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Date of Request: **September 28, 2017**
NCCN Guidelines Panel: **Breast Cancer**

Dear Panel Members,

On behalf of Eli Lilly and Company, we respectfully request the NCCN Breast Cancer Panel to review the enclosed data and consider including VERZENIO™ (abemaciclib) in the Breast Cancer Guidelines and the associated NCCN Drugs and Biologics Compendium™.

FDA STATUS

On September 28, 2017, the US Food and Drug Administration approved abemaciclib for use in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (mBC) with disease progression following endocrine therapy, and as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.[1,2]

RATIONALE

Abemaciclib is an orally administered CDK4 & 6 inhibitor administered on a twice-daily continuous schedule. Two pivotal trials have demonstrated the safety and efficacy of abemaciclib either in combination with fulvestrant or as a monotherapy in HR+/HER- mBC.[2]

MONARCH 1 was a phase 2, single-arm study which evaluated the safety and efficacy of abemaciclib as monotherapy in women with refractory HR+, HER2- mBC whose disease progressed on or after both endocrine therapy and chemotherapy. The 12-month primary analysis of investigator-assessed objective response rate (ORR) is summarized in Table 1.[2,3] Efficacy results of the 18-month analysis were consistent with the 12-month results of MONARCH 1. The median overall survival (OS) time with additional 6 months of follow-up was 22.3 months and a median duration of treatment response of 8.9 months.[4] The most common adverse reactions (≥20%) reported of any grade included diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia. Diarrhea was the most common side effect. The majority of cases were low grade with grade 1 or 2 diarrhea occurring in 70% of patients treated with abemaciclib monotherapy. Neutropenia was observed in 37% of patients treated with abemaciclib monotherapy with grade 3 and 4 neutropenia reported in 19% and 5% of patients, respectively. Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters without affecting glomerular function.[2]

Table 1. MONARCH 1 Efficacy Results (Intent-to-Treat Population)[2]

	Abemaciclib 200 mg N=132	
	Investigator Assessed	**Independent Review**
Objective response rate, n (%)	**26 (19.7)**	**23 (17.4)**
95% confidence interval, %	13.3, 27.5*	11.4, 25.0
Median duration of response	**8.6 months**	**7.2 months**
95% confidence interval, %	5.8, 10.2	5.6, Not Reached

* 15% not excluded[3]

MONARCH 2 was a randomized, double-blind, phase 3 study in women with HR+, HER2- mBC in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting.[2] The primary efficacy results from MONARCH 2 are summarized in Table 2. Median progression-free survival (PFS) assessment based on a blinded independent radiologic review was consistent with the investigator assessment.[2] Consistent PFS benefit was seen across all patient subgroups analyzed. At the time of data cutoff, OS results were not mature and will be disclosed when available.[5] The most common adverse reactions reported (≥20%) of any grade in the abemaciclib arm included diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache.[2] Diarrhea was the most common side effect. The majority of diarrhea cases were low grade with grade 1 or 2 diarrhea occurring in 73% of patients in the abemaciclib plus fulvestrant arm and 24% in the fulvestrant arm. Grade 3 diarrhea occurred in 13% of patients in the abemaciclib plus fulvestrant arm. Permanent discontinuation of abemaciclib study drug due to diarrhea was infrequent (1%).[2] The majority (70%) of patients in the abemaciclib arm who experienced diarrhea did not require treatment modification (i.e., dose interruption, dose reduction, or discontinuation).[5] In the abemaciclib plus fulvestrant arm, neutropenia was observed in 46% of all patients. Grade ≥3 neutropenia was reported in 27% of patients.[2] Febrile neutropenia was infrequent and not associated with severe infection.[5]

Table 2. MONARCH 2 Efficacy Results (ITT Population, Investigator Assessment)[2]

	Abemaciclib + Fulvestrant	**Placebo + Fulvestrant**
Progression-free survival	**N=446**	**N=223**
Number of patients with an event, n (%)	222 (49.8)	157 (70.4)
Median, months (95% confidence interval)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% confidence interval)	0.553 (0.449, 0.681)	
P-value	p<.0001	
Objective response for patients with measurable disease	**N=318**	**N=164**
Objective response rate, n (%)	153 (48.1)	35 (21.3)
95% confidence interval	42.6, 53.6	15.1, 27.6

Abbreviation: ITT = intent-to-treat.

RESOURCES / REFERENCES

The following resources are submitted to assist the committee with their review:

1. FDA Approval Letter
2. VERZENIO™ (abemaciclib) Prescribing Information
3. Dickler M, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer. *Clin Cancer Res*. 2017;23(17):5218-5224.
4. Rugo HS, et al. MONARCH 1: Final overall survival analysis of a phase 2 study of abemaciclib, a CDK4 and CDK6 inhibitor, as monotherapy, in patients with HR+/HER2- breast cancer, after chemotherapy for advanced disease. Oral Presentation. AACR 2017. Abstract CT044.
5. Sledge GW, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884.

Thank you for considering this request. Please do not hesitate to contact us with any questions.

Sincerely,

William R. Schelman, MD, PhD
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