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Suzana Giffin, AVP
Merck & Co., Inc.
2000 Galloping Hill Road
P.O. Box 539
Kenilworth, New Jersey 07033-1310
908-740-6708
suzana.giffin@merck.com

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 combination with chemotherapy as neoadjuvant treatment in reference to NCCN Guidelines Version 3.2019 for Breast Cancer.

Specific Changes Requested:

Based on the oral presentation of Keynote 522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC) at the ESMO Congress 2019, Barcelona, Spain, we respectfully request that KEYTRUDA (pembrolizumab), in combination with platinum-based chemotherapy, be added as a preoperative therapy regimen for patients with early triple-negative breast cancer.

Rationale:

The efficacy of pembrolizumab in combination with chemotherapy vs. placebo in combination with chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs. placebo as adjuvant treatment is being investigated in KEYNOTE-522, a phase lll, randomized, double-blind trial that enrolled patients with newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-2. A total of 1,174 patients were randomly allocated at a 2:1 ratio to pembrolizumab or placebo, both added to preoperative chemotherapy with carboplatin + paclitaxel for 4 cycles followed by doxorubicin or epirubicin + cyclophosphamide for an additional 4 cycles. After surgery, patients continued their allocated treatment of pembrolizumab or placebo for nine cycles.

The two primary endpoints are pCR using the definition of ypT0/Tis ypN0 assessed by local pathologist and event-free survival (EFS) assessed by investigator, both in the ITT population. The efficacy results for the endpoint of pCR in the neoadjuvant phase were presented for the IA 1 population of the prespecified first 602 patients (LPLV 24 September 2018). pCR rate (%) (95% CI) in the 401 patients receiving pembrolizumab + chemotherapy as neoadjuvant treatment was 64.8 (59.9, 69.5), and in the 201 patients receiving placebo + chemotherapy 51.2 (44.1,58.3). The difference in % between treatments was 13.6 (5.4, 21.8), p value = 0.00055. At data cutoff of 24 April 2019 there was a favorable trend for EFS for the pembrolizumab group with a hazard ratio of 0.63 (95% CI 0.43–0.93).

The most common treatment related adverse events (incidence ≥20%) in the neoadjuvant phase (data cutoff 24 April 2019) were nausea, alopecia, anemia, neutropenia, fatigue, diarrhea, elevated ALT,

vomiting, asthenia, constipation, decreased neutrophil count, rash and peripheral neuropathy. Grade 3 or higher treatment-related adverse events occurred in 76.8% and 72.2% of the pembrolizumab and placebo groups, respectively.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Keynote 522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC). Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kummel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Jia L, Karantza V, Zhao J, Aktan G, O'Shaughnessy J. ESMO Congress 2019. Oral Presentation 29 September 2019.

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

Sincerely,

Suzana Giffin, AVP
Merck & Co., Inc.
2000 Galloping Hill Road
P.O. Box 539
Kenilworth, New Jersey 07033-1310
908 740-6708
suzana.giffin@merck.com