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 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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References

1. Prasad V, et al. *Nat Rev Clin Oncol*. 2017;14(6):381-390.
2. *Nat Cancer*. 2021;2(3):245-246.
3. Porter ME. *N Engl J Med*. 2010;363(26):2477-2481.
4. Vrinzen CEJ, et al. *Cancer Med*. 2023;12(5):6105-6116.
5. Campolina AG. *Clinics (Sao Paulo)*. 2018;73(suppl 1):e470s.
6. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. 2020.
7. Ezeife DA, et al. *Cancer*. 2020;126(7):1530-1540.
8. Jena AB, et al. *Am J Manag Care*. 2018;24(11):506-509.
9. Sung H, et al. *CA Cancer J Clin*. 2021;71(3):209-249.
10. Lamm DL, Torti FM. *CA Cancer J Clin*. 1996;46(2):93-112.
11. Saginala K, et al. *Med Sci (Basel)*. 2020;8(1):15.
12. Beigi A, et al. *Curr Oncol*. 2021;28(5):3812-3824.
13. von der Maase H, et al. *J Clin Oncol*. 2000;18(17):3068-3077.
14. Bellmunt J, et al. *J Clin Oncol*. 2009;27(27):4454-4461.
15. Valderrama BP, et al. *Clin Transl Oncol*. 2022;24(4):613-624.
16. Challita-Eid PM, et al. *Cancer Res*. 2016;76(10):3003-3013.
17. ASCO. ASCO Value Framework Net Health Benefit Worksheet: Advanced Disease Setting. 2020.
18. Drug Pricing Lab. Drug Abacus. Available at: https://www.drugpricinglab.org/tools/drug-abacus/.
19. ESMO. ESMO MCBS Factsheet. Available at: https://www.esmo.org/content/download/288505/5736229/1/ESMO-MCBS-Factsheet.pdf.
20. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer: NCCN Evidence Blocks™ V.2.2023.
21. Schnipper LE, et al. *J Clin Oncol*. 2015;33(23):2563-2577.
22. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™. Available at: https://www.nccn.org/guidelines/guidelines-with-evidence-blocks.
23. Drug Pricing Lab. What we do. Available at: https://www.drugpricinglab.org/what-we-do/.
24. Cherny NI, et al. *Ann Oncol*. 2015;26(8):1547-1573.
25. Ben-Aharon O, et al. *JAMA Oncol*. 2018;4(3):326-332.
26. Kiesewetter B, et al. *ESMO Open*. 2017;2(3):e000166.
27. Yu PP, et al. *J Immunother Cancer*. 2019;7(1):235.
28. Vivot A, et al. *J Natl Cancer Inst*. 2019;111(5):519-521.
29. Gyawali B, et al. *JAMA Internal Medicine*. 2019;179(7):906-913.
30. ESMO. ESMO-MCBS Scorecards: Enfortumab vedotin EV-301. Available at: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-286-1.
31. ESMO. ESMO-MCBS Scorecards: Enfortumab vedotin EV-201 - cohort 2. Available at: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-275-1.

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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 (v2.2023), 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 (v2.2023), 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	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 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	ESMO	MSKCC	ICER	DAF
Study	Ben-Aharon et al[25]	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 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 OS gain: 3.91 mo OS HR: 0.70 (0.56–0.89) QOL comment pending	PFS control: 5.8 mo ORR: 52% Duration of response: 10.9 mo QOL not a prespecified endpoint
Adjusted final score		
Final noncurative score	4	3
Release date[a]	Aug 31, 2021 Last update: Jun 21, 2022	Jun 14, 2021 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 Evidence Blocks
  - The value of EV as a 2L+ therapy for la/mUC was assessed using 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. 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