# Comparative Narrative Review of Oncology Value Assessment Frameworks: Enfortumab Vedotin (EV) for Treatment of Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

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## Conclusions

- To decrease assessment variability, the development of easy-to-use value frameworks that are transparent, robust, and consider all relevant criteria important to both patients with cancer and their providers should be prioritized and identified
- The high-scoring evaluation of EV in the value frameworks of ESMO-MCBS and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™ indicates that this antibody–drug conjugate may contribute to optimizing outcomes in patients with la/mUC; however, evaluations should be conducted across additional value frameworks

### Author Disclosures

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### Abbreviations

NCCN, National Comprehensive Cancer Network® (NCCN®).



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## Background

- Despite new and beneficial therapies, cancer care is becoming more complex and costly due to escalating drug prices and the availability of vast treatment options that may complicate treatment decision-making[1,2]
- Evaluating the value of a drug is critical to ensure that patients receive the most effective and cost-efficient care[3]
  - A wide range of values matter to patients and other stakeholders, including patient health, quality of life (QOL), treatment cost, impact on caregivers and family, societal impact, and quality of treatment[4]
- Value frameworks have been increasingly used to assess the added value of new oncology therapies to guide decision-making and resource allocation[5,6]
  - Frameworks help identify important criteria for health sector decisions among stakeholders, considering parameters such as clinical benefit, toxicity, QOL by patient-reported outcomes, and cost/affordability[5-7]
  - While they share similarities, they differ in their intended goals, assessment methods, and target users; thus, the same drug may be evaluated differently by different frameworks[5,8]
- Bladder cancer makes up about 3% of all new cancer diagnoses and is responsible for 2% of all cancer-related deaths worldwide[9]
  - Urothelial carcinoma (UC; transitional cell carcinoma) accounts for 90% of all bladder cancer cases[10,11]
    - Individuals with metastatic UC (mUC) have a poor prognosis and diminished QOL[12-14]
- Nearly half of patients with mUC are ineligible for standard first-line (1L) treatment[15]
- A lack of different treatment options in UC treatment highlights an unmet therapeutic need
- This narrative review aims to explore attributes of value frameworks, using the example of enfortumab vedotin (EV), a Nectin-4–directed antibody–drug conjugate for patients with locally advanced or metastatic (la/mUC) previously treated with platinum-based chemotherapy and immunotherapy[16]

## Methods

- Oncology value frameworks from PubMed, gray literature, and the official websites of relevant institutions were identified and compared from January 2022 to March 2023
- The American Society of Clinical Oncology (ASCO) assessment framework (v2.0), European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) (v1.1), National Comprehensive Cancer Network (NCCN) Evidence Blocks (v3.2023), Memorial Sloan Kettering Cancer Center DrugAbacus, Institute for Clinical and Economic Review (ICER) assessment framework, and Drug Assessment Framework (DAF) (v1.0) were compared for general characteristics, criteria used, scoring methodology, and results in the context of UC
- Given its approval as monotherapy in 40 countries for previously treated la/mUC and, in the US, in combination with pembrolizumab for previously untreated la/mUC ineligible for cisplatin, the value of EV for UC within the available oncology frameworks was assessed

## Results

- The ASCO assessment framework (v2.0), ESMO-MCBS (v1.1), NCCN Evidence Blocks (v3.2023), Memorial Sloan Kettering Cancer Center DrugAbacus, ICER assessment framework, and DAF (v1.0) were compared and summarized (**Table 1**)

**Table 1. Summary of Select Value Frameworks Proposed by Relevant Institutions[6,7,17-20]**

| Parameter | ASCO | NCCN Guidelines® | ICER | MSKCC | ESMO | DAF |
|---|---|---|---|---|---|---|
| **General characteristics** | | | | | | |
| Outcome | Net health benefit | Evidence blocks | QALY | DrugAbacus price | ESMO-MCBS scoring | DAF score |
| Stakeholders | Patients, clinicians | Patients, clinicians | Nonprofit organization, decision-makers | Clinicians, decision-makers | Payers, decision-makers | Patients, health care professionals, decision-makers, economists |
| Algorithm/ Expert judgment | Algorithm | Expert judgment | Expert judgment (partially) | Algorithm | Algorithm | Algorithm |
| Version | 1.0 (2015), v2.0 (2016), 2020 update | 1 (2015), updated per indication | 2020–2023 | 2015 (online) | 1.0 (2015), 1.1 (2017) | 1.0 (2019) |
| **Criteria** | | | | | | |
| Efficacy | Noncurative treatment: OS, PFS, response rate; Curative treatment: OS, DFS (max 100 points) | Yes; variable, depends on indication (19 possibilities) | Synthesis of evidence using QALY | No | Curative treatment: OS, PFS, symptom palliation, response rate | OS (max 15 points), PFS (max 12 points), response rate (max 8 points) |
| Safety/Toxicity | Based on frequency and grade of AEs (max 20 points) | Safety, effect on patient's daily life | Grades 3–4, severity of AEs | Severe AEs | Grades 3–4, severity of AEs | AEs (max 10 points) |
| QOL/Symptom of palliation | Yes (max. 10 bonus points for QOL; max 10 bonus points for symptom palliation) | Not considered | Work productivity, QALY, formal and informal care | Not considered | Yes (1 bonus point for QOL) | QOL measures and patient-reported QOL (max 19 points) |
| Other | Tail of the curve (max 16–20 bonus points), treatment-free interval | Quality and consistency of evidence; affordability | Unmet needs, reduction of health disparities | Unmet needs, treatment novelty, cost of research/development, disease burden, treatment duration | Unmet needs and tail of curve (v1.1) | Unmet needs, equity, feasibility, severity and caregiver well-being |
| **Results** | | | | | | |
| Outcome measure | Net health benefit: max 140–180 points (curative and advanced) | Score (1–5) of 5 categories contemplated | Net health benefit expressed as QALY difference | DrugAbacus price | Curative: alphabetical scale; Noncurative: numeric (1–5) | DAF score (max 300 points); Clinical benefit (max 192 points) |
| Cost | Cost of treatment (acquisition and copayment) | Total cost of intervention (affordability for system) | Cost for patient, total cost for payer | Budget impact (mean sale price and mean wholesale price) | Not specified, reserved for payer evaluation | Joint use of DAF and cost parameters |

AE, adverse event; ASCO, American Society of Clinical Oncology; DAF, Drug Assessment Framework; DFS, disease-free survival; ESMO, European Society for Medical Oncology; ICER, Institute for Clinical and Economic Review; MCBS, Magnitude of Clinical Benefit Scale; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; QOL, quality of life.

### United States

- ASCO
  - Developed to help compare the relative value of cancer treatments to the standard of care as a tool for physicians and patients working together to decide the best treatment plan[21]
    - Estimates a net health benefit score for a drug by calculating points based on its clinical benefit, toxicity, cost, and other factors considered relevant[21]
- NCCN Guidelines® with NCCN Evidence Blocks™
  - Graphic representations scoring 5 categories related to efficacy, affordability, quality of evidence, and consistency of evidence supporting the drug being evaluated[22]
- Memorial Sloan Kettering Cancer Center DrugAbacus
  - Employs a value-based approach to estimate prices of oncologic treatments approved in the US from 2001–2015[18,23]
    - Allows comparisons to be made between different types of tumors and between the budget impact and actual impact[18,23]
- ICER
  - Provides information for clinical decisions intended to achieve sustainable access to high-value care for all patients[17]
  - Aims to establish a common model for all stakeholders involved to improve transparency and consistency of the process[17]

### Europe

- ESMO-MCBS
  - Intended to assist in clinical decision-making, promote accessibility, and reduce disparities in access to oncologic treatments[19]
  - Highlights treatments that bring substantial improvements in survival rates, QOL, or both for patients with cancer[24]

### Canada

- DAF
  - Developed by a Canadian-based research team with help from patients, health care professionals, health economists, government representatives, and others[7]
    - Considers 10 criteria: OS, progression-free survival, response rate, QOL, toxicity, unmet need, equity, feasibility, disease severity, and caregiver well-being[7]

### Application of Value Frameworks to Urothelial Carcinoma

- In recent years, oncologic value frameworks have been applied to several indications, including various treatment lines for UC (**Table 2**)[7,20,25-27]

**Table 2. Application of Value Frameworks to Urothelial Carcinoma**

| | ASCO | NCCN Guidelines® | ESMO | MSKCC | ICER | DAF |
|---|---|---|---|---|---|---|
| Study | Ben-Aharon et al[25] | NCCN Guidelines® with NCCN Evidence Blocks™[20] | Kiesewetter et al[26] | DrugAbacus[18,a] | Yu et al[27,b] | Ezeife et al[7] |
| Adaptation | Late life expectancy to evaluate long-term benefit[28] | None | None | None | None | None |
| Assess enfortumab vedotin? | No | Yes | Yes | No | No | No |

[a]Does not specifically mention urothelial cancer, but includes similar cancers such as prostate cancer.
[b]Includes cancer immune checkpoint inhibitors used in urothelial cancer.

ASCO, American Society of Clinical Oncology; DAF, Drug Assessment Framework; ESMO, European Society for Medical Oncology; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network.

### Positioning of Enfortumab Vedotin in the Value Frameworks

- EV has been assessed within 2 value frameworks; ESMO-MCBS and NCCN Guidelines® with NCCN Evidence Blocks™[20]
  - In both frameworks, drug assessment allows comparison of the alternative therapies available for UC; the ESMO scale additionally takes QOL into consideration[29]
- ESMO-MCBS
  - The EV-301 clinical trial comparing EV with chemotherapy yielded a final score of 4 (3 points awarded for efficacy and 1 additional point for QOL) out of a maximum score of 5 based for EV on the primary outcome measure of OS with follow-up beyond 1 year (**Table 3**)

**Table 3. Assessment of Enfortumab Vedotin Using European Society for Medical Oncology's Magnitude of Clinical Benefit Scale[30,31]**

| | | |
|---|---|---|
| **Indication** | | |
| Tumor type | Genitourinary cancer | |
| Tumor subtype | UC | |
| Tumor stage | Locally advanced or metastatic | |
| **Trial name** | **EV-301** | **EV-201 cohort 2** |
| Treatment setting | Adults with la/mUC who previously received platinum-containing chemotherapy and a PD-1/L1 inhibitor | Patients with la/mUC ineligible for cisplatin-containing chemotherapy and received ≥1 prior lines of therapy |
| Control arm | Investigator-chosen chemotherapy (standard docetaxel, paclitaxel, or vinflunine) | Single arm (phase 2) |
| **Primary outcome** | | |
| Primary outcome | OS | ORR |
| Evaluated outcome | OS | ORR |
| Form | 2a | 3 |
| **Outcome data** | | |
| Outcome | OS control: 8.97 mo<br>OS gain: 3.91 mo<br>OS HR: 0.70 (0.56–0.89)<br>QOL comment pending | PFS control: 5.8 mo<br>ORR: 52%<br>Duration of response: 10.9 mo<br>QOL not a prespecified endpoint |
| **Adjusted final score** | | |
| Final noncurative score | 4 | 3 |
| Release date[a] | Aug 31, 2021<br>Last update: Jun 21, 2022 | Jun 14, 2021<br>Last update: Nov 14, 2022 |

[a]At time of publication.

HR, hazard ratio; la/mUC, locally advanced or metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; PD-1/L1, programmed cell death protein 1/ligand 1; PFS, progression-free survival; QOL, quality of life; UC, urothelial carcinoma.

- NCCN Guidelines® with NCCN Evidence Blocks™
  - The value of EV as a 2L+ therapy for la/mUC was assessed using NCCN Guidelines® with NCCN Evidence Blocks™, differentiating between post-chemotherapy and checkpoint inhibitor therapies[20] (**Table 4**)
    - Post-chemotherapy in the 2L setting, EV was positioned higher than erdafitinib, nivolumab, and avelumab based on efficacy and consistency of evidence[20]
    - For patients ineligible for cisplatin, EV was positioned as the preferred regimen due to its greater efficacy, quality, and consistency of evidence relative to its comparators[20]

**Table 4. NCCN Guidelines® with NCCN Evidence Blocks™ for Systemic Therapy for Locally Advanced or Metastatic Urothelial Carcinoma (Stage IV)[20]**

| Regimen | Efficacy | Safety | Quality of evidence | Consistency of evidence | Affordability |
|---|---|---|---|---|---|
| **Post-chemotherapy second-line systemic therapy** | | | | | |
| Preferred | | | | | |
| Pembrolizumab | 4 | 3 | 4 | 4 | 2 |
| Nivolumab | 3 | 3 | 4 | 3 | 2 |
| Avelumab | 3 | 3 | 4 | 3 | 2 |
| Erdafitinib | 3 | 3 | 3 | 3 | 1 |
| Enfortumab vedotin | 4 | 3 | 4 | 4 | 1 |
| Other | | | | | |
| Paclitaxel | 2 | 3 | 3 | 3 | 4 |
| Docetaxel | 2 | 3 | 3 | 3 | 4 |
| Gemcitabine | 2 | 3 | 3 | 3 | 4 |
| **Post-checkpoint inhibitor (cisplatin ineligible) for second-line systemic therapy** | | | | | |
| Preferred | | | | | |
| Enfortumab vedotin | 4 | 3 | 4 | 4 | 1 |
| Gemcitabine and carboplatin | 3 | 3 | 3 | 3 | 4 |
| Other | | | | | |
| Erdafitinib | 3 | 3 | 3 | 3 | 1 |
| Paclitaxel | 2 | 3 | 3 | 3 | 4 |
| Docetaxel | 2 | 3 | 3 | 3 | 4 |
| Gemcitabine | 2 | 3 | 3 | 3 | 4 |
| **Subsequent-line systemic therapy** | | | | | |
| Preferred | | | | | |
| Enfortumab vedotin | 3 | 3 | 4 | 4 | 1 |
| Erdafitinib | 3 | 3 | 3 | 3 | 1 |
| Other | | | | | |
| Sacituzumab govitecan | 3 | 3 | 3 | 3 | 1 |
| Gemcitabine | 2 | 3 | 3 | 3 | 4 |
| Paclitaxel | 2 | 3 | 3 | 3 | 4 |
| Docetaxel | 2 | 3 | 3 | 3 | 4 |
| Ifosfamide, doxorubicin, and gemcitabine | 2 | 2 | 2 | 3 | 3 |
| Gemcitabine and paclitaxel | 2 | 3 | 2 | 3 | 4 |
| Gemcitabine and cisplatin | 2 | 2 | 2 | 3 | 4 |
| Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with growth factor support | 3 | 2 | 2 | 2 | 3 |

## Limitations

- This study used a narrative, rather than systematic, approach, causing potential for bias, and may not encompass the entirety of available evidence
  - A narrative approach was chosen as it is better suited for providing a broad and comprehensive perspective on the topic, compared with a systematic approach
- Only one database (PubMed) was utilized, resulting in relevant sources potentially being missed
  - As PubMed contains a vast majority of published studies, it is reasonable to assume that the most relevant value frameworks and models were likely identified in the PubMed search