Locally Advanced and Metastatic Urothelial Cancer
First-Line Therapy: Immunotherapy

- Platinum-based chemotherapy has been standard for decades
  - Gemcitabine + cisplatin (cisplatin eligible)
  - Gemcitabine + carboplatin (cisplatin ineligible)
  - Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC)
- Better understanding of underlying mechanisms has led to advances with effective immunotherapies
  - Improved outcomes when added to chemotherapy backbone or in previously treated patients
  - Immunotherapies include immune checkpoint inhibitors (ICIs) and antibody–drug conjugates (ADCs)

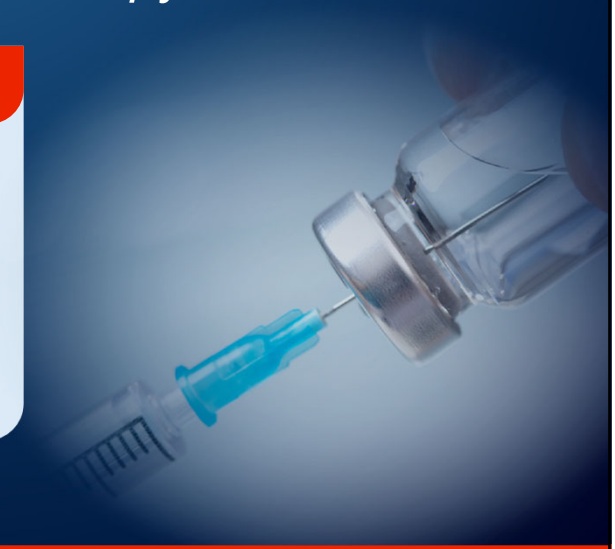
Moussa MJ et al. *Biomedicines*. 2024;12:519. National Comprehensive Cancer Network Guidelines Bladder Cancer v6.2024.

1

Bladder Cancer
Chemotherapy + Immunotherapy

JAVELIN 100 Study

- 4 to 6 cycles of first-line platinum chemotherapy (gemcitabine + cisplatin or carboplatin) followed by avelumab vs BSC
- Median overall survival
  - Avelumab: 21.4 months
  - BSC: 14.3 months
- Avelumab maintenance following platinum-based chemotherapy became standard treatment



BSC, best supportive care
Powles T et al. *N Engl J Med*. 2020;383:1218.

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Bladder Cancer
Chemotherapy + Immunotherapy Combinations

KEYNOTE-361[1]

- Treatment arms
  - Pembrolizumab + platinum/gemcitabine (n=351)
  - Pembrolizumab monotherapy (n=307)
  - Platinum/gemcitabine (n=352)
- Coprimary end points
  - PFS and OS (combination vs chemotherapy)
  - OS (monotherapy vs chemotherapy)

CHECKMATE901[2]

- Treatment arms
  - Nivolumab + gemcitabine/cisplatin (n=304)
  - Gemcitabine/cisplatin (n=304)
- Primary end points: PFS and OS

IMvigor130[3]

- Treatment arms
  - Atezolizumab + platinum/gemcitabine (n=451)
  - Atezolizumab monotherapy (n=362)
  - Platinum/gemcitabine (n=400)
- Coprimary end points
  - PFS and OS (combination vs chemotherapy)
  - OS (monotherapy vs chemotherapy)

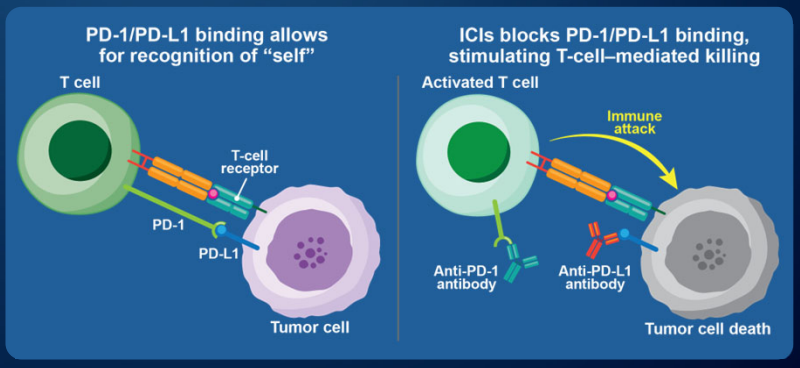
PFS, progression free survival; OS, overall survival

1. Powles T et al. *Lancet Oncol.* 2021;22:931. **2.** Van der Heijden MS et al. *N Engl J Med.* 2023;389:1778. **3.** Galsky MD et al. *Lancet.* 2020;395:1547.

3

Immune Checkpoint Inhibitors

- ICIs stimulate T-cell–mediated killing of tumor cells by blocking recognition of tumor cells as "self"
- Targets include
  - Cytotoxic T lymphocyte–associated antigen 4 (CTLA4)
  - Programmed cell death 1 (PD-1)
  - Programmed cell death ligand 1 (PD-L1)



Centanni M et al. *Clin Pharmacokinet.* 2019;58:835.

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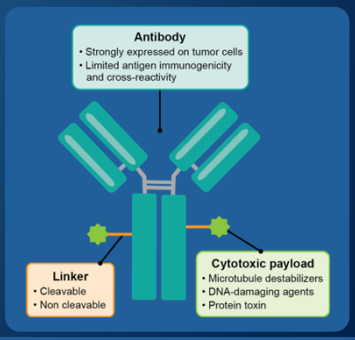
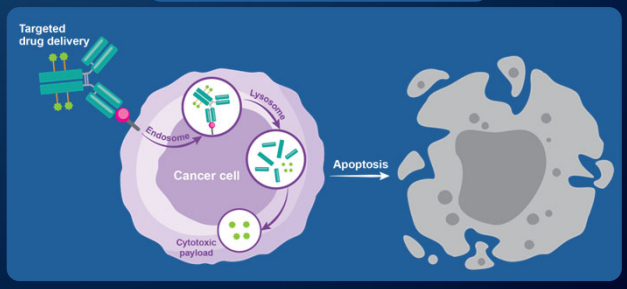
Antibody–Drug Conjugates

- ADCs combine a monoclonal antibody (directed against a tumor-associated antigen) with a cytotoxic drug (payload) connected by a linker
- All three components collectively determine the characteristics/potency of the ADC
- Tumor cell targets include
  - Human epidermal growth factor receptor 2 (HER-2)
  - Trophoblastic cell surface antigen 2 (TROP-2)
  - Nectin-4
- Payloads include
  - Microtubule inhibitor (MMAE)
  - Topoisomerase inhibitors (SN-38, DXd)





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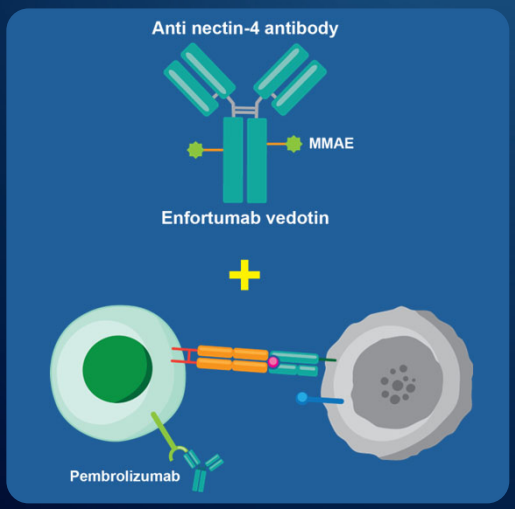
Enfortumab Vedotin (EV) + Pembrolizumab



EV-302/Keynote-A39 Study

- Previously untreated patients randomized 1:1 to EV + pembrolizumab or chemotherapy (gemcitabine + cisplatin or carboplatin)
- Dual primary end points
  - Progression-free survival
  - Overall survival

Powles T et al. *N Engl J Med*. 2024;390:875.

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Guideline Update for Locally Advanced and Metastatic Urothelial Cancer

- EV-302/KEYNOTE-A39 showed superiority of enfortumab vedotin + pembrolizumab (EVP) over chemotherapy
  - PFS = 12.5 months vs 6.3 months
  - OS = 31.5 months vs 16.1 months
  - ORR = 67.7% vs 44.4%
  - CR = 29.1% vs 12.5%

EVP is now preferred first-line therapy regardless of cisplatin eligibility.

PFS, progression free survival; OS, overall survival; ORR, overall response ratio; CR, complete response
Powles T et al. *N Engl J Med.* 2024;390:875. National Comprehensive Cancer Network Guidelines Bladder Cancer v6.2024.

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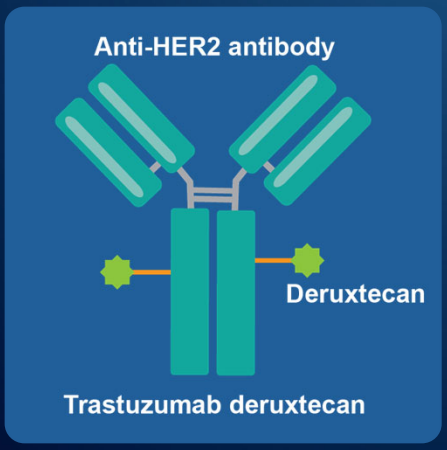
Trastuzumab Deruxtecan for Pretreated Patients With HER2-Expressing Solid Tumors



DESTINY-PanTumor02 Study

- 41 patients with HER2 expressing bladder cancer (IHC 3+/2+)
- Prior therapies
  - 0, 1, or 2: 22 (54%)
  - >2: 19 (46%)
- Overall response rate
  - All: 39.0%
  - IHC3+: 56.3%
  - IHC2+: 35.0%

IHC, immunohistochemistry
Merric-Bernstam F et al. *J Clin Oncol.* 2023;42:47.

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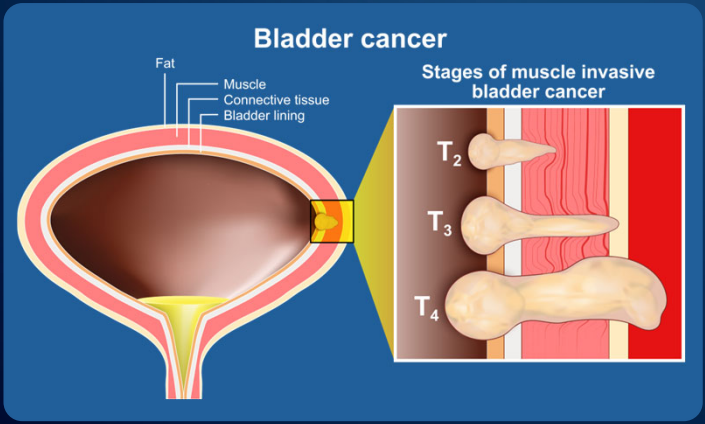
Muscle-Invasive Bladder Cancer



Neoadjuvant therapy

Preferred therapy

- Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC)

Other recommended regimens

- Gemcitabine and cisplatin

National Comprehensive Cancer Network Guidelines Bladder Cancer v6.2024.

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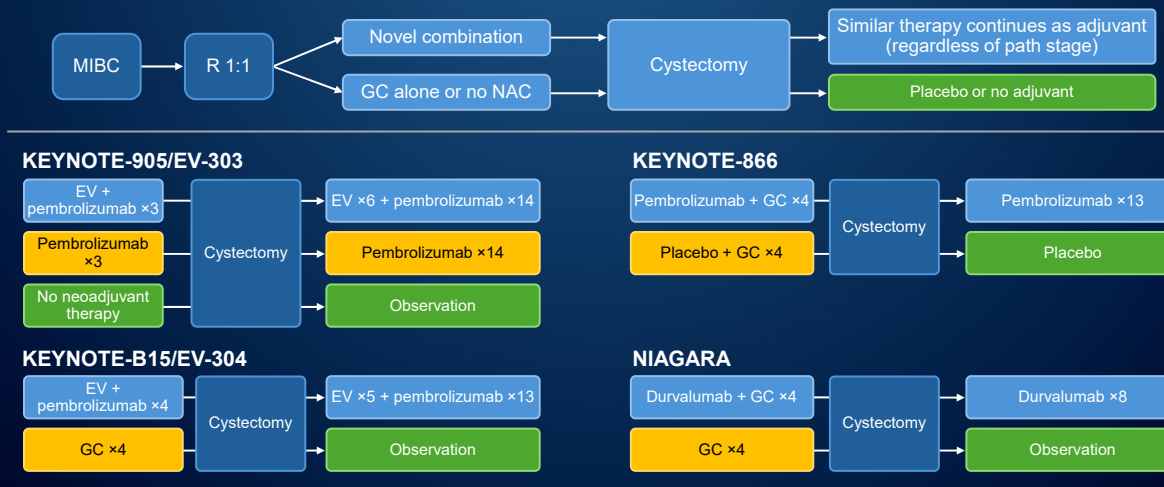
Current MIBC Perioperative Trials



MIBC, muscle-invasive bladder cancer; EV, enfortumab vedotin; GC, gemcitabine + cisplatin; NAC, neoadjuvant chemotherapy

Necchi A et al. *J Clin Oncol*. 2023;41. Abstract TPS585; Galsky MD et al. *Future Oncol*. 2021;17:3137; Powles TB et al. *Annals Oncol*. 2024;35. Abstract S1271; Hoimes CJ et al. *J Clin Oncol*. 2021;39. Abstract TPS4587.

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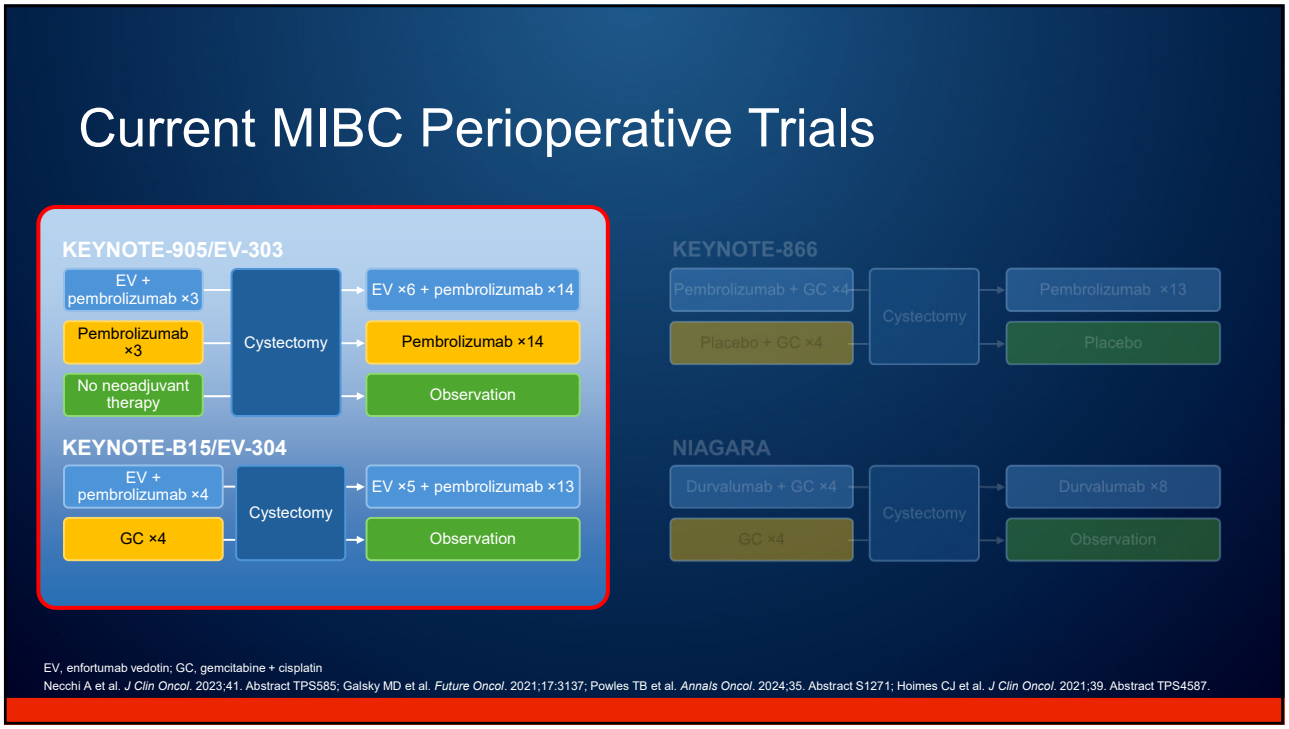
Current MIBC Perioperative Trials
KEYNOTE-905/EV-303
EV + pembrolizumab ×3
Pembrolizumab ×3
No neoadjuvant therapy
Cystectomy
EV ×6 + pembrolizumab ×14
Pembrolizumab ×14
Observation
KEYNOTE-B15/EV-304
EV + pembrolizumab ×4
GC ×4
Cystectomy
EV ×5 + pembrolizumab ×13
Observation
KEYNOTE-866
Pembrolizumab + GC ×4
Placebo + GC ×4
Cystectomy
Pembrolizumab ×13
Placebo
NIAGARA
Durvalumab + GC ×4
GC ×4
Cystectomy
Durvalumab ×8
Observation
EV, enfortumab vedotin; GC, gemcitabine + cisplatin
Necchi A et al. J Clin Oncol. 2023;41. Abstract TPS585; Galsky MD et al. Future Oncol. 2021;17:3137; Powles TB et al. Annals Oncol. 2024;35. Abstract S1271; Hoimes CJ et al. J Clin Oncol. 2021;39. Abstract TPS4587.

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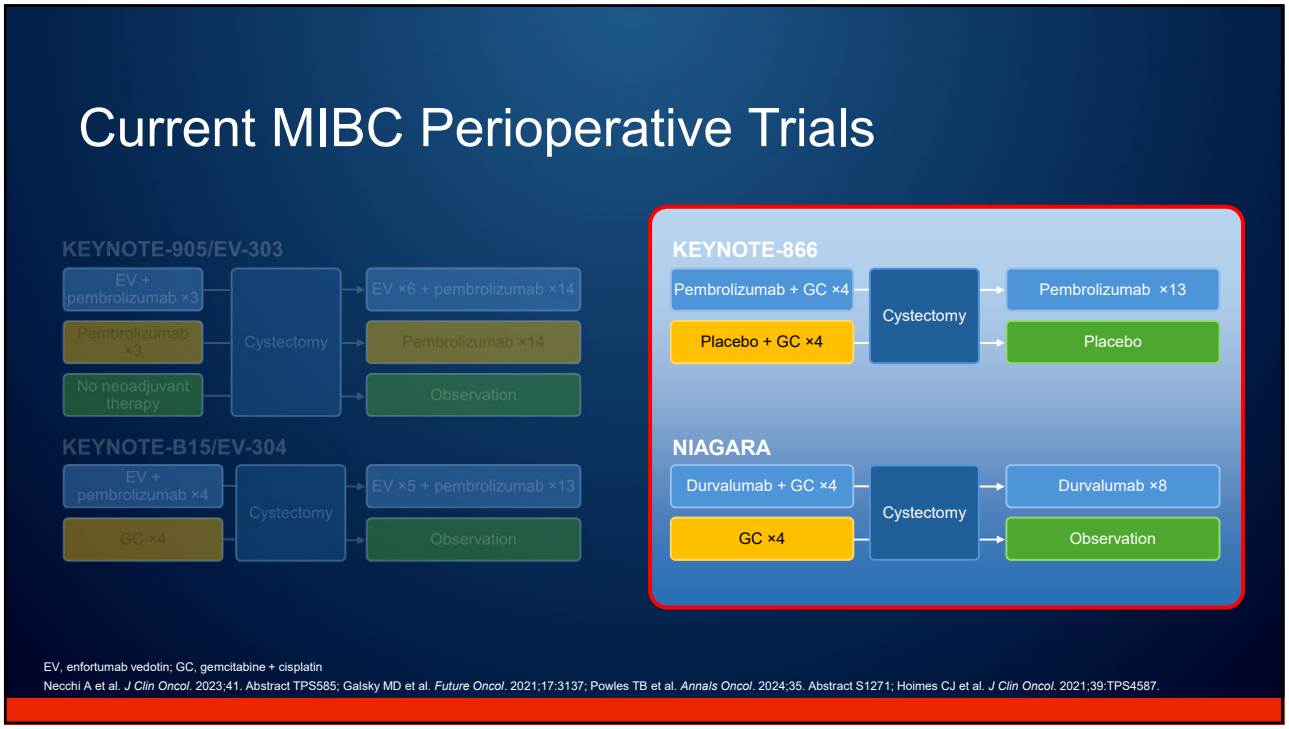
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Flaws With Current Perioperative Trials

- Gemcitabine-cisplatin backbone for all trials
  - Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin now standard
- Adjuvant therapy is assigned regardless of pathologic stage
- pT3/4: why continue to treat with same therapy tumor demonstrated resistance to?
- pT0: why continue to treat a patient who is likely cured?
- Placebo/observation without adjuvant option is no longer standard

Necchi A et al. *J Clin Oncol*. 2023;41. Abstract TPS585; Galsky MD et al. *Future Oncol*. 2021;17:3137; Powles TB et al. *Annals Oncol*. 2024;35. Abstract S1271; Hoimes CJ et al. *J Clin Oncol*. 2021;39:TPS4587; National Comprehensive Cancer Network Guidelines Bladder Cancer v6.2024.

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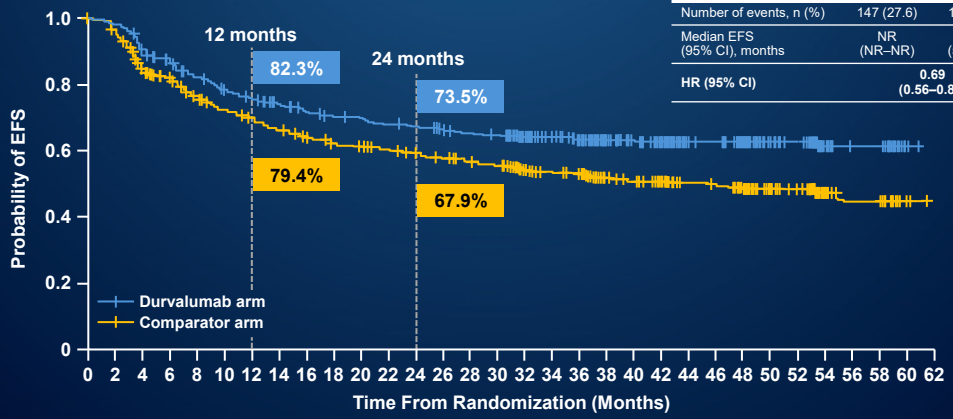
NIAGARA Study
Event-Free Survival

Patients Who Did Not Undergo RC Were Censored



	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	147 (27.6)	186 (35.1)
Median EFS (95% CI), months	NR (NR–NR)	NR (53.2–NR)
HR (95% CI)	0.69 (0.56–0.86)	

EFS was assessed using RECIST v1.1. EFS is defined as the time from randomization to the first: 1) progressive disease that precluded RC; 2) recurrence after RC; 3) date of expected surgery in patients who did not undergo RC; 4) death from any cause. Data cutoff 29 Apr 2024.

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intent-to-treat population; NR, not reached; RC, radical cystectomy; RECIST, Response Evaluation Criteria In Solid Tumors

Powles TB et al. *Annals Oncol*. 2024;35. Abstract S1271.

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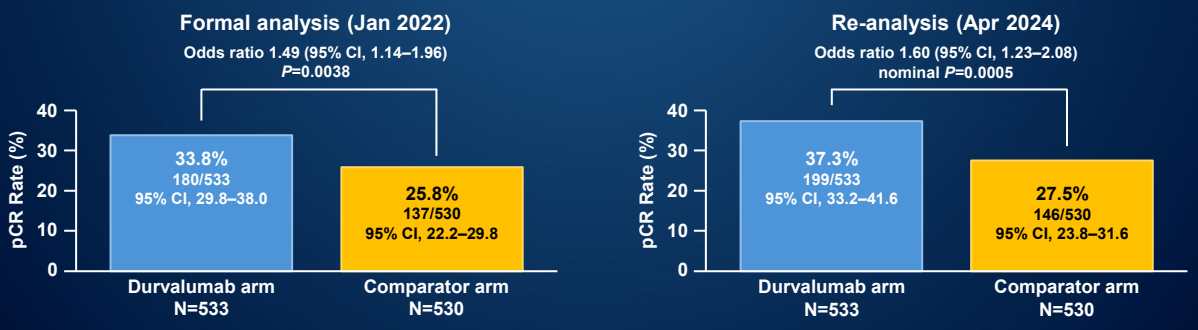
NIAGARA Study
Pathologic Complete Response



- The planned formal analysis for pCR was not statistically significant (threshold for significance, *P*=0.001)
- 59 evaluable samples were incorrectly considered nonresponders rather than their true result

- The re-analysis showed nominal statistical significance in favor of the durvalumab arm
- This analysis includes the results of the 59 omitted samples (28 additional pCRs)

CI, confidence interval; DCO, data cutoff; ITT, intent-to-treat population; pCR, pathologic complete response; RC, radical cystectomy.
Powles TB et al. *Annals Oncol.* 2024;35. Abstract S1271.

7

Putting NIAGARA in Context

Study	Treatment arm	pT0	1-year MFS	2 year MFS	2-year OS %
VESPER[1,2]	ddMVAC	42%	82%	73%	83%
	GC	36%	76%	61%	78%
NIAGARA[3]	GC + durvalumab (pre/post)	37%	82%*	74%*	82%
	GC	28%	79%	68%	75%

*Patients who did not undergo radical cystectomy were censored.

ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine and cisplatin
1. Pfister C et al. *Annals Oncol.* 2021;32:Abstract 6520. **2.** Pfister C et al. *Lancet.* 2024;25:255. **3.** Powles TB et al. *Annals Oncol.* 2024;35. Abstract S1271.

8

Enfortumab Vedotin (EV) + Pembrolizumab
Adverse Events (AEs) of Clinical Interest

Skin reactions

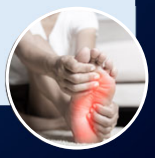
- Seen with both EV and pembrolizumab but more frequently with combination (EVP)
- 70% of patients treated with EVP
- Management ranges from monitoring and emollients or topical steroids to holding or discontinuing both agents, depending on severity

Hyperglycemia/ diabetes mellitus

- Seen with both EV and pembrolizumab but more commonly with EV
- 13% of patients treated with EVP
- Management includes treating with insulin and holding EV and/or pembrolizumab

Peripheral neuropathy

- Anticipated AE with ADCs, rarely with pembrolizumab
- Second most common AE: 67% of patients treated with EVP
- Management ranges from dose reduction and treatment for nerve pain to discontinuing both agents, depending on severity



Brower B et al. *Front Oncol*. 2024;14:1326715.

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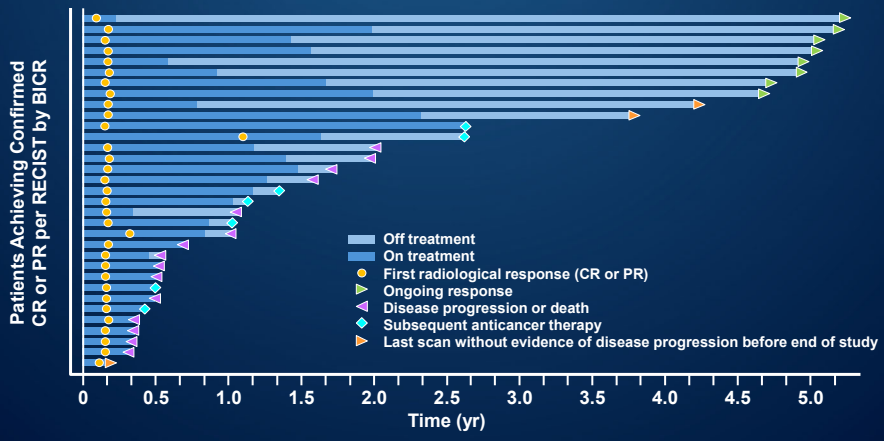
Time to Response and Duration of Response
Study EV-103



Response endured after stopping treatment.

BICR, blinded independent central review; CR, complete response; PR, partial response; RECIST, response evaluation criteria in solid tumors
Rosenberg J et al. *Annals Oncol*. 2024;35. Abstract 1968P.

2

Time to First Onset of Toxicities
Enfortumab Vedotin vs Chemotherapy

Adverse event	Median time to onset, months (range)	
	EV	Chemotherapy
Skin reactions	0.43 (0.03–12.68)	0.66 (0.07–9.56)
Peripheral neuropathy	2.81 (0.03–13.04)	0.85 (0.03–9.07)
Hyperglycemia	0.62 (0.26–13.37)	1.41 (1.41–1.41)

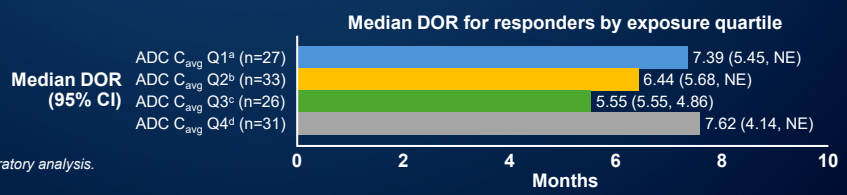
EV, enfortumab vedotin
Rosenberg J et al. *Ann Oncol*. 2023;11:1047.

3

Durable Responses Maintained With EV Despite Dose Modifications (EV-301)

	ADC C_{avg} Q1[a] (n=74)	ADC C_{avg} Q2[b] (n=74)	ADC C_{avg} Q3[c] (n=74)	ADC C_{avg} Q4[d] (n=74)
Median EV ADI (mg/kg/4 week)[e] (range)	2.37 (1.15, 3.77)	2.96 (1.57, 3.82)	3.26 (2.36, 3.86)	3.59 (2.50, 3.93)
Any EV dose delay (%)	59.5	58.1	44.6	26.4
Any EV dose reduction (%)	54.1	39.2	28.4	20.3
To 1.0 mg/kg	52.7	39.2	28.4	20.3
To 0.75 mg/kg	21.6	14.9	6.8	1.4
Median time to EV dose reduction (range), mo	2.02 (0.79, 9.27)	2.96 (0.95, 12)	3.06 (0.72, 6.64)	2.79 (0.89, 9.04)

EV-301:
ORR: 41%
Median time to response:
1.9 months (range: 1.1–5.7)



All data presented are from the post hoc, exploratory analysis.

ADC, antibody-drug conjugate; ADI, absolute dose intensity; C_{avg}, time-averaged exposure over the entire treatment duration; EV, enfortumab vedotin; NE, not evaluable; Q, quartile
Average ADC exposures were divided into 4 quartiles: [a]Q1 represents the EV exposures between 0%–25%; [b]Q2: 25%–50%; [c]Q3: 50%–75%; [d]Q4: 75%–100% (the highest EV exposure quartile); [e]Intended ADI was 3.75 mg/kg/4 weeks.
Petrylak DP et al. *J Clin Oncol*.2024; 42: Abstract 4503.

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