NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	Real-World Treatment Effectiveness of Palbociclib in Combination With An Aromatase Inhibitor as First-Line Therapy in Post-Menopausal Women and Men With Metastatic Breast Cancer
Protocol number	A5481161
Version identifier of the final study report	Version 1.0
Date	31 January 2023
EU Post Authorization Study (PAS) register number	EUPAS41803
Active substance	Palbociclib (PD-0332991)
Medicinal product	IBRANCE® (Palbociclib; PD-0332991)
Research question and objectives	**Primary objective** • To compare OS in post-menopausal women and men treated with palbociclib + AI versus AI alone as first-line therapy for HR+/HER2- MBC **Secondary objectives** • To estimate rwPFS and rwRR in post-menopausal women and men treated with palbociclib + AI versus AI alone as first-line therapy for

	HR+/HER2- MBC during first-line treatment
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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
ATE	average treatment effect
AI	aromatase inhibitor
BC	breast cancer
BMI	body mass index
CCI	Charlson Comorbidity Index
CDK	cyclin-dependent kinase
CDS	Chronic Disease Score
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CR	complete response
EBC	early breast cancer
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EHR	electronic health record
ER	estrogen receptor
ET	endocrine therapy
FAS	full analysis set
[redacted]	[redacted]
FISH	fluorescence in situ hybridization

GPP	Good Pharmacoepidemiology Practices
HER2-	human epidermal growth factor receptor 2 negative
HR+	hormone receptor positive
ICD	International Classification of Diseases / Informed Consent Document
IEC	Independent Ethics Committee
iKM	iKnowMed
ILD	interstitial lung disease
IPTW	inverse probability of treatment weighting
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	the International Society for Pharmacoeconomics and Outcomes Research
ITT	intention -to-treat
LADMF	Limited Access Master Death File
LOT	line of therapy
MBC	metastatic breast cancer
MI	multiple imputation
NDI	National Death Index
NE	not evaluable
nIPTW	normalized inverse probability of treatment weighting
NOS	not otherwise specified
ORR	overall response rate
OS	overall survival

PACL	protocol administrative change letter
PALOMA	**PAL**bociclib **O**ngoing Trials in the **MA**nagement of Breast Cancer
PASS	Post-Authorization Safety Study
PD	progressive disease
PFS	progression free survival
PR	Partial response
PS	propensity score
PSM	propensity score matching
QA	quality assurance
QC	quality control
RCT	randomized clinical trial
RPSFT	rank preserving structural failure time
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 / standard deviation
SMD	standardized mean difference
US	the United States
USON	The US Oncology Network
TNM	Tumor, Node, Metastasis

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]*

* Ontada is an oncology technology and insights business launched by McKesson.

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
[redacted]	[redacted]

* Ontada is an oncology technology and insights business launched by McKesson.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection Part 1 Data Transfer - final baseline data	3Q2021	14 Feb 2022	
SAP (including PS estimation and feasibility assessment)	4Q2021	09 May 2022	
End of data collection Part 2 Data Transfer - final outcome data	2/3Q2022	10 May 2022	
Registration in the EU PAS register	3Q2021	02 July 2021	
Final study report	4Q2022	31 January 2023	

Note: Planned dates were based on Appendix 2, Protocol Section 6.

6. RATIONALE AND BACKGROUND

There are more than 3.5 million women living with a history of BC in the US including women who are still being treated.[1] In 2017, it was estimated that 154,794 American women were living with metastatic BC in the US; of these, 3 out of 4 progressed from an early stage BC.[1] MBC remains an incurable disease with 5-year survival rates of 27%.[2] The goal of treatment for MBC is to prolong the time to disease progression or extend life to the extent possible or improve/maintain quality of life of that survival.[3]

Palbociclib, an oral (cyclin-dependent kinase) CDK 4/6 inhibitor, is approved for HR+/HER2- advanced or MBC in combination with an AI or fulvestrant. 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). An accelerated approval was first granted based on the results from the Phase 2 PALOMA-1 trial[4] in February 2015. The Phase 3 PALOMA-2 study confirmed the findings from the PALOMA-1 trial, demonstrating statistically significant improvement in median PFS in the palbociclib + letrozole arm of 27.6 months compared to 14.5 months in the placebo + letrozole arm (HR of 0.563 [95% CI: 0.461–0.687]; 1-sided $p < 0.0001$).[5] The secondary endpoint of OS for PALOMA-1 showed an HR of 0.897 (95% CI: 0.623, 1.294) with 1-sided p=0.281.[6] The OS results for PALOMA-2 detected a HR of 0.956 (95% CI: 0.777, 1.177); 1-sided p=0.3378)[7].

The safety profile from the PALOMA-1, -2 and -3 trials were consistent, with no new safety signals identified across the Phase 3 studies. Long-term pooled safety analyses of the 3 randomized Phase 2 and 3 studies demonstrated no evidence of specific cumulative or delayed toxicities with palbociclib + endocrine therapy.[8]

Understanding the effectiveness of new treatments in the general population affected by the disease can supplement RCT data and aid in clinical decision making in routine clinical practice.[9]

Refer to Appendix 2, Protocol Section 7 for further information regarding the background supporting the rationale for this study.

This non-interventional study was designated as a PASS and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

This study aimed to assess real-world effectiveness in post-menopausal women and men with HR+/HER2- MBC initiating palbociclib + AI or AI alone as first-line therapy during the index period from 01 February 2015 through 30 June 2020 with additional follow-up until the study data cutoff date of 31 August 2021.

Primary Objective

- To compare OS in post-menopausal women and men treated with palbociclib + AI versus AI alone as first-line therapy for HR+/HER2- MBC

Secondary Objective

- To estimate rwPFS and rwRR in post-menopausal women and men treated with palbociclib + AI versus AI alone as first-line therapy for HR+/HER2 - MBC during first-line treatment.

8. AMENDMENTS AND UPDATES

There were no protocol amendments issued for this study.

Three PACLs were issued during the study. The edits described were clarifications of the protocol that did not impact the safety of patients, the scope of the study, or the scientific quality of the study, and therefore did not qualify as a protocol amendment.

PACL dated 29 Jun 2021	• EU PAS study was registered
PACL dated 14 Sep 2021	• The data-cutoff was extended from 31 May 2021 to 31 August 2021. • In Table 1, Key Variables, the operational definition for physician BC patient was clarified.
PACL dated 12 May 2022	• In Table 1, Key Variables, the operational definitions for practice size and provider-documented tumor assessment were clarified

9. RESEARCH METHODS

The final protocol specifying the study methods is found in Appendix 2, with further details in the SAP found in Appendix 4.

9.1. Study Design

Study 1161 is a retrospective observational cohort study utilizing data sourced from the USON's iKM EHR to compare outcomes for women and men treated with palbociclib + AI or AI alone as first-line treatment for HR+/HER2- MBC. Post-menopausal women and men with HR+/HER2- MBC meeting the inclusion and exclusion criteria were included and analyses were conducted utilizing secondary deidentified data from the USON's iKM EHR in the US. Structured data fields within the iKM EHR database were supplemented by additional unstructured data collected through a targeted chart review and external sources for death data.

Key study design elements are presented in Table 1.

Table 1. Study Design

Protocol Component	Description
Eligibility Criteria	Post-menopausal women and men with HR+/HER2- MBC who had not received prior systemic treatment for their MBC and initiating therapy during the period of 01 February 2015 through 30 June 2020 registered in the USON
Treatment Cohort	Palbociclib + AI versus AI alone as the first-line MBC treatment
Assignment Procedures	Patients were assigned to either cohort at baseline according to their observed first-line MBC treatment received
Observation Period	Began at their start date of the first-line MBC treatment during the period on or after 01 February 2015 through 30 June 2020 to study end (additional follow-up until the study data cutoff date of 31 August 2021). The index date was the start date of first-line MBC treatment.
Primary Endpoint	OS
Intercurrent Event	OS outcome was used regardless of the occurrence of intercurrent events (concomitant or subsequent treatments)
Analysis Plan	An IPTW approach was used to compare palbociclib + AI versus AI alone for the ATE on the primary endpoint OS. A weighted log-rank test with the robust variance estimation was used for the hypothesis testing with the significance level at 1-sided 0.025. HR for OS with the corresponding 2-sided 95% CI was calculated based on a weighted Cox's proportional hazard model. Sensitivity analyses were performed to explore the robustness of the primary analysis results for OS.

Source: Appendix 2, Protocol Section 9.1 and Appendix 4, SAP Section 2.1.

In the absence of provider-documented intention to prescribe multiple treatments in a combination, treatment started within 60 days of the first agent was to be considered a combination regimen. LOT were operationally defined as a course of care that continued until disease progression or unacceptable toxicity. As such, advancement/end in LOT were assigned if there was 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 was switching among AIs (exemestane, letrozole, anastrozole) did not constitute a change in LOT, unless the change in AI was due to documented progression.

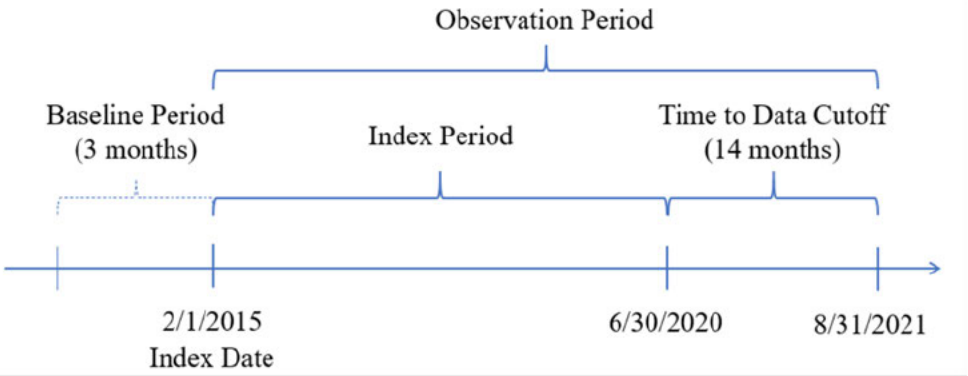
9.2. Setting

This study used secondary deidentified EHR data that involve patients who have been diagnosed with HR+/HER2- MBC and received treatment within the USON. The USON

includes 1200 affiliated physicians operating in over 470 sites of care in the US and treats approximately 1 million US cancer patients annually.[10]

The date of initiation of palbociclib + AI or AI alone as first-line therapy for a patient initiating treatment on or after 01 February 2015 and on or before 30 June 2020 is defined as the index period to identify eligible patients. Data included additional follow-up until the study data cutoff date of 31 August 2021 (Figure 1).

Figure 1. Study Flowchart



a. For illustration purposes, the calendar axis may have not been proportional to scale.
b. Some variables (eg, comorbidities) may have had an extended baseline period (any time prior to index date).
Source: Appendix 4, SAP Section 2.1.

9.3. Subjects

9.3.1. Inclusion Criteria

Patients were required to meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. At least 18 years old at initial recorded MBC diagnosis.
2. Post-menopausal women and men with an MBC diagnosis (see Appendix 2, Protocol Table 1 for definition).
3. Diagnosis of MBC at any point in patient history as recorded in the USON EHR iKM database.
    a. Diagnosis of BC were determined through a review of iKM's discrete diagnosis and histology fields, which were populated during the routine course of care (specifically, the provider selected "breast cancer" from a list of diagnosis; ICD codes were not used).

b. Evidence of a metastatic diagnosis date in the USON iKM EHR, as confirmed by unstructured clinical documents.

i. To initially identify patients with metastatic disease status, using structured data, 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. Subsequent chart review confirmed documentation of metastatic disease.

4. Confirmed HR+/HER2- status as defined as

a. HR+: ER+ or PR+ test.

b. HER2-: any HER2 negative test and the absence of a positive test (immunohistochemistry 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 February 2015 through index treatment period 30 June 2020.

- Palbociclib + AI as first-line treatment for MBC.

or

- 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.

EHR data available from the USON site(s) where the patient received treatment were accessible for research purposes.

9.3.2. Exclusion Criteria

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

1. Evidence of prior treatment with any CDK 4/6 inhibitors (including palbociclib, ribociclib or abemaciclib) in the EBC or MBC setting.

2. First structured activity (clinical visit) greater than 120 days after MBC diagnostic date with subsequent chart review to also confirm no initial MBC treatment outside USON.

3. Receipt of treatment indicated for another primary cancer during the study observation period or history of another primary cancer within the USON iKM EHR database.

4. Enrolled in any interventional clinical trials during study observation period (post initiation of treatment after 01 February 2015 and before 31 August 2021).

9.4. Variables

All variables were assessed using the operational definitions shown in Appendix 2, Protocol Table 1. Most data originated from 1 of 2 sources: the iKM EHR database (structured data) or chart review (unstructured data), although some variables may have been derived from these raw data sources (eg, age from date of birth). Derived and transformed data needed for the analysis are described and presented along with the operational definitions in Appendix 2, Protocol Table 1. Supplemental vitality status was sourced from other databases, including the NDI and LADMF, and a commercial death database hosted by Datavant.[11]

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

Variables described as being captured at "baseline" were captured within 90 days prior to the index date. Exceptions included variables described as being captured with "prior medical history" were sourced from patients' entire medical history within the USON prior to index treatment initiation. If multiple values were available during the time period of measurement, either baseline or prior medical history, the 1 closest (in absolute value) to treatment initiation was used.

Some data elements were captured from both iKM and chart review. Although the chart review data were expected to provide a richer source of information, if data were available from both sources for a single patient, then chart review data were superseded by what was available in the structured iKM data for the final analysis. Refer to Section 9.10 further details on quality control.

As this study was expected to obtain an exception and waiver of informed consent from the US Oncology IRB, a deidentified dataset was used for analysis. To comply with applicable data regulations and to reduce the risk of patient reidentification, the deidentified dataset was certified through an expert determination process before it was transferred to Pfizer. This expert determination was performed by an experienced professional with appropriate statistical and scientific training. During the process, this individual confirmed which data elements can be transferred in the deidentified dataset. Some of the variables anticipated in the protocol were modified based on guidance received during expert determination, including the granularity of dates, race categories and geographic location.

9.5. Data Sources and Measurement

Appendix 2, Protocol Table 1 represents the data elements that were evaluated through this study and their associated source.

The data source for this retrospective real-world study was the iKM EHR database and included structured and unstructured data (chart review). Most study data originated from the EHR system of the USON, iKM. The USON included >1200 affiliated physicians operating in >470 sites of care in the US treating approximately 1.2 million US cancer patients annually[12]. The iKM EHR captured 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, and laboratory testing results;
- Treatment information such as dosages and treatment administration.

Structured data fields within the iKM EHR database were supplemented by additional unstructured data collected through chart review (see Section 9.4). Electronic chart review data were collected by means of a secure, web-based eCRF by healthcare professionals with oncology experience.

Study 1161 only used data from USON practices utilizing full EHR capacities of iKM. Data management and administrative processing were supported by McKesson's QA procedures.

Additionally, iKM has previously been used to evaluate patient profiles, treatment patterns and outcomes among MBC patients and the results have been consistent with other published studies.[13,14,15,16]

Death information were sourced from structured and unstructured records of death in the iKM EHR database. Also, external Governmental sources were utilized consisting of the LADMF of the Social Security Administration and the NDI of the Centers for Disease Control were additional sources of vital status (death). McKesson had certification to access the LADMF of the Social Security Administration. Lastly, the commercial Datavant mortality dataset, a database of publicly-available death records (ie, obituaries) were utilized. If there was discrepancy in date of death among the above sources the following hierarchy were used to select the date of death prioritizing governmental data sources: 1. NDI, 2. LADMF, 3. EHR, 4. Datavant.

Details on additional data sources, including death information with multiple data sources, are discussed in Appendix 2, Protocol Section 9.4 and Appendix 4, SAP Section 2.1.3.

9.6. Bias

Potential sources of bias and efforts to access and address the bias are discussed in Section 11.2.

9.7. Study Size

The primary objective of this study was to demonstrate superiority of palbociclib + AI over AI alone in prolonging OS for post-menopausal women and men with HR+/HER2- MBC as first-line treatment in the US clinical practice setting. The study was designed to test the null hypothesis H_{10} $\lambda \geq 1$ versus H_{1A}: $\lambda < 1$, palbociclib + AI cohort versus AI alone cohort. λ stands for the HR.

[redacted] Assuming an approximately 1:1 ratio of palbociclib + AI to AI monotherapy cohorts, a total of 750 OS events were required to have at least 85% power to detect a HR of 0.80 using a 1-sided log-rank test at a significance level of 0.025 based on the exponential distribution assumptions of OS for both cohorts. With a close to 2:1 ratio of treatment to control cohorts, 750 OS events would have at least 82% power to detect a HR of 0.80 at a 1-sided significance level of 0.025.

An estimated approximately 2000 patients with close to a 1:1 ratio between palbociclib + AI and AI alone cohorts were planned to be included based on examination of structured iKM data applying inclusion/exclusion criteria between 01 Feb 2015 to 30 June 2020.

Data cutoff of 31 August 2021 was predetermined based on an estimated number of eligible patients and estimated number of deaths in the overall cohort, prior to chart review and prior to knowledge of death events in the treatment cohorts.

The final number of eligible patients included in the study was 1288 post-chart reviews to verify inclusion in the study. Among the 1288 patients, there was nearly a 2:1 ratio of patients in each treatment arm; 838 were treated with palbociclib plus AI and 450 were treated with AI monotherapy as first-line treatment for HR+/HER2- MBC. Additionally, there were only 674 total death events reported during the study period.

Eligible patients with HR+/HER2- MBC were included into the following cohorts to be analyzed for the primary and secondary objectives:

- Palbociclib + AI: Postmenopausal women and men treated with palbociclib + AI as the first-line treatment for HR+/HER2- MBC.
- AI alone: Postmenopausal women and men treated with an AI alone as the first-line treatment of HR+/HER2- MBC.

9.8. Data Transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the Appendix 4 SAP, which is dated, filed and maintained by the sponsor.

9.9. Statistical Methods

Details on the methodology of planned statistical analysis are described in the Appendix 4, SAP.

9.9.1. Main Summary Measures

9.9.1.1. Analysis Sets/Subgroup Populations

- **FAS**: The FAS was the postmenopausal women and men patients who were treated with palbociclib + AI or AI monotherapy as first-line treatment for HR+/HER2- MBC in the US clinical practice setting from USON database who met the inclusion/exclusion criteria of the study protocol.

- **Safety Analysis Set**: The safety analysis set was the same as the FAS.

- **Subgroups**: The subgroups were defined according to patient demographics and baseline characteristics as appropriate, based on availability of the data and sample sizes.

    - Age (<55 years, 55 to <65 years, 65 to <75 years, ≥75 years)
    - Race (White, Black, Asian/Other, Not documented)
    - BMI (Normal/Underweight, Overweight/Obese, Unknown)
    - Smoking status (Current/Former, Never, Not documented)
    - ECOG performance status (0, 1, 2/3/4, Not documented)
    - Visceral disease (Yes, No)
    - Bone-only disease (Yes, No)
    - Number of disease sites (1, 2, ≥3)
    - Stage at initial diagnosis (I, II, III, IV, Not documented)
    - Disease histology (Ductal, Lobular, Other, Not documented)
    - CCI score (0, 1, ≥2)

- CDS (Low risk, Medium/High risk)
- Disease-free interval (De novo metastatic, ≤12 months, >12 months, Unknown)
- Prior adjuvant hormonal treatment (Yes, No)
- Prior neo/adjuvant chemotherapy (Yes, No)
- Index treatment of palbociclib + letrozole or letrozole alone (Yes, No)

9.9.1.2. Efficacy/Effectiveness Endpoint(s)

9.9.1.2.1. Primary Endpoint

OS is defined as the time (in months) from the date of initiation of the index treatment (palbociclib + AI or AI alone) to the date of death due to any cause. Date of death based on multiple data sources was derived following the prespecified hierarchy: 1. NDI, 2. LADMF, 3. EHR, 4. Datavant. Patients without documented death within the study observation period were censored at the date of last contact known to be alive in the datasets. Patients' last contact date were captured through chart review as a verified physical or direct phone or virtual encounter with the practice as evidenced by treatment administration, measurement of vital signs, laboratory sample collection or other office procedures.

9.9.1.2.2. Secondary Endpoints

rwPFS was defined as the time from date of index treatment (palbociclib + AI or AI alone) to the date of the first documentation of a PD by the treating clinician based on radiology or other source types (eg, clinical assessment, pathology, laboratory evidence) or death due to any cause, whichever occurred first during first-line treatment. Patients without documentation of a real-world PD or death during first-line treatment were censored at the end of their first-line treatment or the date of last contact, whichever occurred first. Those patients known to be alive without on-treatment tumor assessments were censored at the date of initiation of the index treatment.

rwTR was reported based on treating clinician's assessment of radiological evidence for change in burden of disease over the course of treatment (specifically, first-line therapy containing palbociclib, AI). Assessments were not performed on a schedule and responses were not confirmed by subsequent assessments. Each assessment was classified as follows:

- **CR**: Documented as "a complete response" to therapy; indication patient was in "remission"; "all lesions" had disappeared or "no evidence of disease").
- **PR**: 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 was still present).

- **SD**: Documented as disease was stable (not progressed or not improved; eg, Stable appearance of lobe nodules) or Mixed response, which was a combination of improved and worsened disease.

- **PD**: Documented as disease had "progressed"; or worsening of disease.

- **NE**: No determination of disease status can be made based on radiologic assessment. Not evaluated.

rwRR was defined as the proportion of patients with a real-world best response of CR or PR during first-line treatment. Patients with a real-world best response of CR or PR were those patients with a CR or PR without a PD at any prior assessment which occurred at least 30 days after the initiation of index treatment during first-line treatment.

9.9.2. Main Statistical Methods

The non-randomized nature of observational studies can lead to selection bias which may influence the choice of treatment and outcomes for patients. PS methods that had become a standard and critical piece of best practice analysis can effectively control for baseline confounding by balancing measured baseline confounders and creating comparable treatment and control groups. The SAP including the PS estimation and feasibility assessment utilizing prespecified baseline patient characteristics was finalized prior to access and analysis of any outcomes data.

9.9.2.1. Propensity Score

The primary goal of a PS-based analysis was used to reduce the bias inherent in comparative observational data analysis that was due to measured confounders. The statistical adjustment balanced the 2 treatment cohorts regarding all key baseline covariates that were associated with outcome and/or the treatment selection.

The PS was defined as the probability of a patient receiving the treatment under the study conditional on measured baseline characteristics and comorbidities. It combined multidimensional characteristics into a single dimension summary score that can be used for confounding control. Conditioning on the PS, each patient had the same chance of receiving treatment and therefore PS was a tool to mimic randomization when randomization was not available.

Under certain assumptions, the PS was a balancing score, which meant the treatment assignment was independent of the potential outcome, given the PS. However, in the setting of retrospective observational trial, the true PS of a patient was unknown. Thus, to use PS to control for bias when estimating effectiveness of treatment, proper steps including selection of covariates, missing covariates values in estimating PS (see Section 9.9.3) and PS estimation model were taken to estimate the PS. Details were described in Appendix 4, Appendix 4, SAP Section 7.1.1. A multivariable logistic regression model was used to model the treatment assignment (ie, palbociclib + AI or AI monotherapy) as a function of the

measured baseline covariates and to estimate the PS (range from 0 to 1). There were no accesses to the outcome variables in these steps of estimating the PS.

9.9.2.2. Inverse Probability of Treatment Weighting

The PS was defined as a patient's probability of treatment selection, conditional on observed baseline covariates. Weighting patients by the inverse probability of treatment received created a synthetic sample in which treatment assignment was independent of measured baseline covariates. IPTW using the PS allowed one to obtain unbiased estimates of average treatment effects. In concept, for patients who were unlikely on the palbociclib + AI treatment, were up-weighted while patients who were over-represented (very likely to be on the palbociclib + AI treatment) were down-weighted, bringing balance in covariates across the treatment cohorts. [19]

More details on IPTW method were described in Appendix 4, SAP Section 7.1.3.

nIPTW based on the PS was used in the primary analysis of OS and main analyses of rwPFS and rwRR to estimate the effectiveness of palbociclib + AI versus AI monotherapy as first-line treatment for postmenopausal women and men with HR+/HER2- MBC in a real-world setting. After normalization, the total number of patients in the weight-adjusted population remained the same as the unadjusted population. Refer to Appendix 4, SAP Section 7.2 for details on the statistical analysis of nIPTW.

9.9.2.3. Propensity Score Matching

PSM based on the PS was used as the sensitivity analysis of OS and the secondary analyses of rwPFS and rwRR to estimate the effectiveness of palbociclib + AI versus AI monotherapy as first-line MBC treatment for post-menopausal women and men with HR+/HER2- MBC in a real-world setting. The 1:1 matching in the two treatment cohorts based on the PS was implemented using the nearest neighbor matching without replacement and a caliper of 0.1. More details on PSM method were described in Appendix 4, SAP Section 7.1.4.

9.9.2.4. Propensity Score Stratification

PS stratification (quintiles) based on the PS was used as the sensitivity analysis of OS and the secondary analysis of rwPFS to estimate the effectiveness of palbociclib + AI versus AI monotherapy as first-line MBC treatment for post-menopausal women and men with HR+/HER2- MBC in a real-world setting. More details on PS stratification were described in Appendix 4, SAP Section 7.1.5.

9.9.2.5. Feasibility Assessment

A feasibility assessment examined whether the observational real-world data were sufficient to produce reliable and valid estimates using the planned analyses to meet the study objectives and the estimand of interest. The success of PS implementation was judged by the balance between treatment cohorts for each measured potential confounder after the PS adjustment.

The following process was implemented to determine whether there was sufficient overlap between the patient populations of the 2 treatment cohorts:

- Compute the SMD in each level of each baseline covariate
- Graphically assess differences in the full distribution of each covariate between two treatment cohorts

An absolute SMD <0.1 indicated negligible difference and variable considered well balanced between cohorts.

More details of feasibility assessment were described Appendix 4, SAP Section 7.1.2.

9.9.2.6. Assessment of Prescriber Bias on Treatment Assignment

Inherent prescriber bias in the RWE studies were mitigated or removed with the use of PSs. Since PS was estimated as the probability of receiving a given treatment, it informed physician tendency in treatment assignment based on patient characteristics. Patients in the FAS were grouped into 5 strata based on quintiles of the PS with patients in Strata 1 (ie, the lowest 20th quintile) representing the lowest likelihood of being prescribed palbociclib + AI and those in Strata 5 (ie, the highest 20th quintile) representing the highest likelihood of being prescribed palbociclib + AI. Percentage of patients by strata were summarized for each baseline variable and trends were identified that indicate the physician prescribing tendencies. Important baseline variables that had direct influence on prescriber decision were retained in the final PS model for PS generation.

9.9.2.7. Evaluating the Impact of Unmeasured Confounding

Details of the possible sensitivity analysis (eg, E-value, tipping point analysis) to explore inferences when unmeasured confounding cannot be overcome were described in Appendix 4, SAP Section 7.1.7.

9.9.2.8. General Methods

General methods including analyses for time-to-event endpoints (OS and rwPFS), binary endpoints, continuous data and categorical data were described in Appendix 4, SAP Section 7.1.8.

9.9.3. Missing Values

The PS methods to control for confounding was sensitive to the presence of missing data in measured covariates. Missing information on any categorical variable of baseline characteristics was either captured as “Not documented” or assigned as a new category of “Unknown” and was included in the multivariable logistic regression model for the PS estimation. Further imputation of missing values was not performed in estimating PSs.

For patients who did not have any tumor assessments post index treatment, the missing rwTR were assigned as NE and these patients were counted as non-responders in the assessment of rwRR based on the FAS.

9.9.4. Primary Analyses

PS were first estimated by a multivariable logistic regression model using baseline patient demographic characteristics, disease characteristics, and prior treatment characteristics variables selected a-priori based on clinical judgement as potential confounders (Table 2).

Table 2. Baseline Characteristics Variables Selected for Generating PS

Variable	Source(s)	Operation Definition
Baseline demographics and clinical characteristics		
Age	iKM structured data (derived)	<55 years, 55-<65 years, 65-<75 years, ≥75 years
Race	iKM structured data	White, Black, Asian/Other, Not documented
BMI	iKM structured data (derived)	Normal/Underweight, Overweight/Obese, Unknown
Smoking status	iKM structured data	Current/Former, Never, Not documented
Disease characteristics		
ECOG performance status	iKM structured data	0, 1, 2/3/4, Not documented
Visceral disease	iKM structured data + chart review (derived)	Yes, No
Bone-only disease	iKM structured data + chart review (derived)	Yes, No
Number of disease sites	iKM structured data + chart review (derived)	1, 2, ≥3
Stage at initial diagnosis	iKM structured data	I, II, III, IV, Not documented
Disease histology	iKM structured data	Ductal, Lobular, Other, Not documented
CCI score	Chart review	0, 1, ≥2
CDS*	Structured data (derived)	Low risk, Medium risk, High risk
Prior treatment characteristics		
Disease-free interval	iKM structured data + chart review (derived)	De novo metastatic, ≤12 months, >12 months, Unknown
Prior adjuvant hormonal treatment	iKM structured data (derived)	Yes, No
Prior neo/adjuvant chemotherapy	iKM structured data (derived)	Yes, No
Treatment initiation time	iKM structured data + chart review	2015, 2016, 2017, 2018, 2019, 2020

* Low, medium and high risk were defined as a CDS score being ≤5, 6, and ≥7 points, respectively.[20]
Source: Appendix 4 SAP, Table 5.

nIPTW based on the PS were used in the primary OS analysis to estimate the effectiveness of palbociclib + AI vs. AI monotherapy as first-line treatment for postmenopausal women and men with HR+/HER2- MBC in a real-world setting.

- A weighted log-rank test based on nIPTW with the robust variance estimation was used to compare OS time between the 2 treatment cohorts with the 1-sided significance level of 0.025.
- HR for OS with the corresponding 2-sided 95% CI were calculated based on weighted Cox's proportional hazards model.
- OS time associated with each treatment cohort were summarized using the weighted Kaplan-Meier method and displayed graphically. The median OS with the corresponding 2-sided 95% CI was reported.
- The OS rates summarized using the weighted Kaplan-Meier method and corresponding 2-sided 95% CIs were reported for each treatment cohort at specific time points.
- Frequency (number and percentage) of patients with OS event and censoring reasons were presented by treatment cohort.
- Duration of follow-up for OS in the treatment cohorts were summarized using the reverse Kaplan-Meier method including the median time of follow-up for OS and associated 2-sided 95% CI.

9.9.5. Sensitivity Analyses

Sensitivity analyses were performed to explore the robustness of the primary analysis results for OS.

PSM based on the PS was used as a sensitivity analysis of OS to estimate the effectiveness of palbociclib + AI vs.AI monotherapy as first-line MBC treatment for post-menopausal women and men with HR+/HER2- MBC in a real-world setting.

- A log-rank test was used to compare OS time between the 2 treatment cohorts generated by PSM with a nominal significance level at 1-sided 0.025.
- HR for OS with the corresponding 2-sided 95% CI was calculated based on Cox's proportional hazards model in the two treatment cohorts generated by PSM.
- OS time associated with each treatment cohort was summarized using the Kaplan-Meier method and displayed graphically. The median OS with the corresponding 2-sided 95% CI was reported.

- The OS rates summarized using Kaplan-Meier method and corresponding 2-sided 95% CIs were reported for each treatment cohort at specific time points.

- Frequency (number and percentage) of patients with OS event and censoring reasons were presented by treatment cohort.

PS stratification (quintiles) based on the PS was used as a sensitivity analysis of OS to estimate the effectiveness of palbociclib + AI vs. AI mono as first-line treatment for post-menopausal women and men with HR+/HER2- MBC in a real-world setting.

- A stratified log-rank test based on quintiles was used to compare OS time between the 2 treatment cohorts with a nominal 1-sided significance level of 0.025.

- HR for OS with the corresponding 2-sided 95% CI was calculated based on stratified Cox's proportional hazards model.

Potential impact of COVID-19 related deaths was planned to be assessed if ≥5% of the patients died due to COVID-19 related reasons. A competing risk analysis was to be performed treating COVID-19 related death as a competing event and the cumulative incidence function to be compared between the treatment cohorts.

Additional sensitivity analyses may have included methods described in Section 9.9.2.7 to evaluate the potential impact of unmeasured confounding for OS.

9.9.6. Amendments to the Statistical Analysis Plan

SAP version 1.0 was based on the protocol version 1.0 dated 25 June 2021 and PACL dated 14 September 2021.

The SAP was finalized after the baseline characteristics data were received and PS analyses were performed. Details on PS estimation and corresponding feasibility assessments were presented in Appendix 4, SAP Section 9.2. Access to the clinical outcome data did not occur until after the SAP was finalized.

Changes to the previous SAP drafts were summarized below:

SAP Date	Changes to the Previous SAP Drafts	Rationale
11 November 2020	NA	[redacted].
20 December 2021	• Updated the data cutoff date from 31 December 2020 to 31 August 2021. • Updated Tables 2, 3, 6 and SAP Appendix 1. • Included editorial and consistency changes throughout the document	Per protocol updates extending the study follow-up period, patient attribution and study date variable definitions.
09 May 2022	• Replaced Tables 2 and 3 with a patient attrition chart in current Figure 2.	Final patient attrition chart was generated post chart abstraction.
	• Updated Table 6 on the categorization of some baseline characteristics variables selected for generating PS.	Updated categorization of the baseline variables based on further literature review and final baseline data.
	• Section 7.1.5 PSM - updated the caliper for PSM from 0.2 to 0.1.	Used a narrower caliper to improve the PS performance of PSM without compromise of number of patients matched.
	• Added Section 7.1.6 to describe assessment of prescriber bias on treatment assignment.	[redacted]

	• Deleted ratio of PS variances assessments in relevant sections of feasibility assessments.	Current feasibility assessments were considered sufficient.
	• Included additional editorial and consistency changes throughout the document.	

9.10. Quality Control

With the exception of supplementary vitality status, study data originated in the iKM EHR, which is an oncology-specific EHR that has been deployed across USON to record outpatient practice encounter histories for patients under community-based care. Structured fields of the iKM EHR were used to initially screen for study eligible patients and for select study variables (specified in the study protocol). Patients' eligibility and additional study data were captured through a manual chart review, which included human-level review of unstructured and structured fields of the iKM EHR. All study data were merged into a single study dataset, which was deidentified and securely transferred to Pfizer for analysis. Several layers of QC were incorporated into the data collection and analytic file construction.

Chart abstraction was performed by certified tumor registrars and/or oncology care nurses with specialized chart review training specific to oncological abstraction methods. The chart abstractors were trained on study-specific requirements and had access to proprietary chart review training guidelines that provide more detail about general considerations about abstraction. To reduce potential observer bias, all study training materials focused on details related to the accurate and consistent capture of study data, with limited background on the study objectives provided. In particular, chart abstractors were not informed of the study hypotheses nor that that primary study objective of A5481161 was assessment of OS.

Abstraction activities were facilitated by an electronic data capture system that is 21 CFR Part 11 compliant, OpenClinica. An eCRF was jointly developed by the Ontada and Pfizer study teams based on the study protocol specifications and Ontada's standard abstraction guidelines. OpenClinica promotes standardized abstraction of study data elements through incorporation of skip logic and error flags that provide real-time guidance to abstractors during chart review (eg, instructions are included on each page of the eCRF and logic checks are included).

Questions that arose during the course of chart review were addressed according to a standard process that entailed submitting questions to the Ontada Data Quality Specialist via

a question log hosted on a secure network shared drive that was also used to capture responses to the questions. Each question was logged and answers were documented by the Data Quality Specialist in the log for reference throughout the study.

Following initial abstraction, source data verification for variables as described below, by Data Quality Specialists was performed for abstracted charts to confirm that the information from the original EHR was correctly, consistently and comprehensively abstracted. While the original QC plan assumed at least 25% of eligible charts would be selected for source data verification, in total, 76.3% of all eligible charts underwent this level of review. Additionally, verification of ineligibility was performed for all disqualified charts.

Among charts selected for source data verification, the following key variables were targeted for review and corrected if needed. If errors were identified during this process for other variables, those were reviewed/corrected as well:

- Menopausal status
- Distant metastatic sites
- Performance status
- Last contact date
- Death date
- Patient disposition at follow-up
- Cause of death
- Initial diagnosis date
- Metastatic diagnosis date
- Stage at diagnosis
- CCI
- Pneumonitis/ILD (toxicity)

Throughout the course of the study and quality monitoring, abstractor performance was assessed. Abstractors that did not meet performance thresholds removed from the study and all of their prior abstracted charts underwent full source data verification (of the entire chart) as described above.

Once initial source data verification was complete, the OpenClinica data were exported so that predetermined quality checks could be executed by the Ontada Biostatisticians (see Figure 2). For the final transfers of baseline and follow-up data, 198 individual analytic checks were run. These checks were run against the entire analytic file (100% of eligible patient data).

To supplement this analytic QC, an export of the analytic file was used to provide human-level review of the entire analytic file by the Ontada Outcomes Researcher, Physician Investigator and other clinical staff. The scope of this clinical-level review included, but was not limited to:

- For every data element, determination if the proportion of patients with "missing," "unknown" or "not documented" values is higher than expected;
- Review of free-text responses to "other" questions, to determine if these responses should be re-categorized or confirmed through source data verification;
- LOT assignments of patients who discontinued the initial palbociclib + AI or AI mono regimen for reasons other than disease progression or toxicities;
- Distribution of observed treatments and treatment sequences to identify potentially anomalous therapies;
- Non-standard palbociclib dosing and frequency;
- Data output cross-referenced with data specifications document to ensure consistency and completeness;
- Review of the number of last contact dates and death dates with imputed dates to determine if additional source data verification is needed.

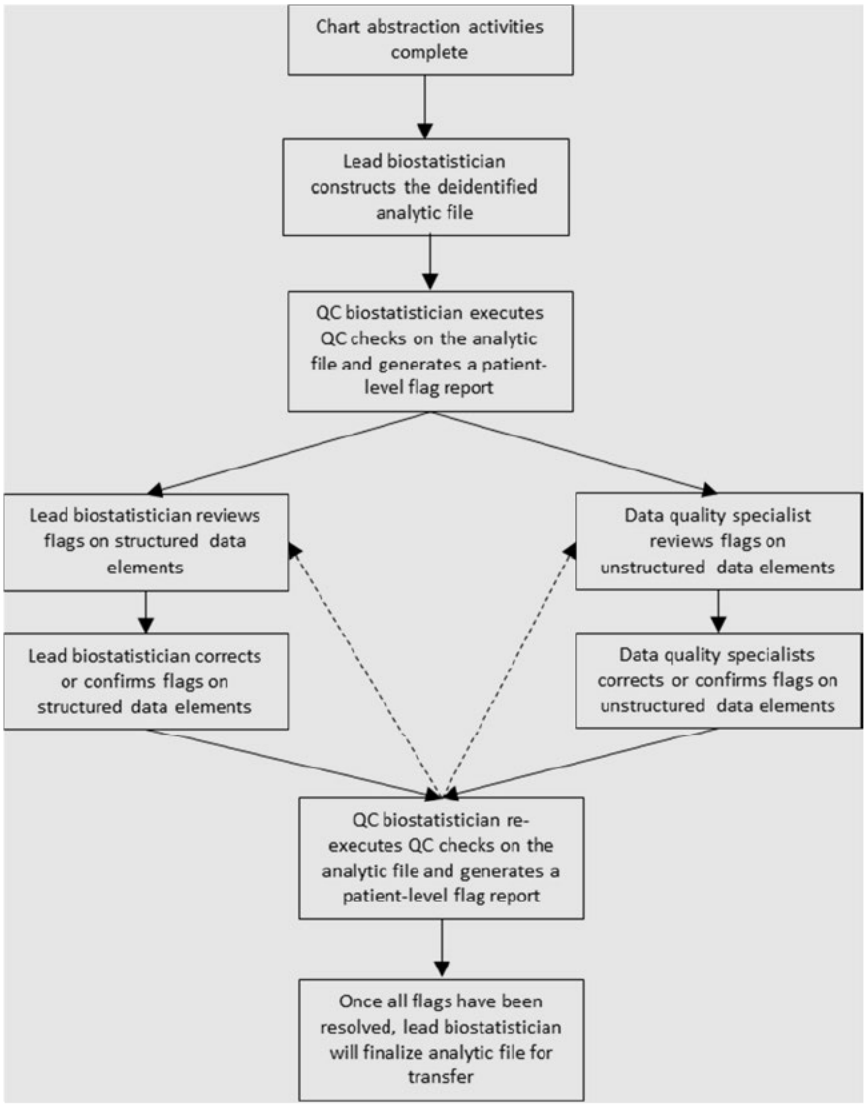
Each clinical and analytic check generated patient-level "flags" that represented potential errors in the analytic file. Using the approach described in the next paragraph, each flag underwent review and records were kept to indicate if the flag was either 1) an error that was corrected or 2) an anomalous data element that was confirmed correct.

For potential errors that originate from structured data, the Ontada Biostatistician reviewed the structured data records to correct or confirm if changes to the dataset were needed. For potential errors that originated from unstructured data, source data verification was performed by a Data Quality Specialist. For unstructured data flags, a list of the flags by individual patient were sent to the Ontada Data Quality Specialist for review. The Data Quality Specialist reviewed the EHR records of the patient to confirm the accuracy and completeness of data captured.

Following review and correction (if needed) of all flags in the study dataset, the analytic QC checks were re-run and the process repeated until all flags were resolved.

All SAS programming and data transfer materials were reviewed by a second Ontada Biostatistician.

Figure 2. Analytic QC Schema



This was a retrospective study, therefore issues of quality control at study sites, eg, data clarification queries, did not apply, as the team was unable to follow-up with the treating physician for clarification. Analyses were programmed according to the specifications in the protocol's SAP and all code and other technical artifacts were documented and stored following established programming practices on Pfizer servers and in Pfizer's Global Document Management System.

9.11. Protection of Human Subjects

Subject information and consent

Not Applicable. This protocol relied on secondary use of data collected in the EHR of USON.

The Ontada team submitted a request for exemption, waiver of informed consent and authorization to the US Oncology IRB. This project involved the study of existing data and records; study information was transmitted to Pfizer in such a manner that research participants could not be directly identified. As such, this study was granted exemption status and waiver of authorization can be approved, allowing the retrospective study to proceed without informed consent.

IEC/IRB

IEC/IRB review was not required for this secondary data study. A waiver of informed consent and authorization to the IRB was received.

Ethical Conduct of the Study

As discussed in Appendix 2, Protocol Section 10.4, the study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in GPP issued by the ISPE research practices, Good Practices for Outcomes Research issued by the ISPOR, and Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making, and similar standards.

10. RESULTS

10.1. Patients

A total of 1288 patients were included in the study, 838 patients in the palbociclib + AI cohort and 450 patients in the AI monotherapy cohort, after applying inclusion and exclusion criteria with reasons specified in Figure 3, using EHR structured data and chart review to confirm eligibility.

In the FAS, 710 (84.7%) patients in the palbociclib + AI cohort and 319 (70.9%) patients in the AI monotherapy cohort had at least 1 tumor assessment on treatment (Table 3).

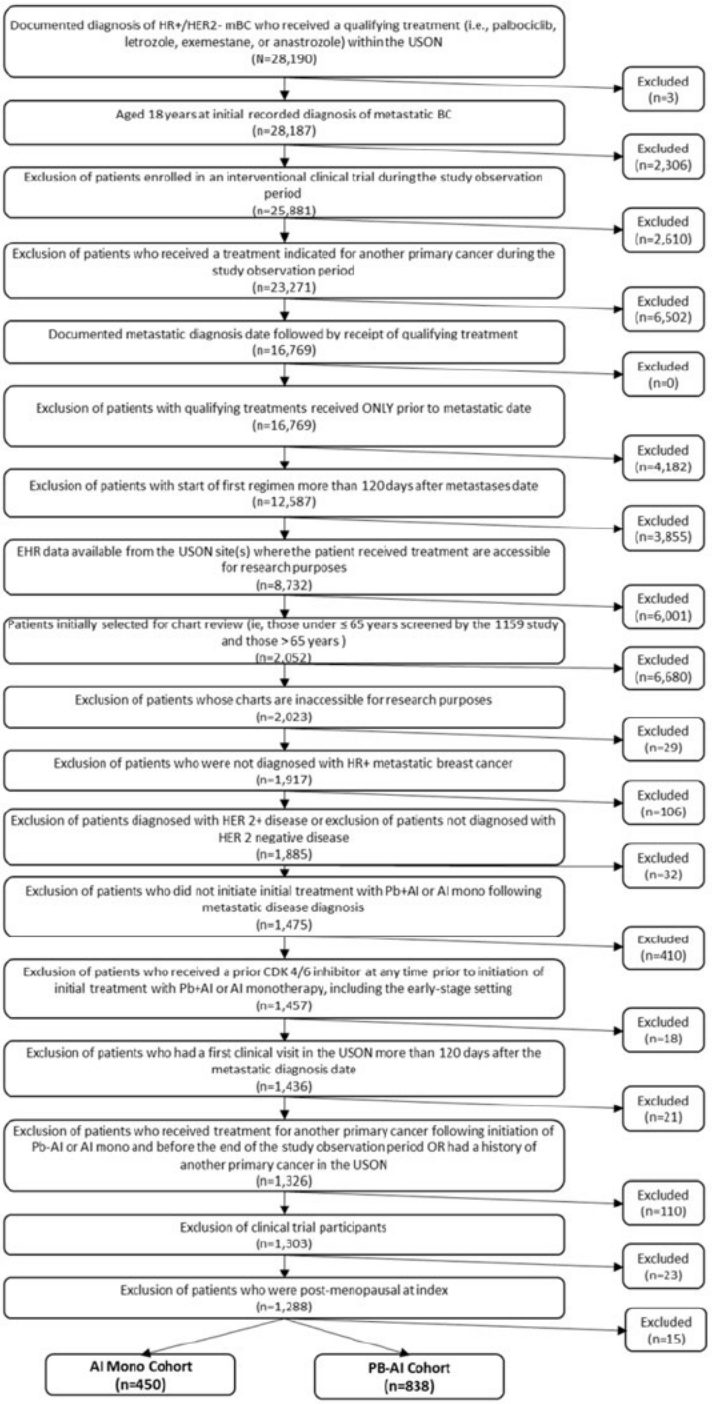
In the FAS, 546 (65.2%) patients in the palbociclib plus AI cohort and 339 (75.3%) patients in the AI monotherapy cohort discontinued treatment, with progressive disease as the most frequent reason for discontinuation of first-line treatment for MBC (Table 3). As of the data cutoff date of 31 Aug 2021, 185 (22.1%) patients in the palbociclib plus AI cohort and 93 (20.7%) of patients in the AI monotherapy cohort were ongoing on treatment with first-line therapy for MBC.

Table 3. Patient Evaluability and Disposition (Protocol A5481161)

	Palbociclib + AI (N=838) n (%)	AI Mono (N=450) n (%)
Evaluability:		
Full analysis set	838 (100.0)	450 (100.0)
Full analysis set with at least 1 imaging-based tumor assessment on treatment	710 (84.7)	319 (70.9)
Disposition phase: Index Treatment		
Discontinued	546 (65.2)	339 (75.3)
Reason for discontinuation		
Death	34 (4.1)	38 (8.4)
Progressive disease	313 (37.4)	187 (41.6)
Toxicity	118 (14.1)	22 (4.9)
Decline in performance status	5 (0.6)	7 (1.6)
Financial/insurance	1 (0.1)	1 (0.2)
Hospice	28 (3.3)	39 (8.7)
Patient preference	25 (3.0)	10 (2.2)
Physician decision	21 (2.5)	18 (4.0)
Other	1 (0.1)	1 (0.2)
Not documented	0	16 (3.6)
Completed	0	0
Ongoing	292 (34.8)	111 (24.7)
Disposition phase: Follow-up		
Patients entered in follow-up phase	441 (52.6)	241 (53.6)
Discontinued	254 (30.3)	148 (32.9)
Reason for discontinuation		
Death	55 (6.6)	31 (6.9)
Progressive disease	64 (7.6)	32 (7.1)
Toxicity	18 (2.1)	8 (1.8)
Decline in performance status	28 (3.3)	7 (1.6)
Financial/insurance	0	1 (0.2)
Hospice	66 (7.9)	51 (11.3)
Patient preference	13 (1.6)	11 (2.4)
Physician decision	9 (1.1)	4 (0.9)
Other	0	2 (0.4)
Not documented	1 (0.1)	1 (0.2)
Completed	2 (0.2)	0
Ongoing	185 (22.1)	93 (20.7)

PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:28) Source Data: adds Table Generation: 30AUG2022 (15:06)
Output File: ./rWE1161/A5481161_final/adds_s001
Table 14.1.1.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Figure 3. Patient Attrition (01 February 2015 - 30 June 2020)



Source: Appendix 4, SAP Figure 2.

10.2. Descriptive Data

10.2.1. Before and After nIPTW Adjustment

10.2.1.1. Patient Characteristics

Patient baseline characteristics, including demographic and clinical characteristics, healthcare setting and provider characteristics, disease characteristics and prior treatment characteristics, before and after nIPTW adjustment are presented by cohorts for the FAS (N=1288) in Table 4. PS were generated by a multivariable logistic regression model using 16 selected variables listed in Table 2.

In the unadjusted population, the median age was 67.5 and 72.0 years in palbociclib + AI and AI monotherapy cohorts, respectively, and 24.0% vs 42.4% of patients were aged ≥75 years in palbociclib + AI vs AI monotherapy arm. In the palbociclib + AI and AI monotherapy cohorts, 37.8% and 41.6% of patients had Stage IV disease at initial diagnosis; 24.3% and 32.4% of patients had bone-only disease, 59.1% and 53.8% had 3 or more disease sites, 30.0% and 19.1% of patients received prior neo/adjuvant chemotherapy and 45.6% and 36.2% of patients received prior adjuvant hormonal treatment, respectively.

After nIPTW adjustment, all 16 selected baseline variables used in the final PS model at each level had an absolute SMD <0.1 as shown in Table 4, demonstrating good balance between the 2 treatment cohorts with respect to the key baseline variables considered to be potential confounders.

Additional graphic plots are presented to visually assess the overlap and balance between the 2 treatment cohorts before and after the IPTW adjustment:

- The plots of SMDs between the 2 treatment cohorts for the 16 selected baseline variables at each variable level before and after IPTW adjustment are presented in Figure 14.1.2.2. After IPTW adjustment, the SMD of each baseline variable is in the range of -0.1 to 0.1 as shown in the shaded region, which indicates a good balance achieved;

- Box plots of overall PS distribution are presented in Figure 14.1.2.4. The differences in the PS distributions between the 2 treatment cohorts was negligible in the IPTW weighted population compared to those in the unweighted population, indicating good balance was achieved after weighting;

- Histogram plots of overall PS distribution before and after the IPTW adjustment are presented in Figure 14.1.2.5. The right panel with histogram of PS distributions on the weighted population indicates good excellent overlap between the 2 treatment cohorts;

- Cumulative distribution of PS before and after IPTW are presented in Figure 14.1.2.6. The area between the 2 curves represents the PS distribution difference between the

2 treatment cohorts. The larger the area, the bigger the difference. Compared to the upper panel of all observation (unweighted observations), the lower panel of weighted observations indicates that the difference between the 2 cohorts was negligible after applying IPTW.

Table 4. Patient Baseline Characteristics with nIPTW - Full Analysis Set (Protocol A5481161)

	Unadjusted			nIPTW Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences
Age (Years)*, n (%)						
<55	79 (9.4)	21 (4.7)	-0.1868	64 (7.6)	31 (6.9)	-0.0293
55-<65	249 (29.7)	95 (21.1)	-0.1986	225 (26.8)	126 (28.0)	0.0264
65-<75	309 (36.9)	143 (31.8)	-0.1075	294 (35.1)	157 (34.9)	-0.0042
≥75	201 (24.0)	191 (42.4)	0.3997	255 (30.4)	136 (30.2)	-0.0047
Mean (SD)	67.2 (10.0)	71.5 (10.2)	0.4348	68.6 (10.2)	68.9 (10.0)	0.0337
Median (min,max)	67.5 (33.0, 85.0)	72.0 (43.0, 85.0)		69.0 (33.0, 85.0)	70.0 (43.0, 85.0)	
Sex, n (%)						
Male	6 (0.7)	3 (0.7)	-0.0060	5 (0.6)	2 (0.4)	-0.0393
Female	832 (99.3)	447 (99.3)	0.0060	833 (99.4)	448 (99.6)	0.0393
Race*, n (%)						
White	605 (72.2)	332 (73.8)	0.0356	611 (72.9)	324 (72.0)	-0.0189
Black	43 (5.1)	22 (4.9)	-0.0111	47 (5.6)	26 (5.8)	0.0092
Asian/Other	33 (3.9)	21 (4.7)	0.0359	34 (4.1)	17 (3.8)	-0.0155
Not documented	157 (18.7)	75 (16.7)	-0.0542	146 (17.4)	83 (18.4)	0.0242
Menopausal Status, n (%) [1]						
Pre/Peri-menopausal	0	0		0	0	
Post-menopausal [2]	838 (100.0)	450 (100.0)		838 (100.0)	450 (100.0)	
Body Mass Index*, n(%) [3]						

Table 4. Patient Baseline Characteristics with nIPTW - Full Analysis Set (Protocol A5481161)

	Unadjusted			nIPTW Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences
Overweight/Obese	511 (61.0)	251 (55.8)	-0.1057	498 (59.4)	259 (57.6)	-0.0363
Normal/Underweight	216 (25.8)	105 (23.3)	-0.0568	210 (25.1)	120 (26.7)	0.0349
Unknown	111 (13.2)	94 (20.9)	0.2042	130 (15.5)	71 (15.8)	0.0072
Smoking Status*, n (%)						
Current/Former	308 (36.8)	163 (36.2)	-0.0111	305 (36.4)	169 (37.6)	0.0222
Never	469 (56.0)	254 (56.4)	0.0096	470 (56.1)	247 (54.9)	-0.0252
Not documented	61 (7.3)	33 (7.3)	0.0021	63 (7.5)	35 (7.8)	0.0067
Family History of Cancer, n (%)						
Yes	580 (69.2)	289 (64.2)	-0.1060	566 (67.5)	305 (67.8)	0.0060
No	149 (17.8)	94 (20.9)	0.0788	158 (18.9)	83 (18.4)	-0.0113
Unknown	109 (13.0)	67 (14.9)	0.0543	113 (13.5)	62 (13.8)	0.0046
Practice Location, n (%)						
Midwest	131 (15.6)	80 (17.8)	0.0575	133 (15.9)	79 (17.6)	0.0442
Northeast	39 (4.7)	30 (6.7)	0.0872	45 (5.4)	29 (6.4)	0.0437
South	298 (35.6)	119 (26.4)	-0.1981	293 (35.0)	113 (25.1)	-0.2191
West	370 (44.2)	221 (49.1)	0.0995	367 (43.8)	230 (51.1)	0.1468
Rural/Urban, n (%)						
Metro	570 (68.0)	283 (62.9)	-0.1080	568 (67.8)	286 (63.6)	-0.0903
Non-metro	9 (1.1)	20 (4.4)	0.2069	8 (1.0)	20 (4.4)	0.2100
Unknown	259 (30.9)	147 (32.7)	0.0378	262 (31.3)	145 (32.2)	0.0194
Practice Size, n (%)						
≥ 2000 patients/2018	644 (76.8)	303 (67.3)	-0.2134	648 (77.3)	308 (68.4)	-0.2039
1500 - < 2000 patients/2018	80 (9.5)	50 (11.1)	0.0514	78 (9.3)	52 (11.6)	0.0761
1000 - < 1500 patients/2018	56 (6.7)	41 (9.1)	0.0901	54 (6.4)	37 (8.2)	0.0655

Table 4. Patient Baseline Characteristics with nIPTW - Full Analysis Set (Protocol A5481161)

	Unadjusted			nIPTW Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences
500 - < 1000 patients/2018	34 (4.1)	35 (7.8)	0.1582	36 (4.3)	32 (7.1)	0.1255
< 500 patients/2018	24 (2.9)	21 (4.7)	0.0948	22 (2.6)	21 (4.7)	0.1111
Patient Volume, n (%)						
≤10 patients/2018	9 (1.1)	7 (1.6)	0.0423	9 (1.1)	6 (1.3)	0.0325
11-49 patients/2018	43 (5.1)	21 (4.7)	-0.0215	44 (5.3)	18 (4.0)	-0.0578
≥50 patients/2018	786 (93.8)	422 (93.8)	-0.0007	785 (93.7)	425 (94.4)	0.0365
Treatment Initiation Time*, n (%)						
2015	99 (11.8)	112 (24.9)	0.3427	136 (16.2)	72 (16.0)	-0.0080
2016	141 (16.8)	100 (22.2)	0.1365	162 (19.3)	86 (19.1)	-0.0035
2017	157 (18.7)	103 (22.9)	0.1025	164 (19.6)	87 (19.3)	-0.0041
2018	185 (22.1)	77 (17.1)	-0.1253	172 (20.5)	101 (22.4)	0.0438
2019	191 (22.8)	46 (10.2)	-0.3436	154 (18.4)	82 (18.2)	-0.0036
2020	65 (7.8)	12 (2.7)	-0.2305	50 (6.0)	22 (4.9)	-0.0470
Hormone Receptor Status, n (%)						
ER positive only	161 (19.2)	70 (15.6)	-0.0966	163 (19.5)	72 (16.0)	-0.0929
PR positive only	2 (0.2)	0	-0.0692	2 (0.2)	0	-0.0672
ER and PR positive	675 (80.5)	380 (84.4)	0.1026	673 (80.3)	378 (84.0)	0.0986
Negative HER2 Status, n (%) [1]						
Yes	838 (100.0)	450 (100.0)		838 (100.0)	450 (100.0)	
No	0	0		0	0	
ESR1 Status, n (%)						
Positive	15 (1.8)	5 (1.1)	-0.0568	14 (1.7)	4 (0.9)	-0.0752
Negative	82 (9.8)	38 (8.4)	-0.0466	76 (9.1)	35 (7.8)	-0.0510
Unknown	741 (88.4)	407 (90.4)	0.0657	747 (89.1)	412 (91.6)	0.0765

Table 4. Patient Baseline Characteristics with nIPTW - Full Analysis Set (Protocol A5481161)

	Unadjusted			nIPTW Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences
BRCA 1/2 Status, n (%)						
Positive	33 (3.9)	4 (0.9)	-0.1997	29 (3.5)	3 (0.7)	-0.1932
Negative	182 (21.7)	68 (15.1)	-0.1711	166 (19.8)	74 (16.4)	-0.0866
Unknown	623 (74.3)	378 (84.0)	0.2395	643 (76.7)	373 (82.9)	0.1515
NGS Status, n (%)						
Positive	69 (8.2)	11 (2.4)	-0.2597	60 (7.2)	12 (2.7)	-0.2138
Negative	679 (81.0)	385 (85.6)	0.1216	679 (81.0)	384 (85.3)	0.1160
Unknown	90 (10.7)	54 (12.0)	0.0397	99 (11.8)	54 (12.0)	0.0076
Disease Sites, n (%) [4]						
Ascites	9 (1.1)	4 (0.9)	-0.0188	8 (1.0)	5 (1.1)	0.0297
Bone	668 (79.7)	352 (78.2)	-0.0366	666 (79.5)	346 (76.9)	-0.0619
Brain	27 (3.2)	20 (4.4)	0.0637	25 (3.0)	23 (5.1)	0.1071
Breast	58 (6.9)	37 (8.2)	0.0492	54 (6.4)	35 (7.8)	0.0490
Liver	156 (18.6)	64 (14.2)	-0.1188	142 (16.9)	76 (16.9)	-0.0017
Lung	234 (27.9)	116 (25.8)	-0.0484	218 (26.0)	120 (26.7)	0.0137
Lymph nodes	392 (46.8)	181 (40.2)	-0.1325	376 (44.9)	183 (40.7)	-0.0862
Soft tissue	11 (1.3)	14 (3.1)	0.1225	10 (1.2)	16 (3.6)	0.1534
Pleural effusion	71 (8.5)	31 (6.9)	-0.0595	71 (8.5)	30 (6.7)	-0.0658
Skin	41 (4.9)	27 (6.0)	0.0488	44 (5.3)	25 (5.6)	0.0151
Other [5]	479 (57.2)	235 (52.2)	-0.0993	458 (54.7)	244 (54.2)	-0.0082
Visceral Disease*, n(%) [6]						
Yes	393 (46.9)	177 (39.3)	-0.1532	368 (43.9)	193 (42.9)	-0.0202
No	445 (53.1)	273 (60.7)	0.1532	470 (56.1)	257 (57.1)	0.0202
Bone-only Disease*, n(%)						
Yes	204 (24.3)	146 (32.4)	0.1804	233 (27.8)	132 (29.3)	0.0314

Table 4. Patient Baseline Characteristics with nIPTW - Full Analysis Set (Protocol A5481161)

	Unadjusted			nIPTW Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences
No	634 (75.7)	304 (67.6)	-0.1804	605 (72.2)	318 (70.7)	-0.0314
Number of Disease Site(s)*, n (%)						
1	135 (16.1)	108 (24.0)	0.1980	168 (20.0)	89 (19.8)	-0.0105
2	208 (24.8)	100 (22.2)	-0.0613	203 (24.2)	119 (26.4)	0.0517
≥3	495 (59.1)	242 (53.8)	-0.1069	467 (55.7)	242 (53.8)	-0.0368
Disease-free Interval*, n (%) [7]						
De novo metastatic	321 (38.3)	188 (41.8)	0.0709	331 (39.5)	171 (38.0)	-0.0276
≤12 Months	144 (17.2)	51 (11.3)	-0.1679	128 (15.3)	72 (16.0)	0.0210
>12 Months	287 (34.2)	130 (28.9)	-0.1155	271 (32.3)	146 (32.4)	0.0053
Unknown	86 (10.3)	81 (18.0)	0.2235	109 (13.0)	60 (13.3)	0.0098
Stage at Initial Diagnosis*, n (%)						
Stage I [8]	129 (15.4)	59 (13.1)	-0.0653	119 (14.2)	64 (14.2)	0.0005
Stage II	187 (22.3)	92 (20.4)	-0.0456	184 (22.0)	105 (23.3)	0.0328
Stage III	108 (12.9)	55 (12.2)	-0.0201	102 (12.2)	54 (12.0)	-0.0009
Stage IV	317 (37.8)	187 (41.6)	0.0762	327 (39.0)	169 (37.6)	-0.0316
Not documented	97 (11.6)	57 (12.7)	0.0334	106 (12.6)	58 (12.9)	0.0053
Disease Histology*, n (%)						
Ductal	521 (62.2)	290 (64.4)	0.0472	526 (62.8)	280 (62.2)	-0.0095
Lobular	109 (13.0)	65 (14.4)	0.0418	116 (13.8)	64 (14.2)	0.0089
Other	52 (6.2)	38 (8.4)	0.0860	58 (6.9)	34 (7.6)	0.0193
Not documented	156 (18.6)	57 (12.7)	-0.1643	138 (16.5)	72 (16.0)	-0.0094
Prior Neo/Adjuvant Chemotherapy*, n (%)						
Yes	251 (30.0)	86 (19.1)	-0.2540	222 (26.5)	131 (29.1)	0.0583
No	587 (70.0)	364 (80.9)	0.2540	616 (73.5)	319 (70.9)	-0.0583

Table 4. Patient Baseline Characteristics with nIPTW - Full Analysis Set (Protocol A5481161)

	Unadjusted			nIPTW Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences
Prior Adjuvant Hormonal Treatment*, n (%)						
Yes	382 (45.6)	163 (36.2)	-0.1913	355 (42.4)	199 (44.2)	0.0389
No	456 (54.4)	287 (63.8)	0.1913	483 (57.6)	251 (55.8)	-0.0389
ECOG Performance Status*, n (%)						
0	158 (18.9)	73 (16.2)	-0.0693	146 (17.4)	75 (16.7)	-0.0193
1	346 (41.3)	156 (34.7)	-0.1368	334 (39.9)	176 (39.1)	-0.0168
2/3/4	106 (12.6)	85 (18.9)	0.1718	121 (14.4)	67 (14.9)	0.0101
Not documented	228 (27.2)	136 (30.2)	0.0667	236 (28.2)	132 (29.3)	0.0262
Charlson Comorbidity Index (CCI) Score*, n (%)						
0	718 (85.7)	364 (80.9)	-0.1287	702 (83.8)	382 (84.9)	0.0299
1	77 (9.2)	37 (8.2)	-0.0343	72 (8.6)	34 (7.6)	-0.0351
≥2	43 (5.1)	49 (10.9)	0.2133	64 (7.6)	34 (7.6)	-0.0048
Chronic Disease Score (CDS)*, n (%) [9]						
Low risk	787 (93.9)	377 (83.8)	-0.3262	758 (90.5)	407 (90.4)	-0.0030
Medium risk	7 (0.8)	6 (1.3)	0.0481	8 (1.0)	4 (0.9)	0.0042
High risk	44 (5.3)	67 (14.9)	0.3245	72 (8.6)	39 (8.7)	0.0017
Prior History of Interstitial Lung Disease (ILD), n (%)						
Yes	2 (0.2)	2 (0.4)	0.0353	2 (0.2)	2 (0.4)	0.0269
No	836 (99.8)	448 (99.6)	-0.0353	836 (99.8)	448 (99.6)	-0.0269
Prior History of Pneumonitis, n (%)						
Yes	1 (0.1)	1 (0.2)	0.0249	1 (0.1)	3 (0.7)	0.0849
No	837 (99.9)	449 (99.8)	-0.0249	837 (99.9)	447 (99.3)	-0.0849

Table 4. Patient Baseline Characteristics with nIPTW - Full Analysis Set (Protocol A5481161)

	Unadjusted			nIPTW Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences

[1] Standardized mean difference is not calculated for the categorical variables with only one level.
[2] Post-menopausal also includes male patients.
[3] Body Mass Index (kg/m², BMI) = weight (kg) / (0.01*[height (cm)])²; BMI ≥25 is classified as overweight/obese. BMI < 25 is classified as normal/underweight.
[4] Patients can be in more than one disease site. [5]. Other includes the rest of the disease sites not listed.
[6] Visceral disease was defined as metastatic disease in the liver, lung and/or pleura.
[7] Time from end of (neo)adjuvant therapy to date of metastatic breast cancer diagnosis. [8] Stage I includes Stage I and Stage 0.
[9] Low, medium and high risk were defined as a CDS score being ≤5, 6, and ≥7 points, respectively.
* Variables used in the propensity score model.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:27) Source Data: adsl Table Generation: 14SEP2022 (11:47)
Output File: ./rWE1161/A5481161_final/adsl_ns001_2
Table 14.1.2.1 Palbociclib (PD-0332991) is for Pfizer internal use.

10.2.1.2. Patient Characteristics in Patients with Tumor Assessment

Patient baseline characteristics, including demographic and clinical characteristics, disease characteristics and prior treatment characteristics, before and after nIPTW adjustment are presented by cohorts for a subgroup of patients who had at least 1 tumor assessment on treatment (N=1029) in Table 14.1.5.1. PS were generated by a multivariable logistic regression model using 16 selected variables listed in Table 2.

In general, baseline demographic and clinical characteristics were largely similar to the FAS population. After nIPTW adjustment, all the selected baseline variables at every level had an absolute SMD <0.1 (Table 14.1.5.1), indicating good balance between the 2 treatment cohorts with respect to measured potential confounders.

10.2.2. Before and After PSM Adjustment

10.2.2.1. Patient Characteristics

Patient baseline characteristics, including demographic and clinical characteristics, disease characteristics and prior treatment characteristics, before and after PSM adjustment are presented by cohorts for the FAS (N=1288) in Table 5. PS were generated by a multivariable logistic regression model using 16 selected variables listed in Table 2.

The unadjusted baseline variables were various in absolute SMDs, see details in Section 10.2.1.1.

After PSM adjustment, most of the selected variables, except prior adjuvant hormonal treatment and prior neo/adjuvant chemotherapy, had an absolute SMD <0.1 (Table 5) at every level and demonstrated an overall good balance between the 2 treatment cohorts with respect to measured confounders.

Additional graphic plots were presented to visually assess the overlap and balance between the 2 treatment cohorts before and after PSM:

- The plots of SMD between the 2 treatment cohorts for the selected baseline variables at each variable level before and after applying PSM are presented in Figure 14.1.3.2. After IPTW adjustment, the SMD of most baseline variables are in the range of -0.1 to 0.1 as shown in the shaded region, which indicates an overall good balance achieved;

- PS distributions by treatment cohort with PSM is illustrated in a cloud plot presented in Figure 14.1.3.3;

- Histogram plots of PS before and after PSM are presented in Figure 14.1.3.4, which consistently support balance being achieved in the matched population as the overlap between the 2 treatment cohorts are greater in the right panel (after PSM);

- Cumulative plots of PS distribution before and after PSM are presented in Figure 14.1.3.5, which indicates smaller difference in the weighted matched population and consistently support balance being achieved after PSM.

Table 5. Patient Baseline Characteristics with PSM - Full Analysis Set (Protocol A5481161)

	Unadjusted			PSM Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=384)	AI Mono (N=384)	Standardized Mean Differences
Age (Years) , n (%)						
<55	79 (9.4)	21 (4.7)	-0.1868	25 (6.5)	21 (5.5)	-0.0439
55-<65	249 (29.7)	95 (21.1)	-0.1986	96 (25.0)	91 (23.7)	-0.0303
65-<75	309 (36.9)	143 (31.8)	-0.1075	134 (34.9)	134 (34.9)	0.0000
≥75	201 (24.0)	191 (42.4)	0.3997	129 (33.6)	138 (35.9)	0.0492
Mean (SD)	67.2 (10.0)	71.5 (10.2)	-0.4348	69.3 (9.9)	70.1 (9.9)	-0.0801
Median (min,max)	67.5 (33.0, 85.0)	72.0 (43.0, 85.0)		69.0 (44.0, 85.0)	70.0 (43.0, 85.0)	
Race, n (%)						
White	605 (72.2)	332 (73.8)	0.0356	288 (75.0)	283 (73.7)	-0.0298
Black	43 (5.1)	22 (4.9)	-0.0111	24 (6.3)	21 (5.5)	-0.0333
Asian/Other	33 (3.9)	21 (4.7)	0.0359	16 (4.2)	17 (4.4)	0.0128
Not documented	157 (18.7)	75 (16.7)	-0.0542	56 (14.6)	63 (16.4)	0.0504
Body Mass Index, n (%) [1]						
Overweight/Obese	511 (61.0)	251 (55.8)	-0.1057	230 (59.9)	216 (56.3)	-0.0739
Normal/Underweight	216 (25.8)	105 (23.3)	-0.0568	89 (23.2)	96 (25.0)	0.0426
Unknown	111 (13.2)	94 (20.9)	0.2042	65 (16.9)	72 (18.8)	0.0476
Smoking Status, n (%)						
Current/Former	308 (36.8)	163 (36.2)	-0.0111	144 (37.5)	140 (36.5)	-0.0216
Never	469 (56.0)	254 (56.4)	0.0096	213 (55.5)	215 (56.0)	0.0105

Table 5. Patient Baseline Characteristics with PSM - Full Analysis Set (Protocol A5481161)

	Unadjusted			PSM Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=384)	AI Mono (N=384)	Standardized Mean Differences
Not documented	61 (7.3)	33 (7.3)	0.0021	27 (7.0)	29 (7.6)	0.0200
ECOG Performance Status, n (%)						
0	158 (18.9)	73 (16.2)	-0.0693	58 (15.1)	62 (16.1)	0.0287
1	346 (41.3)	156 (34.7)	-0.1368	145 (37.8)	143 (37.2)	-0.0108
2/3/4	106 (12.6)	85 (18.9)	0.1718	65 (16.9)	66 (17.2)	0.0069
Not documented	228 (27.2)	136 (30.2)	0.0667	116 (30.2)	113 (29.4)	-0.0171
Visceral Disease, n (%) [2]						
Yes	393 (46.9)	177 (39.3)	-0.1532	158 (41.1)	160 (41.7)	0.0106
No	445 (53.1)	273 (60.7)	0.1532	226 (58.9)	224 (58.3)	-0.0106
Bone-only Disease, n (%)						
Yes	204 (24.3)	146 (32.4)	0.1804	118 (30.7)	116 (30.2)	-0.0113
No	634 (75.7)	304 (67.6)	-0.1804	266 (69.3)	268 (69.8)	0.0113
Number of Disease Sites, n (%)						
1	135 (16.1)	108 (24.0)	0.1980	90 (23.4)	82 (21.4)	-0.0500
2	208 (24.8)	100 (22.2)	-0.0613	95 (24.7)	88 (22.9)	-0.0428
≥3	495 (59.1)	242 (53.8)	-0.1069	199 (51.8)	214 (55.7)	0.0784
Stage at Initial Diagnosis, n (%)						
Stage I [3]	129 (15.4)	59 (13.1)	-0.0653	47 (12.2)	49 (12.8)	0.0157
Stage II	187 (22.3)	92 (20.4)	-0.0456	91 (23.7)	78 (20.3)	-0.0818
Stage III	108 (12.9)	55 (12.2)	-0.0201	50 (13.0)	45 (11.7)	-0.0396
Stage IV	317 (37.8)	187 (41.6)	0.0762	148 (38.5)	164 (42.7)	0.0849
Not documented	97 (11.6)	57 (12.7)	0.0334	48 (12.5)	48 (12.5)	0.0000
Disease Histology, n (%)						
Ductal	521 (62.2)	290 (64.4)	0.0472	248 (64.6)	244 (63.5)	-0.0217

Table 5. Patient Baseline Characteristics with PSM - Full Analysis Set (Protocol A5481161)

	Unadjusted			PSM Adjusted		
	Palbociclib + AI (N=838)	AI Mono (N=450)	Standardized Mean Differences	Palbociclib + AI (N=384)	AI Mono (N=384)	Standardized Mean Differences
Lobular	109 (13.0)	65 (14.4)	0.0418	53 (13.8)	54 (14.1)	0.0075
Other	52 (6.2)	38 (8.4)	0.0860	29 (7.6)	32 (8.3)	0.0289
Not documented	156 (18.6)	57 (12.7)	-0.1643	54 (14.1)	54 (14.1)	0.0000
Charlson Comorbidity Index (CCI) Score, n (%)						
0	718 (85.7)	364 (80.9)	-0.1287	322 (83.9)	319 (83.1)	-0.0210
1	77 (9.2)	37 (8.2)	-0.0343	32 (8.3)	33 (8.6)	0.0094
≥2	43 (5.1)	49 (10.9)	0.2133	30 (7.8)	32 (8.3)	0.0191
Chronic Disease Score (CDS), n (%) [4]						
Low risk	787 (93.9)	377 (83.8)	-0.3262	342 (89.1)	341 (88.8)	-0.0083
Medium risk	7 (0.8)	6 (1.3)	0.0481	5 (1.3)	5 (1.3)	0.0000
High risk	44 (5.3)	67 (14.9)	0.3245	37 (9.6)	38 (9.9)	0.0088
Disease-free Interval, n (%) [5]						
De novo metastatic	321 (38.3)	188 (41.8)	0.0709	149 (38.8)	165 (43.0)	0.0848
≤12 Months	144 (17.2)	51 (11.3)	-0.1679	56 (14.6)	46 (12.0)	-0.0768
>12 Months	287 (34.2)	130 (28.9)	-0.1155	124 (32.3)	116 (30.2)	-0.0450
Unknown	86 (10.3)	81 (18.0)	0.2235	55 (14.3)	57 (14.8)	0.0148
Prior Adjuvant Hormonal Treatment, n (%)						
Yes	382 (45.6)	163 (36.2)	-0.1913	164 (42.7)	145 (37.8)	-0.1010
No	456 (54.4)	287 (63.8)	0.1913	220 (57.3)	239 (62.2)	0.1010
Prior Neo/Adjuvant Chemotherapy, n (%)						
Yes	251 (30.0)	86 (19.1)	-0.2540	102 (26.6)	85 (22.1)	-0.1033
No	587 (70.0)	364 (80.9)	0.2540	282 (73.4)	299 (77.9)	0.1033
Treatment Initiation Time, n (%)						

Table 5. Patient Baseline Characteristics with PSM - Full Analysis Set (Protocol A5481161)

	Unadjusted			PSM Adjusted		
	Palbociclib + AI (N=838)	**AI Mono (N=450)**	**Standardized Mean Differences**	**Palbociclib + AI (N=384)**	**AI Mono (N=384)**	**Standardized Mean Differences**
2015	99 (11.8)	112 (24.9)	0.3427	78 (20.3)	75 (19.5)	-0.0196
2016	141 (16.8)	100 (22.2)	0.1365	83 (21.6)	88 (22.9)	0.0313
2017	157 (18.7)	103 (22.9)	0.1025	87 (22.7)	89 (23.2)	0.0124
2018	185 (22.1)	77 (17.1)	-0.1253	73 (19.0)	75 (19.5)	0.0132
2019	191 (22.8)	46 (10.2)	-0.3436	52 (13.5)	45 (11.7)	-0.0549
2020	65 (7.8)	12 (2.7)	-0.2305	11 (2.9)	12 (3.1)	0.0153

[1] Body Mass Index (kg/m², BMI) = weight (kg) / (0.01*[height (cm)])²; BMI ≥25 is classified as overweight/obese. BMI < 25 is classified as normal/underweight.
[2] Visceral disease was defined as metastatic disease in the liver, lung and/or pleura.
[3] Stage I includes Stage I and Stage 0.
[4] Low, medium and high risk were defined as a CDS score being ≤5, 6, and ≥7 points, respectively.
[5] Time from end of (neo)adjuvant therapy to date of metastatic breast cancer diagnosis.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:27) Source Data: adsl Table Generation: 29AUG2022 (11:55)
Output File: ./rWE1161/A5481161 final/adsl ns001 1
Table 14.1.3.1 Palbociclib (PD-0332991) is for Pfizer internal use.

10.2.2.2. Patient Characteristics in Patients with Tumor Assessment

Patient baseline characteristics, including demographic and clinical characteristics, disease characteristics and prior treatment characteristics, before and after PSM adjustment are presented by cohorts for a subgroup of patients who had at least 1 tumor assessment on treatment (N=1029) in (Table 14.1.5.2). PS were generated by a multivariable logistic regression model using 16 selected variables listed in Table 2.

The unadjusted baseline variables were various in absolute SMDs, see details in Section 10.2.1.2.

After PSM adjustment, most of the selected variables had an absolute SMD <0.1 at every level, except the variables of age ≥75 years and mean age, visceral disease (yes and no) and CDS of low risk, the SMD of which were >0.1 (Table 14.1.5.2). Overall, there is a good balance between the 2 treatment cohorts.

10.2.3. PS Stratification Adjustment

Patients were divided into 5 strata based on quintiles of the PS with the first quintiles (highest likelihood of being prescribed AI monotherapy) and the fifth quintiles (highest likelihood of being prescribed palbociclib + AI) representing the lowest and highest 20% of the PS. PS quintiles and key baseline variables can elucidate reasoning behind prescriber assignment of treatment. These assessments ensured such variables with potential confounding effect would be included in the final PS model for estimating the PSs.

Prescriber patterns across PS strata for each of the 16 baseline variables are summarized in Table 6. As shown in the table, only 4.3% of patients in the oldest age group (≥75 years) were in strata 5 (highest likelihood of being prescribed palbociclib + AI) while 45.9% of these patients were in strata 1 (lowest likelihood of being prescribed palbociclib + AI) indicating there was a tendency for physicians to treat older patients with AI monotherapy rather than palbociclib + AI. In contrast, patients in the youngest age group (<55 years) were clustered towards the higher quintile strata indicating they were more likely to be prescribed palbociclib + AI. As such, PS quintiles and key baseline variables can elucidate reasoning behind prescriber assignment of treatment. Overall, it indicated that the physician may tend to prescribe palbociclib + AI as treatment for those patients with better ECOG performance status (0 and 1), lower CCI score (0 and 1), low risk category of the CDS, those with Stage I/II disease at initial diagnosis, patients with visceral disease, those who received prior neo/adjuvant chemotherapy or hormonal treatment, or those who initiated their treatment in 2019 and 2020 vs earlier years.

Additional graphic plots were presented to visually assess the balance between the 2 treatment cohorts before and after the PS stratification.

- Figure 14.1.4.1 provides the averaged SMDs between the 2 treatment cohorts across 5 strata for the 16 selected baseline variables at each level. Recommended ranges for stratum-specific SMD are currently not available in the literature. The shaded area captures SMDs across strata in the range of -0.25 to 0.25, indicating an overall good balance between treatment cohorts with PS stratification.

- Figure 14.1.4.3 presents box plots of the overall PS distribution between the 2 treatment cohorts within strata. Overall, overlap of the 2 treatment cohorts within strata was acceptable. Due to the smaller samples size in each stratum, within-strata SMDs may not be comparable to the overall SMDs and in general would be greater, eg, a residual imbalance was observed in stratum 1 for the PS.

Table 6. Prescriber Pattern Across Propensity Score Strata - Full Analysis Set (Protocol A5481161)

	N	Quintile Strata [1] 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)
Age (Years)						
< 55	100	1 (1.0)	7 (7.0)	21 (21.0)	25 (25.0)	46 (46.0)
55-<65	344	25 (7.3)	51 (14.8)	87 (25.3)	89 (25.9)	92 (26.7)
65-<75	452	51 (11.3)	114 (25.2)	94 (20.8)	91 (20.1)	102 (22.6)
≥ 75	392	180 (45.9)	86 (21.9)	56 (14.3)	53 (13.5)	17 (4.3)
Race						
White	937	196 (20.9)	187 (20.0)	192 (20.5)	189 (20.2)	173 (18.5)
Black	65	10 (15.4)	16 (24.6)	11 (16.9)	16 (24.6)	12 (18.5)
Asian/Other	54	10 (18.5)	19 (35.2)	8 (14.8)	11 (20.4)	6 (11.1)
Not documented	232	41 (17.7)	36 (15.5)	47 (20.3)	42 (18.1)	66 (28.4)
Body Mass Index [2]						
Overweight/Obese	762	140 (18.4)	131 (17.2)	145 (19.0)	160 (21.0)	186 (24.4)
Normal/Underweight	321	41 (12.8)	69 (21.5)	81 (25.2)	68 (21.2)	62 (19.3)
Unknown	205	76 (37.1)	58 (28.3)	32 (15.6)	30 (14.6)	9 (4.4)
Smoking Status						
Current/Former	471	86 (18.3)	100 (21.2)	93 (19.7)	102 (21.7)	90 (19.1)
Never	723	154 (21.3)	141 (19.5)	141 (19.5)	135 (18.7)	152 (21.0)
Not documented	94	17 (18.1)	17 (18.1)	24 (25.5)	21 (22.3)	15 (16.0)
ECOG Performance Status						
0	231	32 (13.9)	41 (17.7)	48 (20.8)	53 (22.9)	57 (24.7)
1	502	62 (12.4)	102 (20.3)	107 (21.3)	108 (21.5)	123 (24.5)

Table 6. Prescriber Pattern Across Propensity Score Strata - Full Analysis Set (Protocol A5481161)

	N	Quintile Strata [1] 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)
2/3/4	191	75 (39.3)	40 (20.9)	34 (17.8)	24 (12.6)	18 (9.4)
Not documented	364	88 (24.2)	75 (20.6)	69 (19.0)	73 (20.1)	59 (16.2)
Visceral Disease [3]						
Yes	570	80 (14.0)	97 (17.0)	120 (21.1)	125 (21.9)	148 (26.0)
No	718	177 (24.7)	161 (22.4)	138 (19.2)	133 (18.5)	109 (15.2)
Bone-only Disease						
Yes	350	111 (31.7)	80 (22.9)	64 (18.3)	57 (16.3)	38 (10.9)
No	938	146 (15.6)	178 (19.0)	194 (20.7)	201 (21.4)	219 (23.3)
Number of Disease Site(s)						
1	243	91 (37.4)	57 (23.5)	30 (12.3)	38 (15.6)	27 (11.1)
2	308	52 (16.9)	55 (17.9)	64 (20.8)	63 (20.5)	74 (24.0)
≥ 3	737	114 (15.5)	146 (19.8)	164 (22.3)	157 (21.3)	156 (21.2)
Stage at Initial Diagnosis						
I/II [4]	467	78 (16.7)	80 (17.1)	93 (19.9)	94 (20.1)	122 (26.1)
III/IV	667	143 (21.4)	147 (22.0)	133 (19.9)	136 (20.4)	108 (16.2)
Not documented	154	36 (23.4)	31 (20.1)	32 (20.8)	28 (18.2)	27 (17.5)
Disease Histology						
Ductal	811	174 (21.5)	168 (20.7)	158 (19.5)	156 (19.2)	155 (19.1)
Lobular	174	39 (22.4)	36 (20.7)	37 (21.3)	35 (20.1)	27 (15.5)
Other	90	21 (23.3)	31 (34.4)	21 (23.3)	13 (14.4)	4 (4.4)
Not documented	213	23 (10.8)	23 (10.8)	42 (19.7)	54 (25.4)	71 (33.3)
Charlson Comorbidity Index (CCI) Score						
0	1082	188 (17.4)	218 (20.1)	226 (20.9)	224 (20.7)	226 (20.9)
1	114	20 (17.5)	20 (17.5)	19 (16.7)	26 (22.8)	29 (25.4)
≥ 2	92	49 (53.3)	20 (21.7)	13 (14.1)	8 (8.7)	2 (2.2)

Table 6. Prescriber Pattern Across Propensity Score Strata - Full Analysis Set (Protocol A5481161)

	N	Quintile Strata [1] 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)
Chronic Disease Score (CDS) [5]						
Low risk	1164	180 (15.5)	229 (19.7)	244 (21.0)	254 (21.8)	257 (22.1)
Medium risk	13	4 (30.8)	6 (46.2)	1 (7.7)	2 (15.4)	0
High risk	111	73 (65.8)	23 (20.7)	13 (11.7)	2 (1.8)	0
Disease-free Interval [6]						
De novo metastatic	509	113 (22.2)	116 (22.8)	104 (20.4)	102 (20.0)	74 (14.5)
≤ 12 Months	195	18 (9.2)	24 (12.3)	33 (16.9)	51 (26.2)	69 (35.4)
> 12 Months	417	50 (12.0)	84 (20.1)	89 (21.3)	89 (21.3)	105 (25.2)
Unknown	167	76 (45.5)	34 (20.4)	32 (19.2)	16 (9.6)	9 (5.4)
Prior Neo/Adjuvant Hormonal Treatment						
Yes	545	64 (11.7)	98 (18.0)	106 (19.4)	125 (22.9)	152 (27.9)
No	743	193 (26.0)	160 (21.5)	152 (20.5)	133 (17.9)	105 (14.1)
Prior Neo/Adjuvant Chemotherapy						
Yes	337	16 (4.7)	50 (14.8)	68 (20.2)	91 (27.0)	112 (33.2)
No	951	241 (25.3)	208 (21.9)	190 (20.0)	167 (17.6)	145 (15.2)
Treatment Initiation Time						
2015	211	104 (49.3)	67 (31.8)	33 (15.6)	7 (3.3)	0
2016	241	62 (25.7)	67 (27.8)	67 (27.8)	41 (17.0)	4 (1.7)
2017	260	62 (23.8)	68 (26.2)	66 (25.4)	47 (18.1)	17 (6.5)
2018	262	23 (8.8)	38 (14.5)	63 (24.0)	83 (31.7)	55 (21.0)
2019	237	4 (1.7)	15 (6.3)	26 (11.0)	64 (27.0)	128 (54.0)
2020	77	2 (2.6)	3 (3.9)	3 (3.9)	16 (20.8)	53 (68.8)

Table 6. Prescriber Pattern Across Propensity Score Strata - Full Analysis Set (Protocol A5481161)

		Quintile Strata [1]				
	N	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)

N is the total number of patients at each level of the baseline variable; percentages are calculated relative to N.
[1] Strata were defined as the quintiles of the propensity score with the first quintile and fifth quintile representing the lowest and highest 20% of the propensity scores, respectively.
[2] BMI ≥25 is classified as overweight/obese. BMI
[3] Visceral disease was defined as metastatic disease in the liver, lung and/or pleura.
[4] Stage I includes Stage I and Stage 0.
[5] Low, medium and high risk were defined as a CDS score being ≤5, 6, and ≥7 points, respectively.
[6] Time from end of (neo) adjuvant therapy to date of metastatic disease.
PFIZER CONFIDENTIAL SDTM Creation: 18AUG2022 (14:32) Source Data: adsl Table Generation: 23AUG2022 (15:31)
Output File: ./rWE1161/A5481161_final/pop_ps
Table 14.1.4.5 Palbociclib (PD-0332991) is for Pfizer internal use.

10.2.4. Treatments

The treatments received by patients in the palbociclib + AI and AI monotherapy cohorts are presented in Table 7.

- In the palbociclib + AI cohort, the majority of patients (84.2%) received letrozole as the AI in combination with palbociclib, 12.9% received anastrozole and 3.9% received exemestane. In the AI monotherapy cohort, 50.7% of patients received letrozole, 42.7% of patients received anastrozole and 12.0% patients received exemestane as the AI.

- The median duration of treatment was 16.36 and 11.76 months in the pabociclib + AI and AI monotherapy cohorts, respectively.

- Three hundred and thirty-eight (40.3%) patients had at least 1 palbociclib dose changed in the palbociclib + AI cohort. Of the 338 patients, toxicity was reported in 321 patients as the reason for dose change.

Table 7. Summary of Study Treatments (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Patients with AI, n (%)		
Letrozole	706 (84.2)	228 (50.7)
Anastrozole	108 (12.9)	192 (42.7)
Exemestane	33 (3.9)	54 (12.0)
Duration of Treatment (months)		
n	838	450
Mean (SD)	19.28 (15.474)	17.24 (17.105)
Median (min,max)	16.36 (0.3, 74.3)	11.76 (0.0, 74.3)
Patients with at Least One Palbociclib Dose Change, n (%)	338 (40.3)	NA
Reasons for Any Change of Palbociclib, n (%)		
Lack of response	2 (0.2)	NA
Patient preference	8 (1.0)	NA
Toxicity	321 (38.3)	NA
Other	15 (1.8)	NA
Unknown	15 (1.8)	NA

Table 7. Summary of Study Treatments (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)

Duration of treatment = (stop date - start date +1)/30.4375 for first line metastatic treatment.
PFIZER CONFIDENTIAL SDTM Creation: 22AUG2022 (11:52) Source Data: adexsum adsl Table Generation: 22AUG2022 (11:53)
Output File: ./rWE1161/A5481161_final/adex_s001
Table 14.4.1 Palbociclib (PD-0332991) is for Pfizer internal use.

10.3. Outcome Data

Not Applicable.

10.4. Main Results

10.4.1. Overall Survival

nIPTW was used to estimate the effectiveness of palbociclib + AI vs AI monotherapy as primary analysis, and PSM and PS stratification (quintiles) were used as the sensitivity analyses (Section 9.9.4 and Section 9.9.5). Prespecified subgroup analyses of OS were conducted according to the baseline patient demographics and disease characteristics. Following OS analysis was conducted based on the data with the cutoff date of 31 August 2021.

Summary of OS by treatment in unadjusted FAS is presented in Table 14.2.1.1.4 and Table 8:

- The median follow-up time for the unadjusted OS was 43.7 months overall (95% CI: 42.1, 46.5), 40.0 months (95% CI: 37.7, 42.3) in the palbociclib + AI cohort and 53.4 months (95% CI: 49.9, 58.2) in the AI monotherapy cohort (Table 14.2.1.1.4). The imbalance in follow-up time between the 2 treatment cohorts was mainly due to confounding by treatment initiation time in the unadjusted population (Section 10.2.3).

- A total of 675 death events were observed, 395 (47.1%) in the palbociclib + AI cohort and 280 (62.2%) in the AI monotherapy cohort.

- The median OS was 43.3 months (95% CI: 39.4, 46.0) in the palbociclib + AI cohort and 34.5 months (95% CI: 30.9, 38.7) in the AI monotherapy cohort. The observed HR was 0.820 (95% CI: 0.703, 0.957) with 1-sided p-value = 0.0058.

- The survival probabilities from 6 months to 60 months were all numerically higher in the palbociclib + AI cohort compared with the AI monotherapy cohort.

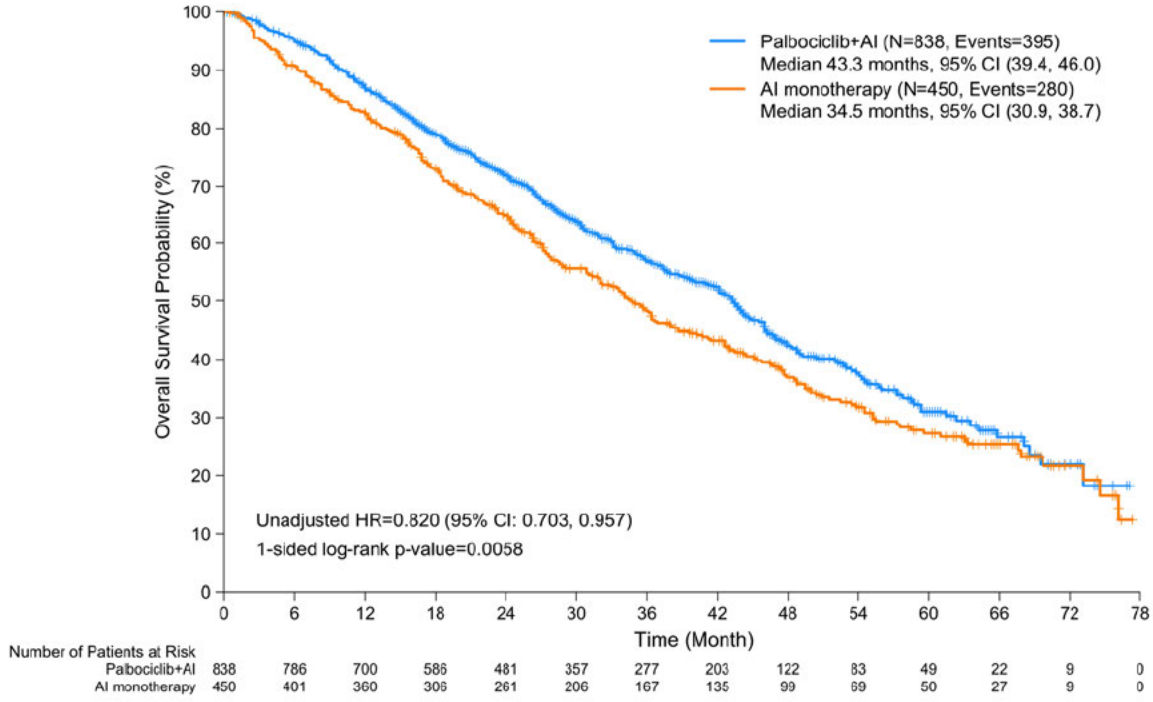
The Kaplan-Meier plot of OS by treatment cohort for the unadjusted FAS is presented in Figure 4.

Table 8. Summary of Overall Survival (Unadjusted) - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Patients with event, n (%)	395 (47.1)	280 (62.2)
Patients censored, n (%)	443 (52.9)	170 (37.8)
Reason for censoring, n (%)		
Alive in follow-up	368 (43.9)	125 (27.8)
Transferred care	41 (4.9)	25 (5.6)
Lost to follow-up [1]	34 (4.1)	20 (4.4)
Probability of being event-free (95% CI) [2]		
at 6 months	0.953 (0.936, 0.965)	0.908 (0.877, 0.931)
at 12 months	0.867 (0.842, 0.889)	0.824 (0.785, 0.856)
at 24 months	0.719 (0.686, 0.749)	0.648 (0.601, 0.691)
at 36 months	0.570 (0.531, 0.606)	0.483 (0.433, 0.531)
at 48 months	0.423 (0.379, 0.467)	0.369 (0.320, 0.419)
at 60 months	0.310 (0.260, 0.361)	0.273 (0.223, 0.325)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	21.4 (18.9, 23.7)	16.8 (14.8, 18.7)
Median	43.3 (39.4, 46.0)	34.5 (30.9, 38.7)
Q3	68.6 (62.4, NE)	67.6 (55.2, 74.5)
Unadjusted Comparison vs AI Mono		
Hazard Ratio [4]	0.820	
95% CI [4]	0.703, 0.957	
1-sided p-value [5]	0.0058	

[1] Includes participants deemed to be lost to follow-up in the US Oncology Network.
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Based on the Brookmeyer and Crowley method.
[4] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Palbociclib + AI compared to AI Mono;
[5] p-value from the log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:55) Source Data: adtte Table Generation: 19AUG2022 (15:36)
Output File: ./rWE1161/A5481161 final/adtte os s001
Table 14.2.1.1.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Figure 4. Kaplan-Meier Plot of Overall Survival (Unadjusted) - Full Analysis Set



Source: Table 8, Figure 14.2.1.1.2

10.4.1.1. Primary Analysis – nIPTW Adjustment

OS by Treatment

The analysis of FAS with nIPTW adjustment is summarized in Table 14.2.1.2.3 and Table 9 by treatment:

- The median follow-up time for OS with nIPTW adjustment was 43.7 months (95% CI: 41.4, 46.5) in the palbociclib + AI cohort and 44.0 months (95% CI: 40.7, 48.1) in the AI monotherapy cohort (Table 14.2.1.2.3).
- A total of 675 death events were observed, 429 (51.1%) in the palbociclib + AI cohort and 246 (54.7%) in the AI monotherapy cohort.
- The median OS was 42.1 months (95% CI: 36.8, 44.4) in the palbociclib + AI cohort and 35.7 months (95% CI: 30.9, 42.6) in the AI monotherapy cohort (HR=0.898 [95% CI: 0.752, 1.071]; 1-sided p-value=0.1165).
- The survival probabilities were numerically higher in the palbociclib + AI cohort compared with the AI monotherapy cohort at 6 months (94.5% vs 92.3%), 12 months

(85.6% vs 84.3%), 24 months (71.0% vs 67.1%), 36 months (54.8% vs 49.2%), 48 months (41.0% vs 38.7%) and 60 months (30.4% vs 29.8%).

The Kaplan-Meier plot of OS by treatment cohort for FAS with nIPTW adjustment is presented in Figure 5.

OS by Subgroups

The analysis of FAS with nIPTW adjustment conducted by prespecified subgroups is summarized in Table 14.2.1.2.4.

The forest plot of OS in the subgroups with nIPTW adjustment is presented in Figure 6. The figure presents the HRs and 95% CIs from the analysis of OS in each of the subgroups.

Table 9. Summary of Overall Survival with nIPTW Adjustment - Full Analysis Set (Protocol A5481161)

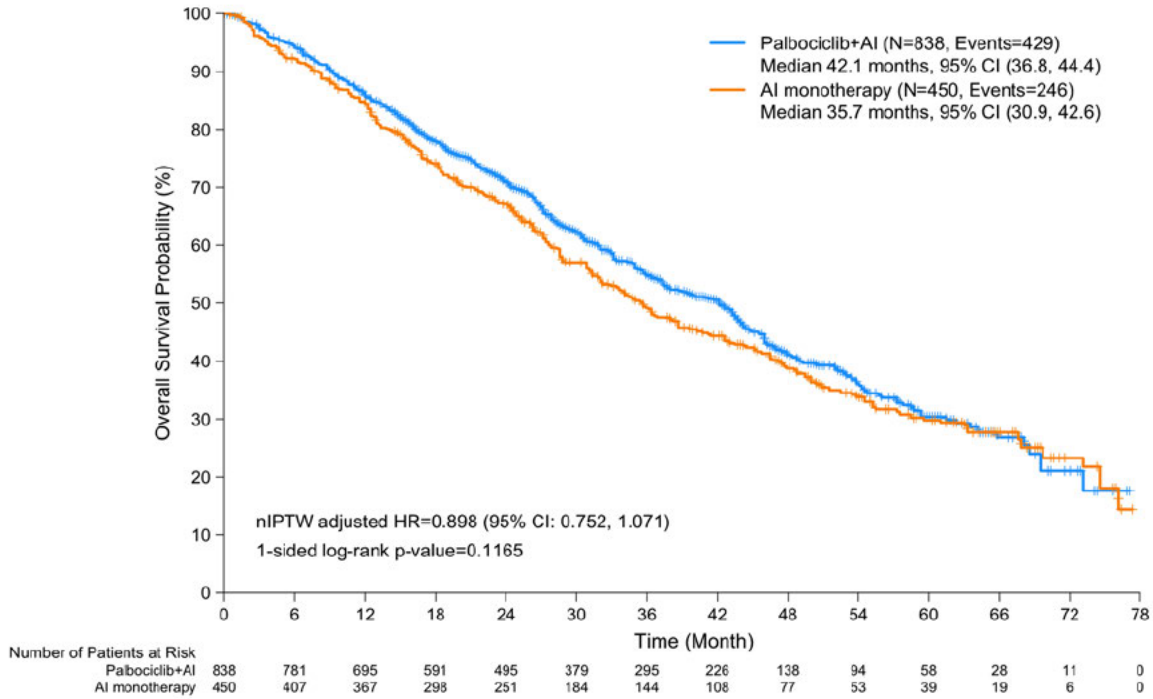
	Palbociclib + AI (N=838)	AI Mono (N=450)
Patients with event, n (%)	429 (51.1)	246 (54.7)
Patients censored, n (%)	409 (48.9)	204 (45.3)
Reason for censoring, n (%)		
Alive in follow-up	336 (40.1)	149 (33.1)
Transferred care	38 (4.6)	29 (6.5)
Lost to follow-up [1]	35 (4.2)	26 (5.7)
Probability of being event-free (95% CI) [2]		
at 6 months	0.945 (0.925, 0.959)	0.923 (0.886, 0.948)
at 12 months	0.856 (0.829, 0.880)	0.843 (0.797, 0.880)
at 24 months	0.710 (0.675, 0.742)	0.671 (0.614, 0.721)
at 36 months	0.548 (0.507, 0.587)	0.492 (0.432, 0.549)
at 48 months	0.410 (0.365, 0.455)	0.387 (0.329, 0.445)
at 60 months	0.304 (0.254, 0.356)	0.298 (0.240, 0.358)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	20.7 (17.7, 23.5)	17.1 (14.1, 20.5)
Median	42.1 (36.8, 44.4)	35.7 (30.9, 42.6)
Q3	68.6 (61.4, NE)	69.7 (58.4, NE)
Adjusted by nIPTW Comparison vs AI Mono		
Hazard Ratio [4]	0.898	
95% CI [4]	0.752, 1.071	
1-sided p-value [5]	0.1165	

Table 9. Summary of Overall Survival with nIPTW Adjustment - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)

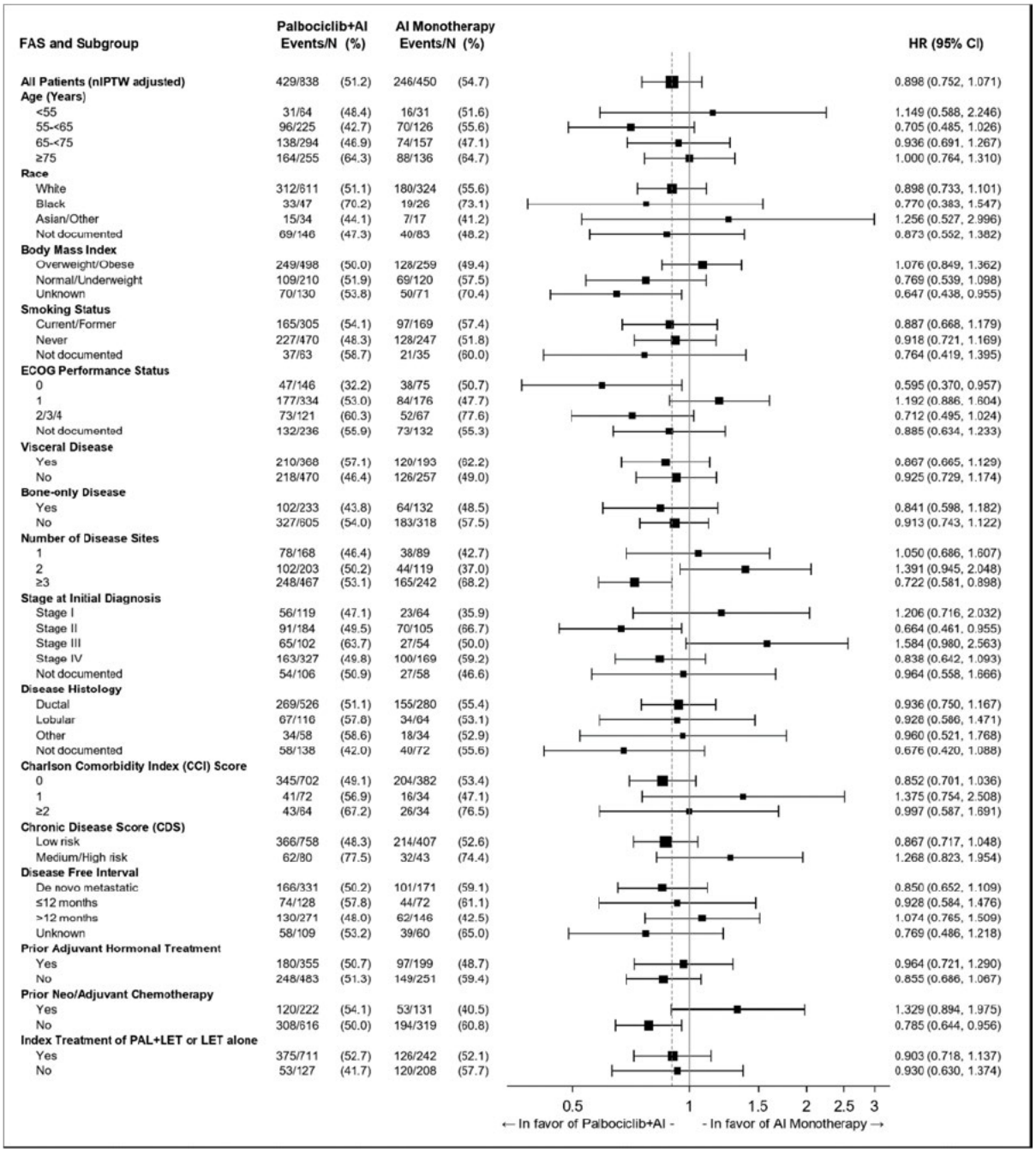
Weighted counts from nIPTW adjustment are displayed with rounding. All percentages are based on actual weighted counts.
[1] Includes patients deemed to be lost to follow-up in the US Oncology Network.
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Based on the Brookmeyer and Crowley method.
[4] Hazard ratio based on weighted Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Palbociclib + AI compared to AI Mono;
[5] p-value from the weighted log-rank test with robust variance estimator.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:55) Source Data: adtte Table Generation: 30AUG2022 (17:14)
Output File: ./rWE1161/A5481161 final/adtte os s001 2
Table 14.2.1.2.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Figure 5. Kaplan-Meier Plot of Overall Survival Analysis with nIPTW Adjustment - Full Analysis Set



Source: Table 9, Figure 14.2.1.2.2

Figure 6. Forest Plot of Overall Survival by Subgroups with nIPTW Adjustment – Full Analysis Set



Source: Table 14.2.1.2.4, Figure 14.2.1.5.2

10.4.1.2. Sensitivity Analysis – PSM Adjustment

The results in the sensitivity analysis using PSM method were consistent with the assessments of the primary analysis.

OS by Treatment

The analysis of FAS matched by PSM is summarized in Table 14.2.1.3.3 and Table 10 by treatment:

- The median follow-up time for FAS with PSM adjustment was 47.9 months (95% CI: 44.4, 51.5) in the palbociclib + AI cohort and 50.4 months (95% CI: 46.5, 54.3) in the AI monotherapy cohort (Table 14.2.1.3.3).
- A total of 439 death events were observed, 211 (54.9%) in the palbociclib + AI cohort and 228 (59.4%) in the AI monotherapy cohort.
- The median OS was 43.3 months (95% CI: 35.7, 46.9) in the palbociclib + AI cohort and 34.5 months (95% CI: 28.8, 38.7) in the AI monotherapy cohort (HR=0.855 [95% CI: 0.709, 1.031]; 1-sided p-value=0.0507).
- The survival probabilities were numerically higher in the palbociclib + AI cohort compared with the AI monotherapy cohort at 6 months (94.0% vs 90.5%), 12 months (86.3% vs 82.0%), 24 months (71.3% vs 64.5%), 36 months (54.9% vs 47.6%), 48 months (42.7% vs 38.0%) and 60 months (31.1% vs 28.8%).

The Kaplan-Meier plot of OS by treatment cohort for FAS with PSM adjustment is presented in Figure 7.

OS by Subgroups

The analysis of OS for FAS with PSM adjustment conducted by prespecified subgroups is summarized in Table 14.2.1.3.4.

The forest plot of OS in the subgroups with PSM adjustment is presented in Figure 8. The figure presents the HRs and 95% CIs from the analysis of OS in each of the subgroups.

Table 10. Summary of Overall Survival with PSM Adjustment - Propensity Score Matched Patients (Protocol A5481161)

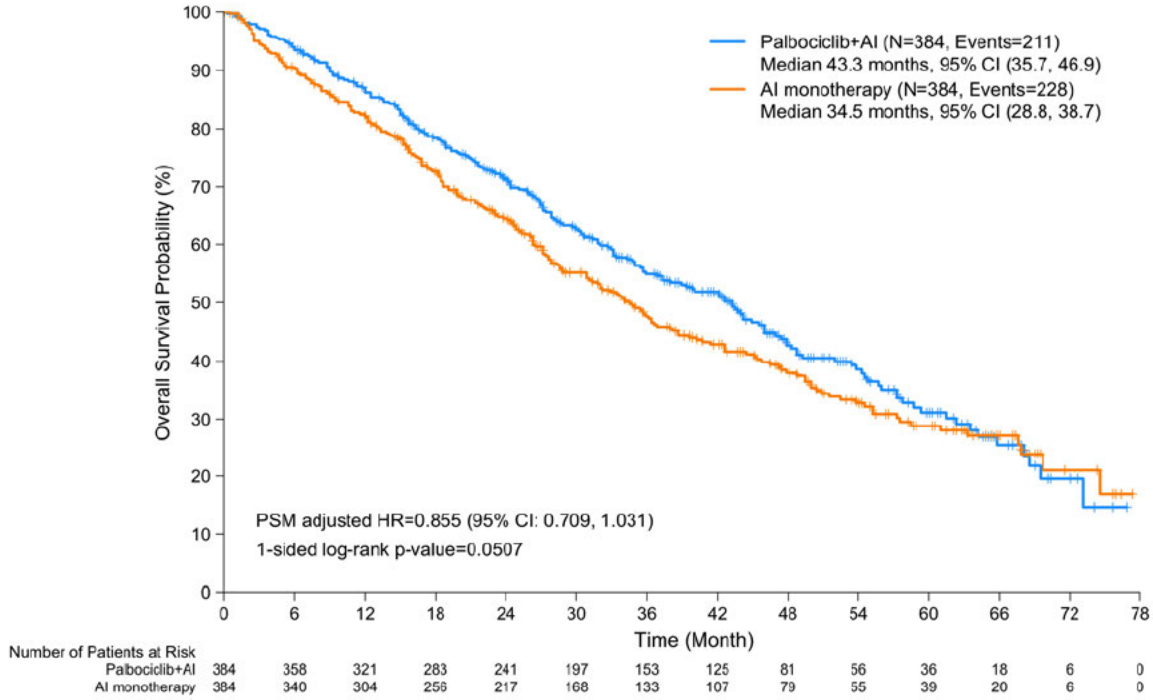
	Palbociclib + AI (N=384)	AI Mono (N=384)

Table 10. Summary of Overall Survival with PSM Adjustment - Propensity Score Matched Patients (Protocol A5481161)

	Palbociclib + AI (N=384)	AI Mono (N=384)
Patients with event, n (%)	211 (54.9)	228 (59.4)
Patients censored, n (%)	173 (45.1)	156 (40.6)
Reason for censoring, n (%)		
Alive in follow-up	140 (36.5)	113 (29.4)
Transferred care	16 (4.2)	23 (6.0)
Lost to follow-up [1]	17 (4.4)	20 (5.2)
Probability of being event-free (95% CI) [2]		
at 6 months	0.940 (0.911, 0.960)	0.905 (0.871, 0.931)
at 12 months	0.863 (0.824, 0.894)	0.820 (0.777, 0.855)
at 24 months	0.713 (0.664, 0.757)	0.645 (0.594, 0.692)
at 36 months	0.549 (0.494, 0.601)	0.476 (0.422, 0.529)
at 48 months	0.427 (0.369, 0.484)	0.380 (0.325, 0.435)
at 60 months	0.311 (0.249, 0.376)	0.288 (0.232, 0.347)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	21.0 (17.1, 24.4)	16.6 (13.8, 18.7)
Median	43.3 (35.7, 46.9)	34.5 (28.8, 38.7)
Q3	68.1 (59.4, NE)	67.9 (57.3, NE)
Adjusted by PSM Comparison vs AI Mono		
Hazard Ratio [4]	0.855	
95% CI [4]	0.709, 1.031	
1-sided p-value [5]	0.0507	

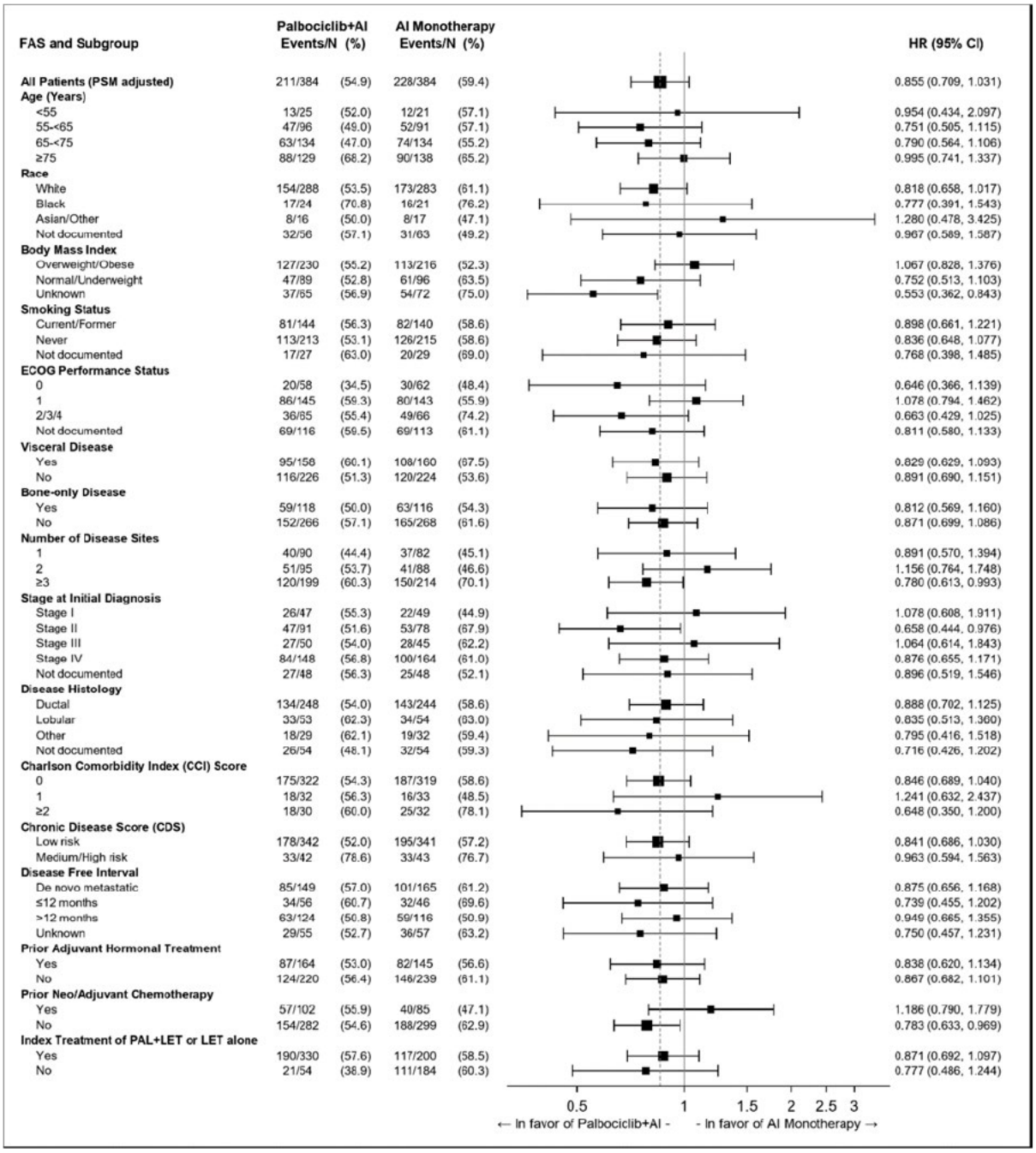
[1] Includes participants deemed to be lost to follow-up in the US Oncology Network.
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Based on the Brookmeyer and Crowley method.
[4] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Palbociclib + AI compared to AI Mono;
[5] p-value from the log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:55) Source Data: adtte Table Generation: 30AUG2022 (15:48)
Output File: ./rWE1161/A5481161 final/adtte os s001 1
Table 14.2.1.3.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Figure 7. Kaplan-Meier Plot of Overall Survival Analysis with PSM Adjustment - Propensity Score Matched Patients



Source: Table 10, Figure 14.2.1.3.2

Figure 8. Forest Plot of Overall Survival by Subgroups with PSM Adjustment - Propensity Score Matched Patients



Source: Table 14.2.1.3.4, Figure 14.2.1.6.2

10.4.1.3. Sensitivity Analysis – PS Stratification Using Quintiles

The results in the sensitivity analysis using PS Stratification (Quintiles) method were consistent with the assessments of the primary analysis.

The analysis of FAS with PS Stratification (Quintiles) is summarized in Table 11 by treatment:

- A total of 675 death events were observed, 395 (47.1%) in the palbociclib + AI cohort and 280 (62.2%) in the AI monotherapy cohort.
- The median OS was 43.3 months (95% CI: 39.4, 46.0) in the palbociclib + AI cohort and 34.5 months (95% CI: 30.9, 38.7) in the AI monotherapy cohort (HR=0.875 [95% CI: 0.742, 1.032]; 1-sided p-value = 0.0565).
- The survival probabilities were numerically higher in the palbociclib + AI cohort compared with the AI monotherapy cohort at 6 months (95.3% vs 90.8%), 12 months (86.7% vs 82.4%), 24 months (71.9% vs 64.8%), 36 months (57.0% vs 48.3%), 48 months (42.3% vs 36.9%) and 60 months (31.0% vs 27.3%).

Table 11. Summary of Overall Survival with Propensity Score Stratification - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Patients with event, n (%)	395 (47.1)	280 (62.2)
Patients censored, n (%)	443 (52.9)	170 (37.8)
Reason for censoring, n (%)		
Alive in follow-up	368 (43.9)	125 (27.8)
Transferred care	41 (4.9)	25 (5.6)
Lost to follow-up [1]	34 (4.1)	20 (4.4)
Probability of being event-free (95% CI) [2]		
at 6 months	0.953 (0.936, 0.965)	0.908 (0.877, 0.931)
at 12 months	0.867 (0.842, 0.889)	0.824 (0.785, 0.856)
at 24 months	0.719 (0.686, 0.749)	0.648 (0.601, 0.691)
at 36 months	0.570 (0.531, 0.606)	0.483 (0.433, 0.531)
at 48 months	0.423 (0.379, 0.467)	0.369 (0.320, 0.419)
at 60 months	0.310 (0.260, 0.361)	0.273 (0.223, 0.325)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	21.4 (18.9, 23.7)	16.8 (14.8, 18.7)
Median	43.3 (39.4, 46.0)	34.5 (30.9, 38.7)
Q3	68.6 (62.4, NE)	67.6 (55.2, 74.5)

Table 11. Summary of Overall Survival with Propensity Score Stratification - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Stratified Analysis [4]		
Comparison vs AI Mono		
Hazard Ratio [5]	0.875	
95% CI [5]	0.742, 1.032	
1-sided p-value [6]	0.0565	

[1] Includes participants deemed to be lost to follow-up in the US Oncology Network.
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Based on the Brookmeyer and Crowley method.
[4] Stratified by quintiles of propensity score
[5] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Palbociclib + AI compared to AI Mono;
[6] p-value from the log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:55) Source Data: adtte Table Generation: 19AUG2022 (15:36)
Output File: ./rWE1161/A5481161 final/adtte os s001 3
Table 14.2.1.1.3 Palbociclib (PD-0332991) is for Pfizer internal use.

10.4.1.4. Supplementary Analyses

Supplementary analyses were performed with different estimand strategies to provide additional insights into the understanding of the OS assessed in the primary analysis. Refer SAP Section 7.2.2.3 for details of the statistical analyses.

10.4.1.4.1. Multivariable Analysis

Multivariable Cox regression analysis was summarized for FAS after nIPTW in Table 14.2.1.2.5. OS results were consistent after additionally adjusting for relevant baseline factors of potential prognostic impact on OS.

10.4.1.4.2. Adjustment for Subsequent Treatment With CDK4/6 Inhibitors

10.4.1.4.2.1. Subsequent Anticancer Treatments

The summary of subsequent anticancer treatments by category and by treatment cohorts for patients who discontinued first-line treatment are summarized in Table 14.4.2.1 (unadjusted), Table 12 (after nIPTW adjustment) and Table 14.4.2.3 (after PSM adjustment), respectively.

In the palbociclib plus AI cohort and AI monotherapy cohort with nIPTW adjustment, 35.1% and 56.2% of patients received CDK 4/6 inhibitor(s) post discontinuation of first-line

treatment, respectively. Palbociclib was the most frequently used CDK 4/6 inhibitor (144/197 and 147/178 of patients, respectively).

Table 12. Summary of Subsequent Anticancer Treatments with nIPTW Adjustment - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Patients who discontinued first-line treatment, n (%) [1]	561 (67.0)	317 (70.5)
Number of LOTs after first-line, n (%) [2]		
1	156 (27.8)	87 (27.3)
2	116 (20.6)	62 (19.5)
3	84 (15.0)	39 (12.4)
4	44 (7.8)	23 (7.4)
≥5	36 (6.4)	22 (7.1)
Median (min,max)	2.0 (1.0, 10.0)	2.0 (1.0, 14.0)
Any subsequent treatment received, n (%) [2]	436 (77.7)	234 (73.7)
Endocrine Therapy	384 (68.5)	224 (70.6)
Fulvestrant	293 (52.2)	171 (53.8)
Exemestane	110 (19.6)	42 (13.3)
Letrozole	86 (15.3)	65 (20.5)
Anastrozole	25 (4.5)	35 (10.9)
Tamoxifen	13 (2.3)	28 (8.8)
Other	0	0 (0.1)
Chemotherapy	229 (40.9)	105 (33.1)
CDK 4/6 Inhibitor	197 (35.1)	178 (56.2)
Palbociclib	144 (25.6)	147 (46.2)
Abemaciclib	56 (9.9)	31 (9.8)
Ribociclib	14 (2.6)	15 (4.7)
mTOR Inhibitor	115 (20.4)	28 (8.7)
PI3K Inhibitor	46 (8.1)	12 (3.7)
PARP Inhibitor	9 (1.7)	1 (0.4)
Antiandrogen	6 (1.1)	4 (1.1)
Angiogenesis Inhibitor	3 (0.5)	0
Other	2 (0.4)	3 (1.0)
EGFR Inhibitor	1 (0.1)	0
Anti-HER2 Therapy	0	1 (0.2)
Any second-line treatment received, n (%) [2]	436 (77.7)	234 (73.7)
Endocrine Therapy	350 (62.3)	209 (66.0)
Fulvestrant	218 (38.8)	118 (37.1)
Letrozole	76 (13.5)	53 (16.8)
Exemestane	48 (8.6)	22 (6.9)

Table 12. Summary of Subsequent Anticancer Treatments with nIPTW Adjustment - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Anastrozole	19 (3.3)	25 (7.9)
Tamoxifen	6 (1.1)	13 (4.0)
Other	0	0
CDK 4/6 Inhibitor	153 (27.3)	139 (43.8)
Palbociclib	126 (22.4)	116 (36.6)
Abemaciclib	23 (4.1)	12 (3.8)
Ribociclib	6 (1.1)	11 (3.4)
Chemotherapy	77 (13.6)	31 (9.7)
mTOR Inhibitor	48 (8.6)	3 (0.8)
PI3K Inhibitor	20 (3.5)	1 (0.2)
Antiandrogen	2 (0.3)	1 (0.2)
Other	2 (0.3)	0
PARP Inhibitor	1 (0.3)	0

Weighted counts from nIPTW adjustment are displayed with rounding. All percentages are based on actual weighted counts.
[1] Percentages were relative to the number of patients in the respective treatment cohort.
[2] Percentages were relative to the number of patients who discontinued first-line treatment in the respective treatment cohort.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:27) Source Data: adcm Table Generation: 01SEP2022 (16:11)
Output File: ./rWE1161/A5481161 final/adcm ns003 niptw
Table 14.4.2.2 Palbociclib (PD-0332991) is for Pfizer internal use.

10.4.1.4.2.2. RPSFT Analysis

In the unadjusted AI monotherapy cohort, 166 (50.3%) patients received CDK 4/6 inhibitor(s) post first-line therapy (Table 14.4.2.1). To correct for the potential confounding impact on OS for the patients in the AI monotherapy cohort subsequently treated with palbociclib or other CDK 4/6 inhibitor(s), a sensitivity analysis of OS was carried out using the RPSFT method to estimate the counterfactual OS of the AI monotherapy cohort that would have been observed as if subsequent treatment of CDK 4/6 inhibitors had not occurred, assuming palbociclib and other CDK 4/6 inhibitors have a similar treatment effect in this patient population.

After adjusting for the effect of palbociclib and/or other CDK 4/6 inhibitors as subsequent treatment in the AI monotherapy cohort, the median OS for the AI monotherapy cohort was reduced to 32.6, 33.4, and 31.7 months, in the unadjusted, nIPTW adjusted, and PSM adjusted analyses, respectively (Table 13). The nIPTW-adjusted HR was 0.825 (bootstrap 95% CI: 0.645, 1.030) and the PSM-adjusted HR was 0.785 (bootstrap 95% CI: 0.605, 0.989)

and improvements in HRs confirming impact of subsequent CDK 4/6 inhibitor use compared to the HRs obtained using conventional statistical methods (Table 13).

The results of RPSFT analyses are summarized in Table 13 and displayed graphically in Figure 14.2.1.7.2 (unadjusted), Figure 14.2.1.7.3 (with nIPTW adjustment) and Figure 14.2.1.7.4 (with PSM adjustment).

Table 13. Summary of Overall Survival by Conventional and RPSFT Analyses – Full Analysis Set

	Palbociclib + AI	AI Mono
Conventional Analysis (Unadjusted)		
N	838	450
Median (95% CI[1]), months	43.3 (39.4, 46.0)	34.5 (30.9, 38.7)
Hazard Ratio[2] (95% CI)	0.820 (0.703, 0.957)	
P-value[3]	0.0058	
RPSFT Analysis (Unadjusted)		
N	838	450
Median (95% CI[1]), months	43.3 (39.4, 46.0)	32.6 (27.9, 36.0)
Hazard Ratio[2] (95% CI[4])	0.752 (0.604, 0.928)	
Conventional Analysis (nIPTW adjusted)		
N	838	450
Median (95% CI[1]), months	42.1 (36.8, 44.4)	35.7 (30.9, 42.6)
Hazard Ratio[5] (95% CI)	0.898 (0.752, 1.071)	
P-value[6]	0.1165	
RPSFT Analysis (nIPTW adjusted)		
N	838	450
Median (95% CI[1]), months	42.1 (36.8, 44.4)	33.4 (29.2, 38.3)
Hazard Ratio[5] (95% CI[4])	0.825 (0.645, 1.030)	
Conventional Analysis (PSM adjusted)		
N	384	384
Median (95% CI[1]), months	43.3 (35.7, 46.9)	34.5 (28.8, 38.7)
Hazard Ratio[2] (95% CI)	0.855 (0.709, 1.031)	
P-value[3]	0.0507	
RPSFT Analysis (PSM adjusted)		
N	384	384
Median (95% CI[1]), months	43.3 (35.7, 46.9)	31.7 (27.4, 35.6)
Hazard Ratio[2] (95% CI[4])	0.785 (0.605, 0.989)	

Source: Table 8, Table 9, Table 10
Abbreviations: CI = confidence interval; N = number of patients; nIPTW = normalized inverse probability treatment weighting; PSM = propensity score matching; RPSFT = rank preserving structural failure time.
[1] Based on the Brookmeyer and Crowley Method.
[2] Based on Cox proportional hazards model. Under proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of palbociclib + AI.
[3] 1-sided log-rank test.
[4] Based on 5,000 bootstraps with bias correction.
[5] Based on weighted Cox proportional hazards model.
[6] 1-sided weighted log-rank test with robust variance estimator.

10.4.2. Real-World Progression-Free Survival

rwPFS was a secondary endpoint. nIPTW based on PS were used to estimate the effectiveness of palbociclib + AI vs AI monotherapy as the main analysis, PSM and PS stratification (quintiles) based on the PS were used as the secondary analyses (Appendix 4 SAP, Section 7.2.3.1). Prespecified subgroup analyses of rwPFS were conducted according to the baseline patient demographics and disease characteristics. Following rwPFS analysis was conducted based on the data with the cutoff date of 31 August 2021.

The rwPFS based on the unadjusted FAS is summarized in Table 14.2.2.1.3 and Table 14.2.2.1.1 by treatment:

- A total of 806 events were observed, 477 (56.9%) in the palbociclib + AI cohort and 329 (73.1%) in the AI monotherapy cohort.
- The unadjusted median PFS was 21.2 months (95% CI: 19.1, 23.0) in the palbociclib + AI cohort and 15.7 months (95% CI: 13.1, 18.4) in the AI monotherapy cohort (HR=0.718 [95% CI: 0.624, 0.827]; 1-sided p-value <0.0001).

The Kaplan-Meier plot of rwPFS by treatment cohort for unadjusted FAS is presented in Figure 14.2.2.1.2. The follow-up duration of rwPFS for unadjusted FAS is summarized in Table 14.2.2.1.3.

10.4.2.1. Main Analysis – nIPTW Adjustment

rwPFS by Treatment

The rwPFS based on FAS with nIPTW adjustment is summarized in Table 14 by treatment:

- The median rwPFS was 21.0 months (95% CI: 18.7, 22.6) in the palbociclib + AI cohort and 15.7 months (95% CI: 13.1, 19.1) in the AI monotherapy cohort (HR = 0.750 [95% CI: 0.638, 0.882], 1-sided p-value = 0.0002).

The Kaplan-Meier plot of rwPFS by treatment cohort for FAS with nIPTW adjustment is presented in Figure 9. The follow-up duration of rwPFS for FAS with nIPTW adjustment is summarized in Table 14.2.2.2.3.

rwPFS by Subgroups

The analysis of rwPFS for FAS with nIPTW adjustment conducted by subgroups was summarized in Table 14.2.2.5.3.

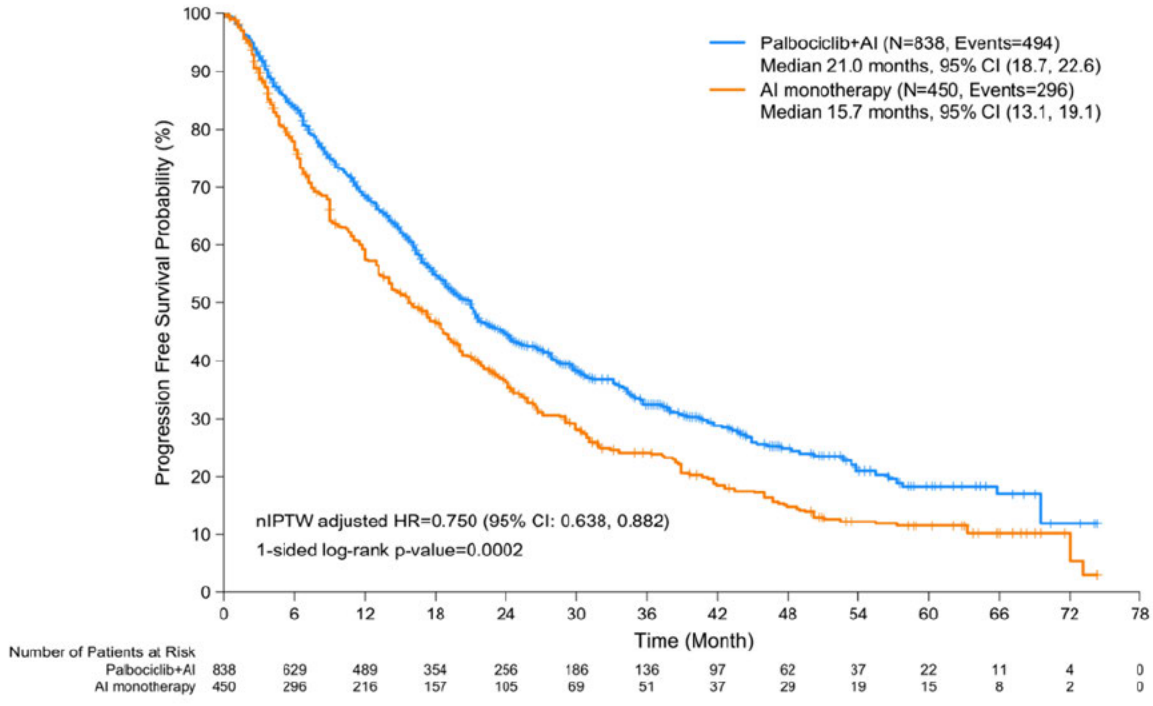
The forest plot of rwPFS in the selected subgroups with nIPTW adjustment is presented in Figure 10. The figure presents the HRs and 95% CIs from the analysis of rwPFS in each of the subgroups. The HR for rwPFS favored palbociclib + AI in most subgroups.

Table 14. Summary of Real-World Progression-Free Survival with nIPTW Adjustment - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Patients with event, n (%)	494 (58.9)	296 (65.7)
Patients censored, n (%)	344 (41.1)	154 (34.3)
Reason for censoring, n (%)		
No on-treatment tumor assessment	66 (7.9)	39 (8.7)
Start of new anti-cancer therapy	64 (7.7)	35 (7.9)
Lost to follow-up/Transferred care	30 (3.6)	22 (4.9)
In follow-up without an event	184 (21.9)	57 (12.7)
Probability of being event-free (95% CI) [1]		
at 6 months	0.840 (0.810, 0.865)	0.778 (0.724, 0.823)
at 12 months	0.685 (0.648, 0.718)	0.575 (0.514, 0.632)
at 24 months	0.445 (0.405, 0.484)	0.363 (0.305, 0.422)
at 36 months	0.324 (0.284, 0.365)	0.241 (0.190, 0.296)
at 48 months	0.249 (0.207, 0.293)	0.148 (0.106, 0.196)
at 60 months	0.183 (0.137, 0.235)	0.115 (0.078, 0.160)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	9.0 (7.9, 10.8)	6.5 (5.1, 7.4)
Median	21.0 (18.7, 22.6)	15.7 (13.1, 19.1)
Q3	47.4 (41.7, 56.6)	32.0 (28.6, 41.2)
Adjusted by nIPTW Comparison vs AI Mono		
Hazard Ratio [3]	0.750	
95% CI [3]	0.638, 0.882	
1-sided p-value [4]	0.0002	

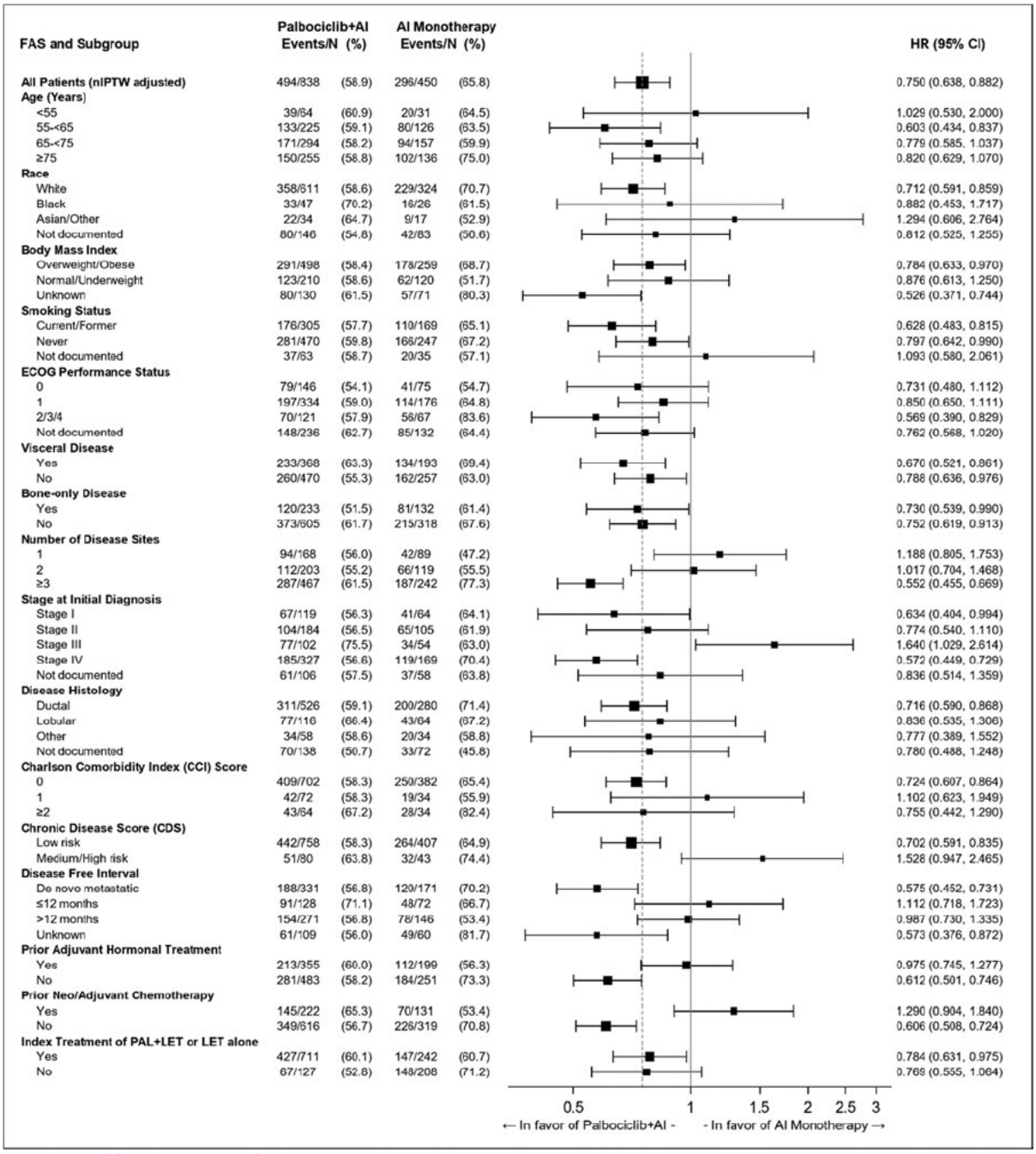
Numbers under individual categories may not add to combined categories due to weighting and rounding with nIPTW. Weighted counts from nIPTW adjustment are displayed with rounding. All percentages are based on actual weighted counts.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] Based on the Brookmeyer and Crowley method.
[3] Hazard ratio based on weighted Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Palbociclib + AI compared to AI Mono;
[4] p-value from the weighted log-rank test with robust variance estimator.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:55) Source Data: adtte Table Generation: 30AUG2022 (17:12)
Output File: ./rWE1161/A5481161 final/adtte pfs s001 2
Table 14.2.2.2.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Figure 9. Kaplan-Meier Plot of Real-World Progression-Free Survival with nIPTW Adjustment - Full Analysis Set



Source: Table 14, Figure 14.2.2.2.2

Figure 10. Forest Plot of Real-World Progression-Free Survival by Subgroups with nIPTW Adjustment - Full Analysis Set



Source: Table 14.2.2.5.3, Figure 14.2.2.5.4

10.4.2.2. Secondary Analyses - PSM Adjustment

The results in the secondary analysis using PSM method were consistent with the assessments of the primary analysis.

rwPFS by Treatment

The rwPFS based on PSM adjusted FAS is summarized in Table 15 by treatment:

- The median rwPFS was 21.0 months (95% CI: 17.7, 24.4) in the palbociclib + AI cohort and 14.8 months (95% CI: 12.2, 17.3) in the AI monotherapy cohort (HR = 0.707 [95% CI: 0.594, 0.841], 1-sided p-value <0.0001).

The Kaplan-Meier plot of rwPFS by treatment cohort for FAS with PSM adjustment is presented in Figure 11. The follow-up duration of rwPFS for FAS with PSM adjustment is summarized in Table 14.2.2.3.3.

rwPFS by Subgroups

The analysis of rwPFS for FAS with PSM adjustment conducted by subgroups was summarized in Table 14.2.2.5.5.

The forest plot of rwPFS in the selected subgroups with PSM adjustment is presented in Figure 12. The figure presents the HRs and 95% CIs from the analysis of rwPFS in each of the subgroups.

Table 15. Summary of Real-World Progression-Free Survival with PSM Adjustment - Propensity Score Matched Patients (Protocol A5481161)

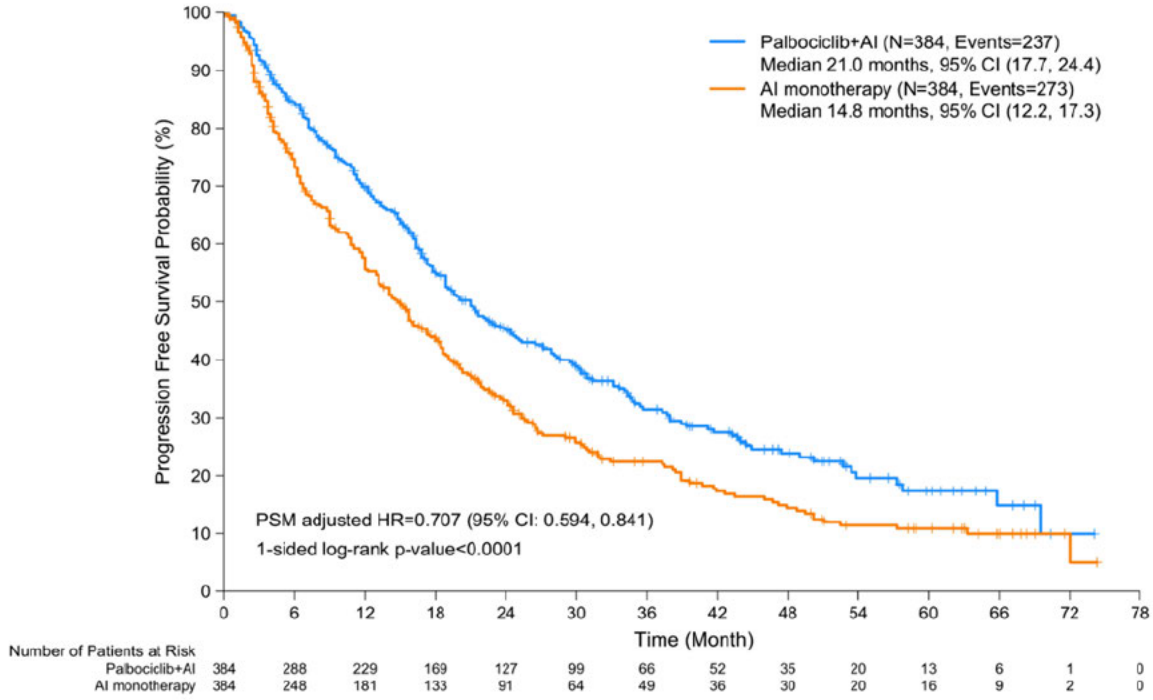
	Palbociclib + AI (N=384)	AI Mono (N=384)
Patients with event, n (%)	237 (61.7)	273 (71.1)
Patients censored, n (%)	147 (38.3)	111 (28.9)
Reason for censoring, n (%)		
No on-treatment tumor assessment	32 (8.3)	28 (7.3)
Start of new anti-cancer therapy	31 (8.1)	27 (7.0)
Lost to follow-up/Transferred care	16 (4.2)	13 (3.4)
In follow-up without an event	68 (17.7)	43 (11.2)
Probability of being event-free (95% CI) [1]		
at 6 months	0.845 (0.803, 0.879)	0.747 (0.697, 0.790)
at 12 months	0.699 (0.647, 0.744)	0.555 (0.500, 0.607)
at 24 months	0.452 (0.396, 0.505)	0.329 (0.278, 0.381)
at 36 months	0.314 (0.260, 0.369)	0.224 (0.178, 0.274)
at 48 months	0.239 (0.187, 0.294)	0.144 (0.104, 0.191)
at 60 months	0.173 (0.120, 0.235)	0.108 (0.072, 0.152)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	9.7 (7.6, 11.8)	5.8 (4.2, 6.7)

Table 15. Summary of Real-World Progression-Free Survival with PSM Adjustment - Propensity Score Matched Patients (Protocol A5481161)

	Palbociclib + AI (N=384)	AI Mono (N=384)
Median	21.0 (17.7, 24.4)	14.8 (12.2, 17.3)
Q3	44.9 (38.0, 57.3)	30.6 (25.3, 38.9)
Adjusted by PSM Comparison vs AI Mono		
Hazard Ratio [3]	0.707	
95% CI [3]	0.594, 0.841	
1-sided p-value [4]	<.0001	

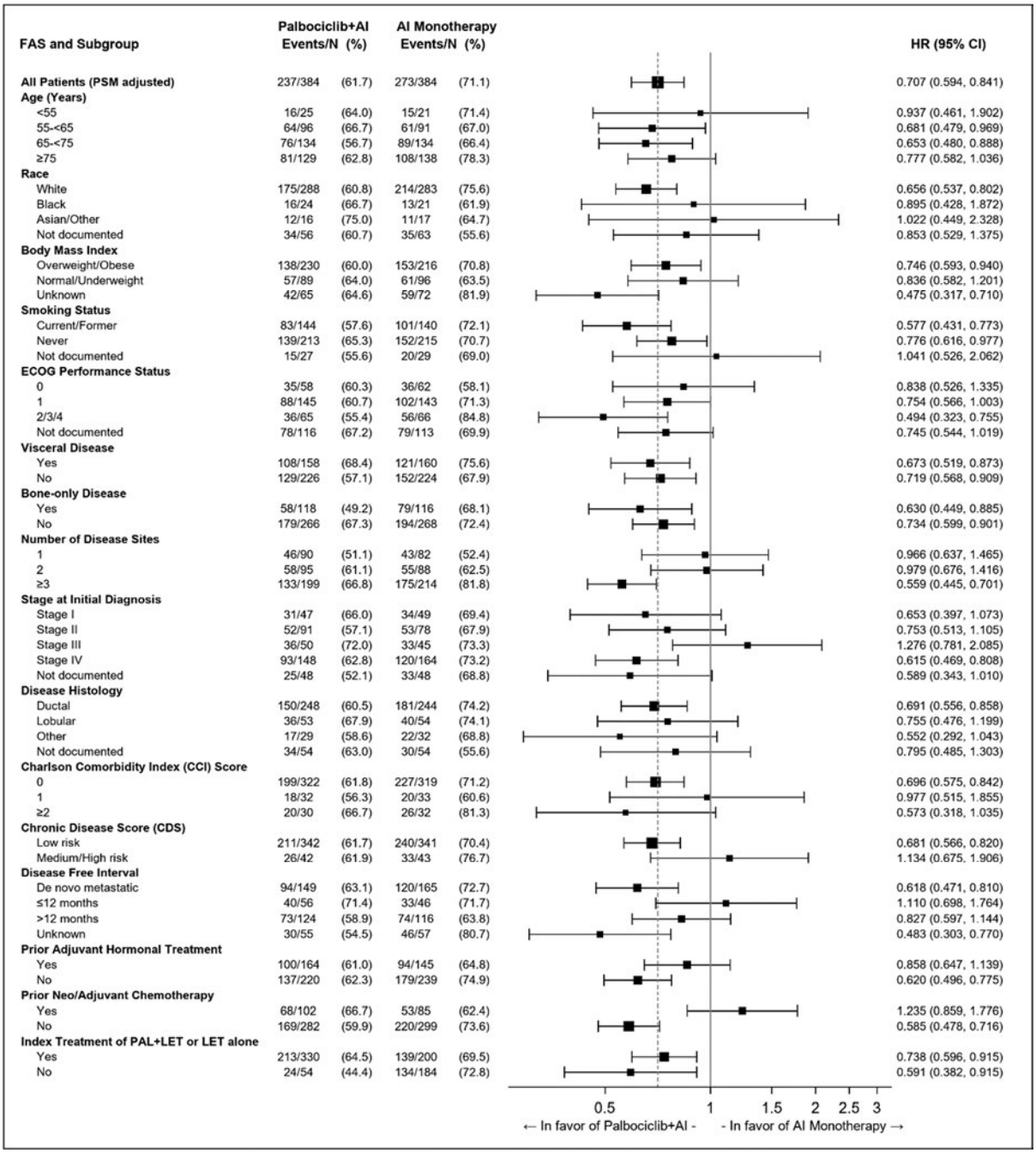
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] Based on the Brookmeyer and Crowley method.
[3] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Palbociclib + AI compared to AI Mono;
[4] p-value from the log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:55) Source Data: adtte Table Generation: 30AUG2022 (15:58)
Output File: ./rWE1161/A5481161 final/adtte pfs s001 1
Table 14.2.2.3.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Figure 11. Kaplan-Meier Plot of Real-World Progression-Free Survival with PSM Adjustment - Propensity Score Matched Patients



Source: Table 15, Figure 14.2.2.3.2

Figure 12. Forest Plot of Real-World Progression-Free Survival by Subgroups with PSM Adjustment - Propensity Score Matched Patients



Source: Table 14.2.2.5.5, Figure 14.2.2.5.6

10.4.2.3. Secondary Analyses – PS Stratification (Quintiles)

The results in the secondary analysis using PS stratification were consistent with the assessments of the primary analysis.

The rwPFS based on FAS with PS stratification is summarized in Table 14.2.2.4.1 by treatment:

- The median rwPFS was 21.2 months (95% CI: 19.1, 23.0) in the palbociclib + AI cohort and 15.7 months (95% CI: 13.1, 18.4) in the AI monotherapy cohort (HR = 0.715 [95% CI: 0.613, 0.834], 1-sided p-value <0.0001).

10.4.3. Real-World Tumor Response

nIPTW were used to estimate the effectiveness of palbociclib + AI vs AI monotherapy as main analysis, PSM was used as the secondary analysis (Appendix 4 SAP, Section 7.2.3.2). Following rwRR analysis was conducted based on the data with the cutoff date of 31 August 2021.

10.4.3.1. Main Analysis – nIPTW Adjustment

rwTR in FAS

The rwTR and rwRR based on FAS before and after nIPTW adjustment are presented in Table 16. The real-world response (CR + PR) rate (95% CI) adjusted by nIPTW was 50.6% (47.2%, 54.0%) in the palbociclib + AI cohort and 29.7% (25.7%, 34.1%) in the AI monotherapy cohort. The odds ratio (95% CI) of palbociclib + AI vs AI monotherapy was 2.426 (1.902, 3.095).

rwTR in Patients With Tumor Assessment

The rwTR of FAS who had at least 1 imaging-based tumor assessment on treatment is presented in Table 17. The real-world response (CR + PR) rate (95% CI) adjusted by nIPTW in patients with tumor assessment was 59.8% (56.1%, 63.3%) in the palbociclib + AI cohort and 39.9% (34.7%, 45.4%) in the AI monotherapy cohort. The odds ratio (95% CI) of palbociclib + AI vs AI monotherapy was 2.240 (1.711, 2.934).

Table 16. Real-World Tumor Response Unadjusted and with nIPTW Adjustment - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Real-World Best Overall Response Unadjusted, n (%)		
Complete response (CR)	61 (7.3)	26 (5.8)
Partial response (PR)	376 (44.9)	102 (22.7)

Table 16. Real-World Tumor Response Unadjusted and with nIPTW Adjustment - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)
Stable disease (SD) [1]	184 (22.0)	101 (22.4)
Progressive disease (PD)	87 (10.4)	70 (15.6)
Not evaluable (NE)	130 (15.5)	151 (33.6)
No tumor assessment on index treatment	9 (1.1)	36 (8.0)
Tumor assessment within 30 days of start of index treatment	5 (0.6)	11 (2.4)
Tumor assessment is not imaging based	6 (0.7)	7 (1.6)
Not done	110 (13.1)	97 (21.6)
Real-World Tumor Response Unadjusted		
Real-World Response (CR+PR) Rate, n (%)	437 (52.1)	128 (28.4)
95% CI [2]	48.8, 55.5	24.5, 32.8
Comparison vs. AI Mono		
Odds Ratio [3]	2.741	
95% CI [3]	2.130, 3.535	
1-sided p-value [3]	<.0001	
Real-World Best Overall Response Adjusted by nIPTW, n(%)		
Complete response (CR)	56 (6.7)	36 (8.0)
Partial response (PR)	368 (43.9)	98 (21.7)
Stable disease (SD) [1]	187 (22.3)	97 (21.5)
Progressive disease (PD)	82 (9.7)	65 (14.5)
Not evaluable (NE)	145 (17.3)	154 (34.3)
No tumor assessment on index treatment	9 (1.1)	45 (10.0)
Tumor assessment within 30 days of start of index treatment	8 (0.9)	8 (1.9)
Tumor assessment is not imaging based	7 (0.8)	6 (1.3)
Not done	122 (14.5)	95 (21.1)
Real-World Tumor Response adjusted by nIPTW		
Real-World Response (CR+PR) Rate, n (%)	424 (50.6)	134 (29.7)
95% CI [2]	47.2, 54.0	25.7, 34.1
Comparison vs. AI Mono		
Odds Ratio [4]	2.426	
95% CI [4]	1.902, 3.095	
1-sided p-value [4]	<.0001	

Table 16. Real-World Tumor Response Unadjusted and with nIPTW Adjustment - Full Analysis Set (Protocol A5481161)

	Palbociclib + AI (N=838)	AI Mono (N=450)

Patients under individual categories may not add to combined categories due to weighting and rounding with nIPTW adjustment.
Weighted counts from nIPTW adjustment are displayed with rounding. All percentages are based on actual weighted counts.
[1] Including Mixed Response (MR) collected from CRF page.
[2] Based on the Wilson Score Method.
[3] Based on CMH Method.
[4] Based on weighted rwRR using the CMH Method.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:55) Source Data: rs Table Generation: 31AUG2022 (16:30)
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Table 14.6.1.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Table 17. Real-World Tumor Response Unadjusted and with nIPTW Adjustment - Full Analysis Set with At Least 1 Imaging-Based Tumor Assessment on Treatment (Protocol A5481161)

	Palbociclib + AI (N=710)	AI Mono (N=319)
Real-World Best Overall Response Unadjusted, n (%)		
Complete response (CR)	61 (8.6)	26 (8.2)
Partial response (PR)	376 (53.0)	102 (32.0)
Stable disease (SD) [1]	179 (25.2)	96 (30.1)
Progressive disease (PD)	80 (11.3)	54 (16.9)
Not evaluable (NE)	14 (2.0)	41 (12.9)
No tumor assessment on index treatment	9 (1.3)	34 (10.7)
Tumor assessment within 30 days of start of index treatment	5 (0.7)	7 (2.2)
Real-World Tumor Response Unadjusted		
Real-World Response (CR+PR) Rate, n (%)	437 (61.5)	128 (40.1)
95% CI [2]	57.9, 65.1	34.9, 45.6
Comparison vs. AI Mono		
Odds Ratio[3]	2.388	
95% CI[3]	1.806, 3.159	
1-sided p-value[3]	<.0001	
Real-World Best Overall Response Adjusted by nIPTW, n(%)		
Complete response (CR)	57 (8.0)	31 (9.7)
Partial response (PR)	368 (51.8)	96 (30.2)

Table 17. Real-World Tumor Response Unadjusted and with nIPTW Adjustment - Full Analysis Set with At Least 1 Imaging-Based Tumor Assessment on Treatment (Protocol A5481161)

	Palbociclib + AI (N=710)	AI Mono (N=319)
Stable disease (SD) [1]	188 (26.5)	91 (28.5)
Progressive disease (PD)	76 (10.7)	52 (16.4)
Not evaluable (NE)	21 (3.0)	49 (15.2)
No tumor assessment on index treatment	9 (1.3)	43 (13.6)
Tumor assessment within 30 days of start of index treatment	12 (1.7)	5 (1.6)
Real-World Tumor Response adjusted by nIPTW		
Real-World Response (CR+PR) Rate, n (%)	425 (59.8)	127 (39.9)
95% CI [2]	56.1, 63.3	34.7, 45.4
Comparison vs. AI Mono		
Odds Ratio [4]	2.240	
95% CI [4]	1.711, 2.934	
1-sided p-value [4]	<.0001	

Patients under individual categories may not add to combined categories due to weighting and rounding with nIPTW adjustment.
Weighted counts from nIPTW adjustment are displayed with rounding. All percentages are based on actual weighted counts.
[1] Including Mixed Response (MR) collected from CRF page.
[2] Based on the Wilson Score Method.
[3] Based on CMH Method.
[4] Based on weighted rwRR using the CMH Method.
PFIZER CONFIDENTIAL SDTM Creation: 18AUG2022 (17:14) Source Data: adrs adsl Table Generation: 31AUG2022 (16:30)
Output File: ./rWE1161/A5481161_final/adrs_bor_ns003
Table 14.6.1.2 Palbociclib (PD-0332991) is for Pfizer internal use.

10.4.3.2. Secondary Analysis – PSM Adjustment

The results in the secondary analysis using PSM method were consistent with the assessments of the main analysis.

rwTR in FAS

The rwTR and rwRR based on FAS after PSM adjustment are presented in Table 18. The real-world response (CR + PR) rate (95% CI) adjusted by nIPTW was 47.1 (42.2%, 52.1%)

in the palbociclib + AI cohort and 27.1% (22.9%, 31.7%) in the AI monotherapy cohort. The odds ratio (95% CI) of palbociclib + AI vs AI monotherapy was 2.401 (1.756, 3.283).

rwTR in Patients With Tumor Assessment

The rwTR of FAS who had at least 1 imaging-based tumor assessment on treatment is presented in Table 19. The real-world response (CR + PR) rate (95% CI) adjusted by PSM in patients with tumor assessment was 58.0 (52.1%, 63.6%) in the palbociclib + AI cohort and 40.9% (35.3%, 46.8%) in the AI monotherapy cohort. The odds ratio (95% CI) of palbociclib + AI vs AI monotherapy was 1.990 (1.398, 2.832).

Table 18. Real-World Tumor Response with PSM Adjustment - Propensity Score Matched Patients (Protocol A5481161)

	Palbociclib + AI (N=384)	AI Mono (N=384)
Real-World Best Overall Response Adjusted by PSM, n (%)		
Complete response (CR)	23 (6.0)	22 (5.7)
Partial response (PR)	158 (41.1)	82 (21.4)
Stable disease (SD) [1]	94 (24.5)	81 (21.1)
Progressive disease (PD)	36 (9.4)	62 (16.1)
Not evaluable (NE)	73 (19.0)	137 (35.7)
No tumor assessment on index treatment	5 (1.3)	34 (8.9)
Tumor assessment within 30 days of start of index treatment	3 (0.8)	11 (2.9)
Tumor assessment is not imaging based	3 (0.8)	7 (1.8)
Not done	62 (16.1)	85 (22.1)
Real-World Tumor Response Adjusted by PSM		
Real-World Response (CR+PR) Rate, n (%)	181 (47.1)	104 (27.1)
95% CI [2]	42.2, 52.1	22.9, 31.7
Comparison vs. AI Mono		
Odds Ratio [3]	2.401	
95% CI [3]	1.756, 3.283	
1-sided p-value [3]	<.0001	

[1] Including Mixed Response (MR) collected from CRF page.
[2] Based on the Wilson Score Method.
[3] Based on CMH Method.
PFIZER CONFIDENTIAL SDTM Creation: 18AUG2022 (17:14) Source Data: adrs adsl Table Generation: 22AUG2022 (15:29)
Output File: ./rWE1161/A5481161_final/adrs_bor_m_ns001
Table 14.6.2.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Table 19. Real-World Tumor Response with PSM Adjustment - Propensity Score Matched Patients with At Least 1 Imaging-Based Tumor Assessment On Treatment (Protocol A5481161)

	Palbociclib + AI (N=276)	AI Mono (N=276)
Real-World Best Overall Response Adjusted by PSM, n (%)		
Complete response (CR)	21 (7.6)	22 (8.0)
Partial response (PR)	139 (50.4)	91 (33.0)
Stable disease (SD) [1]	74 (26.8)	79 (28.6)
Progressive disease (PD)	35 (12.7)	47 (17.0)
Not evaluable (NE)	7 (2.5)	37 (13.4)
No tumor assessment on index treatment	4 (1.4)	32 (11.6)
Tumor assessment within 30 days of start of index treatment	3 (1.1)	5 (1.8)
Real-World Tumor Response Adjusted by PSM		
Real-World Response (CR+PR) Rate, n (%)	160 (58.0)	113 (40.9)
95% CI [2]	52.1, 63.6	35.3, 46.8
Comparison vs. AI Mono		
Odds Ratio [3]	1.990	
95% CI [3]	1.398, 2.832	
1-sided p-value [3]	<.0001	

[1] Including Mixed Response (MR) collected from CRF page.
[2] Based on the Wilson Score Method.
[3] Based on CMH Method.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2022 (09:55) Source Data: adrs Table Generation: 22AUG2022 (10:15)
Output File: ./rWE1161/A5481161 final/adrs bor m ns001 ta
Table 14.6.2.2 Palbociclib (PD-0332991) is for Pfizer internal use.

[redacted]

[redacted]

10.5. Other Analyses

None.

10.6. Adverse Events / Adverse Reactions

The number of cases of pneumonitis or ILD which occurred while on first-line treatment plus 30 days after treatment discontinuation, directly attributable to the treatment were reported.

In the palbociclib + AI cohort, the ADRs (based on statements of explicit attribution identified during medical chart abstraction of unstructured data) pneumonitis and ILD were reported in 5 patients during the first-line treatment (Table 14.5.1 and Listing 16.2.7). Individual deaths are listed in Listing 16.2.7.1.

In accordance with the A5481161 study protocol, other AEs with explicit attribution to a Pfizer product identified during unstructured data review of patients' medical records were reported in the safety database and reviewed. Events were consistent with the known Palbociclib safety profile.

11. DISCUSSION

11.1. Key Results

Real-world evidence of effectiveness in an approved medication is an important complement to evidence from RCTs. Real-world data representing a multisite and heterogeneous sample of patients across the US have been previously used to assess effectiveness outcomes in approved oncology medication in the USON database across different tumor types.[21,22,23,24,25,26,27]

Study 1161 aimed to compare the effectiveness of palbociclib + AI compared to AI monotherapy as first-line therapy for HR+/HER2- MBC during the index period from 01 February 2015 through 30 June 2020 until the data cutoff date of 31 August 2021 using data obtained from structured data within the EHR system of the USON iKM database and unstructured data collected through targeted chart review.

Overall, the results showed an associated benefit for patients treated with palbociclib combination therapy compared to AI alone in this analysis of effectiveness for first line treatment using OS, rwPFS (by treatment and subgroups) and rwRR (including patients with tumor assessments). Although the study demonstrated a numerical improvement associated with the palbociclib + AI arm in OS as assessed by nIPTW (42.1 months (95% CI: 36.8, 44.4) vs. 35.7 months (95% CI: 30.9, 42.6) respectively (HR=0.898 [95% CI: 0.752, 1.071]; 1-sided p-value = 0.1165) the finding was not statistically significant. The median OS in the PSM sensitivity analysis was 43.3 months (95% CI: 35.7, 46.9) in the palbociclib + AI cohort and 34.5 months (95% CI: 28.8, 38.7) in the AI monotherapy cohort (HR=0.855 [95% CI:

0.709, 1.031]; 1-sided p-value = 0.0507). The RPSFT analysis adjusting for subsequent treatment with palbociclib or other CDK 4/6 inhibitor(s) in the AI monotherapy cohort showed improved HR in all 3 analyses (unadjusted, nIPTW adjusted, and PSM adjusted), demonstrating the impact of subsequent CDK 4/6i treatment which may lead to underestimate of the treatment effect of palbociclib + AI in the first line. The majority of those treated with CDK 4/6 inhibitors post first-line therapy were with palbociclib (144/197 and 147/178 in the palbociclib + AI and AI cohorts, respectively).

The median rwPFS adjusted by nIPTW was 21.0 months (95% CI: 18.7, 22.6) in the palbociclib + AI cohort vs 15.7 months (95% CI: 13.1, 19.1) in the AI monotherapy cohort (HR=0.750 [95% CI: 0.638, 0.882]; 1-sided p-value = 0.0002). The median rwPFS adjusted by PSM was 21.0 months (95% CI: 17.7, 24.4) in the palbociclib + AI cohort and 14.8 months (95% CI: 12.2, 17.3) in the AI monotherapy cohort (HR = 0.707 [95% CI: 0.594, 0.841], 1-sided p-value <0.0001). In the FAS, rwRR adjusted by nIPTW was 50.6 (47.2%, 54.0%) in the palbociclib + AI cohort and 29.7% (25.7%, 34.1%) in the AI monotherapy cohort (odds ratio [95% CI] = 2.426 [1.902, 3.095]). Similarly, in patients with at least 1 tumor assessment, rwRR adjusted by nIPTW was 59.8% (56.1%, 63.3%) in the palbociclib + AI cohort and 39.9% (34.7%, 45.4%) in the AI monotherapy cohort (odds ratio [95% CI] = 2.240 [1.711, 2.934]).

11.2. Limitations

11.2.1. Internal Validity of Study Design

Potential sources of bias included but not limited to:

1. Imbalance in cohort size
2. Measurement errors/misclassifications.
3. Information bias.
4. Confounding.

To minimize these bias risks:

1. A targeted chart review was performed to verify patients' eligibility and data elements that may not have been reliably captured if only relying on structured fields. With chart review, progress notes and additional free-text were reviewed to provide a much richer source of information. All patients in the study sample underwent chart review.
2. The study observation period began on the date palbociclib was approved for the treatment of MBC so that the study cohorts both represented the treatment landscape after this approval. Using a contemporaneous comparator group helped reduce potential confounding by examining the same period of time.

3. An ITT approach was used for analysis. As an example, there was an assumption that all prescribed oral therapies were taken as it would not be possible to confirm if dispensed oral therapies were taken. In addition, statistical methodology, such as IPTW and PSM, were employed to mitigate against potential confounding due to selection biases. It is important to emphasize that using PS methodology to balance the baseline characteristics between the 2 treatment cohorts was conducted independently and prior to access of the outcome data. Therefore, estimation of PS, generation of IPTW/nIPTW and feasibility assessment were not influenced by the outcome data. The following 2 steps were implemented using a staggered approach in the McKesson data transfer:

    - **Step 1**: Baseline characteristics data were transferred first to Pfizer to perform balancing process using PS analysis, ie, generate PSs and conduct feasibility assessment with IPTW/nIPTW, PSM and PS quintile stratification. For each method, the PS was re-run so that the baseline covariates were balanced between the 2 cohorts for the subsequent outcome analysis.

    - **Step 2**: Only after the balancing process was completed for each planned analysis and SAP was finalized, the data containing outcome variables (death, tumor assessments) were transferred to Pfizer to perform the comparative effectiveness analyses.

11.2.2. External Validity of Study Design

Not all USON practices were included in the dataset. The USON utilizes the iKM EHR and decision-support technology which may influence treatment patterns. The rwPFS and tumor response endpoints in USON network have not been validated. The results of this study were most generalizable to other community oncology practices that adhere to evidence-based treatment guidelines.

11.2.3. Analysis Limitations

As a retrospective observational study, data entry errors at the point of care may have occurred and influenced the results. To reduce this risk, a targeted chart review was performed to capture or verify data elements that may not be reliably sourced through structured data. Additionally, Section 9.10 described the quality control process that was taken to ensure data from the EHR were captured correctly, which included additional verification of outlying and missing values.

11.2.4. Limitations Due to Missing Data and/or Incomplete Data

Although data quality checks were conducted, it was possible that some variables of interest may not have been as complete across the entire population. To reduce this risk, a targeted chart review was performed to capture or verify data elements that may not have been reliably sourced through structured data.

Prescriber bias is a component of real-world treatment patterns in the absence of randomization and with a change in standard of care. This could be adjusted for when confounders were known with statistical approaches including PSM and IPTW. Addressing unobserved variables presented greater challenges and required the ability to discern their influence. The USON iKM EHR dataset represented information collected as part of routine clinical practice and thus had limitations typical of data collected for purposes other than research.

11.2.5. Comorbid Conditions

Although the CCI was a variable abstracted from charts in USON, the data available reflected only the information entered by the treating oncologist and thus may have not captured comorbidity not directly treated during the course of therapy. The CDS was also utilized as an additional measure of multimorbidity burden. The CDS used medication data to identify classes of drugs which could be used as surrogates for whether or not a patient had a chronic disease.[28,29] The CDS had shown correlations with self-rated health status, functional status, hospitalization rates, and mortality. Missing comorbid conditions were important if they were likely to affect mortality however epidemiological data for patients with HR+/HER2- advanced or MBC demonstrated the majority of patients died from progression of BC,[30] thus reducing the effect of comorbid conditions as an influence on mortality for this population.

ECOG performance status was a structured field in the USON EHR however data may have not always been reported by physicians for all patients. This study also included ECOG as a variable included as part of chart level review. Logistic regression models had shown baseline ECOG performance score to be an important variable associated with treatment choice by the physician. In the MBC population, although treatment selection may have been influenced by ECOG, the vast majority of patients die of progression of disease therefore this was unlikely to impact mortality as an independent variable.

“Missing” was included as a categorical level for the baseline ECOG variable in PS model to be able to adjust for confounding if present.

11.3. Interpretation

The results of this real-world study provide support for the clinical benefit of palbociclib in combination with AI as first-line treatment of postmenopausal women and men with HR+/HER2-MBC in routine practice. Real-world evidence is important to understand the effectiveness of a treatment under daily clinical practice in a broad, general patient population, unlike a clinical trial setting with specific inclusion and exclusion criteria.

This real-world study assessed OS, rwPFS and rwRR in 1288 patients with HR+/HER2-MBC, treated with palbociclib + AI or AI alone in community practices across the US from the USON. The final number of eligible patients was less than originally targeted along with a nearly 2:1 ratio of palbociclib and AI to AI patients instead of an expected 1:1 and 675 total

death events instead of 750. Imbalance in baseline demographic and clinical characteristics between the cohorts was observed in the unadjusted population suggesting bias by treatment assignment. These characteristics were well balanced after nIPTW and PSM, correcting for the unadjusted differences. Results were consistent across primary and sensitivity analysis. The clinical trial endpoint of OS can be confounded in disease states with long post-progression survival as patients can receive multiple subsequent treatments. After RPSFT adjustment for subsequent CDK 4/6 inhibitor treatment in the AI monotherapy arm, an improvement in the HR can be seen, suggesting the impact of subsequent treatments in the primary OS analysis which may underestimate the treatment effect of palbociclib + AI.

These results of this study are consistent with other analyses of real-world data evaluating effectiveness of palbociclib in routine clinical practice. Of note, the most recently published comparative analysis utilizing a contemporaneous control arm was the Rugo et al 2022 P REALITY X study found statistically significant associated OS benefit for the palbociclib combination arm and aligned rwPFS benefit of. In an analysis of 2,888 patients, after stabilized IPTW, median OS (95% CI) was significantly longer among patients receiving palbociclib + AI vs AI alone (49.1 [45.2-57.7] vs 43.2 [37.6-48.0] months; HR = 0.76 [95% CI, 0.65–0.87]; P <0.0001). PFS (95% CI) is 19.3 (17.5-20.7) vs 13.9 (12.5-15.2) months, respectively (HR = 0.70 [95% CI, 0.62-0.78]; P <0.0001).[31]

11.4. Generalizability

Not all community oncology practices were included in the USON. They had to utilize the iKM EHR and decision-support technology which provides guidance on treatment guidelines. Therefore, the results of this study may not be generalizable outside of USON to other community oncology practices and those that do not utilize a similar evidence-based treatment guideline decision-support technology.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

The real-world OS, rwPFS and real-world tumor response assessments provide evidence to support the clinical benefit of palbociclib in combination with AI as first-line treatment of postmenopausal women and men with HR+/HER2- MBC. The benefit/risk profile for the use of palbociclib in combination with AI in this setting appears favorable.

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15. LIST OF SOURCE TABLES AND FIGURES

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