KEYTRUDA® (pembrolizumab) as Adjuvant Therapy for Certain Patients With Renal Cell Carcinoma

Identification of Eligible Patients

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

This indication is based on data from the KEYNOTE-564 trial.

Based on the patient population included in KEYNOTE-564, the following populations are eligible for adjuvant treatment with KEYTRUDA:

Prespecified Disease Risk Categories in KEYNOTE-564	AJCC Prognostic Stage Groups for RCC (8th Ed.)[1]				Histology
	Stage	T	N	M	
Intermediate-High Risk of Recurrence	Stage II	pT2	N0	M0	Grade 4 or sarcomatoid
	Stage III	pT3	N0	M0	Any grade
High Risk of Recurrence	Stage III	pT1, pT2, or pT3	N1	M0	Any grade
	Stage IV	pT4	N0	M0	Any grade
	Stage IV	pT4	N1	M0	Any grade
M1 NED	M1 No Evidence of Disease				

Patients with M1 disease are classified as stage IV (any T, any N, M1) per AJCC prognostic stage groups for RCC (8th ed.), and includes patients with histology of any grade.[1]

AJCC = American Joint Committee on Cancer; M0 = no distant metastasis; M1 = distant metastasis; N0 = no regional lymph node metastasis; N1 = metastasis in regional lymph node(s); NED = no evidence of disease; pT = pathological primary tumor.

SELECTED SAFETY INFORMATION

- 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, and the accompanying Prescribing Information. The Medication Guide also is available.

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Definitions of Stage II, III, and IV RCC per AJCC Prognostic Stage Groups for RCC (8th Ed.)[1]

	Primary Tumor (T)		Regional Lymph Node (N)	Distant Metastasis (M)
Stage II	T2	T2a: Tumor is >7 cm but ≤10 cm in greatest dimension, limited to the kidney T2b: Tumor is >10 cm, limited to the kidney	N0	M0
Stage III	T1	T1a: Tumor is ≤4 cm in greatest dimension, limited to the kidney T1b: Tumor is >4 cm but ≤7 cm in greatest dimension, limited to the kidney	N1	M0
	T2	T2a: Tumor is >7 cm but ≤10 cm in greatest dimension, limited to the kidney T2b: Tumor is >10 cm, limited to the kidney	N1	M0
	T3	T3a: Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia T3b: Tumor extends into the vena cava below the diaphragm T3c: Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava	N0 or N1	M0
Stage IV	T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)	Any N	M0
	Any T		Any N	M1

AJCC = American Joint Committee on Cancer; M0 = no distant metastasis; M1 = distant metastasis; N0 = no regional lymph node metastasis; N1 = metastasis in regional lymph node(s); RCC = renal cell carcinoma.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions

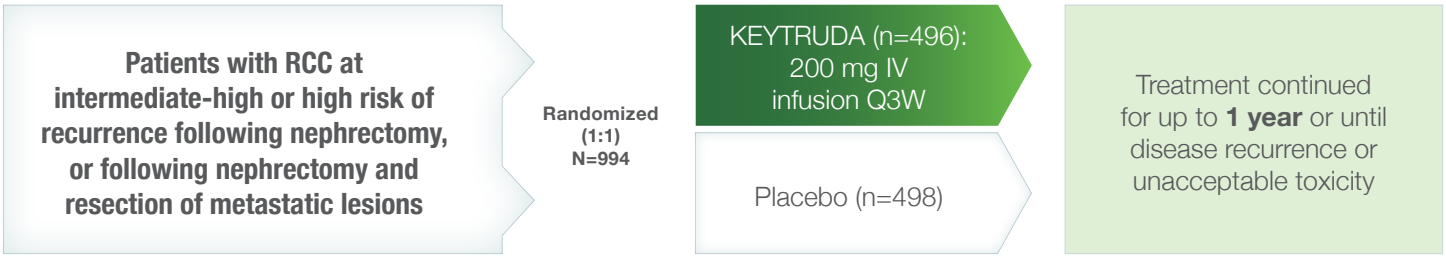
- KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the programmed death ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and 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.

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

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

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1 and 3–7, and the accompanying Prescribing Information.

KEYNOTE-564: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial[2]



- **Major efficacy outcome measure:** Disease-free survival (DFS)[2,a]
- **Additional outcome measure:** Overall survival (OS)

Patient Inclusion Criteria

Intermediate-High Risk of Recurrence	High Risk of Recurrence	M1 NED
pT2 with Grade 4 or sarcomatoid, N0, M0	pT4, any grade, N0, M0	M1 No evidence of disease
pT3, any grade, N0, M0	Any pT, any grade, N1, M0	

Nephrectomy

- Partial nephroprotective or radical complete nephrectomy with negative surgical margins ≥4 weeks prior to the time of screening.
- M1 NED patients also had complete resection of solid, isolated, soft tissue metastatic lesion(s).

Patient 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.

[a]DFS, as assessed by the investigator, is defined as the time from randomization to the first documented local or distant recurrence of RCC or death due to any cause, whichever occurred first.[2]

IV = intravenous; M0 = no distant metastasis; M1 = distant metastasis; N0 = no regional lymph node metastasis; N1 = metastasis in regional lymph node(s); NED = no evidence of disease; pT = pathological primary tumor; Q3W = every 3 weeks; 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. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1, 2, and 4–7, and the accompanying Prescribing Information.

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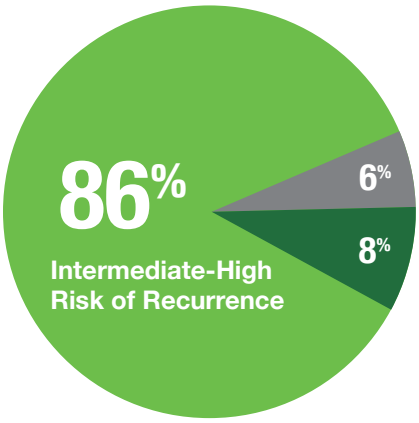
KEYNOTE-564: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial[2] *(continued)*

Study Population Characteristics



- **Median age:** 60 years (range: 25 to 84 years), 33% aged 65 years or older
- **Male:** 71%
- **ECOG PS of 0:** 85%; **ECOG PS of 1:** 15%
- **N0:** 94%
- **Sarcomatoid features:** 11%
- **Radical nephrectomy:** 92%
- **Partial nephrectomy:** 8%
- **Patients with T3 tumors[3,a]:** 89%

[a]90% (n=444/496) in the KEYTRUDA group; 88% (n=437/498) in the placebo group.[3]

ECOG PS = Eastern Cooperative Oncology Group performance status; M1 = distant metastasis; N0 = no regional lymph node metastasis; NED = no evidence of disease.

Learn more about KEYNOTE-564 at keytrudahcp.com.

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.

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.

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KEYTRUDA® (pembrolizumab) Injection 100 mg

SELECTED SAFETY INFORMATION *(continued)*

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

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

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

Hypophysitis

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

Thyroid Disorders

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

- Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). It led to permanent discontinuation of KEYTRUDA in <0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

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.

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.

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

SELECTED SAFETY INFORMATION *(continued)*

Increased Mortality in Patients With Multiple Myeloma

- In trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with an anti–PD-1/PD-L1 treatment in this combination is not recommended outside of controlled trials.

Embryofetal Toxicity

- Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA and advise them to use effective contraception during treatment and for 4 months after the last dose.

Adverse Reactions

- In KEYNOTE-564, when KEYTRUDA was administered as a single agent for the adjuvant treatment of renal cell carcinoma, serious adverse reactions occurred in 20% of patients receiving KEYTRUDA; the serious adverse reactions (≥1%) were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis (1% each). Fatal adverse reactions occurred in 0.2% including 1 case of pneumonia. Discontinuation of KEYTRUDA due to adverse reactions occurred in 21% of 488 patients; the most common (≥1%) were increased ALT (1.6%), colitis (1%), and adrenal insufficiency (1%). The most common adverse reactions (≥20%) were musculoskeletal pain (41%), fatigue (40%), rash (30%), diarrhea (27%), pruritus (23%), and hypothyroidism (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 last dose.

ALT = alanine aminotransferase; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1–6, and the accompanying Prescribing Information. The Medication Guide also is available.

For additional copies of the Prescribing Information, please call 800-672-6372, visit keytrudahcp.com, or contact your Merck representative.

References: 1. Rini BI, McKiernan JM, Chang SS, et al. Kidney. In: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Springer International Publishing; 2017:739–748. **2.** Choueiri TK, Tomczak P, Park SH, et al; for the KEYNOTE-564 investigators. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med*. 2021;385(8):683–694. **3.** Powles T, Tomczak P, Park SH, et al; for the KEYNOTE-564 investigators. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2022;23(9):1133–1144.

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