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NCCN Guidelines Panel: Head and Neck Cancers

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

Specific changes requested:

We respectfully request the category of evidence and consensus for KEYTRUDA (pembrolizumab) to be changed from category 2A to category 1 recommendation in patients with non-nasopharyngeal, recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy (section CHEM-A).

FDA Approval:

KEYTRUDA (pembrolizumab) is approved for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. 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.

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

Rationale:

A multicenter, open-label, randomized phase III study (KEYNOTE-040; NCT02252042) of pembrolizumab vs. standard of care (SOC) was conducted in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). Key eligibility criteria included SCC of the oral cavity, oropharynx, hypopharynx or larynx; disease progression during or after platinum-containing treatment for recurrent or metastatic disease (or both) or had recurrence or progression within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease; ECOG PS 0 or 1. Patients received pembrolizumab every 3 weeks for up to 24 months or SOC (methotrexate, docetaxel or cetuximab). The primary endpoint was overall survival (OS) in the ITT population with a pre-specified significance boundary α=0.0175 (one-sided). Overall patient baseline characteristics were generally balanced between treatment groups (N=247 in the pembrolizumab arm; N=248 in the SOC arm).[2]

At the time of the protocol-specified final analysis (data cutoff: May 15, 2017), death had occurred in 179 (72%) of 247 patients in the pembrolizumab group and 198 (80%) of 248 patients in the SOC group, with survival status unconfirmed for 12 patients (3 in pembrolizumab group; 9 in SOC group). The HR for death for pembrolizumab vs. SOC was 0.82 (95% CI: 0.67–1.01; one-sided p=0.0316), which did not meet the efficacy boundary. After confirming the survival status of the 12 outstanding patients (same data cutoff), a post-hoc analysis showed the number of deaths in the ITT population increased to 181 (73%) of 247 in the pembrolizumab group and 207 (83%) of 248 in the SOC group, with a HR of 0.80 (95% CI: 0.65–0.98; nominal p=0.0161). In a post-hoc exploratory analysis in the SOC

group, the 31 patients who received subsequent immune checkpoint inhibitor (ICI) had longer OS than the 70 patients who received other subsequent therapy and the 147 patients who received no subsequent therapy (median OS of 20.1 months vs. 9.7 months vs. 4.5 months). In a post-hoc sensitivity analysis in which patients in both treatment groups were censored at the time of first subsequent ICI, the HR for death was 0.72 (95% CI: 0.58–0.88; nominal p=0.0008). Treatment-related adverse events (TR-AEs) of any grade occurred in 155 patients (63%) and 196 patients (84%) in the pembrolizumab and SOC arms, respectively; Grade 3-5 TR-AEs occurred in 13% vs. 36% of patients in the pembrolizumab and SOC arms, respectively. Discontinuation rates were 6% and 5%, death rates were 2% and 1% for pembrolizumab and SOC, respectively. There were no new or unexpected toxicities in the pembrolizumab arm.[2]

The clinically meaningful survival benefit and favorable safety profile of pembrolizumab compared with SOC (methotrexate, docetaxel or cetuximab), in patients with R/M HNSCC who progressed during or after platinum-based therapy, support our request for the change to category 1 recommendation.[2]

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

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

2. Cohen EEW, Soulières D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. The Lancet; Published Online November 30, 2018; http://dx.doi.org/10.1016/ S0140-6736(18)31999-8

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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