Non-Interventional Study Protocol
A5481159

Real-World Tumor Response of Palbociclib in Combination with an Aromatase Inhibitor as First Line Therapy in Pre/perimenopausal Women with Metastatic Breast Cancer

Statistical Analysis Plan

Version: 1.0

Author: PPD

Date: 27 September 2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
AI	aromatase inhibitor
BC	breast cancer
BMI	body mass index
CDK	cyclin-dependent kinase
CMH	Cochran–Mantel–Haenszel
CR	complete response
ECOG	Eastern Cooperative Oncology Group
EHR	electronic health record
ER	estrogen receptor
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
HR	hazard ratio
ICD	International Classification of Diseases
IHC	International Council for Harmonisation
iKM	iknowMed
ILD	interstitial lung disease
IPTW	inverse probability of treatment weighting
LOT	line of therapy
MBC	metastatic breast cancer
MI	multiple imputation
nIPTW	normalized inverse probability of treatment weighting
NOS	not otherwise specified
PD	progressive disease
PR	partial response
PS	propensity score
PSM	propensity score matching
rwCR	real world complete response
rwPR	real world partial response
rwRR	real world response rate
rwTR	real world tumor response
SAP	statistical analysis plan
SD	Stable disease
std dev	standard deviation
TNM	Tumor, Node, Metastasis
US	United States
USON	United States Oncology Network
USPI	United States Prescribing Information

AMENDMENTS FROM PREVIOUS VERSION(S)

CCI [redacted]

[redacted]

In the protocol and draft SAP, the number of patients in the final datasets based on structured data was 316 (139 in palbociclib plus AI cohort and 177 in AI monotherapy cohort). After chart review to confirm patient eligibility, the actual number of patients who met inclusion/exclusion criteria is 196 (116 in palbociclib plus AI and 80 in AI monotherapy cohorts). Figure 1 shows the patient attrition.

Since the number of patients in the control cohort (AI monotherapy) is less than that in the treatment cohort (palbociclib plus AI), a significant number of patients in the treatment cohort did not have a match in the control cohort. Using a greedy nearest neighbor matching strategy (with caliper 0.1), 64 patients from each cohort were matched. Even when the caliper was extended to 0.2, only 69 patients were matched from each cohort. Therefore, due to the risk of substantial loss of information, the PSM method is not considered appropriate for the primary analysis.

Based on baseline data, following changes were made to the draft SAP CCI [redacted]

1) Perform the primary analysis using IPTW to adjust for imbalance of potential confounding factors between the 2 cohorts.
2) PSM method will be used as a sensitivity analysis.
3) Remove sensitivity analysis 3 (tumor response data imputation for patients who had no tumor assessment data). There were total 20 patients (10% of 196) without any imaging-based tumor assessments; 13 (11.2%) in palbociclib plus AI cohort and 7 (8.8%) in the AI monotherapy cohort. Given the proportion of patients without tumor assessments between the two cohorts are similar, and the total number is relatively low, this sensitivity analysis is removed.
4) Remove sensitivity analysis 4. The subgroup analysis was proposed to estimate rwRR in patients after the initial approval of palbociclib in 2015 in the US. Patients included in this analysis were to have been those who meet inclusion and exclusion criteria during an index period from 01 February 2015 to 30 June 2020.

This sensitivity analysis is removed because of an insufficient number of patients in the control cohort.

5) Propose a new sensitivity analysis 3 to address potential impact of missing values among the 8 selected baseline factors used for PS estimation and further to the primary analysis.
6) Added details to the following items:
    a. Line of therapy
    b. Algorithm for deriving real world responder (rwCR/rwPR)

PS estimation using multivariate logistic regression model was completed. The details on PS generation and PS performance assessments are presented in Appendix 2.

1. INTRODUCTION

Palbociclib is an oral CDK 4/6 inhibitor, approved for the treatment of adult patients with HR-positive, HER2-negative MBC in combination with (1) an AI as initial endocrine-based therapy in postmenopausal women or in men; or (2) fulvestrant in patients with disease progression following endocrine therapy. Since its approval in February 2015, palbociclib has rapidly become a standard-of-care in the treatment of HR-positive, HER2-negative MBC.

Palbociclib was approved in the US based on improved median PFS demonstrated in 3 pivotal clinical trials: PALOMA-1 and PALOMA-2 (initial endocrine-based therapy in combination with letrozole for advanced disease) and PALOMA-3 (in combination with fulvestrant after progression on or after prior endocrine therapy). Of note, pre-/perimenopausal women were not included in the PALOMA-1 or -2 trials investigating palbociclib plus letrozole, therefore palbociclib is not currently approved as first-line treatment for pre-/perimenopausal women with ER-positive, HER2-negative MBC.

While pre-/perimenopausal women were not included in the PALOMA 1/2 studies in combination with an AI for initial endocrine-based therapy for MBC, the PALOMA 3 study did include pre or perimenopausal women. The subgroup of 108/521 (21%) pre or perimenopausal women randomized to palbociclib + fulvestrant + goserelin versus placebo + fulvestrant + goserelin showed a longer median PFS of 9.5 months versus 5.6 months, respectively (HR = 0.50; 95% CI: 0.29, 0.87). [4]

Study 1159 is intended to add to the body of evidence for palbociclib in support of an update to the IBRANCE® USPI to expand the indication for palbociclib to pre-/perimenopausal women with HR-positive, HER2-negative MBC treated with palbociclib plus AI in the first line setting.

2. OVERVIEW OF STUDY 1159

2.1. Study Design

Study 1159 is designed to estimate rwRR in pre-/perimenopausal patients treated with palbociclib plus AI compared to AI monotherapy as first-line therapy for HR-positive, HER2-negative MBC.

This is a retrospective observational cohort study utilizing data derived from the USON's iKM EHR database combined with chart review to estimate the rwRR for each of the 2 treatment cohorts. Patients with HR-positive, HER2-negative MBC who have not received any prior systemic anti-cancer treatment for their advanced disease and initiated palbociclib plus AI or AI monotherapy treatment as first-line therapy during the period on or after 01 January 2010 through 30 June 2020 in the iKM EHR database will be identified and included in the analyses. Structured data fields within the iKM EHR database will be supplemented by additional unstructured data collected through a targeted chart review.

The date of the initiation of palbociclib plus AI or AI monotherapy as the first-line of therapy in the metastatic setting for a patient initiating treatment on or after 01 January 2010 and on or before 30 June 2020 is defined as the index period to identify the eligible patients. Data also include an additional follow up for 6 months from the end of the index period, and it leads to the study cut-off date to 31 December 2020.

LOT will be operationally defined as a course of care that continues until disease progression or unacceptable toxicity. As such, advancement/end in LOT will be assigned if there is a change in regimen (change in combinations of therapies or monotherapies prescribed as a single course of care) documented due to progression or toxicity. The only exception is switching among AIs (exemestane, letrozole, anastrozole) will not constitute a change in LOT, unless the change in AI is due to documented progression.

In the absence of provider-documented intention to prescribe multiple treatments in a combination, treatments started within 60 days of the first agent will be considered a combination regimen. In the case of regimens consisting of multiple treatments, the duration of the regimen will be the start and stop dates of the earliest and latest dates of the individual treatments, respectively.

Real-world tumor responses are assessed based on the treating clinician's assessment of radiological evidence for change in burden of disease over the course of treatment. Assessments were not performed on a schedule and responses were not confirmed by subsequent assessment. Each assessment will be classified as follows:

- **Complete response**: Documented as "a complete response" to therapy; indication patient is in "remission", "all lesions" have disappeared, or "no evidence of disease".
- **Partial response**: Documented as partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease (decrease in disease volume even though disease is still present).
- **Stable disease**: Documented as disease is stable (not progressed or not improved, eg stable appearance of lobe nodules) or mixed response (combination of improved and worsened disease).
- **Progressive disease**: Documented as disease has "progressed", or worsening of disease.
- **Not evaluated**: No documentation of status of disease.

The primary endpoint is rwRR defined as either CR or PR based on all recorded response assessments during first-line therapy captured with chart review, which occurred at least 30 days after therapy initiation.

2.2. Study Population

Patients who are 18 years of age or older and were pre-/perimenopausal at MBC diagnosis, had HR-positive, HER2-negative confirmed and initiated palbociclib plus AI or AI monotherapy as first-line therapy in the metastatic setting during the period from 01 January 2010 through 30 June 2020 will be included in the analyses. Eligible patients

will be identified from structured data fields within the iKM EHR database and unstructured data collected through chart review.

Structured data will be used to screen patients who received treatment within the USON based on the eligibility criteria described in the attrition table below describing the patient attrition based on initial screening.

Study-eligible patients who received first-line AI monotherapy or palbociclib-AI combination therapy will be selected to undergo a targeted chart review. During the course of abstraction, patients' eligibility for the study will be verified and some of these patients may be found to be ineligible. Reasons for disqualification will be captured and reported.

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. At least 18 years old at initial recorded MBC diagnosis.
2. Pre or perimenopausal at MBC diagnosis
3. Diagnosis of MBC at any point in patient history as recorded in the iKM database
   a. Diagnosis of BC will be determined through a review of iKM's discrete diagnosis and histology fields, which are populated during the routine course of care (specifically, the provider will select "breast cancer" from a list of diagnoses; ICD codes will not be used).
   b. Evidence of stage IV or recurrent MBC with a metastatic diagnosis date in the USON iKM EHR, as confirmed by unstructured clinical documents.
      - To identify patients with metastatic disease status, patients must have at least 1 of the following indicators: 1) receipt of a numbered LOT, 2) Stage IV disease, 3) TNM staging with M value of 1, 4) record of location of metastatic disease or 5) current or prior disease status containing reference to metastatic disease.
4. Confirmed HR-positive, HER2-negative status as defined as:
   a. HR-positive: ER-positive or PR-positive test
   b. HER2-negative: any HER2 negative test and the absence of a positive test (IHC positive 3+, FISH positive/amplified, positive NOS)
5. Received 1 of the following regimens as first-line treatment for MBC during the period from 01 January 2010 through index period 30 June 2020 until the data cutoff date of 31 December 2020.
   a. Palbociclib plus AI as first-line treatment for MBC.

   or

   b. Monotherapy AI as first-line treatment for MBC.
6. Received care at a USON site(s) utilizing the full EHR capacities of iKM at the time of treatment.
7. EHR data available from the USON site(s) where the patient received treatment are accessible for research purposes.

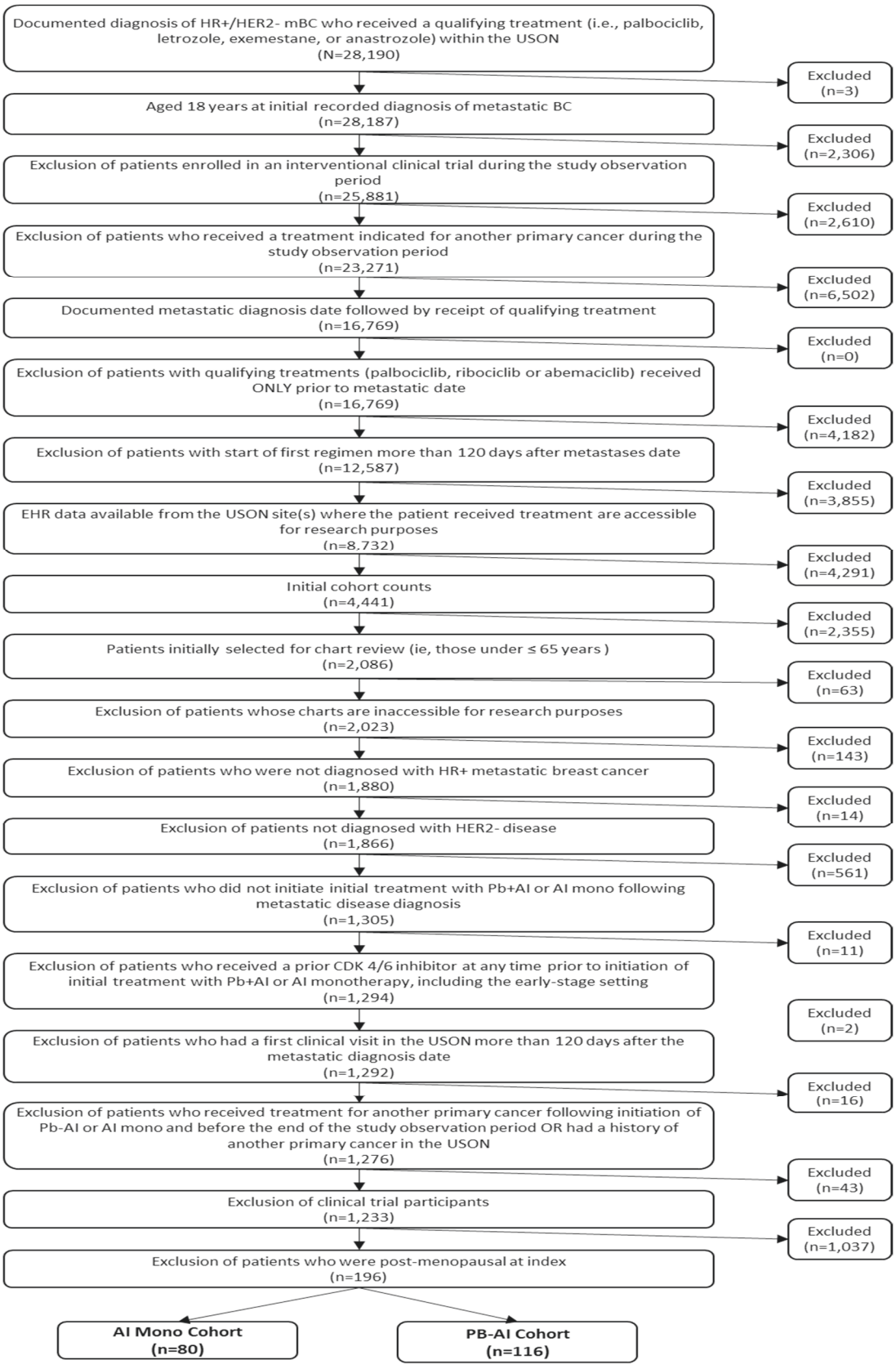
Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Evidence of prior treatment with CDK 4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) in the early BC or MBC setting.
2. First structured activity (clinical visit) greater than 120 days after MBC diagnostic date with chart review to confirm no initial MBC treatment outside USON.
3. Receipt of treatment indicated for another primary cancer during the study observation period (after initiation of palbociclib plus AI or AI monotherapy and before 31 December 2020) or history of another primary cancer within USON.
4. Enrolled in any interventional clinical trial after initiation of palbociclib plus AI or AI monotherapy and before 31 December 2020.

Figure 1 displays the patient attrition flowchart.

Figure 1. Study 1159 Patient Attrition (01 January 2010 - 31 December 2020)



2.3. Data Source

The data source for this retrospective study is the iKM HER database and includes structured and unstructured data (chart review data).

Most study data will originate from the EHR system of the USON, iKM. The USON includes 1380 affiliated physicians operating in over 480 sites of care in the US treating approximately 1.2 million US cancer patients annually. [3] The iKM EHR captures outpatient practice encounter histories for patients under community-based care within the USON, including, but not limited to:

- patient demographics such as age and gender,
- clinical information such as disease diagnosis,
- diagnosis stages,
- performance status information,
- laboratory testing results,
- treatment information such as dosages and treatment administration.

Structured data fields within the iKM EHR database will be supplemented by additional unstructured data collected through chart review.

The variables to be collected from the data sources are listed in Table 2.

For variables that are listed as being sourced from both structured and unstructured fields, chart review is recommended and, in some cases, may be required. Specifically, many of these are variables that are available in structured fields but have been found to be more reliably and comprehensively captured through chart review of unstructured fields. Other variables require information that can only be sourced through chart review (eg, response and progression).

Variables described as being captured at “baseline” will be captured at the date closest to the index date initiation within 90 days. Variables described as being captured with “prior medical history” will be sourced from patients’ entire medical history within the USON prior to index treatment initiation. If multiple values are available during the time period of measurement, either baseline or prior medical history, the one closest (in absolute value) to treatment initiation will be used.

Some data elements will be captured from both iKM and chart review. Since the chart review data are expected to provide a richer source of information, if data are available from both sources for a single patient, then chart review data will supersede what is available in the structured iKM data for the final analysis.

2.4. Treatment/Cohort Labels

Eligible patients who received first-line AI monotherapy or palbociclib-AI combination therapy will be assigned into 2 cohorts and labelled as:

Cohort A: Palbociclib plus AI

Cohort B: AI monotherapy

3. STUDY OBJECTIVES

The primary objective is to estimate the rwRR for pre-/peri-menopausal patients treated with palbociclib plus AI compared to AI monotherapy as first-line therapy for HR-positive, HER2-negative MBC.

4. HYPOTHESES AND DECISION RULES

No formal hypothesis testing will be performed.

5. ANALYSIS SETS/POPULATIONS

It was projected that approximately 300 patients would be included with close to a 1:1 ratio between palbociclib plus AI and AI monotherapy cohorts based on examination of structured iKM data applying inclusion/exclusion criteria between 01 January 2010 and 30 June 2020. The actual total number of eligible patients is 196 post-chart review. Among the 196 patients, 116 were treated with palbociclib plus AI, 80 were treated with AI monotherapy as first-line treatment for HR-positive, HER2-negative MBC.

5.1. Effectiveness Analysis Set

The treatment effect (rwRR) will be analyzed in the following analysis sets.

Full Analysis Set: The full analysis set is the pre-/peri-menopausal patients who were treated with palbociclib plus AI or AI monotherapy as first-line treatment for HR-positive, HER2-negative MBC in the US clinical practice setting from the USON database who meet the inclusion/exclusion criteria of the study protocol.

Analysis set for patients with tumor assessments: This analysis set is a subgroup of patients in the full analysis set who had at least 1 tumor assessment on treatment.

Analysis set generated by PSM for full analysis set: This analysis set is a subgroup of patients generated by PSM from the full analysis set.

Analysis set generated by PSM for patients with tumor assessments: This analysis set is a subgroup of patients generated by PSM for patients who had at least 1 tumor assessment on treatment.

5.2. Safety Analysis Set

The safety analysis set is the same as the full analysis set.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy/Effectiveness Endpoint(s)

The primary endpoint is rwRR defined as the proportion of real-world tumor response consisting of CR or PR based on all recorded response assessments during first-line therapy captured with chart review.

6.2. Safety Endpoints

The number of cases of pneumonitis and ILD which are directly attributable to the treatment which occurred while on first line treatment plus 30 days will be reported for each treatment cohort.

7. HANDLING OF MISSING VALUES

For the purpose of generating the PS, missing information on any baseline characteristic variable will be assigned the category of "Unknown" and be used in the logistic regression model.

For patients who did not have any postbaseline tumor assessment information, the missing rwTR will be assigned as non-responder (Not Evaluated).

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Real World Tumor Response

Real-world tumor response over the course of treatment (specifically, first-line therapy containing palbociclib, AI) in the real-world setting was reported based on clinicians' assessment of changes in disease burden during treatment following radiologic imaging tests performed to evaluate disease burden. Real-world tumor response will be extracted from the EHR as documented as a part of routine clinical care at each real-world response assessment timepoint and categorized as CR, PR, SD, PD, or not evaluated.

The real-world tumor response will be derived for each patient who had at least 1 on-treatment tumor assessment. Patients with a tumor response of CR or PR are those patients with a CR or PR without a PD at any prior assessment. Confirmation of response is not required at a subsequent assessment for the assignment of tumor response of CR or PR. Real-world tumor response rate will be summarized for each treatment cohort.

8.1.2. Algorithm to Derive a Responder

A responder is defined as a patient who had at least 1 documented CR or PR at least 30 days after initiation of palbociclib plus AI or AI monotherapy. In addition, if the patient had documented PD during the course of the treatment, tumor assessments after the PD will be excluded from derivation of responders.

The response rate will be evaluated in the first-line therapy either during the treatment period of palbociclib plus AI in the treated cohort, or during the treatment period of an AI monotherapy in the control cohort.

In this study, the advancement in LOT occurs only when a disease progression or unacceptable toxicity has been documented. It is possible that there is more than 1 regimen in a patient's first-line therapy. In those cases, only the tumor assessments that occurred during treatment with palbociclib plus an AI (treated cohort) or AI monotherapy (control cohort) will be considered for derivation of responders.

8.1.3. Propensity Score (PS)

Because of the lack of randomization in this real world non-interventional study, PS-based analysis will be used to control the potential imbalance in baseline demographic and clinical characteristics between the 2 comparison cohorts in the statistical analyses. [1,2]

The PS is the probability of treatment assignment conditional on observed baseline characteristics. The PS allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the particular characteristics of a randomized controlled trial.

The PS is defined as the probability of receiving the active treatment (Z=1 vs Z=0), conditional on observed baseline covariates (X): $P_i = Pr(Z_i=1 \mid X_i)$ for a participant *i*. It is a balancing score: conditional on the PS, the distribution of measured baseline covariates is expected to be the same between palbociclib plus AI cohort and AI monotherapy cohort.

Similar to randomized clinical trials, PS methods allow one to estimate marginal, rather than conditional measures of treatment effect. The reason for this can be clearly seen for matching, stratification, and weighting: one is comparing average outcomes between samples of cohort A and cohort B subjects who have the same distribution of observed baseline covariates.

Clinically relevant baseline variables associated with treatment assignment and treatment outcome (tumor response) will be selected based on clinical judgement and be used in logistic regression model to estimate PS.

A PS (value from 0 to 1) will be generated using a multivariable binomial logistic regression model with treatment (palbociclib + AI vs AI monotherapy) as dependent variable and selected informative baseline factors as covariates. Once the PS is estimated, it is important to make sure the measured covariates are balanced in order to reduce overt bias. Several methods can be used to assess the balance including:

- **Standardized mean differences of each covariate between treatment groups**. Standardized mean differences could be used to quantify the magnitude of the difference between baseline characteristics of two cohorts. A standardized difference of 0.1 or less will be considered as well balanced between the two cohorts.
- **Graphic of the PS distribution**. The distribution of the PS between the two cohorts should overlap. Nonoverlapping distributions suggest that one or more baseline covariates are strongly predictive of treatment selection.

8.1.4. Propensity Score Matching (PSM)

PSM creates mutually exclusive sets of observations that have similar PSs. Each set has at least 1 treated unit and at least one control unit. The distribution of observed variables will be similar between treated units and control units in the matched sample.

PS will be used for distance measure for the matching. Given the definition of the PS, 2 patients can have different covariates values and still have the same PS. Thus, PSs produce a set of matched pairs with similar distributions of the covariates, but does not require close or exact matches for each individual matched pair of patients.

The use of "caliper" removes the potential for poorly matched patients by setting a maximum acceptable distance for any matched pair. A caliper of 0.1 standard deviations of the linear PS will be used for the study. The matching is done without replacement. The number of treated/control patients allowed in each matched set is 1:1. The greedy nearest neighbor matching strategy is applied.

The standardized mean difference and the variance ratio of matched values for each covariate are the common tools for feasibility assessment.

8.1.5. Inverse Probability of Treatment Weighting (IPTW)

Weighting patients by the inverse probability of treatment received creates a synthetic sample in which treatment assignment is independent of measured baseline covariates. IPTW using the PS allows one to obtain unbiased estimates of average treatment effects. IPTW can be calculated based on the PS for each patient. The weight for the jth patient with PS P_j is:

$W_j = 1 / P_j$ if in the treated group

$W_j = 1 / (1 – P_j)$ if in the control group

Note: P_j is the probability of receiving the active treatment.

When using IPTW, a good practice is to normalize weights and make the sum of the total of weights within one cohort be 1. It can be achieved by dividing each patient's weight by the sum of all weights in that cohort. The nIPTW weight for patient j in a cohort with N patients can be calculated as:

$$W_j^* = W_j \times \frac{N}{\sum_{j=1}^{N} W_j}$$

After normalization, the total number of patients in the weighted population will stay the same as unweighted population.

8.1.6. Imputation of Missing Values for Baseline Covariates in Sensitivity Analyses

Missing values in baseline variables are not uncommon in real world data. Because the PS of a patient is the conditional probability of treatment given all observed covariates, missing data for any covariate can make the PS estimation more challenging. In primary

analysis, missing data are assigned to a new category of "Unknown" when PSs are estimated in multivariate logistic regression model.

To address the potential impact of missing values on PS estimation, and further on the estimation of the primary endpoint rwRR, the proportion and pattern of missing values will be evaluated, and sensitivity analyses may be performed using appropriate imputation methods (e.g. Multiple Imputation method [5]) to impute missing values for variables with missing data.

8.2. Statistical Analyses

The full analysis set is the primary population for estimating the PS, evaluating effectiveness and safety. All data analyses will be executed using statistical software SAS version 9.4 or later.

8.2.1. Estimate PS and Assess Feasibility

The PS will be generated by a logistic regression model using the baseline demographic and disease characteristics in Table 1 as covariates. The final PS will be based on informative variables from the multivariate logistic regression model.

Table 1. Selected Variables for the Estimation of PS

Baseline Characteristics	Value
Race	Black, White, Unknown
BMI (overweight)	Yes (≥25), No (<25), Unknown
Metastatic sites	Bone only, Visceral disease, non-visceral disease
Number of metastatic site(s)	1, 2, 3+
Stage at diagnosis	I, II, III, IV, Unknown
ECOG performance status score	0, 1, 2+, Unknown
Prior neo/adjuvant chemotherapy	Yes, No
Disease-free interval	< 12 months, ≥12 months, De Novo, Unknown

It is important to emphasize that using PS methodology to balance the baseline characteristics between the 2 cohorts will be performed independently of tumor response outcome. To fulfil this requirement, data transfer from USON will be divided into 2 steps:

Step 1: Baseline and disease characteristics will be transferred first to perform balancing using PS analysis and make the PS match, calculate IPTW weights, and generate quintile strata. For each different patient population, the PS will be re-run so that the baseline characteristics are balanced between the 2 cohorts for the analysis.

Step 2: Only after the balancing process is completed for each planned analysis, CCI [redacted] the data containing outcome variables (tumor assessments) will be transferred to Pfizer to perform the analyses for estimating the treatment effect (rwRR).

8.2.2. Primary Analyses of rwRR

The primary endpoint is rwRR, which is defined as the proportion of real-world tumor response of CR or PR based on response assessments captured with chart review during first line therapy.

The primary analysis is to estimate the rwRR between the 2 cohorts (palbociclib plus AI vs AI monotherapy) using the IPTW method to adjust for the potential imbalance of the eight baseline demographic and clinical characteristics (Section 8.2.1) between the 2 treatment cohorts.

The rwRR will be estimated for each treatment cohort and compared for patients in the analysis set adjusted by nIPTW.

- The number and percentage of patients with a best response of CR, PR, SD, PD, and NE will be tabulated.
- A weighted proportion of patients based on nIPTW achieving rwRR (CR or PR) will be summarized along with the corresponding exact 2-sided 95% CI calculated using a method based on Wilson score method.
- Odds ratio for rwRR with the corresponding 2-sided 95% CIs will be calculated based on weighted rwRR using the CMH method.

Analyses using nIPTW method will be performed in the following 2 analysis sets. PS will be re-estimated for each analysis set.

1. Full analysis set. Patients who had no tumor assessments documented on treatment will be considered as non-responders in the assessment of rwRR.
2. Analysis set for patients with at least one tumor assessment.

8.2.3. Sensitivity Analyses of rwRR

Sensitivity analysis will be performed to examine the robustness of the primary analysis.

Sensitivity analysis 1: PSM

Unlike IPTW method in which all patients were included in the analysis, PSM method generates a paired subset of patients based on each patient's PS (Section 8.1.4). In this analysis, rwRR will be estimated in the subset of patients who are 1:1 matched in the 2 cohorts.

- Similar to the primary analysis: The proportion of patients with real-world tumor response (CR or PR) will be summarized along with the corresponding exact 2-sided 95% CI calculated using a method based on Wilson score method.
- Odds ratio for rwRR will be calculated with the corresponding 2-sided 95% CI.

Sensitivity analysis 2: Stratification by PS.

This analysis will divide patients into 5 equal-sized groups using quintiles of the estimated PS. The treatment effect of rwRR (odds ratio) will be estimated using the CMH method stratified by PS quintiles.

Sensitivity analysis 3: Missing value imputation for selected baseline covariates.

This sensitivity analysis is to evaluate the impact of missing values of the eight selected baseline covariates on PS estimation and further on the estimation of the primary endpoint (rwRR). Multiple imputation or other data imputation methods may be explored when appropriate.

8.2.4. Other Analyses

Descriptive analyses:

- For categorical variables (eg, region, race, and stage at initial diagnosis), data will include the frequency (number of cases) and percentage of total patients observed in each category;
- For continuous variables (eg, age and time from initial breast cancer diagnosis to metastatic diagnosis), variables will be presented as the mean, standard deviation, median, 25th and 75th percentiles and ranges (minimum and maximum) in some cases.

The calculation of percentages will always include the missing category in the case of missing values. Continuous variables may be categorized into intervals, with the distribution of patients (N, %) provided.

9. REFERENCES

1. Austin, P. C., and Stuart, E. A. (2015a). "Moving towards Best Practice When Using Inverse Probability of Treatment Weighting (IPTW) Using the Propensity Score to Estimate Causal Treatment Effects in Observational Studies. "Statistics in Medicine 34:3661–3679.
2. Austin, P. C., and Stuart, E. A. (2015b). "The Performance of Inverse Probability of Treatment Weighting and Full Matching on the Propensity Score in the Presence of Model Misspecification When Estimating the Effect of Treatment on Survival Outcomes." Statistical Methods in Medical Research 26:1654–1670.
3. The US Oncology Network. https://www.usoncology.com/our-company. Accessed 23 September 2021.
4. Loibl S, Turner NC, Ro J, et al. Palbociclib combined with fulvestrant in premenopausal women with advanced breast cancer and prior progression on endocrine therapy: PALOMA-3 Results. Oncologist 2017;22(9):1028-38.
5. Rubin DB. Multiple imputations in sample surveys - a phenomenological Bayesian approach to nonresponse. Imputation and Editing of Faulty or Missing Survey Data, U.S. Department of Commerce, Washington D.C., 1-22. Proceedings of the Section on Survey Research Methods, American Statistical Association, 1978. Retrieved from: 1978: MULTIPLE IMPUTATIONS IN SAMPLE SURVEYS - A PHENOMENOLOGICAL BAYESIAN APPROACH TO NONRESPONSE (asasrms.org).

10. APPENDICES

Appendix 1. Data Variables to be Collected (Table 2)

Appendix 2. PS generation and PS Performance Assessments

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
Demographic and patient characteristics			
Hormone receptor status	iKM structured data + chart review	Prior medical history	Patients who have a documented hormone receptor-positive status, either estrogen and/or progesterone, will be included in the study. Categories: ER positive only PR positive only ER and PR positive
Human epidermal growth factor receptor 2-negative status	iKM structured data + chart review	Prior medical history	Patients who have a documented human epidermal growth factor receptor 2-negative status will be included in the study. Documentation of human epidermal growth factor receptor 2 will be captured as recorded in the iKM EHR database.
Sex	iKM structured data + chart review	Prior medical history	Patients will be categorized as: Male Female No information For patients lacking a documented menopausal status, sex assigned at birth will be verified through chart review.
Age	iKM structured data (derived)	Baseline	Patient's age (in years) at the date of diagnosis, which will be calculated as the integer of [(diagnosis date – date of birth + 1) / 365.25].
Age groups	iKM structured data (derived)	Baseline	Multiple age categories will be created based on the continuous age data: <30 ≥30-45 ≥45 No information
Race	iKM structured data	Prior medical history	Categorized as: White/Caucasian Black/African American Other No information
Height	iKM structured data	Baseline	Patient's height in meters.
Weight	iKM structured data	Baseline	Patient's weight in kilograms.
BMI at index date	iKM structured data (derived)	Baseline	BMI value as calculated from height and weight values will be provided.

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
Smoking history	iKM structured data	Baseline	Categorized as: Never smoked Current smoker Former smoker No information
Family history of cancer	iKM structured data + chart review	Prior to medical history	Categorized as: Yes No information
Menopausal status	iKM structured data + chart review	Baseline	Menopausal status will be first categorized as explicitly documented by physician as: Pre-menopausal Peri-menopausal Among patients lacking a physician-documented menopausal status record, pre-menopausal status will be assigned to those whose sex assigned at birth is female, who are aged less than 60 years and meet either of the following criteria: • No documented history of a prior bilateral oophorectomy • and received an LHRH analog AND/OR • Not amenorrhoeic
Healthcare setting and provider characteristics			
Practice location	iKM structured data (derived)	Baseline	The US census region of the USON clinic where the patient received care at the index visit: **Midwest**: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota and South Dakota **Northeast**: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Pennsylvania, New Jersey and New York **South**: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma and Texas **West**: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, California, Oregon and Washington State Missing clinic values will be captured in a "no information" category. Some of the regions may need to be collapsed if there are small sample sizes (eg, South versus non-South). This determination will be confirmed after reviewing sample sizes and the added value to the study with McKesson's Privacy and Compliance team.

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
[redacted]	[redacted]	[redacted]	CCI [redacted]
Practice size	iKM structured data (derived)	01 Jan 2018 – 31 Dec 2018	The number of patients seen at the USON clinic where the patient receive care for his/her index visit in the year 2018: <50 patients/ year 50-99 patients/year 100-149 patients/year ≥150 patients/year
Physician BC patient volume	iKM structured data (derived)	01 Jan 2018 – 31 Dec 2018	The number of BC patients seen by the physician who provided care for the patient's index visit in the year 2018: <10 patients/ year 11-49 patients/year >50 patients/year
Disease characteristics			
Time since initial BC diagnosis	iKM structured data + chart review (derived)	Medical history prior to index	The duration of time, in weeks, between the date of BC diagnosis and presentation of metastatic disease. To assess BC diagnoses that occurred prior to index, patients' available medical history in iKM will searched. The completeness of this history will vary based on the length of disease and the time within the USON. Records may also be incomplete for patients with an initial BC diagnosis that occurred outside of the USON. Diagnosis of BC will be determined through a review of iKM's discrete diagnosis and histology fields, which are populated during the routine course of care (International Classification of Diseases [ICD] codes will not be used). If no initial diagnosis date is documented, the first recorded diagnosis date in iKM will be used. This date will be used in calculations, not reported separately.
Time since MBC diagnosis	iKM structured data + chart review (derived)	Medical history prior to index	The duration of time, in weeks, between the index date and presentation of metastatic disease. Date of first recorded diagnosis of metastatic disease within the EHR. Patients will be qualified initially based on the date identified in the structured data; this will be confirmed during chart review among patients selected for chart review. Ultimately, the primary source will be the chart if available. Patients without recorded evidence of metastatic disease will be excluded from the study. Structured data will confirm the patient as metastatic and as available, indicate the earliest associated date of any of these criteria: 1) Stage IV disease

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
			2) Tumor, Node, Metastasis (TNM) stage with M value of 1 3) Record of location of metastatic disease 4) Current or prior disease status containing reference to metastatic disease
Distant metastatic site(s)	iKM structured data + chart review	Medical history prior to index	Baseline metastatic location(s) will be captured as documented in patients' charts. Note, patients that lack documented metastatic sites can indicate that metastases were not documented in the chart, not necessarily that patients did not have metastases.
Visceral/non-visceral status Bone only	iKM structured data + chart review (derived)	Medical history prior to index	Categorized as outlined below (not mutually exclusive) except for bone only, in which patients will have bone as their only metastatic site(s) identified: **Visceral**: Liver Lung Pleura **Other (not exhaustive)**: Adrenal gland Ascites Axilla Bilateral intraocular Brain Breast Bronchus Cervical nodes Cervix Chest wall Duodenum, retroperitoneum & mesentery Esophagus Eye Fallopian tube Gallbladder Gastrointestinal tract/stomach Genital organ Intestinal tract Kidney Large intestine Leptomeningeal Leptomeninges Lymph nodes – distant

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
			Lymph nodes – NOS Lymph nodes – regional Mediastinum Muscle Omentum Other parts of nervous system Other respiratory organ Other urinary organ Ovary Pancreas Pericardial effusion Pericardium Peritoneum Pleural effusion Rectum Retroperitoneum Skin Small intestine Soft tissue Spinal cord Spleen **Bone (not exhaustive):** Bone Bone marrow Pelvis Ribs Skull Spine
Count of metastatic site(s)	iKM structured data + chart review (derived)	Baseline	The total count of metastatic site(s) at index: No information 1 2 3 4+ Note, “no information” can indicate that metastases were not documented in the chart, not necessarily that patients did not have metastases.

Table 2. Study A5481159 Key Variables

<table>
<tr><th>Variable</th><th>Source(s)</th><th>Period of Measurement</th><th>Operational Definition</th></tr>
<tr><td>Stage at diagnosis</td><td>iKM structured data</td><td>Medical history prior to index</td><td>Categorized as:
Stage 0
Stage IA
Stage IB
Stage IIA
Stage IIB
Stage IIIA
Stage IIIB
Stage IIIC
Stage IV
No information</td></tr>
<tr><td>Eastern Cooperative Oncology Group (ECOG) performance status</td><td>iKM structured data + chart review</td><td>Baseline</td><td>The ECOG performance status score is a rating of a patient’s disease status, daily living activities and quality of life, with low scores indicating greater functioning than high scores:
0
1
0/1
2
2+
3+
No information
Karnofsky performance status is a similar measure and will be converted to ECOG using the methodology outlined below.
<table>
<tr><th>Karnofsky Performance Status</th><th>ECOG Performance Status</th><th>ECOG Performance Status Description</th></tr>
<tr><td>100</td><td>0</td><td>Fully active</td></tr>
<tr><td>80, 90</td><td>1</td><td>Restricted in physically strenuous activity</td></tr>
<tr><td>60, 70</td><td>2</td><td>Ambulatory and capable of self-care but unable to work</td></tr>
<tr><td>40, 50</td><td>3</td><td>Capable only of limited self-care</td></tr>
<tr><td>10, 20, 30</td><td>4</td><td>Completely disabled</td></tr>
<tr><td>0</td><td>5</td><td>Dead</td></tr>
</table></td></tr>
</table>

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
CCI (Charlson Comorbidity Index) score	Chart review	Prior medical history	Calculated based on the presence of 17 Charlson comorbidities at MBC diagnosis. Comorbidities and associated obfuscated dates documented prior to or on the index date will be captured and summarized as: Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hemiplegia or paraplegia, chronic pulmonary disease, peptic ulcer disease, diabetes with chronic complications, diabetes without chronic complications, renal disease, rheumatologic disease, dementia, mild liver disease, moderate or severe liver disease, any malignancy including leukemia and lymphoma, metastatic solid tumor, HIV/AIDS. In addition, history of interstitial lung disease (ILD) and pneumonitis will be noted but not included in the CCI score. Two approaches will be used to capture comorbidities documented in patients' medical records. First, comorbidities explicitly documented by providers will be captured and reported. Separately, patients with suspected comorbidities based on receipt of medications associated with those conditions will be identified. To identify suspected comorbidities, an extract of all concomitant meds documented pre-index for the study population cohorts will be generated with patients' entire treatment history documented in the structured data. The study team, including clinical experts and the Physician Investigator, will review the frequency distributions of the medications and map these to chronic conditions. For analysis purposes, comorbidities explicitly documented by providers versus those imputed by medication use will be differentiated.
Disease histology	iKM structured data	***Prior medical history***	Categorized as: Ductal Lobular Mixed Metaplastic Tubular Mucinous Other No information
BRCA 1/2 status	iKM structured data + chart review	***Prior medical history***	Categorized as: Positive Negative No information
ESR1 status	iKM structured data + chart review	***Prior medical history***	Categorized as: Positive Negative

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
			No information
NGS status	iKM structured data + chart review	***Prior medical history***	Categorized as: Positive Negative No information
Treatment characteristics			
Pre-index treatment(s)	iKM structured data + chart review	Medical history prior to index	Patients' treatments received prior to index, along with obfuscated dates. This includes prior adjuvant hormonal treatment or prior neo-adjuvant/adjuvant chemotherapy.
Adjuvant treatment end dates	iKM structured data + chart review	Medical history prior to index	Obfuscated date of adjuvant treatment discontinuation.
Endocrine sensitivity	iKM structured data + chart review (derived)	Medical history prior to index	Relapse more than 12 months after completing adjuvant endocrine therapy
Disease-free interval	iKM structured data + chart review (derived)	Medical history prior to index	Obfuscated dates between discontinuation of adjuvant therapy and the start of treatment for unresectable and/or metastatic disease.
Radiotherapy	iKM structured data + chart review	Medical history prior to index and study observation period	All radiotherapy, along with obfuscated dates, received prior to or during the study observation period will be captured. During analysis, 2 variables will be constructed: "Concomitant radiotherapy" will be defined as radiotherapies given during 1L treatment "Prior radiotherapy" will be defined as all radiotherapies prior to index date
Index treatment regimen	iKM structured data + chart review	Study observation period	Patients' index treatment will be categorized based on the cohort descriptions in Protocol Section 9.1: Palbociclib combination therapy with an AI (letrozole, exemestane or anastrozole) or AI monotherapy
Date of treatment initiation during the patient identification period (ie, index date)	iKM structured data + chart review	Study observation period	The obfuscated date of initiation with a palbociclib-based combination regimen or AI monotherapy (letrozole, exemestane or anastrozole) during the study identification period. If a regimen consists of more than one drug with drugs given on different dates, the date of the first administration of any drug will be used.
Index treatment end date(s)	iKM structured data + chart review	Study observation period	Obfuscated date of final treatment for each drug or regimen. If a regimen consists of more than one drug with drugs ending on different dates, the date of the last administration of any drug will be used. It is possible that the patient's treatment stop date is not documented if the patient dies, is lost-to follow-up or is still on-therapy. The final treatment date, death date or end of study date will be used, whichever is earliest.
Index line of therapy (LOT)	iKM structured data	Study observation period	LOT will be operationally defined as a course of care that continues until disease progression or unacceptable toxicity. As such, advancement in LOT will be assigned if there is a change in regimen due to documented progression. The only exception is switching between AIs (exemestane, letrozole, anastrozole) will not constitute a change in LOT, unless the change in AI is due to documented progression.

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
Number of cycles (index treatment)	iKM structured data	Study observation period	The number of provider-documented therapy cycles received for the index treatment.
Index treatment schedule (cycle length and frequency)	iKM structured data + chart review	Study observation period	The planned frequency and cycle length of the index treatment.
Index treatment schedule changes	iKM structured data + chart review	Study observation period	Each index treatment (either AI monotherapy or palbociclib combination therapy) schedule change will be captured and reported, along with the obfuscated date.
Index palbociclib treatment starting dose	iKM structured data + chart review	Study observation period	The actual index treatment starting palbociclib dosage received. Categories to be presented: 75 mg 100 mg 125 mg Other No information
Palbociclib combination regimen	iKM structured data + chart review	Study observation period	Classification of patients into the following treatment groups: Palbociclib-letrozole Palbociclib-anastrozole Palbociclib-exemestane
Reason for palbociclib dose changes	Chart review	Study observation period	Data for palbociclib dose change reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason patients discontinued treatment will be abstracted: Lack of response Patient preference Toxicity Other No information Reviewers will specify other reasons; these will be reported if any represent >5% of patients.
Reason for treatment discontinuation (all treatment lines)	Chart review	Study observation period	Data for discontinuation reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason patients discontinued treatment will be abstracted: Provider-documented disease progression Toxicity Decline in performance status Financial/insurance

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
			Completed planned treatment Death Hospice Patient preference Physician preference Other No information Reviewers will specify other reasons.
Reason for treatment initiation (all treatment lines)	Chart review	Study observation period	Data for treatment initiation reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason for treatment initiation will be abstracted: Initial diagnosis Initial diagnosis with unresectable disease Initial diagnosis with metastatic disease Progressive disease Other reasons; non-progression Toxicity on prior therapy Reason not specified Reviewers will specify other reasons.
Post-index treatment(s)	iKM structured data + chart review	Study observation period	Patients' treatments received after index, along with obfuscated dates.
Provider-documented tumor assessments			
Provider-documented tumor assessment	Chart review	Study observation period	In prospective clinical trials, response is generally assessed according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria. However, the parameters underlying these criteria are less reliably available in retrospective, observational studies. Instead, for this study, provider documented assessments of tumor response will be used. No attempts will be made to mimic the RECIST guidelines. Response assessments documented for the index treatment (depending on cohort). It is possible that patients have multiple response assessments in their charts during this period. All documented responses to the index treatment (AI monotherapy or palbociclib combination therapy) described within progress notes (along with the associated, obfuscated progress note date) will be captured. For each tumor assessment, it will be documented if a scan report was documented as the basis of the assessment. Tumor assessments will be classified as: **Complete response**: Documented as "a complete response" to therapy; indication patient is in "remission"; "all lesions" have disappeared or "no evidence of disease").

Table 2. Study A5481159 Key Variables

Variable	Source(s)	Period of Measurement	Operational Definition
			Partial response: Documented as partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease (decrease in disease volume even though disease is still present). **Stable disease**: Documented as disease is stable (not progressed or not improved; e.g. Stable appearance of lobe nodules and Mixed response: Combination of improved and worsened disease. **Progressive disease**: Documented as disease has "progressed"; or worsening of disease. Not evaluated: No documentation of status of disease.
Clinical outcomes			
Last USON visit date	Chart review	Study observation period	Patients' last visit date will be captured through chart review as a verified physical encounter with the practice as evidenced by treatment administration, measurement of vital signs, laboratory specimen collection or other office procedures. For patients with a death date, this last visit date should occur prior to the death date.
Death date	iKM structured data + LADMF/NDI + chart review	Study observation period	Obfuscated date of death will be captured from the LADMF, NDI as well as iKM. If dates conflict between the 3 sources, the NDI, followed by the LADMF date will be prioritized. If severe data discordance is observed (i.e., death is reported to occur prior to the index date and/or there is a difference of more than 6 months between them), then the iKM death date, as verified through chart review, will be used.
Pneumonitis and interstitial lung disease	Chart review	Study observations period	Explicit attribution to treatment within chart will be documented. Yes/No

Source: Study A5481159 protocol section 9.3 Table 1.

Document Approval Record

Document Name:	Oct 2021 SAP RWE A5481159 Non-Interventional Study Statistical Analysis Plan v1.0
Document Title:	Oct 2021 SAP RWE A5481159 Non-Interventional Study Statistical Analysis Plan v1.0

Signed By:	Date(GMT)	Signing Capacity
PPD	04-Oct-2021 15:32:37	Final Approval