Bladder cancer updates

Petros Grivas, MD PhD

Professor, Dept. of Medicine, Division of Hem-Onc
Clinical Director, Genitourinary Cancers Program
University of Washington
Professor, Clinical Research Division
Fred Hutchinson Cancer Center
Twitter/X: @PGrivasMDPhD

University of Washington Bladder Cancer Multispecialty Clinic

Timeline

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

January 2015
5th Tuesday added (when occurring)

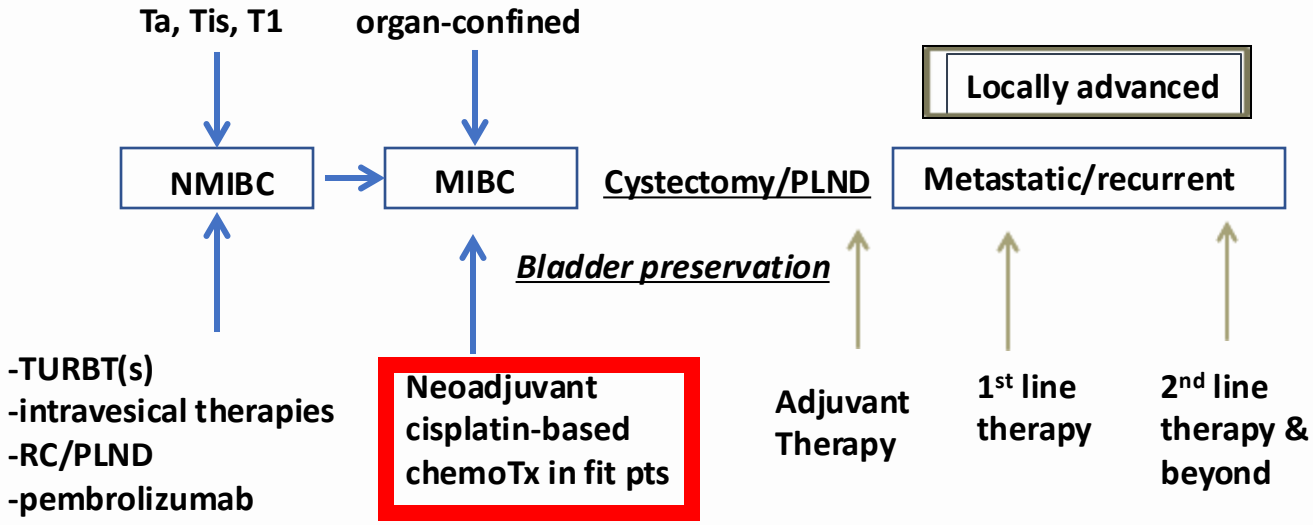
January 2016
Weekly Conference

Participants

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

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

Disease / treatment settings



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.

"*Take home points*" on neoadjuvant chemotherapy

- **Disease-free & overall survival benefit with cisplatin-based combinations (level I evidence)**
- **Non-cisplatin Tx in perioperative setting has no proven benefit**
- **Accelerated (dose dense) MVAC shorter & less toxic vs 'classic/conventional MVAC'**
- **Retrospective datasets; S1314 & VESPER phase 3 trials: aMVAC (with G-CSF) every 2 weeks is my preferred regimen; gemcitabine/cisplatin (21-day) is an acceptable alternative**
- **Conventional plan for 4 cycles for cN0 stage; consideration of 4-6 cycles in cN+ ('induction' chemo)**
- **Consider nephrostomy tubes for hydronephrosis with impaired eGFR, esp. if plan for cisplatin**
- **Consider 24-hour urine collection as needed for creatinine clearance in borderline eGFR cases**
- **Consider audiology assessment as needed based on hearing & patient preference**
- **Novel trials focus on immunotherapy & ADCs, biomarkers of response, bladder preservation**
- **NIAGARA phase 3 trial is positive (see ESMO'24), awaiting other phase 3 trials; we need more work for validated biomarkers with clinical utility**

Smith D et al. J Urol. 2008; 180(6): 2384–2388
Grivas P et al. UROLOGY 82: 111e117, 2013
Choueiri T et al., *J Clin Oncol 32:1889–1894*
Plimack J et al. J Clin Oncol 32:1895–1901
Blick et al. 2012 Cancer
Flaig TW, et al. 2021 1;27(9):2435-41
Pfister C et al. JCO 41,no.17_suppl; LBA4507

NIAGARA trial: press release

Durvalumab + chemo elicited a statistically significant & clinically meaningful improvement in event-free survival & overall survival (primary & secondary endpoint) in this phase III trial (NCT03732677) vs neoadjuvant chemo in pts with MIBC: data will be presented soon

Ongoing peri-op phase III trials evaluating chemo/ICI vs chemo:

-Gem/Cis +/- pembrolizumab

-Gem/Cis +/- nivolumab

Ongoing peri-op phase III trials evaluating EV + ICI:

-Keynote B15, Keynote 905, VOLGA

Neoadjuvant trial for cisplatin-unfit pts with histology subtype/variant MIBC

NCT05581589

Key Eligibility

- Muscle Invasive Bladder Cancer (cT2-T4aN0-N1M0 or cT1-4aN1M0)
- Candidates for radical cystectomy
- Variant histology as defined in eligibility criteria
- Cisplatin-ineligible or refuses cisplatin

Sacituzumab Govitecan

10mg/kg on days 1 & 8
Every 21 days x 3 cycles

TURBT → Radical Cystectomy & Pelvic Lymph Node Dissection

Endpoints

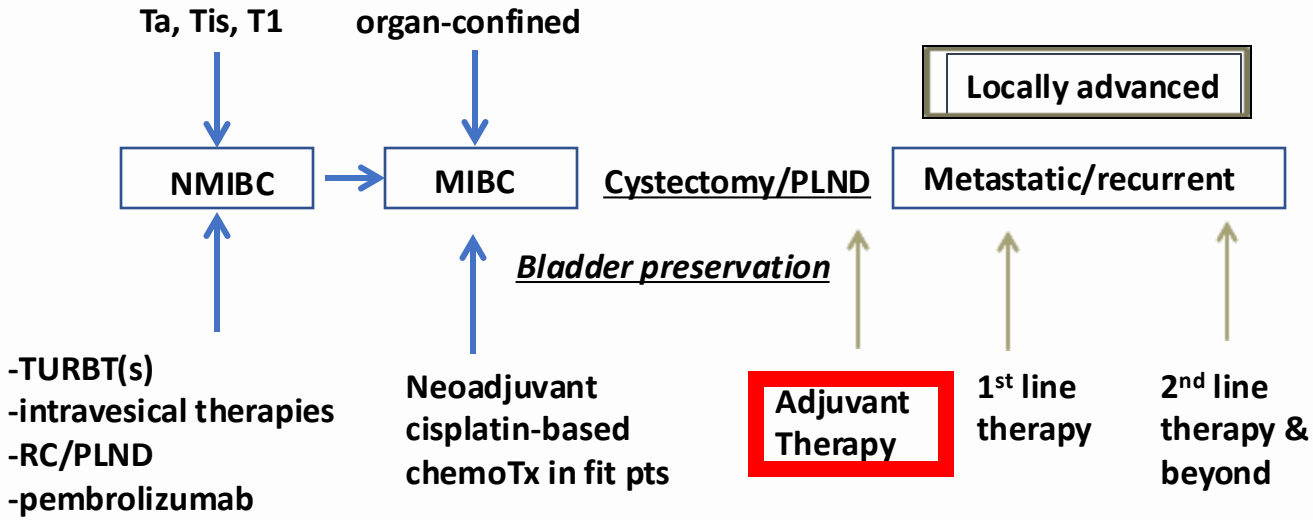
Primary:

- Pathologic complete response rate

Secondary:

- Toxicity
- Two-year recurrence free survival
- Translational studies with tissue, blood, urine, stool

Disease / treatment settings



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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

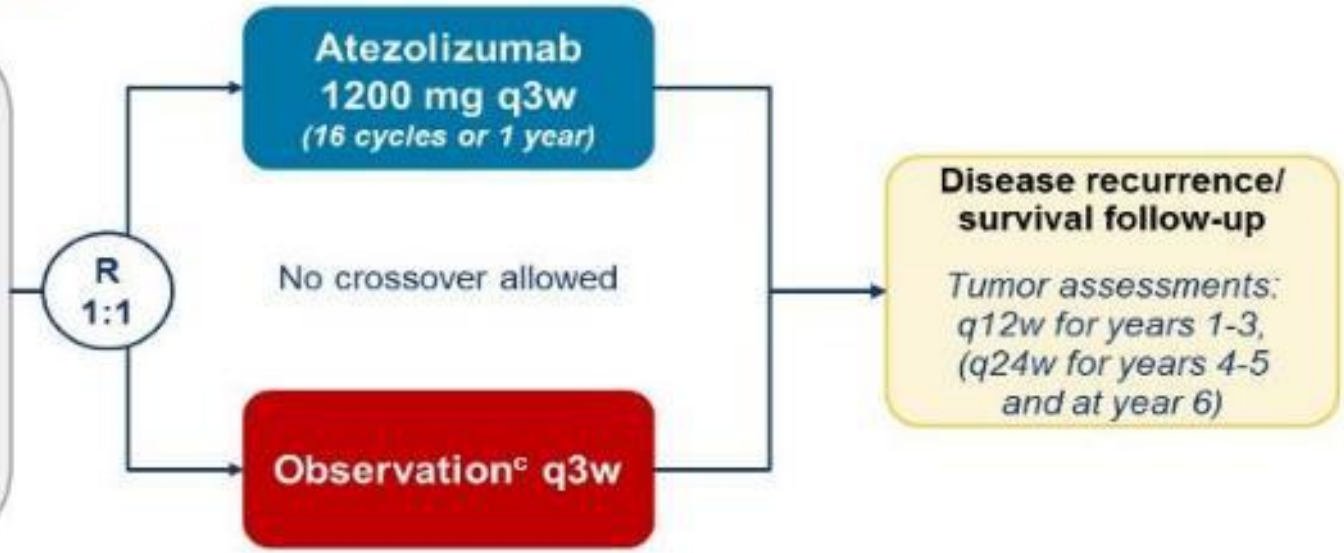
Adjuvant Chemotherapy for Bladder Cancer: Using Population-Based Data to Fill a Void of Prospective Evidence

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*

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**



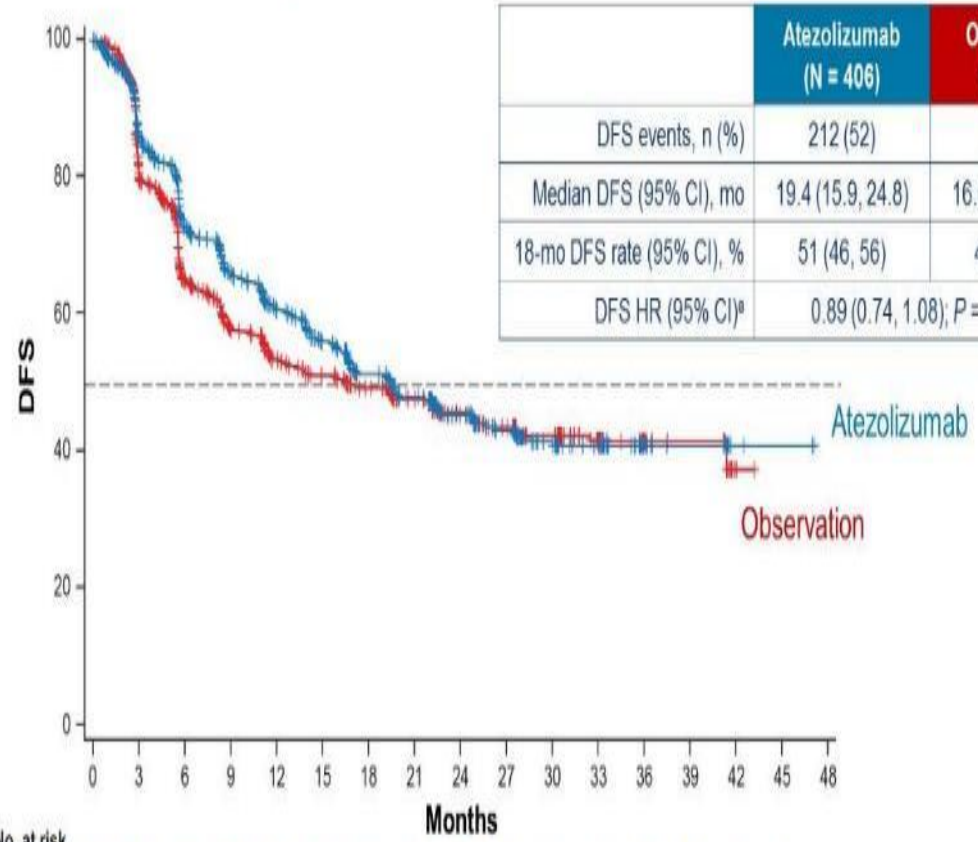
Stratification factors

- 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.

DFS in ITT Population

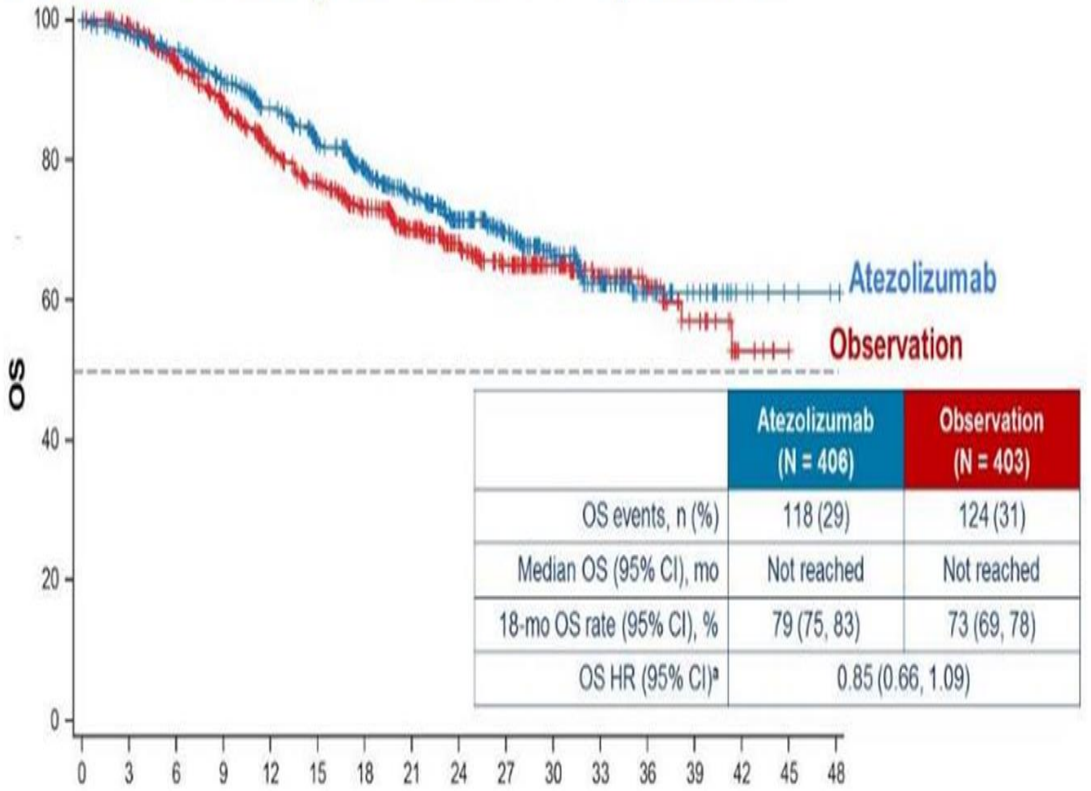


	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

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 PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SKSAD3

Presented By Maha Hussain at TBD

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.

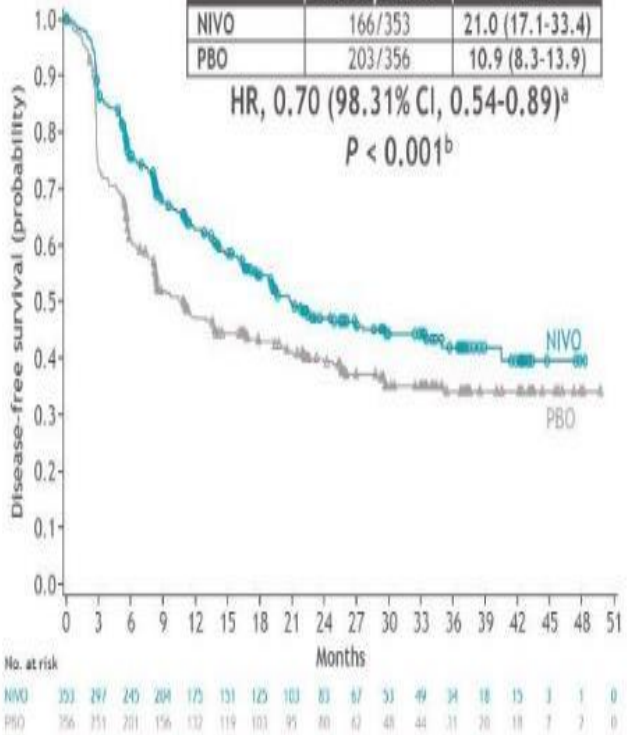
Disease-free survival

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]

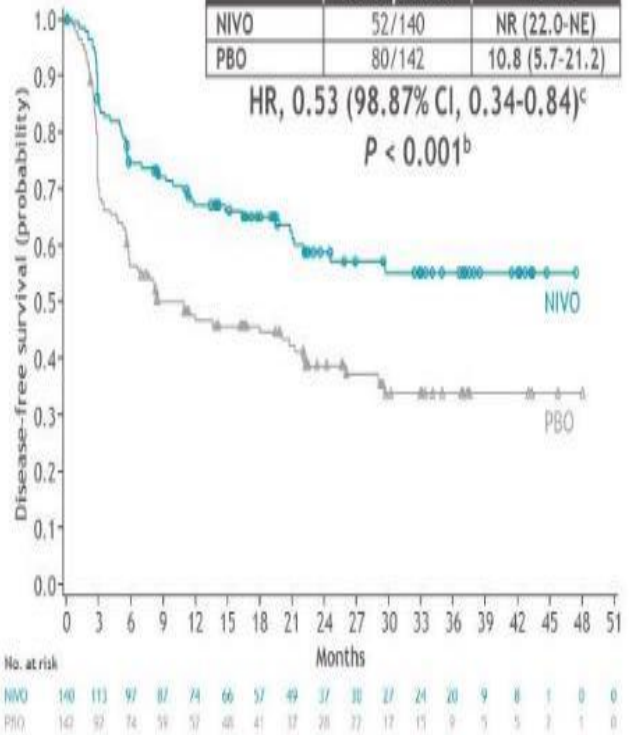


PD-L1 ≥ 1%

	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.

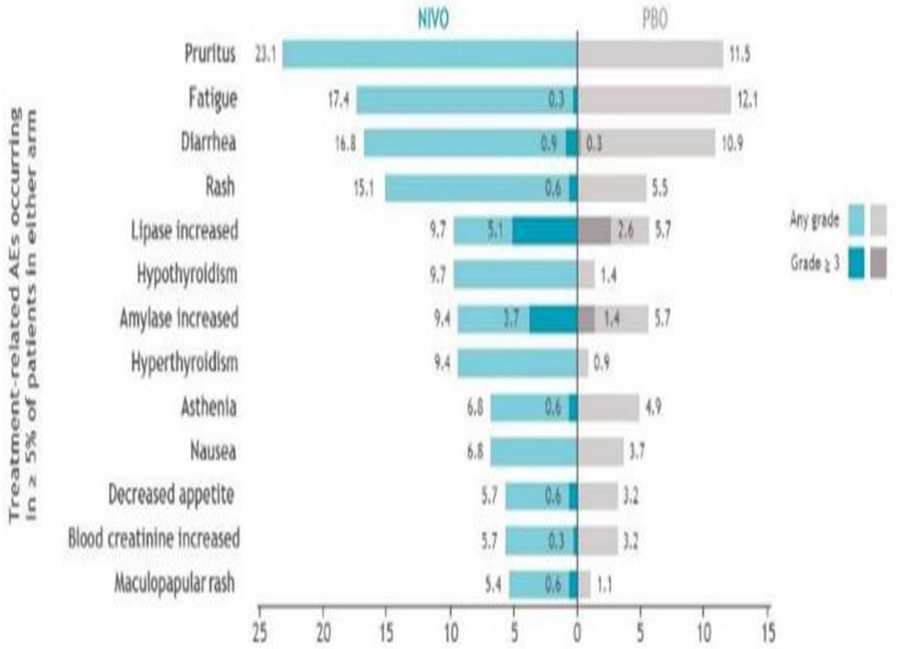
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.

[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



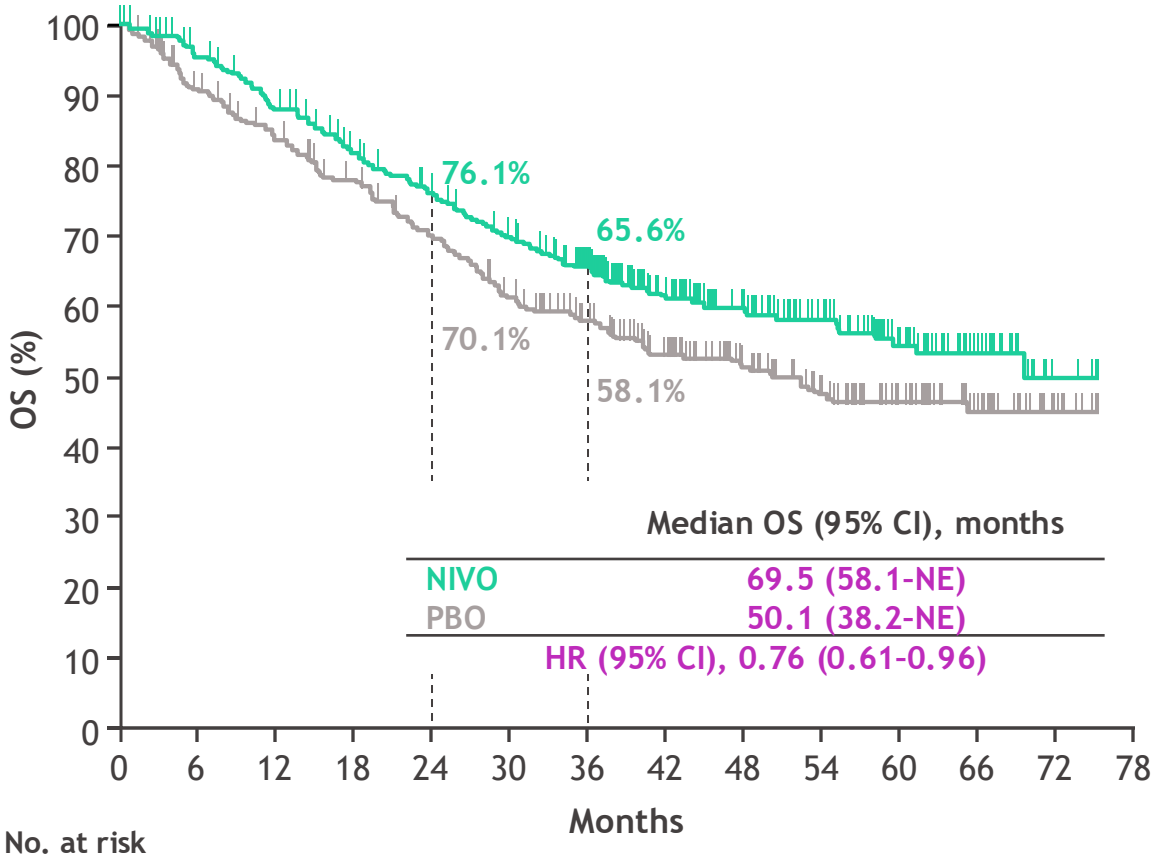
[a]Includes all treated patients. [b]There were 2 treatment-related deaths due to pneumonitis in the NIVO arm. There were no treatment-related deaths in the PBO arm.

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

Overall survival

- Interim OS data favored NIVO versus PBO in the ITT and tumor PD-L1 ≥ 1% populations

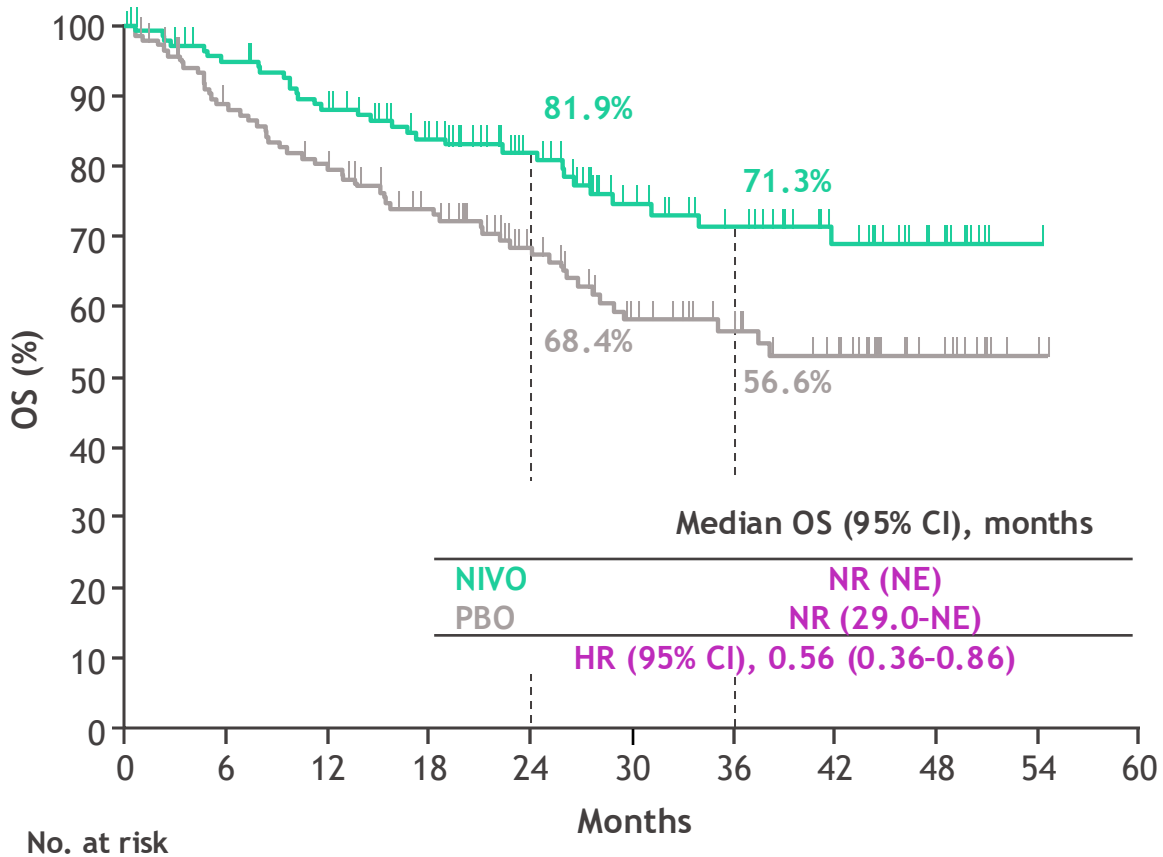
ITT



No. at risk

NIVO	353	326	298	268	244	220	188	150	123	92	60	33	4	0
PBO	356	308	281	254	226	194	167	136	109	79	56	32	10	0

PD-L1 ≥ 1%



No. at risk

NIVO	140	127	115	93	73	52	41	29	11	1	0
PBO	142	116	104	87	65	46	36	26	12	2	0

OS follow-up is ongoing, as the prespecified statistical boundary for significance was not met at the time of these analyses. Median (minimum) follow-up in the ITT population, 36.1 (31.6) months; median (minimum) follow-up in PD-L1 ≥ 1% population, 23.4 (11.4) months. OS was defined as time from date of randomization to date of death (from any cause).

A031501 AMBASSADOR: Study Design

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

NCT03244384

Key Eligibility

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

OR

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

Stratify

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

N=739

R 1:1

Pembrolizumab 200 mg q3W 1 year (18 cycles)

Observation

Dual Primary Endpoints

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

Key Secondary Endpoints

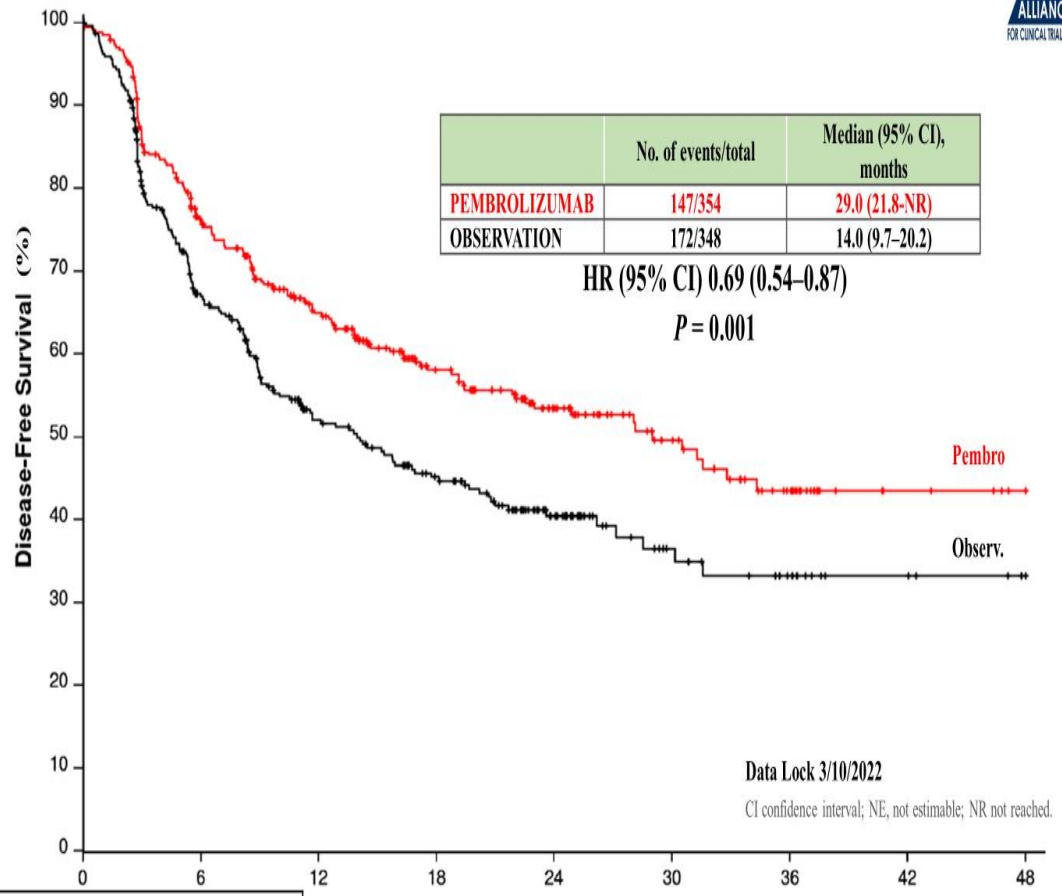
- DFS/OS PD-L1 +/-
- Safety

Correlative Endpoints

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

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

A031501 AMBASSADOR: Disease-Free Survival (ITT)



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

HR (95% CI) 0.69 (0.54–0.87)

P = 0.001

Data Lock 3/10/2022

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

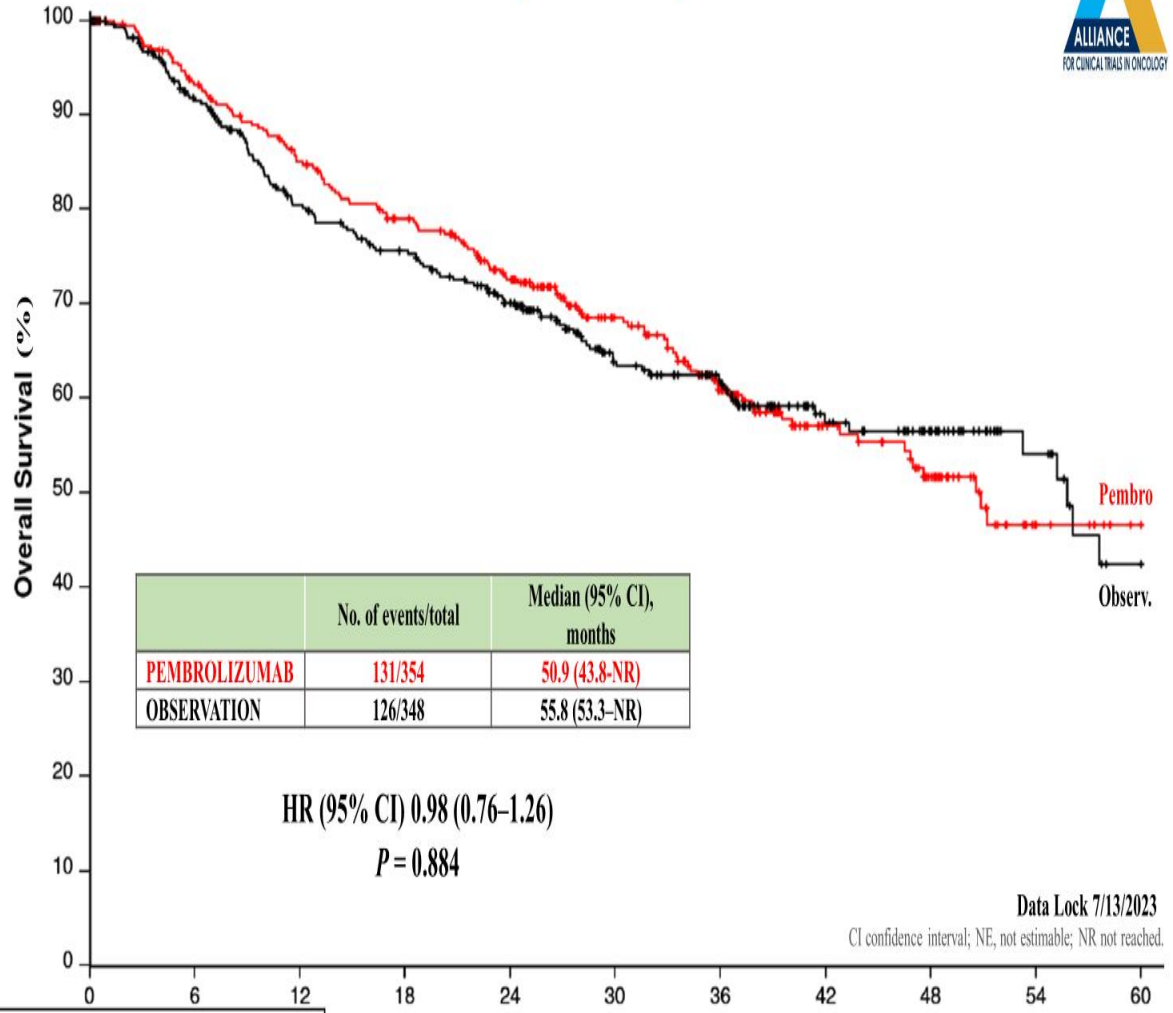
Median follow-up (range) 22.3 months (0.03-48.9)

Patients-at-Risk

Pembro	354	238	178	123	80	45	26	6	2
Observ.	348	192	125	97	53	23	13	6	1

ASCO Genitourinary Cancers Symposium #GU24 PRESENTED BY:

A031501 AMBASSADOR: (interim) Overall Survival



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

HR (95% CI) 0.98 (0.76–1.26)

P = 0.884

Data Lock 7/13/2023

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

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

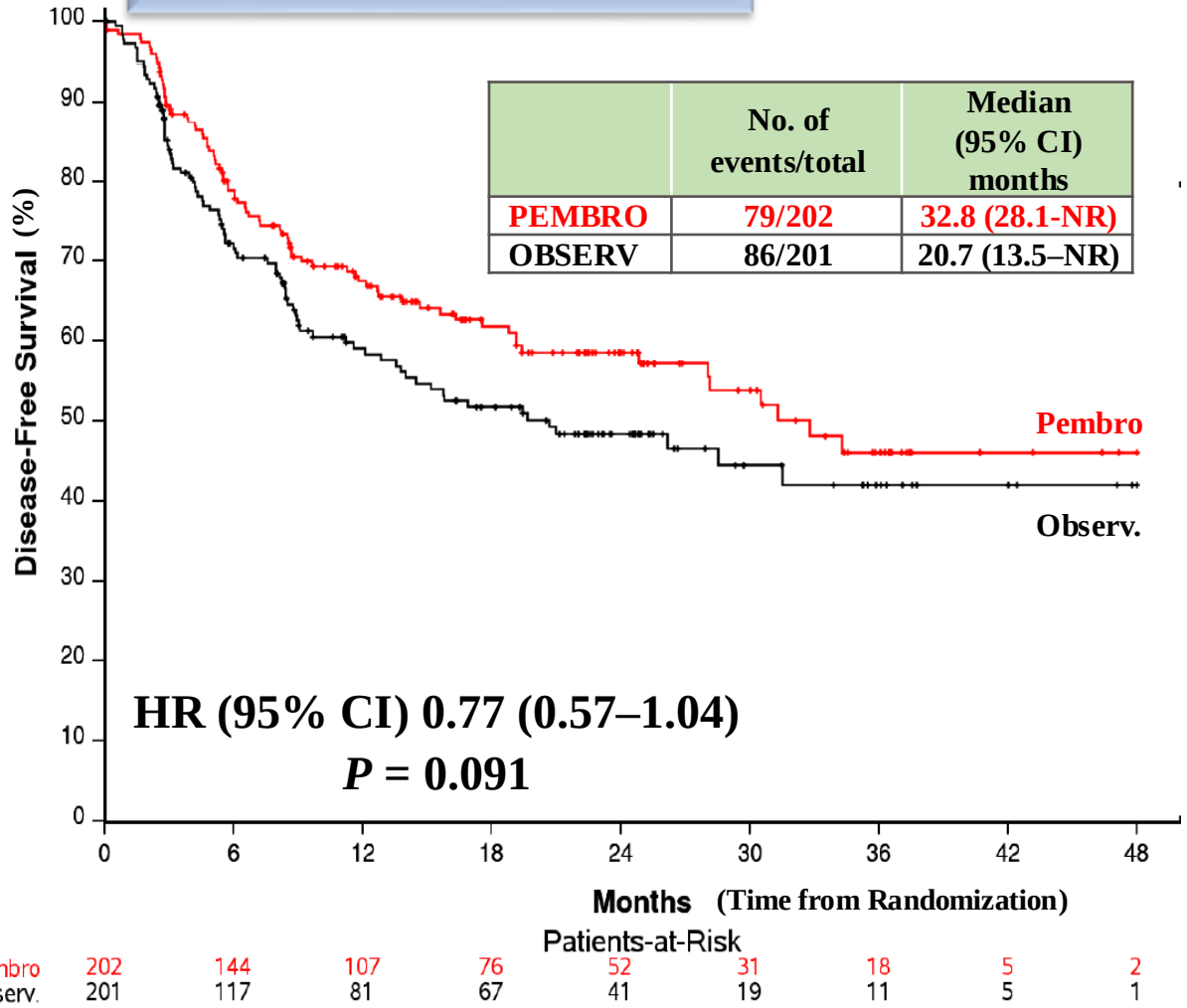
Patients-at-Risk

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

ASCO Genitourinary Cancers Symposium #GU24 PRESENTED BY: Andrea B. Apolo, MD @apolo_andrea ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

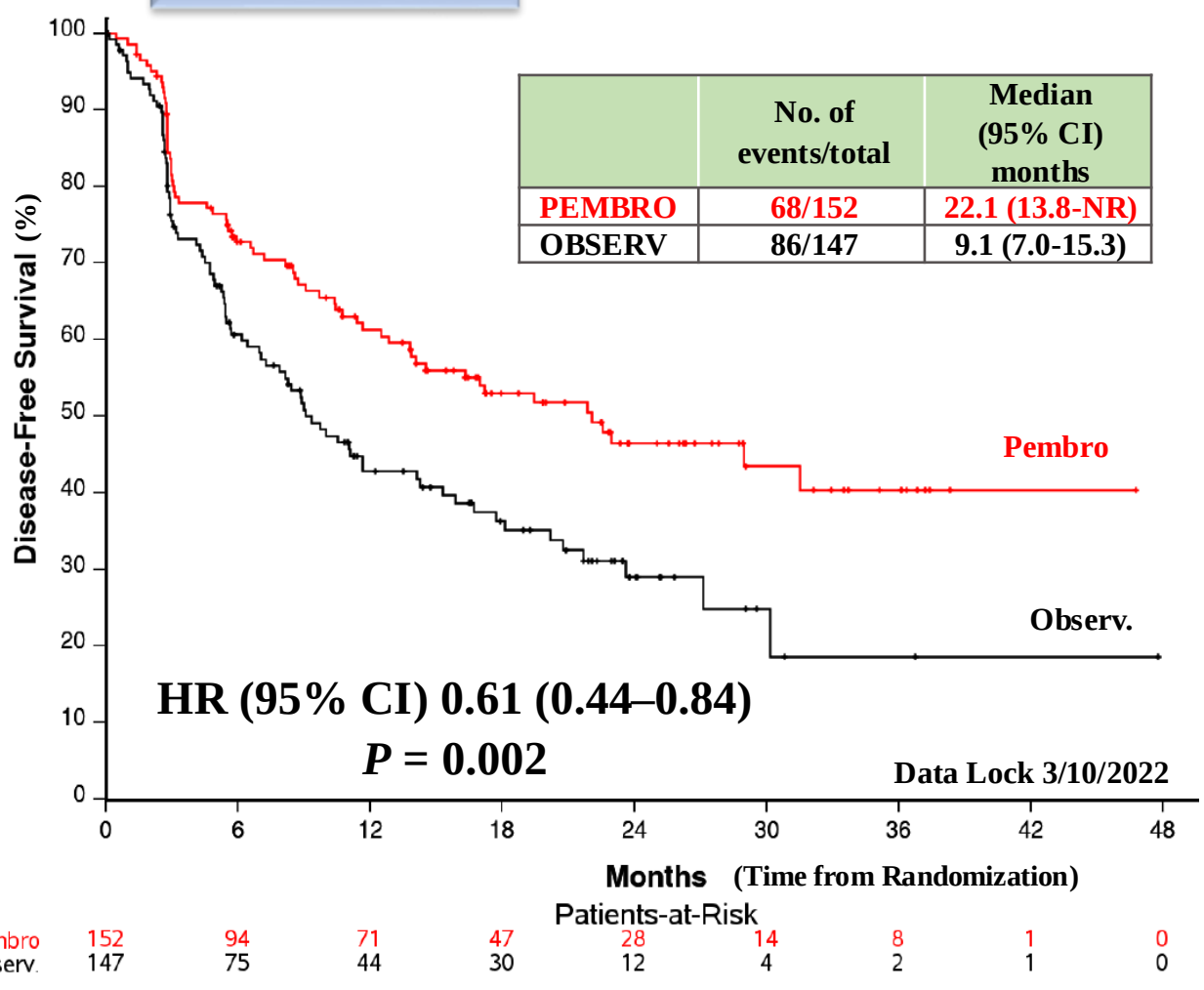
A031501 AMBASSADOR: Disease-Free Survival by PD-L1* Status

PD-L1-Positive CPS ≥ 10%



	No. of events/total	Median (95% CI) months
PEMBRO	79/202	32.8 (28.1-NR)
OBSERV	86/201	20.7 (13.5–NR)

PD-L1-Negative



	No. of events/total	Median (95% CI) months
PEMBRO	68/152	22.1 (13.8-NR)
OBSERV	86/147	9.1 (7.0-15.3)

*Dako PD-L1 immunohistochemistry 22C3 pharmDx assay

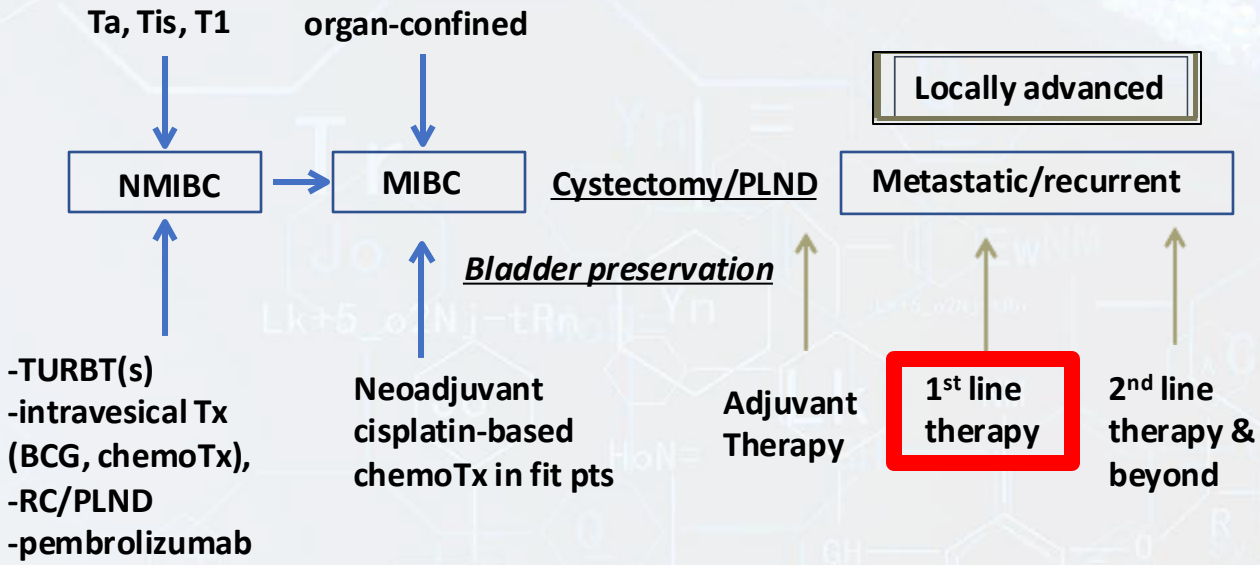
CI, confidence interval; NE, not estimable; NR, not reached.

Data Lock 3/10/2022

'Take home' messages

- **Clinical trials or cisplatin-based chemoTx for cisplatin-fit pts; *is NIAGARA trial practice-changing?* (ESMO'24)**
- **Cisplatin eligibility based on Galsky et al. criteria –JCO 2011- (variability in eGFR threshold, hearing loss)**
- **Cisplatin-fit pts who did not receive NAC and have pT3/4 and/or cN+ MIBC: adjuvant cisplatin-based chemoTx**
- **Adjuvant nivolumab prolonged DFS vs placebo in Checkmate-274 trial: differences between FDA vs EMA approval based on PD-L1; trend towards OS benefit -> awaiting final OS analysis (impact from NIAGARA trial data?)**
- **Adjuvant pembrolizumab prolonged DFS vs observation regardless of PD-L1 in AMBASSADOR trial (no OS benefit in premature analysis); *FDA approval??***
- **ctDNA by Signatera assay has very interesting data and seems highly prognostic, but clinical utility and predictive value need to be proven in the adjuvant setting (awaiting trials: TOMBOLA, IMvigor011, MODERN)**
- **Histology/variant subtypes represent a major challenge with worse prognosis: a focus of our research program**

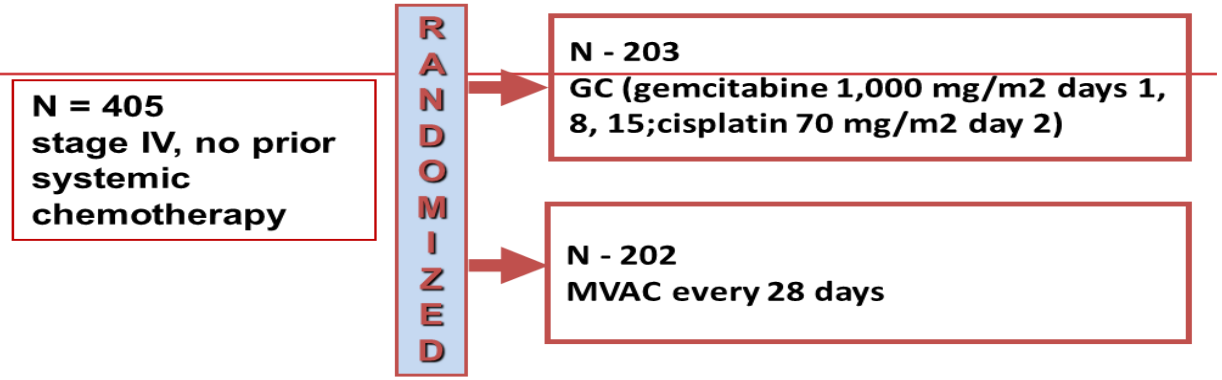
Disease / treatment settings



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)



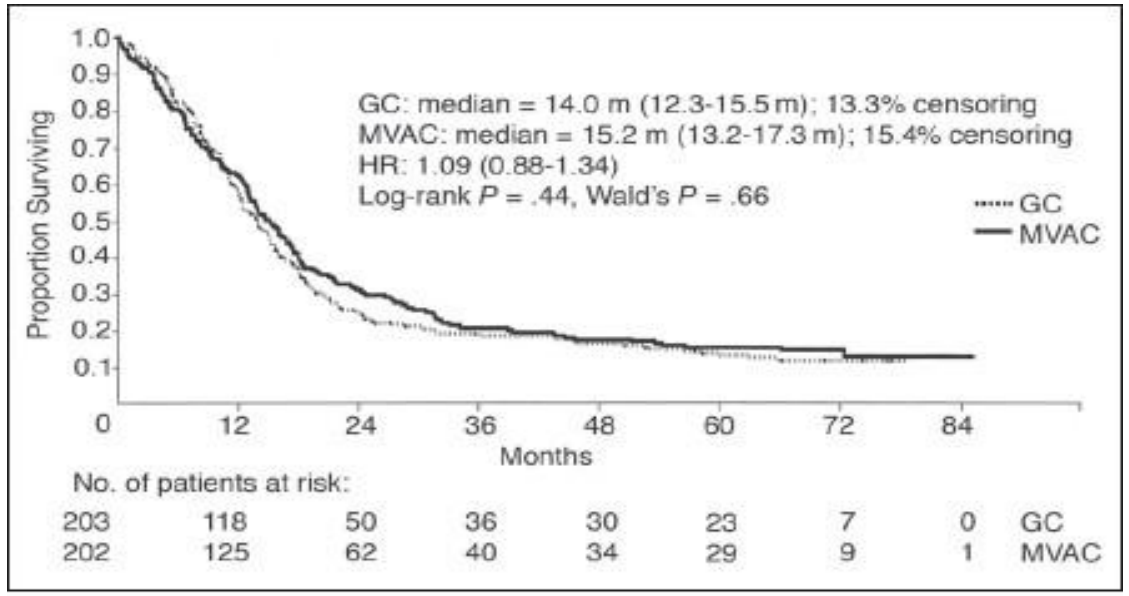


Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

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.

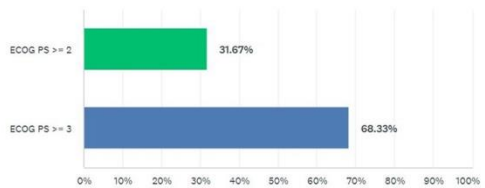
Methods:

- 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.

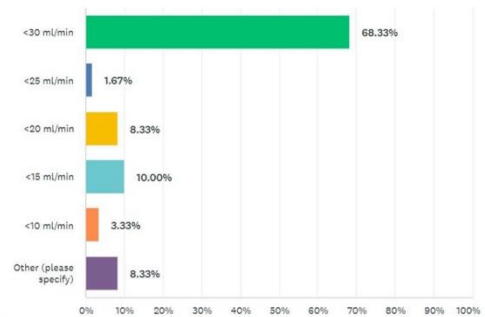
Results:

- 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’

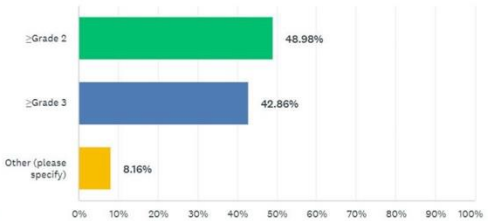
1. What threshold ECOG PS should be used to define "platinum-ineligibility"?



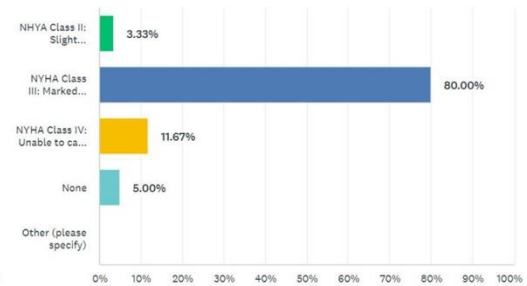
2. What threshold Cr Cl should be used for "platinum-ineligibility"?



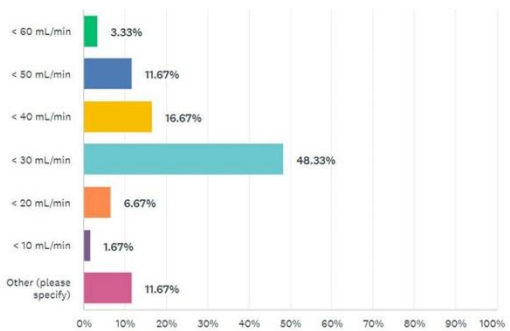
3. What grade of peripheral neuropathy would you consider for "platinum-ineligibility"?



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

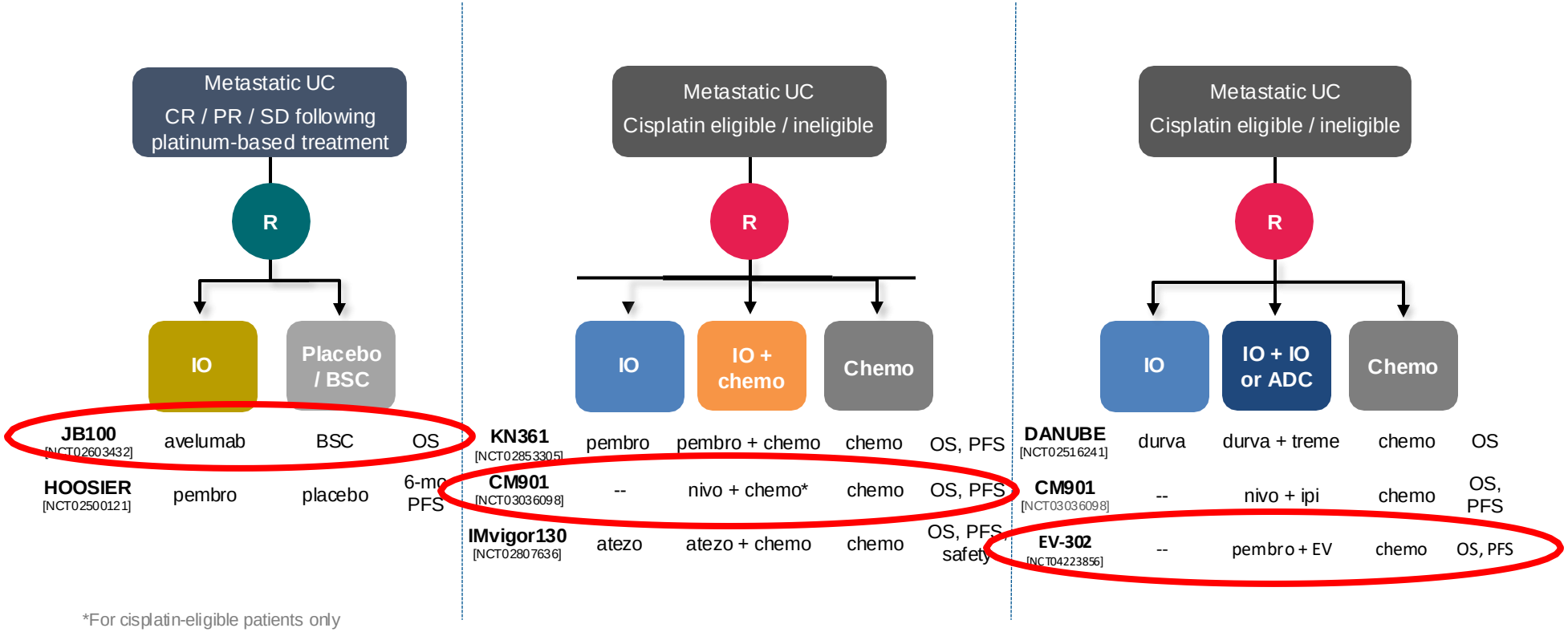
These criteria are proposed to guide treatment recommendations and standardization of eligibility criteria for defining “platinum-ineligible’ pts.

Acknowledgement: Al the respondents who completed the survey

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

Cleveland Clinic

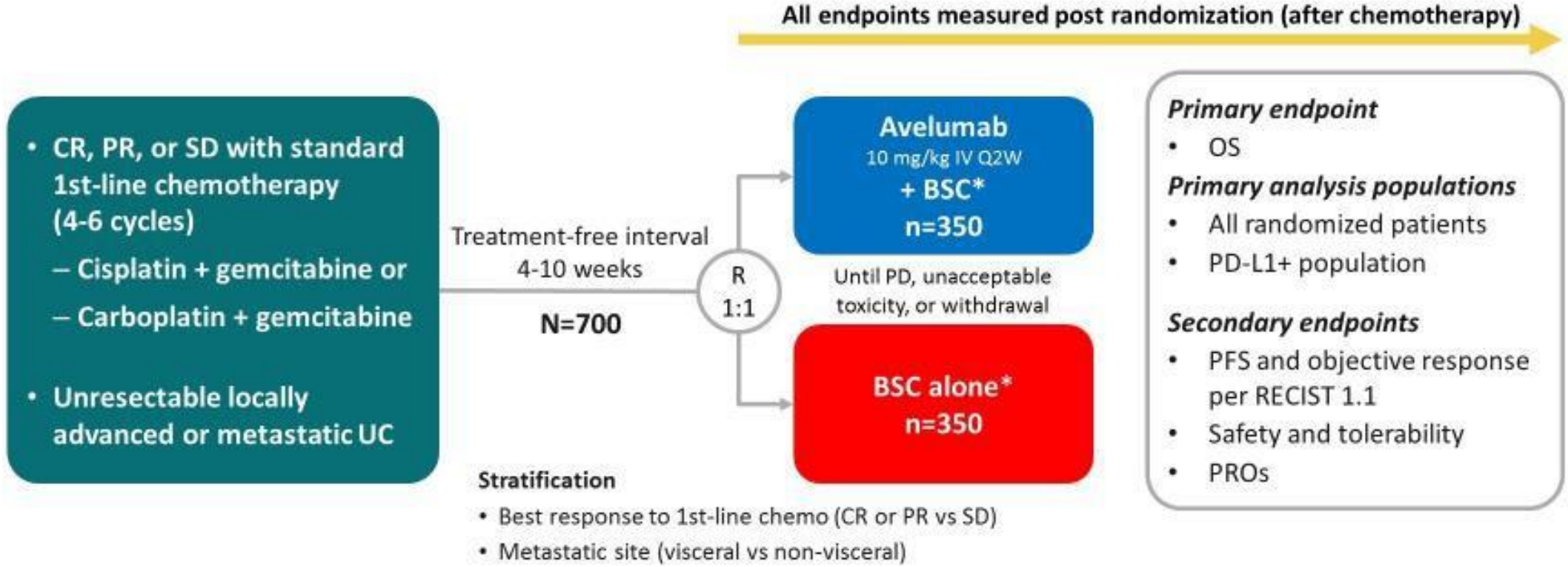
Different strategies aiming to impact 1L SoC



*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)



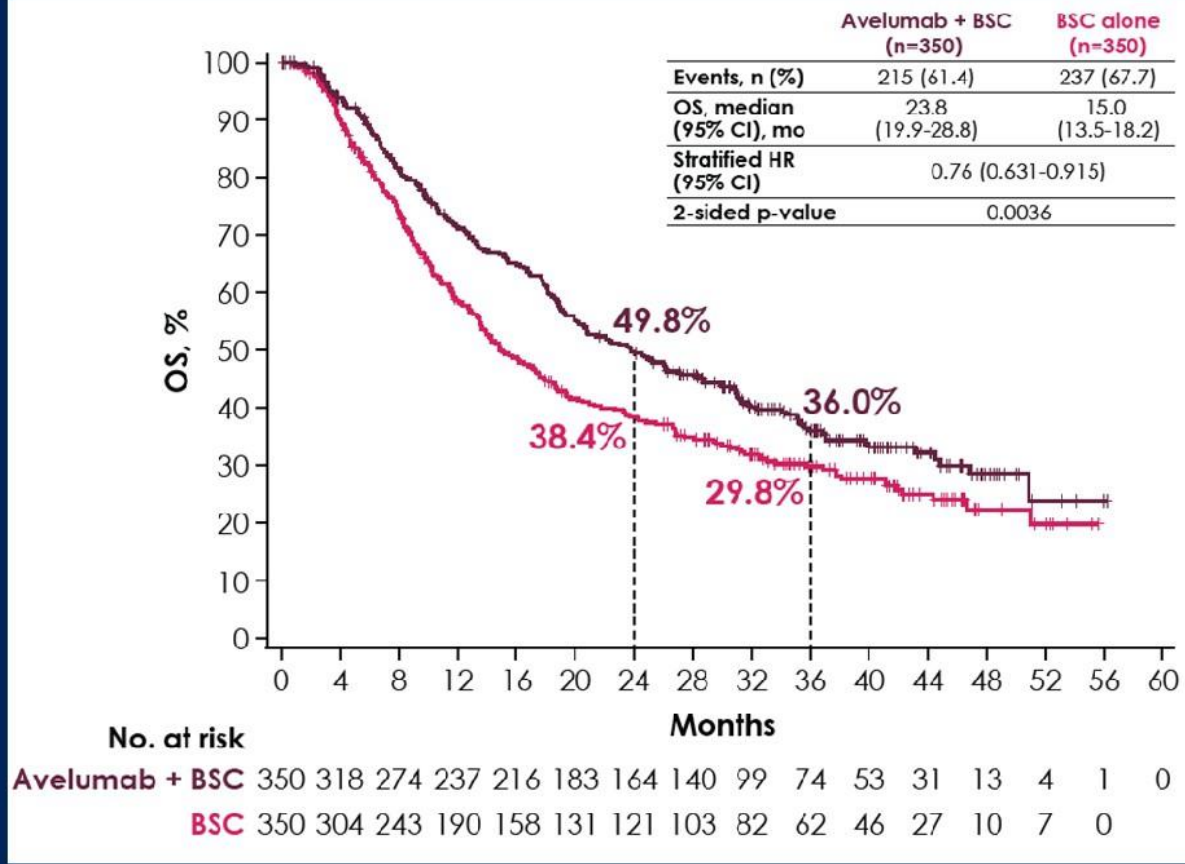
PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

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

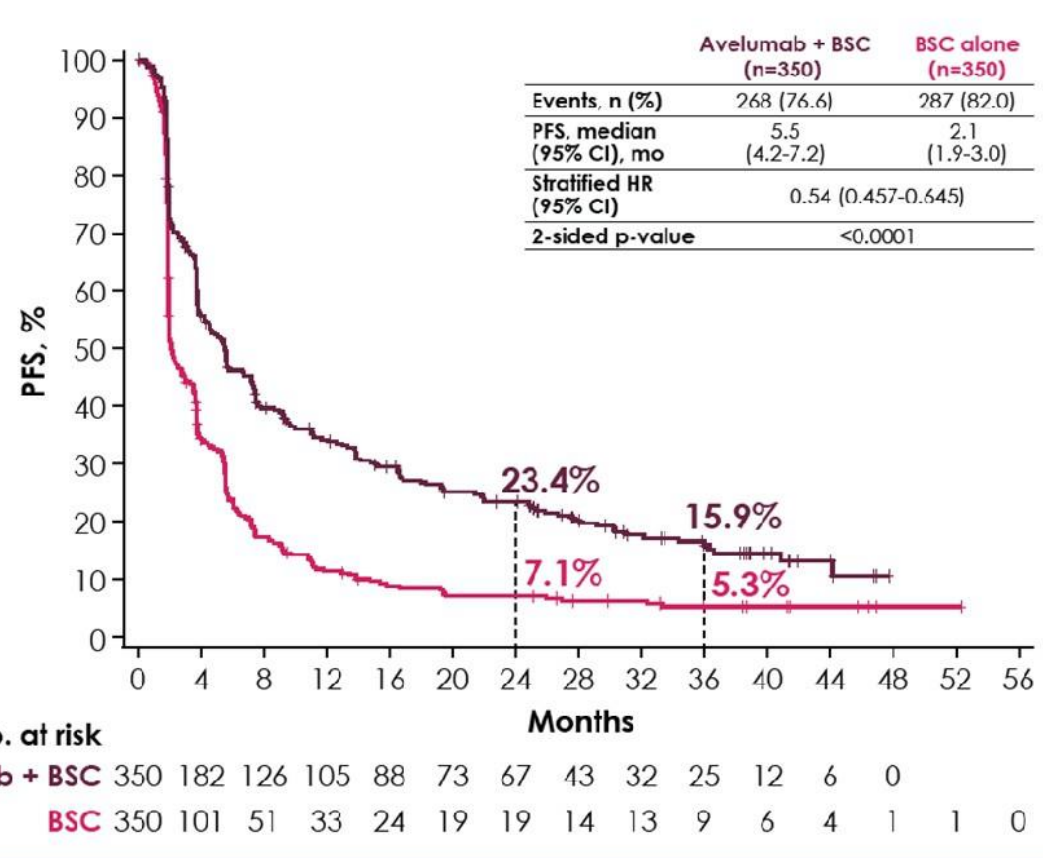
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

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

OS



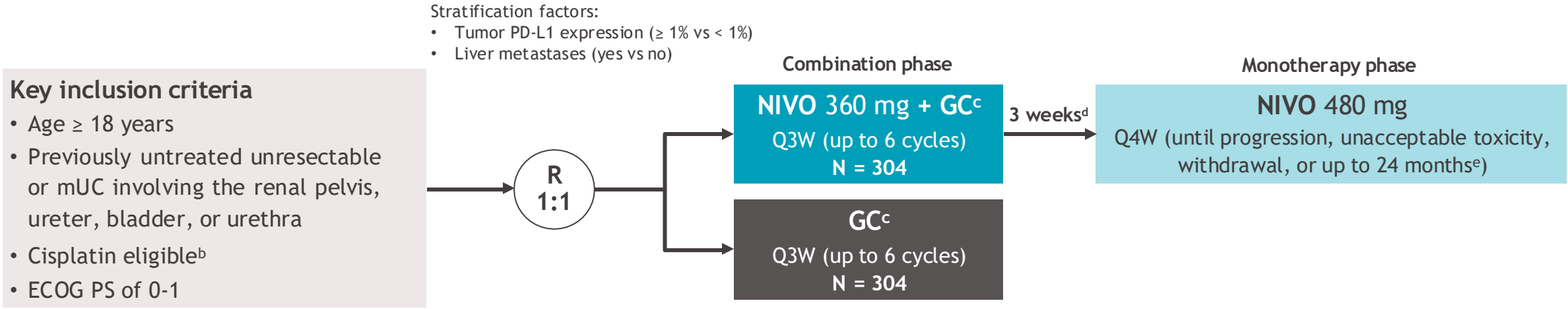
Investigator-assessed PFS



HR, hazard ratio.

PRESENTED BY: Thomas Powles, MD

Study design (NIVO+GC vs GC in cisplatin-eligible patients)[a]

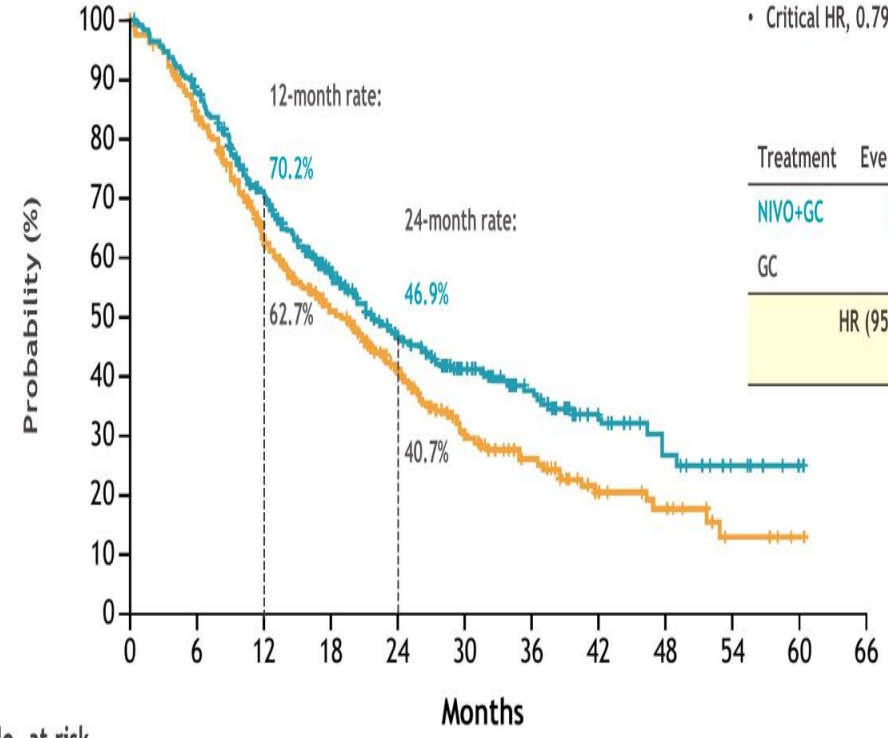


Median (range) study follow-up 33.6 (7.4–62.4) months

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

[a]Further CheckMate 901 study design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Cisplatin eligibility was determined in the study population by a GFR ≥ 60 mL/min (assessed by direct measurement, ie, creatinine clearance, or, if not available, using the Cockcroft-Gault formula), and absence of CTCAE v.4 grade ≥ 2 hearing loss and grade ≥ 2 peripheral neuropathy. [c]Patients who discontinued cisplatin alone could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to six cycles in total). [d]NIVO monotherapy should begin 3 weeks after the last dose of NIVO+GC combination. [e]Represents a maximum of 24 months from the first dose of NIVO administered as part of the NIVO+GC combination.
BICR, blinded independent central review; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q × W, every × weeks; R, randomization.

OS (primary endpoint)



OS final analysis statistical boundaries:
- *P* value boundary, 0.0311
- Critical HR, 0.7980

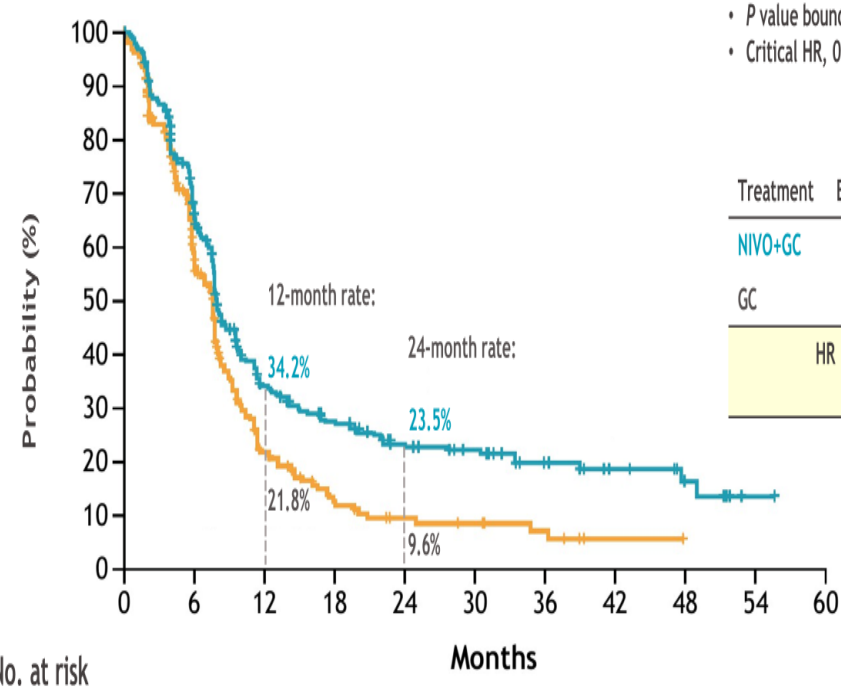
Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7-22.4)
HR (95% CI), 0.78 (0.63-0.96) *P* = 0.0171		

No. at risk

NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

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

PFS per BICR (primary endpoint)



PFS final analysis statistical boundaries:
- *P* value boundary, 0.01
- Critical HR, 0.7734

Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1-7.8)
HR (95% CI), 0.72 (0.59-0.88) *P* = 0.0012		

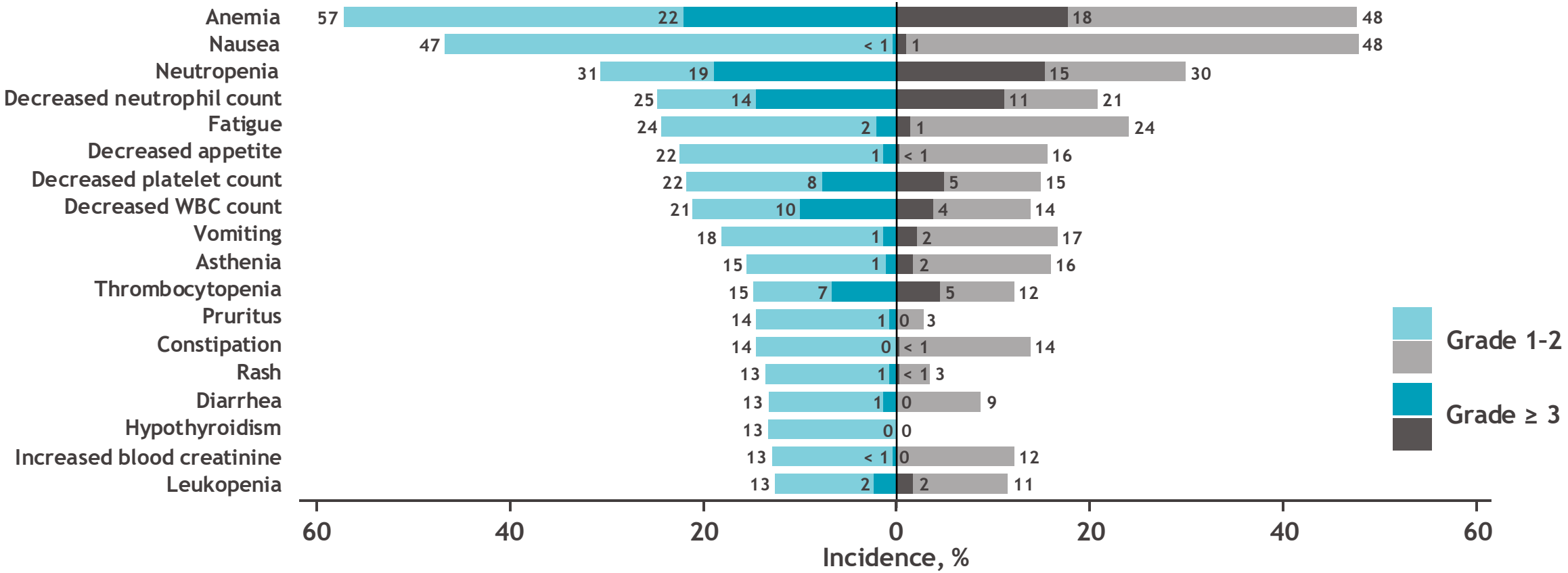
No. at risk

NIVO+GC	304	179	82	57	41	31	19	11	6	1	0	
GC	304	119	35	17	10	8	5	1	0	0	0	

Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as the time from date of randomization to date of first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who died without reported progression were considered to have progressed on the date of death. Patients who did not progress or die were censored on the last evaluable tumor assessment date. Patients without on-study tumor assessments who did not die were censored on the date of randomization. **Patients who started any subsequent anticancer therapy without prior reported progression were censored at the last evaluable tumor assessment before initiation of subsequent anticancer therapy.**
RECIST, Response Evaluation Criteria in Solid Tumors.

Treatment-related AEs in all treated patients

	NIVO+GC (n = 304)		GC (n = 288)	
Treatment-related AE, %[a]	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
Any	97	62	93	52
Leading to DC	21	11	17	8



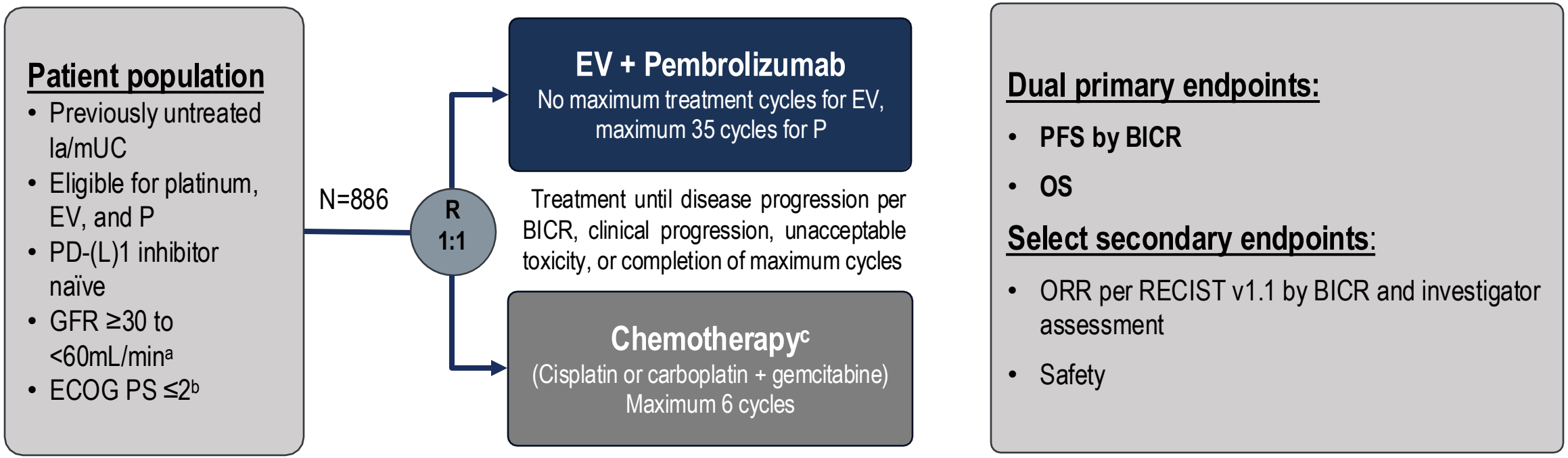
[a]Includes events that occurred in treated patients between first dose and 30 days after last dose of study therapy. Tornado plot displays individual treatment-related AEs occurring at any grade in ≥ 10% of treated patients in either arm. [b]One grade 5 event occurred in each arm (sepsis in the NIVO+GC arm and acute kidney injury in the GC arm).
DC, discontinuation; WBC, white blood cell.

Summary

- NIVO+GC demonstrated statistically significant and clinically meaningful improvements in OS and PFS versus GC alone as first-line treatment for unresectable or mUC
- ORR and CR rates were notably higher with NIVO+GC and the concurrent ICI and chemotherapy combination was associated with deep and durable responses
  - The CR rate was almost double (21.7% vs 11.8%) and the DoCR almost 3 times longer (37.1 vs 13.2 months) with NIVO+GC, despite a maximum of 2 years of NIVO treatment
- The combination of NIVO plus GC resulted in no new toxicity signals, and the safety profile was consistent with the established safety of either agent in prior UC trials
- NIVO+GC is the first frontline concurrent ICI plus chemotherapy combination to improve OS in this setting, with results supporting NIVO plus cisplatin-based chemotherapy as a new SOC for patients with unresectable or mUC

ICI, immune checkpoint inhibitor.

EV-302/KEYNOTE-A39 (NCT04223856)



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

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

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

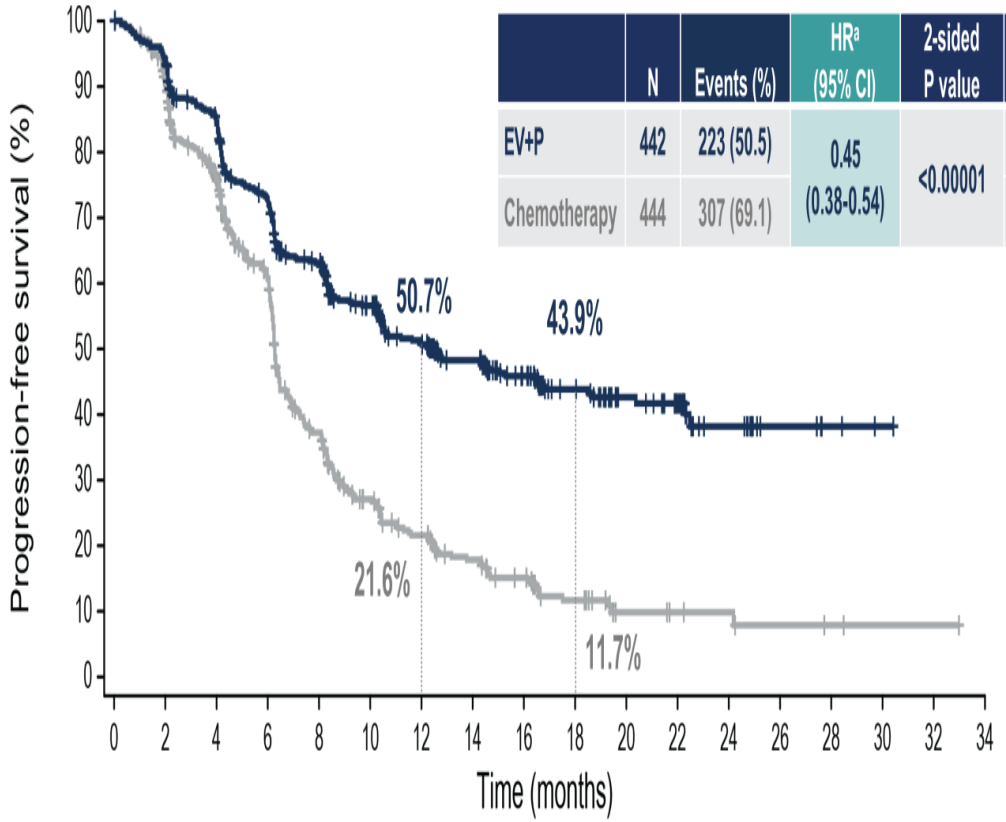
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors
[a]Measured by the Cockcroft-Gault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

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

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

Data cutoff: 08 Aug 2023

PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

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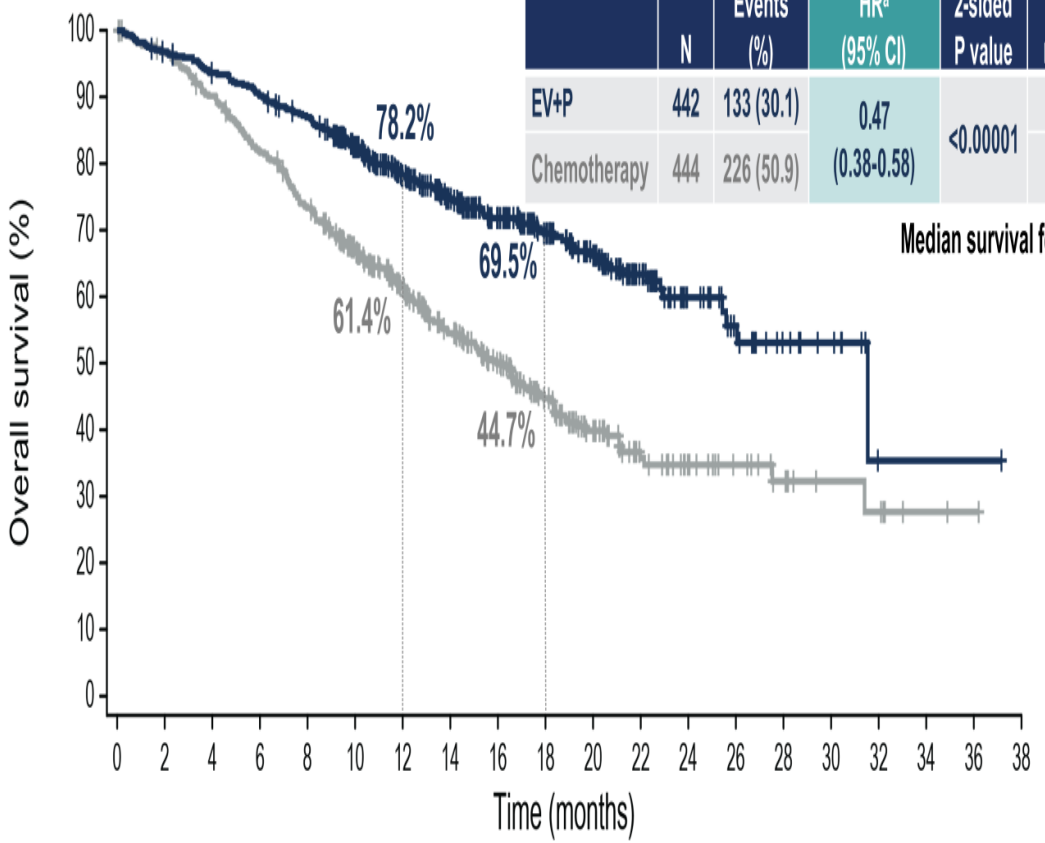
Overall Survival

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

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



N at risk

EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Data cutoff: 08 Aug 2023

OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

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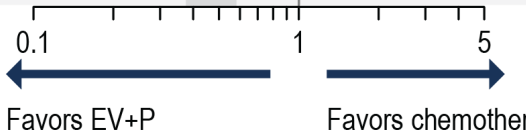
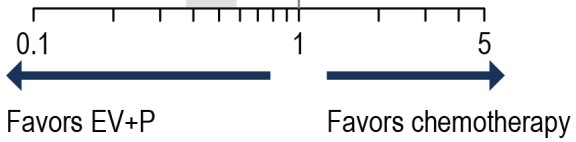
Subgroup Analysis of OS

OS benefit in all pre-specified subgroups was consistent with results in overall population

Subgroup	mOS, months (Events/N) EV+P	Chemotherapy	Hazard Ratio (95% CI)
Overall	31.5 (133/442)	16.1 (226/444)	0.47 (0.38–0.58)
Age			
<65 years	NR (39/144)	19.7 (58/135)	0.46 (0.30–0.71)
≥65 years	31.5 (94/298)	14.6 (168/309)	0.48 (0.38–0.63)
Race			
White	26.1 (104/308)	15.3 (162/290)	0.47 (0.36–0.60)
Other	NR (29/134)	19.3 (64/154)	0.46 (0.29–0.72)
Region			
North America	25.6 (40/103)	21.2 (42/85)	0.71 (0.44–1.12)
Europe	NR (56/172)	13.9 (110/197)	0.40 (0.28–0.56)
Rest of world	NR (37/167)	16.4 (74/162)	0.41 (0.27–0.61)
Sex			
Female	25.4 (32/98)	14.6 (54/108)	0.51 (0.32–0.80)
Male	31.5 (101/344)	16.6 (172/336)	0.47 (0.36–0.60)
ECOG PS			
0	NR (44/223)	18.4 (94/215)	0.36 (0.25–0.53)
1-2	25.4 (89/219)	13.1 (131/227)	0.54 (0.41–0.72)
Primary disease site of origin			
Upper tract	NR (38/135)	18.4 (45/104)	0.53 (0.34–0.83)
Lower tract	31.5 (94/305)	15.6 (180/339)	0.46 (0.36–0.59)
Liver metastases			
Present	19.1 (43/100)	10.1 (67/99)	0.47 (0.32–0.71)
Absent	NR (90/342)	17.9 (159/345)	0.47 (0.36–0.61)
PD-L1 expression			
Low (CPS <10)	NR (53/184)	15.5 (99/185)	0.44 (0.31–0.61)
High (CPS ≥10)	31.5 (79/254)	16.6 (125/254)	0.49 (0.37–0.66)
Cisplatin eligibility			
Eligible	31.5 (69/244)	18.4 (106/234)	0.53 (0.39–0.72)
Ineligible	NR (64/198)	12.7 (120/210)	0.43 (0.31–0.59)
Metastatic disease site			
Visceral metastases	25.6 (108/318)	13.6 (182/318)	0.47 (0.37–0.60)
Lymph node only	NR (22/103)	27.5 (39/104)	0.46 (0.27–0.78)
Renal function[a]			
Normal	26.1 (24/84)	18.4 (44/95)	0.51 (0.30–0.86)
Mild	NR (42/165)	16.4 (78/162)	0.44 (0.30–0.65)
Moderate/Severe	31.5 (67/193)	13.3 (104/187)	0.50 (0.37–0.69)



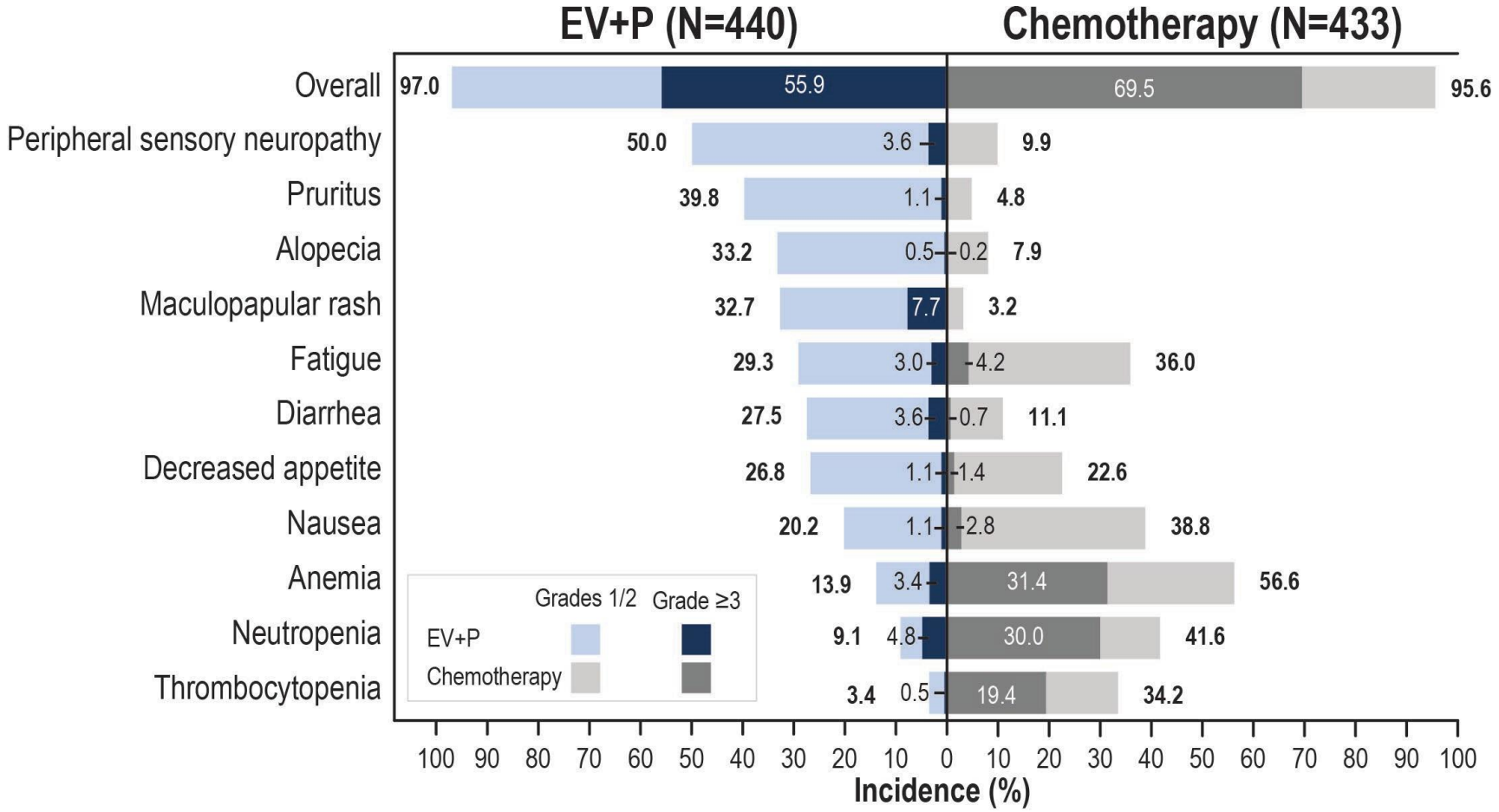


Data cutoff: 08 August 2023

[a]Renal function categories defined as: Normal (≥90 mL/min), Mild (≥60 to <90 mL/min), Moderate/Severe (≥15 to <60 mL/min)

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:
- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

Data cutoff: 08 Aug 2023

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TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm
TRAEs, treatment-related adverse events

Conclusion

Two phase 3 trials in the first-line treatment of advanced/metastatic urothelial carcinoma have demonstrated an improvement in overall survival:

Nivo+GemCis and EV+Pembro

The combination of Nivo+GemCis is the first chemo/IO combination to show a survival benefit with a mOS 21.7 months, however, the combination of EV+Pembro almost doubled the mOS vs chemo (OS 31.5 months), making it the New Standard of Care for patients in this setting.

Many challenges and questions arise when "Welcoming EV+Pembro as a new SOC", including

1] What treatment then becomes the best second-line therapy?

2] Can we dose deescalate EV, in EV+Pembro?

3 What is the underlying biology leading to the great response and OS and how do we build on this?

4 What is the efficacy of EV+Pembro in earlier states of disease (MIBC and NMIBC)?

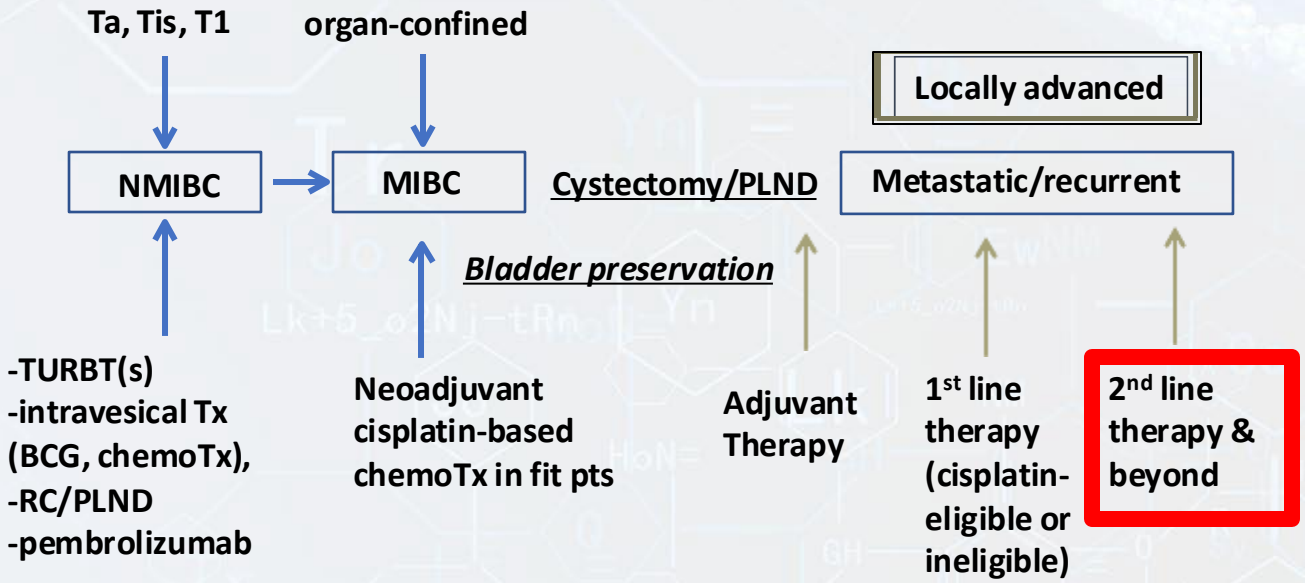
5 EV+Pembro is expensive, will patients, insurance, and public systems be able to afford this treatment?

6] What about patients who received anti-PD(L)1 in prior therapy setting? Timing of progression matters?

Presented by Andrea B. Apolo, MD

@apolo_andrea

Disease / treatment settings

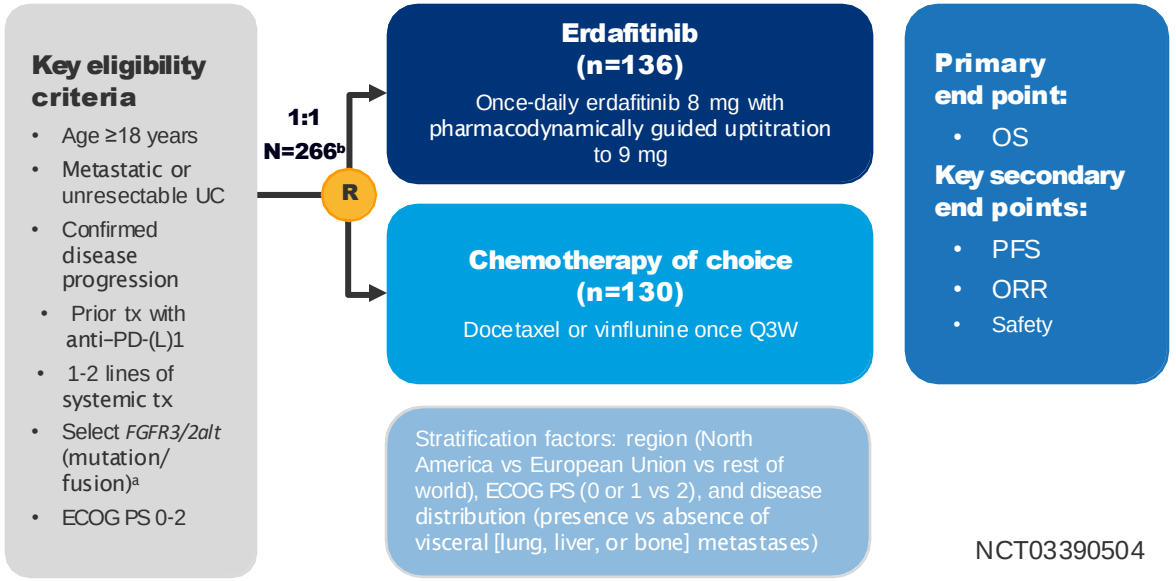


	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase III Randomized vs chemotherapy	Phase II Single Arm	Phase III Randomized vs Chemotherpay	Phase Ib	Phase I/II
Number of Patients	931	265	542	249 (161 pts ≥ 6 mos f/u)	191
Dosing	1200mg every 3 weeks	3mg/kg every 2 weeks	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

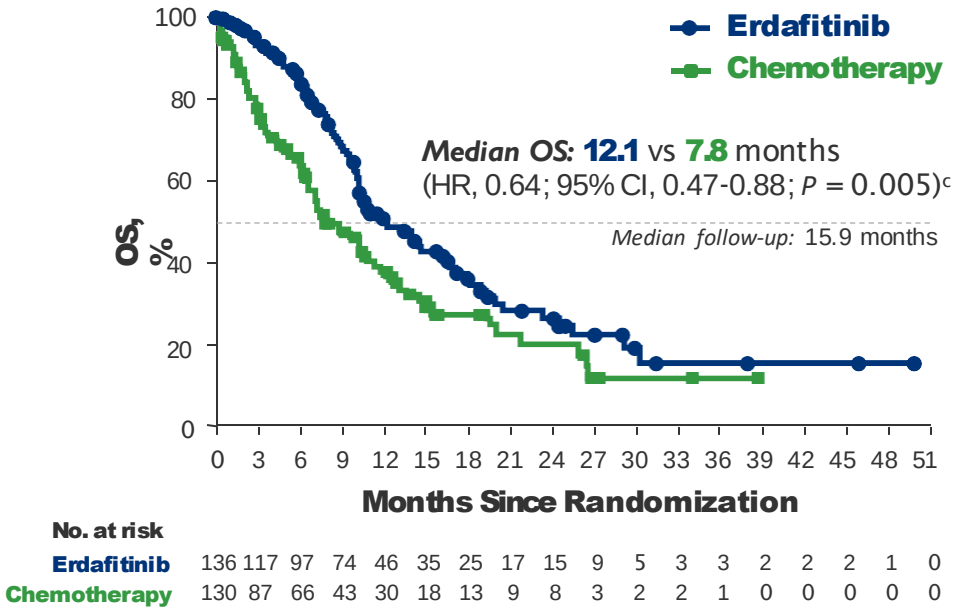
THOR Cohort 1: Erdafitinib Versus Investigator's Choice of Chemotherapy in Patients With *FGFR*-altered mUC

THOR cohort 1 study design



- Based on superior efficacy at a preplanned interim analysis, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

Erdafitinib demonstrated superior efficacy versus chemotherapy in patients with *FGFR*-altered mUC[1]



- ***Median PFS:*** **5.6** vs **2.7** months (HR, 0.58; 95% CI, 0.44-0.78; *P* = 0.0002)
- ***ORR:*** **45.6%** vs **11.5%** (relative risk, 3.94; 95% CI, 2.37-6.57; *P* < 0.001)

[a]Molecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥1 of the following translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1, FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C; [b]Number of patients randomized at the time of the interim analysis (data cutoff January 15, 2023); [c]The significance level for stopping for efficacy was *P* = 0.019, corresponding to a HR of 0.69.

CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.

1. Loriot Y, et al. *J Clin Oncol.* 2023;41(Suppl 17):LBA4619.

Phase 3 THOR Study: Erdafitinib vs Pembrolizumab in Patients With Metastatic Urothelial Carcinoma and Select *FGFR* Alterations

Cohort 2

Key eligibility criteria

- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression on 1 prior tx
- Naive to anti–PD-(L)1 tx
- Select *FGFR3/2alt* (mutation/fusion)[a]
- ECOG PS 0-2

1:1
N=351[b]
R

Erdafitinib
(n=175)
Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

Pembrolizumab
(n=176)
200 mg once every 3 weeks

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

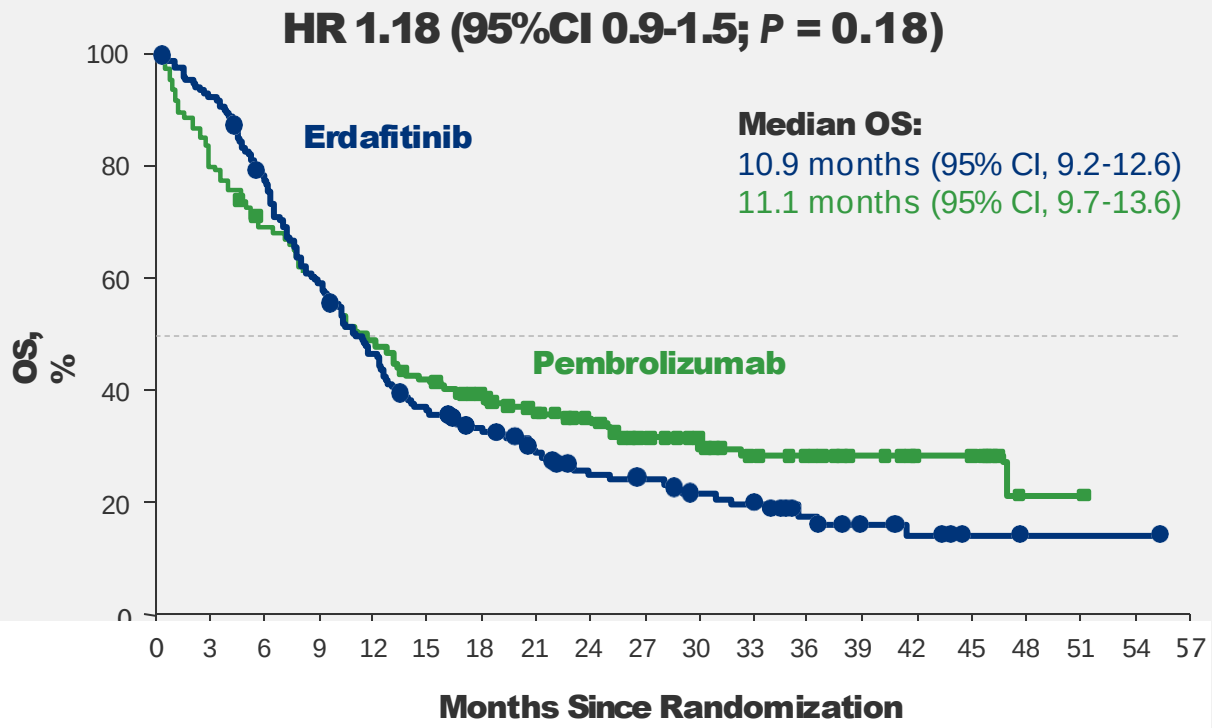
Primary end point
- OS

Secondary end points
- PFS
- ORR
- Safety

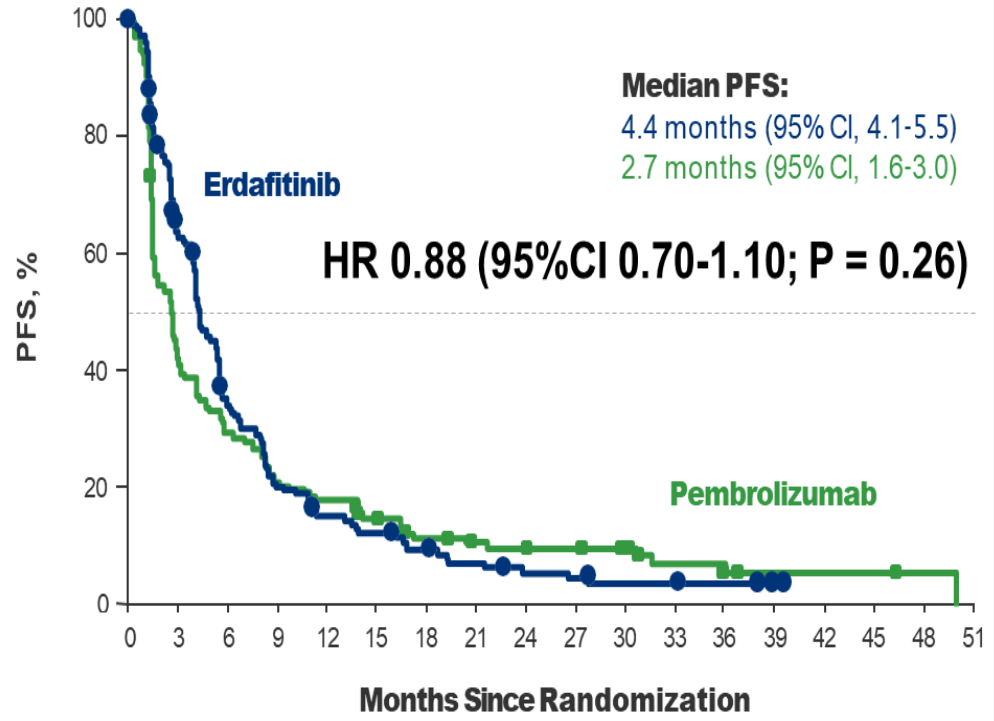
NCT03390504

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

No Significant Difference in OS & PFS Between Erda vs Pembro



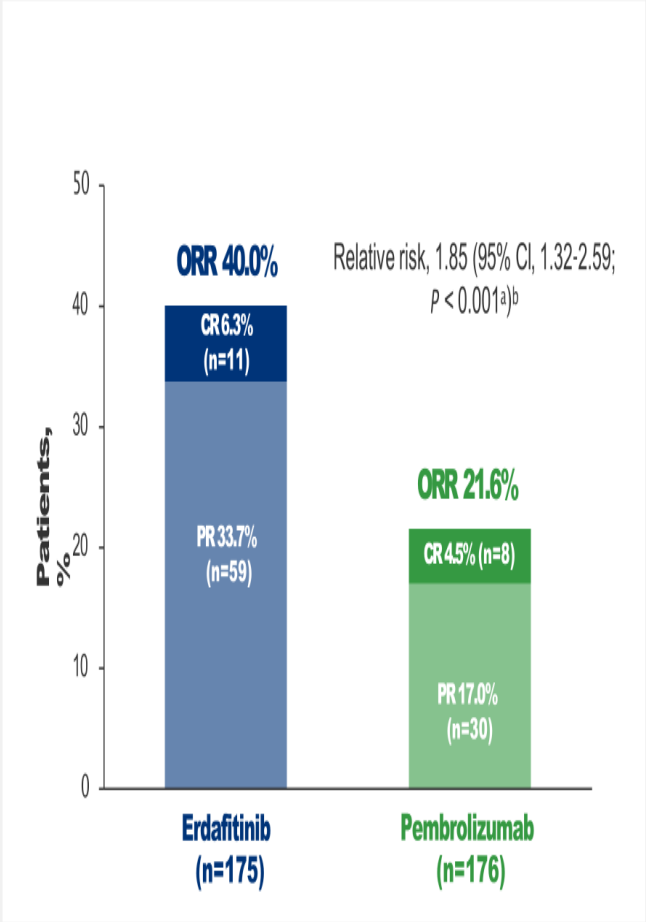
No. at risk																				
Erdafitinib	175	160	131	100	78	60	52	41	30	28	23	21	13	9	7	2	1	1	1	0
Pembrolizumab	176	148	119	103	84	72	60	52	43	34	29	23	19	11	8	8	1	1	0	0



No. at risk																				
Erdafitinib	175	107	57	34	23	19	14	10	7	6	4	4	3	1	0	0	0	0		
Pembrolizumab	176	75	50	36	30	23	16	13	12	11	9	5	3	2	2	2	1	0		

[a]Nominal *P* value, due to primary end point not being met.

ORR: 40.0% With Erdafitinib and 21.6% With Pembrolizumab



- ORR 40.0% (95%CI 32.7-47.7) for erdafitinib and 21.6% (95%CI15.8-28.4) for pembrolizumab
- Median DOR 4.3 months (95%CI 3.7-6.9) for erdafitinib and 14.4 months (95%CI 7.4-27.8) for pembrolizumab

CR, complete response; DOR, duration of response; PR, partial response.
[a]Nominal *P* value, due to primary end point not being met; [b]Relative risk, 95% CI, and *P* value are estimated using Cochran-Mantel-Haenszel procedure with ECOG PS (0 or 1 vs 2) as stratification factor.

Safety Profiles Were Consistent With the Known Profiles Of Erdafitinib and Pembrolizumab (1/3)

Most Frequent[a] Treatment-Related AEs in the Erdafitinib Group

Patients with events, n (%)[a]	Erdafitinib (n=173)		Pembrolizumab (n=173)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
≥1 treatment-related AE	169 (97.7)	75 (43.4)	105 (60.7)	21 (12.1)
Hyperphosphatemia	126 (72.8)	1 (0.6)	0	0
Stomatitis	78 (45.1)	15 (8.7)	5 (2.9)	0
Diarrhea	77 (44.5)	6 (3.5)	10 (5.8)	0
Dry mouth	61 (35.3)	1 (0.6)	5 (2.9)	0
Onycholysis	41 (23.7)	10 (5.8)	0	0
Palmar-plantar erythrodysesthesia syndrome	38 (22.0)	16 (9.2)	0	0
Hyponatremia	13 (7.5)	9 (5.2)	1 (0.6)	1 (0.6)

- In the erdafitinib group:
  - 26 (15.0%) of patients discontinued erdafitinib due to treatment-related AEs[b]
  - 23 (13.3%) patients had serious treatment-related AEs
  - No deaths due to treatment-related AEs occurred
  - Treatment-related AEs with erdafitinib were mostly manageable with dose modifications and supportive care

[a]AEs by preferred term are listed if events of any grade occurred in ≥25% in the erdafitinib group or if events of grade 3-4 occurred in ≥5% of patients of patients in the erdafitinib group.
[b]Most frequent treatment-related AEs leading to discontinuation of erdafitinib included gastrointestinal disorders (9 patients), eye disorders (9 patients), and skin and subcutaneous tissue disorders (6 patients).
AE, adverse event.

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/m² or paclitaxel 175 mg/m² or vinflunine 320 mg/m² 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.

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

	Enfortumab vedotin (N=296)		Chemotherapy (N=291)	
Treatment-related adverse event, n (%)	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

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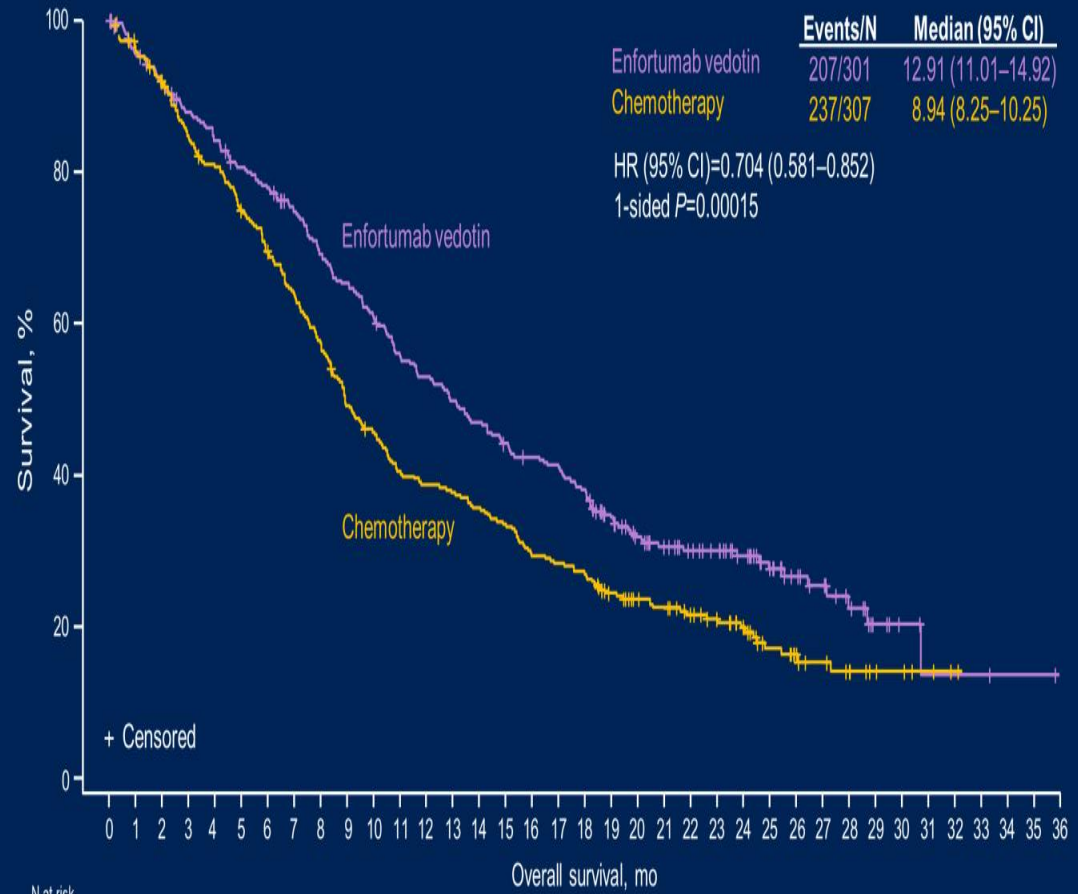
Overall Survival



	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

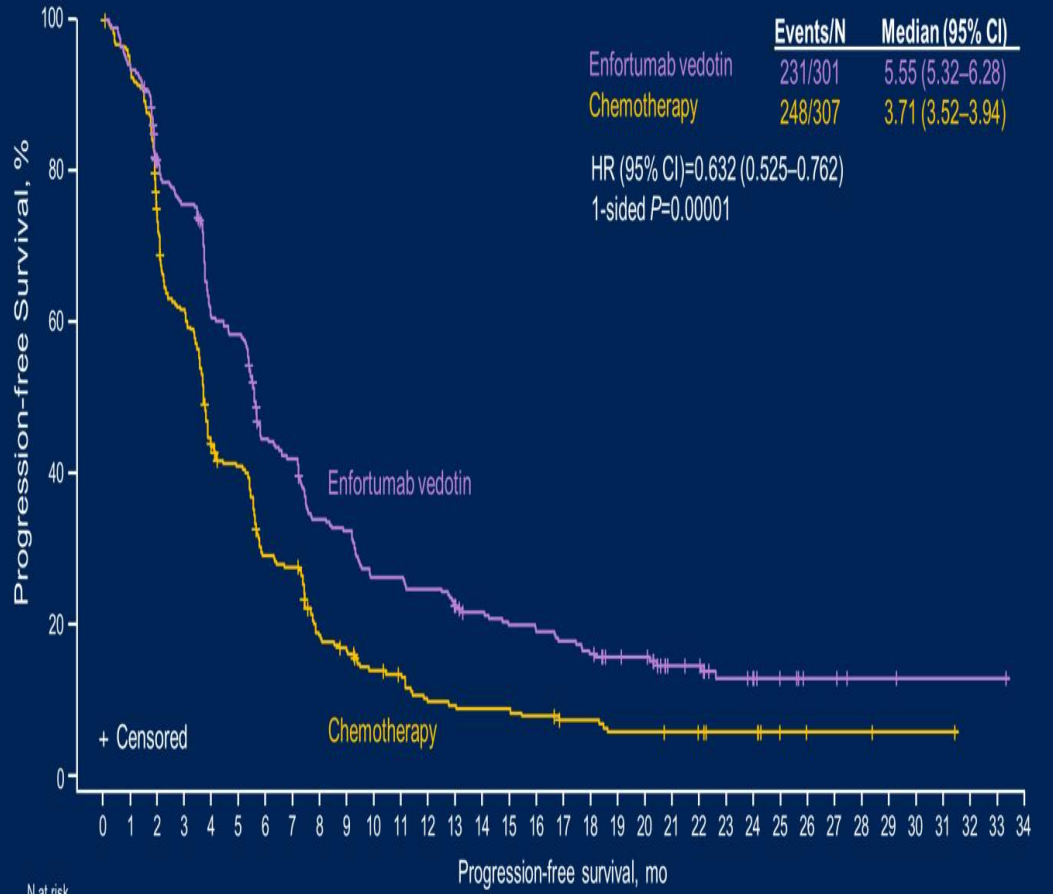
N at risk

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

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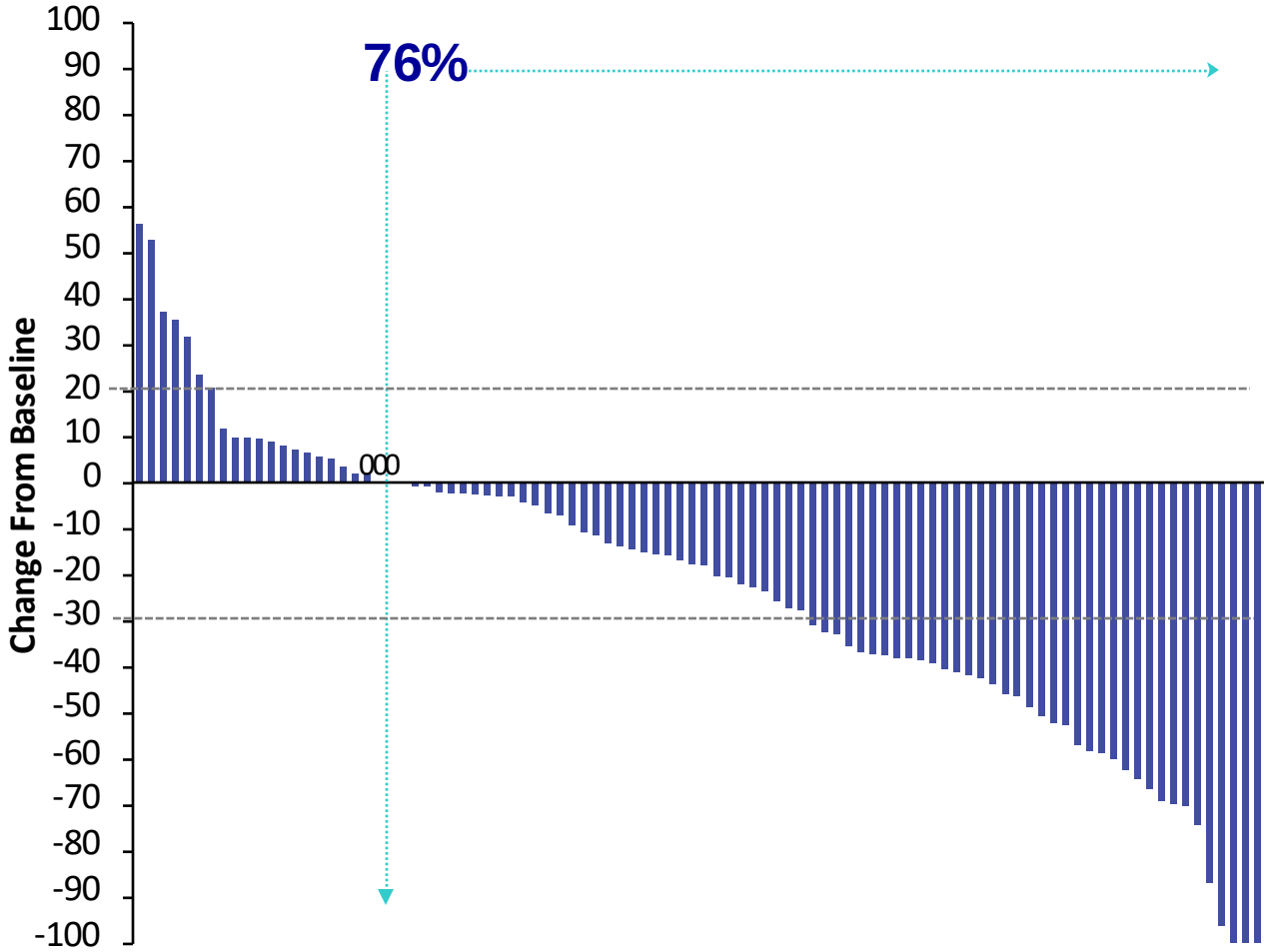
TROPHY-U-01 Cohort 1 Response and Reduction in Tumor Size

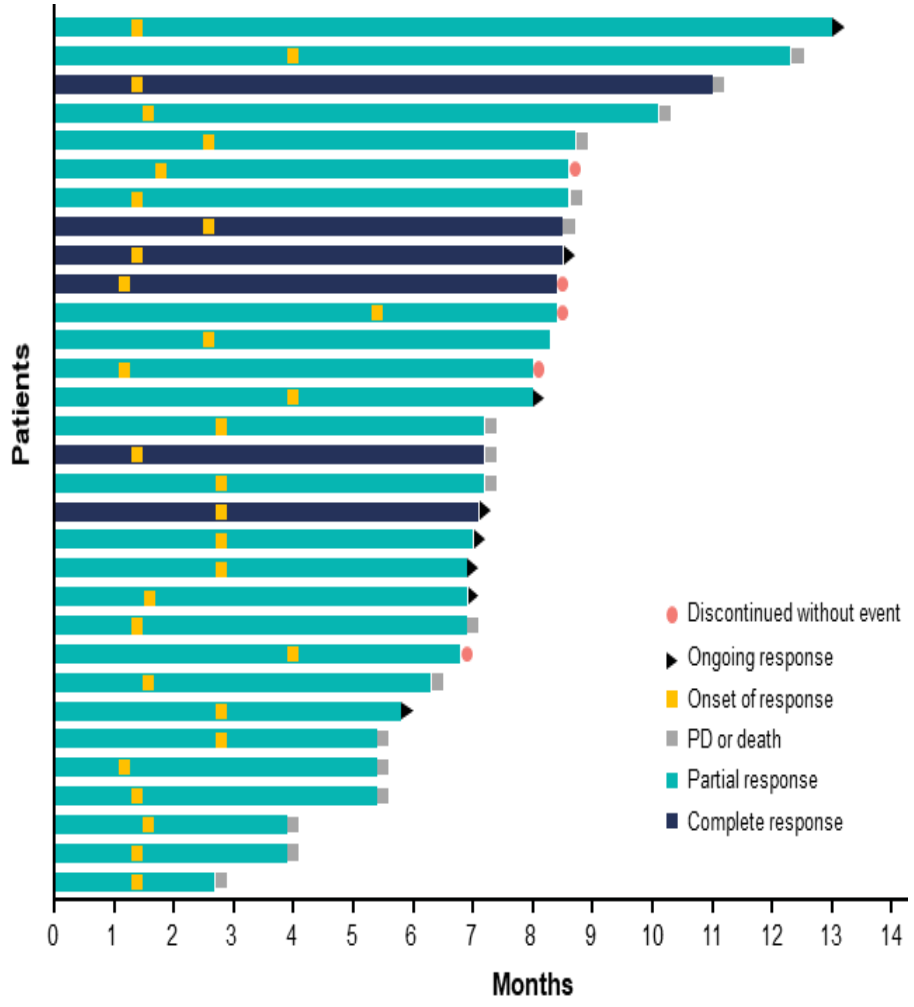
Endpoint	Cohort 1 (N=113)
ORR, n (%) [95% CI]	**31 (27) [19, 37]**
CR, n (%)	6 (5)
PR, n (%)	25 (22)
Median duration of response, mos [95% CI] (Range)	**5.9** [4.70, 8.60] (1.4–11.7)
Median time to onset of response, mos (Range)	1.6 (1.2–5.5)

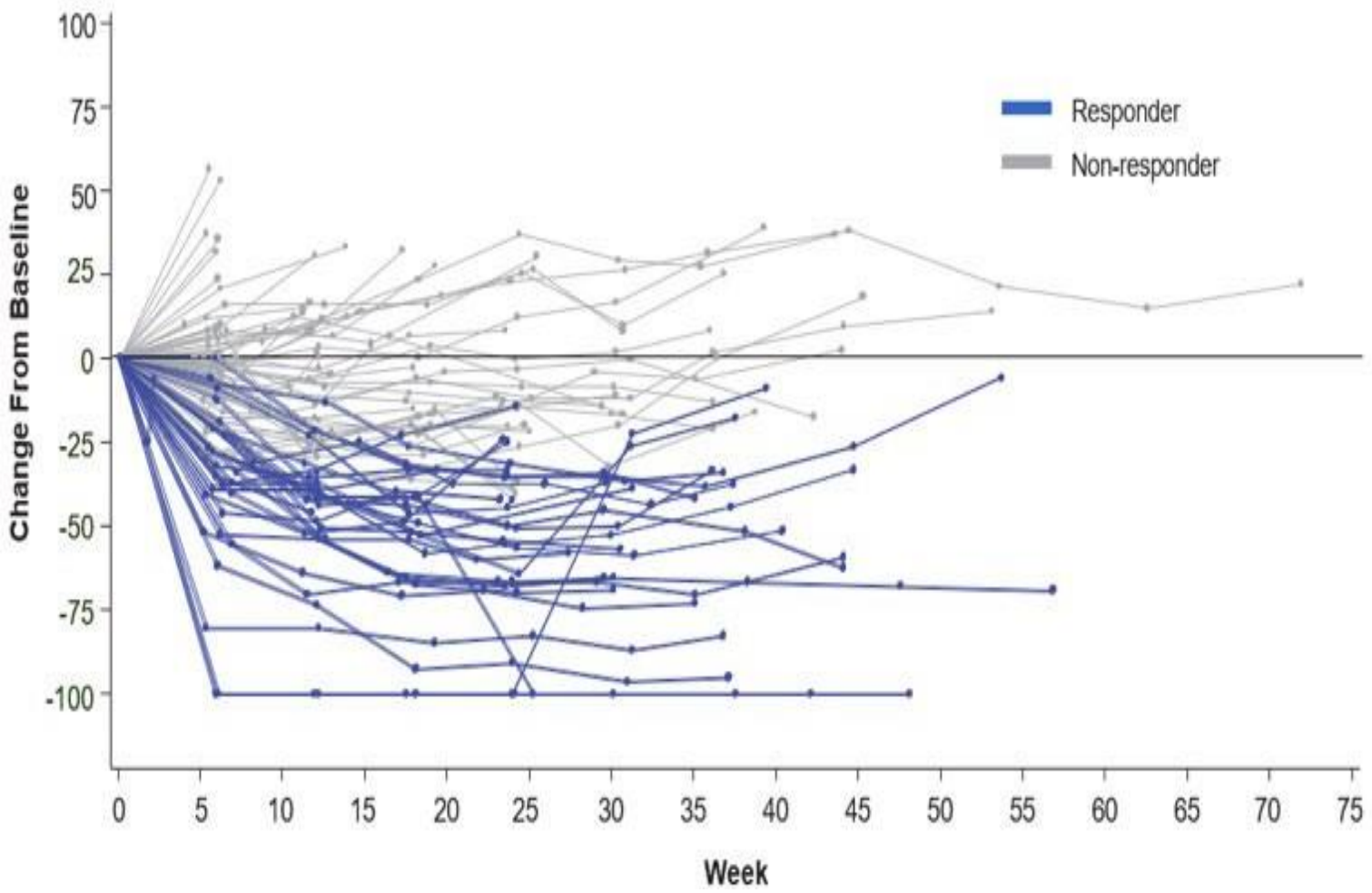


[a]Assessments were per Blinded Independent Review Assessment, RECIST 1.1.
CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; TTR, time to response.

[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**

TROPHY-U-01 Cohort 1 Durability of Response





Tagawa ST, et al. J Clin Oncol 2021; 39:2474-85

TROPHY-U-01 Cohort 1 Treatment-Related Adverse Events ≥20% any grade or ≥5% Grade ≥3 (n=113)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	**Neutropenia**	**46**	**22**	**12**
	Leukopenia	26	12	5
	Anemia	34	14	0
	Lymphopenia	12	5	2
	Febrile neutropenia	**10**	**7**	**3**
Gastrointestinal	**Diarrhea[b]**	**65**	**9**	**1**
	Nausea	**58**	**4**	**0**
	Vomiting	28	1	0
General disorders & administrative site conditions	**Fatigue**	**50**	**4**	**0**
Skin & subcutaneous tissue	**Alopecia**	**47**	**0**	**0**
Metabolism & nutrition	Decreased appetite	36	3	0
Infections & infestations	Urinary tract infection	8	6	0

- 7 (6%) pts discontinued due to TRAEs
  - 3 discontinued due to neutropenia or its complications
- 30% G-CSF usage
- 1 treatment-related death (sepsis due to febrile neutropenia)

Median treatment cycles: 6 (range: 1–22); worst grade CTCAE reported

Tagawa ST, et al. J Clin Oncol 2021; 39:2474-85

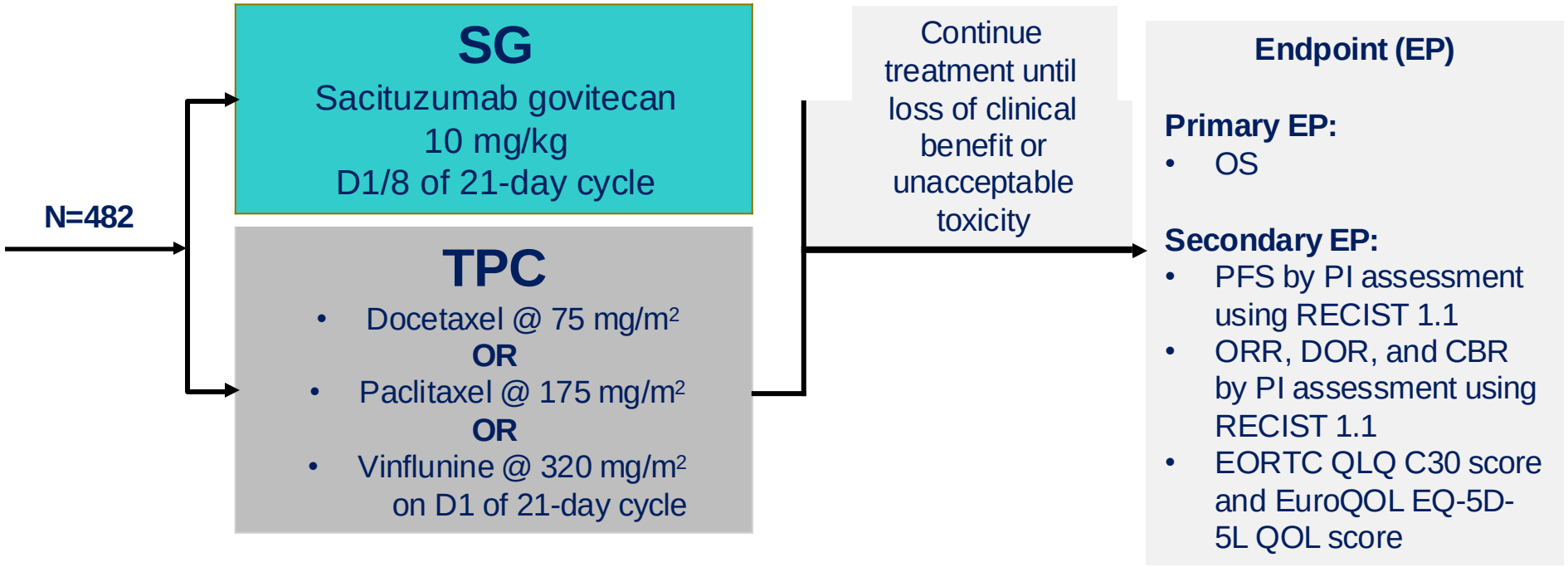
TROPiCS-04 Design

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

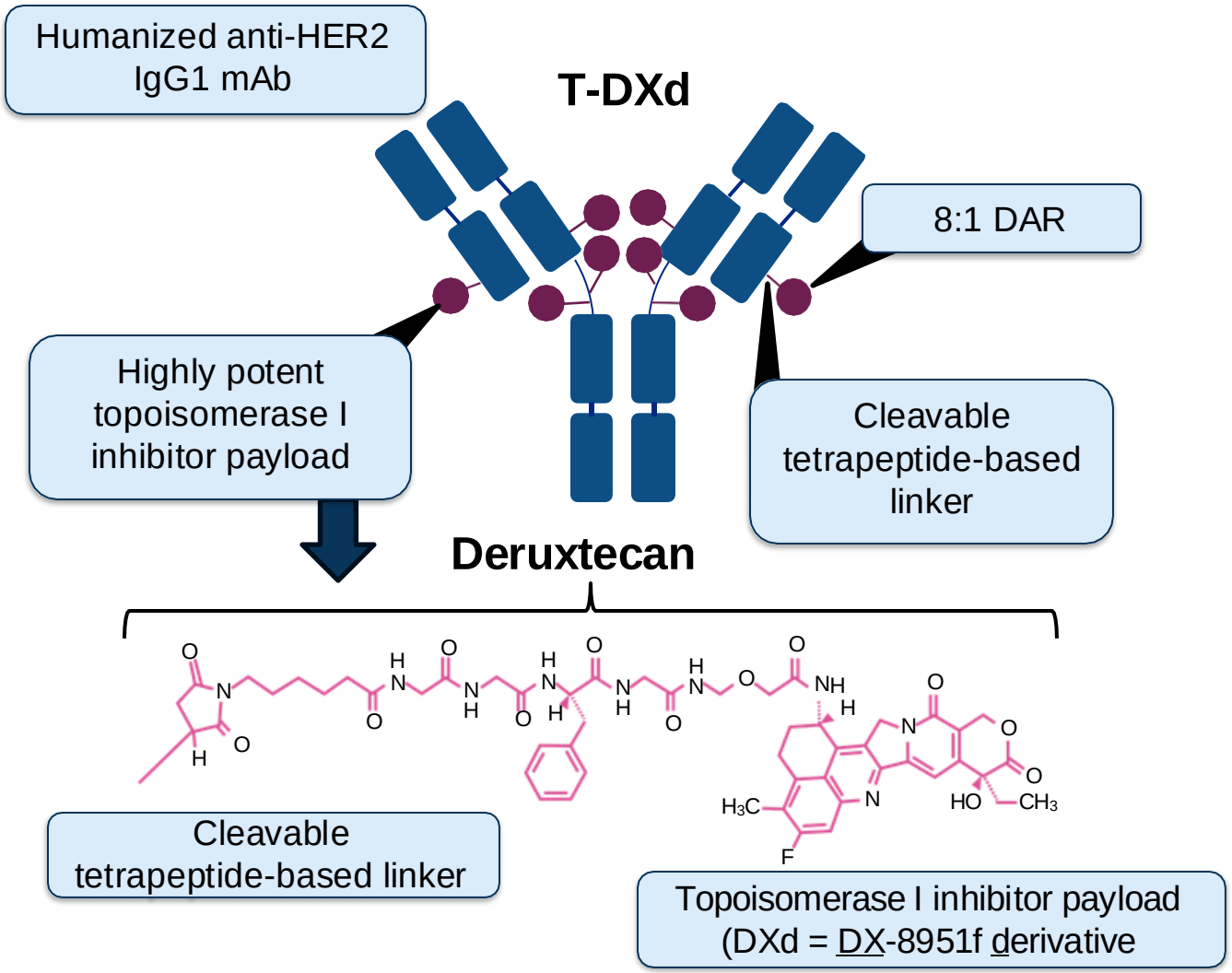


Press release: trial did not meet the primary endpoint (OS)

Neutropenic deaths noted: need for G-CSF as primary prophylaxis!

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

Trastuzumab Deruxtecan (T-DXd): Anti-HER2 ADC



Seven Key Attributes[1-5]

- Payload MOA: topoisomerase I inhibitor
- High potency of payload
- High DAR: ~8
- Payload with short systemic half-life
- Stable linker payload
- Tumor-selective cleavable linker
- Bystander antitumor effect

1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108.
3. Trail PA et al. *Pharmacol Ther*. 2018;181:126-142. 4. Okamoto H et al. *Xenabiotica*. 2020;50:1242-1250. 5. Nagi Y et al. *Xenobiotica*. 2019;49:1086-1096.

DESTINY-PanTumor02: T-DXd in HER2-Expressing Solid Tumors[1-4,a]

An open-label, multicenter study (NCT04482309)

Key Eligibility Criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring)[b]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0-1

T-DXd
5.4 mg/kg
Q3W

40 per cohort[c]

- Endometrial cancer
- Cervical cancer
- Ovarian cancer
- Bladder cancer
- Other tumors[d]
- Biliary tract cancer
- Pancreatic cancer

- **Primary endpoint:** confirmed ORR (investigator)
- **Secondary endpoints:** DOR, DCR, PFS, OS, safety
- **Exploratory analysis:** subgroup analysis by HER2 status

Baseline Characteristics

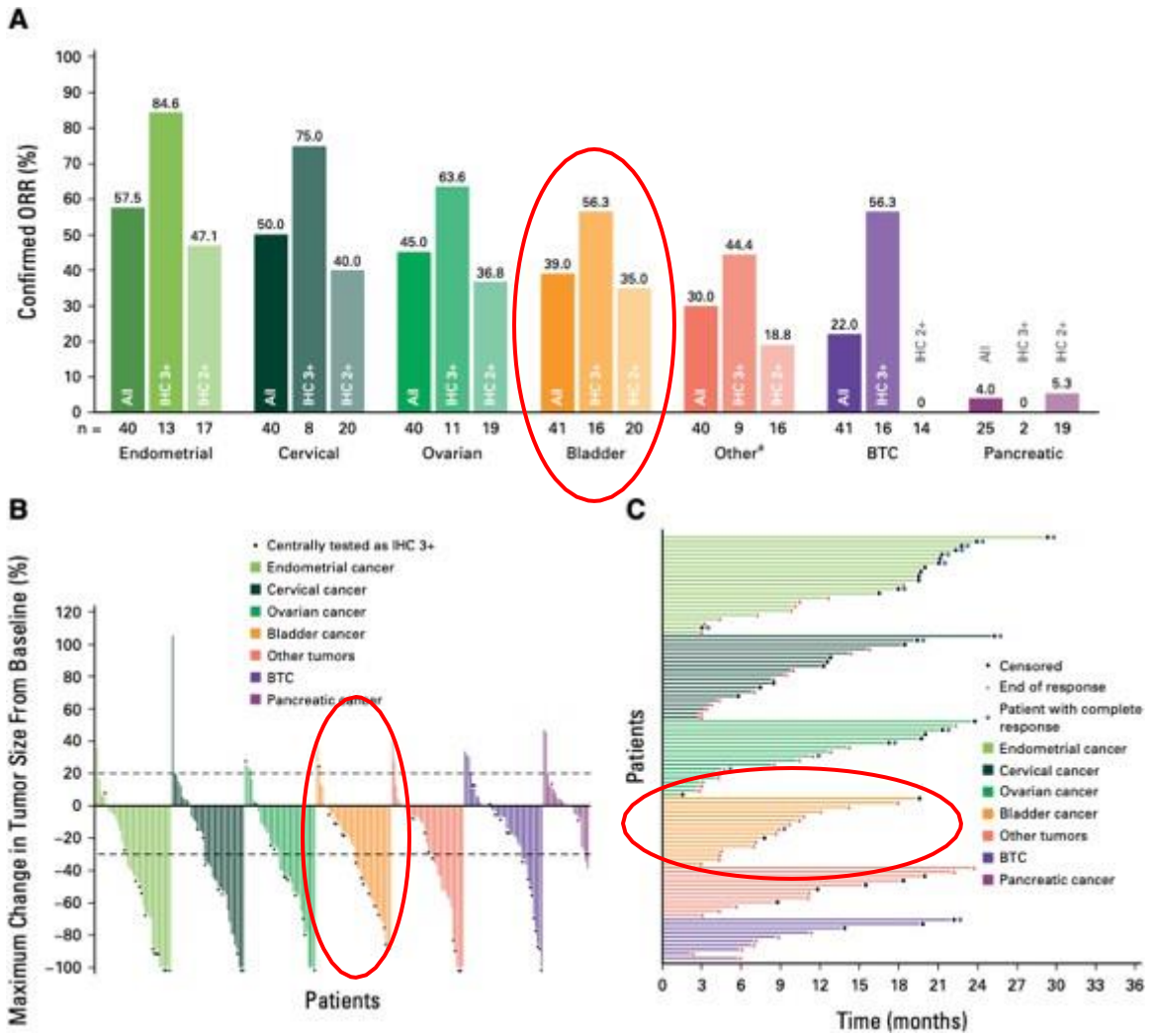
- 267 pts received treatment; 202 (75.7%) based on local HER2 testing
  - 111 (41.6%) pts were IHC 3+ based on HER2 test (local or central) at enrollment; primary efficacy analysis (all patients)
  - 75 (28.1%) pts were IHC 3+ on central testing; sensitivity analysis on efficacy endpoints (subgroup analyses)
- Median age 62 (23-85);109 (41%) pts had received ≥3 lines of therapy

[a] Primary analysis data cutoff: June 8, 2023; median follow-up: 12.75 mo. [b] Patients were eligible for either test. All patients were centrally confirmed.
[c] Planned recruitment, cohorts with no objective responses in the first 15 patients were to be closed. [d] Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, NSCLC, gastric cancer, and CRC.

1. https://clinicaltrials.gov/study/NCT04482309. 2. Hofmann M et al. *Histopathology*. 2008;52:797-805. 3. Meric-Bernstam F et al. ESMO 2023. Abstract LBA34.
4. Meric-Bernstam F et al. *J Clin Oncol*. 2024;42:47-58.

DESTINY-PanTumor02 Trial Results: UC Cohort

Tumor Response



Meric-Bernstam F et al. *J Clin Oncol.* 2023;42:47-58.

UC Cohort Outcomes

	Overall (N=41)	HER2 IHC 3+ (n=16)	HER2 IHC 2+ (n=20)
mPFS, mo	7.0	7.4	7.8
mOS, mo	12.8	13.4	13.1
ORR, %	39.0	56.3	35.0
mDOR, mo	8.7	-	-

Tumor-Agnostic FDA Approval for T-DXd[1-3]

Updated NCCN Guidelines for Bladder Cancer[1]

Second- or subsequent-line therapy:
T-DXd for HER2-positive tumors (IHC 3+ or 2+)
Useful in certain circumstances

Accelerated FDA Approval[2]

For adults with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

1. NCCN Bladder Cancer Guidelines V4.2024. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2.
3. ENHERTU (fam-trastuzumab deruxtecan-nxki) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf.

Advanced Urothelial Ca Therapy Algorithm

Disease State	Preferred Option	Other Options
Metastatic, no prior therapy (1L)	Pembrolizumab/Enfortumab-vedotin	-Gem/Cis + nivolumab (cisplatin-fit) -Gem + (Cis or Carbo) f/b avelumab switch maintenance (if no progression) *-Pembrolizumab (platinum/EV-unfit)* *-Single agent chemo (platinum/EV-unfit)*
Metastatic (prior therapy)	Platinum-based chemo (after EV/P) *OR* Erdafitinib (tumors with *FGFR3* activating mutation or fusion) OR Enfortumab-vedotin (if not used prior) OR Pembrolizumab (if IO not used prior)	Sacituzumab-govitecan T-DXd (HER2 IHC +3)
Metastatic (≥2 prior therapies)	Erdafitinib (tumors with *FGFR3* activating mutation or fusion) OR Enfortumab-vedotin *(*if not used prior) OR Sacituzumab-govitecan OR Pembrolizumab (if IO not used prior), T-DXd (HER2 IHC +3)	Taxane (US) Vinflunine (EU)

Clinical trials are critical throughout disease spectrum & treatment settings!

Petros Grivas

Thanks☺

Patient & families!

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

@PGrivasMDPhD