Metastatik Ürotelyal Kanserlerde Tedavi Seçenekleri

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Ders Planı

- Giriş
  - Metastatik Hastalık
- Sisplatine uygun hastada birinci basamak
- Sisplatine uygun olmayan hastada birinci basamak
- İkinci basamak ve sonrası tedavi seçenekleri
- Gelecek perspektif
- Özet

Metastatik Mesane Kanseri
Birinci Basamak Kemoterapi

Selected randomized clinical trial comparisons of chemotherapy for metastatic bladder cancer

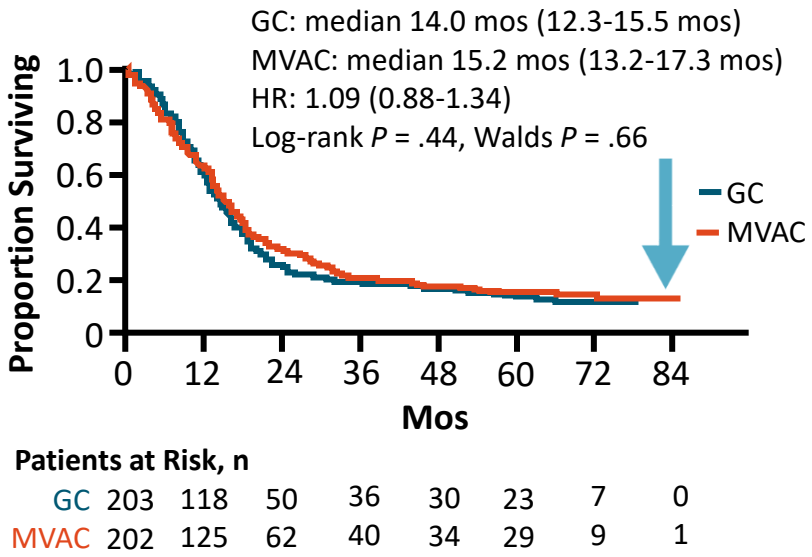
Study (year of publication)	*n*	Interventions	Response rate (%)	Median OS (months)	Toxicity
Logothetis *et al.*[36] (1990)	110	MVAC versus CISCA	65 versus 46; $P<0.05$	15.5 versus 10.1; $P=0.0003$	MVAC>CISCA
Loehrer *et al.*[37] (1992)	269	MVAC versus cisplatin	39 versus 12; $P<0.0001$	12.5 versus 8.2; $P=0.0002$	MVAC>cisplatin
Mead *et al.*[39] (1998)	214	CMV versus MV	46 versus 19 (*P* value not reported)	7.0 versus 4.5; $P=0.0065$	CMV>MV
von der Maase *et al.*[70,71] (2000,2005)	405	GC versus MVAC	49 versus 46; $P=0.51$	14.0 versus 15.2; $P=0.66$	MVAC>GC
Sternberg *et al.*[75,76] (2001, 2006)	263	ddMVAC versus MVAC	72 versus 58; $P=0.016$	15.1 versus 14.9 (*P* value not reported; 5-year OS was 21.8% versus 13.5%, $P=0.04$)	MVAC>ddMVAC
Bamias *et al.*[84] (2013)	130	ddGC versus ddMVAC	32 versus 27; $P=0.67$	18 versus 19; $P=0.98$	ddMVAC>ddGC

CISCA, cisplatin, cyclophosphamide, and doxorubicin; CMV, cisplatin, methotrexate, and vinblastine; ddGC,dose-densegemcitabine and cisplatin; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine and cisplatin; MV, methotrexate and vinblastine; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; *n*, number of patients; OS, overall survival.

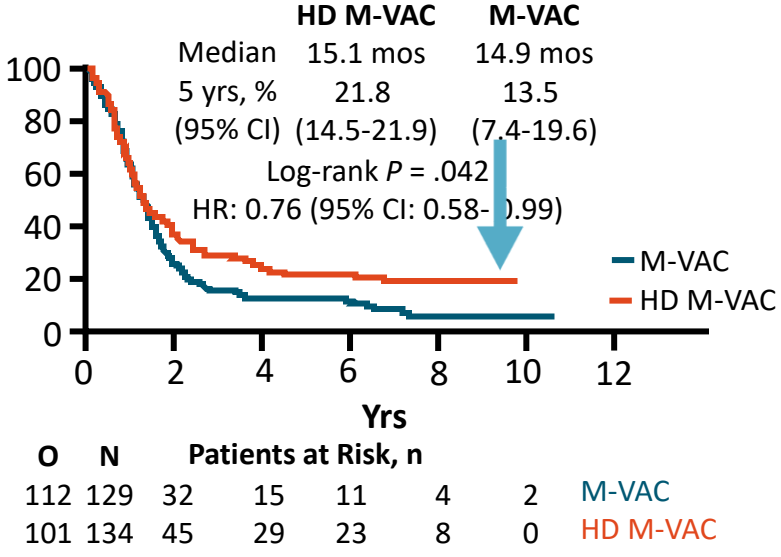
Metastatik Birinci Basamak Kemoterapi Sonuçları

Sisplatin Uygun

Gemcitabine + Cisplatin[1,2]
ORR: 49%
CR: 12%
Median OS: 14.0 mos

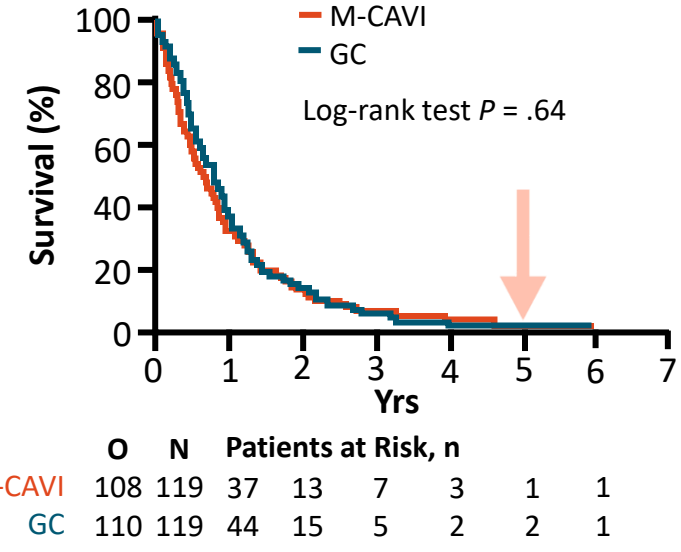


Dose Dense MVAC[3]
ORR: 72%
CR: 25%
Median OS: 15.1 mos



Sisplatin uygun değil

Gemcitabine + Carboplatin[4]
ORR: 36%
CR: 3%
Median OS: 9.3 mos



1. von der Maase H, et al. J Clin Oncol. 2005;23:4602-4608. 2. von der Maase H, et al. J Clin Oncol. 2000;18:3068-3077.
3. Sternberg CN, et al. Eur J Cancer. 2006;42:50-54. 4. De Santis M, et al. J Clin Oncol. 2012;30:191-199.

Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçimi

PRINCIPLES OF SYSTEMIC THERAPY

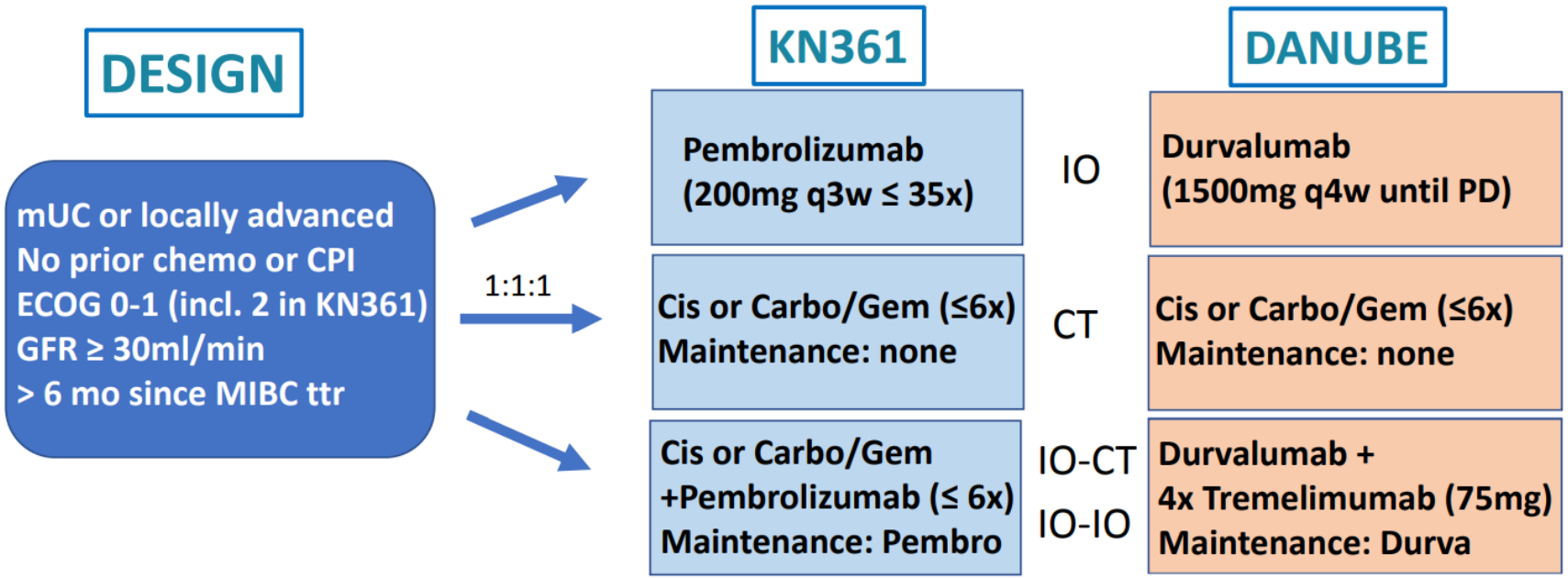
First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Pembrolizumab and enfortumab vedotin-ejfv[15] (category 1) **Other recommended regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,13] • Nivolumab, gemcitabine, and cisplatin (category 1) followed by nivolumab maintenance therapy[14] (category 1) **Useful under certain circumstances** • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,13]
Cisplatin ineligible	**Preferred regimens** • Pembrolizumab and enfortumab vedotin-ejfv[15,17] (category 1) **Other recommended regimens** • Gemcitabine and carboplatin[16] followed by avelumab maintenance therapy (category 1)[a,13] **Useful under certain circumstances** • Gemcitabine[18] • Gemcitabine and paclitaxel[19] • Ifosfamide, doxorubicin, and gemcitabine[21] (for patients with good kidney function and good performance status) • Pembrolizumab[22] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab[20] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

Sisplatin Kombinasyonlu Kemoterapiye Uygun Olmayan Hasta Grubu

- ECOG PS ≥ 2
- Kreatinin klirensi < 60ml/dk
- İşitme kaybı olması grade2>
- Periferik nöropati grade2>
- KKY olması (NYHA class III)

Galsky MD et al. A consensus definition of patient with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy.Lancet 2011

Metastatik Ürotelyal Kanserlerde Birinci Basamak
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri



	KEYNOTE 361 (N=1010)	DANUBE (N=1032)
Stratification	Cis/Carbo investigator choice PD-L1: CPS ≥10	Cisplatin eligibilty PD-L1: ≥25% IC and/or TC positive Liver and/or lung metastases
Primary endpoints	PFS and OS: IO-CT vs CT (total) OS: IO vs CT (total and PD-L1 +) **Sequential testing!**	OS: IO-IO vs CT (ITT) OS: IO vs CT (PD-L1 +)
Minimum follow up	22 months (median 31.7)	34 months (median 41.2)

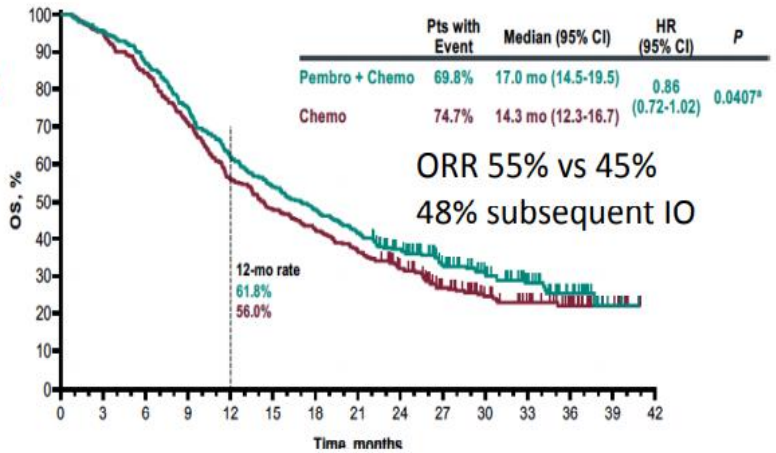
Metastatik Ürotelyal Kanserlerde Birinci Basamak
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

Overall survival

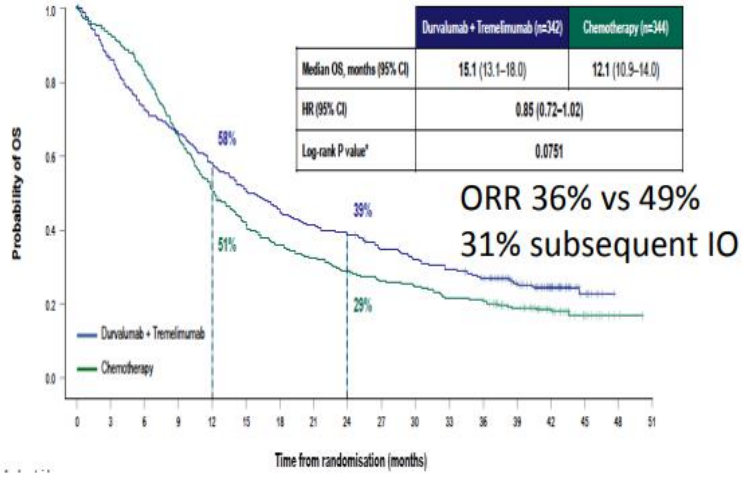
Combination vs Chemo

TOTAL population (ITT)

KEYNOTE 361 –IO-CT vs CT (1˚EP)



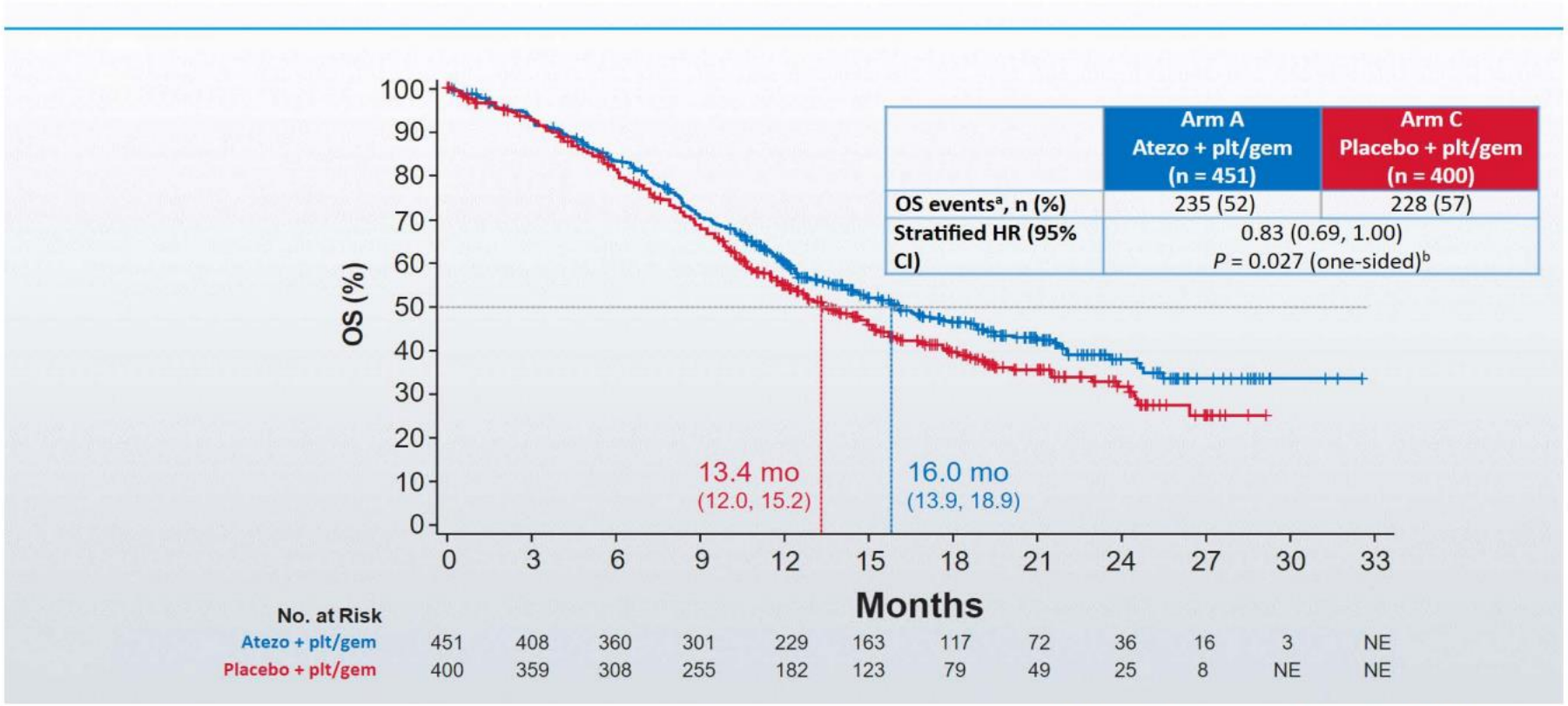
DANUBE – IO-IO vs CT (1˚EP)



Platin bazlı kemoterapi+ Pembrolizumab, Durvalumab+Tremelimumab kombinasyonları platin bazlı(karboplatin/sisplatin +gemsitabin) tedavisine göre üstünlük göstermedi

Metastatik Ürotelyal Kanserlerde Birinci Basamak
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

IMvigor130 Interim OS: ITT (Arm A vs Arm C)



Galsky et al, Lancet 2020 May; Grande ESMO 2019

Platin bazlı kemoterapi+ Atezolizumab, kombinasyonu platin bazlı(karboplatin/sisplatin +gemsitabin) tedavisine göre üstünlük göstermedi

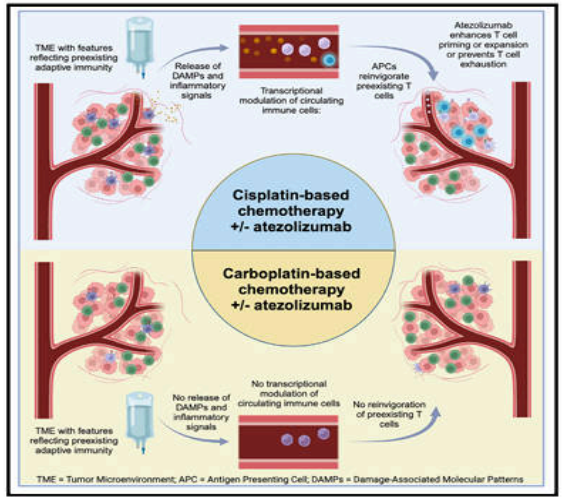
Sisplatin Ürotelyal Kanserlerde immünomodülatör

Cell Reports Medicine

Article

Immunomodulatory effects and improved outcomes with cisplatin- versus carboplatin-based chemotherapy plus atezolizumab in urothelial cancer

Graphical abstract



Authors

Matthew D. Galsky, Xiangnan Guan, Deepali Rishipathak, ..., Peter C. Black, Enrique Grande, Sanjeev Mariathasan

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matthew.galsky@mssm.edu (M.D.G.), mariathasan.sanjeev@gene.com (S.M.)

In brief

Galsky et al. demonstrate that durable cancer control with cisplatin versus carboplatin is most prominent in patients with pretreatment tumors demonstrating features of restrained adaptive immunity. *In vitro*, they demonstrate that cisplatin versus carboplatin exerts direct immunomodulatory effects on cancer cells, promoting dendritic cell activation and antigen-specific T cell killing.

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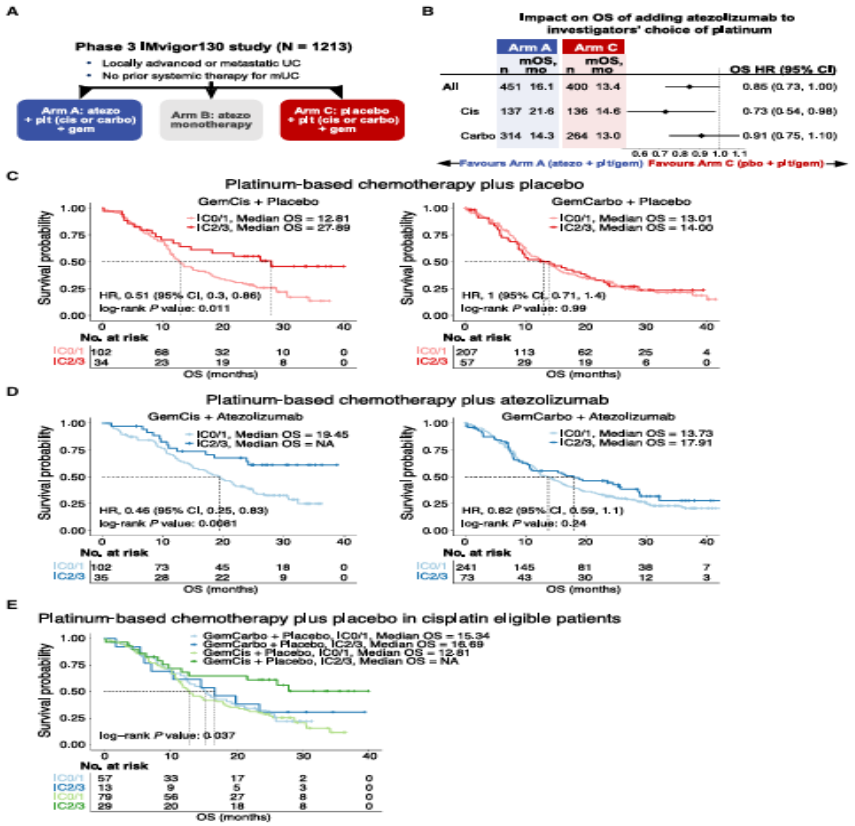
Cell Reports Medicine

Article



GemCis tedavisi, GemCarbo ± atezolizumaba kıyasla, dolaşımdaki immün hücrelerde antijen sunumu ve T hücresi aktivasyonuna ilişkin gen ekspresyonunu artırır. İn vitro veriler, sisplatinin karboplatine göre tümör hücreleri üzerinde daha güçlü immünomodülatör etkiler göstererek dendritik hücre aktivasyonu ve antijen-spesifik T hücresi sitotoksisitesini desteklediğini göstermektedir.

IMvigor130 çalışması, atezolizumab'un gemcitabin ve sisplatin (GemCis) ile kombinasyonunun, gemcitabin ve karboplatin (GemCarbo) rejimine kıyasla daha olumlu sonuçlar verdiğini göstermiştir.

Galsky M, Cell Reports Medicine 2024.

Ürotelyal Kanserlerde Renal Yetmezlik ile İmmünoterapi Etkinliği Azalıyor

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY ASSOCIATION FOR CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

ABSTRACT #434954

Immune checkpoints blockade therapies' efficacy and toxicity in patients with impaired renal function in metastatic bladder cancer.

Deniz Tural, Cagatay Arslan, Fatih Selcukbiricik, Omer Fatih Olmez, Mustafa Erman, Yüksel Ürün, Dilek Erdem, Saadettin Kilickap; Department of Medical Oncology, University of Health Sciences, Bakirköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey; Izmir Economy University Medical Park Hospital, Karsiyaka, Turkey; Koc University Hospital, Istanbul, Turkey; Istanbul Medipol University, Medical Faculty, Department of Medical Oncology, Istanbul, Turkey; Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey; Ankara University Faculty of Medicine, Cebeci, Turkey; Samsun Medicalpark Hospital, Atakum, Turkey; Istinye University Faculty of Medicine, Department of Medical Oncology, Liv Hospital, Ankara, Turkey

**Note: The appearance of your abstract here is an approximation of how the abstract would appear in print, if accepted.

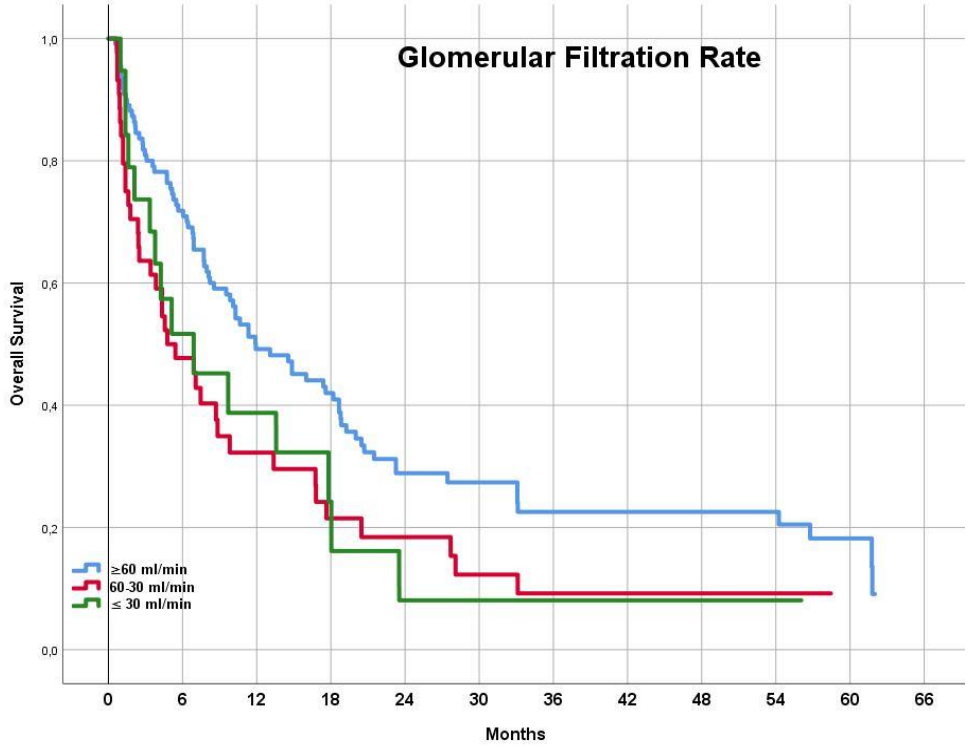
Background:

In this study, we reported the real-life results of data from impaired renal patients with urothelial carcinoma who were treated with immune checkpoint blockade therapies (ICT).

Methods:

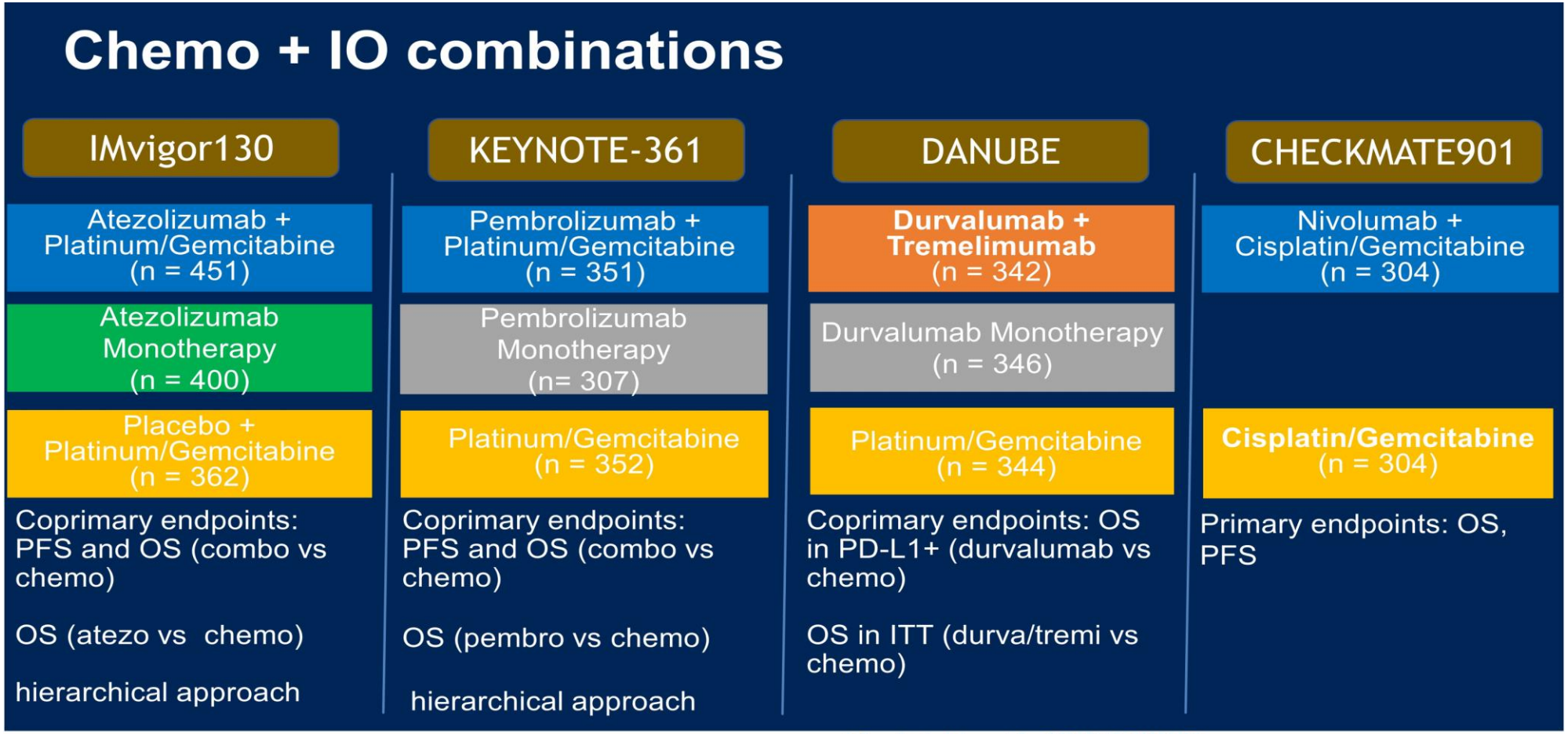
This study included metastatic urothelial carcinoma patients treated with at least one course of ICT. Impaired renal function was defined as a glomerular filtration rate [GFR] less than 60 mL/min. The patients were categorized into 3 different groups GFR≥60mL/min (normal), 60–30mL/min (low), and less than 30 mL/min (very low) based on GFR. The primary endpoints were the overall response rate (ORR), overall survival (OS), duration of response with ICT, and safety. Median follow-up and OS were estimated using the Kaplan-Meier method.

Results:



The Median OS rate for GFR normal, low and very low groups were 11.9 (7.2–16.5) months, 4.7 (1.8–7.7), and 6.8 (1.1–13.6) months, p=0.015, respectively.

Metastatik Mesane Kanseri Birinci Basamak
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri



PRESENTED BY: Pooja Ghatalia

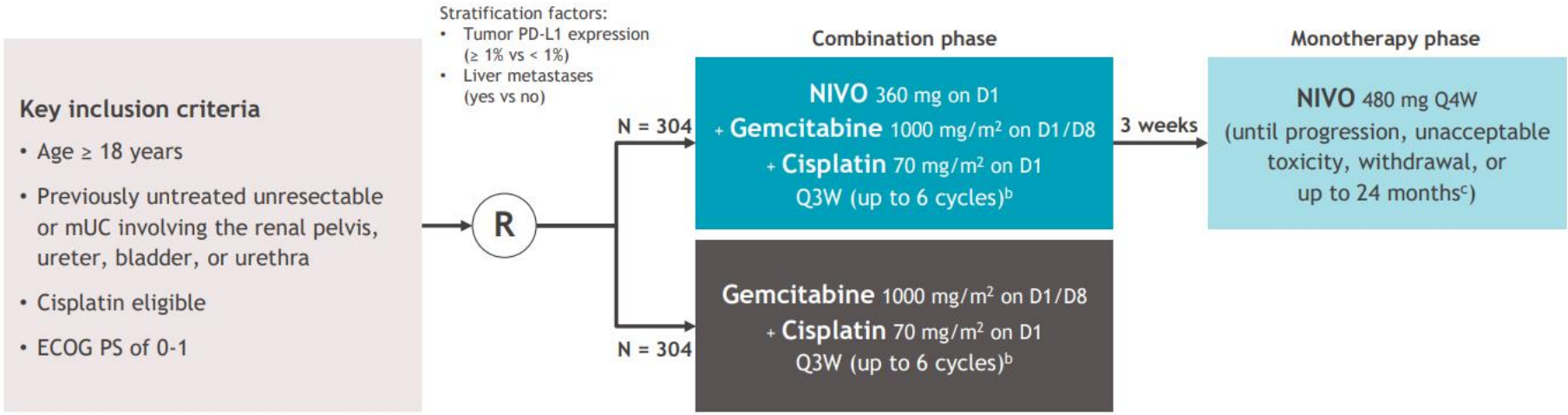
1.Grande et al. Lancet Onc 2024 PMID 38101433
2.Powles et al. Lancet Onc 2021 PMID 34051178
3.Powles et al. Lancet Onc 20201 PMID 32971005
4.Van der Heijden et al. NEJM 2023 PMID 37870949

Sisplatine uygun hastalarda İmmün kontrol noktası inhibitörleri ile kombinasyon

CheckMate 901

Study design

- NIVO + gemcitabine-cisplatin vs gemcitabine-cisplatin 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%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO + gemcitabine-cisplatin combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA, USA).
BICR, blinded independent central review; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; 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.

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

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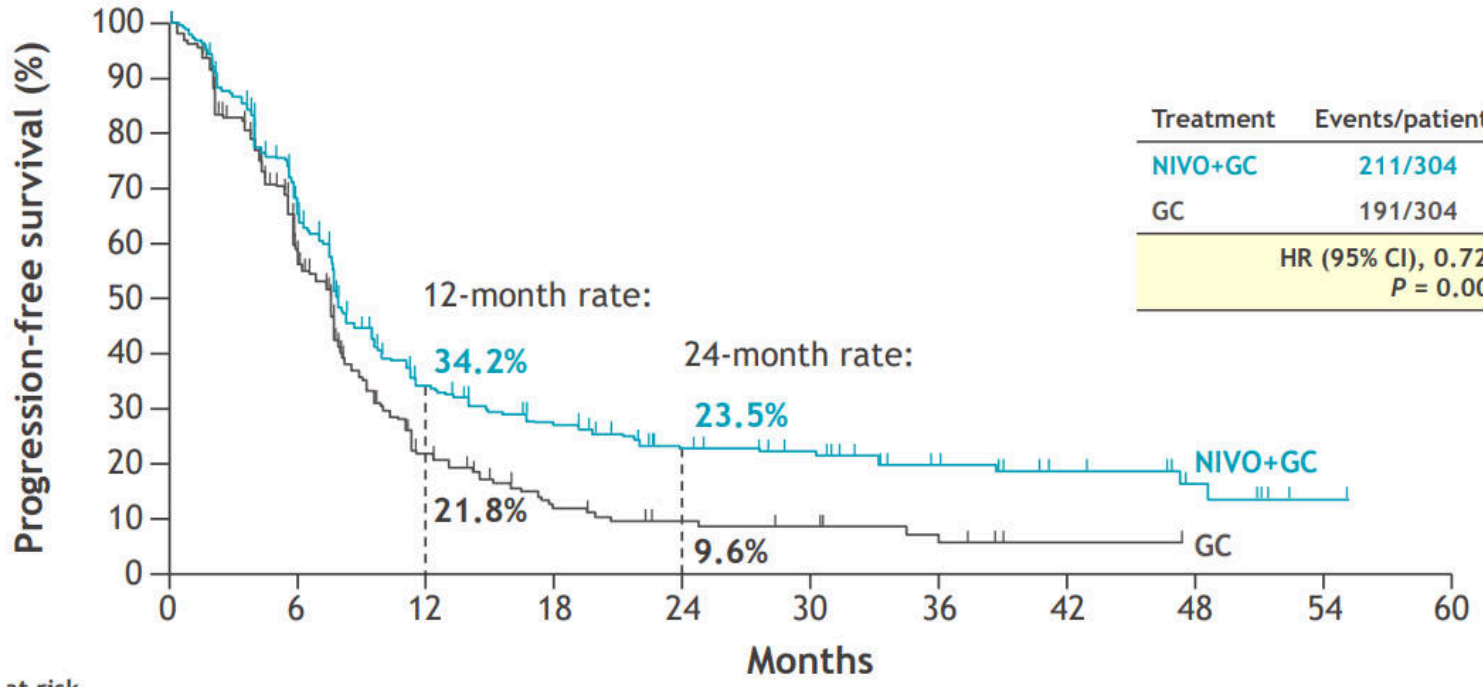
PFS per BICR (primary endpoint)



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 time from randomization to first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who did not progress or die were censored at last evaluable tumor assessment. Patients without on-study tumor assessments who did not die were censored at randomization. **Patients who started any subsequent anticancer therapy without prior reported progression were censored at last evaluable tumor assessment before initiation of subsequent therapy.**

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

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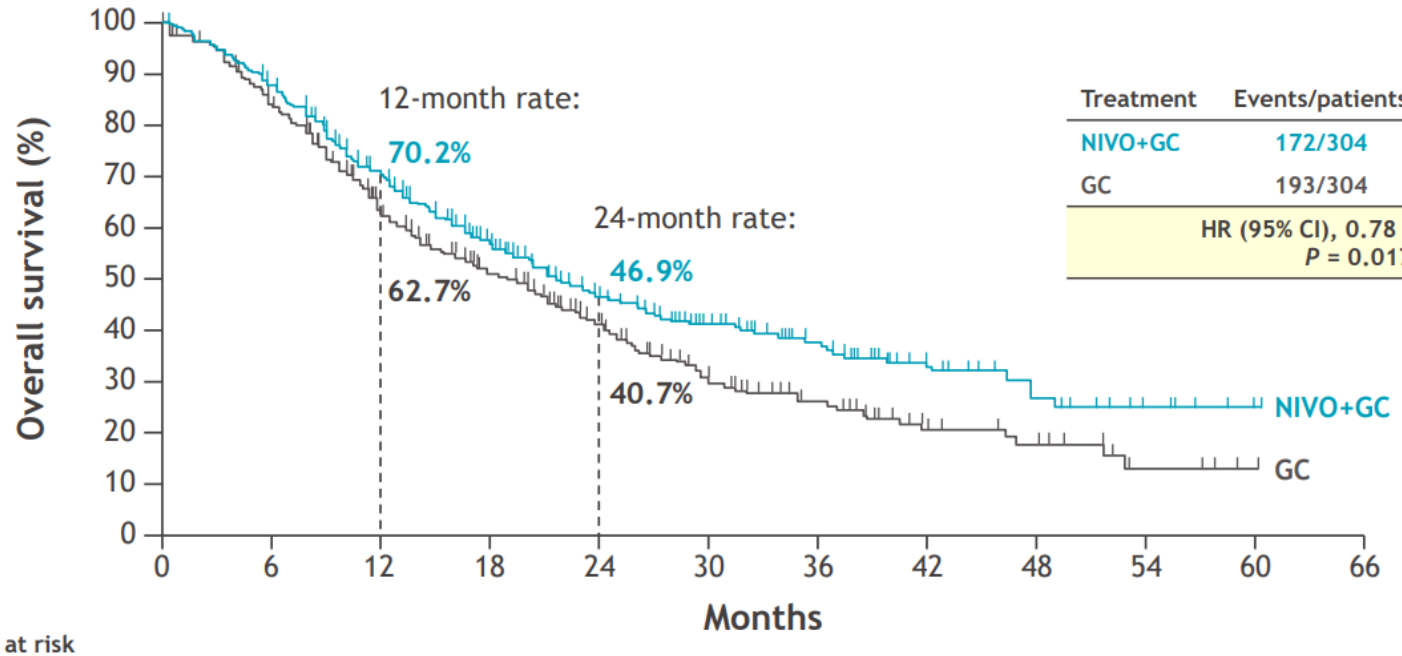
OS (primary endpoint)



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

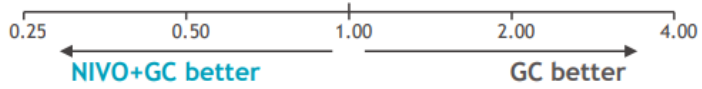
Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with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

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

CheckMate 901

OS in subgroups

Subgroup	No. of patients	NIVO+GC No. of events/no. of patients	GC No. of events/no. of patients	Unstratified HR for death (95% CI)
Overall (N = 608)		172/304	193/304	0.78 (0.63-0.95)
Age, years				
< 65	298	85/150	100/148	0.69 (0.51-0.92)
≥ 65 and < 75	236	65/120	66/116	0.89 (0.63-1.26)
≥ 75	74	22/34	27/40	0.86 (0.49-1.52)
Sex				
Male	470	133/236	147/234	0.76 (0.60-0.97)
Female	138	39/68	46/70	0.82 (0.54-1.26)
Race				
White	436	123/211	145/225	0.80 (0.63-1.02)
Asian	138	38/75	36/63	0.71 (0.45-1.12)
Other	32	11/18	10/14	0.84 (0.35-1.97)
Region				
US	40	18/19	15/21	1.92 (0.95-3.88)
Asia	133	36/72	34/61	0.73 (0.46-1.17)
Europe	276	72/134	90/142	0.73 (0.53-0.99)
Rest of the world	159	46/79	54/80	0.73 (0.49-1.08)
ECOG PS				
0	324	74/162	87/162	0.70 (0.51-0.95)
1	[illegible]	[illegible]	[illegible]	0.85 (0.64-1.11)
PD-L1 expression				
≥ 1%	221	64/111	67/110	0.75 (0.53-1.06)
< 1% or indeterminate	387	108/193	126/194	0.80 (0.62-1.04)
Liver metastases				
Yes	128	45/64	48/64	0.77 (0.51-1.16)
No	480	127/240	145/240	0.77 (0.61-0.98)
Previous systemic anticancer therapy				
Yes	156	44/88	41/68	0.90 (0.59-1.38)
No	452	128/216	152/236	0.76 (0.60-0.96)



All randomized patients. HRs were not computed for subgroup categories (except for age, sex, race, and region) with < 10 patients per treatment group. Categories without a meaningful estimate of the HR are not shown. PD-L1 expression and liver metastases are per interactive response technology. There were no patients with indeterminate PD-L1 status. Previous systemic anticancer therapy refers to neoadjuvant/adjuvant treatments for patients undergoing radical resection or as part of a bladder-sparing approach in muscle-invasive bladder cancer.

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

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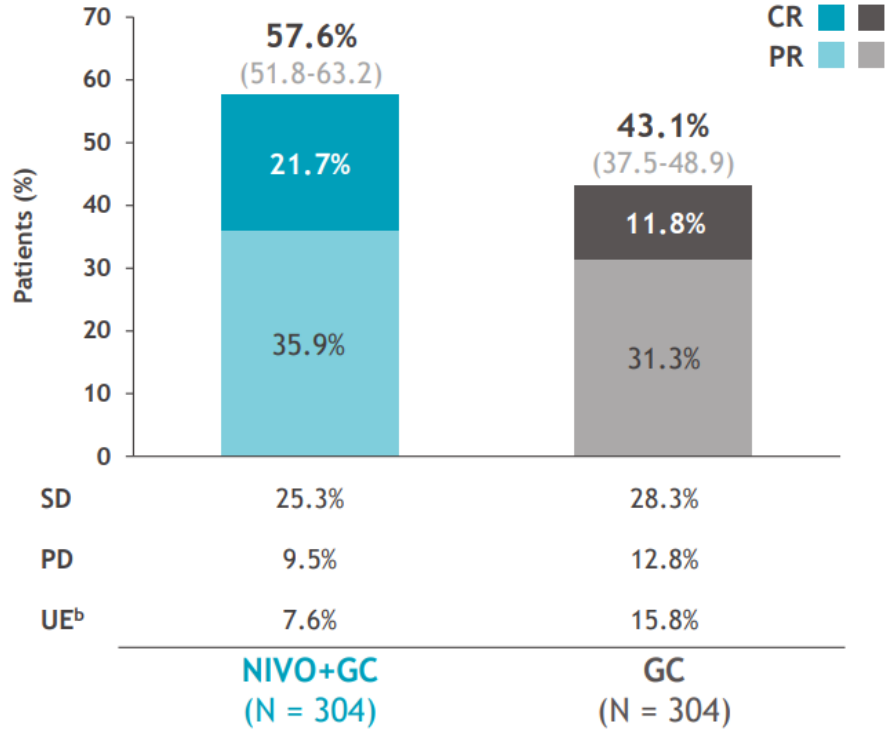
Objective response outcomes (exploratory endpoints)

ORR (95% CI) and BOR per BICR[a]



Time to and duration of responses

Any objective response[c]	NIVO+GC (n = 175)	GC (n = 131)
Median TTR (Q1-Q3), months	2.1 (2.0-2.3)	2.1 (2.0-2.2)
Median DoR (95% CI), months	9.5 (7.6-15.1)	7.3 (5.7-8.9)

Complete response[d]	NIVO+GC (n = 66)	GC (n = 36)
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

[a]In all randomized patients. [b]The most common reasons for UE response included death before first tumor assessment, withdrawal of consent, treatment stopped due to toxicity, patient never treated, and receipt of subsequent anticancer therapy before first tumor assessment. [c]Based on patients with an objective response per BICR (PR or CR as BOR). [d]Based on patients with a CR per BICR.
BOR, best overall response; CR, complete response; DoCR, duration of complete response; DoR, duration of objective response; NE, not estimable; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease; TTCR, time to complete response; TTR, time to objective response; UE, unevaluable.

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

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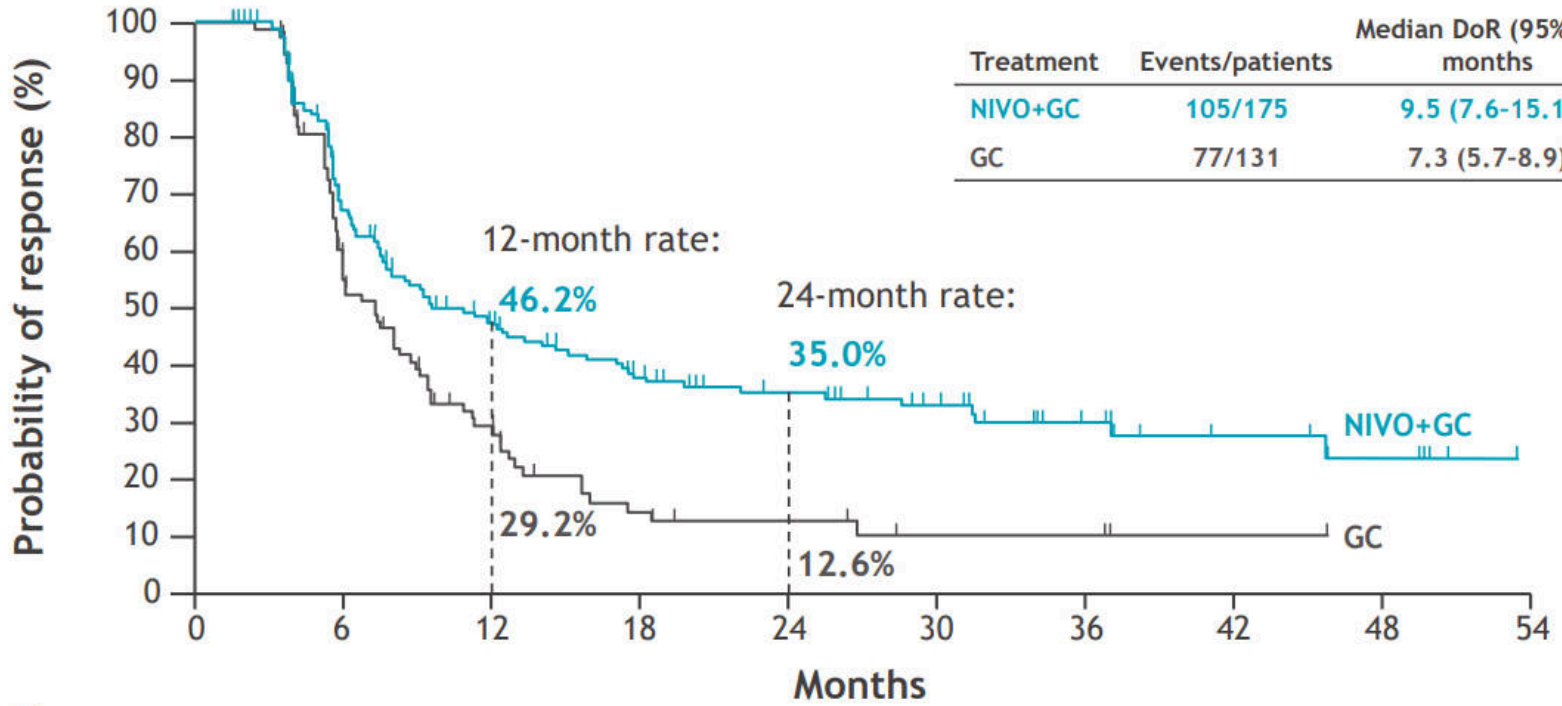
Duration of objective response per BICR



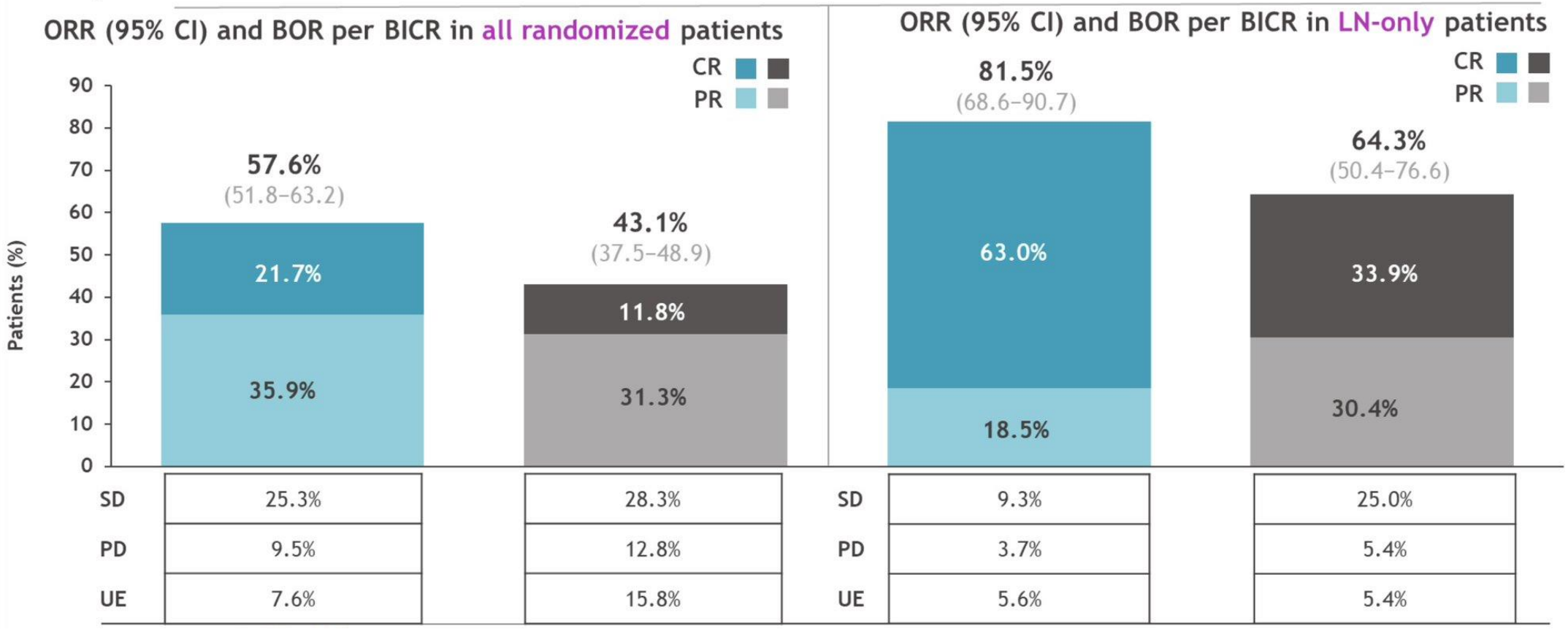
Treatment	Events/patients	Median DoR (95% CI), months
NIVO+GC	105/175	9.5 (7.6-15.1)
GC	77/131	7.3 (5.7-8.9)

No. at risk										
NIVO+GC	175	104	64	47	34	26	15	9	5	0
GC	131	49	22	9	6	3	3	1	0	0

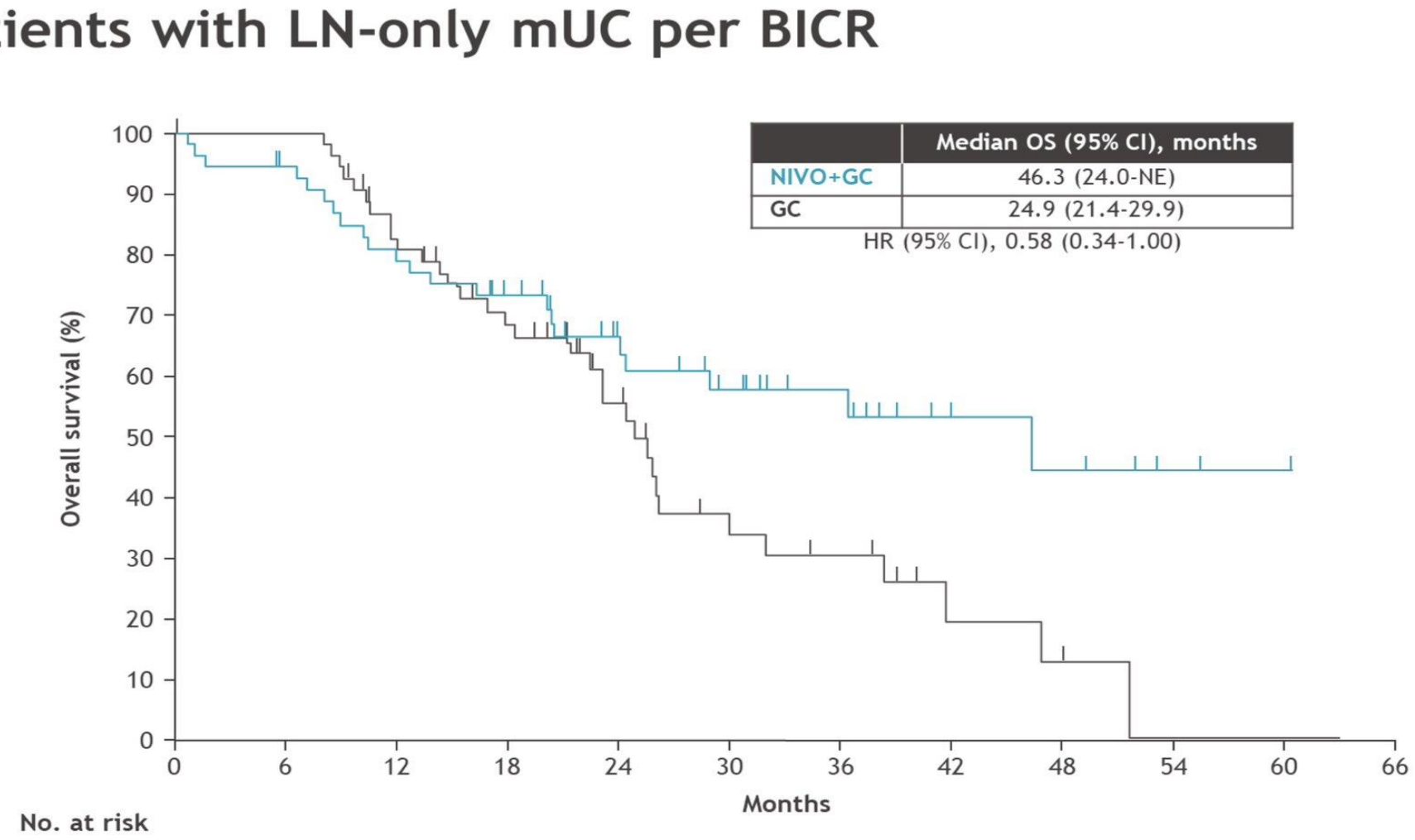
Sisplatin+Gemsitabin+Nivolumab
Yalnız lenf nodu metastazı olanlarda yanıt

Response per BICR: patients with LN-only mUC

- CR rates for NIVO+GC-treated patients with LN-only mUC were approximately twice that of GC-treated patients



Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab Yalnız lenf nodu metastazı olanlarda Genel sağkalım

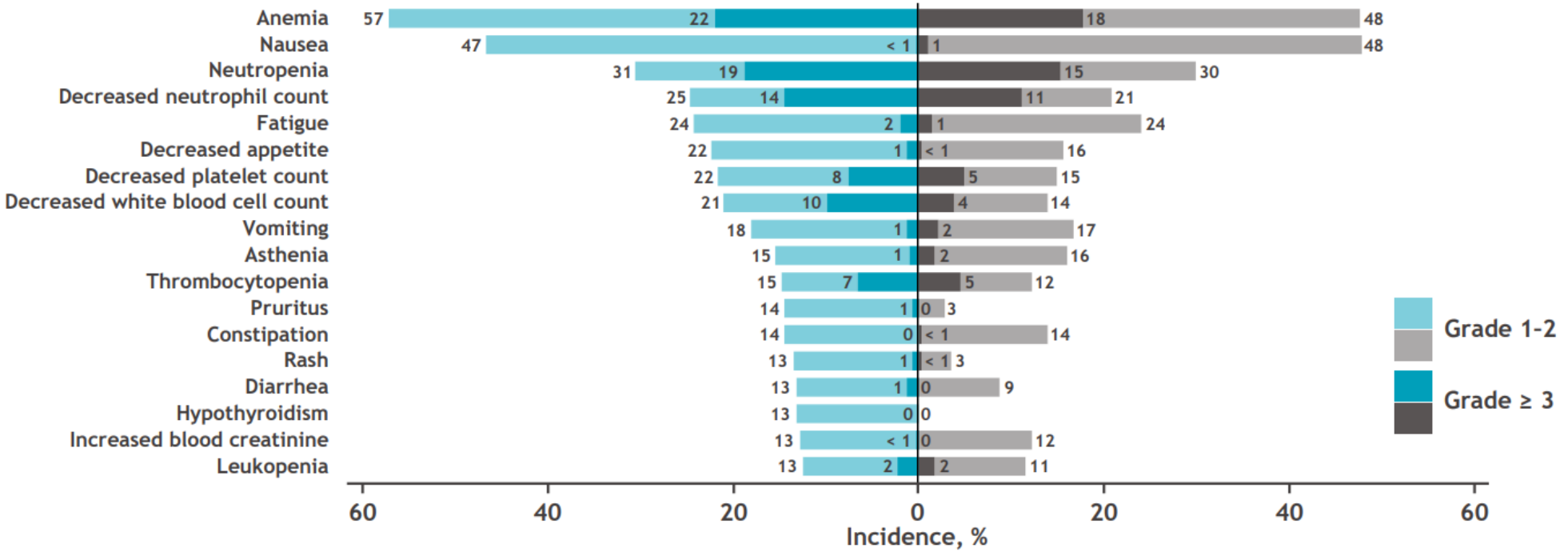


Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

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 discontinuation	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).
AE, adverse event.

Ürotelyal Kanserlerde Platin Direnci İmmünoterapi Direnci ile İlişkili

International Journal of Clinical Oncology (2022) 27:585–591
https://doi.org/10.1007/s10147-021-02072-x

ORIGINAL ARTICLE

Response to first-line chemotherapy regimen is associated with efficacy of ımmune checkpoint blockade therapies in patients with metastatic urothelial carcinoma

Deniz Tural[1] · Fatih Selçukbiricik[2] · Ömer Fatih Ölmez[3] · Ahmet Taner Sümbül[4] · Mustafa Erman[5] · Hasan Şenol Coşkun[6] · Mehmet Artaç[7] · Saadettin Kılıçkap[8]

Received: 16 August 2021 / Accepted: 2 November 2021 / Published online: 11 November 2021

Abstract

Background Atezolizumab (ATZ) has demonstrated antitumor activity in previous studies in patients with metastatic platinum-resistant urothelial carcinoma. However, the response rate of ATZ was modest. Therefore, finding biologic or clinical biomarkers that could help to select patients who respond to the immune checkpoint blockade remains important.

Patients and methods In this study, we present the retrospective analysis of 105 patients with urothelial cancer treated with ATZ after progression on first-line chemotherapy. Data of patients were obtained from patient files and hospital records. The association between response to first-line chemotherapy and ATZ was using Fisher's exact test. Median follow-up was calculated using the reverse Kaplan–Meier method. OS was estimated by using the Kaplan–Meier method.

Results The median follow-up time was 23.5 months. Forty (74.1%) of patients who experienced clinical benefit after firs-line chemotherapy also had clinical benefit after atezolizumab, while only 14 (25.9%) of patients with initial PD after first-line chemotherapy subsequently experienced clinical benefit with ATZ ($p=0.001$). The median OS on ATZ of 14.8 and 3.4 months for patients with clinical benefit and progressive disease in response to first-line chemotherapy, respectively ($p=0.001$). Three of the adverse prognostic factors according to the Bellmunt criteria were independent factors of short survival: liver metastases {Hazard ratio [HR] = 1.9; $p=0.04$}, ECOG PS ≥ 1 (HR = 2.7; $p=0.001$), and Hemoglobin level below 10 mg/dl (HR = 2.8; $p<0.001$). In addition, patients with clinical benefit from first-line chemotherapy (HR = 0.39; $p<0.001$) maintained a significant association with OS in multivariate analysis.

Conclusions Our study demonstrated that clinical benefit from first-line chemotherapy was independent prognostic factors on OS in patients' use of ATZ as second-line treatment in metastatic bladder cancer. Furthermore, these findings are important for stratification factors for future immunotherapy study design in patients with bladder cancer who have progressed after first-line chemotherapy.

Keywords Atezolizumab · Urothelial carcinoma · Bladder cancer · Chemotherapy · Immunotherapy · Outcomes

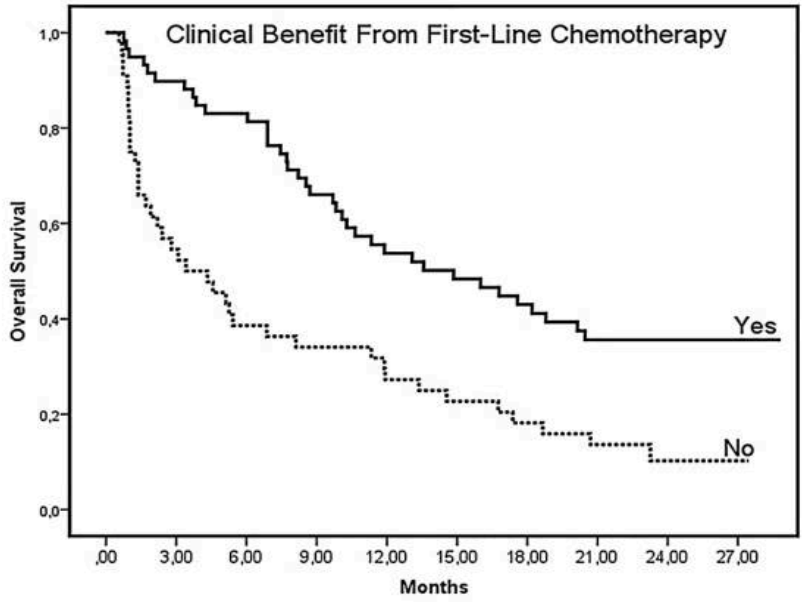
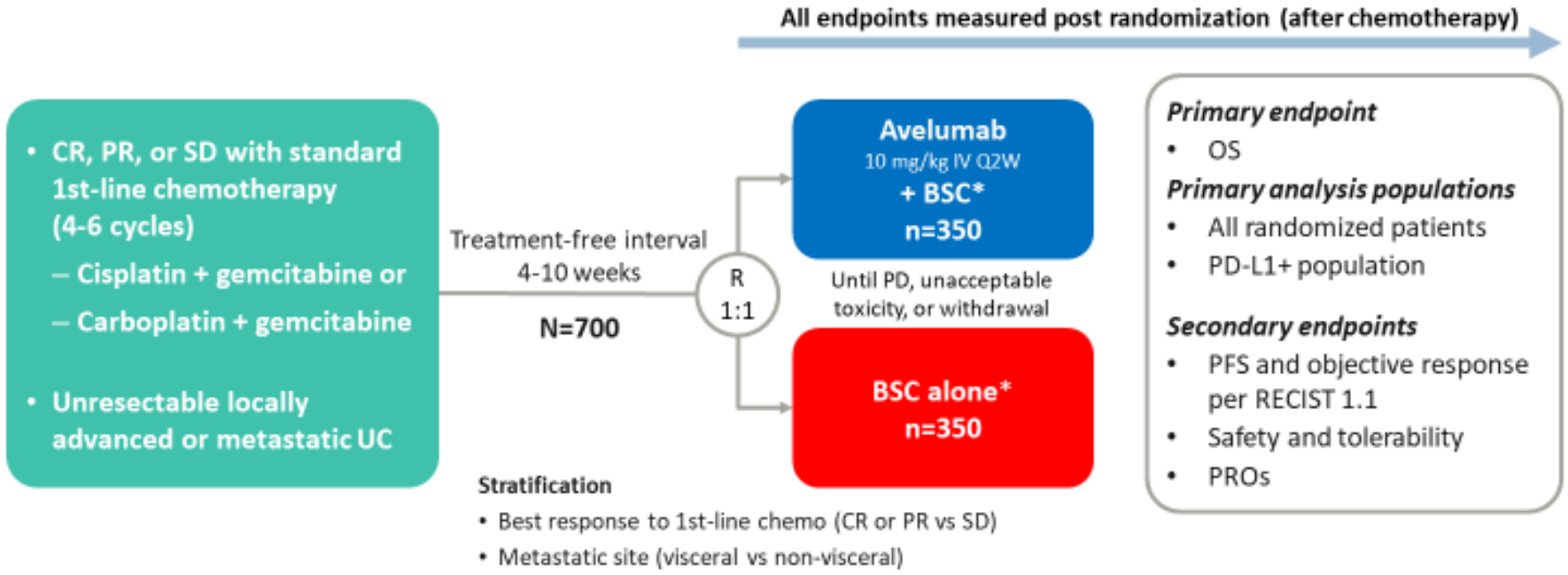


Fig. 2 Kaplan–Meier curves association of clinically benefited from the first-line treatment and overall survival

The median OS on ATZ of 14.8 and 3.4 months for patients with clinical beneft and progressive disease in response to frst-line chemotherapy, respectively (p=0.001).

Metastatik Ürotelyal Kanserlerde Birinci Basamak Tedavi
Platin bazlı kemoterapi Sonrası İdame Avelumab

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 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

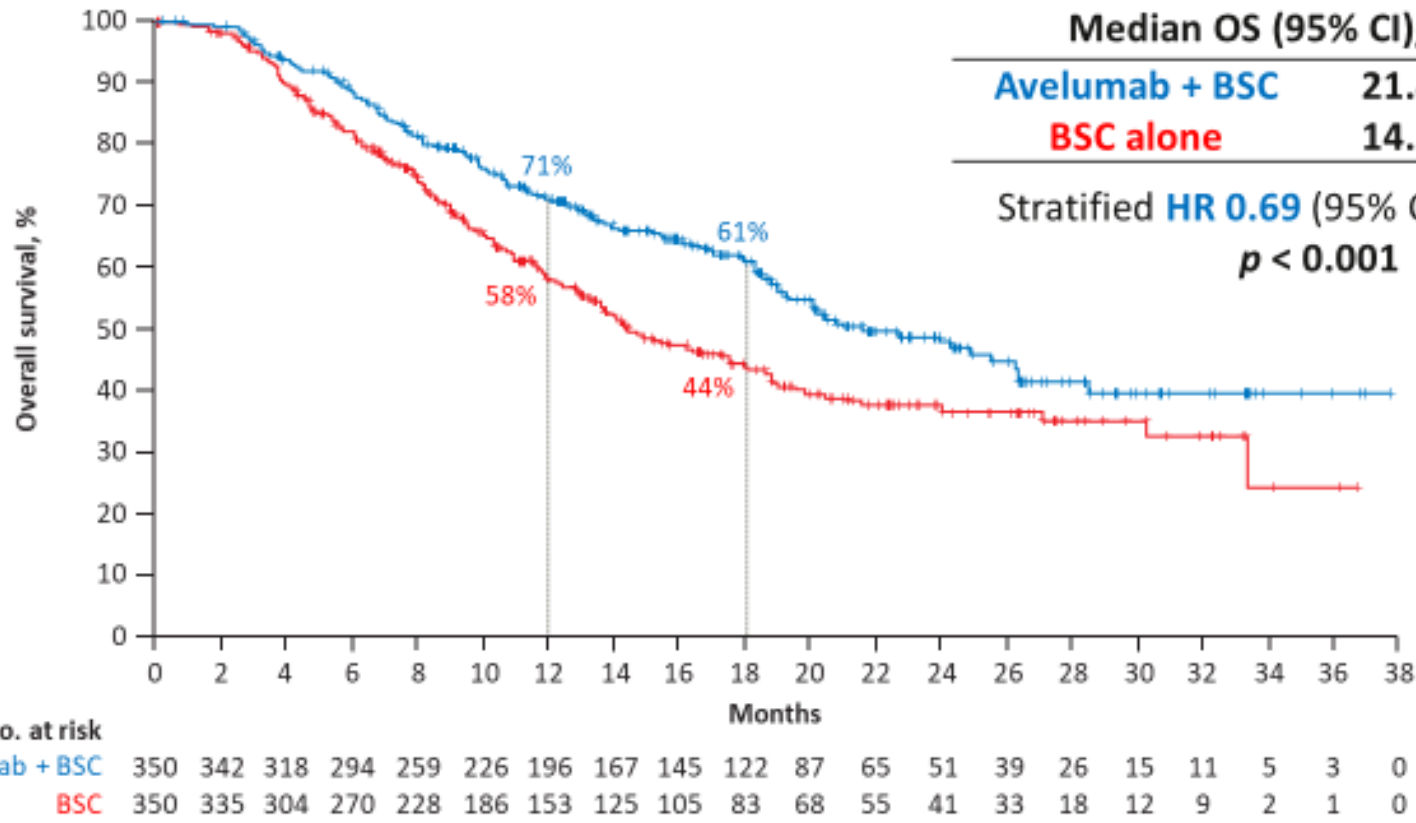
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Powles T et al. ASCO 2020;Abstract LBA1.

Courtesy of Arjun V. Balar, MD

Metastatik Ürotelyal Kanserlerde Birinci Basamak Tedavi
Platin bazlı kemoterapi Sonrası İdame Avelumab

OS in the overall population



Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)
***p* < 0.001**

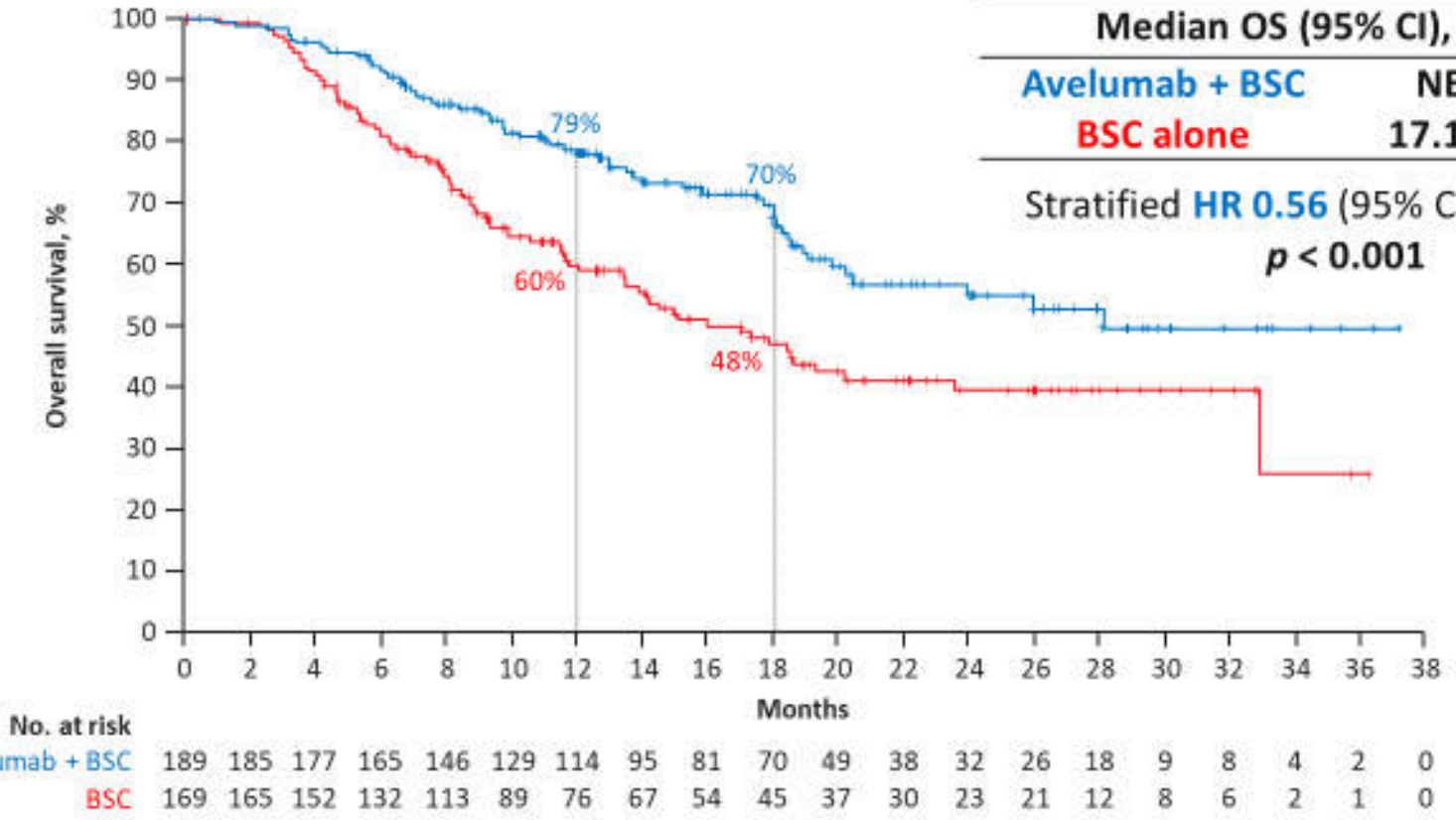
OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

Powles T et al. ASCO 2020;Abstract LBA1.

Courtesy of Arjun V. Balar, MD

Metastatik Ürotelyal Kanserlerde Birinci Basamak Tedavi
Platin bazlı kemoterapi Sonrası idame Avelumab

OS in the PD-L1+ population



Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)

***p* < 0.001**

No. at risk																				
Avelumab + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

Powles T et al. ASCO 2020;Abstract LBA1.

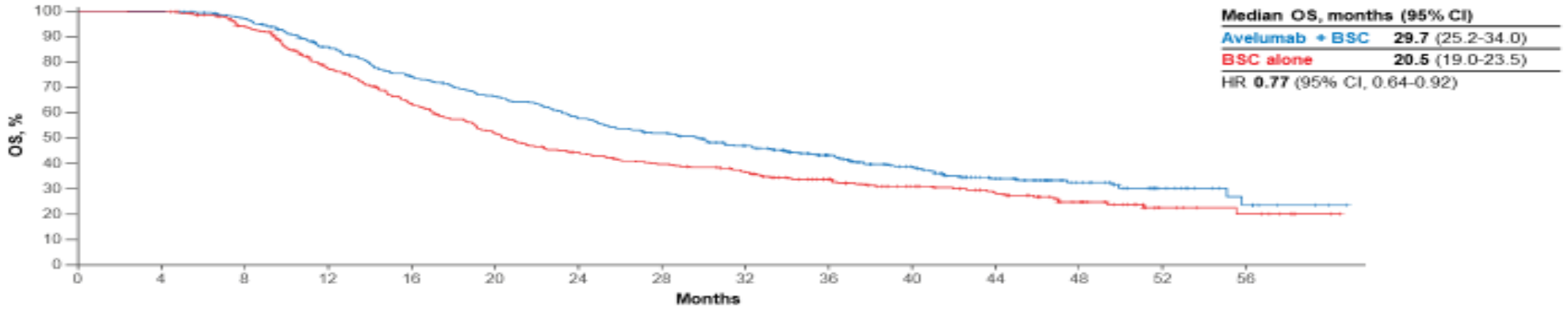
Courtesy of Arjun V. Balar, MD

Metastatik Ürotelyal Kanserlerde Birinci Basamak Tedavi
Platin bazlı kemoterapi Sonrası idame Avelumab

Long-term Analysis | Data Cut-off: 4th June 2021

OS From the Start of 1L CT in All Randomized Patients[1]

Post hoc analysis



No. at risk															
Avelumab + BSC	350	350	334	288	247	220	191	171	145	114	86	58	36	17	7
BSC	350	349	317	255	207	168	141	125	111	89	68	54	33	12	8

In the overall population, median OS measured from the start of 1L chemotherapy was 29.7 months (95% CI, 25.2-34.0) in the avelumab + BSC arm and 20.5 months (95% CI,19.0-23.5) in the BSC alone arm (HR, 0.77 [95% CI, 0.636-0.921])

1L, first-line; BSC, best supportive care; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival.
1. Sridhar SS, et al. Poster 508. Presented at: ASCO GU Symposium; February 16-18, 2023; San Fransisco, CA.

Birinci basamak platin bazlı kemoterapiye yanıt vermeyen hastalar idame İmmün kontrol noktası inhibitörlerine cevap verebilir mi

Patient characteristics	*n*	%
Median age (years) 65 (min.:37; max.: 86)		
Gender (male)	90	85.7
Site of primary tumor		
Bladder	92	87.6
Upper tract	13	12.4
ECOG-PS		
0	27	25.7
1	74	70.5
2	4	3.8
Baseline creatinine clearance <60 ml/min	38	36.2
Baseline hemoglobin concentration <10 g/dl	30	28.6
Smoking status		
Current smoker	27	25.7
Ex-smoker	53	50.5
Never smoker	25	23.8
Metastatic site at baseline		
Visceral	84	80
Liver	16	15.2
Lymph node only	15	14.3
Number of bellmunt risk factors		
0	19	18
1	55	52.4
2	26	24.8
3	5	4.8
Metastatic at the time of diagnosis	45	42.9
Neoadjuvant chemotherapy	21	20
Pelvic radiotherapy	33	31.4
Cystectomy	43	41
Previous chemotherapy		
Cisplatin-based	59	56
Carboplatin-based	46	44
Median Number of cycles of platinum-based first-line chemotherapy	4	2–6
Best response to first-line treatment		
Complete response (CR)	5	4.8
Partial response (PR)	38	36.2
Stable disease (SD)	16	15.2
Progressive disease (PD)	46	43.8
Time relapsed since the last chemotherapy		
3 months ≥	18	17
3 months<	87	83

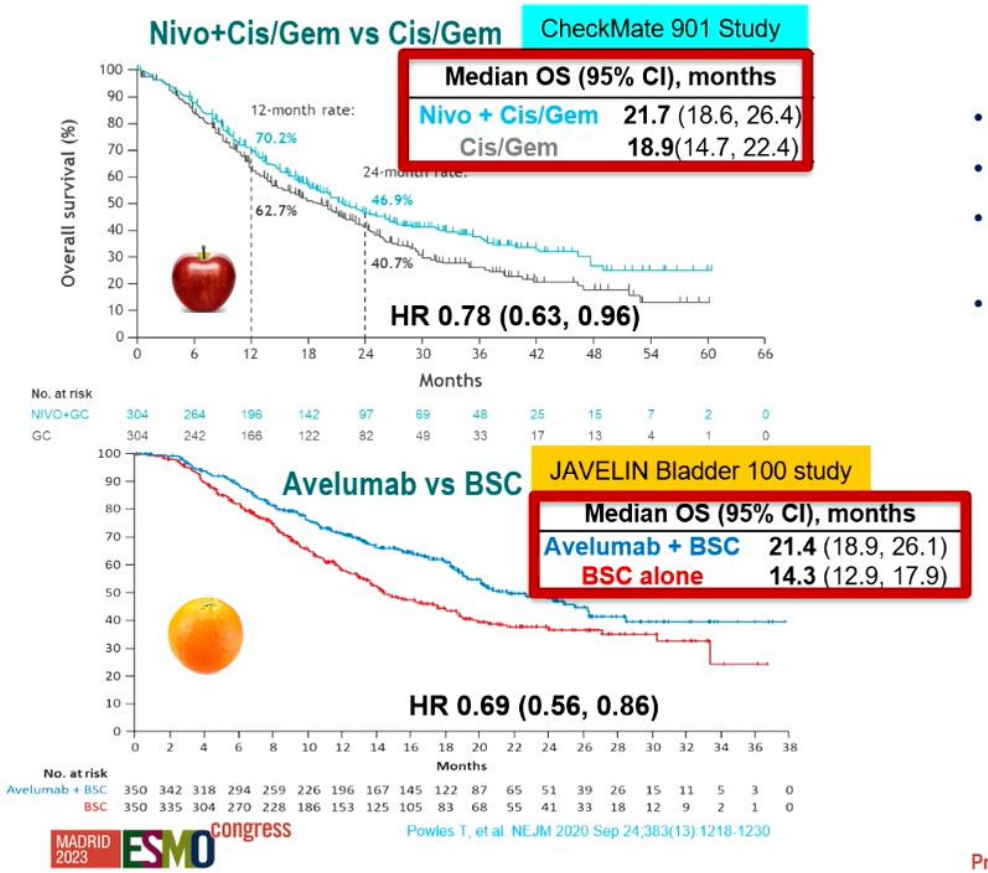
All patients	10	7–13.1	N/A
Best response to first-line treatment			
CR + PR + SD	14.8	8.3–21.4	0.001
PD	3.4	0.5–6.4	
Number of cycles of platinum-based first-line chemotherapy			
4 cycle ≤ 7.8 0.1			
4 cycle > 11.7			
Age (years)			
≤65	8.7	4.2–13.1	0.7
>65	10	5.9–14.2	
Gender			
Male 9.8 6.9–12.7 0.5			
Female 11.9 4.2–19.6			
Smoking status			
Yes	10.2	6.9–13.5	0.9
No	7.72	1.9–13.6	
Location of the tumor			
Upper tract	5.1	2.7–7.4	0.14
Bladder	10.3	6.9–13.6	
ECOG-PS			
0	18.4	14.5–22.3	0.002
1 ≥	8.1	4.2–12	
Baseline creatinine clearance			
<60 ml/min	4.4	2.4–6.3	0.008
≥60 ml/min	14.5	8.3–20.8	
Baseline hemoglobin concentration			
<10 g/dl	3.5	1.5–6.1	0.001
≥10 g/dl	13.4	8.5–18.2	
Metastatic at the time of diagnosis			
Yes	8.4	5.8–11.9	0.3
No	10.8	5.27–15.2	
Lymph node only metastasis			
Yes	14.5	3–26	0.2
No	8.5	5.6–11.4	
Visceral metastasis			
Yes	8.7	5.1–12.3	0.7
No	11.8	6.8–16.9	
Liver metastasis			
Yes	1.4	0.7–2.7	0.001
No	11.4	7.8–14.9	
Number of bellmunt risk factors			
0	20.2	16–24.3	0.001
1	14.2	11.4–16.9	
2	6	3.6–8.5	
3	1.2	0.6–1.9	
Cystectomy			
Yes	10.6	4.6–17	0.3
No	9.7	7.9–12.1	

- İlk seri platin bazlı tedavilere klinik yanıt oranı %56
- Yanıt veren hastaların immün kontrol noktası inhibitörlerinde elde edilen klinik yanıt %74.1
- **İlk basamak platin bazlı kemoterapi altında progresyon gösteren hastaların immün kontrol noktası inhibitörlerine klinik yanıt oranı %25.9**
- Javelin 100 bladder çalışma popülasyonuna dahi edilmeyen hastaların beli bir oranı immün kontrol noktası inhibitörlerinden fayda görebilir

Tural D, International journal of clinical oncology 2022

Metastatik Ürotelyal Kanserlerde Birinci Basamak Tedavi Seçeneği
Sisplatin Gemsitabin Nivolumab vs. Platin bazlı kemoterapi sonrası Avelumab

Both sequential and combination chemo and CPI have efficacy



- We cannot directly compare these studies
- Different patient populations
- Avelumab maintenance study included only responders to 1L chemo
- Length of maintenance CPI therapy was similar: ~6 months for both

Andrea Apolo
Invited Discussant LBA6 and LBA7

Presented by Andrea B. Apolo, MD

Metastatik Ürotelyal Kanseri Sisplatin Uygun Olmayanlarda Birinci Basamak Enfortumab Vedotin + Pembrolizumab Sonuçları

EV-103 Cohort K: Phase 1b/2 Trial

Cohort K
- Unresectable la/mUC
- Cisplatin ineligible
- No prior treatment for la/mUC

N=149 → R 1:1

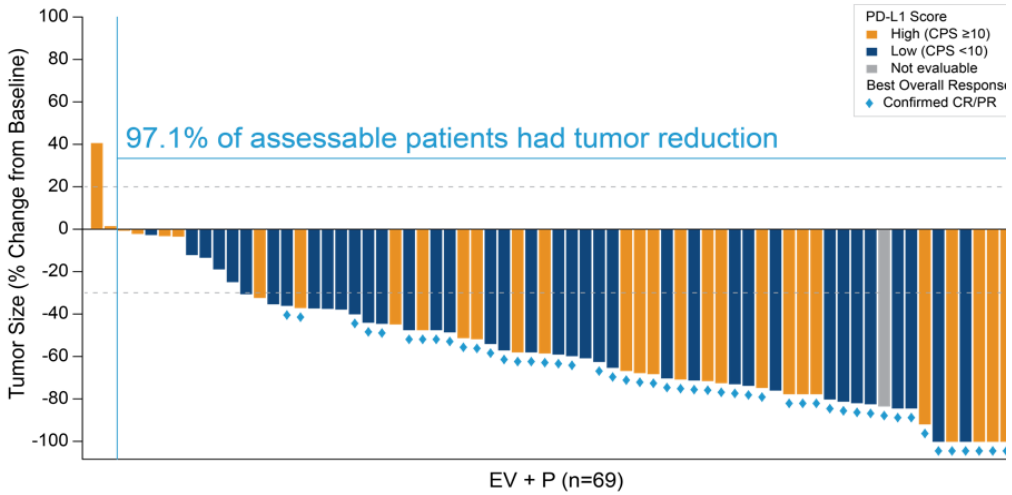
- n=76: EV 1.25 mg/kg days 1 and 8 of a 3-week cycle + Pembrolizumab 200 mg on day 1 of a 3-week cycle
- n=73: EV 1.25 mg/kg days 1 and 8 of a 3-week cycle

Primary Endpoint
- ORR per BICR

Secondary Endpoints
- ORR per investigator assessment
- DOR
- Disease control rate
- PFS
- OS
- Safety

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

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



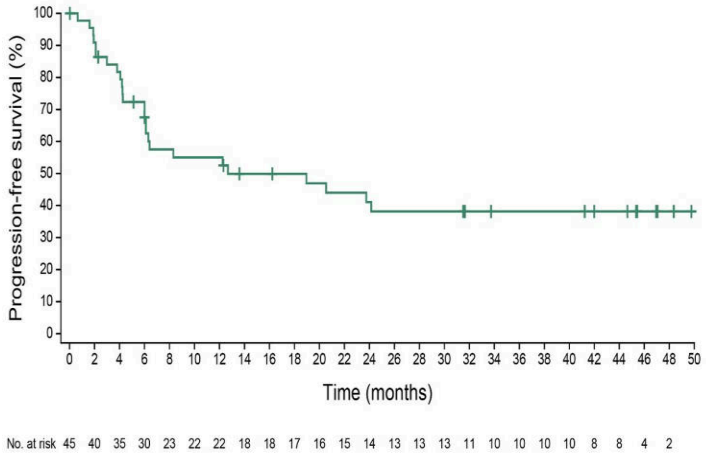
BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

Rosenberg JE, et al. ESMO 2022. Abstract 2895/LBA73.

Enfortumab vedotin ve Pembrolizumab kombinasyonu Sisplatin uygun olmayan Ürotelyal kanserlerde Sonuçları EV103 -EV/pemrolizumab

Progression-Free Survival by BICR

41.1% of patients were progression-free at 24 months

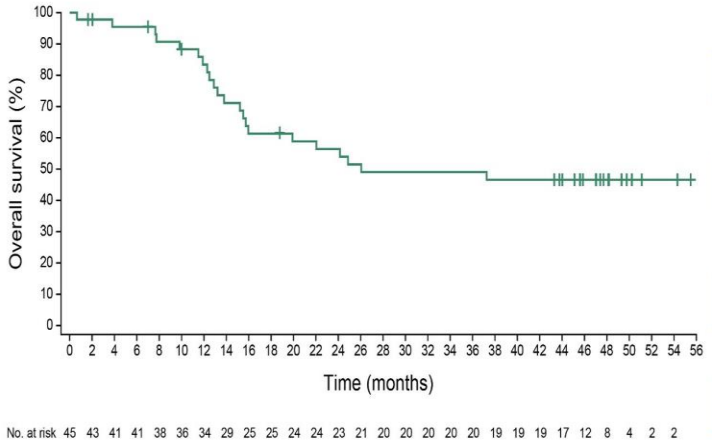


	Dose Escalation + Cohort A (N = 45)
PFS events, n	25
Median PFS (95% CI[a])	12.7 months (6.11-NE)
PFS rate[b] at:	
6 months, % (95% CI[a])	72.4 (56.47-83.26)
12 months, % (95% CI[a])	55.0 (38.84-68.58)
24 months, % (95% CI[a])	41.1 (25.69-55.88)

BICR = blinded independent central review; CI = confidence interval; NE = not estimable; PFS = progression-free survival
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)
[b]As estimated using Kaplan-Meier method

Overall Survival

Median survival exceeds 2 years



	Dose Escalation + Cohort A (N = 45)
OS events, n	22
Median OS (95% CI[a])	26.1 months (15.51-NE)
OS rate[b] at:	
6 months, % (95% CI[a])	95.4 (83.00-98.84)
12 months, % (95% CI[a])	83.4 (68.25-91.72)
24 months, % (95% CI[a])	56.4 (40.03-69.91)
Median follow-up time	47.0 months

CI = confidence interval; NE = not estimable; OS = overall survival
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)
[b]As estimated using Kaplan-Meier method

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Dr. Shilpa Gupta, MD
Presentation is property of the author and ASCO
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Enfortumab vedotin ve pembrolizumab kombinasyonu Sisplatin uygun olmayan Ürotelyal kanserlerde Birinci Basamak Uzun Dönem Tedavi Sonuçları
EV103 -EV/pemrolizumab

Figure 4. PFS per RECIST by BICR

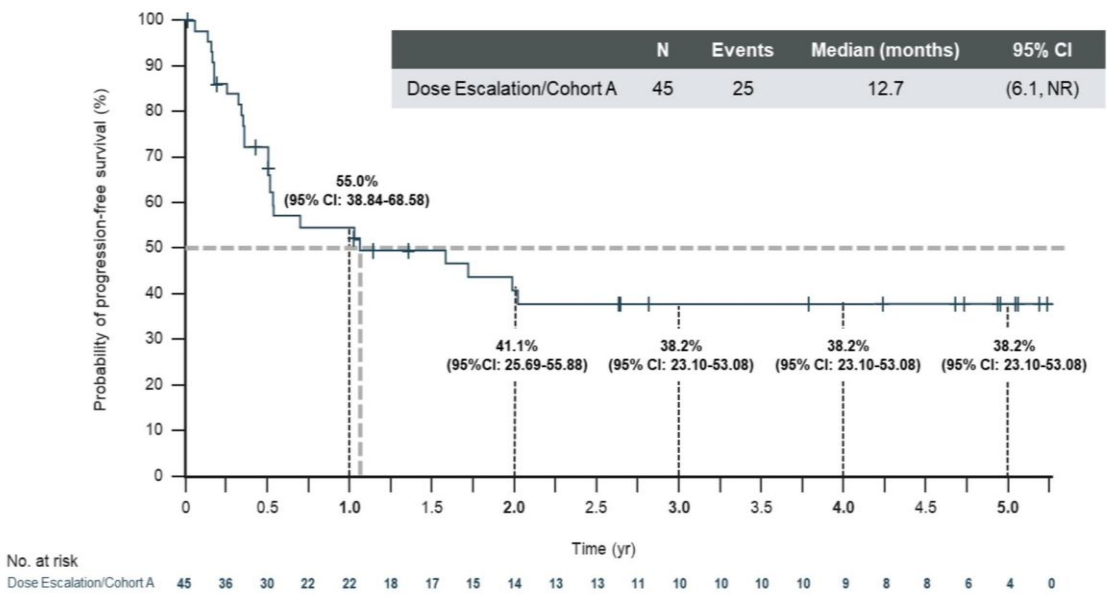
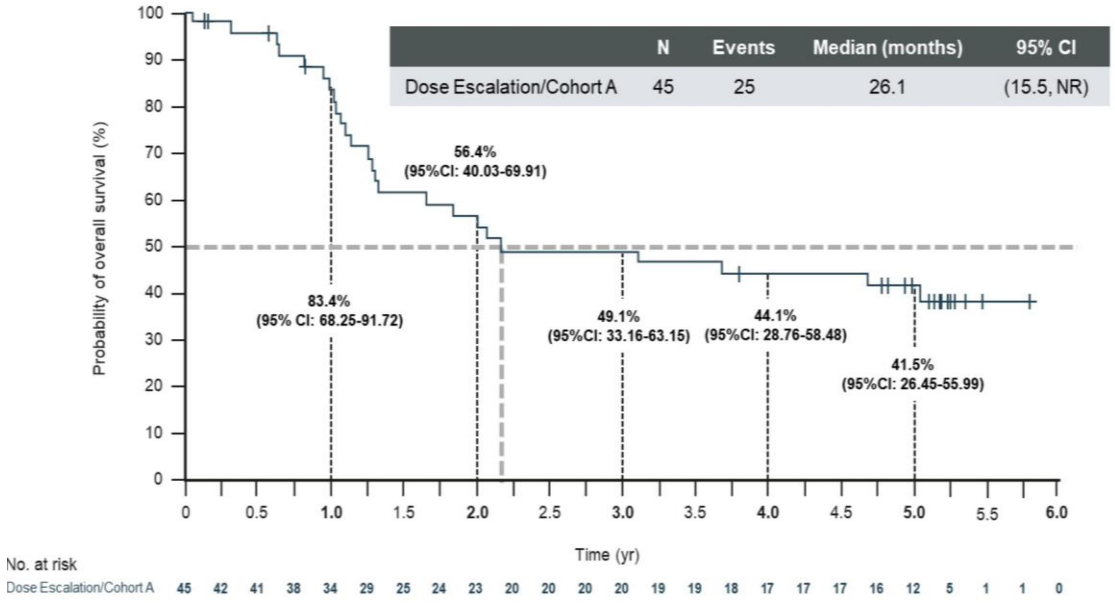


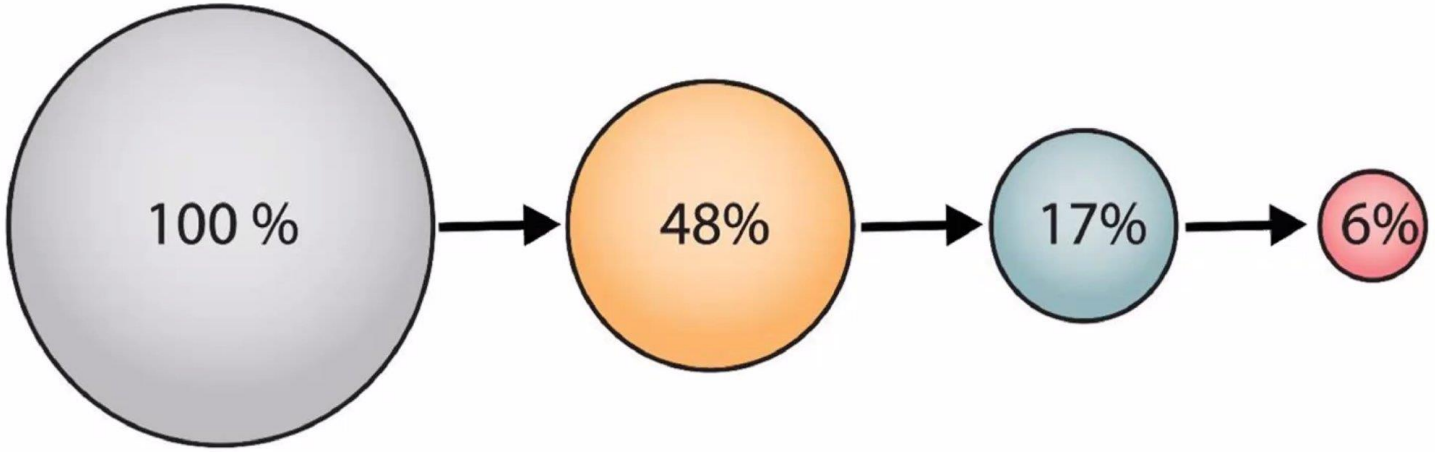
Figure 5. OS



Enfortumab vedotin ve pembrolizumab kombinasyonu sisplatin uygun olmayan hastalarda 5-yılık sağkalım %40

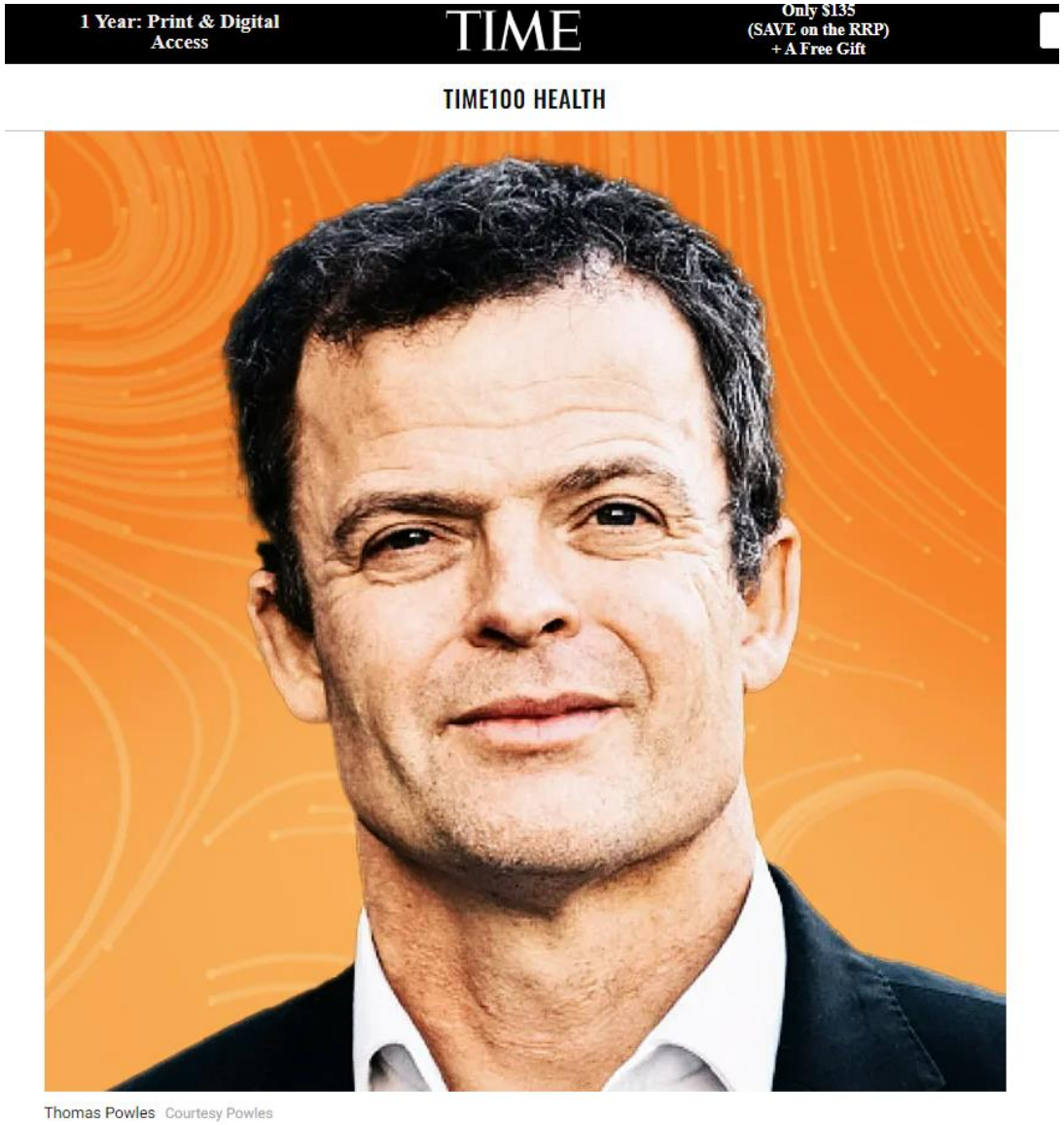
Neden en etkili tedavi ilk sırada verilmeli

Utilization of Systemic Therapy for Advanced Urothelial Carcinoma



Swami U, et al. *Cancer Treat Res Commun.* 2021;27:100325.

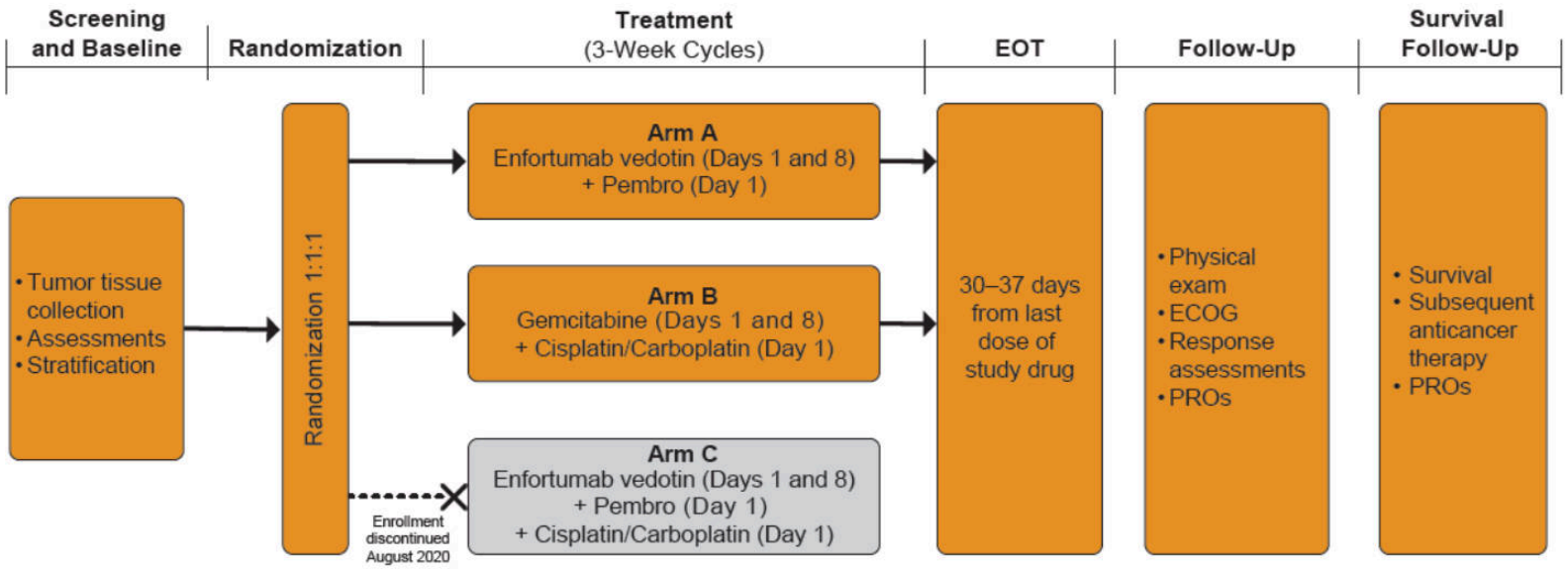
TIME Dergisine Kapak Olan Çalışmanın Sonuçları Açıklandı



Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

EV-302 Randomized Phase 3 Trial Schema

Eligibility
- Locally advanced or metastatic urothelial carcinoma
- 1st line systemic therapy
- Platinum-eligible



EOT= End of Treatment; Pembro=pembrolizumab; PROs=patient reported outcomes

- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

Primary Endpoints: PFS, OS
Secondary Endpoints: ORR, DOR, DCR, QOL, PRO, Safety

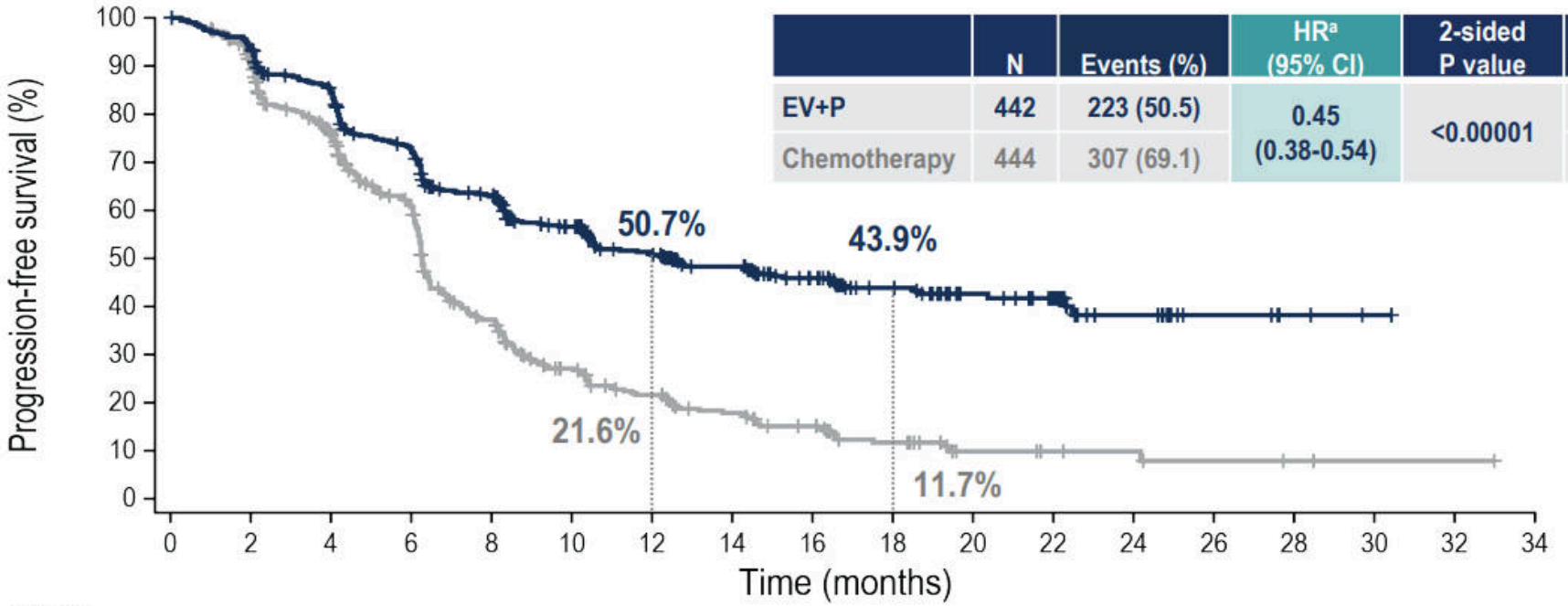
Powles T, ESMO 2023

Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

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)



Powles T, ESMO 2023

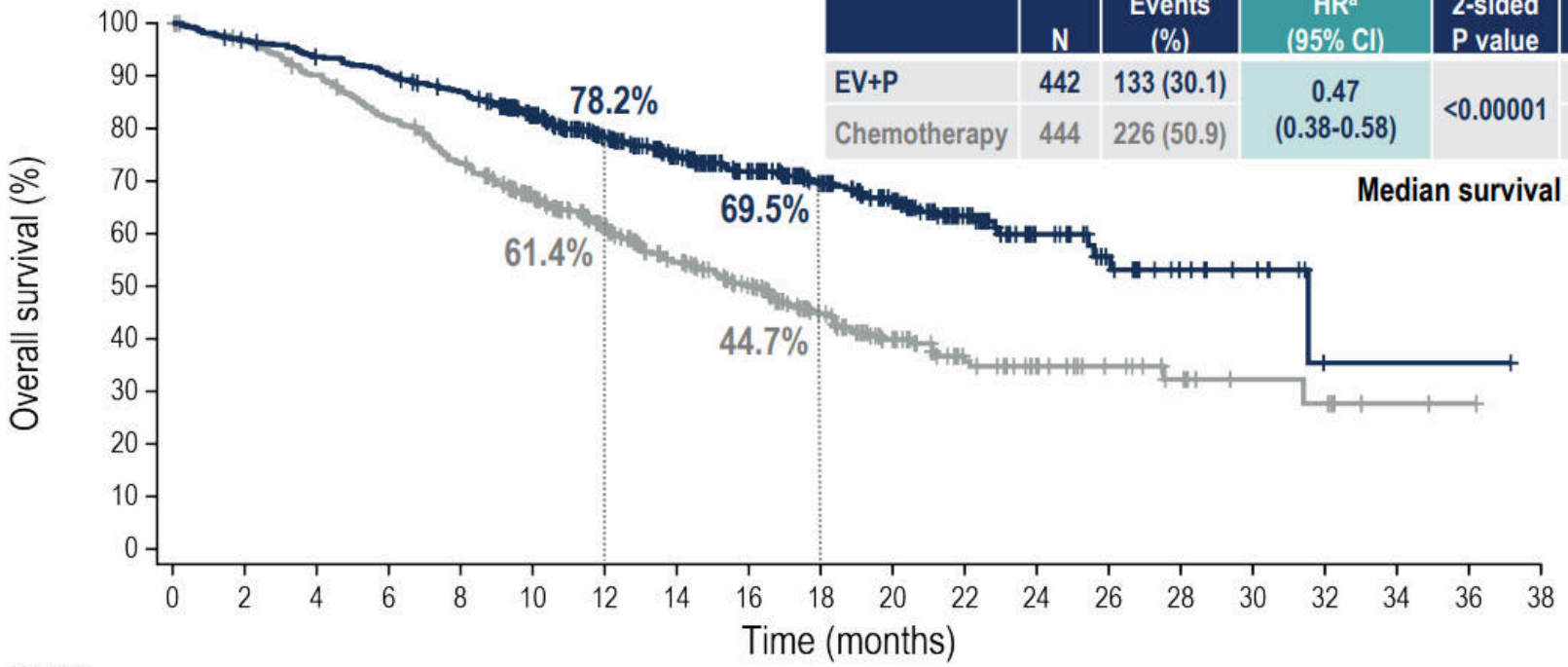
Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

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

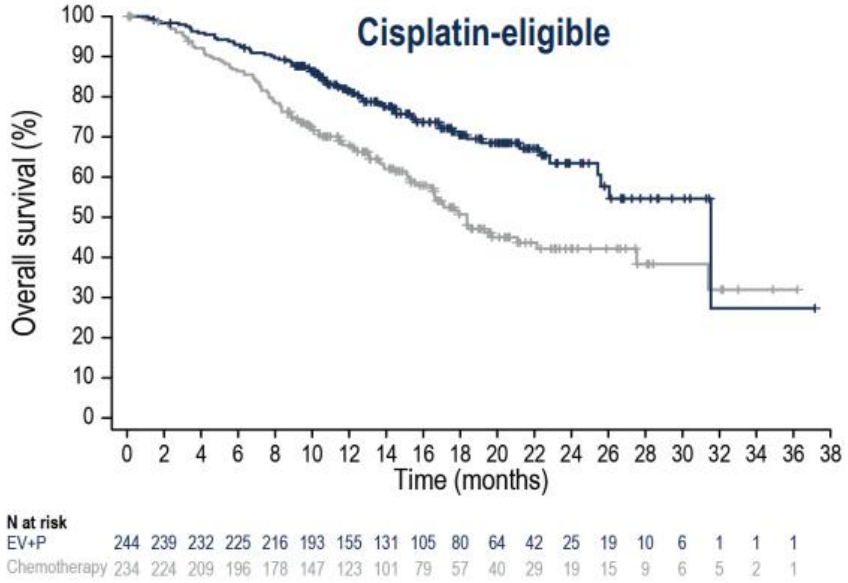


Powles T, ESMO 2023

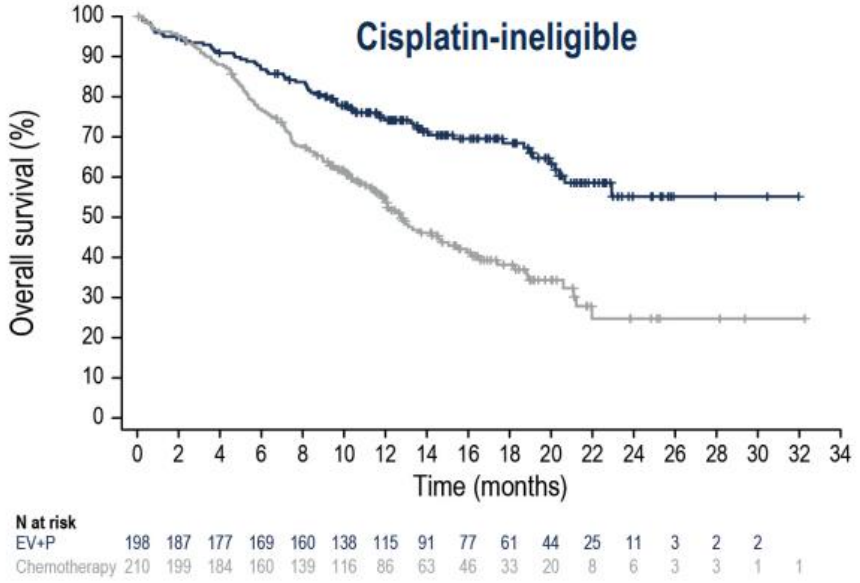
Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility



	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)



	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)

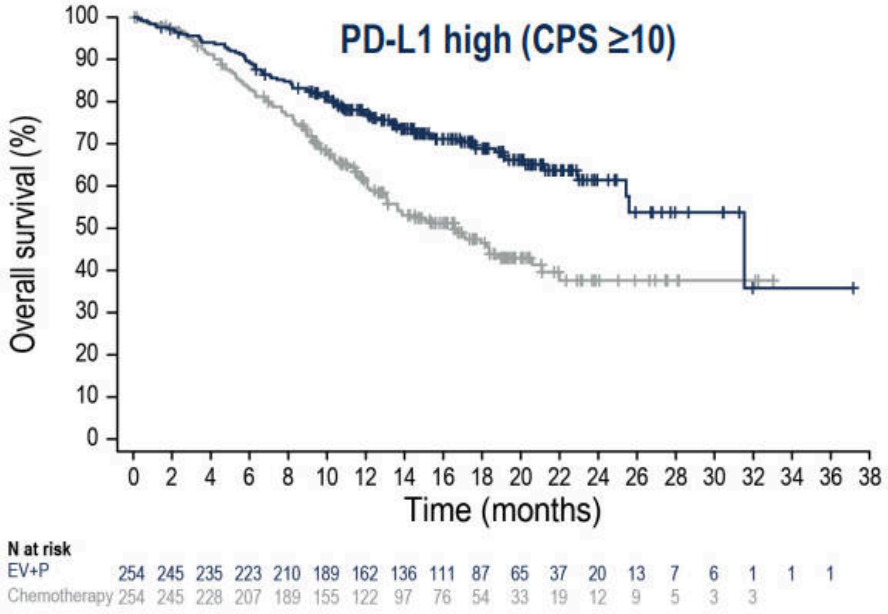
Data cutoff: 08 Aug 2023

Powles T, ESMO 2023

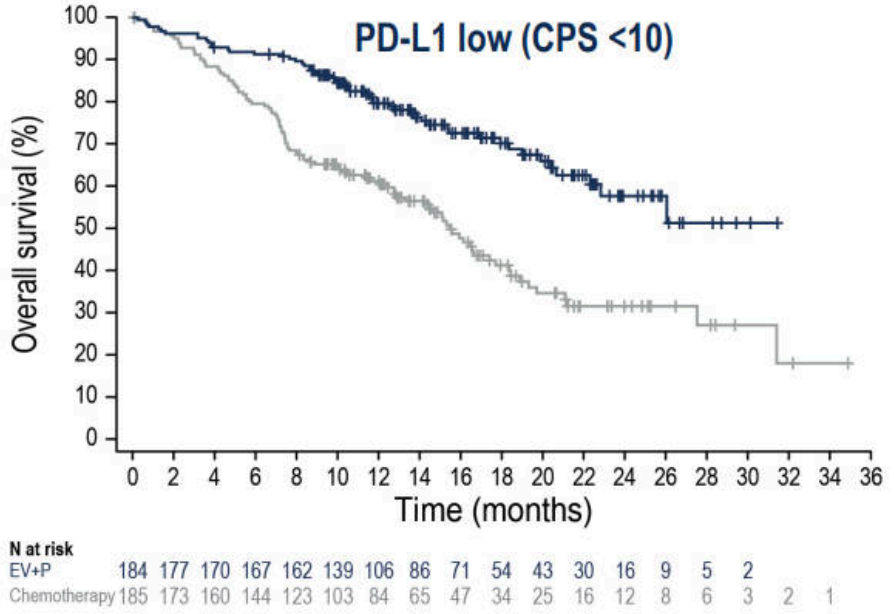
Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

OS Subgroup Analysis: PD-L1 Expression

OS benefit was consistent with overall population regardless of PD-L1 expression status



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	79	0.49 (0.37-0.66)	31.5 (25.4-NR)
Chemotherapy	125		16.6 (13.1-20.6)



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	53	0.44 (0.31-0.61)	NR (22.3-NR)
Chemotherapy	99		15.5 (12.9-17.7)

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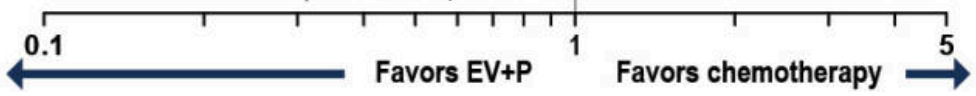
Metastatik Ürotelyal Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

Subgroup Analysis of OS

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

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)

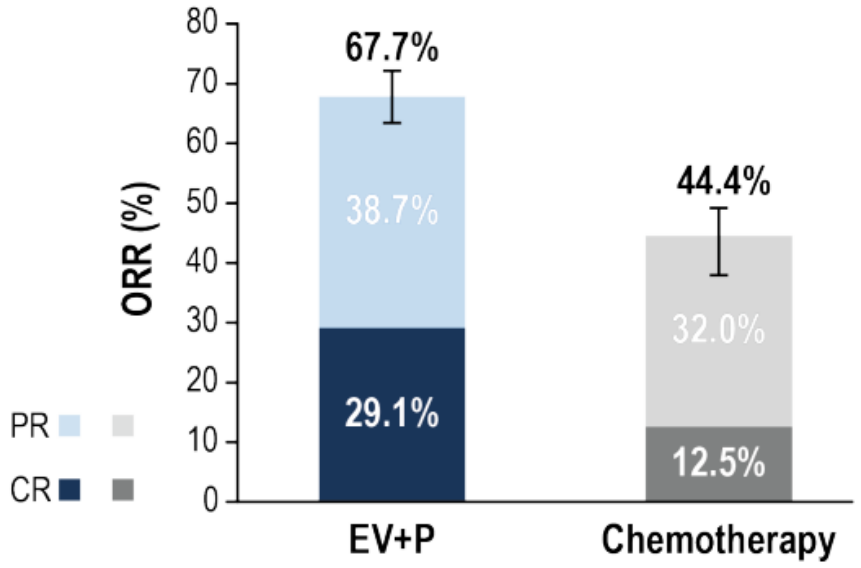


Powles T, ESMO 2023

Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)

Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

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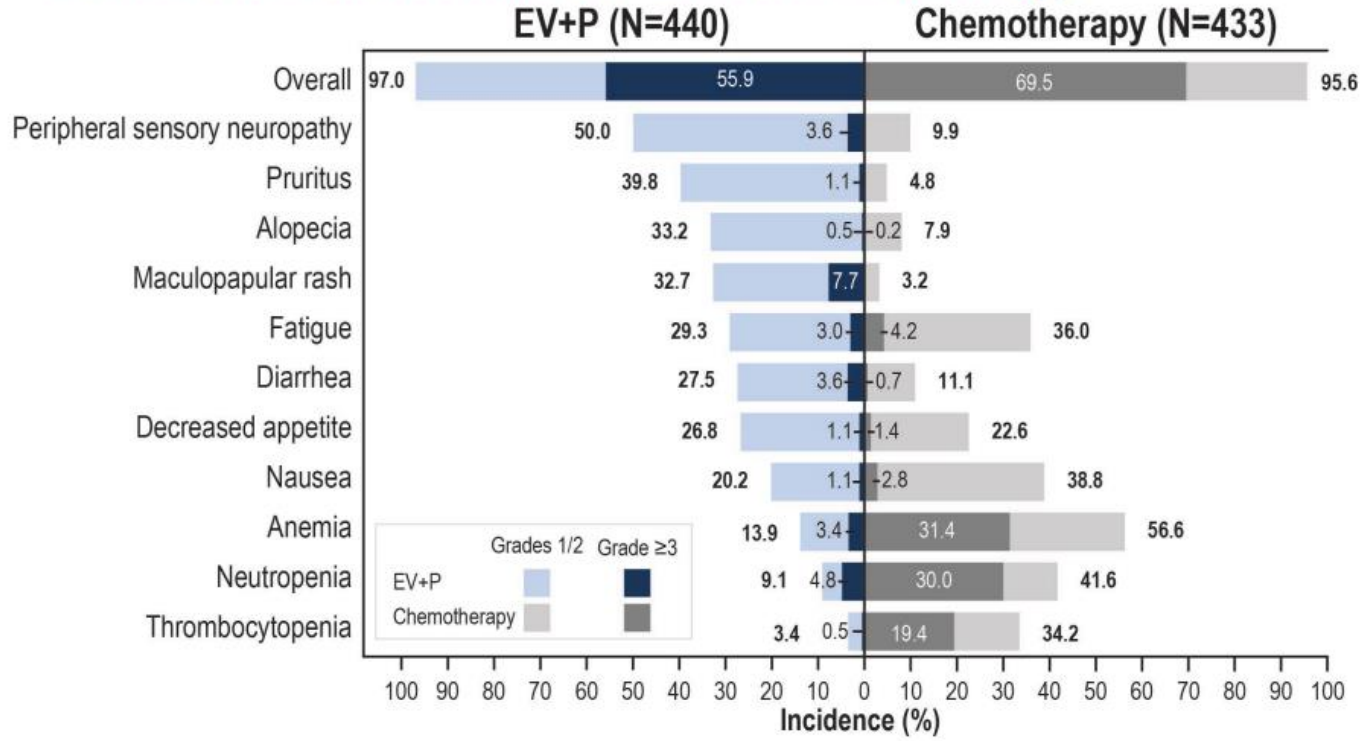
Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

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

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Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

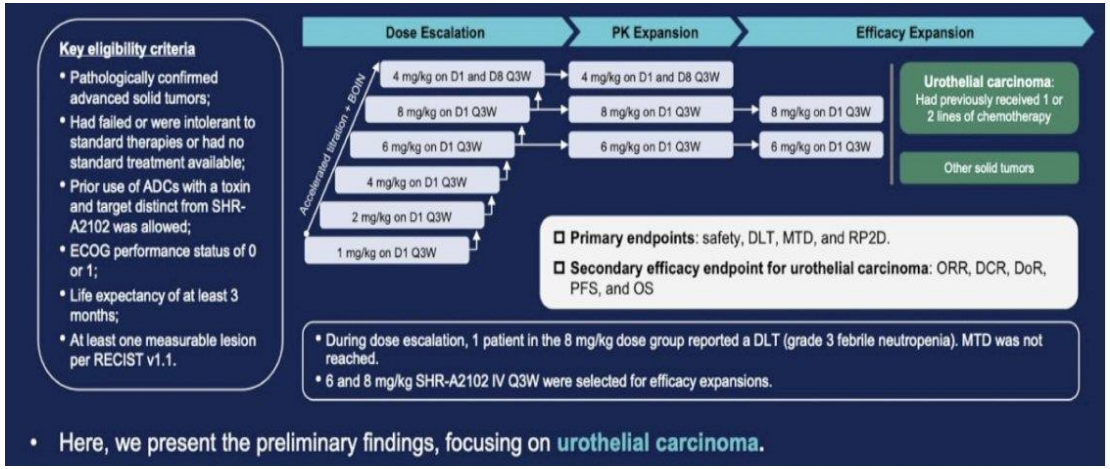
EV Treatment-Related Adverse Events of Special Interest*

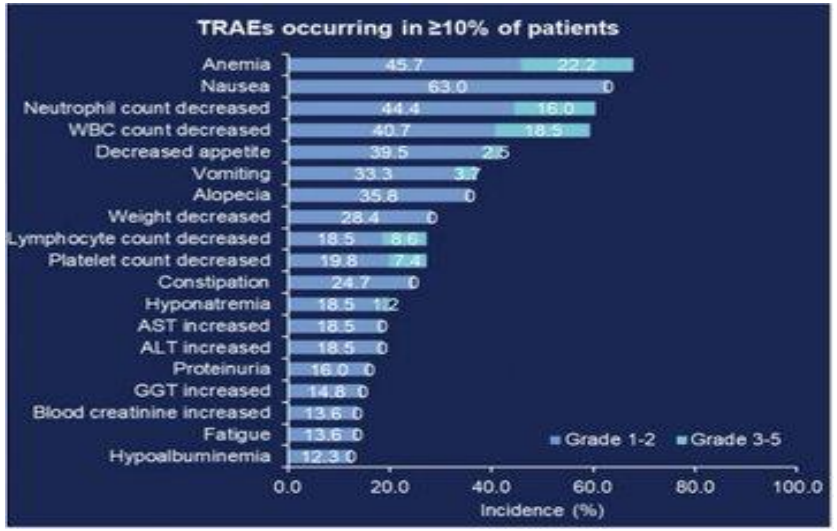
Majority of treatment-related AESIs were low grade

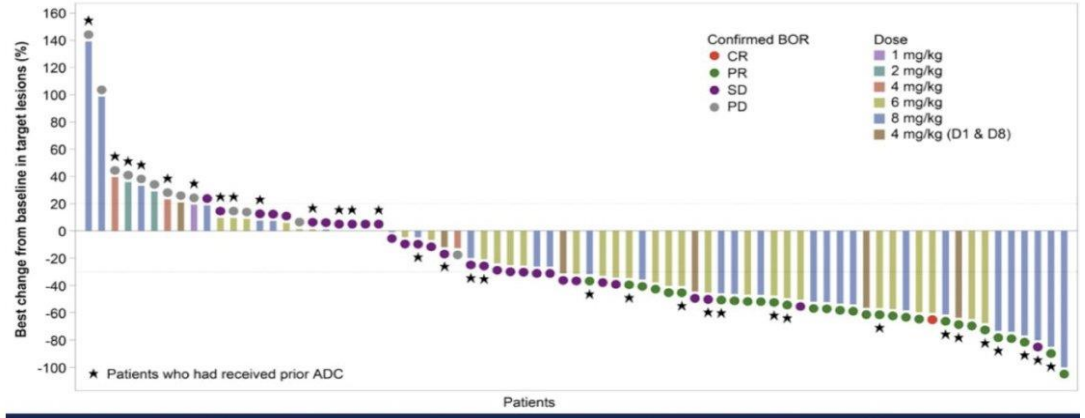
	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
Ocular disorders	94 (21.4)	0 (0.0)	12 (2.8)	0 (0.0)
Dry eye	82 (18.6)	0 (0.0)	8 (1.8)	0 (0.0)
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0 (0.0)
Infusion-related reactions	9 (2.0)	0 (0.0)	9 (2.1)	0 (0.0)

Powles T, ESMO 2023

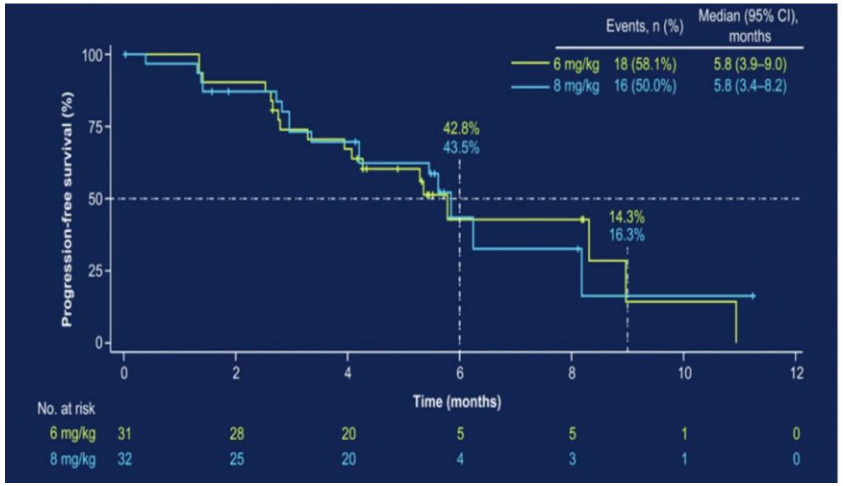
Yeni Nectin-4(SHR-A2102) Tedavi Seçenekleri







	6 mg/kg (N=31)	8 mg/kg (N=32)	4 mg/kg (D1 & D8) (N=11)	All (N=81)
ORR, % (95% CI)	41.9% (24.5–60.9)	50.0% (31.9–68.1)	18.2% (2.3–51.8)	38.3% (27.7–49.7)
DCR, % (95% CI)	90.3% (74.3–98.0)	84.4% (67.2–94.7)	54.5% (23.4–83.3)	76.5% (65.8–85.3)



Bixia Tang, MD, ASCO GU 2025

Metastatik Ürotelyal Kanseri İkinci Basamak Sonrası Tedavi Seçimi

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Bladder Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-platinum or other chemotherapy)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1 post-platinum)[24]	**Other recommended regimens** • Paclitaxel[30] or docetaxel[31] • Gemcitabine[18] • Pembrolizumab and enfortumab vedotin-ejfv (category 2B)[17]
Alternative preferred regimens • Immune checkpoint inhibitor ▸ Nivolumab[25] ▸ Avelumab[26,27] • Erdafitinib[d,28] • Enfortumab vedotin-ejfv[e,29]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[22] • Gemcitabine and paclitaxel[19] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimens for cisplatin ineligible, chemotherapy naïve • Enfortumab vedotin-ejfv[29] • Gemcitabine and carboplatin • Erdafitinib[d,28]	**Other recommended regimens** • Paclitaxel or docetaxel[31] • Gemcitabine[18]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2] • Erdafitinib[d,28]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[22] • Gemcitabine and paclitaxel[19]

Metastatik Ürotelyal Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Bladder Cancer

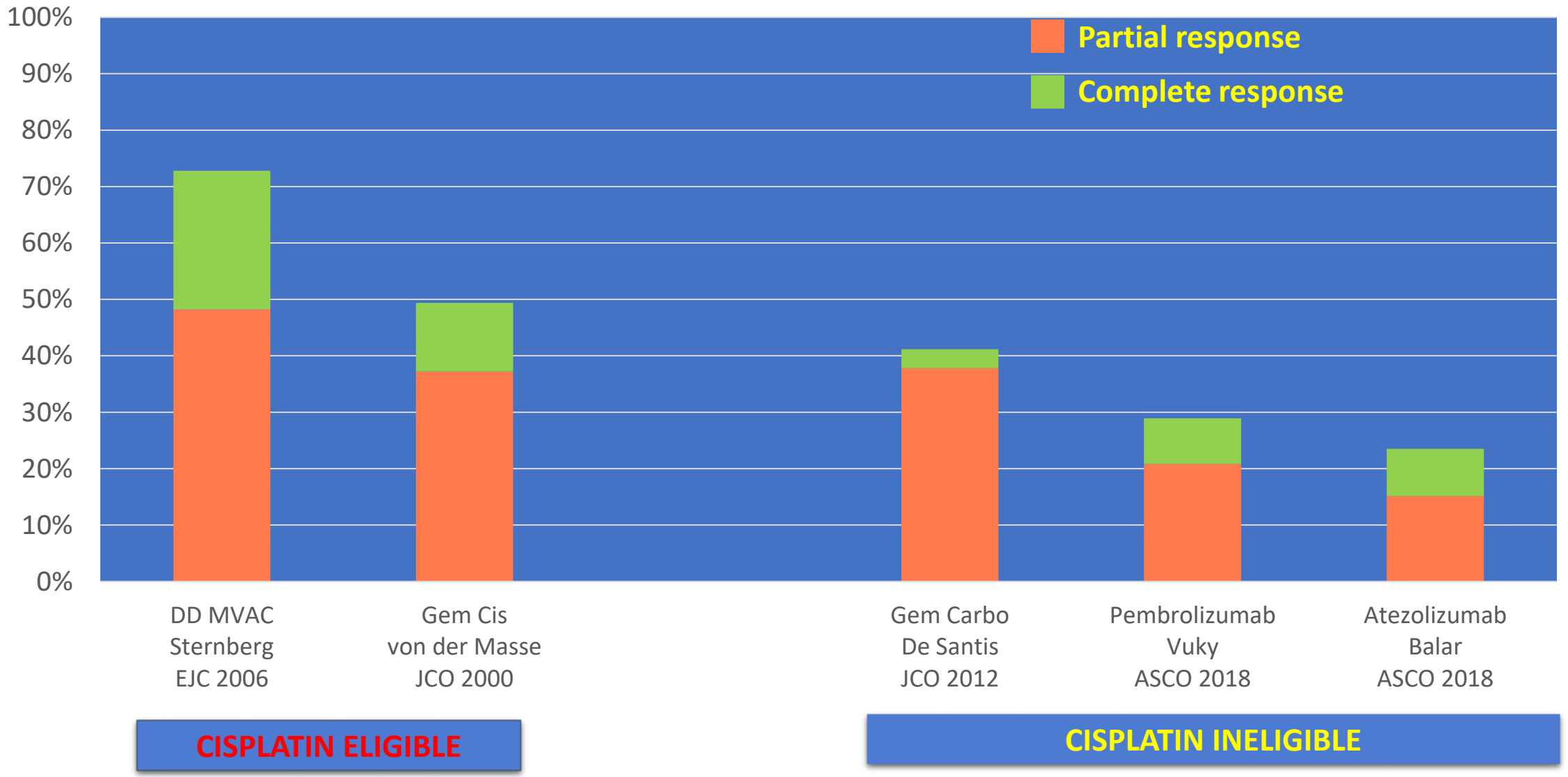
NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)		
Previous immunotherapy and enfortumab vedotin-ejfv (no previous chemotherapy)		
Preferred regimens • DDMVAC with growth factor support[2] • Gemcitabine and cisplatin[4] • Gemcitabine and carboplatin (category 2B) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7)	**Other recommended regimens** • Paclitaxel[22] or docetaxel[23] • Gemcitabine[24]	**Useful in certain circumstances** • Gemcitabine, cisplatin, and nivolumab (category 2B)
Previous chemotherapy (no previous immunotherapy or enfortumab vedotin-ejfv)[c]		
Preferred regimens • Pembrolizumab (category 1 post-platinum)[25] • Enfortumab vedotin-ejfv and pembrolizumab[16] • Enfortumab vedotin-ejfv[26] • Nivolumab[27] (category 2B) • Avelumab[28,29] (category 2B) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7)	**Other recommended regimens** • Paclitaxel[22] or docetaxel[23] • Gemcitabine[24]	**Useful in certain circumstances** • DDMVAC with growth factor support[2] (category 2B) • Ifosfamide, doxorubicin, and gemcitabine[30] (category 2B) • Gemcitabine and paclitaxel[31] (category 2B) • Gemcitabine and cisplatin[4] (category 2B)
Previous immunotherapy (no previous chemotherapy or enfortumab vedotin-ejfv)		
Preferred regimens • Enfortumab vedotin-ejfv[26] • Enfortumab vedotin-ejfv and pembrolizumab • Gemcitabine and carboplatin • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2] • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7)	**Other recommended regimens** • Paclitaxel[22] or docetaxel[23] • Gemcitabine[24]	**Useful in certain circumstances** • Gemcitabine, cisplatin, and nivolumab (category 2B) • Ifosfamide, doxorubicin, and gemcitabine[30](category 2B) • Gemcitabine and paclitaxel[31] (category 2B)
Previous chemotherapy and immunotherapy (no previous enfortumab vedotin-ejfv)[d,e]		
Preferred regimens • Enfortumab vedotin-ejfv[32,33](category 1) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7)	**Other recommended regimens** • Enfortumab vedotin-ejfv and pembrolizumab • Paclitaxel[22] or docetaxel[23] • Gemcitabine[24] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2] • Ifosfamide, doxorubicin, and gemcitabine[30] (category 2B) • Gemcitabine and paclitaxel[31] (category 2B)	**Useful in certain circumstances** • Sacituzumab govitecan-hziy[34]

Metastatik Ürotelyal Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi İlk Seride aldığı Tedavi Seçeneğine göre Değişir

Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları



Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

- International, randomized, open-label phase III study **KEYNOTE-045**

Stratified by ECOG PS (0/1 vs 2), Hg (< 10 vs ≥ 10 g/dL), liver mets (yes vs no), and time since last CT (< vs ≥ 3 mos)

Adult patients with predominantly transitional cell UC of the renal pelvis, ureter, bladder, or urethra; **PD after 1-2 lines of platinum-based CT** or recurrence < 12 mos after perioperative platinum-based CT; ECOG PS 0-2
(N = 542)

Pembrolizumab
200 mg IV Q3W
(n = 270)

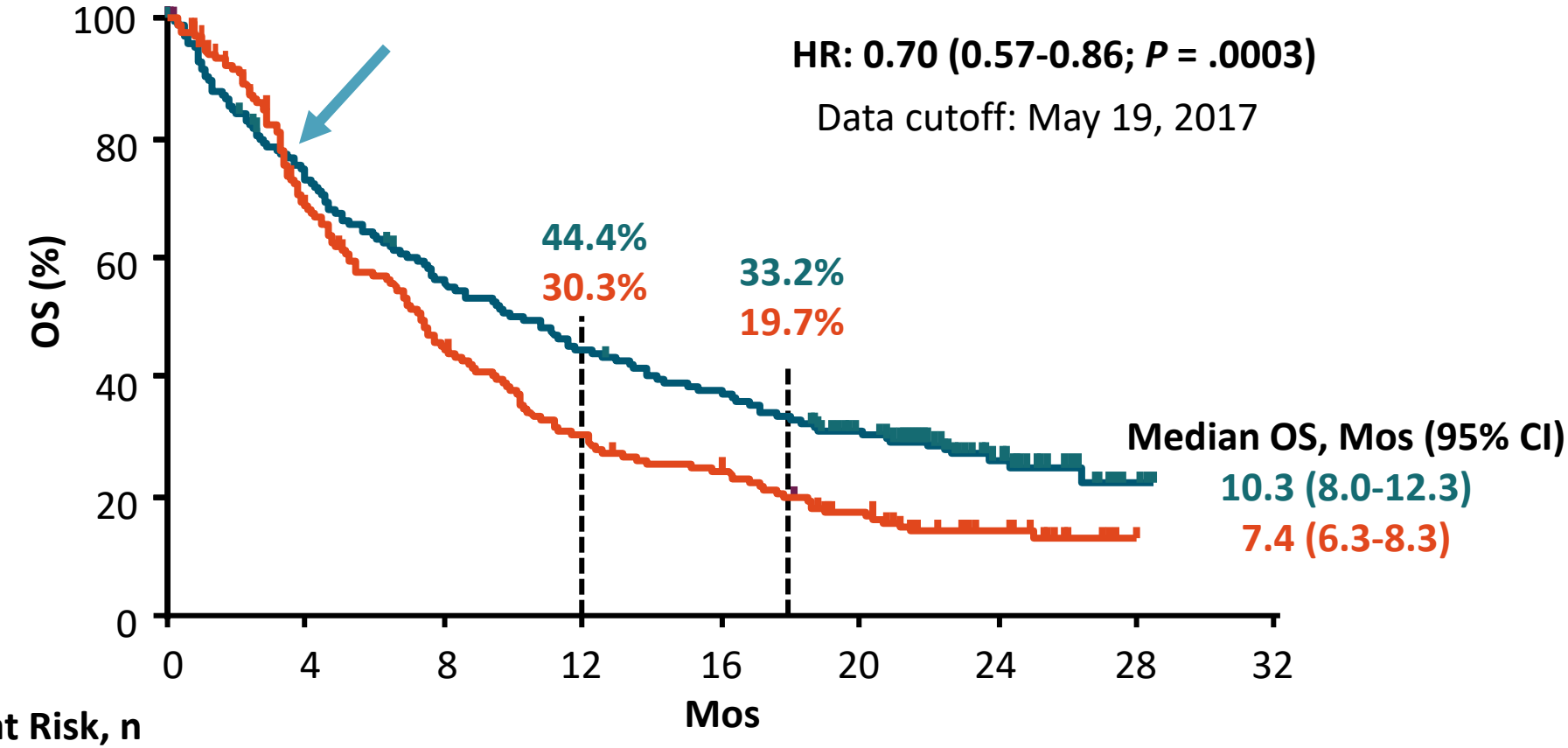
Paclitaxel 175 mg/m^2 IV Q3W or
Docetaxel 75 mg/m^2 IV Q3W or
Vinflunine 320 mg/m^2 IV Q3W
(n = 272)

Treatment continued for 2 yrs or until PD, unacceptable toxicity, or withdrawal of consent

- Primary endpoints: OS, PFS
- Secondary endpoints: ORR, DoR, safety

Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

KEYNOTE-045: OS

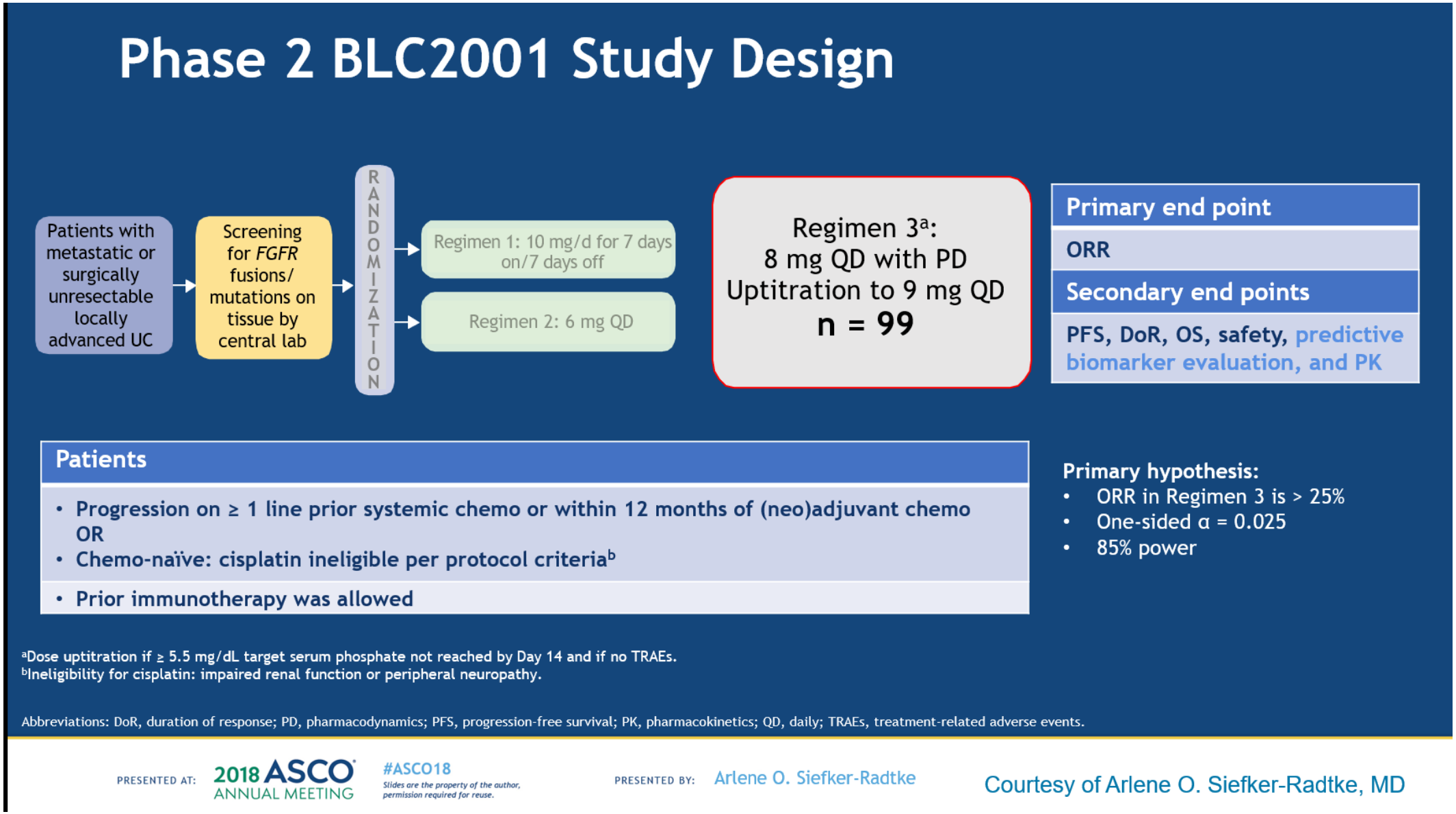


Patients at Risk, n

Pembrolizumab	270	194	147	116	98	67	23
Chemotherapy	272	171	109	73	58	35	13

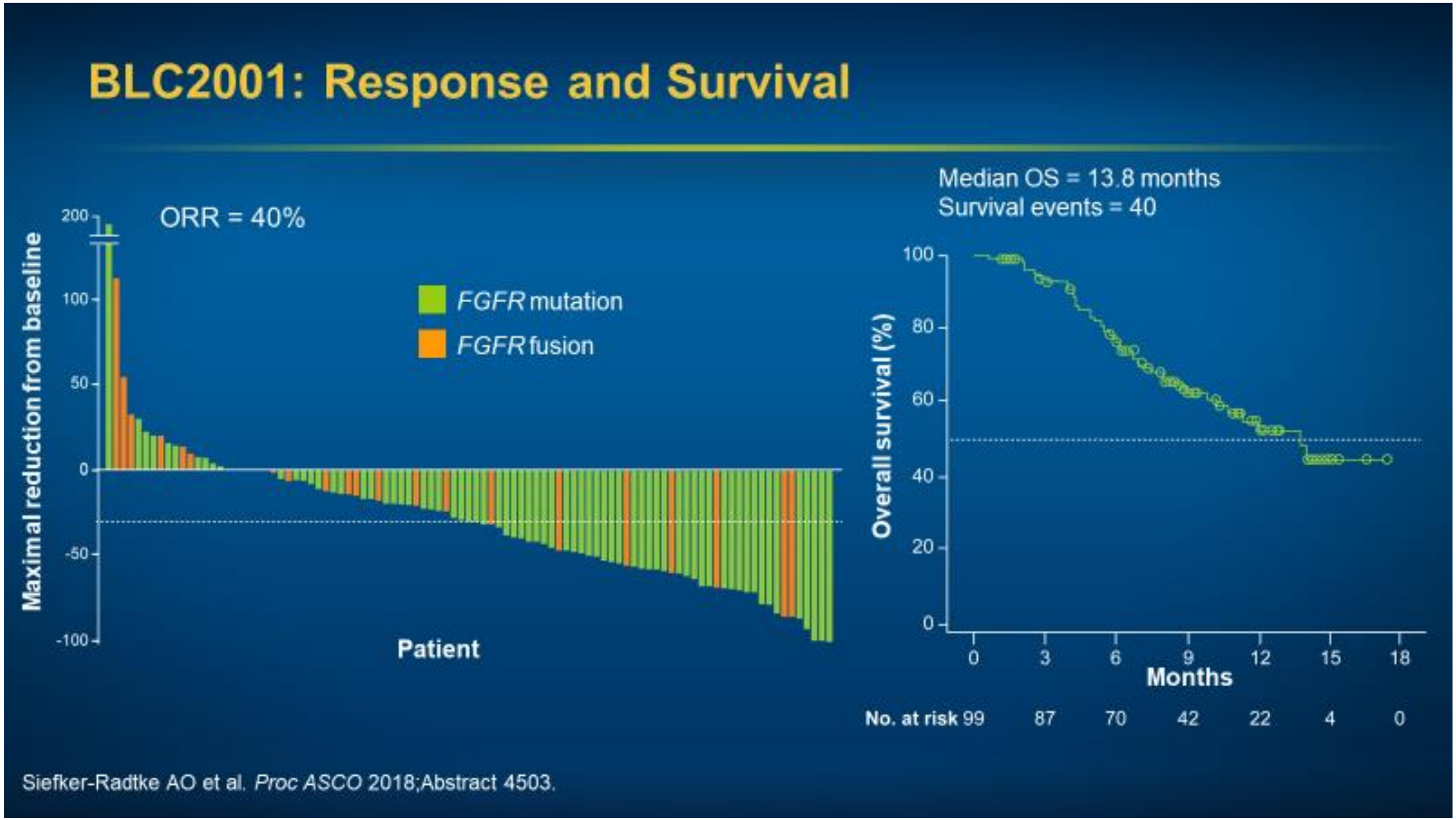
de Wit R, et al. ESMO 2017. Abstract LBA37_PR.

Metastatik Ürotelyal Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi



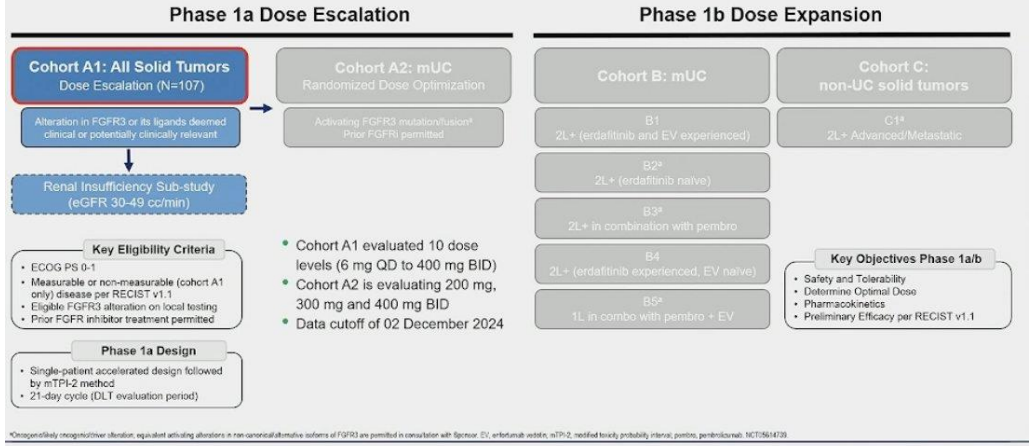
Courtesy of Arlene O. Siefker-Radtke, MD

Metastatik Ürotelyal Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi



Yeni Potent FGFR3 İnhibitörleri

FORAGER-1 Study Design, Eligibility, Objectives

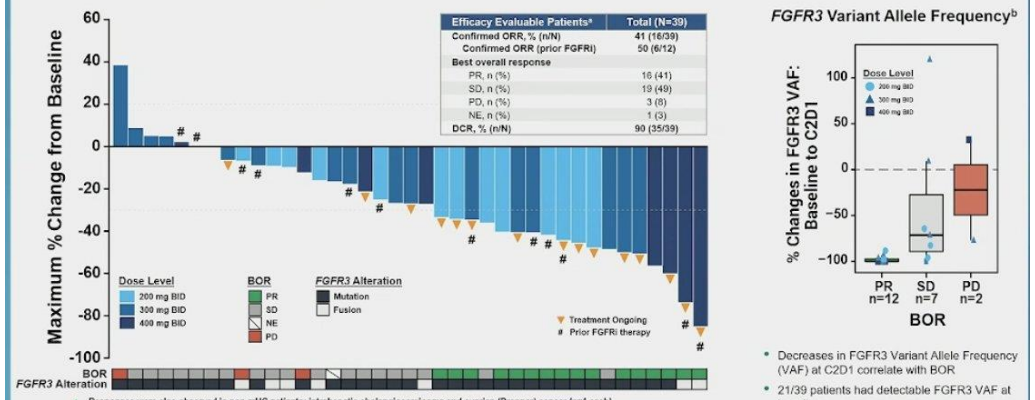


Safety

Treatment-Emergent AEs ≥20%	All Patients (N=107)		200 mg, 300 mg, 400 mg BID (n=70)	
All TEAEs, %	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3[e]**
Any	98	45	100	46
Diarrhea	63	3	76	4
Fatigue	26	<1	29	1
ALT increased	22	7	29	9
AST increased	22	7	29	9
Decreased appetite	21	3	24	1
AEs of interest, %				
Skin disorders[a]	42	3	46	4
Hand-foot (PPE)	6	2	9	3
Hyperphosphatemia[b]	26	<1	36	1
Eye disorders[c]	19	-	21	-
Retinopathy	4	-	4	-
Stomatitis	18	<1	23	1
Nail disorders[d]	16	-	19	-
Dry mouth	14	-	17	-
Dose modifications, %				
Dose reductions due to TEAEs	10		14	
Discontinuations due to TEAEs	5		6	

- Median follow-up time: 5.0 (0.4-19.9+) months
- 10 dose levels evaluated (6 mg QD – 400 mg BID)
- No DLTs observed during dose escalation
- At the higher dose levels (200, 300, 400 mg BID)
  - 25 (36%) remain on treatment at data cutoff
  - Most TEAEs were grade 1-2
  - High-grade FGFR-1, 2, and 4 related AEs typical for erdafitinib[f] were very rare
  - Dose reductions/discontinuations were uncommon[g]

Radiographic Response and *FGFR3* Variant Allele Frequency in *FGFR3*-Altered Efficacy Evaluable mUC Patients Receiving ≥200 mg BID (n=39)



- Responses were also observed in non mUC patients: intrahepatic cholangiocarcinoma and ovarian (Brenner) cancer (n=1 each).

FGFR3 Variant Allele Frequency[b]

- Decreases in FGFR3 Variant Allele Frequency (VAF) at C2D1 correlate with BOR
- 21/39 patients had detectable FGFR3 VAF at baseline

Conclusions

- LY3866288 (LOXO-435) demonstrates
  - Promising preliminary efficacy in patients with *FGFR3*-altered metastatic urothelial carcinoma treated with ≥200 mg BID
    - 41% (16/39) of patients with an activating *FGFR3* mutation or fusion had a confirmed response with a 90% DCR
    - 50% (6/12) of patients who previously received an FGFR inhibitor had a confirmed response
  - Favorable safety profile
    - Diarrhea was the most common TEAE and was predominantly low grade and manageable
    - High-grade FGFR-1, 2, and 4 mediated AEs (e.g. nail/skin disorders and ocular toxicity) typical of pan-FGFR inhibitors were very rare
- Randomized dose finding is currently enrolling patients to 200 mg, 300 mg, and 400 mg BID to select an optimal dose for further development
- Select expansion cohorts, including enfortumab vedotin + pembrolizumab + LY3866288 (LOXO-435) in 1L *FGFR3*-altered mUC patients will open in Q1 2025

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors (NCT03219333)

Arjun V. Balar, Bradley McGregor, Jonathan Rosenberg, Michiel S. van der Heijden, Se Hoon Park, Jae Lyun Lee, Michael R. Harrison, Elisabeth I. Heath, Mark N. Stein, Yohann Loriot, Andrea Necchi, Joyce Steinberg, Shang-Ying Liang, Eric Kim, Janet Trowbridge, Mary Campbell, Daniel P. Petrylak, and Evan Y. Yu

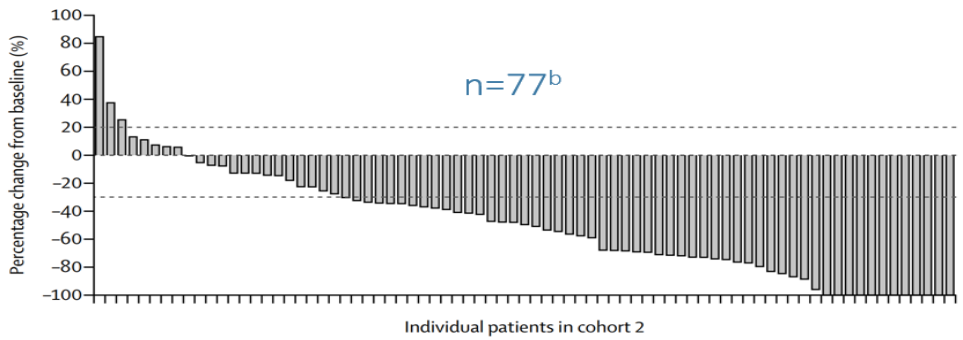
Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

EV-201 Cohort 2 Supports FDA Approval for Cisplatin-Ineligible Patients

Confirmed Best Overall Response per BICR

	Cohort 2 (n=89)
Objective response rate 95% CI	46 (52%) 41-62
Best overall response	
Complete response	18 (20%)
Partial response	28 (31%)
Stable disease	27 (30%)
Progressive disease	8 (9%)
Not evaluable[a]	8 (9%)

Change in Target Lesions From Baseline



Median duration of treatment: 6 months

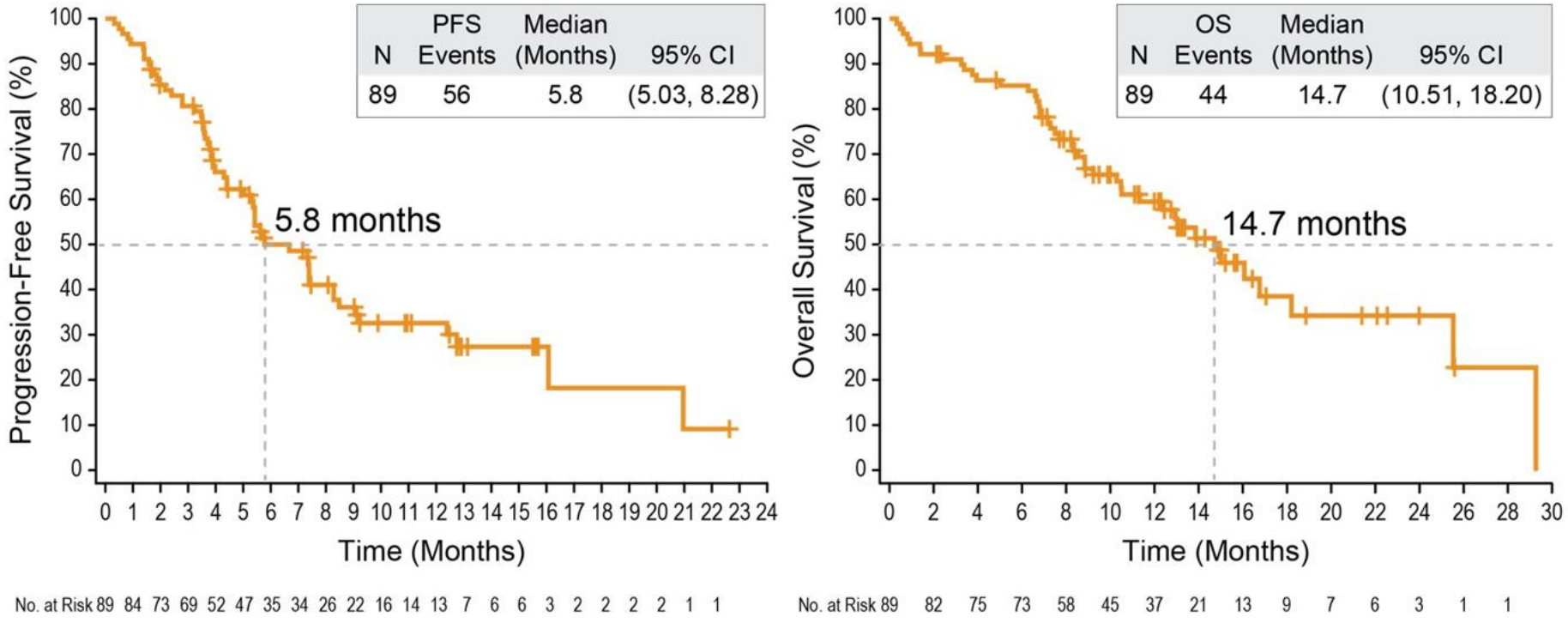
[a] Includes 5 patients who did not have a response assessment postbaseline, 2 patients whose postbaseline assessment did not meet the minimum interval requirement for stable disease, and 1 patient whose response cannot be assessed due to incomplete anatomy.

[b] Data are not available for 12 patients due to no response assessment of response postbaseline (n=5), incomplete assessment of target lesions postbaseline (n=1), or no measurable disease at baseline per BICR (n=6).

Yu EY, et al. *Lancet Oncol.* 2021;22(6):872-882.

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

EV-201 Cohort 2: Progression-Free Survival and Overall Survival



Median follow-up: 13.4 months

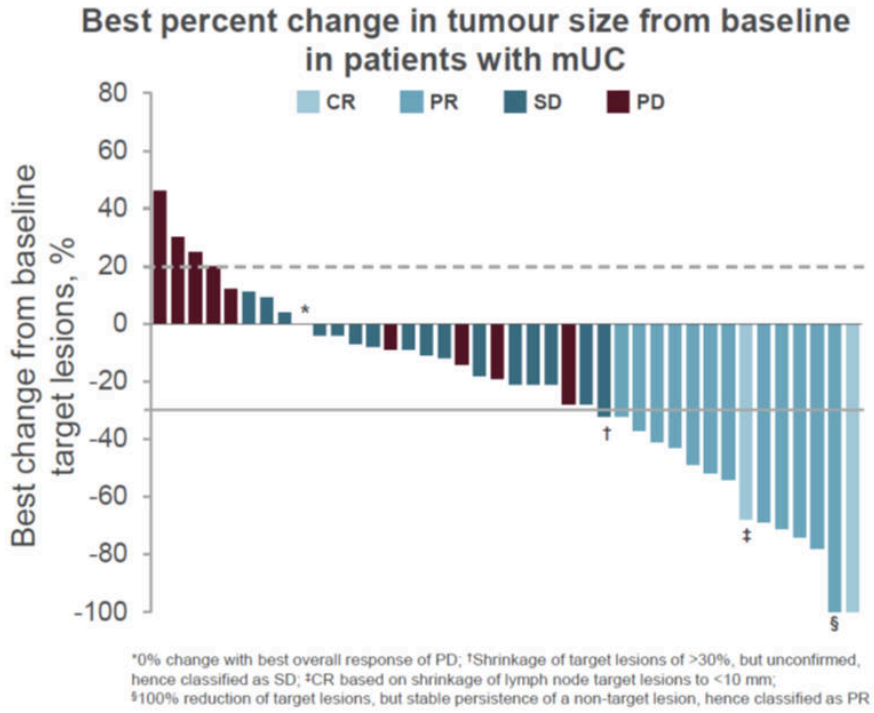
Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

Sacituzumab govitecan for mUC: Efficacy

Sacituzumab govitecan (SG): Humanised ADC comprised of an anti-Trop-2 glycoprotein linked with SN-38, an active metabolite of irinotecan

NCT01631552: Phase I/II study of SG in patients with epithelial cancers (PS 0–1)

ORR in patients with previously treated mUC (N=45)		
ORR by subgroup	**ORR, % (n/N)**	**95% CI**
Overall	31 (14/45)	18–47
Lines of prior therapy ≤2 prior lines ≥3 prior lines	 39 (11/28) 18 (3/17)	 22–59 4–43
Prior checkpoint inhibitors	24 (4/17)	7–50
Prior platinum and checkpoint inhibitors	27 (4/15)	8–55

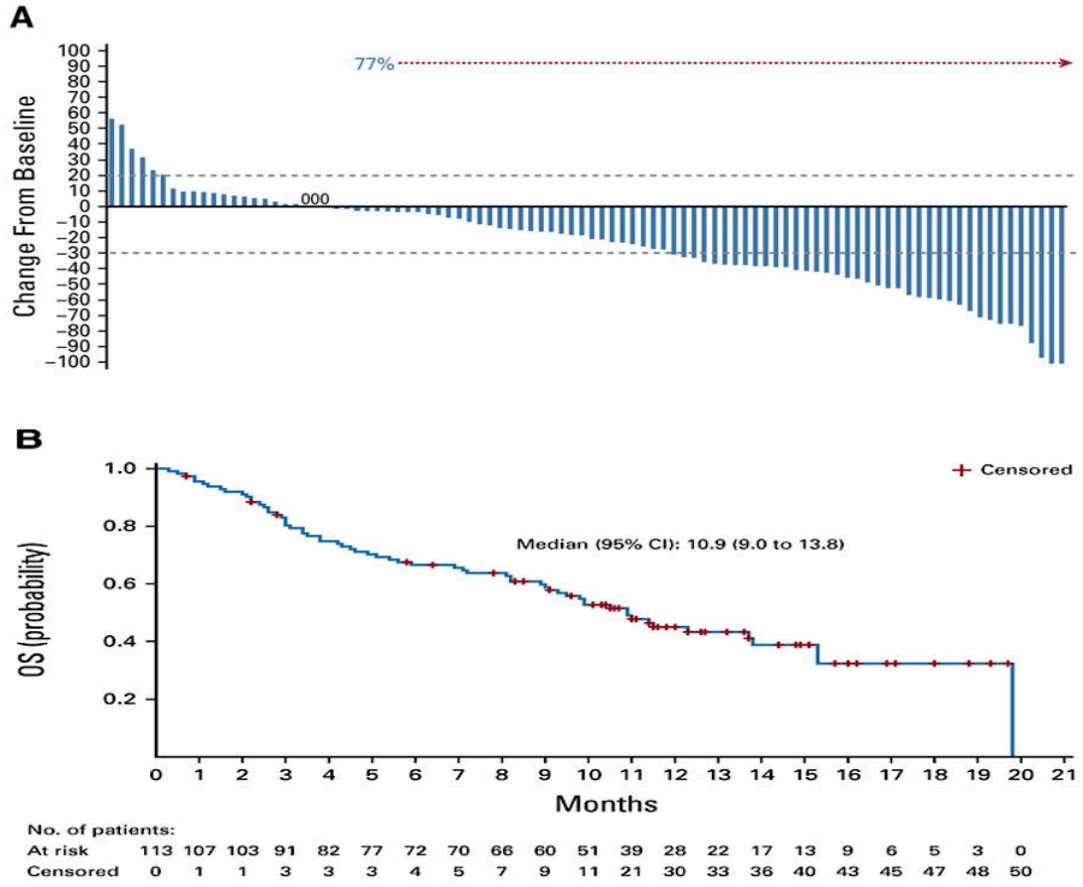


Tagawa ST et al. ASCO GU 2019;Abstract 354.

Courtesy of Thomas Powles, MBBS, MRCP, MD

Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

Sacituzumab Govitecan



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

Tagawa, et al. JCO 2021

Datopotamad-Deruxtecan(DXd) çoklu tedavi almış hastalarda kısmi yanıt

ASCO Genitourinary Cancers Symposium

Datopotamab deruxtecan (Dato-DXd) in locally advanced/metastatic urothelial cancer: updated results from the phase 1 TROPION PanTumor01 study

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Study Design

- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC composed of an anti-TROP2 mAb covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- TROPION-PanTumor01 is an ongoing, phase 1, multi-cohort, multicenter, open-label, dose-escalation and dose-expansion study evaluating Dato-DXd in patients with several types of previously treated advanced solid tumors, including urothelial cancer

Key eligibility criteria
- Unresectable locally advanced/metastatic (stage III or IV) urothelial carcinoma (included renal pelvis, ureter, urinary bladder, and urethra)
- Previous treatment with ≥1 line of therapy including an immune checkpoint inhibitor
- ECOG PS 0–1
- Unselected for TROP2 expression
- No prior treatment with DXd-ADCs or TROP2-directed therapies

→ **Dato-DXd** 6 mg/kg Q3W (N=40)

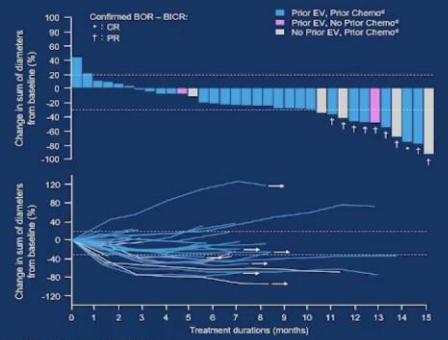
Primary endpoints
- Safety and tolerability

Secondary endpoints (by BICR[a])
- ORR
- DOR
- DCR
- PFS

BICR, blinded independent review committee; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, objective response rate; Q3W, every 3 weeks.
Data cut off: April 22, 2024. Median follow-up was 10.0 months (range, 5.0–28.2). [a]Evaluated per RECIST v1.1. 1. Okajima D, et al. Mol Cancer Ther. 2021;20:2329–40.

Response and Change in Tumor Burden

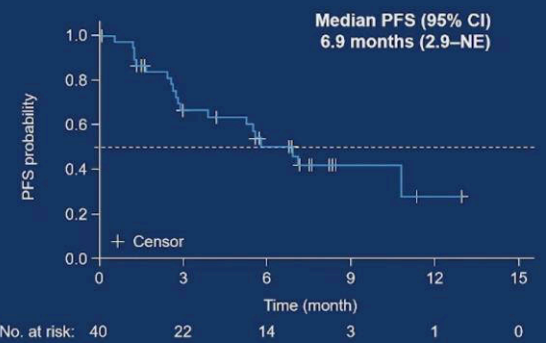
Response by BICR[a]	Dato-DXd (N=40)
ORR[b], n (%) [95% CI]	**10 (25.0)** [12.7–41.2]
DCR[c], n (%) [95% CI]	**31 (77.5)** [61.5–89.2]
BOR, n (%)	
CR	1 (2.5)
PR	9 (22.5)
SD	20 (50.0)
Non-CR/non-PD	1 (2.5)
PD	5 (12.5)
NE	4 (10.0)
DOR, median (95% CI), **months**	NE (2.6–NE)
6-month DOR rate, % (95% CI)	76.2 (33.2–93.5)



ORR by investigator was 30.0% (n=12); all were PR

BOR, best overall response; CI, confidence interval; CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Evaluated by BICR per RECIST v1.1. [b]Responses with confirmation of CR/PR. [c]CR + PR + SD + non-CR/non-PD. [d]All patients received prior immunotherapy.

Progression-Free Survival



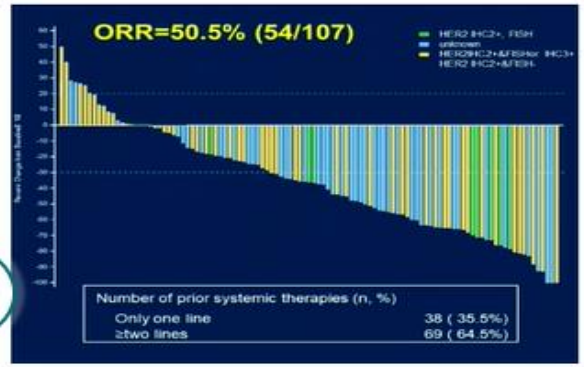
Gelecek Perspektif

Does CPI combine best with ADCs with MMAE payloads?

Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

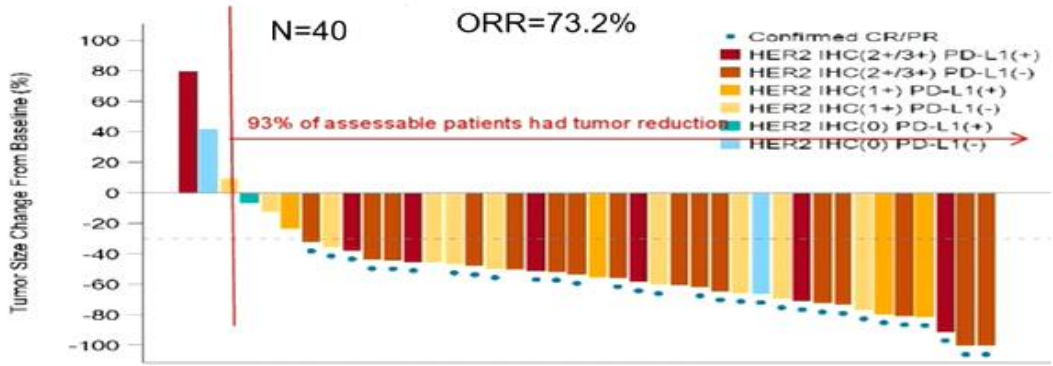
Disitamab vedotin

N=107 In the Second or Third-line setting



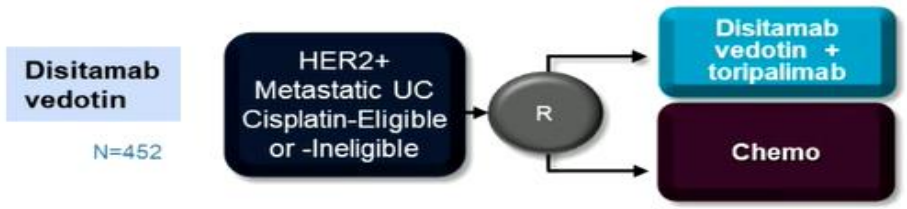
Sheng, et al. ASCO 2022 abstract 4518

Disitamab vedotin + toripalimab



Sheng, X., et al. ASCO 2023

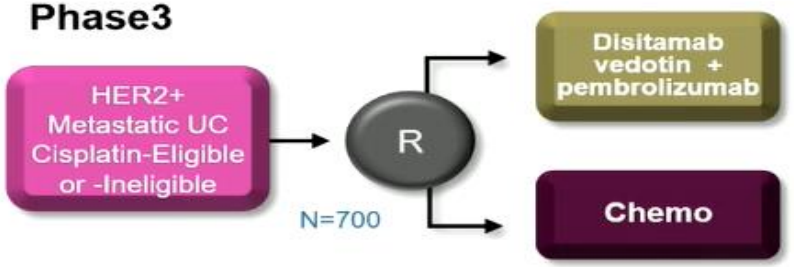
Phase 3



Presented by Andrea B. Apolo, MD

@apolo_andrea

Phase3



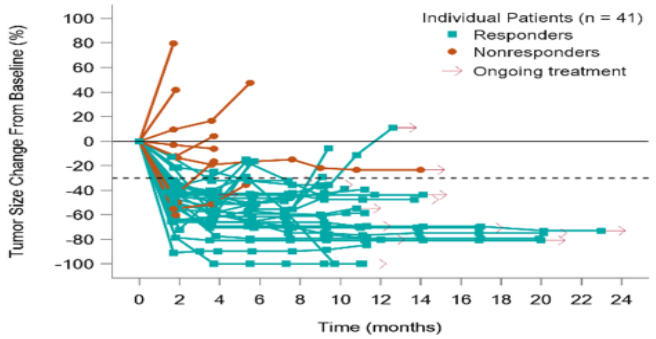
Gelecek Perspektif

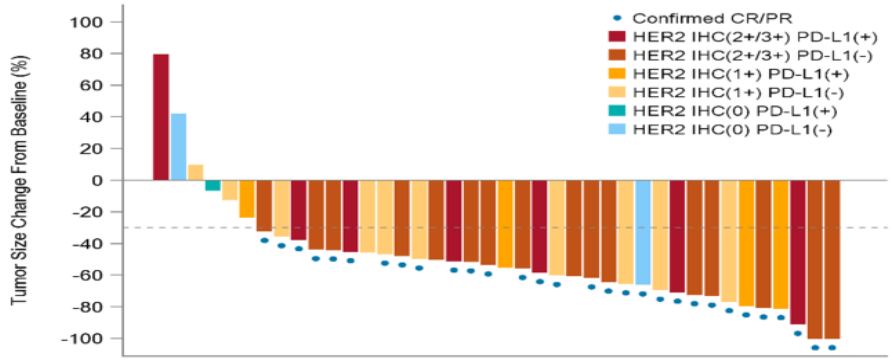
Phase 1b/2 Study C014: Disitamab vedotin + Toripalimab in Urothelial Cancer

Patients with locally advanced or metastatic malignant urothelial carcinoma, unable to tolerate or refused cisplatin, or previously treated with 1 line of systemic therapy (including progression within 12 months of neo-adjuvant therapy)

Efficacy	Total (N=41)
cORR by IRC	**73.2%**
cORR for treatment-naïve patients (n=25)	**76.0%**
mPFS	**9.2** months
2-year OS	**63.2%**
CR	**9.8%**
PR	**63.4%**

cORR by HER2 and PD-L1 Expression Status		
	PD-L1 (+)	**PD-L1 (-)**
HER2 IHC 2+, 3+	75% (n=8)	87.5% (n=16)
HER2 IHC 1+	50% (n=4)	70% (n=10)
HER2 IHC 0	0 (n=1)	50% (n=2)





Sheng, et al. Abs 4566, ASCO 2023.

HER2 Mesane kanserinde Yeni Hedef Molekül

Is HER2 a good target for ADCs in UC?

Location	Her 2 IHC*		
	≥1+	2+	3+
Primary (n = 114)	84 (74%)	36 (32%)	5 (4%)
Lymph node (n = 38)	35 (92%)	17 (45%)	4 (11%)

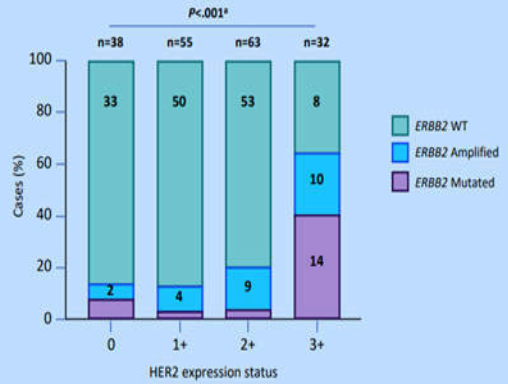
*Dako HercepTest system

Press, ASCO, 2013

Relationship Between *HER2* Alteration by NGS and HER2 Expression by IHC

HER2 IHC

0 = 18.8%
1+ = 29.7%
2+ = 33.7%
3+ = 17.8%



ERBB2 alterations (mutations and/or amplifications) were identified by MSK IMPACT in ≈20% of urothelial cancers

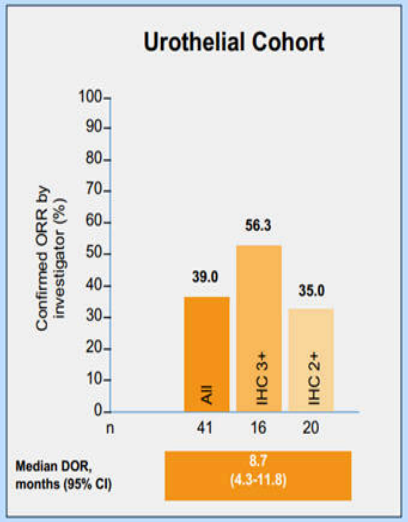
Aggen et al, ASCO GU 2023

HER2 Mesane kanserinde Yeni Hedef Molekül

Anti-HER2 Antibody-Drug Conjugates

	Antibody	Payload	Linker
Trastuzumab emtansine (T-DM1)	Trastuzumab	DM1	Lysine-SMCC
Trastuzumab deruxtecan	Trastuzumab	DXd	Cleavable
Disitamab vedotin (RC48)	Disitamab	MMAE	Cleavable
MRG002	Humanized anti-HER2	MMAE	Cleavable
SYD985	Trastuzumab	Seco-duocarmycin	Cleavable

Phase II DESTINY-PanTumor02 Trastuzumab Deruxtecan



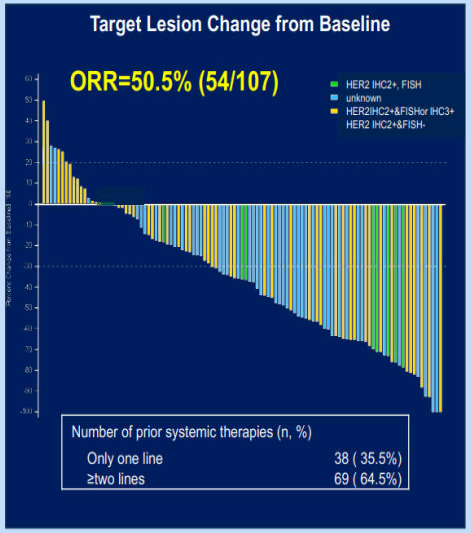
All Patients

	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (n=125)
ORR, % (95% CI)	37.1 (31.3, 43.2)	61.3 (49.4, 72.4)	27.2 (19.6, 35.9)
Median DOR, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

Meric-Bernstam et al, ESMO,2023; Meric-Bernstam et al, JCO 2024.

HER2 Mesane kanserinde Yeni Hedef Molekül

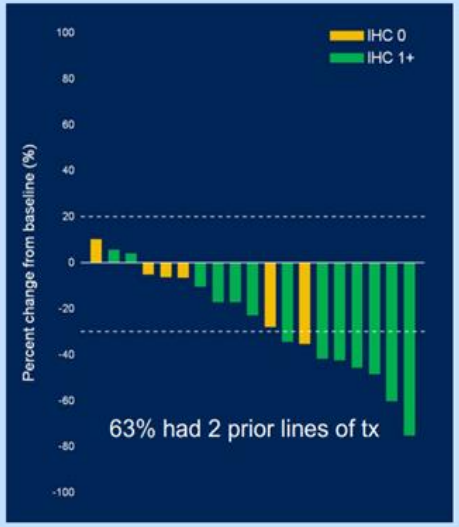
RC48 (Disitamab Vedotin) in HER2 2-3+ mUC



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

Sheng et al, ASCO, 2022. Sheng et al, JCO, 2023.

RC48 (Disitamab Vedotin) in HER2 1+ mUC



Confirmed ORR	
n (%)	5 (26.3%)
95%CI	9.1%, 51.2%

Subgroups	cORR (%, 95% CI)
IHC 0 (n=6)	0
IHC 1+ (n=13)	38.5 (13.9, 68.4)

Xu et al, ASCO, 2022

HER2 Mesane kanserinde Yeni Hedef Molekül

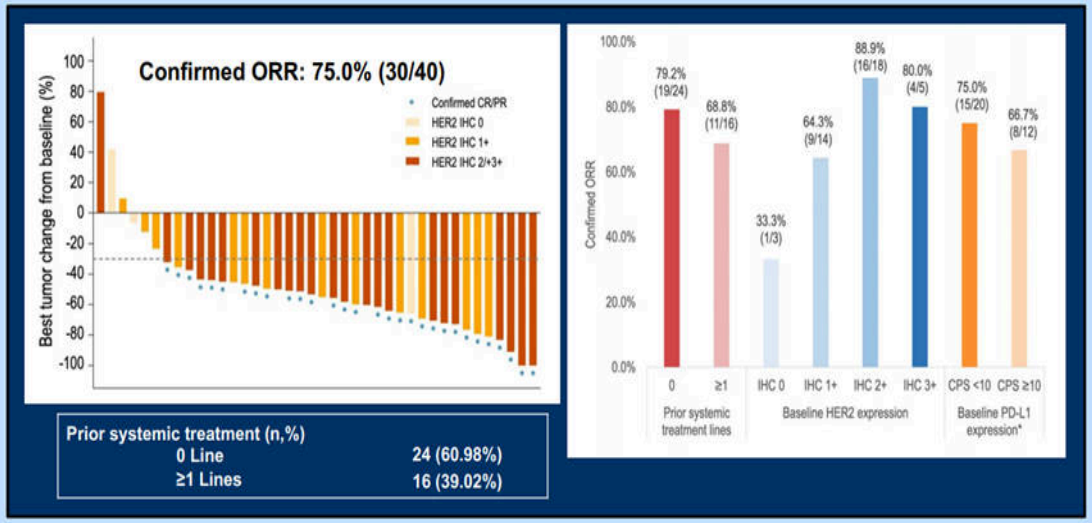
Trastuzumab Deruxtecan + Nivolumab

	Cohort 3: HER2-high n=30	Cohort 4: HER2-low n=4
cORR (CR + PR), n (%) [95% CI]	11 (36.7) [19.9-56.1]	–
Best overall response, n (%)		
CR	4 (13.3)	0
PR	7 (23.3)	2 (50.0)
SD	12 (40.0)	1 (25.0)
PD	5 (16.7)	1 (25.0)
NE	2 (6.7)	0
DoR, median (95% CI), months	13.1 (4.1-NE)	NE
TTR, median (range), months	1.9 (1.2-6.9)	–
PFS, median (95% CI), months	6.9 (2.7-14.4)	NE
OS, median (95% CI), months	11.0 (7.2-NE)	NE
Treatment duration, median (range), months		
T-DXd	3.9 (1-21)	–
Nivolumab	4.1 (1-20)	–

- **36.7%** cORR
- **HER2 IHC 3+: 62.5% (5/8)** patients had a confirmed objective response, including 2 CR (25%)
- HER2 IHC 2+: 27.3% (6/22) patients had a confirmed objective response, including 2 CR (9.1%
- **6.9** months, mPFS
- **11** months, mOS

Galsky et al, ASCO GU, 2022. Hamilton et al, Clin Cancer Res, 2024.

RC48 + Toripalimab



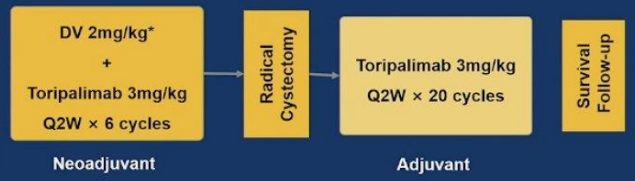
Zhou et al, ESMO, 2024

HER2 Mesane kanserinde Yeni Hedef Molekül

Study design

Key Eligible Criteria:

- Histologically confirmed urothelial carcinoma;
- MIBC at stage of cT2-T4a, N0-1, and M0;
- Eligible for radical cystectomy (RC) + pelvic lymph node dissection (PLND);
- HER2 expression: IHC 1+, 2+, or 3+.



- **Primary endpoint:** Pathologic complete response (pCR, defined as ypT0N0) rate.
- **Secondary endpoints:** Pathological response rate (defined as ≤ypT1N0M0)#; event-free survival (EFS); overall survival (OS)^; adverse events.

The preliminary results of this trial showed promising efficacy and acceptable safety.[1] Herein, we present updated results including the pathological response, event-free survival, safety, and other outcomes with a longer follow-up (data cutoff: Dec 3, 2024).

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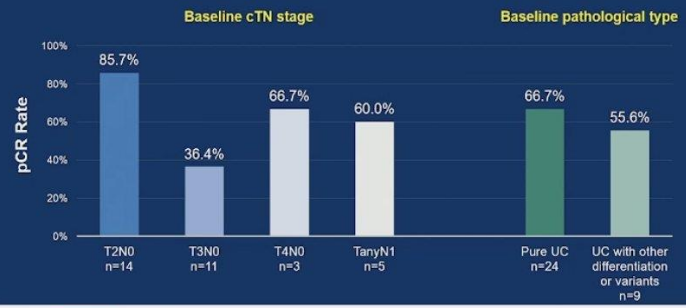
Subgroup analysis

- The pCR rate for the T2N0 patients appeared higher than those for the other subgroups.
- The pCR rates were generally consistent between patients with pure UC and patients with UC with other differentiation or variants.



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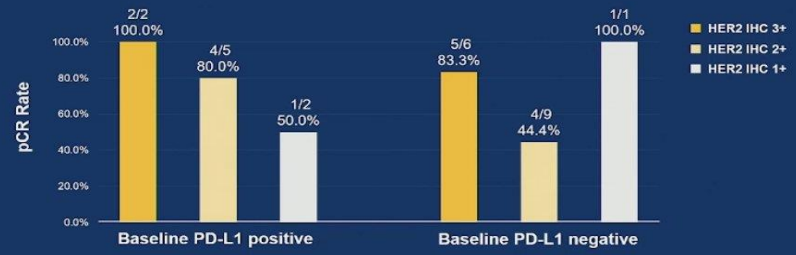
Subgroup analysis

- The pCR rate for the HER2 IHC 3+ subgroup was numerically higher than those for IHC 1+ and IHC 2+ subgroups regardless of PD-L1 status.



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Conclusion

- RC48-017 is the first prospective study showing that ADC in combination with a PD-1 inhibitor as perioperative treatment provided prominent outcomes in operable MIBC.
  - pCR rate: 63.6% (95% CI: 45.1-79.6)
  - 12-month EFS rate: 92.5% (95% CI: 72.8- 98.1)
- Neoadjuvant DV plus toripalimab did not delay RC procedures or impact patients' ability to undergo RC. Safety profile was manageable with no new safety signals.
- The results indicated that neoadjuvant DV plus perioperative toripalimab had promising efficacy and acceptable safety in patients with HER2-expressing MIBC, warranting further investigation.

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Kombinasyon Tedavileri

Selected Ongoing Trials of ADCs + Immunotherapy in mUC					
Treatments	**Alias**	**Ph**	**Population**	**Primary Endpoint**	**NCT Number**
Disitamab Vedotin + Pembrolizumab	DV-001	III	1st line HER2+	PFS, OS	NCT05911295
Disitamab Vedotin + Toripalimab		III	1st line HER2+	PFS, OS	NCT05302284
Zelenectide Pevedotin + Pembro	DURAVELO-2	III	1st line	PFS	NCT06225596
EV + SG + Pembrolizumab	DAD-IO	II	1st line	ORR	NCT04724018
Datopotamab-DXd + Volrustomig or Rilvegostomig	TROPION-Pan Tumor 03	II	1st or 2nd line	ORR, AEs	NCT05489211
SG + Avelumab	JAVELIN Bl. Medley	II	1st line	PFS, AEs	NCT05327530
EV + Pembro + Sacituzumab TMT or investigational agents	KEYMAKER-U04	I/II	1st line	ORR, PFS	NCT05845814
EV or SG + Atezolizumab	MORPHEUS-UC	Ib/II	Post-platinum	ORR	NCT03869190
SG + Zimberelimab (aPD-1) + Domvanalimab (aTIGIT)	TROPHY-U01 Cohort 7	I/II	1st line	ORR	NCT03547973
BGB-C354 (B7-H3 ADC) + Tislelizumab		I	Later line	AEs, ORR	NCT06422520

EV: Enfortumab Vedotin. SG: Sacituzumab Govitecan

Sonuç

- Enfortumab vedotin ve pembrolizumab sisplatin uygunluğundan ve PD-L1 düzeyinden bağımsız standart tedavi
- Evre IV mesane kanserinde birinci basamak tedavide Enfortumab vedotin +pembrolizumab alamayacak hastalarda sisplatine uygun hastalarda sisplatin+gemsitabin+nivolumab bir seçenek
- Sisplatin alamayacak hastalarda platin bazlı kemoterapi sonrası klinik yarar(CR/PR/SD) olanlarda Avelumab idame tedavi olarak bir seçenek
- Platin bazlı kemoterapi alamayacak hastalarda birinci basamak tedavide (ECOG PS≥2, komorbidite vs.) PD-L1 düzeyinden bağımsız Pembrolizumab önerilebilir

Sonuç

- ❑ İkinci basamak ve sonrası tedavi seçeneğini birinci basamakta aldığı tedavi belirler
- ❑ CPS PD-L1 ≥ 10, yalnız lenf nod metastazı olan hastalarda immüne checkpoint inhibitörleri
- ❑ FGFR2 ve FGFR3 alterasyonları olanlarda Erdafitinib
- ❑ İmmüne checkpoint inhibitörü sonrası Enfortumab vedotin
- ❑ Enfortumab vedotin sonrası sacituzumab govitecan
- ❑ HER-2 +3 pozitif olanlarda Trastuzumab deruxtecan
- ❑ Sacituzumab govitecan sonrası(Vinflunine ve taksan vb.) kemoterapi seçenekleri