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**Panel:** Breast Cancer

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:
        a) 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:
        a) 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]
        b) 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)
        a) 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)
        a) Add footnote: "Abemaciclib and ribociclib have demonstrated statistically significant OS benefit in Phase 3 trials in combination with fulvestrant."[1-3]
        b) 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 cancer[5], 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 guidelines[6] 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.
2. Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor–positive, ERBB2-negative breast cancer that progressed on endocrine therapy — MONARCH 2: A randomized clinical trial. [published online September 29, 2019]. *JAMA Oncol*.
3. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. 2019;381(4):307-316.
4. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.
5. VERZENIO® (abemaciclib) Prescribing Information
6. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4). *Ann Oncol*. 2018;29:1634-1657.


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

Sincerely,


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