GUIDE TO SCORING PD-L1 EXPRESSION USING COMBINED POSITIVE SCORE (CPS)

PD-L1 = programmed death ligand 1.
Immune-Mediated Pneumonitis

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

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

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.

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 ≥1), as determined by an FDA-approved test. 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 cervical cancer 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.

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 ≥1) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy or as first-line therapy for advanced disease, including Grades 3–5 in 1.6% of patients.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression after one or more prior lines of systemic therapy.

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.

KEYTRUDA is indicated for the first-line treatment of patients with advanced cervical cancer, including Grades 3–5 in 1.6% of patients.

KEYTRUDA is indicated for the first-line treatment of patients with recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/ neu-targeted therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic gastric or gastroesophageal adenocarcinoma 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.

KEYTRUDA is indicated for the treatment of patients with metastatic or with unresectable, recurrent HNSCC.

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy or as first-line therapy for advanced disease, including Grades 3–5 in 1.5% of patients.

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 1.6% of patients.

SELECTION SAFETY INFORMATION

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% (19/300) 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 1.6% of patients.

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 3 or 4 or recurrent Grade 2 pneumonitis.

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.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide is also available.
Accurate assessment of CPS depends on following proper procedures

**Determine specimen adequacy**
- A minimum of 100 viable tumor cells is needed to determine PD-L1 expression.

**Evaluate controls**
- Ensure that in-house controls and control cell line slide demonstrate acceptable staining.

**Evaluate PD-L1 staining**
- Estimate the number of PD-L1-staining cells (CPS numerator) and the total number of viable tumor cells (CPS denominator).

**Calculate CPS and determine PD-L1 expression level**
\[
CPS = \frac{\# \text{ of PD-L1–positive cells}}{\text{Total } \# \text{ of PD-L1–positive + PD-L1–negative tumor cells}} \times 100
\]
- Report results and eligibility.

**CPS ≥1:** Appropriate patients may be eligible for KEYTRUDA as monotherapy

**CPS ≥10:** Appropriate patients may be eligible for KEYTRUDA as monotherapy

**CPS < 1**

**CPS < 10**

**SELECTED SAFETY INFORMATION**

**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 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.

**Immunemediated 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. 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.

**SELECTED SAFETY INFORMATION (continued)**

**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 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.**

**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. 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.**

**Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.**

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PD-L1 expression status helps inform treatment decisions with KEYTRUDA

Examples of gastric tumor specimens using PD-L1 IHC 22C3 pharmDx

• Immune-mediated skin reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For 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

SELECTED SAFETY INFORMATION (continued) Immune-Mediated Skin Reactions (continued)
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

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Examples of ESCC tumor specimens using PD-L1 IHC 22C3 pharmDx

PD-L1 staining on both tumor cells and certain tumor-associated immune cells are evaluated when determining the CPS numerator.1

Partial and complete membrane staining:

- Tumor cells and immune cells demonstrating convincing partial, and/or complete, linear membrane staining at any intensity (including weak [1+]) should be included in the CPS numerator (gastric specimen). Note that MICs can have membrane and/or cytoplasmic staining.

- Tumor cells with convincing partial or complete linear membrane staining (at any intensity) that is perceived as distinct from cytoplasmic staining.

- Lymphocytes and macrophages (MICs) within the tumor nests and/or adjacent supporting stroma with convincing membrane and/or cytoplasmic staining (at any intensity). MICs must be directly associated with the response against the tumor.

- MICs = mononuclear inflammatory cells.

CPS assessment includes tumor-associated immune cells within lymph nodes, but not non–tumor-associated immune cells.

CPS calculation:

\[
\text{CPS} = \frac{\text{# of PD-L1–positive cells}}{\text{Total # of viable tumor cells}} \times 100
\]

CPS is reported as a whole number. Although the result of the calculation can exceed 100, the maximum score is defined as CPS 100.

SELECTED SAFETY INFORMATION (continued)

Other Immune-Mediated Adverse Reactions (continued)

- 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, hemorrhagic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including classical Hodgkin lymphoma, and postmarketing use.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.
PD-L1 expression in clinical trials with Keytruda

M/uR HNSCC

CPS ≥1 in the KEYNOTE-048 study

CPS ≥1 in the KEYNOTE-059 study

Advanced gastric or GEJ cancer

CPS ≥1 in the KEYNOTE-180 study

Advanced ESCC

CPS ≥1 in Cohort E of the KEYNOTE-158 study

SELECTED SAFETY INFORMATION (continued)

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. 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-refractory 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 programmed death receptor-1 (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-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 occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma and new or worsening hypothyroidism.

• 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 (49%), constipation (37%), vomiting (32%), mucosal inflammation (31%), diarrhea (29%), decreased appetite (29%), stomatitis (26%), and cough (22%).

• In KEYNOTE-045, 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%), muscular skeletal 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 pneumonia (2.5% of patients).
Biomarker status can be a road map for personalizing treatment.

Prepare a report that includes CPS as a number between 0 and 100 to help inform treatment decisions with KEYTRUDA.¹

Selected safety information (continued)

Adverse reactions (continued)

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%).

• The most common adverse reactions for KEYTRUDA (reported in ≥20% of patients) were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

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

Lactation

• 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.

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