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Submission Request

National Comprehensive Cancer Network® (NCCN®)

RE: MONALEESA-2 Overall Survival Data for Ribociclib in First-line Treatment of HR+/HER2- Metastatic Breast Cancer

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NCCN Guidelines Panel:	Breast Cancer

To Whom It May Concern:

On behalf of Novartis Pharmaceuticals Corporation, I respectfully request that the NCCN Breast Cancer Panel review newly presented data on significantly improved overall survival (OS) in support of positioning ribociclib as the "preferred" CDK4/6 inhibitor over other CDK4/6 inhibitors for the treatment of recurrent unresectable (local or regional) and for stage IV (M1) disease for patients who are estrogen receptor (ER) and/or progesterone receptor (PR)-positive, HER2-negative and postmenopausal or premenopausal receiving ovarian ablation or suppression.[1]

Specific Changes

Please consider the following:

- **BINV-P, Preferred Regimens, First-line Therapy**: Please rephrase to "Aromatase inhibitor + CDK4/6 inhibitor, ribociclib (category 1)" with new footnote * below
- **BINV-P, Preferred Regimens, First-line Therapy:** Please rephrase to "Fulvestrant + CDK4/6 inhibitor, ribociclib (category 1)" with new footnote * below
- **New footnote ***: "Ribociclib is the only CDK4/6 inhibitor to demonstrate significant improvement in overall survival in combination with various endocrine therapies (eg, aromatase inhibitor, fulvestrant) across 3 published Phase III randomized controlled trials. Based on these results, ribociclib is preferred over other CDK4/6 inhibitors." [1,2,3]
- **Discussion:** Please update discussion accordingly.[1,2,3]

FDA Clearance

KISQALI (ribociclib) is a kinase inhibitor indicated in combination with[4]:

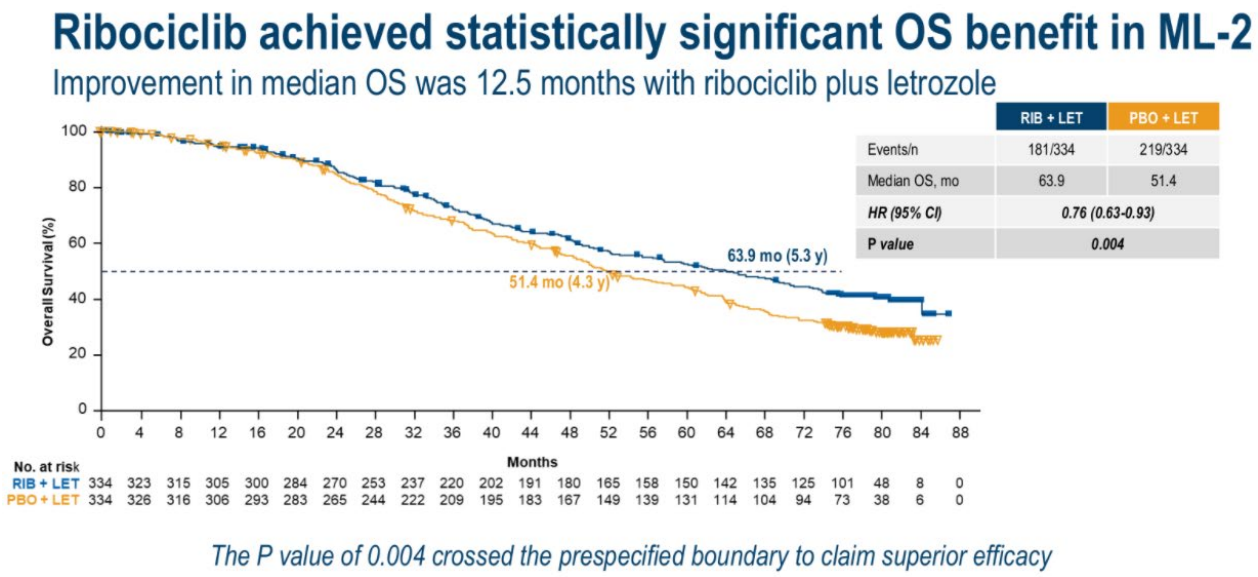
- an aromatase inhibitor as initial endocrine-based therapy for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer as initial endocrine based therapy; or
- fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

Rationale: On September 19, 2021, the final analysis of overall survival for the randomized, double-blind, placebo-controlled, Phase III, MONALEESA-2 trial of ribociclib in combination with letrozole in patients with advanced breast cancer and no prior therapy for advanced disease was presented at ESMO.[1] Ribociclib for the first-line (1L) treatment of ER and/or PR positive, HER-2 negative, recurrent unresectable or stage IV breast cancer now distinguishes itself as the **only** CDK4/6 inhibitor to

demonstrate significant improved overall survival across 3 major published randomized clinical trials (RCTs) used in combination with various endocrine therapies (eg, aromatase inhibitor, fulvestrant).[1,2,3] As such, ribociclib fully meets the NCCN definition for consideration as the only CDK4/6 inhibitor to be designated as "preferred" by the NCCN Panel.

Key Supporting Literature: In the MONALEESA-2 final overall survival analysis, the overall HR for OS was 0.765 (95% CI, 0.628 to 0.932; p = 0.004). The *P*-value crossed the prespecified boundary to claim superior efficacy. An improvement in the median OS (mOS) was 12.5 months with ribociclib plus letrozole. The mOS was 63.9 months (95% CI, 52.4 to 71.0) in the ribociclib arm and was 51.4 months (95% CI, 47.2 to 59.7) in the placebo arm. The estimated overall survival probability at 60 months was 52.3% (95% CI, 46.5% to 57.7) in the ribociclib arm and 43.9% (95% CI, 38.3% to 49.4%) in the placebo arm. The estimated overall survival probability at 72 months was 44.2% (95% CI, 38.5% to 49.8%) in the ribociclib arm and 32.0% (95% CI, 26.8% to 37.3%) in the placebo arm. As such, the OS benefit of ribociclib increases over time, despite more patients on the placebo arm receiving a subsequent CDK4/6 inhibitor.[1] Building on the body of evidence supporting ribociclib's overall survival benefit reported for MONALEESA-3 and MONALEESA-7, MONALEESA-2 now has the longest mOS ever reported in HR+, HER2- metastatic breast cancer with a mOS of 63.9 months in the ribociclib plus letrozole arm (previously it was MONALEESA-7 with mOS of 58.7 months in the ribociclib plus NSAI arm).[1,2,5]

Figure 1. Kaplan-Meier Plot of Overall Survival (Full Analysis Set)[1]



These definitive results distinguish ribociclib as the only CDK4/6 inhibitor to demonstrate significant improvement in OS for patients with metastatic disease in 1L across major RCTs in combination with an aromatase inhibitor, letrozole (in MONALEESA-2), with fulvestrant (MONALEESA-3), and with various endocrine therapies (MONALEESA-7, note that ribociclib is not indicated for concomitant use with tamoxifen).[1,2,3] Again, the results of the MONALEESA-2 trial establish the mOS attained as the longest mOS reported in any of the trials across all 3 CDK4/6 inhibitors.[1,5]

Briefly, the MONALEESA-3 trial reported, in The New England Journal of Medicine (NEJM), improved OS for ribociclib for postmenopausal women in combination with fulvestrant with an HR of 0.72 (95% CI, 0.57 to 0.92; p = 0.00455) for all patients at 42 months with 57.8% alive in the ribociclib arm compared to 45.9% in the placebo plus fulvestrant arm. The OS benefit was consistently observed across all subgroups, including as first-line treatment with an HR of 0.70 (95% CI, 0.48 to 1.02).[2] In the MONALEESA-7 trial, as also published in NEJM, the estimated overall survival at 42 months for ribociclib

plus endocrine therapy was 70.2% vs 46.0% in the placebo plus endocrine therapy group with an HR of 0.71 (95% CI, 0.54 to 0.95; p = 0.00973) for pre- or perimenopausal women. The survival benefit seen in the subgroup of 495 patients who received an aromatase inhibitor was consistent with that in the overall intention-to-treat population (HR = 0.70; 95% CI, 0.50 to 0.98). For patients with metastatic disease who had not received prior chemotherapy, the HR for OS was 0.73 (95% CI, 0.54 to 1.00).[3]

In summary, ribociclib in combination (with an aromatase inhibitor, fulvestrant and various endocrine therapies) as 1L treatment demonstrated significantly improved survival in the MONALEESA-2, -3, and -7 trials in the "all patients" group for all 3 trials compared to endocrine therapy alone. Also, a consistent OS benefit was observed in most subgroups, including de novo patients, patients with or without prior chemotherapy, patients with ≥ 3 or < 3 metastatic sites, and endocrine naive/sensitive/resistant patients.[1,2,3]

Safety: The safety profile of ribociclib in the MONALEESA-2 study (n = 334 for ribociclib arm) is consistent with results published for MONALEESA-3 and MONALEESA-7. No new safety signals were noted with ribociclib after 6.5 years of follow-up.[1] As reported in the prescribing information for the MONALEESA-2 study, the most common adverse events (>20% in the ribociclib arm and ≥ 2% higher than placebo) were neutropenia, nausea, fatigue, diarrhea, alopecia, leukopenia, vomiting, constipation, headache, and back pain. The most common Grade 3/4 adverse reactions occurring at a frequency of ≥5% included neutropenia, leukopenia, abnormal liver function tests, and lymphopenia.[4]

Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving ribociclib plus letrozole and in 3% of patients receiving placebo plus letrozole. Among patients receiving ribociclib plus letrozole, 7% were reported to have permanently discontinued both ribociclib and letrozole and 7% were reported to have permanently discontinued ribociclib alone due to ARs. Among patients receiving placebo plus letrozole, 2% were reported to have permanently discontinued both and 0.9% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of ribociclib in patients receiving ribociclib plus letrozole were ALT increased (4%), AST increased (3%), and vomiting (2%). Antiemetics and antidiarrheal medications were used to manage symptoms as clinically indicated.[4]

On-treatment deaths, regardless of causality, were reported in 3 cases (0.9%) of ribociclib plus letrozole treated patients vs one case (0.3%) of placebo plus letrozole treated patients. Causes of death on ribociclib plus letrozole included one case each of the following: progressive disease, death (cause unknown), and sudden death (in the setting of Grade 3 hypokalemia and Grade 2 QT prolongation).[4]

Quality of Life: Across the 3 Phase III MONALEESA trials, Health-Related Quality of Life (HRQoL) and pain were evaluated using EORTC QLQ-C30 questionnaires. HRQoL was maintained from baseline and similar between treatment arms in MONALEESA-2 and MONALEESA-3, while patients who received ribociclib had an improved HRQoL during treatment in MONALEESA-7.[6,7,8]

In a pooled HRQoL analysis of MONALEESA patients who received first-line endocrine therapy across the 3 trials (n = 1528), ribociclib delayed deterioration in HRQoL. Time to deterioration for Global Health Status (GHS), pain, and emotional functioning scores were longer with ribociclib vs placebo.[9]

- Median time to definitive deterioration (TTDD) ≥10% for GHS was 39.6 months for the ribociclib arms and 33.1 months for placebo arms (HR = 0.79 [95% CI, 0.66 to 0.94]).
- Median TTDD ≥ 10% for pain was not reached for ribociclib or placebo arms (HR = 0.77 [95% CI, 0.61 to 0.97]).
- Median TTDD ≥ 10% for emotional functioning was 46.9 months for ribociclib arms and 35.9 months for placebo arms (HR = 0.71 [95% CI, 0.59 to 0.85]).

Cost: The conservative, rigorous economic assessment group for the UK, National Institute for Health and Care Excellence (NICE), recommended "ribociclib as a treatment option for the first-line treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer" based upon a review conducted by an Evidence Review Group appointed by NICE.[10] Further, a recent published

study showed that when combining pharmacological costs of drugs with the measure of efficacy represented by the progression-free survival across lines of therapy, ribociclib was less expensive than the other CDK4/6 inhibitors in 1L with an aromatase inhibitor and, also as subsequent therapy.[11]

Finally, ribociclib offers a method for "down-dosing" by reducing the number of tablets taken.[4] This obviates the need for waiting to obtain a new prescription, thus potentially creating health care system efficiency by avoiding further inconvenience or delay for the patient and physician.

Summary: NCCN defines "Preferred Status" for an intervention as based upon superior efficacy, safety, and evidence; and when appropriate affordability. Ribociclib for the 1L treatment of ER and/or PR positive, HER-2 negative, recurrent unresectable or stage IV breast cancer distinguishes itself as the **only** CDK4/6 inhibitor to demonstrate significant improved overall survival across all 3 major published RCTs in combination with various endocrine therapies.[1,2,3] Further, NICE, the economic assessment body for the UK, has recommended ribociclib for the first-line treatment of hormone-receptor positive, human epidermal growth factor negative breast cancer.[10] As such, ribociclib fully meets the NCCN definition for consideration as the only CDK4/6 inhibitor to be designated as "preferred" by the NCCN Panel.

We recognize and thank the NCCN Breast Cancer Panel for its diligent and generous work in a volunteer capacity and appreciate any consideration given to our request.

Sincerely,

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Enclosures: Copy of Prescribing Information and referenced primary literature; author disclosures within included references

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