MGB network only).

- **EDB4:** For the EDB4 database, the following logic is applied.
  - Identify patients with evidence of a metastasis from the diagnosis table in which the earliest date associated with evidence of metastasis is captured as a structured field (metastasis date).
  - Identify all potential antineoplastic drugs typically used in advanced/metastatic breast cancer (see list below\*). Only these are considered.
  - Identify patients who received any of the MONARCH-3 drugs within the exposure assessment window as the first antineoplastic treatment on or after the metastasis date.
  - Identify and exclude patients who received abemaciclib before the metastasis date.
  - Follow-up begins after the end of the exposure assessment window.

**\*Antineoplastic drugs considered:** abemaciclib, alpelisib, anastrozole, atezolizumab, bevacizumab, capecitabine, capivasertib, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, elacestrant, entrectinib, epirubicin, eribulin, etoposide, everolimus, exemestane, fluorouracil, fulvestrant, gemcitabine, goserelin, inavolisib, ixabepilone, larotrectinib, letrozole, methotrexate, nab-paclitaxel, olaparib, paclitaxel, palbociclib, pembrolizumab, pertuzumab, ribociclib, sacituzumab, talazoparib, tamoxifen, toremifene, trastuzumab, and vinorelbine.

#### 6.6.5. Context and rationale for outcome(s) of interest

The primary outcome for the database study was defined to emulate the OS outcome for the trial, time from end of exposure assessment window to death due to any reason (OS). Operational definitions:

- **EDB1:** Time in [days, months and years] from end of exposure assessment window to death due to any reason. The date of death is de-identified to month-level granularity or (rarely) to year-level granularity and the date of death is therefore imputed to the 15th of a month or mid-year/July 2 of the year of death, respectively. If there is no indication that a patient died during the study period, the patient is censored. The censoring date is defined as the last visit or treatment encounter or data cut-off date, whichever occurred earlier. The OS endpoint is operationalized using a parameterized R function `edb1_get_os()` and more details can be found in the attached pdf documentation.
- **EDB3:** Time in [days, months and years] from end of exposure assessment window to death due to any reason. The date of death is de-identified to month-level granularity and the day of death is therefore imputed to the 15th of a month. Patients without evidence of death are censored at the earlier of the last recorded activity date or the data cut-off date. Activity dates are defined as documented in Table 4. Death dates are compiled from Electronic Medical Records (EMR), manual curation, and third-party death data, linked via de-identified tokens generated from hashed personally identifiable information (PII). Sources of death dates are prioritized as follows: (1) manual curation, (2) EMR, and (3) third-party sources. For privacy reasons, the final reported death date is shifted to the nearest Sunday within four days of the actual date. Manually curated death dates follow a prioritization hierarchy of source

documentation: death certificate first, followed by scanned obituaries or death announcements, and lastly exact dates reported by providers without other supporting documentation. The OS endpoint calculation uses a parameterized R function (*edb3\_get\_os()*), with detailed documentation provided in the attached PDF.

- **EDB4:** Time in [days, months and years] from end of exposure assessment window to death due to any reason. The date of death is de-identified to month-level granularity and the day of death is therefore imputed to the 15<sup>th</sup> of a month. If there is no indication that a patient died during the study period, the patient is censored. The censoring date is defined as the last date of vital signs recorded as proof that the patient was alive at that time (de-identified to week-level granularity) or data cut-off date, whichever occurred earlier. The OS endpoint is operationalized using a parameterized R function *edb4\_get\_os()* and more details can be found in the attached pdf documentation.

**Table 4. Relevant clinical activities considered to derive last activity date for censoring.**

| Table / clinical activity considered   | Dates considered   |
|--|--|
| Adverse events   | Event date   |
| Therapy (cellular, systemic, radiation, surgery)   | Start and end dates or declined intervention date, surgery date, assessed resection dates              |
| Palliative care referral   | Referral date  |
| Visits   | Contact/visit date   |
| Vitals   | Assessed date  |
| Labs   | Lab date   |
| Biomarkers   | Specimen collection date   |
| Patient observation period   | Start and end dates  |
| Demographics   | Date of most recent contact with provider, date patient was diagnosed with a second primary malignancy |
| Performance assessments  | Documented date, reported date   |
| Secondary diagnoses  | Diagnosis date   |
| Progression, histology, lymphovascular invasion, metastatic sites, pancoast tumor, perineural invasion | Assessed date  |

|           |               |
|-----------|---------------|
| Stage/TNM | Assessed date |
| Smoking   | Assessed date |

#### 6.6.6. Context and rationale for follow up

Only intention-to-treat (ITT) analyses will be conducted. Although cross-over from the exposure to the comparator can be expected, which usually biases the estimated treatment effect toward the null, this limitation also applies to the MONARCH-3 trial. In the final OS analysis reported by Goetz et al. (2024), 284 patients (86.6%) in the abemaciclib-plus-letrozole/anastrozole arm and 154 patients (93.3%) in the placebo-plus-letrozole/anastrozole arm had discontinued study treatment. After discontinuation, 38 patients (11.6%) in the abemaciclib arm and 52 patients (31.5%) in the placebo arm received a CDK4/6 inhibitor as part of subsequent therapy, which effectively constituted crossover.<sup>7</sup>

An as-treated analysis is not considered since in the context of oncology, reasons for discontinuation usually are due to toxicity, death or progression/non-response to the current treatment, all of which are highly correlated with the outcome under study which would hence lead to bias due to informative censoring.

#### 6.6.7. Context and rationale for covariates.

We identified a series of covariates that are strong prognostic factors for the outcome and auxiliary covariates which may be useful to impute missing data. Such covariates comprise demographics, covariates indicating disease-severity, cancer-specific covariates as well as pathological and genetic factors. In addition, selected labs and vitals are considered since they were shown to carry a high amount of prognostic information as described in Becker, Weberpals, et al.<sup>11</sup> For these variables, additional plausibility checks and transformations are carried out. In detail, labs and vitals are individually checked if they cross a certain biologically implausible threshold (e.g., a heart rate of 0) in which cases the values are set missing and imputed in a next step. These thresholds were compiled by experienced practicing physicians and medical oncologists and are listed in appendix **Table 9** and **Table 10**.

Note that not all covariates are available across all databases used for this trial emulation. In the analytical stage, the most comprehensive model will be fit for each database individually.

**Table 5. Operational definitions of key covariates used for trial emulation.**

| Characteristic     | Harmonized analysis variable name | R function to derive covariate (see pdf in appendix) | Details <sup>1</sup>                                     | Variable encoding   | Assessment window                      |
|--------------------|-----------------------------------|--|--|---|--|
| Age at index date  | dem_age_index                     | edbx_get_demographics()                              | Age measured at index date                               | Binary (<60, 65+); modelled continuously in ROPRO <sup>11</sup> | [0;0]                                  |
| Year of index date | c_year_index                      | De novo derived from dt_index                        | Calendar year in which patient initiated study treatment | Nominal (<2020, 2020+)  | [0;0]                                  |
| Family history     | dem_family_history                | edbx_get_demographics()                              | Family history of cancer. Not available in EDB1.         | Logical (TRUE, FALSE)   | [0;0] (no specific date is associated) |

| Characteristic            | Harmonized analysis variable name | R function to derive covariate (see pdf in appendix) | Details <sup>1</sup>   | Variable encoding   | Assessment window                               |
|---------------------------|-----------------------------------|--|--|---|---|
| Race                      | dem_race                          | edbx_get_demographics()                              | Race categorized as in the original RCT  | Nominal (White, Asian, Other)   | [0;0]   |
| Ethnicity                 | dem_ethnicity                     | edbx_get_demographics()                              | Ethnicity  | Hispanic, Non-Hispanic  | [0;0]   |
| Region                    | dem_region                        | edbx_get_demographics()                              | US region patient receives care in; if given on a state level, region is manually mapped (see <b>Table 11</b> )  | Nominal (Northeast, South, West, Midwest)   | [0;0]   |
| Practice type             | dem_practice                      | edbx_get_demographics()                              | Setting patient is receiving care at. Not available in EDB3 and EDB4.  | Nominal (academic, community, academic & community)   | [-inf;0]  |
| Socio-economic status     | dem_ses                           | edbx_get_demographics()                              | Socioeconomic status (SES) index based on residence area of patient Not available in EDB3 and EDB4.  | Nominal (from '1 - Lowest SES' through '5 - Highest SES')   | [-inf;0]  |
| Smoking                   | c_smoking_history                 | edbx_get_demographics()                              | History of current or former (= TRUE) or never (= FALSE) smoking on or anytime before index date; if there are multiple records per patient, any evidence of former/current smoking is prioritized. In EDB1, "smoking history" is unavailable for breast cancer. | Binary logical (TRUE, FALSE)  | [-inf;0]  |
| ECOG                      | c_ecog                            | edbx_get_ecog()                                      | ECOG performance status measured closest to index date within assessment window. In case of ties, the lower ECOG value is selected   | Nominal (0, 1, 2, 3, 4); modelled as ordinal numeric in ROPRO <sup>11</sup> due to I/E criteria ECOG is modelled as a binary (0, 1) covariate | [-90;0]   |
| Stage                     | c_stage_initial_dx                | edbx_get_diagnosis_solid()                           | AJCC summary group stage at initial diagnosis  | Ordinal numeric (from 0 to IV with sub-categories, e.g., IA) <sup>11</sup>  | [-inf;0] at initial diagnosis of primary cancer |
| De novo metastatic status | c_de_novo_mets_dx                 | edbx_get_diagnosis_solid()                           | Evidence of presence of one or multiple metastases at/before initial diagnosis   | Binary logical (TRUE, FALSE)  | [-inf;0] at initial diagnosis of primary cancer |

| Characteristic  | Harmonized analysis variable name | R function to derive covariate (see pdf in appendix)            | Details <sup>1</sup>   | Variable encoding       | Assessment window  |
|---|-----------------------------------|---|--|-------------------------|--|
| Number of metastatic sites                                    | c_number_met_sites                | edbx_get_diagnosis_solid() / edbx_get_number_met_site_s_solid() | Number of metastatic sites for a given patient before/on index date  | Integer                 | [-inf;X];<br>Proprietary business-rule-based covariate assessment window |
| Time between initial diagnosis to index date                  | c_time_dx_to_index_quartiles      | edbx_get_diagnosis_solid()                                      | Time in days between initial diagnosis to index date. Quartiles will be used because there may be “negative” times intervals due to date imprecision of the lines of therapy.                            | Categorical (quartiles) | [-initial dx;0]  |
| Time between earliest evidence of a metastatic and index date | c_time_met_dx_to_index_quartiles  | edbx_get_diagnosis_solid()                                      | Time in days between earliest evidence of a metastatic diagnosis and index date. Quartiles will be used because there may be “negative” times intervals due to date imprecision of the lines of therapy. | Categorical (quartiles) | [met dx;0]   |
| Albumin   | c_albumin_g_l_cont                | edbx_get_labs()   | Closest albumin measurement (in serum/plasma) relative to index date in g/L. In case of ties, the lower is selected  | Continuous              | [-90;0]  |
| Alkaline phosphatase (ALP) <sup>2</sup>                       | c_alp_u_l_cont                    | edbx_get_labs()   | Closest alkaline phosphatase measurement (in serum/plasma) relative to index date in U/L. In case of ties, the lower is selected   | Continuous              | [-90;0]  |
| Alanine aminotransferase (ALT) <sup>2</sup>                   | c_alt_u_l_cont                    | edbx_get_labs()   | Closest alanine transaminase measurement (in serum/plasma) relative to index date in U/L. In case of ties, the lower is selected   | Continuous              | [-90;0]  |
| Aspartate aminotransferase (AST)                              | c_ast_u_l_cont                    | edbx_get_labs()   | Closest aspartate aminotransferase measurement (in serum/plasma) relative to index date in U/L. In case of ties, the lower is selected. Only used to compute AST-ALT ratio.                              | Continuous              | [-90;0]  |
| AST/ALT ratio   | c_ast_alt_ratio_cont              | edbx_get_labs()   | AST/ALT ratio calculated from c_ast_u_l_cont/c_alt_u_l_cont  | Continuous              | [-90;0]  |
| Bilirubin <sup>2</sup>  | c_bilirubin_mg_dl_cont            | edbx_get_labs()   | Closest bilirubin measurement (in serum/plasma) relative to index date in mg/dL. In case of ties, the lower is selected  | Continuous              | [-90;0]  |

| Characteristic                           | Harmonized analysis variable name   | R function to derive covariate (see pdf in appendix) | Details <sup>1</sup>   | Variable encoding           | Assessment window |
|--|-------------------------------------|--|--|-----------------------------|-------------------|
| Calcium <sup>2</sup>                     | c_calcium_mg_dl_cont                | edbx_get_labs()                                      | Closest calcium measurement (in serum/plasma) relative to index date in mg/dL. In case of ties, the lower is selected  | Continuous                  | [-90;0]           |
| Chloride                                 | c_chloride_mmol_l_cont              | edbx_get_labs()                                      | Closest chloride measurement (in serum/plasma) relative to index date in mmol/L. In case of ties, the lower is selected  | Continuous                  | [-90;0]           |
| Eosinophils/100 leukocytes <sup>2</sup>  | c_eosinophils_leukocytes_ratio_cont | edbx_get_labs()                                      | Eosinophils/100 leukocytes in blood. In case of ties, the lower  | Continuous                  | [-90;0]           |
| Estrogen receptor status                 | c_er_status                         | edbx_get_biomarker()                                 | Evidence of estrogen receptor status.  | binary (positive/ negative) | [-inf; 0]         |
| Glucose <sup>2</sup>                     | c_glucose_mg_dl_cont                | edbx_get_labs()                                      | Closest glucose measurement (in serum/plasma) relative to index date in mg/dL. In case of ties, the lower is selected  | Continuous                  | [-90;0]           |
| Granulocyte/leukocyte ratio <sup>2</sup> | c_granulocytes_leukocytes_ratio     | edbx_get_labs()                                      | Closest granulocyte/leukocyte ratio measurement (in blood) relative to index date. In case of ties, the lower is selected. Used to compute granulocyte/lymphocyte ratio            | Continuous                  | [-90;0]           |
| Hemoglobin                               | c_hemoglobin_g_dl_cont              | edbx_get_labs()                                      | Closest hemoglobin measurement (in blood) relative to index date in g/L. In case of ties, the lower is selected  | Continuous                  | [-90;0]           |
| Lactate dehydrogenase (LDH) <sup>3</sup> | c_ldh_u_l_cont                      | edbx_get_labs()                                      | Closest LDH measurement (in serum or plasma) relative to index date in U/L. In case of ties, the lower is selected   | Continuous                  | [-90;0]           |
| Lymphocytes                              | c_lymphocyte_10_9_l_cont            | edbx_get_labs()                                      | Closest lymphocytes measurement (in blood) relative to index date in 10 <sup>9</sup> /L. In case of ties, the lower is selected. Only used to compute neutrophil/lymphocyte ratio. | Continuous                  | [-90;0]           |
| Lymphocyte/leukocyte ratio <sup>2</sup>  | c_lymphocyte_leukocyte_ratio_cont   | edbx_get_labs()                                      | Closest lymphocyte/leukocyte ratio measurement (in blood) relative to index date. In case of ties, the lower is selected. Used   | Continuous                  | [-90;0]           |

| Characteristic                           | Harmonized analysis variable name  | R function to derive covariate (see pdf in appendix) | Details <sup>1</sup>  | Variable encoding           | Assessment window |
|--|------------------------------------|--|---|-----------------------------|-------------------|
|  |                                    |  | to compute neutrophil/lymphocyte ratio  |                             |                   |
| Monocytes <sup>2</sup>                   | c_monocytes_10_9_l_cont            | edbx_get_labs()                                      | Closest monocytes measurement (in blood) relative to index date in 10 <sup>9</sup> /L. In case of ties, the lower is selected.  | Continuous                  | [-90;0]           |
| Neutrophils                              | c_neutrophil_10_9_l_cont           | edbx_get_labs()                                      | Closest neutrophils measurement (in blood) relative to index date in 10 <sup>9</sup> /L. In case of ties, the lower is selected. Only used to compute neutrophil/lymphocyte (NLR) ratio.          | Continuous                  | [-90;0]           |
| Neutrophil/lymphocyte ratio <sup>2</sup> | c_neutrophil_lymphocyte_ratio_cont | edbx_get_labs()                                      | Neutrophil/lymphocyte (NLR) ratio calculated from c_neutrophil_10_9_l_cont/ c_lymphocyte_10_9_l_cont  | Continuous                  | [-90;0]           |
| Platelets                                | c_platelets_10_9_l_cont            | edbx_get_labs()                                      | Closest platelets measurement (in blood) relative to index date in 10 <sup>9</sup> /L. In case of ties, the lower is selected   | Continuous                  | [-90;0]           |
| Progesterone receptor status             | c_pr_status                        | edbx_get_biomarker()                                 | Evidence of any PR mutation present. If patient has multiple measurements, any evidence of a mutation is prioritized. In case of ties, the closest measurement relative to index date is selected | Binary (positive/ negative) | [-inf;0]          |
| Protein                                  | c_protein_g_l_cont                 | edbx_get_labs()                                      | Closest protein measurement (in serum/plasma) relative to index date in g/L. In case of ties, the lower is selected   | Continuous                  | [-90;0]           |
| Urea nitrogen <sup>2</sup>               | c_urea_nitrogen_mg_dl_cont         | edbx_get_labs()                                      | Closest urea nitrogen measurement (in serum/plasma) relative to index date in mg/dL. In case of ties, the lower is selected   | Continuous                  | [-90;0]           |
| Systolic blood pressure <sup>2</sup>     | c_sbp_cont                         | edbx_get_vitals()                                    | Closest systolic blood pressure (in mmHg) measurement. In case of ties, the lower is selected   | Continuous                  | [-90;0]           |
| Diastolic blood pressure                 | c_dbp_cont                         | edbx_get_vitals()                                    | Closest diastolic blood pressure (in mmHg) measurement. In case of ties, the lower is selected.   | Continuous                  | [-90;0]           |

| Characteristic                     | Harmonized analysis variable name | R function to derive covariate (see pdf in appendix) | Details <sup>1</sup>  | Variable encoding | Assessment window |
|------------------------------------|-----------------------------------|--|---|-------------------|-------------------|
| Body mass index (BMI) <sup>2</sup> | c_bmi_cont                        | edbx_get_vitals()                                    | Closest BMI measurement (in kg/m <sup>2</sup> ) relative to index date. In case of ties, the lower is selected. | Continuous        | [-90;0]           |
| Heart rate <sup>2</sup>            | c_hr_cont                         | edbx_get_vitals()                                    | Closest heart rate measurement (in bpm) relative to index date. In case of ties, the lower is selected          | Continuous        | [-90;0]           |
| Oxygen saturation                  | c_oxygen_cont                     | edbx_get_vitals()                                    | Closest oxygen saturation measurement (in bpm) relative to index date. In case of ties, the lower is selected   | Continuous        | [-90;0]           |

<sup>1</sup>x stands for the pseudonymized number of the respective database, i.e., EDB1, EDB3 or EDB4

<sup>2</sup> For calculation of ROPRO prognostic score<sup>11</sup>, this variable is log transformed.

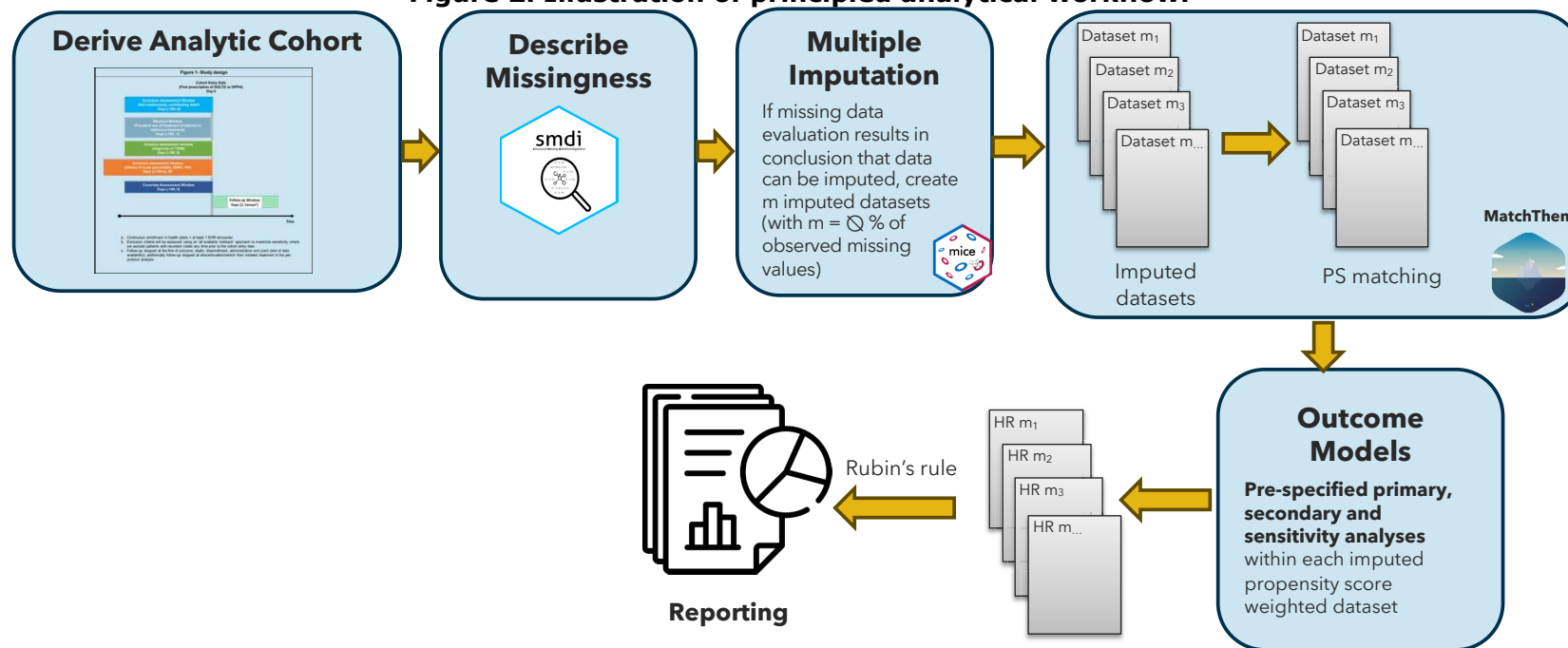
<sup>3</sup> For calculation of ROPRO prognostic score<sup>11</sup>, this variable is log-log transformed.

## 6.7. Data analysis

### 6.7.1. Context and rationale for analysis plan

To emulate the MONARCH-3 trial, the following analytical workflow will be used (Figure 2). First, an analytical cohort with covariates on key eligibility criteria and prognostic factors will be derived across all databases. To ensure reproducibility and consistency throughout the entire ENCORE project, the internally developed *encore.io* R package streamlines this process using the functions referenced in Table 5. Operational definitions of key covariates used for trial emulation.(code documentation see appendix).<sup>16</sup> The analytical cohort will be derived by first identifying a metastatic breast cancer inception cohort of initiators of abemaciclib plus letrozole/anastrozole or letrozole/anastrozole alone in the first-line setting as described in section 6.6.4. Next, key eligibility criteria will be applied in which patients with missing values are considered eligible in the respective attrition steps to allow thorough missing data investigations.

**Figure 2. Illustration of principled analytical workflow.**



Once a full analytic cohort is built, principled missing data investigations will be employed to empirically assess assumptions on potentially underlying missingness mechanisms according to Rubin's classification of missing data (i.e., missing completely at random [MCAR], missing at random [MAR] and missing not at random [MNAR]).<sup>17</sup> To that end, we will adopt a principled process on missing data that was developed as part of an FDA Sentinel Innovation Center causal inference workstream that empirically evaluates different aspects across partially observed covariates based on three group diagnostics (Table 6).<sup>18,19</sup> In brief, the first group diagnostics computes distributions and absolute standardized mean differences (ASMD) between patients with and without an observed value for a given partially observed covariates. If missingness can be explained by observed covariates such as in MAR mechanisms, patient characteristics will significantly differ which will (in analogy to propensity scores) be indicated by ASMDs > 0.1. In addition, Hotelling's<sup>20</sup> and Little's<sup>21</sup> tests additionally provide formal hypothesis tests for such comparisons in which high test statistics and a rejection of the null hypothesis would provide evidence for differences in the distribution of patient characteristics and suggest the underlying mechanism is not MCAR or MNAR. Group 2 diagnostics assess the ability to predict missingness based on observed covariates by fitting a classification model to predict the missingness indicator of the partially observed covariate. To that end, we will fit a random forest (RF) classification model using observed covariates with a 70/30 train-test split of the complete cohort. A sufficiently high area under the receiver operating characteristic curve (AUC) metric of the test dataset may demonstrate that missingness can be predicted well and could point towards MAR as a likely mechanism as opposed to an AUC~0.5 which would suggest MCAR or MNAR. Group 3 diagnostics evaluates the association between the missingness indicator of the partially observed covariates and the outcome (OS). If the missingness of a confounder cannot be explained or approximated by observed covariates and a difference in the outcome is observed depending on the missingness indicator (e.g.,  $HR_{\text{missingness indicator}} \neq 1$ ), this may be indicative of an underlying MNAR mechanism. These empirical diagnostics will be implemented through the smdi R package<sup>22</sup> and be further enhanced by clinical expert knowledge.

**Table 6. Diagnostics to empirically differentiate and characterize missing data mechanisms.**

| Diagnostic metric | Group 1 Diagnostics  |  | Group 2 Diagnostics  | Group 3 Diagnostics   |
|-------------------|--|--|--|---|
|                   | Absolute standardized mean difference (ASMD)   | P-value Hotelling <sup>20</sup> Little <sup>21</sup>   | Area under the receiver operating curve (AUC)  | Log HR (missingness indicator)  |
| Purpose           | Comparison of distributions between patients with vs. without observed value of the partially observed covariate.  |  | Assessing the ability to predict missingness based on observed covariates.   | Check whether missingness of a covariate is associated with the outcome (differential missingness).   |
| Example value     | ASMD = 0.1   | p-value < 0.001  | AUC = 0.5  | log HR = 0.1 (0.05 to 0.2)  |
| Interpretation    | <p><u>&lt;0.1<sup>a</sup></u>: no imbalances in observed patient characteristics; missingness may be likely completely at random or not at random (~MCAR, ~MNAR).</p> <p><u>&gt;0.1<sup>a</sup></u>: imbalances in observed patient characteristics; missingness may be likely at random (~MAR).</p> | High test statistics and low p-values indicate differences in baseline covariate distributions and null hypothesis would be rejected (~MAR). | <p>AUC values ~ 0.5 indicate completely random or not at random prediction (~MCAR, ~MNAR).</p> <p>Values meaningfully above 0.5 indicate stronger relationships between covariates and missingness (~MAR).</p> | <p>No association in either univariate or adjusted model and no meaningful difference in the log HR after full adjustment (~MCAR).</p> <p>Association in univariate but not fully adjusted model (~MAR).</p> <p>Meaningful difference in the log HR also after full adjustment (~MNAR).</p> |

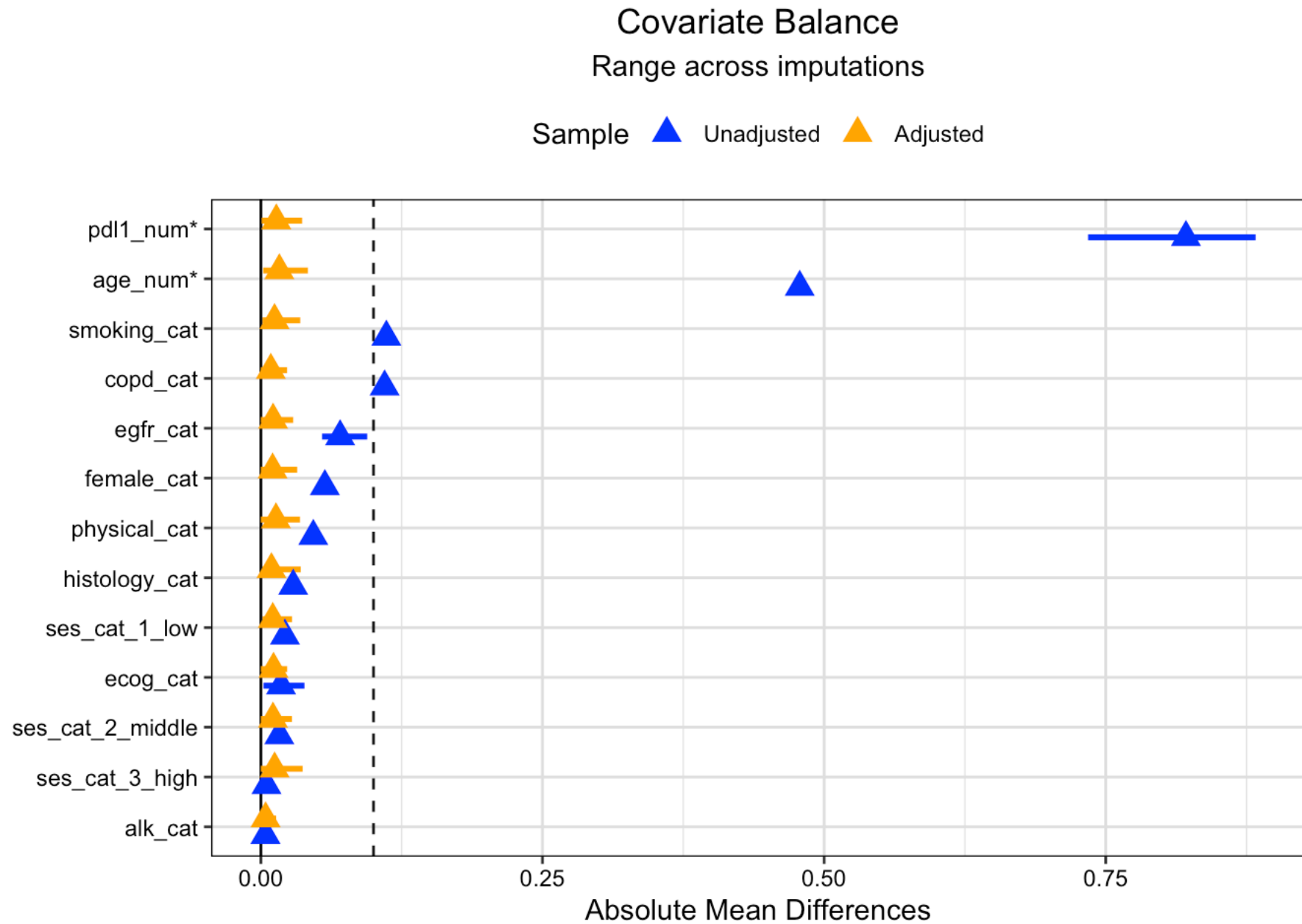
Abbreviations: ASMD = Median absolute standardized mean difference across all covariates, AUC = Area under the curve, CI = Confidence interval, MAR = Missing at random mechanism in which the missingness probability depends on observed covariates, MCAR = Missing completely at random mechanism in which each patients has the same missingness probability, MNAR(unmeasured) = Missing not at random mechanism in which the missingness can only be explained by a covariate which is not observed in the underlying dataset, MNAR(value) = Missing not at random mechanism in which the missingness just depends on the actual value of the partially observed confounder of interest itself.

<sup>a</sup> Analogous to propensity score-based balance measures.<sup>23</sup>

While the MAR assumption is a strong assumption to hold across all considered covariates, it was shown that especially in the context of partially observed covariate data (as opposed to missing exposure and outcome data), only mechanisms in which a covariate causes its own missingness leads to critical bias (MNAR).<sup>24,25</sup> In such situations, multiple imputation can have significant advantages over a complete case analysis since additional information (auxiliary covariates and missing indicator

variables) can be included in imputation algorithms which can make the MAR assumption holding more plausible and increase efficiency in treatment effect estimates since all patients and critical covariates can be retained and variances can be realistically estimated, considering both the general sampling error and the error introduced by missing data.<sup>26,27</sup> Hence, multiple imputation with flexible, non-parametric random forest imputation algorithms<sup>28</sup> (mice R package<sup>29</sup>) will be used for this trial emulation. The number of imputed datasets ( $m$ ) will be determined for each database separately based on the average proportion missingness observed in the analytic cohort and results from the above-referenced missing data investigations will inform the choice of appropriate sensitivity analyses.

**Figure 3. Covariate balance across imputed datasets (simulated example).**



To estimate the treatment effects for abemaciclib plus letrozole/anastrozole using propensity score matching across imputed datasets we will apply the “within” approach using the “MatchThem” R package.<sup>30,31</sup> That is, propensity score matching and the estimation of the treatment effect are performed in each imputed dataset separately and resulting treatment effect estimates are combined using Rubin’s rule. In this study, this will be implemented by matching eligible patients on their propensity to initiate abemaciclib plus letrozole/anastrozole using a 1:1 nearest neighbor matching algorithm without replacement and a caliper of 1% of the standard deviation of the propensity score. The resulting covariates balance will be assessed by computing and visualizing ASMDs before and after matching across datasets. As compared to a single dataset matching approach, this can lead to a range of ASMDs per covariate due to random variation across imputed datasets for which an example (using simulated data) is illustrated in Figure 3. If sufficient balance can be established, a Cox proportional hazards regression model will be fit to estimate the marginal average treatment effect in the matched population. Confidence intervals will be estimated using cluster-robust standard errors.<sup>32</sup> As a secondary endpoint, we will additionally estimate the median OS survival time difference between the two exposure groups using the Kaplan-Meier method. It should be noted that due to administrative and de-identification purposes, the date of death is often only available at the month- or year-granularity level, in which case the date of death will be imputed to the 15<sup>th</sup> of a month or July 2<sup>nd</sup> of a year, respectively (depending on the database). In rare cases, this can lead to negative/implausible follow-up times if the date of death is very close to the index date. These patients will be excluded from the analysis.

The final hazard ratio and median OS survival time difference estimates for each database will then be combined using Rubin’s rule.<sup>29,33</sup> To arrive at a single estimate across databases, the final estimates will be summarized through a meta-analytic fixed effects model.<sup>34</sup> A summary of the analytic approach is summarized in Table 7 and an example workflow with simulated data and annotated code can be found [here](#).

## A. Analyses

**Table 7. Primary, secondary, and subgroup analysis specification**

|  |  |
|--|--|
| <b>Hypothesis:</b>                             | Initiation of abemaciclib plus letrozole/anastrozole decreases the hazard of all-cause mortality as compared to initiation of letrozole/anastrozole alone  |
| <b>Exposure contrast:</b>                      | Initiation of abemaciclib plus letrozole/anastrozole vs letrozole/anastrozole alone  |
| <b>Primary outcome:</b>                        | Time to all-cause mortality (OS)   |
| <b>Databases used:</b>                         | EDB1 (primary analysis); EDB3 and EDB4 (sensitivity analysis)  |
| <b>Time period:</b>                            | From 2017 (approval year for abemaciclib) - 2023   |
| <b>Analytic software:</b>                      | R 4.3.2. Version control of code and R packages will be established through git and Posit package manager, respectively. All packages are frozen to their most recent version as of April 25, 2024.  |
| <b>Model(s):<br/>(provide details or code)</b> | See example code <a href="#">here</a> . The annotated code for the trial emulation will be hosted at <a href="https://drugapi.gitlab-pages.partners.org/encore/monarch3-nct-02246621/">https://drugapi.gitlab-pages.partners.org/encore/monarch3-nct-02246621/</a> (access only through MGB network for authorized personnel)  |
| <b>Confounding adjustment method</b>           | <i>Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.</i>   |
|  | 1:1 propensity score nearest neighbor matching without replacement and a caliper of 1% of propensity score standard deviation  |
| <b>Missing data methods</b>                    | <i>Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.</i>   |
|  | Multiple imputation by chained equations using a random forest imputation model across all covariate types. The number of imputed datasets will be determined by the average proportion of missing values across all partially observed covariates. Imputation models will include all variables of the substantive model, i.e., exposure, outcome, confounders/prognostic factors and additional auxiliary covariates.                                |
| <b>Subgroup Analyses</b>                       | <i>List all subgroups</i>  |
|  | In subgroup analysis, multiple imputation, propensity score matching and balance assessment will be conducted within each subgroup separately. The treatment effect will be estimated for each stratum separately (stratum-specific effects). <ol style="list-style-type: none"> <li>1. Age (&lt;65, ≥65)</li> <li>2. Race (Asian vs. Non-Asian)</li> <li>3. ECOG (0, 1)</li> <li>4. Hormone receptor status (ER and PR-positive vs. Other)</li> </ol> |

**Table 8. Sensitivity analyses – rationale, strengths and limitations.**

|                | What is being varied? How?   | Why?<br>(What do you expect to learn?)   | Strengths of the sensitivity analysis compared to the primary                                      | Limitations of the sensitivity analysis compared to the primary  |
|----------------|--|--|--|--|
| Sensitivity #1 | Caliper matching on ROPRO prognostic score instead of propensity score   | Matching patients on validated prognostic score may be more beneficial to control for (unmeasured) confounding   | Matches patients on validated prognostic score that incorporates weights of key prognostic factors | Limited experience on how to optimally use prognostic scores and should be seen as an <u>experimental</u> sensitivity analysis |
| Sensitivity #2 | ATO weighting instead of matching  | Weights that resemble the average treatment effect in the overlap population (ATO) create a clinical equipoise population which is comparable to an RCT  | ATO weighting usually results in excellent balance and clinical equipoise                          | Estimates the average treatment effect among the overlap patients which may not be comparable to target population anymore     |
| Sensitivity #3 | SMR/ATT weighting instead of matching. Here symmetric trimming (i.e., setting all weights lower/higher than that at a given quantile to the weight at the quantile) of extreme weights may be considered with the quantiles chosen based on weight distribution and resulting balancing performance. | SMR weighting retains all patients and resembles the same estimand as matching   | ATT weighting retains all patients   | Patients with extreme weights after trimming may bias the analysis   |
| Sensitivity #4 | Censoring date is changed to 3 months before data cut-off date   | For all databases, information on mortality comes from different data sources which are updated asynchronously. To account for the potential lag of updated mortality information ( <i>ghost-time bias</i> <sup>37</sup> ), the censoring for patients without mortality event in the whole patient identification period will be moved to last sign of patients being alive/visit or 3 months before data cut-off date, whichever occurred earlier. <sup>38</sup> | Approach implements a more conservative censoring rule   | Approach addresses ghost-time bias by censoring patients without a recorded death event earlier                                |
| Sensitivity #5 | Delta imputation models for MNAR (tipping point analysis)  | Primary multiple imputation analysis assumes MAR which   | Estimates impact of deviations from MAR assumption on final  | Delta parameters must be assumed and results are complex to interpret in   |

|                 |  | may not hold for every covariate  | treatment effect estimates for key covariates  | multivariate missingness settings; just most important covariates or those with highest suspicion of being MNAR will be evaluated  |
|-----------------|--|---|--|--|
| Sensitivity #6  | Re-weighting of strong risk factors and/or treatment effect modifiers distribution to match that of MONARCH-3                                  | In the presence of effect modification, treatment effect estimates may be different if the distribution of strong risk factors/effect modifiers is different in the emulated cohort versus the trial cohort | Re-weighting adjusts for differences in distributions of key risk factors and/or treatment effect modifiers (see subgroup analysis in Table 7) | Re-weighting risk factors/potential effect modifiers to match the MONARCH-3 trial and simultaneously balancing them across treatment groups may be challenging due to differences in measurement   |
| Sensitivity #7  | Including patients who have had at least 1 visit 90 days prior to treatment initiation   | EHRs are often lacking data continuity, and this analysis uses the requirement of 1 visit as a proxy for continuous observation periods   | Considers aspect of data continuity  | There may be patients who are put on treatment immediately in which case they are falsely excluded   |
| Sensitivity #8  | Using all available calendar time  | This analysis explores potential confounding related to calendar time, evolving clinical practice patterns, and access to therapies.  | Aims to assess the extent of confounding introduced by changes in time, treatment practices, and access to therapies.                          | We expect the results to be more confounded due to calendar time.  |
| Sensitivity #9  | Missingness is handled by restricting to patients with complete observations on a subset of the most important confounders (“complete cases”). | Instead of imputing data, this sensitivity analysis restricts the analysis cohort to patients with complete observations on key confounders   | Data will not be imputed and missingness is assumed to be missing completely at random   | The restriction to complete cases will significantly decrease sample size. To limit the attrition of patients with partially observed covariates, it won’t be possible to use all covariates used in the main analysis propensity score model, but only consider key covariates with overall low proportions of missingness (age, sex, etc.) |
| Sensitivity #10 | Exclusion of patients with >1 year between metastasis diagnosis and index date   | This sensitivity analysis varies the inclusion criteria by excluding patients whose index date (treatment start) is >1 year after their metastatic diagnosis date which is                                  | Helps ensure that treatment reflects initial first-line treatment of metastatic disease, not late-line therapy.                                | Exclusion of further patients results in a smaller cohort size which may reduce statistical power.   |

|                 |   |  |   |  |
|-----------------|---|--|---|--|
|                 |   | clinically unrealistic or implausible for a first-line treatment                                   |   |  |
| Sensitivity #11 | Addition of EDB3 and EDB4   | EDB3 and EDB4 are not considered in primary analyses for reasons given in section 6.1.1.           | Increased sample size and potentially broader coverage of general US cancer population                            | See limitations listed in section 6.1.1 regarding potential immortal time and selection bias due to left truncation as well as small cohort size leaving residual imbalance on prognostic factors. |
| Sensitivity #12 | Descriptive analysis of switching/crossover patterns in the trial and its emulation | This sensitivity analysis assesses crossover patterns comparatively in the trial and its emulation | Help to understand the potential concordance/discordance of treatment effects between the trial and its emulation | Analysis is on the description level, which may limit conclusions  |

## 7. Limitation of the methods

- Missingness in prognostic factors is a major challenge which is addressed in this emulation by multiple imputation using a non-parametric imputation algorithm. Multiple imputation usually assumes that missingness can be explained by observed characteristics, which may be empirically evaluated using principled missingness diagnostics, but the true underlying missingness mechanisms are usually unknown. Nevertheless, multiple imputation makes use of additional information (auxiliary covariates) which can render the underlying missingness assumptions more plausible. In addition, assumptions for alternative missing data approaches like complete case analysis or the “missing indicator approach” come with even stronger assumptions and additionally have the limitation of significantly reduced sample sizes, especially when comprehensively adjusting for known confounders and prognostic factors.
- Data continuity is a major challenge in EHR databases since “guaranteed” observable periods (such as continuous enrolment periods in administrative claims data) do not exist which may lead to measurement error in key covariates and exposure misclassification. Sensitivity analysis #7 tries to address this requiring patients to have had at least one visit before the index date which increases the likelihood that a patient was not only diagnosed at the respective center but is also regularly seen.
- Balancing patients on calendar year is not possible since calendar year shows instrumental variable-like behaviors (see Figure 11), i.e., it perfectly predicts treatment assignment and does not have any association with the outcome other than through the exposure. This assumption is formally untestable but clinically reasonable since there has not been any other significant change in treatment paradigms for MONARCH-3–like postmenopausal, HR-positive, HER2-negative metastatic breast cancer populations other than introduction of abemaciclib plus letrozole/anastrozole. The improvements in radiation of brain metastases may be the only exception, but it is expected that this may be of negligible significance for the scope of this emulation.

## 8. Protection of human subjects

This study has been approved by the Brigham and Women's Hospital Institutional Review Board.

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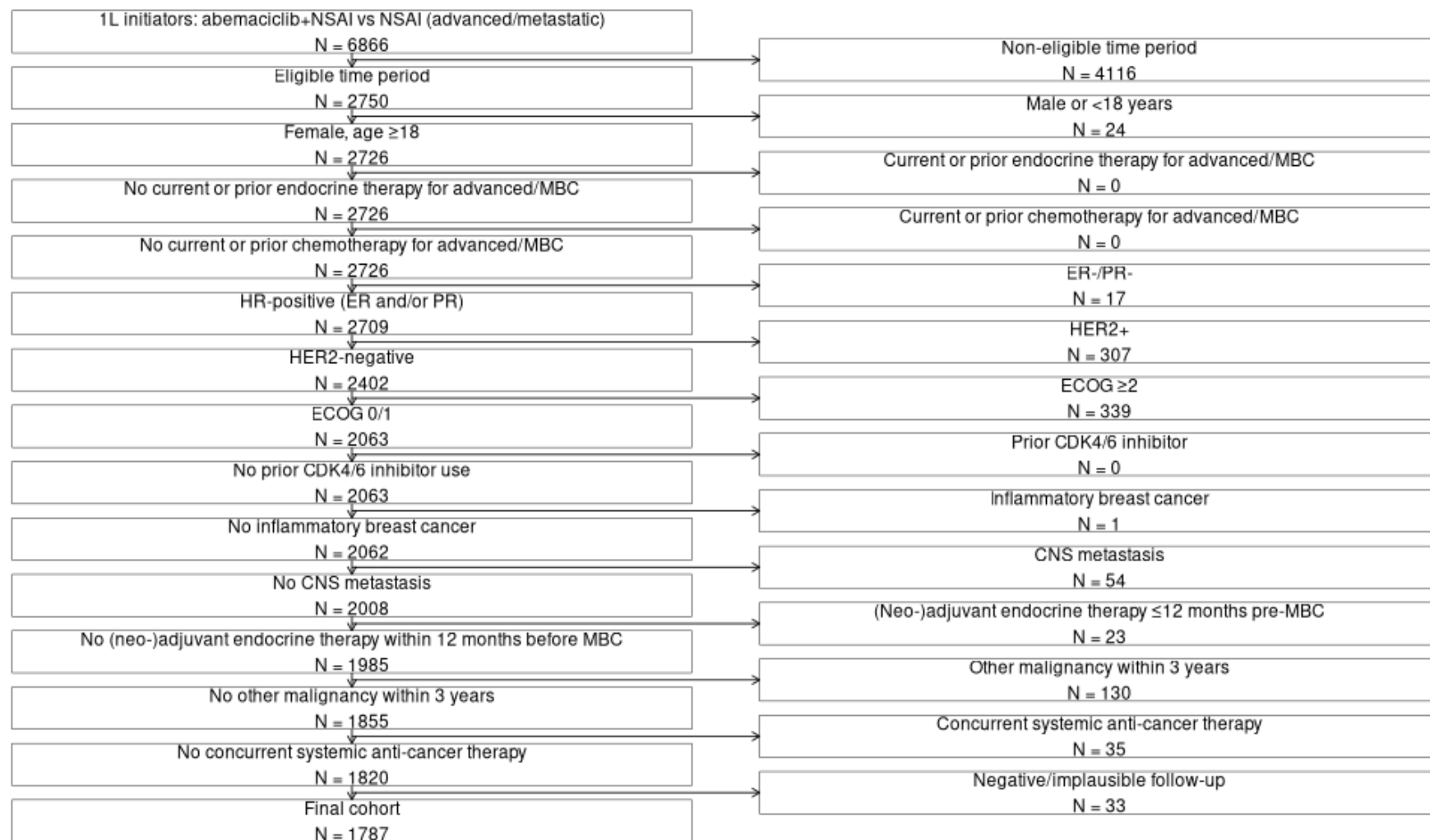
## 10. Appendices

### 10.1. CONSORT diagrams

The following CONSORT attrition diagrams depict the process to select eligible MONARCH-3-like populations in EDB1, EDB3 and EDB4 for the main analysis, respectively.

**Figure 4. CONSORT attrition to select eligible MONARCH-3-like populations in EDB1.**

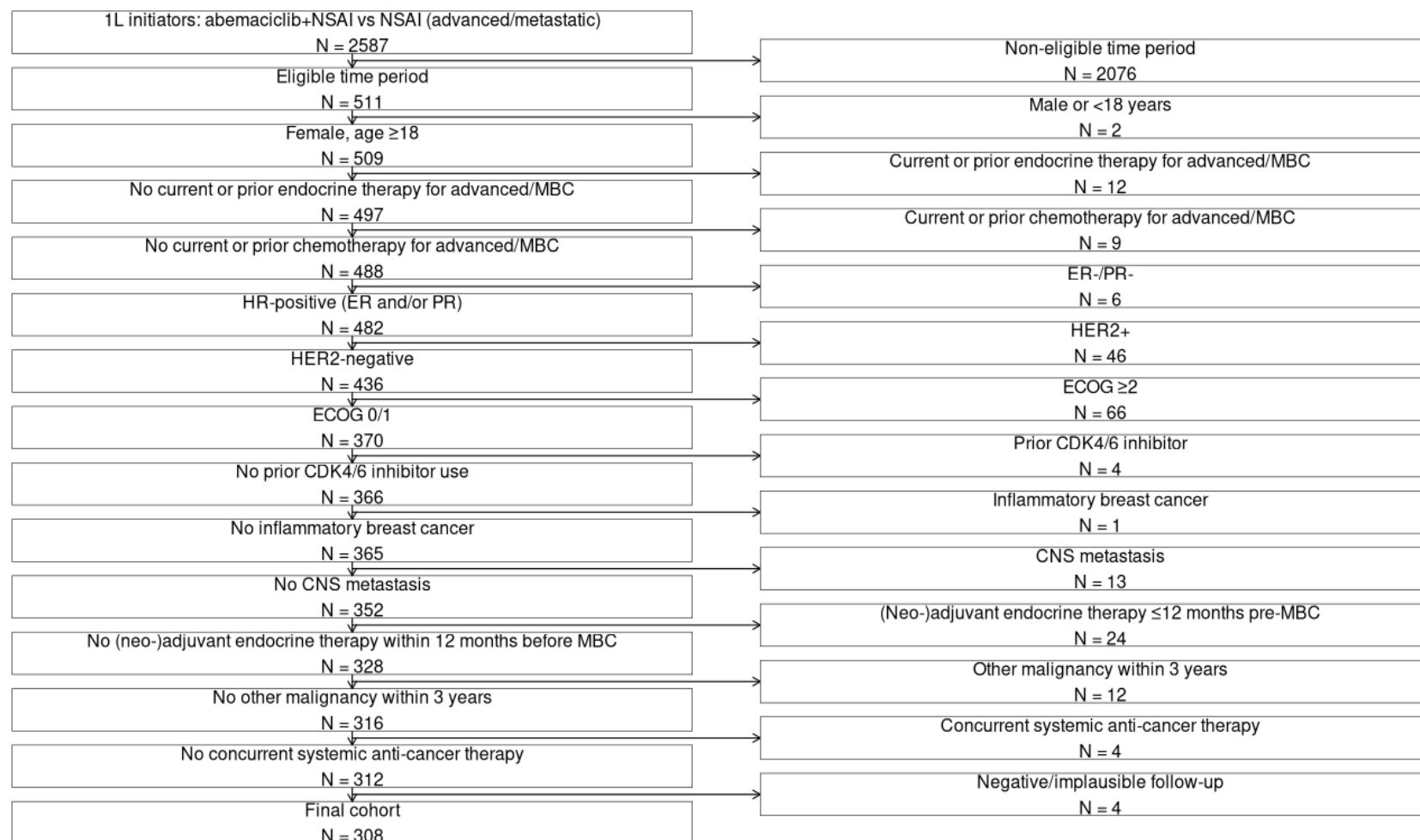
## edb1 attrition



Abbreviations: NAI = non-steroidal aromatase inhibitor (letrozole/anastrozole); MBC = metastatic breast cancer; HER2 = human epidermal growth factor receptor 2; CNS = central nervous system

**Figure 5. CONSORT attrition to select eligible MONARCH-3-like populations in EDB3.**

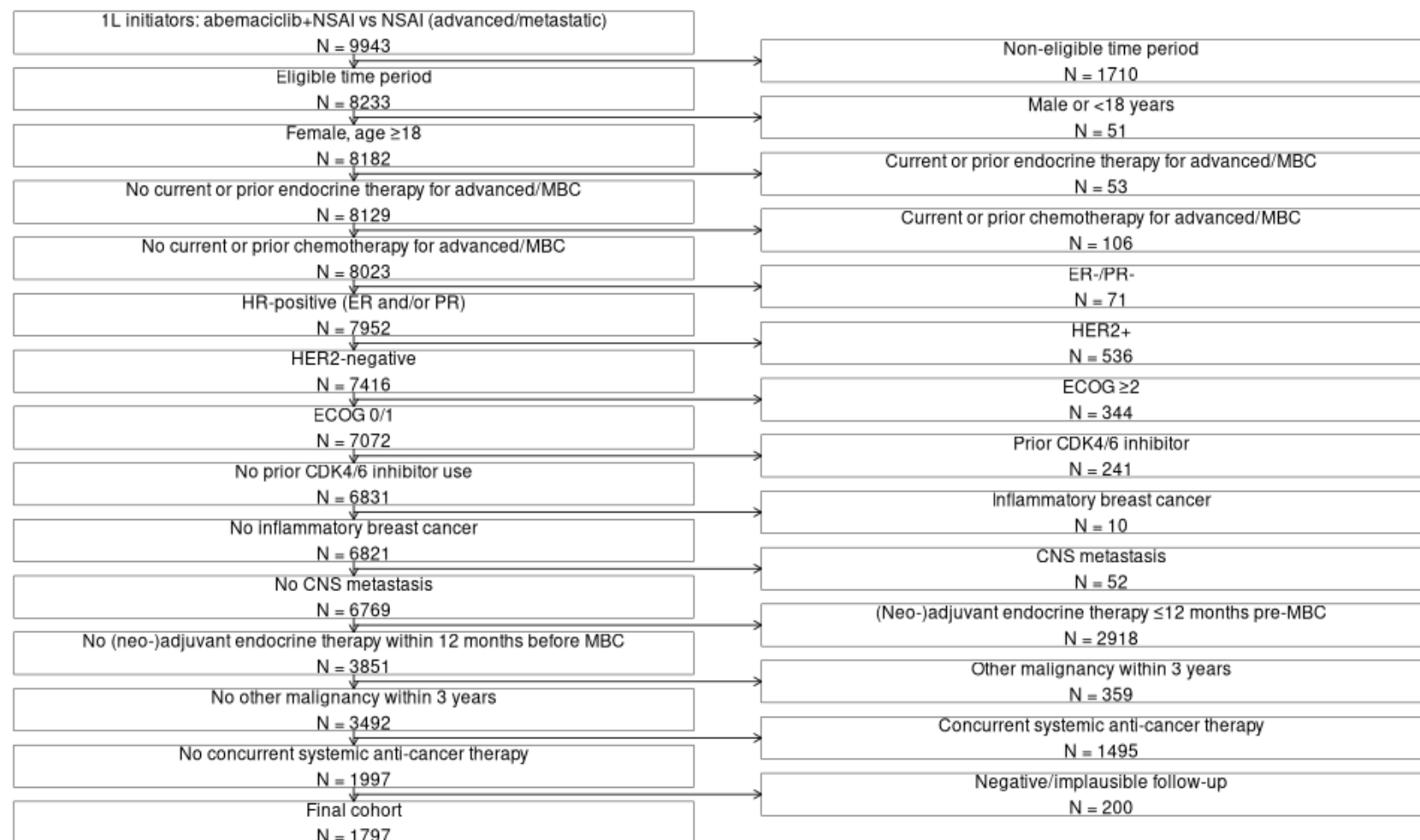
## edb3 attrition



Abbreviations: NAI = non-steroidal aromatase inhibitor (letrozole/anastrozole); MBC = metastatic breast cancer; HER2 = human epidermal growth factor receptor 2; CNS = central nervous system

**Figure 6. CONSORT attrition to select eligible MONARCH-3-like populations in EDB4.**

## edb4 attrition



Abbreviations: NAI = non-steroidal aromatase inhibitor (letrozole/anastrozole); MBC = metastatic breast cancer; HER2 = human epidermal growth factor receptor 2; CNS = central nervous system

## **10.2. Covariate balance figures**

The following figures illustrate the balance of key covariates included in propensity score models among eligible MONARCH-3-like populations in EDB1, EDB3 and EDB4, respectively.

Figure 7. EDB1 covariate balance of covariates included in propensity score model before and after matching.

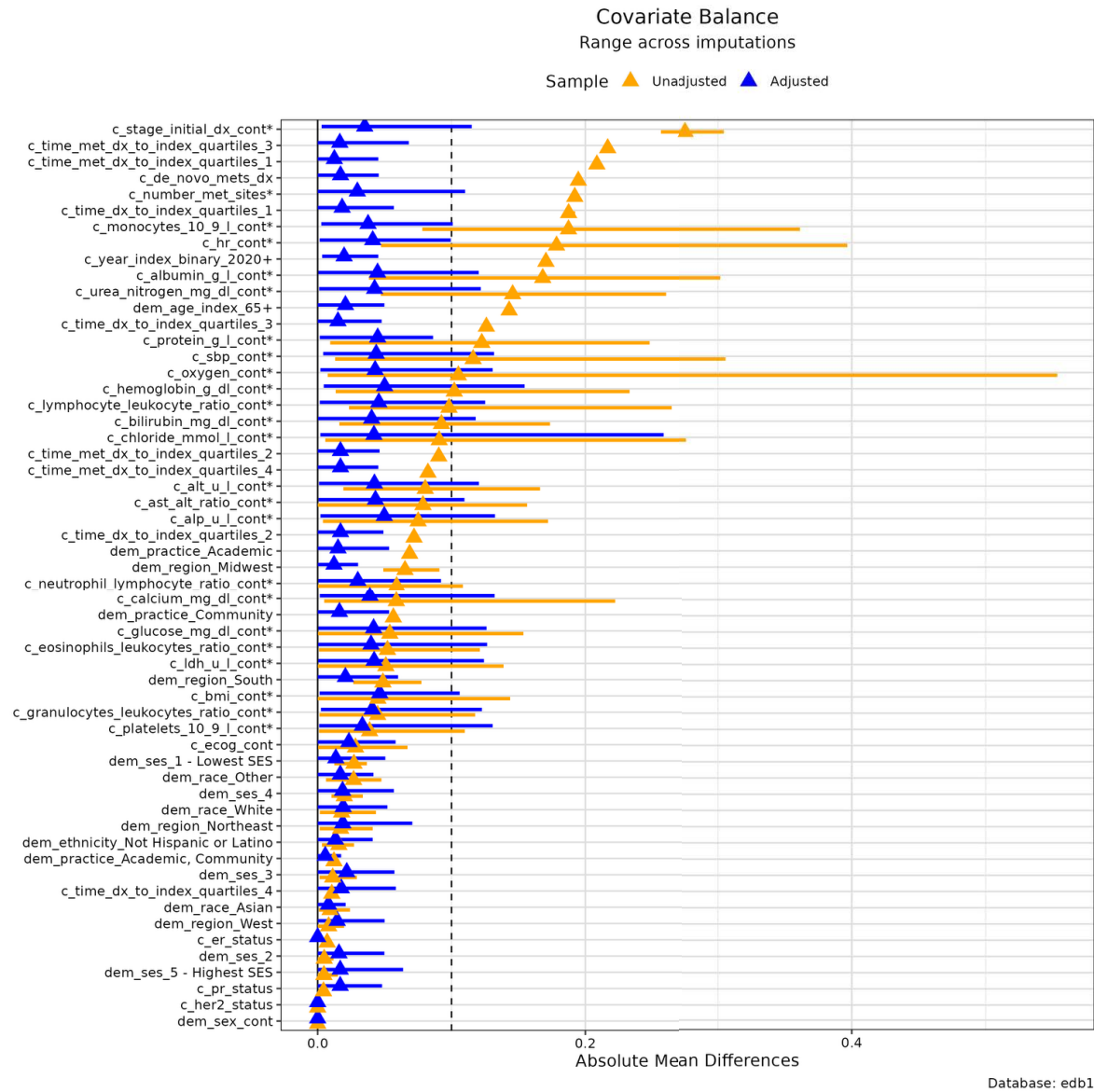


Figure 8. EDB3 covariate balance of covariates included in propensity score model before and after matching.

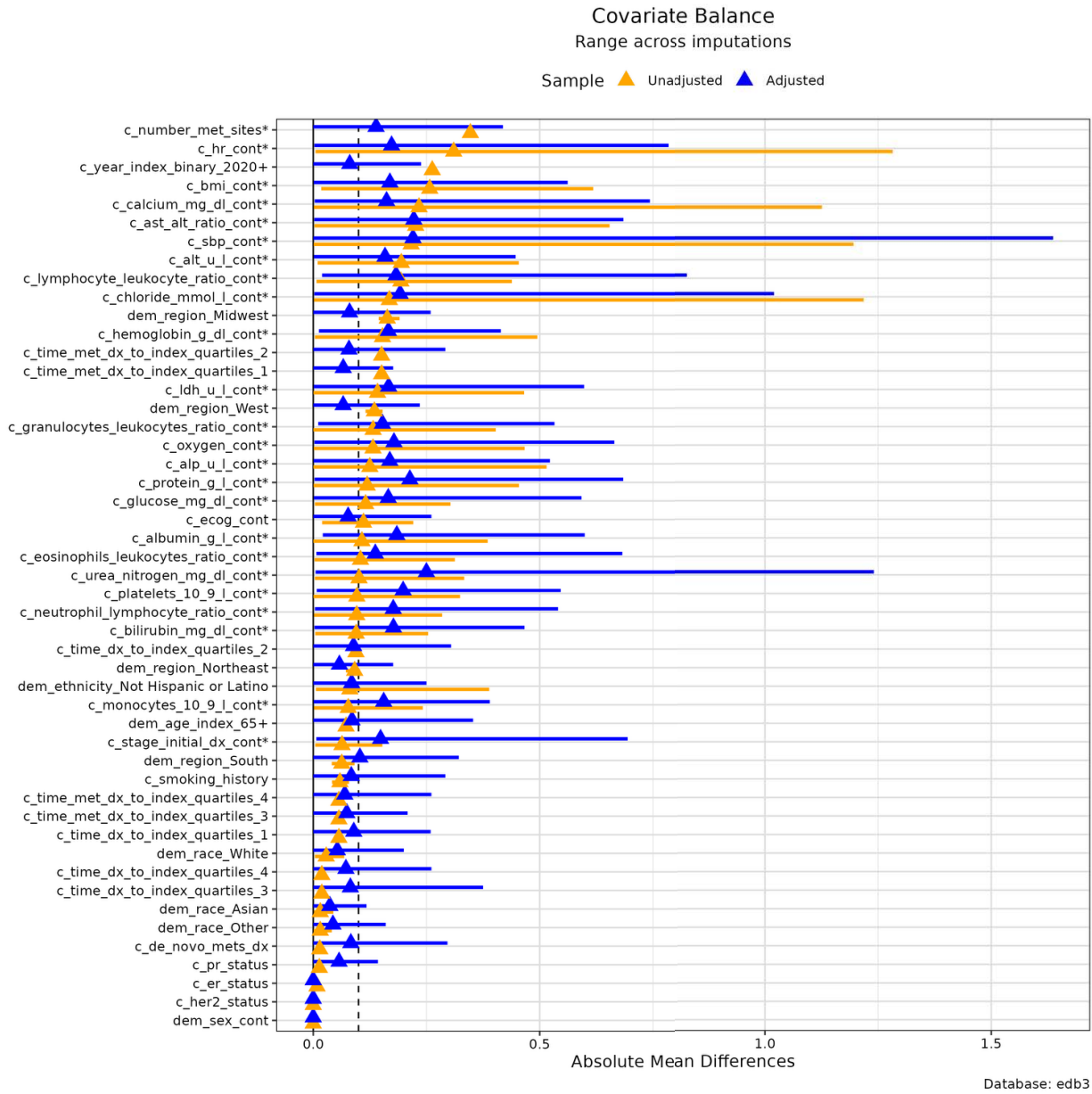
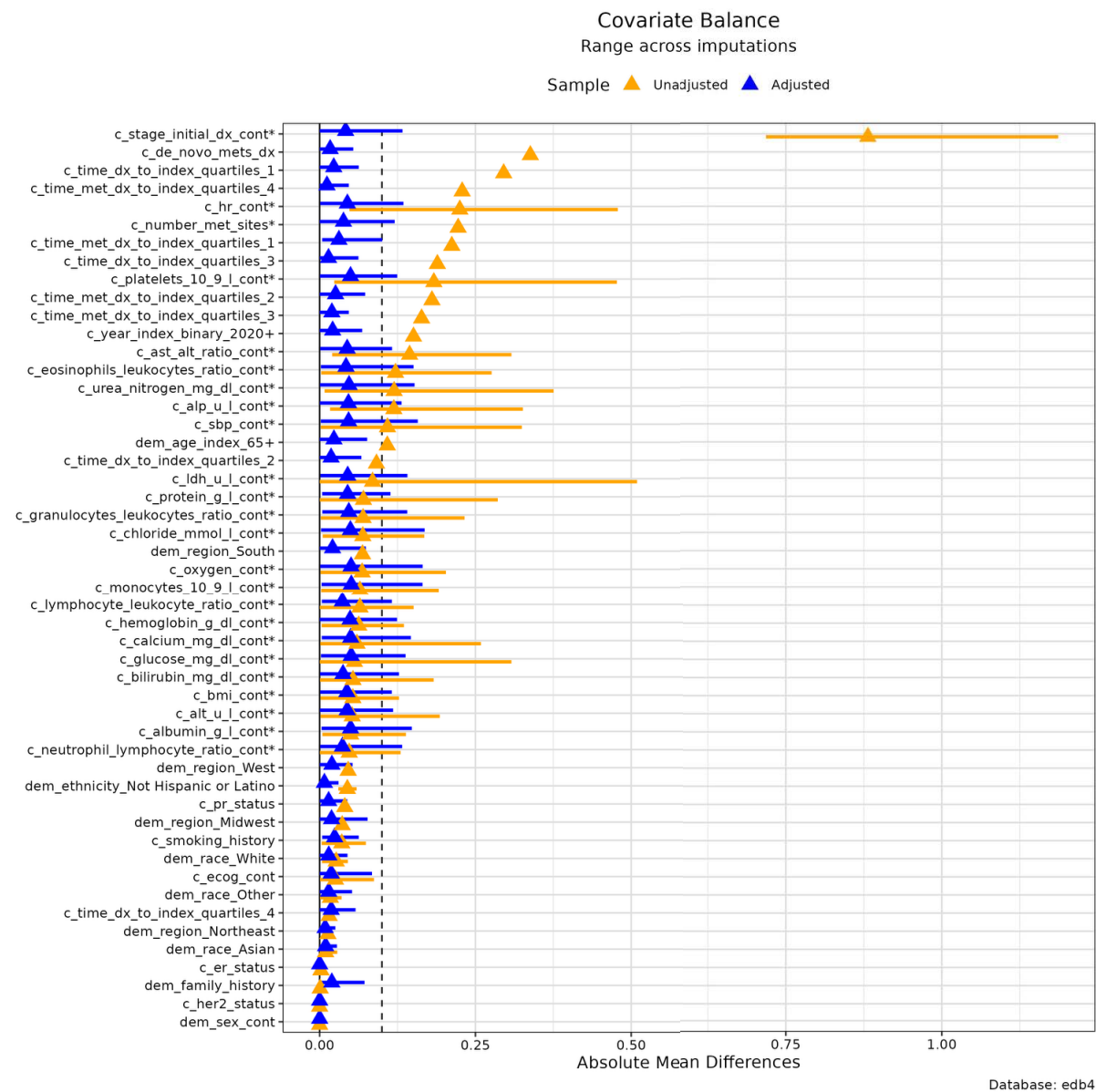


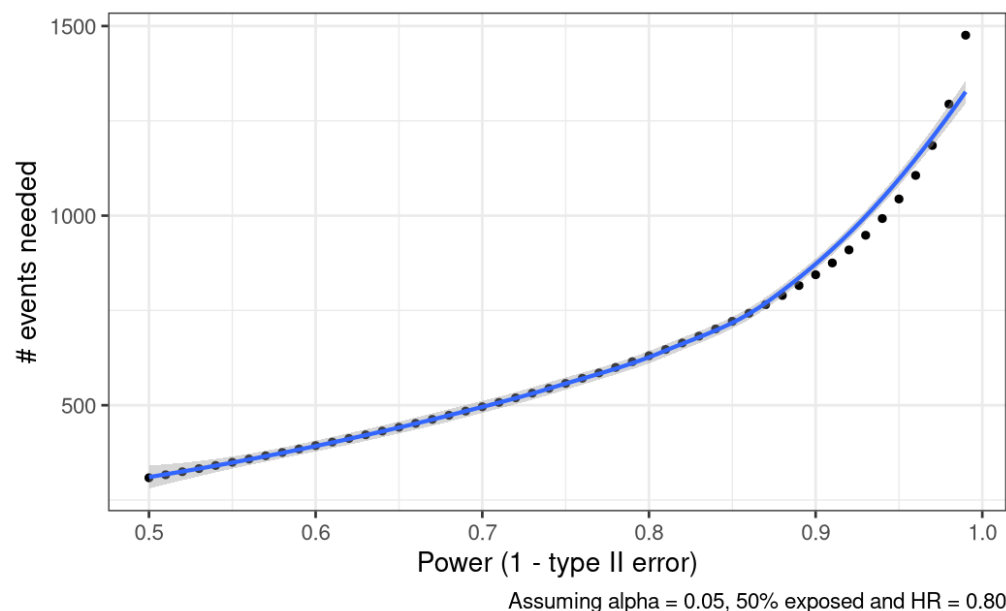
Figure 9. EDB4 covariate balance of covariates included in propensity score model before and after matching.



### 10.3. Sample size/power calculations

Power estimations are computed based on the average number of observed events across imputed and matched datasets according to the methodology described by Schoenfeld.<sup>39</sup> The OS result was null in the trial, therefore, we are not expecting to observe a strong effect in the emulation. Because our 1:1-matched sample in EDB1 ( $n = 580$ ) used in the primary analysis is larger than the trial sample ( $n = 493$ ), we expect its confidence intervals to be narrower (EDB1) or similar (EDB4). In contrast, EDB3 ( $n = 54$ ) and EDB4 ( $n = 480$ ) (sensitivity analysis), are smaller than the trial sample, therefore we expect wider confidence intervals.

**Figure 10 Number of events needed to achieve X power for overall-survival outcome**



#### Primary analysis:

- We are not well powered to detect the expected near null effect based on trial results. Based on a total of 194 events in the 1:1-matched set in EDB1, we would achieve a power of 0.34 to detect an effect as large or larger than  $HR = 0.80$ . However, our expectation is that the observed effect size in the emulation will be near null, with tighter confidence intervals than the trial.

-

Thus, our study will be underpowered for the OS outcome, akin to the original trial that was not powered for OS.

#### 10.4. Additional Figures and Tables

**Table 9.** Lab measurement plausibility thresholds.

| Lab and standardized unit       | Lower plausibility threshold | Upper plausibility threshold |
|---------------------------------|------------------------------|------------------------------|
| c_albumin_g_l                   | 10                           | 200                          |
| c_alp_u_l                       | 1                            | 2000                         |
| c_alt_u_l                       | 1                            | 90000                        |
| c_ast_u_l                       | 1                            | 90000                        |
| c_bilirubin_mg_dl               | 0.1                          | 80                           |
| c_calcium_mg_dl                 | 0.1                          | 20                           |
| c_chloride_mmol_l               | 0.1                          | 200                          |
| c_eosinophils_leukocytes_ratio  | 0                            | 100                          |
| c_glucose_mg_dl                 | 0.1                          | 2000                         |
| c_granulocytes_leukocytes_ratio | 0                            | 100                          |
| c_hemoglobin_g_dl               | 0.1                          | 20                           |
| c_ldh_u_l                       | 0.1                          | Inf                          |
| c_lymphocyte_10_9_l             | 0                            | 1e+06                        |
| c_lymphocyte_leukocyte_ratio    | 0                            | 100                          |
| c_monocytes_10_9_l              | 0                            | 1e+06                        |
| c_neutrophil_10_9_l             | 0                            | 1e+06                        |
| c_platelets_10_9_l              | 0                            | 5000                         |
| c_protein_g_l                   | 1                            | 300                          |
| c_urea_nitrogen_mg_dl           | 0.1                          | 250                          |

**Table 10.** Vital sign measurement plausibility thresholds.

| Vital sign | Lower plausibility threshold | Upper plausibility threshold |
|------------|------------------------------|------------------------------|
| c_sbp      | 50                           | 250                          |
| c_dbp      | 30                           | 150                          |
| c_bmi      | 10                           | 80                           |
| c_bsa      | 0.5                          | 3.5                          |
| c_height   | 0.5                          | 3                            |
| c_oxygen   | 50                           | 100                          |
| c_pain     | 0                            | 10                           |
| c_hr       | 20                           | 250                          |
| c_resp     | 5                            | 50                           |
| c_temp     | 86                           | 113                          |
| c_weight   | 20                           | 300                          |

**Table 11.** Mapping from State to Region.

| State | Region    |
|-------|-----------|
| CT    | Northeast |
| ME    | Northeast |
| MA    | Northeast |
| NH    | Northeast |
| RI    | Northeast |
| VT    | Northeast |
| DE    | Northeast |
| NJ    | Northeast |
| NY    | Northeast |
| PA    | Northeast |
| IL    | Midwest   |
| IN    | Midwest   |
| MI    | Midwest   |
| OH    | Midwest   |
| WI    | Midwest   |
| IA    | Midwest   |
| KS    | Midwest   |
| MN    | Midwest   |
| MO    | Midwest   |
| NE    | Midwest   |
| ND    | Midwest   |

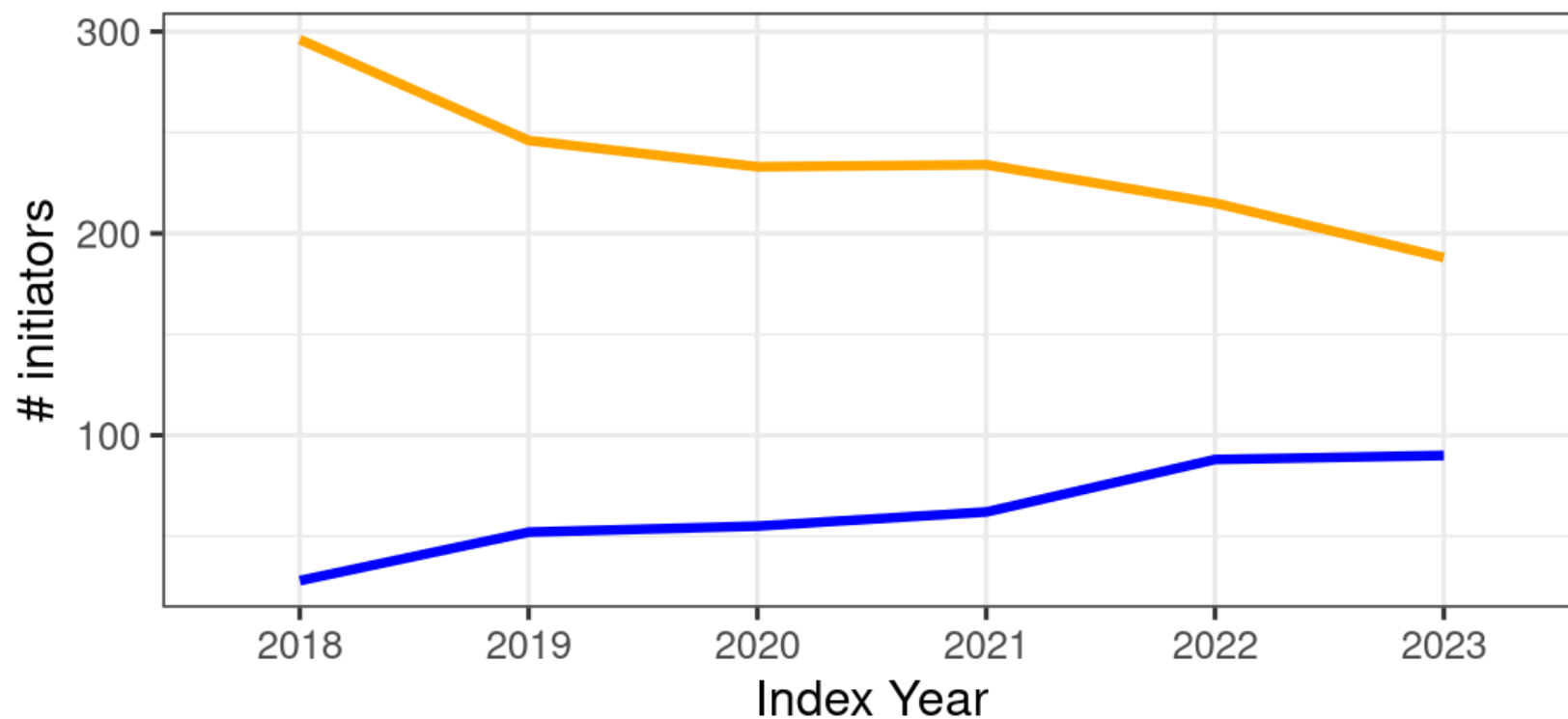
|    |         |
|----|---------|
| SD | Midwest |
| FL | South   |
| GA | South   |
| MD | South   |
| NC | South   |
| SC | South   |
| VA | South   |
| DC | South   |
| WV | South   |
| AL | South   |
| KY | South   |
| MS | South   |
| TN | South   |
| AR | South   |
| LA | South   |
| OK | South   |
| TX | South   |
| AZ | West    |
| CO | West    |
| ID | West    |
| MT | West    |
| NV | West    |
| NM | West    |

|    |      |
|----|------|
| UT | West |
| WY | West |
| AK | West |
| CA | West |
| HI | West |
| OR | West |
| WA | West |

Figure 11. Treatment initiation trends by calendar year and treatment in EDB1.

## Treatment initiation trends in edb1

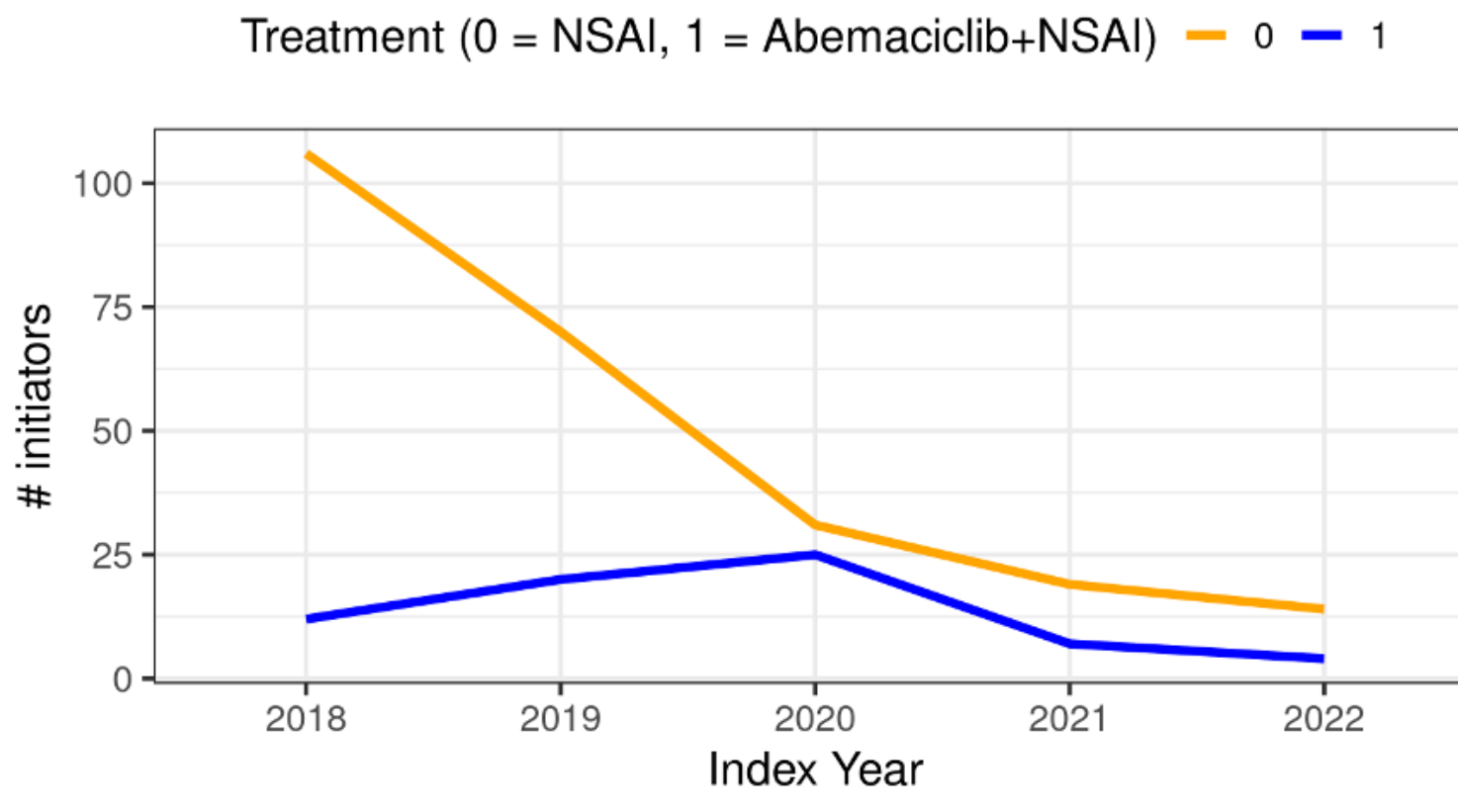
Treatment (0 = NSAI, 1 = Abemaciclib+NSAI) — 0 — 1



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole)

Figure 12. Treatment initiation trends by calendar year and treatment in EDB3.

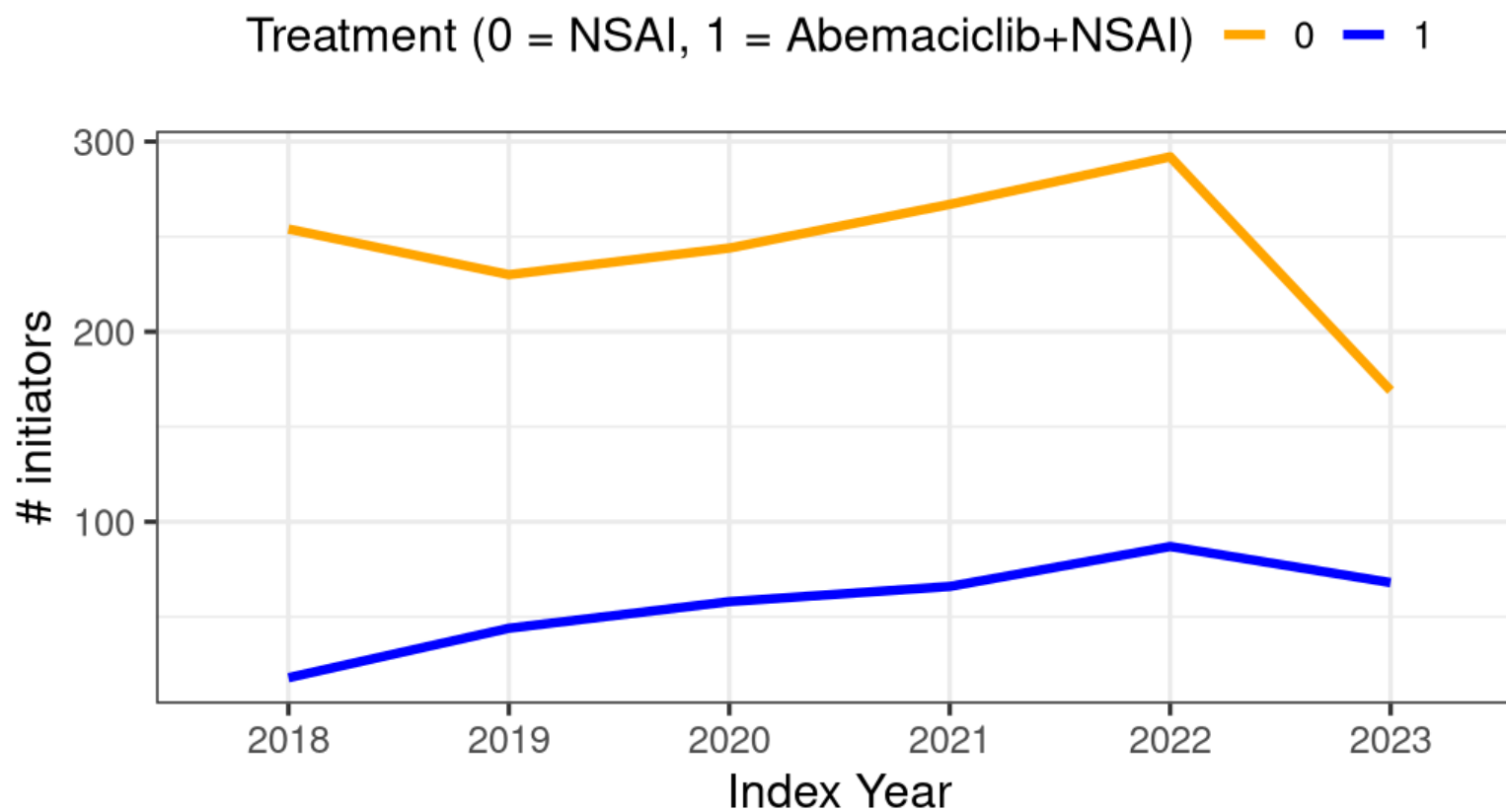
## Treatment initiation trends in edb3



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole)

Figure 13. Treatment initiation trends by calendar year and treatment in EDB4.

## Treatment initiation trends in edb4



Abbreviations: NSAI = non-steroidal aromatase inhibitor (letrozole/anastrozole)

**NCTID** [NCT02246621](https://www.dropbox.com/scl/fi/nz84xecsr70oa048pqu5s/MONARCH3_Protocol.pdf?rlkey=vgp46zxbuj47ba945sdev06vi&st=xmvvbgwz&dl=0)  
**Acronym** **MONARCH3**  
**Protocol** [https://www.dropbox.com/scl/fi/nz84xecsr70oa048pqu5s/MONARCH3\\_Protocol.pdf?rlkey=vgp46zxbuj47ba945sdev06vi&st=xmvvbgwz&dl=0](https://www.dropbox.com/scl/fi/nz84xecsr70oa048pqu5s/MONARCH3_Protocol.pdf?rlkey=vgp46zxbuj47ba945sdev06vi&st=xmvvbgwz&dl=0)  
**PMID** 28968163  
**Indication** Breast cancer  
**Line of Therapy** Metastatic (first-line)  
**Exposure** Abemaciclib plus nonsteroidal aromatase inhibitor - abemaciclib 150 mg orally twice daily, continuous schedule, in combination with either letrozole 2.5 mg orally once daily (continuous) or anastrozole 1 mg orally once daily (continuous).  
**Comparisons** Placebo plus nonsteroidal aromatase inhibitor - placebo orally twice daily, continuous schedule, in combination with either letrozole 2.5 mg orally once daily (continuous) or anastrozole 1 mg orally once daily (continuous).  
**Emulated outcome** Overall survival (secondary endpoint in original trial)

| Key Inclusion/Exclusion Criteria |  |                         |                  |                  |                  | Comment  |
|----------------------------------|--|-------------------------|------------------|------------------|------------------|--|
| Criteria                         | RCT eligibility criteria (taken from the original trial protocol)  | Relevance for emulation | Emulation [EDB1] | Emulation [EDB3] | Emulation [EDB4] |  |
| Inclusion                        | <p>Have a diagnosis of HR+, HER2- breast cancer. Although not required as a protocol procedure, metastatic disease should be considered for biopsy whenever possible to reassess HR and HER2 status if clinically indicated.</p> <ul style="list-style-type: none"> <li>• To fulfill the requirement for HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least one of the hormone receptors (ER, progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).</li> <li>• To fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization (ISH) as defined in the relevant ASCO/CAP guidelines (Wolff et al. 2013).</li> </ul> | Relevant                | Possible         | Possible         | Possible         | <p>Keep if HR+ (ER+ or PR+) or missing because:</p> <p>- Abemaciclib + letrozole is indicated for HR+/HER2-negative metastatic breast cancer.</p> <p>Keep if HER2-negative or HER2 status unknown because:</p> <p>- Ribociclib + letrozole is indicated for HR+/HER2-negative metastatic breast cancer.</p> <p>- Letrozole monotherapy was historically the standard first-line treatment for HR+/HER2-negative metastatic breast cancer before CDK4/6 inhibitors became standard of care</p> <p>- In HER2+ HR+ metastatic breast cancer, letrozole is not typically given alone; instead, it is usually combined with anti-HER2 therapy (e.g., trastuzumab ± pertuzumab).</p> |
| Inclusion                        | Have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease  | Relevant                | Possible         | Possible         | Possible         |  |
| Inclusion                        | <p>Have postmenopausal status, defined as meeting one of the following conditions:</p> <ul style="list-style-type: none"> <li>• Prior bilateral oophorectomy</li> <li>• Age ≥60 years</li> <li>• Age &lt;60 years and amenorrheic (non-treatment-induced amenorrhea secondary to tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months. Follicle-stimulating hormone (FSH) and estradiol must be in the postmenopausal range.</li> </ul>   | Relevant                | Limited          | Limited          | Limited          | To protect privacy, most databases only provide month- or year-level granularity of dates; post-menopausal status can be defined based on age and inferred by the fact that abemaciclib was administered (indication in postmenopausal women)  |

|           |   |                   |                   |                   |                   |   |
|-----------|---|-------------------|-------------------|-------------------|-------------------|---|
| Inclusion | Have one of the following as defined by the RECIST v1.1:<br><br>• Measurable disease<br><br>• Nonmeasurable bone-only disease. Nonmeasurable bone-only disease may include any of the following: blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lyticblastic bone lesions without a measurable soft tissue component.  | Relevant          | Limited           | Limited           | Limited           | We are assuming that all subjects in RWD have measurable disease if they are receiving treatment          |
| Inclusion | Have a PS of ≤1 on the ECOG scale   | Relevant          | Possible          | Possible          | Possible          | ECOG implementation possible; high % missingness likely   |
| Inclusion | Have adequate organ function, including:<br>• hematologic: absolute neutrophil count (ANC) ≥1.5 × 10 <sup>9</sup> /L, platelets ≥100 × 10 <sup>9</sup> /L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.<br>• hepatic: bilirubin ≤1.5 times the upper limit of normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 times ULN (or ALT and AST ≤5 times ULN if liver metastases are present).<br>• renal: serum creatinine ≤1.5 times ULN. | Relevant          | Not implementable | Not implementable | Not implementable | Not captured well   |
| Inclusion | Have discontinued previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture at least 2 weeks prior to randomization and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy   | Limited relevance | Not implementable | Not implementable | Not implementable | Not captured well   |
| Inclusion | Are female and ≥18 years of age   | Relevant          | Possible          | Possible          | Possible          |   |
| Inclusion | Are able to swallow capsules  | Limited relevance | Not implementable | Not implementable | Not implementable |   |
| Inclusion | Have given written informed consent prior to any study-specific procedures  | Limited relevance | Not implementable | Not implementable | Not implementable |   |
| Inclusion | Are reliable, willing to be available for the duration of the study, and are willing to follow study procedures.  | Limited relevance | Not implementable | Not implementable | Not implementable |   |
| Inclusion | Restriction to period 2017-2023   | Relevant          | Possible          | Possible          | Possible          | 2017 was the approval year for abemaciclib, and 2023 is the end of the available data stream              |
| Exclusion | Have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.  | Relevant          | Not implementable | Not implementable | Not implementable | Since treatment was given, it is reasonable to assume that patients did not have severe organ dysfunction |
| Exclusion | Have inflammatory breast cancer.  | Relevant          | Possible          | Possible          | Possible          | Record of inflammatory breast cancer  |
| Exclusion | Have clinical evidence or a history of CNS metastasis. Screening is not required for enrollment   | Relevant          | Possible          | Possible          | Possible          | Record of CNS metastases  |
| Exclusion | Are currently receiving or have previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer. [Note: A patient may be enrolled if she received prior (neo)adjuvant endocrine therapy (including , but not limited to anti-estrogens or aromatase inhibitors) for localized disease. In addition, a patient may be enrolled if she has received ≤2 weeks of NSAI in this disease setting immediately preceding screening and agrees to discontinue NSAI until study treatment initiation.]   | Relevant          | Possible          | Possible          | Possible          | Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole          |
| Exclusion | Have received prior (neo)adjuvant endocrine therapy (e.g., anti-estrogens or aromatase inhibitors) with a disease-free interval ≤12 months from completion of treatment.  | Relevant          | Possible          | Possible          | Possible          |   |

|           |  |                   |                   |                   |                   |  |
|-----------|--|-------------------|-------------------|-------------------|-------------------|--|
| Exclusion | Are currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer. [Note: Patients may be enrolled if they received prior (neo)adjuvant chemotherapy for localized disease.]   | Relevant          | Possible          | Possible          | Possible          | Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole         |
| Exclusion | Have received prior treatment with everolimus  | Relevant          | Not implementable | Not implementable | Not implementable | Not well captured  |
| Exclusion | Have received prior treatment with any CDK4/6 inhibitor (or participated in any CDK4/6 inhibitor clinical trial for which treatment assignment is still blinded)   | Relevant          | Possible          | Possible          | Possible          |  |
| Exclusion | Have initiated bisphosphonates or approved RANK ligand (RANK-L) targeted agents (for example, denosumab) <7 days prior to randomization  | Relevant          | Not implementable | Not implementable | Not implementable | Not well captured  |
| Exclusion | Are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and Lilly clinical research physician (CRP) is required to establish eligibility | Limited relevance | Not implementable | Not implementable | Not implementable | Not captured well  |
| Exclusion | Have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomization for a nonmyelosuppressive or myelosuppressive agent, respectively.  | Limited relevance | Not implementable | Not implementable | Not implementable | Not captured well  |
| Exclusion | Have had major surgery within 14 days prior to randomization to allow for post-operative healing of the surgical wound and site(s)   | Relevant          | Not implementable | Not implementable | Not implementable | Since treatment was given, it is reasonable to assume that patients did not undergo recent major surgery |
| Exclusion | Have received recent (within 28 days prior to randomization) yellow fever vaccination  | Limited relevance | Not implementable | Not implementable | Not implementable | Not captured well  |
| Exclusion | Have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis).   | Relevant          | Not implementable | Not implementable | Not implementable | Not captured well  |
| Exclusion | Have a personal history within the last 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest  | Relevant          | Not implementable | Not implementable | Not implementable | Not captured well  |

|           |  |                   |                   |                   |                   |  |
|-----------|--|-------------------|-------------------|-------------------|-------------------|--|
| Exclusion | Have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.        | Relevant          | Limited           | Limited           | Limited           | EDB4 does not contain records on diagnoses of other malignancies besides breast cancer. Prior non-breast cancer malignancy within 3 years is approximated with advanced prior treatments based on recommendation by the data vendor for EDB4 |
| Exclusion | Have received an autologous or allogeneic stem-cell transplant   | Limited relevance | Not implementable | Not implementable | Not implementable | Not available  |
| Exclusion | Have active bacterial or fungal infection or detectable viral infection (for example, human immunodeficiency virus [HIV] or viral hepatitis). Screening is not required for enrollment | Limited relevance | Not implementable | Not implementable | Not implementable | Since treatment was given, it is reasonable to assume that patients did not have active bacterial or fungal infection or detectable viral infection  |
| Exclusion | Record of systemic anticancer therapy other than exposure/comparator on index date   | Relevant          | Possible          | Possible          | Possible          | Not an explicit RCT criterion, added for database study  |

**NCTID** [NCT02246621](https://www.dropbox.com/scl/fi/nz84xecsr70qa048pqu5s/MONARCH3_Protocol.pdf?rlkey=vgp46zxbui47ba945sdev06vi&st=xmvvbwqz&dl=0)  
**Acronym** **MONARCH3**  
**Protocol** [https://www.dropbox.com/scl/fi/nz84xecsr70qa048pqu5s/MONARCH3\\_Protocol.pdf?rlkey=vgp46zxbui47ba945sdev06vi&st=xmvvbwqz&dl=0](https://www.dropbox.com/scl/fi/nz84xecsr70qa048pqu5s/MONARCH3_Protocol.pdf?rlkey=vgp46zxbui47ba945sdev06vi&st=xmvvbwqz&dl=0)  
**PMID** 28968163  
**Indication** Breast cancer  
**Line of Therapy** Metastatic (first-line)  
**Exposure** Abemaciclib plus nonsteroidal aromatase inhibitor - abemaciclib 150 mg orally twice daily, continuous schedule, in combination with either letrozole 2.5 mg orally once daily (continuous) or anastrozole 1 mg orally once daily (continuous).  
**Comparisons** Placebo plus nonsteroidal aromatase inhibitor - placebo orally twice daily, continuous schedule, in combination with either letrozole 2.5 mg orally once daily (continuous) or anastrozole 1 mg orally once daily (continuous).  
**Emulated outcome** Overall survival (secondary endpoint in original trial)

| Measurement eligibility criteria |  |  |   |   |  | Comment  | encore.io function                            |
|----------------------------------|--|--|---|---|--|--|---|
| Criteria                         | Criteria rule as defined in original protocol  | Time point/period of emulated measurement [days] | Emulation [EDB1]  | Emulation [EDB3]  | Emulation [EDB4]   |  |   |
| Inclusion 1                      | Have a diagnosis of HR+, HER2- breast cancer. Although not required as a protocol procedure, metastatic disease should be considered for biopsy whenever possible to reassess HR and HER2 status if clinically indicated.<br>• To fulfill the requirement for HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least one of the hormone receptors (ER, progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).<br>• To fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization (ISH) as defined in the relevant ASCO/CAP guidelines (Wolff et al. 2013). | [-inf; 0]  | - Any hormone-positive or hormone-missing status to or on index date<br><br>- Any HER2-negative or HER2-missing status prior to or on index date  | - Any hormone-positive or hormone-missing status to or on index date<br><br>- Any HER2-negative or HER2-missing status prior to or on index date  | - Any hormone-positive or hormone-missing status to or on index date<br><br>- Any HER2-negative or HER2-missing status prior to or on index date   | - If estrogen receptor or progesterone receptor missing and a patient received the exposures of interest, then is likely to be positive given the alignment with the indication for the exposures of interest<br><br>- If HER2 is missing and a patient received the exposures of interest, then HER2 is likely to be negative given the alignment with the indication for the exposures of interest | edbx_get_biomarker()<br>edbx_get_her2()       |
| Inclusion 2                      | Have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease  | [-inf; 0]  | First line of therapy needs to be for "Advanced" setting (LoT table);<br><br>No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date | First line of therapy needs to be for "Advanced" setting (LoT table);<br><br>No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date | Any evidence of at least one distant metastasis at any time before the index date (inclusive). This captures both de novo metastatic patients and those who progressed/developed metastases before/on the index date. First therapy for advanced disease after date of first metastasis.<br><br>No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date | EDB4 does not have a well-curated line of therapy variable   | EDB4: Derived from edbx_get_diagnosis_solid() |
| Inclusion 3                      | Have postmenopausal status, defined as meeting one of the following conditions:<br>• Prior bilateral oophorectomy<br>• Age ≥60 years<br>• Age <60 years and amenorrheic (non-treatment-induced amenorrhea secondary to tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months. Follicle-stimulating hormone (FSH) and estradiol must be in the postmenopausal range.  | NA   | NA  | NA  | NA   | Although not directly captured in RWD, it is likely to be fulfilled given the alignment with the indication for the exposures of interest  |   |

|             |  |                  |  |  |  |  |                            |
|-------------|--|------------------|--|--|--|--|----------------------------|
| Inclusion 4 | Have one of the following as defined by the RECIST v1.1:<br><br>• Measurable disease<br><br>• Nonmeasurable bone-only disease. Nonmeasurable bone-only disease may include any of the following: blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lyticblastic bone lesions without a measurable soft tissue component.   | NA               | NA   | NA   | NA   | It is reasonable to assume that all patients in RWD had measurable disease if they received treatment        |                            |
| Inclusion 5 | Have a Performance status of ≤1 on the ECOG scale  | [-90; 0]         | ECOG = 0   1   | ECOG = 0   1   | ECOG = 0   1   |  | edbx_get_ecog()            |
| Inclusion 6 | Are female and ≥18 years of age  | [0; 0]           | Female and age ≥18 years   | Female and age ≥18 years   | Female and age ≥18 years   |  | edbx_get_demographic()     |
| Inclusion 7 | Restriction to period 2017-2023  | [0; 0]           | Years 2017-2023  | Years 2017-2023  | Years 2017-2023  |  |                            |
| Exclusion 1 | Have inflammatory breast cancer.   | [-inf; -0]       | Record of inflammatory breast cancer   | Record of inflammatory breast cancer   | Record of inflammatory breast cancer   |  |                            |
| Exclusion 2 | Have clinical evidence or a history of CNS metastasis. Screening is not required for enrollment  | [-inf; 0]        | Record of CNS metastases prior to or on index date   | Record of CNS metastases prior to or on index date   | Record of CNS metastases prior to or on index date   |  | edbx_get_diagnosis_solid() |
| Exclusion 3 | Are currently receiving or have previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer. [Note: A patient may be enrolled if she received prior (neo)adjuvant endocrine therapy (including, but not limited to anti-estrogens or aromatase inhibitors) for localized disease. In addition, a patient may be enrolled if she has received ≤2 weeks of NSAI in this disease setting immediately preceding screening and agrees to discontinue NSAI until study treatment initiation.] | NA               | NA   | NA   | NA   | Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole/anastrozole |                            |
| Exclusion 4 | Have received prior (neo)adjuvant endocrine therapy (e.g., anti-estrogens or aromatase inhibitors) with a disease-free interval ≤12 months from completion of treatment.   | [MBC-365; MBC-1] | Treatment with (neo)adjuvant endocrine therapy <=12 months from MBC  | No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date | No systemic anti-cancer therapy following initial record potentially indicating metastatic disease and prior to index date |  |                            |
| Exclusion 5 | Are currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer. [Note: Patients may be enrolled if they received prior (neo)adjuvant chemotherapy for localized disease.]   | NA               | NA   | NA   | NA   | Automatically excluded as first-line therapy will exclusively consider abemaciclib and letrozole/anastrozole |                            |
| Exclusion 6 | Have received prior treatment with any CDK4/6 inhibitor (or participated in any CDK4/6 inhibitor clinical trial for which treatment assignment is still blinded)   | [-inf; -1]       | Prior treatment with CDK4/6  | Prior treatment with CDK4/6  | Prior treatment with CDK4/6  |  |                            |
| Exclusion 7 | Have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.  | [-1095; 0]       | Record of cancer diagnosis within 1095 days prior to or on index day   | Record of cancer diagnosis within 1095 days prior to or on index day   | Record of non-index cancer treatment within 1095 days prior to or on index day   | No diagnosis table for EDB4 available  |                            |
| Exclusion 8 | Record of systemic anticancer therapy other than exposure/comparator on index date   | [0; 0]           | Exclusion if treatment is any other than abemaciclib-plus-letrozole/anastrozole or letrozole/anastrozole alone | Exclusion if treatment is any other than abemaciclib-plus-letrozole/anastrozole or letrozole/anastrozole alone             | Exclusion if treatment is any other than abemaciclib-plus-letrozole/anastrozole or letrozole/anastrozole alone             |  |                            |

MBC = first metastatic breast cancer date