Five-Year Survival Data for Merck’s KEYTRUDA® (pembrolizumab) in Advanced Non-Small Cell Lung Cancer (NSCLC) from First KEYNOTE Trial at 2019 ASCO Annual Meeting

Release Date:
Saturday, June 1, 2019 7:30 am EDT

Terms:
Oncology Corporate News Latest News #ASCO #Merck #MRK $MRK Merck MRK MSD NYSE:MRK

Dateline City:
KENILWORTH, N.J.

Longest Follow-Up Data for KEYTRUDA in Lung Cancer to Date Showed Five-Year Overall Survival Rate of 23.2% with KEYTRUDA in Treatment-Naïve Patients and 15.5% in Previously Treated Patients with Advanced NSCLC in KEYNOTE-001 Trial

Updated Overall Survival Analysis and New Data for Disease Progression After Next-Line Treatment (Progression-Free Survival 2) from KEYNOTE-189 Trial in Metastatic Nonsquamous NSCLC Also to be Presented

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced the presentation of five-year efficacy and safety data for KEYTRUDA, Merck’s anti-PD-1 therapy, as monotherapy in patients with advanced non-small cell lung cancer (NSCLC) from the first KEYNOTE trial (Phase 1b KEYNOTE-001). In this study, KEYTRUDA demonstrated a five-year overall survival (OS) rate of 23.2% in treatment-naïve patients (n=101) and 15.5% in previously treated patients (n=449). Of note, the five-year OS rate among patients whose tumors expressed PD-L1 (tumor proportion score [TPS] ≥50%) was 29.6% in treatment-naïve patients (n=27) and 25.0% in previously treated patients (n=138). These findings, which represent the longest follow-up for KEYTRUDA in lung cancer, will be highlighted at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract #LBA9015) during the official press program and presented during a poster discussion on Sunday, June 2.

"Lung cancer is the leading cause of cancer death, and historically, the five-year survival rate has been around 5% for patients in the U.S. with advanced non-small cell lung cancer," said Edward B. Garon, MD, MS, associate professor of medicine, Jonsson Comprehensive Cancer Center, University of California, Los Angeles. "As a treating physician, it is encouraging to see the results of KEYNOTE-001, in which pembrolizumab showed a five-year overall survival rate of 23.2% in treatment-naïve patients and 15.5% in previously treated patients."

After 60.6 months (range, 51.8 to 77.9) of median follow-up, results from KEYNOTE-001 demonstrated the effect of KEYTRUDA monotherapy across primary and secondary endpoints, including OS, objective response rate (ORR) and duration of response (DOR).

<table>
<thead>
<tr>
<th>Events (n/N)</th>
<th>Median OS, mo (95%, CI)</th>
<th>60-mo OS rate (%)</th>
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<tr>
<td>Treatment-naïve</td>
<td>75/101*</td>
<td>22.3 (17.1-32.3)</td>
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<td>TPS ≥50%</td>
<td>17/27</td>
<td>35.4 (20.3-63.5)</td>
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<td>TPS 1%-49%</td>
<td>43/52</td>
<td>19.5 (10.7-26.3)</td>
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<td>Previously treated</td>
<td>375/449†</td>
<td>10.5 (8.6-13.2)</td>
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The investigator-reported ORR was 41.6% (95% CI, 31.9-51.8) in treatment-naïve patients and 22.9% (95% CI, 19.1-27.1) in previously treated patients. Median DOR was 16.8 months (range, 2.1+ to 55.7+) and 38.9 months (range, 1.0+ to 71.8+), respectively.

Among the 60 patients who received two or more years of treatment with KEYTRUDA, the five-year OS rate was 78.6% in treatment-naïve patients and 75.8% in previously treated patients. The ORR in these patients was 86% and 91%, respectively. Median DOR was 52.0 months (range, 10.2 to 55.7+) in treatment-naïve patients and was not reached (range, 12.5 to 71.8+) in previously treated patients.

The safety profile of KEYTRUDA was consistent with what has been seen in previously reported studies among patients with advanced NSCLC. Treatment-related adverse events (TRAEs) of any grade occurred in 71% (n=388) of patients receiving KEYTRUDA; grade 3-5 TRAEs occurred in 13% (n=69) of patients. Immune-mediated adverse events were reported in 17% (n=92) of patients. Hypothyroidism was the most commonly reported immune-mediated adverse event, followed by pneumonitis, hyperthyroidism and skin toxicities.

“Five-year survival is a significant milestone for patients with advanced non-small cell lung cancer, and it is encouraging to see the long-term overall survival rates from our first KEYNOTE study,” said Dr. Roy Baynes, senior vice president and chief medical officer, Merck Research Laboratories. “These five-year data provide important insights into the long-term safety and efficacy of KEYTRUDA in patients with advanced non-small cell lung cancer.”

Additional Lung Cancer Data from KEYNOTE-189 (Abstract #9013)

New and updated data from the Phase 3 KEYNOTE-189 trial evaluating KEYTRUDA in combination with ALIMTA® (pemetrexed) and platinum (cisplatin or carboplatin) for the first-line treatment of metastatic nonsquamous NSCLC compared with pemetrexed plus platinum alone, will also be presented on Sunday, June 2 at ASCO (Abstract #9013). An updated analysis of the OS endpoint showed that after a median follow-up of 18.7 months (range, 0.2 to 30.9), KEYTRUDA in combination with pemetrexed-platinum chemotherapy reduced the risk of death by 44% compared with chemotherapy alone (HR=0.56 [95% CI, 0.45-0.70]; median OS 22.0 months vs. 17.0 months). An improvement in progression-free survival (PFS) was also observed, with a 52% reduction in the risk of progression or death compared with chemotherapy alone (HR=0.48 [95% CI, 0.40-0.58]; median PFS 9.0 months vs. 4.9 months). Fifty-four percent of patients in the chemotherapy alone arm received subsequent immunotherapy, including 41% who received in-study crossover.

New findings at ASCO from KEYNOTE-189 also include the first-time presentation of the progression-free survival 2 (PFS2) study endpoint, a clinical endpoint used to assess the impact of next-line treatment on disease control, in the entire study population and different PD-L1 subgroups. Among patients who received KEYTRUDA in combination with chemotherapy, findings showed a 51% reduction in risk from time of randomization to objective tumor progression on next-line treatment or death from any cause, whichever comes first, compared with patients who received chemotherapy alone (HR=0.49 [95% CI, 0.40-0.59]; median PFS2 17.0 months vs. 9.0 months). Results were consistent across all three PD-L1 categories evaluated – with a 54% reduction in patients with a TPS <1% (HR=0.46 [95% CI, 0.33-0.66]), a 41% reduction in patients with a TPS of 1-49% (HR=0.59 [95% CI, 0.41-0.86]), and a 53% reduction in patients with a TPS ≥50% (HR=0.47 [95% CI, 0.33-0.69]).

Grade 3-5 adverse events from any cause occurred in 71.9% (n=291) of patients who received KEYTRUDA in combination with chemotherapy and 66.8% (n=135) in the chemotherapy alone arm. Adverse events leading to discontinuation of any treatment component occurred in 33.6% (n=136) of patients who received KEYTRUDA in combination with chemotherapy and 16.3% (n=33) in the chemotherapy alone arm. There were two deaths in the KEYTRUDA combination arm from immune-mediated adverse events and infusion reactions. KEYNOTE-189 was conducted in collaboration with Eli Lilly and Company, the makers of pemetrexed (ALIMTA®).

Study Design of KEYNOTE-001 (Abstract #LBA9015)

KEYNOTE-001 (ClinicalTrials.gov, NCT01295827) is a Phase 1b multicenter, open-label, multi-cohort trial evaluating KEYTRUDA in various advanced cancers, including 550 patients with either treatment-naïve or previously treated advanced NSCLC. Patients received 2 mg/kg or 10 mg/kg of KEYTRUDA every three weeks (Q3W) or 10 mg/kg of KEYTRUDA every two weeks until unacceptable toxicity or disease progression. The primary endpoint was ORR; secondary endpoints included PFS, OS and DOR.

Study Design of KEYNOTE-189 (Abstract #9013)

KEYNOTE-189 (ClinicalTrials.gov, NCT02578680) is a pivotal Phase 3, randomized, double-blind, placebo-controlled trial of 616 untreated patients with metastatic nonsquamous NSCLC and no EGFR or ALK genomic tumor aberrations designed to evaluate the efficacy of KEYTRUDA in combination with pemetrexed and cisplatin or carboplatin (n=410), compared with pemetrexed and cisplatin or carboplatin alone (n=206). Patients were randomized 2:1 to receive KEYTRUDA 200 mg, cisplatin or carboplatin, and pemetrexed intravenously Q3W for four cycles followed by KEYTRUDA 200 mg for up to 24 months and pemetrexed Q3W (n=410); or cisplatin or carboplatin and pemetrexed intravenously Q3W for four cycles followed by pemetrexed Q3W (n=206). Treatment continued until progression of disease or unacceptable toxicity. The dual primary endpoints were OS and PFS; secondary endpoints included ORR and DOR.

About Lung Cancer
Lung cancer, which forms in the tissues of the lungs, usually within cells lining the air passages, is the leading cause of cancer death worldwide. Each year, more people die of lung cancer than die of colon and breast cancers combined. The two main types of lung cancer are non-small cell and small cell. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 85% of all cases. Small cell lung cancer (SCLC) accounts for about 10 to 15% of all lung cancers. Between 2008 and 2014, the five-year survival rate for patients diagnosed in the U.S. with advanced NSCLC was only 5%. Moreover, approximately 50% of metastatic NSCLC patients in the U.S. will not receive second-line therapy.

**About KEYTRUDA® (pembrolizumab) Injection, 100mg**

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.

**KEYTRUDA® (pembrolizumab) Indications and Dosing**

**Melanoma**

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma. The recommended dose of KEYTRUDA in patients with unresectable or metastatic melanoma is 200 mg administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity.

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with melanoma is 200 mg administered as an intravenous infusion over 30 minutes every three weeks until disease recurrence, unacceptable toxicity, or for up to 12 months in patients without disease recurrence.

**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 stage IIIB NSCLC who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 [tumor proportion score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

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.

In NSCLC, the recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

When administering KEYTRUDA in combination with chemotherapy, KEYTRUDA should be administered prior to chemotherapy when given on the same day. See also the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA, as appropriate.

**Head and Neck Cancer**

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. 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. In HNSCC, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

**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. In adults with cHL, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. In pediatric patients with cHL, KEYTRUDA is administered as an intravenous infusion over 30 minutes at a dose of 2 mg/kg (up to a maximum of 200 mg) every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

**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.

In adults with PMBCL, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. In pediatric patients with PMBCL, KEYTRUDA is administered as an intravenous infusion over 30 minutes at a dose of 2 mg/kg (up to a maximum of 200 mg) every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

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 [combined positive score (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.

In locally advanced or metastatic urothelial carcinoma, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

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.

In adult patients with MSI-H cancer, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. In pediatric patients with MSI-H cancer, KEYTRUDA is administered as an intravenous infusion over 30 minutes at a dose of 2 mg/kg (up to a maximum of 200 mg) every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

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. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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
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%).

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.

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.

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. Grades 3 and 4 increased ALT and AST were seen in 20% and 13% of patients, respectively. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. For elevated liver enzymes, interrupt KEYTRUDA and axitinib, and consider administering corticosteroids as needed.

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 patients with HNSCC, occurring in 15% (28/192) of patients. 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.

KEYTRUDA can cause immune-mediated nephritis and renal dysfunction. 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% (7/405) 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, 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 Grade 2 or greater exfoliative dermatitis or TEN. Withhold KEYTRUDA for Grade 2; permanently discontinue for Grade 3 or 4 exfoliative dermatitis or TEN.
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 permanent 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%).

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, confusion, 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-007, 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.

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 (1.3%), axitinib only (1.3%), and the combination (8%). The most common adverse reactions (≥1%) resulting in permanent discontinuation of KEYTRUDA, axitinib or the combination were hepatotoxicity (13%), diarrhea/coilitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). When KEYTRUDA was used in combination with axitinib, the most common adverse reactions (≥20%) were diarrhea (56%), fatigue/asthenia (52%), hypertension (48%), hepatotoxicity (39%), hypothyroidism (35%), decreased appetite (30%), palmar-plantar erythrodysesthesia (28%), nausea (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 breastfeed 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 immuno-oncology 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.

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. 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

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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