May 24, 2019

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Alpelisib in Combination With Fulvestrant for Postmenopausal Women and Men With PIK3CA-Mutant, HR-positive, HER2-negative, Advanced or Metastatic Breast Cancer Who Progressed On or After an Endocrine-based Regimen

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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 Version 1.2019 and the associated Drugs & Biologics Compendium™, we are enclosing data related to treatment with recently FDA-approved Piqray® (alpelisib) in combination with fulvestrant for your consideration:

- Data to support the use of alpelisib in combination with fulvestrant for the treatment of hormone receptor-positive (HR+)/human epidermal growth factor receptor-2-negative (HER2-) advanced or metastatic breast cancer with a PIK3CA mutation following progression on or after an endocrine-based regimen.

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Alpelisib + fulvestrant for HR+/HER2- advanced breast cancer with a PIK3CA mutation
SOLAR-1 is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of the combination of alpelisib + fulvestrant vs. placebo + fulvestrant in postmenopausal women and men with HR+/HER2- advanced or metastatic breast cancer which progressed on or after aromatase inhibitor (AI) therapy with or without a CDK4/6 inhibitor (N = 572). The primary endpoint is median progression-free survival (PFS) based on investigator assessment using RECIST v1.1 criteria in the PIK3CA mutant cohort (n = 341); overall survival (OS) in the PIK3CA mutant cohort and safety are secondary endpoints. At a median follow-up of 20 months, median PFS was significantly prolonged in the alpelisib + fulvestrant arm vs. the placebo + fulvestrant arm (11.0 versus 5.7 months; HR = 0.65 [95% CI: 0.50-0.85]; *P*<.001). Median OS was not yet reached.[1]

In the overall study population, the most common adverse events (>35%) in the alpelisib + fulvestrant arm versus placebo + fulvestrant arm were hyperglycemia (63.7% vs. 9.8%), diarrhea (57.7% vs. 15.7%), nausea (44.7% vs. 22.3%), decreased appetite (35.6% vs. 10.5%) and rash (35.6% vs. 5.9%). The most frequently reported Grade 3 or 4 adverse events for the alpelisib + fulvestrant versus placebo + fulvestrant arms, respectively, included: hyperglycemia (36.6% vs. 0.7%), rash (9.9% vs. 0.3%), maculopapular rash (8.8% vs. 0.3%) and diarrhea (6.7% vs. 0.3%). Discontinuation rates for alpelisib and placebo were 25.0% and 4.2%, respectively. Alpelisib was discontinued in 18 patients due to hyperglycemia, and in nine, due to rash.[1]

Specific changes recommended for the Guidelines & Compendium

- Please consider including the combination of alpelisib + fulvestrant as a preferred treatment regimen for systemic treatment of HR+/HER2- advanced or metastatic breast cancer in

postmenopausal women or men with a PIK3CA mutation in sections BINV-21 and BINV-P, and related discussion sections.
- Please consider including testing for PIK3CA mutations with an FDA-approved test to confirm PIK3CA status for patients who may benefit from PI3K-directed therapy as part of the workup for recurrent or stage IV (M1) disease in section BINV-18.

FDA status
Alpelisib is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR+, HER2-, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.[2]

Rationale for recommended changes
- Based on the FDA-approved labeled indication and data from the pivotal SOLAR-1 trial, the combination of alpelisib + fulvestrant has demonstrated efficacy and safety in postmenopausal women and men with HR+/HER2- advanced or metastatic breast cancer with a PIK3CA mutation after progression on or after AI therapy with or without a CDK4/6 inhibitor.
- With an approved agent, testing for PIK3CA mutations identifies patients who may benefit from PI3K-directed therapy.

Literature support

1. Andre F, Ciruelos E, Rubovsky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med. 2019; 380: 1929-1940. DOI: 10.1056/NEJMoa1813904.
2. Piqray [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2019.

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We appreciate the opportunity to provide this 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 email at Neilda.Baron@novartis.com.

Thank you for your time and consideration.

Sincerely,

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Novartis Pharmaceuticals Corporation

Enclosures: Prescribing Information and referenced primary literature; author disclosures included within reference.