How do these treatments impact subsequent line of therapy

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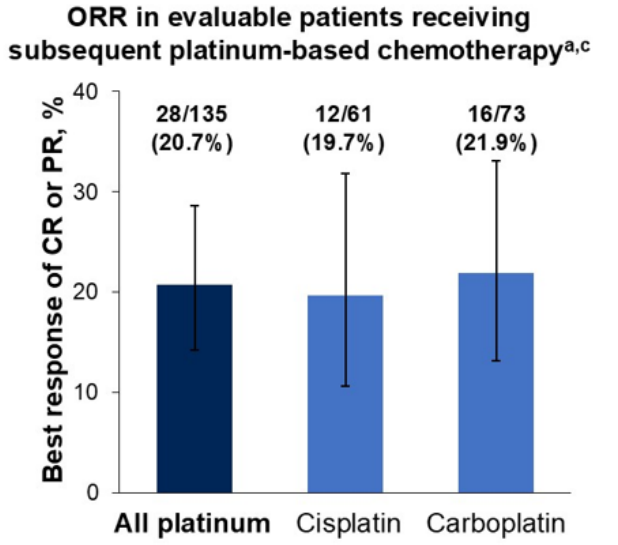
Subsequent therapy: Enfotumab + Pembrolizumab

In the chemotherapy arm, the most common first subsequent treatment was a PD-(L)1 inhibitor

	EV+P (n=442)	Chemotherapy (n=444)
Patients who received subsequent anticancer therapies, n (%)	192 (43.4)	324 (73.0)
Systemic therapy	173 (39.1)	304 (68.5)
First subsequent systemic therapy, n (%)		
Platinum-containing chemotherapy[a]	135 (30.5)	20 (4.5)
Carboplatin-based therapy	73 (16.5)	10 (2.3)
Cisplatin-based therapy	61 (13.8)	9 (2.0)
PD-(L)1 inhibitor therapy[b]	17 (3.8)	265 (59.7)
Maintenance	0	142 (32.0)
Avelumab	0	135 (30.4)
Pembrolizumab	0	5 (1.1)
EV+P-based therapy	2 (0.5)	2 (0.5)
Other PD-(L)1 inhibitor therapy	15 (3.4)	121 (27.3)
Atezolizumab	1 (0.2)	44 (9.9)
Pembrolizumab	14 (3.2)	72 (16.2)
Other[c]	21 (4.8)	19 (4.3)

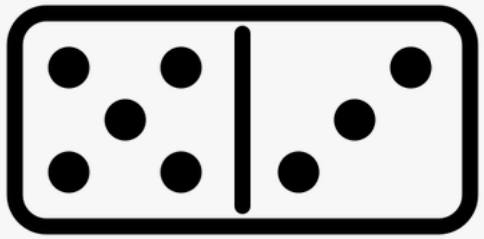


Median OS from start of platinum-based chemotherapy was 10.9 months (95% CI 8.3, 12.8

Attrition rate estimated:

- **EV+P: 84/276 ≈ 30.4%**
- **Chemio: 49/373 ≈ 13.1%**

Powles T. ASCO 206



EV+ Pembro

PD

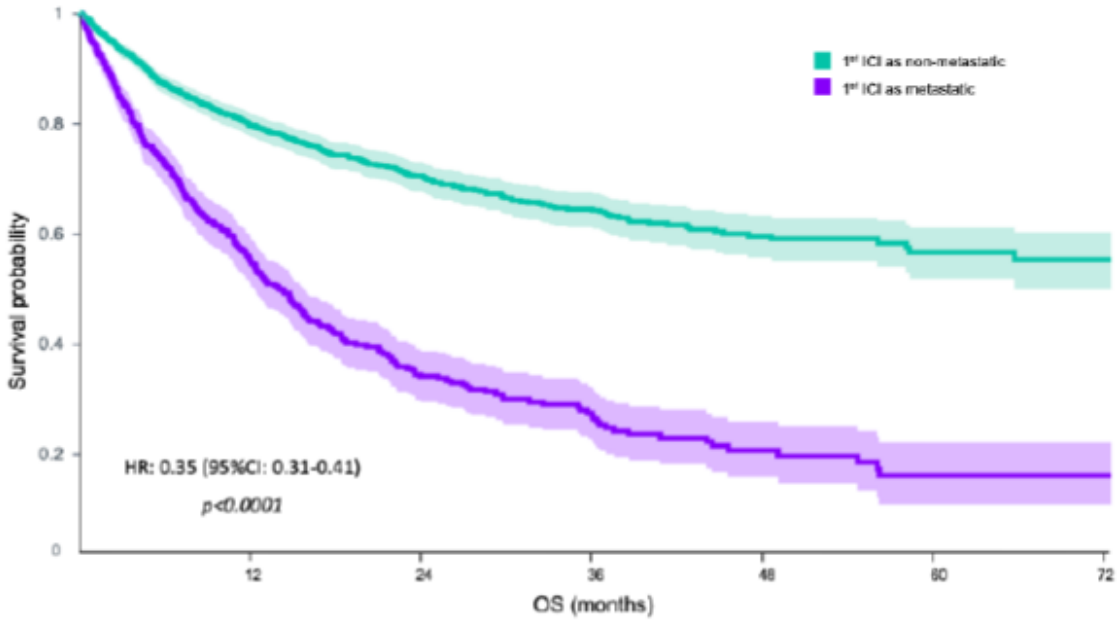
What would experts do after EV + Pembrolizumab?

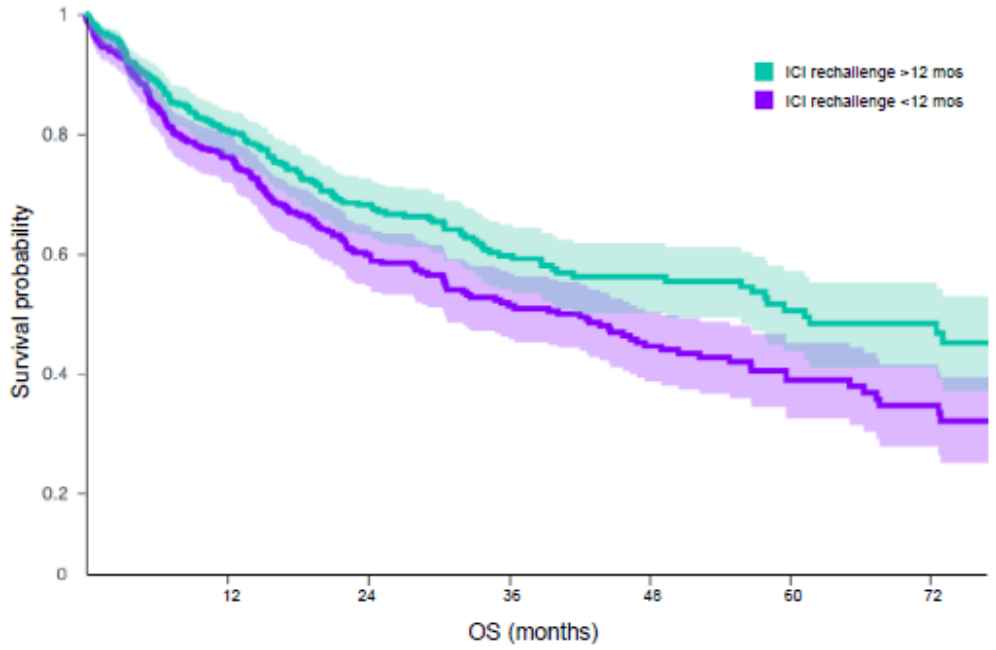
Characteristics	% (*n*)
Time in practice postfellowship	
>20 y	17 (13)
16-20 y	9 (7)
11-15 y	19 (15)
6-10 y	17 (13)
0-5 y	38 (30)
Type of practice setting	
Academic	90 (64)
Community	10 (7)
Number of patients with mUC seen/y	
>25 patients	72 (56)
11-25 patients	21 (16)
6-10 patients	5 (4)
1-5 patients	3 (2)

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* susceptible alterations	87 (62)	7 (5)
SG	56 (40)	30 (21)
ICI-combo trial	54 (38)	35 (25)
Non-ICI trial	80 (57)	8 (6)
Continue EVP for progression in 1-2 sites after using local therapy (eg, radiation)	83 (59)	8 (6)

Tawagi K et al. Clin Genitourinary Cancer 2026

Immuntherapy rechallenge in UC: friends or foes? RWD

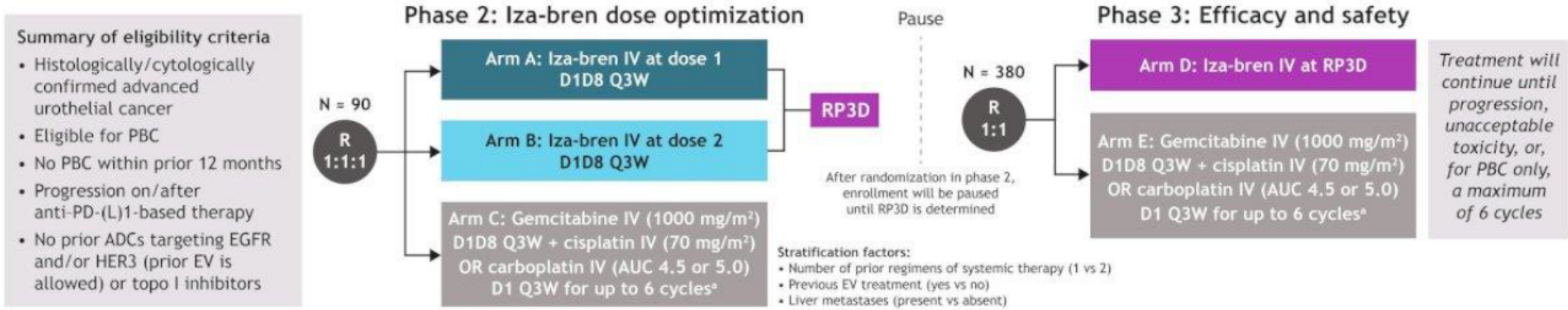




Maiorano BA. Et al ESMO open 2025

ICI rechallage: what is the optimal drug?

ADC anti-EGFR and HER3



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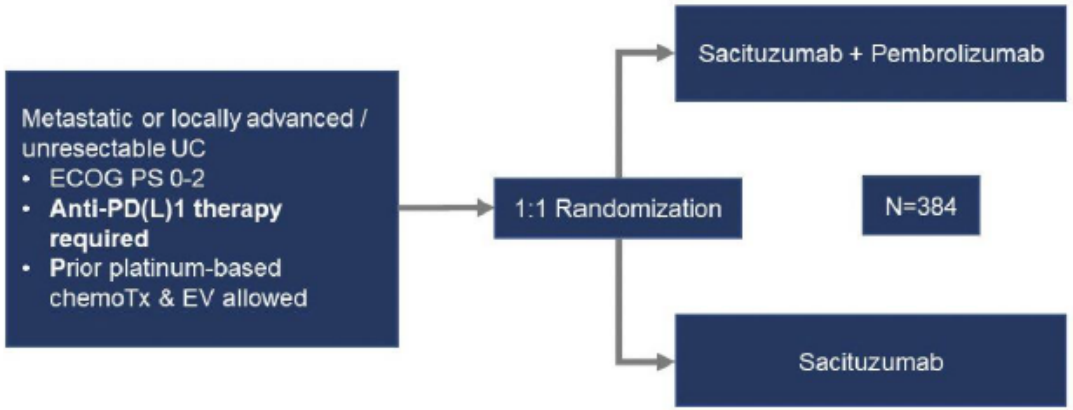
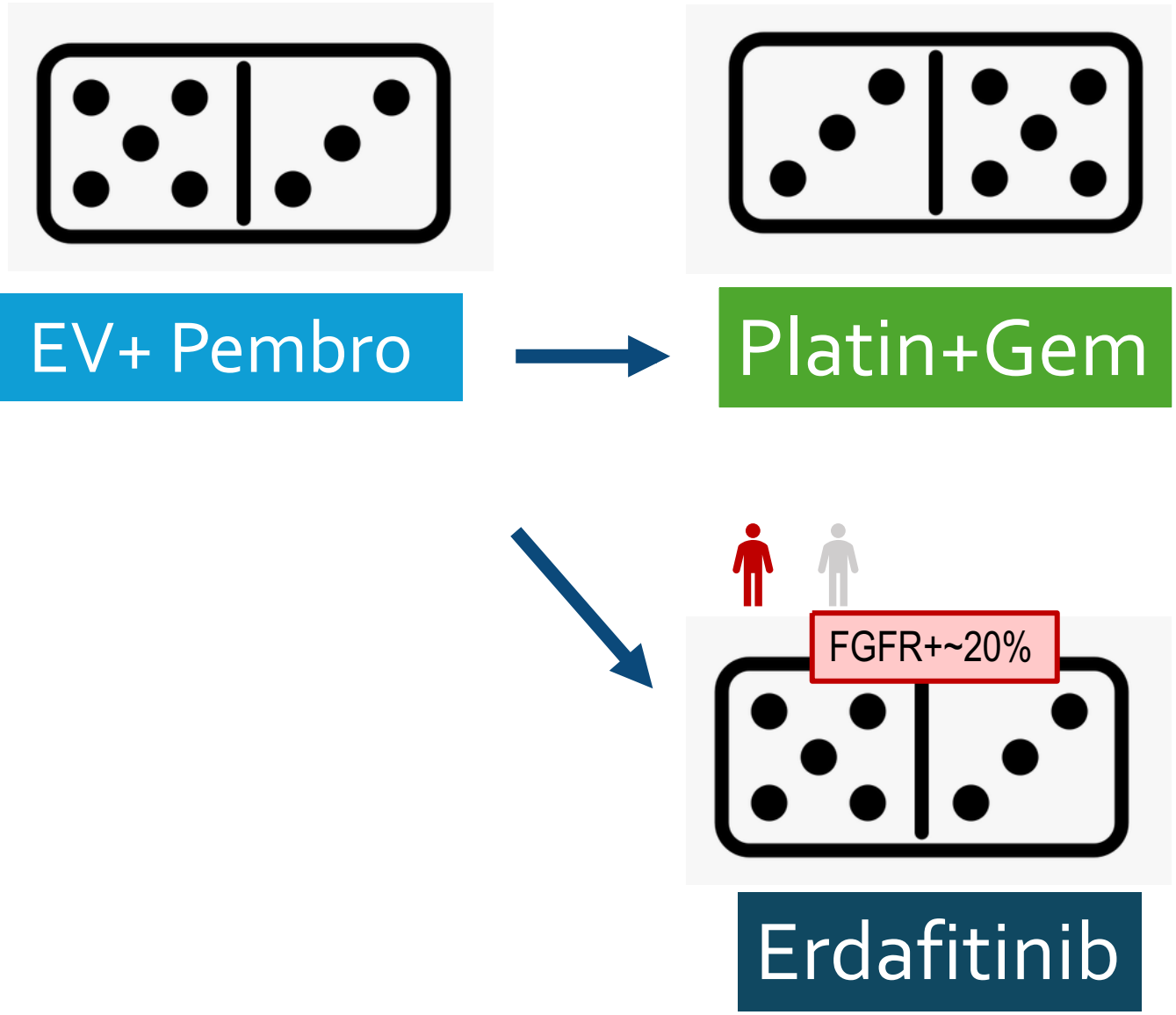
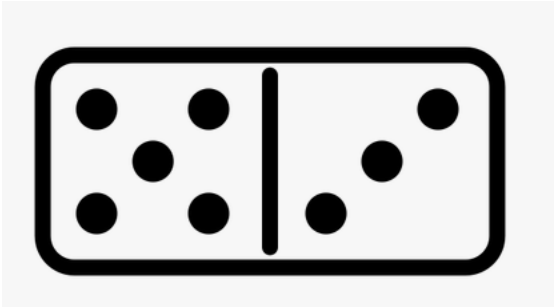
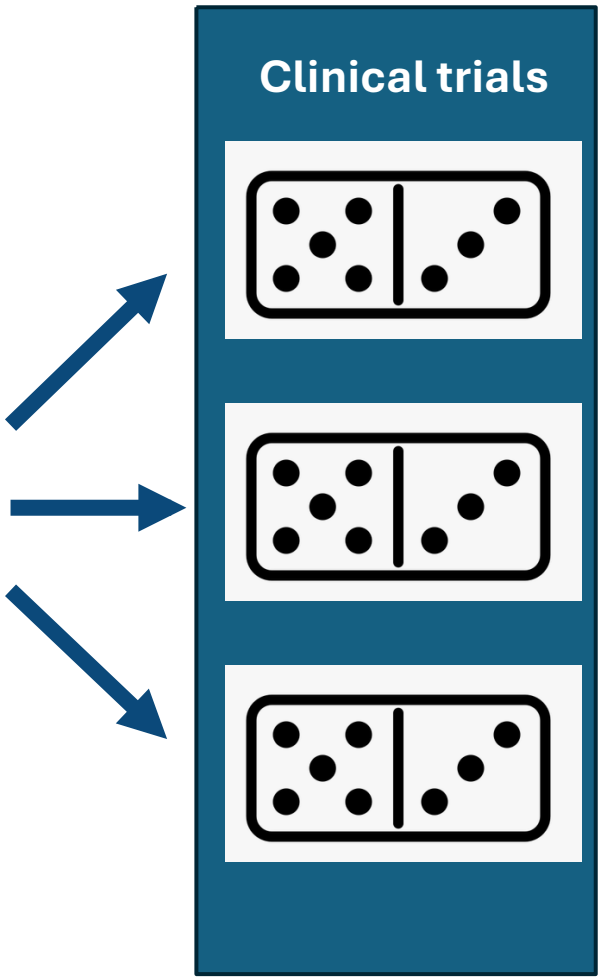
Sacituzumab Govitean-hziy



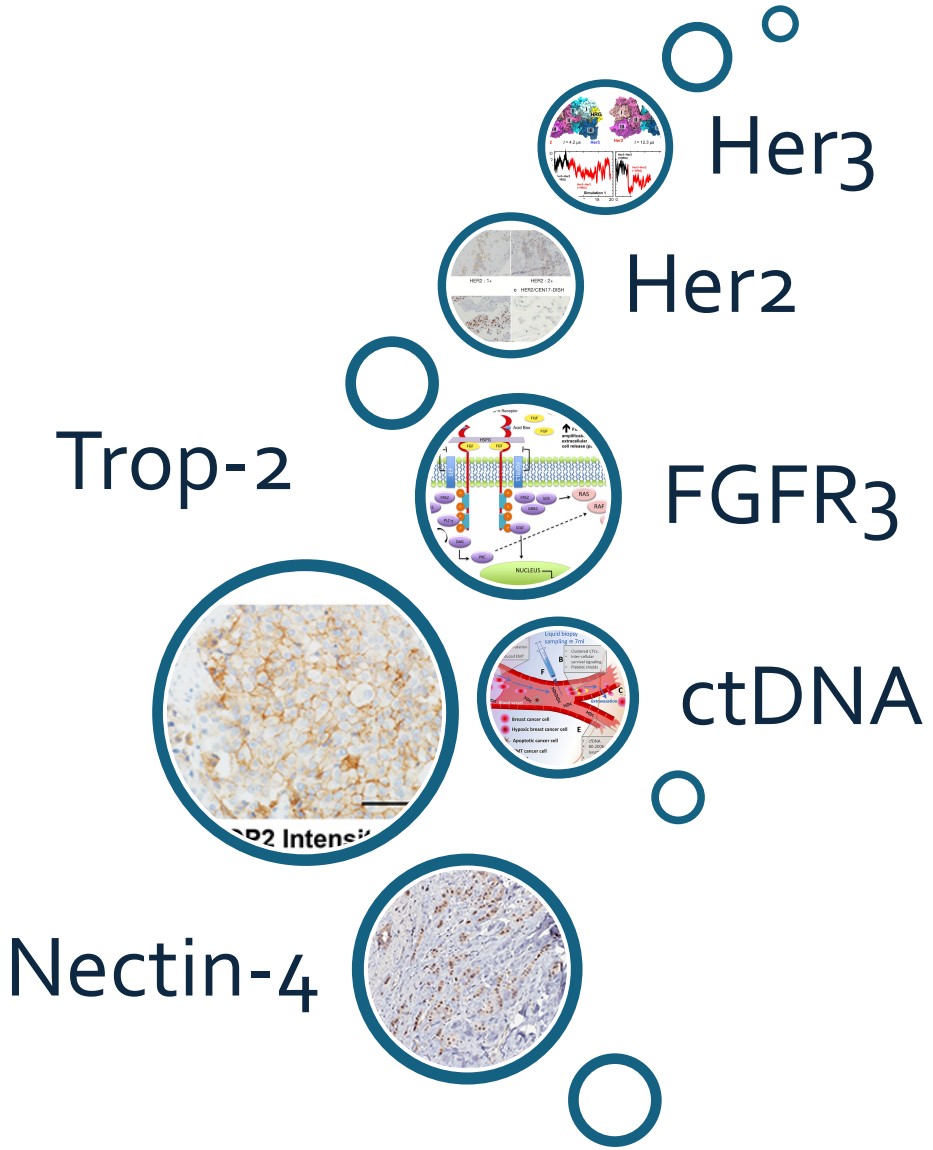

EV+ Pembro
Platin+Gem
FGFR+~20%
Erdafitinib

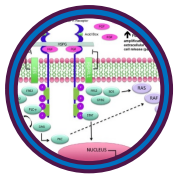


EV+ Pembro



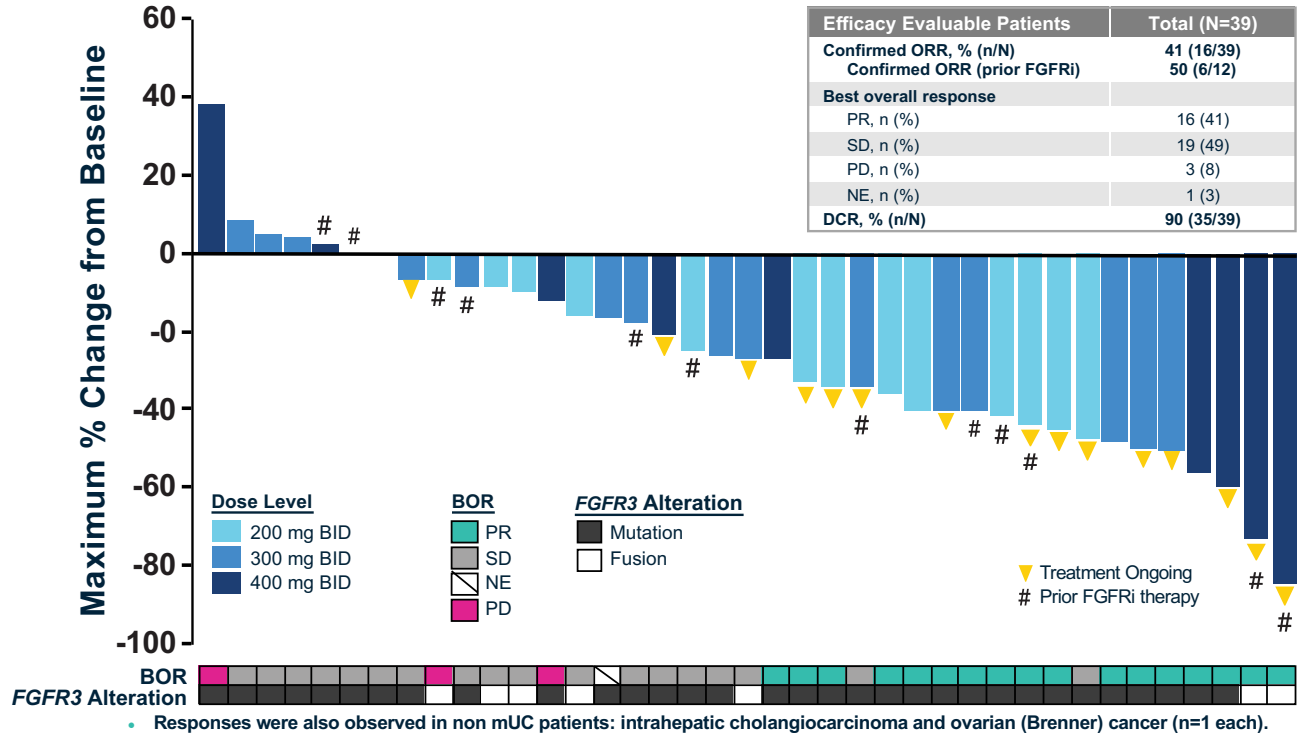
Biomarkers of Interest in Urothelial carcinoma





New FGFR3 Inhibitors

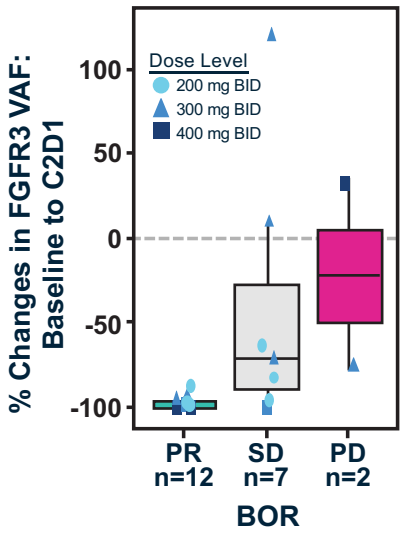
Phase 1 study of LY3866288 (LOXO-435), a potent, highly isoform-selective FGFR3 inhibitor (FGFR3i) in advanced solid tumors with FGFR3 alterations: Initial results from FORAGER-1



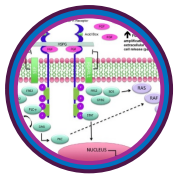
Efficacy Evaluable Patients	Total (N=39)
Confirmed ORR, % (n/N)	41 (16/39)
Confirmed ORR (prior FGFRi)	50 (6/12)
Best overall response	
PR, n (%)	16 (41)
SD, n (%)	19 (49)
PD, n (%)	3 (8)
NE, n (%)	1 (3)
DCR, % (n/N)	90 (35/39)

- Responses were also observed in non mUC patients: intrahepatic cholangiocarcinoma and ovarian (Brenner) cancer (n=1 each).

***FGFR3* Variant Allele Frequency**



- Median time to response was 1.4 (1.2-2.6 months)
- 12 (75%) of 16 confirmed responders remain on treatment; median duration of response is immature



Safety: LY3866288 and other FGFR3i

LY38662881

Treatment-Emergent AEs ≥20%				
	All Patients (N=107)		200 mg, 300 mg, 400 mg BID (n=70)	
All TEAEs, %	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any	98	45	100	46
Diarrhea	63	3	76	4
Fatigue	26	<1	29	1
ALT increased	22	7	29	9
AST increased	22	7	29	9
Decreased appetite	21	3	24	1
AEs of interest, %				
Skin disorders	42	3	46	4
Hand-foot (PPE)	6	2	9	3
Hyperphosphatemia	26	<1	36	1
Eye disorders	19	-	21	-
Retinopathy	4	-	4	-
Stomatitis	18	<1	23	1
Nail disorders	16	-	19	-
Dry mouth	14	-	17	-
Dose modifications, %				
Dose reductions due to TEAEs	10		14	
Discontinuations due to TEAEs	5		6	

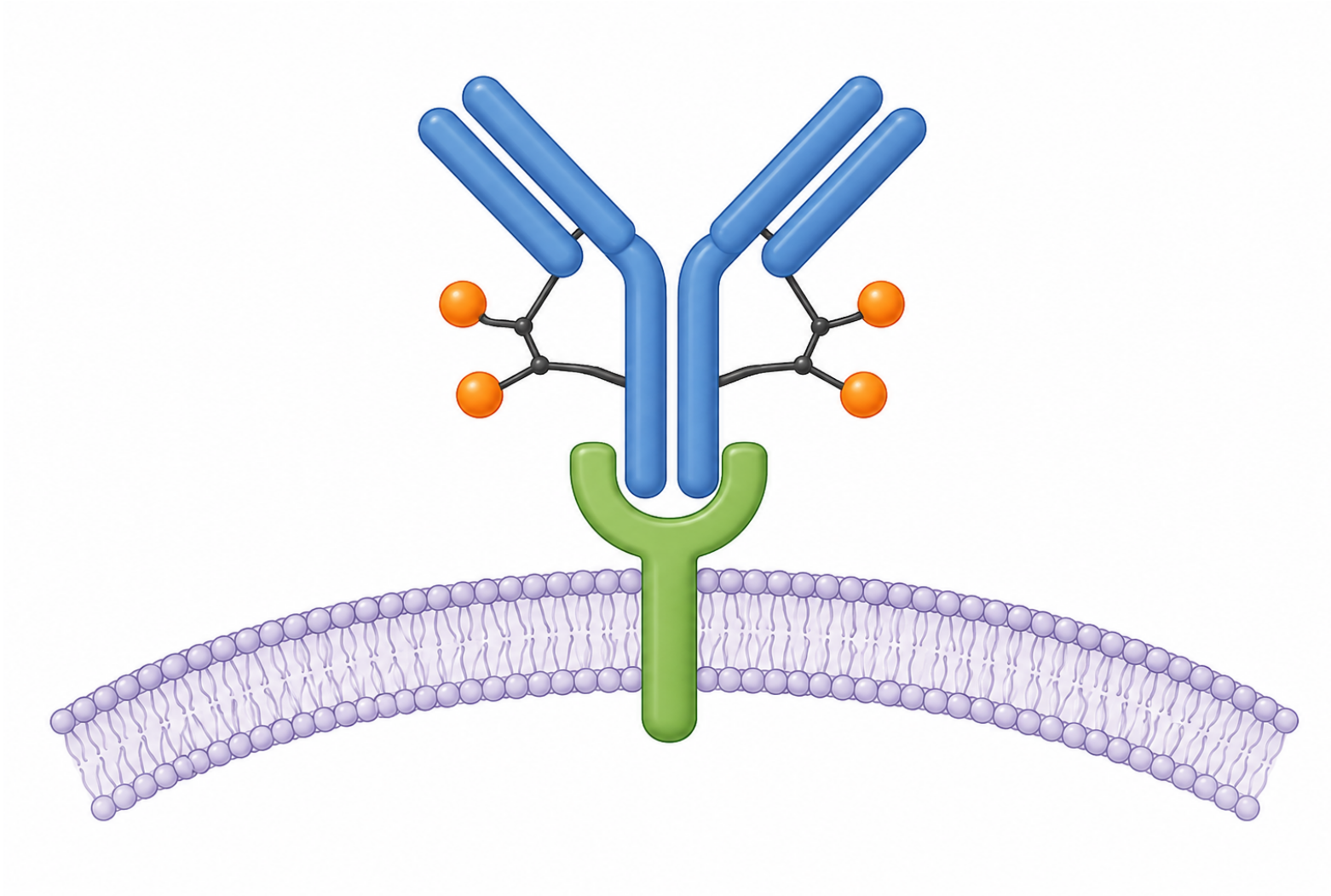
Other FGFR3i

Patients with events, n (%)	Erdafitinib (n=135)
≥1 treatment-related AE (any grade)	**131 (97.0)**
Hyperphosphatemia	**106 (78.5)**
Diarrhea	**74 (54.8)**
Stomatitis	**62 (45.9)**
Dry mouth	**52 (38.5)**
PPE syndrome	**41 (30.4)**
≥1 treatment-related AE leading to discontinuation of study treatment	11 (8.1)

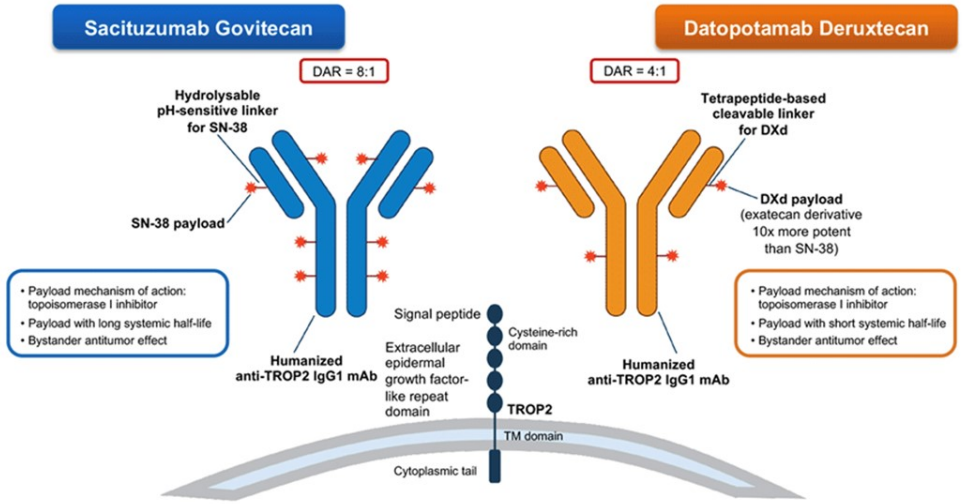
- High-grade FGFR3 related AEs typical for other FGFR3i were very rare
- Dose reductions/discontinuations were uncommon (14.1% in erdafitinib group, median follow-up 5 months) (median follow-up 5 months)

Iyer G et al., J Clin Oncol. 2023. Presented at ASCO GU 2023 (Abstract 662); Loriot Y et al., New Engl J Med. 2023 (Suppl S6)

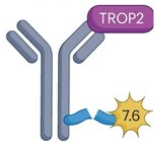
ADCs



Ab-anti TROP2

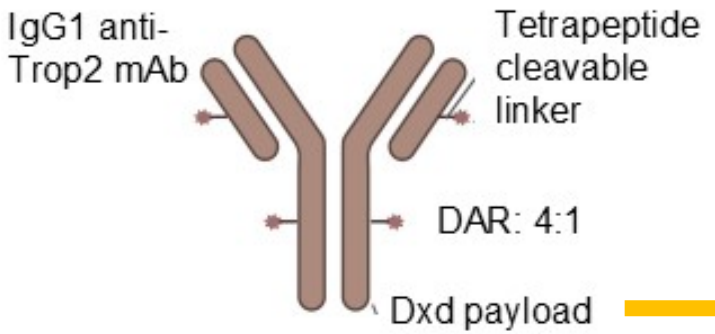


Parisi C et al. Cancer Treat Rev. 2023;118:102572.



Trop2

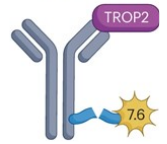
Datopotamab Deruxtecan



Topoisomerase I inhibitor

Phase I TROPION-PanTumor-01
n=40 mUC cohort, 2L+[10]

Phase 1 trial: Datopotemab Derutexan



Key eligibility criteria

- Unresectable locally advanced/metastatic (stage III or IV) urothelial carcinoma (included renal pelvis, ureter, urinary bladder, and urethra)
- Previous treatment with ≥1 line of therapy including an immune checkpoint inhibitor
- ECOG PS 0–1
- Unselected for TROP2 expression
- No prior treatment with DXd-ADCs or TROP2-directed therapies

→ **Dato-DXd** 6 mg/kg Q3W **(N=40)**

Primary endpoints

- Safety and tolerability

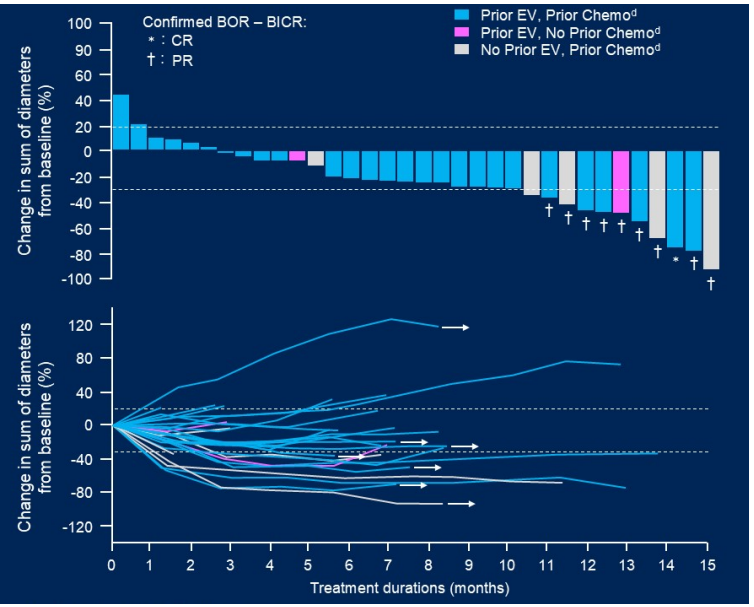
Secondary endpoints (by BICR[a])

- ORR
- DOR
- DCR
- PFS

5% pts with brain mets
83% prior EV

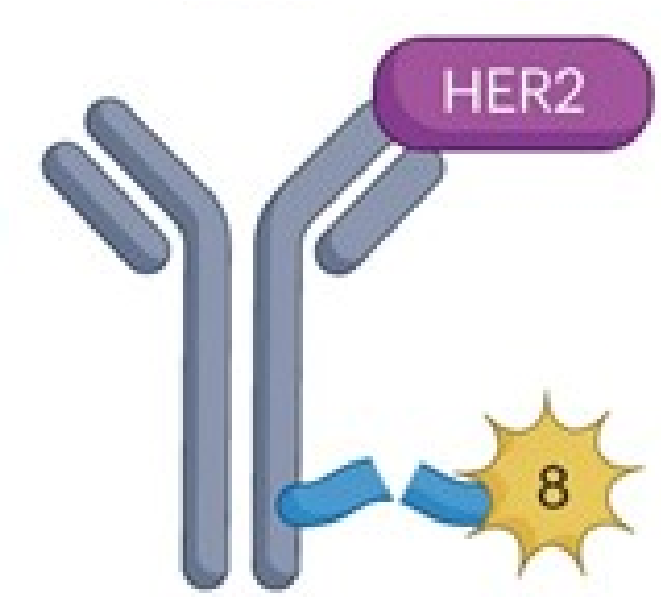
Response by BICR[a]	Dato-DXd (N=40)
ORR[b], n (%) [95% CI]	**10 (25.0)** [12.7–41.2]
DCR[c], n (%) [95% CI]	**31 (77.5)** [61.5–89.2]
BOR, n (%)	
CR	1 (2.5)
PR	9 (22.5)
SD	20 (50.0)
Non-CR/non-PD	1 (2.5)
PD	5 (12.5)
NE	4 (10.0)
DOR, median (95% CI)**, months**	NE (2.6–NE)
6-month DOR rate, % (95% CI)	76.2 (33.2–93.5)

ORR by investigator was 30.0% (n=12); all were PR

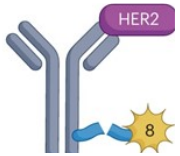


Funda Meric-Bemstam et al abstr JCO 2025

Ab-anti HER 2



HER2-directed ADCs in mUC: Promising results



Deruxtecan (topo-isomerase Ii)

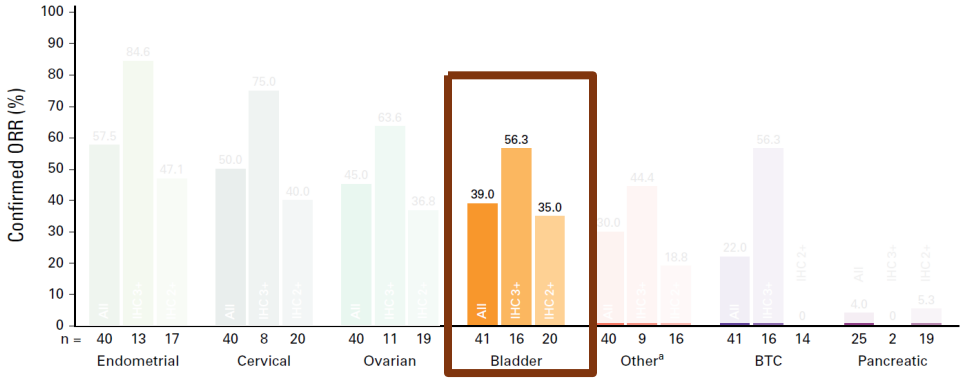
Phase II DESTINY-PanTumor02 (Bladder): Trastuzumab Deruxtecan[1,2]

n = 41 mUC, 2L+, HER2 IHC 2+/3+

Primary endpoint: ORR

→ T-Dxd 5.4 mg/kg q3w

Trastuzumab Deruxtecan	
ORR	39.0% (95% CI 24.2, 55.5)
mPFS	7.0 mo (95% CI, 4.2-9.7)
mOS	12.8 mo (95% CI, 11.2-15.1)



Funda Meric-Bernstam et al. JCO 2023

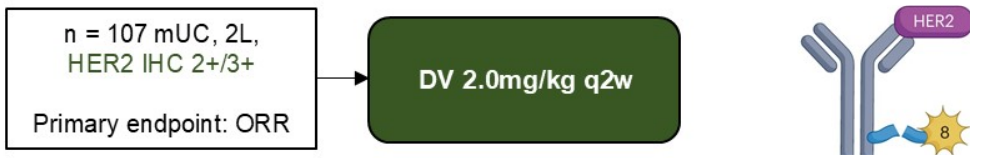
Phase II RC48-C005, RC48-C009: Disitimab Vedotin[3]

n = 107 mUC, 2L, HER2 IHC 2+/3+

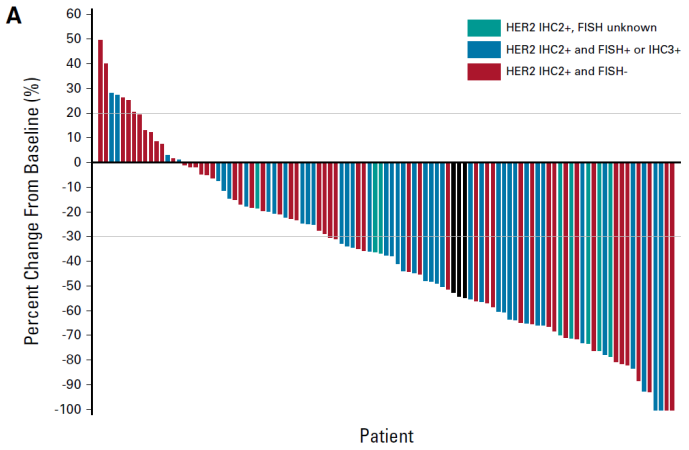
Primary endpoint: ORR

→ DV 2.0mg/kg q2w

Disitimab Vedotin	
ORR	50.5% (95% CI, 4.6-60.3)
mPFS	5.9 mo (95% CI, 4.3-7.2)
mOS	14.2 mo (95% CI, 9.7-18.8)



MMAE (microtubule inhibitor)



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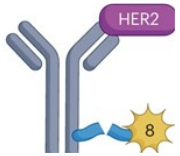


MMAE
(microtubule inhibitor)

Phase III Disitamab V vs chemotherapy (1L)

Key Inclusion criteria

- No prior systemic treatment for unresectable locally advanced or metastatic UC
- Central lab-confirmed HER2 IHC 1+, 2+, or 3+
- Measurable disease per RECIST v1.1
- Eligible for ciscplatin or carboplatin
- ECOG PS 0 or 1

R
1 : 1

N=243

Disitamab vedotin + Toripalimab

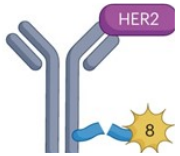
no set maximum cycles

N=241

Gemcitabine + Cisplatin/Carboplatin

a maximum of 6 cycles

Xinan Sheng et al. NEJM 2025



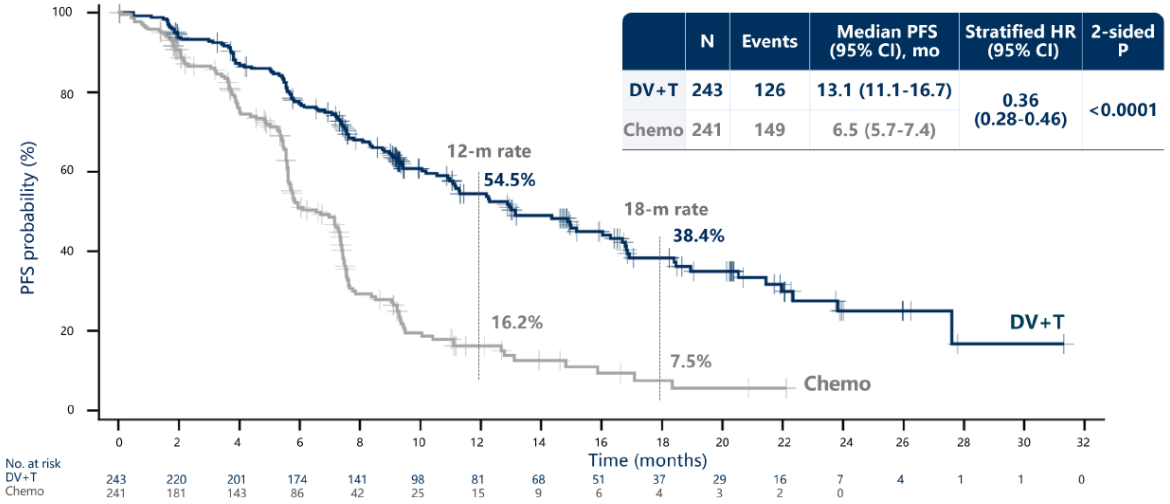
MMAE
(microtubule inhibitor)

Phase III Disitamab V vs chemotherapy (1L)

Evidence gap in the post-enfortumab setting

Progression-free Survival according to BIRC

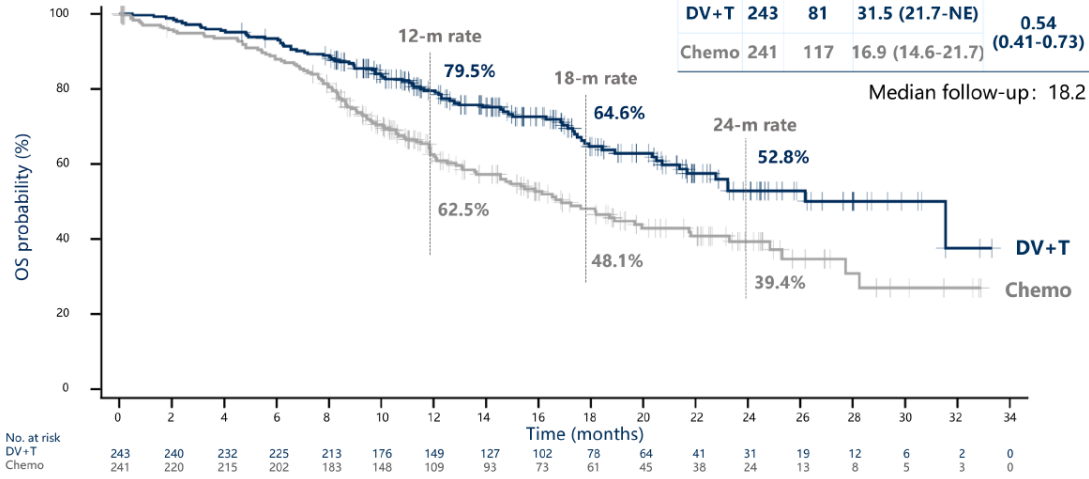
Clinically meaningful reduction in the risk of progression or death by 64% with DV+T



	N	Events	Median PFS (95% CI), mo	Stratified HR (95% CI)	2-sided P
DV+T	243	126	13.1 (11.1-16.7)	0.36 (0.28-0.46)	<0.0001
Chemo	241	149	6.5 (5.7-7.4)		

Overall Survival

Clinically meaningful reduction in the risk of death by 46% with DV+T



	N	Events	Median OS (95% CI), mo	Stratified HR (95% CI)	2-sided P
DV+T	243	81	31.5 (21.7-NE)	0.54 (0.41-0.73)	<0.0001
Chemo	241	117	16.9 (14.6-21.7)		

Median follow-up: 18.2 months

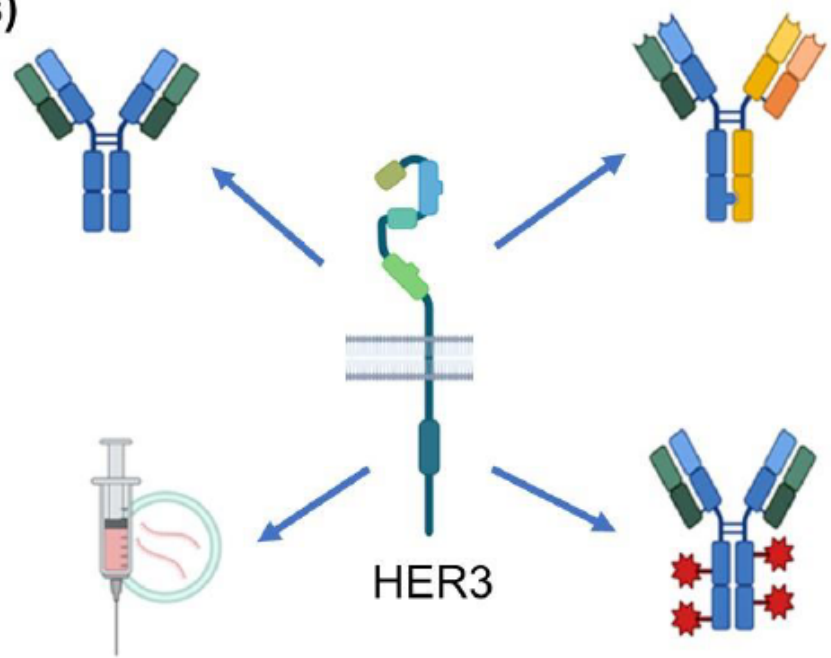
Xinan Sheng et al. NEJM 2025

Examples of Drugs Targeting HER3

New target and bispecifics

Monoclonal Antibodies (mABs)
Patritumab
HMBD-001
SIBP-03
GSK2849330

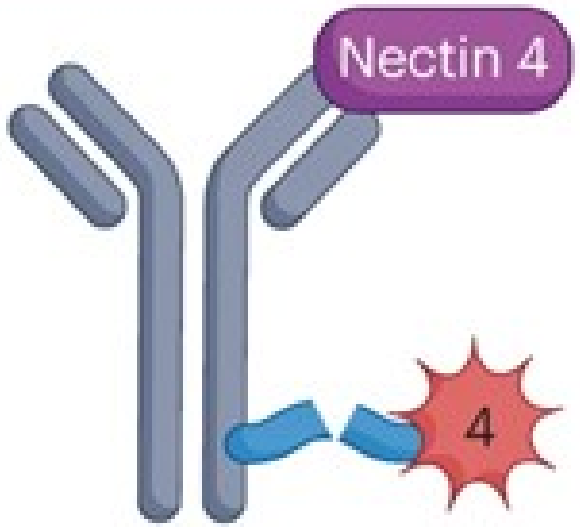
Vaccines
Dendritic cell vaccines
pING-hHER3FL (plasmid DNA)



Bispecific Antibodies (bABs)
Zenocutuzumab (HER2 x HER3)
SI-B001 (EGFR x HER3)

Antibody Drug Conjugates (ADCs)
Patritumab deruxtecan
YL202/BNT326
ENV-501
SHR-A2009
SIBP-A13
AK138D1
AMT-562
EO-1022
DB-1310
Iza-bren /BL-B01D1 (EGFR x HER3 bispecific)
BCG022 (MET x HER3 bispecific)
DM002 (MUC1 x HER3 bispecific)

Ab-anti Nectin 4



Nectin-4 expression post-EVP

61 tissue pre e post EV

Figure 2: Changes in membranous (TOP) and cytoplasmic (BOTTOM) Nectin4 expression by resistance pattern (A), and among patients with residual disease at definitive surgery (B)

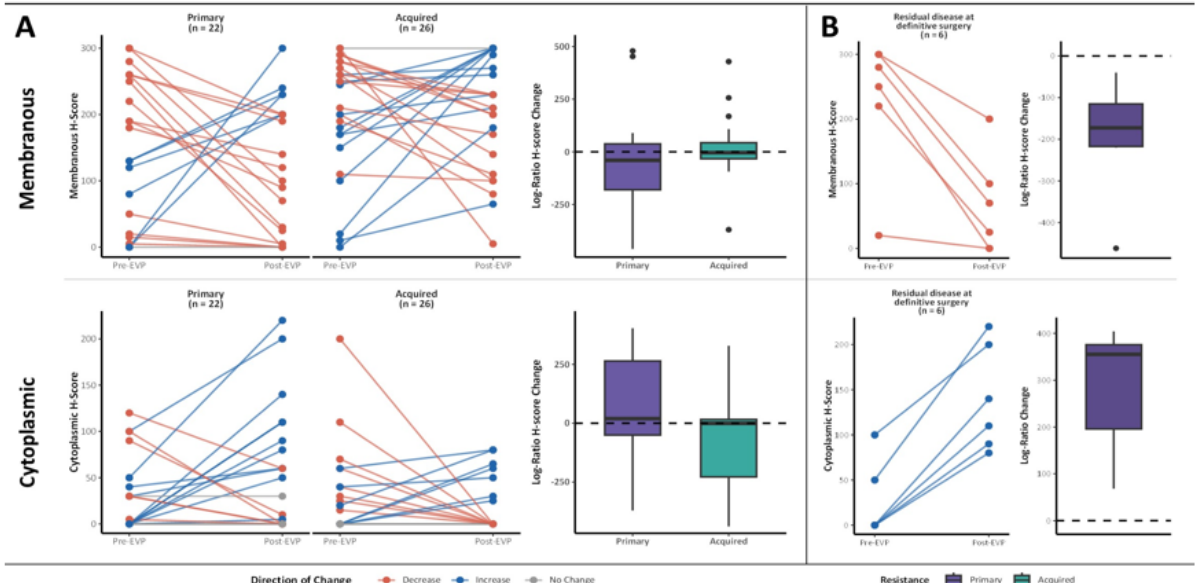
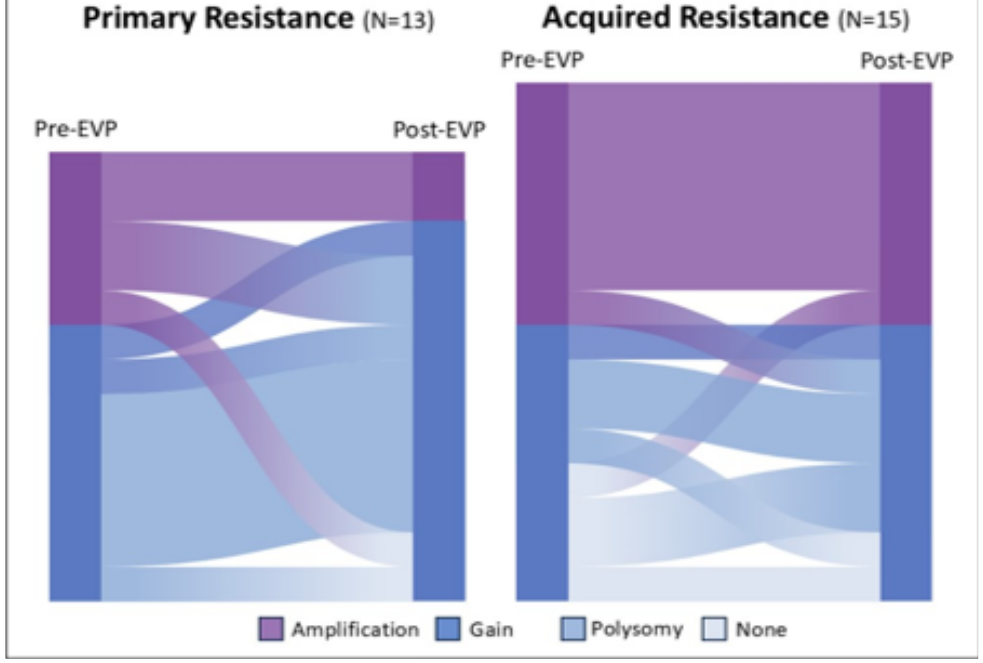


Figure 3: Changes in NECTIN4 FISH by resistance



Conclusions

- In a paired analysis, most tumors retained membranous Nectin4 expression post-EVP, and complete target loss was rare, supporting the rationale for Nectin4-directed strategies in the post-EVP setting.
- Nectin4 dynamics did not differ significantly by resistance pattern, though the numerically higher log change in mNectin4 in primary resistance and the observed patterns in the perioperative setting warrants further investigation in larger cohorts.

Sternschuss M. Et al #abstr 552910 ASCO 26

Nectin-4 Targeted Agents in Development

Nectin 4 Targeted agents under development	Payload	Linker
Zelenectide pevedotin (BT8009)	MMAE	Bicycle Drug Conjugate peptidase-cleavable sarcosine spacer chain / valine-citrulline
Bulumtatug fuvedotin (9MW2821)	MMAE	protease-cleavable
CRB-701 (SYS6002)	MMAE	Cleavable
ETx-22 (LY4101174)	Topo-1 Exatecan	Cleavable Maleimide-beta-glucuronide poly-sarcosine
BAT8007	Topo-1	Enzymatically cleavable
IPH4502	Topo-1 Exatecan	Cleavable, hydrophilic
ADRX-0706	AP052 (tubulin inhibitor)	Protease-cleavable

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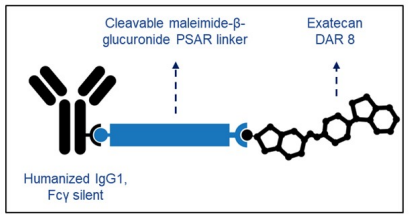
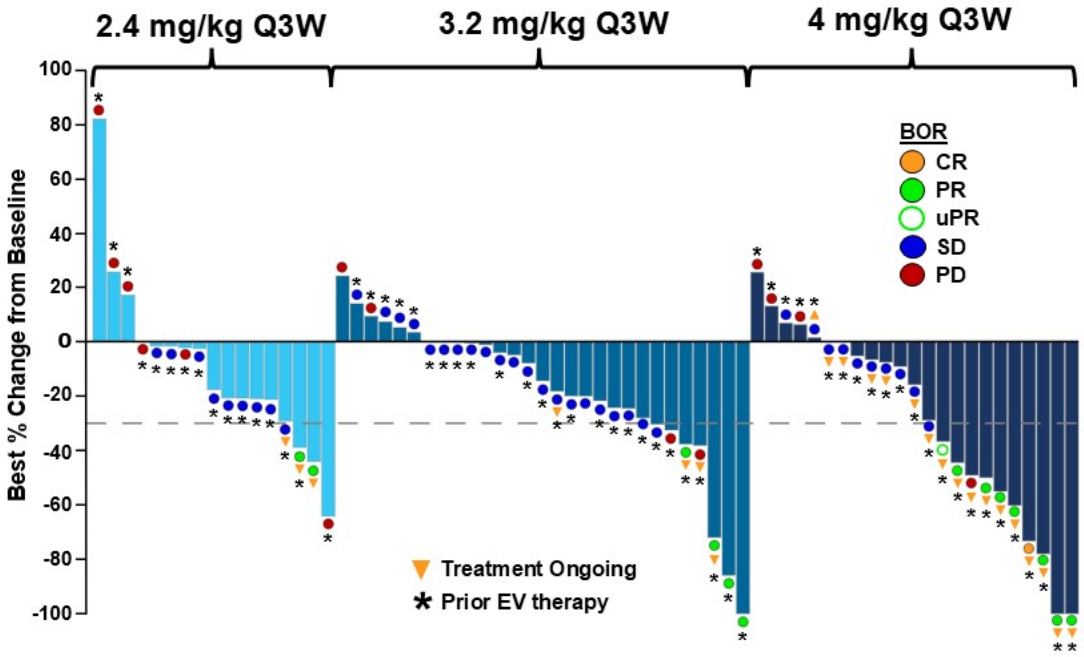


LY4101174 (next generationamti-nectin 4 ADC)

Composed of a humanized IgG1 antibody linked to the Topo-I inhibitor (exatecan)

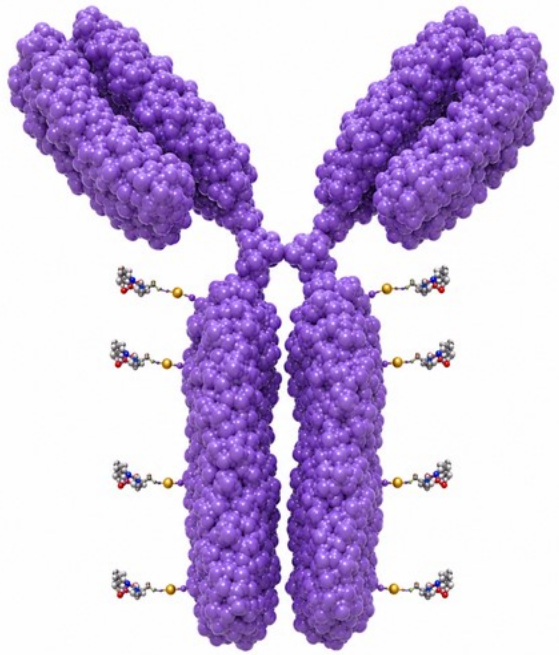
Efficacy Evaluable Participants[a]	Total Q3W (n=76)	2.4 mg/kg Q3W (n=19)	3.2 mg/kg Q3W (n=32)	4 mg/kg Q3W (n=25)
ORR, % (n)	**20 (15)**	**11 (2)**	**13 (4)**	**36 (9)**
CR, n (%)	1 (1)	-	-	1 (4)
PR, n (%)	14[b] (18)	2 (11)	4 (13)	8[b] (32)
SD, n (%)	40 (53)	9 (47)	21 (66)	10 (40)
DCR, % (n)	**72 (55)**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



- 93% prior EV
- ORR 36%
- **Hematologic toxcities →**
- **discontinuation due to toxicities and low efficacy**

Xin Gao J Clin Oncol 44, 2026 (suppl 16; abstr 4517) ASCO 26

LY4052031 and enfortumab vedotin both target nectin-4 but linker and payload are different

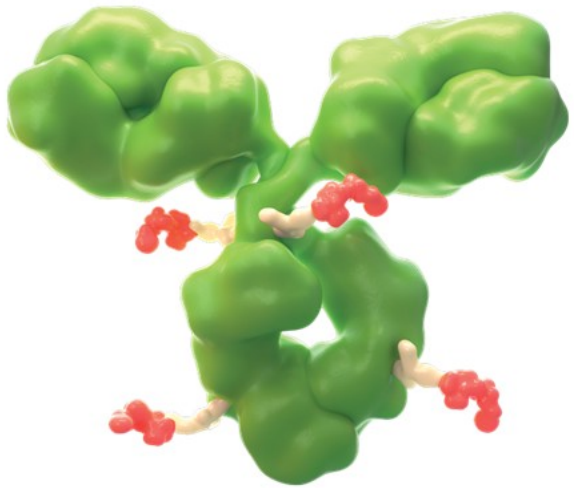


LY4052031

- Nectin-4 ADC
- Topo-I inhibitor, camp98, payload
- A cleavable peptide linker
- Drug antibody ratio (DAR) of 8

Enfortumab vedotin

✓ ≠ ≠ ≠



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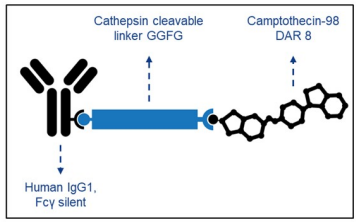
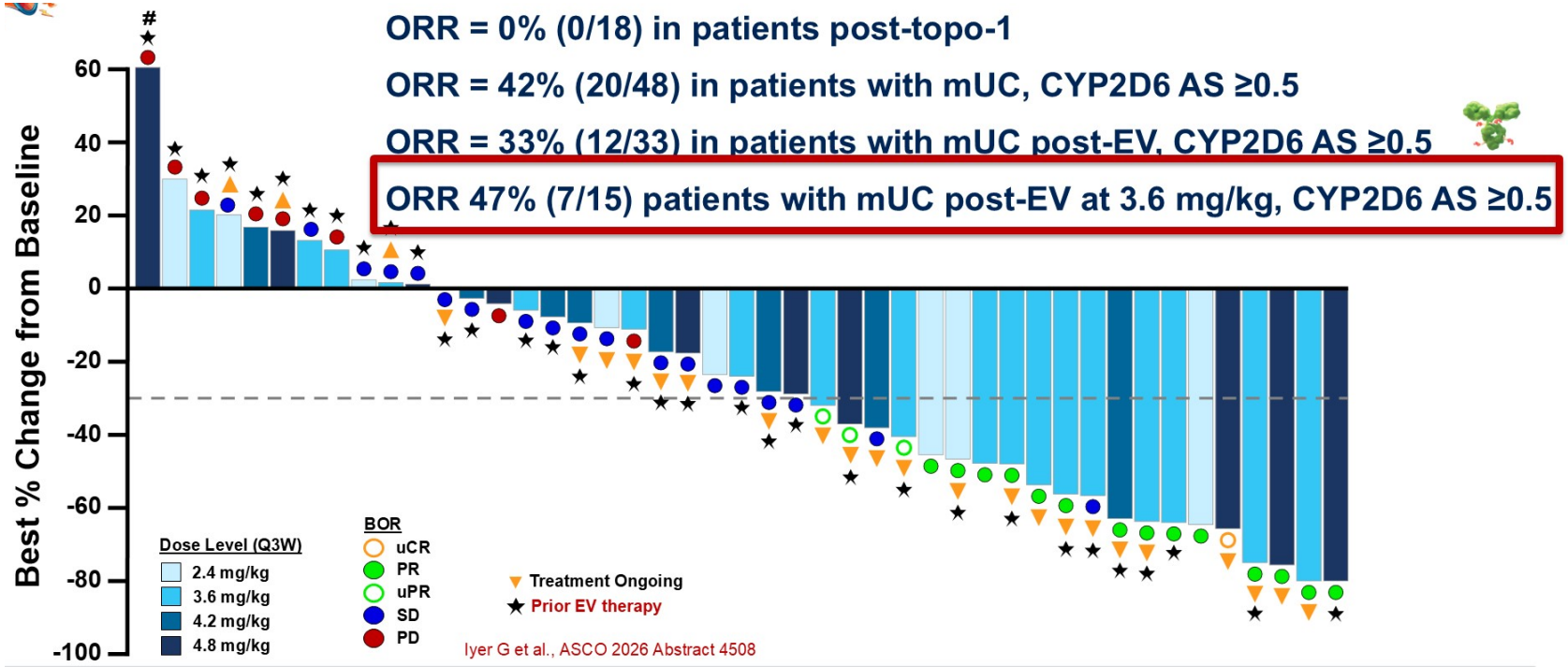


Nexus-01 LY4052031 anti-nectin4

Nex generation anti-nectin-4 target novel Topo-I inhibitor payload (camp98) →DAR8

Preclincal data suggest EV resistence may be mediated bt P-gp-mediated payload efflux



- Clerance of camp98 is mediated by hepaticCYP2D6 genotyping → high risk for severe toxicity
- Median duration of response 7.4 months (95%, CI 2.7-NE) among 9 confimed responders
- 67% of responders are ongoing

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Take home message

EV + pembrolizumab has reshaped first-line treatment of metastatic urothelial carcinoma, creating new challenges for subsequent therapy.

Evidence supporting treatment selection after EV + pembrolizumab remains limited, and current practice is largely guided by expert opinion and retrospective data.

Clinical trials and biomarker-driven strategies will be crucial to optimize treatment sequencing in the post-EV + pembrolizumab era.

Thank you

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