# NON-INTERVENTIONAL (NI) STUDY REPORT

## Study Information

| | |
|---|---|
| **Title** | Safety of Palbociclib Among Breast Cancer Patients in the United States |
| **Protocol number** | A5481105 |
| **Version identifier of the final study report** | 2.0 |
| **Date** | 12 June 2020 |
| **EU Post Authorisation Study (PAS) register number** | EUPAS21948 |
| **Active substance** | Palbociclib<br>ATC: L01XE33 |
| **Medicinal product** | Palbociclib (Trade name: Ibrance®) |
| **Research question and objectives** | Research question:<br>What are the incidence rates of selected safety events among new users of palbociclib in a real-world setting?<br>Primary Objective:<br>1. Describe patient characteristics and incidence rates of safety events among all new users of palbociclib<br>Secondary Objectives:<br>1. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib: a) concomitant fulvestrant new users; b) concomitant letrozole new users; and c) no new use of letrozole or |

| | |
|---|---|
| | fulvestrant (at the time of palbociclib initiation)<br>2. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib who also meet algorithm-defined advanced stage estrogen receptor positive (ER+)/ human epidermal growth factor receptor 2 negative (HER2-) breast cancer: a) concomitant fulvestrant new users; b) concomitant letrozole new users; and c) no new use of letrozole or fulvestrant (at the time of palbociclib initiation)<br>3. Compare and evaluate the incidence rates of safety events (including acute liver injury (ALI)) between new users of palbociclib with fulvestrant to new users of the following subgroups of fulvestrant users alone (historical comparator group from pre-2015): a) any new users of fulvestrant alone; and b) new users of fulvestrant alone who meet algorithm-defined ER+/HER2- breast cancer<br>4. Compare and evaluate the incidence rates of ALI between new users of palbociclib with fulvestrant users alone (contemporaneous comparator group identified after 01 FEB 2015)<br>*5.* Validate potential cases of ALI in new users of palbociclib and new users of fulvestrant through medical record adjudication |
| **Author** | Daniel C. Beachler, PhD, MHS<br>Associate Director, Safety and Epidemiology<br>HealthCore, Inc.<br>123 Justison St. Suite 200<br>Wilmington, DE 19801<br>Phone: 302-230-2089<br>Fax: 302-230-2020 |

| | |
|---|---|
| | E-mail: dbeachler@healthcore.com<br><br>Cynthia de Luise, PhD, MPH<br>Senior Director (Epidemiologist)- Safety Surveillance Research, Worldwide Medical and Safety, Pfizer, Inc<br>235 E 42nd Street, Mail Stop 219/8/01<br>New York, NY 10017 USA<br>Email: cynthia.deluise@pfizer.com |

# TABLE OF CONTENTS

LIST OF TABLES ..... 7
LIST OF FIGURES ..... 7
1. ABSTRACT (STAND-ALONE DOCUMENT) ..... 9
2. LIST OF ABBREVIATIONS ..... 9
3. INVESTIGATORS ..... 12
4. OTHER RESPONSIBLE PARTIES ..... 13
5. MILESTONES ..... 14
6. RATIONALE AND BACKGROUND ..... 15
7. RESEARCH QUESTION AND OBJECTIVES ..... 16
8. AMENDMENTS AND UPDATES ..... 18
9. RESEARCH METHODS ..... 20
9.1. Study design ..... 20
9.2. Setting ..... 20
9.3. Subjects ..... 21
9.3.1. Inclusion criteria ..... 21
9.3.2. Exclusion criteria ..... 21
9.3.3. Study population ..... 21
9.3.3.1. New users of palbociclib with fulvestrant (secondary Objectives 1a and 2a) ..... 23
9.3.3.2. New users of palbociclib with letrozole (Secondary Objectives 1b and 2b) ..... 24
9.3.3.3. Other new users of palbociclib ..... 25
9.3.3.4. New users of fulvestrant (historical comparator group) ..... 25
9.3.3.5. New users of fulvestrant (contemporaneous comparison group) ..... 25
9.3.3.6. Provisional ALI cases ..... 26
9.4. Variables ..... 27
9.4.1. Exposure definition and assessment ..... 27
9.4.2. Outcome definitions and assessment ..... 29
9.4.3. Covariate definitions and assessment ..... 30
9.4.3.1. Covariate definitions and assessment for active surveillance study ..... 30

9.4.3.2. Covariate definitions for signal refinement activities .....30
9.5. Data sources and measurement .....30
9.6. Bias .....31
9.7. Study Size .....31
9.8. Data transformation .....32
9.9. Statistical methods .....32
9.9.1. Main summary measures .....32
9.9.2. Main statistical methods .....32
9.9.2.1. Descriptive and propensity score adjusted analyses – Primary Objective and Secondary Objectives 1-3 .....32
9.9.2.2. Descriptive and propensity score adjusted analyses - Secondary Objective 4 .....34
9.9.2.3. Descriptive and propensity score adjusted analyses – Secondary Objective 5 .....34
9.9.3. Missing values .....35
9.9.4. Sensitivity analyses .....35
9.9.5. Amendments to the statistical analysis plan .....36
9.10. Quality control .....36
9.11. Protection of human subjects .....37
9.12. Patient Information .....37
10. RESULTS .....38
10.1. Participants .....38
10.1.1. Active surveillance study .....38
10.1.2. Signal refinement analyses .....39
10.2. Descriptive data .....40
10.3. Outcome data .....42
10.4. Main results .....43
10.4.1. Active Surveillance Study .....43
10.4.2. ALI algorithm signal refinement analyses .....46
10.4.2.1. ALI algorithm signal refinement – historical comparator .....47
10.4.2.2. ALI algorithm signal refinement – contemporaneous comparator .....48

10.4.2.3. ALI algorithm signal refinement – medical record adjudication and case narratives ....50
10.5. Other analyses ....52
10.5.1. Active Surveillance Study ....52
10.5.2. ALI algorithm signal refinement ....52
10.6. Adverse events / adverse reactions ....54
11. DISCUSSION ....55
11.1. Key results ....55
11.1.1. Active Surveillance Study ....55
11.1.2. ALI Signal Refinement Analyses ....56
11.2. Limitations ....57
11.2.1. Lack of validated outcomes (except of ALI) and ICD-9/10 mapping ....57
11.2.2. Multiple comparisons (outcomes) ....58
11.2.3. Unmeasured confounding ....58
11.2.4. Limited sample size for rarer outcomes ....59
11.3. Interpretation ....59
11.3.1. Active Surveillance Study ....59
11.3.2. ALI signal refinement analyses ....60
11.3.2.1. Overview ....60
11.3.2.2. Adjustment for ALI risk factors and additional ALI algorithms ....60
11.3.2.3. Contemporaneous comparator group ....60
11.3.2.4. Medical record validation ....62
11.4. Generalizability ....63
12. OTHER INFORMATION ....63
13. CONCLUSIONS ....63
14. REFERENCES ....65
15. LIST OF SOURCE TABLES AND FIGURES ....67

## LIST OF TABLES

Table 1. Amendments to the Protocol ....18
Table 2. Patient features and coefficients in the regression model for advanced stage ER+/HER2- Breast Cancer....24
Table 3. Formation of study cohorts....39
Table 4. Select characteristics of breast cancer patients using palbociclib identified in the HIRD ....41
Table 5. Incidence of select safety events in all new users of palbociclib ....43
Table 6. Select characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparator group) after propensity score matching....44
Table 7. Select incidence rates and adjusted hazard ratios of safety events in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparator)....46
Table 8. Unadjusted and adjusted hazard ratios of ALI in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparator)....47
Table 9. ICD-9 and ICD-10 codes that identified as the primary ALI event ....48
Table 10. Unadjusted and adjusted hazard ratios of ALI in new users of palbociclib and fulvestrant and new users of fulvestrant alone (contemporaneous comparator) ....49
Table 11. ALI algorithm signal refinement – validation of claims algorithms compared to medical record adjudication....51

## LIST OF FIGURES

Figure 1. Description of study population and their study sizes....23
Figure 2. Examples of treatment episode construction with 30-day allowable gap....28
Figure 3. Unadjusted and propensity score adjusted hazard ratios of ALI in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical and contemporaneous comparators) ....50
Figure 4. E-value to explain the association between palbociclib and the primary ALI algorithm (in historical fulvestrant analyses) ....53

**Annex 1. List of stand-alone documents**

Appendix 1. SIGNATURES

Appendix 2. PROTOCOL

Appendix 3. STUDY TABLES AND FIGURES

## 1. ABSTRACT (STAND-ALONE DOCUMENT)

## 2. LIST OF ABBREVIATIONS

| Abbreviation or Special Term | Definition |
|---|---|
| AASLD | American Association for the Study of Liver Diseases |
| AC | Adjudication Committee |
| ADIN | Action, Decision, Issue, Notification |
| AE | Adverse event |
| AEM | Adverse event monitoring |
| ALI | Acute liver injury |
| ALP | Abnormal alkaline phosphatase |
| ALT | Abnormal alanine transaminase |
| AST | Abnormal aspartate transaminase |
| aHR | Adjusted hazard ratio |
| CCQP | Cancer Care Quality Program |
| CDK | Cyclin-dependent kinase |
| CFR | Code of Federal Register |
| CIOMS | Council for International Organizations of Medical Sciences |
| CPT | Current Procedural Terminology |
| CT | Computed tomography |
| DCI | Deyo-Charlson Index |
| DILI | Drug induced liver injury |
| DSA | Data Sharing Agreement |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |

| Abbreviation or Special Term | Definition |
|---|---|
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| ER | Estrogen Receptor |
| ER+ | Estrogen Receptor positive |
| FDA | Food and Drug Administration |
| GEP | Good Epidemiological Practice |
| GPI | Generic Product Identifier |
| GPP | Good Pharmacoepidemiology Practices |
| HCPCS | Healthcare Common Procedure Coding System |
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIRD | HealthCore Integrated Research Database℠ |
| HIRE | HealthCore Integrated Research Environment |
| HIV | Human Immunodeficiency Virus |
| HR+ | Hormone Receptor positive |
| IEA | International Epidemiological Association |
| IEC | Independent Ethics Committee |
| ISPE | International Society for Pharmacoepidemiology |
| ICD-9-CM | International Classification of Diseases, Ninth Revision, Clinical Modification |
| ICD-10-CM | International Classification of Diseases, Tenth Revision, Clinical Modification |
| ILD | Interstitial Lung Disease |
| IRB | Institutional Review Board |

| Abbreviation or Special Term | Definition |
|---|---|
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| LDH | Lactic acid dehydrogenase |
| MRI | Magnetic resonance imaging |
| NDC | National Drug Code |
| NIS | Non-interventional study |
| PAS | Post authorisation study |
| PASS | Post-Authorisation Safety Study |
| PHI | Protected Health Information |
| PPV | Positive predictive value |
| SOP | Standard Operating Procedure |
| QC | Quality control |
| US | United States |

## 3. INVESTIGATORS

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Title | Affiliation |
|---|---|---|
| Cynthia de Luise, PhD, MPH | Senior Director, Epidemiologist- Safety Surveillance Research | Pfizer, Inc. |
| Daniel C. Beachler, PhD, MHS | Associate Director, Safety & Epidemiology | HealthCore, Inc. |

## 4. OTHER RESPONSIBLE PARTIES

| Responsible Party Name and Affiliation | Role in the study |
|---|---|
| Ruihua Yin, MS<br>HealthCore, Inc.<br>Andover, MA | Data analysis |
| Aziza Jamal-Allial, PhD, MS<br>HealthCore, Inc.<br>Watertown, MA | Data analysis |
| Devon Taylor, MPH<br>HealthCore, Inc.<br>Wilmington, DE | Project management |
| Stephan Lanes, PhD, MPH<br>HealthCore, Inc.<br>Andover, MA | Study design development and interpretation |

## 5. MILESTONES

| Milestone | Planned date | Actual date | Comments |
|---|---|---|---|
| Start of data collection (start of database data extraction for active surveillance study) | 02 January 2018 | 08 January 2018 | |
| <Registration in the EU PAS register> | 07 January 2018 | 07 January 2018 | |
| End of data collection (end of database data extraction for active surveillance study) | 02 March 2018 | 02 March 2018 | |
| Start of data management/analysis for ALI signal refinement activities | 30 November 2018 | 30 November 2018 | |
| Start of medical record data collection | 01 March 2019 | 01 March 2019 | |
| End of medical record data collection | 28 June 2019 | 28 June 2019 | |
| End of data management/analysis for ALI signal refinement activities | 06 August 2019 | 19 August 2019 | |
| Final study report | 15 November 2019 | 12 June 2020 | |

## 6. RATIONALE AND BACKGROUND

This is a non-interventional, real-world, active surveillance and signal refinement study to assess the safety of palbociclib in the treatment of patients with breast cancer. Palbociclib (Pfizer, Inc.) is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor that received accelerated approval by the United States (US) Food and Drug Administration (FDA) in February 2015 and by the European Medicines Agency (EMA) in November 2016 (1). The FDA first approved palbociclib for the treatment of advanced stage ER+/HER2- breast cancer in combination with letrozole as the first hormonal based therapy in women who have gone through menopause. Subsequently, in February 2016, palbociclib was approved for use in combination with fulvestrant in women with hormone receptor positive (HR+)/HER2- breast cancer with disease progression following hormonal therapy (1). Results from recent randomized controlled trials (PALOMA 2 and PALOMA 3) (2, 3) demonstrated that palbociclib significantly prolonged progression-free survival when used in combination with letrozole or fulvestrant. However, adverse events (AEs) were more common in the palbociclib arms compared to the control arms in the trials. For example, discontinuation due to AEs was 2.6% in the palbociclib-fulvestrant arm compared to 1.7% in the placebo-fulvestrant arm (2, 3). Commonly occurring AEs in the palbociclib arms of the trials included neutropenia, leukopenia, and anemia (2, 3).

Our previous work (Pfizer-HealthCore study A5481080: "Standing Cohorts of Individuals with Early or Advanced Estrogen Receptor Positive (ER+)/Human Epidermal Growth Factor Negative (HER2-) (ER+/HER2-) Breast Cancer") (4) developed and validated a claims algorithm for advanced stage ER+/HER2- breast cancer utilizing predictive modeling in a subset of breast cancer patients with clinically confirmed stage and biomarker data. These standing cohorts provided incidence rates of events of potential relevance for safety (henceforth termed safety events), which were defined via algorithms consisting of ICD-9-CM and ICD-10-CM codes from claims, in the target population for palbociclib, largely before the introduction of palbociclib onto the market. These safety events were a priori selected by Pfizer based on data from clinical trials, published literature, known class effects.

Since its approval, the safety of palbociclib in patients with and without ER+/HER2- breast cancer and how it compares to the safety profile of other breast cancer treatments has not been well established in real-world settings. The exploratory active surveillance portion of this study examined the event rates for the same pre-specified safety events that were included in study A5481080 among all new palbociclib users, and in the subset with the algorithm-defined advanced ER+/HER2- breast cancer (4, 5). In the active surveillance portion of this study, the event rates of pre-specified safety events among individuals initiating palbociclib with fulvestrant were compared with those who received fulvestrant alone (monotherapy) prior to the FDA approval of palbociclib in 2015. We selected this historical comparator of fulvestrant monotherapy based on several considerations. Fulvestrant monotherapy was used as the comparator arm in some of the palbociclib trials,(2) the indication for fulvestrant between 2011-2014 was similar to the subsequent indications of palbociclib with fulvestrant (initiate therapy after cancer progression following hormonal therapy) suggesting good compatibility,(6, 7) and there was a robust number of eligible

patients who initiated fulvestrant monotherapy between 2011-2014, as it was the standard of care at the time.

In the exploratory of active surveillance portion of this study, acute liver injury (ALI), was one of the pre-defined safety events. Prior pharmacoepidemiologic studies have defined ALI in a variety of ways including a wide range of hepatitic-related events. In this study, ALI was pre-defined using ICD-9/10 diagnosis codes indicating elevated liver enzymes or liver necrosis. Based on initial results from the active surveillance portion of the study, subsequent signal refinement activities were conducted for ALI as described in the protocol amendment). This included defining ALI with additional algorithms, including a primary ALI algorithm which included hepatitic failure or liver necrosis but not elevated liver enzymes. The active surveillance study involved further assessment through medical record validation and additional sensitivity analyses. This included a contemporaneous comparator of fulvestrant monotherapy which, although restricted in sample size, would not be impacted by temporal effects (e.g., ICD-9 to ICD-10 code transition) that could affect the historical comparator group.(8)

Drug-induced hepatotoxicity is an important forms of drug toxicity because of its potential severity, and is often studied in observational post-marketing evaluations.(9) Palbociclib trials revealed an elevated liver enzymes, including grade 3 and 4 elevations, but trials were not powered to detect severe outcomes such as hepatic failure, and the product label does not include a warning for hepatotoxicity.(7) Palbociclib randomized trials identified few cases of liver failure, although one trial reported a numerical excess of hepatic failure and elevated transaminase incidence in the palbociclib arm (2, 3, 10). A recent report described two cases of a type of ALI (pseudocirrhosis and liver failure, one fatal) and concluded palbociclib was the most likely cause (11). Recently, Raschi and De Ponti (2019) analyzed the FDA Adverse Event Reporting System (FAERS) which included 224 palbociclib patients with serious liver reports, 83 (26%) of whom with hepatic failure.(12) The product labels of the two other CDK4/6 inhibitors, ribociclib and abemaciclib, each recommends prospective monitoring of liver function tests before and during therapy.(13, 14) Meta-analyses of the randomized trials of all CDK4/6 inhibitors noted elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with CDK4/6 use.(15, 16)

This non-interventional study (NIS) was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer.

## 7. RESEARCH QUESTION AND OBJECTIVES

The Primary Objective and Secondary Objectives 1-3 described below are part of an initial exploratory active surveillance study. Based on initial findings from the active surveillance study suggestive of a potential increased risk of ALI with palbociclib, a signal refinement study was initiated. Secondary Objectives 4-5 are a part of ALI signal refinement activities (as described in the protocol A5481105 amendment dated 06 December 2018) along with ALI analyses contained within Secondary Objective 3.

Research Question:

What are the incidence rates of safety events among new users of palbociclib in a real-world setting?

Primary Objective:

1. Describe patient characteristics and incidence rates of safety events among all new users of palbociclib.

Secondary Objectives:

1. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib:

    1. Concomitant fulvestrant new users;

    2. Concomitant letrozole new users; and

    3. No new use of letrozole or fulvestrant at the time of palbociclib initiation.

2. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib who also meet algorithm-defined advanced stage ER+/HER2- breast cancer:

    a) Concomitant fulvestrant new users;

    b) Concomitant letrozole new users; and

    c) No new use of letrozole or fulvestrant at the time of palbociclib initiation.

3. Compare and evaluate the incidence rates of safety events (including ALI) between new users of palbociclib with fulvestrant and new users of the following subgroups of fulvestrant new users alone (historical comparator group identified prior to February 2015):

    a) Any new users of fulvestrant alone;

    b) Propensity score matched new users of fulvestrant alone;

    c) New users of fulvestrant alone who also meet algorithm-defined ER+/HER2- breast cancer; and

    d) Propensity score matched new users of fulvestrant alone who also meet algorithm-defined ER+/HER2- breast cancer.

4. Compare and evaluate the incidence rates of ALI between new users of palbociclib with fulvestrant and new users of fulvestrant alone between 01 February 2015 and 30

September 2017 (contemporaneous comparator groups identified after 01 February 2015):

a. Any new user of fulvestrant alone; and

b. Propensity score matched new user of fulvestrant alone.

5. Validate potential cases of ALI in new users of palbociclib and new users of fulvestrant through medical record adjudication

   a. Any new users of palbociclib; and

   b. Any new users of fulvestrant alone (historical and contemporaneous comparator groups).

## 8. AMENDMENTS AND UPDATES

### Table 1. Amendments to the Protocol

| Amendment number | Date | Substantial or administrative amendment | Protocol section(s) changed | Summary of amendment | Reason |
|---|---|---|---|---|---|
| 1 | 10/15/18 | Administrative | 8.3.1, 8.3.2, 8.3.3.4 | Follow-up time for new users of fulvestrant (in the historical comparator group) were censored on 01 February 2015, in order to exclude any person-time when a patient may have been able to initiate palbociclib (for Secondary Objective 3). This censoring date was not specified in the original version of the protocol/SAP. | The censoring date for the historical comparator group was not specified in the protocol, and follow-up time when patients may have switched to palbociclib should not be included in a historical comparator group in order to minimize the risk of bias. |
| 2 | 10/15/18 | Substantial | 8.3.2, Annex 2 | For the acute liver injury (ALI) safety event, three additional definitions were included to further examine severe hepatic failure related endpoints, such as hepatic failure and liver transplantation, and to exclude liver related lab (transaminase) codes (Annex 2). One of these algorithms is based on an algorithm recently used in a post-authorization safety study that was informed by a Mini-Sentinel validation study, while the others will provide more sensitive and specific definitions. | To provide further examination of the rate of severe acute liver failure events in the study population, given that the initial results using the original unvalidated algorithm included elevated liver lab codes and other algorithms that have been more widely used in the literature. |

## Table 1. Amendments to the Protocol

| Amendment number | Date | Substantial or administrative amendment | Protocol section(s) changed | Summary of amendment | Reason |
|---|---|---|---|---|---|
| 3 | 10/15/18 | Substantial | 9.2.3.6, Annex 1A, 1B | Addition of a medical record review plan and adjudication committee charter for the validation of possible ALI events identified in this study. The medical record review plan included clinical adjudication of events through a case reporting form, and development of case narratives. | Adjudication of possible ALI events given that claims algorithms for ALI have demonstrated poor accuracy in other published work. |
| 4 | 10/15/18 | Substantial | 9.2.3.5, 9.3.3, 9.7.3 | A contemporaneous comparator group of new users of fulvestrant only will be compared to new users of palbociclib with fulvestrant. If standardized differences were mostly <0.10 after propensity score matching, we will conduct comparative analyses for ALI using this comparator group similar to those done using the historic comparator group. | Literature has suggested the ICD-9 to ICD-10 transition can have an impact on the incidence of certain safety events. While there are no publications to date noting this for ALI, a contemporaneous comparator group could have advantages through the assessment of groups during the same time period. |
| 5 | 10/15/18 | Substantial | 9.3.3, 9.7.3, 9.7.4 | Additional analyses regarding ALI including: (a) revised propensity score adjusted analyses including more covariates that may be associated with ALI, (b) adjusted rates and relative risk based on validated results, and (c) an evaluation of the incidence of ALI events around the ICD-9/ICD-10 transition. | Provide further context regarding the measured relative risk of ALI with palbociclib. |
| 6 | 11/25/19 | Substantial | 8.9.4, 9.5.2, 10.3.2.3 | Additional analyses evaluating the amount of follow-up time in the palbociclib group and the fulvestrant comparator groups, and analyses evaluating the risk of ALI stratified by the amount of follow-up time. | Evaluation of whether the longer study period for the historical comparator group (January 2011-January 2015 vs. February 2015-September 2017) may have impacted the measured relative risk of ALI with palbociclib compared to historical fulvestrant. |

# 9. RESEARCH METHODS

## 9.1. Study design

This active surveillance study and subsequent signal refinement analyses is a retrospective longitudinal new user cohort design utilizing health insurance claims data among breast cancer patients initiating palbociclib or fulvestrant. Incidence rates of pre-specified safety events were calculated among all new users of palbociclib, and we compared new users of palbociclib and fulvestrant to new users of fulvestrant alone (historical comparator group), after matching by propensity score. The goal in selecting a comparator was to identify individuals similar to individuals who received palbociclib but who did not receive palbociclib. Because palbociclib quickly became the "standard of care" for women with advanced stage HR+/HER- after initiation, a potential concern was that individuals who could have received palbociclib, but did not, might not be comparable to women who received palbociclib according to factors related to their risk of safety events. A historical comparator prior to the introduction of palbociclib was selected to avoid possible selection bias associated with decision to treat individuals with palbociclib. The ALI signal refinement activities also included a contemporaneous comparator cohort as a secondary analysis, given that the historical comparator could be impacted by temporal effects. A further description of the strengths and limitations of each comparator group is provided in Section 11.3.2.3.

## 9.2. Setting

This study was conducted using the HealthCore Integrated Research Database (HIRD). The HIRD is a longitudinal claims database from commercial health plan members in the Northeastern, Mid-Atlantic, Southeastern, Midwest, Central, and Western regions of the United States (US). Most analyses were from 01 February 2015 until 30 September 2017, after palbociclib was approved by the FDA. Secondary Objective 3 also included data for individuals who were newly dispensed fulvestrant alone from 01 January 2011 until 31 January 2015 ("historical comparator group"), before the FDA approved palbociclib. For this comparison group, we did not include new users of fulvestrant alone after the FDA approval of palbociclib because the availability and nonuse of palbociclib was considered to make them less comparable to patients receiving palbociclib than a historical comparator group that did not have access to palbociclib. New users of fulvestrant alone after the FDA approval of palbociclib (contemporaneous comparator group) were only used to evaluate the risk of ALI in Secondary Objective 4 as part of signal refinement activities. This was conducted given the historical comparator could be impacted by temporal effects (e.g., ICD-9 to ICD-10 code transition).(8)

Patient enrollment data, inpatient and outpatient medical care, outpatient prescription drug use, and healthcare charges were tracked for each patient in the database. In the HIRD, diagnoses and procedures were identified by ICD-9-CM and ICD-10, Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes, for both outpatient visits and inpatient stays. Drug claims were captured by National Drug Codes (NDCs), which were then translated to broader categories of coding such as Generic Product Identifier (GPI) codes. Information on physician specialty is also retained in the HIRD.

## 9.3. Subjects

### 9.3.1. Inclusion criteria

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

1. At least one dispensing for palbociclib from 01 February 2015 through 31 September 2017 OR dispensing for fulvestrant from 01 January 2011 through 31 January 2015 (for Secondary Objective 3) OR dispensing for fulvestrant from 01 February 2015 through 31 September 2017 (for Secondary Objective 4); AND

2. Aged 18 years or older at time of first dispensing of a study drug; AND

3. At least three months membership in the HIRD with no dispensings of palbociclib (or any other CDK4/6 inhibitor such as ribociclib) before the first dispensing of palbociclib, as a minimal baseline period to define new use and characterize baseline risk.

    1. For Secondary Objectives 2, 3, and 4 for some of the analyses we restricted to individuals with algorithm-defined advanced stage ER+/HER2- breast cancer further described in Section 9.3.3 (5). The date of algorithm-defined advanced ER+/HER2- breast cancer must have occurred before or within three months of the first dispensing of palbociclib for inclusion in this subcohort (further described in Section 9.3.3).

    2. For Secondary Objectives 3 and 4, at least three months membership in the HIRD with no dispensings of palbociclib OR fulvestrant OR another CDK4/6 inhibitor before the first dispensing of palbociclib OR fulvestrant, as a minimal baseline period to define new use and characterize baseline risk.

### 9.3.2. Exclusion criteria

There were no additional exclusion criteria for this study.

### 9.3.3. Study population

The study included all new users of palbociclib aged ≥18 years meeting the inclusion criteria in Section 9.3.1.

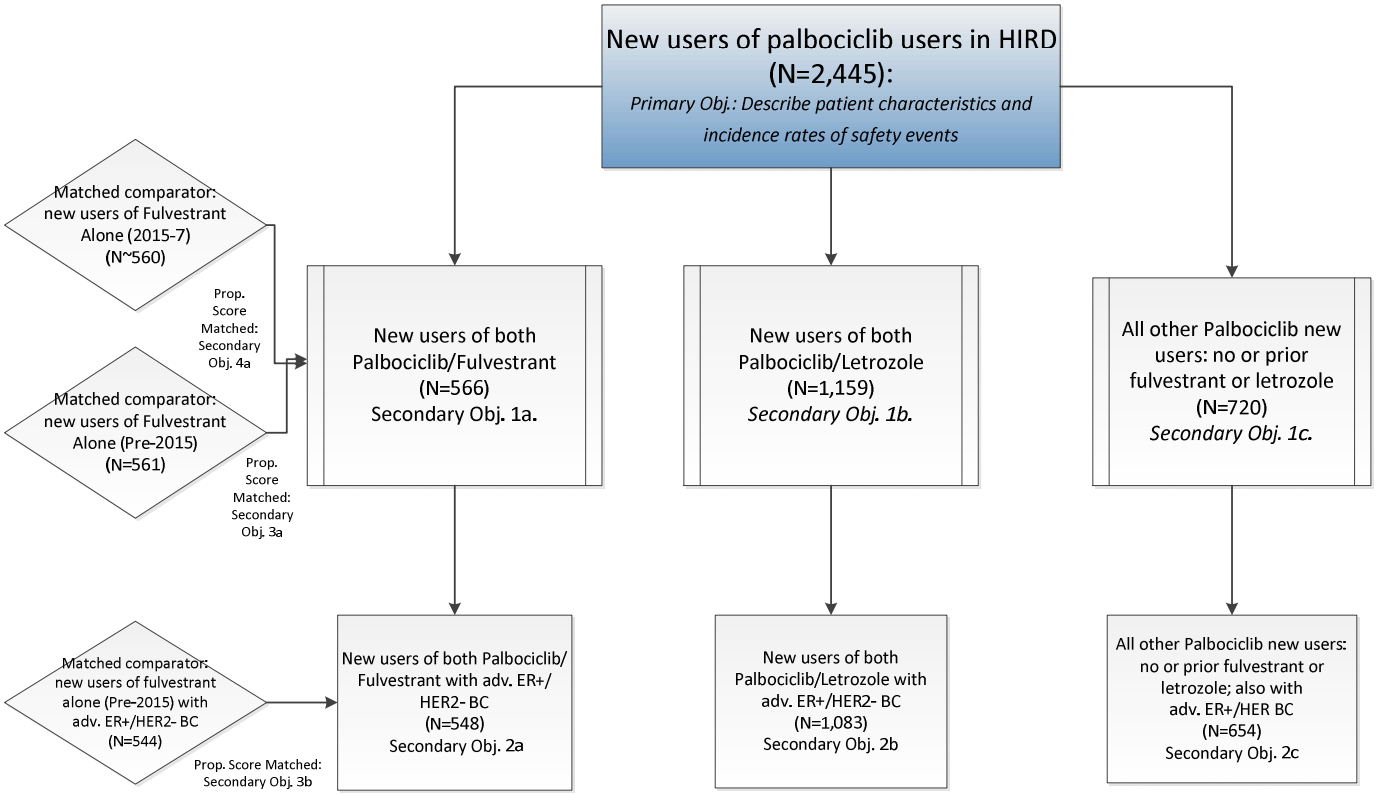
This group of new users of palbociclib was then stratified into three mutually exclusive hierarchical subcohorts:

1. New users of both palbociclib with fulvestrant
2. New users of both palbociclib with letrozole
3. Other new users of palbociclib: those who did not newly initiate fulvestrant or letrozole (i.e. all other new users of palbociclib who were not included in subcohorts 1 or 2 above). This included new users who did not use fulvestrant or letrozole around

the time they initiated palbociclib, and those individuals who had a history of using fulvestrant or letrozole prior to initiating palbociclib.

Creation of the study subcohorts and further subgroups are depicted in Figure 1 and described further below.

**Figure 1. Description of study population and their study sizes**




Abbreviations: HIRD, HealthCore Integrated Research Database; Prop., propensity; adv., advanced; Obj., objective; N, number; ER+, estrogen receptor positive; HER2, human epidermal growth factor receptor 2; BC, breast cancer.

#### 9.3.3.1. New users of palbociclib with fulvestrant (secondary Objectives 1a and 2a)

For Secondary Objective 1a, we restricted individuals in this subcohort to include those who had at least three months membership in the HIRD before the first dispensing of palbociclib or fulvestrant. The first dispensing of fulvestrant (administered through an injection) must have occurred within 30 days before or after a patient's first palbociclib dispensing (administered orally) to qualify for this subcohort.

For Secondary Objective 2a, we further restricted to individuals who met our validated algorithm for advanced stage ER+/HER2- breast cancer that was previously defined in our recent study (A5481080) and in Table 2 below (5). his analysis assesses incidence rates of safety events among individuals very likely to be in the subgroup for which palbociclib is indicated. The algorithm includes treatments, procedures and diagnosis codes positively or inversely associated with advanced stage ER+/HER2- breast cancer and was found to have a positive predictive value (PPV) of 91.4% and a sensitivity of 53.9% at the chosen predictive probability cut-off point of 70%. In order to achieve a higher sensitivity, we utilized a predictive probability cut-off point of 50% which has a PPV of 85.5% and a sensitivity of 68.2%. Using the 50% cut-off point instead of the 70% cut-off increased the sensitivity, and thus increased the number of concomitant new users of palbociclib with fulvestrant with

algorithm-defined advanced ER+/HER2- breast cancer while retaining a high PPV. This allowed further power to examine uncommon safety endpoints.

**Table 2. Patient features and coefficients in the regression model for advanced stage ER+/HER2- Breast Cancer**

| Features associated with confirmed advanced stage ER+/HER2- breast cancer (True Positives) | | Features associated with confirmed not advanced stage ER+/HER2- breast cancer (False Positives, i.e., other types of breast cancer) | |
|---|---|---|---|
| **Patient feature** | **Coefficient** | **Patient feature** | **Coefficient** |
| Fulvestrant | 2.3029 | Intercept | -2.7882 |
| Secondary malignancy to other specified sites (metastasis) | 1.9304 | HER2 positive therapy (Trastuzumab, Lapatinib, Ado-trastuzumab, Pertuzumab) | -6.0778 |
| Palbociclib | 1.533 | Lumpectomy in last six months | -0.7586 |
| Secondary malignancy to respiratory or digestive systems (metastasis) | 1.0335 | Mastectomy in last six months | -0.5514 |
| Tamoxifen | 0.7931 | Diagnostic imaging in last 6 months | -0.4185 |
| Everolimus | 0.7409 | Tomosynthesis | -0.4046 |
| Radical mastectomy in the last six months | 0.6261 | Corticosteroids | -0.3006 |
| Letrozole | 0.6211 | Antifungals | -0.2937 |
| Anastrazole | 0.4478 | Chemotherapy | -0.2642 |
| Denosumab or Pamidronate | 0.396 | | |
| Exemestane | 0.3617 | | |
| Secondary malignancy to lymph nodes of head, face, and neck (metastasis) | 0.3364 | | |

Abbreviations: ER+, estrogen receptor positive; HER2, human epidermal growth factor receptor 2.

The date when a patient reached a predictive probability of at least 50% for the algorithm-defined advanced stage ER+/HER2- breast cancer was defined as the date of advanced stage ER+/HER2- breast cancer. In order for a patient to be included in the "advanced ER+/HER2- breast cancer" subgroup analyses (Secondary Objective 2a), this advanced stage ER+/HER2- breast cancer date must have occurred before or within three months of the first dispensing of palbociclib.

### 9.3.3.2. New users of palbociclib with letrozole (Secondary Objectives 1b and 2b)

For Secondary Objective 1b, we restricted individuals in this subcohort to include those who had at least three months membership in the HIRD with no dispensings of palbociclib or letrozole before the first dispensing of palbociclib or letrozole. For this subcohort, the first dispensing of letrozole must have occurred within 90 days before or after a patient's first palbociclib dispensing, and the patient must not have qualified as a "new user of palbociclib and fulvestrant," subcohort described in Section 9.3.3.1.

For Secondary Objective 2b, we further restricted to individuals who met our validated algorithm for advanced stage ER+/HER2- breast cancer as described in Section 9.3.3.1.

#### 9.3.3.3. Other new users of palbociclib

Secondary Objective 1c included all new users of palbociclib who did not qualify for the first two subcohorts described in Section 9.3.3.1 and Section 9.3.3.2. This included new users who did not use fulvestrant or letrozole around the time they initiated palbociclib, and those individuals who had a history of using fulvestrant or letrozole prior to initiating palbociclib.

Secondary Objective 2c further restricted to individuals who met our validated algorithm for advanced stage ER+/HER2- breast cancer as described in Section 9.3.3.1.

#### 9.3.3.4. New users of fulvestrant (historical comparator group)

Secondary Objective 3a included a comparator group of patients who newly initiated fulvestrant between 01 January 2011 and 31 January 2015 before the FDA approval of palbociclib, given that the main historical comparator could be impacted by temporal effects (e.g., ICD-9 to ICD-10 code transition). Similar to the other new user definitions, we required at least three months membership in the HIRD with no dispensings of fulvestrant before the first dispensing of fulvestrant, as a minimal baseline period to define new use and characterize baseline risk. Follow-up time for new users of fulvestrant was censored on 01 February 2015, in order to exclude any person-time when a patient may have been able to initiate palbociclib.

These patients were then propensity score matched to concomitant new users of palbociclib with fulvestrant described in Section 9.3.3.1 . The propensity score matching is also further described in Section 9.9.2

For Secondary Objective 3b, we further restricted to individuals who met our validated algorithm for advanced stage ER+/HER2- breast cancer as described in Section 9.5.

As a part of signal refinement activities, we conducted the described analyses for Secondary Objective 3a (using the comparator population), among the four described ALI algorithms described in Annex 2 of the protocol.

#### 9.3.3.5. New users of fulvestrant (contemporaneous comparison group)

As a part of signal refinement activities, for Secondary Objective 4a, we included a comparator group of patients who newly initiated fulvestrant (without palbociclib) between 01 February 2015 and 31 September 2017 after the FDA approval of palbociclib.

The historical comparison group (Section 9.3.3.4) was selected for Secondary Objective 3 with the expectation that this group would be similar to new users of palbociclib with fulvestrant given similar indications, however, the historical comparison group is evaluated during a time in which ICD-9 diagnosis codes were utilized, whereas the palbociclib with fulvestrant group is restricted mostly to time in which ICD-10 diagnosis codes are used (8). Thus, in Secondary Objective 4a we examined a “contemporaneous” comparison group of

new users of fulvestrant using the same ICD-10 coding system in the palbociclib and fulvestrant group. This comparison group of new users of fulvestrant had no history of palbociclib before or within one month of fulvestrant initiation. Thus, this contemporaneous comparison group included patients who initiated fulvestrant monotherapy rather than initiating palbociclib, after palbociclib was approved by the FDA. So while the indications for fulvestrant monotherapy remained consistent through the historical and contemporaneous periods, it is possible that the contemporaneous fulvestrant monotherapy group may be less common and more likely to differ from the palbociclib group in regards to disease severity and other factors.

Similar to the other new user definitions, we required at least three months membership in the HIRD prior to the first dispensing of fulvestrant, as a minimal baseline period to define new use and characterize baseline risk.

These patients then were propensity score matched to concomitant new users of palbociclib with fulvestrant described in Section 9.9.2.2.

#### 9.3.3.6. Provisional ALI cases

As a part of signal refinement activities for Secondary Objective 5, we assessed all provisional ALI cases identified in any of the four ALI algorithms (described in Annex 2 of the protocol) through medical record validation (Annexes 1A and 1B). Given that previous validation studies of claims-based algorithms for ALI have suggested limitations in either sensitivity or specificity, (17) we used multiple algorithms for ALI to assess the robustness of the results with respect to ALI definition.

The primary ALI algorithm for the signal refinement analyses was an algorithm used in another PASS (18) that was informed by the Mini-Sentinel validation study (17), which restricted to inpatient diagnoses for ALI and acute liver failure. The second algorithm included codes for liver necrosis and elevated liver enzymes and was the original algorithm used as part of the active surveillance study. The third algorithm was a broad definition for ALI and included all codes from the first and second algorithms at any setting, as well as other codes identified in other ALI studies.(17, 19) Finally, the fourth algorithm was a narrow definition for ALI that restricted to primary inpatient codes that had a high PPV in the Mini-Sentinel validation study. (17)  The codes are included in Annex 2 of the protocol and the ALI algorithms are further described in the Medical Record Review Plan (Annexes 1A of the protocol).

The validation study included all available cases identified in any of the five subgroups in this study: new users of palbociclib with fulvestrant, new users of palbociclib with letrozole, other new users of palbociclib, new users of fulvestrant alone (historical comparator group), and new users of fulvestrant alone (contemporaneous comparator group). Records for some of the cases were unable to be requested due to privacy requests, and other records requested were not provided by the provider.

The validation study involved review of medical records by at least two independent clinicians with an expertise in hepatology. Possible cases identified by the claims algorithms were assessed and adjudicated as confirmed ALI cases or non-cases based on criteria developed by the US FDA Center for Drug Evaluation and Research, the Pharmaceutical Research and Manufacturers of America, and the American Association for the Study of Liver Diseases (AASLD). This criteria required elevation in at least one liver enzyme test, specific timing of the enzyme tests, and lack of chronic liver disease.(9, 20) Subsequently, cases that were deemed confirmed by the adjudicators as ALI had case narratives developed by one hepatologist. The case narratives described further details from the medical record including any possible attribution to the study drug. The validation study methods (adjudication and case narrative development) are further described in the Medical Record Review Plan in Annex 1A and Adjudication Committee Charter in Annex 1B of the protocol.

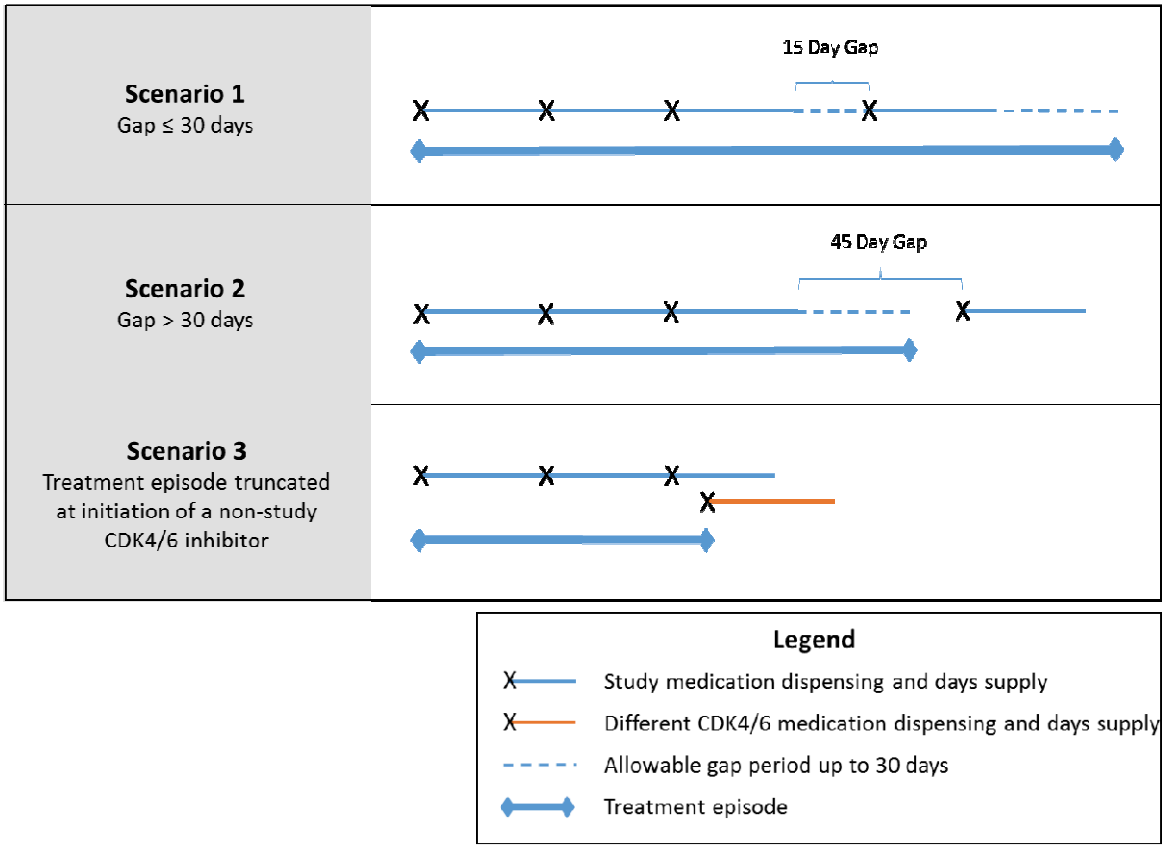
## 9.4. Variables

### 9.4.1. Exposure definition and assessment

Exposure to different therapies for treating breast and other cancers were assessed using the pharmacy and medical claims data available in the HIRD for each cohort member, as was done in the recent standing cohorts study (A5481080) (5). Pharmacy claims exposures were identified using NDC and GPI codes for the specific medications of interest. In the medical claims, CPT and HCPCS procedure codes were utilized to identify the administration of medications of interest.

For each cohort except for the comparator groups as described in Secondary Objectives 3 and 4, the index date (i.e. the start of follow-up) was defined as the date of the first dispensing of palbociclib. For the comparator groups described in Secondary Objectives 3 and 4, the index date was defined as the date of the first dispensing of fulvestrant. Exposure episodes for study medication were created using dispensing date, plus the number of days supplied, plus 30 days to account for possible non-adherence and non-concordance of dispensing date and administration (e.g., patients may obtain new medication before previous medication has been completed). Consecutive dispensings defined in this manner were concatenated into a single continuous episode. Palbociclib exposure episodes were truncated by discontinuation (>30 days from most recent exposed day without another dispensing) or switch to another CDK4/6 inhibitor. Historical fulvestrant exposure episodes for Secondary Objective 3 were similarly truncated by discontinuation (>30 days from most recent exposed day without another dispensing), or on 01 February 2015 when palbociclib was approved for the US market. Contemporaneous fulvestrant exposure episodes for Secondary Objective 4 were also truncated by discontinuation (>30 days from most recent day without another dispensing), or with any dispensing of palbociclib. Analyses focused on the safety events of interest occurring during the exposure episodes of the study medications unless otherwise specified (Figure 2).

**Figure 2. Examples of treatment episode construction with 30-day allowable gap**




Abbreviation: CDK, cyclin-dependent kinase.

For example, in scenario 2 (Figure 2), assuming the days supply is 30 days, this individual had 75 days in between her third and fourth dispensing. He/she would be considered exposed for the first 60 days (30 days supply + 30 day extension period), but then considered unexposed for the next 15 days. So, if he/she had a safety event during those 15 days, it would not be included. However, after the full 75 days, the patient has a new dispensing, and any safety event occurring after that dispensing within a treatment episode would be counted. The two episodes would be separated with the 15-day gap and would not be concatenated in this scenario.

Treatment episodes (i.e. person-time classified as exposed to study drugs) were constructed for each patient by concatenating consecutive episodes. Treatment episode length for individuals in the concomitant new users of palbociclib and fulvestrant subgroup (Section 9.3.3.1) and concomitant new users of palbociclib and letrozole (Section 9.3.3.2) subgroup were based on the use of palbociclib alone given that palbociclib use was of primary interest. For example, if a patient discontinued fulvestrant after six months but continued on palbociclib for three additional months, the treatment episode continues until the end of the palbociclib use (nine months). We separately report the amount of "palbociclib alone" person-time for each of these groups in the analyses.

### 9.4.2. Outcome definitions and assessment

Patients were followed forward from the index date to the earliest of the following dates:

- End of the study period for palbociclib groups and contemporaneous fulvestrant alone comparator group (31 September 2017);
- End of historical comparator study period for new user of fulvestrant alone comparator group (01 February 2015).
- End of continuous health plan enrollment (left health plan or death);
- End of palbociclib (or relevant) treatment episode (Section 9.4.1), except for secondary malignancy endpoint;
- First dispensing of palbociclib for the contemporaneous fulvestrant alone comparator group
- First occurrence of one of the outcomes (safety events) of interest. Note that follow-up for that specific outcome ended, but follow-up for other outcomes continued.

We identified 42 pre-specified safety endpoints of interest from codes recorded in claims (Appendix 2). The occurrence of the following 42 safety events of interest were identified in the HIRD using claims algorithms for the initial active surveillance study: neutropenia, febrile neutropenia, leukopenia, alopecia, vomiting, QT prolongation, fatigue, serious infection, brain/spinal infection, pericardial/myocardial infection, pulmonary infection, GI infection, ear/nose/throat infection, skin/bones/joint infection, hepatitis B infection, influenza infection, other infection, diarrhea, interstitial lung disease/pneumonitis, anemia, nausea, thrombocytopenia, pulmonary embolism, venous embolism and thrombosis, embolism and thrombosis of unspecified artery, cataracts and other ocular disorders, stomatitis and mucositis, fever, anorexia, peripheral neuropathy, sudden cardiac death, diabetes mellitus, type 2 diabetes mellitus, hyperglycemia, ALI/liver failure, abnormal alanine transaminase (ALT), abnormal aspartate transaminase (AST), abnormal alkaline phosphatase (ALP), secondary malignancies, and non-melanoma skin cancer. Incident events are of interest, so any individuals with a history of one of the safety events of interest on or prior to the index date was excluded from the computation of incidence for that specific event. The exceptions were for common events such as vomiting, fatigue, nausea, and diarrhea, along with pulmonary embolism and related venous thrombotic events in which individuals were allowed to have a history of these events on or prior to index date to evaluate the occurrence of repeat events during follow-up. Outcomes were assessed during the follow-up period of the treatment episodes using claims data in the HIRD and include the following safety events of interest: leukopenia, pulmonary embolism, anemia, and serious infections using claims definitions specified in the protocol (Appendix 2).

For select outcomes of interest we examined two separate case-identifying algorithms. These outcomes included neutropenia, febrile neutropenia, leukopenia, and anemia. Outcome definitions were previously developed based on literature reviews and subject matter/clinical

knowledge and are identical for those used in Pfizer-HealthCore study A5481080 and are described in Annex 2 of the protocol.

For ALI signal refinement analyses, four case-identifying algorithms for ALI were developed as further described in Section 9.3.3.6, and evaluated through medical record adjudication, and described in the Medical Record Review Plan in Annex 1A of the protocol.

Coding algorithms for identifying the other safety events of interest in the HIRD can be found in Annex 2 of the protocol.

### 9.4.3. Covariate definitions and assessment

#### 9.4.3.1. Covariate definitions and assessment for active surveillance study

Covariates were assessed prior to the initiation of palbociclib (or fulvestrant for Secondary Objective 3), including demographics, medical history, cancer therapy history, healthcare utilization, medication use (breast cancer and non-breast cancer related), and co-morbidities included in descriptive analyses. These covariates were considered potential confounders and were considered for inclusion in the propensity score (described in Section 9.9.2). The presence of these variables was assessed in the six months on or before the index date. For patients with less than six months of baseline (i.e. those with between three and six month eligibility prior to initiation) we included all available baseline time when they were eligible to evaluate covariates). The coding algorithms for a subset of these covariates, including the breast cancer treatments and co-morbidities, are shown in the protocol (Appendix 2). Other coding algorithms are available upon request.

#### 9.4.3.2. Covariate definitions for signal refinement activities

For ALI related analyses, we also evaluated the prevalence of diagnoses for chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure in the six months prior to palbociclib or fulvestrant initiation given their association with ALI. In addition, we included use of drugs with a known association with liver injury (Table 3 of protocol) (9) in the six months prior to palbociclib or fulvestrant as covariates to consider as potential confounders for inclusion in the propensity score.

### 9.5. Data sources and measurement

The study was conducted in the HIRD, a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from health plan members across the US. The HIRD has member enrollment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data (available on a subset of patients), and health care utilization may be tracked for health plan members in the database dating back to January 2006.

The algorithm utilized for advanced stage ER+/HER2- breast cancer was validated in study A5481080 using the HealthCore Integrated Research Environment (HIRE) Oncology resource. The HIRE Oncology data is an enhancement to the HIRD and includes clinical data pertinent to oncology in a subset of the HIRD's cancer patients. The clinical data in the HIRE

Oncology program are obtained by the Cancer Care Quality Program (CCQP), which is a program initiated in the summer of 2014 by the Anthem Inc. health plans, and are shown to be comparable to medical records (21). The developed claims-based algorithm performed well with a PPV of 91% and a sensitivity of 54% at a predictive probability cut-off of 0.70. When utilizing a predictive probability cut-off of 0.50 as planned in this study, the PPV remained high (86%) with a higher sensitivity (68%) (5).

The safety event outcomes were defined using claims definitions (defined in Appendix 2) and were not validated via medical records in this study (except for ALI as described in Annex 1 of the protocol). Other outcomes could also be validated in follow-up studies.

### 9.6. Bias

For Secondary Objective 3, control of confounding was addressed by propensity score matching. The propensity scores (described in Section 9.9.2) were estimated using covariates measured during the baseline period and did not include factors not reliably available in claims such as body mass index and smoking status. In a sensitivity analysis for ALI, we evaluated the minimum strength required for both the palbociclib-confounder and confounder-ALI relationships to explain the estimated association between palbociclib and disease (e.g., the E-value, as defined in VanderWeele TJ et al.) (22). Additionally, the safety events (outcomes) of interest may have been misclassified. They were identified using diagnosis and procedure codes in the HIRD and the accuracy of this approach is unknown, as events were not validated using medical record adjudication (except for ALI). It is possible that this approach could lead either to the identification of safety events that are false positives and fail to capture actual events (false negatives). For select outcomes, we included sensitive and specific definitions of the outcome to provide a range of potential rates for that outcome. For ALI, for which validation was conducted, outcome accuracy was adjusted using quantitative bias analyses, which involved providing PPV-corrected incidence rates calculated by multiplying the crude incidence rates by the PPV of each algorithm (23).

### 9.7. Study Size

The study included eligible patients utilizing palbociclib from 2015 through 2017, and eligible patients utilizing fulvestrant (without palbociclib) from 2011 through 2015 and separately from 2015 through 2017. There were 2,445 eligible patients in HIRD who were new users of palbociclib and 2,285 of them having algorithm-defined advanced stage ER+/HER2- breast cancer (Figure 1). The number of new users concurrently initiating palbociclib and fulvestrant was 566, and the number of patients treated with fulvestrant (without palbociclib) was 2,316 from January 2011- January 2015 and 961 from February 2015 to September 2017. After 1:1 propensity score matching (described in Section 9.9.2), we had 561 matched patients with palbociclib and fulvestrant and 561 treated with fulvestrant (without palbociclib) (Figure 1) for the historical comparator analyses, and 292 matched patients with palbociclib and fulvestrant and 292 treated with fulvestrant (without palbociclib) for the contemporaneous comparator analyses.

This study examined 42 safety events that varied considerably in prevalence, thus the degree of precision in effect estimates also varied by each safety event (outcome). Further analyses,

including medical record validation, were conducted for ALI, as noted in Annex 1A of the protocol, but this outcome was not pre-specified as the primary outcome of this study.

### 9.8. Data transformation

Categorizations were selected to match the previous Standing Cohort Study (Pfizer-HealthCore study A5481080: "Standing Cohorts of Individuals with Early or Advanced ER+/HER2- Breast Cancer"). Categorizations were selected at the study protocol development based on either the expected distribution of the covariate or based on recognized categories used in literature. There were no transformations of any of the covariates or outcomes.

### 9.9. Statistical methods

#### 9.9.1. Main summary measures

The distributions of variables describing demographics, medical history, cancer therapy history, healthcare utilization, medication use, and co-morbidities (included in Table 1 of Annex 3 of the protocol) are described for the total palbociclib and fulvestrant cohorts and separately for each of the subcohorts outlined in Figure 1, and further described in the protocol (Appendix 2). Characteristics including demographics, medical history, imaging, breast cancer treatment patterns, healthcare utilization, co-morbidities and non-breast cancer related medication use identified from claims were described using measures of central tendency (mean, standard deviation, median, and interquartile range) for continuous variables and frequencies of categorical variables.

#### 9.9.2. Main statistical methods

##### 9.9.2.1. Descriptive and propensity score adjusted analyses – Primary Objective and Secondary Objectives 1-3

Hazard ratios were computed comparing the risk of each safety event between new users of palbociclib with fulvestrant and propensity score matched new users of fulvestrant using Cox proportional hazard regression analysis in the two study cohorts (all users and all users with algorithm-defined advanced stage ER+/HER2- breast cancer). The incidence of the safety events of interest was computed by dividing the total number of events that were identified by the total at-risk person-time accumulated for all cohort members for that specific event. Only cohort members who did not have any history of one of the events of interest contributed to the computation of at-risk person-time for that event (unless otherwise specified). Confidence intervals for the incidence estimates were computed using methods based on the Poisson distribution.

For Secondary Objective 3 analyses, results among patients newly initiating palbociclib with fulvestrant were compared to patients newly initiating fulvestrant alone (prior to the FDA approval of palbociclib in 2015). Descriptive analyses and incidence rates of safety events were presented for both groups as described in Section 9.4.1. Unadjusted hazard ratios for each safety event comparing palbociclib with fulvestrant new users to fulvestrant-only new users were conducted utilizing Cox proportional hazards regression modeling.

Propensity score matching was utilized to adjust for measured (observed) potential confounders including demographics, medical history, imaging, breast cancer treatment patterns, healthcare utilization, co-morbidities and non-breast cancer related medication. A logistic regression model was used to identify covariates that are predictors of any of the outcomes of interest for the propensity score. Variables were included regardless of their measured relation to the exposures, as simulation studies suggest that inclusion of these variables can increase the precision of the estimated effect of the exposure without increasing bias (24).

The distribution of the propensity scores was examined graphically and compared between new users of palbociclib and fulvestrant. Patients whose propensity score laid outside the region of overlap were excluded (trimmed). We then stratified the population into 10 mutually exclusive strata defined by the deciles of the propensity score using the distribution of the palbociclib (with fulvestrant) exposed population. Each palbociclib/fulvestrant new user was then be matched to one (1:1) new user of fulvestrant alone by propensity score stratum (25).

To assess comparability, absolute standardized differences were computed for each covariate, as further described in the protocol (Appendix 2) (26). Baseline covariates with a standardized difference greater than 0.1 and covariates considered particularly relevant were included the propensity score. The following variables were included in the propensity score: age, region, Deyo-Charlson Index (DCI), number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen dispensing, everolimus dispensing, anastrazole dispensing, denosumab or pamidronate dispensing, exemestane dispensing, chemotherapy dispensing, corticosteroids dispensing, diagnostic imaging, breast cancer surgery, letrozole dispensing, HER2 positive therapy, radiation therapy, CT (computed tomography) imaging, mammography, MRI (magnetic resonance imaging), anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, and cerebrovascular disease. A separate propensity score was calculated within each cohort analysis (all new users and new users restricted to advanced stage ER+/HER2- breast cancer), as described above. The same variables were included in this propensity score.

For ALI events specifically as part of signal refinement analyses, we created a separate propensity score that included additional baseline covariates (medications, diagnoses) that may be particularly associated with hepatic outcomes that are noted in Section 9.4.2. The propensity score development was the same as described above with the exception that mutually exclusive strata were defined by the quartiles (instead of deciles) of the propensity score using the distribution of the palbociclib (with fulvestrant) exposed population to improve ability to identify a sufficient number of comparator matches. The propensity score included the following variables: age, region, DCI, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrazole, denosumab or pamidronate, exemestane, chemotherapy,

corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2+ therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, chronic liver disease or Alcoholism, chronic or acute disease of gallbladder or pancreas, hepatic, biliary or pancreatic cancer, congestive heart failure, any medication associated with ALI, including acetaminophen, allopurinol, amiodarone, amitriptyline, clavulanic acid, aripiprazole, baclofen, ciprofloxacin, clindamycin, clopidogrel, duloxetine, estrogens, fluoxetine, ketoconazole, lisinopril, losartan, mirtazapine, nitrofurantoin, NSAIDs, omeprazole, paroxetine, phenothiazine, sertraline, statins, tetracycline, trazodone, and trimethoprim.

In addition, we conducted sensitivity analyses to stratify the main ALI results by whether a patient had one of the following ALI risk factors (chronic liver disease, alcoholism, chronic or acute hepatitis, chronic or acute disease of gallbladder or pancreas, hepatic, biliary, or pancreatic cancer, congestive heart disease, or prescription acetaminophen use).

As a part of ALI signal refinement analyses, we also evaluated whether the transition from ICD-9 to ICD-10 affected the incidence of ALI, as has been noted for a few outcomes (8). We examined the incidence rate of the primary ALI algorithms among palbociclib and fulvestrant users in the ICD-9 period (01 April 2014 to 30 September 2015) and compared it to the ALI incidence rate among palbociclib users in the ICD-10 period (01 October 2015 to 30 March 2017). ALI incidence rates were reported in nine month increments. This analysis was also separately conducted among all individuals in the HIRD (i.e. including individuals without breast cancer) to provide a large sample size for this analysis.

#### 9.9.2.2. Descriptive and propensity score adjusted analyses - Secondary Objective 4

For analyses in Secondary Objective 4, which were all part of ALI signal refinement analyses, results among patients newly initiating palbociclib with fulvestrant were compared to patients newly initiating fulvestrant alone (after the FDA approval of palbociclib in February 2015 – contemporaneous comparator group). Similar to the analyses described in Section 9.7.1., descriptive analyses were presented for both groups using measures of central tendency for continuous variables and frequencies of categorical variables. Propensity score matching was utilized as described in Section 9.9.2 for ALI events, which included the additional baseline covariates that may be associated with hepatic outcomes (Section 9.9.2). Comparability was evaluated using standardized differences.

Additional comparative analyses using the contemporaneous comparators for all of the ALI algorithms were conducted (calculating incidence rates and unadjusted and adjusted hazard ratios as described in Section 9.9.2).

#### 9.9.2.3. Descriptive and propensity score adjusted analyses – Secondary Objective 5

As a part of signal refinement, descriptive analyses were performed among each of the provisional ALI outcomes identified by the four algorithms. Descriptive characteristics were similar to those included in the comparative study described in Section 9.9.2 and included covariates, such as medications noted in Table 3 of the protocol. In addition, we also

provided descriptive statistics of the other conditions and medications pre-specified in the adjudication questionnaire (specified in the medical record plan – Annex 1A). Information from case narratives for each confirmed ALI case were also obtained (further specified in Annex 1A of the protocol) and findings were described qualitatively in Section 11.1.2.

Among the patients with possible ALI events in which medical records were obtained, we assessed the accuracy of each of the ALI algorithms both overall and stratified by the five exposure groups (palbociclib with fulvestrant, palbociclib with letrozole, other palbociclib, fulvestrant monotherapy (historical comparator), and fulvestrant monotherapy (contemporaneous comparator) (i), as counts permitted. PPVs and 95% confidence intervals were reported for each of the groups as further specified in the medical record plan – Annex 1A. The comparative analyses were then re-analyzed using the information obtained through the medical record review, with the outcome restricted to confirmed cases identified through medical record adjudication, and provisional cases (in which records could be retrieved) adjusting for outcome accuracy and provided adjusted point estimates and confidence intervals. Outcome accuracy was adjusted using quantitative bias analyses, which involved calculating PPV-corrected incidence rates calculated by multiplying the crude incidence rates by the PPV of each algorithm (23, 27).

The HRs for ALI (presented in Tables 1-8 in Appendix 3) were presented restricting to confirmed ALI events, and separately including confirmed ALI events and provisional ALI events adjusted for PPVs within each treatment. Since there was a limited number of adjudicated cases in each treatment group, we also presented estimates of the amount of differential outcome misclassification needed to attenuate the palbociclib-ALI association to the null (HR=1.0) when assuming 100% sensitivity and 100% PPV in the fulvestrant monotherapy group.

### 9.9.3. Missing values

Laboratory values are available for a portion of the study population. For the main “incident” analyses of lab values, to qualify for follow-up we required a normal lab value prior to the index date, and to qualify for an event we required an abnormal lab value after the index date for inclusion (defined further in Appendix 2). "Prevalent and Incident" analyses only required an abnormal value of a lab measure after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

### 9.9.4. Sensitivity analyses

For the active surveillance study, all analyses were conducted among patients who met the predictive model for advanced stage ER+/HER2- as a measure of “on-label” users. We also examined the incidence of a “sensitive” and a “specific” definition for an outcome for select safety events of interest.

For the signal refinement study, several sensitivity analyses were conducted:

- Stratified the main ALI results by whether a patient had an ALI risk factor (prescription acetaminophen use, chronic liver disease, alcoholism, chronic or acute hepatitis, chronic or acute disease of gallbladder or pancreas, hepatic, biliary, or pancreatic cancer, and congestive heart disease)

- Evaluated the incidence of the primary ALI algorithm over time, in the palbociclib and fulvestrant group, as well as the overall HIRD. This analysis was conducted to evaluate whether the change from ICD-9 diagnosis codes to ICD-10 diagnosis codes on 01 October 2015 in the US may have impacted the incidence of ALI in our database.

- Examined the effect of unmeasured confounding by calculating the e-value (the association between the confounder-exposure and the confounder-outcome that are needed to attenuate the association of interest to null)(22)

- Examined the effect of outcome misclassification for the ALI outcome. (28)

- Examined the amount of follow-up time in the palbociclib-fulvestrant use group and the comparator group, and evaluated the incidence rates and hazard ratios of ALI stratified by the amount of follow-up time.

### 9.9.5. Amendments to the statistical analysis plan

None.

## 9.10. Quality control

The study was tracked at various levels to help ensure that all aspects including project delivery, infrastructure, quality processes, resource management, and financial issues were addressed. To help ensure the highest level of quality on every project, HealthCore has established several layers of quality assurance throughout the project lifecycle.

- Role Based Control Checks: each member of the team is responsible to perform thorough quality control checks on their work; in addition, the Principal Investigator and Research Project Manager are accountable for quality of all deliverables.

- Quality Check Points: centralized “checkpoints” have been implemented during the data management cycle to help ensure accurate translation of programming requests.

- Quality Assurance Standards: standard review procedures have been developed and are applied throughout the project lifecycle.

- Automation: HealthCore has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability and accuracy for each project.

HealthCore’s research team documents study progress and scientific and quality review of all study activities and deliverables (e.g., protocol, data management, data analysis, reports,

manuscripts, etc.) in an ADIN (Action, Decision, Issue, Notification) log and in a Quality Control (QC) Log. The ADIN Log provides documentation of study progress, action items, issues/issue resolution, and notifications, and is updated weekly during internal project team meetings. In addition, the QC Log documents the quality control measures performed for each study activity during the conduct of the study.

All programming required for study database extraction and creation of the analytic datasets from the HIRD was performed in accordance with HealthCore Programming Standards. The HealthCore Programming Standards are a set of documents describing data extraction methods that are referenced in HealthCore Standard Operating Procedures (SOPs) and provide a guideline for basic, frequently used terms and definitions and respective coding information to maintain operational consistency. Data validation occurred throughout the data management and analysis process. Data quality checks include, but are not limited to, programming checks by an individual who is not the main programmer for the study, internal dataset consistency, and checks to ensure that protocol criteria were met.

### 9.11. Protection of human subjects

Subject information and consent

Not Applicable.

### 9.12. Patient Information

HealthCore maintains Data Sharing Agreements (DSAs) and Business Associate Agreements with covered entities that provide Protected Health Information (PHI) incorporated into the HIRD. HealthCore's access, use, and disclosure of PHI are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 Code of Federal Register (CFR) Part 160 and Subparts A and E of Part 164]. HealthCore does not access, use, or disclose PHI other than as permitted by HIPAA and its Business Associate Agreements. When using PHI for research, this typically means PHI will be used to create limited data sets for research, or when that is not feasible, we may obtain a specific waiver of the HIPAA authorization requirements from an institutional review board (IRB). HealthCore also takes into consideration other federal and state laws and regulations that might limit use of certain types of data more than HIPAA, including those laws related to identifiable records related to substance abuse and human immunodeficiency virus (HIV).

The current study was designed as an analysis based on medical and pharmacy claims data from a large insured population in the US, with information regarding ALI obtained from medical records. Protected Health Information (PHI) must be accessed from medical records in order to adjudicate the safety endpoint of ALI. A HIPAA Waiver of Authorization was applied for from an IRB prior to any PHI was identified. PHI was redacted from medical records prior to adjudication activities (further described in Annex 1A of protocol).

At no time during the conduct of this study will HealthCore provide individual or provider identifying information to the Sponsor. Pfizer will not attempt to re-identify any results

provided for the study. There was no active enrollment or active follow-up of study subjects for this study.

All parties complied with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures included omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data was stored at HealthCore's office in encrypted electronic form and was password protected to ensure that only authorized study staff have access. HealthCore implemented appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), , FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets,

There was prospective approval of the study protocol, protocol amendments, and other relevant documents from the relevant IRBs/IECs.

## 10. RESULTS

### 10.1. Participants

#### 10.1.1. Active surveillance study

During the study period of 01 January 2015 to 30 September 2017, there were 23.4 million - patients with medical and pharmacy data available in the HIRD, of which 2,795 patients received at least one dispensing of palbociclib. There were 2,445 patients who met inclusion criteria for this study, with 2,285 of them also meeting the predictive model algorithm criteria for having advanced stage ER+/HER2- breast cancer (Table 0 in Appendix 3; and Table 3 below). Among the 2,445 eligible new users of palbociclib, there were 566 new users of palbociclib and fulvestrant, 1,159 new users of palbociclib with letrozole, and 720 all other new users of palbociclib (which included prevalent users of fulvestrant or letrozole). There were 2,316 eligible patients who received at least one dispensing of fulvestrant in the historical comparator period of 01 January 2011 to 31 January 2015. After propensity score matching, there were 561 new users of palbociclib and fulvestrant matched to 561 new users of fulvestrant users (Table 3).

**Table 3. Formation of study cohorts**

| | Total | | Total with advanced stage ER+/HER2- breast cancer* | |
|---|---|---|---|---|
| | N | % | N | % |
| Received palbociclib during the study period (01 Jan 2015 to 30 Sept 2017) | 2,795 | 100% | 2,600 | 100% |
| ≥18 years of age | 2,795 | 100% | 2,600 | 100% |
| ≥three months of health plan coverage | 2,445 | 87.48 % | 2,285 | 87.88 % |
| ≥three months with no dispensing of palbociclib or other CDK4/6 inhibitor before first dispensing of palbociclib | 2,445 | 87.48 % | 2,285 | 87.88 % |
| New users of palbociclib with fulvestrant | 566 | 23.15 % | 548 | 23.98 % |
| New users of palbociclib with letrozole | 1,159 | 47.40 % | 1,083 | 47.40 % |
| All other new users of palbociclib | 720 | 29.65 % | 654 | 28.62 % |
| Historical comparison group for Secondary Objective 3 | | | | |
| Received fulvestrant during the study period (01 Jan 2011 to 31 Jan 2015) | 3,315 | 100% | 2,983 | 100% |
| ≥18 years of age | 3,315 | 100% | 2,983 | 100% |
| ≥three months of health plan coverage | 2,773 | 83.65 % | 2,495 | 83.64 % |
| ≥three months with no dispensing of fulvestrant before first dispensing of fulvestrant | 2,316 | 69.86 % | 2,061 | 69.09 % |
| All propensity score matched patients with fulvestrant | 561 | 16.92 % | 544 | 18.24 % |

Abbreviations: N, number; ER+, Estrogen Receptor Positive; HER2-, Human Epidermal Growth Factor 2 Negative; Jan, January; Sept, September; CDK, cyclin-dependent kinase.
*Patients with advanced stage ER+/HER2- breast cancer (as defined by predictive model; this advanced stage ER+/HER2- breast cancer date must have occurred before or within three months of the first dispensing of study drug of interest (palbociclib or fulvestrant).

### 10.1.2. Signal refinement analyses

For the subsequent ALI signal refinement analyses, we utilized the cohorts noted in the initial active surveillance study in Section 10.1.1 and also evaluated a separate contemporaneous fulvestrant-only comparison group in secondary Objective 4.

In the additional analyses involving the historical fulvestrant comparison group, we added additional ALI risk factors to the propensity score and used quartiles instead of deciles for the matching as described in Section 9.9.2. After this propensity score matching, there were 565 new users of palbociclib with fulvestrant and 565 new users of historical fulvestrant.

For the separate contemporaneous fulvestrant comparison group, we identified 961 new users of fulvestrant alone between 01 February 2015 and 30 September 2017. We then created a propensity score, which included the additional ALI risk factors and used quartiles for

matching. After matching, we were only able identify matches for 292 new users of palbociclib with fulvestrant with 292 contemporaneous new users of fulvestrant given baseline differences between the two groups (e.g., metastasis to respiratory and digestive systems: palbociclib with fulvestrant=45% vs. contemporaneous fulvestrant monotherapy=35%; Table 1-4B in Appendix 3).

Subsequently, we validated all ALI outcomes available from any of the four algorithms through medical record adjudication as part of Secondary Objective 5 as described in Section 9.9.2.3. In total, there were 185 potential cases of ALI from any of the four algorithms. Of these, there were 52 cases that were unable to have their medical records requested due to plan-based privacy restrictions. Among the other 133 potential cases requested from the provider, 52 medical records were retrieved, with 29 potential cases meeting the primary ALI claims algorithm defined as "confirmed" (Table 1-9 in Appendix 3). Subsequently a hepatologist developed case narrative on each of these 29 confirmed ALI cases.

### 10.2. Descriptive data

Among all palbociclib initiators in the HIRD (n=2,445), a majority were between the ages of 45 and 64 (60.9%), had previously used an aromatase inhibitor (62.5%), had a secondary malignancy (87.4%), and met a predictive model algorithm for having advanced stage ER+/HER2- breast cancer (93.5%) (Table 1-1 in Appendix 3; and Table 4 below). As expected, most patients were females, although 53 males were dispensed palbociclib (2.2%). While healthcare utilization was common (mean outpatient visits in last six months = 39.7), surgery (mastectomy/lumpectomy), chemotherapy, and radiation therapy in the six months prior to palbociclib initiation were less common (each <20%). The most common non-breast cancer related medication use prior to palbociclib initiation included antidepressants (30.5%), antihypertensives (26.7%), and corticosteroids (24.8%), and lipid lowering agents (21.6%). Common co-morbidities included cerebrovascular disease, pure hypercholesterolemia, pathologic fracture, and osteoporosis (each ≥8.0%) (Table 1-1 in Appendix 3 and Table 4 below).

Descriptive data were relatively similar among three palbociclib subgroups: new users with each having a mean age of around 60 years, approximately 40 outpatient visits the prior six months, and a mean DCI index around eight. There were a few notable differences between the three groups. New users of palbociclib with fulvestrant were more likely to be identified in recent years (2017), in the south, taking antihypertensives and lipid lowering agents than the other two groups. New users of palbociclib with letrozole were more likely to initiate in earlier years (2015), have a secondary malignancy, use CT or diagnostic imaging, and have a pathologic fracture than the other two groups. In contrast, other new users of palbociclib were more likely to be male, from the west, and recently received chemotherapy (Table 1-1 in Appendix 3 and Table 4 below).

**Table 4. Select characteristics of breast cancer patients using palbociclib identified in the HIRD**

| Characteristics* | All new users of palbociclib | | New users of palbociclib with fulvestrant | | New users of palbociclib with letrozole | | All other new users of palbociclib (no new use of fulvestrant or letrozole) | |
|---|---|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD |
| **Overall** | **2,445** | **100%** | **566** | **100%** | **1,159** | **100%** | **720** | **100%** |
| Age at index date (in years) | 59.79 | 11.62 | 59.47 | 11.38 | 59.21 | 11.27 | 60.95 | 12.29 |
| Sex | | | | | | | | |
| Male | 53 | 2.17 | ≤10 | 1.59 | 14 | 1.21 | 30 | 4.17 |
| Female | 2392 | 97.83 | 557 | 98.41 | 1145 | 98.79 | 690 | 95.83 |
| Calendar year of index date | | | | | | | | |
| 2015 | 791 | 32.35 | 99 | 17.49 | 456 | 39.34 | 236 | 32.78 |
| 2016 | 942 | 38.53 | 269 | 47.53 | 406 | 35.03 | 267 | 37.08 |
| 2017 | 712 | 29.12 | 198 | 34.98 | 297 | 25.63 | 217 | 30.14 |
| Geographic region of residence | | | | | | | | |
| Midwest | 400 | 16.36 | 95 | 16.78 | 185 | 15.96 | 120 | 16.67 |
| South | 581 | 23.76 | 159 | 28.09 | 288 | 24.85 | 134 | 18.61 |
| Northeast | 696 | 28.47 | 166 | 29.33 | 340 | 29.34 | 190 | 26.39 |
| West | 768 | 31.41 | 146 | 25.80 | 346 | 29.85 | 276 | 38.33 |
| Secondary malignancy to any site (metastasis) | 2137 | 87.40 | 496 | 87.63 | 1044 | 90.08 | 597 | 82.92 |
| Lymph nodes of head, face, and neck metastasis | 690 | 28.22 | 154 | 27.20 | 356 | 30.72 | 180 | 25.00 |
| Respiratory and digestive system metastasis (includes liver metastasis) | 1058 | 43.27 | 257 | 45.41 | 490 | 42.28 | 311 | 43.19 |
| Metastasis to other specified sites | 2017 | 82.49 | 463 | 81.80 | 978 | 84.38 | 576 | 80.00 |
| Deyo-Charlson comorbidity index (DCI) | 8.39 | 1.90 | 8.52 | 1.76 | 8.48 | 1.70 | 8.13 | 2.25 |
| Advanced stage ER+/HER2- breast cancer | 2,285 | 93.46 | 548 | 96.82 | 1,083 | 93.44 | 654 | 90.83 |
| Radiation therapy | 483 | 19.75 | 112 | 19.79 | 233 | 20.10 | 138 | 19.17 |
| Chemotherapy | 472 | 19.30 | 100 | 17.67 | 218 | 18.81 | 154 | 21.39 |
| CT related imaging | 602 | 24.62 | 139 | 24.56 | 333 | 28.73 | 130 | 18.06 |
| Number of outpatient visits | 39.67 | 25.20 | 38.58 | 23.63 | 39.51 | 23.78 | 40.79 | 28.42 |

**Table 4. Select characteristics of breast cancer patients using palbociclib identified in the HIRD**

| Characteristics* | All new users of palbociclib | | New users of palbociclib with fulvestrant | | New users of palbociclib with letrozole | | All other new users of palbociclib (no new use of fulvestrant or letrozole) | |
|---|---|---|---|---|---|---|---|---|
| Aromatase inhibitor | 1527 | 62.45 | 326 | 57.60 | 815 | 70.32 | 386 | 53.61 |
| HER2+ therapy | 72 | 2.94 | 15 | 2.65 | 35 | 3.02 | 22 | 3.06 |
| Tamoxifen | 552 | 22.58 | 140 | 24.73 | 270 | 23.30 | 142 | 19.72 |
| Fulvestrant | 621 | 25.40 | 238 | 42.05 | 112 | 9.66 | 271 | 37.64 |
| Denosumab or pamidronate | 836 | 34.19 | 206 | 36.40 | 359 | 30.97 | 271 | 37.64 |
| Everolimus | 150 | 6.13 | 40 | 7.07 | 52 | 4.49 | 58 | 8.06 |
| Antihypertensives | 653 | 26.71 | 173 | 30.57 | 293 | 25.28 | 187 | 25.97 |
| Corticosteroids | 606 | 24.79 | 148 | 26.15 | 308 | 26.57 | 150 | 20.83 |
| Lipid lowering agent | 528 | 21.60 | 132 | 23.32 | 251 | 21.66 | 145 | 20.14 |
| Pathologic fracture | 211 | 8.63 | 46 | 8.13 | 110 | 9.49 | 55 | 7.64 |
| Pure hypercholesterolemia | 215 | 8.79 | 48 | 8.48 | 105 | 9.06 | 62 | 8.61 |

Abbreviations: HIRD, HealthCore Integrated Research Database; N, number; SD, standard deviation; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; CT, computed tomography.
*All characteristics are measured as presence within six months prior to palbociclib initiation, unless otherwise specified.

Descriptive results among patients who met the predictive model algorithm for ER+/HER2- advanced stage breast cancer were largely similar to the overall sample, with the only notable difference being that there were less patients in the ER+/HER2- advanced stage breast cancer group who received a HER-2 positive therapy (1.1% vs. 2.9%; Table 2-1 in Appendix 3). New users of palbociclib and fulvestrant and palbociclib and letrozole were both more likely to be included in the ER+/HER2- breast cancer group than the other new users of palbociclib (96.8% and 93.4% vs. 90.8%; Table 1-1 in Appendix 3).

### 10.3. Outcome data

The number of outcomes identified for the active surveillance study among all new users of palbociclib are described in Table 1-2 in Appendix 3. Similarly, the number of outcomes are described for each of the subgroups of new users of palbociclib in Table 1-3 in Appendix 3. There was no "primary outcome" in this active surveillance study as we examined 42 safety events with results further described in Section 10.4 and Section 10.5. Results are considered exploratory in part given the number of outcomes measured. Subsequent analyses were conducted as part of the ALI signal refinement analyses. Tables 1-8 and 1-9 in Appendix 3 provide further results and information on the different ALI outcome algorithms.

## 10.4. Main results

### 10.4.1. Active Surveillance Study

The incidence rates of safety events after the initiation of palbociclib among all new users are described in Table 1-2 in Appendix 3, and in Table 5 below (for select safety events). Safety events common to palbociclib users after initiation included neutropenia, anemia, interstitial lung disease (ILD)/pneumonitis, and serious infections (each incidence rate>20 per 100 person-years). Less common safety events included sudden cardiac death, stomatitis and mucositis, and febrile neutropenia (each incidence rate<4 per 100 person-years). The initial algorithm included in the active surveillance study for ALI was comprised of codes including those indicating elevated liver lab results (now described as Algorithm 2 – original with labs algorithm), and was also a rarely occurring event reported in claims (IR=3.1, 95% CI=2.3-4.1). Note, while elevated liver enzyme results may be a more common occurrence in practice, they may often not be directly reported in claims (i.e. limited sensitivity).

**Table 5. Incidence of select safety events in all new users of palbociclib**

| Event | All new users of palbociclib (N=2,445) | | | | |
|---|---|---|---|---|---|
| | # Events | P-YRS at risk | IR (per 100 person-years) | | |
| | | | IR | 95% Lower CI | 95% Upper CI |
| Anemia | 536 | 1358 | 39.5 | 36.2 | 43.0 |
| Neutropenia | 473 | 1352 | 35.0 | 31.9 | 38.3 |
| Interstitial lung disease (ILD)/pneumonitis | 352 | 1437 | 24.5 | 22.0 | 27.2 |
| Serious infection | 293 | 1472 | 19.9 | 17.7 | 22.3 |
| Fatigue* | 230 | 1330 | 17.3 | 15.1 | 19.7 |
| Nausea* | 200 | 1409 | 14.2 | 12.3 | 16.3 |
| Thrombocytopenia | 149 | 1497 | 10.0 | 8.4 | 11.7 |
| Leukopenia | 99 | 1496 | 6.6 | 5.4 | 8.1 |
| QT prolongation | 80 | 1514 | 5.3 | 4.2 | 6.6 |
| Pulmonary embolism | 45 | 1505 | 3.0 | 2.2 | 4.0 |
| Febrile neutropenia | 44 | 1530 | 2.9 | 2.1 | 3.9 |
| Acute liver injury (Algorithm 2) | 47 | 1553 | 3.1 | 2.3 | 4.1 |
| Stomatitis and mucositis | 35 | 1529 | 2.3 | 1.6 | 3.2 |

Abbreviations: IR, incidence rate; CI, confidence interval, P-YRS, person years.
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

Table 1-3 in Appendix 3 describes the incidence rates of safety events among the three palbociclib new users groups. The incidence rate of many of the safety events were similar across the three palbociclib groups including neutropenia, leukopenia, QT prolongation, stomatitis and mucositis (Appendix 3). The incidence of some safety events were elevated in the new users of palbociclib with fulvestrant compared to the other user groups, including serious infections (25.6 per 100 person-years vs. 17.5 per 100 person-years and 20.28 per 100 person-years), ALI (Algorithm 2- original with labs) (4.0 per 100-person years vs. 2.7 and 3.0 per 100-person years), and anemia (26.1 per 100 person-years vs. 21.2 and 20.3 per 100 person-years) (Table 1-3 in Appendix 3).

Table 1-4A in Appendix 3 provides descriptive statistics comparing new users of palbociclib with fulvestrant with a historical comparison group of new users of fulvestrant alone (pre-2015). Prior to any propensity score matching, the two groups were relatively similar on many of the measured factors including factors related to cancer therapy history such as chemotherapy and radiation therapy, hormone therapy use, and most of the measured co-morbidities (Table 1-4A in Appendix 3). However, there were some notable differences between the groups many suggesting new users of palbociclib-fulvestrant may have more advanced breast cancer. While new fulvestrant users were older on average, the palbociclib-fulvestrant users were more likely to have a secondary malignancy (metastasis) to lymph nodes of head, face, and neck (27.2% vs. 20.6%), respiratory and digestive systems (45.4% vs. 33.7%) and to other specified sites (81.8% vs. 73.8%), a higher DCI score (8.5 vs. 7.9), and certain breast cancer related medications such as tamoxifen, everolimus, denosumab, or pamidronate (Table 1-4A in Appendix 3). After propensity score matching, these measured factors were all largely balanced with standardized differences ≤0.10 (Table 1-4A in Appendix 3 and Table 6 below).

**Table 6. Select characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparator group) after propensity score matching**

| Baseline Characteristics* | After Propensity Score Matching | | | | |
|---|---|---|---|---|---|
| | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (pre-2015) | | Standardized difference |
| | N/Mean | %/SD | N/Mean | %/SD | |
| **Overall** | **561** | **100%** | **561** | **100%** | |
| Age at index date (in years) | 59.5 | 11.0 | 59.9 | 13.3 | 0.04 |
| Secondary malignancy (metastasis) | 491 | 87.5 | 488 | 87.0 | 0.02 |
| Secondary malignancy (metastasis) – respiratory and digestive systems | 254 | 45.3 | 252 | 44.9 | 0.01 |
| Deyo-Charlson comorbidity index (DCI) | 8.5 | 1.8 | 8.56 | 1.6 | 0.03 |

**Table 6. Select characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparator group) after propensity score matching**

| Baseline Characteristics* | After Propensity Score Matching | | | | |
|---|---|---|---|---|---|
| | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (pre-2015) | | Standardized difference |
| Radiation therapy | 112 | 20.0 | 117 | 20.9 | 0.02 |
| Chemotherapy | 99 | 17.7 | 98 | 17.5 | 0.00 |
| Aromatase inhibitor | 321 | 57.2 | 303 | 54.0 | 0.06 |
| HER2+ therapy | 15 | 2.7 | 14 | 2.5 | 0.01 |
| Tamoxifen | 140 | 25.0 | 135 | 24.1 | 0.02 |
| Fulvestrant | 236 | 42.1 | 0 | 0.0 | n/a |
| Denosumab or pamidronate | 201 | 35.8 | 197 | 35.1 | 0.01 |
| Everolimus | 39 | 7.0 | 37 | 6.6 | 0.01 |
| Anticonvulsants | 122 | 21.8 | 123 | 21.9 | 0.00 |
| Corticosteroids | 146 | 26.0 | 146 | 26.0 | 0.00 |
| Pathologic fracture | 46 | 8.2 | 51 | 9.1 | 0.03 |

Abbreviations: N, number; SD, standard deviation, HER2, human epidermal growth factor receptor 2.
*All characteristics are measured as presence within six months prior to the index date (palbociclib or fulvestrant initiation), unless otherwise specified.

Tables 1-5 and 1-6 in Appendix 3 provide the incidence rates of safety events in new users of palbociclib with fulvestrant and new users of fulvestrant alone, along with unadjusted and propensity score hazard ratios comparing the two groups. When compared to a historical group of new users of fulvestrant monotherapy, new users of palbociclib who also initiated fulvestrant were more likely to develop neutropenia, leukopenia, anemia, stomatitis and mucositis, and ALI (Algorithm 2- original with labs) in both unadjusted and propensity score adjusted analyses (HRs>1.6; Tables 1-5 and 1-6 of Appendix 3; and Table 7 below). Many of the other examined safety event rates were similar when comparing new users of palbociclib and fulvestrant to new fulvestrant monotherapy users including serious infections, type 2 diabetes, QT prolongation, second primary cancers, and pulmonary embolism (HRs<1.4; Tables 1-5 and 1-6 of Appendix 3; and Table 7 below).

**Table 7. Select incidence rates and adjusted hazard ratios of safety events in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparator)**

| Event | After Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib and fulvestrant (n=561) | | | | | New users of fulvestrant alone (pre-2015) (n=561) | | | | | Adjusted Hazard Ratios | | |
| | # Events | P-YRS | IR (per 100 P-YRS) | | | # Events | P-YRS | IR (per 100 P-YRS) | | | HR | 95% LCL | 95% UCL |
| | | | IR | 95% LCL | 95% UCL | | | IR | 95% LCL | 95% UCL | | | |
| Neutropenia | 104 | 283 | 36.7 | 30.0 | 44.5 | 17 | 368 | 4.6 | 2.7 | 7.4 | 7.8 | 4.7 | 13.0 |
| Leukopenia | 17 | 316 | 5.4 | 3.1 | 8.6 | ≤10 | 370 | 0.8 | 0.2 | 2.4 | 6.4 | 1.9 | 21.9 |
| QT prolongation | 20 | 313 | 6.4 | 3.9 | 9.9 | 13 | 368 | 3.5 | 1.9 | 6.0 | 1.8 | 0.9 | 3.5 |
| Stomatitis and mucositis | ≤10 | 320 | 2.8 | 1.3 | 5.3 | ≤10 | 372 | 0.5 | 0.1 | 1.7 | 5.0 | 1.1 | 23.1 |
| Serious infection | 79 | 307 | 25.7 | 20.4 | 32.1 | 82 | 358 | 22.9 | 18.2 | 28.5 | 1.1 | 0.8 | 1.5 |
| Anemia | 134 | 281 | 47.7 | 40.0 | 56.5 | 91 | 347 | 26.2 | 21.1 | 32.2 | 1.8 | 1.4 | 2.3 |
| Thrombocytopenia | 33 | 315 | 10.5 | 7.2 | 14.7 | 17 | 370 | 4.6 | 2.7 | 7.4 | 2.3 | 1.3 | 4.1 |
| Pulmonary embolism | 14 | 316 | 4.4 | 2.4 | 7.4 | 15 | 368 | 4.1 | 2.3 | 6.7 | 1.0 | 0.5 | 2.1 |
| Acute liver injury (Algorithm 2) | 13 | 321 | 4.1 | 2.2 | 6.9 | ≤10 | 373 | 0.8 | 0.2 | 2.4 | 4.8 | 1.4 | 16.9 |

Abbreviations: CI, confidence interval; IR, incidence rate; n, number; PT, person-time; HR, hazard ratio; LCL, lower confidence level; UCL, upper confidence level; P-YRS, person-years.

### 10.4.2. ALI algorithm signal refinement analyses

To further investigate the risk of ALI after palbociclib use, we conducted subsequent signal refinement analyses which included development of additional ALI algorithms, adjustment for ALI risk factors, a separate (contemporaneous) comparator group, validation, and other sensitivity analyses.

As a first step, we developed three additional algorithms to define ALI. This included the development of a "primary ALI algorithm" (also called algorithm 1) to supplement the original ALI algorithm from the active surveillance algorithm (now called algorithm 2 or original algorithm with labs), along with broad (algorithm 3) and narrow (algorithm 4) definitions. Further details on these algorithms are provided in Section 9.3.3.6 above.

### 10.4.2.1. ALI algorithm signal refinement – historical comparator

As a part of the signal refinement study, we evaluated additional risk factors for ALI including chronic liver disease, hepatitis, and medications associated with liver injury and included them in the propensity score matching between the palbociclib with fulvestrant group and the historical comparator of fulvestrant monotherapy (Table 1-7 in Appendix 3) to better address potential confounding related to an ALI outcome. Before propensity score matching, there were several ALI risk factors more prevalent in the palbociclib-fulvestrant group than the fulvestrant only group (e.g., any medication associated with liver injury: 82.5% vs. 75.5%; chronic liver disease or alcoholism: 13.1% vs. 10.6%). After propensity score matching, covariates identified as important risk factors for ALI were balanced between the two groups (standardized differences<0.10; Table 1-7 in Appendix 3).

Table 8 and Figure 3 below provides each unadjusted and adjusted ALI algorithm result comparing palbociclib with fulvestrant and the historical fulvestrant monotherapy comparator. The incidence of the primary ALI algorithm (Algorithm 1) was 4.0 per 100 person-years in the palbociclib with fulvestrant group, and 1.3 per 100 person-years in the fulvestrant monotherapy historical comparator group (Table 1-8AB in Appendix 3). The unadjusted HR was 2.8 (95%CI=1.4-5.6), and results were similar after propensity score matching (aHR = 3.0, 95%CI=1.1-8.4). Results were also largely similar for the second ALI algorithm (original algorithm with labs) and third ALI algorithm (broad). There were no ALI events identified when using the fourth ALI algorithm (narrow), which restricted to select codes and required the code to be noted in the principal inpatient diagnosis position (Annex 2 of the protocol; Appendix 2).

**Table 8. Unadjusted and adjusted hazard ratios of ALI in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparator)**

| Event | Unadjusted Hazard Ratios | | | Adjusted Hazard Ratios* | | |
|---|---|---|---|---|---|---|
| | HR | 95% LCL | 95% UCL | aHR | 95% LCL | 95% UCL |
| Acute liver injury (primary algorithm) | 2.8 | 1.4 | 5.6 | 3.0 | 1.1 | 8.4 |
| Acute liver injury - 2 (original with labs algorithm) | 3.1 | 1.5 | 6.2 | 2.2 | 0.9 | 5.4 |
| Acute liver injury - 3 (broad algorithm) | 5.4 | 3.4 | 8.5 | 4.6 | 2.3 | 9.1 |
| Acute liver injury – 4 (narrow algorithm) | -- | -- | -- | -- | -- | -- |

Abbreviations: LCL, lower confidence limit; UCL, confidence limit; HR, hazard ratio; aHR, adjusted hazard ratio.
*Propensity score matching using variables noted in Section 9.9.2

There were 13 ALI events identified by the primary algorithm in the propensity score matched new user of palbociclib and fulvestrant group. This algorithm was met most

commonly by the ICD-10 codes K72.00 and K72.90, referring to hepatic failure (Table 9). For the ALI events identified by the primary algorithm in the propensity score matched historical comparator of new users of fulvestrant alone, the algorithm was fulfilled most commonly by the ICD-9 codes referring to 572.2 and 570 hepatic encephalopathy and acute necrosis of the liver (Table 9).

**Table 9. ICD-9 and ICD-10 codes that identified as the primary ALI event**

| Propensity score matched Palbociclib with Fulvestrant cohort | | | |
|---|---|---|---|
| **ALI ICD-10 Code** | **Description** | **Count** | **Percentage *** |
| K72.00 | Acute and subacute hepatic failure without coma | ≤10 | n/a |
| K72.90 | Hepatic failure, unspecified without coma | ≤10 | n/a |
| K72.91 | Hepatic failure, unspecified with coma | ≤10 | n/a |
| **Propensity score matched Historical Fulvestrant Comparator cohort** | | | |
| **ALI ICD-9 Code** | **Description** | **Count** | **Percentage *** |
| 572.2 | Hepatic encephalopathy | ≤10 | n/a |
| 570 | Acute necrosis of liver | ≤10 | n/a |
| 572.4 | Hepatorenal syndrome | ≤10 | n/a |

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision, ALI, acute liver injury.
*Percentages may not add up to 100%, given that a patients may have had multiple eligible ICD-9/ICD-10 codes from the algorithm on the same event day.

### 10.4.2.2. ALI algorithm signal refinement – contemporaneous comparator

In additional analyses, we evaluated the risk of ALI using a contemporaneous fulvestrant-only comparator group, given the temporal limitations to the historical fulvestrant comparator group with respect to ICD 9/10 coding. Table 1-4B in Appendix 3, provides comparisons of the characteristics for the palbociclib with fulvestrant group with the contemporaneous comparator group. Before propensity score matching, the contemporaneous fulvestrant comparator group was less likely to have certain risk factors such as secondary malignancy to respiratory and digestive systems (34.5% vs. 45.4%) or other sites (68.9% vs. 81.8%) and any medication associated with liver injury (71.7% vs. 82.5%; Table 1-4B in Appendix B).

Identifying comparable propensity score matches for the palbociclib with fulvestrant group with the contemporaneous comparator group was less successful than the historical comparator group, given the lower sample size and less compatibility of the contemporaneous comparator group. As such, only 292 of the 566 (52%) new users of palbociclib with fulvestrant were able to be matched within the same quartile of the propensity score of the contemporaneous new users of fulvestrant monotherapy. Among those who were matched, most of the key covariates including all measurable ALI risk factors were balanced (standardized difference<0.10) after matching between groups. However there were still modest differences after matching in some potentially important

confounders, such as age, as the mean age of new users of palbociclib with fulvestrant was 64 vs. 66 for new users of fulvestrant monotherapy (Table 1-4B, Appendix 3).

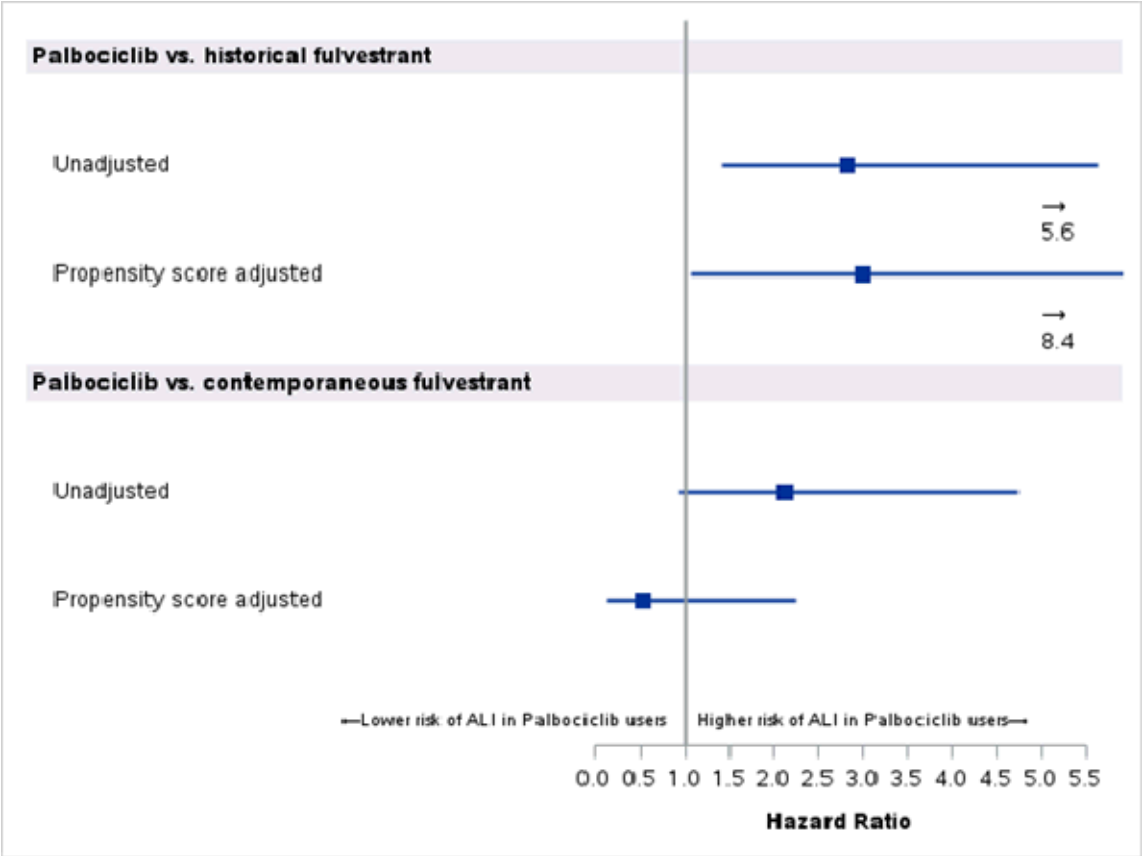
Table 10 below provides unadjusted and adjusted hazard ratios for all four ALI algorithm results comparing palbociclib with fulvestrant and the contemporaneous fulvestrant comparator. The incidence of the primary ALI algorithm was 4.0 per 100 person-years in the palbociclib with fulvestrant group, and 2.0 per 100 person-years in the fulvestrant alone historical comparator group (Table 1-8CD in Appendix 3). The unadjusted HR was 2.1, 95%CI=0.9-4.7, and results were less precise but attenuated across the null after propensity score matching (aHR = 0.5, 95%CI=0.1-2.2; Table 10 and Figure 3). While these point estimates differ from those presented with the historical comparator described in section 9.4.2.1, in regards to random error, the results from both comparison groups are consistent with regions of overlap of the 95% CI of the HRs estimates (Figure 3). Results were also largely similar for the second ALI algorithm (original algorithm with labs), and the third ALI algorithm (broad) (Table 1-8CD in Appendix 3). Similar to the historical comparator, there were no ALI events identified when using the fourth ALI algorithm (narrow), which restricted to select codes and required the code to be noted in the principal inpatient diagnosis position (Annex 2 of the protocol; Appendix 2).

**Table 10. Unadjusted and adjusted hazard ratios of ALI in new users of palbociclib and fulvestrant and new users of fulvestrant alone (contemporaneous comparator)**

| | Unadjusted Hazard Ratios | | | Adjusted Hazard Ratios* | | |
|---|---|---|---|---|---|---|
| **Event** | **HR** | **95% LCL** | **95% UCL** | **aHR** | **95% LCL** | **95% UCL** |
| Acute liver injury (primary algorithm) | 2.1 | 0.9 | 4.7 | 0.5 | 0.1 | 2.2 |
| Acute liver injury - 2 (original with labs algorithm) | 1.5 | 0.7 | 3.0 | 0.7 | 0.2 | 2.4 |
| Acute liver injury - 3 (sensitive algorithm) | 2.3 | 1.4 | 3.8 | 1.2 | 0.6 | 2.5 |
| Acute liver injury - 4 (specific algorithm) | -- | -- | -- | -- | -- | -- |

Abbreviations: LCL, lower confidence limit; UCL, confidence limit; HR, hazard ratio; aHR, adjusted hazard ratio.
*Propensity score matching using variables noted in Section 9.2.1

**Figure 3. Unadjusted and propensity score adjusted hazard ratios of ALI in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical and contemporaneous comparators)**




### 10.4.2.3. ALI algorithm signal refinement – medical record adjudication and case narratives

All 185 patients that met any of the four ALI claims algorithms in any of the palbociclib or fulvestrant group had medical records requested from the providers related to the ALI claim(s). We retrieved the relevant medical records from 52 patients, with 29 having met the primary ALI claims algorithm (Table 11; Table 1-9 in Appendix 3). Records from the other 133 patients who met the ALI algorithm were unable to be collected from the provider of interest due to privacy restrictions or the provider declined to participate. The response rate was highest in the palbociclib with fulvestrant group (36%), followed by the fulvestrant monotherapy groups (28%), and followed by the other palbociclib groups (9%).

Table 11 provides the positive predictive values (PPVs) for each of the ALI algorithms that were adjudicated. Among the 29 cases meeting the primary ALI claims algorithm with adjudicated results, 21 were noted as confirmed ALI cases, four were confirmed as non-cases, and the other four were classified as provisional given lack of sufficient information from the record. Thus, when restricting to confirmed cases and non-cases, the PPV was 84% (95%CI=64%-95%; Table 11; Table 1-9 in Appendix 3). ALI algorithms 2 and 3 had

modestly lower PPVs (Algorithm 2: 72%, Algorithm 3: 73%), while ALI algorithm 4 only had one case available to adjudicate (The one ALI algorithm 4 case was not among the main palbociclib/fulvestrant or comparative fulvestrant groups).

The sample size was limited when stratifying results by the different treatment groups. For the primary ALI algorithm, there were six adjudicated cases in the palbociclib and fulvestrant group, nine adjudicated cases in the historical fulvestrant comparator group, and four adjudicated cases in the contemporaneous fulvestrant comparator group. The PPVs ranged from 75 to 100% in these small groups (Table 1-9 in Appendix 3). The palbociclib with fulvestrant group and historical fulvestrant comparator groups both had PPVs of 75%, and the contemporaneous comparator group had a PPV of 100% (Table 1-9 in Appendix 3).

**Table 11. ALI algorithm signal refinement – validation of claims algorithms compared to medical record adjudication**

| Code or Combination of Codes | Number of provisional cases with collected medical record | Number of Confirmed Cases and Non-cases | Number of Confirmed Cases | PPV (95% CI) | 95% CI | |
|---|---|---|---|---|---|---|
| **Acute Liver Injury - All adjudication results** | | | | | | |
| Algorithm 1 (primary algorithm) | 29 | 25 | 21 | 0.84 | 0.64 | 0.95 |
| Algorithm 2 (original with labs) | 29 | 25 | 18 | 0.72 | 0.51 | 0.88 |
| Algorithm 3 (broad) | 52 | 40 | 29 | 0.73 | 0.56 | 0.85 |
| Algorithm 4 (narrow) | ≤10 | 0 | 0 | 0.00 | 0.00 | --- |

Abbreviations: ALI, acute liver injury; PPV, positive predictive value; CI, confidence interval.

Case narratives were developed by an expert hepatologist on all 32 cases deemed to be confirmed as ALI after adjudication (including three that occurred after palbociclib or fulvestrant discontinuation). However, given that not all medical records were able to be collected for adjudication, case narratives were developed only for a subset of cases (e.g., 3 of the 13 palbociclib with fulvestrant cases identified by the primary ALI algorithm and 6 of the 22 in the historical fulvestrant comparator group). The hepatologist was blinded with respect to the treatment the patient received. Among the 32 cases, the hepatologist noted that the case was unlikely to be drug induced liver injury (DILI) in 28 (87.5%) of the cases based on information in the medical record. Among the other four cases, the hepatologist did not exclude DILI, but he did not directly attribute any of the four cases to either palbociclib or fulvestrant. In the four possible cases that the reviewer suggested could be DILI, one record noted the patient was previously exposed to acetaminophen, another record noted autoimmune hepatitis, and for the other two, liver metastases and lack of preceding liver tests was noted.

There were notes about liver metastases in 28 of 32 (87.5%) of case narratives, with a majority of them noting that liver metastases likely had a prominent role in the ALI diagnosis. Among the 28 cases with noted liver metastases, 23 (82.1%) had an ICD-9/ICD-10 diagnosis code for secondary malignancy (metastasis) to a respiratory or digestive system (which includes the liver).

## 10.5. Other analyses

### 10.5.1. Active Surveillance Study

Analyses were also conducted on patients who met our predictive-model algorithm for ER+/HER2- breast cancer. Results were largely similar in this subgroup of patients in regard to the descriptive statistics and incidence rates of safety events when compared to those in the main analysis (Tables 2-2 and 2-3 in Appendix 3). Also similar to the main analyses, the characteristics of palbociclib with fulvestrant users compared to fulvestrant alone were similar particularly after propensity score matching (Table 2-4 in Appendix 3).

In the advanced stage ER+/HER2- breast cancer subgroup, the unadjusted results comparing new users of palbociclib with fulvestrant compared to fulvestrant alone were largely similar to the unadjusted results in the overall population. While results were also largely similar in the adjusted results, there were few notable differences in this subgroup. The adjusted results suggest a slightly stronger association between palbociclib-fulvestrant use and leukopenia (adjusted hazard ratio (aHR): 10.7, 95%CI= 2.48-46.48), stomatitis and mucositis (aHR: 10.89, 95%CI= 1.38-85.96), and peripheral neuropathy (aHR: 2.21, 95%CI=1.10-4.41), while the association with ALI (Algorithm 2- original with labs algorithm) was modestly lower (aHR: 1.78, 95%CI=0.76-4.16; Table 2-6 in Appendix 3). While hazard ratios may have differed for these events in the advanced stage ER+/HER2- breast cancer subgroup, these three outcomes were relatively uncommon (each incidence rate less than six per 100-person-years), so these findings do not result in a large difference on the absolute scale.

### 10.5.2. ALI algorithm signal refinement

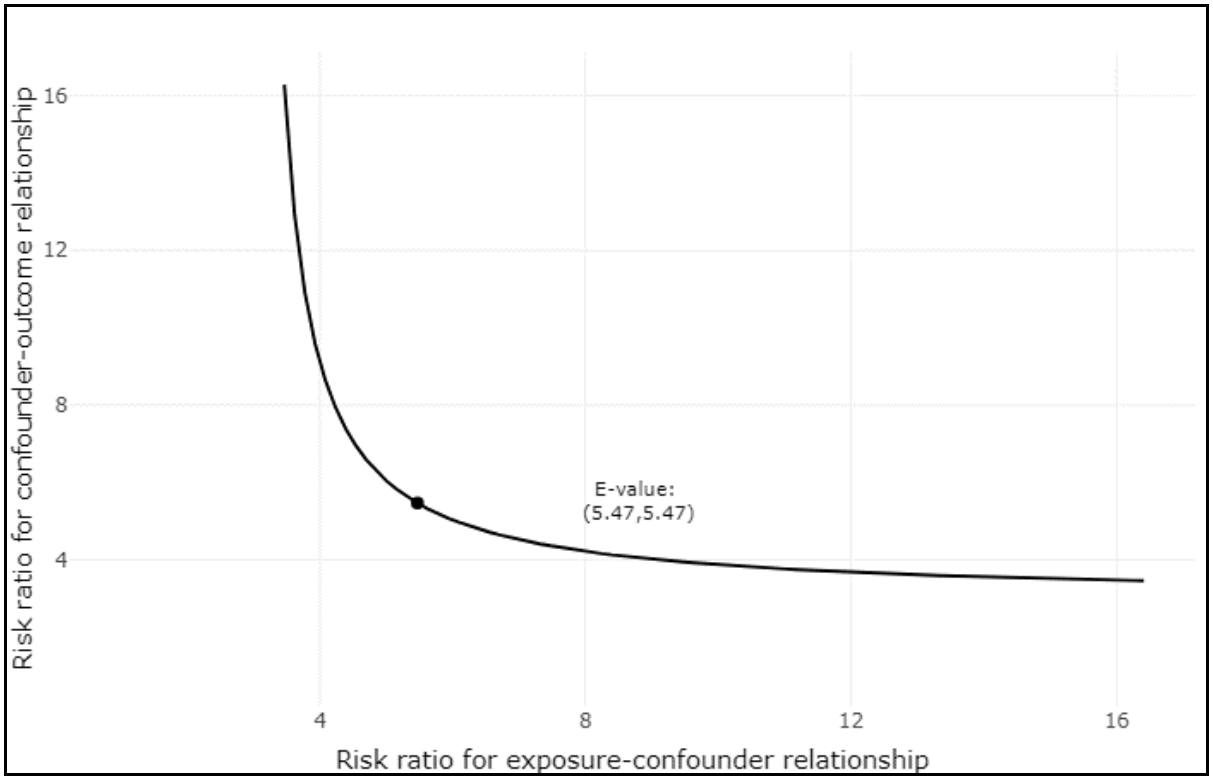
As a part of signal refinement study, we conducted a sensitivity analysis evaluating the incidence of the primary ALI algorithm over time, in the palbociclib and fulvestrant group, as well as the overall HIRD. This analysis was conducted to evaluate whether the change from ICD-9 diagnosis codes to ICD-10 diagnosis codes on October 1, 2015 in the US may have impacted the incidence of ALI in our database. In the overall HIRD population, there were 21,643 ALI events identified between April 2014 and March 2017, and the incidence of ALI was slightly higher in the periods when ICD-10 codes were used. ALI incidence ranged from 0.32 per 100 person-years from April 2014 to December 2014 to 0.37 per 100 person-years from July 2016 to March 2017 (Table 1-10; Appendix 3). Analyses restricted to palbociclib and fulvestrant group were small and limited to ~21 events combined. Point estimates for ALI incidence varied over time in these groups, but the confidence intervals were wide (Table 1-10; Appendix 3).

In a separate sensitivity analyses in Tables 1-8AD, we evaluated the number of ALI events that occurred among those with or without at least one risk factor for ALI (e.g., chronic liver disease, prescription acetaminophen, etc.). Table 1-8AD notes that the vast majority of ALI

events were among those with at least one risk factor for ALI (e.g., 85% of the ALI events in the historical comparison analyses). The hazard ratio results were largely similar across the two groups, though estimates for those without an ALI risk factor were particularly limited in power.

To provide an estimate of the effect of potential unmeasured confounding, we calculated the E-value, which is the minimum strength required for both the palbociclib-confounder and the confounder-ALI relationship to explain away the estimated association between palbociclib and ALI (i.e. attenuate the association to the null). For the association noted between palbociclib and primary ALI algorithm in the historical comparator analysis (aHR=3.0, 95%CI=1.1, 8.4), a risk factor would need to have an association of at least RR=5.47 between palbociclib and the confounder, and an association of at least 5.47 between the confounder and ALI to attenuate the observed association to the null (Figure 4).

**Figure 4. E-value to explain the association between palbociclib and the primary ALI algorithm (in historical fulvestrant analyses)**




*Minimum strength required for both the palbociclib-confounder and confounder-ALI relationships to explain away the estimated relationship between palbociclib and ALI. The E-value for the 95% CI to remain significant is 1.34

We also separately evaluated the effect of outcome misclassification, by adjusting our comparative estimates by our PPVs from our validation study results. Table 1-8A-D provides the results of the association adjusted for the PPV adjusted results. The results adjusting for the PPV were largely similar to the main results, although there was variation noted for the ALI Algorithm 2 in the historical comparator analysis (Table 1-8A-D; Appendix 3).

In a hypothetical scenario where we assume 100% sensitivity and 100% PPV in the historical fulvestrant monotherapy group, the amount of differential outcome misclassification needed to attenuate the palbociclib-ALI association (aHR=3.0, 95%CI=1.1-8.4) to the null would require a PPV of 33% in palbociclib-fulvestrant group. However, with the same assumptions it would only require a PPV of 91% in the palbociclib-fulvestrant group to attenuate the lower bound of the confidence interval below 1.0.

In a final sensitivity analysis, we evaluated the amount of follow-up time in each group, and found that the average follow-up time was similar in each of the groups (mean follow-up time: palbociclib-fulvestrant=6.9 months; historical fulvestrant=7.4 months; contemporaneous fulvestrant=7.0 months). This is despite the fact that the study period for the historical fulvestrant group (January 2011 to January 2015) was longer than the study period for the other two groups (February 2015 to September 2017). In each of the groups, we found the vast majority of the ALI events occurred within the first six months of follow-up (Tables 1-8AB and 1-8CD; Appendix 3), and the risk of ALI was still higher in new users of palbociclib-fulvestrant than the historical new users of fulvestrant monotherapy during this first six month time period (HR=2.4, 95%CI=1.1-5.3; aHR=2.0, 95%CI=0.7-5.8; Table 1-8AB; Appendix 3).

### 10.6. Adverse events / adverse reactions

The active surveillance study includes claims data that were converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports.

Based on active surveillance results, additional signal refinement analyses were performed for the purposes of evaluating ALI. In this refinement activity, each provisional case of ALI was identified by an algorithm applied against the structured claims data. An Adjudication Committee (AC) consisting of three clinicians reviewed the available patient medical records of each provisional case of ALI to confirm ALI case status. The AC were provided medical records that have been redacted of all PHI as well as any mention of study medications (e.g., palbociclib or fulvestrant).

Each available provisional case of ALI required human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database.

The reviewer (AC committee member) was obligated to report AEs with explicit attribution to any Pfizer drug that appeared in the reviewed information (defined per the patient population and study period specified in the protocol; Appendix 2). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to

the AE. The requirements for reporting safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety as further described in Section 11.2 of the Protocol (Appendix 2).

Based on the adjudicator's review there were no AEs (or ALI in particular) specifically attributable to any Pfizer drug based on their review, and thus none were reported.

## 11. DISCUSSION

### 11.1. Key results

#### 11.1.1. Active Surveillance Study

This exploratory study is one of the first evaluations of palbociclib use in a real world population. This study suggests that palbociclib is commonly used in US patients with advanced stage ER+/HER2- breast cancer, as over 2,000 patients in the HIRD initiated palbociclib within its first two years of approval.

Select population characteristics of palbociclib initiators in the HIRD were similar to characteristics among patients receiving palbociclib in randomized trials (2, 3). For example, palbociclib initiators had a mean age of 60 years (Table 1-1 in Appendix 3), a majority had recently received an aromatase inhibitor prior to palbociclib initiation (Table 1-1 in Appendix 3), and we estimate that over 90% of the population had advanced stage ER+/HER2- breast cancer around the time of palbociclib initiation. There were also a few differences in this study's population compared to the trial populations, including a lower prevalence of chemotherapy use immediately prior to palbociclib initiation (2, 3).

In this real world population, there were a number of safety events commonly identified after palbociclib initiation including neutropenia, serious infection, fatigue, anemia, interstitial lung disease/pneumonitis, and nausea, which all occurred at a rate of 15 per 100 person-years or higher (Table 1-2 in Appendix 3). Many of these events were also commonly occurring in the palbociclib randomized trials (2, 3). For example, the trials showed that over 75% of patients develop neutropenia after palbociclib initiation, while fatigue, anemia, upper respiratory infections, and nausea occurred in over 10% of patients. While interstitial lung disease/pneumonitis and second primary cancers were also commonly detected in this study they were identified in less than 10% of patients in the trials. The incident second primary cancers identified in this study may often represent metastases from breast cancer rather than novel secondary cancers, as our previous standing cohort study (5) suggested that about two thirds of these events were occurring at non-specific sites, which may indicate a metastasis/disease progression rather than a new primary cancer.

This study did not measure survival or progression-free survival, which in randomized trials was approximately twice as long in the palbociclib arms than in comparative treatment arms (2, 3). This study supports the trials' findings that certain safety events are more common with palbociclib use, particularly myelosuppression events (2, 3). Comparing all new users of palbociclib with fulvestrant to a historical comparison group of new users of fulvestrant monotherapy, we observed significantly higher rates of neutropenia, leukopenia, stomatitis and mucositis, anemia, thrombocytopenia, and ALI Algorithm 2 (original with labs) (Tables

1-5 and 1-6 in Appendix 3). Each of these events was also found to be more common in the palbociclib arm of the randomized trial (2), except for clinical ALI (defined in the trials as hepatic failure or drug-induced liver injury). These "clinical" ALI related events were rarely detected in the trials although one of the palbociclib trials reported higher prevalence of AST (52% vs. 34%) and ALT (43% vs. 30%) among users of palbociclib with letrozole than placebo with letrozole. (1)

In this observational study, the incidence of ALI defined by the original algorithm was uncommon but still notable for an important event (incidence rate ~3 per 100 person-years). Pulmonary embolism and serious infections were events of interest given results from prior trials (1), but in this study there was no increased risk of these events. Other events such as QT prolongation, type 2 diabetes, and second primary cancer also occurred at a similar incidence as the comparator (Tables 1-5 and 1-6 in Appendix 3). For most safety events examined, this large real-world study is consistent with the risk profile of palbociclib suggested in the palbociclib randomized trials.

### 11.1.2. ALI Signal Refinement Analyses

In subsequent ALI signal refinement analyses, we conducted several additional activities to refine the assessment of the risk of ALI in palbociclib users.

First, we conducted comparative analyses controlling for additional ALI risk factors and using different algorithms for ALI, including an algorithm used in another post-authorization safety study (18) that was informed by the Mini-Sentinel validation study (17). Results across this primary algorithm and the other two ALI algorithms with identifiable cases were relatively consistent with unadjusted and adjusted results suggesting an increased risk of ALI in new users of palbociclib with fulvestrant than a historical comparator group of new users of fulvestrant monotherapy. A fourth ALI algorithm was a narrow algorithm restricted to select codes required to be noted in the principal inpatient diagnosis position did not identify any ALI cases, implying many of the ALI cases in the other three algorithms were not the primary diagnosis of the inpatient stay.

To address the potential for misclassification bias, we attempted to validate the three ALI algorithms that had available cases in this study by medical record adjudication. We found that each ALI algorithm had a relatively high PPV greater than 70%, with the primary ALI algorithm having the highest PPV of 84%. The PPV estimates across different groups of palbociclib and fulvestrant were too imprecise to reliably assess the potential differences in PPV between treatment groups.

Among the ALI cases with available medical records, the hepatologist who constructed case narratives attributed the majority of confirmed ALI cases to liver metastases and none were classified as directly attributable to palbociclib or fulvestrant in the medical record, although another hepatologist adjudicating diagnoses suggested possible DILI in the presence of metastatic disease. In a patient with advanced cancer with liver or bone metastases, it can be particularly difficult for clinical review to reliably rule out idiosyncratic DILI because of its variable phenotype As noted in Rohan et al., there is no universally accepted causality

assessment method to assess adverse drug reaction through expert judgment given their lack of consistency and reproducibility.(29)

We also conducted ALI analyses comparing new users of palbociclib with fulvestrant with a contemporaneous comparator group of new users of fulvestrant monotherapy. While the results of these analyses were imprecise, they did not suggest any increased risk of ALI for palbociclib users for each of the three ALI algorithms with available cases. However, the number of cases was smaller and the confidence intervals were wide for the contemporaneous comparator analyses, as they spanned from strong negative associations to moderate positive associations. Results using the contemporaneous comparator were likely more affected by confounding bias and random error than the historical comparator. Further discussion of this bias, and other potential explanations for the divergent results when using separate comparators are provided in sections 11.2 and 11.3.

## 11.2. Limitations

There were several limitations to this study, that we evaluated in sensitivity analyses to assess their impact on the results of this study.

### 11.2.1. Lack of validated outcomes (except of ALI) and ICD-9/10 mapping

The safety events (outcomes) of interest were identified using diagnosis and procedure codes in the HIRD and the accuracy of this approach is uncertain but is generally better for more serious events that are likely to require hospitalization. It is possible that non-cases may have been included as cases (i.e. false positives), and that cases may have been missed (i.e. false negatives). In particular, we would expect more frequent conditions such as fatigue, vomiting, and diarrhea to be not commonly captured with diagnosis codes, and results for these events are likely to underestimate actual incidence rates. The current study does not include medical record review to validate these safety events of interest except for ALI, but this could be considered as part of a subsequent study. For select outcomes such as ALI, leukopenia and neutropenia, we include sensitive and specific definitions of the outcome to provide a range of potential rates for that outcome in Appendix 3. For ALI, we also attempted to validate the available outcomes with medical record adjudication and conducted quantitative bias analyses to provide estimates accounting for outcome misclassification as described in Section 10.5.2. These analyses suggested that the ALI algorithms used were largely accurate, according to the clinical definition from the FDA working group, and there is, at most, a limited role in outcome misclassification on impacting the ALI findings. However, it should be noted, that meeting a confirmed ALI case by the FDA working group, does not imply that the event was drug induced.

Additionally, ICD-9 diagnosis codes were used to define safety events in the historical fulvestrant monotherapy comparison group, while mostly ICD-10 diagnosis codes were used to define safety events in the palbociclib group. The ICD-10 codes were mapped from the ICD-9 codes, but it is possible that differences between the two groups could be at least partially explained by the two coding systems. In a sensitivity analysis for ALI, we noted the incidence of ALI in the HIRD did not substantially increase across the ICD-9 to ICD-10

period, suggesting this is an unlikely explanatory factor in those analyses (Table 1-10; Appendix 3).

### 11.2.2. Multiple comparisons (outcomes)

We examined 42 safety event outcomes in this exploratory active surveillance study, without specifying any primary outcomes. No adjustment was made in the analysis for multiple comparisons, partially because these safety outcomes were pre-specified based on a potential relationship with palbociclib driven by evidence from the clinical trials of palbociclib and other cancer therapies. This study's findings should be interpreted in light of all pertinent data since the inclusion of dozens of safety events increases the probability of a spurious finding caused by random error. Thus this question would be better assessed through replication.

### 11.2.3. Unmeasured confounding

For Secondary Objective 3, the adjustment for confounding was addressed via propensity score matching. The propensity scores were estimated based only on covariates measured at baseline and thus do not account for changes that may arise during the follow-up period. While propensity scores have demonstrated the ability to control for numerous measured confounders, they cannot control for confounding from unmeasured or unknown factors that are not available in claims (such as body mass index and smoking status) if those unmeasured factors are not associated with the measured risk factors/surrogates that are controlled for by the propensity score. Additionally, for second malignancy (metastasis) related covariates, the codes available were restricted to information on the presence or absence of any metastasis to specific sites, but did not provide further information on the further extent of metastasis and or metastatic tumor burden which could have differed between the palbociclib and fulvestrant groups.

In the ALI analysis using a contemporaneous comparator group, in particular, there was evidence that the palbociclib with fulvestrant group had more advanced disease than the fulvestrant comparator group (e.g., secondary malignancy (metastasis) to respiratory/digestive systems: 45% vs. 34%). While we controlled for these factors in propensity score matching, the propensity score could only identify contemporaneous fulvestrant matches in a subset of palbociclib-fulvestrant patients, and it is possible there is still unmeasured confounding due to limited sensitivity/specificity of measured covariates or covariates that were unable to be measured. One may expect if there was residual confounding due to more severe disease (i.e. channeling) in palbociclib users it may bias the estimate in the alternative direction (i.e. positive association rather than inverse), although other potential covariates, such as the older mean age of the fulvestrant comparator (66 vs. 64), could modestly bias the association in the inverse direction. More specifically, after propensity score matching, the group aged ≥65 accounted for 45% of the palbociclib group and 57% of the contemporaneous comparator group after propensity score matching.

To provide an estimate of the effect of potential unmeasured confounding, we calculated the E-value, which is the minimum strength required for both the palbociclib-confounder and the confounder-ALI relationship to explain the estimated association between palbociclib and

ALI (i.e. attenuate the association to the null) as described in Section 10.4.2. This analysis suggested that it would require a strong unmeasured confounder that is not associated with the measured risk factors (with a 5-fold association with the exposure and the outcome) to explain away the observed association seen when using the historical fulvestrant monotherapy comparator. Given that this historical fulvestrant monotherapy comparator was more similar to new users of palbociclib with fulvestrant than the contemporaneous comparator in terms of measured covariates, unmeasured confounding may be less likely to be the explanatory factor in the signal seen with the historical fulvestrant monotherapy comparator.

#### 11.2.4. Limited sample size for rarer outcomes

While this study is larger than the currently published trials and other studies examining palbociclib, we had limited sample size to observe relatively uncommon events. This can be seen as a small number of cases can have a relatively strong impact on effect size, particularly for rare outcomes such as ALI. This is reflected in the study's relatively wide confidence intervals for ALI and other rare safety events. Replication in large samples would strengthen our findings and provide further clarity on the effect size of the association, if there is one.

### 11.3. Interpretation

#### 11.3.1. Active Surveillance Study

This study suggests that palbociclib use has been commonly initiated among US commercially insured patients particularly among patients with advanced stage ER+/HER2- breast cancer. This includes patients with comorbidities. The mean DCI in this population was high (8.4 (Table 1-1 in Appendix 3)), but that was in part driven by metastatic cancer which accounts for a score of six. Patients initiating palbociclib often were dispensed medications indicative of cardiovascular disease, diabetes, and depression, and a smaller subset had recent acute events such as major adverse cardiac events and stroke. Cerebrovascular disease was particularly prevalent in this study population, although the diagnosis code defined algorithm used to define this condition may prioritize sensitivity over specificity. While the prevalence of comorbidities was not presented in detail in the palbociclib trial literature, the palbociclib-fulvestrant trial was restricted to patients with adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of zero or one (no more than a mild degree of disability) (2). It is possible that this study's population may have had more comorbidities than patients in the trials,(30) and thus potentially more risk for certain subsequent disease events.

The safety events examined in this study were identified using pre-defined algorithms consisting of ICD-9 and ICD-10 diagnosis codes (Section 9.4.2 and Section 11.2.1). The incidence rates and comparative risk of the events compared to historical comparators were largely consistent with the palbociclib randomized trials with a few notable findings for pulmonary embolism, serious infections, and ALI.

We did not observe an increased risk of pulmonary embolism in this study, while the palbociclib-fulvestrant trial did observe a suggestion of a potential association (2). However,

pulmonary embolism in particular was an uncommon event in the trial (three cases), and this observational study with a modestly larger sample size did not suggest an increased risk.

Similarly, we did not observe an association between palbociclib use and serious infections in this study. The palbociclib-fulvestrant trial suggested a modest association with infection, primarily of severity grade one or two (2). Our algorithm for serious infection required at least one inpatient or emergency room visit related to the infection, so it is likely that infections of lesser severity were not captured in this study.

An interpretation regarding ALI and the signal refinement analyses is further described in Section 11.3.2.

### 11.3.2. ALI signal refinement analyses

#### 11.3.2.1. Overview

In the active surveillance study, an algorithm for ALI found an elevated risk with palbociclib and fulvestrant initiation compared to a historical comparator group of new users of fulvestrant. This is an uncommon event that is difficult to assess in modestly sized trials. Palbociclib's label lists a higher prevalence of AST and ALT in the palbociclib arm than the placebo arm in one of the trials. (1) The registered randomized trials noted a few liver safety issues (e.g., two grade 3 or higher hepatic failure events in the palbociclib plus fulvestrant arm compared to zero in the fulvestrant arm), with one hepatic death not from treatment-related toxic effects (10). A recent case report also noted two pseudocirrhosis cases that were judged as likely attributable to palbociclib, with one of the cases leading to death.(11) While there were limited number of primary ALI events in the active surveillance study (n=13) among palbociclib-fulvestrant users), we observed an increased risk of ALI comparing all new-users of palbociclib-fulvestrant to a historical comparator group of new users of fulvestrant monotherapy.

After observing this association, we initiated the subsequent ALI signal refinement study which involved three main components: (1) adjusting for additional ALI risk factors and examining additional ALI algorithms, (2) examining an additional (contemporaneous) comparator group, and (3) validating the ALI outcomes through medical record adjudication.

#### 11.3.2.2. Adjustment for ALI risk factors and additional ALI algorithms

For the first component of the signal refinement activities using alternative algorithms for ALI and adjusting for additional ALI risk factors, we continued to observe an elevated risk of ALI in new-users of palbociclib-fulvestrant in the main analyses. This suggests that the initial finding in the active surveillance study was not solely explained by nuances in the algorithm (e.g., codes related to transaminase elevations) or by lack of adjustment of certain measured ALI risk factors.

#### 11.3.2.3. Contemporaneous comparator group

In contrast to the results for ALI observed when using a historical comparator group, when separately comparing ALI risk in new users of palbociclib with fulvestrant to a

contemporaneous comparator group of new users of fulvestrant monotherapy, there was no evidence of an increased risk of ALI in adjusted analyses. This comparator was specifically included to remove the temporal effects such as the change over from ICD-9 to ICD-10 codes to define diagnoses such as ALI. However, our sensitivity analysis examining the effect of ICD-9 to ICD-10 changeover suggested it would likely have little effect and is unlikely to explain the divergent results between the historical and contemporaneous comparator groups.

The contemporaneous fulvestrant comparator group was less comparable to the palbociclib group both before and after matching, and more prone to residual confounding than the historical fulvestrant comparator group. This could be because the contemporaneous fulvestrant comparator group had the option of initiating palbociclib, but the patient selected instead to initiate fulvestrant monotherapy (not palbociclib) and this selection could have been driven in part by age, the severity of the disease, and/or concerns about quality of life. On the other hand, the historical fulvestrant comparator group included patients who did not have this treatment choice and may be more similar to new users of palbociclib with fulvestrant.

Supporting this notion, the contemporaneous new users of fulvestrant were less comparable to palbociclib-fulvestrant new users than the historical new users of fulvestrant monotherapy in select covariates such as age, presence of secondary malignancies, use of HER2+ therapy, and use any medication related to liver injury. This along with the limited sample size of the contemporaneous comparator limited the ability to propensity score match these patients to palbociclib-fulvestrant users, and unmeasured confounding may still be present.

Label changes over time can also sometimes have an impact on the composition of new users. Fulvestrant was originally approved in 2002 as a monotherapy for treatment of postmenopausal women with HR+ metastatic breast cancer with progression following antiestrogen therapy, and an additional indication approved in February 2016 for use in HR+/HER2- metastatic breast cancer (in combination with palbociclib) with disease progression after endocrine therapy. This indication would impact our active drug group (palbociclib with fulvestrant), so those in our comparator group after February 2016 would include women who did not initiate palbociclib per this new indication. A separate additional indication was approved in August 2017 for monotherapy for those with HR+/HER2- breast cancer who had not undergone endocrine therapy previously, but is unlikely to impact this study given that follow-up in this study ended in September 2017(6).

Additionally, it should be noted that the duration of the study period for the historical fulvestrant-only comparator group (January 2011-January 2015) was longer than among patients in the contemporaneous comparator group (February 2015-September 2017). However, we only evaluated events and person-time while on the relevant treatments, and we found that the average follow-up time was similar among the historical fulvestrant group compared to the contemporaneous groups. This may be driven partially by the particularly low survival among advanced stage HR+/HER2- breast cancer patients before the introduction of palbociclib. Further analyses, stratifying the ALI results by the amount of follow-up time, did not suggest that the different study period lengths were a strong

explanatory factor in the diverging ALI results between the historical and contemporaneous comparator groups. However, the stratified results were limited by a low number of ALI events (e.g. 13 ALI events in all new users of palbociclib-fulvestrant– which were then stratified into three groups).

#### 11.3.2.4. Medical record validation

In the third and last component of the ALI signal refinement analyses, expert hepatologists reviewed medical records to adjudicate diagnoses of potential cases identified by the ALI algorithms. Prior to our validation study, there was uncertainty that algorithm-identified cases of ALI were accurately identified, and results could have been impacted by outcome misclassification. The original ALI algorithm was defined using ICD-9 or ICD-10 diagnosis codes indicating acute or subacute hepatic failure or necrosis of the liver, or by a diagnosis code indicating nonspecific elevation of levels of transaminase or lactic acid dehydrogenase (LDH). Thus, in our subsequent research in signal refinement, we also considered other algorithms that were validated in other settings.

In our validation study, we found that each of the ALI algorithms tended to identify cases that were subsequently confirmed by adjudicators as ALI, as the PPV for the three algorithms ranged from 72% to 84%. Previous validation studies, including a mini-Sentinel study, have noted somewhat lower PPVs and have suggested that the accuracy of different potential liver injury algorithms can vary by diagnosis and setting (17, 31, 32).

Outcome misclassification can bias results, particularly if the misclassification is differential (23). As noted in Section 11.1.2, the PPVs across different groups of palbociclib and fulvestrant did not strongly suggest differential misclassification with the historical comparator. However, it was more consistent with differential misclassification with the contemporaneous comparator, noting that the small sample size of the validation study (e.g., <10 cases adjudicated from each of separate comparator groups) particularly limited the assessment of differential misclassification.

In addition to the validation, a causality assessment of available cases was conducted through case narratives. Causality assessment of case reports is often used to identify potential safety signals. Data from case reports are more limited in ruling out a drug involvement when an adverse event follows drug exposure. Specifically, a patient with an adverse event can have multiple risk factors, identification of other risk factors does not rule out an etiologic role for a drug. Among the ALI cases with available medical records, the hepatologist who constructed case narratives attributed most of the confirmed ALI cases to consequences of liver metastases. For this study, the hepatologist noted that four of 32 confirmed ALI cases examined were possibly DILI and while palbociclib or fulvestrant cannot be ruled out as possible causal factors by case review alone (particularly idiosyncratic DILI),(33) the hepatologist did not classify any cases as directly attributable to palbociclib or fulvestrant based on the medical records. Liver metastases prior to initiation of palbociclib-fulvestrant or fulvestrant monotherapy, was included in the “secondary malignancy to respiratory and digestive systems” covariate which was included in propensity score. Before propensity score matching, the palbociclib group was more likely than the comparator groups to have secondary malignancies (metastases) to respiratory/digestive systems at baseline, and the

sensitivity of this variable compared to information from the case narrative was imperfect (of the 28 cases noted to have liver metastases by the adjudicator, 23 (82%) had code indicating a metastasis to respiratory/digestive system). The fact that there is likely at least some mismeasurement in this covariate suggests there is potential residual confounding related to this variable. Additionally, this covariate likely does not capture the extent of the aggressiveness of the breast cancer completely.

### 11.4. Generalizability

This study was conducted in a large database of US commercially insured patients. Compared with the general population, coverage of the HIRD is skewed towards younger ages. Since breast cancer incidence increases with age, the patients identified in the HIRD may not be representative of the general population of palbociclib or fulvestrant users. However, the participants in this study had similar ages to patients in the randomized trials of palbociclib. As with any study, this study conducted in the HIRD will be most generalizable to commercially insured individuals, and generalizability to other populations is less certain.

In a subgroup analysis, we examined the characteristics of palbociclib users and conducted comparative safety analyses among patients who had an advanced stage ER+/HER2- breast cancer. The indication for palbociclib was expanded in 2016 to include those with advanced HR+/HER2- breast cancer, which includes individuals with progesterone receptor positive (PR+) or ER+ breast cancer. The vast majority of HR+ cases are also ER+; in our clinical HIRE Oncology database approximately 98% of HR+/HER2- breast cancers were also ER+/HER2- breast cancers. Because the ER+ and HR+ breast cancers almost entirely overlap, the existing algorithm would identify HR+ breast cancer with similar accuracy to ER+ breast cancer.

## 12. OTHER INFORMATION

Not applicable

## 13. CONCLUSIONS

Palbociclib is commonly used in US patients with advanced stage ER+/HER2- breast cancer. In this real-world study of commercially insured individuals in the US, pre-selected safety events of interest associated with palbociclib use were generally consistent with those identified in randomized trials.

Randomized trials have demonstrated a higher incidence of elevated transaminases with CDK4/6 inhibitors including palbociclib, but palbociclib trials were underpowered to detect ALI so limited by size and duration. In this retrospective claims study, the risk of ALI was elevated when comparing new users of palbociclib with fulvestrant to a historical comparator group of new users of fulvestrant monotherapy in this active surveillance study and in the subsequent analyses of the signal refinement study. However, case narratives did not attribute any cases directly to palbociclib, and there was no apparent elevated ALI risk when comparing this cohort to a contemporaneous comparator group of new users of fulvestrant monotherapy. The number of cases for the contemporaneous comparator was small and the confidence intervals were wide, spanning from strong negative associations to moderate

positive associations. Overall, results for contemporaneous comparators were more affected by random error and confounding bias (e.g., age) than analyses involving the historical comparator.

Taken as a whole, this retrospective claims database study suggests a potential association between palbociclib and increased risk of ALI. However, given the limitations of this study as well as clinical trials and case reports, additional data and further study would be of interest to better inform on the safety of palbociclib and its possible impact on ALI risk.

## 14. REFERENCES

1. Administration USFD. Palbociclib (IBRANCE) 2017 [Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm549978.htm.
2. Turner NC, Ro J, Andre F, Loi S, Verma S, Iwata H, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015;373(3):209-19.
3. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016;375(20):1925-36.
4. Beachler DC, de Luise C, Yin R, Gangemi K, Cochetti PT, Lanes S. Predictive model algorithms identifying early and advanced stage ER+/HER2- breast cancer in claims data. Pharmacoepidemiology and drug safety. 2018.
5. Beachler DC, Yin R., Cochetti, P.T.; Jemison, J.; Gangemi, K.; de Luise, C.; Lanes, S.;. Identifying breast cacner stage and ER/HER2 status in claims data using predictive models. 33rd International Conference of Pharmacoepidemiology and Therapeutic Risk Management (ICPE); Montreal, CA2017.
6. AstraZeneca. Faslodex (fulvestrant) [package insert] 2017 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021344s034lbl.pdf.
7. IBRANCE (palbociclib) [package insert], Pfizer Inc., New York, NY. 2017.
8. Panozzo CA, Woodworth TS, Welch EC, Huang TY, Her QL, Haynes K, et al. Early impact of the ICD-10-CM transition on selected health outcomes in 13 electronic health care databases in the United States. Pharmacoepidemiology and drug safety. 2018;27(8):839-47.
9. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354(7):731-9.
10. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17(4):425-39.
11. Vuppalanchi R, Saxena R, Storniolo AMV, Chalasani N. Pseudocirrhosis and liver failure in patients with metastatic breast cancer after treatment with palbociclib. Hepatology. 2017;65(5):1762-4.
12. Raschi E, De Ponti F. Strategies for Early Prediction and Timely Recognition of Drug-Induced Liver Injury: The Case of Cyclin-Dependent Kinase 4/6 Inhibitors. Front Pharmacol. 2019;10:1235.
13. FDA. Kisqali (ribociclib) 2017 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf.
14. Sammons SL, Topping DL, Blackwell KL. HR+, HER2- Advanced Breast Cancer and CDK4/6 Inhibitors: Mode of Action, Clinical Activity, and Safety Profiles. Curr Cancer Drug Targets. 2017;17(7):637-49.
15. Sultan AS, S.; Ball, S.; Quirch, M.; Arevalo, M.; Myat, Y.M.; Aung, Y.; Zaw, M.H.; Thein, K.Z.;. Risk Of Gastrointestinal and Hepatic Toxicities in Patients with Hormone Receptor-Positive HER2-Negative Metastatic Breast Cancer Treated With CDK4/6 Inhibitors. Journal of the National Comprehensive Cancer Network (JNCCN). 2019;17(3.5).
16. Zaw M, ; Rhein K.Z.,; Tun, A.; Han, M.M.; Thar, Y.Y.; Nayak, A.; Guevara, E.;. A systematic review and meta-analysis of randomized controlled trials to evaluate the risk of gastrointestinal and hepatic toxicities in patients with hormone receptor-positve HER2-

negative metastatic breast cancer treated with CDK 4/6 inhibitors. American Society of Clinical Oncology; Chicago, IL2017.
17. Lo Re V, 3rd, Haynes K, Goldberg D, Forde KA, Carbonari DM, Leidl KB, et al. Validity of diagnostic codes to identify cases of severe acute liver injury in the US Food and Drug Administration's Mini-Sentinel Distributed Database. Pharmacoepidemiology and drug safety. 2013;22(8):861-72.
18. Lo Re V, Carbonari DM, Saine ME, Newcomb CW, Roy JA, Liu Q, et al. Postauthorization safety study of the DPP-4 inhibitor saxagliptin: a large-scale multinational family of cohort studies of five outcomes. BMJ Open Diabetes Res Care. 2017;5(1):e000400.
19. Chan KA, Truman A, Gurwitz JH, Hurley JS, Martinson B, Platt R, et al. A cohort study of the incidence of serious acute liver injury in diabetic patients treated with hypoglycemic agents. Arch Intern Med. 2003;163(6):728-34.
20. FDA Working Group. P*h*RMA/FDA/AASLD drug-induced hepatotoxicity white paper: postmarketing considerations. US Department of Health and Human Services, Food and Drug Administration; 2000 November.
21. Kern DM, Barron JJ, Wu B, Ganetsky A, Willey VJ, Quimbo RA, et al. A validation of clinical data captured from a novel Cancer Care Quality Program directly integrated with administrative claims data. Pragmat Obs Res. 2017;8:149-55.
22. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268-74.
23. Fox MP, Lash TL, Greenland S. A method to automate probabilistic sensitivity analyses of misclassified binary variables. Int J Epidemiol. 2005;34(6):1370-6.
24. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. American journal of epidemiology. 2006;163(12):1149-56.
25. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.
26. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083-107.
27. Outcome Misclassification [Available from: https://apps.p-95.com/ISPE/.
28. Brenner H, Gefeller O. Use of the positive predictive value to correct for disease misclassification in epidemiologic studies. Am J Epidemiol. 1993;138(11):1007-15.
29. Hire RCK, P.J.; Gaikwad, N.N.;. Causality Assessment in Pharmacovigilance: A Step Towards Quality Care. Scholars Journal of Applied Medical Sciences. 2013;1(5):386-92.
30. Unger JM, Hershman DL, Fleury ME, Vaidya R. Association of Patient Comorbid Conditions With Cancer Clinical Trial Participation. JAMA Oncol. 2019;5(3):326-33.
31. Katz AJ, Ryan PB, Racoosin JA, Stang PE. Assessment of case definitions for identifying acute liver injury in large observational databases. Drug Saf. 2013;36(8):651-61.
32. Bui CL, Kaye JA, Castellsague J, Calingaert B, McQuay LJ, Riera-Guardia N, et al. Validation of acute liver injury cases in a population-based cohort study of oral antimicrobial users. Curr Drug Saf. 2014;9(1):23-8.
33. European Association for the Study of the Liver. Electronic address eee, Clinical Practice Guideline Panel C, Panel m, representative EGB. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222-61.

## 15. LIST OF SOURCE TABLES AND FIGURES

Not Applicable

# Document Approval Record

| | |
|---|---|
| **Document Name:** | A5481105 NI Study Report |
| **Document Title:** | A5481105 |

| Signed By: | Date(GMT) | Signing Capacity |
|---|---|---|
| Campbell, Ulka | 15-Jun-2020 15:17:16 | Final Approval |
| De Bernardi, Barbara | 16-Jun-2020 10:47:49 | Final Approval |

**Appendix 3: Safety of Palbociclib Among Breast Cancer Patients in the United States: A retrospective cohort study**
**Final - February 14th, 2020**


| Table of Contents | |
|---|---|
| Table 0 | Formation of study cohorts |
| Figure 1 | Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users |
| **Analyses including all new users (individuals with or without advanced stage ER+/HER2- breast cancer)** | |
| Table 1-1 | Characteristics of breast cancer patients utilizing palbociclib identified in the HIRD |
| Table 1-2 | Incidence of the safety events of interest in all new users of palbociclib |
| Table 1-3 | Incidence of the safety events of interest in new users of palbociclib subgroups |
| Table 1-4A | Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparison group) |
| Figure 2 | Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users (historical comparison group) |
| Table 1-4B | Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (contemporaneous comparison group) |
| Figure 3 | Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users (contemporaneous comparison group) |
| Table 1-5 | Incidence rates and unadjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone |
| Table 1-6 | Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone |
| Table 1-7 | Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparison group - including ALI risk factors) |
| Table 1-8AB | Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group)<br>Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group) |
| Table 1-8CD | Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (contemporaneous comparison group)<br>Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (contemporaneous comparison group) |
| Table 1-9 | Positive predictive values of all diagnosis codes and combinations of codes for adjudicated cases of ALI |
| Table 1-10 | Incidence of ALI between April 2014 and March 2017 |
| Figure 4 | E-value to explain away the association between palbociclib and the primary ALI algorithm |
| **Analyses restricted to new users with advanced stage ER+/HER2- breast cancer** | |
| Table 2-1 | Characteristics of advanced stage ER+/HER2- breast cancer patients utilizing palbociclib identified in the HIRD |
| Table 2-2 | Incidence of the safety events of interest in all new users of palbociclib with advanced stage ER+/HER2- breast cancer |
| Table 2-3 | Incidence of the safety events of interest in new users of palbociclib subgroups with advanced stage ER+/HER2- breast cancer |
| Table 2-4 | Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone with algorithm-defined advanced stage ER+/HER2- breast cancer |
| Table 2-5 | Incidence rates and unadjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone with advanced stage ER+/HER2- breast cancer |
| Table 2-6 | Incidence rates and adjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone with advanced stage ER+/HER2- breast cancer |
| Table 2-7AB | Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group) with algorithm-defined advanced stage ER+/HER2- Breast cancer<br>Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group) with algorithm-defined advanced stage ER+/HER2- Breast cancer |

*Return to Table of Contents*

**Table 0.** Formation of study cohorts

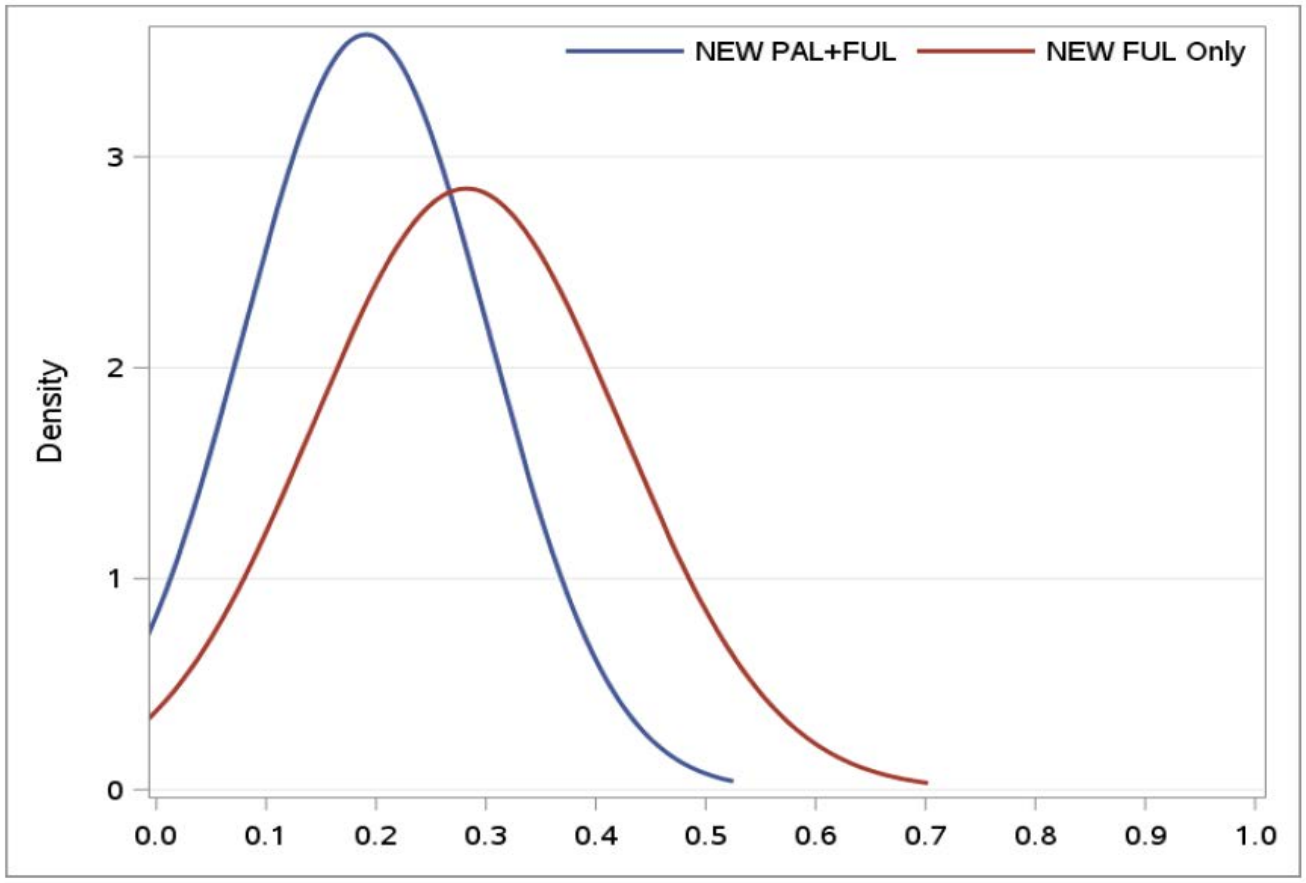
| | Total | | Total with advanced stage ER+/HER2- breast cancer* | |
|---|---|---|---|---|
| | **N** | **%** | **N** | **%** |
| Received palbociclib during the study period (01 Jan 2015 to 30 Sept 2017) | 2,795 | 100.00% | 2,600 | 100.00% |
| >=18 years of age | 2,795 | 100.00% | 2,600 | 100.00% |
| >=3 months of health plan coverage | 2,445 | 87.48% | 2,285 | 87.88% |
| >=3 months with no dispensing of palbociclib or CDK4/6 inhibitor before first dispensing of palbociclib | 2,445 | 87.48% | 2,285 | 87.88% |
| New users of palbociclib with fulvestrant | 566 | 23.15% | 548 | 23.98% |
| New users of palbociclib with letrozole | 1,159 | 47.40% | 1,083 | 47.40% |
| All other new users of palbociclib | 720 | 29.65% | 654 | 28.62% |
| Comparison group for Secondary Objective 3 | | | | |
| Received fulvestrant during the study period (01 Jan 2011 to 31 Jan 2015) | 3,315 | 100.00% | 2,983 | 100.00% |
| >=18 years of age | 3,315 | 100.00% | 2,983 | 100.00% |
| >=3 months of health plan coverage | 2,773 | 83.65% | 2,495 | 83.64% |
| >=3 months with no dispensing of fulvestrant before first dispensing of fulvestrant | 2,316 | 69.86% | 2,061 | 69.09% |
| All propensity score matched patients with fulvestrant | 561 | 16.92% | 544 | 18.24% |

Abbreviations: N, number; ER+, Estrogen Receptor Positive; HER2-, Human Epidermal Growth Factor Negative; Jan, January; Sept, September; CDK, cyclin-dependent kinase.

*Patients with advanced stage ER+/HER2- breast cancer (as defined by predictive model; this advanced stage ER+/HER2- breast cancer date must have occurred before or within three months of the first dispensing of study drug of interest (palbociclib or fulvestrant).

*Return to Table of Contents*

**Figure 1.** Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users




Abbreviations: PAL, palbociclib; FUL, fulvestrant.

*Return to Table of Contents*

**Table 1.1.** Characteristics of breast cancer patients utilizing palbociclib identified in the HIRD
**[Primary Objective 1 and Secondary Objective 1]**

| Characteristics* | All new users of palbociclib | | New users of palbociclib with fulvestrant | | New users of palbociclib with letrozole | | All other new users of palbociclib (no new use of fulvestrant or letrozole) | |
|---|---|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD |
| **Overall** | **2,445** | **100%** | **566** | **100%** | **1,159** | **100%** | **720** | **100%** |
| | | | | | | | | |
| **Demographics** | | | | | | | | |
| Age at index date (in years) | 59.8 | 11.6 | 59.5 | 11.4 | 59.2 | 11.3 | 61.0 | 12.3 |
| Age (years) | | | | | | | | |
| <45 | 226 | 9.2 | 51 | 9.0 | 117 | 10.1 | 58 | 8.1 |
| 45-64 | 1490 | 60.9 | 362 | 64.0 | 719 | 62.0 | 409 | 56.8 |
| 65+ | 729 | 29.8 | 153 | 27.0 | 323 | 27.9 | 253 | 35.1 |
| Sex | | | | | | | | |
| Male | 53 | 2.2 | ≤10 | n/a | 14 | 1.2 | 30 | 4.2 |
| Female | 2392 | 97.8 | 557 | 98.4 | 1145 | 98.8 | 690 | 95.8 |
| Calendar year of index date | | | | | | | | |
| 2015 | 791 | 32.4 | 99 | 17.5 | 456 | 39.3 | 236 | 32.8 |
| 2016 | 942 | 38.5 | 269 | 47.5 | 406 | 35.0 | 267 | 37.1 |
| 2017 | 712 | 29.1 | 198 | 35.0 | 297 | 25.6 | 217 | 30.1 |
| Geographic region of residence | | | | | | | | |
| Midwest | 400 | 16.4 | 95 | 16.8 | 185 | 16.0 | 120 | 16.7 |
| South | 581 | 23.8 | 159 | 28.1 | 288 | 24.8 | 134 | 18.6 |
| Northeast | 696 | 28.5 | 166 | 29.3 | 340 | 29.3 | 190 | 26.4 |
| West | 768 | 31.4 | 146 | 25.8 | 346 | 29.9 | 276 | 38.3 |
| Duration of health plan enrollment prior to index date (years) | 3.45 | 2.1 | 3.46 | 2.1 | 3.2 | 2.0 | 3.8 | 2.0 |
| **Medical History** | | | | | | | | |
| Other primary cancer prior to first breast cancer diagnosis code | 1055 | 43.1 | 223 | 39.4 | 532 | 45.9 | 300 | 41.7 |
| Secondary malignancy (metastasis) | 2137 | 87.4 | 496 | 87.6 | 1044 | 90.1 | 597 | 82.9 |
| Lymph nodes of head, face, and neck | 690 | 28.2 | 154 | 27.2 | 356 | 30.7 | 180 | 25.0 |
| Respiratory and digestive systems | 1058 | 43.3 | 257 | 45.4 | 490 | 42.3 | 311 | 43.2 |
| Other specified sites | 2017 | 82.5 | 463 | 81.8 | 978 | 84.4 | 576 | 80.0 |
| Deyo-Charlson comorbidity index (DCI) | 8.39 | 1.9 | 8.52 | 1.8 | 8.48 | 1.7 | 8.13 | 2.3 |
| Secondary malignant neoplasm of breast | 265 | 10.8 | 66 | 11.7 | 125 | 10.8 | 74 | 10.3 |
| Breast cancer (female) diagnosis code | 2365 | 96.7 | 558 | 98.6 | 1138 | 98.2 | 669 | 92.9 |
| InSitu breast cancer | 208 | 8.5 | 44 | 7.8 | 124 | 10.7 | 40 | 5.6 |
| Advanced stage ER+/HER2- breast cancer | 2,285 | 93.5 | 548 | 96.8 | 1,083 | 93.4 | 654 | 90.8 |
| **Cancer Therapy History** | | | | | | | | |
| **Radiation therapy** | 483 | 19.8 | 112 | 19.8 | 233 | 20.1 | 138 | 19.2 |
| External Beam | 483 | 19.8 | 112 | 19.8 | 233 | 20.1 | 138 | 19.2 |
| **Surgery** | 88 | 3.6 | 11 | 1.9 | 59 | 5.1 | 18 | 2.5 |
| Mastectomy in the last six months | 36 | 1.47 | ≤10 | n/a | 28 | 2.42 | ≤10 | n/a |
| Lumpectomy in the last six months | 35 | 1.43 | ≤10 | n/a | 23 | 1.98 | ≤10 | n/a |
| Radical Mastectomy in the last six months | 40 | 1.64 | ≤10 | n/a | 25 | 2.16 | ≤10 | n/a |
| **Chemotherapy** | 472 | 19.30 | 100 | 17.67 | 218 | 18.81 | 154 | 21.39 |
| Infusion based chemo (procedure) | 14 | 0.57 | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| **Imaging** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| CT related imaging in the last six months | 602 | 24.62 | 139 | 24.56 | 333 | 28.73 | 130 | 18.06 |
| MRI for needle placement | ≤10 | n/a | 0 | 0.00 | ≤10 | n/a | 0 | 0.00 |
| Diagnostic imaging in the last six months | 385 | 15.75 | 72 | 12.72 | 251 | 21.66 | 62 | 8.61 |
| Mammography | 55 | 2.25 | ≤10 | n/a | 37 | 3.19 | ≤10 | n/a |
| MRI related imaging | 168 | 6.87 | 25 | 4.42 | 116 | 10.01 | 27 | 3.75 |
| Tomosynthesis (3D mammography) | 62 | 2.54 | 18 | 3.18 | 35 | 3.02 | ≤10 | n/a |
| **Healthcare Utilization (six months prior to index date)** | | | | | | | | |
| Number of outpatient visits | 39.7 | 25.2 | 38.6 | 23.6 | 39.5 | 23.8 | 40.8 | 28.4 |
| Number of outpatient visits to an oncologist | 0.0 | 0.2 | 0.0 | 0.2 | 0.0 | 0.3 | 0.0 | 0.1 |
| Number of inpatient hospitalizations | 0.3 | 0.7 | 0.3 | 0.7 | 0.3 | 0.6 | 0.4 | 0.8 |
| Number of inpatient hospitalizations for breast cancer | 0.1 | 0.3 | 0.0 | 0.2 | 0.1 | 0.4 | 0.1 | 0.4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Number of inpatient hospitalizations for any cancer | 0.3 | 0.7 | 0.3 | 0.6 | 0.3 | 0.6 | 0.3 | 0.8 |
| Number of emergency department visits | 0.3 | 0.7 | 0.3 | 0.8 | 0.3 | 0.6 | 0.2 | 0.6 |
| **Medication Use (breast cancer related in past six months)** | | | | | | | | |
| Palbociclib | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Aromatase Inhibitor | 1527 | 62.5 | 326 | 57.6 | 815 | 70.3 | 386 | 53.6 |
| Letrozole | 1019 | 41.7 | 116 | 20.5 | 703 | 60.7 | 200 | 27.8 |
| Anastrazole | 391 | 16.0 | 136 | 24.0 | 142 | 12.3 | 113 | 15.7 |
| Exemestane | 286 | 11.7 | 86 | 15.2 | 94 | 8.1 | 106 | 14.7 |
| HER2 positive Therapy | 72 | 2.9 | 15 | 2.7 | 35 | 3.0 | 22 | 3.1 |
| Trastuzumab | 105 | 4.3 | 25 | 4.4 | 43 | 3.7 | 37 | 5.1 |
| Lapatinib | ≤10 | n/a | ≤10 | n/a | 0 | 0.00 | ≤10 | n/a |
| Ado-trastuzumab | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Pertuzumab | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Tamoxifen | 552 | 22.6 | 140 | 24.7 | 270 | 23.3 | 142 | 19.7 |
| Fulvestrant | 621 | 25.4 | 238 | 42.1 | 112 | 9.7 | 271 | 37.6 |
| Denosumab or Pamidronate | 836 | 34.2 | 206 | 36.4 | 359 | 31.0 | 271 | 37.6 |
| Everolimus | 150 | 6.1 | 40 | 7.1 | 52 | 4.5 | 58 | 8.1 |
| **Medication Use (not breast cancer related)** | | | | | | | | |
| Anticonvulsants | 468 | 19.1 | 126 | 22.3 | 201 | 17.3 | 141 | 19.6 |
| Antidepressants | 746 | 30.5 | 178 | 31.4 | 348 | 30.0 | 220 | 30.6 |
| Antidiabetics | 292 | 11.9 | 67 | 11.8 | 134 | 11.6 | 91 | 12.6 |
| Antifungals | 125 | 5.1 | 28 | 4.9 | 64 | 5.5 | 33 | 4.6 |
| Antihypertensives | 653 | 26.7 | 173 | 30.6 | 293 | 25.3 | 187 | 26.0 |
| Antimycobacterials | 499 | 20.4 | 109 | 19.3 | 230 | 19.8 | 160 | 22.2 |
| Antivirals | 131 | 5.4 | 32 | 5.7 | 68 | 5.9 | 31 | 4.3 |
| Corticosteroids | 606 | 24.8 | 148 | 26.1 | 308 | 26.6 | 150 | 20.8 |
| Oral contraceptive use (progestin) | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a | 0 | 0.00 |
| Oral contraceptive use (combination) | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| Oral contraceptive use (unspecified) | 26 | 1.06 | ≤10 | n/a | 13 | 1.12 | ≤10 | n/a |
| Lipid lowering agent | 528 | 21.60 | 132 | 23.32 | 251 | 21.66 | 145 | 20.14 |
| Vaginal estrogen (local hormone treatment) | ≤10 | n/a | 0 | 0.00 | ≤10 | n/a | ≤10 | n/a |
| Macrolides | 22 | 0.90 | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| Sedatives/hypnotics | 228 | 9.33 | 57 | 10.07 | 102 | 8.80 | 69 | 9.58 |
| Selective estrogen receptor modulators | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| Unopposed estrogen hormone replacement therapy (HRT) | ≤10 | n/a | 0 | 0.00 | ≤10 | n/a | 0 | 0.00 |
| **Co-morbidities (six months prior to index date)** | | | | | | | | |
| Pathologic fracture | 211 | 8.6 | 46 | 8.1 | 110 | 9.5 | 55 | 7.6 |
| Osteoporosis | 196 | 8.0 | 56 | 9.9 | 79 | 6.8 | 61 | 8.5 |
| Uterine malignancies | 12 | 0.5 | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| Pure hypercholesterolemia | 215 | 8.8 | 48 | 8.48 | 105 | 9.06 | 62 | 8.61 |
| Major adverse cardiac events (MACE) | 57 | 2.3 | 20 | 3.53 | 24 | 2.07 | 13 | 1.81 |
| Acute myocardial infarction (MI) | 11 | 0.4 | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| Cerebrovascular disease | 1197 | 49.0 | 301 | 53.18 | 550 | 47.45 | 346 | 48.06 |
| Stroke | 48 | 2.0 | 16 | 2.83 | 21 | 1.81 | 11 | 1.53 |
| Hyperglycemia | 104 | 4.3 | 27 | 4.77 | 52 | 4.49 | 25 | 3.47 |
| Deyo-Charlson Index (DCI) | | | | | | | | |
| 0-3 | 125 | 5.1 | 19 | 3.36 | 44 | 3.80 | 62 | 8.61 |
| 4-7 | 30 | 1.2 | 12 | 2.12 | ≤10 | n/a | ≤10 | n/a |
| 8-11 | 2214 | 90.6 | 512 | 90.5 | 1073 | 92.6 | 629 | 87.4 |
| 12 or more | 76 | 3.1 | 23 | 4.1 | 32 | 2.8 | 21 | 2.9 |

Abbreviations: HIRD, HealthCore Integrated Research Database; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.

*All characteristics are measured as presence within six months prior to the index date (new use of palbociclib), unless otherwise specified.

*Return to Table of Contents*

**Table 1.2.** Incidence of the safety events of interest in all new users of palbociclib
**[Primary Objective 1]**

| Event | All new users of palbociclib (N=2,445) | | | | |
|---|---|---|---|---|---|
| | # Events | PT at risk | IR (per 100 person-years) | | |
| | | | IR | 95% Lower CI | 95% Upper CI |
| Neutropenia (sensitive) | 473 | 1,352 | 35.0 | 31.9 | 38.3 |
| Neutropenia (specific) | 313 | 1,417 | 22.1 | 19.7 | 24.7 |
| Febrile neutropenia (sensitive) | 44 | 1,530 | 2.9 | 2.1 | 3.9 |
| Febrile neutropenia (specific) | 11 | 1,538 | 0.7 | 0.4 | 1.3 |
| Leukopenia (sensitive) | 99 | 1,496 | 6.6 | 5.4 | 8.1 |
| Leukopenia (specific) | 98 | 1,496 | 6.6 | 5.3 | 8.0 |
| Alopecia | 12 | 1,535 | 0.8 | 0.4 | 1.4 |
| Vomiting* | 127 | 1,466 | 8.7 | 7.2 | 10.3 |
| QT prolongation | 80 | 1,514 | 5.3 | 4.2 | 6.6 |
| Fatigue* | 230 | 1,330 | 17.3 | 15.1 | 19.7 |
| Serious infection | 293 | 1,472 | 19.9 | 17.7 | 22.3 |
| Brain/spinal infection | ≤10 | n/a | 0.65 | 0.31 | 1.19 |
| Pericardial/myocardial infection | 0 | 1,540 | 0.00 | 0 | 0 |
| Pulmonary infection | 137 | 1,506 | 9.10 | 7.64 | 10.75 |
| GI infection | 12 | 1,539 | 0.78 | 0.40 | 1.36 |
| Genitourinary/renal infection | 140 | 1,496 | 9.36 | 7.87 | 11.04 |
| Dental infection | ≤10 | n/a | 0.06 | 0.00 | 0.36 |
| Ear, nose, and throat infection | 83 | 1,500 | 5.54 | 4.41 | 6.86 |
| Skin, bones, and joint infection | 82 | 1,512 | 5.42 | 4.31 | 6.73 |
| Hepatitis B infection | ≤10 | n/a | 0.20 | 0.04 | 0.57 |
| Influenza infection | ≤10 | n/a | 0.39 | 0.14 | 0.85 |
| Other infection | 284 | 1,445 | 19.66 | 17.44 | 22.08 |
| Diarrhea* | 61 | 1,496 | 4.08 | 3.12 | 5.24 |
| Interstitial lung disease/pneumonitis | 352 | 1,437 | 24.49 | 22.00 | 27.19 |
| Anemia (sensitive) | 536 | 1,358 | 39.47 | 36.20 | 42.96 |
| Anemia (specific) | 318 | 1,448 | 21.96 | 19.62 | 24.52 |
| Nausea* | 200 | 1,409 | 14.19 | 12.29 | 16.30 |
| Thrombocytopenia | 149 | 1,497 | 9.95 | 8.42 | 11.68 |
| Pulmonary embolism* | 45 | 1,505 | 2.99 | 2.18 | 4.00 |
| No history | 54 | 1,517 | 3.56 | 2.67 | 4.64 |
| Other venous embolism and thrombosis* | 64 | 1,489 | 4.30 | 3.31 | 5.49 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 45 | 1,509 | 2.98 | 2.18 | 3.99 |
| No history of "other venous embolism and thrombosis" | 94 | 1,509 | 6.23 | 5.03 | 7.62 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 61 | 1,520 | 4.01 | 3.07 | 5.16 |
| Embolism and thrombosis of unspecified artery | ≤10 | n/a | 0.19 | 0.04 | 0.57 |
| Cataracts and other ocular disorders | 94 | 1,498 | 6.28 | 5.07 | 7.68 |
| Stomatitis and mucositis | 35 | 1,529 | 2.29 | 1.59 | 3.18 |
| Fever | 152 | 1,499 | 10.14 | 8.59 | 11.89 |

| | | | | | |
|---|---|---|---|---|---|
| Anorexia | 30 | 1,532 | 1.96 | 1.32 | 2.80 |
| Peripheral neuropathy | 109 | 1,497 | 7.28 | 5.98 | 8.78 |
| Sudden cardiac death | ≤10 | n/a | 0.26 | 0.07 | 0.67 |
| Diabetes mellitus | 176 | 1,464 | 12.02 | 10.31 | 13.93 |
| Type 2 Diabetes mellitus | 175 | 1,466 | 11.94 | 10.24 | 13.85 |
| Hyperglycemia | 31 | 1,526 | 2.03 | 1.38 | 2.88 |
| Liver failure (Acute liver injury) | 47 | 1,533 | 3.07 | 2.25 | 4.08 |
| Abnormal ALT (incident)^ | 31 | 544 | 5.70 | 3.87 | 8.09 |
| Abnormal ALT (incident or prevalent)^ | 74 | 684 | 10.83 | 8.50 | 13.59 |
| Abnormal AST (incident)^ | 36 | 583 | 6.18 | 4.33 | 8.55 |
| Abnormal AST (incident or prevalent)^ | 83 | 687 | 12.08 | 9.62 | 14.97 |
| Abnormal ALP (incident)^ | 25 | 642 | 3.89 | 2.52 | 5.75 |
| Abnormal ALP (incident or prevalent)^ | 66 | 704 | 9.38 | 7.25 | 11.93 |
| Secondary malignancies (second primary cancers) | 413 | 1,376 | 30.01 | 27.18 | 33.05 |
| Non-melanoma skin cancer | 37 | 1,517 | 2.44 | 1.72 | 3.36 |

Abbreviations: N, number; GI, gastrointestinal; PT, person-time; IR, incidence rate; CI, confidence interval; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L; incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

*Return to Table of Contents*

**Table 1.3.** Incidence of the safety events of interest in new users of palbociclib subgroups
**[Secondary Objective 1]**

| Event | New users of palbociclib and fulvestrant (n=566) | | | | | New users of palbociclib and letrozole (n=1,159) | | | | | All other new users of palbociclib (no new use of fulvestrant or letrozole) (n=720) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | |
| | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI |
| Neutropenia (sensitive) | 107 | 285 | 37.54 | 30.77 | 45.37 | 240 | 709 | 33.87 | 29.72 | 38.44 | 126 | 359 | 35.11 | 29.25 | 41.81 |
| Neutropenia (specific) | 71 | 298 | 23.82 | 18.60 | 30.05 | 154 | 744 | 20.69 | 17.55 | 24.22 | 88 | 374 | 23.50 | 18.85 | 28.95 |
| Febrile neutropenia (sensitive) | 11 | 321 | 3.42 | 1.71 | 6.12 | 20 | 810 | 2.47 | 1.51 | 3.82 | 13 | 399 | 3.26 | 1.73 | 5.57 |
| Febrile neutropenia (specific) | ≤10 | n/a | 0.93 | 0.19 | 2.72 | ≤10 | n/a | 0.62 | 0.20 | 1.44 | ≤10 | n/a | 0.74 | 0.15 | 2.17 |
| Leukopenia (sensitive) | 17 | 318 | 5.34 | 3.11 | 8.56 | 56 | 785 | 7.13 | 5.39 | 9.26 | 26 | 393 | 6.62 | 4.33 | 9.70 |
| Leukopenia (specific) | 17 | 318 | 5.34 | 3.11 | 8.56 | 55 | 785 | 7.00 | 5.28 | 9.12 | 26 | 393 | 6.62 | 4.33 | 9.70 |
| Alopecia | ≤10 | n/a | 0.31 | 0.01 | 1.72 | ≤10 | n/a | 0.99 | 0.43 | 1.95 | ≤10 | n/a | 0.75 | 0.15 | 2.18 |
| Vomiting* | 32 | 309 | 10.36 | 7.09 | 14.63 | 47 | 771 | 6.10 | 4.48 | 8.11 | 48 | 387 | 12.40 | 9.15 | 16.44 |
| QT prolongation | 20 | 315 | 6.35 | 3.88 | 9.80 | 37 | 801 | 4.62 | 3.25 | 6.37 | 23 | 398 | 5.78 | 3.66 | 8.67 |
| Fatigue* | 53 | 284 | 18.69 | 14.00 | 24.45 | 98 | 692 | 14.17 | 11.50 | 17.27 | 79 | 355 | 22.27 | 17.63 | 27.75 |
| Serious infection | 79 | 309 | 25.56 | 20.24 | 31.86 | 135 | 773 | 17.46 | 14.64 | 20.67 | 79 | 389 | 20.28 | 16.06 | 25.28 |
| Brain/spinal infection | ≤10 | n/a | 1.24 | 0.34 | 3.17 | ≤10 | n/a | 0.74 | 0.27 | 1.61 | 0 | 404 | 0.00 | 0 | 0 |
| Pericardial/myocardial infection | 0 | 324 | 0.00 | 0 | 0 | 0 | 812 | 0.00 | 0 | 0 | 0 | 404 | 0.00 | 0 | 0 |
| Pulmonary infection | 34 | 318 | 10.69 | 7.40 | 14.94 | 70 | 791 | 8.85 | 6.90 | 11.18 | 33 | 397 | 8.32 | 5.73 | 11.68 |
| GI infection | ≤10 | n/a | 0.62 | 0.07 | 2.23 | ≤10 | n/a | 0.74 | 0.27 | 1.61 | ≤10 | n/a | 0.99 | 0.27 | 2.54 |
| Genitourinary/Renal infection | 35 | 314 | 11.16 | 7.78 | 15.53 | 73 | 785 | 9.30 | 7.29 | 11.69 | 32 | 397 | 8.06 | 5.51 | 11.38 |
| Dental infection | 0 | 324 | 0.00 | 0 | 0 | ≤10 | n/a | 0.12 | 0.00 | 0.69 | 0 | 404 | 0.00 | 0 | 0 |
| Ear, nose, and throat infection | 14 | 320 | 4.37 | 2.39 | 7.34 | 51 | 784 | 6.50 | 4.84 | 8.55 | 18 | 395 | 4.55 | 2.70 | 7.20 |
| Skin, bones, and joint infection | 17 | 319 | 5.33 | 3.10 | 8.53 | 46 | 793 | 5.80 | 4.25 | 7.73 | 19 | 399 | 4.76 | 2.86 | 7.43 |
| Hepatitis B infection | 0 | 324 | 0.00 | 0 | 0 | ≤10 | n/a | 0.25 | 0.03 | 0.89 | ≤10 | n/a | 0.25 | 0.01 | 1.38 |
| Influenza infection | ≤10 | n/a | 1.24 | 0.34 | 3.18 | 0 | 812 | 0.00 | 0 | 0 | ≤10 | n/a | 0.50 | 0.06 | 1.79 |
| Other infection | 65 | 306 | 21.22 | 16.38 | 27.05 | 146 | 756 | 19.30 | 16.30 | 22.70 | 73 | 382 | 19.11 | 14.98 | 24.03 |
| Diarrhea* | 14 | 316 | 4.42 | 2.42 | 7.42 | 27 | 788 | 3.43 | 2.26 | 4.99 | 20 | 392 | 5.10 | 3.12 | 7.88 |
| Interstitial lung disease/pneumonitis | 103 | 303 | 34.00 | 27.75 | 41.23 | 167 | 749 | 22.29 | 19.04 | 25.94 | 82 | 385 | 21.31 | 16.95 | 26.45 |
| Anemia (sensitive) | 134 | 283 | 47.38 | 39.69 | 56.11 | 276 | 706 | 39.11 | 34.63 | 44.01 | 126 | 369 | 34.11 | 28.41 | 40.61 |
| Anemia (specific) | 79 | 303 | 26.11 | 20.67 | 32.54 | 161 | 761 | 21.15 | 18.01 | 24.68 | 78 | 384 | 20.31 | 16.06 | 25.35 |
| Nausea* | 49 | 297 | 16.48 | 12.19 | 21.79 | 80 | 740 | 10.81 | 8.57 | 13.46 | 71 | 372 | 19.09 | 14.91 | 24.08 |
| Thrombocytopenia | 33 | 318 | 10.39 | 7.15 | 14.60 | 67 | 791 | 8.47 | 6.56 | 10.75 | 49 | 389 | 12.60 | 9.32 | 16.66 |
| Pulmonary embolism* | 14 | 318 | 4.41 | 2.41 | 7.40 | 16 | 791 | 2.02 | 1.16 | 3.29 | 15 | 397 | 3.78 | 2.12 | 6.24 |
| No history | 15 | 319 | 4.70 | 2.63 | 7.75 | 27 | 800 | 3.38 | 2.23 | 4.91 | 12 | 398 | 3.01 | 1.56 | 5.26 |
| Other venous embolism and thrombosis* | 11 | 309 | 3.56 | 1.78 | 6.37 | 28 | 782 | 3.58 | 2.38 | 5.17 | 25 | 398 | 6.28 | 4.07 | 9.27 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | ≤10 | n/a | 2.24 | 0.90 | 4.62 | 17 | 796 | 2.14 | 1.24 | 3.42 | 21 | 400 | 5.25 | 3.25 | 8.02 |
| No history of "other venous embolism and thrombosis" | 23 | 315 | 7.30 | 4.63 | 10.96 | 50 | 794 | 6.30 | 4.67 | 8.30 | 21 | 400 | 5.24 | 3.25 | 8.02 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 16 | 316 | 5.06 | 2.89 | 8.21 | 28 | 802 | 3.49 | 2.32 | 5.05 | 17 | 401 | 4.24 | 2.47 | 6.79 |
| Embolism and thrombosis of unspecified artery | ≤10 | n/a | 0.31 | 0.01 | 1.72 | 0 | 812 | 0.00 | 0 | 0 | ≤10 | n/a | 0.50 | 0.06 | 1.79 |
| Cataracts and other ocular disorders | 19 | 316 | 6.01 | 3.62 | 9.38 | 54 | 787 | 6.86 | 5.16 | 8.96 | 21 | 395 | 5.32 | 3.29 | 8.13 |
| Stomatitis and mucositis | ≤10 | n/a | 2.80 | 1.28 | 5.31 | 11 | 807 | 1.36 | 0.68 | 2.44 | 15 | 401 | 3.74 | 2.10 | 6.17 |
| Fever | 37 | 318 | 11.65 | 8.20 | 16.05 | 77 | 787 | 9.78 | 7.72 | 12.23 | 38 | 394 | 9.64 | 6.82 | 13.23 |
| Anorexia | ≤10 | n/a | 3.10 | 1.49 | 5.70 | 14 | 807 | 1.74 | 0.95 | 2.91 | ≤10 | n/a | 1.49 | 0.55 | 3.24 |
| Peripheral neuropathy | 24 | 316 | 7.59 | 4.86 | 11.29 | 48 | 790 | 6.08 | 4.48 | 8.06 | 37 | 391 | 9.46 | 6.66 | 13.04 |
| Sudden cardiac death | 0 | 324 | 0.00 | 0 | 0 | ≤10 | n/a | 0.37 | 0.08 | 1.08 | ≤10 | n/a | 0.25 | 0.01 | 1.38 |
| Diabetes mellitus | 46 | 310 | 14.84 | 10.87 | 19.80 | 103 | 761 | 13.53 | 11.04 | 16.41 | 27 | 393 | 6.87 | 4.53 | 9.99 |
| Type 2 Diabetes mellitus | 46 | 310 | 14.83 | 10.86 | 19.78 | 103 | 761 | 13.53 | 11.04 | 16.41 | 26 | 394 | 6.60 | 4.31 | 9.67 |
| Hyperglycemia | ≤10 | n/a | 1.55 | 0.50 | 3.62 | 20 | 801 | 2.50 | 1.52 | 3.85 | ≤10 | n/a | 1.49 | 0.55 | 3.25 |
| Liver failure (Acute liver injury) | 13 | 323 | 4.03 | 2.14 | 6.89 | 22 | 807 | 2.73 | 1.71 | 4.13 | 12 | 403 | 2.98 | 1.54 | 5.20 |
| Abnormal ALT (incident)^ | ≤10 | n/a | 7.37 | 3.37 | 13.99 | ≤10 | n/a | 3.38 | 1.55 | 6.41 | 13 | 155 | 8.37 | 4.46 | 14.32 |
| Abnormal ALT (incident or prevalent)^ | 18 | 156 | 11.57 | 6.86 | 18.29 | 31 | 335 | 9.24 | 6.28 | 13.12 | 25 | 193 | 12.99 | 8.40 | 19.17 |
| Abnormal AST (incident)^ | ≤10 | n/a | 7.02 | 3.21 | 13.33 | 13 | 295 | 4.41 | 2.35 | 7.53 | 14 | 160 | 8.77 | 4.79 | 14.71 |
| Abnormal AST (incident or prevalent)^ | 21 | 152 | 13.77 | 8.53 | 21.06 | 31 | 342 | 9.06 | 6.16 | 12.86 | 31 | 193 | 16.10 | 10.94 | 22.85 |
| Abnormal ALP (incident)^ | ≤10 | n/a | 5.04 | 2.02 | 10.38 | ≤10 | n/a | 2.15 | 0.86 | 4.43 | 11 | 177 | 6.20 | 3.09 | 11.09 |
| Abnormal ALP (incident or prevalent)^ | 17 | 152 | 11.15 | 6.50 | 17.86 | 24 | 356 | 6.74 | 4.32 | 10.03 | 25 | 195 | 12.80 | 8.29 | 18.90 |
| Secondary malignancies (second primary cancer) | 106 | 290 | 36.49 | 29.88 | 44.14 | 205 | 715 | 28.66 | 24.87 | 32.87 | 102 | 371 | 27.52 | 22.44 | 33.40 |
| Non-melanoma skin cancer | ≤10 | n/a | 2.19 | 0.88 | 4.51 | 17 | 799 | 2.13 | 1.24 | 3.41 | 13 | 398 | 3.27 | 1.74 | 5.59 |

Abbreviations: n, number; GI, gastrointestinal; PT, person-time; IR, incidence rate; CI, confidence interval; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; DVT, deep vein thrombosis.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

*Return to Table of Contents*

**Table 1.4A.** Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparison group)
**[Secondary Objective 3a]**

| Characteristics* | Before Propensity Score Matching | | | | | After Propensity Score Matching^ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (pre-2015) | | Standardized difference | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (pre-2015) | | Standardized difference |
| | N/Mean | %/SD | N/Mean | %/SD | | N/Mean | %/SD | N/Mean | %/SD | |
| **Overall** | **566** | **100%** | **2,316** | **100%** | | **561** | **100%** | **561** | **100%** | |
| | | | | | | | | | | |
| **Demographics** | | | | | | | | | | |
| Age at index date (in years) | 59.3 | 11.0 | 64.1 | 12.9 | 0.4 | 59.5 | 11.0 | 59.9 | 13.3 | 0.04 |
| Age (years) | | | | | | | | | | |
| <45 | 51.0 | 9.0 | 127.0 | 5.5 | 0.1 | 49.0 | 8.7 | 63.0 | 11.2 | 0.08 |
| 45-64 | 362.0 | 64.0 | 1121.0 | 48.4 | 0.3 | 360.0 | 64.2 | 306.0 | 54.5 | 0.20 |
| 65+ | 153.0 | 27.0 | 1068.0 | 46.1 | 0.4 | 152.0 | 27.1 | 192.0 | 34.2 | 0.16 |
| Sex | | | | | | | | | | |
| Male | ≤10 | n/a | 30 | 1.30 | 0.0 | ≤10 | n/a | ≤10 | n/a | 0.10 |
| Female | 557 | 98.4 | 2286 | 98.7 | 0.0 | 552 | 98.4 | 558 | 99.5 | 0.10 |
| Calendar year of index date | | | | | | | | | | |
| 2011 | 0 | 0.00 | 612 | 26.4 | n/a | 0 | 0.00 | 103 | 18.4 | n/a |
| 2012 | 0 | 0.00 | 507 | 21.9 | n/a | 0 | 0.00 | 138 | 24.6 | n/a |
| 2013 | 0 | 0.00 | 569 | 24.6 | n/a | 0 | 0.00 | 159 | 28.3 | n/a |
| 2014 | 0 | 0.00 | 628 | 27.1 | n/a | 0 | 0.00 | 161 | 28.7 | n/a |
| 2015 | 99 | 17.5 | 0 | 0.00 | n/a | 98 | 17.5 | 0 | 0.00 | n/a |
| 2016 | 269 | 47.5 | 0 | 0.00 | n/a | 267 | 47.6 | 0 | 0.00 | n/a |
| 2017 | 198 | 35.0 | 0 | 0.00 | n/a | 196 | 34.9 | 0 | 0.00 | n/a |
| Geographic region of residence | | | | | | | | | | |
| Midwest | 95 | 16.8 | 422 | 18.2 | 0.04 | 95 | 16.9 | 93 | 16.6 | 0.01 |
| South | 159 | 28.1 | 690 | 29.8 | 0.04 | 157 | 28.0 | 165 | 29.4 | 0.03 |
| Northeast | 166 | 29.3 | 580 | 25.0 | 0.10 | 164 | 29.2 | 158 | 28.2 | 0.02 |
| West | 146 | 25.8 | 624 | 26.9 | 0.03 | 145 | 25.8 | 145 | 25.8 | 0.00 |
| **Medical History** | | | | | | | | | | |
| Other primary cancer prior to first breast cancer diagnosis code | 223 | 39.4 | 1026 | 44.3 | 0.1 | 222 | 39.6 | 271 | 48.3 | 0.18 |
| Secondary malignancy (metastasis) | 496 | 87.6 | 1823 | 78.7 | 0.2 | 491 | 87.5 | 488 | 87.0 | 0.02 |
| Lymph nodes of head, face, and neck | 154 | 27.2 | 476 | 20.6 | 0.2 | 151 | 26.9 | 150 | 26.7 | 0.00 |
| Respiratory and digestive systems | 257 | 45.4 | 781 | 33.7 | 0.2 | 254 | 45.3 | 252 | 44.9 | 0.01 |
| Other specified sites | 463 | 81.8 | 1710 | 73.8 | 0.2 | 458 | 81.6 | 458 | 81.6 | 0.00 |
| Deyo-Charlson comorbidity index (DCI) without cancer codes | 8.5 | 1.8 | 7.85 | 2.3 | 0.3 | 8.5 | 1.8 | 8.56 | 1.6 | 0.03 |
| Secondary malignant neoplasm of breast | 66 | 11.7 | 204 | 8.8 | 0.1 | 65 | 11.6 | 67 | 11.9 | 0.01 |
| Breast cancer (female) diagnosis code | 558 | 98.6 | 2262 | 97.7 | 0.1 | 553 | 98.6 | 556 | 99.1 | 0.05 |
| InSitu breast cancer | 44 | 7.8 | 151 | 6.5 | 0.0 | 42 | 7.5 | 39 | 7.0 | 0.02 |
| **Cancer Therapy History** | | | | | | | | | | |
| **Radiation therapy** | 112 | 19.8 | 386 | 16.7 | 0.1 | 112 | 20.0 | 117 | 20.9 | 0.02 |
| External Beam | 112 | 19.8 | 386 | 16.7 | 0.1 | 112 | 20.0 | 117 | 20.9 | 0.02 |
| **Surgery** | 11 | 1.9 | 68 | 2.9 | 0.1 | 11 | 2.0 | 13 | 2.3 | 0.02 |
| Mastectomy in the last six months | ≤10 | n/a | 32 | 1.38 | 0.09 | ≤10 | n/a | ≤10 | n/a | 0.06 |
| Lumpectomy in the last six months | ≤10 | n/a | 25 | 1.08 | 0.06 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Radical mastectomy in the last six months | ≤10 | n/a | 22 | 0.95 | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| **Chemotherapy** | 100 | 17.67 | 429 | 18.52 | 0.02 | 99 | 17.65 | 98 | 17.47 | 0.00 |
| Infusion based chemo (procedure) | ≤10 | n/a | 31 | 1.34 | 0.11 | ≤10 | n/a | 12 | 2.14 | 0.16 |
| **Imaging** | | | | | | | | | | |
| CT related imaging in the last six months | 139 | 24.56 | 501 | 21.63 | 0.07 | 138 | 24.60 | 146 | 26.02 | 0.03 |
| MR related imaging for needle placement | 0 | 0.00 | ≤10 | n/a | . | 0 | 0.00 | ≤10 | n/a | . |
| Diagnostic imaging in the last six months | 72 | 12.72 | 461 | 19.91 | 0.20 | 72 | 12.83 | 79 | 14.08 | 0.04 |
| Mammography | ≤10 | n/a | 107 | 4.62 | 0.19 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| MRI related imaging | 25 | 4.42 | 91 | 3.93 | 0.02 | 25 | 4.46 | 26 | 4.63 | 0.01 |
| Tomosynthesis (3D mammography) | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| **Healthcare Utilization (six months prior to index date)** | | | | | | | | | | |
| Number of outpatient visits | 37.6 | 21.7 | 36.5 | 24.6 | 0.0 | 37.7 | 21.8 | 39.3 | 24.2 | 0.07 |
| Number of outpatient visits to an oncologist | 0.0 | 0.2 | 0.0 | 0.3 | 0.0 | 0.0 | 0.2 | 0.0 | 0.3 | 0.08 |
| Number of inpatient hospitalizations | 0.3 | 0.7 | 0.3 | 0.7 | 0.0 | 0.3 | 0.7 | 0.4 | 0.8 | 0.14 |
| Number of inpatient hospitalizations for breast cancer | 0.0 | 0.2 | 0.3 | 0.6 | 0.5 | 0.0 | 0.2 | 0.3 | 0.7 | 0.58 |
| Number of inpatient hospitalizations for any cancer | 0.3 | 0.6 | 0.3 | 0.7 | 0.1 | 0.3 | 0.6 | 0.4 | 0.7 | 0.15 |
| Number of emergency department visits | 0.3 | 0.8 | 0.2 | 0.6 | 0.1 | 0.3 | 0.8 | 0.3 | 0.7 | 0.03 |
| **Medication Use (breast cancer related)** | | | | | | | | | | |
| Palbociclib | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Aromatase inhibitor | 326 | 57.6 | 1285 | 55.5 | 0.04 | 321 | 57.2 | 303 | 54.0 | 0.06 |
| Letrozole | 116 | 20.5 | 429 | 18.5 | 0.05 | 113 | 20.1 | 116 | 20.7 | 0.01 |
| Anastrazole | 136 | 24.0 | 611 | 26.4 | 0.05 | 135 | 24.1 | 138 | 24.6 | 0.01 |
| Exemestane | 86 | 15.2 | 358 | 15.5 | 0.01 | 85 | 15.2 | 76 | 13.5 | 0.05 |
| HER2 positive therapy | 15 | 2.7 | 127 | 5.5 | 0.14 | 15 | 2.7 | 14 | 2.5 | 0.01 |
| Trastuzumab | 25 | 4.4 | 159 | 6.9 | 0.11 | 24 | 4.3 | 27 | 4.8 | 0.03 |
| Lapatinib | ≤10 | n/a | 16 | 0.69 | 0.05 | ≤10 | n/a | ≤10 | n/a | n/a |
| Ado-trastuzumab | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Pertuzumab | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Tamoxifen | 140 | 24.73 | 379 | 16.36 | 0.21 | 140 | 24.96 | 135 | 24.06 | 0.02 |
| Fulvestrant | 238 | 42.05 | 0 | 0.00 | n/a | 236 | 42.07 | 0 | 0.00 | n/a |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Denosumab or Pamidronate | 206 | 36.40 | 424 | 18.31 | 0.41 | 201 | 35.83 | 197 | 35.12 | 0.01 |
| Everolimus | 40 | 7.07 | 84 | 3.63 | 0.15 | 39 | 6.95 | 37 | 6.60 | 0.01 |
| **Medication Use (not breast cancer related)** | | | | | | | | | | |
| Anticonvulsants | 126 | 22.3 | 347 | 15.0 | 0.19 | 122 | 21.7 | 123 | 21.9 | 0.00 |
| Antidepressants | 178 | 31.4 | 631 | 27.2 | 0.09 | 175 | 31.2 | 184 | 32.8 | 0.03 |
| Antidiabetics | 67 | 11.8 | 252 | 10.9 | 0.03 | 66 | 11.8 | 75 | 13.4 | 0.05 |
| Antifungals | 28 | 4.9 | 119 | 5.1 | 0.01 | 28 | 5.0 | 35 | 6.2 | 0.05 |
| Antihypertensives | 173 | 30.6 | 623 | 26.9 | 0.08 | 171 | 30.5 | 135 | 24.1 | 0.14 |
| Antimycobacterials | 109 | 19.3 | 446 | 19.3 | 0.00 | 107 | 19.1 | 117 | 20.9 | 0.04 |
| Antivirals | 32 | 5.7 | 112 | 4.8 | 0.04 | 32 | 5.7 | 30 | 5.3 | 0.02 |
| Corticosteroids | 148 | 26.1 | 416 | 18.0 | 0.20 | 146 | 26.0 | 146 | 26.0 | 0.00 |
| Oral contraceptive use (progestin) | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Oral contraceptive use (combination) | ≤10 | n/a | ≤10 | n/a | 0.02 | ≤10 | n/a | ≤10 | n/a | n/a |
| Oral contraceptive use (unspecified) | ≤10 | n/a | 23 | 0.99 | 0.02 | ≤10 | n/a | ≤10 | n/a | n/a |
| Lipid lowering agent | 132 | 23.32 | 556 | 24.01 | 0.02 | 130 | 23.17 | 121 | n/a | 0.04 |
| Vaginal estrogen (local hormone treatment) | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | ≤10 | 0.18 | n/a |
| Macrolides | ≤10 | n/a | 22 | 0.95 | 0.06 | ≤10 | n/a | ≤10 | n/a | 0.08 |
| Sedatives/hypnotics | 57 | 10.07 | 291 | 12.56 | 0.08 | 57 | 10.16 | 63 | 11.23 | 0.03 |
| Selective estrogen receptor modulators | ≤10 | n/a | ≤10 | n/a | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.08 |
| Unopposed estrogen hormone replacement therapy (HRT) | 0 | 0.00 | ≤10 | 0.43 | n/a | 0 | 0.00 | ≤10 | 0.53 | n/a |
| **Co-morbidities (six months prior to index date)** | | | | | | | | | | |
| Pathologic fracture | 46 | 8.13 | 173 | 7.47 | 0.02 | 46 | 8.20 | 51 | 9.09 | 0.03 |
| Osteoporosis | 56 | 9.89 | 225 | 9.72 | 0.01 | 55 | 9.80 | 52 | 9.27 | 0.02 |
| Uterine malignancies | ≤10 | n/a | 11 | 0.47 | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Pure hypercholesterolemia | 48 | 8.48 | 237 | 10.23 | 0.06 | 48 | 8.56 | 54 | 9.63 | 0.04 |
| Major adverse cardiac events (MACE) | 20 | 3.53 | 83 | 3.58 | 0.00 | 20 | 3.57 | 23 | 4.10 | 0.03 |
| Acute myocardial infarction (MI) | ≤10 | n/a | 23 | 0.99 | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.10 |
| Cerebrovascular disease | 301 | 53.18 | 1148 | 49.57 | 0.07 | 296 | 52.76 | 277 | 49.38 | 0.07 |
| Stroke | 16 | 2.83 | 63 | 2.72 | 0.01 | 16 | 2.85 | 15 | 2.67 | 0.01 |
| Hyperglycemia | 27 | 4.77 | 55 | 2.37 | 0.13 | 23 | 4.10 | 29 | 5.17 | 0.05 |
| Deyo-Charlson Index (DCI) | | | | | | | | | | |
| 0-3 | 19 | 3.36 | 259 | 11.18 | 0.30 | 19 | 3.39 | 17 | 3.03 | 0.02 |
| 4-7 | 12 | 2.12 | 57 | 2.46 | 0.02 | 12 | 2.14 | ≤10 | n/a | 0.12 |
| 8-11 | 512 | 90.46 | 1937 | 83.64 | 0.20 | 508 | 90.55 | 517 | 92.16 | 0.06 |
| 12 or more | 23 | 4.06 | 63 | 2.72 | 0.07 | 22 | 3.92 | 23 | 4.10 | 0.01 |

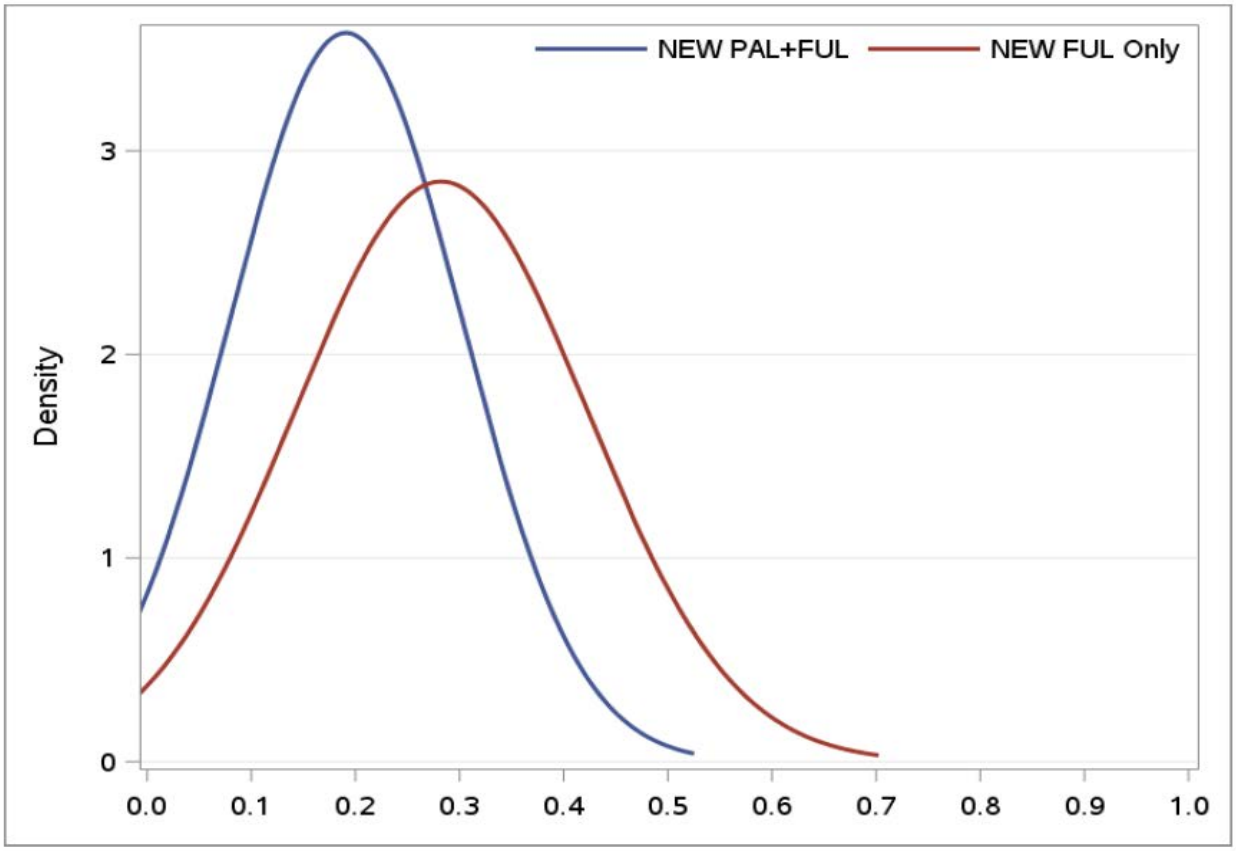
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.

*All characteristics are measured as presence within six months prior to the index date, unless otherwise specified.

^The following variables were included in the propensity score: age, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrazole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, and cerebrovascular disease.

*Return to Table of Contents*

**Figure 2.** Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users (historical comparison grou




Abbreviations: PAL, palbociclib; FUL, fulvestrant.

*Return to Table of Contents*

**Table 1.4B.** Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (contemperaneous comparison group)
**[Secondary Objective 4a]**

| Characteristics* | Before Propensity Score Matching | | | | | After Propensity Score Matching^ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (Feb. 2015 or later) | | Standardized difference | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (Feb. 2015 or later) | | Standardized difference |
| | N/Mean | %/STD | N/Mean | %/STD | | N/Mean | %/STD | N/Mean | %/STD | |
| **Overall** | **566** | **100%** | **961** | **100%** | | **292** | **100%** | **292** | **100%** | |
| **Demographics** | | | | | | | | | | |
| Age at index date (in years) | 59.5 | 11.4 | 66 | 13.5 | 0.52 | 64.1 | 10.8 | 65.6 | 12.7 | 0.13 |
| Age (years) | | | | | | | | | | |
| <45 | 51 | 9.0 | 54 | 5.6 | 0.13 | ≤10 | n/a | 16 | 5.5 | 0.14 |
| 45-64 | 337 | 59.5 | 381 | 39.6 | 0.41 | 153 | 52.4 | 110 | 37.7 | 0.30 |
| 65+ | 178 | 31.4 | 526 | 54.7 | 0.48 | 131 | 44.9 | 166 | 56.8 | 0.24 |
| Gender | | | | | | | | | | |
| Male | ≤10 | n/a | 15 | 1.6 | 0.00 | ≤10 | n/a | ≤10 | n/a | 0.07 |
| Female | 557 | 98.4 | 946 | 98.4 | 0.00 | 284 | 97.3 | 287 | 98.3 | 0.07 |
| Calendar year of index date | | | | | | | | | | |
| 2015 | 99 | 17.5 | 444 | 46.2 | 0.65 | 91 | 31.2 | 97 | 33.2 | 0.04 |
| 2016 | 269 | 47.5 | 325 | 33.8 | 0.28 | 125 | 42.8 | 114 | 39.0 | 0.08 |
| 2017 | 198 | 35.0 | 192 | 20.0 | 0.34 | 76 | 26.0 | 81 | 27.7 | 0.04 |
| Geographic region of residence | | | | | | | | | | |
| Midwest | 95 | 16.8 | 175 | 18.2 | 0.04 | 48 | 16.4 | 59 | 20.2 | 0.10 |
| South | 159 | 28.1 | 249 | 25.9 | 0.05 | 69 | 23.6 | 72 | 24.7 | 0.02 |
| Northeast | 166 | 29.3 | 264 | 27.5 | 0.04 | 84 | 28.8 | 87 | 29.8 | 0.02 |
| West | 146 | 25.8 | 273 | 28.4 | 0.06 | 91 | 31.2 | 74 | 25.3 | 0.13 |
| Duration of health plan enrollment prior to index date (days) | 1264 | 758.3 | 1322 | 721.5 | 0.08 | 1331 | 755.9 | 1406 | 751.2 | 0.10 |
| **Medical History** | | | | | | | | | | |
| Other primary cancer prior to first breast cancer diagnosis code | 223 | 39.4 | 365 | 38.0 | 0.03 | 125 | 42.8 | 123 | 42.1 | 0.01 |
| Secondary malignancy (metastasis) | | | | | | | | | | |
| Lymph nodes of head, face, and neck | 154 | 27.2 | 211 | 22.0 | 0.12 | 77 | 26.4 | 62 | 21.2 | 0.12 |
| Respiratory and digestive systems | 257 | 45.4 | 332 | 34.5 | 0.22 | 119 | 40.8 | 108 | 37.0 | 0.08 |
| Other specified sites | 463 | 81.8 | 662 | 68.9 | 0.30 | 216 | 74.0 | 217 | 74.3 | 0.01 |
| Deyo-Charlson comorbidity index (DCI) | 8.52 | 1.8 | 7.94 | 2.7 | 0.26 | 8.31 | 2.0 | 8.24 | 2.4 | 0.03 |
| Secondary malignant neoplasm of breast | 66 | 11.7 | 90 | 9.4 | 0.07 | 35 | 12.0 | 36 | 12.3 | 0.01 |
| Breast Cancer (Female) diagnosis code | 558 | 98.6 | 924 | 96.1 | 0.15 | 284 | 97.3 | 282 | 96.6 | 0.04 |
| InSitu Breast Cancer | 44 | 7.8 | 63 | 6.6 | 0.05 | 15 | 5.1 | 16 | 5.5 | 0.02 |
| History of Breast Cancer | 327 | 57.8 | 358 | 37.3 | 0.42 | 147 | 50.3 | 132 | 45.2 | 0.10 |
| **Cancer Therapy History** | | | | | | | | | | |
| **Radiation therapy** | 112 | 19.8 | 173 | 18.0 | 0.05 | 54 | 18.5 | 63 | 21.6 | 0.08 |
| Implantation (Brachytherapy) | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| External Beam | 112 | 19.8 | 173 | 18.0 | 0.05 | 54 | 18.5 | 63 | 21.6 | 0.08 |
| **Surgery** | 11 | 1.9 | 33 | 3.4 | 0.09 | ≤10 | n/a | 12 | 4.1 | 0.10 |
| Mastectomy in the last six months | ≤10 | n/a | 12 | 1.2 | 0.08 | ≤10 | n/a | ≤10 | n/a | 0.11 |
| Lumpectomy in the last six months | ≤10 | n/a | 17 | 1.8 | 0.12 | ≤10 | n/a | ≤10 | n/a | 0.12 |
| Radical Mastectomy in the last six months | ≤10 | n/a | ≤10 | n/a | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.06 |
| **Chemotherapy** | 100 | 17.7 | 126 | 13.1 | 0.13 | 42 | 14.4 | 40 | 13.7 | 0.02 |
| Infusion based chemo (procedure) | ≤10 | n/a | ≤10 | n/a | 0.05 | ≤10 | n/a | ≤10 | n/a | 0.14 |
| **Imaging** | | | | | | | | | | |
| CT related imaging in the last six months | 139 | 24.6 | 178 | 18.5 | 0.15 | 62 | 21.2 | 64 | 21.9 | 0.02 |
| MR related imaging for needle placement | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Diagnostic imaging in the last six months | 72 | 12.7 | 154 | 16.0 | 0.09 | 38 | 13.0 | 36 | 12.3 | 0.02 |
| Mammography | ≤10 | n/a | 21 | 2.2 | 0.06 | ≤10 | n/a | ≤10 | n/a | 0.05 |
| MRI related imaging | 25 | 4.4 | 47 | 4.9 | 0.02 | 13 | 4.5 | 13 | 4.5 | 0.00 |
| Tomosynthesis (3D Mammography) | 18 | 3.2 | 15 | 1.6 | 0.11 | 0 | 0.0 | 0 | 0.0 | n/a |
| **Healthcare Utilization (Six months prior to index date)** | | | | | | | | | | |
| Number of outpatient visits | 38.6 | 23.6 | 36.8 | 25.8 | 0.07 | 38.7 | 26.4 | 37.6 | 22.8 | 0.05 |
| Number of outpatient visits to an oncologist | 0.0 | 0.2 | 0.0 | 0.3 | 0.04 | 0.0 | 0.2 | 0.0 | 0.3 | 0.04 |
| Number of inpatient hospitalizations | 0.3 | 0.7 | 0.4 | 0.7 | 0.04 | 0.3 | 0.7 | 0.4 | 0.8 | 0.10 |
| Number of inpatient hospitalizations for breast cancer | 0.0 | 0.2 | 0.1 | 0.4 | 0.25 | 0.1 | 0.3 | 0.1 | 0.4 | 0.11 |
| Number of inpatient hospitalizations for any cancer | 0.3 | 0.6 | 0.3 | 0.7 | 0.03 | 0.3 | 0.6 | 0.4 | 0.7 | 0.12 |
| Number of emergency department visits | 0.3 | 0.8 | 0.3 | 0.7 | 0.03 | 0.3 | 0.8 | 0.3 | 0.6 | 0.03 |
| **Medication Use (breast cancer related)** | | | | | | | | | | |
| Palbociclib | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Hormone Therapy | 326 | 57.6 | 482 | 50.2 | 0.15 | 160 | 54.8 | 158 | 54.1 | 0.0 |
| Letrozole | 116 | 20.5 | 147 | 15.3 | 0.14 | 55 | 18.8 | 51 | 17.5 | 0.0 |
| Anastrazole | 136 | 24.0 | 240 | 25.0 | 0.02 | 67 | 22.9 | 72 | 24.7 | 0.0 |
| Exemestane | 86 | 15.2 | 122 | 12.7 | 0.07 | 42 | 14.4 | 49 | 16.8 | 0.1 |
| HER2 positive Therapy | 15 | 2.7 | 96 | 10.0 | 0.31 | 14 | 4.8 | 16 | 5.5 | 0.0 |
| Trastuzumab | 25 | 4.4 | 131 | 13.6 | 0.33 | 17 | 5.8 | 29 | 9.9 | 0.2 |
| Lapatinib | ≤10 | n/a | ≤10 | n/a | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.0 |
| Ado-trastuzumab | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Pertuzumab | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Tamoxifen | 140 | 24.7 | 189 | 19.7 | 0.1 | 66 | 22.6 | 61 | 20.9 | 0.0 |
| Fulvestrant | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Denosumab or Pamidronate | 206 | 36.4 | 234 | 24.3 | 0.3 | 82 | 28.1 | 85 | 29.1 | 0.0 |
| Everolimus | 40 | 7.1 | 33 | 3.4 | 0.2 | 14 | 4.8 | 17 | 5.8 | 0.0 |
| **Medication Use (not breast cancer related)** | | | | | | | | | | |
| Anticonvulsants | 126 | 22.3 | 146 | 15.2 | 0.18 | 49 | 16.8 | 45 | 15.4 | 0.04 |
| Antidepressants | 178 | 31.4 | 252 | 26.2 | 0.12 | 86 | 29.5 | 83 | 28.4 | 0.02 |
| Antidiabetics | 67 | 11.8 | 112 | 11.7 | 0.01 | 26 | 8.9 | 34 | 11.6 | 0.09 |
| Antifungals | 28 | 4.9 | 42 | 4.4 | 0.03 | 17 | 5.8 | ≤10 | n/a | 0.11 |
| Antihypertensives | 173 | 30.6 | 252 | 26.2 | 0.10 | 80 | 27.4 | 105 | 36.0 | 0.18 |
| Antimycobacterials | 109 | 19.3 | 196 | 20.4 | 0.03 | 56 | 19.2 | 70 | 24.0 | 0.12 |
| Antivirals | 32 | 5.7 | 30 | 3.1 | 0.12 | 17 | 5.8 | 13 | 4.5 | 0.06 |
| Corticosteroids | 148 | 26.1 | 200 | 20.8 | 0.13 | 65 | 22.3 | 76 | 26.0 | 0.09 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Oral contraceptive use (progestin) | ≤10 | n/a | ≤10 | n/a | 0.02 | 0 | 0.0 | ≤10 | n/a | n/a |
| Oral contraceptive use (combination) | ≤10 | n/a | ≤10 | n/a | 0.01 | 0 | 0.0 | ≤10 | n/a | n/a |
| Oral contraceptive use (unspecified) | ≤10 | n/a | 11 | 1.1 | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.14 |
| Lipid lowering agent | 132 | 23.3 | 212 | 22.1 | 0.03 | 67 | 22.9 | 66 | 22.6 | 0.01 |
| Vaginal estrogen (local hormone treatment) | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Macrolides | ≤10 | n/a | 12 | 1.2 | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.08 |
| Sedatives/hypnotics | 57 | 10.1 | 67 | 7.0 | 0.11 | 23 | 7.9 | 21 | 7.2 | 0.03 |
| Selective estrogen receptor modulators | ≤10 | n/a | ≤10 | n/a | 0.03 | 0 | 0.0 | 0 | 0.0 | n/a |
| Unopposed estrogen hormone replacement therapy (HRT) | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | ≤10 | n/a | n/a |
| **Co-morbidities (six months prior to index date)** | | | | | | | | | | |
| Pathologic fracture | 46 | 8.1 | 62 | 6.5 | 0.06 | 20 | 6.8 | 20 | 6.8 | 0.00 |
| Osteoporosis | 56 | 9.9 | 116 | 12.1 | 0.07 | 33 | 11.3 | 36 | 12.3 | 0.03 |
| Uterine malignancies | ≤10 | n/a | ≤10 | n/a | 0.07 | 0 | 0.0 | 0 | 0.0 | n/a |
| Pure hypercholesterolemia | 48 | 8.5 | 99 | 10.3 | 0.06 | 32 | 11.0 | 29 | 9.9 | 0.03 |
| Major adverse cardiac events (MACE) | 20 | 3.5 | 42 | 4.4 | 0.04 | 14 | 4.8 | 12 | 4.1 | 0.03 |
| Acute myocardial infarction (MI) | ≤10 | n/a | ≤10 | n/a | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Cerebrovascular disease | 19 | 3.4 | 47 | 4.9 | 0.08 | 13 | 4.5 | 11 | 3.8 | 0.03 |
| Stroke | 16 | 2.8 | 34 | 3.5 | 0.04 | 12 | 4.1 | ≤10 | n/a | 0.06 |
| Diabetes | 67 | 11.8 | 112 | 11.7 | 0.01 | 26 | 8.9 | 34 | 11.6 | 0.09 |
| Hyperglycemia | 27 | 4.8 | 42 | 4.4 | 0.02 | 11 | 3.8 | ≤10 | n/a | 0.02 |
| Deyo-Charlson Index (DCI) | | | | | | | | | | |
| 0-3 | 19 | 3.4 | 123 | 12.8 | 0.35 | 15 | 5.1 | 30 | 10.3 | 0.19 |
| 4-7 | 12 | 2.1 | 45 | 4.7 | 0.14 | 12 | 4.1 | ≤10 | n/a | 0.06 |
| 8-11 | 512 | 90.5 | 739 | 76.9 | 0.37 | 252 | 86.3 | 238 | 81.5 | 0.13 |
| 12 or more | 23 | 4.1 | 54 | 5.6 | 0.07 | 13 | 4.5 | 15 | 5.1 | 0.03 |
| **ALI related risk factors** | | | | | | | | | | |
| Chronic liver disease or Alcoholism | 74 | 13.1 | 98 | 10.2 | 0.09 | 34 | 11.6 | 32 | 11.0 | 0.02 |
| Chronic or acute hepatitis | ≤10 | n/a | ≤10 | n/a | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Chronic or acute disease of gallbladder or pancreas | 36 | 6.4 | 86 | 8.9 | 0.10 | 25 | 8.6 | 29 | 9.9 | 0.05 |
| Hepatic, Biliary or pancreatic cancer | 160 | 28.3 | 190 | 19.8 | 0.20 | 69 | 23.6 | 71 | 24.3 | 0.02 |
| Congestive heart failure | 29 | 5.1 | 64 | 6.7 | 0.07 | 17 | 5.8 | 20 | 6.8 | 0.04 |
| **Medications association with liver injury** | | | | | | | | | | |
| **Any medication (of list below)** | 467 | 82.5 | 689 | 71.7 | 0.26 | 220 | 75.3 | 226 | 77.4 | 0.05 |
| Acarbose | 0 | 0.0 | 0 | 0.0 | 0.00 | 0 | 0.0 | 0 | 0.0 | n/a |
| Acetaminophen (prescription) | 204 | 36.0 | 292 | 30.4 | 0.12 | 91 | 31.2 | 86 | 29.5 | 0.04 |
| Allopurinol | ≤10 | n/a | 13 | 1.4 | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Amiodarone | ≤10 | n/a | ≤10 | n/a | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.05 |
| Amitriptyline | ≤10 | n/a | ≤10 | n/a | 0.06 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Amoxicillin + clavulanic acid | 33 | 5.8 | 62 | 6.5 | 0.03 | 18 | 6.2 | 23 | 7.9 | 0.07 |
| Anabolic steroids | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Aripiprazole | ≤10 | n/a | ≤10 | n/a | 0.07 | 0 | 0.0 | 0 | 0.0 | n/a |
| Azathioprine | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Baclofen | ≤10 | n/a | ≤10 | n/a | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.08 |
| Bupropion | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Captopril | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Carbamazepine | ≤10 | n/a | ≤10 | n/a | 0.08 | 0 | 0.0 | 0 | 0.0 | n/a |
| Chlorpromazine | ≤10 | n/a | ≤10 | n/a | 0.02 | 0 | 0.0 | 0 | 0.0 | n/a |
| Ciprofloxacin | 46 | 8.1 | 87 | 9.1 | 0.03 | 25 | 8.6 | 28 | 9.6 | 0.04 |
| Clindamycin | 23 | 4.1 | 33 | 3.4 | 0.03 | 10 | 3.4 | 12 | 4.1 | 0.04 |
| Clopidogrel | ≤10 | n/a | 21 | 2.2 | 0.04 | ≤10 | n/a | 6 | 2.1 | 0.00 |
| Cyproheptadine | ≤10 | n/a | ≤10 | n/a | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| Duloxetine | 23 | 4.1 | 32 | 3.3 | 0.04 | 14 | 4.8 | ≤10 | n/a | 0.09 |
| Enalapril | ≤10 | n/a | ≤10 | n/a | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.08 |
| Erythromycins | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Estrogens | 63 | 11.1 | 99 | 10.3 | 0.03 | 34 | 11.6 | 31 | 10.6 | 0.03 |
| Fluoxetine | 12 | 2.1 | 14 | 1.5 | 0.05 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| Flutamide | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| HAART drugs | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Irbesartan | ≤10 | n/a | ≤10 | n/a | 0.06 | 0 | 0.0 | 0 | 0.0 | n/a |
| Isoniazid | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Ketoconazole | ≤10 | n/a | ≤10 | n/a | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Lamotrigine | 2 | 0.4 | ≤10 | n/a | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| Lisinopril | 76 | 13.4 | 87 | 9.1 | 0.14 | 29 | 9.9 | 33 | 11.3 | 0.04 |
| Losartan | 54 | 9.5 | 72 | 7.5 | 0.07 | 23 | 7.9 | 35 | 12.0 | 0.14 |
| Methotrexate | ≤10 | n/a | ≤10 | n/a | 0.06 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| Mirtazapine | ≤10 | n/a | ≤10 | n/a | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.06 |
| Nitrofurantoin | ≤10 | n/a | 31 | 3.2 | 0.09 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| NSAIDs | 129 | 22.8 | 161 | 16.8 | 0.15 | 41 | 14.0 | 58 | 19.9 | 0.16 |
| Omeprazole | 76 | 13.4 | 125 | 13.0 | 0.01 | 34 | 11.6 | 35 | 12.0 | 0.01 |
| Oral contraceptives | ≤10 | n/a | ≤10 | n/a | 0.01 | 0 | 0.0 | ≤10 | n/a | n/a |
| Paroxetine | ≤10 | n/a | 22 | 2.3 | 0.05 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Phenobarbital | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Phenothiazines | 92 | 16.3 | 90 | 9.4 | 0.21 | 25 | 8.6 | 34 | 11.6 | 0.10 |
| Phenytoin | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Pyrazinamide | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Rifampicin | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Risperidone | ≤10 | n/a | ≤10 | n/a | 0.08 | 0 | 0.0 | 0 | 0.0 | n/a |
| Sertraline | 19 | 3.4 | 34 | 3.5 | 0.01 | ≤10 | n/a | 16 | 5.5 | 0.10 |
| Statins | 125 | 22.1 | 197 | 20.5 | 0.04 | 65 | 22.3 | 61 | 20.9 | 0.03 |
| Sulfonamides | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | ≤10 | n/a | n/a |
| Terbinafine | ≤10 | n/a | ≤10 | n/a | 0.02 | 0 | 0.0 | 0 | 0.0 | n/a |
| Tetracyclines | 31 | 5.5 | 44 | 4.6 | 0.04 | 14 | 4.8 | 16 | 5.5 | 0.03 |
| Trazodone | 15 | 2.7 | 24 | 2.5 | 0.01 | 11 | 3.8 | 13 | 4.5 | 0.03 |
| Tricyclics | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Trimethoprim-sulfamethoxazole | 28 | 4.9 | 58 | 6.0 | 0.05 | 13 | 4.5 | 19 | 6.5 | 0.09 |
| Trovafloxacin | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Valproic acid | ≤10 | n/a | ≤10 | n/a | 0.03 | 0 | 0.0 | 0 | 0.0 | n/a |
| Verapamil | ≤10 | n/a | 11 | 1.1 | 0.07 | ≤10 | n/a | ≤10 | n/a | 0.05 |

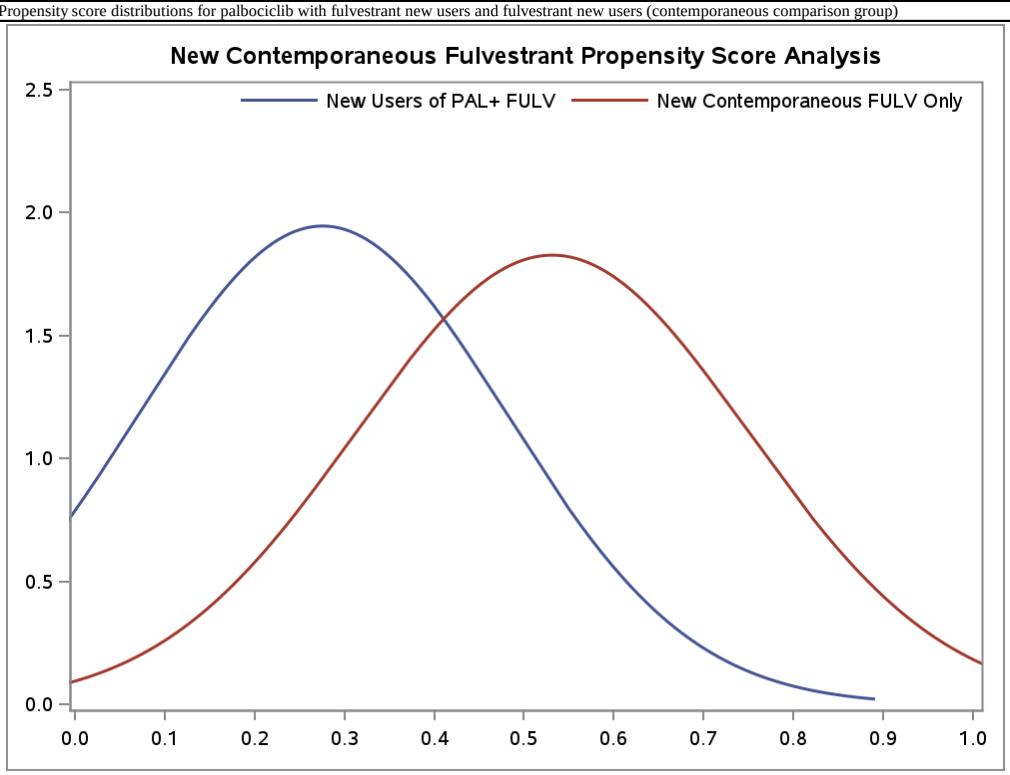
Abbreviations: Feb., February; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; STD, standard deviation; ALI, acute liver injury; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal anti-inflammatory drugs.

*All characteristics are measured as presence within six months prior to the index date, unless otherwise specified.

^The following variables were included in the propensity score: age, calendar year of index date, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrazole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, Chronic liver disease or Alcoholism, Chronic or acute disease of gallbladder or pancreas, Hepatic, Biliary or pancreatic cancer, Congestive heart failure, any medication associated with ALI- Acetaminophen, Allopurinol, Amiodarone, Amitriptyline, + clavulanic acid, Aripiprazole, Baclofen, Ciprofloxacin, Clindamycin, Clopidogrel, Duloxetine, Estrogens, Fluoxetine, Ketoconazole, Lisinopril, Losartan, Mirtazapine, Nitrofurantoin, NSAIDs, Omeprazole, Paroxetine, Phenothiazine, Sertraline, Statins, Tetracycline, Trazodone, and Trimethoprim

Return to Table of Contents

**Figure 3.** Propensity score distributions for palbociclib with fulvestrant new users and fulvestrant new users (contemporaneous comparison group)




Abbreviations: FULV, Fulverstrant; PAL, palbociclib.

*Return to Table of Contents*

**Table 1.5.** Incidence rates and unadjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone **[Secondary Objective 3a]**

| Event | Before Propensity Score Matching[#] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All new users of palbociclib and fulvestrant (n=566) | | | | | All new users of fulvestrant alone (pre-2015) (n=2,316) | | | | | Unadjusted Hazard Ratios | | |
| | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | | HR | 95% LCL | 95%UCL |
| | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI | | | |
| Neutropenia (sensitive) | 107 | 285 | 37.5 | 30.77 | 45.37 | 95 | 1,661 | 5.7 | 4.63 | 6.99 | 6.0 | 4.5 | 7.9 |
| Neutropenia (specific) | 71 | 298 | 23.8 | 18.60 | 30.05 | 68 | 1,664 | 4.1 | 3.17 | 5.18 | 5.4 | 3.9 | 7.6 |
| Febrile neutropenia (sensitive) | 11 | 321 | 3.4 | 1.71 | 6.12 | ≤10 | n/a | 0.6 | 0.28 | 1.09 | 5.2 | 2.2 | 12.2 |
| Febrile neutropenia (specific) | ≤10 | n/a | 0.9 | 0.19 | 2.72 | ≤10 | n/a | 0.1 | 0.01 | 0.43 | 6.8 | 1.1 | 40.8 |
| Leukopenia (sensitive) | 17 | 318 | 5.3 | 3.11 | 8.56 | 13 | 1,682 | 0.8 | 0.41 | 1.32 | 6.3 | 3.1 | 12.9 |
| Leukopenia (specific) | 17 | 318 | 5.3 | 3.11 | 8.56 | 13 | 1,682 | 0.8 | 0.41 | 1.32 | 6.3 | 3.1 | 12.9 |
| Alopecia | ≤10 | n/a | 0.3 | 0.01 | 1.72 | ≤10 | n/a | 0.2 | 0.04 | 0.52 | 1.6 | 0.2 | 15.8 |
| Vomiting* | 32 | 309 | 10.4 | 7.09 | 14.63 | 209 | 1,627 | 12.8 | 11.17 | 14.71 | 0.8 | 0.5 | 1.1 |
| QT prolongation | 20 | 315 | 6.3 | 3.88 | 9.80 | 84 | 1,661 | 5.1 | 4.03 | 6.26 | 1.2 | 0.7 | 1.9 |
| Fatigue* | 53 | 284 | 18.7 | 14.00 | 24.45 | 297 | 1,566 | 19.0 | 16.87 | 21.25 | 0.9 | 0.7 | 1.2 |
| Serious infection | 79 | 309 | 25.6 | 20.24 | 31.86 | 342 | 1,616 | 21.2 | 18.98 | 23.53 | 1.1 | 0.9 | 1.5 |
| Brain/spinal infection | ≤10 | n/a | 1.2 | 0.34 | 3.17 | ≤10 | n/a | 0.1 | 0.01 | 0.43 | 9.6 | 1.8 | 52.5 |
| Pericardial/myocardial infection | 0 | 324 | 0.0 | . | . | ≤10 | n/a | 0.1 | 0.01 | 0.43 | n/a | . | . |
| Pulmonary infection | 34 | 318 | 10.7 | 7.40 | 14.94 | 130 | 1,659 | 7.8 | 6.55 | 9.30 | 1.3 | 0.9 | 1.9 |
| GI infection | ≤10 | n/a | 0.6 | 0.07 | 2.23 | ≤10 | n/a | 0.4 | 0.17 | 0.85 | 1.4 | 0.3 | 6.9 |
| Genitourinary/Renal infection | 35 | 314 | 11.2 | 7.78 | 15.53 | 180 | 1,630 | 11.0 | 9.49 | 12.78 | 0.9 | 0.7 | 1.4 |
| Dental infection | 0 | 324 | 0.0 | . | . | ≤10 | n/a | 0.1 | 0.01 | 0.43 | 0.0 | 0.0 | |
| Ear, nose, and throat infection | 14 | 320 | 4.4 | 2.39 | 7.34 | 55 | 1,664 | 3.3 | 2.49 | 4.30 | 1.3 | 0.7 | 2.3 |
| Skin, bones, and joint infection | 17 | 319 | 5.3 | 3.10 | 8.53 | 71 | 1,659 | 4.3 | 3.34 | 5.40 | 1.2 | 0.7 | 2.0 |
| Hepatitis B infection | 0 | 324 | 0.0 | . | . | 38 | 1,661 | 2.3 | 1.62 | 3.14 | n/a | . | . |
| Influenza infection | ≤10 | n/a | 1.2 | 0.34 | 3.18 | ≤10 | n/a | 0.2 | 0.06 | 0.61 | 4.8 | 1.2 | 19.3 |
| Other infection | 65 | 306 | 21.2 | 16.38 | 27.05 | 557 | 1,463 | 38.1 | 34.99 | 41.38 | 0.5 | 0.4 | 0.7 |
| Diarrhea* | 14 | 316 | 4.4 | 2.42 | 7.42 | 90 | 1,655 | 5.4 | 4.37 | 6.69 | 0.8 | 0.4 | 1.3 |
| Interstitial lung disease/pneumonitis | 103 | 303 | 34.0 | 27.75 | 41.23 | 342 | 1,594 | 21.5 | 19.24 | 23.85 | 1.5 | 1.2 | 1.9 |
| Anemia (sensitive) | 134 | 283 | 47.4 | 39.69 | 56.11 | 372 | 1,564 | 23.8 | 21.43 | 26.33 | 1.8 | 1.5 | 2.2 |
| Anemia (specific) | 79 | 303 | 26.1 | 20.67 | 32.54 | 123 | 1,652 | 7.4 | 6.19 | 8.89 | 3.3 | 2.5 | 4.4 |
| Nausea* | 49 | 297 | 16.5 | 12.19 | 21.79 | 267 | 1,601 | 16.7 | 14.74 | 18.80 | 0.9 | 0.7 | 1.3 |
| Thrombocytopenia | 33 | 318 | 10.4 | 7.15 | 14.60 | 58 | 1,680 | 3.5 | 2.62 | 4.46 | 2.8 | 1.8 | 4.3 |
| Pulmonary embolism* | 14 | 318 | 4.4 | 2.41 | 7.40 | 46 | 1,668 | 2.8 | 2.02 | 3.68 | 1.5 | 0.8 | 2.7 |
| No history | 15 | 319 | 4.7 | 2.63 | 7.75 | 39 | 1,673 | 2.3 | 1.66 | 3.19 | 1.9 | 1.0 | 3.4 |
| Other venous embolism and thrombosis* | 11 | 309 | 3.6 | 1.78 | 6.37 | 104 | 1,635 | 6.4 | 5.20 | 7.71 | 0.5 | 0.3 | 1.0 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | ≤10 | n/a | 2.2 | 0.90 | 4.62 | 69 | 1,658 | 4.2 | 3.24 | 5.27 | 0.5 | 0.2 | 1.1 |
| No history of "Other venous embolism and thrombosis" | 23 | 315 | 7.3 | 4.63 | 10.96 | 95 | 1,653 | 5.7 | 4.65 | 7.03 | 1.2 | 0.8 | 1.9 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 16 | 316 | 5.1 | 2.89 | 8.21 | 63 | 1,667 | 3.8 | 2.90 | 4.83 | 1.3 | 0.7 | 2.2 |
| Embolism and thrombosis of unspecified artery | ≤10 | n/a | 0.3 | 0.01 | 1.72 | ≤10 | n/a | 0.1 | 0.00 | 0.33 | 4.7 | 0.3 | 75.4 |
| Cataracts and other ocular disorders | 19 | 316 | 6.0 | 3.62 | 9.38 | 104 | 1,633 | 6.4 | 5.20 | 7.72 | 0.9 | 0.6 | 1.5 |
| Stomatitis and mucositis | ≤10 | n/a | 2.8 | 1.28 | 5.31 | ≤10 | n/a | 0.5 | 0.20 | 0.94 | 5.3 | 2.1 | 13.8 |
| Fever | 37 | 318 | 11.6 | 8.20 | 16.05 | 74 | 1,668 | 4.4 | 3.48 | 5.57 | 2.4 | 1.6 | 3.6 |
| Anorexia | ≤10 | n/a | 3.1 | 1.49 | 5.70 | 27 | 1,686 | 1.6 | 1.06 | 2.33 | 1.9 | 0.9 | 3.9 |
| Peripheral neuropathy | 24 | 316 | 7.6 | 4.86 | 11.29 | 53 | 1,668 | 3.2 | 2.38 | 4.16 | 2.2 | 1.4 | 3.6 |
| Sudden cardiac death | 0 | 324 | 0.0 | . | . | ≤10 | n/a | 0.2 | 0.06 | 0.61 | n/a | . | . |
| Diabetes mellitus | 46 | 310 | 14.8 | 10.87 | 19.80 | 215 | 1,608 | 13.4 | 11.64 | 15.28 | 1.0 | 0.7 | 1.4 |
| Type 2 Diabetes mellitus | 46 | 310 | 14.8 | 10.86 | 19.78 | 207 | 1,609 | 12.9 | 11.17 | 14.74 | 1.1 | 0.8 | 1.5 |
| Hyperglycemia | ≤10 | n/a | 1.5 | 0.50 | 3.62 | 14 | 1,685 | 0.8 | 0.45 | 1.39 | 1.9 | 0.7 | 5.3 |
| Liver failure (Acute liver injury) | 13 | 323 | 4.0 | 2.14 | 6.89 | 20 | 1,685 | 1.2 | 0.73 | 1.83 | 3.1 | 1.5 | 6.2 |
| Abnormal ALT (incident)^ | ≤10 | n/a | 7.4 | 3.37 | 13.99 | 34 | 558 | 6.1 | 4.22 | 8.51 | 1.1 | 0.5 | 2.3 |
| Abnormal ALT (incident or prevalent)^ | 18 | 156 | 11.6 | 6.86 | 18.29 | 81 | 634 | 12.8 | 10.14 | 15.87 | 0.8 | 0.5 | 1.4 |
| Abnormal AST (incident)^ | ≤10 | n/a | 7.0 | 3.21 | 13.33 | 46 | 555 | 8.3 | 6.07 | 11.06 | 0.8 | 0.4 | 1.6 |
| Abnormal AST (incident or prevalent)^ | 21 | 152 | 13.8 | 8.53 | 21.06 | 101 | 627 | 16.1 | 13.12 | 19.56 | 0.8 | 0.5 | 1.3 |
| Abnormal ALP (incident)^ | ≤10 | n/a | 5.0 | 2.02 | 10.38 | 27 | 586 | 4.6 | 3.04 | 6.70 | 0.9 | 0.4 | 2.2 |
| Abnormal ALP (incident or prevalent)^ | 17 | 152 | 11.2 | 6.50 | 17.86 | 90 | 637 | 14.1 | 11.36 | 17.36 | 0.7 | 0.4 | 1.2 |
| Secondary malignancies (second primary cancer) | 106 | 290 | 36.5 | 29.88 | 44.14 | 515 | 1,506 | 34.2 | 31.32 | 37.29 | 1.0 | 0.8 | 1.2 |
| Non-melanoma skin cancer | ≤10 | n/a | 2.2 | 0.88 | 4.51 | 63 | 1,647 | 3.8 | 2.94 | 4.89 | 0.5 | 0.2 | 1.2 |

Abbreviations: n, number; GI, gastrointestinal; PT, person-time; IR, incidence rate; CI, confidence interval; HR, hazard ratios, LCL, lower confidence limit; UCL, upper confidence limit; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; DVT, deep vein thrombosis.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

*Return to Table of Contents*

**Table 1.6.** Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone **[Secondary Objective 3a]**

| Event | After Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib and fulvestrant (n=561) | | | | | New users of fulvestrant alone (pre-2015) (n=561) | | | | | Adjusted Hazard Ratios | | |
| | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | | aHR | 95% LCL | 95%UCL |
| | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI | | | |
| Neutropenia (sensitive) | 104 | 283 | 36.7 | 29.99 | 44.47 | 17 | 368 | 4.6 | 2.69 | 7.40 | 7.8 | 4.7 | 13.0 |
| Neutropenia (specific) | 71 | 296 | 24.0 | 18.73 | 30.25 | 14 | 368 | 3.8 | 2.08 | 6.38 | 6.3 | 3.6 | 11.2 |
| Febrile neutropenia (sensitive) | ≤10 | n/a | 3.1 | 1.50 | 5.76 | ≤10 | n/a | 0.3 | 0.01 | 1.50 | 11.1 | 1.4 | 87.1 |
| Febrile neutropenia (specific) | ≤10 | n/a | 0.9 | 0.19 | 2.73 | 0 | 373 | 0.0 | . | 0.99 | n/a | . | . |
| Leukopenia (sensitive) | 17 | 316 | 5.4 | 3.13 | 8.61 | ≤10 | n/a | 0.8 | 0.17 | 2.37 | 6.4 | 1.9 | 21.9 |
| Leukopenia (specific) | 17 | 316 | 5.4 | 3.13 | 8.61 | ≤10 | n/a | 0.8 | 0.17 | 2.37 | 6.4 | 1.9 | 21.9 |
| Alopecia | ≤10 | n/a | 0.3 | 0.01 | 1.73 | 0 | 373 | 0.0 | . | 0.99 | n/a | 0.0 | . |
| Vomiting* | 31 | 307 | 10.1 | 6.87 | 14.34 | 50 | 347 | 14.4 | 10.69 | 18.98 | 0.7 | 0.4 | 1.1 |
| QT prolongation | 20 | 313 | 6.4 | 3.90 | 9.87 | 13 | 368 | 3.5 | 1.88 | 6.04 | 1.8 | 0.9 | 3.5 |
| Fatigue* | 52 | 282 | 18.4 | 13.77 | 24.18 | 82 | 341 | 24.1 | 19.13 | 29.86 | 0.7 | 0.5 | 1.0 |
| Serious infection | 79 | 307 | 25.7 | 20.37 | 32.07 | 82 | 358 | 22.9 | 18.24 | 28.47 | 1.1 | 0.8 | 1.5 |
| Brain/spinal infection | ≤10 | n/a | 1.2 | 0.34 | 3.19 | 0 | 373 | 0.0 | . | 0.99 | n/a | . | . |
| Pericardial/myocardial infection | 0 | 322 | 0.0 | . | . | 0 | 373 | 0.0 | . | 0.99 | n/a | . | . |
| Pulmonary infection | 34 | 316 | 10.8 | 7.45 | 15.04 | 29 | 369 | 7.9 | 5.27 | 11.30 | 1.4 | 0.8 | 2.3 |
| GI infection | ≤10 | n/a | 0.6 | 0.08 | 2.25 | ≤10 | n/a | 0.5 | 0.07 | 1.94 | 1.1 | 0.2 | 8.1 |
| Genitourinary/Renal infection | 35 | 311 | 11.2 | 7.83 | 15.63 | 33 | 364 | 9.1 | 6.24 | 12.72 | 1.2 | 0.7 | 1.9 |
| Dental infection | 0 | 322 | . | . | . | ≤10 | n/a | 0.5 | 0.07 | 1.94 | n/a | . | . |
| Ear, nose, and throat infection | 14 | 318 | 4.4 | 2.41 | 7.38 | 18 | 367 | 4.9 | 2.91 | 7.75 | 0.8 | 0.4 | 1.7 |
| Skin, bones, and joint infection | 17 | 317 | 5.4 | 3.12 | 8.59 | 17 | 366 | 4.6 | 2.71 | 7.44 | 1.1 | 0.6 | 2.2 |
| Hepatitis B infection | 0 | 322 | 0.0 | . | . | ≤10 | n/a | 1.9 | 0.76 | 3.92 | n/a | . | . |
| Influenza infection | ≤10 | n/a | 1.2 | 0.34 | 3.20 | ≤10 | n/a | 0.5 | 0.07 | 1.94 | 2.3 | 0.4 | 12.9 |
| Other infection | 65 | 304 | 21.4 | 16.49 | 27.23 | 136 | 323 | 42.1 | 35.30 | 49.76 | 0.5 | 0.4 | 0.7 |
| Diarrhea* | 14 | 314 | 4.5 | 2.43 | 7.47 | 25 | 365 | 6.8 | 4.43 | 10.10 | 0.6 | 0.3 | 1.2 |
| Interstitial lung disease/pneumonitis | 103 | 301 | 34.2 | 27.93 | 41.51 | 85 | 353 | 24.1 | 19.22 | 29.75 | 1.4 | 1.1 | 1.9 |
| Anemia (sensitive) | 134 | 281 | 47.7 | 39.98 | 56.52 | 91 | 347 | 26.2 | 21.13 | 32.22 | 1.8 | 1.4 | 2.3 |
| Anemia (specific) | 79 | 301 | 26.3 | 20.81 | 32.75 | 33 | 366 | 9.0 | 6.21 | 12.68 | 2.9 | 1.9 | 4.3 |
| Nausea* | 49 | 296 | 16.6 | 12.26 | 21.92 | 71 | 339 | 21.0 | 16.38 | 26.45 | 0.8 | 0.5 | 1.1 |
| Thrombocytopenia | 33 | 315 | 10.5 | 7.20 | 14.69 | 17 | 370 | 4.6 | 2.67 | 7.35 | 2.3 | 1.3 | 4.1 |
| Pulmonary embolism* | 14 | 316 | 4.4 | 2.43 | 7.44 | 15 | 368 | 4.1 | 2.28 | 6.73 | 1.0 | 0.5 | 2.1 |
| No history | 15 | 317 | 4.7 | 2.65 | 7.80 | 12 | 369 | 3.2 | 1.68 | 5.67 | 1.4 | 0.7 | 3.0 |
| Other venous embolism and thrombosis* | 11 | 307 | 3.6 | 1.79 | 6.41 | 26 | 360 | 7.2 | 4.72 | 10.58 | 0.5 | 0.2 | 1.0 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | ≤10 | n/a | 2.3 | 0.91 | 4.65 | 15 | 368 | 4.1 | 2.28 | 6.73 | 0.5 | 0.2 | 1.3 |
| No history of "Other venous embolism and thrombosis" | 22 | 313 | 7.0 | 4.40 | 10.64 | 25 | 362 | 6.9 | 4.47 | 10.20 | 1.0 | 0.6 | 1.8 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 15 | 315 | 4.8 | 2.67 | 7.87 | 15 | 369 | 4.1 | 2.28 | 6.71 | 1.2 | 0.6 | 2.4 |
| Embolism and thrombosis of unspecified artery | ≤10 | n/a | 0.3 | 0.01 | 1.73 | ≤10 | n/a | 0.3 | 0.01 | 1.50 | 1.1 | 0.1 | 17.4 |
| Cataracts and other ocular disorders | 19 | 314 | 6.0 | 3.64 | 9.45 | 27 | 363 | 7.4 | 4.91 | 10.83 | 0.8 | 0.4 | 1.4 |
| Stomatitis and mucositis | ≤10 | n/a | 2.8 | 1.29 | 5.34 | ≤10 | n/a | 0.5 | 0.07 | 1.94 | 5.0 | 1.1 | 23.1 |
| Fever | 36 | 316 | 11.4 | 7.99 | 15.79 | 22 | 368 | 6.0 | 3.75 | 9.06 | 1.9 | 1.1 | 3.2 |
| Anorexia | ≤10 | n/a | 3.1 | 1.50 | 5.74 | ≤10 | n/a | 1.3 | 0.44 | 3.13 | 2.3 | 0.8 | 6.6 |
| Peripheral neuropathy | 24 | 314 | 7.6 | 4.89 | 11.36 | 17 | 368 | 4.6 | 2.69 | 7.40 | 1.6 | 0.9 | 3.0 |
| Sudden cardiac death | 0 | 322 | 0.0 | . | . | 0 | 373 | 0.0 | . | 0.99 | n/a | . | . |
| Diabetes mellitus | 46 | 308 | 14.9 | 10.94 | 19.93 | 66 | 346 | 19.1 | 14.74 | 24.24 | 0.8 | 0.5 | 1.1 |
| Type 2 Diabetes mellitus | 46 | 308 | 14.9 | 10.93 | 19.91 | 65 | 347 | 18.7 | 14.47 | 23.89 | 0.8 | 0.5 | 1.2 |
| Hyperglycemia | ≤10 | n/a | 1.6 | 0.51 | 3.64 | ≤10 | n/a | 0.8 | 0.17 | 2.36 | 2.0 | 0.5 | 8.4 |
| Liver failure (Acute liver injury) | 13 | 321 | 4.1 | 2.16 | 6.93 | ≤10 | n/a | 0.8 | 0.17 | 2.35 | 4.8 | 1.4 | 16.9 |
| Abnormal ALT (incident)^ | ≤10 | n/a | 6.6 | 2.84 | 12.98 | ≤10 | n/a | 5.7 | 2.29 | 11.75 | 1.0 | 0.4 | 2.8 |
| Abnormal ALT (incident or prevalent)^ | 17 | 155 | 11.0 | 6.39 | 17.57 | 16 | 142 | 11.2 | 6.43 | 18.26 | 0.8 | 0.4 | 1.6 |
| Abnormal AST (incident)^ | ≤10 | n/a | 7.1 | 3.23 | 13.42 | ≤10 | n/a | 4.9 | 1.78 | 10.58 | 1.3 | 0.5 | 3.6 |
| Abnormal AST (incident or prevalent)^ | 20 | 152 | 13.2 | 8.06 | 20.38 | 19 | 144 | 13.2 | 7.94 | 20.59 | 0.9 | 0.5 | 1.7 |
| Abnormal ALP (incident)^ | ≤10 | n/a | 5.1 | 2.04 | 10.43 | ≤10 | n/a | 2.2 | 0.46 | 6.55 | 2.0 | 0.5 | 7.6 |
| Abnormal ALP (incident or prevalent)^ | 16 | 152 | 10.6 | 6.04 | 17.15 | 16 | 143 | 11.2 | 6.41 | 18.20 | 0.7 | 0.3 | 1.5 |
| Secondary malignancies (second primary cancer) | 105 | 289 | 36.4 | 29.76 | 44.04 | 133 | 340 | 39.2 | 32.78 | 46.40 | 0.9 | 0.7 | 1.2 |
| Non-melanoma skin cancer | ≤10 | n/a | 2.2 | 0.89 | 4.54 | ≤10 | n/a | 0.8 | 0.17 | 2.37 | 3.2 | 0.8 | 13.2 |

Abbreviations: GI, gastrointestinal; n; number; PT, person-time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; DVT, deep vein thrombosis.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

w34

**Table 1.7.** Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone (historical comparison group - including ALI risk factors)
**[Secondary Objective 3a]**

| Characteristics* | Before Propensity Score Matching | | | | | After Propensity Score Matching^ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (Pre-2015) | | Standardized difference | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (Pre-2015) | | Standardized difference |
| | N/Mean | %/STD | N/Mean | %/STD | | N/Mean | %/STD | N/Mean | %/STD | |
| **Overall** | **566** | **100%** | **2,316** | **100%** | | **565** | **1.00** | **565** | **1.00** | |
| | | | | | | | | | | |
| **Demographics** | | | | | | | | | | |
| Age at index date (in years) | 59.5 | 11.4 | 64.1 | 12.9 | 0.40 | 59.5 | 11.4 | 60.0 | 12.9 | 0.04 |
| Age (years) | | | | | | | | | | |
| <45 | 51 | 9.0 | 127 | 5.5 | 0.14 | 51 | 9.0 | 53 | 9.4 | 0.01 |
| 45-64 | 337 | 59.5 | 1121 | 48.4 | 0.32 | 336 | 59.5 | 307 | 54.3 | 0.10 |
| 65+ | 178 | 31.4 | 1068 | 46.1 | 0.40 | 178 | 31.5 | 205 | 36.3 | 0.10 |
| Gender | | | | | | | | | | |
| Male | ≤10 | n/a | 30 | 1.3 | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.10 |
| Female | 557 | 98.4 | 2286 | 98.7 | 0.02 | 556 | 98.4 | 556 | 98.4 | 0.00 |
| Calendar year of index date | | | | | | | | | | |
| 2011 | 0 | 0.0 | 612 | 26.4 | n/a | 0 | 0.0 | 118 | 20.9 | n/a |
| 2012 | 0 | 0.0 | 507 | 21.9 | n/a | 0 | 0.0 | 113 | 20.0 | n/a |
| 2013 | 0 | 0.0 | 569 | 24.6 | n/a | 0 | 0.0 | 151 | 26.7 | n/a |
| 2014 | 0 | 0.0 | 628 | 27.1 | n/a | 0 | 0.0 | 183 | 32.4 | n/a |
| 2015 | 99 | 17.5 | 0 | 0.0 | n/a | 99 | 17.5 | 0 | 0.0 | n/a |
| 2016 | 269 | 47.5 | 0 | 0.0 | n/a | 269 | 47.6 | 0 | 0.0 | n/a |
| 2017 | 198 | 35.0 | 0 | 0.0 | n/a | 197 | 34.9 | 0 | 0.0 | n/a |
| Geographic region of residence | | | | | | | | | | |
| Midwest | 95 | 16.8 | 422 | 18.2 | 0.04 | 95 | 16.8 | 103 | 18.2 | 0.04 |
| South | 159 | 28.1 | 690 | 29.8 | 0.04 | 159 | 28.1 | 143 | 25.3 | 0.06 |
| Northeast | 166 | 29.3 | 580 | 25.0 | 0.10 | 165 | 29.2 | 154 | 27.3 | 0.04 |
| West | 146 | 25.8 | 624 | 26.9 | 0.03 | 146 | 25.8 | 165 | 29.2 | 0.08 |
| Duration of health plan enrollment prior to index date (days) | 1263.9 | 758.3 | 694.1 | 422.9 | 0.93 | 1264.2 | 759.0 | 744.6 | 444.5 | 0.84 |
| **Medical History** | | | | | | | | | | |
| Other primary cancer prior to first breast cancer diagnosis code | 223 | 39.40 | 1026 | 44.30 | 0.10 | 223 | 39.47 | 265 | 46.90 | 0.15 |
| Secondary malignancy (metastasis) | | | | | | | | | | |
| Lymph nodes of head, face, and neck | 154 | 27.2 | 476 | 20.6 | 0.16 | 153 | 27.1 | 160 | 28.3 | 0.03 |
| Respiratory and digestive systems | 257 | 45.4 | 781 | 33.7 | 0.24 | 257 | 45.5 | 244 | 43.2 | 0.05 |
| Other specified sites | 463 | 81.8 | 1710 | 73.8 | 0.19 | 462 | 81.8 | 458 | 81.1 | 0.02 |
| Deyo-Charlson comorbidity index (DCI) | 8.52 | 1.8 | 7.85 | 2.3 | 0.31 | ≤10 | n/a | 8.44 | 1.7 | 0.05 |
| Secondary malignant neoplasm of breast | 66 | 11.7 | 204 | 8.8 | 0.09 | 66 | 11.7 | 64 | 11.3 | 0.01 |
| Breast Cancer (Female) diagnosis code | 558 | 98.6 | 2262 | 97.7 | 0.07 | 557 | 98.6 | 556 | 98.4 | 0.01 |
| InSitu Breast Cancer | 44 | 7.8 | 151 | 6.5 | 0.05 | 43 | 7.6 | 45 | 8.0 | 0.01 |
| History of Breast Cancer | 370 | 65.4 | 1338 | 57.8 | 0.16 | 349 | 61.8 | 370 | 65.5 | 0.08 |
| **Cancer Therapy History** | | | | | | | | | | |
| **Radiation therapy** | 112 | 19.8 | 386 | 16.7 | 0.08 | 112 | 19.8 | 109 | 19.3 | 0.01 |
| Implantation (Brachytherapy) | 0 | 0.0 | 2 | 0.1 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| External Beam | 112 | 19.8 | 386 | 16.7 | 0.08 | 112 | 19.8 | 109 | 19.3 | 0.01 |
| **Surgery** | 11 | 1.9 | 68 | 2.9 | 0.06 | 11 | 1.9 | 13 | 2.3 | 0.02 |
| Mastectomy in the last six months | ≤10 | n/a | 32 | 1.4 | 0.09 | ≤10 | n/a | ≤10 | n/a | 0.06 |
| Lumpectomy in the last six months | ≤10 | n/a | 25 | 1.1 | 0.06 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Radical Mastectomy in the last six months | ≤10 | n/a | 22 | 0.9 | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| **Chemotherapy** | 100 | 17.7 | 429 | 18.5 | 0.02 | 100 | 17.7 | 105 | 18.6 | 0.02 |
| Infusion based chemo (procedure) | ≤10 | n/a | 31 | 1.3 | 0.11 | ≤10 | n/a | 12 | 2.1 | 0.16 |
| **Imaging** | | | | | | | | | | |
| CT related imaging in the last six months | 139 | 24.6 | 501 | 21.6 | 0.07 | 139 | 24.6 | 132 | 23.4 | 0.03 |
| MR related imaging for needle placement | 0 | 0.0 | 3 | 0.1 | --- | 0 | 0.0 | ≤10 | n/a | --- |
| Diagnostic imaging in the last six months | 72 | 12.7 | 461 | 19.9 | 0.20 | 72 | 12.7 | 80 | 14.2 | 0.04 |
| Mammography | ≤10 | n/a | 107 | 4.6 | 0.19 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| MRI related imaging | 25 | 4.4 | 91 | 3.9 | 0.02 | 25 | 4.4 | 24 | 4.2 | 0.01 |
| Tomosynthesis (3D Mammography) | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| **Healthcare Utilization (Six months prior to index date)** | | | | | | | | | | |
| Number of outpatient visits | 38.58 | 23.6 | 36.5 | 24.6 | 0.05 | 39 | 23.7 | 39.2 | 25.0 | 0.02 |
| Number of outpatient visits to an oncologist | 0.02 | 0.2 | 0.0 | 0.3 | 0.04 | 0 | 0.2 | 0.0 | 0.2 | 0.00 |
| Number of inpatient hospitalizations | 0.33 | 0.7 | 0.3 | 0.7 | 0.04 | 0 | 0.7 | 0.4 | 0.8 | 0.08 |
| Number of inpatient hospitalizations for breast cancer | 0.03 | 0.2 | 0.3 | 0.6 | 0.51 | 0 | 0.2 | 0.3 | 0.7 | 0.55 |
| Number of inpatient hospitalizations for any cancer | 0.29 | 0.6 | 0.3 | 0.7 | 0.06 | 0 | 0.6 | 0.4 | 0.7 | 0.10 |
| Number of emergency department visits | 0.31 | 0.8 | 0.2 | 0.6 | 0.11 | 0 | 0.8 | 0.3 | 0.6 | 0.09 |
| **Medication Use (breast cancer related)** | | | | | | | | | | |
| Palbociclib | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Hormone Therapy | 326 | 57.6 | 1285 | 55.5 | 0.04 | 325 | 57.5 | 293 | 51.9 | 0.11 |
| Letrozole | 116 | 20.5 | 429 | 18.5 | 0.05 | 115 | 20.4 | 121 | 21.4 | 0.03 |
| Anastrazole | 136 | 24.0 | 611 | 26.4 | 0.05 | 136 | 24.1 | 128 | 22.7 | 0.03 |
| Exemestane | 86 | 15.2 | 358 | 15.5 | 0.01 | 86 | 15.2 | 74 | 13.1 | 0.06 |
| HER2 positive Therapy | 15 | 2.7 | 127 | 5.5 | 0.14 | 15 | 2.7 | 19 | 3.4 | 0.04 |
| Trastuzumab | 25 | 4.4 | 159 | 6.9 | 0.11 | 25 | 4.4 | 33 | 5.8 | 0.06 |
| Lapatinib | ≤10 | n/a | 16 | 0.7 | 0.05 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Ado-trastuzumab | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Pertuzumab | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Tamoxifen | 140 | 24.7 | 379 | 16.4 | 0.21 | 140 | 24.8 | 125 | 22.1 | 0.06 |
| Fulvestrant | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Denosumab or Pamidronate | 206 | 36.4 | 424 | 18.3 | 0.41 | 205 | 36.3 | 178 | 31.5 | 0.10 |
| Everolimus | 40 | 7.1 | 84 | 3.6 | 0.15 | 40 | 7.1 | 33 | 5.8 | 0.05 |
| **Medication Use (not breast cancer related)** | | | | | | | | | | |
| Anticonvulsants | 126 | 22.3 | 347 | 15.0 | 0.19 | 125 | 22.1 | 115 | 20.4 | 0.04 |
| Antidepressants | 178 | 31.4 | 631 | 27.2 | 0.09 | 177 | 31.3 | 176 | 31.2 | 0.00 |
| Antidiabetics | 67 | 11.8 | 252 | 10.9 | 0.03 | 67 | 11.9 | 75 | 13.3 | 0.04 |
| Antifungals | 28 | 4.9 | 119 | 5.1 | 0.01 | 28 | 5.0 | 35 | 6.2 | 0.05 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Antihypertensives | 173 | 30.6 | 623 | 26.9 | 0.08 | 173 | 30.6 | 179 | 31.7 | 0.02 |
| Antimycobacterials | 109 | 19.3 | 446 | 19.3 | 0.00 | 109 | 19.3 | 120 | 21.2 | 0.05 |
| Antivirals | 32 | 5.7 | 112 | 4.8 | 0.04 | 32 | 5.7 | 33 | 5.8 | 0.01 |
| Corticosteroids | 148 | 26.1 | 416 | 18.0 | 0.20 | 147 | 26.0 | 142 | 25.1 | 0.02 |
| Oral contraceptive use (progestin) | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Oral contraceptive use (combination) | ≤10 | n/a | ≤10 | n/a | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| Oral contraceptive use (unspecified) | ≤10 | n/a | 23 | 1.0 | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| Lipid lowering agent | 132 | 23.3 | 556 | 24.0 | 0.02 | 131 | 23.2 | 137 | 24.2 | 0.02 |
| Vaginal estrogen (local hormone treatment) | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | ≤10 | n/a | n/a |
| Macrolides | ≤10 | n/a | 22 | 0.9 | 0.06 | ≤10 | n/a | ≤10 | n/a | 0.08 |
| Sedatives/hypnotics | 57 | 10.1 | 291 | 12.6 | 0.08 | 57 | 10.2 | 63 | 11.2 | 0.03 |
| Selective estrogen receptor modulators | ≤10 | n/a | ≤10 | n/a | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.08 |
| Unopposed estrogen hormone replacement therapy (HRT) | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | ≤10 | n/a | n/a |
| **Co-morbidities (six months prior to index date)** | | | | | | | | | | |
| Pathologic fracture | 46 | 8.1 | 173 | 7.5 | 0.02 | 46 | 8.1 | 43 | 7.6 | 0.02 |
| Osteoporosis | 56 | 9.9 | 225 | 9.7 | 0.01 | 56 | 9.9 | 41 | 7.3 | 0.09 |
| Uterine malignancies | ≤10 | n/a | 11 | 0.5 | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Pure hypercholesterolemia | 48 | 8.5 | 237 | 10.2 | 0.06 | 48 | 8.5 | 65 | 11.5 | 0.10 |
| Major adverse cardiac events (MACE) | 20 | 3.5 | 83 | 3.6 | 0.00 | 20 | 3.5 | 21 | 3.7 | 0.01 |
| Acute myocardial infarction (MI) | ≤10 | n/a | 23 | 1.0 | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.10 |
| Cerebrovascular disease | 19 | 3.4 | 104 | 4.5 | 0.05 | 19 | 3.4 | 21 | 3.7 | 0.02 |
| Stroke | 16 | 2.8 | 63 | 2.7 | 0.01 | 16 | 2.8 | 16 | 2.8 | 0.00 |
| Diabetes | 67 | 11.8 | 252 | 10.9 | 0.03 | 67 | 11.9 | 75 | 13.3 | 0.04 |
| Hyperglycemia | 27 | 4.8 | 55 | 2.4 | 0.13 | 26 | 4.6 | 19 | 3.4 | 0.06 |
| Deyo-Charlson Index (DCI) | | | | | | | | | | |
| 0-3 | 19 | 3.4 | 259 | 11.2 | 0.30 | 19 | 3.4 | 23 | 4.1 | 0.04 |
| 4-7 | 12 | 2.1 | 57 | 2.5 | 0.02 | 12 | 2.1 | ≤10 | n/a | 0.12 |
| 8-11 | 512 | 90.5 | 1937 | 83.6 | 0.20 | 511 | 90.4 | 517 | 91.5 | 0.04 |
| 12 or more | 23 | 4.1 | 63 | 2.7 | 0.07 | 23 | 4.1 | 20 | 3.5 | 0.03 |
| **ALI related risk factors** | | | | | | | | | | |
| Chronic liver disease or Alcoholism | 74 | 13.1 | 246 | 10.6 | 0.09 | 74 | 13.1 | 69 | 12.2 | 0.03 |
| Chronic or acute hepatitis | ≤10 | n/a | ≤10 | n/a | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| Chronic or acute disease of gallbladder or pancreas | 36 | 6.4 | 145 | 6.3 | 0.01 | 36 | 6.4 | 34 | 6.0 | 0.01 |
| Hepatic, Biliary or pancreatic cancer | 160 | 28.3 | 458 | 19.8 | 0.18 | 160 | 28.3 | 143 | 25.3 | 0.07 |
| Congestive heart failure | 29 | 5.1 | 159 | 6.9 | 0.07 | 29 | 5.1 | 29 | 5.1 | 0.00 |
| **Medications association with liver injury** | | | | | | | | | | |
| **Any medication (of list below)** | 467 | 82.51 | 1749 | 75.52 | 0.17 | 466 | 82.48 | 466 | 82.48 | 0.00 |
| Acarbose | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Acetaminophen (prescription) | 204 | 36.04 | 899 | 38.82 | 0.06 | 204 | 36.11 | 202 | 35.75 | 0.01 |
| Allopurinol | ≤10 | n/a | 19 | 0.82 | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| Amiodarone | ≤10 | n/a | 14 | 0.60 | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| Amitriptyline | ≤10 | n/a | 35 | 1.51 | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Amoxicillin + clavulanic acid | 33 | 5.83 | 116 | 5.01 | 0.04 | 33 | 5.84 | 28 | 4.96 | 0.04 |
| Anabolic steroids | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Aripiprazole | ≤10 | n/a | ≤10 | n/a | 0.07 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Azathioprine | ≤10 | n/a | ≤10 | n/a | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Baclofen | ≤10 | n/a | 16 | 0.69 | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Bupropion | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Captopril | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Carbamazepine | ≤10 | n/a | ≤10 | n/a | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| Chlorpromazine | ≤10 | n/a | ≤10 | n/a | 0.04 | 0 | 0.00 | 0 | 0.00 | n/a |
| Ciprofloxacin | 46 | 8.13 | 238 | 10.28 | 0.07 | 46 | 8.14 | 39 | 6.90 | 0.05 |
| Clindamycin | 23 | 4.06 | 74 | 3.20 | 0.06 | 23 | 4.07 | 25 | 4.42 | 0.02 |
| Clopidogrel | ≤10 | n/a | 57 | 2.46 | 0.06 | ≤10 | n/a | ≤10 | n/a | 0.01 |
| Cyproheptadine | ≤10 | n/a | ≤10 | n/a | 0.05 | 0 | 0.00 | 0 | 0.00 | n/a |
| Duloxetine | 23 | 4.06 | 66 | 2.85 | 0.06 | 23 | 4.07 | 24 | 4.25 | 0.01 |
| Enalapril | ≤10 | n/a | 33 | 1.42 | 0.07 | ≤10 | n/a | ≤10 | n/a | 0.07 |
| Erythromycins | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Estrogens | 63 | 11.13 | 265 | 11.44 | 0.01 | 63 | 11.15 | 63 | 11.15 | 0.00 |
| Fluoxetine | 12 | 2.12 | 47 | 2.03 | 0.01 | 12 | 2.12 | 11 | 1.95 | 0.01 |
| Flutamide | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| HAART drugs | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Irbesartan | ≤10 | n/a | ≤10 | n/a | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Isoniazid | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Ketoconazole | ≤10 | n/a | ≤10 | n/a | 0.07 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| Lamotrigine | ≤10 | n/a | 17 | 0.73 | 0.05 | ≤10 | n/a | ≤10 | n/a | 0.11 |
| Lisinopril | 76 | 13.43 | 237 | 10.23 | 0.10 | 76 | 13.45 | 80 | 14.16 | 0.02 |
| Losartan | 54 | 9.54 | 121 | 5.22 | 0.17 | 54 | 9.56 | 48 | 8.50 | 0.04 |
| Methotrexate | ≤10 | n/a | 14 | 0.60 | 0.07 | ≤10 | n/a | ≤10 | n/a | 0.06 |
| Mirtazapine | ≤10 | n/a | 34 | 1.47 | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Nitrofurantoin | 10 | 1.77 | 71 | 3.07 | 0.08 | ≤10 | n/a | 13 | 2.30 | 0.04 |
| NSAIDs | 129 | 22.79 | 398 | 17.18 | 0.13 | 128 | 22.65 | 124 | 21.95 | 0.02 |
| Omeprazole | 76 | 13.43 | 305 | 13.17 | 0.01 | 76 | 13.45 | 81 | 14.34 | 0.03 |
| Oral contraceptives | ≤10 | n/a | ≤10 | n/a | 0.02 | 0 | 0.00 | 0 | 0.00 | n/a |
| Paroxetine | ≤10 | n/a | 30 | 1.30 | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Phenobarbital | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Phenothiazines | 92 | 16.25 | 276 | 11.92 | 0.12 | 92 | 16.28 | 84 | 14.87 | 0.04 |
| Phenytoin | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | ≤10 | n/a | n/a |
| Pyrazinamide | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Rifampicin | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | ≤10 | n/a | n/a |
| Risperidone | ≤10 | n/a | ≤10 | n/a | 0.02 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Sertraline | 19 | 3.36 | 72 | 3.11 | 0.01 | 19 | 3.36 | 23 | 4.07 | 0.04 |
| Statins | 125 | 22.08 | 502 | 21.68 | 0.01 | 124 | 21.95 | 121 | 21.42 | 0.01 |
| Sulfonamides | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | ≤10 | n/a | n/a |
| Terbinafine | ≤10 | n/a | ≤10 | n/a | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.06 |
| Tetracyclines | 31 | 5.48 | 69 | 2.98 | 0.12 | 31 | 5.49 | 33 | 5.84 | 0.02 |
| Trazodone | 15 | 2.65 | 60 | 2.59 | 0.01 | 15 | 2.65 | 20 | 3.54 | 0.05 |
| Tricyclics | 0 | 0.00 | ≤10 | n/a | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Trimethoprim-sulfamethoxazole | 28 | 4.95 | 123 | 5.31 | 0.00 | 28 | 4.96 | 30 | 5.31 | 0.02 |
| Trovafloxacin | 0 | 0.00 | 0 | 0.00 | n/a | 0 | 0.00 | 0 | 0.00 | n/a |
| Valproic acid | ≤10 | n/a | ≤10 | n/a | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.08 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Verapamil | ≤10 | n/a | 22 | 0.95 | 0.05 | ≤10 | n/a | ≤10 | n/a | 0.00 |

Abbreviations: Feb., February; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; STD, standard deviation; ALI, acute liver injury; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal anti-inflammatory drugs.

*All characteristics are measured as presence within six months prior to the index date, unless otherwise specified.

^The following variables were included in the propensity score: age, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrazole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, Chronic liver disease or Alcoholism, Chronic or acute disease of gallbladder or pancreas, Hepatic, Biliary or pancreatic cancer, Congestive heart failure, any medication associated with ALI- Acetaminophen, Allopurinol, Amiodarone, Amitriptyline, + clavulanic acid, Aripiprazole, Baclofen, Ciprofloxacin, Clindamycin, Clopidogrel, Duloxetine, Estrogens, Fluoxetine, Ketoconazole, Lisinopril, Losartan, Mirtazapine, Nitrofurantoin, NSAIDs, Omeprazole, Paroxetine, Phenothiazine, Sertraline, Statins, Tetracycline, Trazodone, and Trimethoprim.

*Return to Table of Contents*

**Table 1-8A.** Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group)

| | Before Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All new users of palbociclib and fulvestrant (N=566) | | | | | All new users of fulvestrant alone (pre-2015) (N=2,316) | | | | | Unadjusted Hazard Ratios | | |
| Event | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | | HR | 95% LCL | 95%UCL |
| | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI | | | |
| **Overall** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | 13 | 323 | 4.0 | 2.1 | 6.9 | 22 | 1,686 | 1.3 | 0.8 | 2.0 | 2.8 | 1.4 | 5.6 |
| Acute liver injury (original with labs algorithm) | 13 | 323 | 4.0 | 2.1 | 6.9 | 20 | 1,685 | 1.2 | 0.7 | 1.8 | 3.1 | 1.5 | 6.2 |
| Acute liver injury (sensitive algorithm) | 39 | 317 | 12.3 | 8.7 | 16.8 | 35 | 1,682 | 2.1 | 1.5 | 2.9 | 5.4 | 3.4 | 8.5 |
| Acute liver injury (specific algorithm) | 0 | 324 | 0 | . | 1.1 | 0 | 1,689 | 0 | . | 0.2 | -- | -- | -- |
| **Among patients with a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | 11 | 188 | 5.8 | 2.9 | 10.5 | 19 | 912 | 2.1 | 1.3 | 3.3 | 2.6 | 1.2 | 5.5 |
| **Among patients without a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 1.5 | 0.2 | 5.4 | ≤10 | n/a | 0.4 | 0.1 | 1.1 | 3.5 | 0.6 | 20.9 |
| **Stratified by amount of follow-up-time (primary algorithm)** | | | | | | | | | | | | | |
| Acute liver injury - ≤5.9 months of follow-up | ≤10 | n/a | 4.8 | 2.3 | 8.8 | 17 | n/a | 2.0 | 1.2 | 3.2 | 2.4 | 1.1 | 5.3 |
| Acute liver injury - 6 to 11.9 months of follow-up | ≤10 | n/a | 3.9 | 0.8 | 11.2 | ≤10 | n/a | 0.8 | 0.2 | 2.3 | 4.7 | 0.9 | 23.2 |
| Acute liver injury - ≥12 months of follow-up | 0 | 35 | 0 | 0.0 | . | ≤10 | n/a | 0.4 | 0.1 | 1.6 | -- | -- | --- |
| **Restricting to confirmed cases** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 0.9 | 0.2 | 2.7 | ≤10 | n/a | 0.4 | 0.2 | 0.7 | 2.6 | 0.4 | 12.2 |
| Acute liver injury (original with labs algorithm) | ≤10 | n/a | 0.9 | 0.2 | 2.7 | ≤10 | n/a | 0.3 | 0.1 | 0.7 | 3.1 | 0.5 | 16.1 |
| Acute liver injury (sensitive algorithm) | ≤10 | n/a | 1.6 | 0.5 | 3.6 | ≤10 | n/a | 0.4 | 0.2 | 0.8 | 3.0 | 0.6 | 11.7 |
| Acute liver injury (specific algorithm) | 0 | 324 | 0.0 | . | 1.1 | 0 | 1,689 | 0.0 | . | 0.2 | -- | -- | -- |
| **Confirmed cases and PPV adjusted results^** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm)^ | ≤10 | n/a | 3.0 | 1.5 | 5.4 | 16.5 | 1,686 | 1.0 | 0.6 | 1.5 | 2.8 | 1.4 | 5.6 |
| Acute liver injury (original with labs algorithm)^ | 12.0 | 323 | 3.7 | 2.0 | 6.3 | 11.4 | 1,685 | 0.7 | 0.4 | 1.2 | 1.8 | 0.9 | 3.6 |
| Acute liver injury (sensitive algorithm)^ | 27.7 | 322 | 8.6 | 5.8 | 12.3 | 22.4 | 1,682 | 1.3 | 0.9 | 2.0 | 4.9 | 3.1 | 7.7 |
| Acute liver injury (specific algorithm)^ | 0 | 324 | 0 | . | 1.1 | 0 | 1,689 | 0 | . | 0.2 | -- | -- | -- |

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure, or prescription acetaminophen use.

^Assuming 100% sensitivity for each algorithm

Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; HR, hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury

**Table 1-8B.** Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group)

| | After Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib and fulvestrant (N=565) | | | | | New users of fulvestrant alone (pre-2015) (N=565) | | | | | Adjusted Hazard Ratios[&] | | |
| Event | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | | aHR | 95% LCL | 95%UCL |
| | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI | | | |
| **Overall** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | 13 | 322 | 4.0 | 2.2 | 6.9 | ≤10 | n/a | 1.2 | 0.4 | 2.9 | 3.0 | 1.1 | 8.4 |
| Acute liver injury (original with labs algorithm) | 13 | 322 | 4.0 | 2.2 | 6.9 | ≤10 | n/a | 1.7 | 0.7 | 3.6 | 2.2 | 0.9 | 5.4 |
| Acute liver injury (sensitive algorithm) | 39 | 317 | 12.3 | 8.8 | 16.8 | ≤10 | n/a | 2.5 | 1.2 | 4.6 | 4.6 | 2.3 | 9.1 |
| Acute liver injury (specific algorithm) | 0 | 323 | 0 | . | 1.1 | 0 | 402 | 0 | . | 0.9 | -- | -- | -- |
| **Among patients with a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | 11 | 188 | 5.8 | 2.9 | 10.5 | ≤10 | n/a | 2.5 | 0.8 | 5.8 | 2.3 | 0.8 | 6.5 |
| **Among patients without a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 1.5 | 0.2 | 5.4 | 0 | n/a | 0 | . | 1.9 | -- | -- | -- |
| **Stratified by amount of follow-up-time (primary algorithm)** | | | | | | | | | | | | | |
| Acute liver injury - ≤5.9 months of follow-up | ≤10 | n/a | 4.8 | 2.3 | 8.8 | ≤10 | n/a | 2.4 | 0.8 | 5.5 | 2.0 | 0.7 | 5.8 |
| Acute liver injury - 6 to 11.9 months of follow-up | ≤10 | n/a | 3.8 | 0.8 | 11.2 | 0 | 90 | 0.0 | 0.0 | 4.1 | --- | --- | -- |
| Acute liver injury - ≥12 months of follow-up | 0 | 35 | 0.0 | 0.0 | . | 0 | 100 | 0.0 | 0.0 | 3.7 | --- | --- | --- |
| **Restricting to confirmed cases** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 0.9 | 0.2 | 2.7 | ≤10 | n/a | 0.2 | 0.0 | 1.2 | 3.7 | 0.3 | 196.1 |
| Acute liver injury (original with labs algorithm) | ≤10 | n/a | 0.9 | 0.2 | 2.7 | ≤10 | n/a | 0.2 | 0.0 | 1.2 | 3.7 | 0.3 | 196.1 |
| Acute liver injury (sensitive algorithm) | ≤10 | n/a | 1.6 | 0.5 | 3.6 | ≤10 | n/a | 0.3 | 0.0 | 1.2 | 6.2 | 0.7 | 294.0 |
| Acute liver injury (specific algorithm) | 0 | 323 | 0 | 0 | 0 | 0 | 402 | 0.0 | 0.0 | 0.9 | 0 | 0 | 0 |
| **Confirmed cases and PPV adjusted results** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm)^ | ≤10 | n/a | 3.0 | 1.5 | 5.4 | ≤10 | n/a | 1.2 | 0.5 | 2.7 | 4.0 | 1.4 | 11.2 |
| Acute liver injury (original with labs algorithm)^ | 12.0 | 322 | 3.7 | 2.0 | 6.3 | ≤10 | n/a | 0.6 | 0.1 | 1.7 | 0.7 | 0.3 | 1.8 |
| Acute liver injury (sensitive algorithm)^ | 27.7 | 321 | 8.6 | 5.9 | 12.3 | ≤10 | n/a | 0.8 | 0.3 | 2.1 | 2.1 | 1.1 | 4.3 |
| Acute liver injury (specific algorithm)^ | 0 | 323 | 0 | . | 1.1 | 0 | 402 | 0 | 0 | 0.6 | -- | -- | -- |

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure, or prescription acetaminophen use.

^Assuming 100% sensitivity for each algorithm

[&]The following variables were included in the propensity score: age, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrazole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, Chronic liver disease or Alcoholism, Chronic or acute disease of gallbladder or pancreas, Hepatic, Biliary or pancreatic cancer, Congestive heart failure, any medication associated with ALI- Acetaminophen, Allopurinol, Amiodarone, Amitriptyline, + clavulanic acid, Aripiprazole, Baclofen, Ciprofloxacin, Clindamycin, Clopidogrel, Duloxetine, Estrogens, Fluoxetine, Ketoconazole, Lisinopril, Losartan, Mirtazapine, Nitrofurantoin, NSAIDs, Omeprazole, Paroxetine, Phenothiazine, Sertraline, Statins, Tetracycline, Trazodone, and Trimethoprim.

Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury; PPV, positive predictive value

*Return to Table of Contents*

**Table 1-8C** Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (contemporaneous comparison)

| | Before Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All new users of palbociclib and fulvestrant (N=566) | | | | | All new users of fulvestrant alone (2015 or later) (N=961) | | | | | Unadjusted Hazard Ratios | | |
| | | | IR (per 100 person-years) | | | | | IR (per 100 person-years) | | | | | |
| Event | # Events | PT at risk | IR | 95% Lower CI | 95% Upper CI | # Events | PT at risk | IR | 95% Lower CI | 95% Upper CI | HR | 95% LCL | 95%UCL |
| **Overall** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | 13 | 323 | 4.0 | 2.1 | 6.9 | 11 | 553 | 2.0 | 1.0 | 3.6 | 2.1 | 0.9 | 4.7 |
| Acute liver injury (original with labs algorithm) | 13 | 323 | 4.0 | 2.1 | 6.9 | 16 | 550 | 2.9 | 1.7 | 4.7 | 1.5 | 0.7 | 3.0 |
| Acute liver injury (sensitive algorithm) | 39 | 317 | 12.3 | 8.7 | 16.8 | 29 | 549 | 5.3 | 3.5 | 7.6 | 2.3 | 1.4 | 3.8 |
| Acute liver injury (specific algorithm) | 0 | 324 | 0 | . | 1.1 | 0 | 553 | 0 | . | 0.7 | -- | -- | -- |
| **Among patients with a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary) | 11 | 188 | 5.8 | 2.9 | 10.5 | ≤10 | n/a | 3.2 | 1.5 | 6.1 | 1.9 | 0.8 | 4.6 |
| **n** | | | | | | | | | | | | | |
| Acute liver injury (primary) | ≤10 | n/a | 1.5 | 0.2 | 5.4 | ≤10 | n/a | 0.7 | 0.1 | 2.7 | 2.2 | 0.3 | 15.4 |
| **Stratified by amount of follow-up-time (primary algorithm)** | | | | | | | | | | | | | |
| Acute liver injury - ≤5.9 months of follow-up | ≤10 | n/a | 4.8 | 2.3 | 8.8 | ≤10 | n/a | 3.1 | 1.5 | 5.6 | 1.6 | 0.7 | 3.9 |
| Acute liver injury - 6 to 11.9 months of follow-up | ≤10 | n/a | 3.9 | 0.8 | 11.2 | ≤10 | n/a | 0.8 | 0.0 | 4.3 | 4.9 | 0.5 | 47.0 |
| Acute liver injury - ≥12 months of follow-up | 0 | 35 | 0.0 | 0.0 | . | 0 | 96 | 0.0 | 0.0 | . | --- | --- | --- |
| **Restricting to confirmed cases** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 0.9 | 0.2 | 2.7 | ≤10 | n/a | 0.7 | 0.2 | 1.9 | 1.3 | 0.3 | 5.7 |
| Acute liver injury (original with labs algorithm) | ≤10 | n/a | 0.9 | 0.2 | 2.7 | ≤10 | n/a | 0.9 | 0.3 | 2.1 | 1.0 | 0.2 | 4.3 |
| Acute liver injury (sensitive algorithm) | ≤10 | n/a | 1.6 | 0.5 | 3.6 | ≤10 | n/a | 0.9 | 0.3 | 2.1 | 1.7 | 0.5 | 5.9 |
| Acute liver injury (specific algorithm) | 0 | 324 | 0 | 0 | 0 | 0 | 554 | 0 | . | 0.7 | -- | -- | -- |
| **Confirmed cases and PPV adjusted results** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm)^ | ≤10 | n/a | 3.0 | 1.5 | 5.4 | 11 | 554 | 2.0 | 1.1 | 3.4 | 2.8 | 1.3 | 6.3 |
| Acute liver injury (original with labs algorithm)^ | 12.0 | 323 | 3.7 | 2.0 | 6.3 | 16 | 553 | 2.9 | 1.7 | 5 | 1.5 | 0.7 | 3.0 |
| Acute liver injury (sensitive algorithm)^ | 27.7 | 322 | 8.6 | 5.8 | 12.3 | 29 | 553 | 5.2 | 3.6 | 7.4 | 3.3 | 2.0 | 5.3 |
| Acute liver injury (specific algorithm)^ | 0 | 324 | 0 | . | 1.1 | 0 | 553 | 0 | . | 0.7 | -- | -- | -- |

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure, or prescription acetaminophen use

^Assuming 100% sensitivity

Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; HR, hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury.

**Table 1-8D** Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (contemporaneous comparison)

| | After Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib and fulvestrant (N=292) | | | | | New users of fulvestrant alone (2015 or later) (N=292) | | | | | Adjusted Hazard Ratios[&] | | |
| | | | IR (per 100 person-years) | | | | | IR (per 100 person-years) | | | | | |
| Event | # Events | PT at risk | IR | 95% Lower CI | 95% Upper CI | # Events | PT at risk | IR | 95% Lower CI | 95% Upper CI | aHR | 95% LCL | 95%UCL |
| **Overall** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 1.6 | 0.3 | 4.7 | ≤10 | n/a | 3.6 | 1.2 | 8.4 | 0.5 | 0.1 | 2.2 |
| Acute liver injury (original with labs algorithm) | ≤10 | n/a | 2.7 | 0.9 | 6.3 | ≤10 | n/a | 4.3 | 1.6 | 9.5 | 0.7 | 0.2 | 2.4 |
| Acute liver injury (sensitive algorithm) | 18 | 183 | 9.8 | 5.8 | 15.5 | 12 | n/a | 8.7 | 4.5 | 15.2 | 1.2 | 0.6 | 2.5 |
| Acute liver injury (specific algorithm) | 0 | 186 | 0 | . | 2.0 | 0 | 139 | 0 | . | 2.7 | -- | -- | -- |
| **Among patients with a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 2.1 | 0.3 | 7.5 | ≤10 | n/a | 5.3 | 1.5 | 13.6 | 0.5 | 0.1 | 2.5 |
| **Among patients without a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 1.1 | 0 | 6.2 | ≤10 | n/a | 1.6 | 0 | 8.8 | 0.8 | 0 | 13.4 |
| **Stratified by amount of follow-up-time (primary algorithm)** | | | | | | | | | | | | | |
| Acute liver injury - ≤5.9 months of follow-up | ≤10 | n/a | 1.8 | 0.2 | 6.4 | ≤10 | n/a | 4.5 | 1.2 | 11.4 | 0.4 | 0.1 | 2.3 |
| Acute liver injury - 6 to 11.9 months of follow-up | ≤10 | n/a | 2.1 | 0.1 | 11.6 | ≤10 | n/a | 3.5 | 0.1 | 19.4 | 0.7 | 0.0 | 10.8 |
| Acute liver injury - ≥12 months of follow-up | 0 | 26 | 0.0 | 0.0 | 0.0 | 0 | 20 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Restricting to confirmed cases** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm) | ≤10 | n/a | 0.5 | 0.0 | 3.0 | ≤10 | n/a | 0.7 | 0 | 4.0 | 0.8 | 0.1 | 58.7 |
| Acute liver injury (original with labs algorithm) | ≤10 | n/a | 0.5 | 0.0 | 3.0 | ≤10 | n/a | 1.4 | 0.2 | 5.2 | 0.4 | 0 | 7.1 |
| Acute liver injury (sensitive algorithm) | ≤10 | n/a | 1.1 | 0.1 | 3.9 | ≤10 | n/a | 1.4 | 0.2 | 5.2 | 0.7 | 0.1 | 10.2 |
| Acute liver injury (specific algorithm) | 0 | 186 | 0 | . | 2.0 | 0 | 139 | 0 | . | 2.7 | -- | -- | -- |
| **Confirmed cases and PPV adjusted results** | | | | | | | | | | | | | |
| Acute liver injury (primary algorithm)^ | ≤10 | n/a | 3.0 | 1.5 | 5.4 | ≤10 | n/a | 3.6 | 1.2 | 8.4 | 0.5 | 0.1 | 2.2 |
| Acute liver injury (original with labs algorithm)^ | ≤10 | n/a | 3.7 | 2.0 | 6.3 | ≤10 | n/a | 4.3 | 1.6 | 9.5 | 0.7 | 0.2 | 2.4 |
| Acute liver injury (sensitive algorithm)^ | 18 | 322 | 8.6 | 5.8 | 12.3 | 12 | 138 | 8.7 | 4.5 | 15.2 | 1.2 | 0.6 | 2.5 |
| Acute liver injury (specific algorithm)^ | 0 | 324 | 0 | . | 1.1 | 0 | 139 | 0 | . | 2.7 | -- | -- | -- |

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart failure, or prescription acetaminophen use

^Assuming 100% sensitivity

[&]The following variables were included in the propensity score: age, calendar year of index date, region, Deyo-Charlson Index, number of outpatient visits, number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrazole, denosumab or pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, cerebrovascular disease, Chronic liver disease or Alcoholism, Chronic or acute disease of gallbladder or pancreas, Hepatic, Biliary or pancreatic cancer, Congestive heart failure, any medication associated with ALI- Acetaminophen, Allopurinol, Amiodarone, Amitriptyline, + clavulanic acid, Aripiprazole, Baclofen, Ciprofloxacin, Clindamycin, Clopidogrel, Duloxetine, Estrogens, Fluoxetine, Ketoconazole, Lisinopril, Losartan, Mirtazapine, Nitrofurantoin, NSAIDs, Omeprazole, Paroxetine, Phenothiazine, Sertraline, Statins, Tetracycline, Trazodone, and Trimethoprim

Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury; PPV, positive predictive value.

*Return to Table of Contents*

**Table 1-9** Positive Predictive Values of All Diagnosis Codes and Combinations of Codes for Adjudicated Cases of ALI

| Code or Combination of Codes | Number of provisional cases identified by algorithm | Number of provisional case with collected medical record | Number of Confirmed Cases and Non-cases | Number of Confirmed Cases | PPV (95% CI) | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Acute Liver Injury - All adjudication results** | | | | | | | |
| **Algorithm 1 (primary algorithm)** | ---- | 29 | 25 | 21 | 0.84 | 0.64 | 0.95 |
| **Algorithm 2 (original with labs algorithm)** | ---- | 29 | 25 | 18 | 0.72 | 0.51 | 0.88 |
| **Algorithm 3 (sensitive algorithm)** | ---- | 52 | 40 | 29 | 0.73 | 0.56 | 0.85 |
| **Algorithm 4 (specific algorithm)** | ---- | ≤10 | 0 | 0 | 0.00 | 0.00 | --- |
| | | | | | | | |
| **Algorithm 1 (primary algorithm)** | 70 | 20 | 17 | 14 | 0.84 | 0.64 | 0.95 |
| Subsets of codes (Individual codes with counts >10) | | | | | | | |
| Most common code - K76.89 (Other specified diseases of liver) | 59 | --- | ≤10 | ≤10 | 1.00 | 0.29 | 1.00 |
| Second most common code - K72.90 (Hepatic failure, unspecified without coma) | 59 | --- | 19 | 19 | 1.00 | 0.82 | 1.00 |
| Algorithm 1 (Palbociclib index use) | 37 | ≤10 | ≤10 | ≤10 | 0.80 | 0.28 | 0.99 |
| **Algorithm 1 (Palbociclib with fulvestrant)** | **13** | **≤10** | **≤10** | **≤10** | **0.75** | **0.19** | **0.99** |
| Algorithm 1 (Palbociclib with letrozole) | 14 | ≤10 | ≤10 | ≤10 | 1.00 | 0.03 | 1.00 |
| Algorithm 1 (Other palbociclib) | ≤10 | 0 | 0 | 0 | --- | 0.00 | 0.00 |
| Algorithm 1 (Fulvestrant index use) | 33 | 13 | 12 | ≤10 | 0.83 | 0.52 | 0.98 |
| **Algorithm 1 (Fulvestrant - historical)** | **22** | **≤10** | **≤10** | **≤10** | **0.75** | **0.35** | **0.97** |
| **Algorithm 1 (Fulvestrant - contemporaneous)** | **11** | **≤10** | **≤10** | **≤10** | **1.00** | **0.40** | **1.00** |
| Algorithm 1 - assuming all provisional cases after palbociclib are negative | 37 | ≤10 | ≤10 | ≤10 | 0.57 | 0.18 | 0.90 |
| Algorithm 1 - assuming all provisional cases after palbociclib are positive | 37 | ≤10 | ≤10 | ≤10 | 0.86 | 0.42 | 1.00 |
| **Algorithm 2 (original with labs algorithm)** | 83 | 20 | 17 | 12 | 0.71 | 0.44 | 0.90 |
| Algorithm 2 (Palbociclib index use) | 47 | ≤10 | ≤10 | ≤10 | 0.60 | 0.15 | 0.95 |
| **Algorithm 2 (Palbociclib with fulvestrant)** | **13** | **≤10** | **≤10** | **≤10** | **1.00** | **0.29** | **1.00** |
| Algorithm 2 (Palbociclib with letrozole) | 22 | ≤10 | ≤10 | 0 | 0.00 | 0.00 | 0.98 |
| Algorithm 2 (Other palbociclib) | 12 | ≤10 | ≤10 | 0 | 0.00 | 0.00 | 0.98 |
| Algorithm 2 (Fulvestrant index use) | 36 | 12 | 12 | ≤10 | 0.75 | 0.43 | 0.95 |
| **Algorithm 2 (Fulvestrant - historical)** | **20** | **≤10** | **≤10** | **≤10** | **0.57** | **0.18** | **0.90** |
| **Algorithm 2 (Fulvestrant - contemporaneous)** | **16** | **≤10** | **≤10** | **≤10** | **1.00** | **0.48** | **1.00** |
| Algorithm 2 - assuming all provisional cases after palbociclib are negative | 47 | ≤10 | ≤10 | ≤10 | 0.38 | 0.09 | 0.76 |
| Algorithm 2 - assuming all provisional cases after palbociclib are positive | 47 | ≤10 | ≤10 | ≤10 | 0.75 | 0.35 | 0.97 |
| **Algorithm 3 (sensitive algorithm)** | 185 | 39 | 28 | 20 | 0.71 | 0.51 | 0.87 |
| Algorithm 3 (Palbociclib index use) | 121 | 21 | 12 | ≤10 | 0.67 | 0.35 | 0.90 |
| **Algorithm 3 (Palbociclib with fulvestrant)** | **39** | **14** | **≤10** | **≤10** | **0.71** | **0.29** | **0.96** |
| Algorithm 3 (Palbociclib with letrozole) | 54 | ≤10 | ≤10 | ≤10 | 0.67 | 0.09 | 0.99 |
| Algorithm 3 (Other palbociclib) | 28 | ≤10 | ≤10 | ≤10 | 0.50 | 0.01 | 0.99 |
| Algorithm 3 (Fulvestrant index use) | 64 | 18 | 16 | 12 | 0.75 | 0.48 | 0.93 |
| **Algorithm 3 (Fulvestrant - historical)** | **35** | **12** | **11** | **≤10** | **0.64** | **0.31** | **0.89** |
| **Algorithm 3 (Fulvestrant - contemporaneous)** | **29** | **≤10** | **≤10** | **≤10** | **1.00** | **0.48** | **1.00** |
| Algorithm 3 - assuming all provisional cases after palbociclib are negative | 121 | **≤10** | 21 | ≤10 | 0.38 | 0.18 | 0.62 |
| Algorithm 3 - assuming all provisional cases after palbociclib are positive | 121 | 21 | 21 | 17 | 0.81 | 0.58 | 0.95 |
| **Algorithm 4 (specific algorithm)** | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 (Palbociclib index use) | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 (Palbociclib with fulvestrant) | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 (Palbociclib with letrozole) | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 (Other palbociclib) | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 (Fulvestrant index use) | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 (Fulvestrant - historical) | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 (Fulvestrant - contemporaneous) | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 - assuming all provisional cases after palbociclib are negative | 0 | 0 | 0 | 0 | ---- | ---- | ---- |
| Algorithm 4 - assuming all provisional cases after palbociclib are positive | 0 | 0 | 0 | 0 | ---- | ---- | ---- |

Abbreviations: ALI, acute liver injury; PPV, positive predictive value; CI, confidence interval.

*Return to Table of Contents*

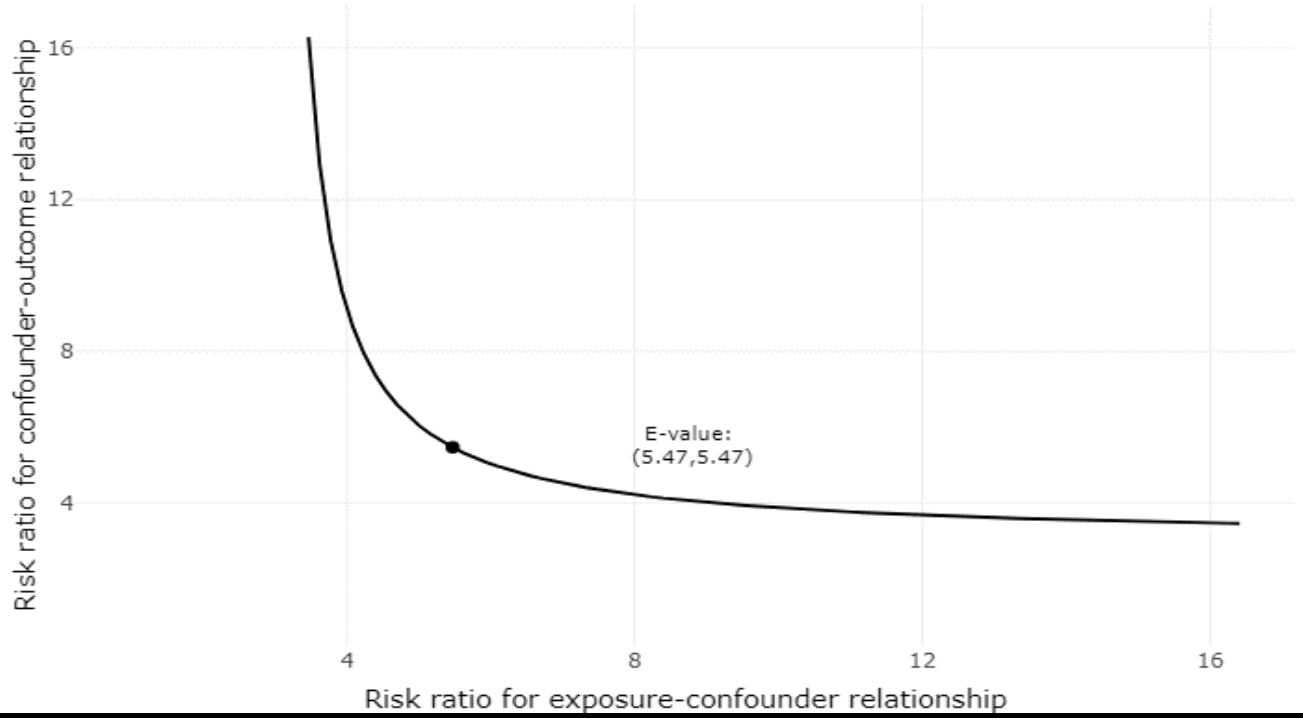
**Table 1-10** Incidence of ALI between April 2014 and March 2017

| Event | April 2014 to December 2014 | | | January 2015 to September 2015 | | | October 2015 to June 2016 | | | July 2016 to March 2017 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IR (per 100 person-years) | | | IR (per 100 person-years) | | | IR (per 100 person-years) | | | IR (per 100 person-years) | | |
| | IR | 95% Lower CI | 95% Upper CI | IR | 95% Lower CI | 95% Upper CI | IR | 95% Lower CI | 95% Upper CI | IR | 95% Lower CI | 95% Upper CI |
| **Overall - All HIRD** | | | | | | | | | | | | |
| Acute liver injury (primary) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| **Palbociclib users** | | | | | | | | | | | | |
| Acute liver injury (primary) | . | . | . | 0 | 0 | 31.1 | 28.4 | 3.4 | 102.5 | 37.9 | 12.3 | 88.5 |
| **Fulvestrant only users** | | | | | | | | | | | | |
| Acute liver injury (primary) | 10.8 | 2.2 | 31.5 | 32.09 | 10.73 | 76.29 | 27.7 | 9.0 | 64.7 | 10.7 | 1.3 | 38.5 |

Abbreviations: ALI, acute liver injury; IR, incidence rate; CI, confidence interval; HIRD, HealthCore Integrated Research Database.

*Return to Table of Contents*

**Figure 4. E-value to explain away the association between palbociclib and the primary ALI algorithm***




*Minimum strength required for both the palbociclib-confounder and confounder-ALI relationships to explain away the estimated relationship between palbociclib and ALI. The E-value for the 95% CI to remain significant is 1.34
Abbreviations: ALI, acute liver injury; CI, confidence interval.

*Return to Table of Contents*

**Table 2.1.** Characteristics of advanced stage ER+/HER2- breast cancer patients utilizing palbociclib identified in the HIRD **[Secondary Objective 2]**

| Characteristics | All new users of Palbociclib | | New users of palbociclib with fulvestrant | | New users of palbociclib with letrozole | | All other new users of palbociclib (no new use of fulvestrant or letrozole) | |
|---|---|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD |
| **Overall** | **2,285** | **1.0** | **548** | **1.0** | **1,083** | **1.0** | **654** | **1.0** |
| | | | | | | | | |
| **Demographics** | | | | | | | | |
| Age at index date (in years) | 59.9 | 11.6 | 59.6 | 11.3 | 59.2 | 11.3 | 61.2 | 12.3 |
| Age (years) | | | | | | | | |
| <45 | 207 | 9.1 | 47 | 8.6 | 110 | 10.2 | 50 | 7.6 |
| 45-64 | 1391 | 60.9 | 352 | 64.2 | 671 | 62.0 | 368 | 56.3 |
| 65+ | 687 | 30.1 | 149 | 27.2 | 302 | 27.9 | 236 | 36.1 |
| Gender | | | | | | | | |
| Male | 44 | 1.9 | ≤10 | n/a | 12 | 1.1 | 23 | 3.5 |
| Female | 2241 | 98.1 | 539 | 98.4 | 1071 | 98.9 | 631 | 96.5 |
| Calendar year of index date | | | | | | | | |
| 2015 | 746 | 32.6 | 97 | 17.7 | 425 | 39.2 | 224 | 34.3 |
| 2016 | 881 | 38.6 | 260 | 47.4 | 381 | 35.2 | 240 | 36.7 |
| 2017 | 658 | 28.8 | 191 | 34.9 | 277 | 25.6 | 190 | 29.1 |
| Geographic region of residence | | | | | | | | |
| Midwest | 378 | 16.5 | 93 | 17.0 | 175 | 16.2 | 110 | 16.8 |
| South | 545 | 23.9 | 154 | 28.1 | 267 | 24.7 | 124 | 19.0 |
| Northeast | 654 | 28.6 | 159 | 29.0 | 318 | 29.4 | 177 | 27.1 |
| West | 708 | 31.0 | 142 | 25.9 | 323 | 29.8 | 243 | 37.2 |
| Duration of health plan enrollment prior to index date (years) | 3.43 | 2.1 | 3.43 | 2.1 | 3.22 | 2.0 | 3.77 | 2.0 |
| **Medical History** | | | | | | | | |
| Other primary cancer prior to first breast cancer diagnosis code | 985 | 43.1 | 216 | 39.4 | 498 | 46.0 | 271 | 41.4 |
| Secondary malignancy (metastasis) | 2032 | 88.9 | 481 | 87.8 | 990 | 91.4 | 561 | 85.8 |
| Lymph nodes of head, face, and neck | 634 | 27.7 | 149 | 27.2 | 324 | 29.9 | 161 | 24.6 |
| Respiratory and digestive systems | 1007 | 44.1 | 251 | 45.8 | 465 | 42.9 | 291 | 44.5 |
| Other specified sites | 1943 | 85.0 | 448 | 81.8 | 947 | 87.4 | 548 | 83.8 |
| Deyo-Charlson comorbidity index (DCI) without cancer codes | 8.45 | 1.8 | 8.52 | 1.8 | 8.53 | 1.6 | 8.26 | 2.1 |
| Secondary malignant neoplasm of breast | 255 | 11.2 | 64 | 11.7 | 121 | 11.2 | 70 | 10.7 |
| Breast cancer (female) diagnosis code | 2225 | 97.4 | 540 | 98.5 | 1065 | 98.3 | 620 | 94.8 |
| InSitu breast cancer | 193 | 8.4 | 44 | 8.0 | 112 | 10.3 | 37 | 5.7 |
| **Cancer Therapy History** | | | | | | | | |
| **Radiation therapy** | 455 | 19.9 | 108 | 19.7 | 224 | 20.7 | 123 | 18.8 |
| External Beam | 455 | 19.9 | 108 | 19.7 | 224 | 20.7 | 123 | 18.8 |
| **Surgery** | 78 | 3.4 | 11 | 2.0 | 52 | 4.8 | 15 | 2.3 |
| Mastectomy in the last six months | 28 | 1.2 | ≤10 | n/a | 22 | 2.0 | ≤10 | n/a |
| Lumpectomy in the last six months | 31 | 1.4 | ≤10 | n/a | 21 | 1.9 | ≤10 | n/a |
| Radical mastectomy in the last six months | 37 | 1.6 | ≤10 | n/a | 23 | 2.1 | ≤10 | n/a |
| **Chemotherapy** | 437 | 19.1 | 95 | 17.3 | 201 | 18.6 | 141 | 21.6 |
| Infusion based chemo (procedure) | 12 | 0.5 | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| **Imaging** | | | | | | | | |
| CT related imaging in the last six months | 563 | 24.6 | 131 | 23.9 | 316 | 29.2 | 116 | 17.7 |
| MR related imaging for needle placement | ≤10 | n/a | 0 | 0.0 | ≤10 | 0.1 | n/a | . |
| Diagnostic imaging in the last six months | 358 | 15.7 | 70 | 12.8 | 230 | 21.2 | 58 | 8.9 |
| Mammography | 48 | 2.1 | ≤10 | n/a | 33 | 3.0 | ≤10 | n/a |
| MRI related imaging | 148 | 6.5 | 24 | 4.4 | 102 | 9.4 | 22 | 3.4 |
| Tomosynthesis (3D mammography) | 58 | 2.5 | 18 | 3.3 | 31 | 2.9 | ≤10 | n/a |
| **Healthcare Utilization** | | | | | | | | |
| Number of outpatient visits | 39.6 | 25.3 | 38.3 | 23.8 | 39.5 | 23.8 | 41.0 | 28.4 |
| Number of outpatient visits to an oncologist | 0.0 | 0.2 | 0.02 | 0.2 | 0.0 | 0.3 | 0.0 | 0.1 |
| Number of inpatient hospitalizations | 0.3 | 0.7 | 0.33 | 0.7 | 0.3 | 0.6 | 0.3 | 0.8 |
| Number of inpatient hospitalizations for breast cancer | 0.1 | 0.3 | 0.03 | 0.2 | 0.1 | 0.4 | 0.1 | 0.4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Number of inpatient hospitalizations for any cancer | 0.3 | 0.7 | 0.29 | 0.6 | 0.3 | 0.6 | 0.3 | 0.8 |
| Number of emergency department visits | 0.3 | 0.7 | 0.31 | 0.8 | 0.3 | 0.6 | 0.2 | 0.6 |
| **Medication Use (breast cancer related)** | | | | | | | | |
| Palbociclib | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Aromatase inhibitor | 1440 | 63.0 | 316 | 57.7 | 772 | 71.3 | 352 | 53.8 |
| Letrozole | 964 | 42.2 | 112 | 20.4 | 663 | 61.2 | 189 | 28.9 |
| Anastrazole | 368 | 16.1 | 133 | 24.3 | 137 | 12.7 | 98 | 15.0 |
| Exemestane | 270 | 11.8 | 82 | 15.0 | 92 | 8.5 | 96 | 14.7 |
| HER2 positive therapy | 24 | 1.1 | ≤10 | n/a | 12 | 1.1 | ≤10 | n/a |
| Trastuzumab | 24 | 1.1 | ≤10 | n/a | 11 | 1.0 | ≤10 | n/a |
| Lapatinib | ≤10 | n/a | ≤10 | n/a | 0 | 0.0 | 0 | 0.0 |
| Ado-trastuzumab | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Pertuzumab | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Tamoxifen | 531 | 23.2 | 137 | 25.0 | 262 | 24.2 | 132 | 20.2 |
| Fulvestrant | 601 | 26.3 | 234 | 42.7 | 109 | 10.1 | 258 | 39.4 |
| Denosumab or Pamidronate | 806 | 35.3 | 196 | 35.8 | 348 | 32.1 | 262 | 40.1 |
| Everolimus | 144 | 6.3 | 39 | 7.1 | 51 | 4.7 | 54 | 8.3 |
| **Medication Use (not breast cancer related)** | | | | | | | | |
| Anticonvulsants | 431 | 18.9 | 120 | 21.9 | 184 | 17.0 | 127 | 19.4 |
| Antidepressants | 696 | 30.5 | 169 | 30.8 | 328 | 30.3 | 199 | 30.4 |
| Antidiabetics | 269 | 11.8 | 64 | 11.7 | 126 | 11.6 | 79 | 12.1 |
| Antifungals | 116 | 5.1 | 27 | 4.9 | 61 | 5.6 | 28 | 4.3 |
| Antihypertensives | 606 | 26.5 | 168 | 30.7 | 273 | 25.2 | 165 | 25.2 |
| Antimycobacterials | 460 | 20.1 | 104 | 19.0 | 213 | 19.7 | 143 | 21.9 |
| Antivirals | 121 | 5.3 | 29 | 5.3 | 63 | 5.8 | 29 | 4.4 |
| Corticosteroids | 563 | 24.6 | 137 | 25.0 | 288 | 26.6 | 138 | 21.1 |
| Oral contraceptive use (progestin) | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a | 0 | 0.0 |
| Oral contraceptive use (combination) | ≤10 | n/a | ≤10 | 0.2 | ≤10 | n/a | ≤10 | n/a |
| Oral contraceptive use (unspecified) | 24 | 1.1 | ≤10 | 1.3 | 13 | 1.2 | ≤10 | n/a |
| Lipid lowering agent | 489 | 21.4 | 129 | 23.5 | 231 | 21.3 | 129 | 19.7 |
| Vaginal estrogen (local hormone treatment) | ≤10 | n/a | 0 | 0.0 | ≤10 | n/a | ≤10 | n/a |
| Macrolides | 21 | 0.9 | ≤10 | 1.6 | ≤10 | n/a | ≤10 | n/a |
| Sedatives/hypnotics | 213 | 9.3 | 52 | 9.5 | 94 | 8.7 | 67 | 10.2 |
| Selective estrogen receptor modulators | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| Unopposed estrogen hormone replacement therapy (HRT) | ≤10 | n/a | 0 | 0.0 | ≤10 | n/a | 0 | 0.0 |
| **Co-morbidities (six months prior to index date)** | | | | | | | | |
| Pathologic fracture | 204 | 8.9 | 45 | 8.2 | 106 | 9.8 | 53 | 8.1 |
| Osteoporosis | 185 | 8.1 | 52 | 9.5 | 75 | 6.9 | 58 | 8.9 |
| Uterine malignancies | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| Pure hypercholesterolemia | 204 | 8.9 | 47 | 8.6 | 101 | 9.3 | 56 | 8.6 |
| Major adverse cardiac events (MACE) | 55 | 2.4 | 20 | 3.6 | 22 | 2.0 | 13 | 2.0 |
| Acute myocardial infarction (MI) | 11 | 0.5 | ≤10 | n/a | ≤10 | n/a | ≤10 | n/a |
| Cerebrovascular disease | 1116 | 48.8 | 292 | 53.3 | 514 | 47.5 | 310 | 47.4 |
| Stroke | 46 | 2.0 | 16 | 2.9 | 19 | 1.8 | 11 | 1.7 |
| Hyperglycemia | 97 | 4.2 | 26 | 4.7 | 50 | 4.6 | 21 | 3.2 |
| Deyo-Charlson Index (DCI) | | | | | | | | |
| 0-3 | 93 | 4.1 | 19 | 3.5 | 31 | 2.9 | 43 | 6.6 |
| 4-7 | 28 | 1.2 | 12 | 2.2 | ≤10 | n/a | ≤10 | n/a |
| 8-11 | 2090 | 91.5 | 494 | 90.1 | 1012 | 93.4 | 584 | 89.3 |
| 12 or more | 74 | 3.2 | 23 | 4.2 | 31 | 2.9 | 20 | 3.1 |

Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.

*Return to Table of Contents*

**Table 2.2.** Incidence of the safety events of interest in all new users of palbociclib with advanced stage ER+/HER2- breast cancer **[Secondary Objective 2]**

| Event | All new users of palbociclib with advanced stage ER+/HER2- breast cancer (n=2,285) | | | | |
|---|---|---|---|---|---|
| | # Events | PT at risk | IR (per 100 person-years) | | |
| | | | IR | 95% Lower CI | 95% Upper CI |
| Neutropenia (sensitive) | 447 | 1,259 | 35.5 | 32.29 | 38.96 |
| Neutropenia (specific) | 293 | 1,319 | 22.2 | 19.74 | 24.90 |
| Febrile neutropenia (sensitive) | 43 | 1,422 | 3.0 | 2.19 | 4.07 |
| Febrile neutropenia (specific) | ≤10 | n/a | 0.7 | 0.34 | 1.29 |
| Leukopenia (sensitive) | 91 | 1,390 | 6.5 | 5.27 | 8.04 |
| Leukopenia (specific) | 91 | 1,390 | 6.5 | 5.27 | 8.04 |
| Alopecia | 11 | 1,427 | 0.8 | 0.38 | 1.38 |
| Vomiting* | 119 | 1,361 | 8.7 | 7.24 | 10.46 |
| QT prolongation | 73 | 1,409 | 5.2 | 4.06 | 6.52 |
| Fatigue* | 218 | 1,232 | 17.7 | 15.43 | 20.21 |
| Serious infection | 278 | 1,365 | 20.4 | 18.04 | 22.91 |
| Brain/spinal infection | ≤10 | n/a | 0.7 | 0.34 | 1.29 |
| Pericardial/myocardial infection | 0 | 1,431 | 0.0 | . | . |
| Pulmonary infection | 127 | 1,400 | 9.1 | 7.56 | 10.79 |
| GI infection | ≤10 | n/a | 0.7 | 0.34 | 1.29 |
| Genitourinary/renal infection | 131 | 1,388 | 9.4 | 7.89 | 11.20 |
| Dental infection | ≤10 | n/a | 0.1 | 0.00 | 0.39 |
| Ear, nose, and throat infection | 77 | 1,394 | 5.5 | 4.36 | 6.90 |
| Skin, bones, and joint infection | 78 | 1,405 | 5.5 | 4.39 | 6.93 |
| Hepatitis B infection | ≤10 | n/a | 0.1 | 0.02 | 0.51 |
| Influenza infection | ≤10 | n/a | 0.4 | 0.15 | 0.91 |
| Other infection | 264 | 1,343 | 19.7 | 17.36 | 22.18 |
| Diarrhea* | 57 | 1,389 | 4.1 | 3.11 | 5.32 |
| Interstitial lung disease/pneumonitis | 329 | 1,337 | 24.6 | 22.01 | 27.41 |
| Anemia (sensitive) | 510 | 1,264 | 40.3 | 36.92 | 44.00 |
| Anemia (specific) | 302 | 1,346 | 22.4 | 19.97 | 25.11 |
| Nausea* | 189 | 1,306 | 14.5 | 12.49 | 16.69 |
| Thrombocytopenia | 146 | 1,389 | 10.5 | 8.87 | 12.36 |
| Pulmonary embolism* | 43 | 1,399 | 3.1 | 2.22 | 4.14 |
| No history | 52 | 1,411 | 3.7 | 2.75 | 4.83 |
| Other venous embolism and thrombosis* | 60 | 1,384 | 4.3 | 3.31 | 5.58 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 41 | 1,402 | 2.9 | 2.10 | 3.97 |
| No history of "Other venous embolism and thrombosis" | 89 | 1,404 | 6.3 | 5.09 | 7.80 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 57 | 1,413 | 4.0 | 3.06 | 5.23 |
| Embolism and thrombosis of unspecified artery | ≤10 | n/a | 0.1 | 0.02 | 0.51 |
| Cataracts and other ocular disorders | 89 | 1,393 | 6.4 | 5.13 | 7.86 |
| Stomatitis and mucositis | 34 | 1,421 | 2.4 | 1.66 | 3.34 |
| Fever | 144 | 1,392 | 10.3 | 8.72 | 12.18 |
| Anorexia | 28 | 1,424 | 2.0 | 1.31 | 2.84 |
| Peripheral neuropathy | 100 | 1,391 | 7.2 | 5.85 | 8.74 |
| Sudden cardiac death | ≤10 | n/a | 0.3 | 0.08 | 0.72 |
| Diabetes mellitus | 164 | 1,363 | 12.0 | 10.26 | 14.02 |
| Type 2 Diabetes mellitus | 163 | 1,364 | 11.9 | 10.18 | 13.93 |
| Hyperglycemia | 31 | 1,417 | 2.2 | 1.49 | 3.11 |

| | | | | | |
|---|---|---|---|---|---|
| Liver failure (Acute liver injury) | 46 | 1,424 | 3.2 | 2.36 | 4.31 |
| Abnormal ALT (incident)^ | 28 | 504 | 5.6 | 3.69 | 8.04 |
| Abnormal ALT (incident or prevalent)^ | 69 | 636 | 10.8 | 8.44 | 13.72 |
| Abnormal AST (incident)^ | 33 | 541 | 6.1 | 4.20 | 8.57 |
| Abnormal AST (incident or prevalent)^ | 77 | 639 | 12.0 | 9.51 | 15.06 |
| Abnormal ALP (incident)^ | 23 | 594 | 3.9 | 2.45 | 5.81 |
| Abnormal ALP (incident or prevalent)^ | 63 | 655 | 9.6 | 7.39 | 12.30 |
| Secondary malignancies (second primary cancer) | 378 | 1,279 | 29.6 | 26.65 | 32.69 |
| Non-melanoma skin cancer | 35 | 1,409 | 2.5 | 1.73 | 3.45 |

Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person-time; IR, incidence rate; CI, confidence interval; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

*Return to Table of Contents*

**Table 2.3.** Incidence of the safety events of interest in new users of palbociclib subgroups with advanced stage ER+/HER2- breast cancer
[Secondary Objective 2]

| Event | New users of palbociclib and fulvestrant (n=548) | | | | | New users of palbociclib and letrozole (n=1,083) | | | | | All other new users of palbociclib (no new use of fulvestrant or letrozole) (n=654) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | |
| | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI |
| Neutropenia (sensitive) | 104 | 278 | 37.4 | 30.58 | 45.35 | 228 | 653 | 34.91 | 30.53 | 39.75 | 115 | 328 | 35.08 | 28.96 | 42.10 |
| Neutropenia (specific) | 70 | 289 | 24.2 | 18.85 | 30.56 | 144 | 687 | 20.97 | 17.69 | 24.69 | 79 | 343 | 23.01 | 18.22 | 28.68 |
| Febrile neutropenia (sensitive) | 11 | 312 | 3.5 | 1.76 | 6.30 | 20 | 744 | 2.69 | 1.64 | 4.15 | 12 | 365 | 3.28 | 1.70 | 5.74 |
| Febrile neutropenia (specific) | ≤10 | n/a | 1.0 | 0.20 | 2.80 | ≤10 | n/a | 0.67 | 0.22 | 1.56 | ≤10 | n/a | 0.54 | 0.07 | 1.95 |
| Leukopenia (sensitive) | 17 | 309 | 5.5 | 3.21 | 8.81 | 52 | 721 | 7.21 | 5.39 | 9.46 | 22 | 361 | 6.10 | 3.82 | 9.24 |
| Leukopenia (specific) | 17 | 309 | 5.5 | 3.21 | 8.81 | 52 | 721 | 7.21 | 5.39 | 9.46 | 22 | 361 | 6.10 | 3.82 | 9.24 |
| Alopecia | ≤10 | n/a | 0.3 | 0.01 | 1.77 | ≤10 | n/a | 1.08 | 0.46 | 2.12 | ≤10 | n/a | 0.54 | 0.07 | 1.96 |
| Vomiting* | 30 | 301 | 10.0 | 6.73 | 14.25 | 46 | 707 | 6.51 | 4.77 | 8.68 | 43 | 354 | 12.16 | 8.80 | 16.37 |
| QT prolongation | 19 | 306 | 6.2 | 3.74 | 9.69 | 33 | 738 | 4.47 | 3.08 | 6.28 | 21 | 364 | 5.76 | 3.57 | 8.81 |
| Fatigue* | 51 | 276 | 18.5 | 13.78 | 24.33 | 94 | 634 | 14.83 | 11.98 | 18.15 | 73 | 322 | 22.66 | 17.76 | 28.50 |
| Serious infection | 77 | 300 | 25.7 | 20.25 | 32.06 | 129 | 709 | 18.20 | 15.20 | 21.63 | 72 | 356 | 20.22 | 15.82 | 25.46 |
| Brain/spinal infection | ≤10 | 314 | 1.3 | 0.35 | 3.26 | ≤10 | n/a | 0.80 | 0.30 | 1.75 | 0 | 370 | 0.00 | . | . |
| Pericardial/myocardial infection | 0 | 315 | 0.0 | . | . | 0 | 747 | 0.00 | . | . | 0 | 370 | 0.00 | . | . |
| Pulmonary infection | 33 | 309 | 10.7 | 7.35 | 15.00 | 64 | 728 | 8.79 | 6.77 | 11.23 | 30 | 363 | 8.26 | 5.57 | 11.80 |
| GI infection | ≤10 | 314 | 0.6 | 0.08 | 2.30 | ≤10 | 746 | 0.80 | 0.29 | 1.75 | ≤10 | n/a | 0.54 | 0.07 | 1.95 |
| Genitourinary/Renal infection | 34 | 304 | 11.2 | 7.74 | 15.61 | 69 | 721 | 9.57 | 7.45 | 12.12 | 28 | 363 | 7.71 | 5.12 | 11.14 |
| Dental infection | 0 | 315 | 0.0 | . | . | ≤10 | n/a | 0.13 | 0.00 | 0.75 | 0 | 370 | 0.00 | . | . |
| Ear, nose, and throat infection | 14 | 311 | 4.5 | 2.46 | 7.55 | 46 | 721 | 6.38 | 4.67 | 8.50 | 17 | 362 | 4.70 | 2.74 | 7.52 |
| Skin, bones, and joint infection | 16 | 310 | 5.2 | 2.95 | 8.38 | 45 | 730 | 6.17 | 4.50 | 8.25 | 17 | 366 | 4.65 | 2.71 | 7.44 |
| Hepatitis B infection | 0 | 315 | 0.0 | . | . | ≤10 | n/a | 0.13 | 0.00 | 0.75 | ≤10 | n/a | 0.27 | 0.01 | 1.51 |
| Influenza infection | ≤10 | n/a | 1.3 | 0.35 | 3.27 | 0 | 747 | 0.00 | . | . | ≤10 | n/a | 0.54 | 0.07 | 1.96 |
| Other infection | 64 | 297 | 21.5 | 16.58 | 27.50 | 135 | 697 | 19.38 | 16.25 | 22.94 | 65 | 349 | 18.62 | 14.37 | 23.73 |
| Diarrhea* | 14 | 308 | 4.6 | 2.49 | 7.64 | 26 | 723 | 3.60 | 2.35 | 5.27 | 17 | 359 | 4.73 | 2.76 | 7.58 |
| Interstitial lung disease/pneumonitis | 100 | 294 | 34.0 | 27.66 | 41.35 | 156 | 689 | 22.63 | 19.22 | 26.48 | 73 | 354 | 20.61 | 16.16 | 25.92 |
| Anemia (sensitive) | 133 | 274 | 48.6 | 40.67 | 57.57 | 261 | 651 | 40.07 | 35.36 | 45.24 | 116 | 339 | 34.22 | 28.28 | 41.04 |
| Anemia (specific) | 78 | 294 | 26.6 | 21.00 | 33.16 | 152 | 701 | 21.70 | 18.38 | 25.43 | 72 | 352 | 20.45 | 16.00 | 25.76 |
| Nausea* | 47 | 289 | 16.3 | 11.94 | 21.61 | 79 | 677 | 11.67 | 9.24 | 14.55 | 63 | 340 | 18.55 | 14.26 | 23.74 |
| Thrombocytopenia | 33 | 308 | 10.7 | 7.37 | 15.03 | 66 | 726 | 9.09 | 7.03 | 11.57 | 47 | 355 | 13.24 | 9.73 | 17.60 |
| Pulmonary embolism* | 14 | 308 | 4.5 | 2.48 | 7.62 | 15 | 727 | 2.06 | 1.16 | 3.40 | 14 | 364 | 3.85 | 2.10 | 6.46 |
| No history | 15 | 310 | 4.8 | 2.71 | 7.98 | 26 | 735 | 3.54 | 2.31 | 5.18 | 11 | 366 | 3.01 | 1.50 | 5.38 |
| Other venous embolism and thrombosis* | 11 | 300 | 3.7 | 1.83 | 6.57 | 27 | 720 | 3.75 | 2.47 | 5.46 | 22 | 364 | 6.04 | 3.78 | 9.14 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | ≤10 | n/a | 2.3 | 0.93 | 4.76 | 16 | 733 | 2.18 | 1.25 | 3.55 | 18 | 367 | 4.91 | 2.91 | 7.76 |
| No history of "Other venous embolism and thrombosis" | 23 | 306 | 7.5 | 4.77 | 11.28 | 48 | 731 | 6.56 | 4.84 | 8.70 | 18 | 367 | 4.91 | 2.91 | 7.76 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 16 | 307 | 5.2 | 2.98 | 8.46 | 27 | 738 | 3.66 | 2.41 | 5.32 | 14 | 367 | 3.81 | 2.08 | 6.39 |
| Embolism and thrombosis of unspecified artery | 0 | 315 | 0.0 | . | . | 0 | 747 | 0.00 | . | . | ≤10 | n/a | 0.54 | 0.07 | 1.96 |
| Cataracts and other ocular disorders | 18 | 308 | 5.8 | 3.46 | 9.24 | 50 | 723 | 6.91 | 5.13 | 9.11 | 21 | 361 | 5.81 | 3.60 | 8.89 |
| Stomatitis and mucositis | ≤10 | n/a | 2.9 | 1.32 | 5.46 | 11 | 741 | 1.48 | 0.74 | 2.66 | 14 | 367 | 3.81 | 2.08 | 6.40 |
| Fever | 34 | 309 | 11.0 | 7.62 | 15.38 | 75 | 723 | 10.38 | 8.16 | 13.01 | 35 | 361 | 9.70 | 6.76 | 13.49 |
| Anorexia | ≤10 | n/a | 2.9 | 1.31 | 5.45 | 13 | 741 | 1.75 | 0.93 | 3.00 | ≤10 | n/a | 1.63 | 0.60 | 3.54 |
| Peripheral neuropathy | 22 | 308 | 7.1 | 4.47 | 10.80 | 46 | 724 | 6.35 | 4.65 | 8.47 | 32 | 358 | 8.93 | 6.11 | 12.61 |
| Sudden cardiac death | 0 | 315 | 0.0 | . | . | ≤10 | n/a | 0.40 | 0.08 | 1.17 | ≤10 | n/a | 0.27 | 0.01 | 1.51 |
| Diabetes mellitus | 44 | 301 | 14.6 | 10.62 | 19.63 | 95 | 701 | 13.54 | 10.96 | 16.56 | 25 | 361 | 6.93 | 4.49 | 10.23 |
| Type 2 Diabetes mellitus | 44 | 301 | 14.6 | 10.61 | 19.61 | 95 | 702 | 13.54 | 10.95 | 16.55 | 24 | 361 | 6.64 | 4.25 | 9.88 |
| Hyperglycemia | ≤10 | 313 | 1.6 | 0.52 | 3.72 | 20 | 736 | 2.72 | 1.66 | 4.20 | ≤10 | n/a | 1.63 | 0.60 | 3.55 |
| Liver failure (Acute liver injury) | 13 | 314 | 4.1 | 2.21 | 7.09 | 22 | 742 | 2.97 | 1.86 | 4.49 | 11 | 369 | 2.98 | 1.49 | 5.33 |
| Abnormal ALT (incident)^ | ≤10 | n/a | 7.6 | 3.47 | 14.39 | ≤10 | n/a | 2.86 | 1.15 | 5.89 | 12 | 140 | 8.57 | 4.43 | 14.97 |
| Abnormal ALT (incident or prevalent)^ | 17 | 151 | 11.3 | 6.55 | 18.02 | 28 | 312 | 8.99 | 5.97 | 12.99 | 24 | 174 | 13.82 | 8.86 | 20.56 |
| Abnormal AST (incident)^ | ≤10 | n/a | 7.1 | 3.25 | 13.51 | 11 | 272 | 4.04 | 2.02 | 7.23 | 13 | 142 | 9.13 | 4.86 | 15.61 |
| Abnormal AST (incident or prevalent)^ | 20 | 148 | 13.5 | 8.23 | 20.80 | 28 | 317 | 8.83 | 5.87 | 12.77 | 29 | 174 | 16.69 | 11.18 | 23.98 |
| Abnormal ALP (incident)^ | ≤10 | n/a | 4.4 | 1.63 | 9.65 | ≤10 | 300 | 2.34 | 0.94 | 4.81 | ≤10 | 159 | 6.27 | 3.01 | 11.54 |
| Abnormal ALP (incident or prevalent)^ | 16 | 148 | 10.8 | 6.16 | 17.50 | 24 | 330 | 7.27 | 4.66 | 10.82 | 23 | 177 | 13.01 | 8.24 | 19.51 |
| Secondary malignancies (second primary cancer) | 102 | 282 | 36.2 | 29.53 | 43.96 | 194 | 654 | 29.68 | 25.65 | 34.17 | 82 | 344 | 23.86 | 18.97 | 29.61 |
| Non-melanoma skin cancer | ≤10 | n/a | 2.3 | 0.91 | 4.65 | 17 | 734 | 2.32 | 1.35 | 3.71 | 11 | 365 | 3.01 | 1.50 | 5.39 |

Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person-time; IR; incidence rate; CI, confidence interval; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

*Return to Table of Contents*

**Table 2.4.** Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone with algorithm-defined advanced stage ER+/HER2- breast cance
**[Secondary Objective 3b]**

| Characteristics of patients with advanced stage ER+/HER2- Breast Cancer | Before Propensity Score Matching | | | | | After Propensity Score Matching^ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (pre-2015) | | Standardized difference | New users of palbociclib with fulvestrant | | New users of fulvestrant alone (pre-2015) | | Standardized difference |
| | N/Mean | %/SD | N/Mean | %/SD | | N/Mean | %/SD | N/Mean | %/SD | |
| **Overall** | **548** | **1.0** | **2,061** | **1.0** | | **544** | **1.0** | **544** | **1.0** | |
| | | | | | | | | | | |
| **Demographics** | | | | | | | | | | |
| Age at index date (in years) | 59.7 | 10.9 | 64.0 | 12.8 | 0.37 | 59.8 | 10.9 | 60.2 | 12.2 | 0.04 |
| Age (years) | | | | | | | | | | |
| <45 | 47 | 8.6 | 107 | 5.2 | 0.13 | 45 | 8.3 | 41 | 7.5 | 0.03 |
| 45-64 | 352 | 64.2 | 1010 | 49.0 | 0.31 | 351 | 64.5 | 327 | 60.1 | 0.09 |
| 65+ | 149 | 27.2 | 944 | 45.8 | 0.39 | 148 | 27.2 | 176 | 32.4 | 0.11 |
| Gender | | | | | | | | | | |
| Male | ≤10 | n/a | ≤10 | n/a | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.07 |
| Female | 539 | 98.4 | 2036 | 98.8 | 0.04 | 535 | 98.3 | 539 | 99.1 | 0.07 |
| Calendar year of index date | | | | | | | | | | |
| 2011 | 0 | 0.0 | 541 | 26.2 | n/a | 0 | 0.0 | 119 | 21.9 | n/a |
| 2012 | 0 | 0.0 | 453 | 22.0 | n/a | 0 | 0.0 | 102 | 18.8 | n/a |
| 2013 | 0 | 0.0 | 509 | 24.7 | n/a | 0 | 0.0 | 144 | 26.5 | n/a |
| 2014 | 0 | 0.0 | 558 | 27.1 | n/a | 0 | 0.0 | 179 | 32.9 | n/a |
| 2015 | 97 | 17.7 | 0 | 0.0 | n/a | 96 | 17.6 | 0 | 0.0 | n/a |
| 2016 | 260 | 47.4 | 0 | 0.0 | n/a | 259 | 47.6 | 0 | 0.0 | n/a |
| 2017 | 191 | 34.9 | 0 | 0.0 | n/a | 189 | 34.7 | 0 | 0.0 | n/a |
| Geographic region of residence | | | | | | | | | | |
| Midwest | 93 | 17.0 | 370 | 18.0 | 0.03 | 93 | 17.1 | 92 | 16.9 | 0.00 |
| South | 154 | 28.1 | 603 | 29.3 | 0.03 | 152 | 27.9 | 155 | 28.5 | 0.01 |
| Northeast | 159 | 29.0 | 519 | 25.2 | 0.09 | 158 | 29.0 | 160 | 29.4 | 0.01 |
| West | 142 | 25.9 | 569 | 27.6 | 0.04 | 141 | 25.9 | 137 | 25.2 | 0.02 |
| **Medical History** | | | | | | | | | | |
| Other primary cancer prior to first breast cancer diagnosis code | 216 | 39.4 | 927 | 45.0 | 0.11 | 216 | 39.7 | 252 | 46.3 | 0.13 |
| Secondary malignancy (metastasis) | 481 | 87.8 | 1696 | 82.3 | 0.15 | 477 | 87.7 | 458 | 84.2 | 0.10 |
| Lymph nodes of head, face, and neck | 149 | 27.2 | 428 | 20.8 | 0.15 | 146 | 26.8 | 143 | 26.3 | 0.01 |
| Respiratory and digestive systems | 251 | 45.8 | 740 | 35.9 | 0.20 | 248 | 45.6 | 252 | 46.3 | 0.01 |
| Other specified sites | 448 | 81.8 | 1612 | 78.2 | 0.09 | 444 | 81.6 | 427 | 78.5 | 0.08 |
| Deyo-Charlson comorbidity index (DCI) without cancer codes | 8.49 | 1.9 | 8.07 | 2.1 | 0.21 | 8.49 | 1.9 | 8.48 | 1.8 | 0.01 |
| Secondary malignant neoplasm of breast | 64 | 11.7 | 190 | 9.2 | 0.08 | 63 | 11.6 | 73 | 13.4 | 0.06 |
| Breast cancer (female) diagnosis code | 540 | 98.5 | 2016 | 97.8 | 0.05 | 536 | 98.5 | 537 | 98.7 | 0.02 |
| InSitu breast cancer | 44 | 8.0 | 128 | 6.2 | 0.07 | 42 | 7.7 | 48 | 8.8 | 0.04 |
| **Cancer Therapy History** | | | | | | | | | | |
| **Radiation therapy** | 108 | 19.7 | 348 | 16.9 | 0.07 | 108 | 19.9 | 102 | 18.8 | 0.03 |
| External Beam | 108 | 19.7 | 348 | 16.9 | 0.07 | 108 | 19.9 | 102 | 18.8 | 0.03 |
| **Surgery** | 11 | 2.0 | 52 | 2.5 | 0.03 | 11 | 2.0 | 11 | 2.0 | 0.00 |
| Mastectomy in the last six months | ≤10 | n/a | 21 | 1.0 | 0.05 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| Lumpectomy in the last six months | ≤10 | n/a | 19 | 0.9 | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.03 |
| Radical Mastectomy in the last six months | ≤10 | n/a | 20 | 1.0 | 0.01 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| **Chemotherapy** | 95 | 17.3 | 369 | 17.9 | 0.01 | 94 | 17.3 | 100 | 18.4 | 0.03 |
| Infusion based chemo (procedure) | ≤10 | n/a | 25 | 1.2 | 0.10 | ≤10 | n/a | 11 | 2.0 | 0.15 |
| **Imaging** | | | | | | | | | | |
| CT related imaging in the last six months | 131 | 23.9 | 465 | 22.6 | 0.03 | 130 | 23.9 | 126 | 23.2 | 0.02 |
| MR related imaging for needle placement | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | ≤10 | n/a | n/a |
| Diagnostic imaging in the last six months | 70 | 12.8 | 384 | 18.6 | 0.16 | 70 | 12.9 | 70 | 12.9 | 0.00 |
| Mammography | ≤10 | n/a | 90 | 4.4 | 0.19 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| MRI related imaging | 24 | 4.4 | 77 | 3.7 | 0.03 | 24 | 4.4 | 27 | 5.0 | 0.03 |
| Tomosynthesis (3D Mammography) | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| **Healthcare Utilization (six months prior to index date)** | | | | | | | | | | |
| Number of outpatient visits | 37.2 | 21.9 | 36.13 | 24.3 | 0.05 | 37.21 | 21.9 | 37.56 | 23.4 | 0.02 |
| Number of outpatient visits to an oncologist | 0.02 | 0.2 | 0.03 | 0.4 | 0.03 | 0.02 | 0.2 | 0.03 | 0.3 | 0.05 |
| Number of inpatient hospitalizations | 0.29 | 0.7 | 0.34 | 0.7 | 0.07 | 0.29 | 0.7 | 0.4 | 0.7 | 0.16 |
| Number of inpatient hospitalizations for breast cancer | 0.03 | 0.2 | 0.26 | 0.6 | 0.51 | 0.03 | 0.2 | 0.34 | 0.7 | 0.61 |
| Number of inpatient hospitalizations for any cancer | 0.25 | 0.6 | 0.3 | 0.7 | 0.08 | 0.25 | 0.6 | 0.38 | 0.7 | 0.20 |
| Number of emergency department visits | 0.3 | 0.8 | 0.23 | 0.6 | 0.10 | 0.3 | 0.8 | 0.3 | 0.7 | 0.00 |
| **Medication Use (breast cancer related)** | | | | | | | | | | |
| Palbociclib | | | | | | | | | | |
| Aromatase inhibitor | 316 | 57.7 | 1161 | 56.3 | 0.03 | 312 | 57.4 | 295 | 54.2 | 0.06 |
| Letrozole | 112 | 20.4 | 400 | 19.4 | 0.03 | 109 | 20.0 | 114 | 21.0 | 0.02 |
| Anastrazole | 133 | 24.3 | 544 | 26.4 | 0.05 | 132 | 24.3 | 132 | 24.3 | 0.00 |
| Exemestane | 82 | 15.0 | 327 | 15.9 | 0.02 | 82 | 15.1 | 79 | 14.5 | 0.02 |
| HER2 positive therapy | ≤10 | n/a | 27 | 1.3 | 0.00 | ≤10 | n/a | ≤10 | n/a | 0.02 |
| Trastuzumab | ≤10 | n/a | 33 | 1.6 | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.00 |
| Lapatinib | ≤10 | n/a | ≤10 | n/a | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Ado-trastuzumab | 0 | 0.0 | 0 | 0.0 | 0.00 | 0 | 0.0 | 0 | 0.0 | n/a |
| Pertuzumab | 0 | 0.0 | 0 | 0.0 | 0.00 | 0 | 0.0 | 0 | 0.0 | n/a |
| Tamoxifen | 137 | 25.0 | 357 | 17.3 | 0.19 | 137 | 25.2 | 135 | 24.8 | 0.01 |
| Fulvestrant | 234 | 42.7 | 0 | 0.0 | n/a | 232 | 42.6 | 0 | 0.0 | n/a |
| Denosumab or Pamidronate | 196 | 35.8 | 391 | 19.0 | 0.38 | 192 | 35.3 | 187 | 34.4 | 0.02 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Everolimus | 39 | 7.1 | 84 | 4.1 | 0.13 | 38 | 7.0 | 31 | 5.7 | 0.05 |
| **Medication Use (not breast cancer related)** | | | | | | | | | | |
| Anticonvulsants | 120 | 21.9 | 300 | 14.6 | 0.19 | 117 | 21.5 | 111 | 20.4 | 0.03 |
| Antidepressants | 169 | 30.8 | 558 | 27.1 | 0.08 | 167 | 30.7 | 166 | 30.5 | 0.00 |
| Antidiabetics | 64 | 11.7 | 227 | 11.0 | 0.02 | 63 | 11.6 | 69 | 12.7 | 0.03 |
| Antifungals | 27 | 4.9 | 99 | 4.8 | 0.01 | 27 | 5.0 | 40 | 7.4 | 0.10 |
| Antihypertensives | 168 | 30.7 | 551 | 26.7 | 0.09 | 167 | 30.7 | 135 | 24.8 | 0.13 |
| Antimycobacterials | 104 | 19.0 | 385 | 18.7 | 0.01 | 103 | 18.9 | 113 | 20.8 | 0.05 |
| Antivirals | 29 | 5.3 | 97 | 4.7 | 0.03 | 29 | 5.3 | 34 | 6.3 | 0.04 |
| Corticosteroids | 137 | 25.0 | 370 | 18.0 | 0.17 | 136 | 25.0 | 148 | 27.2 | 0.05 |
| Oral contraceptive use (progestin) | 0 | 0.0 | 0 | 0.0 | n/a | 0 | 0.0 | 0 | 0.0 | n/a |
| Oral contraceptive use (combination) | ≤10 | n/a | ≤10 | n/a | 0.02 | 0 | 0.0 | 0 | 0.0 | n/a |
| Oral contraceptive use (unspecified) | ≤10 | n/a | 20 | 1.0 | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.08 |
| Lipid lowering agent | 129 | 23.5 | 499 | 24.2 | 0.02 | 127 | 23.3 | 119 | 21.9 | 0.04 |
| Vaginal estrogen (local hormone treatment) | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | ≤10 | 0.2 | n/a |
| Macrolides | ≤10 | n/a | 20 | 1.0 | 0.06 | ≤10 | n/a | ≤10 | 0.7 | 0.08 |
| Sedatives/hypnotics | 52 | 9.5 | 251 | 12.2 | 0.09 | 52 | 9.6 | 52 | 9.6 | 0.00 |
| Selective estrogen receptor modulators | ≤10 | n/a | ≤10 | n/a | 0.04 | ≤10 | 0.2 | ≤10 | 0.7 | 0.08 |
| Unopposed estrogen hormone replacement therapy (HRT) | 0 | 0.0 | ≤10 | n/a | n/a | 0 | 0.0 | ≤10 | 0.4 | n/a |
| **Co-morbidities (six months prior to index date)** | | | | | | | | | | |
| Pathologic fracture | 45 | 8.2 | 161 | 7.8 | 0.01 | 45 | 8.3 | 50 | 9.2 | 0.03 |
| Osteoporosis | 52 | 9.5 | 196 | 9.5 | 0.00 | 51 | 9.4 | 45 | 8.3 | 0.04 |
| Uterine malignancies | ≤10 | n/a | 11 | 0.5 | 0.03 | ≤10 | n/a | ≤10 | n/a | 0.07 |
| Pure hypercholesterolemia | 47 | 8.6 | 215 | 10.4 | 0.06 | 47 | 8.6 | 58 | 10.7 | 0.07 |
| Major adverse cardiac events (MACE) | 20 | 3.6 | 73 | 3.5 | 0.01 | 20 | 3.7 | 15 | 2.8 | 0.05 |
| Acute Myocardial Infarction (MI) | ≤10 | n/a | 22 | 1.1 | 0.04 | ≤10 | n/a | ≤10 | n/a | 0.04 |
| Cerebrovascular disease | 292 | 53.3 | 995 | 48.3 | 0.10 | 288 | 52.9 | 250 | 46.0 | 0.14 |
| Stroke | 16 | 2.9 | 54 | 2.6 | 0.02 | 16 | 2.9 | ≤10 | n/a | 0.07 |
| Hyperglycemia | 26 | 4.7 | 49 | 2.4 | 0.13 | 23 | 4.2 | 24 | 4.4 | 0.01 |
| Deyo-Charlson Index (DCI) | | | | | | | | | | |
| 0-3 | 19 | 3.5 | 177 | 8.6 | 0.22 | 19 | 3.5 | 21 | 3.9 | 0.02 |
| 4-7 | 12 | 2.2 | 27 | 1.3 | 0.07 | 12 | 2.2 | ≤10 | n/a | 0.07 |
| 8-11 | 494 | 90.1 | 1798 | 87.2 | 0.09 | 491 | 90.3 | 493 | 90.6 | 0.01 |
| 12 or more | 23 | 4.2 | 59 | 2.9 | 0.07 | 22 | 4.0 | 23 | 4.2 | 0.01 |

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; STD, standard deviation; DVT, deep vein thrombosis; CT, computed tomography; MRI, magnetic resonance imaging.

^The following variables were included in the propensity score: age, region, Deyo-Charlson Index, Number of outpatient visits, Number of emergency room visits, secondary malignancy to lymph nodes of head, face, and neck, secondary malignancy to other specified sites, secondary malignancy to respiratory sites, tamoxifen, everolimus, anastrazole, Denosumab or Pamidronate, exemestane, chemotherapy, corticosteroids, diagnostic imaging, breast cancer surgery, letrozole, HER2 positive therapy, radiation therapy, CT imaging, mammography, MRI imaging, anticonvulsants, antidepressants, sedatives/hypnotics, secondary malignancy to breast, breast cancer diagnosis code, in situ breast cancer diagnosis, hyperglycemia, and cerebrovascular disease.

*Return to Table of Contents*

**Table 2.5.** Incidence rates and unadjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone with advanced stage ER+/HER2- breast cancer **[Secondary Objective 3b]**

| Event | Before Propensity Score Matching | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib and fulvestrant with advanced stage ER+/HER2- breast cancer (n=548) | | | | | New users of fulvestrant alone (pre-2015) with advanced stage ER+/HER2- breast cancer (n=2,061) | | | | | Unadjusted Hazard Ratios | | |
| | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | | HR | 95% LCL | 95%UCL |
| | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI | | | |
| Neutropenia (sensitive) | 104 | 278 | 37.4 | 30.58 | 45.35 | 83 | 1,432 | 5.8 | 4.62 | 7.19 | 6.0 | 4.5 | 8.0 |
| Neutropenia (specific) | 70 | 289 | 24.2 | 18.85 | 30.56 | 57 | 1,435 | 4.0 | 3.01 | 5.15 | 5.7 | 4.0 | 8.2 |
| Febrile neutropenia (sensitive) | 11 | 312 | 3.5 | 1.76 | 6.30 | ≤10 | n/a | 0.6 | 0.28 | 1.17 | 5.1 | 2.1 | 12.4 |
| Febrile neutropenia (specific) | ≤10 | n/a | 1.0 | 0.20 | 2.80 | ≤10 | n/a | 0.1 | 0.00 | 0.38 | 11.7 | 1.2 | 113.0 |
| Leukopenia (sensitive) | 17 | 309 | 5.5 | 3.21 | 8.81 | 13 | 1,451 | 0.9 | 0.48 | 1.53 | 5.7 | 2.7 | 11.7 |
| Leukopenia (specific) | 17 | 309 | 5.5 | 3.21 | 8.81 | 13 | 1,451 | 0.9 | 0.48 | 1.53 | 5.7 | 2.7 | 11.7 |
| Alopecia | ≤10 | n/a | 0.3 | 0.01 | 1.77 | ≤10 | n/a | 0.2 | 0.04 | 0.60 | 1.5 | 0.2 | 14.1 |
| Vomiting* | 30 | 301 | 10.0 | 6.73 | 14.25 | 190 | 1,405 | 13.5 | 11.67 | 15.59 | 0.7 | 0.5 | 1.0 |
| QT prolongation | 19 | 306 | 6.2 | 3.74 | 9.69 | 76 | 1,432 | 5.3 | 4.18 | 6.64 | 1.1 | 0.7 | 1.8 |
| Fatigue* | 51 | 276 | 18.5 | 13.78 | 24.33 | 263 | 1,349 | 19.5 | 17.22 | 22.01 | 0.9 | 0.7 | 1.2 |
| Serious infection | 77 | 300 | 25.7 | 20.25 | 32.06 | 308 | 1,395 | 22.1 | 19.69 | 24.70 | 1.1 | 0.9 | 1.4 |
| Brain/spinal infection | ≤10 | n/a | 1.3 | 0.35 | 3.26 | ≤10 | n/a | 0.1 | 0.02 | 0.50 | 8.6 | 1.6 | 47.2 |
| Pericardial/myocardial infection | 0 | 315 | 0.0 | . | . | ≤10 | n/a | 0.1 | 0.02 | 0.50 | n/a | 0.0 | . |
| Pulmonary infection | 33 | 309 | 10.7 | 7.35 | 15.00 | 119 | 1,432 | 8.3 | 6.88 | 9.94 | 1.2 | 0.8 | 1.8 |
| GI infection | ≤10 | n/a | 0.6 | 0.08 | 2.30 | ≤10 | n/a | 0.4 | 0.15 | 0.90 | 1.5 | 0.3 | 7.4 |
| Genitourinary/Renal infection | 34 | 304 | 11.2 | 7.74 | 15.61 | 161 | 1,412 | 11.4 | 9.71 | 13.31 | 0.9 | 0.6 | 1.3 |
| Dental infection | 0 | 315 | 0.0 | . | . | ≤10 | n/a | 0.1 | 0.02 | 0.50 | n/a | 0.0 | . |
| Ear, nose, and throat infection | 14 | 311 | 4.5 | 2.46 | 7.55 | 47 | 1,437 | 3.3 | 2.40 | 4.35 | 1.3 | 0.7 | 2.4 |
| Skin, bones, and joint infection | 16 | 310 | 5.2 | 2.95 | 8.38 | 61 | 1,432 | 4.3 | 3.26 | 5.47 | 1.2 | 0.7 | 2.0 |
| Hepatitis B infection | 0 | 315 | 0.0 | . | . | 33 | 1,434 | 2.3 | 1.58 | 3.23 | n/a | 0.0 | . |
| Influenza infection | ≤10 | n/a | 1.3 | 0.35 | 3.27 | ≤10 | n/a | 0.2 | 0.04 | 0.60 | 5.7 | 1.3 | 25.5 |
| Other infection | 64 | 297 | 21.5 | 16.58 | 27.50 | 486 | 1,270 | 38.3 | 34.93 | 41.81 | 0.6 | 0.4 | 0.7 |
| Diarrhea* | 14 | 308 | 4.6 | 2.49 | 7.64 | 86 | 1,425 | 6.0 | 4.83 | 7.45 | 0.7 | 0.4 | 1.2 |
| Interstitial lung disease/pneumonitis | 100 | 294 | 34.0 | 27.66 | 41.35 | 311 | 1,372 | 22.7 | 20.22 | 25.33 | 1.4 | 1.2 | 1.8 |
| Anemia (sensitive) | 133 | 274 | 48.6 | 40.67 | 57.57 | 327 | 1,348 | 24.3 | 21.69 | 27.03 | 1.9 | 1.5 | 2.3 |
| Anemia (specific) | 78 | 294 | 26.6 | 21.00 | 33.16 | 108 | 1,423 | 7.6 | 6.22 | 9.16 | 3.3 | 2.5 | 4.5 |
| Nausea* | 47 | 289 | 16.3 | 11.94 | 21.61 | 241 | 1,382 | 17.4 | 15.30 | 19.78 | 0.9 | 0.7 | 1.2 |
| Thrombocytopenia | 33 | 308 | 10.7 | 7.37 | 15.03 | 57 | 1,449 | 3.9 | 2.98 | 5.10 | 2.6 | 1.7 | 3.9 |
| Pulmonary embolism* | 14 | 308 | 4.5 | 2.48 | 7.62 | 43 | 1,438 | 3.0 | 2.16 | 4.03 | 1.4 | 0.8 | 2.6 |
| No history | 15 | 310 | 4.8 | 2.71 | 7.98 | 37 | 1,443 | 2.6 | 1.81 | 3.54 | 1.8 | 1.0 | 3.2 |
| Other venous embolism and thrombosis* | 11 | 300 | 3.7 | 1.83 | 6.57 | 93 | 1,411 | 6.6 | 5.32 | 8.07 | 0.5 | 0.3 | 1.0 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | ≤10 | n/a | 2.3 | 0.93 | 4.76 | 60 | 1,430 | 4.2 | 3.20 | 5.40 | 0.5 | 0.2 | 1.2 |
| No history of "Other venous embolism and thrombosis" | 23 | 306 | 7.5 | 4.77 | 11.28 | 85 | 1,427 | 6.0 | 4.76 | 7.36 | 1.2 | 0.8 | 1.9 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 16 | 307 | 5.2 | 2.98 | 8.46 | 55 | 1,439 | 3.8 | 2.88 | 4.98 | 1.3 | 0.8 | 2.3 |
| Embolism and thrombosis of unspecified artery | 0 | 315 | 0.0 | . | . | ≤10 | n/a | 0.1 | 0.00 | 0.38 | n/a | 0.0 | . |
| Cataracts and other ocular disorders | 18 | 308 | 5.8 | 3.46 | 9.24 | 88 | 1,413 | 6.2 | 5.00 | 7.67 | 0.9 | 0.5 | 1.5 |
| Stomatitis and mucositis | ≤10 | n/a | 2.9 | 1.32 | 5.46 | ≤10 | n/a | 0.6 | 0.24 | 1.08 | 4.8 | 1.8 | 12.4 |
| Fever | 34 | 309 | 11.0 | 7.62 | 15.38 | 68 | 1,438 | 4.7 | 3.67 | 6.00 | 2.2 | 1.4 | 3.3 |
| Anorexia | ≤10 | n/a | 2.9 | 1.31 | 5.45 | 27 | 1,455 | 1.9 | 1.22 | 2.70 | 1.5 | 0.7 | 3.3 |
| Peripheral neuropathy | 22 | 308 | 7.1 | 4.47 | 10.80 | 46 | 1,440 | 3.2 | 2.34 | 4.26 | 2.1 | 1.2 | 3.5 |
| Sudden cardiac death | 0 | 315 | 0.0 | . | . | ≤10 | n/a | 0.1 | 0.02 | 0.50 | n/a | 0.0 | . |
| Diabetes mellitus | 44 | 301 | 14.6 | 10.62 | 19.63 | 194 | 1,388 | 14.0 | 12.08 | 16.09 | 1.0 | 0.7 | 1.4 |
| Type 2 Diabetes mellitus | 44 | 301 | 14.6 | 10.61 | 19.61 | 189 | 1,389 | 13.6 | 11.73 | 15.69 | 1.0 | 0.7 | 1.4 |
| Hyperglycemia | ≤10 | n/a | 1.6 | 0.52 | 3.72 | 11 | 1,454 | 0.8 | 0.38 | 1.35 | 2.1 | 0.7 | 6.0 |
| Liver failure (Acute liver injury) | 13 | 314 | 4.1 | 2.21 | 7.09 | 18 | 1,454 | 1.2 | 0.73 | 1.96 | 3.1 | 1.5 | 6.3 |
| Abnormal ALT (incident)^ | ≤10 | n/a | 7.6 | 3.47 | 14.39 | 34 | 465 | 7.3 | 5.07 | 10.22 | 0.9 | 0.5 | 2.0 |
| Abnormal ALT (incident or prevalent)^ | 17 | 151 | 11.3 | 6.55 | 18.02 | 78 | 530 | 14.7 | 11.63 | 18.36 | 0.7 | 0.4 | 1.2 |
| Abnormal AST (incident)^ | ≤10 | n/a | 7.1 | 3.25 | 13.51 | 45 | 467 | 9.6 | 7.03 | 12.89 | 0.7 | 0.3 | 1.4 |
| Abnormal AST (incident or prevalent)^ | 20 | 148 | 13.5 | 8.23 | 20.80 | 96 | 525 | 18.3 | 14.81 | 22.33 | 0.7 | 0.4 | 1.1 |
| Abnormal ALP (incident)^ | ≤10 | n/a | 4.4 | 1.63 | 9.65 | 25 | 490 | 5.1 | 3.30 | 7.53 | 0.8 | 0.3 | 1.9 |
| Abnormal ALP (incident or prevalent)^ | 16 | 148 | 10.8 | 6.16 | 17.50 | 82 | 535 | 15.3 | 12.20 | 19.03 | 0.6 | 0.4 | 1.1 |
| Secondary malignancies (second primary cancer) | 102 | 282 | 36.2 | 29.53 | 43.96 | 468 | 1,293 | 36.2 | 32.99 | 39.62 | 1.0 | 0.8 | 1.2 |
| Non-melanoma skin cancer | ≤10 | n/a | 2.3 | 0.91 | 4.65 | 57 | 1,421 | 4.0 | 3.04 | 5.20 | 0.5 | 0.2 | 1.2 |

Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person-time; IR, incidence rate; CI, confidence interval; HR, hazard ratio; LCL, lower confidence limit; UCL, upper confidence limit; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

*Return to Table of Contents*

**Table 2.6.** Incidence rates and adjusted hazard ratios of the safety events of interest in new users of palbociclib and fulvestrant and new users of fulvestrant alone with advanced stage ER+/HER2- breast cancer **[Secondary Objective 3b]**

| Event | After Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib and fulvestrant with advanced stage ER+/HER2- breast cancer (n=544) | | | | | New users of fulvestrant alone (pre-2015) with advanced stage ER+/HER2- breast cancer (n=544) | | | | | Adjusted Hazard Ratios | | |
| | # Events | PT at risk | IR (per 100 person-years) | | | # Events | PT at risk | IR (per 100 person-years) | | | aHR | 95% LCL | 95%UCL |
| | | | IR | 95% Lower CI | 95% Upper CI | | | IR | 95% Lower CI | 95% Upper CI | | | |
| Neutropenia (sensitive) | 101 | 277 | 36.5 | 29.74 | 44.36 | 16 | 351 | 4.6 | 2.61 | 7.41 | 7.6 | 4.5 | 12.9 |
| Neutropenia (specific) | 70 | 288 | 24.3 | 18.96 | 30.73 | 11 | 351 | 3.1 | 1.56 | 5.60 | 7.5 | 4.0 | 14.1 |
| Febrile neutropenia (sensitive) | ≤10 | n/a | 3.2 | 1.54 | 5.92 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | 10.8 | 1.4 | 84.4 |
| Febrile neutropenia (specific) | ≤10 | n/a | 1.0 | 0.20 | 2.81 | 0 | 357 | 0.0 | . | 1.03 | n/a | . | . |
| Leukopenia (sensitive) | 17 | 307 | 5.5 | 3.22 | 8.86 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | 18.6 | 2.5 | 139.6 |
| Leukopenia (specific) | 17 | 307 | 5.5 | 3.22 | 8.86 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | 18.6 | 2.5 | 139.6 |
| Alopecia | ≤10 | n/a | 0.3 | 0.01 | 1.78 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | 1.1 | 0.1 | 17.4 |
| Vomiting* | 28 | 299 | 9.4 | 6.23 | 13.55 | 52 | 340 | 15.3 | 11.42 | 20.06 | 0.6 | 0.4 | 1.0 |
| QT prolongation | 19 | 304 | 6.2 | 3.76 | 9.75 | 19 | 346 | 5.5 | 3.31 | 8.57 | 1.1 | 0.6 | 2.1 |
| Fatigue* | 49 | 274 | 17.9 | 13.24 | 23.66 | 68 | 334 | 20.4 | 15.82 | 25.83 | 0.8 | 0.6 | 1.2 |
| Serious infection | 77 | 299 | 25.8 | 20.36 | 32.24 | 78 | 344 | 22.7 | 17.91 | 28.28 | 1.1 | 0.8 | 1.5 |
| Brain/spinal infection | ≤10 | n/a | 1.3 | 0.35 | 3.28 | ≤10 | n/a | 0.6 | 0.07 | 2.02 | 2.2 | 0.4 | 11.8 |
| Pericardial/myocardial infection | 0 | 313 | 0.0 | . | 1.18 | 0 | 357 | 0.0 | . | 1.03 | n/a | . | . |
| Pulmonary infection | 33 | 307 | 10.7 | 7.39 | 15.08 | 26 | 352 | 7.4 | 4.82 | 10.81 | 1.4 | 0.8 | 2.3 |
| GI infection | ≤10 | n/a | 0.6 | 0.08 | 2.31 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | 2.4 | 0.2 | 26.0 |
| Genitourinary/Renal infection | 34 | 303 | 11.2 | 7.78 | 15.69 | 42 | 347 | 12.1 | 8.72 | 16.36 | 0.9 | 0.6 | 1.4 |
| Dental infection | 0 | 313 | 0.0 | . | 1.18 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | 0.0 | 0.0 | . |
| Ear, nose, and throat infection | 14 | 309 | 4.5 | 2.47 | 7.59 | ≤10 | n/a | 2.0 | 0.79 | 4.06 | 2.1 | 0.8 | 5.2 |
| Skin, bones, and joint infection | 16 | 308 | 5.2 | 2.97 | 8.43 | 13 | 353 | 3.7 | 1.96 | 6.29 | 1.3 | 0.6 | 2.8 |
| Hepatitis B infection | 0 | 313 | 0.0 | . | 1.18 | ≤10 | n/a | 1.4 | 0.46 | 3.28 | n/a | . | . |
| Influenza infection | ≤10 | n/a | 1.3 | 0.35 | 3.29 | 0 | 357 | 0.0 | . | 1.03 | n/a | . | . |
| Other infection | 64 | 296 | 21.7 | 16.68 | 27.65 | 124 | 309 | 40.1 | 33.38 | 47.84 | 0.5 | 0.4 | 0.7 |
| Diarrhea* | 14 | 306 | 4.6 | 2.50 | 7.68 | 24 | 347 | 6.9 | 4.44 | 10.30 | 0.6 | 0.3 | 1.2 |
| Interstitial lung disease/pneumonitis | 100 | 292 | 34.2 | 27.82 | 41.58 | 92 | 333 | 27.6 | 22.24 | 33.83 | 1.2 | 0.9 | 1.6 |
| Anemia (sensitive) | 133 | 272 | 48.9 | 40.92 | 57.91 | 82 | 331 | 24.8 | 19.70 | 30.74 | 1.9 | 1.4 | 2.5 |
| Anemia (specific) | 78 | 292 | 26.7 | 21.12 | 33.35 | 37 | 345 | 10.7 | 7.55 | 14.79 | 2.4 | 1.6 | 3.5 |
| Nausea* | 46 | 288 | 16.0 | 11.71 | 21.34 | 72 | 329 | 21.9 | 17.14 | 27.58 | 0.7 | 0.5 | 1.0 |
| Thrombocytopenia | 33 | 307 | 10.8 | 7.41 | 15.11 | 15 | 356 | 4.2 | 2.36 | 6.95 | 2.4 | 1.3 | 4.5 |
| Pulmonary embolism* | 14 | 307 | 4.6 | 2.50 | 7.66 | 12 | 351 | 3.4 | 1.77 | 5.98 | 1.2 | 0.5 | 2.6 |
| No history | 15 | 308 | 4.9 | 2.72 | 8.02 | ≤10 | n/a | 2.8 | 1.36 | 5.20 | 1.6 | 0.7 | 3.6 |
| Other venous embolism and thrombosis* | 11 | 298 | 3.7 | 1.84 | 6.60 | 33 | 337 | 9.8 | 6.74 | 13.75 | 0.4 | 0.2 | 0.7 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | ≤10 | n/a | 2.3 | 0.93 | 4.78 | 22 | 342 | 6.4 | 4.03 | 9.73 | 0.4 | 0.2 | 0.9 |
| No history of "Other venous embolism and thrombosis" | 22 | 304 | 7.2 | 4.53 | 10.95 | 29 | 342 | 8.5 | 5.68 | 12.19 | 0.8 | 0.5 | 1.4 |
| Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT) | 15 | 306 | 4.9 | 2.75 | 8.09 | 19 | 347 | 5.5 | 3.30 | 8.56 | 0.9 | 0.5 | 1.7 |
| Embolism and thrombosis of unspecified artery | 0 | 313 | 0.0 | . | 1.18 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | n/a | . | . |
| Cataracts and other ocular disorders | 18 | 306 | 5.9 | 3.48 | 9.29 | 20 | 349 | 5.7 | 3.50 | 8.86 | 1.0 | 0.5 | 1.8 |
| Stomatitis and mucositis | ≤10 | n/a | 2.9 | 1.32 | 5.49 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | 9.4 | 1.2 | 74.1 |
| Fever | 33 | 307 | 10.7 | 7.39 | 15.07 | 18 | 350 | 5.1 | 3.05 | 8.13 | 2.0 | 1.1 | 3.5 |
| Anorexia | ≤10 | n/a | 2.9 | 1.32 | 5.48 | ≤10 | n/a | 2.5 | 1.16 | 4.80 | 1.1 | 0.4 | 2.8 |
| Peripheral neuropathy | 22 | 307 | 7.2 | 4.49 | 10.86 | ≤10 | n/a | 2.5 | 1.16 | 4.81 | 2.6 | 1.2 | 5.7 |
| Sudden cardiac death | 0 | 313 | 0.0 | . | 1.18 | ≤10 | n/a | 0.3 | 0.01 | 1.56 | 0.0 | 0.0 | . |
| Diabetes mellitus | 44 | 299 | 14.7 | 10.68 | 19.73 | 60 | 337 | 17.8 | 13.59 | 22.92 | 0.8 | 0.5 | 1.2 |
| Type 2 Diabetes mellitus | 44 | 300 | 14.7 | 10.67 | 19.71 | 59 | 337 | 17.5 | 13.32 | 22.57 | 0.8 | 0.5 | 1.2 |
| Hyperglycemia | ≤10 | n/a | 1.6 | 0.52 | 3.74 | ≤10 | n/a | 0.8 | 0.17 | 2.46 | 2.0 | 0.5 | 8.8 |
| Liver failure (Acute liver injury) | 13 | 312 | 4.2 | 2.22 | 7.13 | ≤10 | n/a | 2.0 | 0.79 | 4.06 | 1.9 | 0.8 | 4.8 |
| Abnormal ALT (incident)^ | ≤10 | n/a | 6.8 | 2.92 | 13.35 | 11 | 113 | 9.8 | 4.87 | 17.46 | 0.6 | 0.3 | 1.6 |
| Abnormal ALT (incident or prevalent)^ | 16 | 150 | 10.6 | 6.08 | 17.28 | 20 | 134 | 14.9 | 9.12 | 23.05 | 0.6 | 0.3 | 1.2 |
| Abnormal AST (incident)^ | ≤10 | n/a | 7.2 | 3.28 | 13.61 | 12 | 117 | 10.2 | 5.30 | 17.90 | 0.7 | 0.3 | 1.6 |
| Abnormal AST (incident or prevalent)^ | 19 | 148 | 12.9 | 7.75 | 20.11 | 31 | 134 | 23.2 | 15.76 | 32.91 | 0.5 | 0.3 | 0.9 |
| Abnormal ALP (incident)^ | ≤10 | n/a | 4.5 | 1.64 | 9.71 | ≤10 | n/a | 4.1 | 1.33 | 9.56 | 1.0 | 0.3 | 3.2 |
| Abnormal ALP (incident or prevalent)^ | 15 | 148 | 10.2 | 5.69 | 16.77 | 28 | 133 | 21.0 | 13.96 | 30.35 | 0.4 | 0.2 | 0.7 |
| Secondary malignancies (second primary cancer) | 101 | 280 | 36.0 | 29.36 | 43.80 | 139 | 371 | 37.5 | 31.54 | 44.30 | 0.9 | 0.7 | 1.2 |
| Non-melanoma skin cancer | ≤10 | n/a | 2.3 | 0.91 | 4.67 | ≤10 | n/a | 1.7 | 0.70 | 3.56 | 1.8 | 0.6 | 6.0 |

Abbreviations: GI, gastrointestinal; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person-time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazard ratios; LCL, lower confidence limit; UCL, upper confidence limit; DVT, deep vein thrombosis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date

^Abnormal AST > 40 U/L; Abnormal ALT > 40 U/L; Abnormal ALP > 147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

*Return to Table of Contents*

**Table 2-7A** Incidence rates and unadjusted hazard ratios of the acute liver injury in new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group) with algorithm-defined advanced stage ER+/HER2- Breast cancer

| | Before Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All new users of palbociclib and fulvestrant (n=548) | | | | | All new users of fulvestrant alone (pre-2015) (n=2,061) | | | | | Unadjusted Hazard Ratios | | |
| | | | IR (per 100 person-years) | | | | | IR (per 100 person-years) | | | | | |
| **Event** | **# Events** | **PT at risk** | **IR** | **95% Lower CI** | **95% Upper CI** | **# Events** | **PT at risk** | **IR** | **95% Lower CI** | **95% Upper CI** | **HR** | **95% LCL** | **95%UCL** |
| **Overall** | | | | | | | | | | | | | |
| Acute liver injury (primary) | 13 | 314 | 4.1 | 2.2 | 7.1 | 22 | 1,455 | 1.5 | 1.0 | 2.3 | 2.6 | 1.3 | 5.1 |
| Acute liver injury (original with labs) | 13 | 314 | 4.1 | 2.2 | 7.1 | 18 | 1,454 | 1.2 | 0.7 | 2.0 | 3.1 | 1.5 | 6.3 |
| Acute liver injury (sensitive) | 37 | 308 | 12.0 | 8.5 | 16.5 | 33 | 1,451 | 2.3 | 1.6 | 3.2 | 4.9 | 3.0 | 7.8 |
| Acute liver injury (specific) | 0 | 315 | 0.0 | . | 1.2 | 0 | 1,457 | 0.0 | . | 0.3 | | | |
| **Among patients with a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary) | 11 | 184 | 6 | 3.0 | 10.7 | 19 | 797 | 2 | 1.4 | 3.7 | 2.4 | 1.1 | 5.0 |
| **Among patients without a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary) | ≤10 | n/a | 2 | 0.2 | 5.6 | ≤10 | n/a | 0 | 0.1 | 1.3 | 3.1 | 0.5 | 18.4 |

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart

Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; HR, hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury.

**Table 2-7B** Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone (historical comparison group) with algorithm-defined advanced stage ER+/HER2- Breast cancer

| | After Propensity Score Matching | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | New users of palbociclib and fulvestrant (n=544) | | | | | New users of fulvestrant alone (pre-2015) (n=544) | | | | | Adjusted Hazard Ratios | | |
| | | | IR (per 100 person-years) | | | | | IR (per 100 person-years) | | | | | |
| **Event** | **# Events** | **PT at risk** | **IR** | **95% Lower CI** | **95% Upper CI** | **# Events** | **PT at risk** | **IR** | **95% Lower CI** | **95% Upper CI** | **aHR** | **95% LCL** | **95%UCL** |
| **Overall** | | | | | | | | | | | | | |
| Acute liver injury (primary) | 13 | 312 | 4.2 | 2.2 | 7.1 | ≤10 | n/a | 1.5 | 0.5 | 3.2 | 2.8 | 1.0 | 7.8 |
| Acute liver injury (original with labs) | 13 | 312 | 4.2 | 2.2 | 7.1 | ≤10 | n/a | 2.2 | 1.0 | 4.2 | 1.9 | 0.8 | 4.8 |
| Acute liver injury (sensitive) | 37 | 307 | 12.1 | 8.5 | 16.6 | 15 | 411 | 3.7 | 2.0 | 6.0 | 3.6 | 1.8 | 7.0 |
| Acute liver injury (specific) | 0 | 313 | 0.0 | . | 1.2 | 0 | 413 | 0.0 | . | 0.9 | -- | -- | -- |
| **Among patients with a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary) | 11 | 183 | 6.0 | 3 | 10.8 | ≤10 | 258 | 1.9 | 0.6 | 4.5 | 3.1 | 1.0 | 9.7 |
| **Among patients without a risk factor for ALI*** | | | | | | | | | | | | | |
| Acute liver injury (primary) | ≤10 | n/a | 1.5 | 0.2 | 5.6 | ≤10 | n/a | 0.6 | 0.0 | 3.6 | 1.9 | 0.2 | 21.0 |

*Risk factors for ALI defined as chronic liver disease or alcoholism, chronic or acute hepatitis, chronic or acute disease of the gallbladder or pancreas, or hepatic, biliary or pancreatic cancer, or congestive heart

Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit; ALI, acute liver injury.