CLEE011AIC01 Study Results Abstract for Public Disclosure

Title

REAL-World EvidencE Study for the SAfety and Effectiveness of Ribociclib in Combination with Hormonal Therapy in Patients with HR+/HER2- Advanced or Metastatic Breast Cancer in the Middle East Region: The REALEESA Study

Date

10 June 2026

NIS Type

NIS with both Primary Data Collection and Secondary Use of Data

Keywords

Breast Cancer, Ribociclib, Hormonal Therapy, HR+/HER2-, Effectiveness, Safety

Rationale and background

Breast cancer (BC) is the most prevalent cancer type in women and takes a pole position in cancer-related deaths (Bray *et al.*, 2018; Elezaby *et al.*, 2019).

The increase in BC incidence varied substantially amongst different geographical regions, with which the largest increase was observed in Middle Eastern countries (Li *et al.*, 2019). Such observations concord with national studies from the Middle East, demonstrating an increased incidence of BC to reach 37.1 per 100,000 person-year between 2011 and 2019 (Zahedi *et al.*, 2020).

The standard regimen for patients with early hormone receptor-positive/ human epidermal growth factor receptor 2-negative (HR+/ HER2-) BC usually encompasses a combination of surgical resection with removal of axillary lymph nodes, radiotherapy, and systemic hormonal therapies (with or without chemotherapy) (Senkus *et al.*, 2015). While adjuvant hormonal therapies dramatically reduced the recurrence rate and metastasis in patients with early HR+/HER2- BC (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2015). The oncological outcomes of advanced BC are much less favorable (Waks and Winer, 2019).

HR+ BCs, which represent up to 75% of invasive BCs, are characterized by the presence of receptors for estrogen (ER) and/or progesterone (PgR). Endocrine therapy (ET) remains the therapeutic backbone for treating HR+ patients with advanced/metastatic BC (Cardoso *et al.*, 2017). However, up to 50% of HR+ patients with metastatic BC develop mechanisms of therapeutic resistance to the ET they receive (Osborne and Schiff, 2011).

Recently, several targeted agents have been proposed for the management of advanced/metastatic BC following our better understanding of the underlying mechanisms of resistance in advanced cases. In BC, sustained activation of cyclin-dependent kinase (CDKs) 4/6 was found to play a critical role in the tumorgenicity of breast cancer cells (Yu, Geng and Sicinski, 2001). Ribociclib (LEE011) is an orally bioavailable, selective, small-molecule inhibitor of CDK4/6 that blocks retinoblastoma protein phosphorylation, thereby preventing cell-cycle progression and inducing G1 phase arrest (Kim *et al.*, 2013). Food and Drug Administration (FDA) approval was granted to Ribociclib in March 2017 for the treatment of postmenopausal women with metastatic HR+/ HER2–BC (Shah *et al.*, 2018). In July 2018, this approval was expanded to include the pre/peri-menopausal population based on the MONALEESA 7 trial data.

The combination of CDK4/6 inhibitors with hormonal therapy has emerged in recent years as the new "standard of care" treatment in metastatic HR+ BC. However, in the Middle East region, limited data have been published on the use of CDK4/6 inhibitors on its population, and no data was done on Ribociclib. It is worth observing the safety profile and effectiveness of Ribociclib in combination with hormonal therapy in this geographic region (Heer *et al.*, 2020).

The current observational study aimed to obtain real-world safety data of HR+/HER2– advanced/metastatic breast cancer patients who have received Ribociclib in combination with hormonal therapy in pre-and postmenopausal women or men in Middle Eastern countries. The study also aimed to obtain real-world data about Ribociclib effectiveness in terms of progression-free survival (PFS) and duration of treatment, clinical characteristics, and demographics.

Research question and objectives

Primary objectives

1. To describe real-world safety of HR+/HER2– advanced/ metastatic BC patients who have received Ribociclib in combination with hormonal therapy in pre-and postmenopausal women or men in Middle Eastern countries.

   **Postmenopausal status is defined either by 1. Prior bilateral oophorectomy OR 2. Age ≥ 60 OR 3. Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range per local normal range. If the patient is taking tamoxifen or toremifene and age < 60, then FSH and plasma estradiol levels should be in the postmenopausal range per local normal range (National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2017). Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure menopausal status.*

   ***Premenopausal status is defined as either: 1. The patient had the last menstrual period within the last 12 months, OR 2. If on tamoxifen or toremifene within the past 14 days, plasma estradiol and FSH must be in the premenopausal range per local*

normal range, OR 3. In case of therapy-induced amenorrhea, plasma estradiol and/or FSH must be in the premenopausal range per the local normal range.

Secondary objectives

1. To describe the effectiveness of Ribociclib in combination with hormonal therapy in terms of percentage of progression-free patients, overall response rate (ORR), and duration of treatment of HR+/HER2– advanced/metastatic BC in pre-and postmenopausal women or men in Middle Eastern countries.

   **ORR is defined as the proportion of patients with the best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1. CR = Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR = At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.*

2. Describing clinical characteristics and demographics of HR+/HER2– advanced/metastatic BC patients who have received Ribociclib in combination with hormonal therapy in pre-and postmenopausal women or men in Middle Eastern countries.

Study design

This is a non-interventional, ambispective, observational cohort study describing the real-world safety data of 358 HR+/HER2– advanced/metastatic BC patients who have received ribociclib combined with hormonal therapy in pre-and postmenopausal women or men in Middle Eastern countries.

The investigators had a six-month recruitment period to include the eligible subjects as per the protocol selection criteria. Retrospective patients had been on Ribociclib in combination with hormonal therapy for at least 18 months and stopped the medication before the patient's recruitment.

Ambispective patients had initiated Ribociclib, in combination with hormonal therapy, for at least 12 months before the patient's recruitment date and are still on Ribociclib in combination with hormonal therapy at recruitment. These patients were followed up till progression, death, Ribociclib discontinuation due to adverse events, or till a maximum period of 6 months, whichever came first.

Data were collected from patient electronic medical records (EMR) in the sites chosen for patients who received Ribociclib, in combination with hormonal therapy, in the first or second-line setting available in the relevant institutions.

Setting

- 358 HR+/HER2– advanced/metastatic BC patients who have received ribociclib combined with hormonal therapy in pre-and postmenopausal women or men in Middle Eastern countries.
- 5 Sites.
- Middle Eastern countries: Jordan, Kingdom of Saudi Arabia (KSA), Oman, and United Arab Emirates (UAE).

Subjects and study size, including dropouts

A total of 368 patients was enrolled in the study. The sample size should capture very common adverse events reported in previous studies as well as adverse events ≥ 10% occurring in grade 3 and grade 4 with precision ±2.5%.

Variables

- Demographic information
  - Gender
  - Age
  - Nationality
  - Comorbidity profile (Charlson comorbidity index, CCI) (Charlson *et al.*, 1987)
  - Medical history of previous cancer
  - Family history of breast cancer
  - Menopausal status (Pre/Post)
- Clinical characteristics variables
  - Extent of the disease (Tumor, Node, and Metastasis (TNM)-Stage/ Stage III &IV)
  - Eastern Cooperative Oncology Group (ECOG) performance status
  - Number of metastatic sites/ sites of metastasis
- Ribociclib data
  - Dose
  - Start date
  - End date
  - Line of therapy (1^{st} line – 2^{nd} line)
  - Dose reduction data
  - Dose interruption data
  - Discontinuation data
- Prior line of treatment in case the Ribociclib is 2^{nd}, or more, line therapy
  - Treatment type

  - Agent name
  - Duration
  - Number of cycles
  - Reason of switch to the Ribociclib line of treatment
- Prior line of treatment (adjuvant or neo-adjuvant) in case the Ribociclib is 1st line therapy
  - Treatment type
  - Agent name
  - Disease free interval (DFI)* (>12months/<12months)

    **DFI is defined as the time between the first diagnosis of breast cancer and disease recurrence (Finn et al., 2020)*.
  - (Finn *et al.*, 2020)Treatment free interval**(TFI)

    ***TFI is defined as the time between the end of any (neo)adjuvant therapy and relapse (Finn et al., 2020).*
  - Reason of switch to the Ribociclib line of treatment
- Hormonal therapy data (Including luteinizing hormone-releasing hormone (LHRH) for premenopausal women)
- Other treatment received data, in case of combination
- Concomitant medications received data
- Subsequent therapy data
- Occurrence of progression on Ribociclib therapy line of treatment
- Treatment response data
- Date of death
- Adverse events

Data sources

The Investigator prepared and maintained adequate and accurate source documents designed to record all observations and other pertinent data for each patient treated with the study drug.

Statistical methods

A detailed statistical analysis plan (SAP) was done prior to the analysis of data that described all steps needed in data analysis.

Descriptive statistics were used to summarize serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation or dose modification of therapy, and severity of AEs, baseline

characteristics, and demographic data. Categorical variables were presented by count and percent. Numerical data were tested for normality using the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Normally distributed data is presented using mean and standard deviation, while non-normally distributed variables were summarized using the median and interquartile range.

The proportion of patients progression-free at 18 months and objective response were calculated along with 95% confidence interval. The duration of therapy and median dose intensity were calculated and summarized for the study population. An interim analysis was conducted.

Results

A total of 358 patients were included in the final analysis after exclusion of 10 ineligible cases. Of these, 143 patients (39.9%) were enrolled retrospectively, while 215 patients (60.1%) were enrolled through the ambispective cohort. Most patients were female (99.4%) with a mean (SD) age of 55.1 (11.87) years at data collection and 51.8 (11.84) years at Ribociclib initiation. Jordan represented the largest proportion of participants (n=255; 71.2%). All patients had Stage IV disease with distant metastasis, most frequently involving bone (n=291; 81.3%), lungs (n=117; 32.7%), and liver (n=56; 15.6%). The majority had one metastatic site (n=208; 58.1%), and 83.7% (n=298) had an ECOG score of 0. Comorbidities were infrequent, with diabetes documented in 44 (12.3%) of patients. Ribociclib was initiated at 600 mg/day in 95.5% (n=342) of the cohort; discontinuation occurred in 48.9% (n=175), primarily due to disease progression (n=152; 86.9%).

Safety assessments showed that 69.8% (n=250), 77.4% (n=277), and 80.2% (n=287) of patients reported adverse events (AEs) at 6, 12, and 18 months, respectively, increasing to 83.2% (n=298) by the end of treatment. Across all timepoints, more than 99% of AEs were non-serious, while serious adverse events (SAEs) occurred in 5.2%(n=13), 5.8% (n=16), 6.6% (n=19), and 10.7% (n=32) of patients at 6, 12, 18 months, and treatment end, respectively. Infections were the most common SAE at each assessment, followed by neutropenia. Event-level data recorded 643 AEs at 6 months, 956 at 12 months, 1,268 at 18 months, and 1,481 by the end of treatment. Non-serious events consistently accounted for over 97% of all AEs. Mild events represented the majority throughout the study, while severe events accounted for only 2–3% of all AEs at each timepoint. Neutropenia, infection, and arthralgia were the most commonly reported AEs at both the patient and event levels.

Treatment modifications related to AEs were frequent. By 6, 12, and 18 months, 44.4% (n=111), 48.4% (n=134), and 50.5% (n=145) of patients, respectively, required dose reduction or discontinuation due to AEs, reaching 52.3% (n=156) by treatment completion. Dose interruptions occurred in 26.3% (n=94) of patients by 6 months, 10.6% (n=38) by 12 months, 7.8% (n=28) by 18 months, and 5.1% (n=18) by treatment end, with mean durations ranging from 15 to 34 days. Most interruptions were attributed to AEs, and over half of the affected patients resumed at 600 mg/day.

Regarding treatment effectiveness, 55.9% (n=200) of patients maintained non-progressive disease at 18 months or at treatment completion. At the patient level, complete or partial responses were observed at all assessment points, while stable disease remained the

predominant outcome until the end of treatment, at which point 52.7% (n=187) had stable disease, and 44.2% (n=157) had progression. Among patients receiving first-line Ribociclib, many had prior surgery (n=95;32.9%) and adjuvant systemic therapies, while second-line users commonly had prior chemotherapy (n=54; 78.3%). Most premenopausal women received LHRH agonists. After discontinuation of Ribociclib, 41.3% (n=148) of patients received subsequent therapy, most commonly hormonal therapy (n=74; 50%) or chemotherapy (n=59; 39.9%).

Discussion

Ribociclib is an orally bioavailable, highly selective CDK4/6 inhibitor targeting the dysregulated CDK4/6-Rb pathway in HR+ BC (Curigliano et al., 2017; Dhungana et al., 2025). With its increasing use in real-world practice, several studies have evaluated its safety and effectiveness across different treatment settings (Dhungana et al., 2025). In our study, Ribociclib combined with ET demonstrated a favorable safety and effectiveness profile in both premenopausal and postmenopausal women with HR+/HER2− advanced or metastatic BC.

Although AEs were commonly reported in our cohort, SAEs occurred in a relatively small proportion of patients. Post-marketing FDA Adverse Event Reporting System (FAERS) analyses indicate that many AEs occur early during treatment initiation (Xu, Wang and Shen, 2025). These findings are consistent with clinical trials such as CompLEEment-1 and NATALEE, which similarly reported frequent AEs but relatively limited SAEs and no new long-term safety signals (De Laurentiis et al., 2022; Fasching et al., 2025). Similarly, MONALEESA trials confirmed that most AEs associated with Ribociclib are mild to moderate and that long-term therapy remains generally tolerable (Hortobagyi et al., 2018; Slamon et al., 2018). In our study, infections and neutropenia were the most common SAEs. These findings align with previous studies identifying hematologic toxicities, particularly neutropenia, as the most frequent adverse events associated with Ribociclib (Kalinsky et al., 2023; Dhungana et al., 2025; Fasching et al., 2025). Therefore, neutropenia remains a predictable toxicity that requires careful monitoring during treatment. Consistent with previous studies, treatment discontinuation in our cohort was mainly driven by disease progression rather than adverse events (De Laurentiis et al., 2022; Lu et al., 2022).

In terms of effectiveness, Ribociclib provided meaningful clinical benefit, with more than half of patients maintaining non-progressive disease and an ORR of 22.5%. These results are consistent with pivotal trials such as MONALEESA-3 and MAINTAIN, which demonstrated improved PFS with Ribociclib combined with ET (Slamon et al., 2018; Kalinsky et al., 2023). Overall, our findings support the real-world effectiveness and manageable safety profile of Ribociclib in HR+/HER2− advanced and metastatic BC.

Conclusion

Ribociclib combined with ET shows meaningful clinical benefit and maintains a manageable safety profile in HR+/HER2− advanced or metastatic BC, with most AE being mild and

treatment discontinuation largely driven by disease progression rather than toxicity. Effectiveness and safety outcomes in this study align with major clinical trials, supporting the real-world applicability of Ribociclib and emphasizing the need for routine monitoring, particularly for neutropenia, to optimize patient outcomes.