Important safety information

Clinical use:

Safety and efficacy of KEYTRUDA® in pediatric patients have not been established for urothelial carcinoma.

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, hypoparathyroidism, 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
- Patients with hepatic or renal impairment
- Driving and operating machinery
- Monitoring requirements
- Geriatrics

For more information:

Please consult the Product Monograph at www.merck.ca/static/pdf/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.

KEYNOTE-045

Study design

Multicentre, randomized (1:1), active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. Patients were randomized to receive either KEYTRUDA® 200 mg intravenously every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m² (n=84), docetaxel 75 mg/m² (n=84) or vinflunine 320 mg/m² (n=87). Patients received KEYTRUDA® until unacceptable toxicity or disease progression. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to one additional year. Primary efficacy outcome measures were overall survival and progression-free survival by BICR per RECIST 1.1 at 2nd interim analysis.

References: 1. KEYTRUDA® Product Monograph. Merck Canada Inc. April 19, 2023. **2.** Bellmunt J, Ronald de Wit R, Vaughn D, *et al.* Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med.* 2017;376(11):1015-1026. **3.** Fradet Y, Bellmunt J, Vaughn DJ, *et al.* Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. *Ann Oncol.* 2019;30(6):970-976. **4.** Warren M, Kolinsky M, Canil CM, *et al.* Canadian Urological Association/Genitourinary Medical Oncologists of Canada consensus statement: Management of unresectable locally advanced and metastatic urothelial carcinoma. *Can Urol Assoc J.* 2019;13(10):318-327.

MERCK

Merck Canada Inc., 16750 Trans-Canada Highway, Kirkland, Quebec, Canada, H9H 4M7

MEMBER OF INNOVATIVE MEDICINES CANADA

CA-PDO-00255

REVIEWED BY PAAB

What do you consider for patients with locally advanced or metastatic UC who have progression ≤12 months after **adjuvant/neoadjuvant platinum-containing therapy**?

KEYNOTE-045: KEYTRUDA® vs. investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine)

KEYTRUDA® is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, as monotherapy who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

UC=urothelial carcinoma.

Pr KEYTRUDA® (pembrolizumab)

KEYNOTE-045: Patients **previously treated** with platinum-containing chemotherapy[1,2]

- **21%** of patients had received ≥2 prior systemic regimens in the metastatic setting
- **76%** of patients had received prior cisplatin, **23%** had prior carboplatin, **1%** were treated with other platinum-based regimens

KEYTRUDA® demonstrated a significant improvement in overall survival vs. investigator's choice (IC) of chemotherapy[1,3]*

Interim analysis

Overall survival (primary endpoint): 27% reduction in risk of death demonstrated with KEYTRUDA® vs. IC chemotherapy (HR 0.73 [95% CI: 0.59, 0.91], *p*=0.002; primary endpoint; interim analysis; # of deaths 155/270 patients and 179/272 patients, respectively)

- Median overall survival was 10.3 months (95% CI: 8.0, 11.8) for KEYTRUDA® and 7.4 months (95% CI: 6.1, 8.3) for IC chemotherapy.

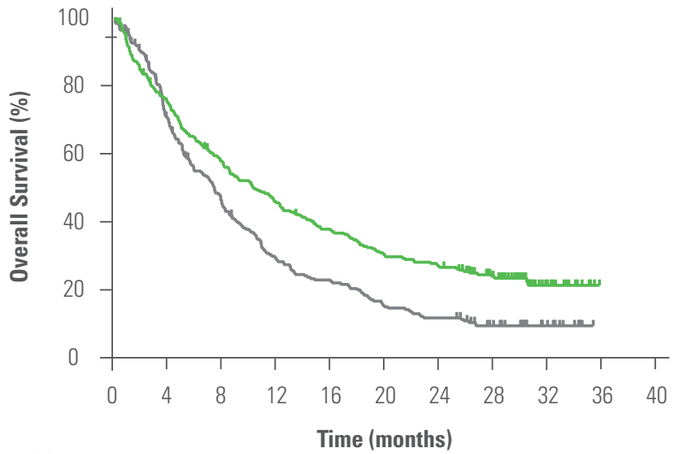
Final descriptive analysis

Overall survival: 30% reduction in risk of death demonstrated with KEYTRUDA® vs. IC chemotherapy (HR 0.70 [95% CI: 0.57, 0.85], *p*<0.001; primary endpoint; final analysis; # of deaths 200/270 and 219/272 patients, respectively)

- Median overall survival was 10.1 months (95% CI: 8.0, 12.3) for KEYTRUDA® and 7.3 months (95% CI: 6.1, 8.1) for IC chemotherapy.

KEYNOTE-045: Patients **previously treated** with platinum-containing chemotherapy[1,2]

Observed overall survival in KEYNOTE-045 (final descriptive analysis, intent to treat population)



n at risk

KEYTRUDA®	270	195	148	116	98	80	67	33	7	0	0
IC Chemotherapy	272	173	109	73	59	42	34	18	4	0	0

In the interim analysis and final descriptive analysis of progression-free survival there was no statistically significant difference between KEYTRUDA® and IC chemotherapy.

Please see back cover for study design.

Consider our data. ***Choose KEYTRUDA®***

CI=confidence interval; HR=hazard ratio.

* Investigator's choice (IC) of chemotherapy of any of the following regimens all given intravenously every 3 weeks: paclitaxel 175 mg/m² (n=84), docetaxel 75 mg/m² (n=84), or vinflunine 320 mg/m² (n=87).

Canadian Urological Association/ Genitourinary Medical Oncologists of Canada consensus statement[4]

Second-line systemic therapy for unresectable, locally advanced and metastatic urothelial carcinoma:

In patients who have progressive disease during or after platinum-based chemotherapy, pembrolizumab is the preferred regimen (if available).

Please see the CUA 2019 consensus guidelines for complete information.