Enfortumab vedotin (Padcev®) as monotherapy for the treatment of patients with locally advanced or metastatic urothelial cancer

General information [1]							
Drug description	Indication						
Enfortumab vedotin (Padcev®) is an antibody-drug							
conjugate that induces cytotoxicity in cancer cells							
by binding to the nectin-4 target on the cell surface	Enfortumab vedotin (Padcev®) as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have						
and forming an ADC-nectin-4 complex. With the	previously received a platinum-containing chemotherapy and a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.						
internalisation and release of the drug component,							
the cycle cell is interrupted and the cells die.							

Current treatment

- In the current NICE pathway for managing locally advanced metastatic bladder cancer, there are no recommended therapies in patients that have progressed after second-line treatment with chemotherapy and PD-1/L1 inhibitors [2].
- Prognosis of advanced urothelial carcinoma [3]:
 - Advances in the management of advanced urothelial (transitional cell) carcinoma using cisplatin-based combination chemotherapy have led to a substantial increase in survival.
 - Despite this progress, metastatic disease is associated with a limited life expectancy, and cures are infrequent.
- Treatment of chemotherapy and immunotherapy-relapsed disease, according to the ESMO [4]:
 - Enfortumab vedotin is recommended as standard treatment in this population.
 - Erdafitinib is an alternative in patients with FGFR alterations with a weaker level of evidence.
 - Chemotherapy can be considered instead of best supportive care, if clinically appropriate.
 - Retreatment with chemotherapy for those patients that relapse after all other treatment options can be considered.
 - Single-agent taxane therapy or vinflunine can be considered.

Single-agent taxane therapy of vinnornine can be considered.								
Regulatory status								
EMA [1]	FDA [5]							
Approval status for this indication : On 24 February 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for	Approval status for this indication: On 9 July 2021, the FDA approved enfortumab vedotin-ejfv (Padcev®) for adult patients with locally advanced or metastatic urothelial cancer who:							
Padcev®.	have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, or							
The CHMP had initially adopted an opinion on 16 December 2021. During the decision-making process further safety information was brought to the attention	are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.							
of the Committee. Following a request from the European Commission, the CHMP	✓ Priority review							
readopted its opinion on 24 February 2022, taking into account the latest information.	✓ Breakthrough therapy designation							
UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 13/04/2022 [6]	The FDA granted accelerated approval in December 2019 to enfortumab vedotin-ejfv for patients with locally advanced or metastatic urothelial cancer who have received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy in the							
The full indication is:	neoadjuvant/adjuvant, locally advanced, or metastatic setting.							
Padcev® as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.	Other indications: none							
Other indications: none								



✓ Medicine is under additional monitoring

Costs [7]

Padcev® powder for concentrate for solution for infusion 20 mq = € 710.41 (ex-factory price)

Padcev® powder for concentrate for solution for infusion 30 mg = € 1,065.62 (ex-factory price)

Warnings and precautions [8]

Serious skin reactions

- Padcev® can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).
- Immediately withhold Padcev® and consider referral for specialised care for suspected SJS or TEN or severe skin reactions.
- Permanently discontinue Padcev® in patients with confirmed SJS or TEN, or Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia:

- Diabetic ketoacidosis may occur in patients with and without pre-existing diabetes mellitus, which may be fatal.
- Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia.
- Withhold Padcev® if blood glucose is >250 mg/dL.

Pneumonitis:

- Severe, life-threatening, or fatal pneumonitis may occur.
- Withhold Padcev® for persistent or recurrent Grade 2 pneumonitis and consider dose reduction.
- Permanently discontinue Padcev® for Grade 3 or 4 pneumonitis.

Peripheral neuropathy:

Monitor patients for new or worsening peripheral neuropathy and consider dose interruption, dose reduction, or discontinuation of Padcev®.

Ocular disorders:

- Ocular disorders, including vision changes, may occur.
- Monitor patients for signs or symptoms of ocular disorders.
- Consider prophylactic artificial tears for dry eyes and treatment with ophthalmic topical steroids after an ophthalmic exam.
- Consider dose interruption or dose reduction of Padcev® when symptomatic ocular disorders occur.

Infusion site extravasation:

- Ensure adequate venous access prior to administration.
- Monitor the infusion site during Padcev® administration and stop the infusion immediately for suspected extravasation.

Embryo-foetal toxicity:

- Padcev® can cause foetal harm.
- Advise of the potential risk to a foetus and to use effective contraception.

7 ta vise c	Advise of the potential risk to a foctor and to use effective contraception.									
Study characteristics [9-13]										
Trial name	e n Intervention (I) Comparator (C) PE Characteristics Biomarker Funding Publication(s)									
EV-301 NCT03474107	608 (301 vs. 307)	Enfortumab vedotin at a dose of 1.25 mg/kg of body weight	Chemotherapy¹ (selected by the investigator	OS	ongoing, global, open-label, randomised, phase 3 trial	-	Astellas Pharma US and Seagen	[12]		



¹ Chemotherapy and was one of the following: docetaxel at a dose of 75 mg/m² of BSA, administered IV over 60 minutes; paclitaxel at a dose of 175 mg/m², administered IV over 3 hours; or vinflunine (in regions where it is approved for treatment of urothelial carcinoma) at a dose of 320 mg/m², administered IV over 20 minutes. The use of vinflunine was capped at 35% of the patients in this trial. The chemotherapy treatments were administered on day 1 of a 21-day cycle.

Safety (I.v. C) Safety (I.v. C) Treatment-related AEs 1-2/8/19/6/(93, 4) or 3-6/3/21/(93.8%) Treatment-related AEs 1-2/8/19/6/(93.8%) Treatment-													
Safety (Us. C) Treatment-related AEs: n=278/296 (39.9% Us. n=267/291 (9.18%) All rear a median follow-up of 1.1 months, the risk of death was 30% lower with Enfortumab vedotin han with chemotherapy. Bedian AEs: 2.88 months (95% C), 10.68-15.21 Us. 8.97 months (95% C), 8.05 + 0.74, p-18 (95% C), 3.25 + 0.36, p-0.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 4.6-9.80 (1.8.05 + 0.74, p-18) (95% C), 0.55 + 0.38, p-0.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 4.6-9.80 (1.8.05 + 0.74, p-18) (95% C), 0.55 + 0.38, p-0.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 4.6-9.80 (1.8.05 + 0.74, p-18) (95% C), 0.51 + 0.38, p-0.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 3.51 + 0.38, p-1.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 3.51 + 0.38, p-1.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 3.51 + 0.38, p-1.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 3.51 + 0.38, p-1.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 3.51 + 0.38, p-1.001 Estimated percentage of patients alive a 1.2 months: 51.9% (95% C), 3.51 + 0.38, p-1.001 Estimated percentage of patients alive a 1.2 months: 61.9% (C), 3.52 + 0.39, p-1.001 Estimated percentage of patients alive a 1.2 months: 61.9% (C), 3.52 + 0.39, p-1.001 Estimated percentage of patients alive a 1.2 months: 61.9% (C), 3.52 + 0.39, p-1.001 Estimated percentage of patients on the second percentage of patie			y means of										
Safety (Ivs. C) OS: After a median follow-up of 13.2 months, the risk of death was 30% lower with Enfortumab vedotin than with chemotherapy. After a median follow-up of 13.2 months, the risk of death was 30% lower with Enfortumab vedotin than with chemotherapy. Median OS: 12.88 months (95% Cl, 10.5% 15.21) vs. 8 g. 7 months (95% Cl, 8.05 to 7.4), HR for death 10.79; 95% Cl, 0.55-0.89; peo. 002 FPES: Treatment with enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. Median PFS: 5.55; months (95% Cl, 5.32-5.82) vs. 3.71 months (95% Cl, 3.52-5.92), p. 8, 20.01 Clinical Response: OS: After a median follow-up of 13.2 months, the risk of death was 30% lower with Enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. Median PFS: 5.55; months (95% Cl, 5.32-5.82) vs. 3.71 months (95% Cl, 3.52-5.92), p. 8, 20.01 Clinical Response: OS: After a median follow-up of 13.2 months, the risk of death was 30% lower with Enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. OS: After a median follow-up of 13.2 months (95% Cl, 5.32-5.82) vs. 3.71 months (95% Cl, 5.32-5.82) vs. 3.71 months (95% Cl, 5.32-5.82) vs. 3.71 months (95% Cl, 5.32-5.82) vs. 3.72 months (95% Cl, 5.32-5.82) vs. 3.73 months vs. 8.11 months OCL: OL: OL: A Cuestionnaire compliance rates at baseline were golf in both groups, during the study, average rates were 70.2% (I) and 6.59% (Cl, 7.76) vs. 7.52 pc.0, but significantly greater detection ration and more variability in Ocl our the first tax weeks. Patients receiving Enfortumab vedotin had significant reduction in pain symptoms (1-2.8, C-1-2.5, qb, 25, C-1-3.3, qb, 25). Cr. 20.31, adjusted difference: 5.73, pc.0.0) but significant worsening of appetite loss (randomisation) ²									
Safety (1vs. C) Treatment-related AEs: n=29/296 (33-9%) vs. n=26/293 (33-9%) vs. n=26/2													
Safety (vs. C) Treatment related AEs: ne-z9/23g (gg.39) vs. ne-25/23g (gg.39) vs. ne-33/23g (gg.39) vs. ne-33/2		· · · · · · · · · · · · · · · · · · ·	-										
Safety (Us. ©) Safety (Us. ©) Safety (Us. ©) Safety (Us. ©) Treatment-related AEs: n=278/256 (33.9%) vs. n=267/251 (93.8%) Median OS: 1.28 months (95% C), 10.58-15.21) vs. 8 gy months (95% C), 8.05-10.74), HR for death 0.70; 95% C), 0.56-0.89; p=0.001 Estimated percentage of patients alive at 12 months: \$12.9% (93.6 C), 4.6-5.80 ovs. 39.2% (95% C), 2.5-6.5.6) PSF. Treatment with enfortural vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. Median PSF. 5, 55 months (95% C), 5.32-5.82) vs. 3.71 months (95% C), 3.52-3.94), HR for progression or death 0.52; 95% C), 0.51-0.75; p=0.001 Clinical Response: Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% C), 3.49-465, vs. 1.73% (93% C), 1.337-128, p=0.001) Complete response: Obj. Disease control: 71.3% (95% C), 6.3-77-00) vs. 53.4% (95% C), 4.75-59.2), p=0.001 Complete response: n abtents who had a complete or partial response: 7.39 months vs. 8.11 months Obj. Disease control: 71.3% (95% C), 6.3-77-00) vs. 53.4% (95% C), 4.75-59.2), p=0.001 Complete response in abtents who had a complete or partial response: 7.39 months vs. 8.11 months Obj. Disease control: 71.3% (95% C), 6.3-77-00 vs. 53.4% (95% C), 4.5-59.2), p=0.001 Complete response in abtents who had a complete or partial response: 7.39 months vs. 8.11 months Obj. Disease control: 71.3% (95% C), 6.3-77-00 vs. 53.4% (95% C), 6.3-77-00 vs. 63.4% (95% C), 6.3-77-00 vs. 63.4% (95% C), 6.3-77-0			, , ,										
Safety (l.s. ©) Safety (l.s. ©) Safety (l.s. ©) After a median follow-up of 1.1 months, the risk of death was 30% lower with Enfortumab vedotin than with chemotherapy. Median OS: 1.2.8 months (93% Cl, 10.58-2.5.21) vs. 8.97 months (93% Cl, 8.05-1.0.74), HR for death 0.70; 95% Cl, 0.56-0.89, p=0.001 Estimated percentage of patients alive at 12 months: 5.13% (95% Cl, 4.6-5.80 vs. 32.946.95% Cl, 3.05-6.4.56) PFS: Treatment with enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. Median PFS: 5.55 months (95% Cl, 5.32-5.82) vs. 3.71 months (95% Cl, 3.52-3.94), HR for progression or death o. 62; 95% Cl, 0.51-0.75; p=0.002 Clinical Response: Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% Cl, 34-9-46.5 vs. 1.79 (95% Cl, 3.73-2.8) p=0.003) Complete response: 4.98% vs. 2.79% Median duration of response in patients who had a complete or partial response: 7.39 months (95% Cl, 4.75-59.2.) p=0.003 Complete response: patients who had a complete or partial response: 7.39 months vs. 8.11 months Col: Oustionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were 70.2% (f) and 6.6.9% (C). Baseline Cl.Q. Cos scores were similar between groups. At view ext. 3, scores on the global health status (GHS) scale were similar between groups (1-2.8, C-5.6); p=2429), but chemotherapy was associated with numerically greater deterioration and more variability in Ool. over the first 12 weeks. Patients receiving Enfortumab vedotin had significant reduction in pain symptoms (1-5.62, C-10.11) adjusted difference: 9-5, pp. 60, sb. 10, significant vorsening of appetite loss (1-8, 55, C-1.25, 6), alloyed difference: 9-5, pp. 60, sb. 10, significant vorsening of appetite loss (1-8, 55, C-1.25, 6), alloyed difference: 9-5, pp. 60, sb. 10, significant vorsening of appetite loss (1-8, 55, C-1.25, 6), alloyed difference: 9-5, pp. 60, sb. 10, significant vorsening of													
OS: 12.88 months (gs% Cl, 10.58-15.21) vs. 8.97 months (gs% Cl, 8.05-10.74), HR for death 0.70; gs% Cl, 0.56-0.89; p=0.005 Estimated percentage of patients alive at 12 months: (gs% Cl, 8.05-10.74), HR for death 0.70; gs% Cl, 0.56-0.89; p=0.005 Estimated percentage of patients alive at 12 months: (gs% Cl, 8.05-10.74), HR for death 0.70; gs% Cl, 0.56-0.89; p=0.005 Estimated percentage of patients alive at 12 months: (gs% Cl, 8.05-10.74), HR for death 0.70; gs% Cl, 0.56-0.89; p=0.005 Estimated percentage of patients alive at 12 months: (gs% Cl, 8.05-10.74), HR for progression or death 0.62; gs% Cl, 0.51-0.75; p=0.001 Median PES: 5, gs months (gs% Cl, 5.32-5, 82) vs. 3.71 months (gs% Cl, 3.52-3.94), HR for progression or death 0.62; gs% Cl, 0.51-0.75; p=0.002 Conflictal Response: Conflictal Response: Conflicted overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 4.0.6% (gs% Cl, 3.47-2.8), p=0.001 Complete response: 4.9% vs. 2.7% Disease control: 7.1.9% (gs% Cl, 6.5-7.77.0) vs. 53.4% (gs% Cl, 4.75-59.2), p=0.001 Complete response: 4.9% vs. 2.7% Disease control: 7.1.9% (gs% Cl, 6.5-7.77.0) vs. 53.4% (gs% Cl, 4.75-59.2), p=0.001 Complete response: 4.9% vs. 2.7% Disease control: 7.1.9% (gs% Cl, 6.5-7.77.0) vs. 53.4% (gs% Cl, 4.75-59.2), p=0.001 Treatment-related AEs leading to withdrawal: m=2/1296 (g.3.9%) vs. n=32/372 (gs.9.6%) vs. n=28/1291 (gs.8%) n=32/372 (gs.9.6%) vs. n=28/1291 (gs.8%) n=32/372 (gs.9.6%) vs. n=28/1291 (gs.8%) n=32/372 (gs.9.6%) vs. n=28/1291 (gs.9%) n=32/372 (gs.9.6%) vs. n=28/1291 (gs.9%) n=32/372 (gs.9.6%) n=32/		2	8-day cycle	-cc:									
After a median follow-up of 1.1.1 months, the risk of death was 30% lower with Enfortumab vedotin than with chemotherapy. Median OS: 12.88 months (95% C1, 10.58-15.21) vs. 8.97 months (95% C1, 0.56-10.74), HR for death 0.70; 95% C1, 0.56-0.89; p=0.001 Estimated percentage of patients alive at 12 months: 51.5% (95% C1, 44.6-58.0) vs. 39.2% (95% C1, 25.6-45.6) PFES: Treatment with enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. Median PFS: 5.55 months (95% C1, 52-2-58.2) vs. 3,71 months (95% C1, 3.52-3.94), HR for progression or death o.62; 95% C1, 0.52-0.02 Clinical Response: Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 4.0.6% (95% C1, 34-9-46.5) Spease control: 7.9.9% (95% C1, 0.53-0.003) Complete response: 4.9% vs. 2.7% Median divation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Col. * Questionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were 70.2% (1) and 6.6% (95% C1, 20.50) spease control: 7.9.9% (95% C1, 0.52-59.2), p<.0.03 Median divation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Col. * Questionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were 70.2% (1) and 6.6% (95% C1, 20.50) spease control rate (1) greater deterioration and more variability in O.0.1 over the first 12 weeks. Patients receiving Enfortumab vedotin than disgnificant reduction in pain symptoms of 1.5.6.2, 2. 1.0.13, 400 (10.60) spease control (1)				Efficacy	(I vs. C)								
Median PS: 12.88 months (95% Cl, 10.98-15,23.1) × 8.89 grownoths (95% Cl, 10.94-6,98.0) vs. 39.2% (95% Cl, 32.6-4.5.6) PFS: Treatment with enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. Median PFS: 55 grownths (95% Cl, 53.2-5.82) vs. 3.71 months (95% Cl, 3.52-3.94), HR for progression or death 0.62; 95% Cl, 0.51-0.75; pc. ∞.03 Clinical Response: Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% Cl, 34.9-46.5 vs. 17.9% (95% Cl, 34.7-22.8); pc.0.001 Complete response: Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% Cl, 34.9-46.5 vs. 17.9% (95% Cl, 35.7-3.8), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53.4% (95% Cl, 4.7.5-9.2), pc.0.001 Median PTS: 52, pc. moths (95% Cl, 66.3.77.0) vs. 53													
Estimated percentage of patients alive at 12 months: 51,5% (65% Cl, 44,6-58 a) vs. 39,2% (65% Cl, 26-45.5) PFS: Treatment with enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. Median PFS: 5,55 months (95% Cl, 532-5.82) vs. 371 months (95% Cl, 352-3.94), HR for progression or death o. 62, 95% Cl, 0.51-075, p=-0.00 Clinical Response: Confirmed voreall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% Cl, 34.9-46.5 vs. 17, 39% (95% Cl, 13.7-22.8) ps.0.001) Complete response: 4.9% vs. 2.7% Disease Control: 73.9% (95% Cl, 13.7-22.8) ps.0.001 Median Juration of response with chemotherapy group: 40.6% (95% Cl, 34.9-46.5 vs. 17, 39% (95% Cl, 43.7-40) vs. 53.4% (95% Cl, 43.7-20.8) ps.0.001 Median Juration of response where similar between groups (1-2.8, Cl-5.0) ps. 24.29), but chemotherapy was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. 5-573, ps.0.6), but significantly different between groups. * Attentive Rev. 21, scores on the global health status (GHS) scale were similar between groups (1-2.8, Cl-5.0), ps.2429), but chemotherapy was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. 5-573, ps.0.6), but significantly different reduction in pain symptoms (1-2.8, Cl-5.0), ps.2429), but chemotherapy was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. 6-573, ps.0.6), but significantly different between groups. * Plates receiving Enfortumab vedotion has significant reduction in pain symptoms (1-2.8, Cl-5.0), ps.2429), but chemotherapy was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. 6-573, ps.0.6), but significantly difference in improvements across all functioning domains (role, physical, emotional), social, cognitive, (HS, and several symptoms scales (pain, fatigue, dyspnea, co		·	-	_									
PFS: Treatment with enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. Median PFS: 5.55 months (95% CI, 9.32-5.82) vs. 3.71 months (95% CI, 3.52-3.94), HR for progression or death o. 6.2; 95% CI, 0.51-0.75 pc. 0.01 Confinical Response: Confinical Response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% CI, 3.49-46.5 vs. ra.38/1.26 (4.65 %) vs. n=128/1.29 (4.0.4%) Complete response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% CI, 3.49-46.5 vs. ra.38/1.28) pc. 0.001) Complete response: 4.9% vs. 2.7% Disease control: 71.9% (95% CI, 6.53-77.0) vs. 53.4% (95% CI, 4.7.5-59.2), pc. 0.001 Complete response: 4.9% vs. 2.7% Disease control: 71.9% (95% CI, 6.63-77.7.0) vs. 53.4% (95% CI, 4.7.5-59.2), pc. 0.001 Complete response: 4.9% vs. 2.7% Disease control: 71.9% (95% CI, 6.63-77.7.0) vs. 53.4% (95% CI, 4.7.5-59.2), pc. 0.001 Treatment-emergent AEs leading to death: n=21/2.96 (71.9%) vs. n=16/2.91 (71.7.5%) Treatment-emergent AEs leading to death: n=21/2.96 (71.9%) vs. n=16/2.91 (71.5.9%) Treatment-emergent AEs leading to death: n=21/2.96 (71.9%) vs. n=11/2.91 (31.9%) vs. n=11/2.91 (31								.56-0.89; p=0.001	Treatment-rela	ated AEs leading to withdrawal: r	1=40/296 (13.5%) vs. n=33/291		
Median PFS: 5.55 months (95% CI, 5.32-5.82) vs. 3.71 months (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 5.32-5.82) vs. 3.71 months (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 5.32-5.82) vs. 3.72 months (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.51-505; provided (95% CI, 3.52-3.94), HR for progression or death o. 52; 95% CI, 0.52-505; provided (95% CI, 3.52-5.95), Pro	Estimat	ed percentage of patien	ts alive at 12	months: 51.5% (95	% CI, 44.6-58.0) v	s. 39.2% (95% C	I, 32.6-45.6)		(11.3%)				
Median PFS: 5.55 months (95% CI, 5.32-5.82) vs. 3.71 months (95% CI, 3.52-3.94), HR for progression or death o.62; 95% CI, 0.51-Clinical Response: Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% CI, 34.9-46.5 vs. 17.9% (95% CI, 1.37-22.8, p-o.001) Complete response: 4.9% vs. 2.7% Disease control: 71.9% (95% CI, 63.77.0) vs. 53.4% (95% CI, 47.5-59.2), p-o.001 Median duration of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Col. ◆ Questionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were yo.2% (I) and 6.5% (C). ◆ Baseline CU.C-3go scores were similar between groups. ◆ At week 12, scores on the global health status (GHS) scale were similar between groups (I: -2.8, C: -5.0; p=.2429), but chemotherapy was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. ◆ Patients receiving Enfortumab vedotin had significant treduction in pain symptoms (I: -12.6; adjusted difference: -5.73, p-0.93), but significant worsening of appetite loss (I: +8.55, C: +1.26; adjusted difference: -5.73, p-0.03), but significant worsening of appetite loss (I: +8.55, C: +1.26; adjusted difference: -5.73, p-0.03), but significant to more variability in QoL over the first 12 weeks. ◆ Patients receiving Enfortumab vedotin had significant to offirmed improvements across all functioning domains (role, physical, emotional, social, cognitive), GHS, and several symptom scales (pain, fatigue, dyspnea, constipation). The greatest difference in improvement was reported for pain (I: 51.6%, C: 28.8%, OR = 2.76,1.81, 4.22). Conclusions: Compared with chemotherapy, patients receiving enfortumab vedotin had numerically less deterioration and variability in QoL during the first 12 weeks of treatment. More patients in I had improvements over Ci in 10 of 15 QLQ. C30 domains; improvement in pain showed the largest benefit.	PFS: Tre	atment with enfortumal	vedotin resu	Ited in significantly	longer PFS than o	chemotherapy a	nd a 38% lowe	r risk of			at resulted in death: n=7/296		
Serious treatment-emergent AEs: n=13/1.926 (4.6.6%) vs. n=128/1.921 (4.0.6%) (5.5%)									-	-			
Cinical Response: Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% Cl, 34,-9-45.5 xl, 7% (95% Cl, 23,7-22.8) p<0.001) Complet response: 4,9% vs. 2,7% Disease control: 71.9% (95% Cl, 66.3-77.0) vs. 53.4% (95% Cl, 47.5-59.2), p<0.001 Median duration of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Col: ◆ Ouestionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were 70.2% (l) and 66.9% (C). ◆ Baseline CLQ-C30 scores were similar between groups. ★ At tweek 12, scores on the global health status (GHS) scale were similar between groups (l:-2.8, C:-5.0; p=.2429), but chemotherapy was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. ◆ Patients receiving Enfortumab vedotin had significant reduction in pain symptoms (l:-5.62, C:+0.11, adjusted difference:-5.73, p<0.05), but significant worsening of appetite loss (l:+8.55, C:+1.26; adjusted difference:-7.29, p<0.05) compared with chemotherapy. ◆ Other symptom scores were not significantly different between groups. ◆ Higher proportions of patients on l vs. C had significant confirmed improvements across all functioning domains (role, physical, emotional, social, cognitive), GHS, and several symptom scales (pain, fatigue, dyspnea, constipation). The greatest difference in improvement was reported for pain (l: 51.6%, C: 28.8%; OR = 2.76,1.81, 4.22). ◆ Conclusions: Compared with chemotherapy, patients receiving enfortumab vedotin had improvements over C in 10 of 15 CLC- 23 domains; improvement in pain showed the largest benefit. ESMOMCBS version 1.1 [14]	Median	PFS : 5.55 months (95% (CI, 5.32-5.82) \	/s. 3.71 months (95%	6 CI, 3.52-3.94), Н	R for progressio	n or death o.6:	2; 95% CI, 0.51-	Overall treatment-emergent AEs: n=290/296 (98.0%) vs. n=288/291 (99.0%)				
Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% Cl, 34,9-46.5 vs. 17,9% (95% Cl, 32,7-22.8); p<0.001) Complete response: 4,9% vs. 2.7% Disease control: 71.9% (95% Cl, 66.3-77.0) vs. 53.4% (95% Cl, 47.5-59.2), p<0.001 Median duration of response in patients who had a complete or partial response: 7,39 months vs. 8.11 months Col: * Ouestionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were 70.2% (I) and 66.9% (C). * Baseline QLQ-C30 scores were similar between groups. * At week 12, scores on the global health status (GHS) scale were similar between groups (1:-2.8, C:-5.0; p=.2429), but chemotherapy was associated with numerically greater deterioration and more variability in Qu. out one to significant worsening of appetite loss (I:+8.55, C:+1.26; adjusted difference: -5.73, p0.5), but significant worsening of appetite loss (I:+8.55, C:+1.26; adjusted difference: -5.73, p0.5), but significant solitons of patients on I vs. C had significant reduction in pain symptoms (I:-5.63, C:+0.11; adjusted difference: physical, emotional, social, cognitive), GHS, and several symptom scales (pain, fatigue, dyspnea, constipation). The greatest difference in improvement was reported for pain (I: 5.15%), C: 2.8% (OR = 2.75, 1.81, 2.2). * Conclusions: Compared with chemotherapy, patients receiving enfortumab vedotin had numerically less deterioration and variability in QoL during the first 12 weeks of treatment. More patients in I had improvements over Cin 10 of 15 QLQ-C30 domains; improvement in pain showed the largest benefit. ESMOMCBS version 1.1 [14]									Serious treatment-emergent AEs: n=138/296 (46.6%) vs. n=128/291 (44.0%)				
Vs. 17.9% (95% CI, 13.7-22.8; p<0.001) Complete response: 4.9% vs. 27,% Median duration of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=11/291 (3.8%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=11/291 (3.8%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=11/291 (3.8%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=11/291 (3.7%) vs. n=11/291 (3.8%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=11/296 (3.7%) vs. n=11/291 (3.8%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=11/291 (3.8%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=11/291 (3.8%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leading to death: n=21/296 (7.1%) vs. n=16/291 (5.5%) Treatment-emergent AEs leadin	Clinical	Response:							Treatment-emergent grade ≥3 AEs: n=210/296 (70.9%) vs. n=193/291 (66.3%)				
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Disease control: 71.9% (95% CI, 66.3-77.0) vs. 53.4% (95% CI, 47.5-59.2), p<0.001 Median duration of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months COL: * Questionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were 70.2% (I) and 66.9% (C). * Baseline QLQ-C30 scores were similar between groups. * At week 12, scores on the global health status (GHS) scale were similar between groups (I: -2.8, C: -5.0; p=.2429), but chemotherapy was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. * Patients receiving Enfortumab vedotin had significant reduction in pain symptoms (I: -2.62, C: +0.11; adjusted difference: -5.73, p<-0.5), but significant worsening of appetite loss (I: +8.55, C: +1.26; adjusted difference: -7.29, p<-0.9) compared with chemotherapy. * Other symptom scores were not significantly different between groups. * Higher proportions of patients on I vs. C had significant confirmed improvements across all functioning domains (role, physical, emotional, social, cognitive), GHS, and several symptom scales (pain, fatigue, dyspnea, constipation). The greatest difference in improvement was reported for pain (I: 51.6%, C: 28.8%, OR = 2.76,1.81, 4.22). * Conclusions: Compared with chemotherapy, patients receiving enfortumab vedotin had numerically less deterioration and variability in QoL during the first 12 weeks of treatment. More patients in I had improvements over C in 10 of 15 QLQ-C30 domains; improvement in pain showed the largest benefit. ESMONCBS version 1.1 [14]	vs. 17.9%	% (95% CI, 13.7-22.8; p<0	.001)										
Treatment-emergent AEs leading to death, excluding disease progression: n=11/296 (3.7%) vs. n=11/291 (3.8%) Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months Columnation of response in patients at baseline were gold in both groups; during the study, average rates were 70.2% (I) and 66.9% (C). At week 12, scores on the global health status (GHS) scale were similar between groups (I: -2.8, C: -5.0; p=.24,29), but chemotherapy was associated with numerically greates difference: -5.73, p.<.05), but significant vorsening of appetite loss (I: -8.55, C: +1.26; adjusted difference: -5.50; pe.24, 29, p.<.05) compared with chemotherapy. Columnation of response were not significant reduction in pain symptom scores at large difference: 7.29, p.<.05) compared with chemotherapy. Columnation of patients on I vs. C had significant reduction in pain symptom scales (pain, fatigue, dyspnea, constipation). The greatest difference in improvement was reported for pain (I: 51.6%, C: 28.8%; OR = 2.76,1.81, 4.22). Columnation of the patients of the	Complet	e response: 4.9% vs. 2.79	%										
Col.:	Disease	control: 71.9% (95% CI , 6	6.3-77.0) vs. 5	3.4% (95% CI , 47.5-	59.2) , p<0.001				(5.5%)				
 Questionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were 70.2% (I) and 66.9% (C). Baseline OLQ-C30 scores were similar between groups. At week 12, scores on the global health status (GHS) scale were similar between groups (I: -2.8, C: -5.0; p=.2429), but chemotherapy was associated with numerically greater deterioration and more variability in OoL over the first 12 weeks. Patients receiving Enfortumab vedotin had significant reduction in pain symptoms (I: -5.62, C: +0.11; adjusted difference: -5.73, p<.05), but significant worsening of appetite loss (I: +8.55, C: +1.26; adjusted difference: 7.29, p<.05) compared with chemotherapy. Other symptom scores were not significantly different between groups. Higher proportions of patients on I vs. C had significant confirmed improvements across all functioning domains (role, physical, emotional, social, cognitive), GHS, and several symptom scales (pain, fatigue, dyspnea, constipation). The greatest difference in improvement was reported for pain (I: 51.6%, C: 28.8%, OR = 2.76,1.81, 4:22). Conclusions: Compared with chemotherapy, patients receiving enfortumab vedotin had numerically less deterioration and variability in OoL during the first 12 weeks of treatment. More patients in I had improvements over C in 10 of 15 QLQ-C30 domains; improvement in pain showed the largest benefit. 	Median	duration of response in p	atients who h	ad a complete or pa	artial response: 7.3	39 months vs. 8.:	11 months						
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Scale Int. Form Mod Til (9570 CI) Score Calculation Fivi Toxicity Que AJ Fivi	Scale	Int. Form MO	G ST M	1G HR (95	% CI) Sco	ore calculation	PM	Toxicity	QoL	AJ	FM		

² All patients who received paclitaxel or docetaxel received premedication to prevent hypersensitivity reactions or fluid retention.



Original	NC	28	≤12 months	OS: +3.91 months	0.70 (0.56-0.89)	HR≤o.65 AND gain ≥ months	3 4	х	NSD	x	4
Adapted	NC	28	≤12 months	OS: +3.91 months	0.70 (0.56-0.89)	HR >0.65-0.70 AND gain ≥1.5 months	2	х	NSD	x	2
	Risk of bias (RCT) [15]										
-	Adequate generation of randomisation sequence		ACIECILIA	ate allocation	concealment	Blinding		ve outcome ing unlikely	Other aspects which increase the risk of bias	Risk of	bias
	yes			-		No, open-label	U	nclear³	yes ⁴	uncle	ar
											First published: 01/2022

Last updated: o6/2022

Abbreviations: AE=adverse event, AJ=adjustment, BSA=body-surface area, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, GHS=global health status, FGFR= fibroblast growth factor receptor, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention. IV=intravenous(IV). NSD=no significant difference. MG=median gain. n=number of patients. OS=overall survival. PD-1=programmed death-receptor-1. PD-L1=programmed death-ligand. PE=primary endpoint. PFS=progression-

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free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SJS= Stevens-Johnson syndrome, ST=standard treatment, TEN=Toxic Epidermal Necrolysis

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 $^{^{\}rm 3}$ EV-301 is currently ongoing; estimated study completion date is 02/2022.

⁴ The trial was designed by the sponsors in collaboration with an advisory committee. Data were collected by the trial investigators, analysed by statisticians employed by the sponsor, and interpreted by all authors. The authors, with writing and editorial support funded by the trial sponsors, developed and approved the manuscript.

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