On behalf of Eli Lilly and Company, I respectfully request the National Comprehensive Cancer Network (NCCN) to review the enclosed information for VERZENIO® (abemaciclib) in combination with fulvestrant in reference to NCCN Guidelines V3.2019 for Breast Cancer.

Overall survival (OS) results of the phase 3 MONARCH 2 study were recently presented as an oral presentation at the Annual Meeting of the European Society for Medical Oncology (ESMO): September 27-October 1; Barcelona, Spain and published in a simultaneous manuscript in *JAMA Oncology*.1-2 MONARCH 2 met its secondary endpoint of OS at a pre-planned interim analysis. This definitive analysis demonstrated that treatment with abemaciclib in combination with fulvestrant resulted in a statistically significant and clinically meaningful improvement in OS compared to fulvestrant alone.1-2

**Specific changes:**
We respectfully suggest the following revisions and/or additions for NCCN consideration in the following sections:

1. **BINV-21, Systemic Treatment of Recurrent or Stage IV (M1) Disease: ER and/or PR Positive, HER2 Negative:**
   - For premenopausal and postmenopausal women with no visceral crisis and prior endocrine therapy within 1 year:
     - Add footnote: “For patients who have not received a prior CDK4/6 inhibitor, abemaciclib and ribociclib have demonstrated statistically significant OS in studies that include this patient population.”1-2
   - For postmenopausal women with no visceral crisis and no prior endocrine therapy within 1 year:
     - Revise footnote mmm to read “Fulvestrant has been combined with CDK4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) in the first-line setting in three randomized trials.”1-4
     - Add footnote: “Abemaciclib and ribociclib have demonstrated statistically significant OS benefit in Phase 3 trials in combination with fulvestrant in studies that include this patient population.”1-3

2. **BINV-P, Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease: HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression:**
   - For preferred regimen: aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib)
     - Revise last sentence of footnote b to read “Fulvestrant has been combined with CDK4/6 inhibitors (i.e., abemaciclib, palbociclib, and ribociclib) in the first-line setting in three randomized trials.”1-4
   - For preferred regimen: fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib)
     - Add footnote: “Abemaciclib and ribociclib have demonstrated statistically significant OS benefit in Phase 3 trials in combination with fulvestrant.”1-3
     - Revise last sentence of footnote b to read “Fulvestrant has been combined with CDK4/6 inhibitors (i.e., abemaciclib, palbociclib, and ribociclib) in the first-line setting in three randomized trials.”1-4

**FDA Clearance:**
Abemaciclib is approved by the FDA in combination with fulvestrant for the treatment of women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer MBC with disease progression following endocrine therapy (ET).5 Abemaciclib is also indicated
- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR+, HER2- advanced or metastatic breast cancer5, and
• as monotherapy for the treatment of adult patients with HR+, HER2- advanced or metastatic breast cancer (MBC) with disease progression following ET and prior chemotherapy in the metastatic setting.5

**Rationale:**
MONARCH 2 was a phase 3, global, randomized, double-blind, placebo-controlled study in 669 women with HR+, HER2- advanced breast cancer (ABC) whose disease had progressed while receiving neoadjuvant or adjuvant ET, within 12 months after adjuvant ET, or while receiving first-line ET for ABC. Patients were randomized in a 2:1 fashion (stratified by metastatic site and ET resistance) to receive abemaciclib plus fulvestrant (n=446) or placebo plus fulvestrant (n=223) until disease progression, death, or withdrawal. The study included pre/peri and postmenopausal women with an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients who had previously received more than one line of ET or any prior chemotherapy for ABC, prior treatment with fulvestrant, everolimus or cyclin dependent kinases 4 and 6 (CDK4 & 6) inhibitors, presence of visceral crisis, or history of central nervous system metastasis were excluded from the study. Baseline characteristics were well balanced. Most patients enrolled had visceral disease (n=373), followed by bone-only disease (n=180) and other sites of disease (n=113). A total of 169 patients had primary ET resistance and 489 had secondary ET resistance. Primary endocrine resistance was defined by ESMO guidelines6 and included patients whose disease relapsed while receiving the first 2 years of (neo)adjuvant ET or progressed while receiving the first 6 months of ET for advanced breast cancer. Of the 446 women randomized to abemaciclib, 263 (59%) received their most recent endocrine therapy in the (neo) adjuvant setting; the combination of abemaciclib and fulvestrant was their first line of therapy in the metastatic setting. The primary end point was investigator-assessed progression-free survival (PFS), and key secondary end points included OS, objective response rate (ORR), and safety.1-2

Patients treated with abemaciclib plus fulvestrant demonstrated a significantly longer median OS of 9.4 months than patients treated with placebo plus fulvestrant regardless of menopausal status (46.7 months vs 37.3 months; HR=0.757; 95% CI: 0.606-0.945, p=0.0137). The OS benefit was consistent across subgroups; among subgroups, more pronounced effects were observed in patients with visceral disease (HR= 0.675; 95% CI: 0.511-0.891) and primary ET resistance (HR=0.686; 95% CI: 0.451-1.043).1,2

In the updated analysis, abemaciclib plus fulvestrant significantly improved PFS (median, 16.9 vs 9.3 months; HR: 0.536; 95% CI: 0.445, 0.645; p<0.0001).2

No new safety signals were observed in this analysis of MONARCH 2, and safety data were consistent with the established safety profile of abemaciclib.1-2

**References:**
The following references are submitted to assist the committee in their review. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors for these publications.

1. Sledge GW, Toi M, Neven P, et al. MONARCH 2: Overall survival of abemaciclib plus fulvestrant in patients with HR+, HER2- advanced breast cancer. Talk presented at: Annual Meeting of the European Society for Medical Oncology (ESMO); September 27-October 1, 2019; Barcelona, Spain.
5. VERZENIO® (abemaciclib) Prescribing Information

We appreciate the Panel’s thorough consideration of this request. Please do not hesitate to contact me with any questions.

Sincerely,

Jessie L. Fahrbach, MD
Vice President, Global Medical Affairs, Lilly Oncology