1. Title Page

Title	Evaluation of Synthetic Data for External Control Arm Analysis – A Case Study using Lung-MAP S1400I
Research question & Objectives	To compare the efficacy of ● Nivolumab + ipilimumab combination therapy versus ● Nivolumab monotherapy in patients with metastatic non-small cell lung cancer using real-world data and synthetic data derived from the same, with the aim of validating synthetic data for use in external control arm analysis.
Protocol version	0.3
Last update date	July 23, 2024
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Study registration	**Site:** n/a **Identifier:** n/a
Sponsor	**Organization:** n/a **Contact:** n/a
Conflict of interest	None

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2. Abstract

Single-arm trials supplemented with external comparator arm(s) (ECA) derived from real-world data are sometimes used when randomized trials are infeasible. However, due to data sharing restrictions, privacy/security concerns, or for logistical reasons, patient-level real-world data may not be available to researchers for analysis. Instead, it may be possible to use generative models to construct synthetic data from the real-world dataset that can then be freely shared with researchers. Although the use of generative models and synthetic data is gaining prominence, the extent to which a synthetic data ECA can replace original data while preserving patient privacy in small samples is unclear.

Objective: To compare the efficacy of nivolumab + ipilimumab combination therapy ("experimental arm") versus nivolumab monotherapy ("control arm") in patients with metastatic non-small cell lung cancer (mNSCLC) using real-world data from two real-world databases ("original ECA"), and synthetic data versions of these datasets ("synthetic ECA"), with the aim of validating synthetic data for use in ECA analysis.

Study design: Non-randomized analyses of treatment efficacy comparing the experimental arm to the (i) original ECA and (ii) synthetic ECA, with baseline confounding adjustment.

Data sources: The experimental arm is from the Lung-MAP no-match substudy S1400I (NCT02785952) provided by National Clinical Trials Network (NCTN) in the United States. The real-world data source for the ECA is data from population-based oncology data from the Canadian province of Alberta, and from Nordic countries in Europe.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
March 12, 2024	0.1	All	First draft	n/a
July 23, 2024	0.2	All	Update	Including additional data source, and expanding sections on benchmarking metrics and specific generative models; Update timelines

4. Milestones

Table 1. Milestones

Milestone	Date
Project initiation ● Finalize study objectives and scope of work ● Establish tasks and timelines ● Provide communication channels	June 2024
Data preparation	September 2024
Statistical analysis including synthetic data generation	November 2024
Discussion of results with all collaborators	December 2024
Manuscript draft and revisions	January 2024
Submission to scientific journal	February 2024

5. Rationale and background

Clinical researchers often encounter challenges in accessing patient-level real-world data for external comparator arms (ECAs) in single-arm trials, attributed to data sharing restrictions, privacy concerns, and logistical constraints. To address this issue, an emerging approach involves utilizing generative models to construct synthetic data that mirrors the statistical properties of real-world datasets. This strategy enables the creation of alternative comparator arms, which can be freely shared and analyzed, circumventing obstacles associated with data availability. However, the extent to which synthetic data faithfully reproduces the characteristics of the original real-world dataset remains uncertain, raising questions about its reliability and validity in the context of single-arm trials.

This research aims to explore the viability of synthetic data in external comparator arms by assessing its fidelity compared to real-world data. The study delves into the current landscape of single-arm trials, emphasizing the limitations in accessing patient-level real-world data and elucidating the role of synthetic data in overcoming these challenges. By investigating the potential benefits and limitations of synthetic data generation methods, the research seeks to provide valuable insights into the reliability of study outcomes derived from ECAs constructed using generative models, thereby contributing to the ongoing discourse on innovative methodologies for enhancing the robustness of single-arm trials amidst data constraints.

The following are details about the Lung-MAP trial used in this study:

What is known about the condition: Squamous cell lung carcinoma is a histological subtype of NSCLC that originates in the squamous cells lining the airways of the lungs. Historically, 25-30% of all cases of NSCLC are squamous cell carcinoma although these percentages can vary regionally and may change over time due to factors such as changes in smoking patterns. Compared to other NSCLC subtypes, such as adenocarcinoma, the presence of actionable genetic variants is less common and there are fewer targeted therapies available for squamous cell advanced/metastatic NSCLC.

What is known about the exposure of interest: Patients diagnosed with squamous mNSCLC often receive Platinum-based chemotherapy regimens as front-line systemic therapy. Following progression, patients will most often receive therapy with immune checkpoint inhibitors that target either the PD-(L)1 pathway, such as nivolumab and atezolizumab, or CTLA-4, such as ipilimumab. The Lung-MAP S1400I trial (NCT02785952) compared overall survival in United States patients with recurrent stage IV squamous NSCLC randomized to receive either nivolumab monotherapy or nivolumab + ipilimumab combination therapy and found no significant difference in mortality rates between these groups.

- Note: Since FDA approval in October 2018, combination therapy with pembrolizumab + chemotherapy has gradually replaced chemotherapy as first-line systemic treatment for patients with squamous aNSCLC. The NCT02785952 study was performed between 2016-2018.

Gaps in knowledge: While the proposed research addresses the innovative use of synthetic data in constructing ECAs for single-arm trials, several gaps in knowledge exist:

1. What metrics should be used to evaluate utility and privacy risks of synthetic ECA compared to the original,
2. What validation strategies should be used to ensure that the synthetic ECA captures inferential results compared to the original ECA
3. What best practices should be followed to ensure reliable synthetic ECA are generated.

What is the expected contribution of this study? This study aims to answer the gaps in knowledge described above using a case study in mNSCLC, as well as describe limitations of this strategy and long-term implications for wider adoption.

6. Research question and objectives

Table 2. Primary and secondary research questions and objective

A. Primary research question and objective

Objective:	To compare the efficacy of nivolumab + ipilimumab combination therapy (“experimental arm”) versus nivolumab monotherapy (“control arm”) in patients with metastatic non-small cell lung cancer (mNSCLC) using real-world data from Alberta, Canada (“original ECA”) and synthetic data derived from the same (“synthetic ECA”), with the aim of validating synthetic data for use in external control arm analysis.

Hypothesis:	This is not a hypothesis-driven study. However, we anticipate that synthetic ECA will be able to recapitulate an original ECA on different benchmarking metrics.
Population *(mention key inclusion-exclusion criteria):*	The following are eligibility criteria for NCT02785952. ● Age 18 years or older at index date ● Diagnosed with pathologically proven stage IV or recurrent squamous NSCLC ● No mixed histologies ● No other previous untreated malignancies ● Progression on one previous treatment with platinum-based chemotherapy ● No EGFR mutation or ALK fusion ● Sufficient tumour tissue for biomarker analysis ● ECOG score of 0 or 1 ● No prior treatment with anti-PD-(L)1/2, CTLA-4 or any immune checkpoint inhibitor ● No active, known or suspected autoimmune diseases except some specific exceptions ● No known allergy or reaction to nivolumab and ipilimumab formulations ● No prior systemic treatment with corticosteroids or immunosuppressants within last 14 days ● No hepatitis B or C antibodies or infection, or HIV or AIDS ● No interstitial lung disease ● No grade III/IV cardiac disease or myocardial infarction within past 6 months The target trial specification is provided below.
Exposure:	Nivolumab + ipilimumab combination therapy
Comparator:	Nivolumab monotherapy
Outcome:	Overall survival
Time *(when follow up begins and ends):*	Follow-up begins at the date of initiation of the index therapy (“index date”) and ends at month 40 after index date or death, whichever is earlier.
Setting:	Stage IV squamous NSCLC
Main measure of effect:	Hazard ratio and restricted mean survival time over 40 months from index date

B. Target trial specification

The target trial specification is provided for the original ECA. Because the synthetic ECA is derived from the same real-world data as the original ECA, the specification is identical.

Protocol element	Target trial	Emulation
Eligibility criteria	• Age 18 years or older at index date • Diagnosed with pathologically proven stage IV or recurrent squamous NSCLC • No mixed histologies • No other previous untreated malignancies • Progression on one previous treatment with platinum-based chemotherapy • No EGFR mutation or ALK fusion • Sufficient tumour tissue for biomarker analysis • ECOG score of 0 or 1 • No prior treatment with anti-PD-(L)1/2, CTLA-4 or any immune checkpoint inhibitor • No active, known or suspected autoimmune diseases except some specific exceptions • No known allergy or reaction to nivolumab and ipilimumab formulations • No prior systemic treatment with corticosteroids or immunosuppressants within last 14 days • No hepatitis B or C antibodies or infection, or HIV or AIDS • No interstitial lung disease • No grade III/IV cardiac disease or myocardial infarction within past 6 months	Same as target trial, except those in red: • Age 18 years or older at index date • Diagnosed with pathologically proven stage IV or recurrent squamous NSCLC • No mixed histologies • No other previous untreated malignancies • Progression on one previous treatment with platinum-based chemotherapy • No EGFR mutation or ALK fusion [mutation status is not available; eligible patients with squamous NSCLC would be unlikely to have EGFR or ALK mutations] • Sufficient tumour tissue for biomarker analysis • ECOG score of 0 or 1 [not available; patients who meet other eligibility criteria and receive systemic treatment of cancer may be inferred to have an eligible performance status] • No prior treatment with anti-PD-(L)1/2, CTLA-4 or any immune checkpoint inhibitor • No active, known or suspected autoimmune diseases except some specific exceptions • No known allergy or reaction to nivolumab and ipilimumab formulations • No prior systemic treatment with corticosteroids or immunosuppressants within last 14 days • No hepatitis B or C antibodies or infection, or HIV or AIDS • No interstitial lung disease • No grade III/IV cardiac disease or myocardial infarction within past 6 months
Treatment regimens	Initiation of (assignment to) one of • Nivolumab administered intravenously at a dose of 3 mg/kg every 14 days (“control arm”)	Same as target trial

	• Nivolumab administered intravenously at a dose of 3 mg/kg every 14 days + ipilimumab given at 1 mg/kg on day 1 of every third cycle (“experimental arm”)	
Treatment assignment	Patients were randomly assigned to the control or experimental arm at baseline	Treatment assignment is assumed random conditional on measured risk factors including age at baseline, sex, ECOG score, presence of liver and bone metastases and index line of therapy
Outcome	All-cause mortality	Same as target trial
Follow-up	Begins at treatment assignment and ends at month 40, study discontinuation or death, whichever occurs first	Same as target trial
Causal contrast	Intention to treat effect on the absolute and relative scales, namely restricted mean survival time and hazard ratio	Same as target trial
Statistical analysis	Kaplan-Meier curves will be reported and restricted mean survival will be calculated using these curves. Hazard ratio will be estimated using Cox proportional hazard model.	Kaplan-Meier curves and hazard ratios will be estimated using models weighted by the inverse probability of treatment assignment. Inverse weights will be estimated using a logistic regression model with treatment assignment indicator as a function of baseline confounders. Point estimates and 95% confidence intervals based on robust standard errors to account for weighting will be documented.

The analysis will be replicated with no change using the original and synthetic ECAs.

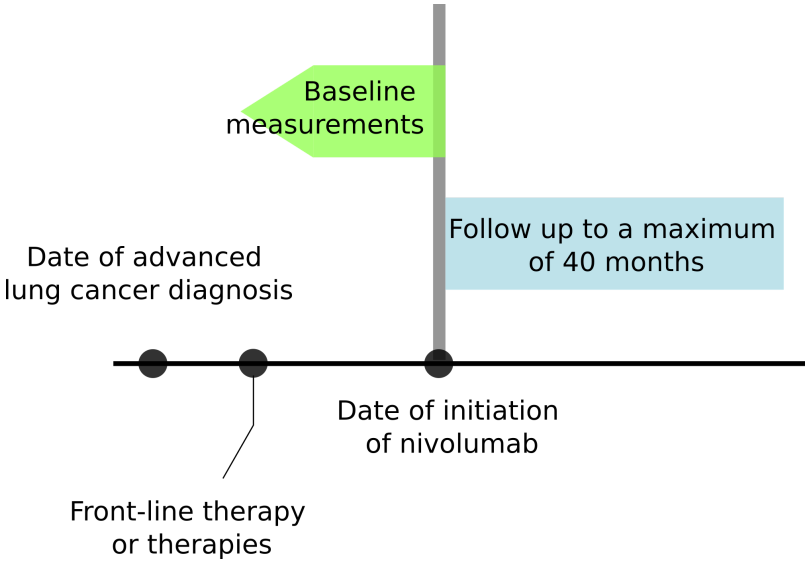
7. Research methods

7.1. Study design

Research design (e.g. cohort, case-control, etc.): External control arm study (non-randomized comparison of trial and real-world patients)

Rationale for study design choice: For assessing the feasibility of using synthetic data for ECA analysis, an ECA design is most appropriate.

7.2. Study design diagram



7.3. Setting

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

The index date is the date of treatment assignment in the Lung-MAP study NCT02785952. The ECA analysis aims to emulate the same.

Table 3 Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry
NCT02785952	Date of randomization	1	Incident use

7.3.2 Context and rationale for study eligibility criteria:

Eligibility criteria for the target trial are identical to those from NCT02785952.

Table 4. Operational Definitions of Inclusion/Exclusion Criteria

Eligibility criteria (Lung-MAP *S1400* + NCT02785952)	**NCT02785952**	**Real-world data**
Age 18 years or older at index date		
Diagnosed with pathologically proven stage IV or recurrent squamous NSCLC		
No mixed histologies		
No other previous untreated malignancies		
Progression on one previous treatment with platinum-based chemotherapy		
No EGFR mutation or ALK fusion		
Sufficient tumour tissue for biomarker analysis		
ECOG 0, 1		
No prior treatment with anti-PD-(L)1/2/CTLA-4/immune checkpoint inhibitor		
No active, known or suspected autoimmune diseases		
No known allergy or reaction to nivolumab + ipilimumab formulations		
No prior systemic corticosteroids or immunosuppressants within last 14 days		
No hepatitis B or C antibodies or infection, or HIV or AIDS		
No interstitial lung disease		
No grade III/IV cardiac disease or myocardial infarction within past 6 months		

Green = identical eligibility criterion applied, Red = eligibility criterion not applied due to lack of measured data elements

7.4. Variables

7.4.1 Context and rationale for exposure(s) of interest

The treatment groups of interest are the same as those in NCT02785952. For real-world studies, we make the concession that any dose and frequency compatible with observed data is permitted, even if not reported.

Treatment regimens in NCT02785952**:**

- Nivolumab administered intravenously at a dose of 3 mg/kg every 14 days
- Nivolumab administered intravenously at a dose of 3 mg/kg every 14 days + ipilimumab given at 1 mg/kg on day 1 of every third cycle

Algorithm to define duration of exposure effect:

n/a

7.4.2 Context and rationale for outcome(s) of interest

Overall survival defined as time from index date to death from any cause is the primary and sole outcome of interest. Overall survival is the most important clinical outcome in aNSCLC.

Table 7. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Measurement characteristics/ validation	Source of algorithm
Overall survival	Time from index date to death from any cause	Yes	Time-to-event	Measured in the trial and real-world dataset reliably	N/A

7.4.3 Context and rationale for follow up

The maximum length of follow-up in the NCT02785952 data cut available to us is approximately 40 months.Click here to enter text.

Table 8. Operational Definitions of Follow Up.

Follow up start	Day 1	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome **Date of death**	Yes	Outcome is death for any reason
End of observation in data	Yes	The administrative end of follow-up in real-world data
Day X following index date *(specify day)*	Yes	40 months from index date
End of study period (specify date)	No	N/A
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	N/A
Date of add to/switch from exposure *(specify algorithm)*	No	N/A
Other date *(specify)*	None	N/A

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

7.4.4 Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

An assumption for unbiased estimation of the treatment effect is adjustment for all confounders of the treatment effect. However, not all risk factors for survival are measured across the data sources. Furthermore, it is impossible to adjust for all risk factors even if they were measured. We only adjust for measured confounding variables in this study.

Table 9. Operational Definitions of Covariates

The following is a tentative list of measured risk factors for overall survival we will attempt to adjust for. Variables marked with an asterisk are missing for the majority of patients in the real-world database.

Characteristic	Details	Type of variable	Assessment window
Age	Age (in years) at randomization	Continuous	Screening variables were assessed within 14 days of registration in NCT02785952
Sex	Sex	Dichotomous (male or female)	
ECOG score*	ECOG performance score (0-1)	Dichotomous	
Liver metastases	Presence of liver metastases at baseline	Dichotomous (present or absent)	
Brain metastases	Presence of brain metastases at baseline	Dichotomous (present or absent)	
Smoking history*	History of smoking	Dichotomous (ever or never)	
Index line	Index line of therapy	Dichotomous (1 or 2+)	

7.5. Data analysis

7.5.1 Context and rationale for analysis plan

The inferential data analysis plan is described conceptually, and the context or rationale for the choices are provided in this section.

Table 10. Primary, secondary, and subgroup analysis specification

A. Primary analysis

Hypothesis:	This is not a hypothesis-driven study. However, we expect that synthetic ECA will be able to recapitulate an original ECA on different quantitative and qualitative benchmarking metrics.
Exposure contrast:	Nivolumab monotherapy versus nivolumab + ipilimumab combination
Outcome:	All-cause mortality
Analytic software:	R version 4.3 Packages: survival, survminer (Package versions and any additional packages used for the analysis will be documented)
Model(s): ***(provide details or code)***	Kaplan-Meier curves will be estimated using standard functions with a treatment indicator, with or without inverse probability weighting. Hazard ratios will be estimated using Cox proportional hazards model with the treatment indicator, either with or without inverse probability weighting. Synthetic data will be generated from the real-world Canadian data using Subsalt platform. The details of synthetic data generation will be provided separately from this document.

	For synthetic data generation, the following is a tentative list of models that will be evaluated: **R package synthpop:** Classification and regression trees (CART) Bagging Random forest Ranger (based on the random forest model) **Python package sdv:** Gaussian copula TVAE based on variational autoencoder (VAE) for tabular data CTGAN based on generative adversarial network (GAN). CT=conditional tabular **Python package synthcity:** Bayesian network CTGAN Denoising diffusion probabilistic models (DDPM) Adversarial random forest (ARF) PATEGAN (Privacy-focused implementation of GAN) PrivBayes (Privacy-focused implementation of Bayesian network) RTVAE based on VAE Other models or implementations of these models may be explored as well.
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.***
	A logistic regression model for treatment assignment will be used to estimate inverse odds of treatment (corresponding to ATT weights) using the following formula: `treatment_indicator ~ age + sex + ecog + smoker + + brainmets + livermets + index_line race`
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.***
	Missing data is expected in baseline covariates in the real-world data. These will be imputed if possible using single imputation including all other baseline covariates, as well as the outcome variable, as predictors.
Subgroup Analyses	***List all subgroups***

	No subgroup analyses are planned.

Table 11. Sensitivity analyses – rationale, strengths and limitations

No sensitivity analyses are planned.

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

n/a

7.6. Data sources

7.6.1 Context and rationale for data sources

Reason for selection: Selection of data sources was based on availability of individual-level data. NCT02785952 was selected from Project Data Sphere. The criteria for selecting a suitable clinical trial dataset for this study were as follows: (i) a lung cancer indication, (ii) a randomized trial with both treatment arms available, (iii) sample size >100 and (iv) testing a non-chemotherapy regimen of clinical importance that is approved for use and commonly administered. NCT02785952 was the only trial on Project Data Sphere that fit these criteria. aNSCLC was chosen because the study authors have substantial experience in this disease setting, and because it is a common indication for drug development, and therefore for regulatory approvals and health technology assessments.

Subsequently, two real-world data sources were identified:

- Administrative cancer data from the province of Alberta, Canada
- Nordic national cancer registry

Strengths of data source(s): Patient-level data is available for important risk factors and overall survival.

Limitations of data source(s): The original ADaM/SDTM dataset is not available, and therefore we only have derived variables in some cases for the trial. No longitudinal data on risk factors or subsequent therapies is available. Some variables, notably ECOG scores, are not available in the real-world data.

Data source provenance/curation: Not available for the trial dataset. However, the distribution of baseline characteristics and Kaplan-Meier estimates match those from the trial publication (not shown here). Both the Canadian and Nordic databases collect cancer data at a national population level and are well-documented and have previously been used for epidemiologic and comparative analyses.

Table 12. Metadata about data sources and software

	Trial data	**Real-world data**	**Real-world data**
Data Source(s):	NCT02785952	Alberta Health	Nordic cancer registry
Study Period:	2015-12-29 to 2019-12-19 based on https://www.clinicaltrials.gov/study/NCT02785952.		
Eligible Cohort Entry Period:	Not known. The data available does not include this information.		
Data Version (or date of last update):	Not known		
Data sampling/extraction criteria:	n/a		
Type(s) of data:	Patient-level data from a randomized clinical trial		
Data linkage:	n/a		
Conversion to CDM*:	None		
Software for data management:	None		

*CDM = Common Data Model

7.7. Data management

Patient-level data from NCT02785952 has been provided by the trial sponsor in a deidentified format. A single copy of this dataset will be stored on a local password-protected computer. Programming code will be stored and backed up in a private and secured cloud repository.

7.8. Quality control

For NCT02785952, we have a limited dataset provided by the trial sponsor. Data from Alberta, Canada and Nordic regions are both validated and analyzed by an expert deeply familiar with the data and its limitations. Although double programming will not be performed, steps will be taken to ensure that there are no programming errors for data processing and analysis that can affect the accuracy of the results, for example, through sanity checks and visualization of intermediate results/outputs in the analysis.

7.9. Study size and feasibility

Because this is an exploratory study, sample size calculations were not formally performed. The primary objective of this study is to compare results between original ECA and synthetic ECA used for ECA analysis, rather than producing unbiased estimates of the treatment effect (which are available from the trial and known). Therefore, the study should be feasible regardless of sample size or adequacy of confounding control. However, sensitivity analyses will be performed for unmeasured confounding.

Table 13. Power and sample size

Not applicable. This is an exploratory study and no formal power calculations were performed.

8. Limitation of the methods

The following is a discussion of potential limitations of the study design, and analytic methods, including issues relating to confounding, bias, generalisability, and random error:

1. Random error – NCT02785952 is a relatively small trial (125 + 127 patients) and therefore the results may have low precision. This limitation exists for any study with small samples, and is a common concern in external control arm studies. Therefore, it may be difficult to disentangle a small difference in results between the original ECA and synthetic ECA if it exists.
2. Inability to emulate the target trial perfectly – Due to lack of data availability, there are limitations for perfectly emulating eligibility criteria from the trial. There is also the possibility that there are other unknown differences in variable recording and derivation across the two datasets. However, the primary objective of this study is to compare results between original ECA and synthetic ECA used for ECA analysis, rather than producing unbiased estimates of the treatment effect, and therefore this limitation may be discussed by comparing ECA results with those from the randomized trial.
3. Generalizability of the results – Our results may not generalize to other settings or other datasets. We will not assert that they do. Instead, we will use this case study to describe best practices for future benchmarking studies or applications using synthetic data for ECA analyses.

9. Protection of human subjects

n/a. This study uses deidentified data.

10. Reporting of adverse events

n/a

11. References

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12. Appendices

n/a