THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Perioperative Therapy in Surgically Resectable Urothelial Carcinoma

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DISCLOSURE INFORMATION

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Advisory Boards: Abbvie, Astellas, AstraZeneca, Basilea, Bicycle Therapeutics, Bristol Myers Squibb, Genentech, G1 Therapeutics, Gilead, Ideaya Biosciences, Immunomedics, Janssen, LOXO-Oncology, Merck Sharp and Dohme, Mirati, Nektar Therapeutics, Seattle Genetics, and Taiho

Clinical trials: Basilea Pharmaceutical, Bristol Myers Squibb, Janssen, Loxo, Merck, Mirati, and Nektar Therapeutics

Speaker (non-promotional): Janssen

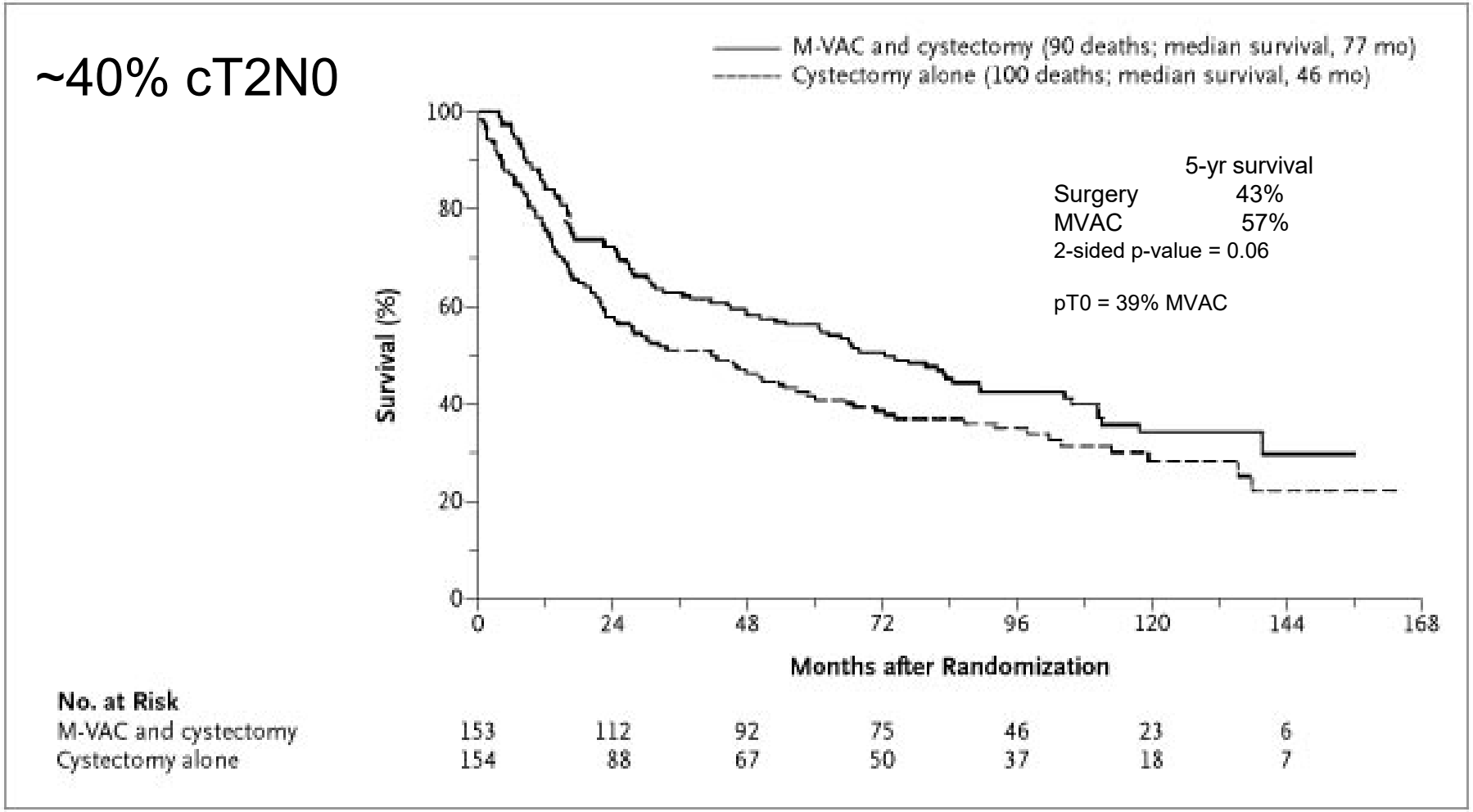

Neoadjuvant Chemotherapy:
Cisplatin remains the standard!

Muscle Invasive: cT2-4aN0 Disease

- Neoadjuvant chemotherapy now standard
  - Cisplatin (not carboplatin!)
  - MVAC historical standard
  - DDMVAC acceptable – improved toxicity and shorter time to surgery
  - Some consider GC
  - Ifosfamide with doxorubicin and gemcitabine
- Adverse prognostic factors
  - Lymphovascular invasion (LVI)
  - Positive EUA
  - Tumor at ureteral orifice/hydronephrosis
  - HG upper tract
  - Extension to local but resectable organs

SWOG Intergroup Trial

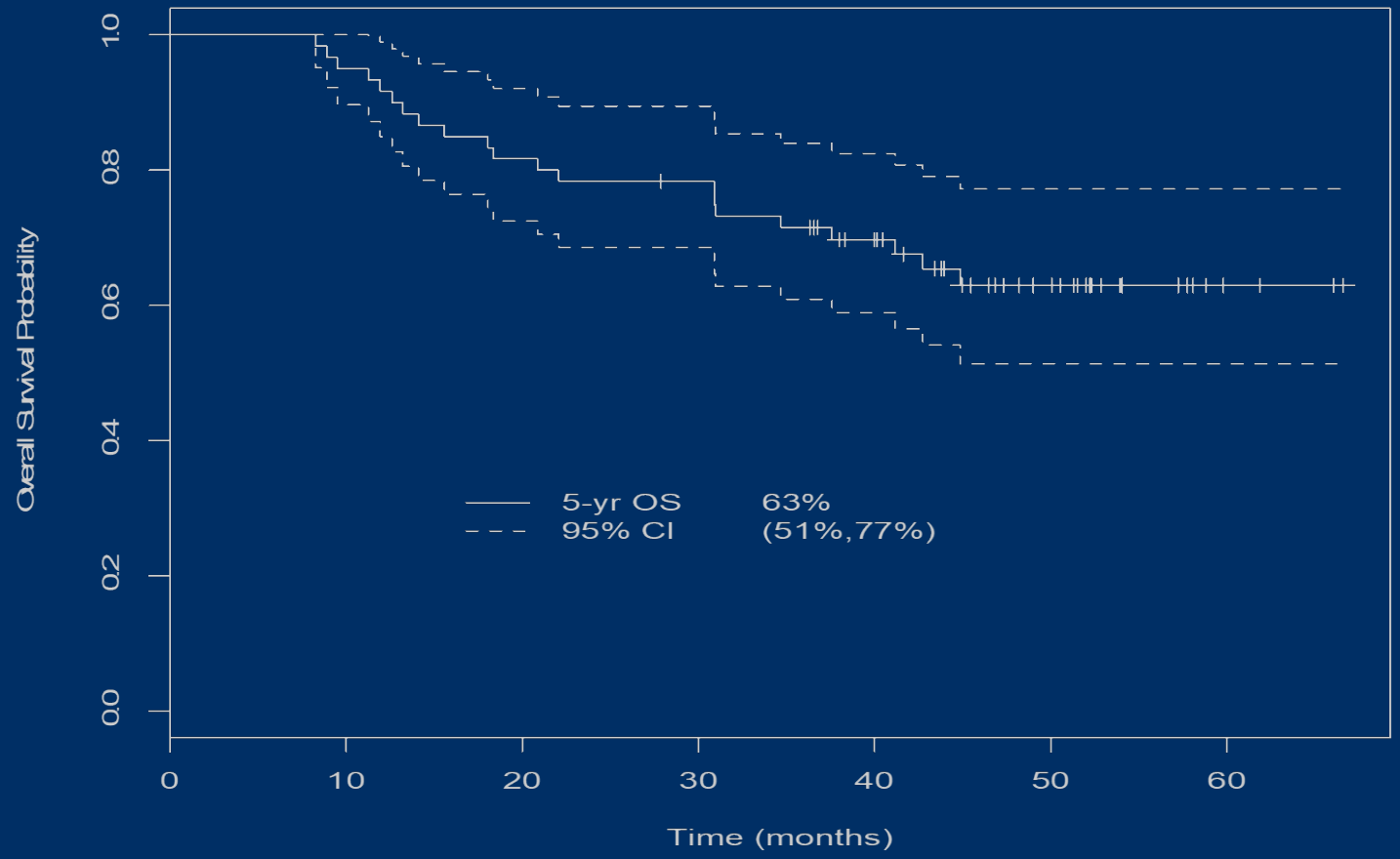
~40% cT2N0



Grossman et al. NEJM 349;9: 859-866, 2003

Dose-Dense Therapy: Neoadjuvant DDMVAC

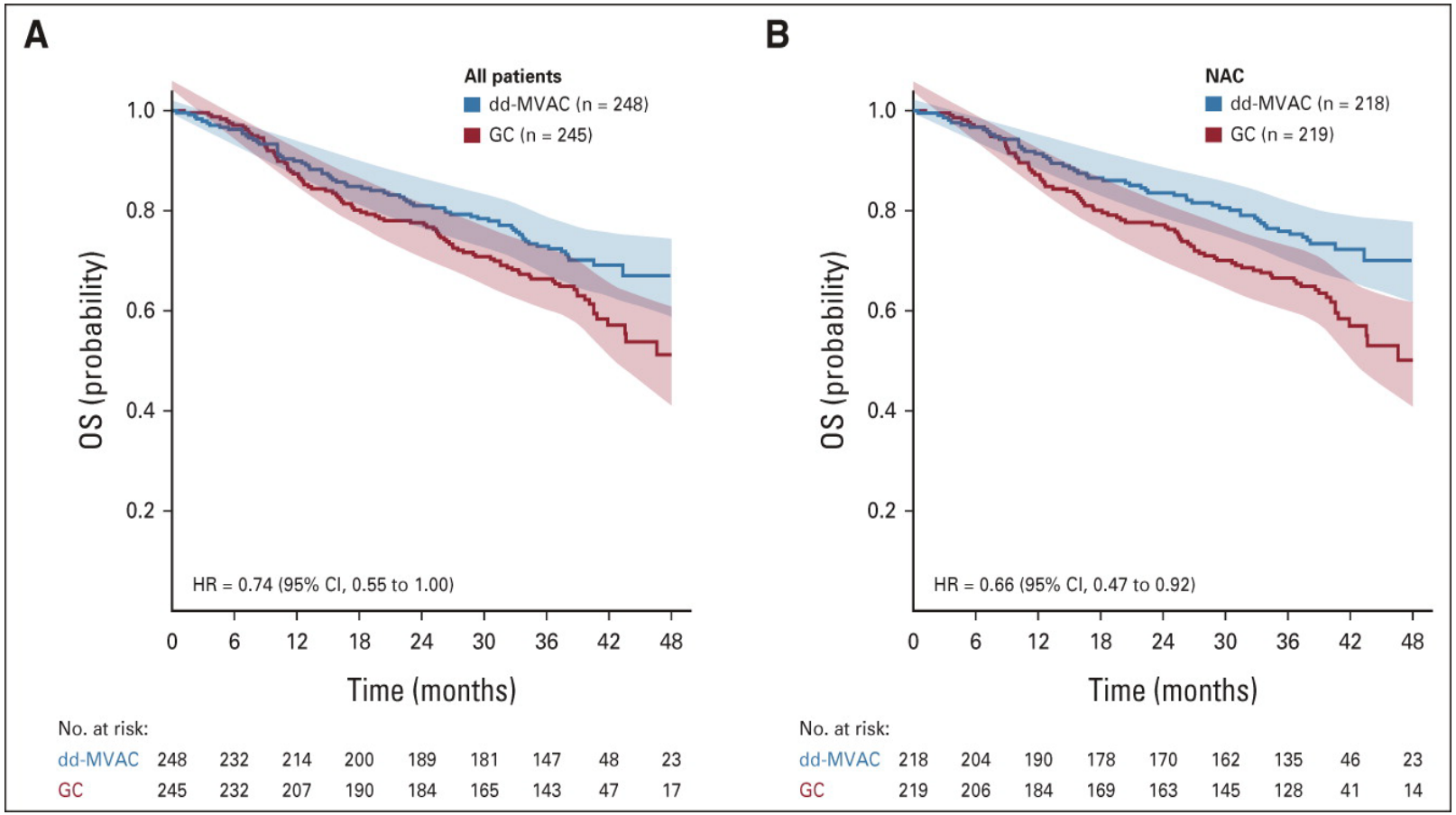
- MVAC q 2 weeks X 4 with Bevacizumab
- High risk patients (predicted ~ 80% likelihood of >= pT3b disease)
- pT0 = 38%, ≤ pT1 = 53%
- 5-year OS 63%
  - Med f/u 49 mo
- Less toxic than traditional MVAC
  - Neutropenic fever 27%
  - Fatigue 12 %
- Bevacizumab: no appreciable benefit
- Similar DDMVAC trials Plimack et al. and Choueiri et el. with similar pT0 rates, short FU



Siefker-Radtke, et al. GUASCO 2015/EurUrol 2016


DDMVAC vs GC

VESPER Trial: Perioperative DDMVAC vs GC

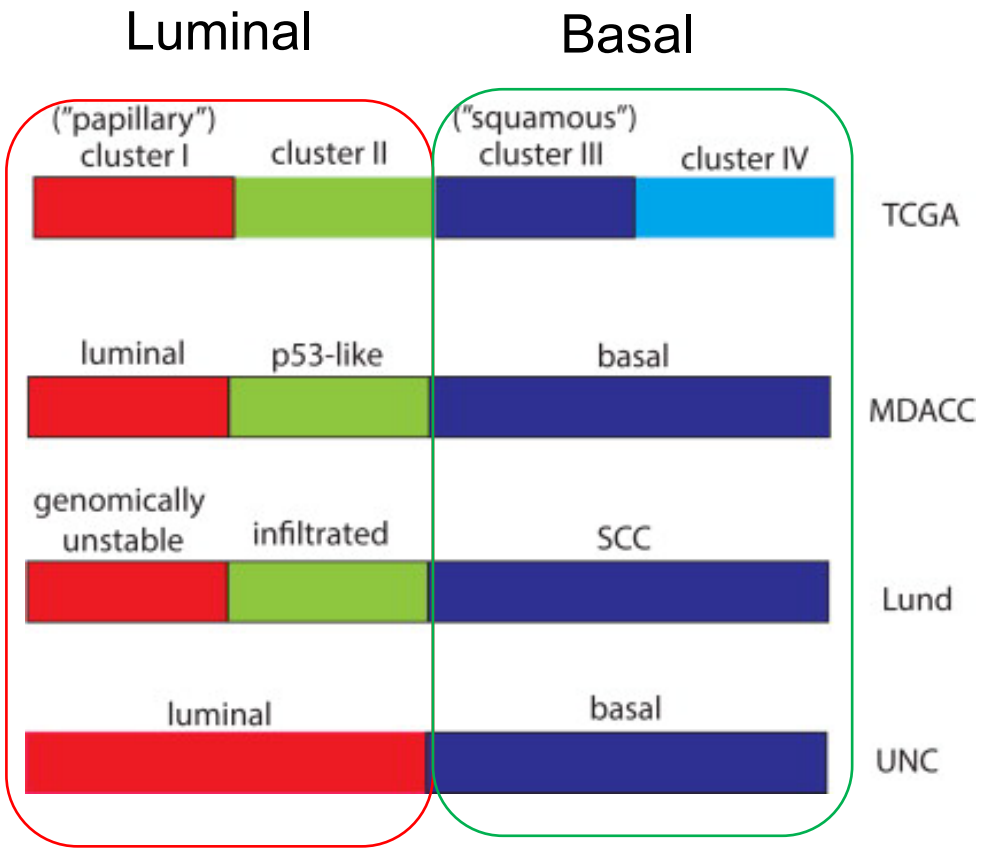


- N=500
  - cT2-4aN0 (neoadjuvant 89%))
    - 90-95% cT2N0
  - >=pT3 any N (adjuvant 11%)
    - 73% N+
- Chemotherapy
  - DDMVAC x 6
  - GC x 4
- Primary endpoint improved PFS not met (HR 0.77 (95% CI 0.57-1.02), P=0.066
  - DDMVAC 3-yr: 64%
  - GC 3-yr: 56%
- OS in neoadjuvant group favored DDMVAC (HR – 0.66 (95% CI 0.47-0.92)

Pfister et al. JCO, 2022


Patient Selection

Gene Expression



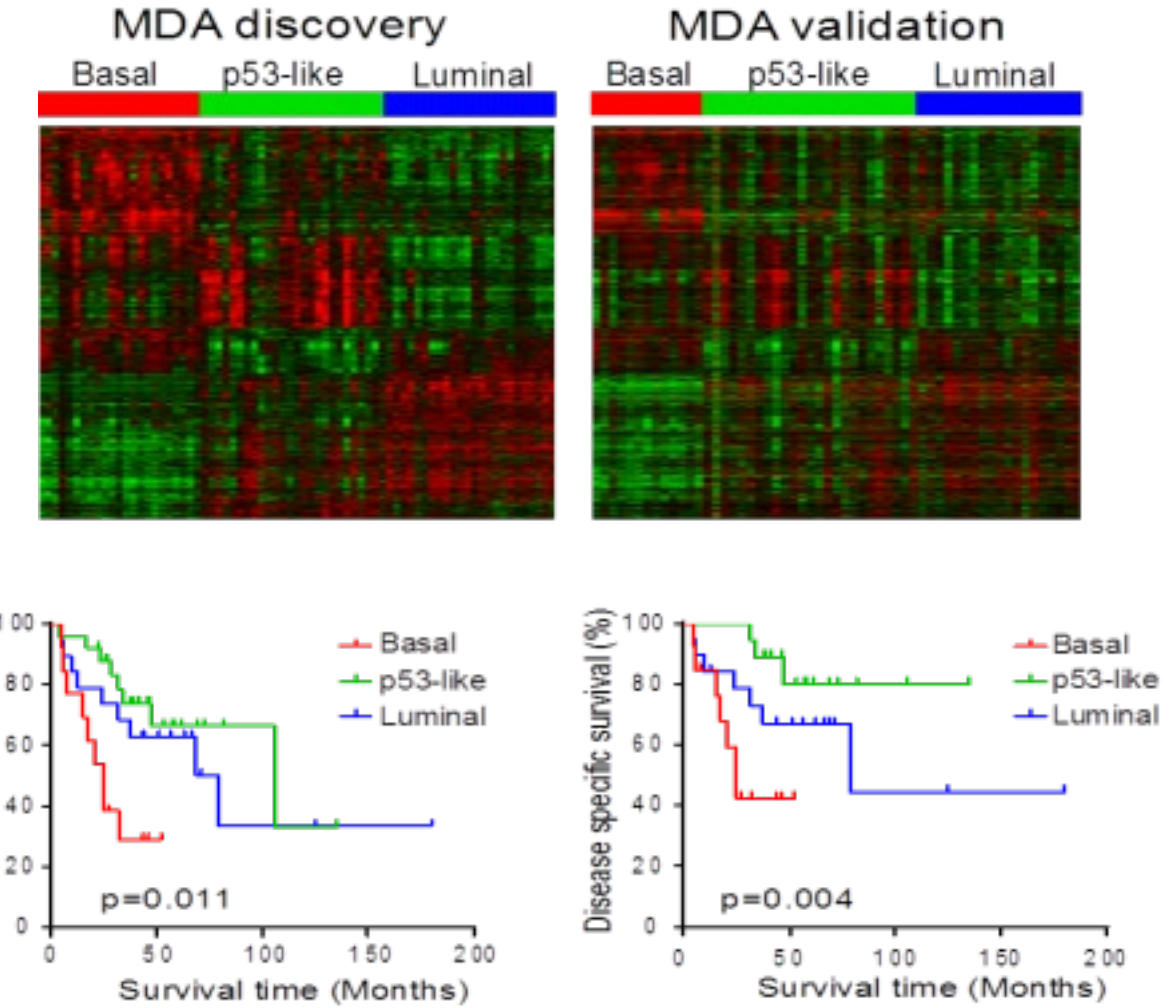
Relationships between the intrinsic subtypes identified by the groups at Lund University, MD Anderson Cancer Center, University of North Carolina, and TCGA centres

David J. McConkey, Woonyoung Choi, Andrea Ochoa, Arlene Siefker-Radtke, Bogdan Czerniak, Colin P.N. Dinney
Therapeutic Opportunities in the Intrinsic Subtypes of Muscle-Invasive Bladder Cancer
Hematology/Oncology Clinics of North America, Volume 29, Issue 2, 2015, 377–394
http://dx.doi.org/10.1016/j.hoc.2014.11.003

Background: Gene Expression

Three intrinsic subtypes:

- Basal
  - Highest proliferation
  - “Stemness”
  - Worst clinical outcomes
- Luminal
  - Intermediate proliferation
  - *FGFR3* mutations
- p53-like
  - Lowest proliferation
  - Stromal markers

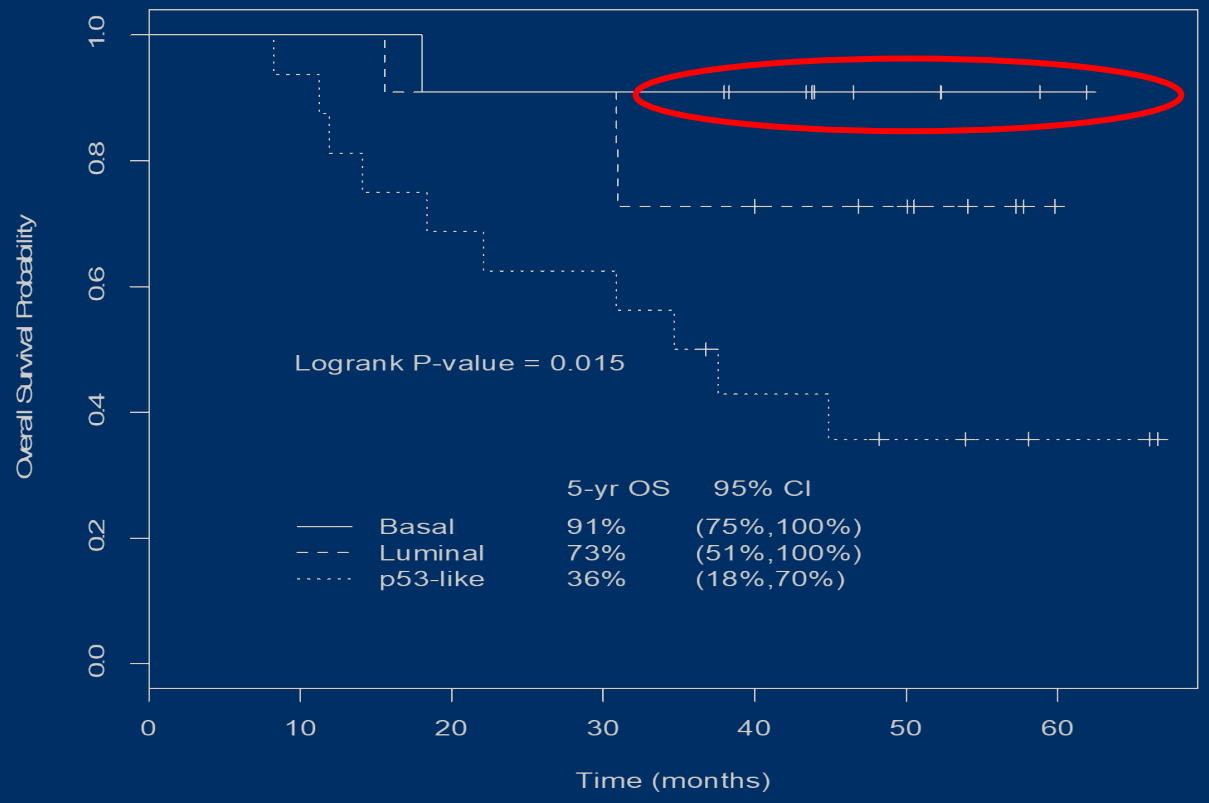


MDA, MD Anderson.

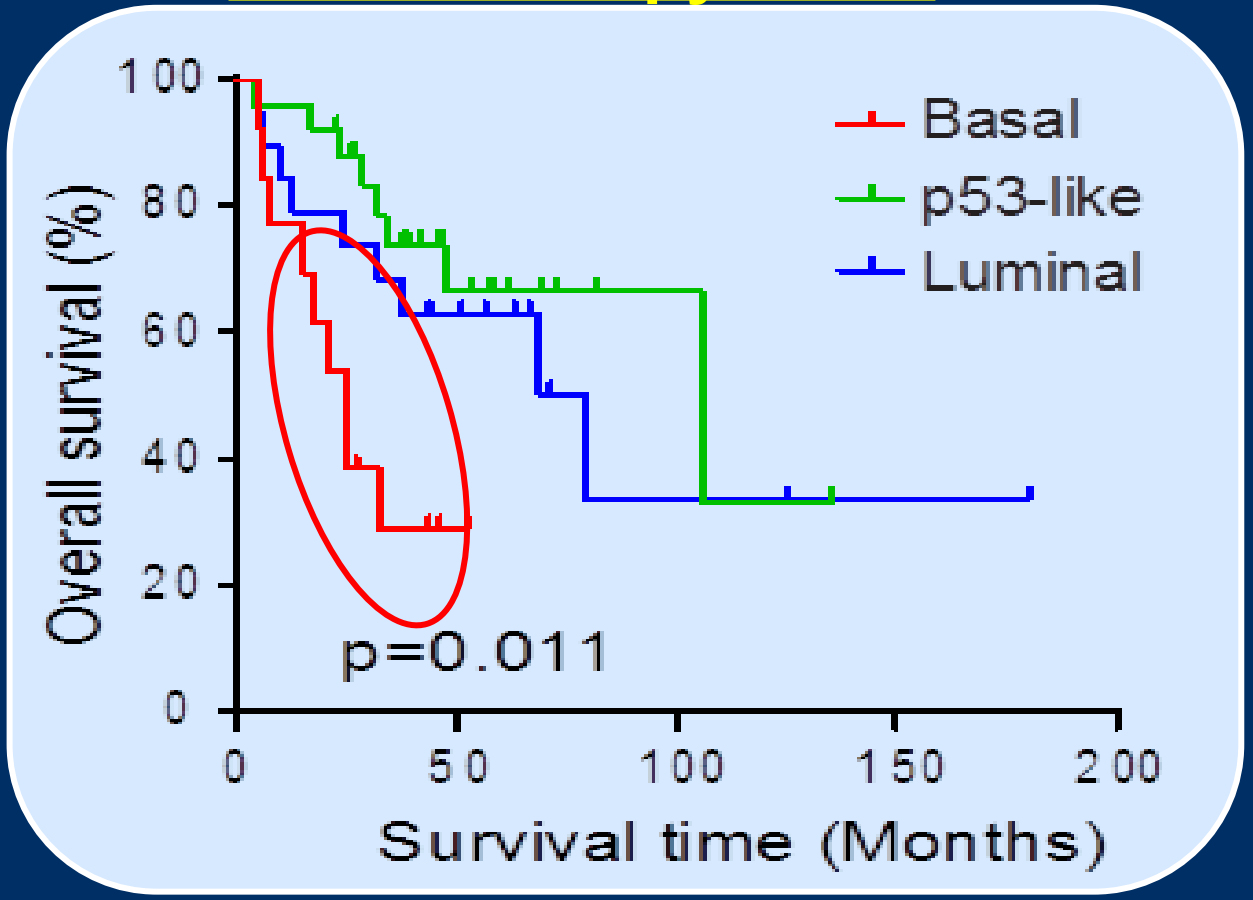
Choi W, at al. Cancer Cell. 2014;25:152-65.

Basal tumors benefit from neoadjuvant chemotherapy: MDACC clinical trials

Neoadjuvant chemotherapy



Chemotherapy Naive



Siefker-Radtke, Choi, McConkey et al. GUASCO 2015, European Urology 2016

Paradigm Shift in Urothelial Cancer

- Urothelial cancer is no longer just 1 disease:

"Basal"

- Chemo-sensitive
- Immune signature

Therapies:

- GC/DDMVAC
- CTLA4?
- PD-1/PDL-1?
- Proteasome inhibitors + chemo?

"p53-like"

- Chemo-resistance
- Stromal enrichment
- Bone mets
- Immune signature

Therapies:

- PD-1/PD-L1?
- Met inhibitors?

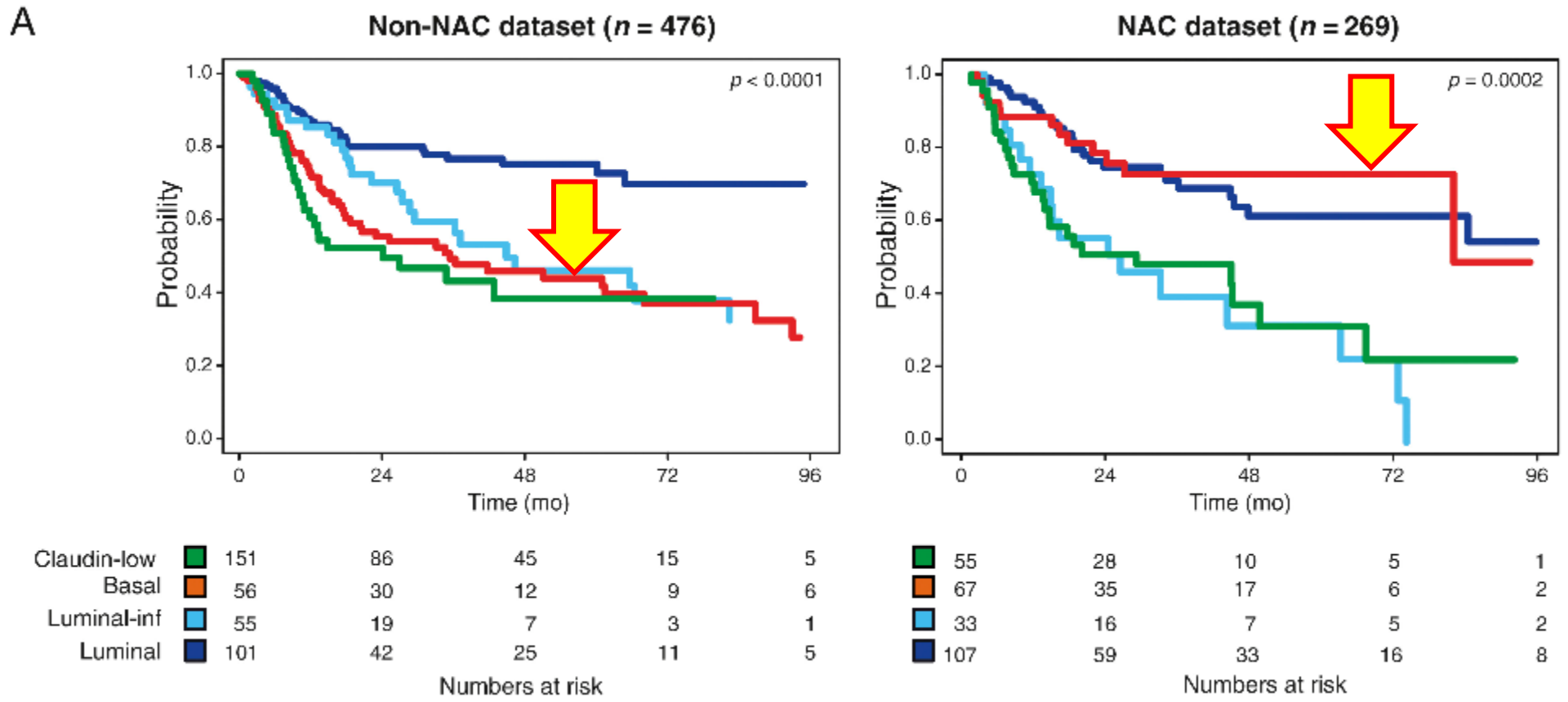
"Luminal"

- Still some chemo-sensitivity
- "FGFR" signature

Therapies:

- GC/DDMVAC
- FGFR inhibitors?
- Proteasome inhibitors + chemo?

Additional retrospective analysis: basal tumours benefit from chemotherapy



Luminal inf, luminal infiltrated, mo, months; NAC, neoadjuvant cisplatin-based chemotherapy.

Seiler R, et al. Eur Urol. 2017;72:544-554.

Paradigm shift in urothelial cancer

- Urothelial cancer is no longer just one disease

"Basal"

- Chemosensitive
- Immune signature
- Angiogenesis

Classification
- CK5/6+

Therapies
- GCb/DD-MVAC
- Immunotherapy
- Angiogenesis

"Basal-Claudin Low"

- Immune signature
- MDSC?
- Does autocrine FGFR signalling play a role?

Classification
- CK5/6+

Therapies
- IDO-IO?
- FGFR inhibitor + IO

"Luminal-P53-like"

- Stromal enrichment
- Chemoresistance
- Immune signature
- Bone metastases

Classification
- CK20+ or GATA3+
- Lack *FGFR* mutations or translocations
- ERBB2-

Therapies
- Immunotherapy
- Bone-targeting agents

"Luminal"

- FGFR-PPAR-ɣ
- Intermediate chemosensitive
- Immunoquiescent

Classification
- *FGFR3* mutations
- *FGFR* translocations
- CK20+ or GATA3+
- ERBB2-

Therapies
- FGFR inhibitors (+IO)
- TUR, initial surgery

"Luminal"

- ERBB2+
- Chemosensitive

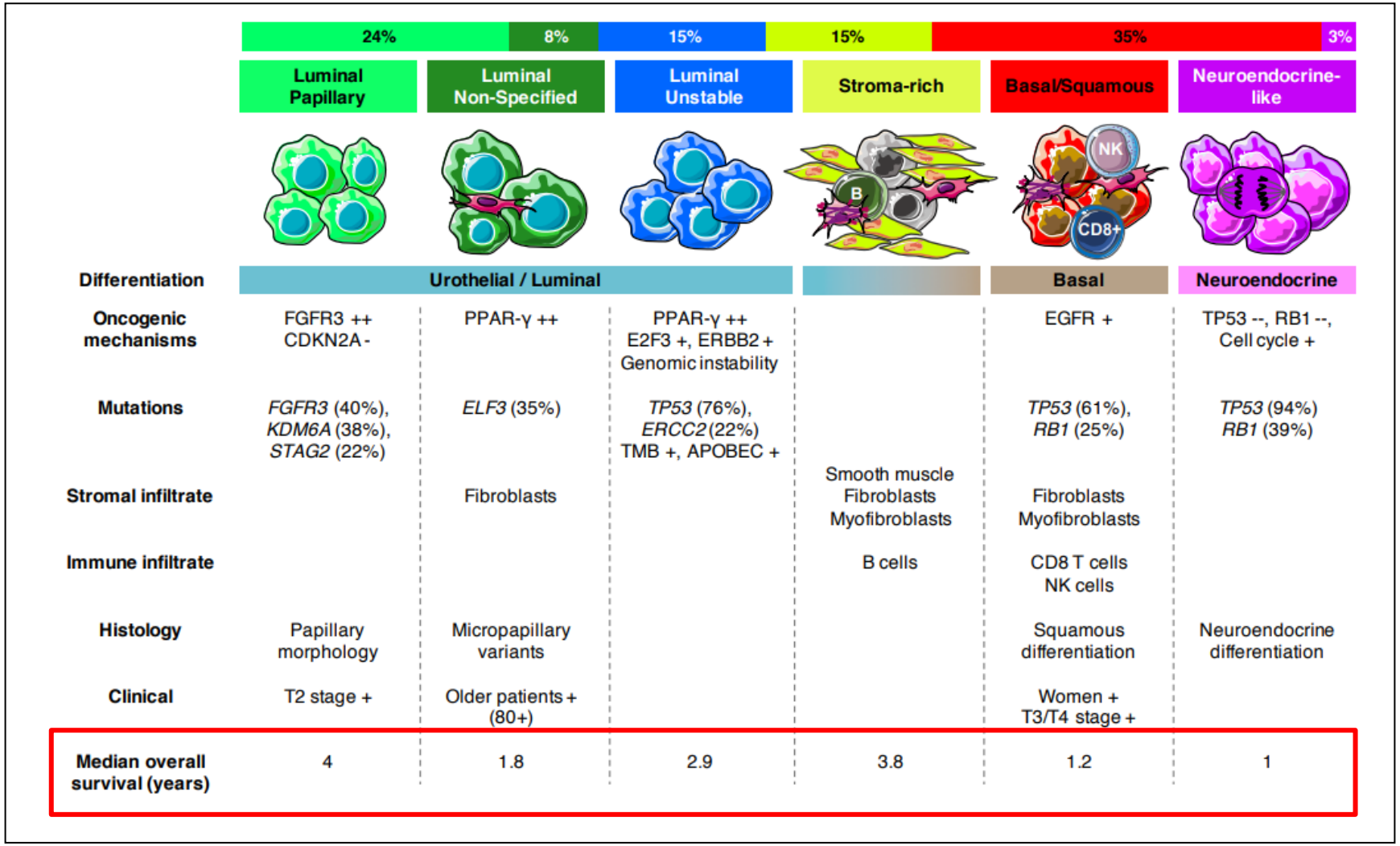
Classification
- ERBB2+
- CK20+ or GATA3+
- WT FGFR

Therapies
- Chemotherapy
- HER2-targeted therapies

CK, cytokeratin; HER2, human epidermal growth factor receptor 2; IDO-IO; indoleamine 2,3-dioxygenas immuno-oncology; MDSC, myeloid-derived suppressor cells; WT, wild type.

Siefker-Radtke AO, et al. ASCO 2018;

Bladder cancer is composed of multiple tumors: Subtypes within subtypes

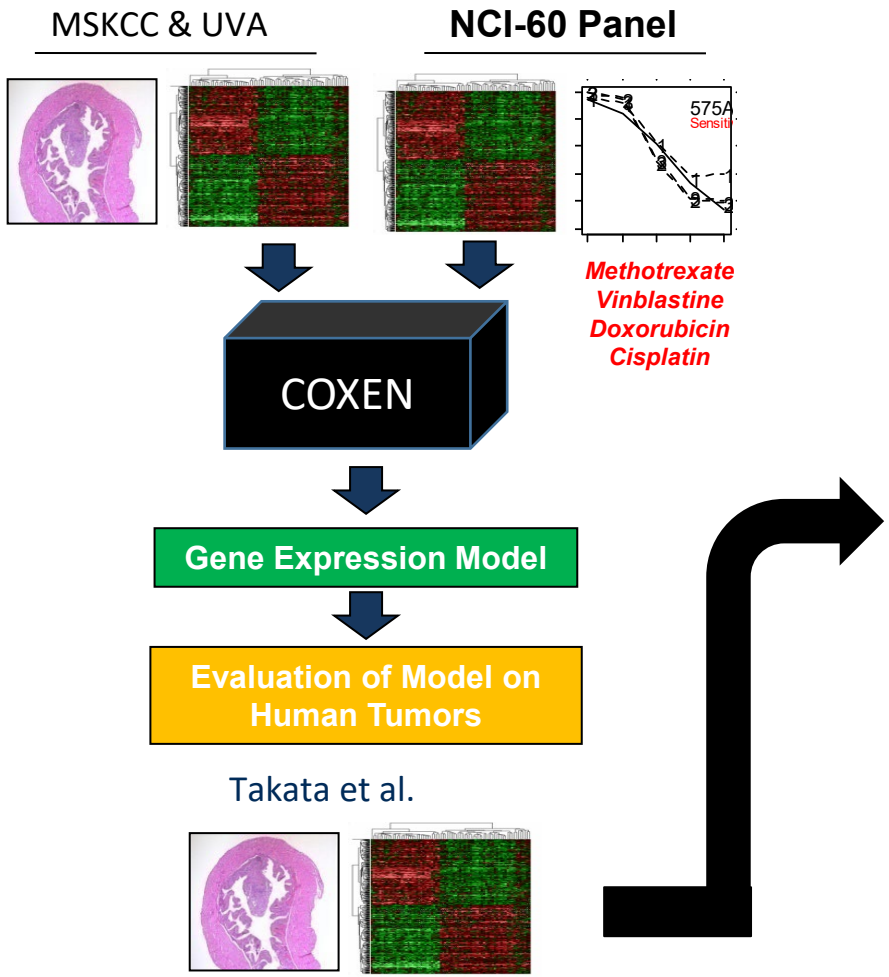


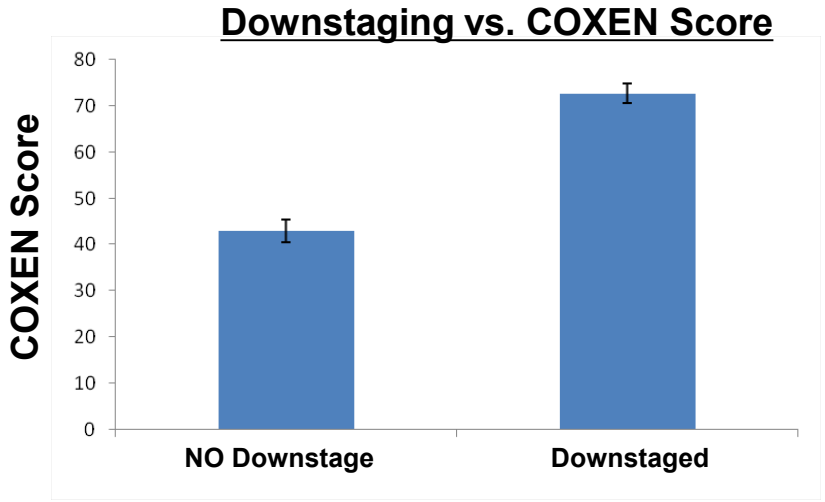
	Luminal Papillary	Luminal Non-Specified	Luminal Unstable	Stroma-rich	Basal/Squamous	Neuroendocrine-like
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 ++ CDKN2A -	PPAR-γ ++	PPAR-γ ++ E2F3 +, ERBB2 + Genomic instability		EGFR +	TP53 --, RB1 --, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%), *STAG2* (22%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology	Micropapillary variants			Squamous differentiation	Neuroendocrine differentiation
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

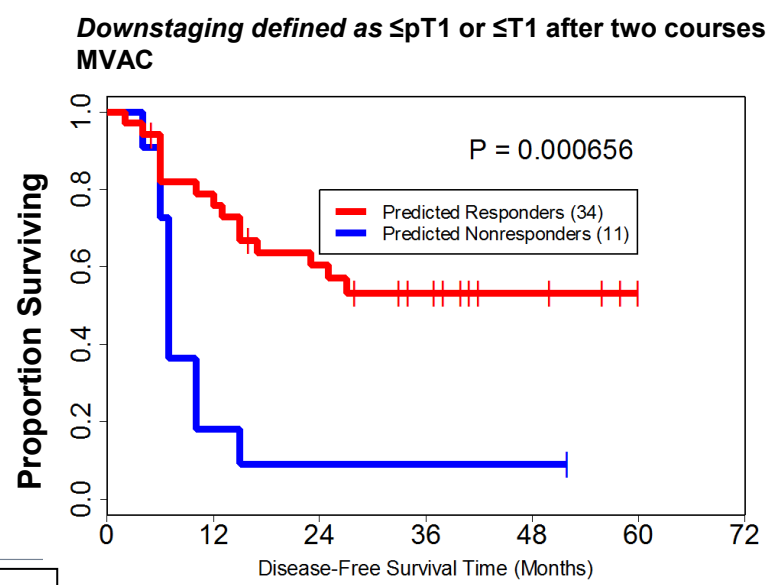
APOBEC, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like; CDKN2A, cyclin-dependent kinase Inhibitor 2A; E2F3, E2F transcription factor 3; NK, natural killer; TMB, tumour mutation burden.

Kamoun A, et al. 2019. Epub ahead of print date.

S1314: COXEN background



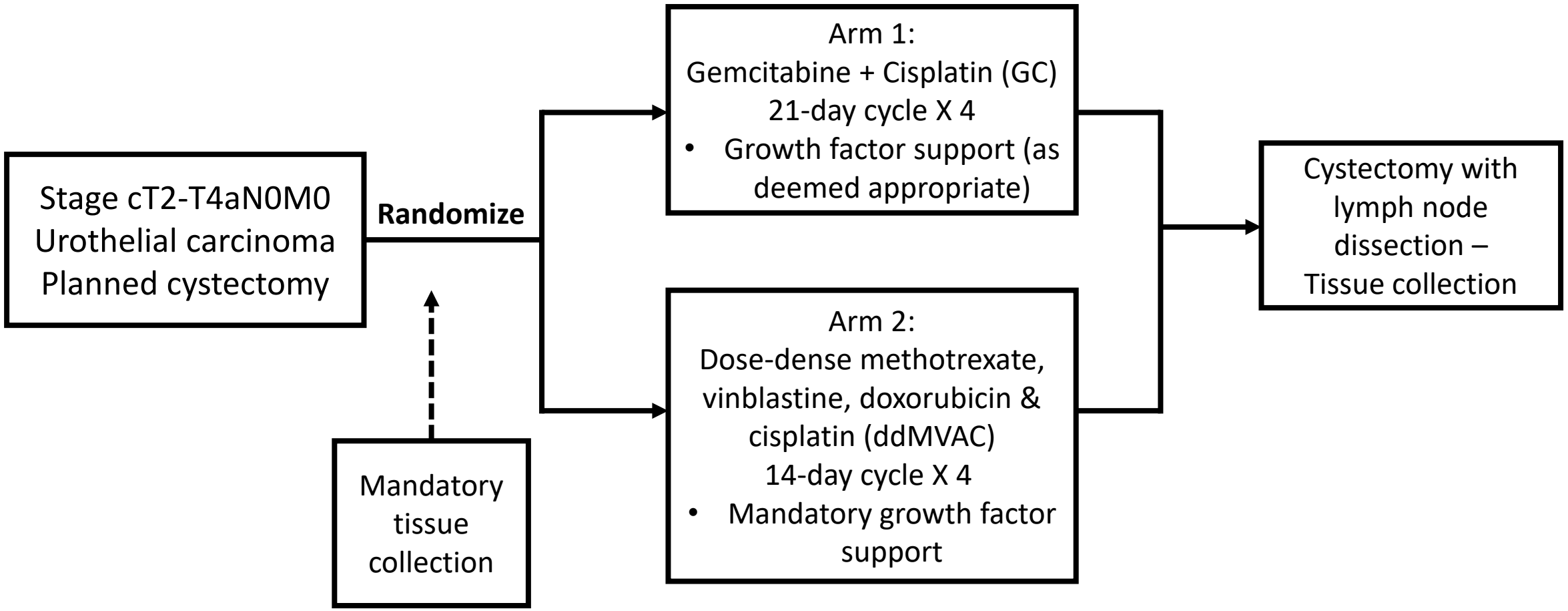




Ref: Clin Can Res 2005;11(7): 2625
Tx: Neoadjuvant MVAC (N=45) + surgery or XRT
Outcome: Downstaging, Overall survival

Slide courtesy of Tom Flaig, MD

S1314: Schema



Coxen Trial Results

Table 3. Results of logistic regression modeling of COXEN score and pathologic response at cystectomy.

COXEN score	Outcome	Arm	*N*	OR (95% CI)[b]	*P*[b]	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
GC[a]	pT0	GC	82	2.63 (0.82–8.36)	0.10	29% (13%–49%)	81% (69%–91%)	44% (22%–69%)	69% (56%–80%)
GC[a]	≤pT1	GC	82	1.75 (0.60–5.34)	0.30	25% (13%–41%)	81% (66%–91%)	47% (34%–60%)	53% (40%–66%)
ddMVAC[a]	pT0	ddMVAC	85	1.12 (0.42–2.95)	0.82	37% (19%–58%)	63% (46%–78%)	33% (17%–53%)	44% (17%–53%)
ddMVAC[a]	≤pT1	ddMVAC	85	0.92 (0.37–2.27)	0.86	34% (21%–49%)	63% (46%–78%)	53% (34%–72%)	69% (55%–81%)
GC[a]	pT0	Pooled	167	1.84 (0.88–3.83)	0.10	33% (21%–47%)	78% (69%–85%)	42% (27%–58%)	70% (61%–78%)
GC[a]	≤pT1	Pooled	167	2.33 (1.11–4.89)	0.02	32% (23%–43%)	81% (71%–89%)	65% (49%–79%)	52% (43%–61%)
ddMVAC[a]	pT0	Pooled	167	0.99 (0.49–2.02)	0.99	31% (19%–45%)	68% (58%–76%)	32% (20%–46%)	67% (58%–76%)
ddMVAC[a]	≤pT1	Pooled	167	0.90 (0.46–1.75)	0.76	30% (21%–41%)	66% (55%–76%)	49% (35%–63%)	46% (37%–56%)

Abbreviations: NPV, negative predictive value; Pooled, GC + ddMVAC arms; PPV, positive predictive value.
[a]Favorable based on prespecified COXEN algorithm and cut-off point.
[b]Adjusted for two stratification factors: clinical stage at baseline (T2 vs. T3, T4a), PS (0 vs. 1) in logistic regression model.

- Individual GC and MVAC coxen scores were not predictive of benefit
- The GC Coxen score predicted benefit when pooling GC and DDMVAC data

Flaig et al. ClinCanRes, 2021


Perioperative Immunotherapy:
Neoadjuvant

Neoadjuvant Pembrolizumab

Table 3. Pathologic Response to Pembrolizumab

Response	All Treated Patients (N = 50)	PD-L1 CPS ≥ 10% (n = 35)	PD-L1 CPS < 10% (n = 15)
Primary end point			
Pathologic complete response, No. (%)	21 (42)	19 (54.3)	2 (13.3)
95% CI	28.2 to 56.8		
Secondary end point			
Pathologic downstaging to pT<2, No. (%)	27 (54)	23 (65.7)	4 (26.7)
95% CI*	39.3 to 68.2		
Treatment failure, No. (%)			
pT2N0	2 (3.8)		
pT3-4N0	6 (12)		
pTanyN+	10 (20)		
Additional MVAC chemotherapy†	5 (10)		
RECIST v1.1 PD	0		

Abbreviations: CPS, combined positive score; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; PD, disease progression; PD-L1, programmed death ligand-1.

*Including pTa (n = 3), pTis (n = 2), and pT1 (n = 1).

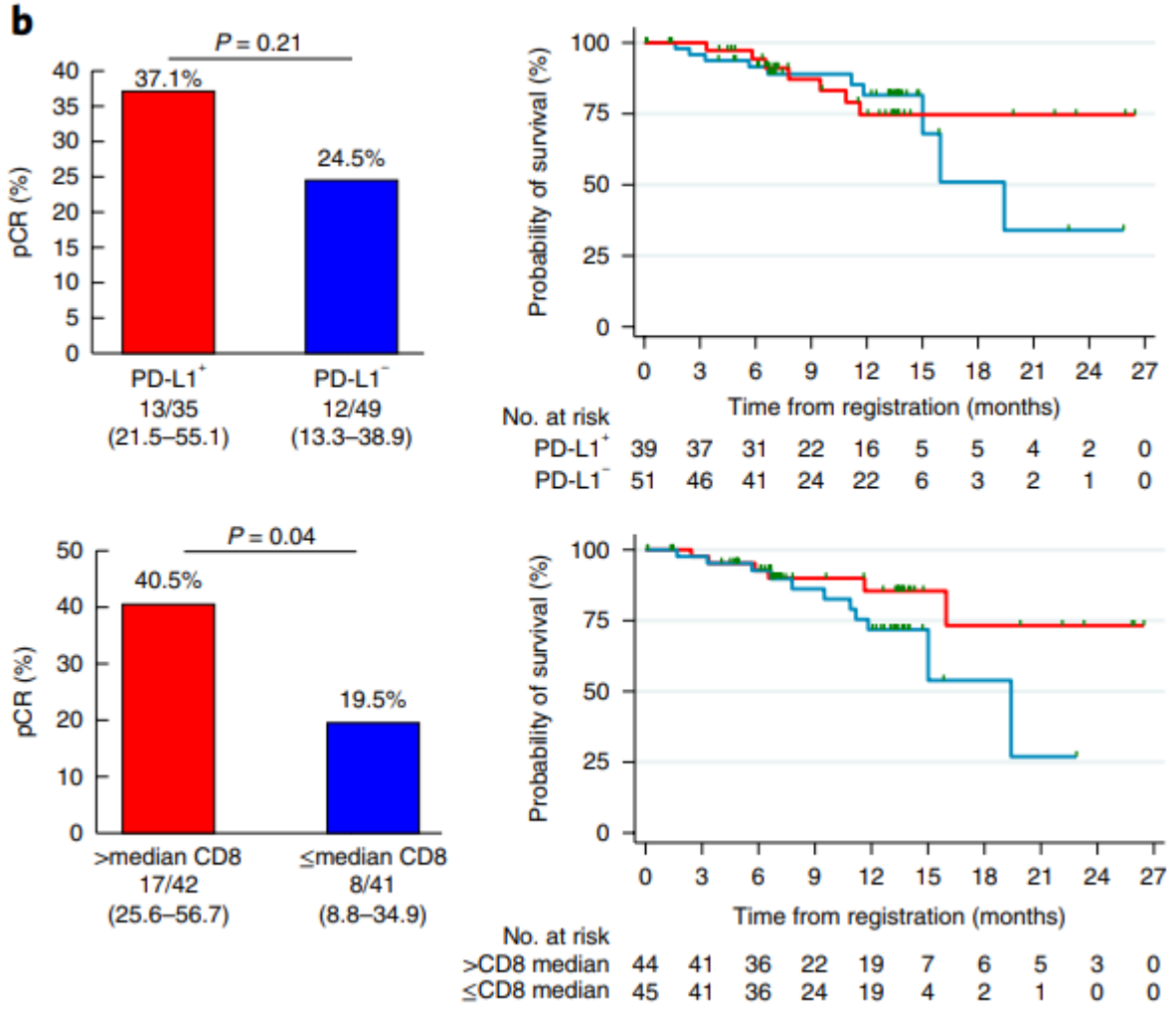
†As a result of investigator decision after the evidence of radiologic nonresponse to pembrolizumab (n = 4) or because of the onset of immune-related, grade 3 transaminase increase (n = 1). These patients achieved pTis (n = 2), pT2pN2 (n = 1), and pT3pN1 (n = 2) stage at radical cystectomy.

- N=50
- Cisplatin ineligible: 92%
- cT2N0 42%
- Staging post TUR MRI of the bladder
- Median tumor volume: 0.7 cm^3 (range 0.4-1.5)
- pT0N0 42%

Necchi et al. JCO 2018

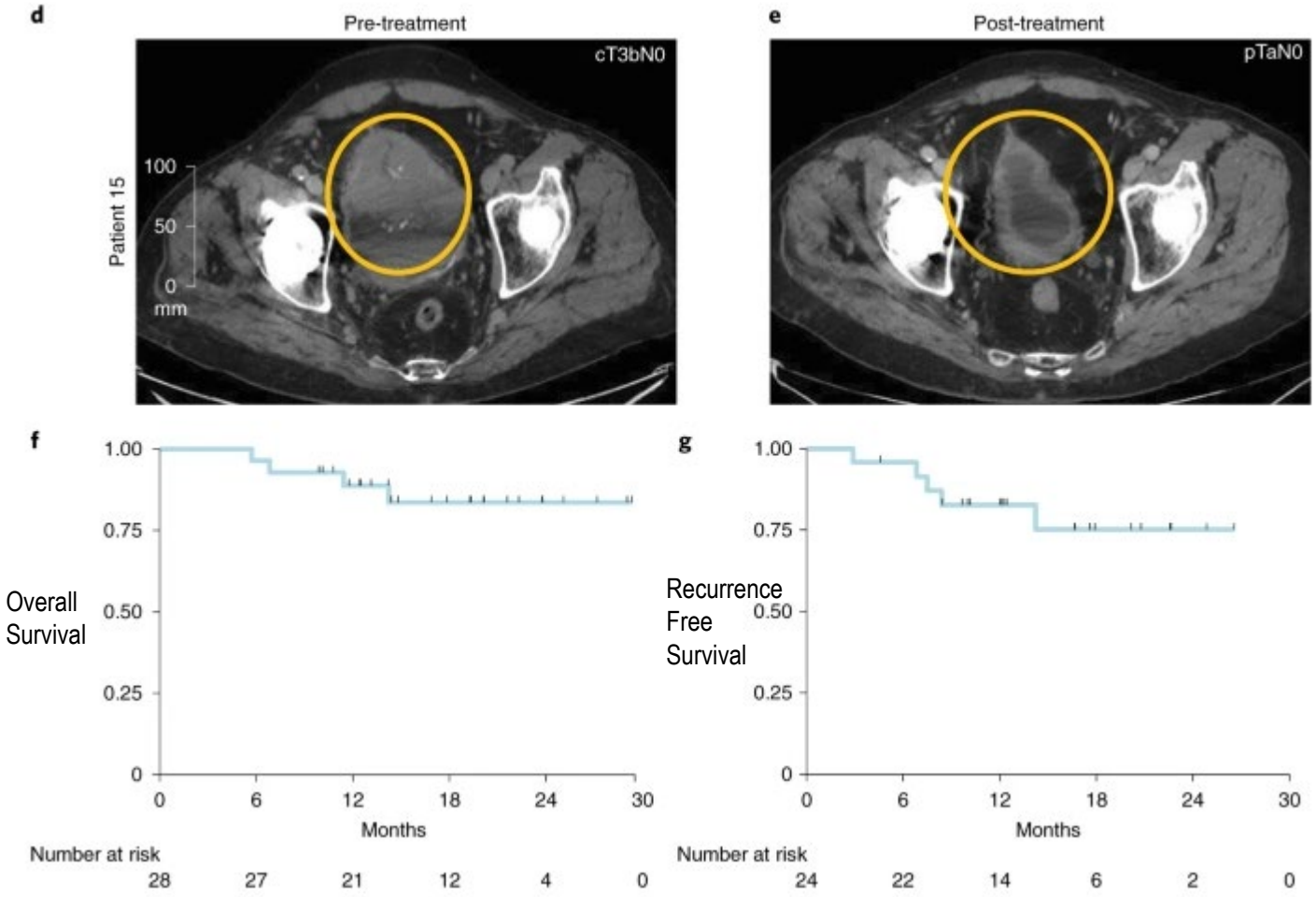
Neoadjuvant Atezolizumab

- N=95, only 88 had cystectomy and were included in the analysis
- GFR<60mL/min: 41%
- cT2N0 74%
- pT0N0 31% (ITT: 28%)



Powles et al. NatMed 2019

Neoadjuvant Durvalumab + Tremelimumab



- N=28
- Cisplatin ineligible:90%
- cT2N0 47%
- pT0N0 37.5%, by ITT: 31.7%

Gao et al. Nat Med 2020


Perioperative Immunotherapy:
Adjuvant

Study design - Adjuvant Nivolumab

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

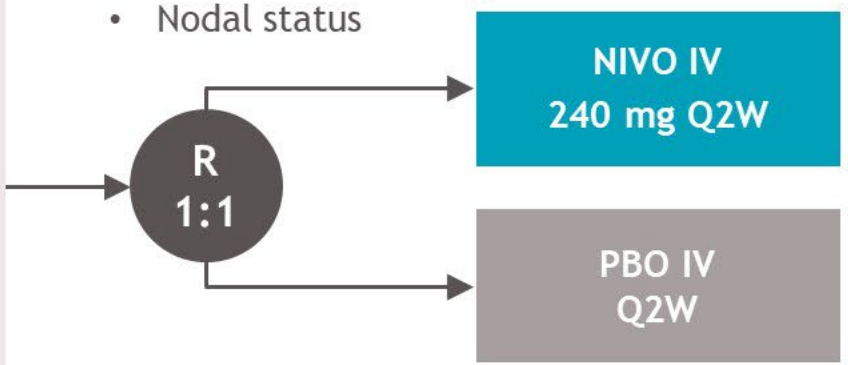
N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



Treat for up to 1 year of adjuvant therapy

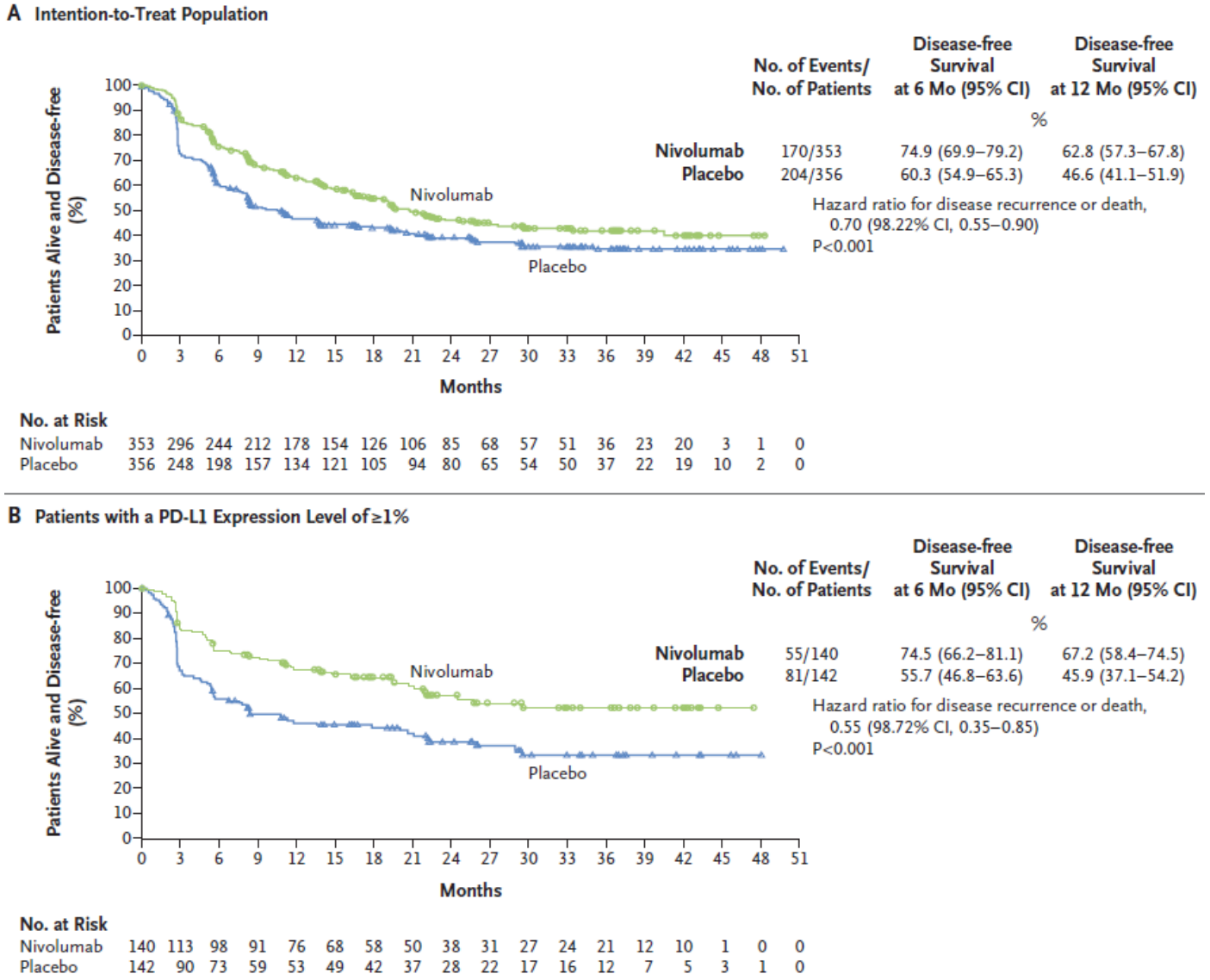
Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

Bajorin, et al. GUASCO 2021

Adjuvant Nivolumab



- N=709, “high-risk”
  - Post cisplatin:ypT2-4a or N+
  - No chemo:pT3-4a or N+
- Must have negative margin surgery
- Adjuvant to start within 120 days
- Disease-free by imaging within 4-weeks
- 1 year adj. nivo
- Median f/u: ~ 20 mo
- Improvement in DFS:
  - Nivo: 20.8 mo
  - Placebo: 10.8
- No survival data presented

Bajorin, et al. NEJM 2021

A031501 AMBASSADOR: Study Design

Phase 3 randomized, open label, multicenter study of adjuvant pembrolizumab vs observation in patients with high-risk muscle-invasive urothelial carcinoma (MIUC)

NCT03244384

Key Eligibility

- Muscle-invasive urothelial carcinoma: bladder, urethra, renal pelvis, ureter
- Post-radical surgery (cystectomy, nephrectomy, nephroureterectomy, or ureterectomy) ≥ 4 but ≤ 16 weeks
- Post-neoadjuvant chemotherapy and ≥ pT2 and/or N+/+margins

OR

- cisplatin-ineligible or refusing and ≥ pT3 and/or pN+/+margins

Stratify

- PD-L1 status*
- Neoadjuvant chemotherapy yes/no
- Pathologic stage:
  - pT2/3/4aN0
  - pT4aN0
  - pT4bNx/N1-3
  - +surgical margins

N=739

R 1:1

Pembrolizumab 200 mg q3W 1 year (18 cycles)

Observation

Dual Primary Endpoints

- **Disease-free survival**
- **Overall survival**

Key Secondary Endpoints
- DFS/OS PD-L1 +/-
- Safety

Correlative Endpoints
- DFS/OS ctDNA +/-
- DFS/OS immune gene signatures
- DFS/OS tumor molecular subtype
- DFS/OS TCR clonality
- QOL

*PD-L1 status was tested centrally and defined using the combined positive score: percentage of PD-L1-positive tumor cells and infiltrating immune cells relative to the total number of tumor cells. PD-L1 positive = CPS ≥ 10%, Dako PD-L1 immunohistochemistry 22C3 pharmDx assay. DFS: disease-free survival (defined as new MIUC, metastatic disease, or death without recurrence); OS: overall survival

A031501 AMBASSADOR: Patient Characteristics

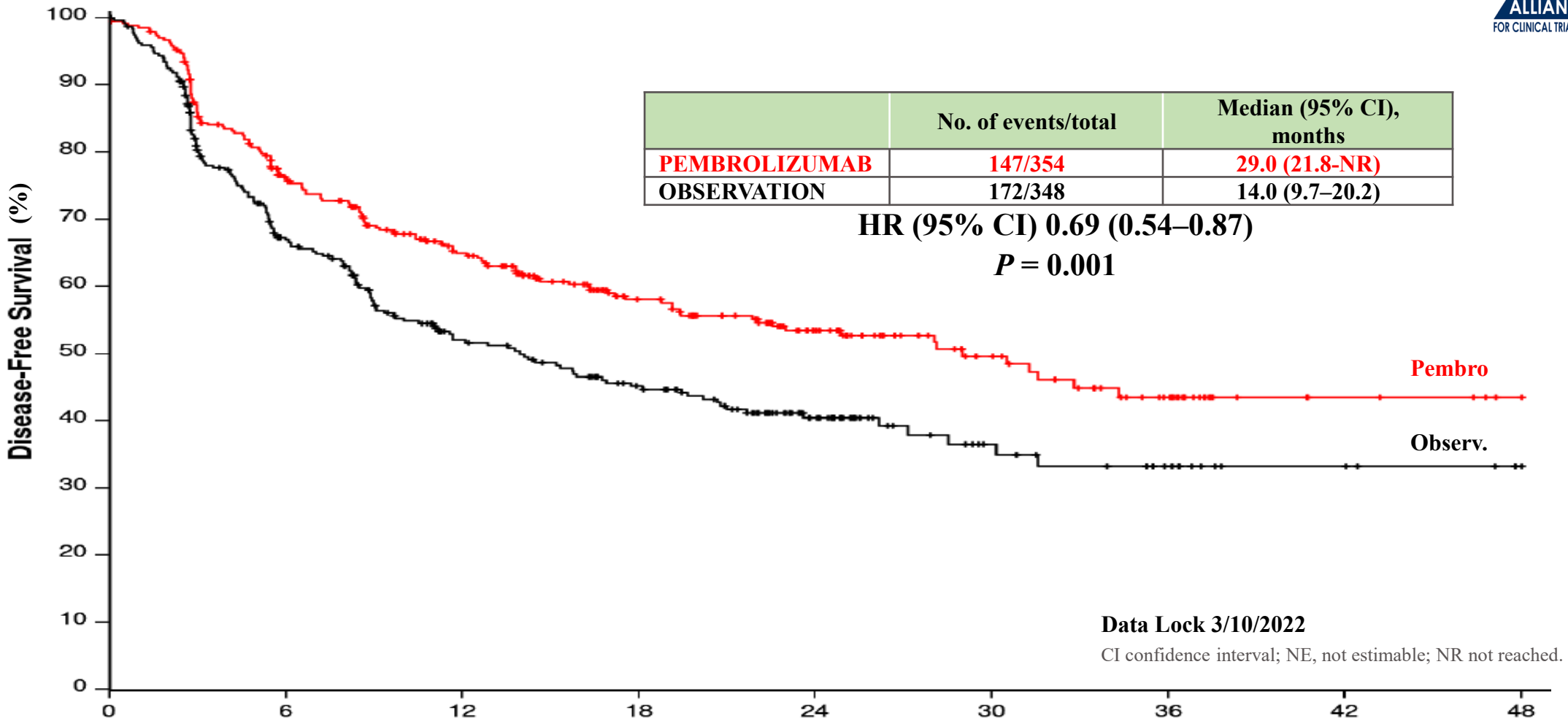
	Pembrolizumab (N=354)	Observation (N=348)
Median age, years (range)	69.0 (22.0-92.0)	68.0 (34.0-90.0)
Race		
White	323 (91.2%)	310 (89.1%)
Black or African American	14 (4.0%)	11 (3.2%)
Asian	5 (1.4%)	10 (2.9%)
American Indian or Alaskan Native	2 (0.6%)	2 (0.6%)
Not reported/Unknown	10 (2.8%)	15 (4.3%)
Gender		
Female	83 (23.4%)	95 (27.3%)
Male	271 (76.6%)	253 (72.7%)
Neoadjuvant therapy		
Yes	231 (65.3%)	218 (62.6%)
Pathologic stage		
+ Surgical margins	9 (2.5%)	8 (2.3%)
pT-any N+ (any)	180 (50.9%)	170 (48.8%)
pT2/3N0 or NX	146 (41.2%)	150 (43.1%)
pT4N0 or NX	19 (5.4%)	20 (5.8%)
PD-L1 status		
Positive (central testing, Dako 22C3, CPS ≥ 10%)	202 (57.1%)	201 (57.8%)
Primary tumor site		
Bladder	267 (75.4%)	264 (75.9%)
Urethra	6 (1.7%)	12 (3.4%)
Upper tract (renal pelvis and ureter)	81 (22.9%)	72 (20.7%)
Histology		
Variant (mixed urothelial histology excluding any neuroendocrine carcinoma)	60 (16.9%)	51 (14.7%)

A031501 AMBASSADOR: Disease-Free Survival (ITT)

	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	147/354	29.0 (21.8-NR)
OBSERVATION	172/348	14.0 (9.7–20.2)

HR (95% CI) 0.69 (0.54–0.87)

***P* = 0.001**

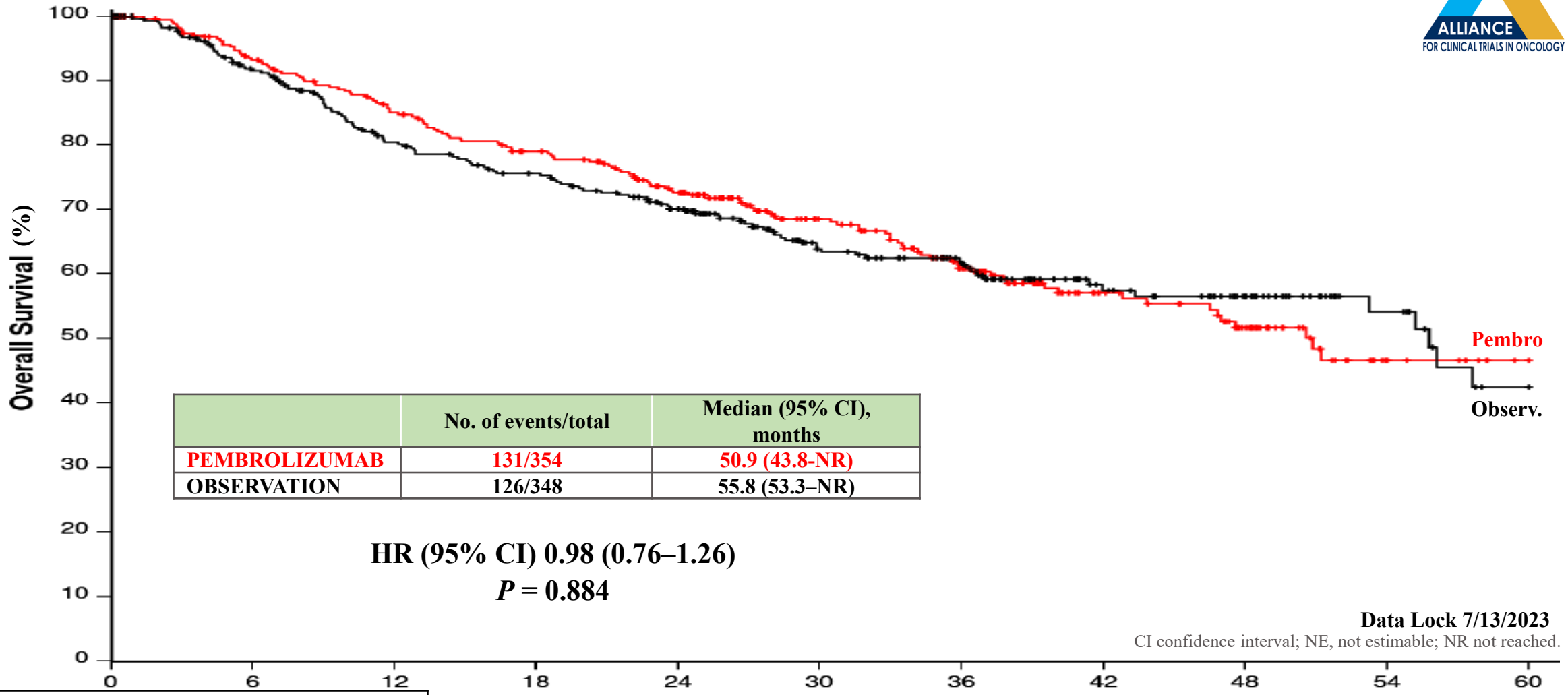


Data Lock 3/10/2022

CI confidence interval; NE, not estimable; NR not reached.

Median follow-up (range) 22.3 months (0.03-48.9)

A031501 AMBASSADOR: (interim) Overall Survival



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	131/354	50.9 (43.8-NR)
OBSERVATION	126/348	55.8 (53.3–NR)

HR (95% CI) 0.98 (0.76–1.26)
***P* = 0.884**

Data Lock 7/13/2023

CI confidence interval; NE, not estimable; NR not reached.

Median follow-up (range) 36.9 months (0-63.9)

Patients-at-Risk

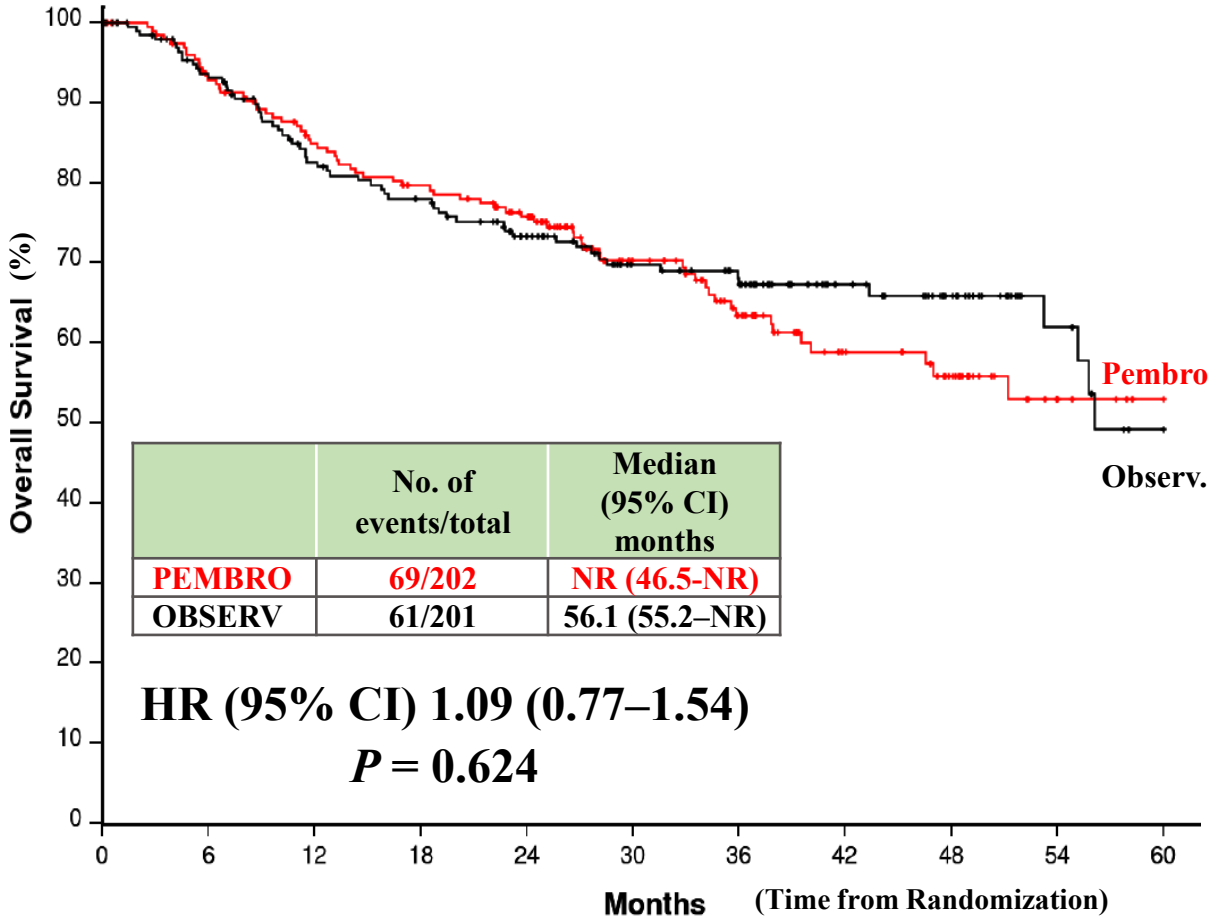
Pembro	354	313	280	253	218	152	115	69	50	17	10
Observ.	348	296	249	227	195	139	117	65	45	23	12

PRESENTED BY: Andrea B. Apolo, MD

@apolo_andrea

A031501 AMBASSADOR: Overall Survival by PD-L1* Status

PD-L1-Positive CPS ≥ 10%

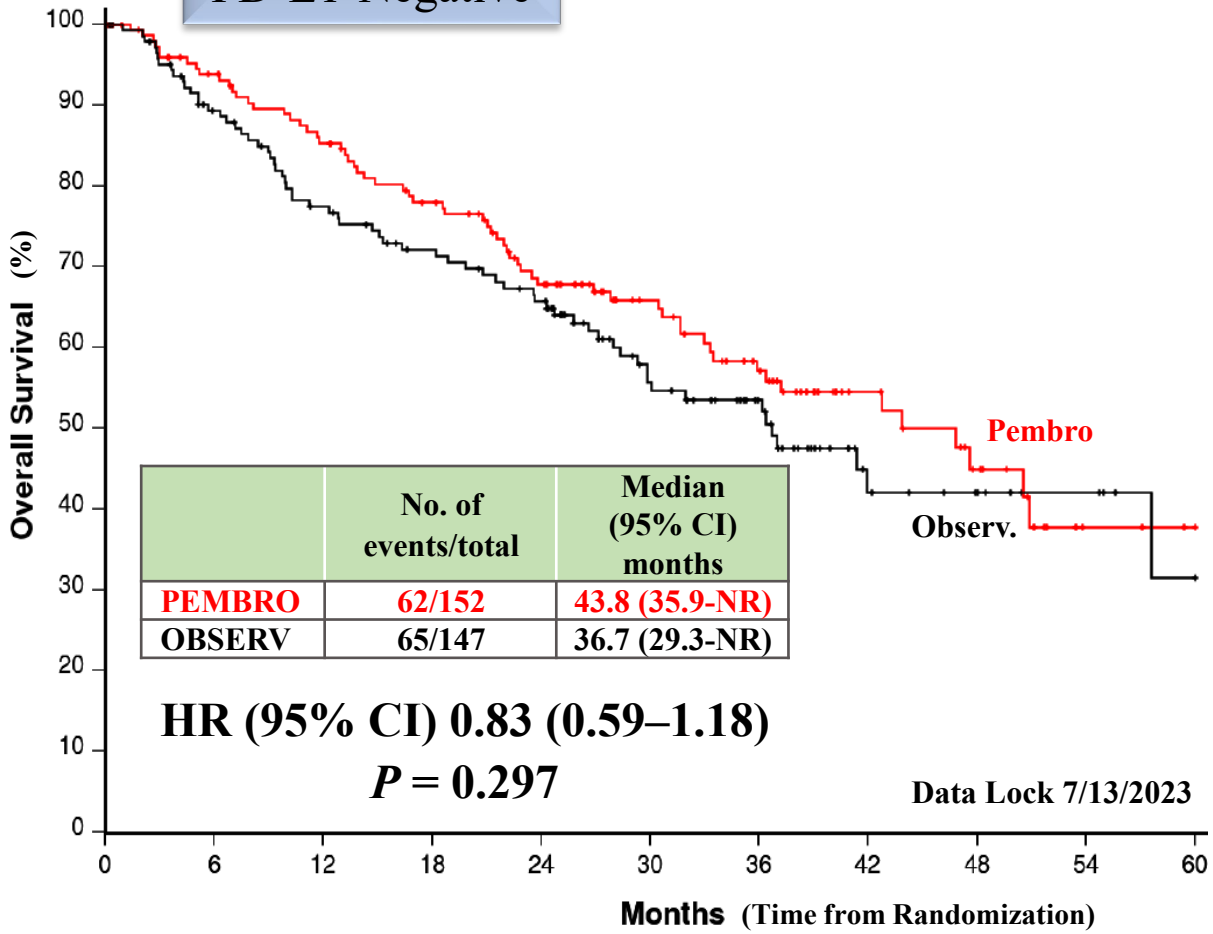


	No. of events/total	Median (95% CI) months
PEMBRO	69/202	NR (46.5-NR)
OBSERV	61/201	56.1 (55.2–NR)

HR (95% CI) 1.09 (0.77–1.54)

***P* = 0.624**

PD-L1-Negative



	No. of events/total	Median (95% CI) months
PEMBRO	62/152	43.8 (35.9-NR)
OBSERV	65/147	36.7 (29.3-NR)

HR (95% CI) 0.83 (0.59–1.18)

***P* = 0.297**

Data Lock 7/13/2023

*Dako PD-L1 immunohistochemistry 22C3 pharmDx assay

CI confidence interval; NE, not estimable; NR not reached.


Combinations with Immunotherapy

Chemotherapy with immunotherapy:

- Two great standards go great together!

+

=

US/FDA Approval

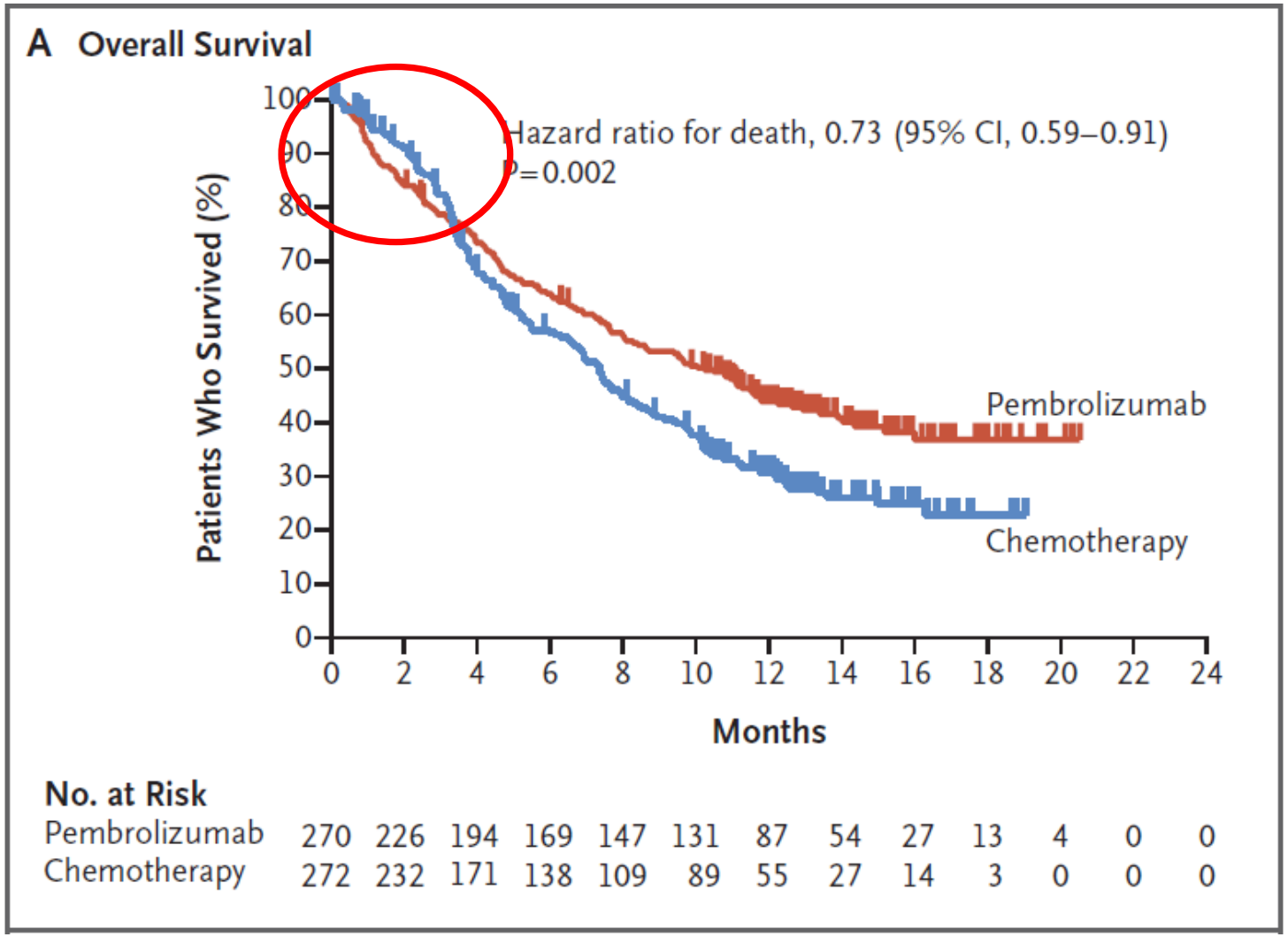
EU/EMA Approval

Reasons to combine chemotherapy with immunotherapy:

- Two great standards go great together
- Control rapidly progressive disease – bulkier cT3b-4a tumor
    - Is there a subset who benefit more from chemotherapy than IO

A subset who needs chemotherapy more than IO?

- Does the cross-over reflect a group of patients who benefit more from chemotherapy than immunotherapy?



Bellmunt et al. NEJM 2017

Reasons to combine chemotherapy with immunotherapy:

- Two great standards go great together
- Control rapidly progressive disease – liver metastases
    - Is there a subset who benefit more from chemotherapy than IO
- Chemotherapy may impact antigen presentation
- Chemotherapy may increase PDL1 expression
    - And overcome a mechanism of resistance with poor outcomes

Methods- Neoadjuvant GC + Pembrolizumab

Study Design: Phase 1b/2 study with 2 cohorts: cisplatin–eligible (I) and –ineligible (II)

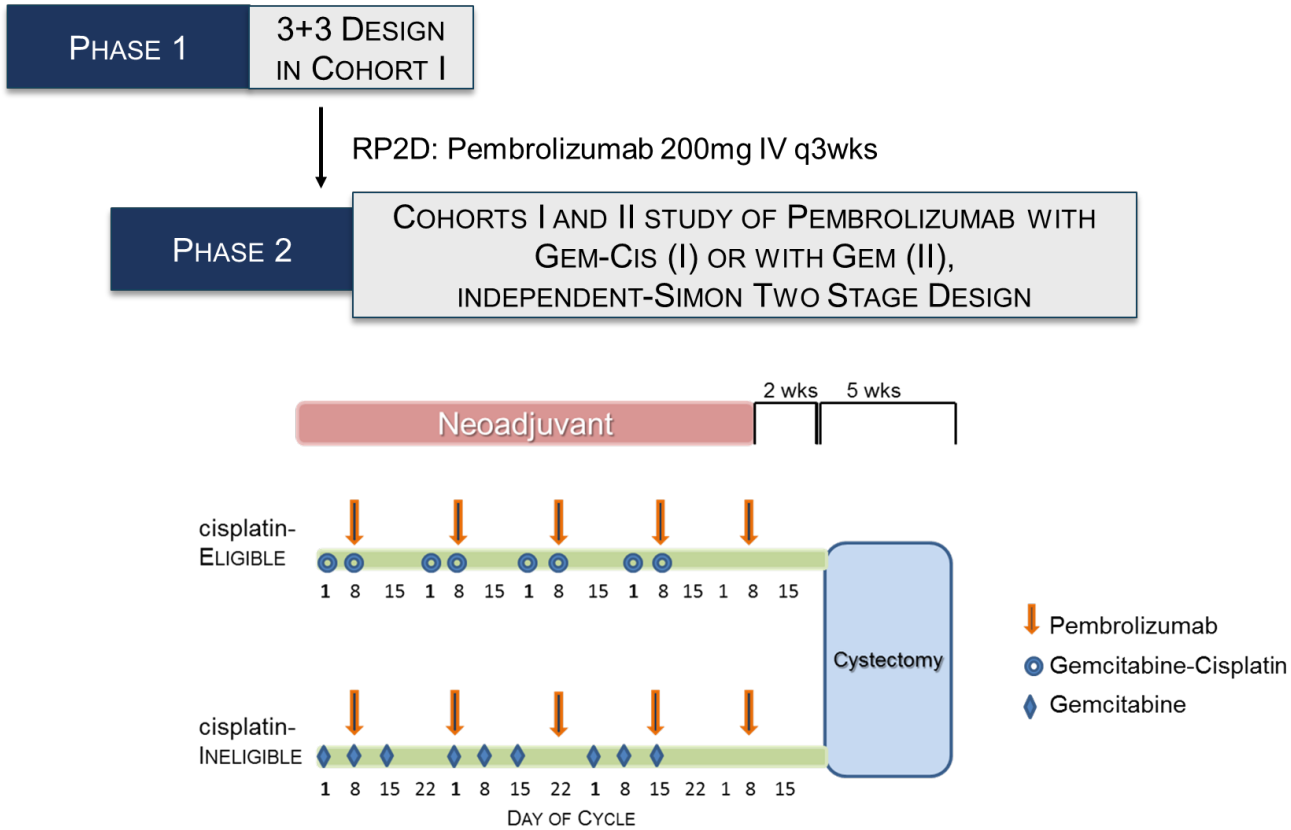


Fig 1: Treatment schematic of the HCRN GU14-188 neoadjuvant chemo-immunotherapy trial in urothelial cancer subjects that meet cisplatin eligible or ineligible criteria.

Hoimes et al. ESMO LBA 2018

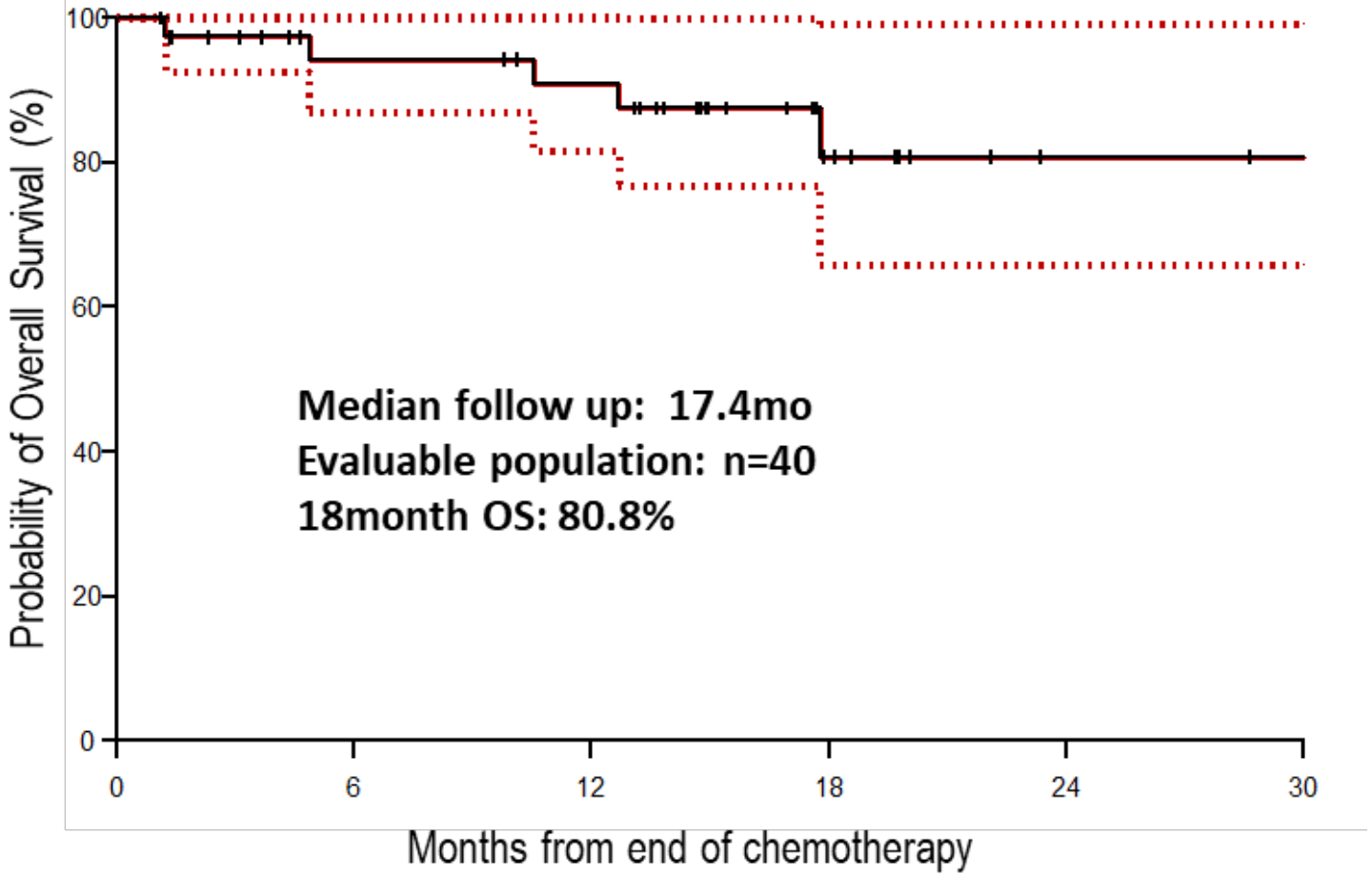
Results – Downstaging and OS

N=40
- cT2: 20 (51%)
- cT3: 18 (44%)
- cT4: 2 (5%)

N=35
- ≤ pT0N0: 15 (42%)
- ≤ pT1N0: 21 (60%)

pStage by ITT n=40
- ≤ pT0N0: 15 (38%)
- ≤ pT1N0: 21 (53%)

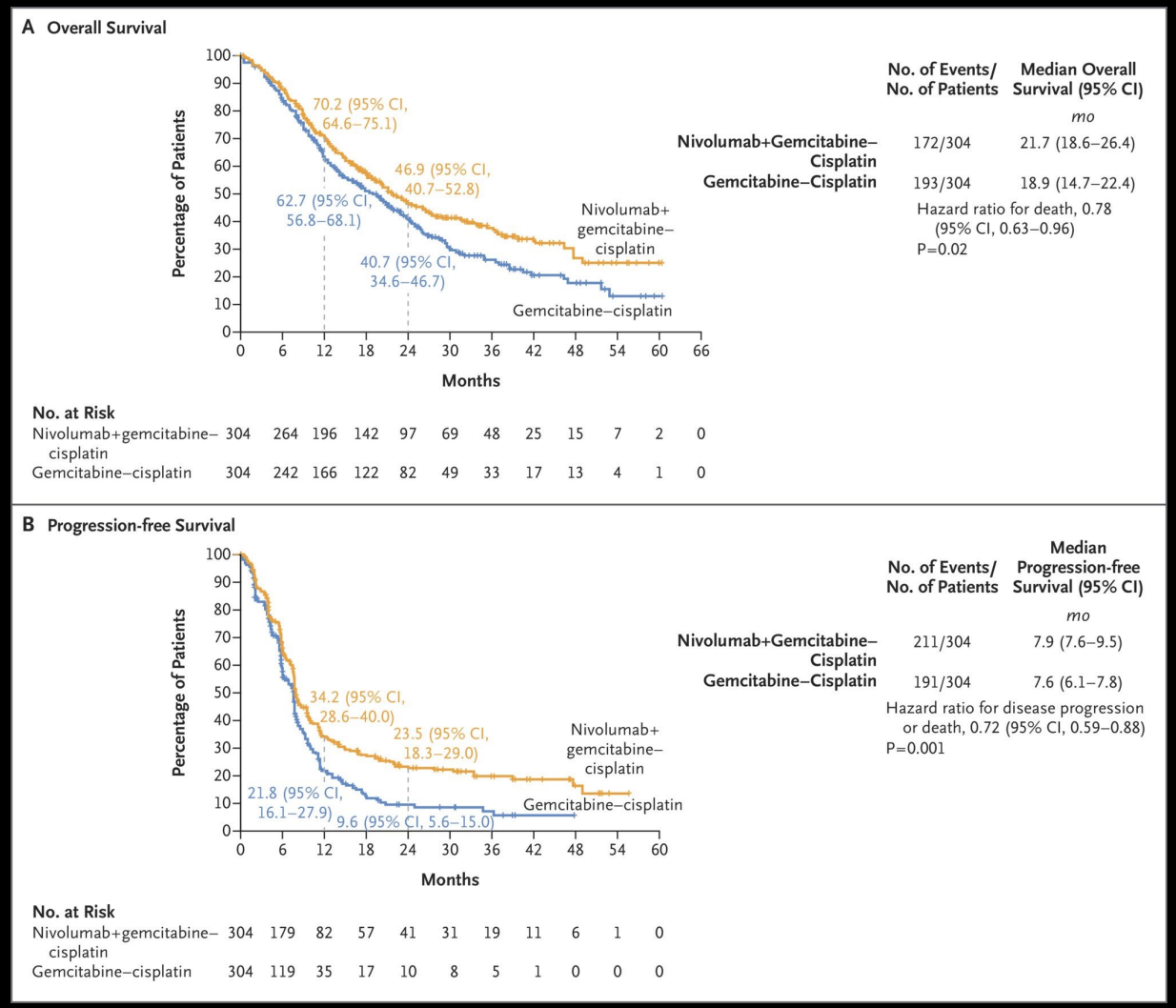
Figure 5. Overall Survival (Evaluable Population)



BARCELONA 2019 ESMO congress

Hoimes et al. ESMO LBA 2018

GC with Nivolumab, Metastatic Urothelial Cancer
Overall Survival and Progression-free Survival.

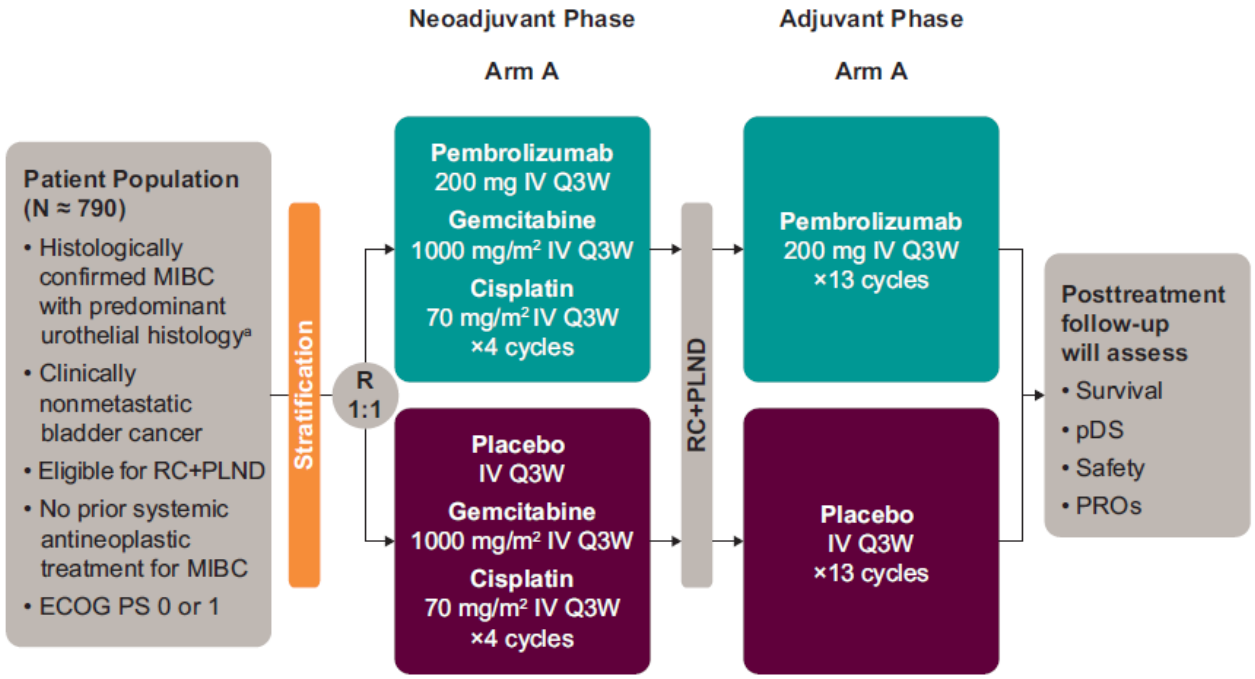


ORR GC: 57.6%
cCR GC: 21.7%

van der Heijden MS et al. N Engl J Med 2023;389:1778-1789

The NEW ENGLAND JOURNAL of MEDICINE

Phase III Neoadjuvant GC + Pembrolizumab



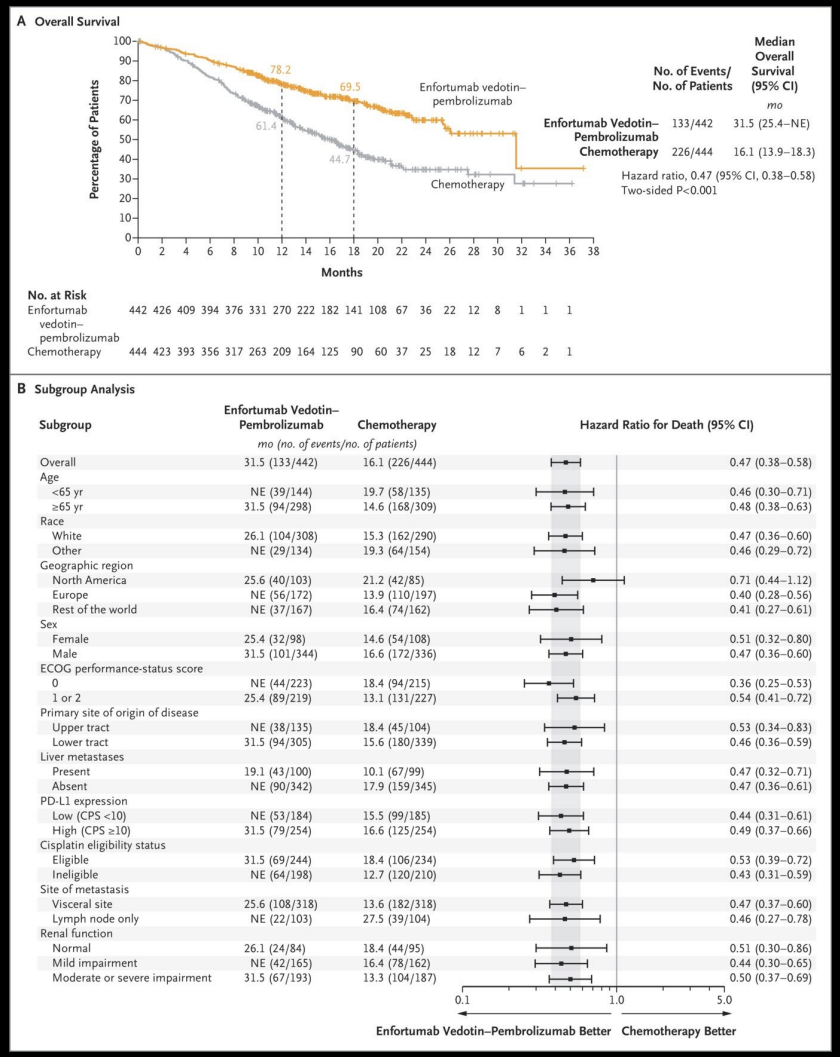
Stratification
- PD-L1 status (CPS ≥10 or <10)
- Disease stage (T2 or T3/4)
- Region (United States or Europe or most of world)

End Points
- **Primary:** pCR,[b] EFS[b]
- **Secondary:** OS,[b] DFS,[b] pDS,[b] safety and tolerability
- **Exploratory:** PROs, biomarkers

BICR, blinded independent central review; CPS, combined positive score; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IV, intravenously; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathological complete response; pDS, pathological downstaging; PLND, pelvic lymph node dissection; PRO, patient-reported outcome; Q3W, every 3 weeks; R, randomization; RC, radical cystectomy.

[a]Histology and presence of muscle invasion will be confirmed by BICR. Patients with mixed histology are eligible provided the urothelial component is ≥50%. Patients whose tumors contain any neuroendocrine component are not eligible. Patients with urothelial carcinomas not originating from the bladder (eg, upper tract [ureters, renal pelvis], urethra) are not eligible.
[b]Tumors expressing PD-L1 CPS ≥10 and tumors in all patients irrespective of CPS.

Enfortumab Vedotin with Pembrolizumab in Metastatic Urothelial Cancer
Analysis of Overall Survival in Overall Population and in Prespecified Subgroups.



ORR EV+P: 67.7%
cCR EV+P: 29.1%

Powles T et al. N Engl J Med 2024;390:875-888

The NEW ENGLAND JOURNAL of MEDICINE

EV-103 Cohort H Study Design

Eligibility:

Cisplatin-ineligible

Clinical stage T2-T4aN0M0

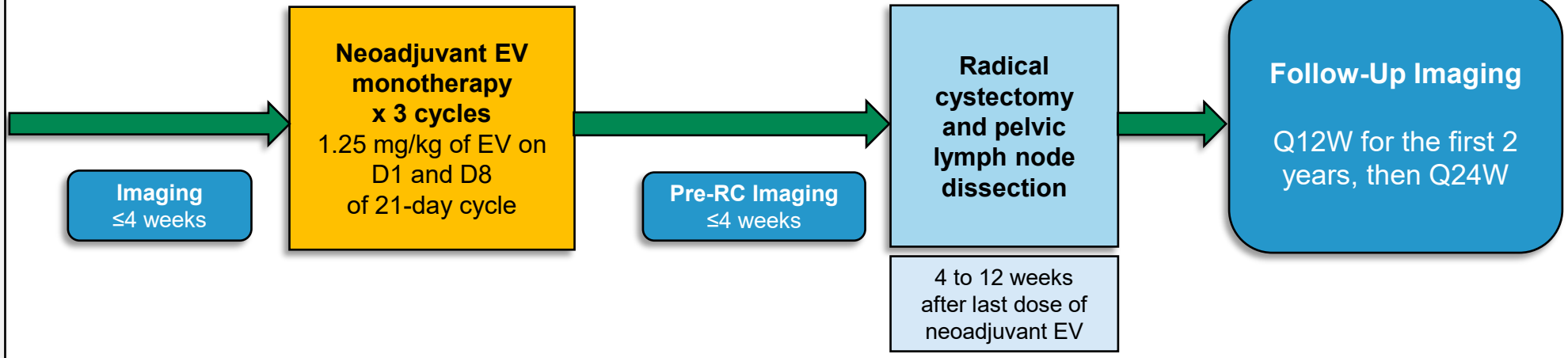
No upper or lower tract disease allowed

≥50% Urothelial carcinoma histology

ECOG 0−2

Medically fit for RC+PLND

TURBT ≤ 90 days from C1D1



Primary endpoint: pCR rate by central pathology review

Secondary endpoints: EFS, OS, DFS, pDS (central review), safety, PROs, biomarkers

DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free survival; EV: Enfortumab vedotin; OS: Overall survival; pCR: pathological Complete Response rate; pDS: pathological Downstaging; RC+PLND: radical cystectomy + pelvic lymph node dissection; PROs: Patient-reported outcomes; TURBT: transurethral resection of bladder tumor

Slides Courtesy of Dan Petrylak, MD

Key Demographic and Disease Characteristics

	Cohort H (N=22)
Male sex, n (%)	20 (90.9)
Median age (range), years	74.5 (56–81)
White race, n (%)	22 (100)
Current or former smoker, n (%)	21 (95.5)
Median enrollment time from diagnosis (range), months	1.6 (1–3)
ECOG performance status	
0	13 (59.1)
1	8 (36.4)
2	1 (4.5)
Current stage, n (%)	
cT2N0	15 (68.2)
cT3N0	6 (27.3)
cT4aN0	1 (4.5)
Histology type, n (%)	
Transitional cell carcinoma (TCC) only	15 (68.2)
TCC with squamous differentiation	3 (13.6)
TCC with other histologic variants	4 (18.2)
TCC+adenocarcinoma	1 (4.5)
TCC+micropapillary	2 (9.1)
TCC+sarcomatoid	1 (4.5)

Data cut date: 9 Sep 2021

Slide Courtesy of Dan Petrylak, MD

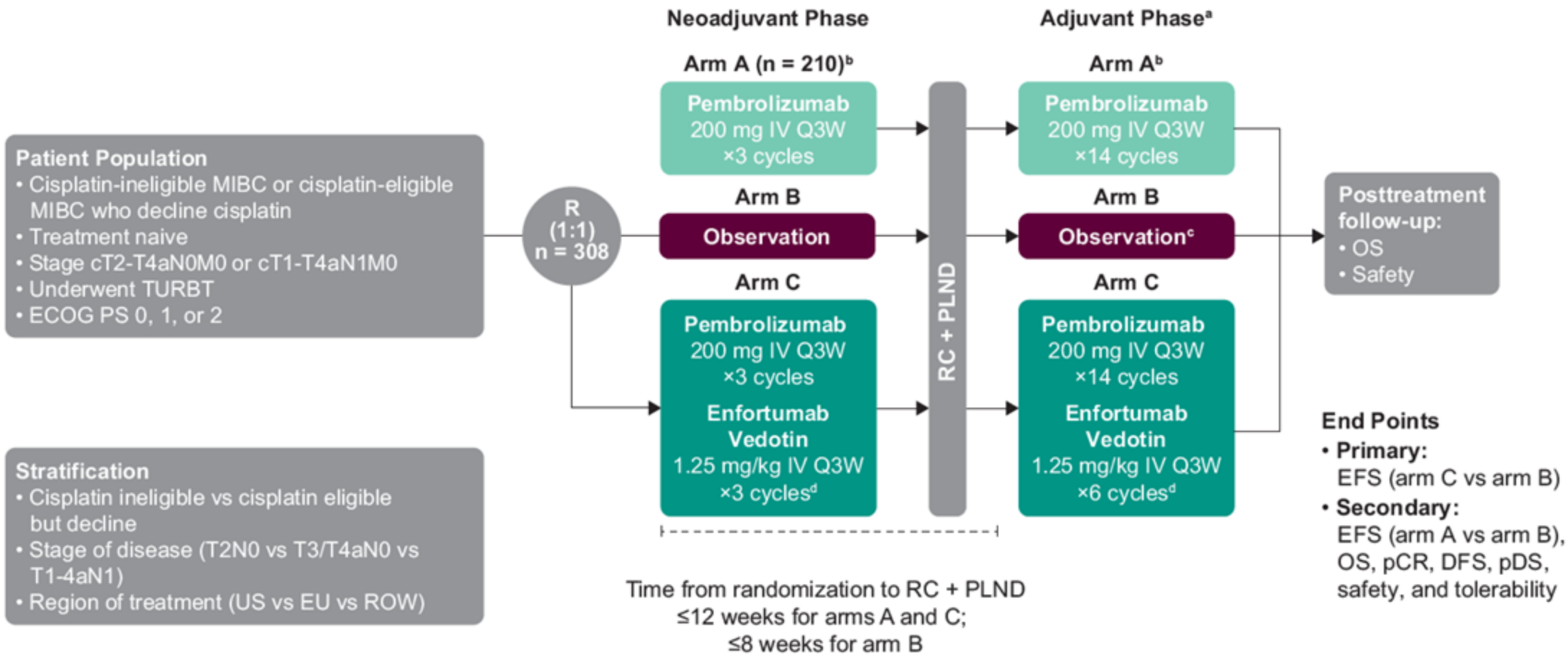
Efficacy: Central Pathology Review

Pathological Response	Central Pathology Results (N=22) n(%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue: ypT0 and N0)	**8 (36.4%)** [17.2–59.3]
Pathological Downstaging Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	**11 (50.0%)** [28.2–71.8]

Data cut date: 9 Sep 2021

Slide Courtesy of Dan Petrylak, MD

KEYNOTE-095/EV-303 Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; IV, intravenously; Q3W, every 3 weeks; R, randomization; ROW, rest of world; TURBT, transurethral resection of the bladder tumor. [a]Until disease progression, unacceptable adverse events (AEs), intercurrent illness preventing further treatment administration, or investigator's or patient's decision to withdraw. [b]Prior to the protocol amendment 8, patients were enrolled in arm A. Enrollment for that arm will be stopped once the current protocol amendment is initiated, and further randomization will focus on arms B and C. [c]Patients at high risk of recurrence after RC + PLND may receive treatment with adjuvant nivolumab per the approved product label. [d]Administered on days 1 and 8 of every 3-week cycle.

Conclusions:

- Cisplatin-based chemotherapy remains the standard for cT2-4aN0 surgically resectable urothelial cancer
- Adjuvant Immunotherapy
  - Improvement in DFS (Nivolumab and pembrolizumab)
  - No improvement in OS (Pembrolizumab, Nivolumab pending)
    - Risk of overtreatment without overall survival benefit?
    - Signatera testing under study!
- Future Combinations with chemotherapy and antibody drug conjugates
  - Treatment of cisplatin-ineligible patients!


Thank you!
“All bladder, all the time!”
Arlene Siefker-Radtke, MD