NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: Safety of Palbociclib among Breast Cancer Patients in the United States:

A retrospective cohort study

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Keywords: Palbociclib, Safety, Real World, Comparative

Rationale and background:
Palbociclib received accelerated approval by the United States (US) Food Drug Administration (FDA) in February 2015 to treat post-menopausal women for advanced stage Hormone Receptor Positive (HR+)/Human Epidermal Growth Factor Negative (HER2-) breast cancer in combination with letrozole as the initial endocrine-based therapy. Subsequently, in February 2016, palbociclib in combination with fulvestrant received approval for the treatment of women with HR+/HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy. Given the limited data on palbociclib use outside of clinical trials, we sought to characterize the utilization and safety of palbociclib in a real-world population.

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 acute liver injury (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.

Primary Objective: Describe patient characteristics and incidence rates of selected safety events among 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:

    - Concomitant fulvestrant new users;
    - Concomitant letrozole new users; and
    - 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 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 selected safety events (including ALI) between new users of palbociclib with fulvestrant and new users of the following subgroups of users of fulvestrant alone (historical comparator group identified from pre-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 group 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 (both historical and contemporaneous comparator groups).

Study design:
Retrospective longitudinal new user study with medical record review

Setting:
HealthCore Integrated Research Database (HIRD), a commercially insured population dispersed across the United States (US)

Subjects and study size, including dropouts:
There were 2,795 users of palbociclib during the study period from February 2015 to September 2017. After applying the exclusion criteria (those <18 years and those with less than three months health eligibility prior to palbociclib initiation), there were 2,445 patients who initiated palbociclib in the HIRD, including 566 new users of palbociclib with fulvestrant and 1,159 new users of palbociclib with letrozole. There were 2,315 new users of fulvestrant monotherapy between January 2011 and January 2015 (historical comparator cohort), and 961 new users of fulvestrant monotherapy between February 2015 and September 2017 (contemporaneous comparator cohort). The historical comparator cohort was the main comparison cohort for safety event analyses, while the contemporaneous comparator cohort was added as a secondary analysis for the ALI safety event.

Variables and data sources:

Exposures:

Exposure to palbociclib, fulvestrant, and letrozole were assessed using pharmacy claims and medical claims. Treatment episodes (i.e. person-time classified as exposed to study drugs) were constructed for each patient by concatenating consecutive dispensing periods (dispensing date + days supply + 30-day extension period).

Outcomes:

Safety event outcomes were assessed using algorithms based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM or ICD-9) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM or ICD-10) diagnosis codes from claims during the follow-up period of the treatment episodes using claims data in the HIRD and included the following safety events of interest including leukopenia, pulmonary embolism, anemia, ALI, and serious infections using claims definitions. The ALI claims definitions were validated through medical record adjudication.

Covariates:

Demographics, medical history, breast and other cancer therapies, healthcare utilization, medication use (breast cancer and non-breast cancer related), and co-morbidities were described for each objective and considered for utilization in propensity score matching for Secondary Objectives 3 and 4.

Results:

Among all 2,445 palbociclib initiators, 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%). 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%). Safety events

common to palbociclib users after initiation included neutropenia, anemia, interstitial lung disease/pneumonitis, and serious infections (each IR>20 per 100 person-years).

Baseline characteristics, including evidence of metastasis, were similar in the new users of palbociclib with fulvestrant and the historical comparator group of new users of the fulvestrant monotherapy after propensity score matching. When compared to the historical comparator group, new users of palbociclib who also initiated fulvestrant were more likely to develop neutropenia, leukopenia, anemia, stomatitis and mucositis, and ALI in both unadjusted and propensity score adjusted analyses. 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, QT prolongation, and pulmonary embolism (HRs<1.4).

After ALI signal refinement analyses, we observed an elevated risk of ALI in new users of palbociclib with fulvestrant compared to new users of historical fulvestrant monotherapy when using alternative algorithms for ALI and adjusting for additional ALI risk factors (e.g., primary ALI algorithm: aHR=3.0, 95% CI=1.1-8.4). In contrast, when separately comparing ALI risk in new users of palbociclib with fulvestrant to a comparator group of contemporaneous new users of fulvestrant monotherapy, no increased risk of ALI was observed with palbociclib use in adjusted analyses (primary ALI algorithm: aHR=0.5, 95%CI=0.1-2.2). After medical record adjudication, the primary ALI algorithm had a positive predictive value (PPV) of 84%. After medical record review, a medical expert attributed most cases to the presence or presumption of liver metastases, although drug induced ALI was noted as a possible cause in at least one case. Reasons for causal attribution were not given.

Discussion:

Palbociclib is commonly used in US patients with advanced ER+/HER2- breast cancer. In this real-world study population, safety events commonly identified after palbociclib use were largely similar to those identified in randomized controlled trials. An event of particular interest, ALI, had an increased risk among new users of palbociclib with fulvestrant when compared to a historical comparator group of new users of fulvestrant monotherapy. This association was supported by most sensitivity analyses, however the number of ALI events were limited and the increased risk was not observed when new users of palbociclib with fulvestrant were compared to a contemporaneous comparator group of new users of fulvestrant monotherapy. Further study in larger populations would better inform the safety of palbociclib and its impact on ALI risk.

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