Clinician Group Input

Generic Drug Name (Brand Name): Ribociclib (KISQALI)
CDA Project Number: PC0395-000
Indication: Ribociclib is indicated:

- For the adjuvant treatment of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative stage II and III early breast cancer, in combination with an aromatase inhibitor.
- In pre- or perimenopausal women, or men, the AI should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Name of Clinician Group: REAL Alliance
Author of Submission: Dr. Karen Gelmon, Medical Oncologist at the BC Cancer Agency, Vancouver Coastal Health Research Institute – VCHRI, Professor of Medicine at the University of British Columbia
REAL Alliance Members in support of this submission: Dr. Jean-Francois Boileau, Dr. Christine Brezden-Masley, Dr. Stephen Chia, Dr. Scott Edwards, Dr. Jan-Willem Henning, Dr. Anil Abraham Joy, Dr. Nathalie Levasseur, Dr. Mita Manna, Dr. Sandeep Sehdev, Dr. Christine Simmons.
Clinicians that agree with the REAL Alliance Clinical Input and in support of the submission: Dr. Nayyer Iqbal, Dr. Maged Salem, Dr. Silvana Spadafora.

1. About Your Clinician Group

The Research Excellence, Active Leadership (REAL) Canadian Breast Cancer Alliance is an equitable standing nucleus committee of multi-disciplinary, clinical-academic oncologists across Canada and Breast Cancer Canada, a patient organization. Formed in December 2023 in recognition that a national ecosystem of leadership should address evidence-based guidance and recommendations for equitable breast cancer clinical management. REAL Alliance publishes national clinical consensus recommendations, routinely updated, for timely health policy, funding, and consistent clinical adoption based on research evidence and medical specialty expertise to ensure optimal outcomes for breast cancer patients across all provinces and territories in Canada.

2. Information Gathering

Our members met virtually and exchanged views via email to discuss our clinical recommendations for ribociclib in patients with hormone receptor positive (HR+), HER-2 negative (HER2-), early-stage breast cancer (EBC) who are at high-risk of recurrence. Our recommendations were compiled to reflect our clinical opinion as medical specialists in breast cancer on what we believe is best for our patients. Our opinion is based on literature review, level 1 data from clinical trials, and recent data releases from international congresses, as well as our collective clinical expertise. We urge CDA to consider our clinical recommendation as per the evidence in this document along with the submissions put forward by patient advocacy groups to make an informed decision regarding the place in therapy for ribociclib in patients with HR+/HER2– EBC at high-risk for recurrence. The collective expertise from this group equates to decades of clinical experience in the management of patients with breast cancer.

3. Current Treatments and Treatment Goals

HR+/HER2- early breast cancer is associated with long-term risk of recurrence

In Canada, breast cancer remains one of the most commonly diagnosed cancers among women, with HR+/HER2– subtype comprising approximately 70% of cases.[1,2] Most women (>90%) with HR+/HER2- tumors will present with EBC and receive multimodal treatment that includes locoregional and systemic therapies. However, despite advances in the treatment of HR+/HER2- EBC, this disease is associated with a long-term risk of recurrence with ~ 50% of recurrences happening more than 5 years after diagnosis.[1,3,4]

Our ultimate goal in treating patients with HR+/HER2- EBC is to cure them of their cancer (i.e., prevent recurrence) and to minimize any treatment-related adverse events. The treatments include surgery, radiotherapy and (neo)adjuvant systemic therapy consisting of chemotherapy and/or endocrine therapy (ET) with oral tamoxifen or aromatase inhibitors.[5,6] The clinical assessments to measure the effectiveness of treatment are recurrence-free survival by measuring invasive disease-free survival (iDFS) and overall survival (OS). Thus, the goals of systemic treatment for EBC are to prolong recurrence-free survival and overall survival (iDFS and OS) while minimizing treatment-related adverse events (AEs) to preserve quality of life.[7]

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

50% of recurrences happen >5 years after diagnosis

Despite the effectiveness of current systemic therapies, relapse remains a significant challenge, highlighting the need for more effective strategies to prevent recurrence in patients with HR+/HER2- EBC. This risk persists not only in the years immediately following diagnosis but can extend for decades, with nearly half of recurrences occurring more than five years after initial treatment.[3] Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) and real-world studies emphasize the long-term risk, with 10-year recurrence rates with lymph node positive patients ranging from 15% to 40%.[8] While patients treated after the year 2000 benefited from improved adjuvant treatments, the long-term risks of distant recurrence persists (figure 1).[8] Even among patients with lymph node negative EBC, the 10-year risk of distant recurrence remains substantial at 7.5% and appears to be increasing at a constant rate with each passing year. At 20 years, the distant recurrence risk for patients with node-negative disease was reported to be as high as 22%.[3] This elevated recurrence for node-negative disease has also been confirmed in recent data from the control arm in the NATALEE trial evaluating a CDK4/6 inhibitor with 5-year adjuvant ET showing a 10% 3-year invasive disease recurrence rate for node-negative patients with a higher risk (T4N0, T3N0, or T2N0 with additional criteria (grade [G]2 with Ki-67≥20% or high genomic risk, or G3).[9] In fact, real-world evidence from the US indicates how this cohort of node-negative HR+/HER2− EBC has a similar recurrence risk as patients with 1-3 affected nodes (N1)(figure 2).[10] While extending ET to 10 years modestly reduces recurrence risk, it does not significantly improve survival and is associated with increased adverse effects, such as bone pain, fractures, and osteoporosis.[11] Furthermore, recurrence usually manifests in the form of distant metastatic disease, which is an incurable disease. Current endocrine therapeutic strategies are failing to prevent the recurrence of advanced breast cancer despite targeting the driver of the disease which is the endocrine receptor. There remains a significant unmet need to optimize treatment of patients with HR+/HER2- breast cancer, in the early-stage setting to prevent recurrences, when the disease is still curable.

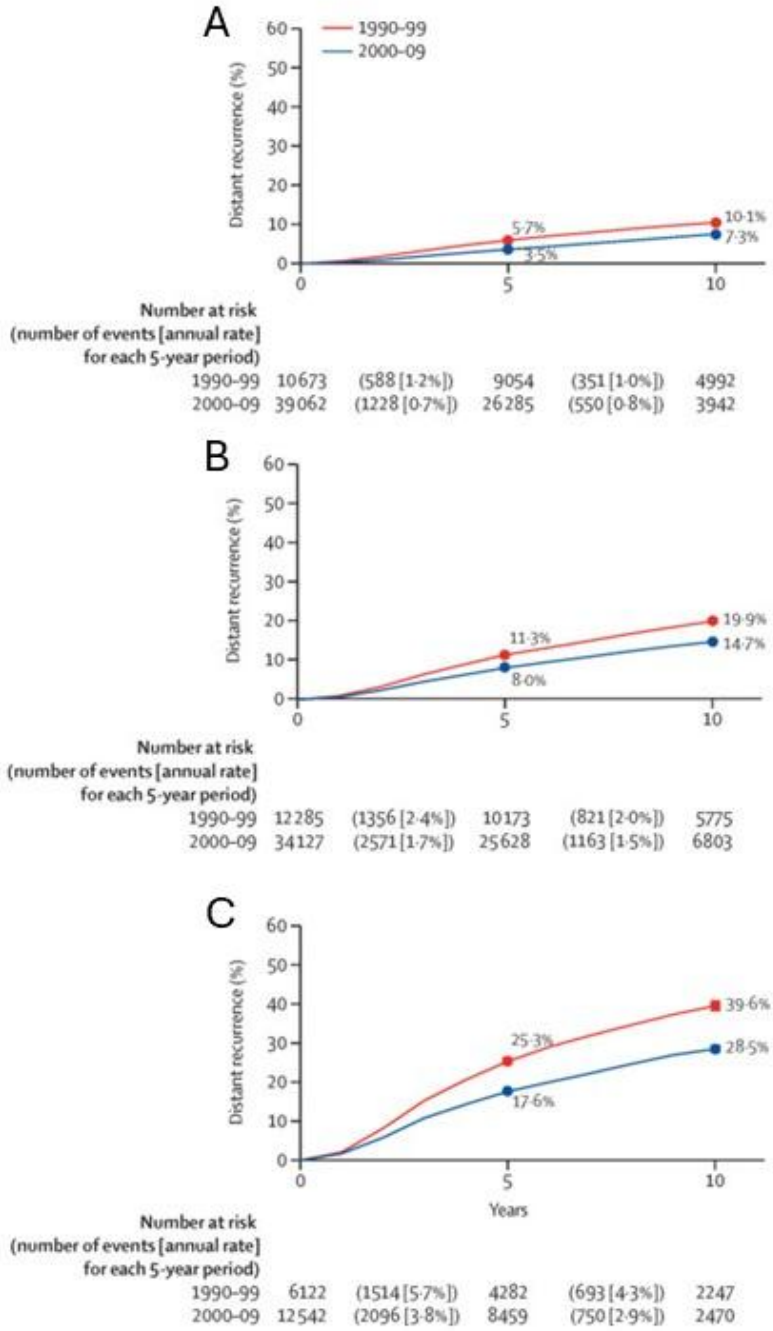

Figure 1. **Risk of distant recurrence by period of enrolment among 155 746 women from 151 trials treated with 5 years of endocrine therapy for HR+ disease.** Molecular risk of distant recurrence in HR+ EBC consistently increases over time despite nodal status in node-negative (A), node-positive N1 (B) and node-positive N2 (C).
Source: Early Breast Cancer Trialists' Collaborative Group. Lancet. 2024 Oct 12;404(10461):1407-1418

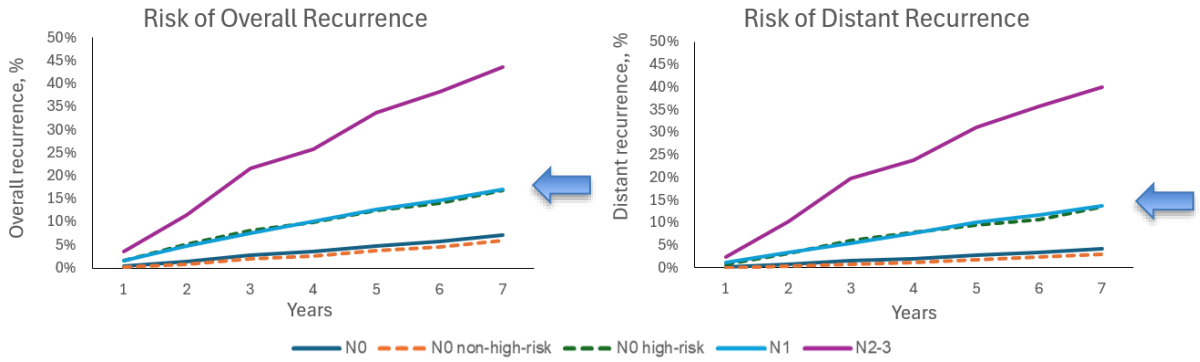

Figure 2. Overall (left) and distant (right) recurrence risk in patients with node negative and node positive HR+/HER2− EBC from 7564 US electronic health records. Real-world data illustrating how N0 high-risk patients have similar risk of both overall and distant recurrence to that of patients with N1 node-positive disease.
Source: Jhaveri K, et al. ESMO 2024. Poster 292P

Emerging evidence supports the role of adding CDK4/6 inhibitors to endocrine therapy in the adjuvant setting to reduce the risk of recurrence for patients with HR+/HER2- EBC.[9,12–15] Both the FDA and the European committee for medicinal products for human use (CHMP) now recognize the benefits of adding CDK4/6 inhibitors to ET in these populations, with abemaciclib and ribociclib approved for such use.[16–18] In addition, the NATALEE clinical trial demonstrated a reduction in risk of recurrence for a population not previously studied (i.e., node-negative disease and a broader population of patients with node-positive disease), while offering a manageable safety profile with less diarrhea compared to other agents in this class.[13,14]

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

NATALEE trial is the first HR+/HER2- EBC randomized trial to include patients with Stage II and Stage III EBC, regardless of nodal status.[9,13,14]

The Phase III NATALEE trial evaluated adjuvant ribociclib + ET in a population of HR+/HER2- patients at risk for recurrence. Patients with Stage II and Stage III disease comprised 40% and 60% of the study population, respectively. Patients with N0 disease (no nodal involvement) accounted for ~27% of the study population and patients with N1 disease made up ~40% of the study population; the remaining evaluated 20% of patients had a higher burden of nodal involvement (N2+).

The results demonstrated that patients treated with ribociclib + ET in the adjuvant setting had a significantly longer iDFS compared to those treated with ET alone at both the 3-year and 4-year landmark analyses. At 3 years, iDFS rates were 90.4% versus 87.1% in favour of ribociclib (HR=0.748; 95% CI: 0.618-0.906; P<0.001).[13] At 4 years, the iDFS rates were 88.5% versus 83.6%, also favouring ribociclib (HR=0.715; 95 CI: 0.609-0.840; P<0.0001).[9,14] **The difference between the groups increased over time, with a delta of 2.7% at 3 years and 4.9% at 4 years.** These results suggest a potential **carry-over effect**, where the benefits of ribociclib persist and the divergence between the treatment curves continues to expand even after the 3-year ribociclib treatment is completed. In other words, while the risk continues to increase over time for the control arm, in the ribociclib study-arm, there is a statistical protective benefit from developing local and distant recurrences.

Notably, there was a consistent iDFS benefit in favour of ribociclib across all key subgroups, including patients with Stage II disease (HR 0.644; 95% CI 0.468-0.887), **patients with N0** disease (HR 0.666; 95% CI 0.397-1.118) and **men/premenopausal women** (HR 0.677; 95% CI 0.523-0.877).[9,14]

Distant disease-free survival (DDFS), a secondary endpoint and surrogate for overall survival, also demonstrated a consistent benefit with ribociclib with the difference between the arms increasing over time (3-year delta of 2.7% and a 4-year delta of 4.5%).[13] This represents a 29% risk reduction at the 4-year landmark analysis.[9,14] Overall survival remains immature, as would be expected in an adjuvant trial with a short follow-up. Other agents have received HTA approval in Canada (and globally) based on trials with iDFS or event-free survival (EFS) as the primary objective.[17,19] The NATALEE trial demonstrated significant disease-free benefits at the 4 year landmark analysis, which is one year after completion of 3 years of treatment.[9,14]

Thus, based on these results, we recommend that ribociclib, in combination with ET, be made available as a treatment option for patients with HR+/HER2- EBC adjuvant setting with node-positive or high-risk node-negative disease as per the NATALEE trial eligibility criteria.

The NATALEE trial demonstrated manageable AEs when adding ribociclib to ET with a 20% discontinuation rate, while on 3-years of therapy.[9] Dose modification due to AEs were mainly observed in the first four months of treatment, consistent with other CDK4/6 inhibitor clinical trials.[20] Neutropenia was the most frequent AE requiring dose reduction or discontinuation in the NATALEE trial. Of note, there are some AEs that are equal in the two arms in the NATALEE trial, as ET alone is known to be associated with some AEs, such as arthralgias, headache, fatigue and hot flushes.

Given our experience with CDK4/6 inhibitors in the metastatic setting, we know the importance of having more than one treatment option. Diarrhea can be a debilitating AE. A patient with EBC is generally fit and well after the peri-operative treatment (surgery/radiation/chemotherapy) is completed. They will often go back to work and resume their regular life. Grade 1 level of diarrhea can significantly disrupt a person's routine with 4 bowel movements a day. Abemaciclib is associated with higher AE grade and incidence of diarrhea.[15] The NATALEE trial demonstrated that the ribociclib + ET combination has a manageable safety profile, where AEs are notably predictable (e.g., liver transaminitis, neutropenia) in the first four months of initiating therapy and are detected with routine bloodwork, as patients are usually asymptomatic.[20] Oncologists have become very competent in monitoring and managing ribociclib associated side effects because this agent is the preferred CDK4/6i in the metastatic setting.[21] Furthermore, the quality-of-life data confirms a minimal effect of AEs on patient's lives, during 3-years of combination therapy.[22] Thus, it is important that clinicians and patients have treatment options within this drug class.[23]

The current treatment paradigm provides adjuvant ET for HR+/HER2- EBC patients over a 5-year period, with some patients who have node positive EBC continuing ET for a longer duration. Following surgery and chemotherapy (where applicable), the addition of combination oral agent adjuvant therapy with ribociclib and ET can be incorporated into current standard practice for 3 of the 5 years with ET.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

We recommend ribociclib for all HR+/HER2- EBC patients at high-risk of recurrence using the NATALEE study criteria, including men and pre and postmenopausal women, regardless of nodal status. This population has been shown to clearly derive iDFS benefit. Of note, the T2N0 sub-population must have grade 2 disease plus an additional risk factor of either high genomic risk (i.e.OncoType Dx / MammaPrint etc.) or Ki67 score of ≥20%, or, have grade 3 disease[9,13,14], **thereby reducing the number of eligible N0 patients** that would routinely be prescribed ET and are currently included in current practice volumes. Ribociclib should ideally start within 12 months of beginning standard (neo)adjuvant ET and continue for 3 years in combination with ET. In patients with a BRCA mutation who undergo a year of adjuvant olaparib therapy, ribociclib initiation may occur slightly beyond the 12-month window. This adjustment accommodates the completion of olaparib without overlapping toxicities. After finishing ribociclib, patients should stay on their regular ET for a total of 5 to 10 years, as recommended by a medical oncologist.

Least suitable patient populations would include patients ineligible for the NATALEE study or contraindicated to CDK4/6 inhibitors.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Monitoring for recurrence would occur only if clinically indicated, as per the current standard of care for ET.

Monitoring is required most notably in the first four months after ribociclib initiation, which includes monitoring of blood work for toxicities and ensuring adherence to ET + ribociclib. AEs are manageable with early intervention including dose reduction and standard supportive care. For baseline cardiac assessment with ECG, the US label indicates that an ECG is required in all patients prior to starting ribociclib and repeated at approximately Day 14 of the first cycle, and as clinically indicated.[24] A similar indication by Health Canada is anticipated.

Current health systems in place can incorporate this follow up monitoring, with consideration of health system monitoring models that utilize pharmacists and nurses, where necessary, at no additional clinical workflow burden.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Ribociclib + ET combination therapy should be discontinued at the first evidence of recurrent disease or in the case of persistent toxicity, as per the product monograph.

5.5 What settings are appropriate for treatment with ribociclib? Is a specialist required to diagnose, treat, and monitor patients who might receive ribociclib?

Oncologists with experience in treating breast cancer patients are required for the initial treatment recommendation and early monitoring of ribociclib + ET combination therapy. Pharmacy/nursing expertise can support the management of oral agents and routine AE screening, including assessing for treatment adherence

6. Additional Information

Of note, and per current standard practice, men and premenopausal women also receive goserelin (ovarian function suppression).

References

1. Breast cancer statistics. Canadian Cancer Society. May 2024. Accessed November 22, 2024. https://cancer.ca/en/cancer-information/cancer-types/breast/statistics

2. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*. 2014;106(5):dju055. doi:10.1093/jnci/dju055

3. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med*. 2017;377(19):1836-1846. doi:10.1056/NEJMoa1701830

4. Pedersen RN, Esen BÖ, Mellemkjær L, et al. The Incidence of Breast Cancer Recurrence 10-32 Years After Primary Diagnosis. *J Natl Cancer Inst*. 2022;114(3):391-399. doi:10.1093/jnci/djab202

5. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. *Ann Oncol*. 2024;35(2):159-182. doi:10.1016/j.annonc.2023.11.016

6. Gradishar W. NCCN Guidelines® Insights: Breast Cancer, Version 5.2024. Accessed October 30, 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

7. Lopez-Tarruella S, Echavarria I, Jerez Y, Herrero B, Gamez S, Martin M. How we Treat HR-Positive, HER2-Negative Early Breast Cancer. *Future Oncol*. 2022;18(8):1003-1022. doi:10.2217/fon-2021-0668

8. Reductions in recurrence in women with early breast cancer entering clinical trials between 1990 and 2009: a pooled analysis of 155 746 women in 151 trials. *The Lancet*. 2024;404(10461):1407-1418. doi:10.1016/S0140-6736(24)01745-8

9. Fasching PA, Stroyakovskiy D, Yardley DA, et al. Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2− Early Breast Cancer: 4-Year Outcomes From the NATALEE Trial.

10. Jhaveri K, Pegram M, Neven P, et al. 292P Real-world evidence on risk of recurrence (ROR) in patients (pts) with node-negative (N0) and node-positive HR+/HER2− early breast cancer (EBC) from US electronic health records (EHR). *Ann Oncol*. 2024;35:S337-S338. doi:10.1016/j.annonc.2024.08.233

11. Goss PE, Ingle JN, Pritchard KI, et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. *N Engl J Med*. 2016;375(3):209-219. doi:10.1056/NEJMoa1604700

12. Rastogi P, O'Shaughnessy J, Martin M, et al. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. *J Clin Oncol Off J Am Soc Clin Oncol*. 2024;42(9):987-993. doi:10.1200/JCO.23.01994

13. Slamon DJ, Stroyakovskiy D, Yardley DA, et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: Primary results from the phase III NATALEE trial. *J Clin Oncol*. 2023;41(17_suppl):LBA500-LBA500. doi:10.1200/JCO.2023.41.17_suppl.LBA500

14. Hortobagyi GN, Lacko A, Sohn J, et al. A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial. *Ann Oncol*. 2024;0(0). doi:10.1016/j.annonc.2024.10.015

15. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(1):77-90. doi:10.1016/S1470-2045(22)00694-5

16. FDA approves ribociclib with an aromatase inhibitor and ribociclib and letrozole co-pack for early high-risk breast cancer. *FDA*. Published online September 17, 2024. Accessed November 28, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ribociclib-aromatase-inhibitor-and-ribociclib-and-letrozole-co-pack-early-high-risk-0

17. FDA D.I.S.C.O. Burst Edition: FDA approval of Verzenio (abemaciclib) with endocrine therapy for patients with HR-positive, HER2-negative, node-positive, early breast cancer. *FDA*. Published online August 9, 2024. Accessed November 28, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-verzenio-abemaciclib-endocrine-therapy-patients-hr-positive

18. Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 14-17 October 2024 | European Medicines Agency (EMA). October 18, 2024. Accessed November 28, 2024. https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-14-17-october-2024

19. Verzenios | European Medicines Agency (EMA). October 29, 2018. Accessed November 28, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/verzenios

20. Barrios CH, Harbeck N, Hortobagyi GN, et al. 113MO NATALEE update: Safety and treatment (tx) duration of ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+/HER2− early breast cancer (EBC). *ESMO Open*. 2024;9. doi:10.1016/j.esmoop.2024.103101

21. Jerzak KJ, Bouganim N, Brezden-Masley C, et al. HR+/HER2- Advanced Breast Cancer Treatment in the First-Line Setting: Expert Review. *Curr Oncol Tor Ont*. 2023;30(6):5425-5447. doi:10.3390/curroncol30060411

22. Fasching PA, Slamon D, Nowecki Z, et al. VP3-2023: Health-related quality of life (HRQoL) in the phase III NATALEE study of adjuvant ribociclib (RIB) plus a nonsteroidal aromatase inhibitor (NSAI) vs NSAI alone in patients (pts) with HR+/HER2- early breast cancer (EBC). *Ann Oncol*. 2023;34(10):951-953. doi:10.1016/j.annonc.2023.08.007

23. Lauro VD, Barchiesi G, Martorana F, et al. Health-related quality of life in breast cancer patients treated with CDK4/6 inhibitors: a systematic review. *ESMO Open*. 2022;7(6). doi:10.1016/j.esmoop.2022.100629

24. Ribociclib (Kisqali) label [Sep, 2024], Novartis Pharmaceuticals Corporation Inc. Accessed December 2, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/209092s019lbl.pdf