December 6, 2017

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of KISQALI® (ribociclib) as First-line Treatment in Premenopausal Women with HR+/HER2- Advanced Breast Cancer

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Date of request:	December 6, 2017
NCCN Guidelines Panel:	Breast Cancer

To Whom It May Concern:

As the Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Breast Cancer v.3.2017 and the associated Drugs and Biologics Compendium™, we have enclosed data related to treatment with KISQALI® (ribociclib) for your consideration:

- Data to support the preferred use of ribociclib in combination with either nonsteroidal aromatase inhibitor (NSAI) or tamoxifen along with ovarian suppression or ablation for the treatment of premenopausal women with hormone receptor-positive/human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced breast cancer

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Ribociclib plus NSAI/tamoxifen for first-line treatment of premenopausal HR+/HER2- advanced breast cancer

This request is for the Panel to consider the inclusion of ribociclib in combination with NSAI/tamoxifen along with ovarian suppression or ablation as the preferred first-line treatment option for premenopausal women with HR+/HER2- advanced breast cancer in the Breast Cancer Guidelines® and the associated NCCN Drugs and Biologics Compendium™.

The data were presented at the 2017 San Antonio Breast Cancer Symposium and will be submitted for publication. The journal manuscript will be submitted to the Panel upon publication.

Mammary **ON**cology **A**ssessment of **LE**E011's (ribociclib) **E**fficacy and **SA**fety-7 (MONALEESA-7) is a Phase III study of 672 premenopausal women with HR+, HER2– advanced breast cancer who had received ≤1 line of chemotherapy and no prior endocrine therapy for their advanced disease. Patients were randomized (1:1) to ribociclib (600 mg/day, 3-weeks-on/1-week-off) or placebo in combination with either tamoxifen (20 mg/day) or an NSAI (letrozole [2.5 mg/day] or anastrozole [1 mg/day]) + goserelin (3.6 mg every 28 days). The median age was 43 years (range, 25-58) in the ribociclib arm and 45 years (range, 29-58) in the placebo arm. The primary endpoint was locally assessed progression-free survival (PFS).The primary analysis was conducted after 318 events occurred and the median time from randomization to the data cutoff date was 19.2 months.[1]

The study met its primary objective: PFS was significantly improved in the ribociclib arm (median PFS = 23.8 months; 95% CI: 19.2–not reached) vs the placebo arm (median PFS = 13.0 months; 95% CI: 11.0–16.4), with a hazard ratio of 0.553 (95% CI: 0.441–0.694; $P = 9.83\times10^{-8}$). [1]

The most frequent all-grade adverse events (AEs; ≥20% of patients; ribociclib arm vs placebo arm) were neutropenia (76% vs 8%), hot flash (34% vs 34%), nausea (32% vs 20%), leukopenia (31% vs 6%), arthralgia (30% vs 27%), anemia (21% vs 10%), fatigue (24% vs 25%), headache (23% vs 24%), and diarrhea (20% vs 19%). Grade 3/4 AEs reported in ≥5% of patients include neutropenia (61% vs 4%) and leukopenia (14% vs 1%) in the ribociclib vs placebo arms. [1]

Specific changes recommended for the Guidelines & Compendium

In section BINV-20 and BINV-N, please consider replacing the current recommendations with inclusion of ribociclib plus NSAI/tamoxifen with ovarian suppression or ablation as the preferred first-line treatment option for premenopausal women with HR+/HER2- advanced breast cancer in those with no prior endocrine therapy within 1 year and update relevant discussion sections.

FDA status

Ribociclib is not FDA approved for the treatment of premenopausal women with 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.[2]

Rationale for recommended change

Data from the MONALEESA-7 study demonstrated that ribociclib used in combination with oral hormonal therapies (tamoxifen or an NSAI) and goserelin was shown to significantly prolong PFS vs endocrine therapy alone as first-line treatment in premenopausal women with HR+/HER2- advanced breast cancer. At the time of this request, MONALEESA-7 is the only randomized Phase III trial with a CDK 4/6 inhibitor in combination with an aromatase inhibitor and tamoxifen in first-line premenopausal and perimenopausal women that was powered to show a difference in PFS.

Literature support

[1]Tripathy D, Sohn J, Im S, et al. First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized Phase III MONALEESA-7 trial. Oral presentation at: San Antonio Breast Cancer Symposium (SABCS); December 5-9, 2017; San Antonio, TX. Presentation GS2-05.

[2] Kisqali [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.

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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: Copy of Prescribing Information and slides presented at San Antonio Breast Cancer Symposium 2017; author disclosures included within reference