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SPECIAL ARTICLE

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

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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 (UC; 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 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 UC (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—pembrolizumab 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, $P < 0.001$]. OS was also significantly prolonged with enfortumab vedotin—pembrolizumab versus platinum-based ChT (median OS, 31.5 months versus 16.1 months, respectively; HR 0.47, 95% CI 0.38-0.58, $P < 0.001$). The overall response rate was 67.7% for enfortumab vedotin—pembrolizumab [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 enfortumab vedotin—pembrolizumab and 26.1% with platinum-based ChT. Grade ≥3 TRAEs occurred in 55.9% of those treated with enfortumab vedotin—pembrolizumab 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 enfortumab vedotin—

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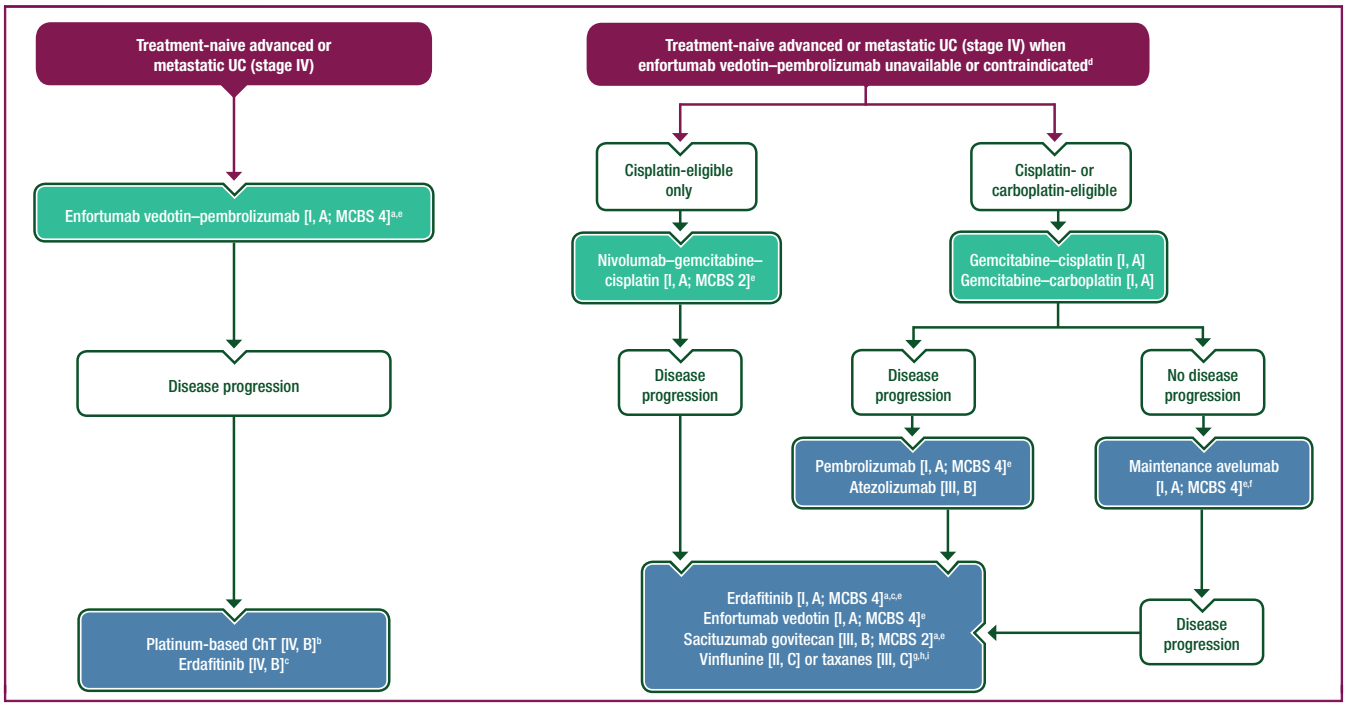

Figure 1. Management of patients with metastatic urothelial carcinoma.
Purple: algorithm title; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities; white: other aspects of management.
ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; 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]Enfortumab vedotin—pembrolizumab 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.

pembrolizumab 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 enfortumab vedotin—pembrolizumab. Discontinuation due to TRAEs of any study drug occurred in 35.0% and 18.5% of patients in the enfor-tumab vedotin—pembrolizumab and the ChT group, respectively.

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. The overall objective response and CR rates were 57.6% and 21.7%, respectively, with nivolumab—gemcitabine—cisplatin versus 43.1% and 11.8%, respectively, 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 et al.[6]

There is now level of evidence I (Table 1) for three treatment strategies in first-line: (i) enfortumab vedotin—pembrolizumab, (ii) nivolumab—gemcitabine—cisplatin for cisplatin-eligible patients or (iii) four to six cycles of platinum-based ChT followed by maintenance avelumab in patients who did not experience disease progression on platinum-based ChT.

Enfortumab vedotin—pembrolizumab is the new standard of care. The vast majority of patients are able to receive enfortumab vedotin—pembrolizumab irrespective of platinum eligibility. Subgroups of patients (e.g. those with a contraindication to pembrolizumab or uncontrolled diabetes) are ineligible for enfortumab vedotin—pembrolizumab and alternatives should be considered, such as platinum-based ChT.

A consensus could not be reached on giving enfortumab vedotin—pembrolizumab after completing adjuvant

Table 1. 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]

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 pretreated patients.[8] Sacituzumab govitecan is also included in the algorithm for heavily pretreated 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 'Management of Advanced/Metastatic Disease' section in the 2022 CPG).[1]

Recommendations

- Enfortumab vedotin—pembrolizumab is recommended as the preferred first-line therapy for advanced or metastatic UC, irrespective of platinum eligibility [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMOMCBS) v1.1 score: 4; Food and Drug Administration (FDA) approved, not European Medicines Agency (EMA) approved].
- After progression on enfortumab vedotin—pembrolizumab, 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 enfortumab vedotin—pembrolizumab should be treated with nivolumab plus up to six cycles of gemcitabine—cisplatin (if cisplatin-eligible only) [I, A; ESMO-MCBS v1.1 score: 2; FDA and EMA approved] or up to six cycles of platinum-based ChT (gemcitabine plus cisplatin or carboplatin) [I, A], followed by maintenance avelumab (for nonprogressing tumours) [I, A; 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):
  - o 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; FDA approved, not EMA approved].
  - o 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 enfortumab vedotin—pembrolizumab, 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 eUpdate 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 2. 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 1.[11]

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Table 2. 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							
First-line therapy							
Enfortumab vedotin −pembrolizuma[b]	Treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing ChT	EV-302/KN-A39[2] Phase III NCT04223856	Platinum-based ChT Median PFS: 6.3 months Median OS: 16.1 months	PFS gain: 6.2 months OS gain: 15.4 months	PFS: 0.45 (0.38-0.54) OS: 0.47 (0.38-0.58)	QoL data pending	4 (Form 2a)
Nivolumab–gemcitabine–cisplatin	First-line treatment of adult patients with unresectable or metastatic UC	CheckMate 901[3] Phase III NCT03036098	Gemcitabine–cisplatin Median PFS: 7.6 months Median OS: 18.9 months	PFS gain: 0.3 months OS gain: 2.8 months	PFS: 0.72 (0.59-0.88) OS: 0.78 (0.63-0.96)	No QoL benefit	2 (Form 2a)
Maintenance therapy							
Avelumab	First-line maintenance treatment of patients with locally advanced or metastatic UC who are progression-free following platinum-based ChT	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)
Further-line therapy							
Enfortumab vedotin	Treatment of patients with locally advanced or metastatic UC who have previously received a platinum-containing ChT and a PD-1 or PD-L1 inhibitor	EV-301[14,15] Phase III NCT03474107	Investigator's choice of ChT (standard docetaxel, paclitaxel or vinflunine) Median OS: 8.94 months	OS gain: 3.97 months	OS: 0.70 (0.58-0.85)	QoL data pending	4 (Form 2a)
Erdafitinib[b]	Treatment of patients with locally advanced or metastatic UC that has susceptible *FGFR3* or *FGFR2* genetic alterations and progressed after one or two previous treatments that included an anti-PD-1 or anti-PD-L1	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)
Pembrolizumab	Treatment of locally advanced or metastatic UC in adults who have received prior platinum-containing ChT	KEYNOTE-045[16-19] Phase III NCT02256436	Investigator's choice of ChT (paclitaxel, docetaxel or vinflunine) 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)	QoL was an exploratory endpoint Fewer grade 3/4 treatment-related AEs versus control ($P < 0.001$) but not affecting daily well-being	4 (Form 2a)
Sacituzumab govitecan[b]	Treatment of patients with locally advanced or metastatic UC who have previously received a platinum-containing ChT and either PD-1 or PD-L1 inhibitor	TROPHY-U-01[9] Phase II NCT03547973	Single arm	ORR: 27.4% Median DoR: 7.2 months Median PFS: 5.4 months		QoL was not a prespecified endpoint	2 (Form 3)

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.

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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 T, Valderrama BP, Gupta S, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. *N Engl J Med*. 2024;390(10):875-888.
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 JÁA, 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].
12. Grivas P, Kopyltsov E, Su PJ, et al. Patient-reported outcomes from JAVELIN Bladder 100: avelumab first-line maintenance plus best supportive care versus best supportive care alone for advanced urothelial carcinoma. *Eur Urol*. 2023;83(4):320-328.
13. Powles T, Park SH, Caserta C, et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN Bladder 100 trial after ≥2 years of follow-up. *J Clin Oncol*. 2023;41(19):3486-3492.
14. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med*. 2021;384(12):1125-1135.
15. Rosenberg JE, Powles T, Sonpavde GP, et al. EV-301 long-term outcomes: 24-month findings from the phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. *Ann Oncol*. 2023;34(11):1047-1054.
16. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026.

17. Vaughn DJ, Bellmunt J, Fradet Y, et al. Health-related quality-of-life analysis from KEYNOTE-045: a phase III study of pembrolizumab versus chemotherapy for previously treated advanced urothelial cancer. *J Clin Oncol*. 2018;36(16):1579-1587.
18. Fradet Y, Bellmunt J, Vaughn DJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. *Ann Oncol*. 2019;30(6):970-976.
19. Balar AV, Castellano DE, Grivas P, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. *Ann Oncol*. 2023;34(3):289-299.