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Real- World Safety Evaluation through Electronic Medical Record: A Transformative Approach to Korean Post-Marketing Surveillance

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ABSTRACT

Existing post-marketing surveillance (PMS) in Korea has been implemented for decades to secure safety data for regulatory purposes. However, the separation from the actual medical environment, difficulty in recruiting patients, and high costs and time-consuming are burdensome to pharmaceutical companies. Electronic medical record (EMR) is emerging as an effective alternative to safety analysis. This study aims to evaluate whether retrospective safety assessments using EMR data can effectively replace traditional PMS.

This study used EMR-based database from tertiary multicenter hospitals in Korea, collected between August 29, 2015, and December 31, 2023. It included patients with HR(+)/HER2(-) advanced or metastatic breast cancer treated with palbociclib combined with an aromatase inhibitor or Fulvestrant. The analysis included both structured data (e.g., diagnosis codes, prescriptions, laboratory results) and unstructured data (e.g., clinical notes and nursing records). Unstructured data were processed using a hybrid approach of rule-based Natural Language Processing (NLP) techniques and Large Language Models (LLMs), including keyword and pattern matching to identify mentions of adverse events or clinical symptoms. Adverse events were defined using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), which enabled the inclusion of rarely occurring events. The definitions of adverse events according to the CTCAE were determined using operational definitions from previous published literature and CTCAE laboratory criteria. In cases where no relevant literature was available, appropriate criteria were established through clinical expert review.

Compared to traditional PMS, we were able to derive various clinical information and incidence of adverse event in more patients with shorter time. Therefore, EMR-based safety analysis can be considered as a realistic and scientific alternative to traditional PMS.

INTRODUCTION

In Korea, post-marketing drug safety management mainly relies on traditional PMS through Drug Use-Results Surveys (DURS), which collect safety and efficacy data during routine clinical practice. However, these studies have major limitations: high cost and resource burden, lack of control groups, selection bias, and insufficient statistical validation — often resulting in descriptive case collection rather than robust evidence generation. Since the primary goal of post-marketing safety is to identify previously unknown adverse drug reactions, more proactive monitoring strategies are needed.

Globally, the importance of Real-World Data (RWD) and Real-World Evidence (RWE) is increasing, with growing use in regulatory decision-making. Although frameworks now support real-world safety data collection, RWD utilization in Korean post-marketing studies remains rare, highlighting the need to explore and expand RWD-based approaches.

IBRANCE®, also known as palbociclib, was first approved for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer in postmenopausal women, in combination with letrozole. IBRANCE® PMS was approved in Korea in 2016 with a regulatory requirement to collect prospective 3,000 cases within 6 years. However, patient enrollment was challenging because most patients were female breast cancer cases, and large hospitals prioritized global clinical trials or investigator-sponsored research over PMS. In 2020, the target sample size was reduced to 1,000 cases, but continuous enrollment remained difficult. As a result, study period was extended by 9 years. Therefore, we planned the IBRANCE DB protocol using EMR-based safety analysis as an alternative, and it was approved by Korea MFDS in July 2024.

This study aims to use a large real-world database to describe breast cancer patients treated with IBRANCE and assess its safety and effectiveness. The primary objective is to evaluate safety, including adverse events during treatment, and identify related risk factors. The secondary objectives are to assess effectiveness through tumor response and compare treatment outcomes across patient groups based on predictors such as age and pathological characteristics.

MATERIALS AND METHODS

Data Source and study population

This study used an electronic medical record (EMR)–based database derived from tertiary, multicenter hospitals in Korea. Data were collected between August 29, 2015, and September 30, 2023.The study included patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) advanced or metastatic breast cancer who were treated with palbociclib in combination with an aromatase inhibitor or fulvestrant.

Exposure Definition

The exposure group consisted of patients with HR(+)/HER2(−) advanced or metastatic breast cancer who received IB RANCE® in combination therapy. Combination therapy was defined as the prescription of letrozole, anastrozole, or fu lvestrant within 28 days following the initiation of IBRANCE®.

Index Date and Follow-up

The index date for all treatment-related events, including adverse events and tumor response assessments, was defin ed as the date of the first IBRANCE® prescription. For safety analysis, the observation period extended from the inde x date to 28 days after the last dose of IBRANCE®. Adverse events were identified and classified according to the Na tional Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. For effectiveness ana lyses, the observation period extended from the index date to the date of death or the censoring date, whichever occu rred first. The censoring date was defined as the date of the last clinical visit or the end of the study period. Effectiven ess outcomes included the assessment of overall survival (OS).

Data processing and management

Data for the IBRANCE database was collected from electronic medical records (EMRs) through a clinical data wareh ouse (CDW). All study data were standardized and de-identified at the time of extraction using the CDW system to en sure patient privacy and data consistency. Both structured and unstructured data were utilized in this study. Structure d data included diagnosis codes based on the International Classification of Diseases, 10th Revision (ICD-10), prescr iption records, laboratory test results, demographic information, and treatment history.

Unstructured data consisted of clinical notes and nursing records documented as free-text clinical charts. These data were processed through an integrated approach combining rule-based logic and generative AI (LLMs), including keyw ord searches and pattern-matching algorithms, to successfully extract patient cohorts and detect adverse events with enhanced sensitivity.

Outcome Assessment

For safety, adverse events were defined and classified according to the National Cancer Institute's Common Terminol ogy Criteria for Adverse Events (CTCAE). Operational definitions of adverse events were derived from previously pub lished literature and CTCAE laboratory criteria. When no applicable definitions were available in the literature, event d efinitions were established through review and consensus by clinical experts.

For Effectiveness, Effectiveness analyses were conducted among patients who received IBRANCE® in combination with an aromatase inhibitor as first-line endocrine therapy and who were prescribed IBRANCE® for a minimum of four treatment cycles.

Data Quality Control

To ensure the validity and reliability of the study data, quality control procedures were implemented in accordance wit h standard data quality management practices. These procedures included consistency checks, completeness asses sments, and logical validation of key variables.

Statistical Analysis

Safety analyses were conducted among patients who received at least one dose of IBRANCE® in combination with let rozole, anastrozole, or fulvestrant. The incidence of adverse events was calculated as the proportion of patients exper iencing at least one adverse event during the observation period. Incidence rates were reported with corresponding 9 5% confidence intervals (CIs).

Effectiveness analyses were performed in patients who received at least four cycles of IBRANCE® in combination with an aromatase inhibitor as first-line endocrine therapy and had a documented treatment response. Effectiveness outc omes were summarized with 95% confidence intervals calculated using the Wilson method. Time-to-event outcomes were analyzed using the Kaplan–Meier method, with 95% confidence intervals estimated for survival curves. Overall s urvival (OS) was defined as the time from the index date to the date of death from any cause or the censoring date, w hichever occurred first. Real-world tumor response (rwTR) was assessed based on clinician-evaluated radiologic and clinical data and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive d isease (PD). The best overall response (BOR) was summarized for each patient over the course of treatment. Objecti ve response rate (ORR) was defined as the proportion of patients who achieved a complete response (CR) or partial r esponse (PR) during the observation period.

Final study outcomes were derived from pooled analyses of site-level data summaries across all participating

institutions.

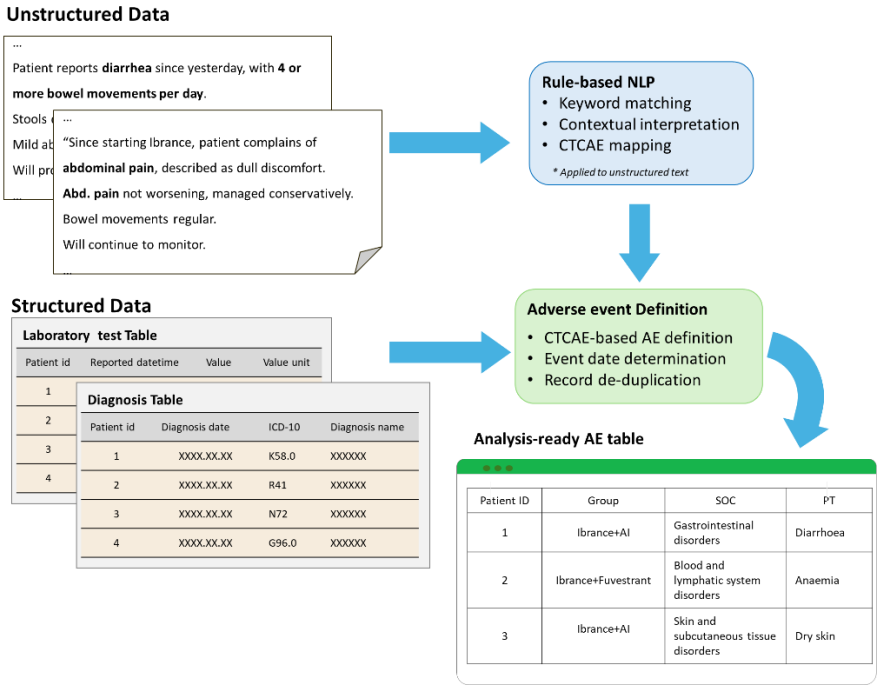

Figure. Workflow for Generating Analysis-Ready AE Data

Limitations and Future Directions

This study has several limitations inherent to the use of retrospective EMR-based data. First, compared with structured post-marketing surveillance (PMS) reporting systems, EMR data may inadequately capture mild, transient, or non-specific adverse events, leading to potential underestimation of event incidence. Second, variations in coding practices, clinical documentation, and data completeness across participating sites may reduce data consistency relative to protocol-driven PMS studies. Third, causal attribution of adverse events is inherently limited in retrospective observational analyses, as EMR-based assessments lack the systematic, physician-adjudicated causality evaluations typically performed in PMS programs. Finally, PMS-specific data elements—such as detailed reasons for treatment discontinuation—are not consistently or comprehensively recorded within routine EMR systems.

Future research should focus on methodological advancements to enhance the utility of EMR data for pharmacovigilance. Development of an integrated EMR–PMS hybrid model may enable automated, PMS-aligned data capture while preserving the advantages of real-world clinical data. The application of advanced natural language processing (NLP) techniques and Large Language Models (LLMs) could further improve the accuracy and completeness of adverse event identification from unstructured clinical text. In addition, promoting national-level standardization of clinical coding and documentation practices would support scalable and consistent EMR-based PMS activities. Finally, inclusion of appropriate comparator cohorts in future studies would strengthen the interpretation and contextualization of safety findings.

CONCLUSION

EMR-based safety analysis provided broader clinical information and identified adverse events in more patients with a shorter time compared to traditional PMS, demonstrating its viability as an alternative approach. Therefore, EMR-based safety analysis can be considered as a realistic and scientific alternative to traditional PMS.

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