European Commission Approves Two New Regimens of Merck’s KEYTRUDA® (pembrolizumab) as First-Line Treatment for Metastatic or Unresectable Recurrent Head and Neck Squamous Cell Carcinoma (HNSCC)

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#MRK
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KEYTRUDA is the First Anti-PD-1 Therapy Approved in Europe for the First-Line Treatment of Head and Neck Cancer as Monotherapy or in Combination with Chemotherapy, in Patients Whose Tumors Express PD-L1 (CPS ≥1)

Approval Based on Significant Overall Survival Findings from Phase 3 KEYNOTE-048 Trial

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the European Commission has approved KEYTRUDA, Merck's anti-PD-1 therapy, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumors express PD-L1 (combined positive score [CPS] ≥1). This approval is based on findings from the pivotal Phase 3 KEYNOTE-048 trial, in which KEYTRUDA, compared with standard treatment (cetuximab with carboplatin or cisplatin plus 5-FU), demonstrated a significant improvement in overall survival (OS) as monotherapy (HR = 0.74 [95% CI, 0.61-0.90]; p=0.00133) and in combination with chemotherapy (HR=0.65 [95% CI, 0.53-0.80]; p=0.00002), in patients whose tumors expressed PD-L1 (CPS ≥1).

“This disease is especially debilitating since it can be highly visible and affect a patient’s appearance and their daily functions, such as eating and speaking,” said Professor Kevin Harrington, investigator for KEYNOTE-048, professor of biological cancer therapies at The Institute of Cancer Research, London, and consultant clinical oncologist at The Royal Marsden NHS Foundation Trust. “Considering the great need for new treatment options, we are encouraged by today’s KEYTRUDA approval in Europe, which will allow certain patients to be treated with immunotherapy earlier in the course of their treatment.”

This approval allows marketing of the KEYTRUDA monotherapy and combination regimen in all 28 EU member states plus Iceland, Lichtenstein and Norway.

“KEYTRUDA is now the first anti-PD-1 treatment option in the first-line setting for metastatic or unresectable recurrent head and neck cancer, a disease that has been treated the same way in the EU for more than a decade,” said Dr. Jonathan Cheng, vice president, clinical research, Merck Research Laboratories. “The European Commission approval underscores our commitment to transforming the way cancer is treated around the world.”

Data Supporting the European Approval

This approval is based on data from the Phase 3 KEYNOTE-048 trial, a multi-center, randomized, open-label, active-controlled trial conducted in 882 patients with histologically confirmed metastatic or recurrent HNSCC of the oral cavity, pharynx or larynx, who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies. Randomization was stratified by tumor PD-L1 expression (Tumor Proportion Score [TPS] ≥50% or <50%), HPV status (positive or negative), and ECOG Performance Status (PS) (0 vs. 1). The dual primary endpoints were OS and progression-free survival (PFS). Patients were randomized 1:1:1 to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every three weeks;
- KEYTRUDA 200 mg intravenously every three weeks, carboplatin AUC 5 mg/mL/min intravenously every three weeks or

...
cisplatin 100 mg/m\textsuperscript{2} intravenously every three weeks and 5-FU 1000 mg/m\textsuperscript{2}/day as a continuous intravenous infusion over 96 hours every three weeks (maximum of six cycles of platinum and 5-FU);
- Cetuximab 400 mg/m\textsuperscript{2} intravenously as the initial dose then 250 mg/m\textsuperscript{2} intravenously once weekly, carboplatin AUC 5 mg/mL/min intravenously every three weeks or cisplatin 100 mg/m\textsuperscript{2} intravenously every three weeks and 5-FU 1000 mg/m\textsuperscript{2}/day as a continuous intravenous infusion over 96 hours every three weeks (maximum of six cycles of platinum and 5-FU).

Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by the investigator, unacceptable toxicity or a maximum of 24 months.

### Efficacy Results for KEYTRUDA as Monotherapy in KEYNOTE-048 with PD-L1 Expression (CPS ≥1)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>KEYTRUDA n=257</th>
<th>Standard Treatment* n=255</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients with event</td>
<td>197 (77%)</td>
<td>229 (90%)</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>12.3 (10.8, 14.3)</td>
<td>10.3 (9.0, 11.5)</td>
</tr>
<tr>
<td>Hazard ratio† (95% CI)</td>
<td>0.74 (0.61, 0.90)</td>
<td></td>
</tr>
<tr>
<td>p-Value‡</td>
<td>0.00133</td>
<td></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients with event</td>
<td>228 (89%)</td>
<td>237 (93%)</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>3.2 (2.2, 3.4)</td>
<td>5.0 (4.8, 6.0)</td>
</tr>
<tr>
<td>Hazard ratio† (95% CI)</td>
<td>1.13 (0.94, 1.36)</td>
<td></td>
</tr>
<tr>
<td>p-Value‡</td>
<td>0.89580</td>
<td></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective response rate§ (95% CI)</td>
<td>19.1% (14.5, 24.4)</td>
<td>35% (29.1, 41.1)</td>
</tr>
<tr>
<td>Complete response</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Partial response</td>
<td>14%</td>
<td>32%</td>
</tr>
<tr>
<td>p-Value¶</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median in months (range)</td>
<td>23.4 (1.5+, 43.0+)</td>
<td>4.5 (1.2+, 38.7+)</td>
</tr>
<tr>
<td>% with duration ≥6 months</td>
<td>81%</td>
<td>36%</td>
</tr>
</tbody>
</table>

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)

### Efficacy Results for KEYTRUDA plus Chemotherapy in KEYNOTE-048 with PD-L1 Expression (CPS ≥1)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>KEYTRUDA + Platinum Chemotherapy + 5-FU n=242</th>
<th>Standard Treatment* n=235</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients with event</td>
<td>177 (73%)</td>
<td>213 (91%)</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>13.6 (10.7, 15.5)</td>
<td>10.4 (9.1, 11.7)</td>
</tr>
<tr>
<td>Hazard ratio† (95% CI)</td>
<td>0.65 (0.53, 0.80)</td>
<td></td>
</tr>
<tr>
<td>p-Value‡</td>
<td>0.00002</td>
<td></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients with event</td>
<td>212 (88%)</td>
<td>221 (94%)</td>
</tr>
<tr>
<td>Metric</td>
<td>Value</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>5.1 (4.7, 6.2)</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.84 (0.69, 1.02)</td>
<td></td>
</tr>
<tr>
<td>p-Value</td>
<td>0.03697</td>
<td></td>
</tr>
</tbody>
</table>

**ORR**

| Objective response rate (95% CI)            | 36% (30.3, 42.8) |
| Complete response                           | 7%             |
| Partial response                            | 30%            |
| p-Value                                    | 0.4586        |

**Duration of Response**

| Median in months (range)                  | 6.7 (1.6+, 39.0+) |
| % with duration ≥6 months                  | 54%             |

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)
¶ Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)

The safety of KEYTRUDA as monotherapy has been evaluated in 5,884 patients with advanced melanoma, resected Stage III melanoma (adjuvant therapy), non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma, urothelial carcinoma, or HNSCC across four doses (2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks) in clinical studies. In this patient population, the median observation time was 7.3 months (range: 1 day to 31 months) and the most frequent adverse reactions with KEYTRUDA were fatigue (32%), nausea (20%), and diarrhea (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions.

The safety of KEYTRUDA in combination with chemotherapy has been evaluated in 1,067 patients with NSCLC or HNSCC receiving 200 mg, 2 mg/kg or 10 mg/kg KEYTRUDA every 3 weeks, in clinical studies. In this patient population, the most frequent adverse reactions were anemia (50%), nausea (50%), fatigue (37%), constipation (35%), diarrhea (30%), neutropenia (30%), decreased appetite (28%) and vomiting (25%). Incidences of Grades 3-5 adverse reactions in patients with NSCLC were 67% for KEYTRUDA combination therapy and 66% for chemotherapy alone and in patients with HNSCC were 85% for KEYTRUDA combination therapy and 84% for chemotherapy plus cetuximab.

**About Head and Neck Cancer**

Head and neck cancer describes a number of different tumors that develop in or around the throat, larynx, nose, sinuses and mouth. Most head and neck cancers are squamous cell carcinomas that begin in the flat, squamous cells that make up the thin surface layer of the structures in the head and neck. Two substances that greatly increase the risk of developing head and neck cancer are tobacco and alcohol. It is estimated that there were more than 705,000 new cases of head and neck cancer diagnosed and over 358,000 deaths from the disease worldwide in 2018. In Europe, it is estimated that there were more than 146,000 newly diagnosed cases of head and neck cancer and around 66,000 deaths from the disease in 2018.

**About KEYTRUDA® (pembrolizumab) Injection**

KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of the body’s immune system to help detect and fight tumor cells. KEYTRUDA is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

Merck has the industry’s largest immuno-oncology clinical research program. There are currently more than 1,000 trials studying KEYTRUDA across a wide variety of cancers and treatment settings. The KEYTRUDA clinical program seeks to understand the role of KEYTRUDA across cancers and the factors that may predict a patient’s likelihood of benefiting from treatment with KEYTRUDA, including exploring several different biomarkers.

**Selected Indications for KEYTRUDA® (pembrolizumab) in the U.S.**

**Melanoma**

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

**Non-Small Cell Lung Cancer**

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [tumor proportion score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one 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.

Head and Neck Squamous Cell Cancer

KEYTRUDA, 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).

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.

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.

Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines 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 the confirmatory trials.

Primary Mediastinal Large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines 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. KEYTRUDA is not recommended for the treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [CPS ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Microsatellite Instability-High (MSI-H) Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

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.

The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

Gastric Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 [CPS ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted 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 the confirmatory trials.
KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

Cervical Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. 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.

Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. 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.

Merkel Cell Carcinoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. 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.

Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

Selected Important Safety Information for KEYTRUDA

Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 3.4% (94/2799) of patients with various cancers receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%). Pneumonitis occurred in 8.2% (65/790) of NSCLC patients receiving KEYTRUDA as a single agent, including Grades 3-4 in 3.2% of patients, and occurred more frequently in patients with a history of prior thoracic radiation (17%) compared to those without (7.7%). Pneumonitis occurred in 6% (18/300) of HNSCC patients receiving KEYTRUDA as a single agent, including Grades 3-5 in 1.6% of patients, and occurred in 5.4% (15/276) of patients receiving KEYTRUDA in combination with platinum and FU as first-line therapy for advanced disease, including Grade 3-5 in 1.5% of patients.

Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis. Colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 2 (0.4%), 3 (1.1%), and 4 (<0.1%). Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA for Grade 4 colitis.

Immune-Mediated Hepatitis (KEYTRUDA) and Hepatotoxicity (KEYTRUDA in Combination With Axitinib)

Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%). Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

Hepatotoxicity in Combination With Axitinib

KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib, and consider administering corticosteroids as needed.

Immune-Mediated Endocrinopathies

KEYTRUDA can cause hypophysitis, thyroid disorders, and type 1 diabetes mellitus. Hypophysitis occurred in 0.6% (17/2799) of patients, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%). Hypothyroidism occurred in 8.5% (237/2799) of patients, including Grade 2 (6.2%) and 3 (0.1%). The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC (16%), receiving KEYTRUDA, as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. Hyperthyroidism occurred in 3.4% (96/2799) of patients, including Grade 2 (0.8%) and 3 (0.1%), and thyroiditis occurred in 0.6% (16/2799) of patients, including Grade 2 (0.3%). Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 0.2% (6/2799) of patients.
Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency), thyroid function (prior to and periodically during treatment), and hyperglycemia. For hypophysitis, administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2 and withhold or discontinue for Grade 3 or 4 hypophysitis. Administer hormone replacement for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for Grade 3 or 4 hyperthyroidism. Administer insulin for type 1 diabetes and withhold KEYTRUDA and administer antihyperglycemics in patients with severe hyperglycemia.

Immune-Mediated Nephritis and Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.1%), and 4 (<0.1%) nephritis. Nephritis occurred in 1.7% (7405) of patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue for Grade 3 or 4 nephritis.

Immune-Mediated Skin Reactions

Immune-mediated rashes, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA.

Other Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving KEYTRUDA and may also occur after discontinuation of treatment. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

The following clinically significant immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and postmarketing use.

Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment vs the risk of possible organ rejection in these patients.

Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% (6/2799) of patients.

Monitor patients for signs and symptoms of infusion-related reactions. For Grade 3 or 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic HSCT after treatment with KEYTRUDA. Of 23 patients with cHL who proceeded to allogeneic HSCT after KEYTRUDA, 6 (26%) developed graft-versus-host disease (GVHD) (1 fatal case) and 2 (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning (1 fatal case). Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor-blocking antibody before transplantation. Follow patients closely for early evidence of transplant-related complications such as hyperacute graft-versus-host disease (GVHD), Grade 3 to 4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions.

In patients with a history of allogeneic HSCT, acute GVHD (including fatal GVHD) has been reported after treatment with KEYTRUDA. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after KEYTRUDA. Consider the benefit of KEYTRUDA vs the risk of GVHD in these patients.

Increased Mortality in Patients With Multiple Myeloma

In trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with a PD-1 or PD-L1 blocking antibody in this combination is not recommended outside of controlled trials.

Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA and advise them to use effective contraception during treatment and for 4 months after the last dose.

Adverse Reactions
In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to permanent discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-054, KEYTRUDA was permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. The most common adverse reaction (≥20%) with KEYTRUDA was diarrhea (28%).

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 20% of 405 patients. The most common adverse reactions resulting in discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions (≥20%) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), diarrhea (31%), decreased appetite (28%), rash (25%), vomiting (24%), cough (21%), dyspnea (21%), and pyrexia (20%).

In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and either paclitaxel or paclitaxel protein-bound in metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 15% of 101 patients. The most frequent serious adverse reactions reported in at least 2% of patients were febrile neutropenia, pneumonia, and urinary tract infection. Adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs 36%) and peripheral neuropathy (31% vs 25%) were observed in the KEYTRUDA and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients; the most common were pneumonitis (3%), death due to unknown cause (1.6%), and pneumonia (1.4%). The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-010, KEYTRUDA monotherapy was discontinued due to adverse reactions in 8% of 682 patients with metastatic NSCLC; the most common was pneumonitis (1.8%). The most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

Adverse reactions occurring in patients with SCLC were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

In KEYNOTE-048, KEYTRUDA monotherapy was discontinued due to adverse events in 12% of 300 patients with HNSCC; the most common adverse reactions leading to permanent discontinuation were sepsis (1.7%) and pneumonia (1.3%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and rash (20%).

In KEYNOTE-048, when KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 16% of 276 patients with HNSCC. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). The most common adverse reactions (≥20%) were nausea (51%), fatigue (49%), constipation (37%), vomiting (32%), mucosal inflammation (31%), diarrhea (29%), decreased appetite (29%), stomatitis (26%), and cough (22%).

In KEYNOTE-012, KEYTRUDA was discontinued due to adverse reactions in 17% of 192 patients with HNSCC. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The most common adverse reactions (≥20%) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy, with the exception of increased incidences of facial edema and new or worsening hypothyroidism.

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 5% of 210 patients with cHL. Serious adverse reactions occurred in 16% of patients; those ≥1% included pneumonia, pneumonitis, pyrexia, dyspnea, GVHD, and herpes zoster. Two patients died from causes other than disease progression: 1 from GVHD after subsequent allogeneic HSCT and 1 from septic shock. The most common adverse reactions (≥20%) were fatigue (26%), pyrexia (24%), cough (24%), musculoskeletal pain (21%), diarrhea (20%), and rash (20%).

In KEYNOTE-170, KEYTRUDA was discontinued due to adverse reactions in 8% of 53 patients with PMBCL. Serious adverse reactions occurred in 26% of patients and included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), cough (26%), fatigue (23%), and dyspnea (21%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with locally advanced or metastatic urothelial carcinoma. Serious adverse reactions occurred in 42% of patients; those ≥2% were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions (≥20%) were fatigue (38%), musculoskeletal pain (24%), decreased appetite (22%), constipation (21%), rash (21%), and diarrhea (20%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 8% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients; those ≥2% were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (38%), musculoskeletal pain (32%), pruritus (23%), decreased appetite (21%), nausea (21%), and rash (20%).

Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.
Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with recurrent or metastatic cervical cancer. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA; the most frequent included anemia (7%), fistula, hemorrhage, and infections (except urinary tract infections) (4.1% each). The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22% each), and decreased appetite (21%).

Adverse reactions occurring in patients with HCC were generally similar to those in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy, with the exception of increased incidences of ascites (8% Grades 3-4) and immune-mediated hepatitis (2.9%). Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (20%), ALT (9%), and hyperbilirubinemia (10%).

Among the 50 patients with MCC enrolled in study KEYNOTE-017, adverse reactions occurring in patients with MCC were generally similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (11%) and hyperglycemia (19%).

In KEYNOTE-426, when KEYTRUDA was administered in combination with axitinib, fatal adverse reactions occurred in 3.3% of 429 patients. Serious adverse reactions occurred in 40% of patients, the most frequent of which (≥1%) included hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%). Permanent discontinuation due to an adverse reaction occurred in 31% of patients; KEYTRUDA only (13%), axitinib only (13%), and the combination (8%). The most common adverse reactions (≥1%) resulting in permanent discontinuation of KEYTRUDA, axitinib or the combination were hepatotoxicity (13%), diarrhea (10%), hypertension (9%), hypoalbuminemia (7%), and cerebrovascular accident (1%). When KEYTRUDA was used in combination with axitinib, the most common adverse reactions (≥20%) were diarrhea (56%), fatigue (52%), nausea (48%), hepatotoxicity (39%), hypothyroidism (35%), decreased appetite (30%), palmar-plantar erythrodysesthesia (28%), stomatitis/mucosal inflammation (27%), dysphonia (25%), rash (25%), cough (21%), and constipation (21%).

Lactation
Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeeding during treatment and for 4 months after the final dose.

Pediatric Use
There is limited experience in pediatric patients. In a trial, 40 pediatric patients (16 children aged 2 years to younger than 12 years and 24 adolescents aged 12 years to 18 years) with various cancers, including unapproved usages, were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range 1–17 doses), with 34 patients (85%) receiving 2 doses or more. The safety profile in these pediatric patients was similar to that seen in adults; adverse reactions that occurred at a higher rate (≥15% difference) in these patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), increased transaminases (28%), and hyponatremia (18%).

Merck's Focus on Cancer
Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck is committed to exploring the potential of immunology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube, LinkedIn.

About Merck
For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world’s most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA
This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health
care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company’s 2018 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).


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