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Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Breast Cancer to review the enclosed data for inclusion of FASLODEX<sup>®</sup> (fulvestrant) in combination with ribociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. This request is based on recently published data from the MONALEESA-3 study.<sup>1</sup>

Specific Changes:

- We respectfully request addition of fulvestrant plus ribociclib to the Breast Cancer guidelines as a combination therapy option for the treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.

FDA Status:

- Fulvestrant is approved by the FDA as a monotherapy option for the treatment of hormone receptor (HR)-positive, human epidermal growth receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.<sup>2</sup>
- Fulvestrant is also indicated for the:
  - Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.<sup>2</sup>
  - Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.<sup>2</sup>

Rationale:

**Monotherapy Trials**

- In the Phase III, randomized, double-blind FALCON trial, fulvestrant 500 mg demonstrated a significant improvement in PFS compared with anastrozole 1 mg [16.6 months vs. 13.8 months; HR 0.797 (95% CI 0.637, 0.999); p=0.0486] when given in the first line setting to endocrine therapy-naïve postmenopausal women with HR+ advanced breast cancer.<sup>3</sup> These results confirmed the clinical benefit of fulvestrant versus anastrozole seen in the FIRST trial.<sup>4,5</sup>

**Combination Therapy Trials**

- In the Phase III, randomized, double-blind, placebo-controlled MONALEESA-3 trial, fulvestrant 500 mg in combination with ribociclib 600 mg once daily demonstrated a significant improvement in PFS compared with fulvestrant 500 mg plus placebo [20.5 months vs. 12.8 months; HR 0.593 (95% CI 0.480, 0.732); p<0.001] for the treatment of HR+, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy or who had received up to one line of prior endocrine therapy in the advanced setting.<sup>1</sup>

- PFS in patients who were treatment naïve in the advanced setting was not reached in the fulvestrant 500 mg plus ribociclib arm and was 18.3 months in the fulvestrant plus placebo arm; HR 0.577 (95% CI 0.415, 0.802).<sup>1</sup>
- The objective response rate for patients with measurable disease was 40.9% for the fulvestrant plus ribociclib arm versus 28.7% in the fulvestrant plus placebo arm.<sup>1</sup>

Reference(s): The following references are submitted in support of this proposal. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. Slamon DJ, 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.  
<http://dx.doi.org/10.1200/JCO.2018.78.9909>. Accessed June 13, 2018.
2. FASLODEX Prescribing Information.
3. Robertson JF, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet*. 2016;388:2997–3005.
4. Robertson JFR, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol*. 2009;27:4530-4535.
5. Robertson JFR, Lindemann JPO, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized ‘FIRST’ study. *Breast Cancer Res Treat*. 2012;136:503-511.

Sincerely,

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