Urothelial cancer updates

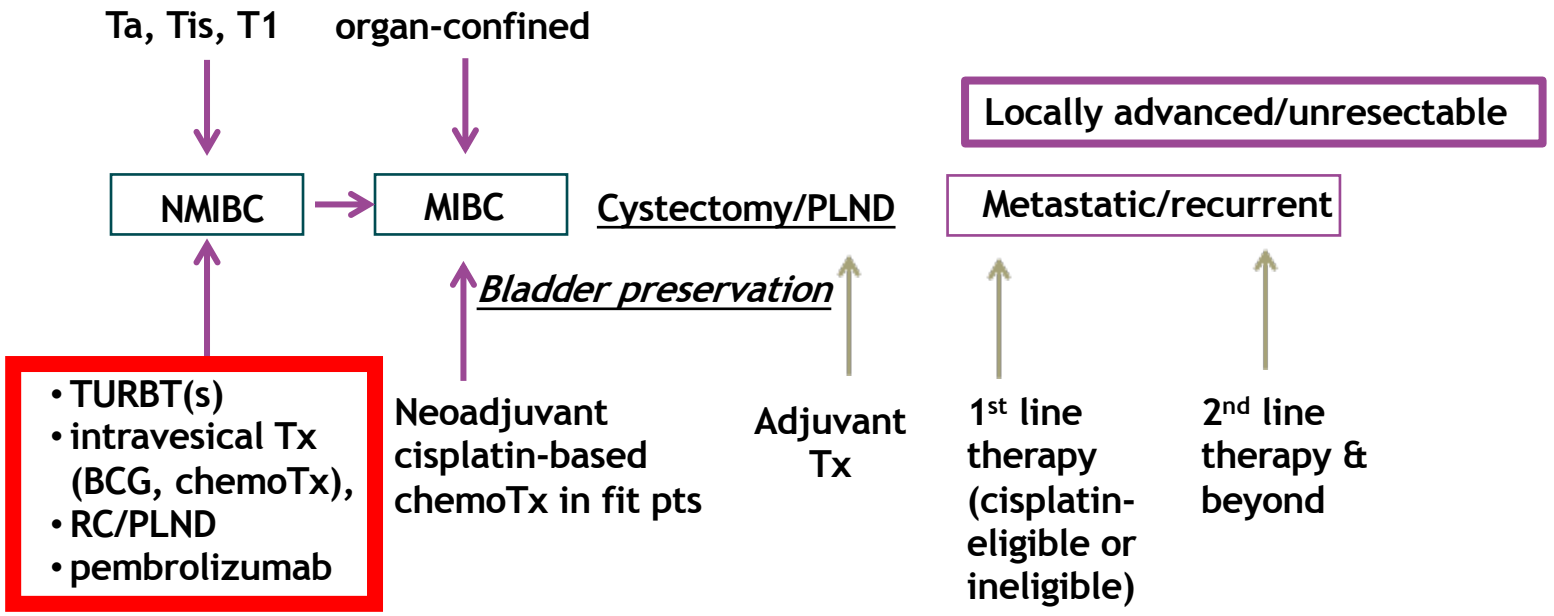
Petros Grivas, MD PhD

Professor, Dept. of Medicine, Division of Medical Oncology
Clinical Director, Genitourinary Cancers Program
University of Washington

Professor, Clinical Research Division
Fred Hutchinson Cancer Center

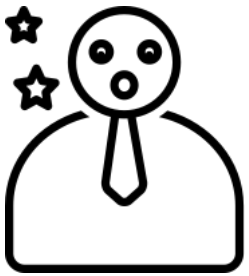
Twitter: @PGrivasMDPhD

Disease / treatment settings



High risk NMIBC states defined by BCG Therapy

BCG Naïve



BCG ‘Exposed’

- Induction only
- Late Relapse

BCG Unresponsive

- BCG Refractory
- Early Relapse

Discussion

Drug	N	CR Rate at Anytime	Median Duration of CR in responders	Median follow up (months)	Cystectomy Free Rate to date	% with Extra Vesical Disease
N-803	80	71%	19.2 Months*	10.7	88%	1
Pembrolizumab[1]	97	41%	16.2 Months	24.1	63%	3
Nadofaragene[2]	103	53%	9.7 Months	19.7	71%	1

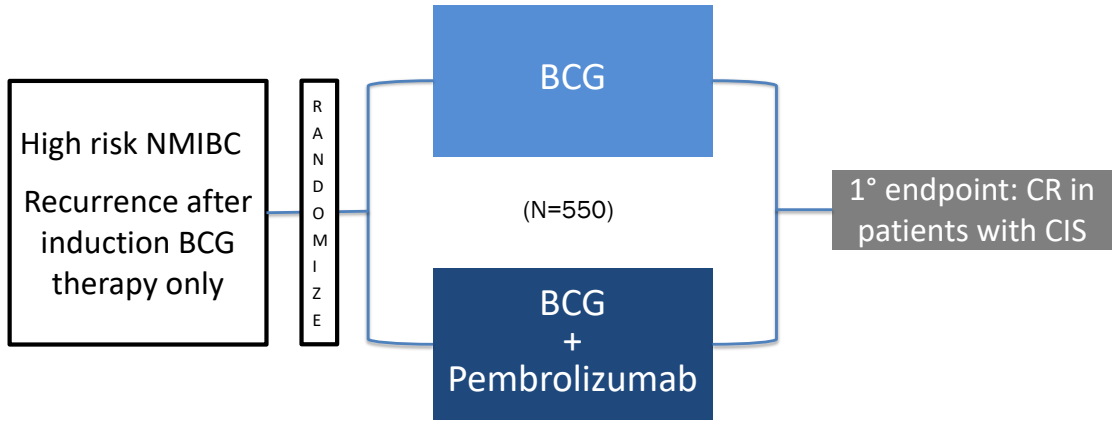
***Kaplan-Meier estimate**

1. ODAC: https://www.fda.gov/media/133542/download, ASCO 2020
2. Boorjian et al. Lancet 2020

Presented By Karim Chamie at 2021 Genitourinary Cancers Symposium

Immune Checkpoint Inhibitors for Earlier NMIBC

BCG "Exposed"

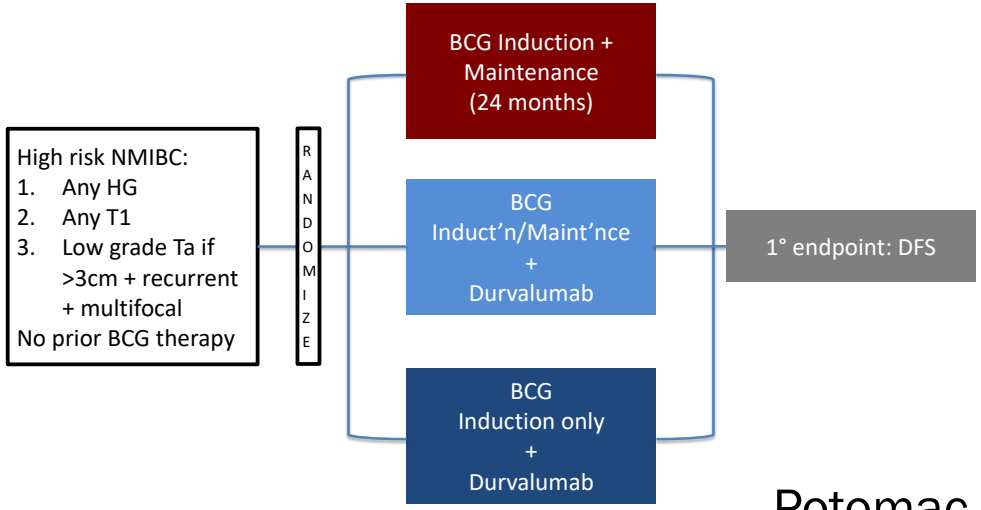


Keynote 676

Similar Trials:

- Checkmate 7G8 with nivolumab (terminated)
- ADAPT-Bladder durvalumab + RT (PI: Hahn)

BCG Naïve

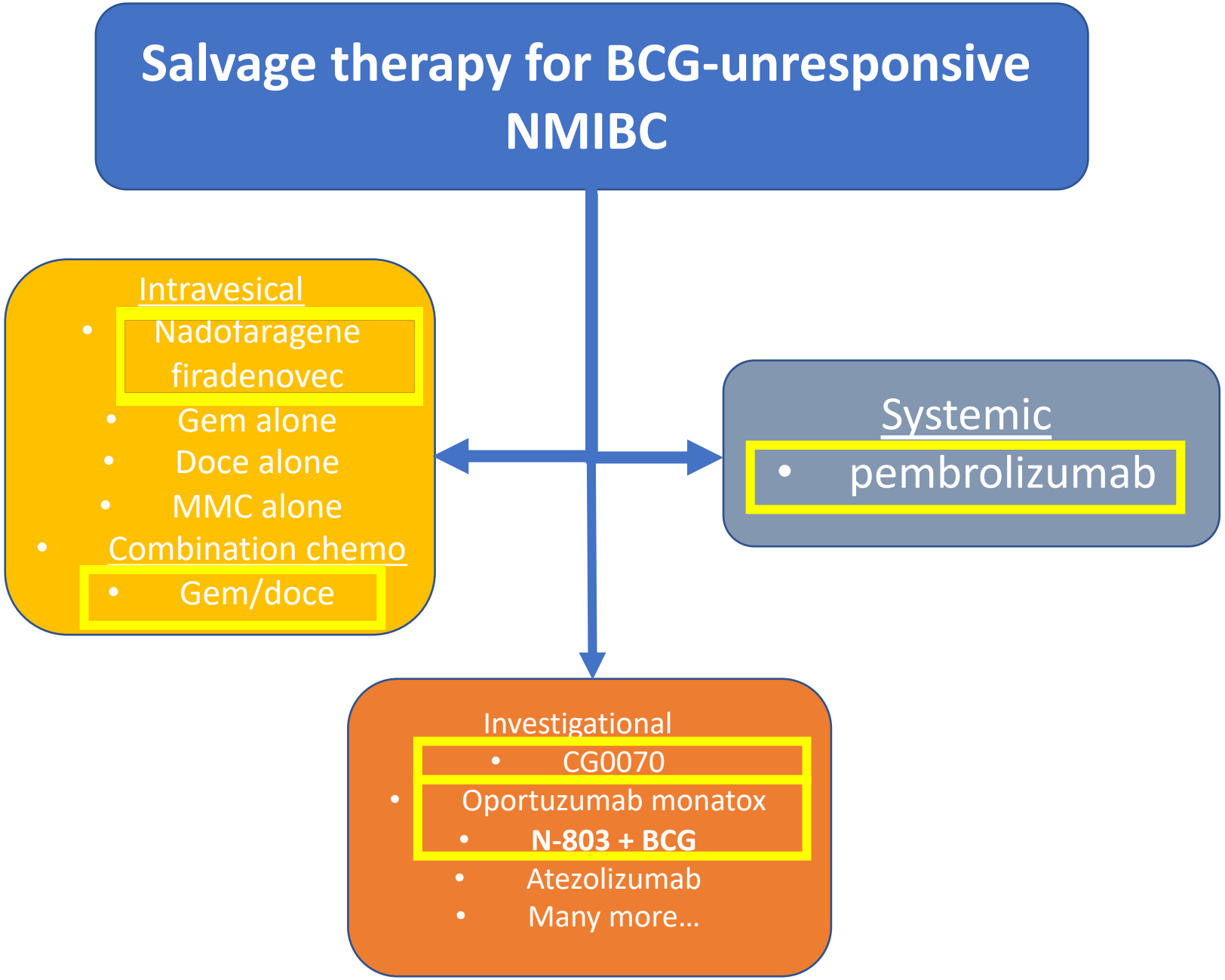


Potomac

Similar Trials:

- ALBAN with atezolizumab
- CREST with sasanlimab (subcutaneous)

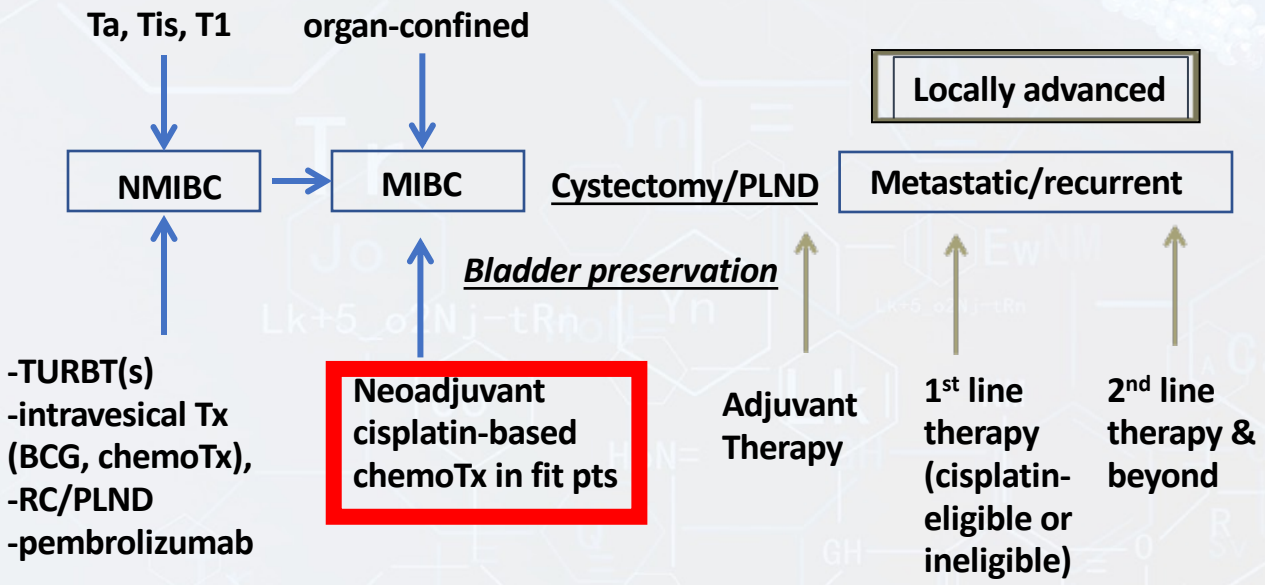
BRIDGE 8212 trial: BCG vs gem/doce (PI: Kates)


Salvage therapy for BCG-unresponsive NMIBC
Intravesical
Nadofaragene firadenovec
Gem alone
Doce alone
MMC alone
Combination chemo
Gem/doce
Systemic
pembrolizumab
Investigational
CG0070
Oportuzumab monatox
N-803 + BCG
Atezolizumab
Many more…

Take home messages in NMIBC

- **BCG remains the treatment of choice and standard for comparison to (& combination with) in current & future trials**
- **Risk stratification is key and requires experience & look at the guidelines**
- **Intravesical nadofaragene firadenovec, intravesical chemotherapy, intravenous pembrolizumab are options for BCG-unresponsive CIS (with or without papillary tumors) in pts who refuse or are unable to undergo curative intent radical cystectomy & PLND**
- **BCG + N-803 data look very promising (awaiting FDA review soon)**
- **Several clinical trials are evaluating intravesical & systemic therapies across the spectrum of NMIBC disease states**

Disease / treatment settings



University of Washington Bladder Cancer Multispecialty Clinic

Timeline

January 2014
Bi-monthly (2nd/4th Tuesday)

January 2015
5th Tuesday added (when occurring)

January 2016
Weekly Conference

Participants

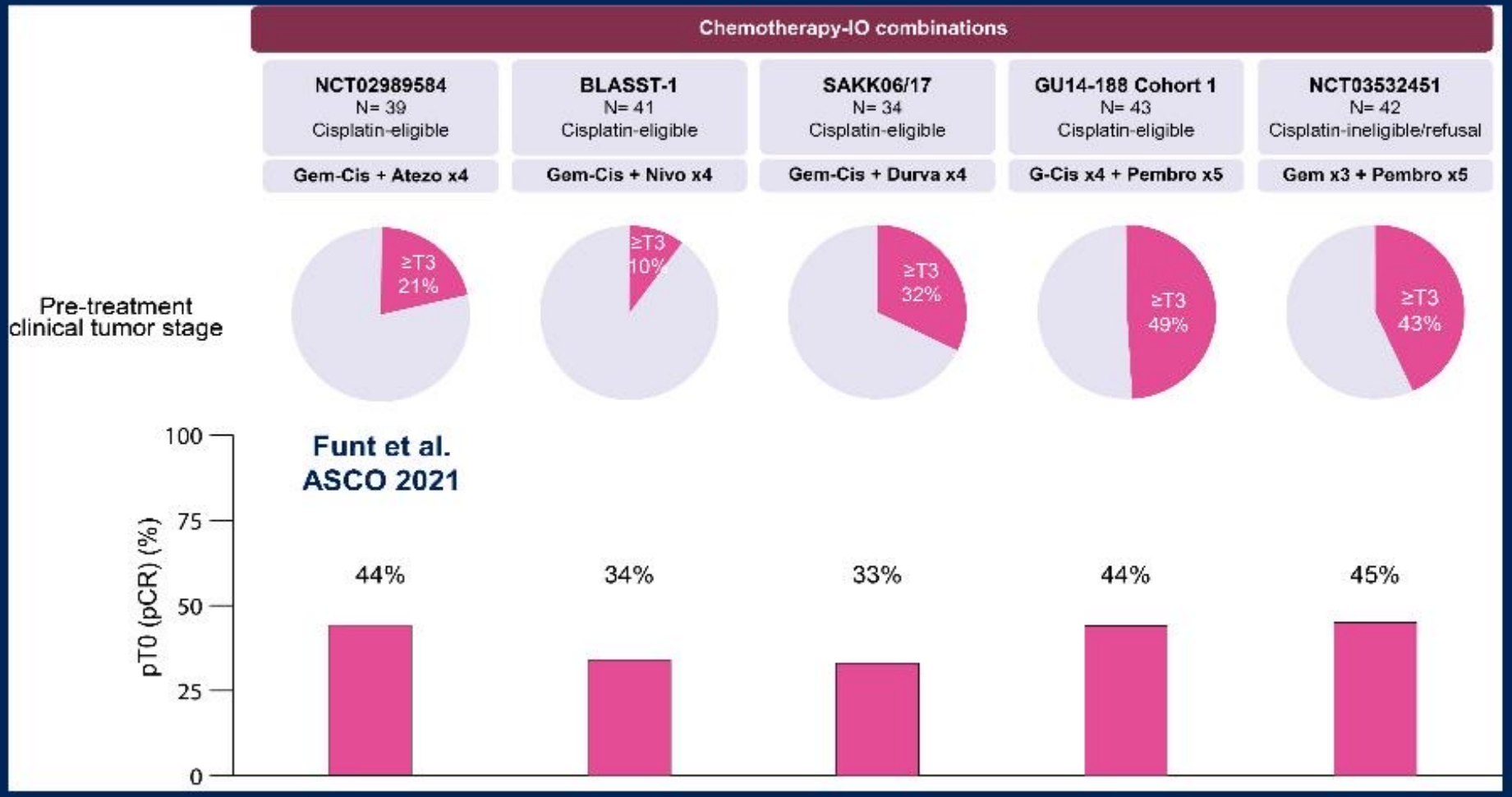
- Physicians
  - Urology
  - Medical Oncology
  - Radiation Oncology
  - GU Pathology
  - GU Radiology
- Nursing
  - NP
  - Ostomy Nurse
  - RN/CNC
- Others (available later for referral)
  - Physical / Occupational Therapy
  - Nutritional Services
  - Social Worker / Case Manager
  - Psychology / Psychiatry
  - Genetics
  - Integrative Medicine
  - Palliative Care

Diamantopoulos et al. *Bladder Cancer* 2019;5:289–98

Advantages of neoadjuvant systemic therapy

- Neoadjuvant cisplatin-based chemotherapy improves OS.
- Often better tolerated.
- Potential for maximizing impact on patient outcomes by administering drug at the earliest point in the natural history of the disease.
- Tissue availability from TURBT and RC offers opportunities to study biomarkers of response in clinical trials.
- Surrogate endpoints of responsiveness to therapy (pCR) enable early risk-stratification to select patients who could benefit from additional therapy.

IO-chemotherapy neoadjuvant combinations for MIBC

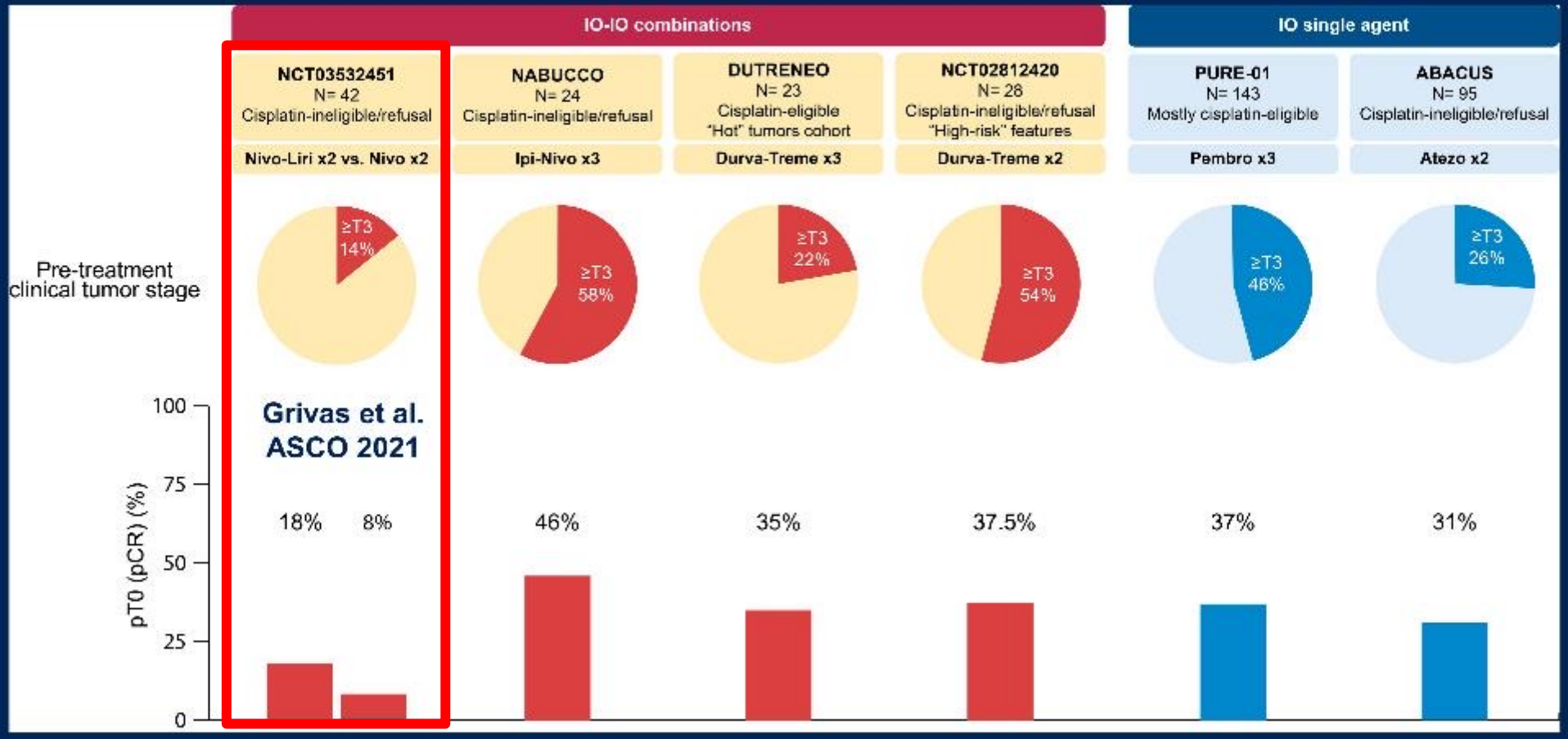


Presented By: **Bishoy M. Faltas MD**

Figure adapted from:
Rey-C´ardenas et al. Cancer Treatment Reviews, 2021.
Rouanne et al. European Urology Oncology, 2020

2021 ASCO ANNUAL MEETING

Neoadjuvant IO single agent and combinations for MIBC

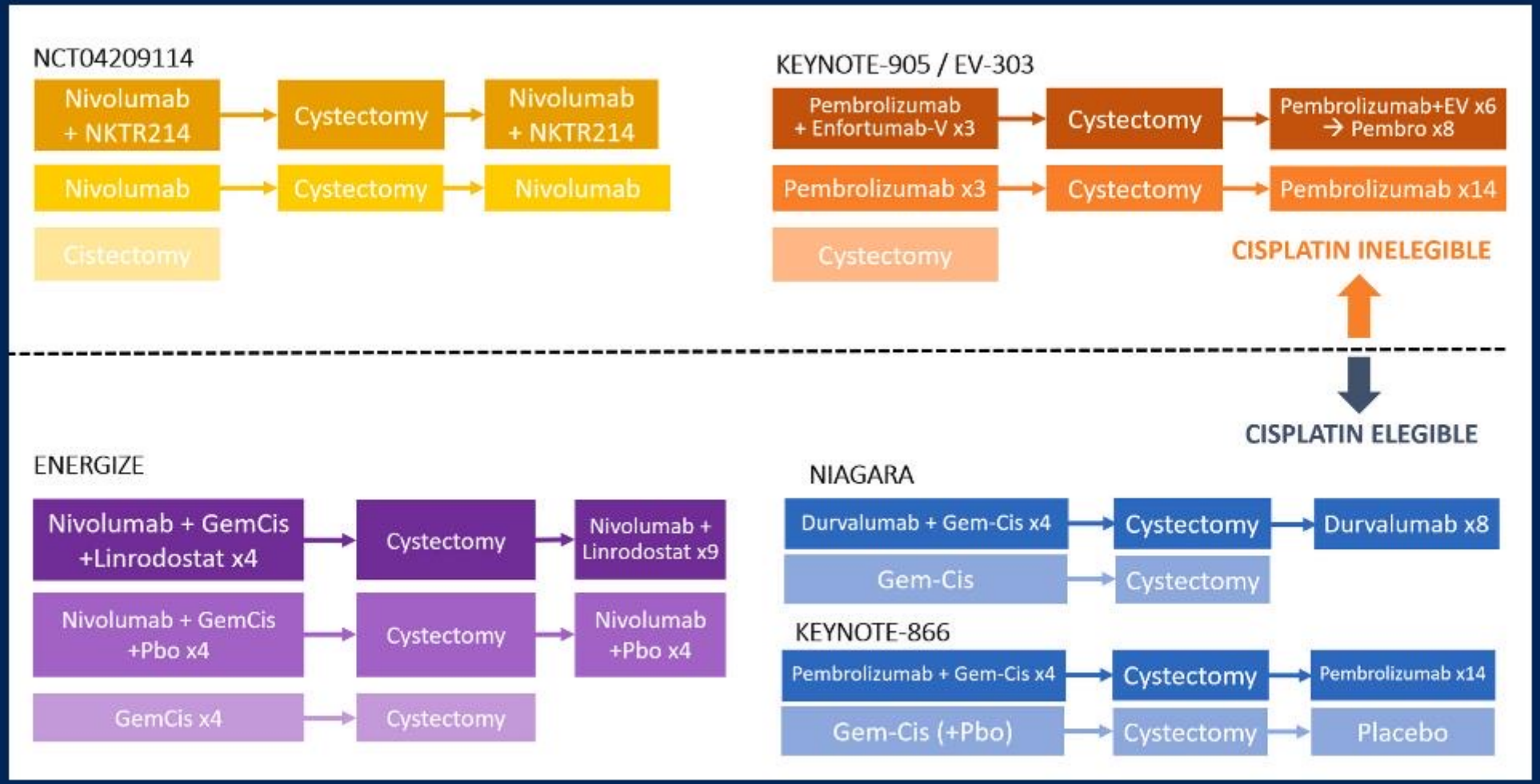


Presented By: **Bishoy M. Faltas MD**

Figure adapted from:
Rey-C´ardenas et al. Cancer Treatment Reviews, 2021.
Rouanne et al. European Urology Oncology, 2020

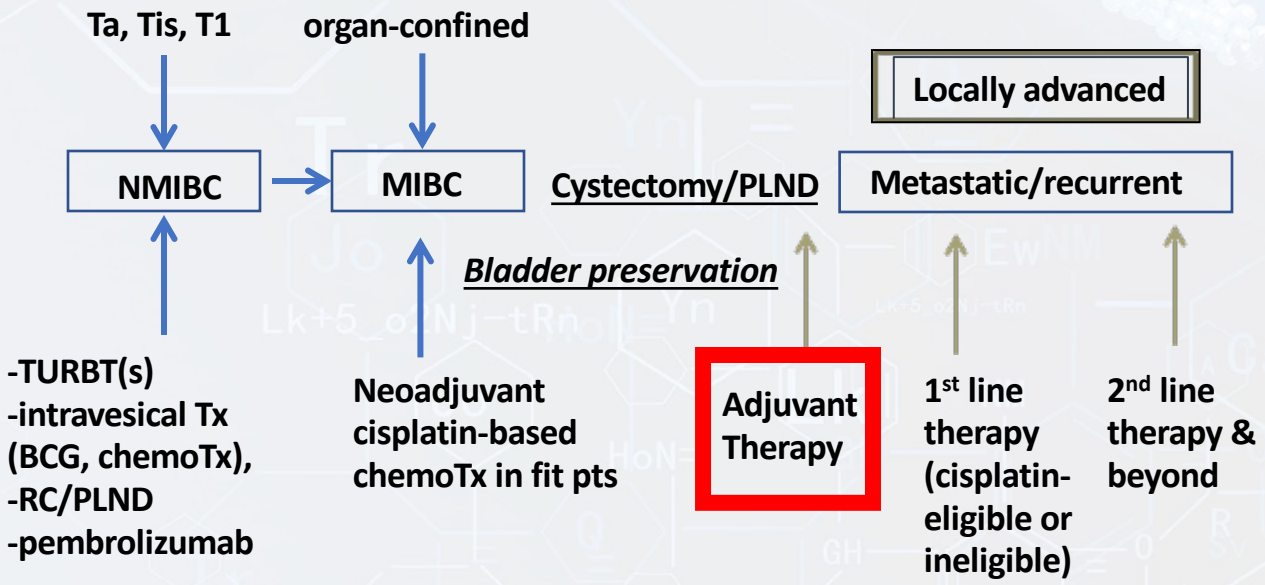
2021 ASCO ANNUAL MEETING

Phase III neoadjuvant IO trials



Rey-C´ardenas et al. Cancer Treatment Reviews, 2021.

Disease / treatment settings



VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Consider gemcitabine/cisplatin or accelerated/dose dense MVAC X 4 cycles for pT3/4 and/or pN+ if cisplatin-fit & did not receive neoadjuvant chemoTx

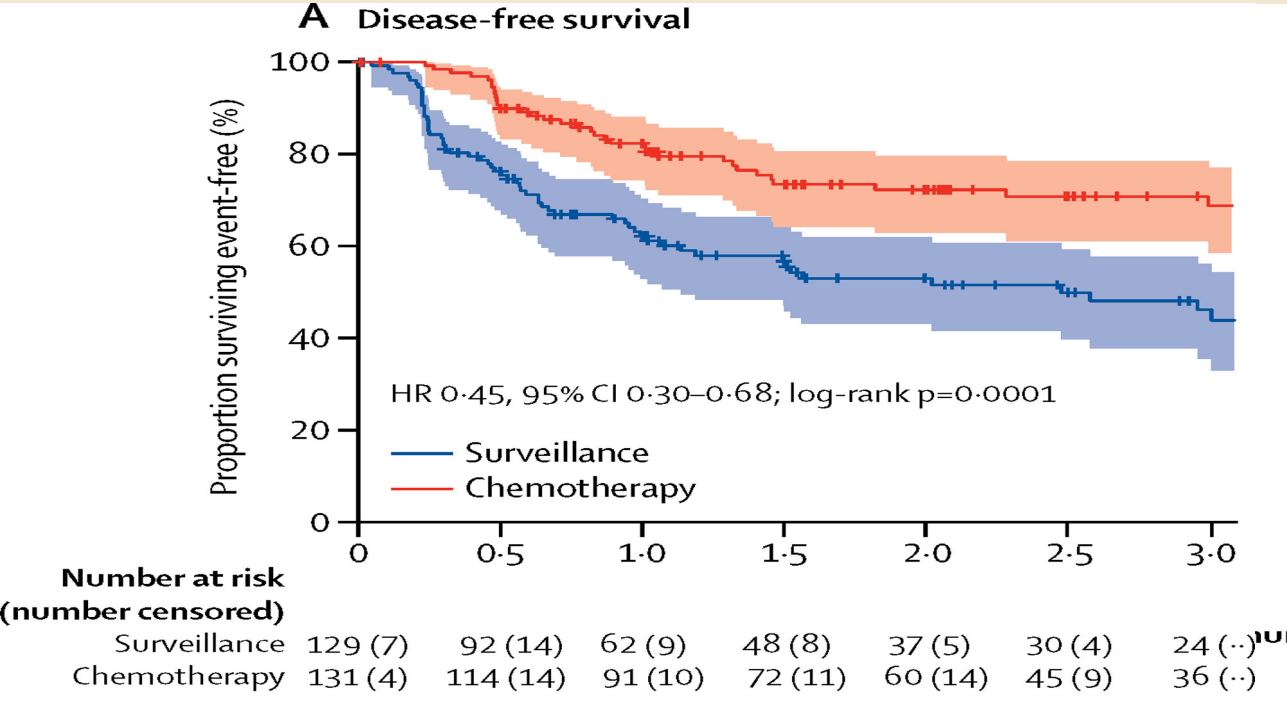
Adjuvant Chemotherapy for Bladder Cancer: Using Population-Based Data to Fill a Void of Prospective Evidence

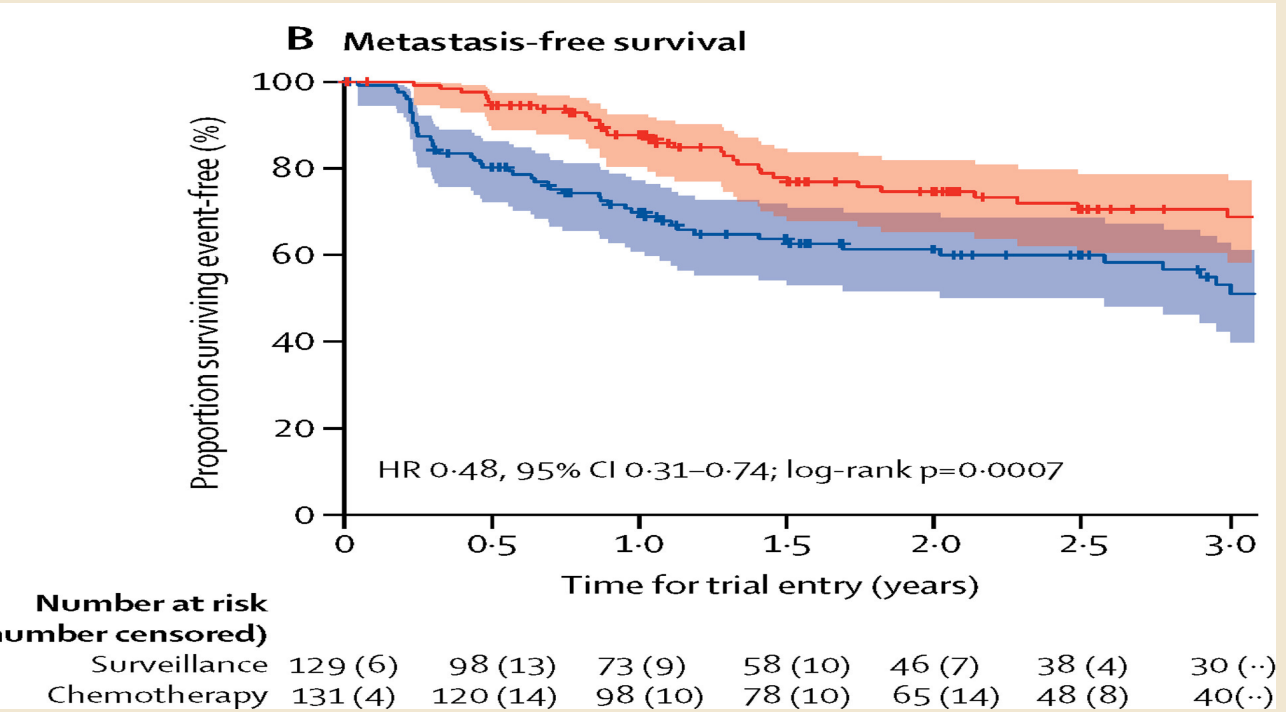
Sumanta K. Pal, *City of Hope Comprehensive Cancer Center, Duarte, CA*
Neeraj Agarwal, *Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*
Petros Grivas, *Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*
Toni Choueiri, *Dana-Farber Cancer Institute, Boston, MA*

Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial

Alison Birtle, MD, Mark Johnson, MD, Prof John Chester, PhD, Prof Robert Jones, PhD, David Dolling, PhD, Richard T Bryan, PhD, Christopher Harris, Andrew Winterbottom, Anthony Blacker, MBChB, Prof James W F Catto, PhD, Prabir Chakraborti, MD, Prof Jenny L Donovan, PhD, Paul Anthony Elliott, PhD, Ann French, MSc, Satinder Jagdev, MDRB, Benjamin Jenkins, MSc, Francis Xavier Keeley, MD, Roger Kockelbergh, MBChB, Prof Thomas Powles, PhD, Prof John Wagstaff, MD, Caroline Wilson, PhD, Rachel Todd, MSc, Rebecca Lewis, BSc, Prof Emma Hall, PhD

The Lancet
Volume 395 Issue 10232 Pages 1268-1277 (April 2020)
DOI: 10.1016/S0140-6736(20)30415-3



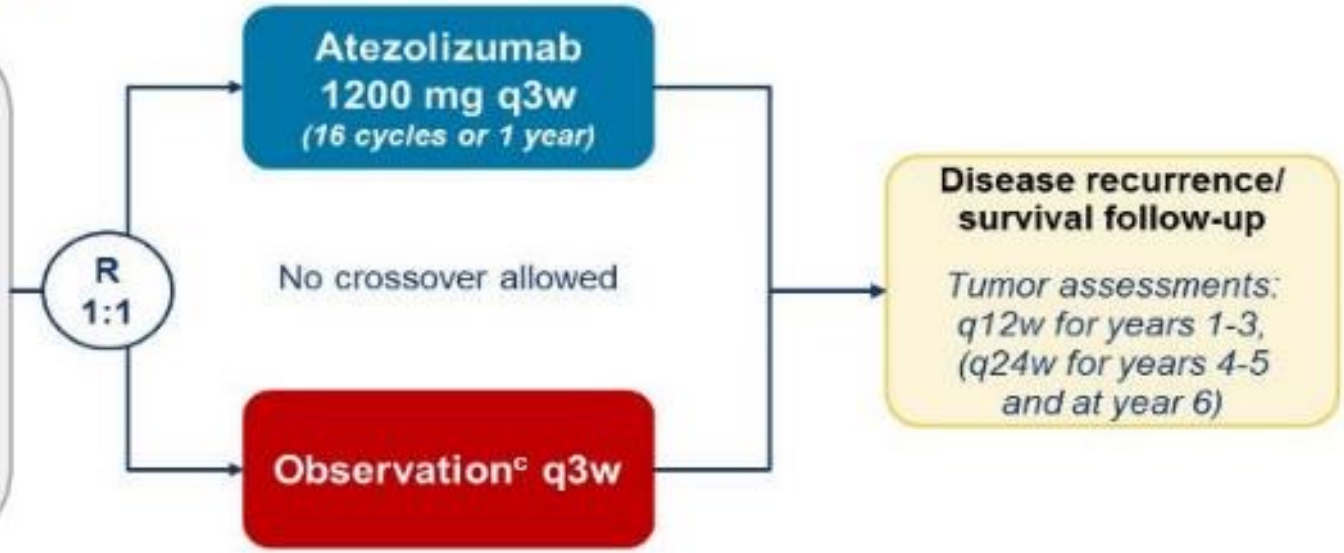


The Lancet 2020 3951268-1277DOI: (10.1016/S0140-6736(20)30415-3)

IMvigor010 Study Design

Key eligibility[a]

- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC[b]**
  - **pT3-T4a or pN+** for patients **not treated with NAC[b]**
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**



Stratification factors

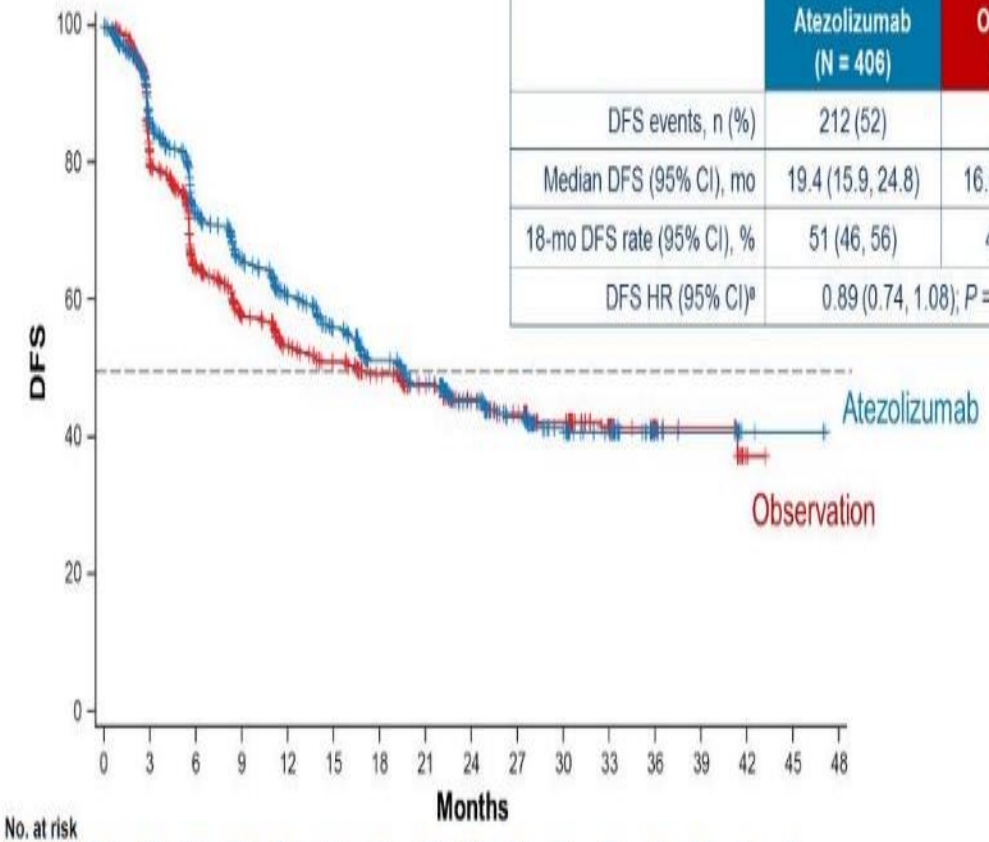
- Number of LNs resected (< 10 vs ≥ 10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤ pT2 vs pT3/pT4)
- PD-L1 status[a] (IC0/1 vs IC2/3)

- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

Presented By Maha Hussain at TBD

DFS in ITT Population

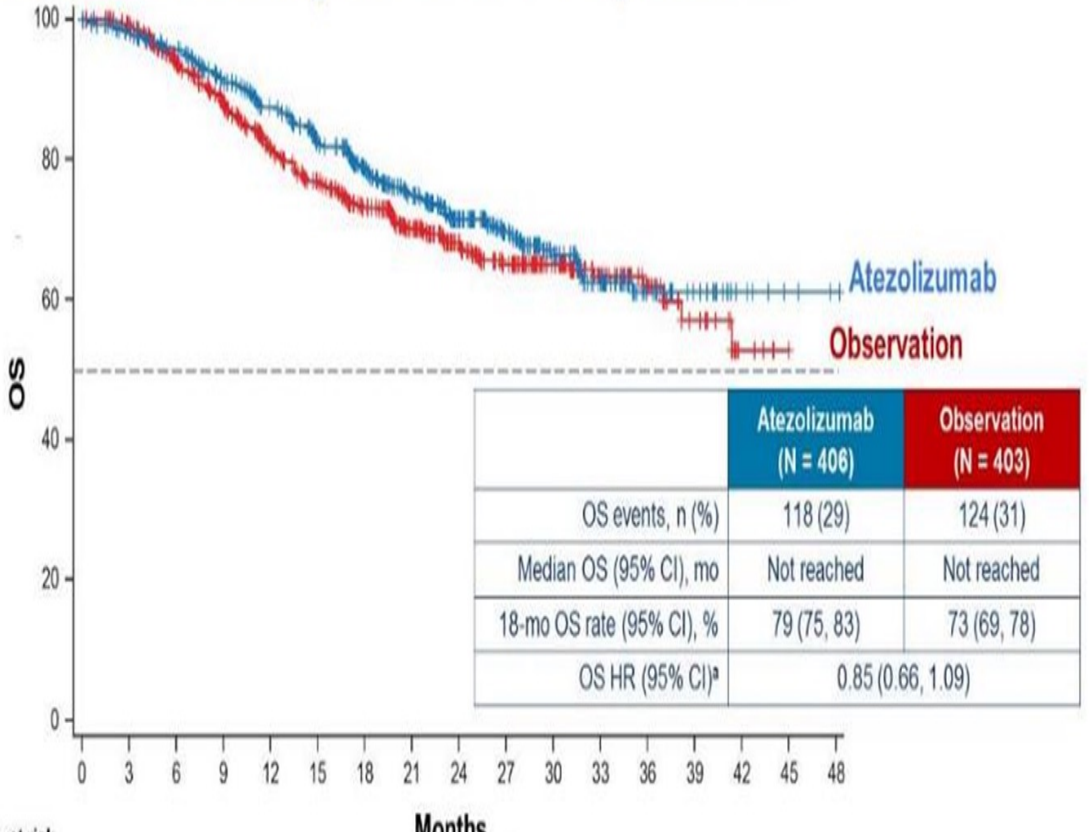


	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

No. at risk																
Atezolizumab	406	332	281	248	223	201	169	142	115	92	67	52	15	10	3	2
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

Interim OS Analysis in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

No. at risk																
Atezolizumab	406	383	369	350	328	306	267	229	185	144	100	72	35	22	8	4	2
Observation	403	377	345	318	289	270	235	199	163	134	100	65	36	20	6	1	

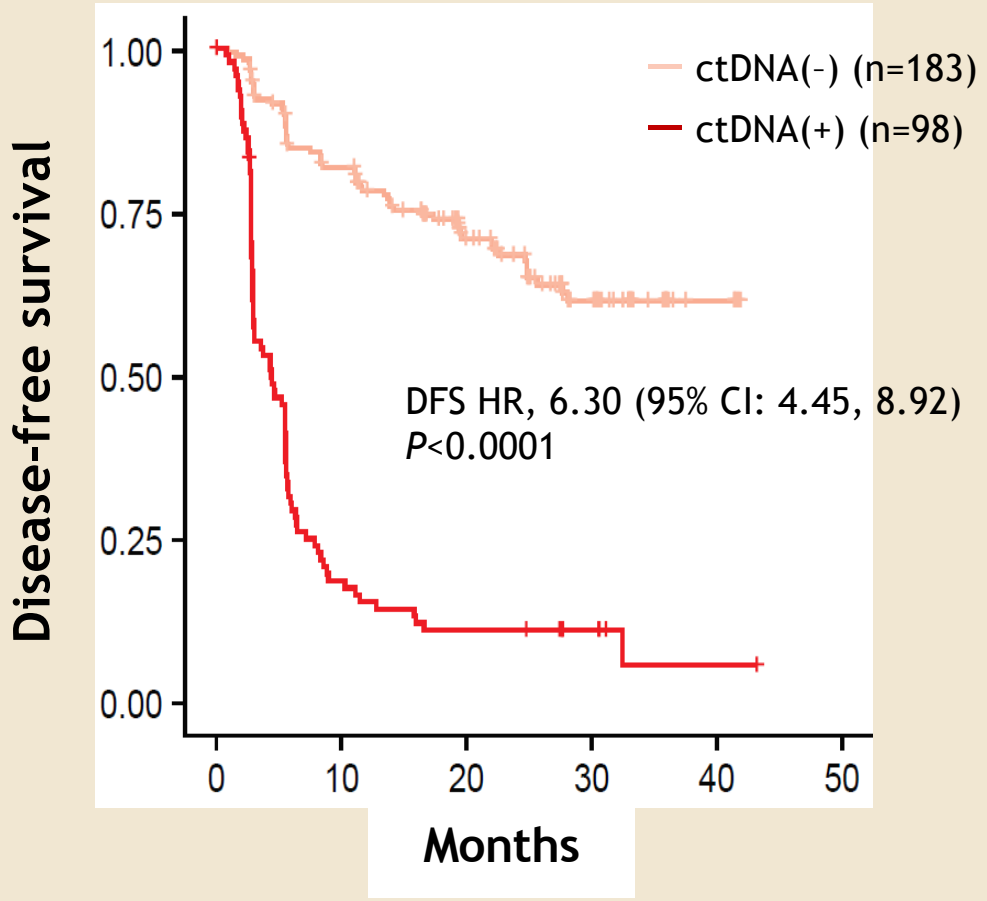
Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author, permission required for reuse. PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SKSAD3

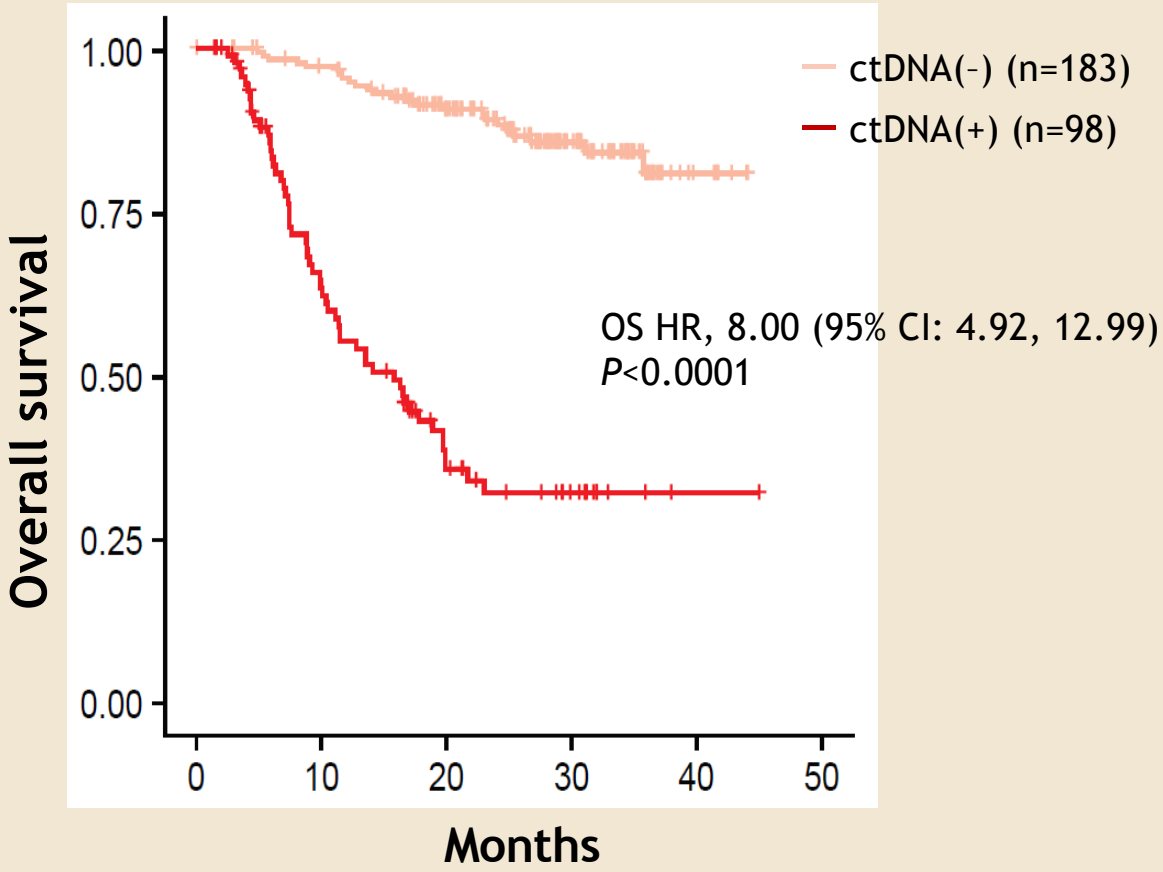
Presented By Maha Hussain at TBD

ctDNA(+) portends poor prognosis

Observation arm



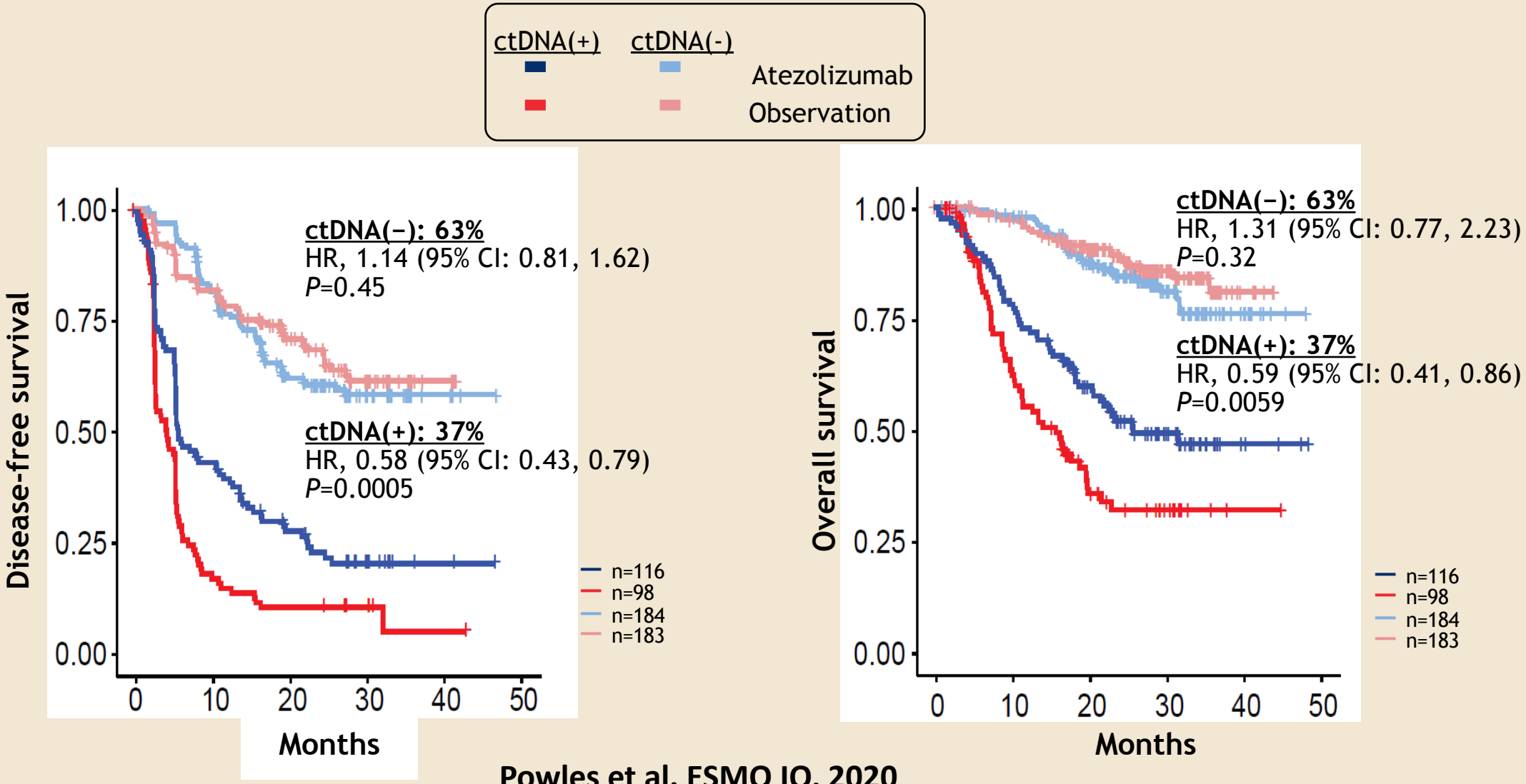
Observation arm



- IMvigor010 confirmed the prognostic value of ctDNA status

Powles et al. ESMO IO, 2020
Powles et al. Nature, 2021

ctDNA(+) associated with improved DFS and OS with atezolizumab vs observation



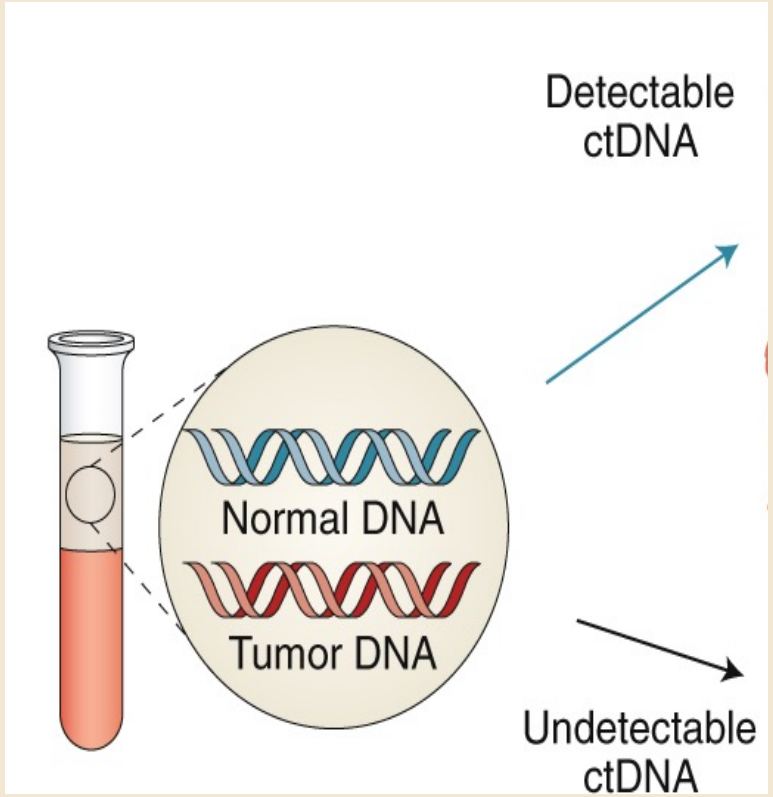
Powles et al. ESMO IO, 2020
Powles et al. Nature, 2021

IMVigor 011 (NCT04660344)

ypT2 and/or ypN+

or

pT3 and/or pN+
(cisplatin-ineligible)



R

Atezolizumab

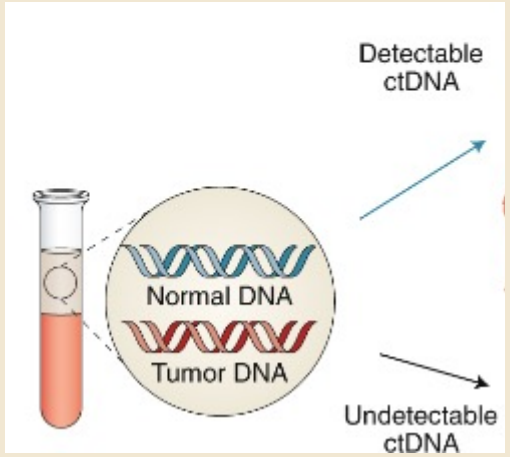
Placebo

Not eligible

Treatment Of Metastatic Bladder Cancer at the Time Of Biochemical reLApse Following Radical Cystectomy (TOMBOLA; NCT04138628)

Radical Cystectomy

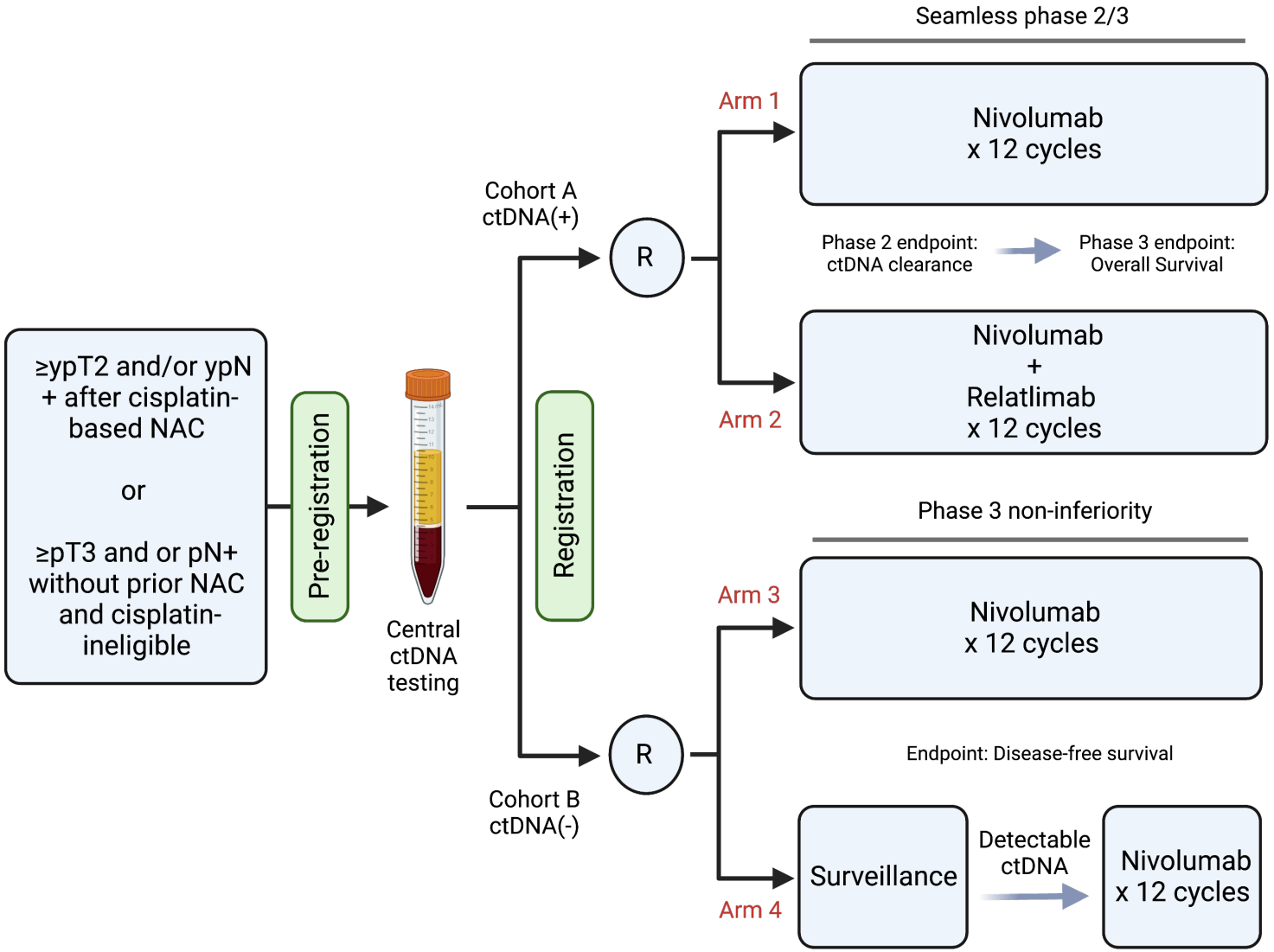
Serial ctDNA testing during follow-up



Atezolizumab

Surveillance

A032103 (MODERN) Schema



Alliance for Clinical Trials in Oncology

PI: Galsky

Study design

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

N = 709

Key inclusion criteria

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

Stratification factors

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

Treat for up to 1 year of adjuvant therapy

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

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

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

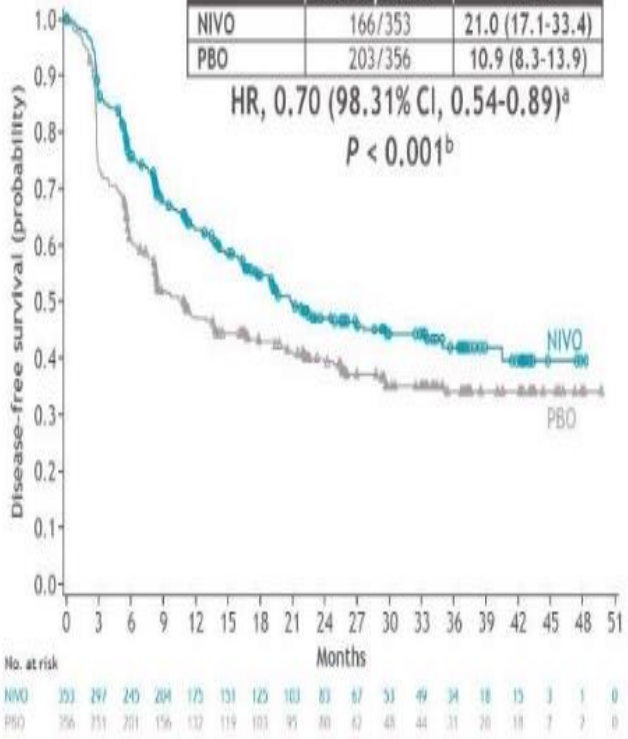
Disease-free survival

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	166/353	21.0 (17.1-33.4)
PBO	203/356	10.9 (8.3-13.9)

HR, 0.70 (98.31% CI, 0.54-0.89)[a]

$P < 0.001$[b]

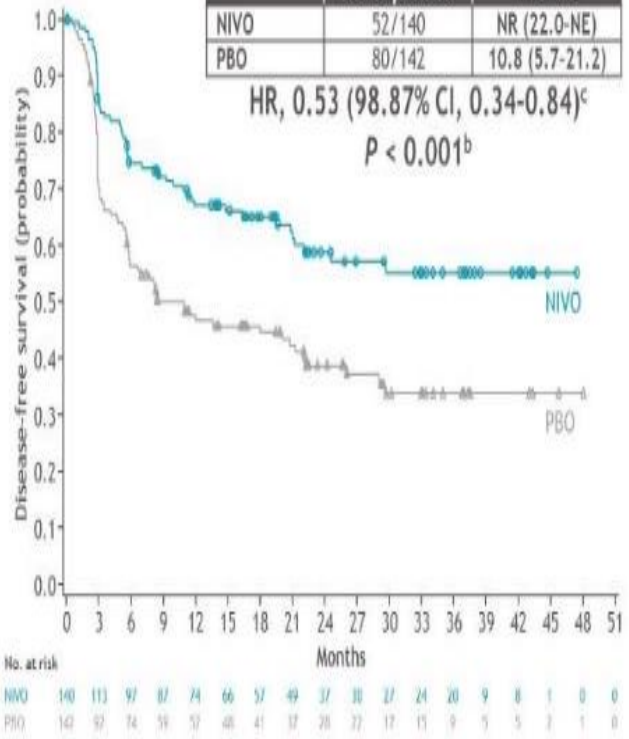


PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	52/140	NR (22.0-NE)
PBO	80/142	10.8 (5.7-21.2)

HR, 0.53 (98.87% CI, 0.34-0.84)[c]

$P < 0.001$[b]



Minimum follow-up, 5.9 months.

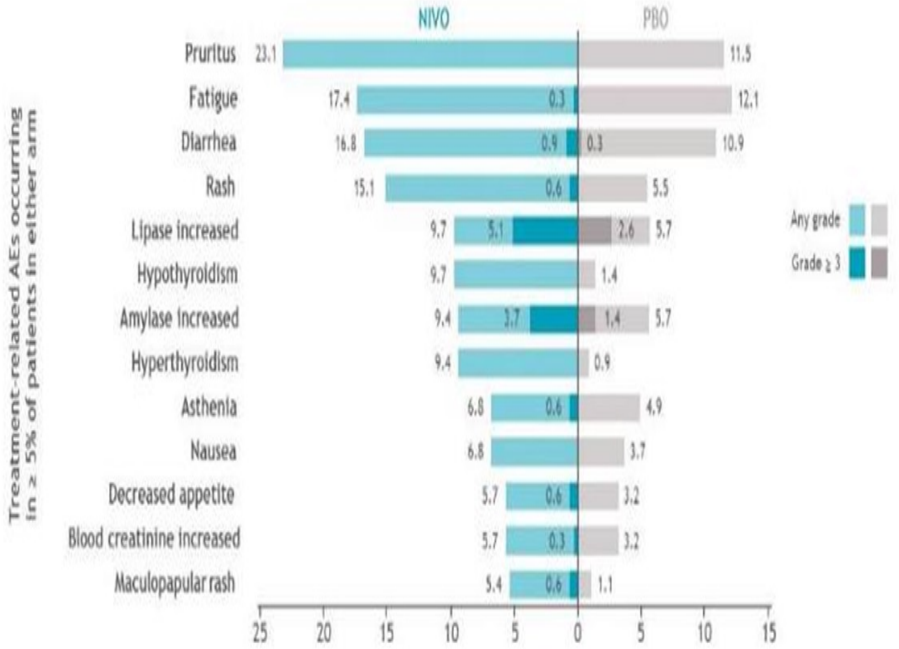
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.

[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).

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

Safety summary in all treated patients

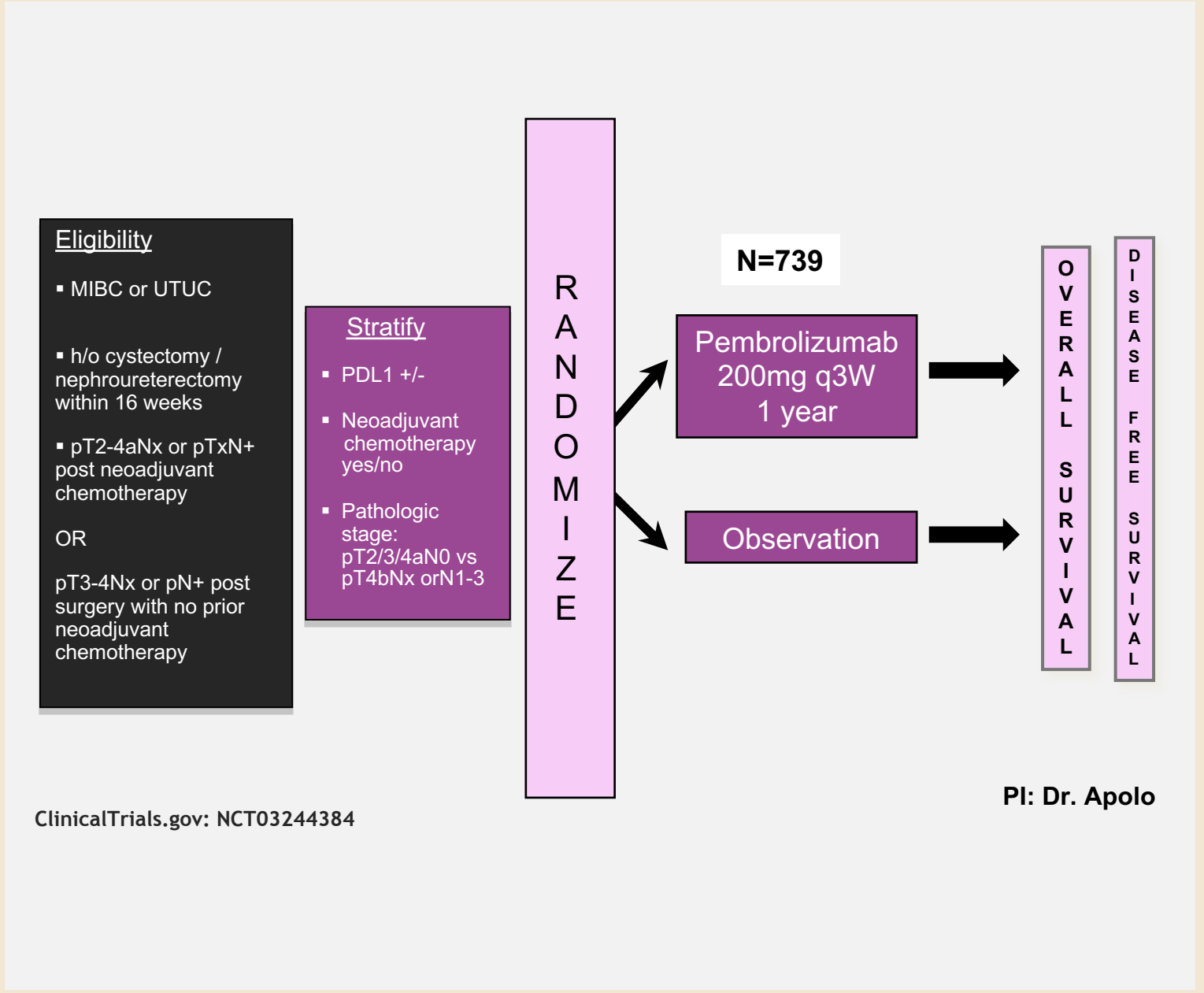
	NIVO (N = 351)[a]		PBO (N = 348)[a]	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any-cause AEs, %	98.9	42.7	95.4	36.8
Treatment-related AEs,[b] %	77.5	17.9	55.5	7.2
Treatment-related AEs leading to discontinuation, %	12.8	7.1	2.0	1.4



[a]Includes all treated patients. [b]There were 2 treatment-related deaths due to pneumonitis in the NIVO arm. There were no treatment-related deaths in the PBO arm.

Includes events reported between the first dose and 30 days after the last dose of study therapy.

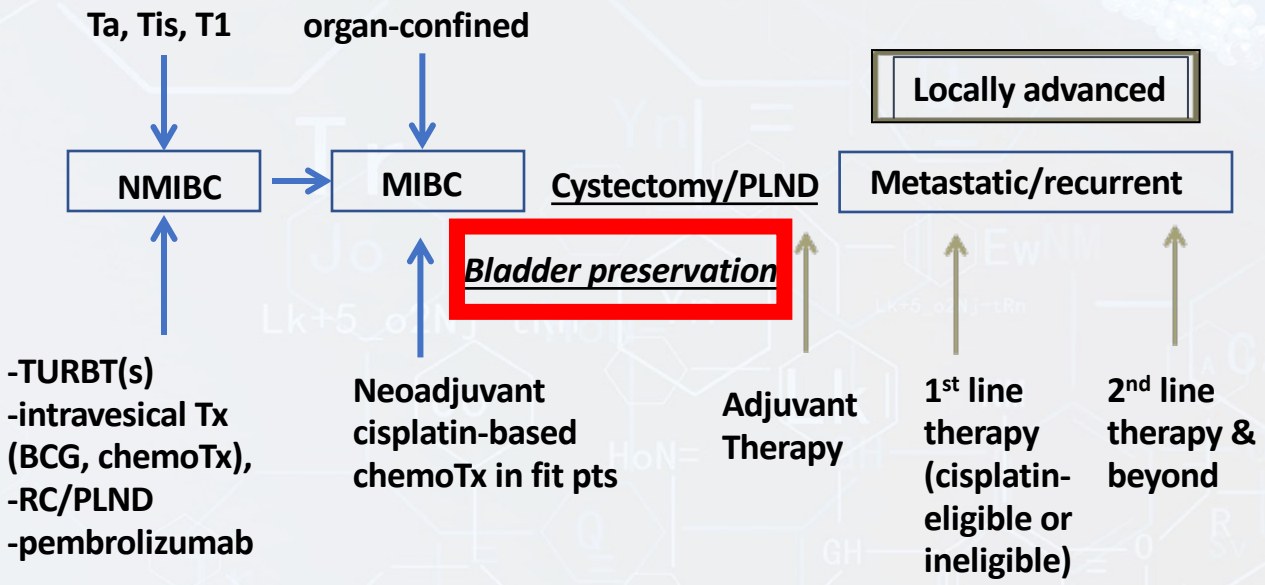
Phase III randomized “Adjuvant study of peMBrolizumAb in muScle invaSive and locAlly aDvanced urOthelial carcinoma” (AMBASSADOR) vs. observation



A few 'take home' messages so far

- **Clinical trials or cisplatin-based chemoTx for cisplatin-eligible pts**
- **Neoadjuvant cisplatin-based chemoTx: SOC prior to RC in fit pts**
- **Adjuvant nivolumab prolonged DFS in CM-274 trial (no OS data): FDA-approved in high risk MIUC in US**
- **AMBASSADOR phase 3 trial accrued 702 out of 739 pts; results pending (closed to accrual)**
- **PROOF302 phase 3 trial with infigratinib vs placebo for pts with tumors harboring FGFR3 activating mutation or fusion (terminated)**
- **ctDNA has emerging very interesting data but remains experimental in the peri-operative setting**
- **Variant histologies represent a major challenge with worse prognosis: a focus of our research program**

Disease / treatment settings



SWOG/NRG 1806: Phase III Trial of Concurrent Chemoradiation With or Without Atezolizumab for Localized Muscle Invasive Bladder Cancer

cT2-T4N0M0 stratify by
- Chemotherapy regimen
- Radiation field
- Performance status
- Clinical stage

Randomize 1:1, 475 patients

CRT (concurrent chemoradiation)

CRT+ Atezo x9

Primary endpoint
BIEFS*

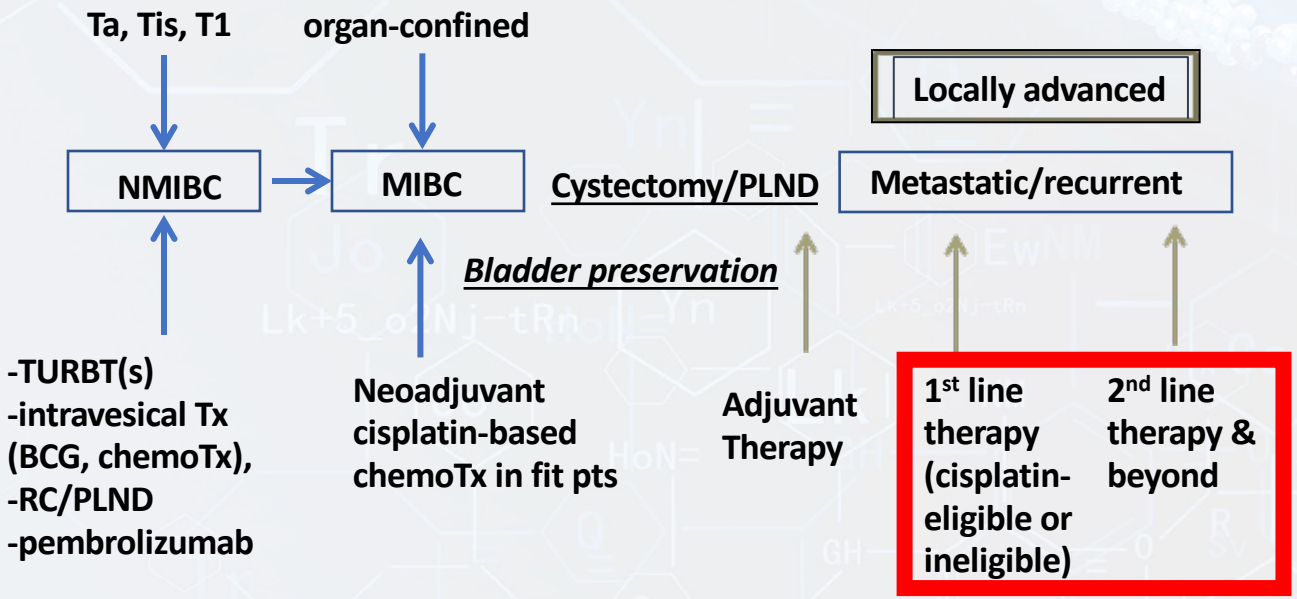
Secondary end point
- OS at 5 years
- Clinical response at 5 mths
- DSS
- MFS
- Toxicity at 1& 2 years
- NMIBC recurrence
- Cystectomy rate
- Global QoI

TM endpoints
- MRE 11
- DDR alterations
- Immune-related biomarkers

*BIEFS (bladder intact event free survival): muscle invasive recurrence in bladder, regional pelvic soft tissue or LN recurrence, distant mets, bladder cancer or toxicity related death or cystectomy

Singh et al. *JCO* 2020;38(6_suppl):TPS586

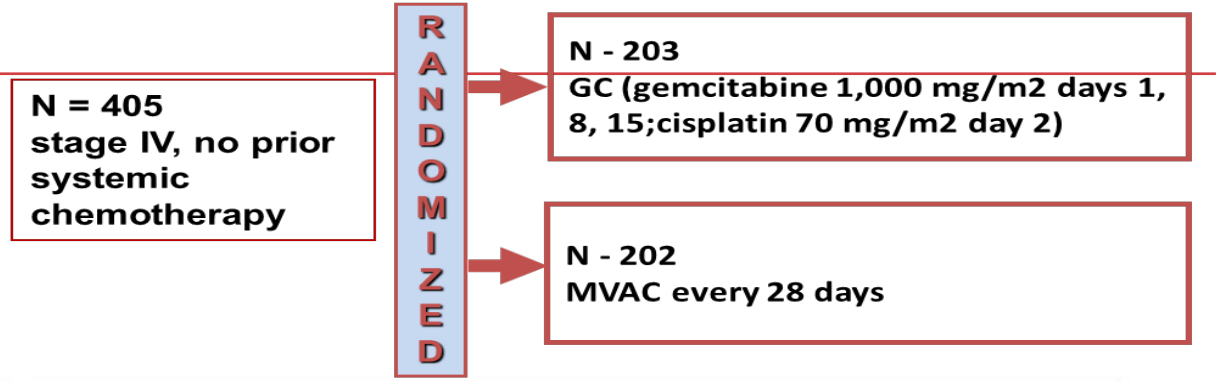
Disease / treatment settings



Metastatic disease (1st line)

- Comparable ORR between GC & 'classic' MVAC
- Median PFS: 7.7m (GC) and 8.3 m (MVAC)
- Median OS (14 vs. 15 months)
- Similar 5-y OS rate (13-15%) (p=0.53)
- Less G ¾ AEs with GC, e.g. neutropenia (71 vs. 82%), neutropenic sepsis (2% vs 14%), mucositis (1% vs 22%)
- Trial was designed to assess if GC is superior and was not powered to demonstrate non-inferiority

Most patients get GC (dose dense MVAC easier & better than older 'classic' MVAC)



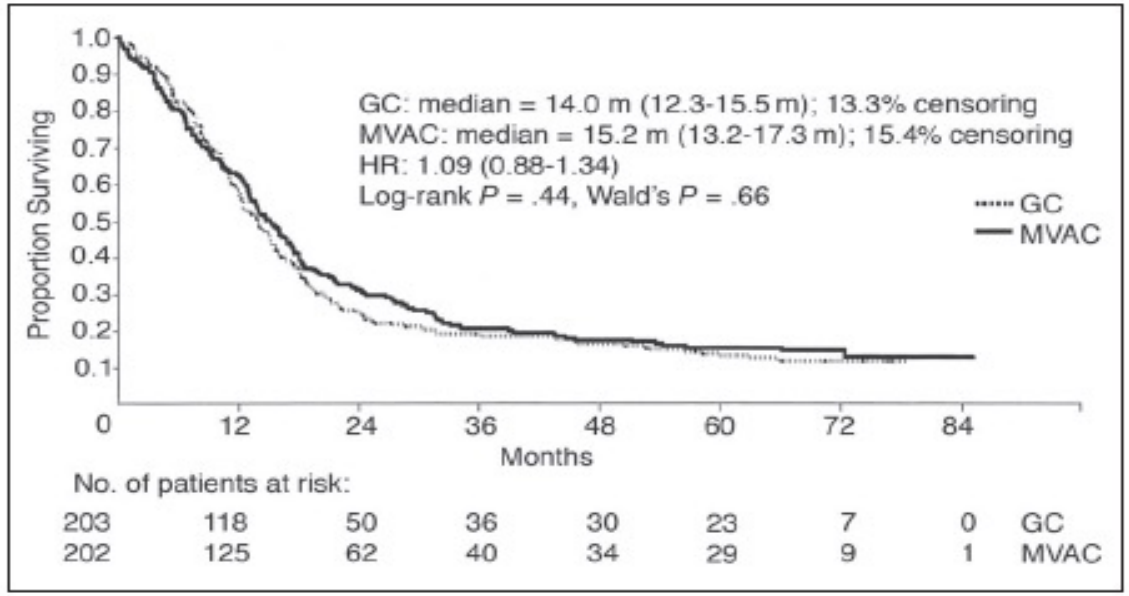


Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

Von der Maase H et al, JCO, 2000 (17): 3068-77

Defining “platinum-ineligible” patients with metastatic urothelial cancer (mUC)

Shilpa Gupta[1], Joaquim Bellmunt[2], Elizabeth R. Plimack[3], Guru P. Sonpavde[4], Petros Grivas[5], Andrea B. Apolo[6], Sumanta K. Pal[7], Arlene O. Siefker-Radtke[8], Thomas W. Flaig[9], Matt D. Galsky[10], Jonathan E. Rosenberg[11]

Platinum-Ineligibility in Bladder Cancer Working Group

[1]Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH; [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [3]Fox Chase Cancer Center, Philadelphia, PA; [4]Dana-Farber Cancer Institute, Boston, MA; [5]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; [6]Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD; [7]City of Hope Comprehensive Cancer Center, Duarte, CA; [8]MD Anderson, Houston, TX; [9]University of Colorado Cancer Center, Aurora, CO; [10]The Tisch Cancer Institute, Mount Sinai, New York, NY,[11]Memorial Sloan Kettering Cancer Center, New York, NY

Background:

- Carboplatin and gemcitabine followed by avelumab maintenance is the current preferred treatment (tx) for cisplatin-ineligible patients (pts) with mUC.
- Although pembrolizumab (P) and atezolizumab (At) were approved as 1L tx for these pts in 2017, the FDA has now restricted the use of 1L P to “platinum ineligible” mUC pts.
- We previously suggested a consensus definition for “platinum-ineligible” pts with mUC (Gupta et al. ASCO GU 2019) and now updated this for standard therapy and clinical trial eligibility in the current tx era.

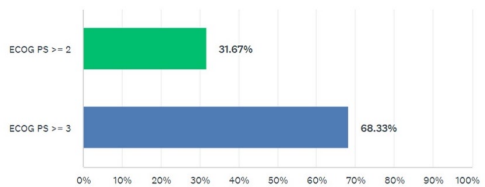
Methods:

- We surveyed 60 genitourinary medical oncologists in the US (similar cohort from initial survey) using an online tool consisting of clinical parameters used in our initial survey with additional questions related to current available tx options.
- We compiled the responses to generate a consensus definition.

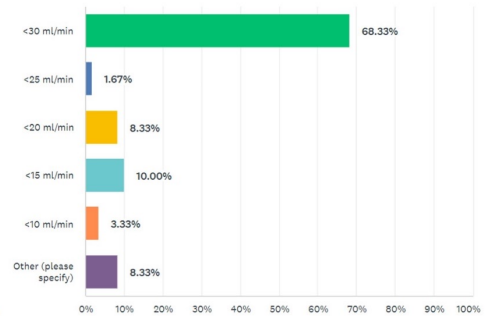
Results:

- All 60 respondents provided 100% responses.
- Survey results for “platinum-ineligibility” are displayed in bar graphs.
- Age was not considered a criteria for “platinum-ineligibility’

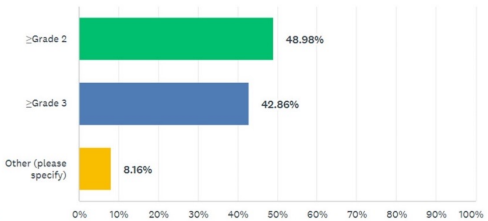
1. What threshold ECOG PS should be used to define "platinum-ineligibility"?



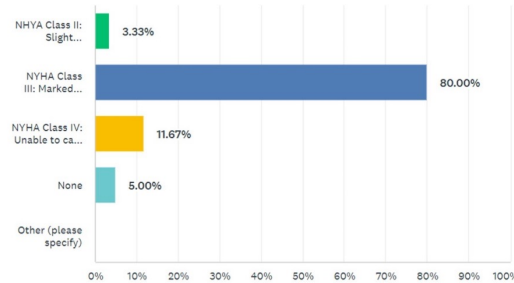
2. What threshold Cr Cl should be used for "platinum-ineligibility"?



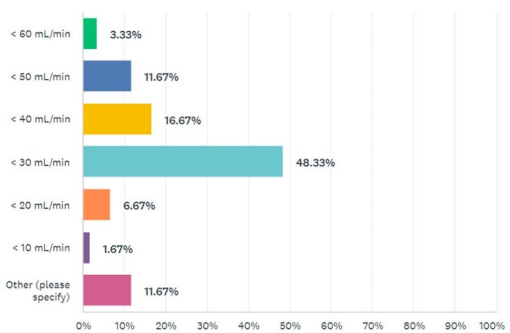
3. What grade of peripheral neuropathy would you consider for "platinum-ineligibility"?



4. What class of Heart Failure do you Consider to define "platinum-ineligibility"?



5. In a patient with ECOG PS 2, what Cr Cl cut-off would you use to define "platinum-ineligibility" differently of what is used for “cisplatin-ineligibility”?



Conclusions:

Based on the survey, any mUC pt meeting one the following 5 parameters should be considered "platinum-ineligible”:

1. ECOG PS > / = 3
2. Cr Cl < 30 ml/min
3. Peripheral neuropathy > / =Grade 2
4. NYHA Heart Failure Class > 3
5. ECOG PS 2 AND Cr Cl < 30 ml/min

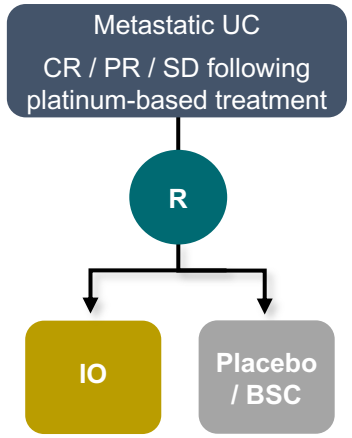
These criteria are proposed to guide treatment recommendations and standardization of eligibility criteria for defining “platinum-ineligible’ pts.

Acknowledgement: Al the respondents who completed the survey

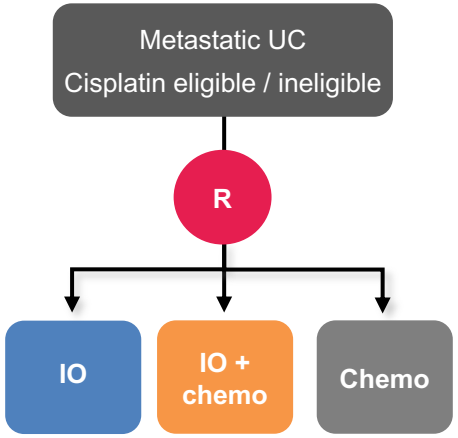
Correspondence: Shilpa Gupta MD, E-mail: Guptas5@ccf.org **@shilpaonc**

Cleveland Clinic

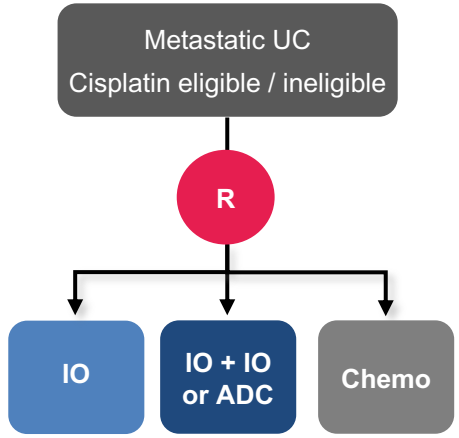
Different strategies aiming to impact 1L SoC



JB100 [NCT02603432]	avelumab	BSC	OS
HOOSIER [NCT02500121]	pembro	placebo	6-mo PFS



KN361 [NCT02853305]	pembro	pembro + chemo	chemo	OS, PFS
CM901 [NCT03036098]	--	nivo + chemo*	chemo	OS, PFS
IMvigor130 [NCT02807636]	atezo	atezo + chemo	chemo	OS, PFS, safety

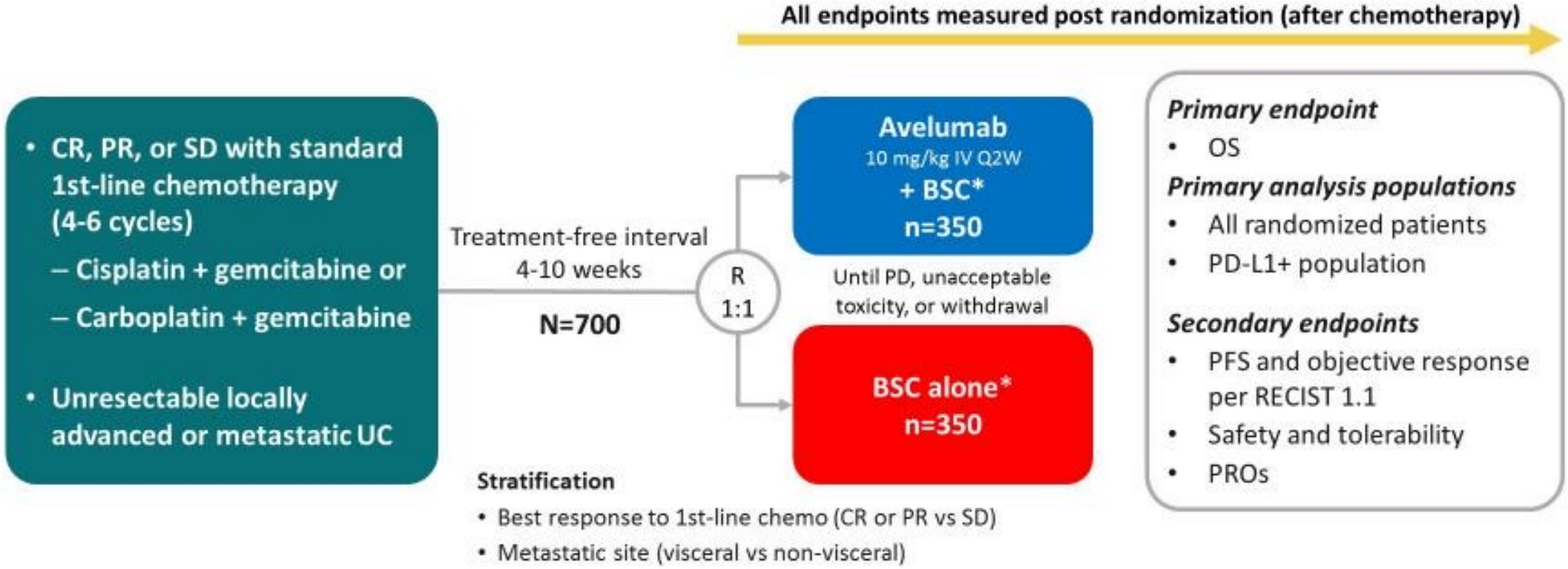


DANUBE [NCT02516241]	durva	durva + treme	chemo	OS
CM901 [NCT03036098]	--	nivo + ipi	chemo	OS, PFS
EV-302 [NCT04223856]	--	pembro + EV	chemo	OS, PFS

*For cisplatin-eligible patients only

1L, first-line; ADC, antibody-drug conjugate; atezo, atezolizumab; BSC, best supportive care; EV, enfortumab vedotin; chemo, chemotherapy; CR, complete response; durva, durvalumab;
IO, immuno-oncology; ipi, ipilimumab; OS, overall survival; nivo, nivolumab; pembro, pembrolizumab; PFS, progression-free survival; PR, partial response; R, randomisation; SD, stable disease;
SoC, standard of care; treme, tremelimumab; UC, urothelial carcinoma. NCT entries available at https://clinicaltrials.gov/ [Accessed August 2020].

JAVELIN Bladder 100 study design (NCT02603432)



PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

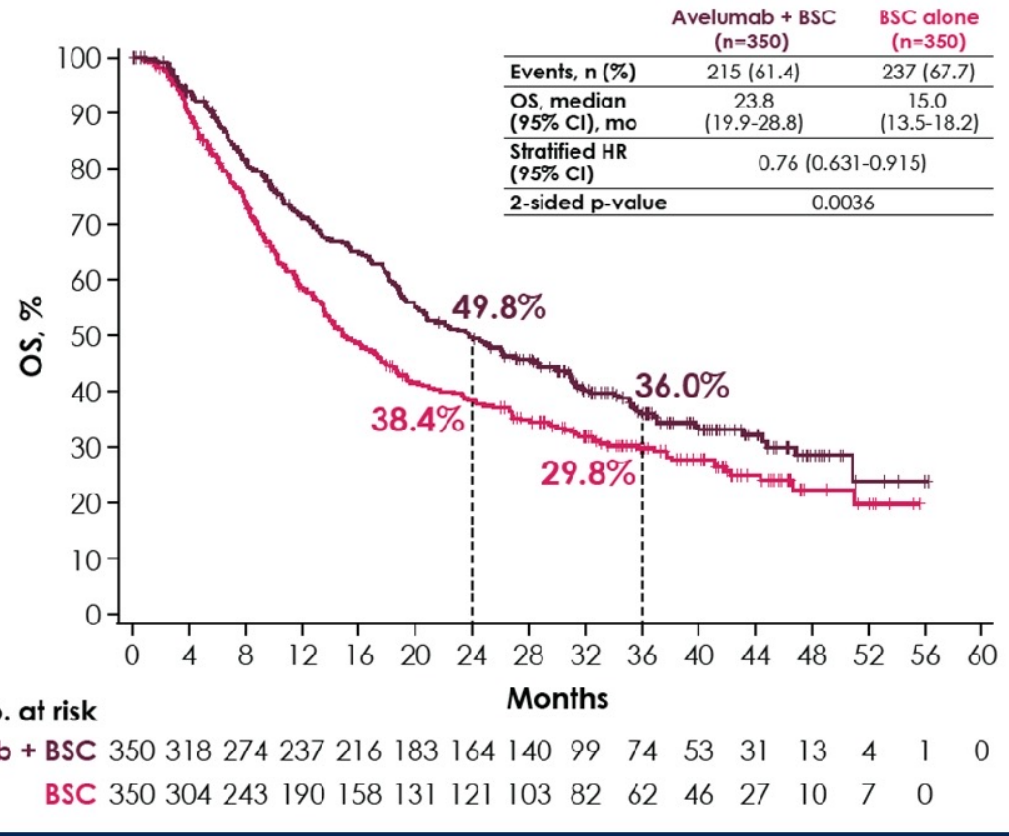
BSC, best supportive care; **CR**, complete response; **IV**, intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W**, every 2 weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

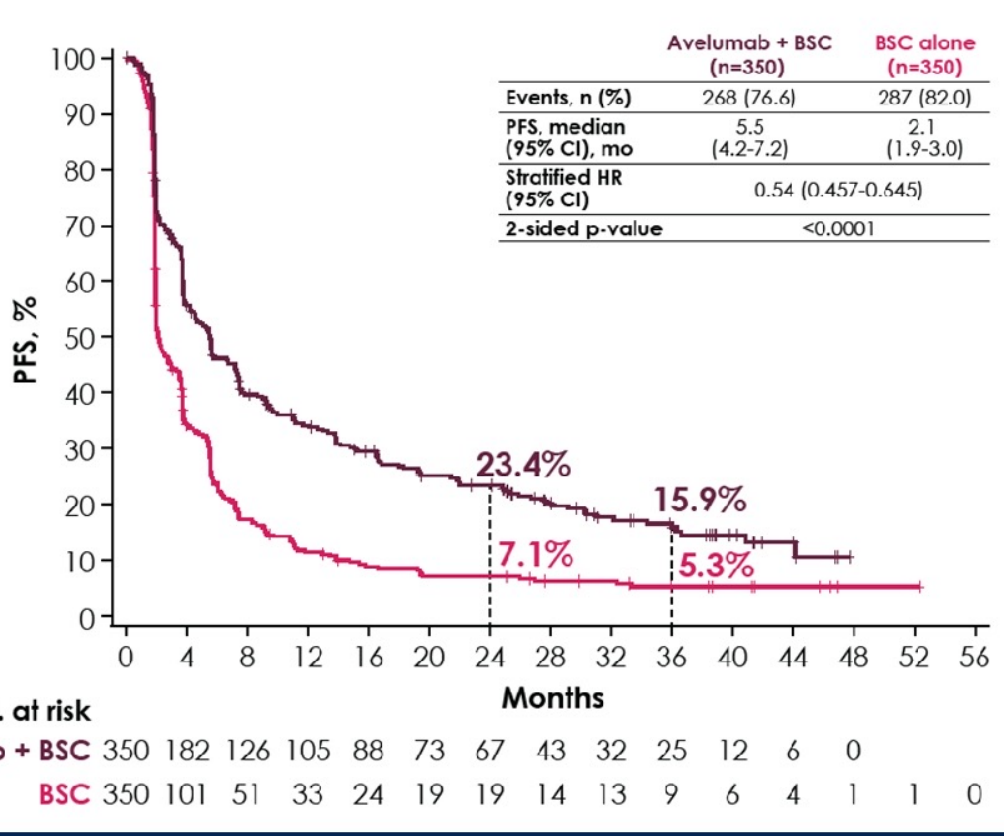
Presented By Thomas Powles at TBD

Long-term follow-up continues to show prolonged OS and PFS with avelumab + BSC vs BSC alone

OS



Investigator-assessed PFS

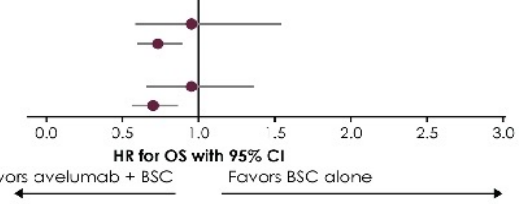


HR, hazard ratio.

PRESENTED BY: Thomas Powles, MD

OS favored avelumab + BSC vs BSC alone across subgroups

Subgroup	No. of events/no. of patients: Avelumab + BSC	BSC	HR for OS (95% CI)*
All patients (stratified†)	215/350	237/350	0.76 (0.631-0.915)
All patients (unstratified)	215/350	237/350	0.75 (0.627-0.908)
Best response to 1L chemotherapy			
CR	43/90	54/89	0.72 (0.482-1.076)
PR	108/163	117/163	0.70 (0.541-0.914)
SD	64/97	66/98	0.84 (0.596-1.188)
Metastatic disease site when initiating 1L chemotherapy			
Visceral	130/191	130/191	0.91 (0.713-1.162)
Nonvisceral	85/159	107/159	0.60 (0.451-0.798)
Age			
<65 years	85/129	71/107	0.89 (0.651-1.224)
≥65 years	130/221	166/243	0.68 (0.544-0.862)
Sex			
Male	163/266	189/275	0.74 (0.596-0.908)
Female	52/84	48/75	0.84 (0.568-1.250)
Race			
White	151/232	162/238	0.78 (0.625-0.975)
Asian	41/75	55/81	0.70 (0.464-1.044)
Other	23/43	20/31	0.80 (0.435-1.470)
Pooled geographic region			
Europe	136/214	146/203	0.71 (0.558-0.892)
North America	7/12	14/22	0.82 (0.330-2.035)
Asia	40/73	49/74	0.73 (0.479-1.108)
Australasia	23/34	18/37	1.29 (0.697-2.398)
Rest of the world	9/17	10/14	0.42 (0.163-1.061)
PD-L1 status at baseline			
Positive	102/189	108/169	0.69 (0.530-0.912)
Negative	101/139	100/131	0.83 (0.630-1.095)
Unknown	12/22	29/50	0.82 (0.418-1.614)
1L chemotherapy regimen			
Gemcitabine + cisplatin	108/183	134/206	0.78 (0.607-1.008)
Gemcitabine + carboplatin	97/147	91/122	0.70 (0.523-0.929)
Gemcitabine + carboplatin + cisplatin‡	10/20	11/20	0.69 (0.294-1.639)
ECOG performance status			
0	125/213	141/211	0.72 (0.563-0.913)
≥1	90/137	96/139	0.81 (0.606-1.078)
Creatinine clearance at baseline			
≥60 mL/min	113/181	125/196	0.84 (0.652-1.085)
<60 mL/min	101/168	109/148	0.64 (0.491-0.845)
Liver lesions at baseline			
Yes	33/43	33/44	0.95 (0.585-1.541)
No	182/307	204/306	0.73 (0.597-0.892)
Lung lesions at baseline			
Yes	59/83	57/83	0.95 (0.658-1.364)
No	156/267	180/267	0.70 (0.564-0.866)



ECOG, Eastern Cooperative Oncology Group. *HRs and CIs were calculated using a Cox proportional hazards model. †Stratified by best response to 1L chemotherapy (CR or PR vs SD) and metastatic disease site when initiating 1L chemotherapy (visceral vs nonvisceral). ‡Patients who switched platinum regimens while receiving 1L chemotherapy.

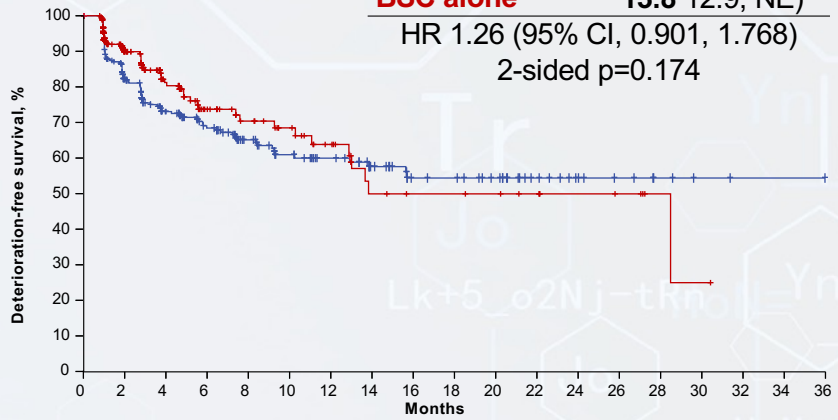
Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

TTD in FBISI-18 DRS-P scores (A) and TTD in FBISI-18 DRS-P scores or death (B) in the overall population

A

Median TTD (95% CI), months	
Avelumab + BSC	**NE** (13.9, NE)
BSC alone	**13.8** 12.9, NE)

HR 1.26 (95% CI, 0.901, 1.768)
2-sided p=0.174

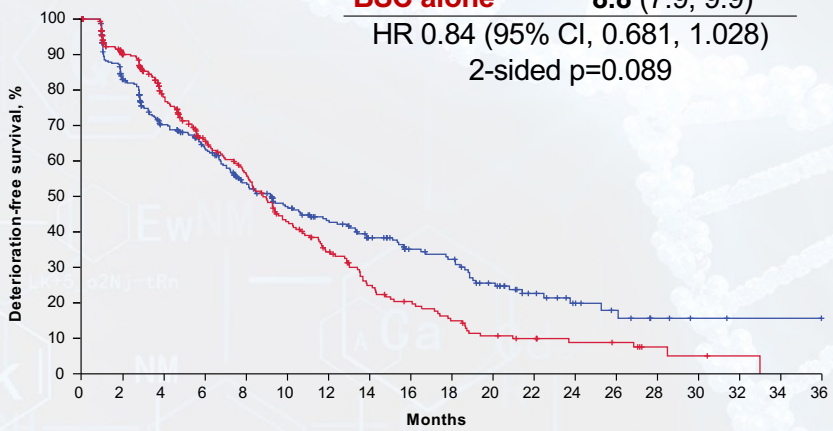


No. at risk																		
Avelumab + BSC	350	206	140	112	84	65	55	42	30	29	24	15	10	7	4	2	1	1	0
BSC	350	155	90	54	40	32	23	14	12	12	11	9	6	5	2	1	0	0	0

B

Median TTD (95% CI), months	
Avelumab + BSC	**9.2** (7.4, 11.7)
BSC alone	**8.8** (7.9, 9.9)

HR 0.84 (95% CI, 0.681, 1.028)
2-sided p=0.089



No. at risk																		
Avelumab + BSC	350	250	195	164	125	100	83	65	50	45	31	19	12	8	4	2	1	1	0
BSC	350	232	178	131	107	78	58	39	30	22	15	12	8	7	3	2	1	0	0

- **NE**, not estimable
- Crossing of curves, inconsistency between HRs, and differences in median TTD suggest that HRs may be nonproportional; therefore results should be interpreted with caution

PATRIOT-II: Observational Study (PI: Grivas)

Objectives: to complement JAVELIN Bladder 100 data gap in chemotherapy and understand the real-world effectiveness, including PROs, of 1LM with Aveluamab in LA/mUC from ~20 US Oncology centers

Patient Population (n=100)

Inclusion Criteria:

- Histologically confirmed LA/mUC
- Adults age 18 or older at dx
- Patients about to be initiated on 1L platinum-containing chemo

Exclusion criteria:

- Pt refusal to participate
- Incomplete history data
- Pregnancy
- Clinical trial participation at time of study enrolment

Patients with LA/mUC who are going to receive platinum-containing chemo.

1) For those do not move onto Avelumab 1LM, collect data up to last dose of chemo;

2) For those who continue onto Avelumab 1LM, continue to collect Avelumab follow up data for up to 1 year, in addition to the chemo data collected.

Selected Endpoints

Key endpoints

- Effectiveness: OS, rwPFS
- Treatment patterns
- rw time to treatment discontinuation,
- rw time to next line of treatment
- Reasons for treatment discontinuation
- Adverse events
- time to onset of irAEs, and high-dose steroid use
- HCRU, hospitalization, and ED visits
- PROs

Key points: 1) Pts will be followed for 1 year after 1LM Avelumab, for those not move onto Avelumab, followed until last dose of chemo. 2) Medical chart data collected at 4 timepoints: @chemo baseline, @Avelumab 1LM initiation, 6 & 12 mo f/u with Avelumab initiation; chart abstraction at last dose of chemo/or disease prog if patient not switching to Avelumab. 3) PRO data collected for max 10 points, including @chemo baseline, W6, @Avelumab initiation, W6, W12, then Q3M up to 1 year and at disease progression if within 1 year; 4) Complement JAVELIN Bladder 100 for information prior to randomization.

rw = real world; OS = overall survival; PFS = progression free survival; HCRU = healthcare resource utilization; irAE = immune-related adverse event; ED= emergency department; PRO = patient-reported-outcome

EV-103: Phase 1b/2 Trial of EV + Pembrolizumab *Cohort A*

Patients with 1L **cisplatin-ineligible** la/mUC (N=45)

Dose escalation	Dose expansion cohort A
EV + pembro	EV + pembro
(n=5)	(n=40)

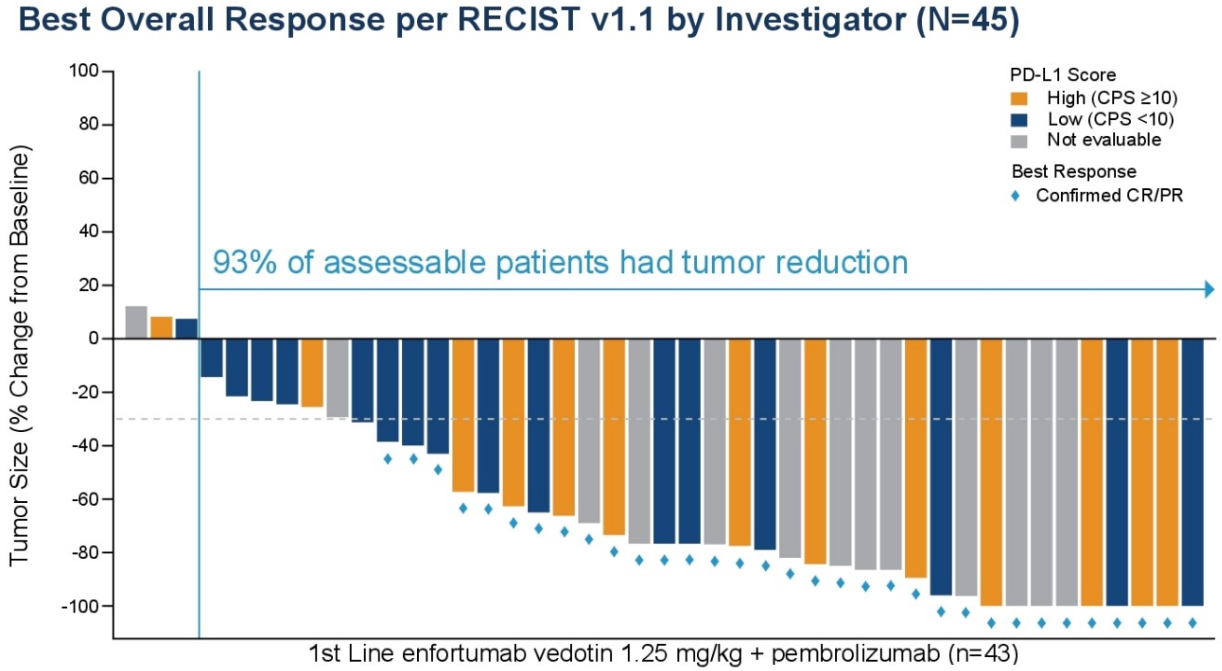
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembrolizumab 200 mg on day 1 of a 3-week cycle

- 84% of patients had visceral disease, and 31% had liver metastasis
- 31% of patients had PD-L1 CPS ≥10

Confirmed ORR 95% CI	**73%** (33/45) (58.1, 85.4)
Complete response	16% (7/45)
Partial response	58% (26/45)

- 57% confirmed ORR in patients with liver metastases

Maximum Target Lesion Reduction from Baseline by PD-L1 Status



la = locally advanced.

Friedlander TW, et al. Presented at: ASCO Annual Meeting; 2021. Abstract 4528.

Overall Response Rate by BICR

EV+P: 64.5% confirmed ORR with rapid responses

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	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)

Data cutoff: 10Jun2022
BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

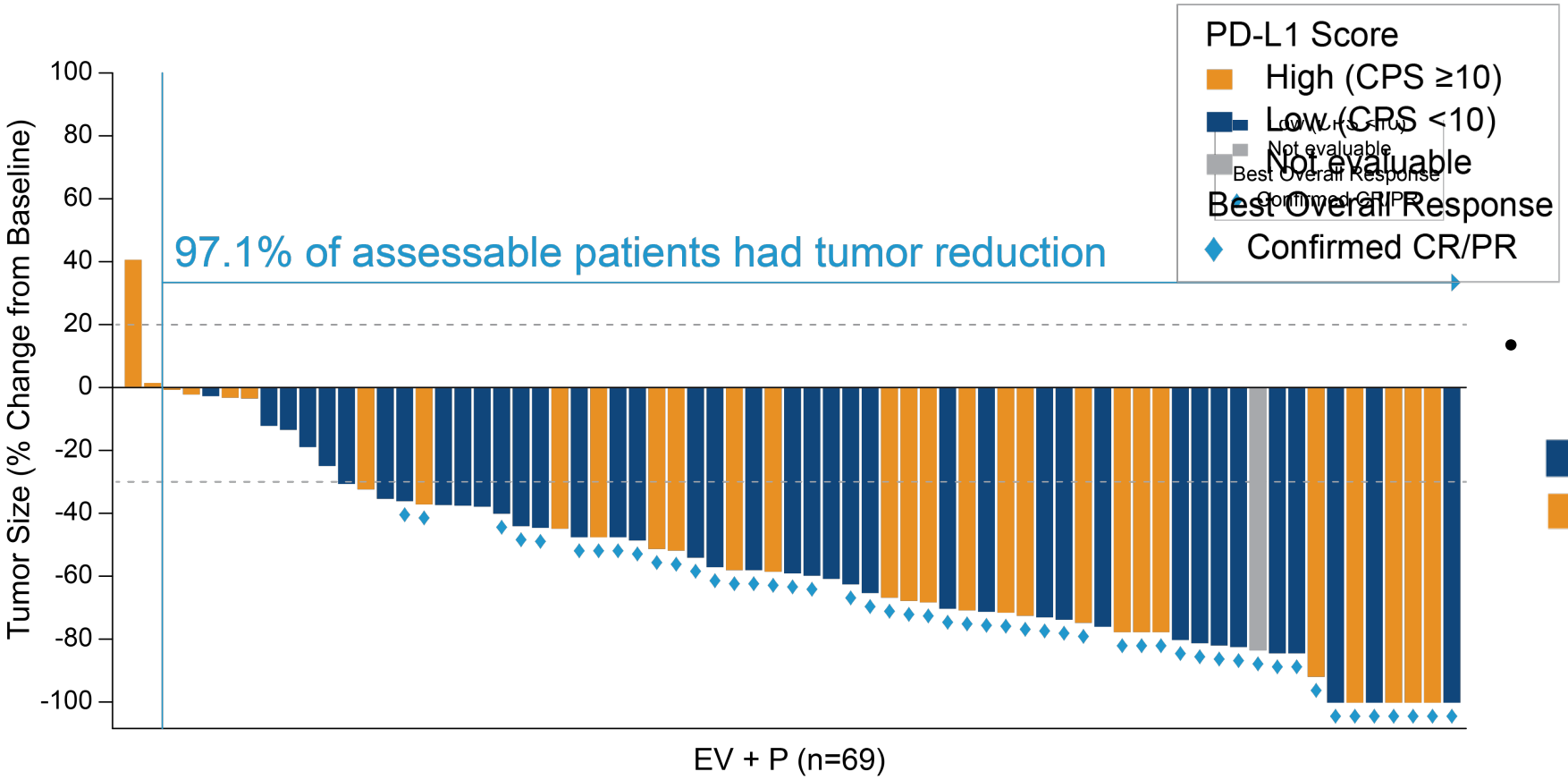
EV+P

- 41/49 (85.7%) of responses observed at first assessment (week 9±1 wk)
- cORRs were consistent across all pre-specified subgroups
- 7/13 (53.8%) cORR observed in patients with liver metastases

EV monotherapy

- Activity is consistent with prior results in 2L+ la/mUC

EV+P: Maximum Percent Reduction from Baseline of Target Lesion by BICR



- Activity seen regardless of PD-L1 status
  - 27/44 (61.4%) cORR in CPS<10
  - 21/31 (67.7%) cORR in CPS≥10

BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

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	35 (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

Serious TRAEs

- **18 (23.7%) EV+P**
- **11 (15.1%) EV Mono**

TRAEs leading to death (per investigator)

- **3 (3.9%) EV+P (Pneumonitis, Respiratory failure, Sepsis)**
- **2 (2.7%) EV Mono (Multiple organ dysfunction, Respiratory failure)**

EV-302: Randomized Phase 3 Trial of Enfortumab Vedotin + Pembrolizumab vs Chemotherapy

Key eligibility criteria:

- Untreated locally advanced or metastatic urothelial cancer
- Eligible for platinum-based chemotherapy and for pembrolizumab

1:1 randomization

Enfortumab vedotin
(Days 1 and 8)
+
Pembrolizumab
(Day 1)
Every 3-week cycle

Gemcitabine
(Days 1 and 8)
+
Cisplatin or Carboplatin
(Day 1)

Every 3-week Cycle

Primary Objectives
- PFS per RECIST by central review
- OS

Secondary Objectives
- PFS per RECIST by investigator
- ORR
- DOR
- DCR
- QOL
- Safety and tolerability

	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase III Randomized vs chemotherapy	Phase II Single Arm	Phase III Randomized vs Chemotherpay	Phase Ib	Phase I/II
Number of Patients	931	265	542	249 (161 pts ≥ 6 mos f/u)	191
Dosing	1200mg every 3 weeks	3mg/kg every 2 weeks	200mg every 3 weeks	10mg/kg every 2 weeks	10mg/kg every 2 weeks
ORR	13.4%	19.6%	21.1%	17%	17.8%
Duration of Response	63% of responses ongoing at median f/u of 21.7 mos	77% of responses ongoing at median f/u of 7 mos	72% of responses ongoing at median f/u of 14.1 mos	96% of responses ongoing at 6 mos f/u	50% of responses lasting ≥ 6 mos
Median OS	8.6 mos	8.7 mos	10.3 mos	6.5 mos	18.2 mos
Median PFS	2.1 mos	2.0 mos	2.1 mos	1.5 mos	1.5 mos
Rate of Grade 3/4 Treatment-related AEs	20%	18%	15%	8%	6.8%

1Powles T, et al. Lancet. 2018;391(10122):748-757.; 2Sharma P, et al. Lancet Oncol. 2017;18(3):312-322.; 3Bellmunt J, et al. N Engl J Med. 2017;376(11):1015-1026.; 4Patel MR, et al. Lancet Oncol. 2018;19(1):51-64.; 5Powles T, et al. JAMA Oncol. 2017;3(9):e172411

BLC2001: Phase 2 Trial of Erdafitinib[1]

- Fifteen percent of patients with MIBC have *FGFR* alterations[2]

Patients

- Unresectable Ia/mUC with prespecified *FGFR3/2* alterations
- ECOG PS 0-2
- History of disease progression during or after ≥1 line of prior systemic chemotherapy, or within 12 months after receiving (neo)adjuvant chemotherapy in the metastatic setting (chemo-refractory patients)
- Were cisplatin ineligible (for impaired renal function or peripheral neuropathy)
- Chemotherapy naïve

Screening for *FGFR* fusions/mutations

Randomized 1:1

Regimen 1

Erdafitinib 10 mg/d
7 days on/7 days off
Locally advanced UC

Regimen 2

Erdafitinib 6 mg/d

Regimen 3

Erdafitinib 8 mg/d with potential for uptitration to 9 mg/d

(n=99)

Primary endpoint

- Confirmed ORR

Secondary endpoints

- PFS, DOR, OS, safety, predictive biomarker evaluation, and PK

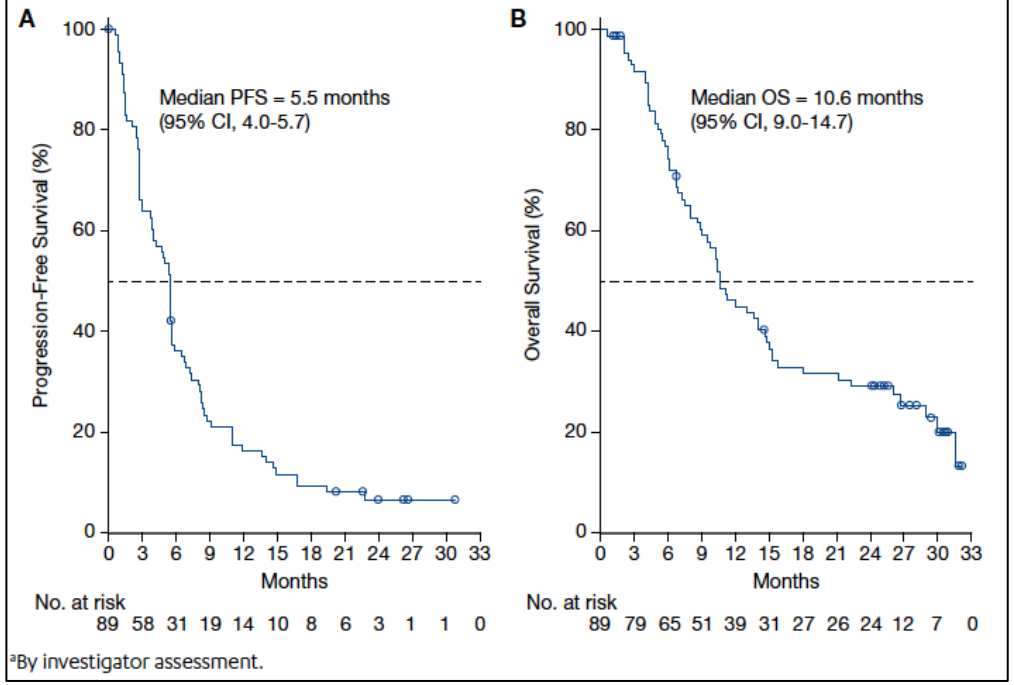
***FGFR* Alterations (n=99)**	
FGFR2 or *FGFR3* fusion, No. (%)	25 (25)
FGFR3 mutation, No. (%)	74 (75)
FGFR2/3 fusions and mutations	0

1. Loriot Y, et al. *N Engl J Med.* 2019;381(4):338-348.
2. Helsten T, et al. *Clin Cancer Res.* 2016;22(1):259-267.

BCL2001: Efficacy

	All Patients (N=99)	*FGFR3* Mutation (n=74)	*FGFR2/3* Fusion (n=25)
ORR, n (%) (95% CI)	40 (**40**) (31-50)	36 (**49**) (37-60)	4 (**16**) (2-30)

Figure 3. A) PFS[a] and B) OS in Patients Who Had Prior Chemotherapy



[a]By investigator assessment.

1. Loriot Y, et al. *N Engl J Med.* 2019;381(4):338-348.

2. Necchi A, et al. ESMO 2020. Presentation 750P.

- **Confirmed response rate 40% (3% CR; 37% PR)**
- **Among 22 pts with prior ICI, confirmed response rate 59%**

Table 2. Efficacy Outcomes by Subgroup

	n	Median DoR[a], mo	n[b]	Median PFS[a], mo	Median OS, mo
FGFR alteration					
FGFRm+f-	33	6.0	70	5.6	12.0
FGFRm-f+	4	6.2	25	2.8	10.3
FGFRm+f+	3	5.6	6	6.9	15.0
Primary tumor location					
Upper tract	11	6.7	25	4.2	10.3
Lower tract	29	6.0	76	5.6	13.8
Presence of visceral metastases					
Yes	30	6.0	78	5.5	10.3
No	10	5.3	23	5.8	14.1
Prior systemic therapy					
None	4	10.9	10	9.8	18.1
1 line	17	6.0	48	5.5	11.3
2 lines	10	6.1	28	5.5	8.0
3 lines	7	4.4	11	5.7	11.2
> 3 lines	2	4.8	4	3.4	12.4
Use of prior chemotherapy					
Yes	35	5.6	89	5.5	10.6
No	5	14.3	12	14.9	20.8
Use of prior IO					
Prior IO	14	6.5	24	5.7	10.9
No prior IO	26	5.6	77	5.5	12.0

[a]By investigator assessment. [b]For PFS and OS.

BCL2001: Safety

Grade ≥3 AEs Occurring in ≥5% of Patients, No. (%)	(N=99)
Stomatitis	10 (10)
Hyponatremia	11 (11)
Asthenia	7 (7)
Nail dystrophy	6 (6)
Hand-foot syndrome	5 (5)
Urinary tract infection	5 (5)

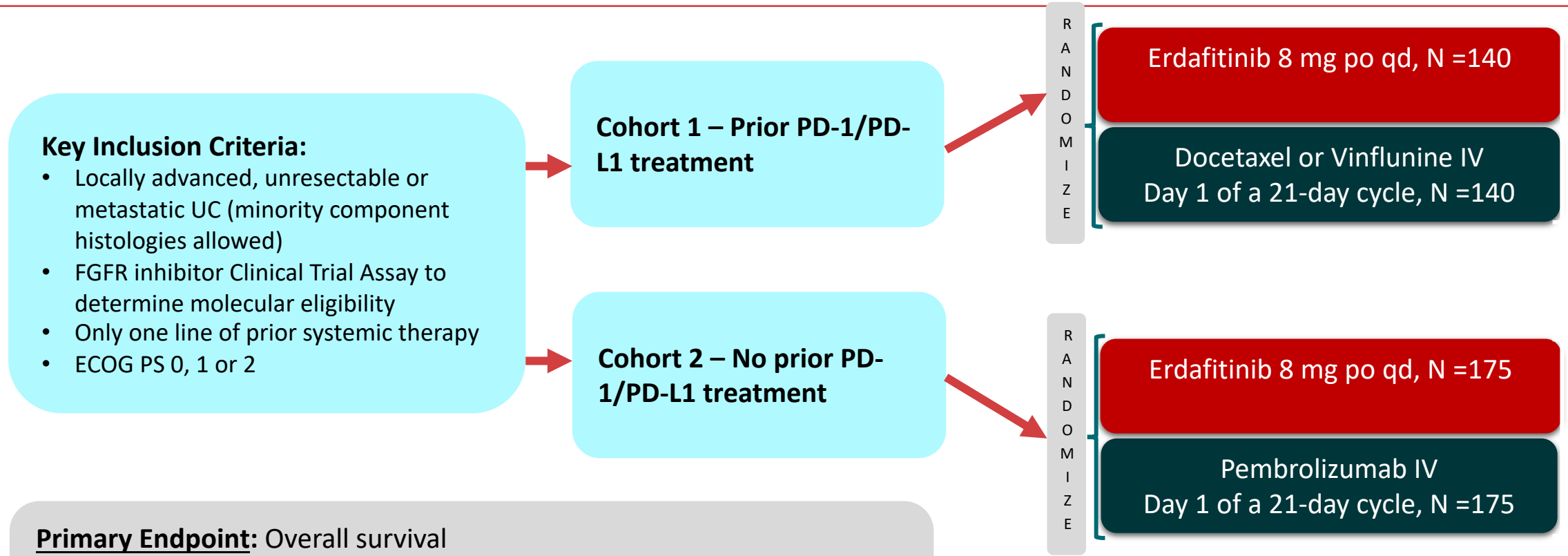
Final Analysis (n=101)

TEAE of Interest	Overall Incidence n (%)
Hyperphosphatemia[a]	79 (78%)
Stomatitis	60 (59%)
Nail disorders	60 (59%)
Skin disorders	55 (55%)
Central serous retinopathy	27 (27%)

1. Loriot Y, et al. *N Engl J Med.* 2019;381(4):338-348.

2. Necchi A, et al. ESMO 2020. Presentation 750P.

Randomized Phase 3 Erdafitinib THOR Trial Schema

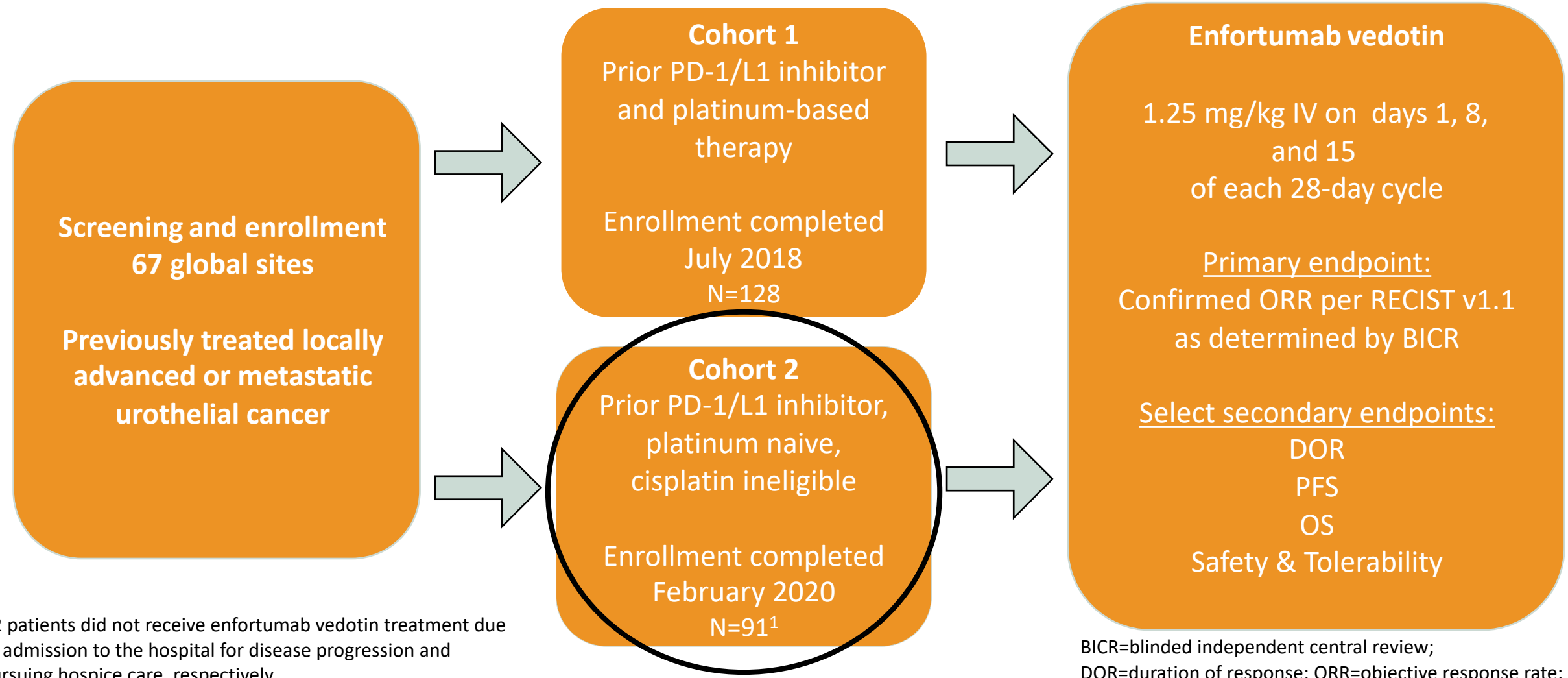


Primary Endpoint: Overall survival

Secondary Endpoints: PFS, ORR, duration of response, safety, patient-reported outcomes, pharmacokinetics.

https://clinicaltrials.gov/ct2/show/NCT03390504

Enfortumab Vedotin (EV-201) Phase 2 Trial



[1] 2 patients did not receive enfortumab vedotin treatment due to admission to the hospital for disease progression and pursuing hospice care, respectively

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

EV-201 Cohort 2 Confirmed Best Overall Response per BICR

ORR per RECIST v 1.1 assessed by BICR	Patients (N=89) %
Confirmed ORR, 95% CI[1]	52 (40.8, 62.4)
Best overall response	%
Complete response	20
Partial response	31
Stable disease	30
Progressive disease	9
Not evaluable[2]	9

ORR = Objective Response Rate; BICR = Blinded Independent Central Review

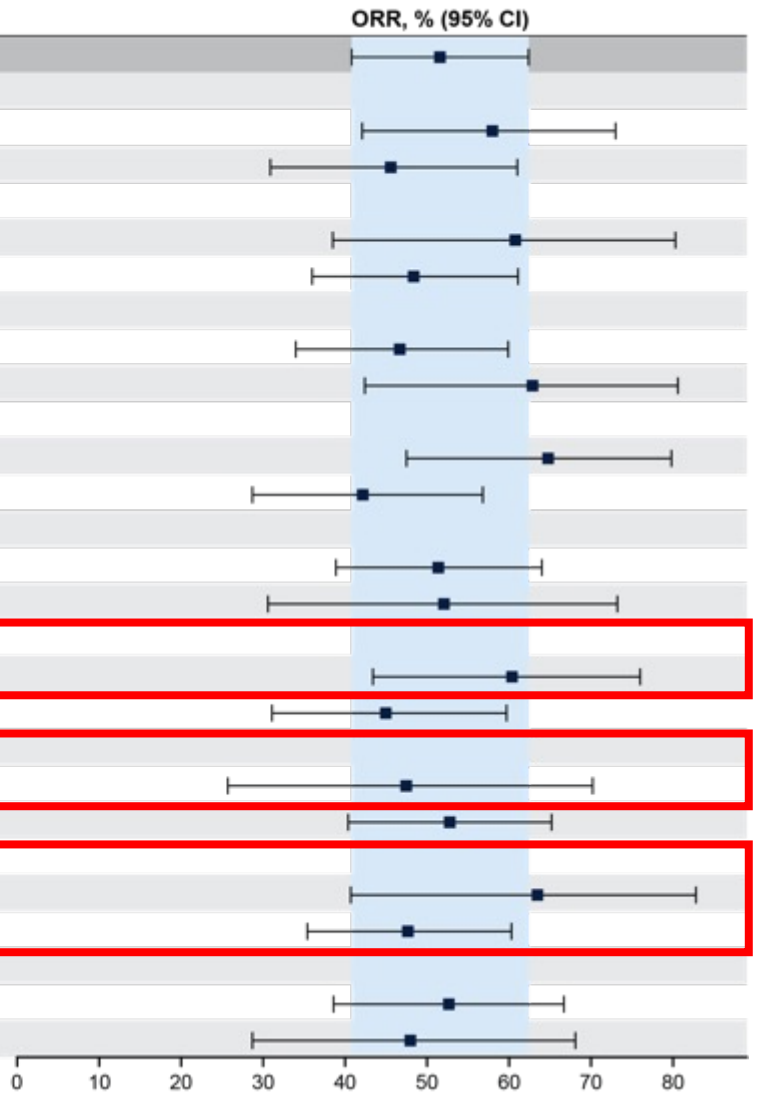
[1] CI = Confidence Interval, Computed using the Clopper-Pearson method

[2] Includes five subjects who did not have response assessment post-baseline, two subjects whose post-baseline assessment did not meet the minimum interval requirement for stable disease, and one subject whose response cannot be assessed due to incomplete anatomy.

EV-201 Cohort 2 Overall Response Rates by Subgroup

Subjects (N=89)

Subgroup	n/N	% (95% CI)
Overall	46/89	52 (40.8, 62.4)
Age		
<75 years	25/43	58 (42.1, 73)
≥75 years	21/46	46 (30.9, 61)
Sex		
Female	14/23	61 (38.5, 80.3)
Male	32/66	48 (36, 61.1)
Race		
White	29/62	47 (34, 59.9)
Non-white	17/27	63 (42.4, 80.6)
ECOG PS		
0	24/37	65 (47.5, 79.8)
1–2	22/52	42 (28.7, 56.8)
Bellmunt risk score		
0–1	34/66	52 (38.9, 64)
≥2	12/23	52 (30.6, 73.2)
Primary tumor sites		
Upper tract	23/38	61 (43.4, 76)
Bladder/Other	23/51	45 (31.1, 59.7)
Liver metastasis		
Yes	10/21	48 (25.7, 70.2)
No	36/68	53 (40.4, 65.2)
Best response to prior CPI		
Responder	14/22	64 (40.7, 82.8)
Non-responder	32/67	48 (35.4, 60.3)
PD-L1 expression		
CPS <10	28/53	53 (38.6, 66.7)
CPS ≥10	13/27	48 (28.7, 68.1)



Responses were observed across all subgroups, including patients:

- with liver metastasis (48%)
- with primary tumor sites in the upper tract (61%)
- who did not respond to prior PD-1/PD-L1 inhibitors (48%)

ECOG PS= Eastern Cooperative Oncology Group Performance Score; CPI = Checkpoint Inhibitor; PD-L1 = programmed death-ligand 1; CPS = combined positive score

EV-201 Cohort 2 Treatment-Related Adverse Events

Treatment-related AEs by preferred term in ≥20% of patients (any Grade) or ≥5% (≥Grade 3)	Patients (N=89) n (%)	
	Any Grade	≥Grade 3
Alopecia	45 (51)	–
Peripheral sensory neuropathy	42 (47)	3 (3)
Fatigue	30 (34)	6 (7)
Decreased appetite	29 (33)	5 (6)
Pruritus	27 (30)	3 (3)
Rash maculo-papular	27 (30)	7 (8)
Dysgeusia	24 (27)	–
Weight decreased	23 (26)	1 (1)
Anemia	22 (25)	5 (6)
Diarrhea	20 (22)	5 (6)
Nausea	20 (22)	1 (1)
Neutropenia	11 (12)	8 (9)
Hyperglycemia	8 (9)	5 (6)
Lipase increased	7 (8)	5 (6)

Treatment-related AEs led to discontinuations in 16% of patients with peripheral sensory neuropathy as the most common reason (4%)

Treatment-Related AEs leading to death:

4 deaths considered to be treatment related by the investigator:

- acute kidney injury
- metabolic acidosis
- multiple organ dysfunction syndrome
- pneumonitis (occurred >30 days of last dose)

3 of these deaths occurred within 30 days of first dose of EV occurred in patients with BMI ≥30 kg/m^2

All 4 deaths: confounded by age (≥75 years) and other comorbidities

Enfortumab Vedotin for Previously Treated Advanced UC

- The 5-year relative survival rate for metastatic bladder cancer is ≈8%[1]
- Enfortumab vedotin (EV), an antibody–drug conjugate directed against Nectin-4, demonstrated overall survival (OS) and progression-free survival (PFS) benefit in patients with locally advanced or metastatic (la/m) urothelial carcinoma (UC) in the open-label, confirmatory phase 3 EV-301 trial (NCT03474107) at the prespecified interim analysis[2]

Efficacy and safety are presented for EV vs chemotherapy over a median follow-up period of ≈2 years

Key eligibility criteria:
- Histologically/Cytologically confirmed UC
- Radiographic progression/ relapse during or after PD-1/L1 treatment for advanced UC
- Prior platinum-containing regimen for advanced UC
- ECOG PS 0–1

1:1 randomization with stratification

Enfortumab vedotin (N=301)
1.25 mg/kg
on days 1, 8, and 15 of each 28-d cycle

Preselected chemotherapy (N=307)
Docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 or vinflunine 320 mg/m^2
on day 1 of each 21-d cycle

Primary end point: Overall survival

Secondary end points:
- Progression-free survival
- Disease control rate
- Overall response rate
- Safety

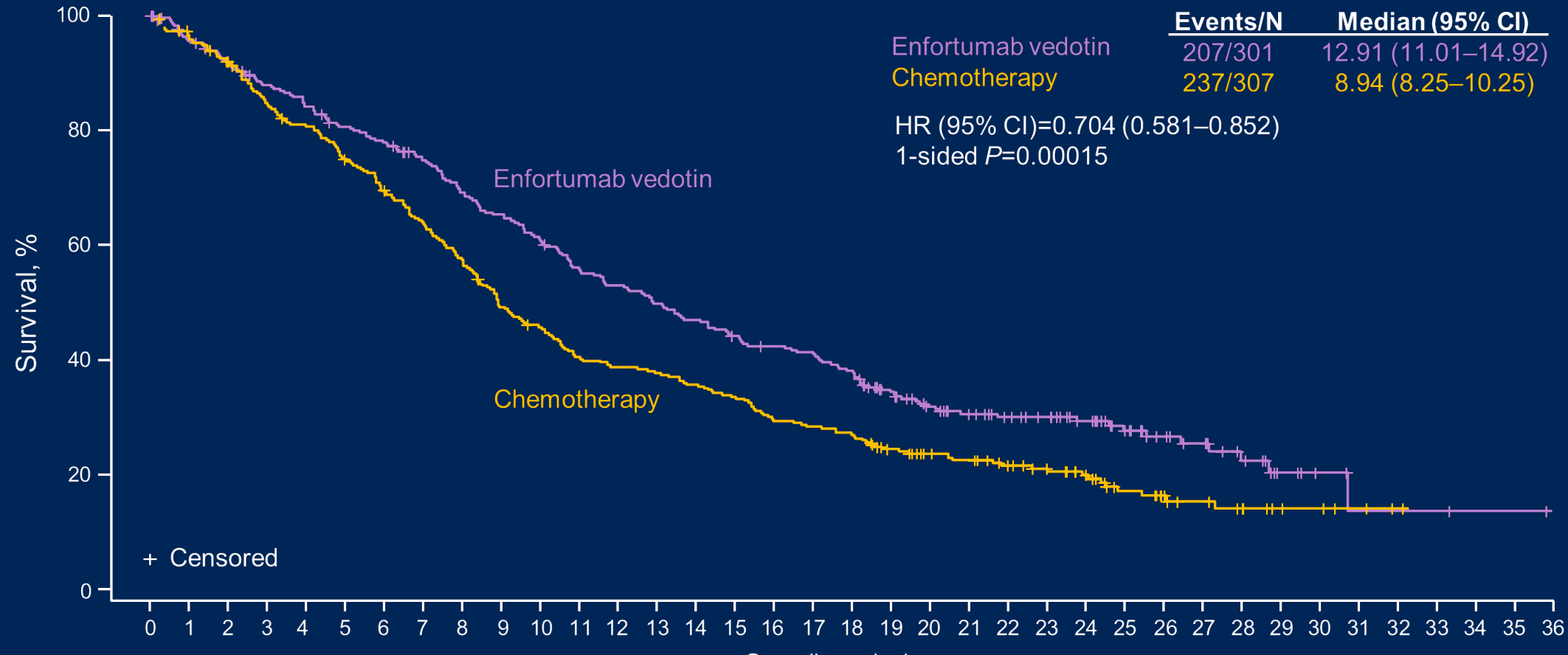
Investigator-assessed per RECIST v1.1

Findings from the prespecified, event-driven OS analysis when 439 deaths occurred are presented

ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; la/m, locally advanced or metastatic; OS, overall survival; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria In Solid Tumors; UC, urothelial carcinoma.

1. National Cancer Institute. https://seer.cancer.gov/statfacts/html/urinb.html. **2.** Powles T, et al. *N Engl J Med*. 2021;384:1125-1135.

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

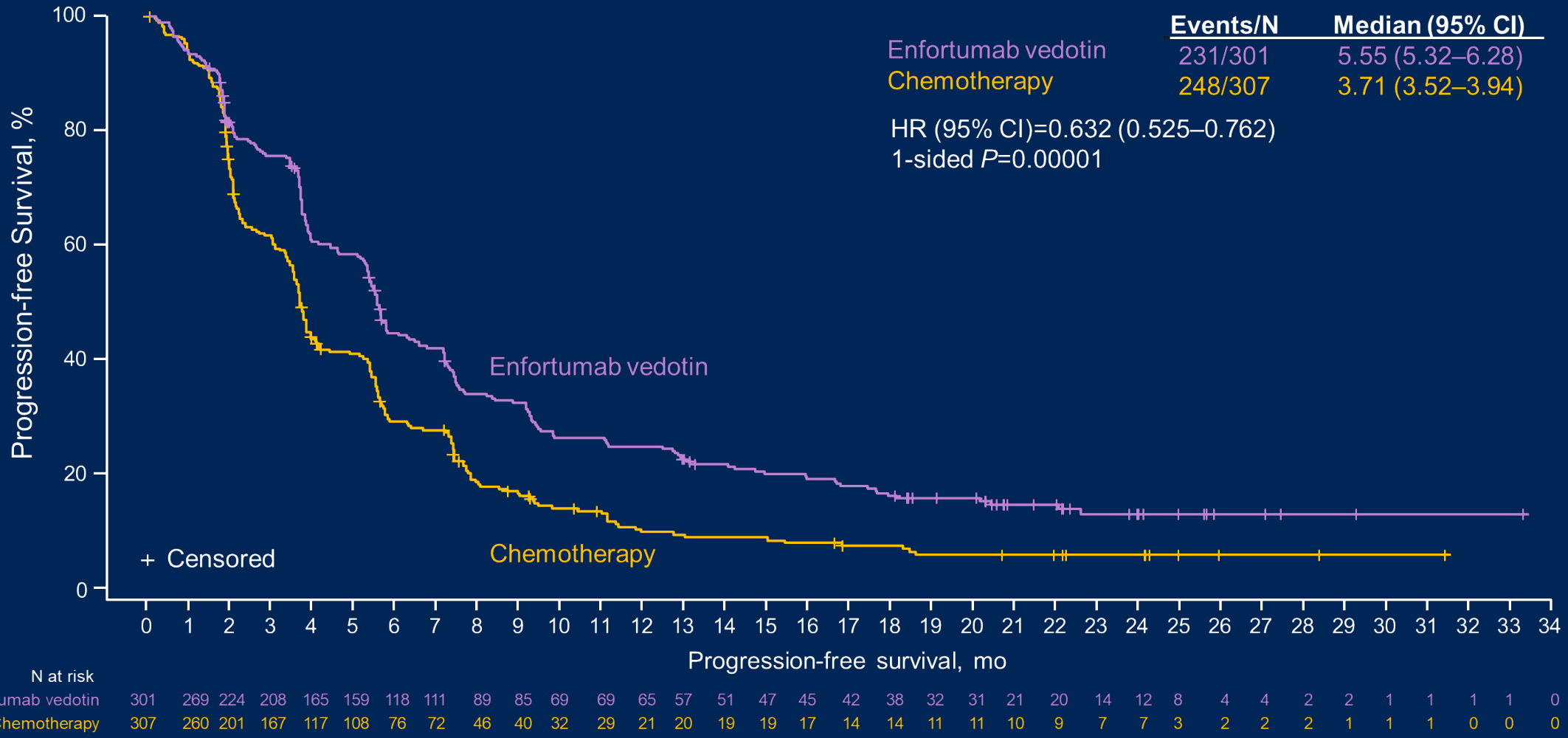
N at risk

Enfortumab vedotin	301	286	272	257	246	234	226	213	197	186	174	159	150	141	133	124	118	115	106	86	73	63	55	50	41	31	24	20	14	7	4	2	2	2	1	1	0
Chemotherapy	307	288	274	250	238	219	203	186	168	142	132	116	111	108	102	96	85	81	78	65	58	54	46	40	32	22	17	13	10	6	5	3	1	0	0	0	0

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

Data cutoff date: July 30, 2021

Progression-Free Survival



	Events/N	Median (95% CI)
Enfortumab vedotin	231/301	5.55 (5.32–6.28)
Chemotherapy	248/307	3.71 (3.52–3.94)

HR (95% CI)=0.632 (0.525–0.762)
1-sided *P*=0.00001

N at risk																																
Enfortumab vedotin	301	269	224	208	165	159	118	111	89	85	69	69	65	57	51	47	45	42	38	32	31	21	20	14	12	8	4	4	2	2	1	1	1	1	0
Chemotherapy	307	260	201	167	117	108	76	72	46	40	32	29	21	20	19	19	17	14	14	11	11	10	9	7	7	3	2	2	2	1	1	1	0	0	0

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

Data cutoff date: July 30, 2021

Safety/Tolerability

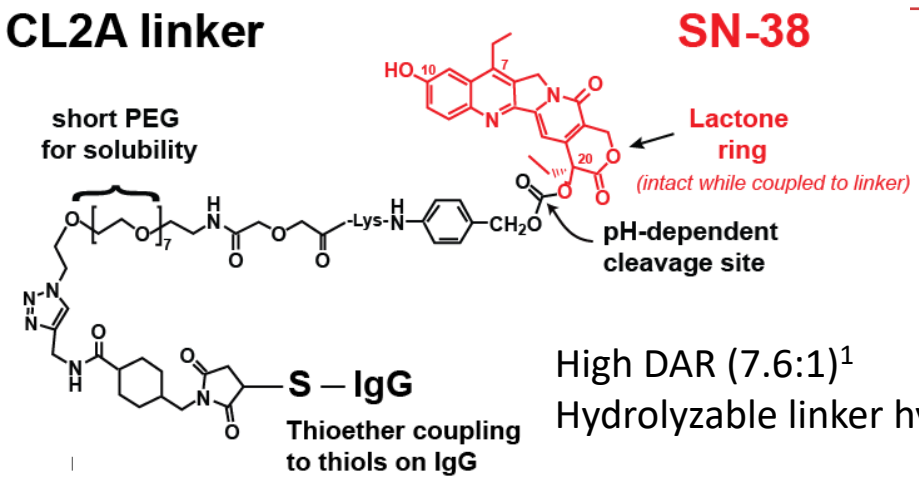
- Median (range) duration rates of treatment were 4.99 mo (0.5-29.9) for EV and 3.45 mo (0.2–26.4) for chemotherapy
- Rates of treatment-related adverse events (TRAEs; 93.9% vs 91.8%) and serious TRAEs (22.6% vs 23.4%) were comparable between EV and chemotherapy groups

Treatment-related adverse event, n (%)	Enfortumab vedotin (N=296)		Chemotherapy (N=291)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Alopecia	135 (45.6)	NR	108 (37.1)	NR
Peripheral sensory neuropathy	103 (34.8)	15 (5.1)	63 (21.6)	6 (2.1)
Pruritus	96 (32.4)	4 (1.4)	14 (4.8)	1 (0.3)
Fatigue	93 (31.4)	20 (6.8)	66 (22.7)	13 (4.5)
Decreased appetite	92 (31.1)	9 (3.0)	69 (23.7)	5 (1.7)
Diarrhea	74 (25.0)	10 (3.4)	49 (16.8)	5 (1.7)
Dysgeusia	73 (24.7)	NR	22 (7.6)	NR
Nausea	71 (24.0)	3 (1.0)	64 (22.0)	4 (1.4)
Maculopapular rash	50 (16.9)	22 (7.4)	5 (1.7)	NR
Anemia	34 (11.5)	8 (2.7)	63 (21.6)	23 (7.9)
Decreased neutrophil count	31 (10.5)	18 (6.1)	51 (17.5)	41 (14.1)
Neutropenia	20 (6.8)	14 (4.7)	25 (8.6)	18 (6.2)
Decreased white blood cell count	15 (5.1)	4 (1.4)	32 (11.0)	21 (7.2)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

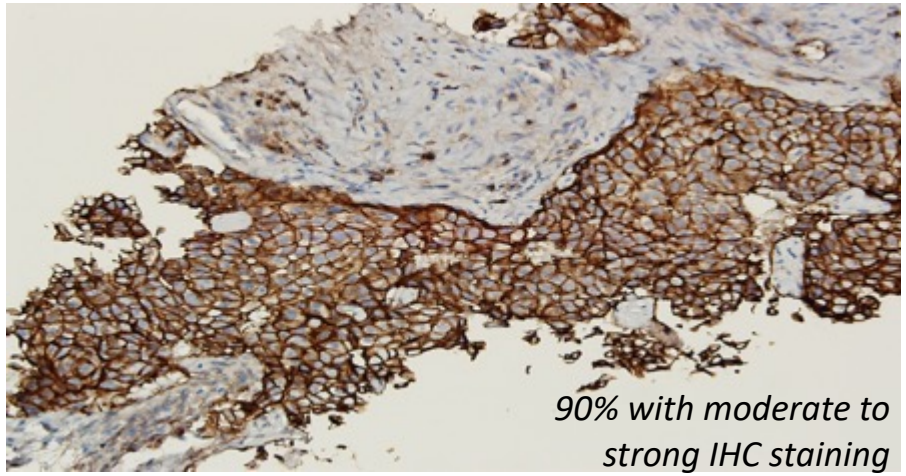
NR, not reported; TRAE, treatment-related adverse event.
Occurring in ≥20% of patients in either treatment group or grade ≥3 TRAEs occurring in ≥5% of patients in either treatment group. Data shown for safety population.

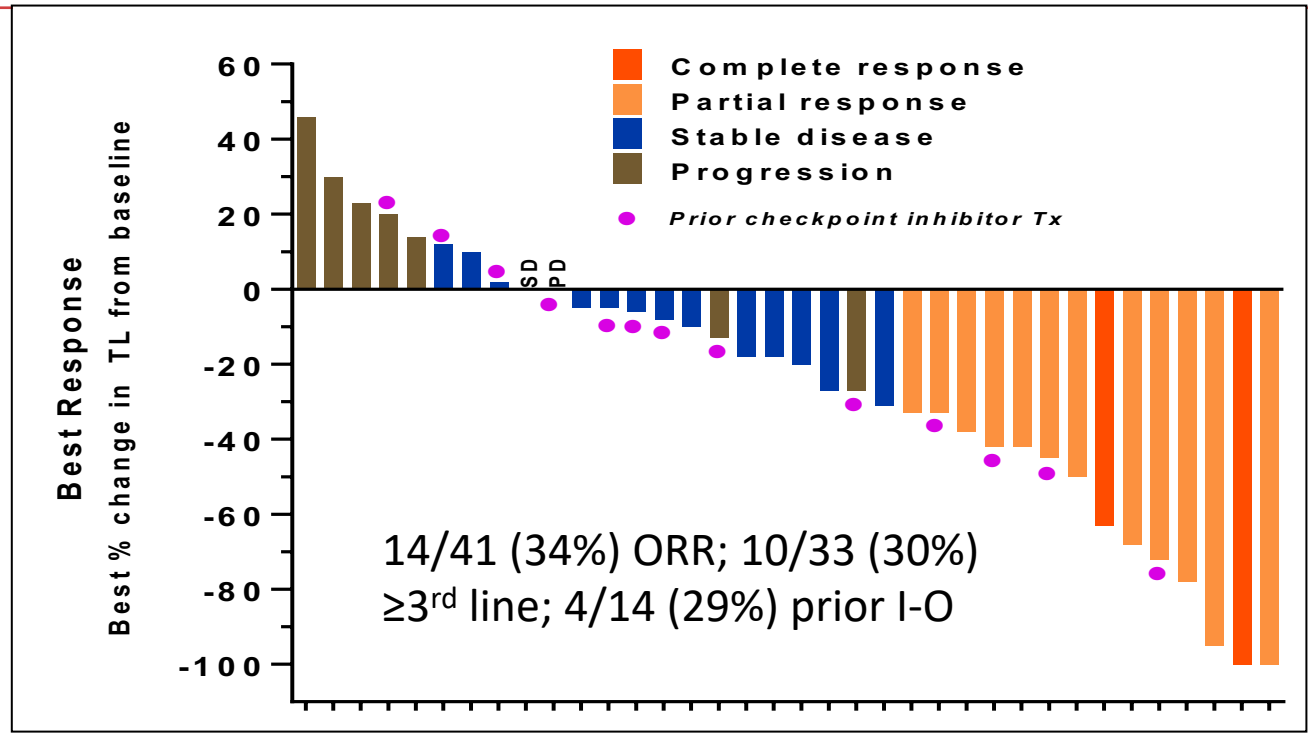
Data cutoff date: July 30, 2021

Sacituzumab govitecan



High DAR (7.6:1)[1]
Hydrolyzable linker hydrolysis[2]





- Final 14/45 (31%) ORR
- Median PFS 7.3 months
- Median OS 18.9 months

1. Cardillo TM, et al. Bioconjug Chem 2015; 26:919-31
2. Govindan SV, et al. Mol Cancer Ther 2013; 12:968-78

Tagawa S, et al. Ann Oncol (2017) 28 (suppl_5):v295-v329
Tagawa S, et al. J Clin Oncol 37, no. 7_suppl (March 1, 2019) 354-354

TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC

TROPHY U-01

Cohort 1* (~100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies → SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 2 (~40 patients): patients with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies → SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 3[a] (up to 61 patients): mUC CPI naïve patients who progressed after prior platinum-based therapies → SG 10 mg/kg Days 1 and 8, every 21 days; Pembrolizumab 200 mg day 1 every 21 days

Cohort 4 (up to 60 patients): mUC platinum-naïve patients → SG Days 1 and 8, every 21 days; Cisplatin[b]

Cohort 5 (up to 60 patients): mUC platinum-naïve patients → SG Days 1 and 8, every 21 days; Cisplatin[c] Avelumab 800 mg every 2 weeks

Continue treatment in the absence of unacceptable toxicity or disease progression

Continue until a maximum of 6 cycles has been completed,[d] disease progression, lack of clinical benefit, toxicity, or withdrawal of consent → **Maintenance avelumab (800 mg every 2 weeks) with SG (Days 1 and 8 every 21 days) for those without disease progression**

Primary Endpoint:
Objective response rate per RECIST 1.1 criteria

Key Secondary Endpoints:
Safety/tolerability, DOR, PFS, OS

Key Inclusion Criteria: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

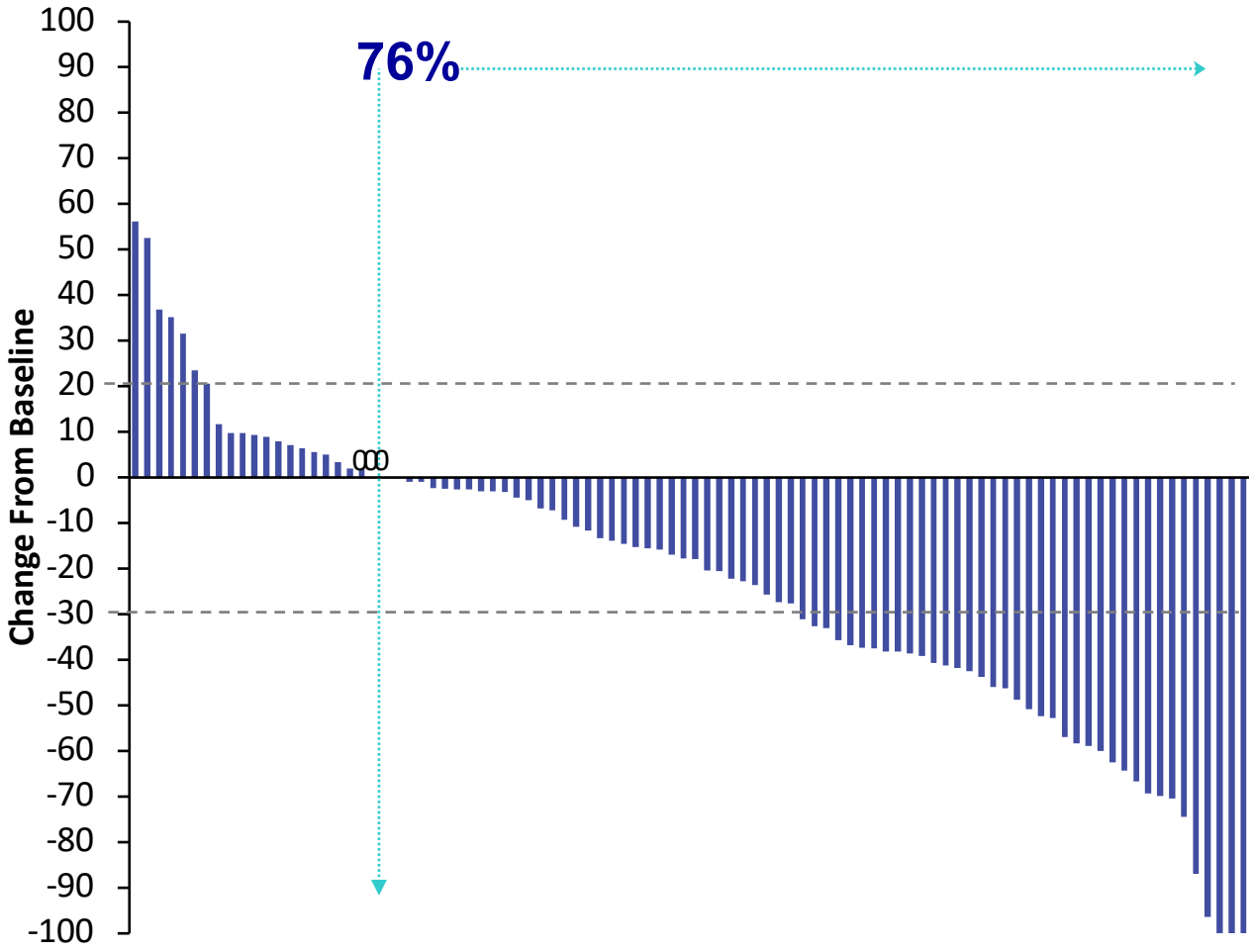
***Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor[1]**

[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

TROPHY-U-01 Cohort 1 Response and Reduction in Tumor Size

Endpoint	Cohort 1 (N=113)
ORR, n (%) [95% CI]	**31 (27) [19, 37]**
CR, n (%)	6 (5)
PR, n (%)	25 (22)
Median duration of response, mos [95% CI] (Range)	**5.9** [4.70, 8.60] (1.4–11.7)
Median time to onset of response, mos (Range)	1.6 (1.2–5.5)



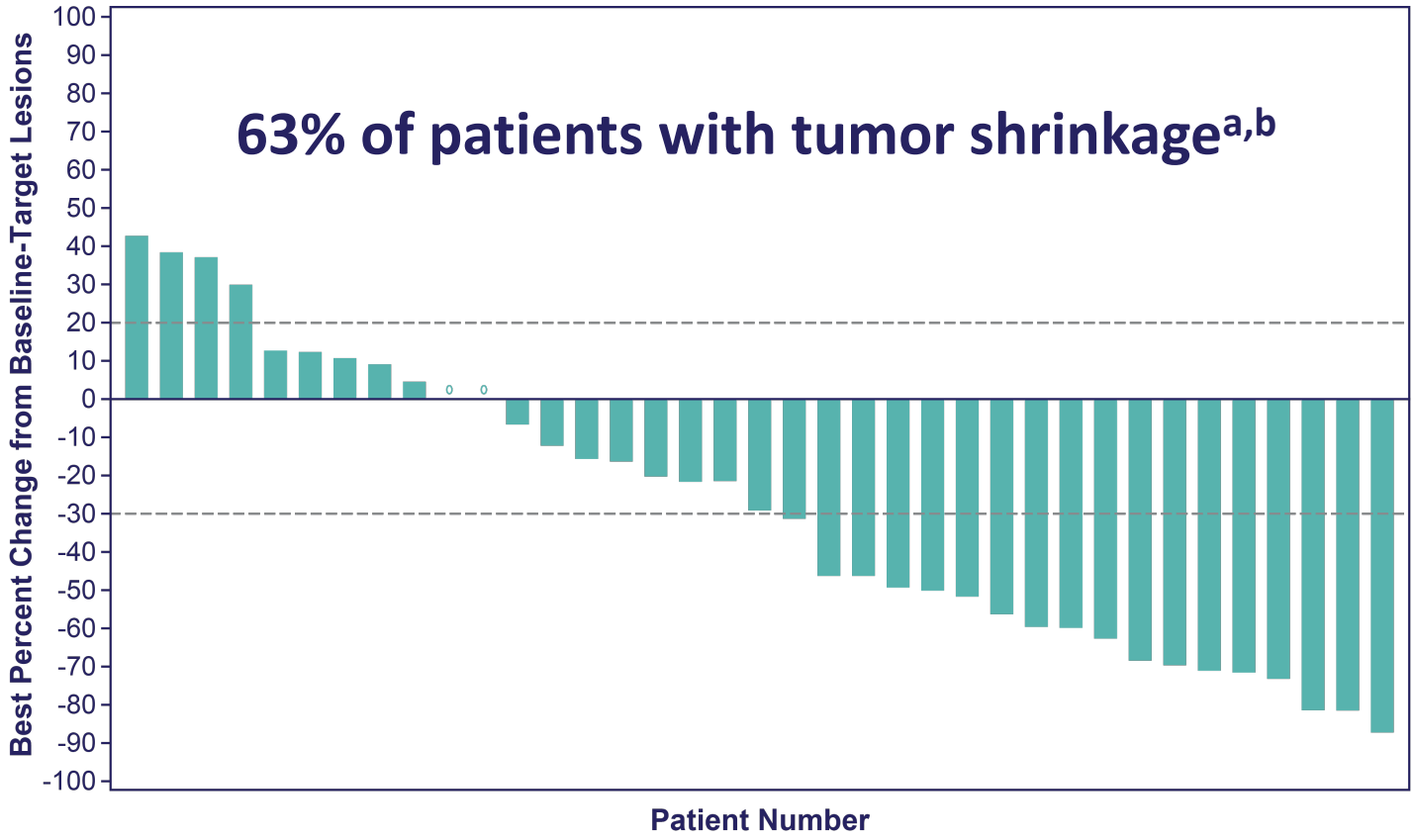
[a]Assessments were per Blinded Independent Review Assessment, RECIST 1.1.
CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; TTR, time to response.

[a]71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality. **Tagawa ST, et al. J Clin Oncol 2021; 39:2474-85**

Overall Response and Best % Change From Baseline in Tumor Size (Cohort 3: Pembro + SG)

TROPHY U-01

- Median follow-up: 5.8 months (data cutoff date: 2021-09-24)
- Median time to response: 2 months (1.3–2.8; n=14)
- Median DOR not yet reached: N/A (2.80-N/A)
- Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached



	Cohort 3[a] (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	**14 (34) [20.1-50.6]**
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	*4 (10)*
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]	25 (61) [44.5-75.8]

[a]Responses assessed by investigator in the intent-to-treat population. [b]Patients without post-baseline assessments are not shown here.
CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

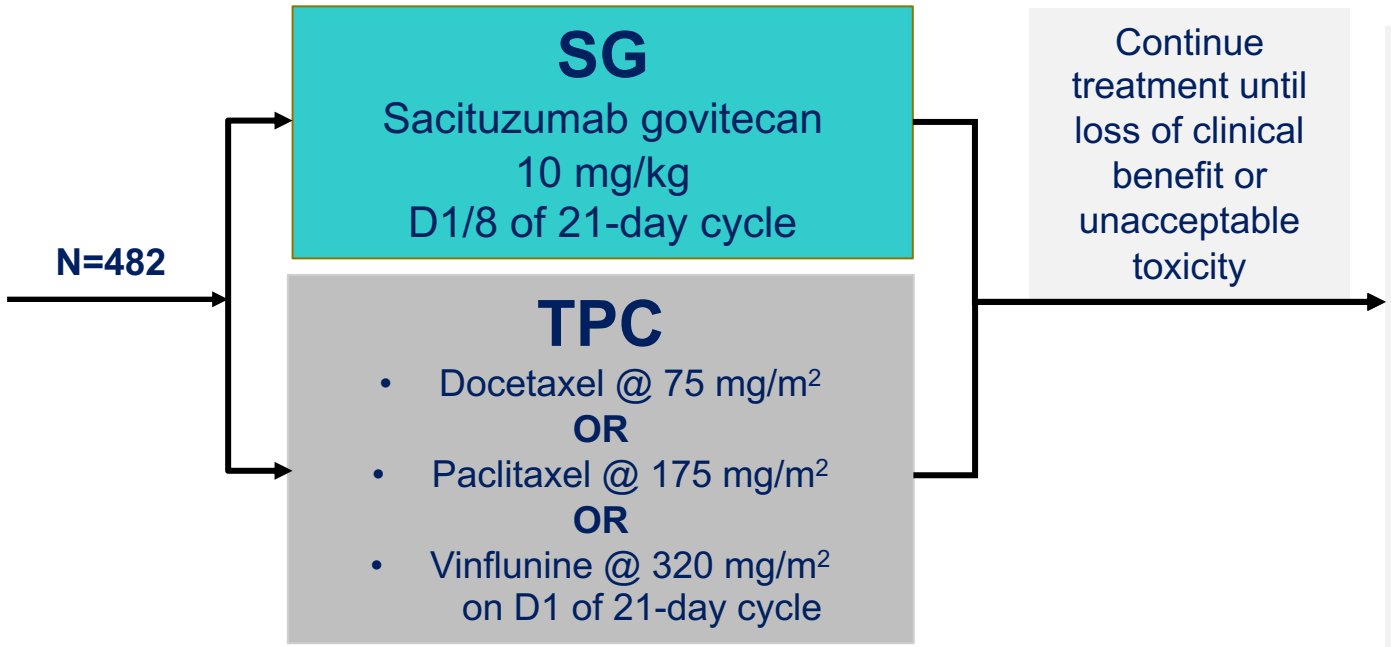
TROPiCS-04 Study Design

Study Population

- Locally advanced unresectable or mUC
- Upper/lower tract tumors
- Mixed histologic types are allowed if urothelial is predominant
- Progression after platinum-based **and** anti–PD-1/PD-L1 therapy

OR

- Platinum in neo/adj setting if progression within 12 months and subsequent CPI



Endpoint (EP)

Primary EP:
- OS

Secondary EP:
- PFS by PI assessment using RECIST 1.1
- ORR, DOR, and CBR by PI assessment using RECIST 1.1
- EORTC QLQ C30 score and EuroQOL EQ-5D-5L QOL score

Grivas et al. 10.1200/JCO.2021.39.6_suppl.TPS498 *JCO* 39, no. 6_suppl

Advanced Urothelial Ca Treatment Algorithm

Disease State	Setting	Preferred Option	Other Options
Metastatic, no prior chemotherapy	**Cisplatin-eligible**	**Cisplatin/gemcitabine f/b avelumab maintenance**	**aMVAC f/b avelumab maintenance**
Metastatic, no prior chemotherapy	**Cisplatin-ineligible**	**Gemcitabine/Carboplatin (in fit patients) f/b avelumab maintenance**	**Pembrolizumab Atezolizumab *Single agent chemotherapy***
Metastatic, prior platinum chemotherapy or relapse within 1 year of perioperative cisplatin-based therapy		**Pembrolizumab OR Erdafitinib (tumors with FGFR2/3 activating alteration) OR Enfortumab vedotin (cisplatin-unfit pts)**	***Avelumab Nivolumab***
Metastatic, prior chemotherapy & immunotherapy		**Enfortumab vedotin OR Sacituzumab govitecan OR Erdafitinib (tumors with FGFR2/3 activating alteration)**	***Taxane (US) Vinflunine (EU)***

Clinical trials are critical throughout disease spectrum & treatment settings!

Petros Grivas

'*Takeaway*' messages / Key Learning Points

- ❑ **Clinical trials or cisplatin-based chemoTx for cisplatin-eligible pts**
- ❑ **Pembrolizumab*:* 1L option only for platinum-unfit in US**
- ❑ **OS with switch maintenance avelumab→ level I evidence after CR/PR/SD on platinum-based chemoTx**
- ❑ **Level I evidence for pembrolizumab in platinum-refractory setting (KN045 trial)**
- ❑ **Selection of salvage therapy depends on various factors, e.g. prior treatments, eligibility for cisplatin/platinum, other medical issues / organ function, performance status, FGFR2/3 genomic status, patient & provider preferences, etc.**
- ❑ **Erdafitinib: accelerated FDA approval post-platinum for tumors with FGFR2 or FGFR3 activating mutation or fusion**
- ❑ **Enfortumab-vedotin FDA-approved as 3L post-platinum/IO & as 2L in cisplatin-ineligible pts**
- ❑ **Sacituzumab-govitecan: accelerated FDA approval post-platinum/IO**
- ❑ **Anti-HER2 ADCs & afatinib look very promising in single arm phase II trials**
- ❑ **Role of anti-CTLA4: only experimental in UC (awaiting NILE trial in 1L mUC setting; VOLGA in peri-op setting)**
- ❑ **ADCs, FGFRi, VEGFi, IO-based & other combos evaluated in various clinical trials (EV/pembro: very promising as 1L Tx)**
- ❑ **Biomarker validation: the *Holy Grail*: variability among clinical trials makes it very hard**

Thank you ☺
Patient & families!

Collaborators, sponsors, institutions, foundations, colleagues, research, admin & clinical staff: TEAMS!

@PGrivasMDPhD