Debate: Neoadjuvant/Adjuvant Enfortumab Vedotin + Pembrolizumab (EVP) vs Cisplatin Based Therapy in MIBC

The question is not whether EVP works…
It's if it should replace cisplatin-based therapy for everyone?

Jordan Ciuro MD

DDHO 2026

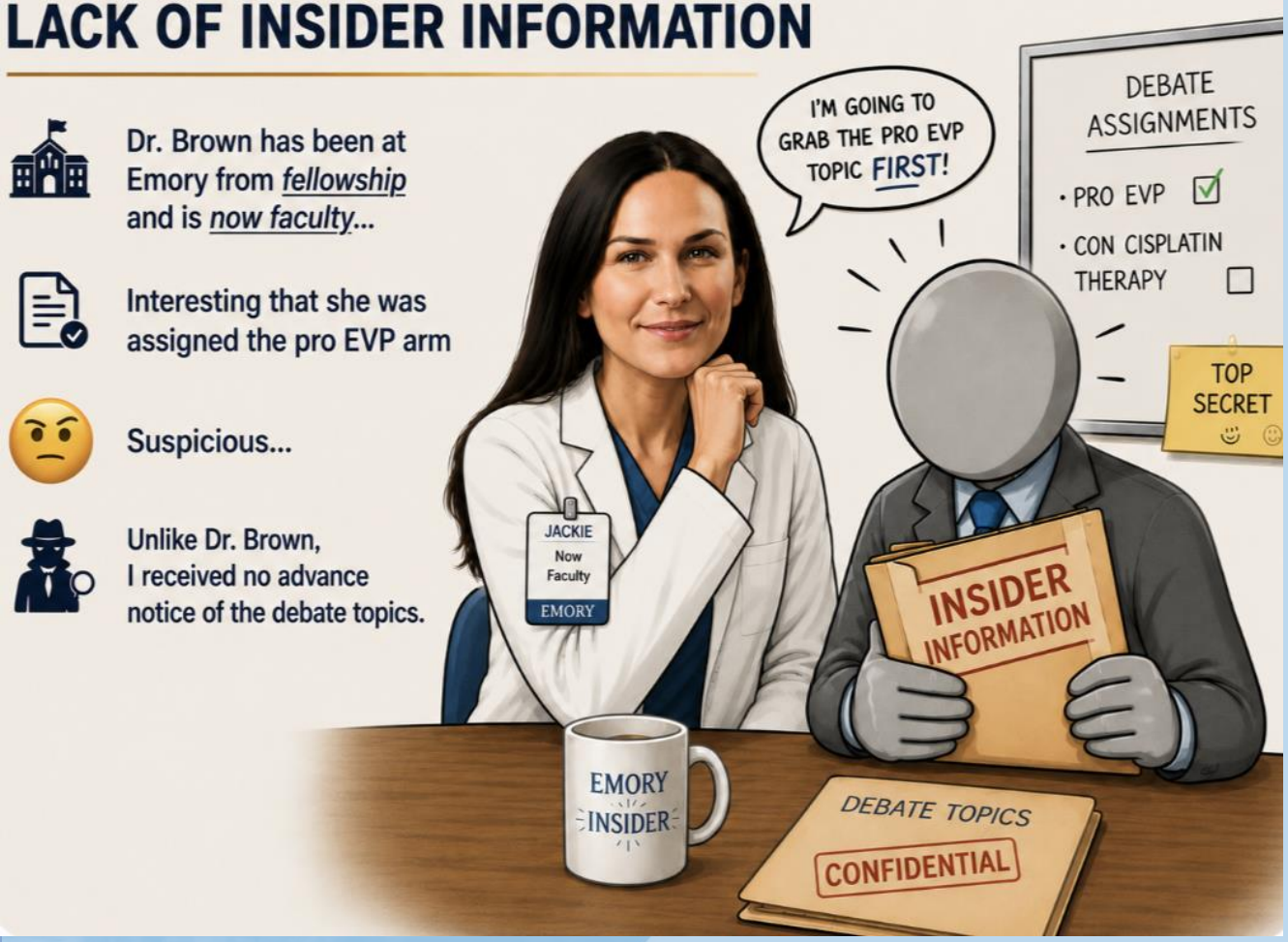
DISCLOSURE:
LACK OF INSIDER INFORMATION

Dr. Brown has been at Emory from *fellowship* and is *now faculty*...

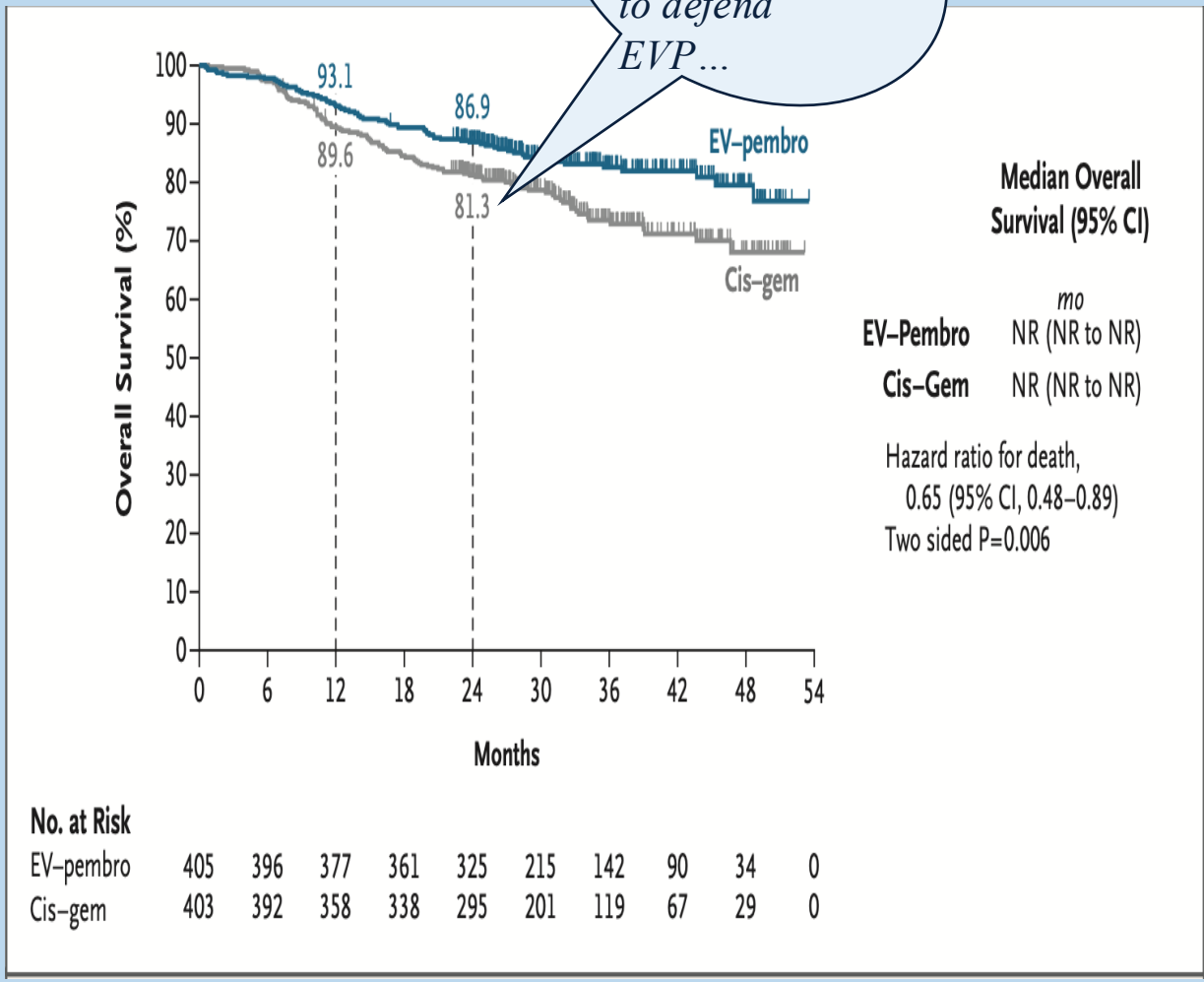
Interesting that she was assigned the pro EVP arm

Suspicious...

Unlike Dr. Brown, I received no advance notice of the debate topics.



I wonder why Dr. Brown would choose to defend EVP…



Things we can agree on…

EVP is highly active in MIBC

EVP has become the preferred regimen for most patients with MIBC

NIAGARA regimen with cisplatin therapy STILL matters

Specifically, today I am going to argue 5 things:

1. We still don’t have the right head-to-head trial comparison
2. The patients enrolled in these trials were different
3. Tumor biology
4. Toxicity
5. Treatment sequencing

Current NCCN MIBC Landscape

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Muscle-Invasive Bladder Cancer

NCCN Guidelines Index
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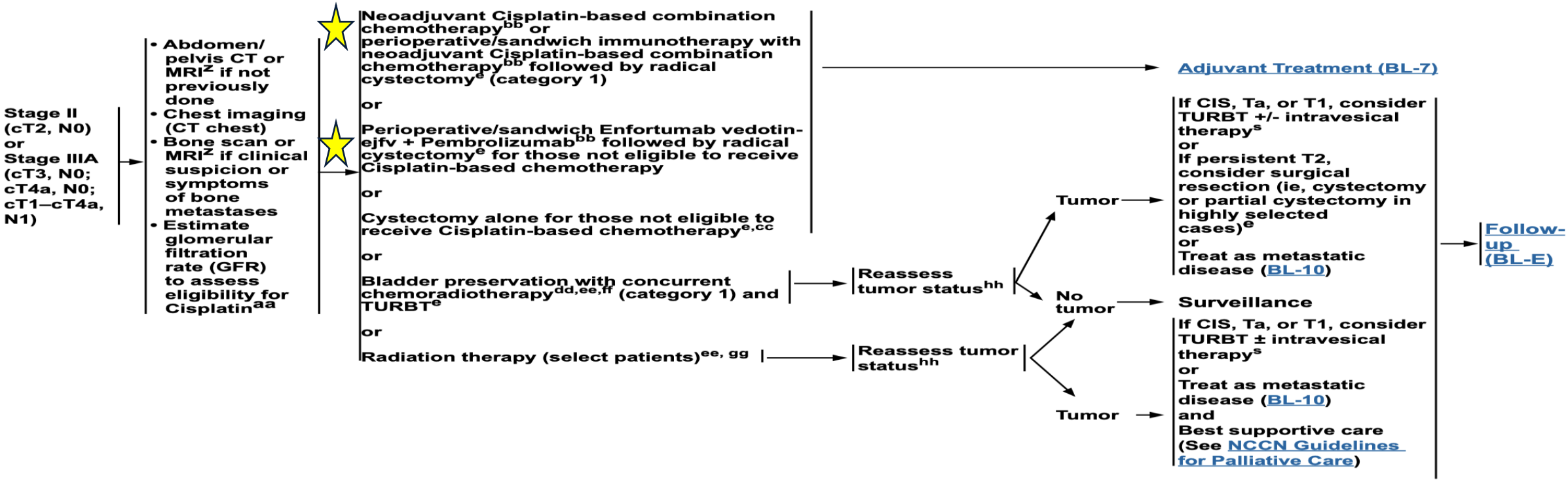
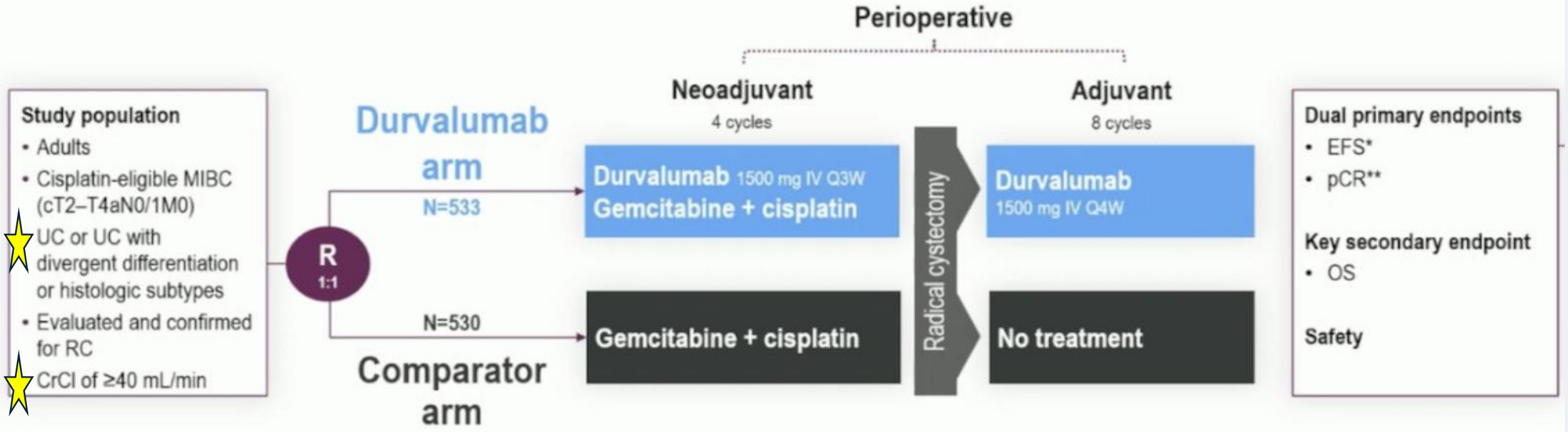
Discussion



NIAGARA: Study Design



Stratification factors

Clinical tumour stage (T2N0 vs >T2N0)

Renal function (CrCl ≥60 mL/min vs ≥40–<60 mL/min)

PD-L1 status (high vs low/negative expression)

Gemcitabine/cisplatin dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 Day 1, then gemcitabine 1000 mg/m^2 Day 8, Q3W for 4 cycles

CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m^2 Days 1 and 8, Q3W for 4 cycles

EFS was defined as:

- Progressive disease that precluded RC
- Recurrence after RC
- Date of expected surgery in patients who did not undergo RC
- Death from any cause

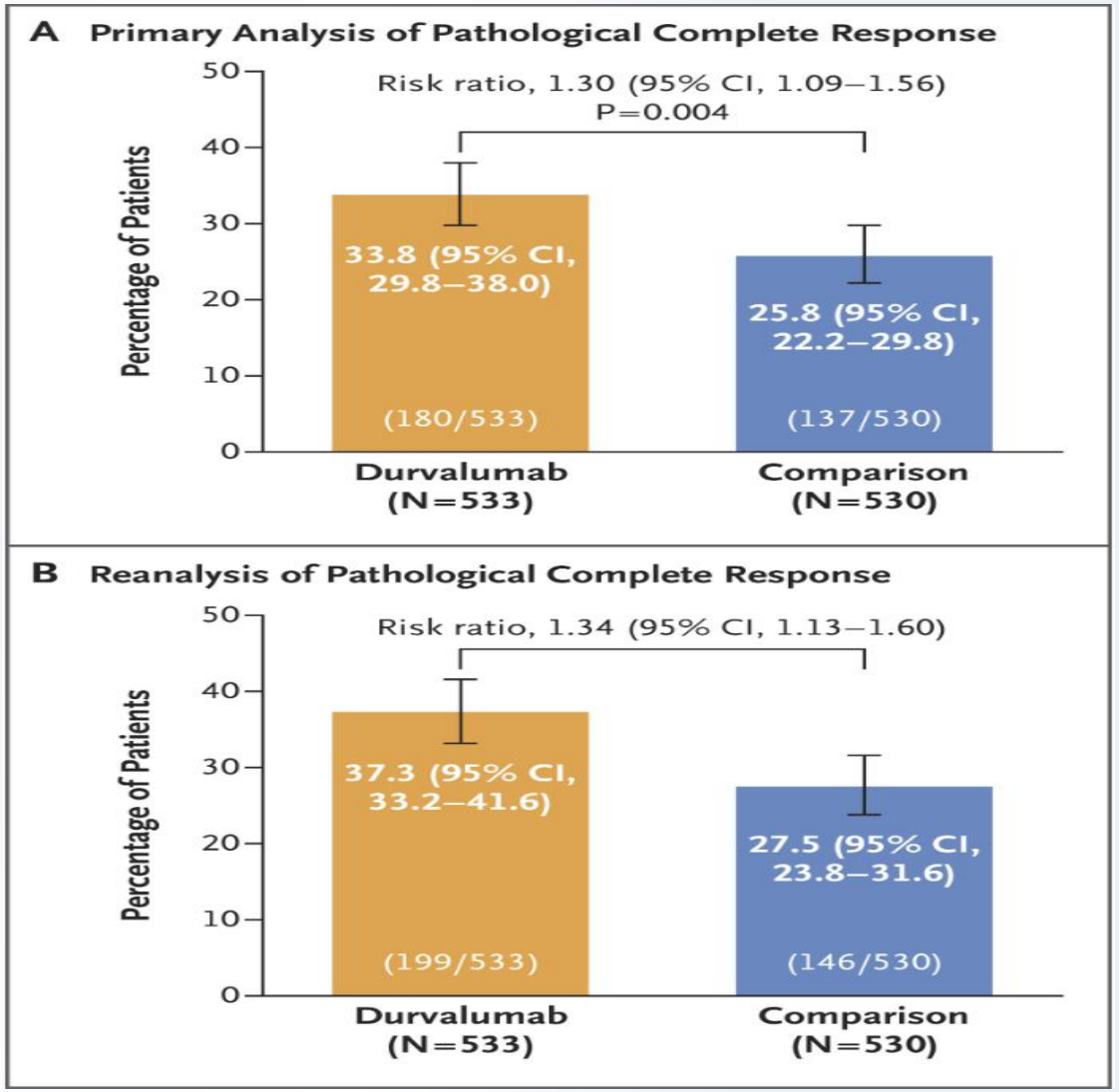
Other endpoints (not reported here): DFS, DSS, MFS, HRQoL, 5-year OS

Slide credit: ESMO 2024

Why NIAGARA Changed Practice?

Statistically significant and clinically meaningful improvement in:

- EFS: HR 0.68 CI 0.56-0.82 p<0.0001
- OS: HR 0.75 CI 0.59-0.93 p=0.0106
- 10% improvement in pathologic complete response rates
- No delay to surgery



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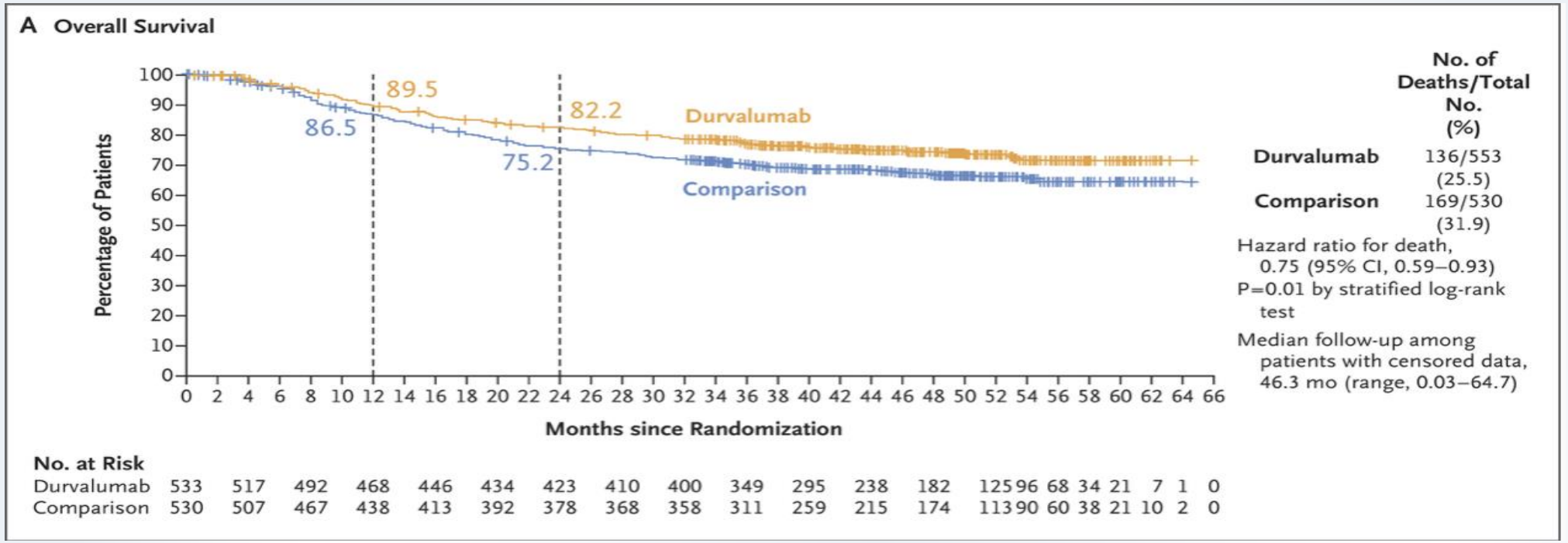

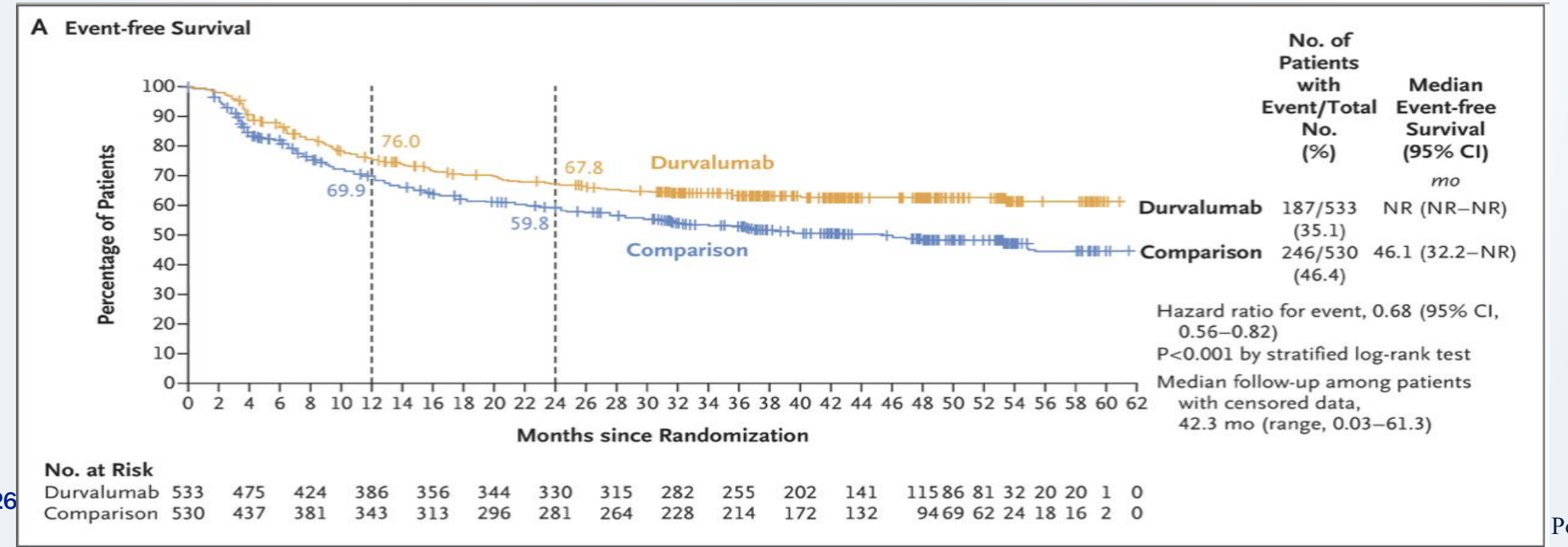

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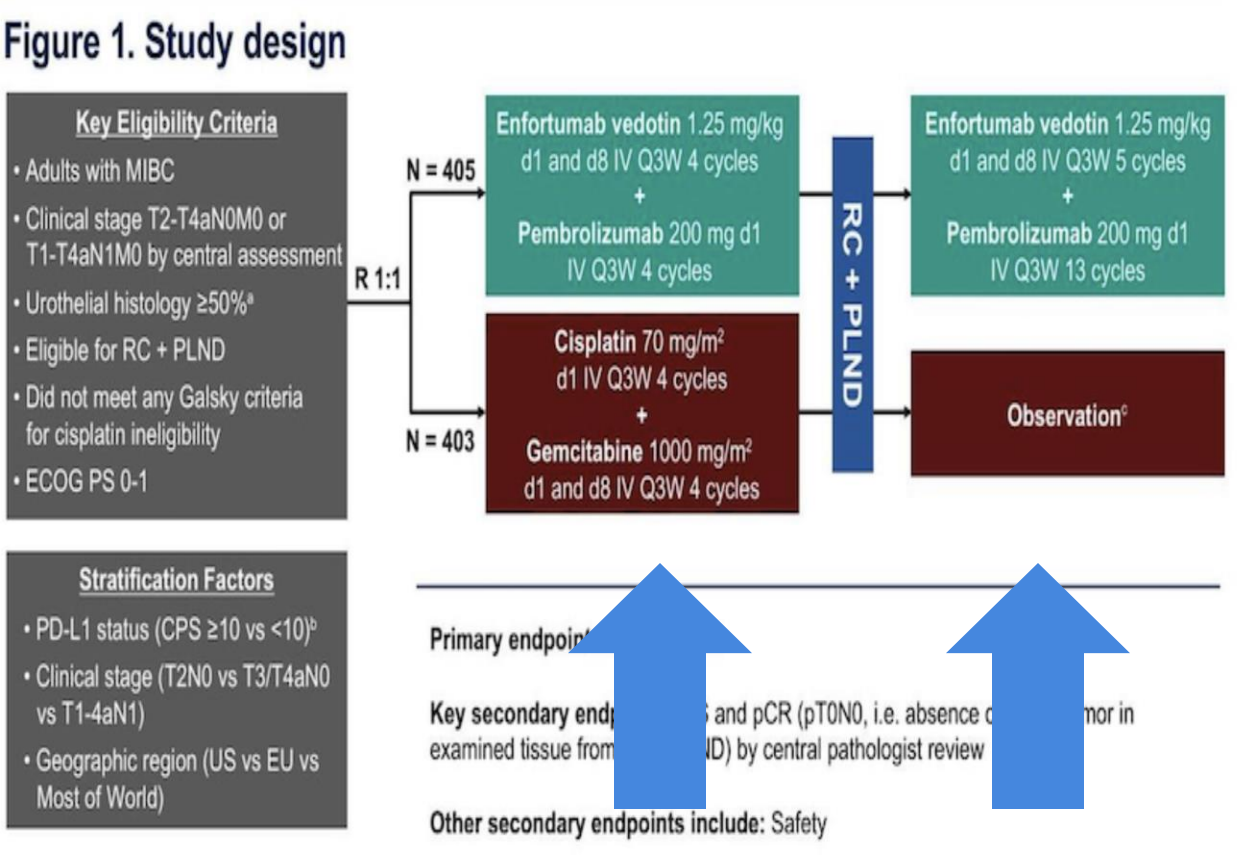
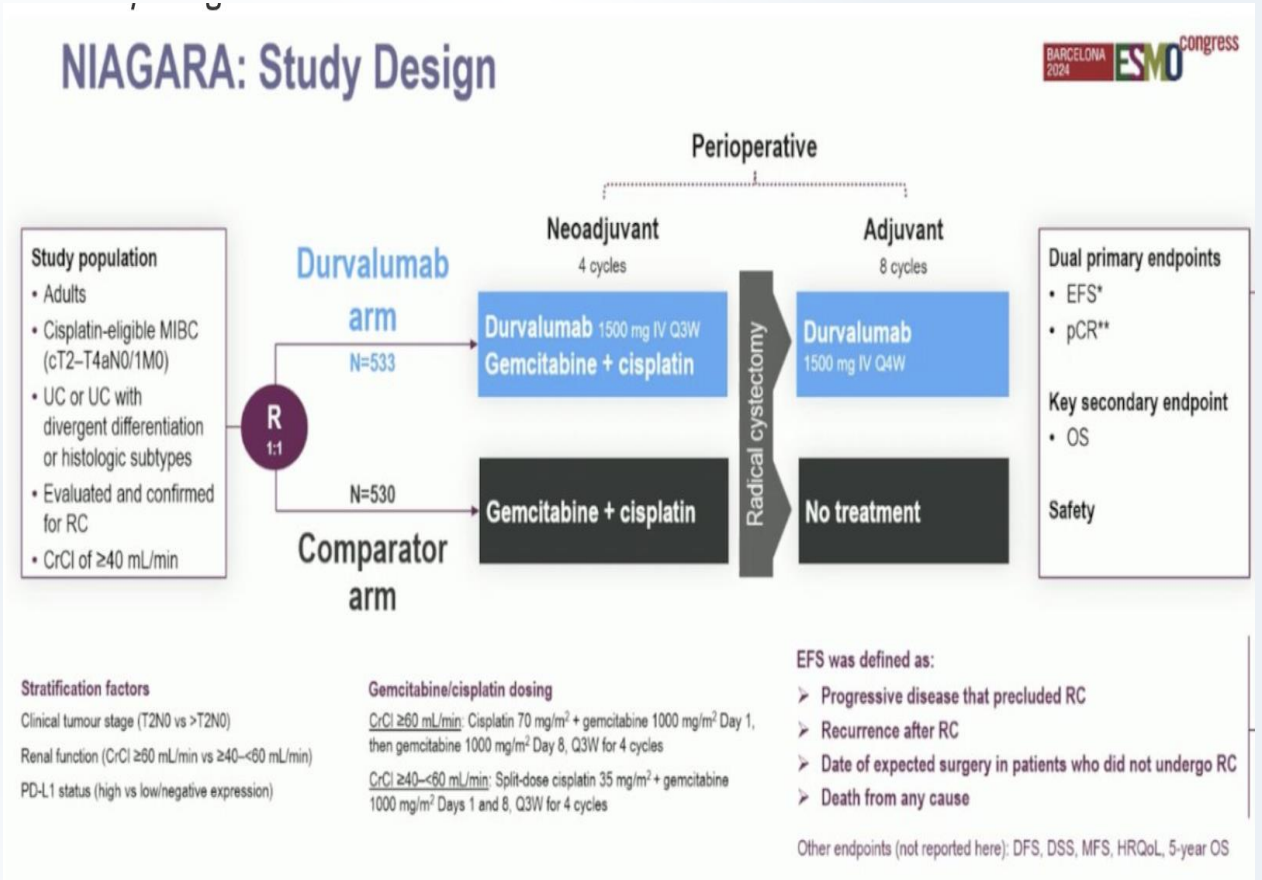
The Missing Head-to-Head Trial…

KEYNOTEB15/EV-304



NIAGARA



Both regimens beat GC alone, but they have never been compared…

Are we comparing the same patients?

NIAGARA

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Durvalumab (N = 533)	Comparison (N = 530)
Age — yr		
Median (range)	65 (34–84)	66 (32–83)
≥75 — no. %	58 (10.9)	63 (11.9)
Sex — no. (%)		
Male	437 (82.0)	433 (81.7)
Female	96 (18.0)	97 (18.3)
Race — no. (%)†		
White	354 (66.4)	358 (67.5)
Asian	152 (28.5)	145 (27.4)
Black	6 (1.1)	4 (0.8)
Other	7 (1.3)	1 (0.2)
Missing data	14 (2.6)	22 (4.2)
Region — no. (%)		
Europe	265 (49.7)	287 (54.2)
Asia	151 (28.3)	143 (27.0)
North America and Australia	66 (12.4)	62 (11.7)
South America	51 (9.6)	38 (7.2)
ECOG performance-status score — no. (%)‡		
0	418 (78.4)	415 (78.3)
1	115 (21.6)	115 (21.7)
Smoking status — no. (%)		
Current	122 (22.9)	130 (24.5)
Former	255 (47.8)	269 (50.8)
Never	144 (27.0)	120 (22.6)
Missing data	12 (2.3)	11 (2.1)
Histologic type — no. (%)§		
Invasive urothelial carcinoma, not otherwise specified	457 (85.7)	441 (83.2)
Urothelial carcinoma with squamous differentiation	38 (7.1)	49 (9.2)
Urothelial carcinoma with glandular differentiation	10 (1.9)	15 (2.8)
Urothelial carcinoma with other histologic subtype	28 (5.3)	25 (4.7)
Tumor stage — no. (%)§¶		
T2N0	215 (40.3)	213 (40.2)
Higher than T2N0	318 (59.7)	317 (59.8)
Regional lymph-node stage — no. (%)§		
N0	505 (94.7)	500 (94.3)
N1	28 (5.3)	30 (5.7)
Creatinine clearance — no. (%)		
≥60 ml/min/1.73 m²	432 (81.1)	430 (81.1)
40 to <60 ml/min/1.73 m²	101 (18.9)	100 (18.9)

EV304

Characteristic, n (%)	EV + pembro N = 405	Cis + gem N = 403
Median age (range), years	66.0 (35–83)	66.0 (37–85)
≥65 years	247 (61.0)	247 (61.3)
Male	327 (80.7)	327 (81.1)
ECOG PS		
0	317 (78.3)	310 (76.9)
1	88 (21.7)	93 (23.1)
Region		
United States	59 (14.6)	59 (14.6)
European Union	206 (50.9)	205 (50.9)
Most of world	140 (34.6)	139 (34.5)
PD-L1 CPS		
≥10	233 (57.5)	230 (57.1)
<10	171 (42.2)	173 (42.9)
Missing	1 (0.2)	0
Tumor stage at baseline (central assessment)[a]		
T2N0	79 (19.5)	77 (19.1)
T3/T4aN0	293 (72.3)	293 (72.7)
T1-4aN1	33 (8.1)	33 (8.2)
Pure urothelial carcinoma histology	370 (91.4)	353 (87.6)
Creatinine clearance		
≥90 mL/min	149 (36.8)	156 (38.7)
≥60 and <90 mL/min	252 (62.2)	245 (60.8)
≥30 and <60 mL/min[b]	4 (1.0)	2 (0.5)

Does Tumor Biology Matter? Variant Histology

Squamous histology:

-
-

Enfortumab Vedotin Plus Pembrolizumab for the Treatment of Locally Advanced or Metastatic Bladder Cancer of Variant Histology

ClinicalTrials.gov ID NCT05756569

Sponsor Emory University

Information provided by Jacqueline Brown, Emory University (Responsible Party)

Last Update Posted 2025-07-28

Recruiting

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UROTHELIAL CARCINOMA

Check for updates

865

Poster Session

Association of urothelial carcinoma with squamous differentiation with Nectin-4 expression and outcomes with enfortumab vedotin (EV) treatment.

Jonas Saal, Niklas Klümper, Stefanie Zschaebitz, Thomas Büttner, Florian Roghmann, Dora Niedersuess-Beke, Friedemann Zengerling, Richard Cathomas,

Background: The Nectin-4 directed antibody-drug conjugate EV has demonstrated high efficacy in metastatic urothelial carcinoma (mUC), but outcomes in patients with divergent histologies remain poorly characterized. Squamous differentiation represents a clinically chal-

patients with squamous histology exhibited inferior clinical outcomes to EV: ORR was lower (20.0% vs 51.6%, p = 0.02), median PFS was 2.8 months vs 6.2 months (HR = 2.52, 95% CI 1.45–4.37, p = 0.001), and median OS was 6.5 months vs 13 months (HR = 2.38, 95% CI 1.26–4.49, p = 0.008). **Conclusions:** Squamous differentiation in advanced urothelial carcinoma is associated with significantly lower membranous Nectin-4 expression and NECTIN4 amplification frequency, corresponding to markedly inferior responses to EV. These findings highlight the critical need for alternative therapeutic targets and novel treatment strategies in this population. Research Sponsor: None.

Toxicity Profile Matters

GC+ Durvalumab (NIAGARA)

- Familiar toxicity profile
- Well established management
- Grade ≳3 TRAE: **40.6%**

EVP (EV-304)

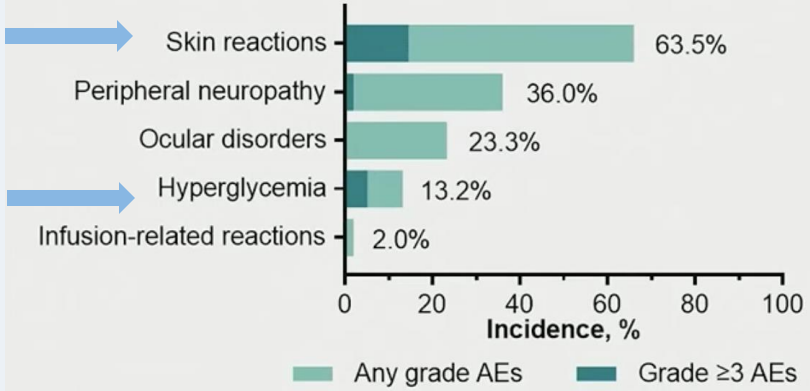
- Grade ≳3 TRAE: **45.5%**
- Unique toxicities:
  - **Severe skin reactions**
  - **Peripheral neuropathy**
  - **Hyperglycemia**
  - **Ocular toxicity**

Treatment AE in EV304

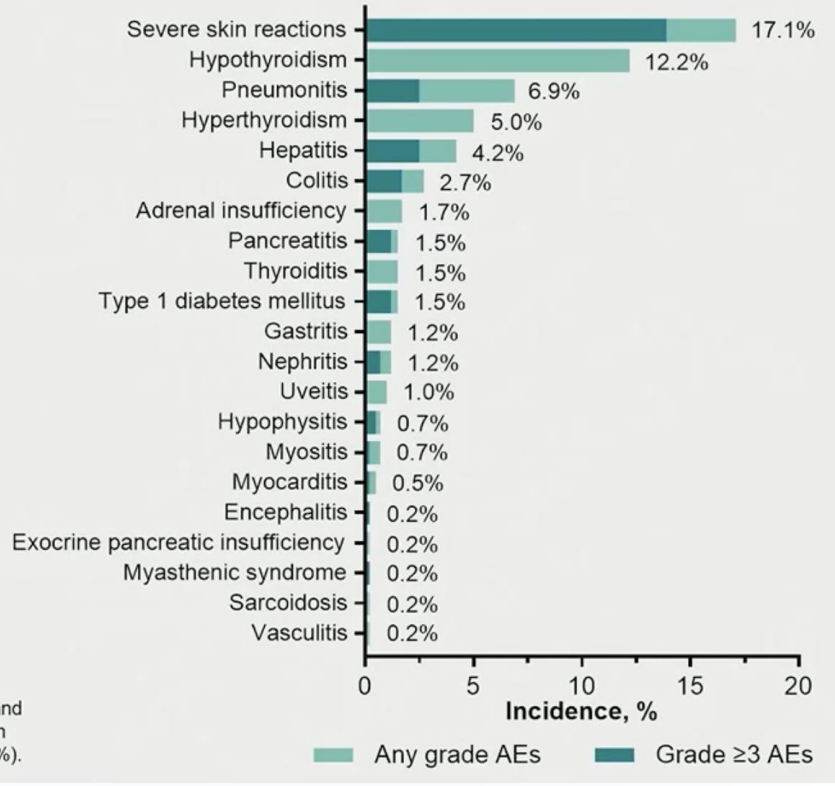
AEs of Special Interest[a]

Safety Analysis Population, EV + Pembro Arm

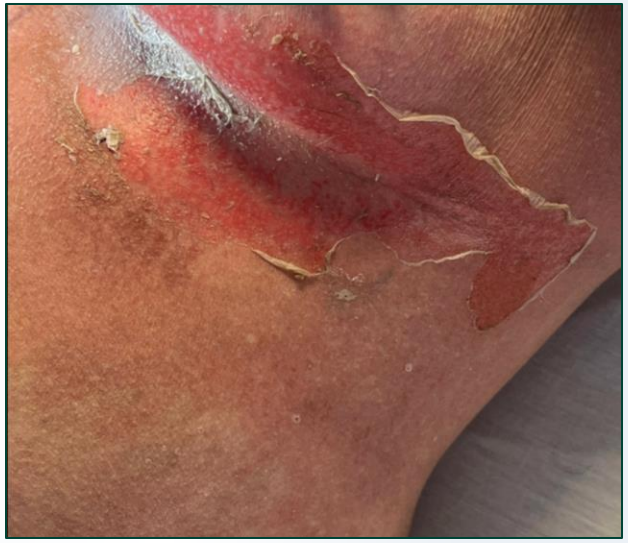
Drug-Related AEs of Special Interest, EV (N = 403)



AEs of Special Interest, Pembro[b,c] (N = 403)



[a]Based on separate prespecified lists of preferred terms (grouped) of known risks associated with EV and pembro treatment. [b]Considered regardless of attribution to study treatment by the investigator. [c]Infusion reactions, reported separately, occurred in 12 pt (3.0%); grade ≥3 infusion reactions occurred in 3 (0.7%).
Data cutoff date: 27 October 2025



EV studies excluded patients with:

- HbA1c ≳8, limited data in diabetics

Galsky GU ASCO 2026 oral presentation
Sport et al J Cutan Pathology 2024

Treatment Burden Matters
Duration? Cost? Global Access?

NIAGARA

- Duration: 4 cy of GC (12w), 8 cy adj durvalumab (32w) = **44w**
- Established chemotherapy
- Lower financial burden
- Widely available globally

EVP

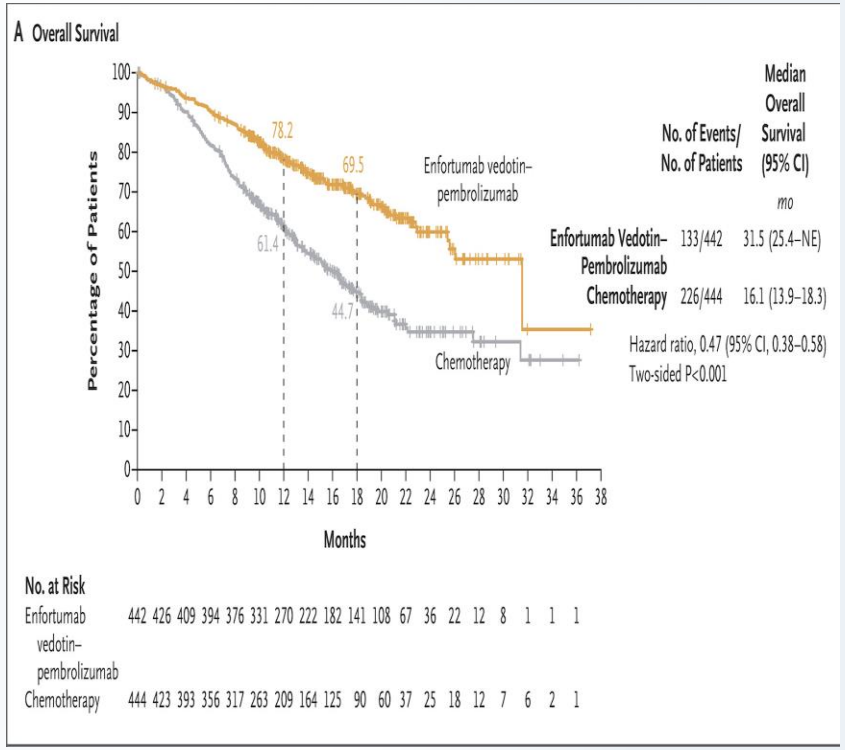
- Duration: 4 cy EVP, 5 cy adj EV and 13 cycles of adj pembro = **27w EVP + 24 weeks pembro = 51w**
- Novel targeted therapy+IO
- Higher financial burden
- Access may be limited

Treatment decisions extend beyond efficacy alone…

An unanswered question: Treatment Sequencing?

- Data from EV-302 evaluating EVP vs SOC chemotherapy in advanced UC improved OS

- Questions we still don't know:
  - Can EVP be effectively reused after perioperative EVP?
  - What is optimal therapy after relapse on adjuvant EVP?
  - Will earlier EV exposure change future treatment options?



Powels et al NEJM 2024

Summary

What we know:

- EVP is a landmark trial
- EVP will become standard for most MIBC
- NIAGARA has OS and clinical utility

What we still don't know:

- EVP vs GC +durvalumab (no head-to head)
- Optimal treatment sequencing
- Best strategy by histology
- Duration of therapy needed? pCR and ctDNA to guide decisions

Who to still consider NIAGARA for?

- Variant histology
- Significant DM or history of skin conditions
- Cost or access limitations

EVP is practice-changing, not practice-uniform

The goal is not to give every patient the same treatment…

it is to give every patient the right treatment