Pembrolizumab (Keytruda®) with enfortumab vedotin (Padcev®) for the first-line treatment of unresectable or metastatic urothelial carcinoma

General information

Drug description

Pembrolizumab (Keytruda®) is a programmed death receptor-1 (PD-1)-blocking antibody.
Enfortumab vedotin (Padcev®) is a Nectin-4-directed antibody and microtubule inhibitor conjugate.

Indication [1]

Pembrolizumab (Keytruda®), in combination with enfortumab vedotin (Padcev®), is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

Incidence [2]

In Austria, in 2022, a total of 1,247 persons were newly diagnosed with bladder cancer. The age-standardised[1] incidence rate was 22.3/100,000 in men and 6.3/100,000 in women.

Current treatment [3]

The Onkopedia treatment recommendation for the treatment of advanced urothelial carcinoma is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [1, 4]

Keytruda®

Approval status for this indication: On 25 July 2024, the CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for Keytruda®.

The CHMP adopted a new indication as follows:

- Keytruda®, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

Other indications: Keytruda® is indicated:

- as monotherapy for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.
- as monotherapy for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.
- in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment for the treatment of resectable non-small cell lung carcinoma (NSCLC) at high risk of recurrence in adults.

FDA [5-7]

Approval status for this indication: On 15 December 2023, the FDA approved enfortumab vedotin-ejfv (Padcev®) in combination with pembrolizumab (Keytruda®) for patients with locally advanced or metastatic urothelial cancer.

Keytruda®

Other indications: Keytruda® is indicated:

- for the treatment of patients with unresectable or metastatic melanoma.
- for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection.
- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumour aberrations.
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, and is:
  - Stage III, where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-

[1] European Standard Population 2013.

- as monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy.
- as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% TPS with no EGFR or ALK positive tumour mutations.
- in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous NSCLC in adults.
- as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Keytruda®.
- as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
- as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10.
- as monotherapy or in combination with platinum and 5-fluorouracil chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1.
- as monotherapy for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.
- in combination with axitinib, for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.
- in combination with lenvatinib, for the first-line treatment of advanced RCC in adults.
- as monotherapy for the adjuvant treatment of adults with RCC at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.
- as monotherapy for adults with MSI-H or dMMR colorectal cancer in the following settings:

  containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda®.
- for the treatment of patients with resectable (tumours ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- as a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.
- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumours express PD-L1 (CPS≥1) as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
- for the treatment of adult patients with relapsed or refractory cHL.
- for the treatment of paediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.
- for the treatment of adult and paediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy. Limitations of Use: Keytruda® is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
- in combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial cancer.
- as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy.
- as a single agent for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy.
- for the treatment of adult and paediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- for the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC as determined by an FDA-approved test.
- in combination with trastuzumab, fluoropyrimidine-and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumour response rate and durability of response.

- first-line treatment of metastatic colorectal cancer;
- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

❖ as monotherapy for the treatment of the following MSI-H or dMMR tumours in adults with:
- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

❖ in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10.

❖ in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, or early-stage TNBC at high risk of recurrence.

❖ in combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic TNBC in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease.

❖ in combination with lenvatinib, for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

❖ in combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.

❖ in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

❖ in combination with fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

❖ in combination with fluoropyrimidine-and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma.

❖ for the treatment of patients with locally advanced or metastatic oesophageal or GEJ (tumours with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
- in combination with platinum-and fluoropyrimidine-based chemotherapy, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumours of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

❖ in combination with chemoradiotherapy, for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer.

❖ in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

❖ as a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

❖ for the treatment of patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD1/PD-L1-containing regimen.

❖ in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer.

❖ for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.

❖ in combination with axitinib, for the first-line treatment of adult patients with advanced RCC.

❖ in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.

❖ for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

❖ in combination with carboplatin and paclitaxel, followed by Keytruda® as a single agent, for the treatment of adult
patients with primary advanced or recurrent endometrial carcinoma.

❖ in combination with lenvatinib, for the treatment of adult patients with advanced endometrial carcinoma that is
mismatch repair proficient as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

❖ as a single agent, for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

❖ for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H (≥10 mutations/megabase) solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on

- ❖ in combination with gemcitabine and cisplatin, for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

Enfortumab vedotin (Padcev®)

Approval status for this indication: On 25 July 2024, the CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for Padcev®.

The CHMP adopted a new indication as follows:

- ❖ Padcev®, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.

Other indications:

- ❖ Padcev® as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor.

✓ **Medicine is under additional monitoring**

tumour response rate and durability of response. Limitations of Use: The safety and effectiveness of Keytruda® in pediatric patients with TMB-H CNS cancers have not been established.

- ❖ for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.
- ❖ for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- ❖ in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic
  TNBC whose tumours express PD-L1 (CPS ≥10) as determined by an FDA approved test.
- ❖ Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg Every 6 Weeks
  - for use at an additional recommended dosage of 400 mg every 6 weeks for cHL and PMBCL in adults. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety.

Padcev®

Other indications: Padcev® is indicated

- ❖ as a single agent for the treatment of adult patients with locally advanced or metastatic urothelial cancer who:
  - have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinumcontaining chemotherapy, or
  - are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

Manufacturer

Keytruda® is manufactured by Merck Sharp & Dohme B.V.
Padcev® is manufactured by Astellas pharma.

Costs [8]

4 ml Keytruda® concentrate for solution for infusion 25 mg/ml = € 3,428.00 (ex-factory price)
Padcev® powder for concentrate for solution for infusion 20 mg = € 710.41 (ex-factory price)

Posology [9, 10]

Keytruda®

- ❖ If specified in the indication, patient selection for treatment with Keytruda® based on the tumour expression of PD-L1 should be confirmed by a validated test.
- ❖ Keytruda®, as monotherapy or as combination therapy, should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-mediated adverse reactions unless otherwise specified in product information.

Padcev®

- ❖ Treatment with Padcev® should be initiated and supervised by a physician experienced in the use of anticancer therapies. Ensure good venous access prior to starting treatment.

Warnings and precautions [9, 10]

Keytruda®

- ❖ Traceability
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- ❖ Assessment of PD-L1 status

- When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is chosen to minimise false negative or false positive determinations.

❖ Immune-mediated adverse reactions
- Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-mediated adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions have also occurred after the last dose of pembrolizumab. Immune-mediated adverse reactions affecting more than one bodysystem can occur simultaneously.
- For suspected immune-mediated adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 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.
- Pembrolizumab may be restarted within 12 weeks after last dose of Keytruda® if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.
- Pembrolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones.
- For detailed description of immune-mediated pneumonitis, colitis, hepatitis, nephritis, endocrinopathies and skin adverse reactions, please see Product Information

❖ Transplant-related adverse reactions
- Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with pembrolizumab versus the risk of possible organ rejection should be considered in these patients.

❖ Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)
- Allogeneic HSCT after treatment with pembrolizumab
  - Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease have been observed in patients with cHL undergoing allogeneic HSCT after previous exposure to pembrolizumab. Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case.
- Allogeneic HSCT prior to treatment with pembrolizumab
  - In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with pembrolizumab. Patients who experienced GVHD after their transplant procedure may be at an increased risk for GVHD after treatment with pembrolizumab. Consider the benefit of treatment with pembrolizumab versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

❖ Infusion-related reactions
- Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving pembrolizumab. For Grades 3 or 4 infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued. Patients with Grades 1 or 2 infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

❖ Use of pembrolizumab in combination with chemotherapy
- Pembrolizumab in combination with chemotherapy should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis.

❖ Patients excluded from clinical studies
- Patients with the following conditions were excluded from clinical studies: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV infection, hepatitis B or hepatitis C infection (except for BTC); active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks.
- Patients with active infections were excluded from clinical studies and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical studies, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

- There are limited data on the safety and efficacy of Keytruda® in patients with ocular melanoma
- After careful consideration of the potential increased risk, pembrolizumab may be used with appropriate medical management in these patients.

❖ Patient card
- All prescribers of Keytruda® must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of KEYTRUDA therapy with the patient. The patient will be provided with the patient card with each prescription

Padcev®

❖ Traceability
- In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

❖ Skin reactions
- Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs.
- Mild to moderate skin reactions, predominantly maculopapular rash, have been reported.
- Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4). Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis.
- Permanently discontinue Padcev® for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions. For Grade 2 worsening, Grade 2 with fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level.

❖ Pneumonitis/ILD
- Severe, life-threatening or fatal pneumonitis/ILD have occurred in patients treated with enfortumab vedotin.
- Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnoea or interstitial infiltrates on radiologic exams. Corticosteroids should be administered for Grade ≥ 2 events (e.g., initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Withhold Padcev® for Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue Padcev® for Grade ≥3 pneumonitis/ILD.

❖ Hyperglycaemia
- Hyperglycaemia and diabetic ketoacidosis, including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with enfortumab vedotin.
- Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m2). Patients with baseline HbA1c ≥8% were excluded from clinical trials. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), Padcev® should be withheld until blood glucose is ≤13.9 mmol/L (≤250 mg/dL) and treat as appropriate.

❖ Peripheral neuropathy
- Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with enfortumab vedotin, including Grade ≥3 reactions. Patients with preexisting peripheral neuropathy Grade ≥2 were excluded from clinical trials. Patients should be monitored for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of enfortumab vedotin. Padcev® should be permanently discontinued for Grade ≥3 peripheral neuropathy.

❖ Ocular disorders
- Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin. Patients should be monitored for ocular disorders. Consider artificial tears for prophylaxis of dry eye and referral for ophthalmologic evaluation if ocular symptoms do not resolve or worsen.

❖ Infusion site extravasation
- Skin and soft tissue injury following enfortumab vedotin administration has been observed when extravasation occurred. Ensure good venous access prior to starting Padcev® and monitor for possible infusion site extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

❖ Embryo-foetal toxicity and contraception

- Pregnant women should be informed of the potential risk to a foetus.
- Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, to use effective contraception during treatment and for at least 12 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for up to 9 months following the last dose of Padcev®.

Study characteristics [11-14]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
EV-302 NCT04223856	886 (1:1)	3-week cycles of enfortumab vedotin (1.25 mg/kg IV on days 1 and 8) and pembrolizumab (200 mg IV on day 1)	3-week cycles of gemcitabine and either cisplatin or carboplatin	PFS by BICR + OS	17.2 months	**ongoing**[2], phase 3, global, open-label, randomised trial	PD-1	Astellas Pharma US and others	EV-302 [14]

Inclusion criteria[3]

- Histologically documented, unresectable, locally advanced or metastatic urothelial carcinoma.
- Measurable disease by investigator assessment according to RECIST v1.1.
- Participants with prior definitive radiation therapy must have measurable disease per RECIST v1.1 that is outside the radiation field or has demonstrated unequivocal progression since completion of radiation therapy.
- Participants must not have received prior systemic therapy for locally advanced or metastatic urothelial carcinoma, with the following exceptions:
  - Participants who received neoadjuvant chemotherapy with recurrence >12 months from completion of therapy are permitted.
  - Participants who received adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy are permitted.
- Must be considered eligible to receive cisplatin- or carboplatin-containing chemotherapy, in the investigator's judgment.

Exclusion criteria

- Previously received enfortumab vedotin or other monomethyl auristatin E-based antibody-drug conjugate.
- Received prior treatment with a PD-(L)-1 inhibitor for any malignancy, including earlier-stage urothelial cancer, defined as a PD-1 inhibitor or PD-L1 inhibitor.
- Prior treatment was received with an agent directed to another stimulatory or co-inhibitory T-cell receptor.
- Received anticancer treatment with chemotherapy, biologics, or investigational agents not otherwise prohibited by exclusion criteria 1-3 that is not completed 4 weeks prior to the first dose of study treatment.
- Uncontrolled diabetes.
- Estimated life expectancy of less than 12 weeks.
- Active CNS metastases.
- Ongoing clinically significant toxicity associated with prior treatment that has not resolved to ≤ Grade 1 or returned to baseline.
- Currently receiving systemic antimicrobial treatment for active infection (viral, bacterial, or fungal) at the time of randomisation. Routine antimicrobial prophylaxis is permitted.

Patient characteristics at baseline (I vs. C, n=442 vs. 444)

- Median age (range): 69 (37–87) vs. 69 (22–91) years
- Age ≥75 years: 23.1% vs. 24.3%
- Male sex: 77.8% vs. 75.7%
- Race or ethnic group:
  - Asian: 22.4% vs. 20.7%
  - Black: 0.7% vs. 1.6%
  - White: 69.7% vs. 65.3%
  - Other: 1.1% vs. 1.8%
  - Unknown or not reported: 6.1% vs. 0.6%
- Geographic region
  - North America: 23.3% vs.19.1%
  - Europe: 38.9% vs. 44.4%
  - Rest of the world: 37.8% vs. 36.5%
- ECOG performance-status score:
  - 0: 50.5% vs. 48.4%
  - 1: 46.2% vs. 48.6%
  - 2: 3.4% vs. 2.5%
  - Data missing: 0% vs. 0.5%
- Body-mass index
  - <25: 46.6% vs. 41.7%
  - 25 to <30: 32.6% vs. 34.9%
  - ≥30: 20.1% vs. 22.7%
  - Data missing: 0.7% vs. 0.7%
- Creatinine clearance:

[2] EV-302 is currently ongoing; the estimated study completion date is 11/2027.
[3] For detailed in-and exclusion criteria, please see trial protocol.

❖ Archival tumour tissue comprising muscle-invasive urothelial carcinoma or a biopsy of metastatic urothelial carcinoma must be provided for PD-L1 testing prior to randomisation. ❖ ECOG PS score of 0, 1, or 2. ❖ Adequate hematologic and organ function.	❖ Known active hepatitis B, active hepatitis C, or HIV infection. ❖ History of another invasive malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. ❖ Documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with NYHA Class IV within 6 months prior to randomisation. ❖ Receipt of radiotherapy within 2 weeks prior to randomisation. ❖ Received major surgery within 4 weeks prior to randomisation. ❖ Known severe (≥ Grade 3) hypersensitivity to any enfortumab vedotin excipient contained in the drug formulation of enfortumab vedotin. ❖ Active keratitis or corneal ulcerations. ❖ History of autoimmune disease that has required systemic treatment in the past 2 years. ❖ History of idiopathic pulmonary fibrosis, organising pneumonia, drug induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. ❖ Prior allogeneic stem cell or solid organ transplant. ❖ Received a live attenuated vaccine within 30 days prior to randomisation.	• ≥60 ml/min: 56.3% vs. 57.9% • <60 ml/min: 43.7% vs. 42.1% ❖ No. of Bajorin risk factors[4]: • 0: 40.5% vs. 41.2% • 1: 59.5% vs. 58.3% • Data missing: 0 vs. 0.5% ❖ H score of nectin-4 expression†† • No. of patients tested: 394 vs. 406 • Median score (range): 280 (0–300) vs. 270 (0–300) ❖ Disease status at randomisation: • Locally advanced: 4.8% vs. 5.4% • Metastatic: 95.2% vs. 94.6% ❖ Primary site of origin of disease: • Upper tract: 30.5% vs. 23.4% • Lower tract: 69.0% vs. 76.4% • Unknown: 0.5% vs. 0.2% ❖ Histologic type • Urothelial carcinoma: 85.7% vs. 84.0% • Urothelial carcinoma, mixed types: 11.3% vs. 11.9% • Variant urothelial carcinoma only: 0.9% vs. 1.6% • Unknown: 2.0% vs. 2.5% ❖ Sites of metastasis • Lymph node only: 23.3% vs. 23.4% • Visceral site: 71.9% vs. 71.6% • Bone: 18.3% vs. 23.0% • Liver: 22.6% vs. 22.3% • Lung: 38.5% vs. 35.4% ❖ Cisplatin eligibility status • Eligible: 54.3% vs. 54.5% • Ineligible: 45.7% vs. 45.5% ❖ PD-L1 expression • High, CPS ≥10: 58.0% vs. 57.9% • Low, CPS <10: 42.0% vs. 42.1%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Data cutoff date 8 August 2023; median duration of follow-up for survival: 7.2 months</u> **Median PFS**: 12.5 months (95% CI, 10.4-16.6) vs. 6.3 months (95% CI, 6.2-6.5); HR for disease progression or death 0.45; 95% CI, 0.38-0.54; p<0.001 **Median OS:** 31.5 months (95% CI, 25.4-not reached) vs. 16.1 months (95% CI, 13.9-18.3); HR for death 0.47; 95% CI, 0.38-0.58; p<0.001 **Estimated patients alive at 12 months**: 78.2% (95% CI, 73.9-81.9) vs. 61.4% (95% CI, 56.6-65.9)	**TRAEs of any grade:** 97.0% vs. 95.6% **TRAES of grade ≥3:** 55.9% vs. 69.5% **TRAES resulting in discontinuation of any treatment:** 35.0% vs. 18.5%

[4] Bajorin risk factors include visceral metastases (metastases to the bone, lung, or liver) and an ECOG performance-status score of 3 or higher. Patients with an ECOG performance-status score of higher than 2 were not eligible for the trial.

Confirmed ORR: 67.7% (95% CI, 63.1-72.1) vs. 44.4% (95% CI, 39.7-49.2); p<0.001 **CR**: 29.1% vs. 12.5% **Median duration of response**: not reached vs. 7.0 months **Patients in remission at 12 months**: 67.3% vs. 35.2% **Patients in remission at 18 months:** 59.6% vs. 19.3% **Subsequent Therapies** Patients who received subsequent anticancer therapies: 31.7% vs. 70.5% Platinum-based therapy as the first subsequent therapy[5]: 78.6% PD-1 or PD-L1 inhibitor–containing therapy as the first subsequent systemic therapy: 1.6% vs. 58.6%	**TRAEs resulting in death[6]:** <1.0% vs. <1%

Patient-reported outcomes

- The median time to pain progression was 14.2 months in I vs. 10.0 months in C; the between-group difference in the time to pain progression was not significant (HR 0.92; 95% CI, 0.72-1.17; p= 0.48
- Therefore, the additional patient-reported outcome in the statistical hierarchy was not formally tested.

ESMO-MCBS version 1.1 [15]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	>12 months ≤24 months	OS: +15.4 months	0.47 (0.38-0.58)	HR≤0.70 AND gain ≥5 months	4	-	improved (not significant)	-	4
Adapted	NC	2A	>12 months ≤24 months	OS: +15.4 months	0.47 (0.38-0.58)	HR≤0.70 AND gain ≥5 months	4	+16.5% TRAEs leading to discontinuation of any study treatment	improved (not significant)	-1[7]	3

Risk of bias (RCT) [16]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no[8] high risk	unclear[9] unclear risk	yes[10] high risk	unclear

Ongoing trials

NCT number/trial name	Description	Estimated study completion date
NCT04223856 / EV-302	Please see above.	11/ 2027
NCT05239624 / EV-ECLIPSE	Enfortumab vedotin in combination with pembrolizumab for locally advanced and/or node-positive urothelial carcinoma prior to surgery (phase 2).	06/2025
NCT03288545 / EV-103	Study of enfortumab vedotin as monotherapy or in combination with other anticancer therapies for the treatment of urothelial cancer (phase 2).	12/2026

[5] Among the patients in the enfortumab vedotin–pembrolizumab group who received subsequent therapies.
[6] In 4 patients in the enfortumab vedotin–pembrolizumab group (multiple organ dysfunction syndrome, immune-mediated lung disease, diarrhoea, and asthenia; 1 patient each) and in 4 patients in the chemotherapy group (sepsis, febrile neutropenia, neutropenic sepsis, and myocardial infarction; 1 patient each).
[7] Toxicity adjustment.
[8] Open-label trial design.
[9] The trial is currently ongoing; final result are not available yet.
[10] The trial was sponsored by Astellas Pharma US; Merck Sharp and Dohme, a subsidiary of Merck; and Seagen. The trial was designed by the sponsors and select members of the steering committee. Medical writers funded by the sponsors provided medical writing and editorial assistance with an earlier version of the manuscript in accordance with Good Publication Practice guidelines.

NCT05845814 / MK-3475-04B/ KEYMAKER-U04	A study of efficacy and safety of pembrolizumab + enfortumab vedotin +/- investigational agents in first-line metastatic urothelial carcinoma (phase 2).	05/2027

Available assessments

- In November 2022, NIHR published a Health Technology Briefing "Enfortumab vedotin with pembrolizumab for previously untreated locally advanced or metastatic urothelial cancer" [17].
- No further assessments were identified via NICE, CDA-AMC, G-BA and ICER.

Other aspects and conclusions: wichtige Informationen **fett**gedruckt**!**

- In July 2024, the **CHMP adopted a new indication** for Keytruda®, in combination with enfortumab vedotin, for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults. In December 2023, the **FDA approved** Padcev® in combination with Keytruda® for patients with locally advanced or metastatic urothelial cancer.
- **EV-302 (NCT04223856)** is an **ongoing**, **phase 3**, global, open-label, randomised trial comparing the efficacy and safety of enfortumab vedotin and pembrolizumab with the efficacy and safety of platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma. Eligible patients had radiologically documented, histologically confirmed, unresectable locally advanced or metastatic urothelial carcinoma; various histologic types such as adenocarcinoma or squamous cell differentiation, were included. Key exclusion criteria were previous PD-1 or PD-L1 inhibitor therapy or other systemic therapy, uncontrolled diabetes, ongoing sensory or motor neuropathy of grade 2 or higher, and previous autoimmune disease for which the patient had received systemic treatment in the previous 2 years.
- The **primary endpoints were PFS by BICR and OS**. Median PFS was 12.5 months vs. 6.3 months (HR for disease progression or death 0.45; 95% CI, 0.38-0.54; p<0.001), median OS was 31.5 months vs. 16.1 months (HR for death 0.47; 95% CI, 0.38-0.58; p<0.001).
- The median time to pain progression was longer in the enfortumab vedotin–pembrolizumab group; however, the difference between groups in the time to disease progression was **not significant**.
- The original and adapted **EMSO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit **grade 4 and 3**, respectively.
- Due to the ongoing status of EV-302 trial, the **risk of bias was considered unclear**. However, it is increased by the open-label trial design and the industry-funded background of the trial.
- Besides EV-302, **no further phase 3 trial** could be identified via ClinicalTrials.gov.
- For the assessed indication, available evidence is rare, and no further ongoing phase 3 trials were identified. Of note, because the results of the interim analysis of OS were significant in EV-302, the interim analysis was considered to be the final analysis.

First published: 09/2024

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ALT alanine aminotransferase, AST=aspartate aminotransferase, ASCT=autologous stem cell transplant, BICR=blinded independent central review, BTC=biliary tract cancer, C=comparator, CDA-AMC=Canada´s Drug Agency, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CPS=Combined Positive Score, CR=complete response, CRC=colorectal cancer, cSCC= Cutaneous Squamous Cell Carcinoma, CT=computed tomography, dMMR=mismatch repair deficient, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GEJ= gastroesophageal junction, GVHD=Graft-versus-Host disease, HIV= human immunodeficiency virus, HNSCC=head and neck squamous cell cancer, HR=hazard ratio, HSCT=haematopoietic stem cell transplant, I=intervention, ICER=Institute for Clinical and Economic Review, ILD=interstitial lung disease, Int.=intention, MG=median gain, MSI-H=microsatellite instability high, n=number of patients, NICE=National Institute for Health Care Excellence, NSCLC=non small cell lung cancer, NYHA=New York Heart Association, ORR=objective response rate, OS=overall survival, PD-1=programmed death receptor-1, PD-L1=programmed death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL= Primary Mediastinal Large B-Cell Lymphoma, QoL=quality of life, RCC=renal cell carcinoma, RECIST=Response Evaluation Criteria in Solid Tumors SAE=serious adverse event, SJS=Sjögren's syndrome, ST=standard treatment, TEN=toxic epidermal necrolysis, TMB-H= Tumor Mutational Burden-High, TPS= Tumor Proportion Score, TRAE=treatment-related adverse event, ULN=upper limit of normal

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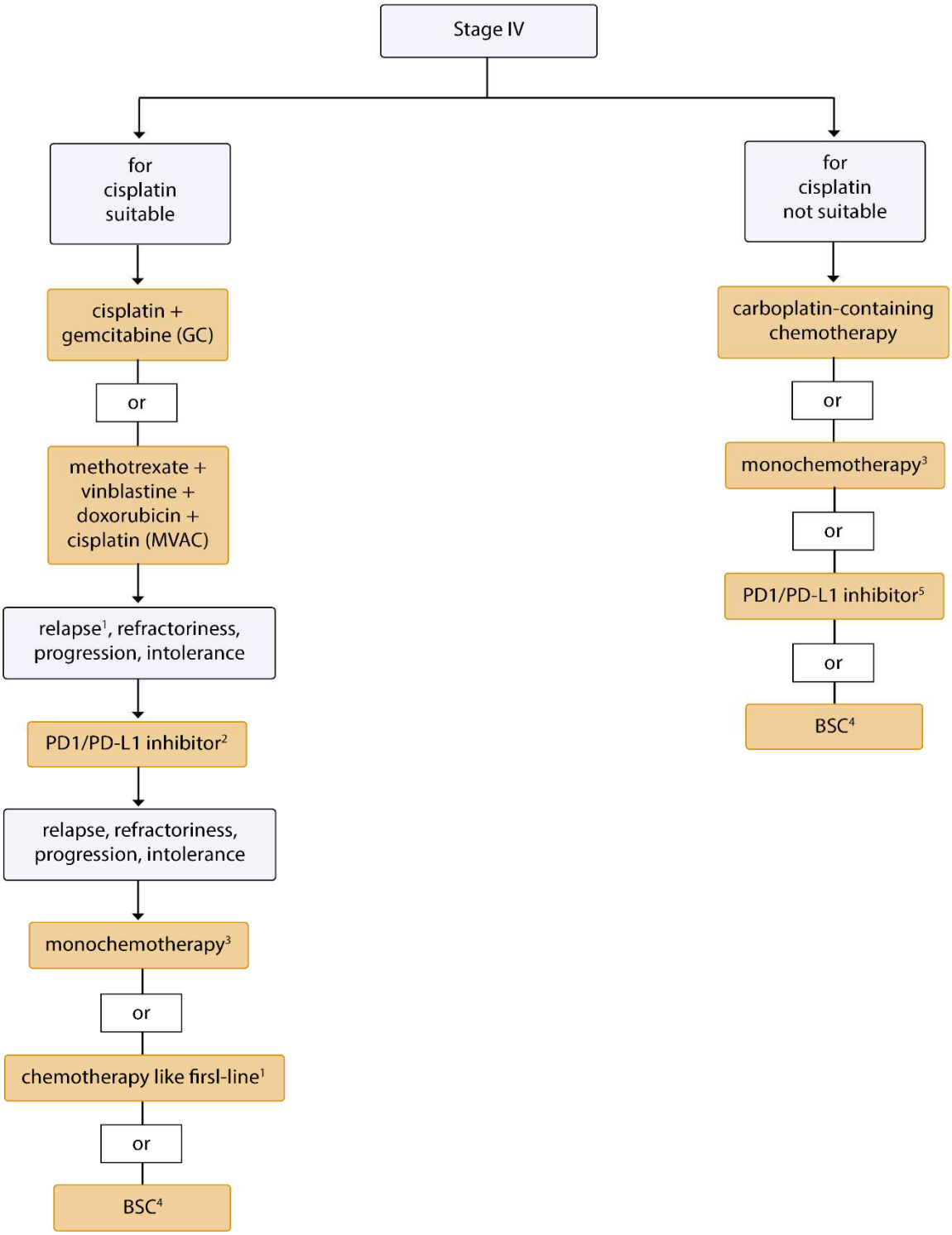
Appendix – Figure 1:



Legend:

curative therapy intention; palliative therapy intention;

[1] *With a remission duration >6 months, a repeat of the first-line therapy is also possible, depending on tolerability*
[2] *PD1/PD-L1 inhibitor: approved are atezolizumab, nivolumab, pembrolizumab*
[3] *Monochemotherapy: vinflunine, carboplatin, docetaxel, gemcitabine, paclitaxel*
[4] *BSC - Best Supportive Care*
[5] *PD1/PD-L1 inhibitor: if PD-L1 expression is positive (combined positive score, CPS): approved are pembrolizumab CPS ≥10%, atezolizumab PD-L1 ≥5%*