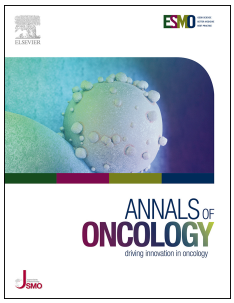

ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma

T. Powles, J. Bellmunt, E. Comperat, M. De Santis, R. Huddart, Y. Loriot, A. Necchi, B.P. Valderrama, A. Ravaud, S.F. Shariat, B. Szabados, M.S. van der Heijden, S. Gillessen, on behalf of the ESMO Guidelines Committee

PII: S0923-7534(24)00075-9

DOI: https://doi.org/10.1016/j.annonc.2024.03.001

Reference: ANNONC 1449

To appear in: *Annals of Oncology*

Received Date: 9 January 2024

Revised Date: 29 February 2024

Accepted Date: 1 March 2024

Please cite this article as: Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Loriot Y, Necchi A, Valderrama BP, Ravaud A, Shariat SF, Szabados B, van der Heijden MS, Gillessen S, on behalf of the ESMO Guidelines Committee, ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma, *Annals of Oncology* (2024), doi: https://doi.org/10.1016/j.annonc.2024.03.001.

ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma

T. Powles[1], J. Bellmunt[2], E. Comperat[3], M. De Santis[4,5], R. Huddart[6], Y. Loriot[7], A. Necchi[8,9], B. P. Valderrama[10], A. Ravaud[11], S. F. Shariat[5,12-14], B. Szabados[1,15], M. S. van der Heijden[16] & S. Gillessen[17,18], on behalf of the ESMO Guidelines Committee*

[1]Barts Cancer Centre, Barts Health NHS Trust, Queen Mary University of London, London, UK; [2]Department of Hematology and Oncology, Dana-Farber Cancer Institute, Harvard Cancer Centre, Boston, USA; [3]Department of Pathology, Medical University Vienna, Austria; [4]Department of Urology, Charité Universitätsmedizin, Berlin, Germany; [5]Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [6]Royal Marsden Hospital, Institute of Cancer Research, London, UK; [7]Department of Medical Oncology, Université Paris-Saclay and Gustave Roussy, Villejuif, France; [8]Vita-Salute San Raffaele University, Milan; [9]Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy; [10]Department of Medical Oncology, University Hospital Virgen del Rocio, Seville, Spain; [11]Department of Medical Oncology, Bordeaux University Hospital, Bordeaux, France; [12]Department of Urology, Weill Cornell Medical College, New York; [13]Department of Urology, University of Texas Southwestern, Dallas, USA; [14]Division of Urology, Department of Special Surgery, University of Jordan, Amman, Jordan; [15]Department of Urology, University College London Hospital NHS Foundation Trust, London, UK; [16]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [17]Oncology Institute of Southern Switzerland (EOC-IOSI), Bellinzona; [18]Università della Svizzera Italina (USI), Lugano, Switzerland

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland.

E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

Type: Special Article

Running header: ESMO Clinical Practice Guidelines eUpdate on bladder cancer

Word count: 2502 (excluding title page, acknowledgements, funding and disclosure sections); References: 19; Tables: 2; Figures: 1.

Key words:

bladder cancer, enfortumab vedotin, fibroblast growth factor receptor inhibitor, nivolumab, pembrolizumab, urothelial carcinoma

Highlights (online only):

- This ESMO Clinical Practice Guideline eUpdate addresses developments in first-line therapy in advanced urothelial carcinoma.
- EV+P is the new standard of care in first-line advanced urothelial carcinoma.
- Nivolumab–cisplatin–gemcitabine or platinum-based ChT and maintenance avelumab are alternatives if EV+P is not possible.

INTRODUCTION

The following ESMO Clinical Practice Guideline (CPG) has been recently updated with new treatment recommendations and an updated algorithm for managing treatment-naive advanced or metastatic urothelial carcinoma (stage IV): Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up.[1]

View the original CPG here: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-genitourinary-cancers/bladder-cancer.

MANAGEMENT OF ADVANCED/METASTATIC DISEASE

Two randomised trials comparing new therapy combinations with standard platinum-based chemotherapy (ChT) in the first-line treatment of advanced or metastatic urothelial carcinoma (UC) have recently reported positive results for progression-free survival (PFS) and overall survival (OS).[2,3] Maintenance avelumab given after clinical benefit with first-line platinum-based ChT has also had positive results on PFS and OS.[4] These three trials have different populations and cannot be directly compared. Together, however, they necessitate the update of the first-line treatment recommendations for advanced or metastatic UC. The treatment algorithm for the management of patients with metastatic urothelial carcinoma (previous Figure 3) has also been updated (**Figure 1**).

In the EV-302/KEYNOTE-A39 trial,[2] patients with previously untreated, locally advanced or metastatic UC (N = 886) were randomised to receive enfortumab vedotin (until disease progression) plus pembrolizumab (maximum 35 cycles) or platinum-based ChT (gemcitabine plus cisplatin or carboplatin, according to guidelines[5]). Maintenance with avelumab was given to 30.4% of patients in the ChT arm. PFS was significantly prolonged with enfortumab vedotin plus pembrolizumab (EV+P) versus platinum-based ChT [median PFS, 12.5 months versus 6.3 months, respectively; hazard ratio (HR) 0.45, 95% confidence interval (CI) 0.38-0.54, $P < 0.00001$]. OS was also significantly prolonged with EV+P versus platinum-based ChT (median OS, 31.5 months versus 16.1 months, respectively; HR 0.47, 95% CI 0.38-0.58, $P < 0.00001$). The overall response rate was 67.7% for EV+P [complete response (CR) rate 29.1%] and 44.4% for platinum-based ChT (CR rate 12.5%).

Treatment with enfortumab vedotin could continue until progression, which has implications for adverse-event (AE) management. Grade 1-2 treatment-related AEs (TRAEs) occurred in 41.1% of patients treated with EV+P and 26.1% with platinum-based ChT. Grade ≥3 TRAEs occurred in 55.9% of those treated with EV+P and 69.5% with platinum-based ChT. Treatment-related deaths occurred in 0.9% of patients in both arms. The most common grade ≥3 TRAEs of special interest for EV+P included skin reactions (15.5%), peripheral neuropathy (6.8%) and hyperglycaemia (6.1%). Grade 1-2 peripheral neuropathy occurred in 56.4% of patients treated with EV+P. Discontinuation due to AEs occurred in 24% of patients.

In the CheckMate 901 trial,[3] patients with previously untreated unresectable or metastatic UC and eligible for cisplatin (N = 608) were randomised to nivolumab plus gemcitabine–cisplatin for up to six cycles, followed by maintenance nivolumab, or gemcitabine–cisplatin for up to six cycles. Both OS (median OS, 21.7 months versus 18.9 months; HR 0.78, 95% CI 0.63-0.96) and PFS (median PFS, 7.9 months versus 7.6 months; HR 0.72, 95% CI, 0.59-0.88) significantly improved with the addition of nivolumab to gemcitabine–cisplatin. Overall objective response and CR rates were 57.6% and 21.7% with nivolumab–gemcitabine–cisplatin versus 43.1% and 11.8% with gemcitabine–cisplatin. In the control arm, 14.5% of patients received avelumab or pembrolizumab before centrally assessed disease progression. Grade ≥3 TRAEs occurred in 61.8% of patients in the nivolumab–gemcitabine–cisplatin arm and 51.7% of patients in the gemcitabine–cisplatin arm. In previous atezolizumab or pembrolizumab trials, results from subsets of patients treated with cisplatin-based ChT showed similar trends, although not statistically tested; therefore, this positive result should not be considered an outlier or unexpected.[6,7] The choice of platinum-based therapy should follow the criteria outlined by Galsky MD, et al (2020).[6]

There is now level of evidence I (**Table 2**) for three treatment strategies in first-line: EV+P, nivolumab–gemcitabine–cisplatin for cisplatin-eligible patients, or four to six cycles of platinum-based ChT followed by maintenance avelumab in patients who did not experience disease progression on platinum-based ChT.

EV+P is the new standard of care. The vast majority of patients are able to receive EV+P irrespective of platinum eligibility. Subgroups of patients (e.g. those with a

contraindication to pembrolizumab or uncontrolled diabetes) are ineligible for EV+P and alternatives should be considered, such as platinum-based ChT.

A consensus could not be reached on giving EV+P after completing adjuvant immune therapy with an immune checkpoint inhibitor (ICI). Therefore, it may be considered.

Other changes to the treatment algorithm include strengthening evidence for erdafitinib in *FGFR*-driven tumours. A survival advantage was demonstrated in a randomised phase III study of selected pre-treated patients.[8] Sacituzumab govitecan is also included in the algorithm for heavily pre-treated disease, based on phase II data with overall response rates of >20%.[9] Otherwise the previous recommendations for subsequent treatment after platinum-based ChT are unchanged (see Section MANAGEMENT OF ADVANCED/METASTATIC DISEASE in the 2022 CPG).[1]

Recommendations

- EV+P is recommended as the preferred first-line therapy for advanced or metastatic UC, irrespective of platinum eligibility [I, A; FDA approved; not EMA approved].

- After progression on EV+P, standard platinum-based ChT without maintenance avelumab in unselected patients or erdafitinib in selected *FGFR*-altered tumours can be recommended [IV, B].

- Rechallenge with a single-agent ICI is not encouraged without further evidence [V, D].

- Patients not able to receive EV+P should be treated with nivolumab plus up to six cycles of gemcitabine–cisplatin (if cisplatin-eligible only) [I, A] (awaiting FDA and EMA decision) or up to six cycles of platinum-based ChT (gemcitabine plus cisplatin or carboplatin) [I, A], followed by maintenance avelumab (for non-progressing tumours) [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4].

- Single-agent ICIs have a limited role in first-line advanced disease and should

not be routinely recommended [I, D].

- There are two changes for treatment after first-line platinum-based ChT and an ICI (given concurrently, sequentially or as second-line therapy):
    - Erdafitinib is recommended in patients with selected *FGFR* DNA fusions and mutations who have previously been treated with ChT and an ICI [I, A; ESMO-MCBS v1.1 score: 4; Food and Drug Administration (FDA) approved, not European Medicines Agency (EMA) approved].
    - Sacituzumab govitecan can be recommended in patients previously treated with ChT and an ICI [III, B; ESMO-MCBS v1.1 score: 2; FDA approved, not EMA approved].
- For patients with progression after EV+P, treatments not previously given may be considered for third- and fourth-line therapy [V, C].

METHODOLOGY

This eUpdate was developed in accordance with the ESMO standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A table of ESMO-MCBS scores is included in **Table 1**. ESMO-MCBS v1.1[10] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this eUpdate. Levels of evidence and grades of recommendation have been applied using the system shown in **Table 2**.[11] Statements without grading were considered justified standard clinical practice by the authors.

ACKNOWLEDGEMENTS

Manuscript editing support was provided by Ioanna Ntai and Jennifer Lamarre (ESMO Guidelines staff); this support was funded by ESMO. Nathan Cherny, Chair

of the ESMO-MCBS Working Group, and Urania Dafni, Giota Zygoura, Georgia Dimopoulou and Tereza Dellaporta of Frontier Science Foundation Hellas provided review and validation of the ESMO-MCBS scores. Nicola Latino (ESMO Scientific Affairs staff) provided coordination and support of the ESMO-MCBS scores and Angela Corstorphine of Kstorfin Medical Communications Ltd (KMC) provided medical writing and editing support in the preparation of the ESMO-MCBS table; this support was funded by ESMO.

FUNDING

No external funding has been received for the preparation of this eUpdate. Production costs have been covered by ESMO from central funds.

DISCLOSURE

TP reports personal fees for advisory board membership from Astellas, AstraZeneca, Bristol Myers-Squibb (BMS), Eisai, Exelixis, Incyte, Ipsen, Johnson & Johnson, Merck, Merck Serono, MSD, Novartis, Pfizer, Roche and Seattle Genetics; personal travel grants from AstraZeneca, Ipsen, MSD, Pfizer and Roche; personal sponsorship for the Uromigos Podcast from Mashup Ltd; institutional honoraria from Gilead; and institutional research grants from Astellas, AstraZeneca, BMS, Eisai, Exelixis, Ipsen, Johnson & Johnson, Merck, Merck Serono, MSD, Novartis, Pfizer, Roche and Seattle Genetics.

JB reports personal fees for advisory board membership from AstraZeneca (bladder cancer), BMS (adjuvant study CM 247), Merck (bladder cancer) and Pfizer (global); personal fees as an invited speaker from Merck (lectures in national meetings) and MSD (ESMO Asia Congress 2020); personal stocks/shares in Bicycle; personal royalties as Section Editor for bladder cancer from UpToDate; institutional fees as coordinating principal investigator (PI) of the INDUCOMAIN trial from MSD and of a prostate cancer study of avelumab plus carboplatin from Pfizer both through the Asia Pacific Regional Office (APRO) Association; and non-renumerated membership of the IMvigor011 study Steering Committee (Genentech) and the American Society of Clinical Oncology (ASCO).

EC reports personal fees as an invited speaker from Janssen; and a non-renumerated advisory role as a consulting pathologist for the European Association of Urology (EAU) guidelines for bladder cancer.

MDS reports fees from 4D (personal for advisory board membership; personal and institutional for Steering Committee membership and an advisory function); AAA (personal for advisory board and Steering Committee memberships); Amgen (personal for advisory board and Steering Committee memberships and an advisory function); Astellas (personal for advisory board membership, an advisory function and as an invited speaker; personal and institutional for Steering Committee membership and an advisory function); AstraZeneca (personal for advisory board and Steering Committee memberships and as an invited speaker; personal and institutional as coordinating PI and for an advisory function); Basilea (personal for advisory board membership; personal and institutional for Steering Committee membership, an advisory function, clinical trials and as local PI); Bayer (personal for advisory board membership; personal and institutional for Steering Committee membership and an advisory function); Bioclin (personal for advisory board membership, advisory functions and as an invited speaker); BMS (personal for advisory board membership; personal and institutional for Steering Committee membership, an advisory function and travel grants); Calithera (institutional as local PI); Eisai (personal for advisory board membership; personal and institutional as local PI, for an advisory function and clinical trials); Ferring (personal for advisory board membership and an advisory function); Gilead (personal for advisory board membership; personal and institutional for Steering Committee membership); Immunomedics/Gilead (personal for advisory board membership; personal and institutional for Steering Committee membership, an advisory function and as local PI); Ipsen (personal for advisory board membership; personal and institutional for Steering Committee membership and an advisory function); Janssen (personal as an invited speaker; personal and institutional for Steering Committee membership and an advisory function); Merck/Serono (personal for advisory board membership; personal and institutional for Steering Committee membership and an advisory function); MSD (personal for advisory board membership and as an invited speaker; personal and institutional for Steering Committee membership, an advisory function,

clinical trials and as local PI); Nektar (institutional for clinical trials and as local PI); Novartis/Sandoz (personal for advisory board membership; personal and institutional for Steering Committee membership and advisory function); Pierre Fabre (personal for advisory board membership and as an invited speaker personal and institutional for Steering Committee membership, an advisory function and as local and coordinating PI); Roche (personal for advisory board membership); Roche/Genentech (personal and institutional for Steering Committee membership and an advisory function); Sandoz (personal for Steering Committee membership and an advisory function); Sanofi (personal for advisory board membership; personal and institutional for Steering Committee membership and an advisory function); SeaGen; (personal for advisory board membership; personal and institutional for Steering Committee membership, an advisory function and as local PI); and non-renumerated membership of the EAU guidelines group for prostate cancer (writing and discussing guidelines for treatment and diagnostics), the ESMO CPGs author group for bladder cancer and the S3-Leitlinie Blasenkrebs (guidelines for the treatment of bladder cancer).

RH reports personal fees for advisory board membership from Astellas, BioNTech, BMS, Merck, MSD, Nektar and Roche; personal fees as an invited speaker from Pfizer and Roche; personal fees for expert testimony from the National Institute of Clinical Excellence; personal and institutional fees for Steering Committee membership from Janssen and Nektar; personal fees for consultancy from Roche; personal fees for a limited liability partnership from the Cancer Centre London; institutional royalties from Janssen; institutional fees as a local PI from Astellas, Basilea, Bicycle, Gilead, Janssen, MSD, Nektar and Roche; institutional fees as a coordinating PI from Cancer Research UK (CRUK); institutional research grants from MSD and Roche; non-renumerated roles as chief investigator or co-investigator on CRUK-funded studies; non-renumerated roles as educational secretary and trustee of the British Uro-oncology group; a non-renumerated role as chair of the NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad); and non-renumerated membership of the consensus guideline group of the Royal College of Radiologists.

YL reports personal fees for advisory board membership from Gilead, Merck KGaA, Pfizer, Seattle Genetics and Taiho; personal fees for advisory board membership and lectures from Astellas, AstraZeneca, BMS, Janssen, MSD and Roche; personal fees for Steering Committee membership from Basilea; institutional fees as a local PI from Astellas, AstraZeneca, BMS, Exelixis, Gilead, Incyte, Janssen, Merck KGaA, MSD and Pfizer; institutional fees for Steering Committee membership and as a coordinating PI from Janssen; institutional research grants from Celsius, Janssen, MSD, Roche and Sanofi; Steering Committee membership for Astellas, Gilead/Immunomedics, MSD and Taiho; and non-renumerated memberships of the American Association for Cancer Research (AACR), the Scientific Committee of Fondation ARC, ASCO and ESMO.

AN reports personal fees for Steering Committee membership from Astellas, AstraZeneca, Bayer, Clovis Oncology, Janssen, Merck and Roche; institutional research grants from AstraZeneca, BMS, Gilead, Ipsen and Merck; a role as coordinating PI for Incyte; a role as local PI for Pfizer; and a non-renumerated leadership role for the Global Society of Rare Genitourinary Tumors (GSRGT), Leadership Role.

BPV reports personal fees for advisory board membership from AAA, Astellas Pharma, AstraZeneca, BMS, EUSA Pharma, Ipsen, Merck, MSD, Pfizer and Recordati; personal fees as an invited speaker from AAA, Almirall Pharma, Astellas Pharma, Bayer, BMS, Merck, MSD and Pfizer; and travel grants from BMS and Pfizer.

AR reports personal fees for advisory board membership from AstraZeneca, BMS, Ipsen, Merck GA and Pfizer; institutional research grants from Ipsen, Merck GA and Pfizer; institutional fees as local PI from AstraZeneca, BMS, Ipsen, Merck GA and Pfizer; travel grants/accommodation compensation for meetings/conferences from BMS, Ipsen, Merck GA and Pfizer; and a non-renumerated role as affiliate of ASCO.

SFS reports personal fees for advisory board membership from Astellas, AstraZeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda and Urogen.

BS reports personal fees for advisory board membership from Merck KGaA; personal fees as an invited speaker from MSD and Pfizer; personal fees for expert testimony from Ellipses and Ipsen; and personal travel grants from Photocure and Roche/Genentech.

MSvdH reports institutional fees for advisory board membership from AstraZeneca, BMS, Janssen, MSD, Pfizer and Seagen; institutional funding for investigator-initiated trials from 4SC, AstraZeneca, BMS and Roche; institutional fees for Steering Committee membership and as local PI from AstraZeneca, BMS, MSD and Seagen; and institutional fees as local and study co-PI from Janssen.

SG reports personal fees for advisory board membership from MSD Merck Sharp & Dohme and Sanofi; personal fees as an invited speaker for DESO, the Swiss Group for Clinical Cancer Research (SAKK) and the Swiss Academy of Multidisciplinary Oncology (SAMO) - International Breast Cancer Study Group (IBCSG); personal travel grants from AstraZeneca and Bayer; other personal fees from Radiotelevisione svizzera (RSI; Swiss television); institutional fees for advisory board membership from AAA International, Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, Innomedica, Modra Pharmaceuticals Holding B.V., MSD Merck Sharp & Dohme, Myriad Genetics, Novartis, Orion and Telixpharma; institutional fees as an invited speaker for ASCO GU, ESMO, EPG Health, Ipsen, Meister ConCept GmbH, SAKK, Silvio Grasso Consulting, the Swiss Society of Medical Oncology and TOLREMO; institutional funding as a co-investigator from Astellas; other institutional fees from Amgen (Steering Committee membership), PeerVoice (interview) and WebMD-Medscape (faculty activity); and a non-remunerated advisory role for ProteoMediX.

REFERENCES

1 Powles T, Bellmunt J, Comperat E, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33(3):244-258.

2 Powles TB, Perez Valderrama B, Gupta S, et al. LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC). *Ann Oncol*. 2023;34(S2):S1340.

3 van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus Gemcitabine-Cisplatin in Advanced Urothelial Carcinoma. *N Engl J Med*. 2023;389(19):1778-1789.

4 Powles T, Park SH, Voog E, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med*. 2020;383(13):1218-1230.

5 Jiang DM, Gupta S, Kitchlu A, et al. Defining cisplatin eligibility in patients with muscle-invasive bladder cancer. *Nat Rev Urol*. 2021;18(2):104-114.

6 Galsky MD, Arija JÁ A, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020;395(10236):1547-1557.

7 Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(7):931-945.

8 Loriot Y, Matsubara N, Park SH, et al. Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med*. 2023;389(21):1961-1971.

9 Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. *J Clin Oncol*. 2021;39(22):2474-2485.

10 Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.

11 Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clin Infect Dis*. 2001;33(2):139-144 [adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994;18(3):421].

FIGURES

Figure 1. Management of patients with metastatic urothelial carcinoma.

Purple: algorithm title; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities; white: other aspects of management.

ChT, chemotherapy; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; EV+P, enfortumab vedotin plus pembrolizumab; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, Magnitude of Clinical Benefit Scale; UC, urothelial carcinoma.

[a]FDA approved; not EMA approved.

[b]Rechallenge with single-agent ICI is not encouraged without further evidence [V, D].

[c]In tumours with selected *FGFR* DNA fusions and mutations.

[d]EV+P is preferred over platinum-based ChT irrespective of platinum eligibility.

[e]ESMO-MCBS v1.1[10] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[f]This should be assessed within 10 weeks of completion of ChT.

[g]Rechallenge with platinum-based ChT may be considered if progression occurred 12 months after the end of previous platinum-based ChT or 12 months after the end of previous platinum-based ChT and maintenance avelumab.

[h]Platinum doublets to be considered if the treatment-free interval from the last platinum-based ChT is >1 year.

[i]To be considered when other therapies are not available.

Table 1. ESMO-MCBS table for therapies/indications in UC

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/ toxicity	ESMO-MCBS score[a]
Metastatic							
Maintenance therapy							
Avelumab	First-line maintenance treatment of patients with locally advanced or metastatic UC who are progression-free following	JAVELIN Bladder 100[4,12,13] Phase III NCT02603432	BSC Median OS: 15.0 months	OS gain: 8.8 months	OS: 0.76 (0.63-0.91)	No QoL benefit	4 (Form 2a)

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/ toxicity	ESMO-MCBS score[a]
	platinum-based ChT						
Further-line therapy							
Enfortumab vedotin	Treatment of patients with locally advanced or metastatic UC who have previously received a platinum-containing ChT	EV-301[14,15] Phase III NCT03474107	Investigator's choice of ChT (standard docetaxel, paclitaxel or vinflunine) Median OS: 8.94 months			QoL data pending	4 (Form 2a)

Therapy	**Disease setting**	**Trial**	**Control**	**Absolute survival gain**	**HR (95% CI)**	**QoL/ toxicity**	**ESMO-MCBS score[a]**
	and a PD-1 or PD-L1 inhibitor			OS gain: 3.97 months	OS: 0.70 (0.58-0.85)		
Erdafitinib[b]	Treatment of patients with locally advanced or metastatic UC that has susceptible *FGFR3* or *FGFR2* genetic alterations and progressed after	THOR - Cohort 1[8] Phase III NCT03390504	Investigator's choice of ChT (docetaxel or vinflunine) Median OS: 7.8 months	OS gain: 4.3 months	OS: 0.64 (0.47-0.88)	QoL data pending	4 (Form 2a)

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/ toxicity	ESMO-MCBS score[a]
	one or two previous treatments that included an anti-PD-1 or anti-PD-L1						
Pembrolizumab	Treatment of locally advanced or metastatic UC in adults who have received prior	KEYNOTE-045[16-19] Phase III NCT02256436	Investigator's choice of ChT (paclitaxel, docetaxel or vinflunine)			QoL was an exploratory endpoint Fewer grade 3/4 treatment-	4 (Form 2a)

Therapy	**Disease setting**	**Trial**	**Control**	**Absolute survival gain**	**HR (95% CI)**	**QoL/ toxicity**	**ESMO-MCBS score[a]**
	platinum-containing ChT		Median OS: 7.2 months 2-year OS: 14.3%	OS gain: 2.9 months 2-year OS gain: 12.6%	OS: 0.71 (0.59-0.86)	related AEs versus control (p<0.001) but not affecting daily well-being	
Sacituzumab govitecan[b]	Treatment of patients with locally advanced or metastatic UC who have	TROPHY-U-01[9] Phase II	Single arm	ORR: 27.4% Median DoR: 7.2 months		QoL was not a prespecified endpoint	2 (Form 3)

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/ toxicity	ESMO-MCBS score[a]
	previously received a platinum-containing ChT and either PD-1 or PD-L1 inhibitor	NCT03547973		Median PFS: 5.4 months			

AE, adverse event; BSC, best supportive care; ChT, chemotherapy; CI, confidence interval; DoR, duration of response; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QoL, quality of life; UC, urothelial carcinoma.

[a]ESMO-MCBS v1.1[10] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[b]FDA approved; not EMA approved.

Table 2. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of Oxford University Press on behalf of the Infectious Diseases Society of America. [11]