KEYTRUDA®
(pembrolizumab) Injection 100 mg

Patient Identification Guide

As part of a treatment regimen for certain cancers,

Consider KEYTRUDA Together With Surgery in the Neoadjuvant and Adjuvant Settings or Adjuvant Setting

TUMOR TYPE	INDICATION	NEOADJUVANT	ADJUVANT	CLINICAL STUDIES
NSCLC	KEYTRUDA is indicated for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.	✓ +	✓	KEYNOTE-671
	KEYTRUDA, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC.		✓	KEYNOTE-091
TNBC	KEYTRUDA is indicated for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.	✓ +	✓	KEYNOTE-522
RCC	KEYTRUDA is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.		✓	KEYNOTE-564
MELANOMA	KEYTRUDA is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB, IIC, or III melanoma following complete resection.		✓	KEYNOTE-716 KEYNOTE-054

NSCLC = non–small cell lung cancer; T2a = tumor >3 cm but ≤5 cm in the greatest dimension; TNBC = triple-negative breast cancer; RCC = renal cell carcinoma.

SELECTED SAFETY INFORMATION

SUMMARY OF IMMUNE-MEDIATED REACTIONS

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time during or after treatment with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of KEYTRUDA. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or permanently discontinued and corticosteroids administered if appropriate.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 2–7, 9–14, and 16, and the accompanying Prescribing Information. The Medication Guide also is available.

KEYNOTE-671: KEYTRUDA® (pembrolizumab) With Chemotherapy as Neoadjuvant Treatment, Then KEYTRUDA as Adjuvant Treatment in Certain Patients With Resectable NSCLC

TUMOR CHARACTERISTICS FOR INCLUSION IN KEYNOTE-671[1,2]:

TUMOR SIZE	NODAL INVOLVEMENT	PRESENCE OF METASTASIS
≥4 cm	N0	M0
	N1	
	N2	
Regardless of PD-L1 expression		

KEYNOTE-671 Key Inclusion Criteria

- Patients with previously untreated and resectable stage II, IIIA, or IIIB (N2) NSCLC per AJCC 8th ed
- Patients were enrolled regardless of PD-L1 expression

KEYNOTE-671 Key Exclusion Criteria

- Active autoimmune disease that required systemic therapy within 2 years of treatment
- A medical condition that required immunosuppression
- A history of interstitial lung disease or pneumonitis requiring steroids

A regimen including KEYTRUDA was evaluated in 797 patients with previously untreated and resectable stage II, IIIA, or IIIB (N2) NSCLC

Study Design[1,2]: KEYNOTE-671 (NCT03425643) was a randomized, double-blind, multicenter, placebo-controlled phase 3 study in patients with previously untreated and resectable stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or a history of interstitial lung disease or pneumonitis that required steroids were ineligible. Patients were randomized[a] (1:1) to receive neoadjuvant KEYTRUDA 200 mg IV or placebo Q3W IV, each of which was given with chemotherapy (cisplatin plus pemetrexed or cisplatin plus gemcitabine) for up to 4 cycles, followed by surgery. Within 4–12 weeks following surgery, adjuvant KEYTRUDA 200 mg IV Q3W or placebo IV Q3W was administered for up to 13 cycles. Treatment continued until completion (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. The trial was not designed to isolate the effect of KEYTRUDA in each phase (neoadjuvant or adjuvant) of the treatment.

[a]Randomization was stratified by stage (II vs III), tumor PD-L1 expression (TPS ≥50% or <50%), histology (squamous vs nonsquamous), and geographic region (East Asia vs non-East Asia).

AJCC = American Joint Committee on Cancer; IV = intravenous; M0 = no metastasis; N0 = no regional lymph node involvement; N1 = metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension; N2 = metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s); NSCLC = non–small cell lung cancer; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks; TPS = tumor proportion score.

SELECTED SAFETY INFORMATION (*continued*)

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.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1, 3–7, 9–14, and 16, and the accompanying Prescribing Information. The Medication Guide also is available.

KEYTRUDA® (pembrolizumab) Injection 100 mg

KEYNOTE-091: KEYTRUDA (pembrolizumab) as Adjuvant Treatment in Patients With Certain Stages of NSCLC After Surgery and Chemotherapy

TUMOR CHARACTERISTICS FOR INCLUSION IN KEYNOTE-091[3,4]:

TUMOR SIZE	NODAL INVOLVEMENT	PRESENCE OF METASTASIS
≥4 cm	N0	M0
	N1	
	N2 without $T4_{inv}$/ $T4_{ipsi}$ Nod	
Regardless of PD-L1 expression		

KEYNOTE-091 Key Inclusion Criteria[5]

- Completely resected stage IB (T2a ≥4 cm), II, or IIIA NSCLC per AJCC 7th ed, regardless of tumor PD-L1 expression
- No prior neoadjuvant radiotherapy and/or neoadjuvant chemotherapy
- No prior adjuvant radiotherapy for the current malignancy
- May or may not have received adjuvant chemotherapy (up to 4 cycles)

KEYNOTE-091 Key Exclusion Criteria

- Active autoimmune disease
- Use of chronic immunosuppressive agents
- History of interstitial lung disease or pneumonitis

KEYTRUDA was evaluated in 1,177 patients with completely resected stage IB (T2a ≥4 cm), II, or IIIA NSCLC[a]

Study Design[5]: KEYNOTE-091 (NCT02504372) was a multicenter, randomized[b], triple-blind, placebo-controlled, phase 3 trial.[5] Patients were randomized (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks. Treatment continued until RECIST v1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity or up to 1 year. Tumor assessments were conducted every 12 weeks for the first year, then every 6 months for years 2 to 3, and then annually through year 5. After year 5, imaging was performed as per local standard of care.

[a]By AJCC 7th edition.

[b]Randomization was stratified by stage (IB vs II vs IIIA), receipt of adjuvant chemotherapy (yes vs no), PD-L1 status (TPS <1% [negative] vs TPS 1–49% vs TPS ≥50%), and geographic region (Western Europe vs Eastern Europe vs Asia vs Rest of World).

AJCC = American Joint Committee on Cancer; M0 = no metastasis; N0 = no regional lymph node involvement; N1 = metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension; N2 = metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s); Nod = separate tumor nodules in a different ipsilateral node; NSCLC = non–small cell lung cancer; PD-L1 = programmed death ligand 1; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1; T2a = tumor >3 but ≤5 cm in the greatest dimension; T4 inv = tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; T4 ipsi = tumor of any size with separate tumor nodules in a different ipsilateral lobe; TPS = tumor proportion score.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

- 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. For patients with TNBC treated with KEYTRUDA in the neoadjuvant setting, monitor blood cortisol at baseline, prior to surgery, and as clinically indicated. 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.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1, 2, 4–7, 9–14, and 16, and the accompanying Prescribing Information. The Medication Guide also is available.

KEYTRUDA® (pembrolizumab) Injection 100 mg

KEYNOTE-522: KEYTRUDA (pembrolizumab) With Chemotherapy as Neoadjuvant Treatment, Then KEYTRUDA as Adjuvant Treatment in Patients With High-Risk Early-Stage TNBC

TUMOR CHARACTERISTICS FOR INCLUSION IN KEYNOTE-522[6]:

TUMOR SIZE	NODAL INVOLVEMENT	PRESENCE OF METASTASIS
>1 cm to ≤2 cm	N+	M0
>2 cm	N+/N-	
Regardless of PD-L1 expression		

KEYNOTE-522 Key Inclusion Criteria

- Patients with newly diagnosed, previously untreated high-risk early-stage TNBC
- Tumor size >1 cm but ≤2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement
- Patients were enrolled regardless of tumor PD-L1 expression

KEYNOTE-522 Key Exclusion Criteria

- Patients with active autoimmune disease that required systemic therapy within 2 years of treatment
- Patients with a medical condition that required immunosuppression

A regimen including KEYTRUDA was evaluated in 1,174 patients with newly diagnosed, previously untreated high-risk early-stage TNBC

Study Design: KEYNOTE-522 was a multicenter, randomized[a] (2:1), double-blind, placebo-controlled trial. Patients were randomized to receive neoadjuvant therapy with KEYTRUDA 200 mg IV or placebo IV every 3 weeks plus paclitaxel and carboplatin for 4 cycles, followed by KEYTRUDA or placebo plus either doxorubicin or epirubicin plus cyclophosphamide for 4 cycles. Following surgery, patients received adjuvant KEYTRUDA or placebo every 3 weeks for 9 cycles.

[a]Randomization was stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and choice of carboplatin (dosed every 3 weeks vs weekly).

IV = intravenous; M0 = no metastasis; N+ = nodal positive; N- = nodal negative; PD-L1 = programmed death ligand 1; T1 = tumor ≤20 mm in greatest dimension; T2 = tumor >20 mm but ≤50 mm in greatest dimension; T3 = tumor >50 mm in greatest dimension; T4 = tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules); TNBC = triple-negative breast cancer.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

- 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.

KEYNOTE-564: KEYTRUDA (pembrolizumab) as Adjuvant Treatment in Certain Patients With RCC

TUMOR CHARACTERISTICS FOR INCLUSION IN KEYNOTE-564[7]:

	TUMOR SIZE/LOCATION	NODAL INVOLVEMENT	PRESENCE OF METASTASIS
Intermediate-High Risk	pT2 with Grade 4 or sarcomatoid features	N0	M0
Intermediate-High Risk	pT3, any grade	N0	M0
High Risk	pT4, any grade	N0	M0
High Risk	Any pT, any grade	N1	M0
M1 NED	Any pT, any grade	N+/N-	M1
Regardless of PD-L1 expression			

KEYNOTE-564 Key Inclusion Criteria[7]

- Patients with intermediate-high risk of recurrence (pT2 with Grade 4 or sarcomatoid, N0, M0; pT3, any grade, N0, M0)
- Patients with high risk of recurrence (pT4, any grade, N0, M0; any pT, any grade, N1, M0)
- Patients with M1 NED (M1 no evidence of disease[a])

KEYNOTE-564 Key Exclusion Criteria

- Patients were excluded from the trial if they had received prior systemic therapy for advanced RCC
- Patients with active autoimmune disease or a medical condition that required immunosuppression were also ineligible

KEYTRUDA was evaluated as adjuvant therapy in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease

Study Design: KEYNOTE-564 was a multicenter, randomized[b] (1:1), double-blind, placebo-controlled trial. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft-tissue metastatic lesion(s) in patients with M1 NED) with negative surgical margins ≥4 weeks prior to the time of screening. Patients were randomized to receive KEYTRUDA 200 mg administered intravenously every 3 weeks or placebo for up to 1 year until disease recurrence or unacceptable toxicity.

[a]Patients with metastatic disease who had undergone complete resection of primary and metastatic lesions.[7]

[b]Randomization was stratified by metastasis status (M0, M1 NED), M0 group, further stratified by ECOG PS (0,1), and by geographic region (US, non-US).

ECOG PS = Eastern Cooperative Oncology Group performance status; M0 = no metastasis; M1 = distant metastasis; N+ = nodal positive; N- = nodal negative; NED = no evidence of disease; N0 = no regional lymph node involvement; N1 = metastasis in regional lymph node(s); PD-L1 = programmed death ligand 1; pT = pathological tumor stage; pT2 = tumor is larger than 7 cm in greatest dimension and limited to the kidney; pT3 = locally advanced disease with invasion of the fat or vasculature of the kidney; pT4 = tumor invades beyond Gerota's fascia; RCC = renal cell carcinoma.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

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.

KEYNOTE-716: KEYTRUDA (pembrolizumab) as Adjuvant Treatment in Certain Patients With Melanoma

TUMOR CHARACTERISTICS FOR INCLUSION IN KEYNOTE-716[8-10]:

TUMOR SIZE	NODAL INVOLVEMENT	PRESENCE OF METASTASIS
T3b (>2.0–4.0 mm, with ulceration) T4a (>4.0 mm, without ulceration) T4b (>4.0 mm, with ulceration)	N-	M0
Regardless of PD-L1 expression		

KEYNOTE-716 Key Inclusion Criteria

- Age ≥12
- Completely resected stage IIB or stage IIC melanoma
- No previous treatment for melanoma beyond complete surgical resection

KEYNOTE-716 Key Exclusion Criteria[11]

- Eastern Cooperative Oncology Group (ECOG) performance status score of >1
- Patients with active autoimmune disease that required systemic therapy within 2 years of treatment
- Patients with a known additional malignancy that is progressing or has required active antineoplastic therapy (including hormonal) within the past 5 years[a]

A regimen including KEYTRUDA was evaluated in 976 patients with completely resected stage IIB or stage IIC melanoma[8]

Study Design: KEYNOTE-716 (NCT03553836) was a multicenter, randomized, double-blind, placebo-controlled trial. A total of 976 patients were randomized[b] (1:1) to receive KEYTRUDA 200 mg or the pediatric (≥12 years old) dose of KEYTRUDA 2 mg/kg intravenously (up to a maximum of 200 mg) every 3 weeks (n=487) or placebo (n=489) for up to 1 year or until disease recurrence or unacceptable toxicity. Patients underwent imaging every 6 months for 1 year from randomization, every 6 months from years 2 to 4, and then once in year 5 from randomization or until recurrence, whichever came first.

[a]Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy were not excluded. Participants with a history of nonulcerated cutaneous/acral primary melanoma <1 mm in depth with no nodal involvement were allowed in this study.[11]

[b]Randomization was stratified by AJCC 8th edition T stage (>2.0–4.0 mm with ulceration vs >4.0 mm without ulceration vs >4.0 mm with ulceration).

AJCC = American Joint Committee on Cancer; M0 = no metastasis; N- = nodal negative; PD-L1 = programmed death ligand 1; T3b = tumor >2.0–4.0 mm with ulceration; T4a = tumor >4.0 mm without ulceration; T4b = tumor >4.0 mm with ulceration.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Pneumonitis (*continued*)

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 7% (41/580) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.2%), Grade 4 (0.3%), and Grade 3 (1%) adverse reactions. Patients received high-dose corticosteroids for a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to discontinuation of KEYTRUDA in 26 (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 63% discontinued KEYTRUDA, and 71% had resolution.

KEYNOTE-054: KEYTRUDA (pembrolizumab) as Adjuvant Treatment in Certain Patients With Melanoma

TUMOR CHARACTERISTICS FOR INCLUSION IN KEYNOTE-054[10,12]:

TUMOR SIZE	NODAL INVOLVEMENT	PRESENCE OF METASTASIS
Any T	N+	M0
Regardless of PD-L1 expression		

KEYNOTE-054 Key Inclusion Criteria[12]

- Age ≥18
- Completely resected stage IIIA (>1 mm lymph node metastasis), IIIB, or IIIC melanoma
- Lymph node dissection and, if indicated, radiotherapy within 13 weeks prior to starting treatment

KEYNOTE-054 Key Exclusion Criteria[12]

- Eastern Cooperative Oncology Group (ECOG) performance status score of >1
- Autoimmune disease
- Uncontrolled infections
- Use of systemic glucocorticoids
- Previous systemic therapy for melanoma

A regimen including KEYTRUDA was evaluated in 1,019 patients with completely resected stage III A (>1 mm lymph node metastasis), IIIB, or IIIC melanoma

Study Design: KEYNOTE-054 (NCT02362594) was a multicenter, randomized (1:1), double-blind, placebo-controlled trial. Patients were randomized[a] to receive KEYTRUDA 200 mg intravenously every 3 weeks or placebo for up to 1 year or until disease recurrence or unacceptable toxicity. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first 2 years, then every 6 months from year 3 to 5, and then annually.

[a]Randomization was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs IIIB vs IIIC 1–3 positive lymph nodes vs IIIC ≥4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated).

M0 = no metastasis; N+ = nodal positive; PD-L1 = programmed death ligand 1; T = primary tumor.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

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.

Continued Collaboration With the Medical Oncologist and MDT[13,14]

Your role in the development of a treatment plan is critical. It's important to have detailed conversations with your medical oncology colleagues and the multidisciplinary team (MDT). Once you have identified that a patient is eligible for surgery, discuss the patient's clinical profile with an oncologist to see if KEYTRUDA in the neoadjuvant and adjuvant settings, or in the adjuvant setting, is indicated.

Points to consider with the medical oncologist and MDT

1. **Clinical and Pathological Evaluation:** Patient history and diagnosis (including tumor characteristics and prognostic stage).[13,15,16]
2. **Prognosis:** Patient's risk of recurrence or progression based on tumor type and stage.[15]
3. **Treatment Before Surgery:** How neoadjuvant treatment may impact the timing and type of surgery.[15,17]
4. **Treatment After Surgery:** How important recovery time is when considering the initiation of adjuvant therapy.[13,15,18]

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

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.

Immune-Mediated Endocrinopathies

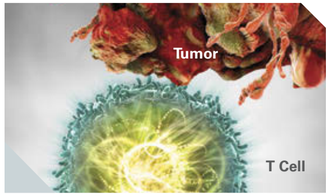
Adrenal Insufficiency

- 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.

KEYTRUDA® (pembrolizumab) Injection 100 mg

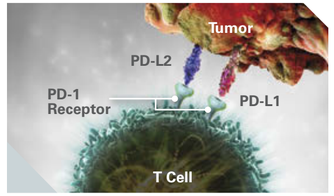
KEYTRUDA binds to the PD-1 receptor, blocking both immune-suppressing ligands, PD-L1 and PD-L2, from interacting with PD-1 to help restore T-cell response and immune response

Restoring active T-cell response could affect both normal healthy cells and tumor cells.



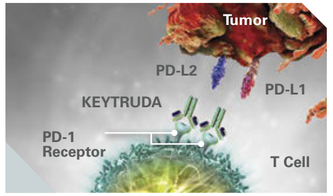
NORMAL IMMUNE RESPONSE

When functioning properly, T cells are activated and can attack tumor cells.



TUMOR EVASION AND T-CELL DEACTIVATION

Some tumors can evade the immune system through the PD-1 pathway. The PD-L1 and PD-L2 ligands on tumors can bind with PD-1 receptors on T cells to inactivate the T cells.



T-CELL REACTIVATION WITH *KEYTRUDA*

KEYTRUDA binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, which helps restore the immune response. While having an effect on the tumor, this could also affect normal healthy cells.

PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Endocrinopathies (*continued*)

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.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Endocrinopathies (*continued*)

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 hyperthyroidism was higher in 580 patients with resected NSCLC, occurring in 11% of patients receiving KEYTRUDA as a single agent as adjuvant treatment, including Grade 3 (0.2%) hyperthyroidism. The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC, occurring in 22% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) 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.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

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.

Selected Safety Information (*continued*)

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% 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 treatments. 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 treatments 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.

SELECTED SAFETY INFORMATION (*continued*)

Adverse Reactions

- When KEYTRUDA was used as monotherapy, the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism.
- When KEYTRUDA was used in combination with chemotherapy, the most common adverse reactions (≥20%) were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, and hypothyroidism.

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 last dose.

Pediatric Use

- In KEYNOTE-051, 173 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 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 25 months).
- Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults were pyrexia (33%), leukopenia (31%), vomiting (29%), neutropenia (28%), headache (25%), abdominal pain (23%), thrombocytopenia (22%), Grade 3 anemia (17%), decreased lymphocyte count (13%), and decreased white blood cell count (11%).

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Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1–7, 9–14, and 16, and the accompanying Prescribing Information. The Medication Guide also is available.

Collaborate With the Medical Oncologist and MDT to Identify Patients Who May Be Eligible for Treatment With KEYTRUDA

NEOADJUVANT AND ADJUVANT SETTINGS

NSCLC

KEYTRUDA is indicated for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

High-risk early-stage TNBC

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

ADJUVANT SETTING

NSCLC

KEYTRUDA, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC.

RCC

KEYTRUDA is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Melanoma

KEYTRUDA is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB, IIC, or III melanoma following complete resection.

MDT = multidisciplinary team; NSCLC = non–small cell lung cancer; RCC = renal cell carcinoma.

SUMMARY OF IMMUNE-MEDIATED REACTIONS

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time during or after treatment with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of KEYTRUDA. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or permanently discontinued and corticosteroids administered if appropriate.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1–7, 9–14, and the accompanying Prescribing Information. The Medication Guide also is available.

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