Merck Presents Promising New Data for Three Investigational Medicines From Diverse and Expansive Oncology Pipeline at ESMO Virtual Congress 2020

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Researchers Share New Data for Vibostolimab (MK-7684), Merck’s Anti-TIGIT Therapy, as Monotherapy and in Combination With KEYTRUDA® (pembrolizumab); First-Time Results for First-in-Class MK-4830 (Anti-ILT4 Therapy); and Late-Breaking Data for MK-6482 (HIF-2α Inhibitor)

Merck to Initiate Phase 3 Study of Vibostolimab in Non-Small Cell Lung Cancer in First Half of 2021

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced the presentation of new data for three investigational medicines in Merck’s diverse and expansive oncology pipeline: vibostolimab (MK-7684), an anti-TIGIT therapy; MK-4830, a first-in-class anti-ILT4 therapy; and MK-6482, an oral HIF-2α inhibitor. Data from cohort expansions of a Phase 1b trial evaluating vibostolimab, as monotherapy and in combination with KEYTRUDA, Merck’s anti-PD-1 therapy, in patients with metastatic non-small cell lung cancer (NSCLC; Abstract #1410P and Abstract #1400P), and first-time Phase 1 data for MK-4830 in patients with advanced solid tumors (Abstract #524O), demonstrated acceptable safety profiles for these two investigational medicines and early signals of anti-tumor activity. Additionally, late-breaking Phase 2 data for MK-6482 showed anti-tumor responses in von Hippel-Lindau (VHL) disease patients with clear cell renal cell carcinoma (RCC) and other tumors (Abstract #LBA26).
“The new data for these three investigational medicines are encouraging and highlight continued momentum in our rapidly expanding oncology pipeline,” Dr. Eric H. Rubin, senior vice president, early-stage development, clinical oncology, Merck Research Laboratories. “Over the past five years, KEYTRUDA has become foundational in the treatment of certain advanced cancers. Our broad oncology portfolio and promising pipeline candidates are a testament to our commitment to bring forward innovative new medicines to address unmet medical needs in cancer care.”

Vibostolimab (Anti-TIGIT Therapy): Early Findings in Metastatic NSCLC (Abstract #1410P and Abstract #1400P)

Vibostolimab in combination with KEYTRUDA was evaluated in patients with metastatic NSCLC who had not previously received anti–PD-1/PD-L1 therapy, but the majority of whom had received ≥1 prior lines of therapy (73%, n=30/41) in Abstract #1410P. In Part B of the first-in-human, open-label, Phase 1 trial (NCT02964013) all patients received vibostolimab (200 or 210 mg) in combination with KEYTRUDA (200 mg) on Day 1 of each three-week cycle for up to 35 cycles. The primary endpoints of the study were safety and tolerability. Secondary endpoints included objective response rate (ORR), duration of response (DOR) and progression-free survival (PFS) based on investigator review per RECIST v1.1. In this anti-PD-1/PD-L1 naïve study, vibostolimab in combination with KEYTRUDA had a manageable safety profile and demonstrated promising anti-tumor activity. Treatment-related adverse events (TRAEs) with vibostolimab in combination with KEYTRUDA occurred in 34 patients (83%). The most frequent TRAEs (≥20%) were pruritus (34%), hypoalbuminemia (29%) and pyrexia (20%). Grade 3-5 TRAEs occurred in six patients (15%). No deaths due to TRAEs occurred. Across all patients enrolled, treatment with vibostolimab in combination with KEYTRUDA demonstrated an ORR of 29% (95% CI, 16-46) and median PFS was 5.4 months (95% CI, 2.1-8.2). The median DOR was not reached (range, 4 to 17+ months). Among patients whose tumors express PD-L1 (tumor proportion score [TPS] ≥1%) (n=13), the ORR was 46% (95% CI, 19-75) and median PFS was 8.4 months (95% CI, 3.9-10.2). Among patients whose tumors express PD-L1 (TPS <1%) (n=12), the ORR was 25% (95% CI, 6-57), and median PFS was 4.1 months (95% CI, 1.9-not reached [NR]). PD-L1 status was not available for 16 patients. Median follow-up for the study was 11 months (range, 7 to 18).

Additional data from a separate cohort of the same Phase 1b trial evaluated vibostolimab as monotherapy (n=41) and in combination with KEYTRUDA (n=38) in patients with metastatic NSCLC whose disease progressed on prior anti-PD-1/PD-L1 therapy (Abstract #1400P). In the study, 78% of patients had received ≥2 lines of prior therapy. In the study, patients received vibostolimab monotherapy (200 or 210 mg) or vibostolimab (200 or 210 mg) in combination with KEYTRUDA (200 mg) on Day 1 of each three-week cycle for up to 35 cycles. The primary endpoints of the study were safety and tolerability. Secondary endpoints included ORR and DOR. Vibostolimab as monotherapy or in combination with KEYTRUDA had a manageable safety profile and demonstrated modest anti-tumor activity in patients whose disease was refractory to PD-1/PD-L1 inhibition, most of whom had previously
received several lines of therapy for advanced disease prior to enrollment. Grade 3-5 TRAEs occurred in 15% of patients receiving vibostolimab monotherapy and 13% of patients receiving vibostolimab in combination with KEYTRUDA. The most common TRAEs (≥10% in either arm) were pruritus, fatigue, rash, arthralgia and decreased appetite. One patient died due to treatment-related pneumonitis in the vibostolimab and KEYTRUDA combination arm. The ORR was 7% (95% CI, 2-20) with vibostolimab monotherapy and 5% (95% CI, <1-18) with vibostolimab in combination with KEYTRUDA. The median DOR was 9 months (range, 9 to 9) with vibostolimab monotherapy and 13 months (range, 4+ to 13) with vibostolimab in combination with KEYTRUDA.

Data from these cohort expansion studies are encouraging and support the continued development of vibostolimab, which is being evaluated alone and in combination with KEYTRUDA across multiple solid tumors, including NSCLC and melanoma. In the ongoing Phase 2 KEYNOTE-U01 umbrella study (NCT04165798), substudy KEYNOTE-01A (NCT04165070) is evaluating vibostolimab in combination with KEYTRUDA plus chemotherapy for the first-line treatment of patients with advanced NSCLC who had not received prior treatment with an anti-PD-1/PD-L1. Merck plans to initiate a Phase 3 study of vibostolimab in NSCLC in the first half of 2021. Ongoing trials in melanoma include the Phase 1/2 KEYNOTE-U02 umbrella study comprised of three substudies evaluating vibostolimab in combination with KEYTRUDA across treatment settings (substudy 02A: NCT04305041, substudy 02B: NCT04305054 and substudy 02C: NCT04303169).

**MK-4830 (Anti-ILT4 Therapy): Initial Results in Advanced Solid Tumors (Abstract #524O)**

In this first-in-human Phase 1, open-label, multi-arm, multi-center, dose escalation study (NCT03564691), MK-4830, Merck’s first-in-class anti-ILT4 therapy, was evaluated as monotherapy (n=50) and in combination with KEYTRUDA (n=34) in patients with advanced solid tumors. The majority of patients enrolled in the study (51%) had received three or more prior lines of therapy. MK-4830 was administered intravenously at escalating doses every three weeks alone or in combination with KEYTRUDA (200 mg every three weeks). The primary endpoints of the dose escalation part of the study were safety and tolerability; Pharmacokinetics was a secondary endpoint, and exploratory objectives included ORR per RECIST v1.1, evaluation of receptor occupancy and immune correlates of response in blood and tumor.

Findings showed that MK-4830 as monotherapy and in combination with KEYTRUDA had an acceptable safety profile and demonstrated dose-related evidence of target engagement in patients with advanced solid tumors. No dose-limiting toxicities were observed; the maximum-tolerated dose was not reached. Any-grade adverse events were consistent with those associated with KEYTRUDA. Treatment-related AEs occurred in 54% (n=28/52) of patients who received MK-4830 in combination with KEYTRUDA and 48% (n=24/50) of patients who received MK-4830 monotherapy; the majority were Grade 1 and 2. Preliminary efficacy data showed an ORR of 24% (n=8/34) in patients who received MK-4830 in combination with KEYTRUDA. All responses occurred in heavily pretreated
patients, including five who had progressed on prior anti-PD-1 therapy (n=5/11). Some patients received more than one year of treatment, and treatment is ongoing in several patients.

These early data support the continued development of MK-4830 in combination with KEYTRUDA in patients with advanced solid tumors. Expansion cohorts of this study include pancreatic adenocarcinoma, glioblastoma, head and neck squamous cell carcinoma (recurrent or metastatic; PD-L1 positive), advanced NSCLC and gastric cancer.

**MK-6482 (HIF-2α Inhibitor): Results in VHL-Associated RCC and Non-RCC Tumors (Abstract #LBA26)**

In this Phase 2, open-label, single-arm trial, MK-6482 was evaluated for the treatment of VHL-associated RCC (NCT03401788). New data include findings for MK-6482 in VHL patients with non-RCC tumors and updated data in VHL patients with RCC. First-time data in VHL-associated RCC were presented in the virtual scientific program of the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting. The study enrolled adult patients with a pathogenic germline VHL variation, measurable localized or non-metastatic RCC, no prior systemic anti-cancer therapy, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Patients received MK-6482 120 mg orally once daily until disease progression, unacceptable toxicity, or investigator’s or patient’s decision to withdraw. The primary endpoint was ORR of VHL-associated RCC tumors per RECIST v1.1 by independent radiology review. Secondary endpoints included DOR, time to response, PFS, efficacy in non-RCC tumors, and safety and tolerability.

Promising clinical activity continues to be observed with MK-6482 in treatment-naïve patients with VHL-associated RCC. Among 61 patients, results showed a confirmed ORR of 36.1% (95% CI, 24.2-49.4); all responses were partial responses, and 38% of patients had stable disease. The median time to response was 31.1 weeks (range, 11.9 to 62.3), and median DOR was not yet reached (range, 11.9 to 62.3 weeks). Additionally, 91.8% (n=56) of patients had a decrease in size of target lesions. Median PFS has not been reached, and the PFS rate at 52 weeks was 98.3%. Median duration of treatment was 68.7 weeks (range, 18.3 to 104.7), and 91.8% of patients were still on therapy after a minimum follow-up of 60 weeks.

In patients with non-RCC tumors, results in those with pancreatic lesions (n=61) showed a confirmed ORR of 63.9% (95% CI, 50.6-75.8), with four complete responses and 35 partial responses. Additionally, 34.4% had stable disease. In those with central nervous system (CNS) hemangioblastoma (n=43), results showed a confirmed ORR of 30.2% (95% CI, 17.2-46.1), with five complete responses and eight partial responses. Additionally, 65.1% had stable disease. In patients with retinal lesions (n=16), 93.8% of patients had improved or stable response.

In this Phase 2 study, TRAEs occurred in 98.4% of patients, and there were no Grade 4-5 TRAEs. The most common all-cause adverse events (≥20%) were anemia (90.2%), fatigue (60.7%), headache (37.7%), dizziness (36.1%) and
nausea (31.1%). Grade 3 all-cause adverse events included anemia (6.6%), fatigue (4.9%) and dyspnea (1.6%). One patient discontinued treatment due to a TRAE (Grade 1 dizziness).

As announced, data spanning more than 15 types of cancer will be presented from Merck's broad oncology portfolio and investigational pipeline at the congress. A compendium of presentations and posters of Merck-led studies is available here. Follow Merck on Twitter via @Merck and keep up to date with ESMO news and updates by using the hashtag #ESMO20.

About Vibostolimab

Vibostolimab is an anti-TIGIT therapy discovered and developed by Merck. Vibostolimab binds to TIGIT and blocks the interaction between TIGIT and its ligands (CD112 and CD155), thereby activating T lymphocytes which help to destroy tumor cells. The effect of combining KEYTRUDA with vibostolimab – blocking both the TIGIT and PD-1 pathways simultaneously – is currently being evaluated across multiple solid tumors, including NSCLC and melanoma.

About MK-4830

MK-4830 is a novel antibody directed against the inhibitory immune checkpoint receptor immunoglobulin-like transcript 4 (ILT4). Unlike current T cell-targeted antibodies (e.g., anti-PD1, anti-CTLA-4), anti-ILT4 is believed to attenuate immunosuppression imposed by tolerogenic myeloid cells in the tumor microenvironment. MK-4830 is currently being evaluated alone and in combination with KEYTRUDA across multiple solid tumors as part of ongoing Phase 1 and 2 trials.

About MK-6482

MK-6482 is an investigational, novel, potent, selective, oral HIF-2α inhibitor that is currently being evaluated in a Phase 3 trial in advanced RCC (NCT04195750), a Phase 2 trial in VHL-associated RCC (NCT03401788), and a Phase 1/2 dose-escalation and dose-expansion trial in advanced solid tumors, including advanced RCC (NCT02974738). Proteins known as hypoxia-inducible factors, including HIF-2α, can accumulate in patients when VHL, a tumor-suppressor protein, is inactivated. The accumulation of HIF-2α can lead to the formation of both benign and malignant tumors. This inactivation of VHL has been observed in more than 90% of RCC tumors. Research into VHL biology that led to the discovery of HIF-2α was awarded the Nobel Prize in Physiology or Medicine in 2019.

About KEYTRUDA® (pembrolizumab) Injection, 100 mg

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 1,200 trials studying KEYTRUDA across a wide variety of cancers and treatment settings. The KEYTRUDA clinical program seeks to understand the role of KEYTRUDA across cancers and the factors that may predict a patient's likelihood of benefiting from treatment with KEYTRUDA, including exploring several different biomarkers.

Selected KEYTRUDA® (pembrolizumab) Indications

Melanoma

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

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

Non-Small Cell Lung Cancer

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

KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

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

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

Small Cell Lung Cancer
KEYTRUDA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least 1 other prior line of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Head and Neck Squamous Cell Cancer

KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [combined positive score (CPS) ≥1] as determined by an FDA-approved test.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Primary Mediastinal Large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. KEYTRUDA is not recommended for 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 [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 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.

KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) 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, 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.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

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

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.

Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

Cervical Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Merkel Cell Carcinoma

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

Tumor Mutational Burden-High
KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] 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) that is not curable by surgery or radiation.

Selected Important Safety Information for KEYTRUDA® (pembrolizumab)

Immune-Mediated Pneumonitis

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

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

Immune-Mediated Colitis

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

Immune-Mediated Hepatitis

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

Hepatotoxicity in Combination With Axitinib

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

Immune-Mediated Endocrinopathies

KEYTRUDA can cause adrenal insufficiency (primary and secondary), hypophysitis, thyroid disorders, and type 1 diabetes mellitus. Adrenal insufficiency occurred in 0.8% (22/2799) of patients, including Grade 2 (0.3%), 3 (0.3%), and 4 (<0.1%). Hypophysitis occurred in 0.6% (17/2799) of patients, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%). Hypothyroidism occurred in 8.5% (237/2799) of patients, including Grade 2 (6.2%) and 3 (0.1%). The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC (16%) receiving KEYTRUDA, as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. Hyperthyroidism occurred in 3.4% (96/2799) of patients, including Grade 2 (0.8%) and 3 (0.1%), and thyroiditis occurred in 0.6% (16/2799) of patients, including Grade 2 (0.3%). Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 0.2% (6/2799) of patients.

Monitor patients for signs and symptoms of adrenal insufficiency, hypophysitis (including hypopituitarism), thyroid function (prior to and periodically during treatment), and hyperglycemia. For adrenal insufficiency or hypophysitis, administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2 adrenal insufficiency or hypophysitis and withhold or discontinue KEYTRUDA for Grade 3 or Grade 4 adrenal insufficiency or 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, including classical Hodgkin lymphoma, 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-002, KEYTRUDA was permanently discontinued due to adverse reactions in 12% of 357 patients with advanced melanoma; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). The most common adverse reactions were fatigue (43%), pruritus (28%), rash (24%), constipation (22%), nausea (22%), diarrhea (20%), and decreased appetite (20%).

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

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

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

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

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

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

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

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

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

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 ≥2% were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions (≥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.

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

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

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with recurrent or metastatic cervical cancer. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA; the most frequent included anemia (7%), fistula, hemorrhage, and infections [except urinary tract infections] (4.1% each). The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22% each), and decreased appetite (21%).
Adverse reactions occurring in patients with hepatocellular carcinoma (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 (≥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 (≥20%) were diarrhea (56%), fatigue/asthenia (52%), hypertension (48%), hepatotoxicity (39%), hypothyroidism (35%), decreased appetite (30%), palmar-planter 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 cSCC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

**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 125 years, Merck, 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 in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. 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 the global outbreak
of novel coronavirus disease (COVID-19); 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 2019 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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