Emulation of the CheckMate 017/057 (NCT01642004 and NCT01673867) trials using specialty oncology electronic health records databases

NCT07485166

29th January, 2026

1. Title Page

Title	Emulation of the CheckMate 017/057 (NCT01642004 and NCT01673867) trials using specialty oncology electronic health records databases
Research question & Objectives	Emulation of the CheckMate 017/057 (NCT01642004 and NCT01673867) trials, which compared Nivolumab to Docetaxel as second-line treatment on the risk of death in patients with advanced non-small cell lung cancer.
Protocol version	V1.0
Last update date	January 29, 2026
Contributors	**Primary investigators contact information:** Xiangzhong Xue, Shirley V. Wang **Contributor names:** Yuxin Wang (programmer)
Study registration	**Site:** clinicaltrials.gov **Identifier:** NCT07485166
Sponsor	**Organization:** Food and Drug Administration **Contact:** n/a
Conflict of interest	SVW has been an ad hoc consultant to ICA Group, Cytel Inc, and MITRE a federally funded research and development center for the Centers for Medicare and Medicaid
Protocol repository	Clinicaltrials.gov
Analytic code repository	https://gitlab-scm.partners.org/drugepi/encore/check-mate-017-057 (access within Mass General Brigham network only)
Quarto study report (including annotated code and output)	https://gitlab-scm.partners.org/drugepi/encore/check-mate-017-057/-/tree/main/public?ref_type=heads (access within Mass General Brigham network only)
***encore.io*[1] version**	0.2.0 (see attached documentation *encore.io_0.2.0.pdf*)
encore.analytics[1] version	0.2.0 (https://janickweberpals.github.io/encore.analytics/)
[1] 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 pooled analysis of CheckMate 017 (NCT01642004) and CheckMate 057 (NCT01673867) using real-world specialty oncology electronic health record data and to investigate the concordance between the trial's original and emulated treatment effect estimates on overall survival (OS). CheckMate 017 and CheckMate 057 were two Phase III, double-blind, randomised studies assessing the efficacy and safety of Nivolumab (3 mg/kg IV every 2 weeks) versus Docetaxel (75 mg/m² IV every 3 weeks) in patients with squamous (CheckMate 017) and nonsquamous (CheckMate 057) advanced Non-small Cell Lung Cancer (NSCLC) and disease progression during or after prior platinum-based chemotherapy.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
January 29, 2026	V1.0	NA	Initial version	NA

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 of 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,[1–4] **EmulatioN of Comparative Oncology trials with Real-world Evidence** (**ENCORE)** is the trial emulation discussed in this protocol 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 pooled analysis of **CheckMate 017 and CheckMate 057**.[5,6] CheckMate 017/057 were two Phase III, double-blind, randomised studies assessing the efficacy and safety of Nivolumab (3 mg/kg IV every 2 weeks) versus Docetaxel (75 mg/m² IV every 3 weeks) in patients with squamous (CheckMate 017) and nonsquamous (CheckMate 057) advanced Non-small Cell Lung Cancer (NSCLC) and disease progression during or after prior platinum-based chemotherapy.

The primary estimate of pooled analysis targeted for emulation is a hazard ratio (HR) for death (overall survival) of 0.68 (95% CI 0.59 to 0.78) with a median overall survival time of 11.1 months (95% CI 9.2 to 13.1) in the nivolumab group and 8.1 months (95% CI, 7.2 to 9.2) in the comparator group.[7] Nivolumab received U.S. FDA approval for the treatment of patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy on March 4, 2015, based on the results of CheckMate 017. Subsequently, on October 9, 2015, the FDA expanded the indication to include patients with metastatic nonsquamous NSCLC with progression on or after platinum-based chemotherapy, supported by evidence from CheckMate 057.

The 5-year pooled OS endpoint was published in the Journal of Clinical Oncology on March 1, 2021.[7]

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.

Objective:	To compare overall survival [OS] in patients who initiated nivolumab versus patients who initiated docetaxel.
Hypothesis:	Initiation of nivolumab improves overall survival time as compared to initiation of docetaxel
Population ***(mention key inclusion-exclusion criteria):***	• Age at least 18 years • Subjects with NSCLC who present with advanced/metastatic (Stage IIIB/ Stage IV) disease • Prior platinum doublet–based chemotherapy regimen for advanced or metastatic NSCLC • Have experienced disease recurrence or progression during or after the prior platinum doublet–based chemotherapy regimen • ECOG 0 or 1
Exposure:	Initiation of nivolumab
Comparator:	Initiation of docetaxel
Outcome:	Time to all-cause mortality (OS)
Time ***(when follow up begins and ends):***	From the day of the end of the treatment assessment window until death or last observed clinical activity/last sign of the patient being alive or data cut-off, whichever occurred earlier
Setting:	Advanced NSCLC with recurrence or progression during or after first-line platinum doublet-based chemotherapy
Main measure of effect:	Primary: Hazard ratio (95% CI) for overall survival Secondary: median overall survival time (difference) in % (95% CI)

aThe treatment assessment window is defined as the period from second-line treatment initiation to a vendor-specified time point in order to fully capture the first-line regimen for advanced NSCLC.

The emulation of the main protocol elements of the CheckMate 017/057 is illustrated side by side in

Protocol component	CheckMate 017/057 RCT	Emulation
Eligibility criteria	Age ≥18 years at randomization	Age ≥18 years at treatment initiation
	Stage IIIB/IV NSCLC, or recurrent/progressive disease after multimodality therapy for locally advanced disease	Line-of-therapy setting is “advanced” (EDB1), “metastatic” (EDB2), or evidence of metastatic disease at treatment initiation (EDB4)
	Received nivolumab or docetaxel as 2L (017/057) or 3L (057)	Treatment with nivolumab or docetaxel is 2L for advanced/metastatic diseases ○ CheckMate 017 evaluated nivolumab versus docetaxel in the second-line setting. CheckMate 057 enrolled predominantly second-line patients, with a smaller proportion treated in the third-line (88% and 12%, respectively). Given that the trial population was primarily second-line and that real-world data are limited in their ability to reliably ascertain third-line treatment, we will focus our emulation on the second-line setting.
	Received one prior platinum doublet–based chemotherapy for advanced/metastatic NSCLC	Patient received 1L platinum doublet–based chemotherapy for advanced/metastatic disease
	Disease recurrence/progression during or after the prior platinum doublet regimen	Excluded patients without documentation of disease progression between initiation of 1L platinum doublet-based chemotherapy and initiation of nivolumab or docetaxel
	ECOG Performance Status 0–1	ECOG 0 or 1 in the 90 days before/on treatment initiation
	No prior docetaxel or nivolumab	Excluded patients with documentation of docetaxel or nivolumab use before treatment initiation
	No prior immunotherapy	Excluded patients with documentation of immunotherapy[a] use before treatment initiation
	No active malignancy / prior malignancy (except non-melanoma skin cancers and specified in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast); if prior malignancy allowed, complete remission ≥2 years and no additional therapy anticipated	Excluded patients with any prior non-lung malignancy diagnosis (except non-melanoma skin cancers and specified in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast)
	No active/known/suspected autoimmune diseases	Excluded patients with documented autoimmune diseases[b] within 2 years before/on treatment initiation

	No interstitial lung disease	Excluded patients with documented interstitial lung disease before/on treatment initiation
	No CNS metastases	Excluded patients with documented CNS metastases before/on treatment initiation
	No ongoing/planned anti-cancer therapies other than study treatments	Excluded patients with any other anti-cancer therapy[c] during the treatment assessment window[c]
Treatment strategies	Nivolumab versus Docetaxel	Nivolumab versus Docetaxel
Assignment procedures	Random assignment to receive either nivolumab or docetaxel in a 1:1 ratio	1:1 matching of patients based on their propensity to initiate nivolumab as opposed to docetaxel
Follow-up period	Time from randomization until death from any cause or censoring of patients who did not die on the basis of the last recorded date that the patient was known to be alive	Time from the end of the treatment assessment window[c] defined by the vendors business rules to identify line of therapy until death from any cause or censoring of patients who did not die on the basis of the last recorded date that the patient was known to be alive
Outcome	Overall survival	Overall survival
Causal contrast	Intent-to-treat effect	As started (observational analogue of intent-to-treat)

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Table 2. Trial emulation table summarizing the main protocol elements of the CheckMate 017/057 trial and the planned emulation.

Protocol component	CheckMate 017/057 RCT	Emulation
Eligibility criteria	Age ≥18 years at randomization	Age ≥18 years at treatment initiation
	Stage IIIB/IV NSCLC, or recurrent/progressive disease after multimodality therapy for locally advanced disease	Line-of-therapy setting is "advanced" (EDB1), "metastatic" (EDB2), or evidence of metastatic disease at treatment initiation (EDB4)
	Received nivolumab or docetaxel as 2L (017/057) or 3L (057)	Treatment with nivolumab or docetaxel is 2L for advanced/metastatic diseases ○ CheckMate 017 evaluated nivolumab versus docetaxel in the second-line setting. CheckMate 057 enrolled predominantly second-line patients, with a smaller proportion treated in the third-line (88% and 12%, respectively). Given that the trial population was primarily second-line and that real-world data are limited in their ability to reliably ascertain third-line treatment, we will focus our emulation on the second-line setting.
	Received one prior platinum doublet–based chemotherapy for advanced/metastatic NSCLC	Patient received 1L platinum doublet–based chemotherapy for advanced/metastatic disease
	Disease recurrence/progression during or after the prior platinum doublet regimen	Excluded patients without documentation of disease progression between initiation of 1L platinum doublet-based chemotherapy and initiation of nivolumab or docetaxel
	ECOG Performance Status 0–1	ECOG 0 or 1 in the 90 days before/on treatment initiation
	No prior docetaxel or nivolumab	Excluded patients with documentation of docetaxel or nivolumab use before treatment initiation
	No prior immunotherapy	Excluded patients with documentation of immunotherapy[a] use before treatment initiation
	No active malignancy / prior malignancy (except non-melanoma skin cancers and specified in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast); if prior malignancy allowed, complete remission ≥2 years and no additional therapy anticipated	Excluded patients with any prior non-lung malignancy diagnosis (except non-melanoma skin cancers and specified in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast)
	No active/known/suspected autoimmune diseases	Excluded patients with documented autoimmune diseases[b] within 2 years before/on treatment initiation

	No interstitial lung disease	Excluded patients with documented interstitial lung disease before/on treatment initiation
	No CNS metastases	Excluded patients with documented CNS metastases before/on treatment initiation
	No ongoing/planned anti-cancer therapies other than study treatments	Excluded patients with any other anti-cancer therapy[c] during the treatment assessment window[c]
Treatment strategies	Nivolumab versus Docetaxel	Nivolumab versus Docetaxel
Assignment procedures	Random assignment to receive either nivolumab or docetaxel in a 1:1 ratio	1:1 matching of patients based on their propensity to initiate nivolumab as opposed to docetaxel
Follow-up period	Time from randomization until death from any cause or censoring of patients who did not die on the basis of the last recorded date that the patient was known to be alive	Time from the end of the treatment assessment window[c] defined by the vendors business rules to identify line of therapy until death from any cause or censoring of patients who did not die on the basis of the last recorded date that the patient was known to be alive
Outcome	Overall survival	Overall survival
Causal contrast	Intent-to-treat effect	As started (observational analogue of intent-to-treat)

[a]Includes the following: ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab, tremelimumab, dostarlimab

[b]Includes the following: Inflammatory bowel disease, Systemic lupus erythematosus, Dermatomyositis, Scleroderma, Vasculitis, Polyarteritis nodosa, Sarcoidosis, Immune thrombocytopenic purpura, Hemolytic anemia, Multiple sclerosis

[c]Proprietary business rules to define initiation of the line of therapy (including exposure assessment window) cannot be shared

EDB1 =ENCORE DataBase 1; EDB2 =ENCORE DataBase 2; EDB4 =ENCORE DataBase 4; 1L = First-line antineoplastic systemic therapy; 2L = Second-line antineoplastic systemic therapy; 3L = Third-line antineoplastic systemic therapy; ECOG = Eastern Cooperative Oncology Group; CNS = central nervous system

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 of 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, NSCLC-specific data are available for EDB1, EDB2 and EDB4. The fitness-for-purpose of the data for the given trial emulation was 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[8,9]).

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 pooled analysis of CheckMate 017/057 trial, EDB2 and EDB4 were found insufficient to be included in the main and sensitivity analyses for the following reasons.

- Rationale for excluding EDB2 from the main and sensitivity analyses: After applying the inclusion/exclusion criteria, EDB2 results in a cohort with a very small sample size even before matching (Figure). Important prognostic covariates are unavailable, which may lead to biased effect estimates due to unmeasured confounding. In addition, related to the small sample size, the cohort identified in EDB2, did not achieve sufficient balance in measurable covariates after propensity score matching (Figure).
- Rationale for excluding EDB4 from the main and sensitivity analyses: As shown in Table 3, the patient identification period in EDB4 starts on 10/01/2018 which is years after the official approval of nivolumab for 2L metastatic NSCLC. This means that a design which includes patients who initiate treatment before this date will suffer from immortal time bias (see Figure). Although we could restrict to patients who enter the cohort after 2018, there was an additional concern that EDB4 lacks information on disease progression (a key inclusion criterion). In addition to these limitations in terms of design and measurement of key study parameters, the cohort size is too small after applying the inclusion/exclusion criteria to achieve balance on key risk factors via propensity score matching and make a meaningful comparison between the two treatment arms (see Figure 6 and Figure 13).

For these reasons, only EDB1 will be used for the primary and sensitivity analyses.

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	EDB2	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	Patient identification period: as of 2/20/2022 with follow-up information through data cut-off on 02/24/2023	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:	Comparison group: Anytime at the start of study drug initiation Exposure group: In or after the year when nivolumab was approved by the FDA (2015)	Comparison group: Anytime at the start of study drug initiation Exposure group: In or after the year when nivolumab was approved by the FDA (2015)	Comparison group: Anytime at the start of study drug initiation Exposure group: In or after the year when nivolumab was approved by the FDA (2015)
Data Version (or date of last update):	Delivery: Jul 11, 2024	Delivery: Sep 8, 2023 Updated (LoT addition): Mar 11, 2024	Delivery: Oct 24, 2023 Updated (demographics): Feb 29, 2024
Data sampling/extraction criteria:	Patients are sampled if they have a confirmed diagnosis of advanced NSCLC via abstraction on or after 1 Jan 2011, and at least 2 EHR visits on or after 1 Jan 2011. Both ICD-9 (162.x) and ICD-10 (C34x or C39.9) codes are used for the initial selection, and advanced diagnosis are then confirmed via abstraction (since ICD codes do not specify advanced diseases).	Patients are sampled if they were diagnosed with NSCLC and do not meet any of the following exclusion criteria: patient is <18 years of age at the time of diagnosis, does not have the malignancy of interest, is not evaluated at the accessible provider site for the malignancy of interest, has concurrent primary malignancies, has no date of diagnosis in EHR, patient chart has no clinician note available in the EHR, is diagnosed with a malignancy after the diagnosis of the malignancy of interest prior to evaluation for the malignancy of interest at the accessible provider site, is only seen once at the provider site for the malignancy of interest, is initially misdiagnosed and treated for another malignancy, but was later confirmed to have the malignancy of interest, is on therapy, active surveillance, or observation for a malignancy diagnosed prior to the diagnosis of the malignancy of interest at the time of diagnosis of the malignancy of interest, is metastatic	NSCLC 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 NSCLC 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.

		(includes leukemias and multiple myeloma) for a malignancy diagnosed prior to the malignancy of interest, with the presence of low grade (inclusive of grades 1 and 2) neuroendocrine histology	
Type(s) of data:	EHR-derived	EHR-derived	EHR-derived
Data linkage[1]:	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 of structured and unstructured data from EHRs and commercially available obituary data including the Social Security Administration death master file	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[2]:	No	No	No
Software for data management:	R 4.3.2	R 4.3.2	R 4.3.2

[1] 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
[2] 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 ensure 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/drugepi/encore/quality (repository is only accessible within the Mass General Brigham network and additionally only to authorized study personnel).

6.4. Study design

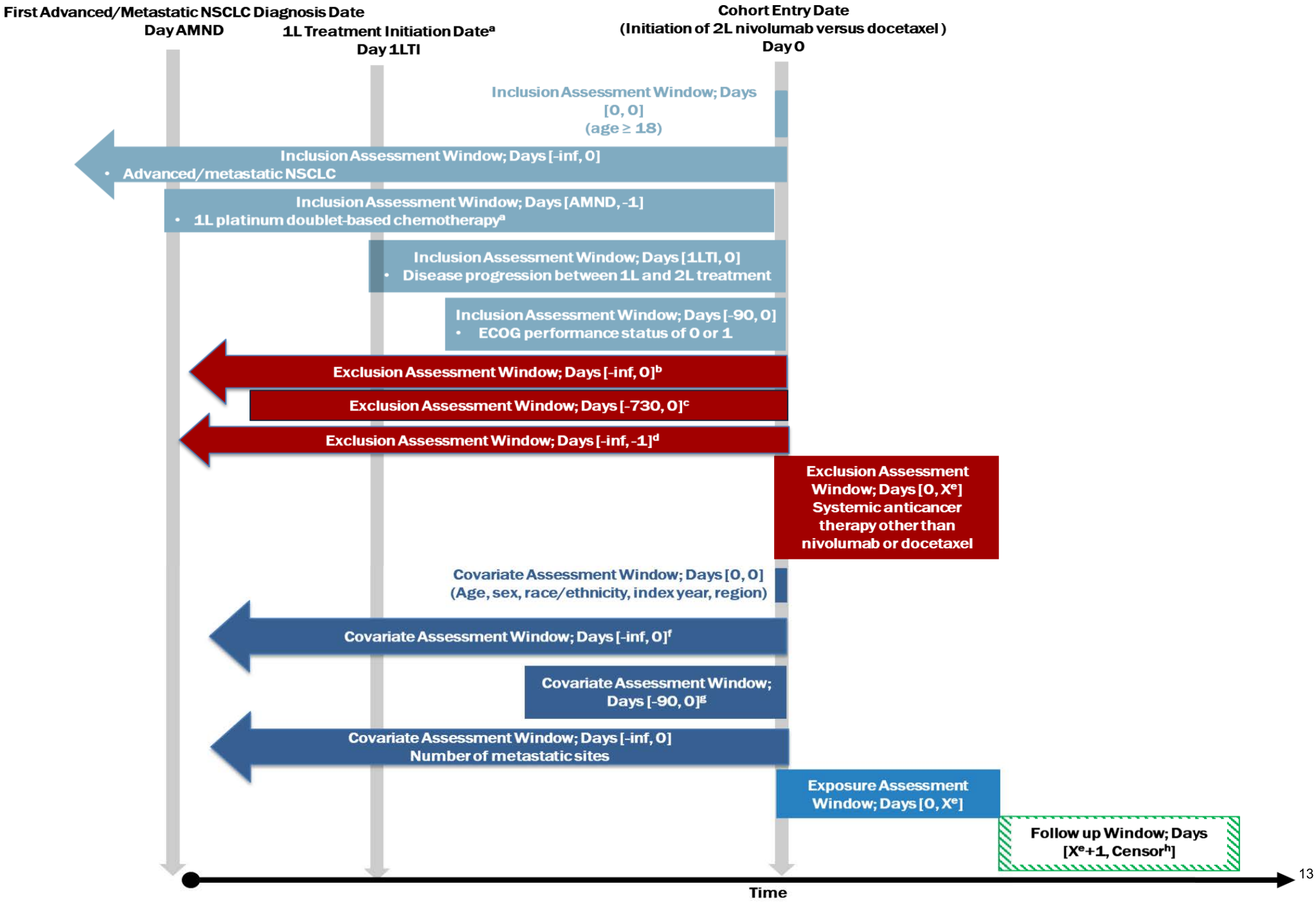
Research design (e.g. cohort, case-control, etc.): Cohort study

Rationale for study design choice: Resembles the principles of the (target) trial emulation framework.[10]

6.5. Study design diagram

Figure 1 depicts study design and variable measurement considerations for the emulation of the CheckMate 017/057 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.[11–15]

Figure 1. Study design illustration for CheckMate 017/057 trial emulation.


First Advanced/Metastatic NSCLC Diagnosis Date
Day AMND
1L Treatment Initiation Date[a]
Day 1LTI
Cohort Entry Date
(Initiation of 2L nivolumab versus docetaxel)
Day 0
Inclusion Assessment Window; Days [0, 0]
(age ≥ 18)
Inclusion Assessment Window; Days [-inf, 0]
• Advanced/metastatic NSCLC
Inclusion Assessment Window; Days [AMND, -1]
• 1L platinum doublet-based chemotherapy[a]
Inclusion Assessment Window; Days [1LTI, 0]
• Disease progression between 1L and 2L treatment
Inclusion Assessment Window; Days [-90, 0]
• ECOG performance status of 0 or 1
Exclusion Assessment Window; Days [-inf, 0][b]
Exclusion Assessment Window; Days [-730, 0][c]
Exclusion Assessment Window; Days [-inf, -1][d]
Exclusion Assessment Window; Days [0, X[e]] Systemic anticancer therapy other than nivolumab or docetaxel
Covariate Assessment Window; Days [0, 0]
(Age, sex, race/ethnicity, index year, region)
Covariate Assessment Window; Days [-inf, 0][f]
Covariate Assessment Window; Days [-90, 0][g]
Covariate Assessment Window; Days [-inf, 0]
Number of metastatic sites
Exposure Assessment Window; Days [0, X[e]]
Follow up Window; Days [X[e]+1, Censor[h]]
Time

a. Initiation of 1L platinum doublet–based chemotherapy. Platinum doublet regimens included cisplatin–pemetrexed, cisplatin–gemcitabine, cisplatin–etoposide, cisplatin–paclitaxel, cisplatin–nab-paclitaxel, cisplatin–docetaxel, cisplatin–vinorelbine, carboplatin–pemetrexed, carboplatin–paclitaxel, carboplatin–nab-paclitaxel, carboplatin–gemcitabine, carboplatin–docetaxel, carboplatin–etoposide, and carboplatin–vinorelbine.

b. Exclusion criteria. Patients with central nervous system metastases, interstitial lung disease, non–lung malignancies (except non-melanoma skin cancer and in situ cancers of the bladder, stomach, colon, cervix/dysplasia, endometrium, melanoma, or breast), autoimmune disease, or prior treatment with docetaxel, nivolumab, or any other immune checkpoint inhibitor were excluded.

c. Autoimmune diseases included inflammatory bowel disease, systemic lupus erythematosus, dermatomyositis, scleroderma, vasculitis, polyarteritis nodosa, sarcoidosis, immune thrombocytopenic purpura, hemolytic anemia, and multiple sclerosis.

d. Immune checkpoint inhibitors included ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab, tremelimumab, and dostarlimab.

e. Proprietary business rules to define initiation of the line of therapy (including exposure assessment window) cannot be shared.

f. De novo metastatic status, time from initial diagnosis to T0, time from first evidence of metastatic disease to T0, smoking, family history, race/ethnicity, etc.

g. Labs (albumin, hemoglobin, etc.) and vitals (BMI, etc.) that are part of the ROPRO prognostic score; see Becker, Weberpals, et al. Ann Oncol 2020 (doi: 10.1016/j.annonc.2020.07.013)

h. 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)

AMND = advanced/metastatic non-small cell lung cancer diagnosis; 1L = First-line antineoplastic systemic therapy; 1LTI = First-line treatment initiation; 2L = Second-line antineoplastic systemic therapy; ECOG = Eastern Cooperative Oncology Group; CNS = central nervous system

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 nivolumab (exposure) or docetaxel (comparator) as 2L systemic antineoplastic treatment for advanced or metastatic NSCLC. 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 reports (CheckMate 017 & CheckMate 057) 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. A flowchart of the study cohort assembly is provided in Appendix 3.

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. A flowchart of the study cohort assembly is provided in Appendix 3.

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

The exposure and comparator were defined to emulate the agents compared in the trials—nivolumab versus docetaxel in a 2L advanced/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. That is, each patient is represented with one row per curated line of therapy with corresponding information on line number, regimens, as well as start and end dates. Based on this table, patients who received nivolumab or docetaxel treatment regimens are identified by their generic names (string match) in 2L. The LOT implicitly only considers regimens that were given in an advanced 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).
- **EDB2**: 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. 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 who received nivolumab or docetaxel treatment regimen by their generic names (string match) in 2L are identified. 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 EDB2' 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 metastatic NSCLC (see list below*). Only these are considered.

  Identify patients who initiated any of the CheckMate 017/057 drugs as their second-line antineoplastic treatment after the date of metastasis. Treatment line identification is established in accordance with the business rules set by the data vendor.

***Antineoplastic drugs considered:** adagrasib, ado-trastuzumab emtansine, afatinib, alectinib, amivantamab-vmjw, atezolizumab, atezolizumab and hyaluronidase-tqjs, bevacizumab, bevacizumab-adcd, bevacizumab-awwb, bevacizumab-bvzr, bevacizumab-maly, bevacizumab-tnjn, binimetinib, brigatinib, cabozantinib, capmatinib, carboplatin, cemiplimab-rwlc, ceritinib, cetuximab, cisplatin, crizotinib, dabrafenib, dacomitinib, datopotomab, docetaxel, durvalumab, encorafenib, ensartinib, entrectinib, erdafitinib, erlotinib, etoposide, fam-trastuzumab deruxtecan-nxki, gefitinib, gemcitabine, ipilimumab, larotrectinib, lazertinib, lorlatinib, mobocertinib, nivolumab, nivolumab-hyaluronidase, osimertinib, paclitaxel, paclitaxel protein bound, pembrolizumab, pembrolizumab and berahyaluronidase alfa-pmph, pemetrexed, pralsetinib, ramucirumab, repotrectinib, selpercatinib, sotorasib, sunvozertinib, taletrectinib, telisotuzumab vedotin-tllv, tepotinib, trametinib, tremelimumab-actl, vandetanib, vemurafenib, vinorelbine, zenocutuzumab-zbco, zongertinib.

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

The primary outcome for the database study was defined to emulate the trial's primary outcome: time from index to death from any cause (overall survival). 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 overall survival endpoint is operationalized using a parameterized R function *edb1_get_os()* and more details can be found in the attached pdf documentation.
- **EDB2**: Time in [days, months, and years] from end of exposure assessment window to death due to any reason. 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 observed activity date or data cut-off date, whichever occurred earlier. Activity dates are defined as documented in Table 4. Dates used to derive time to all-cause mortality may have some associated imprecision such that the date of death is either known completely, the year and month is known or only the year is known. The overall survival endpoint is operationalized using a parameterized R function *edb2_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

- EDB4: Time in from index date 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. 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 overall survival endpoint is operationalized using a parameterized R function *edb4_get_os()* and more details can be found in the attached pdf documentation.

6.6.6. Context and rationale for follow up

Only intention-to-treat (ITT) analyses will be conducted. Although cross-over from the comparator to the exposure can be expected, which biases the exposure treatment effect more towards the null, this also applies to the RCT. According to Horn et al.,[16] in the comparator groups, 8% with squamous NSCLC and 10% with nonsquamous NSCLC received anti–PD-(L)1 or anti–cytotoxic T-lymphocyte–associated antigen 4 immunotherapy after docetaxel treatment.

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.[11] 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 10** and **Table 11**.

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[1]	Variable encoding	Assessment window
Age at initial diagnosis	dem_age_initial_diagnosis	edbx_get_demographics()	Age measured at initial diagnosis of eligible primary tumor	Nominal (<60, 60-69, 70-79, 80+)	[-inf;0] at initial diagnosis of primary cancer
Age at index date	dem_age_index	edbx_get_demographics()	Age measured at index date	Binary (<60, 65+); modelled continuously in ROPRO[11]	[0;0]
Sex	dem_sex	edbx_get_demographics()	Sex	Binary (Male, Female)	[0;0]
Year of index date	c_year_index	De novo derived from dt_index	Calendar year in which patient initiated study treatment	Nominal (<2018, 2018+)	[0;0]
Family history	dem_family_history	edbx_get_demographics()	Family history of cancer	Logical (TRUE, FALSE)	[0;0] (no specific date is associated)
Race	dem_race	edbx_get_demographics()	Race categorized as in the original RCT	Binary (Asian vs non-Asian)	[0;0]
Ethnicity	dem_ethnicity	edbx_get_demographics()	Ethnicity	Hispanic, Non-Hispanic	[0;0]

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details[1]	Variable encoding	Assessment window
Region	dem_region	edbx_get_demographics()	US region patient receives care in; if given on a state level, region is manually mapped (see Table **12**)	Nominal (Northeast, South, West, Midwest)	[0;0]
Practice type	dem_practice	edbx_get_demographics()	Setting patient is receiving care at	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	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	Binary logical (TRUE, FALSE)	[-inf;0]
PD-L1 expression status	C_pdl1_status	EDB1, EDB2: edbx_get_pdl1() EDB4: edb4_get_biomarker()	Evidence of PD-L1 expression level. If a patient has multiple PD-L1 measurements, the measurement closest to the index date is prioritized.	EDB1 and EDB2: PD-L1 expression was reported from IHC (immunohistochemistry) results or a range of values (e.g., 1–10%). We harmonized PD-L1 into three trial-aligned categories: <1%, 1–49%, and ≥50%. EDB4: Binary (negative, positive)	[-90;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[11]; 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., IA1)[11]	[-inf;0] at initial diagnosis of primary cancer

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details[1]	Variable encoding	Assessment window
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
Evidence of metastases	c_met_pre_index	edbx_get_diagnosis_solid()	Evidence of any metastasis before/on the index date	Binary logical (TRUE, FALSE)	[-inf;0]
Number of metastatic sites	c_number_met_sites	edbx_get_diagnosis_solid()	Number of metastatic sites for a given patient before/on the index date	Integer	[-inf;0]
Time between initial diagnosis to index date	c_time_dx_to_index	edbx_get_diagnosis_solid()	Time in days between initial diagnosis to index date	Continuous	[-initial dx;0]
Time between earliest evidence of a metastatic and index date	c_time_met_dx_to_index	edbx_get_diagnosis_solid()	Time in days between earliest evidence of a metastatic and index date	Continuous	[-inf;0]
Histology (adenocarcinoma)	c_histology_match	edbx_get_histology()	Evidence of adenocarcinoma histology (nonsquamous cell for EDB1)	Binary logical (TRUE, FALSE)	[-inf;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) [2]	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) [2]	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. 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[2]	c_bilirubin_mg_dl_cont	edbx_get_labs()	Closest bilirubin measurement (in serum/plasma) relative to index	continuous	[-90;0]

Characteristic	Harmonized analysis variable name	R function to derive covariate (see pdf in appendix)	Details[1]	Variable encoding	Assessment window
			date in mg/dL. In case of ties, the lower is selected		
Calcium[2]	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[2]	c_eosinophils_leukocytes_ratio_cont	edbx_get_labs()	Eosinophils/100 leukocytes in blood. In case of ties, the lower	continuous	[-90;0]
Glucose[2]	c_glucose_mg_dl_cont	edbx_get_labs()	Closest glucose measurement (in serum/plasma) relative to index date in mmol/L. In case of ties, the lower is selected	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)[3]	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 10^9/L. In case of ties, the lower is selected. Used to compute neutrophil/lymphocyte ratio	continuous	[-90;0]
Lymphocyte/leukocyte ratio[2]	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 to compute neutrophil/lymphocyte ratio	continuous	[-90;0]
Monocytes[2]	c_monocytes_10_9_l_cont	edbx_get_labs()	Closest monocytes measurement (in blood) relative to index date in 10^9/L. 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[1]	Variable encoding	Assessment window
Neutrophils	c_neutrophil_10_9_l_cont	edbx_get_labs()	Closest neutrophils measurement (in blood) relative to index date in 10^9/L. In case of ties, the lower is selected. Used to compute neutrophil/lymphocyte (NLR) ratio	continuous	[-90;0]
Neutrophil/lymphocyte ratio[2]	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 10^9/L. In case of ties, the lower is selected	continuous	[-90;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[2]	c_urea_nitrogen_mg_dl_cont	edbx_get_labs()	Closest urea nitrogen measurement (in serum/plasma) relative to index date in mg/L. In case of ties, the lower is selected	continuous	[-90;0]
Systolic blood pressure[2]	c_sbp_cont	edbx_get_vitals()	Closest systolic blood pressure (in mmHg) measurement. In case of ties, the lower is selected	continuous	[-90;0]
Body mass index (BMI)[2]	c_bmi_cont	edbx_get_vitals()	Closest BMI measurement (in kg/m^2) relative to index date. In case of ties, the lower is selected. For ROPRO and in EDB2, BMI is (additionally) computed from individual height and weight measurements	continuous	[-90;0]
Heart rate[2]	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 heart rate measurement (in bpm) relative to index date. In case of ties, the lower is selected	continuous	[-90;0]

[1] x stands for the pseudonymized number of the respective database, i.e., EDB1, EDB2 or EDB4

[2] For calculation of ROPRO prognostic score[11], this variable is log transformed.

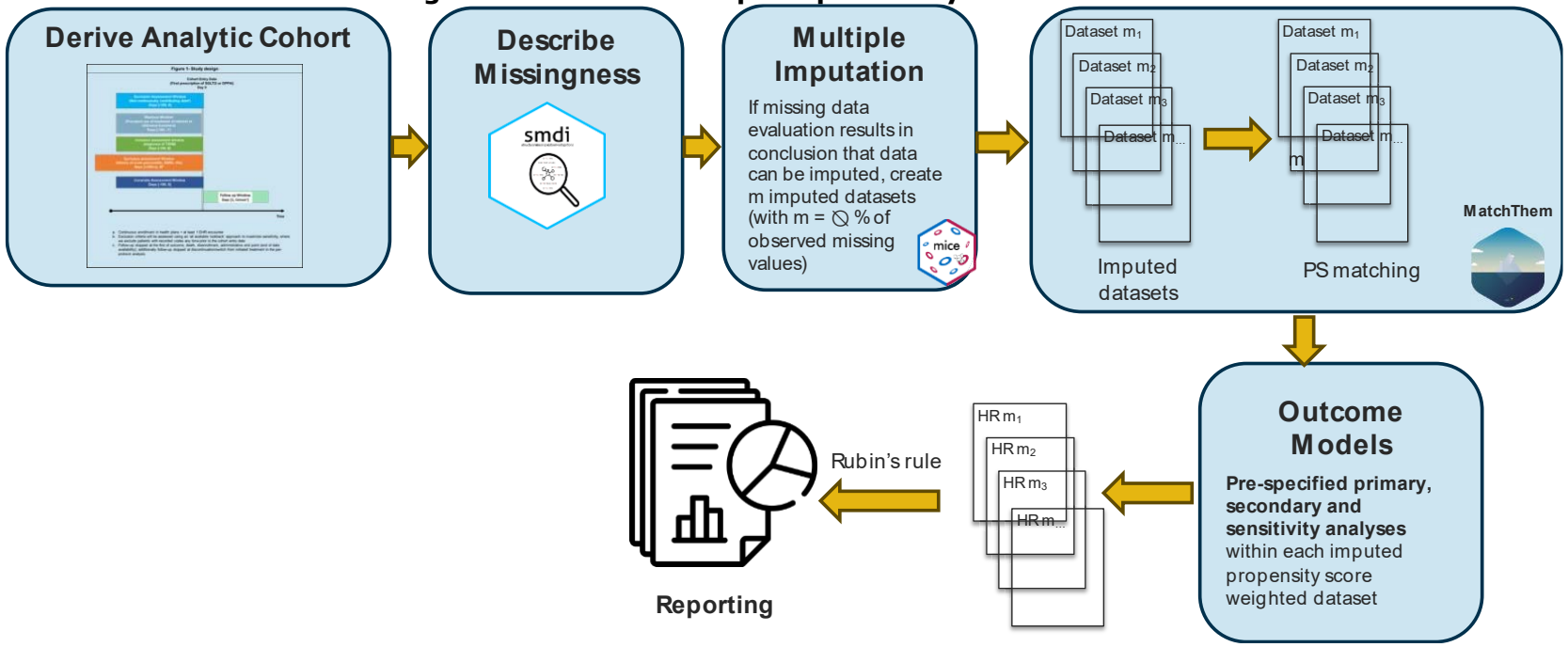
[3] For calculation of ROPRO prognostic score[11], this variable is log-log transformed.

6.7. Data analysis

6.7.1. Context and rationale for analysis plan

To emulate the CheckMate 017/057 trial, the following analytical workflow will be used (Figure). 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. Table 5 (code documentation see appendix).[17] The analytical cohort will be derived by first identifying an advanced NSCLC inception cohort of initiators of nivolumab or docetaxel in the second-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]).[18] To that end, we will adopt a principled process on missing data that was developed as part of a FDA Sentinel Innovation Center causal inference workstream that empirically evaluates different aspects across partially observed covariates based on three group diagnostics (Table 6).[19,20] 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, Hoteling's[21] and Little's[22] 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[23] and be further enhanced by clinical expert knowledge.

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

	Group 1 Diagnostics		Group 2 Diagnostics	Group 3 Diagnostics
Diagnostic metric	Absolute standardized mean difference (ASMD)	P-value Hoteling[21]/ Little[22]	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	<0.1[a]: no imbalances in observed patient characteristics; missingness may be likely completely at random or not at random (~MCAR, ~MNAR). >0.1[a]: imbalances in observed patient characteristics;	High test statistics and low p-values indicate differences in baseline covariate distributions and null hypothesis would be rejected (~MAR).	AUC values ~ 0.5 indicate completely random or not at random prediction (~MCAR, ~MNAR). Values meaningfully above 0.5 indicate stronger relationships between covariates and missingness (~MAR).	No association in either univariate or adjusted model and no meaningful difference in the log HR after full adjustment (~MCAR). Association in univariate but not fully adjusted model (~MAR).

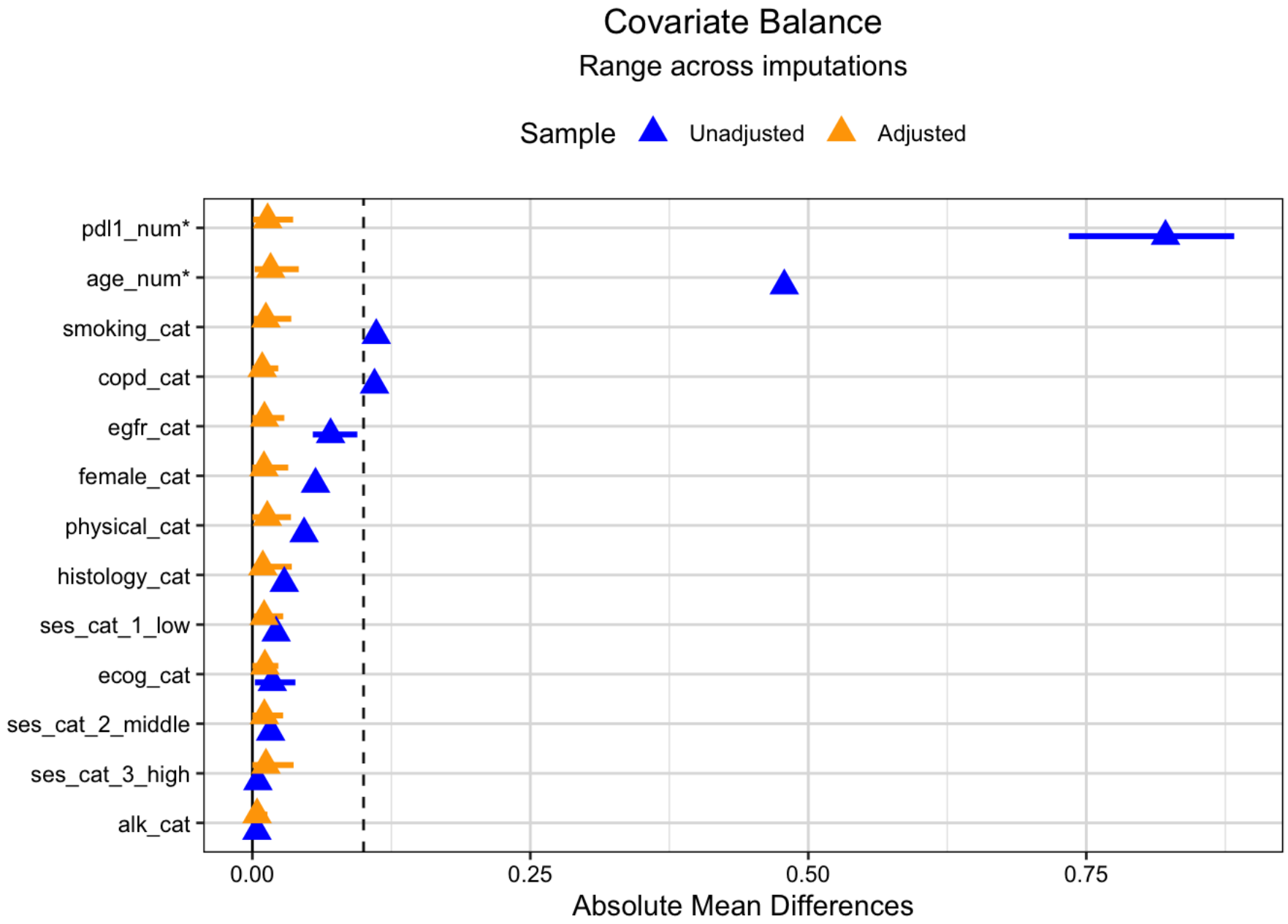
	missingness may be likely at random (~MAR).			Meaningful difference in the log HR also after full adjustment (~MNAR).

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.

[a] Analogous to propensity score-based balance measures.[24]

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).[25] 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.[26,27] Hence, multiple imputation with flexible, non-parametric random forest imputation algorithms[28] (mice R package[29]) 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 nivolumab using propensity score matching across imputed datasets we will apply the "within" approach using the "MatchThem" R package.[30,31] 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 nivolumab using a 1:1 nearest neighbor matching algorithm without replacement, within each histology stratum (squamous vs. nonsquamous), and a caliper of 1% of the standard deviation of the propensity score. The stratum-specific matches will be pooled for the covariate balance assessment and further analysis. The resulting covariate 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 . 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. Since in most databases there are more nivolumab patients than patients in the control arm, the estimand will rather correspond to the ATC than the ATT. Confidence intervals will be estimated using cluster-robust standard errors.[32] As a secondary endpoint, we will additionally estimate the median OS survival time difference between the two treatment 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 15th of a month or July 2nd 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 HR and median OS survival time difference estimates for each database will then be combined using Rubin's rule.[29,33] 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. Primary analysis

Table 7. Primary and subgroup analysis specification

Hypothesis:	Initiation of nivolumab decreases the hazard of all-cause mortality as compared to initiation of docetaxel
Exposure contrast:	Initiation of nivolumab vs. initiation of docetaxel
Outcome:	Time to all-cause mortality (overall survival)
Databases used:	EDB1
Analytic software:	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 24, 2024.
Model(s): *(provide details or code)*	See example code here. The annotated code for the trial emulation will be hosted at https://gitlab.partners.org/drugepi/encore/check-mate-017-057 (access only through MGB network for authorized personnel)
Confounding adjustment method	***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.***
	Within each histology stratum (squamous vs non-squamous), 1:1 propensity score nearest neighbor matching without replacement and using a caliper width of 0.01 standard deviations of the propensity score. The stratum specific matches will be pooled for the main analysis.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	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 substantiative model, i.e., exposure, outcome, confounders/prognostic factors and additional auxiliary covariates.
Subgroup Analyses	***List all subgroups***
	In subgroup analysis, 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). 1. Histology (squamous, nonsquamous)

B. Secondary Analysis

Table 8. Secondary analysis specification.

Hypothesis:	Initiation of nivolumab increases overall survival as compared to initiation of docetaxel
Exposure contrast:	Initiation of nivolumab vs. initiation of docetaxel
Outcome:	Median overall survival time, i.e., time until 50% of the patients in each stratum deceased
Databases used:	EDB1
Analytic software:	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 24, 2024.
Model(s): *(provide details or code)*	See example code here. The annotated code for the trial emulation will be hosted at https://gitlab-scm.partners.org/drugepi/encore/check-mate-017-057/ (access only through MGB network for authorized personnel)
Confounding adjustment method	***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.***
	Within each histology stratum (squamous vs non-squamous), 1:1 propensity score nearest neighbor matching without replacement and using a caliper width of 0.01 standard deviations of the propensity score. The stratum specific matches will be pooled for the main analysis.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	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 substantiative model, i.e., exposure, outcome, confounders/prognostic factors and additional auxiliary covariates.
Subgroup Analyses	***List all subgroups***
	In subgroup analysis, 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). 1. Histology (squamous, nonsquamous)

Table 9. Sensitivity analyses – rationale, strengths and limitations.

	What is being varied? How?	Why? (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 experimental 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 (*ghost-time bias*[34]), the censoring date 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.[35]	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 may not hold for every covariate	Estimates impact of deviations from MAR assumption on final treatment effect estimates for key covariates	Delta parameters must be assumed and results are complex to interpret in multivariate missingness settings; just must 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 CheckMate 017/057	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 CheckMate 017/057 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	EHR 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	Exclusion of patients with docetaxel exposure before March 4, 2015	Descriptive analyses indicate that there was a rapid uptake of new initiators of nivolumab immediately after approval in 2015 and a decrease in docetaxel. This means there is hardly any overlap of patients pre/post 2015, and the calendar cannot be sufficiently balanced	This sensitivity aims to mitigate the potential effects of an imbalance in calendar time	Calendar time will remain imbalanced overall. Unmeasured confounding may have persisted because, after nivolumab approval, patients who continued to receive docetaxel may have differed systematically from those who received nivolumab, with docetaxel potentially representing a suboptimal treatment option during that period.
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	Use EDB4 to estimate the treatment effects	Evaluate the potential impact of selection/immortal time bias on the treatment effects.	N/A	See section 6.1.1 for the limitations of EDB 4

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 #6 tries to address this requiring patients to have had at least one visit before the index date which increases the likelihood that a patients 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 behaviours (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 not directly testable using observational data, and calendar time is likely influenced not only by the introduction of nivolumab but also by subsequent approvals and uptake of other immunotherapies over time. The improvements in the 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.
- We did not adjust for PD-L1 because PD-L1 values were missing for approximately 96% of patients in EDB1 and could not be adequately predicted from observed covariates. Because PD-L1 is an important prognostic factor, failure to control for PD-L1 may have resulted in residual confounding.

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 CheckMate 017/057-like populations in EDB1, EDB2 and EDB4 for the main analysis, respectively.

Figure 4. CONSORT attrition to select eligible CheckMate 017/057-like populations in EDB1.

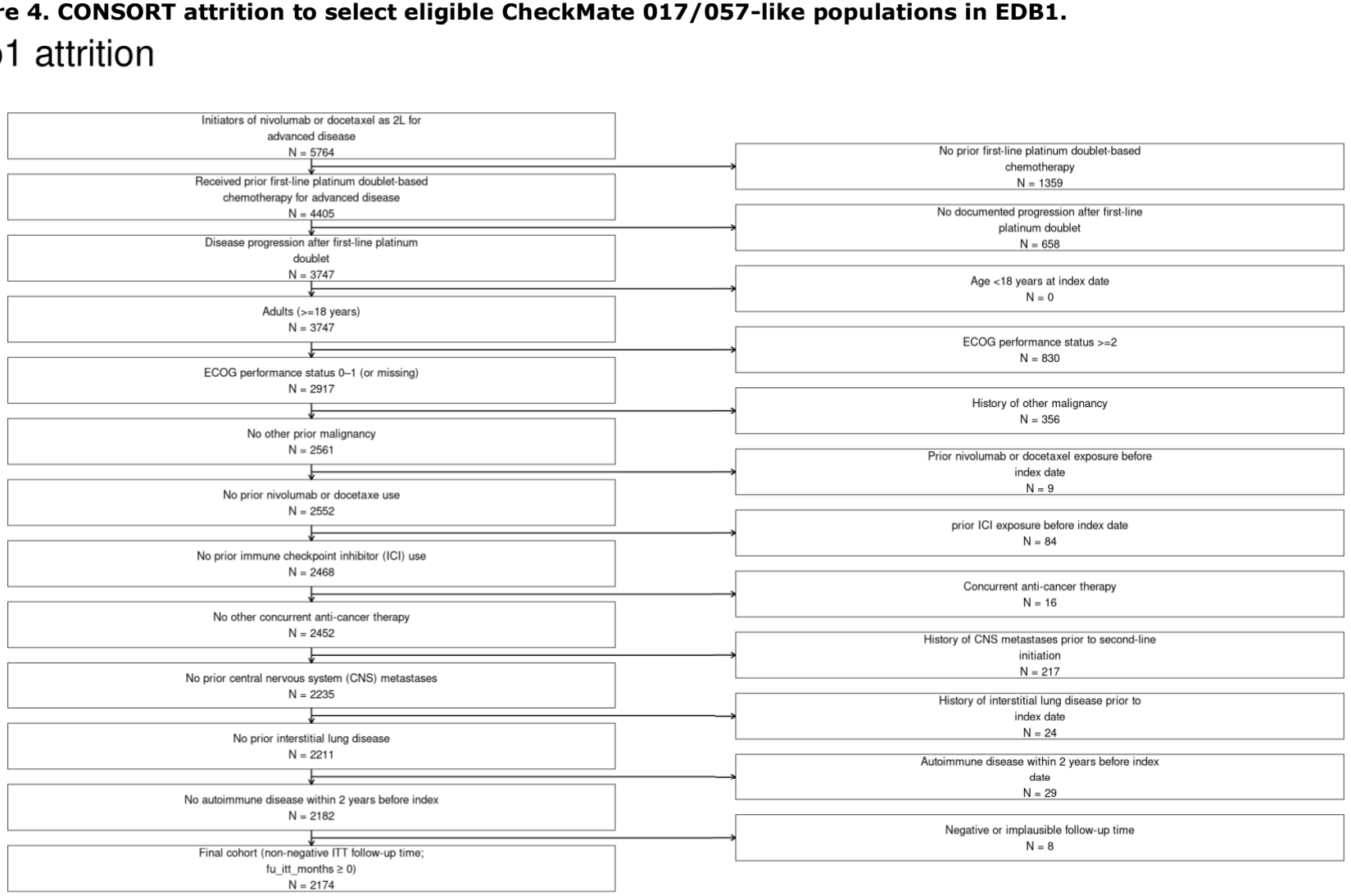


Figure 5. CONSORT attrition to select eligible CheckMate 017/057-like populations in EDB2.

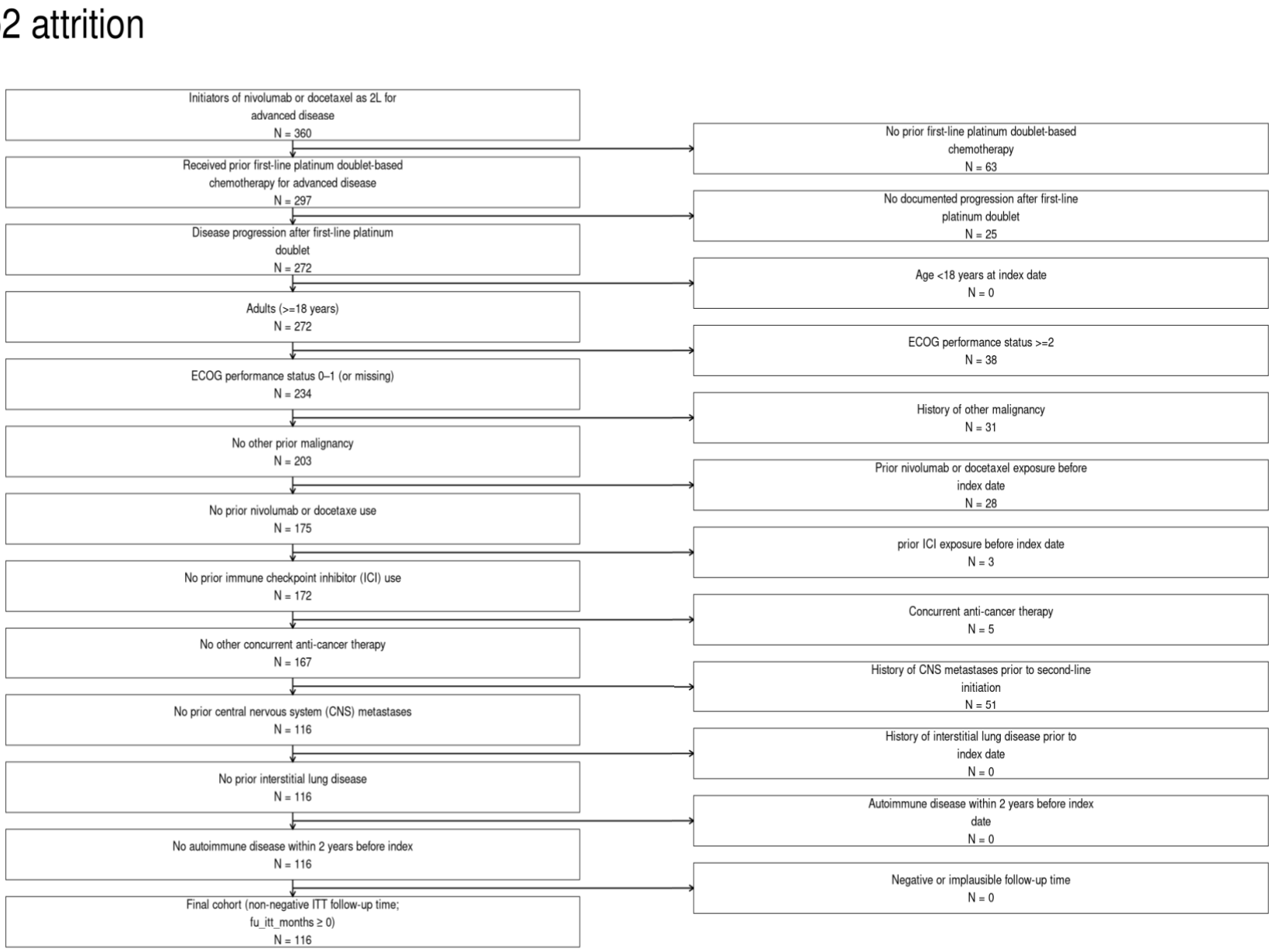
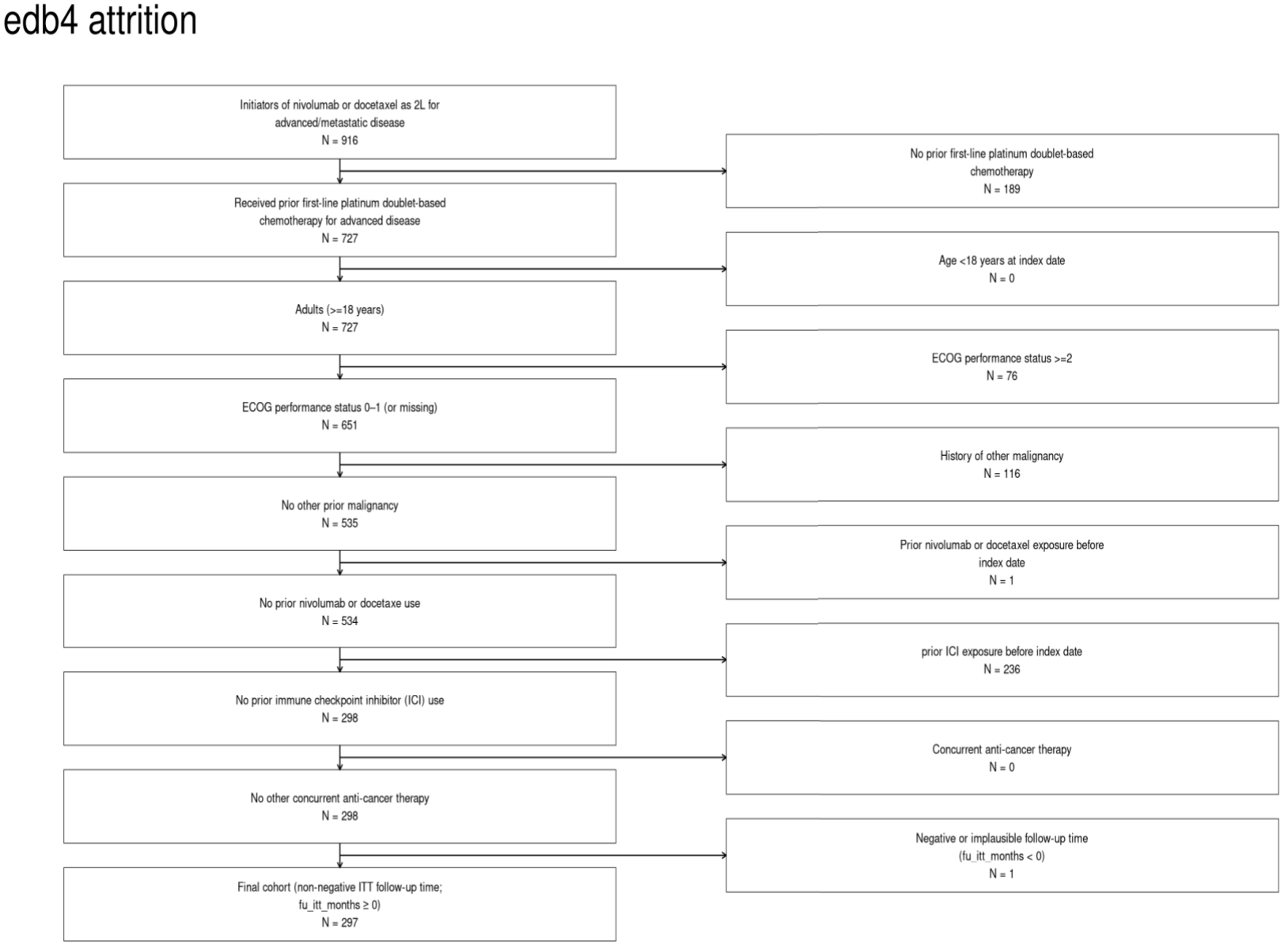


Figure 6. CONSORT attrition to select eligible CheckMate 017/057-like populations in EDB4.



10.2. Covariate balance figures

The following figures illustrate the balance of key covariates included in propensity score models among eligible CheckMate 017/057-like populations in EDB1, EDB2 and EDB4, respectively.

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

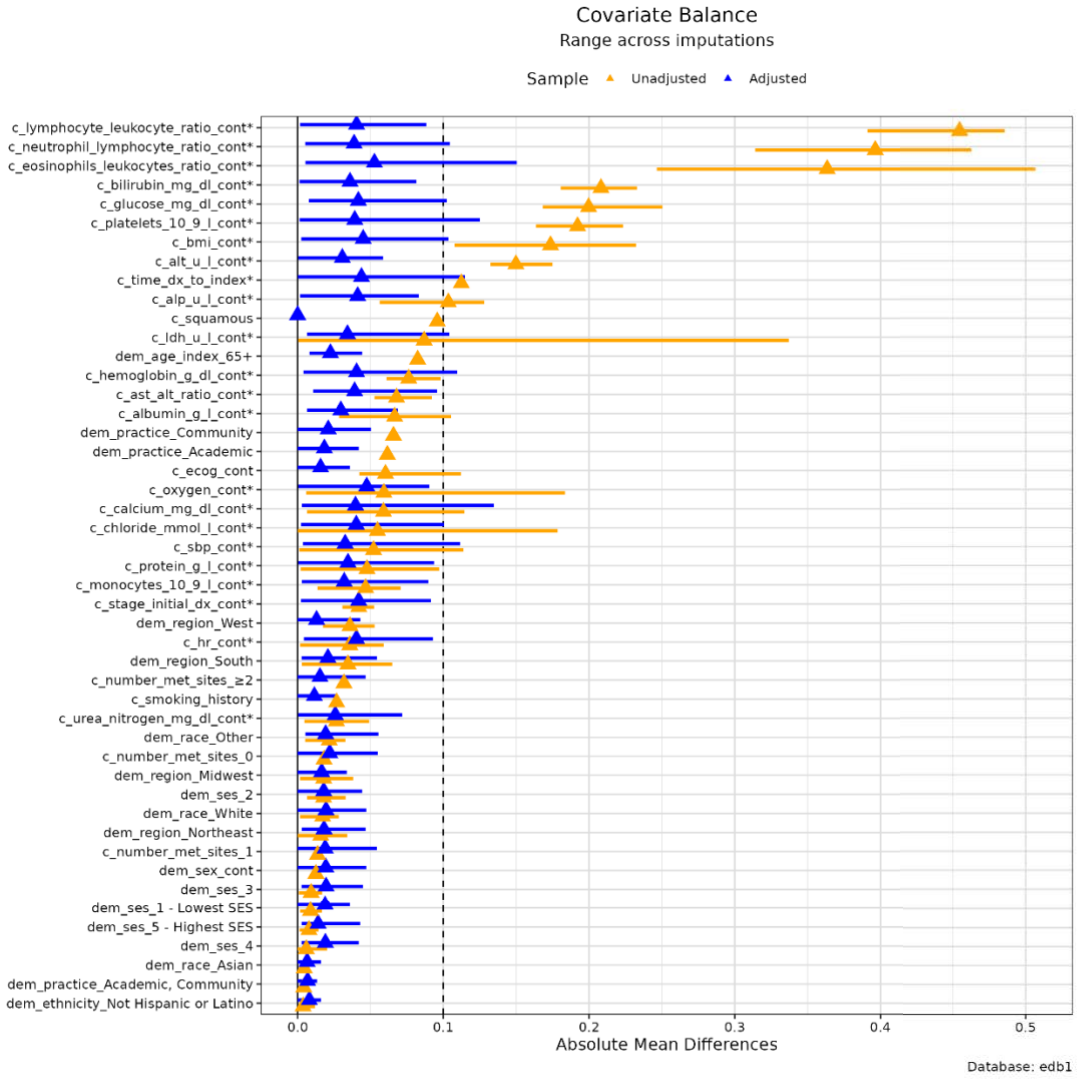


Figure 8. EDB2 covariate balance of covariates included in propensity score model before and after matching.

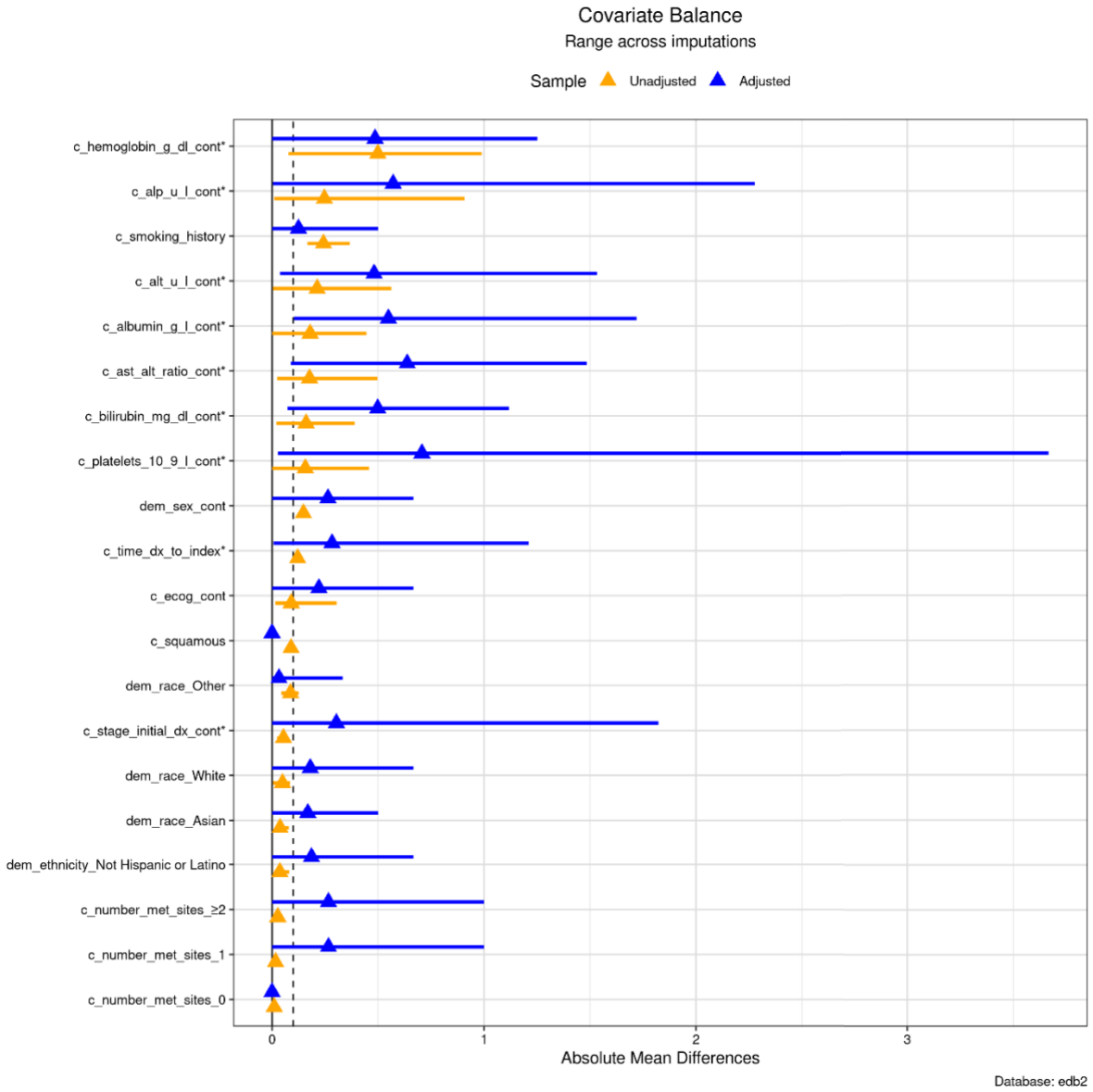
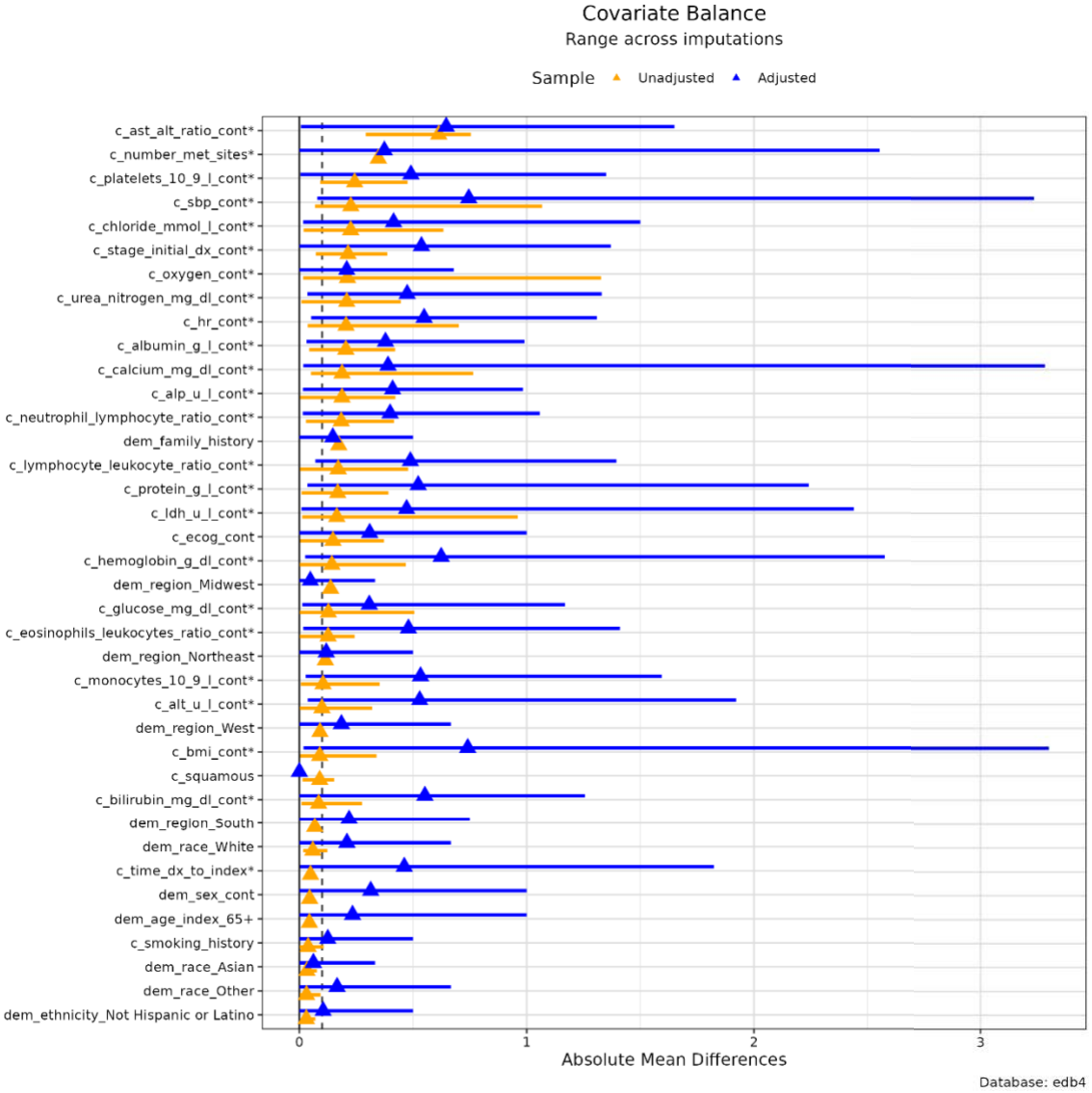


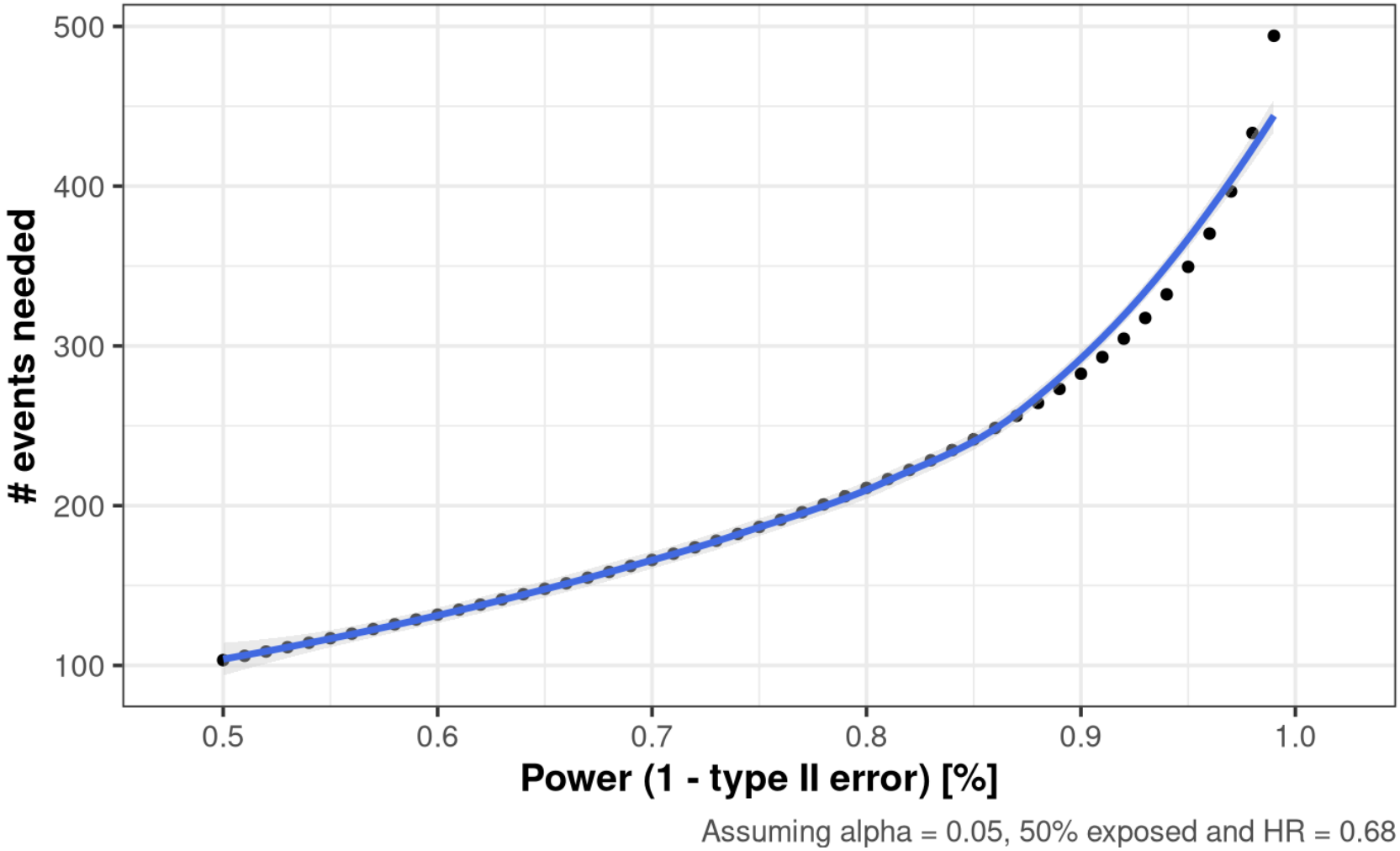
Figure 9. EDB4 covariate balance of covariates included in propensity score model before and after matching.



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.[36] Considering EDB1 only for primary analysis and assuming an HR = 0.68 and an alpha = 0.05 (2-sided), this results in an estimated statistical power (1-estimated type II error) of 99.9%.

Figure 10. Number of events needed to achieve x% power.



10.4. Additional Figures and Tables

Table 10. 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 11. 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 12. 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.

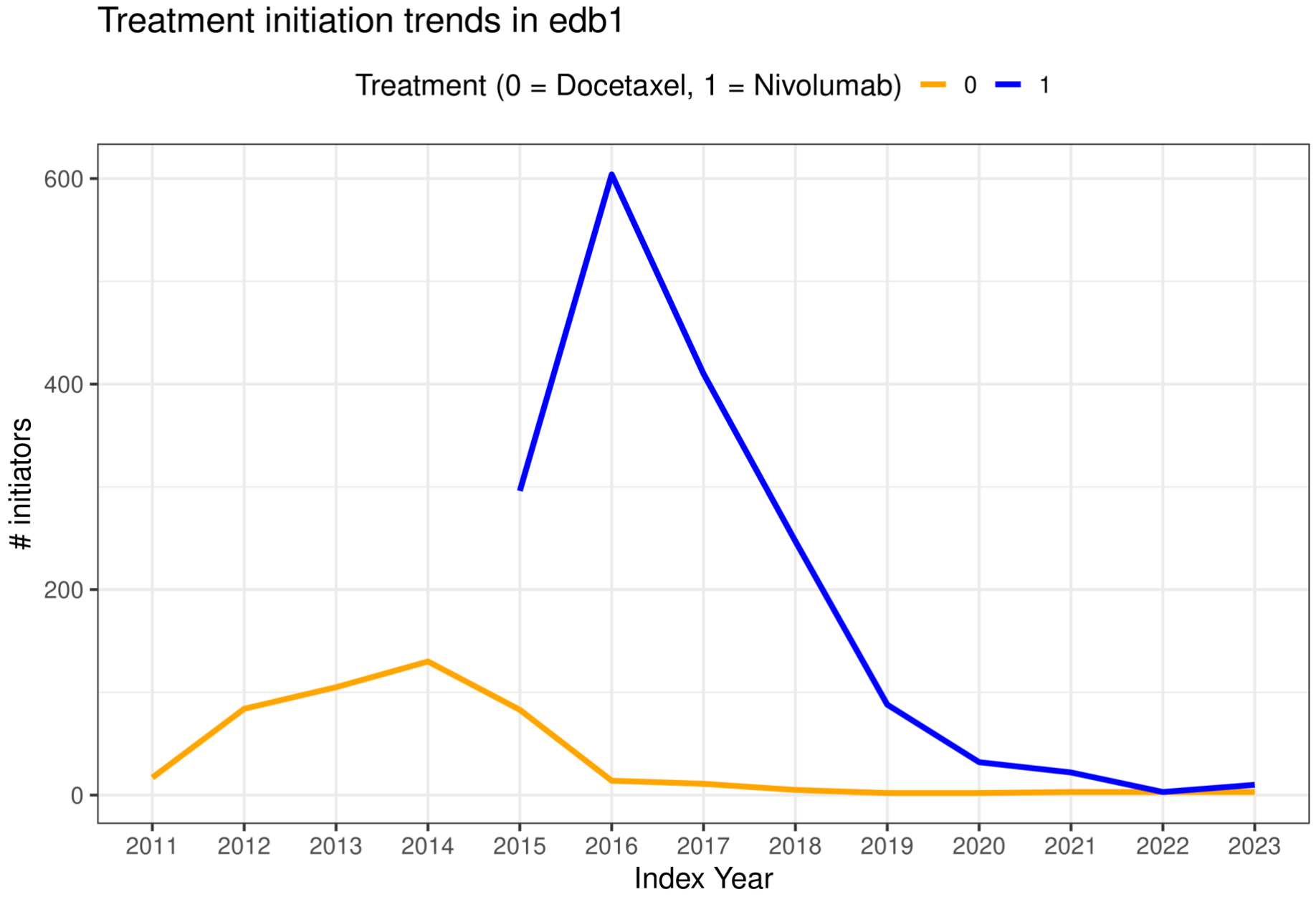


Figure 12. Treatment initiation trends by calendar year and treatment in EDB2.

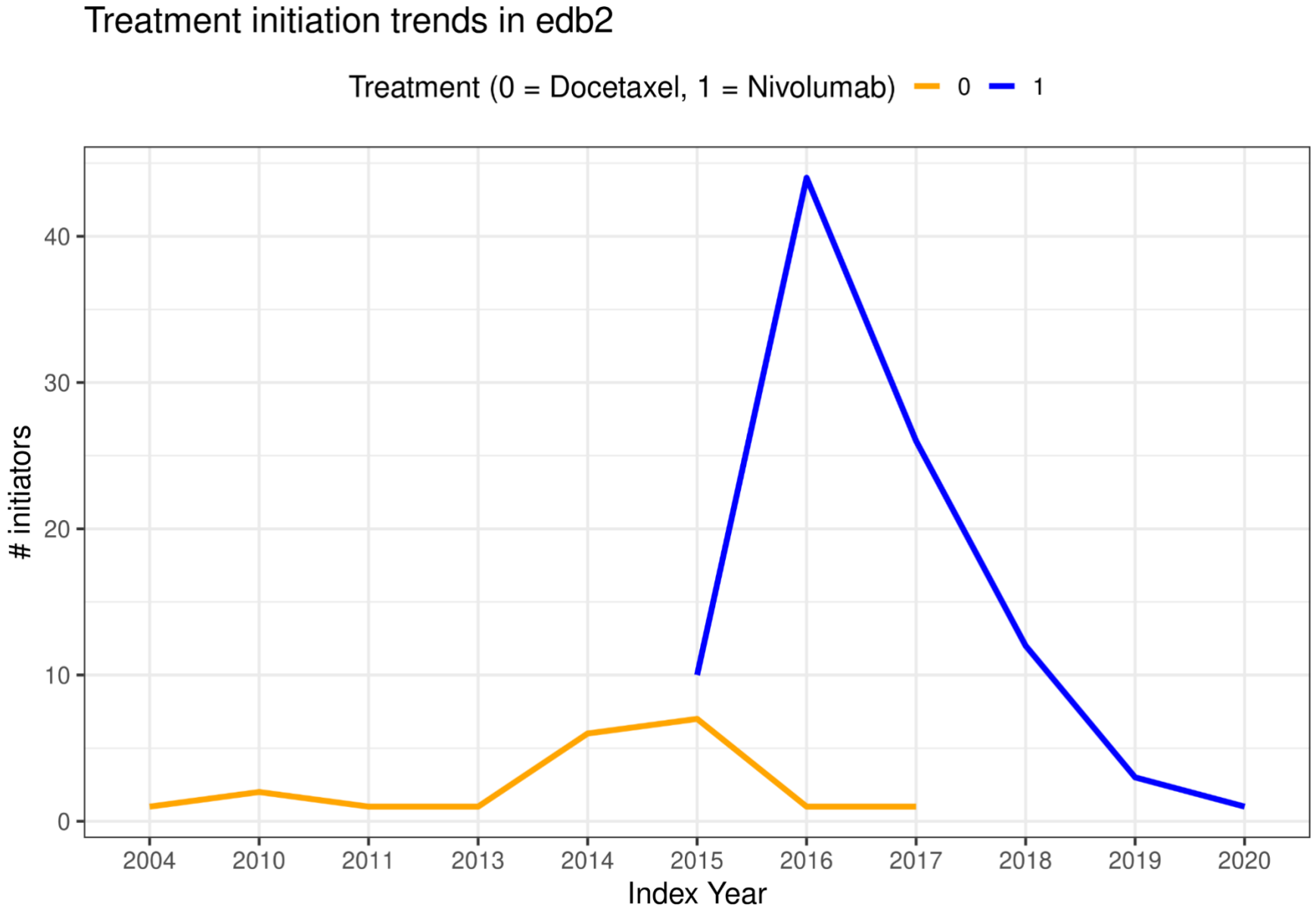
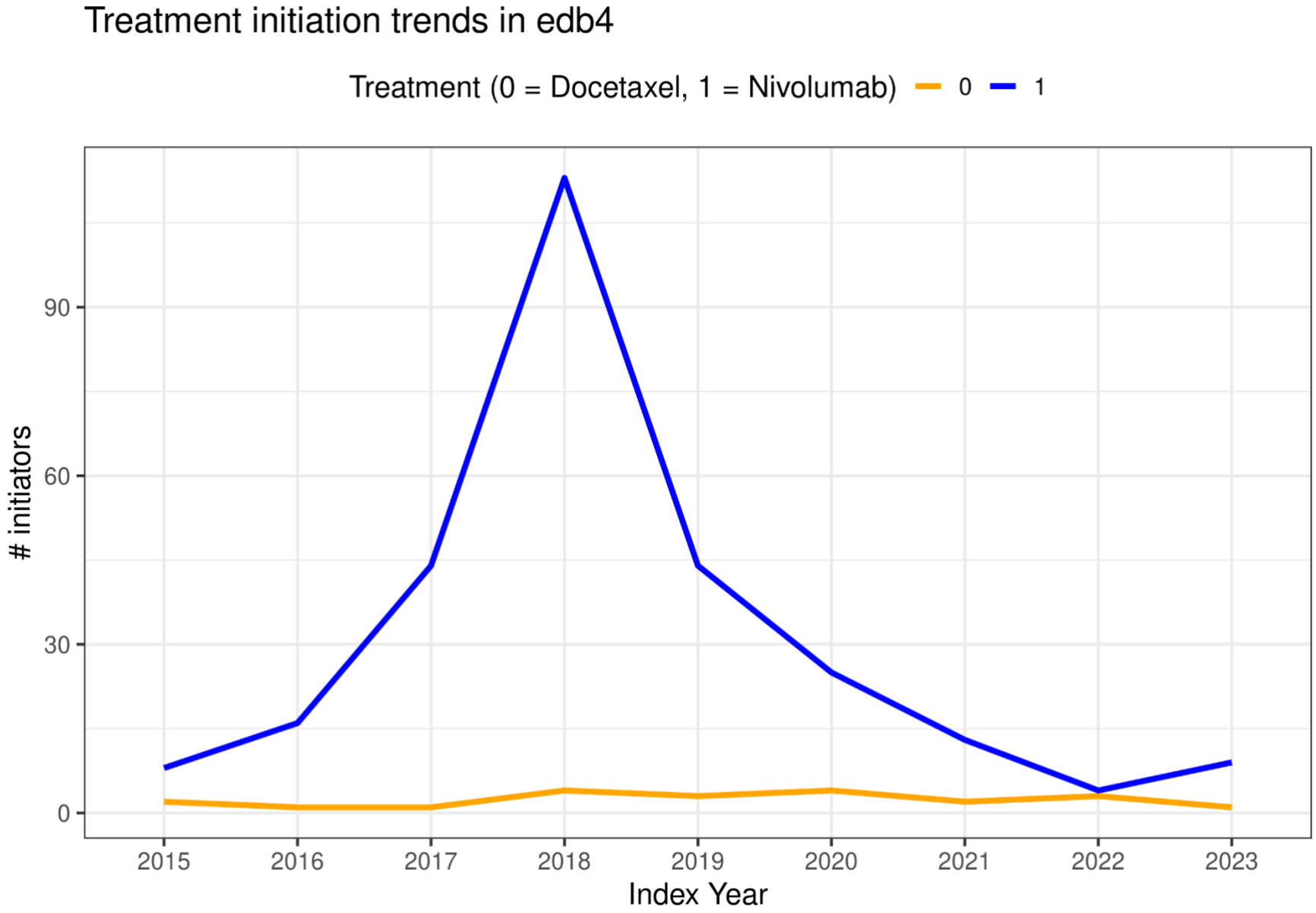


Figure 13. Treatment initiation trends by calendar year and treatment in EDB4.



NCTID NCT01642004
Acronym **CheckMate 017**
Protocol https://ascopubs.org/action/downloadSupplement?doi=10.1200%2FJCO.2017.74.3062&file=protocol_2017.743062-1.pdf
SAP NA
PMID https://www.nejm.org/doi/full/10.1056/NEJMoa1504627
Indication Squamous Non-small cell lung cancer (NSCLC)
Line of Therapy >=2
Exposures Nivolumab 3 mg/kg IV every 2 weeks
Comparisons Docetaxel 75 mg/m² IV every 3 weeks
Emulated outcome Overall survival (primary end point)

An open-label randomized Phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer

Measurement eligibility criteria						
Criteria	**Criteria rule as defined in original protocol**	**Clinical relevance**	**Emulation [EDB1]**	**Emulation [EDB2]**	**Emulation [EDB4]**	**Comment**
Inclusion 1	Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.	Limited Relevance	Not implementable	Not implementable	Not implementable	
Inclusion 2	Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.	Limited Relevance	Not implementable	Not implementable	Not implementable	
Inclusion 3	Men and women ≥ 18 years of age	Relevant	Possible	Possible	Possible	To protect privacy, most databases only provide month- or year-level granularity of dates
Inclusion 4	Subjects with histologically- or cytologically-documented squamous cell NSCLC who present with Stage IIIB/ Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease).	Relevant	Possible	Possible	Possible	
Inclusion 5.1	Subjects must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.	Relevant	Possible	Possible	Possible	
Inclusion 5.2	Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy	Relevant	Possible	Possible	Possible	
Inclusion 5.3	Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.	Limited Relevance	Not implementable	Not implementable	Not implementable	We will not operationalize this criterion because prior (neo)adjuvant platinum/definitive chemoradiation and the recurrence timing are not reliably captured in data.
Inclusion 5.4	Subjects with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible.	Limited Relevance	Possible	Possible	Possible	
Inclusion 6	Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of randomization	Limited Relevance	Not implementable	Not implementable	Not implementable	
Inclusion 7	Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site	Limited Relevance	Not implementable	Not implementable	Not implementable	
Inclusion 8	Eastern Cooperative Oncology Arm (ECOG) performance status of ≤ 1	Relevant	Possible	Possible	Possible	ECOG implementation possible; high % missingness likely
Inclusion 9	A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.4.2. Specimens must be received by the central lab prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.	Limited Relevance	Not implementable	Not implementable	Not implementable	
	All baseline laboratory requirements will be assessed and should be obtained within -14 days of randomization. Screening laboratory values must meet the following criteria	Relevant	Not implementable	Not implementable	Not implementable	
	WBCs ≥ 2000/μL	Relevant	Not implementable	Not implementable	Not implementable	
	Neutrophils ≥ 1500/μL	Relevant	Not implementable	Not implementable	Not implementable	
	Platelets ≥ 100 x 10^3/μL	Relevant	Not implementable	Not implementable	Not implementable	Not well captured
	Hemoglobin ≥ 9.0 g/dL	Relevant	Not implementable	Not implementable	Not implementable	
	Serum creatinine of ≤ 1.5 X ULN or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula) Female CrCl= (140- age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/ dL Male CrCl= (140- age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/ dL	Relevant	Not implementable	Not implementable	Not implementable	
	AST≤ 1.5X ULN	Relevant	Not implementable	Not implementable	Not implementable	
	ALT≤ 1.5X ULN	Relevant	Not implementable	Not implementable	Not implementable	
	Total bilirubin≤ ULN (except subjects with Gilbert Syndrome who must have total bilirubin <3.0 mg/dL)	Relevant	Not implementable	Not implementable	Not implementable	
Inclusion 10	Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to randomization	Limited Relevance	Not implementable	Not implementable	Not implementable	
Inclusion 11	Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 2. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception should be determined in consultation with the investigator. WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours. Contraception should be continued for a period of at least 30 days plus the time required for the investigational drug to undergo five half lives. For women randomized to receive BMS-936558 (nivolumab), this is equivalent to 23 weeks after discontinuation of treatment. For women randomized to receive docetaxel, this is equivalent to 33 days after discontinuation of treatment	Limited Relevance	Not implementable	Not implementable	Not implementable	We assumed these reproductive safety criteria were met as part of routine clinical care for patients receiving systemic cancer therapy (e.g., contraception counseling, pregnancy testing when applicable, and avoidance of breastfeeding).
Inclusion 12	WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.	Limited Relevance	Not implementable	Not implementable	Not implementable	
Inclusion 13	Women must not be breastfeeding	Limited Relevance	Not implementable	Not implementable	Not implementable	
Inclusion 14	Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. The investigator shall review contraception methods and the time period that contraception must be followed. Men that are sexually active with WOCBP must follow instructions for birth control for a period of 90 days plus the time required for the investigational drug to undergo five half lives. For men randomized to receive BMS-936558 (nivolumab), this is equivalent to 31 weeks after discontinuation of treatment. Men randomized to receive docetaxel must follow instructions for birth control as per the SmPC (6 months after discontinuation of treatment), or package insert.	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 1	Subjects with untreated CNS metastases are excluded. Subjects are eligible if CNS metastases are treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).	Relevant	Limited	Limited	Limited	We excluded patients with CNS involvement, defined by diagnoses of brain metastases, cerebral meningeal metastases, or metastases to other parts of the nervous system.
Exclusion 2	Subjects with carcinomatous meningitis	Relevant	Limited	Limited	Limited	

Exclusion 3	Subjects with active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.	Limited Relevance	Limited	Limited	Limited	Patients with a history of clinically significant autoimmune disease within two years prior to treatment initiation were excluded. Autoimmune diseases are likely underdocumented in the data.
Exclusion 4	Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Corticosteroids with minimal systemic absorption (for example topical, inhalational, or as specified in Section 3.4.3), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 5	Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).	Relevant	Possible	Possible	Possible	Patients with any prior exposure to immune checkpoint inhibitors were excluded, including ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab, tremelimumab, and dostarlimab.
Exclusion 6	Prior treatment on the first-line study CA184104	Limited Relevance	Possible	Possible	Possible	Patients with any prior exposure to ipilimumab.
Exclusion 7	Prior treatment with docetaxel	Relevant	Possible	Possible	Possible	
Exclusion 8	Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity	Relevant	Limited	Limited	Limited	Exclude patients with prior diagnosis of interstitial lung disease.
Exclusion 9	Other active malignancy requiring concurrent intervention	Relevant	Possible	Possible	Possible	Exclude patients with current malignancies or a history of malignancy before initiation of second-line therapy.
Exclusion 10	Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period	Relevant	Possible	Possible	Possible	
Exclusion 11	All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.	Relevant	Not implementable	Not implementable	Not implementable	Not well captured
Exclusion 12	Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment	Relevant	Not implementable	Not implementable	Not implementable	
Exclusion 13	Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 14	Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 15	History of severe hypersensitivity reactions to other monoclonal antibodies.	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 16	History of severe hypersensitivity reaction to prior paclitaxel	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 17	History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions.	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 18	WOCBP who are pregnant or breastfeeding	Limited Relevance	Not implementable	Not implementable	Not implementable	We assumed these reproductive safety criteria were met as part of routine clinical care for patients receiving systemic cancer therapy (e.g., contraception counseling, pregnancy testing when applicable, and avoidance of breastfeeding).
Exclusion 19	Women with a positive pregnancy test at enrollment or prior to administration of study medication	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 20	Ongoing or planned administration of anti-cancer therapies other than those specified in this study	Relevant	Possible	Possible	Possible	
Exclusion 21	Use of corticosteroids or other immunosuppressive medications	Limited Relevance	Not implementable	Not implementable	Not implementable	Not well captured
Exclusion 22	Strong CYP3A4 inhibitors	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 23	Treatment with any investigational agent within 14 days of first administration of study treatment	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 24	Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results	Relevant	Not implementable	Not implementable	Not implementable	
Exclusion 25	Prisoners or subjects who are involuntarily incarcerated	Limited Relevance	Not implementable	Not implementable	Not implementable	
Exclusion 26	Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness	Limited Relevance	Not implementable	Not implementable	Not implementable	

Autoimmune diseas inflammatory bowel disease; systemic lupus erythematosus; dermatomyositis; scleroderma; vasculitis; polyarteritis nodosa; sarcoidosis; immune thrombocytopenic purpura; hemolytic anemia; multiple sclerosis

NCTID NCT01673867
Acronym **CheckMate 057**
Protocol https://ascopubs.org/action/downloadSupplement?doi=10.1200%2FJCO.2017.74.3062&file=protocol_2017.743062-2.pdf
SAP NA
PMID https://ascopubs.org/doi/10.1200/JCO.2017.74.3062#suppl-html-sec-2
Indication Nonsquamous Non-small cell lung cancer (NSCLC)
Line of Therapy >=2
Exposures Nivolumab 3 mg/kg IV every 2 weeks
Comparisons Docetaxel 75 mg/m² IV every 3 weeks
Emulated outcome Overall survival

An open-label randomized Phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated metastatic non-squamou

Measurement eligibility criteria					
Criteria	**Criteria rule as defined in original protocol**	**Clinical relevance**	**Emulation [EDB1]**	**Emulation [EDB2]**	**Emulation [EDB4]**
Inclusion 1	Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.	Limited Relevance	Not implementable	Not implementable	Not implementable
Inclusion 2	Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.	Limited Relevance	Not implementable	Not implementable	Not implementable
Inclusion 3	Subjects with histologically or cytologically-documented locally advanced non-squamous cell NSCLC who present with Stage IIIB/Stage IV or recurrent or progressive disease following multi-modality therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease).	Relevant	Possible	Possible	Possible
Inclusion 4	Men and women ≥ 18 years of age	Relevant	Possible	Possible	Possible
Inclusion 5	Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1	Relevant	Possible	Possible	Possible
Inclusion 6	Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of randomization	Limited Relevance	Not implementable	Not implementable	Not implementable
Inclusion 7	Target Lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site	Limited Relevance	Not implementable	Not implementable	Not implementable
Inclusion 8	Subjects who will receive study therapy after acceptable prior therapy as specified below: Subjects who will receive study therapy as second line of treatment: Subjects must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy and could comprise continuation of one or more of the agents used in the first-line therapy regimen or switch to another non cross-resistant agent. The initiation of maintenance therapy requires the lack of progressive disease with front-line therapy.	Relevant	Possible	Possible	Possible
Inclusion 8.1	Treatment given for locally advanced disease is not considered as a line of therapy for advanced disease. Subjects with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible.	Relevant	Possible	Possible	Possible
Inclusion 8.2	Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 9	Subjects who will receive study therapy as third line of treatment must have experienced disease recurrence or progression during or after a separate EGFR or ALK tyrosine kinase inhibitor (TKI) regimen in addition to one prior platinum doublet-based chemotherapy regimen (regardless of order of administration)	Relevant	Limited	Limited	Limited
Inclusion 9.1	Subjects who received an EGFR TKI (erlotinib, gefitinib or experimental) in addition to a platinum-based chemotherapy must have a tumor with a known activating EGFR mutation.	Relevant	Limited	Limited	Limited

Inclusion 9.2	Subjects who received an ALK inhibitor (crizotinib or experimental) in addition to a platinum-based chemotherapy must have a tumor with a known ALK translocation.	Relevant	Limited	Limited	Limited
Inclusion 10	A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.4.2. Specimens must be received by the central lab prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.	Limited Relevance	Not implementable	Not implementable	Not implementable
Inclusion 11	laboratory values must meet the following criteria: WBCs ≥ 2000/µL	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 12	Neutrophils ≥ 1500/µL	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 13	Platelets ≥ 100 x 10^3/µL	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 14	Hemoglobin ≥ 9.0 g/dL	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 15	Serum creatinine of ≤ 1.5 X ULN or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula) Female CrCl= (140- age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/ dL Male CrCl= (140- age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/ dL	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 16	AST ≤ 1.5 X ULN	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 17	ALT ≤ 1.5 X ULN	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 18	Total bilirubin ≤ ULN (except subjects with Gilbert Syndrome who must have total bilirubin <3.0 mg/dL)	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 19	Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to randomization	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 20	Not applicable per Global Amendment No. 6	Relevant	Not implementable	Not implementable	Not implementable
Inclusion 21	This study permits re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.	Relevant	Not implementable	Not implementable	Not implementable
Exclusion 1	Subjects with carcinomatous meningitis	Relevant	Limited	Limited	Limited
Exclusion 2	Subjects with untreated CNS metastases are excluded. Subjects are eligible if metastases are treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).	Relevant	Limited	Limited	Limited
Exclusion 3	Any serious or uncontrolled medical disorder or active infection with hepatitis or HIV that may be reactivated	Relevant	Not implementable	Not implementable	Not implementable
Exclusion 4	Other active malignancy requiring concurrent intervention	Relevant	Limited	Limited	Limited
Exclusion 5	Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required or anticipated to be required during the study period	Relevant	Limited	Limited	Limited
Exclusion 6	Subjects with a condition requiring systemic treatment with either corticosteriods (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Corticosteroids with minimal systemic absorption (for example inhaled, topical, or as specified in Section 3.4.3) and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 7	Subjects with active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted to enroll.	Relevant	Limited	Limited	Limited
Exclusion 8	All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.	Relevant	Not implementable	Not implementable	Not implementable
Exclusion 9	Prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents	Limited Relevance	Not implementable	Not implementable	Not implementable

Exclusion 10	Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L-2, anti-CD-137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).	Relevant	Possible	Possible	Possible
Exclusion 11	Prior treatment with docetaxel	Relevant	Possible	Possible	Possible
Exclusion 12	Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.	Relevant	Limited	Limited	Limited
Exclusion 13	Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.	Relevant	Not implementable	Not implementable	Not implementable
Exclusion 14	Any positive tests for Hepatitis B virus or Hepatitis C virus indicating acute or chronic infection	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 15	Known history of testing positive for Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS).	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 16	History of severe hypersensitivity reactions to other monoclonal antibodies.	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 17	History of severe hypersensitivity reaction to prior paclitaxel	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 18	History of allergy or intolerance (unacceptable adverse event) to study drug components, or Polysorbate-80-containing infusions.	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 19	WOCBP who are pregnant or breastfeeding	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 20	Women with a positive pregnancy test at enrollment or prior to administration of study medication	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 21	Ongoing or planned administration of anti-cancer therapies other than those specified in this study	Relevant	Possible	Possible	Possible
Exclusion 22	Use of corticosteroids or other immunosuppressive medications per exclusion criteria 2d	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 23	Strong CYP3A4 inhibitors	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 24	Treatment with any investigational agent within 14 days of first administration of study treatment	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 25	Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results.	Relevant	Not implementable	Not implementable	Not implementable
Exclusion 26	Prisoners or subjects who are involuntarily incarcerated	Limited Relevance	Not implementable	Not implementable	Not implementable
Exclusion 27	Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness	Limited Relevance	Not implementable	Not implementable	Not implementable

Autoimmune diseas	inflammatory bowel disease; systemic lupus erythematosus; dermatomyositis; scleroderma; vasculitis; polyarteritis nodosa; sarcoidosis; immune thrombocytopenic purpura; hemolytic anemia; multiple sclerosis

NCTID
Acronym **CheckMate 017/057**
Protocol
SAP
PMID https://pubmed.ncbi.nlm.nih.gov/33449799/
Indication Non-small cell lung cancer (NSCLC)
Line of Therapy >=2
Exposures Nivolumab 3 mg/kg IV every 2 weeks
Comparisons Docetaxel 75 mg/m² IV every 3 weeks
Emulated outcome Overall survival (primary end point)

Measurement eligibility criteria							
Criteria	**Criteria rule as defined in original protocol**	**Time point/period of emulated measurement [days]**	**Emulation [EDB1]**	**Emulation [EDB2]**	**Emulation [EDB4]**	**Comment**	**encore.io function**
Inclusion 1	Men and women ≥ 18 years of age	[0;0]	Age at index date (year granularity level)	Age at index date (year granularity level)	Age at index date (year granularity level)		edbx_get_demographics()
Inclusion 2	Subjects with histologically or cytologically-documented NSCLC who present with Stage IIIB/ Stage IV disease or recurrent or progressive disease following multi-modality therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease).	[-inf;0]	Line of therapy needs to be for "Advanced" setting (LoT table)	Line of therapy needs to be for "Metastatic" setting (LoT table)	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.	EDB1 included patients diagnosis with stage IIIB through IV or first recurrence/progression after earlier stage diagnosis. Since advanced NSCLC not amenable to curative surgery or radiotherapy is difficult to ascertain in EHR, EDB2 and EDB4 are restricted to metastatic patients only which is easier to assess.	EDB1 and EDB2: Part of exposure definition EDB4: Derived form edbx_get_diagnosis()
Inclusion 3	Patients received nivolumab or docetaxel as second-line therapy (ChakeMate 017/057) or third-line therapy (ChakeMate 057).	[0;0]	Treatment needs to be the second line of therapy for the advanced setting (LoT table).	Treatment needs to be the second line of therapy for the metastatic setting (LoT table).	Second systematic therapy for advanced disease after date of first metastasis.	In CheckMate 057, third-line patients were a small subgroup (~12%) and had additional, complex eligibility requirements (prior platinum doublet plus prior EGFR/ALK TKI exposure, regardless of order). For third-line eligibility, the trial required patients to have progressed during/after a separate EGFR or ALK TKI regimen in addition to platinum chemotherapy, and to have confirmed activating EGFR mutations (for EGFR TKI users) or confirmed ALK translocations (for ALK inhibitor users). These biomarker-confirmation and detailed treatment-sequencing requirements are difficult to reliably capture in real-world data, increasing the risk of misclassification. We also did not implement the trial allowance for patients who received platinum-based adjuvant/neoadjuvant/definitive chemoradiation for locally advanced disease and recurred within 6 months, because: 1. This subgroup is expected to be rare in our data 2. Key information needed to identify these pathways (early-stage treatment details and timing) is likely incomplete/missing, making accurate implementation unreliable. As a result, we will restrict the emulation to the second-line setting.	EDB1 and EDB2: Part of exposure definition EDB4: de novo coding
Inclusion 4	Subjects must have received one prior platinum doublet–based chemotherapy regimen for advanced or metastatic NSCLC.	[day of aNSCLC/mNSCLC diagnosis; -1]	Patient received first-line platinum doublet-based chemotherapy regimens for aNSCLC	Patient received first-line platinum doublet-based chemotherapy regimens for mNSCLC.	Patient received platinum doublet-based chemotherapy regimens as the first systematic therapy after the date of metastasis.		
Inclusion 5	Subjects must have experienced disease recurrence or progression during or after the prior platinum doublet–based chemotherapy regimen for advanced or metastatic NSCLC.	[day of first-line platinum doublet-based chemotherapy initiation;0]	Evidence of disease progression between the initiation of first-line platinum doublet–based chemotherapy and initiation of second-line therapy.	Evidence of disease progression between the initiation of first-line platinum doublet–based chemotherapy and initiation of second-line therapy.	Not appliable	EDB4 did not provide documentation for the progression information.	
Inclusion 6	Eastern Cooperative Oncology Arm (ECOG) performance status of ≤ 1	[-90;0]	ECOG = 0 | 1	ECOG = 0 | 1	ECOG = 0 | 1		edbx_get_ecog()
Exclusion 1	Treatment with any of the following:						
Exclusion 1.1	Prior treatment with docetaxel or nivolumab	[-inf;-1]	Treatments with docetaxel or nivolumab before the initiation of second-line treatment for aNSCLC.	Treatments with docetaxel or nivolumab before the initiation of second-line treatment for mNSCLC.	Treatments with docetaxel or nivolumab before the initiation of second-line treatment for mNSCLC.		
Exclusion 1.2	Prior treatment with any anti-PD-1, anti-PD-L1, anti-PD-L-2, anti-CD-137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).	[-inf;-1]	Immunotherapy before the second-line treatment for aNSCLC	Immunotherapy before the second-line treatment for mNSCLC	Immunotherapy before the second-line treatment for mNSCLC		
Exclusion 1.3	Ongoing or planned administration of anti-cancer therapies other than those specified in this study	[0, proprietary business rules]	Concurrent any other anti-cancer therapy during the treatment ascertainment window.	Concurrent any other anti-cancer therapy during the treatment ascertainment window.	Concurrent any other anti-cancer therapy during the treatment ascertainment window.		
Exclusion 2	Diagnosis with any of the following before nivolumab/docetaxel initiation:						
Exclusion 2.1	Subjects with active malignancy requiring concurrent intervention or previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required or anticipated to be required during the study period	[-inf; 0]	Exclude patients with any prior non-lung malignancy diagnosis recorded before or on the index date, except non-melanoma skin cancer, carcinoma in situ of bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast.	Exclude patients with any prior non-lung malignancy diagnosis recorded before or on the index date, except non-melanoma skin cancer, carcinoma in situ of bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast.	Exclude patients with a record of non-index cancer treatment prior to or on the index date.	No diagnosis table for EDB4 available	edbx_get_diagnosis_solid( )

Exclusion 2.2	Subjects with active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted to enroll.	[-730;0]	Patients with a history of autoimmune disease within 2 years before treatment initiation were excluded.	Patients with a history of autoimmune disease within 2 years before treatment initiation were excluded.	Patients with a history of autoimmune disease within 2 years before treatment initiation were excluded.	The history of autoimmune disease is likely underdocumented in the data; a 2-year period was selected to capture potential active autoimmune disease.	
Exclusion 2.4	Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.	[-inf; 0]	Exclude patients who were diagnosed with interstitial lung disease before the index date.	Exclude patients who were diagnosed with interstitial lung disease before the index date.	Exclude patients who were diagnosed with interstitial lung disease before the index date.	Interstitial lung disease is likely underdocumented in the data.	
Exclusion 2.5	Subjects with central nervous system (CNS) metastases	[-inf; 0]	Exclude patients who had a diagnosis of brain metastases, cerebral meningeal metastases, or metastases to other parts of nervous system before the index date	Exclude patients who had a diagnosis of brain metastases, cerebral meningeal metastases, or metastases to other parts of nervous system before the index date	Exclude patients who had a diagnosis of brain metastases, cerebral meningeal metastases, or metastases to other parts of nervous system before the index date		

aNSCLC = advanced non-small cell lung cancer, mNSCLC = metastatic non-small cell lung cancer

Immunotherapy	Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, Avelumab, Cemiplimab, Tremelimumab, Dostarlimab
Autoimmune diseases	Inflammatory bowel disease, Systemic lupus erythematosus, Dermatomyositis, Scleroderma, Vasculitis, Polyarteritis nodosa, Sarcoidosis, Immune thrombocytopenic purpura, Hemolytic anemia, Multiple sclerosis
Ongoing or planned administration of ant	adagrasib, ado-trastuzumab emtansine, afatinib, alectinib, amivantamab-vmjw, atezolizumab, atezolizumab and hyaluronidase-tqjs, bevacizumab, bevacizumab-adcd, bevacizumab-awwb, bevacizumab-bvzr, bevacizumab-maly, bevacizumab-tnjn, binimetinib, brigatinib, cabozantinib, capmatinib, carboplatin, cemiplimab-rwlc, ceritinib, cetuximab, cisplatin, crizotinib, dabrafenib, dacomitinib, datopotomab, durvalumab, encorafenib, ensartinib, entrectinib, erdafitinib, erlotinib, etoposide, fam-trastuzumab deruxtecan-nxki, gefitinib, gemcitabine, ipilimumab, larotrectinib, lazertinib, lorlatinib, mobocertinib, osimertinib, paclitaxel, paclitaxel protein bound, pembrolizumab, pembrolizumab and berahyaluronidase alfa-pmph, pemetrexed, pralsetinib, ramucirumab, repotrectinib, selpercatinib, sotorasib, sunvozertinib, taletrectinib, telisotuzumab vedotin-tllv, tepotinib, trametinib, tremelimumab-actl, vandetanib, vemurafenib, vinorelbine, zenocutuzumab-zbco, zongertinib.