Beyond The Guidelines: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Urothelial Bladder Cancer

Part 1 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the American Urological Association Annual Meeting 2023 (AUA2023)

Sunday, April 30, 2023

8:00 AM – 10:00 AM CT

Faculty

Sia Daneshmand, MD

Joshua J Meeks, MD, PhD

Matthew Milowsky, MD

J Alfred Witjes, MD, PhD

Moderator

Arlene Siefker-Radtke, MD

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Prof Daneshmand — Disclosures

Consulting Agreements	Bristol-Myers Squibb Company, CG Oncology, Ferring Pharmaceuticals, Janssen Biotech Inc, Pacific Edge, Pfizer Inc, Photocure, Protara Therapeutics, QED Therapeutics
Contracted Research	Janssen Biotech Inc, Pacific Edge, Photocure, Protara Therapeutics
Stock Options/Ownership — Public Company	TARIS Biomedical LLC (Johnson & Johnson Pharmaceuticals)
Nonrelevant Financial Relationship	Catalyst Clinical Research

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Dr Meeks — Disclosures

Advisory Committee	Astellas, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Imvax Inc, Incyte Corporation, Janssen Biotech Inc, Merck, Pfizer Inc, Prokarium, Seagen Inc, UroGen Pharma
Consulting Agreement	Janssen Biotech Inc
Contracted Research	Epizyme Inc, Merck
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP, STEBA Biotech NV

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Dr Milowsky — Disclosures

Advisory Committee and Consulting Agreement	Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company
Contracted Research	ALX Oncology, Arvinas, Bristol-Myers Squibb Company, Clovis Oncology, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Incyte Corporation, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mirati Therapeutics Inc, Seagen Inc
Stock Options/Ownership — Public Company	Gilead Sciences Inc, Merck, Pfizer Inc
Nonrelevant Financial Relationship	Alliance for Clinical Trials in Oncology, Alliance Foundation Trials LLC, Elsevier (Co-Editor-in-Chief, *Clinical Genitourinary Cancer*), Hoosier Cancer Research Network Inc, Medscape (educational videos)

Dr Siefker-Radtke — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bavarian Nordic, Bristol-Myers Squibb Company, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, IDEAYA Biosciences, Janssen Biotech Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mirati Therapeutics Inc, Nektar, Seagen Inc, Taiho Oncology Inc
Contracted Research	Basilea Pharmaceutica Ltd, Bristol-Myers Squibb Company, Janssen Biotech Inc, Merck, Mirati Therapeutics Inc, Nektar, Takeda Pharmaceuticals USA Inc
Honoraria	Janssen Biotech Inc

Prof Witjes — Disclosures

No relevant conflicts of interest to disclose

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Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

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Clinicians Attending via Zoom

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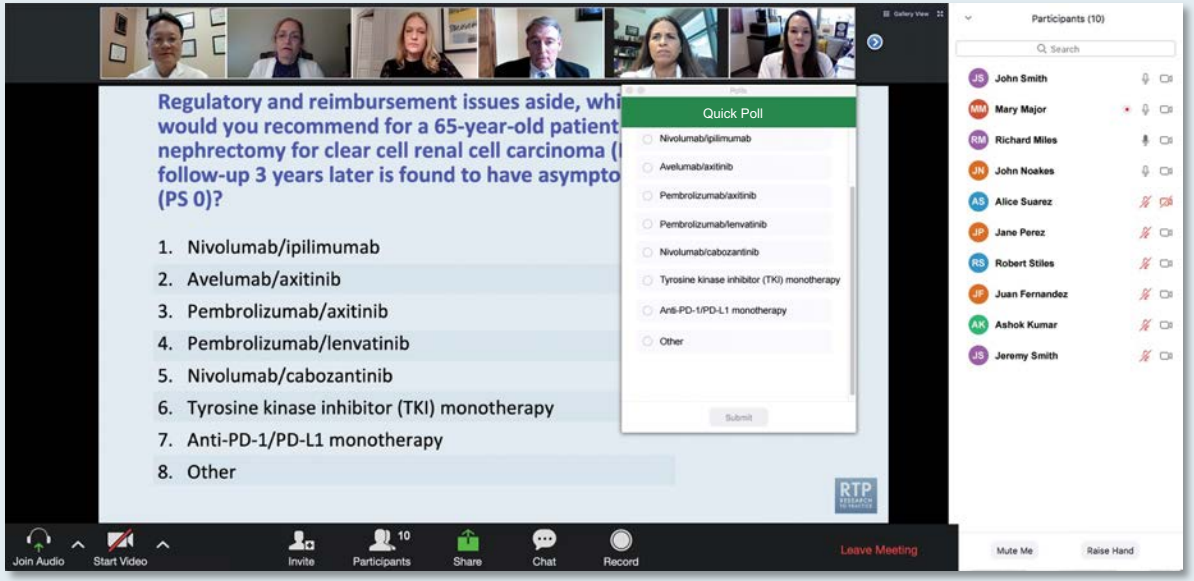
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Agenda

Module 1 – Current Role of Anti-PD-1/PD-L1 Antibodies in the Treatment of Non-Muscle-Invasive Bladder Cancer (NMIBC) — Dr Meeks

Module 2 – Contemporary Management of Muscle-Invasive Bladder Cancer (MIBC) — Prof Witjes

Module 3 – Novel Strategies Under Investigation for Nonmetastatic Urothelial Bladder Cancer (UBC) — Prof Daneshmand

Module 4 – Current and Future Up-Front Management of Metastatic UBC (mUBC) — Dr Milowsky

Module 5 – Selection and Sequencing of Therapy for Relapsed/Refractory mUBC — Dr Siefker-Radtke

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Urothelial Bladder Cancer Survey Respondents

Faculty

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MODULE 1: Current Role of Anti-PD-1/PD-L1 Antibodies in the Treatment of Non-Muscle-Invasive Bladder Cancer (NMIBC)

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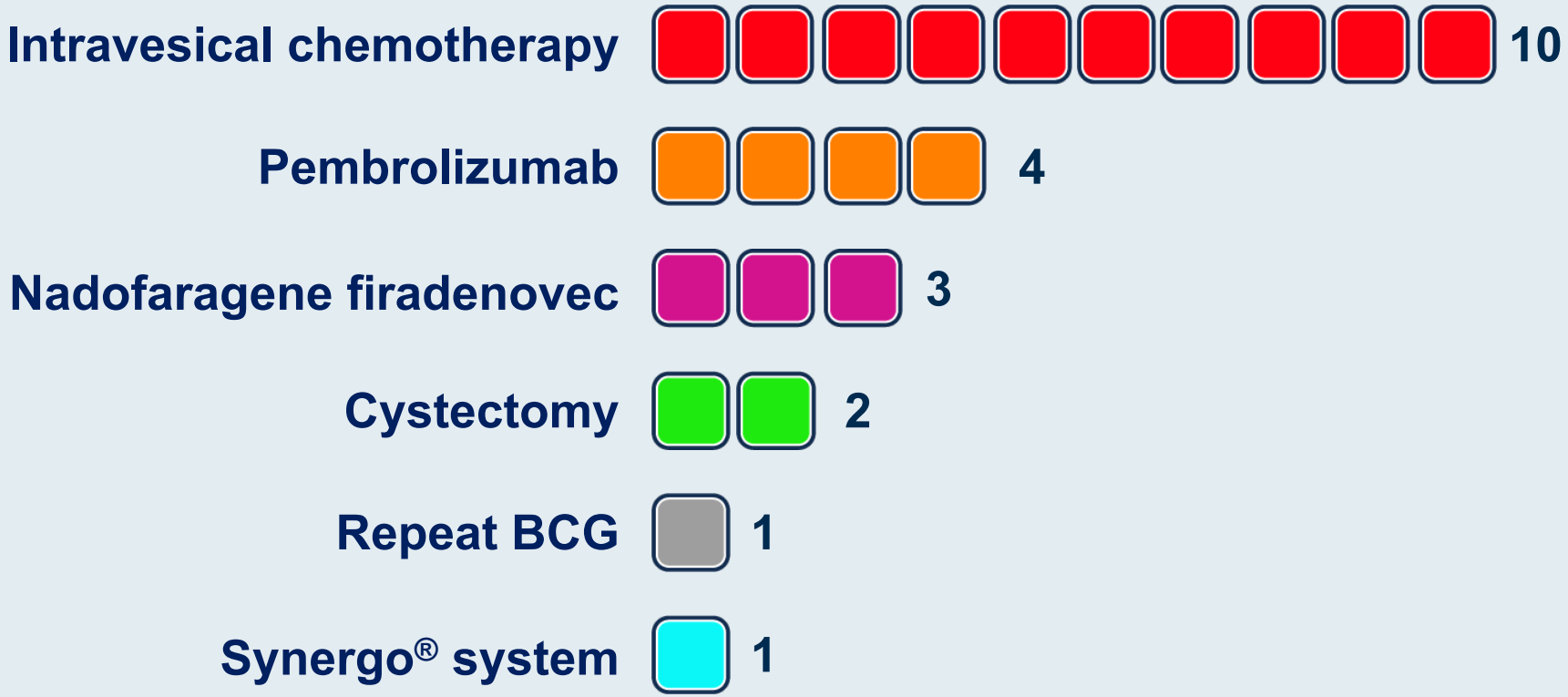
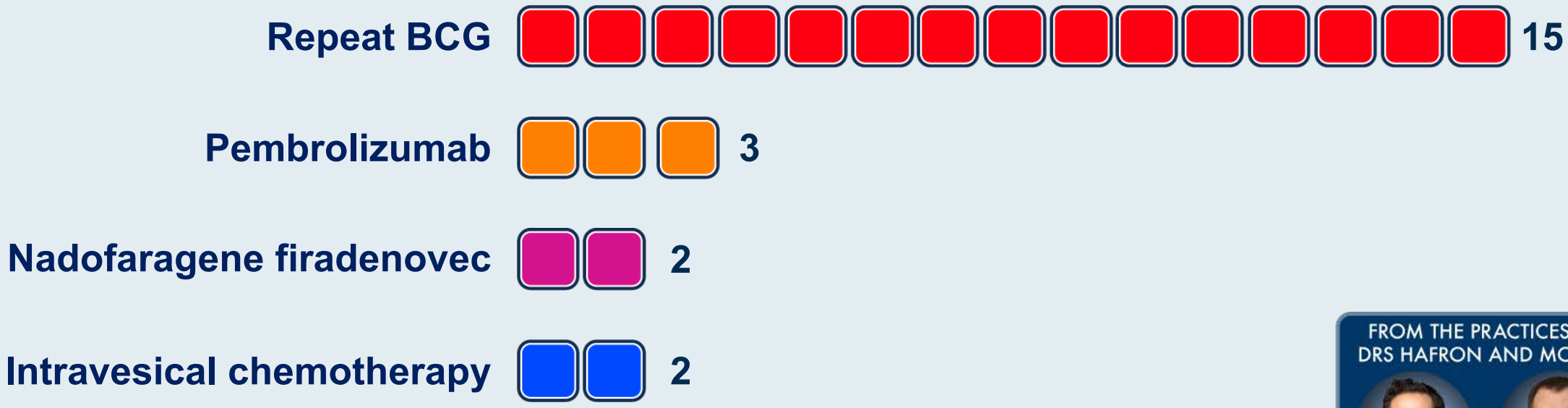
An 83-year-old man undergoing evaluation for hematuria is noted to have erythematous patches on cystoscopy. Biopsy confirms carcinoma in situ (CIS) in a diffuse pattern. Complete resection or fulguration is impossible because of the extent of disease. He receives BCG induction x 6 with maintenance for 18 months before recurrence is noted on cystoscopy. Biopsy confirms CIS recurrence. Regulatory and reimbursement issues aside, what would you recommend?



Survey of urologic oncology clinical investigators

A 59-year-old man presented with hematuria and underwent TURBT with gemcitabine, which showed high-grade T1 urothelial bladder cancer (UBC) without muscle present in the specimen. A CT urogram was negative. Repeat transuretheral resection 6 weeks later shows CIS with muscle present in the specimen. The patient receives induction BCG x 6. At the 3-month post-BCG cystoscopy, cytology is positive but an office cystoscopy is negative. Additional biopsies demonstrate CIS at the dome of the bladder. The patient refuses cystectomy. Regulatory and reimbursement issues aside, what would you recommend?



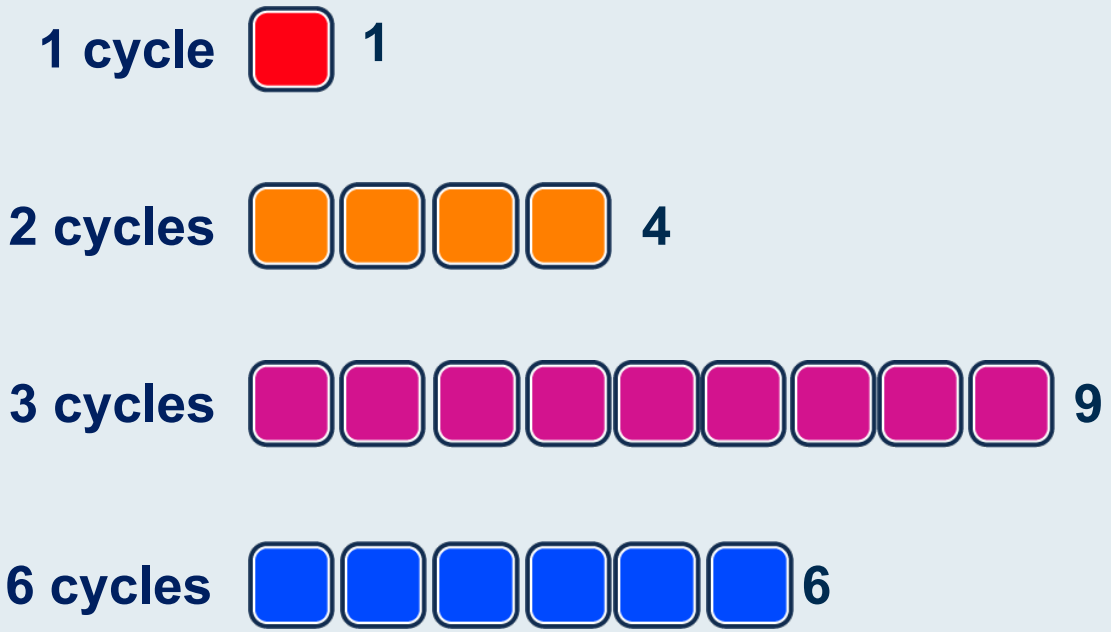
FROM THE PRACTICES OF DRS HAFRON AND MORRIS

Survey of urologic oncology clinical investigators

To what extent has the ongoing shortage of BCG affected your practice?

Survey of urologic oncology clinical investigators

For a patient with BCG-unresponsive non-muscle-invasive UBC (NMIBC) who is receiving pembrolizumab, how many cycles of therapy would you administer without a clinical response before you switched to an alternative treatment?



Survey of urologic oncology clinical investigators

AUA 2023

CHICAGO ★ APR 28-MAY 1

Current Role of Anti-PD-1/PD-L1 Antibodies in Non-Muscle-Invasive Bladder Cancer (NMIBC)

Joshua Meeks, MD, PhD

Associate Professor Urology, Biochemistry and Molecular Genetics

Northwestern University, Feinberg School of Medicine

@JoshMeeks

BCG Unresponsive

Panel: Classification of BCG failures

BCG refractory

Persistent high-grade disease at 6 months after adequate* BCG induction and maintenance treatment or any progression in stage at 3 month assessment (ie, after induction BCG cycle).

BCG relapsing

Recurrence of high-grade disease after a disease-free interval of ≥6 months after adequate* BCG induction and maintenance treatment.

Early relapse: <12 months; intermediate relapse: 12–24 months; late relapse: >24 months.

BCG unresponsive

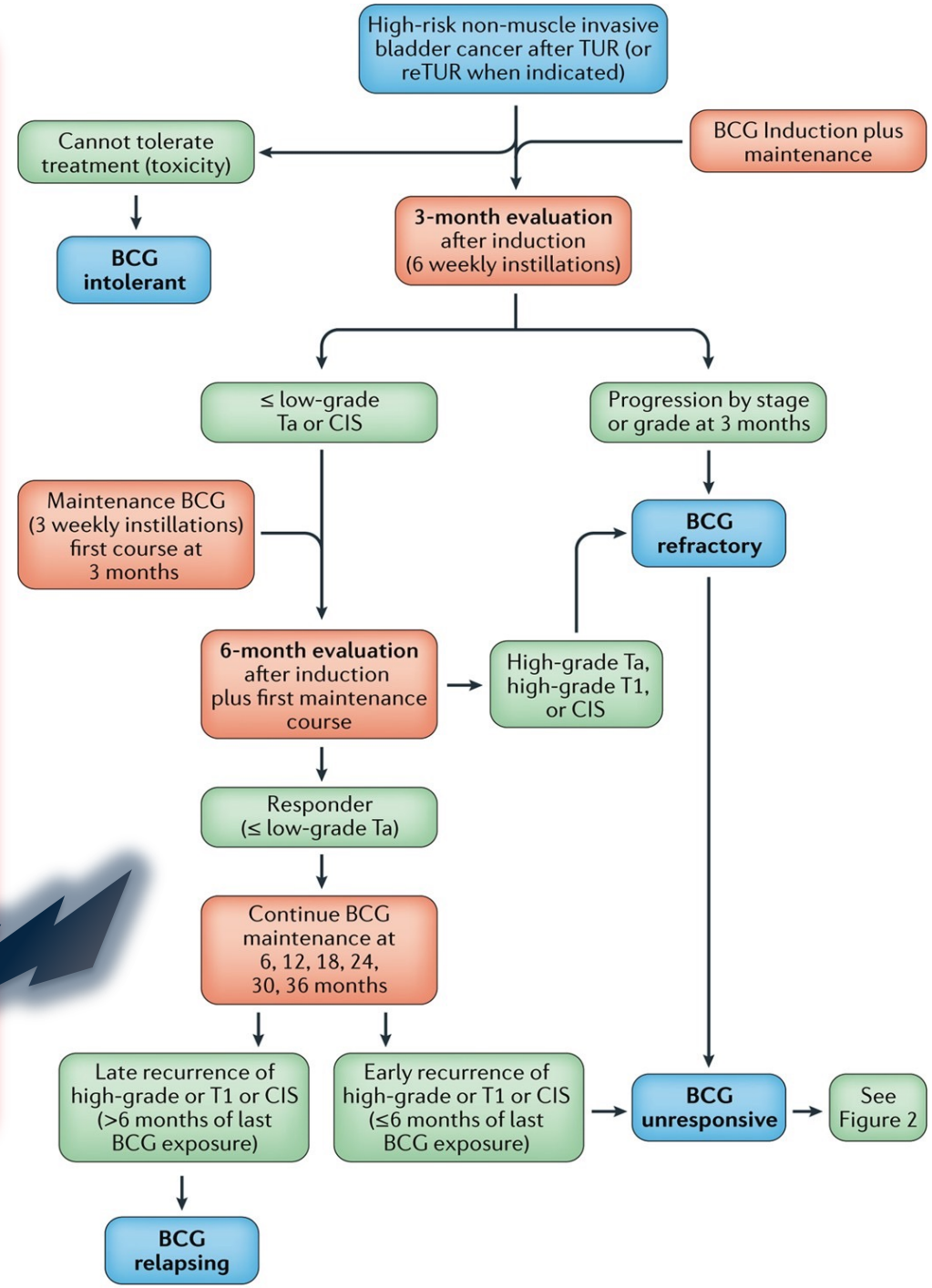
This category (developed for clinical trial design) includes patients with BCG-refractory and BCG-relapsing disease as already defined. The patients with BCG-relapsing disease should have recurrence within 6 months of last BCG exposure (eg, for patients on maintenance treatment).

Patients in the BCG unresponsive subgroup are at highest risk of recurrence and progression.

BCG intolerant

Disease persistence because the patient cannot receive adequate* BCG owing to BCG toxicity.

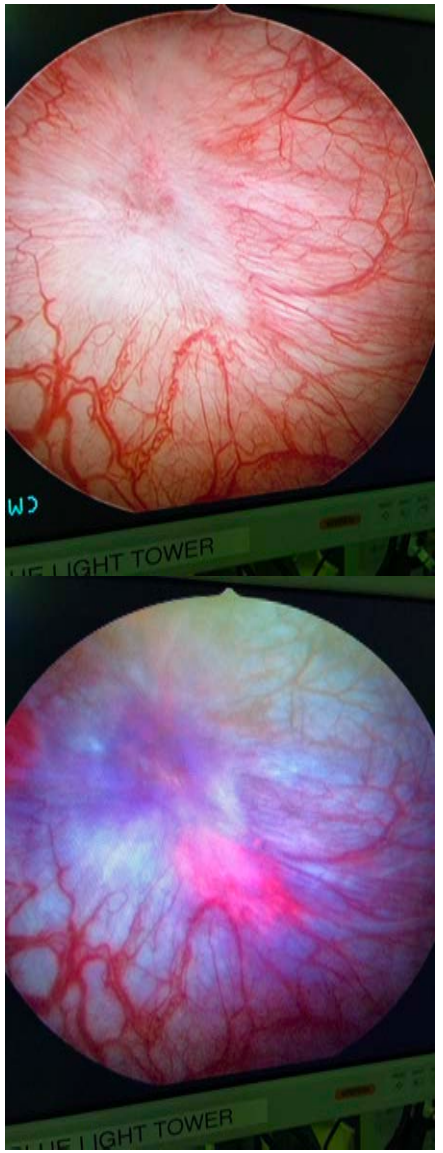
Adapted from Kamat and colleagues.[32] *Adequate BCG treatment is defined as the patient receiving at least five of six planned instillations of induction treatment and at least two of three planned instillations of maintenance treatment over 6 months.



Evaluation

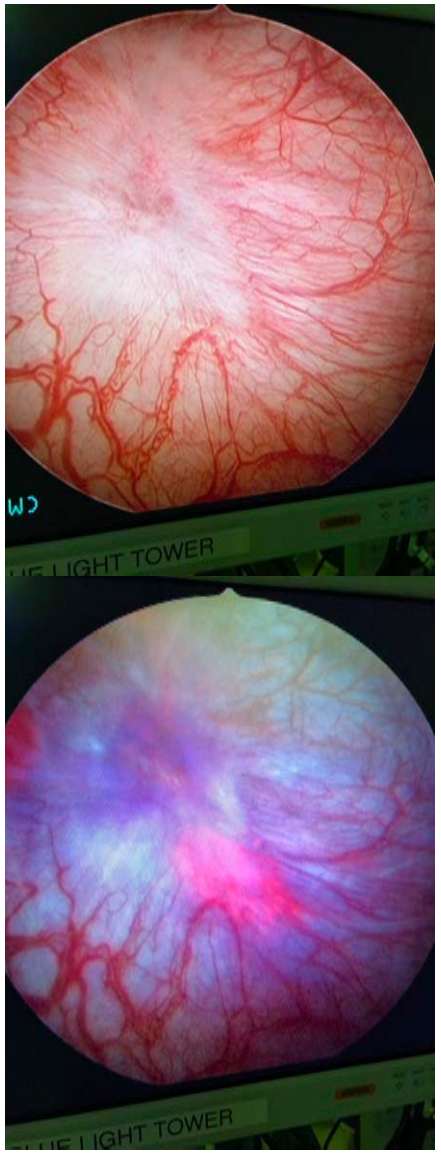
BCG Unresponsive Evaluation

- Solid H&P (voiding and EUA)
- How much BCG and when, anything else?
- Were they ever disease free?
- Could this be UTUC?
- Could it be prostatic?
- CIS or papillary? How much?



BCG Unresponsive Evaluation

- CT urogram (or RPGs)
- Path review?
- BLC (OR>office) Saphira
- Selection cytology of upper tracts
- Prostatic urethral biopsy
- Mapping biopsies



BCG Unresponsive BCa: Current Standards

Intravesical Options

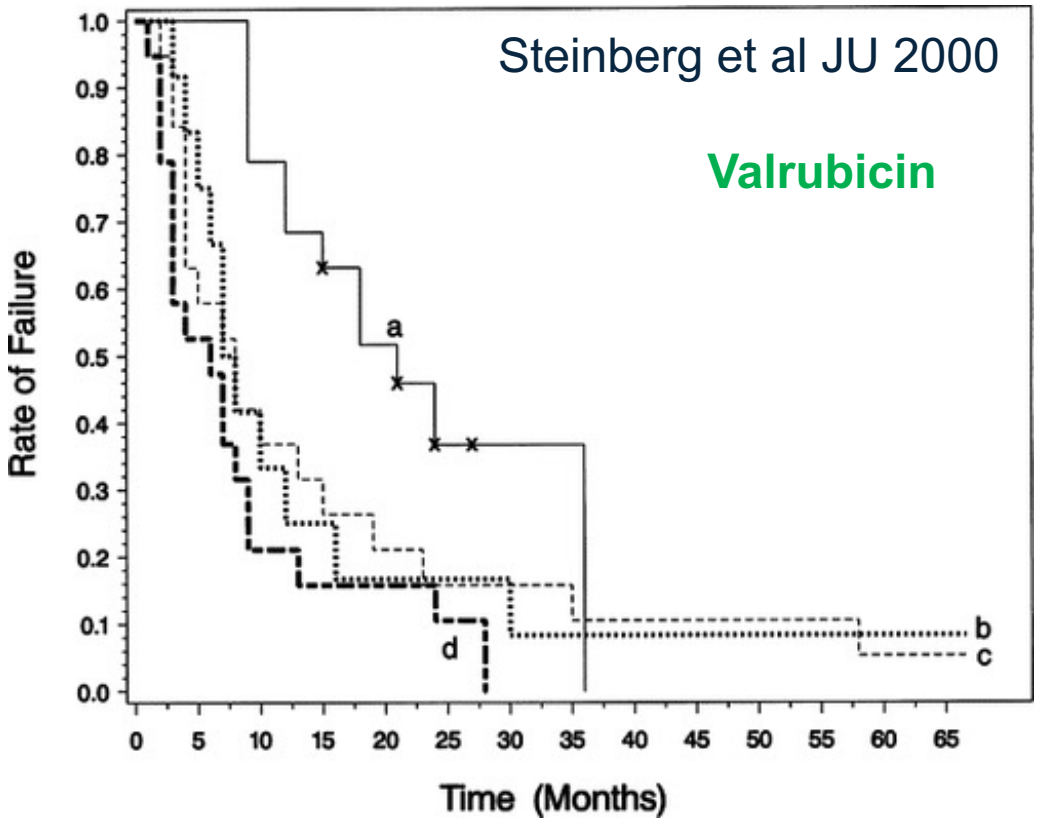
Single Agent Chemotherapy

Table 1 | **Results of intravesical chemotherapy after BCG failure**

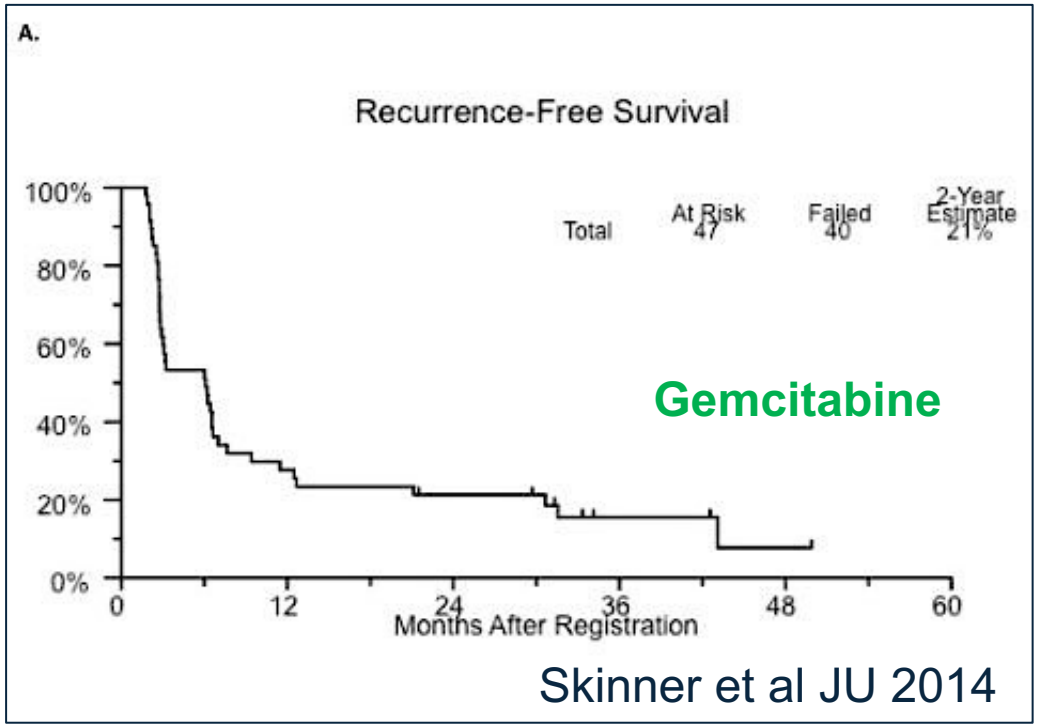
Agent	Outcomes	Studies
Valrubicin	18–21% disease free at 6 months	Steinberg *et al.*[42]
	16% disease free at 12 months	Dinney *et al.*[43]
Gemcitabine	21–28% disease free at 12 months	Dalbagni *et al.*[45]
	21% disease free at 24 months	Dalbagni *et al.*[46]
Docetaxel	40% disease free at 12 months	Laudano *et al.*[50]
Nab Paclitaxel	36% disease free at 12 months	McKiernan *et al.*[52]

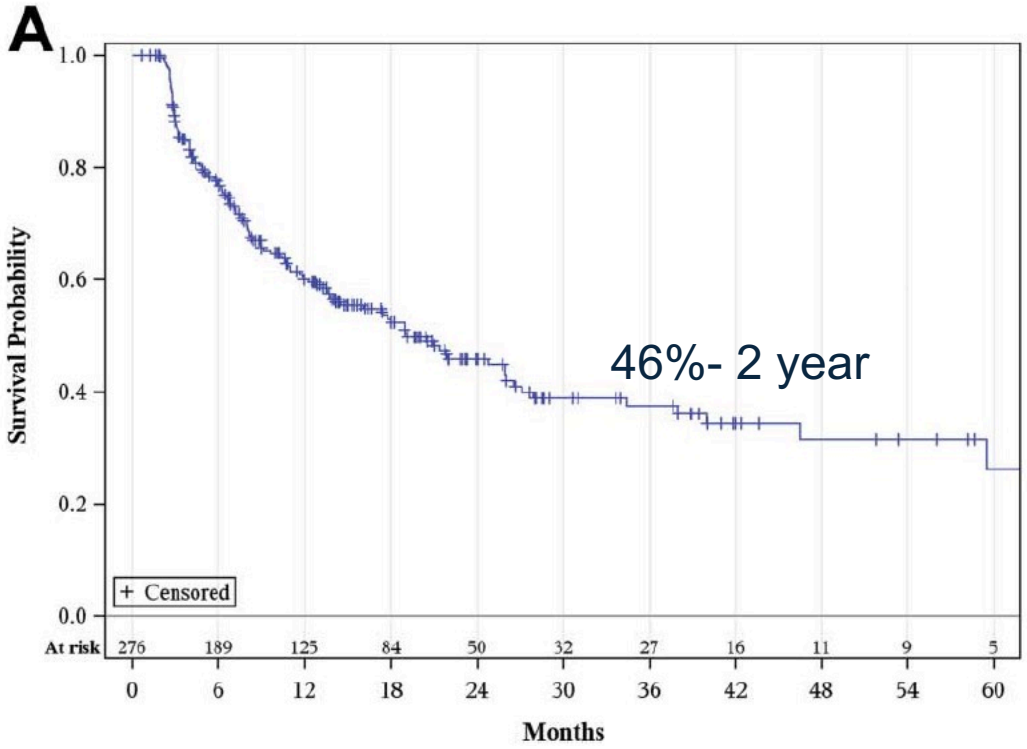
State of the Art Before CPI

90 patients, 19 complete responses (21%) @ 3 and 6 months
44/79 had a cystectomy
11/90 died
Led to FDA approval of valrubicin



47 patients
2 prior courses of BCG
21% Recurrence-free at 24 mo



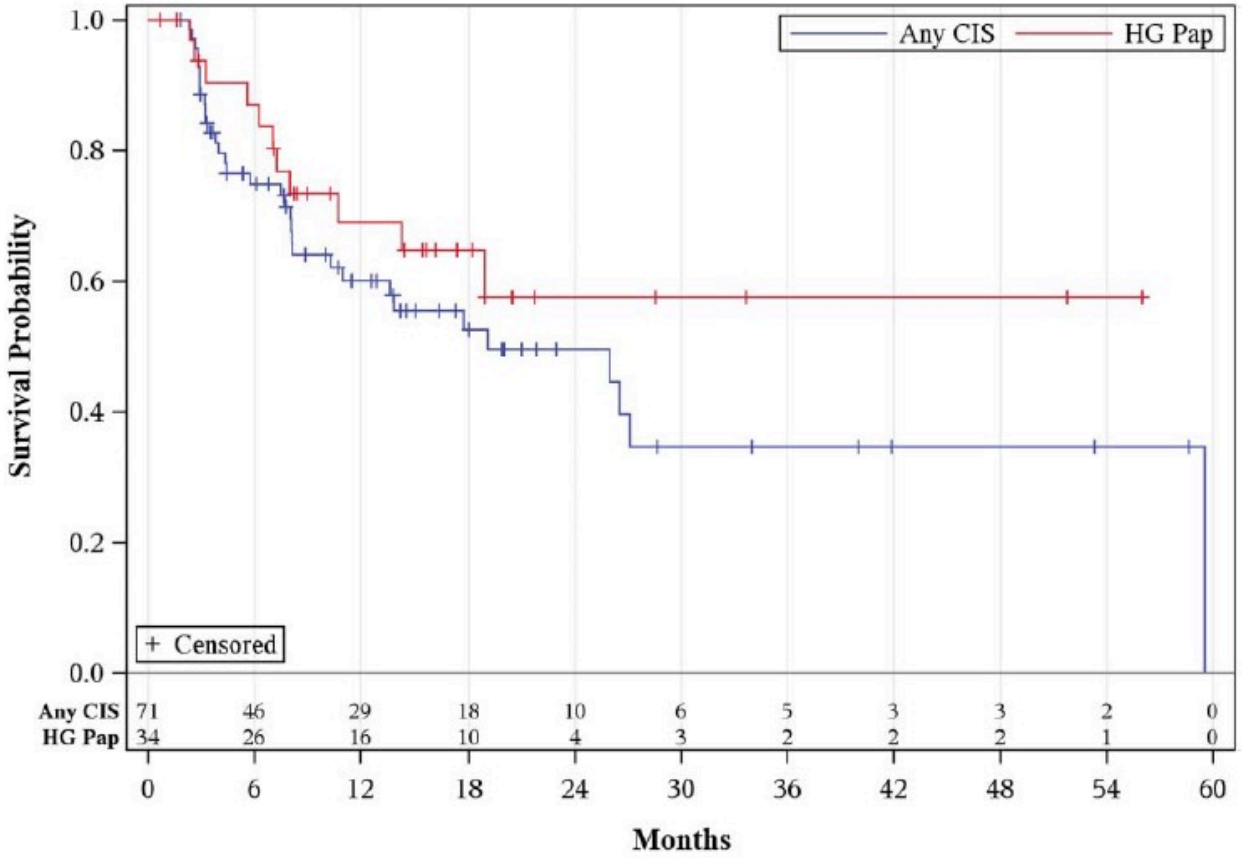


Side Effects of Gemcitabine/Docetaxel Intravesical Therapy

	Level	N = 276	%
Any Side Effects?	No	164	59.4
	Yes	112	40.6
Treatment Schedule Affected by SE?	No	248	90.6
	Yes	26	9.4
	Missing	2	-
Specific Side Effects			
Dysuria?	No	233	84.4
	Yes	43	15.6
Hematuria?	No	247	89.5
	Yes	29	10.5
Urinary Frequency/Urgency?	No	215	77.9
	Yes	61	22.1
Urinary Retention?	No	272	98.6
	Yes	4	1.4

9/276 stopped treatment (3.3%)

BCG Unresponsive

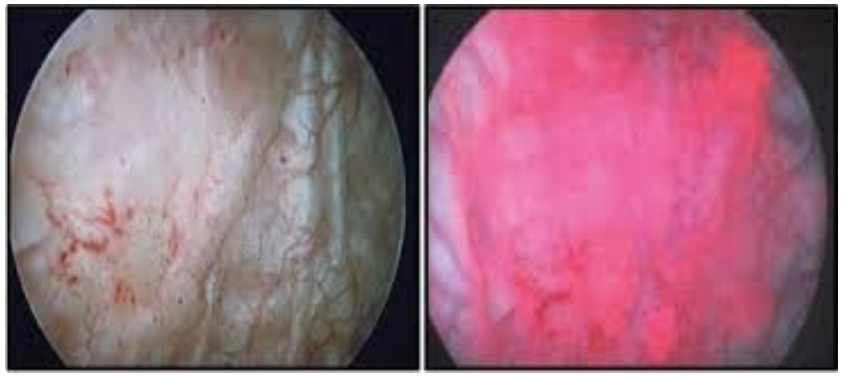
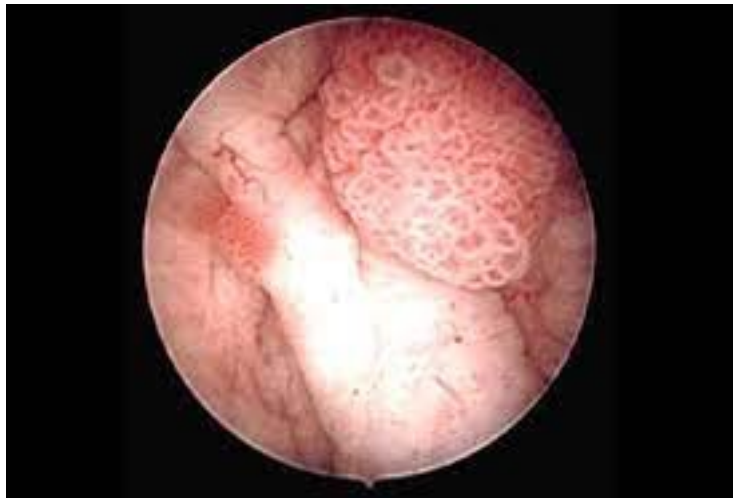


- 60% at 1 year, 46% at 2 years RFS
- 43 underwent RC for recurrence
- T0=7
- Ta-T1=24
- T2 or greater: 11; 11% N+

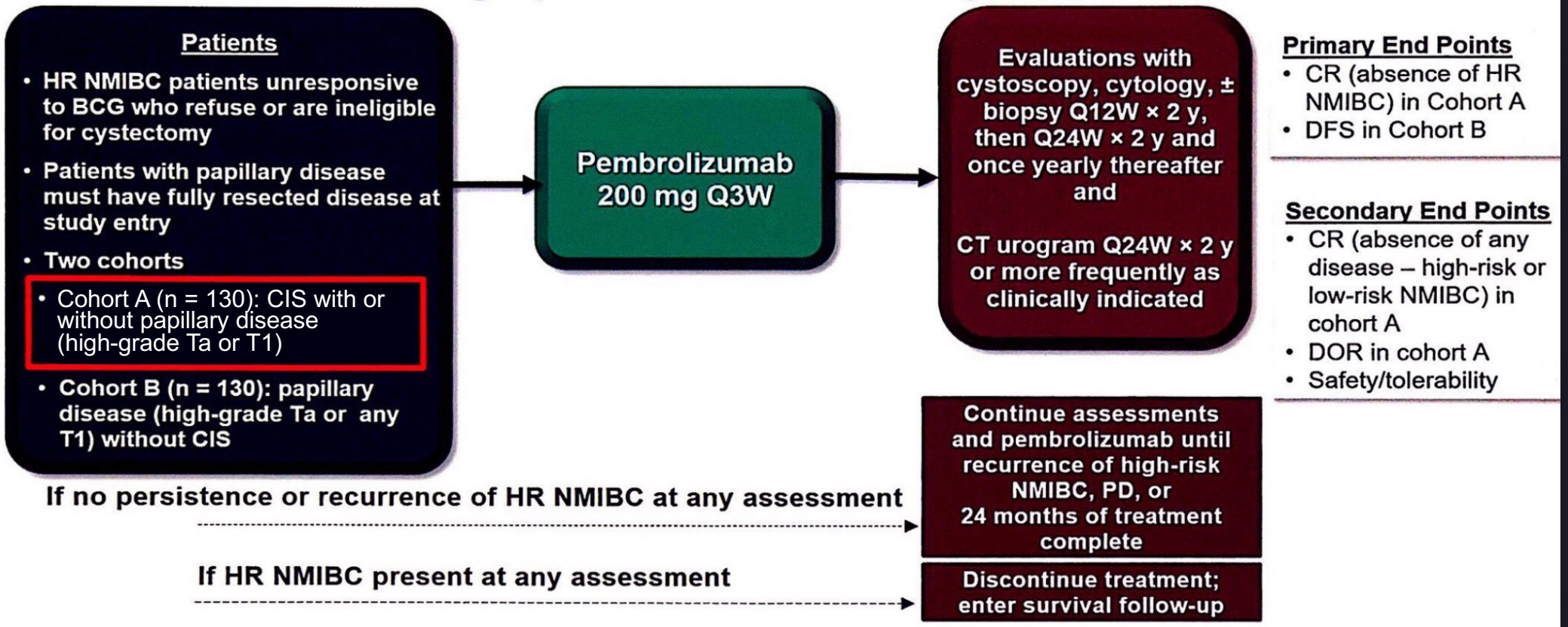
Steinberg RL et al. *J Urol* 2020;203(5):902-09.

Pembrolizumab (Checkpoint Immunotherapy)

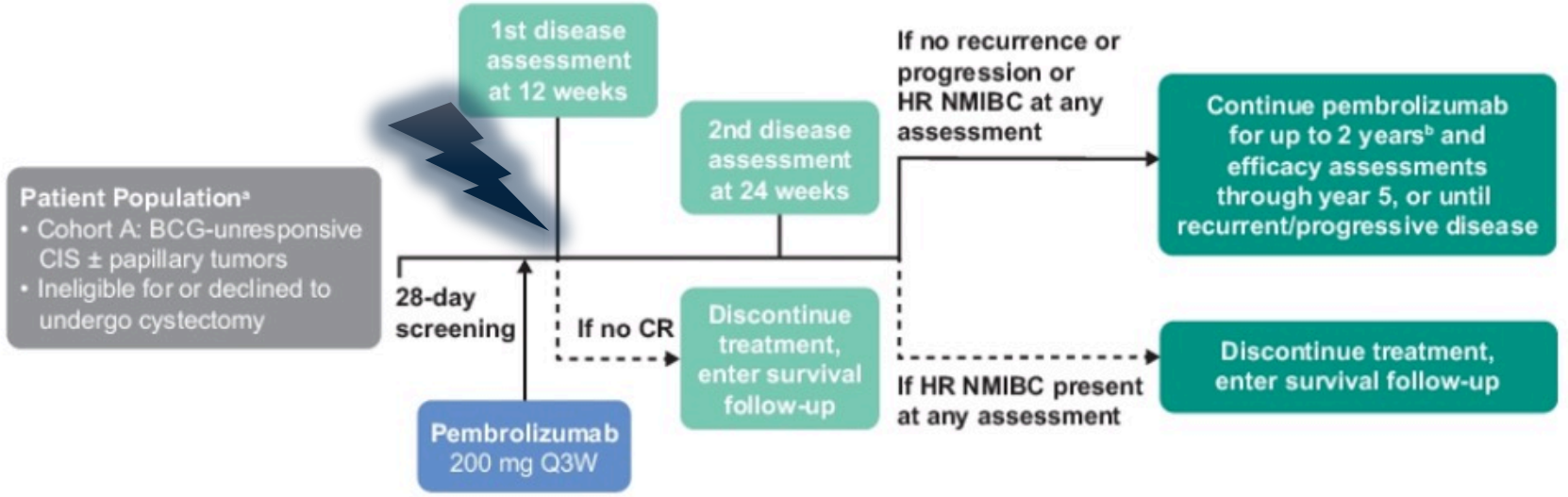
CIS *vs* Papillary NMIBC

Appearance	Disease State	Goal	Expectations	KN57
CIS- flat; ***NB- can also be papillary with CIS**				
	**Ca at start**	**Ca response** *Neg cyto, neg cysto*	**10-20%**	**A**
 papillary	**No Ca**	**No recurrence**	**20-40%**	**B**

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



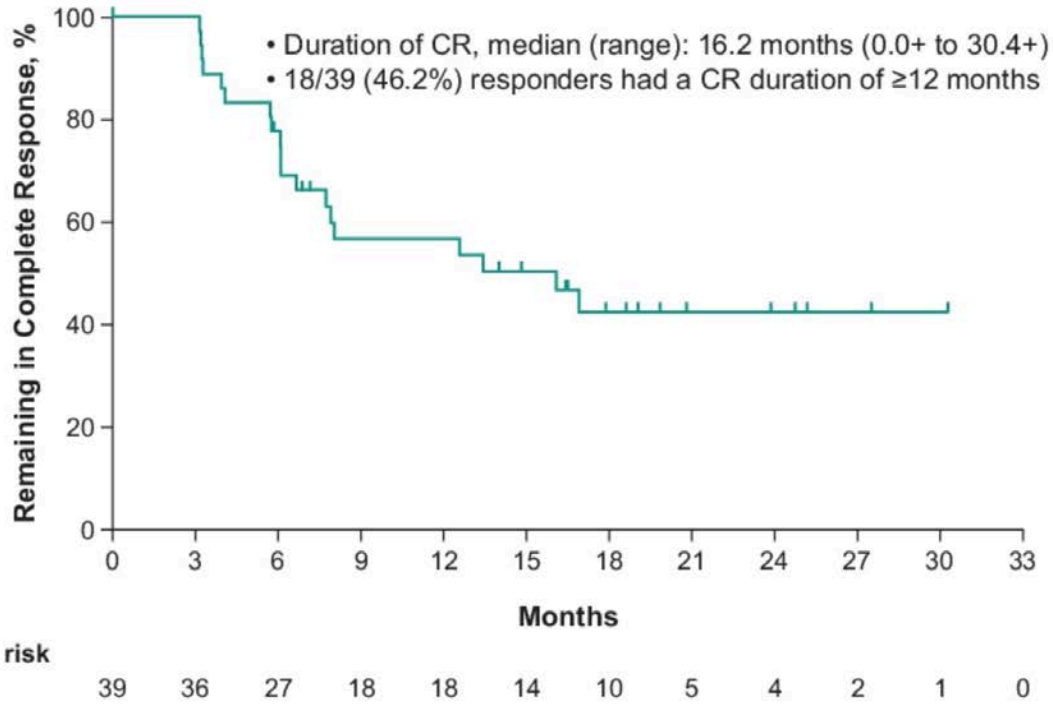
De Wit et al ESMO 2018



Primary End Point
- Complete response rate

Secondary End Points
- Duration of response[c]
- Progression-free survival
- Overall survival
- Safety

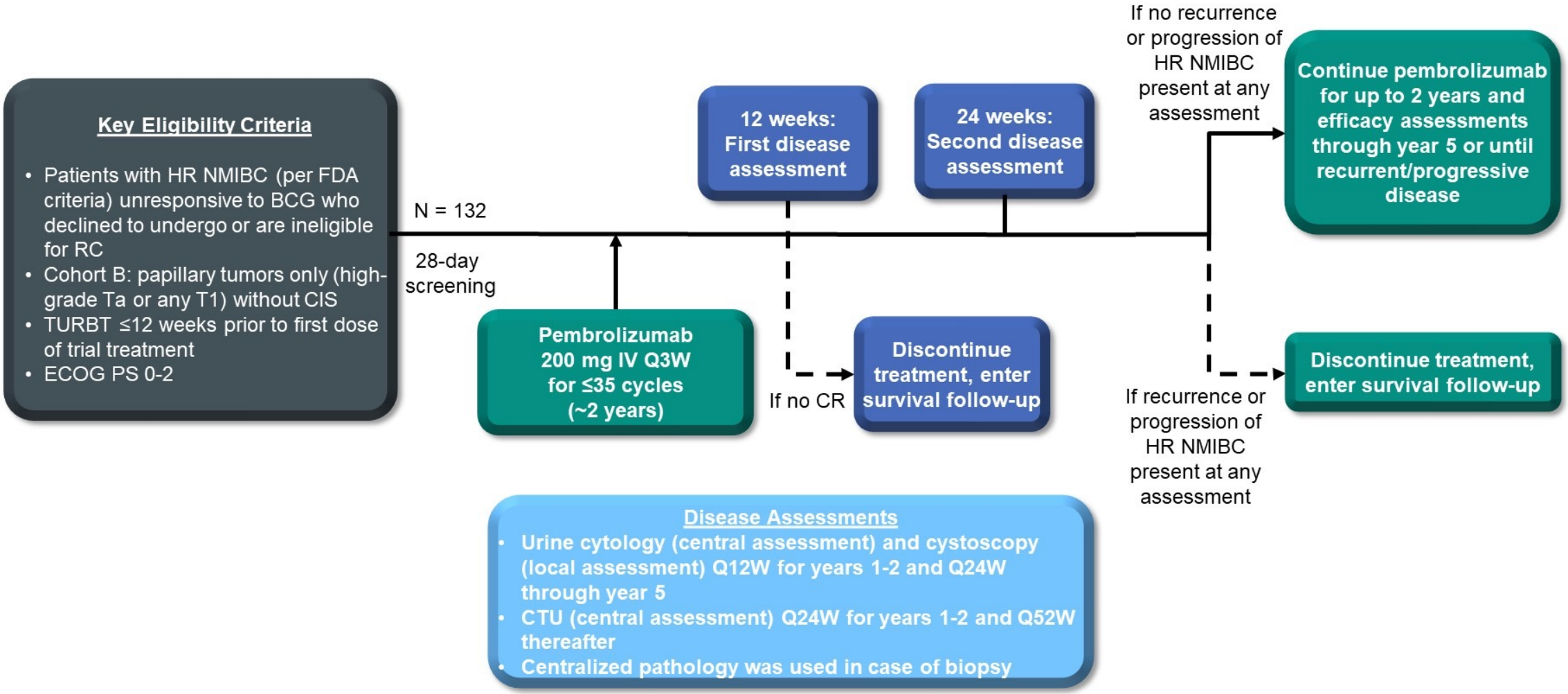
19%
Response
at 12 mo



" + " indicates ongoing response.

[a]Month 0 = time point when initial CR was achieved. The onset of response was 3 months for most patients.

KEYNOTE-057 Study Design: Cohort B



CTU, computed tomography urography; ECOG PS, Eastern Cooperative Oncology Group performance status.

Necchi A et al. *Genitourinary Cancers Symposium* 2023;Abstract LBA442.

Baseline Characteristics

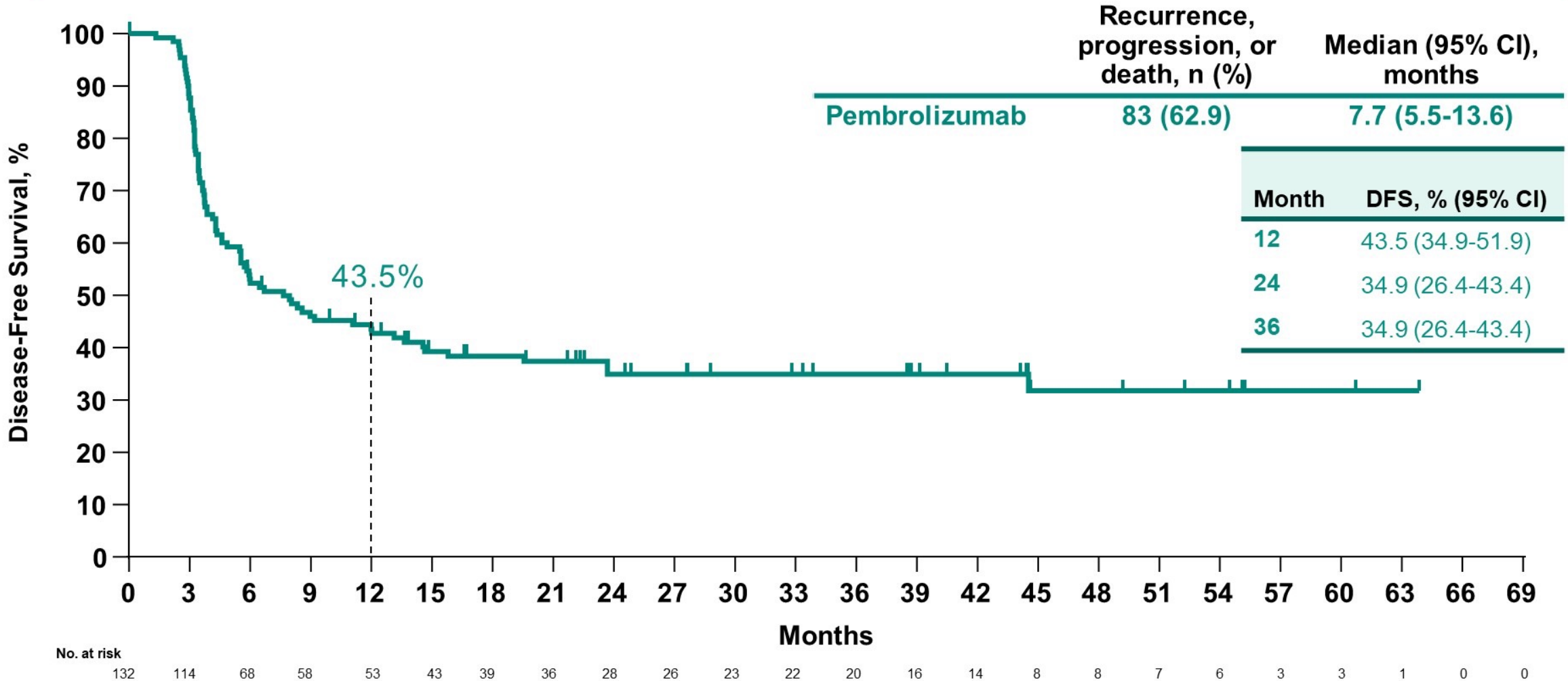
	Cohort B N = 132
Age, median (range), years	72 (37-87)
Male	104 (79)
Geographical region	
US	33 (25)
Non-US	99 (75)
Race	
Asian	22 (17)
Black or African American	2 (1)
White	87 (66)
Missing	21 (16)
ECOG PS	
0	101 (76)
1	28 (21)
2	3 (2)

	Cohort B N = 132
Prior instillations of BCG, median (range)	10 (6-33)
Urothelial histology	132 (100)
Tumor stage prior to study entry	
T1	57 (43)
High-grade Ta	75 (57)
Baseline HR NMIBC status	
Persistent HR NMIBC	35 (26)
Recurrent HR NMIBC	79 (60)
Progressive HR NMIBC	18 (14)

Values are n (%) unless otherwise noted. Data cutoff: October 20, 2022.

Necchi A et al. *Genitourinary Cancers Symposium* 2023;Abstract LBA442.

Disease-Free Survival for HR NMIBC[a]



	Recurrence, progression, or death, n (%)	Median (95% CI), months
Pembrolizumab	83 (62.9)	7.7 (5.5-13.6)

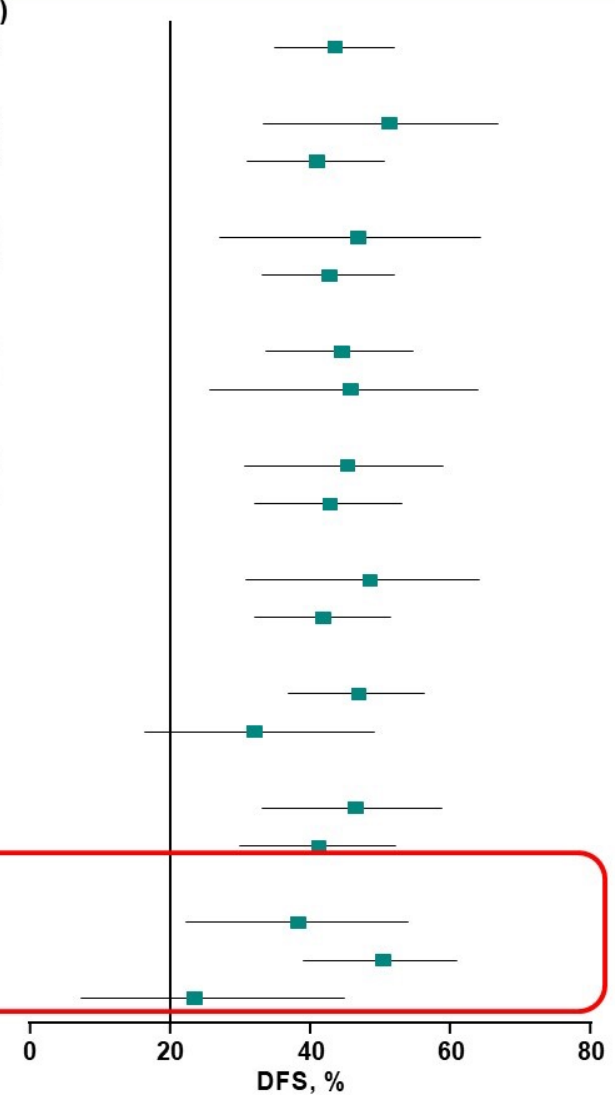
Month	DFS, % (95% CI)
12	43.5 (34.9-51.9)
24	34.9 (26.4-43.4)
36	34.9 (26.4-43.4)

[a]Per central pathology/radiology review. Data cutoff: October 20, 2022.

Necchi A et al. *Genitourinary Cancers Symposium* 2023;Abstract LBA442.

Subgroup Analysis of 12-Month DFS Rate for HR NMIBC by Baseline Characteristics

	Events, n/N	DFS, % (95% CI)
Overall	83/132	43.5 (34.9-51.9)
Age, years		
<65	18/33	51.3 (33.3-66.7)
≥65	65/99	40.9 (31.0-50.5)
Sex		
Female	15/28	46.8 (27.1-64.3)
Male	68/104	42.7 (33.0-52.0)
Race		
White	54/87	44.5 (33.7-54.7)
Non-White	15/24	45.8 (25.6-64.0)
Region (EU)		
EU	27/47	45.3 (30.5-58.9)
Non-EU	56/85	42.8 (32.1-53.0)
Region (US)		
US	23/33	48.5 (30.8-64.1)
Non-US	60/99	41.9 (32.0-51.5)
ECOG PS		
0	60/101	46.9 (36.8-56.3)
1/2	23/31	32.1 (16.4-49.1)
Tumor pattern at study entry		
T1	34/57	46.4 (33.1-58.8)
High-grade Ta	49/75	41.2 (29.9-52.2)
Baseline HR NMIBC disease status		
Persistent	24/35	38.2 (22.3-54.0)
Recurrent	44/79	50.4 (38.9-60.8)
Progressive	15/18	23.5 (7.3-44.9)



Data cutoff: October 20, 2022.

Necchi A et al. *Genitourinary Cancers Symposium* 2023;Abstract LBA442.

Pembrolizumab for BCG unresponsive NMIBC: Underused?

- Cost
- Infusion chairs
- “Systemic therapy”
- Possible toxicity
- Limited efficacy

Pembro for NMIBC (what I do)

- Offered for all, discuss side-effects
- Cysto in OR for BLC w mapping biopsies and cytology at 3 mo
- Best for those far from Chicago
- Good for those that have poor bladder capacity and function
- May make sense for recurrent T1 tumors
- Great for UTUC CIS (poor overall exposure to BCG)
- Move on after 3 mo if no response

What is on the horizon?

Urologists, You'll Never Walk Alone! How Novel Immunotherapy and Modern Imaging May Change the Management of Non–muscle-invasive Bladder Cancer

Gianluca Giannarini [a,], Neeraj Agarwal [b], Andrea B. Apolo [c], Alberto Briganti [d,e], Petros Grivas [f], Shilpa Gupta [g], Ashish M. Kamat [h], Francesco Montorsi [d,e], Morgan Rouprêt [i], Andrea Necchi [d,e,j]*

Note: this slide is purposefully hard to read

Table 1 – Phase 2 and 3 trials testing immune checkpoint inhibitors as single agents or in combinations for the treatment of high-risk NMIBC (searched at ClinicalTrials.gov)

Trial	Phase	Design	Enrolled population	Target number of participants	Experimental arm vs control arm	Route of ICI administration	Primary endpoint (s)
Single-agent							
NCT02625961 KEYNOTE-057	2	Single-arm assignment	BCG-unresponsive	260	Pembrolizumab	Intravenous	CRR, DFS rate
NCT02844816 SWOG 1605	2	Single-arm assignment	BCG-unresponsive	202	Atezolizumab	Intravenous	CRR at 25 wk for Cis, EFS at 18 mo
NCT02901548	2	Single-arm assignment	BCG-refractory Cis	17	Durvalumab	Intravenous	CRR at 6 mo
NCT03504163	2	Single-arm assignment	BCG-naïve	37	Pembrolizumab	Intravenous	Disease-free rate at 6 mo
NCT03759496	2	Single-arm assignment	BCG-refractory	39	Durvalumab	Intravenous	Maximum tolerated dose, high-grade relapse-free rate
NCT04738630	2	Single-arm assignment	BCG-unresponsive	110	HX008 (anti–PD-1 antibody)	Intravenous	CRR at 24 mo, EFS at 36 mo
Combined with BCG							
NCT03519256 CheckMate 9UT	2	Randomised, parallel assignment	BCG-unresponsive	358	Nivolumab vs Nivolumab + BCG vs Nivolumab + BMS-986205 vs Nivolumab + BMS-986205 + BCG	Intravenous	CRR in Cis, CR duration in Cis
NCT03528694 POTOMAC	3	Randomised, parallel assignment	BCG-naïve	1018	Durvalumab + BCG (I + M) vs Durvalumab + BCG (induction only) vs BCG (I + M)	Intravenous	DFS
NCT03711032 KEYNOTE-676	3	Randomised, parallel assignment	Recurrence/persistence after BCG induction (cohort A), BCG-naïve (cohort B)	1525	Cohort A Pembrolizumab + BCG (I + M) vs BCG (I + M) vs Cohort B Pembrolizumab + BCG (I + reduced M) vs Pembrolizumab + BCG (I + full M) vs BCG (I + M)	Intravenous	CCR (cohort A), EFS (cohort B)
NCT03799835 ALBAN	3	Randomised, parallel assignment	BCG-naïve	516	Atezolizumab + BCG (I + M) vs BCG (I + M)	Intravenous	RFS
NCT04149574 CheckMate 7G8	3	Randomised, parallel assignment	Recurrence/persistence after BCG	700	Nivolumab + BCG vs Placebo + BCG	Intravenous	EFS
NCT04165317 CREST	3	Randomised, parallel assignment	BCG-naïve	999	Sasanlimab + BCG (I + M) vs Sasanlimab + BCG (induction only) vs BCG (I + M)	Subcutaneous	EFS
Combined with other agents							
NCT04164082	2	Single-arm assignment	BCG-unresponsive	161	Pembrolizumab + intravesical gemcitabine	Intravenous	CRR at 6 mo (Cis), EFS at 18 mo
NCT04387461 CORE-001	2	Single-arm assignment	BCG-unresponsive	37	Pembrolizumab + intravesical CG0070 (oncolytic adenovirus)	Intravenous	CRR at 12 mo
NCT04640623	2	Randomised, parallel assignment	BCG-unresponsive	200	Cetrelimab + TAR-200 vs TAR-200 vs Cetrelimab	Intravenous	Overall CRR
NCT04730232	2	Single-arm assignment	BCG-naïve, not completely resectable	63	Tislelizumab + intravenous nab-paclitaxel	Intravenous	CRR at the time of TURBT
Combined with EBRT							
NCT03317158 ADAPT-BLADDER	1/2	Randomised, crossover assignment	Recurrence/persistence of intermediate-/high-risk NMIBC after BCG	186	Durvalumab + BCG vs Durvalumab + EBRT vs Retreatment with BCG	Intravenous	RFS at 6 mo
NCT03950362 PREVERT	2	Single-arm assignment	BCG-unresponsive	67	Avelumab + EBRT + avelumab	Intravenous	High-risk RFS at 1 yr

BCG = bacillus Calmette-Guérin; BMS-986205 = inhibitor of indoleamine 2,3-dioxygenase 1; Cis = carcinoma in situ; CR = complete response; CRR = complete response rate; DFS = disease-free survival; EBRT = external beam radiation therapy; EFS = event-free survival; I + M = induction plus maintenance; ICI = immune checkpoint inhibitor; NMIBC = non–muscle-invasive bladder cancer; RFS = recurrence-free survival; TAR-200 = intravesical gemcitabine delivery system; TURBT = transurethral resection of bladder tumour.

Trial number	Phase	Design	Enrolled population	Target number of participants	Experimental arm vs control arm	Route of administration	Primary endpoint(s)
NCT00794950	2	Single-arm assignment	BCG-naïve	43	BCG (induction) + sunitinib	Oral	CRR at 3 mo
NCT01373294	2	Nonrandomised, parallel assignment	BCG-naïve	17	Lenalidomide + BCG vs BCG	Oral	PFS
NCT02015104	2	Randomised, parallel assignment	BCG-failure after ≥1 induction course	32	BCG (induction) + PANVAC vs BCG (induction)	Subcutaneous	RFS
NCT02138734	3	Randomised, parallel assignment	BCG-naïve Cis (cohort A), high-grade Ta/T1 (cohort B)	596	N-803 (IL-15 superagonist complex) + BCG vs BCG	Intravesical	CRR at 12 mo (cohort A), DFS at 24 mo (cohort B)
NCT02365818	2	Single-arm assignment	BCG-unresponsive	66	CG0070 (engineered oncolytic adenovirus)	Intravesical	Durable CRR
NCT02449239	3	Single-arm assignment	BCG-unresponsive	134	Vicinium (antibody-drug conjugate)	Intravesical	CRR (Cis)
NCT02773849	3	Single-arm assignment	BCG-unresponsive	157	Nadofaragene firadenovec	Intravesical	CRR at 12 mo (Cis)
NCT02982395	3	Randomised, parallel assignment	BCG-refractory	36	Docetaxel vs intravesical MMC	Intravesical	RFR at 12 mo
NCT03022825 QUILT-3.032	2/3	Single-arm assignment	BCG-unresponsive	180	N-803 (IL-15 superagonist complex) + BCG	Intravesical	CR (cohorts A and C), DFR at 12 mo (cohort B)
NCT03664869	3	Randomised, parallel assignment	BCG-naïve	300	Sequential BCG + MMC (I + M) vs BCG (I + M)	Intravesical electromotive	Bladder cancer recurrence
NCT03719300	2	Single-arm assignment	BCG-unresponsive	32	BC-819 (inodiftagene vixteplasmid)	Intravesical	CRR at 12 wk (Cis)
NCT03945162	2	Single-arm assignment	BCG-unresponsive	125	TLD1433 (ruthenium-based photosensitiser)	Intravesical	CRR at 12 mo
NCT04172675	2	Randomised, parallel assignment	BCG-unresponsive with FGFR mutations or fusions (cohort 1)	280	Erdafitinib vs Intravesical gemcitabine or MMC/ hyperthermic MMC	Oral	RFS
NCT04311580	2	Single-arm assignment	BCG failure	52	MMC	Intravesical electromotive	Time to first recurrence
NCT04386746	2	Single-arm assignment	BCG-naïve	26	Gemcitabine + docetaxel	Intravesical	CRR at 3 mo
NCT04452591	3	Single-arm assignment	BCG-unresponsive	110	CG0070 (engineered oncolytic adenovirus)	Intravesical	CRR (Cis)
NCT04490993	3	Randomised, parallel assignment	Intermediate/high-risk chemorefractory NMIBC	359	APL-1202 + intravesical epirubicin vs Placebo + intravesical epirubicin	Oral	EFS
NCT04498702	2	Single-arm assignment	Relapse after intravesical chemotherapy or BCG	41	APL-1202	Oral	RFR at 12 mo
NCT04859751	3	Single-arm assignment	BCG-unresponsive	53	VB4-845 (antibody-drug conjugate)	Intravesical	CRR at 6 mo

APL-1202 = methionine aminopeptidase II inhibitor; BCG = Bacillus Calmette-Guérin; Cis = carcinoma in situ; CR = complete response; CRR = complete response rate; DFR = disease-free rate; EFS = event-free survival; I + M = induction plus maintenance; MMC = mitomycin C; NMIBC = non–muscle-invasive bladder cancer; PANVAC = recombinant virus vector vaccine containing genes for human carcinoembryonic antigen and mucin-1, and three co-stimulatory molecules; PFS = progression-free survival; RFR = recurrence-free rate; RFS = recurrence-free survival.

Pembro is just the beginning….

Giannarini G et al. *Eur Urol Oncol* 2022 Jun;5(3):268-72.

POTOMAC Trial Design

Non-Muscle Invasive Bladder Cancer

STATUS: Done, Awaiting Results

NMIBC BCG Naïve
- T1 tumor
- HG/G3
- CIS
- Multiple and recurrent and large (>3cm) Gr1/Gr2 Ta tumors (all 3 should meet)

Stratification Factors
- Higher risk papillary disease (yes versus no)
- CIS (yes versus no)

Higher Risk:
– T1G3, OR
– Multiple AND recurrent AND large (with diameter of largest evaluable node ≥3 cm) tumors

R
N = 975
1:1:1

Arm A
Durva + BCG (I + M)
(N = 325)

BCG induction X 6 cycles	3m	6m	12m	18m	24m
Durvalumab Q4 weeks	→ 12m				

Arm B
Durva + BCG (I only)
(N = 325)

BCG induction X 6 cycles
Durvalumab Q4 weeks → 12m

Arm C
BCG (I + M)
(N = 325)

BCG induction X 6 cycles	3m	6m	12m	18m	24m

Primary endpoint: DFS
Secondary endpoints:
- **DFS at 24 months**
- **OS at 5 yrs**

Note: *BCG re-induction at 3 months for persistent disease. Durva 1500mg IV Q4 wks; BCG 50mg intra-vesically for 2 years

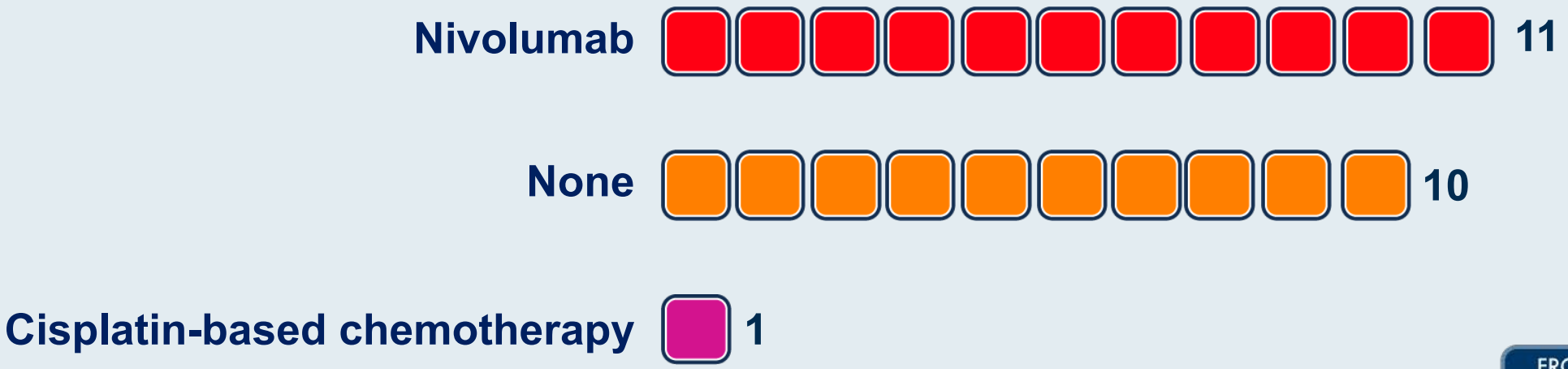
Critical questions-

- Will patients opt for systemic therapy?
- Will the known toxicity of CPIs affect use?
- Will we identify biomarkers for patient selection?

MODULE 2: Contemporary Management of Muscle-Invasive Bladder Cancer (MIBC)

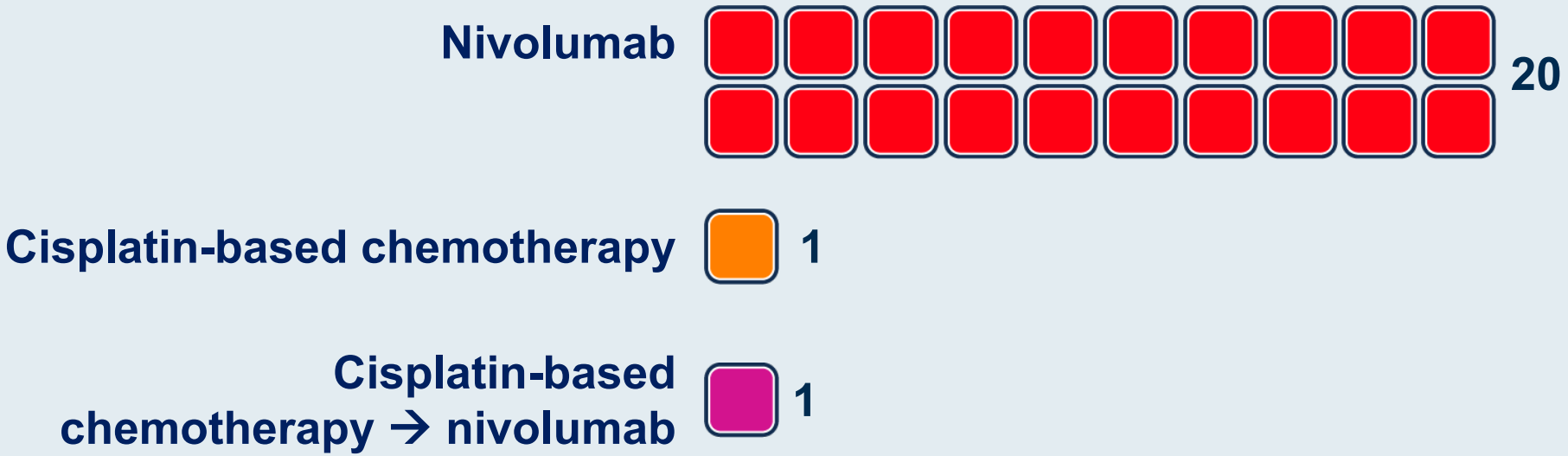
RTP
RESEARCH
TO PRACTICE

A 74-year-old man presents with a history of hematuria, and office cystoscopy shows a large papillary lesion. He undergoes TURBT, which shows T2 transitional cell carcinoma (TCC), and receives neoadjuvant chemotherapy with gemcitabine/cisplatin followed by robotic cystectomy with ileal conduit. Pathology reveals pT2apN0 with negative margins. Regulatory and reimbursement issues aside, which adjuvant systemic therapy, if any, would you recommend?



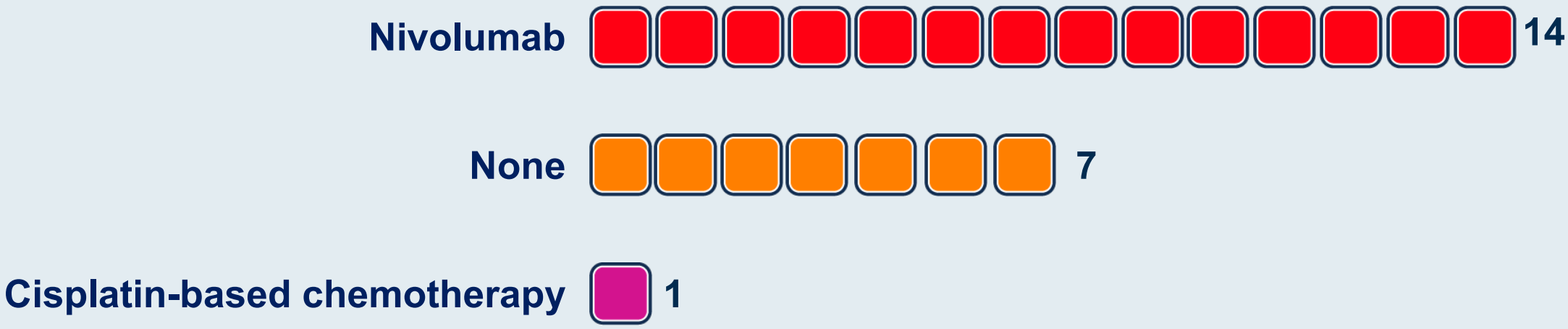
Survey of urologic oncology clinical investigators

An 84-year-old man presents with a 4-cm bladder mass consistent with T2 UBC. Metastatic evaluation is negative. He receives neoadjuvant chemotherapy with gemcitabine/cisplatin followed by robotic cystectomy with ileal conduit. Pathology reveals T3aN1 and 2/16 positive lymph nodes. Regulatory and reimbursement issues aside, which adjuvant systemic therapy, if any, would you recommend?



Survey of urologic oncology clinical investigators

A 67-year-old woman with pT2 UBC and hydronephrosis, suggesting cT3 disease, receives neoadjuvant gemcitabine/cisplatin x 6 and undergoes cystectomy with residual T2 disease. Regulatory and reimbursement issues aside, which adjuvant systemic therapy, if any, would you recommend?



Survey of urologic oncology clinical investigators

AUA 2023

CHICAGO ★ APR 28-MAY 1

Satellite symposium: management of BCa

Contemporary management of MIBC

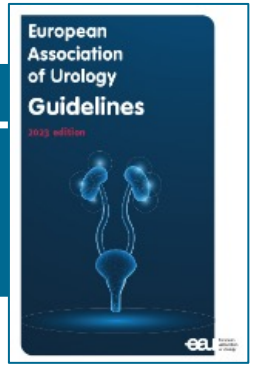
Prof Fred Witjes, Nijmegen, NL
April 30, 2023

1. Clinical and biologic factors that confer a high risk of recurrence in patients with MIBC

- Pathological stage and nodal involvement
- Response to neoadjuvant (chemo)therapy
- Histological subtypes is unclear (is it stage?), except small cell/neuro-endocrine
- Markers……
- Gender (stage?), smoking
- ……

Summary of evidence

There is insufficient evidence to use TMB, molecular subtypes, immune- or other gene expression signatures for the management of patients with urothelial cancer.



Stage and nodal involvement

- Hautman et al: Radical cystectomy for UC in the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients

stage

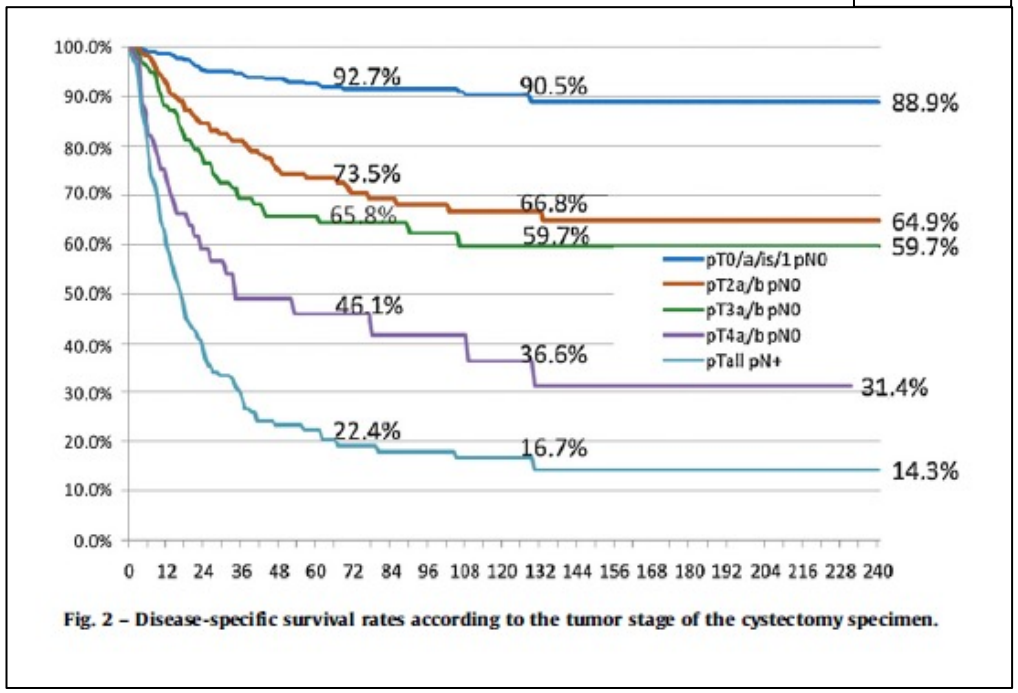


Fig. 2 – Disease-specific survival rates according to the tumor stage of the cystectomy specimen.

nodes

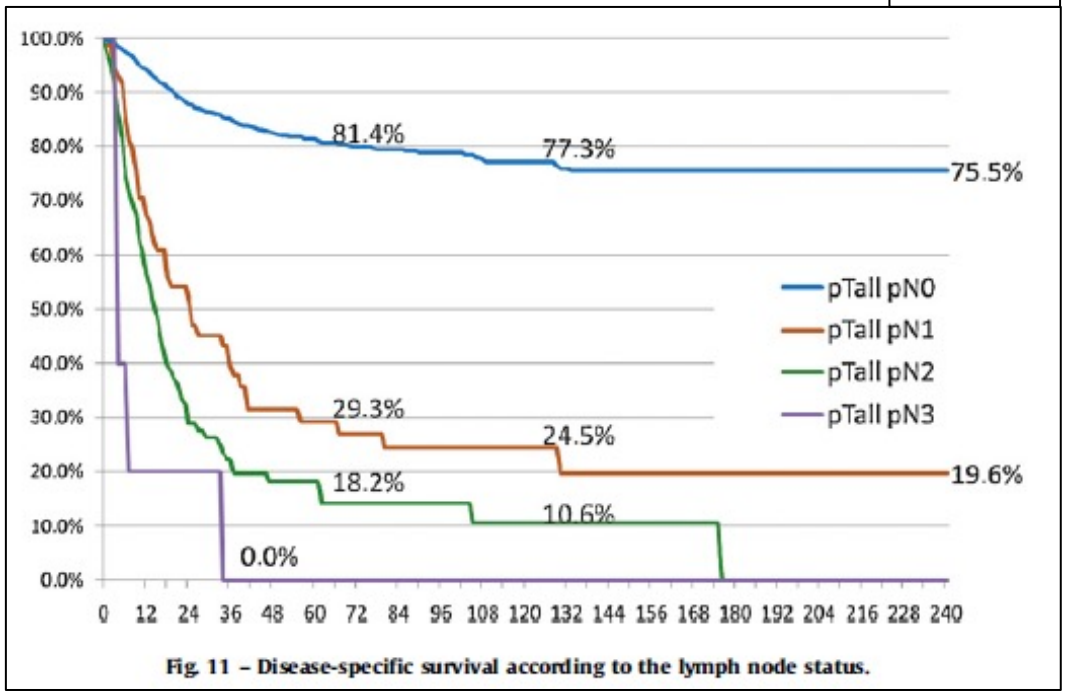


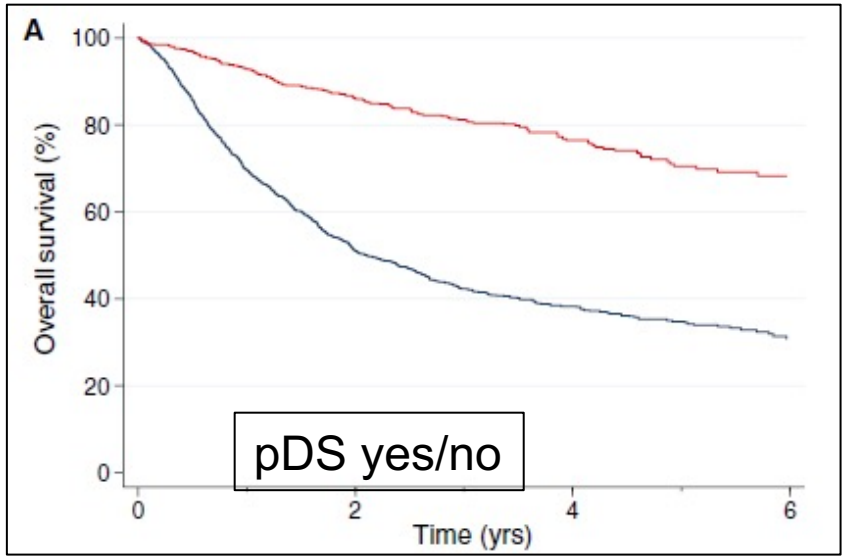
Fig. 11 – Disease-specific survival according to the lymph node status.

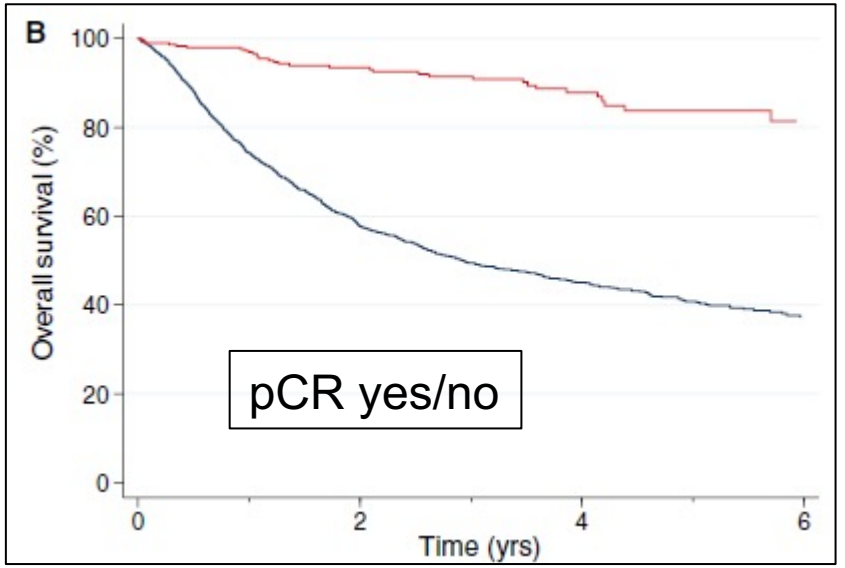
Hautman et al, EurUrol 61 (2012:1039-1047

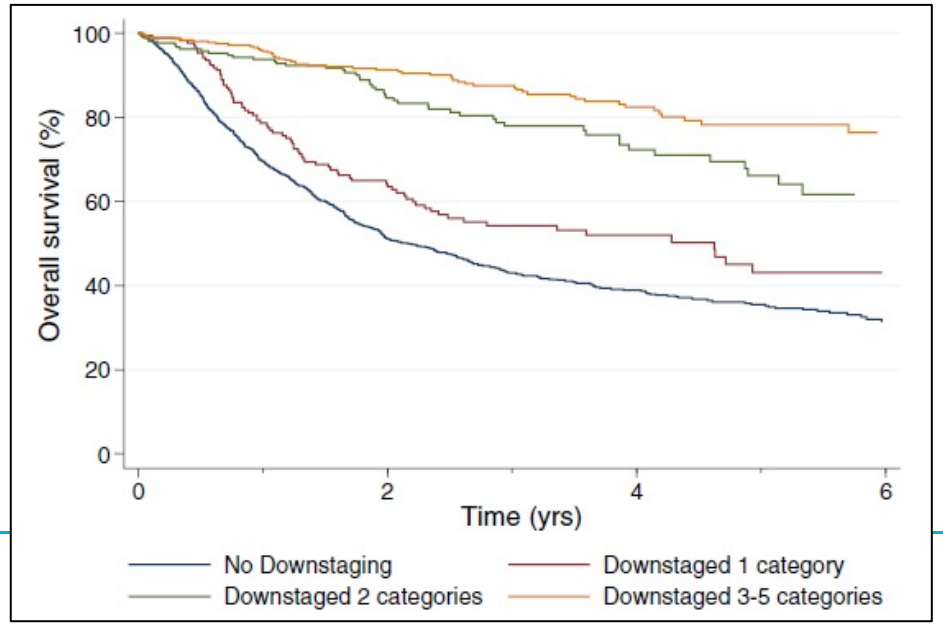
Radboudumc

Downstaging after NAC

- Retrospective, cT2-4N0M0, >2,200 pts
- Endpoint: OS and pathological downstaging (pDS) and pCR
- Results
  - NAC induces pDS +2.07-fold (*P* < .001) compared to RC alone
  - pCR (ypT0) does better than pDS
  - No response does very bad
  - A decrease cT→pT ≥1 point associated with improved OS



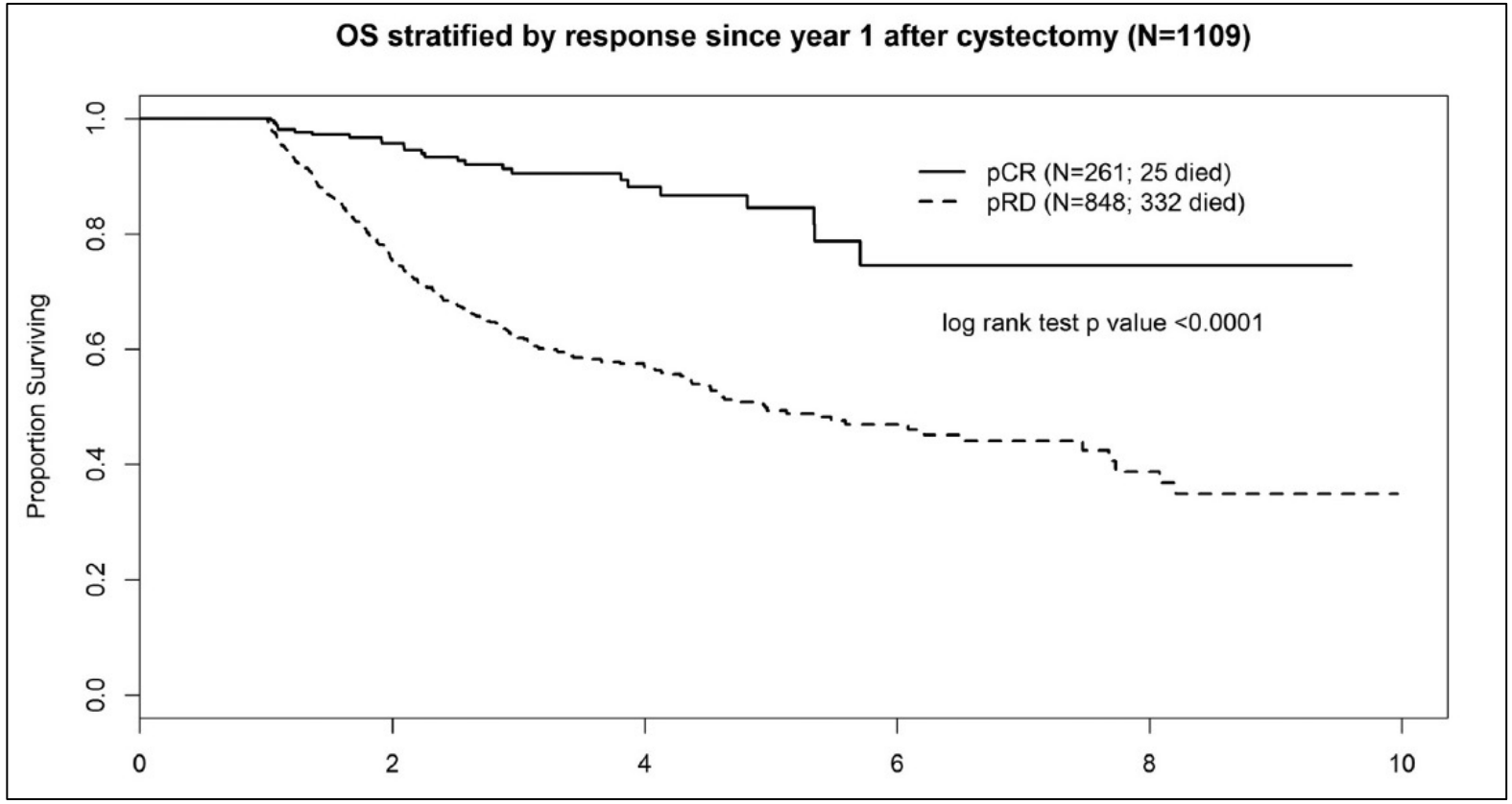




Martini et al, Cancer 2019;125:3155-63

Radboudumc

Downstaging after NAC



- Overall
  - No response: OS <40%
  - Response: OS 70-80%

N. Waingankar et al. Urol Oncol. (2019) 572.e21–572.e28

Radboudumc

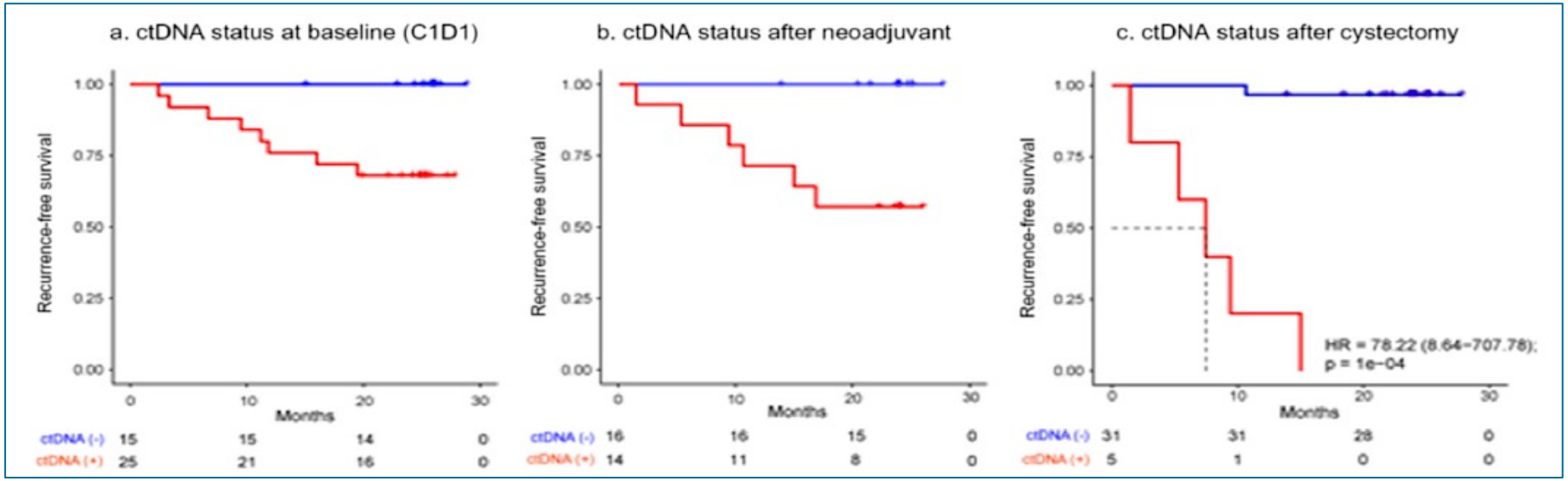
2. ypT0 and other clinically relevant endpoints in early neoadj IO trials

Neoadjuvant phase 2 trials *(2018–2022)*

	chemo		Immuno (combi's)			Chemo and immuno			ADC
	ddMVAC VESPER	GC VESPER	PURE-01	ABACUS	NABUCCO	BLASST-1	SAKK 06/17	LCCC1520	EV 103
Ref	Eur Urol 2020	Eur Urol 2020	JCO 2018	NatMed 2019	ESMO 2019	ASCO GU 2020	ASCO GU 2021	ASCO GU 2021	ASCO GU 2022
Therapy	ddMVAC (x6)	GC	Pembro	Atezo	Nivo+Ipi	Nivo+GC	Durva+GC	Pembro+ Split-Cis/G	EV mono
N=	218	219	80 (UC)	88	24	41	58	39	22
cT2	90%	95%	51%	73%	0	90%	69%%	72%	68%
cN+	0	0	0	0	42%	3%	17%	0	0%
ypT0	**42%**	**36%**	**39%**	**31%**	**46%**	**34%**	**34%**	**36%**	**34%**
ypT≤1	**63%**	**49%**	**56%**	**n.a.**	**58%**	**66%**	**60%**	**56%**	**50%**

Neoadjuvant immunotherapy

- ABACUS: single arm phase II, 2 cycles **Atezolizumab** in 95 pts (Szabados et al., EurUrol 2022;82:212-22)
  - pCR (1st endpoint) was 31%
  - Two-year DFS in patients achieving a pCR was 85%.
  - The ctDNA status was highly prognostic at all time points: no relapses were observed in ctDNA-negative patients at baseline and after neoadjuvant therapy.



Neoadjuvant immunotherapy

- PURE-01: single arm phase II, 3 cycles **Pembrolizumab** in 114 pts (Necchi et al, Eur Urol 2020)
  - ypT0 (1st endpoint) was 37%; pT≤1 (2nd endpoint) was 55% (6/7 in SCC!)
  - **But only PD-L1 CPS and TMB correlated with response**

Covariate	pT0			pT ≤ 1		
	OR	95% CI	*p* value[a]	OR	95% CI	*p* value[a]
TMB (continuous)	1.06	1.01–1.13	0.03	1.10	1.03–1.19	0.01
PD-L1 CPS (continuous)	1.02	1.01–1.04	0.002	1.02	1.01–1.04	0.01
Histology						
Nonpredominant VH (Ref. UC)	1.25	0.32–4.76	0.3	1.17	0.29–5.16	0.8
Predominant VH (Ref. UC)	0.25	0.04–1.05		0.71	0.21–2.30	

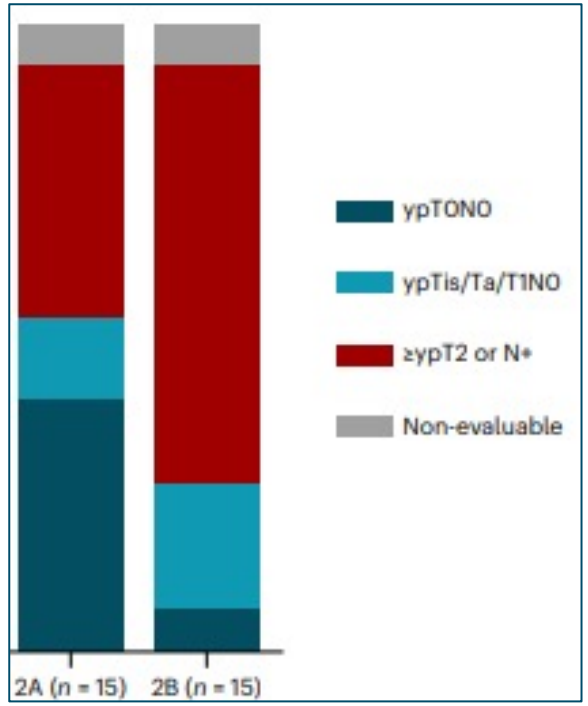
NABUCCO update *(van Dorp et al, short communication Nat Med 2023)*

- Neoadjuvant **ipi/nivo** (cohort 2A 3-1 mg/kg versus cohort 2B 1-3 mg/kg) followed by nivo 3 mg/kg

- Results: pathological CR in 6/15 (43%, cohort A) vs 1/15 pt (7%, cohort B)

- Markers
  - Absence of urinary ctDNA correlated with pCR in bladder but not with PFS
  - **Absence of plasma ctDNA correlated with pCR (OR 45.0, CI 4.9–416.5) and PFS (HR 10.4, CI 2.9–37.5).**

- Author conclusion:
  - high-dose ipilimumab plus nivolumab is required in stage III UC
  - **absence of ctDNA in plasma can predict PFS**



3. Long-term efficacy/safety from the Phase III CheckMate 274 trial comparing nivolumab to placebo after radical surgery for high-risk MIBC

Study design CheckMate 274

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

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 randomization

Stratification factors

- Tumor PD-L1 status (≥ 1% vs < 1% or indeterminate)[b]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

Median (range) follow-up[c] (ITT population),
36.1 (0.0-75.3) months (37.4 months for NIVO, 33.9 months for PBO)
Minimum follow-up[d] (ITT population), 31.6 months
Median (range) follow-up[c] (PD-L1 ≥ 1% population),
37.1 (0.0-75.3) months (39.8 months for NIVO, 33.3 months for PBO)
Database lock, October 20, 2022

Primary endpoints: DFS in all randomized patients (ITT population) and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[e]
Exploratory endpoints included: DMFS, PFS2, safety, HRQoL

[a]NCT02632409. [b]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the validated Dako PD-L1 IHC 28-8 pharmDx immunohistochemistry assay. [c]Defined as time between randomization date and last known date alive (for patients who are alive) and death. [d]Defined as time from clinical cut-off date to last patient's randomization date. [e]OS will be assessed at a future database lock. OS and DSS data are not presented.
DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IV, intravenous; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PFS2, second progression-free survival; Q2W, every 2 weeks; R, randomized.

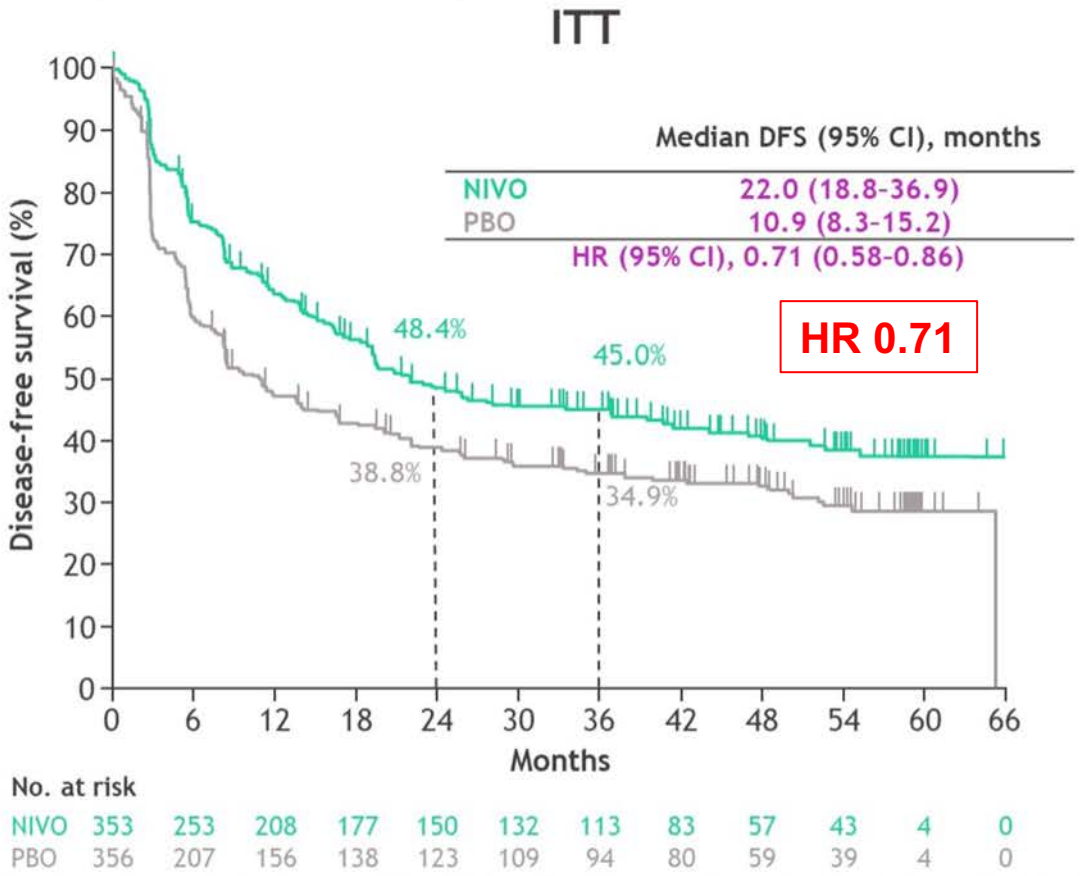
Patients were indeed at high risk for recurrence

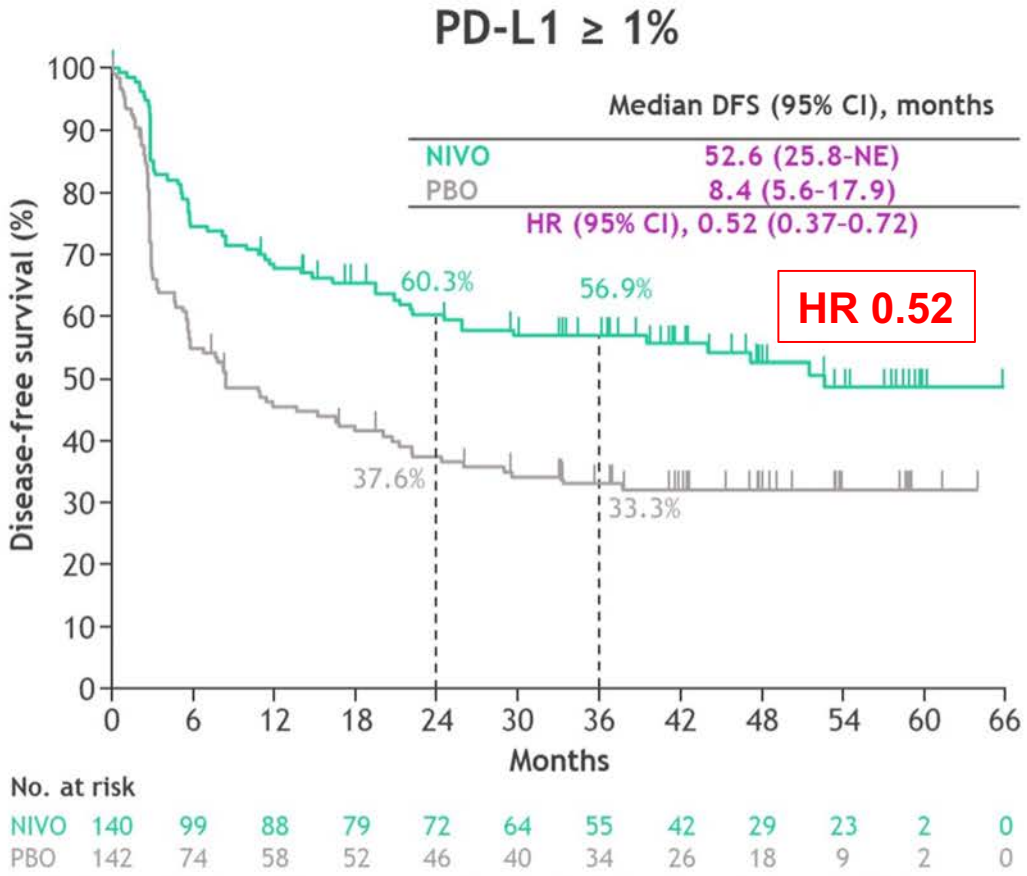
	NIVO (N = 353)	PBO (N = 356)
Mean age (range), years	65.3 (30–92)	65.9 (42–88)
Region, % United States	13.9	14.9
Europe	48.2	48.0
Asia	22.7	20.8
Rest of the world	15.3	16.3
Tumor origin at initial diagnosis, %		
Urinary bladder	79.0	78.9
Upper tract disease	21.0	21.1
PD-L1 ≥ 1% by IVRS, %	39.7	39.9
Prior neoadjuvant cisplatin, %	43.3	43.5
pT stage at resection, % pT0–2	22.7	24.2
pT3	58.4	57.3
pT4a	16.1	17.4
N+ status at resection, %	47.3	47.2

~75%

Disease-free survival (latest update, ASCO 2023)

- Continued DFS benefit was observed with NIVO versus PBO both in the ITT and tumor PD-L1 expression ≥ 1% populations

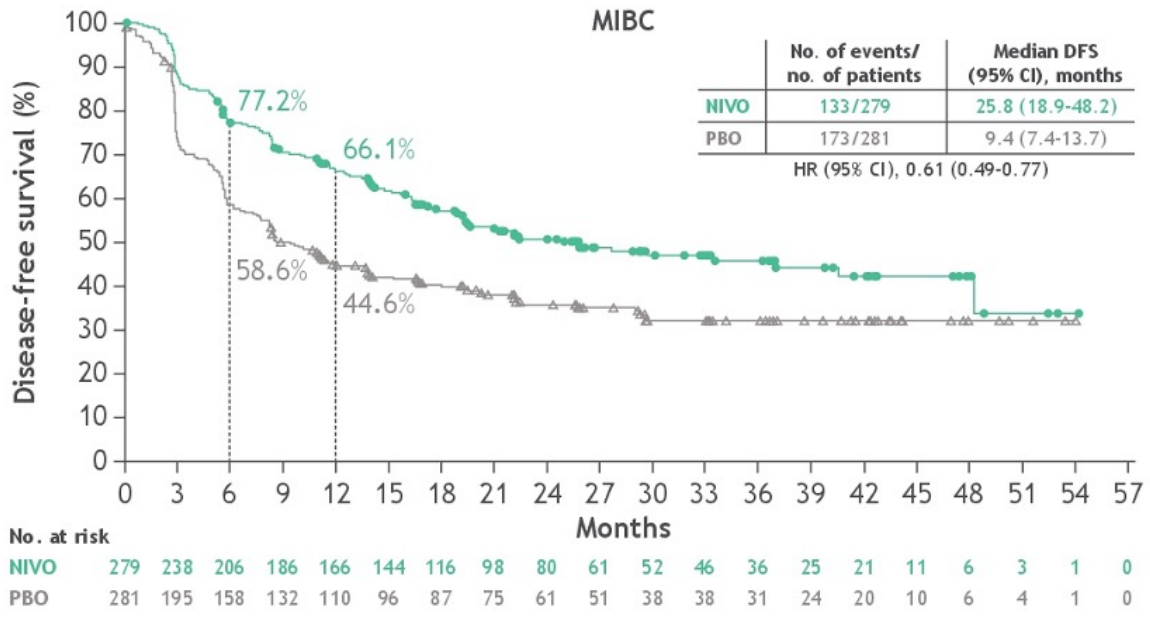




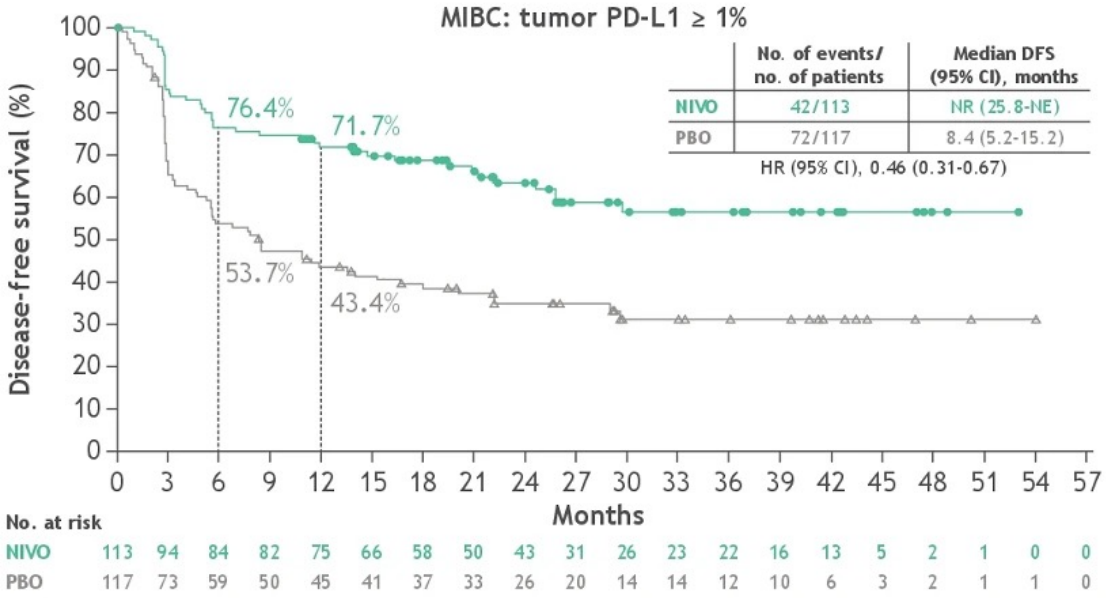
Minimum follow-up in the ITT population, 31.6 months. DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
NE, not estimable.

BCa only

HR 0.71 → 0.61



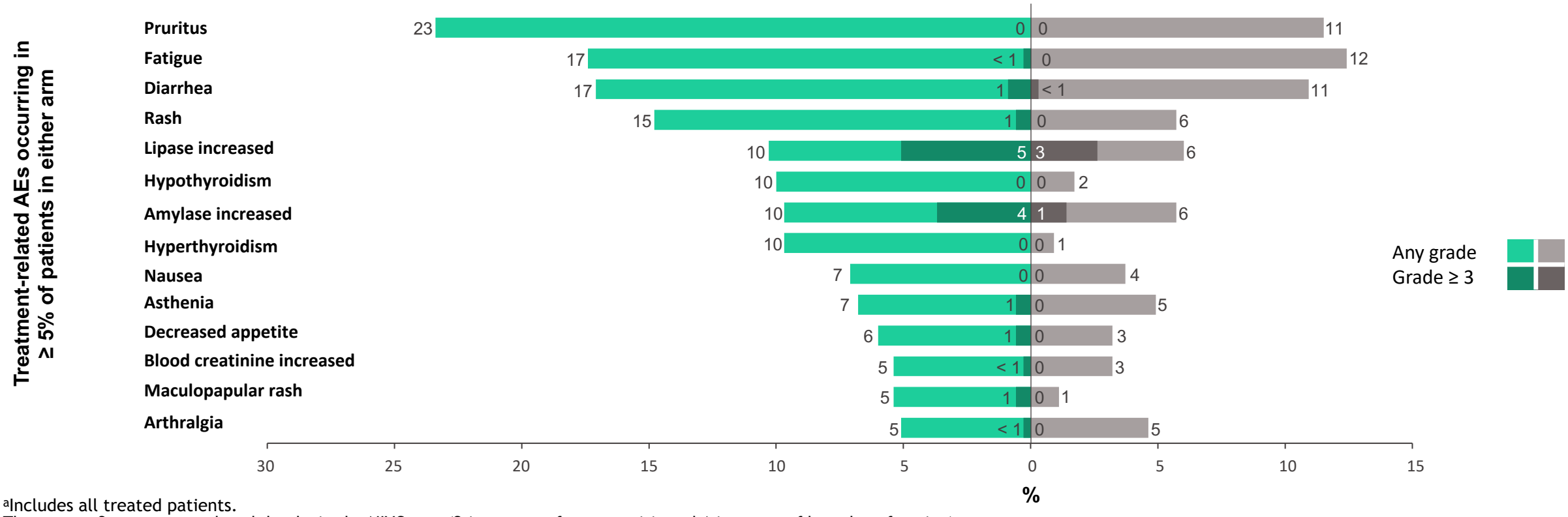
HR 0.52→ 0.46



NE, not estimable; NR, not reached.

Safety summary in all treated patients

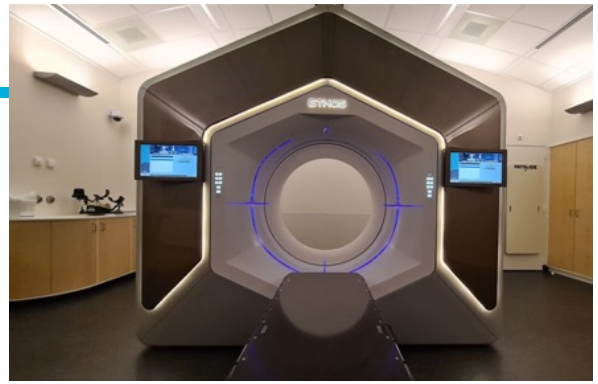
	NIVO (n = 351)[a]		PBO (n = 348)[a]	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Treatment-related AEs, %	79	18	56	7
Treatment-related AEs leading to discontinuation, %	14	7	2	1



[a]Includes all treated patients.
There were 3 treatment-related deaths in the NIVO arm (2 instances of pneumonitis and 1 instance of bowel perforation).
Includes events reported between the first dose and 30 days after the last dose of study therapy.
Minimum follow-up in the ITT population, 31.6 months.
AE, adverse event.

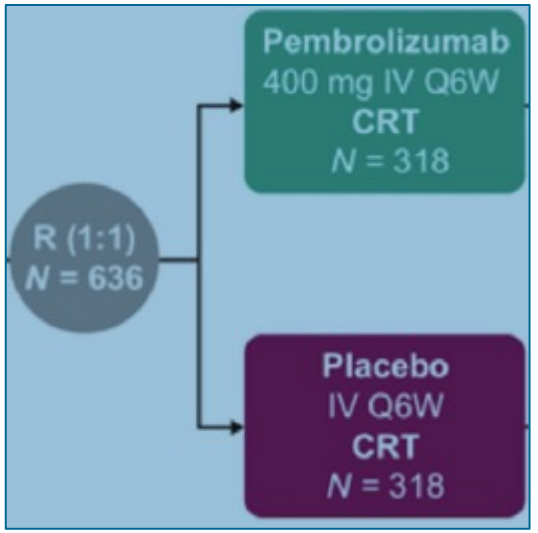
4. Combination of anti-PD-1/PD-L1 with RT or other systemic therapies (eg, chemotherapy, targeted agents, other immunotherapy) in the neoadjuvant and adjuvant settings

Immunotherapy and radiotherapy



- In general: Combining RT and IO leads to immunogenic cell death and an increase in immune markers, thus leading to improved tumor control

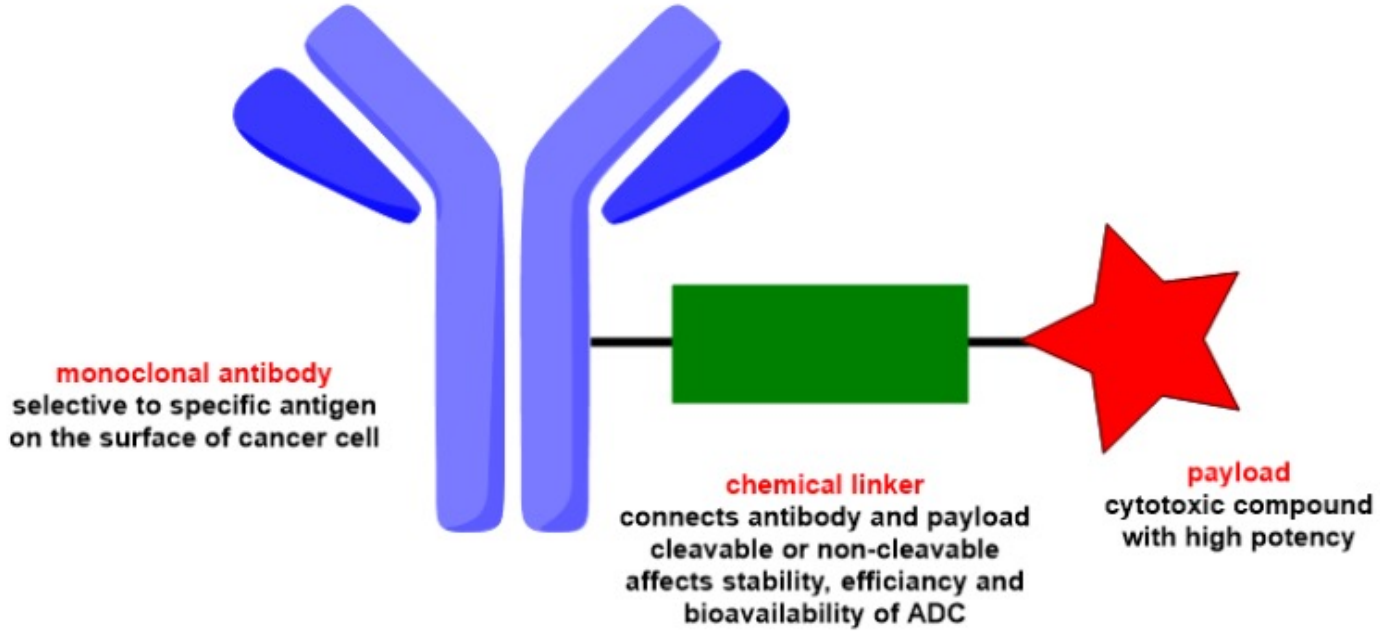
- Two comparative phase 3 RCT's ongoing
  - TMT + 6 months of atezolizumab (NCT03775265, SWOG S1806)
    - Interim analysis of 80 pts reported acceptable toxicity (Singh et al., JCO 2021;39(suppl 6):428)
    - TAR-200 (gemcitabine) plus systemic cetrelimab
  - MK-3475-992 compares ChRad plus pembro or placebo (Williams et al., JCO 2021;39(15 suppl):TPS4586)
    - the primary endpoint of the study is bladder-intact event-free survival

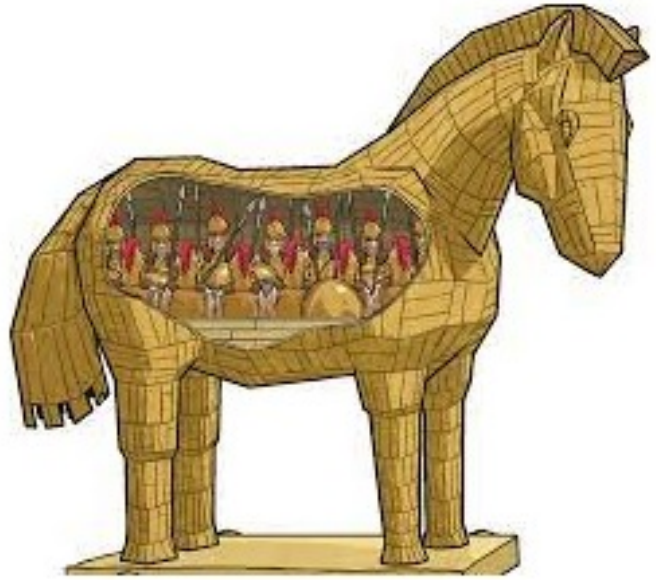


Perioperative treatment: ongoing trials

Agent	Trial	Arms	Setting	N	Status	1º completion	1º endpoint
Nivo ± bempeg[1]	NCT04209114 CA045-009	Neoadj/adj nivo + bempeg Neoadj nivo then adj nivo Cystectomy alone	MIBC (T2-T4a, N0, M0)	540	Recruiting	Aug 2023	pCRR, EFS
Gem/cis + nivo ± linrodostat[2]	NCT03661320 CA017-078	Nivo + gem/cis + linrodostat (IDOi) Nivo + gem/cis Gem/cis	MIBC (T2-T4a, N0, M0)	1200	Recruiting	Nov 2023	pCR, EFS
Pembro + gem/cis[3]	NCT03924856 KEYNOTE-866	Pembro + gem/cis then pembro Neoadj gem/cis	MIBC (T2-T4a, N0, M0, or T1-T4a, N1, M0 with predominant (≥50%) urothelial histology), cisplatin eligible	870	Recruiting	Jun 2025	pCR and EFS in all pts and CPS ≥10
Pembro[4]	NCT03924895 KEYNOTE-905	Pembro Cystectomy alone Neoadj/adj Enfortumab Vedotin + pembro	MIBC (T2-T4a, N0, M0, or T1-T4a, N1, M0 with predominant (≥50%) urothelial histology), cisplatin ineligible	836	Recruiting	Jun 2026	pCR and EFS in all pts and CPS ≥10
Durva[5]	NCT03732677 NIAGRA	Durva + chemo then adj durva Chemo then observation	MIBC (T2-T4a, N0, M0), transitional cell histology	1050	Recruiting	Jun 2023	pCRR, EFS

A potential game changer: Antibody Drug Conjugates (ADC's)





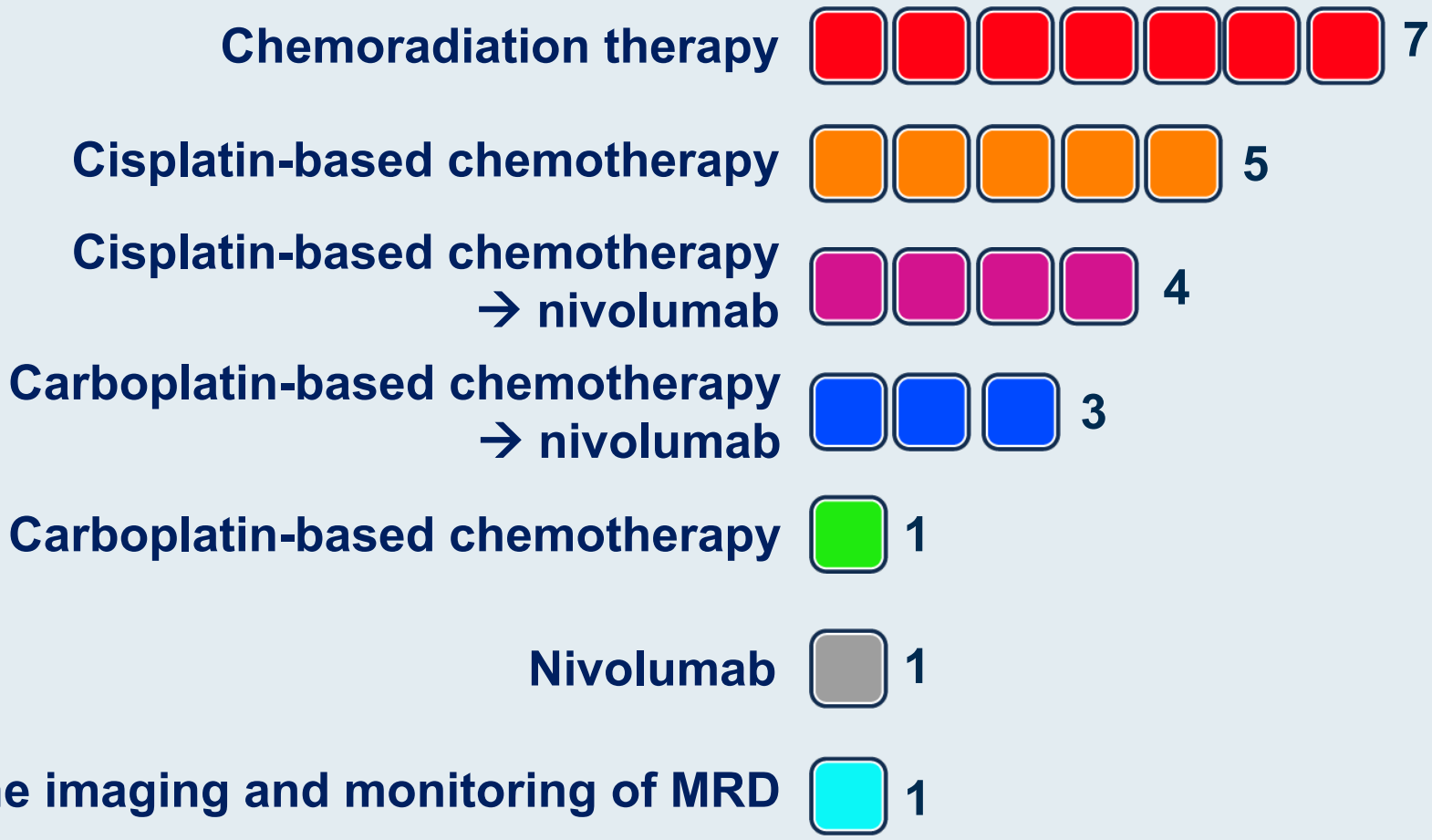
My conclusions

- Stage/grade and response to neoadjuvant therapy (still) the most important risk factors for recurrence
- pCR or ypT0 (PFS?) seems a good surrogate endpoint, but is (still) difficult to predict
- Neoadjuvant immunotherapy seems as good as NAC, but should still be done in trials only
  - IO plus chemo no advantage
  - Marker issue unsolved (CPS, ctDNA)
- CheckMate 274 shows a significantly better PFS of adjuvant Nivo after surgery, even more so in cystectomy patients with a CPS≥1
- Immunotherapy and radiation sounds promising, trials are recruiting
- ADC's are coming

MODULE 3: Novel Strategies Under Investigation for Nonmetastatic Urothelial Bladder Cancer (UBC)

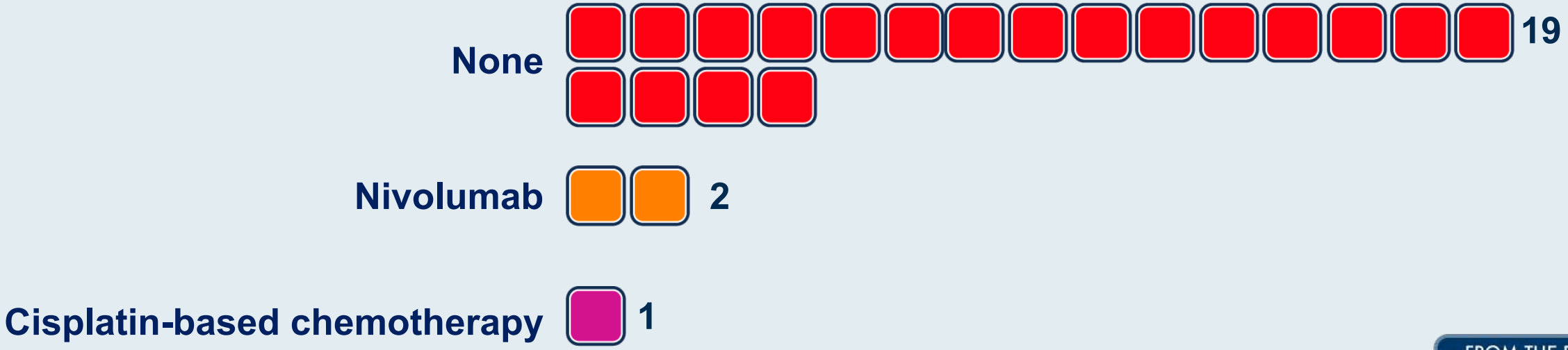
RTP
RESEARCH
TO PRACTICE

An 84-year-old morbidly obese man with diabetes mellitus, mild neuropathy and a glomerular filtration rate (GFR) of 50 undergoes evaluation for hematuria and a large mass is found and shown to be T2 UBC on maximal resection. He refuses cystectomy and requests a bladder-sparing approach. Regulatory and reimbursement issues aside, which treatment would you recommend?



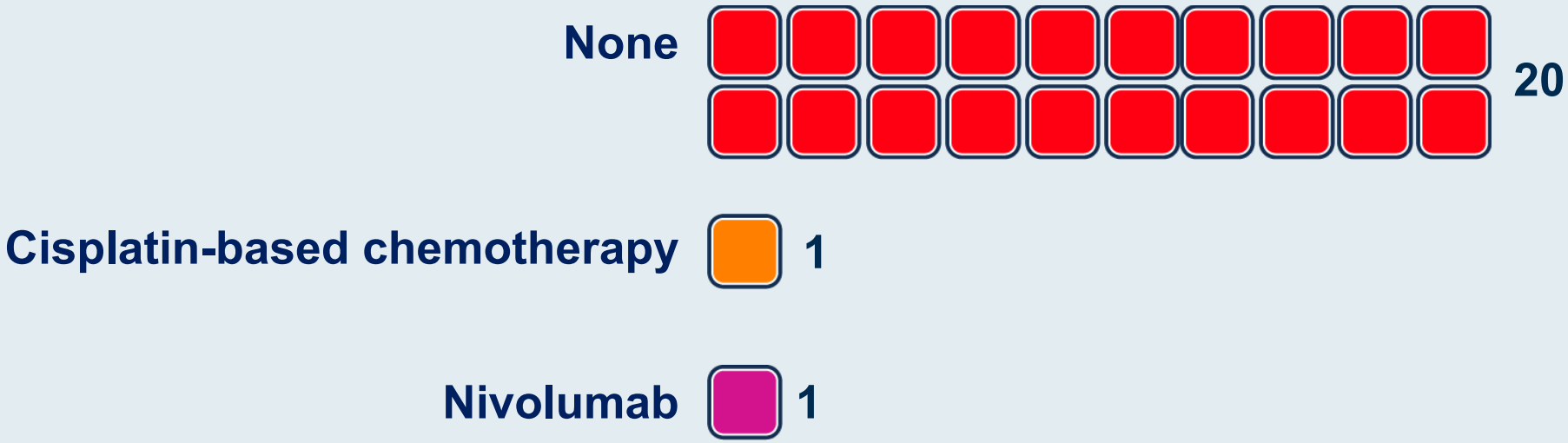
Survey of urologic oncology clinical investigators

A 57-year-old woman presents with gross hematuria and is found to have T2 bladder TCC. CT scan of chest, abdomen and pelvis is negative. She receives neoadjuvant gemcitabine/cisplatin followed by robotic cystectomy with neobladder construction. Pathology reveals pT0N0 and 0/21 positive lymph nodes. Regulatory and reimbursement issues aside, which adjuvant systemic therapy, if any, would you recommend?



Survey of urologic oncology clinical investigators

A 60-year-old man presents with microhematuria and dysuria. He undergoes cystoscopy, which shows diffuse erythema of the bladder. Multiple biopsies are performed, and CIS is shown in 5/5 of the bladder biopsies. Cytology and FISH are positive. CT imaging of chest and abdomen are negative. He undergoes robotic cystectomy with neobladder construction. Pathology shows extensive pTispN0 and 0/9 positive lymph nodes. Regulatory and reimbursement issues aside, which adjuvant systemic therapy, if any, would you recommend?



Survey of urologic oncology clinical investigators

Novel Investigational Strategies for Non-metastatic Urothelial Bladder Cancer

Sia Daneshmand, M.D.

Professor of Urology and Medicine (Oncology) -Clinical Scholar
Director of Urologic Oncology
Director of Clinical Research
Director of Urologic Oncology Fellowship

USC Institute of Urology

Discussion

- Novel intravesical drug delivery system TAR-200 in NMIBC and MIBC
- Clinical trials with TAR-200 with and without the anti-PD-1 antibody cetrelimab in NMIBC (SunRISe-1) and MIBC (SunRISe-2, SunRISe-4)
- Other intravesical drug delivery systems, TAR-210
- Results of Phase II/III QUILT 3.032 trial evaluating N-803 combined with BCG for patients with BCG-unresponsive NMIBC
- Other novel agents (Erdafitinib, Enfortumab Vedotin) for patients with nonmetastatic UBC

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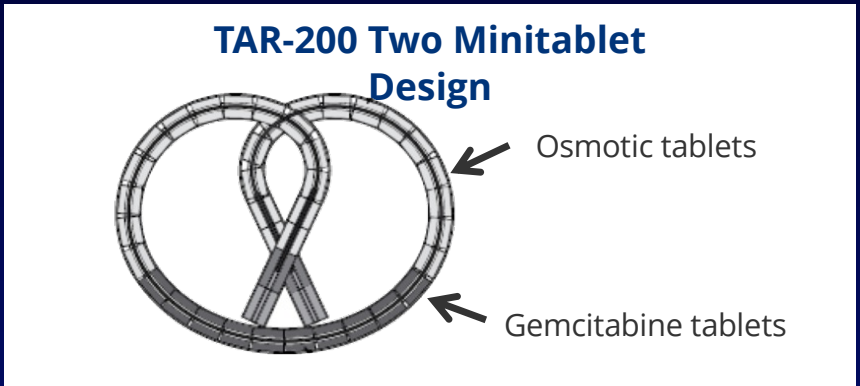
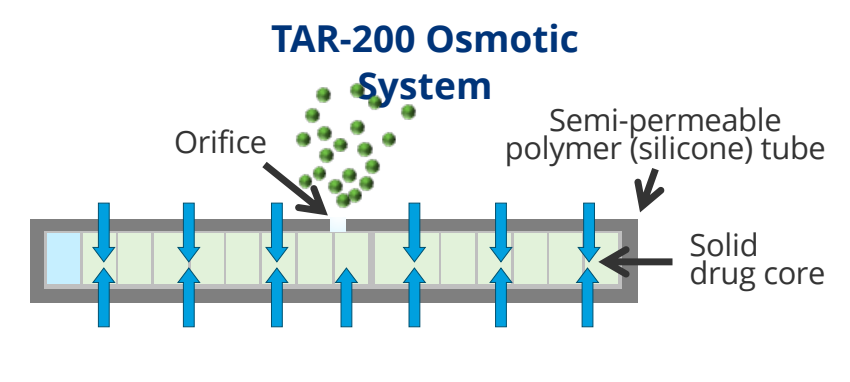
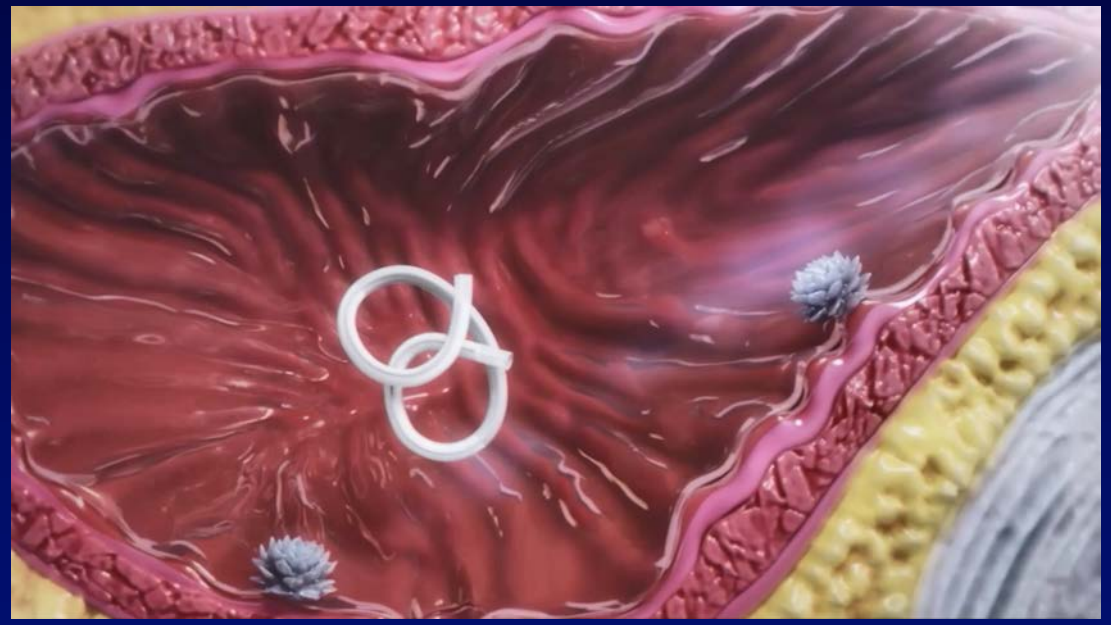
TAR-200 is a Novel Drug Delivery System for Sustained Local Release of Gemcitabine in the Bladder[1-3]







1. Grimberg DC, et al. *Eur Urol Focus*. 2020;6:620-622;
2. Daneshmand S, et al. *Urol Oncol*. 2022;40:344.e1-344.e9; 3. Tyson MD, et al. *J Urol*. 2023:209:890-900.

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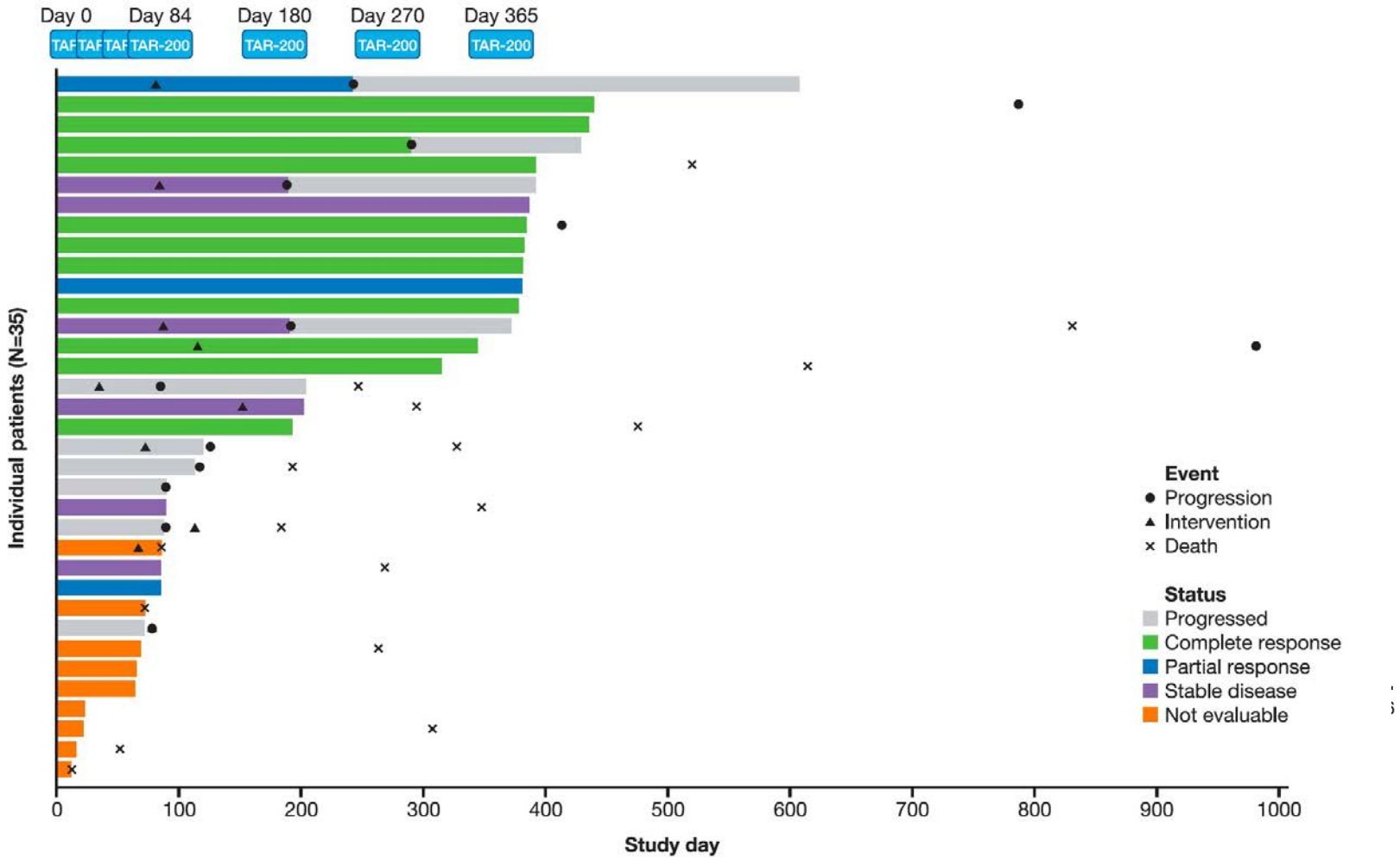
Safety, Tolerability, and Preliminary Efficacy of TAR-200 in Patients With Muscle-invasive Bladder Cancer Who Refused or Were Unfit for Curative-intent Therapy: A Phase 1 Study

THE JOURNAL of UROLOGY®

Mark D. Tyson,[1]* David Morris,[2] Juan Palou,[3] Oscar Rodriguez,[3] Maria Carmen Mir,[4] Rian J. Dickstein,[5] Félix Guerrero-Ramos,[6] Kristen R. Scarpato,[7] Jason M. Hafron,[8]



J Urol 2023 May;209(5):890-900.

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First Results From SunRISe-1 in Patients With BCG-Unresponsive High-Risk Non–Muscle-Invasive Bladder Cancer Receiving TAR-200 in Combination With Cetrelimab, TAR-200, or Cetrelimab Alone

Late Breaking Abstract 02-03 Sunday, April 30, 2023 1:00 PM to 3:00 PM

Siamak Daneshmand,[1] Michiel S. van der Heijden,[2] Joseph M. Jacob,[3] Andrea Necchi,[4] Evanguelos Xylinas,[5] David S. Morris,[6] Philipp Spiegelhalder,[7] Daniel Zainfeld,[8] Taek Won Kang,[9] Justin T. Matulay,[10] Laurence H. Belkoff,[11] Karel Decaestecker,[12] Harm Arentsen,[13]
Shalaka Hampras,[14] Shu Jin,[15] Christopher J. Cutie,[15] Hussein Sweiti,[16] Katharine Stromberg,[14] Jason Martin,[17] Giuseppe Simone[18]

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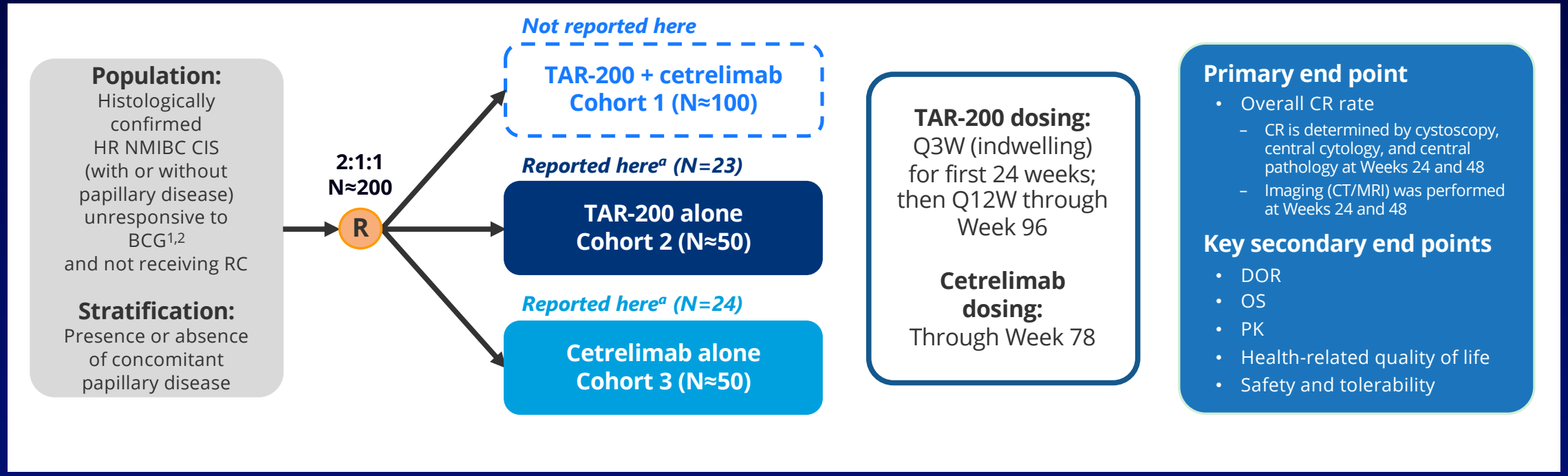
Patients With BCG-Unresponsive High-Risk Non–Muscle-Invasive Bladder Cancer Receiving TAR-200 in Combination With Cetrelimab, TAR-200, or Cetrelimab Alone



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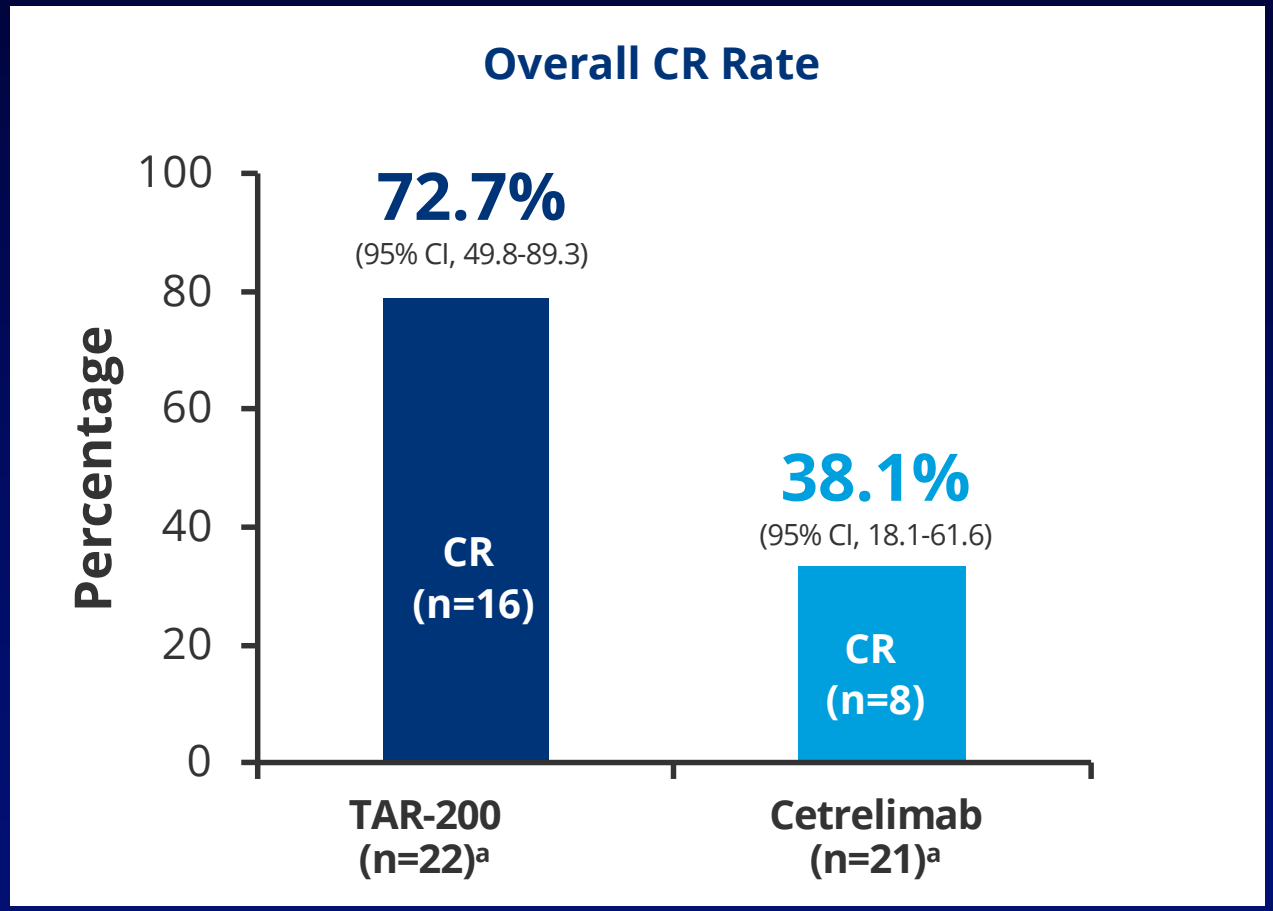
AUA 2023;Abstract 02-03.

Efficacy of TAR-200 and Cetrelimab Monotherapies: 73% of Evaluable Patients Achieved CR With TAR-200



- CR is based on cystoscopy and centrally assessed urine cytology and biopsy at Weeks 24 and 48

AUA 2023;Abstract 02-03.

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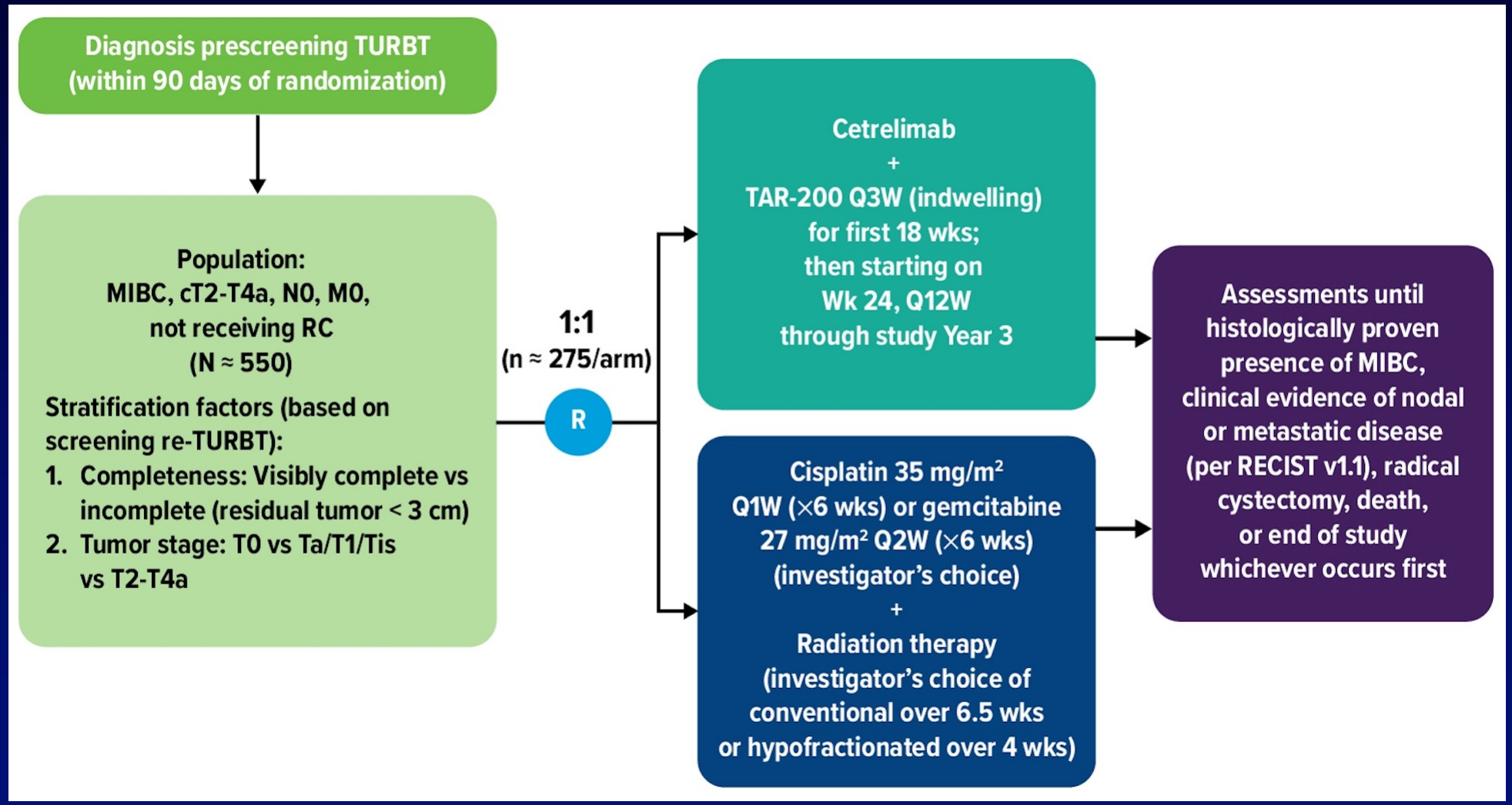
SunRISe-2: TAR-200 in Combination with Cetrelimab versus Concurrent Chemoradiation Therapy for MIBC



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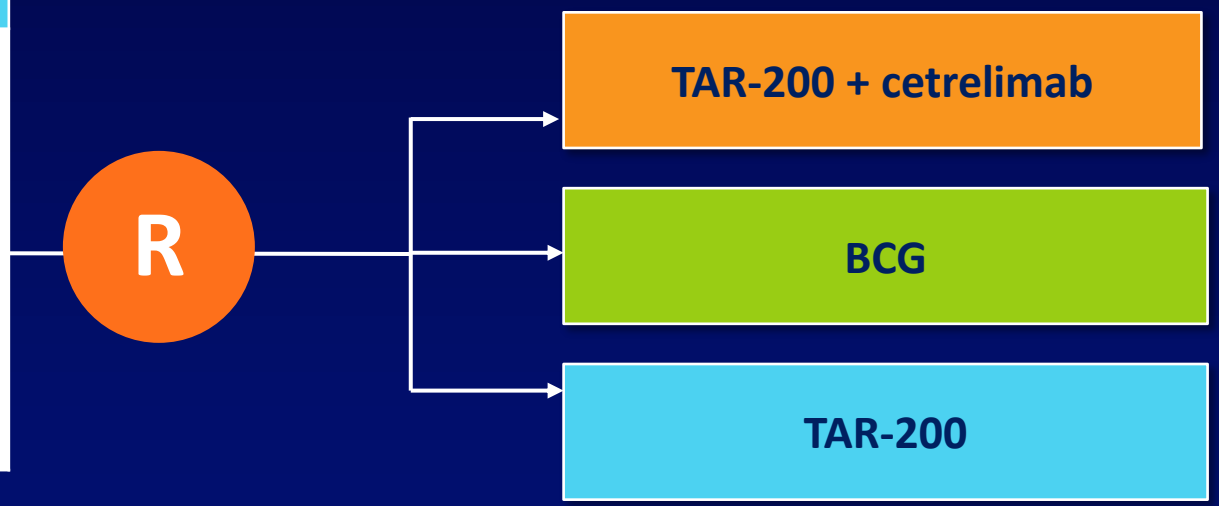
Williams SB et al. ASCO 2021;Abstract TPS4586.

SunRISe-3: TAR-200 in Combination with Cetrelimab or TAR-200 Alone versus Intravesical BCG for BCG-Naïve High-Risk NMIBC

Trial identifier: NCT05714202 (open)
Estimated enrollment: 1,050

Key eligibility

- HR-NMIBC (high-grade Ta, any T1 or carcinoma in situ)
- BCG naïve
- ECOG PS 0-2
- No history of muscle-invasive, locally advanced, nonresectable or metastatic UBC



Primary endpoint: Event-free survival

BCG = Bacillus Calmette-Guérin

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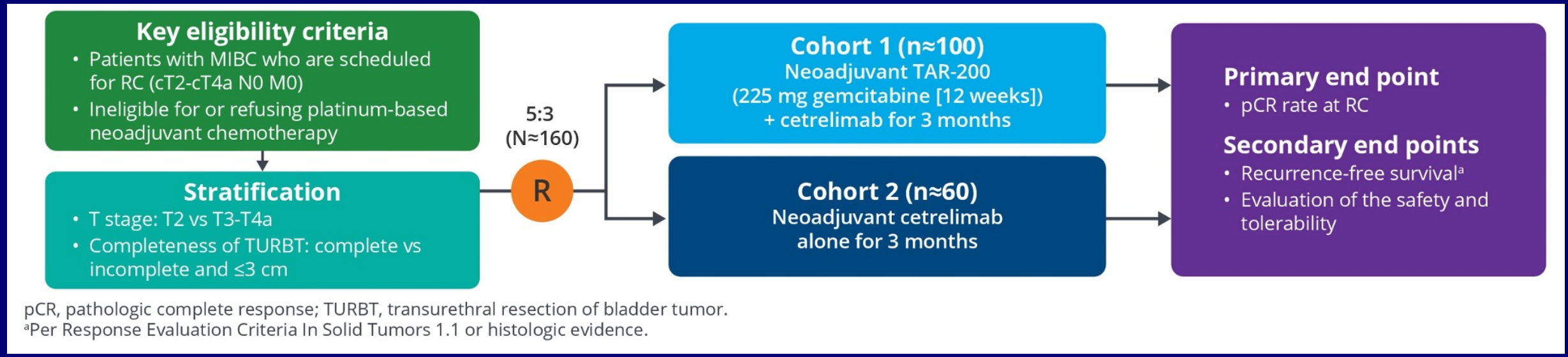
www.clinicaltrials.gov. Accessed April 2023.

SunRISe-4: Ongoing Multicenter Randomized Phase II Study Design



pCR, pathologic complete response; TURBT, transurethral resection of bladder tumor.
[a]Per Response Evaluation Criteria In Solid Tumors 1.1 or histologic evidence.

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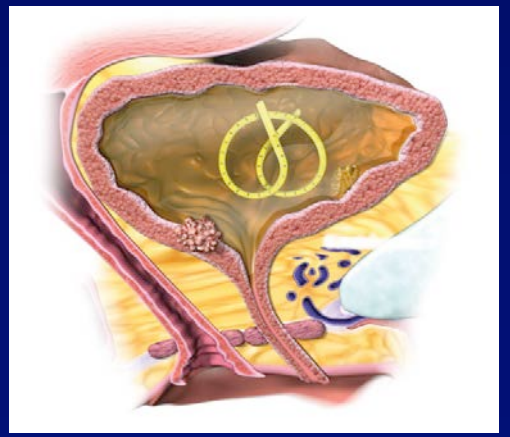
Psutka SP et al. Genitourinary Cancers Symposium 2023;Abstract TPS584.

TAR-210 Phase 1 Study

- NCT05316155 is an open-label multicenter Phase 1 First-in-Human Study for patients with recurrent NMIBC or MIBC

- **TAR-210** is an intravesical drug delivery system designed to provide localized, continuous release of Erdafitinib within the bladder
  - Oral selective pan-FGFR tyrosine kinase inhibitor
  - Approved for locally advanced or metastatic UC with susceptible *FGFR2/3* alterations progressed following platinum



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ASCO GU 2023;Abstract TPS583.

Study Objectives-

FGFR alteration in either urine or tissue

Primary Objectives

- **Part 1 (dose escalation):**
  To determine the recommended Phase 2 dose (RP2D[s]) for TAR-210
- **Part 2 (dose expansion):**
  To determine the safety of TAR-210 administered at the RP2D(s) for up to 12 months

Secondary Objectives

- To assess the PK
- To assess preliminary clinical activity

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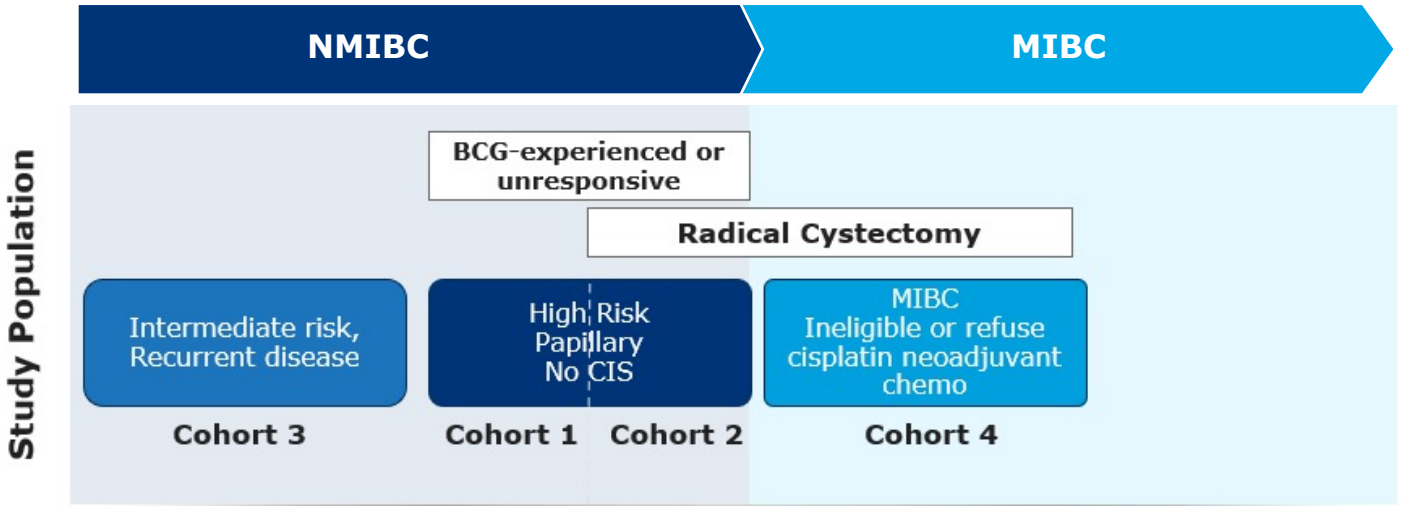
ASCO GU 2023;Abstract TPS583.

Study Design

Patient Populations (4 different FGFR+ cohorts)



FGFR+ alterations vary based on extent of disease in Bladder Ca

- NMIBC FGFR+ rate is ~35-70%
- MIBC FGFR + rate is ~20%

- **Cohort 1:** Recurrent, BCG-unresponsive or BCG-experienced high risk papillary NMIBC. No CIS. Refusing or ineligible for cystectomy.
- **Cohort 2:** Recurrent, BCG-unresponsive or BCG-experienced high risk papillary NMIBC. No CIS. Scheduled for radical cystectomy.
- **Cohort 3:** Recurrent intermediate risk NMIBC with previous history of only low-grade disease.
- **Cohort 4:** MIBC cT2-3N0 scheduled for radical cystectomy who have refused or are ineligible for cisplatin-based neoadjuvant chemotherapy. Cohort 4 are scheduled for radical cystectomy.

ASCO GU 2023;Abstract TPS583.

2022 ASCO ANNUAL MEETING

QUILT 3032: Final clinical results of pivotal trial of IL-15RαFc superagonist N-803 with BCG in BCG-unresponsive CIS and papillary nonmuscle-invasive bladder cancer (NMIBC)

QUILT 3032

Dr. Karim Chamie, UCLA

Slide Courtesy of Dr. Karim Chamie, MD, MSHS – UCLA Department of Urology

NEJM Evidence

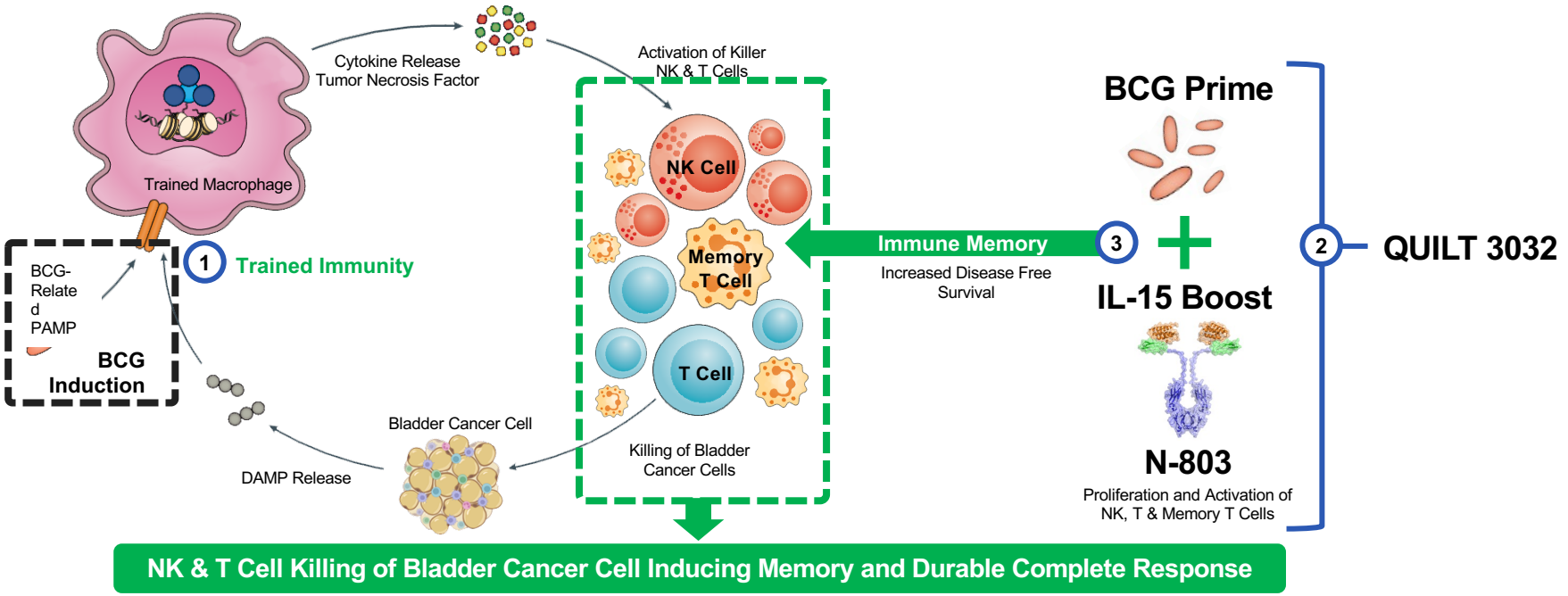
Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

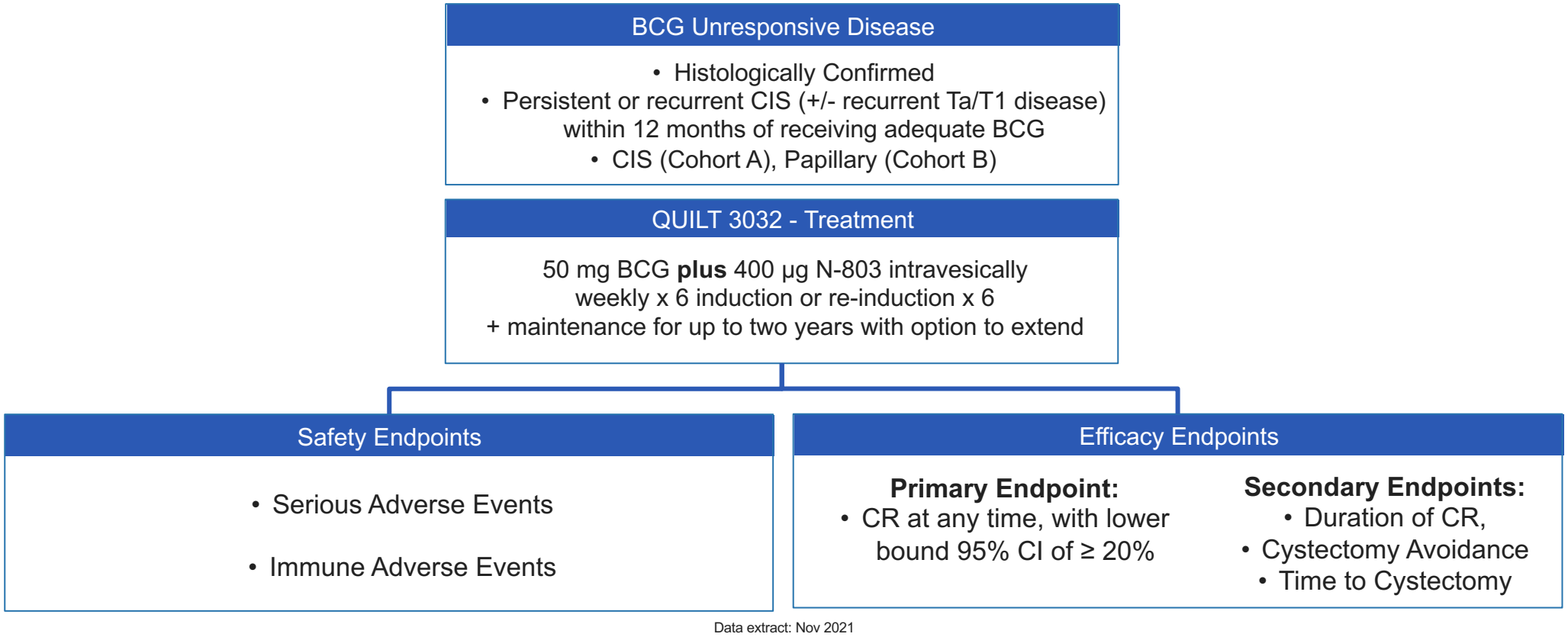
QUILT 3032: BCG Induces Trained Immunity
BCG (Prime) + N-803 (Boost) in NMIBC for Immune Memory



- Slide Courtesy of Dr. Karim Chamie, MD, MSHS – UCLA Department of Urology

QUILT 3032

Phase 2 / 3: IL-15RαFc Superagonist N-803 with BCG in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer CIS & Papillary



Data extract: Nov 2021

Slide Courtesy of Dr. Karim Chamie, MD, MSHS – UCLA Department of Urology

QUILT 3032
Adverse Events: Cohort A (CIS) & Cohort B (Papillary)

Treatment-Related AE's				Treatment-Related SAE's	Immune-Related SAE	Treatment-Related Deaths
GRADE 1-2 (CIS & Papillary)		**GRADE 3 (CIS & Papillary)**				
Adverse Event (AE)	**%**	**Adverse Event (AE)**	**%**			
Dysuria	22%	Arthralgia	<1%	**1%**	**0%**	**0%**
Pollakiuria	20%	Bacteraemia	<1%			
Haematuria	17%	Dysuria	<1%			
Fatigue	16%	Encephalopathy	<1%			
Micturition urgency	12%	Haematuria	<1%			
Chills	7%	Myalgia	<1%			
Bladder spasm	6%	Pain in extremity	<1%			
Pyrexia	5%	Pollakiuria	<1%			
Urinary tract infection	6%	Sepsis	<1%			
Cystitis noninfective	4%	Urinary tract infection	<1%			
Nocturia	3%	Urine flow decreased	<1%			
Diarrhoea	3%					
Nausea	2%					
Bacterial test positive	2%					
Cystitis	2%					
Influenza like illness	2%					
Urinary tract pain	2%					

No Treatment Related Grade 4 or 5 Events

N-803 Activity is **Local to the Bladder** with **Zero Systemic** IL-15 Levels per PK

Clinically Meaningful Efficacy Results Cohort A (CIS)

Complete Response

Median DoR

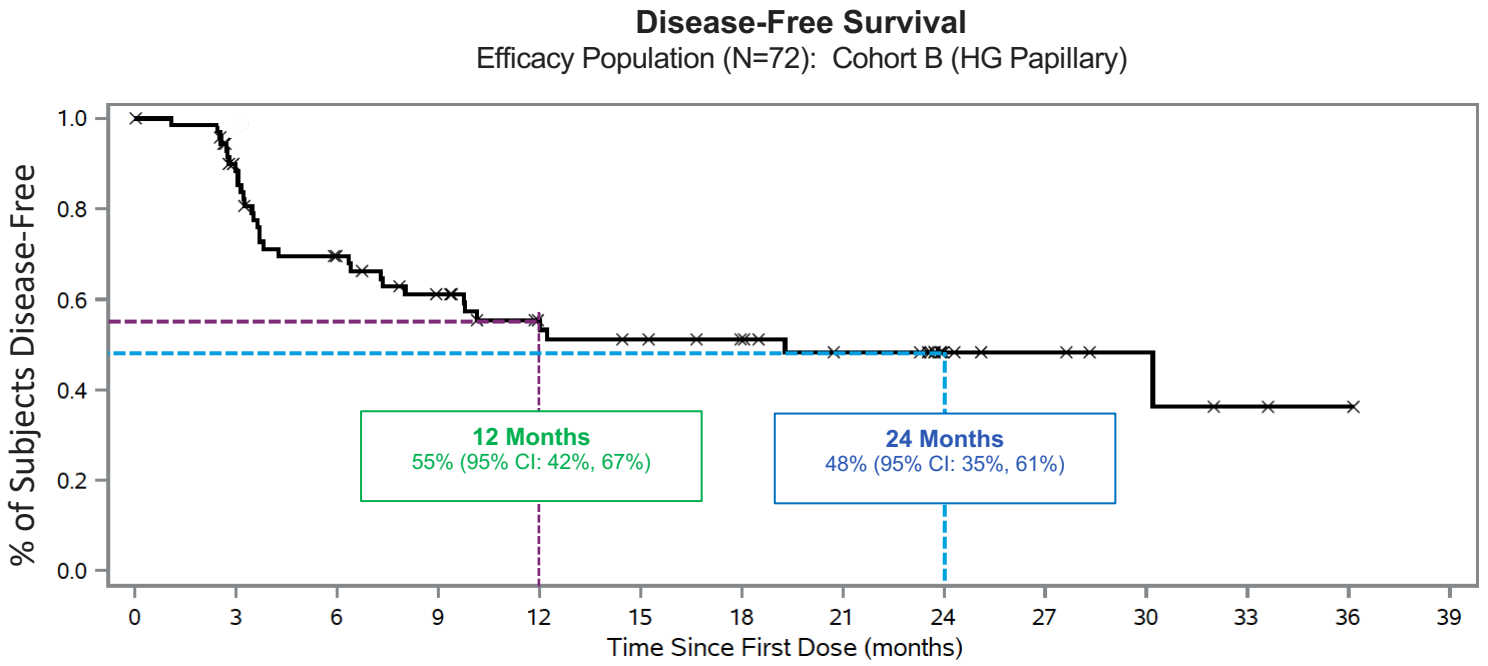
Duration of Response

Overall Intent to Treat Population Efficacy	QUILT 3032
Complete Response (n)	58 / 82
CR Rate	71% (95% CI: 59.6, 80.3)
Median Duration of Response in Months	26.6 Months (95% CI: 9.9, Not Reached)
Duration of Response ≥12 Months per KM	61.6% (95% CI: 47.3, 73.1)
Duration of Response ≥18 Months per KM	56.3% (95% CI: 41.5, 68.8)
Duration of Response ≥24 Months per KM	53.2% (95% CI: 38.0, 66.2)

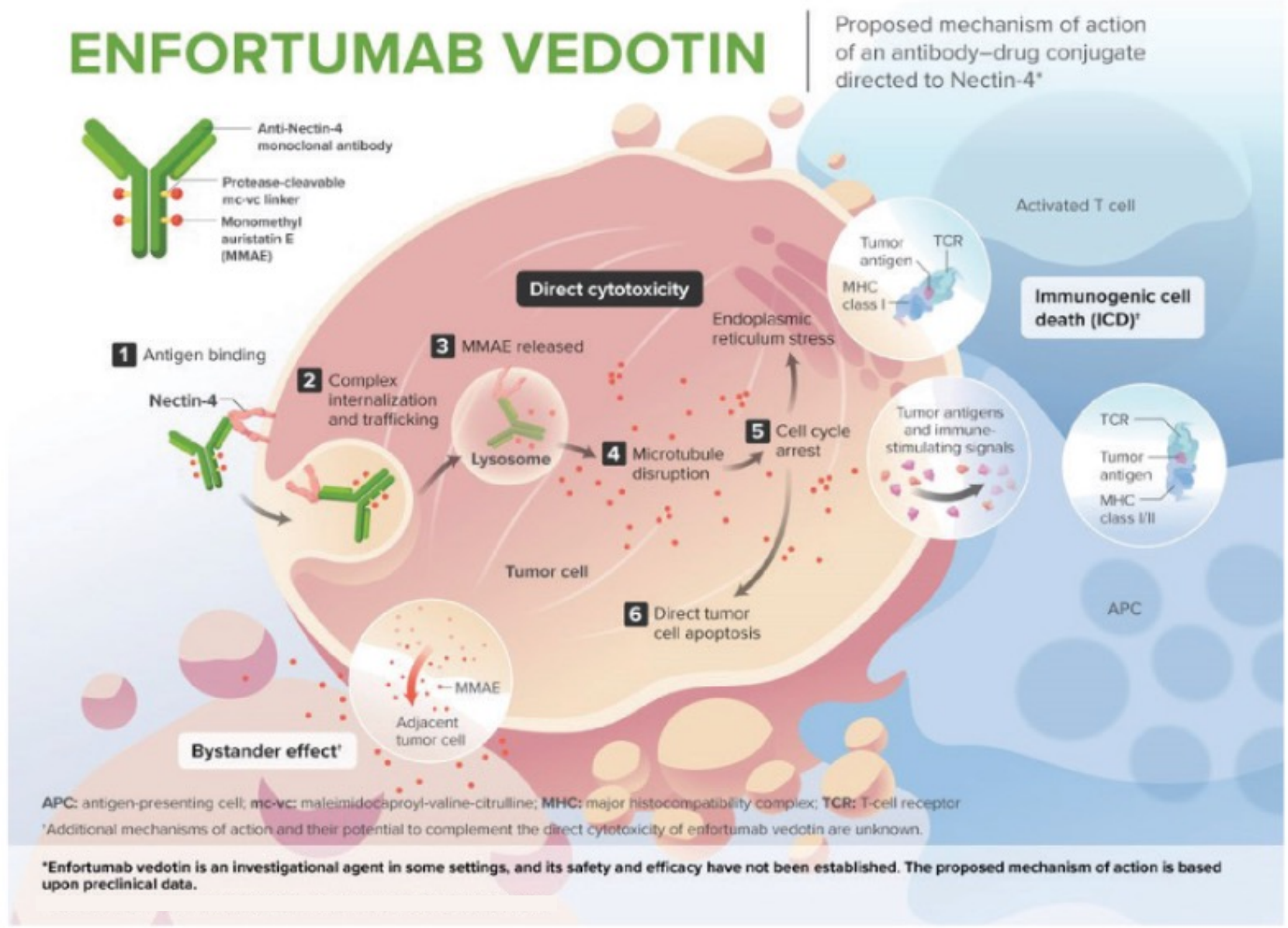
Data Cutoff: January 15, 2022

Durable 24 Month Disease Free Survival in Papillary

- 77 patients have been accrued
- Median DFS: 19.3 months
- 55% DFS rate at 12 months
- 51% DFS rate at 18 months
- 48% DFS rate at 24 months
- Median F/U is 20.7 months
- 72 of 77 (94%) radical cystectomy avoidance



Enfortumab Vedotin Proposed Mechanism of Action



***Enfortumab vedotin is an investigational agent in some settings, and its safety and efficacy have not been established. The proposed mechanism of action is based upon preclinical data.**

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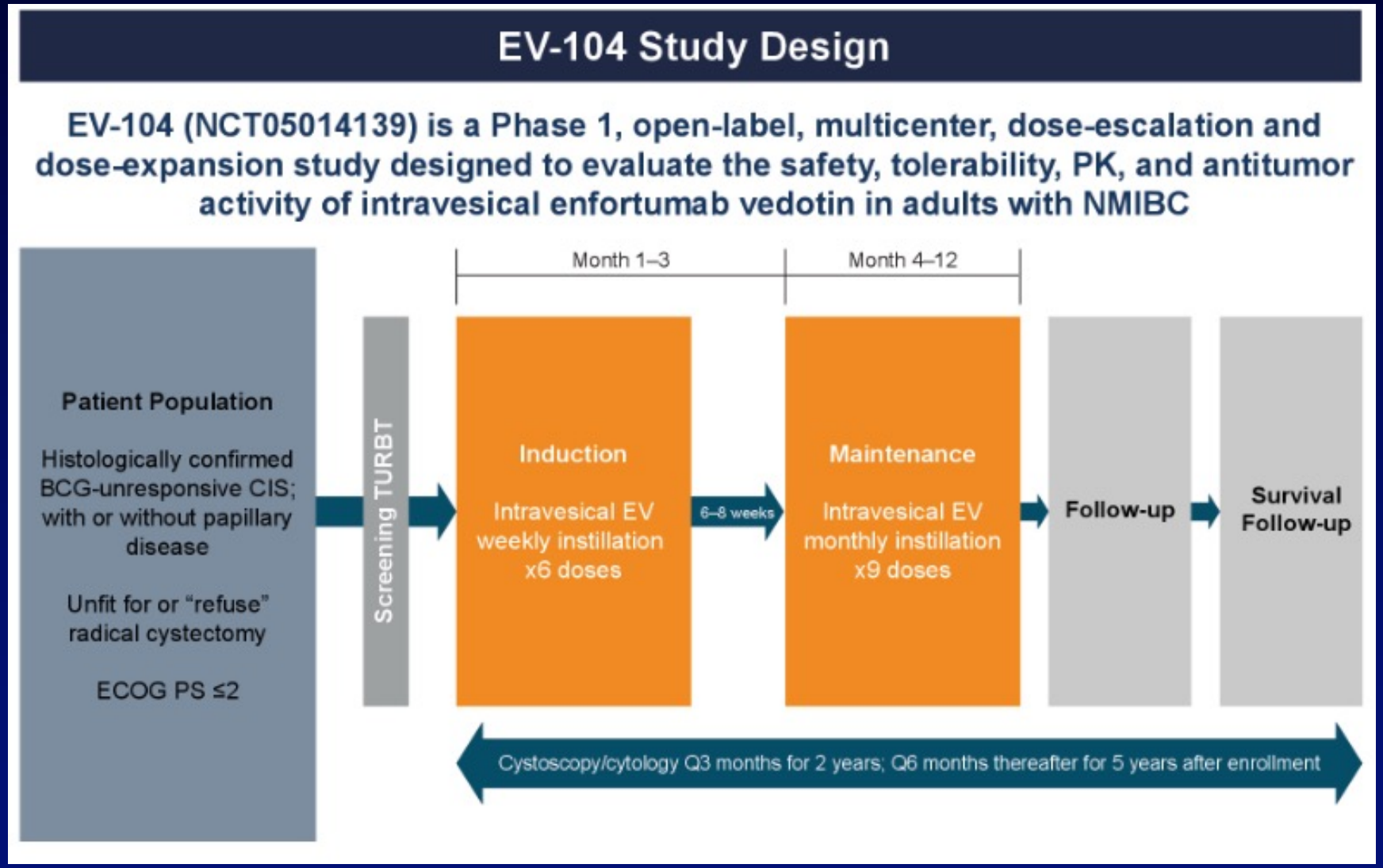
Ashish M. Kamat, Gary D. Steinberg, Brant Allen Inman, Max R. Kates, Edward M. Uchio, Sima P. Porten, Morgan Roupret, Joan Redorta, James W.F. Catto, Girish S. Kulkarni, Thomas Powles, Mark Tyson, Gabriel P. Haas, Yao Yu, Matthew Birrenkott, Yair Lotan



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ASCO-GU 2023;Abstract TPS582.

Eligibility

Key Inclusion Criteria

- High-risk BCG-unresponsive disease
- Histologically confirmed, non-muscle invasive urothelial (transitional cell) carcinoma with carcinoma in situ, with or without papillary disease
- Predominant histologic component (>50%) must be urothelial (transitional cell) carcinoma
- Ineligible for or refusing a cystectomy
- ECOG PS ≤2
- Estimated life expectancy of >2 years

Objectives and Associated Endpoints

Primary Objectives	Primary Endpoints
To evaluate the safety and tolerability of intravesical EV in patients with NMIBC	Type, incidence, severity, seriousness, and relatedness of AEs Type, incidence, and severity of laboratory abnormalities
To identify the MTD or recommended dose of intravesical EV in patients with NMIBC	Incidence of DLTs and cumulative safety by dose level
Key Secondary Objectives	**Key Secondary Endpoints**
To assess the PK of intravesical EV	Estimates of selected PK parameters
To assess the antitumor activity of intravesical EV as measured by CR rate	CR rate at any time on study and CR rates at 3, 6, 12, 18, and 24 months
To assess the duration of CR, PFS, and cystectomy-free survival	Duration of CR, progression-free survival, and cystectomy-free survival

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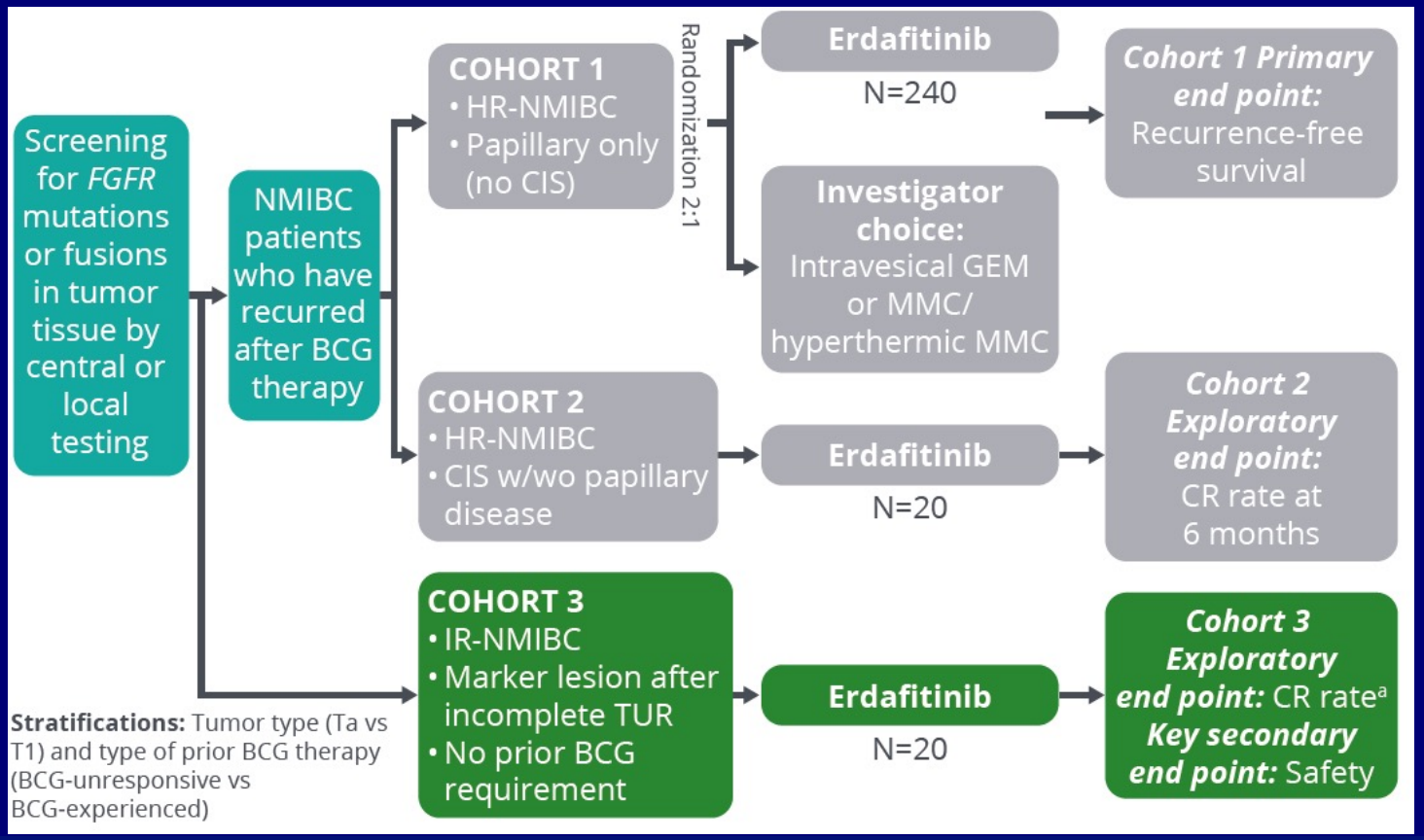
ASCO-GU 2023;Abstract TPS582.

Phase 2 Study of the Efficacy and Safety of Erdafitinib in Patients With Intermediate-Risk Non–Muscle-Invasive Bladder Cancer (IR-NMIBC) With *FGFR3/2* Alterations (*alt*) in THOR-2

Siamak Daneshmand,[1] Renata Zaucha,[2] Benjamin A. Gartrell,[3] Yair Lotan,[4] Syed A. Hussain,[5] Eugene K. Lee,[6] Giuseppe Procopio,[7] Fernando Galanternik,[8] Vahid Naini,[9] Jenna Cody Carcione,[10] Spyros Triantos,[10] Mahadi Baig,[10] Jodi K. Maranchie[11]

FIGURE 1: THOR-2 study design (Cohort 3 presented herein)



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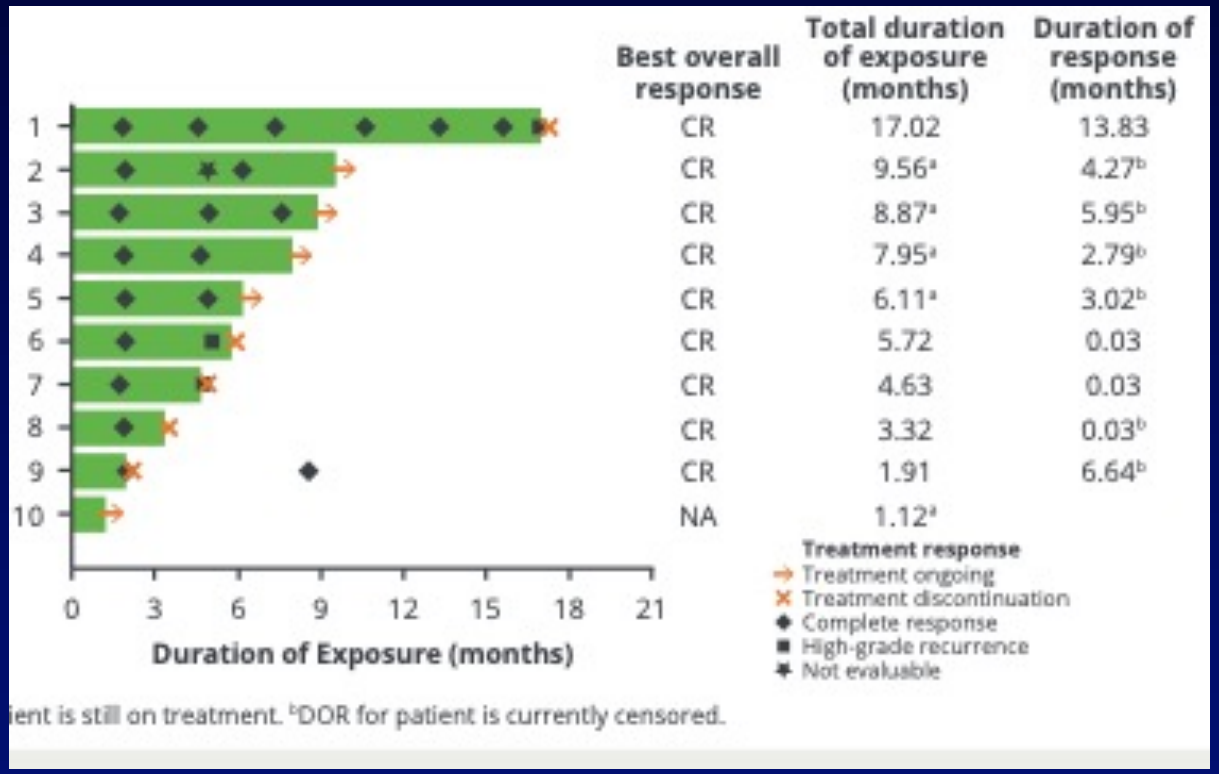
ASCO-GU 2023;Abstract 504.

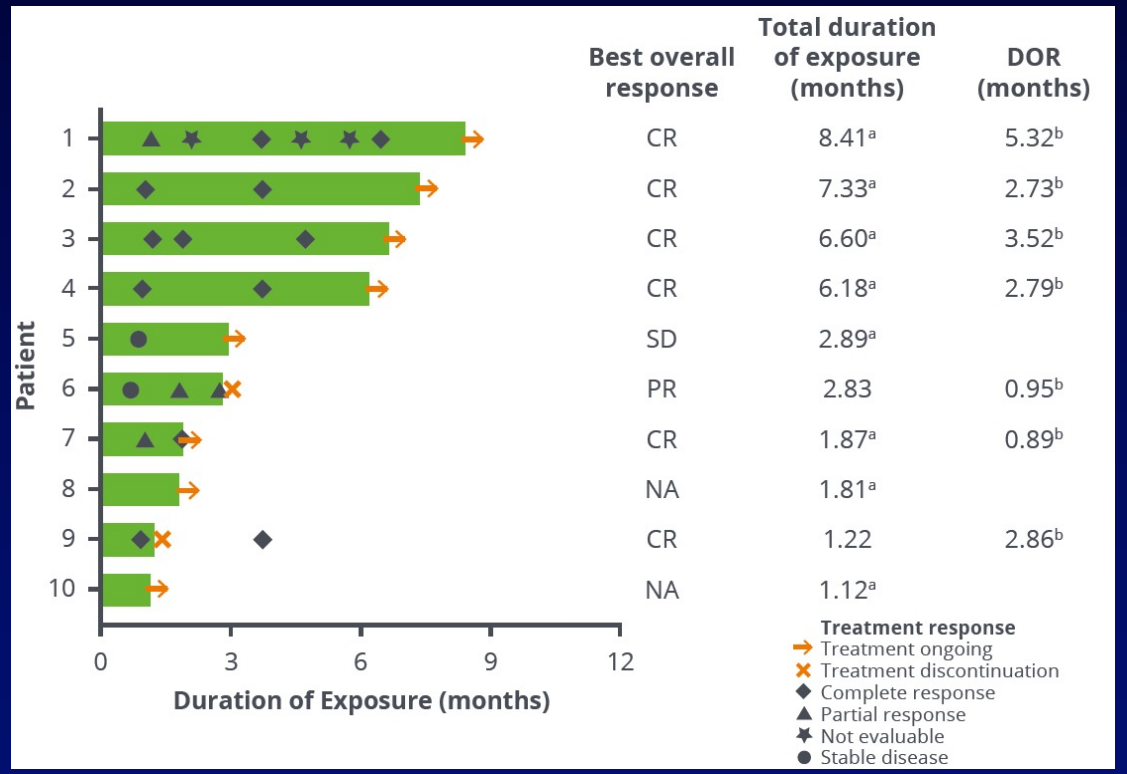
RESULTS

Cohort 2



9/9 evaluable patients had CR rate at C3D1
6/8 (75%) evaluable patients had CR at C6D1

Cohort 3



6 of 8 evaluable patients had a CR
(CR rate, 75.0%) and 1 PR

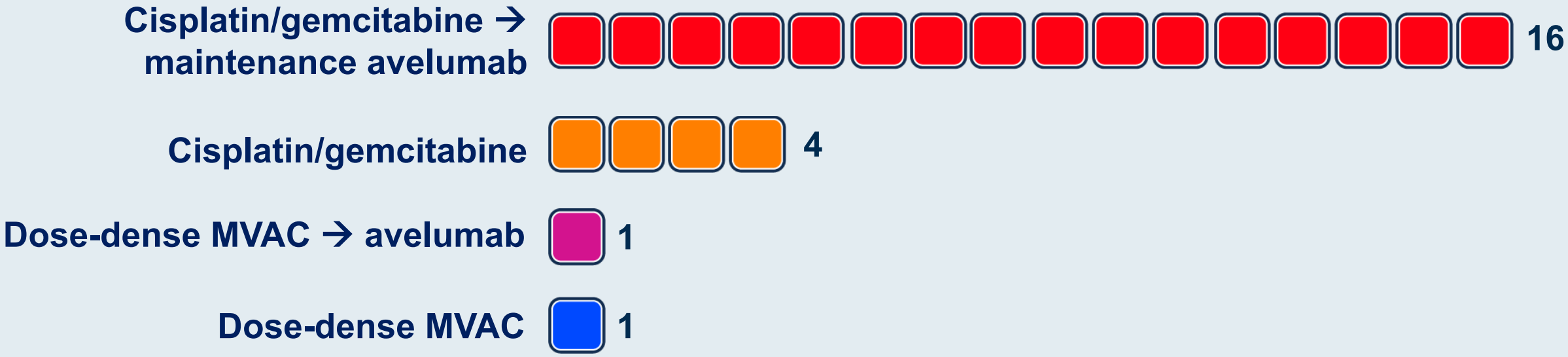
USC Institute of Urology

ASCO-GU 2023;Abstract 504.

MODULE 4: Current and Future Up-Front Management of Metastatic UBC (mUBC)

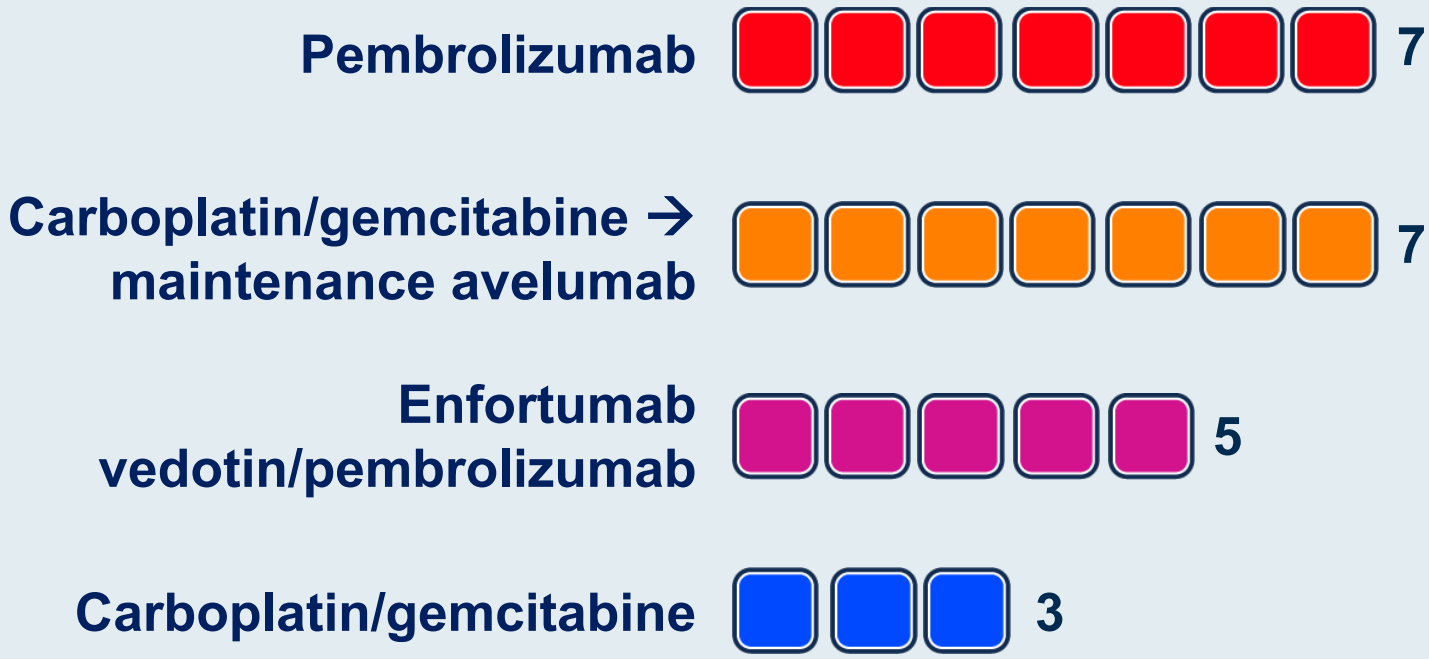
RTP
RESEARCH
TO PRACTICE

What would be your preferred first-line treatment regimen for a 65-year-old patient with metastatic UBC and no prior systemic treatment?



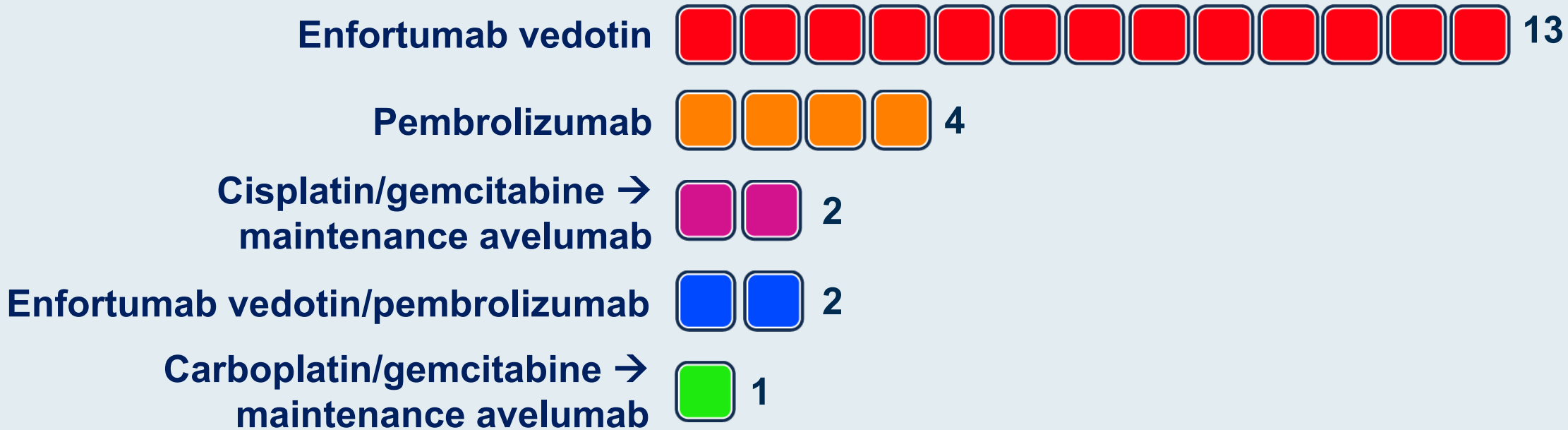
Survey of urologic oncology clinical investigators

What would be your preferred first-line regimen for an 80-year-old patient with metastatic UBC and no prior systemic treatment who is not a candidate for cisplatin-based therapy?



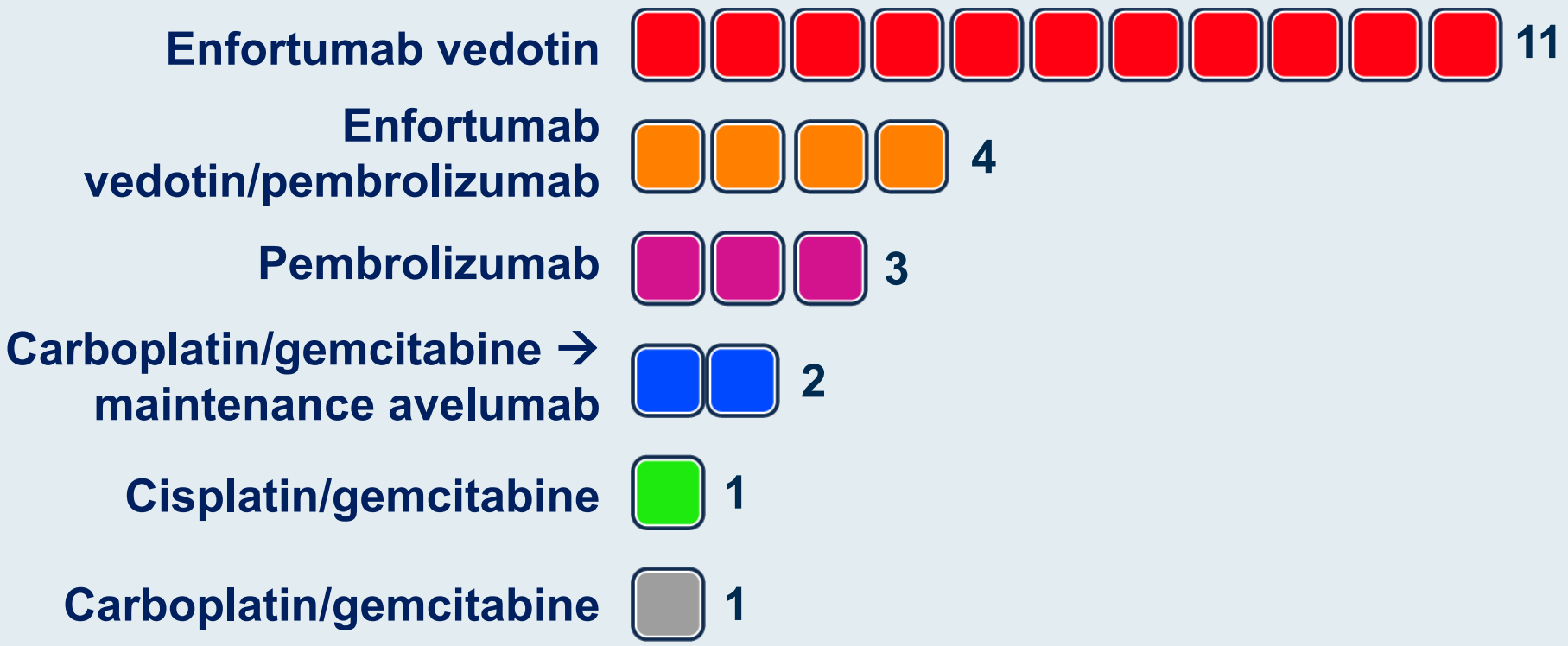
Survey of urologic oncology clinical investigators

A 65-year-old patient receives neoadjuvant chemotherapy followed by cystectomy and then adjuvant nivolumab for FGFR wild-type UBC but develops metastatic disease 9 months after starting nivolumab. Regulatory and reimbursement issues aside, what would you likely recommend?



Survey of urologic oncology clinical investigators

Regulatory and reimbursement issues aside, what would you generally recommend for an 80-year-old platinum-ineligible patient who undergoes cystectomy followed by adjuvant nivolumab for FGFR wild-type UBC but develops liver metastases 9 months after starting nivolumab?



Survey of urologic oncology clinical investigators

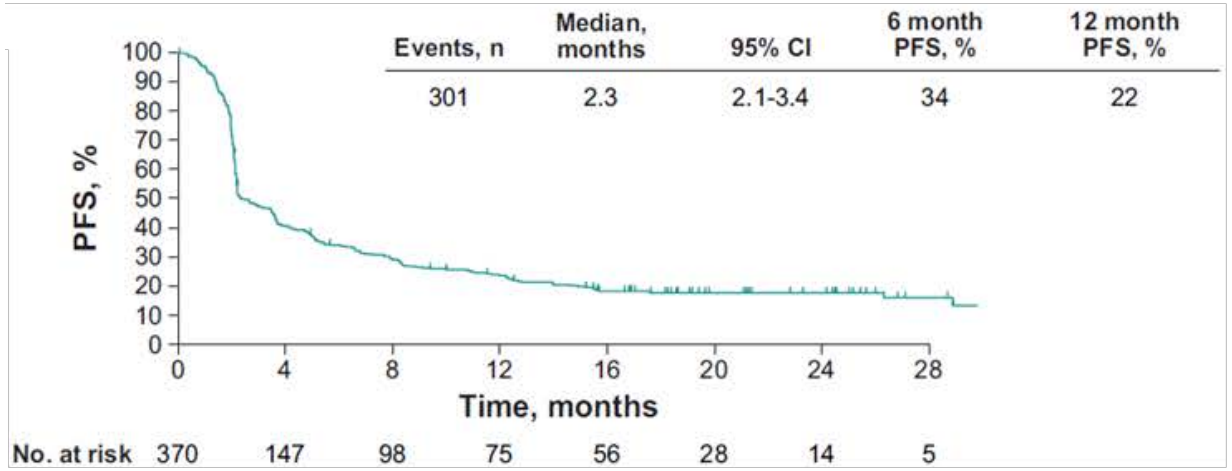
UNC | LINEBERGER COMPREHENSIVE CANCER CENTER

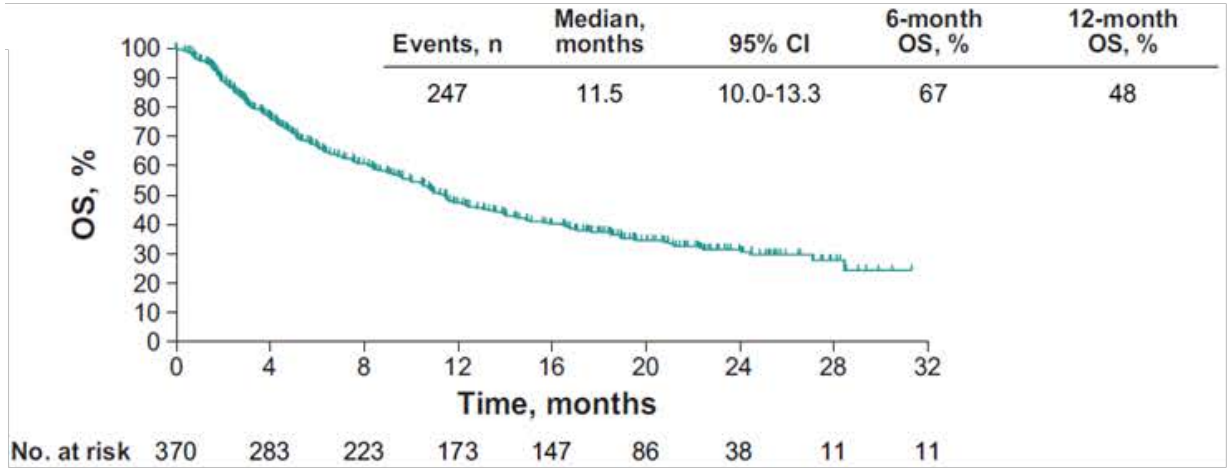
UNC CANCER CARE

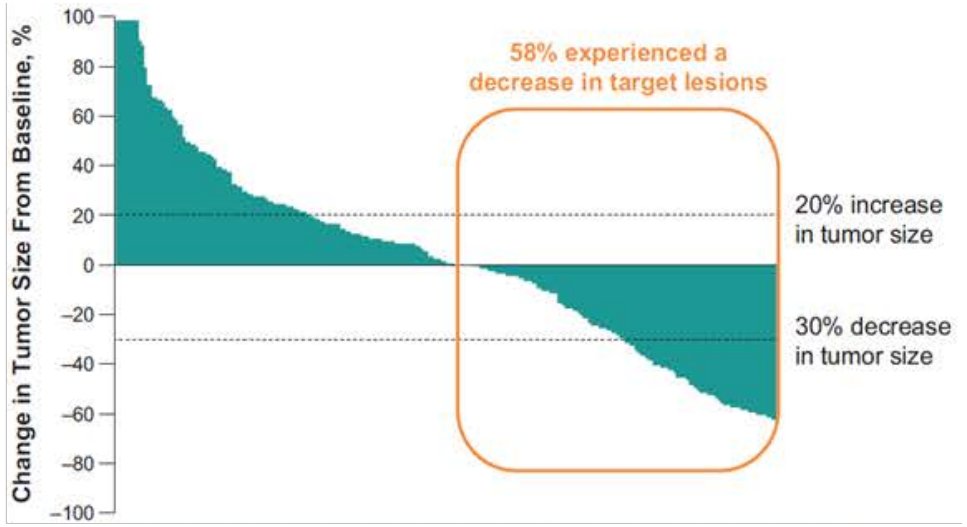
Current and Future Up-Front Management of Metastatic UC (mUC)

Matthew Milowsky, MD
George Gabriel and Frances Gable Villere Distinguished Professor
Section Chief, Genitourinary Oncology

Pembrolizumab as first-line treatment for mUC (KEYNOTE-052)







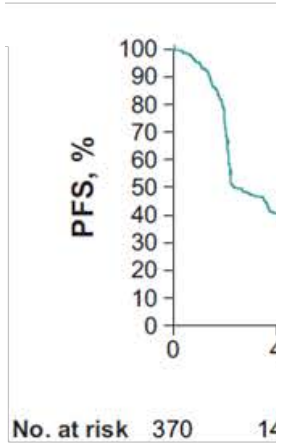
N = 370 patients
Median follow up: 17 months

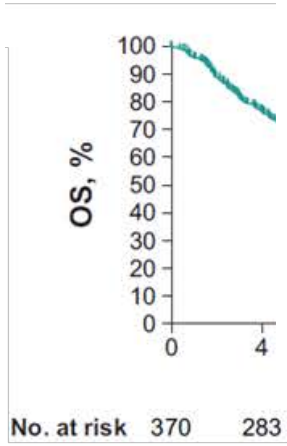
ORR: 29%
Median OS: 11.5 months
48% alive at 12 months

Vuky J, et al. ASCO 2018. Abstract 4524.

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

Pembrolizumab as first-line treatment for mUC (KEYNOTE-052)



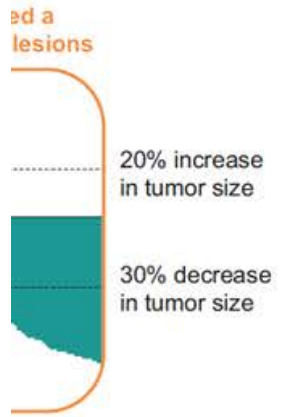


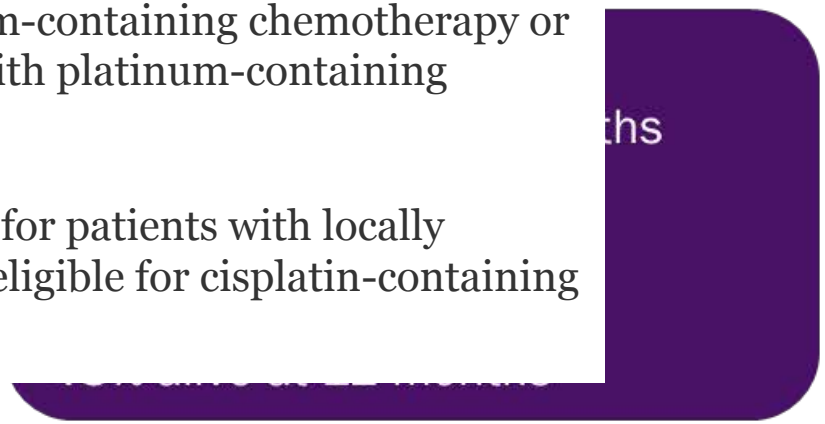
Pembrolizumab: Advanced or Metastatic Urothelial Carcinoma

May 18, 2017

On May 18, 2017, the U.S. Food and Drug Administration granted regular approval to pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

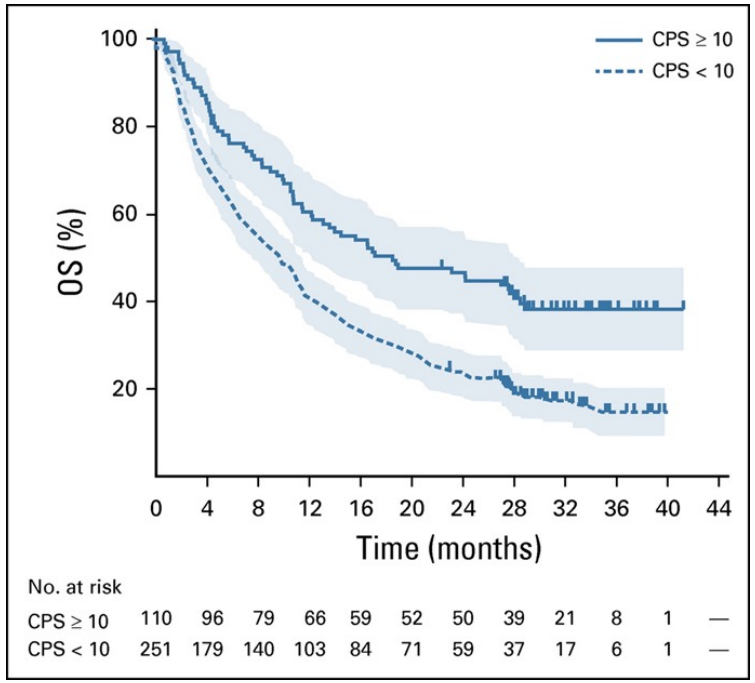
FDA also granted accelerated approval to pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

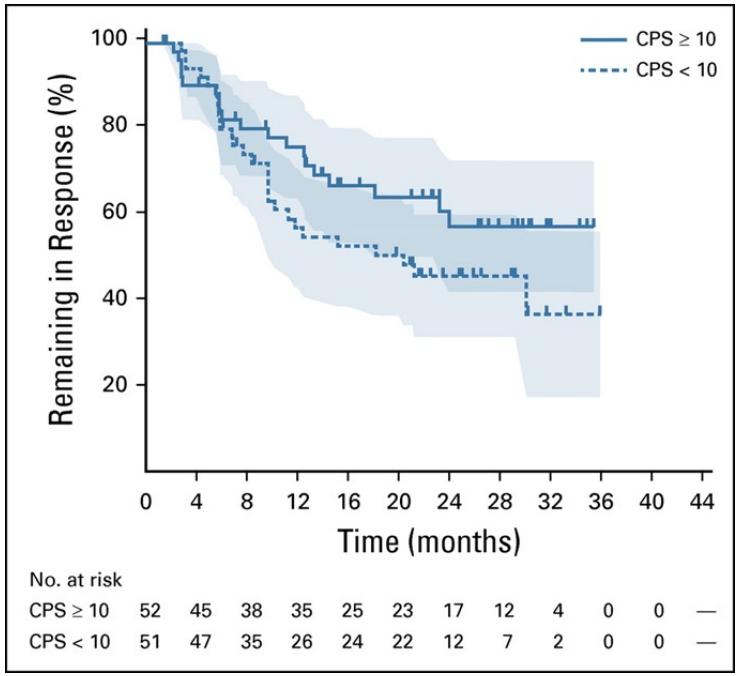




Vuky J, et al. ASCO 2018. Abstract 4524.

Pembrolizumab as first-line treatment for mUC (KEYNOTE-052): CPS ≥ 10 with improved outcomes

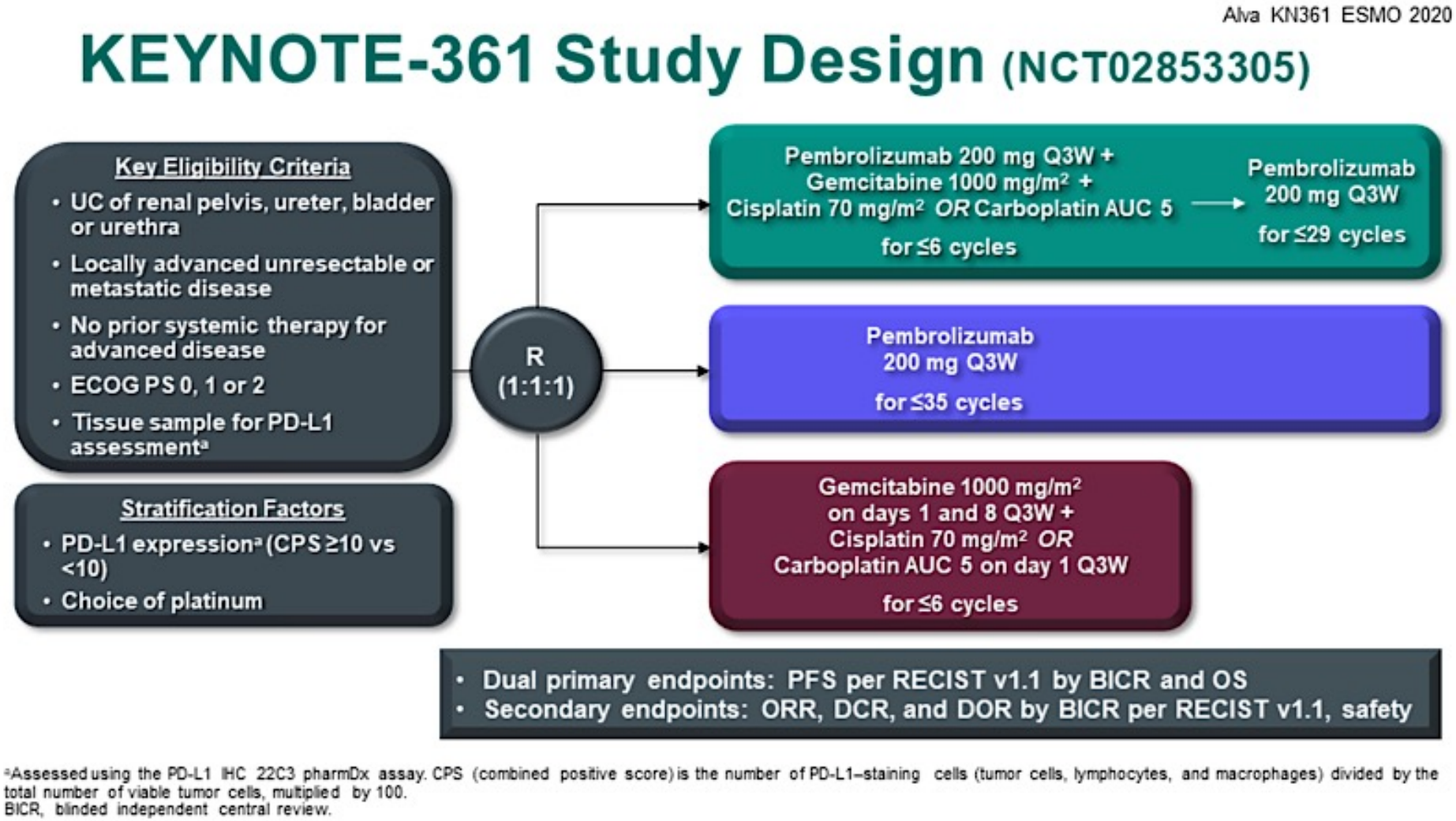




	All Patients (N = 370)		CPS ≥ 10 (n = 110)		CPS < 10 (n = 251)	
Response	Response, No. (%)	95% CI	Response, No. (%)	95% CI	Response, No. (%)	95% CI
Objective response	106 (28.6)	(24.1 to 33.5)	52 (47.3)	(37.7 to 57.0)	51 (20.3)	(15.5 to 25.8)
CR	33 (8.9)	(6.2 to 12.3)	22 (20.0)	(13.0 to 28.7)	10 (4.0)	(1.9 to 7.2)
PR	73 (19.7)	(15.8 to 24.2)	30 (27.3)	(19.2 to 36.6)	41 (16.3)	(12.0 to 21.5)

Vuky J, et al. J Clin Oncol. 2020. 38(23).

KEYNOTE-361: a confirmatory trial



Alva, et al. ESMO. 2020.

FDA Warning (May 18, 2018)

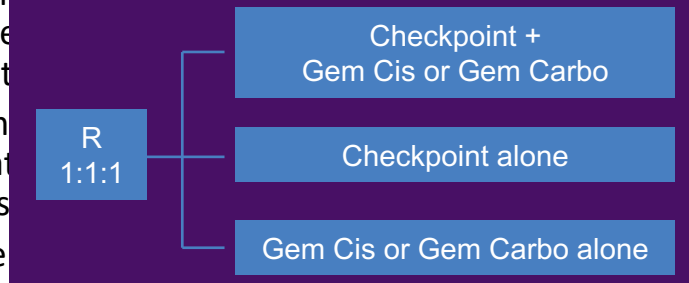
- [5/18/ s, oncology clinical investigators, and the public about decreased surviva monotherapy) in clinical trials to treat patients with metastatic urothe protein programmed death ligand 1 (PD-L1).
- In two (DMC) early reviews found patients in the monotherapy arms c who received was no nufacturers of bo enrolling patients whose tumors have PD-L1 low status to the pembrolizumab or atezolizumab monothe
- The clinical trials compare platinum-based chemotherapy combined with pembrolizumab or atezoliz trials enrolled a third arm of monotherapy with pembrolizumab or atezolizumab to compare to platinum arms remain open only to patients whose tumors have PD-L1 high status. The combination arms and the open. The FDA is reviewing the findings of the ongoing clinical trials and will communicate new informat
- Both pembrolizumab or atezolizumab are currently approved under accelerated approval for the treatm carcinoma patients who are not eligible for cisplatin-containing chemotherapy, irrespective of PD-L1 stat for other approved uses should continue to take their medication as directed by their health care profes
- Health care profes ions enrolled in the ongoing clinical trials we and therefore diffe d to the accelerated approvals of both pemb patients with locall carcinoma who are not eligible for cisplatin-containing chemotherapy. FDA recommends providers select patients for the treatment of locally advanced or metastatic urothelial cancer using the criteria described in Section 14 of each label. These criteria supported the approvals for pembrolizumab and atezolizumab for initial monotherapy in cisplatin-ineligible patients. Pembrolizumab and atezolizumab are also currently approved by the FDA for the treatment of multiple types of other cancers.
- Patients should talk to their doctor if they have questions or concerns about either drug. Health care professionals and patients are encouraged to report any adverse events or side effects related to the use of these products and other similar products to FDA's MedWatch Adverse Event Reporting program.

Alert! Decreased survival associated with the use of pembrolizumab or atezolizumab as monotherapy in clinical trials of patients with metastatic bladder cancer who have *not received prior therapy and who have low expression of PD-L1*

However…

Enrolled cisplatin-eligible and ineligible patients.

The studies cited compare monotherapy with platinum chemotherapy



FDA website. Efficacy Issue for pembrolizumab or atezolizumab.

June/July 2018: FDA and EMA Restrict Indication for First-Line Treatment to Cisplatin-Ineligible Patients and PDL1+

FDA has limited the use of atezolizumab and pembrolizumab for patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing therapy.

The Agency took this action on June 19, 2018, due to decreased survival associated with the use of pembrolizumab or atezolizumab as single therapy (monotherapy) compared to platinum-based chemotherapy in clinical trials to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1 (PD-L1).

The labels of both drugs have been revised to reflect the limitation in the indication. The indi

Pembrolizumab is indicated for the treatment of patients with locally advanced or metastatic n-containing therapy and whose tumors express PD-L1 (Combined Positive Score ≥ 10), or in pat ng chemotherapy regardless of PD-L1 status.

For pembrolizumab, patients must be cisplatin-ineligible and PDL1+ by CPS score [CPS ≥ 10]

Atezolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Are not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area), as determined by an FDA-approved test, or
- Are not eligible for any platinum-containing therapy regardless of PD-L1 status.

For atezolizumab, patients must be cisplatin-ineligible and PDL1+ by IC score [IC ≥ 5%]

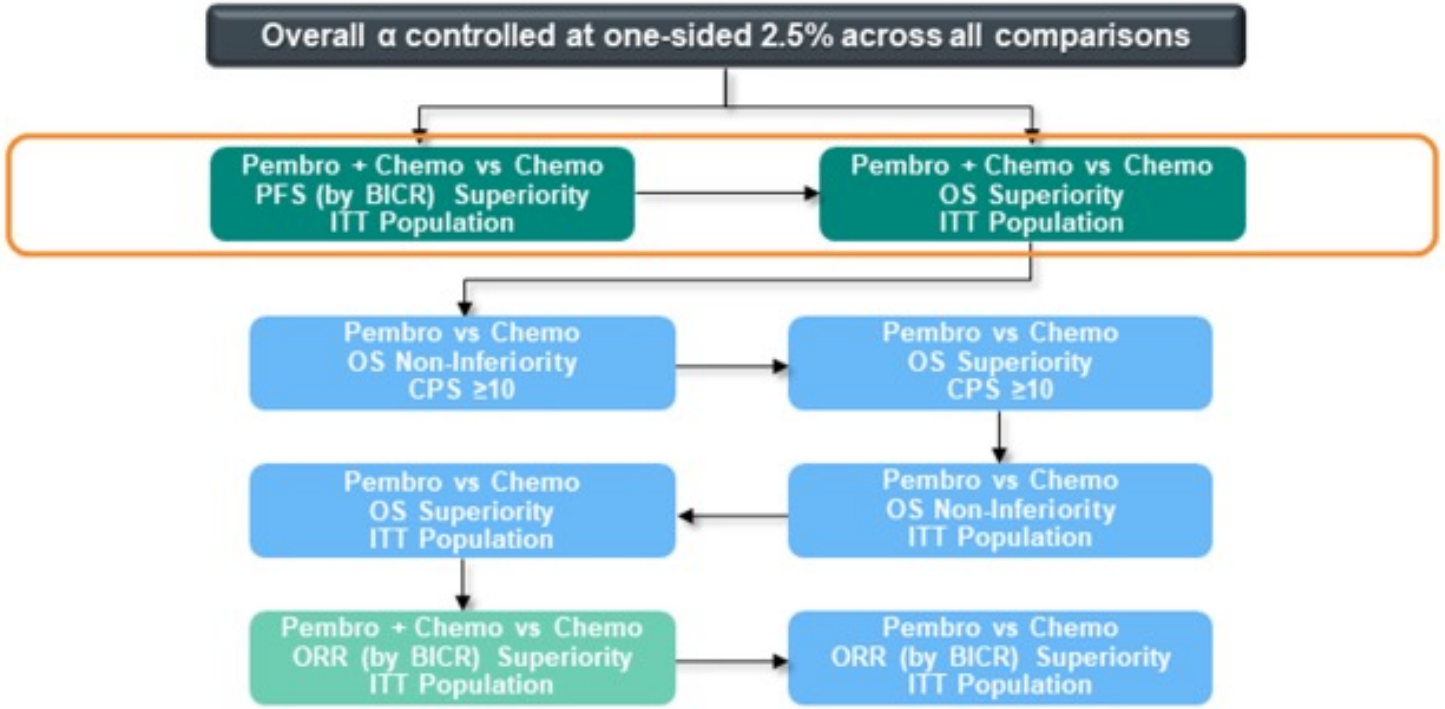
On July 2, 2018, the FDA approved the Ventana PD-L1 (SP142) Assay ld be used to select patients with locally advanced or metastatic urothelial carcinoma for treatme scribing Information for atezolizumab to require use of an FDA-approved test for patient selection.

The tests used in the trial to determine PD-L1 expression are listed in Section 14 of each drug label. The FDA is reviewing the findings of ongoing analyses and will communicate new information regarding the PD-L1 assays and indications as it becomes available.

FDA website. FDA limits use of pembrolizumab and atezolizumab; EMA website. EMA restricts use of pembrolizumab and atezolizumab.

KEYNOTE-361: analysis plan

Alva KN361 ESMO 2020

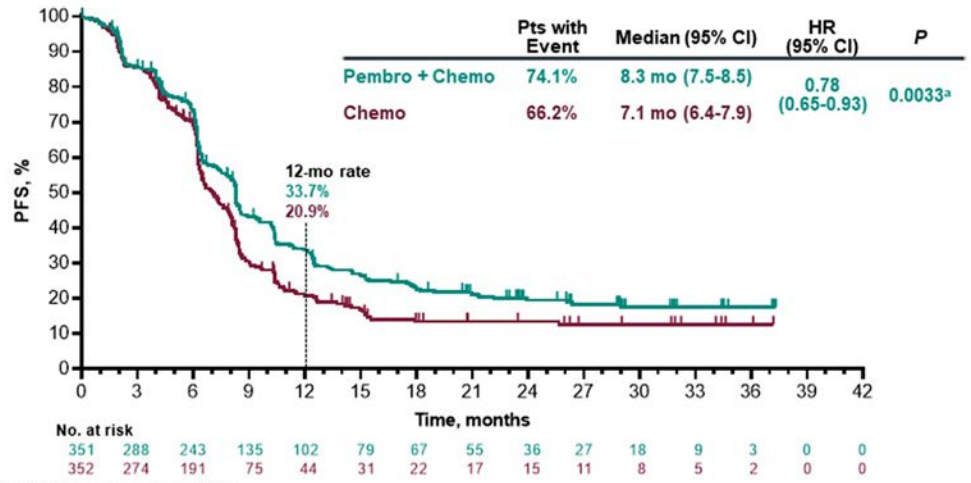


Alva, et al. ESMO. 2020.

KEYNOTE-361: a negative study

Alva KN361 ESMO 2020

PFS by BICR: Pembro + Chemo vs Chemo, ITT Population (Primary Endpoint)

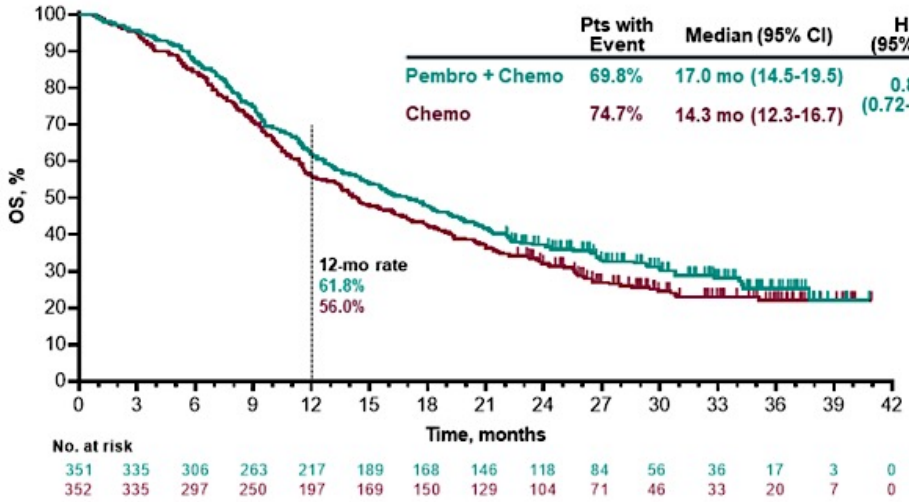


	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	74.1%	8.3 mo (7.5-8.5)	0.78 (0.65-0.93)	0.0033[a]
Chemo	66.2%	7.1 mo (6.4-7.9)		

[a]*P*-value boundary of significance at final analysis ≤0.0019.
PFS assessed per RECIST v1.1. Data cutoff date: April 29, 2020.

Alva KN361 ESMO 2020

OS: Pembro + Chemo vs Chemo, ITT Population



	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407[a]
Chemo	74.7%	14.3 mo (12.3-16.7)		

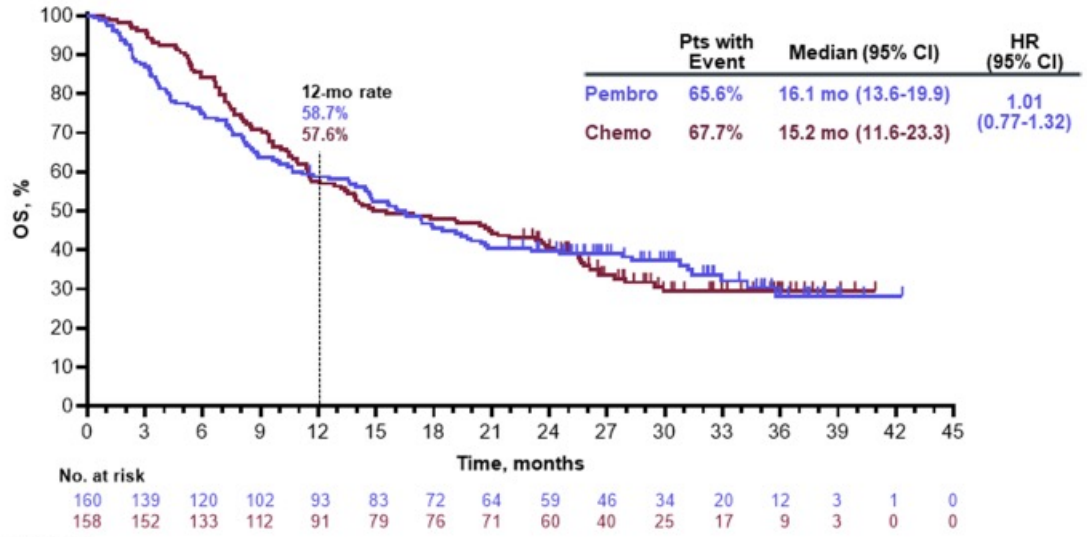
[a]*P*-value boundary of significance at final analysis ≤0.0142. Per the statistical analysis plan, no further formal statistical testing was performed.
Data cutoff date: April 29, 2020.

Alva, et al. ESMO. 2020.

KEYNOTE-361: a negative study

Alva KN361 ESMO 2020

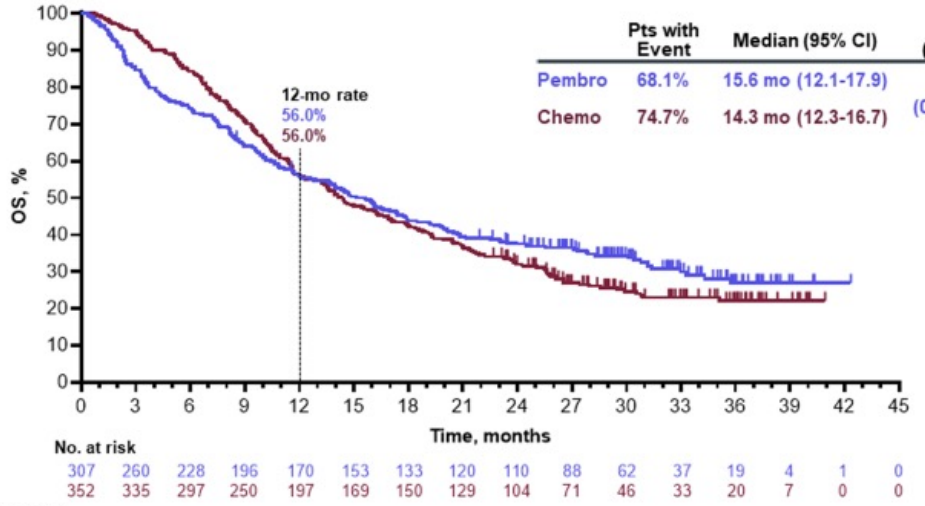
OS: Pembro vs Chemo, Patients With CPS≥10 Tumors



	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	65.6%	16.1 mo (13.6-19.9)	1.01 (0.77-1.32)
Chemo	67.7%	15.2 mo (11.6-23.3)	

Data cutoff date: April 29, 2020.

OS: Pembro vs Chemo, ITT Population



	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	68.1%	15.6 mo (12.1-17.9)	0.92 (0.77-1.11)
Chemo	74.7%	14.3 mo (12.3-16.7)	

Data cutoff date: April 29, 2020.

Alva, et al. ESMO. 2020.

Pembrolizumab as first-line treatment for mUC?

FDA Revises Label for Pembrolizumab in Patients With Advanced Urothelial Carcinoma

By The ASCO Post Staff
September 25, 2021

Get Permission

On August 31, the U.S. Food and Drug Administration (FDA) revised the label for the anti–PD-1 therapy pembrolizumab for its indication in first-line advanced urothelial carcinoma. The FDA converted the indication from an accelerated approval to a full approval. In addition, as part of the label update, this indication has been revised to be for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy.

Previously, pembrolizumab was indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy and whose tumors expressed PD-L1 (combined positive score [CPS] ≥ 10) as determined by an FDA-approved test, or in patients who were not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication received an accelerated approval based on tumor response rate and duration of response.

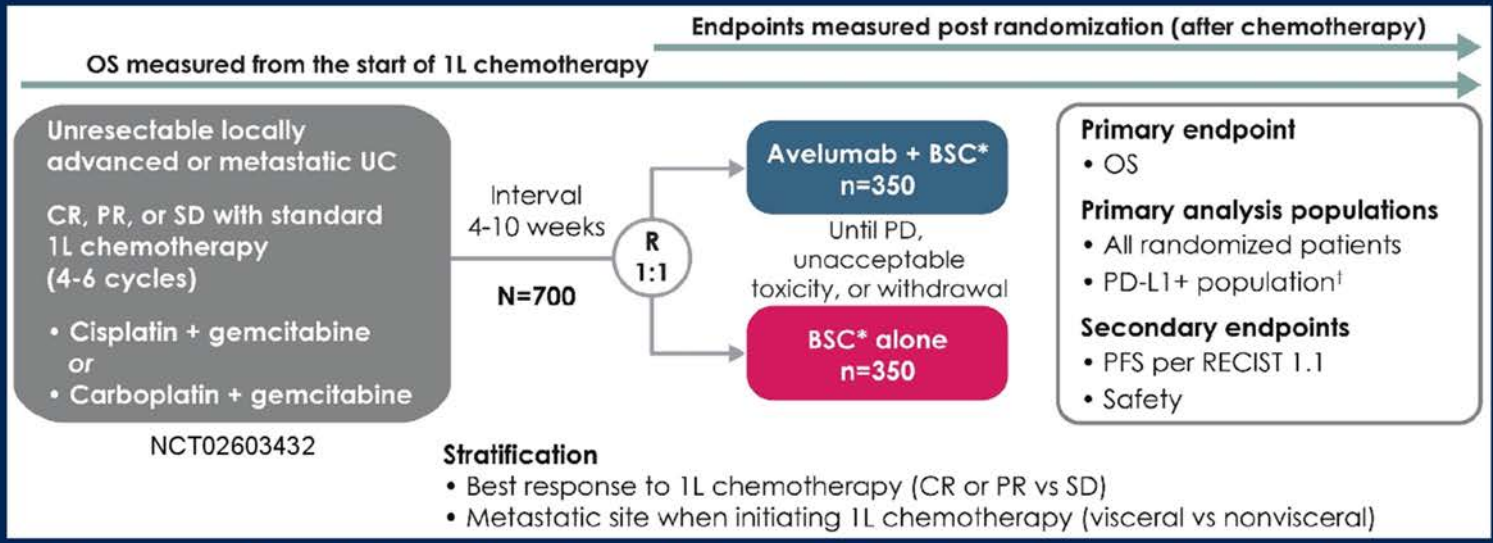
Continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. The subsequent phase III KEYNOTE-361 trial, evaluating pembrolizumab as monotherapy and in combination with chemotherapy for the first-line treatment of patients with advanced or metastatic urothelial carcinoma who were eligible for platinum-containing chemotherapy, did not meet its prespecified dual primary endpoints of overall and progression-free survival compared with standard-of-care chemotherapy.

August 31, 2021

"For the treatment of patients with locally advanced or metastatic UC who are not eligible for ANY platinum-containing chemotherapy"

JAVELIN Bladder 100 Update

JAVELIN Bladder 100 phase 3 study design



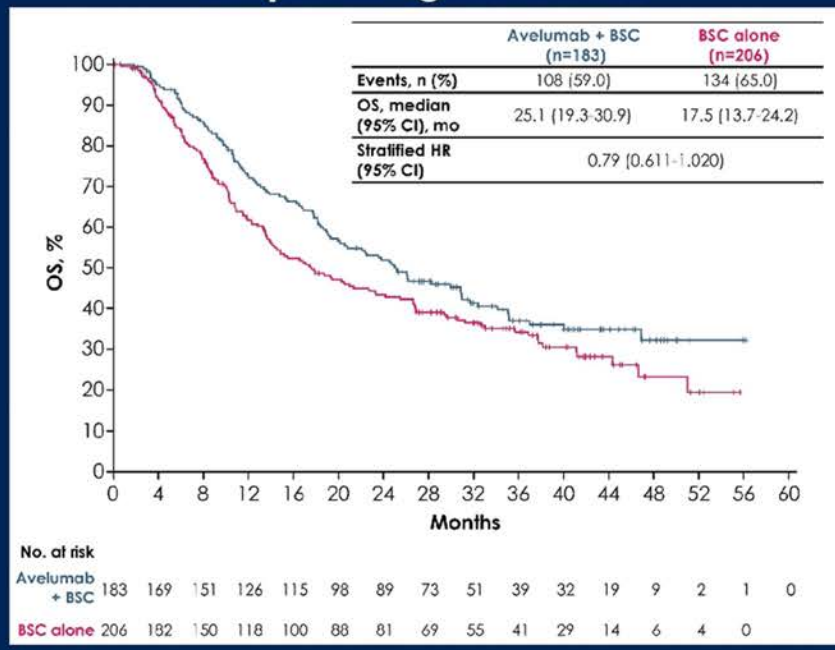
- Avelumab 1L maintenance + BSC significantly prolonged OS and PFS vs BSC alone in patients without progression on 1L platinum-based chemotherapy,[1,2] leading to its approval in various countries worldwide[3,4]
  - With long-term follow-up (data cutoff, June 4, 2021), median OS was 23.8 vs 15.0 months, respectively (HR, 0.76 [95% CI, 0.63-0.91]; 2-sided p=0.0036)[2]
- We report post hoc analyses of long-term outcomes (≥2 years of follow-up in all patients) in subgroups defined by 1L chemotherapy regimen
- Additionally, OS from the start of 1L chemotherapy was analyzed

Sridhar et al. ASCO Genitourinary Cancers Symposium 2023.

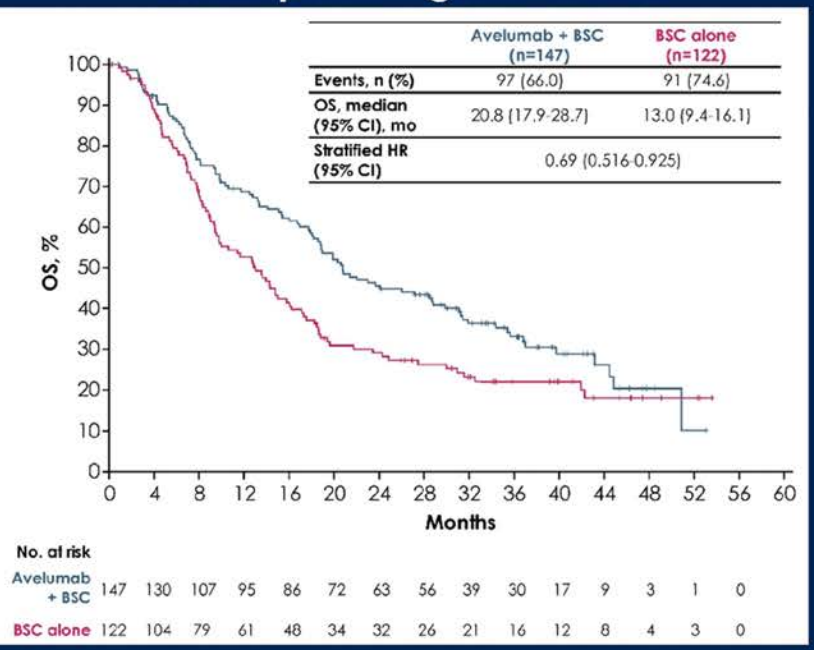
JAVELIN Bladder 100 Update

OS from start of maintenance (randomization)

Cisplatin + gemcitabine



Carboplatin + gemcitabine



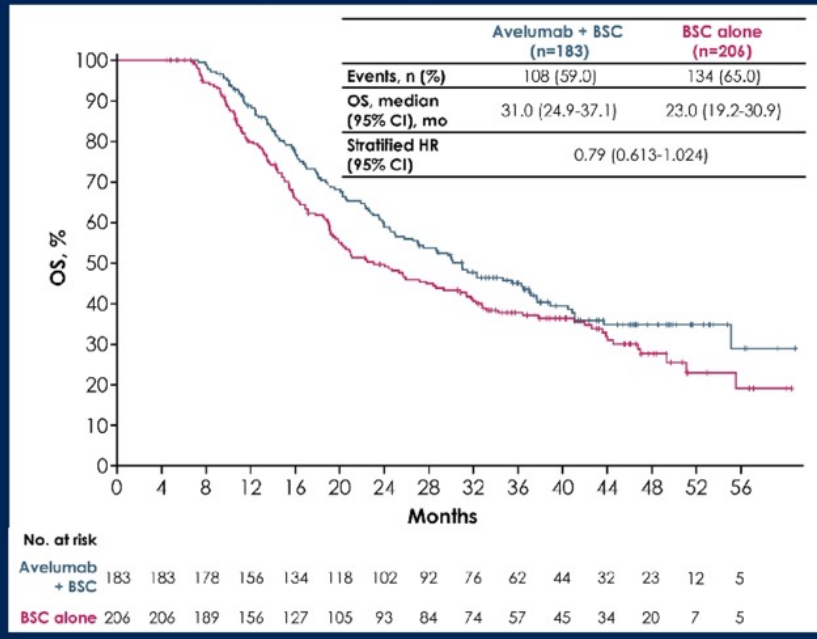
- OS* was longer with avelumab + BSC vs BSC alone in both the cisplatin and carboplatin subgroups
- In both subgroups, investigator-assessed PFS* was also longer with avelumab + BSC vs BSC alone

Sridhar et al. ASCO Genitourinary Cancers Symposium 2023.

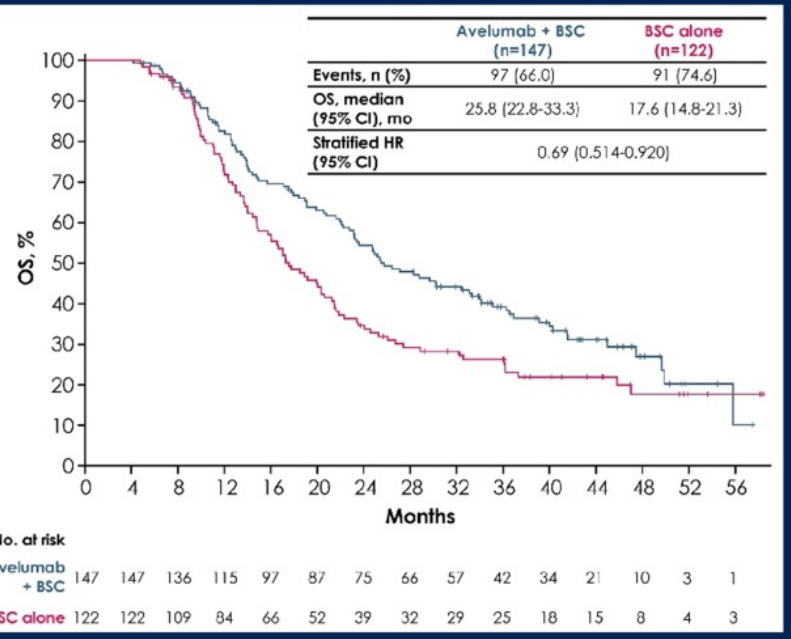
JAVELIN Bladder 100 Update

OS from start of 1L chemotherapy

Cisplatin + gemcitabine



Carboplatin + gemcitabine



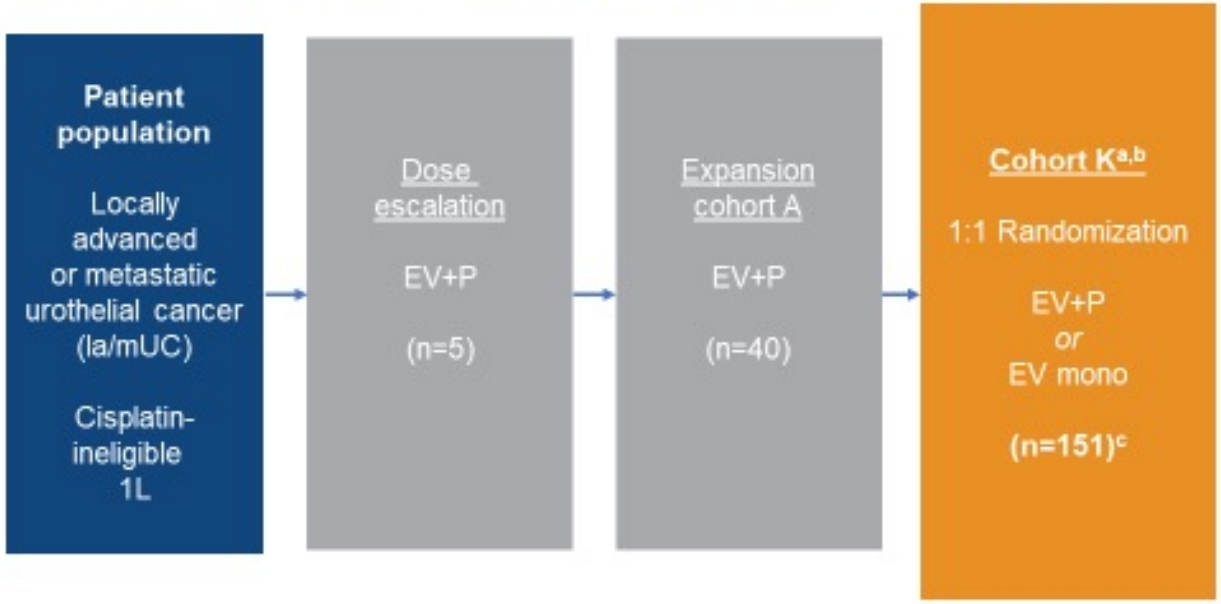
- In the overall population, median OS measured from the start of 1L chemotherapy was 29.7 months with avelumab + BSC and 20.5 months with BSC alone
- OS measured from the start of 1L chemotherapy was also longer with avelumab + BSC vs BSC alone irrespective of 1L chemotherapy regimen

Sridhar et al. ASCO Genitourinary Cancers Symposium 2023.

EV-103 Cohort K: EV mono or EV+P in previously untreated cisplatin-ineligible pts with la/mUC

EV-103 Cohort K

Part of an open-label, multiple cohort, phase 1b/2 study in patients with la/mUC



Study endpoints

- **Primary endpoint:** confirmed ORR by RECIST v1.1 per BICR
- **Key secondary endpoints:** confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS, OS, safety/tolerability, and lab abnormalities
- **Exploratory endpoints**: PK, biomarkers, PFS2, **PROs (EORTC QLQ-C30, BPI-SF**, EQ-5D-5L, HRU)

Statistical considerations

- No formal statistical comparisons between the two treatment arms

Dosing schedule: EV 1.25 mg/kg IV on days 1 and 8, and P 200 mg IV on day 1 of every 3-week cycle.

[b]Cohort K stratification factors: liver metastases (present/absent) and ECOG PS (0 or 1/2); the sample size was based on precision of the estimate for ORR characterized by 95% CIs.

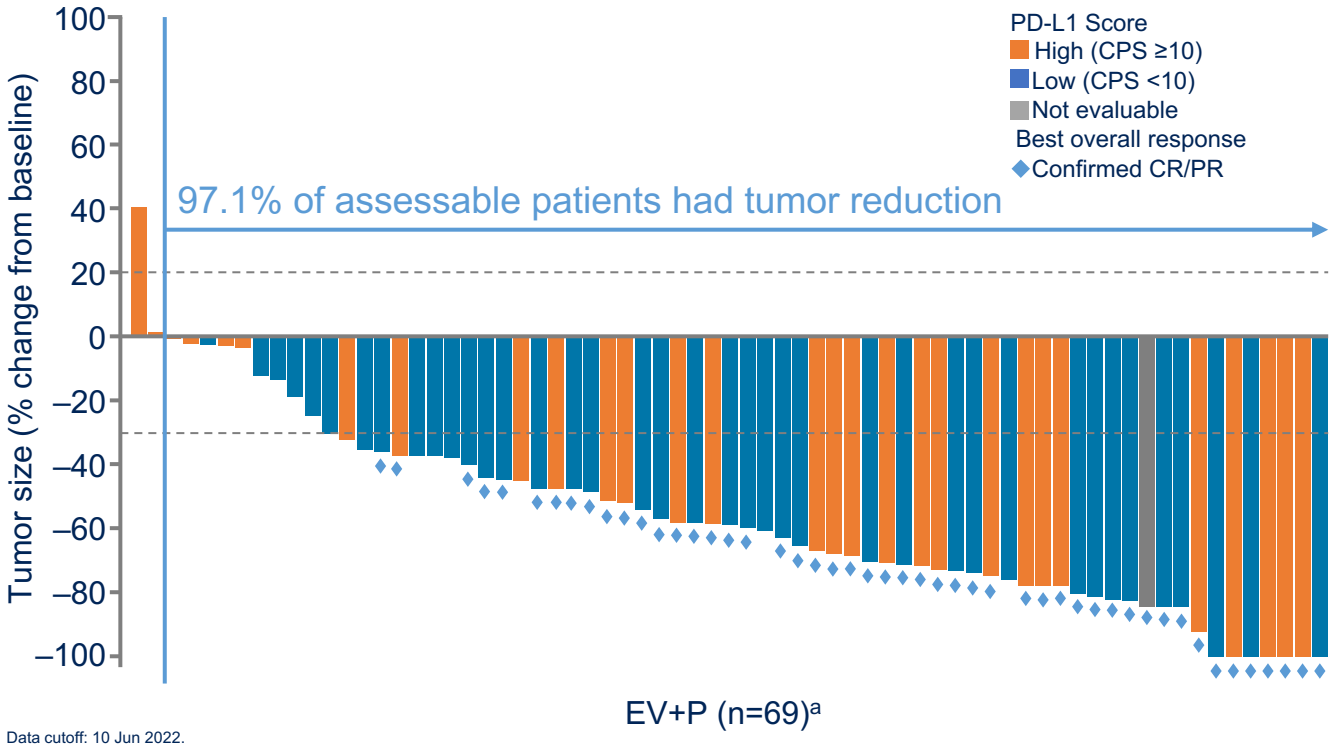
[c]Cohort K completed enrollment on 11 Oct 2021; data cutoff was 10 Jun 2022.

[a]The full analysis set included all patients who enrolled in the study and received study treatment. Of 151 patients who were randomized, 149 were treated; 2 patients were randomized but not treated and so were not included in the safety and efficacy analyses.

1L, first-line; BICR, blinded independent central review; BPI-SF, Brief Pain Inventory Short Form; CI, confidence interval; DCR, disease control rate; DOR, duration of response; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire; EQ-5D-5L, EuroQol-5 dimension-5 level; EV, enfortumab vedotin; HRU, healthcare resource utilization; la/mUC, locally advanced/metastatic urothelial cancer; mono, monotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; P, pembrolizumab; PK, pharmacokinetics; PROs, patient-reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumours.

Milowsky M et al. Genitourinary Cancers Symposium 2023;Abstract 439.

EV-103 Cohort K: EV mono or EV+P in previously untreated cisplatin-ineligible pts with la/mUC



Data cutoff: 10 Jun 2022.

[a]Of 76 patients in the EV+P arm, seven patients were not assessable due to non-measurable disease (n=4), post-baseline assessment that was not evaluable (n=2), and lack of post-baseline assessment (n=1).

[b]**There were no formal statistical comparisons between treatment arms**.

2L, second-line; AEs, adverse events; BICR, blinded independent central review; CI, confidence interval; cORR: confirmed objective response rate; CPS, combined positive score; CR, complete response; EV, enfortumab vedotin; la/mUC, locally advanced/metastatic urothelial cancer; mono, monotherapy; NR, not reached; P, pembrolizumab; PD-L1, programmed death-ligand-1; PR, partial response; TRAEs, treatment-related adverse events.

	EV+P[b] (n=76)	EV mono[b] (n=73)
cORR, n (%) (95% CI)	49 (64.5) (52.7-75.1)	33 (45.2) (33.5-57.3)
Median time to objective response (range), mo	2.07 (1.1-6.6)	2.07 (1.9-15.4)
Median number of treatment cycles (range)	11.0 (1-29)	8.0 (1-33)

EV+P

- 42/49 (85.7%) of responses observed at first assessment (week 9±1 week)
- Most common AEs were fatigue, peripheral sensory neuropathy, alopecia, and maculopapular rash

EV mono

- Activity is consistent with prior results in 2L+ la/mUC
- Safety profile consistent with previous studies

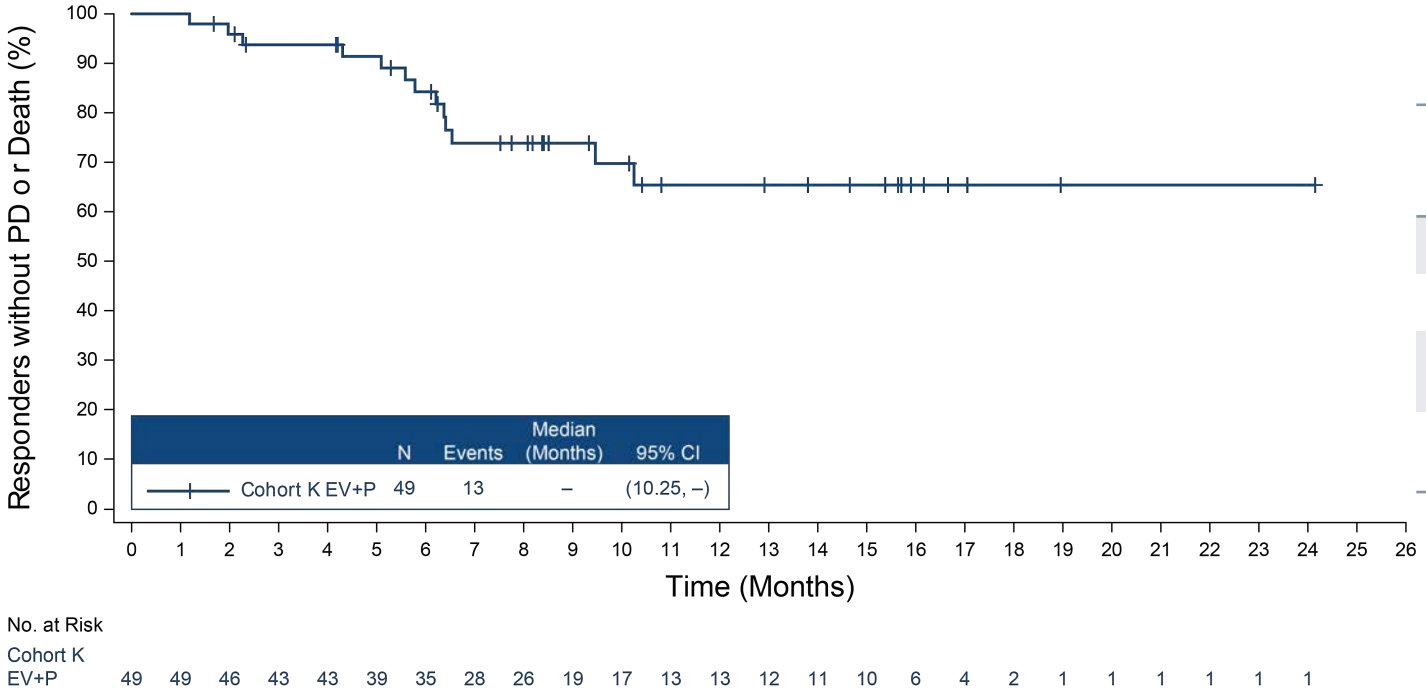
Previously presented at ESMO 2022, Rosenberg et al. Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC).

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

Rosenberg J et al. ESMO 2022; LBA73.

EV-103 Cohort K: EV mono or EV+P in previously untreated cisplatin-ineligible pts with la/mUC

Median DOR for EV+P was not reached; 65.4% of responders were still responding at 12 months



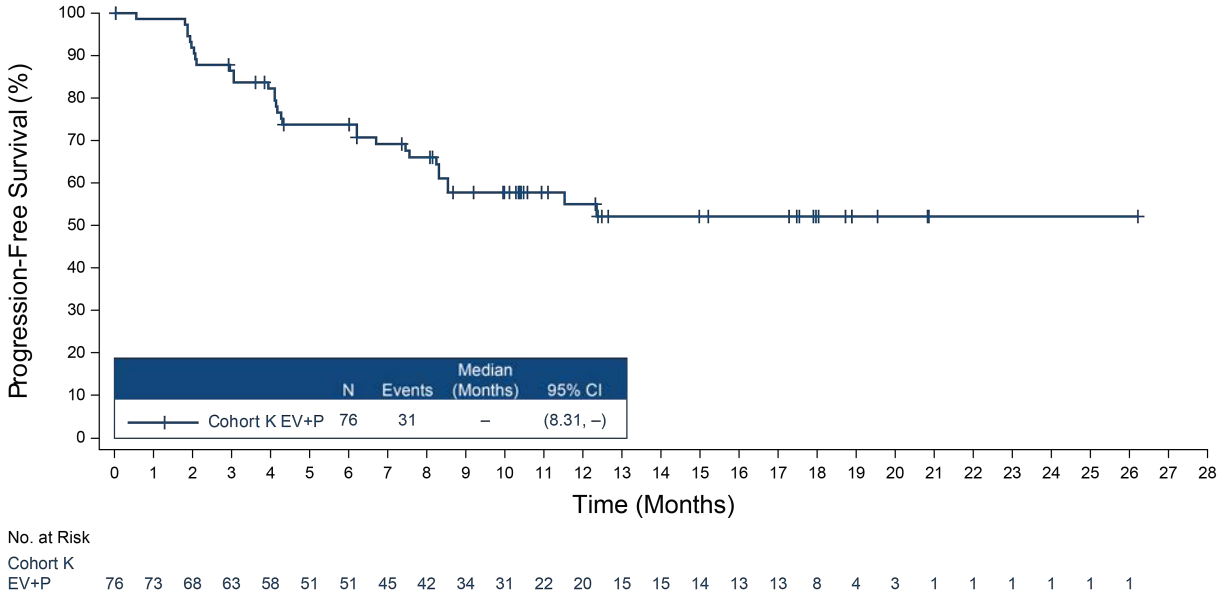
	EV+P (N=76)	EV Mono (N=73)
Responders, n	49	33
Progression events, n	13	14
mDOR (95% CI), mos	- (10.25, -)	13.2 (6.14, 15.97)
DOR ≥12 mos, %	65.4%	56.3%

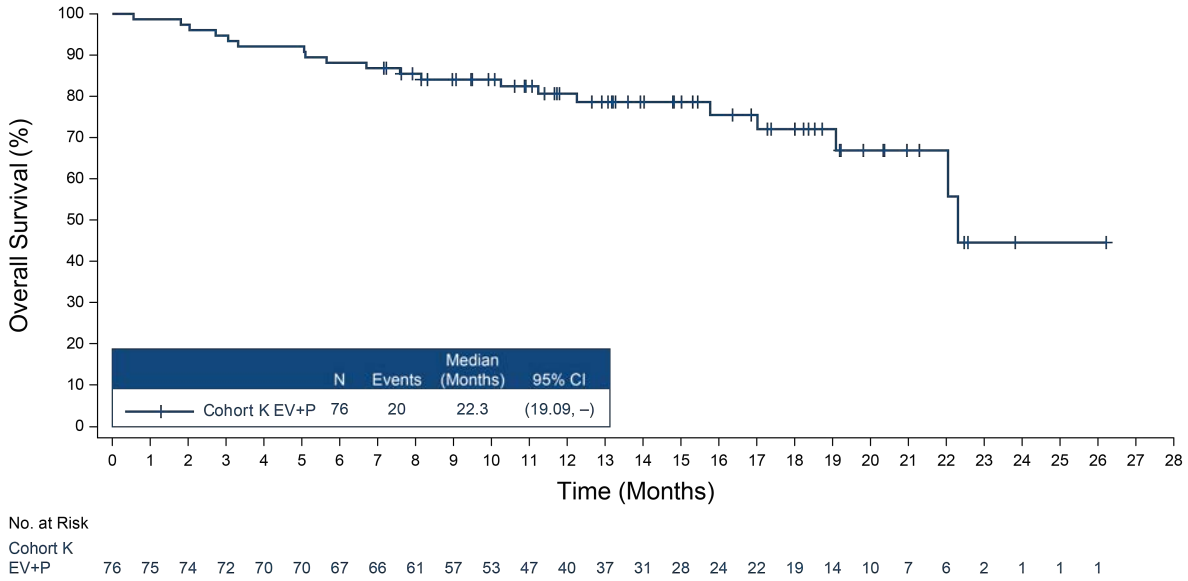
Rosenberg J et al. ESMO 2022; LBA73.

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

EV-103 Cohort K: EV mono or EV+P in previously untreated cisplatin-ineligible pts with la/mUC

Encouraging PFS and OS for EV+P with data expected to continue to evolve with follow-up





	EV+P (N=76)	EV Mono (N=73)
PFS events, n	31	38
mPFS (95% CI), mos	- (8.31, -)	8.0 (6.05, 10.35)
PFS at 12 mos, %	55.1%	35.8%

	EV+P (N=76)	EV Mono (N=73)
OS Events, n	20	26
mOS (95% CI), mos	22.3 (19.09, -)	21.7 (15.21, -)
OS at 12 mos, %	80.7%	70.7%
Median follow-up time, mos	14.8	15.0

Rosenberg J et al. ESMO 2022; LBA73.

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

EV-103 Cohort K: Safety

Treatment-Related Adverse Events (TRAEs)

Most common AEs with EV+P were fatigue, peripheral sensory neuropathy, alopecia, and maculo-papular rash

TRAEs **Any Grades** by Preferred Term ≥20% of Patients	EV+P (N=76) n (%)		EV Mono (N=73) n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Overall	76 (100.0)	48 (63.2)	68 (93.2)	35 (47.9)
Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
Alopecia	45 (46.1)	0	26 (35.6)	0
Rash maculo-papular	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
Pruritus	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
Dysgeusia	23 (30.3)	0	25 (34.2)	0
Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
Decreased appetite	20 (26.3)	0	28 (38.4)	0
Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
Dry eye	15 (19.7)	0	8 (11.0)	0

EV-Treatment-Related Adverse Events of Special Interest

The majority of treatment-related AESIs were grade ≤ 2

Skin reactions were observed more frequently with EV+P

	EV+P (N=76)		EV Mono (N=73)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Skin reactions	51 (67.1)	16 (21.1)	33 (45.2)	6 (8.2)
Peripheral neuropathy	46 (60.5)	2 (2.6)	40 (54.8)	2 (2.7)
Ocular disorders	20 (26.3)	0	21 (28.8)	0
Dry eye	18 (23.7)	0	9 (12.3)	0
Blurred vision	9 (11.8)	0	10 (13.7)	0
Corneal disorders	0	0	4 (5.5)	0
Hyperglycemia	11 (14.5)	5 (6.6)	8 (11.0)	7 (9.6)
Infusion-related reactions	3 (3.9)	0	4 (5.5)	0

Rosenberg J et al. ESMO 2022; LBA73.

FDA Approval: EV plus P

FDA grants accelerated approval to enfortumab vedotin-ejfv with pembrolizumab for locally advanced or metastatic urothelial carcinoma

April 3, 2023

On April 3, 2023, the Food and Drug Administration granted accelerated approval to enfortumab vedotin-ejfv with pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy.

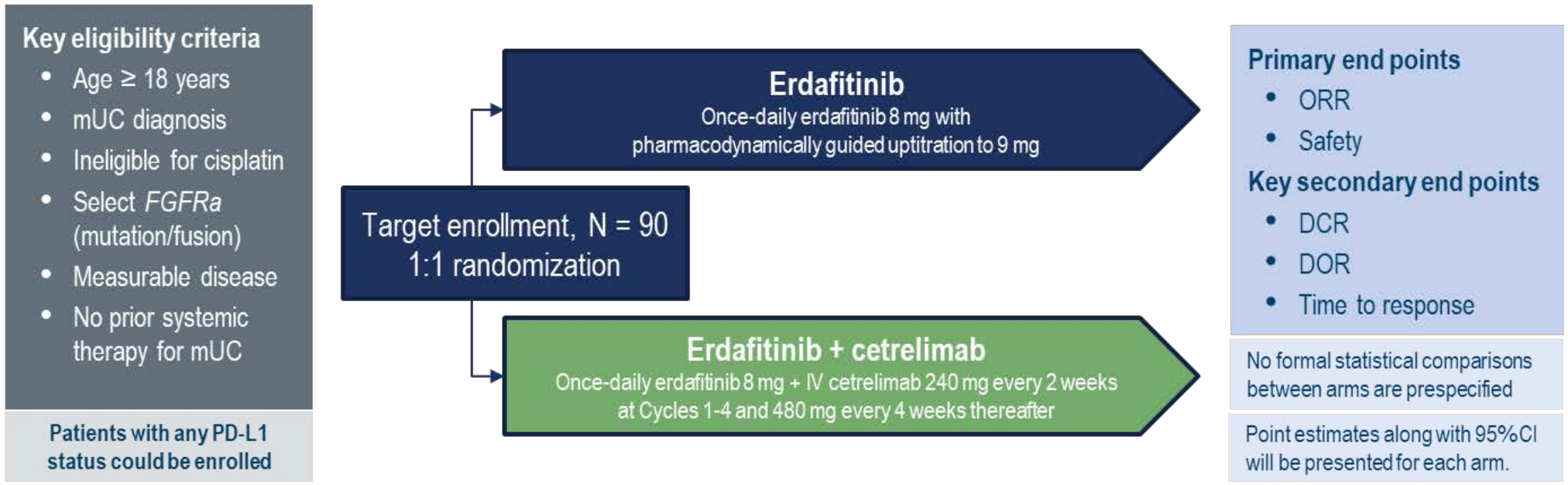
View full prescribing information for enfortumab vedotin-ejfv with pembrolizumab.

Efficacy was evaluated in EV-103/KEYNOTE-869 (NCT03288545), a multi-cohort (dose escalation cohort, Cohort A, Cohort K) study. The dose escalation cohort and Cohort A were single-arm cohorts treating patients with enfortumab vedotin-ejfv plus pembrolizumab while patients on Cohort K were randomized to either the combination or to enfortumab vedotin-ejfv alone. Patients had not received prior systemic therapy for locally advanced or metastatic disease and were ineligible for cisplatin-containing chemotherapy. A total of 121 patients received enfortumab vedotin-ejfv plus pembrolizumab.

FDA website. FDA approval for EV plus pembrolizumab.

Phase 2 NORSE Study: erdafitinib or erdafitinib plus cetrelimab for metastatic or locally advanced UC and FGFR alterations

NORSE Phase 2 Study Design[a]



- *Sample size determination:* Assuming a true ORR of 45% in the erdafitinib arm and 55% in the erdafitinib + cetrelimab arm, n ≈ 45 patients in each arm would result in an estimated ORR that is above a 95% CI lower bound of 30% and 40%, respectively
- A review of safety and efficacy data was planned per the data review committee charter when ~40 patients were response-evaluable

DCR, disease control rate; DOR, duration of response; IV, intravenous; ORR, overall response rate.
[a]Enrollment began in April 2018. The data cut-off for this analysis was July 19, 2021.

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Powles et al. ESMO 2021.

Phase 2 NORSE Study: Baseline Characteristics

NORSE: Baseline Demographics and Disease Characteristics

Characteristic	Erdafitinib (n = 26)	Erdafitinib + Cetrelimab (n = 27)
Age, median (range), years	75 (45-92)	69 (56-91)
Men, n (%)	19 (73%)	20 (74%)
Presence of visceral metastases[a], n (%)	14 (54%)	14 (52%)
ECOG PS, n (%)[b]		
0-1	20 (77%)	17 (63%)
2	6 (23%)	9 (33%)
Primary tumor location, n (%)		
Lower tract	19 (76%)	22 (85%)
Upper tract	6 (24%)	4 (15%)
PD-L1 positive status[c], n (%)		
Yes	2 (8%)	2 (7%)
No	10 (39%)	7 (26%)
Unknown[d]	14 (54%)	18 (67%)
FGFRa[e], n (%)		
Mutations	23 (88%)	18 (67%)
Fusions	3 (12%)	7 (26%)
Mutations and fusions	0	1 (4%)

[a]Lung, liver, or bone. [b]Eastern Cooperative Oncology Group performance status (ECOG PS) was not reported for 1 patient in the erdafitinib + cetrelimab arm. [c]PD-L1 expression level was assessed by immunohistochemistry (Dako 28.8) in tumor tissue provided at screening (PD-L1 positivity if Combined Positive Score ≥ 10). [d]Includes insufficient biopsy tissue, results pending, and test failed. [e]*FGFRa* were reported in 26 patients in the erdafitinib + cetrelimab arm.

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Phase 2 NORSE Study: Efficacy

NORSE: Efficacy

	Erdafitinib (n = 18)	Erdafitinib + Cetrelimab (n = 19)
ORR[a], n (%) [95% CI]	6 (33%) [13%-59%]	13 (68%) [43%-87%]
Complete response, n (%)	1 (6%)	4 (21%)
Partial response, n (%)	5 (28%)	9 (47%)
DOR, median, months [95% CI]	NE [4.4-NE]	6.9 [1.6-NE]
Responses ongoing, n (%)	5 (28%)	10 (53%)
Time to response, median (range), months	2.3 (1-6)	1.8 (1-4)
DCR, n (%) [95% CI]	18 (100%) [82%-100%]	17 (90%) [67%-99%]

[a]All responses included in ORR are confirmed responses.

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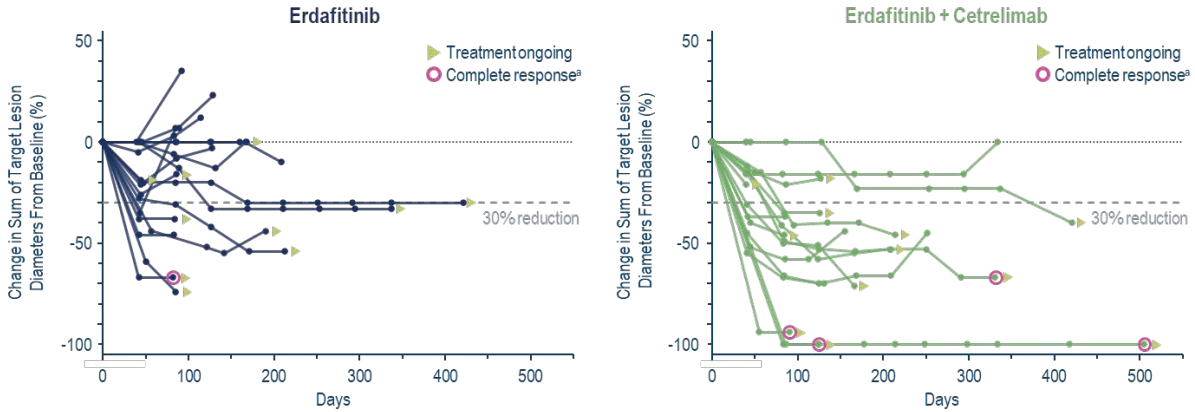
NORSE: Antitumor Activity Over Time



- Patients in both treatment arms had a durable reduction in the sum of target lesion diameters over time
- Median of the maximum reduction in the sum of target lesion diameters was 28% in the erdafitinib arm and 51% in the erdafitinib + cetrelimab arm

[a]Complete responses include patients who had sum of target lesions > 0 mm; in patients with lymph node target lesions, a diameter < 10 mm is required for complete response per RECIST 1.1.

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Phase 2 NORSE Study: Safety

NORSE: Safety Profile

Patients with TEAE, n (%)	Erdafitinib (n = 24)	Erdafitinib + Cetrelimab (n = 24)
TEAE of any grade	23 (96%)	23 (96%)
Most frequent (≥ 25% of patients)		
Hyperphosphatemia	14 (58%)	14 (58%)
Stomatitis	15 (63%)	13 (54%)
Diarrhea	12 (50%)	10 (42%)
Dry mouth	5 (21%)	14 (58%)
Dry skin	5 (21%)	9 (38%)
Anemia	6 (25%)	6 (25%)
Drug-related TEAEs leading to treatment discontinuation[a]	2 (8%)	Erdafitinib and/or cetrelimab: 7 (29%)[b] Both erdafitinib and cetrelimab: 2 (8%)

- The safety profile of erdafitinib + cetrelimab was generally similar to that of erdafitinib alone
- Grade 3-4 TEAEs occurred in 9 patients (38%) in the erdafitinib arm and 12 patients (50%) in the erdafitinib + cetrelimab arm; most frequent were:
  - Erdafitinib arm: anemia (n = 3 patients [12.5%]) and general physical health deterioration (n = 3 [12.5%])
  - Erdafitinib + cetrelimab arm: stomatitis (n = 3 [12.5%]), lipase increased (n = 3 [12.5%]), and fatigue (n = 2 [8.3%])
- 1 death in the erdafitinib + cetrelimab arm was determined to be related to cetrelimab (respiratory failure)

TEAE, treatment-emergent adverse event. [a]No drug-related TEAE of the same type led to discontinuation in > 1 patient. [b]4 patients discontinued only erdafitinib, 1 discontinued only cetrelimab; 2 discontinued both.

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Powles et al. ESMO 2021.

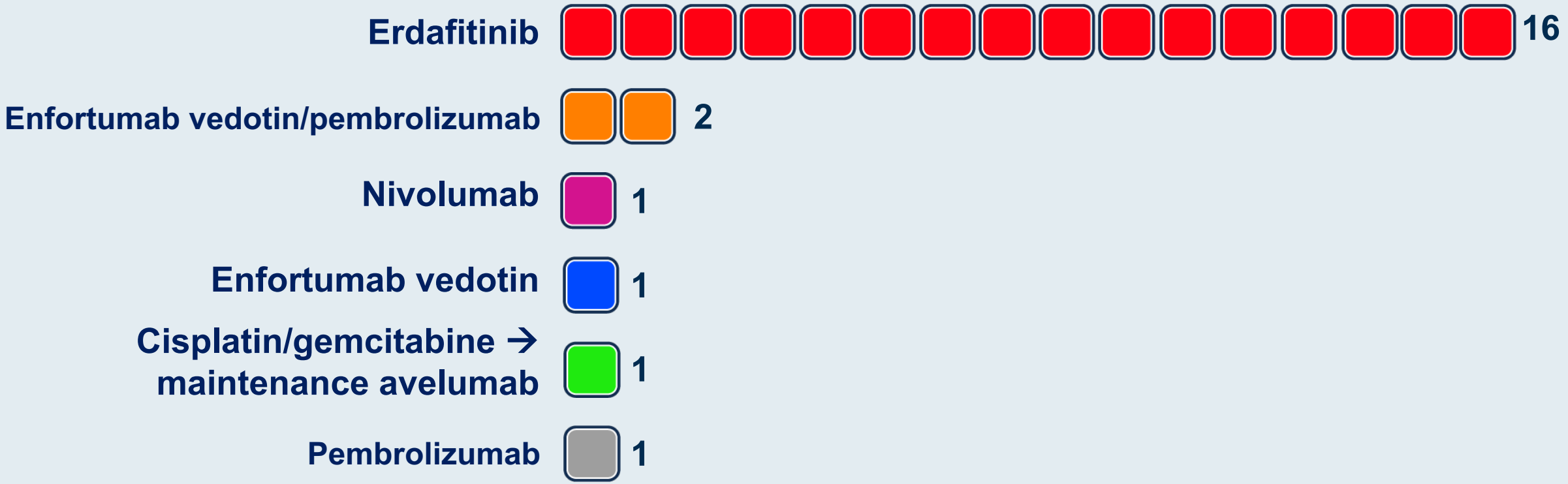
Conclusions

- **Pembrolizumab monotherapy has a more limited role in the first-line treatment for patients with mUC.**
- **Maintenance immunotherapy remains a SOC for patients with mUC who are progression-free following 1L platinum-based chemotherapy.**
- **EV plus P is a new first-line therapeutic option for patients with mUC who are ineligible for cisplatin-containing chemotherapy.**
- **Molecularly selected patients with mUC may benefit from novel combination approaches such as erdafitinib plus cetrelimab.**

MODULE 5: Selection and Sequencing of Therapy for Relapsed/Refractory mUBC

RTP
RESEARCH
TO PRACTICE

A 65-year-old patient receives neoadjuvant chemotherapy followed by cystectomy and then adjuvant nivolumab for FGFR-mutated UBC but develops metastatic disease 9 months after starting nivolumab. Regulatory and reimbursement issues aside, what would you likely recommend?

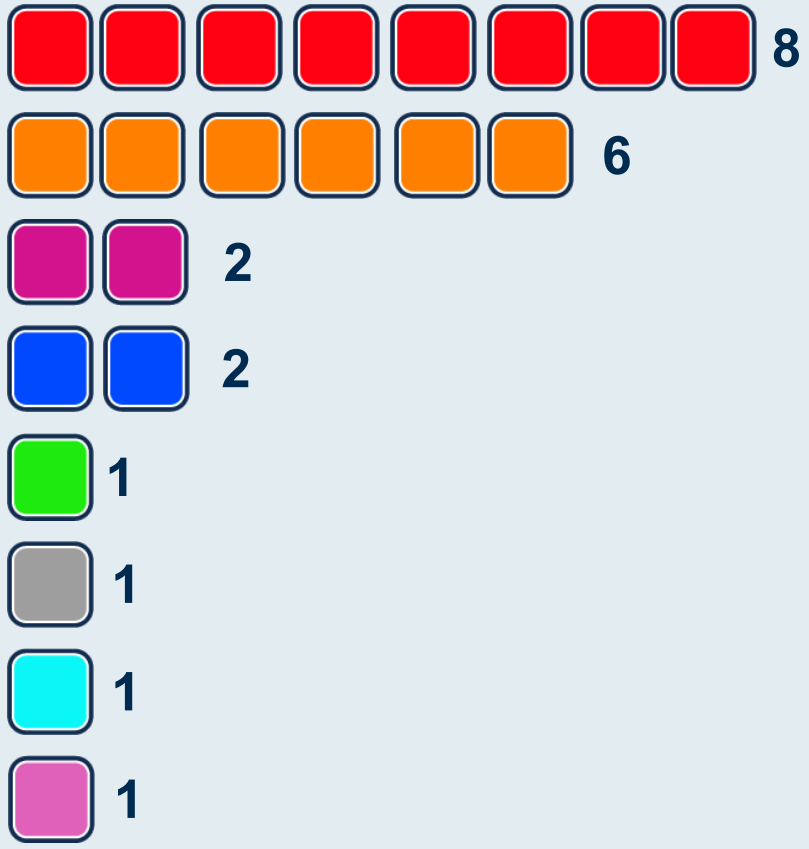


Survey of urologic oncology clinical investigators

Regulatory and reimbursement issues aside, what would you generally recommend for an 80-year-old platinum-ineligible patient who undergoes cystectomy followed by adjuvant nivolumab for FGFR-mutated UBC but develops liver metastases 9 months after starting nivolumab?

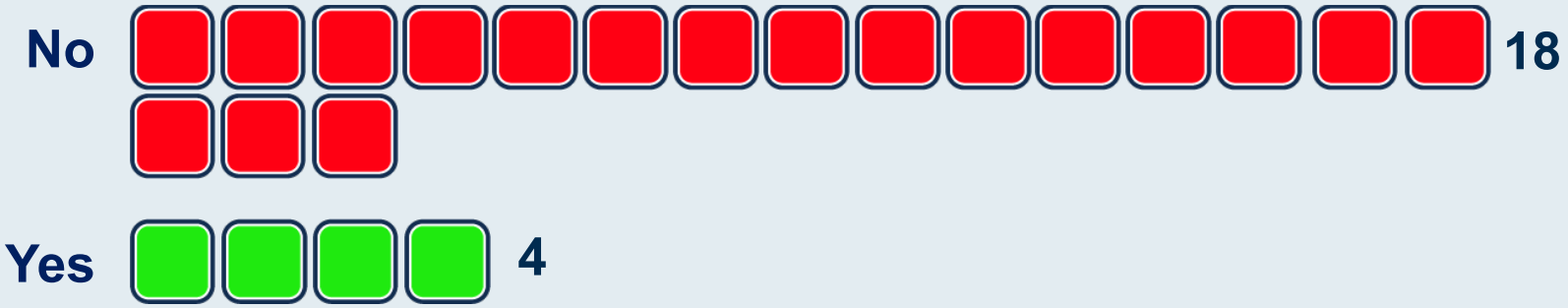
Survey of urologic oncology clinical investigators

An 85-year-old woman underwent cystectomy for pT3N1 disease 3 years ago. She received adjuvant gemcitabine/cisplatin for nodal disease. ECOG PS is 0. Recent surveillance imaging reveals retroperitoneal lymphadenopathy and small lung nodules. FGFR mutated. Regulatory and reimbursement issues aside, what would be your preferred first-line therapy?

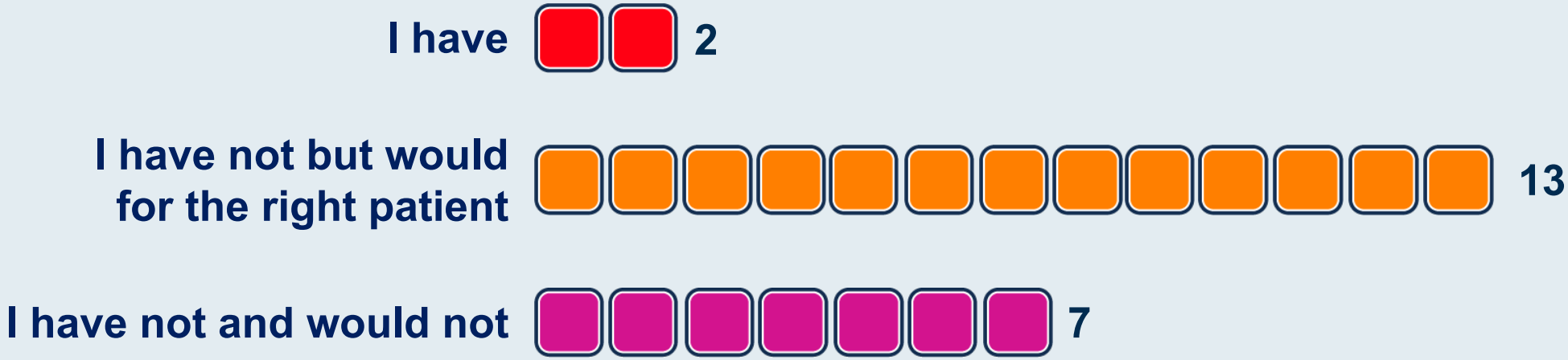


Survey of urologic oncology clinical investigators

Do you generally conduct HER2 testing for your patients with metastatic UBC?



Have you offered or would you offer HER2-targeted therapy to your patients with HER2-positive metastatic UBC outside of a protocol setting?



Survey of urologic oncology clinical investigators

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

Selection and Sequencing: Targeted Therapy in Previously Treated Metastatic Urothelial Cancer

Arlene Siefker-Radtke, MD
Professor
Department of Genitourinary Medical Oncology

CHOOSING A GOOD TARGET

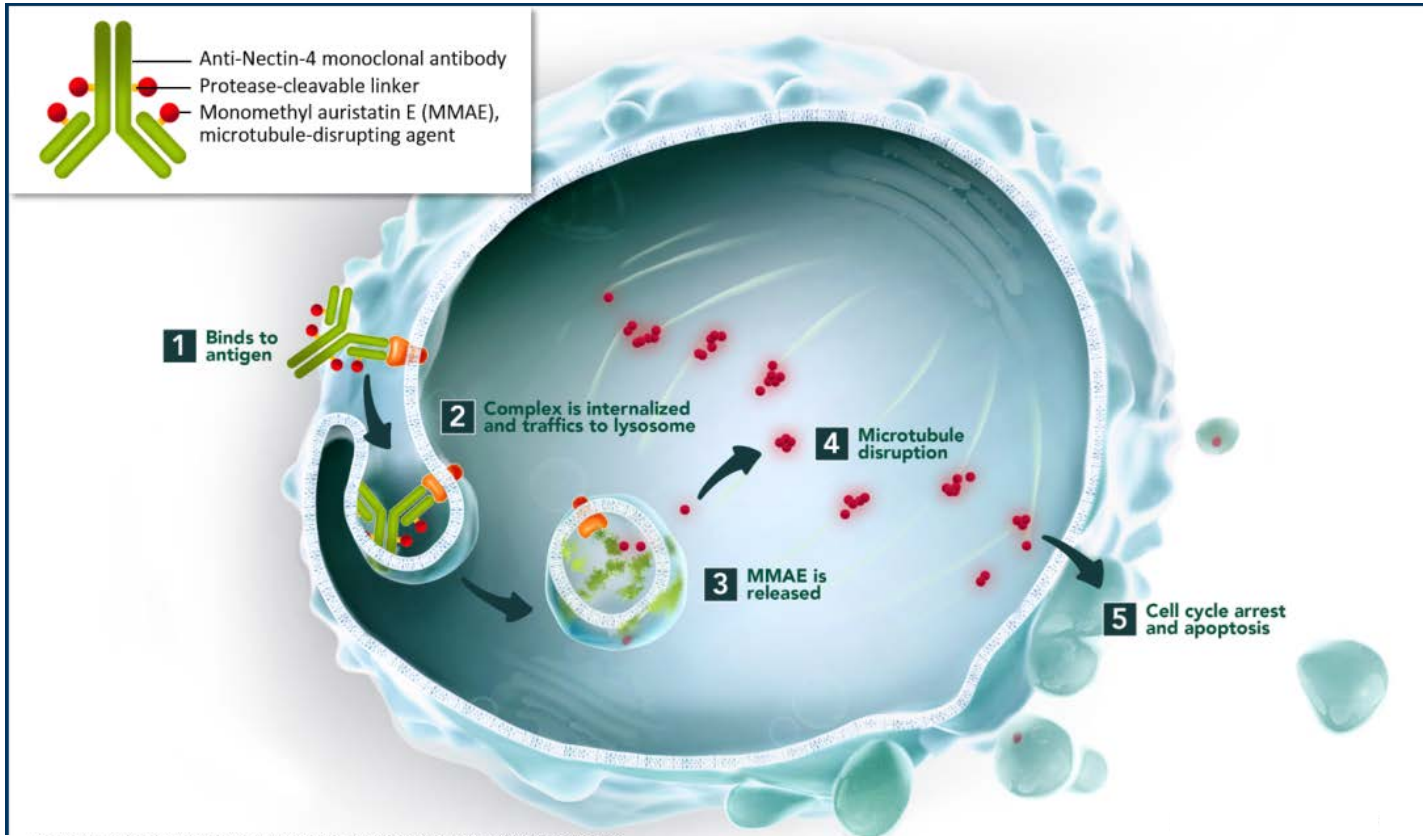
Easily reproducible

- Anyone can do it
- CLIA certification
- Not open to interpretation/everyone agrees
- Does not fluctuate or change

Predicts response or benefit!


Enfortumab Vedotin:
The First Antibody Drug Conjugate in mUC

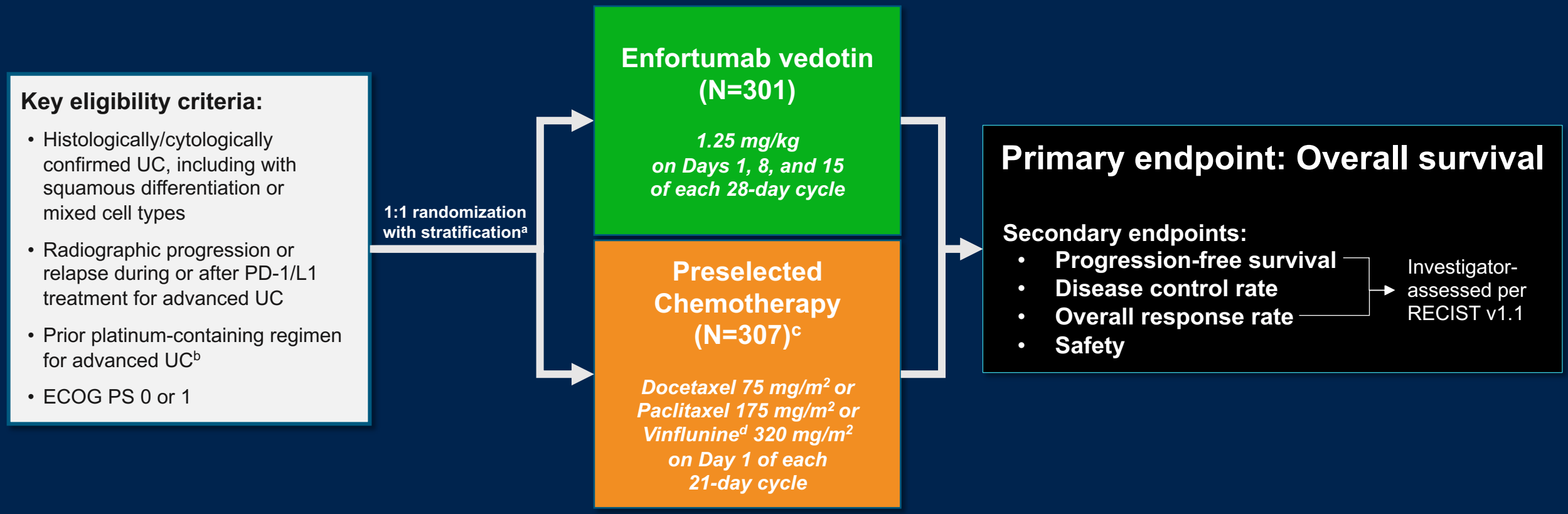
Enfortumab Vedotin



- Fully humanized monoclonal antibody targeting Nectin-4
- Nectin-4
  - A transmembrane cell adhesion molecule
  - Expressed in 93% of mUC patient samples
- “Payload” is auristatin-E, a microtubule disrupting agent
- Antibody is conjugated by a protease cleavable linker

Abstract 393

EV-301 Open-Label Phase 3 Trial Design

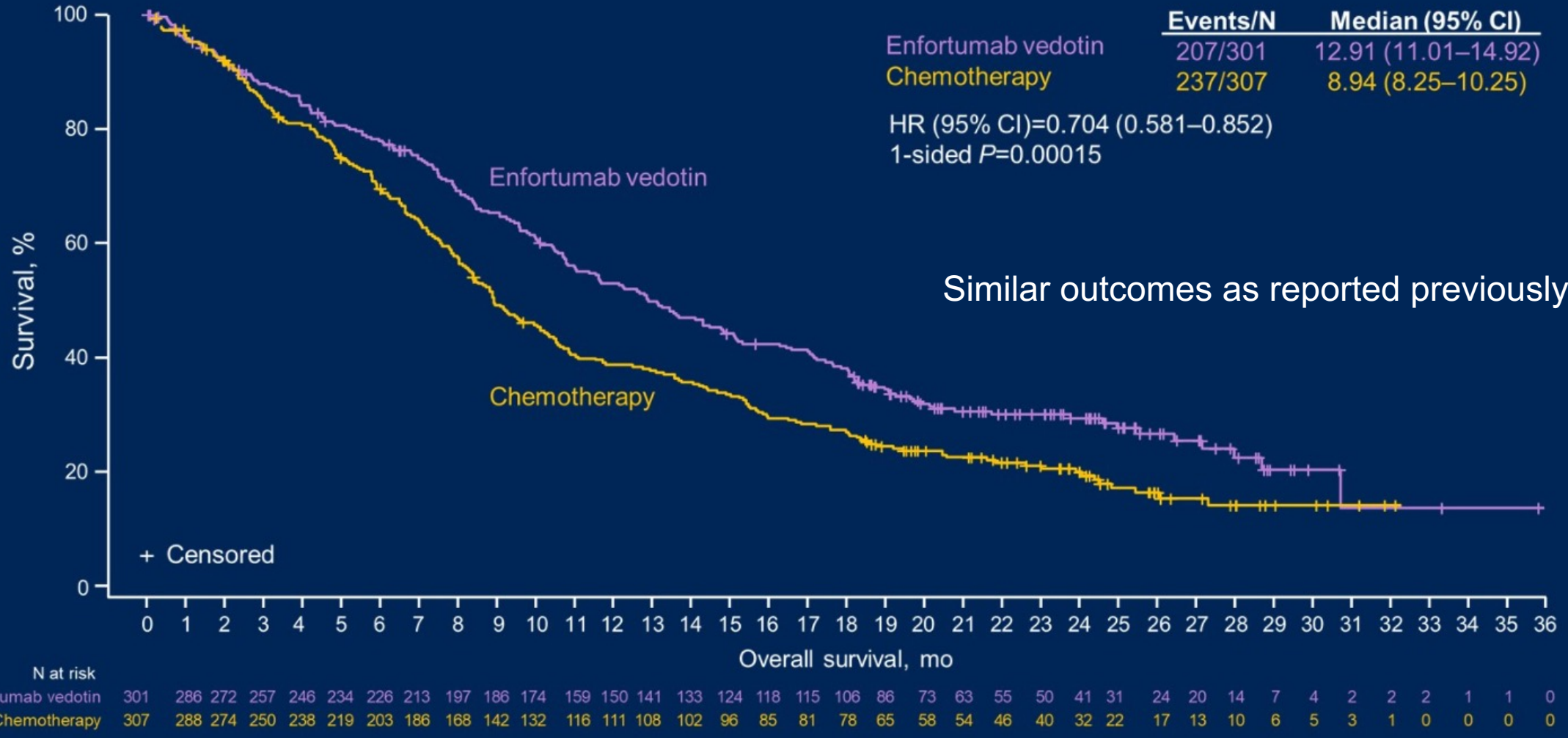


[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

PRESENTED AT: Genitourinary Cancers Symposium

PRESENTED BY: Thomas Powles

Overall Survival



	Events/N	Median (95% CI)
Enfortumab vedotin	207/301	12.91 (11.01–14.92)
Chemotherapy	237/307	8.94 (8.25–10.25)

HR (95% CI)=0.704 (0.581–0.852)
1-sided *P*=0.00015

Similar outcomes as reported previously!

Data shown for intention-to-treat population.
HR, hazard ratio.

Data cutoff date: July 30, 2021

Adverse Events of Special Interest[a] (Safety Population)

Treatment-related adverse event, n (%)	Enfortumab vedotin (N=296)						Chemotherapy (N=291)					
		Grade						Grade				
	Any	1	2	3	4	5	Any	1	2	3	4	5
Rash	133 (44.9)	41 (13.9)	48 (16.2)	43 (14.5)	1 (0.3)	NR	28 (9.6)	21 (7.2)	6 (2.1)	1 (0.3)	0	NR
Severe cutaneous adverse reaction	60 (20.3)	20 (6.8)	25 (8.4)	14 (4.7)	1 (0.3)	NR	22 (7.6)	12 (4.1)	8 (2.7)	2 (0.7)	0	NR
Peripheral neuropathy	142 (48.0)	36 (12.2)	84 (28.4)	22 (7.4)	NR	NR	92 (31.6)	43 (14.8)	41 (14.1)	8 (2.7)	NR	NR
Peripheral neuropathy sensory events	135 (45.6)	35 (11.8)	82 (27.7)	18 (6.1)	NR	NR	89 (30.6)	42 (14.4)	39 (13.4)	8 (2.7)	NR	NR
Peripheral neuropathy motor events	23 (7.8)	6 (2.0)	11 (3.7)	6 (2.0)	NR	NR	7 (2.4)	5 (1.7)	2 (0.7)	0	NR	NR
Dry eye	48 (16.2)	34 (11.5)	12 (4.1)	2 (0.7)	NR	NR	9 (3.1)	6 (2.1)	2 (0.7)	1 (0.3)	NR	NR
Blurred vision	13 (4.4)	11 (3.7)	2 (0.7)	0	NR	NR	6 (2.1)	5 (1.7)	0	1 (0.3)	NR	NR
Corneal disorders	2 (0.7)	2 (0.7)	NR	NR	NR	NR	0	0	NR	NR	NR	NR
Infusion-related reaction	27 (9.1)	12 (4.1)	11 (3.7)	4 (1.4)	NR	NR	14 (4.8)	7 (2.4)	7(2.4)	0	NR	NR
Systemic infusion-related reaction event	24 (8.1)	11 (3.7)	9 (3.0)	4 (1.4)	NR	NR	9 (3.1)	4 (1.4)	5 (1.7)	0	NR	NR
Local infusion-related reaction event	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR	7 (2.4)	5 (1.7)	2 (0.7)	0	NR	NR
Infusion-site reaction	2 (0.7)	0	2 (0.7)	0	NR	NR	5 (1.7)	4 (1.4)	1 (0.3)	0	NR	NR
Extravasation-site reaction	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR
Hyperglycemia	20 (6.8)	3 (1.0)	4 (1.4)	12 (4.1)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0

MedDRA, Medical Dictionary for Regulatory Activities; NR, not reported.

[a]Adverse events of special interest to enfortumab vedotin. Events represent listings by preferred term and are sponsor-specific query/customized medical queries or standard MedDRA queries. Order of adverse events is as it appears in the Supplementary Appendix to the EV-301 primary publication (Powles, et al. *N Engl J Med.* 2021;384:1125-1135).

Data cutoff date: July 30, 2021

Adverse Events of Special Interest[a] (Safety Population)

Treatment-related adverse event, n (%)	Enfortumab vedotin (N=296)						Chemotherapy (N=291)					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash	133 (44.9)	41 (13.9)	48 (16.2)	43 (14.5)	1 (0.3)	NR	28 (9.6)	21 (7.2)	6 (2.1)	1 (0.3)	0	NR
Severe cutaneous adverse reaction										2 (0.7)	0	NR
Peripheral neuropathy										8 (2.7)	NR	NR
Peripheral neuropathy sensory events										8 (2.7)	NR	NR
Peripheral neuropathy motor events										0	NR	NR
Dry eye										1 (0.3)	NR	NR
Blurred vision										1 (0.3)	NR	NR
Corneal disorders										NR	NR	NR
Infusion-related reaction										0	NR	NR
Systemic infusion-related reaction event										0	NR	NR
Local infusion-related reaction event										0	NR	NR
Infusion-site reaction	2 (0.7)	0	2 (0.7)	0	NR	NR	5 (1.7)	4 (1.4)	1 (0.3)	0	NR	NR
Extravasation-site reaction	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR	4 (1.4)	2 (0.7)	2 (0.7)	0	NR	NR
Hyperglycemia	20 (6.8)	3 (1.0)	4 (1.4)	12 (4.1)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0

WARNING: SERIOUS SKIN REACTIONS

See full prescribing information for complete boxed warning.

- **Enfortumab vedotin can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).**
- **Immediately withhold enfortumab vedotin and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue enfortumab vedotin in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions. (2.2), (5.1) (6.1)**

MedDRA, Medical Dictionary for Regulatory Activities; NR, not reported.

[a]Adverse events of special interest to enfortumab vedotin. Events represent listings by preferred term and are sponsor-specific query/customized medical queries or standard MedDRA queries. Order of adverse events is as it appears in the Supplementary Appendix to the EV-301 primary publication (Powles, et al. *N Engl J Med.* 2021;384:1125-1135).

Data cutoff date: July 30, 2021

Metabolism of Enfortumab Vedotin

- Metabolite MMAE
  - 17% recovered in feces over 1 week period
  - 6% recovered in urine over 1 week period
- Dose reduction
  - Renal impairment: No differences in AUC for mild-mod-severe
    - no significant dose reductions
    - Effect on end-stage renal disease/dialysis is unknown
  - Liver impairment: Mild hepatic impairment 48% AUC increase in MMAE
    - Mild hepatic impairment: bilirubin 1-1.5 x ULN with NL AST and ALT or bilirubin ≤ ULN and AST > ULN
    - Frequency of ≥ Grade 3 adverse reactions and deaths in moderate (Child-Pugh B) or severe (Child-Pugh C)
- AVOID use in moderate-severe hepatic impairment

FDA Package insert 12/2019

Monitoring Caveats

- Grade-3-4 hyperglycemia increase in greater BMI and higher HgbA1C
  - HgbA1C ≥ 8 excluded
- HOLD for:
  - Glucose > 250 mg/dL
    - Could be a sign of impaired clearance of MMAE
    - Mechanism unknown
    - ~~Personal hypothesis: impaired glycogen storage as a sign of saturation of liver metabolism~~
    - New Hypothesis: potent tubule stabilization resulting in decreased glucose transport and muscle weakness resulting in decreased glucose utilization and even rhabdomyolysis
  - Peeling skin or bullous skin lesions
    - May have more diffuse rash preceding this
  - Grade 3 diarrhea


Erdafitinib:
The First Biomarker Targeted Therapy in mUC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Siefker-Radtke, for the BLC2001 Study Group*

ABSTRACT

NEJM July 25, 2019.

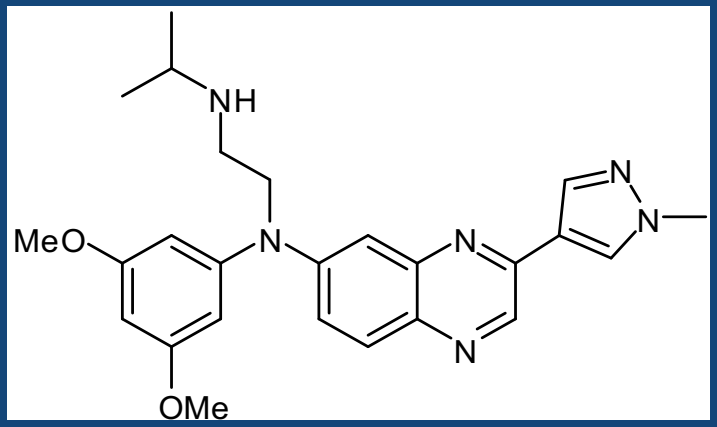
Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study

*Arlene O Siefker-Radtke, Andrea Necchi, Se Hoon Park, Jesús García-Donas, Robert A Huddart, Earle F Burgess, Mark T Fleming, Arash Rezazadeh Kalebasty, Begoña Mellado, Sergei Varlamov, Monika Joshi, Ignacio Duran, Scott T Tagawa, Yousef Zakharia, Sydney Akapame, Ademi E Santiago-Walker, Manish Monga, Anne O'Hagan, Yohann Loriot, on behalf of the BLC2001 Study Group**

The Lancet Oncology, February, 2022.

Erdafitinib Is a Potent FGFR Inhibitor

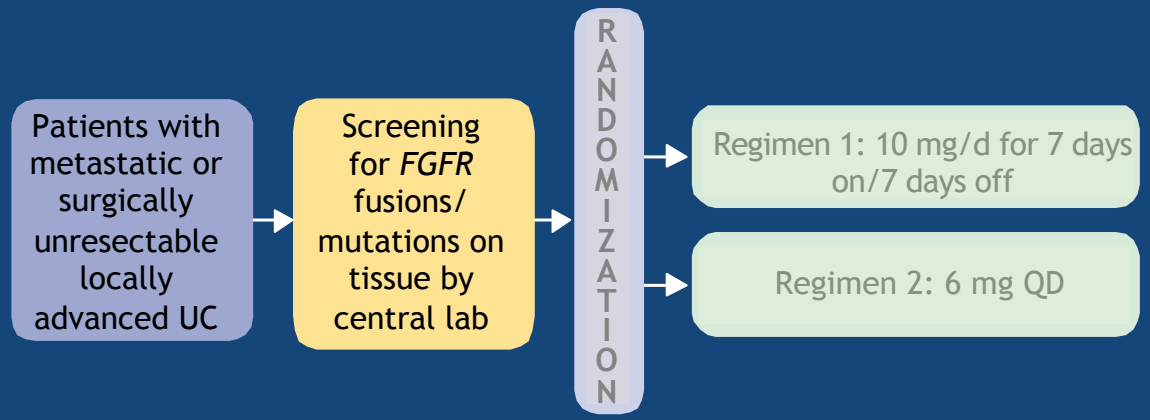
- Erdafitinib* is an oral pan-FGFR (1-4) inhibitor with IC_{50} in the single-digit nanomolar range[1]
- Erdafitinib is taken up by lysosomes, resulting in sustained intracellular release, which may contribute to its long-lasting activity[1]
- Erdafitinib has demonstrated promising activity in patients with metastatic or unresectable UC and other histologies (eg, cholangiocarcinoma) with *FGFR* alterations[2-5]



Abbreviation: IC_{50}, drug concentration at which 50% of target enzyme activity is inhibited.

1. Perera TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020.
2. Tabernero J, et al. *J Clin Oncol*. 2015;33:3401-3408.
3. Soria J-C, et al. ESMO 2016. Abstract 781PD.
4. Loriot Y, et al. ASCO GU 2018. Abstract 411.
5. Siefker-Radtke A, et al. ASCO GU 2018. Abstract 450.

Phase 2 BLC2001 Study Design



Regimen 3[a]:
8 mg QD with PD Uptitration to 9 mg QD
n = 99

Primary end point
ORR
Secondary end points
PFS, DoR, OS, safety, predictive biomarker evaluation, and PK

Patients
• Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR • Chemo-naïve: cisplatin ineligible per protocol criteria[b]
• Prior immunotherapy was allowed

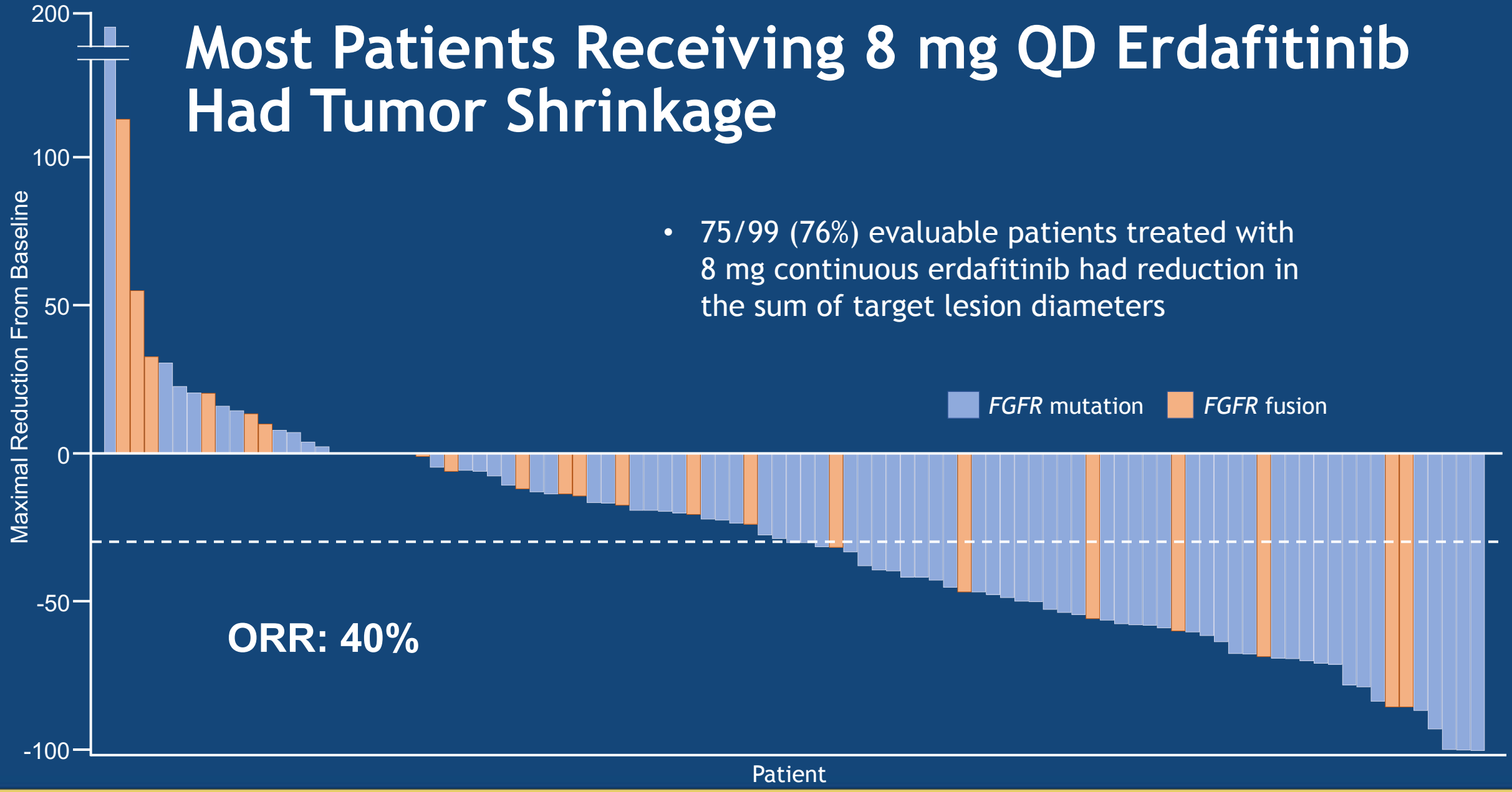
Primary hypothesis:
- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.
[b]Ineligibility for cisplatin: impaired renal function or peripheral neuropathy.

Abbreviations: DoR, duration of response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, daily; TRAEs, treatment-related adverse events.

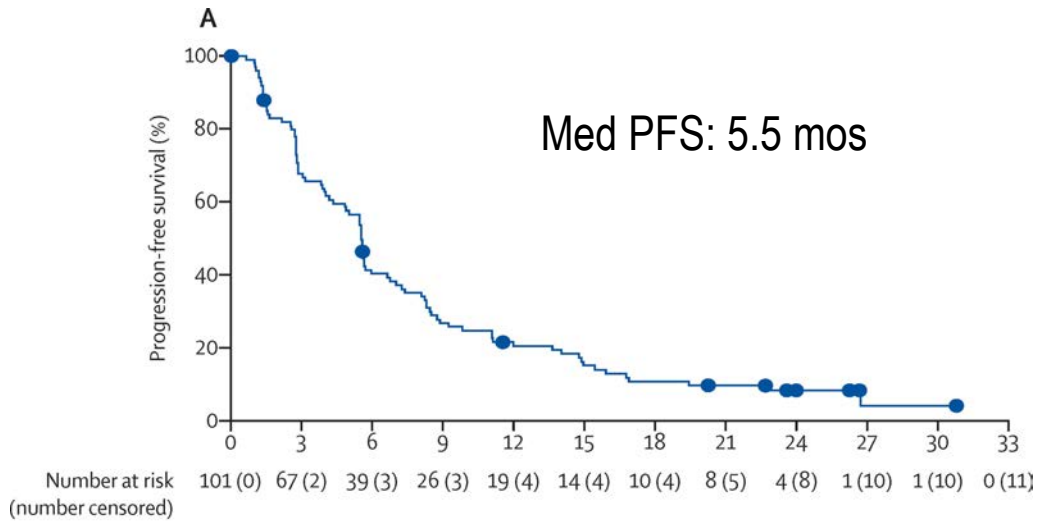
Most Patients Receiving 8 mg QD Erdafitinib Had Tumor Shrinkage

- 75/99 (76%) evaluable patients treated with 8 mg continuous erdafitinib had reduction in the sum of target lesion diameters

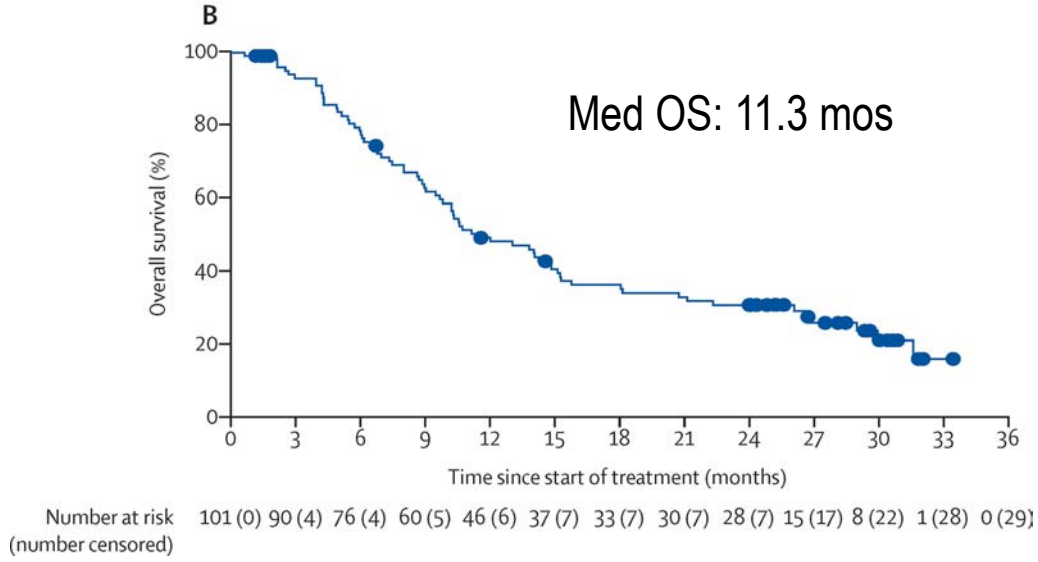


Erdafitinib – Long-term Outcomes

	Participants (n=101)*
Age, years	67 (61–73)
ECOG performance status	
0	51 (50%)
1	43 (43%)
2	7 (7%)
Pretreatment†	
Progressed or relapsed after chemotherapy	89 (88%)
Chemotherapy-naive	12 (12%)
Previous immunotherapy	24 (24%)
Number of lines of previous treatment‡	
0	10 (10%)
1	48 (48%)
2	28 (28%)
≥3	15 (15%)
Visceral metastases§	
Present	78 (77%)
Absent	23 (23%)
Liver	20 (20%)
Lung	57 (56%)
Bone	23 (23%)
Lymph node metastases only	9 (9%)
Other metastases¶	14 (14%)
Haemoglobin concentration, g/dL	
≥10	86 (85%)
<10	15 (15%)
Primary tumour location	
Upper tract	25 (25%)
Lower tract	76 (75%)
Creatinine clearance rate	
<60 mL/min	53 (52%)
≥60 mL/min	48 (48%)
FGFR alteration	
FGFR mutation present and fusion absent	70 (69%)
FGFR mutation absent and fusion present	25 (25%)
FGFR mutation and fusion present	6 (6%)



Med PFS: 5.5 mos



Med OS: 11.3 mos

Siefker-Radtke et al. Lancet Onc, 2022

Erdafitinib – Most Common Treatment-Related AEs

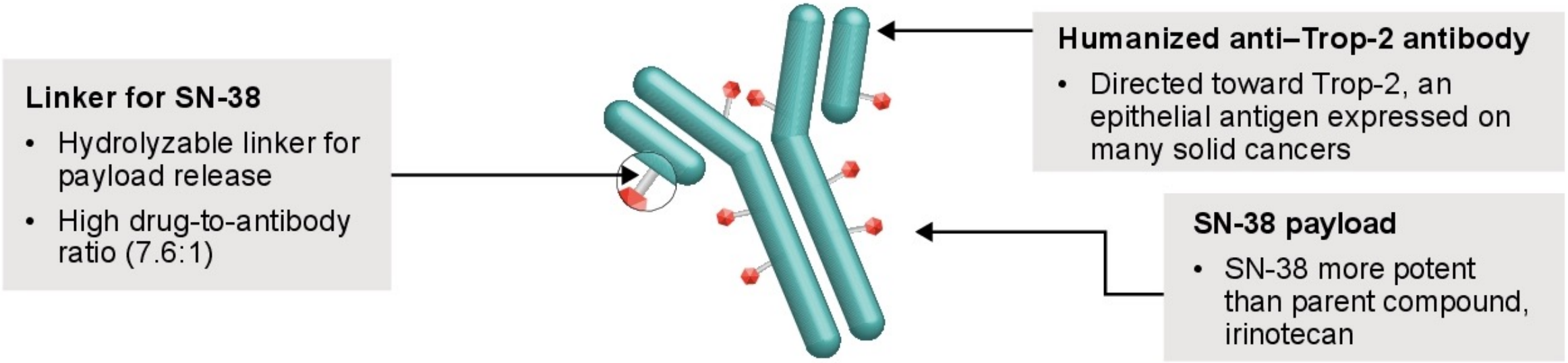
	Grade 1–2	Grade 3	Grade 4	Grade 5*
All treatment-emergent adverse events	29 (29%)	58 (57%)	6 (6%)	8 (8%)
Hyperphosphataemia†	77 (76%)	2 (2%)	0	0
Stomatitis	46 (21%)	14 (14%)	0	0
Diarrhoea	51 (50%)	4 (4%)	0	0
Dry mouth	45 (45%)	1 (1%)	0	0
Decreased appetite	40 (40%)	1 (1%)	0	0
Dysgeusia	39 (39%)	2 (2%)	0	0
Alopecia	34 (34%)	0	0	0
Dry skin	34 (34%)	0	0	0
Fatigue	31 (31%)	2 (2%)	0	0
Constipation	28 (28%)	1 (1%)	0	0
Dry eye	27 (27%)	1 (1%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	20 (20%)	5 (5%)	0	0
Asthaenia	15 (15%)	6 (6%)	0	2 (2%)
Anaemia	17 (17%)	5 (5%)	0	0
Nausea	21 (21%)	1 (1%)	0	0
Alanine aminotransferase increased	17 (17%)	2 (2%)	0	0
Onycholysis	17 (17%)	2 (2%)	0	0
Paronychia	16 (16%)	3 (3%)	0	0
Urinary tract infection	13 (13%)	5 (5%)	0	0
Vision blurred	18 (18%)	0	0	0
Weight decreased	17 (17%)	1 (1%)	0	0
Nail dystrophy	11 (11%)	6 (6%)	0	0

- Majority of events were grade 1-2
- All grade 4 and 5 events were deemed unrelated to erdafitinib by the investigator
- Few patients (N=16) discontinued due to TRAEs
- Most events were treated by dose holds/modification
- More hyperphosphatemia in the non-uptitrated group
- CSR is a known class effect of inhibitors of the MEK and MAPk pathways
  - 27 patients developed CSR
  - Most events occurred within first 3 mo

Siefker-Radtke et al. Lancet Onc, 2022

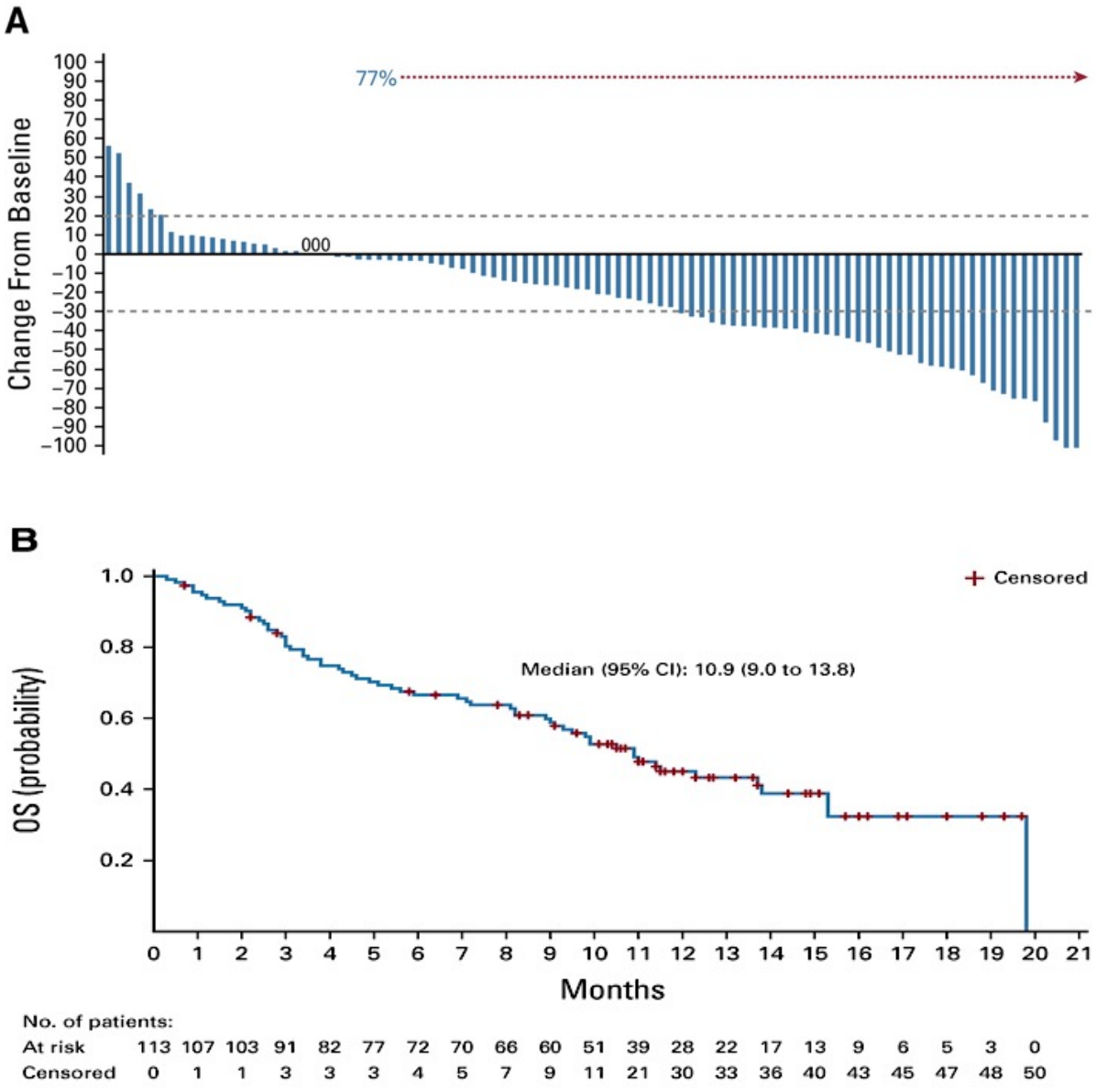

Sacituzumab Govitecan:
The Second Antibody Drug Conjugate in mUC

Sacituzumab Govitecan



- Humanized monoclonal antibody targeting Trop-2 expression
- Trop-2
  - Epithelial antigen expressed on many solid cancers
  - Expressed in ~ 83% of mUC patient samples; testing for expression not necessary
- “Payload” is SN-38, the active metabolite of irinotecan, inhibiting topoisomerase 1
- Payload is conjugated by a hydrolyzable linker

Sacituzumab Govitecan



- N=113, post-platinum and post-IO
- SG 10 mg/kg d1, d8 q 3-wk
- GCSF as clinically indicated
- ORR 27%
- Med PFS: 5.4 mo
- Med OS: 10.9 mo
- Toxicity
  - Neutropenia ≥G3: 34%
  - Diarrhea ≥G3: 10%
- UGT1A homozygous/heterozygous
  - Potential increased risk neutropenia, pre-screening not required

Tagawa, et al. JCO 2021

Sacituzumab Govitecan

TABLE 3. Most Common TRAEs of Any Grade (Observed in ≥ 20% of Patients) orTRAEs Grade ≥ 3 (Observed in ≥ 5% of Patients) (N = 113)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	Neutropenia	46	22	12
	Leukopenia	25	12	5
	Anemia	33	14	0
	Lymphopenia	11	5	2
	Febrile neutropenia	10	7	3
GI	Diarrhea	65	9	1
	Nausea	60	4	0
	Vomiting	30	1	0
General disorders and administrative site conditions	Fatigue	52	4	0
Skin and subcutaneous tissue	Alopecia	47	0	0
Metabolism and nutrition	Decreased appetite	36	3	0
Infections and infestations	Urinary tract infection	8	6	0

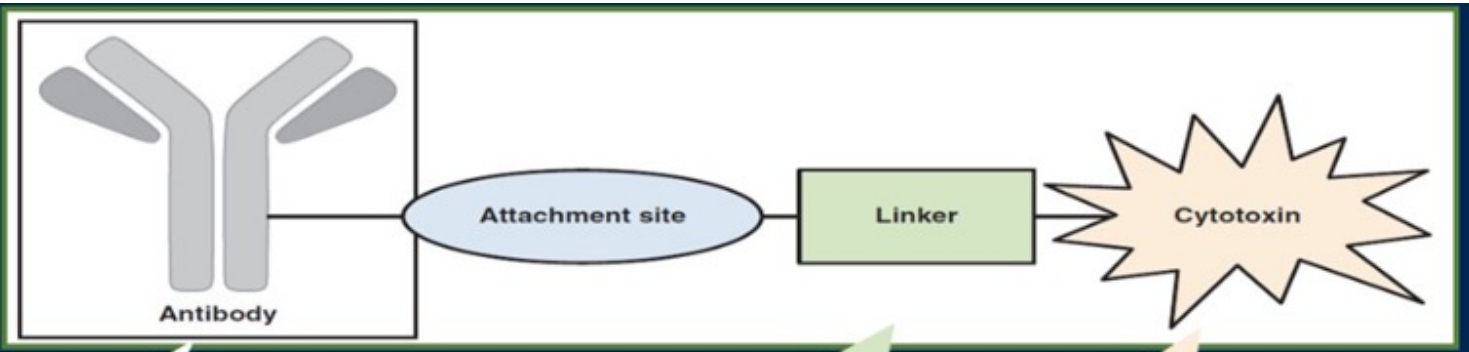
Abbreviation: TRAEs, treatment-related adverse events.

[a]Neutrophil count decreased, WBC count decreased, lymphocyte count decreased, and hemoglobin decreased have been recoded to neutropenia, leukopenia, lymphopenia, and anemia, respectively, for summary purposes.

Tagawa, et al. JCO 2021


Other Targets!

Disitamab Vedotin: HER2



Antibody

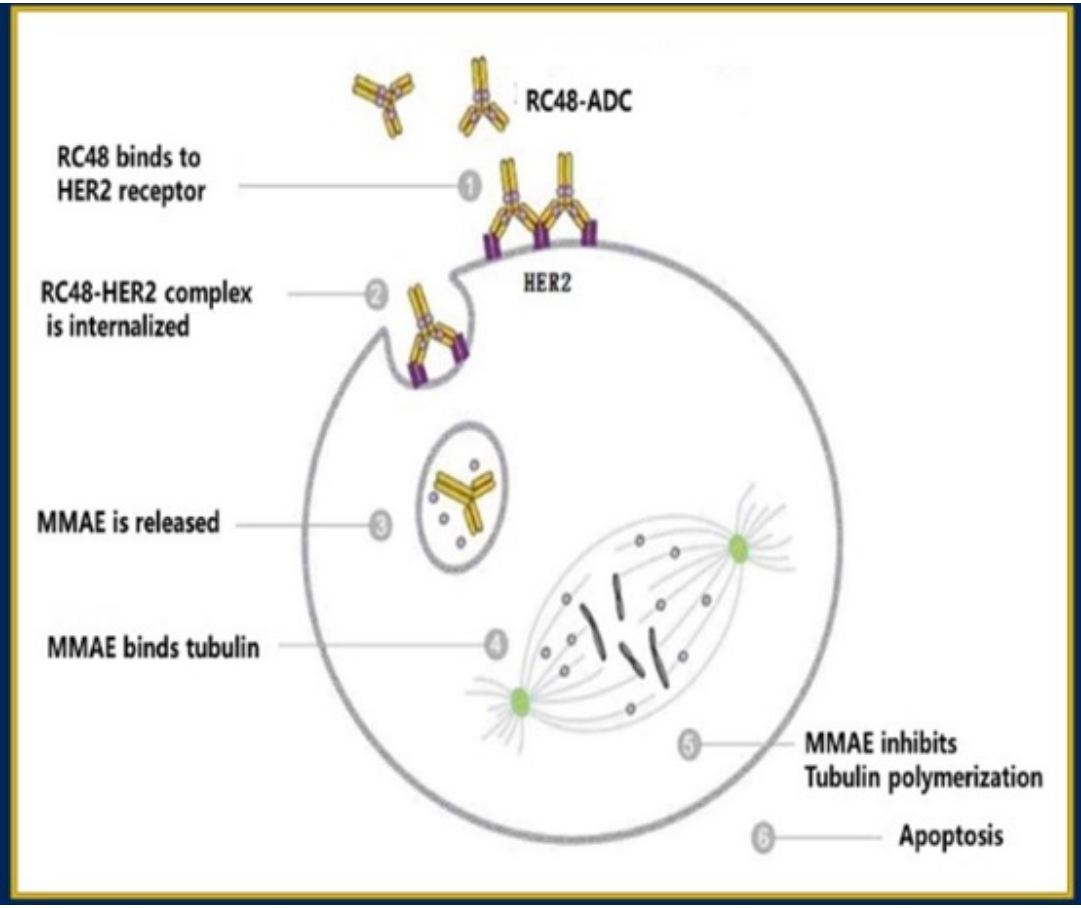
- Newly screened HER2 monoclonal antibody
- Different antigen recognition regions, and preferable affinity compared with trastuzumab

Linker

- Cleavable: A cathepsin cleavable valine–citrulline (VC) linker enables an easier release of payload post to the endocytosis
- Bystander Effect: Payload promotes potent cell killing upon initial release of the ADC and has the ability to kill surrounding tumor cells

Payload

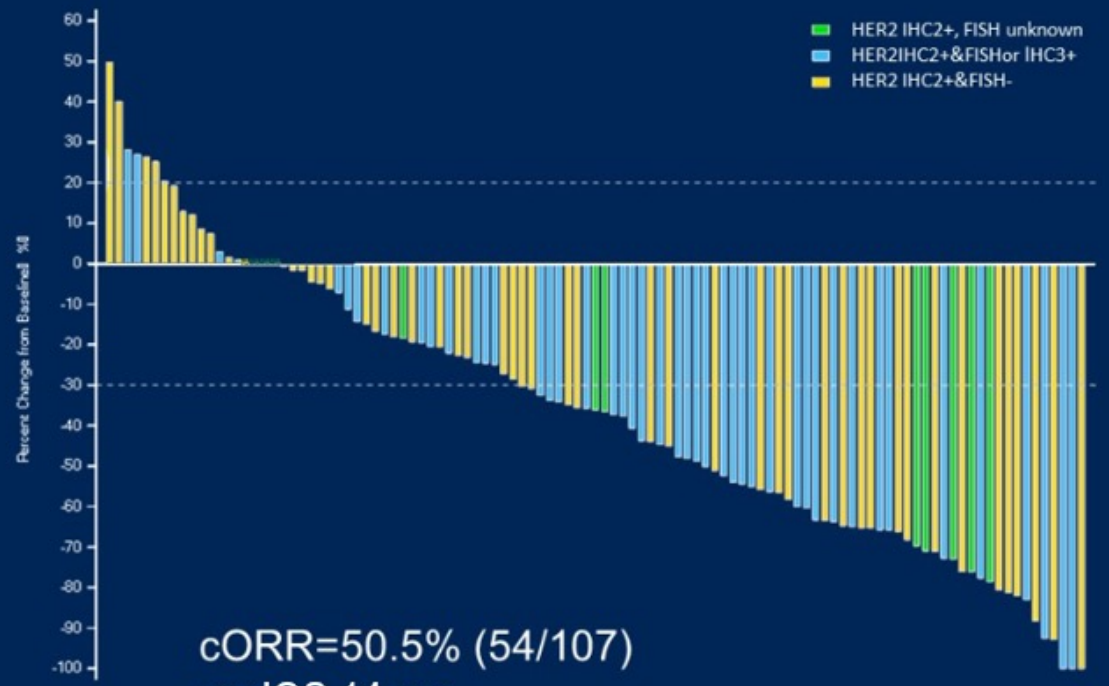
- MMAE: A potent antimitotic drug derived from peptides occurring in marine shell-less mollusc dolabella auricularia called dolastatins
- Inhibits cell division by blocking the polymerisation of tubulin



Sheng, et al, ASCO 2022

Disitamab Vedotin: HER2

Target Lesion Change from Baseline



Patients were enrolled between December 28, 2017 and September 4, 2020
Data cut off : 04-Sep-2021

Subgroup Analysis for cORR

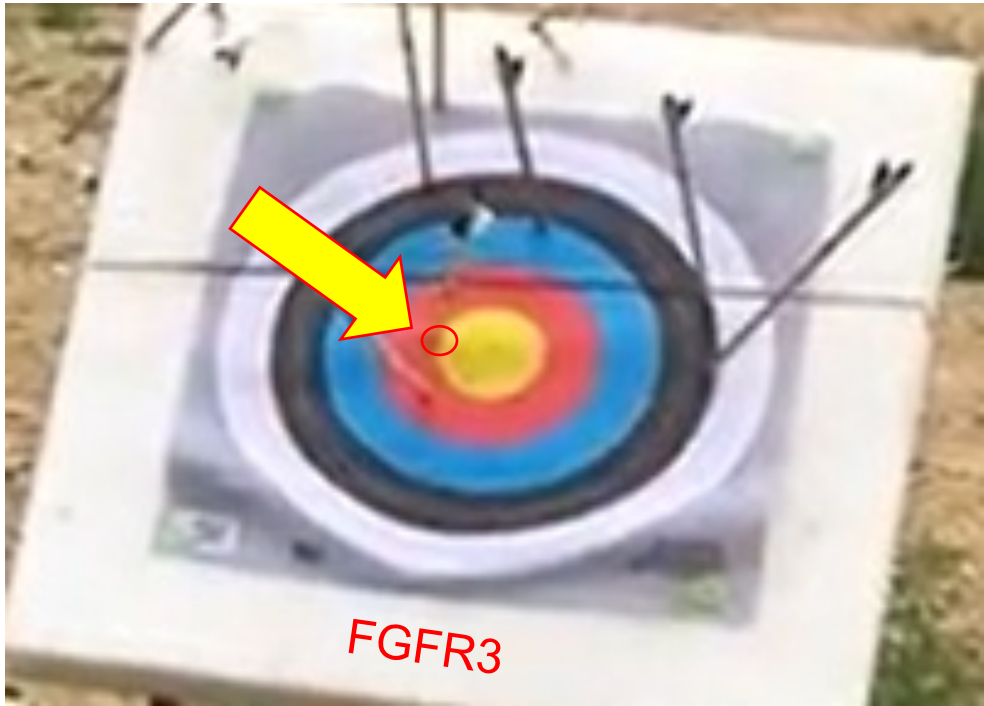
Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 74.5%)
Post 1 line of Chemotherapy (n=38)	50.0% (33.4%, 66.6%)
Post ≥2 Lines of Chemotherapy (n=69)	50.7% (38.4%, 63.0%)

Sheng, et al, ASCO 2022

Conclusions:

- Multiple new agents
  - ADC
  - TKI
- Clinical activity
  - Enfortumab Vedotin and Erdafitinib (~40% ORR) > Sacituzumab Govitecan (~27% ORR) – currently FDA approved!
    - Or is this an effect of more prior treatment in SG?
  - Disitamab Vedotin: see what the future holds
- Each have their specific toxicities
  - Enfortumab Vedotin: watch closely in cirrhosis/fatty liver
  - Erdafitinib: Watch for CSR
  - Sacituzumab Govitecan: Neutropenia and diarrhea
    - Advocate for routine use of GCSF

We are getting closer…



Beyond The Guidelines: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the American Urological Association Annual Meeting 2023 (AUA2023)

Sunday, April 30, 2023

6:00 PM – 8:00 PM

Faculty

Himisha Beltran, MD

Stephen J Freedland, MD

Fred Saad, MD

Neal D Shore, MD

Moderator

Matthew R Smith, MD, PhD

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