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

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.

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)

Immune-mediated adverse reactions are presented based on 2,799 patients with melanoma or NSCLC in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010. The safety profile was generally similar for patients with melanoma and NSCLC.

Pr KEYTRUDA® (pembrolizumab)

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).

Relevant warnings and precautions not presented elsewhere in this document:

- Other immune-mediated adverse events, including uveitis, arthritis, myositis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), vasculitis, Guillain-Barré syndrome, hemolytic anemia, pancreatitis and myelitis.
- Myocarditis and sclerosing cholangitis
- Solid organ transplant rejection
- Driving and operating machinery
- Teratogenic risk
- Not recommended in pregnant women
- In nursing women, a decision should be made whether to discontinue breast-feeding or KEYTRUDA® taking into account the benefit of breast-feeding for the child and the benefit of KEYTRUDA® therapy for the woman
- Has not been studied in patients with moderate or severe hepatic impairment
- Has not been studied in patients with severe renal impairment
- Monitor liver and thyroid function tests and electrolytes during treatment

For more information:

Please consult the product monograph available at www.merck.ca/static/pdf/KEYTRUDA-PM_E.pdf for important information relating to adverse reactions, drug interactions and dosing information 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.

PMBCL=primary mediastinal B-cell lymphoma
cHL=classical Hodgkin Lymphoma

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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Pr KEYTRUDA® (pembrolizumab)

Pr KEYTRUDA® (pembrolizumab)

USING KEYTRUDA®

An algorithm for managing immune-related adverse reactions during treatment with KEYTRUDA®

Pr KEYTRUDA® (pembrolizumab) 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 of 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.

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)	
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®**	

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.