City of Hope

3rd Annual Southern California Genitourinary Cancer Research Forum

Key Updates in Urothelial Cancer

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City of Hope

Disclosures

- I do not have any relevant financial relationships with any ineligible companies.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

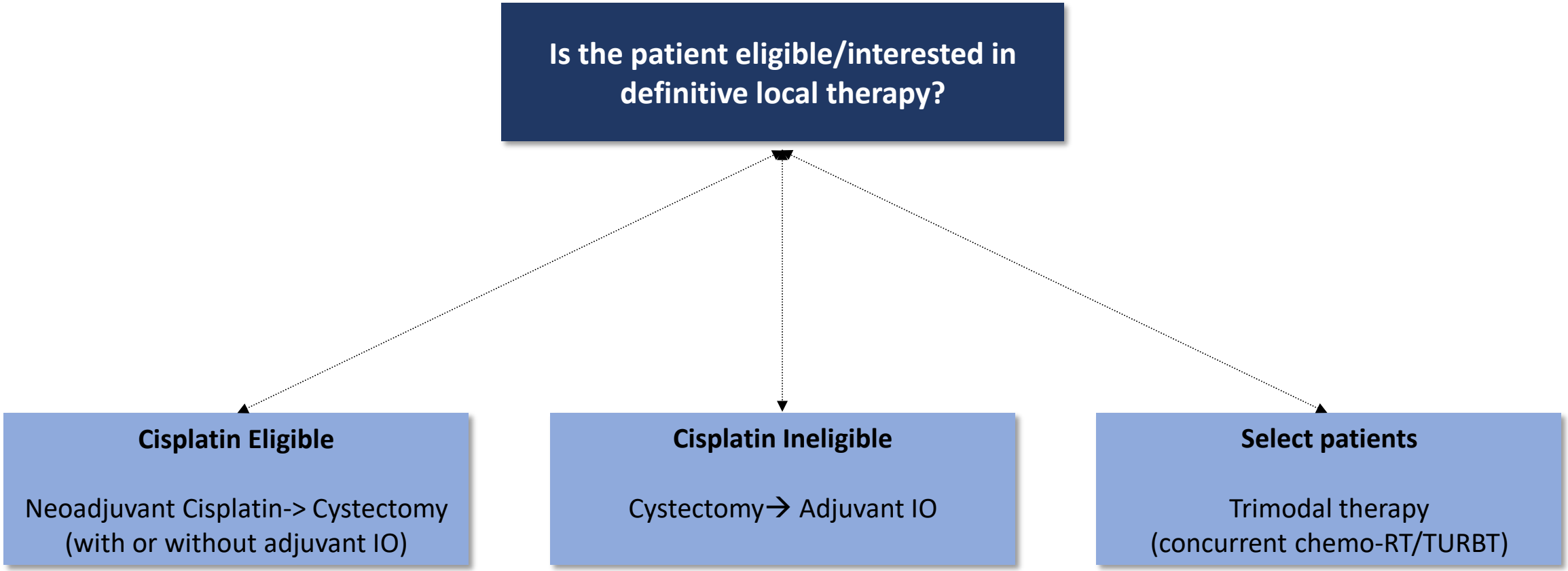
EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

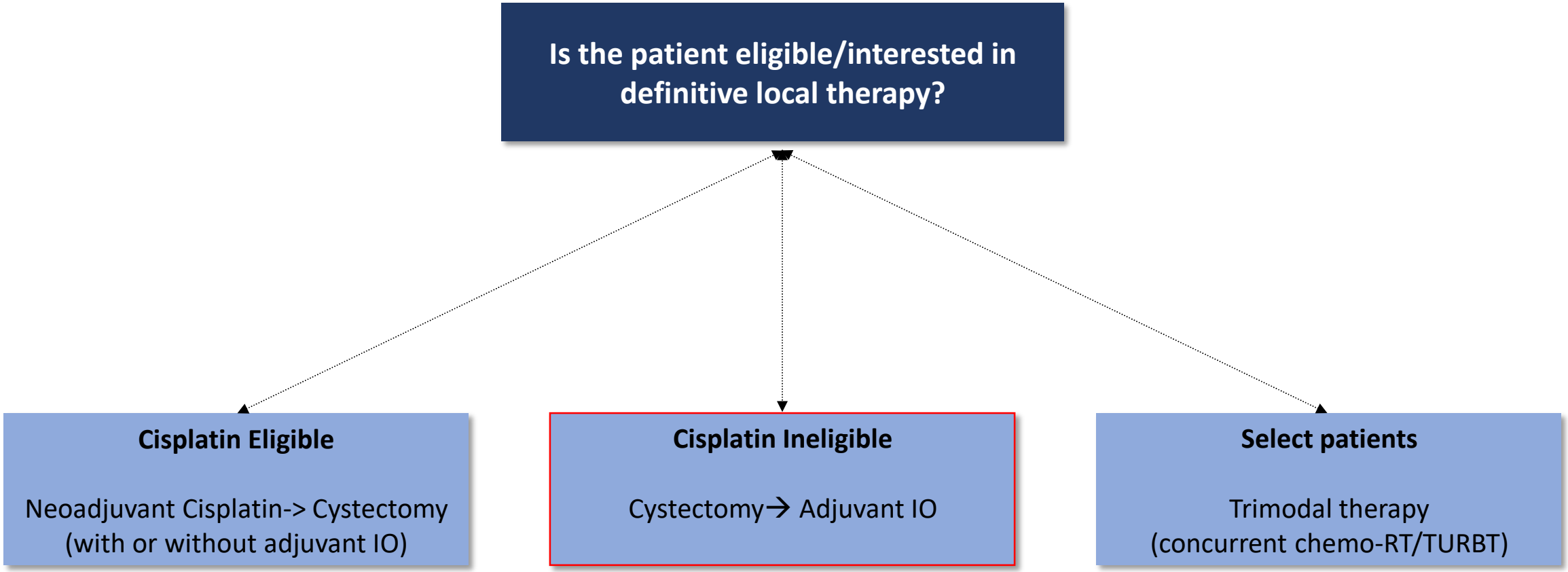
The following CLC & IB components will be addressed in this presentation:

- *The treatment of underrepresented minorities in bladder cancer.*
- *Gender disparities in bladder cancer.*

Current treatment paradigm of MIBC



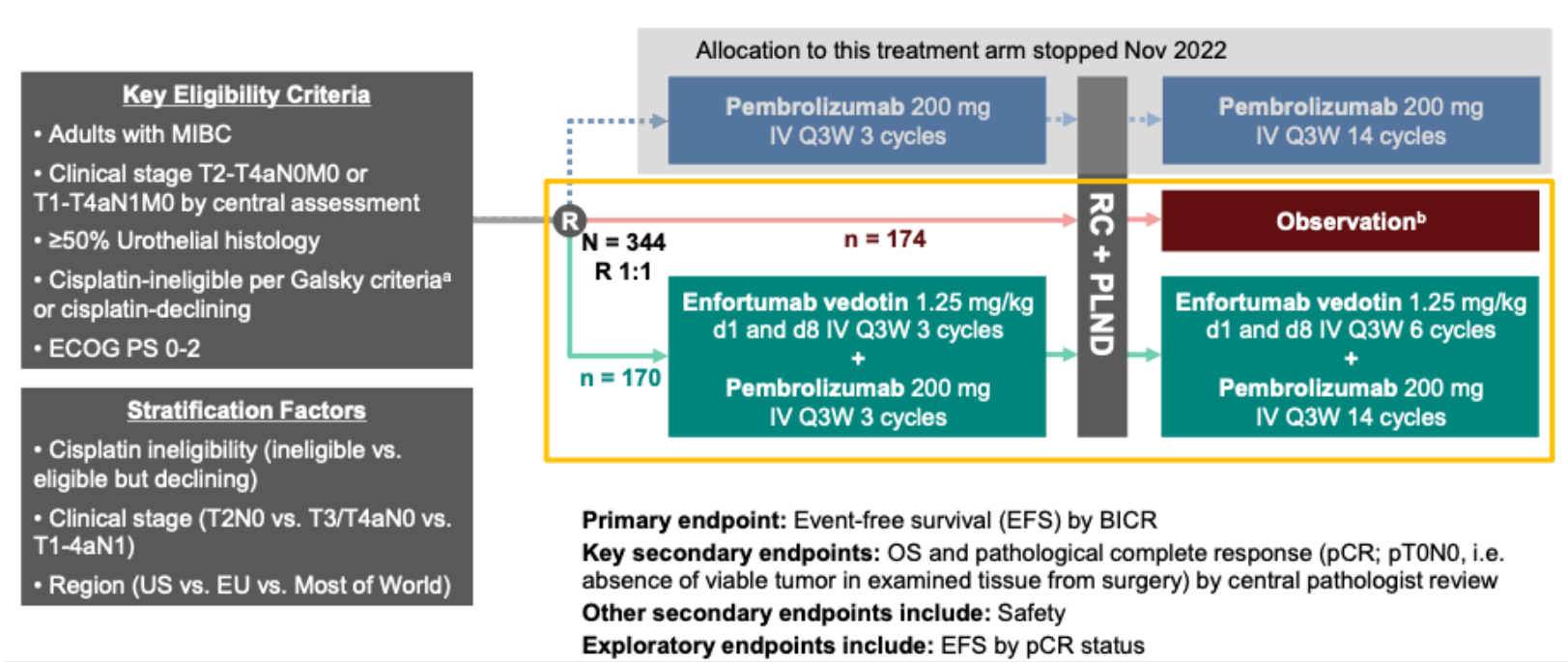
Current treatment paradigm of MIBC



Perioperative Enfortumab Vedotin Plus Pembrolizumab in Cisplatin-ineligible MIBC: Phase 3 KEYNOTE-905 Study

BERLIN 2025 ESMO congress

Perioperative Enfortumab Vedotin Plus Pembrolizumab in Participants With Muscle-invasive Bladder Cancer Who Are Cisplatin-ineligible: Phase 3 KEYNOTE-905 Study



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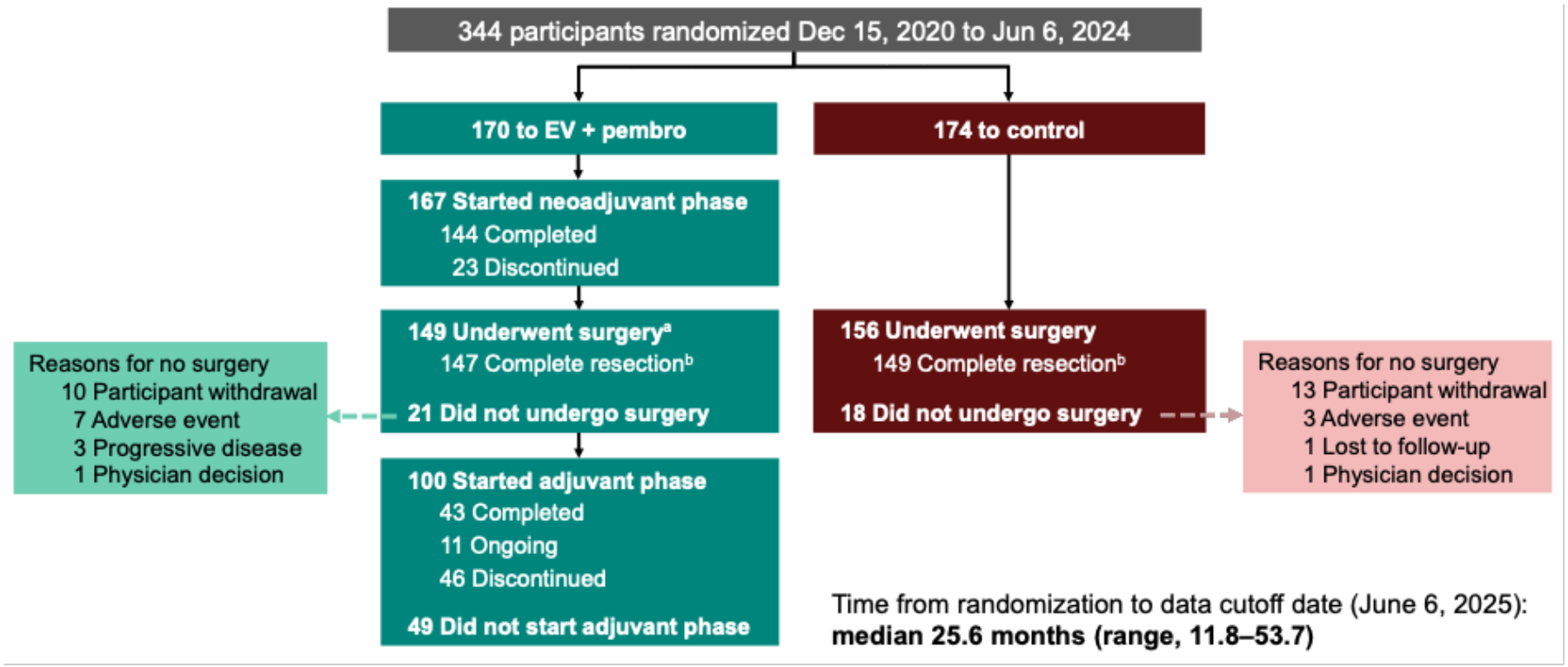
Perioperative Enfortumab Vedotin Plus Pembrolizumab in Cisplatin-ineligible MIBC: Phase 3 KEYNOTE-905 Study



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Baseline Characteristics

Characteristic, n (%)	EV + pembro (N = 170)	Control (N = 174)
Median age (range), years	74.0 (47–87)	72.5 (46–87)
≥65 to <75 years	63 (37.1)	77 (44.3)
≥75 years	78 (45.9)	68 (39.1)
Male	137 (80.6)	131 (75.3)
ECOG PS		
0	102 (60.0)	95 (54.6)
1	47 (27.6)	53 (30.5)
2	21 (12.4)	26 (14.9)
Region		
United States	21 (12.4)	23 (13.2)
European Union	78 (45.9)	77 (44.3)
Most of World	71 (41.8)	74 (42.5)
Cisplatin eligibility status (per Galsky criteria)		
Ineligible	142 (83.5)	139 (79.9)
Eligible but declining	28 (16.5)	35 (20.1)
PD-L1 combined positive score (CPS) ≥10[a]	80 (47.1)	83 (47.7)
Tumor stage at baseline (*centrally assessed using both pathology of TURBT specimen and imaging*)[b]		
T2N0	30 (17.6)	32 (18.4)
T3/T4aN0	133 (78.2)	132 (75.9)
T1-4aN1	7 (4.1)	10 (5.7)
Creatinine clearance		
≥60 mL/min	68 (40.0)	72 (41.4)
≥30 and <60 mL/min	102 (60.0)	101 (58.0)
<30 mL/min	0	1 (0.6)
Pure urothelial carcinoma histology	152 (89.4)	161 (92.5)

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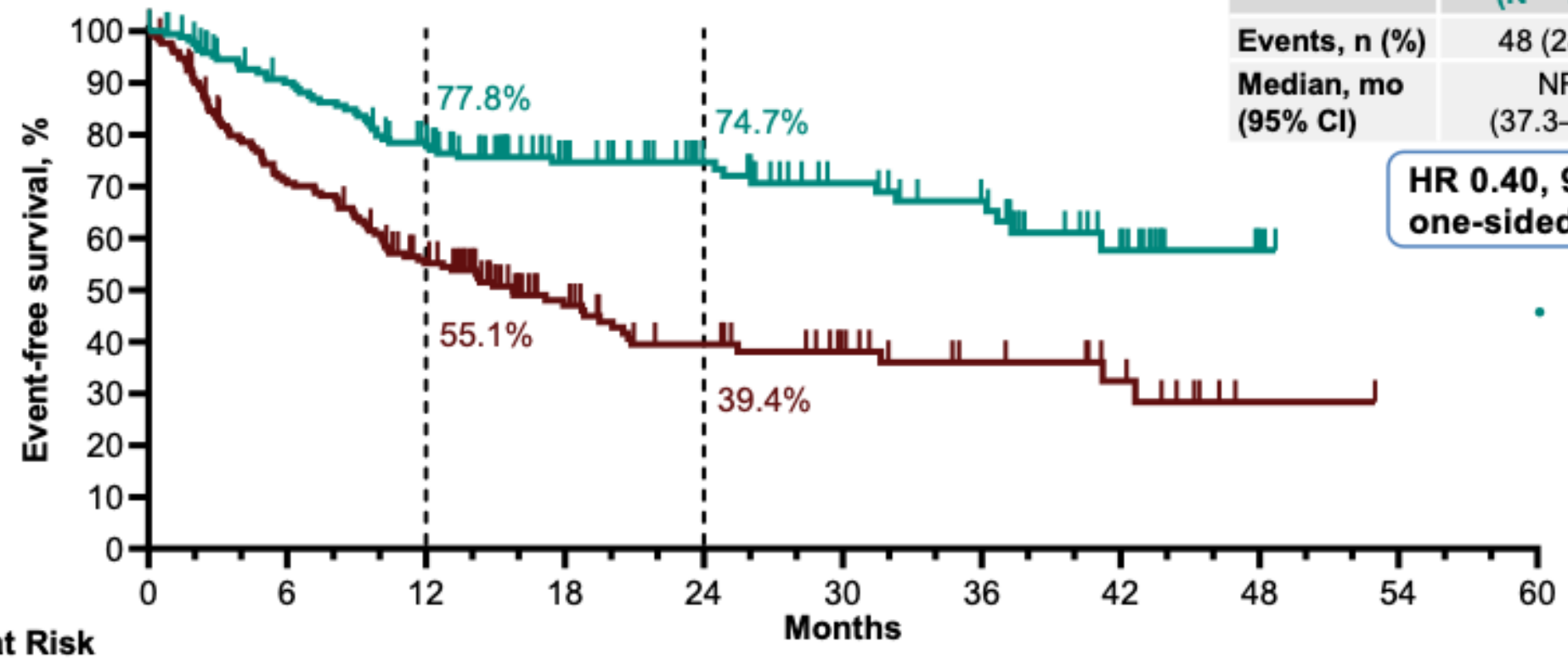
Primary Endpoint: EFS[a] by BICR

ITT Population

	EV + pembro (N = 170)	Control (N = 174)
Events, n (%)	48 (28.2)	95 (54.6)
Median, mo (95% CI)	NR (37.3–NR)	15.7 (10.3–20.5)

HR 0.40, 95% CI 0.28–0.57, one-sided *P* <.0001*



- 29/174 pts (16.7%) in the control arm received adjuvant nivolumab as of data cutoff per local guidelines/prescribing information

No. at Risk

EV + pembro	170	140	116	73	56	42	35	16	3	0	0
Control	174	116	84	48	33	22	14	9	1	0	0

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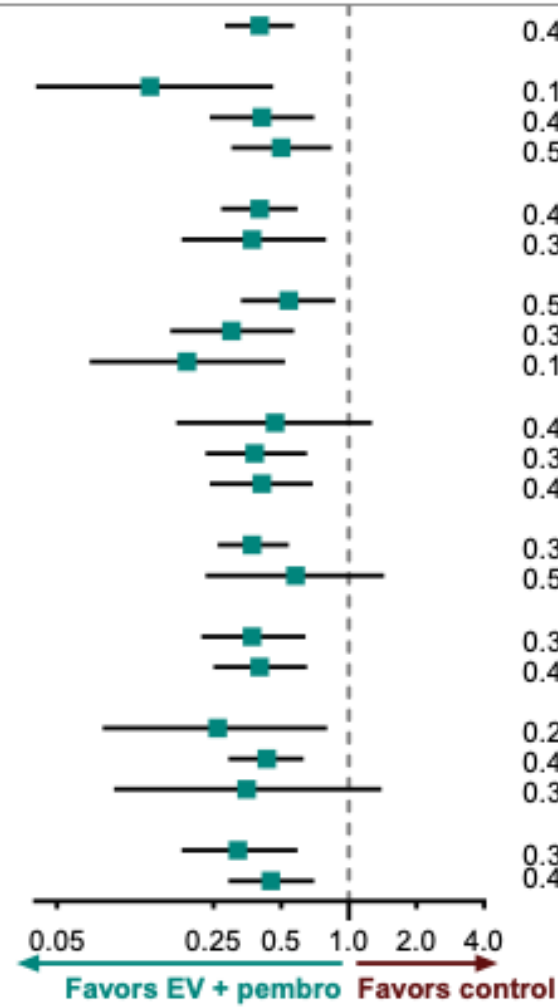
EFS by BICR in Key Subgroups
ITT Population

	Events/Participants EV + pembro	Events/Participants Control	HR (95% CI)
Overall	48/170	95/174	0.40 (0.28-0.57)
Age			
<65 years	3/29	16/29	0.13 (0.04-0.46)
≥65 to <75 years	21/63	44/77	0.41 (0.24-0.70)
≥75 years	24/78	35/68	0.50 (0.30-0.84)
Sex			
Male	37/137	72/131	0.40 (0.27-0.59)
Female	11/33	23/43	0.37 (0.18-0.79)
ECOG PS			
0	26/102	43/95	0.54 (0.33-0.87)
1	16/47	35/53	0.30 (0.16-0.57)
2	6/21	17/26	0.19 (0.07-0.52)
Region			
United States	6/21	11/23	0.47 (0.17-1.27)
European Union	21/78	41/77	0.38 (0.23-0.65)
Most of World	21/71	43/74	0.41 (0.24-0.69)
Cisplatin eligibility			
Ineligible	41/142	81/139	0.37 (0.26-0.54)
Eligible but declining	7/28	14/35	0.58 (0.23-1.44)
PD-L1 CPS			
≥10	21/80	42/83	0.37 (0.22-0.64)
<10	26/87	53/90	0.40 (0.25-0.65)
Tumor stage			
T2N0	4/30	13/32	0.26 (0.08-0.80)
T3/T4aN0	41/133	75/132	0.43 (0.29-0.63)
T1-4aN1	3/7	7/10	0.35 (0.09-1.40)
Creatinine clearance			
≥60 mL/min	16/68	36/72	0.32 (0.18-0.59)
<60 mL/min	32/102	59/102	0.45 (0.29-0.70)



Subgroup levels with <10 events across both treatment arms were not included in forest plots.

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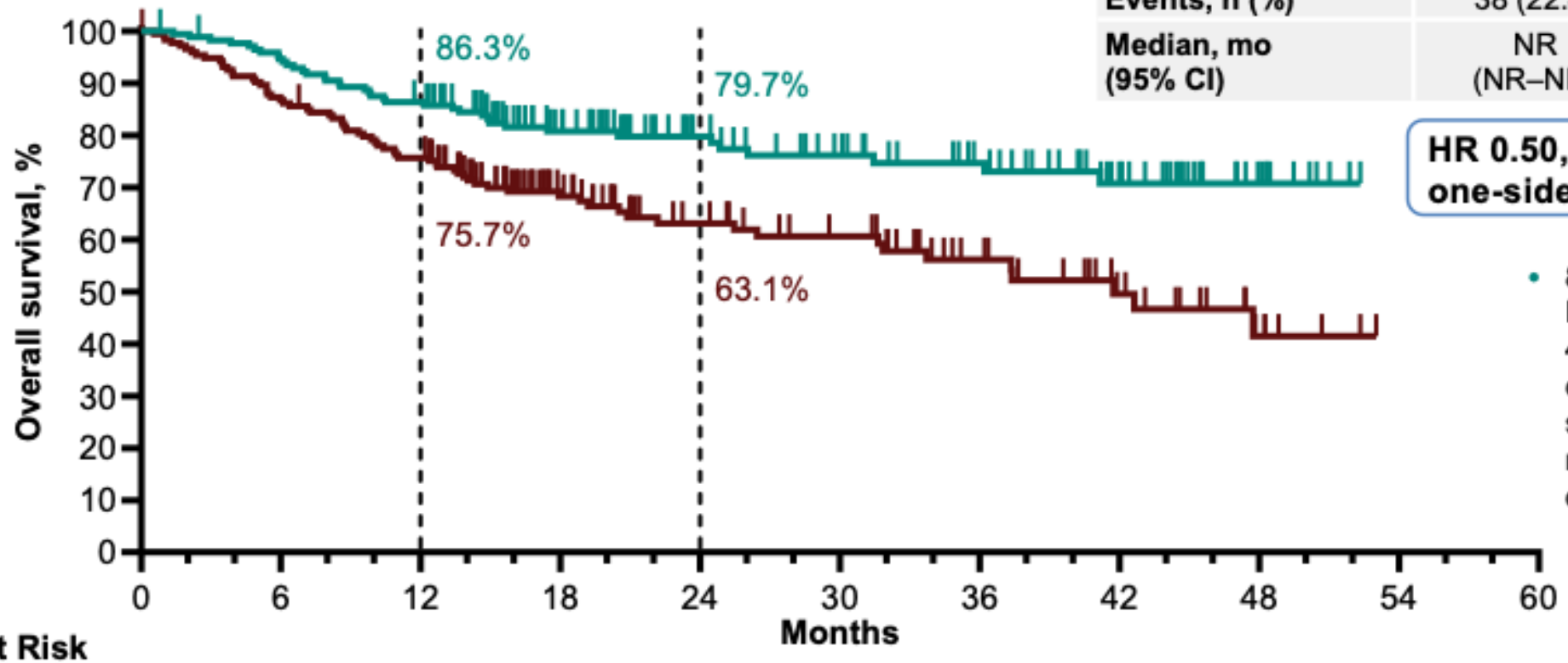
Key Secondary Endpoint: OS
ITT Population

	EV + pembro (N = 170)	Control (N = 174)
Events, n (%)	38 (22.4)	68 (39.1)
Median, mo (95% CI)	NR (NR–NR)	41.7 (31.8–NR)



HR 0.50, 95% CI 0.33–0.74, one-sided *P* =.0002*

- 8/170 pts (4.7%) in the EV + pembro arm and 46/174 (26.4%) in the control arm received subsequent therapy for recurrent/metastatic disease

No. at Risk

EV + pembro	170	159	144	94	68	56	45	28	10	0	0
Control	174	150	130	75	54	45	30	18	6	0	0

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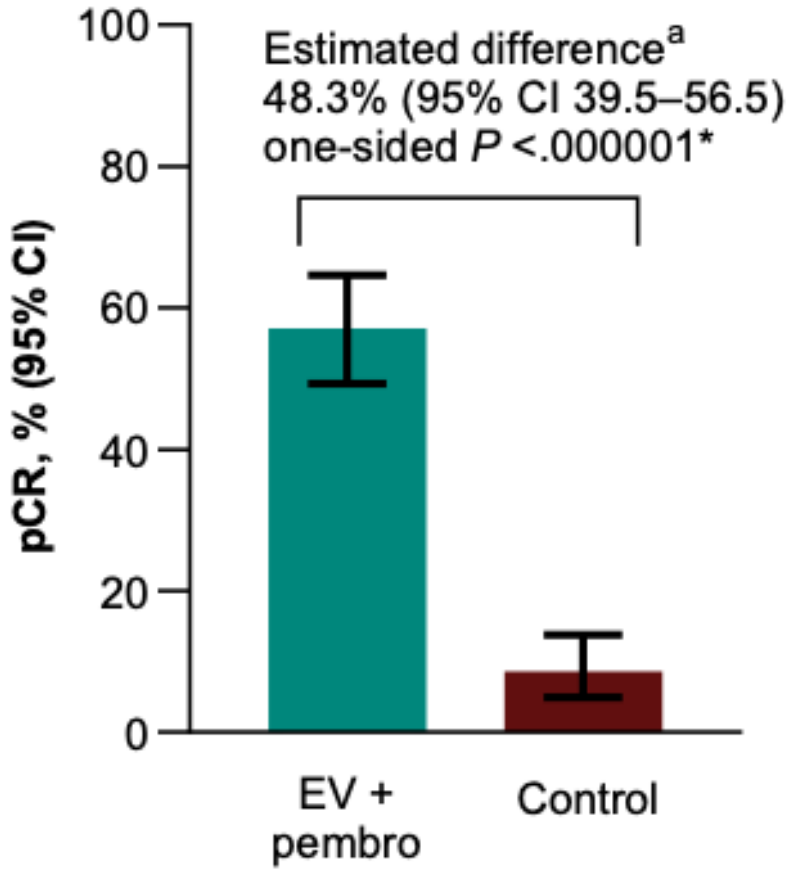
Key Secondary Endpoint: pCR by Central Pathology Review

ITT Population



	EV + pembro (N = 170)	Control (N = 174)
pCR, n	97	15
pCR rate, % (95% CI)	57.1 (49.3–64.6)	8.6 (4.9–13.8)

- **pCR:** absence of viable tumor (pT0N0) in examined tissue from RC + PLND
- Pts who did not undergo surgery, including those with clinical complete response after neoadjuvant therapy, were considered non-responders

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Summary of AEs, All Phases of Treatment
Safety Analysis Population

- Median (range) duration of **neoadjuvant therapy** in the EV + pembro arm (N = 167): 1.6 months (0.03–2.8)
  - Median cycles of neoadjuvant EV + pembro: 3.0 (range, 1.0–3.0)
- Median (range) duration of **adjuvant therapy** in the EV + pembro arm (N = 100): 8.0 months (0.03–12.9)
  - Median (range) number adjuvant cycles of EV was 6.0 (1.0–6.0) and of pembro was 12.0 (1.0–14.0)

	EV + pembro (N = 167)	Control (N = 159)
Any grade TEAE[a]	167 (100)	103 (64.8)
Surgery phase only[b]	99/146 (67.8)	103 (64.8)
Grade ≥3 TEAE	119 (71.3)	73 (45.9)
Surgery phase only	52/146 (35.6)	73 (45.9)
Serious TEAE	97 (58.1)	65 (40.9)
Surgery phase only	42/146 (28.8)	65 (40.9)
AE leading to surgery delay[c]	6/149 (4.0)	1/156 (0.6)
TEAE leading to dose reduction of EV	28 (16.8)	NA
TEAE leading to discontinuation of EV	69 (41.3)	NA
TEAE leading to discontinuation of pembro	57 (34.1)	NA
TEAE leading to death	13 (7.8)*	9 (5.7)
Surgery phase only	4/146 (2.7)	9 (5.7)

TEAE, treatment-emergent adverse event. Data are n (%) when denominator matches header, and n/N (%) when denominator is different.
*Included 2 drug-related deaths (both during neoadjuvant phase: n = 1 myasthenia gravis and n = 1 toxic epidermal necrolysis).

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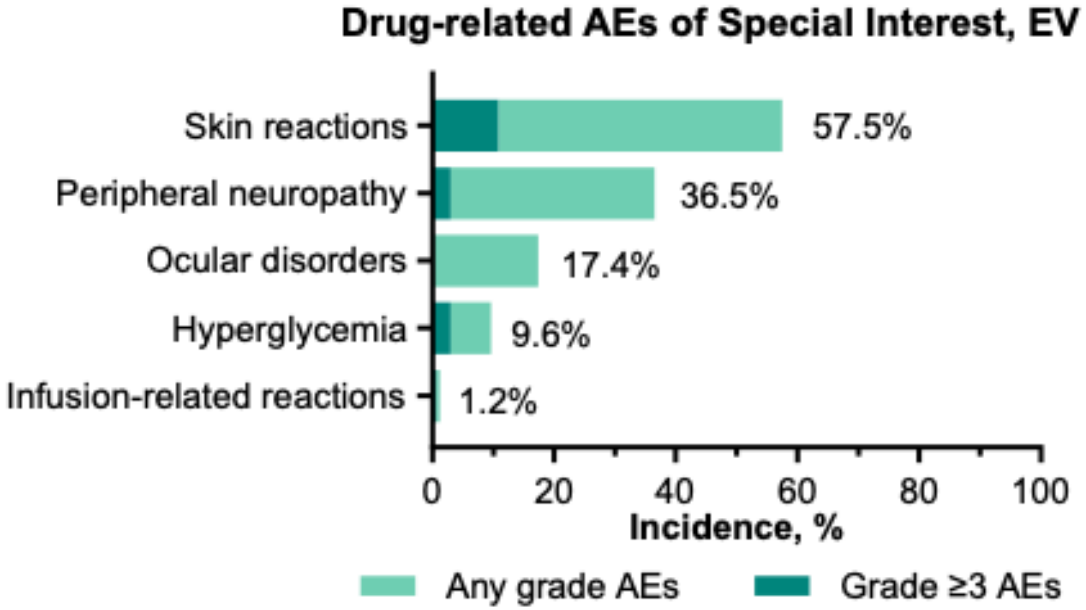
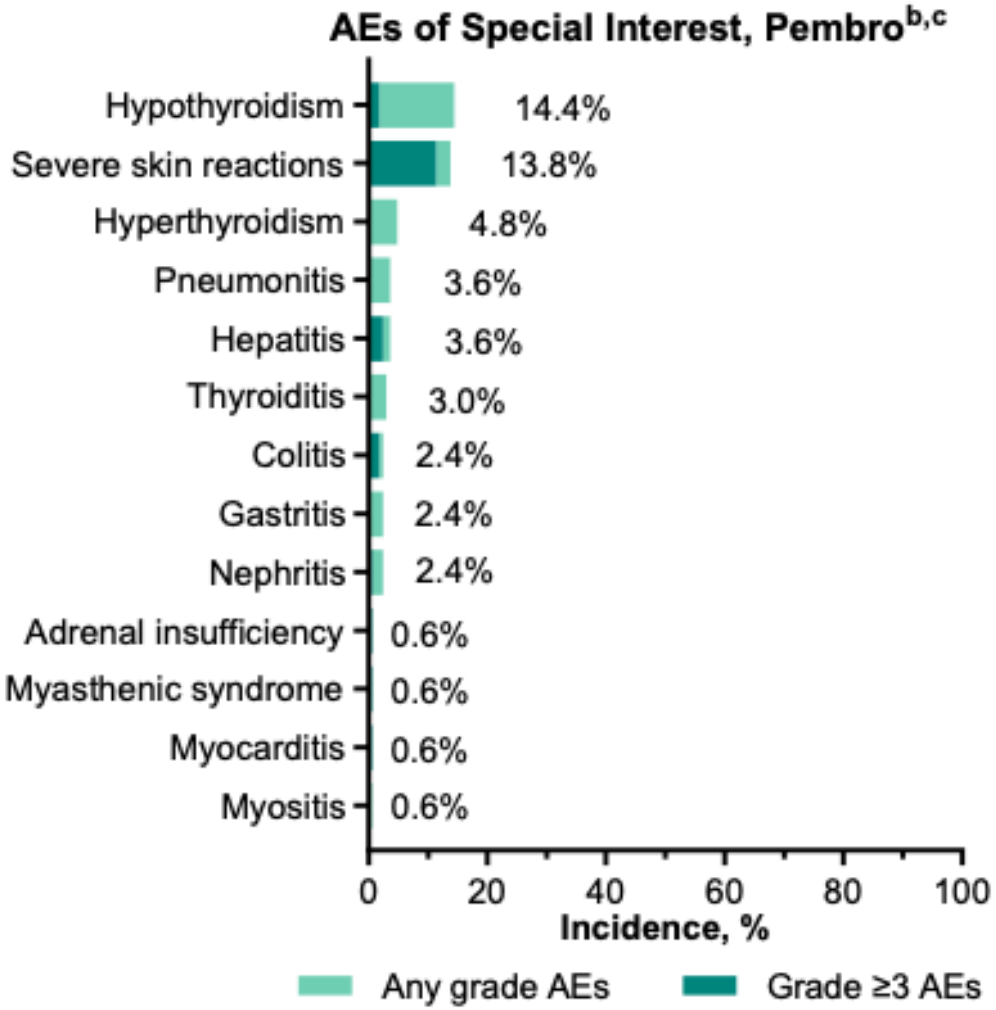
AEs of Special Interest[a]

Safety Analysis Population, EV + Pembro Arm





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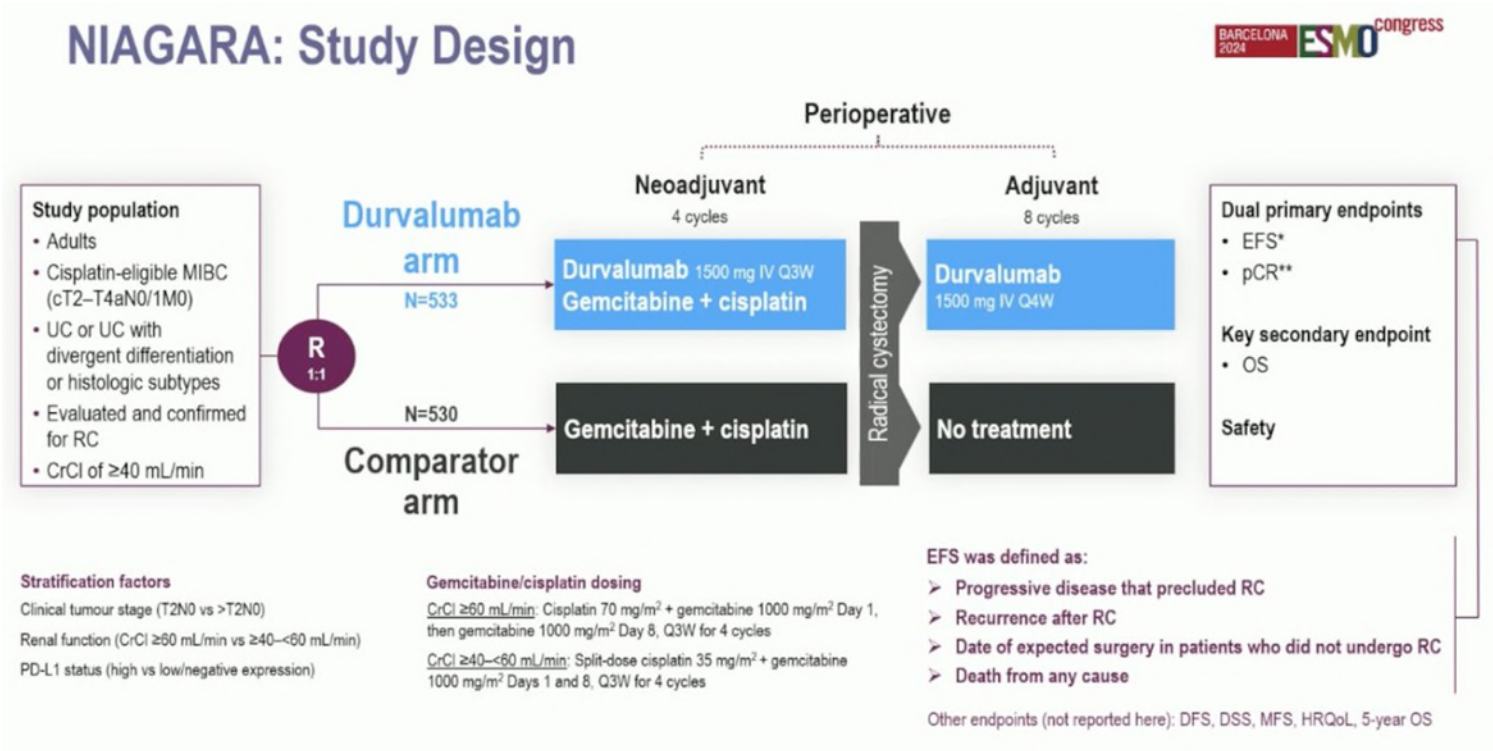
Perioperative chemo-immunotherapy in MIBC: NIAGARA study



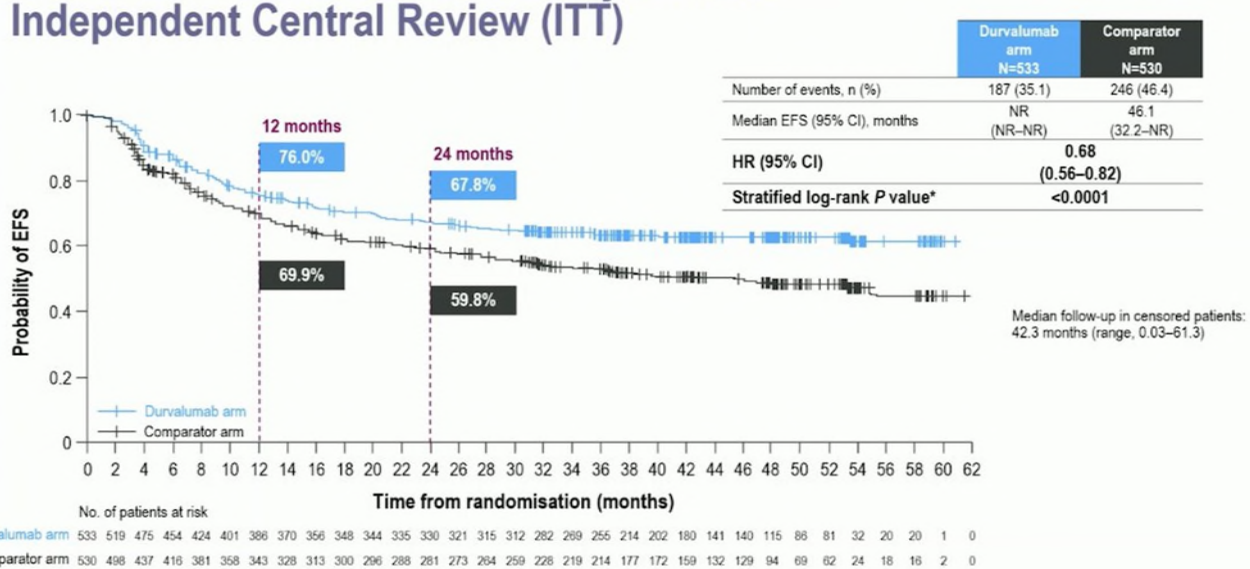
Galsky et al. ESMO 2024; Powles et al. NEJM 2024

Perioperative chemo-immunotherapy in MIBC: NIAGARA study

NIAGARA: Baseline Characteristics (ITT)

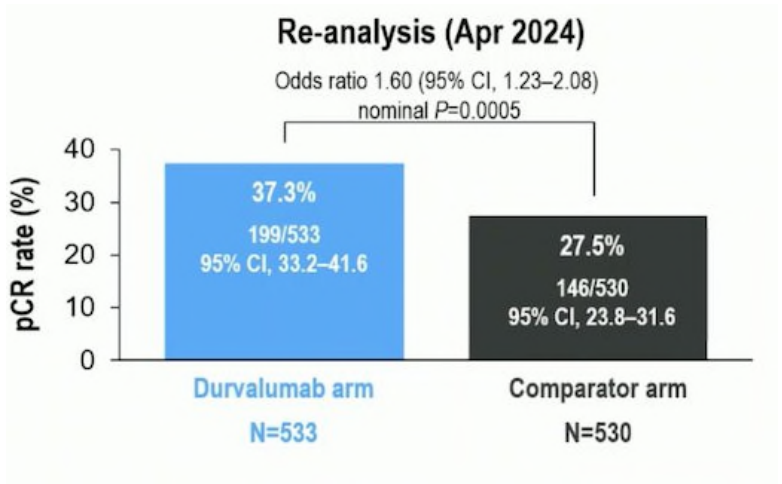
Characteristics		Durvalumab arm N=533	Comparator arm N=530
Age	Median, years (range)	65 (34–84)	66 (32–83)
Sex, %	Male	82	82
Race, %	White	66	68
	Asian	29	27
	Black/Other	2	1
	Not reported	3	4
ECOG PS, %	0	78	78
	1	22	22
Smoker, %	Yes (current or former)	71	75
Renal function*, %	CrCl ≥60 mL/min	81	81
	CrCl ≥40–<60 mL/min	19	19
Tumour stage*, %	T2N0	40	40
	>T2N0	60	60
PD-L1 expression†, %	High	73	73
	Low/negative	27	27
Histology, %	UC	86	83
	UC with divergent differentiation or histologic subtypes	14	17
Regional lymph nodes, %	N0	95	94
	N1	5	6

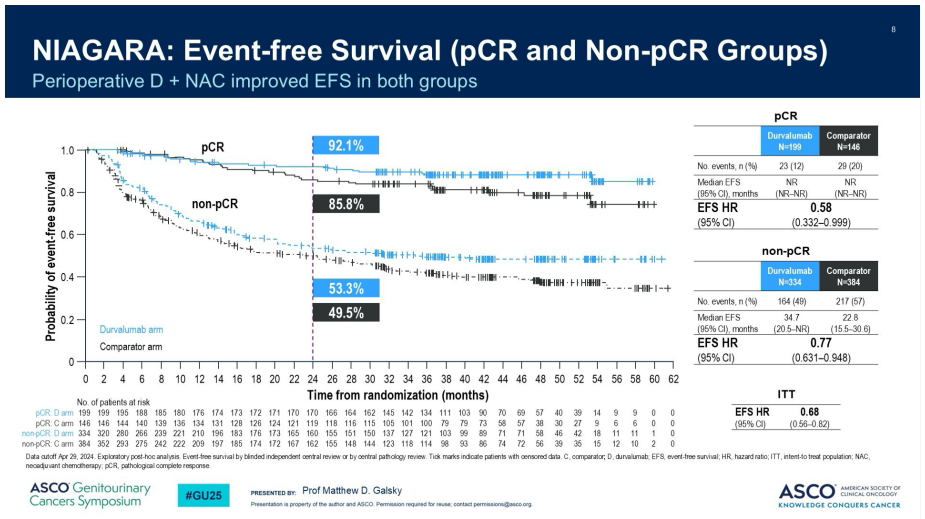
NIAGARA: Event-free Survival by Blinded Independent Central Review (ITT)

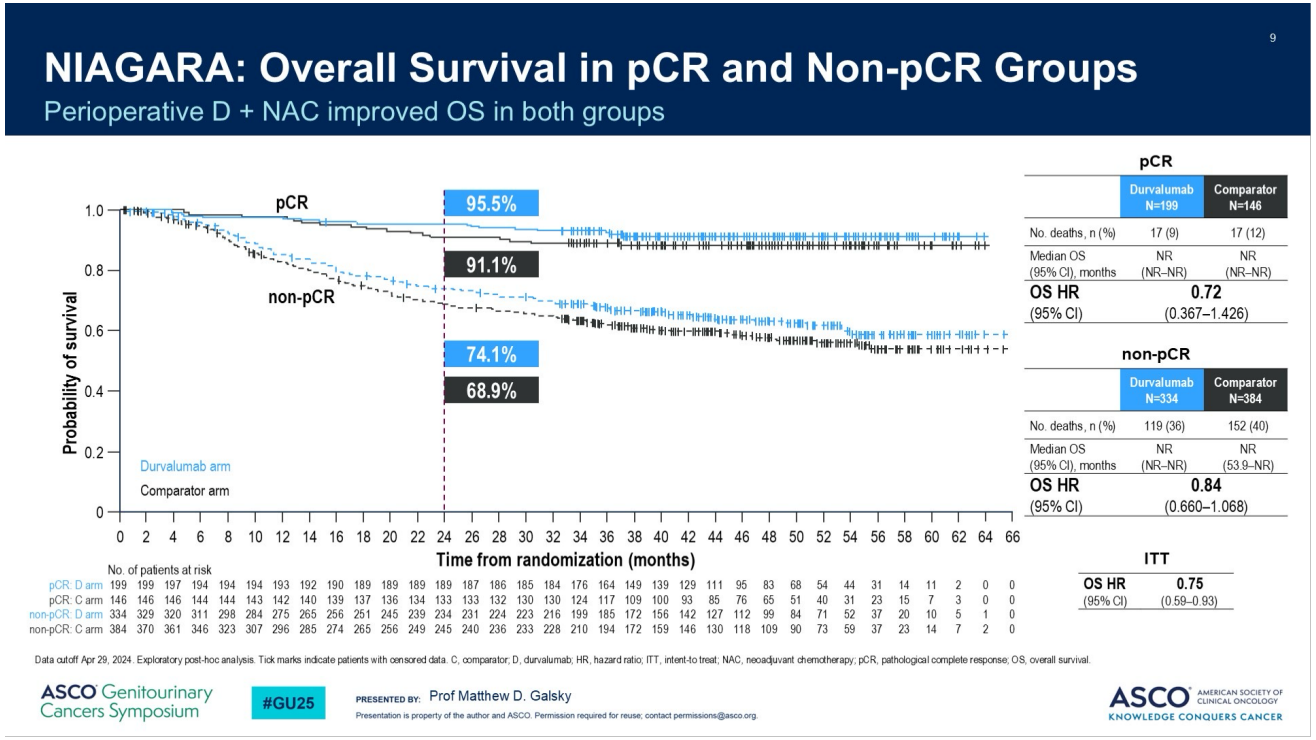


Galsky et al. ESMO 2024; Powles et al. NEJM 2024

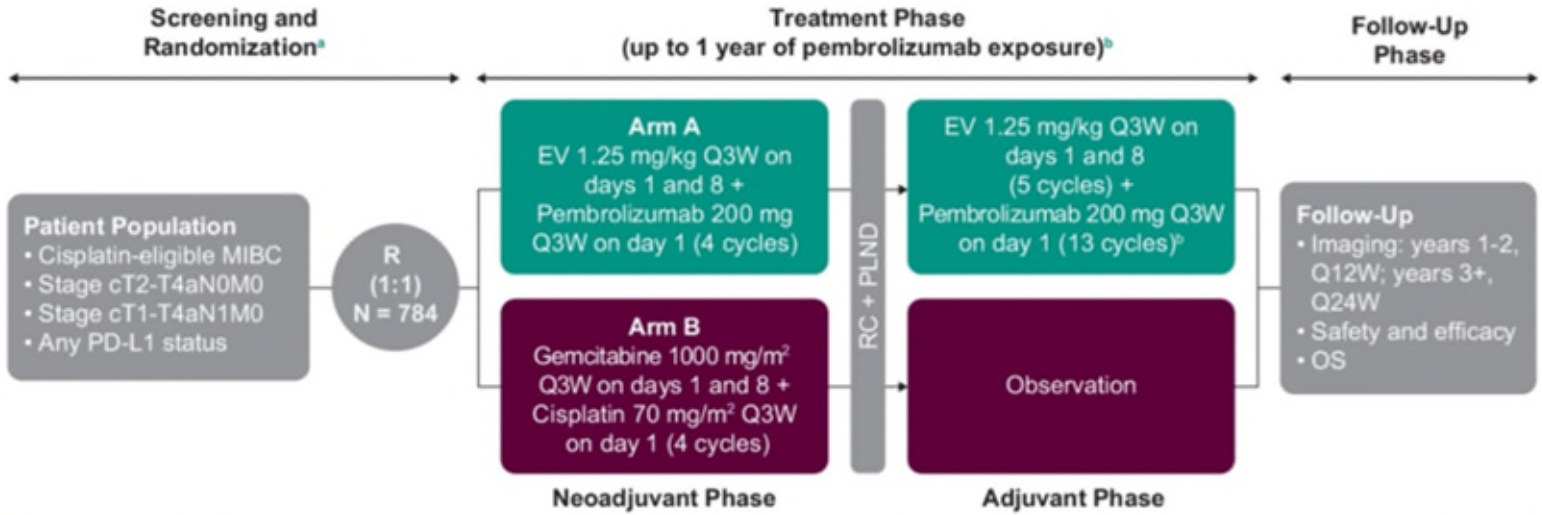
Perioperative chemo-immunotherapy in MIBC: NIAGARA study







Galsky et al. ESMO 2024; Powles et al. NEJM 2024

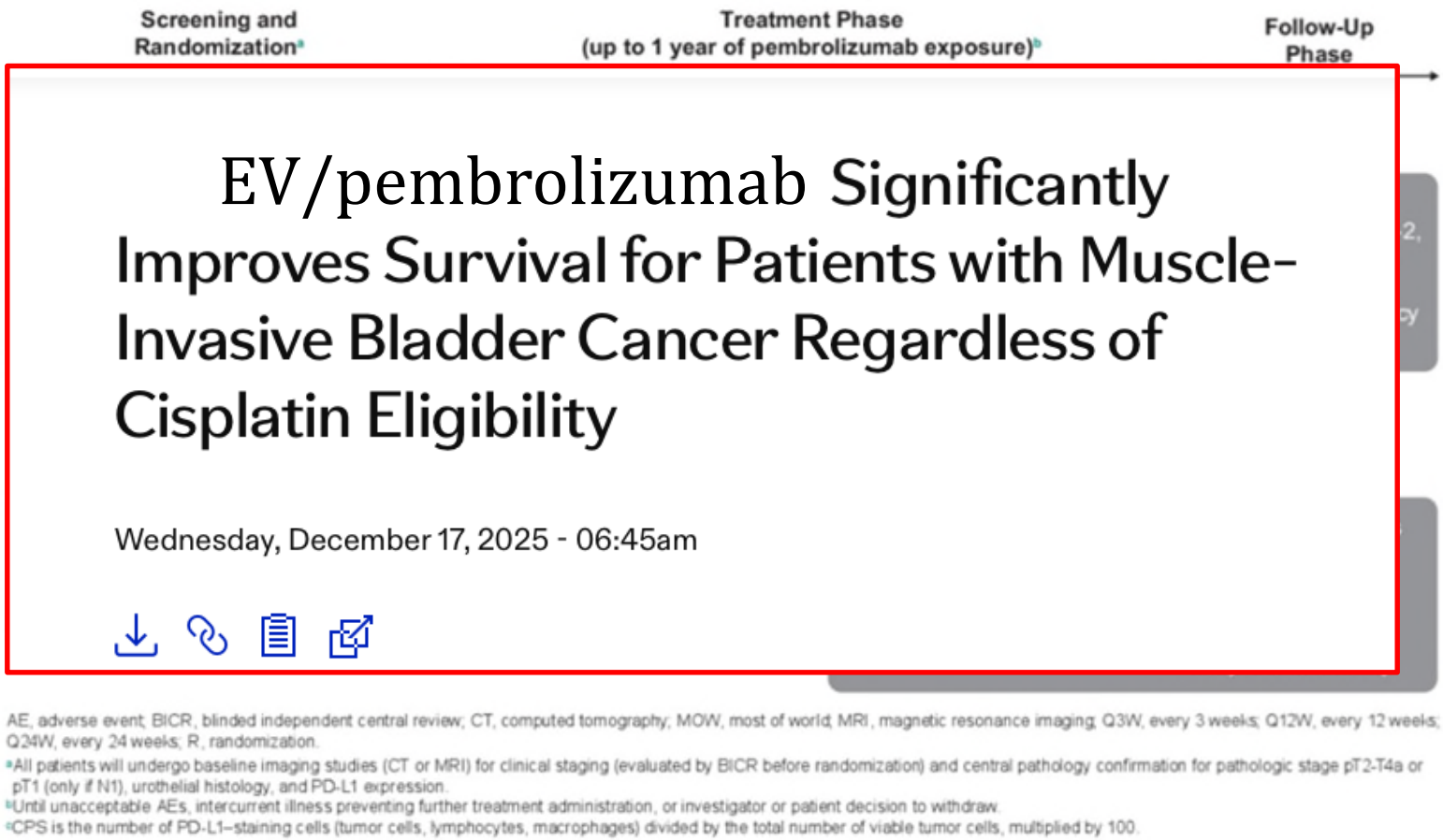


AE, adverse event; BICR, blinded independent central review; CT, computed tomography; MOW, most of world; MRI, magnetic resonance imaging; Q3W, every 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; R, randomization.

[a]All patients will undergo baseline imaging studies (CT or MRI) for clinical staging (evaluated by BICR before randomization) and central pathology confirmation for pathologic stage pT2-T4a or pT1 (only if N1), urothelial histology, and PD-L1 expression.

[b]Until unacceptable AEs, intercurrent illness preventing further treatment administration, or investigator or patient decision to withdraw.

[c]CPS is the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.


Screening and Randomization[a]
Treatment Phase (up to 1 year of pembrolizumab exposure)[b]
Follow-Up Phase
EV/pembrolizumab Significantly Improves Survival for Patients with Muscle-Invasive Bladder Cancer Regardless of Cisplatin Eligibility
Wednesday, December 17, 2025 - 06:45am
AE, adverse event; BICR, blinded independent central review; CT, computed tomography; MOW, most of world; MRI, magnetic resonance imaging; Q3W, every 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; R, randomization.
[a]All patients will undergo baseline imaging studies (CT or MRI) for clinical staging (evaluated by BICR before randomization) and central pathology confirmation for pathologic stage pT2-T4a or pT1 (only if N1), urothelial histology, and PD-L1 expression.
[b]Until unacceptable AEs, intercurrent illness preventing further treatment administration, or investigator or patient decision to withdraw.
[c]CPS is the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

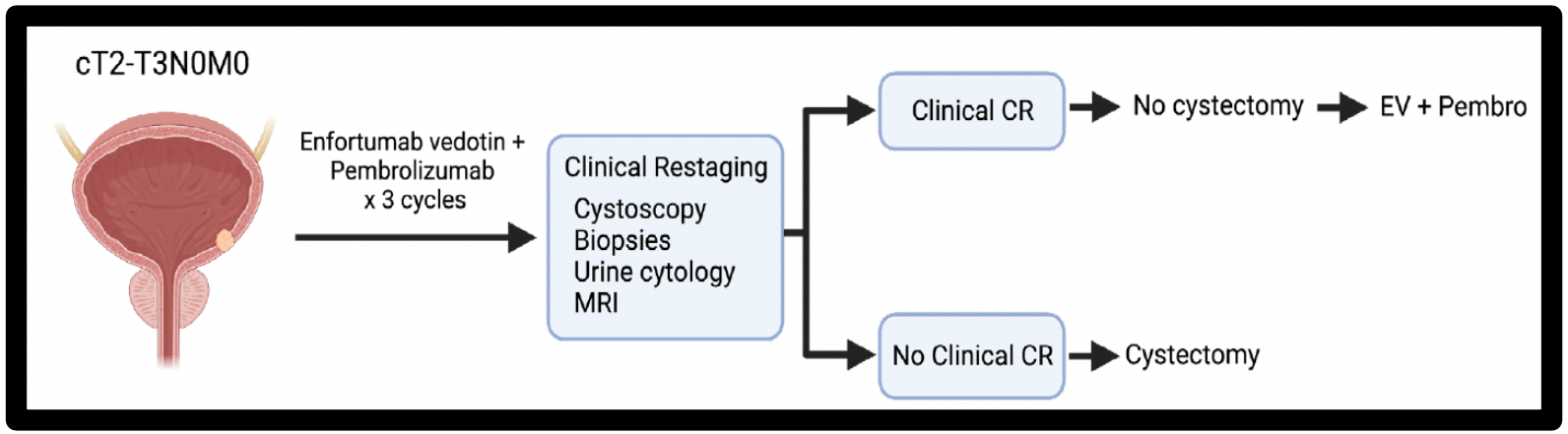
Key questions in the EV/P era of MIBC

- High path-CR rates post neoadjuvant EV/P is encouraging. But do all those 60% of patients need definitive local therapy?
- Can we de-escalate adjuvant therapy in exceptional responders ?
- How do these results apply to patients opting for TMT?

HCRN GU22-598: Phase 2 trial of enfortumab vedotin plus pembrolizumab with selective bladder sparing for treatment of muscle-invasive urothelial cancer of the bladder

Eric J. Miller[1], Tareq Salous[2], Elizabeth R. Plimack[3], Abhishek Tripathi[4], Alexander Z. Wei[5], Menggang Yu[6], Jonathan F. Anker[1], Saad Omar Atiq[1], Matthew D. Galsky[1]

[1]Mount Sinai Tisch Cancer Center, New York, NY; [2]Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN; [3]Fox Chase Cancer Center, Philadelphia, PA; [4]City of Hope Comprehensive Cancer Center, Duarte, CA; [5]Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY;

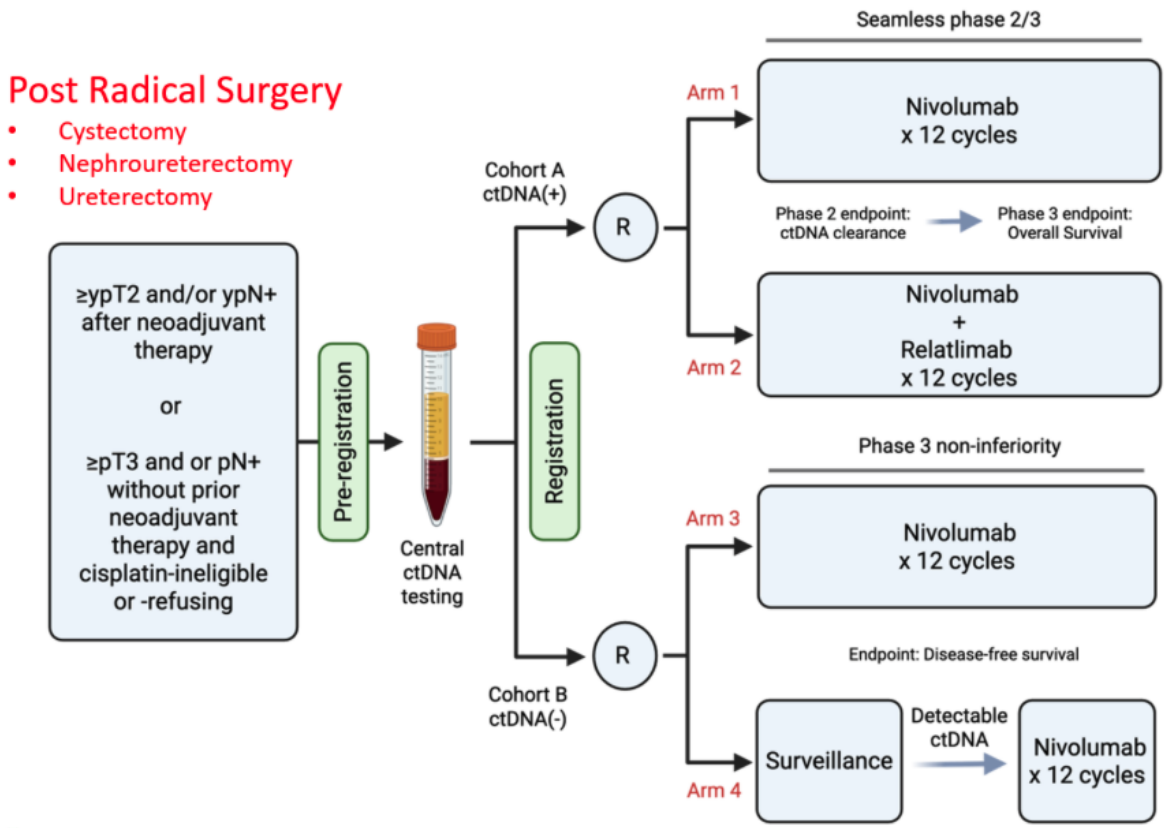


Primary endpoint: cCR rate with EV plus pembrolizumab for MIBC

Secondary endpoint:

- Safety
- PPV of cCR for 2-year bladder-intact event-free survival (BIEFS)
- PPV of cCR for 2-year MFS
- Invasive local recurrence-free survival in patients achieving a cCR and forgoing immediate cystectomy
- OS in patients achieving a cCR, in patients not achieving a cCR, and in the overall cohort

A032103 (MODERN) Schema

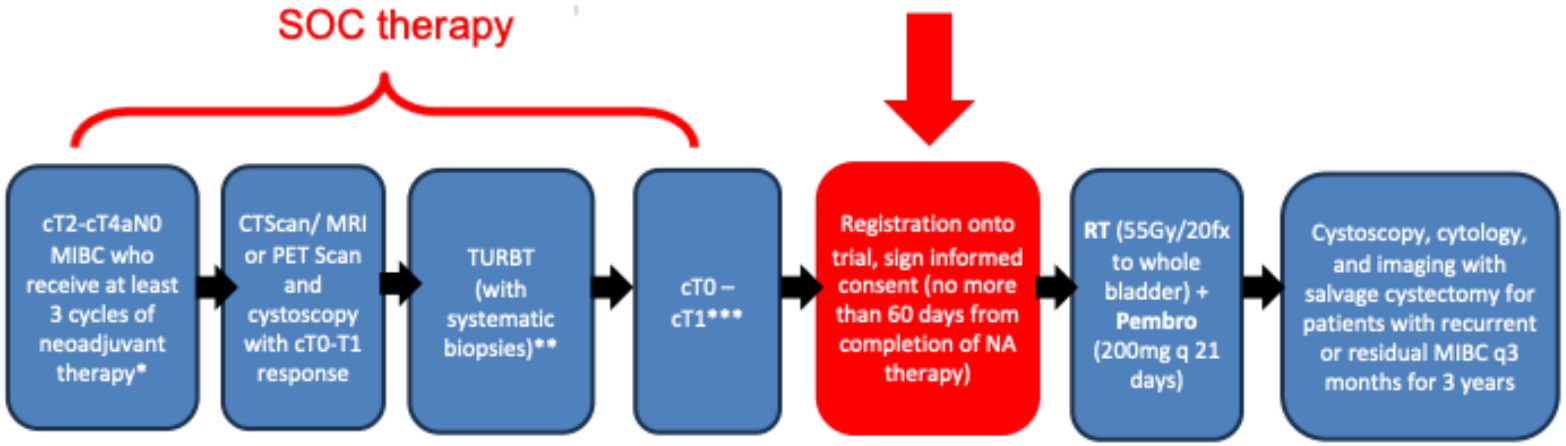


- Eligible patients could have had muscle-invasive urothelial cancers of the bladder, urethra, ureter, or renal pelvis
- For patients who received neoadjuvant systemic therapy, regimens could have included:
  - cisplatin-based chemotherapy
  - cisplatin-based chemotherapy plus PD-1/PD-L1 blockade
  - EV plus Pembro
- Patients who did not receive neoadjuvant chemotherapy should be cisplatin-ineligible or cisplatin-refusing
- Patients with pT2N0 are eligible ONLY if ctDNA(+) by commercial Signatera – note: this is different than ypT2N0 (after neoadjuvant therapy) and such patients eligible if ctDNA(+) or ctDNA(-)

****All ctDNA testing (Signatera) is done within the context of the study and funded by the study (amendment to allow commercial Signatera pending)**

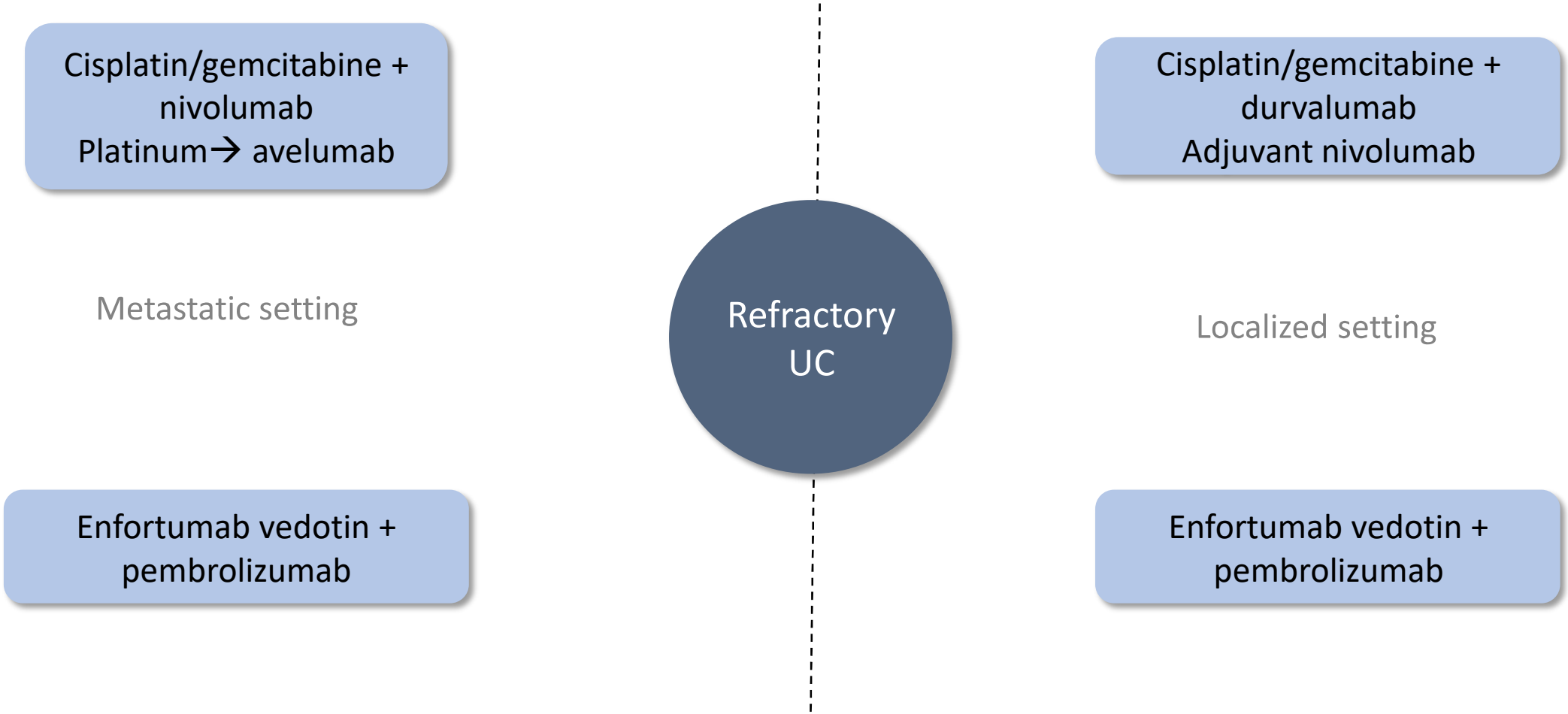
SWOG CANCER RESEARCH NETWORK

S2427: SINGLE ARM PHASE II STUDY OF BLADDER PRESERVATION WITH IMMUNORADIOTHERAPY AFTER A CLINICALLY MEANINGFUL RESPONSE TO NEOADJUVANT THERAPY IN PATIENTS WITH MUSCLE INVASIVE BLADDER CANCER (BRIGHT)

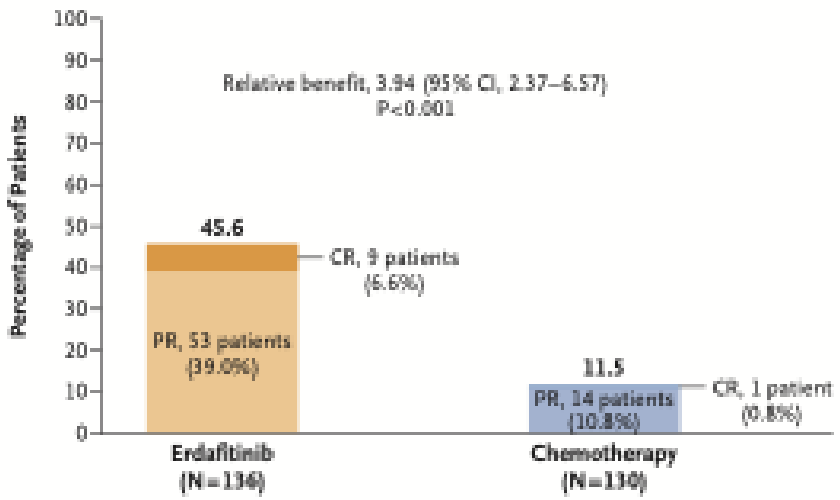


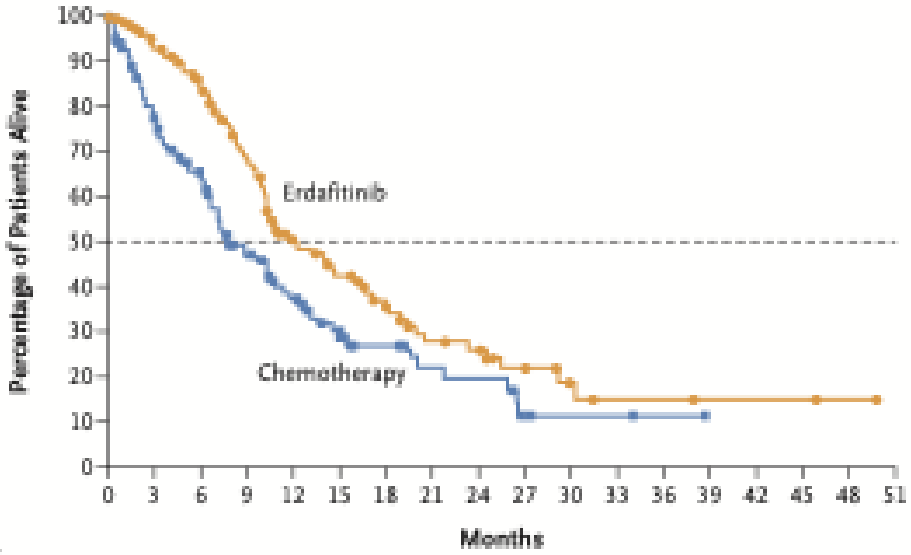
*Patients who receive NAC as the NAT must have at least 3 cycles of cis-based regimen
**Patients found to have >T1 disease on TURBT will proceed to SOC cystectomy
***Diffuse CIS patients will be excluded (>3 cm area of contiguous CIS or >3 separate locations of CIS on TURBT (dome/posterior/left/right/trigone)

Relapsed-refractory Advanced UC



FGFR-3 inhibition in IO-refractory UC: THOR





No. at Risk (no. with censored data)																		
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Erdafitinib	77/136	12.1 (10.3–16.4)
Chemotherapy	78/130	7.8 (6.5–11.1)

Hazard ratio for death, 0.64 (95% CI, 0.47–0.88)
P=0.005

Loriot et al. *NEJM* 2023

Novel FGFR-3 specific inhibitors post EV and IO

- Activating *FGFR3* genetic alterations (most commonly S249C) occur in 15-20% of metastatic urothelial cancers (mUC) and <5% of other solid tumors
- Erdafitinib, a pan FGFR1-4 inhibitor, improves survival in 2L/3L *FGFR3*-altered mUC (OS 12.1 months, confirmed ORR 35%) but has clinical toxicities driven by off-target FGFR-1, 2, and 4 inhibition[1]
- LY3866288 (LOXO-435) is an oral, highly potent and isoform-selective small molecule FGFR3i designed to limit off-target toxicities[2]
- Here we report initial phase 1 dose escalation results from FORAGER-1, a phase 1 study of LY3866288 in *FGFR3*-altered mUC and other advanced solid tumors

LY3866288 is potent against and highly selective for FGFR3 and FGFR3 V555M enzymes while sparing FGFR1 and FGFR2[2]

	Enzyme Inhibition				Fold Selectivity	
	FGFR1 IC_{50} (nM)	FGFR2 IC_{50} (nM)	FGFR3 IC_{50} (nM)	FGFR3 V555M IC_{50} (nM)	FGFR3 over FGFR1	FGFR3 over FGFR2
Erdafitinib	0.3	0.6	0.2	1218.0	1.5x	2.0x
Pemigatinib	0.5	0.3	1.0	752.0	0.5x	0.3x
Infigratinib	0.4	0.7	0.3	579.8	1.3x	0.6x
Futibatinib	0.7	0.4	0.4	14.4	1.8x	1.8x
LY3866288	108.2	19.7	0.3	1.1	361x	66x

[1]Loriot Y. et al. 2023 *N Engl J Med* 389(21):1961-1971. [2]Ballard JA. et. al. 2021 *Mol Cancer Ther* 20 (12_Suppl) P141.

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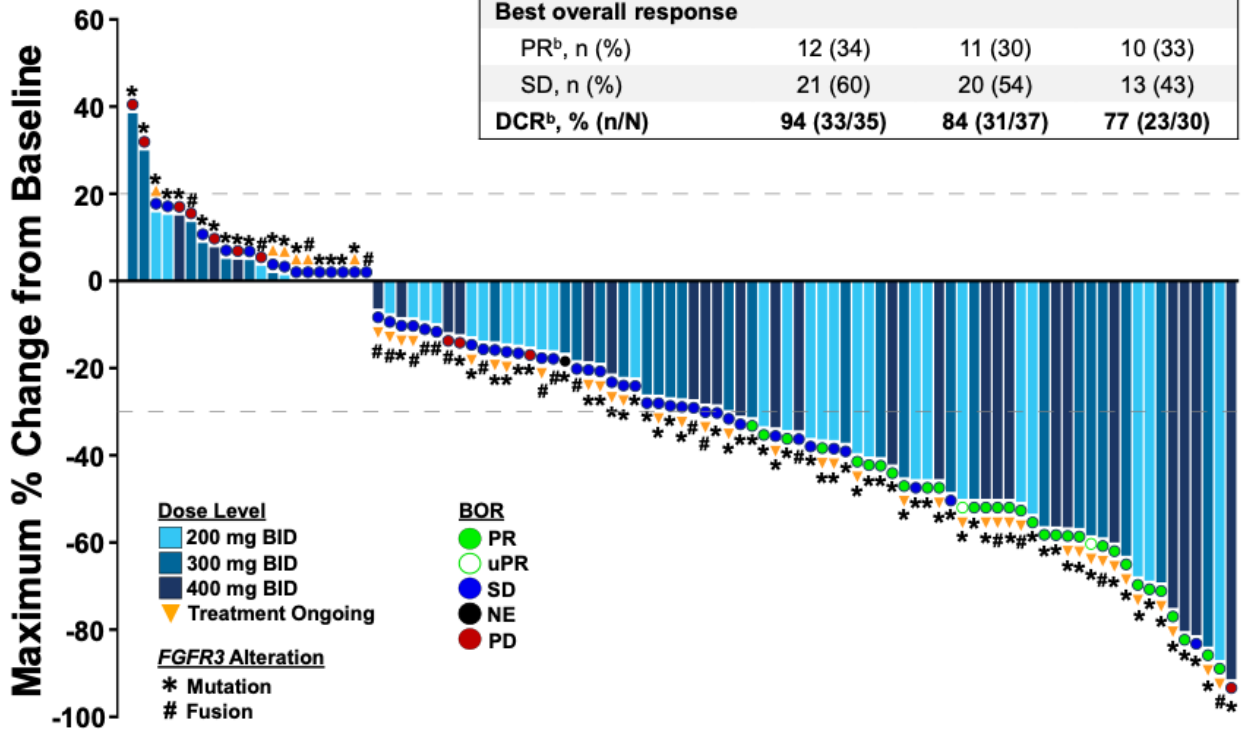
Target population, mUC with mutation/fusion 200 mg, 300 mg and 400 mg BID (n=39)	
Primary tumor location, n (%)	
Upper tract / Lower tract	17 (44) / 22 (56)
Liver metastases, n (%)	
Yes	8 (21)
Bellmunt Score[e], %	
0 / 1 / 2 / 3	18 / 46 / 33 / 3
CrCl/eGFR, n (%)	
≥60 ml/min	22 (56)
Median prior regimens in advanced / metastatic setting (range)	3 (1-6)
Prior Therapy, n (%)	
FGFR inhibitor (progressed/intolerant as reason withdrawn)	11 (28) / 1 (3)
Erdafitinib	10 (26)
AZD4547	2 (5)
PD-1/L1 inhibitor	34 (87)
Platinum chemotherapy	31 (79)
Enfortumab vedotin + Pembrolizumab	9 (23)
Enfortumab vedotin monotherapy	18 (46)
FGFR3 alterations[d], n (%)	
Mutations	32 (82)
Fusions	7 (18)

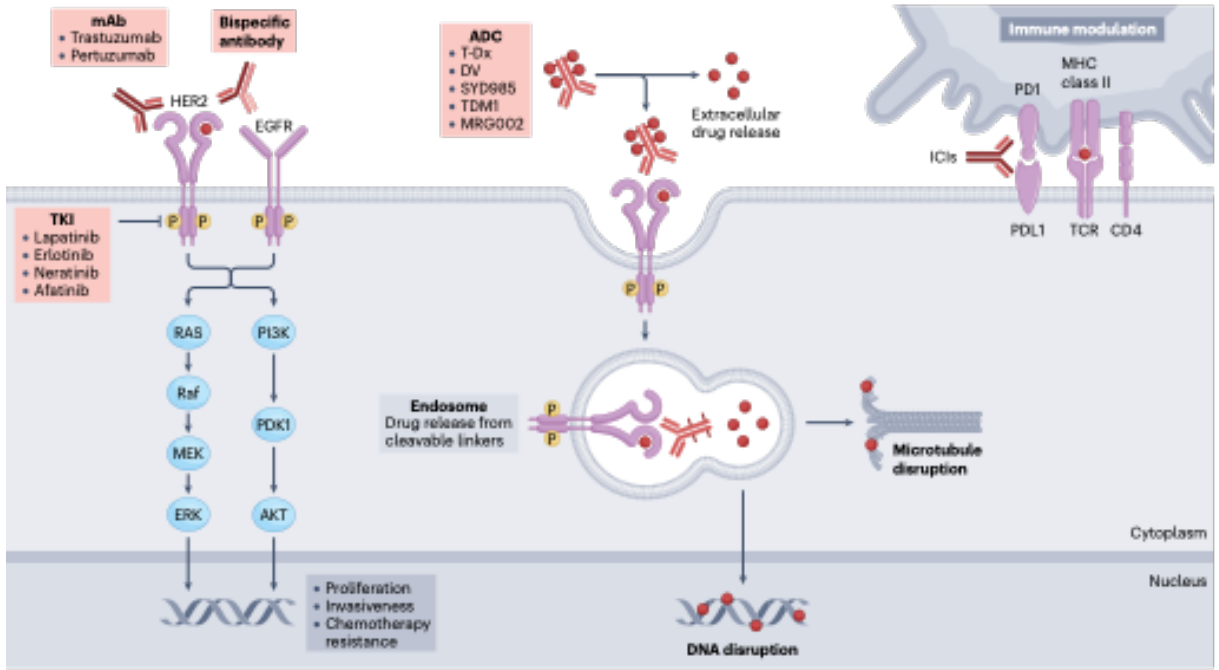
Novel FGFR-3 specific inhibitors post EV and IO

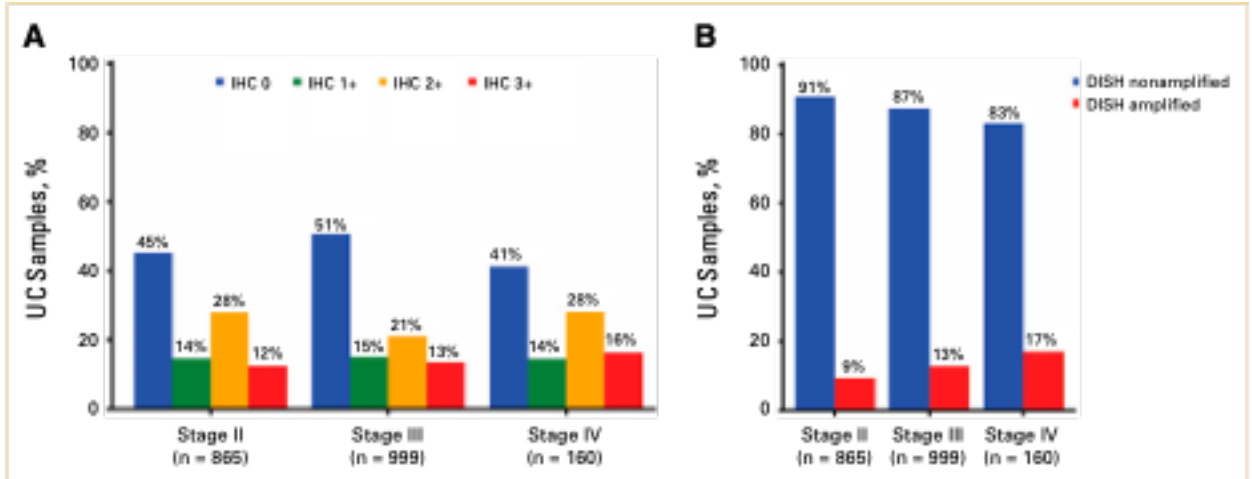
Characteristics	200 mg BID (n=46)	300 mg BID (n=52)	400 mg BID (n=40)
Median age, years (range)	67 (35-88)	72 (42-93)	70 (26-89)
Male, n (%)	31 (67)	31 (60)	29 (73)
Race, White / Asian, n (%)	21 (46) / 19 (41)	30 (58) / 16 (31)	28 (70) / 7 (18)
ECOG PS 1, n (%)	32 (70)	38 (73)	25 (63)
Primary Tumor Location[a], n (%)			
Upper tract/lower tract	20 (44) / 25 (54)	22 (42) / 30 (58)	14 (35) / 26 (65)
FGFR3 alteration[b], n (%)			
Mutation/Fusion	32 (70) / 14 (30)	46 (88) / 6 (12)	31 (78) / 9 (23)
CrCl/eGFR ml/min[c], n (%)			
30-59	16 (35)	18 (35)	16 (40)
≥60	29 (63)	33 (63)	24 (60)
Liver metastases, n (%)	15 (33)	9 (17)	8 (20)
Bellmunt score[d], %			
0 / 1 / 2 / 3	15 / 48 / 33 / 4	21 / 48 / 27 / 4	33 / 45 / 20 / 3
Stable brain metastases, n (%)	3 (7)	1 (2)	1 (3)
Median prior regimens for LA/mUC[e] (range)	2 (1-7)	2 (1-7)	2 (1-7)
Prior Therapy, n (%)			
Platinum chemotherapy	34 (74)	40 (78)	30 (75)
EV[f]	18 (39)	18 (35)	19 (48)
EVP	10 (22)	11 (22)	14 (35)
FGFR inhibitor	11 (24)	15 (29)	10 (25)

Efficacy Evaluable Patients[a]	200 mg BID (n=35)	300 mg BID (n=37)	400 mg BID (n=30)
ORR[b], % (n/N)	**34 (12/35)**	**30 (11/37)**	**33 (10/30)**
Best overall response			
PR[b], n (%)	12 (34)	11 (30)	10 (33)
SD, n (%)	21 (60)	20 (54)	13 (43)
DCR[b], % (n/N)	**94 (33/35)**	**84 (31/37)**	**77 (23/30)**



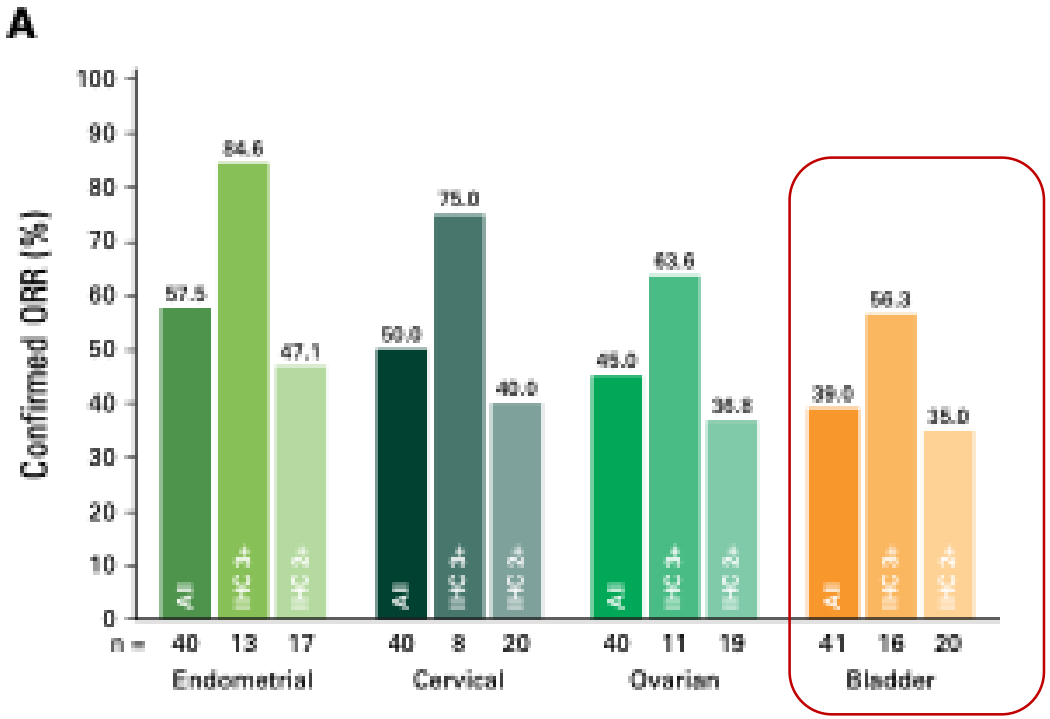
HER-2 inhibition in relapsed refractory urothelial cancer

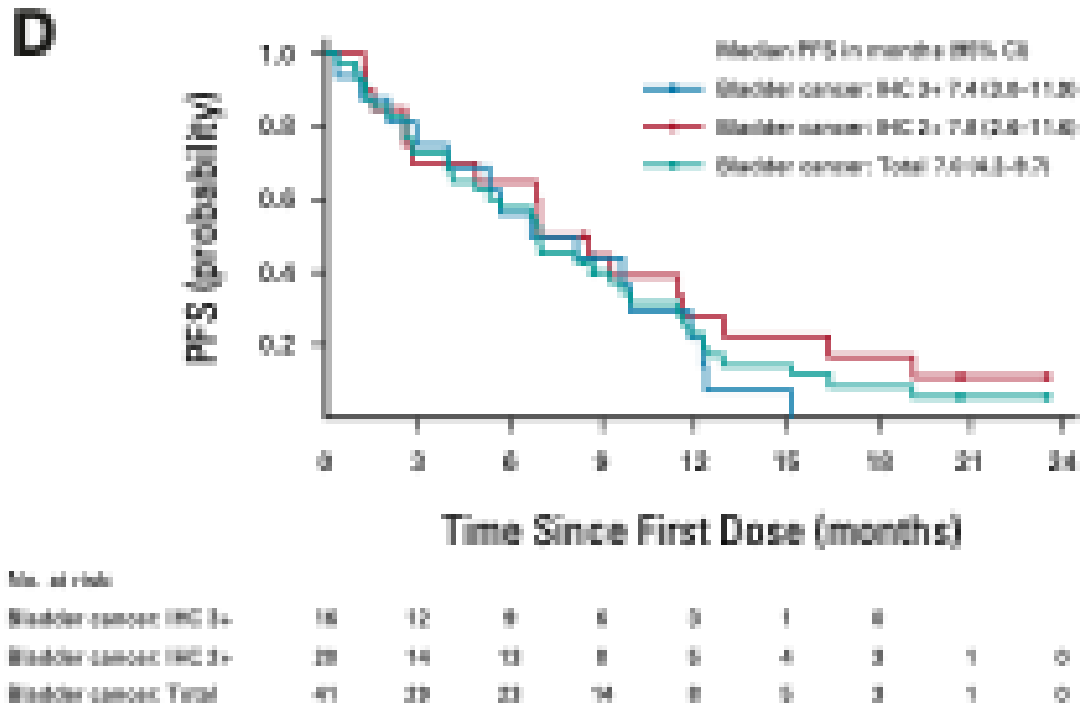




Raggi et al. Nature Rev Urol. 2025; Koskin et al. JCO PO 2025

T-DxD in advanced solid tumors

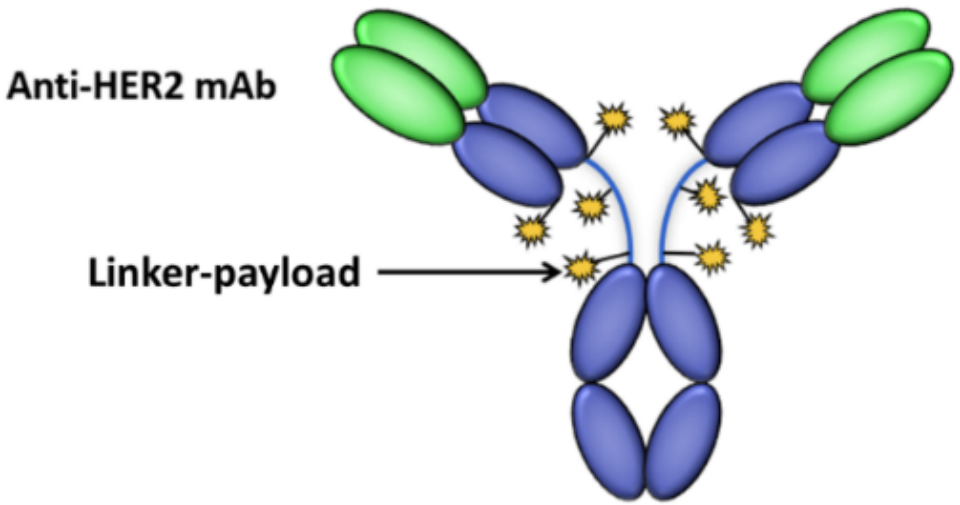


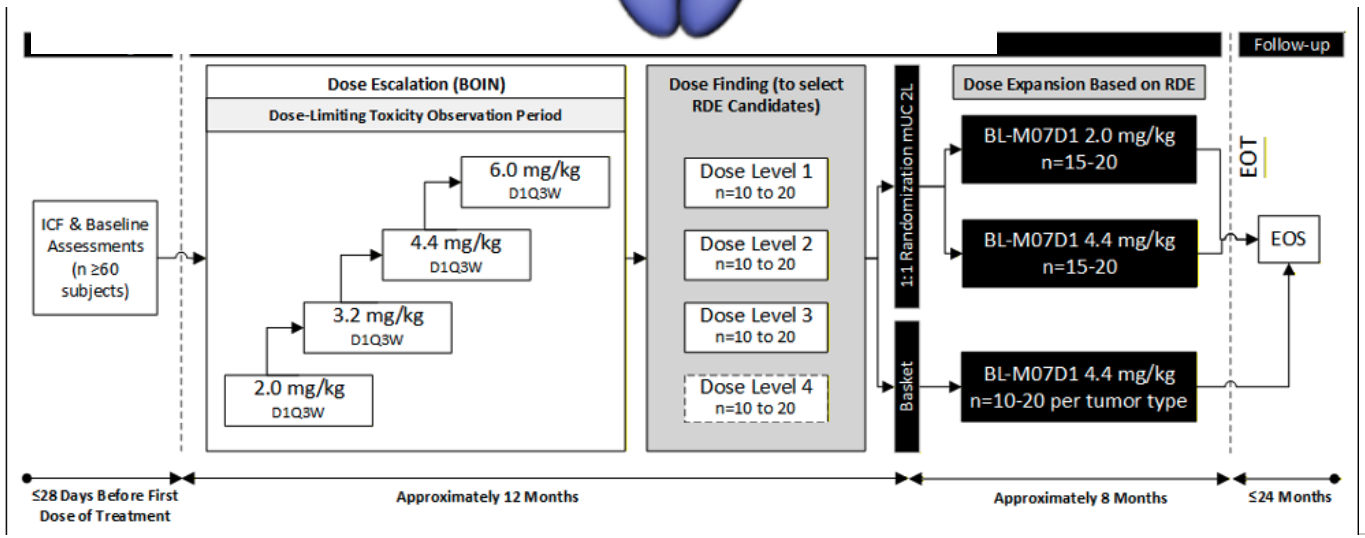


T-DxD approved in all solid tumors with 3+ HER-2 expression

Meric-Bernstam et al. JCO 2023

Novel HER-2 ADCs in advanced urothelial cancer

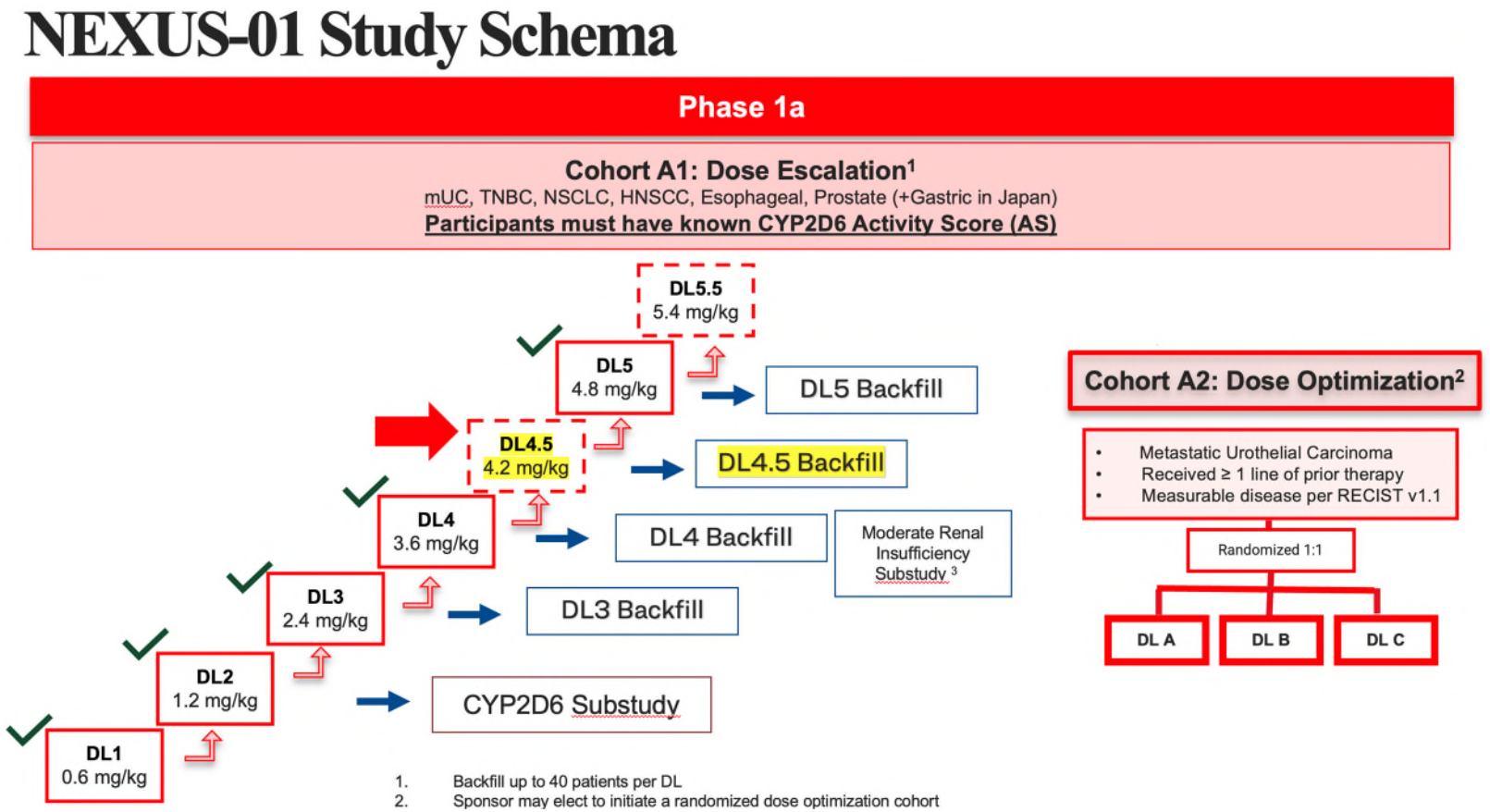




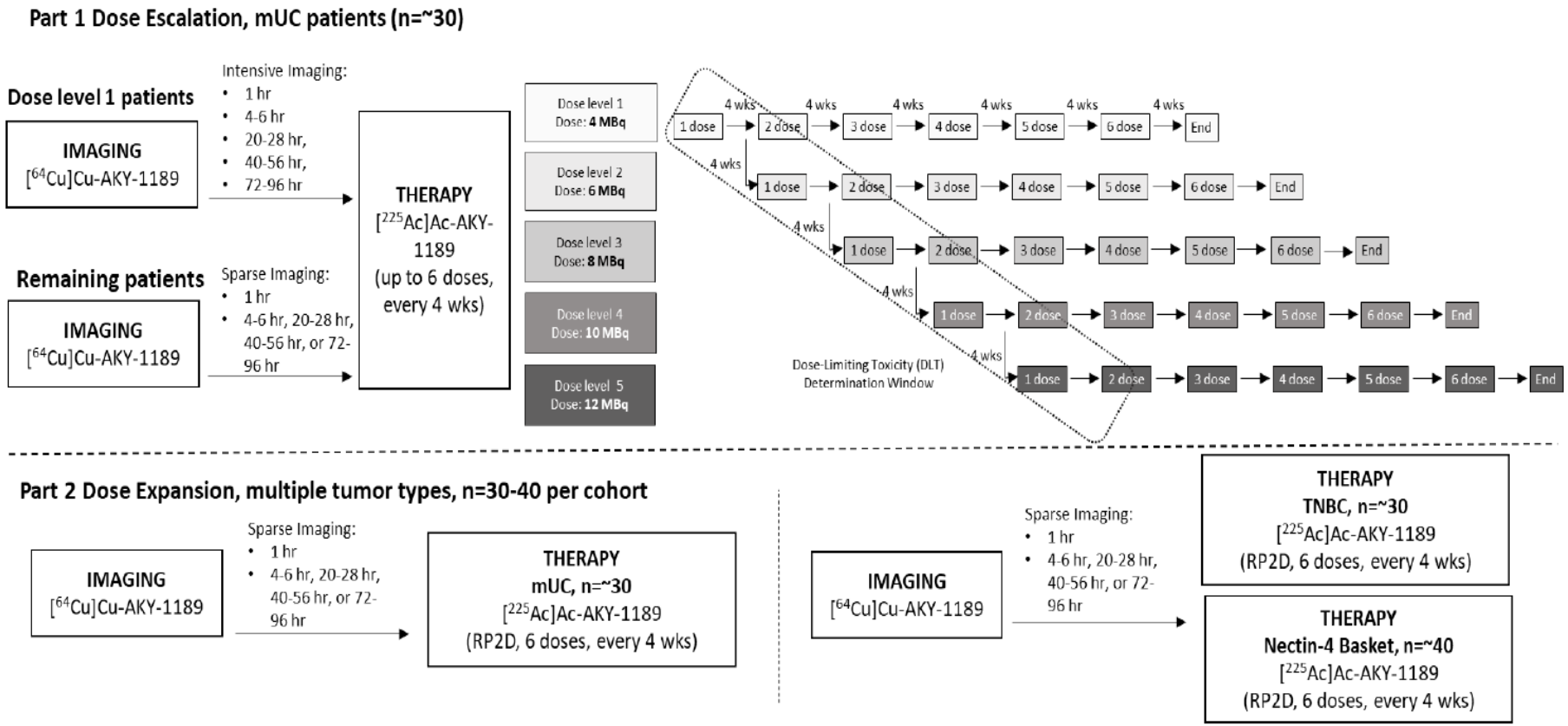
- BL-M07D1 specifically binds to HER2 on the surface of tumor cells, enters tumor cells through endocytosis, releases Ed-04 in lysosomes through digestion, and initiates apoptosis by inhibiting topoisomerase I
- The binding BL-M07D1 to HER2 on the surface of tumor cells blocks the signaling pathways of HER2 and may enhance antitumor activity, and
- The mAb Fc fragment of BL-M07D1 mediates antibody-dependent cellular cytotoxicity (ADCC) to achieve cytotoxic activities.

Any HER-2 expression (1-3+) by IHC or *HER-2* mutation allowed

Nectin-4 targeted therapy beyond EV: ADC approach



Nectin-4 targeted therapy beyond EV: Radiopharmaceutical approach



Conclusions

- Approval of EV/Pembro ushers in new era in the treatment of cisplatin ineligible (and eligible?) patients with localized MIBC
- With improving systemic therapy, important to re-evaluate role of adjuvant, and definitive local therapy to individualize treatment in a risk adapted manner
- Relapsed/metastatic disease may have different biology driving resistance to EV/P upfront
- Novel targeted therapy, ADCs and theranostic approaches under investigation will pave the way for rational and chemo-free approach to relapsed UC