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NCCN Guidelines Panel: Breast Cancer

On behalf of Merck & Co., Inc., I respectfully request the NCCN Breast Cancer Panel to review the enclosed information for KEYTRUDA® (pembrolizumab), in reference to the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

Specific Changes: We respectfully request that pembrolizumab in combination with chemotherapy as preoperative treatment, followed by pembrolizumab as a single agent as adjuvant treatment after surgery be added as a preferred preoperative/adjuvant therapy regimen for patients with high-risk early-stage triple-negative breast cancer in the appropriate sections of the NCCN Breast Cancer Guidelines v5.2021, including page BINV-L 1 of 7.

FDA Clearance:

Triple-Negative Breast Cancer (TNBC)

- KEYTRUDA is indicated for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- KEYTRUDA is indicated in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.

Please refer to the KEYTRUDA prescribing information for other FDA-approved indications.[1]

Rationale:

The efficacy of pembrolizumab in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with pembrolizumab as a single agent was investigated in KEYNOTE-522, a randomized (2:1), multicenter, double-blind, placebo-controlled trial conducted in 1174 patients with newly diagnosed previously untreated high-risk early-stage TNBC[1]. The main efficacy outcomes were pathological complete response (pCR) rate and event free survival (EFS). pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause.

In the pembrolizumab-chemotherapy/pembrolizumab arm (n=784), 494 patients had a pCR [pCR Rate 63.0% (95% CI 59.5-66.4)] compared to 217 patients [pCR Rate 55.6% (95% CI 50.6-60.6)] in the placebo-chemotherapy/placebo arm (n=390), resulting in an estimated treatment difference of 7.5% (1.6-13.4). Based on an earlier pre-specified pCR interim analysis in 602 patients, the pCR rate difference was statistically significant (p=0.00055 compared to a significance level of 0.003).

In a pre-specified interim analysis, the addition of pembrolizumab to neoadjuvant chemotherapy followed by pembrolizumab alone in the adjuvant setting resulted in a statistically significant improvement in event-free survival. The number of patients with an EFS event was 123 (16%) in the pembrolizumab-chemotherapy/pembrolizumab arm, compared to 93 (24%) in the placebo-chemotherapy/placebo arm (HR: 0.63, 95% CI, 0.48-0.82, p=0.00031).

Fatal adverse reactions occurred in 0.9% of patients receiving pembrolizumab, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 44% of patients receiving pembrolizumab. Serious adverse reactions in ≥2% of patients who received pembrolizumab included febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%). The most common adverse reactions of all grades with pembrolizumab-chemotherapy/pembrolizumab (≥20%) were fatigue (70%), nausea (67%), alopecia (61%), rash (52%), constipation (42%), diarrhea and peripheral neuropathy (41% each), stomatitis (34%), vomiting (31%), headache (30%), arthralgia (29%), pyrexia (28%), cough (26%), abdominal pain (24%), decreased appetite (23%), insomnia (21%), and myalgia (20%).

The results from this study support our recommendation that pembrolizumab in combination with chemotherapy be added as a preoperative treatment regimen for patients with high-risk early-stage triple-negative breast cancer, and then as a single agent as adjuvant treatment following surgery.

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

1. Keytruda (pembrolizumab) Prescribing Information. Merck & Co., Inc
2. Schmid P, Cortes J, Dent R, et al. KEYNOTE-522: Phase 3 study of neoadjuvant pembrolizumab + chemotherapy versus placebo + chemotherapy, followed by adjuvant pembrolizumab versus placebo for early-stage triple-negative breast cancer. Presented at ESMO Plenary; July 15-16, 2021; Virtual.

Thank you for considering this request. Below is my contact information should you need to contact me for additional information.

Sincerely,

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