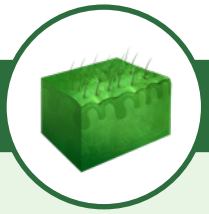
UNDERSTANDING THE END POINTS AND STUDY DESIGNS IN CLINICAL TRIALS EVALUATING *KEYTRUDA*® (pembrolizumab) IN THE NEOADJUVANT AND ADJUVANT SETTINGS OR ADJUVANT SETTING

A clinical end point is a characteristic or variable that directly measures a therapeutic effect of a drug.[1] Clinical trials are designed with end points appropriate to measure an effect in a particular context – for example, in the context of neoadjuvant and adjuvant therapy.[2]

Indications for KEYTRUDA in the neoadjuvant and adjuvant settings or adjuvant setting

Please note that the information included is not a complete review of the clinical data for each of the KEYNOTE trials listed. To learn more about the clinical data associated with the indications and KEYNOTE clinical trials noted on the following pages, please visit **keytrudahcp.com**.



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.

Efficacy end points evaluated in KEYNOTE-054

- **Recurrence-free survival (RFS)** – defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurred first.
- **Distant metastasis–free survival (DMFS)** – defined as a spread of tumor to distant organs or distant lymph nodes.

Efficacy end points evaluated in KEYNOTE-716

- **RFS** – defined as the time between the date of randomization and the date of first recurrence (local, in-transit, or regional lymph nodes or distant recurrence) or death, whichever occurred first.
- **DMFS** – defined as a spread of tumor to distant organs or distant lymph nodes.

Go to KEYNOTE-054 Study Design ▶ Go to KEYNOTE-716 Study Design ▶

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, other transplant (including corneal graft) 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 2–4, 6, 8, 9, 11, and 12, and the accompanying Prescribing Information. The Medication Guide also is available.

KEYTRUDA® (pembrolizumab) Injection 100 mg

Indications for KEYTRUDA in the neoadjuvant and adjuvant settings or adjuvant setting *(continued)*

NON–SMALL CELL LUNG CANCER (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.

Efficacy end points evaluated in KEYNOTE-671

- **Overall survival (OS)** – defined as the time from randomization to death from any cause.[3]
- **Event-free survival (EFS)** – defined as the time from randomization to the first occurrence of local progression that precluded the planned surgery, unresectable tumor, progression or recurrence according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), by the investigator's assessment, or death from any cause.[3]
- **Pathological complete response (pCR)** – defined as the absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0) as assessed on the basis of blinded, central examination by a pathologist.[3]
- **Major pathological response (mPR)** – defined as ≤10% viable tumor cells in resected primary tumor and lymph nodes as assessed on the basis of blinded, central examination by a pathologist.[3]

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

Efficacy end points evaluated in KEYNOTE-091

- **Disease-free survival (DFS)** – defined as time from randomization to locoregional or metastatic recurrence assessed per RECIST v1.1 by investigator review, appearance of a second NSCLC primary or other malignancy, or death from any cause, whichever occurred first.[4]
- **OS** – defined as time from randomization to death from any cause.[4]

Go to KEYNOTE-671 Study Design ▶ Go to KEYNOTE-091 Study Design ▶

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

Indications for KEYTRUDA in the neoadjuvant and adjuvant settings or adjuvant setting *(continued)*

RENAL CELL CARCINOMA (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.

Efficacy end points evaluated in KEYNOTE-564

- **Disease-free survival (DFS)** – defined as time to recurrence, metastasis, or death.
- **Overall survival (OS)** – defined as time from randomization to death due to any cause.[5]

Go to KEYNOTE-564 Study Design

SELECTED SAFETY INFORMATION *(continued)*

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

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

Immune-Mediated Pneumonitis

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

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.

NSCLC = non–small cell lung cancer; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; TNBC = triple-negative breast cancer.

Indications for KEYTRUDA in the neoadjuvant and adjuvant settings or adjuvant setting *(continued)*

TRIPLE-NEGATIVE BREAST CANCER (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.

Efficacy end points evaluated in KEYNOTE-522

- **Pathological complete response (pCR)** – defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) as assessed by the blinded local pathologist at the time of definitive surgery.
- **Event-free survival (EFS)** – defined as the time from randomization to the first occurrence of any of the following events: Progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause.
- **Overall survival (OS)** – defined as the time from randomization to death due to any cause.[6]

Go to KEYNOTE-522 Study Design

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.

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

STUDY DESIGNS FOR CLINICAL TRIALS EVALUATING *KEYTRUDA*® (pembrolizumab) IN THE NEOADJUVANT AND ADJUVANT SETTINGS OR ADJUVANT SETTING

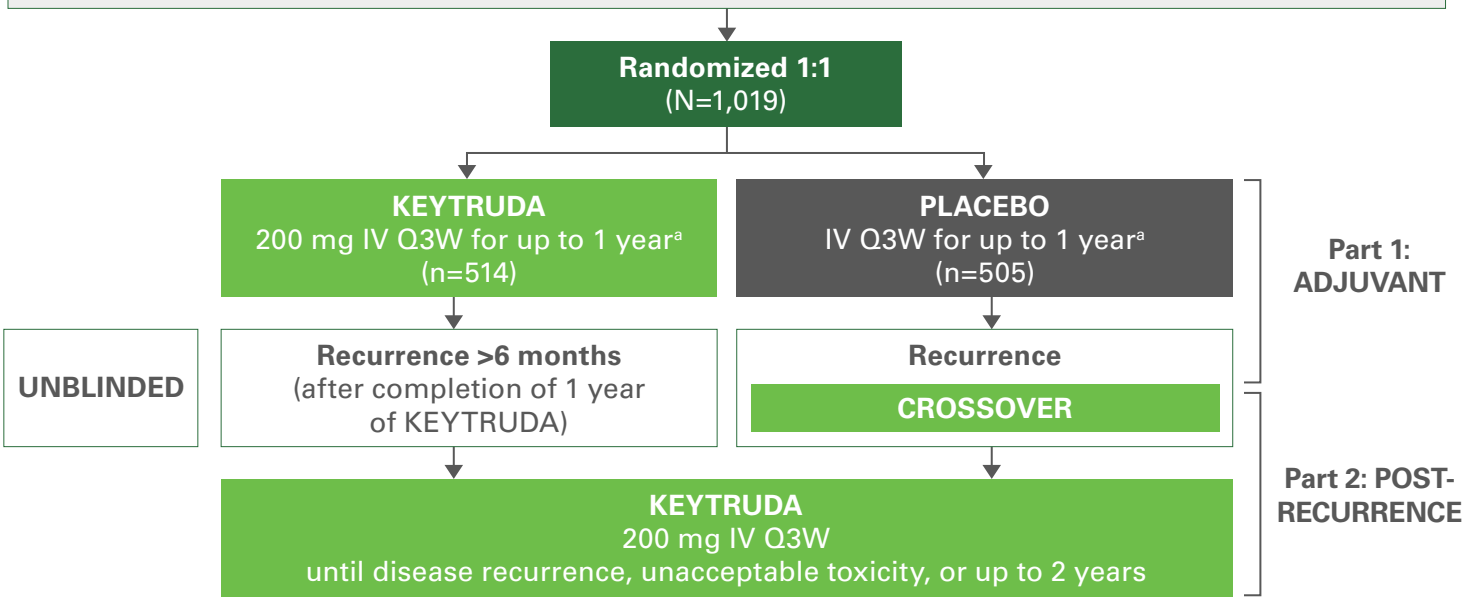
Study Design for KEYNOTE-054[7-9]

Back to KEYNOTE-054 End Points

- KEYNOTE-054 was a multicenter, randomized, double-blind, placebo-controlled trial conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC) that included treatment with KEYTRUDA compared with placebo following complete surgical resection of stage III melanoma, as well as an anti–PD-1 rechallenge crossover design.

Select Eligibility Criteria

- Age ≥18 years
- Completely resected stage IIIA (>1 mm lymph node metastasis), IIIB, or IIIC melanoma (AJCC, 7th ed.)
- PD-L1 expression evaluation
- Lymph node dissection within 13 weeks prior to starting treatment
- Randomization within 13 weeks of surgery
- Radiotherapy within 13 weeks postsurgery, if indicated, prior to starting treatment



Major efficacy outcome measure (primary end point):

- Investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1–positive tumors, where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first.
- New primary melanomas were excluded from the definition of RFS.

Additional efficacy outcome measure (secondary end point):

- The additional efficacy outcome measure was distant metastasis–free survival (DMFS), defined as the time from randomization to the first diagnosis of distant metastasis or date of death (whatever the cause), whichever occurs first.

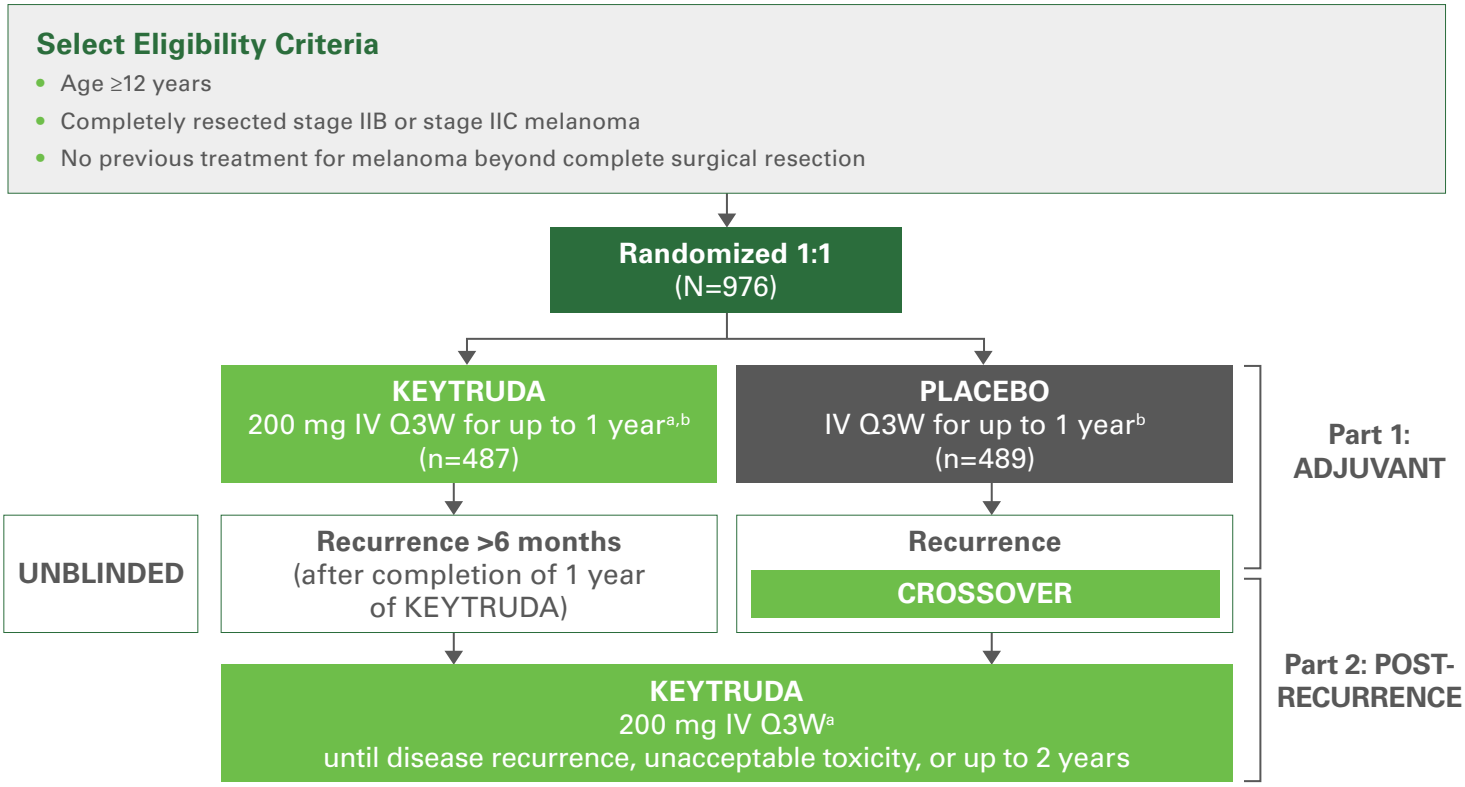
[a]Up to 1 year or until disease recurrence or unacceptable toxicity.

AJCC = American Joint Committee on Cancer; IV = intravenous; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks.

Study Design for KEYNOTE-716[10-12]

Back to KEYNOTE-716 End Points

- KEYNOTE-716 was a multicenter, randomized, double-blind, placebo-controlled trial in patients with completely resected stage IIB or stage IIC melanoma.
- 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).



Major efficacy outcome measure (primary end point):

- The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS), defined as the time between the date of randomization and the date of first recurrence (local, in-transit, or regional lymph nodes, or distant recurrence) or death, whichever occurred first.
- New primary melanomas were excluded from the definition of RFS. 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.

Additional efficacy outcome measure (secondary end point):

- The additional efficacy outcome measure was distant metastasis–free survival (DMFS), defined as the time from randomization to the first diagnosis of distant metastasis per RECIST v1.1. Distant metastasis refers to cancer that has spread from the original (primary) tumor and beyond local tissues and lymph nodes to distant organs or distant lymph nodes.

[a]Or the pediatric (≥12 years old) dose of KEYTRUDA, 2 mg/kg (up to a maximum of 200 mg) IV every 3 weeks. [b]Up to 1 year or until disease recurrence or unacceptable toxicity.
AJCC = American Joint Committee on Cancer; IV = intravenous; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

SELECTED SAFETY INFORMATION *(continued)*

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

Immune-Mediated Endocrinopathies *(continued)*

Thyroid Disorders (continued)

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

Study Design for KEYNOTE-671[3]

Back to KEYNOTE-671 End Points

- KEYNOTE-671 was a randomized, double-blind, multicenter, placebo-controlled, phase 3 study in patients with resectable stage II, IIIA, or IIIB (N2) NSCLC per AJCC, 8th edition.

Key Eligibility Criteria

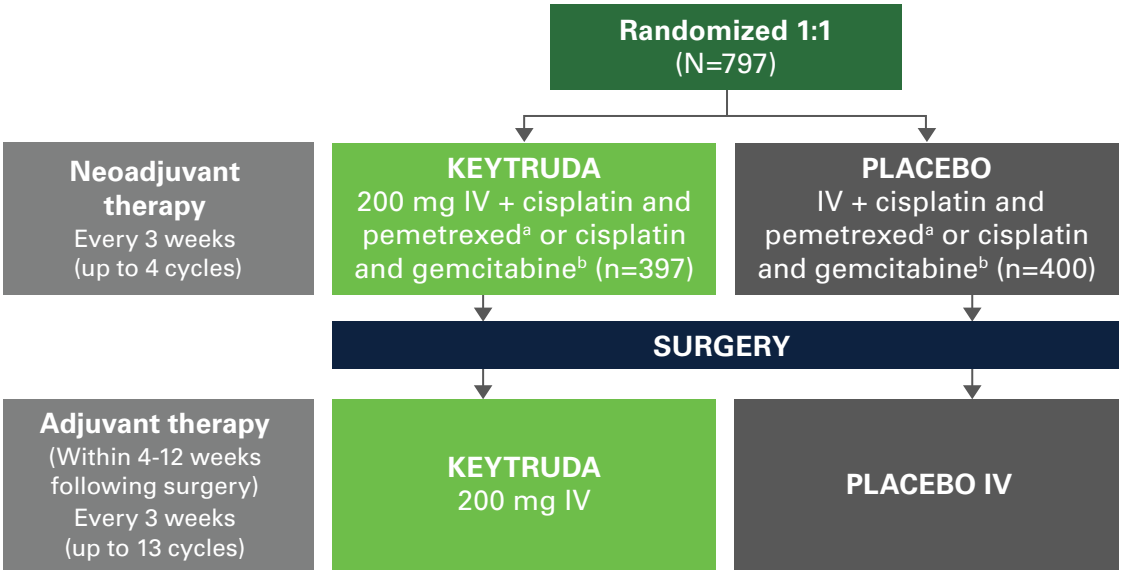
- Patients with previously untreated and resectable stage II, IIIA, or IIIB (N2) NSCLC per AJCC, 8th edition
- Regardless of PD-L1 expression

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 that required steroids

Stratification Factors:

- Stage (II vs III)
- Tumor PD-L1 expression (TPS <50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (East Asia vs non–East Asia)



Treatment continued until either:

- 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
- Unacceptable toxicity

- **Major efficacy outcome measures:** Overall survival (OS) and event-free survival (EFS)[c]
- Additional efficacy outcome measures: Pathological complete response (pCR) rate[d] and major pathological response (mPR) rate[d]

The trial was not designed to isolate the effect of KEYTRUDA in each phase (neoadjuvant or adjuvant) of treatment.

[a]Cisplatin 75 mg/m^2 IV Q3W on day 1 + pemetrexed 500 mg/m^2 IV on day 1 of each 21-day cycle. [b]Cisplatin 75 mg/m^2 IV Q3W on day 1 + gemcitabine 1,000 mg/m^2 IV on days 1 and 8 of each 21-day cycle. [c]Assessed according to investigator review. [d]Assessed by blinded independent pathology review.

AJCC = American Joint Committee on Cancer; IV = intravenous; NSCLC = non–small cell lung cancer; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks; TPS = tumor proportion score.

Study Design for KEYNOTE-091[4]

Back to KEYNOTE-091 End Points

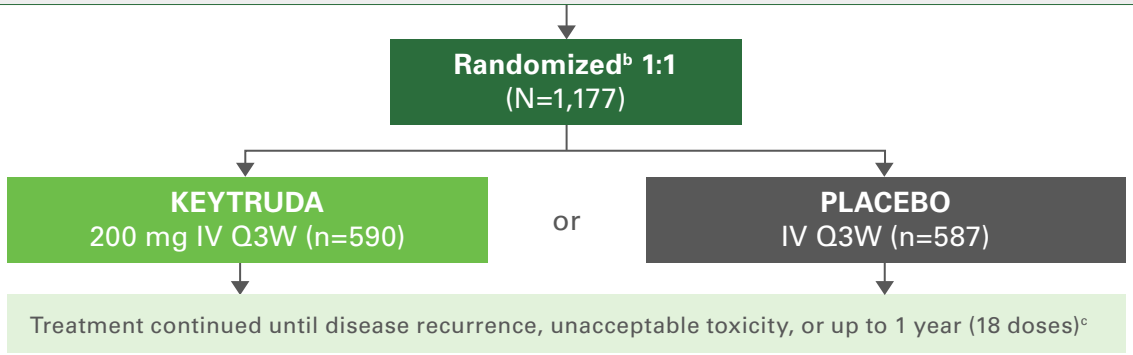
- KEYNOTE-091 was a multicenter, randomized, triple-blind, placebo-controlled trial in patients with resected stage IB (T2a ≥4 cm), II, or IIIA NSCLC.[a]

Key Eligibility Criteria

- Completely resected stage IB (T2a ≥4 cm), II, or IIIA NSCLC per AJCC 7th edition, 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)

Key Exclusion Criteria

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



- **Major efficacy outcome measure:** Disease-free survival (DFS)[d] in the overall population.
- Additional efficacy outcome measure: Overall survival (OS) in the overall population.

[a]As defined per AJCC 7th edition. [b]Randomization was stratified by stage (IB vs II vs IIIA), adjuvant chemotherapy (no adjuvant chemotherapy vs adjuvant chemotherapy), 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). [c]RECIST v1.1–defined disease recurrence as determined by the investigator. [d]DFS was defined as time from randomization to locoregional or metastatic recurrence assessed per RECIST v1.1 by investigator review, appearance of a second NSCLC primary or other malignancy, or death from any cause, whichever occurred first.

AJCC = American Joint Committee on Cancer; IV = intravenous; NSCLC = non–small cell lung cancer; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TPS = tumor proportion score.

SELECTED SAFETY INFORMATION *(continued)*

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

Immune-Mediated Endocrinopathies *(continued)*

Thyroid Disorders (continued)

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.

NSCLC = non–small cell lung cancer.

Study Design for KEYNOTE-564[5,13]

Back to KEYNOTE-564 End Points

- KEYNOTE-564 was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in patients with intermediate-high or high risk of recurrence of RCC post nephrectomy or M1 NED post nephrectomy and resection of metastatic lesions.

Key Eligibility Criteria

- Intermediate-high or high risk of recurrent RCC or M1 NED
- Partial or radical nephrectomy[a] with negative surgical margins ≥4 weeks prior to the time of screening
- No active autoimmune disease or a medical condition that required immunosuppression
- No prior systemic therapy for advanced RCC

Stratification Factors

- Metastasis status (M0, M1 NED)
- Within M0: ECOG PS (0,1), geographic region (US, non-US)

Randomized 1:1
(N=994)

KEYTRUDA
200 mg IV Q3W (n=496)

or

PLACEBO
IV Q3W (n=498)

- Treatment continued for up to 1 year or until disease recurrence or unacceptable toxicity.
- Imaged every 12 weeks for the first year, then every 16 weeks from year 2 to 4, and then every 24 weeks thereafter.

- **Main efficacy outcome measure:** Investigator-assessed disease-free survival (DFS).
- Additional secondary outcome measure: Overall survival (OS).
- Median time from randomization to data cutoff was 24.1 months (range: 14.9 to 41.5).

[a]M1 NED participants had complete resection of solid, isolated, soft tissue metastatic lesion(s).

ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous; M0 = no metastasis; M1 = distant metastasis; NED = no evidence of disease; Q3W = every 3 weeks; RCC = renal cell carcinoma.

SELECTED SAFETY INFORMATION *(continued)*

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

Immune-Mediated Nephritis With Renal Dysfunction

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

Immune-Mediated Dermatologic Adverse Reactions

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

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

Study Design for KEYNOTE-522

Back to KEYNOTE-522 End Points

- KEYNOTE-522 was a randomized, multicenter, double-blind, placebo-controlled trial evaluating the efficacy and safety of KEYTRUDA in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) given as a neoadjuvant treatment and continued as a single agent as adjuvant treatment after surgery, in newly diagnosed, previously untreated, high-risk early-stage TNBC patients.

Key Inclusion Criteria

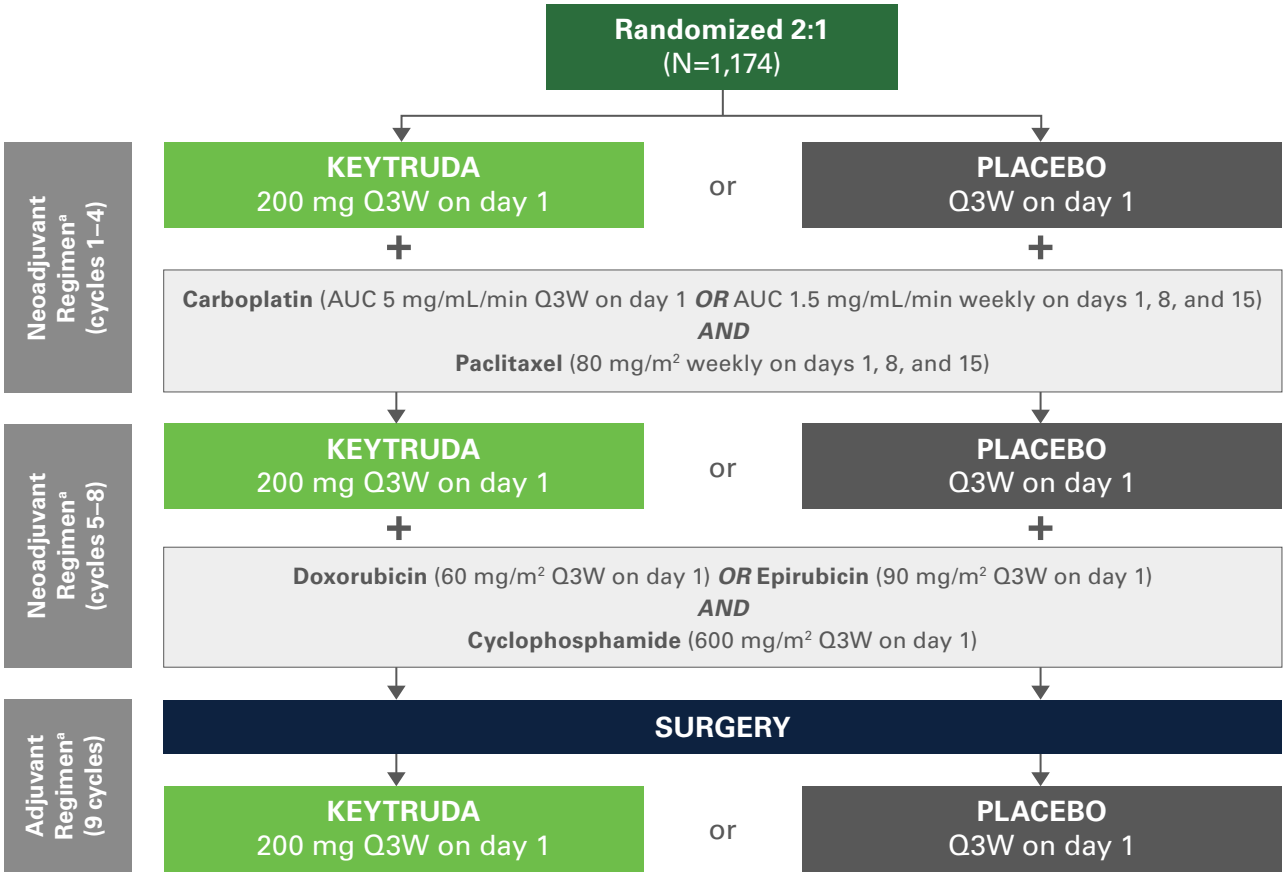
- Patients with newly diagnosed, previously untreated, high-risk early-stage TNBC:
  - Tumor size >1 cm but ≤2 cm in diameter with nodal involvement, or tumor size >2 cm in diameter regardless of nodal involvement
- Patients were enrolled regardless of PD-L1 expression.

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

Stratification Factors

- Nodal status (positive vs negative)
- Tumor size (T1/T2 vs T3/T4)
- Choice of carboplatin (Q3W vs weekly)



- **Main efficacy outcome measures included:** Pathological complete response (pCR) rate[b] and event-free survival (EFS).[c]
- Additional efficacy outcome measure: Overall survival (OS).

[a]All study medications were administered intravenously. [b]pCR (ypT0/Tis ypN0) was defined as absence of invasive cancer in the breast and lymph nodes and was assessed by the blinded local pathologist at the time of definitive surgery. [c]EFS was defined as the time from randomization to the first occurrence of any of the following events: Progression of disease that precluded definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause.

AUC = area under the curve; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks; TNBC = triple-negative breast cancer.

SELECTED SAFETY INFORMATION *(continued)*

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

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, other transplant (including corneal graft) 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.

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-054, when KEYTRUDA was administered as a single agent to patients with stage III melanoma, 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-716, when KEYTRUDA was administered as a single agent to patients with stage IIB or IIC melanoma, adverse reactions occurring in patients with stage IIB or IIC melanoma were similar to those occurring in 1011 patients with stage III melanoma from KEYNOTE-054.
- In KEYNOTE-671, adverse reactions occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as single-agent adjuvant treatment, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.
- The most common adverse reactions (reported in ≥20%) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, and hypothyroidism.
- In the neoadjuvant phase of KEYNOTE-671, when KEYTRUDA was administered in combination with platinum-containing chemotherapy as neoadjuvant treatment, serious adverse reactions occurred in 34% of 396 patients. The most frequent (≥2%) serious adverse reactions were pneumonia (4.8%), venous thromboembolism (3.3%), and anemia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated lung disease (0.3%). Permanent discontinuation of any study drug due to an adverse reaction occurred in 18% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy; the most frequent adverse reactions (≥1%) that led to permanent discontinuation of any study drug were acute kidney injury (1.8%), interstitial lung disease (1.8%), anemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).
- Of the KEYTRUDA-treated patients who received neoadjuvant treatment, 6% of 396 patients did not receive surgery due to adverse reactions. The most frequent (≥1%) adverse reaction that led to cancellation of surgery in the KEYTRUDA arm was interstitial lung disease (1%).
- In the adjuvant phase of KEYNOTE-671, when KEYTRUDA was administered as a single agent as adjuvant treatment, serious adverse reactions occurred in 14% of 290 patients. The most frequent serious adverse reaction was pneumonia (3.4%). One fatal adverse

NSCLC = non–small cell lung cancer; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.

SELECTED SAFETY INFORMATION *(continued)*

Adverse Reactions *(continued)*

reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 12% of patients who received KEYTRUDA as a single agent, given as adjuvant treatment; the most frequent adverse reactions (≥1%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1%), and musculoskeletal pain (1%).

- The most common adverse reactions for KEYTRUDA as a single agent (reported in ≥20% of patients) were fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism.
- Adverse reactions observed in KEYNOTE-091 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). Two fatal adverse reactions of myocarditis occurred.
- 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%).
- In KEYNOTE-522, when KEYTRUDA was administered with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent (n=778) to patients with newly diagnosed, previously untreated, high-risk early-stage TNBC, fatal adverse reactions occurred in 0.9% of patients, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA; those ≥2% were febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%). KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥1%) resulting in permanent discontinuation were increased ALT (2.7%), increased AST (1.5%), and rash (1%). The most common adverse reactions (≥20%) in patients receiving KEYTRUDA were fatigue (70%), nausea (67%), alopecia (61%), rash (52%), constipation (42%), diarrhea and peripheral neuropathy (41% each), stomatitis (34%), vomiting (31%), headache (30%), arthralgia (29%), pyrexia (28%), cough (26%), abdominal pain (24%), decreased appetite (23%), insomnia (21%), and myalgia (20%).

Lactation

- Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the 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 (30%), 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%).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NSCLC = non–small cell lung cancer; TNBC = triple-negative breast cancer.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1–4, 6, 8, 9, and 11, and the accompanying Prescribing Information. The Medication Guide also is available.

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