USING KEYTRUDA®

A guide to **monitoring and managing adverse reactions during treatment** with **KEYTRUDA®**

PrKEYTRUDA® (pembrolizumab)

Clinically significant immune-mediated adverse reactions can occur during treatment with PrKEYTRUDA® (pembrolizumab). This guide provides important information about monitoring patients for adverse reactions. It also includes recommendations for managing potential immune-mediated adverse reactions.

INDICATIONS

KEYTRUDA® is indicated for:

Treatment of adult patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

Treatment of adult patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor.

First-line treatment, as monotherapy, of adult patients with metastatic NSCLC or Stage III disease where patients are not candidates for surgical resection or definitive chemoradiation, expressing PD-L1 (TPS ≥1%) as determined by a validated test, with no EGFR or ALK genomic tumour aberrations. A positive association was observed between the level of PD-L1 expression and the magnitude of the treatment benefit.

Treatment of adult patients with metastatic NSCLC as monotherapy, whose tumours express PD-L1 (TPS ≥1%) as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung carcinoma; PD-L1=programmed cell death ligand 1; TPS=Tumour Proportion Score

DOSING

Dosing schedules

Dose	Indication	Administered intravenously
200 mg or 400 mg	**Previously untreated metastatic NSCLC** (TPS ≥1%)	Over 30 minutes every 3 weeks (200 mg) or every 6 weeks (400 mg) until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg in patients without disease progression†
	Previously treated metastatic NSCLC (TPS ≥1%)	Over 30 minutes every 3 weeks (200 mg) or every 6 weeks (400 mg) until disease progression or unacceptable toxicity†
	Unresectable or metastatic melanoma	

† See the Product Monograph for complete dosing, dosing adjustments and administration recommendations.

- Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA® with close monitoring; premedication with antipyretic and antihistamine may be considered.
- For severe or life-threatening infusion reactions (Grade ≥3), stop infusion and permanently discontinue KEYTRUDA®.
- Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression may remain on treatment until disease progression is confirmed.

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MONITOR FOR ADVERSE REACTIONS

Immune-mediated adverse reaction overview

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA® and consider administration of corticosteroids. Please refer to pages 8-11 for recommendations on managing adverse reactions by grade.[1]

Adverse reaction	Monitoring patients	Ask patients to immediately report
Immune-mediated pneumonitis	• Monitor patients for signs and symptoms of pneumonitis • If pneumonitis is suspected, evaluate with radiographic imaging	• Shortness of breath • Chest pain • Coughing
Immune-mediated colitis	• Monitor patients for signs and symptoms of colitis	• Diarrhea • More bowel movements than usual • Black, tarry, sticky stools • Stools with blood or mucus • Severe stomach pain or tenderness • Nausea • Vomiting
Immune-mediated hepatitis	• Monitor patients for changes in liver function	• Nausea or vomiting • Feeling less hungry • Pain on the right side of stomach • Yellowing of skin or whites of eyes • Dark urine • Bleeding or bruising more easily than normal
Immune-mediated nephritis and renal dysfunction	• Monitor patients for changes in renal function	• Changes in the amount or colour of urine
Immune-mediated endocrinopathies, including adrenal insufficiency (primary and secondary), hypophysitis, hyperthyroidism, hypothyroidism and thyroiditis	• Monitor for signs and symptoms of adrenal insufficiency • Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism) • Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders • Hyperthyroidism may be managed symptomatically • Hypothyroidism may be managed with replacement therapy, without treatment interruption and without corticosteroids	• Rapid heartbeat • Weight loss • Increased sweating • Weight gain • Hair loss • Feeling cold • Constipation • Voice getting deeper • Muscle aches • Dizziness or fainting • Headaches that will not go away or unusual headache • Feeling more hungry or thirsty • Urinating more often than usual
Type 1 diabetes mellitus	• Monitor patients for hyperglycemia or other signs or symptoms of diabetes	• Hunger or thirst • A need to urinate more often • Weight loss

Severe skin reactions	• Monitor patients for suspected severe skin reactions and exclude other causes
	• Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported
		• Skin abnormalities such as:
		  ○ Rash
		  ○ Itching
		  ○ Blistering
		  ○ Peeling
		  ○ Sores
		• Ulcers in mouth or in lining of nose, throat or genital area

Other important immune-mediated adverse reactions	• Monitor patients for signs and symptoms of the following: uveitis, arthritis, myositis, encephalitis, sarcoidosis, myasthenic syndrome/ myasthenia gravis (including exacerbation), vasculitis, Guillain-Barré syndrome, hemolytic anemia, pancreatitis, myelitis and hypoparathyroidism • Increased risk of rejection in solid organ transplant recipients, myocarditis and sclerosing cholangitis were reported in other clinical studies or in post-marketing use	• Change in eyesight • Muscle problems (i.e., muscle pain or weakness) • Severe or persistent muscle or joint pains • Weakness and rapid fatigue of muscles or weakness and tingling in arms and legs • Muscle cramps or spasms • Confusion, fever, memory problems or seizures • Swollen lymph nodes, rash or tender lumps on skin, cough or eye pain • Low red blood cell count • Abdominal pain • Nausea • Vomiting • Shortness of breath • Irregular heartbeat • Feeling tired • Chest pain • Pain, numbness, tingling or weakness in the arms or legs • Bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation • Red skin lesions • Numbness and weakness • Pain in the upper right part of the stomach • Swelling of the liver or spleen • Fatigue • Itching • Yellowing of the skin or the whites of the eyes
Infusion-related reactions	• Monitor for signs and symptoms of infusion-related reactions	• Shortness of breath • Itching or rash • Dizziness • Fever • Wheezing • Flushing • Feeling like passing out

Talk with your patients about immune-mediated and other adverse reactions that can occur during treatment with KEYTRUDA®.

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SELECTED IMMUNE-MEDIATED ADVERSE REACTIONS

The information presented in the following tables is based on the Reference Safety Data (KEYNOTE-001, -002, -006 and -010) described in the Product Monograph. The dosing schedule in the clinical trials differs from the recommended dosing in the KEYTRUDA® Product Monograph. The recommended dosing schedule for KEYTRUDA® is 200 mg every 3 weeks or 400 mg every 6 weeks (see page 3 of this guide).

Selected immune-mediated adverse reactions in patients with metastatic NSCLC or unresectable or metastatic melanoma[1]

Adverse reaction	KEYTRUDA® 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks (n=2,799)				
	All Grades (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Pneumonitis	3.4	1.3	0.9	0.3	0.1
Colitis	1.7	0.4	1.1	<0.1	0
Hepatitis	0.7	0.1	0.4	<0.1	0
Nephritis	0.3	0.1	0.1	<0.1	0
Adrenal insufficiency	0.8	0.3	0.3	<0.1	0
Hypophysitis	0.6	0.2	0.3	<0.1	0
Hypothyroidism	8.5	6.2	0.1	0	0
Hyperthyroidism	3.4	0.8	0.1	0	0
Type 1 diabetes mellitus	0.2	<0.1	0.1	0.1	0

- In individual studies of patients with NSCLC treated with KEYTRUDA® as monotherapy (total n=2,602), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%.[1]
- Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, some with fatal outcome, have been reported in patients treated with KEYTRUDA®.[1]
- KEYTRUDA® can cause other clinically important immune-mediated adverse reactions, including severe and fatal cases.[1]
- The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% (unless otherwise indicated) of patients treated with KEYTRUDA® in the reference data set: uveitis, arthritis (1.5%), myositis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), vasculitis, Guillain-Barré syndrome, hemolytic anemia, pancreatitis, myelitis and hypoparathyroidism. Myocarditis and sclerosing cholangitis were reported in other clinical studies with KEYTRUDA® or in post-marketing use. Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with KEYTRUDA®.[1]

Median time to onset and duration of selected immune-mediated adverse reactions in patients with metastatic NSCLC or unresectable or metastatic melanoma[1]

Adverse reaction	KEYTRUDA® 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks (n=2,799)	
	Time to onset months (range)	Duration months (range)
Pneumonitis	3.3 (2 days to 19.3 months)	1.5 (1 day to 17.2+ months)
Colitis	3.5 (10 days to 16.2 months)	1.3 (1 day to 8.7+ months)
Hepatitis	1.3 (8 days to 21.4 months)	1.8 (8 days to 20.9+ months)
Nephritis	5.1 (12 days to 12.8 months)	3.3 (12 days to 8.9+ months)
Adrenal insufficiency	5.3 months (26 days to 16.6 months)	Not reached (4 days to 1.9+ years)
Hypophysitis	3.7 (1 day to 11.9 months)	4.7 (8+ days to 12.7+ months)
Hypothyroidism	3.5 (1 day to 18.9 months	Not reached (2 days to 27.7+ months)
Hyperthyroidism	1.4 (1 day to 21.9 months)	2.1 (3 days to 15.0+ months)

- Treatment with KEYTRUDA® may increase the risk of rejection in solid organ transplant recipients.[1]
- The following was reported in other clinical studies with KEYTRUDA® or in post-marketing use: myocarditis and sclerosing cholangitis.[1]
- Severe (Grade ≥3) or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2,799 patients receiving KEYTRUDA® in the Reference Safety Data set.[1]

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KEYTRUDA®: MANAGING IMMUNE-MEDIATED ADVERSE REACTIONS[1]

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA®. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA®, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions have also occurred after the last dose of KEYTRUDA®. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA® and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

Refer to the CTCAE v.4.0 definitions[2] for grading the severity of an adverse reaction.

Adverse reaction†		Management	Follow-up
Pneumonitis	Moderate (Grade 2)	**Withhold KEYTRUDA® and administer corticosteroids** (initial dose of 1 to 2 mg/kg/day prednisone.‡ Upon improvement to Grade 1 or less, taper over at least 1 month)	**Resume treatment with KEYTRUDA®** **WHEN:** • Adverse reactions remain at Grade 1 or less, following corticosteroid taper over at least 1 month
	Severe or life-threatening (Grade 3 or 4) or recurrent moderate (Grade 2)	**Permanently discontinue KEYTRUDA® and administer corticosteroids** (see prednisone dose above). Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for **Grade 2 or greater pneumonitis**.	**Permanently discontinue KEYTRUDA®** **WHEN:** • For any life-threatening (Grade 4) adverse reaction (except for endocrinopathies that are controlled with replacement hormones) • If a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA® • If corticosteroid dosing cannot be reduced to ≤10 mg prednisone‡ per day within 12 weeks • For Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of KEYTRUDA® may be considered after corticosteroids taper, if needed. Otherwise treatment should be discontinued
Colitis	Moderate or severe (Grade 2 or 3)	**Withhold KEYTRUDA® and administer corticosteroids** (initial dose of 1 to 2 mg/kg/day prednisone.‡ Upon improvement to Grade 1 or less, taper over at least 1 month)	
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	**Permanently discontinue KEYTRUDA® and administer corticosteroids** (see prednisone dose above)	
Hepatitis	Moderate (Grade 2) with AST/ALT >3 to 5 x ULN or total bilirubin >1.5 to 3 x ULN	**Withhold KEYTRUDA® and administer corticosteroids** (initial dose of 0.5 to 1 mg/kg/day prednisone.‡ Upon improvement to Grade 1 or less, taper over at least 1 month)	
	Grade ≥3: AST/ALT >5 x ULN or total bilirubin >3 x ULN or for patients with liver metastasis who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥50% relative to baseline and lasts ≥1 week	**Permanently discontinue KEYTRUDA® and administer corticosteroids** (initial dose of 1 to 2 mg/kg/day prednisone.‡ Upon improvement to Grade 1 or less, taper over at least 1 month)	
Nephritis and renal dysfunction	Moderate (Grade 2) with creatinine >1.5 to ≤3 x ULN	**Withhold KEYTRUDA® and administer corticosteroids** (initial dose of 1 to 2 mg/kg/day prednisone.‡ Upon improvement to Grade 1 or less, taper over at least 1 month)	
	Severe or life-threatening (Grade 3 or 4) (Grade ≥3 with creatinine >3 x ULN)	**Permanently discontinue KEYTRUDA® and administer corticosteroids** (see prednisone dose above)	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis; ULN=upper limit of normal

† Grades are defined according to the CTCAE v4.0.
‡ Prednisone or equivalent.

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KEYTRUDA®: MANAGING IMMUNE-MEDIATED ADVERSE REACTIONS[1] (CONT'D)

Adverse reaction†	Management		Follow-up
Adrenal insufficiency or hypophysitis	Moderate (Grade 2)	**Withhold KEYTRUDA® and administer corticosteroids** and hormone replacement as clinically indicated	
	Severe or life-threatening (Grade 3 or 4)	**Withhold or discontinue KEYTRUDA® and administer corticosteroids** and hormone replacement as clinically indicated	
Hypothyroidism	**Administer replacement hormones** without treatment interruption and without corticosteroids		
Hyperthyroidism	Manage symptomatically		
	Severe or life-threatening (Grade 3 or 4)	**Withhold or discontinue KEYTRUDA®. Manage symptomatically**	
Type 1 diabetes	With Grade >3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or with ketoacidosis	**Administer insulin. Withhold KEYTRUDA®** in cases of severe hyperglycemia until metabolic control is achieved	
Other immune-mediated adverse reactions	Moderate or severe (Grade 2 or 3)	**Withhold KEYTRUDA® and administer corticosteroids.** Upon improvement to Grade 1 or less, taper over at least 1 month	
	Life-threatening (Grade 4) or recurrent severe (Grade 3) or severe or life-threatening (Grade 3 or 4) myocarditis, encephalitis or Guillain-Barré syndrome	**Permanently discontinue KEYTRUDA® and administer corticosteroids**	
Skin reactions or SJS or TEN	Severe skin reactions (Grade 3) or suspected SJS or TEN§	**Withhold KEYTRUDA® and administer corticosteroids** § Refer to specialized care for assessment and treatment.	
	Severe skin reactions (Grade 4) or confirmed SJS or TEN§	**Permanently discontinue KEYTRUDA® and administer corticosteroids** § Refer to specialized care for assessment and treatment.	
Infusion-related reactions	Patients with mild or moderate infusion reaction	**Continue KEYTRUDA® with close monitoring;** premedication with antipyretic and antihistamine may be considered	
	Severe or life-threatening (Grade 3 or 4)	**Stop infusion and permanently discontinue KEYTRUDA®**	

Resume treatment with KEYTRUDA®

WHEN:

- Adverse reactions remain at Grade 1 or less, following corticosteroid taper over at least 1 month

Permanently discontinue KEYTRUDA®

WHEN:

- For any life-threatening (Grade 4) adverse reaction (except for endocrinopathies that are controlled with replacement hormones)
- If a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA®
- If corticosteroid dosing cannot be reduced to ≤10 mg prednisone‡ per day within 12 weeks
- For Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of KEYTRUDA® may be considered after corticosteroids taper, if needed. Otherwise treatment should be discontinued

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis; ULN=upper limit of normal

† Grades are defined according to the CTCAE v4.0.
‡ Prednisone or equivalent.

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CTCAE GRADING DEFINITIONS[2†]

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	**Moderate**	**Severe or medically significant**	**Life-threatening consequences**	**Death-related**
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[‡]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[§]	Life-threatening consequences; urgent intervention indicated	Death related to adverse event

Adverse event	Grade 2	Grade 3	Grade 4
Pulmonary disorders			
Pneumonitis	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Gastrointestinal disorders			
Colitis	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated
Hepatic disorders			
ALT increased	Asymptomatic with ALT >3.0-5.0 x ULN; >3 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia	>5.0-20.0 x ULN; >5 x ULN for >2 weeks	>20.0 x ULN

Adverse event	Grade 2	Grade 3	Grade 4
AST increased	Asymptomatic with AST >3.0-5.0 x ULN; >3 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia	>5.0-20.0 x ULN; >5 x ULN for >2 weeks	>20.0 x ULN
Blood bilirubin increased	>1.5-3.0 x ULN	>3.0-10.0 x ULN	>10.0 x ULN
Endocrine disorders			
Adrenal insufficiency	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hypothyroidism	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hyperthyroidism	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hyperglycemia	Fasting glucose value >160-250 mg/dL; fasting glucose value >8.9-13.9 mmol/L	>250-500 mg/dL; >13.9-27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Renal disorders			
Creatinine increased	>1.5-3.0 x baseline; >1.5-3.0 x ULN	>3.0 baseline; >3.0-6.0 x ULN	>6.0 x ULN

† CTCAE v4.0.
‡ Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
§ Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase;
CTCAE=Common Terminology Criteria for Adverse Events; ULN=upper limit of normal

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MONITOR FOR ADVERSE REACTIONS
Summary of safety profile

The data described in this section are termed the Reference Safety Data set. The Reference Safety Data set is the data against which safety data from other indicated populations were compared. The Reference Safety Data reflect exposure to KEYTRUDA® as monotherapy in:

2,799 patients (pooled population)

- 1,567 patients with melanoma
  - 699 previously treated with ipilimumab
  - 868 naive to ipilimumab
- 1,232 patients with NSCLC

The pooled population of 2,799 patients were studied in:

- Three randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010)
  - 912 patients with melanoma
  - 682 patients with NSCLC
- One open-label, uncontrolled, dose-comparative trial (KEYNOTE-001)
  - 655 patients with melanoma
  - 550 patients with NSCLC

Safety is described for the pooled population of the Reference Safety Data set studied across three doses:

- 2 mg/kg every 3 weeks, and
- 10 mg/kg every 2 or 3 weeks

The dosing schedules described for the Reference Safety Data set differ from the recommended dosing in the KEYTRUDA® Product Monograph. The recommended dosing schedule for KEYTRUDA® is 200 mg every 3 weeks or 400 mg every 6 weeks (see page 3 of this guide).

The median treatment duration was 4.2 months (range 1 day to 30.4 months) including:

- 1,153 patients treated for greater than or equal to 6 months and
- 600 patients treated for greater than or equal to 1 year

KEYTRUDA® was discontinued for treatment-related adverse reactions in 5% of melanoma and NSCLC patients.

Treatment-related SAEs reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA®.

Of these treatment-related SAEs, those occurring in more than ten patients (out of 2,799) were: pneumonitis (n=44), colitis (n=25), diarrhea (n=17) and pyrexia (n=10)

NSCLC=non-small cell lung carcinoma; SAE=serious adverse event

Clinical use:

Safety and efficacy of KEYTRUDA® have not been established for pediatric patients with conditions other than relapsed or refractory cHL, relapsed or refractory PMBCL or melanoma (Stage IIB or IIC).

Use of KEYTRUDA® in specific populations:

- **Teratogenic risk:** KEYTRUDA® can cause fetal harm. Pregnant women or women with childbearing potential should be advised of the potential risk to the fetus.
- **Pregnant women:** There are no data on the use of pembrolizumab in pregnant women. KEYTRUDA® has the potential to be transmitted from the mother to the developing fetus. KEYTRUDA® is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. For women of childbearing potential, pregnancy status should be established prior to initiating KEYTRUDA®. Women should be advised to use highly effective contraception and take active measures to avoid pregnancy during treatment with KEYTRUDA® and for at least 4 months after the last dose of KEYTRUDA®.
- **Nursing women:** It is unknown whether KEYTRUDA® is secreted in human milk. Because many drugs are secreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue KEYTRUDA®, taking into account the benefit of breast-feeding for the child and the benefit of KEYTRUDA® therapy for the woman. Because of the potential for serious adverse reactions in breastfed infants from KEYTRUDA®, advise women not to breast-feed during treatment and for at least 4 months after the last dose.
- **Pediatrics (<18 years of age):** There is limited experience with KEYTRUDA® in pediatric patients compared with in adult patients. The mechanism of action of pembrolizumab in pediatric patients is expected to be similar to that in adult patients. Therefore, adverse reactions of KEYTRUDA® reported in adult patients can occur in pediatric patients. In a single Phase I/II trial that enrolled pediatric patients with advanced tumours, immune-mediated adverse reactions were observed. The observed immune-mediated adverse reactions included pneumonitis, colitis, thyroid disorders (hyperthyroidism, hypothyroidism and thyroiditis) and skin reactions. Infusion reactions were also observed. The developmental effect of KEYTRUDA® on pediatric patients has not been established. Monitor pediatric patients for signs and symptoms of immune-mediated adverse reactions, and/or infusion reactions, and manage as is described throughout the WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the Product Monograph. Efficacy for pediatric patients with cHL, PMBCL and Stage IIB or IIC melanoma (aged 12 years and older) is extrapolated from the results in the respective adult populations.
- **Geriatrics (>65 years of age):** No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population. Limited safety information is available for KEYTRUDA® in cHL patients ≥65 years of age.
- **Hepatic impairment:** No dose adjustment is needed for patients with mild hepatic impairment. KEYTRUDA® has not been studied in patients with moderate or severe hepatic impairment.
- **Renal impairment:** No dose adjustment is needed for patients with mild (eGFR <90 and ≥60 mL/min/1.73 m^2) or moderate (eGFR <60 and ≥30 mL/min/1.73 m^2) renal impairment. KEYTRUDA® has not been studied in patients with severe (eGFR <30 and ≥15 mL/min/1.73 m^2) renal impairment.

eGFR=estimated Glomerular Filtration Rate

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For more information:

Please consult the product monograph available at www.merck.ca/static/pdf/KEYTRUDA-PM_E.pdf for important information relating to contraindications, warnings, precautions, adverse reactions, drug interactions, dosing information and conditions of clinical use, which have not been discussed in this document.

The product monograph is also available by calling us at 1-800-567-2594 or by email at medinfocanada@merck.com.

Should you have any questions regarding KEYTRUDA® therapy, please contact our Medical Information Centre at 1-800-567-2594.

References: 1. KEYTRUDA® Product Monograph. Merck Canada Inc. April 19, 2023. **2.** National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) v4.0.* National Cancer Institute. May 28, 2009. CTC and CTCAE Version Archive. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed December 15, 2022.

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