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## MEDIA & INVESTOR RELEASE

# Novartis Kisqali® NATALEE analysis reinforces consistent reduction in risk of recurrence across key subgroups of patients with early breast cancer

- *Late-breaking NATALEE subgroup analysis to be presented at ESMO shows invasive disease-free survival (iDFS) benefit remains consistent in all subgroups, including in patients with stage II tumors, node-negative disease and those who are 65 or older*[1]

- *The data reinforce previously presented results which reported that investigational use of Kisqali® (ribociclib) plus endocrine therapy (ET) significantly lowered the risk of cancer recurrence across a broad population of patients with stage II and III HR+/HER2- early breast cancer (EBC), while also maintaining patients' quality of life in the adjuvant setting*[1,2,3]

- *The outcomes of patients treated with ET alone in this NATALEE analysis confirm an unmet need across all study subgroups, including patients with node-negative or stage II disease*[1]

**Basel, October 20, 2023** — Novartis will present late-breaking results from a prespecified exploratory subgroup analysis of invasive disease-free survival (iDFS) from the pivotal Phase III NATALEE trial at the European Society for Medical Oncology (ESMO) Congress 2023. After 27.7 months of follow-up, the iDFS benefit with Kisqali® (ribociclib) plus endocrine therapy (ET) was consistent across key prespecified subgroups, compared to ET alone, in patients with stage II and III hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC) (see table below)[1]. Results were also consistent with those in the overall trial population, reinforcing that the benefit was not driven by a specific patient subgroup[1,2].

**iDFS results across key prespecified subgroups[1]:**

| Subgroup | Treatment Arm, n | 3-year iDFS rate, % | HR (95% CI) |
|---|---|---|---|
| AJCC Stage II | ribociclib + ET, 1011<br>ET alone, 1034 | 94<br>91 | 0.76<br>(0.53-1.10) |
| AJCC Stage III | ribociclib + ET, 1528<br>ET alone, 1512 | 87<br>84 | 0.74<br>(0.59-0.93) |
| N0 | ribociclib + ET, 285<br>ET alone, 328 | 94<br>89 | 0.63<br>(0.34-1.17) |

| | | | |
|---|---|---|---|
| N1-N3 | ribociclib + ET, 2261<br>ET alone, 2219 | 90<br>87 | 0.77<br>(0.63-0.94) |
| Premenopausal women & men | ribociclib + ET, 1126<br>ET alone, 1132 | 91<br>89 | 0.72<br>(0.53-0.98) |
| Postmenopausal women | ribociclib + ET, 1423<br>ET alone, 1420 | 90<br>86 | 0.78<br>(0.61-1.00) |
| <65 years old | ribociclib + ET, 2142<br>ET alone, 2186 | 90<br>87 | 0.77<br>(0.62-0.94) |
| ≥65 years old | ribociclib + ET, 407<br>ET alone, 366 | 90<br>86 | 0.72<br>(0.46-1.14) |
| Ki-67 ≤20% | ribociclib + ET, 1199<br>ET alone, 1236 | 92<br>90 | 0.80<br>(0.59-1.08) |
| Ki-67 >20% | ribociclib + ET, 920<br>ET alone, 938 | 89<br>84 | 0.75<br>(0.56-1.00) |

“Subgroup analyses provide a more comprehensive picture of clinical benefit for patients and are critical to guiding treatment decisions, as they help indicate how different breast cancer subgroups might respond to treatment,” said Aditya Bardia, M.D., Attending Physician, Medical Oncology, Mass General Cancer Center and Associate Professor, Medicine, Harvard Medical School and NATALEE trial investigator. “Given the outcomes of patients treated with endocrine therapy alone, this analysis outlines the potential benefit of adding ribociclib to endocrine therapy to reduce the risk of recurrence. These data provide important insight into how we think about residual risk in this population and make adjuvant treatment decisions for patients with localized breast cancer.”

“Despite endocrine therapy, cancer recurrence remains unpredictable, and too many patients diagnosed with stage II or III HR+/HER2- early breast cancer experience their cancer coming back. This analysis further reinforces the potential of ribociclib to address the need for a new adjuvant option that reduces the ongoing risk of recurrence consistently across many types of at-risk patients,” said Jeff Legos, Executive Vice President, Global Head of Oncology Development at Novartis. “These results from the NATALEE trial add to the wealth of efficacy, safety and quality of life data suggesting that ribociclib, if approved, could provide healthcare providers with a new option to help keep their patients living well and cancer-free.”

Further analysis of the NATALEE trial is ongoing. Additional data, including the final efficacy analysis of the NATALEE trial, will be shared at upcoming medical meetings.

**About NATALEE**

NATALEE is a global Phase III multi-center, randomized, open-label trial to evaluate the efficacy and safety of ribociclib with ET as adjuvant treatment versus ET alone in patients with stage II and III HR+/HER2- EBC, being conducted in collaboration with TRIO[2]. The adjuvant ET in both treatment arms was a non-steroidal aromatase inhibitor (NSAI; anastrozole or letrozole) and goserelin if applicable[2]. The primary endpoint of NATALEE is iDFS as defined by the Standardized Definitions for Efficacy End Points (STEEP) criteria[2]. A total of 5,101 adult patients with HR+/HER2- EBC across 20 countries were randomized in the trial[2].

Results previously announced at the American Society of Clinical Oncology (ASCO) Annual Meeting 2023 showed ribociclib plus ET, compared to ET alone, lowered the risk of cancer recurrence by 25.2% (HR=0.748; 95% CI: 0.618, 0.906; p=0.0014), along with consistent clinically meaningful iDFS benefit across key pre-specified subgroups: AJCC Tumor Stage II (HR=0.761; 95% CI: 0.525, 1.103), AJCC Tumor Stage III (HR=0.740; 95% CI: 0.592, 0.925), node-negative disease (HR=0.630; 95% CI: 0.341, 1.165), node-positive disease (HR=0.771; 95% CI: 0.630, 0.944), pre-menopausal women and men (HR=0.722; 95% CI: 0.530, 0.983),

post-menopausal women (HR=0.781; 95% CI: 0.613, 0.997)[2]. Ribociclib data across all secondary efficacy endpoints was also consistent, including distant disease-free survival (DDFS) (26% risk reduction) and recurrence-free survival (RFS) (28% risk reduction), with a trend for improvement in overall survival (OS) (HR=0.759; 95% CI: 0.539, 1.068)*[2].

For these previously announced results, median study duration of follow-up was 34 months (range 21-48 months) with clinical benefits observed after approximately two years[2]. NATALEE explored a lower starting dose (400 mg) of ribociclib than the dose approved for treatment in metastatic breast cancer (MBC) (600 mg) with the goal to minimize disruptions to patient quality of life without compromising efficacy. The safety profile of ribociclib at 400 mg was observed to have lower rates of symptomatic adverse events (AEs) and less need for dose modifications when administered up to three years[2]. The most frequently reported AEs of special interest (grade 3 or higher) were neutropenia (43.8%) and liver-related AEs (e.g. elevated transaminases) (8.3%)[2].

**Results based on pre-specified interim analysis for OS at time of primary iDFS analysis; additional follow-up is planned to obtain more mature OS data[2].*

**About Early Breast Cancer**
More than 90% of patients diagnosed with breast cancer have EBC[4]. Despite adjuvant ET, approximately one-third of those diagnosed with stage II and more than half of those diagnosed with stage III HR+/HER2- EBC experience cancer recurrence[5,6]. The risk of recurrence continues over decades with more than half of breast cancer recurrences occurring five or more years after diagnosis[5,7]. For many of these patients, there are currently no targeted therapeutic options outside of the standard chemotherapy and ET[8].

**About Kisqali® (ribociclib)**
Kisqali has consistently demonstrated OS benefit while preserving or improving quality of life across three Phase III trials in MBC[9-20]. Updates to the NCCN Guidelines® for breast cancer, released in January 2023, recommend ribociclib (Kisqali) as the only Category 1 preferred CDK4/6 inhibitor for first-line treatment of patients with HR+/HER2- MBC when combined with an aromatase inhibitor (AI)[21]. Additionally, Kisqali has the highest rating of any CDK4/6 inhibitor on the ESMO Magnitude of Clinical Benefit Scale, achieving a score of five out of five for first-line pre-menopausal patients with HR+/HER2- advanced breast cancer[22]. Further, Kisqali in combination with either letrozole or fulvestrant has uniquely, among other CDK4/6 inhibitors, received a score of four out of five for post-menopausal patients with HR+/HER2- advanced breast cancer treated in the first line[23].

Kisqali has been approved in 99 countries worldwide, including by the United States Food and Drug Administration (FDA) and the European Commission. In the U.S., Kisqali is approved for the treatment of adult patients with HR+/HER2- advanced or MBC in combination with an AI as initial ET or fulvestrant as initial ET or following disease progression on ET in post-menopausal women or in men. In the EU, Kisqali is approved for the treatment of women with HR+/HER2- advanced or MBC in combination with either an AI or fulvestrant as initial ET or following disease progression. In pre- or peri-menopausal women, the ET should be combined with a luteinizing hormone-releasing hormone agonist[20].

Novartis is committed to continuing to study Kisqali in breast cancer. Novartis is collaborating with SOLTI, which is leading the HARMONIA study to test whether Kisqali changes tumor biology to enable a better response to ET compared to Ibrance®** (palbociclib) for patients with HR+/HER2-, HER2-enriched subtype[24] MBC, and with the Akershus University Hospital in Norway on the NEOLETRIB trial, a neoadjuvant Phase II trial studying the effects of Kisqali in HR+/HER2- EBC to discover the potentially unique underlying mechanism of action[25].

Kisqali was developed by the Novartis Institutes for BioMedical Research (NIBR) under a research collaboration with Astex Pharmaceuticals.

Please see full Prescribing Information for Kisqali, available at www.Kisqali.com

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**About Novartis**

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Reimagine medicine with us: Visit us at https://www.novartis.com and connect with us on LinkedIn, Facebook, X/Twitter and Instagram.

**References**


1. Bardia A et al. Abstract: Invasive disease–free survival (iDFS) across key subgroups from the Phase III NATALEE study of ribociclib (RIB) + a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+/HER2− early breast cancer (EBC). Results to be presented at European Society for Medical Oncology (ESMO) Congress on 23 October 2023. Madrid, Spain.
2. Slamon D, Stroyakovskiy D, Yardley D, 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. Presented at the American Society of Clinical Oncology Annual Meeting, June 2, 2023. Chicago, USA.
3. Fasching P, Slamon D et al. Health-related quality of life in the phase 3 NATALEE study of adjuvant ribociclib plus a NSAI vs NSAI alone in patients with HR+/HER2− early breast cancer). Presentation at European Society for Medical Oncology (ESMO) Virtual Plenary on 14 September 2023.
4. Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States [published correction appears in *JAMA*. 2015 Jun 9;313(22):2287]. *JAMA*. 2015;313(2):165-173. doi:10.1001/jama.2014.17322
5. Pan H, Gray R, Braybrooke J, et al; EBCTCG. 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

6. Pan H, Gray R, Braybrooke J, et al; EBCTCG. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377(19):1836-1846;(suppl). doi:10.1056/NEJMoa1701830
7. Gomis R, Gawrzak S. Tumor cell dormancy. Mol Oncol. 2017;11(1):62-78.
8. American Cancer Society. Treatment of breast cancer stages I-III. Revised April 12, 2022. Available at: https://www.cancer.org/cancer/breast-cancer/treatment/treatment-of-breast-cancer-by-stage/treatment-of-breast-cancer-stages-i-iii.html/ Accessed October 2023.
9. Yardley DA, Yap YS, et al. Pooled exploratory analysis of survival in patients (pts) with HR+/HER2- advanced breast cancer (ABC) and visceral metastases (mets) treated with ribociclib (RIB) + endocrine therapy (ET) in the MONALEESA (ML) trials. Poster presented at the European Society of Medical Oncology Congress. September 9-13, 2022. Paris, France.
10. Neven P, Fasching PA, et al. Updated overall survival (OS) results from the first-line (1L) population in the Phase III MONALEESA-3 trial of postmenopausal patients with HR+/HER2- advanced breast cancer (ABC) treated with ribociclib (RIB) + fulvestrant (FUL). Mini oral presented at the European Society for Medical Oncology Breast Cancer Congress. May 4, 2022. Paris, France.
11. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. *New England Journal of Medicine*. 2022;386(10):942-950. doi:10.1056/NEJMoa2114663
12. Hortobagyi GN, et al. Overall survival (OS) results from the phase III MONALEESA (ML)-2 trial of postmenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. Proffered paper presented at the European Society of Medical Oncology Congress, September 16-21, 2021. Lugano, Switzerland.
13. Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *New England Journal of Medicine*. 2019;381(4):307-316. doi:10.1056/nejmoa1903765
14. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. *New England Journal of Medicine*. 2020;382(6):514-524. doi:10.1056/NEJMoa1911149
15. Slamon DJ, Neven P, Chia S, et al. Overall survival (OS) results of the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor 2–negative (HER2−) advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). Presented at the European Society of Medical Oncology Congress, September 29, 2019, Barcelona, Spain.
16. Slamon D, Neven P, Chia S, et al. Updated overall survival (OS) results from the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2− advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB. Presented at the American Society of Clinical Oncology Annual Meeting, June 5, 2021. Chicago, USA.
17. Tripathy D, Im S-A, Colleoni M, et al. Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with HR+/HER2− advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. Presented at the San Antonio Breast Cancer Symposium, December 9, 2020. Texas, USA.
18. Yardley D, Nusch A, Yap YS, et al. Overall survival (OS) in patients (pts) with advanced breast cancer (ABC) with visceral metastases (mets), including those with liver mets, treated with ribociclib (RIB) plus endocrine therapy (ET) in the MONALEESA (ML) -3 and -7 trials. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. June 2020. Chicago, USA.
19. O'Shaughnessy J, Stemmer SM, Burris HA, et al. Overall survival subgroup analysis by metastatic site from the Phase III MONALEESA-2 study of first-line ribociclib + letrozole in postmenopausal patients with HR+/HER2− advanced breast cancer. Presented at the San Antonio Breast Cancer Symposium, December 7-10, 2021. Texas, USA.
20. Kisqali (ribociclib) Prescribing Information.
21. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) - Breast Cancer. NCCN Guidelines. Published March 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf/ Accessed October 2023.
22. European Society for Medical Oncology – Magnitude of Clinical Benefit Scale Scorecard. Published April 20, 2020. Updated August 21, 2020. Available at: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-158-1/ Accessed October 2023.
23. European Society for Medical Oncology – Magnitude of Clinical Benefit Scale Scorecard. Published March 29, 2022. Available at: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-9-1/ Accessed October 2023.
24. Ribociclib vs. palbociclib in patients with advanced breast cancer within the HER2-enriched intrinsic subtype (HARMONIA). Identifier NCT05207709. Revised April 4, 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05207709/ Accessed October 2023.
25. Novartis and Vestre Viken Hospital Trust (2022, April 1 – 2024, December 1). Neoadjuvant Treatment of Locally-Advanced Breast Cancer Patients with ribociclib and letrozole (NEOLETRIB). Identifier NCT05163106. Available at: https://clinicaltrials.gov/ct2/show/NCT05163106/ Accessed October 2023.



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