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NCCN Guidelines Panel: Small Cell Lung Cancer

On behalf of Merck & Co., Inc., I respectfully request that the NCCN Small Cell Lung Cancer Panel review the enclosed information for KEYTRUDA® (pembrolizumab), in reference to small cell lung cancer (SCLC).

Specific Changes: We would like to inform the NCCN Small Cell Lung Cancer Panel of the voluntary withdrawal of the U.S. indication for KEYTRUDA (pembrolizumab) for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

FDA Clearance: The withdrawal of the following indication was done in consultation with the FDA.

- *Small Cell Lung Cancer:* KEYTRUDA is indicated for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least 1 other prior line of therapy. 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 confirmatory trials.

This decision does not affect other indications for KEYTRUDA. Please refer to the KEYTRUDA prescribing information for the FDA-approved indications.[1]

Rationale:
Merck's consultation with the FDA on this withdrawal is part of an industry-wide evaluation of indications based on accelerated approvals that have not yet met their post-marketing requirements.

The accelerated approval for KEYTRUDA in metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least 1 other prior line of therapy was granted in June 2019 based on tumor response rate and durability of response data from KEYNOTE-158 (cohort G) and KEYNOTE-028 (cohort C1). Continued approval for this indication was contingent upon completion of the post-marketing requirement establishing superiority of KEYTRUDA as determined by overall survival (OS). As announced in January 2020, KEYNOTE-604, the confirmatory Phase 3 trial for this indication, met one of its dual primary endpoints of PFS but did not reach statistical significance for the other primary endpoint of OS.

Merck has initiated KEYLYNK-013, a Phase 3 study examining pembrolizumab plus concurrent chemo-radiation therapy compared to standard of care in patients with limited stage SCLC. This study is currently enrolling (Clinical Trial Number NCT04624204).

The following information from the KEYNOTE-158 and KEYNOTE 604 studies was previously submitted to this Panel for consideration. [2,3]

KEYNOTE-158
KEYNOTE-158 was a phase 2 multicohort study that was conducted to evaluate pembrolizumab in patients with advanced SCLC regardless of biomarker status. Enrolled patients had prior progression on or intolerance to standard therapy and received pembrolizumab 200 mg every 3 weeks for 2 years or until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR; RECIST v1.1, central review). Secondary endpoints included progression free survival (PFS), OS, duration of response (DOR) and safety. At the data cutoff date (Jan 15, 2018), median follow-up was 9.3 months (range, 0.5–22.3). Among 107 SCLC patients enrolled, 61 (57%) had received 2 or more lines of prior therapies for recurrent/metastatic disease and 16 (15%)

had stable brain metastasis. PD-L1-positive was defined as PD-L1 combined positive score ≥1. Tumors were PD-L1–positive in 39% and PD-L1–negative in 47% of patients (14% non-evaluable). ORR was 18.7% in the overall population (20/107; 95% CI, 11.8–27.4), 35.7% (15/42; 95% CI, 21.6–52.0) in patients with PD-L1–positive tumors, and 6.0% (3/50; 95% CI, 1.3–16.5) in PD-L1–negative tumors. Overall, median DOR had not been reached (range, 2.1+ to 18.7+) and 12 patients had DOR ≥12 months by Kaplan Meier curve estimation. Median PFS was 2.0 months (95% CI, 1.9–2.1) in all patients, 2.1 months (95% CI, 2.0–8.1) in patients with PD-L1–positive tumors, and 1.9 months (95% CI, 1.6–2.0) in PD-L1–negative tumors. Median OS was 8.7 months (95% CI, 5.6–12.0) overall, 14.9 months (95% CI, 5.6–NR) in patients with PD-L1–positive tumors, and 5.9 months (95% CI, 3.3–10.1) in PD-L1–negative tumors. Treatment-related AEs occurred in 64 patients (60%) with Grade ≥3 AEs in 13 patients (12%); there were two fatal treatment-related AEs (pneumonia and encephalopathy). The most common AEs (≥10%) were fatigue (14%), pruritus (12%), hypothyroidism (12%), decreased appetite (10%) and nausea (10%).[2]

KEYNOTE-604

KEYNOTE-604 was a randomized, double-blind, phase III study comparing pembrolizumab plus etoposide and platinum-based chemotherapy (EP) and placebo plus EP in patients with previously untreated extensive-stage (ES)-SCLC. The dual primary endpoints were PFS (RECIST version 1.1, blinded central review) and OS. Secondary endpoints included ORR and DOR. At the second interim analysis, which was the protocol-specified final analysis for PFS, pembrolizumab plus EP significantly improved PFS (hazard ratio [HR], 0.75; 95% CI, 0.61 to 0.91; P = 0.0023). Twelve-month PFS estimates were 13.6% with pembrolizumab plus EP and 3.1% with placebo plus EP. At final analysis, pembrolizumab plus EP prolonged OS compared with placebo plus EP (HR, 0.80; 95% CI, 0.64 to 0.98; P = 0.0164); however, the significance threshold of P = 0.0128 was not met. The estimated OS rates at 24 months were 22.5% in the pembrolizumab plus EP group and 11.2% in the placebo plus EP group. ORR was 70.6% (95% CI, 64.2% to 76.4%) in the pembrolizumab plus EP group and 61.8% (95% CI, 55.1% to 68.2%) in the placebo plus EP group; at 1 year, the estimated proportion of ongoing responses was 19.3% and 3.3%, respectively. Any-cause adverse events were grade 3-4 in 76.7% and 74.9%, grade 5 in 6.3% and 5.4%, and led to discontinuation of any drug in 14.8% and 6.3% in the pembrolizumab plus EP and placebo plus EP groups, respectively. As the success criterion for the dual primary hypothesis for PFS was met, KEYNOTE-604 is considered a positive study.[3]

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Chung HC, Lopez-Martin J, Kao S, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer: KEYNOTE-158. Presented at: American Society of Clinical Oncology (ASCO); June 1-5, 2018; Chicago IL, USA. J Clin Oncol. 2018;36(suppl 15):8506. doi:10.1200/JCO.2018.36.15_suppl.8506.
3. Rudin C, Awad M, Navarro A, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol. 2020;38(21):2369-2379. doi: 10.1200/JCO.20.00793.

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

Sincerely,

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