IV GO NORTE INTERNATIONAL GU DEBATES
OCTOBER 2nd - 3rd 2025
#GonorteGUDebates

ADC Combos in the Perioperative Setting: Will Efficacy Outperform the Potential Risks?

Vadim S. Koshkin, MD

Associate Professor of Clinical Medicine
Division of Hematology/Oncology, Department of Medicine
University of California San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, CA

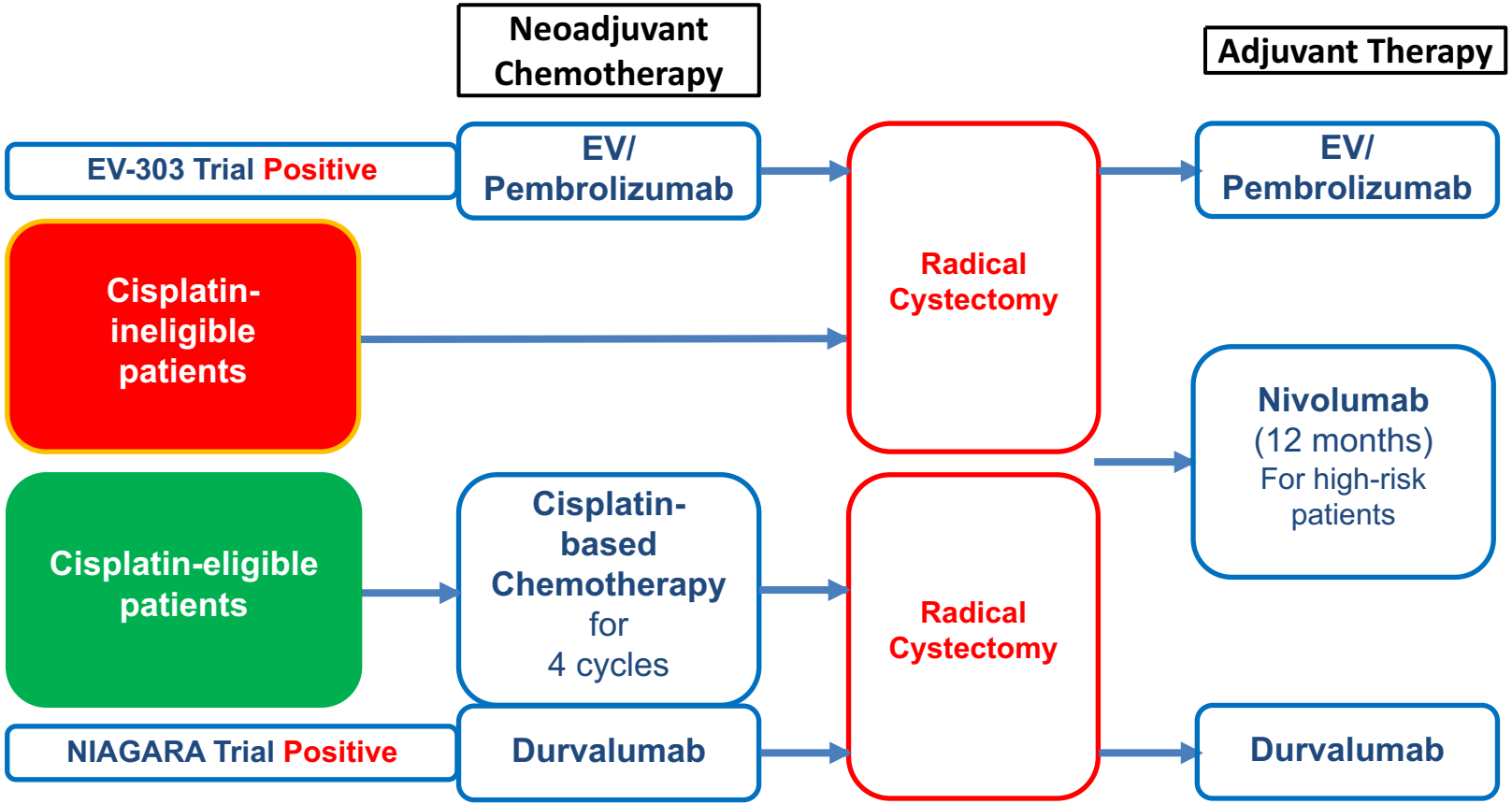
Disclosures

Research Support (Institution): Curium, Eli Lilly, Endocyte/Novartis, Gilead, Merck, Nektar, Seagen/Pfizer and Taiho

Research Funding: Eli Lilly, Astellas/Merck, Prostate Cancer Foundation

Consulting or Advisory Role: Astellas, AstraZeneca, Bicycle Therapeutics, BMS, Janssen, Loxo Oncology, MSD, Pfizer/Seagen, Roche, Tempus

Perioperative Setting: Evolving Standard of Care



Recent Advances in Perioperative Treatment: Two Positive Registrational Studies and Others to Come

	Clinical Trial	N	Treatment Arms	Control Arm
CISPLATIN ELIGIBLE	NIAGARA[3]	1063	Durvalumab + GC	GC
	KEYNOTE-866[1]	907	Pembrolizumab + GC	GC
	KEYNOTE-B15/EV-304[2]	784	Pembrolizumab + EV	GC
	ENERGIZE[4]	861	Nivolumab + GC	GC
CISPLATIN INELIGIBLE	KEYNOTE-905/EV-303[5]	857	A: Pembro + EV B: Pembro monotherapy	RC
	VOLGA[6]	830	A: Durva/Tremi + EV B: Durva + EV	RC

1. NCT03924856. 2. NCT04700124. 3. NCT03732677. 4. NCT03661320.
5. NCT03924895. 6. NCT04960709. 7. NCT04871529.

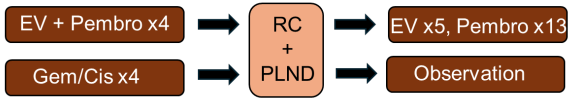
EV: Enfortumab vedotin
GC: Gemcitabine/cisplatin
RC: Radical cystectomy

@koshkin85 @vadimkoshkin.bsky.social

Registrational Perioperative Trials with ADC: Enfortumab Vedotin / ICI Combinations

Cisplatin-eligible

EV-304/KN-B15 (NCT04700124):



Primary endpoint:
Event free survival (EFS)

N=808

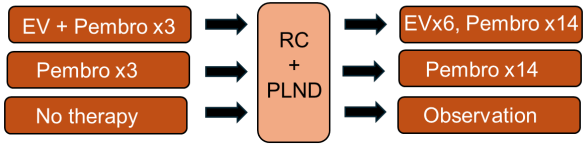
Secondary endpoints:
OS, pCR, DFS, AE

Inclusion criteria:
- cT2 - T4a
- cN0-N1 M0
- ≥ 50% urothelial histology
- Cisplatin-eligible
- all adj. ttr vs observation

Cisplatin-ineligible

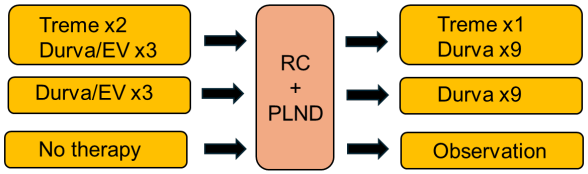
EV-303/KN-905 (NCT03924895):

N=595



VOLGA (NCT04960709):

N=712



Inclusion criteria:
- cT2 - T4a
- cN0-N1 M0
- ≥ 50% urothelial histology
- **Cisplatin-ineligible**
- all adj. ttr vs observation

Primary Endpoints:
- EFS
  - EV 303: EV+P vs no ttr
  - VOLGA: separate for active arms vs no ttr

Secondary Endpoints:
- OS, pCR, DFS, AE

Potential Impact on Future Treatment in Perioperative Setting

- Possible new SOC
- High CR rates may support bladder sparing approaches (clinical trials)
- No all patients may need extensive adjuvant treatment

Slide c/o M Milowsky, R. Cathomas

@koshkin85 @vadimkoshkin.bsky.social

EV-Based Regimens As Bladder-Sparing Approaches with Radiotherapy in MIBC

EV-PRIME: Phase Ib/II Trial of EV/Pembrolizumab with Concurrent RT for Patients with MIBC Interested in Bladder Preservation *(PI V. Koshkin)*

Phase Ib

3+3 Dose escalation of EV, Until Recommended Phase 2 dose (RP2D) is reached (n=6-18 Patients)

EV Dose Level 1: 0.75 mg/kg
EV Dose Level 2: 1.00 mg/kg
EV Dose Level 3: 1.25 mg/kg
(all with concurrent Pembrolizumab and standard fractionation RT as below)

Phase II

MIBC Patients (cT2-4aN0M0)

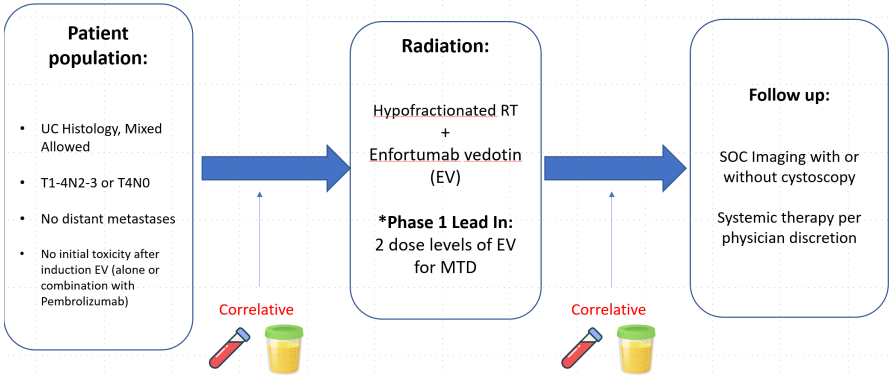
- Patients eligible for bladder-sparing trimodality therapy
- Ineligible for or unwilling to undergo radical cystectomy

Concurrent RT with Systemic Treatment of Each Dose Level of EV (Phase Ib) OR RP2D (Phase II) (n=29 patients)

Enfortumab vedotin (Day 1 and Day 8 of a 21-day cycle) x 2 cycles
AND
Pembrolizumab 200 mg (day 1 of 21-day cycle) x 2 cycles
WITH
Concurrent RT (64 Gy in 32 fractions of 2 Gy; 6.5 weeks total)

Pembrolizumab 200 mg (Day 1 of 21-day cycle) x 15 cycles (1 year total)
AND
Enfortumab vedotin
(Day 1 and Day 8 of a 21-day cycle) x 3 cycles

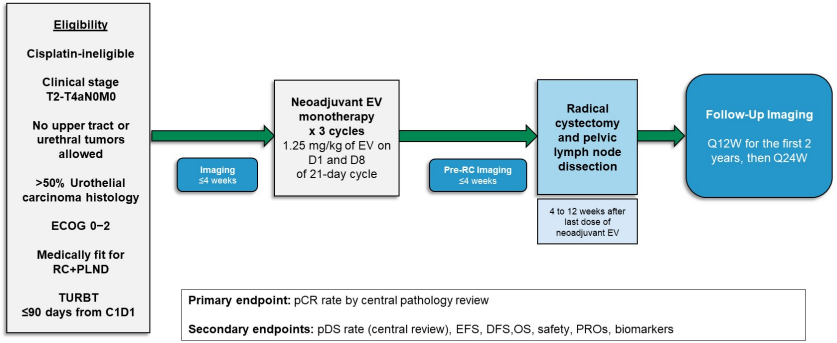
CONSOLIDATE: Phase I/II Trial of EV with Hypofractionated RT (PI C. Hassanzadeh)



@koshkin85 @vadimkoshkin.bsky.social

EV Neoadjuvant and Perioperative Data

EV-103 Cohort H Study Design

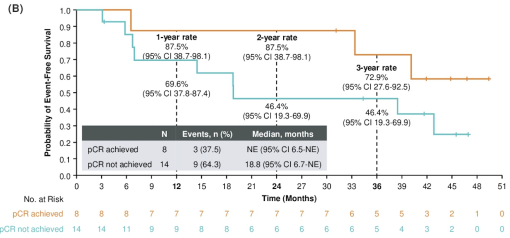


Primary endpoint: pCR rate by central pathology review

Secondary endpoints: pDS rate (central review), EFS, DFS,OS, safety, PROs, biomarkers

Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue: ypT0 and N0)	**8 (36.4%)** [17.2–59.3]
Pathological Downstaging Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	**11 (50.0%)** [28.2–71.8]

Investigator Assessed EFS by pCR



Safety Data

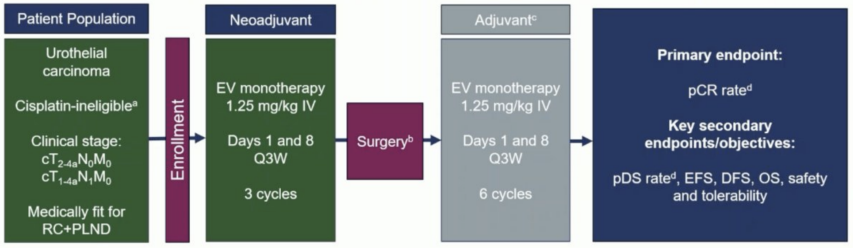
- 19/22 Patients completed all 3 cycles of neoadjuvant EV
- All 22 patients underwent surgery without delay

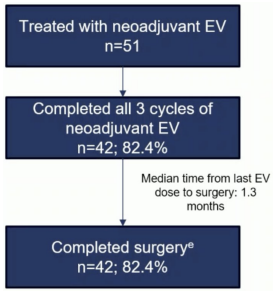
Safety: Treatment Emergent Adverse Events

EV-related TEAEs seen in ≥20% patients by preferred term	EV Mono (N=22)
Overall (all Grades)	22 (100)
Fatigue	10 (45.5)
Alopecia	8 (36.4)
Dysgeusia	8 (36.4)
Diarrhea	6 (27.3)
Nausea	6 (27.3)
Peripheral sensory neuropathy	6 (27.3)
Dry eye	5 (22.7)
Rash maculo-papular	5 (22.7)

- Overall, 4 (18%) patients had Grade ≥3 EV-related TEAEs
  - Grade 3 EV-related TEAEs included: asthenia, dehydration, erythema multiforme, hyperglycemia, post procedural urine leak, rash maculo-papular, small intestinal obstruction
- No EV-related Grade 4 TEAEs or deaths were observed
- 3 deaths occurred on the study:
  - Acute kidney injury
  - Cardiac arrest (related to RC+PLND)
  - Pulmonary embolism (related to RC+PLND)

EV-103 Cohort L: Perioperative EV in Cisplatin-Ineligible MIBC





Pathological Response	Central Pathology Review (n=50[a]) n (%) [95% CI[b]]
pCR (defined as absence of viable tumor tissue: ypT0N0)	17 (34.0) [21.2, 48.8]
pDS[c] (defined as patients with <ypT2, including pT0, pTis, pTa, pT1, and N0)	21 (42.0) [28.2, 56.8]

EV AEs in Neoadjuvant Setting

EV-related TEAEs[a] (n=51) n (%)	Any grade	Grade ≥3
Overall	46 (90.2)	20 (39.2)
Fatigue	27 (52.9)	1 (2.0)
Rash maculo-papular	16 (31.4)	6 (11.8)
Nausea	15 (29.4)	-
Alopecia	14 (27.5)	-
Peripheral sensory neuropathy	14 (27.5)	1 (2.0)
Pruritis	12 (23.5)	-
Hyperglycemia	7 (13.7)	6 (11.8)

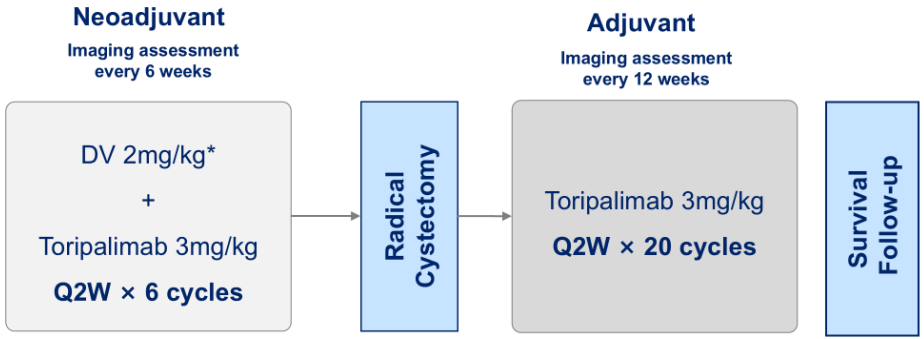
- One patient with EV-related death prior to surgery
- 31.4% pf pts had a RC-related TEAE ≥ grade 3
- No surgeries delayed due to EV-related TEAEs

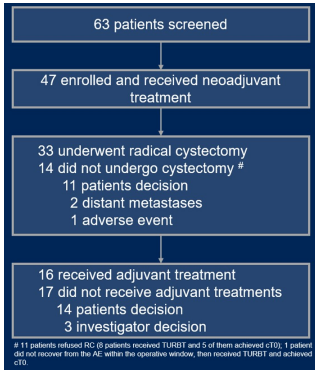
Petrylak *et al. ASCO GU* 2022, Mar *et al ASCO* 2025, Sridhar et al ESMO 2023

@koshkin85 @vadimkoshkin.bsky.social

Disitamab vedotin (HER2-targeting ADC) + Toripalimab in MIBC

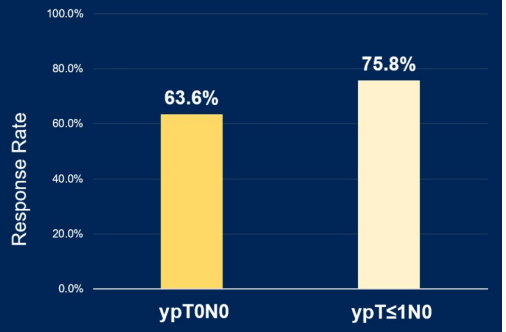
Eligibility: HER2 ≥ 1+: (10.6% pts with HER2 IHC 1+, 57.4% IHC 2+, and 31.9% IHC 3+)





	Patients Received RC N=33
Pathological response	
pCR (ypT0N0), n (%)	**21 (63.6)**
95% CI	45.1-79.6
Pathological response (≤ypT1N0M0), n (%)	**25 (75.8)**
95% CI	57.7-88.9
Pathological staging, n (%)	
ypT0N0	21 (63.6)
ypT≤1N0	4 (12.1)
ypTisNx*	1 (3.0)
ypT2N0	4 (12.1)
ypT3N0	3 (9.1)
ypT4 or ypTanyN+	0

Pathological tumor response was assessed by the local pathologists based on the postoperative pathology.
*Pelvic lymph-node dissection was not performed.

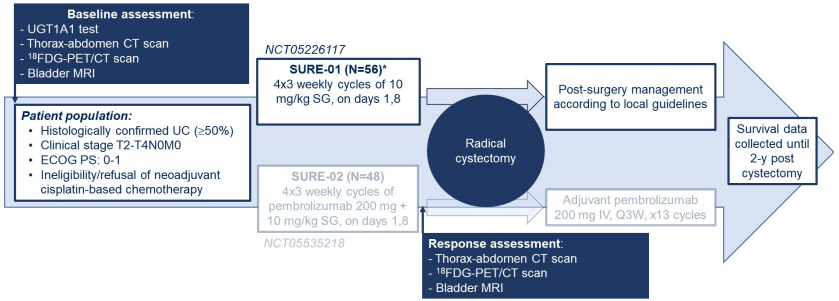


Treatment-Related Adverse Events

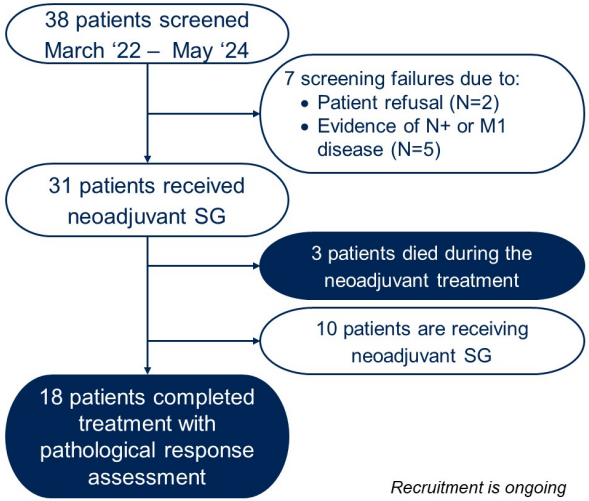
Overall study period (except otherwise specified)	All patients (N=47) n (%)
Treatment-emergent adverse events (TEAEs)	47 (100)
Grade ≥3	13 (27.7)
Grade ≥3 (neoadjuvant phase)	8 (17.0)
Grade ≥3 (adjuvant phase)	4/16* (25.0)
Serious adverse events	11 (23.4)
Leading to dose reduction	1 (2.1)
Leading to discontinuation of study treatment	8 (17.0)
Leading to discontinuation of neoadjuvant treatment	6 (12.8)
Leading to patient not undergoing radical cystectomy	1 (2.1)
Leading to discontinuation of adjuvant treatment	3/16* (18.8)
Treatment-related adverse events#	46 (97.9)
Grade ≥3	10 (21.3)
Serious adverse events	6 (12.8)

Sheng et al. *ASCO GU* 2025

Sacituzumab Govitecan Neoadjuvant Trial: SURE-01



Primary Endpoint: ypT0N0 rate; ***Secondary Endpoints***: ypT≤1N0 rate, EFS, OS, QoL, Safety (CTCAE v.5.0)



Recruitment is ongoing

Protocol amended due to TRAEs after initial 8 patients

- G3-4 Neutropenia: 6/8 (75%).
- Timing of G3-4 TRAE onset: after C1D8 in 5/6 patients.
- G3-4 Diarrhea: 4/8 (50%; all after C1D8).
- Dose-reductions of SG: 6/8 (75%), the remaining 2 patients had treatment discontinuation/death.
- One treatment-related Grade 5 event (sepsis).
- One treatment-unrelated Grade 5 event.

KEY PROTOCOL CHANGES[a]

Dose reduction of sacituzumab govitecan to 7.5 mg/Kg from C1D1.

Introduction of G-CSF use (Peg-GCSF) as primary prophylaxis since C1D9.

Exclusion of patients who had ≥3 risk factors for febrile neutropenia as indicated by the ASCO guidelines.*

Treatment-Related Adverse Events

Most common TRAEs	Any grade, N (%)	≥G3, N (%)
Anemia	31 (73.8)	1 (2.4)
Neutropenia	10 (23.8)	8 (19.0)
Alopecia	18 (42.8)	0
Diarrhea	16 (38.0)	7 (16.7)
Fatigue	13 (30.9)	0
Creatinine increase	11 (26.2)	3 (7.1)
Nausea/Vomiting	8 (19.0)	0
Sepsis/Fever	6 (14.3)	5 (11.9)
Urinary Infection	4 (9.5)	0

In the first 8 pts: 6 ≥G3 neutropenia (75%), 4 ≥G3 diarrhea (50%), 4 serious TRAEs (50%); 75% dose reduction, 2 treatment discontinuations/deaths (1 G5 TRAE, 1 G5 unrelated AE)

Efficacy Outcomes

Best overall response	ITT population (N=37), N (%; 95%CI)
ypT0N0-x	**12 (32.4; 18.0-49.8)**
ypT≤1N0-x	14 (37.8; 23.5-57.7)
ypT2N0-x	2 (5.4; 0-14.7)
ypT3-4N0-x	9 (24.3; 5.2-32.4)
$ypT_{any}N+$	7 (18.9; 7.6-36.2)
PD/death	4 (10.8; 1.0-24.0)
Refused surgery	2 (5.4; 0-14.7)

Cigliola et al. *ASCO* 2024, Maiorano et al. *ASCO* 2025

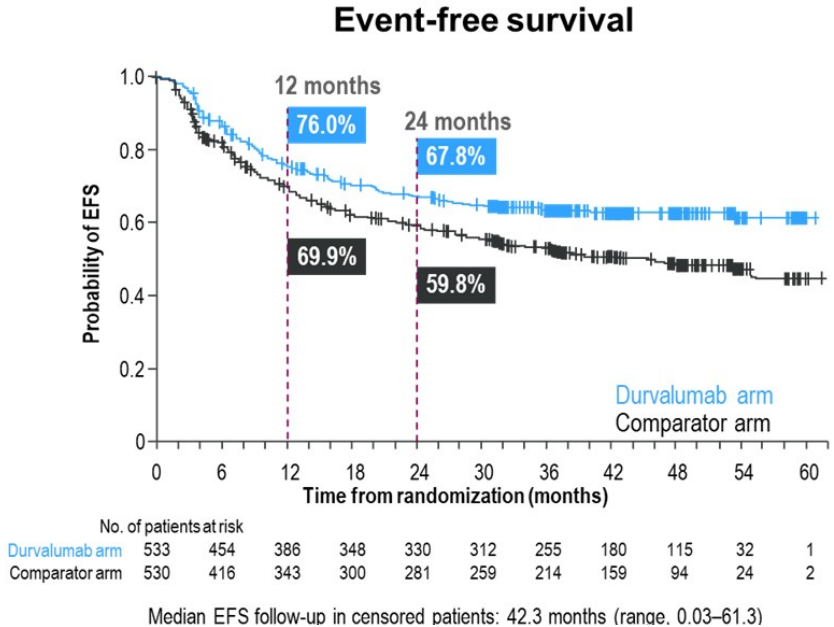
@koshkin85 @vadimkoshkin.bsky.social

NIAGARA: Cis/Gem + Durvalumab the Current Standard for Perioperative Treatment

For perioperative durvalumab + NAC with radical cystectomy vs NAC with radical cystectomy alone:

- **Event-free survival**[1]: HR, 0.68 (95% CI 0.56-0.82), ***P*<0.0001**
- **Overall survival**[1]: HR, 0.75 (95% CI 0.59-0.93), ***P*=0.0106**
- **pCR rate**[1]: 37.3% vs 27.5%
- **pCR/non-pCR groups**[2]: perioperative durvalumab + NAC improved EFS and OS in both groups[a]
- **Radical cystectomy rate**[1]: 88% vs 83%
- **Safety**[1]: addition of durvalumab to NAC was tolerable and manageable, with no new safety signals

Perioperative durvalumab + NAC was approved for use in MIBC by the US FDA on 28 March 2025.

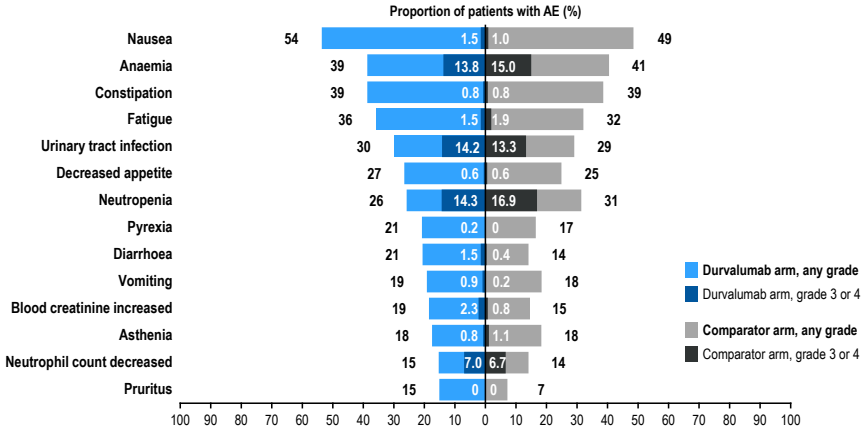


Powles et al. *NEJM* 2024, Powles et al. *ASCO GU* 2025

@koshkin85 @vadimkoshkin.bsky.social

Lessons from NIAGARA: Safety and Adverse Events

NIAGARA: Most Frequently Reported AEs (Overall)



NIAGARA: AE Summary (Safety Population)

Overall study period (unless otherwise stated)	Durvalumab arm N=530	Comparator arm N=526
AEs of any cause, n (%)	527 (99)	525 (100)
Grade 3 or 4	368 (69)	355 (68)
Serious AEs	326 (62)	287 (55)
Outcome of death	27 (5)	29 (6)
Leading to discontinuation of study treatment	112 (21)	80 (15)
Leading to discontinuation of neoadjuvant durvalumab	50 (9)	---
Leading to discontinuation of NAC	**72 (14)**	**80 (15)**
Leading to patient not undergoing RC	**6 (1)**	**7 (1)**
Leading to delay in surgery*	**9 (2)**	**6 (1)**
Leading to discontinuation of adjuvant durvalumab	30/383† (8)	---
AEs possibly related to any treatment, n (%)‡	502 (95)	487 (93)
Grade 3 or 4 (treatment related)	215 (41)	215 (41)
Outcome of death (treatment related)	3 (0.6)	3 (0.6)
Any-grade immune-mediated AEs	111 (21)	16 (3)

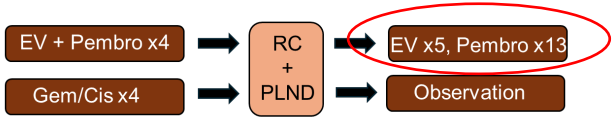
Powles et al. *ESMO* 2024

@koshkin85 @vadimkoshkin.bsky.social

Registrational Perioperative Trials with ADC: Enfortumab Vedotin / ICI Combinations

Cisplatin-eligible

EV-304/KN-B15 (NCT04700124):



Inclusion criteria:
- cT2 - T4a
- cN0-N1 M0
- ≥ 50% urothelial histology
- Cisplatin-eligible
- all adj. ttr vs observation

Primary endpoint:
Event free survival (EFS)

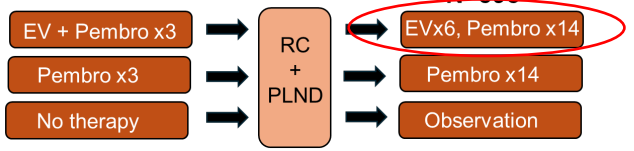
N=808

Secondary endpoints:
OS, pCR, DFS, AE

Cisplatin-ineligible

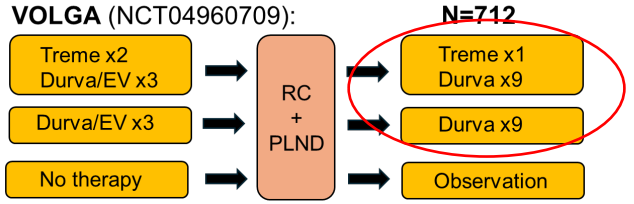
EV-303/KN-905 (NCT03924895):

N=595



VOLGA (NCT04960709):

N=712



Inclusion criteria:
- cT2 - T4a
- cN0-N1 M0
- ≥ 50% urothelial histology
- **Cisplatin-ineligible**
- all adj. ttr vs observation

Primary Endpoints:
- EFS
  - EV 303: EV+P vs no ttr
  - VOLGA: separate for active arms vs no ttr

Secondary Endpoints:
- OS, pCR, DFS, AE

Will removing adjuvant EV (VOLGA study) result in equivalent efficacy while mitigating additional toxicity?

Future Questions from These Trials

- What percentage of patients will be completing adjuvant EV / other adj. treatment?
- How do we select patients for adjuvant treatment? Do all patients need this?
- Are we overtreating patients with pCR and ctDNA- following surgery?

Slide c/o M Milowsky, R. Cathomas

@koshkin85 @vadimkoshkin.bsky.social

EV+P adverse Events and Their Timing

Dermatologic Toxicity

70% of those receiving **PADCEV + pembrolizumab**

Peripheral Neuropathy

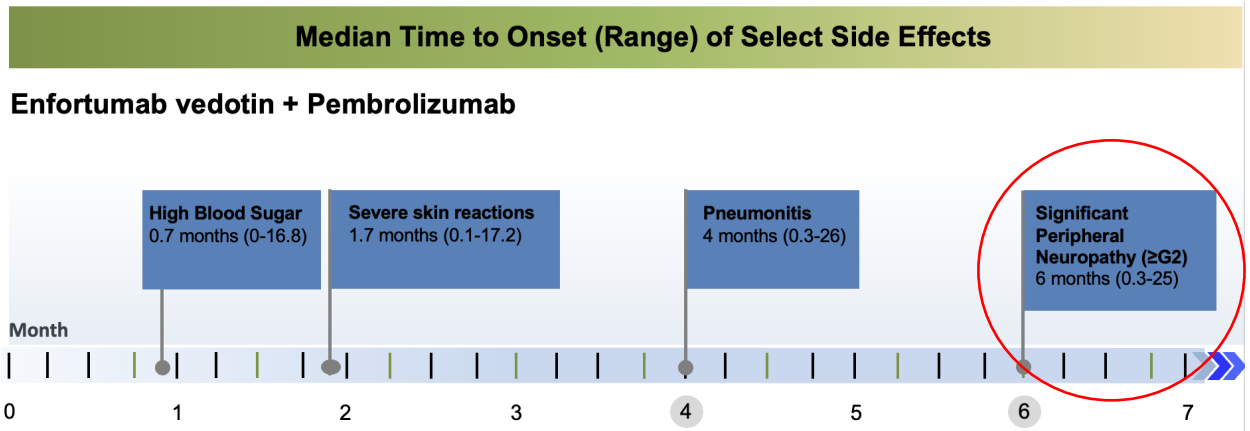
67% of those receiving **PADCEV + pembrolizumab**

Pneumonitis /ILD

10% of those receiving **PADCEV + pembrolizumab**

Hyperglycemia

19% of those receiving **PADCEV + pembrolizumab**



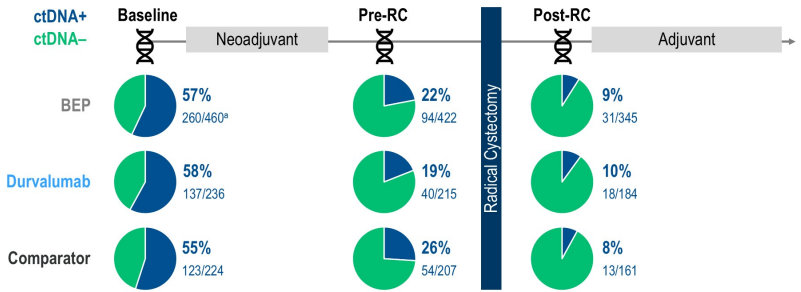
PADCEV [Package Insert] 2025

@koshkin85 @vadimkoshkin.bsky.social

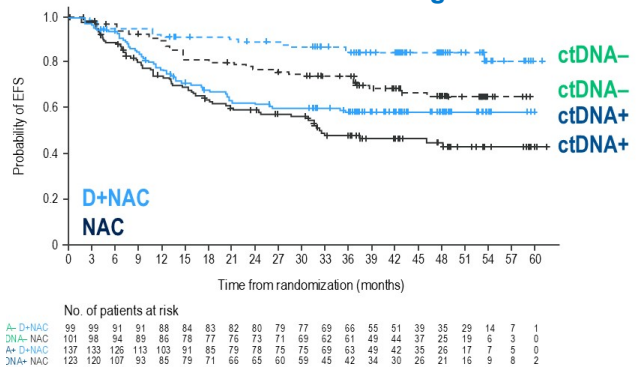
NIAGARA: ctDNA Prognostic of Outcomes at All Timepoints

NIAGARA: ctDNA Detection Rates

ctDNA+ rates decreased after neoadjuvant treatment and radical cystectomy

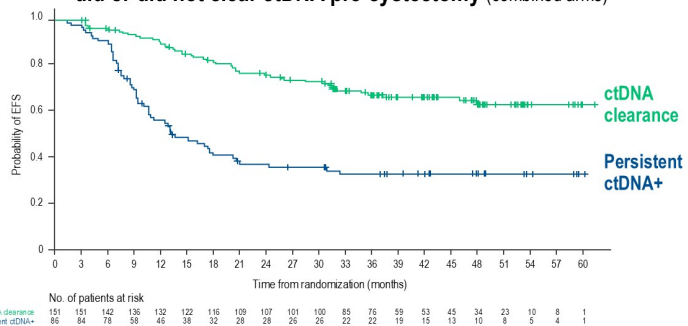


NIAGARA: Baseline ctDNA Prognostic of EFS



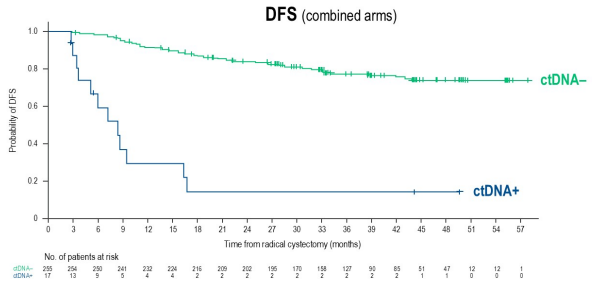
ctDNA–: D+NAC vs NAC	**HR, 0.45** (95% CI, 0.24–0.84)
ctDNA+: D+NAC vs NAC	**HR, 0.73** (95% CI, 0.51–1.05)

EFS in the baseline ctDNA+ population that did or did not clear ctDNA pre-cystectomy (combined arms)



ctDNA clearance vs persistent ctDNA+	**HR, 0.32** (95% CI, 0.22–0.47)

NIAGARA Post-Cystectomy: ctDNA Detection Was Prognostic for DFS



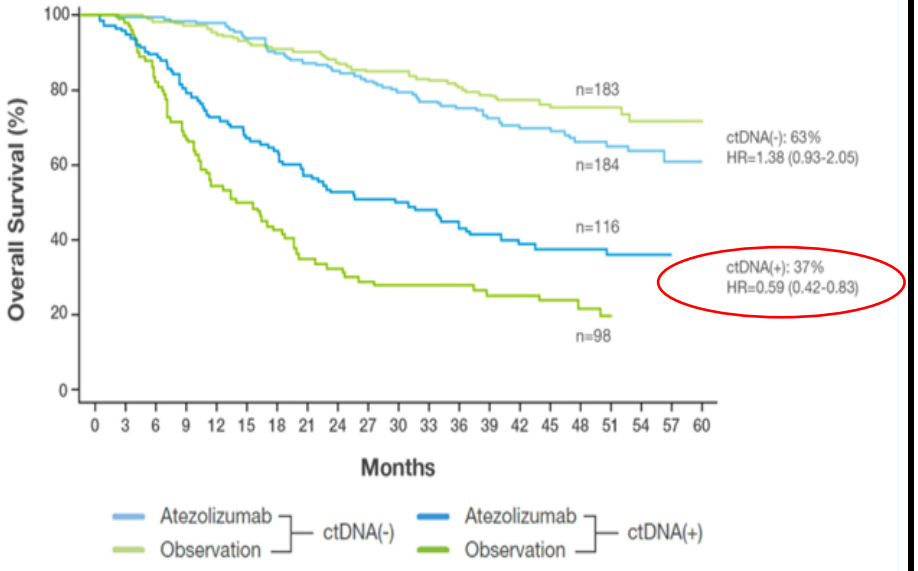
ctDNA– vs ctDNA+	**HR, 0.09** (95% CI, 0.05–0.18)

Powles et al. *ASCO GU* 2024

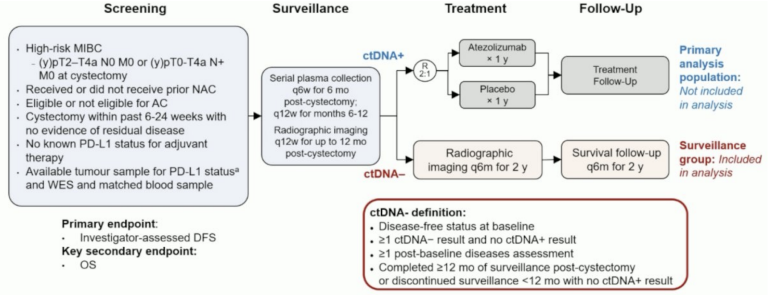
@koshkin85 @vadimkoshkin.bsky.social

Using ctDNA to Select Patients for Adjuvant Treatment?

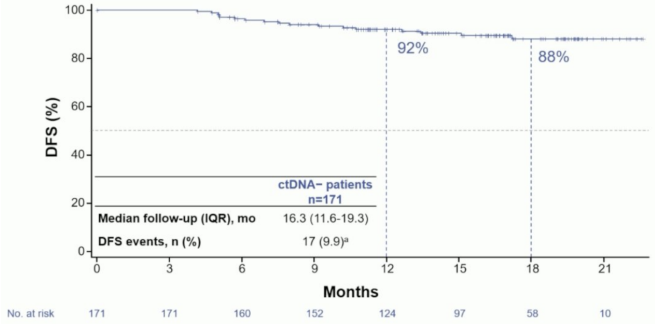
IMvigor 010: OS by ctDNA Status After Cystectomy



IMvigor011 Trial



DFS in ctDNA- Patients (median f/u of 16.3 months)



AUGUST 18, 2025

IMvigor011 Bladder Cancer Trial Achieves Positive Results, with Signatera™ Strongly Predicting Adjuvant Immunotherapy Benefit

Powles et al. *Nature* 2021, Powles et al ASCO 2025, Powles *et al EAU* 2024

@koshkin85 @vadimkoshkin.bsky.social

Key Considerations for ADC Combinations in the Perioperative Setting

- ADC and EV-based regimens becoming established in the perioperative setting.
- Have to consider cumulative toxicities differently in this curative-intent population.
- Are there patients who are overtreated with additional adjuvant therapy?
- Novel prognostic and predictive biomarkers to potentially address these questions.

Thank you!

vadim.koshkin@ucsf.edu

@koshkin85

@vadimkoshkin.bsky.social