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Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of KISQALI® (ribociclib) in Combination with Fulvestrant for HR+/HER2- Advanced Breast Cancer

Name: Neilda Baron, MD
Company/Organization: Novartis Pharmaceuticals Corporation
Address: One Health Plaza, Building 345
East Hanover, NJ 07936
Phone: 862-778-5494
E-mail: Neilda.baron@novartis.com
Date of request: XXXXX
NCCN Guidelines Panel: Breast Cancer

To Whom It May Concern:

As the NCCN Breast Cancer Panel reviews the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Breast Cancer v.1.2018 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with KISQALI® (ribociclib) for your consideration:

- Data to support the use of ribociclib in combination with fulvestrant as treatment in the first- and second-line setting of postmenopausal women with hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced or metastatic breast cancer.

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Ribociclib plus fulvestrant in the first- and second-line treatment setting for HR+/HER2- advanced breast cancer

This request is for the Panel to consider the inclusion of ribociclib in combination with fulvestrant as a treatment option in sections BINV-20 and BINV-N of the Breast Cancer Guidelines and the associated NCCN Drugs and Biologics Compendium™.

Data from the interim analysis of the Phase III study, Mammary ONcology Assessment of LEE011's Efficacy and SAfety-3 (MONALEESA-3, NCT02422615) demonstrated that the combination of ribociclib plus fulvestrant significantly prolonged progression-free survival (PFS) compared to treatment with fulvestrant alone (hazard ratio [HR] = 0.593, 95% CI: 0.480-0.732, $P < .001$). At the time of the data cutoff, the median PFS in the ribociclib plus fulvestrant arm was 20.5 months (95%CI: 18.5 – 23.5) versus 12.8 months (95%CI: 10.9 - 16.3) in the placebo plus fulvestrant arm. The median PFS for patients who were treatment-naïve (de novo and disease-free interval >12 months from completion of (neo)adjuvant endocrine therapy) in the advanced setting subgroup was not reached versus 18.3 months (HR = 0.577; 95% CI, 0.415 to 0.802), respectively. Patients in the subgroup of those who had received up to one line of prior endocrine therapy for advanced disease had a median PFS of 14.6 versus 9.1 months, respectively (HR = 0.565; 95% CI, 0.428 to 0.744).¹

Adverse reactions of any grade ($\geq 30\%$ in either arm) were neutropenia (69.6% vs 2.1%), nausea (45.3% vs 28.2%), and fatigue (31.5% vs 33.2%) in the ribociclib plus fulvestrant arm

versus the placebo plus fulvestrant arm, respectively. Grade 3 adverse events reported in $\geq 10\%$ of patients in either arm (ribociclib plus fulvestrant vs placebo plus fulvestrant) were neutropenia (46.6% vs 0%) and leukopenia (13.5% vs 0%); the only grade 4 event reported in $\geq 5\%$ of patients was neutropenia (6.8% vs 0%).¹

Specific changes recommended for the Guidelines & Compendium

- Please consider adding ribociclib plus fulvestrant to the treatment algorithm (BINV-20) for
 - ER and/or PR positive/HER2-, no prior endocrine therapy within 1 year, postmenopausal women
 - ER and/or PR positive/HER2-, prior endocrine therapy within 1 year
- Please consider including ribociclib plus fulvestrant as an option for the treatment of HR+/HER2- postmenopausal women with recurrent or stage IV breast cancer in section BINV-N and update relevant discussion sections.

FDA status

Ribociclib is not approved in combination with fulvestrant for HR+/HER2- advanced breast cancer. Ribociclib is approved in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer.

Rationale for recommended change

Based on the data from the MONALEESA-3 study, ribociclib plus fulvestrant has demonstrated significantly longer PFS compared to fulvestrant alone.

Literature support

1. Slamon D, Neven P, Chia S et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: MONALEESA-3. *J Clin Oncol*. 2018 Jun 3. [E-pub ahead of print] doi.org/10.1200/JCO.2018.78.9909

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Breast Cancer Panel. If you have any questions or require additional information, please do not hesitate to contact me at 1-862-778-5494 or via e-mail at Neilda.baron@novartis.com.

Thank you for your time and consideration.

Sincerely,

Neilda Baron, MD
Executive Director, Medical Information Oncology
Novartis Pharmaceuticals Corporation

Enclosures: Electronic copy of referenced primary literature and Prescribing Information; Author disclosures within included references