

Metastatik Ürotelyal Kanserlerde Tedavi Seçenekleri

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Koç Üniversitesi Hastanesi Tıbbi Onkoloji

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)	<i>n</i>	Interventions	Response rate (%)	Median OS (months)	Toxicity
Logothetis <i>et al.</i> ³⁶ (1990)	110	MVAC versus CISCA	65 versus 46; $P<0.05$	15.5 versus 10.1; $P= 0.0003$	MVAC>CISCA
Loehrer <i>et al.</i> ³⁷ (1992)	269	MVAC versus cisplatin	39 versus 12; $P<0.0001$	12.5 versus 8.2; $P= 0.0002$	MVAC>cisplatin
Mead <i>et al.</i> 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 <i>et al.</i> ^{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 <i>et al.</i> ^{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 <i>et al.</i> 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-dense gemcitabine 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

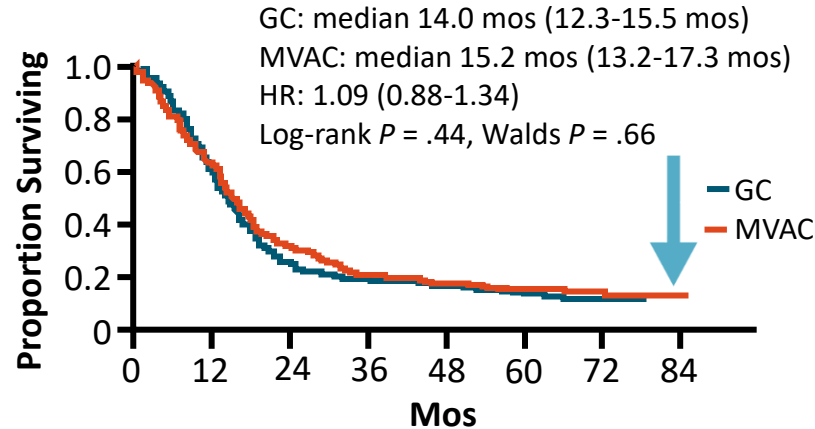
Sisplatin Uygun

Gemcitabine + Cisplatin^[1,2]

ORR: 49%

CR: 12%

Median OS: 14.0 mos



Patients at Risk, n

GC 203 118 50 36 30 23 7 0

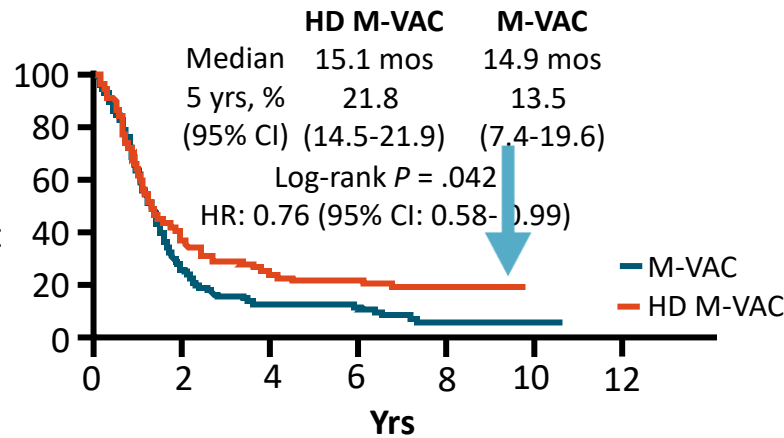
MVAC 202 125 62 40 34 29 9 1

Dose Dense MVAC^[3]

ORR: 72%

CR: 25%

Median OS: 15.1 mos



O N Patients at Risk, n

112 129 32 15 11 4 2 M-VAC

101 134 45 29 23 8 0 HD M-VAC

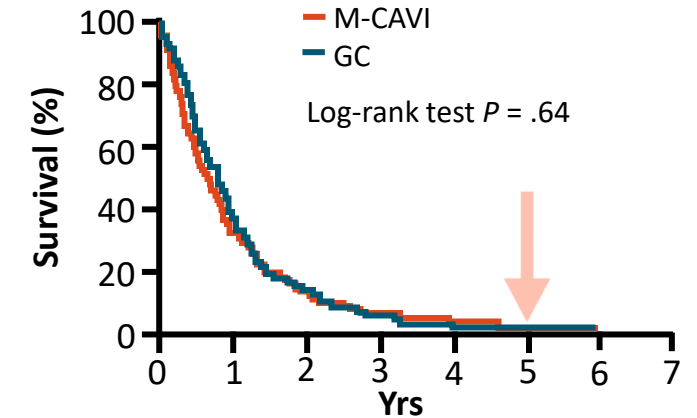
Sisplatin uygun değil

Gemcitabine + Carboplatin^[4]

ORR: 36%

CR: 3%

Median OS: 9.3 mos



O N Patients at Risk, n

M-CAVI 108 119 37 13 7 3 1 1

GC 110 119 44 15 5 2 2 1

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

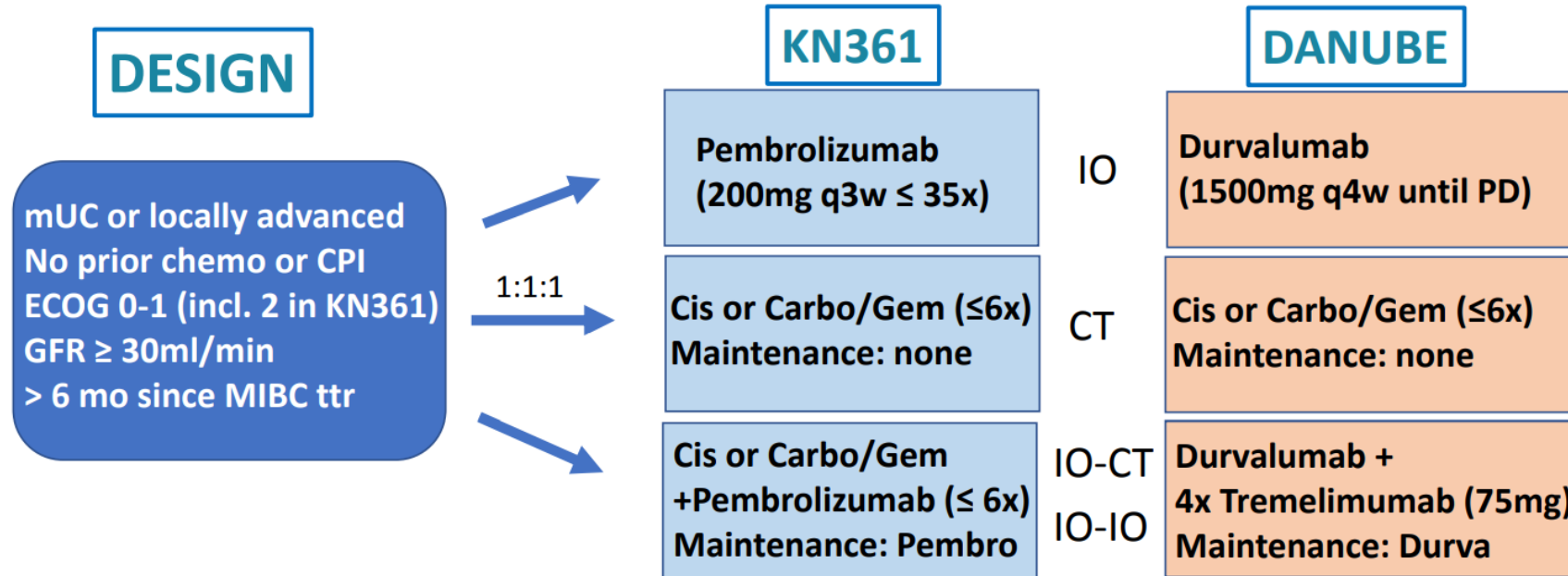
First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	<u>Preferred regimens</u> • Pembrolizumab and enfortumab vedotin-ejfv¹⁵ (category 1) <u>Other recommended regimens</u> • Gemcitabine and cisplatin⁴ (category 1) followed by avelumab maintenance therapy (category 1)^{a,13} • Nivolumab, gemcitabine, and cisplatin (category 1) followed by nivolumab maintenance therapy¹⁴ (category 1) <u>Useful under certain circumstances</u> • DDMVAC with growth factor support (category 1)^{2,8} followed by avelumab maintenance therapy (category 1)^{a,13}
Cisplatin ineligible	<u>Preferred regimens</u> • Pembrolizumab and enfortumab vedotin-ejfv^{15,17} (category 1) <u>Other recommended regimens</u> • Gemcitabine and carboplatin¹⁶ followed by avelumab maintenance therapy (category 1)^{a,13} <u>Useful under certain circumstances</u> • Gemcitabine¹⁸ • Gemcitabine and paclitaxel¹⁹ • Ifosfamide, doxorubicin, and gemcitabine²¹ (for patients with good kidney function and good performance status) • Pembrolizumab²² (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab²⁰ (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 $< 60\text{ml/dk}$
- ☐ 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



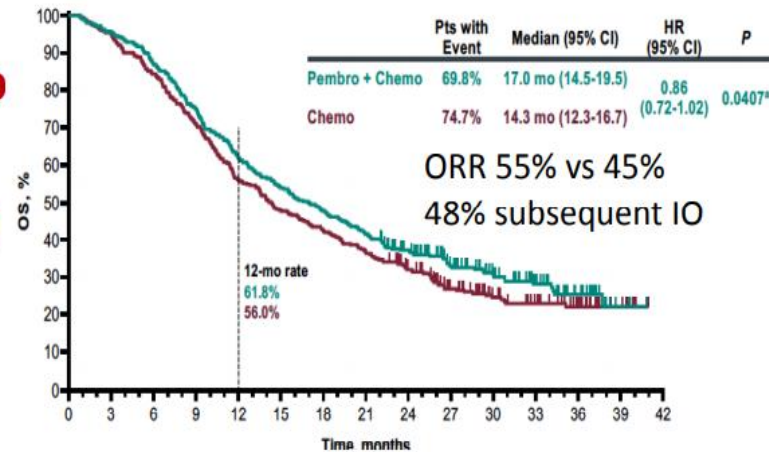
	KEYNOTE 361 (N=1010)	DANUBE (N=1032)
Stratification	Cis/Carbo investigator choice PD-L1: CPS ≥10	Cisplatin eligibilty PD-L1: ≥25% IC and/or TC positive Liver and/or lung metastases
Primary endpoints	PFS and OS: IO-CT vs CT (total) OS: IO vs CT (total and PD-L1 +) Sequential testing!	OS: IO-IO vs CT (ITT)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

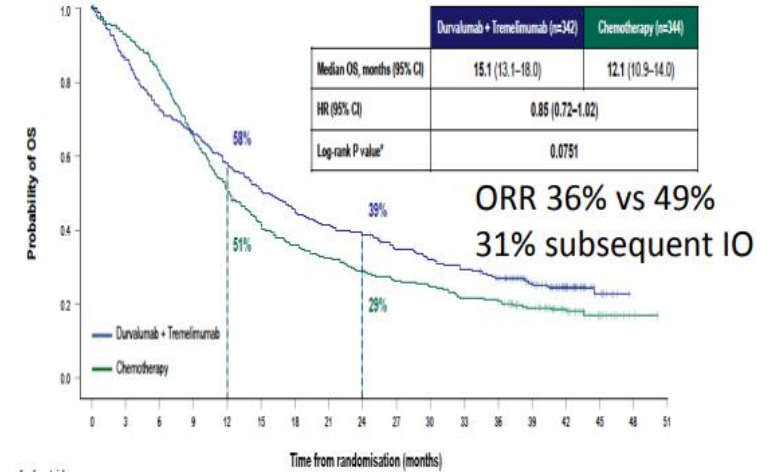
Overall survival

Combination vs Chemo
TOTAL population (ITT)

KEYNOTE 361 –IO-CT vs CT (1°EP)



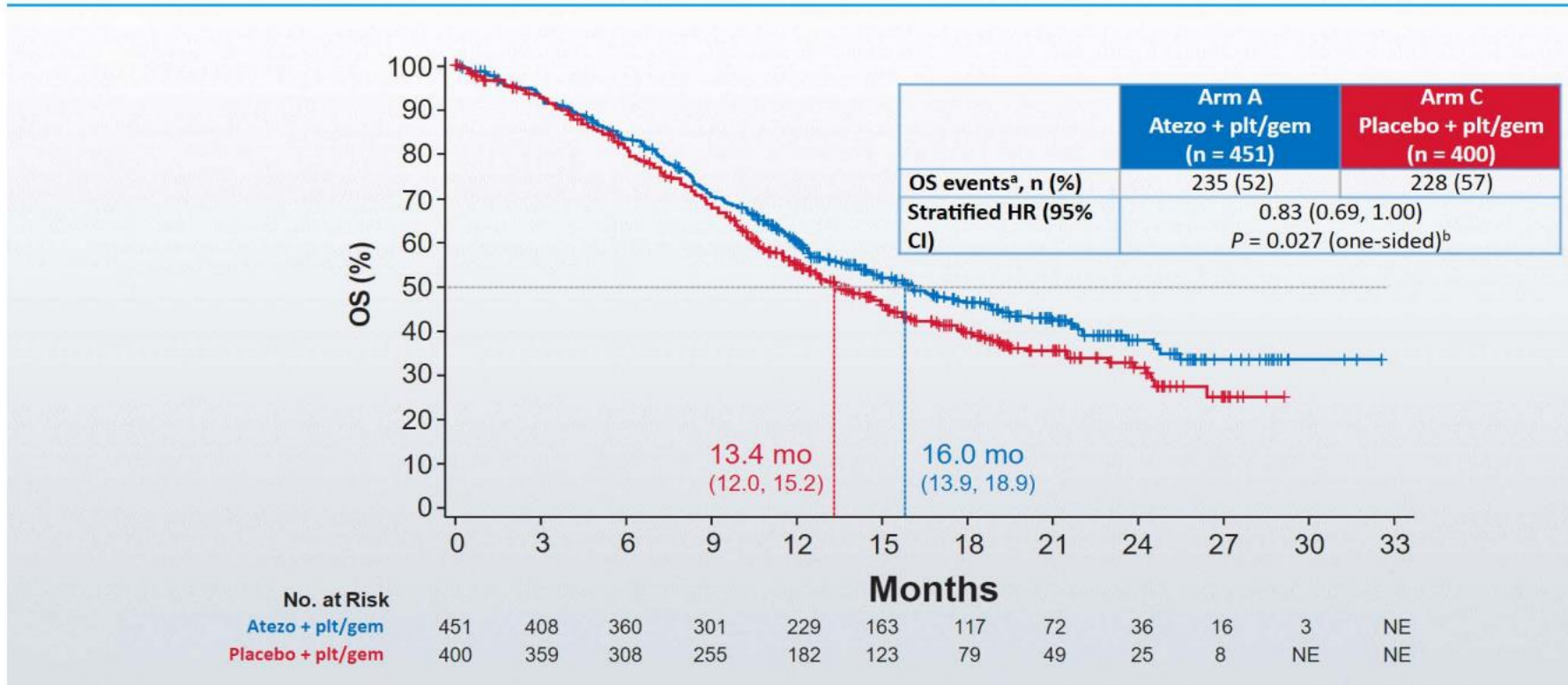
DANUBE – IO-IO vs CT (1°EP)



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

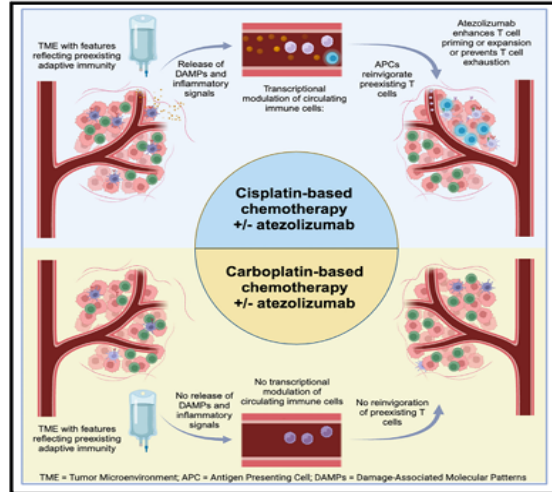


CellPress
OPEN ACCESS

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

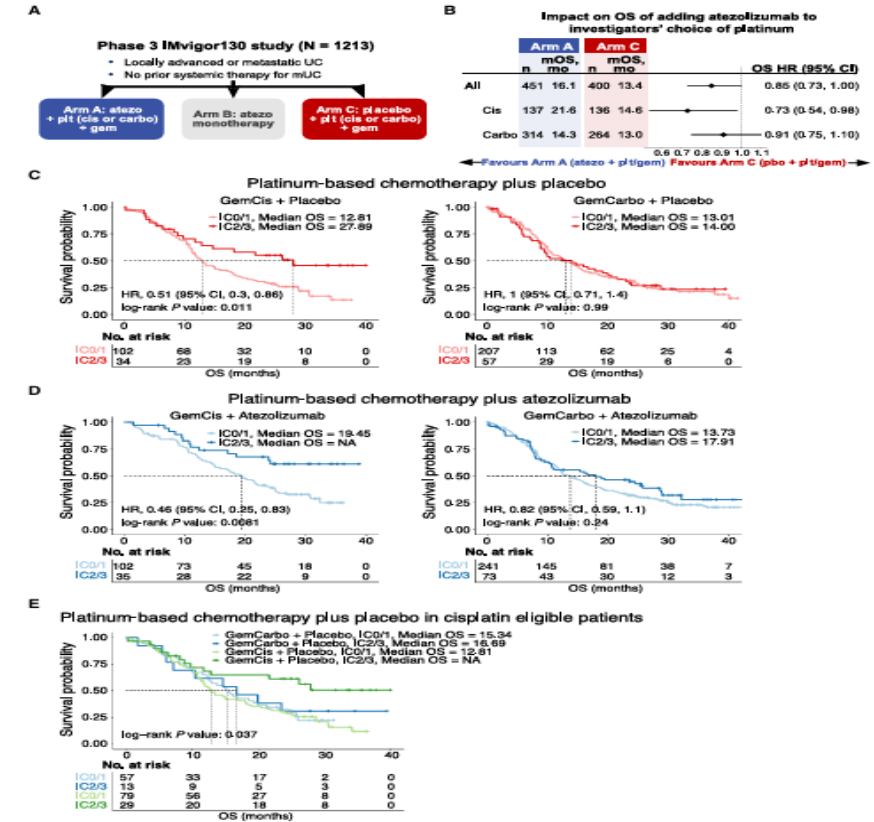
Correspondence

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.

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



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

Ürotelyal Kanserlerde Renal Yetmezlik ile İmmünoterapi Etkinliği Azalıyor

ASCO ABSTRACT #434954
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
ASSOCIATION FOR CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

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, Bakırköy 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.

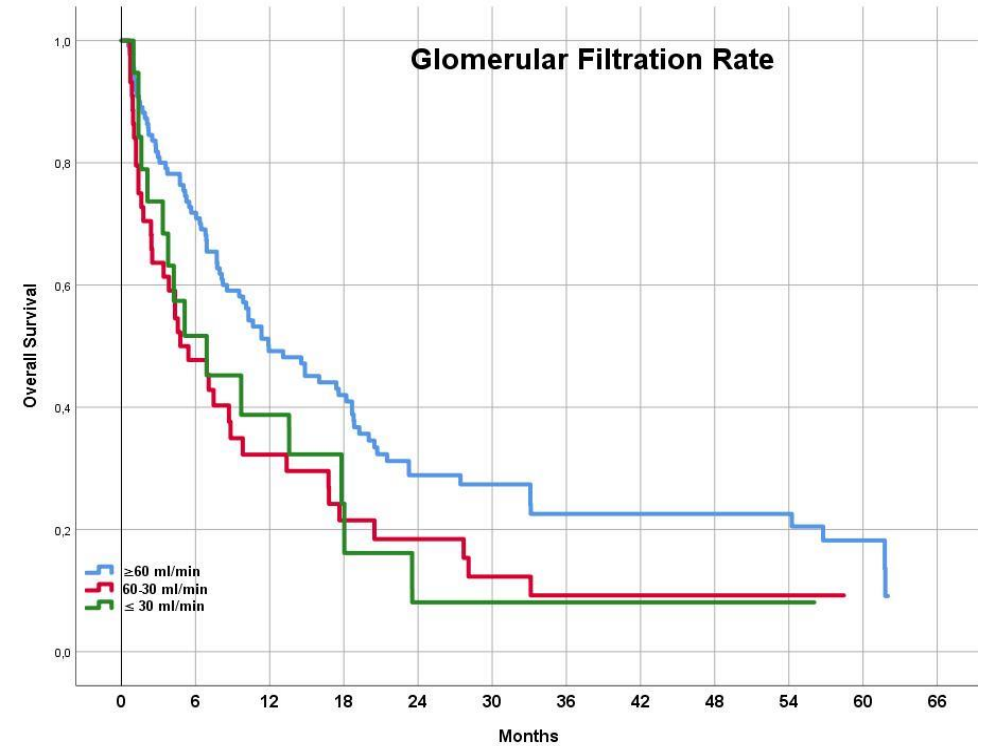
Background:

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 $\geq$ 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

Chemo + IO combinations

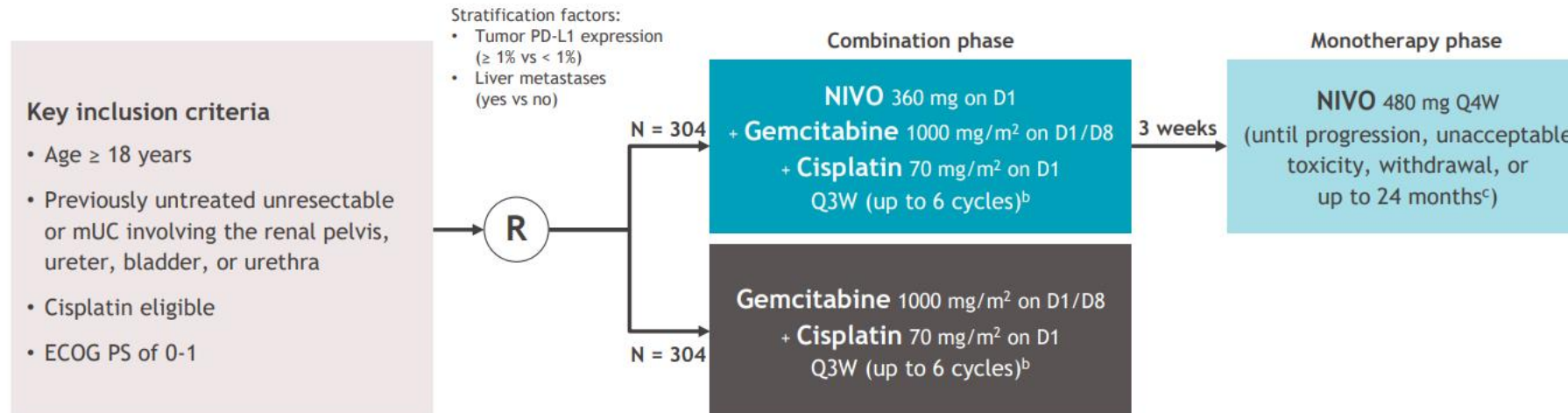
IMvigor130	KEYNOTE-361	DANUBE	CHECKMATE901
Atezolizumab + Platinum/Gemcitabine (n = 451)	Pembrolizumab + Platinum/Gemcitabine (n = 351)	Durvalumab + Tremelimumab (n = 342)	Nivolumab + Cisplatin/Gemcitabine (n = 304)
Atezolizumab Monotherapy (n = 400)	Pembrolizumab Monotherapy (n = 307)	Durvalumab Monotherapy (n = 346)	
Placebo + Platinum/Gemcitabine (n = 362)	Platinum/Gemcitabine (n = 352)	Platinum/Gemcitabine (n = 344)	Cisplatin/Gemcitabine (n = 304)
Coprimary endpoints: PFS and OS (combo vs chemo)	Coprimary endpoints: PFS and OS (combo vs chemo)	Coprimary endpoints: OS in PD-L1+ (durvalumab vs chemo)	Primary endpoints: OS, PFS
OS (atezo vs chemo)	OS (pembro vs chemo)	OS in ITT (durva/tremi vs chemo)	
hierarchical approach	hierarchical approach		

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 $\geq 1\%$,^d HRQoL

Key exploratory endpoints: ORR per BICR, safety

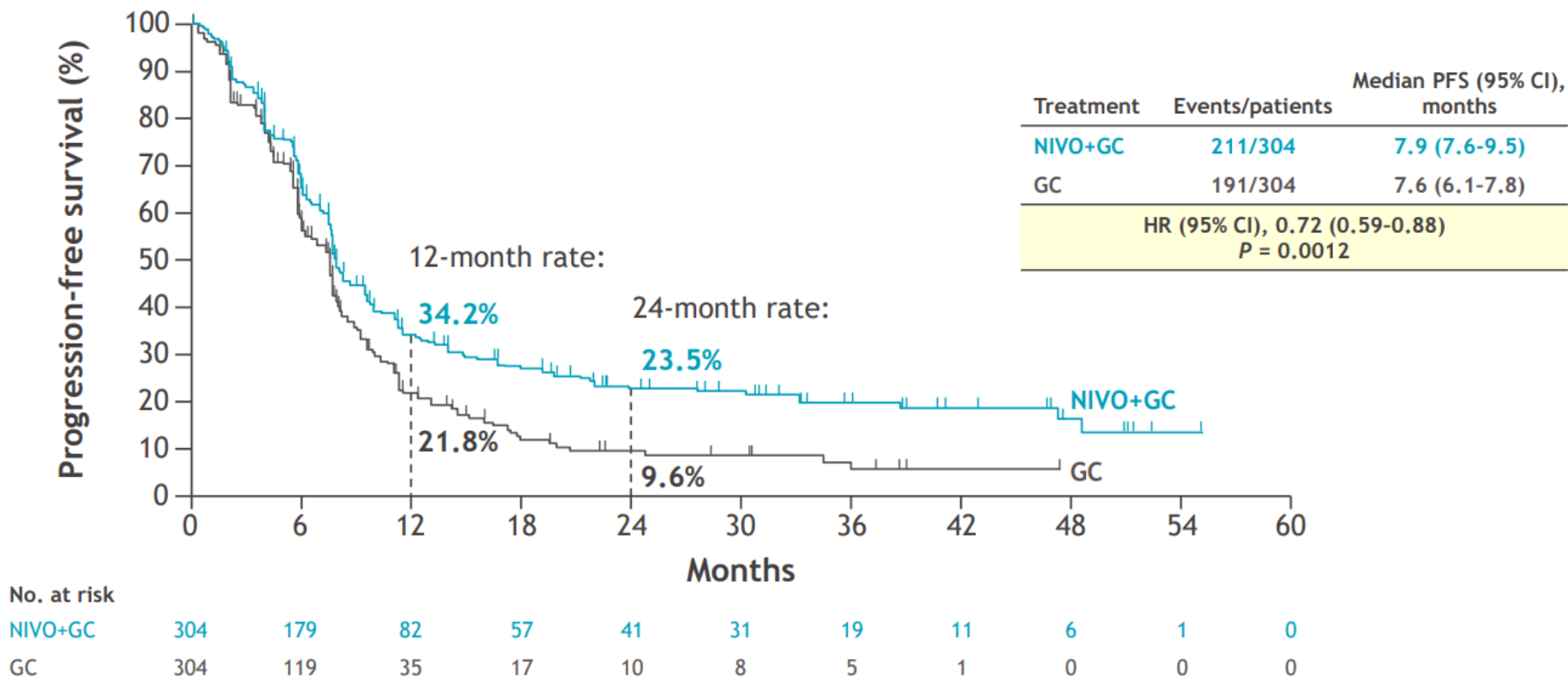
^aFurther CheckMate 901 trial design details are available at <https://clinicaltrials.gov/ct2/show/NCT03036098>. ^bPatients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). ^cA maximum of 24 months from first dose of NIVO administered as part of the NIVO + gemcitabine-cisplatin combination. ^dPD-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; QxW, every x weeks; R, randomization.

Sisplatine uygun hastalarda Cisplatin+Gemsitabin+Nivolumab

CheckMate 901

PFS per BICR (primary endpoint)

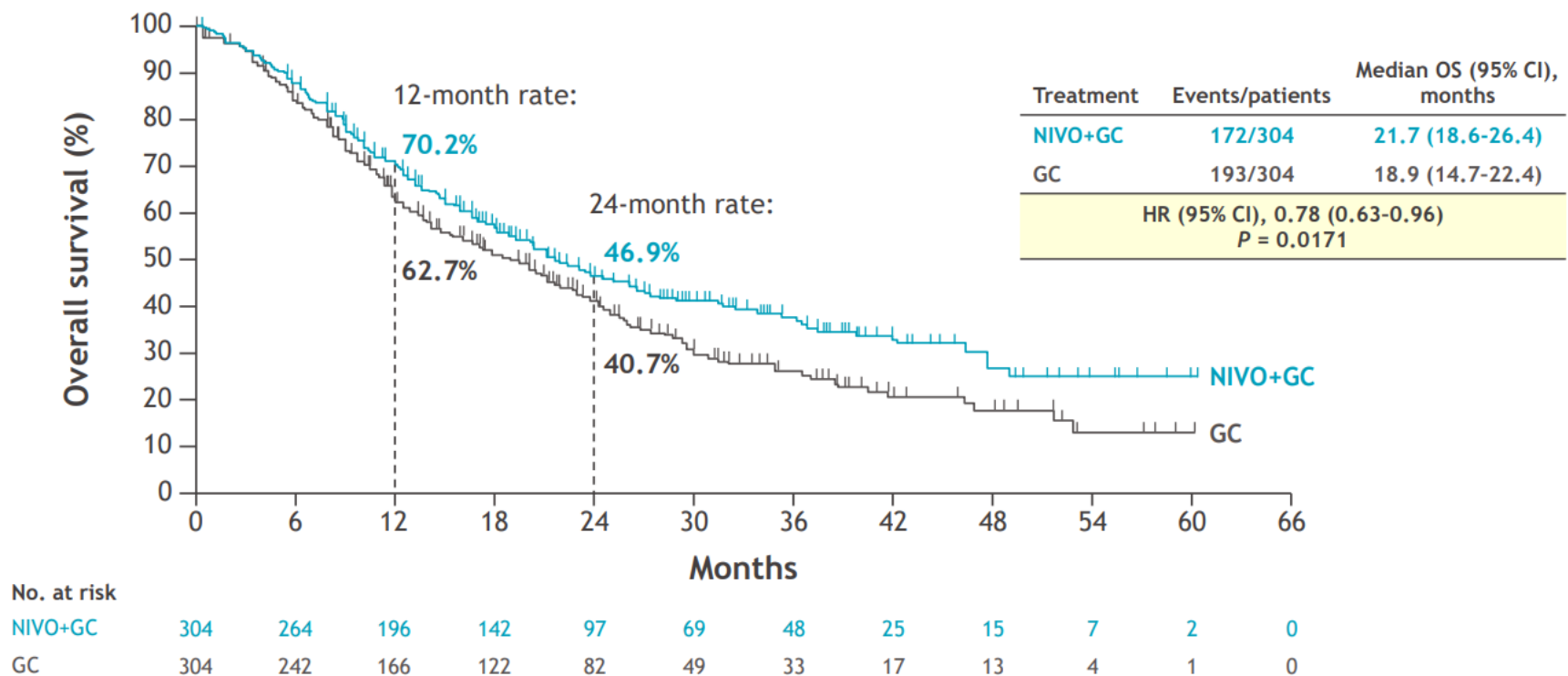


Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as time from randomization to first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who did not progress 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 Cisplatin+Gemsitabin+Nivolumab

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OS (primary endpoint)

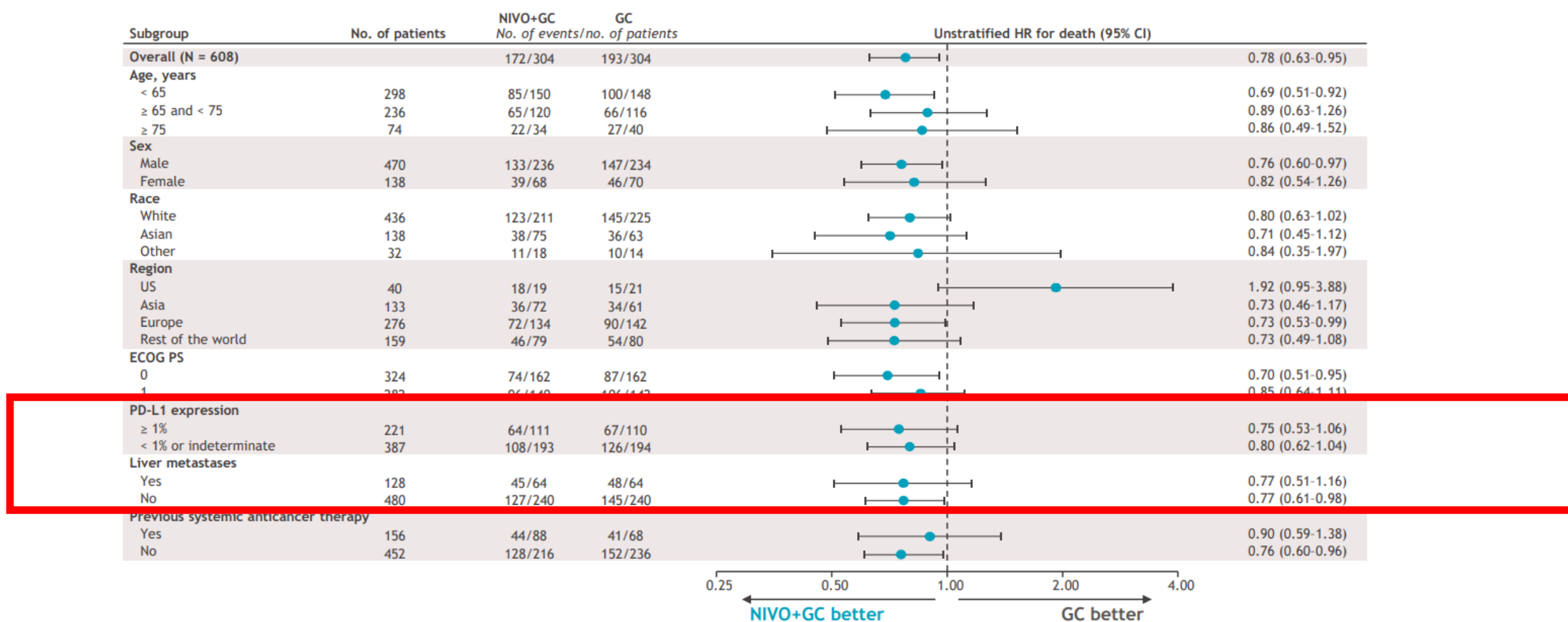


Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with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

Sisplatine uygun hastalarda Cisplatin+Gemsitabin+Nivolumab

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OS in subgroups

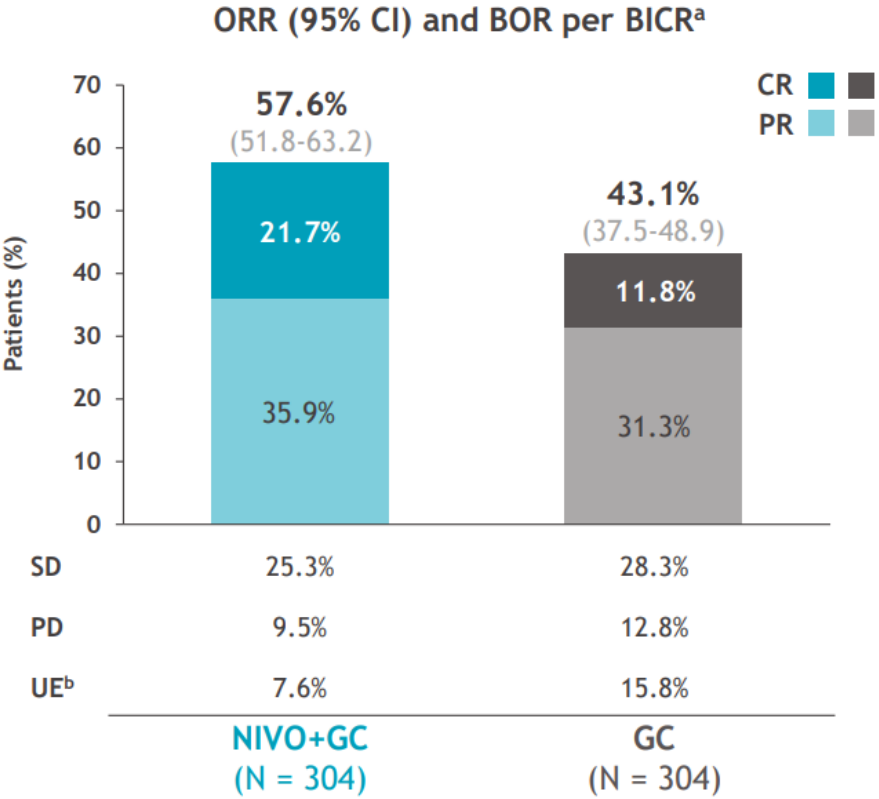


All randomized patients. HRs were not computed for subgroup categories (except for age, sex, race, and region) with < 10 patients per treatment group. Categories without a meaningful estimate of the HR are not shown. PD-L1 expression and liver metastases are per interactive response technology. There 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

CheckMate 901

Objective response outcomes (exploratory endpoints)



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)

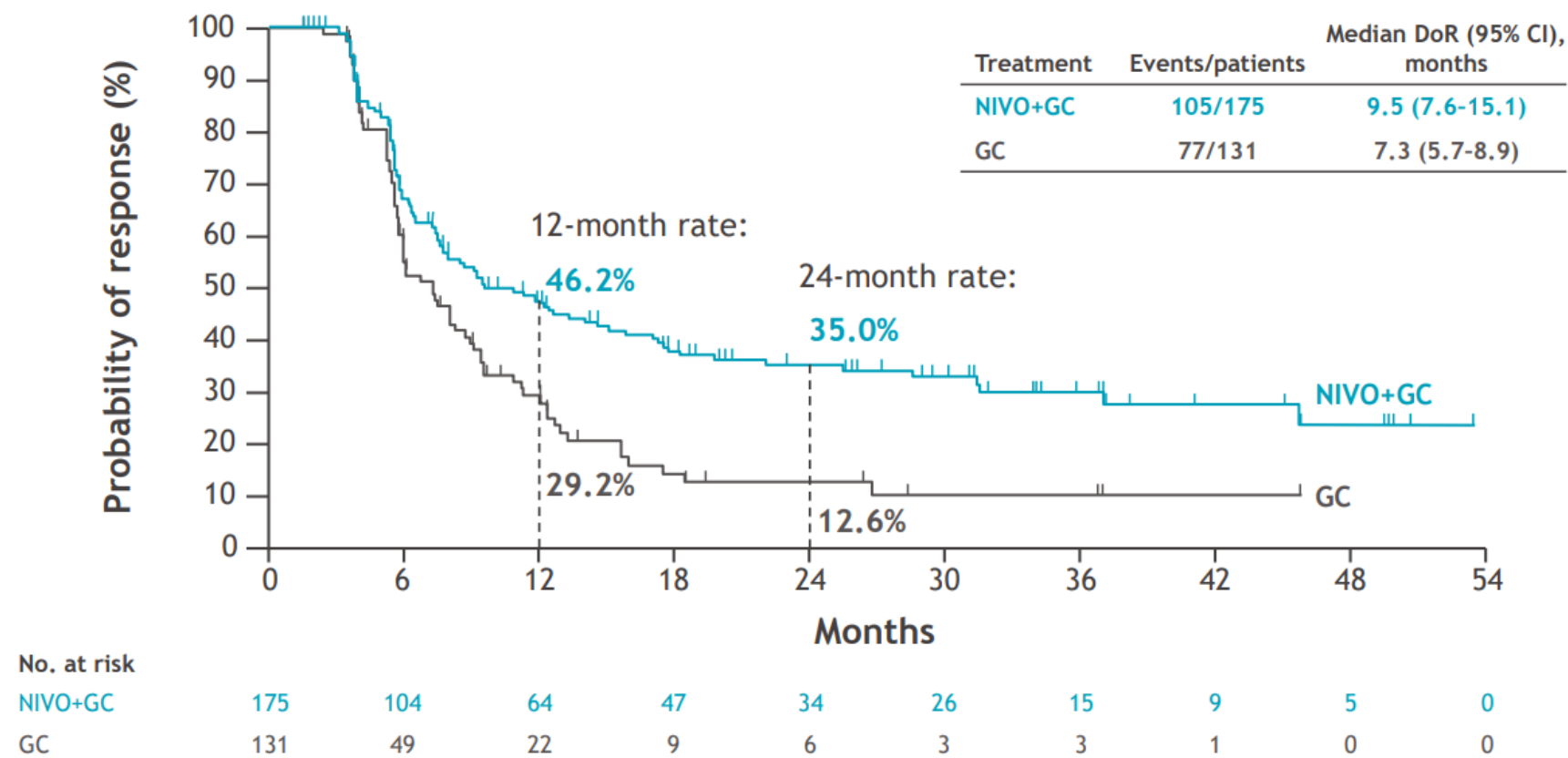
Complete response ^d	NIVO+GC (n = 66)	GC (n = 36)
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

^aIn all randomized patients. ^bThe 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. ^cBased on patients with an objective response per BICR (PR or CR as BOR). ^dBased 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

CheckMate 901

Duration of objective response per BICR

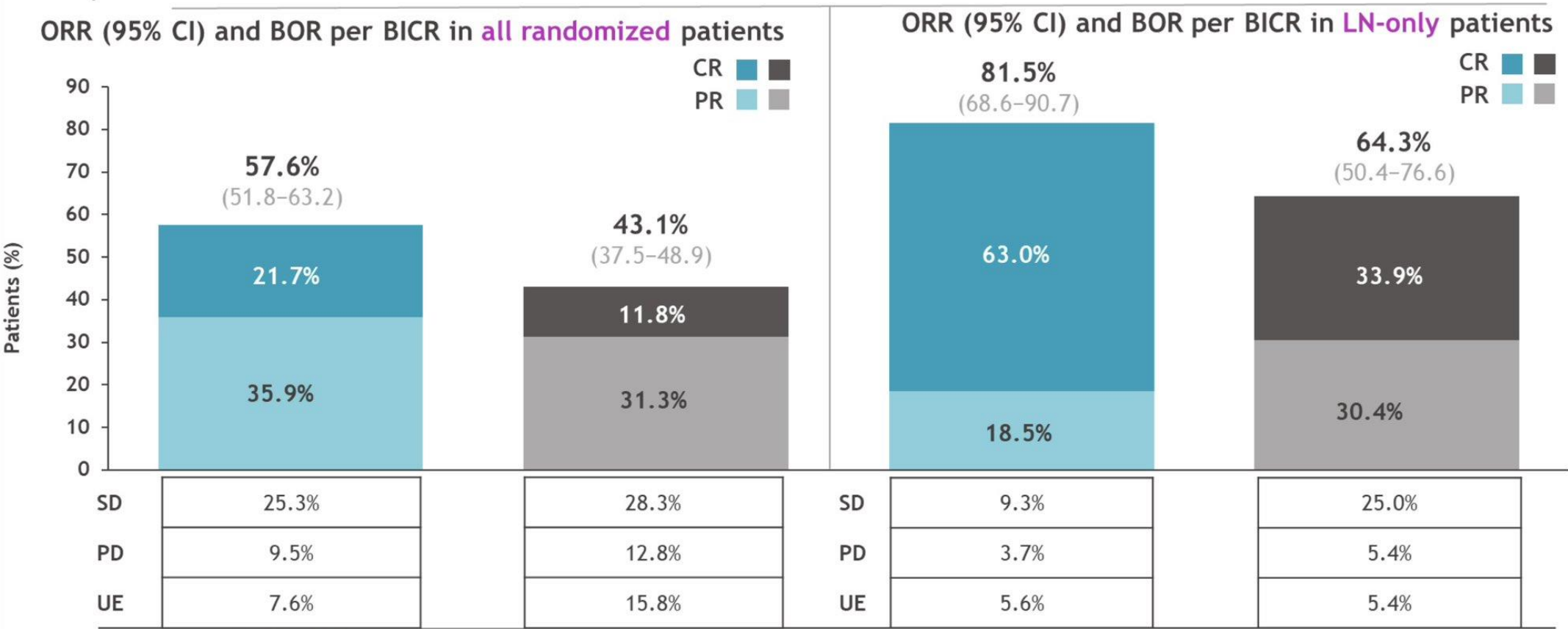


Sisplatin+Gemsitabin+Nivolumab

Yalnız lenf nodu metastazı olanlarda yanıt

Response per BICR: patients with LN-only mUC

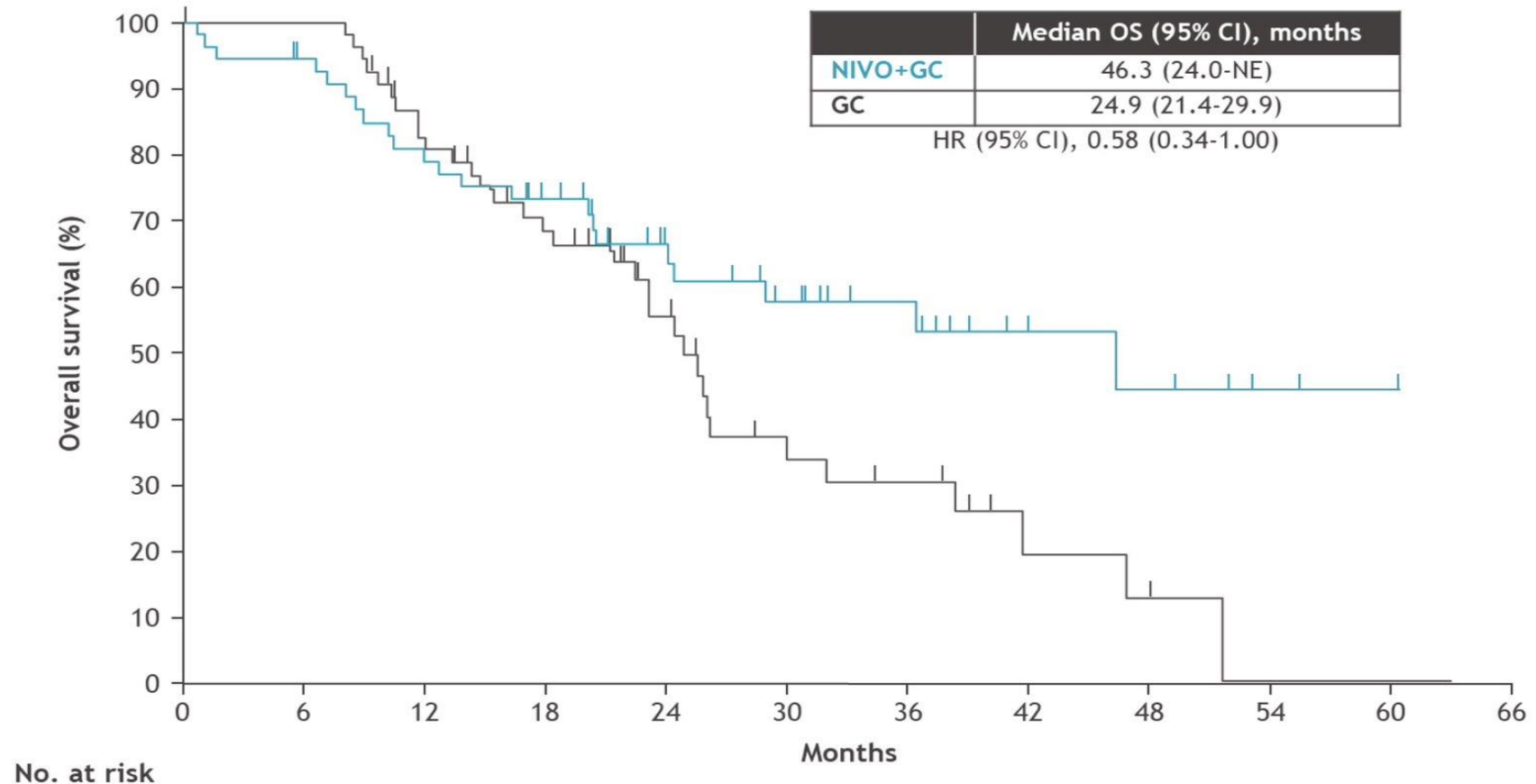
- CR rates for NIVO+GC-treated patients with LN-only mUC were approximately twice that of GC-treated patients



Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

Yalnız lenf nodu metastazı olanlarda Genel sağkalım

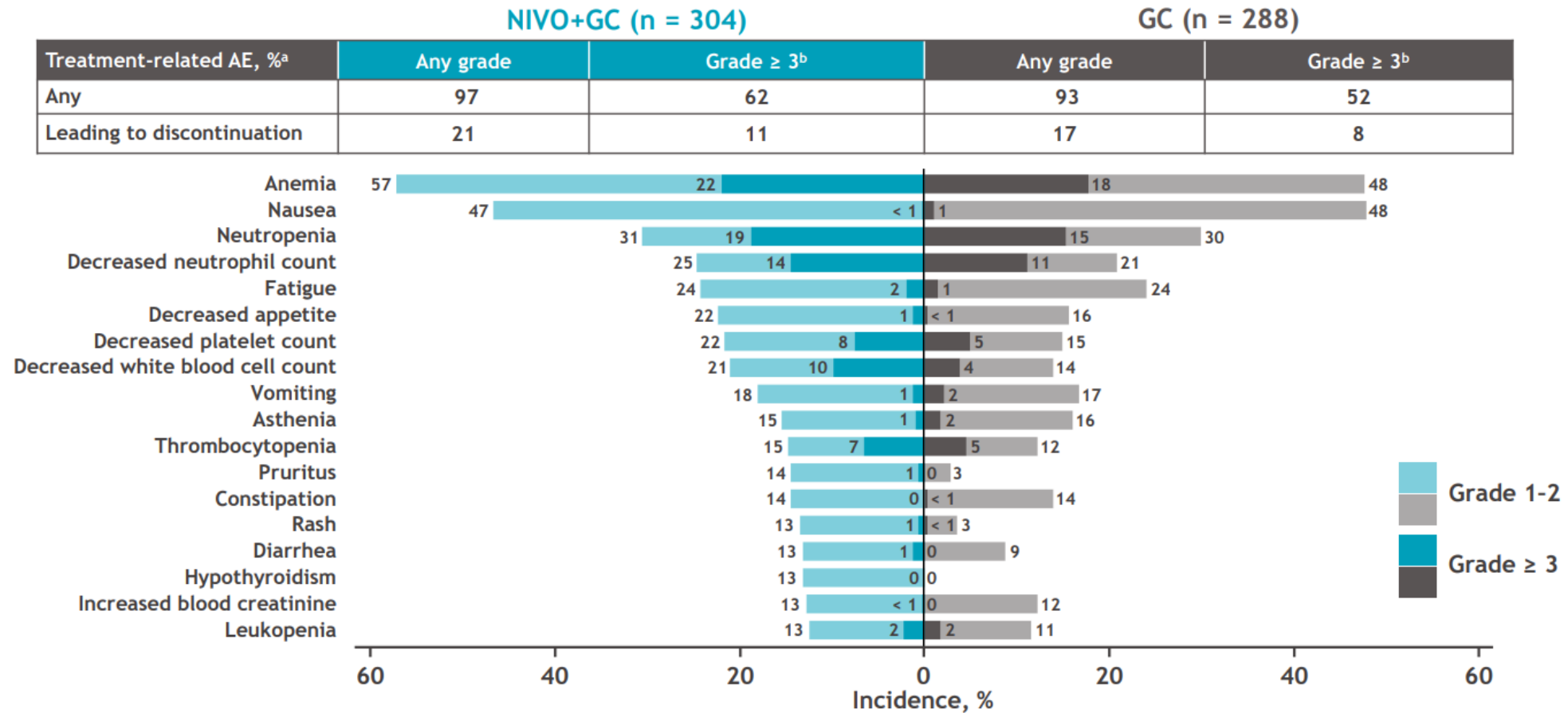
OS: patients with LN-only mUC per BICR



Sisplatin uygun hastalarda KT+İmmünoterapi

CheckMate 901

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). 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 immune checkpoint blockade therapies in patients with metastatic urothelial carcinoma

Deniz Tural¹ · Fatih Selçukbiricik² · Ömer Fatih Ölmez³ · Ahmet Taner Sümbül⁴ · Mustafa Erman⁵ · Hasan Şenol Coşkun⁶ · Mehmet Artaç⁷ · Saadetin Kılıçkap⁸

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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 first-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

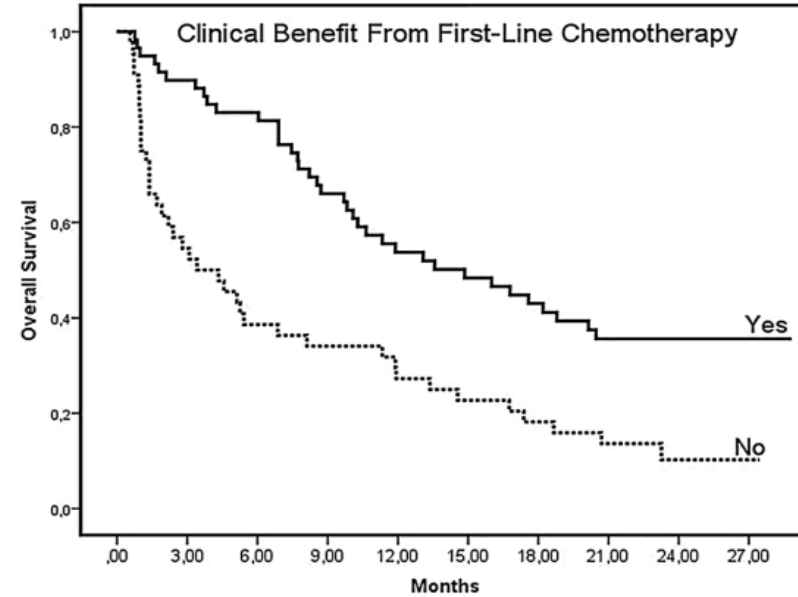
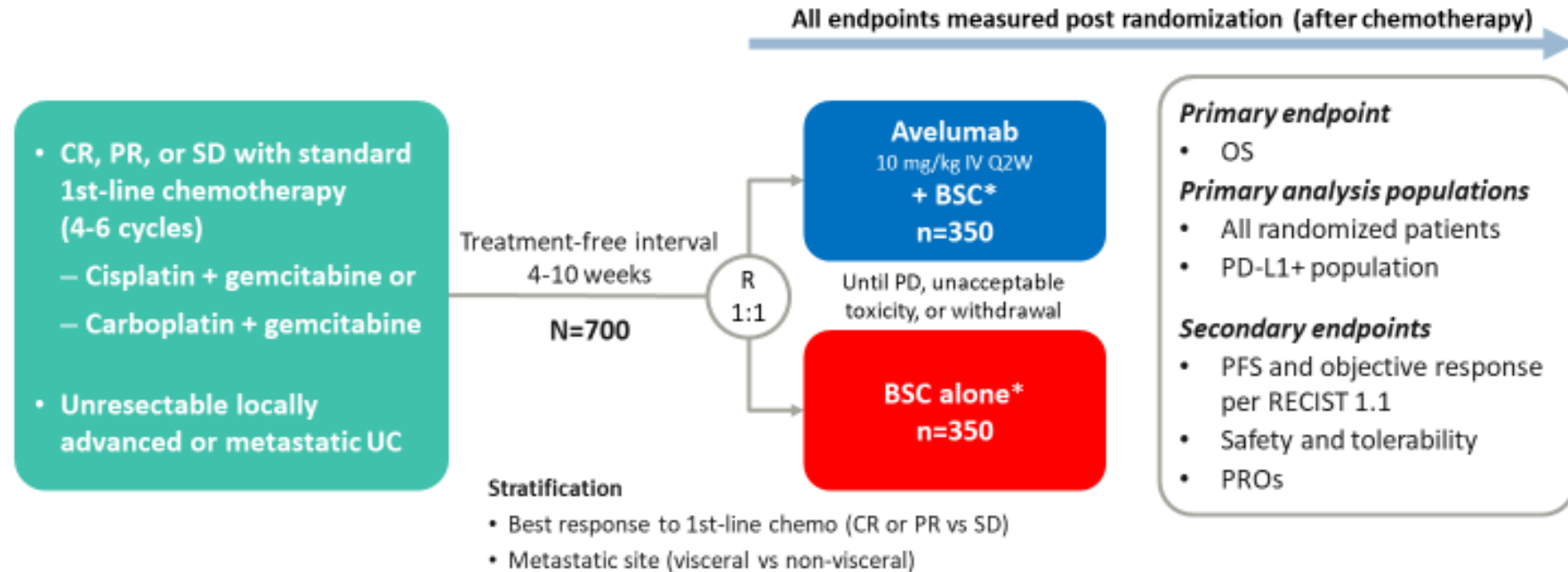


Fig. 2 Kaplan–Meier curves association of clinically benefited from the first-line treatment and overall survival

The median OS on ATZ of 14.8 and 3.4 months for patients with clinical benefit and progressive disease in response to first-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 $\geq 25\%$ 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 SP263 assay; 358 patients (51%) had a PD-L1-positive tumor

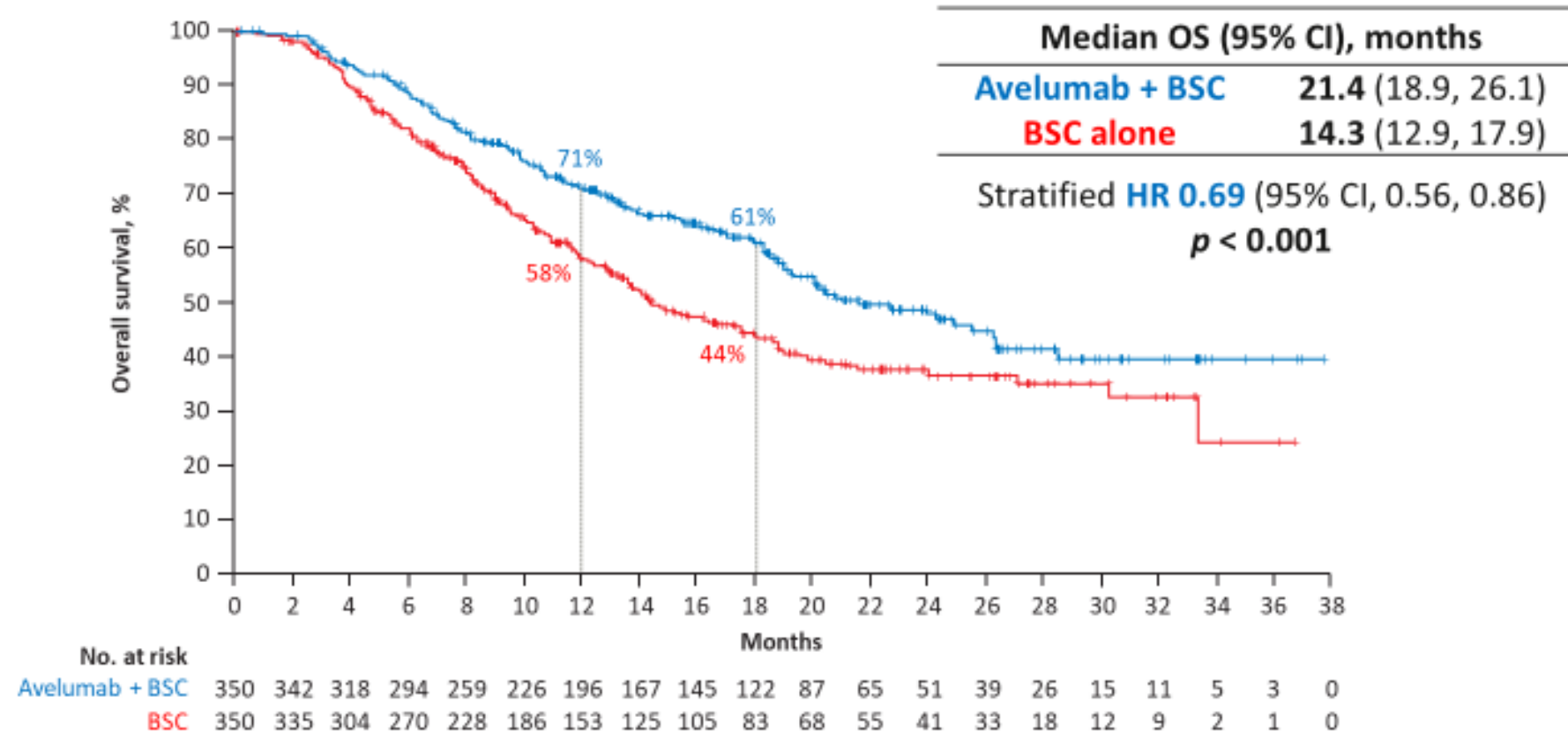
BSC, best supportive care; CR, complete response; IV, intravenous; PR, partial response; PRO, patient reported outcome; Q2W, every 2 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease

*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

Metastatik Ürotelyal Kanserlerde Birinci Basamak Tedavi

Platin bazlı kemoterapi Sonrası İdame Avelumab

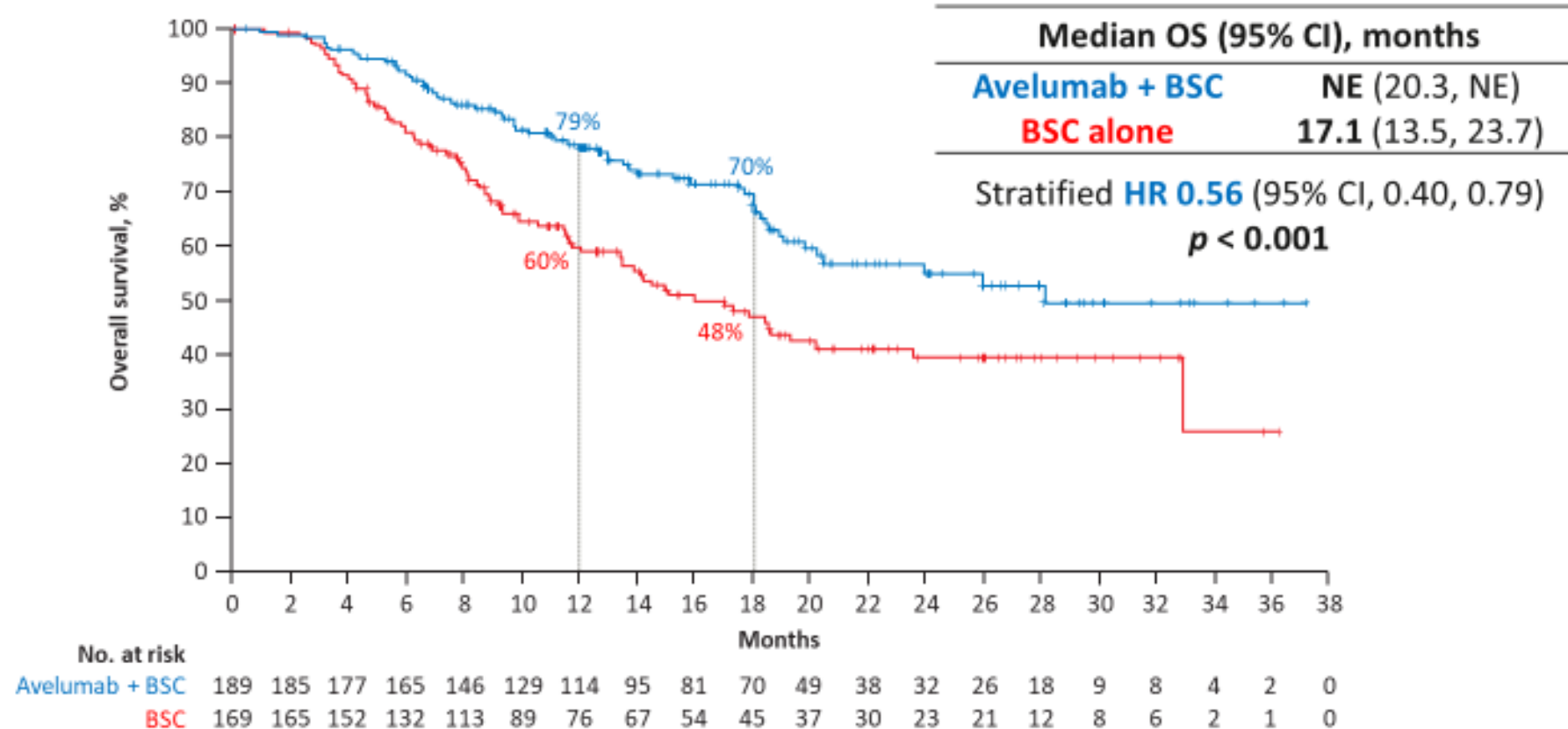
OS in the overall population



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

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

OS in the PD-L1+ population



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

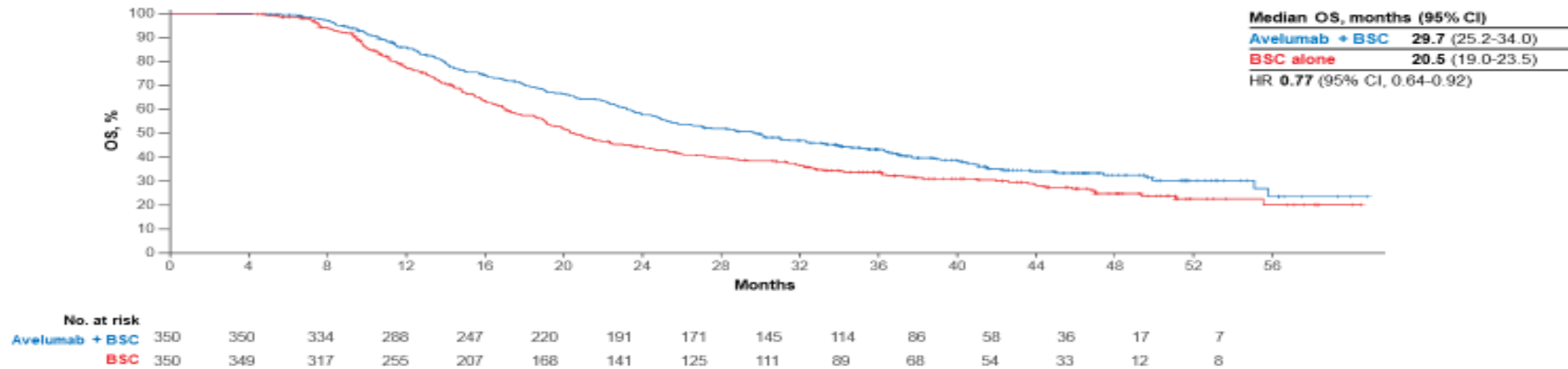
Metastatik Ürotelyal Kanserlerde Birinci Basamak Tedavi Platin bazlı kemoterapi Sonrası idame Avelumab

Long-term Analysis

Data Cut-off: 4th June 2021

OS From the Start of 1L CT in All Randomized Patients¹

Post hoc analysis



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 Francisco, 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

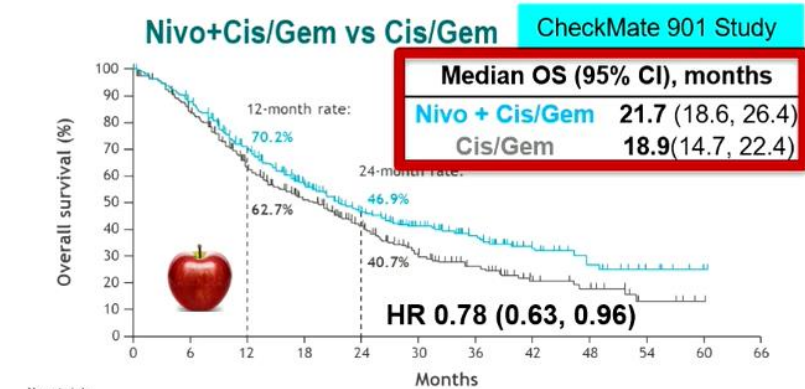
All patients	10	7-13.1	N/A
Best response to first-line treatment			
CR + PR + SD	14.8	8.3-21.4	0.001
PD	3.4	0.5-6.4	
Number of cycles of platinum-based first-line chemotherapy			
4 cycle ≤ 7.8	0.1		
4 cycle > 11.7			
Age (years)			
≤ 65	8.7	4.2-13.1	0.7
> 65	10	5.9-14.2	
Gender			
Male	9.8	6.9-12.7	0.5
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 belli bir oranı immün kontrol noktası inhibitörlerinden fayda görebilir

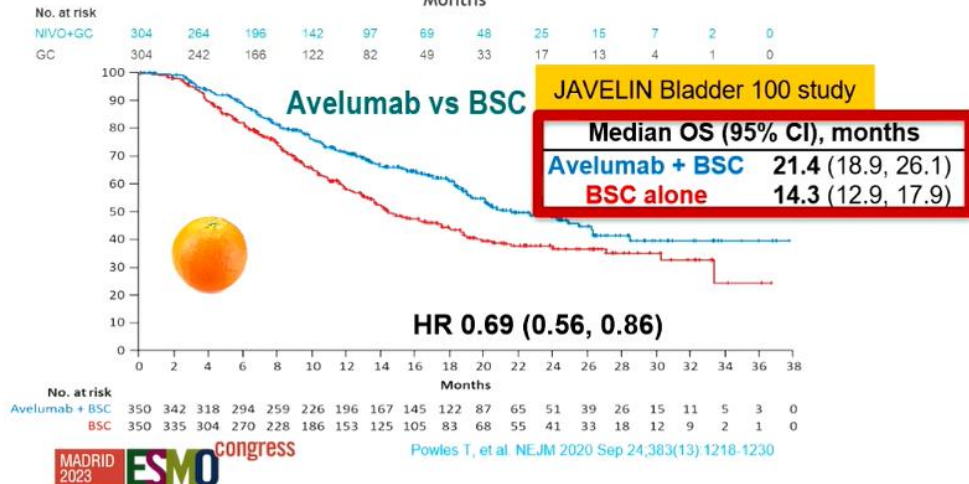
Metastatik Ürotelyal Kanserlerde Birinci Basamak Tedavi Seçeneği

Sisplatin Gempitabin 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 Ia/mUC
- Cisplatin ineligible
- No prior treatment for Ia/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

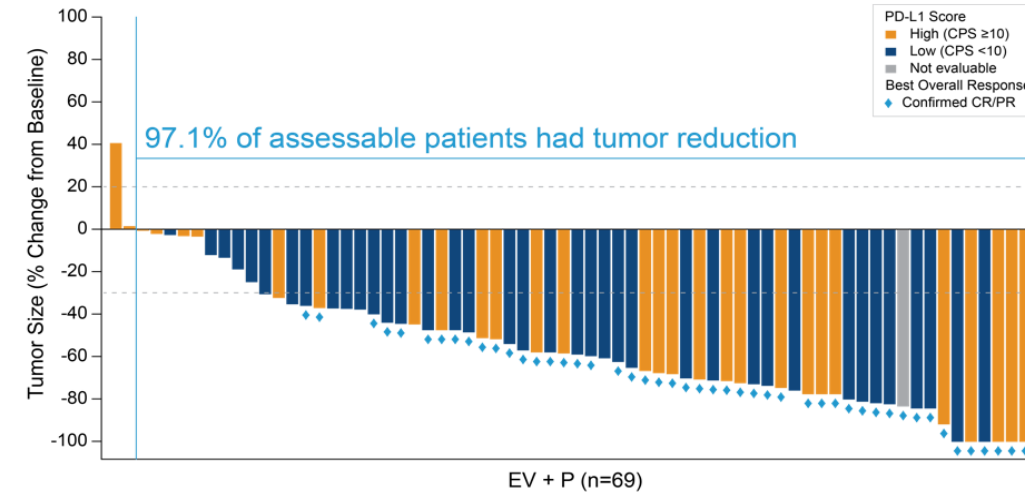
Primary Endpoint

- 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

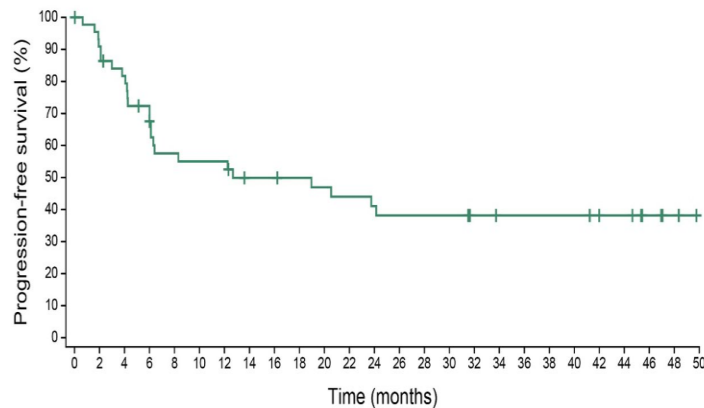
BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

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



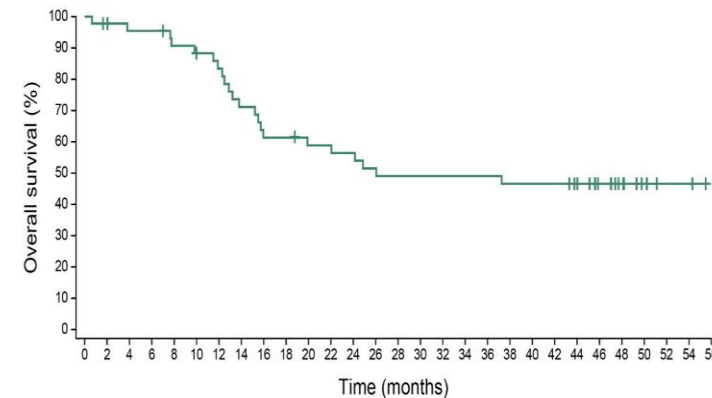
No. at risk 45 40 35 30 22 22 18 17 16 15 13 13 11 10 10 8 8 4 2

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
^aCI was calculated using the complementary log-log transformation method (Collett, 1994)
^bAs estimated using Kaplan-Meier method

Overall Survival

Median survival exceeds 2 years



No. at risk 45 43 41 38 36 34 29 25 25 24 23 21 20 20 20 20 19 19 17 12 8 4 2 2

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
^aCI was calculated using the complementary log-log transformation method (Collett, 1994)
^bAs estimated using Kaplan-Meier method

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

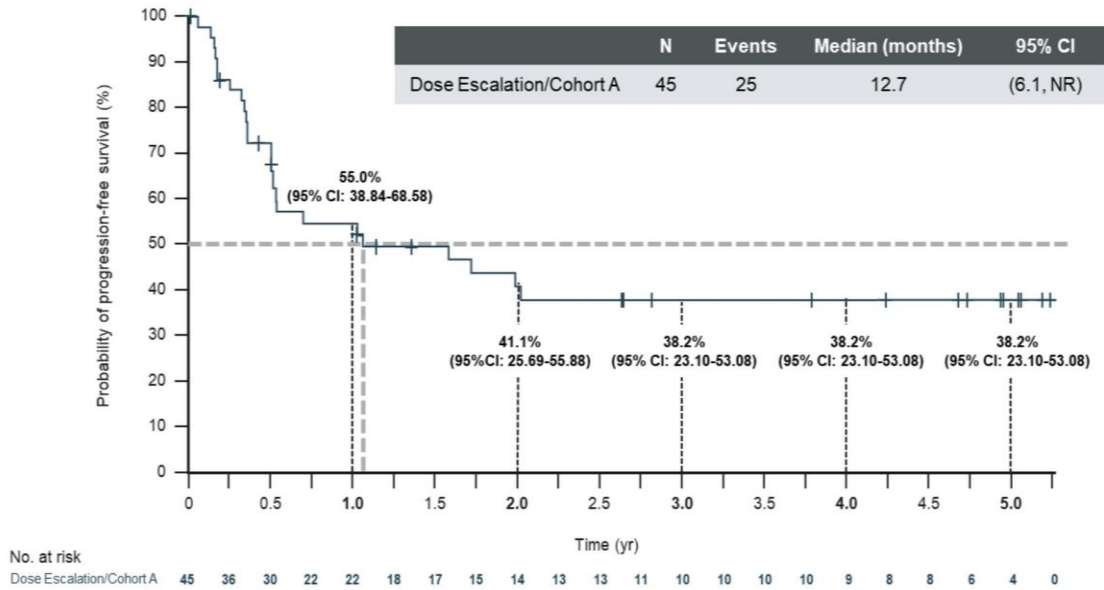
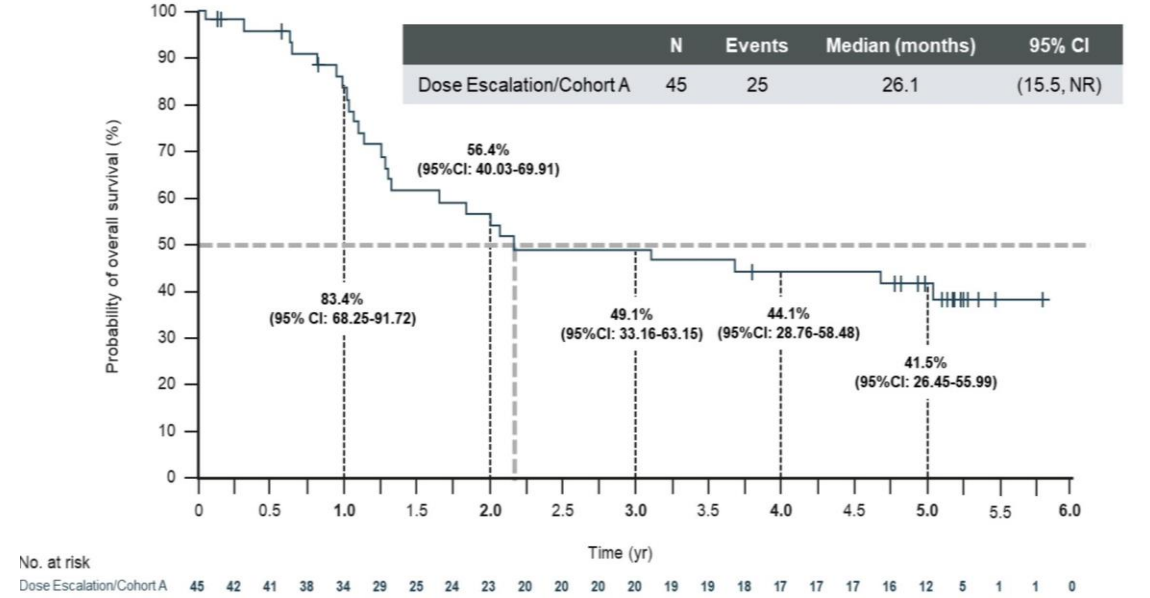


Figure 5. OS

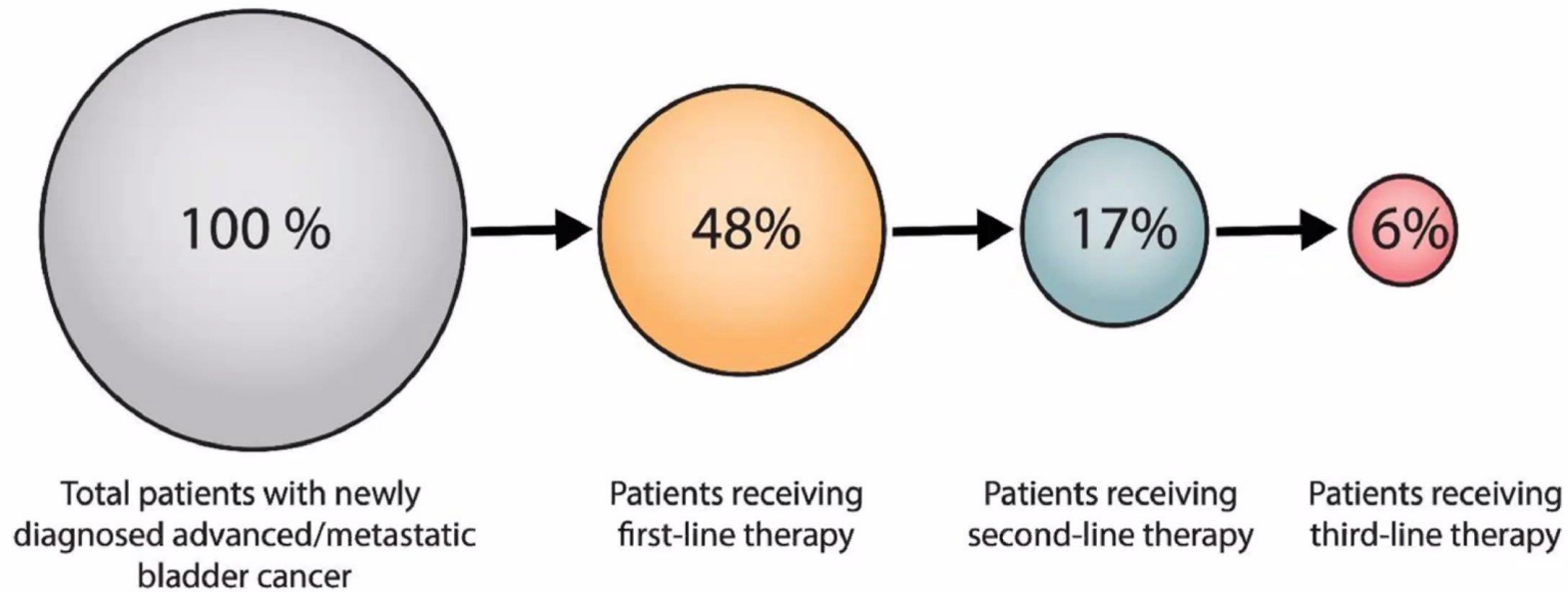


Enfortumab vedotin ve pembrolizumab kombinasyonu sisplatin uygun olmayan hastalarda 5-yıllık sağkalım %40

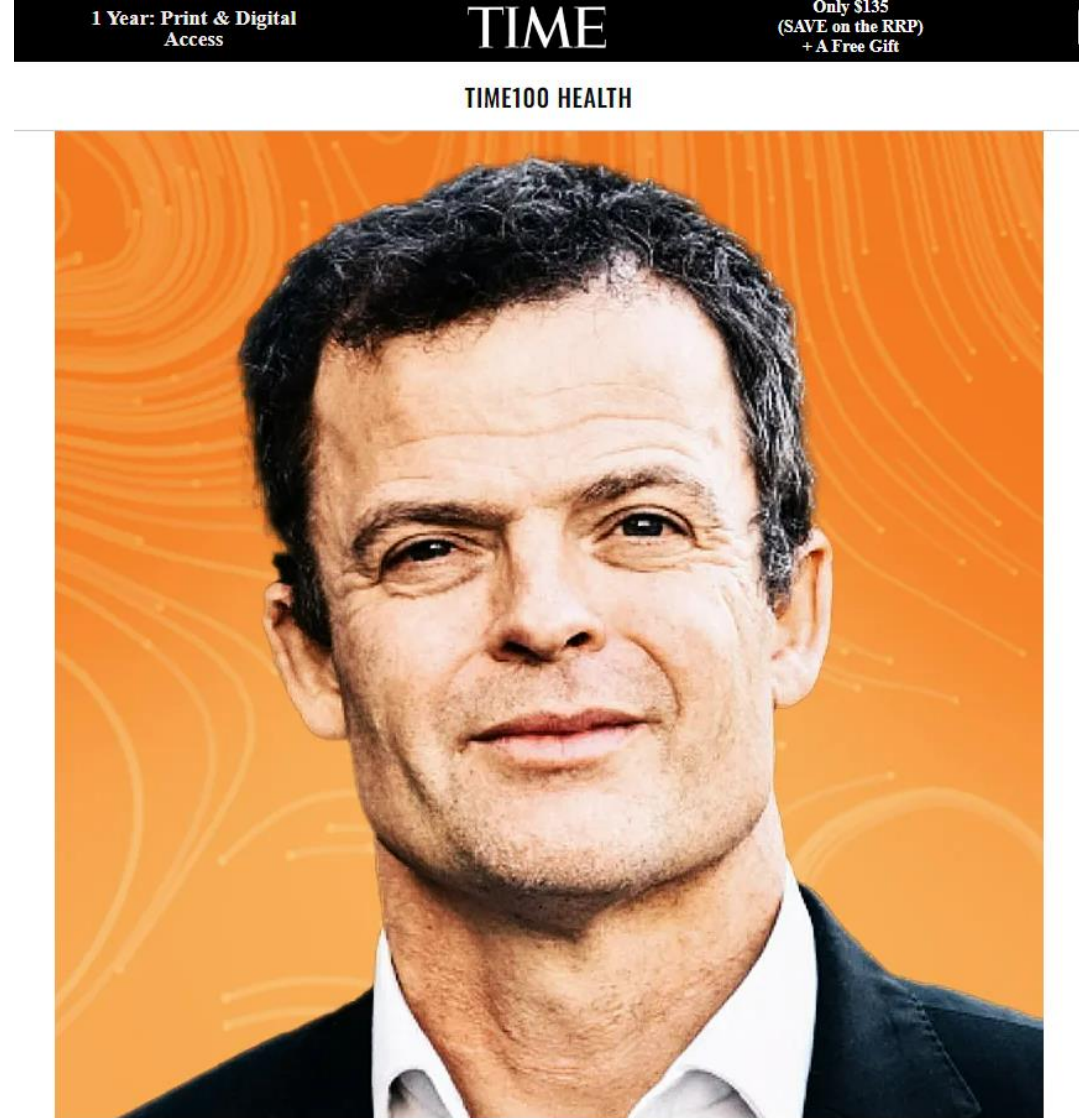
Neden en etkili tedavi ilk sırada verilmeli



Utilization of Systemic Therapy for Advanced Urothelial Carcinoma



TIME Dergisine Kapak Olan Çalışmanın Sonuçları Açıklandı



Thomas Powles Courtesy Powles

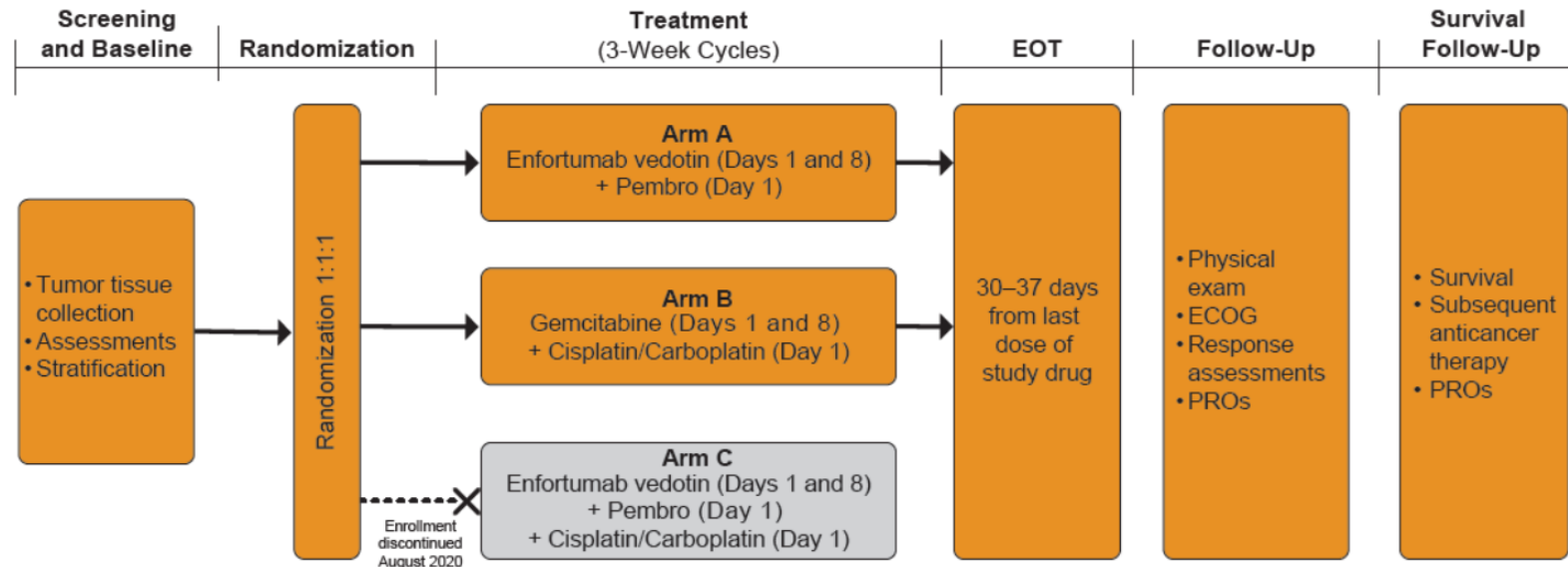
Metastatik Mesane Kanseri Birinci Basamak Tedavi

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

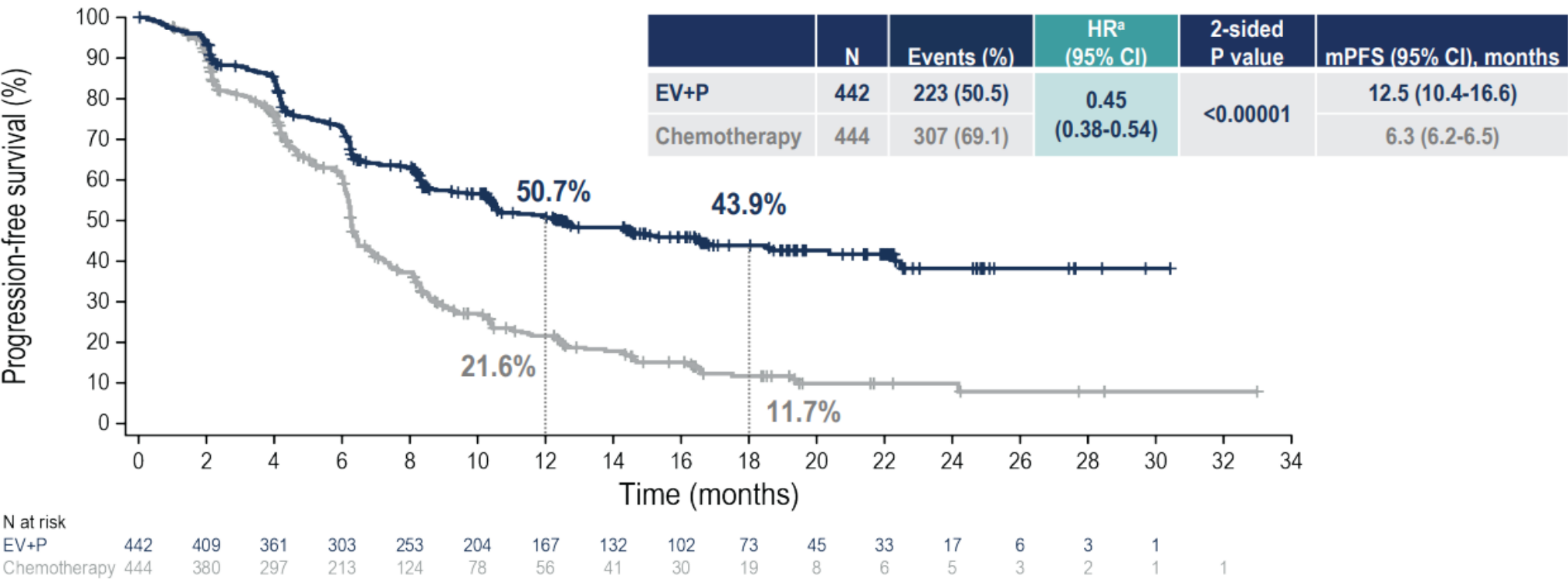
Primary Endpoints: PFS, OS
Secondary Endpoints: ORR, DOR, DCR, QOL, PRO, Safety

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

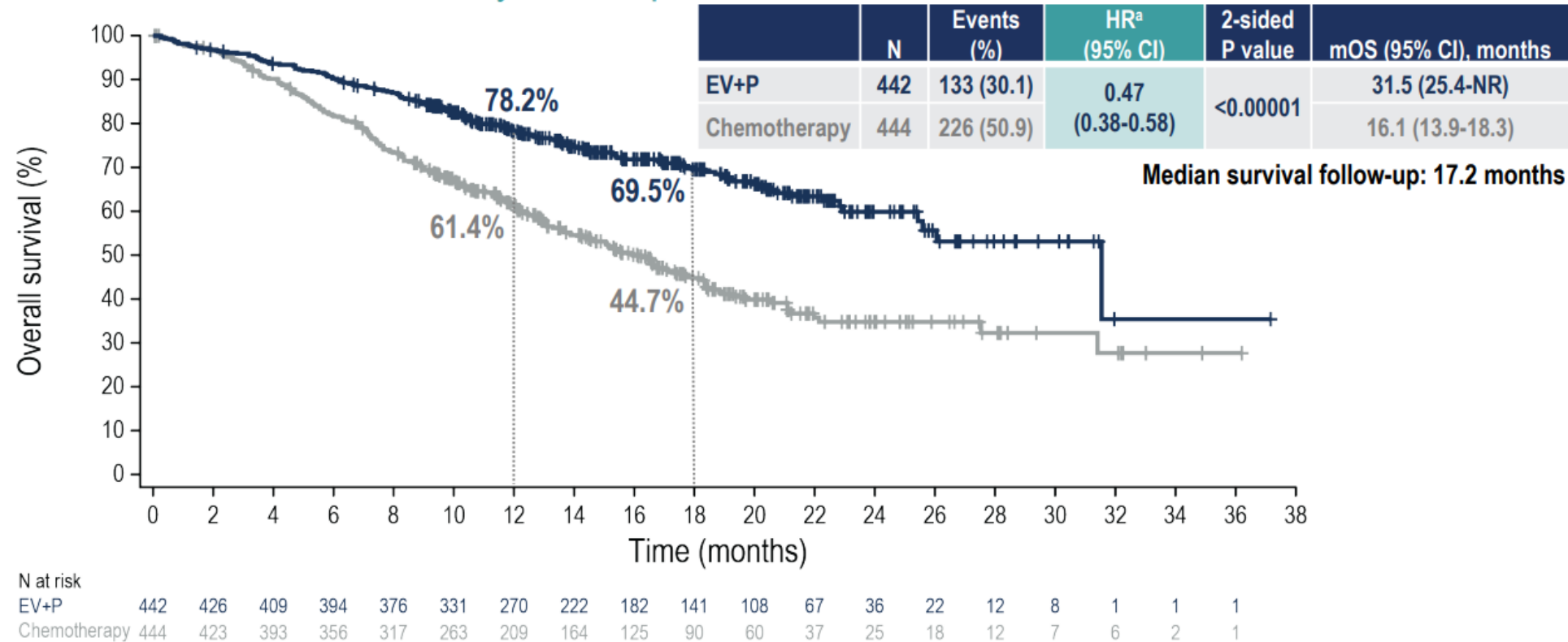


Metastatik Mesane Kanseri Birinci Basamak Tedavi

EV-302 -EV/pemrolizumab

Overall Survival

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

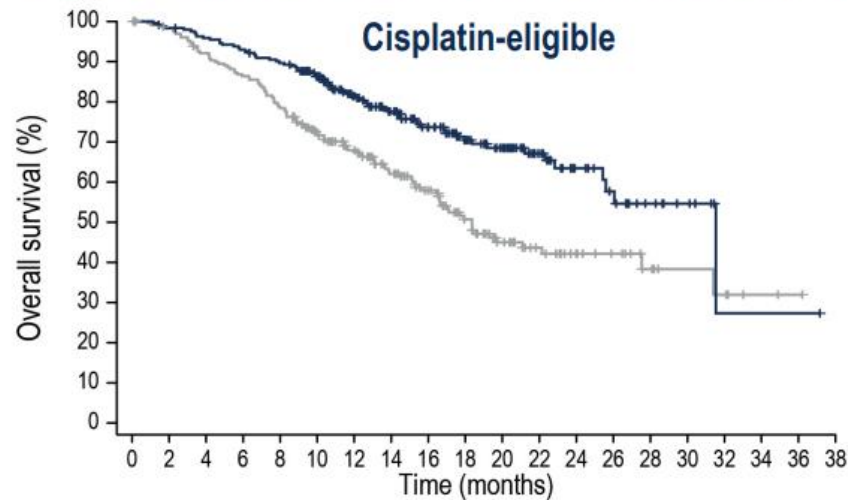


Metastatik Mesane Kanseri Birinci Basamak Tedavi

EV-302 -EV/pemrolizumab

OS Subgroup Analysis: Cisplatin Eligibility

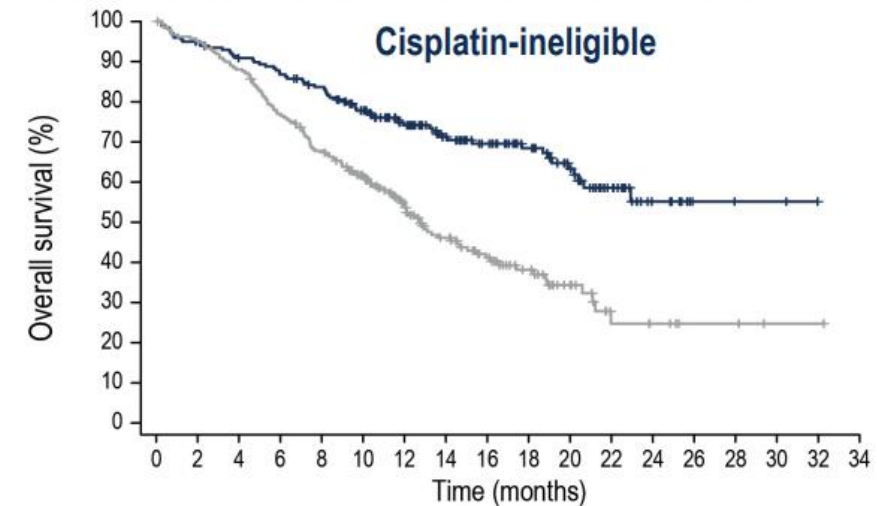
OS benefit was consistent with overall population regardless of cisplatin eligibility



N at risk												
EV+P	244	239	232	225	216	193	155	131	105	80	64	42
Chemotherapy	234	224	209	196	178	147	123	101	79	57	40	29

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

Data cutoff: 08 Aug 2023



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

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

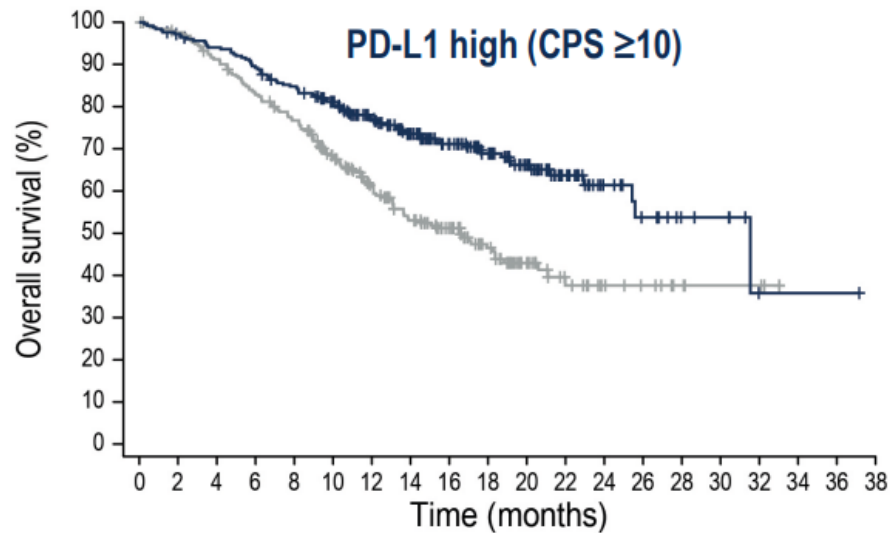
Powles T, ESMO 2023

Metastatik Mesane Kanseri Birinci Basamak Tedavi

EV-302 -EV/pemrolizumab

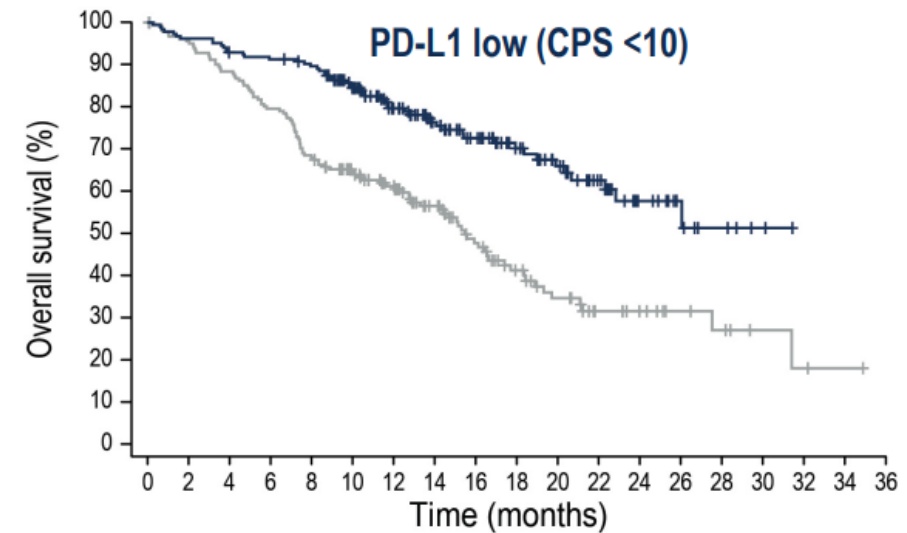
OS Subgroup Analysis: PD-L1 Expression

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



N at risk													
EV+P	254	245	235	223	210	189	162	136	111	87	65	37	20
Chemotherapy	254	245	228	207	189	155	122	97	76	54	33	19	12

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



N at risk													
EV+P	184	177	170	167	162	139	106	86	71	54	43	30	16
Chemotherapy	185	173	160	144	123	103	84	65	47	34	25	16	12

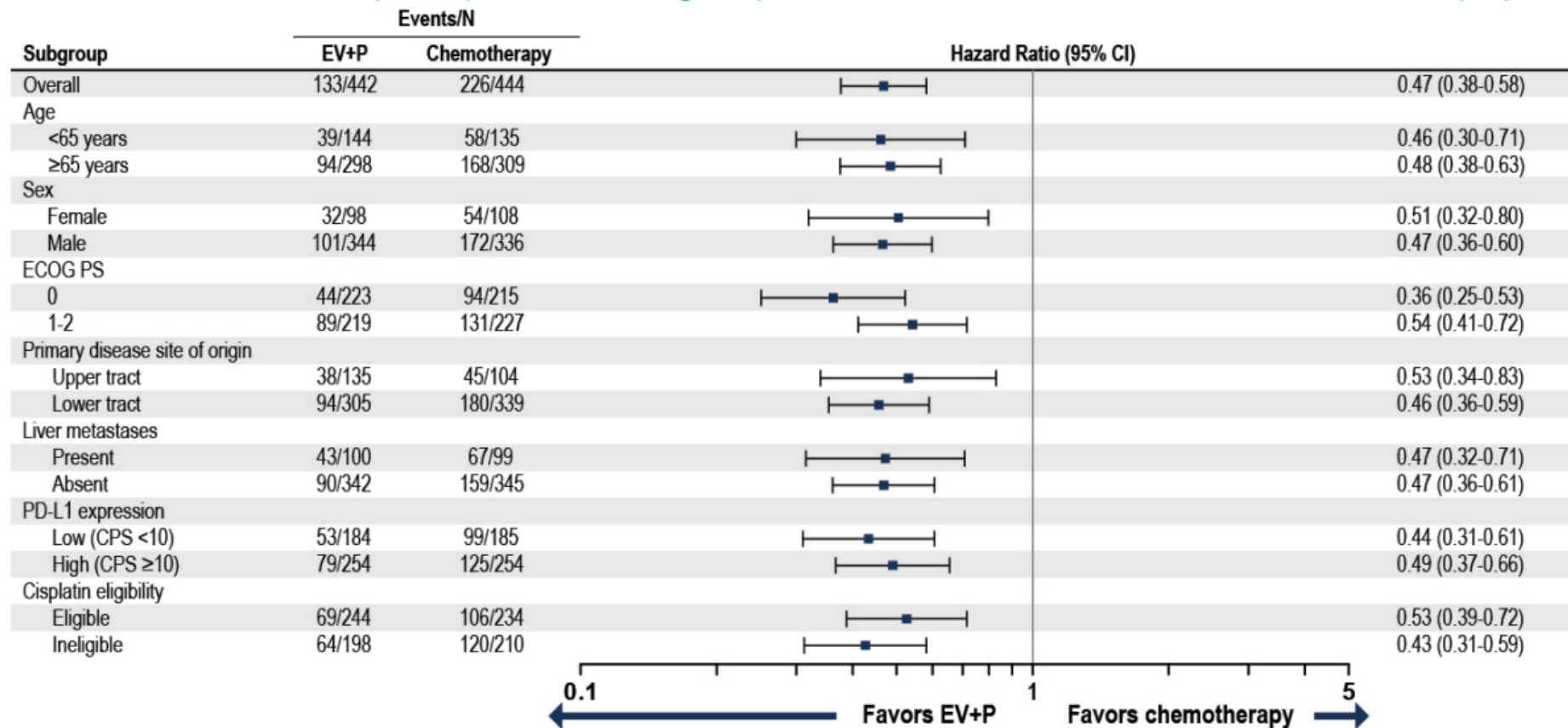
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	53	0.44	NR (22.3-NR)
Chemotherapy	99	(0.31-0.61)	15.5 (12.9-17.7)

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

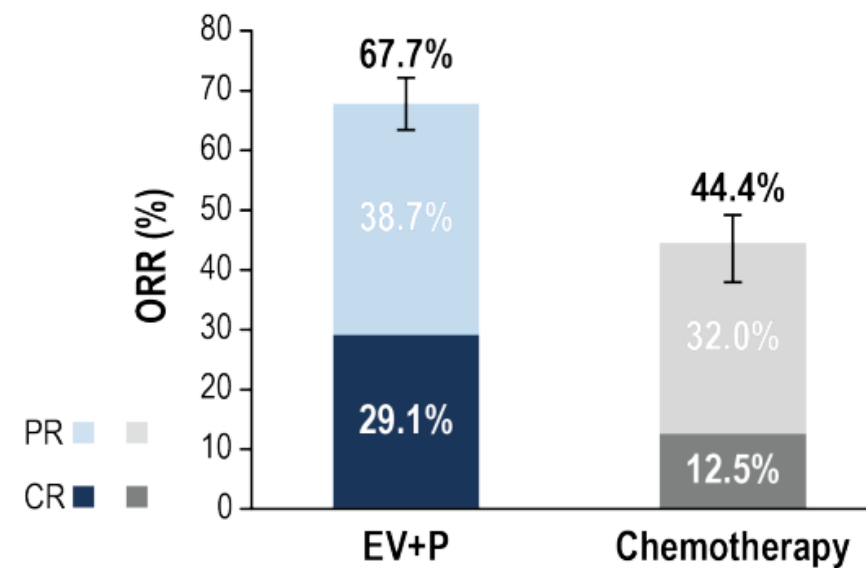


Metastatik Mesane Kanseri Birinci Basamak Tedavi

EV-302 -EV/pemrolizumab

Confirmed Overall Response per BICR

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



Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)
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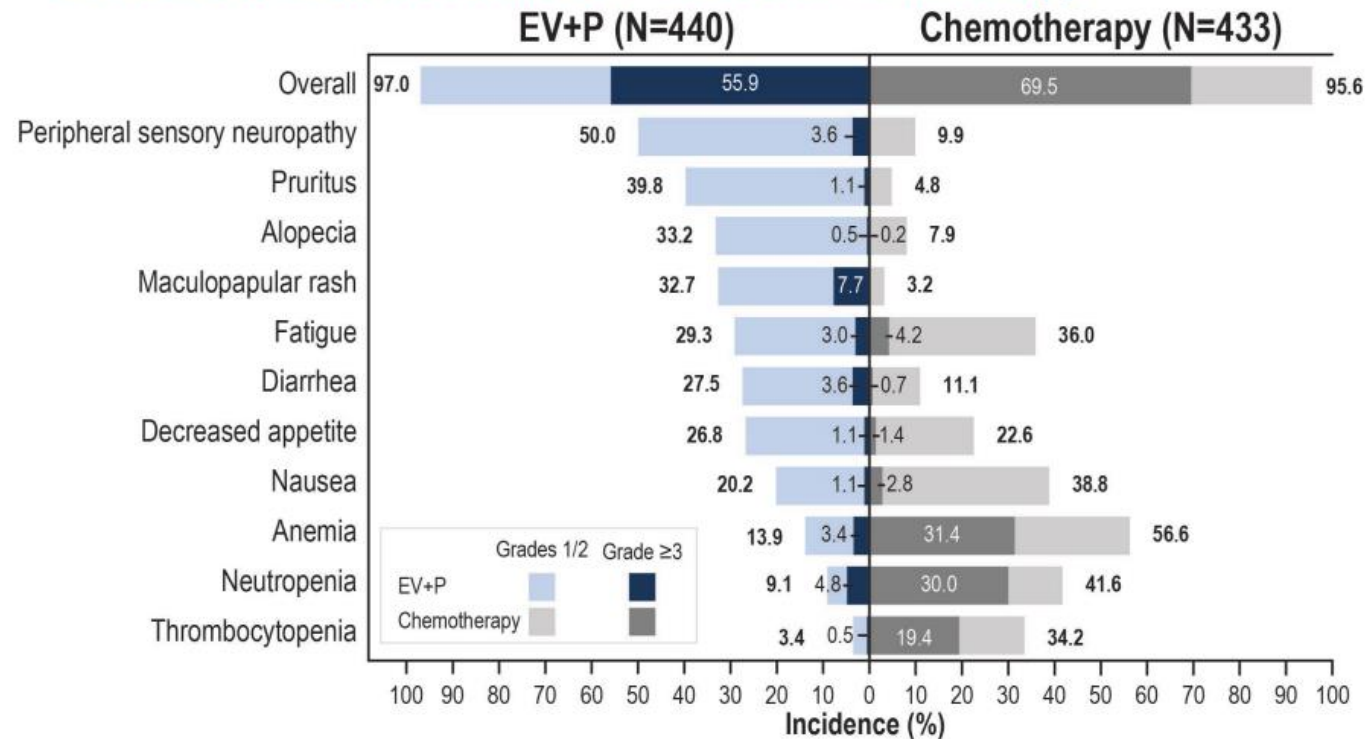
	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	296 (67.7) (63.1-72.1)	196 (44.4) (39.7-49.2)
2-sided P value	<0.00001	
Best overall response ^a , n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment ^b	21 (4.8)	36 (8.2)

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

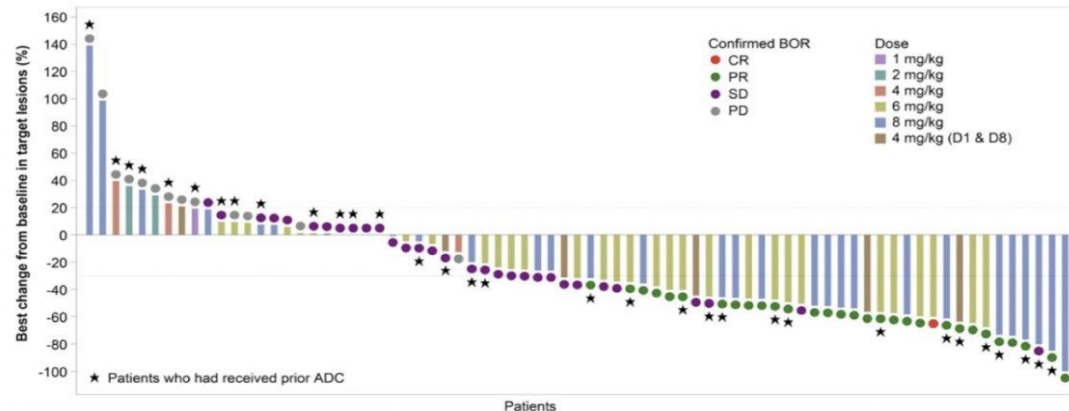
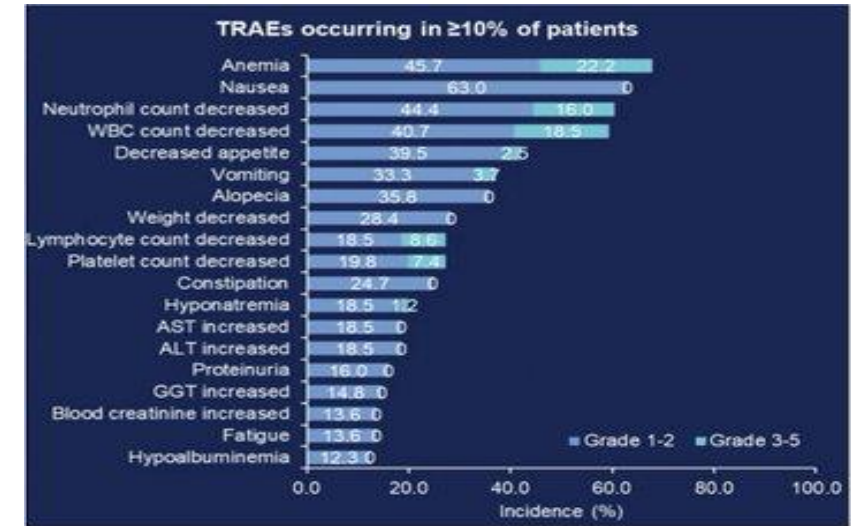
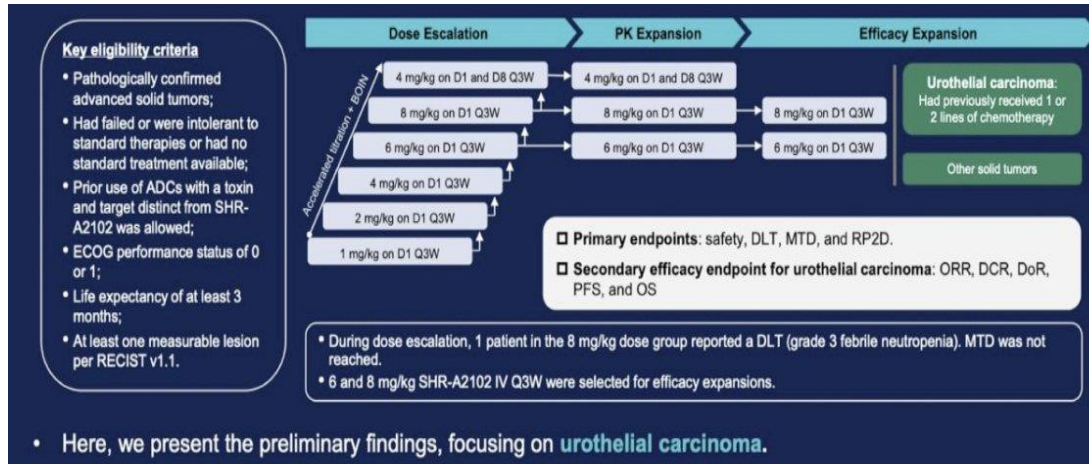
Metastatik Mesane Kanseri Birinci Basamak Tedavi EV-302 -EV/pemrolizumab

EV Treatment-Related Adverse Events of Special Interest*

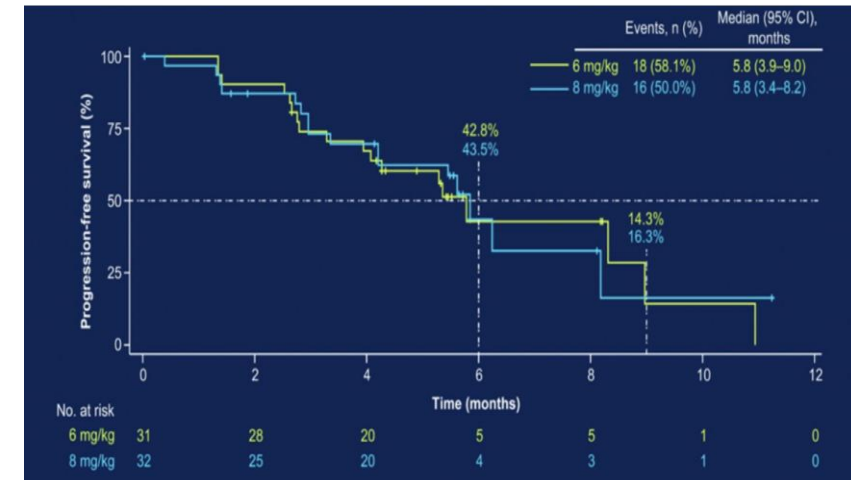
Majority of treatment-related AEs were low grade

	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)

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)



Metastatik Ürotelyal Kanseri İkinci Basamak Sonrası Tedavi Seçimi



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NCCN Guidelines Version 4.2024 Bladder Cancer

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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 • Paclitaxel³⁰ or docetaxel³¹ • Gemcitabine¹⁸ • Pembrolizumab and enfortumab vedotin-ejfv (category 2B)¹⁷
Alternative preferred regimens • Immune checkpoint inhibitor ▶ Nivolumab²⁵ ▶ Avelumab^{26,27} • Erdafitinib^{d,28} • Enfortumab vedotin-ejfv^{e,29}	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine²² • Gemcitabine and paclitaxel¹⁹ • Gemcitabine and cisplatin⁴ • DDMVAC with growth factor support²

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-ejfv²⁹ • Gemcitabine and carboplatin • Erdafitinib^{d,28}	Other recommended regimens • Paclitaxel or docetaxel³¹ • Gemcitabine¹⁸
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin⁴ • DDMVAC with growth factor support² • Erdafitinib^{d,28}	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine²² • Gemcitabine and paclitaxel¹⁹

Metastatik Ürotelyal Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi



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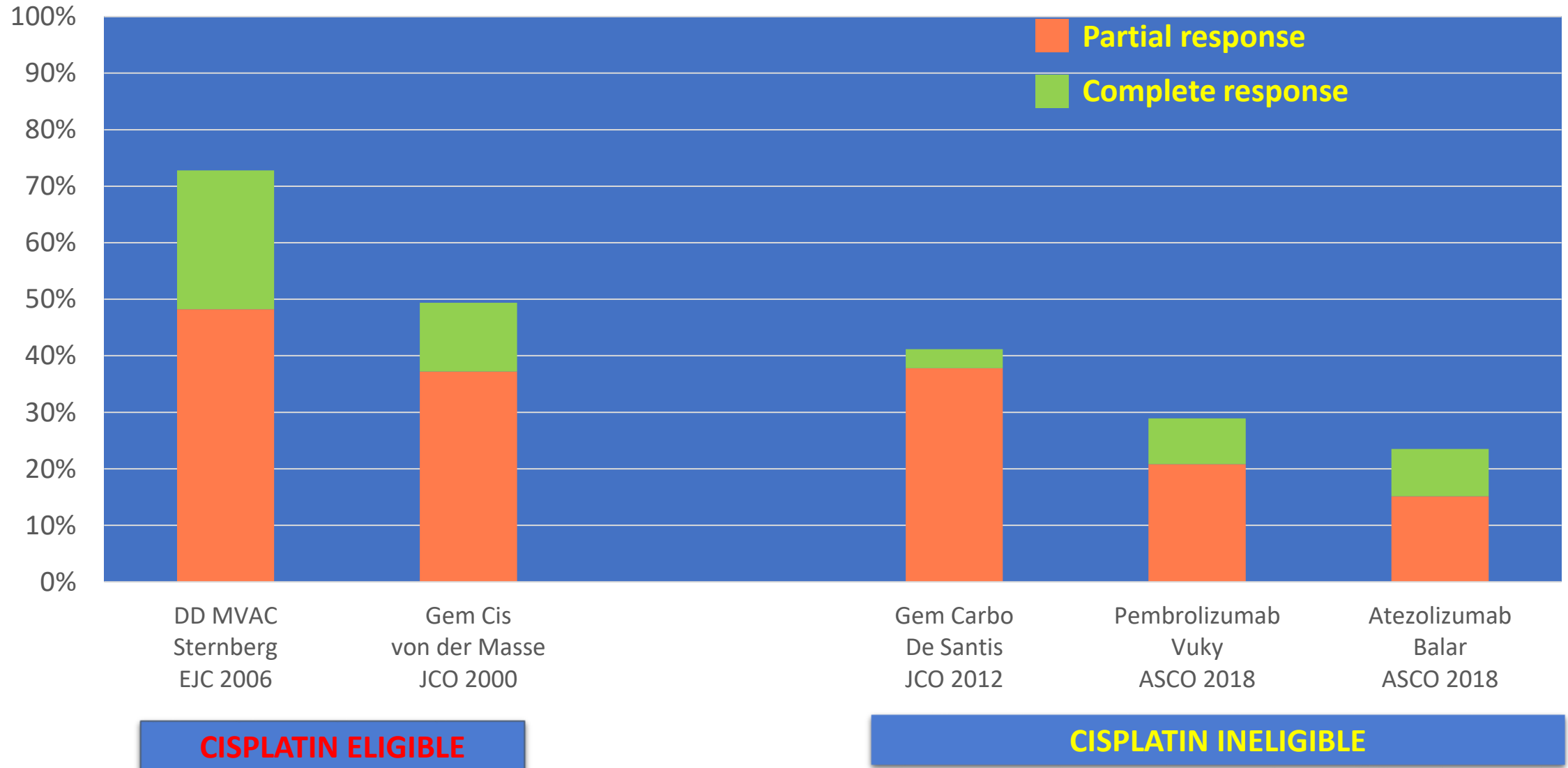
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PRINCIPLES OF SYSTEMIC THERAPY

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 support² • Gemcitabine and cisplatin⁴ • Gemcitabine and carboplatin (category 2B) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7)	Other recommended regimens • Paclitaxel²² or docetaxel²³ • Gemcitabine²⁴	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 pembrolizumab¹⁶ • Enfortumab vedotin-ejfv²⁶ • Nivolumab²⁷ (category 2B) • Avelumab^{28,29} (category 2B) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7)	Other recommended regimens • Paclitaxel²² or docetaxel²³ • Gemcitabine²⁴	Useful in certain circumstances • DDMVAC with growth factor support² (category 2B) • Ifosfamide, doxorubicin, and gemcitabine³⁰ (category 2B) • Gemcitabine and paclitaxel³¹ (category 2B) • Gemcitabine and cisplatin⁴ (category 2B)
Previous immunotherapy (no previous chemotherapy or enfortumab vedotin-ejfv)		
Preferred regimens • Enfortumab vedotin-ejfv²⁶ • Enfortumab vedotin-ejfv and pembrolizumab • Gemcitabine and carboplatin • Gemcitabine and cisplatin⁴ • DDMVAC with growth factor support² • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7)	Other recommended regimens • Paclitaxel²² or docetaxel²³ • Gemcitabine²⁴	Useful in certain circumstances • Gemcitabine, cisplatin, and nivolumab (category 2B) • Ifosfamide, doxorubicin, and gemcitabine³⁰ (category 2B) • Gemcitabine and paclitaxel³¹ (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 • Paclitaxel²² or docetaxel²³ • Gemcitabine²⁴ • Gemcitabine and cisplatin⁴ • DDMVAC with growth factor support² • Ifosfamide, doxorubicin, and gemcitabine³⁰ (category 2B) • Gemcitabine and paclitaxel³¹ (category 2B)	Useful in certain circumstances • Sacituzumab govitecan-hziy³⁴

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

Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları

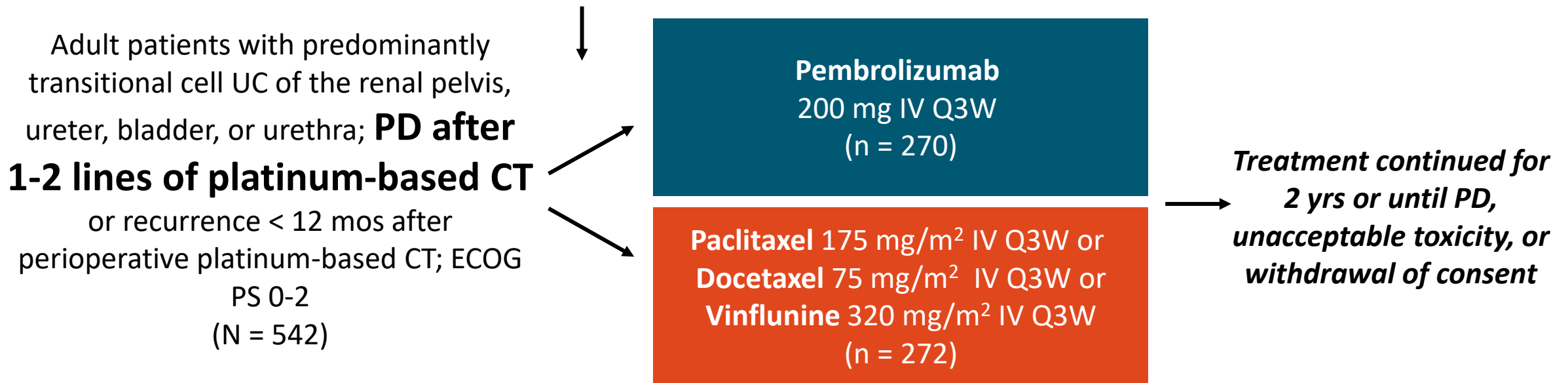


Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

- International, randomized, open-label phase III study

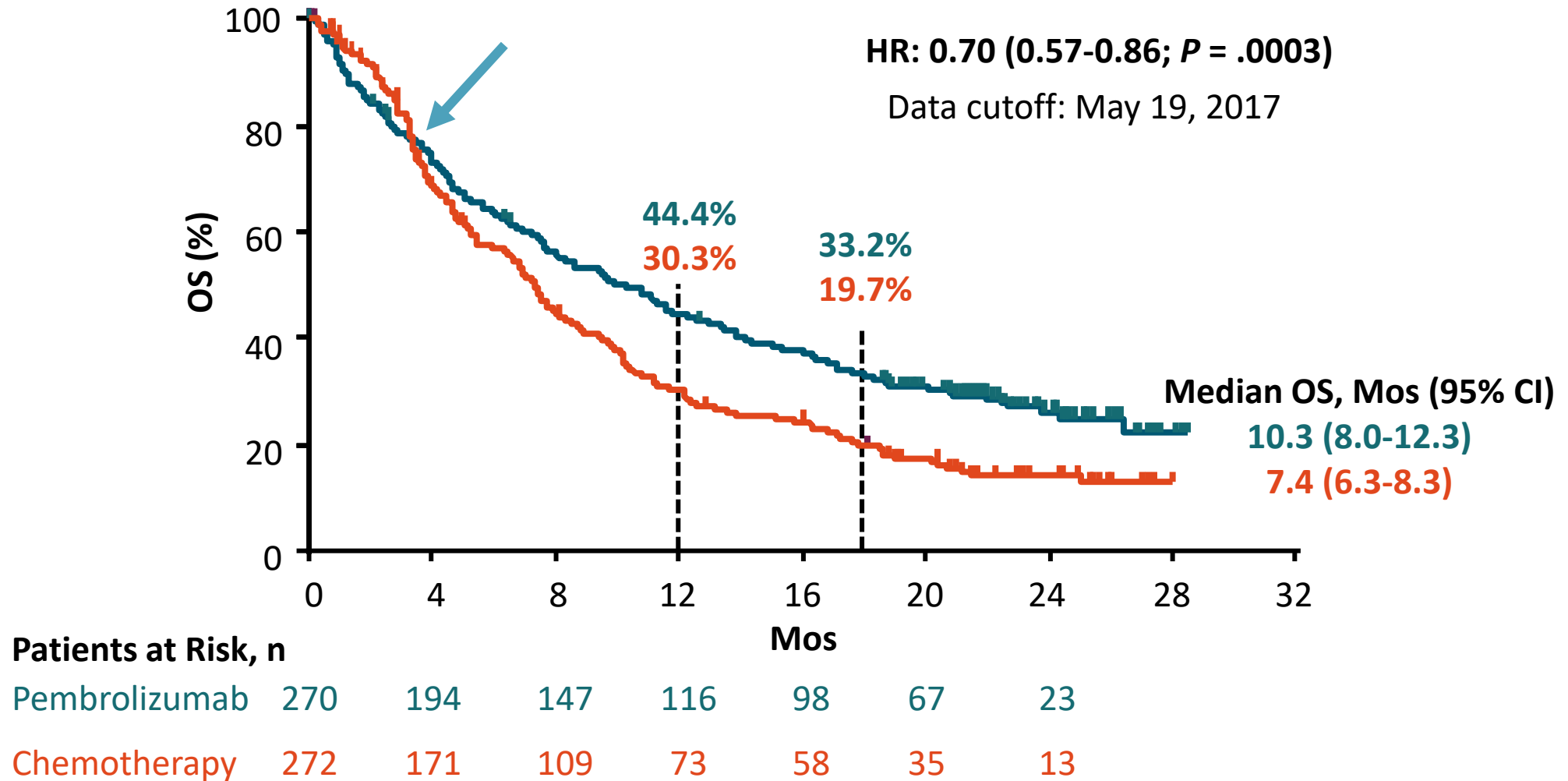
Stratified by ECOG PS (0/1 vs 2), Hg (< 10 vs ≥ 10 g/dL), liver mets (yes vs no), and time since last CT (< vs ≥ 3 mos)

KEYNOTE-045



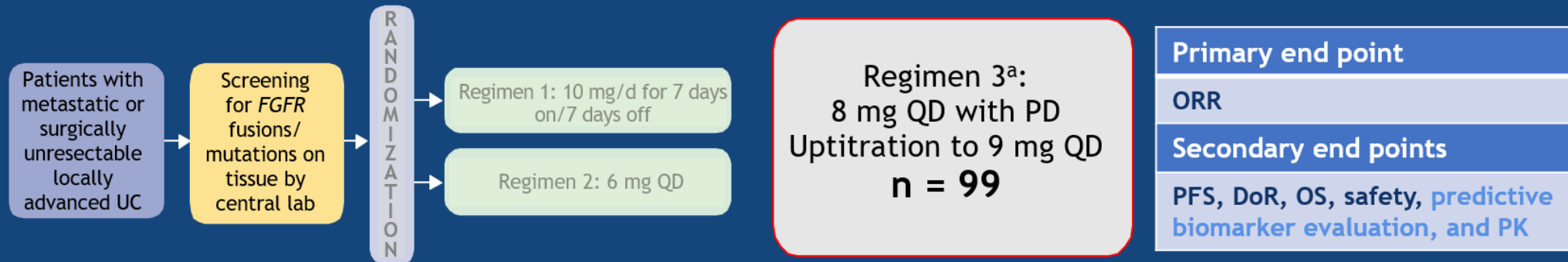
- Primary endpoints: OS, PFS
- Secondary endpoints: ORR, DoR, safety

KEYNOTE-045: OS



Metastatik Ürotelyal Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

Phase 2 BLC2001 Study Design



Patients

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

Primary hypothesis:

- ORR in Regimen 3 is $> 25\%$
- One-sided $\alpha = 0.025$
- 85% power

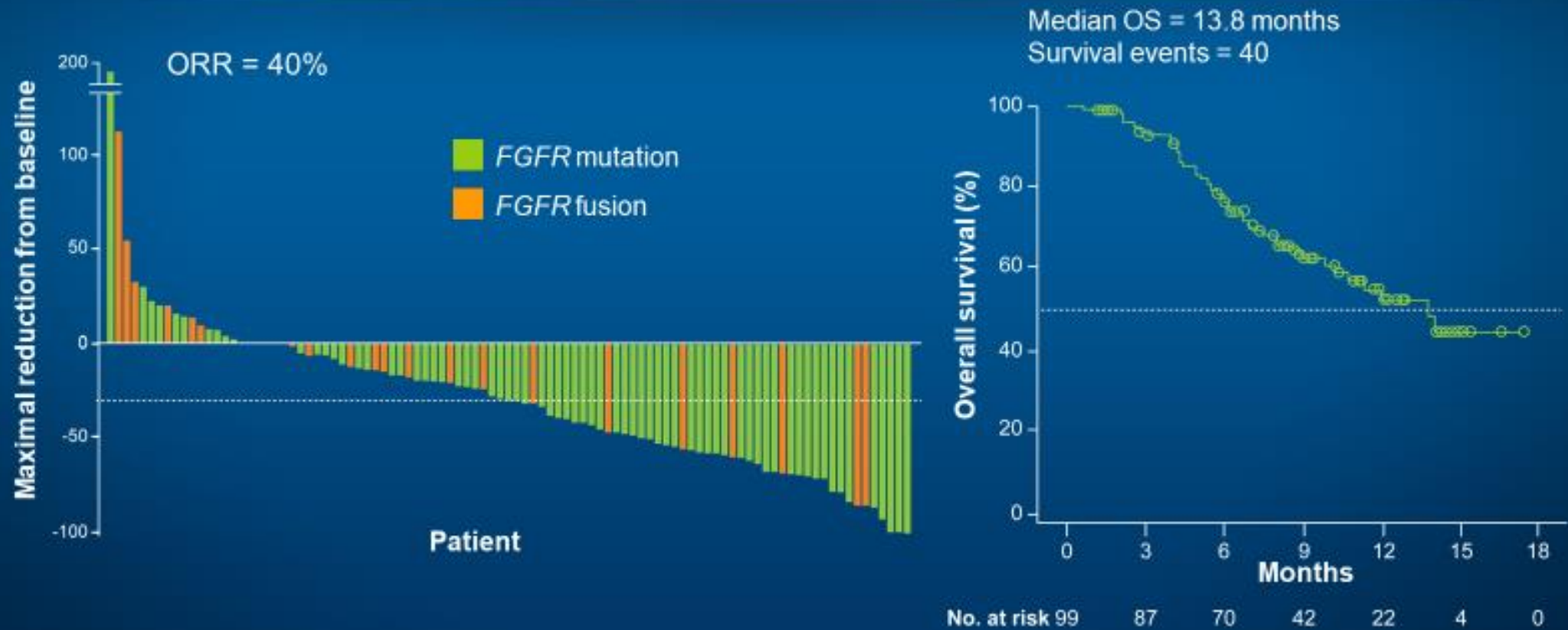
^aDose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.

^bIneligibility for cisplatin: impaired renal function or peripheral neuropathy.

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

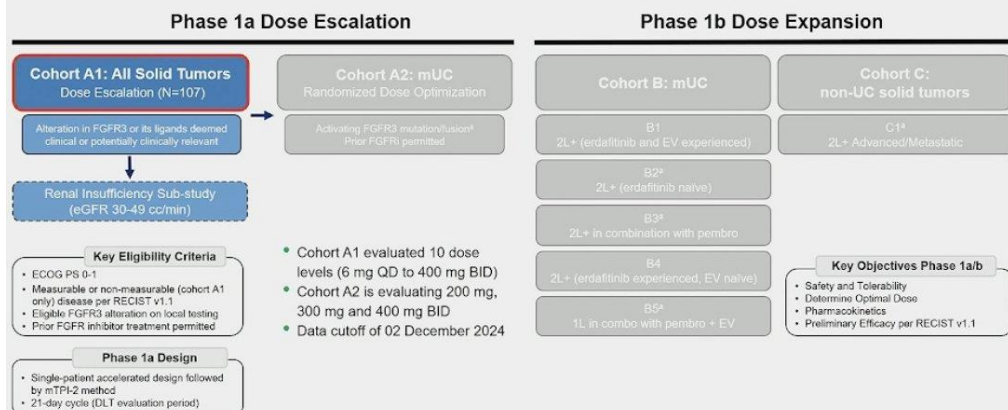
Metastatik Ürotelyal Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

BLC2001: Response and Survival



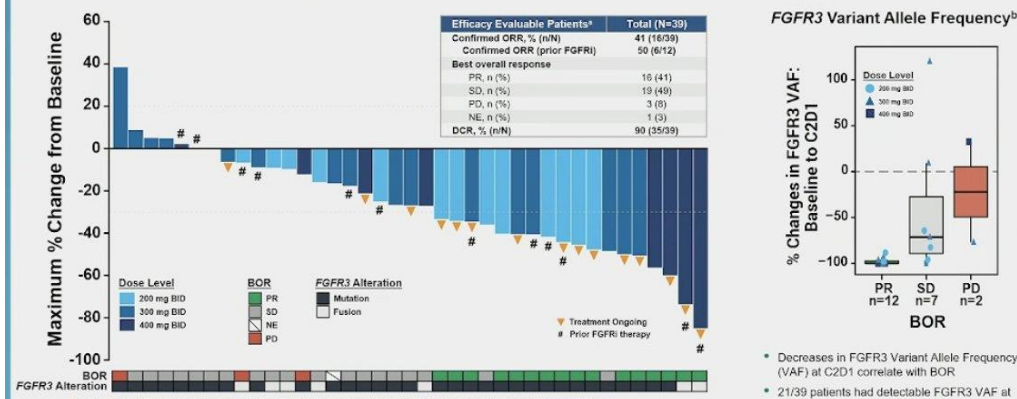
Yeni Potent FGFR3 İnhibitörleri

FORAGER-1 Study Design, Eligibility, Objectives



*Oncogenically reconstituted (over expression of activating alterations in non-canonical alternative isoforms of EGFR) are omitted in consultation with factor IV, indicating within mTP-2, modified to inhibit internal system, peribulbular, NCT05614739

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



Data cutoff date of 02 Dec 2024. *Efficacy-evaluable patients are those with measurable disease who had at least 1 post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment.

Safety

Treatment-Emergent AEs ≥20%				
	All Patients (N=107)		200 mg, 300 mg, 400 mg B (n=70)	
All TEAEs, %	Any Grade	Grade ≥3	Any Grade	Grade ≥3
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	

Data cutoff date of 22 Dec 2004. Safety was evaluated across all patients tested, regardless of dose or tumor type. Includes rash, dry skin, PPE, rash maculopapular, stomatitis, pruritus, dermatitis allergic, night sweats, skin fissures, blister, dermatitis acneiform/skin, hyperhidrosis, hyperkeratosis, neurodermatitis, subacute dermatitis, and skin ulcer. 113 patients received pharmacologic intervention (1 at 200 mg, 6 at 300 mg, 4 at 400 mg). Includes vision blurred, dry eye, blepharitis, eye pruritus, lacrimation increased, ocular hyperemia, eyelid hemorrhage, subconjunctival fluid, swelling of eyelid, vision moderately reduced, and vision blurred. Includes nail ridges, discoloration, onycholysis, onychia, and psoriasis. 14 patients had grade 4 events. ALT/AST increased, hypoproteinemia, hypocalcemia, and neutrophil count decreased. 2 events occurred – acute cholecystitis and cholecystitis. Includes vitreous body opacities, and PPE. ALT/AST increased in 2, diarrhea in 2, and stomatitis in 2. Some root causes were for dose reduction, ALT, albumin, aspartate aminotransferase, AST, aspartate aminotransferase, PPE, plasma protein, erythrocytes.

- 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 erdafitinib¹ were very rare
 - Dose reductions/discontinuations were uncommon²

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

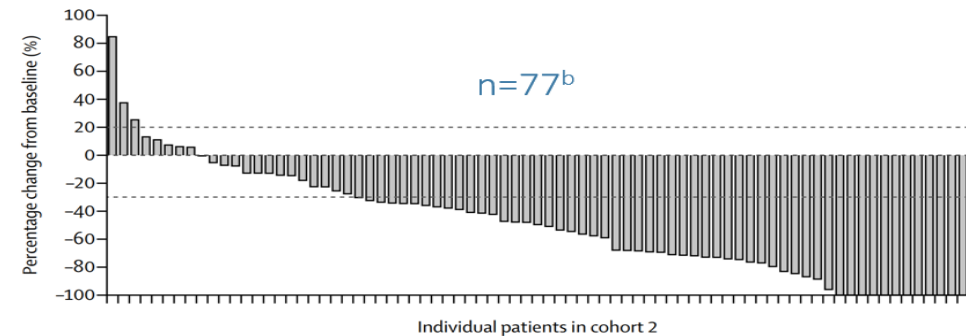
	Cohort 2 (n=89)
Objective response rate	46 (52%)
95% CI	41-62
Best overall response	
Complete response	18 (20%)
Partial response	28 (31%)
Stable disease	27 (30%)
Progressive disease	8 (9%)
Not evaluable ^a	8 (9%)

^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.

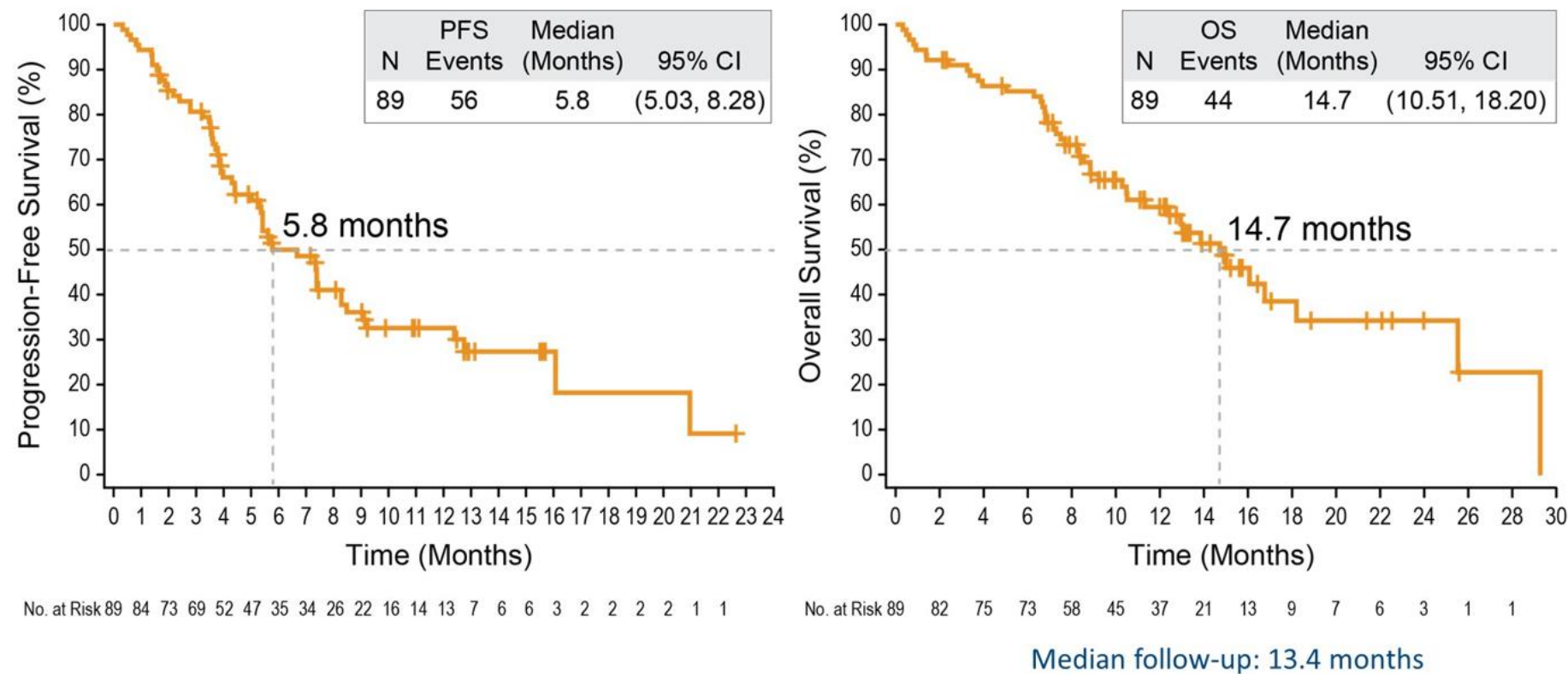
Change in Target Lesions From Baseline



Median duration of treatment: 6 months

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

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



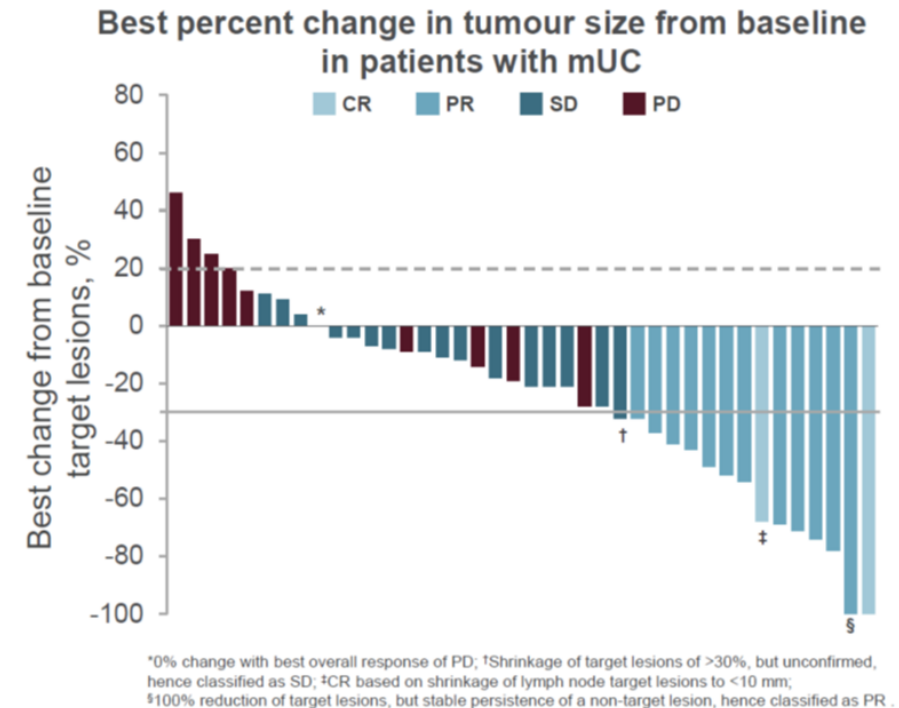
Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

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

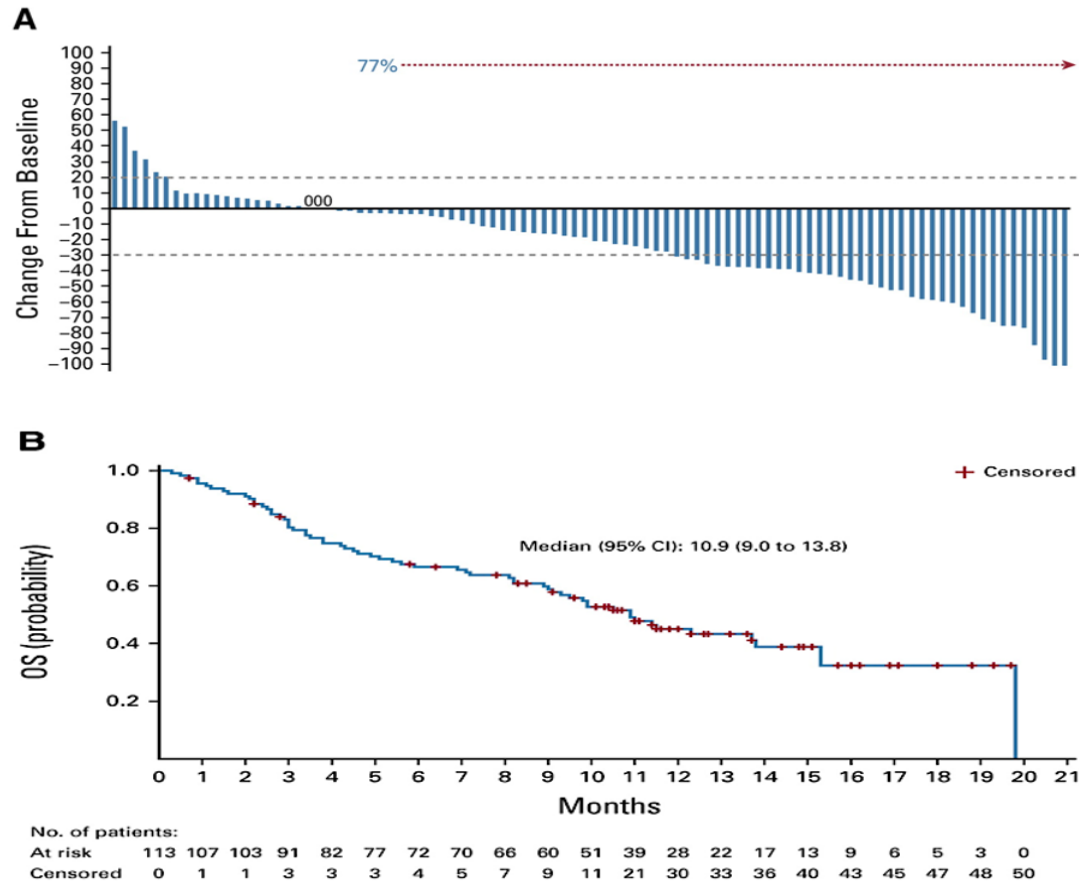
NCT01631552: Phase I/II study of SG in patients with epithelial cancers (PS 0–1)

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	39 (11/28)	22–59
≥3 prior lines	18 (3/17)	4–43
Prior checkpoint inhibitors	24 (4/17)	7–50
Prior platinum and checkpoint inhibitors	27 (4/15)	8–55



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 $\geq$ G3: 34%
 - Diarrhea $\geq$ G3: 10%
- UGT1A homozygous/heterozygous
 - Potential increased risk neutropenia, pre-screening not required

Datopotamab-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

Funda Meric-Bernstam,¹ Omar Alhalabi,² Aaron Lisberg,³ Alexandra Drakaki,³ Benjamin Garnezy,⁴ Takahiro Kogawa,⁵ Alexander Spira,⁶ Mohamad Salkeni,⁶ Xin Gao,⁷ Anthony Tolcher,⁸ Manali Bhawe,⁹ Deborah Doroshow,¹⁰ Jeannie Hoffman-Censits,¹¹ Gunnar Klauß,¹² Yoshiaki Kaga,¹³ Yasuyuki Kakurai,¹⁴ Takahiro Kojima¹⁵

¹Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, University of Texas, Houston, TX, USA; ²Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ³Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine, University of California Los Angeles (UCLA), Los Angeles, CA, USA; ⁴Sarah Cannon Research Institute, Nashville, TN, USA; ⁵Department of Advanced Medical Development, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; ⁶Virginia Cancer Specialists (VCS) Research Institute, Fairfax, VA, USA; ⁷Department of Medicine, Division of Hematology and Oncology, Massachusetts General Hospital, Harvard Medical School, Harvard University, Boston, MA, USA; ⁸NEXT Oncology, San Antonio, TX, USA; ⁹Department of Hematology/Oncology, Emory University, Atlanta, GA, USA; ¹⁰Division of Hematology & Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, NY, USA; ¹¹Departments of Medical Oncology & Urology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins Medical Institutions, Baltimore, MD, USA; ¹²Global Oncology, RAD, Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; ¹³Clinical Science, Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; ¹⁴Data Intelligence, Daiichi Sankyo, Co., Ltd., Tokyo, Japan; ¹⁵Department of Urology, Aichi Cancer Center, Nagoya, Japan

ASCO Genitourinary
Cancers Symposium

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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 linker¹
- 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*)

- 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, 0.0-29.2). *Evaluated per RECIST v1.1.1. Ochiai D, et al. Mol Cancer Ther. 2021;20:2329-40.

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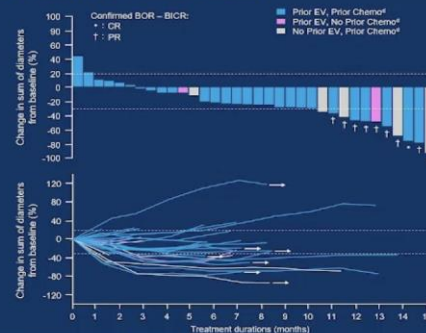
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Response and Change in Tumor Burden

Response by BICR*	Dato-DXd (N=40)
ORR ^a , n (%) [95% CI]	10 (25.0) [12.7-41.2]
DCR ^a , 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

BICR, best overall response; CI, confidence interval; CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease. *Evaluated by BICR per RECIST v1.1.1. ^aResponses with confirmation of CR/PR. ^bCR + PR + SD + non-CR/non-PD. ^cAll patients received prior immunotherapy.



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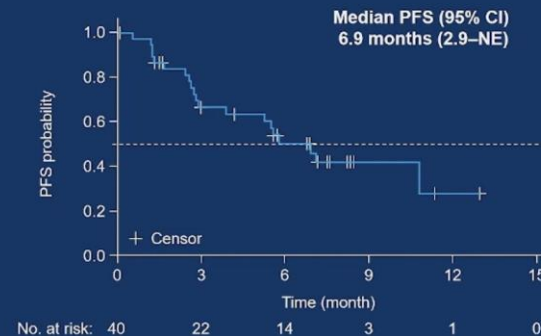
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Progression-Free Survival



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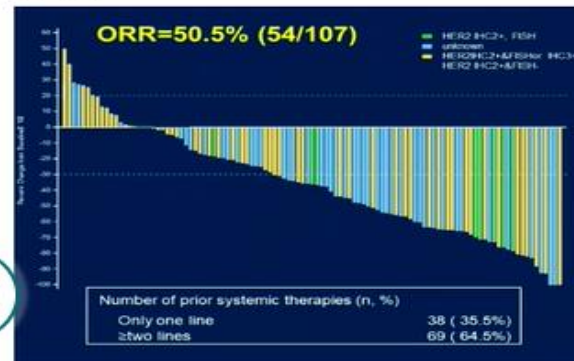
Gelecek Perspektif

Does CPI combine best with ADCs with MMAE payloads?

Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

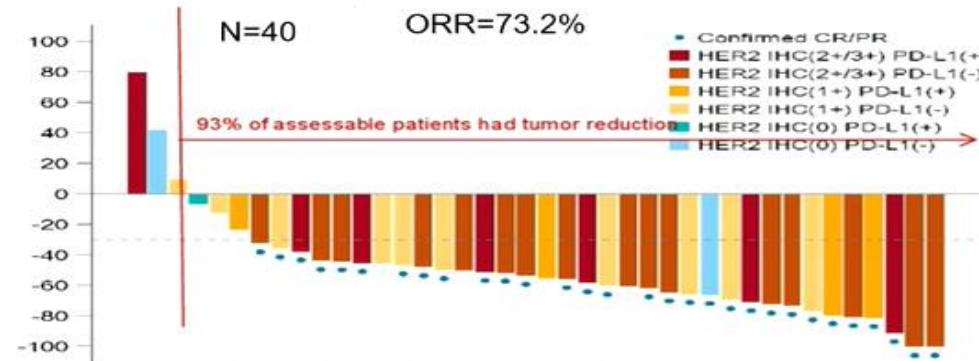
Disitamab vedotin

N=107 In the Second or Third-line setting



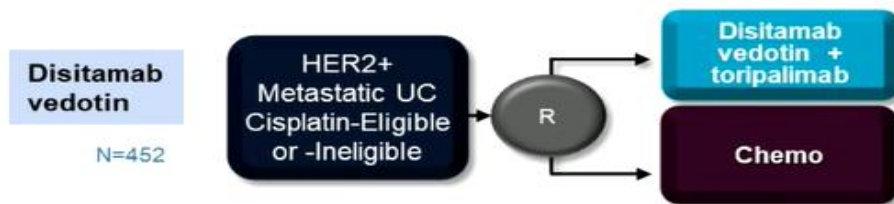
Sheng, et al. ASCO 2022 abstract 4518

Disitamab vedotin + toripalimab

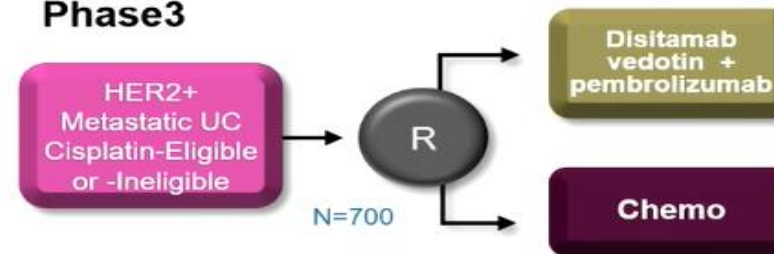


Sheng, X., et al. ASCO 2023

Phase 3



Phase3



Presented by Andrea B. Apolo, MD

✉ @apolo_andrea

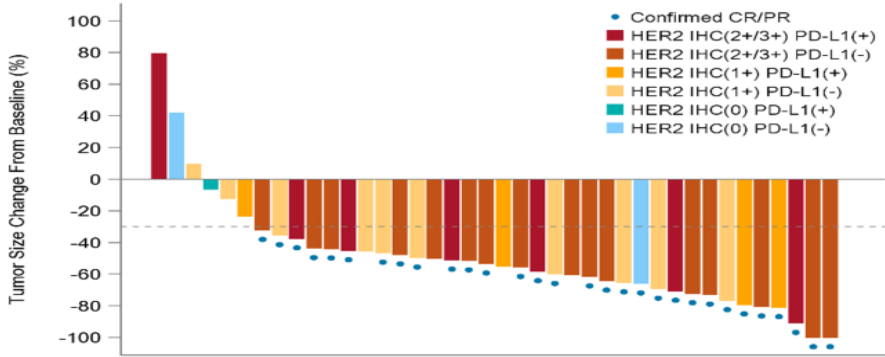
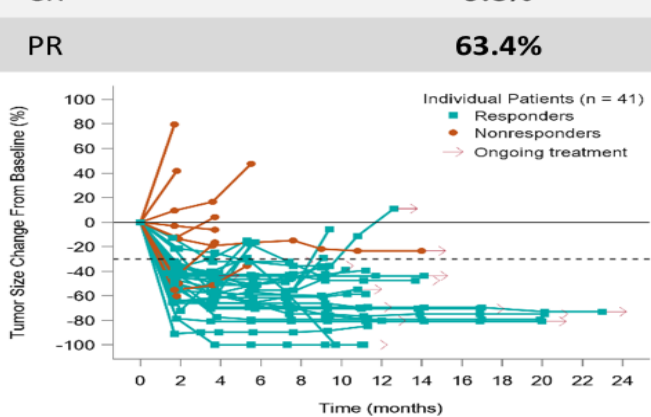
Gelecek Perspektif

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%)

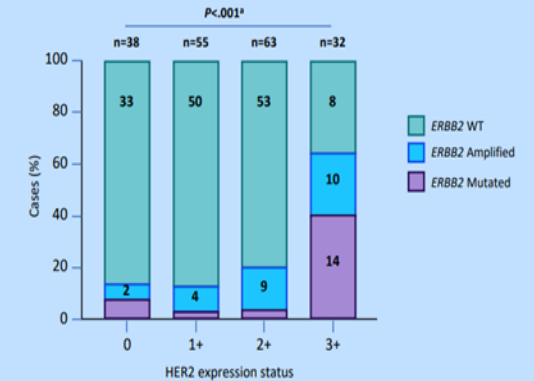
*Dako HercepTest system

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

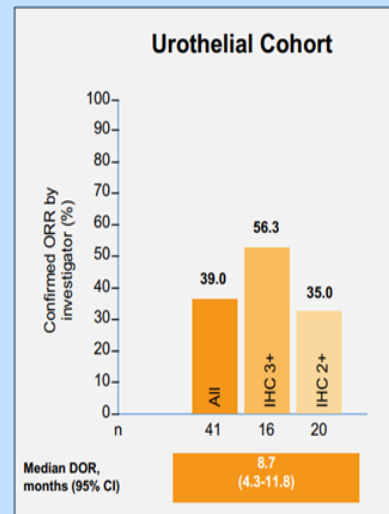
Aggen et al, ASCO GU 2023

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



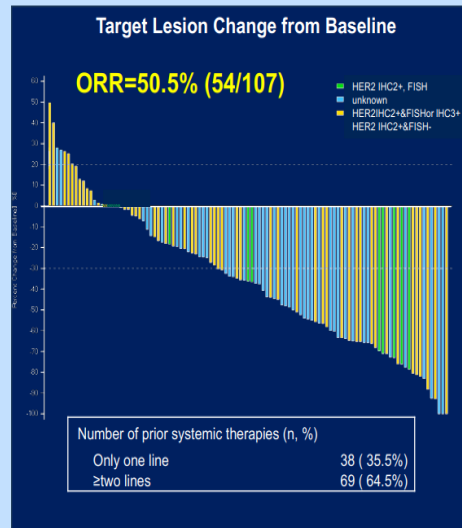
All Patients

	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

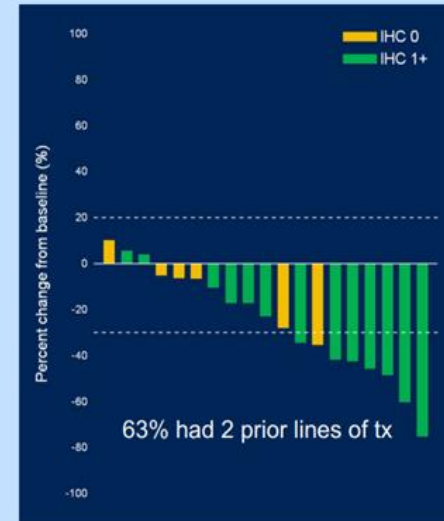
RC48 (Disitamab Vedotin) in HER2 2-3+ mUC



Subgroups	cORR (% , 95% CI)
<i>HER2 status</i>	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
<i>Metastasis site</i>	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
<i>Prior therapies</i>	
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

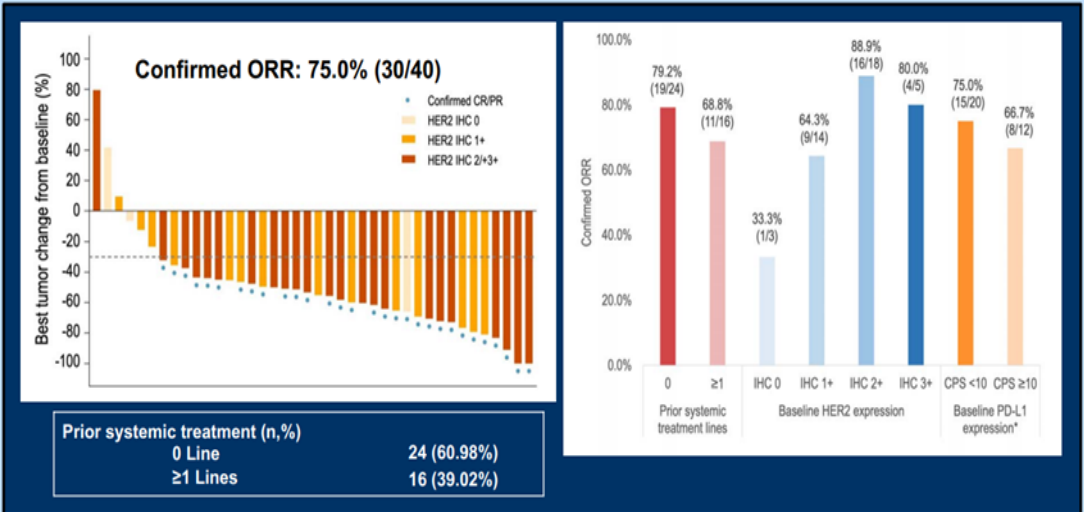
Trastuzumab Deruxtecan + Nivolumab

	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	3.9 (1-21)	–
T-DXd	4.1 (1-20)	–
Nivolumab		

- **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



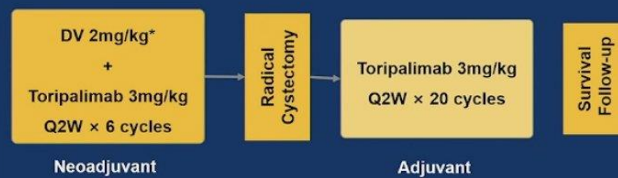
Zhou et al, ESMO, 2024

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 $\geq$ 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).

Pathological tumor response was assessed by the local pathologists and investigators based on the postoperative pathology. Radiological assessment was performed by the investigators per RECIST v1.1. [#]Operative status of T3/T4a using the local urologist's assessment. [^]OS data was not mature and not reported here. 1. Sheng, et al. J Clin Oncol. 2024; 42(11):sup4588.

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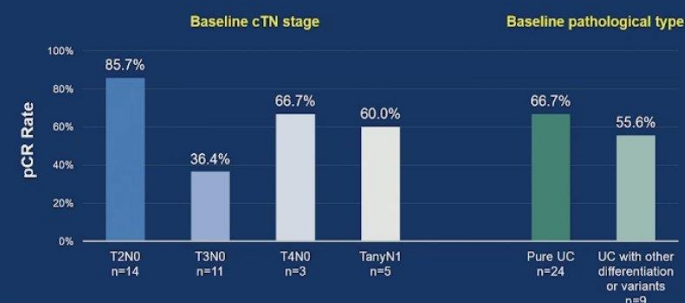
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Subgroup analysis

- 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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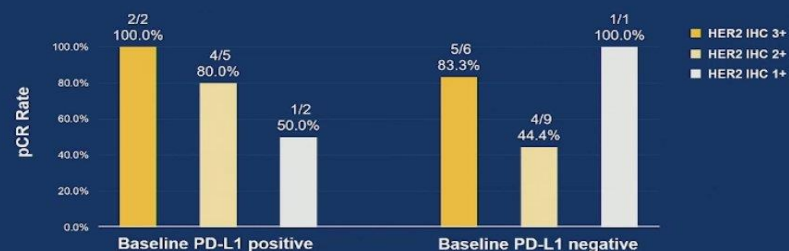
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Subgroup analysis

- 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	1 st line HER2+	PFS, OS	NCT05911295
Disitamab Vedotin + Toripalimab		III	1 st line HER2+	PFS, OS	NCT05302284
Zelenectide Pevedotin + Pembro	DURAVELO-2	III	1 st line	PFS	NCT06225596
EV + SG + Pembrolizumab	DAD-IO	II	1 st line	ORR	NCT04724018
Datopotamab-DXd + Volrustomig or Rilvegostomig	TROPION-Pan Tumor 03	II	1 st or 2 nd line	ORR, AEs	NCT05489211
SG + Avelumab	JAVELIN Bl. Medley	II	1 st line	PFS, AEs	NCT05327530
EV + Pembro + Sacituzumab TMT or investigational agents	KEYMAKER-U04	I/II	1 st 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	1 st 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 $\geq$ 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