

Targeted Therapy Approaches

for Metastatic
Urothelial Carcinoma



Faculty

Petros Grivas, MD, PhD

Professor, Clinical Director

GU Cancers Program

University of Washington

Fred Hutchinson Cancer Center

Seattle, Washington

Mary W. Dunn, MSN, RN, OCN, NP-C

Adult Oncology Nurse Practitioner

University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

Faculty Disclosures

- **Dr. Grivas:** Consulting - 4D Pharma, Aadi Bioscience, Astellas, Asieris Pharmaceuticals, AstraZeneca, BostonGene, Bristol Myers Squibb, CG Oncology, Dyania Health, Exelixis, Fresenius Kabi, Genentech, Gilead Sciences, Guardant Health, ImmunityBio, Infinity Pharmaceuticals, Janssen, Lucence, Merck KGaA, Mirati Therapeutics, MSD, Pfizer, PureTech, QED Therapeutics, Regeneron, Roche, Seattle Genetics, Silverback Therapeutics, Strata Oncology, UroGen Pharma; institutional research funding - Acrivon, ALX Oncology, Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm Group, G1 Therapeutics, Gilead Sciences, GlaxoSmithKline, Merck KGaA, Mirati Therapeutics, MSD, Pfizer, QED Therapeutics
- **Ms. Dunn** has disclosed no relevant financial relationship with any ineligible company (commercial interest)



Program Information

- This program is provided by HMP Education, an HMP Global company
- Supported by an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC. and Seagen

Learning Objectives

- Describe the clinical challenges and unmet needs associated with treatment selection and sequence to manage mUC
- Evaluate the safety, efficacy, and toxicity data associated with available first-, second, and subsequent-line therapies for mUC including targeted therapies
- Incorporate multidisciplinary and patient-centered care to manage adverse events and address treatment barriers

mUC = metastatic urothelial carcinoma.

Submit Your Questions and Post-Event Survey

- Scan the QR Code to submit your questions
- Scan the QR Code at the end to complete the Post-Event Survey for a chance to win a \$25 Gift Card!
- Look out for the Key Learning Point Icon throughout the talk!



Overview

Epidemiology

82,290 new cases (62,420 men; 19,870 women)

16,710 deaths (12,160 men, 4550 women)

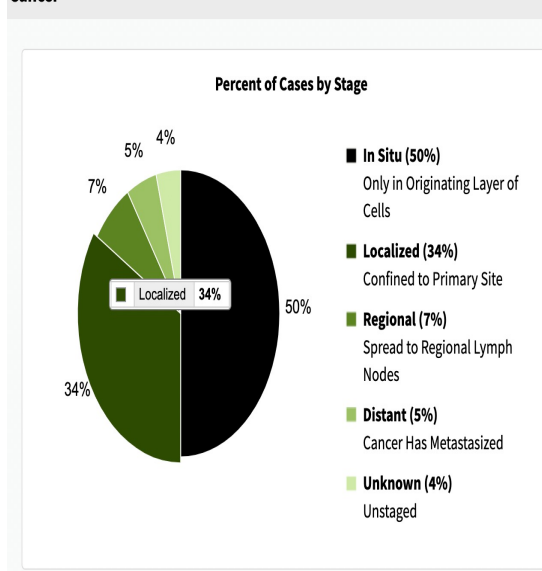
4th most common cancer in men; 6th most common overall (both sexes combined)

Average age of diagnosis: 73 years

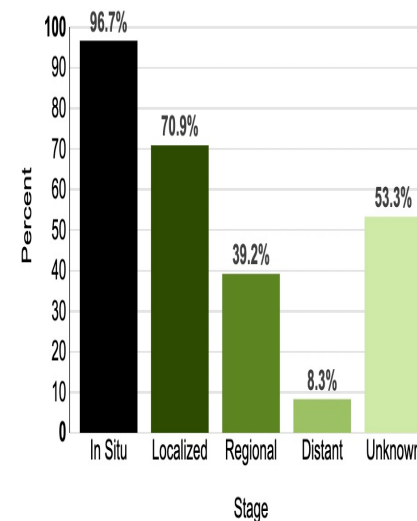
1 in 28 men; 1 in 91 women

Survival depends on stage, met sites, ECOG PS

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Bladder Cancer



5-Year Relative Survival



ECOG PS = Eastern Cooperative Oncology Group performance status.

American Cancer Society (ACS) [www.cancer.org]. Last updated January 13, 2023. <https://www.cancer.org/cancer/types/bladder-cancer/about/key-statistics.html>. Surveillance, Epidemiology, and End Results (SEER) Program [www.seer.cancer.gov].

<https://seer.cancer.gov/statfacts/html/urinb.html>.

- Urothelial most common histologic subtype
- Bladder wall has 4 distinct layers (urothelial, lamina propria, muscularis propria, perivesical fat)
- Grade: Low and high

Humphrey 2016; Kaseb 2022; Raj 2019

T-Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue layer
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle
T2b	Tumor invades deep muscle
T3	Tumors invade perivesical tissue
T3a	Tumors invade microscopically
T3b	Tumors invade macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, seminal vesicles, uterus or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N-Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis
N2	Metastasis in multiple regional lymph nodes in true pelvis
N3	Metastasis in common iliac lymph node(s)
M-Distant metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

Overview for mUC Presentation and Diagnosis

Clinical presentation can be variable

- Hematuria
- Irritative urinary symptoms
- Urinary retention
- Bone, flank, other pain
- Fatigue/weakness, loss of stamina
- Anorexia, weight loss, asthenia
- Asymptomatic with recurrence on scans s/p treatment with curative intent

Diagnosis

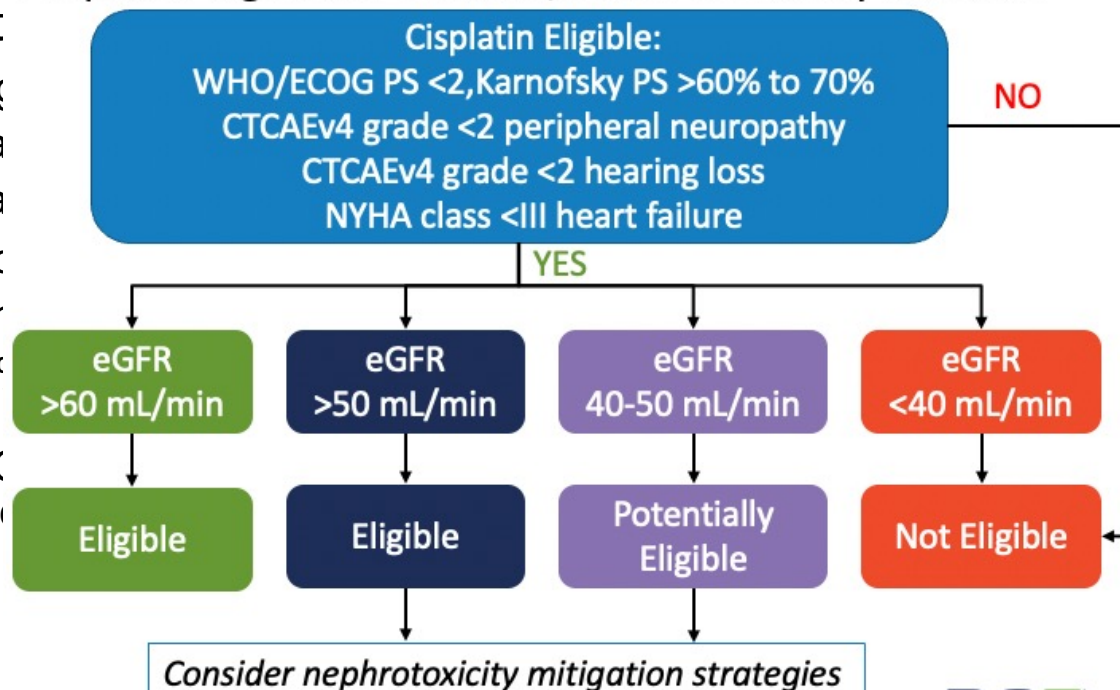
- Recurrence s/p treatment with curative intent (more common)
 - Abnormal imaging
 - Potential biopsy if needed
- *De novo* metastatic stage (less common)
 - Biopsy (TURBT, biopsy of suspicious lesions)
 - Urine cytology
 - Upper tract imaging (part of CT CAP or MRI)

s/p = status post; TURBT = trans urethral resection of bladder tumour; CT = computed tomography; CAP = chest, abdomen, pelvis; MRI = magnetic resonance imaging.

Therapeutic Approaches: Treatment Selection

Proposed algorithm in **MIBC**, based on kidney function

- Considerat
 - Physiolog
 - Performa
 - Prior trea
 - Medical c
 - Renal fur
 - Up to 50% ineligible due to EC hearing, (



cisplatin
JC
 y PS > 60-70%
 heral
 ing loss
 are

Tx = treatment; NYHA = New York Heart Association; CrCl = creatinine clearance; CTCAE = Common Terminology Criteria for Adverse Events; WHO = World Health Organization; eGFR = estimated glomerular filtration rate.
 Galsky MD, et al. *Lancet Oncol.* 2011;12(3):211-214. Jiang DM, et al. *Nat Rev Urol.* 2021;18(2):104-114.

Therapeutic Approaches:

NCCN

Cisplatin-

- Gemcitabine/cisplatin → switch maintenance if no progression
- Dose-dense methotrexate + vinorelbine + cisplatin → avelumab maintenance if no



ESMO

**atin-ineligible
preferred regimens)**

carboplatin → avelumab maintenance

avelumab (ineligible for any

avelumab + enfortumab vedotin

NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology.

Powles T, et al. *N Engl J Med*. 2020;383(13):1218-1230. Sternberg CN, et al. *J Clin Oncol*. 2001;19(10):2638-2646. Von der Maase H, et al. *J Clin Oncol*. 2000;18(17):3068-77. De Santis M, et al. *J Clin Oncol*. 2012;30(2):191-199. Powles T, et al. *N Engl J Med*. 2021;384(12):1125-1135. Holmes CJ, et al. *J Clin Oncol*. 2023;41(1):22-31.

Therapeutic Approaches: NCCN 2nd Line—Before ESMO

Post-platinum chemotherapy

- Pembrolizumab
- Erdafitinib (selected pts)
- Enfortumab vedotin
- *Nivolumab*
- *Avelumab*
- ~~Atezolizumab~~
- ~~Durvalumab~~

Post-checkpoint inhibitor

- Cisplatin-eligible/chemoTx-naïve
 - Gemcitabine/cisplatin
 - ddMVAC
- Cisplatin-ineligible/chemoTx-naïve
 - Enfortumab vedotin
 - Gemcitabine/carboplatin

Therapeutic Approaches: NCCN \geq 3rd Line—Before ESMO

Preferred

- Enfortumab vedotin
- Erdafitinib (selected pts)

Other

- Sacituzimab govitecan

- If pts already received platinum-based chemoTx and CPI (if eligible)
- Appropriate as 2nd line therapy for pts who received 1st line platinum-based chemoTx - > switch maintenance avelumab
- Subsequent Tx lines depend on prior therapies, ECOG PS, medical comorbidities, organ function, therapy burden, efficacy, toxicity, level of evidence, provider familiarity, patient preferences, tumor NGS testing, among other factors

CPI = checkpoint inhibitor; NGS = next-generation sequencing.

Powles T, et al. *N Engl J Med.* 2021;384(12):1125-1135. Rosenberg JE, et al. *J Clin Oncol.* 2019;37(29):2592-2600. Tagawa ST, et al. *J Clin Oncol.* 2021;39(22):2474-2485.



Therapeutic Approaches: Sequencing

Challenges

- Selecting the optimal sequence for a patient
- Medical comorbidities, poor ECOG PS
- Long-term survival with combination chemo reported in good-risk patients (excellent PS, no visceral or bone mets, normal albumin/nutrition)
- Not all pts achieve benefit from chemotherapy and ICI, making treatment selection and optimal sequencing complex and often challenging
- ICI efficacy may be influenced by various factors, including PD-L1 status, TMB, metastatic site, patient characteristics, further complicating treatment selection (we lack accurate predictive biomarkers despite extensive studies in that field)

Chemotherapeutic agents*

- Gemcitabine/cisplatin
- Methotrexate, vinblastine, doxorubicin, cisplatin
- Gemcitabine/carboplatin
- Paclitaxel or docetaxel

Immune checkpoint inhibitors

- PD-1 inhibitors
 - Pembrolizumab
 - Nivolumab
- PD-L1 inhibitors
 - Avelumab

Other Agents

- Erdafitinib (FGFR inhibitor)
- Enfortumab-vedotin
- Sacituzumab govitecan

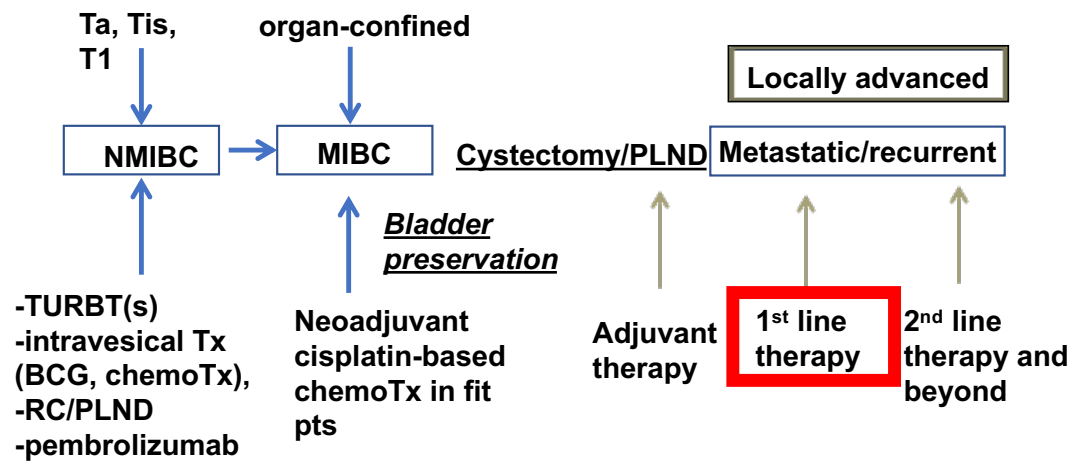
*Not an all-inclusive list.

ICI = immune checkpoint inhibitor; PD-L = programmed death-ligand; TMB = tumor mutational burden; FGFR = fibroblast growth factor receptor.

Data Review: First Line Therapeutic Approaches

Petros Grivas, MD

Disease/Treatment Settings



NMIBC = non-muscle-invasive bladder cancer; MIBC = muscle-invasive bladder cancer; BCG = Bacillus Calmette-Guerin; RC = radical cystectomy; PLND = pelvic lymph node dissection.

Metastatic Disease (1st Line)

- Comparable ORR between GC and “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 $\frac{3}{4}$ AEs with GC, eg 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 and better than older “classic” MVAC)

ORR = objective response rate; GC = gemcitabine plus cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; OS = overall survival; AE = adverse event.

Von der Maase H, et al. *J Clin Oncol*. 2000;18(17):3068-3077.

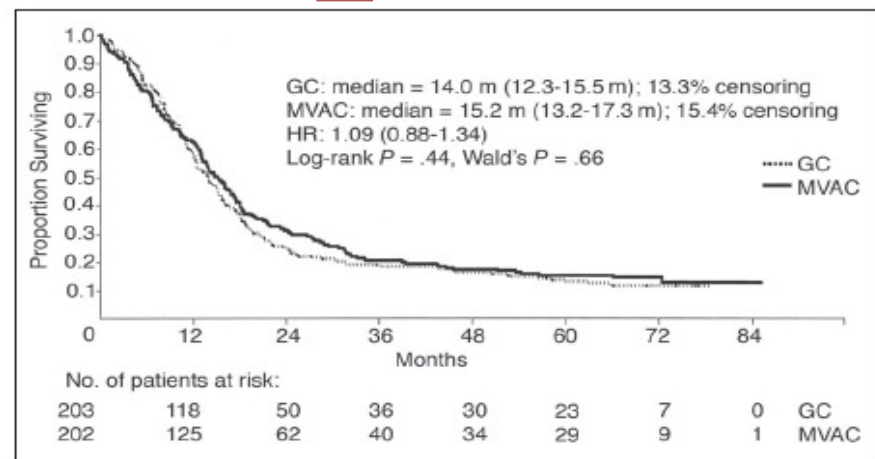
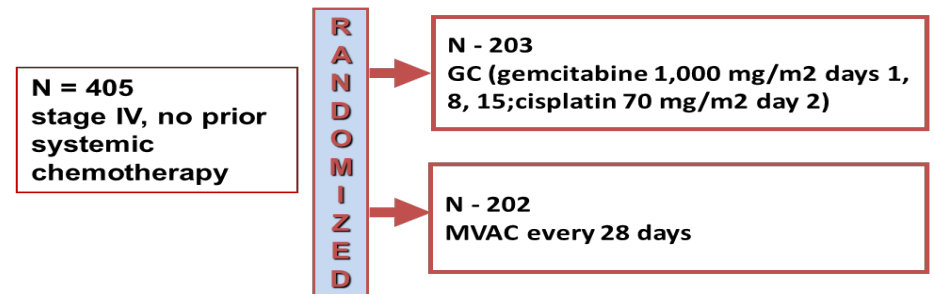


Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

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

Shilpa Gupta¹, Joaquim Bellmunt², Elizabeth R. Plimack³, Guru P. Sonpavde⁴, Petros Grivas⁵, Andrea B. Apolo⁶, Sumanta K. Pal⁷, Arlene O. Siefker-Radtke⁸, Thomas W. Flaig⁹, Matt D. Galsky¹⁰, Jonathan E. Rosenberg¹¹

Platinum-Ineligibility in Bladder Cancer Working Group

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

Background:

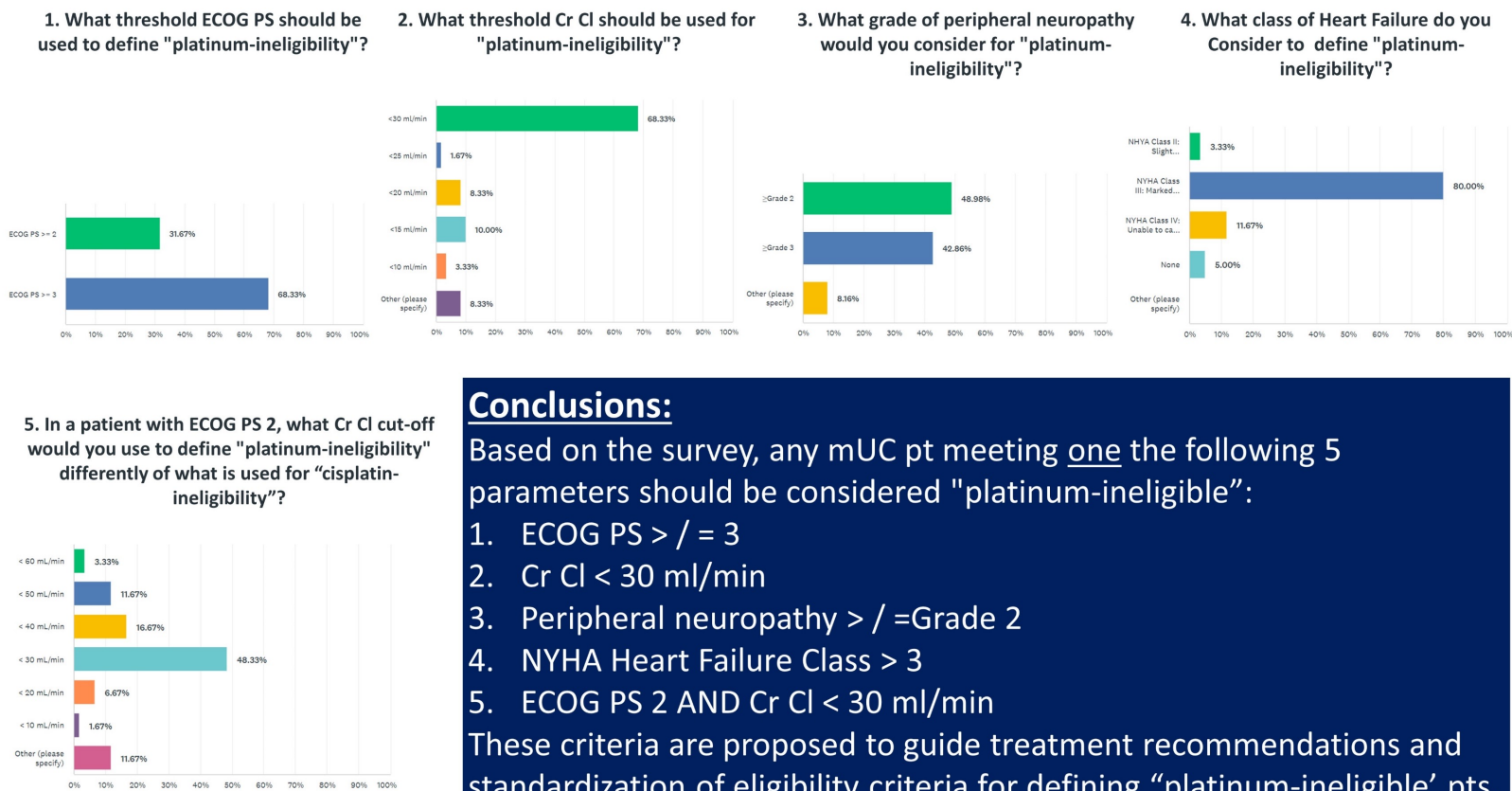
- Carboplatin and gemcitabine followed by avelumab maintenance is the current preferred treatment (tx) for cisplatin-ineligible patients (pts) with mUC.
- Although pembrolizumab (P) and atezolizumab (At) were approved as 1L tx for these pts in 2017, the FDA has now restricted the use of 1L P to “platinum 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”



Conclusions:

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

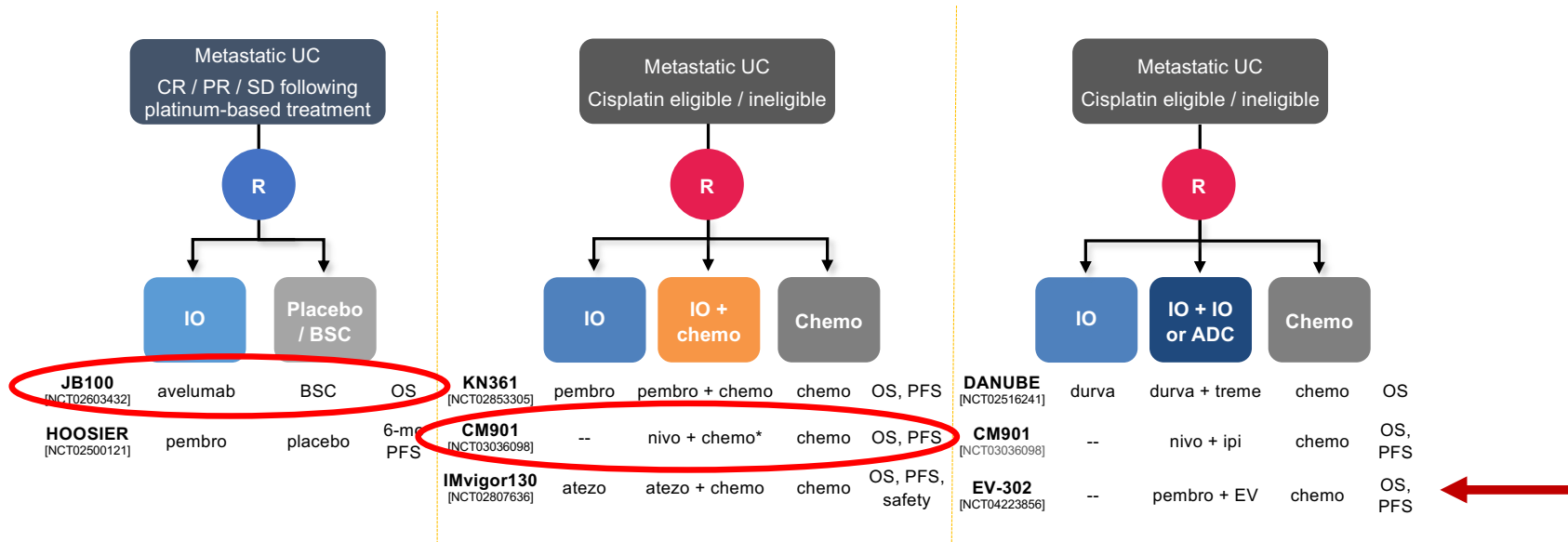
1. ECOG PS > / = 3
2. Cr Cl < 30 ml/min
3. Peripheral neuropathy > / =Grade 2
4. NYHA Heart Failure Class > 3
5. ECOG PS 2 AND Cr Cl < 30 ml/min

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

Acknowledgement: All the respondents who completed the survey

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

Different Strategies Aiming to Impact 1L SoC

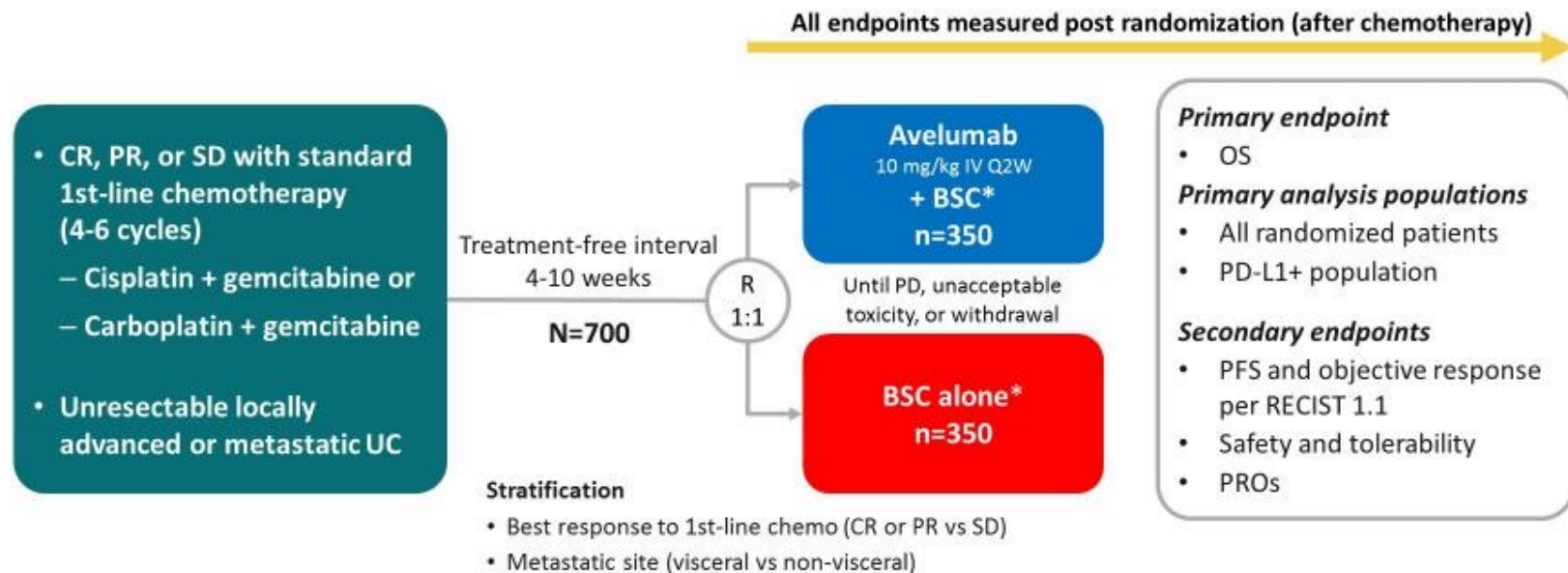


*For cisplatin-eligible patients only.

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 = randomization; SD = stable disease; SoC = standard of care; treme = tremelimumab; UC = urothelial carcinoma.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated June 6, 2023. <https://clinicaltrials.gov/study/NCT02603432>. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 30, 2022. <https://clinicaltrials.gov/study/NCT02500121>. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 8, 2023. <https://clinicaltrials.gov/study/NCT02853305>. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated November 6, 2023. <https://clinicaltrials.gov/study/NCT03036098>. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated June 9, 2023. <https://clinicaltrials.gov/study/NCT02807636>. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 13, 2023. <https://clinicaltrials.gov/study/NCT02516241>. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated November 1, 2023. <https://clinicaltrials.gov/study/NCT04223856>.

JAVELIN Bladder 100 Study Design (NCT02603432)



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

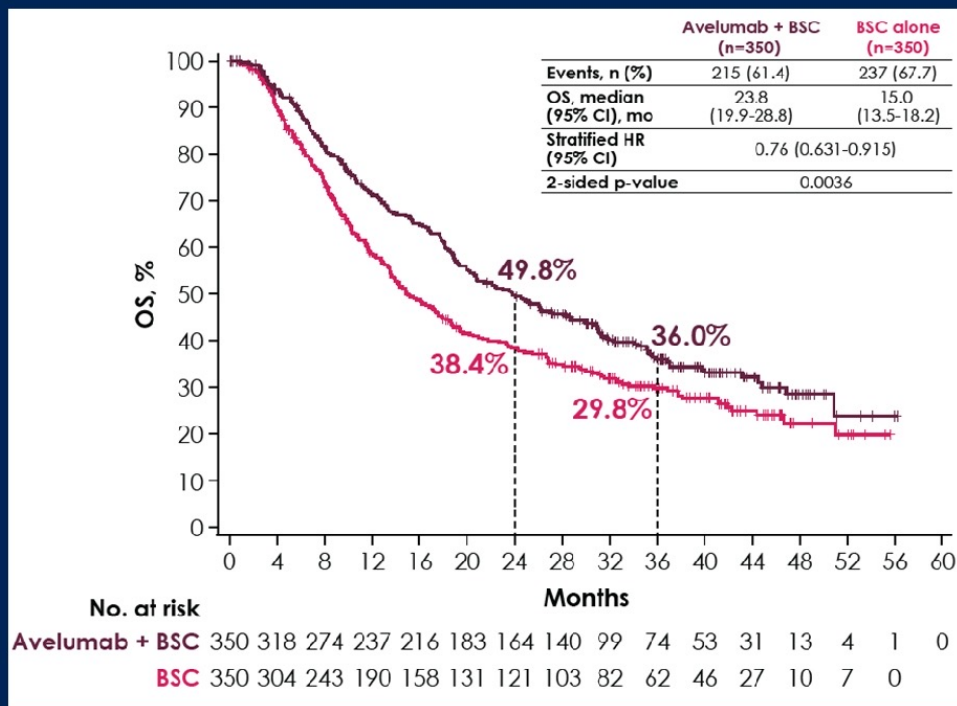
BSC, best supportive care; **CR**, complete response; **IV**, intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W**, every 2 weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*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

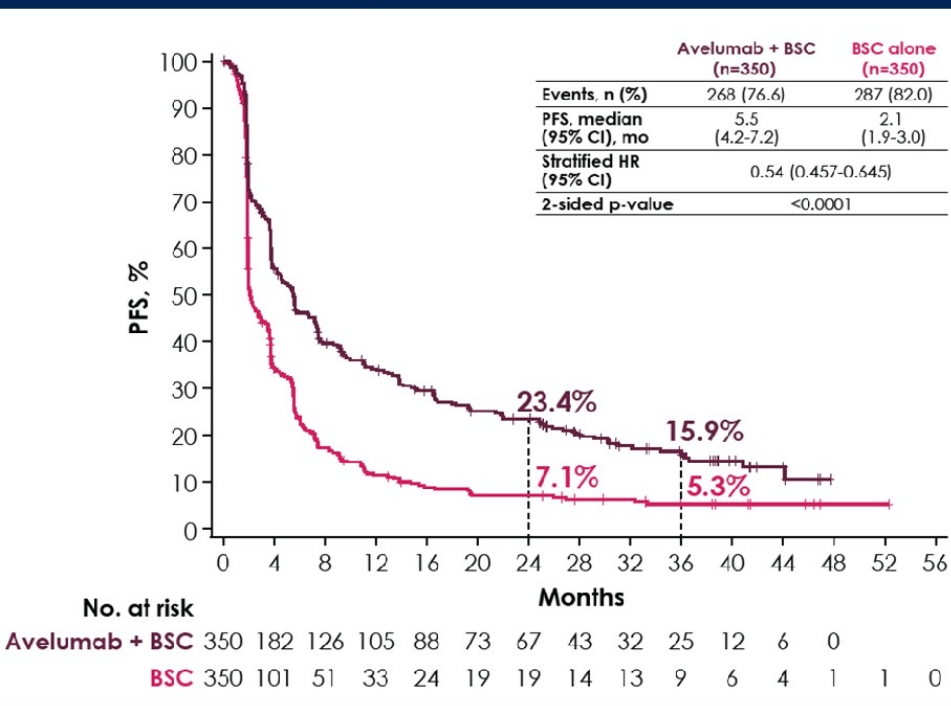
Powles T. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; virtual.

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

OS

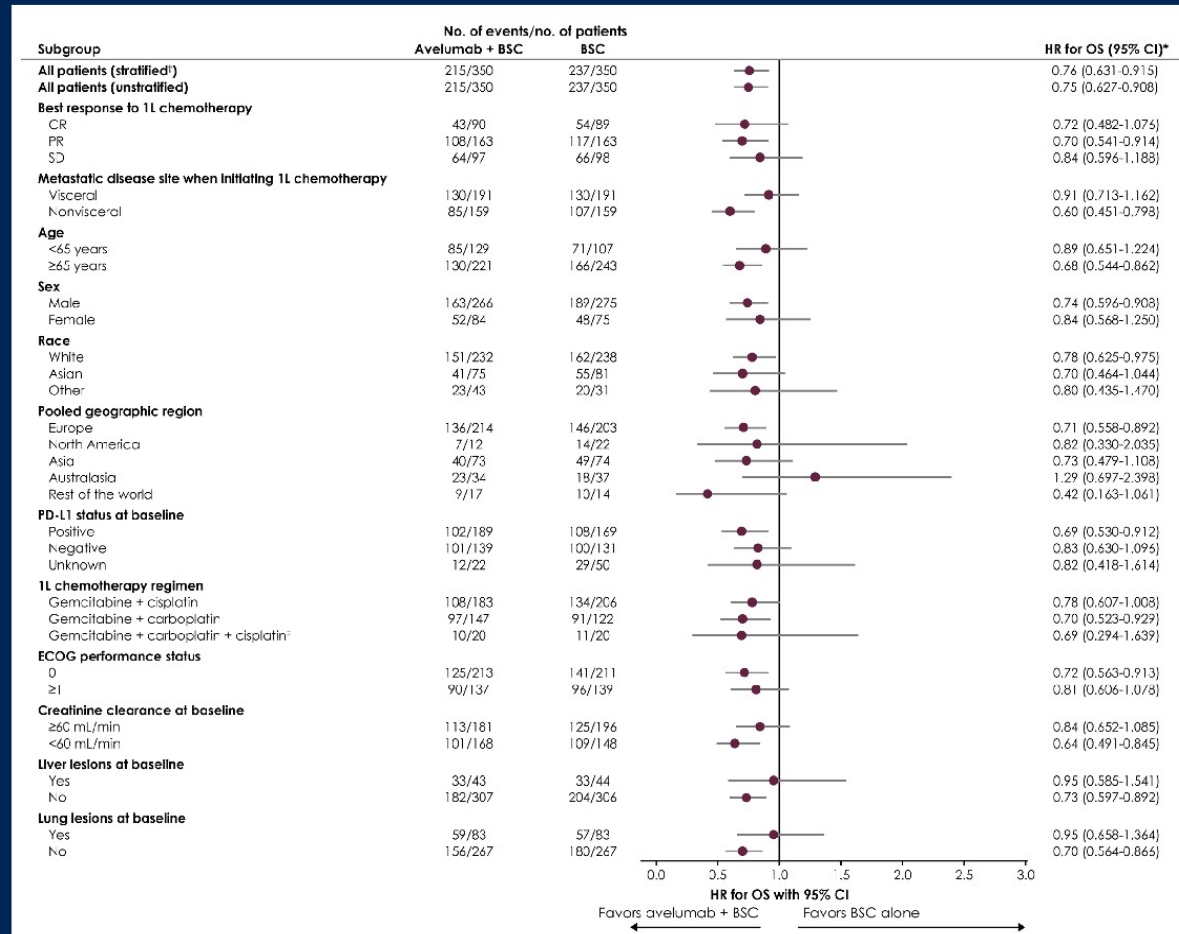


Investigator-assessed PFS



HR, hazard ratio.

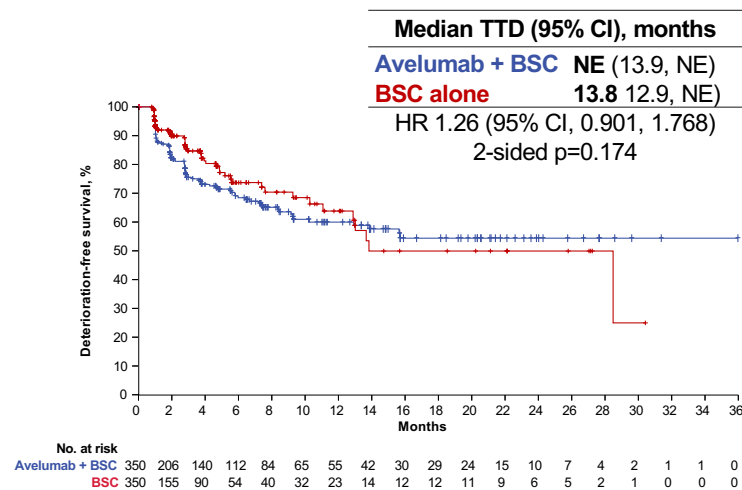
OS favored avelumab + BSC vs BSC alone across subgroups



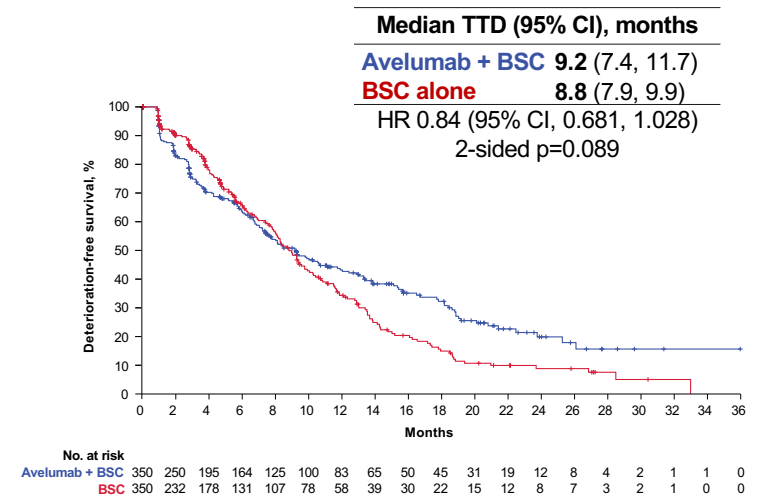
ECOG, Eastern Cooperative Oncology Group. *HRs and CIs were calculated using a Cox proportional hazards model. †Stratified by best response to 1L chemotherapy (CR or PR vs SD) and metastatic disease site when initiating 1L chemotherapy (visceral vs nonvisceral). ‡Patients who switched platinum regimens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

TTD in FBISI-18 DRS-P Scores (A) and TTD in FBISI-18 DRS-P Scores or Death (B) in the Overall Population

A



B



Crossing of curves, inconsistency between HRs, and differences in median TTD suggest that HRs may be nonproportional; therefore results should be interpreted with caution.

NE = not estimable; FBISI = The National Comprehensive Cancer Network FACT Bladder Symptom Index; DRS-P = Disease-Related Symptoms-Physical; TTD = time to deterioration.

Grivas P, et al. *Eur Urol.* 2023;83(4):320-328.

Study Design (NIVO+GC vs GC in Cisplatin-Eligible Patients)^a

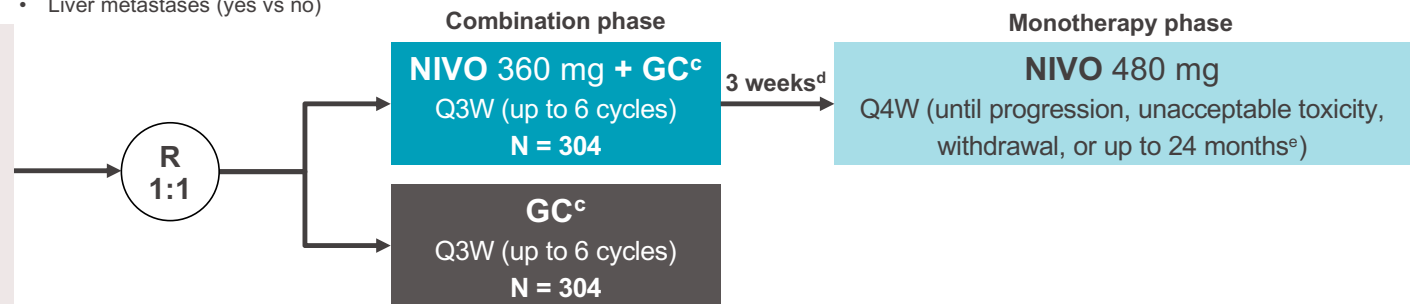
Stratification factors:

- Tumor PD-L1 expression ($\geq 1\%$ vs $< 1\%$)
- Liver metastases (yes vs no)

Key inclusion criteria

- Age ≥ 18 years
- Previously untreated unresectable or mUC involving the renal pelvis, ureter, bladder, or urethra
- Cisplatin eligible^b
- ECOG PS of 0-1

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 $\geq 1\%$, HRQoL

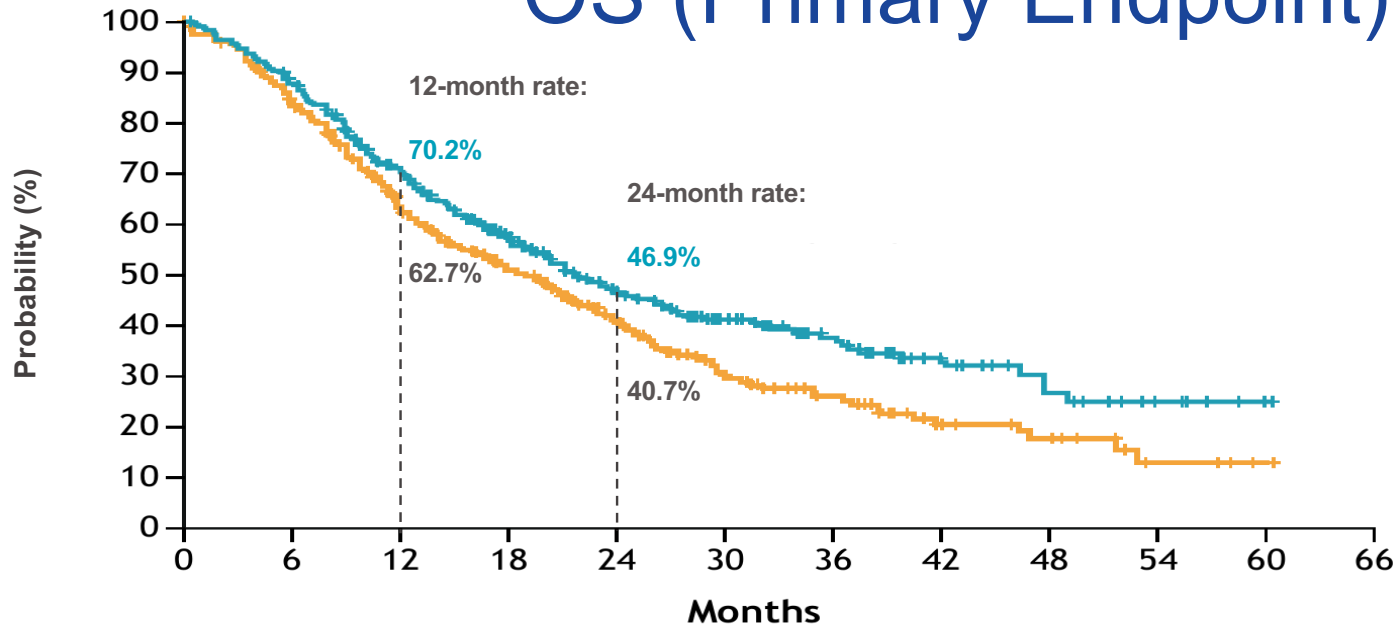
Key exploratory endpoints: ORR per BICR, safety

^aFurther CheckMate 901 study design details are available at <https://clinicaltrials.gov/ct2/show/NCT03036098>. ^bCisplatin 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. ^cPatients who discontinued cisplatin alone could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to six cycles in total). ^dNIVO monotherapy should begin 3 weeks after the last dose of NIVO+GC combination. ^eRepresents a maximum of 24 months from the first dose of NIVO administered as part of the NIVO+GC combination.

BICR = blinded independent central review; HRQoL = health-related quality of life; Q \times W, every \times weeks.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated November 6, 2023. <https://clinicaltrials.gov/study/NCT03036098>.

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		

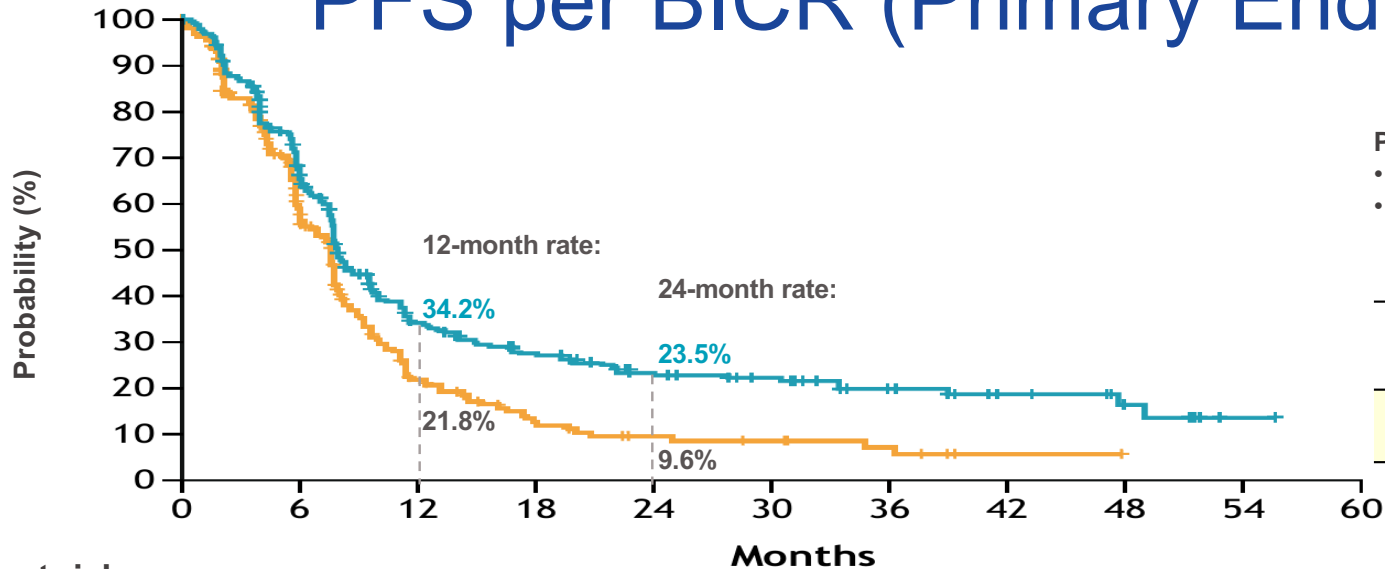
No. at risk

	0	6	12	18	24	30	36	42	48	54	60	66
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.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated November 6, 2023. <https://clinicaltrials.gov/study/NCT03036098>.

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) <i>P</i> = 0.0012		

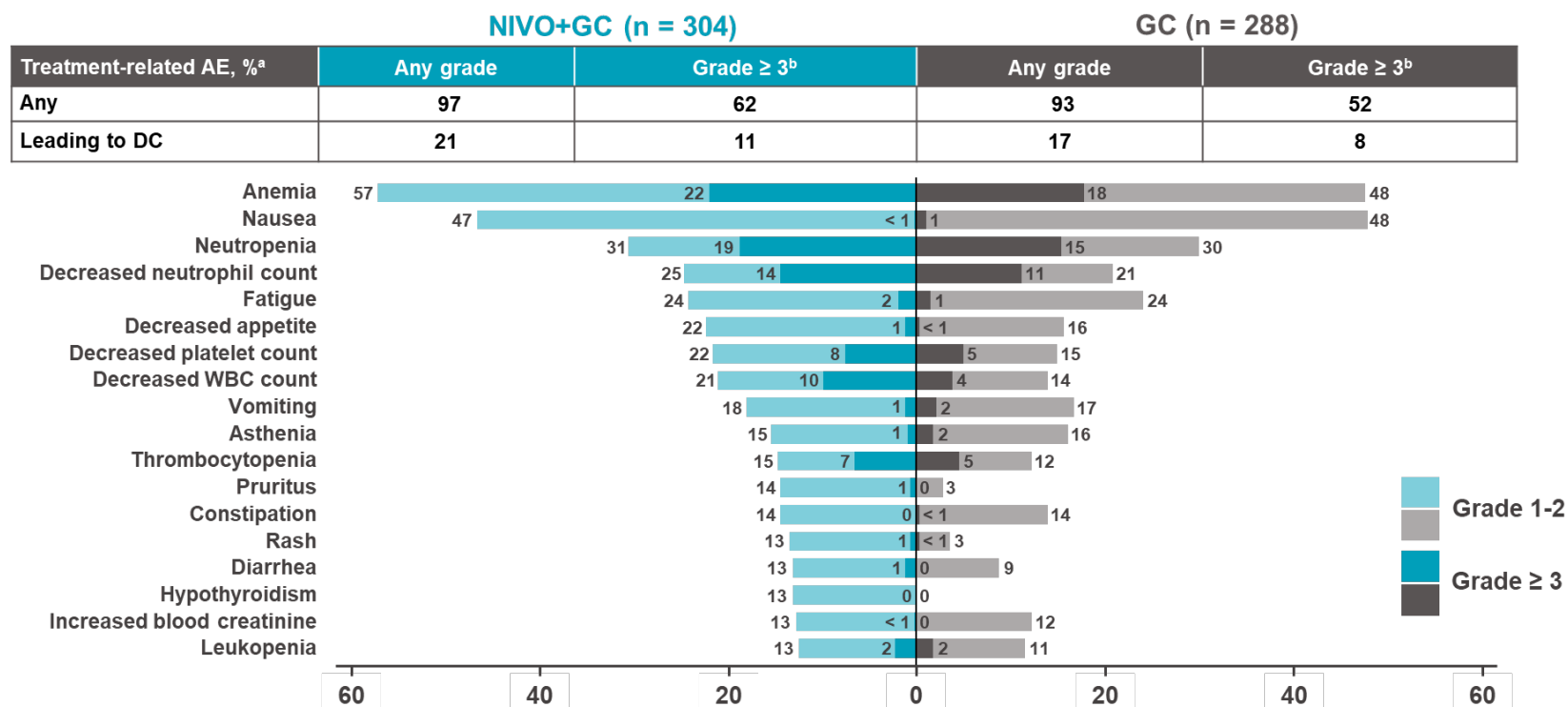
No. at risk

	0	6	12	18	24	30	36	42	48	54	60
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.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated November 6, 2023. <https://clinicaltrials.gov/study/NCT03036098>.

Treatment-Related AEs in All Treated Patients



^aIncludes 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. ^bOne 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.

DC = discontinuation; WBC = white blood cell.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated November 6, 2023. <https://clinicaltrials.gov/study/NCT03036098>.

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

DoCR = duration of complete response.

Cohort K: 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)

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

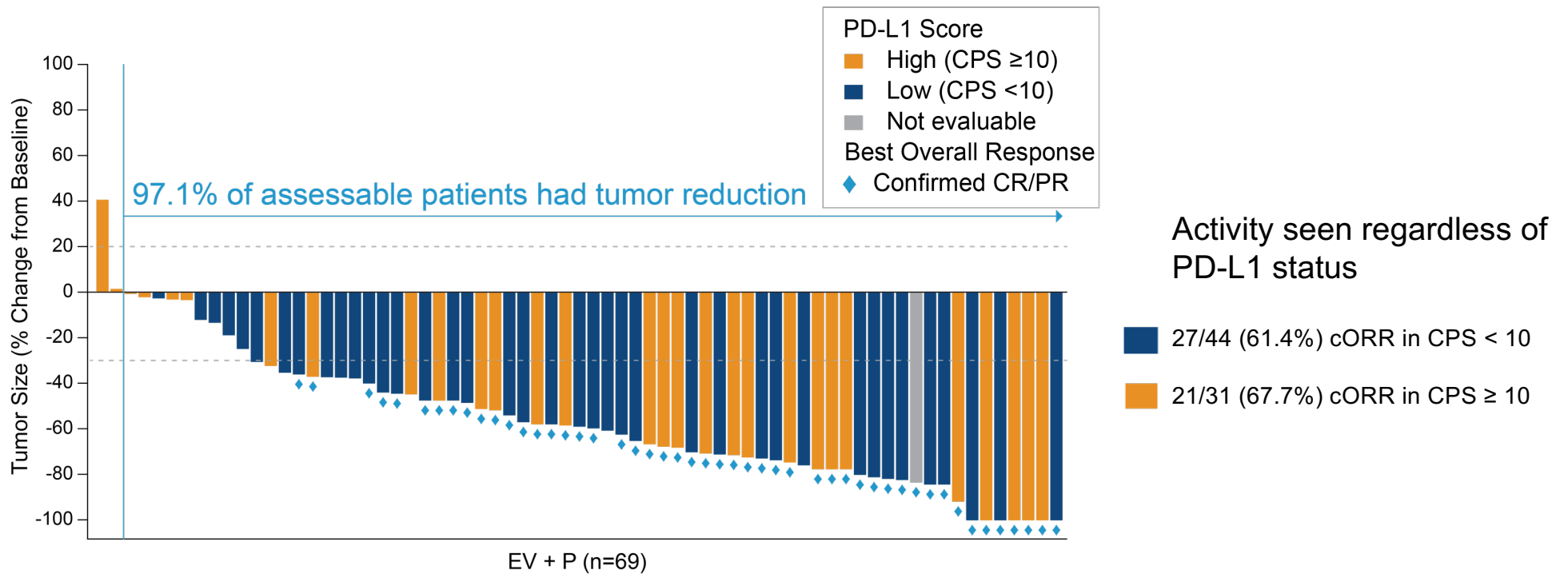
- Activity is consistent with prior results in 2L+ la/mUC

Data cutoff: June 10, 2022.

cORR = confirmed objective response rate; NR = not reached; EV = enfortumab vedotin; P = pembrolizumab; 2L = second-line; la = locally advanced.

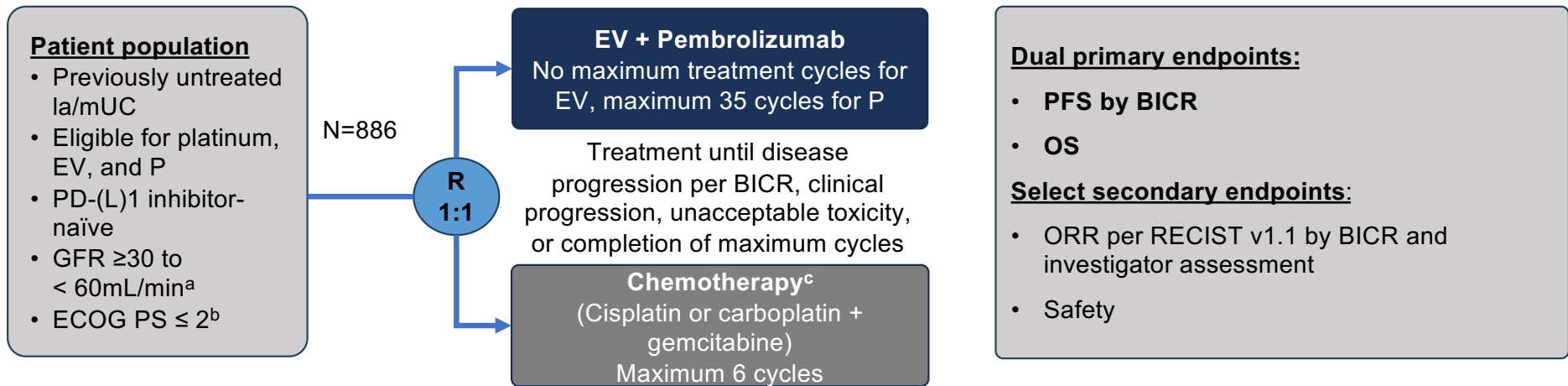
Rosenberg JE. Presented at European Society for Medical Oncology (ESMO) Congress; September 9-13, 2022; Paris, France. Abstract LBA73.

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



CPS = combined positive score.
 Rosenberg JE. ESMO Congress; September 9-13, 2022; Paris, France. Abstract LBA73.

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

Data cutoff: August 8, 2023; FPI: April 7, 2020, LPI: November 9, 2022.

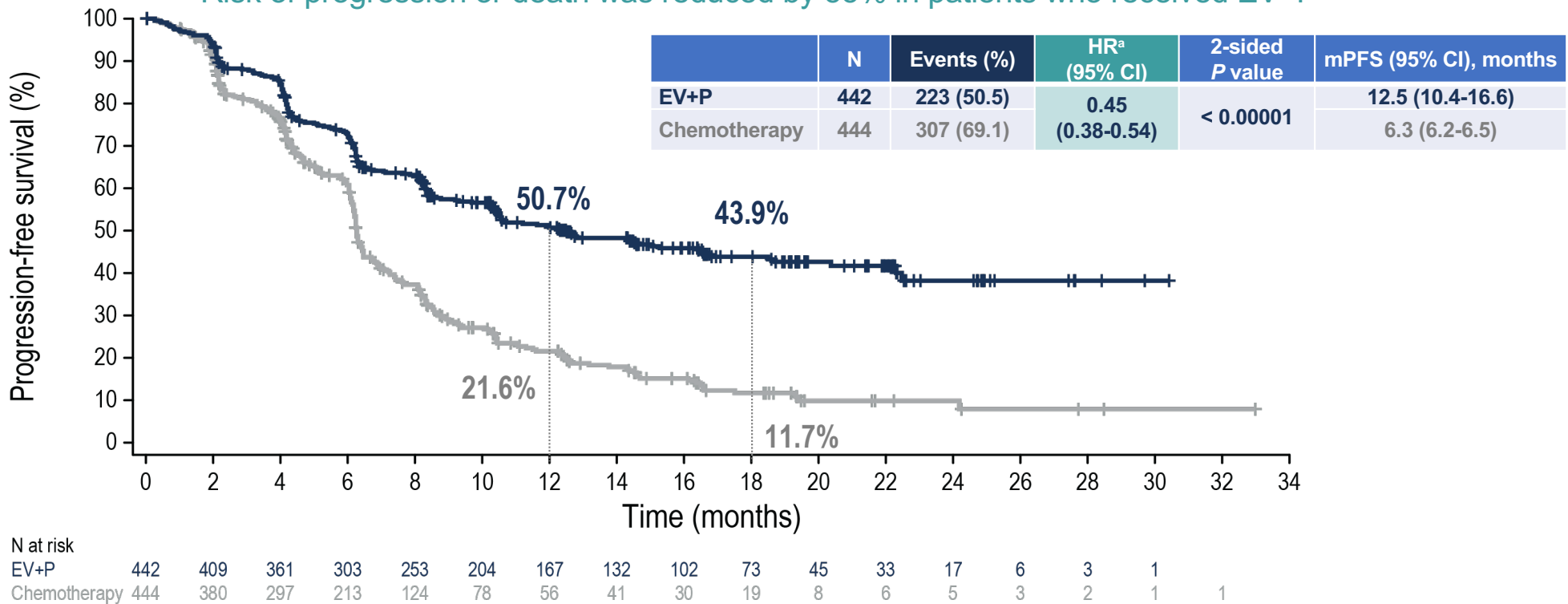
^aMeasured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine. ^bPatients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥ 10 g/dL, GFR ≥ 50 mL/min, may not have NYHA class III heart failure. ^cMaintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy.

FPI = first patient in; LPI = last patient in.

Powles T, et al. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA6.

Progression-Free Survival per BICR

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



Data cutoff: August 8, 2023. PFS at 12 and 18 months as estimated using Kaplan-Meier method.

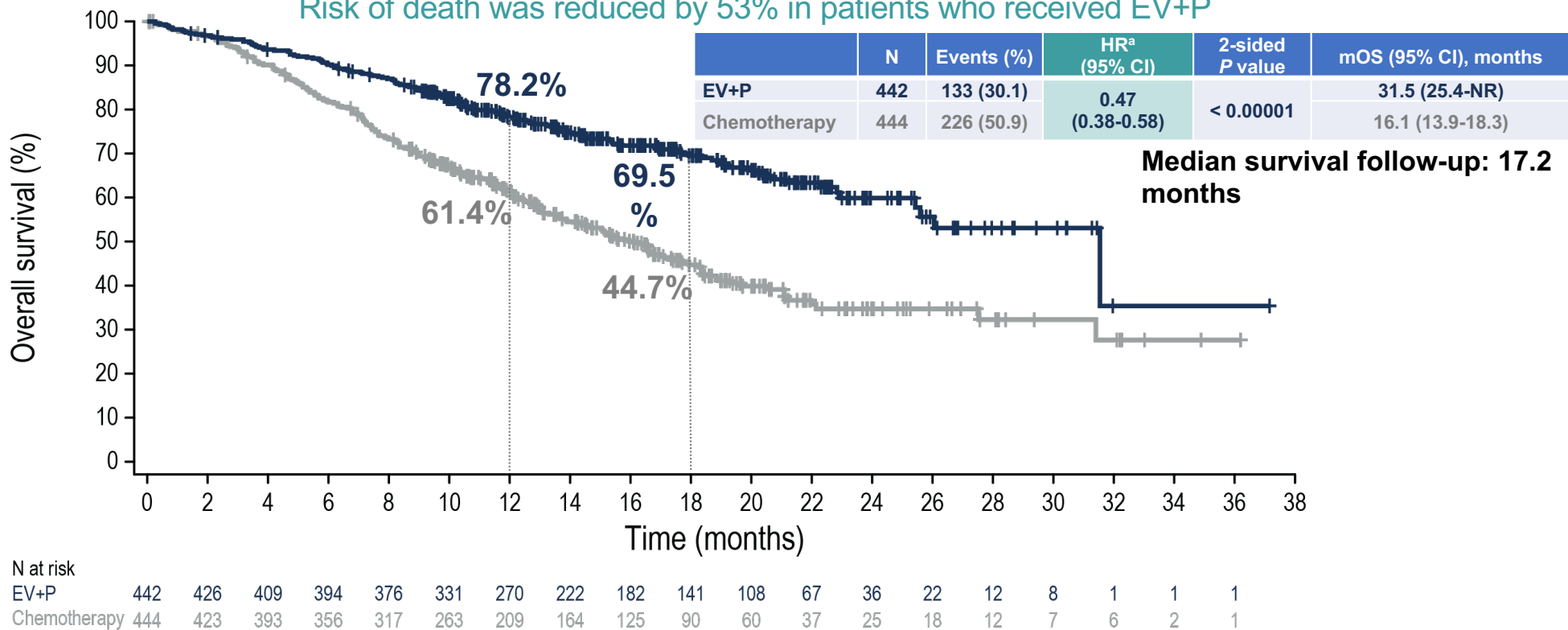
^aCalculated using stratified Cox proportional hazards model; a hazard ratio < 1 favors the EV+P arm.

mPFS = median progression-free survival.

Powles T, et al. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA6.

Overall Survival

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



Data cutoff: August 8, 2023. OS at 12 and 18 months was estimated using Kaplan-Meier method.

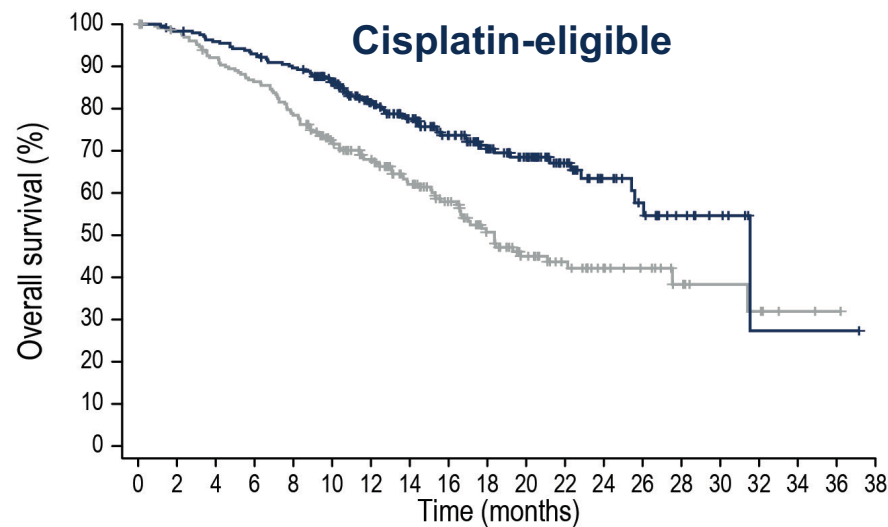
^aCalculated using stratified Cox proportional hazards model; a hazard ratio < 1 favors the EV+P arm.

mOS = median overall survival.

Powles T, et al. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA6.

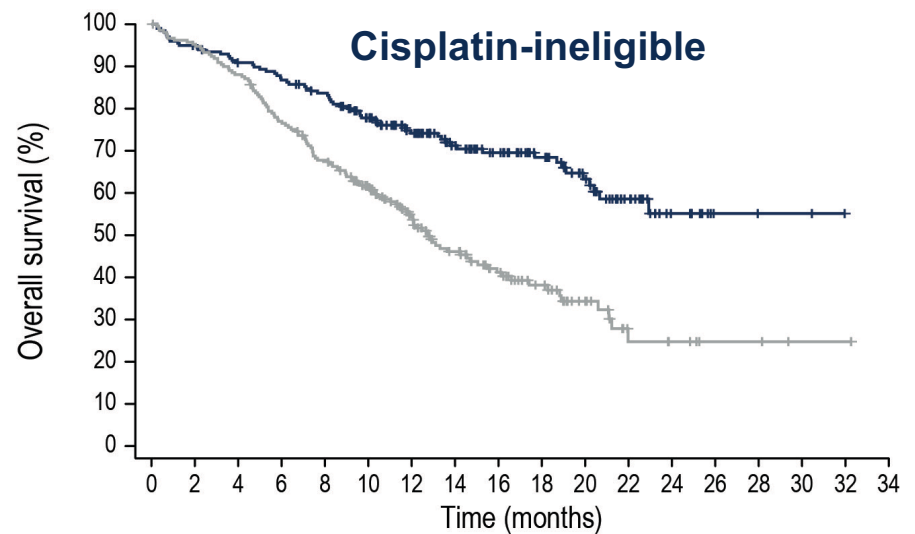
OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility



N at risk	
EV+P	244 239 232 225 216 193 155 131 105 80 64 42 25 19 10 6 1 1 1
Chemotherapy	234 224 209 196 178 147 123 101 79 57 40 29 19 15 9 6 5 2 1

	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	69	0.53 (0.39-0.72)	31.5 (25.4-NR)
Chemotherapy	106		18.4 (16.4-27.5)



N at risk	
EV+P	198 187 177 169 160 138 115 91 77 61 44 25 11 3 2 2
Chemotherapy	210 199 184 160 139 116 86 63 46 33 20 8 6 3 3 1 1

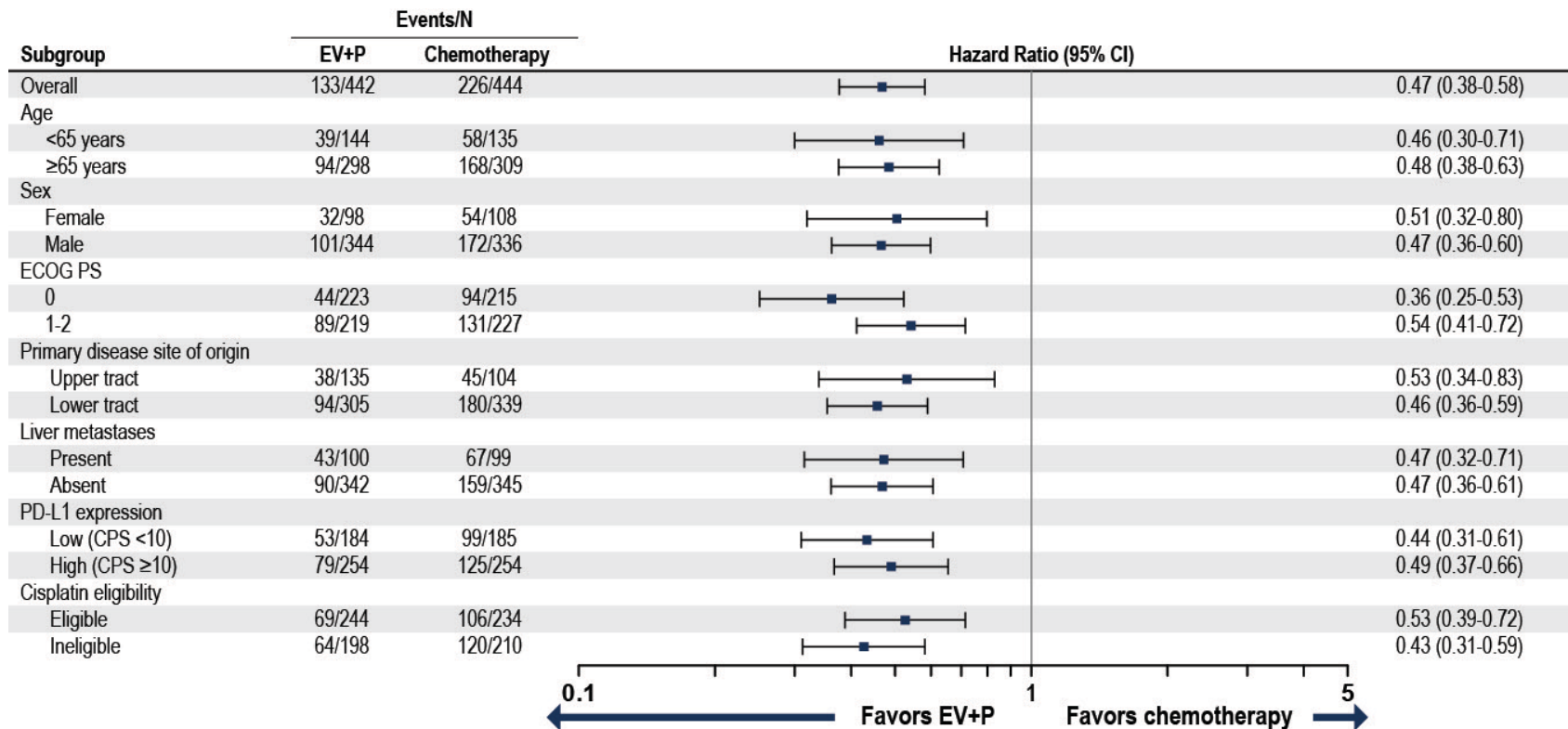
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43 (0.31-0.59)	NR (20.7-NR)
Chemotherapy	120		12.7 (11.4-15.5)

Data cutoff: August 8, 2023.

Powles T, et al. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA6.

Subgroup Analysis of OS

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

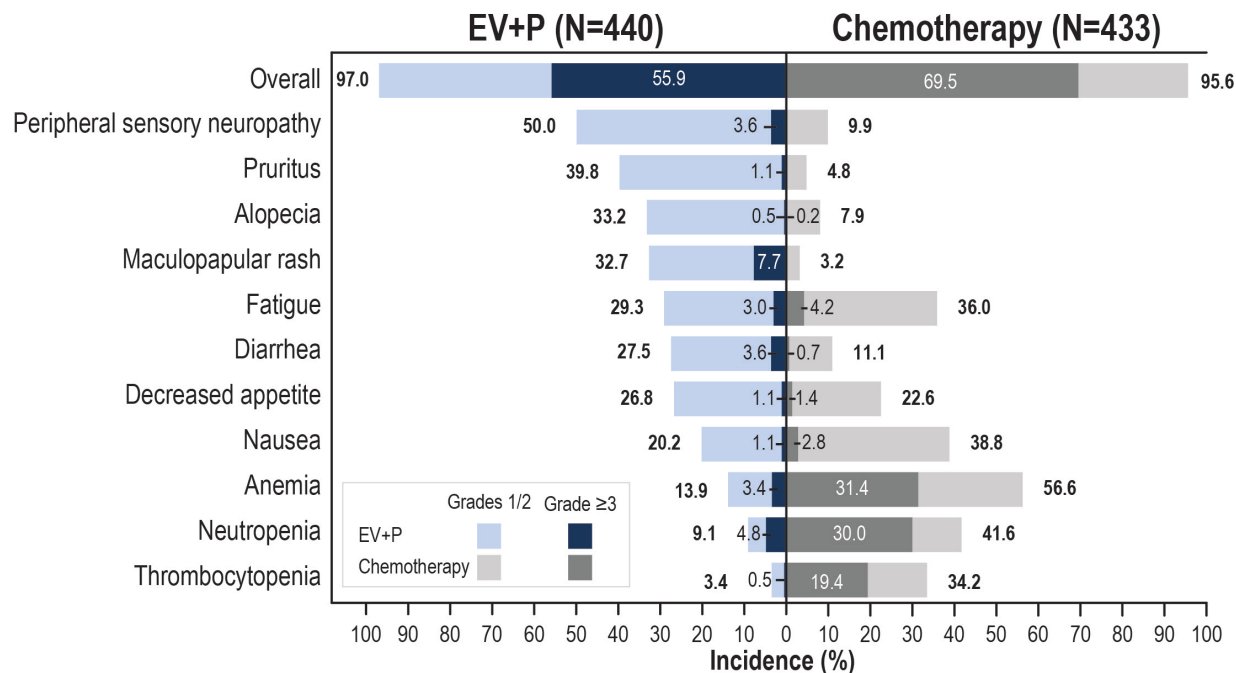


Data cutoff: August 8, 2023.

Powles T, et al. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA6.

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: August 8, 2023. 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.

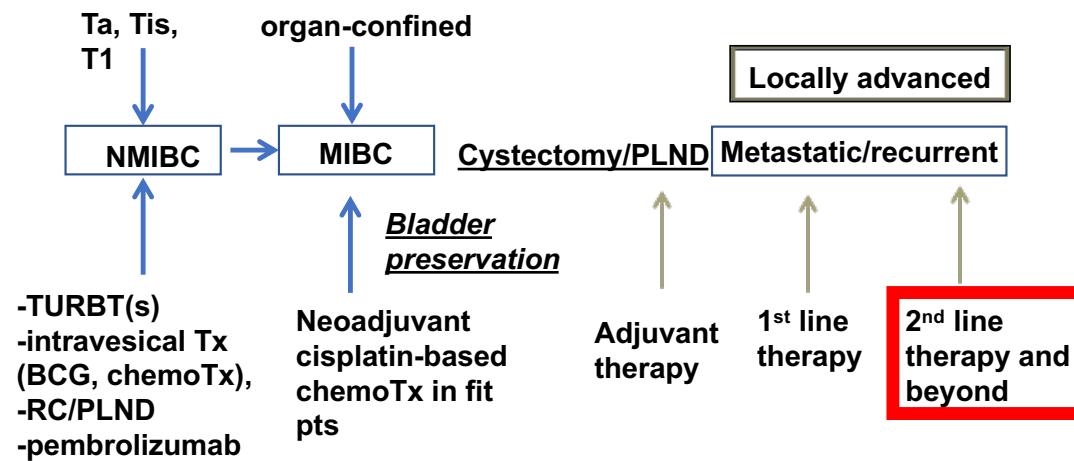
Powles T, et al. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA6.

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
 - What treatment then becomes the best second-line therapy?
 - Can we dose de-escalate EV, in EV+pembro?
 - What is the underlying biology leading to the great response and OS, and how do we build on this?
 - What is the efficacy of EV+pembro in earlier states of disease (MIBC and NMIBC)?
 - EV+pembro is expensive; will patients, insurance, and public systems be able to afford this treatment?
 - **What about patients who received anti-PD(L)1 in prior therapy setting? Timing of progression matters?**

Data Review: Second Line Therapeutic Approaches and Beyond

Disease/Treatment Settings

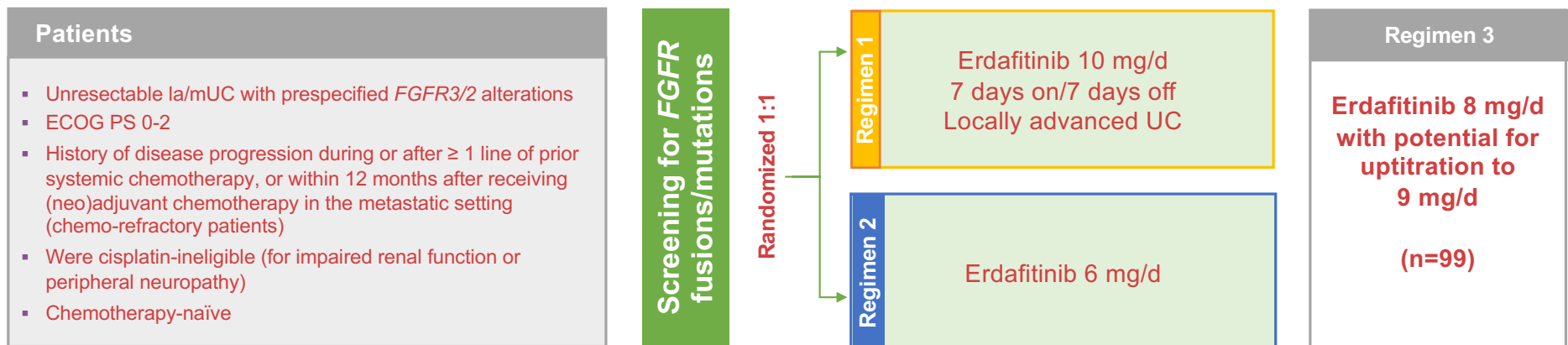


	Atezolizumab ¹	Nivolumab ²	Pembrolizumab ³	Avelumab ⁴	Durvalumab ⁵
Phase	Phase III Randomized vs chemotherapy	Phase II Single Arm	Phase III Randomized vs Chemotherapy	Phase Ib	Phase I/II
Number of Patients	931	265	542	249 (161 pts ≥ 6 mos f/u)	191
Dosing	1200mg every 3 weeks	3mg/kg every 2 weeks	200mg 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%

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

BLC2001: Phase 2 Trial of Erdafitinib

Fifteen percent of patients with MIBC have *FGFR* alterations



Primary endpoint

- Confirmed ORR

Secondary endpoints

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

FGFR Alterations (n=99)

<i>FGFR2</i> or <i>FGFR3</i> fusion, no. (%)	25 (25)
<i>FGFR3</i> mutation, no. (%)	74 (75)
<i>FGFR2/3</i> fusions and mutations	0

DOR = duration of response; PK = pharmacokinetic.

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

BCL2001: Efficacy

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

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

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

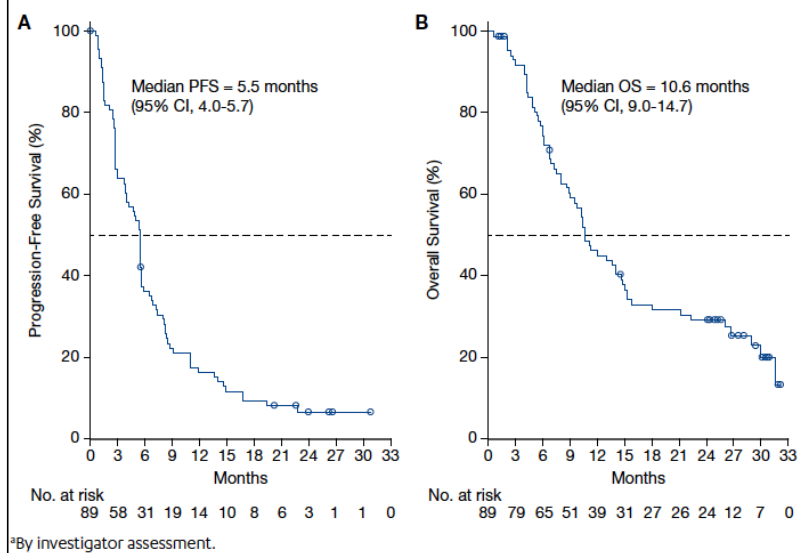


Table 2. Efficacy Outcomes by Subgroup

	n	Median DoR ^b , mo	n ^b	Median PFS ^a , mo	Median OS, mo
FGFR alteration					
<i>FGFRm</i> +/-	33	6.0	70	5.6	12.0
<i>FGFRm</i> -/+	4	6.2	25	2.8	10.3
<i>FGFRm</i> +/+	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

^aBy investigator assessment. ^bFor PFS and OS.

Loriot Y, et al. *N Engl J Med.* 2019;381(4):338-348. Necchi A, et al. Presented at: ESMO Congress; September 19-21, 2020; virtual. Abstract 750P.

Novel Therapy: Erdafitinib Clinical Pearls

- Novel mechanism of action (MOA), 1st targeted therapy and orally available option in UC treatment
 - MOA: Pan-FGFR inhibitor (FGFR 1-4)
 - Approved for FGFR 2-3 mutations or fusions
- 8 mg PO daily (w/ or w/o food) with dose increase to 9 mg daily if criteria are met
 - Day 14-21 phosphorus < 5.5 mg/dL
 - No ocular disorders
 - No grade ≥ 2 AEs
- Increase occurred in 41% of pts
- Restricted distribution (specialty pharmacy): tablets: 3 mg, 4 mg, 5 mg

Adverse Reaction (8 mg/day)	All Grade (%)	Grade 3-4 (%)
Any	100	67
Gastrointestinal disorders	92	24
Metabolism and nutrition disorders	90	16
General disorders and admin. site conditions	69	13
Skin and subcutaneous disorders	75	16
Eye disorders	62	11
Nervous system disorders	57	5
Infections and infestations	56	20
Respiratory, thoracic, and mediastinal disorders	40	7
Renal and urinary tract disorders	38	10
Musculoskeletal and connective tissue disorders	31	0

PO = by mouth.

US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed September 30, 2021.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212018s000lbl.pdf.

Erdafitinib Ocular Toxicity

- Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) was reported in 25% of patients
 - First onset of 50 days
 - Grade 3 in 3% of patients
 - Usually resolves or improves after dose hold
 - Ongoing in 13% of patients at the study cutoff
 - 9% dose interruptions, 14% reductions, 3% discontinuations
- Dry eye symptoms occurred in 28% of patients, with grade 3 in 6% of patients
 - All patients should receive dry eye prophylaxis with ocular demulcents as needed
- Monthly ophthalmological examinations during the first 4 months of treatment, every 3 months afterwards, and urgently at any time for visual symptoms
 - Assessment of visual acuity, slit lamp examination, fundoscopy, optical coherence tomography



Toxicity Management of Erdafitinib

Dosing in Hyperphosphatemia

5.6-6.9 mg/dL (1.8-2.3 mmol/L)	Continue
7.0-9.0 mg/dL (2.3-2.9 mmol/L)	Assess weekly and resume normal dose once < 5.5 mg/dL or baseline; may dose reduce by 1 level if abnormal by > 1 week
> 9.0 mg/dL (> 2.9 mmol/L)	Assess weekly and resume at 1 dose level lower once < 5.5 mg/dL or baseline
> 10.0 mg/dL (> 3.2 mmol/L) or significant impairment in renal function or grade 3 hypercalcemia	Assess weekly and resume at 2 dose levels lower once <5.5 mg/dL or baseline

Dose Reduction Levels

Dose	1st reduction	2nd reduction	3rd reduction	4th reduction	5th reduction
9 mg →	8 mg	6 mg	5 mg	4 mg	Stop
8 mg →	6 mg	5 mg	4 mg	Stop	

Dosing in CSR/RPED

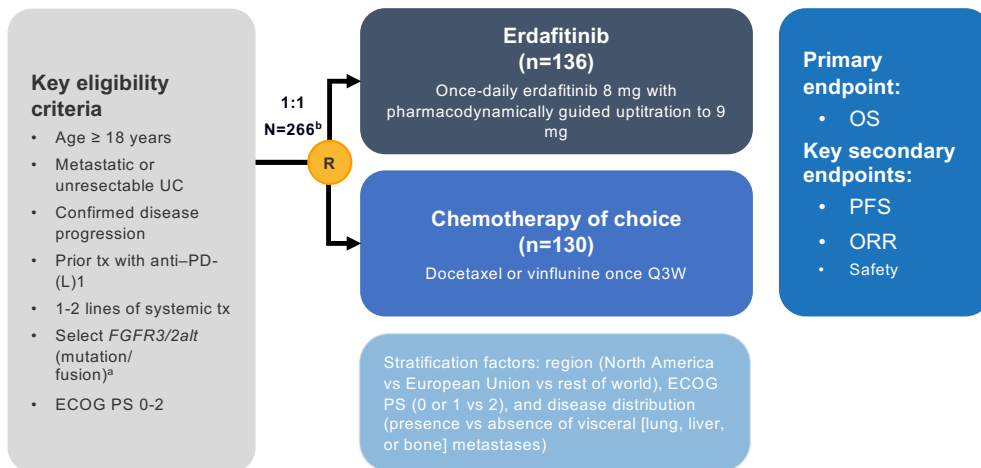
Grade 1: Asymptomatic; clinical or diagnostic observations only	<ul style="list-style-type: none"> Withhold until resolution; if resolves within 4 weeks, resume at the next lower dose level If no recurrence for a month, consider re-escalation If stable for 2 consecutive eye exams but not resolved, resume at the next lower dose level
Grade 2: Visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline	Withhold until resolution; if resolves within 4 weeks, may resume at the next lower dose level
Grade 3: Visual acuity worse than 20/40 or > 3 lines of decreased vision from baseline	<ul style="list-style-type: none"> Withhold until resolution; if resolves within 4 weeks, may resume 2 dose levels lower If recurs, consider permanent discontinuation
Grade 4: Visual acuity 20/200 or worse in affected eye	Permanently discontinue

US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed September 30, 2021.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212018s000lbl.pdf.

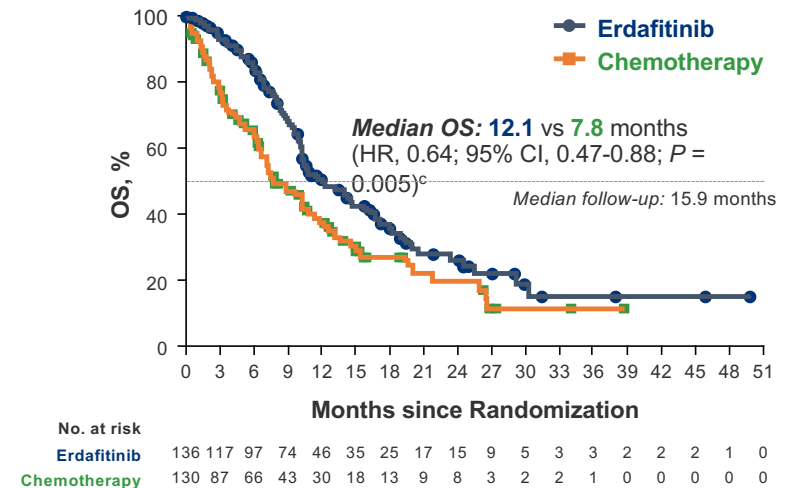
THOR Cohort 1: Erdafitinib versus Investigator's Choice of Chemotherapy in Patients with *FGFR*-Altered mUC

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



- **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; $P<0.001$)

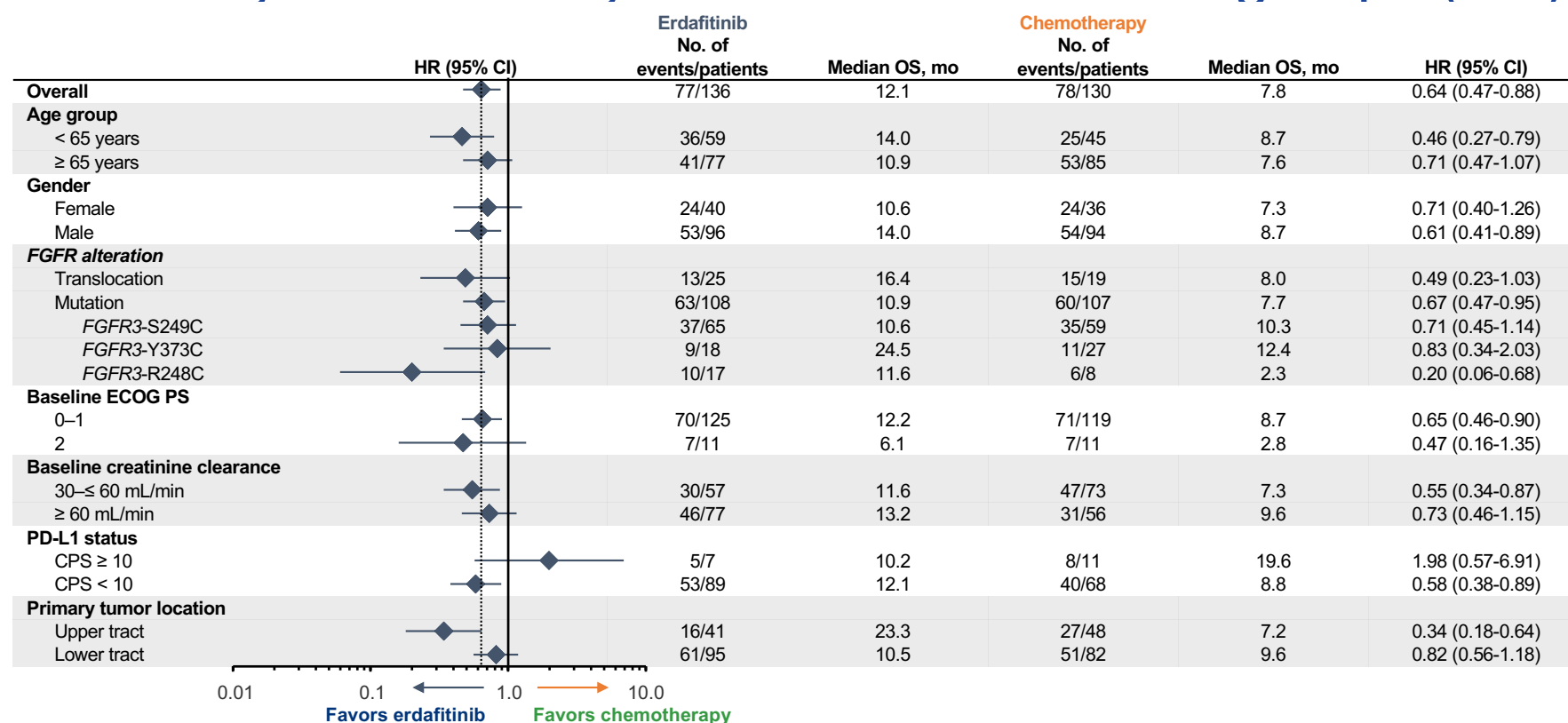
^aMolecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have \geq 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; ^bNumber of patients randomized at the time of the interim analysis (data cutoff January 15, 2023); ^cThe significance level for stopping for efficacy was $P=0.019$, corresponding to an HR of 0.69.

IDMC = independent data monitoring committee; Q3W = every 3 weeks.

Loriot Y, et al. *J Clin Oncol*. 2023;41(Suppl 17):LBA4619. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated October 11, 2023.

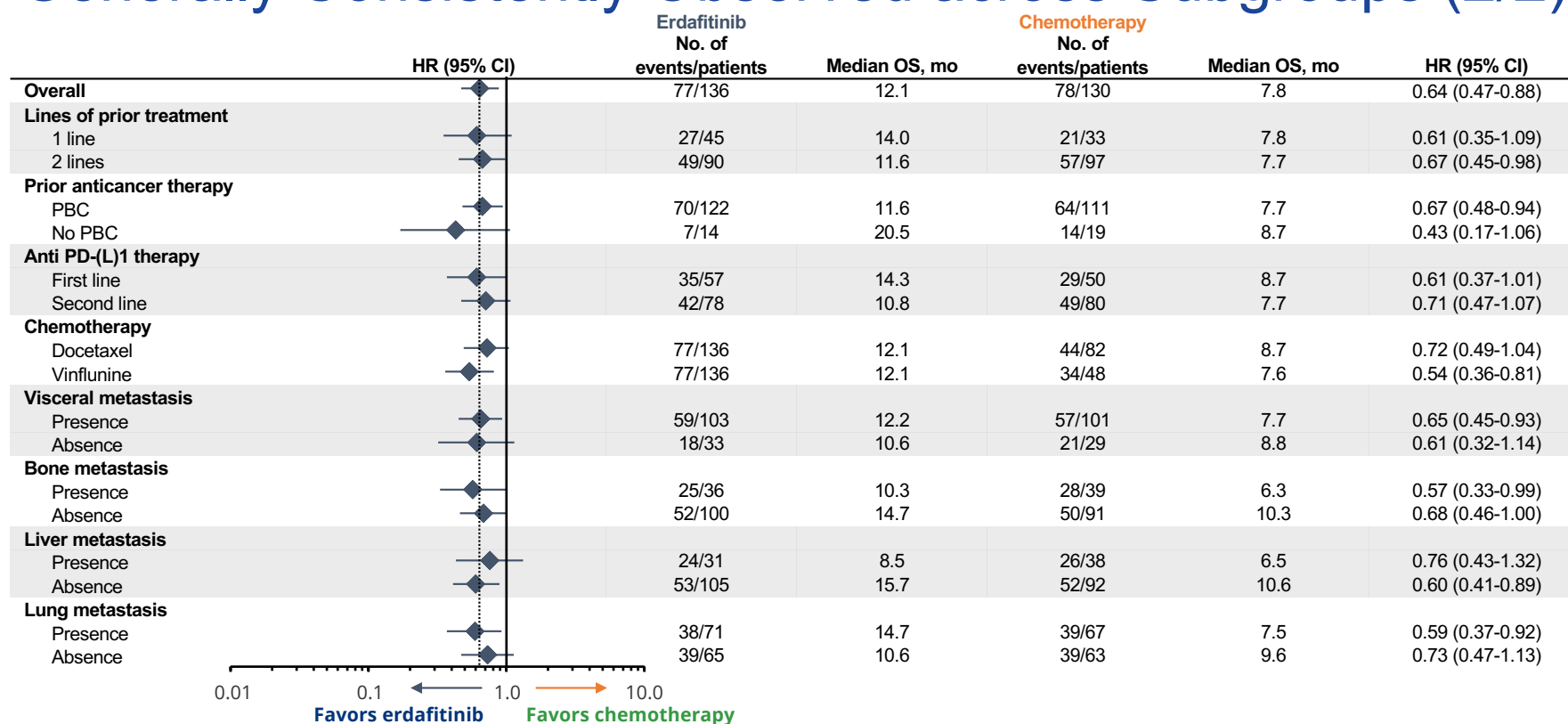
<https://clinicaltrials.gov/study/NCT03390504>.

OS Benefit with Erdafitinib versus Chemotherapy Was Generally Consistently Observed across Subgroups (1/2)



Loriot Y. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain.

OS Benefit with Erdafitinib versus Chemotherapy Was Generally Consistently Observed across Subgroups (2/2)

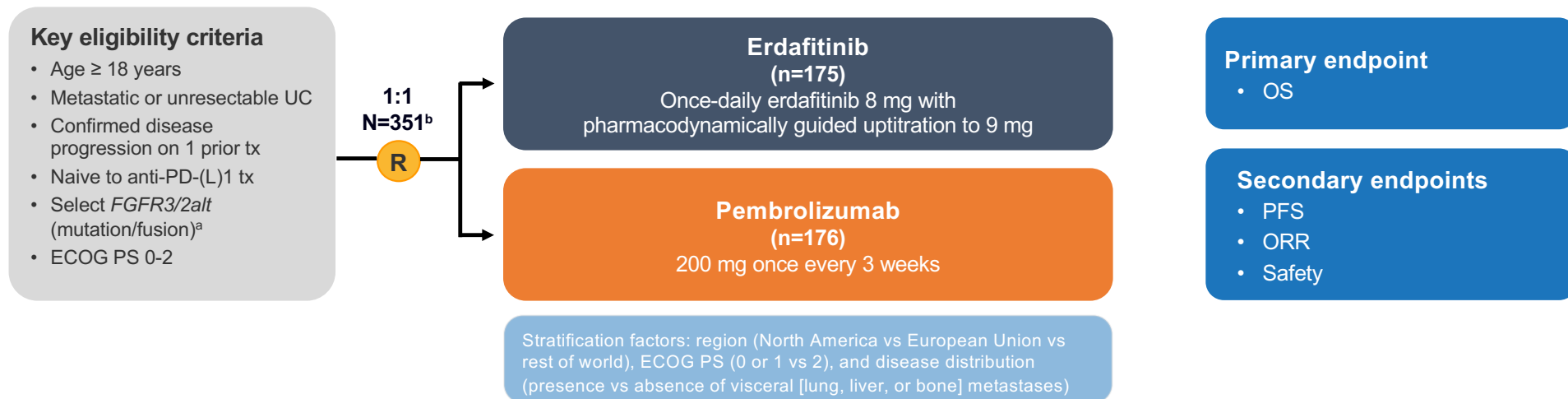


PBC = platinum-based chemotherapy.

Loriot Y. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain.

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

Cohort 2

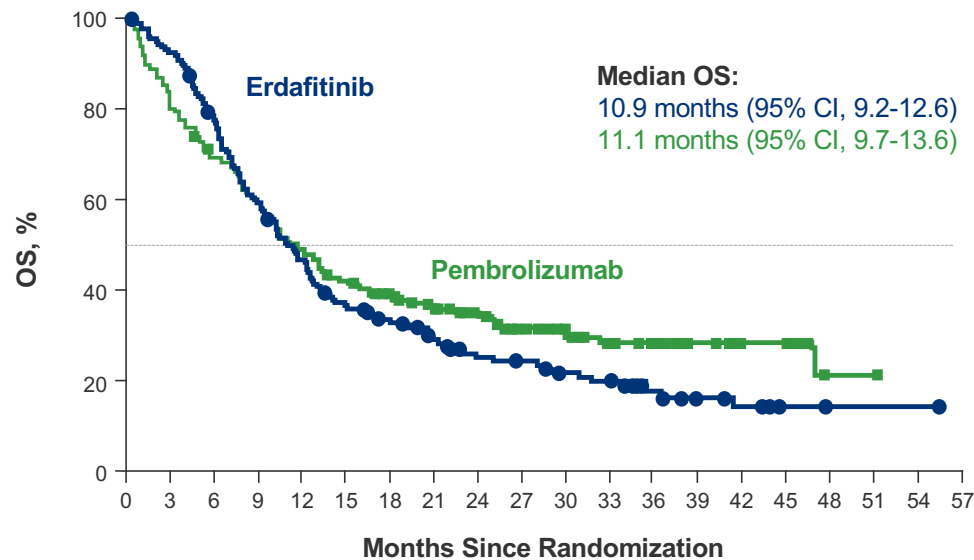


^aMolecular eligibility was confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. 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. ^bNumber of patients randomized at the time of the interim analysis (data cutoff January 15, 2023).

FGFR3/2alt = *FGFR3/2* alterations.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated October 11, 2023. <https://clinicaltrials.gov/study/NCT03390504>.

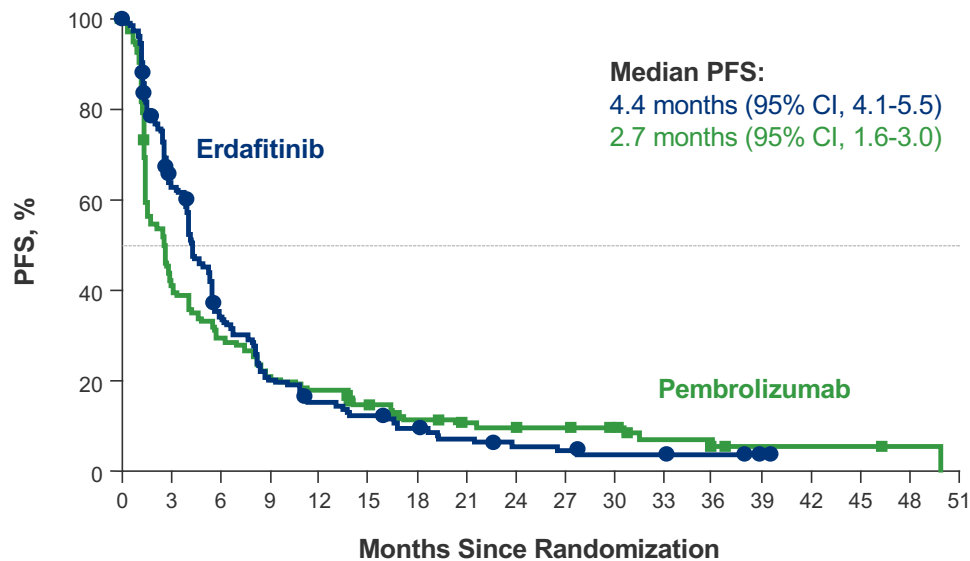
No Significant Difference Was Found in Overall Survival between Erdafitinib and Pembrolizumab



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
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

- Primary endpoint was not met
- Median OS 10.9 months (95% CI 9.2-12.6) for erdafitinib and 11.1 months (95% CI 9.7-13.6) for pembrolizumab
- HR 1.18 (95% CI 0.9-1.5; $P=0.18$)

Median PFS: 4.4 Months with Erdafitinib and 2.7 Months with Pembrolizumab

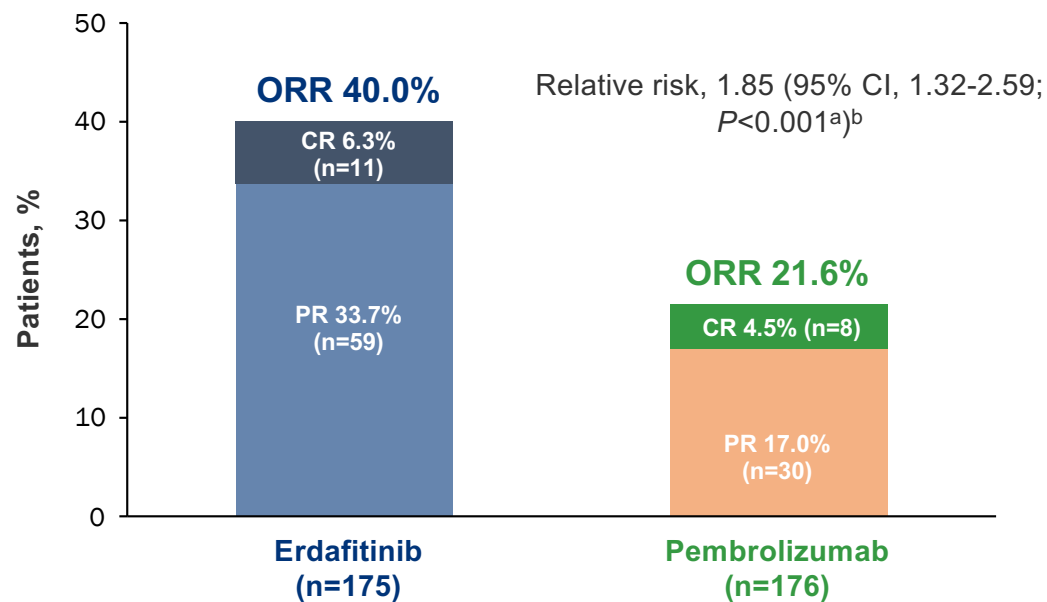


- Median PFS 4.4 months (95% CI 4.1-5.5) for erdafitinib and 2.7 months (95% CI 1.6-3.0) for pembrolizumab
- HR 0.88 (95% CI 0.70-1.10; $P=0.26$)^a

No. at risk	Months Since Randomization																	
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
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

^aNominal P value, due to primary endpoint not being met.
 Siefker-Radtke A. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain.

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%CI 15.8-28.4) 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

^aNominal *P* value, due to primary endpoint not being met; ^bRelative risk, 95% CI, and *P* value are estimated using Cochran-Mantel-Haenszel procedure with ECOG PS (0 or 1 vs 2) as stratification factor.

Siefker-Radtke A. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain.

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

^aAEs 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 in the erdafitinib group. ^bMost 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).

Siefker-Radtke A. Presented at ESMO Congress; October 20-24, 2023; Madrid, Spain.



Enfortumab Vedotin for Previously Treated Advanced UC

- The 5-year relative survival rate for metastatic bladder cancer is $\approx 8\%$ 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 analysis²

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

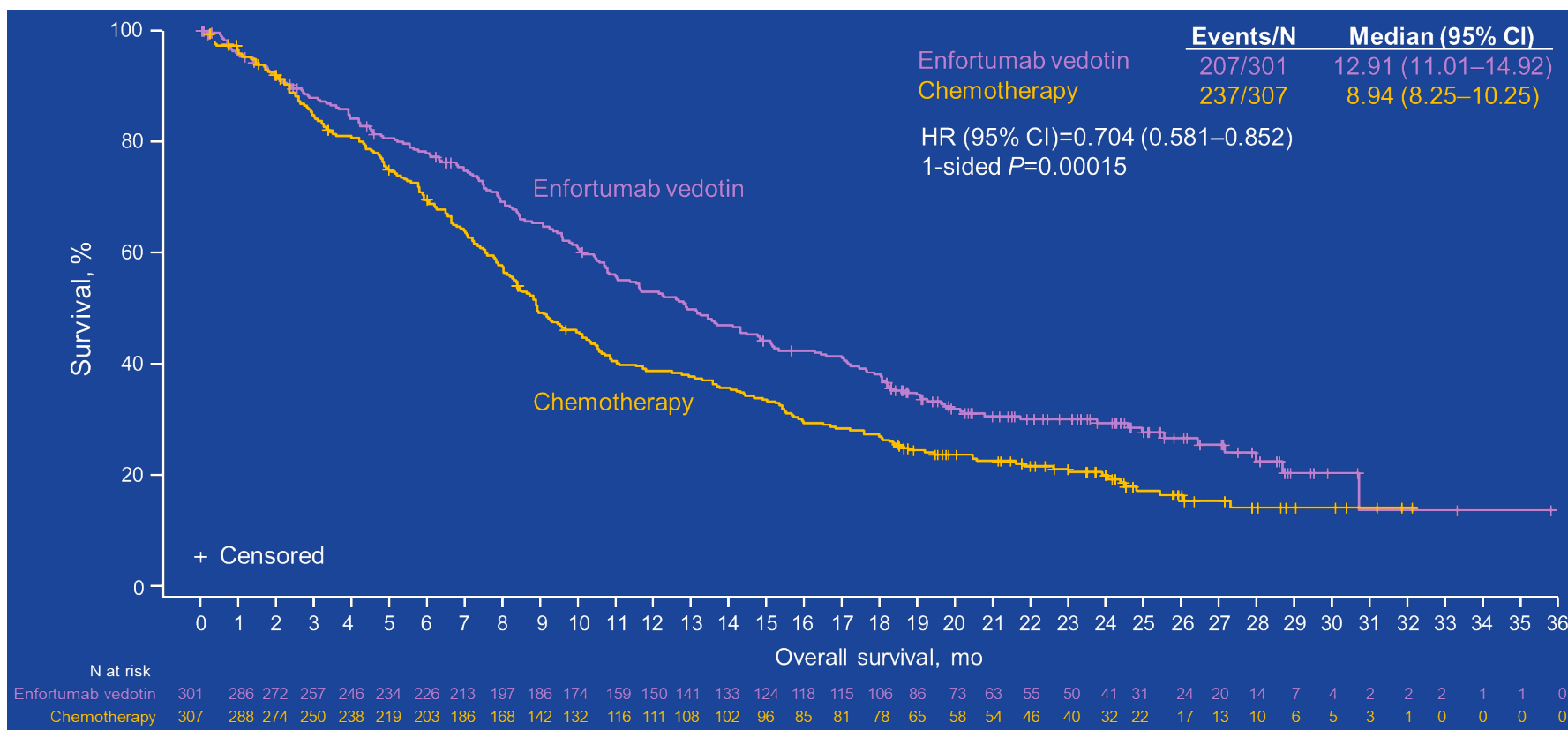
Secondary end points:

- 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

SEER Program [www.seer.cancer.gov]. <https://seer.cancer.gov/statfacts/html/urinb.html>. Powles T, et al. *N Engl J Med*. 2021;384(12):1125-1135. Rosenberg JE. Presented at ASCO Annual Meeting; June 3-7, 2022; Chicago, Illinois. Abstract 4516.

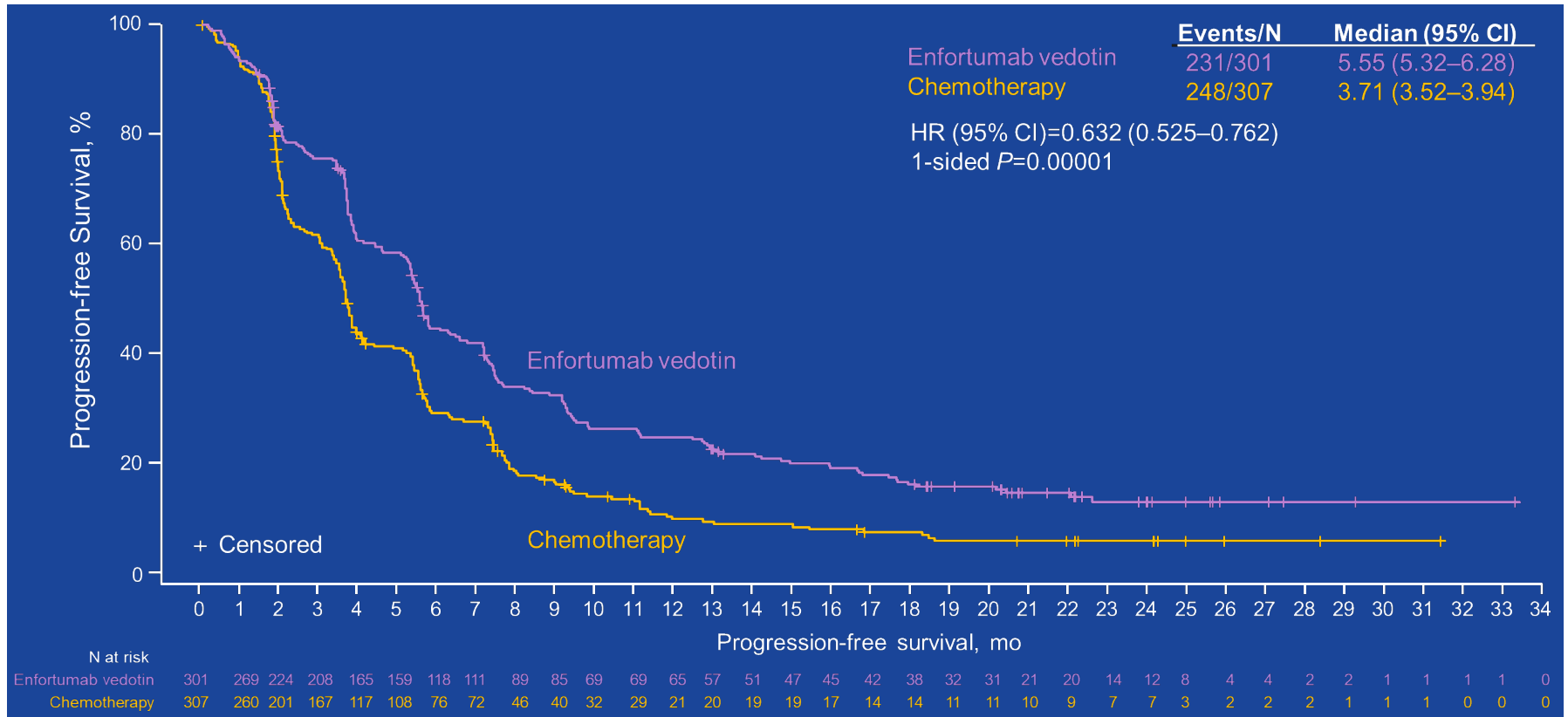
Overall Survival



Data shown for intention-to-treat population. Data cutoff date: July 30, 2021.

Rosenberg JE. Presented at ASCO Annual Meeting; June 3-7, 2022; Chicago, Illinois. Abstract 4516.

Progression-Free Survival



Data shown for intention-to-treat population. Data cutoff date: July 30, 2021.

Rosenberg JE. Presented at ASCO Annual Meeting; June 3-7, 2022; Chicago, Illinois. Abstract 4516.

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

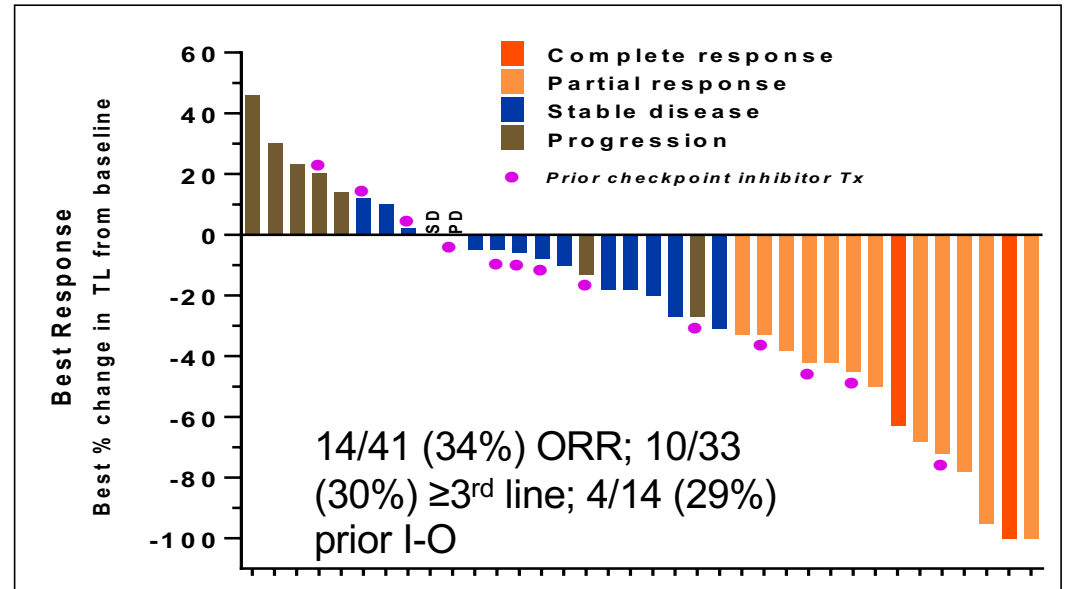
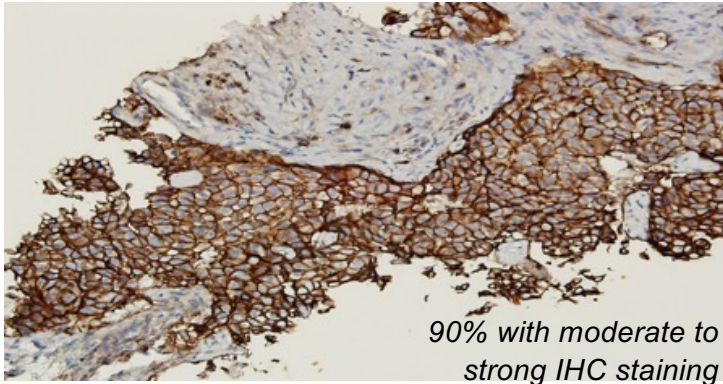
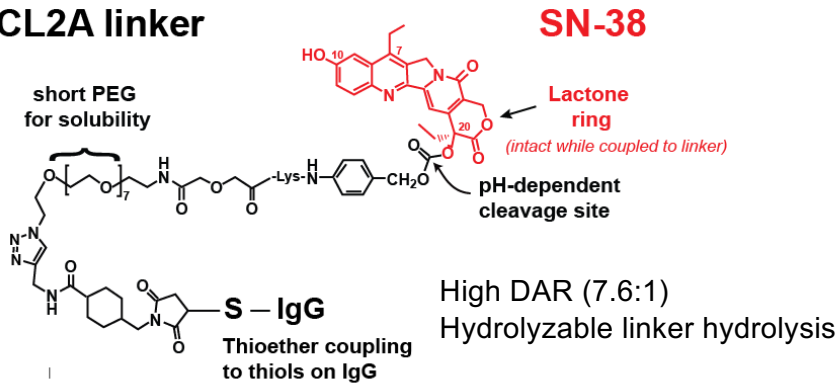
Treatment-related adverse event, n (%)	Enfortumab vedotin (N=296)		Chemotherapy (N=291)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Alopecia	135 (45.6)	NR	108 (37.1)	NR
Peripheral sensory neuropathy	103 (34.8)	15 (5.1)	63 (21.6)	6 (2.1)
Pruritus	96 (32.4)	4 (1.4)	14 (4.8)	1 (0.3)
Fatigue	93 (31.4)	20 (6.8)	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)

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.

Rosenberg JE. Presented at ASCO Annual Meeting; June 3-7, 2022; Chicago, Illinois. Abstract 4516.

Sacituzumab Govitecan

CL2A linker



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

Cardillo TM, et al. *Bioconjug Chem.* 2015; 26(5):919-931. Govindan SV, et al. *Mol Cancer Ther.* 2013;12:968-978. Tagawa S, et al. *Ann Oncol.* 2017;28(Suppl 5):v295-v329. Tagawa S, et al. *J Clin Oncol.* 2019;37(7 Suppl):354.

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

Cohort 1* (~100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies

Cohort 2 (~40 patients): patients with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies

Cohort 3^a (up to 61 patients): mUC CPI naïve patients who progressed after prior platinum-based therapies

Cohort 4 (up to 60 patients): mUC platinum-naïve patients

Cohort 5 (up to 60 patients): mUC platinum-naïve patients

SG 10 mg/kg
Days 1 and 8, every 21 days →

SG 10 mg/kg
Days 1 and 8, every 21 days →

SG 10 mg/kg
Days 1 and 8, every 21 days →
Pembrolizumab 200 mg
day 1 every 21 days

SG
Days 1 and 8, every 21 days →
Cisplatin^b
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

Primary Endpoint:

Objective response rate per RECIST 1.1 criteria

Key Secondary Endpoints:

Safety/tolerability, DOR, PFS, OS

Maintenance avelumab (800 mg every 2 weeks) with SG (days 1 and 8 every 21 days) for those without disease progression

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

^aExclusions for cohort 3 only: active autoimmune disease or history of interstitial lung disease. ^bIn patients with CrCl ≥ 60 mL/min; ^cIn patients with creatinine clearance 50-60 mL/min. ^dFor 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.

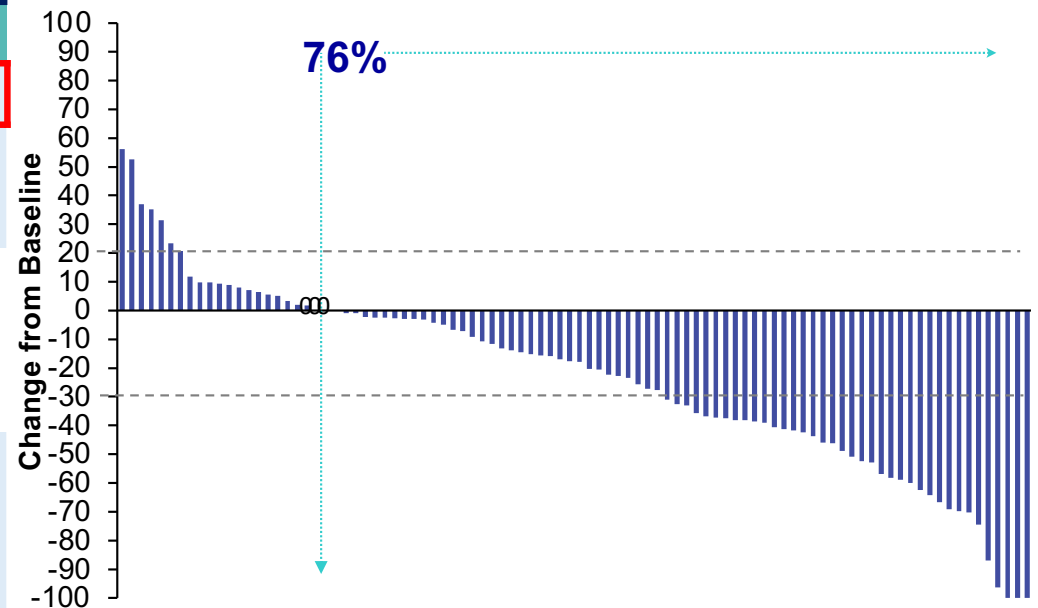
CBR = clinical benefit rate; SG = sacituzumab govitecan.

US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761115s023lbl.pdf.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated October 19, 2023. <https://clinicaltrials.gov/study/NCT03547973>.

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)

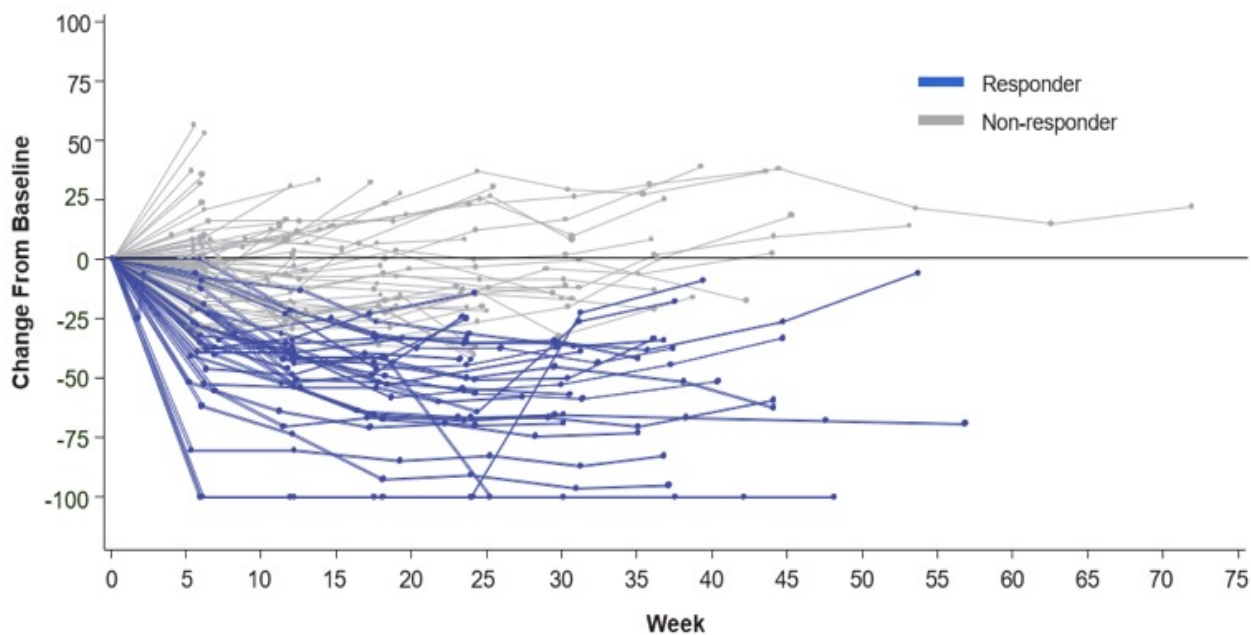
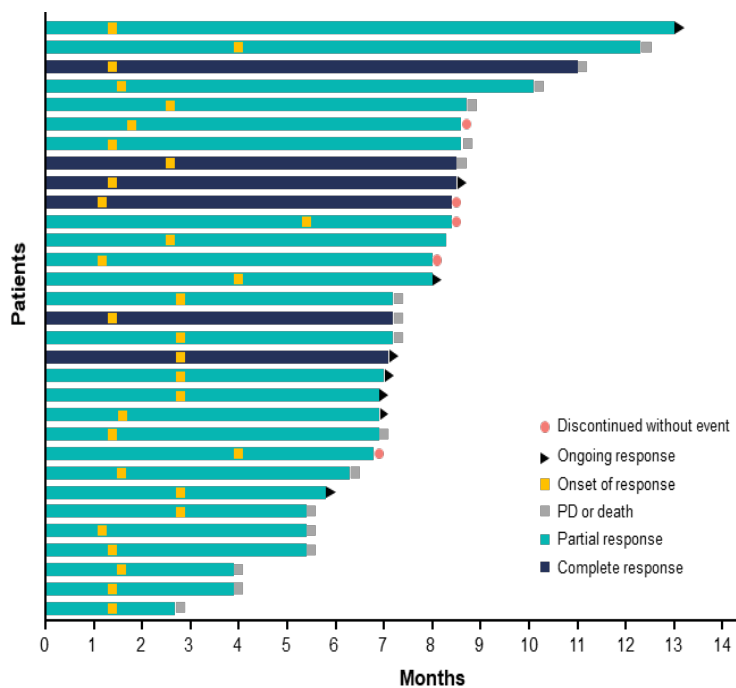


Assessments were per blinded independent review assessment, RECIST 1.1. 71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality.

TTR = time to response.

Tagawa ST, et al. *J Clin Oncol.* 2021;39(22):2474-2485

TROPHY-U-01 Cohort 1 Durability of Response



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	Neutropenia	46	22	12
	Leukopenia	26	12	5
	Anemia	34	14	0
	Lymphopenia	12	5	2
	Febrile neutropenia	10	7	3
Gastrointestinal	Diarrhea	65	9	1
	Nausea	58	4	0
	Vomiting	28	1	0
General disorders and administrative site conditions	Fatigue	50	4	0
Skin and subcutaneous tissue	Alopecia	47	0	0
Metabolism and nutrition	Decreased appetite	36	3	0
Infections and infestations	Urinary tract infection	8	6	0

- 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.

G-CSF = granulocyte colony stimulating factor.

Tagawa ST, et al. *J Clin Oncol*. 2021;39(22):2474-2485

Advanced Urothelial Ca Tx Algorithm before ESMO 2023

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

Clinical trials are critical throughout disease spectrum and treatment settings!

f/b = followed by.

Advanced Urothelial Ca Tx Algorithm after ESMO 2023

Disease State	Preferred Option	Other Options
Metastatic, no prior chemotherapy (1L)	Pembrolizumab/enfortumab-vedotin	Gem/cis + nivolumab (cisplatin-fit) -Gem/carbo (in cisplatin-unfit patients) f/b avelumab switch maintenance -Pembrolizumab (platinum-unfit) -Single agent chemoTx (platinum-unfit)
Metastatic (prior therapy)	Platinum-based chemotherapy (after EV/P) OR erdafitinib (tumors with FGFR2/3 activating mutation or fusion) OR enfortumab-vedotin (if not used prior) OR pembrolizumab (if IO not used prior)	Sacituzumab-govitecan
Metastatic (≥ 2 prior therapies)	Erdafitinib (tumors with FGFR2/3 activating mutation or fusion) OR enfortumab-vedotin (if not used prior) OR sacituzumab-govitecan	Taxane (US) Vinflunine (EU)

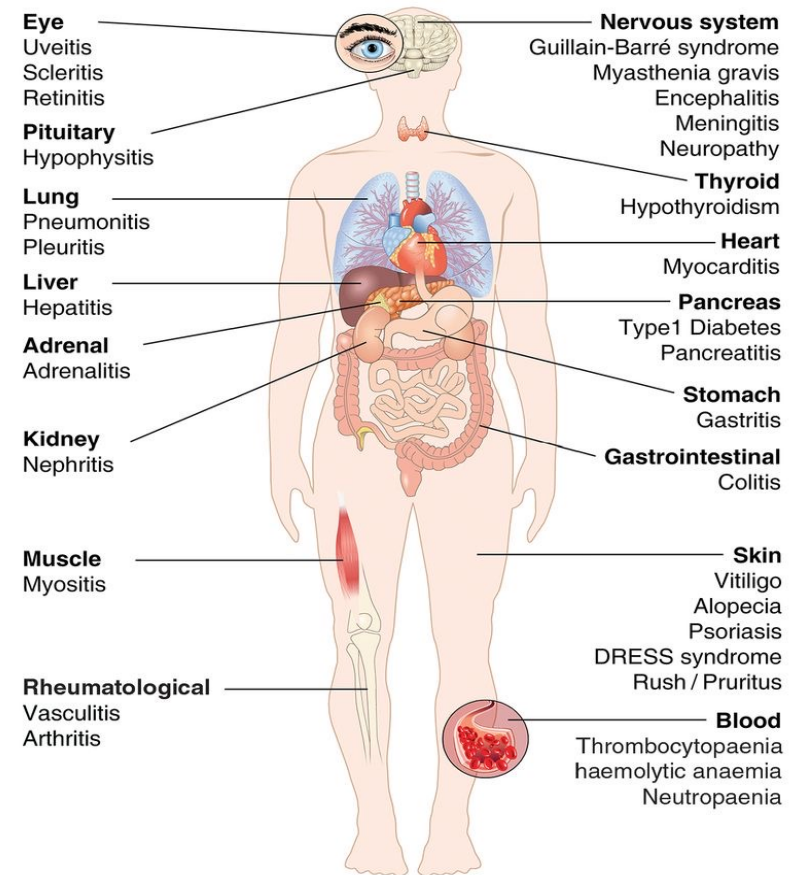
Clinical trials are critical throughout disease spectrum and treatment settings!

IrAE Management Pearls, Education, and Collaboration

Mary Dunn, NP-C

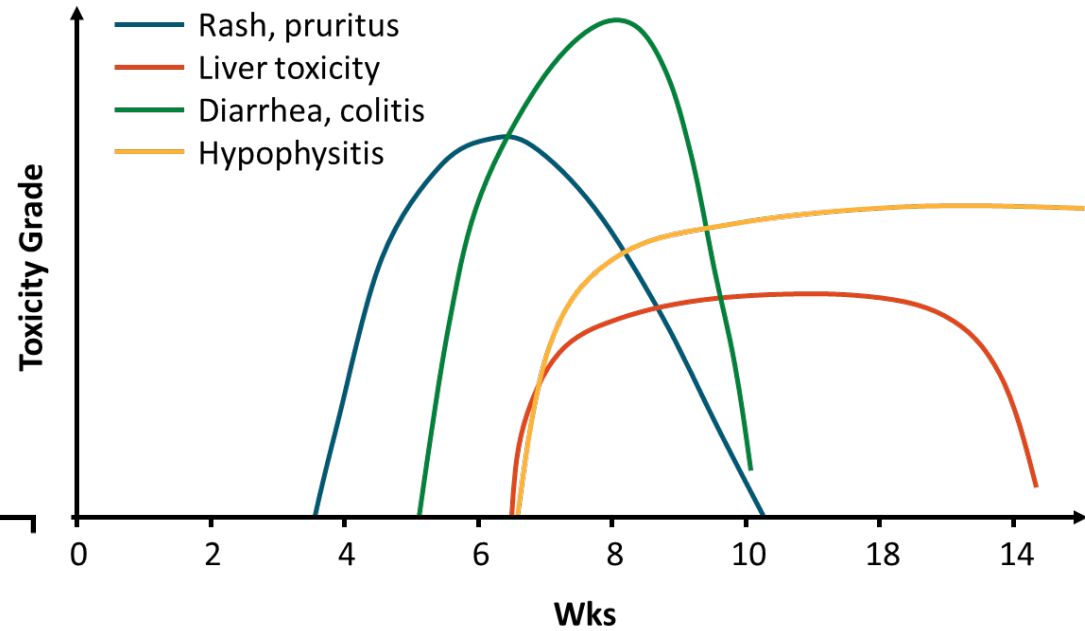
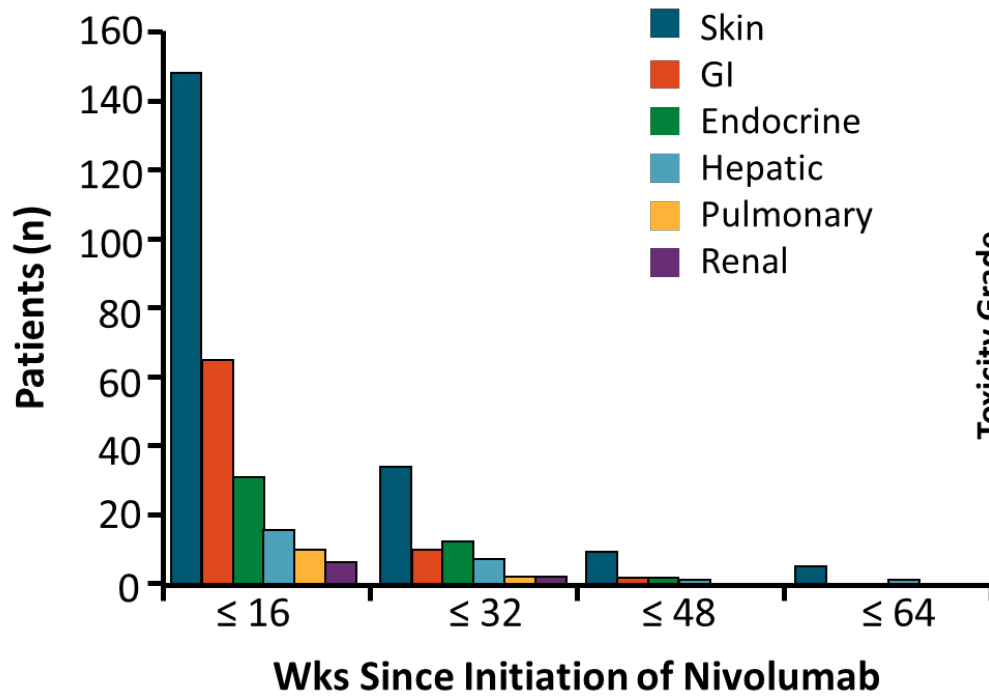
Immune-Related AEs (irAEs)

- ICIs introduce the potential for transformative, durable responses in multiple malignancies
- ICIs also introduce potential for toxicity
- irAEs
 - Activation of immune system that can “target” host tissues/organs
 - Can mimic (or flare) pre-existing autoimmune conditions
 - Pathophysiology not well understood
 - Treatment with immunosuppressive agents

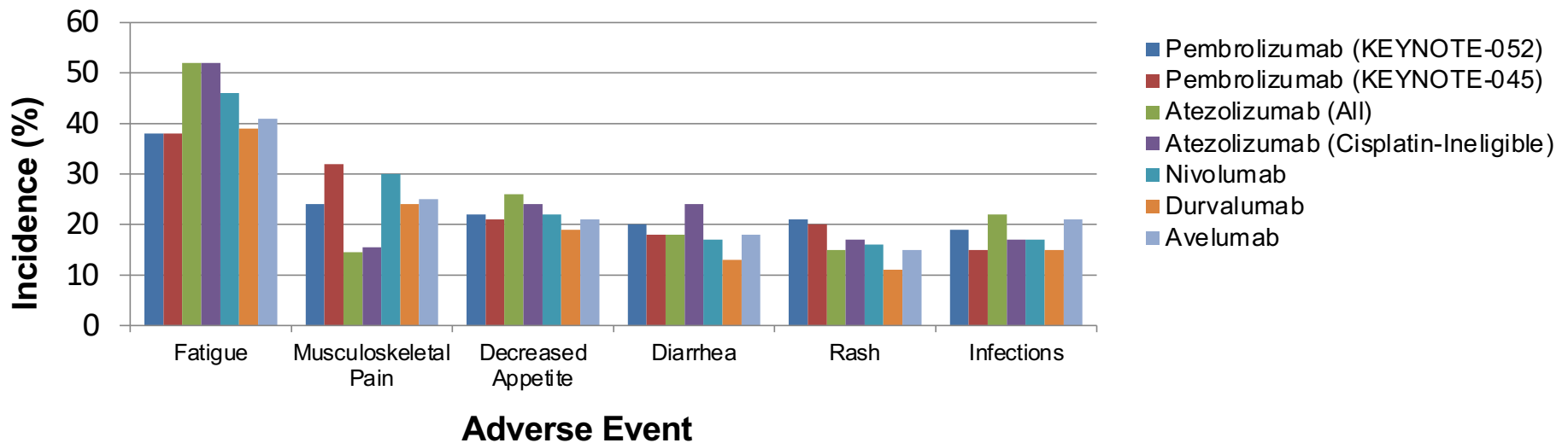


DRESS = drug rash with eosinophilia and systemic symptoms.
 Varricchi G, et al. *ESMO Open*. 2017;2(4):e000247.

Onset of irAEs



Select All-Grade AEs in $\geq 10\%$ of Patients with UC



US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed September 30, 2021.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s133lbl.pdf. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed

September 30, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761034s049s051lbl.pdf.

US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed September 30, 2021.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125527s000lbl.pdf.

US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed September 30, 2021.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761069s042lbl.pdf.

US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Accessed September 30, 2021.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761049s005lbl.pdf.

Generic Toxicity Management of irAEs

- Corticosteroids remain cornerstone of care for immune-mediated adverse events
 - Resolved most irAEs among UC trials
 - Mild skin reactions can be treated with topical steroids
 - Higher grade/persistent toxicity requires systemic steroids
 - Oral preferred; IV may be used when absorption compromised (eg, colitis)
- Moderate cases (grade 2)
 - Hold drug, re-dose if toxicity improves, consider low-dose steroids (prednisone 0.5-1 mg/kg/day)
- Severe cases (grades 3/4)
 - Start high-dose steroids (prednisone 1-2 mg/kg/day) with a slow taper (≥ 1 month)
 - Infliximab 5 mg/kg once every 2 weeks can be used
- Endocrine side effects
 - Hormonal replacement as needed

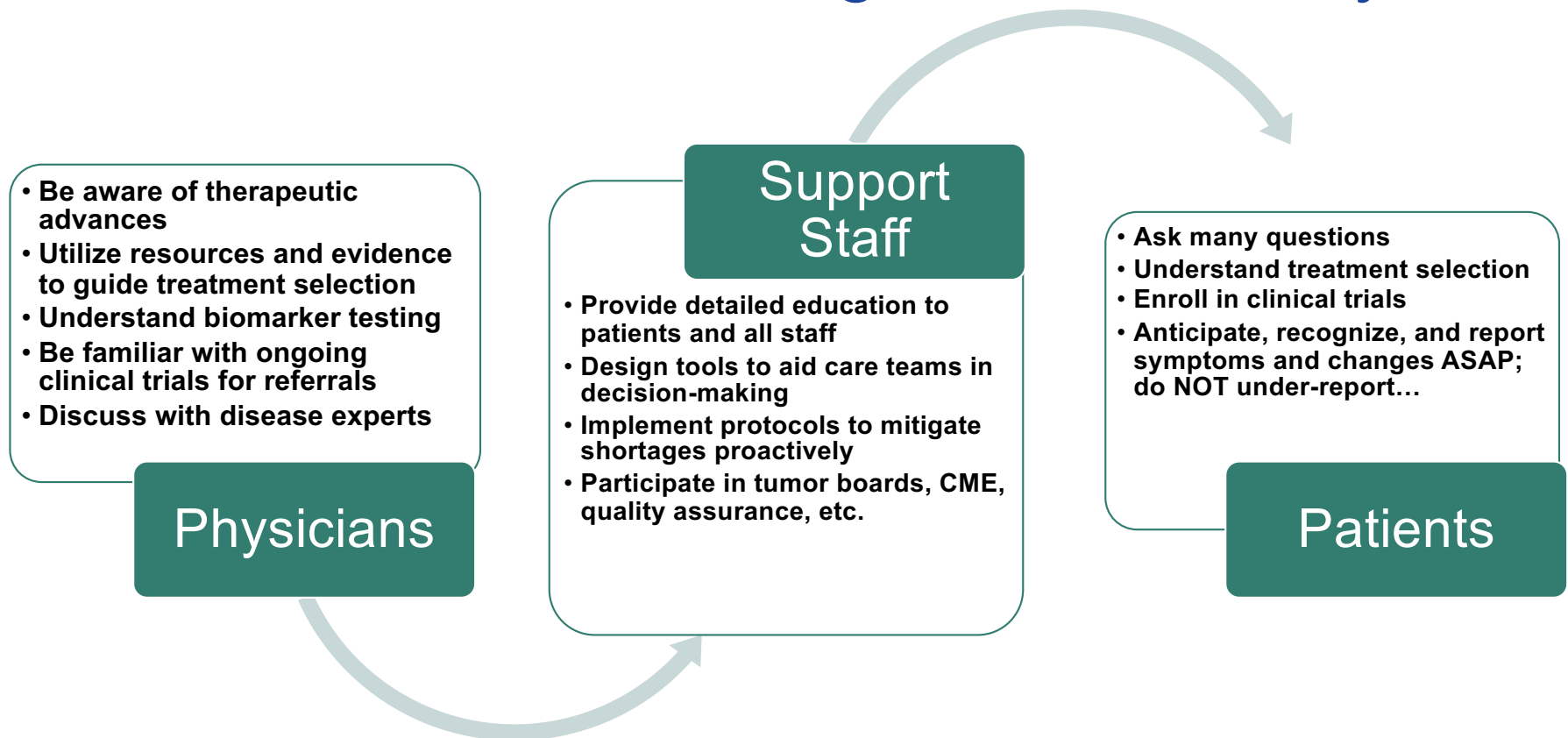
CTCAE Grade	Corticosteroids	Other Adjunctive Therapies	Immunotherapy Action
1	Not required	Not required	Continue
2	Topical or systemic steroids	Not required	Hold temporarily
3	Systemic steroids	If no response to steroids after 3-5 days	Discontinue and may consider resuming therapy* based on risk/benefit
4	Systemic steroids	If no response to steroids after 3-5 days	Discontinue

*Doses are either given or held. There are no dose reductions.

IV = intravenous.

Petrylak DP. *Clin Genitourin Cancer*. 2017;15(3S):S3-S17. Weber JS, et al. *J Clin Oncol*. 2012;30(21):2691-2697. Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68

Shared Decision-Making Involves Everyone

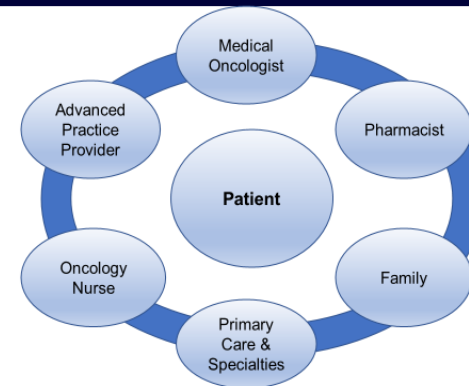


CME = continuing medical education.

Multidisciplinary Approach

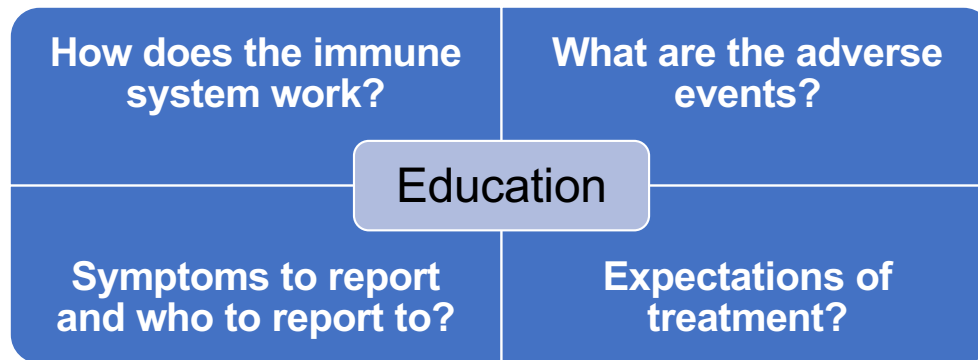
- Patient: Preparing for treatment
 - Shared decision-making
 - Assess/identify risk for AEs
 - Patient/family education
 - Educational tools
 - Ask about clinical trials
- Program strategies
 - Education
 - Identify immuno-oncology and precision oncology champions
 - Tumor boards, registries, databases, etc.
 - Care coordination, navigation, monitoring
 - Clinical trials and referral networks

Multidisciplinary Team Approach



Education Is KEY!

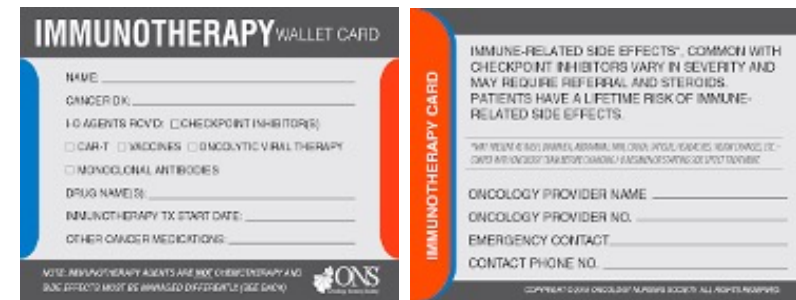
- Information about mechanism of action
- Understanding risks of irAEs
- How checkpoint inhibitors differ from chemotherapy and other oral cancer therapies
- Early recognition and treatment of immune-related adverse events
- How to recognize irAEs and knowing to monitor even when treatment has ended
- Importance of ongoing communication with oncology multidisciplinary care team



Kennedy LC, et al. *J Natl Compr Canc Netw*. 2019;17(6):750-757. VanderWalde A, et al. [www.accc-cancer.org]. Last updated November-December 2018. Accessed September 30, 2021. https://www.accc-cancer.org/docs/documents/oncology-issues/articles/nd18/best-practices-for-implementing-cancer-immunotherapy-in-the-community.pdf?sfvrsn=fdd7fdcd_12.

Education for Patients & Caregivers

- Special populations (e.g., autoimmune disorders, transplants, steroid, other chronic illness)
- Report anything new!
- Treatment delays, dose reductions
- Immunotherapy wallet cards
- Additional resources
 - NCCN, ASCO, ESMO, ONS, SITC, ACCC



IMMUNOTHERAPY WALLET CARD

NAME: _____

CANCER DX: _____

IO AGENTS RCVD: CHECKPOINT INHIBITOR(S)
 CAR-T VACCINES MODULATORY VIRAL THERAPY

MONOCLONAL ANTIBODIES

DRUG NAME(S): _____

IMMUNOTHERAPY TX START DATE: _____

OTHER CANCER MEDICATIONS: _____

NOTE: IMMUNOTHERAPY AGENTS ARE NOT CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY (SEE DRUG)

©2019 ONS (ONCOLOGY NURSING SOCIETY). ALL RIGHTS RESERVED.

IMMUNOTHERAPY CARD

IMMUNE-RELATED SIDE EFFECTS*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

*BY VISIT # 8 (SEE PANEL ABOVE), WE COVER YOUR SYMPTOMS REGARDLESS OF HOW MANY TIMES YOU VISIT US FOR MANAGEMENT OF YOUR SYMPTOMS.

ONCOLOGY PROVIDER NAME: _____

ONCOLOGY PROVIDER NO.: _____

EMERGENCY CONTACT: _____

CONTACT PHONE NO.: _____

©2019 ONS (ONCOLOGY NURSING SOCIETY). ALL RIGHTS RESERVED.

Contact your oncology provider's office if you experience any of these symptoms:

- Fever (oral temperature greater than 100.4°F)
- New or worsening cough, chest pain, or shortness of breath
- New or worsening fatigue or activity intolerance with or without palpitations
- Diarrhea (loose stools) or more bowel movements than usual
- Abdominal pain and/or blood in stools
- Skin rash, with or without itching
- Blurry vision, double vision, or other vision problems
- Numbness or tingling in hands and/or feet
- Unusual weakness or pain of legs, arms, or face
- Dark urine (tea-colored) and/or change in urination frequency
- Headaches that will not go away or unusual headaches
- **Any new or worsening symptoms**

©2019 ONS (ONCOLOGY NURSING SOCIETY). ALL RIGHTS RESERVED.

IMMUNOTHERAPY WALLET ID CARD

PATIENT NAME: _____

EMERGENCY CONTACT NAME & TEL.: _____

ONCOLOGY TEAM PRIMARY CONTACT: _____

CANCER DIAGNOSIS: _____

NAME OF IO AGENT(S): _____

ONCOLOGY PROVIDER NAME: _____

PROVIDER HOURS: MON. THRU FRI. _____ AM to _____ PM

TEL. _____ AFTER-HOURS TEL. _____

This patient is receiving IMMUNOTHERAPY for cancer treatment. Side effects may differ from standard chemotherapy but with PROMPT recognition and management, most side effects are treatable. Please contact the oncology provider's office for assistance in managing immune-related adverse events.

Education for Providers

Relevant providers

- Primary care providers
- Emergency department
- Hospitalists
- Urgent care
- Sub-specialists (IO champions)
- Advanced practice providers
- Pharmacists, nurses, etc.

Strategies/tools for education

- Community outreach
- Tumor boards
- Grand rounds/seminars
- CME access, MOC
- National and locoregional meetings
- “irAE/toxicity teams” (outpatient/inpatient)

MOC = maintenance of certification.

Barriers

Disparities

- Women and Black patients less likely to receive prompt hematuria evaluation
- Women, Black, Hispanic, and those of lower SES are likely to have more advanced disease
- Black patients have higher mortality rates
- Risk of recurrence higher in women

How can we mitigate?

- Public health awareness re: risk factors
 - Tobacco use, obesity, hypertension, occupational exposures
- Implement health policies to improve social inequities
- Facilitate access to healthcare programs for underserved populations
- Primary care services to minority and underinsured populations
- Educating primary care providers re: hematuria evaluation
- Refer women to urology for hematuria eval
- Screen for financial distress at time of diagnosis



Thanks Much😊

Patients and families!

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

@PGrivasMDPhD

Q&A

Scan to Submit your Questions or
Complete the Post-Event Survey!



Access accreditation information
or claim CE credit by scanning
the QR code

