Advanced urothelial carcinoma: Expert guidance to navigate an evolving therapeutic landscape

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Optimizing treatment choices: Integrating emerging first-line therapies in advanced bladder cancer

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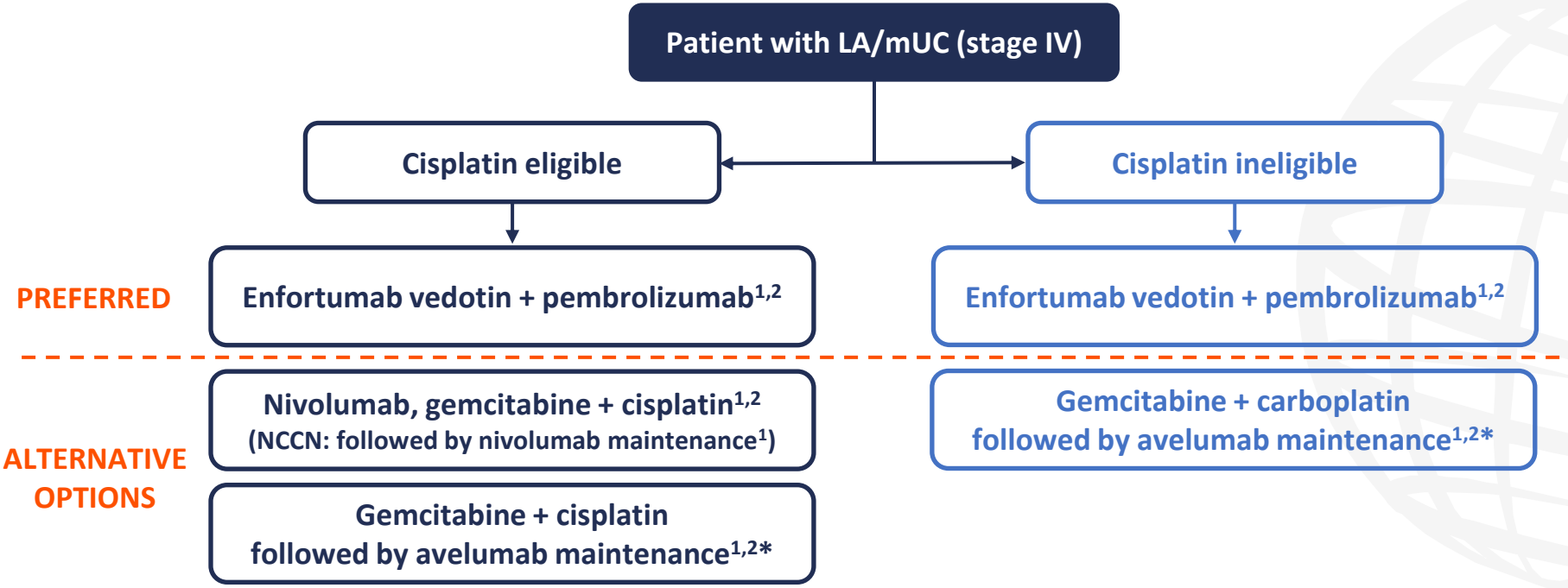
How is the first-line treatment of advanced urothelial carcinoma evolving?

ESMO and NCCN guidelines: First-line treatment recommendations



*Avelumab maintenance only if no progression on first-line platinum-containing chemotherapy.[1,2]

ESMO, European Society for Medical Oncology; LA/mUC, locally advanced/metastatic urothelial carcinoma; NCCN, National Comprehensive Cancer Network.

1. NCCN. Bladder Cancer V4.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed 23 May 2024); 2. Powles T, et al. *Ann Oncol.* 2024:S0923-7534(24)00075-9 (online ahead of print).

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What data have driven the updates to the recommended first-line treatments?

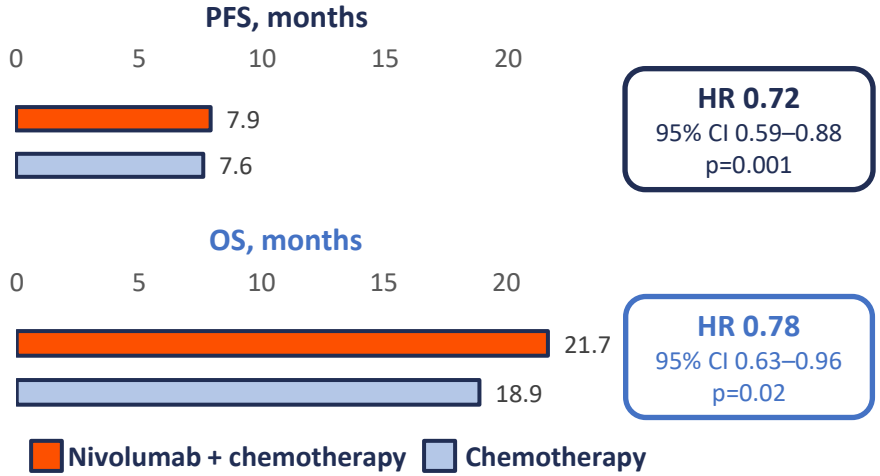
Trial data for updated first-line treatment options

Checkmate-901[1]

Phase III, multinational, open-label, randomized trial

N=608; previously untreated unresectable/mUC

Nivolumab + gemcitabine + cisplatin (n=304)
Gemcitabine + cisplatin (n=304)

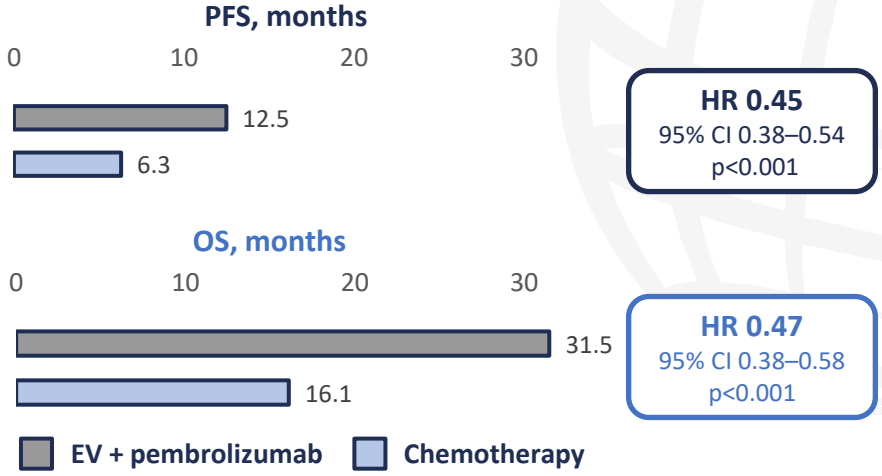


EV-302[2]

Phase III, global, open-label, randomized trial

N=886; previously untreated LA/mUC

Enfortumab vedotin + pembrolizumab (n=442)
Gemcitabine + cisplatin or carboplatin (n=444)



CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; LA/mUC, locally advanced/metastatic urothelial carcinoma; OS, overall survival; PFS, progression free survival.

1. van der Heijden MS, et al. *N Engl J Med*. 2023;389:1778–89; 2. Powles TB, et al. *N Engl J Med.* 2024;390:875–88.

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Which factors inform the decision to use enfortumab vedotin plus pembrolizumab in the first-line setting?

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Factors to consider when using enfortumab vedotin plus pembrolizumab

Significant peripheral neuropathy or poorly controlled diabetes at baseline	• Peripheral neuropathy has occurred with enfortumab vedotin, and patients with pre-existing peripheral neuropathy grade ≥2 were excluded from clinical trials[1] • Hyperglycaemia and DKA have occurred in patients with and without pre-existing diabetes mellitus treated with enfortumab vedotin, and patients with baseline HbA1c ≥8% were excluded from clinical trials[1]
Autoimmune disease requiring immunosuppressive therapy	• In patients on immunosuppressive therapy for active autoimmune disease, the efficacy of ICIs may be reduced and management of irAEs is more challenging[2] • Patients with previous autoimmune disease for which they had received systemic treatment in the previous 2 years were excluded from the EV-302 trial[3]
Performance status >2	• Patients with an ECOG performance status >2 were excluded from the EV-302 trial[3]

DKA, diabetic ketoacidosis; ECOG, Eastern Cooperative Oncology Group; HbA1c, glycated haemoglobin; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

1. EMA. Enfortumab vedotin SmPC. Available at: www.ema.europa.eu/en (accessed 23 April 2024); 2. Rakshit S, Molina JR. *J Thorac Dis*. 2020;12:7032–8;
3. Powles TB, et al. *N Engl J Med.* 2024;390:875–88.

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How do you select a first-line treatment for a patient who is not going to receive enfortumab vedotin plus pembrolizumab?

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What other treatments are being investigated in the first-line setting?

Examples of ongoing neo(adjuvant) and first-line trials

(Neo)adjuvant approaches

- Durvalumab + enfortumab vedotin ± tremelimumab (NCT04960709)
- Pembrolizumab (NCT03244384)
- Atezolizumab (ctDNA positive) (NCT04660344)
- ctDNA-guided nivolumab ± relatlimab (NCT05987241)
- Tislelizumab ± APL-1202 (MetAP2 inhibitor) (NCT04813107)
- Pembrolizumab + gemcitabine (NCT02365766)

Maintenance

- Cabozantinib + avelumab (NCT05092958)

HER2 targeting

- Disitamab vedotin + toripalimab (NCT05302284)
- Disitamab vedotin + pembrolizumab (NCT05911295)

ICI + chemotherapy

- Tislelizumab + chemotherapy (NCT03967977)
- Durvalumab ± tremelimumab + chemotherapy (NCT03682068)
- Toripalimab + chemotherapy (PD-L1 positive) (NCT04568304)
- Tislelizumab + chemotherapy ± trilaciclib (CDK4/6i) (NCT06364904)

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumour DNA; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; MetAP2, methionine aminopeptidase 2; PD-L1, programmed death-ligand 1.

ClinicalTrials.gov. Available at: www.clinicaltrials.gov (accessed 16 May 2024).

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Transitioning to the second line: Integrating treatments with precision sequencing in advanced bladder cancer

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What are the second-line treatment options in advanced urothelial carcinoma?

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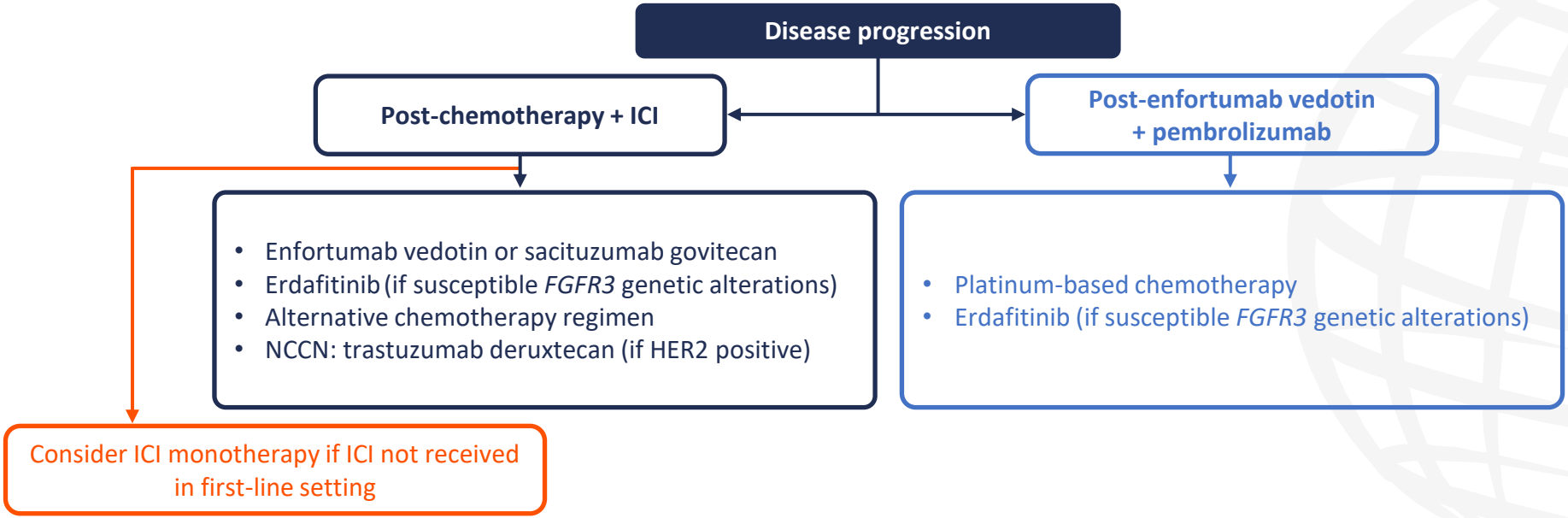
ESMO and NCCN guidelines: Key second-line treatment options for LA/mUC



ESMO, European Society for Medical Oncology; FGFR3, fibroblast growth factor receptor 3; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; LA/mUC, locally advanced/metastatic urothelial carcinoma; NCCN, National Comprehensive Cancer Network.

1. NCCN. Bladder Cancer V4.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed 23 May 2024); 2. Powles T, et al. *Ann Oncol.* 2024:S0923-7534(24)00075-9 (online ahead of print).

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What data have led to updates in the second-line treatment algorithm for advanced urothelial carcinoma?

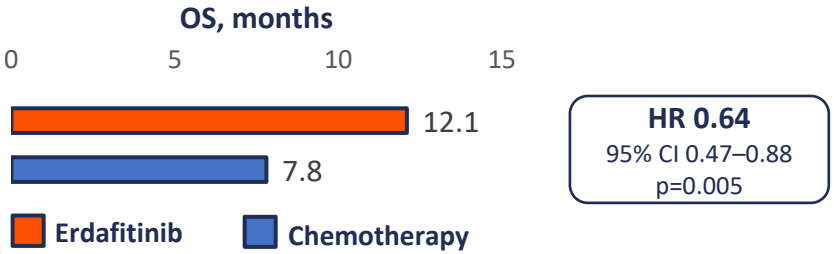
Trial data for updated second-line treatment options

THOR Cohort 1[1]

Phase III, global, randomized trial

N=266; LA/mUC with progression; *FGFR3/2* alterations

Erdafitinib (n=136)
Chemotherapy (docetaxel or vinflunine; n=130)



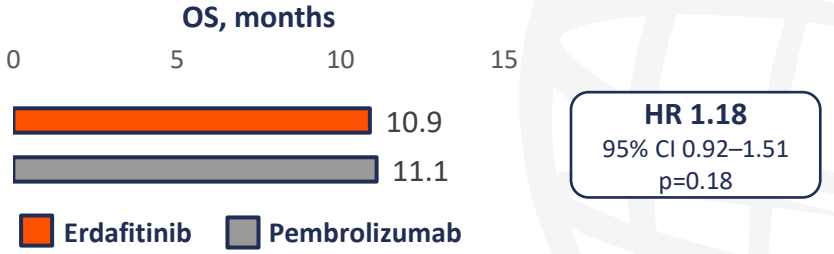
HR 0.64
95% CI 0.47–0.88
p=0.005

THOR Cohort 2[2]

Phase III, global, open-label, randomized trial

N=351; unresectable/mUC with progression;
FGFR3/2 alterations; ICI naive

Erdafitinib (n=175)
Pembrolizumab (n=176)



HR 1.18
95% CI 0.92–1.51
p=0.18

TROPHY-U-01[3]

Phase II, open-label study

Cohort 1; N=113
LA/mUC with progression
after chemotherapy + ICI

Sacituzumab govitecan

ORR: 28%
Median PFS: 5.4 months
Median OS: 10.9 months
Median follow-up of 10.5 months

CI, confidence interval; FGFR3/2, fibroblast growth factor receptor 3/2, HR, hazard ratio; ICI, immune checkpoint inhibitor; LA/mUC, locally advanced/metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Loriot Y, et al. *N Engl J Med*. 2023;389:1961–71; 2. Siefker-Radtke AO, et al. *Ann Oncol*. 2024;35:107–17; 3. Loriot Y, et al. *Ann Oncol*. 2024;35:392–401.

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Which factors should be considered when selecting the most appropriate second-line treatment?

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Which recent data support the use of immune checkpoint inhibitors or antibody–drug conjugates in the second-line setting?

Recent trial data and real-world findings for ADCs and ICIs in the second-line setting

ADCs

- Real-world data confirmed the safety profile of **sacituzumab govitecan** and feasibility of prescribing after enfortumab vedotin[1]
- 24-month data with **enfortumab vedotin** from the EV-301 trial showed durable response rates and OS outcomes[2]
- Real-world outcomes for patients with previously treated advanced UC who received **enfortumab vedotin** were consistent with clinical trials[3–5]

ICIs

- Data from multiple centres found that **ICI therapy** has durable results with acceptable adverse events when used in the real world[6,7]
- One retrospective analysis found **atezolizumab** and **pembrolizumab** to be effective treatment options[8]

ADC, antibody–drug conjugate; ICI, immune checkpoint inhibitor; OS, overall survival; UC, urothelial carcinoma.

1. Parikh M, et al. *J Clin Oncol*. 2024;24:Abstr. 608; 2. Rosenberg JE, et al. *Ann Oncol*. 2023;34:1047–54; 3. Zschäbitz S, et al. *EU Open Science*. 2023;53:31–7; 4. Endo Y, et al. *Curr Oncol*. 2024;31:759–68; 5. Miyake M et al. *JPN J Clin Oncol*. 2024;54:329–38; 6. Su R, et al. *Cancer Med*. 2023;12:10587–96; 7. Tural D, et al. *Clin Genitourin Cancer*. 2023;21:334–41; 8. Váradi M, et al. *Sci Rep*. 2023;13:17378.

What other treatments are in the pipeline for the second-line setting?

Ongoing clinical trials in the second-line setting

Patients who have received prior (platinum-based) chemotherapy	Estimated study completion dates
Bispecific antibody	
Phase II: SI-B003 (PD-1/CTLA-4) ± BL-B01D1 (EGFRxHER3) (NCT05965856)	12/2025
Monoclonal antibody	
Phase II: Atezolizumab and CYT107 (IL-7) (NCT03513952)	10/2024
Phase II: Atezolizumab ± eribulin mesylate (NCT03237780)	01/2025
Patients who have received prior PD-(L)1 therapy	
Phase II: Pemetrexed + etrumadenant (A2a and A2b adenosine receptor antagonist) + zimberelimab (NCT05335941)	09/2025
Patients who have received either and/or both prior chemotherapy or PD-(L)1 therapy	
Nectin-4-targeted treatment	
Phase III: 9MW2821 (NCT06196736)	12/2028
HER2-targeted treatment	
Phase II: Trastuzumab and pyrotinib (NCT05318339)	12/2024
Phase II: Disitamab vedotin ± pembrolizumab (NCT04879329)	03/2026
Phase III: MRG002 (NCT05754853)	01/2027

ADC, antibody-drug conjugate; CTLA-4; cytotoxic T-lymphocyte associated protein 4; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; ICI, immune checkpoint inhibitor; IL-7, interleukin 7; PD-(L)1, programmed cell death protein-1/programmed cell death-ligand 1.

ClinicalTrials.gov. Available at: www.clinicaltrials.gov (accessed 28 April 2024).

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Patient safety: Managing adverse events in advanced bladder cancer

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What are the key safety considerations when using enfortumab vedotin plus pembrolizumab?

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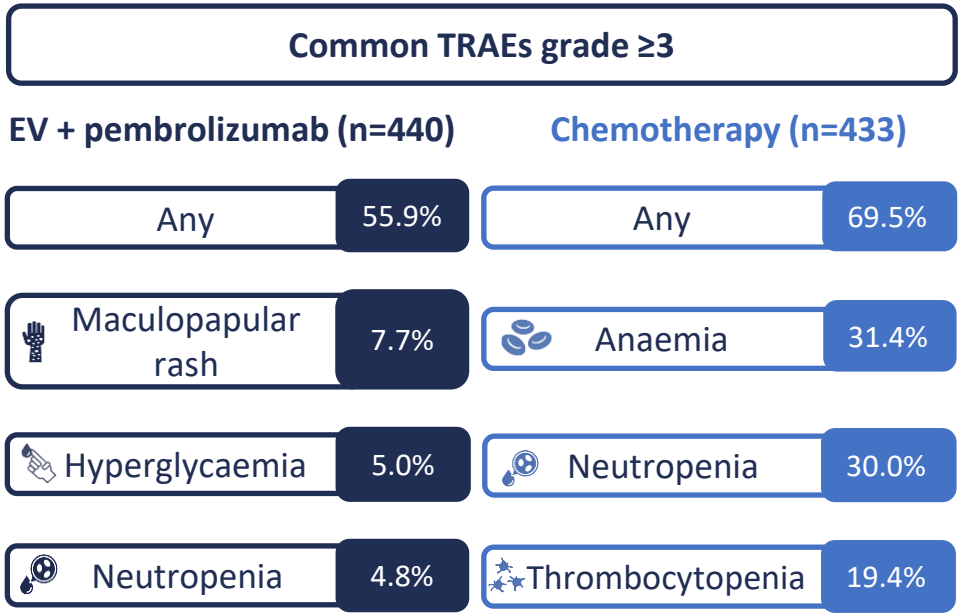
Enfortumab vedotin + pembrolizumab adverse events



AEs of special interest (grade ≥3) previously associated with EV

Skin reactions	15.5%
Peripheral neuropathy	6.8%
Hyperglycaemia	6.1%

AEs of special interest (grade ≥3) previously associated with pembrolizumab

Severe skin reactions	11.8%
Pneumonitis	3.6%
Hepatitis	1.8%

Most AEs of special interest were manageable with dose modifications

AE, adverse event; EV, enfortumab vedotin; TRAE, treatment-related adverse event.

Powles TB, et al. *N Engl J Med.* 2024;390:875–88.

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Which side effects may occur when using an immune checkpoint inhibitor, and how should these be monitored for and managed?

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Immune checkpoint inhibitor adverse events[1–4]

Colitis

Monitor for signs and symptoms

Hepatitis

Monitor ALT, AST and bilirubin

Nephritis

Monitor serum creatinine

Pneumonitis

Monitor for signs and symptoms

Hypo/hyperthyroidism

Monitor thyroid function, and for signs and symptoms

Management strategies include corticosteroids, withholding drug and treatment discontinuation, depending on grade

- Management strategies include corticosteroids, withholding drug and treatment discontinuation, depending on grade
- **For hypothyroidism:** use thyroid replacement therapy
- **For hyperthyroidism:** use antithyroid medication

ALT, alanine transaminase; AST, aspartate transaminase.

1. EMA. Atezolizumab SmPC; 2. EMA. Pembrolizumab SmPC; 3. EMA. Avelumab SmPC. 4. EMA. Nivolumab SmPC.
All SmPC available at: www.ema.europa.eu/en (accessed 23 April 2024).

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What are the key side effects to consider when using antibody–drug conjugates, and how can they be identified and managed?

Adverse events of special interest with enfortumab vedotin

Peripheral neuropathy

Musculoskeletal and neurological assessments

- Grade 2: withhold until grade ≤1
- Grade ≥3: permanently discontinue

Skin reactions

Monitor from first cycle and throughout treatment

- Mild-to-moderate skin reactions: topical corticosteroids or antihistamines
- Suspected SJS, TEN or bullous lesions: immediately withhold and refer to specialized care
- Confirmed SJS or TEN, grade 4 or recurrent grade 3: permanently discontinue
- Grade 2 worsening, grade 2 with fever or grade 3: withhold until grade ≤1

Ocular

Ophthalmological examinations

- Consider artificial tears for dry eye prophylaxis
- If ocular symptoms worsen or do not resolve: ophthalmologic evaluation

Hyperglycaemia

Monitor blood glucose prior to dosing and periodically throughout treatment

- If blood glucose elevated (>13.9 mmol/L/>250 mg/dL): withhold until ≤13.9 mmol/L (≤250 mg/dL)

Refer to product information for dose modifications

SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.

EMA. Enfortumab vedotin SmPC. Available at: www.ema.europa.eu/en (accessed 23 April 2024).

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Adverse events of special interest with sacituzumab govitecan

Diarrhoea

Patient reported

- If non-infectious cause, initiate loperamide
- Grade 3 or 4 at time of scheduled treatment: withhold and resume when resolved to grade ≤1
- Additional supportive measures, e.g. fluid and electrolyte substitution, may be used as clinically indicated

Nausea and vomiting

Patient reported

- Premedicate with a two- or three-drug combination regimen
- Grade 3 nausea or grade 3 or 4 vomiting at time of scheduled treatment: withhold and resume with additional supportive measures when resolved to grade ≤1
- Additional antiemetics and other supportive measures as clinically indicated

Hypersensitivity

Observe during infusion and for further 30 mins

- Pre-infusion treatment, including antipyretics, H1 and H2 blockers, or corticosteroids
- If infusion-related reaction develops: slow or interrupt infusion; permanently discontinue if life-threatening reaction occurs

Neutropenia

Signs of infection; monitor blood cell counts

- Do not administer if absolute neutrophil count is below 1,500/m^3 on Day 1 of any cycle or if the neutrophil count is below 1,000/mm^3 on Day 8 of any cycle, or in cases of neutropenic fever
- Administer G-CSF as clinically indicated

Refer to product information for dose modifications

G-CSF, granulocyte-colony stimulating factor.

FDA. Sacituzumab govitecan PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2023/761115s035lbl.pdf (accessed 23 April 2024).

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What side effects may occur when using FGFR inhibitors, and how can they be identified and managed?

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Erdafitinib adverse events

Common AEs grade ≥3[1–3]

- Anaemia
- Asthenia
- Hyperphosphataemia
- Hyponatraemia
- Onycholysis
- Palmar-plantar erythrodysesthesia syndrome
- Stomatitis

AEs of special interest[4]

Nail and skin reactions

Patient reported

- Grade 3: withhold until grade ≤1 or baseline
- Grade 4: permanently discontinue

CSR/RPED

Ophthalmological examinations

- Dry eye prophylaxis as needed
- If CSR/RPED occurs, withhold; discontinue if it does not resolve within 4 weeks or if grade 4

Hyperphosphataemia

Serum phosphate level monitoring

- Dietary phosphate restriction
- Consider oral phosphate binder if serum phosphate is >7.0 mg/dL
- If serum phosphate ≥9.0 mg/dL, withhold treatment until level returns to <7.0 mg/dL

Refer to product information for dose modifications

AE, adverse event; CSR, central serous retinopathy; RPED, retinal pigment epithelial detachment.

1. Loriot Y, et al. *N Engl J Med*. 2019;381:338–48; 2. Loriot Y, et al. *N Engl J Med.* 2023;389:1961–71; 3. Siefker-Radtke AO, et al. *Ann Oncol.* 2024;35:107–17;
4. FDA. Erdafitinib PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2024/212018s007s008s009lbl.pdf (accessed 23 April 2024).

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How can the multidisciplinary team be utilized to improve identification and monitoring of side effects?