**Note to Reviewers:**

This resource is annotated to PI (uspi-mk3475-iv-2208r060) and the associated SSI (US-KEY-05642). This job aligns to the parent job US-LAM-02165 and uses lavender boxes to indicate changes from the ADT HCP KN-189 Video NSCLC (US-LAM-02165).

**Gallery:**

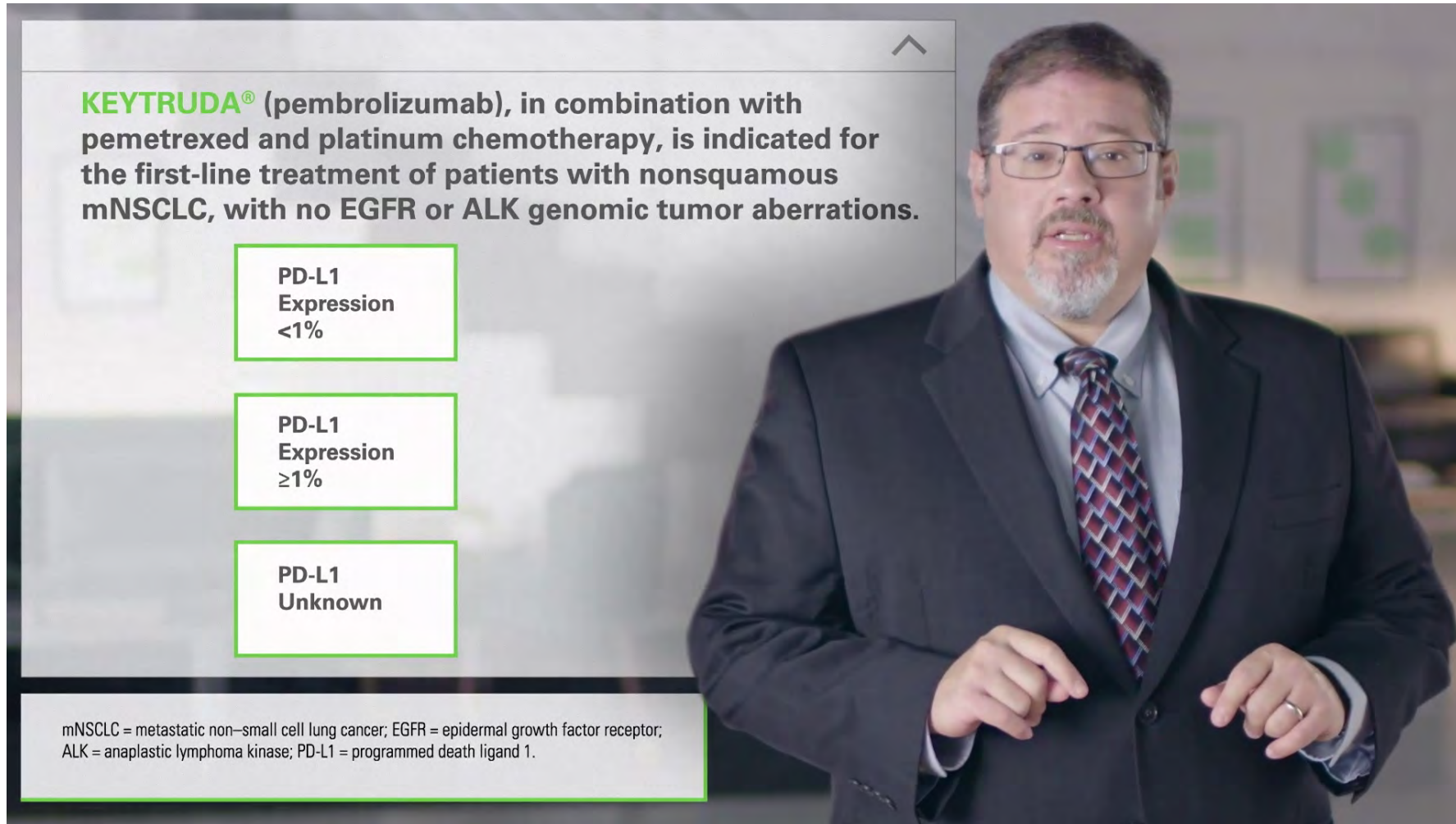
- All associated references (Linked Documents)



**Howard (Jack) West, MD**

**Script**

Treatment options for my patients with metastatic nonsquamous non–small cell lung cancer have increased over the past decade.



**KEYTRUDA®** (pembrolizumab), in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with nonsquamous mNSCLC, with no EGFR or ALK genomic tumor aberrations.

- PD-L1 Expression <1%
- PD-L1 Expression  $\geq$ 1%
- PD-L1 Unknown

mNSCLC = metastatic non–small cell lung cancer; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; PD-L1 = programmed death ligand 1.

### Script

In my practice, an important development for the first-line treatment of nonsquamous metastatic non–small cell lung cancer was the approval of KEYTRUDA in combination with pemetrexed and platinum chemotherapy for patients without EGFR or ALK genomic tumor aberrations, regardless of PD-L1 expression. Before we begin discussing the data for KEYTRUDA, let's take a look at Selected Safety Information.

## KEYTRUDA® (pembrolizumab): 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.

KEYTRUDA can cause **severe or life-threatening infusion-related reactions**, including hypersensitivity and anaphylaxis. Monitor patients 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.

Based on its mechanism of action, KEYTRUDA can cause **fetal harm when administered to a pregnant woman**. Female patients of reproductive potential should be advised of the potential hazard to a fetus.

### Script

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.

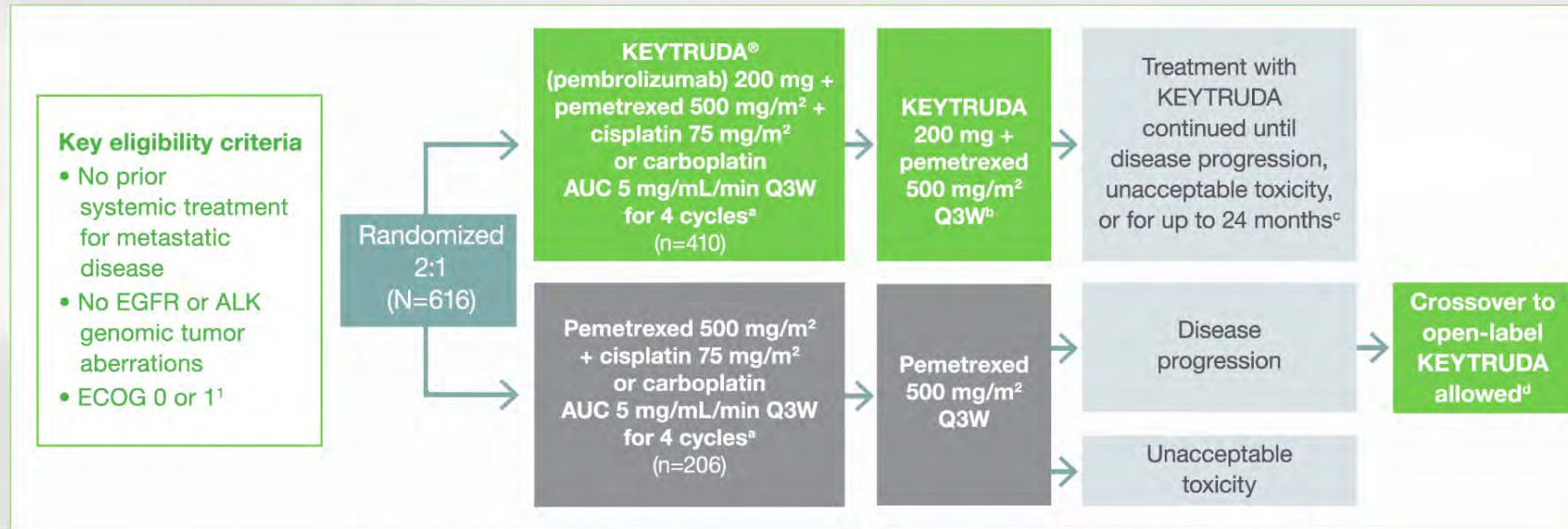
KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis. It can also cause fetal harm when administered to a pregnant woman.



Script

Now let's get into the clinical trial data.

## KEYNOTE-189: Phase 3, randomized, multicenter, double-blind, active-controlled study in patients with nonsquamous mNSCLC, regardless of PD-L1 tumor expression status<sup>1</sup>



<sup>a</sup>All patients received 4 cycles of the investigator's choice of cisplatin 75 mg/m<sup>2</sup> or carboplatin AUC 5 mg/mL/min + pemetrexed 500 mg/m<sup>2</sup>, all administered intravenously Q3W, followed by pemetrexed 500 mg/m<sup>2</sup> Q3W.

<sup>b</sup>KEYTRUDA was given Q3W for up to a total of 35 cycles with pemetrexed maintenance therapy.<sup>1</sup>

<sup>c</sup>Administration of KEYTRUDA was permitted beyond RECIST v1.1-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.

<sup>d</sup>Patients in the plat/pem-alone group who had disease progression verified by BICR could cross over to receive KEYTRUDA as monotherapy.<sup>1</sup>

AUC = area under the curve; BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; plat/pem = (cisplatin or carboplatin) and pemetrexed; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors version 1.1.

**Reference: 1.** Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; for the KEYNOTE-189 investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med.* 2018;378(22):2078–2092.

## Script

KEYTRUDA was evaluated in KEYNOTE-189—a randomized trial in patients with nonsquamous metastatic non-small cell lung cancer who had no prior systemic treatment for metastatic disease, no EGFR or ALK genomic tumor aberrations, and an ECOG performance status of 0 or 1. The trial compared KEYTRUDA plus a platinum agent and pemetrexed, which we will abbreviate as KEYTRUDA plus plat/pem in this video, vs plat/pem alone.

Patients who progressed on plat/pem alone could cross over to open-label KEYTRUDA as monotherapy. Take a moment to review the study design for KEYNOTE-189.

- **Primary efficacy outcome measures: OS and PFS, assessed by BICR per RECIST v1.1, with allowance of a maximum of 10 target lesions and a maximum of 5 target lesions per organ.<sup>1</sup>**
- Secondary efficacy outcome measures: ORR and DOR as assessed by BICR per RECIST v1.1, with allowance of a maximum of 10 target lesions and a maximum of 5 target lesions per organ.<sup>1</sup>
- Patients were stratified by tumor PD-L1 status (TPS <1%; TPS ≥1%), cisplatin or carboplatin, and smoking history.
- Patients with an autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or patients who had received more than 30 Gy of thoracic radiation within 6 months were ineligible.

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; DOR = duration of response; TPS = tumor proportion score.

**Reference 1.** Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; for the KEYNOTE-189 investigators. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med.* 2018;378(22):2078–2092.

## Script

The primary efficacy outcome measures were overall survival and progression-free survival. Secondary efficacy outcome measures were objective response rate and duration of response. As specified on the slide, patients who required systemic therapy due to an autoimmune disease, who required immunosuppression, or who received certain doses of thoracic radiation were ineligible.

IN THE FIRST-LINE TREATMENT OF NONSQUAMOUS mNSCLC WITH NO EGFR OR ALK GENOMIC TUMOR ABERRATIONS

## DURABLE OVERALL SURVIVAL WITH KEYTRUDA® (pembrolizumab) + PLAT/PEM VS PLAT/PEM ALONE

Superior Overall Survival With KEYTRUDA + Plat/pem vs Plat/pem Alone at Initial Analysis  
(median follow-up time: 10.5 months)<sup>1</sup>

**51%** REDUCTION IN THE RISK OF DEATH with KEYTRUDA + plat/pem vs plat/pem alone  
(HR=0.49; 95% CI, 0.38–0.64;  $P<0.0001$ )<sup>a</sup>

- Events observed: 31% (127/410) with KEYTRUDA + plat/pem and 52% (108/206) with plat/pem alone
- **Median OS was not reached:** (95% CI, NR–NR) with KEYTRUDA + plat/pem vs 11.3 months (95% CI, 8.7–15.1) with plat/pem alone

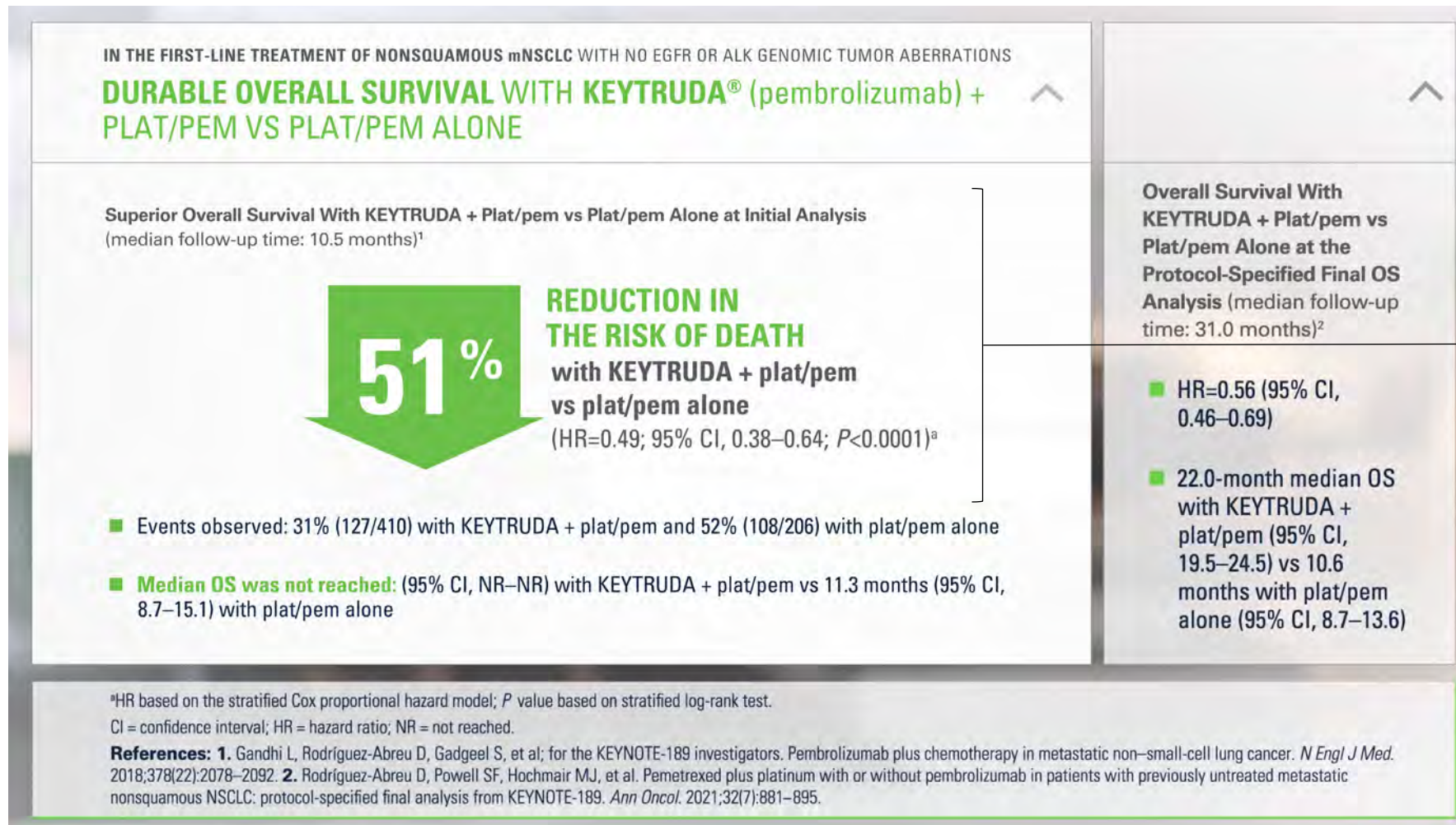
<sup>a</sup>HR based on the stratified Cox proportional hazard model;  $P$  value based on stratified log-rank test.  
CI = confidence interval; HR = hazard ratio; NR = not reached.

**References:** 1. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; for the KEYNOTE-189 investigators. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med.* 2018;378(22):2078–2092. 2. Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Oncol.* 2021;32(7):881–895.

Calc (risk reduction):  $(1 - 0.49) \times 100 = 51\%$

### Script

In KEYNOTE-189, durable overall survival was observed with KEYTRUDA plus plat/pem vs plat/pem alone. At initial analysis, which had a median follow-up time of 10.5 months, superior overall survival was observed with KEYTRUDA plus plat/pem vs plat/pem alone as the risk of death was reduced by half. The percentage of patients with an event was 31% with KEYTRUDA plus plat/pem vs 52% with plat/pem alone.



## Script

At protocol-specified final overall survival analysis, which had a median follow-up time of 31.0 months, median overall survival with KEYTRUDA plus plat/pem was 22.0 months vs 10.6 months with plat/pem alone.

As a reminder, these overall survival data included both nonexpressers and expressers of PD-L1.

IN THE FIRST-LINE TREATMENT OF NONSQUAMOUS mNSCLC WITH NO EGFR OR ALK GENOMIC TUMOR ABERRATIONS  
**EXPLORATORY ANALYSIS (MEDIAN FOLLOW-UP TIME: 64.6 MONTHS)<sup>1</sup>**  
 Overall Survival, Regardless of PD-L1 Expression



- 22-month median OS with KEYTRUDA + plat/pem (95% CI, 19.5–24.5) and 10.6 months with plat/pem alone (9)
- Events observed: 80.2% (329/410) with KEYTRUDA + plat/pem and 88.8% (183/206) with plat/pem alone<sup>1</sup>

**LIMITATION:** This post hoc analysis (median follow-up time: 64.6 months) in KEYNOTE-189 was exploratory in nature and occurred after the protocol-specified final analysis. No formal statistical testing was planned for this analysis and, therefore, no statistical conclusions can be drawn. Trial participants in either study arm could receive subsequent anti-cancer therapy.<sup>1</sup>

**CROSSOVER RATE:** 57.3% (118/206) of patients crossed over from plat/pem to anti-PD-(L)1 therapy on (n=84) or off (n=34) study.<sup>1,a</sup>

<sup>a</sup>Some patients received >1 subsequent anti-PD-(L)1 therapy.

**Reference:** 1. Data available on request from Merck & Co., Inc., Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package US-LAM-02720.

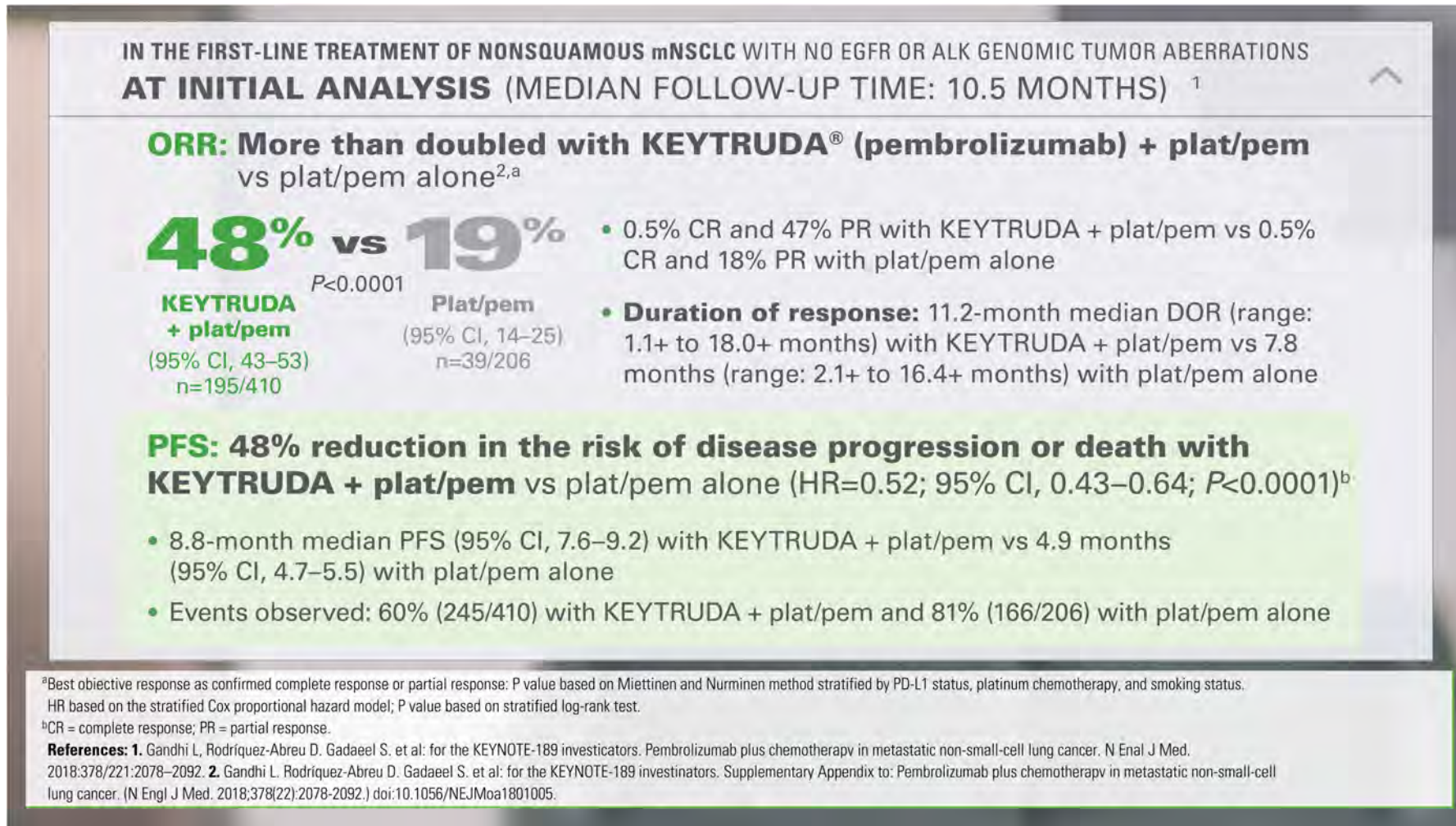
**Note to PRT:**

Content for 5-year OS data was added and is in alignment with US-LAM-02720 and presentation in US-LAM-02165.

## Script

In an exploratory post-hoc analysis of KEYNOTE-189 that included 5 years of follow-up, the overall survival rate at years 1, 2, 3, 4, and 5, respectively, was 70%, 46%, 31%, 24%, and 19% with KEYTRUDA plus plat/pem and 48%, 27%, 17%, 14%, and 11% with plat/pem alone. The median overall survival for patients was 22.0 months with KEYTRUDA plus plat/pem and 10.6 months with plat/pem alone. As a reminder, these overall survival data included both nonexpressers and expressers of PD-L1.

A limitation of this post-hoc analysis is that it was exploratory in nature and was based on an extended follow-up, which had a median of 64.6 months. No formal statistical testing was planned for this analysis and, therefore, no statistical conclusions can be drawn. **Trial participants in either study arm should receive subsequent anti-cancer therapy. The rate of patients who crossed over from plat/pem to anti-PD-(L)1 therapy on or off study was 57.3%.**



## Script

Shown are the results for objective response rate and progression-free survival **at initial analysis with median follow up time 10.5 months**, both of which showed the superiority of KEYTRUDA plus plat/pem vs plat/pem alone.

Median duration of response was also measured and showed 11.2 months for KEYTRUDA plus plat/pem vs 7.8 months for plat/pem alone.

Please take a moment to look at the results for these end points.

## Safety Profile

### Treatment Discontinuation

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%).

### Treatment Interruption

Adverse reactions leading to interruption of KEYTRUDA occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), thrombocytopenia (5%), diarrhea (4%), pneumonia (4%), increased blood creatinine (3%), dyspnea (2%), febrile neutropenia (2%), upper respiratory tract infection (2%), increased ALT (2%), and pyrexia (2%).

ALT = alanine aminotransferase.

**KEYTRUDA**  
(pembrolizumab) injection 100mg

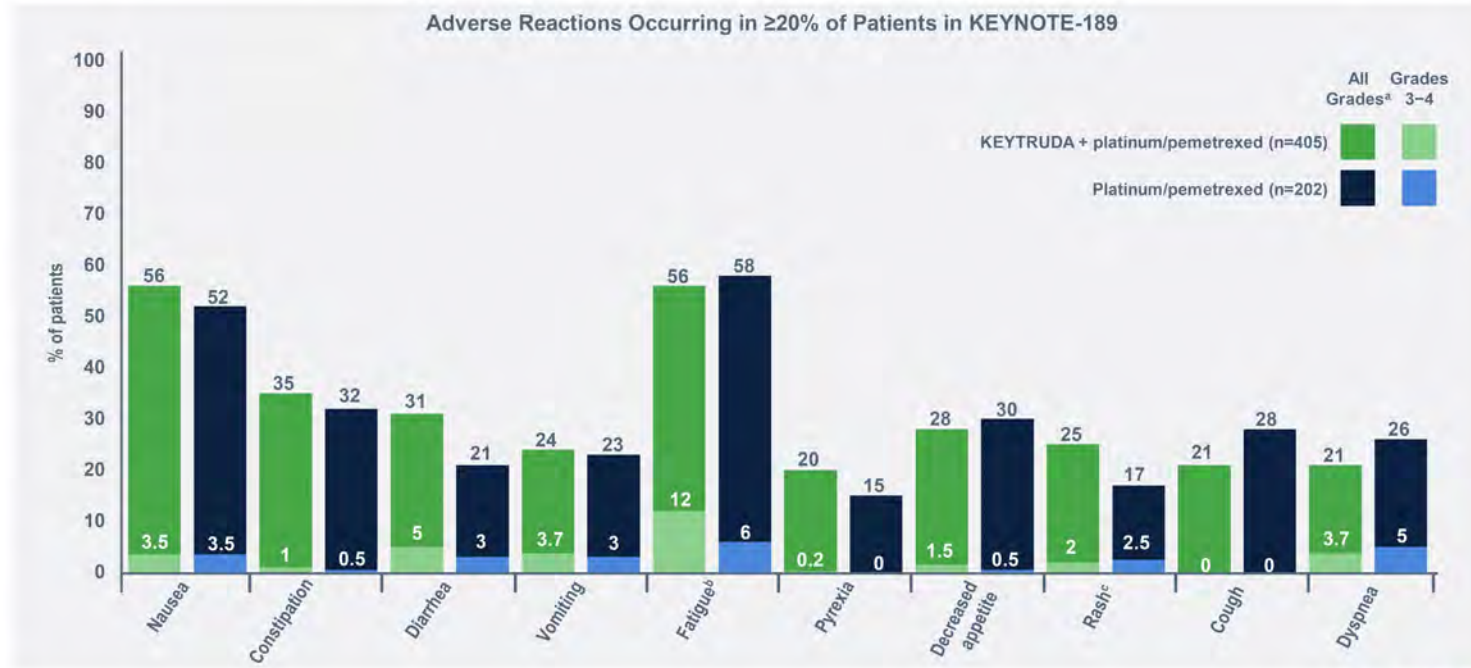
## Script

In KEYNOTE 189, KEYTRUDA was discontinued for adverse reactions in 20% of patients.

The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis and acute kidney injury.

Adverse reactions leading to the interruption of KEYTRUDA occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were as follows: neutropenia, fatigue/asthenia, anemia, thrombocytopenia, diarrhea, pneumonia, increased blood creatinine, dyspnea, febrile neutropenia, upper respiratory tract infection, increased ALT, and pyrexia.

## Safety Profile



Graded per NCI-CTCAE v4.03. <sup>a</sup>Includes asthenia and fatigue. <sup>b</sup>Includes genital rash, rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.  
 NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

**KEYTRUDA**  
 (pembrolizumab) INJECTION 100mg

Added a period at the end of the abbreviation.

## Script

This graph summarizes the adverse reactions that occurred in at least 20% of patients treated with KEYTRUDA and platinum/pemetrexed, which included: nausea, constipation, diarrhea, vomiting, fatigue/asthenia, pyrexia, decreased appetite, rash, cough, and dyspnea.

Please take a moment to review this information.



Script

Let's continue to review the safety profile of KEYTRUDA.

## KEYTRUDA® (pembrolizumab): 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.

### Note to PRT:

- Common Content and corresponding annotations have been globally updated to US-KEY-05680.

## Script

KEYTRUDA belongs to a class of drugs that potentially induces immune-mediated adverse reactions. These 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 any time after starting treatment, including after discontinuation. 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. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. If immune-mediated adverse reactions are suspected, exclude alternative etiologies and institute medical management promptly.

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 as indicated on the screen. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

## KEYTRUDA® (pembrolizumab): INCIDENCE OF SELECTED IMMUNE-MEDIATED ADVERSE REACTIONS

Adverse Reaction	KEYTRUDA (N=2,799)				
	All Grades % (n)	Grade 2 %	Grade 3 %	Grade 4 %	Fatal %
Pneumonitis	3.4 (94)	1.3	0.9	0.3	0.1
Colitis	1.7 (48)	0.4	1.1	<0.1	—
Hepatitis	0.7 (19)	0.1	0.4	<0.1	—
Adrenal insufficiency	0.8 (22)	0.3	0.3	<0.1	—
Hypophysitis	0.6 (17)	0.2	0.3	<0.1	—
Hyperthyroidism	3.4 (96)	0.8	0.1	—	—
Hypothyroidism	8 (237)	6.2	0.1	—	—
Nephritis	0.3 (9)	0.1	0.1	<0.1	—
Dermatologic adverse reactions	1.4 (38)	0.1	1	—	—

- The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.
- Of 2,799 patients receiving KEYTRUDA, thyroiditis occurred in 16 (0.6%) patients, including Grade 2 (0.3%), and type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 6 (0.2%) patients.

### Script

This screen gives an overview of selected immune-mediated adverse reactions associated with KEYTRUDA. These include pneumonitis, colitis, hepatitis, adrenal insufficiency, hypophysitis, hyperthyroidism, nephritis, dermatologic reactions, thyroiditis, type 1 diabetes mellitus (which can present with diabetic ketoacidosis), and, most commonly, hypothyroidism. This table shows the incidence of selected immune-mediated adverse reactions by overall incidence and Grades 2, 3, 4, and 5.

It is important to note that the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Please take a moment to review the information on the screen.

## KEYTRUDA® (pembrolizumab): MANAGEMENT OF SELECTED IMMUNE-MEDIATED ADVERSE REACTIONS

Adverse Reaction	KEYTRUDA (N=2,799)		Systemic Corticosteroids Required, % (n/N)	Resolution Rate
	Permanently Discontinued, % (n)	Withheld, % (n)		
Pneumonitis	1.3 (36)	0.9 (26)	67 (63/94)	59% of 94
Colitis	0.5 (15)	0.5 (13)	69 (33/48)	85% of 48
Hepatitis	0.2 (6)	0.3 (9)	68 (13/19)	79% of 19
Adrenal insufficiency	<0.1 (1)	0.3 (8)	77 (17/22)	—
Hypophysitis	0.1 (4)	0.3 (7)	94 (16/17)	—
Thyroiditis	0	<0.1 (1)	—	—
Hyperthyroidism	<0.1 (2)	0.3 (7)	—	—
Hypothyroidism	<0.1 (1)	0.5 (14)	—	—
Type 1 diabetes mellitus	<0.1 (1)	<0.1 (1)	—	—
Nephritis	0.1 (3)	0.1 (3)	89 (8/9)	56% of 9
Dermatologic adverse reactions	0.1 (2)	0.6 (16)	40 (15/38)	79% of 38

- Additional immunosuppressant therapy was required in 4.2% of patients with colitis and in 11% of patients with hepatitis.
- Of those with adrenal insufficiency or hypophysitis who required systemic corticosteroids, the majority of patients remained on systemic corticosteroids.
- The majority of patients with hypothyroidism required long-term thyroid hormone replacement.
- All patients with type 1 diabetes mellitus required long-term insulin therapy.
- All patients who were withheld<sup>a</sup> reinitiated KEYTRUDA after symptom improvement; of those:
  - 23% had recurrence of pneumonitis or colitis.
  - None had recurrence of hepatitis or nephritis.
  - 6% had recurrence of dermatologic adverse reactions.

<sup>a</sup>This is applicable to all patients who were withheld KEYTRUDA due to the immune-mediated adverse reactions presented, except thyroiditis.

### Script

This screen shows how the selected immune-mediated adverse reactions associated with KEYTRUDA observed in clinical trials were managed. This includes the percentage of patients whose adverse reaction led to permanent discontinuation of treatment, treatment being withheld, systemic corticosteroid administration, and the resolution of the selected immune-mediated adverse reactions.

Additional immunosuppressant therapy was required in 4.2% of patients with colitis and in 11% of patients with hepatitis.

Of those with adrenal insufficiency or hypophysitis who required systemic corticosteroids, the majority of patients remained on systemic corticosteroids.

The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

All patients with type 1 diabetes mellitus required long-term insulin therapy.

This screen also shows information about patients who were withheld and reinitiated KEYTRUDA.

Please take a moment to review this information.

## KEYTRUDA® (pembrolizumab): SELECTED IMMUNE-MEDIATED AND OTHER 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.
- 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

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

### Script

Importantly, 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.

Additional clinically significant immune-mediated adverse reactions, which 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, are presented on the screen for your review. Severe or fatal cases have been reported for some of these adverse reactions.

**KEYTRUDA® (pembrolizumab):**  
**SELECTED IMMUNE-MEDIATED AND OTHER ADVERSE REACTIONS (CONTINUED)**

- KEYTRUDA can cause **severe or life-threatening infusion-related reactions**, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2,799 patients.
- **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 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.
- 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.

GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; PD-1 = programmed death receptor-1;  
PD-L1 = programmed death ligand 1.

**Script**

KEYTRUDA can also cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis.

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 GVHD, acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause).

It's also important to note that, in multiple myeloma, treatment of patients with an anti-PD-1/PD-L1 treatment in combination with a thalidomide analogue and dexamethasone is not recommended.

**KEYTRUDA® (pembrolizumab):**  
**MONITORING AND MANAGEMENT OF 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.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (eg, endocrinopathies and dermatologic reactions) are discussed on the following slides.

Additional monitoring and management considerations for selected immune-mediated adverse reactions are also discussed.

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

### Script

KEYTRUDA is associated with immune-mediated adverse reactions, which may be severe or fatal. Early identification and management of such reactions are essential to ensure safe use of KEYTRUDA. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. If immune-mediated adverse reactions are suspected, exclude alternative etiologies and institute medical management promptly.

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 as indicated on the screen. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (eg, endocrinopathies and dermatologic reactions) are discussed on the following screens.

Additional monitoring and management considerations for selected immune-mediated adverse reactions are also discussed.

**KEYTRUDA® (pembrolizumab):****MONITORING AND MANAGEMENT OF SELECT IMMUNE-MEDIATED ADVERSE REACTIONS****Adverse Reaction****Monitoring and Management of Patients****Colitis**

- Colitis may present with diarrhea.
- CMV 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.

CMV = cytomegalovirus.

**Script**

Now let's review specific considerations for monitoring and managing certain immune-mediated adverse reactions.

Immune-mediated colitis may present with diarrhea. In patients with corticosteroid-refractory immune-mediated colitis, CMV infection/reactivation has been reported. Consider repeating infectious workup in these patients to exclude alternative etiologies.

**KEYTRUDA® (pembrolizumab):****MONITORING AND MANAGEMENT OF SELECT IMMUNE-MEDIATED ADVERSE REACTIONS (CONTINUED)**

Adverse Reaction	Monitoring and Management of Patients
<b>Endocrinopathies</b>	
<b>Adrenal insufficiency</b>	<ul style="list-style-type: none"> <li>■ KEYTRUDA can cause primary or secondary adrenal insufficiency.</li> <li>■ For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity.</li> </ul>
<b>Hypophysitis</b>	<ul style="list-style-type: none"> <li>■ Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects.</li> <li>■ Hypophysitis can cause hypopituitarism.</li> <li>■ Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity.</li> </ul>
<b>Thyroid disorders</b>	<ul style="list-style-type: none"> <li>■ Thyroiditis can present with or without endocrinopathy.</li> <li>■ Hypothyroidism can follow hyperthyroidism.</li> <li>■ Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity.</li> </ul>
<b>Type 1 diabetes mellitus</b>	<ul style="list-style-type: none"> <li>■ Type 1 diabetes mellitus can present with diabetic ketoacidosis.</li> <li>■ Monitor patients for hyperglycemia or other signs and symptoms of diabetes.</li> <li>■ Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity.</li> </ul>

**Script**

Monitoring and management considerations for patients with immune-mediated endocrinopathies are shown here.

KEYTRUDA can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity.

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.

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.

Type 1 diabetes mellitus 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.

**KEYTRUDA® (pembrolizumab):****MONITORING AND MANAGEMENT OF SELECT IMMUNE-MEDIATED ADVERSE REACTIONS (CONTINUED)**

Adverse Reaction	Monitoring and Management of Patients
<b>Dermatologic adverse reactions</b>	<ul style="list-style-type: none"><li>■ Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity.</li></ul>
<b>Other immune-mediated adverse reactions</b> <i>Ocular</i>	<ul style="list-style-type: none"><li>■ Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment.</li><li>■ Various grades of visual impairment, including blindness, can occur.</li><li>■ 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.</li></ul>

**Script**

Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity.

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.

**KEYTRUDA® (pembrolizumab):  
INFUSION-RELATED REACTIONS****Adverse Reaction****Monitoring and Management of Patients****Infusion-related reactions**

- Monitor for signs and symptoms of infusion-related reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.
- For Grade 1 or Grade 2 reactions, interrupt or slow the rate of infusion.
- For Grade 3 or Grade 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

**Script**

Monitor patients 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.

**KEYTRUDA® (pembrolizumab):**  
**COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)**

### Allogeneic HSCT before or after anti-PD-1/PD-L1 treatments

#### Monitoring Patients

- Follow patients closely for evidence of transplant-related complications such as hyperacute GVHD, acute and chronic GVHD, hepatic VOD, and steroid-requiring febrile syndrome.

#### Management of Patients

- Intervene promptly.

- Consider the benefit vs risks of using anti-PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.

GVHD = graft-versus-host disease; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; VOD = veno-occlusive disease.

#### Script

Patients who receive an allogeneic hematopoietic stem cell transplant before or after anti-PD-1/PD-L1 treatments should be followed closely for evidence of transplant-related complications.

Consider the benefit vs risks of using anti-PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.

## KEYTRUDA® (pembrolizumab): USE IN SPECIFIC POPULATIONS

### Pregnancy

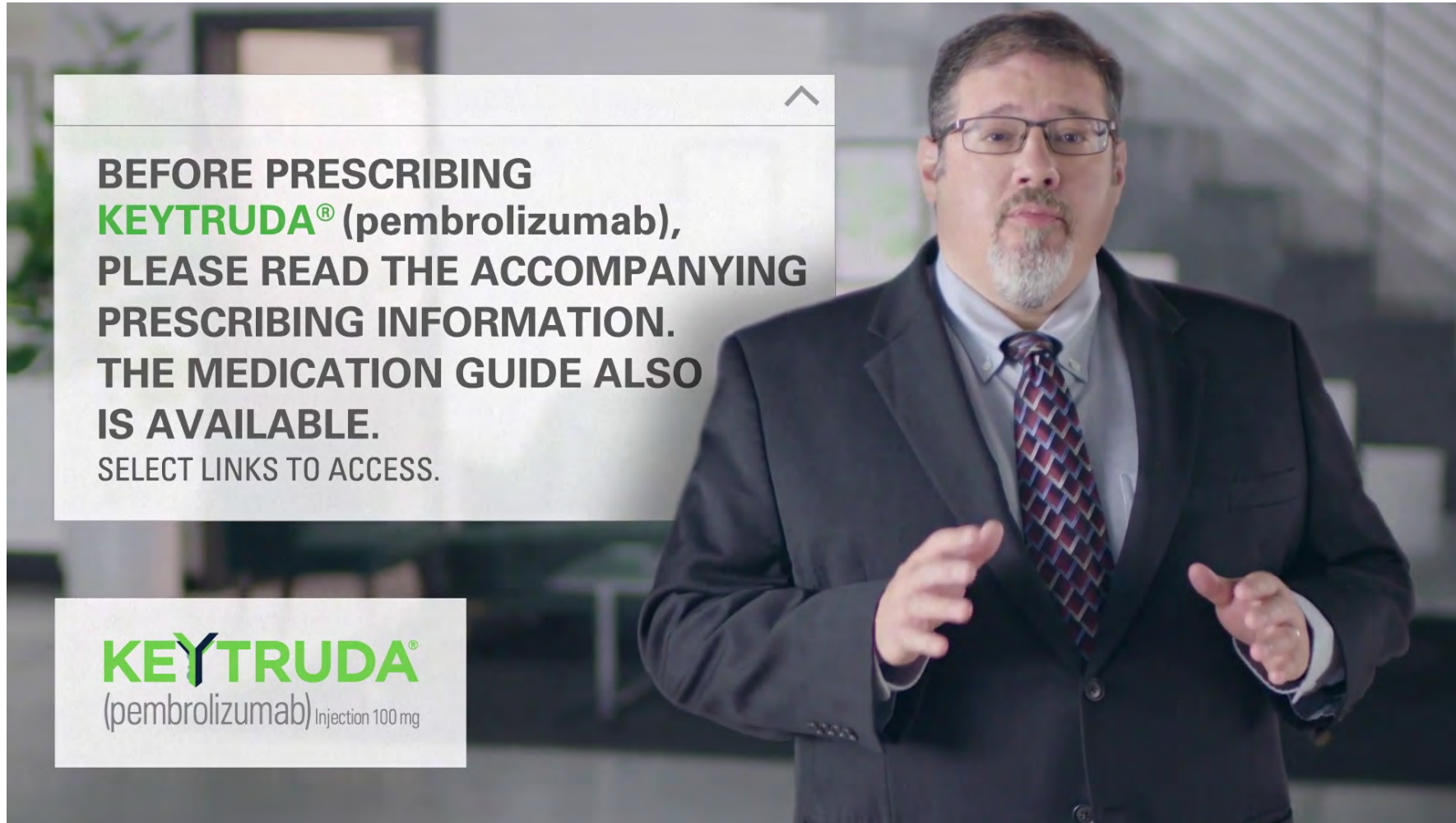
- Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA and advise them to use effective contraception during treatment and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

### Lactation

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

### Script

It is important to know that KEYTRUDA can cause harm to a fetus if administered to a pregnant woman. Patients of reproductive potential should be advised to use effective contraception and not to breastfeed during treatment and for 4 months after the final dose.

A man with glasses and a goatee, wearing a dark suit, light blue shirt, and patterned tie, is speaking and gesturing with his hands. He is positioned in the center-right of the frame. On the left side, there is a white text box with a grey background and a small upward-pointing arrow in the top right corner. Below this text box is a white box containing the KEYTRUDA logo and product information. The background is a blurred office setting.

**BEFORE PRESCRIBING  
KEYTRUDA® (pembrolizumab),  
PLEASE READ THE ACCOMPANYING  
PRESCRIBING INFORMATION.  
THE MEDICATION GUIDE ALSO  
IS AVAILABLE.  
SELECT LINKS TO ACCESS.**

**KEYTRUDA®**  
(pembrolizumab) Injection 100 mg

## Script

For more details and before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

**KEYTRUDA**<sup>®</sup>  
(pembrolizumab) Injection 100 mg



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Updated job number and copywrite text to align to current guidance.