

NEWS RELEASE

KEYTRUDA® (pembrolizumab) Plus Chemotherapy Before Surgery and Continued as a Single Agent After Surgery Showed Statistically Significant Event-Free Survival (EFS) Result Versus Neoadjuvant Chemotherapy Alone in High-Risk Early-Stage TNBC

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KEYNOTE-522 Is the First Phase 3 Study With an Immunotherapy to Show Positive EFS Results in High-Risk Early-Stage Triple-Negative Breast Cancer

Merck Has Submitted These Data From KEYNOTE-522 to the US FDA for Review

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced positive event-free survival (EFS) data from the pivotal neoadjuvant/adjuvant Phase 3 study KEYNOTE-522. The trial investigated neoadjuvant KEYTRUDA, Merck's anti-PD-1 therapy, plus chemotherapy followed by adjuvant KEYTRUDA as monotherapy (the KEYTRUDA regimen) compared with neoadjuvant chemotherapy followed by adjuvant placebo (the chemotherapy-placebo regimen) in patients with high-risk early-stage triple-negative breast cancer (TNBC). This is the first time an anti-PD-1/L1 therapy has demonstrated a statistically significant EFS result as combined neoadjuvant and adjuvant therapy for these patients. These results are being presented today during a European Society for Medical Oncology (ESMO) Virtual Plenary.

After a median follow-up of 39 months, the KEYTRUDA regimen reduced the risk of EFS events by 37% (HR=0.63 [95% CI, 0.48-0.82]; p=0.00031) versus the chemotherapy-placebo regimen – a statistically significant and clinically meaningful EFS result. EFS was defined as the time from randomization to the first occurrence of either disease progression that precluded definitive surgery, a local/distant recurrence, a second primary cancer, or death from

any cause. As previously announced, KEYNOTE-522 met the dual primary endpoint of pathological complete response (pCR) at the first interim analysis. The trial is continuing to allow for additional follow-up of overall survival (OS), a key secondary endpoint. At this fourth interim analysis, although these data have not crossed the boundary for statistical significance, there was a 28% reduction in the risk of death with the KEYTRUDA regimen versus the chemotherapy-placebo regimen (HR=0.72 [95% CI, 0.51-1.02]; p=0.03214). The safety profile of the KEYTRUDA regimen was consistent with the known profiles of each regimen, and no new safety concerns were identified.

“Given the high rates of recurrence within the first five years of diagnosis, patients with high-risk early-stage TNBC need new treatment options,” said Dr. Peter Schmid, lead, Centre for Experimental Cancer Medicine, Barts Cancer Institute in London, England. “KEYNOTE-522 was designed to study whether the combined neoadjuvant and adjuvant regimen with KEYTRUDA could help treat the cancer earlier. Now, with more than three years of follow-up, we see the potential of this approach. These event-free survival data are very encouraging for patients and show that this combination of KEYTRUDA plus chemotherapy as neoadjuvant therapy, followed by single-agent KEYTRUDA as adjuvant therapy, may offer women with high-risk early-stage TNBC a new treatment option for this aggressive disease.”

“These highly anticipated event-free survival results in this TNBC population build upon earlier findings from the KEYNOTE-522 trial and further support the potential use of KEYTRUDA in these patients,” said Dr. Vicki Goodman, vice president, clinical research, Merck Research Laboratories. “KEYNOTE-522 is the first large randomized Phase 3 study to report a statistically significant and clinically meaningful EFS result among patients with stage II and stage III TNBC. We have submitted these data to the FDA and are working closely with the agency on its review of our application.”

KEYTRUDA is currently approved under accelerated approval in the U.S. in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10) as determined by an FDA-approved test.

Merck is rapidly advancing a broad portfolio in women’s cancers with an extensive clinical development program for KEYTRUDA and several other investigational and approved medicines across multiple gynecologic and breast cancers. The KEYTRUDA clinical development program for TNBC encompasses several internal studies and external collaborative trials, including the ongoing studies KEYNOTE-242 and KEYNOTE-355.

Study Design and Additional Data From KEYNOTE-522

KEYNOTE-522 is a Phase 3, randomized, double-blind trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03036488), NCT03036488). The dual primary endpoints are pCR, defined as pathological stage ypT0/Tis ypN0 at the time of definitive surgery, and EFS, defined as the time from randomization to the first occurrence of either disease progression that precluded definitive

surgery, a local/distant recurrence, a second primary cancer, or death from any cause in all patients randomized. Secondary endpoints include pCR rate using alternative definitions, OS in all patients randomized, pCR rate according to all definitions, EFS and OS in patients whose tumors express PD-L1 (CPS ≥ 1), safety and health-related quality of life assessments. The study enrolled 1,174 patients who were randomized 2:1 to receive either:

- The KEYTRUDA regimen: KEYTRUDA (every three weeks) plus paclitaxel (weekly) and carboplatin (weekly or every three weeks) for four cycles, followed by KEYTRUDA plus cyclophosphamide and either doxorubicin or epirubicin (every three weeks) for four cycles as neoadjuvant therapy prior to surgery, followed by nine cycles of KEYTRUDA (every three weeks) as adjuvant therapy post-surgery (n=784)
- The chemotherapy-placebo regimen: Placebo (every three weeks) plus paclitaxel (weekly) and carboplatin (weekly or every three weeks) for four cycles, followed by placebo plus cyclophosphamide and either doxorubicin or epirubicin (every three weeks) for four cycles as neoadjuvant therapy prior to surgery, followed by nine cycles of placebo (every three weeks) as adjuvant therapy post-surgery (n=390)

As previously announced, KEYNOTE-522 met the success criterion for the dual primary endpoint of pCR at the first interim analysis; pCR was observed in 64.8% of patients treated with KEYTRUDA plus chemotherapy (n=401), an increase of 13.6% (p=0.00055) from 51.2% in patients treated with placebo plus chemotherapy (n=201). At the fourth interim analysis, KEYNOTE-522 met the success criterion for the dual primary endpoint of EFS. The study is continuing to allow for additional follow-up of OS.

At three years, 84.5% of patients treated with the KEYTRUDA regimen were alive and did not experience an EFS event compared to 76.8% of patients treated with the chemotherapy-placebo regimen.

In pre-specified exploratory subgroup analyses of EFS, the EFS benefit seen with the KEYTRUDA regimen was independent of PD-L1 expression. In the PD-L1-positive subgroup (n=973), defined as CPS ≥ 1 , treatment with the KEYTRUDA regimen reduced the risk of EFS events by 33% (HR=0.67 [95% CI, 0.49-0.92]) versus the chemotherapy-placebo regimen. In the PD-L1-negative subgroup (n=197), defined as CPS < 1 , treatment with the KEYTRUDA regimen reduced the risk of EFS events by 52% (HR=0.48 [95% CI, 0.28-0.85]) versus the chemotherapy-placebo regimen.

In a pre-specified but non-randomized exploratory analysis of EFS by pCR outcome, the reduction in EFS events with the KEYTRUDA regimen was observed independent of pCR outcome at definitive surgery.

Treatment-related adverse events (TRAEs) were examined in the neoadjuvant phase, the adjuvant phase and the combined phases. TRAEs in the neoadjuvant phase have been previously reported. At the time of this data cutoff, no patients were still receiving protocol treatment. For the combined neoadjuvant and adjuvant phases, TRAEs occurred in 98.9% of patients receiving the KEYTRUDA regimen (n=783) and 99.7% of patients receiving the

chemotherapy-placebo regimen (n=389); Grade 3-5 TRAEs occurred in 77.1% versus 73.3%, respectively. TRAEs led to death in 0.5% of patients receiving the KEYTRUDA regimen (n=4) and 0.3% of patients receiving the chemotherapy-placebo regimen (n=1). No new safety concerns were identified. In the adjuvant phase, TRAEs occurred in 53.7% of patients receiving adjuvant KEYTRUDA (n=588) and 48.6% of patients receiving adjuvant placebo (n=331), including 6.3% and 2.7%, respectively, who had at least one Grade ≥ 3 event.

Immune-mediated adverse events (AEs) and infusion reactions of any grade in the combined neoadjuvant and adjuvant phases occurred in 43.6% of patients receiving the KEYTRUDA regimen and 21.9% of patients receiving the chemotherapy-placebo regimen. The most common of these events (occurring in $\geq 10\%$ of patients) were infusion reactions (18.0%) and hypothyroidism (15.1%) in patients receiving the KEYTRUDA regimen and infusion reactions (11.6%) in patients receiving the chemotherapy-placebo regimen. Immune-mediated AEs led to death in 0.3% of patients receiving the KEYTRUDA regimen (n=2) and no patients receiving the chemotherapy-placebo regimen. In the adjuvant phase, immune-mediated AEs and infusion reactions occurred in 10.2% of patients receiving adjuvant KEYTRUDA and 6.0% of patients receiving adjuvant placebo, including 2.9% and 0.3%, respectively, who had at least one Grade ≥ 3 event.

About Triple-Negative Breast Cancer (TNBC)

Triple-negative breast cancer is an aggressive type of breast cancer that characteristically has a high recurrence rate within the first five years after diagnosis. While some breast cancers may test positive for estrogen receptors, progesterone receptors or overexpression of human epidermal growth factor receptor 2 (HER2), TNBC tests negative for all three. Approximately 10-15% of patients with breast cancer are diagnosed with TNBC. TNBC tends to be more common in people who are younger than 40 years of age, who are African American or who have a BRCA1 mutation.

About KEYTRUDA® (pembrolizumab) Injection, 100 mg

KEYTRUDA is an anti-programmed death receptor-1 (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 1,500 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.

Selected KEYTRUDA® (pembrolizumab) Indications 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) $\geq 1\%$] 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 $\geq 1\%$) 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.

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 (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 patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

KEYTRUDA is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

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. KEYTRUDA is not recommended for 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 confirmatory trials.

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

KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High or Mismatch Repair Deficient 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.

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.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Gastric Cancer

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. 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.

Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

- in combination with platinum- and fluoropyrimidine-based chemotherapy, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.

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 (MCC). 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.

Tumor Mutational Burden-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. 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 TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥ 10) as

determined by an FDA-approved test. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Selected Important Safety Information for KEYTRUDA

Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the programmed death ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can affect more than one body system simultaneously, and can occur at any time after starting treatment or after discontinuation of treatment. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti-PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

Pneumonitis occurred in 8% (31/389) of adult patients with cHL receiving KEYTRUDA as a single agent, including Grades 3-4 in 2.3% of patients. Patients received high-dose corticosteroids for a median duration of 10 days (range: 2 days to 53 months). Pneumonitis rates were similar in patients with and without prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 5.4% (21) of patients. Of the patients who developed pneumonitis, 42% interrupted KEYTRUDA, 68% discontinued KEYTRUDA, and 77% had resolution.

Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) reactions. Systemic corticosteroids were required in 69% (33/48); additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Colitis resolved in 85% of the 48 patients.

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA as a Single Agent

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 68% (13/19) of patients; additional immunosuppressant therapy was required in 11% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Hepatitis resolved in 79% of the 19 patients.

KEYTRUDA with Axitinib

KEYTRUDA in combination with axitinib can cause hepatic toxicity. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider monitoring more frequently 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. With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased alanine aminotransferase (ALT) (20%) and increased aspartate aminotransferase (AST) (13%) were seen, at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥ 3 times upper limit of normal (ULN) (Grades 2-4, n=116), ALT resolved to

Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT \geq 3 times ULN was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT \geq 3 ULN subsequently recovered from the event.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

KEYTRUDA can cause primary or secondary adrenal insufficiency. For Grade 2 or higher, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity. Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 77% (17/22) of patients; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hypophysitis

KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Thyroid Disorders

KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). None discontinued, but KEYTRUDA was withheld in <0.1% (1) of patients.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2

(0.8%). It led to permanent discontinuation of KEYTRUDA in <0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in 389 adult patients with cHL (17%) receiving KEYTRUDA as a single agent, including Grade 1 (6.2%) and Grade 2 (10.8%) hypothyroidism.

Type 1 Diabetes Mellitus (DM), Which Can Present With Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity. Type 1 DM occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 89% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Nephritis resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, has occurred with anti-PD-1/PD-L1 treatments. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 40% (15/38) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence. The reactions resolved in 79% of the 38 patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other anti-PD-1/PD-L1 treatments. Severe or fatal cases have been reported for some of these adverse reactions. Cardiac/Vascular: Myocarditis, pericarditis, vasculitis; Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis; Musculoskeletal and Connective Tissue: Myositis/polymyositis rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica; Endocrine: Hypoparathyroidism; Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving KEYTRUDA. Monitor for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 reactions. For Grade 3 or Grade 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti-PD-1/PD-L1 treatment. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti-PD-1/PD-L1 treatment and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti-PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.

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 an anti-PD-1/PD-L1 treatment 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 ($\geq 20\%$) 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 ($\geq 1\%$) 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 ($\geq 20\%$) 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 ($\geq 20\%$) 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 with advanced NSCLC; 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 ($\geq 20\%$) 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 ($\geq 20\%$) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

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 ($\geq 20\%$) 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 ($\geq 20\%$) 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 ($\geq 20\%$) 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-204, KEYTRUDA was discontinued due to adverse reactions in 14% of 148 patients with cHL. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA; those $\geq 1\%$ were pneumonitis, pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients died from causes other than disease progression: 2 from complications after allogeneic HSCT and 1 from unknown cause. The most common adverse reactions ($\geq 20\%$) were upper respiratory tract infection (41%), musculoskeletal pain (32%),

diarrhea (22%), and pyrexia, fatigue, rash, and cough (20% each).

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 $\geq 1\%$ were 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 ($\geq 20\%$) 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 ($\geq 20\%$) 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 $\geq 2\%$ were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions ($\geq 20\%$) 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 $\geq 2\%$ were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions ($\geq 20\%$) in patients who received KEYTRUDA were fatigue (38%), musculoskeletal pain (32%), pruritus (23%), decreased appetite (21%), nausea (21%), and rash (20%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Serious adverse reactions occurred in 28% of patients; those $\geq 2\%$ were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions ($\geq 20\%$) were fatigue (29%), diarrhea (24%), and rash (24%).

Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-811, when KEYTRUDA was administered in combination with trastuzumab, fluoropyrimidine- and

platinum-containing chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 6% of 217 patients with locally advanced unresectable or metastatic HER2+ gastric or GEJ adenocarcinoma. The most common adverse reaction resulting in permanent discontinuation was pneumonitis (1.4%). In the KEYTRUDA arm versus placebo, there was a difference of $\geq 5\%$ incidence between patients treated with KEYTRUDA versus standard of care for diarrhea (53% vs 44%) and nausea (49% vs 44%).

The most common adverse reactions (reported in $\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, and weight loss.

In KEYNOTE-590, when KEYTRUDA was administered with cisplatin and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation, KEYTRUDA was discontinued due to adverse reactions in 15% of 370 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA ($\geq 1\%$) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). The most common adverse reactions ($\geq 20\%$) with KEYTRUDA in combination with chemotherapy were nausea (67%), fatigue (57%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

Adverse reactions occurring in patients with esophageal cancer who received KEYTRUDA as a monotherapy 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 ($\geq 20\%$) 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 ($\geq 1\%$) were 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 were hepatotoxicity (13%), diarrhea/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). The most common adverse reactions ($\geq 20\%$) 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%).

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

Adverse reactions occurring in patients with recurrent or metastatic cSCC or locally advanced cSCC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-355, when KEYTRUDA and chemotherapy (paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin) were administered to patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting (n=596), fatal adverse reactions occurred in 2.5% of patients, including cardio-respiratory arrest (0.7%) and septic shock (0.3%). Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with chemotherapy; the serious reactions in $\geq 2\%$ were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%). KEYTRUDA was discontinued in 11% of patients due to adverse reactions. The most common reactions resulting in permanent discontinuation ($\geq 1\%$) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions ($\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue (48%), nausea (44%), alopecia (34%), diarrhea and constipation (28% each), vomiting and rash (26% each), cough (23%), decreased appetite (21%), and headache (20%).

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

In KEYNOTE-051, 161 pediatric patients (62 pediatric patients aged 6 months to younger than 12 years and 99

pediatric patients aged 12 years to 17 years) were administered KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 24 months).

Adverse reactions that occurred at a $\geq 10\%$ higher rate in pediatric patients when compared to adults were pyrexia (33%), vomiting (30%), leukopenia (30%), upper respiratory tract infection (29%), neutropenia (26%), headache (25%), and Grade 3 anemia (17%).

Merck's Focus on Cancer

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Please see Prescribing Information for KEYTRUDA (pembrolizumab) at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf and Medication Guide for KEYTRUDA at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_mg.pdf.

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