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

Black Boxes in mUC: What to do Beyond ADC-CPI Progression What is the Clinical Evidence?

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

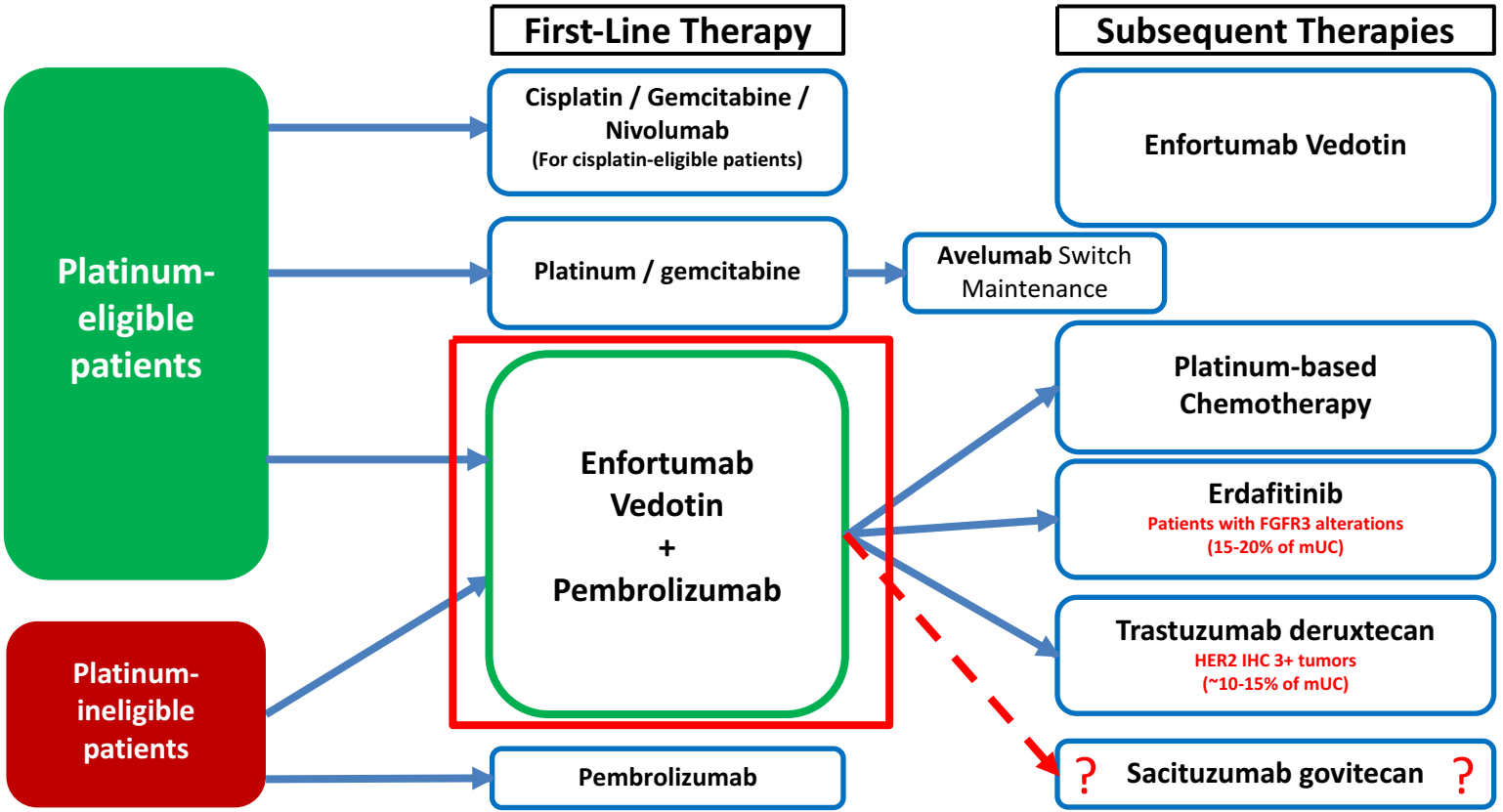
Disclosures

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

Metastatic Urothelial Carcinoma Treatment Landscape in 2025



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Recent Advances in Perioperative Treatment: EV+ICI Combinations Will Likely be Used Earlier

	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 mono	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

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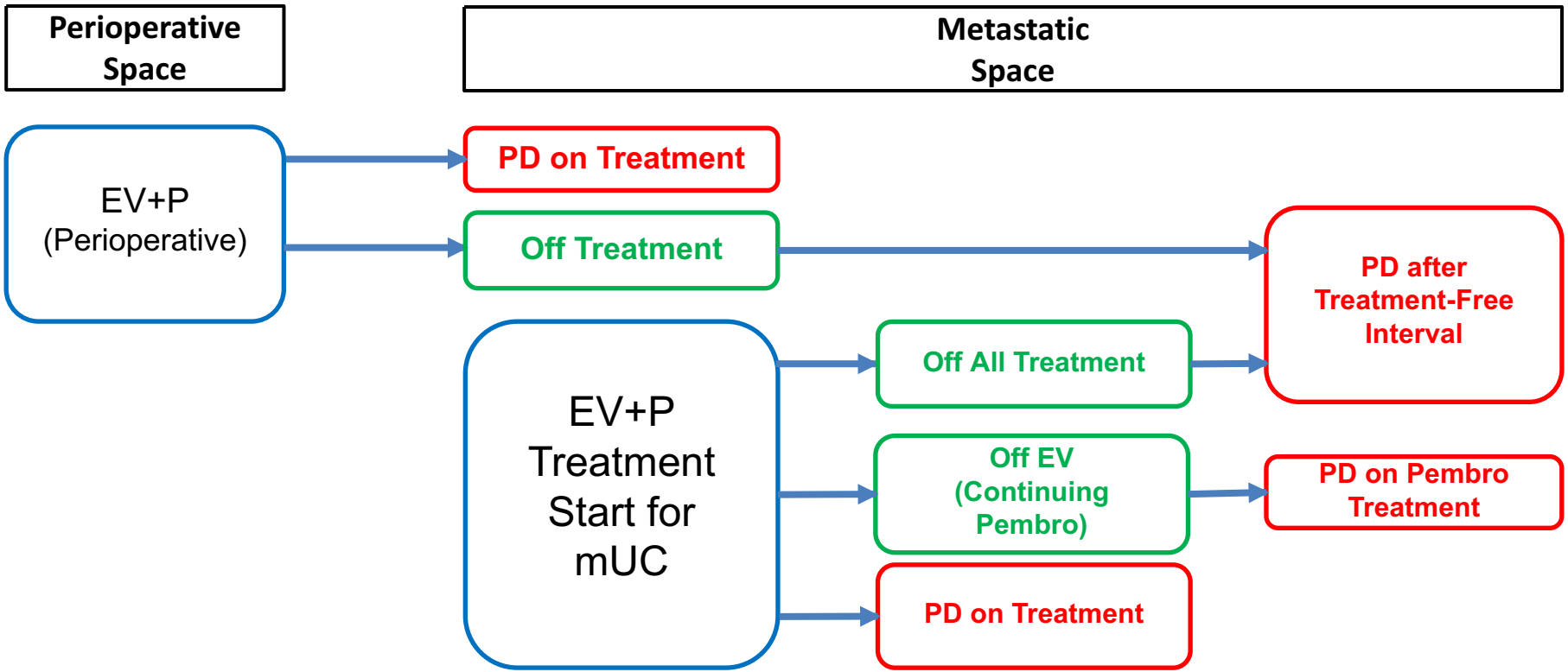
What is the Next Treatment After EV+P for Pateints with mUC Who Need It?

- No prospective data currently
- Retrospective data emerging
- Treatment context matters
- Distinction between prior exposure to EV+P and progression on EV+P?

Patients with Prior EV/P Exposure and/or Progression



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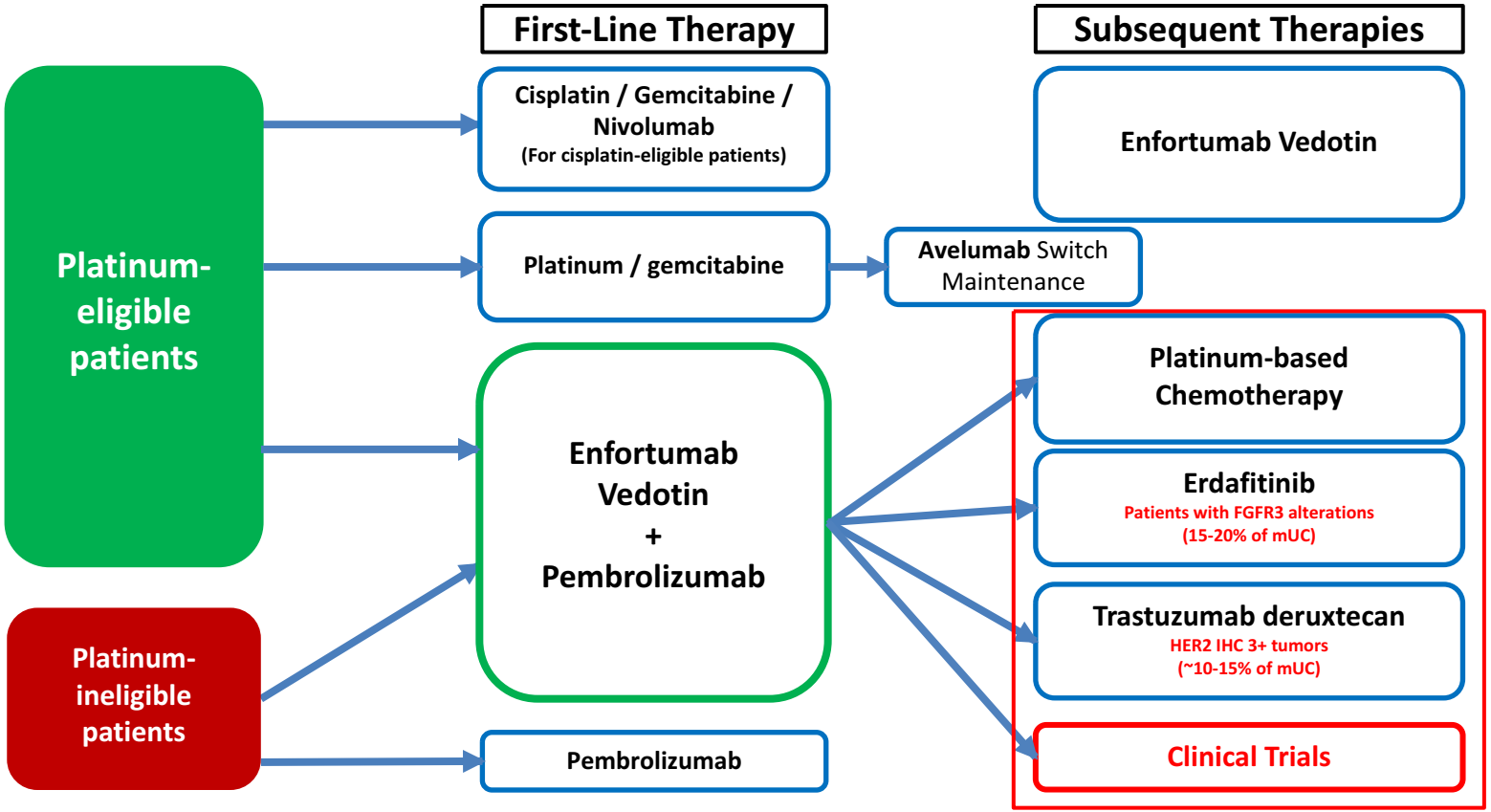

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Options Oncologists Prefer After EV/P: Survey Outcomes

Question: ***If a patient has progression on first-line Enfortumab vedotin + Pembrolizumab, how likely are you to give each of the following options as second-line treatment?***

- Survey responses received from 71 of 227 (31%) bladder-focused oncologists

- After progression on EV/Pembro, most oncologists favored **platinum-based chemotherapy (PBC)** ***without ICI switch maintenance***, or **erdafitinib** (***in FGFR3-altered tumors***) as **2L therapies**
- For **2L clinical trials**, more oncologists favored ***non-ICI containing*** **regimens**

2L Treatment after EVP	Somewhat or very likely to use, % (n)	Somewhat or very unlikely to use, % (n)
Gemcitabine + Cisplatin + Nivolumab	11 (8)	80 (57)
PBC with switch maintenance ICI	31 (22)	62 (44)
PBC without switch maintenance ICI	77 (55)	13 (9)
Erdafitinib for *FGFR3*-altered patients	87 (62)	7 (5)
ICI-combination trial	54 (38)	35 (25)
Non-ICI trial	80 (57)	8 (6)
Continue EVP for progression in 1-2 sites after using local therapy (e.g. radiation)	83 (59)	8 (6)
Sacituzumab*	56 (40)	30 (21)

Chablani et al. ASCO GU 2025

More Expert Opinion: The Uromigos Score

Frist line therapy

Enfortumab vedotin and pembrolizumab

Uromigos score 3.0

Immune checkpoint inhibitor in ADC/chemo ineligible
Uromigos score 1.9

Subsequent therapy

HER-2/FGFR negative or prior targeted therapy

Platinum chemotherapy Uromigos score 2.8

PD

PD (in biomarker positives)

HER-2/FGFR biomarker positive

TDXD in HER-2+ve Uromigos score 2.9

Platinum chemotherapy Uromigos 2.4

Erdafitinib in FGFR3+ve Uromigos score 2.1

PD

Other chemotherapy options

Uromigos score
3 Undisputed Standard
2 Potentially inferior and/or reasonable option
1 limited role
0 avoid

Treatments with scores <1.75 and not included

1st line platinum chemotherapy with sequenced avelumab Uromigos score 1.5

1st line platinum chemo with concurrent nivolumab Uromigos score 1.4

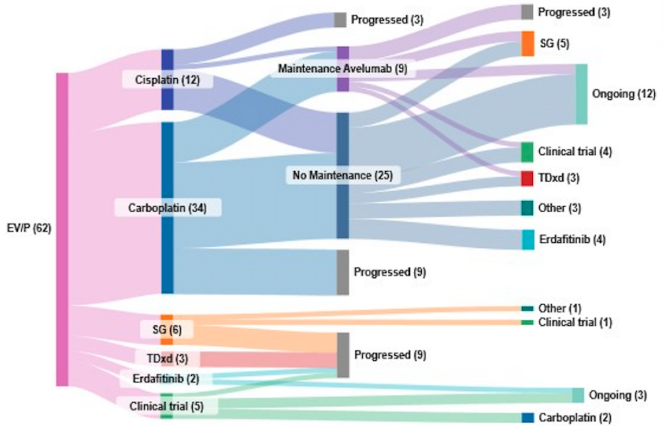
Sacituzumab Govitecan 3rd line Uromigos score 0.7

Slide Courtesy of Tom Powles

Platinum-Based Chemotherapy Following EV+P: Retrospective Data

Among 236 patients treated at MSKCC with 1L EV+P from 10/2018-12/2024, 62 received any subsequent treatment

- 46 patients (74%) received platinum-based chemo



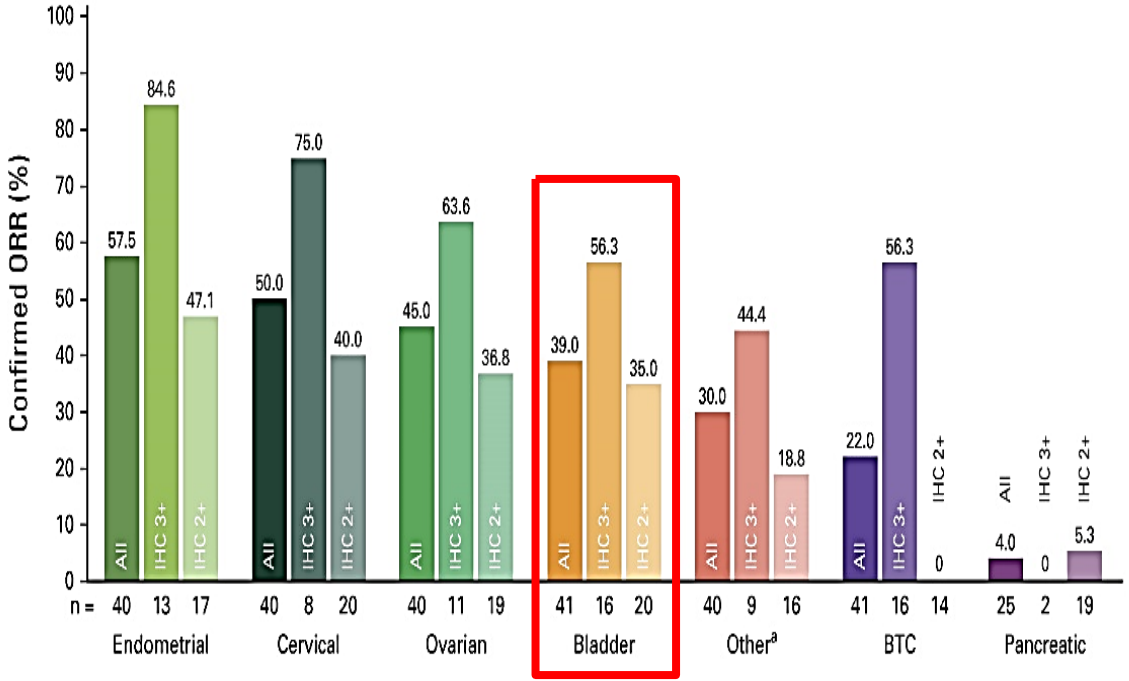
		Any platinum N=46	Carboplatin N=34	Cisplatin N=12
Best response	CR	2 (4.4%)	2 (5.9%)	0 (0%)
	PR	20 (44%)	14 (41%)	6 (55%)
	SD	9 (20%)	8 (24%)	1 (9.1%)
	PD	14 (31%)	10 (29%)	4 (36%)
	Unknown	1	0	1
ORR (95% CI)		49% (34%, 64%)	47% (30%, 65%)	55% (23%, 83%)
Median DOR months (95% CI)		4.6 (3.6, 7.7)	3.8 (2.9, -)	5.7 (4.6, -)
Median PFS months (95% CI)		4.6 (3.6, 5.7)	4.6 (3.6, 6.6)	5.7 (2.4, -)
Median OS months (95% CI)		11 (9.7, 17)	10 (9.7, -)	11 (4.6, -)

	MSKCC (New York, USA)	Samsung Medical Center (Seoul, S Korea)	Dana Farber Cancer Institute (Boston, USA)
Patients (N) with EV/P in 1L	236	37	101
Patients (N) with platinum-based chemotherapy (PBC) in 2L	46	10	13
ORR with PBC	48% (2 CR, 20 PR)	10% (1 PR)	N/A
Clinical benefit rate with PBC (CR,PR,SD)	66% (2 CR, 20 PR, 9 SD)	40% (1 PR, 3 SD)	55%
Median PFS	4.6 months	3.4 months	N/A
Median OS	11.0 months	8.0 months	N/A

Sternschuss et al. ASCO 2025, Galera *et al. ASCO 2025 ePoster*, Kim *et al. ASCO GU 2025*

Trastuzumab Deruxtecan in Treatment-Refractory Patients (HER2-Positive)

DESTINY-PanTumor02: Phase 2 Study of Trastuzumab deruxtecan Monotherapy in HER2-Expressing (IHC 2+/3+) Patients With 1+ Prior Lines of Treatment



Bladder Cohort	All (n=41)	IHC 3+ (n=16)	IHC 2+ (n=20)
Investigator-assessed ORR	39%	56%	35%
Median PFS, mos	7.0	7.4	7.8
Median OS, mos	12.8	13.4	13.1

FDA APPROVED

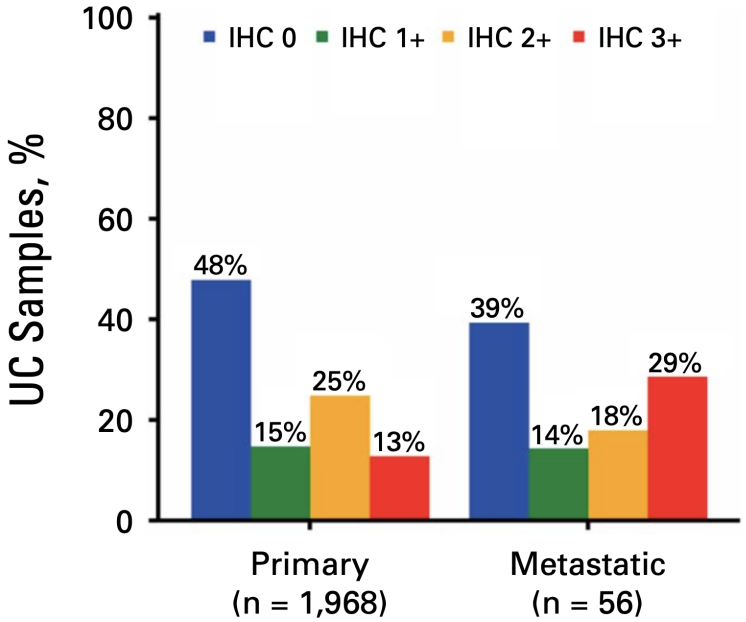
For HER2-positive (IHC 3+) tumors

Meric-Bernstam *et al. JCO* 2024

HER2 Expression in Advanced Urothelial Cancer

Standardized testing with immunohistochemistry (IHC) assay in a large, commercially sourced, global cohort of tumor samples with advanced primary or mUC **(N=2024)**

- **13% with IHC 3+ HER2 expression**
  - Current FDA approval for trastuzumab deruxtecan
- **>50% with HER2 expression (1+, 2+, 3+)**
  - Potential benefit with HER2-targeted therapy



FGFR3-Altered Patients: THOR Trial of Erdafitinib vs Chemotherapy in Pretreated Patients With mUC and *FGFR3* Alterations

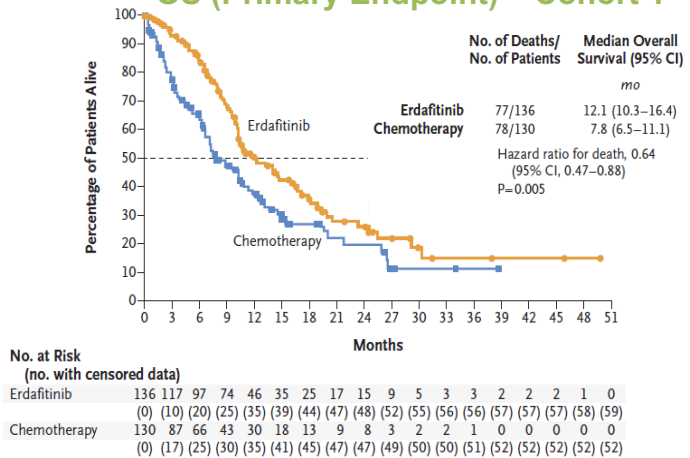
- Unresectable or mUC
- Confirmed progression on/after 1-2 prior therapies
- Select *FGFR* aberrations

Cohort 1
Prior treatment with PD-1/PD-L1 Inhibitor
R 1:1
Arm A: Erdafitinib
Arm B: Docetaxel or vinflunine

Cohort 2
No prior treatment with PD-1/PD-L1 Inhibitor
R 1:1
Arm A: Erdafitinib
Arm B: Pembrolizumab

Primary endpoint: OS
Secondary endpoints: DOR, ORR, PFS, PK, PROs, safety

OS (Primary Endpoint) – Cohort 1

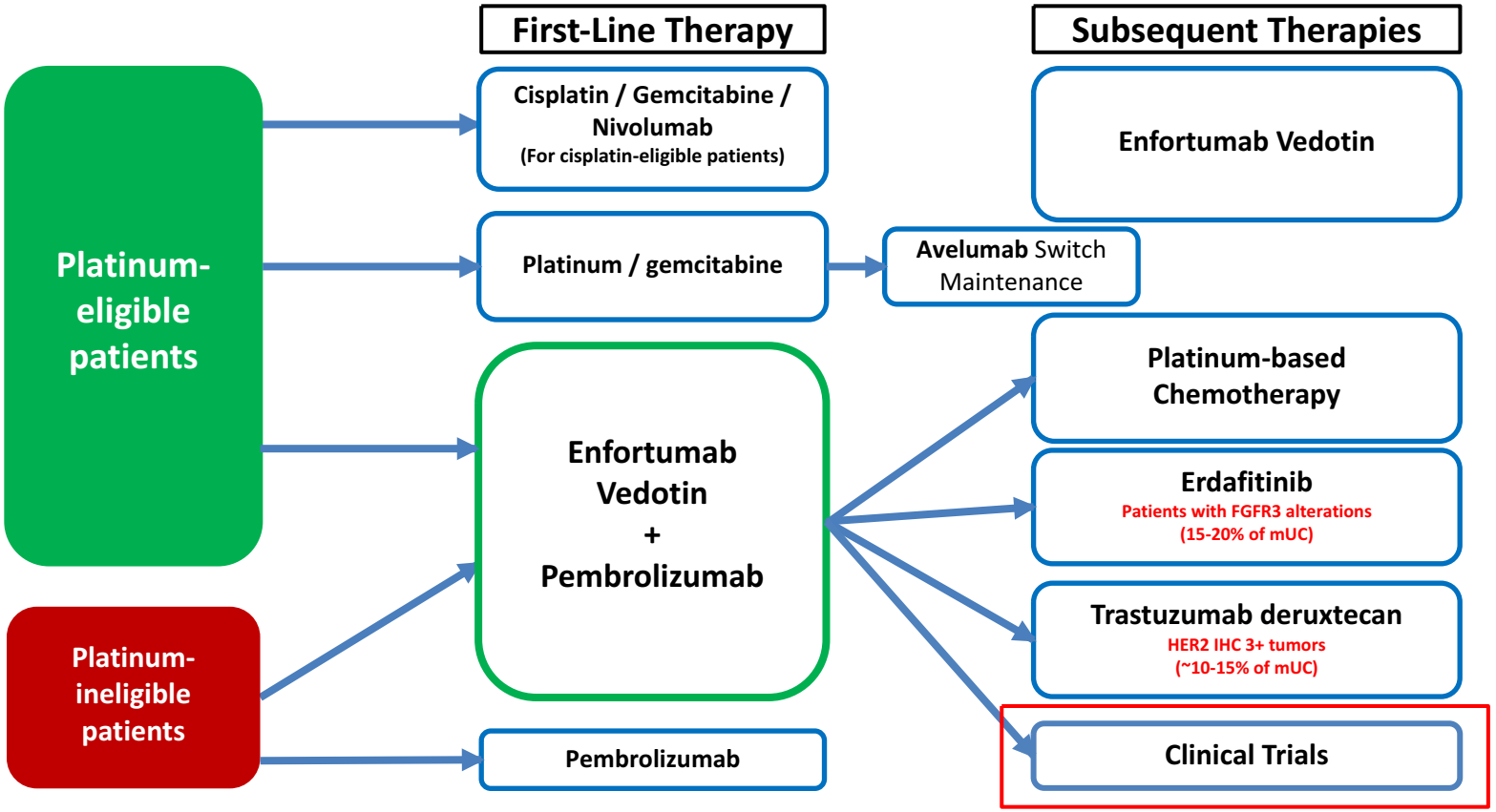


Cohort 1	Erdafitinib (n=136)	Chemo (n=130)
ORR (INV), %	45.6	11.5
CR	6.6	0.8
PR	39.0	10.8
mPFS, months (95% CI)	5.6 (4.4-5.7)	2.7 (1.8-3.7)

Erdafitinib now indicated for patients with **Ia/mUC and susceptible *FGFR3*** alterations whose disease has **progressed after at least one line of prior systemic therapy**

Loriot *et al. NEJM*, 2023

Metastatic Urothelial Carcinoma Treatment Landscape in 2025



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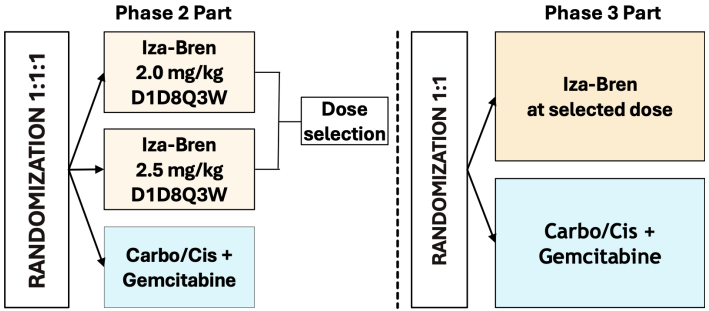
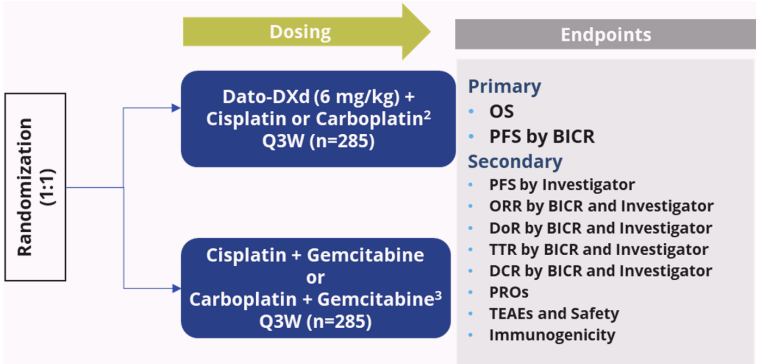
Registrational Trials in the Post EV/P Setting

IZABRIGHT-Bladder01 (HER3/EGFR ADC)

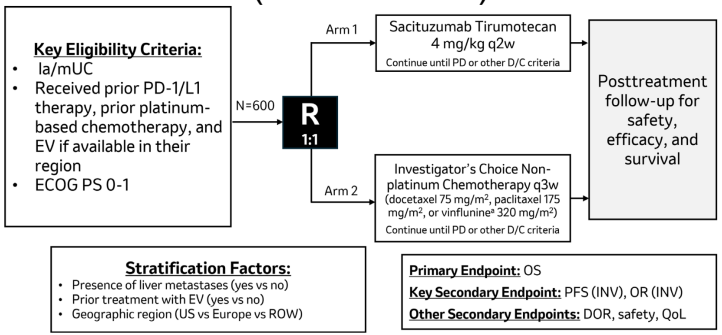


Study design schema of IZABRIGHT-Bladder01: Dual primary endpoints of OS & PFS

TROPION-Urothelial03 (TU03) (TROP2 ADC)



MK2870-031 (TROP2 ADC)



Other Investigational Agents in Post-EV+P Space

Biomarker-Selected

- HER2-Targeted: (Disitamab Vedotin)
- Next-generation FGFR3-inhibitors

Alternate Nectin-4 Targeted Therapies

- Nectin4-Targeted ADCs (Topo1 Payload or Others)
- Nectin4-Targeted RLT
- Dual-targeting ADCs (Nectin4/Trop2)

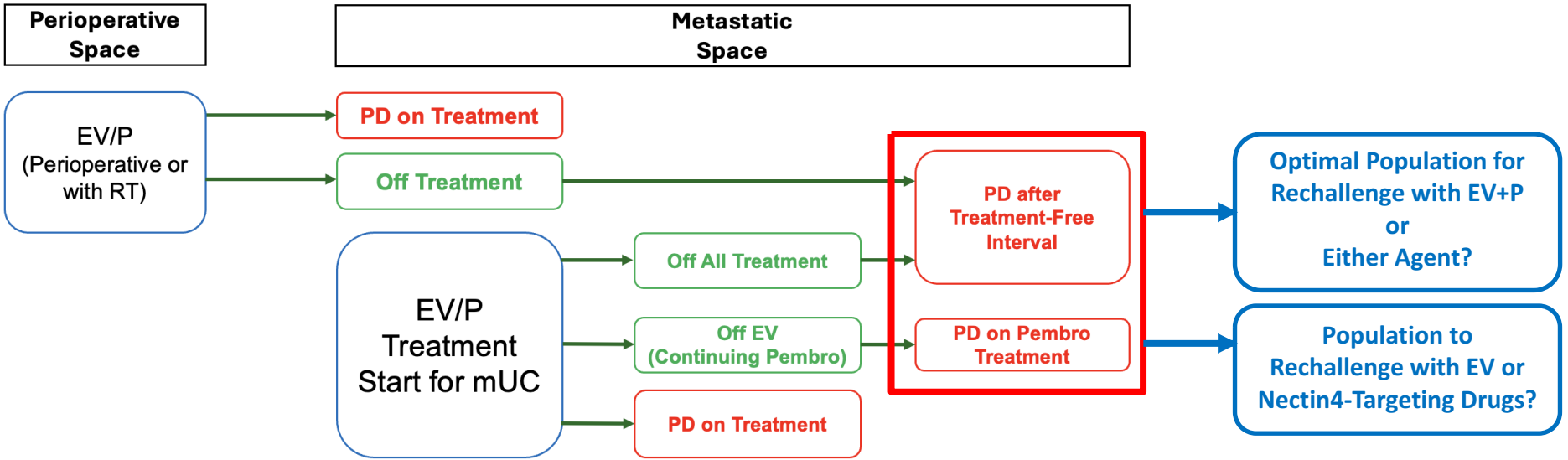
Combinations for ICI Rechallenge

- Pembrolizumab + Nectin4 ADC (Topo1 Payload)
- Pembrolizumab + SG
- Bispecific Antibody (Nectin4/CD28) + Pembrolizumab

Role for Rechallenge with EV +/- P or Similar Agents

- Which patients can be rechallenged successfully?
  - How relevant is time from prior treatment?
- Role for Rechallenge with Nectin4 Targeting Drugs?
- Which patients can be rechallenged with ICI?
- Role for retrospective studies and future clinical trials to answer these questions?

Other Options for Patients Who Have Not Progressed on EV-Based Treatment?



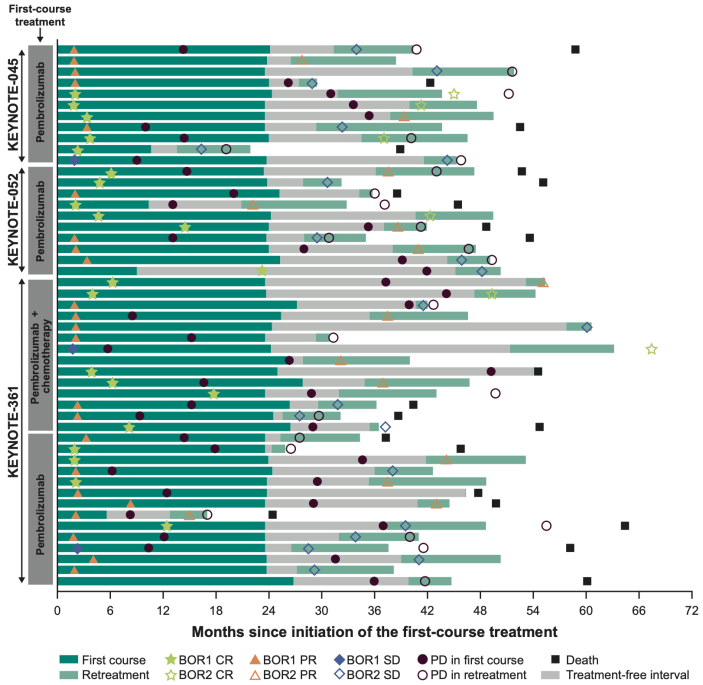
Rechallenge with Pembrolizumab after Prior Pembrolizumab-Based Regimens

Post-Hoc Analysis of KEYNOTE Pembrolizumab Trials (KEYNOTE-045, KEYNOTE-052, KEYNOTE-361)

- Patients with CR or completing full course of treatment (35 cycles; 2 years) could stop Pembrolizumab
- Could then be rechallenged if PD occurred off treatment

49 patients were retreated with Pembro and analyzed

- Median treatment-free interval: 10.7 months
- Retreatment ORR: 41%, DCR: 82%
- Median time to response: 2 months
- From start of retreatment:
  - Median PFS: 9.5 months
  - Median OS: 25.7 months
  - Median DOR (for responders): 14.0 months



- Pembrolizumab rechallenge is effective for patients with prior clinical benefit on Pembrolizumab-based regimens
- This is a highly selected patient population; approach for all patients is unclear

Koshkin et al. *Eur Urol* 2024

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EV+Pembrolizumab Treatment after Prior ICI

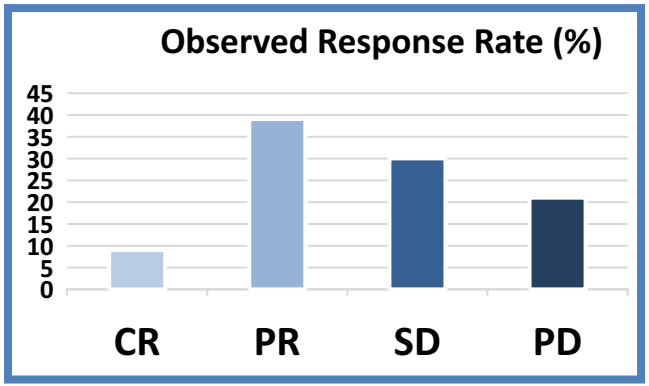
UNITE Study

- Retrospective cohort study
- Investigating outcomes of patients with mUC treated with targeted agents, including EV-based combinations
- Over 17 sites and 900 patients in the United States

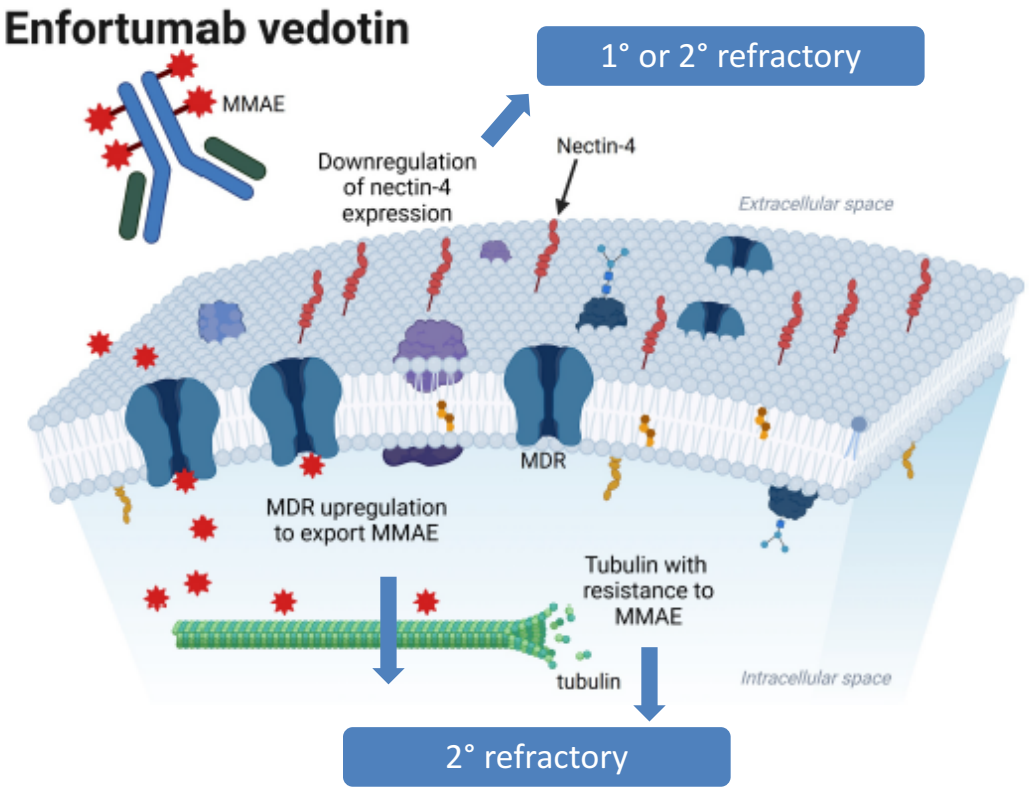
EV+Pembrolizumab:
202 Patients From 14 sites

- Subset of 43 patients who previously received ICI

Treatment and Survival Outcomes (n=43)	
Median Follow Up	14 months
Median Overall Survival	15.4 mos (95% CI: 8.7 – NR)
Median Progression-Free Survival	6.9 mos (95% CI: 3.91 – 12.2)
Observed Response Rate	48% (95% CI: 31 - 66) [16/33]
Disease Control Rate (CR/PR/SD)	79% (95% CI: 65 - 93) [26/33]



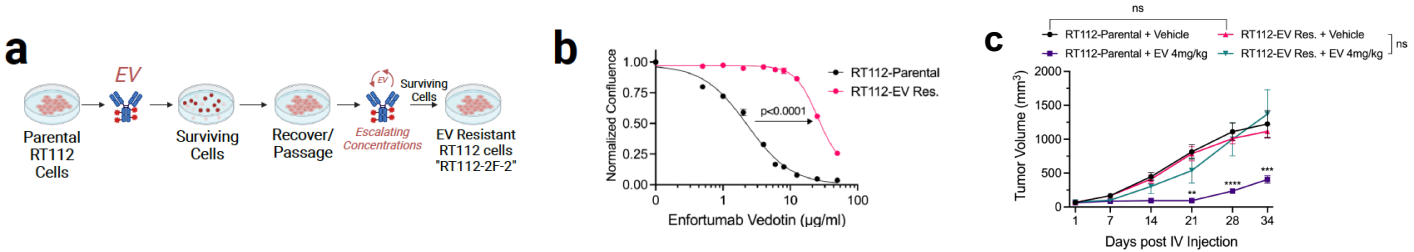
Can We Rechallenge with Nectin4-Targeting Agents? Mechanisms of Resistance to EV



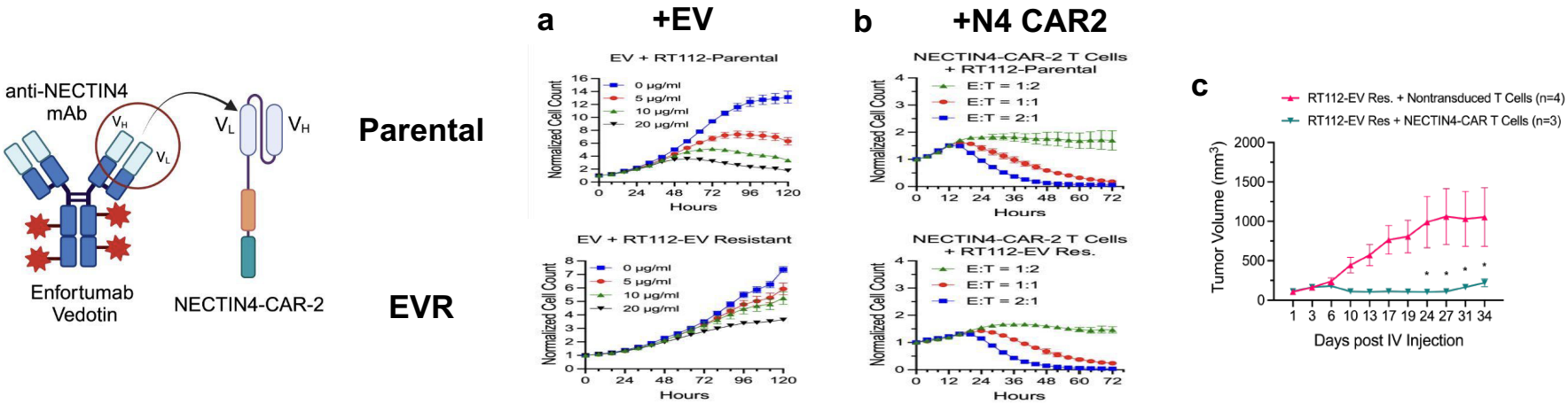
Slide c/o Ali Khaki

Jang & Brown. *Explor Target Antitumor Ther* 2025

NECTIN4 is retained in EV-resistant cells, suggesting that switching of treatment modalities is a viable approach



NECTIN4 Targeted CAR T's retain activity against EV-resistant cells



Chang, Chou et al, *Nat Communications,* 2025

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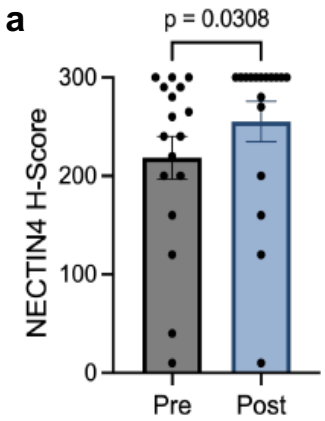
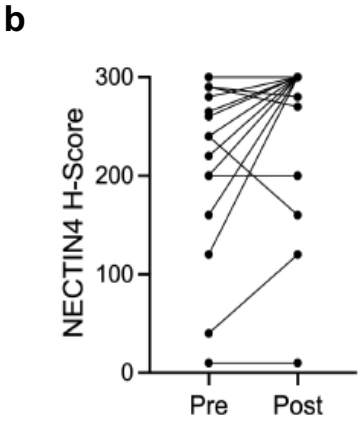
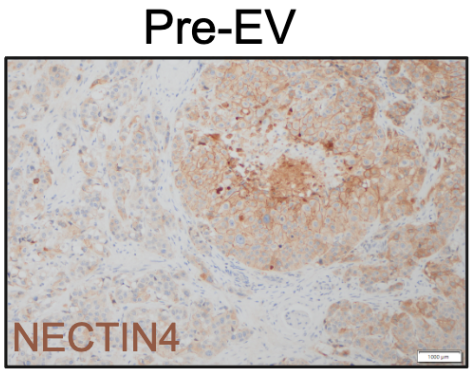
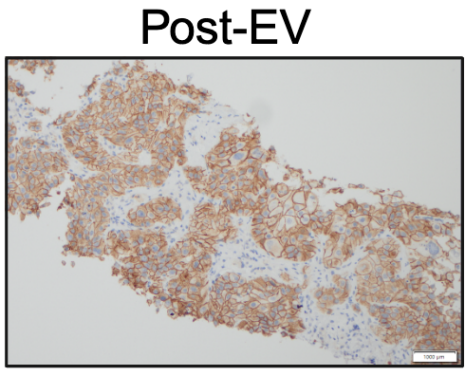
NECTIN4 Expression is Retained in Biopsies Following EV Treatment









Rationale for Rechallenging with Nectin4-Targeting Agents after Progression on EV+Pembrolizumab

C/o: Carissa Chu, David Solit Hikmat Al-Ahmadie, Jonathan Rosenberg, Jon Chou

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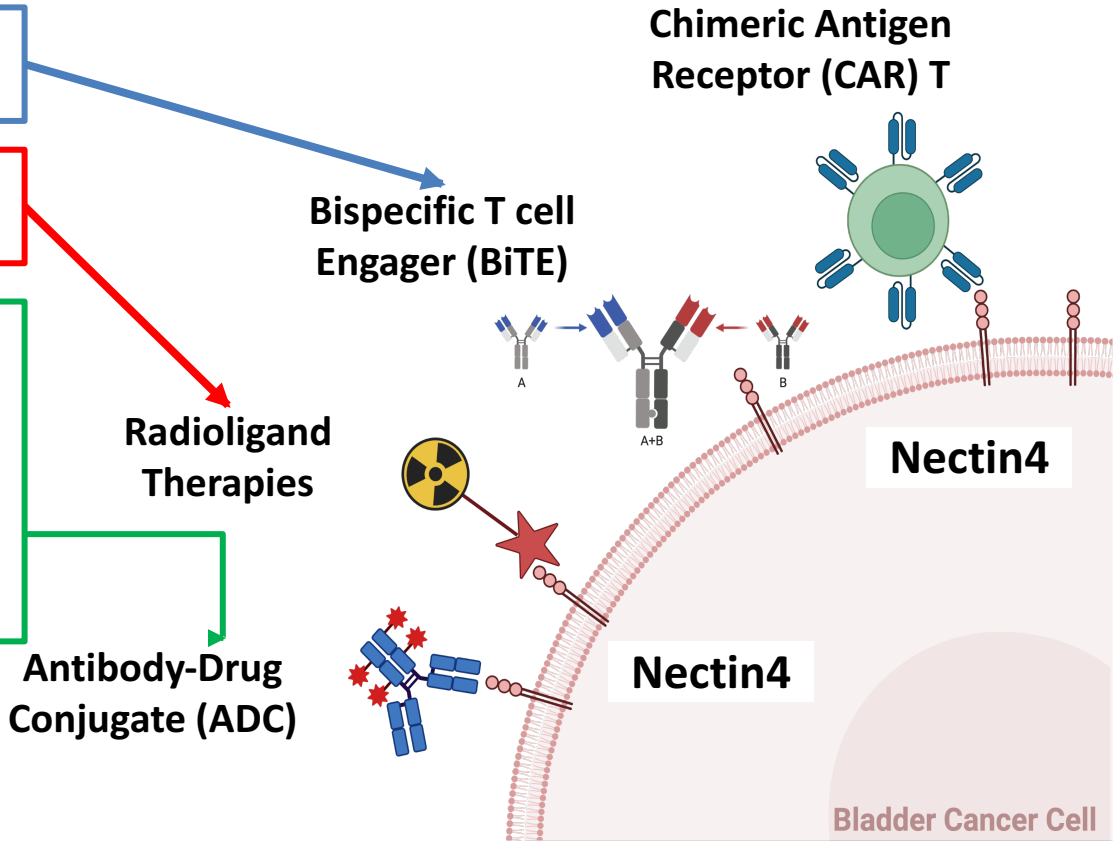
Future Trials Targeting Nectin4

RNDO-564: CD28/Nectin-4 Bispecific antibody

[^{225}Ac]Ac-AKY-1189: RLT targeting Nectin-4

Next generation Nectin4 Targeting ADCs

- Nectin4 Targeting ADCs with Topo1 Payload
- Nectin4/TROP2 Dual-Targeting ADC (Topo1 Payload): AVZO-103



Slide image c/o Jon Chou

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Summary

- EV + Pembrolizumab is becoming the key regimen for patients with aUC
  - Moving earlier to perioperative setting
- Creates important questions regarding treatment space following EV+P
- Heterogeneous patient populations requiring personalized approaches
- Roles for novel and targeted agents, clinical trials and potential for treatment rechallenge in selected patients

Thank you!

vadim.koshkin@ucsf.edu

@koshkin85

@vadimkoshkin.bsky.social