EUROPEAN APPROVAL BASED ON RESULTS FROM PIVOTAL PHASE 3 TRIAL KEYNOTE-189 DEMONSTRATING KEYTRUDA IN COMBINATION WITH PEMETREXED AND PLATINUM CHEMOTHERAPY SIGNIFICANTLY IMPROVED OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL COMPARED WITH CHEMOTHERAPY ALONE

KEYTRUDA is the First Anti-PD-1 Therapy Approved in Combination with Chemotherapy in Europe for First-Line Use in Patients with Metastatic NSCLC

KENILWORTH, N.J.—10/09/2018 (BUSINESS WIRE)—
Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the European Commission has approved KEYTRUDA, the company's anti-PD-1 therapy, in combination with pemetrexed (ALIMTA®) and platinum chemotherapy for the first-line treatment of metastatic nonsquamous non-small cell lung cancer (NSCLC) in adults whose tumors have no *EGFR* or *ALK* positive mutations. This approval, the first in Europe for an anti-PD-1 therapy in combination with chemotherapy, is based on data from the pivotal Phase 3 KEYNOTE-189 trial in patients with metastatic nonsquamous NSCLC regardless of PD-L1 tumor expression status, which demonstrated a significant survival benefit for the combination of KEYTRUDA with chemotherapy as compared with standard-of-care chemotherapy alone – reducing the risk of death in these patients by half (HR=0.49 [95% CI, 0.38-0.64]; p<0.00001).
"We are very pleased that the European Commission has approved KEYTRUDA in combination with chemotherapy based on the significant survival benefit demonstrated in the KEYNOTE-189 trial," said Dr. Roger M. Perlmutter, president, Merck Research Laboratories. "This approval is a first in Europe and adds to the rapidly growing role of KEYTRUDA as a foundation for the treatment of lung cancer."

The approval allows marketing of the KEYTRUDA combination in all 28 EU member states plus Iceland, Lichtenstein and Norway, at the approved dose of 200 mg every three weeks until disease progression or unacceptable toxicity. KEYTRUDA is also approved in Europe as a monotherapy for the first-line treatment of metastatic squamous or nonsquamous NSCLC in patients whose tumors have high PD-L1 expression (tumor proportion score [TPS] of 50 percent or more) with no *EGFR* or *ALK* positive tumor mutations (KEYNOTE-024) and for previously-treated patients with locally advanced or metastatic NSCLC whose tumors express PD-L1 (TPS of 1 percent or more) and who have received at least one prior chemotherapy regimen (KEYNOTE-010).

"Lung cancer is the leading cause of cancer death in Europe, and we are committed to doing everything in our power to help address it," said Frank Clyburn, president, Merck Oncology. "Today KEYTRUDA is now approved across Europe for the treatment of appropriate patients with metastatic nonsquamous non-small cell lung cancer as both a monotherapy and in combination with chemotherapy."

Data Supporting the Approval

The approval was based on data from KEYNOTE-189, a Phase 3, multicenter, randomized, active-controlled, double-blind trial. Key eligibility criteria were metastatic nonsquamous NSCLC, no prior systemic treatment for metastatic NSCLC, and no *EGFR* or *ALK* genomic

tumor aberrations. Patients with autoimmune disease that required systemic therapy within two years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

Patients were randomized to receive KEYTRUDA 200 mg, cisplatin or carboplatin, and pemetrexed intravenously every three weeks for four cycles followed by KEYTRUDA 200 mg for up to 24 months and pemetrexed every three weeks (n=410); or placebo with cisplatin or carboplatin and pemetrexed intravenously every three weeks for four cycles followed by pemetrexed every three weeks (n=206). Treatment continued until progression of disease or unacceptable toxicity, or a maximum of 24 months. For patients who completed 24 months of therapy or had a complete response, treatment with KEYTRUDA could be reinitiated for disease progression and administered for up to one additional year.

Primary efficacy outcome measures were overall survival (OS) and progression-free survival (PFS) as assessed by blinded independent central review (BICR) using RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). Secondary efficacy outcome measures were overall response rate (ORR) and duration of response (DOR). Patients receiving placebo plus chemotherapy who experienced disease progression could cross over to receive KEYTRUDA as monotherapy. The KEYNOTE-189 study was conducted in collaboration with Eli Lilly and Company, the makers of pemetrexed (ALIMTA®).

In KEYNOTE-189, there was a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with pemetrexed and platinum chemotherapy alone – with a reduction in the risk of death by 51 percent (HR=0.49 [95% CI, 0.38-0.64]; p<0.00001) and a 48 percent reduction in the risk of progression or death (HR=0.52 [95% CI, 0.43-0.64]; p<0.00001). The ORR was 48 percent (95% CI, 43-53) for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared to 19 percent (95% CI, 14-25) for patients randomized to pemetrexed and platinum chemotherapy alone (p<0.0001). The median DOR for patients randomized to receive KEYTRUDA in combination with pemetrexed and platinum chemotherapy was 11.2 months (range, 1.1+ to 18.0+ months) compared to 7.8 months (range, 2.1+ to 16.4+ months) for patients randomized to receive pemetrexed and platinum chemotherapy alone.

The safety of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was evaluated in 488 patients with nonsquamous NSCLC receiving 200 mg, 2 mg/kg or 10 mg/kg pembrolizumab every three weeks, in two clinical studies (KEYNOTE-189 and KEYNOTE-021). In this patient population, the most frequent adverse reactions were nausea (47%), anemia (37%), fatigue (38%), neutropenia (22%), decreased appetite (21%), diarrhea (20%) and vomiting (19%). Incidences of Grade 3-5 adverse reactions were 47 percent for KEYTRUDA combination therapy and 37 percent for chemotherapy alone.

For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA