May 12, 2020

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Alpelisib + Fulvestrant for First-Line Treatment of PIK3CA-Mutant Advanced Breast Cancer

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NCCN Guidelines Panel:	Breast Cancer

To Whom It May Concern:

As the NCCN Breast Cancer Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Breast Cancer V.4.2020 and the associated Drugs & Biologics Compendium®, we are enclosing data related to treatment with alpelisib in combination with fulvestrant for your consideration:

- Data to support the use of alpelisib in combination with fulvestrant as a preferred first-line treatment option for PIK3CA-mutant HR+/HER2- recurrent/Stage IV breast cancer

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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 whose disease had progressed or recurred on or after aromatase inhibitor (AI) therapy (N=572). Randomization occurred 1:1 and was split into two cohorts based on PIK3CA mutation status (mutant [n=341] and non-mutant [n=231]). The primary endpoint is median progression-free survival (PFS) based on investigator assessment using RECIST v1.1 criteria in the PIK3CA-mutant cohort.[1]

In the PIK3CA-mutant cohort, 52.1% of patients received alpelisib + fulvestrant as first-line treatment for advanced disease after recurrence on adjuvant AI therapy compared to 51.7% in the placebo + fulvestrant arm.[1]

The median PFS in the PIK3CA-mutant cohort 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). Analysis of PFS in the subgroup of patients receiving first-line treatment for advanced disease revealed an HR of 0.71 (95% CI: 0.49-1.03).[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 adding "For PIK3CA-mutated tumors, see additional targeted therapy options (see BINV-R)" to the list of Preferred Regimens for First-Line Therapy as a systemic treatment option for HR+/HER2- recurrent or Stage IV breast cancer in BINV-P. Also, please consider adding the footnote "If there is disease progression while on an alpelisib-containing regimen, there are no data to support an additional line of therapy with another alpelisib regimen" to the bullet "For PIK3CA-mutated tumors..." under the list of Preferred Regimens for Second- and Subsequent-Line Therapy.
- Please consider changing the NCCN Category of Preference for alpelisib + fulvestrant to "Preferred" instead of "Preferred second-line therapy" in BINV-R.
- Please consider changing the NCCN Compendium Listing to "Treatment of recurrent or stage IV (M1) HR+, HER2- ...as first- or second-line therapy in combination with fulvestrant..." instead of "Treatment of recurrent or stage IV (M1) HR+, HER2- ...as second-line therapy or beyond in combination with fulvestrant...".

FDA status

Alpelisib is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, 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

- More than half (52.1%) of the PIK3CA-mutant cohort in the pivotal SOLAR-1 trial received alpelisib + fulvestrant as first-line treatment for advanced breast cancer after recurrence on adjuvant AI therapy.

- The combination of alpelisib + fulvestrant in SOLAR-1 has demonstrated efficacy and safety, including in the subgroup of patients who received first-line treatment for advanced disease.

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.