The evolving role of antibody–drug conjugates in the treatment of urothelial carcinoma

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Beyond checkpoint inhibitors: What is the role of antibody–drug conjugates in metastatic urothelial carcinoma?

Bladder cancer in numbers

Globally in 2020:

573,278 new cases of bladder cancer

Bladder cancer was the 10th most commonly diagnosed cancer (6th in men)

Bladder cancer was responsible for 212,536 deaths

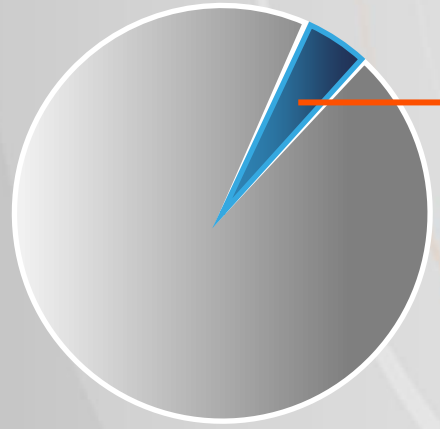
Sung H, et al. *CA Cancer J Clin*. 2021;71:209–49.

Urothelial carcinoma in numbers

90% of bladder cancer is urothelial carcinoma[1]

Metastatic urothelial carcinoma: incidence and survival

5% metastatic disease[1]



5-year survival for metastatic disease is only **6.4%**[2]

1. Saginala K, et al. *Med Sci (Basel).* 2020;8:15; 2. NIH. Cancer Stat Facts: Bladder cancer. Available at: https://seer.cancer.gov/statfacts/html/urinb.html (accessed 17 December 2021).

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Unmet needs in the treatment of urothelial carcinoma

Cisplatin is the standard treatment in mUC; however, **50% of patients** are often considered ineligible[1]

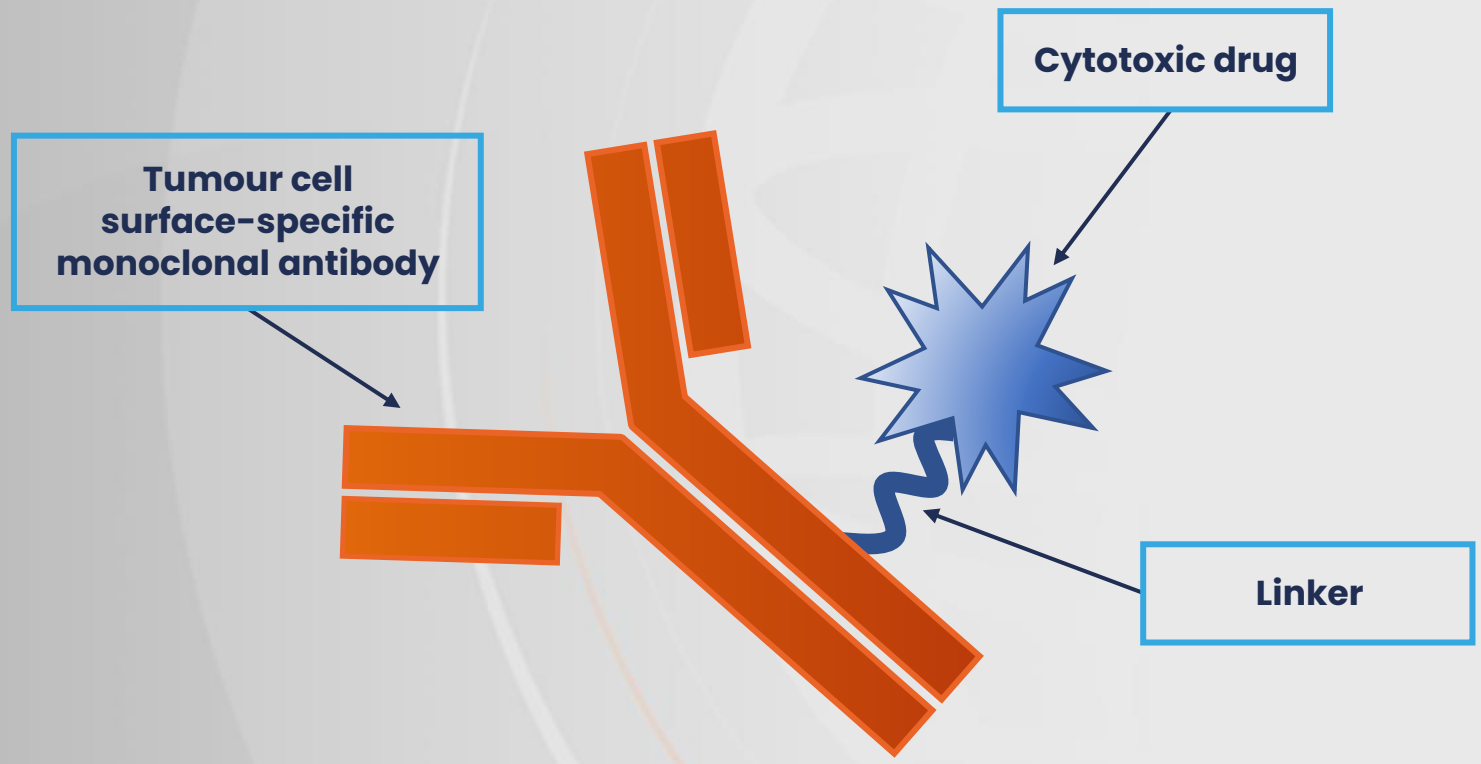
Carboplatin has inferior outcomes vs cisplatin[1]

If a patient is PD-L1-positive, ICIs are an option; however, **~70% of patients do not respond** and require further treatment[2]

ICI, immune checkpoint inhibitor; mUC, metastatic urothelial carcinoma; PD-L1, programmed death-ligand 1.

1. Mollica V, et al. *Cancers (Basel)*. 2020;12:1449; 2. Lopez-Beltran A, et al. *Cancers (Basel)*. 2021;113:131.

Antibody–drug conjugates are a new approach in metastatic urothelial carcinoma



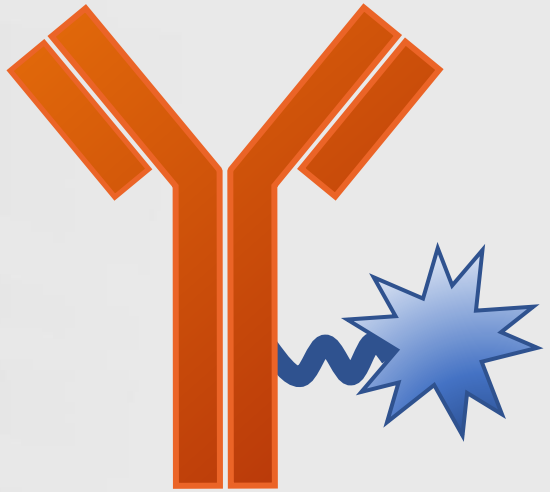
Bouchard H, et al. *Bioorg Med Chem Lett*. 2014;24:5357–63.

Antibody–drug conjugates are a new approach in metastatic urothelial carcinoma

Monoclonal antibodies conjugated to cytotoxic drug or radionuclide

Improves potency and effectiveness of monoclonal antibodies

Allows for targeted delivery of toxic payload to tumour cells, minimizing non-specific, systemic toxicity



Panowski S, et al. *MAbs*. 2014;6:34–45.

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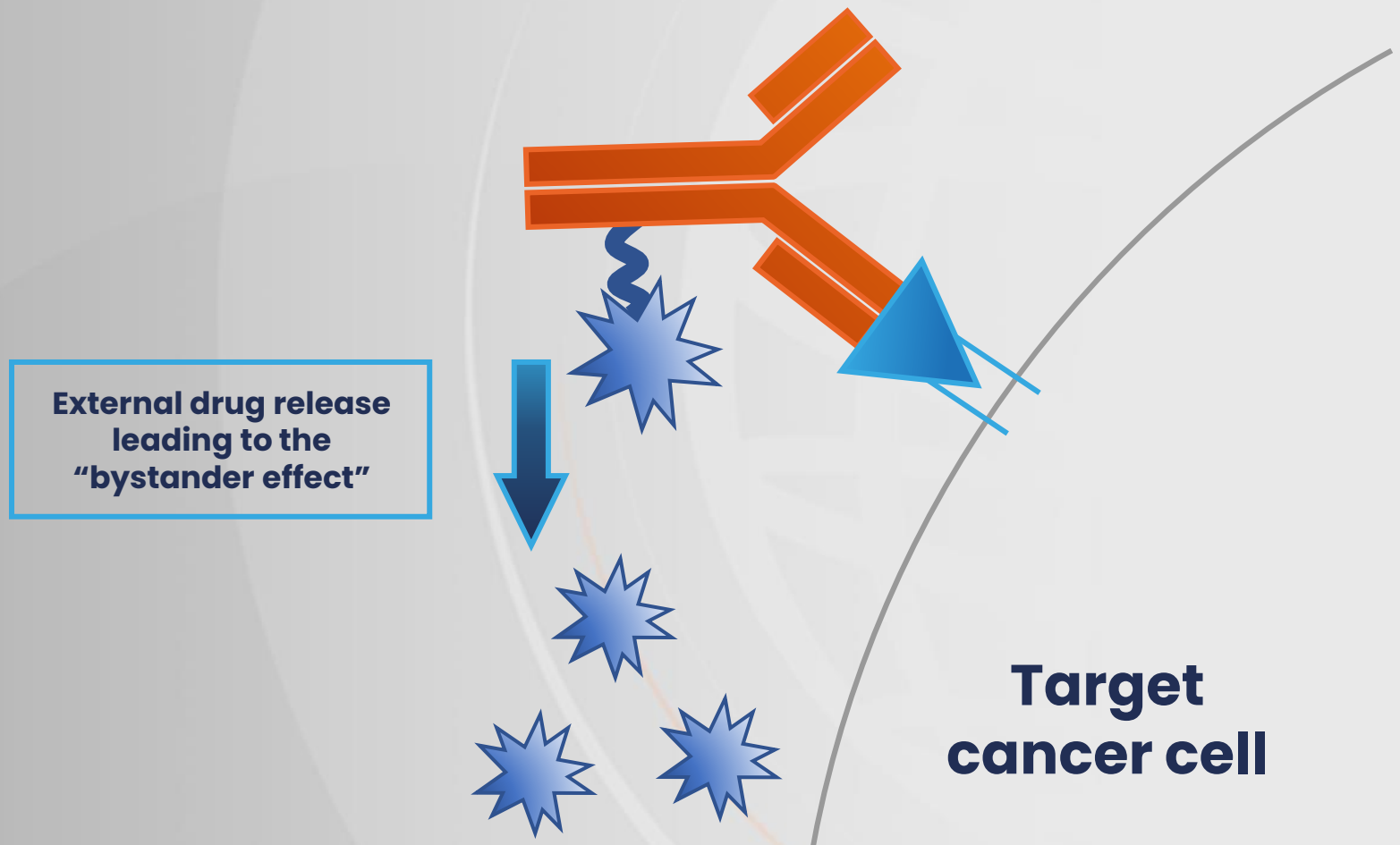
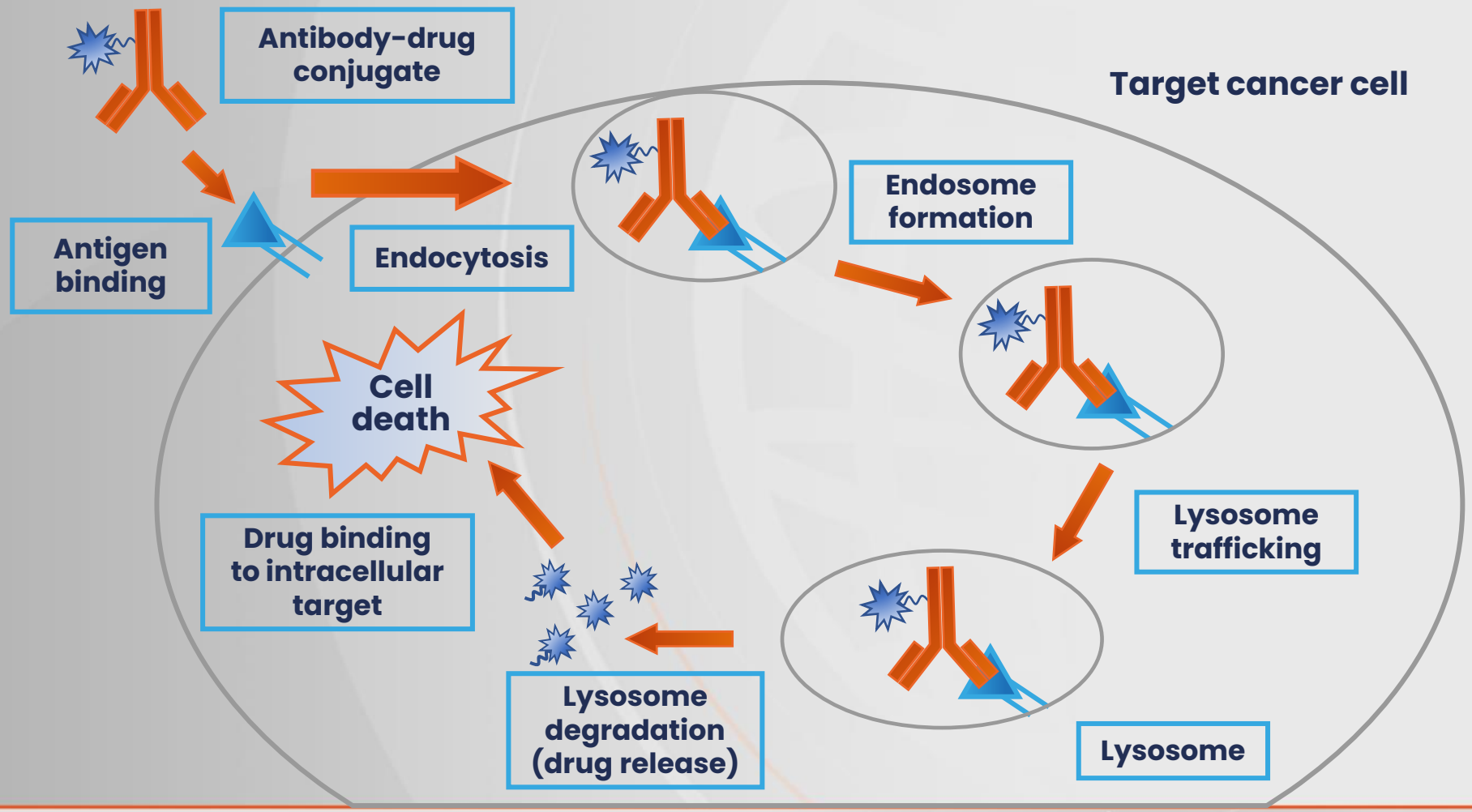
Antibody–drug conjugates: Mechanism of action



Staudacher AH, Brown MP. *Br J Cancer*. 2017;117:1736–42.

Antibody–drug conjugates: Mechanism of action



Bouchard H, et al. *Bioorg Med Chem Lett*. 2014;24:5357–63.

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Antibody-drug conjugates for urothelial carcinoma

Enfortumab vedotin

Target: Nectin-4
Transmembrane cell adhesion molecule highly expressed in cancer cells, including urothelial carcinoma

Monomethyl auristatin E
microtubule inhibitor payload

FDA full approval, July 2021

Adult patients with locally advanced or metastatic urothelial cancer who:

- Have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy

OR

- Are ineligible for cisplatin-containing chemotherapy and have previously received ≥1 prior line of therapy

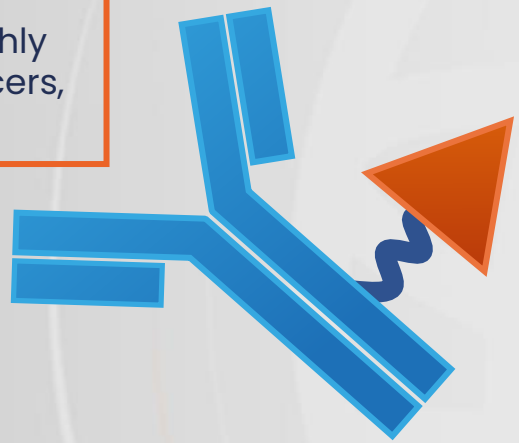
FDA, Food and Drug Administration; PD-1, programmed cell death protein 1.

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Antibody-drug conjugates for urothelial carcinoma

Sacituzumab govitecan

Target: Trop-2
Cell surface antigen highly expressed by many cancers, including mUC



SN-38
topoisomerase inhibitor payload

FDA accelerated approval, April 2021

Adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor

Trop-2, trophoblast cell surface antigen 2.
FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021).

Metastatic urothelial carcinoma NCCN treatment guidelines

First-line treatment options

Preferred regimens for cisplatin-eligible patients

Gemcitabine and cisplatin, avelumab maintenance

DDMVAC with growth factor support, avelumab maintenance

Preferred regimens for cisplatin-ineligible patients

Gemcitabine and carboplatin, avelumab maintenance

Pembrolizumab or atezolizumab (PD-L1-positive only or not eligible for any platinum)

DDMVAC, dose-dense methotrexate, vinblastine, doxorubicin and cisplatin; NCCN, National Comprehensive Cancer Network.

NCCN Clinical Practice Guidelines in Oncology, Bladder Cancer, Version 6.2021, December 6, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed 17 December 2021).

Metastatic urothelial carcinoma NCCN treatment guidelines

Second-line treatment options, post-platinum

Preferred regimen

Pembrolizumab

Alternate preferred regimens

Immune checkpoint inhibitor (nivolumab/avelumab)

Erdafitinib (*FGFR3/2* genetic alterations)

Enfortumab vedotin

FGFR, fibroblast growth factor receptor.

NCCN Clinical Practice Guidelines in Oncology, Bladder Cancer, Version 6.2021, December 6, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed 17 December 2021).

Metastatic urothelial carcinoma NCCN treatment guidelines

Second-line treatment options, post-checkpoint inhibitor (chemotherapy naïve)

Preferred regimens for cisplatin-eligible patients

Gemcitabine and cisplatin

DDMVAC with growth factor support

Preferred regimens for cisplatin-ineligible patients

Enfortumab vedotin

Gemcitabine and carboplatin

NCCN Clinical Practice Guidelines in Oncology, Bladder Cancer, Version 6.2021, December 6, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed 17 December 2021).

Metastatic urothelial carcinoma NCCN treatment guidelines

Subsequent-line treatment options

Preferred regimens

Enfortumab vedotin

Erdafitinib (*FGFR3/2* genetic alterations)

Other recommended regimens include:
Sacituzumab govitecan

NCCN Clinical Practice Guidelines in Oncology, Bladder Cancer, Version 6.2021, December 6, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed 17 December 2021).

Metastatic urothelial carcinoma ESMO treatment guidelines

Enfortumab vedotin is a recommended treatment option in patients who have relapsed after first-line single-agent immunotherapy

Enfortumab vedotin is recommended as standard treatment in patients with chemotherapy- and immunotherapy-relapsed disease

Enfortumab vedotin is not currently EMA approved (December 2021)

EMA, European Medicines Agency; ESMO, European Society for Medical Oncology.
Powles T, et al. *Ann Oncol*. 2021: DOI: https://doiorg/10.1016/j.annonc.2021.11.012 (Online ahead of print).

Conclusions

Patients who progress on chemotherapy and immune checkpoint inhibitors have a poor prognosis

ADCs pair a potent cytotoxic drug with an antibody which targets only the cancer cells

ADCs could fulfil an unmet need for treatment in patients who will not benefit from chemotherapy or immune checkpoint inhibitors

ADC, antibody–drug conjugate.

Cabrera JM, et al. *Advances in Oncology*. 2021;1:273–82.

Improving outcomes with antibody–drug conjugates in urothelial carcinoma: Where are we now and next steps?

EV-201: Phase II study of enfortumab vedotin

Study design

Enfortumab vedotin
1.25 mg/kg IV on days 1, 8 and 15 of each 28-day cycle

Cohort 1[1]

n=125

- Locally advanced unresectable or metastatic urothelial carcinoma
- Previously treated with PD-1/PD-L1 inhibitor and platinum-based therapy

Cohort 2[2]

n=89

- Locally advanced unresectable or metastatic urothelial carcinoma
- Platinum-naïve and cisplatin ineligible
- Previous treatment with PD-1/PD-L1 inhibitor

Primary endpoint
- Confirmed ORR as determined by BICR

Secondary endpoints
- Investigator-assessed ORR
- DOR
- PFS by BICR
- OS
- Safety and tolerability

BICR, blinded independent central review; DOR, duration of response; IV, intravenous; ORR, overall response rate; OS, overall survival; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1. Rosenberg JE, et al. *J Clin Oncol*. 2019;37:2592–600; 2. McGregor BA, et al. American Society of Clinical Oncology Virtual Congress, 4–8 June 2021. Poster 4524.

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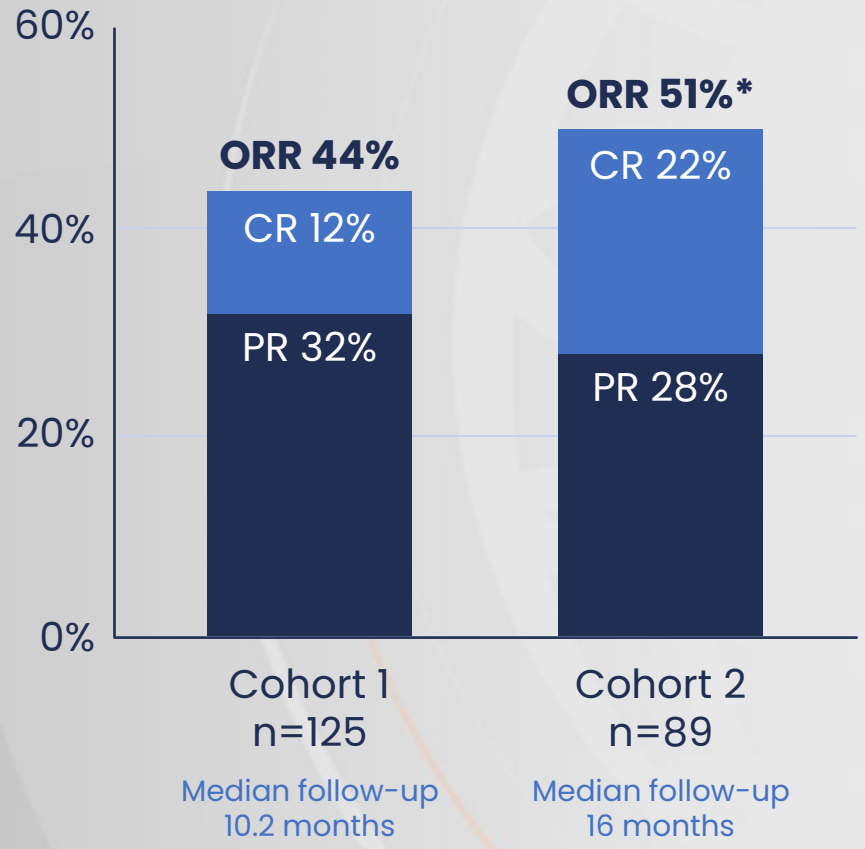
EV-201: Phase II study of enfortumab vedotin

Primary endpoint: ORR[1,2]



*Data rounded to whole numbers.
CR, complete response; PR, partial response.
1. Rosenberg JE, et al. *J Clin Oncol*. 2019;37:2592–600; 2. McGregor BA, et al. American Society of Clinical Oncology Virtual Congress, 4–8 June 2021. Poster 4524.

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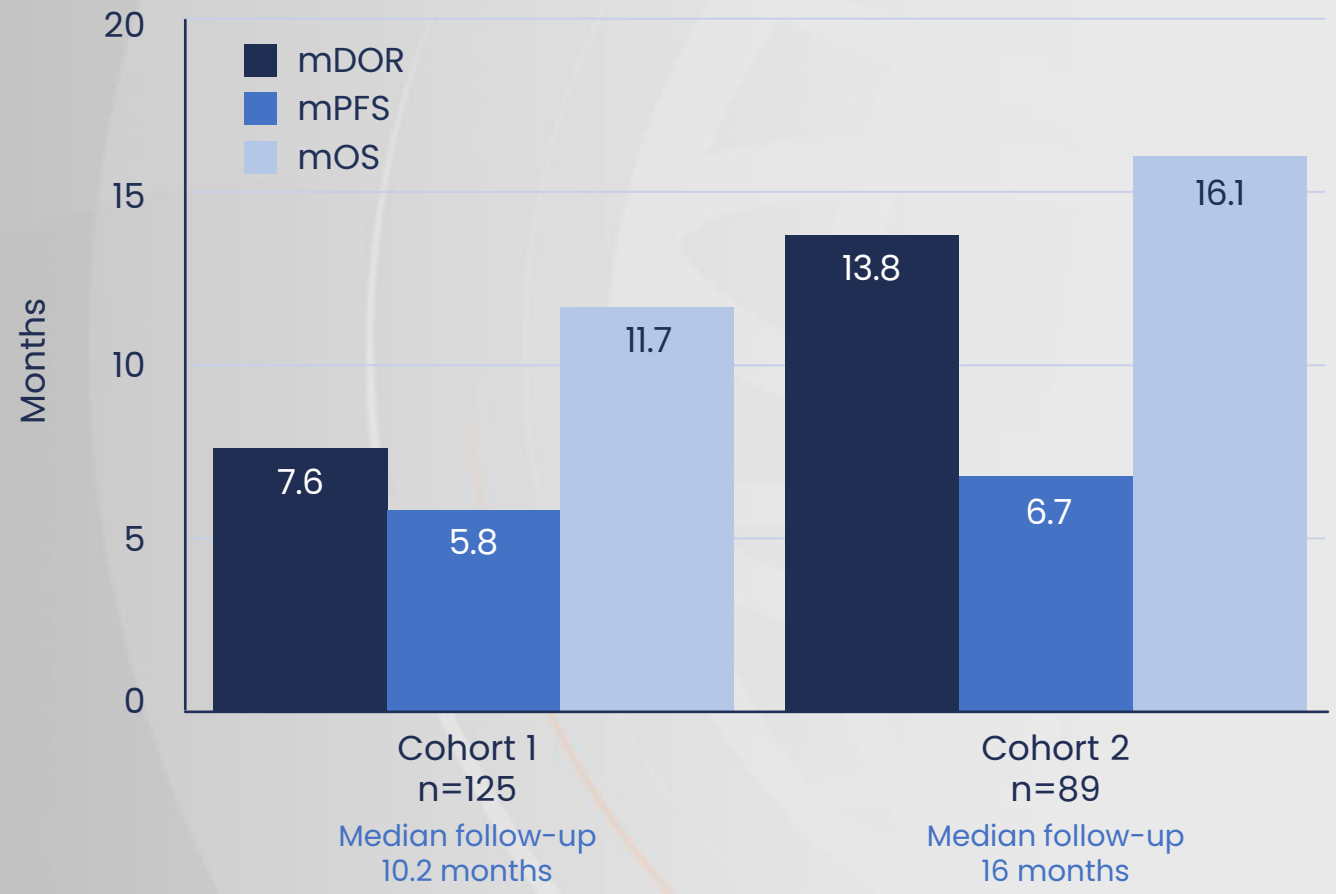
EV-201: Phase II study of enfortumab vedotin

Secondary endpoints[1,2]



mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival.

1. Rosenberg JE, et al. *J Clin Oncol*. 2019;37:2592–600; 2. McGregor BA, et al. American Society of Clinical Oncology Virtual Congress, 4–8 June 2021. Poster 4524.

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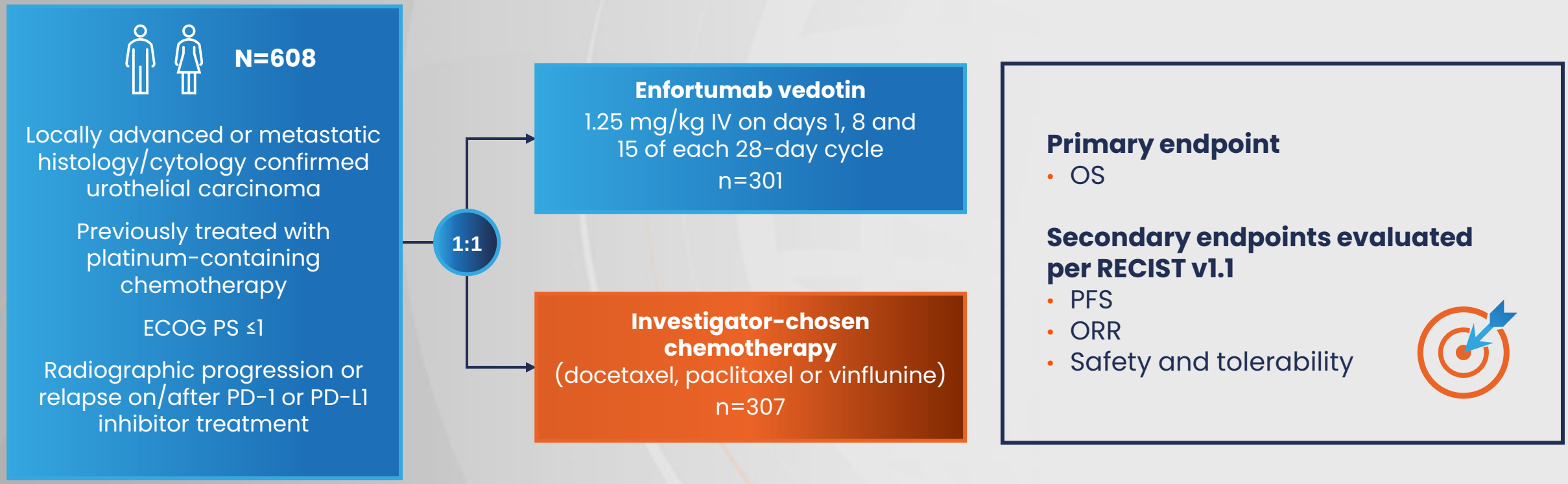
EV-301: Phase III study of enfortumab vedotin

Study design

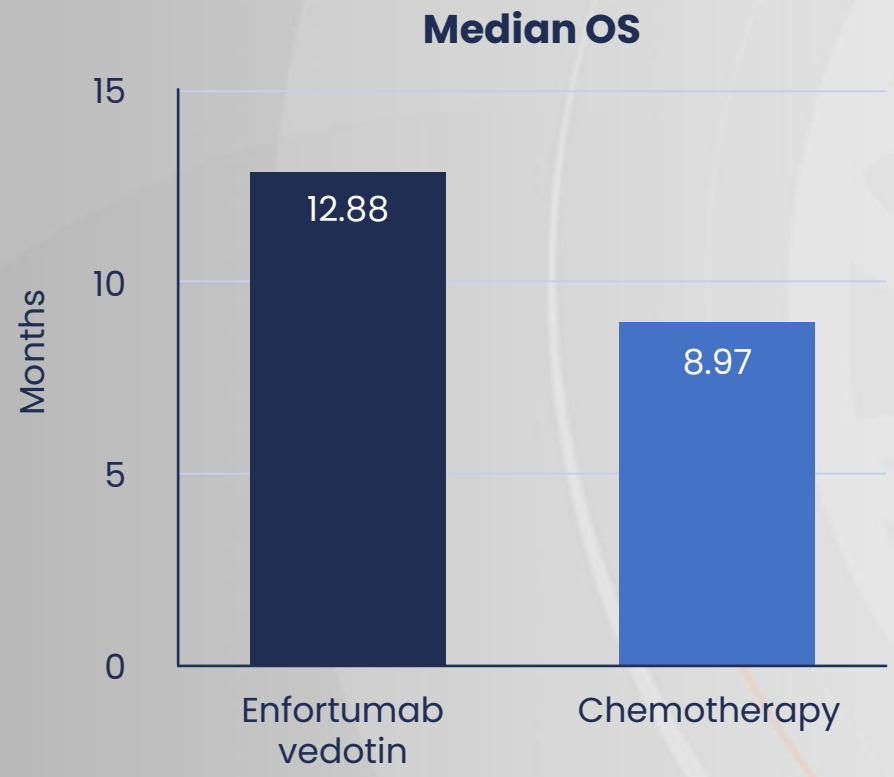


ECOG PS, Eastern Cooperative Oncology Group Performance Status; RECIST, Response Evaluation Criteria in Solid Tumors.

Powles T, et al. *N Engl J Med*. 2021;384:1125–35.

EV-301: Study met primary endpoint of OS

At interim analysis, EV improved OS by 30% versus chemotherapy



Median follow-up:
11.1 months

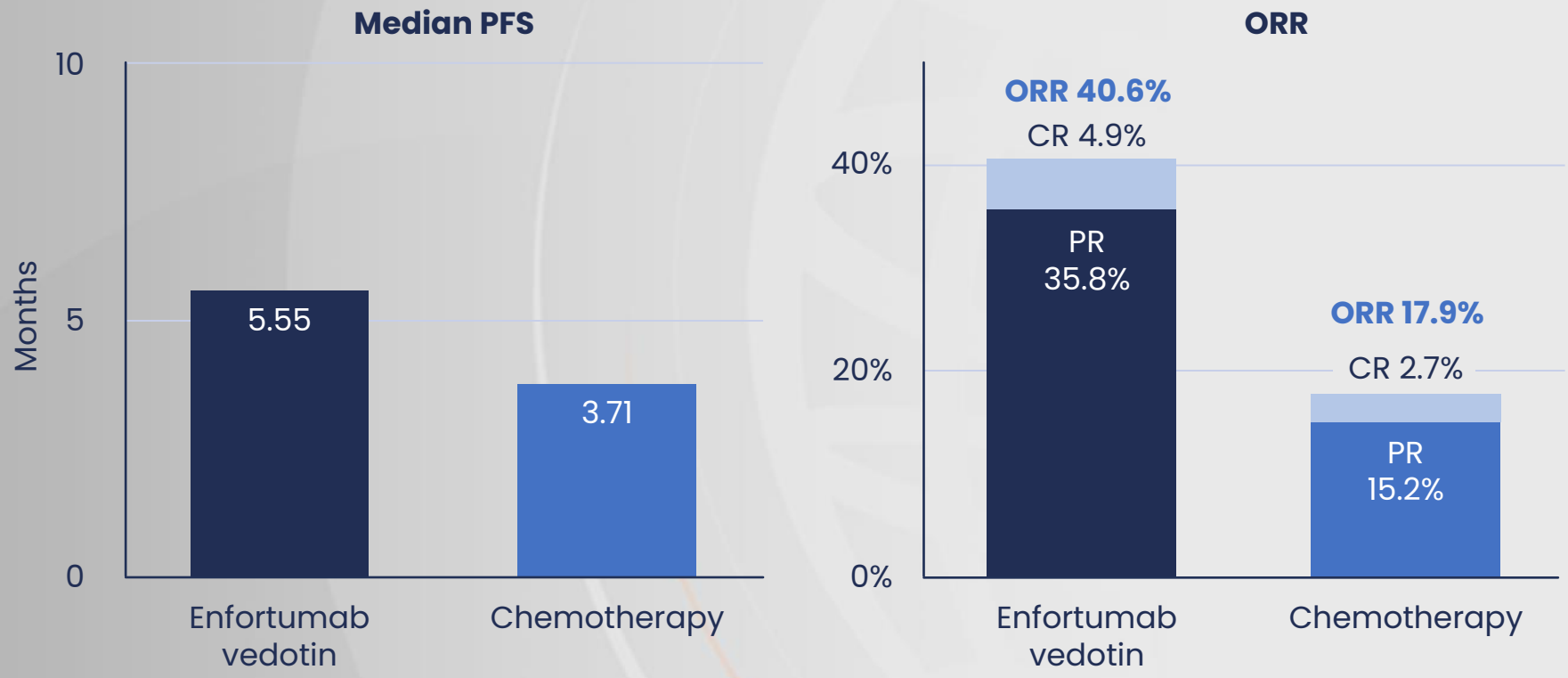
HR 0.70
(95% CI, 0.56–0.89) p=0.001

CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio.

Powles T, et al. *N Engl J Med*. 2021;384:1125–35.

EV-301: Phase III study of enfortumab vedotin

Secondary endpoints



Median follow-up: 11.1 months

Powles T, et al. *N Engl J Med*. 2021;384:1125–35.

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TROPHY-U-01: Phase II study of sacituzumab govitecan

Study design[1,2]

Patients with histologically confirmed, locally advanced or metastatic urothelial carcinoma

- Measurable disease by RECIST v1.1
- ECOG PS ≤1
- Adequate hepatic, renal and haematologic function, and no known Gilbert syndrome

Cohort 1 n=113

Progressed after prior platinum-based and/or ICI-based therapy

Cohort 2 n=22

Ineligible for platinum-based therapy and progressed after prior ICI-based therapy

Sacituzumab govitecan
10 mg/kg IV on days 1 and 8 of each 21-day cycle

Primary endpoint

- Confirmed ORR as determined by BICR

Secondary endpoints

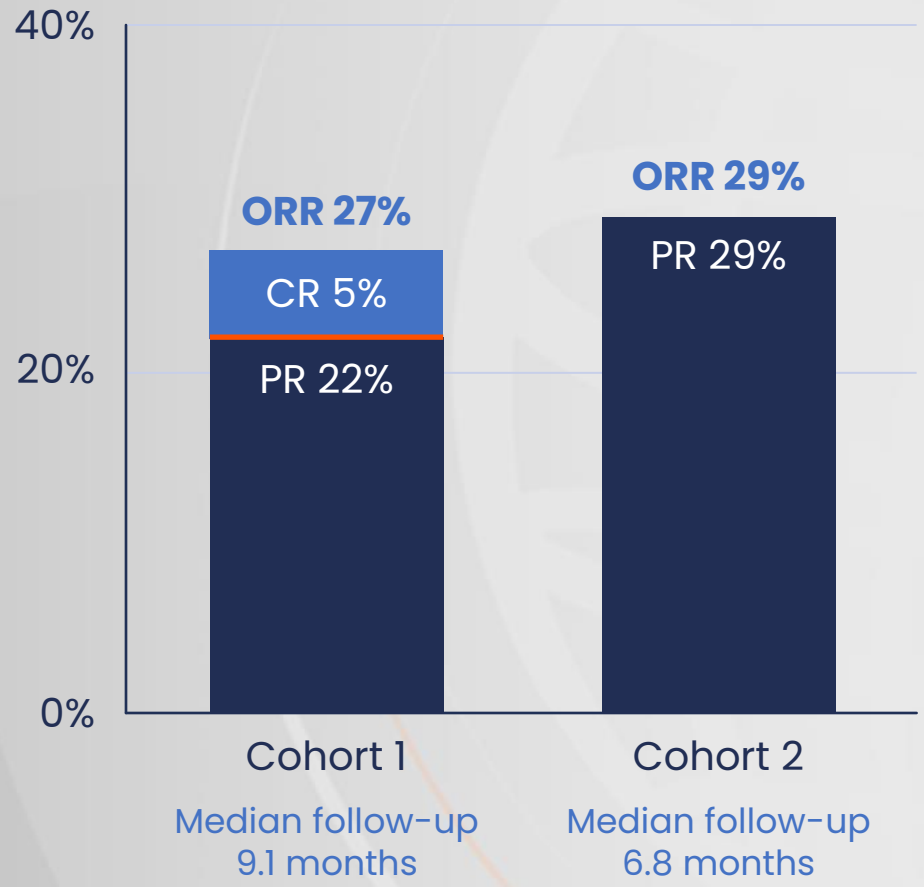
- DOR
- PFS
- OS
- Safety and tolerability

ICI, immune checkpoint inhibitor.

1. Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474–85; 2. Loriot Y, et al. Presented at: European Society for Medical Oncology Virtual Congress, 16–21 September 2021. Poster 700P.

TROPHY-U-01: Phase II study of sacituzumab govitecan

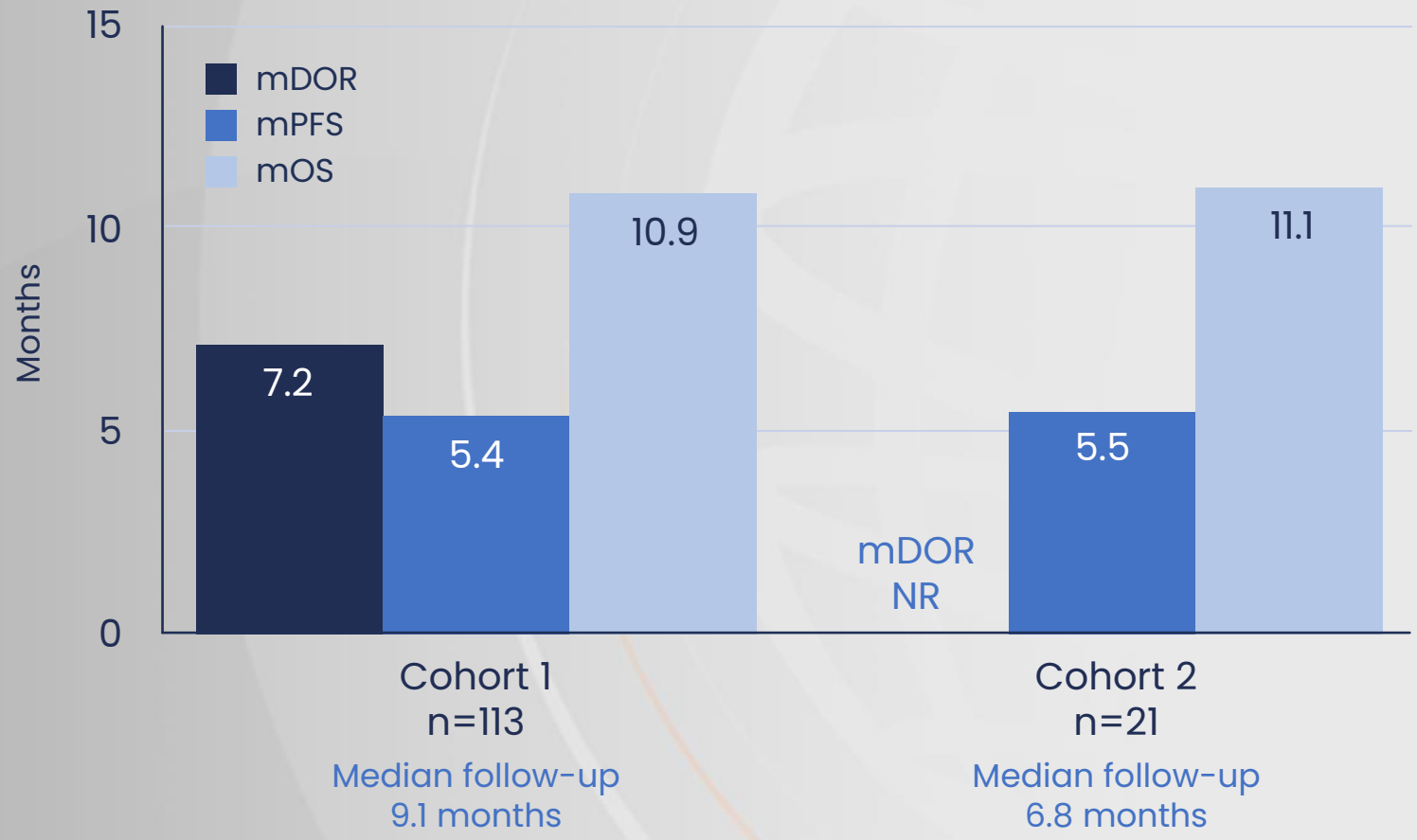
Primary endpoint: ORR[1,2]



1. Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474–85; 2. Petrylak DP, et al. Presented at: ASCO Meeting, Chicago, USA, 29 May–2 June 2020. Poster 5027.

TROPHY-U-01: Phase II study of sacituzumab govitecan

Secondary endpoints[1,2]



NR, not reached.

1. Tagawa ST, et al. *J Clin Oncol.* 2021;39:2474–85; 2. Petrylak DP, et al. Presented at: ASCO Meeting, Chicago, USA, 29 May–2 June 2020. Poster 5027.

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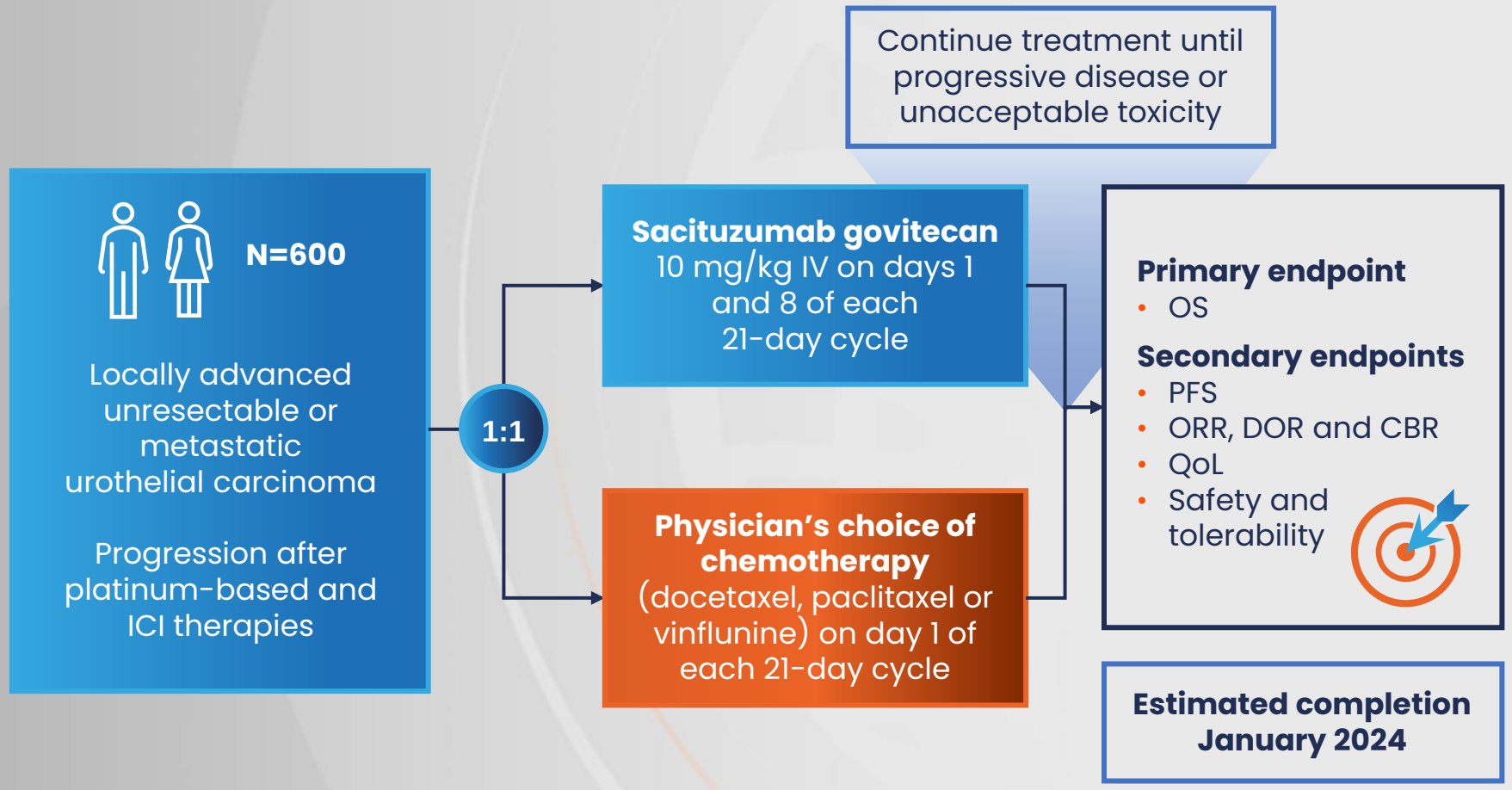
TROPiCS-04: Phase III study of sacituzumab govitecan

Study design[1,2]



CBR, clinical benefit rate; QoL, quality of life.

1. Grivas P, et al. Presented at: ASCO GU Meeting, San Francisco, USA, 17–19 February 2021. Poster TPS498;
2. ClinicalTrials.gov. Available at: https//clinicaltrials.gov/ct2/show/NCT04527991 (accessed 17 December 2021).

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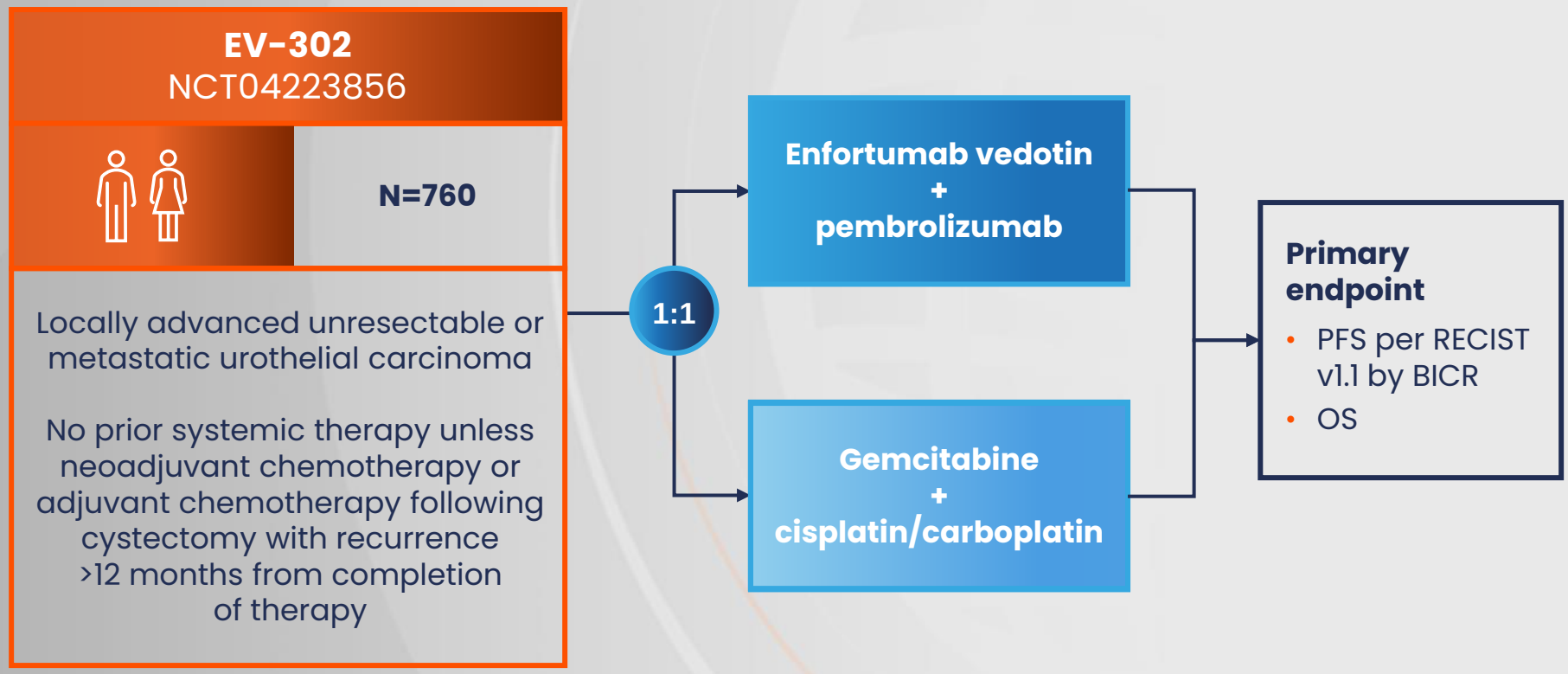
Future directions with enfortumab vedotin

Combination with checkpoint inhibitor[1,2]



1. van der Heijden M, et al. *Ann Oncol*. 2020;31(Suppl. 4)S605–6; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04223856 (accessed 17 December 2021).

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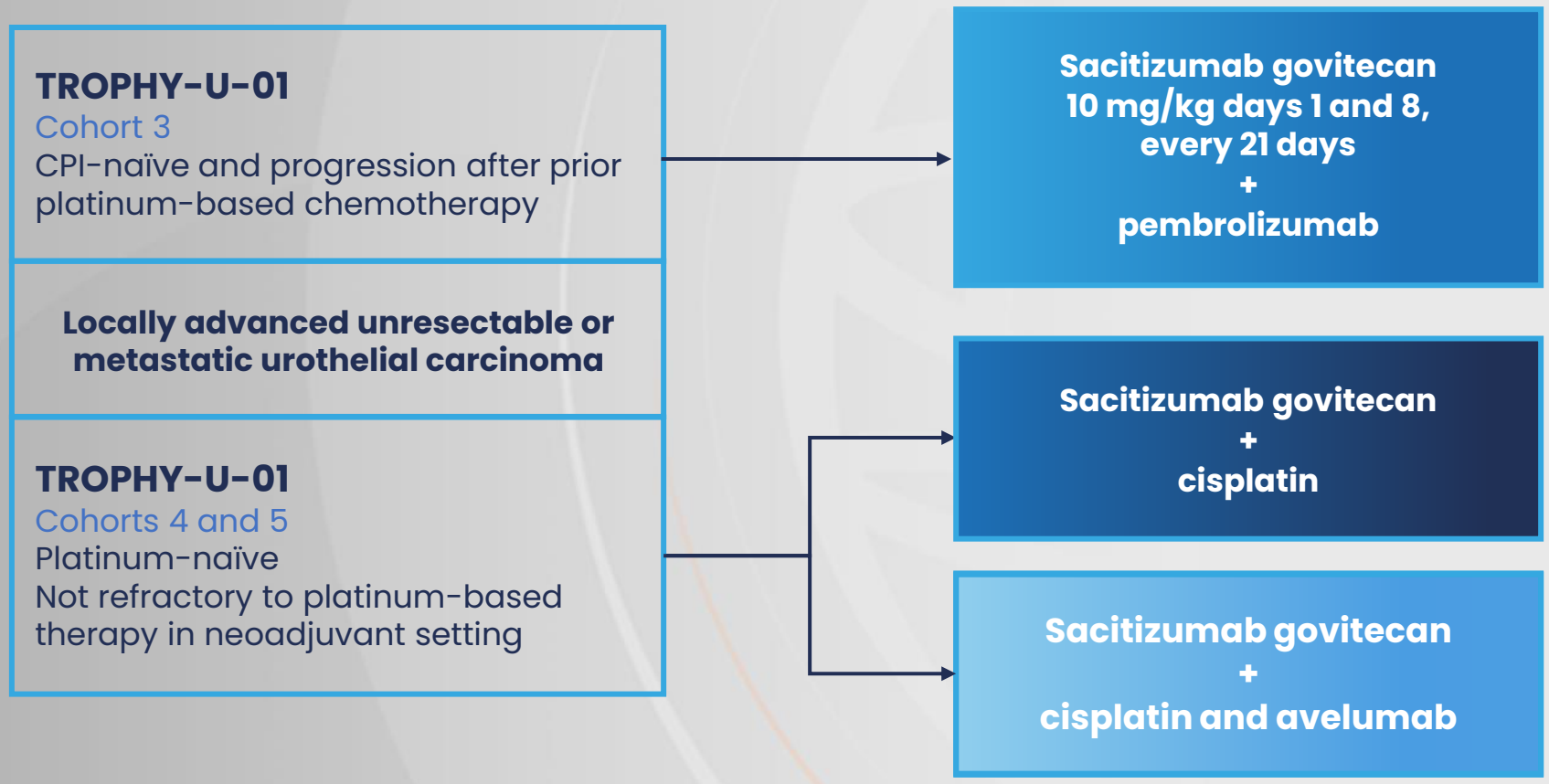
Future directions with sacituzumab govitecan

Combination with platinum-based therapies and/or checkpoint inhibitors[1,2]



CPI, checkpoint inhibitor.

1. Loriot Y, et al. Presented at: European Society for Medical Oncology Virtual Congress, 16–21 September 2021. Poster 700P;
2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03547973 (accessed 17 December 2021).

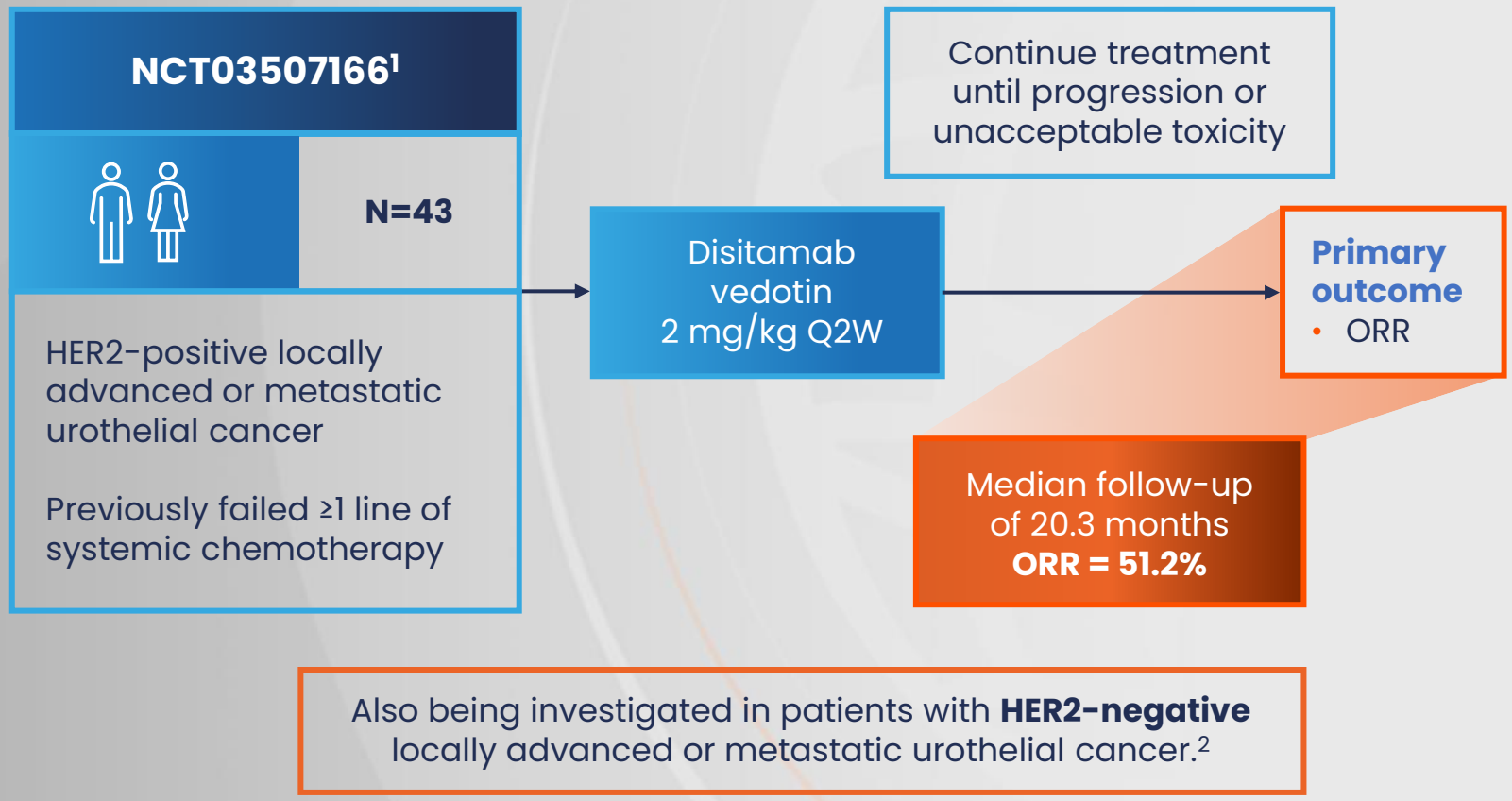
Future directions: HER2-targeting antibody–drug conjugates

HER2, human epidermal growth factor receptor 2. MMAE, monomethyl auristatin E.

Deeks ED. *Drugs*. 2021;81:1929–35.

Future directions: HER2-targeting antibody–drug conjugates

Disitamab vedotin



Q2W, every 2 weeks.

1. Sheng X, et al. *Clin Cancer Res*. 2021;27:43–51; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04073602 (accessed 17 December 2021).

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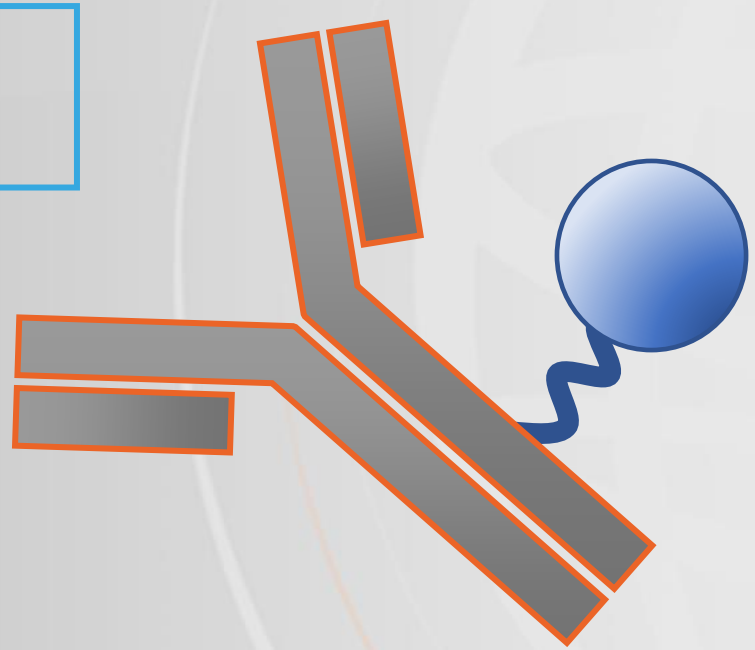
Future directions: HER2-targeting antibody–drug conjugates

Anti-HER2 antibody



Deruxtecan topoisomerase I inhibitor payload

Trastuzumab deruxtecan

Cabrera JM, et al. *Advances in Oncology*. 2021;1:273–82.

Future directions: HER2-targeting antibody–drug conjugates

Trastuzumab deruxtecan

DESTINY-PanTumor02
Phase II HER2-positive solid tumours (NCT04482309)

- Cohort 2: Bladder cancer

Phase I in **combination with nivolumab** in advanced breast and urothelial cancer (NCT03523572)

- Cohort 3: Advanced/metastatic urothelial carcinoma with HER2 expression of IHC 2+ or 3+ and progression on prior platinum-based therapy
- Cohort 4: Advanced/metastatic urothelial carcinoma with HER2 expression of IHC 1+ and progression on prior platinum-based therapy

IHC, immunohistochemistry.
Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 17 December 2021).

Additional ADCs targeting HER2 are under investigation

MRG002[1]

- MMAE payload
- Phase II HER2-positive unresectable locally advanced or metastatic urothelial cancer (NCT04839510)

Trastuzumab emtansine[2]

- DM-1 payload
- Phase II in HER2-overexpressing solid tumours (KAMELEON; NCT02999672)

Trastuzumab duocarmazine[3]

- Duocarmycin payload
- Phase I in solid tumours (NCT02277717)

ADC, antibody–drug conjugate.

1. Li J, et al. *J Clin Oncol*. 2020;38 (15 Suppl.); 2. Barok M, et al. *Breast Cancer Res*. 2014;16:209; 3. Banerji U, et al. *Lancet Oncol*. 2019;20:1124–35.

Additional ADCs targeting Trop-2 are under investigation

STI-3258[1]

- SN-38 payload
- Phase I in relapsed or refractory solid tumours (NCT05060276)

ESG-4012[2]

- SN-38 payload
- Phase I/II in solid tumours (NCT04892342)

SKB264[2]

- Belotecan-derived payload
- Phase I/II in advanced unresectable/metastatic solid tumours, refractory to standard therapies (NCT04152499)

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT05060276 (accessed 17 December 2021); 2. Sorrento Therapeutics. News release 2021. Available at: https://investors.sorrentotherapeutics.com/news-releases/news-release-details/sorrento-announces-its-subsidiary-levena-and-its-partner-escugen (accessed 17 December 2021); 3. Liu Y, et al. *J Clin Oncol*. 2020;38 (15 Suppl.).

An ADC targeting FGFR3 is under investigation

LY3076226

- **Ravtansine** (DM4) is a maytansinoid
- Phase I in advanced or metastatic cancer including urothelial cancer (NCT02529553)

FGFR3, fibroblast growth factor receptor 3.
Kollmannsberger C, et al. *Invest New Drugs*. 2021;39:1613–23.

Conclusions

Enfortumab vedotin significantly prolonged survival vs chemotherapy in patients with locally advanced unresectable or metastatic urothelial carcinoma[1]

Sacituzumab govitecan showed notable efficacy in patients with metastatic urothelial carcinoma who had progressed on prior platinum-based chemotherapy and ICI[2]

Several ADCs approved for other tumour types are being studied in patients with urothelial carcinoma with many emerging ADCs in early development[3]

1. Powles T, et al. *N Engl J Med*. 2021;384:1125–35; 2. Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474–85; 3. Cabrera JM, et al. *Advances in Oncology*. 2021;1:273–82.

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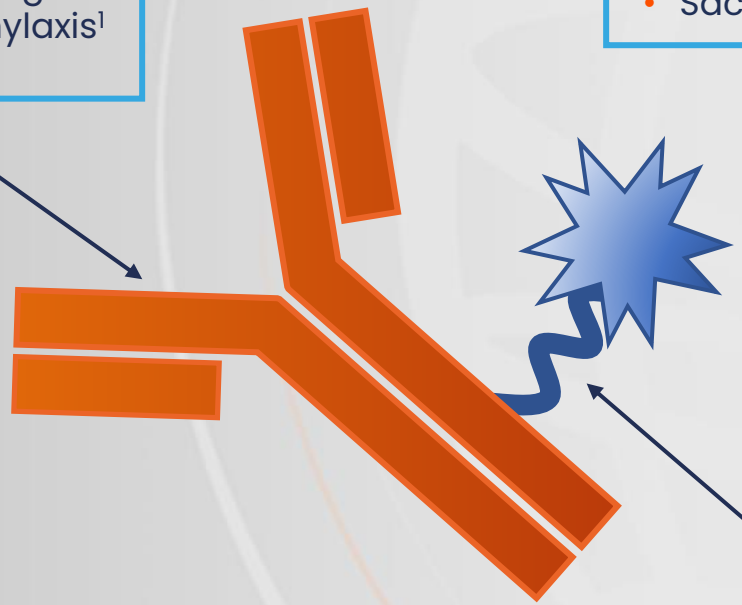
Optimizing the safety of antibody–drug conjugates in urothelial carcinoma: What are the possible adverse events and how do we manage them?

Safety considerations of antibody–drug conjugates

Immune reactions to antibody may lead to IRR, from mild allergic reactions to anaphylaxis[1]

Drug-to-antibody ratio[2,3]

- Enfortumab vedotin, 3.8:1
- Sacituzumab govitecan, 7.6:1



Cleavable linkers have the potential to prematurely release the cytotoxic payload in the blood stream[1]

IRR, infusion-related reactions.

1. Wolska-Washer A, Robak T. *Drug Saf*. 2019;42:295–314; 2. Jain RK, et al. *Cancer Manag Res*. 2020;12:8379–86; 3. Barroso-Sousa R, Tolaney SM. *BioDrugs*. 2021;35:159–74.

TEAEs in EV-301 with enfortumab vedotin

	Patients (%)
Any grade TEAE	93.9
TEAE leading to:	
Dose reduction	32.4
Dose interruption	51.0
Treatment withdrawal	13.5

TEAE, treatment-emergent adverse event.
Powles T, et al. *N Engl J Med*. 2021;384:1125–35.

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TEAEs in EV-301 with enfortumab vedotin

	Any grade* (%)	Grade ≥3* (%)
Alopecia	45.3	0
Peripheral sensory neuropathy	33.8	3.0
Pruritus	32.1	1.4
Fatigue	31.1	6.4
Decreased appetite	30.7	3.0
Diarrhoea	24.3	3.4
Dysgeusia	24.3	0
Nausea	22.6	1.0
Maculopapular rash	16.2	7.4
Decreased neutrophils	10.1	6.1

*Most common TEAEs of any grade observed in ≥20% of patients or grade ≥3 observed in ≥5% of patients.

Powles T, et al. *N Engl J Med*. 2021;384:1125–35.

EV-301: TEAEs of special interest with enfortumab vedotin

	Any grade (%)	Grade ≥3 (%)
Skin reactions	47.0	14.5
Peripheral neuropathy	46.3	5.1
Ocular disorders	18.6	0.7
IRRs	8.8	1.4
Hyperglycaemia	6.4	3.7

Powles T, et al. *N Engl J Med*. 2021;384:1125–35.

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Skin reactions with enfortumab vedotin

Monitoring for skin reactions

Closely monitor patients for skin reactions

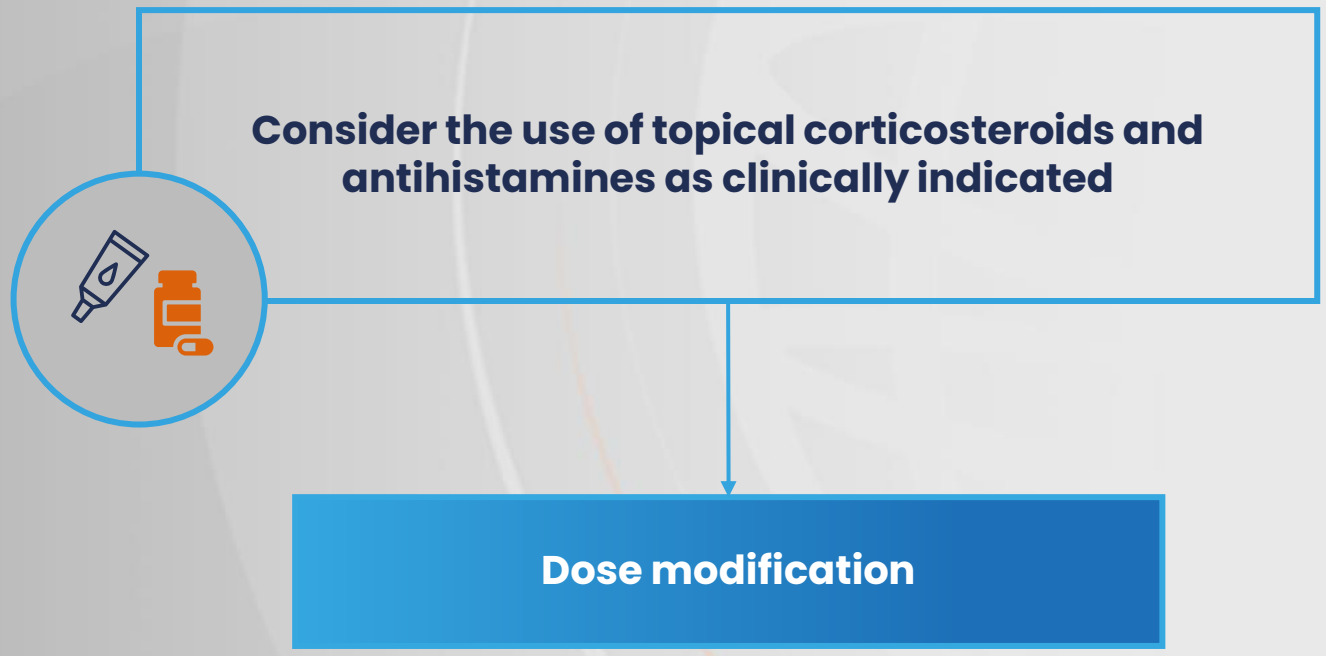
SJS or TEN predominantly occurs during the first cycle of treatment, but may occur later

FDA, Food and Drug Administration; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Skin reactions with enfortumab vedotin

Managing skin reactions



FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Skin reactions with enfortumab vedotin

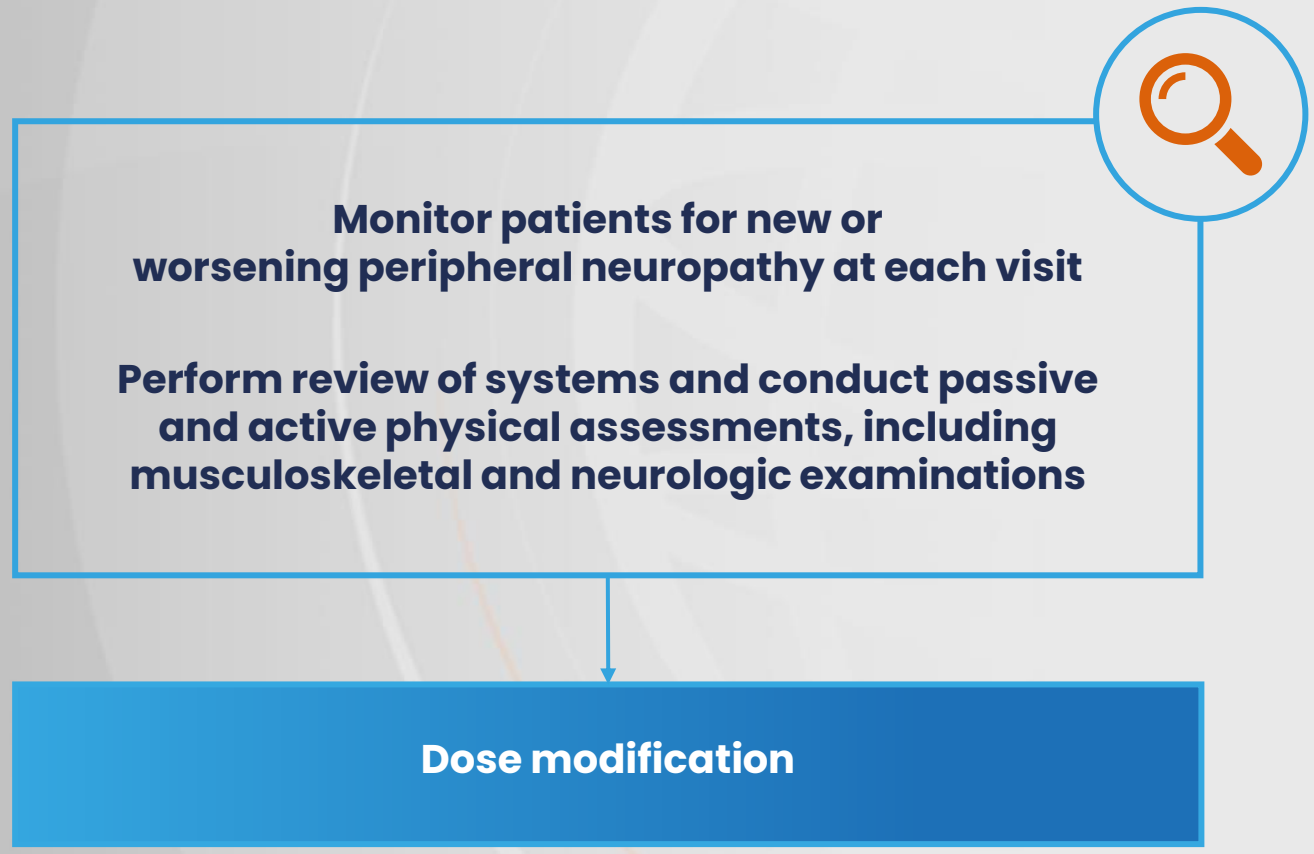
Dose modifications for skin reactions

Severity	Dose modification
Grade 3	Withhold until grade ≤1 Resume at same dose or consider dose reduction by one level
Suspected SJS/TEN	Withhold and consult a specialist to confirm diagnosis
Confirmed SJS/TEN Grade 4 or recurrent grade 3 skin reactions	Permanently discontinue

FDA. Enfortumab vedotin, prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021)

Peripheral neuropathy with enfortumab vedotin

Monitoring for peripheral neuropathy[1,2]



1. FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021);
2. Pace A, et al. *Clin J Oncol Nurs*. 2021;25:E1–9.

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Peripheral neuropathy with enfortumab vedotin

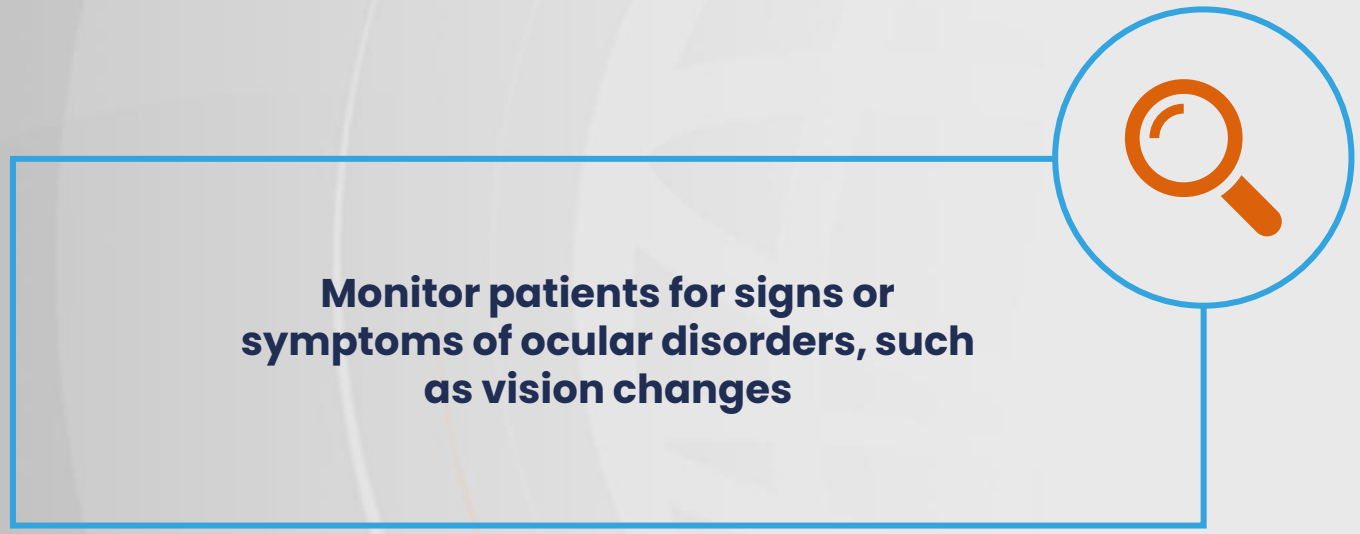
Dose modifications for peripheral neuropathy

Severity	Dose modification
Grade 2	**First occurrence:** Withhold until grade ≤1 Resume at the same dose level **Recurrence:** Withhold until grade ≤1 Resume treatment reduced by one dose level
Grade ≥3	Permanently discontinue

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Ocular disorders with enfortumab vedotin

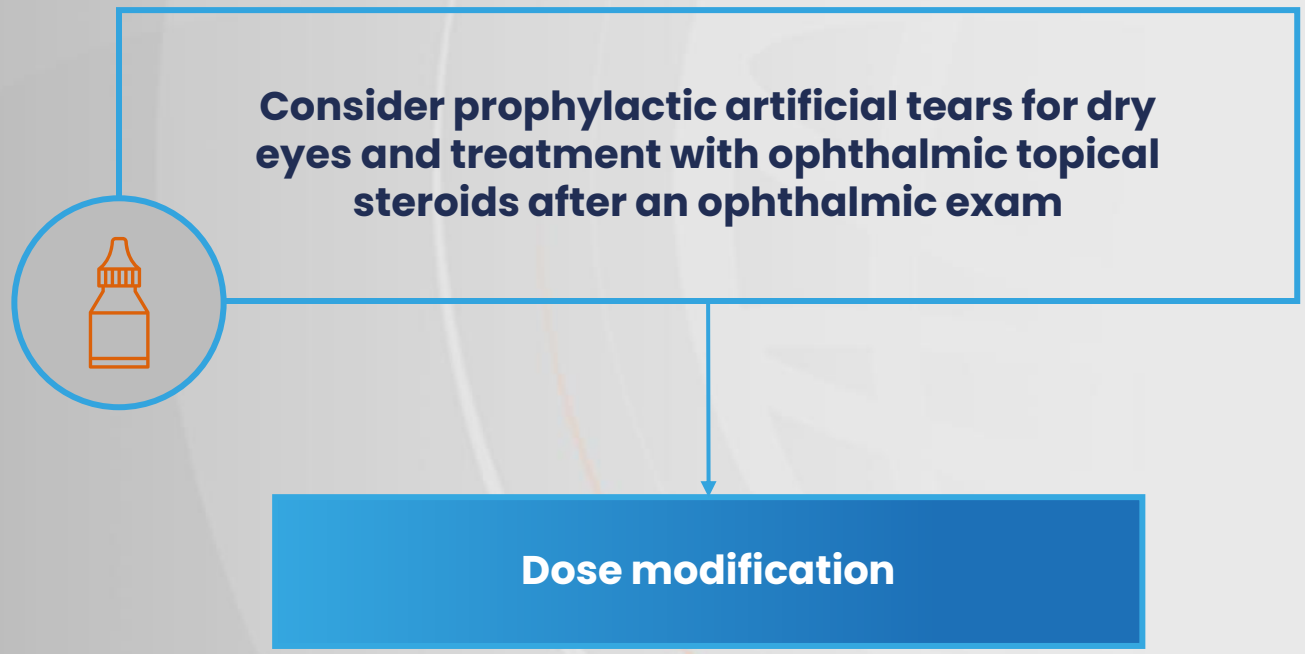
Monitoring for ocular disorders



FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Ocular disorders with enfortumab vedotin

Mitigation and management of ocular disorders



FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Ocular disorders with enfortumab vedotin

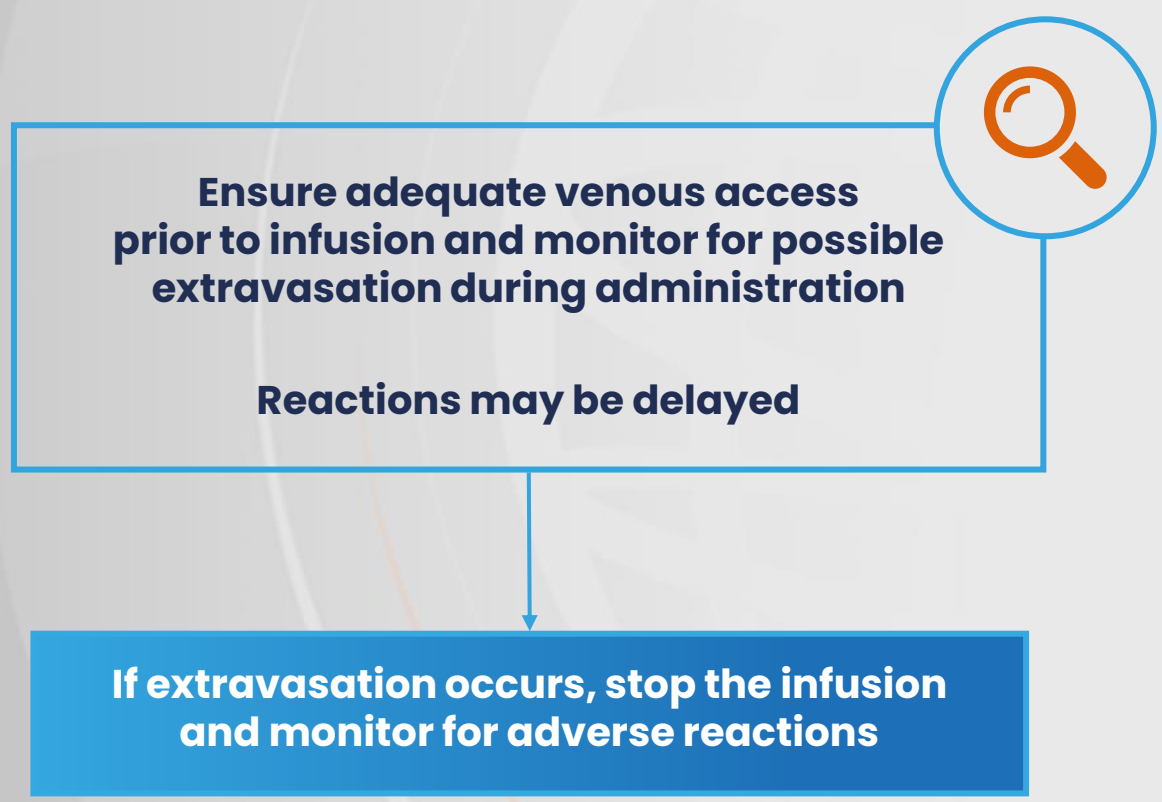
Dose modifications for ocular disorders

Severity	Dose modification
Grade 3	Withhold until grade ≤1, Resume treatment at the same dose level or consider dose reduction by one dose level
Grade 4	Permanently discontinue

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Infusion site extravasation with enfortumab vedotin

Monitoring for and managing infusion site extravasation



FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

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Hyperglycaemia with enfortumab vedotin

Monitoring for hyperglycaemia

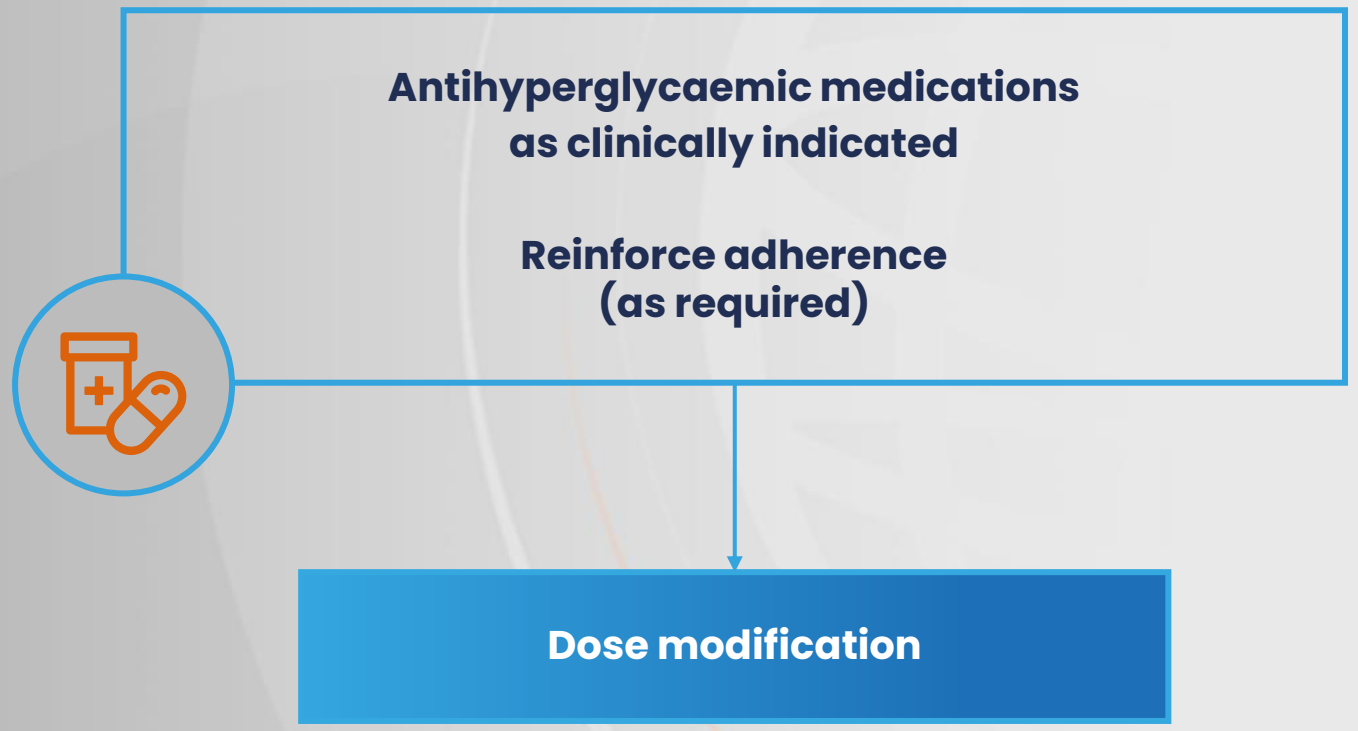
Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycaemia

Diabetic ketoacidosis may occur in patients with and without pre-existing diabetes mellitus, which may be fatal

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Hyperglycaemia with enfortumab vedotin

Managing hyperglycaemia[1,2]



1. Pace A, et al. *Clin J Oncol* Nurs. 2021;25:E1–9;
2. FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

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Hyperglycaemia with enfortumab vedotin

Dose modifications for hyperglycaemia

Severity	Dose modification
Blood glucose >250 mg/dL	Withhold until elevated blood glucose has improved to ≤250 mg/dL Resume treatment at the same dose level

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Pneumonitis with enfortumab vedotin

Monitoring for pneumonitis

Monitor patients for signs and symptoms indicative of pneumonitis:

- **Hypoxia**
- **Cough**
- **Dyspnoea**
- **Interstitial infiltrates on radiologic exams**

Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations

Dose modification

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Pneumonitis with enfortumab vedotin

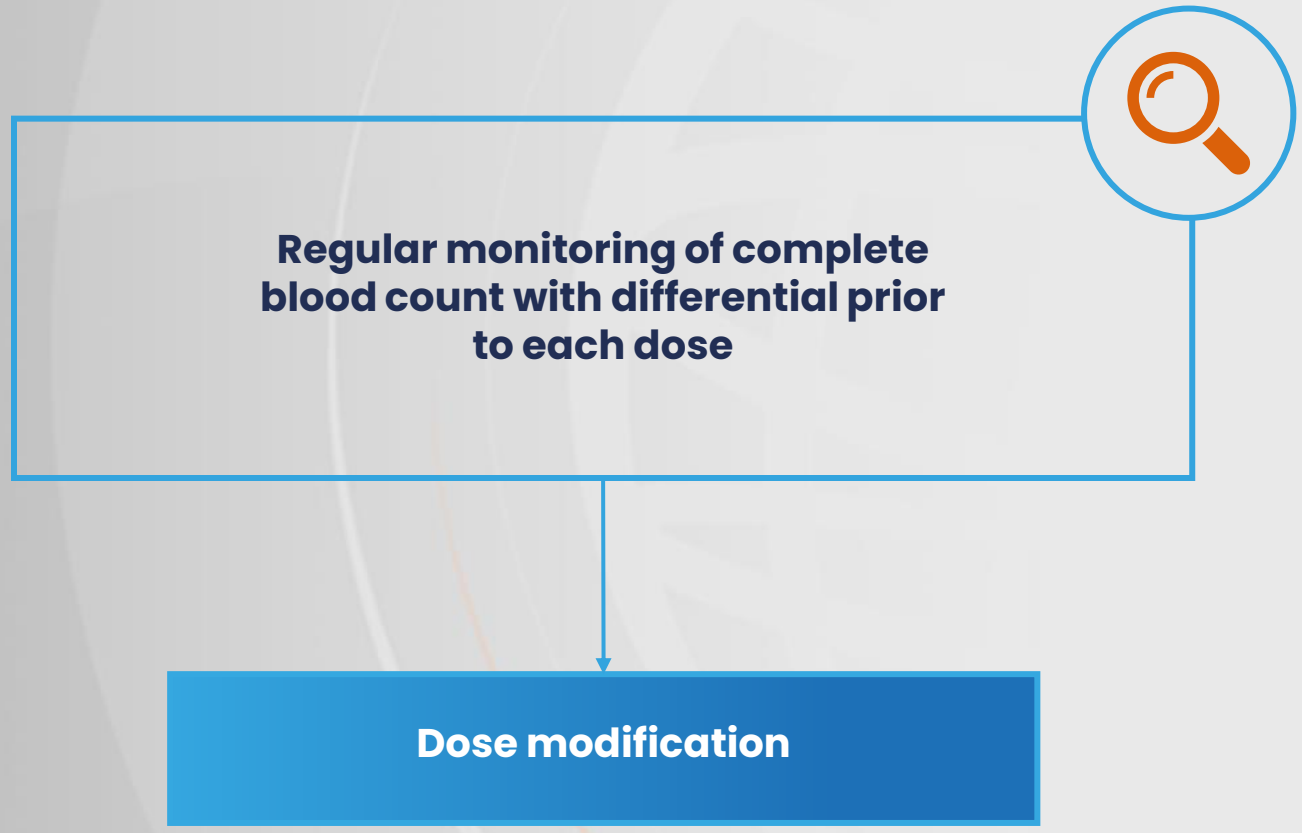
Dose modifications for pneumonitis

Severity	Dose modification
Persistent or recurrent grade 2	Withhold until grade ≤1 Resume treatment at the same dose level or consider dose reduction by one dose level
Grade ≥3	Permanently discontinue

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

Haematologic toxicity with enfortumab vedotin

Monitoring for haematologic toxicity



Pace A, et al. *Clin J Oncol Nurs*. 2021;25:E1–9.

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Haematologic toxicity with enfortumab vedotin

Dose modifications for haematologic toxicity

Severity	Dose modification
Grade 3 or grade 2 thrombocytopenia	Withhold until grade ≤1 Resume treatment at the same dose level or consider dose reduction by one dose level
Grade 4	Withhold until grade ≤1 Reduce dose by one dose level or discontinue treatment

FDA. Enfortumab vedotin, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf (accessed 17 December 2021).

TEAEs in TROPHY-U-01 with sacituzumab govitecan

	Patients (%)
Any grade TEAE	94.7
TEAE leading to:	
Dose reduction	39
Dose interruption	45
Treatment withdrawal	6

Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474–85.

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TEAEs in TROPHY-U-01 with sacituzumab govitecan

	Any grade* (%)	Grade ≥3* (%)
Diarrhoea	65	10
Nausea	60	4
Fatigue	52	4
Alopecia	47	0
Neutropenia	46	34
Decreased appetite	36	3
Anaemia	33	14
Vomiting	30	1
Leukopenia	25	17
Lymphopenia	11	7
Febrile neutropenia	10	10
UTI	8	6

*Most common TEAEs of any grade observed in ≥20% of patients or grade ≥3 observed in ≥5% of patients.
UTI, urinary tract infection.
Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474–85.

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Neutropenia with sacituzumab govitecan

Monitoring for neutropenia

Monitor neutrophil count and temperature for signs of fever

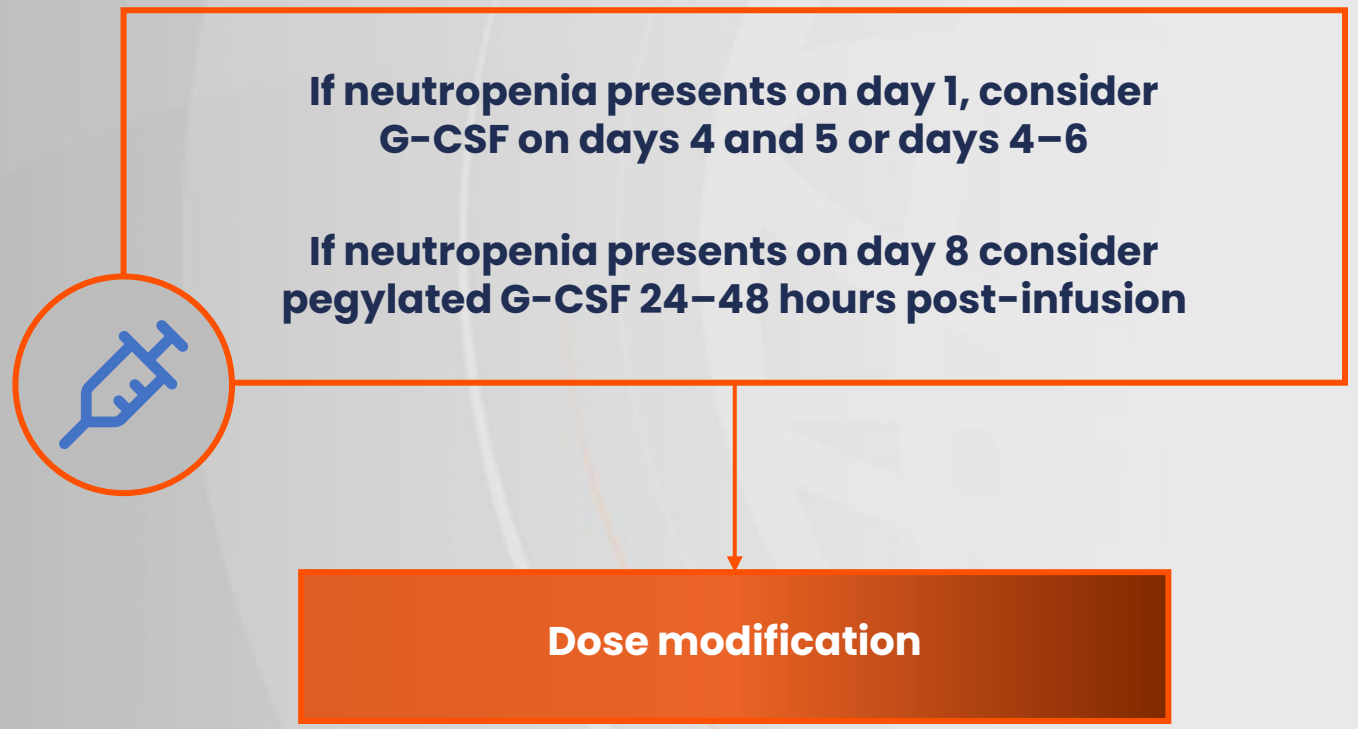
Patients who are known to have reduced UGT1A1 activity should be monitored closely for severe neutropenia

UGT1A1, uridine diphosphate-glucuronosyl transferase 1A1.

FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021).

Neutropenia with sacituzumab govitecan

Managing neutropenia[1,2]



G-CSF, granulocyte-stimulating factor.

1. FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021);
2. Spring LM, et al. *Oncologist*. 2021;26:827–34.

Neutropenia with sacituzumab govitecan

Dose modifications for neutropenia

Severity	Dose modification
Grade 4 neutropenia ≥7 days **OR** Grade 3 febrile neutropenia **OR** At time of scheduled treatment, grade 3–4 neutropenia which delays dose by 2 or 3 weeks for recovery to grade ≤1	**First event** 25% dose reduction **Second event** 50% dose reduction **Third event** Discontinue treatment
At time of scheduled treatment, grade 3–4 neutropenia which delays dose beyond 3 weeks for recovery to grade ≤1	Discontinue treatment

FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021).

Hypersensitivity and IRRs with sacituzumab govitecan

Monitoring for hypersensitivity and IRRs[1,2]

Hypersensitivity reactions including severe anaphylactic reactions have been observed within 24 hours of dosing

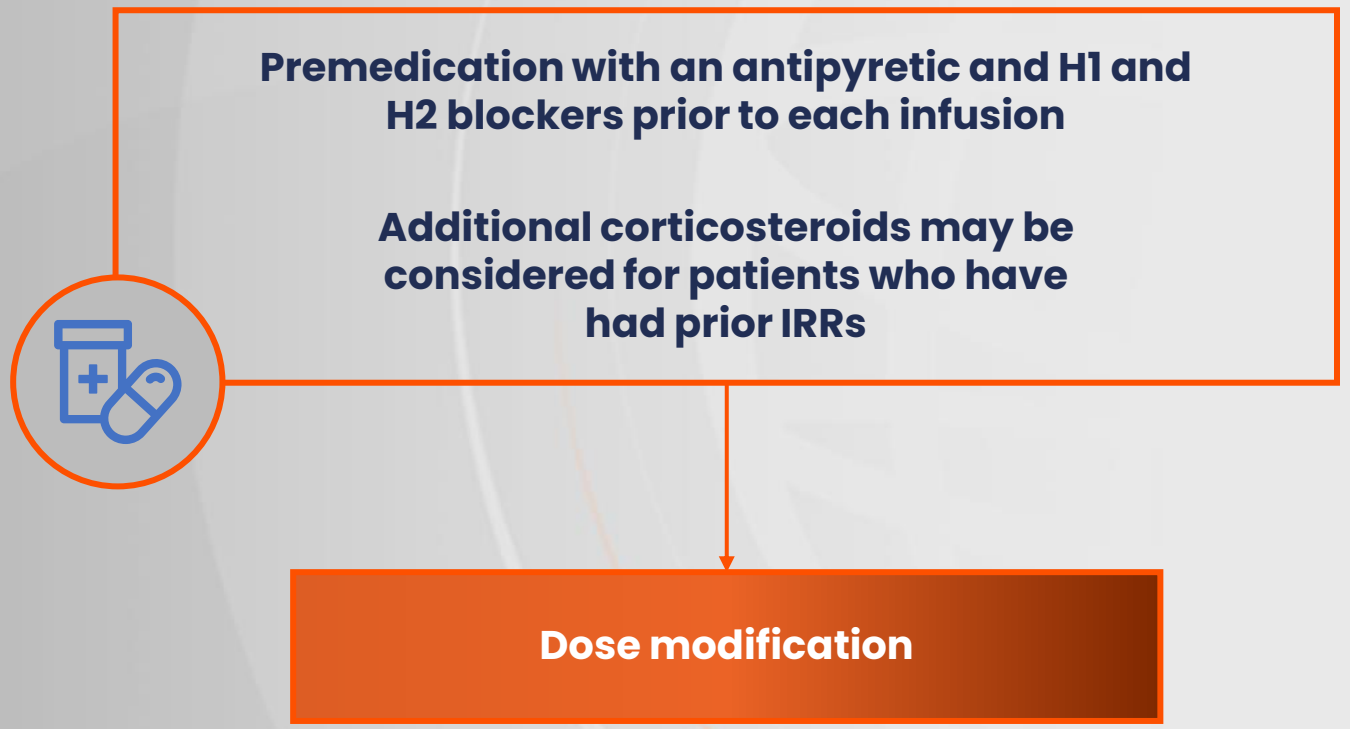
Monitor patients for at least 30 minutes after infusion for signs of:

- **Cardiac arrest**
- **Hypotension**
- **Wheezing**
- **Angioedema**
- **Swelling**
- **Pneumonitis**
- **Skin reactions**

1. FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021);
2. Spring LM, et al. *Oncologist.* 2021;26:827–34.

Hypersensitivity and IRRs with sacituzumab govitecan

Mitigation and management of hypersensitivity and IRRs[1,2]



1. FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021);
2. Spring LM, et al. *Oncologist*. 2021;26:827–34.

Diarrhoea and cholinergic syndrome with sacituzumab govitecan

Monitoring for diarrhoea and cholinergic syndrome[1,2]

Monitor for signs of acute diarrhoea or early cholinergic syndrome during or shortly after infusion:

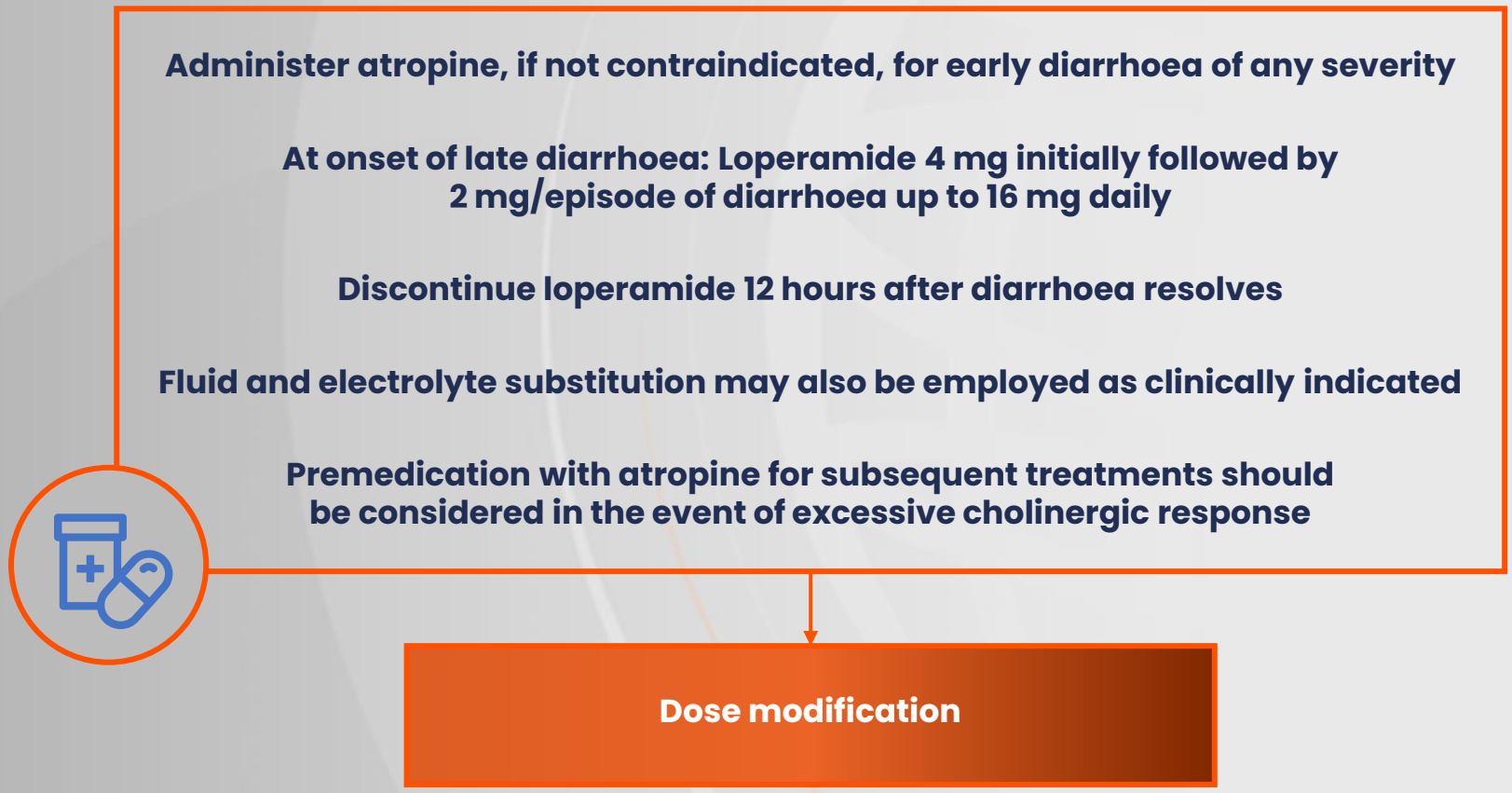
- **Abdominal cramping**
- **Diarrhoea**
- **Sweating**
- **Excessive salivation**

Initiate treatment if no infectious cause

1. FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021);
2. Spring LM, et al. *Oncologist*. 2021;26:827–34.

Diarrhoea and cholinergic syndrome with sacituzumab govitecan

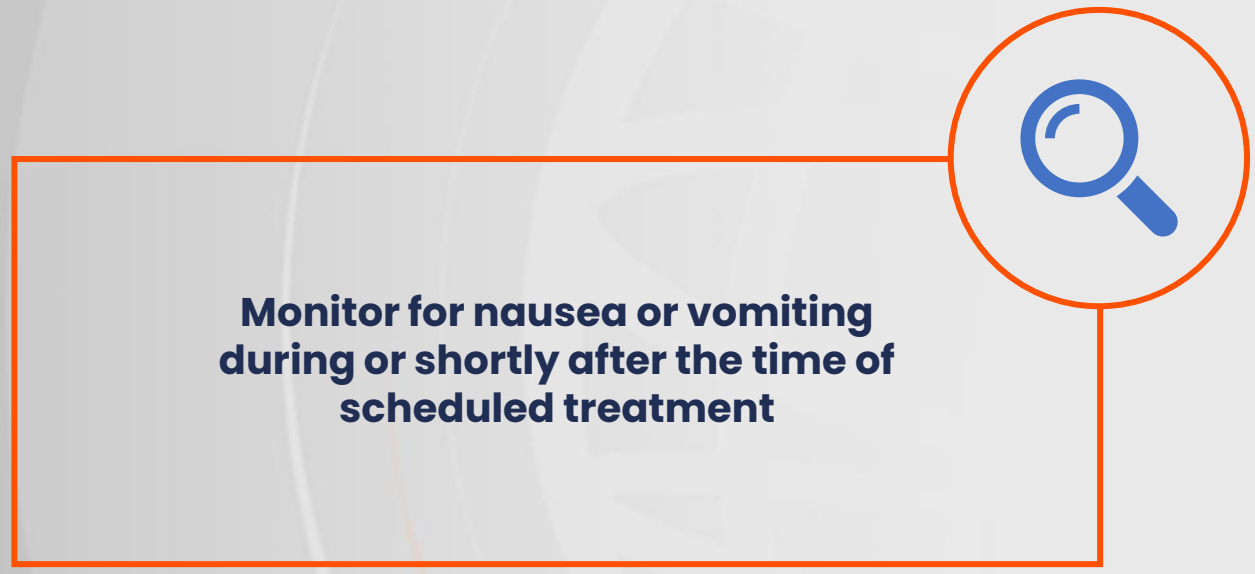
Managing diarrhoea and cholinergic syndrome[1,2]



1. FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021);
2. Spring LM, et al. *Oncologist*. 2021;26:827–34.

Nausea and vomiting with sacituzumab govitecan

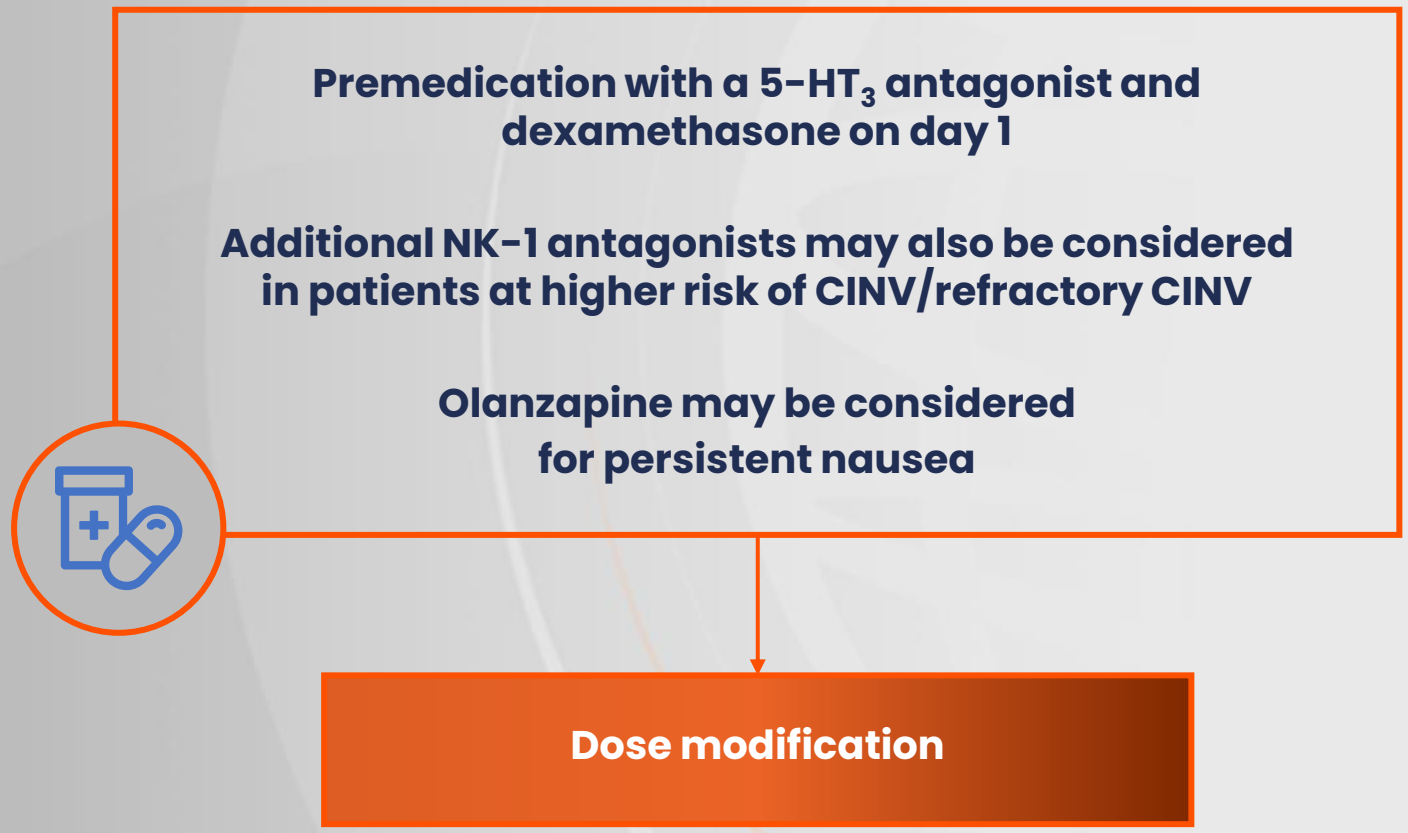
Monitoring for nausea and vomiting



FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021).

Nausea and vomiting with sacituzumab govitecan

Managing nausea and vomiting[1,2]



CINV, chemotherapy-induced nausea and vomiting; NK-1, neurokinin 1.

1. FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021);
2. Spring LM, et al. *Oncologist*. 2021;26:827–34.

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Non-haematologic toxicity with sacituzumab govitecan

Dose modification strategy for non-haematologic toxicity

Grade 4

OR

Any uncontrolled grade ≥3 GI event

OR

Other grade ≥3 event persisting >48 hours
despite optimal medical management

OR

At time of scheduled treatment, grade ≥3 event
which delays dose by 2–3 weeks for recovery to grade ≤1

First event

25% dose reduction

Second event

50% dose reduction

Third event

Discontinue treatment

GI, gastrointestinal.

FDA. Sacituzumab govitecan, prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf (accessed 17 December 2021).

Safety of ADCs in combination therapy

EV-103: enfortumab vedotin in combination with pembrolizumab, N=45

	Any grade* (%)	Grade ≥3* (%)
Peripheral neuropathy	55.6	4.4
Fatigue	51.6	11.1
Alopecia	48.9	0
Diarrhoea	46.7	4.4
Decreased appetite	40.0	2.2
Maculopapular rash	35.6	11.1
Dysgeusia	33.3	0
Pruritus	33.3	2.2
Nausea	28.9	0
Decreased weight	24.4	2.2
Dry skin	22.2	0
Increased ALT/AST	20.0	0
Anaemia	20.0	8.9
One treatment-related death reported: multiple organ dysfunction syndrome		

*Any grade TEAE occurring in ≥20% of patients.
ADC, antibody–drug conjugate; ALT, alanine aminotransferase; AST, aspartate transaminase.
Friedlander TW, et al. Presented at: American Society of Clinical Oncology Virtual Congress, 4–8 June 2021. Poster 4528.

Conclusions

There are common TEAEs associated with ADCs[1]

Healthcare professionals must be aware of which TEAEs may occur to monitor for and manage them throughout the treatment course[1]

ADCs in combination therapy appear to be tolerable[2]

1. Wolska-Washer A, Robak T. *Drug Saf*. 2019;42:295–314; 2. Friedlander TW, et al. Presented at: American Society of Clinical Oncology Virtual Congress, 4–8 June 2021. Poster 4528.