Systemic Therapy in Urothelial Carcinoma

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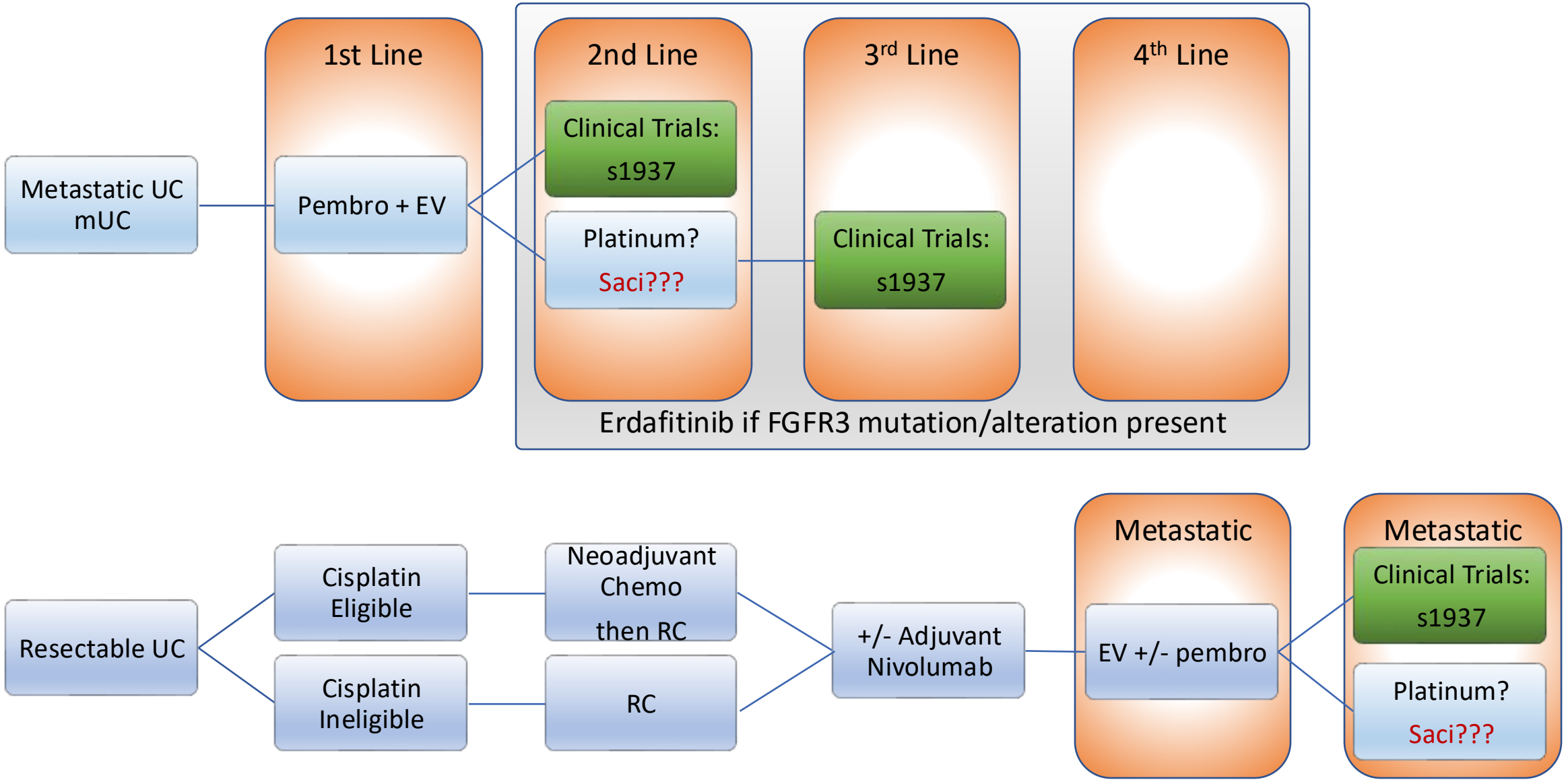
August 24, 2024

Current Standard of Care for UC



The NEW ENGLAND JOURNAL of MEDICINE

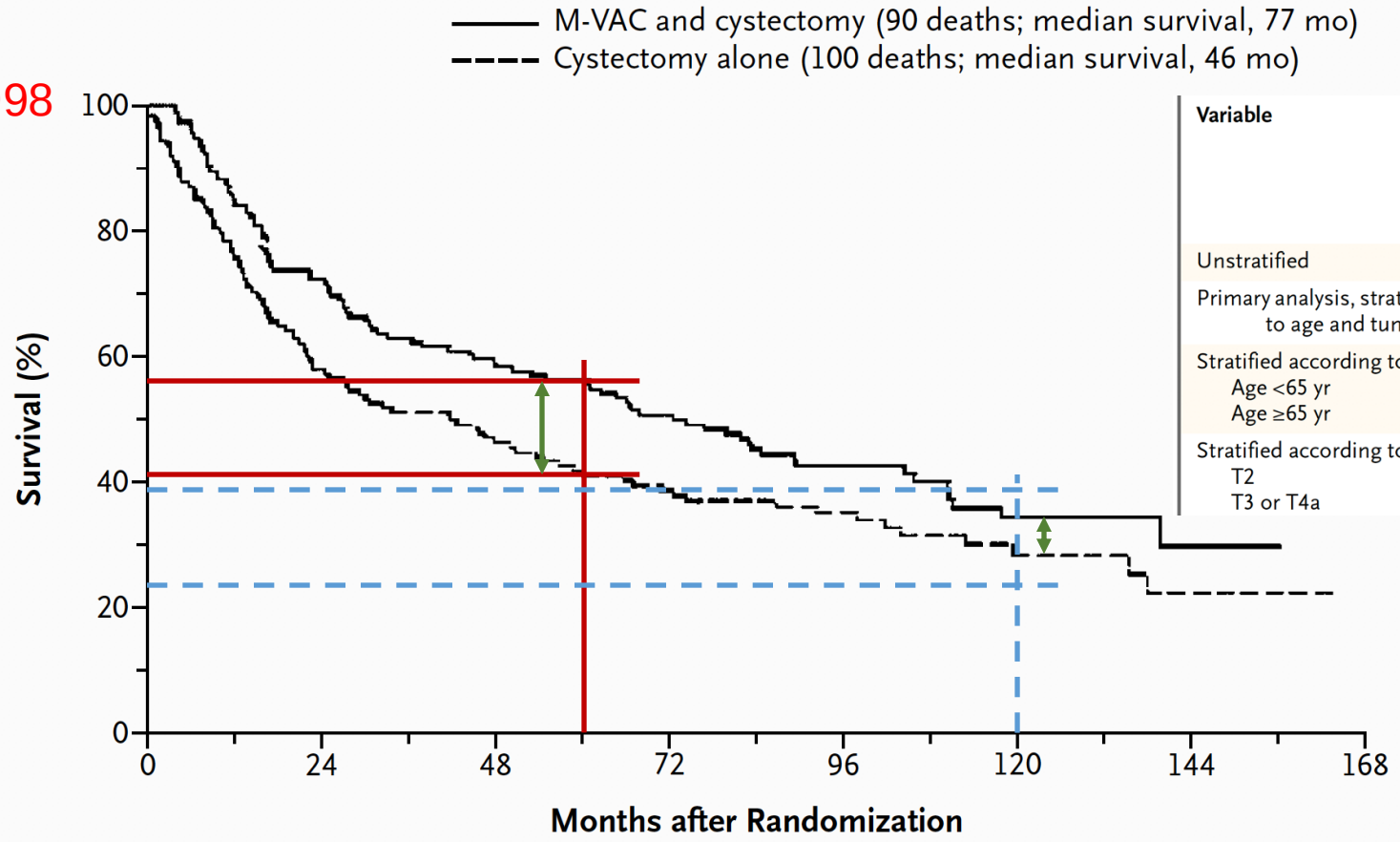
ORIGINAL ARTICLE

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

H. Barton Grossman, M.D., Ronald B. Natale, M.D., Catherine M. Tangen, Dr.P.H., V.O. Speights, D.O., Nicholas J. Vogelzang, M.D., Donald L. Trump, M.D., Ralph W. deVere White, M.D., Michael F. Sarosdy, M.D., David P. Wood, Jr., M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.

N ENGL J MED 349;9 WWW.NEJM.ORG AUGUST 28, 2003

August 1987 to July 1998



Variable	Median Survival		P Value†
	M-VAC and Cystectomy	Cystectomy Alone	
	months		
Unstratified	77	46	0.05
Primary analysis, stratified according to age and tumor stage			0.06
Stratified according to age			0.05
Age <65 yr	104	67	
Age ≥65 yr	61	30	
Stratified according to tumor stage			0.05
T2	105	75	
T3 or T4a	65	24	

No. at Risk

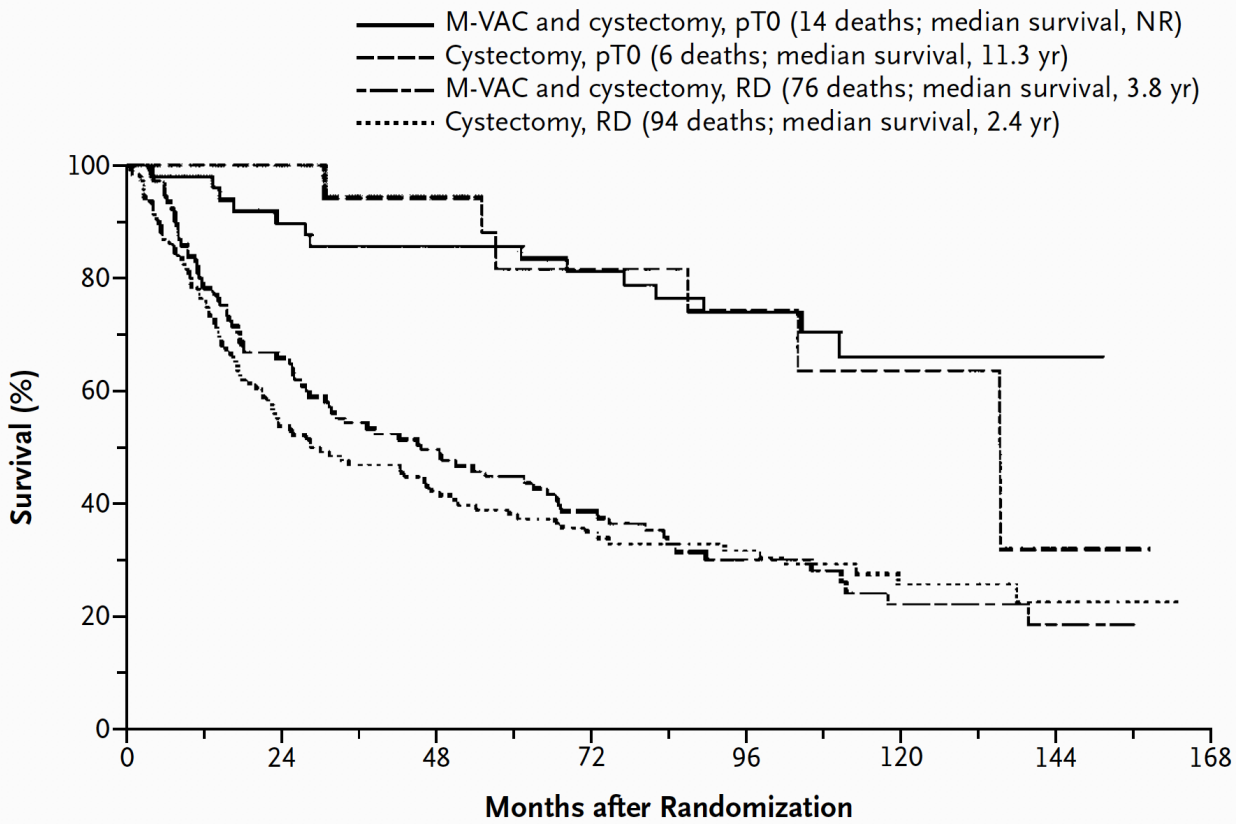
M-VAC and cystectomy	153	112	92	75	46	23	6
Cystectomy alone	154	88	67	50	37	18	7

Figure 1. Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis.

38% pT0 for MVAC
15% pT0 for Cystectomy

85% of pT0 alive at 60 months

pT0 as a surrogate for OS remains controversial



No. at Risk							
M-VAC and cystectomy, pT0	48	43	40	37	26	12	2
Cystectomy, pT0	18	17	15	12	10	4	1
M-VAC and cystectomy, RD	105	69	52	38	20	11	4
Cystectomy, RD	136	71	52	37	27	14	6

Figure 2. Survival According to Treatment Group and Whether Patients Were Pathologically Free of Cancer (pT0) or Had Residual Disease (RD) at the Time of Cystectomy.

M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin, and NR not reached.

Frontline Chemotherapy

Long Term Results: GC vs MVAC *Von der Maase JCO 2005*

	GC	MVAC
ORR	49.4%	45.7%
CR	12.2%	11.9%
SD	33.5%	32.5%
ITT ORR	44.5%	38.1%

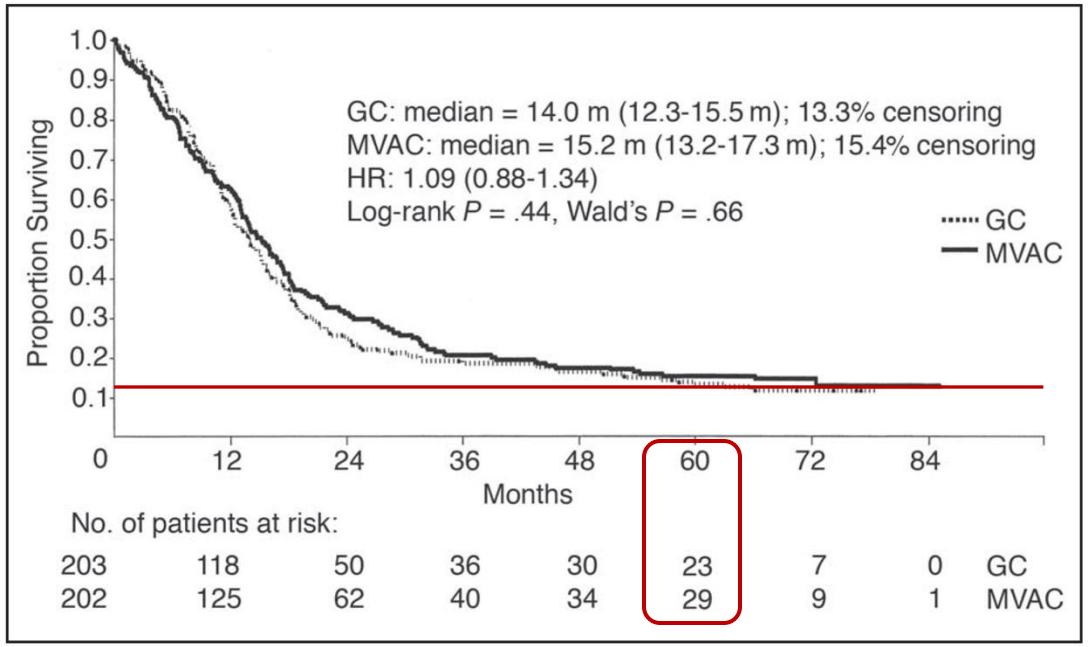


Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

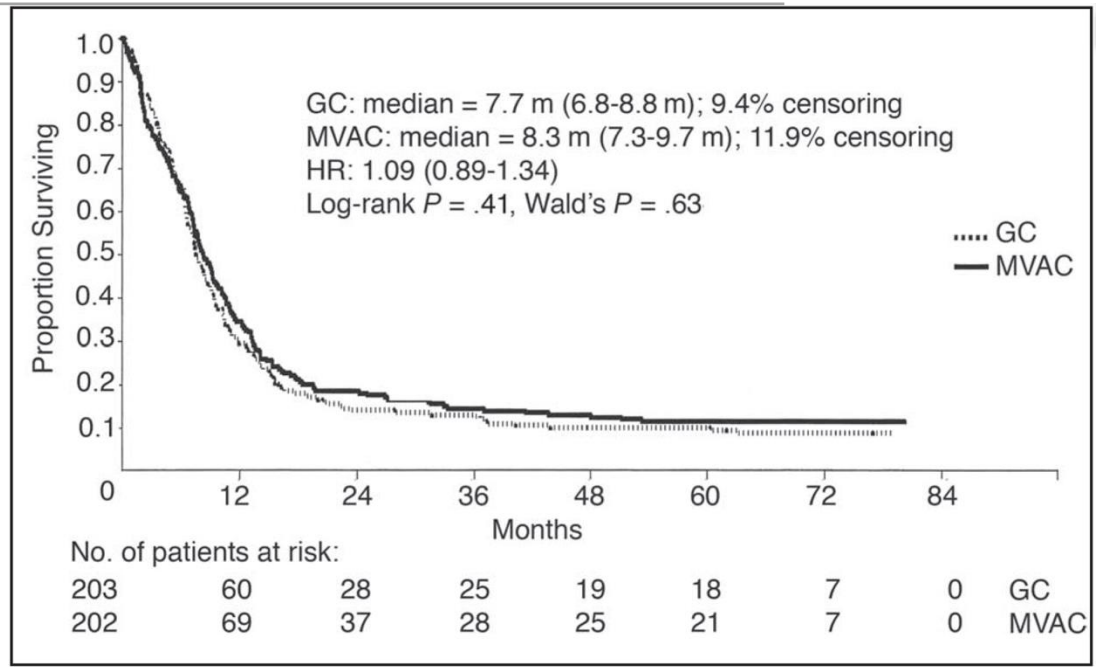
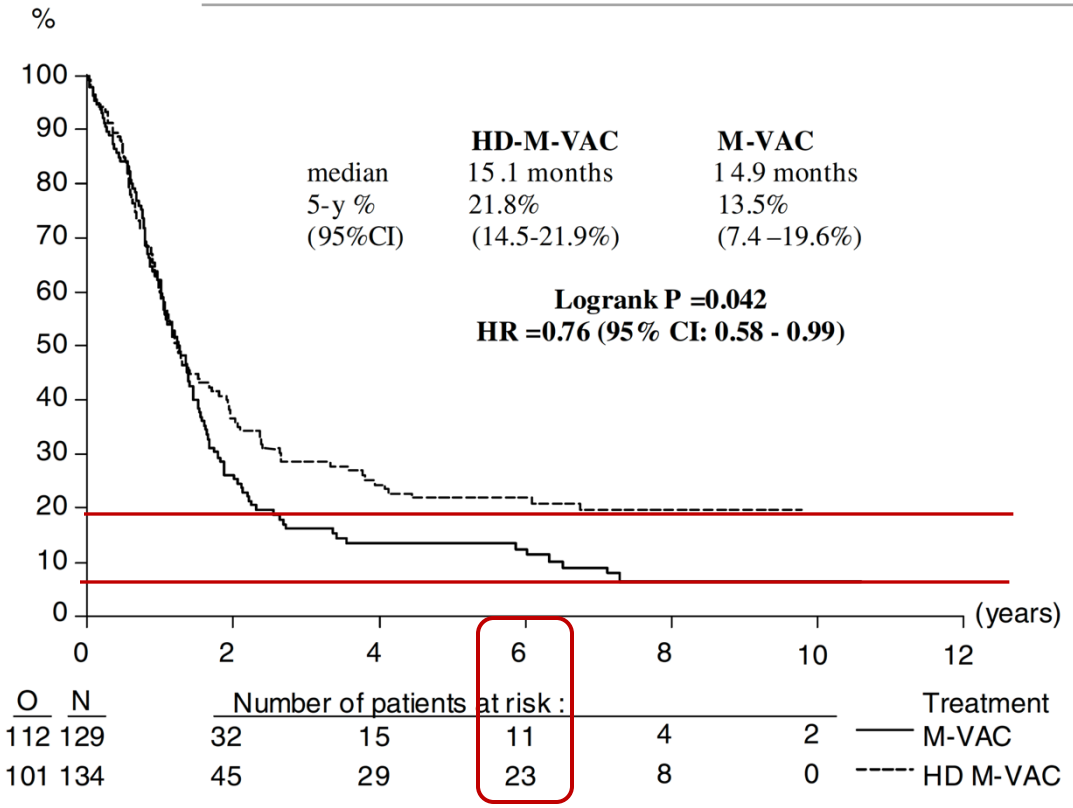


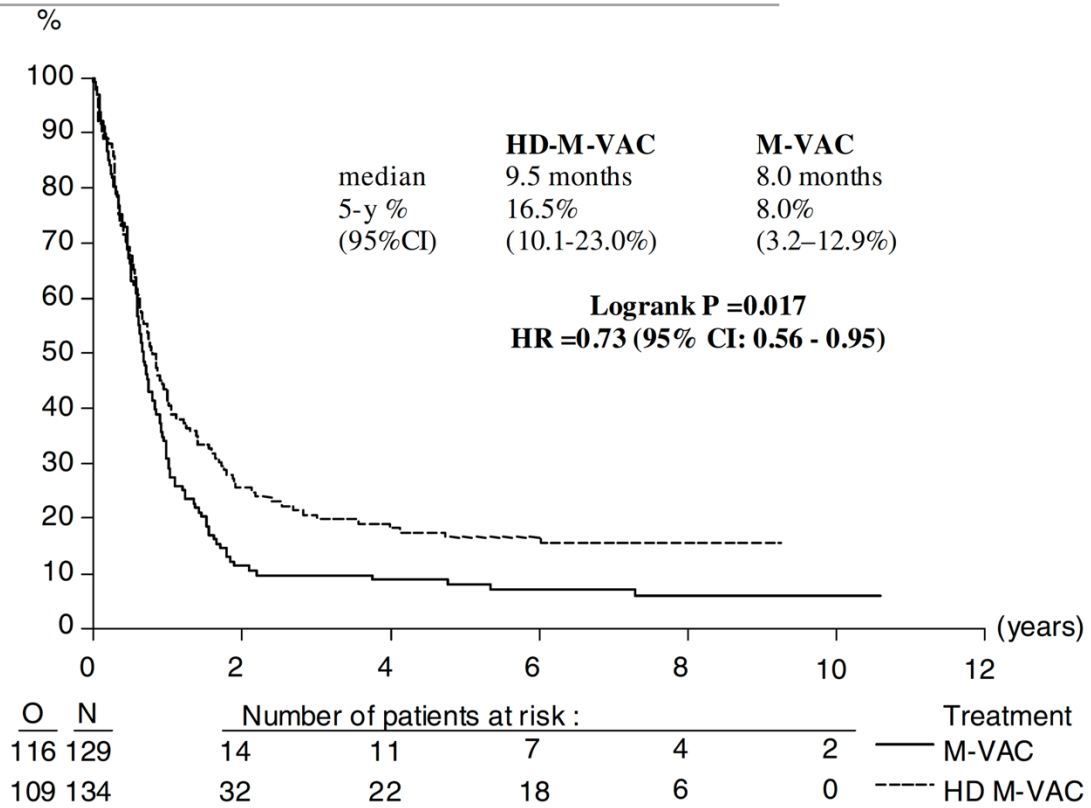
Fig 2. Kaplan-Meier curves for progression-free survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

Frontline Chemotherapy

ddMVAC vs MVAC *Sternberg Eur J Cancer 2006*

	ddMVAC	MVAC
ORR	72%	58%
CR	25%	11%
SD	-%	-%
ITT ORR	64%	50%





1) Is one regimen better (GC vs ddMVAC)?

2) Is one better for select patients?

SWOG S1314: A randomized phase II study of coexpression extrapolation (COXEN) with neoadjuvant chemotherapy for bladder cancer.

Thomas W. Flaig, Catherine M. Tangen, Siamak Daneshmand, Ajjai Shivaram Alva, Seth P. Lerner, M. Scott Lucia, David James McConkey, Dan Theodorescu, Amir Goldkorn, Matthew I. Milowsky, Rick Bangs, Gary R. MacVicar, Bruno R. Bastos, Daniel Gustafson, Melissa Plets, Ian Murchie Thompson Jr.

Division of Medical Oncology, School of Medicine, University of Colorado, Aurora, CO; Fred Hutchinson Cancer Research Center, Seattle, WA; Institute of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA; University of Michigan, Ann Arbor, MI; Baylor College of Medicine, Houston, TX; University of Colorado Anschutz Medical Campus, Aurora, CO; Johns Hopkins School of Medicine, Baltimore, MD; Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai, Los Angeles, CA; Division of Medical Oncology, Department of Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; SWOG, San Antonio, TX; Illinois CancerCare PC, Peoria, IL; Cleveland Clinic Florida, Weston, FL; Colorado State University, Fort Collins, CO; CHRISTUS Medical Center Hospital, San Antonio, TX

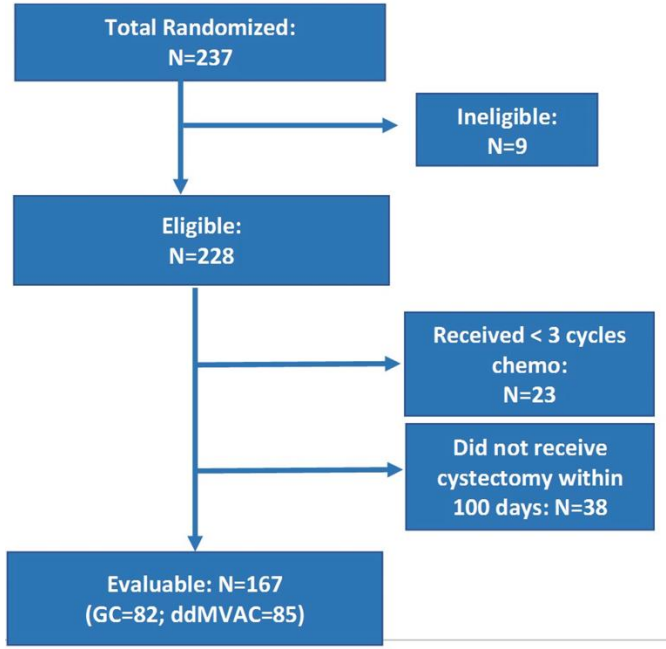
SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Presented By Thomas Flaig at 2019 ASCO Annual Meeting

S1314: Descriptive data on pathologic response by treatment arm in evaluable subjects

N=167	GC (N=82)	ddMVAC (N=85)
Chemotherapy Response		
CR (pT0)	28 (35%)	27 (32%)
PR (downstaged to ≤T1)	12 (15%)	20 (24%)
CR + PR	*40 (50%)*	*47 (56%)*
Non-responders	42 (50%)	38 (44%)



No statistically significant difference between the two.

Not powered for OS.

2023 ASCO ANNUAL MEETING

MULTICENTER RANDOMIZED PHASE III OF DOSE DENSE MVAC OR GC AS PERIOPERATIVE CHEMOTHERAPY FOR MUSCLE INVASIVE BLADDER CANCER

Overall Survival at 5 years in the GETUG/AFU V05 VESPER trial

Ch Pfister, G Gravis, A Flechon, C Chevreau, H Mahammedi, B Laguerre, A Guillot,

F Joly, Y Allory, V Harter and S Culine for the Vesper trial investigators

Getug

Association Française d'Urologie
www.urofrance.org

Trial design (1)

Chemotherapy

- **4 cycles of GC** Gemcitabine 1250 mg/m² d1 and d8
  Cisplatin 70 mg/m² d1 **every 3**
- **6 cycles of ddMVAC** Methotrexate 30 mg/m² d1
  Vinblastine 3 mg/m² d2
  Doxorubicin 30 mg/m² d2
  Cisplatin 70 mg/m² d2
  + G-CSF support from d3 to d9 **every 2**

Trial design (2)

Inclusion criteria

- Pure or mixed urothelial bladder cancer *(neuroendocrine excluded)*
- ECOG PS < 2 and all criteria for cisplatin eligibility
- Written informed consent

AND

- ≥ T2, N0 *(LN ≤ 10 mm on CT scan)*, M0 (Neoadjuvant CT)
- > pT2 or pN+ and M0 (Adjuvant CT)

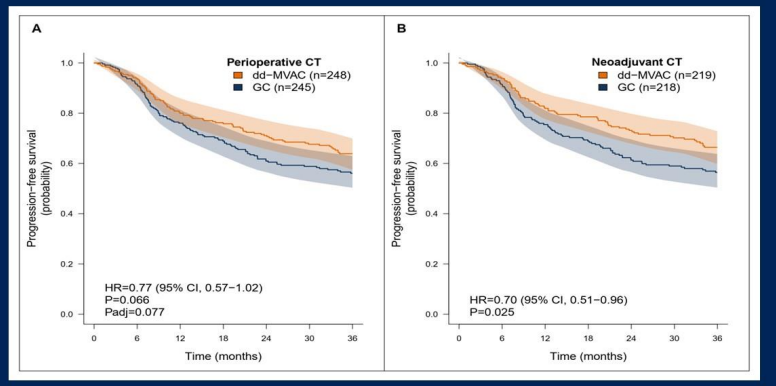
Trial design (3)

- **500 patients included in 28 centers from 2013 to 2018**

  (493 patients available for intent-to-treat analysis)
- **Adjuvant** (n=56) **and Neoadjuvant** (n=437) (88%)
- **Primary end-point :** Progression Free Survival at 3 years
- **Final analysis :** Overall and Specific Survival at 5 years

PFS at 3 years

2021 ESMO congress 16-21 September 2021



Perioperative dd-MVAC improve 3-y PFS over GC

In the neoadjuvant group, better bladder tumor local control with a significant improvement on 3-y PFS in the dd-MVAC arm

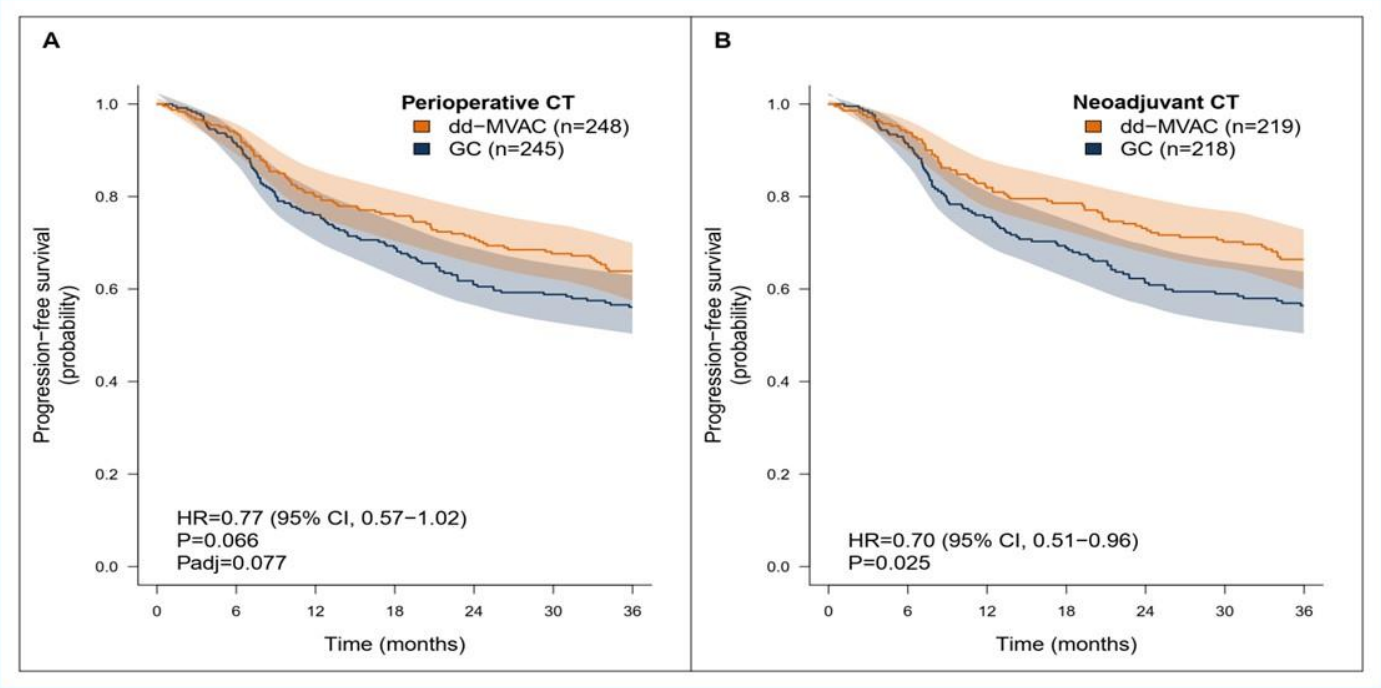
Pfister et al. J Clin Oncol 2022

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: C Pfister - 5-y OS Vesper

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

PFS at 3 years

2021 ESMO congress
16-21 September 2021



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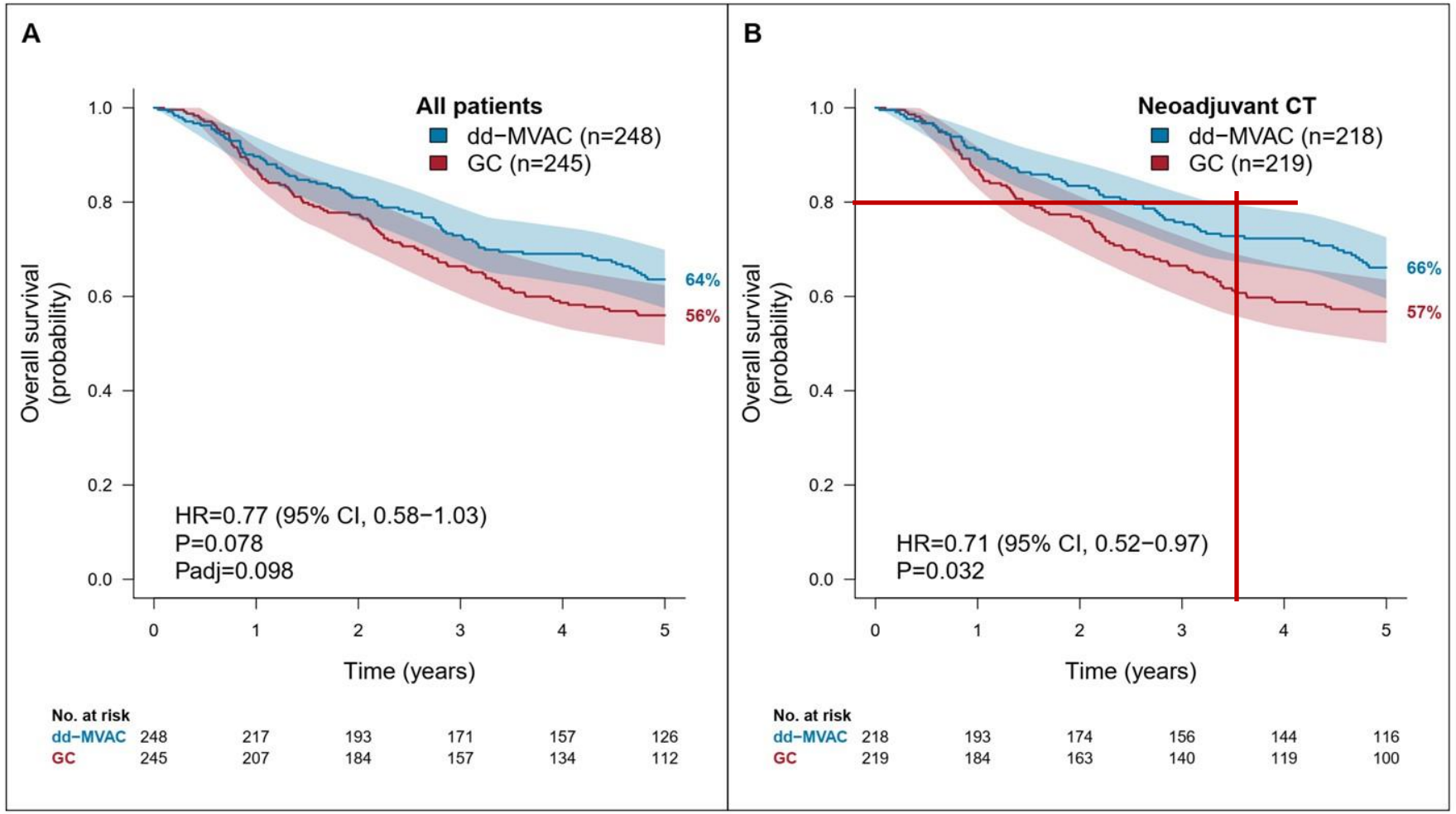
Results (1) Overall Survival at 5 years



Conclusions/Take-Home Messages

- Vesper trial is a milestone in the history of CT for MIBC
- The study did NOT meet its primary endpoint:
  PFS 3-year rate: 64% *v* 56%, hazard ratio [HR] = 0.77 [95% CI, 0.57 to 1.02], *P* = .066- JCO 2022
- **ypT0N0 42% vs 36%, p=0.2**
- No OS 5-year rate benefit in the overall group. But
  overall survival at 5 years was improved in the neoadjuvant dd-MVAC group versus the GC group (66% [95% CI 60-73]vs 57% [50-64], HR 0·71 [95% CI 0·52-0·97])
- **40% in neoadjuvant and 60% in adjuvant setting could not get 6 cycles**

PURE-01 (NCT02736266): Neoadjuvant pembrolizumab before radical cystectomy for MIBC

- Fit and planned for cystectomy
- Predominant (i.e. 50% at least) UC histology
- cT≤3bN0 stage
- Residual disease after TURB (surgical opinion, cystoscopy or radiological presence)
- GFR ≥20 ml/min (Cockcroft – Gault formula)
- ECOG-PS 0-1

3×3 weekly cycles of pembrolizumab 200 mg IV

Additional DD-MVAC x 4 cycles in non-responding pts (investigator choice)

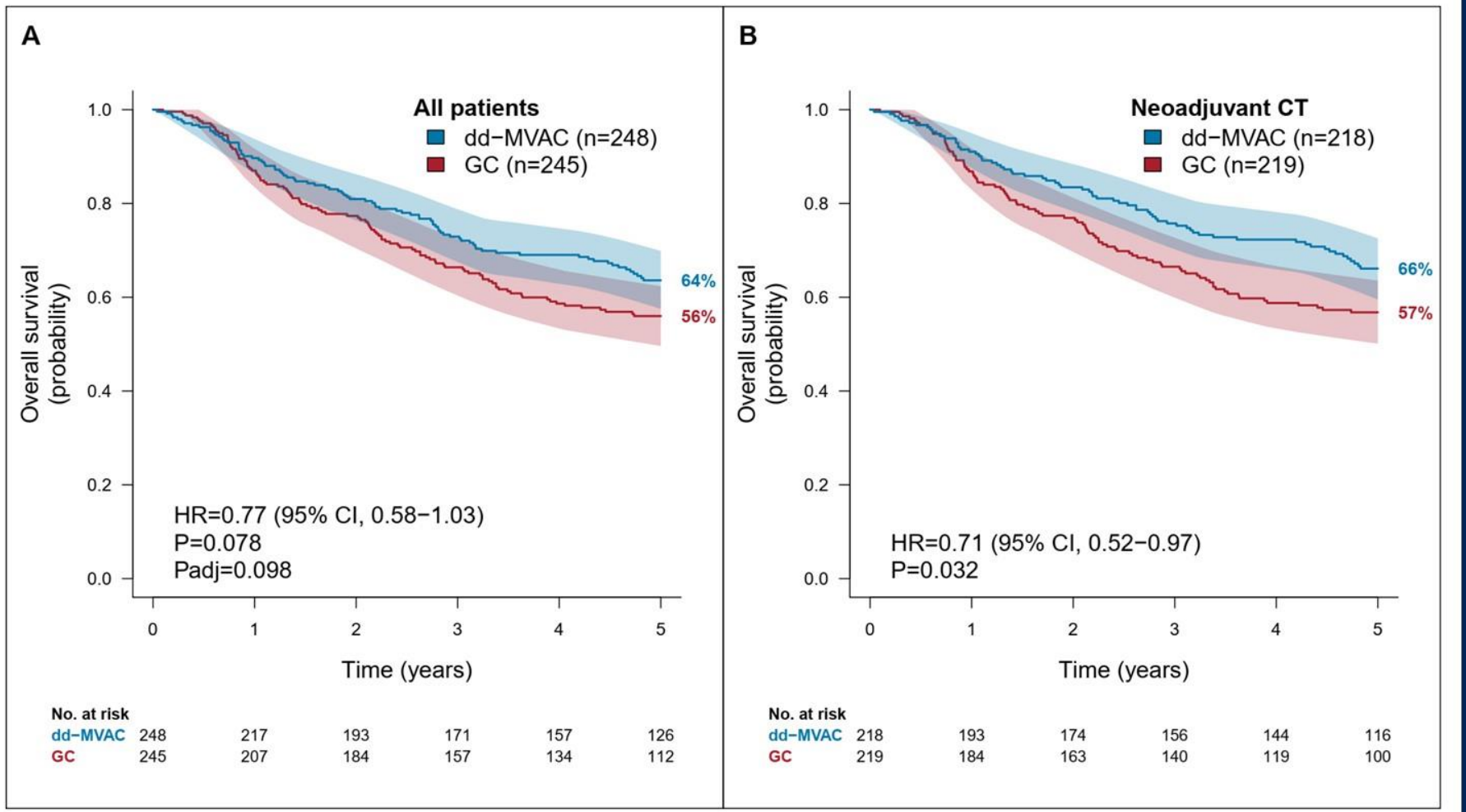
- Cystectomy
- Post-cystectomy management according to EAU guidelines
- Survival data collected until 2-y post cystectomy

Pre-post treatment tissue/blood sample collection for biomarker analyses

Pre-post treatment imaging: multiparametric bladder MRI (mpMRI); ^{18}FDG-PET/CT scan, T/A CT scan

- Pathologic complete response (pT0) in ITT population is the primary endpoint
- The H_1 is pT0 ≥25% and H_0 pT0≤15%
- **71 pts** will be enrolled, with **43 pts** at first stage according to MinMax design
- pT0 limits for H0 rejection: **6 (1st stage); 14 (2nd stage)**
- 80% power and a one-sided test of significance at the 10% level
- Data cut-off: May 10th, 2018: Median Follow-up: 8 months

Results (1) Overall Survival at 5 years



PURE-01

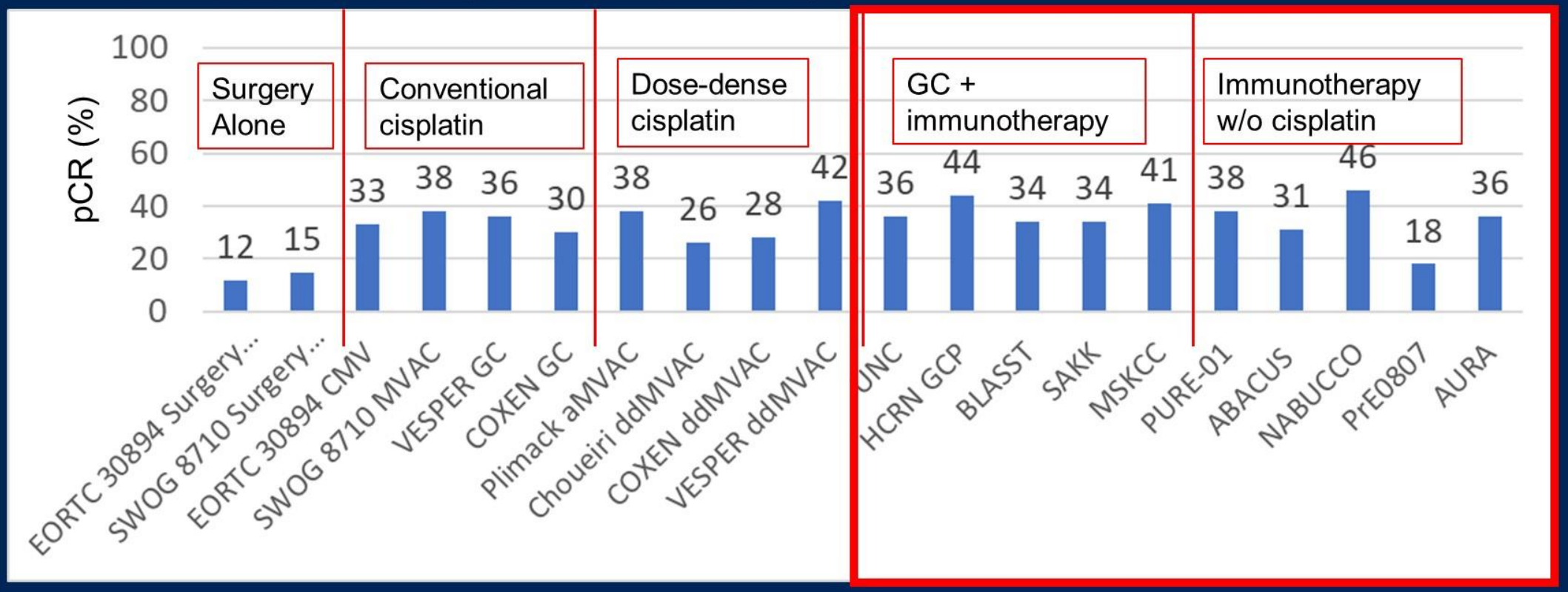
Table 2. Univariable and multivariable Cox regression models predicting EFS.

	Univariable analyses		Multivariable analyses	
Variable	**HR (95%CI)**	***P*[a]**	**HR (95%CI)**	***P*[a]**
Age (continuous)	1.00 (0.97–1.04)	0.6	—	—
Sex (Male vs. Female)	1.15 (0.44–3.00)	0.8	—	—
Previous NMIBC	0.76 (0.17–3.33)	0.7	—	—
Previous BCG	0.72 (0.12–4.20)	0.7	—	—
Histology:				
• Pure UC (ref.)				
• Non-predominant VH (ref.)	2.51 (0.91–6.92)	0.07	—	—
• Predominant VH	0.76 (0.28–2.06)	0.6	—	—
TMB (Mut/Mb; continuous)	0.95 (0.90–1.00)	0.09	0.95 (0.91–1.00)	0.1
CPS (%; continuous)	0.96 (0.95–0.98)	0.001	0.97 (0.95–0.99)	0.003
Clinical T-stage:				
• cT2N0 (ref.)				
• cT3–4N0	2.50 (1.20–5.17)	0.01	2.20 (1.09–4.45)	0.03

Abbreviations: BCG, Bacillus Calmette-Guérin; CPS, combined positive score; HR, hazard ratio; NMIBC, non-muscle-invasive bladder cancer; ref., reference group; TMB, tumor mutational burden; UC, urothelial carcinoma; VH, variant histology.

[a]Two-sided Wald test *P* value.

Is the addition of chemotherapy to immunotherapy necessary?



Grossman et al. NEJM 2003
Flaig et al, CCR 2021
Gupta et al, JCO 38,6_supp (Feb 2020).
Necchi et al, JCO 2018
Grivas et al, ASCO Annual Mtg 2021; abstr 4518

EORTC 30894, JCO 2011
Rose et al, GU ASCO 2021, abstr 396.
Cathomas et al, GU ASCO 2021, abstr 430.
Powles et al, Nat Med 2019
Kaimakliotis et al, ASCO Annual Mtg 2020;abstr 5019

Pfister et al, Euro Urol 2021
Hoimes et al, ESMO 2018, abstr 5681.
Funt et al, ASCO Annual Meeting, abstr 4517.
Van Dijk et al, ASCO Annual Mtg 2020;abstr 5020

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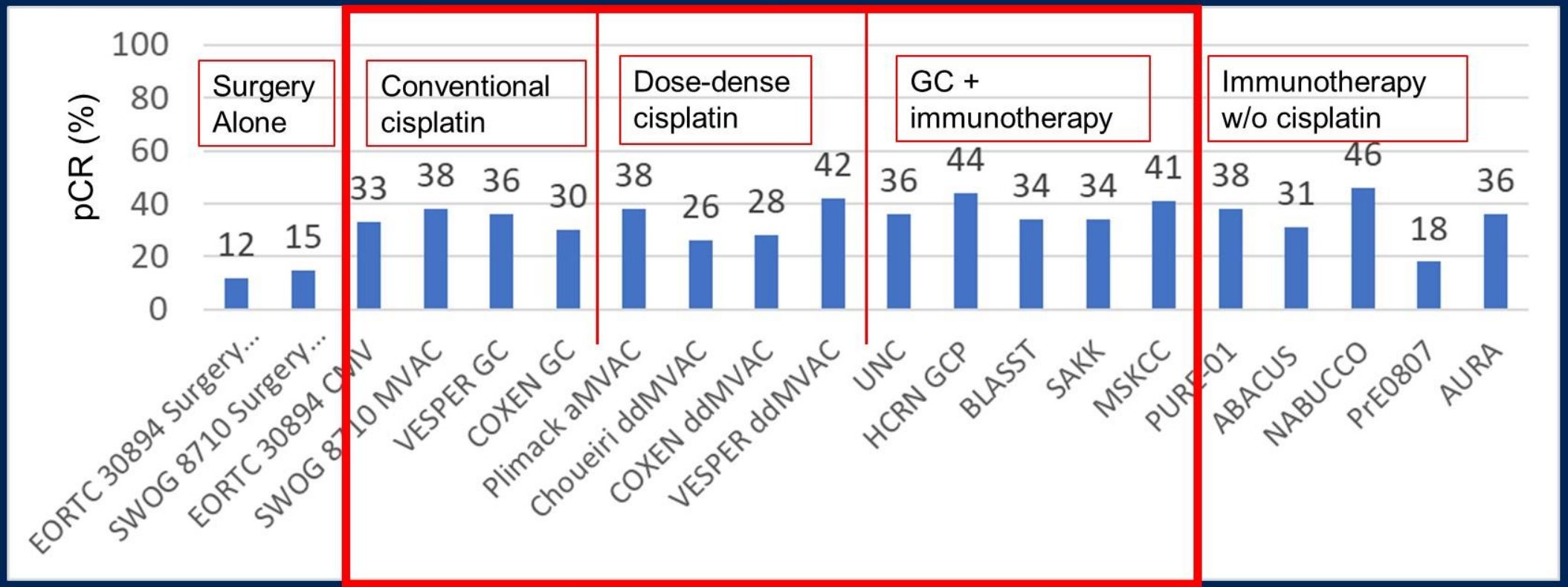
Is the addition of immunotherapy to chemotherapy necessary?



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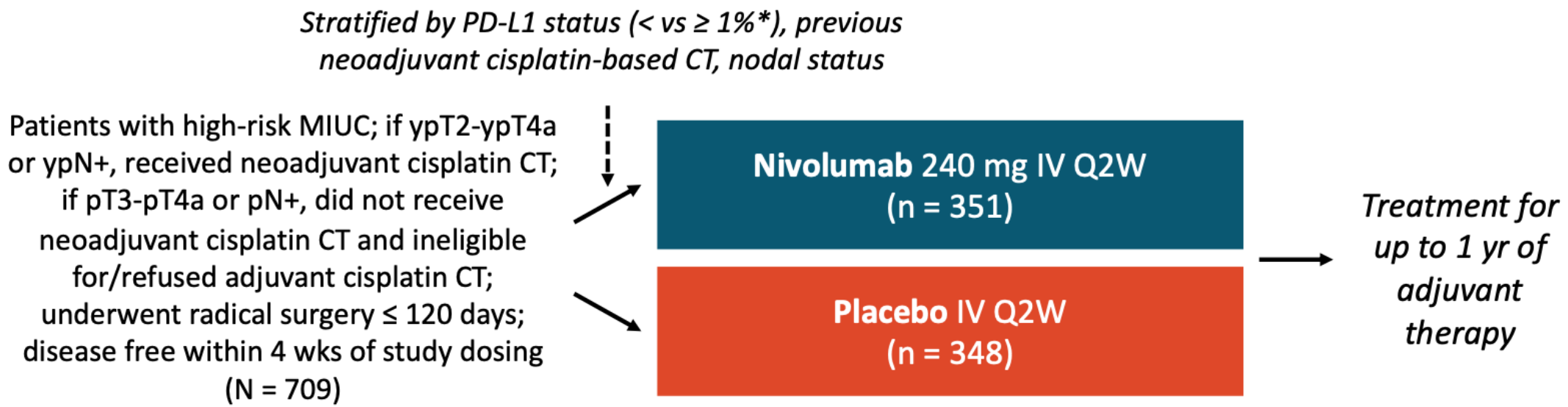
What endpoints should be used for neoadjuvant trials in bladder cancer?

- pCR – individual-level and trial-level surrogacy for time-to-event endpoints (EFS, DFS, OS) is not clear in MIBC
  - Magnitude of pathologic response improvement that translates into meaningful clinical benefit?
- pCR may be used to guide subsequent therapy on a trial level i.e., more therapy for those without pCR (used in breast cancer and c/w CheckMate 274 and more to come related to ctDNA)
- Current trials must have “highly granular patient-related, tumor-related and treatment-related characteristics” to inform design of future trials

Nat Rev Urol. 2022 Jan;19(1):37-46.

CheckMate 274: Adjuvant Nivolumab vs Placebo After Radical Surgery ± Neoadjuvant CT in High-Risk MIUC

- First analysis of international, randomized, double-blind phase III trial



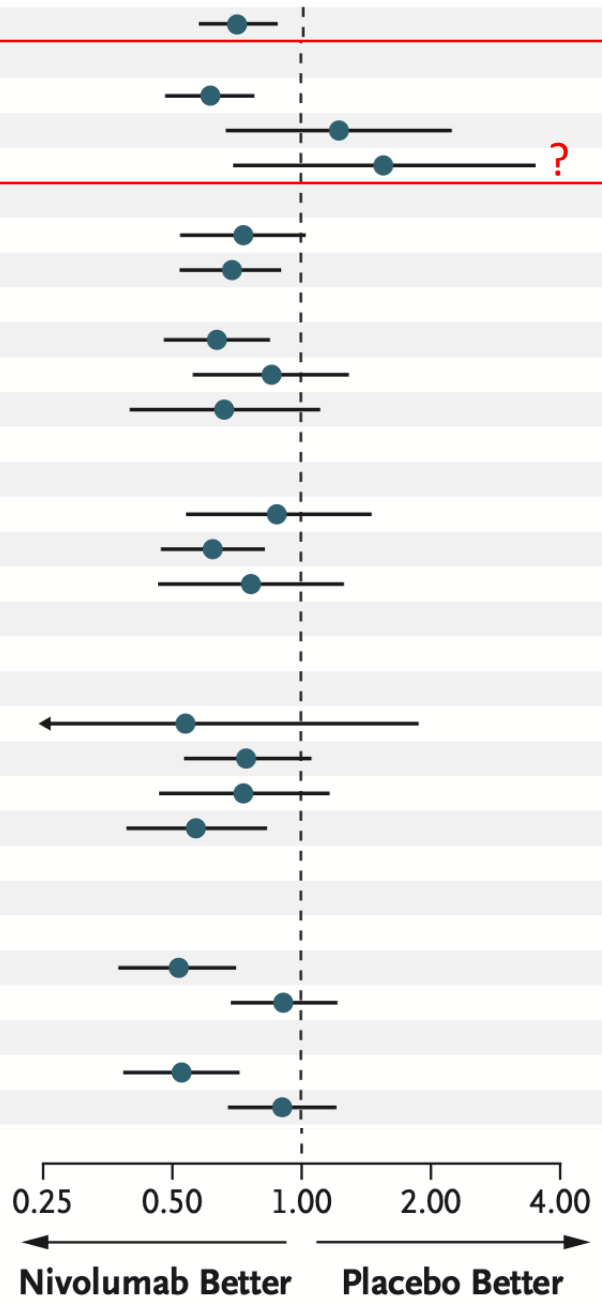
- **Primary endpoints:** DFS is ITT population, DFS in all randomized patients with PD-L1 ≥ 1%

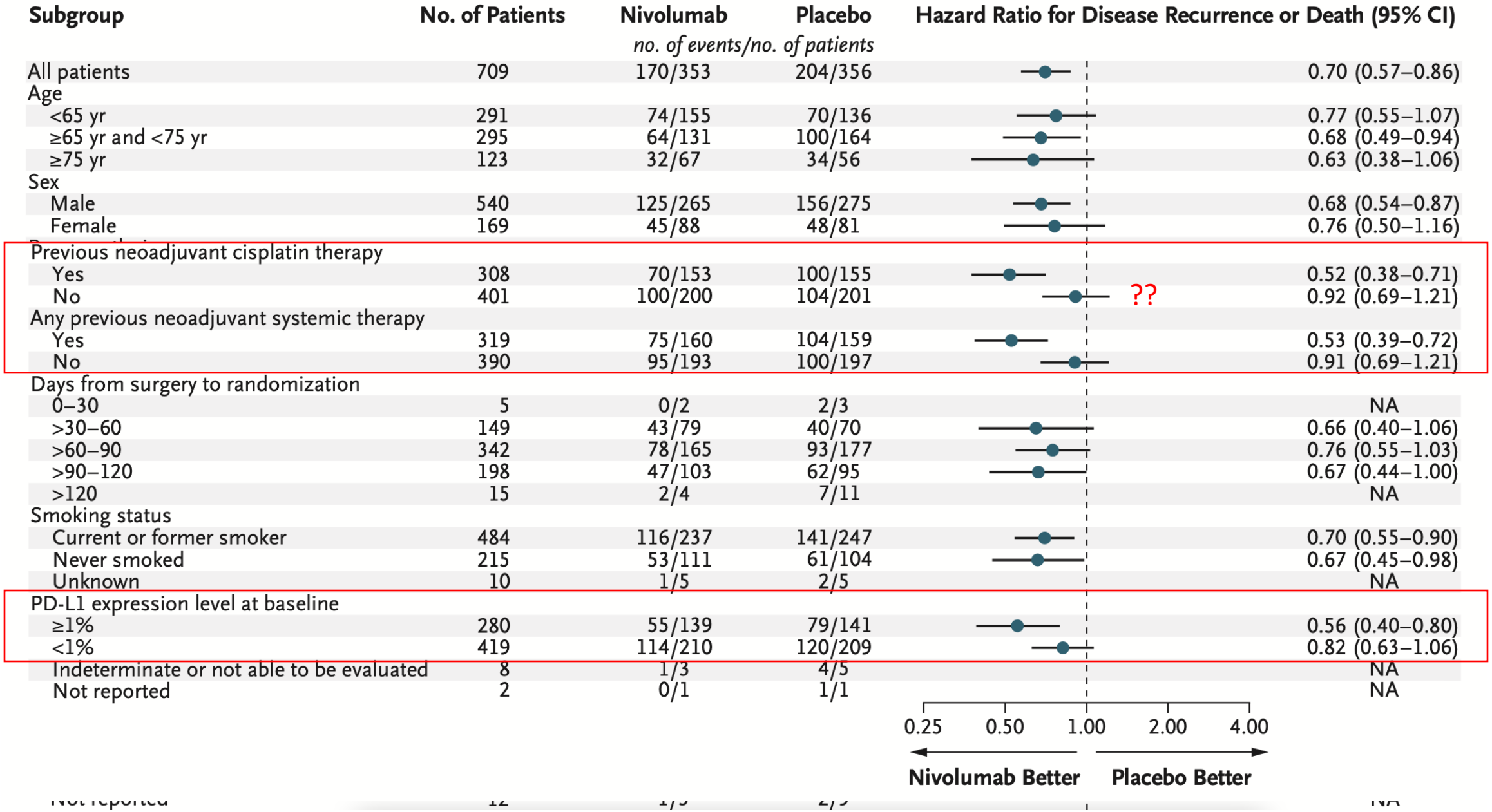
- **Secondary endpoints:** nonurothelial tract recurrence-free survival, disease-specific survival, OS†
- **Exploratory endpoints:** distant metastasis–free survival, safety, HRQoL

*Per PD-L1 IHC 28-8 PharmDx assay.
†OS data immature at time of analysis.

Bajorin. ASCO GU 2021. Abstr 391. NCT02632409.

Subgroup	No. of Patients	Nivolumab	Placebo	Hazard Ratio for Disease Recurrence or Death (95% CI)
		no. of events/no. of patients		
All patients	709	170/353	204/356	0.70 (0.57–0.86)
Initial tumor origin				
Urinary bladder	560	129/279	166/281	0.62 (0.49–0.78)
Renal pelvis	96	24/44	25/52	1.23 (0.67–2.23)
Ureter	53	17/30	13/23	1.56 (0.70–3.48)
Minor histologic variants				
Yes	286	70/145	76/141	0.73 (0.53–1.02)
No	423	100/208	128/215	0.69 (0.53–0.90)
Nodal status				
N+	335	95/167	116/168	0.64 (0.48–0.85)
N0 or NX with <10 nodes removed	193	46/94	50/99	0.85 (0.57–1.28)
N0 with ≥10 nodes removed	179	29/91	37/88	0.67 (0.41–1.10)
Not reported	2	0/1	1/1	NA
Pathological tumor stage				
pT0–2	166	35/80	40/86	0.88 (0.54–1.43)
pT3	410	97/206	120/204	0.63 (0.48–0.82)
pT4a	119	36/57	40/62	0.77 (0.47–1.25)
Other	12	1/9	3/3	NA
Not reported	2	1/1	1/1	NA
Pathological tumor stage and nodal status				
pT2N–	54	6/25	10/29	0.54 (0.16–1.86)
pT3,4N–	317	68/158	78/159	0.75 (0.54–1.05)
pT0–4N1	143	39/71	45/72	0.74 (0.47–1.15)
pT0–4N2,3	192	56/96	71/96	0.57 (0.40–0.83)
pTisN–	1	0/1	0	NA
Not reported	2	1/2	0	NA
Previous neoadjuvant cisplatin therapy				
Yes	308	70/153	100/155	0.52 (0.38–0.71)
No	401	100/200	104/201	0.92 (0.69–1.21)
Any previous neoadjuvant systemic therapy				
Yes	319	75/160	104/159	0.53 (0.39–0.72)
No	390	95/193	100/197	0.91 (0.69–1.21)
Not reported	2	0/1	1/1	NA




Subgroup
No. of Patients
Nivolumab
Placebo
Hazard Ratio for Disease Recurrence or Death (95% CI)
no. of events/no. of patients
All patients 709 170/353 204/356 0.70 (0.57–0.86)
Age
<65 yr 291 74/155 70/136 0.77 (0.55–1.07)
≥65 yr and <75 yr 295 64/131 100/164 0.68 (0.49–0.94)
≥75 yr 123 32/67 34/56 0.63 (0.38–1.06)
Sex
Male 540 125/265 156/275 0.68 (0.54–0.87)
Female 169 45/88 48/81 0.76 (0.50–1.16)
Previous neoadjuvant cisplatin therapy
Yes 308 70/153 100/155 0.52 (0.38–0.71)
No 401 100/200 104/201 0.92 (0.69–1.21)
??
Any previous neoadjuvant systemic therapy
Yes 319 75/160 104/159 0.53 (0.39–0.72)
No 390 95/193 100/197 0.91 (0.69–1.21)
Days from surgery to randomization
0–30 5 0/2 2/3 NA
>30–60 149 43/79 40/70 0.66 (0.40–1.06)
>60–90 342 78/165 93/177 0.76 (0.55–1.03)
>90–120 198 47/103 62/95 0.67 (0.44–1.00)
>120 15 2/4 7/11 NA
Smoking status
Current or former smoker 484 116/237 141/247 0.70 (0.55–0.90)
Never smoked 215 53/111 61/104 0.67 (0.45–0.98)
Unknown 10 1/5 2/5 NA
PD-L1 expression level at baseline
≥1% 280 55/139 79/141 0.56 (0.40–0.80)
<1% 419 114/210 120/209 0.82 (0.63–1.06)
Indeterminate or not able to be evaluated 8 1/3 4/5 NA
Not reported 2 0/1 1/1 NA
0.25
0.50
1.00
2.00
4.00
Nivolumab Better
Placebo Better

CheckMate 274: Efficacy Outcomes

Median, Mos	ITT		PD-L1 ≥ 1%	
	Nivolumab (n = 353)	Placebo (n = 356)	Nivolumab (n = 140)	Placebo (n = 142)
DFS (primary endpoints)	21.0	10.9	NR	10.8
▪ **HR for DFS**	0.70 (98.31% CI: 0.54-0.89); *P* < .001		0.53 (98.87% CI: 0.34-0.84); *P* < .001	
NUTRFS	24.6	13.7	NR	10.9
▪ HR for NUTRFS	0.72 (95% CI: 0.58-0.89)		0.54 (95% CI: 0.38-0.77)	
DMFS	35.0	29.0	NR	21.2
▪ HR for DMFS	0.74 (95% CI: 0.58-0.93)		0.60 (95% CI: 0.41-0.88)	

- Study met its primary endpoints: nivolumab significantly prolonged DFS vs placebo in the ITT population and patients with PD-L1 ≥ 1% (both *P* < .001)
- Nivolumab prolonged DFS vs placebo in most subgroups of ITT population except for patients with initial tumor origin in renal pelvis (HR: 1.16; 95% CI: 0.63-2.13) and ureter (HR: 1.55; 95% CI: 0.70-3.45)

Bajorin. ASCO GU 2021. Abstr 391.

Slide credit: clinicaloptions.com

Upper Tract:

Improved Disease-Free Survival With Adjuvant Chemotherapy After Nephroureterectomy for Upper Tract Urothelial Cancer: Final Results of the POUT Trial

Alison Jane Birtle, MD, MBBS, MRCP, FRCR[1,2,3]; Robert Jones, PhD, MBChB[4,5]; John Chester, PhD, MRCP, MBBS[6]; Rebecca Lewis, BSc[7];

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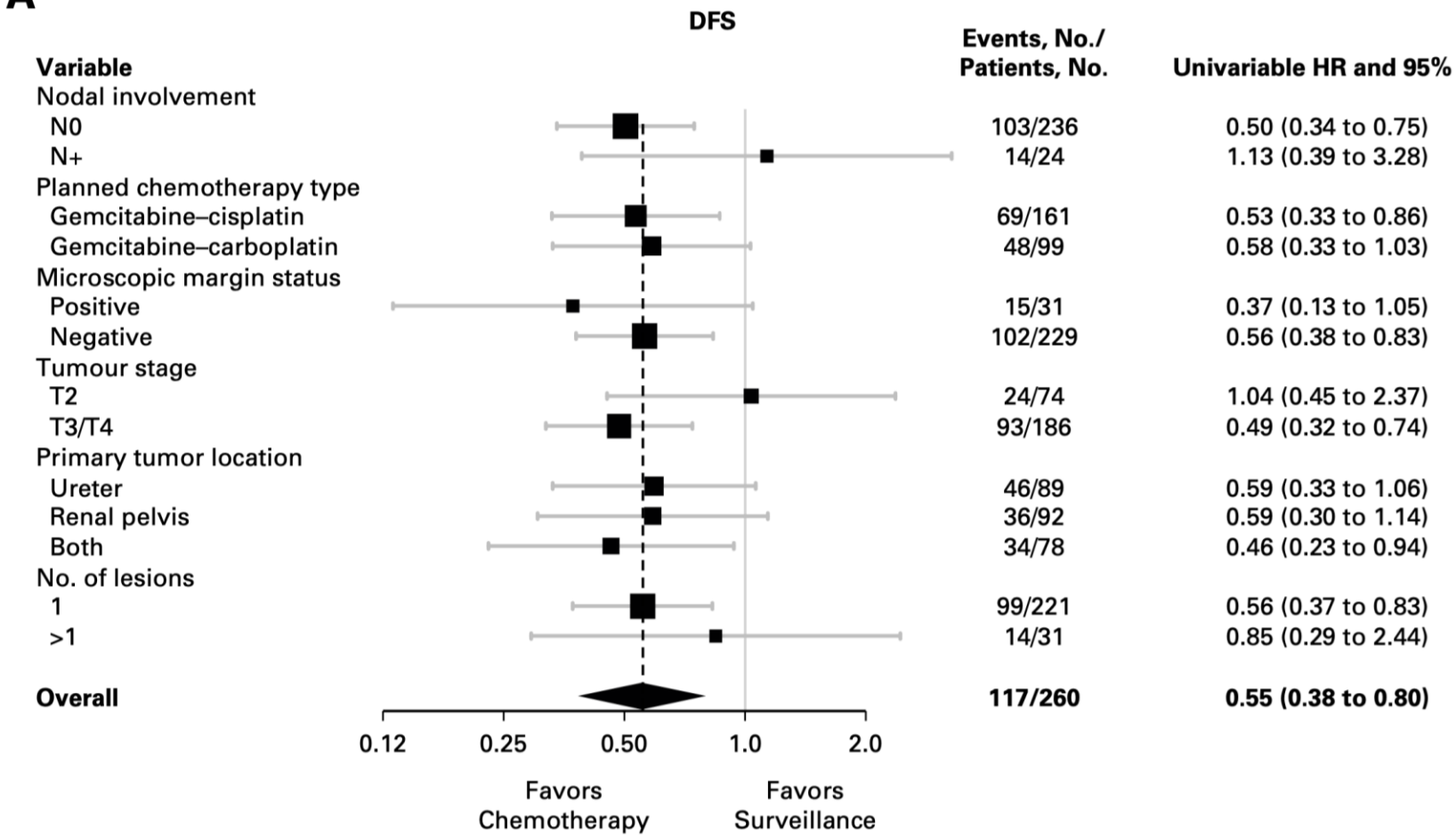
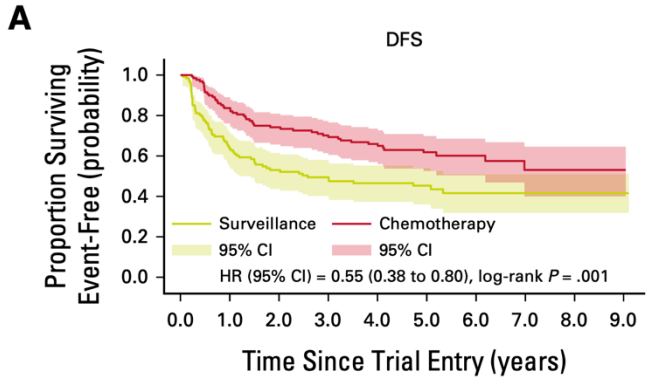
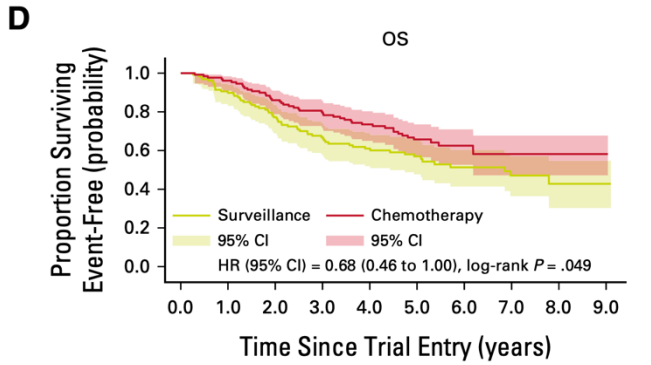






J Clin Oncol 42:1466-1471

MADRID 2023 ESMO congress

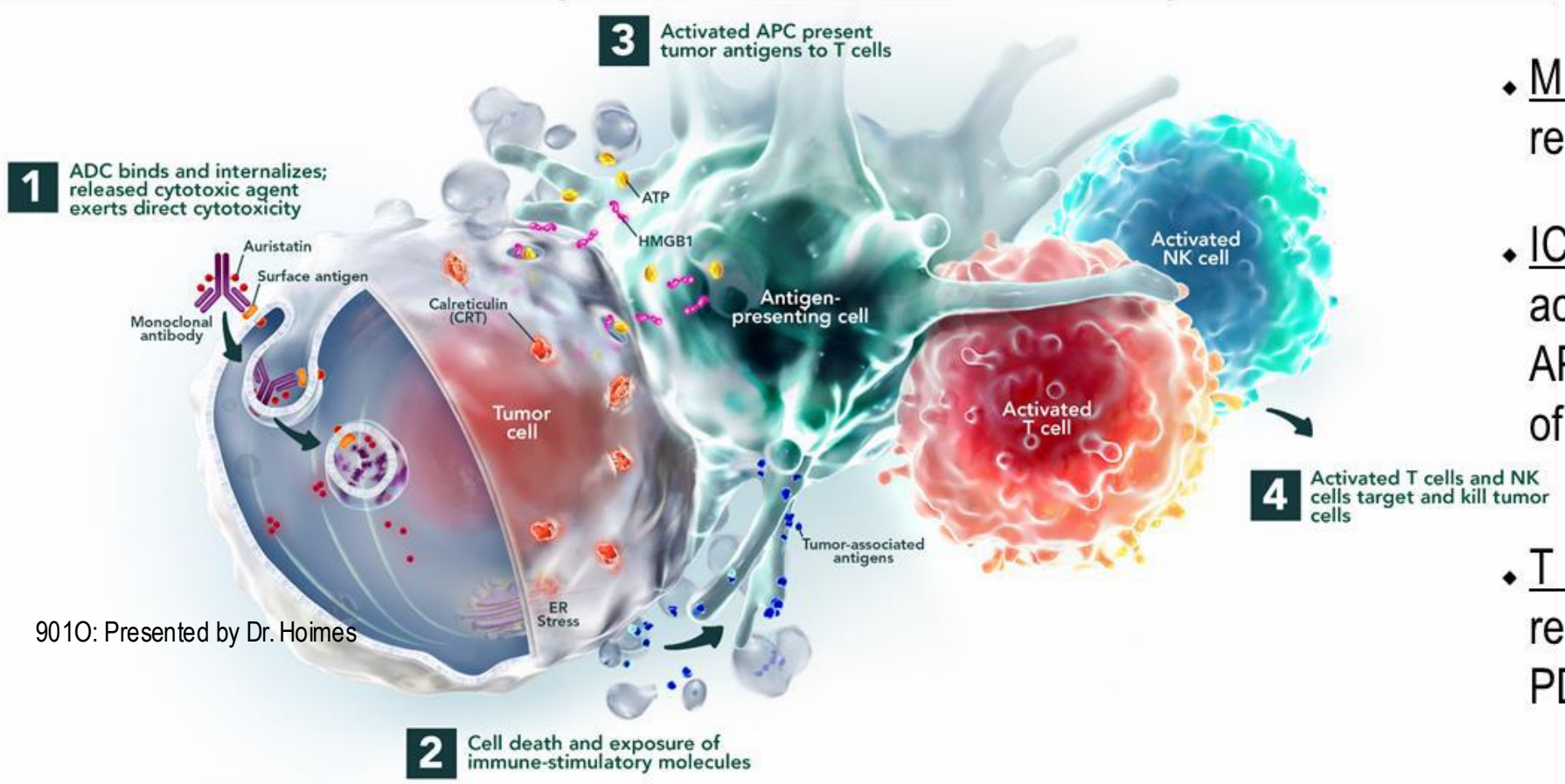
EV-302/KEYNOTE-A39: Open-Label, Randomized Phase 3 Study of Enfortumab Vedotin in Combination with Pembrolizumab vs Chemotherapy in Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma

Thomas Powles, Begona Perez-Valderrama, Shilpa Gupta, Jens Bedke, Eiji Kikuchi, Jean Hoffman-Censits, Gopa Iyer, Christof Vulsteke, Se Hoon Park, Sang Joon Shin, Daniel Castellano Gauna, Giuseppe Fornarini, Jian-Ri Li, Mahmut Gumus, Nataliya Mar, Sujata Narayanan, Xuesong Yu, Seema Gorla, Blanca Homet Moreno, Michiel Van der Heijden

FPN: LBA6

RATIONALE FOR COMBINING ENFORTUMAB VEDOTIN + PEMBROLIZUMAB

ADCs[1] linked to monomethyl auristatin E (MMAE) induce immunogenic cell death (ICD) in preclinical and in vitro data, and may enhance anti-tumor immunity

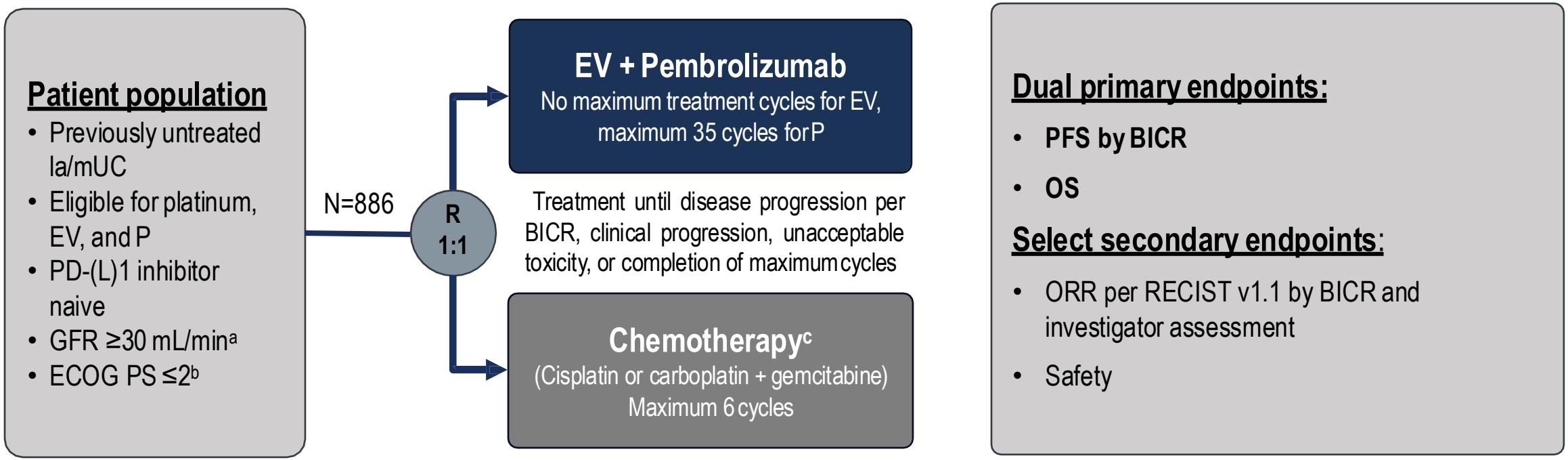


- MMAE disrupts microtubules resulting in ICD due to ER stress
- ICD releases innate immune-activating molecules resulting in APC activation and presentation of tumor antigens to T cells
- T cells mount antigen-specific response augmented by PD-1/L1 inhibitors

901O: Presented by Dr. Hoimes

[1] Brentuximab vedotin, ladiratuzumab vedotin, and tisotumab vedotin. References: Cao et al. *AACR* 2016. Cao et al. *Cancer Res* 2017;77(13 suppl): Abstract 5588. Cao et al. *Cancer Res* 2018;78(13 Suppl): Abstract 2742. Alley et al. *Cancer Res* 2019;79(13 Suppl): Abstract 221.

EV-302/KEYNOTE-A39 (NCT04223856)



Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors
[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine
[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure
[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy

Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

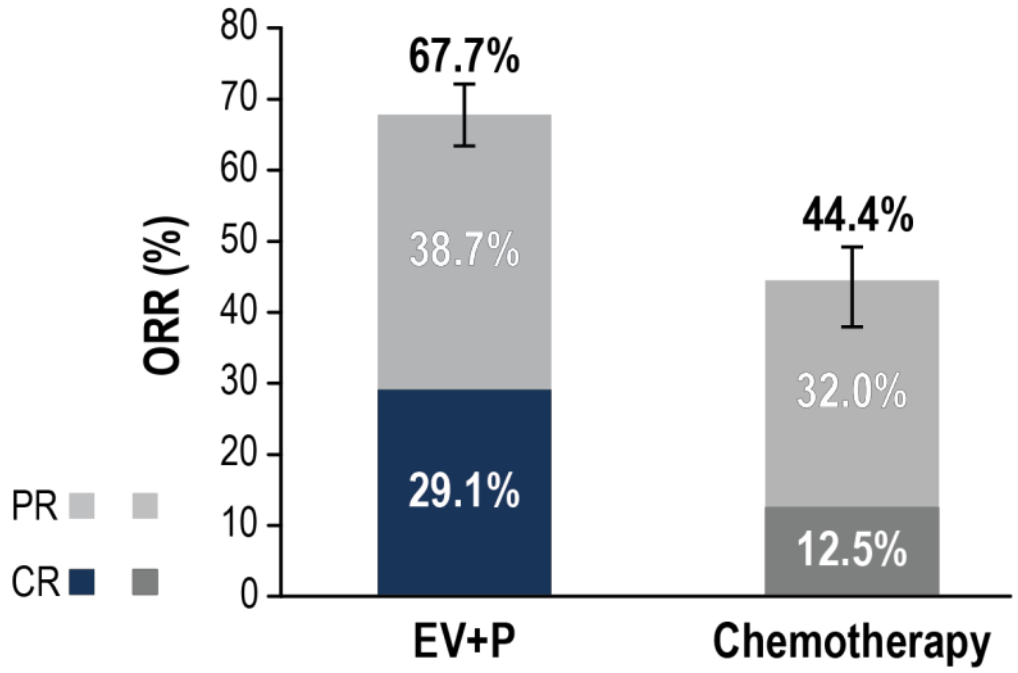
Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	223/442	307/444	0.45 (0.38-0.54)
Age			
<65 years	75/144	88/135	0.45 (0.32-0.62)
≥65 years	148/298	219/309	0.45 (0.36-0.56)
Sex			
Female	55/98	74/108	0.49 (0.34-0.71)
Male	168/344	233/336	0.44 (0.36-0.54)
ECOG PS			
0	93/223	146/215	0.36 (0.28-0.48)
1-2	130/219	161/227	0.53 (0.42-0.68)
Primary disease site of origin			
Upper tract	69/135	70/104	0.50 (0.35-0.71)
Lower tract	152/305	236/339	0.44 (0.35-0.54)
Liver metastases			
Present	66/100	78/99	0.53 (0.38-0.76)
Absent	157/342	229/345	0.43 (0.35-0.52)
PD-L1 expression			
Low (CPS <10)	105/184	127/185	0.50 (0.38-0.65)
High (CPS ≥10)	116/254	176/254	0.42 (0.33-0.53)
Cisplatin eligibility			
Eligible	117/244	149/234	0.48 (0.38-0.62)
Ineligible	106/198	158/210	0.43 (0.33-0.55)

mOS, median overall survival; NR, not reached

[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)
Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

Data cutoff: 08 Aug 2023

CR, complete response; DOR, duration of response; PR, partial response
[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response
[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline

EV Treatment-Related Adverse Events of Special Interest*

Majority of treatment-related AESIs were low grade

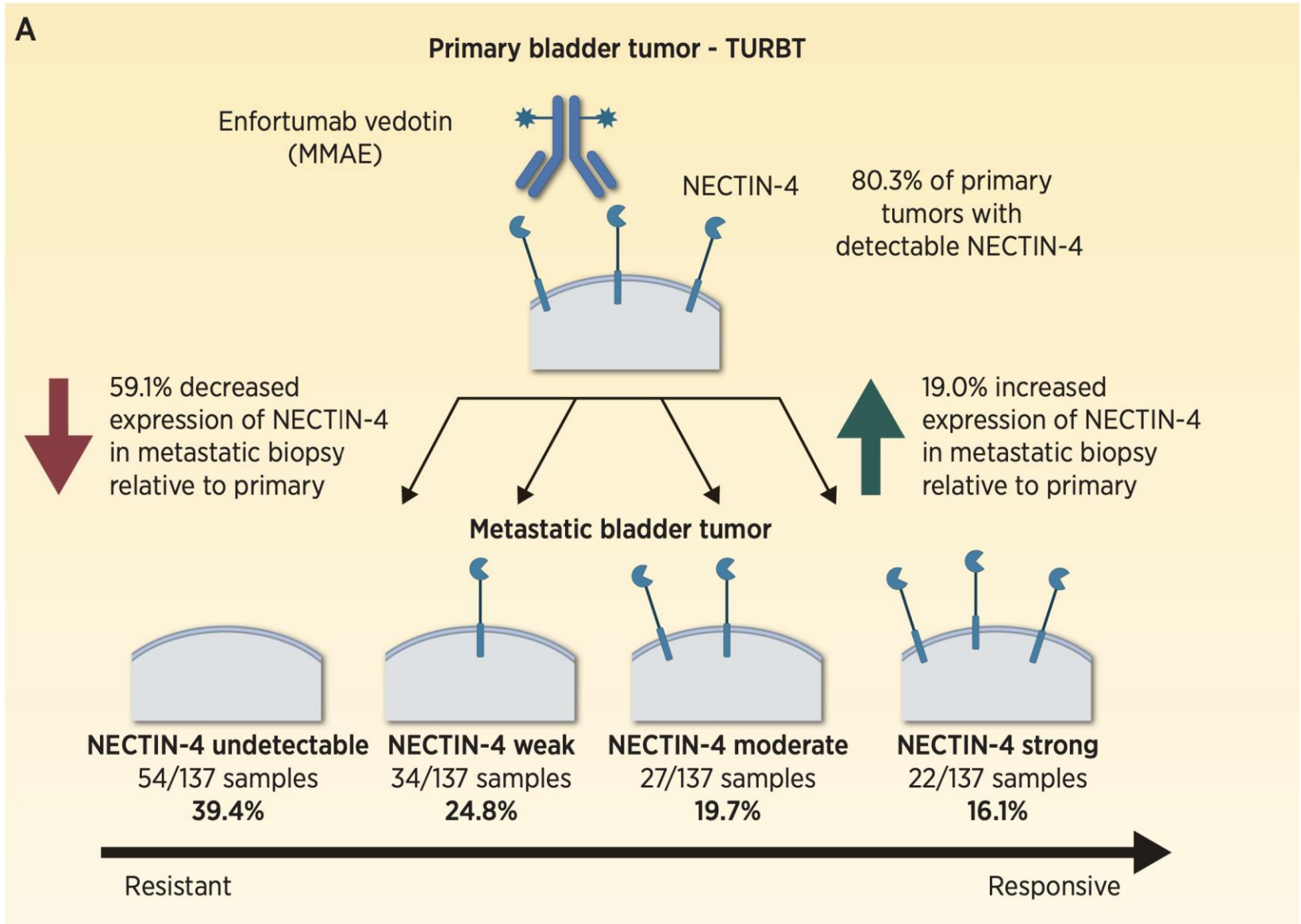
	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
Ocular disorders	94 (21.4)	0 (0.0)	12 (2.8)	0 (0.0)
Dry eye	82 (18.6)	0 (0.0)	8 (1.8)	0 (0.0)
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0 (0.0)
Infusion-related reactions	9 (2.0)	0 (0.0)	9 (2.1)	0 (0.0)

Data cutoff: 08 Aug 2023

*There are differences in the rates of skin reactions reported for EV treatment-related AESIs and P TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and P monotherapies, respectively
AESI, adverse event of special interest

Scratching the Surface: NECTIN-4 as a Surrogate for Enfortumab Vedotin Resistance

David H. Aggen[1], Carissa E. Chu[2], and Jonathan E. Rosenberg[1]

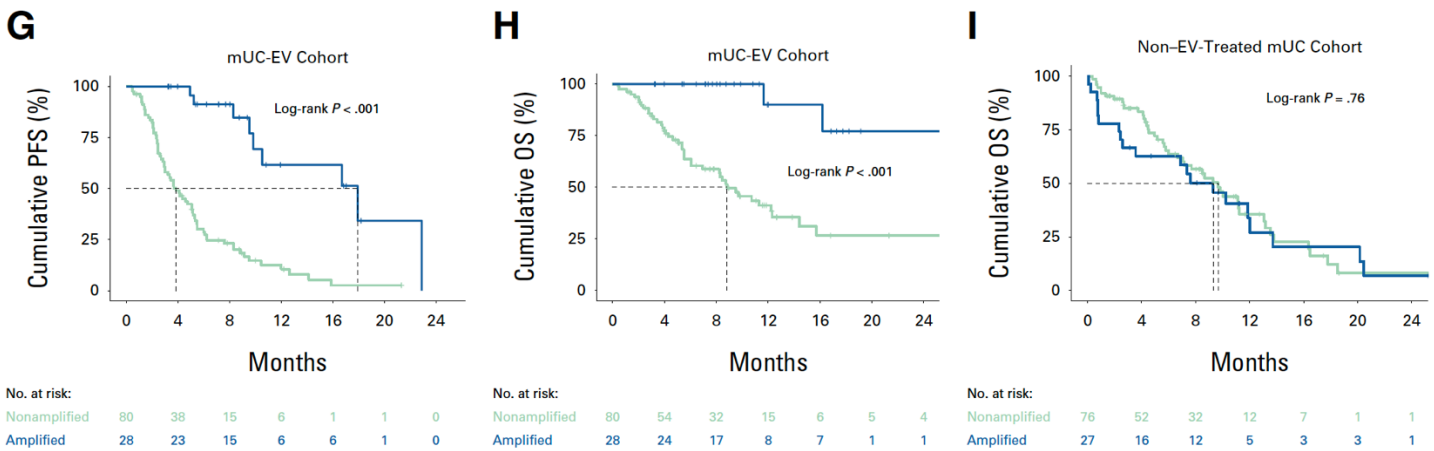


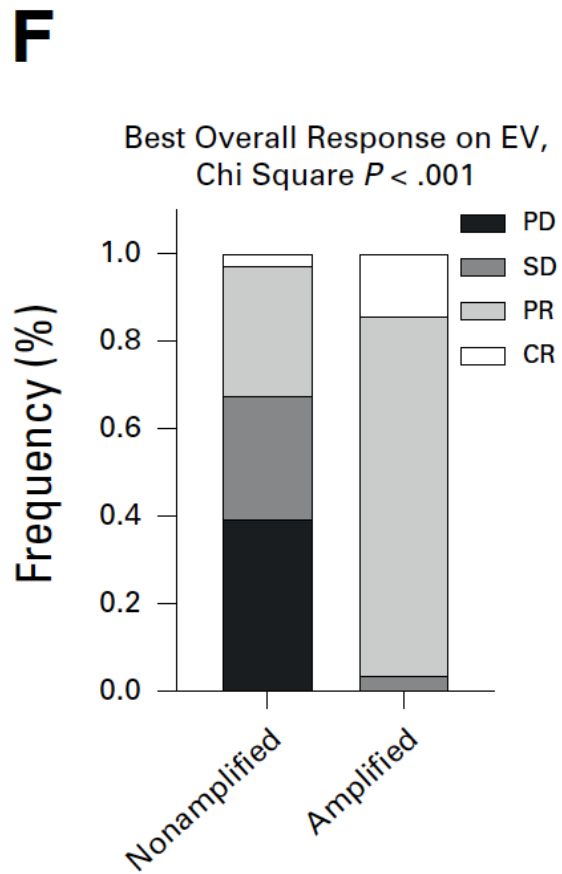
NECTIN4 Amplification Is Frequent in Solid Tumors and Predicts Enfortumab Vedotin Response in Metastatic Urothelial Cancer

Niklas Klümper, MD[1,2,3,4]; Ngoc Khanh Tran[1,2,3]; Stefanie Zschäbitz, MD[5]; Oliver Hahn, MD[6]; Thomas Büttner, MD[1,3];

MATERIALS AND METHODS We established a *NECTIN4*-specific fluorescence in situ hybridization (FISH) assay to assess the predictive value of *NECTIN4* CNVs in a multicenter EV-treated mUC patient cohort (mUC-EV, n = 108). CNVs were correlated with membranous NECTIN4 protein expression, EV treatment responses, and outcomes. We also assessed the prognostic value of *NECTIN4* CNVs measured in metastatic biopsies of non–EV-treated mUC (mUC-non-EV, n = 103). Furthermore, we queried The Cancer Genome Atlas (TCGA) data sets (10,712 patients across 32 cancer types) for *NECTIN4* CNVs.

RESULTS *NECTIN4* amplifications are frequent genomic events in muscle-invasive bladder cancer (TCGA bladder cancer data set: approximately 17%) and mUC (approximately 26% in our mUC cohorts). In mUC-EV, *NECTIN4* amplification represents a stable genomic alteration during metastatic progression and associates with enhanced membranous NECTIN4 protein expression. Ninety-six percent (27 of 28) of patients with *NECTIN4* amplifications demonstrated objective responses to EV compared with 32% (24 of 74) in the nonamplified subgroup ($P < .001$). In multivariable Cox analysis adjusted for age, sex, and





J Clin Oncol 00:1-10

Abstract 456262: Association of EphrinB2 (B2) expression with overall survival (OS) and resistance to PD1/L1 inhibitors in metastatic urothelial carcinoma (mUC)

Sarmad Sadeghi[1], Nataliya Mar[2], Denice Tsao-Wei[3], Karam Ashouri[3], Imran Siddiqi[1], Jon P Cogan[4], Alexandra Jackovich[5], Dory Freeman[6], Jillian O'Toole[6], Thomas W. Flaig[7], Parkash S. Gill[1], Arash Rezazadeh[2], Guru P. Sonpavde[8], Joaquim Bellmunt[6]

1 Norris Comprehensive Cancer Center, Los Angeles, CA; 2 University of California, Irvine Medical Center, Orange, CA; 3 University of Southern California, Los Angeles, CA; 4 Vasgene Therapeutics, Inc, Los Angeles, CA; 5 Rutgers New Jersey Medical School, Newark, NJ; 6 Dana-Farber Cancer Institute, Boston, MA; 7 University of Colorado Anschutz Medical Campus, Aurora, CO; 8 AdventHealth Cancer Institute, Orlando, FL

Background

EphrinB2 is a transmembrane protein expressed in developing arterial capillary endothelium; it is minimally expressed in adults but re-expressed in tumors and tumor blood vessel. Its expression is a poor prognostic marker (TCGA). High EphrinB2 expression in tumor blood vessels functions as a gate-keeper by preventing immune cells in the circulation from migrating into the tumor.

The trial of pembrolizumab+sEphB4-HSA (an EphrinB2 inhibitor) in mUC showed a higher response rate in EphrinB2 high patients compared to pembrolizumab historical data- 52% vs 21%- JCO PMID 35984996. This raised the question whether immunotherapy alone could overcome the poor prognostic effect of EphrinB2?

Objectives

This retrospective study was designed to examine the response to immunotherapy monotherapy in patients with mUC and correlate it with EphrinB2 expression.

Methods

Patients with mUC who received a PD1/PDL1 antibody after prior systemic therapy who had tissue available for analysis were eligible. Demographics, disease characteristics, and radiographic response data were also required and collected.

In situ hybridization was used to assess the expression EphrinB2 in tumor specimens from 3 participating site: University of Southern California (USC), Dana Farber Cancer Institute (DFCI), and University of California, Irvine (UCI).

- EphrinB2 is a biomarker of resistance to PD1/L1 inhibitors in mUC and predicts low response rate and poor overall survival.
- EphrinB2 inhibition may overcome the resistance to PD1/PDL1 inhibitors in patients whose tumors express high levels of EphrinB2
- The role of EphrinB2 in resistance to immunotherapy merits further investigation.

For questions or comments please contact Sarmad Sadeghi sarmadsa@med.usc.edu

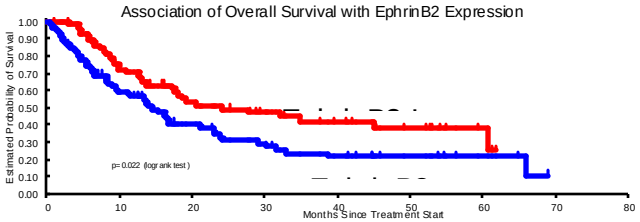
Results

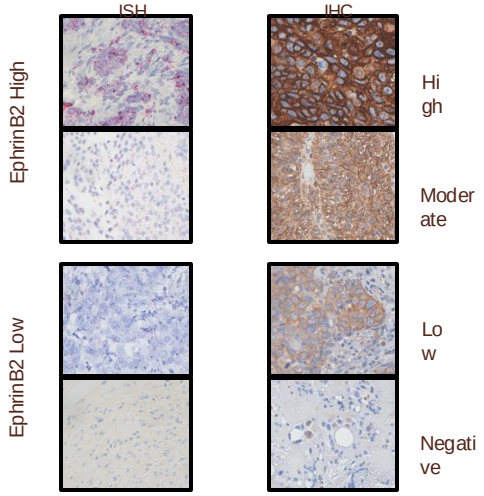
	All N=143	USC n=49	DFCI, n=55	UCI, n=39	P
Median Age (range)	73 (48-91)	72 (48-87)	73 (48-91)	74 (48-90)	0.82
Male (%)	101 (71%)	37 (76%)	36 (65%)	28 (72%)	0.53
ECOG 0, 1, >1 (%)	42, 35, 23	51, 22, 27	40, 40, 21	33, 44, 23	0.23
Visceral Metastases (%)	79 (55%)	26 (53%)	36 (65%)	17 (44%)	0.11
Responders (ORR)*	28 (21%)	10 (20%)	11 (20%)	7 (22%)	1
EphrinB2 Low Cases	55 (40%)	21 (43%)	19 (35%)	15 (47%)	**0.005**
Responders (ORR)	18 (33%)	6 (29%)	7 (37%)	5 (33%)	
EphrinB2 High Cases	81 (60%)	28 (57%)	36 (65%)	17 (53%)	
Responders (ORR)	10 (12%)	4 (14%)	4 (11%)	2 (12%)	
Median OS in months (95% CI)	17.2 (13.5, 23.8)	16 (8.1, 30.1)	14.5 (9.0, 18.0)	32 (13.3, 60.8)	0.32
EphrinB2 Low Cases	60 (42%)	21 (43%)	19 (35%)	20 (51%)	**0.022**
Median OS in months (95% CI)	24 (13.7, 60.8)	24 (9.2, NA)	17.5 (7.3, 27.6)	45.1 (10.8, 60.8)	
EphrinB2 High Cases	83 (58%)	28 (57%)	36 (65%)	19 (49%)	
Median OS in months (95% CI)	14.5 (9.4, 21.0)	8.8 (3.8, 30.1)	13.8 (8.2, 16.7)	21 (9.4, 32.8)	

* 7 patients were inevaluable for response

Results (Continued)

PD1/L1 inhibitors included pembrolizumab 78%, atezolizumab 17%, nivolumab, avelumab, and durvalumab in 3, 1, and 1%, respectively.





Conclusion and Future Directions

The role of EphrinB2 in resistance to immunotherapy merits further investigation.

Whether EphrinB2 inhibition also improves outcomes of non-immunotherapy regimens remains unclear.

MADRID 2023 ESMO congress

Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: results from the phase 3 CheckMate 901 trial

Michiel S. van der Heijden,[1] Guru Sonpavde,[2a] Thomas Powles,[3] Andrea Necchi,[4b] Mauricio Burotto,[5] Michael Schenker,[6] Juan Pablo Sade,[7] Aristotelis Bamias,[8] Philippe Beuzeboc,[9] Jens Bedke,[10c] Jan Oldenburg,[11] Yüksel Ürün,[12] Dingwei Ye,[13] Zhisong He,[14] Begoña P. Valderrama,[15] Yoshihiko Tomita,[16] Jeiry Filian,[17] Daniela Purcea,[18] Federico Nasroulah,[17] Matthew D. Galsky[19]

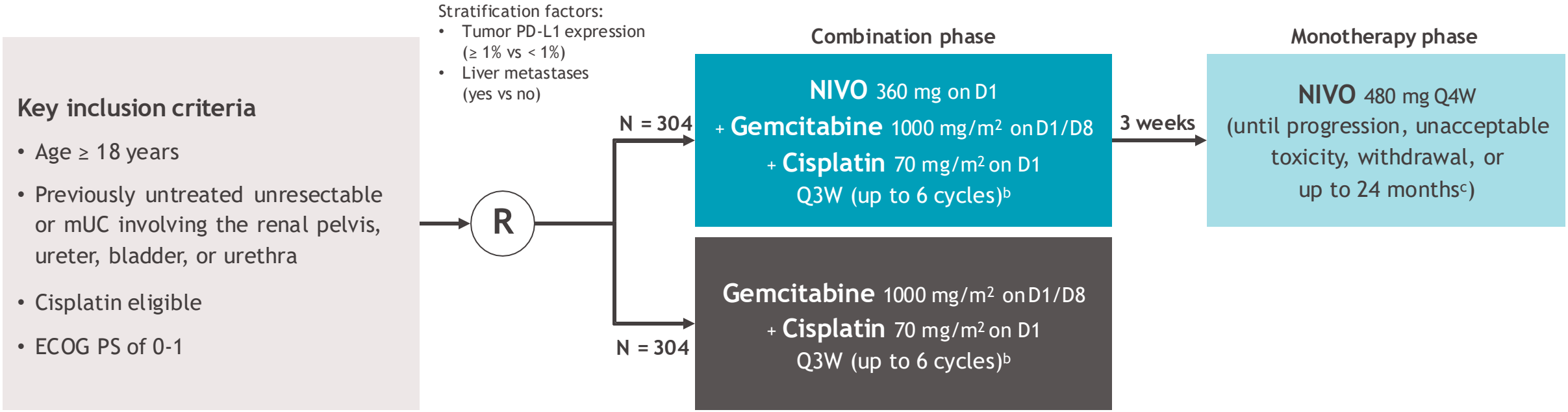
[1]Netherlands Cancer Institute, Amsterdam, the Netherlands; [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [3]Barts Cancer Institute, Queen Mary University of London, London, UK; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Bradford Hill Clinical Research Center, Santiago, Chile; [6]University of Medicine and Pharmacy, Craiova, Romania; [7]Alexander Fleming Institute, Buenos Aires, Argentina; [8]National and Kapodistrian University of Athens, ATTIKON University Hospital, Athens, Greece; [9]Hopital Foch, Suresnes, France; [10]Eberhard Karls University Tübingen, Tübingen, Germany; [11]Akershus University Hospital (Ahus), Lørenskog, Norway; [12]Ankara University, Ankara, Turkey; [13]Fudan University Shanghai Cancer Center, Shanghai, China; [14]Peking University First Hospital, Beijing, China; [15]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [16]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [17]Bristol Myers Squibb, Princeton, NJ, USA; [18]Bristol Myers Squibb, Boudry, Switzerland; [19]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[a]Current affiliation is AdventHealth Cancer Institute and University of Central Florida, Orlando, FL, USA. [b]Current affiliation is IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy. [c]Current affiliation is Klinikum Stuttgart, Katharinenhospital, Stuttgart, Germany.

Presentation number LBA7

Study design

- NIVO + gemcitabine-cisplatin vs gemcitabine-cisplatin in cisplatin-eligible patients[a]

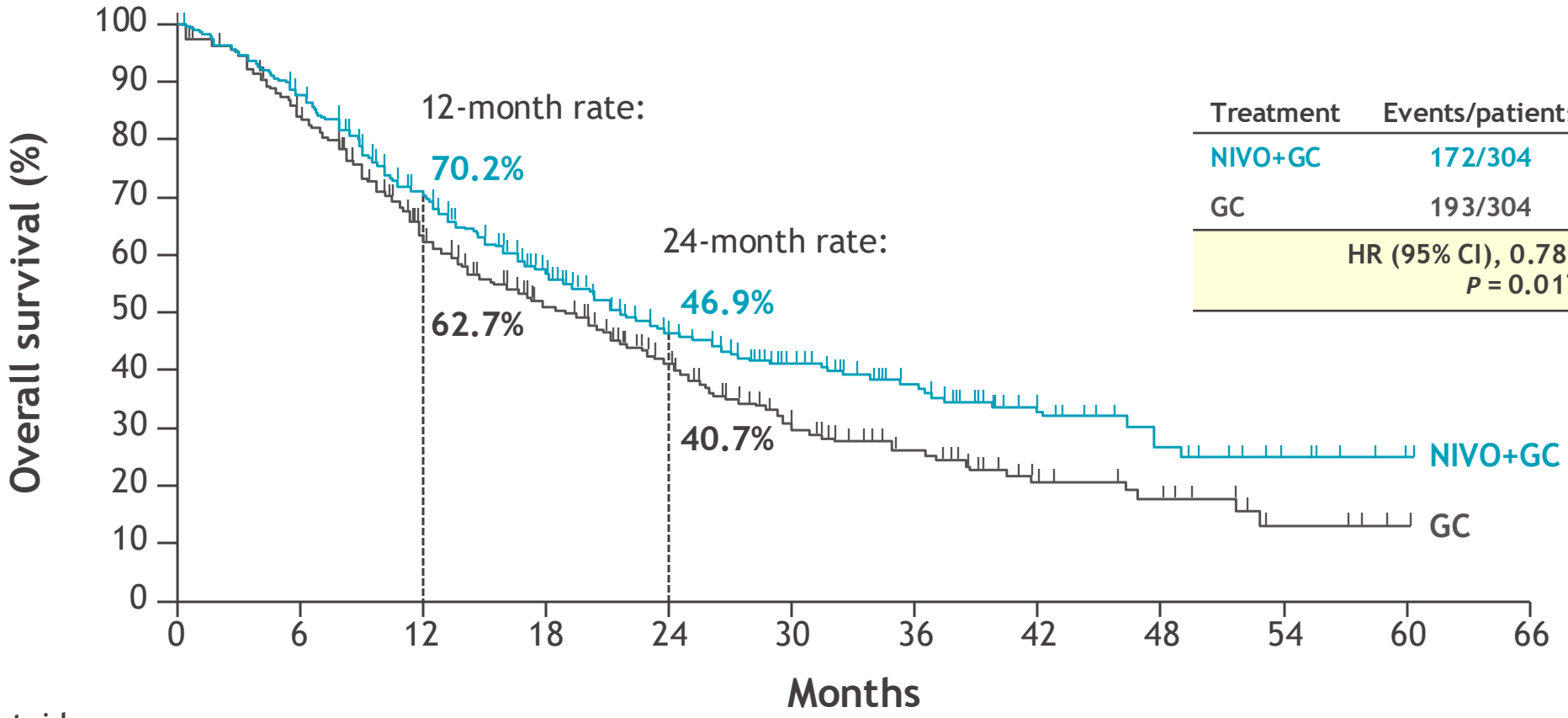


Median (range) study follow-up, 33.6 (7.4–62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO + gemcitabine-cisplatin combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA, USA).
BICR, blinded independent central review; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q×W, every × weeks; R, randomization.

OS (primary endpoint)



Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7-22.4)

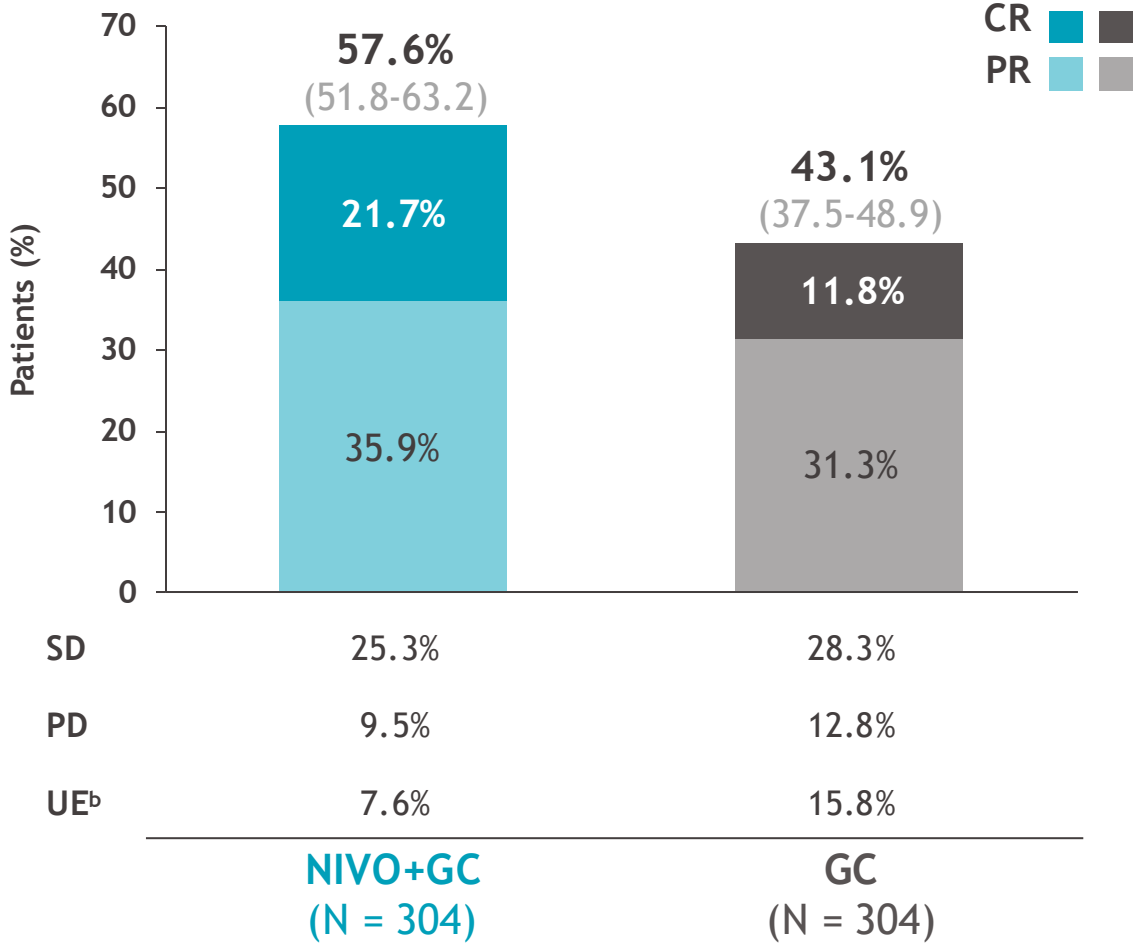
HR (95% CI), 0.78 (0.63-0.96)
P = 0.0171

No. at risk												
NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with no follow-up, OS was censored at randomization.

Objective response outcomes (exploratory endpoints)

ORR (95% CI) and BOR per BICR[a]



Time to and duration of responses

Any objective response[c]	NIVO+GC (n = 175)	GC (n = 131)
Median TTR (Q1-Q3), months	2.1 (2.0–2.3)	2.1 (2.0–2.2)
Median DoR (95% CI), months	9.5 (7.6–15.1)	7.3 (5.7–8.9)

Complete response[d]	NIVO+GC (n = 66)	GC (n = 36)
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

[a]In all randomized patients. [b]The most common reasons for UE response included death before first tumor assessment, withdrawal of consent, treatment stopped due to toxicity, patient never treated, and receipt of subsequent anticancer therapy before first tumor assessment. [c]Based on patients with an objective response per BICR (PR or CR as BOR). [d]Based on patients with a CR per BICR.
BOR, best overall response; CR, complete response; DoCR, duration of complete response; DoR, duration of objective response; NE, not estimable; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease; TTCR, time to complete response; TTR, time to objective response; UE, unevaluable.

Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Selected FGFR Aberrations

Cohort 1

Key eligibility criteria

- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- Prior tx with anti–PD-(L)1
- 1-2 lines of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)[a]
- ECOG PS 0-2

1:1
N=266[b]
R

Erdafitinib
(n=136)
Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

Chemotherapy of Choice
(n=130)
docetaxel or vinflunine once every 3 weeks

Stratification factors: region (North America vs European Union vs rest of world), ECOG PS (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases)

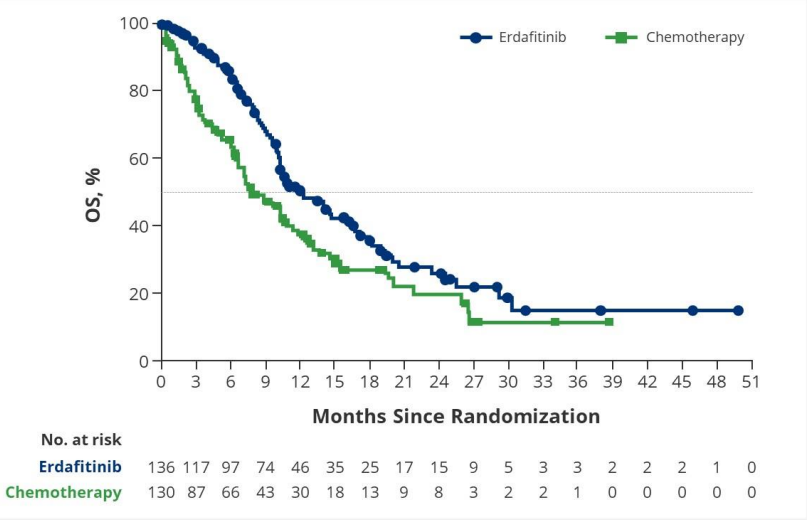
Primary end point:
- OS

Key secondary end points:
- PFS
- ORR
- Safety

NCT03390504

[a]Molecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥1 of the following translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C.
[b]Number of patients randomized at the time of the interim analysis (data cutoff January 15, 2023).
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; *FGFR3/2alt*, *FGFR3/2* alterations; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.

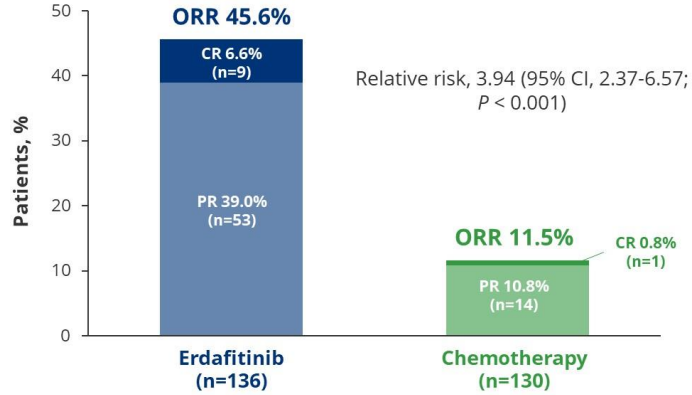
Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy



- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; $P = 0.005$)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; OS, overall survival.
[a]The significance level for stopping for efficacy was p=0.019, corresponding to a HR of 0.69.

Objective Response Rate Was Significantly Higher for Erdafitinib Versus Chemotherapy[a]



The Safety Profiles Were Consistent With the Known Profiles of Erdafitinib and Chemotherapy (2/2)

Patients with AEs of interest, n (%)	Erdafitinib (n=135)		Chemotherapy (n=112)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Nail disorders[a]	90 (66.7)	15 (11.1)	6 (5.4)	0
Skin disorders[b]	74 (54.8)	16 (11.9)	14 (12.5)	0
Eye disorders (excluding central serous retinopathy)[c]	57 (42.2)	3 (2.2)	6 (5.4)	0
Central serous retinopathy[d]	23 (17.0)	3 (2.2)	0	0

[a]Nail disorders: nail bed bleeding, nail discoloration, nail disorder, nail dystrophy, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, paronychia, onychomadesis.
[b]Skin disorders: blister, dry skin, erythema, hyperkeratosis, palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, skin atrophy, skin exfoliation, skin fissures, skin lesion, skin ulcer, toxic skin eruption, xeroderma.
[c]Eye disorders (excluding central serous retinopathy): blepharitis, cataract, cataract subcapsular, conjunctival hemorrhage, conjunctival hyperemia, conjunctival irritation, corneal erosion, corneal infiltrates, dry eye, eye inflammation, eye irritation, eye pain, foreign body sensation in eyes, keratitis, lacrimation increased, night blindness, ocular hyperemia, photophobia, vision blurred, visual acuity reduced, visual impairment, xanthopsia, xerophthalmia, chorioretinitis, conjunctivitis, ulcerative keratitis.
[d]Central serous retinopathy: retinal detachment, vitreous detachment, retinal edema, retinopathy, chorioretinopathy, detachment of retinal pigment epithelium, detachment of macular retinal pigment epithelium, macular detachment, serous retinal detachment, subretinal fluid, retinal thickening, chorioretinitis, serous retinopathy, maculopathy, choroidal effusion.
AE, adverse event.

THOR Cohort 1: Conclusions

- Erdafitinib significantly extended OS in patients with advanced/mUC with *FGFRalt* after prior treatment with anti–PD-(L)1, with a median OS of 1 year
  - Erdafitinib provided a 36% reduction in risk of death compared to chemotherapy
  - The OS benefit of erdafitinib was consistent across clinically relevant subgroups
  - Erdafitinib provided significantly longer PFS and greater ORR versus chemotherapy
- Erdafitinib safety profile was consistent with the BLC2001 study[1,2]
- The phase 3 THOR study supports the clinical efficacy of erdafitinib as the standard of care option for patients with mUC with *FGFRalt* after anti–PD-(L)1 treatment
- The OS benefit of erdafitinib in patients with mUC with *FGFRalt* supports molecular testing for *FGFRalt* in all patients with mUC

FGFRalt, *FGFR* alterations; mUC, metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
1. Loriot Y, et al. *N Engl J Med.* 2019;381:338-348; 2. Siefker-Radtke AO, et al. *Lancet Oncol.* 2022;23:248-258.

Her2 ADC

Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

Funda Meric-Bernstam, MD[1]; Vicky Makker, MD[2,3]; Ana Oaknin, MD[4]; Do-Youn Oh, MD[5]; Susana Banerjee, PhD[6]; Antonio González-Martín, MD[7]; Kyung Hae Jung, MD[8]; Iwona Ługowska, MD[9]; Luis Manso, MD[10]; Aránzazu Manzano, MD[11]; Bohuslav Melichar, MD[12]; Salvatore Siena, MD[13]; Daniil Stroyakovskiy, MD[14]; Anitra Fielding, MBChB[15]; Yan Ma, MSc[16]; Soham Puvvada, MD[15]; Norah Shire, PhD[15]; and Jung-Yun Lee, MD[17]

DOI https://doi.org/10.1200/JCO.23.02005

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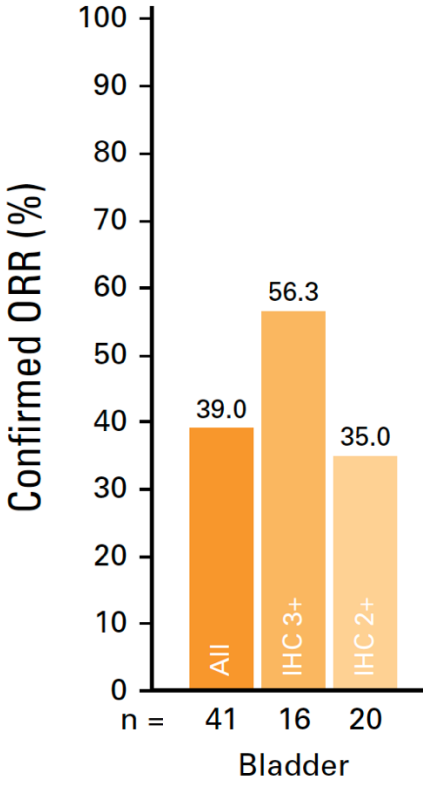

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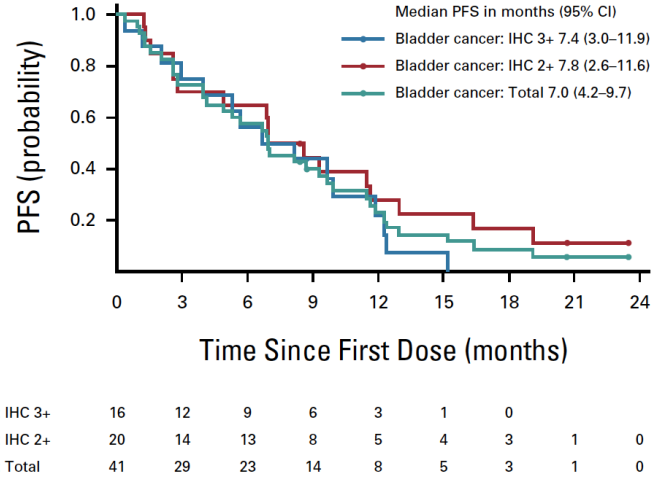

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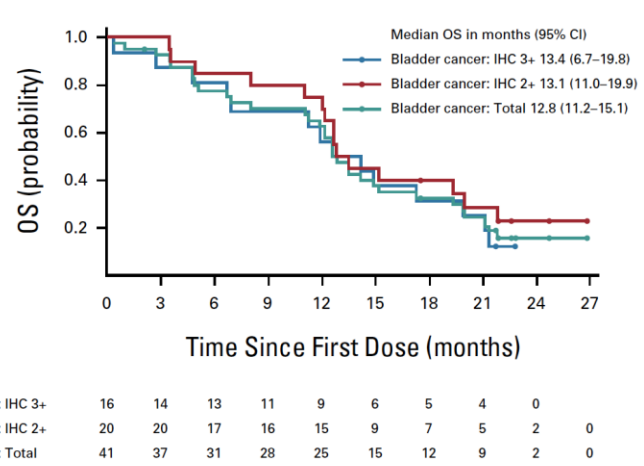

TABLE 2. Incidence of Drug-Related Adverse Events

Adverse Event	Bladder Cancer (n = 41)
Drug-related adverse events, No. (%)	38 (92.7)
Grade ≥3	17 (41.5)
Serious adverse events	4 (9.8)
Leading to discontinuation	4 (9.8)
Leading to dose modification[a]	15 (36.6)
Associated with death	1 (2.4)
Most common drug-related adverse events (>10% of total patients), No.	
Nausea	21 (51.2)
Anemia	12 (29.3)
Diarrhea	13 (31.7)
Fatigue	11 (26.8)
Vomiting	6 (14.6)
Neutropenia	11 (26.8)
Decreased appetite	8 (19.5)
Asthenia	3 (7.3)
Alopecia	5 (12.2)
Thrombocytopenia	6 (14.6)

J Clin Oncol 42:47-58

Her2 ADC

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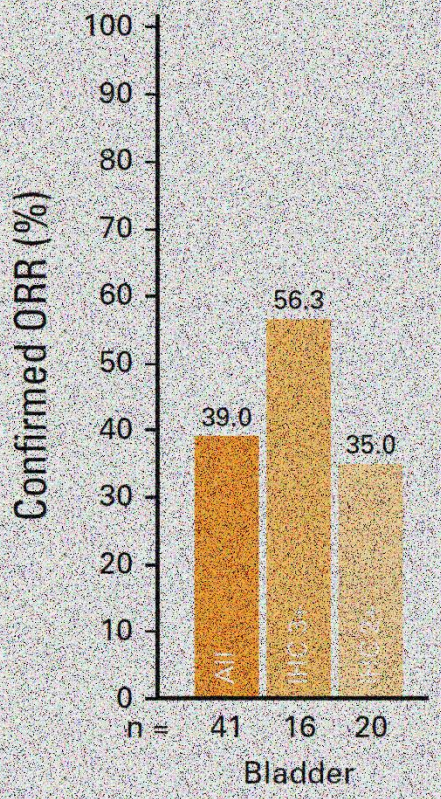

No. at risk:
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Table 2. HER2 Status by UC Stage[a]: Assay Results

Stage	N	N (row %) HER2+	HER2-low	HER2-zero
Stage I	7	1 (14)	0	6 (86)
Stage II	133	17 (13)	46 (35)	70 (53)
Stage III	192	37 (19)	50 (26)	102 (55)
Stage IV	30	2 (7)	7 (23)	21 (70)
All	362	57 (16)	103 (28)	202 (56)

a Stage information as supplied by the tissue vendor. Staging may have been based on clinical information or on tissue samples different from those included in the current study

Table 3. Summary of HER2 Status

HER2 Status	N	Percentage of samples (95% CI)
HER2+ and HER2-low	160	44.2% (39.2%–49.3%)
HER2+/overexpression	57	15.7% (12.4%–19.9%)
HER2-low	103	28.5% (24.1%–33.3%)
HER2-zero	202	55.8% (50.7%–60.8%)

lated Adverse Events

	Bladder Cancer (n = 41)
(%)	38 (92.7)
	17 (41.5)
	4 (9.8)
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	15 (36.6)
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	3 (7.3)
	5 (12.2)
	6 (14.6)

Koshkin et al, ASCO GU 2023, J Clin Oncol 41, 2023 (suppl 6; abstr 556)

Systemic Therapy in Urothelial Carcinoma

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August 24, 2024

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