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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 on KEYTRUDA (pembrolizumab), in reference to NCCN Guidelines V3.2019 for Head and Neck Cancers.

Specific changes requested:

We respectfully request that the recommendation for KEYTRUDA (pembrolizumab) in combination with platinum and fluorouracil chemotherapy in the first-line therapy of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) be changed from **category 2A to category 1** (section CHEM A; page 2 of 6) based on high level evidence (**overall survival data**) demonstrated in the global, randomized, controlled KEYNOTE-048 study.

We also respectfully request that the recommendation for KEYTRUDA monotherapy in the first-line therapy of patients with recurrent or metastatic HNSCC that expresses PD-L1 combined positive score (CPS) ≥1 be changed from **category 2A to category 1** (section CHEM A; page 2 of 6) based on high level evidence (**overall survival data**) demonstrated in the study KEYNOTE-048.

FDA approval:

KEYTRUDA (pembrolizumab), in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).[1]

KEYTRUDA, as a single agent, is indicated for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.[1]

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.[1]

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

Rationale:

A multicenter, randomized, active-controlled, open-label, ongoing phase III study (KEYNOTE-048; NCT02358031) was conducted in the first-line treatment of patients with recurrent or metastatic (R/M) HNSCC. Patients were randomized (1:1:1) to receive pembrolizumab monotherapy, pembrolizumab and chemotherapy (carboplatin or cisplatin + 5-FU), or the EXTREME regimen (cetuximab + carboplatin or cisplatin + 5-FU). Progression-free survival (PFS) and overall survival (OS) were dual primary endpoints and were analyzed in these populations: CPS ≥20, CPS ≥1, and total population. Key secondary endpoints included safety, objective response rate (ORR), PFS at 6 months and 12 months, and quality of life measures.[2-4]

Results from the second interim analysis (data cutoff date: June 13, 2018): Pembrolizumab monotherapy significantly improved OS vs. the EXTREME regimen in the CPS ≥20 population with a hazard ratio (HR) of 0.61 (95% CI, 0.45-0.83; P=0.0007) as well as in the CPS ≥1 population with a HR of 0.78 (95% CI, 0.64-0.96; P=0.0086) and was non-inferior in the total population with a HR of 0.85 (95% CI, 0.71-1.03, P=0.0456). There was no PFS or ORR benefit for pembrolizumab monotherapy over the EXTREME regimen in these populations. Median duration of response (DOR) for pembrolizumab monotherapy patients in the CPS ≥20 population was 20.9 months (range: 2.7 to 34.8+) vs. 4.2 months (range: 1.2+ to 22.3+) for EXTREME regimen patients. Median DOR for pembrolizumab monotherapy in the CPS ≥1 population was 20.9 months (range: 1.5+ to 34.8+) vs. 4.5 months (range: 1.2+ to 28.6+) for EXTREME regimen patients. Pembrolizumab monotherapy had a favorable safety profile vs. EXTREME regimen, with a lower incidence of any-grade, grade 3-4, and grade 5 treatment-related adverse events (AEs), and a lower incidence of treatment-related AEs leading to discontinuation.[2,4]

Pembrolizumab in combination with chemotherapy significantly improved OS vs. EXTREME regimen in the total population regardless of PD-L1 status with a HR of 0.77 (95% CI, 0.63-0.93; P=0.0034). There was no PFS or ORR benefit for pembrolizumab plus chemotherapy over the EXTREME regimen. Median DOR for pembrolizumab plus chemotherapy patients in the total population was 6.7 months (range: 1.6+ to 30.4+) vs. 4.3 months (range: 1.2+ to 27.9+). Pembrolizumab plus chemotherapy had a comparable safety profile vs. the EXTREME regimen. There was a similar incidence of any-grade, grade 3-4, and grade 5 treatment-related AEs. There was no unexpected toxicity in the pembrolizumab plus chemotherapy arm.[2,4]

Results from the final analysis (data cutoff date: February 25, 2019): Pembrolizumab monotherapy continued to demonstrate improved OS vs. EXTREME regimen in the CPS ≥20 population with a HR of 0.58 (95% CI, 0.44-0.78) as well as in the CPS ≥1 population with a HR of 0.74 (95% CI, 0.61-0.90). The threshold for superiority of OS for pembrolizumab alone vs. cetuximab with chemotherapy in the total population was not met; HR: 0.83 (95% CI, 0.70-0.99, P=0.0199). Pembrolizumab monotherapy had a favorable safety profile vs. the EXTREME regimen, with lower incidences of grade 3-5 treatment-related adverse events (AEs), immune-mediated or infusion-related reactions, and treatment-related AEs leading to discontinuation.[3,4]

Pembrolizumab in combination with chemotherapy continued to demonstrate improved OS vs. the EXTREME regimen in the total population regardless of PD-L1 status with a HR of 0.72 (95% CI, 0.60-0.87). Superior OS was also demonstrated in the CPS ≥20 population (HR 0.60, 95% CI, 0.45-0.82, P=0.0004) and in the CPS ≥1 population (HR 0.65, 95% CI, 0.53-0.80, P<0.0001) compared to the EXTREME regimen. Pembrolizumab plus chemotherapy had a comparable safety profile vs. the EXTREME

regimen. There was a similar incidence of any-grade, grade 3-5, and grade 5 treatment-related AEs. There was no unexpected toxicity in the pembrolizumab plus chemotherapy arm.[3,4]

The data from the KEYNOTE-048 study has now been published in a peer-reviewed, medical oncology journal.[4]

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

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

2. Burtness B, Harrington K, Greil R et al. KEYNOTE-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC). Presented at European Society for Medical Oncology (ESMO); October 19-23, 2018; Munich, Germany.

3. Rischin D, Harrington K, Greil R, et al. Protocol-Specified Final Results of the KEYNOTE-048 Trial of Pembrolizumab as First-Line Therapy for Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC). Presented at American Society for Clinical Oncology (ASCO); May 31 – June 4, 2019; Chicago, IL.

4. Burtness B, Harrington K, Greil R et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous-cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet Oncol.* 2019. https://doi.org/10.1016/S0140-6736(19)32591-7.

Thank you for considering this request. Should you need additional information, please do not hesitate to contact me.

Sincerely,

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