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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 V1.2019 for Head and Neck Cancers.

Specific changes requested:

We respectfully request the NCCN panel to consider the inclusion of KEYTRUDA monotherapy as a category 1 first-line treatment recommendation in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that expresses PD-L1 combined positive score (CPS) ≥1 in the appropriate sections of the guidelines, including section CHEM-A.

We also respectfully request the NCCN panel to consider the inclusion of KEYTRUDA in combination with chemotherapy with a platinum and fluorouracil as a category 1 first-line treatment recommendation in patients with recurrent or metastatic HNSCC in the appropriate sections of the guidelines, including section CHEM-A.

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 to evaluate pembrolizumab or pembrolizumab plus chemotherapy versus standard of care of cetuximab plus chemotherapy (EXTREME regimen) in the first-line treatment of patients with recurrent or metastatic (R/M) HNSCC. Key eligibility criteria included confirmed R/M HNSCC in the oropharynx (with known p16 status), oral cavity, hypopharynx or larynx considered incurable by local therapies, with no prior systemic therapy administered in the R/M setting, and ECOG PS of 0 or 1. Patients were randomized (1:1:1) to receive pembrolizumab monotherapy, pembrolizumab and chemotherapy (carboplatin or cisplatin + 5-FU), or 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.[2,3]

Results from the second interim analysis were submitted to the panel on 10/23/2018 (data cutoff date: June 13, 2018). Pembrolizumab monotherapy significantly improved OS vs. 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). 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]

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. 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]

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). Results for OS in the total population were consistent with the prior interim analysis with a HR of 0.83 (95% CI, 0.70-0.99, P=0.0199). Pembrolizumab monotherapy had a favorable safety profile vs. 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. Pembrolizumab in combination with chemotherapy continued to demonstrate improved OS vs. 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. 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]

The totality of these data supports our requests for the inclusion of pembrolizumab monotherapy (CPS ≥1 population) and pembrolizumab in combination with chemotherapy (irrespective of biomarker) as category 1 first-line treatment in patients with R/M HNSCC.[2,3] FDA approval of KEYTRUDA as monotherapy (CPS ≥1) or in combination with platinum and fluorouracil for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC occurred on June 10, 2019.[1] This approval was based on review of the data from the second interim analysis presented at European Society for Medical Oncology (ESMO); October 19-23, 2018; Munich, Germany.[2]

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.


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

Sincerely,


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