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NCCN Guidelines Panel: Esophageal and Esophagogastric Junction Cancers

On behalf of Merck & Co., Inc., I respectfully request the NCCN Esophageal and Esophagogastric Junction Cancers Panel to review the enclosed information for KEYTRUDA (pembrolizumab), in reference to NCCN Guidelines V2.2018 for Esophageal and Esophagogastric Junction Cancers.

Specific changes requested:

We respectfully request the addition of KEYTRUDA (pembrolizumab) as a second-line treatment for patients with recurrent locally advanced or metastatic adenocarcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10], and for patients with recurrent locally advanced or metastatic squamous-cell carcinoma (SCC) of the esophagus in the appropriate sections of the NCCN guidelines, including the section ESOPH-F (4/13).

FDA Approval:

Esophageal Cancer

KEYTRUDA (pembrolizumab) is not approved for the second-line treatment of patients with advanced esophageal cancer, with the exception of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) esophageal and gastroesophageal cancer that has progressed following prior treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.[1]

Please refer to the KEYTRUDA Prescribing Information for other FDA-approved indications.[1]

Rationale:

A multicenter, open label, randomized phase 3 study (KEYNOTE-181 Study; NCT02564263) was conducted to evaluate pembrolizumab (N=314) compared to investigator's choice (paclitaxel, docetaxel or irinotecan; N=314) in patients with advanced/metastatic adenocarcinoma or squamous-cell carcinoma (SCC) of the esophagus or Siewert type 1 adenocarcinoma of the GEJ who had progressed on or after 1 prior therapy. The three primary endpoints were overall survival (OS) in patients with PD-L1 CPS ≥10, OS in patients with SCC and OS in all patients (ITT); the study would be considered positive if any one of the three primary endpoints is met. The secondary endpoints were progression-free survival (PFS), objective response rate (ORR) and safety.[2]

In patients whose tumors had PD-L1 CPS ≥10 (n=222/628), pembrolizumab significantly improved OS compared to chemotherapy with a hazard ratio (HR) of 0.69 (95% CI, 0.52-0.93); one-sided p=0.0074 (significance threshold for OS: α=0.9%; p≤0.0085). The ORR was 21.5% for pembrolizumab vs. 6.1% for chemotherapy; PFS HR was 0.73 (95% CI, 0.54-0.97) with estimated 12-month PFS rates of 21% for pembrolizumab and 7% for chemotherapy.[2]

In patients with SCC (n=401/628), there was a clinically meaningful improvement in OS with pembrolizumab compared to chemotherapy with a HR of 0.78 (95% CI, 0.63-0.96); one-sided p=0.0095, which narrowly missed statistical significance per the pre-specified statistical plan (significance threshold for OS: α=0.8%; p≤0.0077). The estimated 12-month OS rates were 39% for pembrolizumab and 25% for chemotherapy, and 18-month OS rates were 23% and 12% for pembrolizumab and chemotherapy, respectively. The ORR was 16.7% for pembrolizumab vs. 7.4% for chemotherapy, and the PFS HR was 0.92 (95% CI, 0.75-1.13) with estimated 12-month PFS rates of 15% for pembrolizumab and 9% for chemotherapy. In the ITT population (N=628), while also directionally favorable, the difference in OS was not statistically significant between pembrolizumab and chemotherapy with a HR of 0.89 (95% CI, 0.75-1.05); one-sided p=0.0560 (significance threshold for OS: α=0.8%; p≤0.0077).[2]

Treatment-related adverse events (TRAEs) occurred in 64.3% of patients taking pembrolizumab (N=314) compared with 86.1% for chemotherapy (N=296). There was a lower frequency of grade 3-5 TRAEs with pembrolizumab versus chemotherapy (18.2% vs 40.9%). TRAEs led to discontinuation of study treatment in 18 (6.1%) patients treated with pembrolizumab and 19 (6.4%) patients receiving chemotherapy. Treatment related deaths were 1.5% and 1.7% in pembrolizumab and chemotherapy groups, respectively. Pembrolizumab monotherapy showed an improved safety profile compared to chemotherapy, and consistent with the established safety profile in other indications. Based on the favorable benefit-risk profile and current unmet medical need, the totality of this data supports our request for the inclusion of pembrolizumab monotherapy in previously treated advanced esophageal and GEJ carcinoma patients.[2]

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.

2. Kojima T, Muro K, Francois E et al. Pembrolizumab Versus Chemotherapy as Second-line Therapy for Advanced Esophageal Cancer: The Phase 3 KEYNOTE-181 Study. Presented at 2019 Gastrointestinal Cancers Symposium; January 17-19; San Francisco, CA.

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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