Report Padcev® - enfortumab vedotin

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: enfortumab vedotin **Brand Name:** Padcev **Originator/licensee**: Astellas Pharma Europe B.V. **Classification:** NCE **ATC code:** L01FX13 **Orphan Status:** **Eu:** No **Us:**No **Mechanism of action:** Enfortumab vedotin is an ADC. The antibody is a human IgG1 directed against Nectin-4, an adhesion protein located on the surface of cells. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. MMAE disrupts the microtubule network within the cell, inducing cell cycle arrest and apoptotic cell death[1].	**Authorized Indication:** **EMA:** enfortumab vedotin as monotherapy is indicated for the treatment of adult pts with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD□1 or PD-L1 inhibitor [2]. **FDA:** indicated for the treatment of adult pts with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting [1] **Route of administration:**IV **Licensing status** **EU CHMP P.O. date:** 16/12/2021 **FDA M.A. date:** 18/12/2019 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No **ABBREVIATIONS:** **ADC:** antibody-drug conjugate **AE:** adverse event **BCG**: bacillus Calmette-Guérin **CHMP:** Committee for Medicinal Products for Human Use **CP**: complete response **M.A.:** Marketing Authorization **MIBC:** muscle-invasive bladder carcinoma **MMAE:** monomethyl auristatin E **NMIBC**: non-muscle-invasive bladder carcinoma **PR:** partial response **PD-1:** programmed death receptor-1 **PD-L1:** programmed death-ligand 1 **P.O.:** Positive Opinion **Pts:** patients **RECIST**: Response Evaluation Criteria in Solid Tumours **SoC**: Standard of care	**Summary of clinical EFFICACY:** The efficacy of enfortumab vedotin was evaluated in a phase II, single-arm trial (**NCT03219333**). Enfortumab vedotin was administered to 125 pts with locally advanced or metastatic urothelial carcinoma who were previously treated with platinum chemotherapy and anti–PD-1/L1 therapy. Enfortumab vedotin 1.25mg/kg was administered intravenously on days 1, 8 and 15 of every 28-day cycle. Efficacy of enfortumab vedotin was assessed by imaging (computed tomography or magnetic resonance) every eight weeks, then every 12 weeks after one year. CR or PR, as defined by RECIST version 1.1, were confirmed with repeated scans 4-5 weeks after initialresponse. The primary efficacy endpoint was confirmed objective responserate as assessed by blinded independent central review. At data cutoff, the median follow-up was 10.2 months (range: 0.5 to 16.5 months). Confirmed objective response rate was 44% (95%CI: 35.1% to 53.2%), including a 12% CR. Median time to response was 1.84 months (range: 1.2 to 9.2), and median duration of response was 7.6 months (range: 0.95 to 11.30) [3]. **Summary of clinical SAFETY:** Main safety results of **NCT03219333** trial are summarized in the table below: Any AE: 100% Treatment-related AEs: 94% Grade ≥3 treatment-related AEs: 54% Treatment-related serious AEs: 19% Treatment-related AEs resulting in treatment discontinuation: 12% There were no treatment-related deaths during the safety reporting period (i.e. from study day 1 through 30 days after the last study treatment). However, one death that occurred outside the safety reporting period, as a result of interstitial lung disease, was reported as treatment-related. The most frequent (any grade) treatment-related AEs were fatigue (50%), alopecia (49%), decreased appetite (44%), dysgeusia (40%), peripheral sensory neuropathy (40%), nausea (39%) and diarrhea (32%). [3] **Ongoing studies:** ● ***For the same indication:****Yes* ● ***For other indications:*** *Yes*[a] [a]NCT04223856: ongoing phase 3 study of enfortumab vedotin in combination with pembrolizumab vs chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer **Discontinued studies (for the same indication):**No **References:** 1.https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761137s000lbl.pdf 2.https://www-ema-europa-eu.translate.goog/en/medicines/human/summaries-opinion/padcev?_x_tr_sl=en&_x_tr_tl=it&_x_tr_hl=it&_x_tr_pto=op,sc 3.https://pubmed.ncbi.nlm.nih.gov/31356140/ 4.https://www.drugs.com/price-guide/padcev# 5.https://pubmed.ncbi.nlm.nih.gov/28543959/ 6.https://www.cancer.net/cancer-types/bladder-cancer/introduction 7.https://www.aiom.it/wp-content/uploads/2020/12/2020_LG_AIOM_Urotelio.pdf 8.https://pubmed.ncbi.nlm.nih.gov/28489981/ 9.https://pubmed.ncbi.nlm.nih.gov/31443960/ 10.https://pubmed.ncbi.nlm.nih.gov/32360052/ 11.https://www.ioveneto.it/pathology/tumore-della-vescica/ 12.https://clinicaltrials.gov/	**Cost of therapy:** In the USA the cost for Padcev® powder for IV injection is around $2,479 for a 20mg, and $3,713.09 for a 30mg supply [4]. **Epidemiology:** Nearly all cases of urothelial carcinoma are represented by bladder cancer, whereas upper tract urothelial carcinoma is a rare subset, accounting for 5-10% of all urothelial malignancies [5]. On the other hand, approximately 90% of bladder tumors are urothelial carcinomas, and other less frequent types of bladder cancer are represented by squamous cell carcinoma and adenocarcinoma [6]. In Italy, it has been estimated that almost 280,000 living people have a previous diagnosis of bladder cancer, and in 2019 29,700 new cases of bladder cancer were recorded (24,000 among men vs 5,700 women). The proportion of pts who recover is approximately 59% of men and 69% of women, and on average 16 years are requiredto consider a patient recovered [7]. Most pts present non–muscle-invasive disease at diagnosis, but up to 25% have muscle-invasive disease and present or subsequently develop metastatic disease [8]. **POSSIBLE PLACE IN THERAPY:** for early-stage/in situ urothelial NMIBC, surgical resection represents the first therapeutic approach, followed by adjuvant intravesical instillations of a chemotherapeutic agent (mitomycin) or of BCG, which stimulates the local immune response. Radical cystectomy is the recommended treatment in highest-risk NMIBC and nonmetastatic MIBC, preceded by cisplatin-based neoadjuvant chemotherapy. For metastatic MIBC, standard 1st-line treatment for fit pts (e.g. with good renal function) is represented by cisplatin-based combination chemotherapy, such as gemcitabine plus cisplatin regimen. 2nd-line therapy is mainly based on immunotherapy with PD-1/PD-L1 inhibitors, including pembrolizumab, nivolumab andatezolizumab [7, 9-11]. **OTHER INDICATIONS IN DEVELOPMENT:**metastatic castration-resistant prostate cancer;other locally advanced or metastatic malignant solid tumors (HR+/HER2- breast cancer, triple negative breast cancer, squamous non-small cell lung cancer, non-squamous non-small cell lung cancer, head and neck cancer, gastric or gastroesophageal junction or esophageal adenocarcinoma). [12] **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:**Yes **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Already approved by FDA: avelumab, erdafitinib,sacituzumabgovitecan. Ongoing phase 3 studies: ipilimumab (in combination with nivolumab or SoC), epacadostat (in combination with pembrolizumab), ramucirumab (in combination with docetaxel). [12] *Service reorganization:No *Possible off label use: Yes .

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