Oportuzumab monatox for the treatment of noninvasive urothelial carcinoma in situ (CIS) previously treated with Bacillus Calmette-Guérin (BCG)

General information

Drug description [1]	Indication [2]
Oportuzumab monatox (Vicineum®, Vicinium™, Vysyneum™, VB4-845) is a recombinant fusion protein comprising a humanised anti-EpCAM single-chain antibody linked to Pseudomonas exotoxin A. Once bound to the cancer cell, Oportuzumab monatox is internalised and the toxin moiety released into the cytosol where it induces apoptosis. Oportuzumab monatox has been developed for locoregional delivery. Intravesical administration limits systemic exposure while maximising local drug concentration, thereby increasing the therapeutic window.	Oportuzumab monatox (Vicinium™) has been developed for the treatment of Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC).

Incidence

In Austria in 2020, for bladder cancer, the age standardised incidence rate[1] was 15.2 per 100,000 persons per year (25.8/100,000 in men and 7.0/100,000 in women). In 2020, 1,381 persons were newly diagnosed with bladder cancer [3].
The worldwide age-standardised incidence rate (in 2020, per 100,000 person/year) is 9.5 in men and 2.4 in women. In the European Union the age-standardised incidence rate is 20/100,000 for men and 4.6/100,000 for women (in 2020) [4].
75% of bladder cancers are NMIBCs [5, 6].

Current treatment [7]

For the treatment of NMIBC, the ESMO recommends:

- Treatment of NMIBC should follow a risk-stratified approach with TURBT and intravesical chemotherapy or BCG in intermediate- and high-risk patients (I, A).
- Subsets of patients with very-high-risk disease should be offered radical cystectomy. Radical cystectomy should be carried out in CIS or high-grade T1 unresponsive to BCG due to the high risk of progression (III, B).
- In patients who are BCG-unresponsive and -ineligible for or refuse cystectomy, pembrolizumab or nadofaragene firadenovec can be considered; however, more robust data are required before stronger recommendations can be made for these and other bladder-sparing approaches in BCG-unresponsive disease (III, C). A multidisciplinary approach is required for these patients (IV, C).

For the treatment of NMIBC, the DGHO recommends the following [5]:

- ❖ TURBT is indicated:
  - In patients with an incomplete TUR.
  - In patients without histopathological evidence of muscular tissue (except for pTa, low risk).
  - In pT1 tumours.
  - In patients with high risk tumours (other than pTis, CIS).
- ❖ Bladder instillation therapy
  - Early bladder chemotherapy instillation can be offered after complication-free TURBT.
  - Alternatively, and only in patients with intermediate or high risk, a subsequent intravesical instillation of chemotherapy (mitomycin C or BCG) can be useful.
  - In patients with high-risk NMIBC cystectomy provides an option; if unsuitable or declined by the patient, a bladder-preserving therapy (consisting of TURBT and radiotherapy) can be offered.

Regulatory status

[1] For the European Standard Population 2013.

EMA	FDA
Approval status for this indication: not approved On 20 August 2021, DLRC Pharma Services withdrew its application for marketing authorisation of Oportuzumab monatox DLRC Pharma Services for the treatment and prevention of recurrence of cancer of the bladder and the prevention of recurrence of papillary tumours [8]. "Following receipt of a Complete Response Letter from FDA, Sesen Bio is halting further regulatory activities relating to Oportuzumab monatox in Europe until there is more clarity from the FDA on the next steps in the US. Therefore, the withdrawal is based on global regulatory priorities (Withdrawal letter, DLRC Pharma Services LTD [9]). **Other indications**: none	**Approval status for this indication**: not approved On 13 August 2021, the manufacturer (Sesen Bio) announced that it received a Complete Response Letter from the FDA regarding its Biologics License Application for Vicineum™ (Oportuzumab monatox-qqrs) for the treatment of BCG-unresponsive NMIBC. The FDA has determined that it cannot approve the BLA for Vicineum™ in its present form and has provided recommendations specific to additional clinical/statistical data and analyses in addition to Chemistry, Manufacturing and Controls (CMC) issues pertaining to a recent pre-approval inspection and product quality. The company plans to request a Type A meeting as soon as possible with the FDA to discuss the next steps needed before the application may be approved [10]. **Other indications**: none

Manufacturer

DLRC Pharma Services is the applicant for Oportuzumab monatox in Europe; Sesen Bio Inc. is the sponsor of product development.

Costs

Currently, there is no cost information available for the European market.
According to ICER, the price of Oportuzumab monatox was set at $150,000 per year (for a total of 36 doses in the first year), an estimated price net of rebates communicated by Sesen Bio [11].

Study characteristics [2, 12]: only abstract available

Trial name	n	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
NCT02449239	134[2]	**Induction** 30 mg of Oportuzumab monatox in 50 mL of saline administered 2x/week for 6 weeks followed by 1x/week for 6 weeks, for a total of 12 weeks. **Maintenance** 30 mg of Oportuzumab monatox in 50 mL of saline administered	-	Complete response rate (CRR)[3]	NA	single-arm, multicentre, registrational, phase 3 trial[4]	-	Sesen Bio Inc.	NCT02449239 [2] (Abstract only)

[2] BCG-unresponsive NMIBC patients were defined as refractory or relapsing within 6 months (n=126) and relapsing within 6-11 months (n=7) after adequate BCG therapy.
[3] In patients with CIS with or without resected papillary disease following initiation of Vicinium therapy.
[4] According to ClinicalTrials.gov, the estimated study completion date for NCT02449239 was May 2022 and study results are submitted; however, to date there is only abstract data available.

		1x/week every other week for up to 104 weeks							

Inclusion criteria [8]	Exclusion criteria [8]	Patient characteristics at baseline
❖ Histologically confirmed NMIBC (transitional cell carcinoma): CIS (with or without papillary disease), any grade T1 papillary disease, or high-grade Ta papillary disease based on a biopsy within 8 weeks of the initial dose of study treatment ❖ Adequate prior BCG treatment ❖ Refractory or relapsed disease following adequate BCG treatment ❖ Male or non-pregnant, non-breastfeeding female, aged ≥18 years ❖ Karnofsky performance status ≥ 60 ❖ Adequate organ function	❖ Urethral or upper tract transitional cell carcinoma within the past 2 years ❖ Hydronephrosis ❖ Intravesicular or other chemotherapy treatment within 2 weeks[5] ❖ History of recurrent severe urinary tract infections per investigator judgment ❖ Other malignancies within 2 years before the first dose of study treatment[6] ❖ QTc interval of >470 msec by the Fridericia formula at the screening ECG ❖ Patients who cannot tolerate intravesical administration or intravesical surgical manipulation ❖ Local or severe allergy to any components of the drug regimen	Not available.

Efficacy (abstract data)	Safety (abstract data)
Data: May 2019 **CIS patients (n=89):** **CRR at 3 months**: 40% **Median duration of response**: 9.4 months (95%CI, 5.1-NE) Of the 3-month CIS responders, 52% remained disease-free for 12 months after starting treatment. **Papillary patients (n=38):** **Recurrence-free rate at 3 months**: 71% **Recurrence-free rate at 6 months**: 58% **Recurrence-free rate at 12 months**: 50% **Recurrence-free rate at 24 months**: 37% **Median time to recurrence**: 13.2 months (95% CI, 5.6-NE) **Overall** **Recurrence-free responders vs. non-responders at 3 months**: 34.0 vs. 20.7 months, p≤0.001 **Rate of radical cystectomy for responders vs. non-responders at 3 months**: 10 vs. 32% **Preliminary OS at 2 years**: 96% (95% CI, 92-100)	**Treatment-related AEs**: 52%[7] **Frequency of AEs**: similar between 54-69, 70-79 and ≥80 age groups **Severe treatment-related AEs**: 4 in 3 patients[8] **Treatment discontinuation due to AEs**: 3%

Patient-reported outcomes
Not available.

[5] Or any investigational agent within 4 weeks prior to the initial dose of study drug.
[6] Except for superficial skin cancer or localised solid tumours deemed cured by surgery and not treated with systemic anticancer therapy and not expected to require anticancer therapy in the next 2 years.
[7] The majority of treatment-related AEs was grade 1-2.
[8] Including cholestatic hepatitis (grade 4), renal failure (grade 5), acute kidney injury (grade 3) and pyrexia (grade 2).

ESMO-MCBS version 1.1 [13]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Not applicable.											

Risk of bias - study level (case series) [14]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?

Overall risk of bias: not evaluable

Ongoing trials [15]

NCT number/ trial name	Description	Estimated study completion date	
NCT03258593	A phase I single-arm study of the combination of durvalumab (MEDI4736) and Vicineum (Oportuzumab monatox, VB4-845) in subjects with high-grade **NMIBC** previously treated with BCG.	12/2024	[16]
NCT04859751	An open-label, single arm, multicentre study to evaluate the efficacy and safety of intravesical VB4-845 injection in patients with **NMIBC.**	12/2023	[17]

Available assessments

- Summarised information on Oportuzumab monatox identified via ICER can be found in the "Final Evidence Report and Policy Recommendations on New Therapies for Bladder Cancer" [18] and "The effectiveness and value of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab for BCG-unresponsive non-muscle-invasive bladder cancer" [19].
- Currently, there is no assessment available from G-BA; however, an ongoing trial of Oportuzumab monatox (NCT03258593) is referenced in an assessment of Durvalumab (Imfinzi®) [20].
- Currently, there are no assessments available from NICE and CADTH.

Other aspects and conclusions

- Oportuzumab monatox is currently **NOT** approved by the EMA and the FDA.
- In August 2021, the FDA **denied the approval** of the Biologics License Application for Vicineum™ and provided recommendations specific to additional clinical/statistical data and analyses in addition to CMC issues. Consequently, DLRC Pharma Services **withdrew** its application for marketing authorisation of Oportuzumab monatox DLRC Pharma Services for the European Market.
- The FDA application was based on data from NCT02449239, a single-arm phase 3 trial investigating Vicineum™ in BCG-unresponsive NMIBC in 134 patients. Although the estimated study completion date was May 2022, **only abstract data are available**. Hence, currently, the ESMO-MCBS is **not applicable**, and the risk of bias is **not evaluable**.
- Safety, efficacy and PROs data will be added as soon as they are available.

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Abbreviations: AE=adverse event, AJ=adjustment, BCG=Bacillus Calmette-Guerin, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CIS=carcinoma in situ, CMC=Chemistry, Manufacturing and Controls, CRR=complete response rate, ECG= electrocardiogram, 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, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health and Care Excellence, NE=not evaluable, NMIBC= non-muscle-invasive bladder cancer, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TURBT=transurethral resection of the bladder tumour

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