

#guardsymposium2026
X @GuardConsortium



GUARD INTERNATIONAL SYMPOSIUM

GU-Alliance for Research and Development

PRESENCIAL RETRANSMITIDO EN DIRECTO
FACE-TO-FACE AND LIVE STREAMING



16-18 SEPTIEMBRE 2026

Espacio Maldonado, Madrid

#guardsymposium2026
X @GuardConsortium



Future Perspectives on ADCs and Biomarkers

Jonathan Rosenberg, MD

Declarations of Interest

Commercial Interests	Nature of Relationship
Acrivon, Astellas, AstraZeneca, BMS, Eli Lilly, Pfizer	Institutional trial funding
Aktis, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Domain Therapeutics, Eli Lilly, EMD Serono, Generate Biomedicines, Gilead, Greywolf Therapeutics, Johnson and Johnson, Merck, Pfizer, Samsung Bioepis, Summit Therapeutics, Tyra Biosciences	Consulting fees
Pfizer, Bristol Myers Squibb, Astellas, AstraZeneca	Steering Committees
Astellas, Merck	Honoraria
Merck	Travel

The next ADC wave in UC

Target diversification

HER2 and TROP2 now have meaningful clinical validation

EGFR×HER3 and new targets broaden the antigen landscape.

Payload diversification

Topo-I payloads increasingly dominate next-generation programs

New cytotoxics needed

Sequencing treatments

Can an ADC can work after EV?
More important than ADC-naïve disease.

Next-generation Nectin-4 ADCs strategies

Better MMAE engineering

9MW2821 • SYS6002/CRB-701

Site-specific conjugation and linker stability to reduce free payload and widen the therapeutic window.

Payload switch

SHR-A2102 • LY4052031 • LY4101174

Topo-I payloads test whether Nectin-4 remains targetable in those patients where resistance is primarily payload-mediated.

Post-EV proof to date

LY4052031 • LY4101174

Early responses after EV suggest Nectin-4 remains a viable target after front-line EV + pembrolizumab.

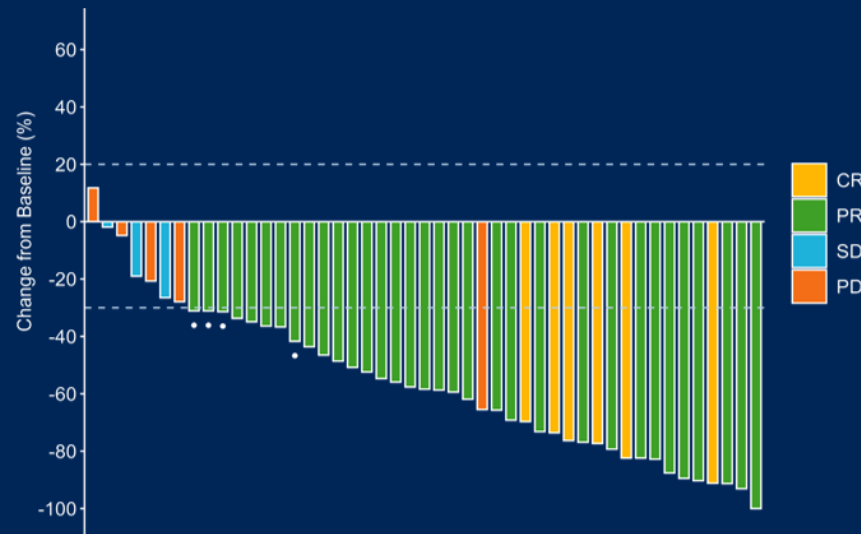
Can we build a better EV?

Bulumtug fuvedotin + toripalimab

Efficacy - ORR

47 patients with la/mUC had at least one tumor assessment after baseline according to RECIST v1.1.

- ORR 83.0% (95%CI 69.2-92.4); DCR 89.4% (95%CI 76.9-96.5) in the overall population.



✓ Treatment-naïve patients for la/mUC (n=40; all BFv 1.25mg/kg combination):

ORR 87.5%, cORR 80.0%, DCR 92.5%

✓ Previously treated patients for la/mUC (n=7; 3 pts for BFv 1.0mg/kg combination, 4 pts for BFv 1.25mg/kg combination):

ORR 57.1%, cORR 42.9%, DCR 71.4%

- BFv 1.0mg/kg (n=3), all chemo progressed only, ORR 33.3%, DCR 66.7%.

- BFv 1.25mg/kg (n=4), all chemo progressed including 3 pts ICI progressed, ORR 75.0%, DCR 75.0%.

Data cut off: 1 Dec 2025

ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease;
• PR, unconfirmed partial response; Chemo, chemotherapy; ICI, immune checkpoint inhibitor.

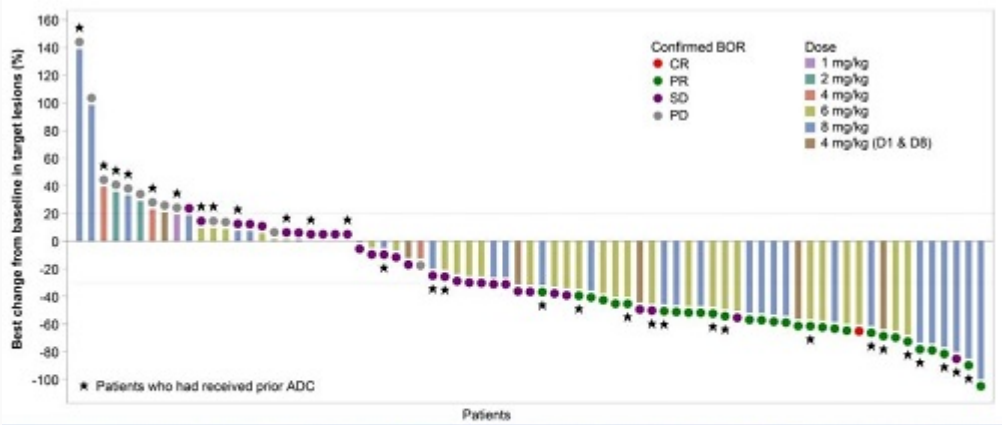
#guardsymposium2026
X @GuardConsortium

More stable linker, but different toxicity profile

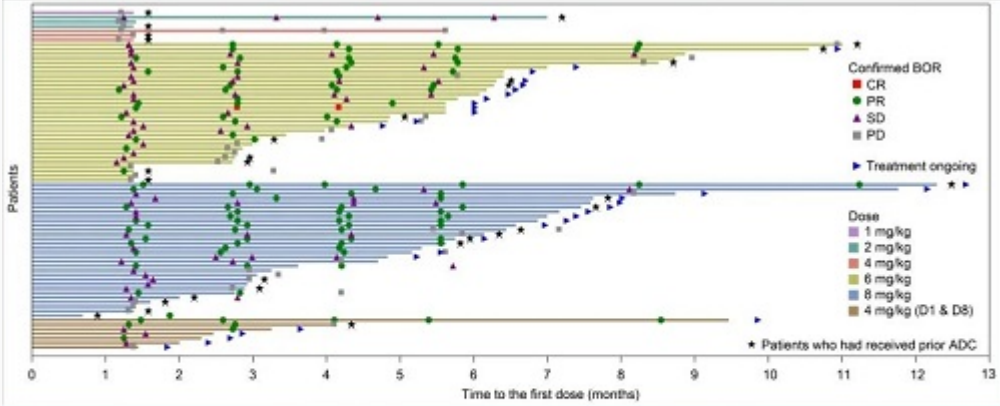
- myelosuppression, more LFT abnormalities, maybe less neuropathy



SHR-A2102 Nectin-4 Topo1 ADC



	6 mg/kg (N=31)	8 mg/kg (N=32)	4 mg/kg (D1 & D8) (N=11)	All (N=81)
ORR, % (95% CI)	41.9% (24.5–60.9)	50.0% (31.9–68.1)	18.2% (2.3–51.8)	38.3% (27.7–49.7)
DCR, % (95% CI)	90.3% (74.3–98.0)	84.4% (67.2–94.7)	54.5% (23.4–83.3)	76.5% (65.8–85.3)



	6 mg/kg (N=13)	8 mg/kg (N=16)	4 mg/kg (D1 & D8) (N=2)	All (N=30)
Response ongoing, n (%)	7 (53.9%)	11 (68.8%)	1 (50.0%)	19 (61.3%)
DoR, median (95% CI), months	7.6 (2.6–8.2)	5.5 (4.2–NR)	NA (2.8–NR)	7.6 (4.2–NR)
6-month DoR rate, % (95% CI)	59.5% (23.5–83.0)	43.5% (8.3–75.7)	50.0% (0.60–91.0)	53.1% (27.8–73.1)

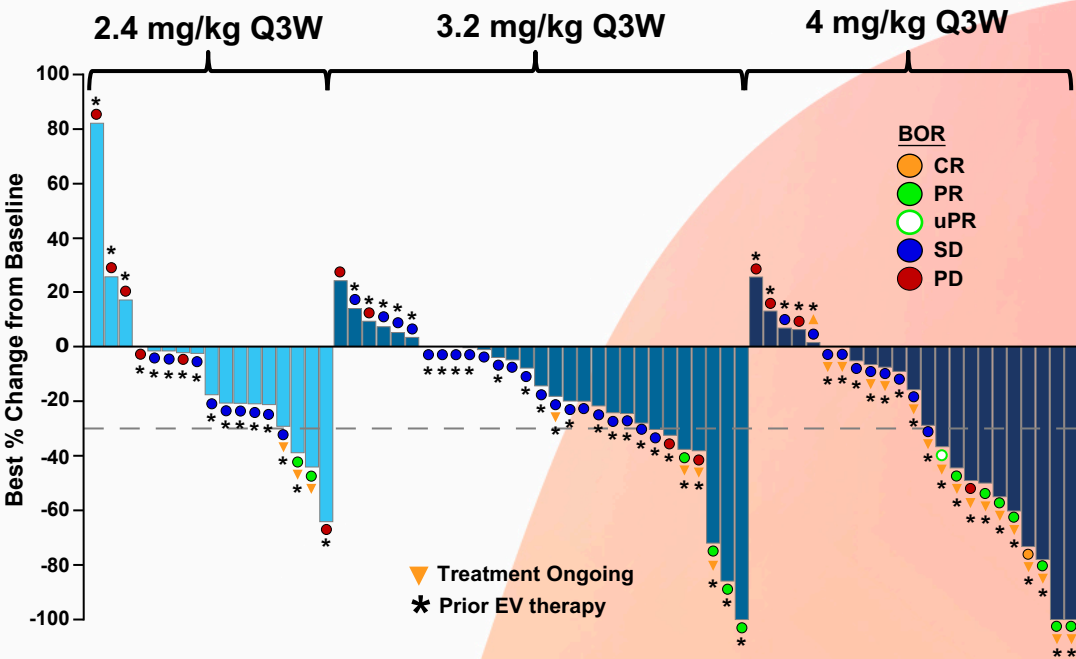
41.9% ORR in prior HER2
ADC-treated patients (DV?)

Efficacy Outcome	All Patients (N = 31)
Best overall response, n (%)	
Confirmed partial response (PR)	13 (41.9%)
Stable disease (SD)	10 (32.3%)
Progressive disease (PD)	7 (22.8%)
Not evaluable (NE)	1 (3.2%)
Confirmed ORR, % (95% CI)	41.9% (24.6 – 60.9)
DCR, % (95% CI)	74.2% (55.4 – 88.1)
Duration of response (DoR)	
Response ongoing, n (%)	7 (53.8%)
Median DoR, months (95% CI)	8.3 (2.8 – NB)
6-month DoR rate, % (95% CI)	52.4% (20.1 – 77.0)

Abbreviations: ORR, objective response rate; DCR, disease control rate;
DoR, duration of response; CI, confidence interval; NR, not reached.

LY4101174: Nectin-4 Topo1i ADC in pre-treated mUC

Efficacy Evaluable Participants ^a	Total Q3W (n=76)	2.4 mg/kg Q3W (n=19)	3.2 mg/kg Q3W (n=32)	4 mg/kg Q3W (n=25)
ORR, % (n)	20 (15)	11 (2)	13 (4)	36 (9)
CR, n (%)	1 (1)	-	-	1 (4)
PR, n (%)	14 ^b (18)	2 (11)	4 (13)	8 ^b (32)
SD, n (%)	40 (53)	9 (47)	21 (66)	10 (40)
DCR, % (n)	72 (55)	58 (11)	78 (25)	76 (19)



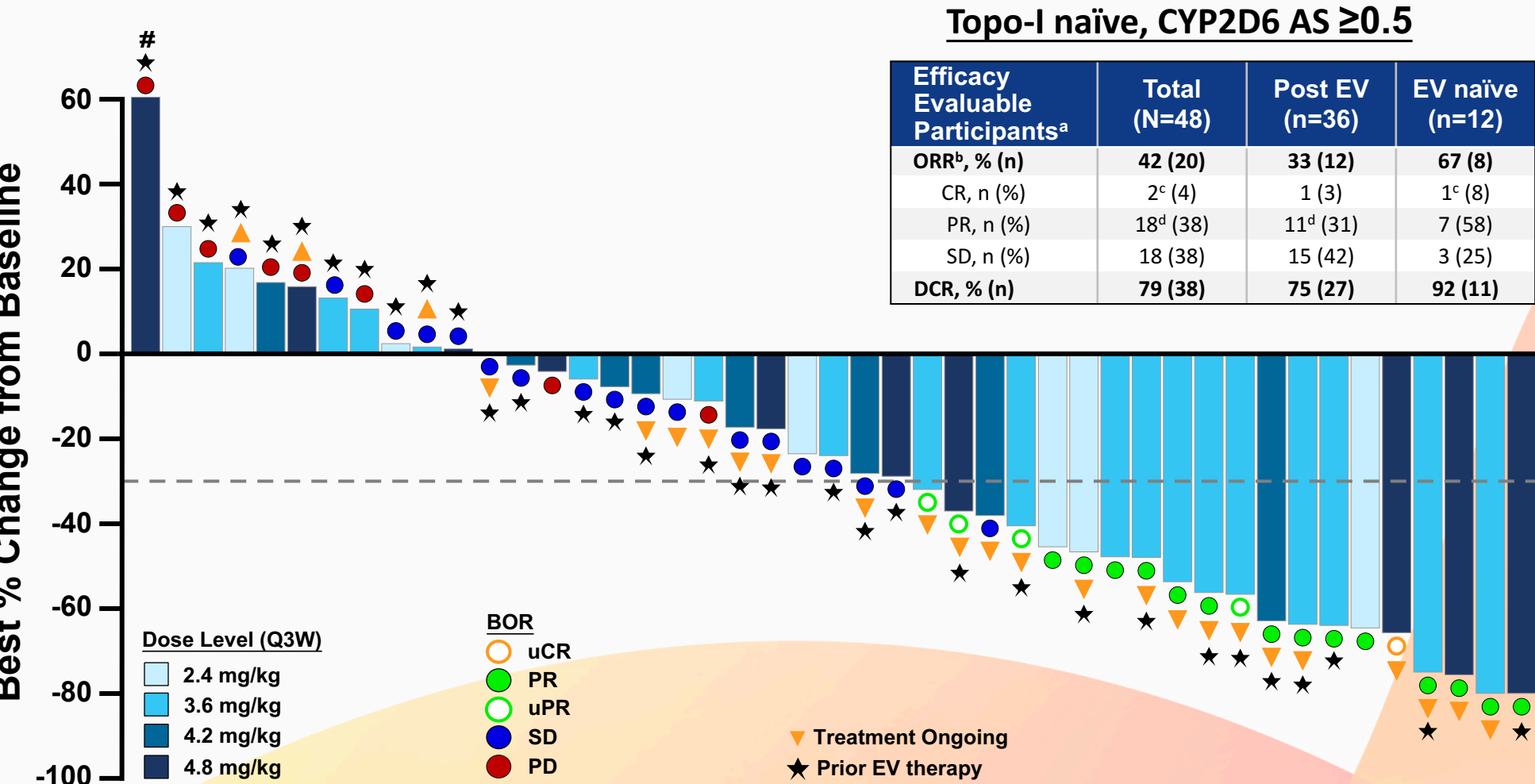
In a heavily pretreated population (93% prior EV), preliminary efficacy suggests Nectin-4 remains an actionable target



While 4 mg/kg demonstrated promising antitumor activity (ORR 36%), grade ≥ 3 hematologic toxicities compromised dose intensity and precluded further dose escalation

NEXUS-01: LY4052301

Nectin-4 TOPO1i: Antitumor Activity in mUC



No confirmed responses were observed in Topo-I ADC pretreated participants (n=18)

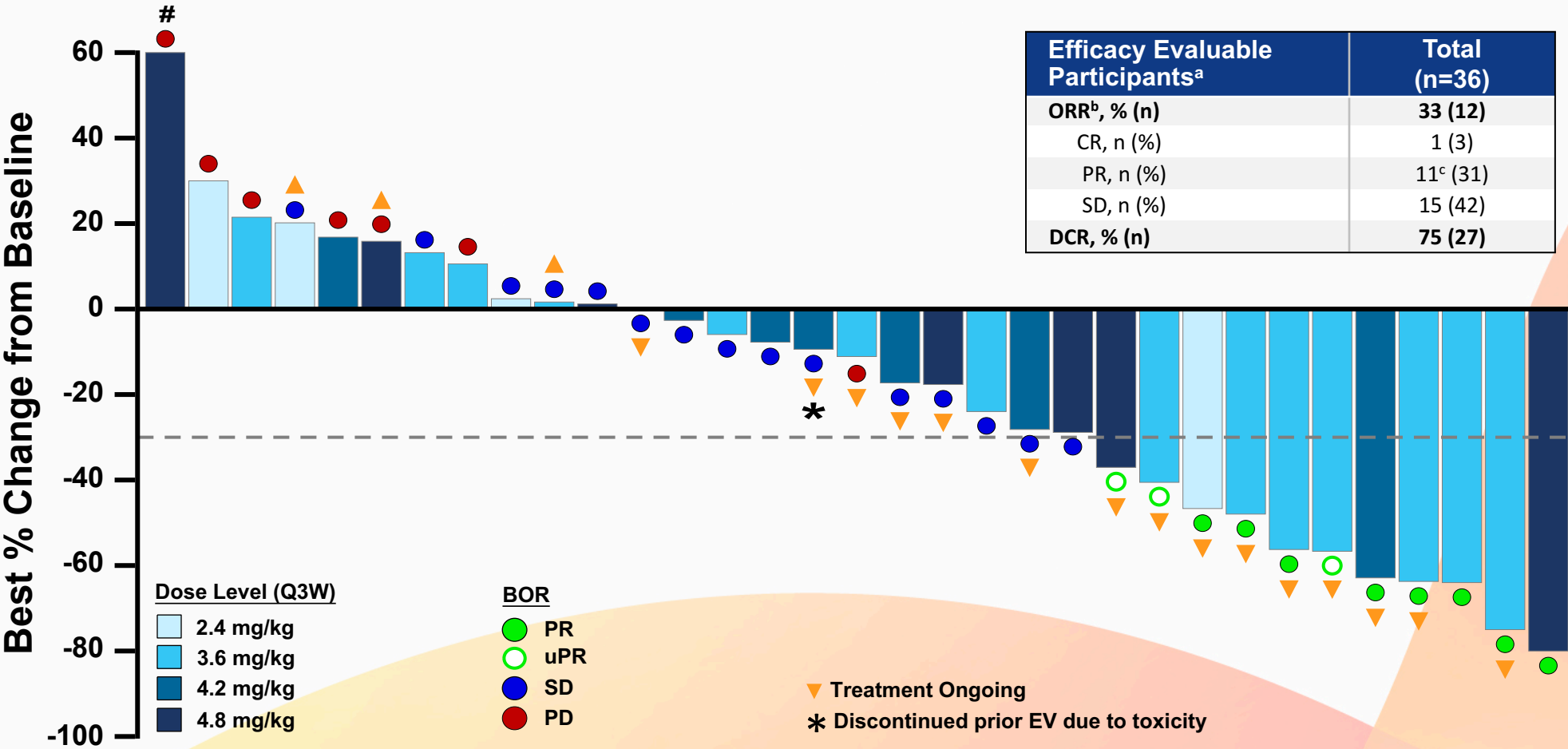
#guardsymposium2026
@GuardConsortium



NEXUS-01: LY4052301

Nectin-4 TOPO1i: Antitumor Activity in mUC Post EV

Topo-I naïve, CYP2D6 AS ≥ 0.5



- LY4052301 demonstrated promising antitumor activity post EV
- ORR 47% (7/15) at 3.6 mg/kg

#guardsymposium2026
@GuardConsortium



Beyond Nectin-4: what targets and agents are in development

HER2 and TROP2 lead the alternative-target landscape; bispecific and novel antigen targets are coming

Agent	Target	Payload	Clinical signal	Reference
Disitamab vedotin	HER2	MMAE	DV + toripalimab: ORR 76.1%; improved OS; validates HER2 in UC First-line strategy, though testing post-EV ongoing	N Engl J Med 2025;393:2324-2337
MRG002	HER2	MMAE	ORR 53%; independent HER2 signal	Eur J Cancer. 2024; 205:114096
SHR-A1811	HER2	Topo-I	UC: ORR 46.2%; DOR 10.1 mo (N=39) Payload-switch question after HER2-MMAE	Signal Transduct Target Ther. 2026; 11:104
Dato-DXd	TROP2	DXd / Topo-I	ORR 25%; 83% prior EV	J Clin Oncol. 2025;43(5_suppl):663
Sac-TMT	TROP2	Belotecan-derived Topo-I	2L ORR 45.5%; ≥3L ORR 26.3%	J Clin Oncol. 2025;43(5_suppl):796
Iza-bren	EGFR × HER3	Novel Topo-I	ORR 44.1%; dual-target concept	J Clin Oncol. 2025; 43(32):3505-3515

MRG002: Trastuzumab vedotin

MMAE ADC

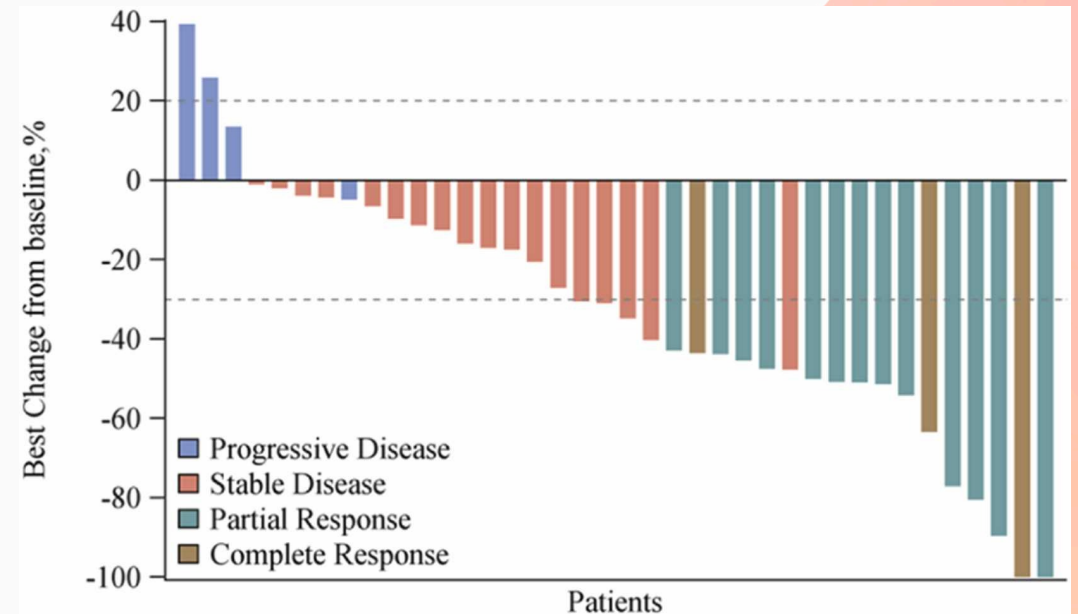
43 patients

HER2 2+/3+

At least 1 prior therapy

No prior ADC exposure

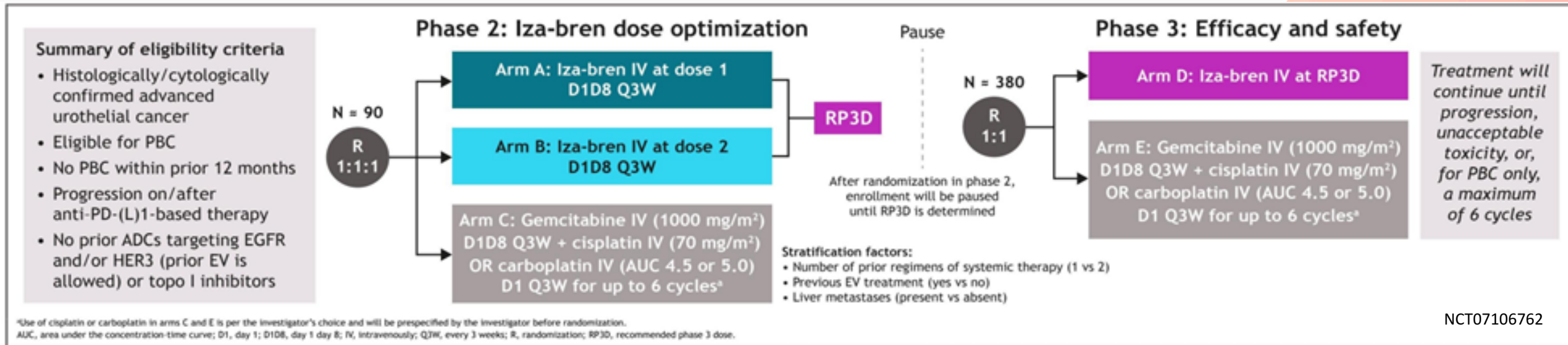
ORR 53.4%



EGFRxHER3

BL-B01D1 Izalontamab brengitecan at 2.2 mg/kg in mUC

80% ORR with 1 prior line of therapy (n=15), 26.3% with more than one line of therapy (n=19)



-100 |

TROPION-UROTHELIAL-04 tests whether a TROP2-DXd-based treatment can improve outcomes in the perioperative EV era

CLINICAL RATIONALE

TROPION-PanTumor03

Dato-DXd + rilvegostomig

1L cis-
ineligible
68.2%

2L post-
platinum
38.9%

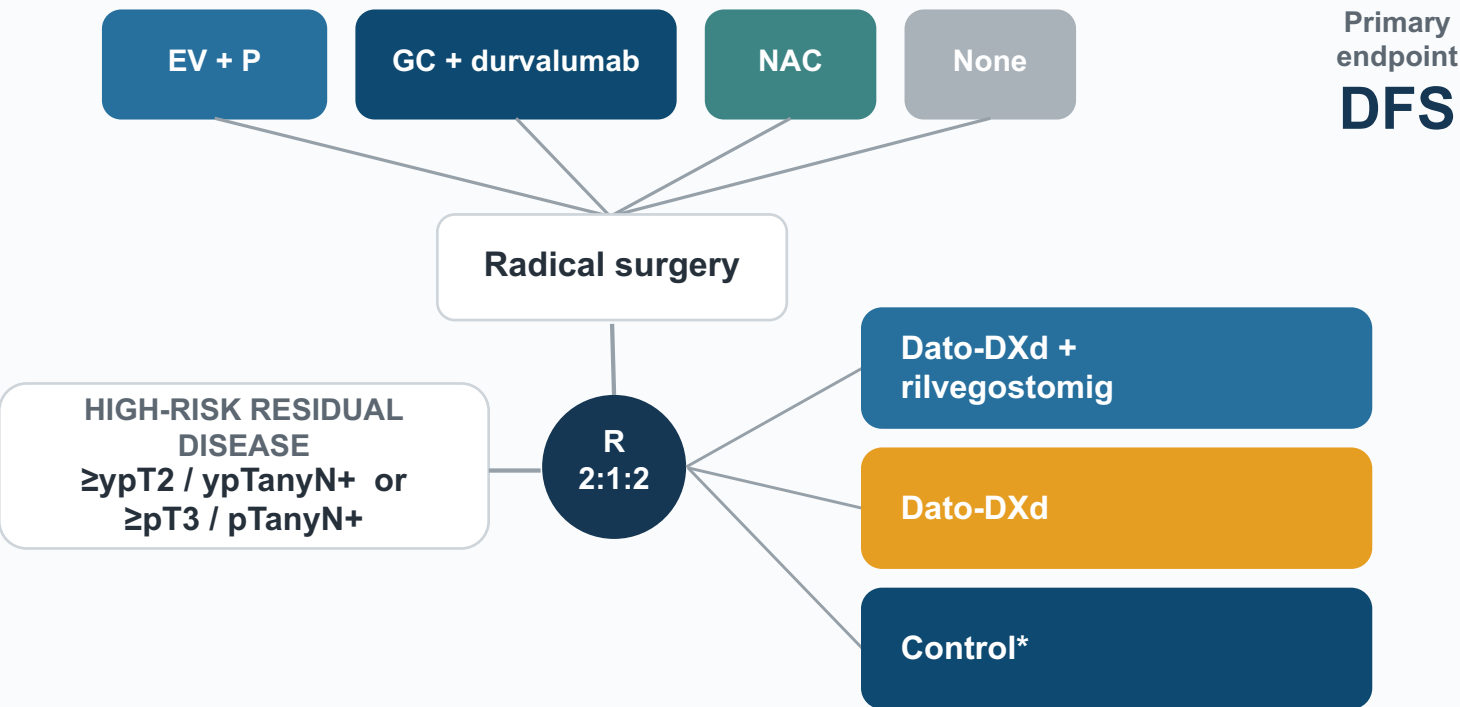
TROPION-PanTumor01

Dato-DXd monotherapy
83% prior EV

ORR 25% BICR
27.5% investigator

TROPION-Urothelial04 | Phase III | N=915 NCT07720284

NEOADJUVANT



*Control may include nivolumab, durvalumab or EV + P based on pre-surgical therapy

**Different target + different payload
(+ different checkpoint)**

The mUC treatment landscape is becoming a target × payload matrix

	Nectin-4	HER2	TROP2	EGFR×HER3	TA-MUC1 / B7-H3
MMAE / auristatin	9MW2821 SYS6002	Disitamab MRG002			
SN-38			Sacituzumab govitecan*		
DXd / exatecan-like Topo-I	SHR-A2102 LY4052031 LY4101174	SHR-A1811	Dato-DXd OBI-992		DS-3939a BGB-C354
Belotecan-derived Topo-I			Sac-TMT		
Novel Topo-I / other	ADRX-0706			Iza-bren	

*urothelial indication withdrawn after phase III OS failure.

Current challenges in post-EV+P ADC development

Target biology

Expression level and heterogeneity

Ability to internalize

Persistence after prior ADC

Tumor vs normal-tissue distribution

Payload biology

Cross-resistance after MMAE

Potential for bystander effect

Marrow, mucosal, pulmonary and neurologic toxicity

ADC engineering

Drug:antibody ratio

Linker stability affecting deconjugation

Free-payload exposure and pharmacokinetics

Development strategy

Post-EV efficacy

Biomarker selection?

Combination feasibility?

Can it move to earlier lines of therapy?

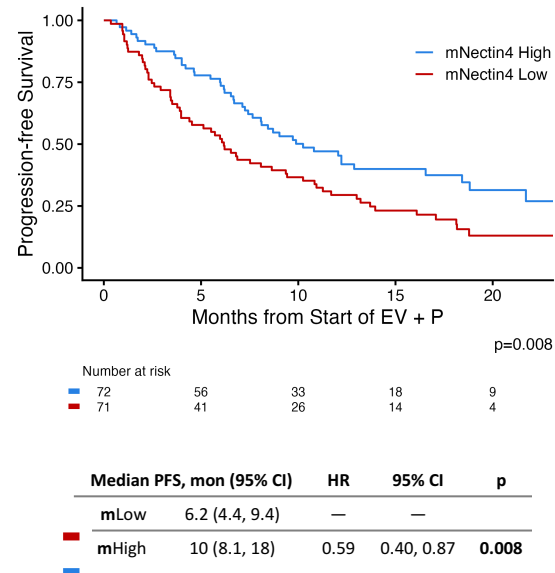
#guardsymposium2026
X @GuardConsortium



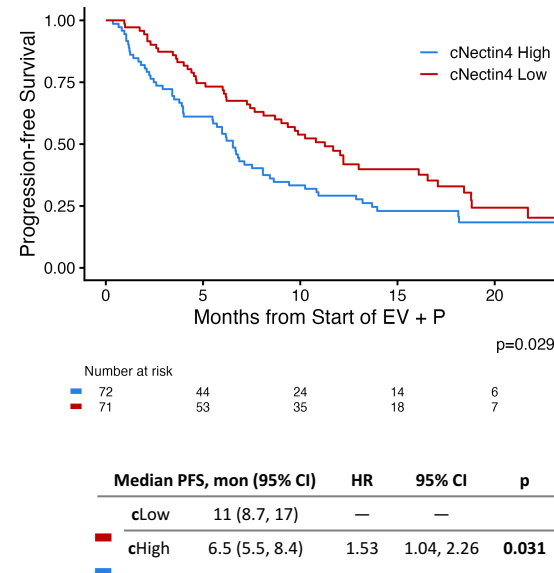
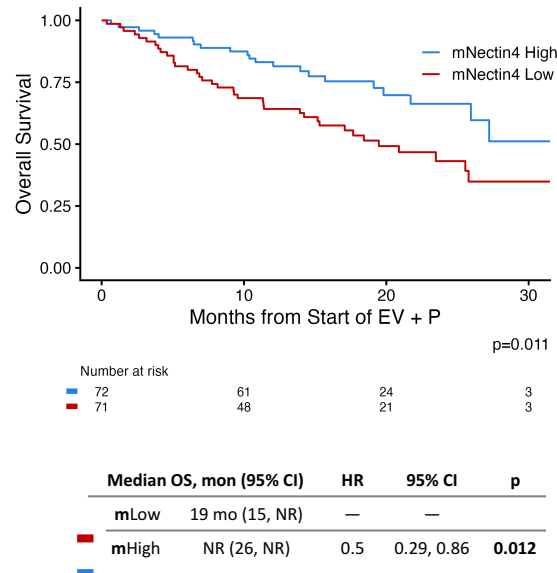
ADC Biomarker strategies in mUC

The Nectin-4 biomarker story may be more subtle and complex

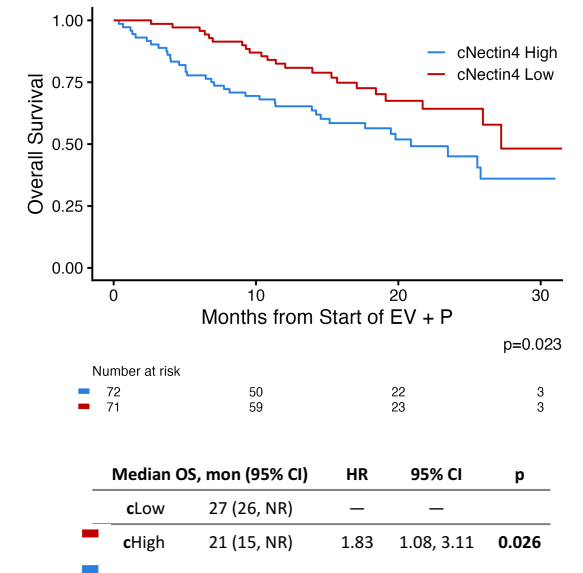
EVP outcome by Nectin-4 localization



PFS and OS by Membranous Nectin-4 expression

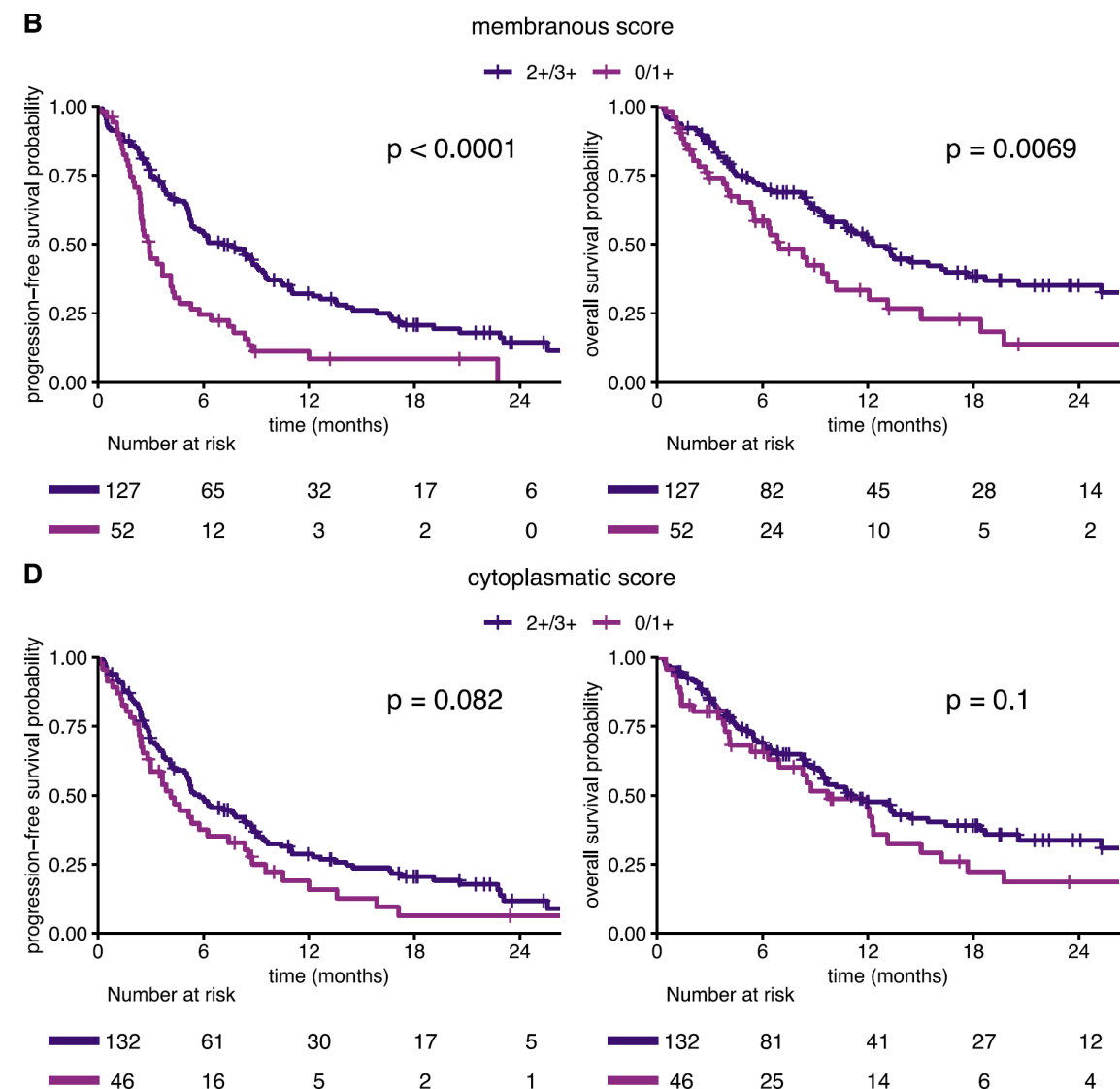


PFS and OS by Cytoplasmic Nectin-4 expression



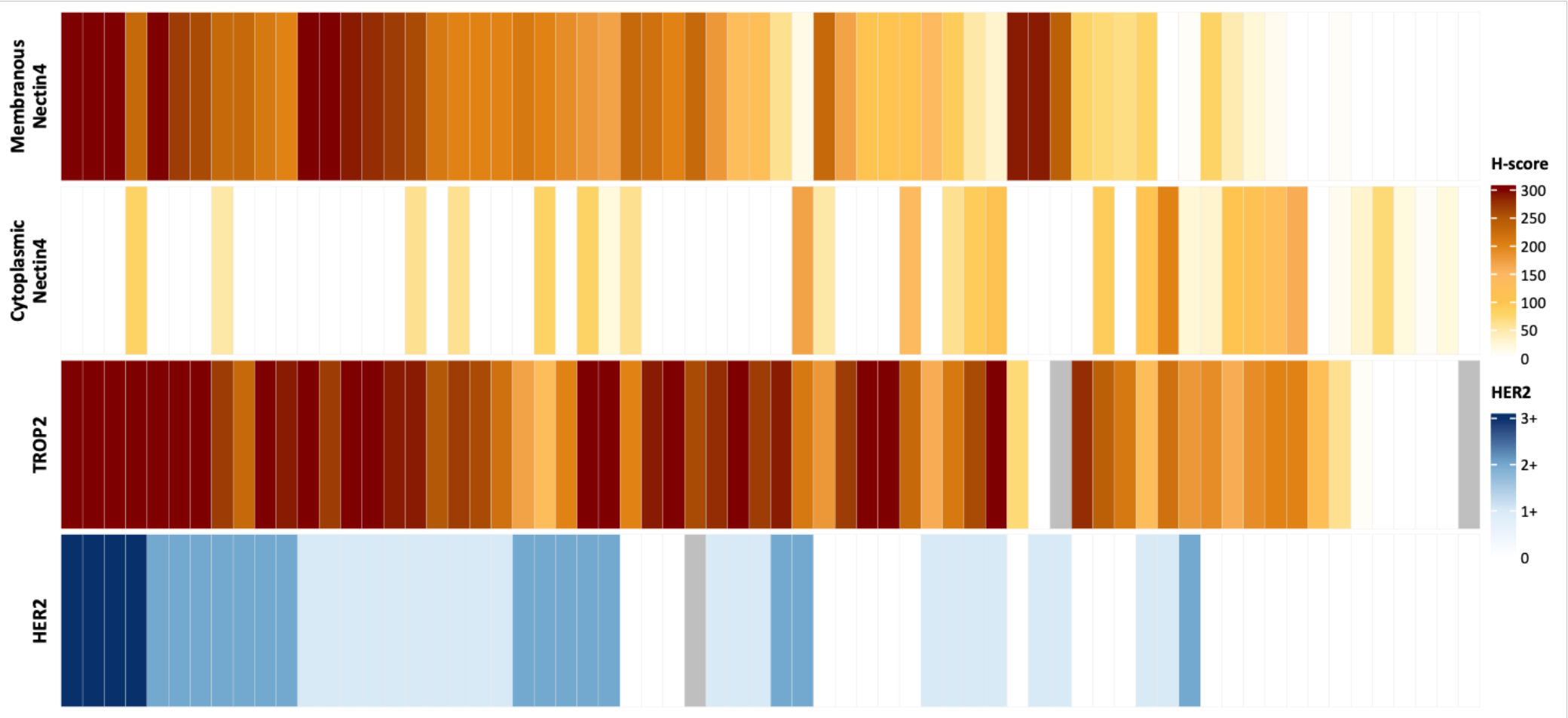
- Cellular localization of Nectin-4 likely appears to matter
- High Nectin-4 on the membrane is associated with PFS and OS improvements compared to low levels
- Cytoplasmic Nectin-4 levels have the opposite relationship

Membranous localization associated with response to treatment with EV monotherapy



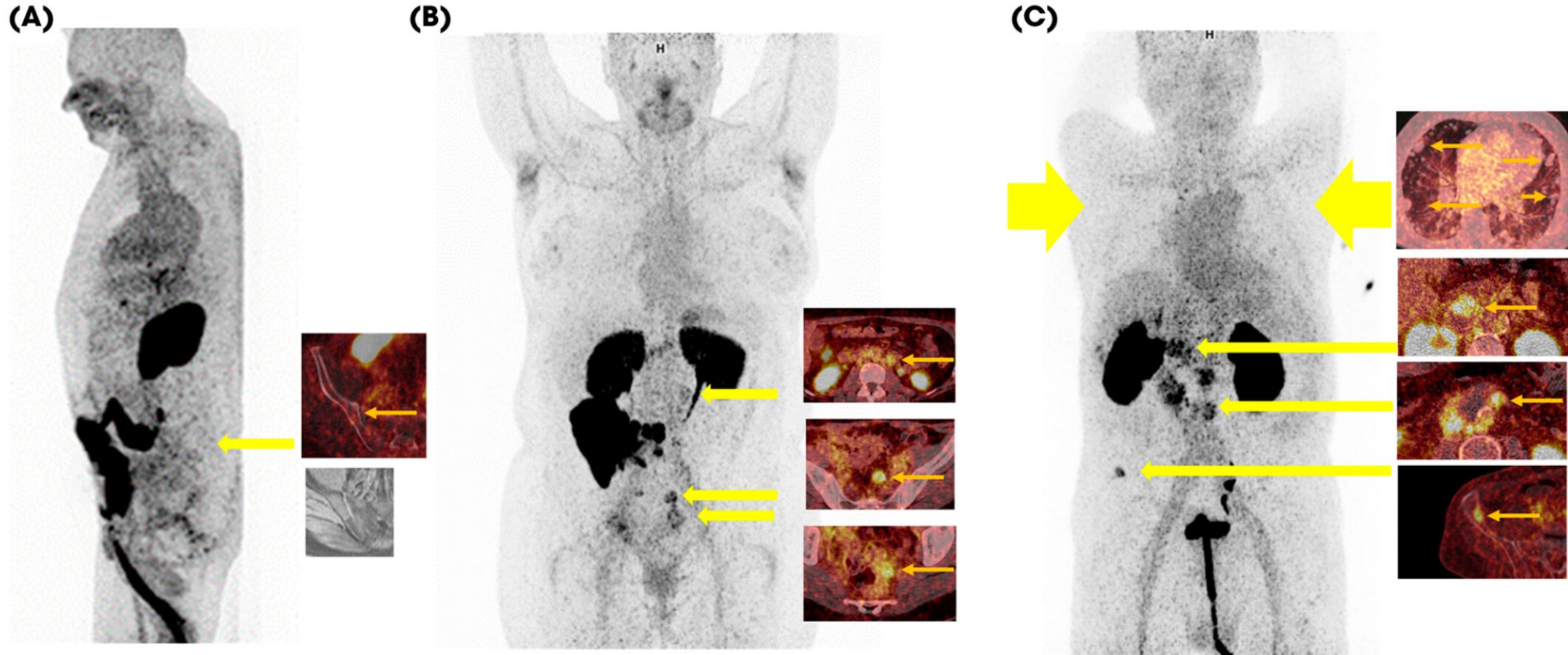
Post-EV/P Biopsies show varied levels of mNectin-4 by IHC

TROP-2 Expression Present Post EV/P



Nectin-4 PET reveals spatial heterogeneity of expression

Whole-body imaging can identify Nectin-4 positive and negative disease within the same patient



A single biopsy does not represent the whole-body Nectin-4 expression landscape

Could molecular imaging help guide ADC sequencing?

Potential future paradigm

Human validation of the imaging biomarker

62 patients / 16 tumor types • ^{68}Ga -N188 SUVmax correlated with membranous Nectin-4 by IHC ($r = 0.458$; $P = .005$) • no correlation with cytoplasmic staining

Baseline
Nectin-4 PET

EV + P

Progression

Repeat
Nectin-4 PET

TARGET RETAINED

Same target + different payload

TARGET LOST OR HETEROGENEOUS

Consider an alternate ADC target

Key question: can dynamic target imaging predict benefit from a subsequent ADC better than archival tissue?

#guardsymposium2026
X @GuardConsortium

Zhang J, et al. *J Nucl Med*. 2024;65(Suppl 1):12S–18S.
Miederer M, et al. *BJU Int*. 2026;137:166–172.



Conclusions

ADC development in urothelial cancer needs to shift from individual drugs toward rational sequencing strategies

EV/P sets a high bar

- Post-EV activity is the clinically relevant question for new ADCs
- ADC-naïve response rates alone may be increasingly difficult to interpret
- Combination approaches are being investigated

Resistance mechanisms may be diverse

- EV resistance does not necessarily equal loss of Nectin-4
- Target biology, payload resistance and ADC engineering may each contribute

There may be >1 rational next ADC

- Retain Nectin-4 but change payload / engineering
- Or switch both target and payload — e.g., TROP2/DXd or HER2/DXd

Biomarker assessment may not be one-time event

- Expression, membrane localization and heterogeneity may all matter
- Archival tissue may not reflect current whole-body target availability
- Molecular imaging could ultimately help guide sequencing

Which ADC should come next, when, and for whom.



Thank you!

