UPDATES IN BLADDER CANCER:
A REVIEW OF THE 2024 ASCO AND ESMO ANNUAL MEETINGS

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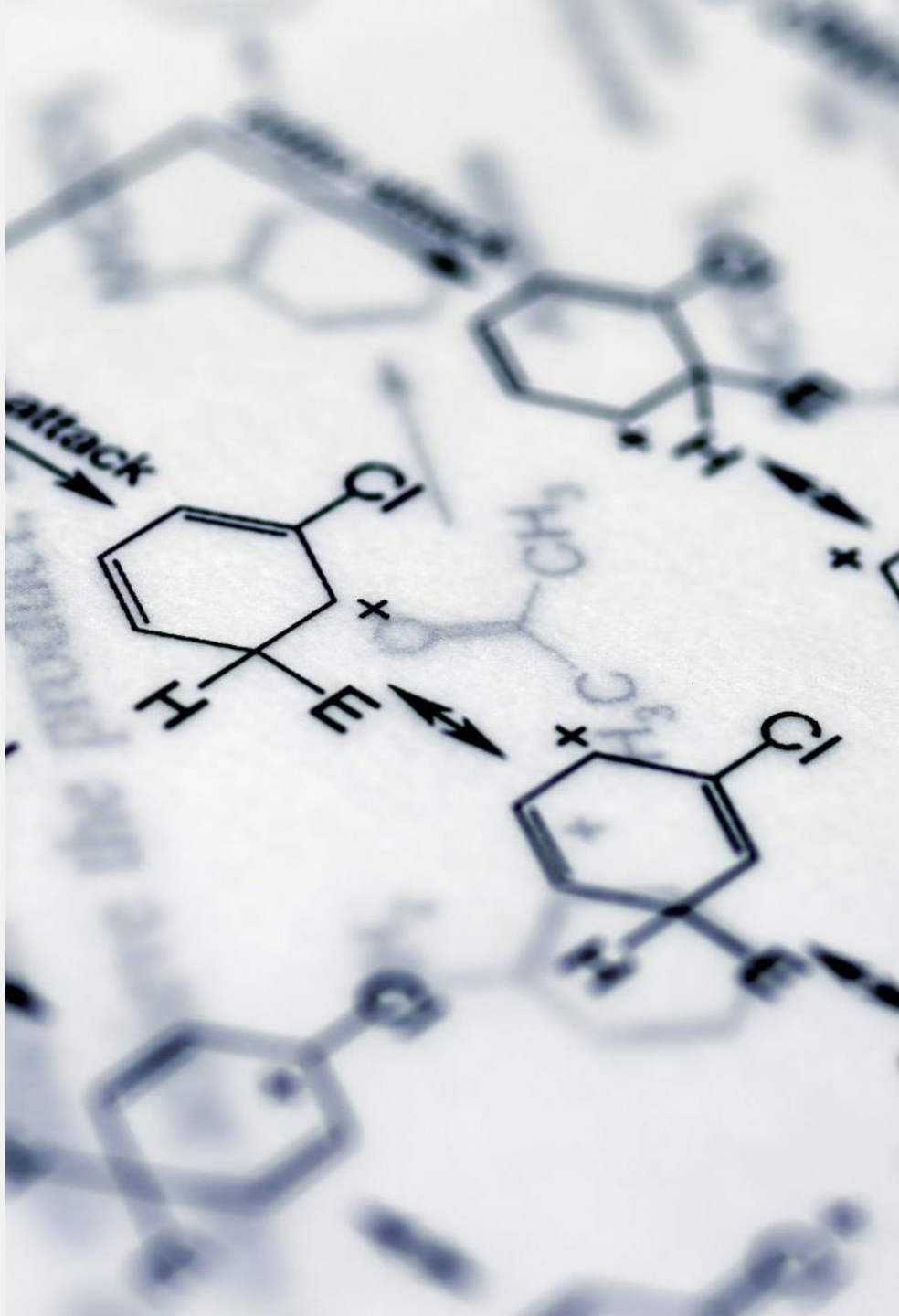
ASCO ANNUAL MEETING

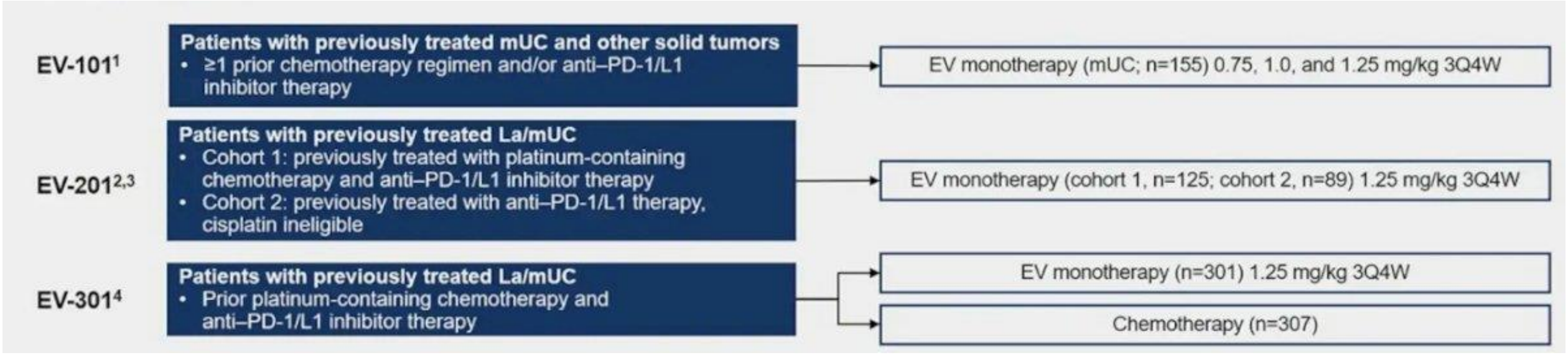
- 1. Exposure and outcomes for enfortumab vedotin in locally advanced/metastatic urothelial carcinoma (UC)
- 2. ULTMA: FOLFIRINOX in the first-line setting for urachal cancer
- 3. DV-001: disitamab vedotin plus pembrolizumab for metastatic UC with HER2 expression

2024 ASCO ANNUAL MEETING

ENFORTUMAB EXPOSURE AND OUTCOMES

- Enfortumab vedotin (EV) is currently approved in second-/third-line setting
- EV plus pembrolizumab is currently approved for use in the first-line setting for locally advanced/metastatic urothelial carcinoma based off EV-302
- EV dosing is 1.25 mg/kg, and can be modified per physician judgement (reduction or interruptions)
- Study sought to evaluate association between EV plasma exposure with safety and efficacy based off EV monotherapy trials

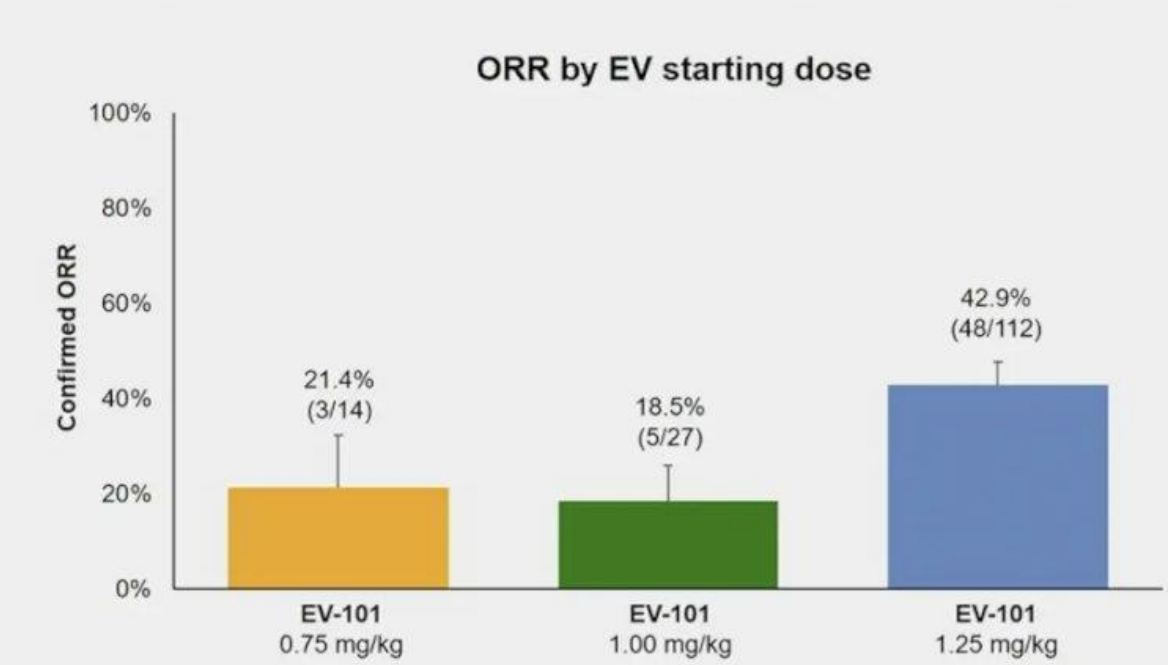


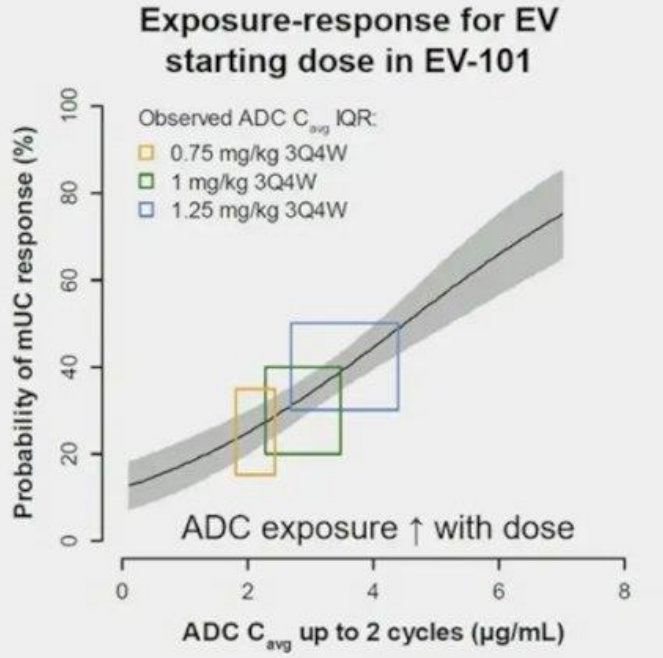


EV MONOTHERAPY TRIALS

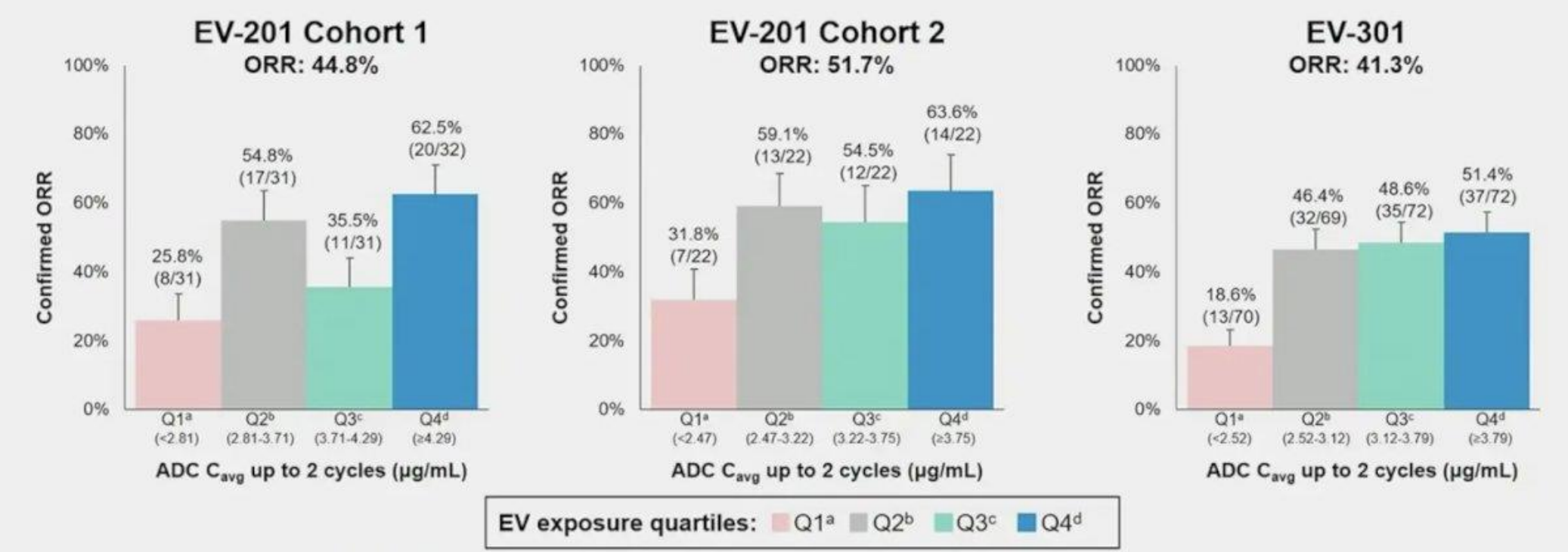
Petrylak D, et al. 2024 ASCO Annual Meeting. Chicago, IL.

OBJECTIVE RESPONSE RATE IN EV-101



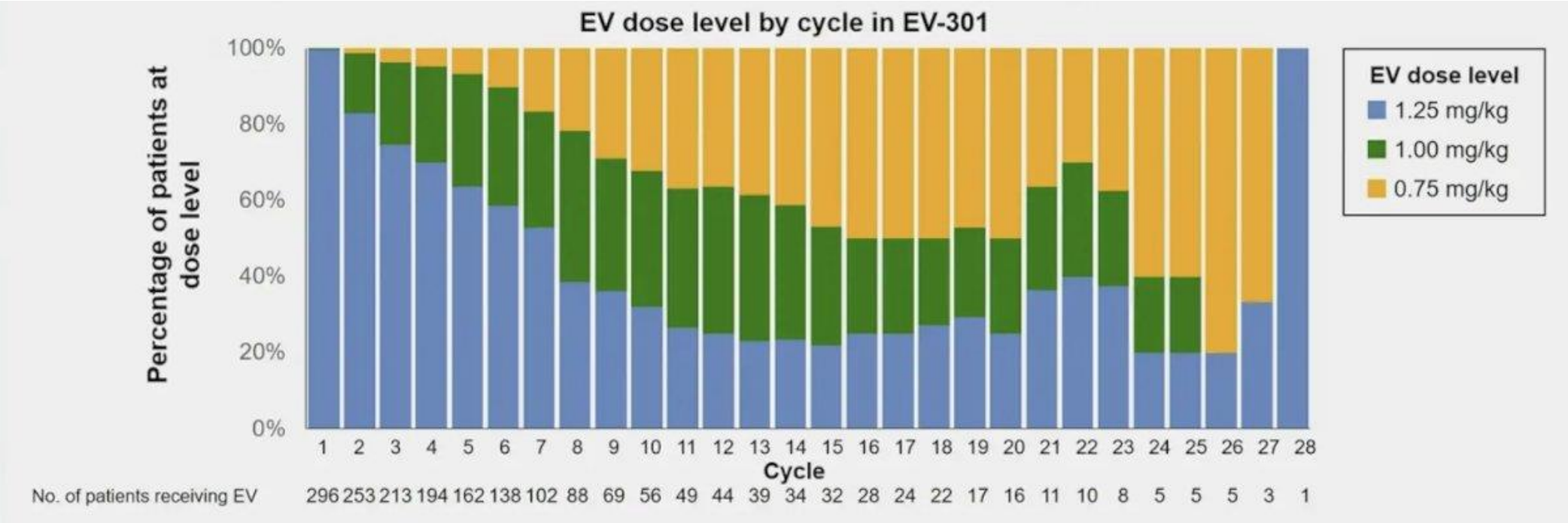


Petrylak D, et al. 2024 ASCO Annual Meeting. Chicago, IL.



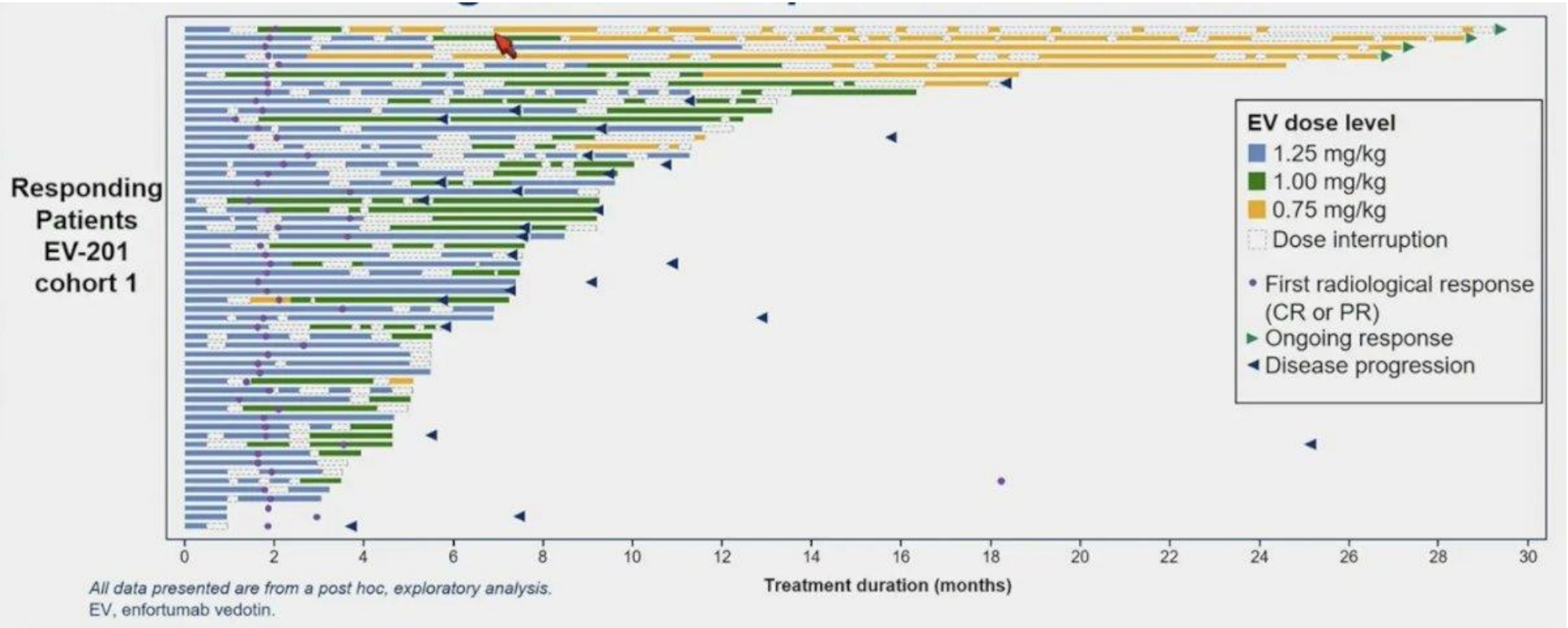
EV EXPOSURE IN EV-201 AND EV-301

Petrylak D, et al. 2024 ASCO Annual Meeting. Chicago, IL.



EV DOSE LEVEL IN EV-301

Petrylak D, et al. 2024 ASCO Annual Meeting.



EV DOSE LEVEL IN EV-201

Petrylak D, et al. 2024 ASCO Annual Meeting.

EV DOSING AND RESPONSE

- Higher EV dose intensity was associated with higher response to EV in prior monotherapy trials
- Responses seen regardless of dose adjustment or interruptions for EV in prior monotherapy trials
- Await data for EV plus pembrolizumab as studied in EV-302

ULTMA: FOLFIRINOX IN URACHAL CANCER

- Urachal cancer is a rare malignancy that is historically associated with bladder cancer that presents at advanced stages[1]
- Prior studies employing next generation sequencing have suggested urachal cancer is more similar with colorectal cancer than bladder cancer[2]
- ULTMA was a single-arm, prospective trial evaluating FOLFIRINOX in the first-line setting conducted at five centers in South Korea, with 21 patients enrolled between April 2021 and November 2023

1. Benjamin DJ…Rezazadeh Kalebasty A. JAMA Oncology. 2023.
2. Benjamin DJ…Rezazadeh Kalebasty A. ASCO Genitourinary Cancers Symposium. 2024.

ULTMA: INCLUSION CRITERIA

- Histologically confirmed adenocarcinoma of bladder/urachal remnant that is clinically consistent with urachal cancer.
  - Origin in the anterior wall or dome of the bladder
  - Predominant invasion of muscularis or deeper tissues
  - No obvious origin from the overlying urothelium (relative normal-looking urothelial mucosa)
  - No primary adenocarcinoma elsewhere
- Patients with locally advanced, recurrent, or metastatic disease not amenable to surgery, radiotherapy, or combined modality therapy with curative intent
- Measurable disease according to RECIST v1.1
- ECOG performance status 0–1
- Adequate bone marrow, hepatic, and renal function

Lee JL, et al. 2024 ASCO Annual Meeting.

ULTMA: FOLFIRINOX DOSING

- Oxaliplatin 85 mg/m^2 over two hours, Irinotecan 150 mg/m2 over 1.5 hours, Leucovorin 400 mg/m^2 over two hours, and 5-FU 2,400 mg/m^2 over 46 hours
- Prophylactic pegteograstim 6 mg subcutaneously on day 3
- Prophylactic antibiotics mandatory for the first two cycles (levofloxacin 750 mg orally daily from days 4 to 7)
- Antiemetics per the investigator's discretion
- Repeated every two weeks up to 12 cycles (or until progression or unacceptable toxicities). Study drugs can be administered after 12 cycles to the subjects deriving a benefit from the study medication

Lee JL, et al. 2024 ASCO Annual Meeting.

ULTMA: STUDY POPULATION

Male	15(71%)	Sites of metastases	
Age, median	50 (28-68)	Lung	10 (48%)
ECOG 0/1	3 (14%)/18 (86%)	Lymph node	8 (38%)
Initially metastatic	13 (62%)	Peritoneum	7 (33%)
Recurrent	8 (38%)	Pelvic cavity	2 (10%)
Prior surgery	16 (76%)	Liver	1 (5%)
Prior adjuvant chemotherapy	2 (10%)	Bone	1 (5%)
		Brain	1 (5%)

Lee JL, et al. 2024 ASCO Annual Meeting.

	No. of pts/percentage
Complete Response (CR)	2(9.5%)
Partial Response (PR)	11(52.4%)
Stable Disease (SD)	8(38.1%)
Progressive Disease (PD)	0

Overall response rate was 61.9% (95% CI, 41.1-82.7)

ULTMA: CLINICAL RESPONSES

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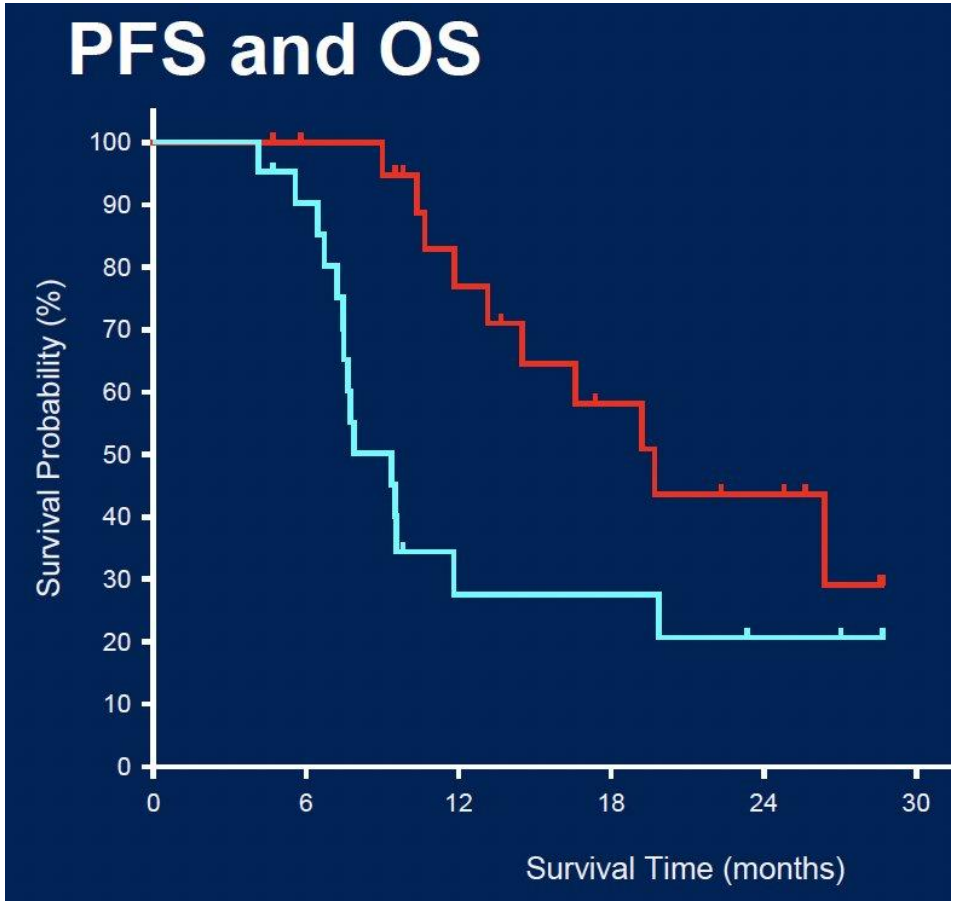
ULTMA: SURVIVAL OUTCOMES

- Median progression-free survival (PFS) was 9.3 months (95% CI, 6.7—11.9)
- Estimated median overall survival was 26.4 months (95% CI, 14.7—38.1)



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ULTMA: ADVERSE EVENTS

Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	0	0	0	0
Neutropenia	0	0	1 (4.8%)	0
Anemia	0	0	2 (9.5%)	0
Thrombocytopenia	0	3 (14.3%)	1 (4.8%)	0
ALT elevation	2 (9.5%)	3 (14.3%)	0	0
AST elevation	2 (9.5%)	1 (4.8%)	0	0
ALP elevation	1 (4.8%)			
Nausea	6 (28.6%)	8 (38.1%)	1 (4.8%)	0
Vomiting	2 (9.5%)	2 (9.5%)	0	0

	Grade 1	Grade 2	Grade 3	Grade 4
Anorexia	4 (19.0%)	1 (4.8%)	0	0
Diarrhea	4 (19.0%)	1 (4.8%)	1 (4.8%)	0
Stomatitis	0	3 (14.3%)	0	0
Fatigue	2 (9.5%)	6 (28.6%)	0	0
Peripheral neuropathy	11 (52.4%)	5 (23.8%)	0	0
Febrile neutropenia	0	0	0	0
Hiccups	4 (19.0%)	1 (4.8%)	0	0
Abdominal pain	2 (9.5%)	2 (9.5%)	1 (4.8%)	0
Laryngopharyngeal dysesthesia	1 (4.8%)	2 (9.5%)	0	0

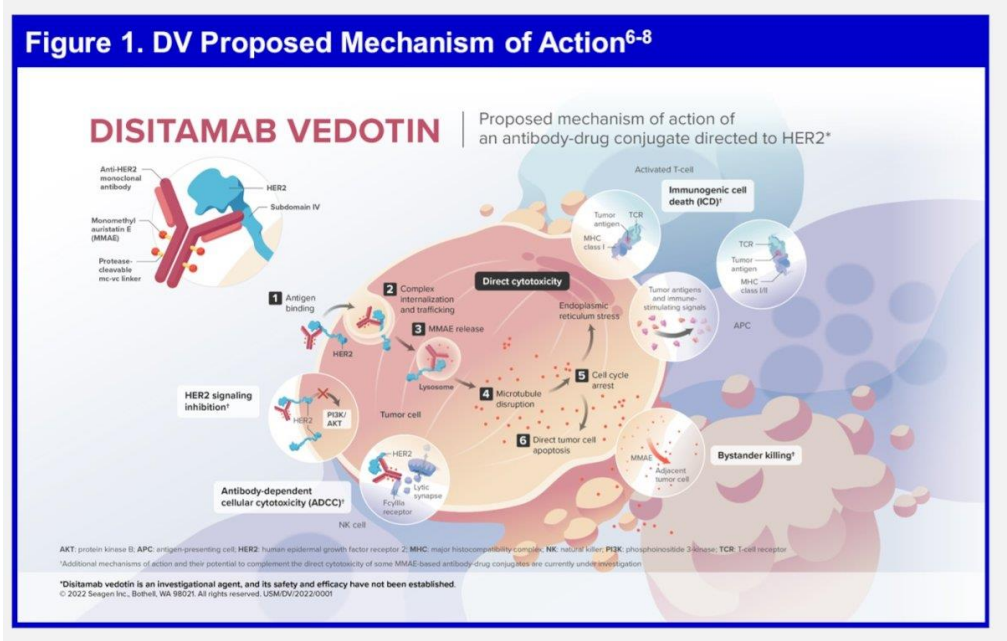
Lee JL, et al. 2024 ASCO Annual Meeting.

ULTMA: FOLFIRINOX IN URACHAL CANCER

- First prospective trial evaluating systemic therapy for urachal cancer
- Modified FOLFIRINOX demonstrated efficacy as well as safety and tolerability
- Possible first-line treatment option in advanced urachal cancer

DV-001: DISITAMAB VEDOTIN PLUS PEMBROLIZUMAB

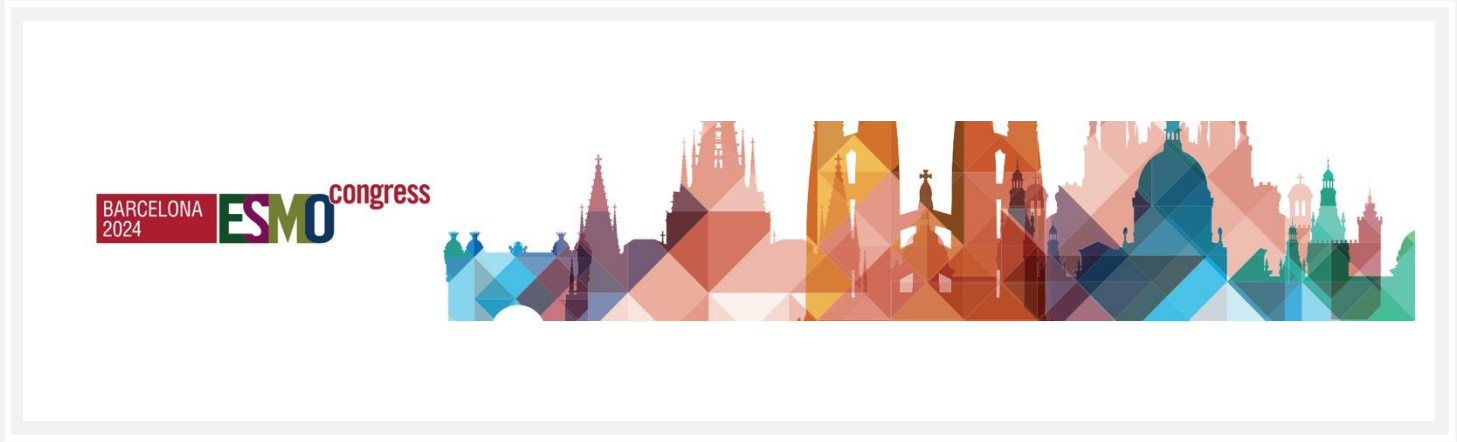
- HER2 expression found in urothelial carcinoma
- Disitamab vedotin is an antibody drug conjugate conjugated to MMAE (monomethyl auristatin E)
- DV-001 is an open-label, randomized phase III trial evaluating DV plus pembrolizumab versus chemotherapy in untreated HER2-expressing locally advanced/metastatic urothelial carcinoma

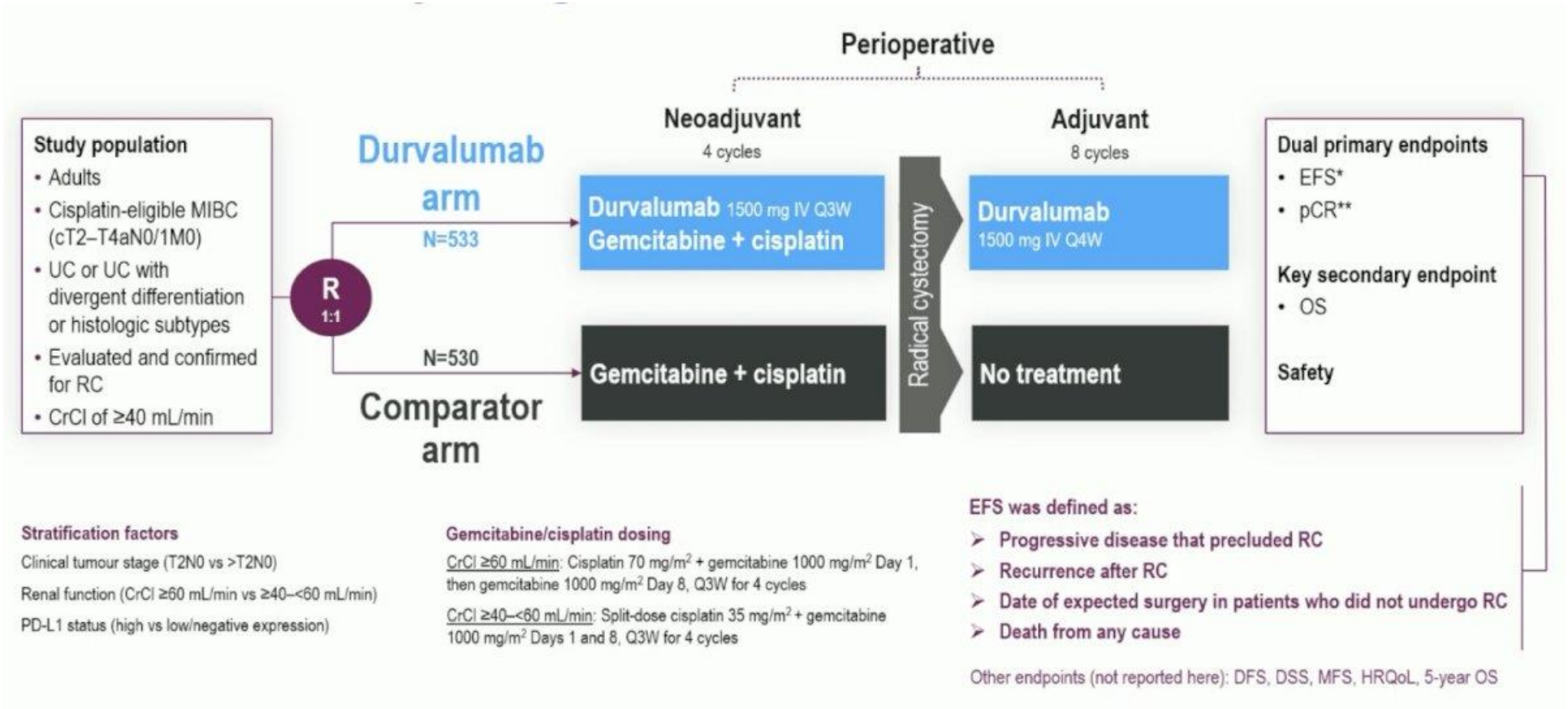


Galsky M, et al. 2024 ASCO Annual Meeting.

ESMO CONGRESS 2024

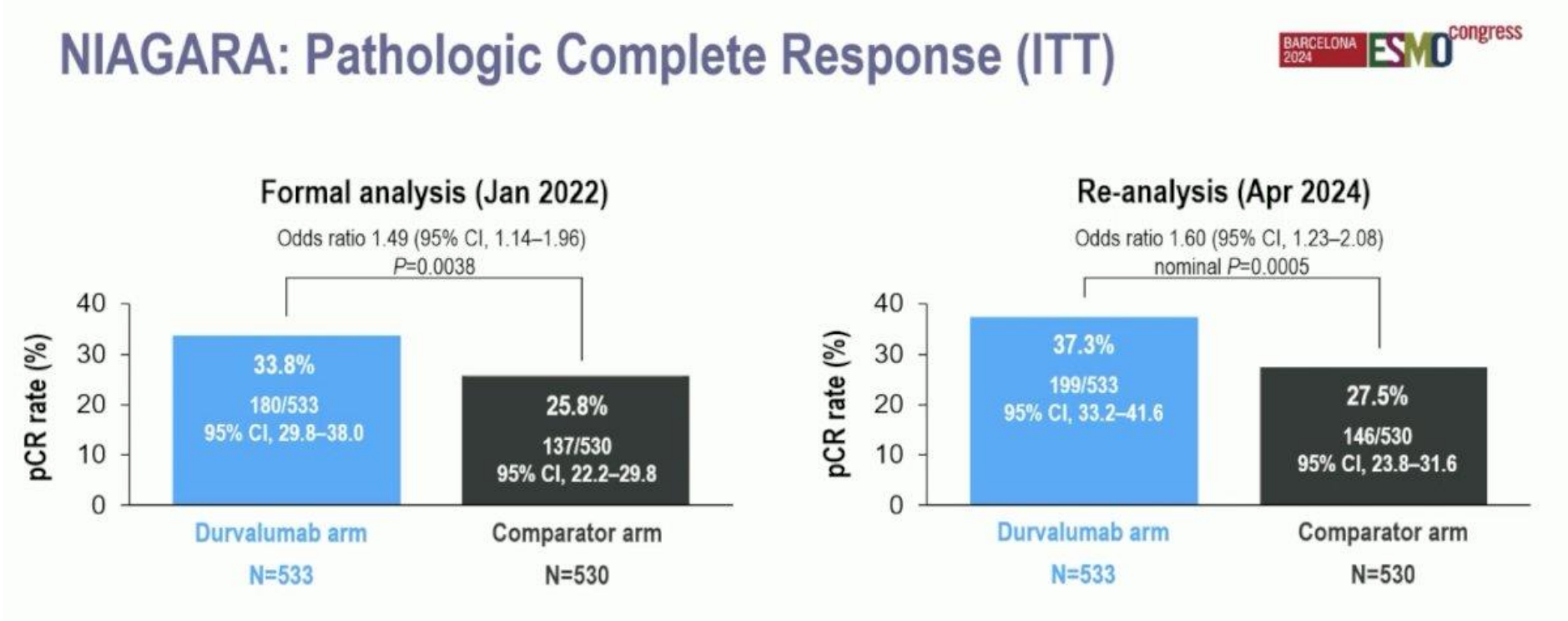
1. NIAGARA: peri-operative chemotherapy and durvalumab for MIBC
2. AMBASSADOR: adjuvant pembrolizumab following surgery
3. TOMBOLA: monitoring with circulating tumor DNA (ctDNA) following cystectomy





NIAGARA: PLATINUM CHEMOTHERAPY PLUS DURVALUMAB

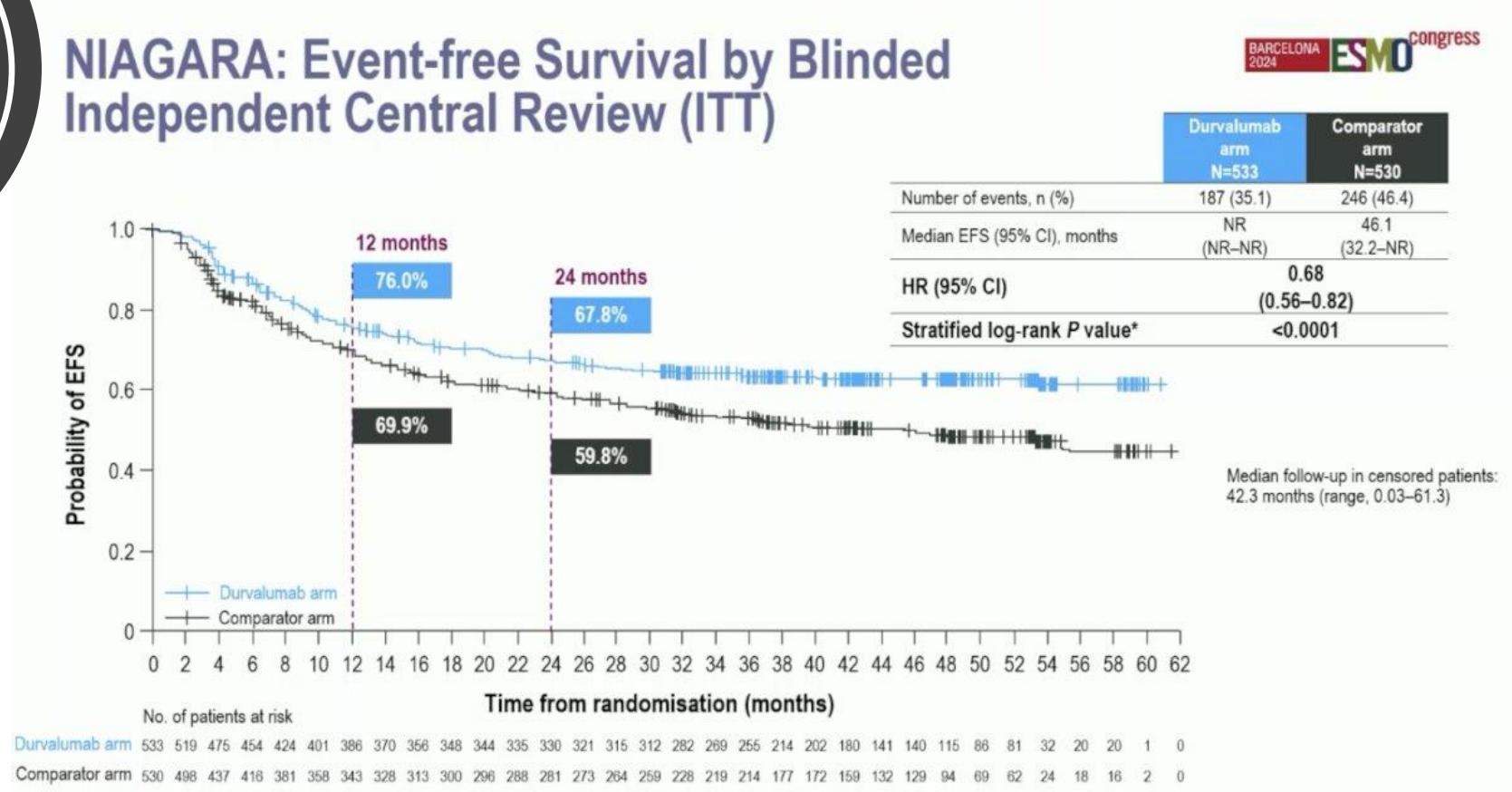
Powles T, et al. ESMO Congress 2024. Barcelona, Spain.



PATHOLOGIC COMPLETE RESPONSE

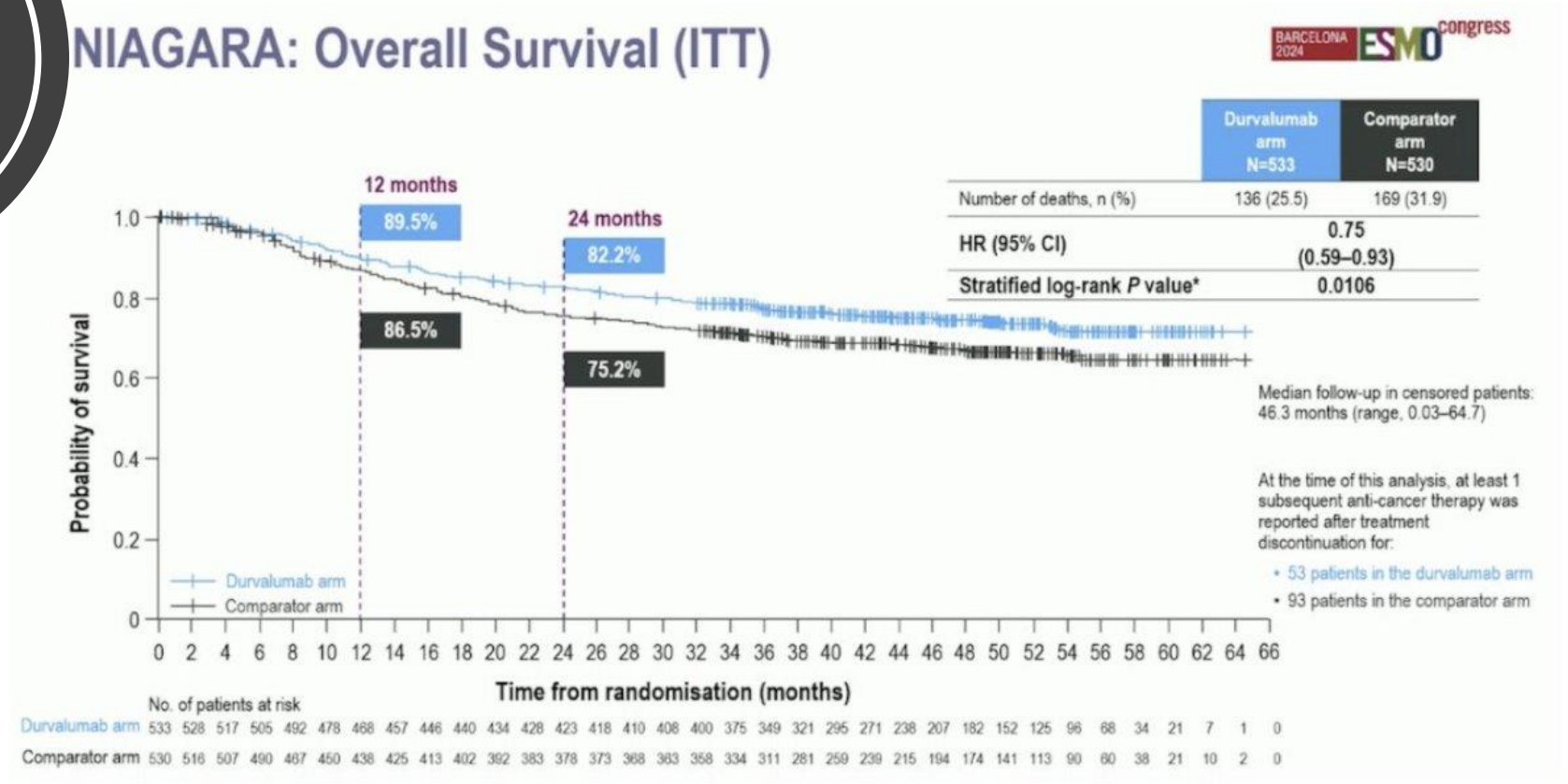
Powles T, et al. ESMO Congress 2024. Barcelona, Spain.

EVENT FREE SURVIVAL



Powles T, et al. ESMO Congress 2024. Barcelona, Spain.

OVERALL SURVIVAL



Powles T, et al. ESMO Congress 2024. Barcelona, Spain.

ADVERSE EVENTS

Overall study period (unless otherwise stated)	Durvalumab arm N=530	Comparator arm N=526
AEs of any cause, n (%)	**527 (99)**	**525 (100)**
Grade 3 or 4	**368 (69)**	**355 (68)**
Serious AEs	326 (62)	287 (55)
Outcome of death	**27 (5)**	**29 (6)**
Leading to discontinuation of study treatment	112 (21)	80 (15)
Leading to discontinuation of neoadjuvant durvalumab	50 (9)	---
Leading to discontinuation of NAC	72 (14)	80 (15)
Leading to patient not undergoing RC	6 (1)	7 (1)
Leading to delay in surgery*	9 (2)	6 (1)
Leading to discontinuation of adjuvant durvalumab	30/383† (8)	---
AEs possibly related to any treatment, n (%)‡	502 (95)	487 (93)
Grade 3 or 4 (treatment related)	**215 (41)**	**215 (41)**
Outcome of death (treatment related)	**3 (0.6)**	**3 (0.6)**
Any-grade immune-mediated AEs	**111 (21)**	**16 (3)**

Powles T, et al. ESMO Congress 2024. Barcelona, Spain.

NIAGARA: CONCLUSION

- First peri-operative phase III trial to demonstrate benefits in event-free survival and overall survival with addition of immune checkpoint inhibitor to chemotherapy
- Inclusion of patients with CrCl between 40-60 mL/min who received split-dose cisplatin, and for those with CrCl > 60 mL/min, full dose cisplatin

AMBASSADOR: ADJUVANT PEMBROLIZUMAB

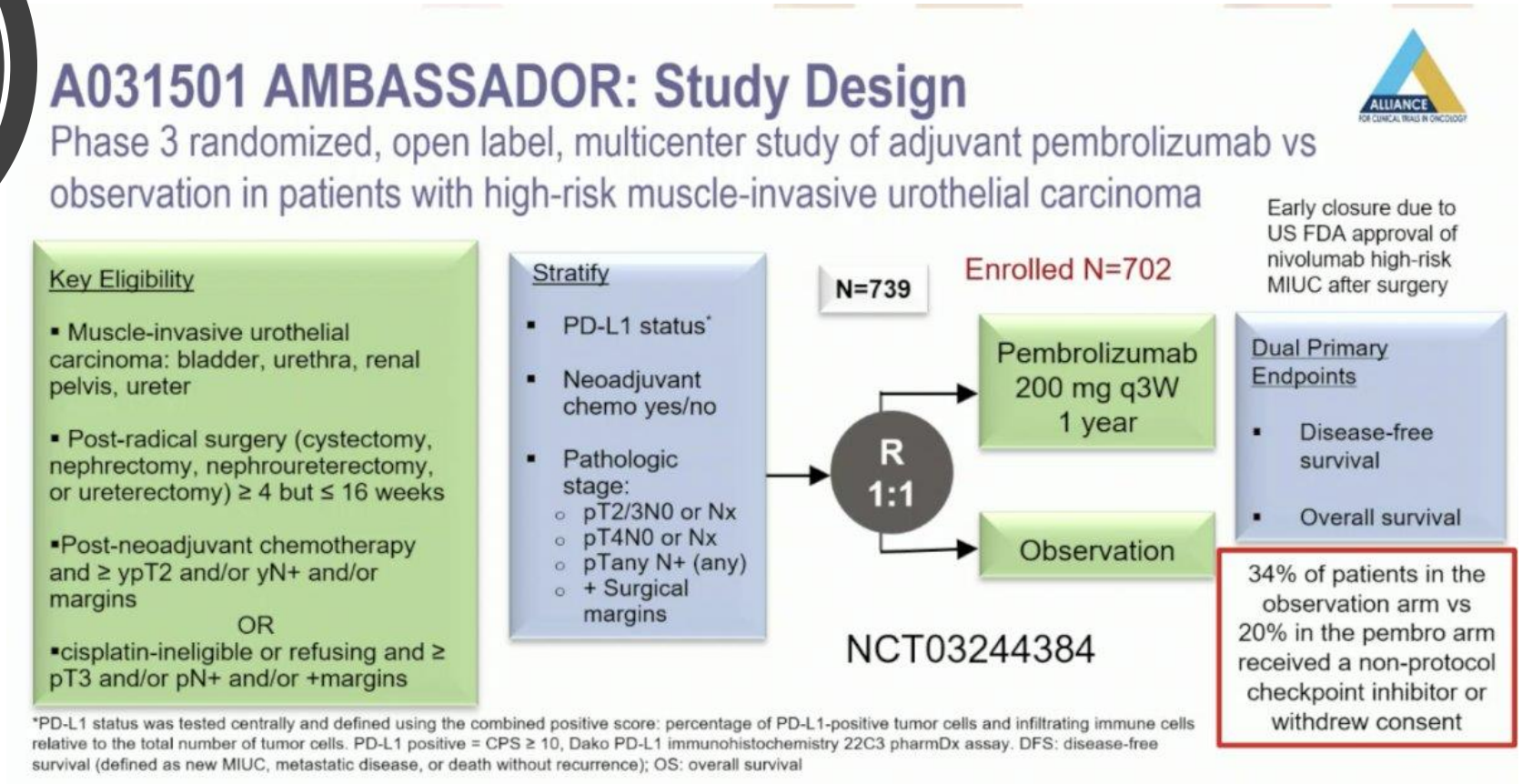
- Phase III randomized trial evaluating pembrolizumab versus observation in muscle-invasive and locally advanced urothelial carcinoma following surgery

- Results initially presented in January 2024 at ASCO Genitourinary Cancers Symposium demonstrated statistically significant improvement in disease-free survival (DFS) but interim analysis showed no benefit in overall survival[1]

- Updated DFS results presented at ESMO Congress 2024

1. Apolo A, et al. ASCO Genitourinary Cancers Symposium. 2024.

STUDY DESIGN



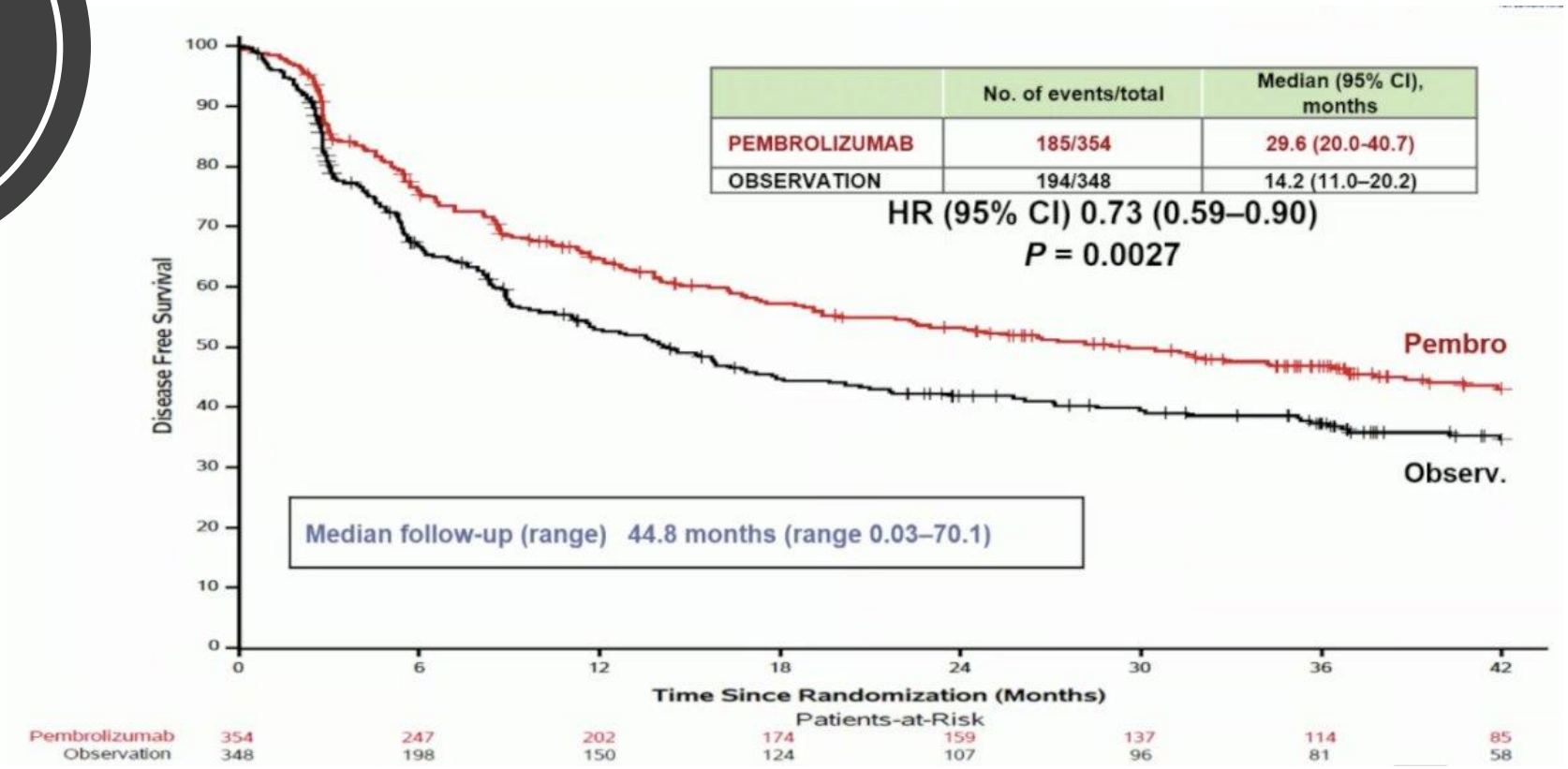
Apolo A, et al. ESMO Congress 2024. Barcelona, Spain.

	Pembrolizumab (N=354)	Observation (N=348)	Total (N=702)
Median age, years (range)	69.0 (22.0-92.0)	68.0 (34.0-90.0)	68.0 (22.0, 92.0)
Race			
White	323 (91.2%)	310 (89.1%)	633 (90.2%)
Black or African American	14 (4.0%)	11 (3.2%)	25 (3.6%)
Asian	5 (1.4%)	10 (2.9%)	15 (2.1%)
American Indian or Alaskan Native	2 (0.6%)	2 (0.6%)	4 (0.6%)
Not reported/Unknown	10 (2.8%)	15 (4.3%)	25 (3.6%)
Gender			
Female	83 (23.4%)	95 (27.3%)	178 (25.4%)
Male	271 (76.6%)	253 (72.7%)	524 (74.6%)
Neoadjuvant therapy			
Yes	229 (64.7%)	218 (62.6%)	447 (63.7%)
Pathologic stage			
+ Surgical margins	9 (2.5%)	8 (2.3%)	17 (2.4%)
pTany N+ (any)	180 (50.9%)	170 (48.8%)	350 (49.9%)
pT2/3N0 or NX	146 (41.2%)	150 (43.1%)	296 (42.2%)
pT4N0 or NX	19 (5.4%)	20 (5.8%)	39 (5.6%)
PD-L1 status			
Positive (Dako 22C3, CPS ≥ 10)	203 (57.3%)	201 (57.8%)	404 (57.5%)
Primary tumor site			
Bladder	267 (75.4%)	263 (75.6%)	530 (75.5%)
Urethra	6 (1.7%)	12 (3.4%)	18 (2.6%)
Upper tract (renal pelvis and ureter)	81 (22.9%)	73 (21.0%)	154 (21.9%)
Histology			
Variant (mixed urothelial histology)	38 (10.7%)	32 (9.2%)	70 (10.0%)

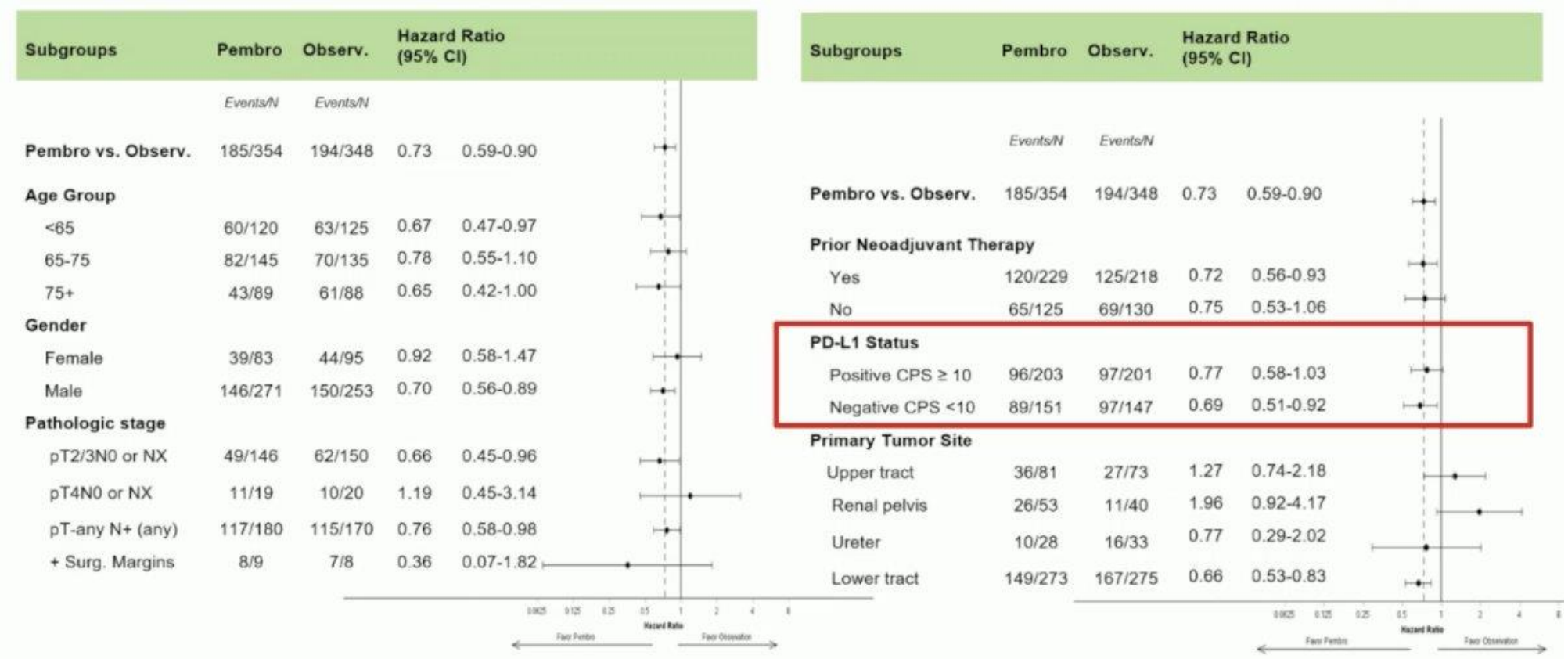
AMBASSADOR: PATIENT CHARACTERISTICS

Apolo A, et al. ESMO Congress 2024. Barcelona, Spain.

UPDATED DFS



Apolo A, et al. ESMO Congress 2024. Barcelona, Spain.

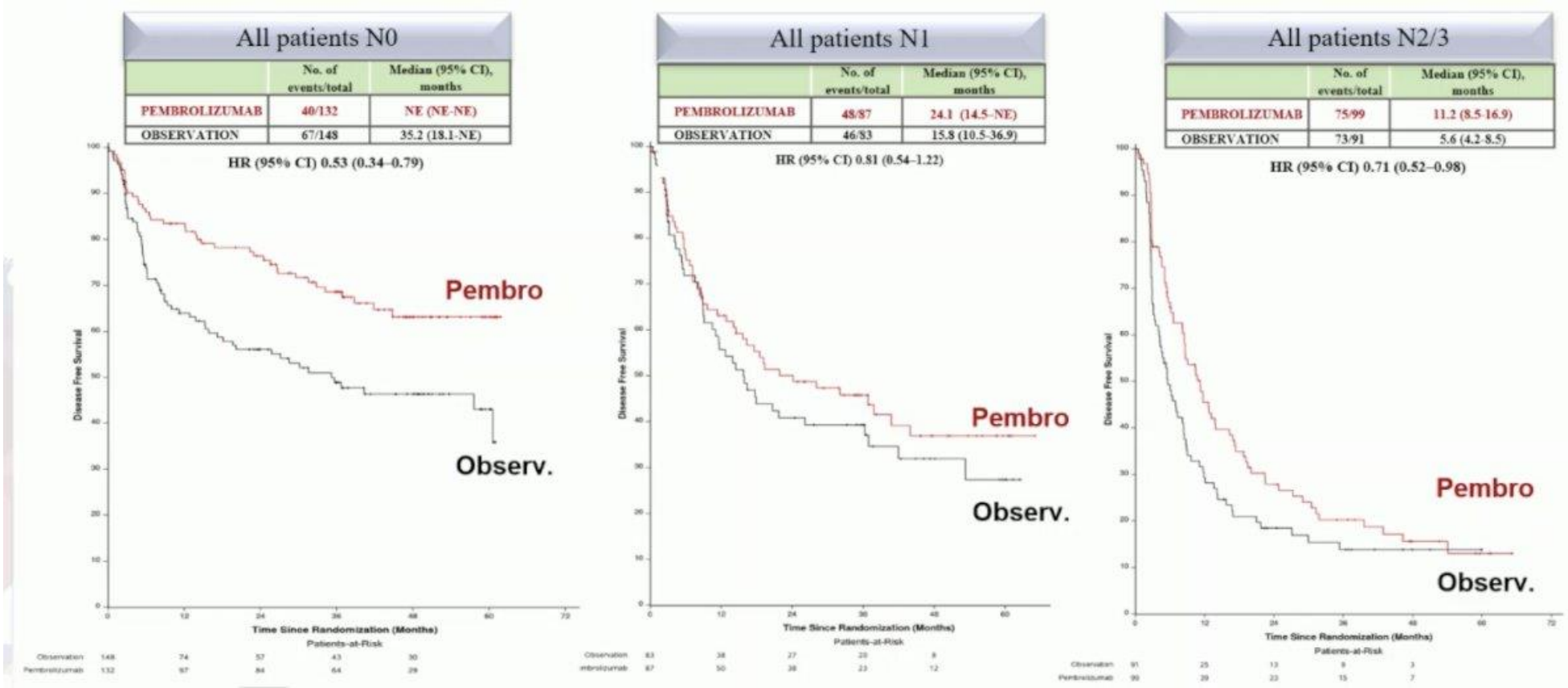


Subgroups	Pembro Events/N	Observ. Events/N	Hazard Ratio (95% CI)	
Pembro vs. Observ.	185/354	194/348	0.73	0.59-0.90
Age Group				
<65	60/120	63/125	0.67	0.47-0.97
65-75	82/145	70/135	0.78	0.55-1.10
75+	43/89	61/88	0.65	0.42-1.00
Gender				
Female	39/83	44/95	0.92	0.58-1.47
Male	146/271	150/253	0.70	0.56-0.89
Pathologic stage				
pT2/3N0 or NX	49/146	62/150	0.66	0.45-0.96
pT4N0 or NX	11/19	10/20	1.19	0.45-3.14
pT-any N+ (any)	117/180	115/170	0.76	0.58-0.98
+ Surg. Margins	8/9	7/8	0.36	0.07-1.82

Subgroups	Pembro Events/N	Observ. Events/N	Hazard Ratio (95% CI)	
Pembro vs. Observ.	185/354	194/348	0.73	0.59-0.90
Prior Neoadjuvant Therapy				
Yes	120/229	125/218	0.72	0.56-0.93
No	65/125	69/130	0.75	0.53-1.06
PD-L1 Status				
Positive CPS ≥ 10	96/203	97/201	0.77	0.58-1.03
Negative CPS <10	89/151	97/147	0.69	0.51-0.92
Primary Tumor Site				
Upper tract	36/81	27/73	1.27	0.74-2.18
Renal pelvis	26/53	11/40	1.96	0.92-4.17
Ureter	10/28	16/33	0.77	0.29-2.02
Lower tract	149/273	167/275	0.66	0.53-0.83

AMBASSADOR: PD-L1 STATUS

Apolo A, et al. ESMO Congress 2024. Barcelona, Spain.



AMBASSADOR: NODAL STATUS

Apolo A, et al. ESMO Congress 2024. Barcelona, Spain.

AMBASSADOR: CONCLUSION

- Adjuvant pembrolizumab demonstrated improvement in disease-free survival compared to placebo in muscle-invasive and locally advanced bladder cancer following surgery

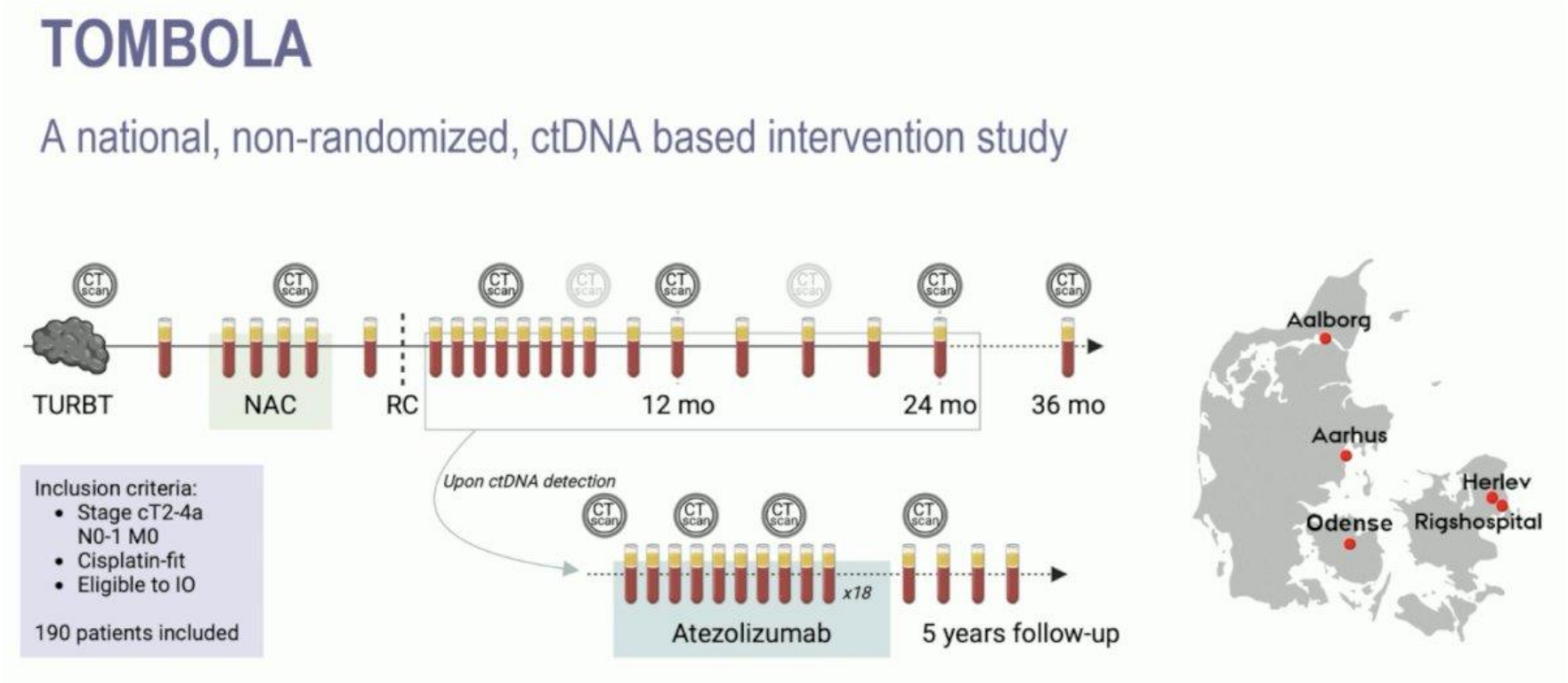
- Benefit seen regardless of PD-L1 status or nodal status

TOMBOLA: CIRCULATING TUMOR DNA

- Prior analysis from the phase III trial of adjuvant atezolizumab versus observation in operative urothelial carcinoma demonstrating patients with positive ctDNA had improved DFS and OS with atezolizumab compared to observation (DFS hazard ratio = 0.58, 95% CI 0.43-0.79, p = 0.0024; OS hazard ratio 0.59, 95% CI 0.41-0.86)[1]

- TOMBOLA was a non-randomized ctDNA-based interventional study conducted at five centers in Denmark for patients who underwent neoadjuvant chemotherapy followed by cystectomy

1. Powles T, et al. Nature. 2021.



TOMBOLA: STUDY DESIGN

Jensen JB, et al. 2024 ESMO Congress. Barcelona, Spain.

Patient characteristics

Table 1: Clinical Characteristics - All patients

Variable	Patients, N = 179	ctDNA status post RC		p-value[1]
		Positive, N = 93	Negative, N = 73	
Age, Median (IQR)	65 (60, 71)	66 (61, 72)	63 (60, 70)	0.4
Sex, n (%)				0.2
Female	37 (21%)	16 (47%)	18 (53%)	
Male	142 (79%)	77 (58%)	55 (42%)	
T stage at RC, n (%)				0.003
T0	75 (42%)	33 (45%)	40 (55%)	
Ta-T1	27 (15%)	15 (56%)	12 (44%)	
T2	29 (16%)	15 (52%)	14 (48%)	
T3-T4a	37 (21%)	30 (81%)	7 (19%)	
*Tx**	11 (6.1%)	0 (NA%)	0 (NA%)	
N stage at RC, n (%)				0.12
N0	144 (80%)	75 (53%)	66 (47%)	
N1-N2	23 (13%)	17 (74%)	6 (26%)	
*Nx**	12 (6.7%)	1 (50%)	1 (50%)	
Clinical high risk, n (%)				0.044
Yes	69 (39%)	45 (65%)	24 (35%)	
*No***	110 (61%)	48 (49%)	49 (51%)	

exact test

Clinical high risk = pT2 or higher and/or N+ for patients treated with neoadjuvant chemotherapy. RC = Radical cystectomy. IQR = Interquartile range.* Missing information. ** For 13 patients, pT and/or pN status is missing.

Jensen JB, et al. 2024 ESMO Congress. Barcelona, Spain.

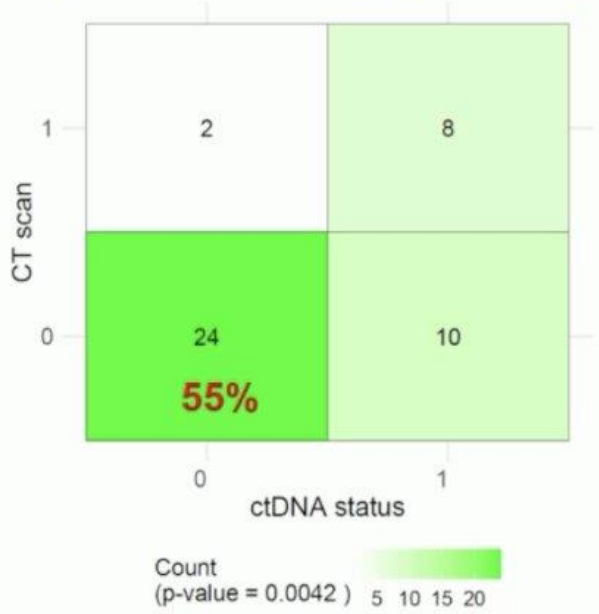
RELAPSE AFTER CYSTECTOMY

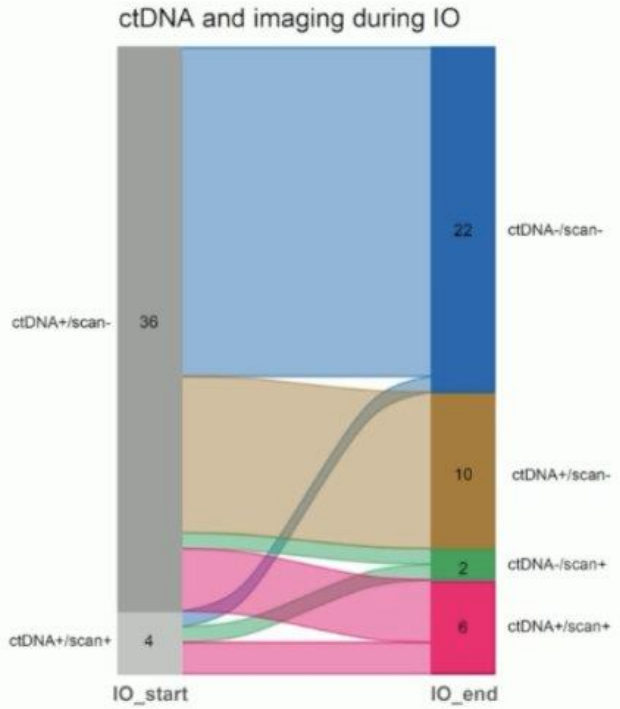
- 56% of patients were ctDNA positive after radical cystectomy
- Among patients who were ctDNA negative, only 2 (3%) developed metastases on CT imaging during follow-up
- 55% of the 44 patients with positive ctDNA status converted to negative ctDNA status after starting immunotherapy with no evidence of disease on CT imaging

TOMBOLA: CONTINUED

Primary endpoint

NED (No evidense of disease) (CT and ctDNA-) following immunotherapy





Jensen JB, et al. 2024 ESMO Congress. Barcelona, Spain.

TOMBOLA: CONCLUSION

- Additional evidence for role of ctDNA in monitoring for recurrence post-cystectomy in MIBC, and to guide use of adjuvant immunotherapy

- Await results of prospective trial (IMvigor-011) utilizing ctDNA for use of adjuvant immune checkpoint inhibitor post-cystectomy in MIBC

THANK YOU

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