Pr KEYTRUDA® (pembrolizumab)

An immunotherapy option in metastatic or unresectable recurrent

HEAD AND NECK CANCER

KEYTRUDA® is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have PD-L1 expression (Combined Positive Score [CPS] ≥ 1) as determined by a validated test.

KEYTRUDA® is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.[1]

- Patient Profiles →
- Safety Profile →
- Trial Design →
- Dosing →
- Efficacy Results →
- Guidelines →

PD-L1=programmed death-ligand 1.

Consider KEYTRUDA®

For your patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC)

Andre*, 52 years old

Meet Andre →

Marianne*, 65 years old

Meet Marianne →

Robert*, 48 years old

Meet Robert →

William*, 67 years old

Meet William →

* Fictitious patient profile. May not be representative of all patients.

Do you have a patient like **Andre**?*

"I knew there was a chance that my cancer would come back."

Background

Age: 52 years old
Factory general manager
Married, 2 children
Heavy smoker (~25 cigarettes/day)
Moderate alcohol use (1–2 drinks/day)

Imaging/biopsy results

- Pulmonary lesions identified through CT scan; biopsy confirms lesions as distant metastases (Stage IVC)
- Exam reveals large lesion on oropharynx and several enlarged lymph nodes
- CT confirms the invasion of surrounding structures/encroachment of left internal carotid artery
- Complete resection was determined unfeasible
- Persistent hoarseness, dysphagia, presence of an asymptomatic neck mass

Clinical notes

- Initially diagnosed with resectable, locally advanced Stage III laryngeal SCC
- He was treated with external beam radiotherapy plus concurrent administration of platinum chemotherapy, and is now in remission after 10 months
- HPV-negative
- PD-L1 CPS: 10
- ECOG PS: 1

Diagnosis: Unresectable recurrent Stage IVC HNSCC

Consider KEYTRUDA® for your unresectable recurrent HNSCC patients like

Andre*

CPS=combined positive score; CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group performance status; HNSCC=head and neck squamous cell carcinoma; HPV=human papillomavirus; PD-L1=programmed death-ligand 1; SCC=squamous cell carcinomas.
* Fictitious patient profile. May not be representative of all patients.

Do you have a patient like **Marianne**?*

"I had never heard of this kind of cancer, and then I was diagnosed with it... twice."

Background

Age: 65 years old
Retired teacher, enjoys gardening
Married, 3 children and 2 grandsons
Moderate alcohol use (1 drink/day)

Imaging/biopsy results

- CT scan identified locoregional recurrence in the oral cavity with extensive invasion of local structures
    - A multidisciplinary tumour board determined lesion to be unresectable
- Lymph node dissection confirms 1 cervical node involved without extranodal extension (Stage IVA)

Clinical notes

- Initially diagnosed with Stage III oral cavity SCC
- She underwent surgery to remove primary tumour and resection of ipsilateral lymph nodes; then received radiotherapy/cisplatin following surgery and was in remission after definitive treatment
- HPV-positive
- PD-L1 CPS: 26
- ECOG PS: 1

Diagnosis: Unresectable recurrent stage III oral cavity SCC

Consider KEYTRUDA® for your unresectable recurrent HNSCC patients like

Marianne*

CPS=combined positive score; CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group performance status; FU=fluorouracil; HNSCC=head and neck squamous cell carcinoma; HPV=human papillomavirus; PD-L1=programmed death-ligand 1.
*Fictitious patient case. May not be reflective of all patients.

Do you have a patient like **Robert**?*

“I never expected this to happen to me. I thought I was healthy.”

Background

Age: 48 years old
General contractor
Married, no children
Occasional alcohol use
Quit smoking 3 years ago

Imaging/biopsy results

- Patient referred by family physician for evaluation
- 5.5 cm lesion identified on left soft palate
- Multiple metastatic lesions in lung, liver and surrounding bone

Clinical notes

- HPV-negative
- PD-L1 CPS: < 1
- ECOG PS: 1

Diagnosis: Metastatic Stage IVC HNSCC

Consider KEYTRUDA® for your metastatic HNSCC patients like

Robert*

CPS=combined positive score; ECOG PS=Eastern Cooperative Oncology Group performance status; HNSCC=head and neck squamous cell carcinoma; HPV=human papillomavirus; PD-L1=programmed death-ligand 1.
*Fictitious patient case. May not be reflective of all patients.

Do you have a patient like **William**?*

"I knew that smoking increased my risk of cancer, but I quit years ago."

Background

Age: 67 years old
Parole officer
Divorced, 2 children and 5 grandchildren
Quit smoking 17 years ago
Quit drinking 3 years ago

Imaging/biopsy results

- Patient referred for a focused examination of the head and neck with white light endoscopy and further testing as required
- 3 cm lesion identified on left tonsil
- 2 metastatic lesions to left-lower lung

Clinical notes

- HPV-positive
- PD-L1 CPS: 1
- ECOG PS: 1

Diagnosis: Metastatic Stage IVC HNSCC

Consider KEYTRUDA® for your metastatic HNSCC patients like

William*

CPS=combined positive score; ECOG PS=Eastern Cooperative Oncology Group performance status; HNSCC=head and neck squamous cell carcinoma; HPV=human papillomavirus; PD-L1=programmed death-ligand 1.
*Fictitious patient case. May not be reflective of all patients.

Study design | Endpoints | Demographics

Pivotal trial KEYNOTE-048: KEYTRUDA® as a first-line monotherapy or in combination with platinum chemotherapy and FU for HNSCC[1]

KEYNOTE-048 study design

Phase III, multicentre, randomized, open-label, active-controlled study encompassing 882 patients.

882 patients

Patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies.

1:1:1

Monotherapy: KEYTRUDA® 200 mg every 3 weeks (n=301)

Combination therapy: KEYTRUDA® 200 mg every 3 weeks, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and FU 1000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum chemotherapy and FU; n=281)

Standard treatment: Cetuximab 400 mg/m^2 load then 250 mg/m^2 once weekly, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and FU 1000 mg/m2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum chemotherapy and FU; n=300)

24 months

- Treatment with KEYTRUDA® continued until RECIST 1.1-defined disease progression (determined by the investigator), unacceptable toxicity, or up to a maximum of 24 months.
    - KEYTRUDA® patients who stopped treatment with stable disease or better were eligible for up to one year of additional therapy if they progressed after stopping study treatment. Administration of KEYTRUDA® was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.
- Assessment of tumour status was performed at Week 9, then every 6 weeks for the first year, followed by every 9 weeks through 24 months.
- Randomization was stratified by tumour PD-L1 expression, HPV status, and ECOG PS.

AUC=area under the curve; ECOG PS=Eastern Cooperative Oncology Group performance status; FU=fluorouracil; HPV=human papillomavirus; PD-L1=programmed death-ligand 1; RECIST=response evaluation criteria in solid tumours.

Endpoints[1]

Primary endpoints

- Overall survival and progression-free survival, assessed by BICR according to RECIST 1.1

Select secondary endpoints

- Objective response rate, assessed by BICR according to RECIST 1.1

Select exploratory endpoint

- Duration of response

BICR=blinded independent central review; RECIST=response evaluation criteria in solid tumours.

Selected baseline demographics[1]

	KEYTRUDA® monotherapy (n=301)	KEYTRUDA® + platinum chemotherapy and FU (n=281)	Cetuximab + platinum chemotherapy and FU (n=300)
Age, median (range)	62 (22-94)	61 (20-85)	61 (22-84)
Male, %	83%	80%	87%
White, %	73%	72%	75%
Asian, %	19%	21%	18%
ECOG PS 0, %	40%	39%	40%
PS 1, %	60%	61%	60%
Former/current smoker, %	79%	80%	78%
HPV positive, %	21%	21%	22%
CPS ≥1, %	85%	86%	85%
CPS ≥20, %	44%	45%	41%
Cancer stage at study entry IVA	20%	18%	20%
IVB	4%	5%	7%
IVC	72%	72%	68%

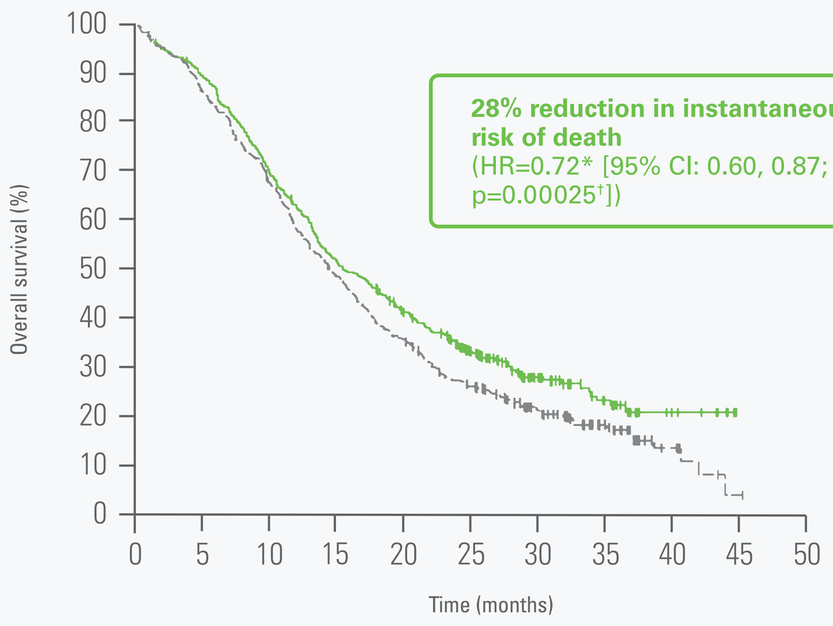
BICR=blinded independent central review; CPS=combined positive score; RECIST=response evaluation criteria in solid tumours.

Co-primary endpoint: OS

KEYTRUDA® + platinum chemotherapy and FU demonstrated significantly improved

overall survival vs. cetuximab + platinum chemotherapy and FU (HR=0.72* [95% CI: 0.60, 0.87; p=0.00025†]) in patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies in the KEYNOTE-048 study (ITT population)[1]

Overall survival for KEYTRUDA® + platinum chemotherapy and FU vs. cetuximab + platinum chemotherapy and FU at final analysis



KEYTRUDA® + platinum chemotherapy and FU	281	227	169	122	94	77	55	29	5	0	0
Cetuximab + platinum chemotherapy and FU	278	227	147	100	66	45	23	6	1	0	0

Adapted from the KEYTRUDA® Product Monograph.

Number of patients with event:
- **76%** (213/281) KEYTRUDA® + platinum chemotherapy and FU
- **89%** (247/278) cetuximab + platinum chemotherapy and FU

Median in months:
- KEYTRUDA® + platinum chemotherapy and FU 13.0 (95% CI: 10.9, 14.7)
- Cetuximab + platinum chemotherapy and FU 10.7 (95% CI: 9.3, 11.7)

* Based on stratified Cox proportional hazard model

† Based on stratified log-rank test

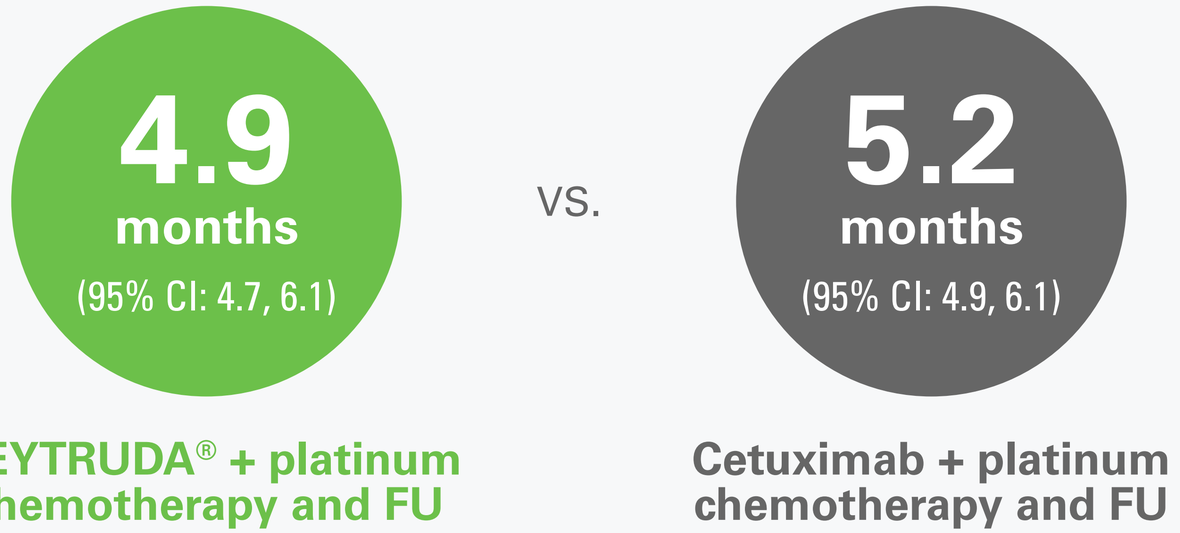
CI=confidence interval; FU=fluorouracil; HNSCC=head and neck squamous cell carcinoma; HR=hazard ratio; ITT=intent-to-treat.

Co-primary endpoint: progression-free survival

Progression-free survival results from KEYTRUDA® + platinum chemotherapy and FU vs. cetuximab + platinum chemotherapy and FU in patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies in the KEYNOTE-048 study (ITT population)

The co-primary endpoint of PFS was not statistically significant at the final analysis (HR=0.93* [95% CI: 0.78, 1.11; *p*=0.2121†]).

Number of patients with event:
- **89%** (250/281) KEYTRUDA® + platinum chemotherapy and FU
- **94%** (260/278) cetuximab + platinum chemotherapy and FU



CONSIDER KEYTRUDA® in combination with platinum chemotherapy and FU for your eligible patients.

* Based on stratified Cox proportional hazard model

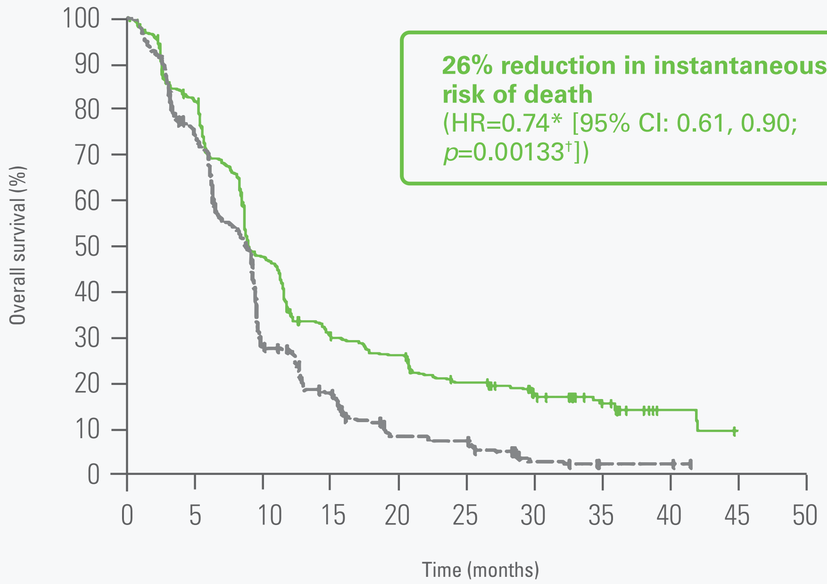
† Based on stratified log-rank test

CI=confidence interval; FU=fluorouracil; HNSCC=head and neck squamous cell carcinoma; HR=hazard ratio; ITT=intent-to-treat.

Co-primary endpoint: overall survival

KEYTRUDA® as a monotherapy demonstrated significantly improved overall survival vs. cetuximab + platinum chemotherapy and FU (HR=0.74* [95% CI: 0.61, 0.90; p=0.00133†]) in patients with a CPS ≥1 metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies in the KEYNOTE-048 study[1]

Overall survival for KEYTRUDA® monotherapy vs. cetuximab + platinum chemotherapy and FU in patients with a CPS ≥1 at final analysis



KEYTRUDA® monotherapy	257	196	152	110	91	70	43	21	13	1	0
Cetuximab + platinum chemotherapy and FU	255	207	131	89	59	40	21	9	5	0	0

Adapted from the KEYTRUDA® Product Monograph.

Number of patients with event:
- **77%** (197/257) KEYTRUDA® monotherapy
- **90%** (229/255) cetuximab + platinum chemotherapy and FU

Median in months:
- **12.3** (95% CI: 10.8, 14.3) KEYTRUDA® monotherapy
- **10.3** (95% CI: 9.0, 11.5) cetuximab + platinum chemotherapy and FU

* Based on stratified Cox proportional hazard model.
† Based on stratified log-rank test
CI=confidence interval; FU=fluorouracil; HNSCC=head and neck squamous cell carcinoma; HR=hazard ratio; ITT=intent-to-treat.

Co-primary endpoint: progression-free survival

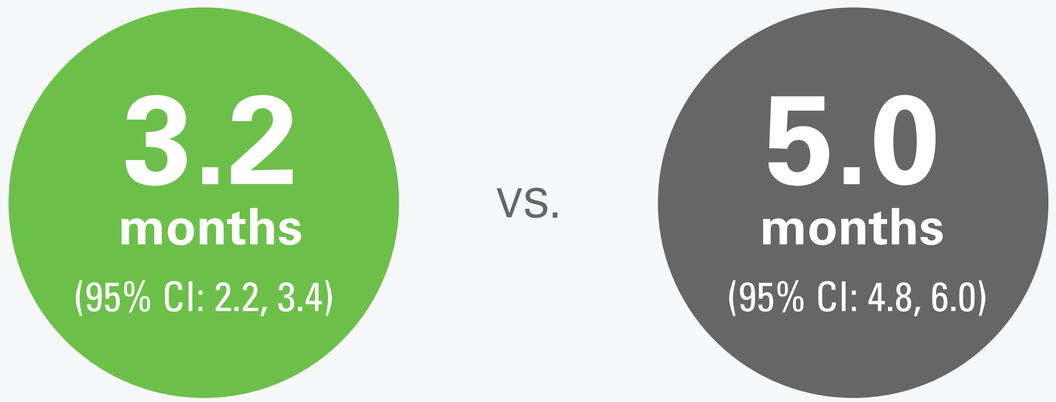
Progression-free survival results of **KEYTRUDA® monotherapy** vs. cetuximab + platinum chemotherapy and FU in patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies in the KEYNOTE-048 study[1]

The co-primary endpoint PFS did not reach statistical significance.

The co-primary endpoint of PFS was not statistically significant at the final analysis (HR=1.13* [95% CI: 0.94, 1.36; *p*=0.8958†]).

Number of patients with event:

- **89%** (228/257) KEYTRUDA® monotherapy
- **93%** (237/255) cetuximab + platinum and FU



HR=1.13* 95% CI: 0.94, 1.36; *p*=0.8958†

CONSIDER KEYTRUDA®
as a monotherapy for your eligible patients.

Exploratory analysis

A positive association was observed between CPS expression and treatment benefit.

* Based on stratified Cox proportional hazard model
† Based on stratified log-rank test
CI=confidence interval; FU=fluorouracil; HNSCC=head and neck squamous cell carcinoma; HR=hazard ratio.

Duration of response, median (exploratory endpoint)[1]

In patients with a CPS ≥1

KEYTRUDA® monotherapy	Cetuximab + platinum chemotherapy and FU
20.9 months (range: 1.5+, 34.8+)	4.5 months (range: 1.2+, 30.6+)

In the ITT patient population

KEYTRUDA® + platinum chemotherapy and FU	Cetuximab + platinum chemotherapy and FU
6.7 months (range: 1.6+, 30.4+)	4.3 months (range: 1.2+, 27.9+)

Safety profile observed in HNSCC with KEYNOTE-048[1]

Most common adverse events (reported in ≥10% of patients) with either KEYTRUDA® monotherapy, KEYTRUDA® + platinum chemotherapy and FU, or cetuximab + platinum chemotherapy and FU, any grade*

Adverse event, % (n)	KEYTRUDA® monotherapy (n=300)	KEYTRUDA® + platinum chemotherapy and FU (n=276)	Cetuximab + platinum chemotherapy and FU (n=287)
Anemia	4.0 (12)	48.6 (134)	41.1 (118)
Nausea	4.0 (12)	45.3 (125)	45.6 (131)
Neutropenia	1.0 (3)	33.0 (91)	31.0 (89)
Fatigue	14.3 (43)	30.4 (84)	28.9 (83)
Mucosal inflammation	2.7 (8)	27.9 (77)	26.5 (76)
Thrombocytopenia	1.3 (4)	27.2 (75)	21.6 (62)
Vomiting	2.3 (7)	27.2 (75)	22.3 (64)
Stomatitis	0.7 (2)	25.0 (69)	24.4 (70)
Decreased appetite	5.3 (16)	22.5 (62)	21.6 (62)
Platelet count decreased	0.3 (1)	18.5 (51)	16.0 (46)
Diarrhea	5.7 (17)	18.1 (50)	26.5 (76)
Neutrophil count decreased	0.3 (1)	16.3 (45)	18.8 (54)
White blood cell count decreased	0.7 (2)	13.0 (36)	15.0 (43)
Hypothyroidism	13.0 (39)	13.0 (36)	0.3 (1)
Leukopenia	0.7 (2)	12.3 (34)	13.2 (38)
Asthenia	2.3 (7)	11.6 (32)	10.5 (30)
Blood creatinine increased	0.7 (2)	11.2 (31)	5.6 (16)
Hypomagnesemia	1.0 (3)	10.5 (29)	33.1 (95)
Constipation	3.0 (9)	10.1 (28)	10.8 (31)

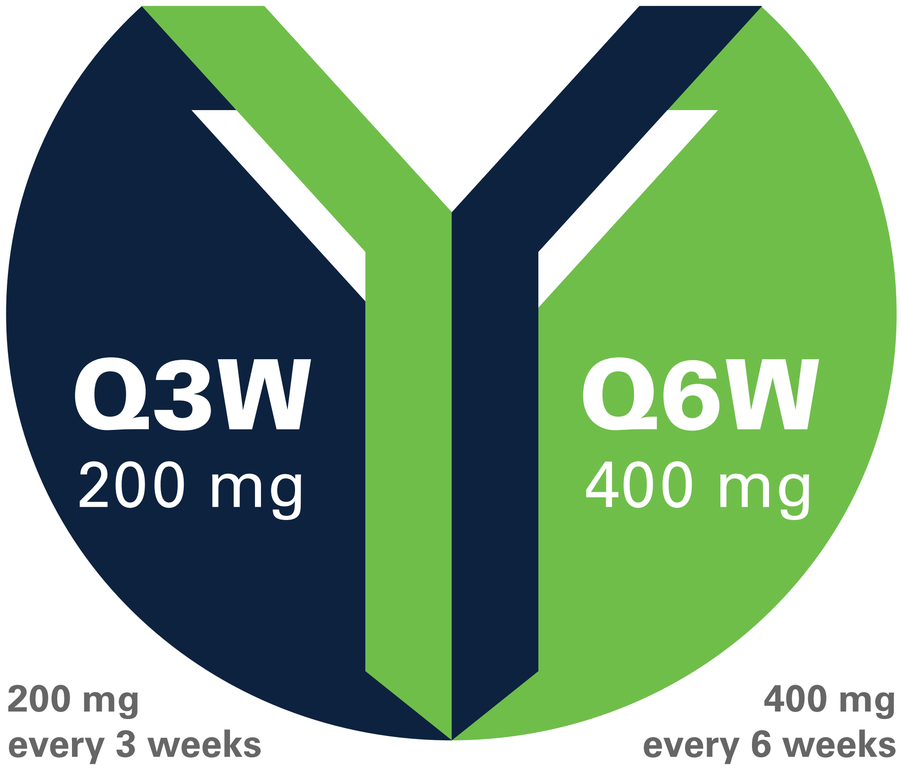
Adapted from the KEYTRUDA® Product Monograph.
* All patients as treated population.

Treatment discontinuation due to treatment-related adverse events was 5.0% for KEYTRUDA® monotherapy (n=300) and 25.0% for KEYTRUDA® + platinum chemotherapy and FU (n=276).

FU=fluorouracil; HNSCC=head and neck squamous cell carcinoma.

Dosing with KEYTRUDA®[1]

KEYTRUDA® offers the flexibility of two dosing options. The recommended dose of KEYTRUDA® can be provided as either:



Administered as an intravenous infusion over 30 minutes

Q3W=every 3 weeks; Q6W=every 6 weeks.

Continue until:

- Unacceptable toxicity
- Disease progression
- Up to 24 months or to 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression

When administering KEYTRUDA® in combination with chemotherapy, administer KEYTRUDA® prior to chemotherapy when given on the same day.

Missed dose

- Administer the missed dose as soon as possible
- Adjust the schedule of administration to maintain Q3W or Q6W dosing

KEYTRUDA® offers two dosing options. Consider which regimen is appropriate for your patients.

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.

Please see the KEYTRUDA® Product Monograph for complete information on dosing and administration.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancers

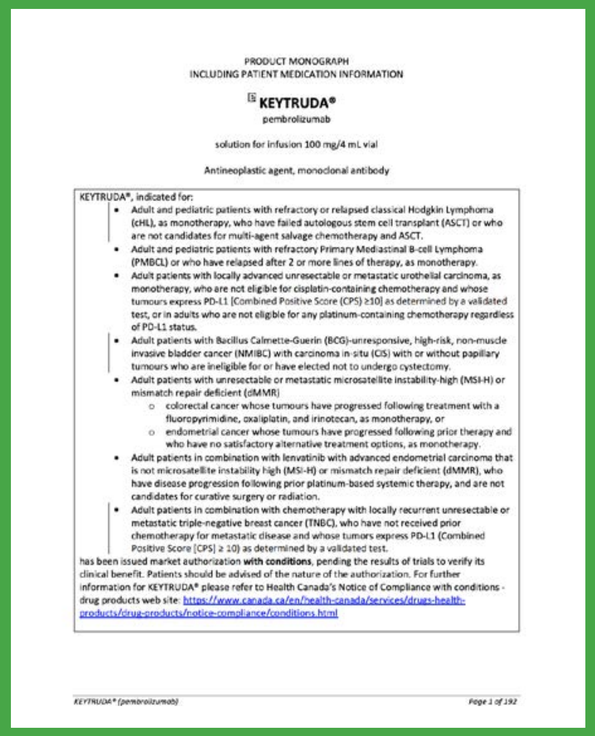
Systemic therapy recommendations for recurrent, unresectable, or metastatic cancer (with no surgery or radiotherapeutic option)[3]

- Pembrolizumab monotherapy is a **preferred first-line regimen** treatment option for patients with CPS ≥1 (category 1 if CPS ≥20).
- Pembrolizumab/platinum (cisplatin or carboplatin/5-FU) therapy is a **preferred first-line regimen** treatment option.

Please see the NCCN Guidelines® for detailed recommendations, including other options.

CPS=combined positive score; FU=fluorouracil; NCCN=National Comprehensive Cancer Network® (NCCN®).

Resources



PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **KEYTRUDA®**
pembrolizumab

solution for infusion 100 mg/4 mL vial

Antineoplastic agent, monoclonal antibody

KEYTRUDA®, indicated for:

- Adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT.
- Adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.
- Adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
- Adult patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy.
- Adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
  - endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.
- Adult patients in combination with lenvatinib with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation.
- Adult patients in combination with chemotherapy with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC), who have not received prior chemotherapy for metastatic disease and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10) as determined by a validated test.

has been issued market authorization **with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KEYTRUDA® please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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KEYTRUDA®
Product Monograph

KEYNOTE-048 publication
Burtness *et al*.

Important safety information

Clinical use:

Safety and efficacy of KEYTRUDA® in pediatric patients have not been established for head and neck cancer.

Relevant warnings and precautions:

- Immune-mediated adverse reactions, including severe and fatal cases:
  - Pneumonitis
  - Colitis
  - Hepatitis
  - Nephritis and renal dysfunction
  - Endocrinopathies including adrenal insufficiency, hypophysitis, type 1 diabetes mellitus and thyroid disorders
  - Severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Other immune-mediated adverse events including uveitis, arthritis, myositis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis, vasculitis, Guillain-Barré syndrome, hemolytic anemia, pancreatitis, myelitis, myocarditis, sclerosing cholangitis
- Solid organ transplant rejection
- Allogeneic stem cell transplant after and before treatment
- Severe infusion-related reactions
- Embryofetal toxicity
- Women should avoid pregnancy and breastfeeding during treatment and for at least 4 months after it
- Advise nursing women not to breastfeed during treatment and for at least 4 months after the last dose
- Patients with hepatic or renal impairment
- Driving and operating machinery
- Monitoring requirements

For more information:

Please consult the Product Monograph at https://www.merck.ca/confirm-monograph.xhtml?file=KEYTRUDA-PM_E.pdf for important information regarding adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling us at 1-800-567-2594 or by email at medinfocanada@merck.com.

References

1. KEYTRUDA® Product Monograph. Merck Canada Inc. September 14, 2022. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancers V.1.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed February 28, 2022. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way. **3.** Merck Manuals Professional Edition. Overview of Head and Neck Tumors - Ear, Nose, and Throat Disorders. Available at: https://www.merckmanuals.com/en-ca/professional/ear,-nose,-and-throat-disorders/tumors-of-the-head-and-neck/overview-of-head-and-neck-tumors#. Accessed: October 12, 2022.

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