Merck’s KEYTRUDA (pembrolizumab) Significantly Improved Overall Survival Compared to Standard of Care, as Monotherapy and in Combination with Chemotherapy, as First-Line Treatment for Patients with Recurrent or Metastatic Head and Neck Cancer

Release Date:
Monday, October 22, 2018 10:30 am EDT

Terms:
Oncology Newsroom  Research and Development News  Corporate News  Latest News  #Merck  #MRK  $MRK

Dateline City:
KENILWORTH, N.J.

Survival Benefit Observed with KEYTRUDA Monotherapy in Patients Whose Tumors Expressed PD-L1 with CPS≥20 and CPS≥1 and in Total Patient Population for KEYTRUDA in Combination with Chemotherapy

KEYTRUDA is the First Anti-PD-1 Therapy to Demonstrate a Survival Benefit as First-Line Therapy for Head and Neck Cancer that has Recurred or Metastasized

Results from Pivotal Phase 3 KEYNOTE-048 Trial Presented Today at the ESMO 2018 Congress during the Presidential Symposium

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced the first presentation of interim data from the pivotal Phase 3 KEYNOTE-048 trial investigating KEYTRUDA, Merck’s anti-PD-1 therapy, as both monotherapy and in combination with chemotherapy, for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). These interim results are being presented today during the Presidential Symposium at the ESMO 2018 Congress (Abstract # LBA8_PR) and are included in the official Press Program.

Interim data from KEYNOTE-048 showed KEYTRUDA monotherapy improved overall survival (OS), a primary endpoint of the study, by 39 percent (HR 0.61 [95% CI, 0.45-0.83]; p=0.0007) in patients whose tumors expressed PD-L1 with Combined Positive Score (CPS) ≥20, and by 22 percent (HR 0.78 [95% CI, 0.64-0.96]; p=0.0086) in patients with CPS≥1, compared to the EXTREME regimen (cetuximab with carboplatin or cisplatin plus 5-fluorouracil (5-FU), the current standard of care. In addition, KEYTRUDA in combination with chemotherapy (carboplatin or cisplatin plus 5-FU) (KEYTRUDA combination) demonstrated improved OS compared to the EXTREME regimen by 23 percent (HR 0.77 [95% CI, 0.63-0.93]; p=0.0034), regardless of PD-L1 expression. At the final analysis, superiority for OS will be evaluated for KEYTRUDA monotherapy in the total population and KEYTRUDA combination in patients whose tumors express PD-L1 at CPS≥20 or ≥1; at this interim analysis, based upon the prespecified testing algorithm, non-inferiority for KEYTRUDA monotherapy in the total population was demonstrated and statistical significance was not achieved for the KEYTRUDA combination in the subset of patients whose tumors expressed PD-L1 at CPS≥20 or ≥1. Additionally, at this time point there was no difference in progression-free-survival (PFS), a dual primary endpoint of the study, in any of the groups studied. There were no new safety concerns identified with the use of KEYTRUDA in KEYNOTE-048.

“In this study, KEYTRUDA showed the potential to significantly prolong survival when used as first-line therapy for patients whose head and neck cancer had recurred or spread,” said Dr. Barbara Burtness, lead investigator for KEYNOTE-048, professor of medicine at Yale School of Medicine and co-director, Development Therapeutics Research Program, Yale Cancer Center. “This is a devastating cancer when it recurs, and there has not been any advance in first-line treatment for over a decade. It is thrilling to see these new data, which have the potential to alter the standard of care in the first-line treatment of head and neck cancer.”
“KEYTRUDA is the first anti-PD-1 therapy to show superior overall survival as first-line treatment compared to the EXTREME regimen, the current standard of care in patients with recurrent or metastatic head and neck cancer,” said Dr. Roy Baynes, senior vice president and head of Global Clinical Development, chief medical officer, Merck Research Laboratories. “Recurrent or metastatic head and neck cancer is a very challenging disease. Merck would like to thank the patients and investigators for participating in this important study, which is helping to advance our understanding of the potential of KEYTRUDA and PD-1 inhibition in the first-line setting.”

KEYTRUDA is currently approved in 61 countries for the treatment of second-line recurrent or metastatic HNSCC, including the U.S. and Europe. Merck plans to file a supplemental Biologics License Application (sBLA) with the U.S. Food and Drug Administration (FDA) for a first-line indication based on KEYNOTE-048 data and will include data from the Phase 3 KEYNOTE-040 trial as supportive data. Based on these results, Merck has withdrawn the sBLA for KEYNOTE-040 for KEYTRUDA as a second-line treatment in patients with recurrent or metastatic HNSCC, which was previously assigned a Prescription Drug User Fee Act (PDUFA) or target action date of Dec. 28, 2018. The results from KEYNOTE-048 will also be submitted to regulatory authorities worldwide.

Study Design and Additional Data from KEYNOTE-048 (Abstract # LBA8_PR)

KEYNOTE-048, a randomized, open-label Phase 3 trial (ClinicalTrials.gov, NCT02358031), evaluated KEYTRUDA monotherapy or KEYTRUDA combination, compared with the EXTREME regimen, as first-line treatment in 882 patients with recurrent or metastatic HNSCC. The dual primary endpoints were OS and PFS. The secondary endpoints were PFS (at 6 months and 12 months), objective response rate (ORR) and time to deterioration in Quality of Life Global Health Status/Quality of Life Scales of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire and Safety. Duration of response (DOR) was evaluated as part of a pre-specified exploratory analysis. The primary and secondary endpoints, as well as exploratory DOR analysis, were evaluated in patients whose tumors expressed PD-L1 with CPS ≥20 and CPS ≥1, and in the total population, regardless of PD-L1 expression, based on a fixed sequential testing strategy. At the time of the analysis, the median follow-up was 11.7 months for KEYTRUDA monotherapy, 13.0 months for KEYTRUDA combination and 10.7 months for the EXTREME regimen, respectively.

In the first comparison group, OS in the CPS ≥20 population was significantly longer with KEYTRUDA monotherapy (14.9 months) (n=133) compared to the EXTREME regimen (10.7 months) (n=122) (HR 0.61 [95% CI, 0.45-0.83]; p=0.0007). There was no difference in PFS between the study arms (HR 0.99 [95% CI, 0.75-1.29]; p=0.5). ORR was 23.3 percent for KEYTRUDA monotherapy and 36.1 percent for the EXTREME regimen, respectively. The median DOR was substantially longer with KEYTRUDA monotherapy (20.9 months) compared to the EXTREME regimen (4.2 months).

Similarly, OS in the CPS ≥1 population was significantly longer with KEYTRUDA monotherapy (12.3 months) (n=257) compared to the EXTREME regimen (10.3 months) (n=255) (HR 0.78 [95% CI, 0.64-0.96]; p=0.0086). There was no difference in PFS between the study arms (HR 1.16 [95% CI, 0.96-1.39]). ORR was 19.1 percent for KEYTRUDA monotherapy and 34.9 percent for the EXTREME regimen, respectively. The median DOR was substantially longer with KEYTRUDA (20.9 months) compared to the EXTREME regimen (4.5 months).

In the second comparison group, OS in the total population was significantly longer with the KEYTRUDA combination (13.0 months) (n=281) compared to the EXTREME regimen (10.7 months) (n=278) (HR 0.77 [95% CI, 0.63-0.93]; p=0.0034). There was no difference in PFS between the study arms (HR 0.92; 95% CI, 0.77-1.10). ORR was 35.6 percent for the KEYTRUDA combination and 36.3 percent for the EXTREME regimen, respectively. The median DOR was longer with KEYTRUDA monotherapy (6.7 months) compared to the EXTREME regimen (4.3 months).

There were no new safety concerns identified with the use of KEYTRUDA in KEYNOTE-048. Grade 3-5 treatment-related adverse events (TRAEs) occurred in 16.7 percent, 71.0 percent and 69.0 percent (n=198/287) of patients in the KEYTRUDA monotherapy, KEYTRUDA combination and the EXTREME regimen arms, respectively. TRAEs resulting in discontinuation occurred in 4.7 percent, 22.8 percent and 19.9 percent of patients in the KEYTRUDA monotherapy, KEYTRUDA combination and the EXTREME regimen arms, respectively. There were no TRAEs observed with an incidence of ≥15% in all arms. The most common TRAEs (occurring in ≥15% of patients) in the KEYTRUDA combination arm included anemia (48.2%), nausea (44.9%), neutropenia (33.0%), fatigue (30.4%), mucosal inflammation (27.9%), thrombocytopenia (27.2%), vomiting (27.2%), stomatitis (24.3%), decreased appetite (22.5%), platelet count decreased (18.5%), diarrhea (17.8%) and neutrophil count decreased (16.7%).

Immune-mediated adverse events in patients receiving KEYTRUDA monotherapy or combination therapy were hypothyroidism (18.0% and 15.2%, respectively), pneumonitis (6.0% and 5.4%, respectively), hyperthyroidism (2.7% and 4.7%, respectively), severe skin reactions (2.7% and 0.7%, respectively), infusion reactions (1.3% and 2.2%, respectively), colitis (1.0% and 2.5%, respectively), nephritis (0.7% in both arms), pancreatitis (0.7% and 0.4%, respectively), hypophysitis (0.3% and 0.4%, respectively); hepatitis (0.7% monotherapy only); myocardiitis and thyroiditis (0.4% each, combination only); and adrenal insufficiency, encephalitis and uveitis (0.3% each, monotherapy only). Treatment-related deaths occurred in 3 patients in the KEYTRUDA monotherapy arm [auto-inflammatory disease, disseminated intravascular coagulation, and pneumonitis (n=1 each)]; 10 patients in the KEYTRUDA combination arm [septic shock (n=5), cerebral ischemia, hemorrhage, interstitial lung disease, sepsis, and tumor hemorrhage (n=1 each)]; and 8 patients in the EXTREME regimen arm [pneumonia (n=3), sepsis (n=2), and hypoxia, osteomyelitis, and pulmonary artery thrombosis (n=1 each)].

Additional Information About KEYNOTE-048

KEYNOTE-048 enrolled 882 patients with recurrent or metastatic HNSCC who were randomized to one of three regimens as first-line therapy, as follows:

- KEYTRUDA monotherapy (200 mg fixed dose every three weeks [Q3W]) for up to 24 months (n=301); or
- KEYTRUDA (200 mg fixed dose Q3W) in combination with cisplatin (100 mg/m² IV Q3W) or carboplatin (AUC 5 IV Q3W) plus 5-FU (1000 mg/m²/day IV continuous from Day 1-4 Q3W) (maximum six cycles), followed by additional KEYTRUDA monotherapy maintenance therapy until progression of disease, toxicity or until the patient had received a maximum of 24 months total treatment (n=281); or...
• EXTREME regimen including cetuximab at a loading dose (400 mg/m² IV) followed by weekly doses (250 mg/m² IV) in combination with cisplatin (100 mg/m² IV Q3W) or carboplatin (AUC 5 IV Q3W) plus 5-FU (1000 mg/m²/day IV) continuous from Day 1-4 Q3W (maximum six cycles), followed by additional cetuximab monotherapy maintenance therapy until progression of disease or toxicity (n=300).

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. The leading modifiable risk factors for head and neck cancer include tobacco and heavy alcohol use. Other risk factors include infection with certain types of HPV, also called human papillomaviruses. Worldwide, an estimated 835,000 new head and neck cancer cases will be diagnosed in 2018, and an estimated 431,000 people will die from the disease this year. In the U.S., there were an estimated 63,000 new cases diagnosed in 2017.

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 850 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 benefitting 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 at a fixed dose of 200 mg every three weeks until disease progression or unacceptable toxicity.

Lung Cancer

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, as a single agent, is also 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 metastatic NSCLC, KEYTRUDA is administered at a fixed dose of 200 mg 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 pemetrexed and carboplatin or cisplatin, 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 is administered at a fixed dose of 200 mg 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 three 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 HNSCC, KEYTRUDA is administered at a dose of 2 mg/kg (up to a maximum of 200 mg) every three weeks until disease progression, 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
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 is administered at a fixed dose of 200 mg every three weeks until disease progression, 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 is administered at a fixed dose of 200 mg every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. In children with MSI-H cancer, KEYTRUDA is administered 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 [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. The recommended dose of KEYTRUDA is a fixed dose of 200 mg 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 a fixed dose of 200 mg every three weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

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 receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%), and occurred more frequently in patients with a history of prior thoracic radiation (6.9%) compared to those without (2.9%). 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 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 for Grade 4 colitis.

In adults with PMBCL, KEYTRUDA is administered at a fixed dose of 200 mg 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 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.

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 for Grade 4 colitis.
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.

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 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.

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% (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

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 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 developed graft-versus-host disease (GVHD) (1 fatal case) and 2 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 clinical 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 clinical trials.

**Embryofetal Toxicity**

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant during treatment, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of KEYTRUDA.

**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-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-010, KEYTRUDA monotherapy was discontinued due to adverse reactions in 8% of 682 patients with metastatic NSCLC. The most common adverse event resulting in permanent discontinuation of KEYTRUDA 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, 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, 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 urethral 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 urethral 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%).

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%).

**Lactation**

It is not known whether KEYTRUDA is excreted in human milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

**Pediatric Use**

There is limited experience in pediatric patients. In a study in 40 pediatric patients with advanced melanoma, lymphoma, or PD-L1-positive advanced, relapsed, or refractory solid tumors, the safety profile was similar to that seen in adults treated with KEYTRUDA. Toxicities 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%), hypertransaminasemia (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 immun-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 2017 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).

Please see Prescribing Information for KEYTRUDA at
http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf and

Medication Guide for KEYTRUDA at

Language:
English

Contact:
Merck Media
Pamela Eisele, 267-305-3558
or
Elizabeth H. Sell, 267-305-3877
or
Investors
Teri Loxam, 908-740-1986
or
Michael DeCarbo, 908-740-1807

Ticker Slug:
Ticker: MRK
Exchange: NYSE
@Merck

Source URL: https://www.mrknewsroom.com/news-release/oncology-newsroom/mercks-keytruda-pembrolizumab-significantly-improved-overall-survival