

Metastatik Mesane ve Üst Üriner Sistem Kanserlerinde Klinik Pratiğimizi Değiştiren Çalışmalar

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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

❑ Neoadjuvan/Adjuvan çalışmalar

❑ 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

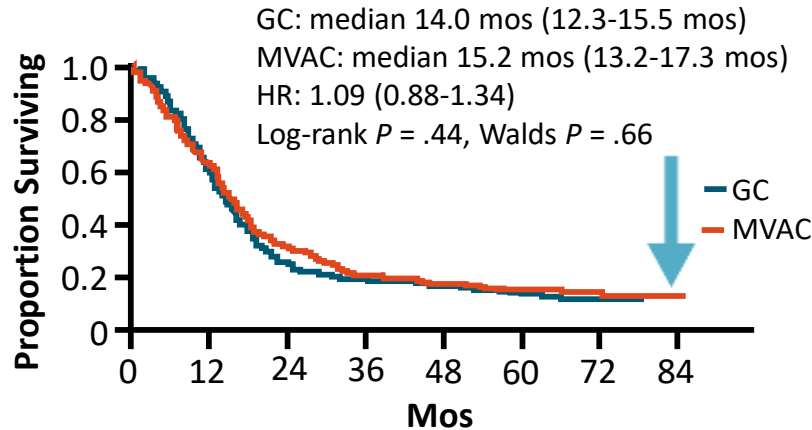
Sisplatin Uygun

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

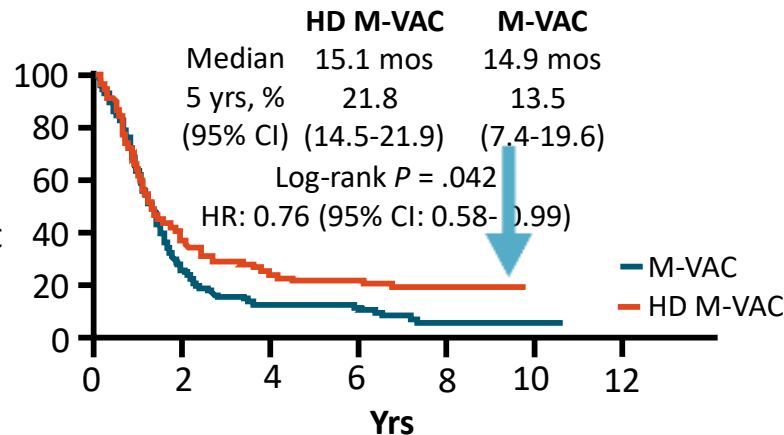
MVAC 202 125 62 40 34 29 9 1

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

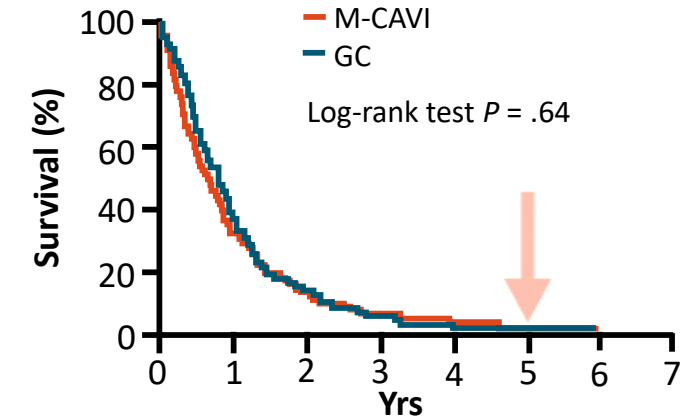
Sisplatin uygun değil

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.

Hangi Kemoterapi Rejimi ? dd-MVAC/GC

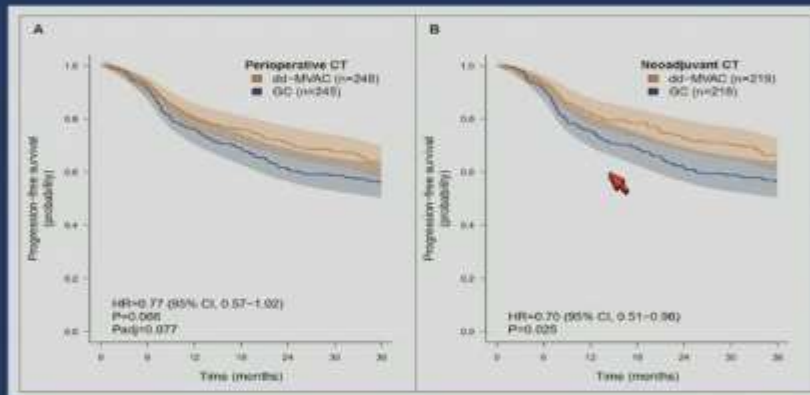
Trial design (3)

- 500 patients included in 28 centers from 2013 to 2018
(493 patients available for intent-to-treat analysis)
- Adjuvant (n=56) and Neoadjuvant (n=437) (88%)
- Primary end-point : Progression Free Survival at 3 years
- Final analysis : Overall and Specific Survival at 5 years



Hangi Kemoterapi Rejimi ? dd-MVAC/GC

PFS at 3 years



Perioperative dd-MVAC improved 3-y PFS over GC

In the **neoadjuvant** group, better bladder tumor local control with a **significant improvement** on 3-y PFS in the dd-MVAC arm

Pfister et al. J Clin Oncol 2022

2023 ASCO
ANNUAL MEETING

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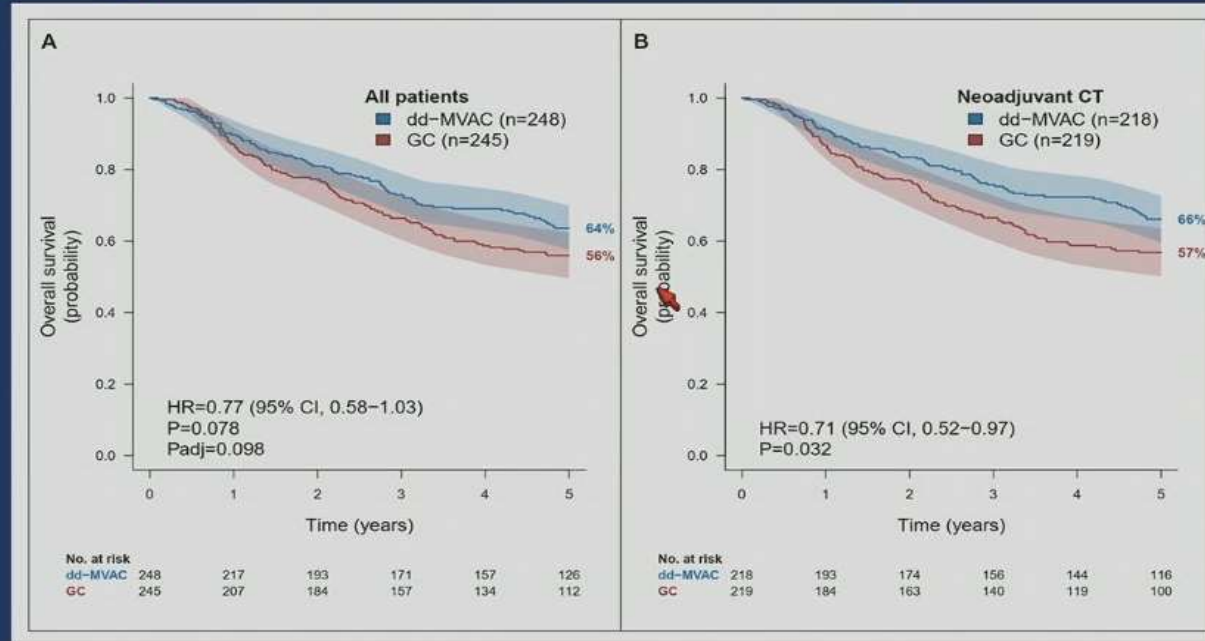


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Hangi Kemoterapi Rejimi ? dd-MVAC/GC

Results (1)

Overall Survival at 5 years



In the neoadjuvant subgroup, overall survival at 5 years was improved in the dd-MVAC group versus the GC group 66% vs 57% .

Sonuç: 4 GC ≠ 6 dd-MVAC , 6 GC = 6 dd-MVAC?

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Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçimi



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 4.2024 Bladder Cancer

[NCCN Guidelines Index](#)
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[Discussion](#)

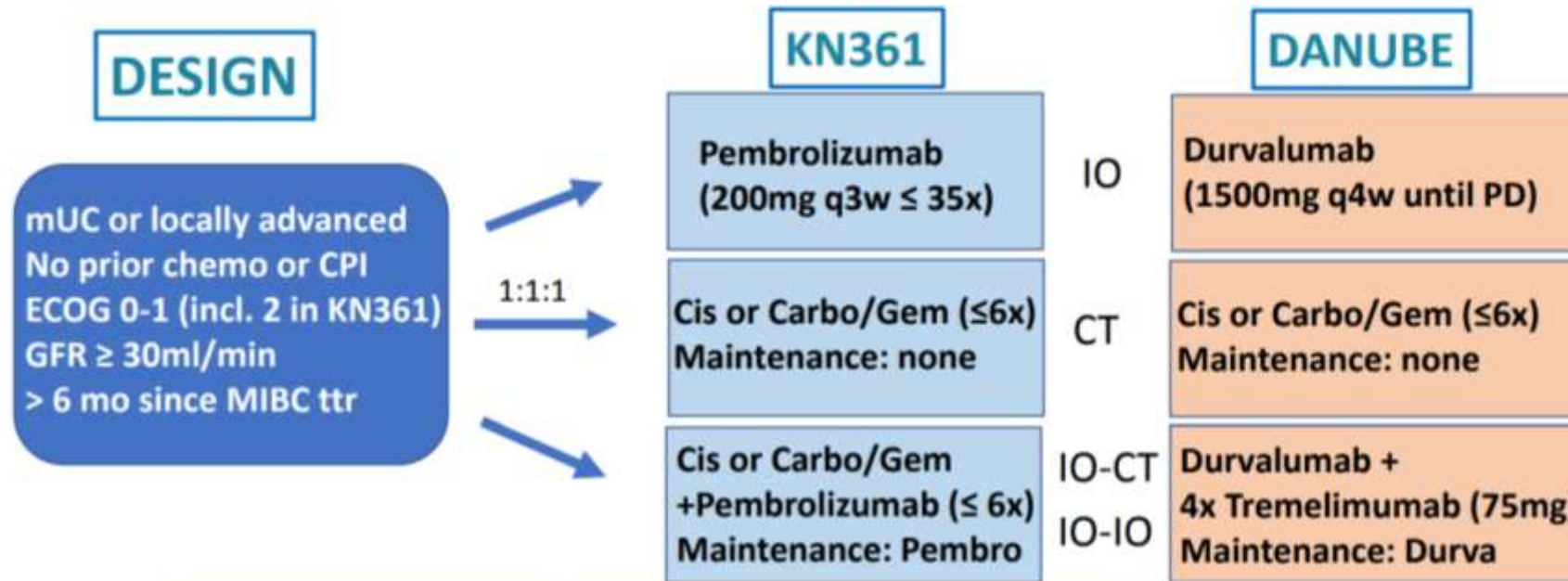
PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	Preferred regimens • Pembrolizumab and enfortumab vedotin-ejfv¹⁵ (category 1) Other recommended regimens • 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) 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 carboplatin¹⁶ followed by avelumab maintenance therapy (category 1)^{a,13} Useful under certain circumstances • 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)

Metastatik Mesane Kanseri 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 Mesane Kanseri Birinci Basamak

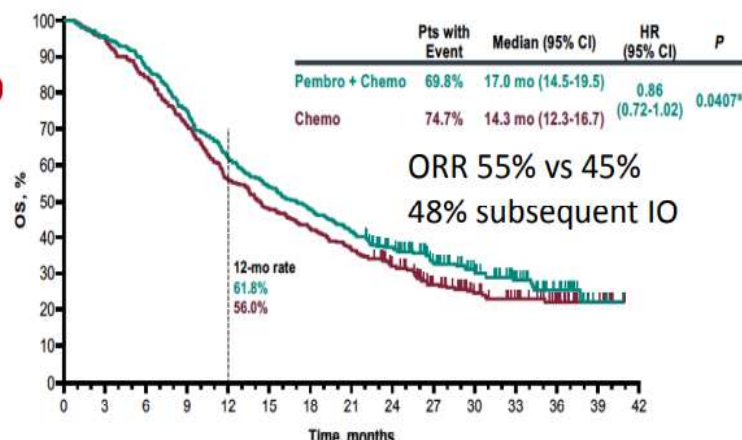
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

Overall survival

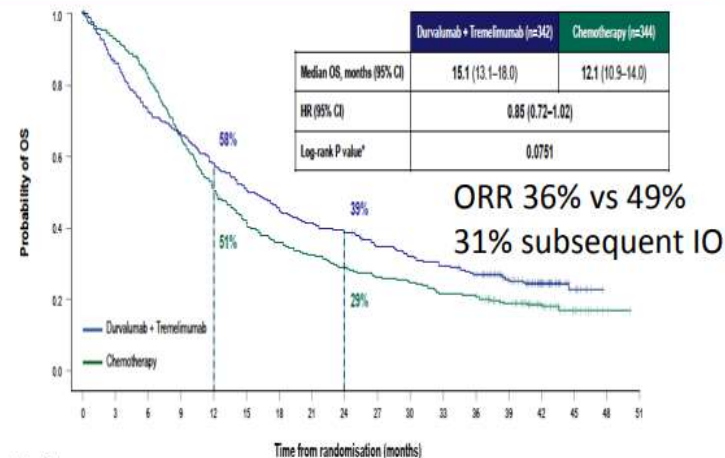
Combination vs Chemo

TOTAL population (ITT)

KEYNOTE 361 –IO-CT vs CT (1°EP)

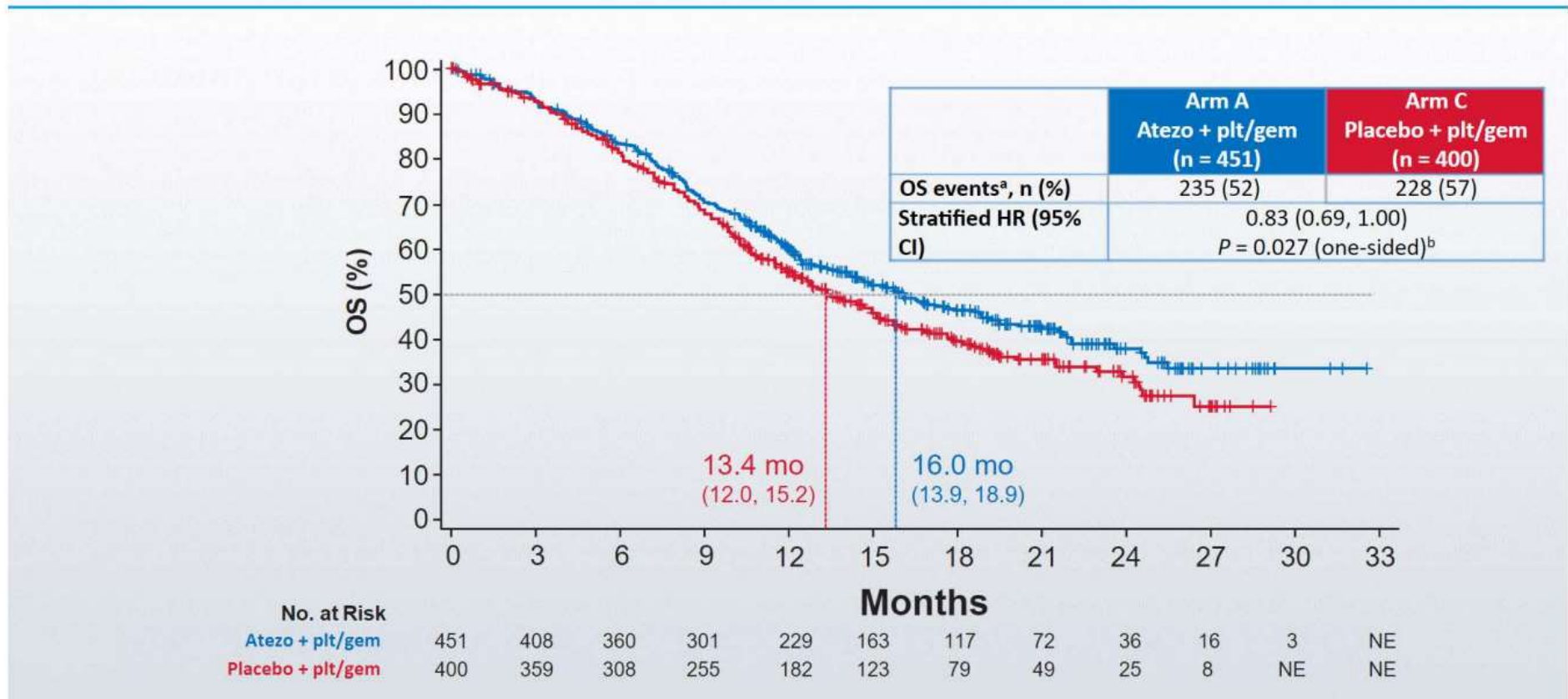


DANUBE – IO-IO vs CT (1°EP)



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

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



Sisplatin Ürotelyal Kanserlerde immünomodülatör

Cell Reports
Medicine

Article

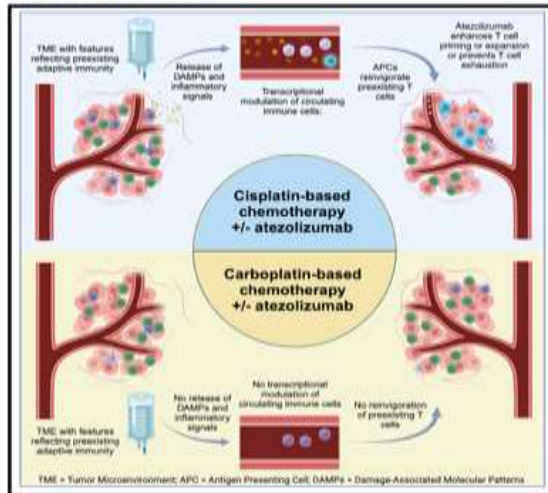


CellPress
OPEN ACCESS

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

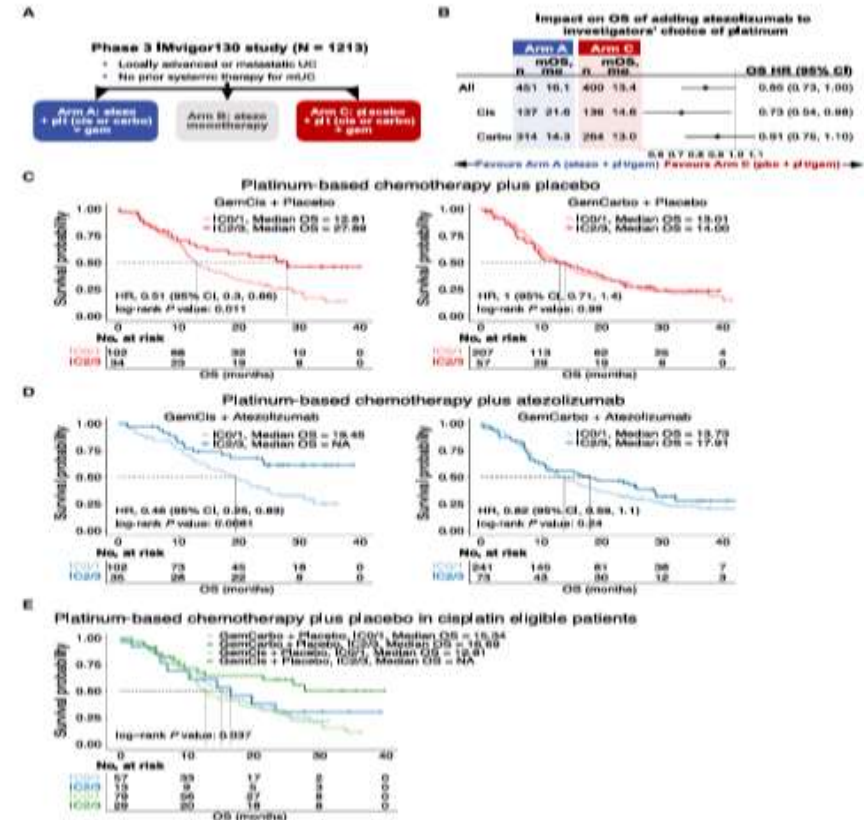
matthew.galsky@mssm.edu (M.D.G.), mariathasan.sanjeev@gene.com (S.M.)

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.

Highlights

- Patients with tumors showing preexisting adaptive immunity benefit more from cisplatin
- Cisplatin versus carboplatin modulates immune-related transcriptional programs
- Tumor cells primed by cisplatin versus carboplatin are sensitive to T cell killing



(legend on next page)

Ürotelyal Kanserlerde Renal Yetmezlik ile İmmünoterapi Etkinliği Azalıyor

ASCO[®] ABSTRACT #434954

AMERICAN SOCIETY OF CLINICAL ONCOLOGY
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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.

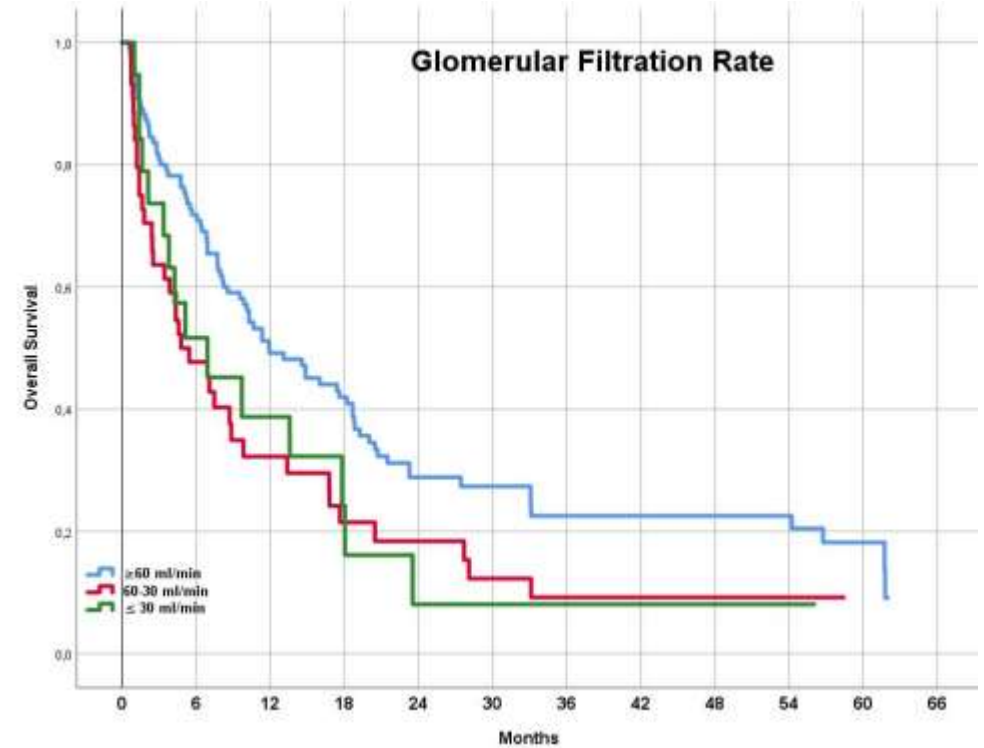
Background:

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

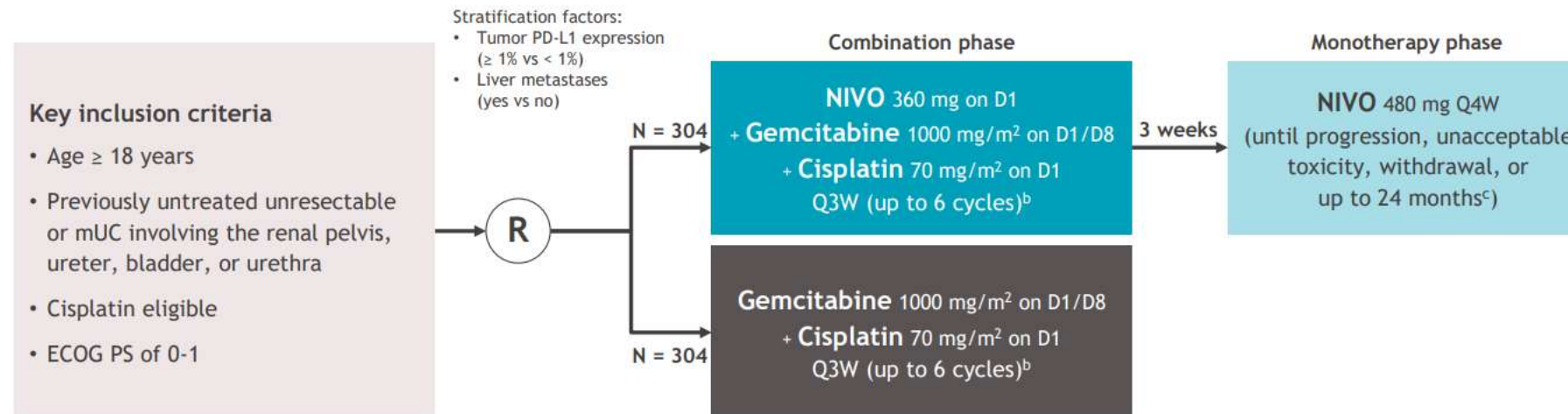
Chemo + IO combinations			
IMvigor130	KEYNOTE-361	DANUBE	CHECKMATE901
Atezolizumab + Platinum/Gemcitabine (n = 451)	Pembrolizumab + Platinum/Gemcitabine (n = 351)	Durvalumab + Tremelimumab (n = 342)	Nivolumab + Cisplatin/Gemcitabine (n = 304)
Atezolizumab Monotherapy (n = 400)	Pembrolizumab Monotherapy (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 KT+İmmünoterapi

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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

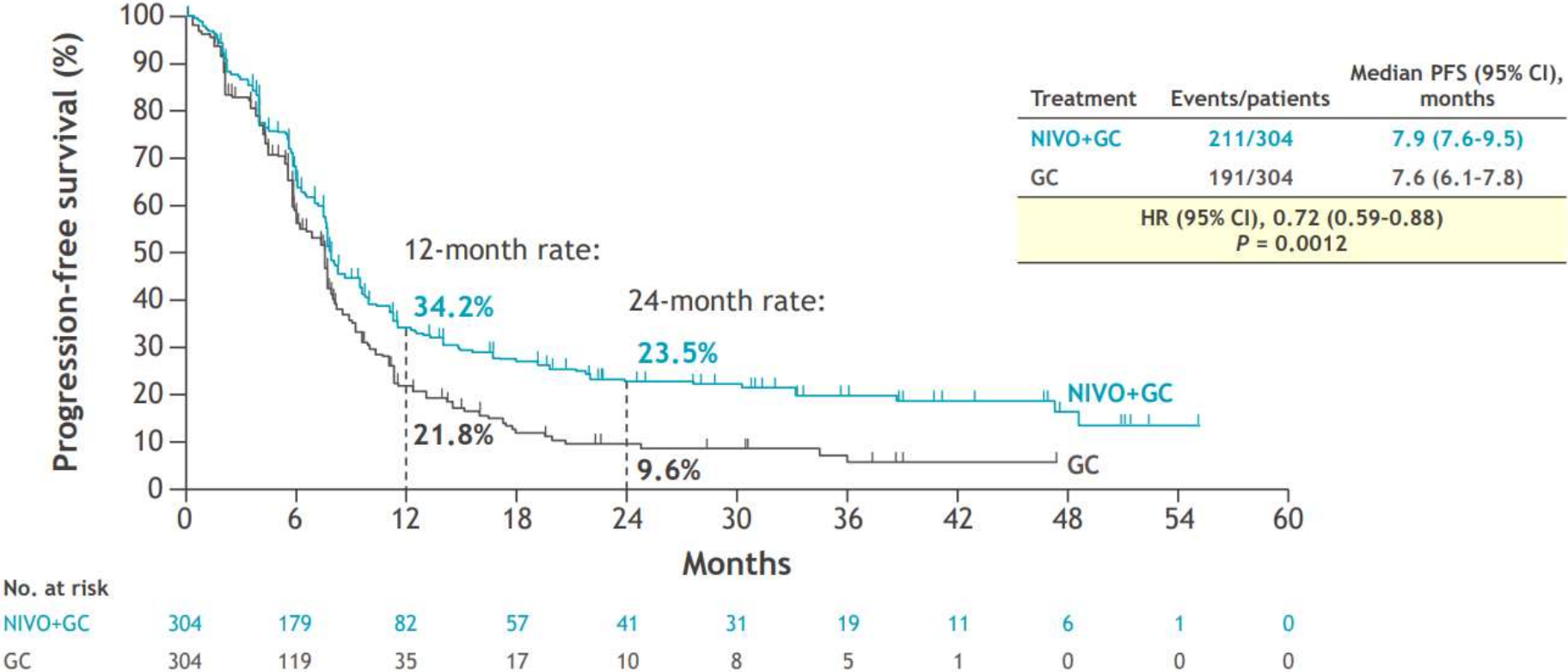
^aFurther CheckMate 901 trial design details are available at <https://clinicaltrials.gov/ct2/show/NCT03036098>. ^bPatients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). ^cA maximum of 24 months from first 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

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PFS per BICR (primary endpoint)

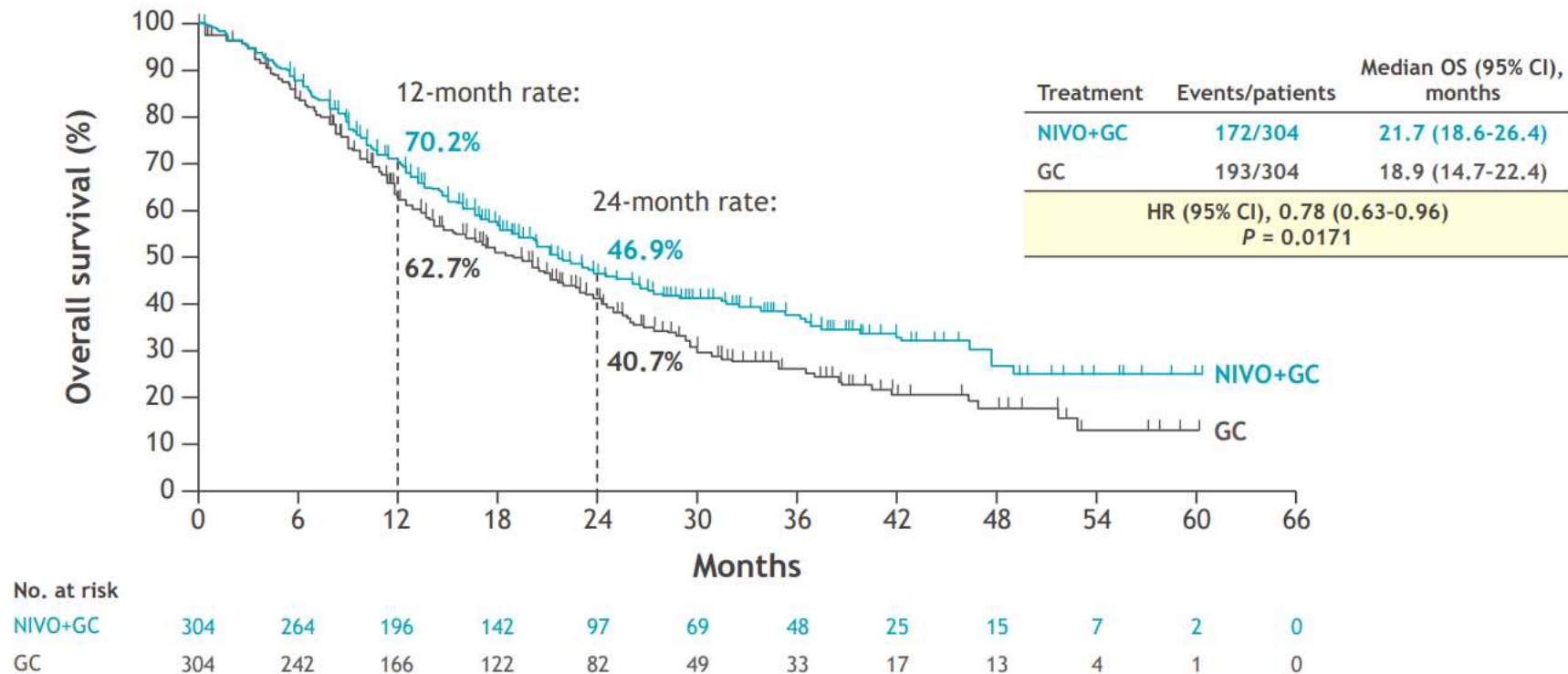


Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as time from randomization to first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who did not progress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

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OS (primary endpoint)

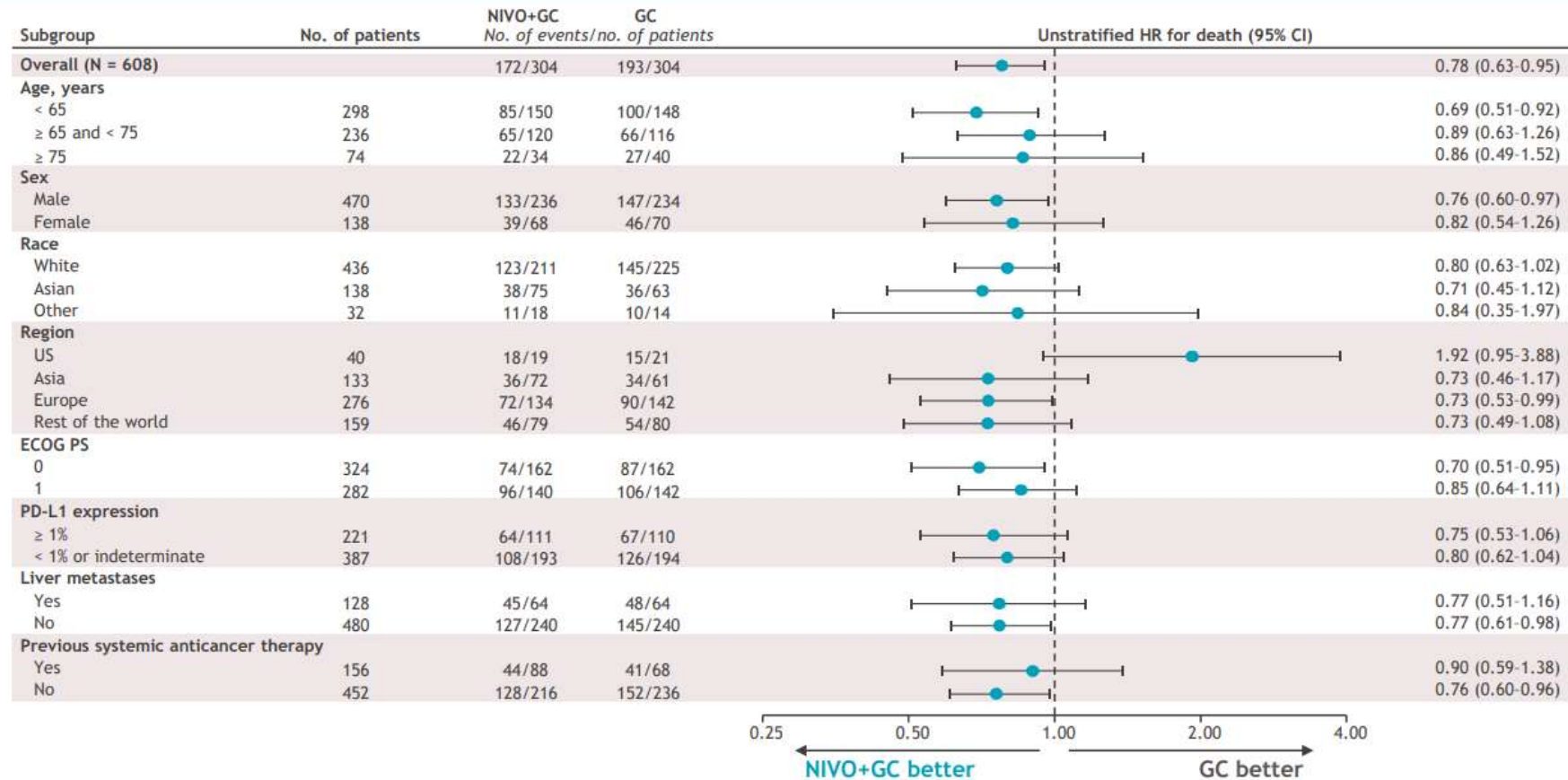


Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with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

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

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OS in subgroups

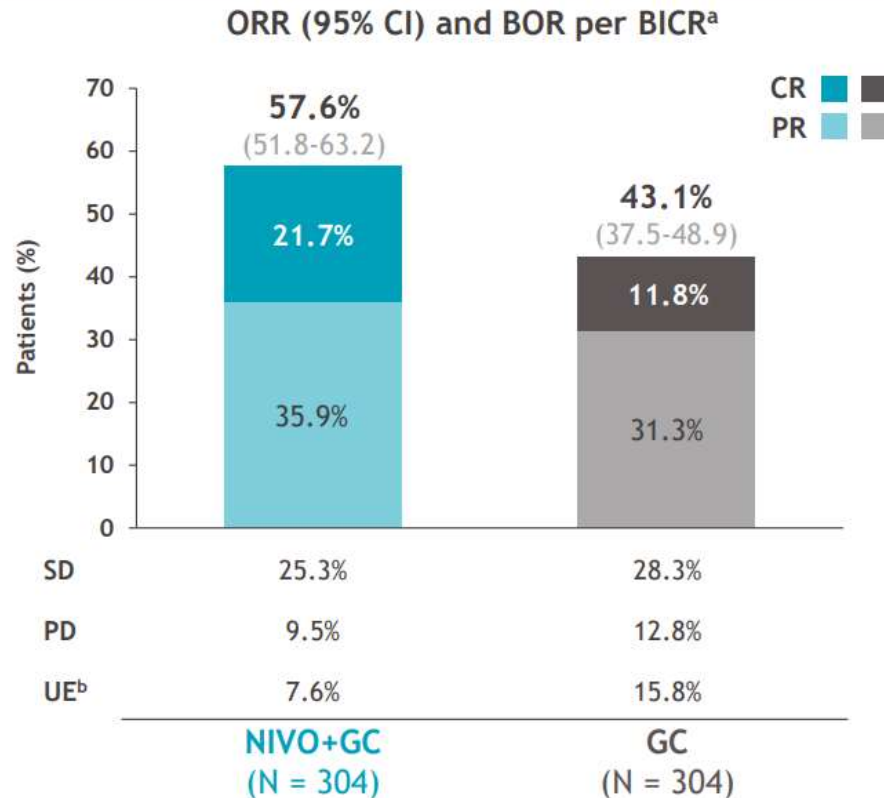


All randomized patients. HRs were not computed for subgroup categories (except for age, sex, race, and region) with < 10 patients per treatment group. Categories without a meaningful estimate of the HR are not shown. PD-L1 expression and liver metastases are per interactive response technology. There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

Sisplatine uygun hastalarda Cisplatin+Gemsitabin+Nivolumab

CheckMate 901

Objective response outcomes (exploratory endpoints)



Time to and duration of responses

	NIVO+GC (n = 175)	GC (n = 131)
Any objective response ^c		
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)

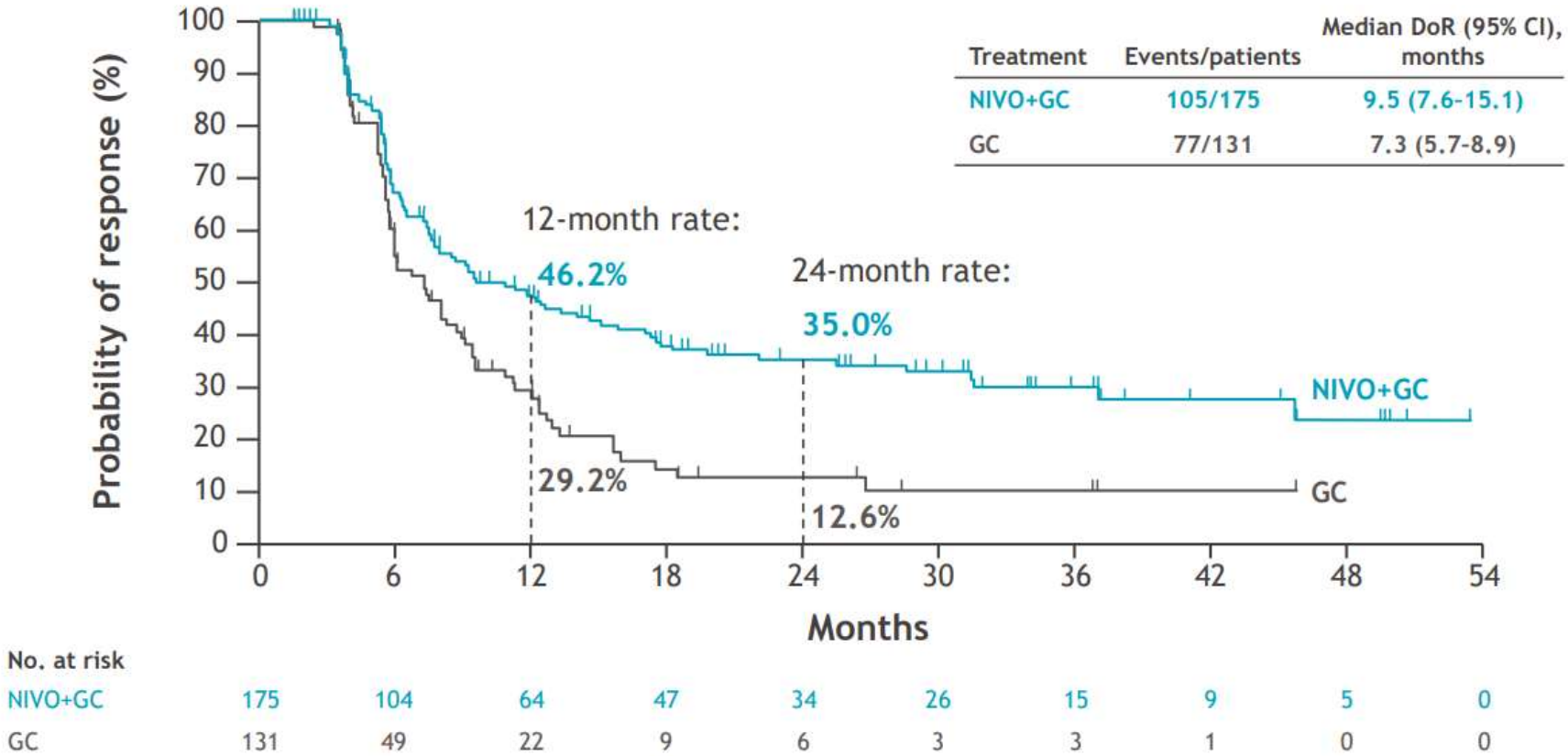
	NIVO+GC (n = 66)	GC (n = 36)
Complete response ^d		
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

^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 Cisplatin+Gemsitabin+Nivolumab

CheckMate 901

Duration of objective response per BICR

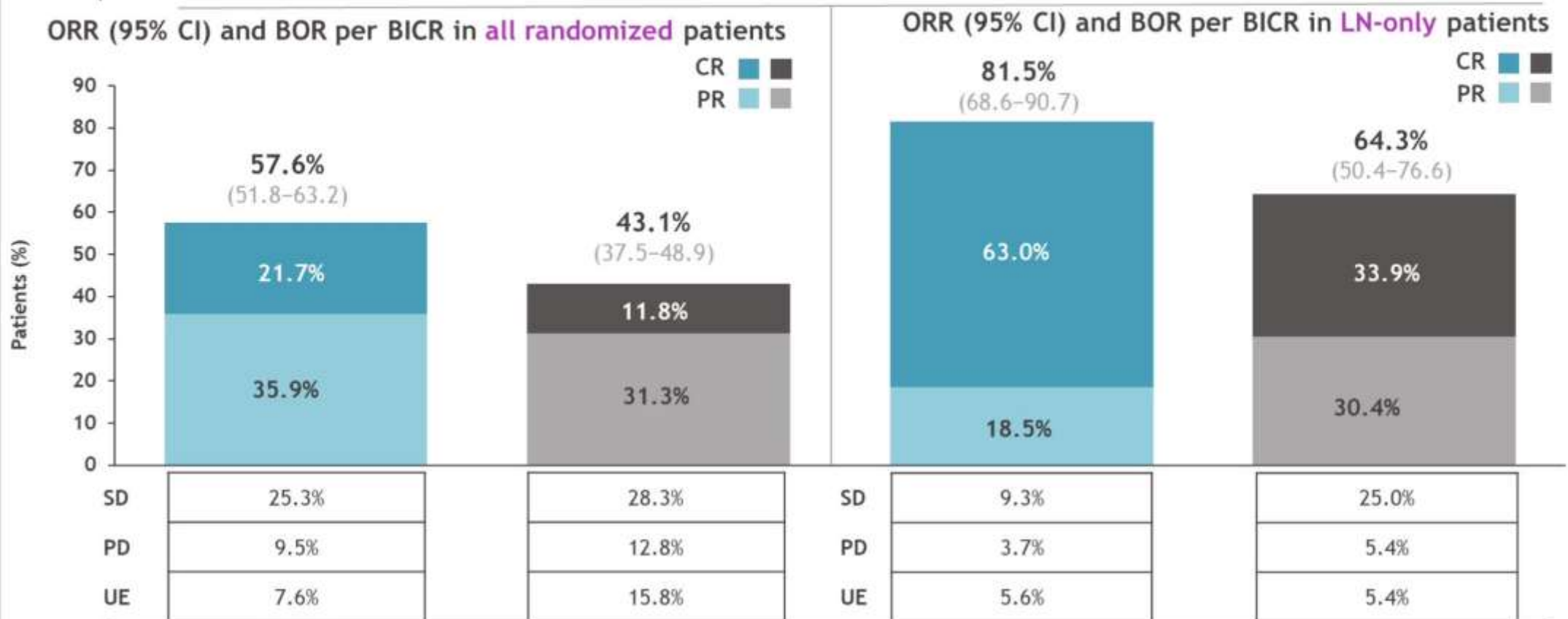


Sisplatin+Gemsitabin+Nivolumab

Yalnız lenf nodu metastazı olanlarda yanıt

Response per BICR: patients with LN-only mUC

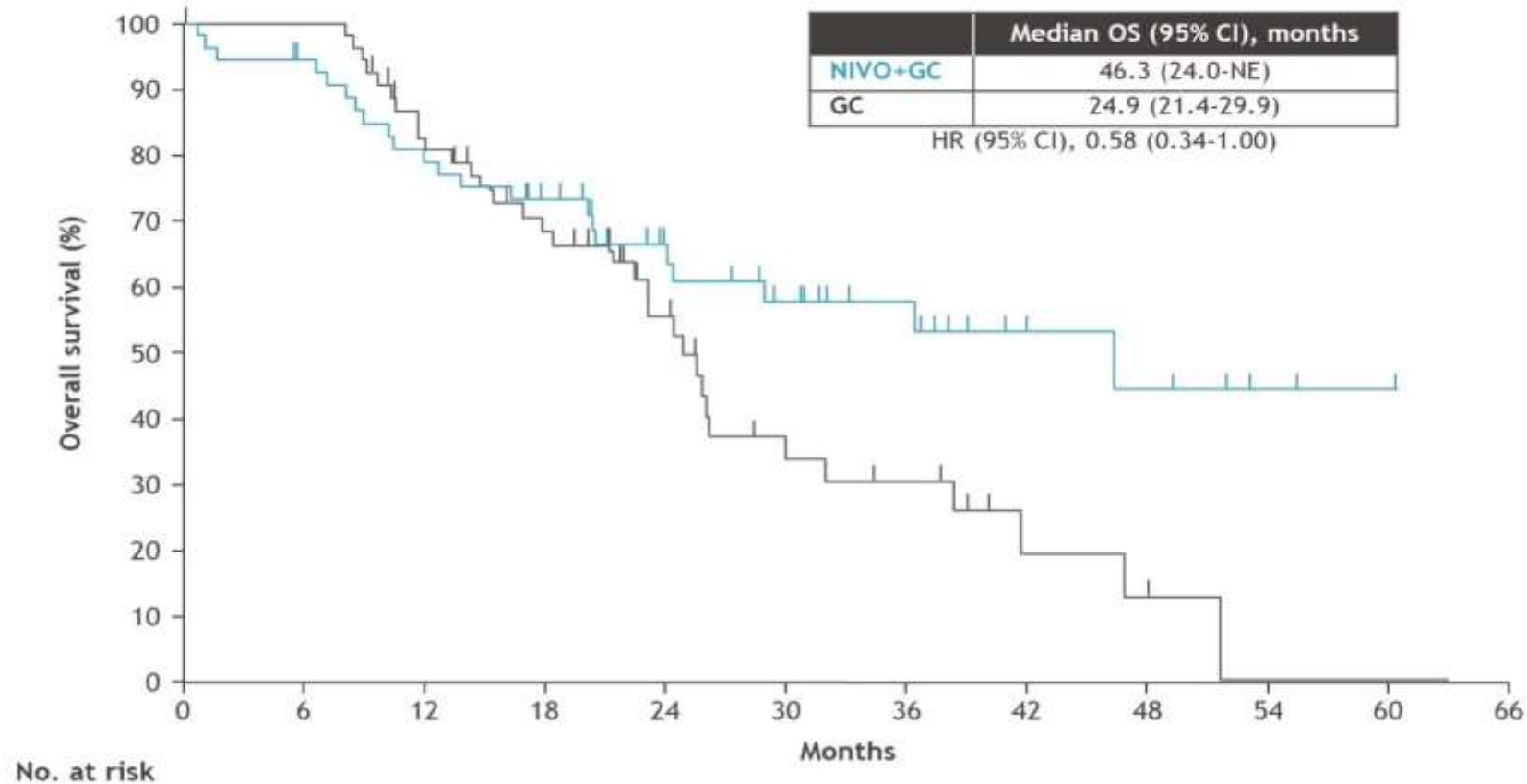
- CR rates for NIVO+GC-treated patients with LN-only mUC were approximately twice that of GC-treated patients



Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

Yalnız lenf nodu metastazı olanlarda Genel sağkalım

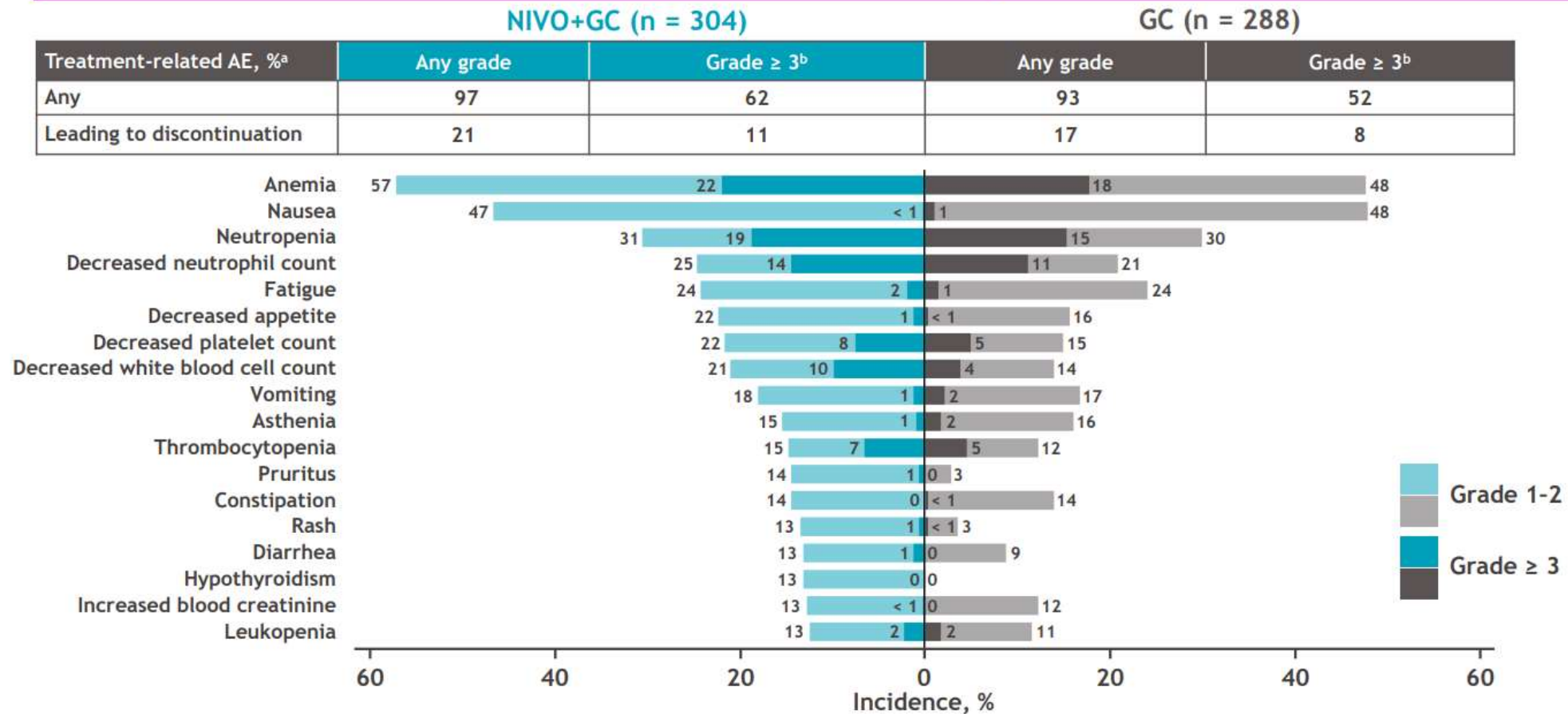
OS: patients with LN-only mUC per BICR



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 · Saadettin 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

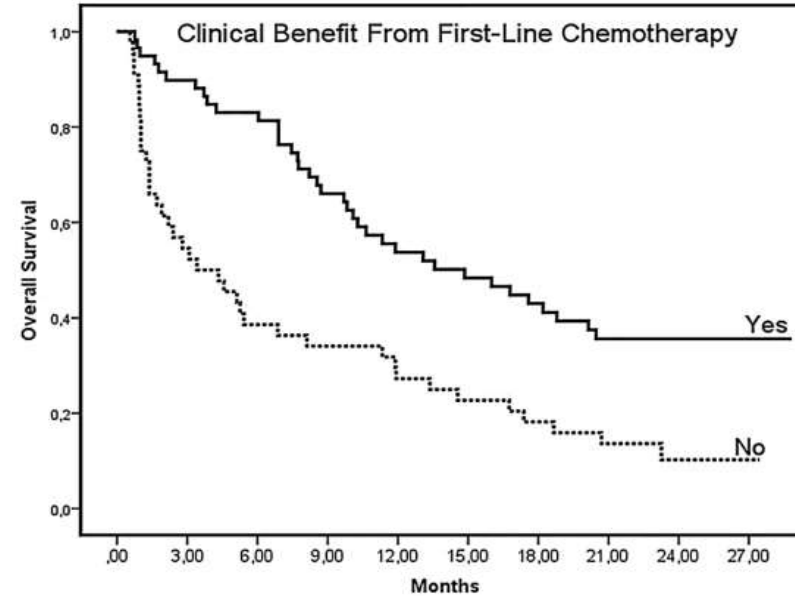
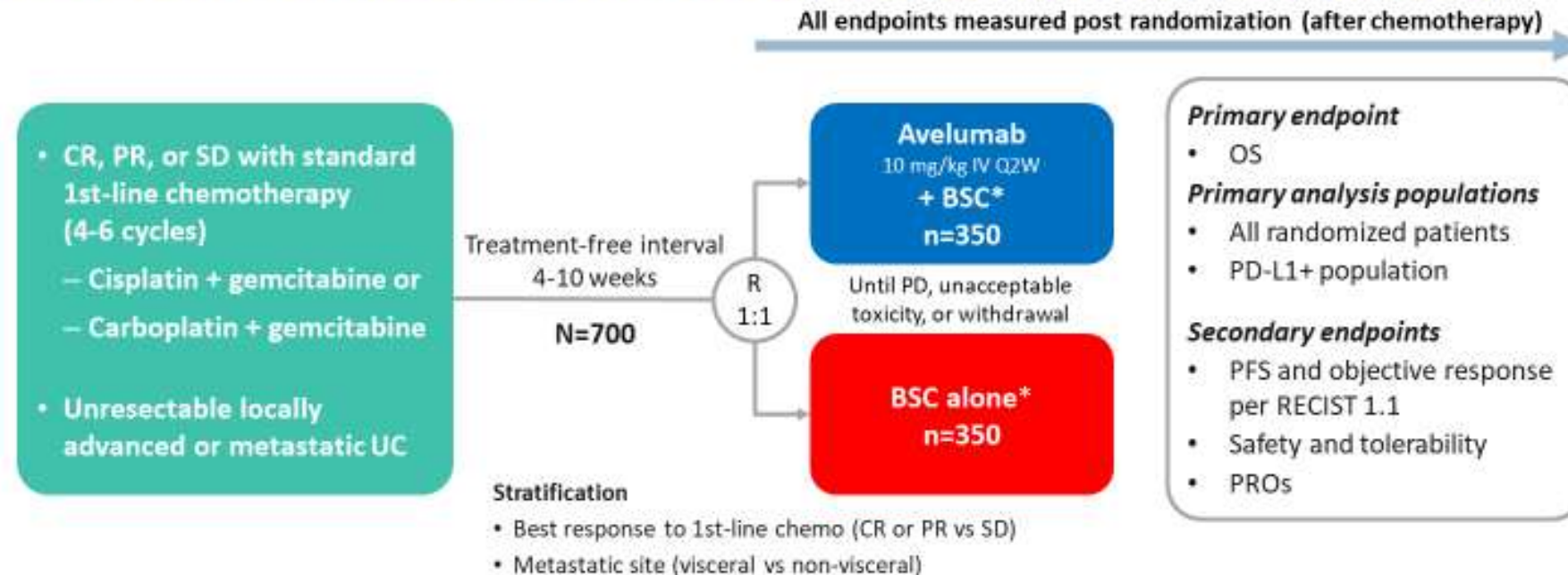


Fig. 2 Kaplan–Meier curves association of clinically benefited from the first-line treatment and overall survival

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 Mesane Kanseri Birinci Basamak Tedavi Platin bazlı kemoterapi Sonrası İdame Avelumab

JAVELIN Bladder 100 study design (NCT02603432)



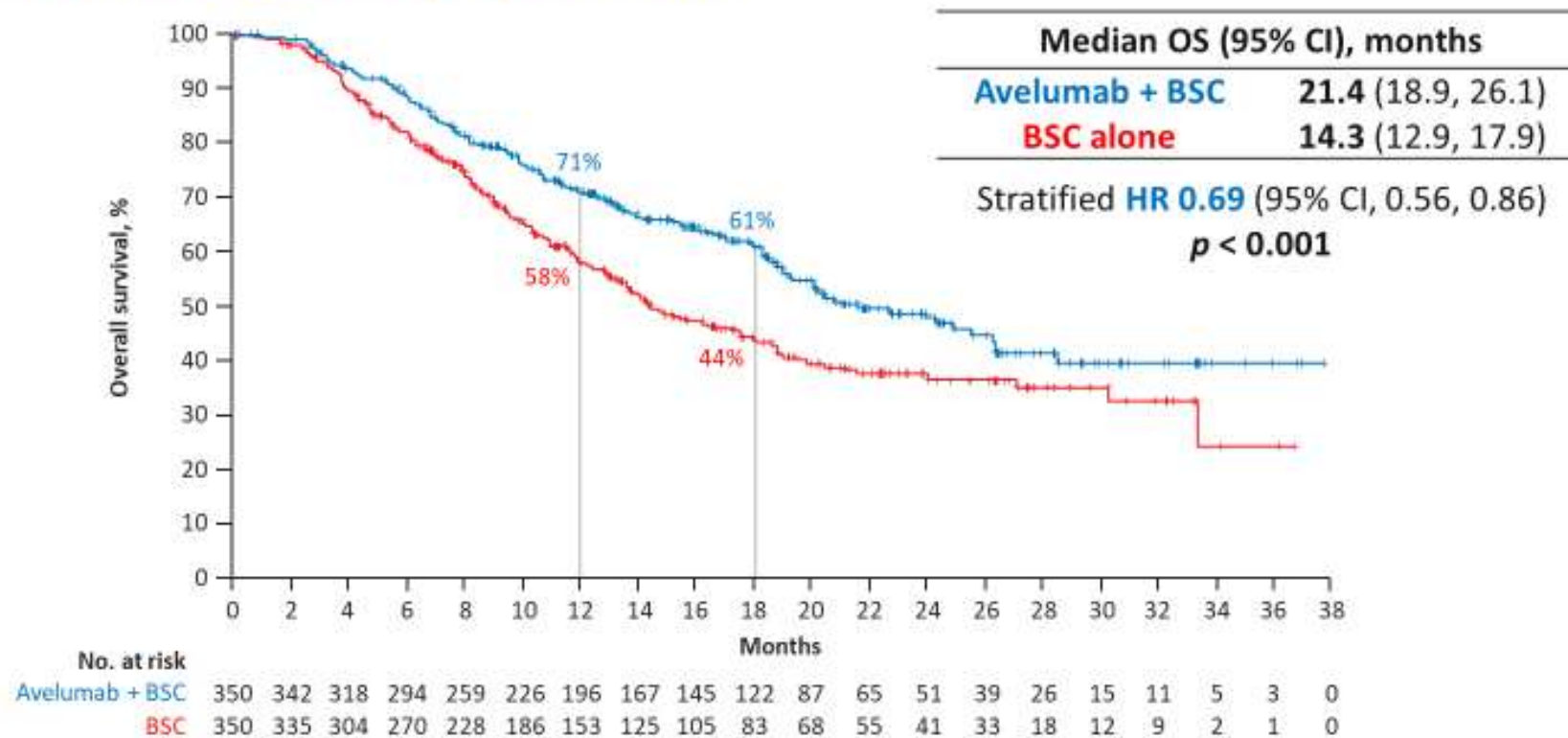
PD-L1+ status was defined as PD-L1 expression in $\geq 25\%$ of tumor cells or in $\geq 25\%$ or 100% of tumor-associated immune cells if the percentage of immune cells was $>1\%$ or $\leq 1\%$, respectively, using the SP263 assay; 358 patients (51%) had a PD-L1-positive tumor

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 Mesane Kanseri Birinci Basamak Tedavi Platin bazlı kemoterapi Sonrası İdame Avelumab

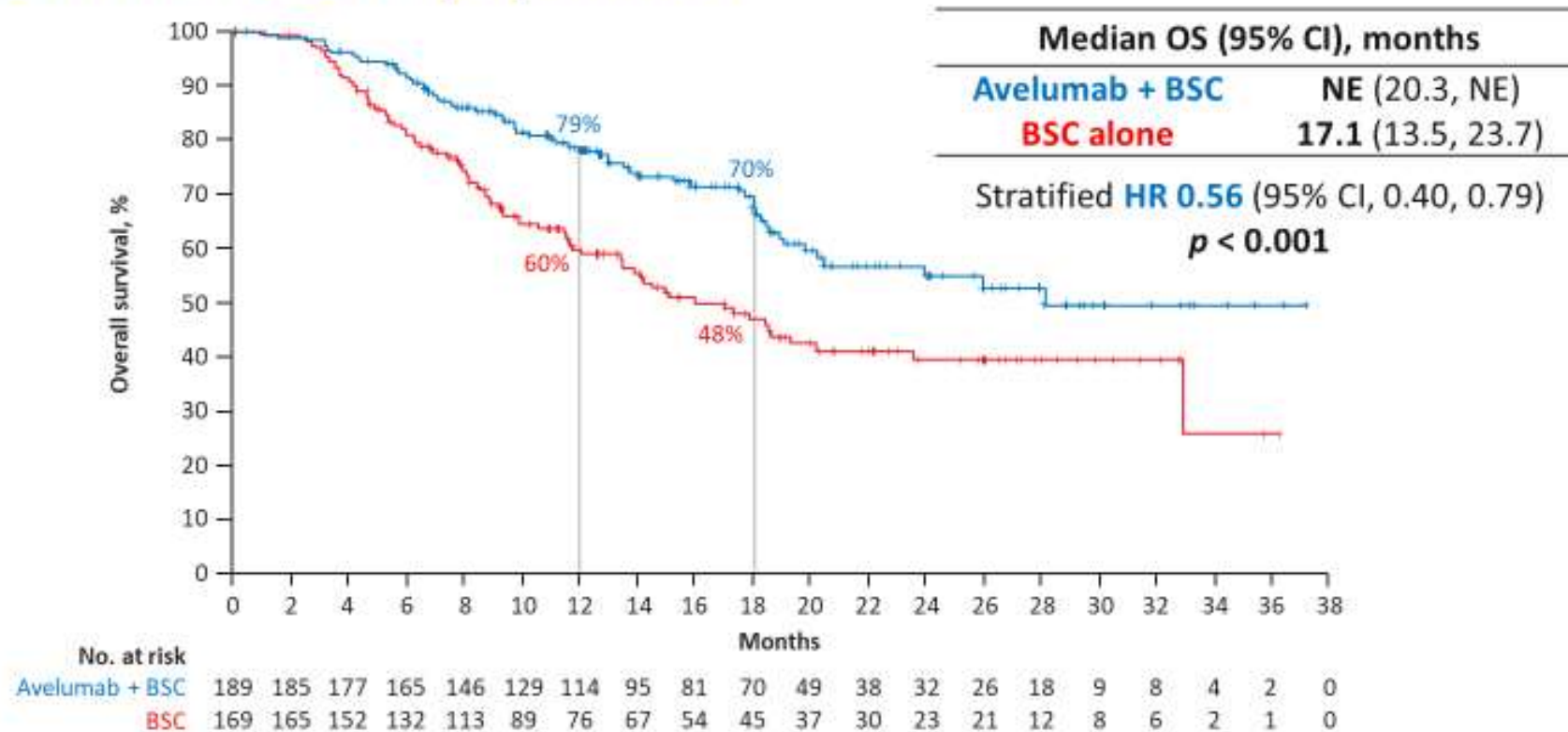
OS in the overall population



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 Mesane Kanseri Birinci Basamak Tedavi Platin bazlı kemoterapi Sonrası İdame Avelumab

OS in the PD-L1+ population



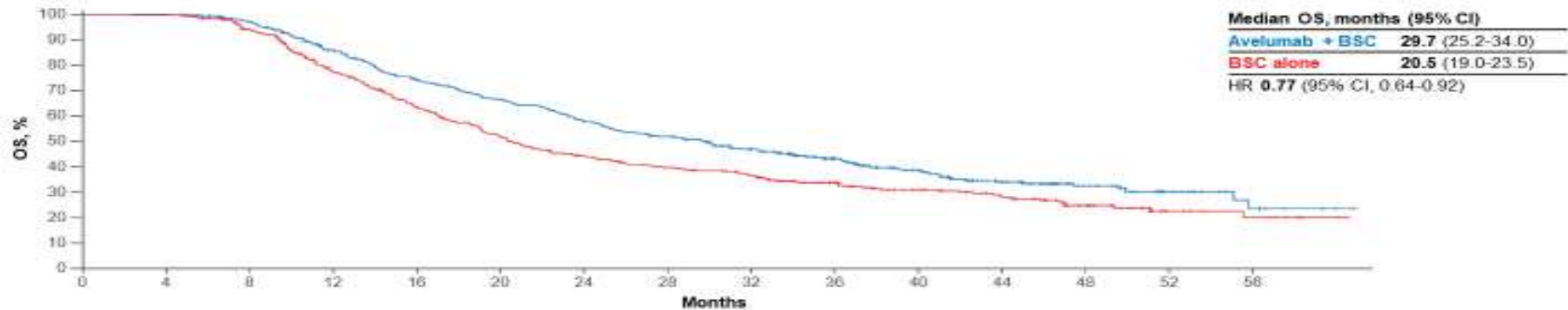
OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function ($P < 0.0014$). NE, not estimable

Metastatik Mesane Kanseri Birinci Basamak Tedavi Platin bazlı kemoterapi Sonrası İdame Avelumab

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

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

Post hoc analysis



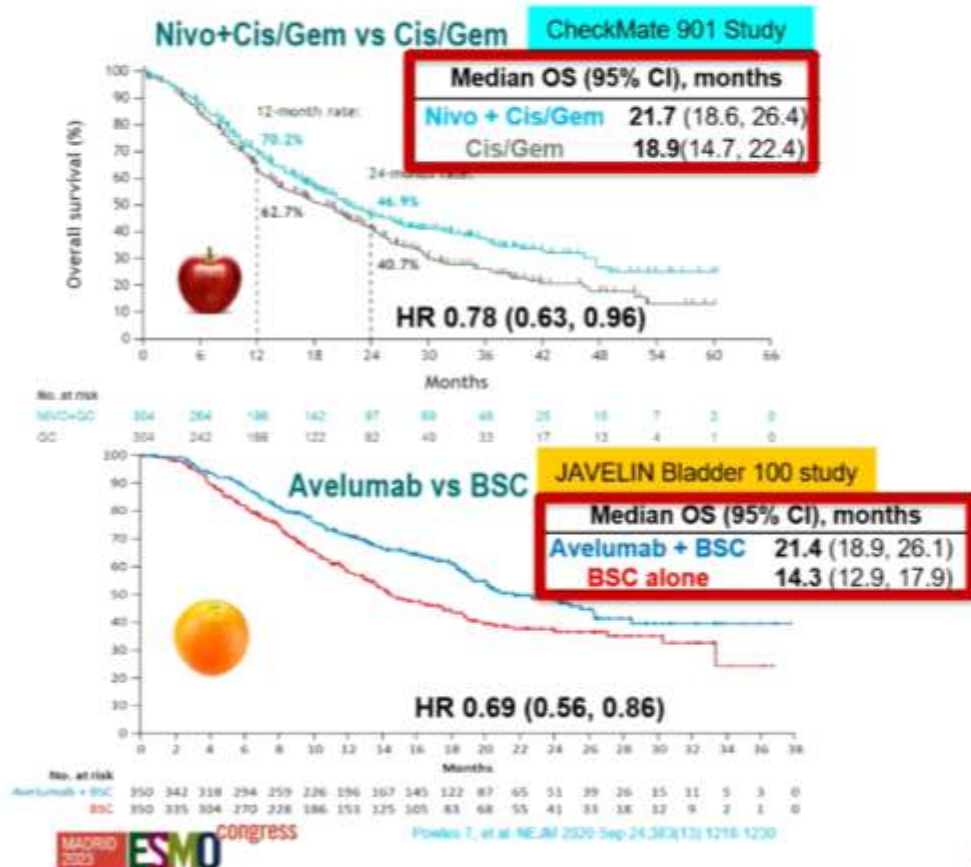
No. at risk															
Avelumab + BSC	350	350	334	288	247	220	191	171	145	114	86	58	36	17	7
	BSC	350	349	317	255	207	168	141	125	111	89	68	54	33	12

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])

Metastatik Mesane Kanseri 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

Metastatik Mesane Kanseri Sisplatin Uygun Olmayanlarda Birinci Basamak Enfortumab+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

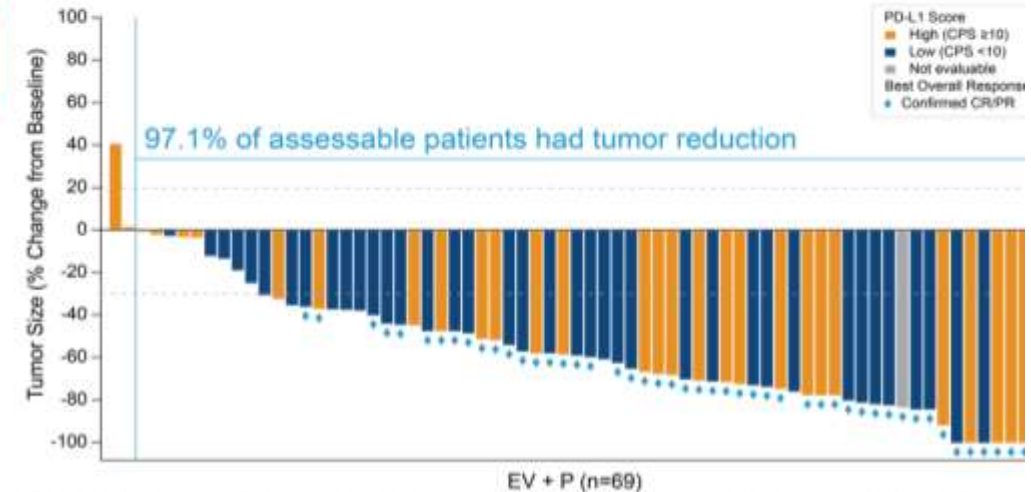
Primary Endpoint

- 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: 10 Jun 2022

BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

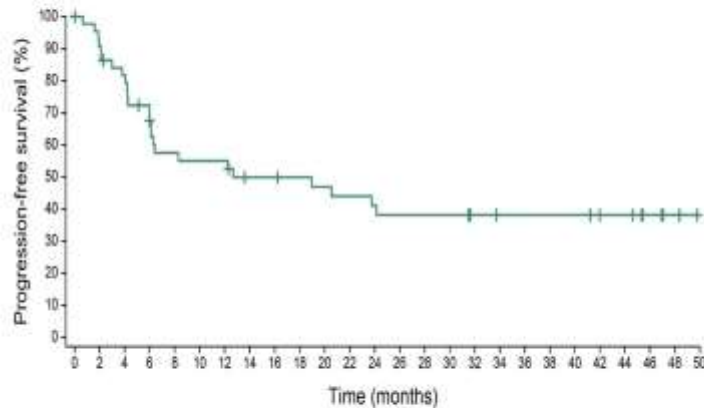
BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

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



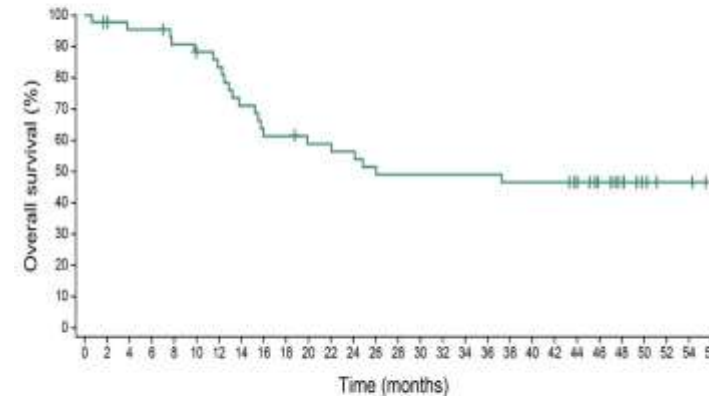
No. at risk 45 40 35 30 23 22 18 17 16 15 13 13 11 10 10 10 8 8 4 2

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).
^bNot estimated using Kaplan-Meier method.

Overall Survival

Median survival exceeds 2 years



No. at risk 45 43 41 41 38 36 34 29 25 25 24 24 23 21 20 20 20 20 19 19 18 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).
^bNot 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

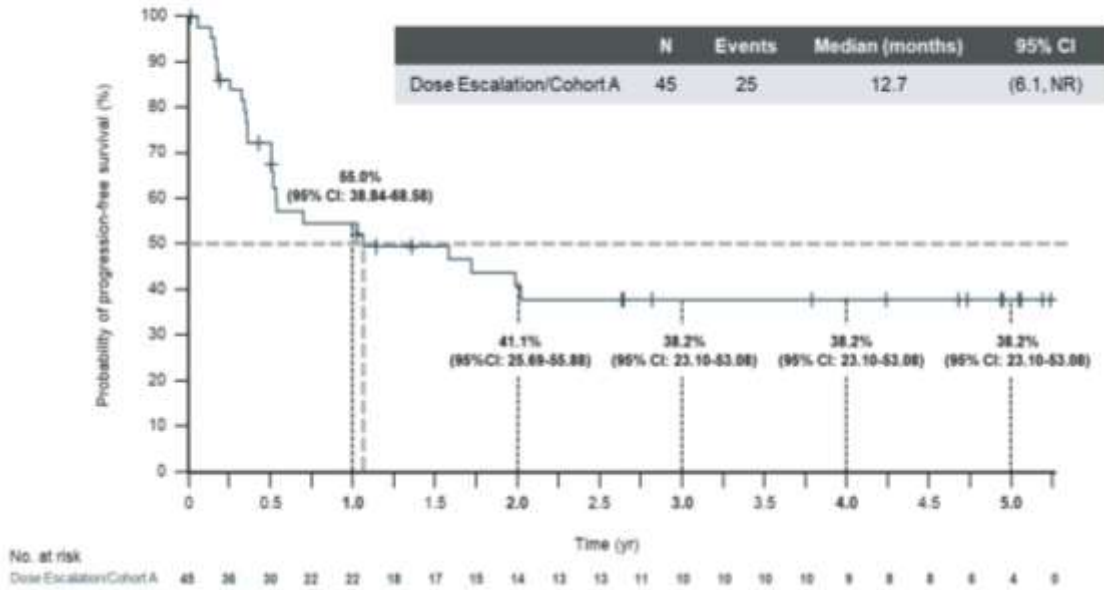
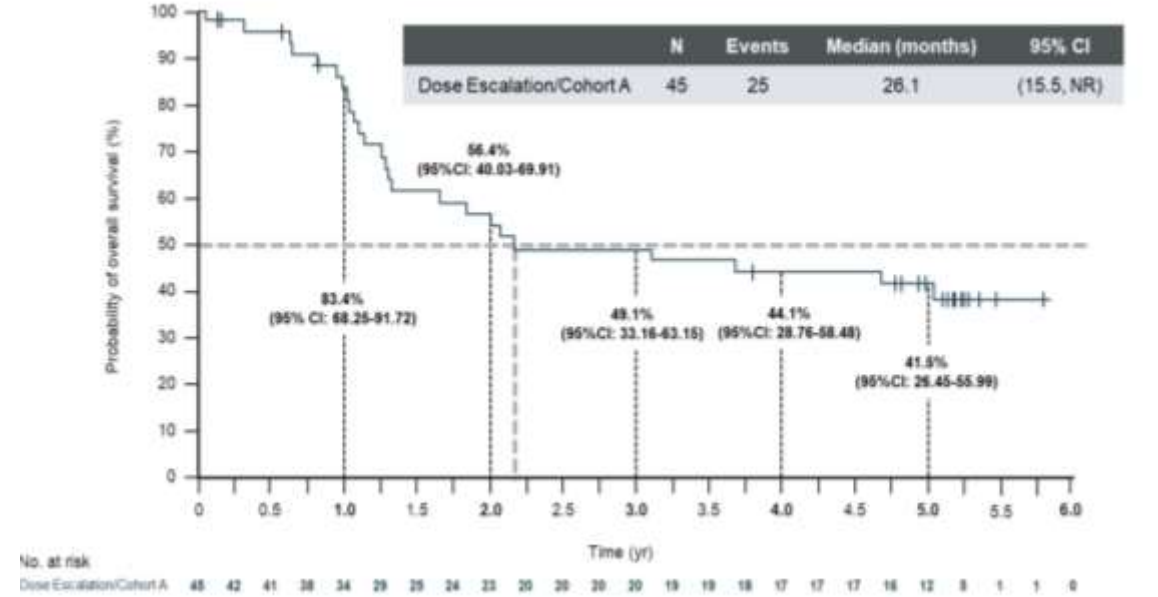


Figure 5. OS

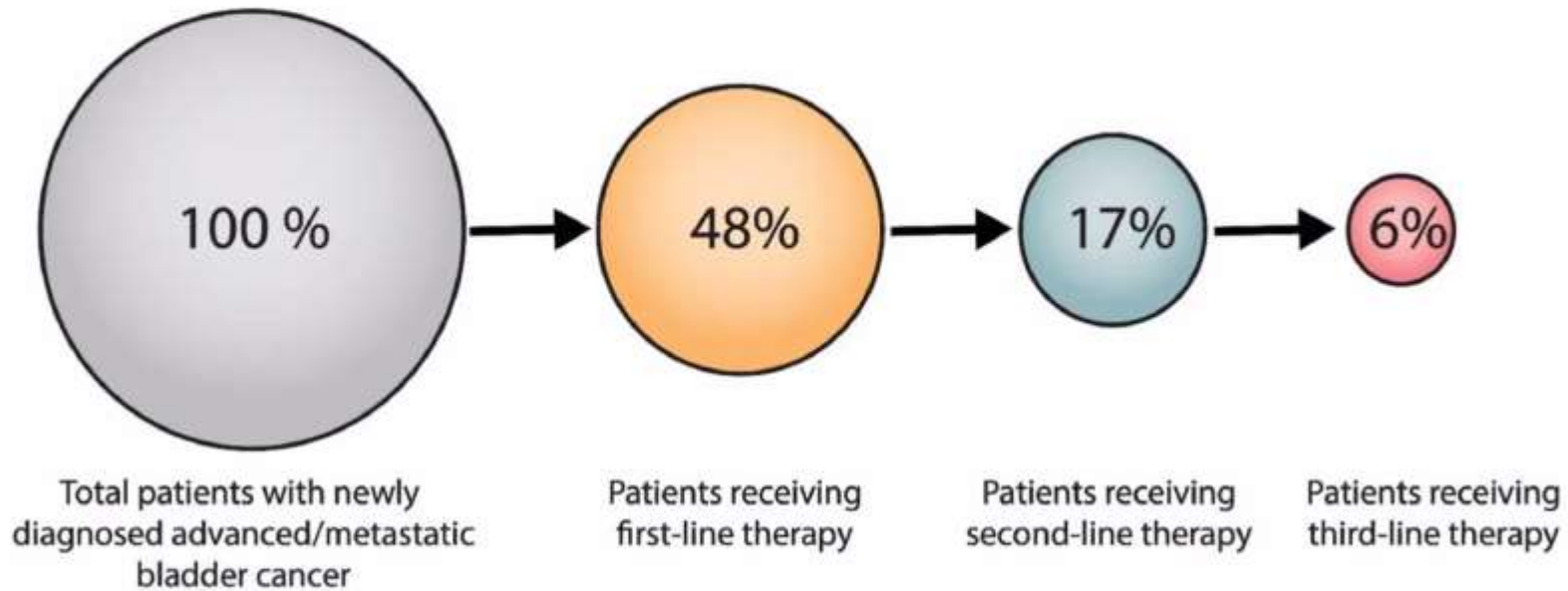


Enfortumab vedotin ve pembrolizumab kombinasyonu sisplatin uygun olmayan hastalarda 5-
yılık sağkalım %40

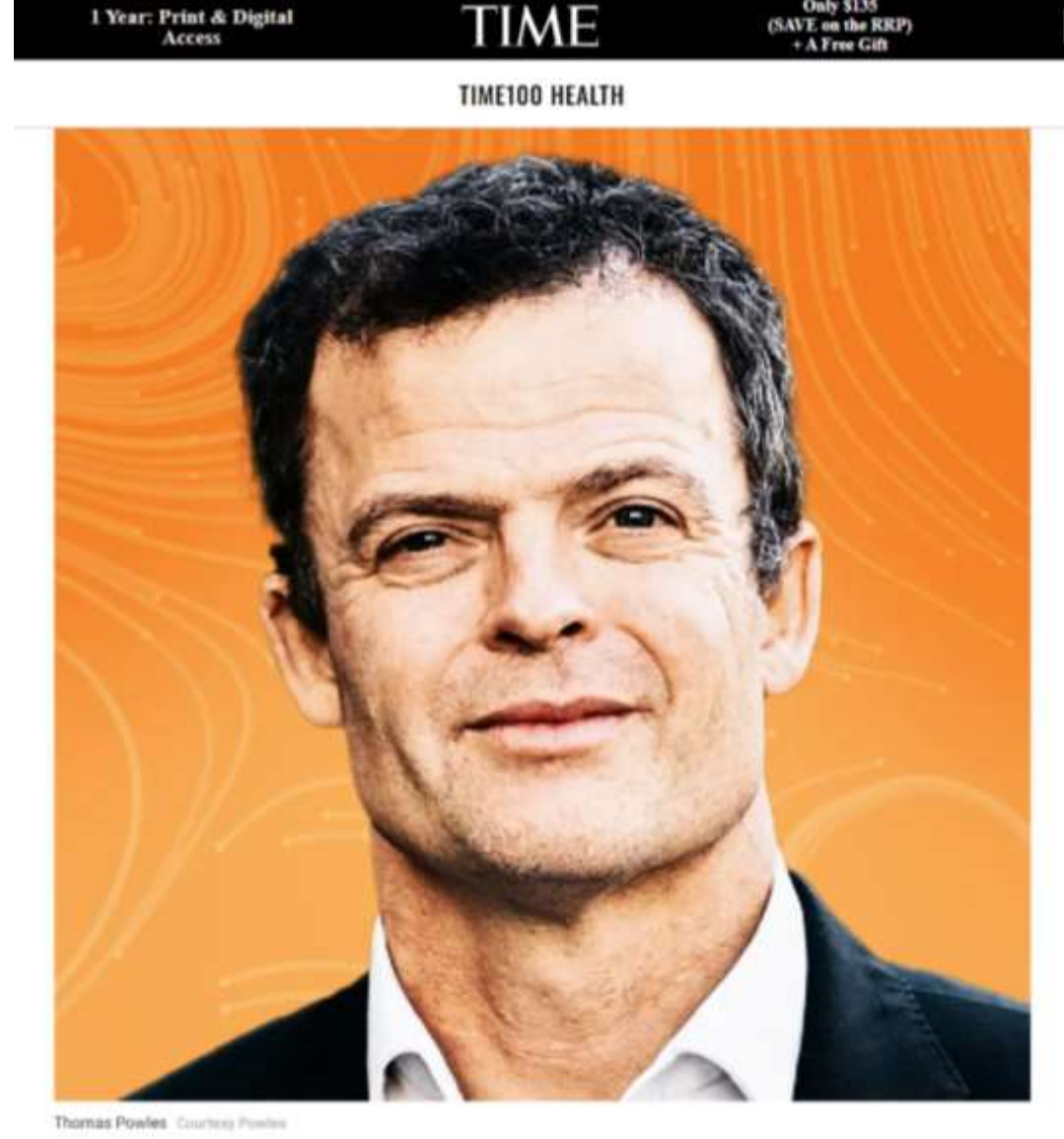
En Etkili Tedavi En kısa Zamanda Vermek



Utilization of Systemic Therapy for Advanced Urothelial Carcinoma



TIME Dergisine Kapak Olan Çalışmanın Sonuçları Açıklandı



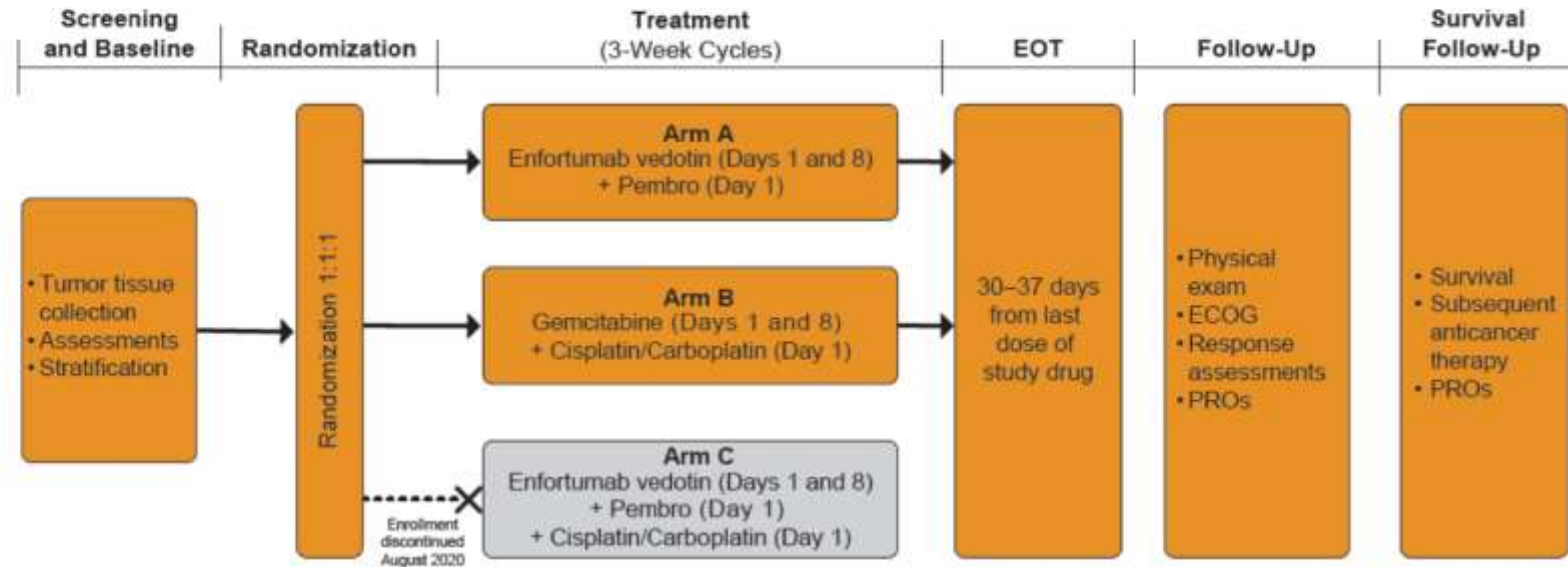
Metastatik Mesane Kanseri Birinci Basamak Tedavi

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

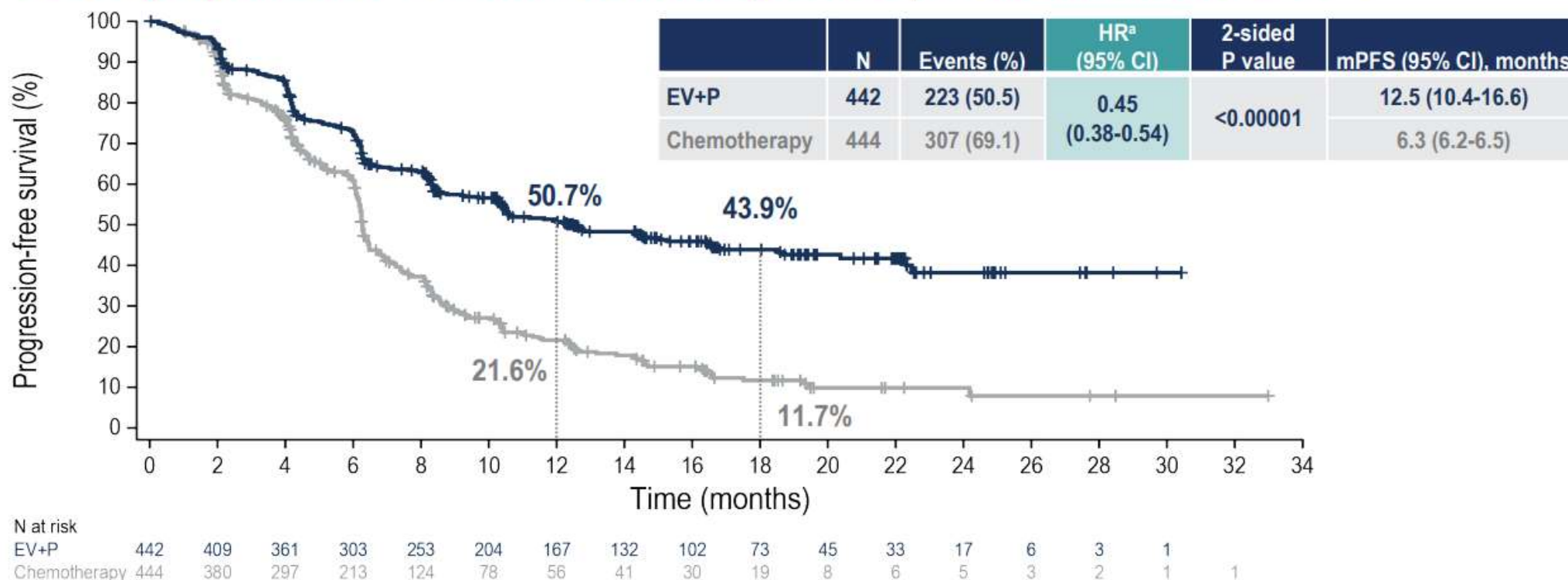
Primary Endpoints: PFS, OS
Secondary Endpoints: ORR, DOR, DCR, QOL, PRO, Safety

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



Data cutoff: 08 Aug 2023



Powles et al.

PFS at 12 and 18 months as estimated using Kaplan-Meier method

HR, hazard ratio; mPFS, median progression-free survival

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

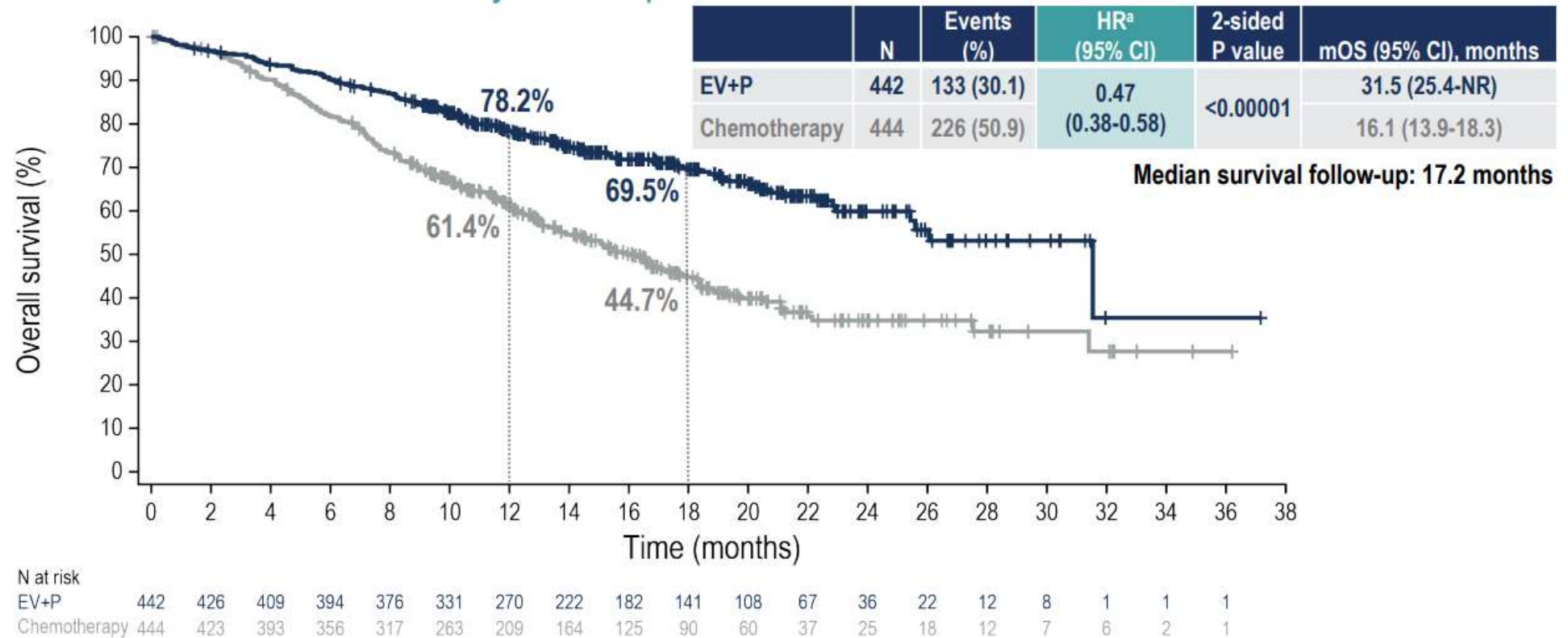
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Metastatik Mesane Kanseri Birinci Basamak Tedavi

EV-302 -EV/pemrolizumab

Overall Survival

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



Data cutoff: 08 Aug 2023



Powles et al.

OS at 12 and 18 months was estimated using Kaplan-Meier method

mOS, median overall survival; NR, not reached

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

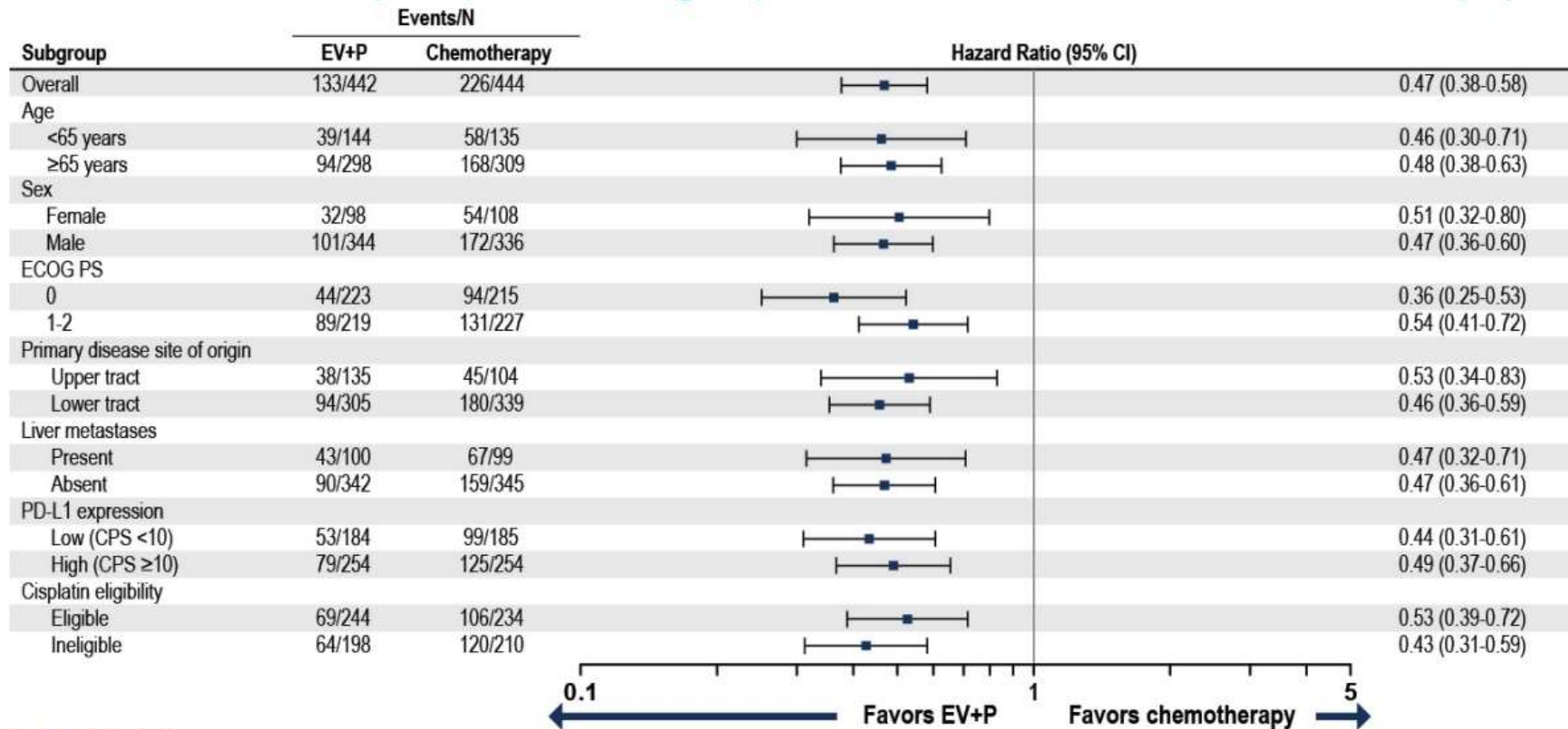
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Metastatik Mesane Kanseri Birinci Basamak Tedavi

EV-302 -EV/pemrolizumab

Subgroup Analysis of OS

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



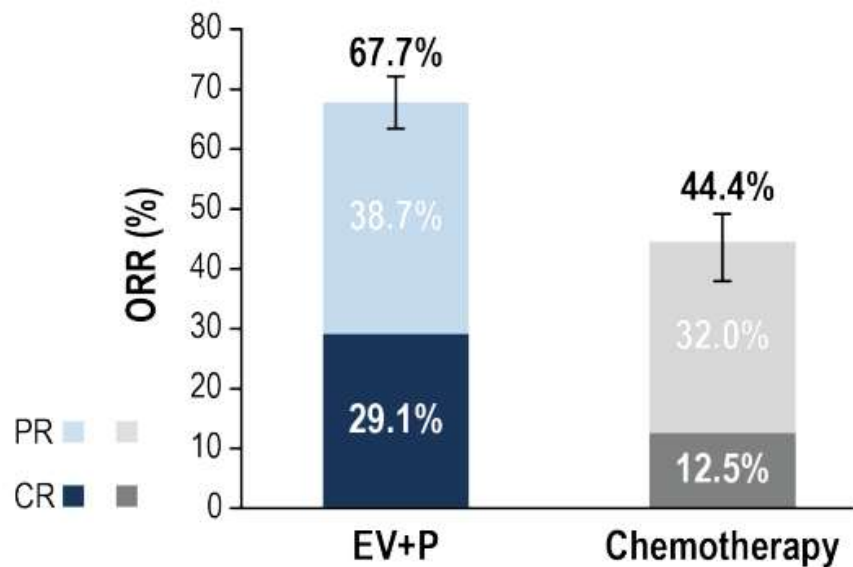
Data cutoff: 08 Aug 2023

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



Median DOR (95% CI)	EV+P	Chemotherapy
	NR (20.2, NR)	7.0 (6.2, 10.2)

	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)

CR, complete response; DOR, duration of response; PR, partial response

^aBest overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response

^bPatients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline

Data cutoff: 08 Aug 2023



Powles et al.

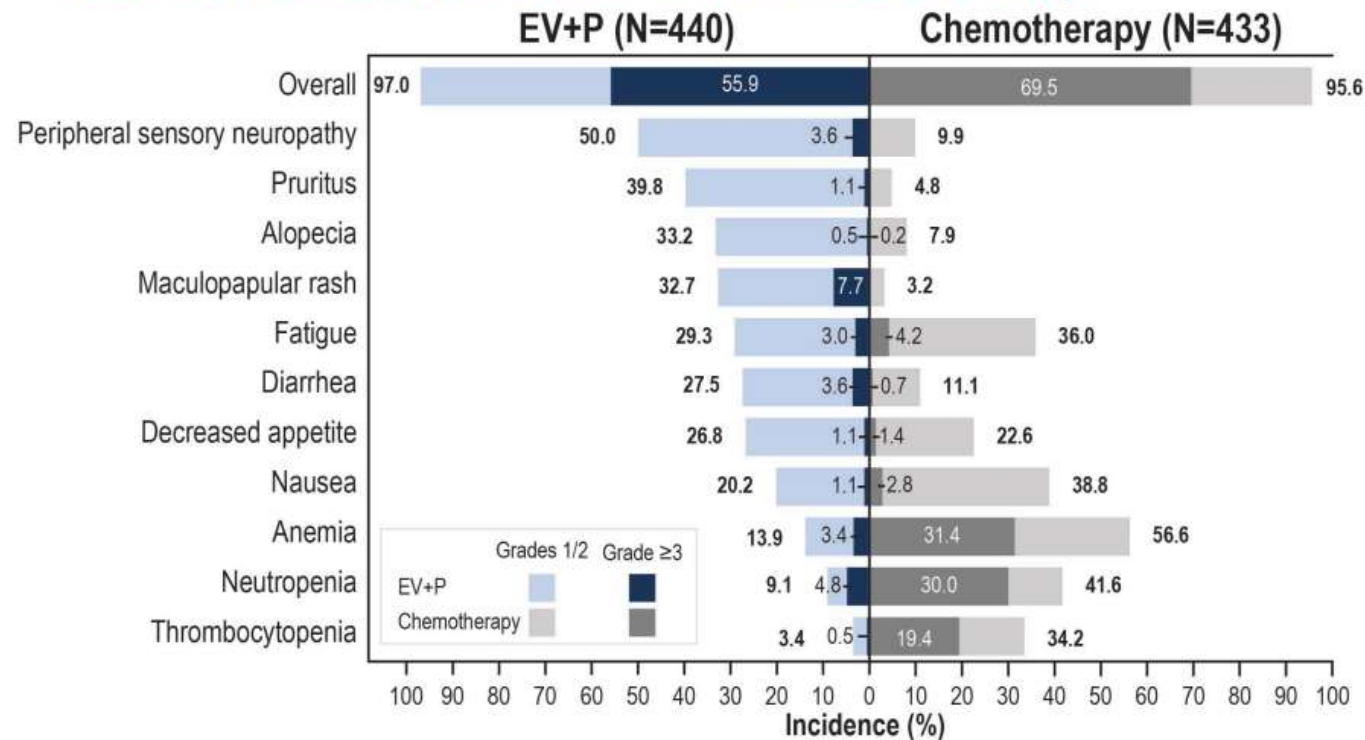
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Metastatik Mesane Kanseri Birinci Basamak Tedavi

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

Data cutoff: 08 Aug 2023

MADRID 2023 ESMO congress

Powles et al.

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

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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 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)

Data cutoff: 08 Aug 2023



Powles et al.

*There are differences in the rates of skin reactions reported for EV treatment-related AEs and P TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and P monotherapies, respectively
AE, adverse event of special interest

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Mesane Kanserinde Neoadjuvan İmmünoterapi çalışmaları

Phase 2 studies exploring neoadjuvant IO in bladder cancer

	PURE-01	ABACUS	NABUCCO			DUTRE NEO	MDACC	PrE0807	MSKCC	
	Pembro	Atezo	Ipi > Ipi/Nivo > Nivo	Ipi ³ + Nivo ¹	Ipi ¹ + Nivo ³	Durva + Treme	Durva + Treme	Nivo+ Liri	Nivo ³	Ipi ³ + Nivo ¹
N	143	88	24	15	15	23	28	30	15	15
cT2	49%	73%	0	0	0	78%	43%	87%	54%	46%
cN1-3	0	0	42%	47%	53%	9%	0	3%	0	0
pCR	39%	31%	46%	43%	7%	35%	38%	18%	13%	7%

Bandini et al, Ann Oncol, 2020; Powles, Nat Med, 2019; van Dijk, Nat Med, 2019; Van Dorp, Ann Oncol, 2021; Grande, ASCO, 2020; Gao, Nat Med, 2020; Grivas, ASCO, 2021; Guercio, ASCO GU 2022

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer

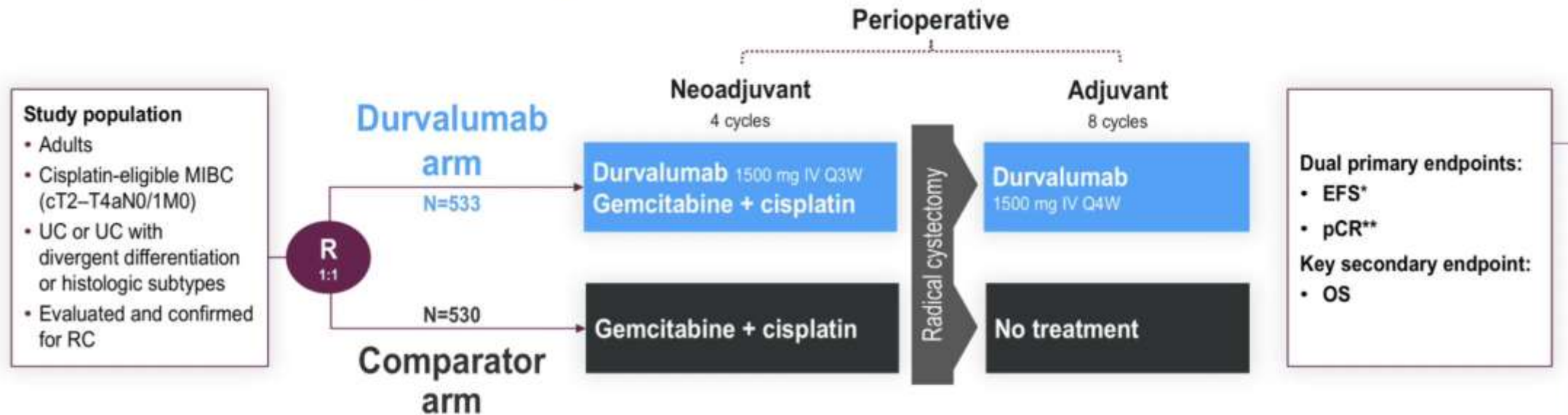
T. Powles, J.W.F. Catto, M.D. Galsky, H. Al-Ahmadie, J.J. Meeks, H. Nishiyama,
T.Q. Vu, L. Antonuzzo, P. Wiechno, V. Atduev, A.G. Kann, T.-H. Kim, C. Suárez,
C.-H. Chang, F. Rghmann, M. Özgüroğlu, B.J. Eigl, N. Oliveira, T. Buchler,
M. Gadot, Y. Zakharia, J. Armstrong, A. Gupta, S. Hois, and M.S. van der Heijden,
for the NIAGARA Investigators*



Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan

NIAGARA: Study Design

BARCELONA 2024 ESMO congress



Stratification factors

Clinical tumour stage (T2N0 vs >T2N0)
Renal function (CrCl ≥60 mL/min vs ≥40–<60 mL/min)
PD-L1 status (high vs low/negative expression)

Gemcitabine/cisplatin dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m² + gemcitabine 1000 mg/m² Day 1, then gemcitabine 1000 mg/m² Day 8, Q3W for 4 cycles
CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m² + gemcitabine 1000 mg/m² Days 1 and 8, Q3W for 4 cycles

EFS was defined as:

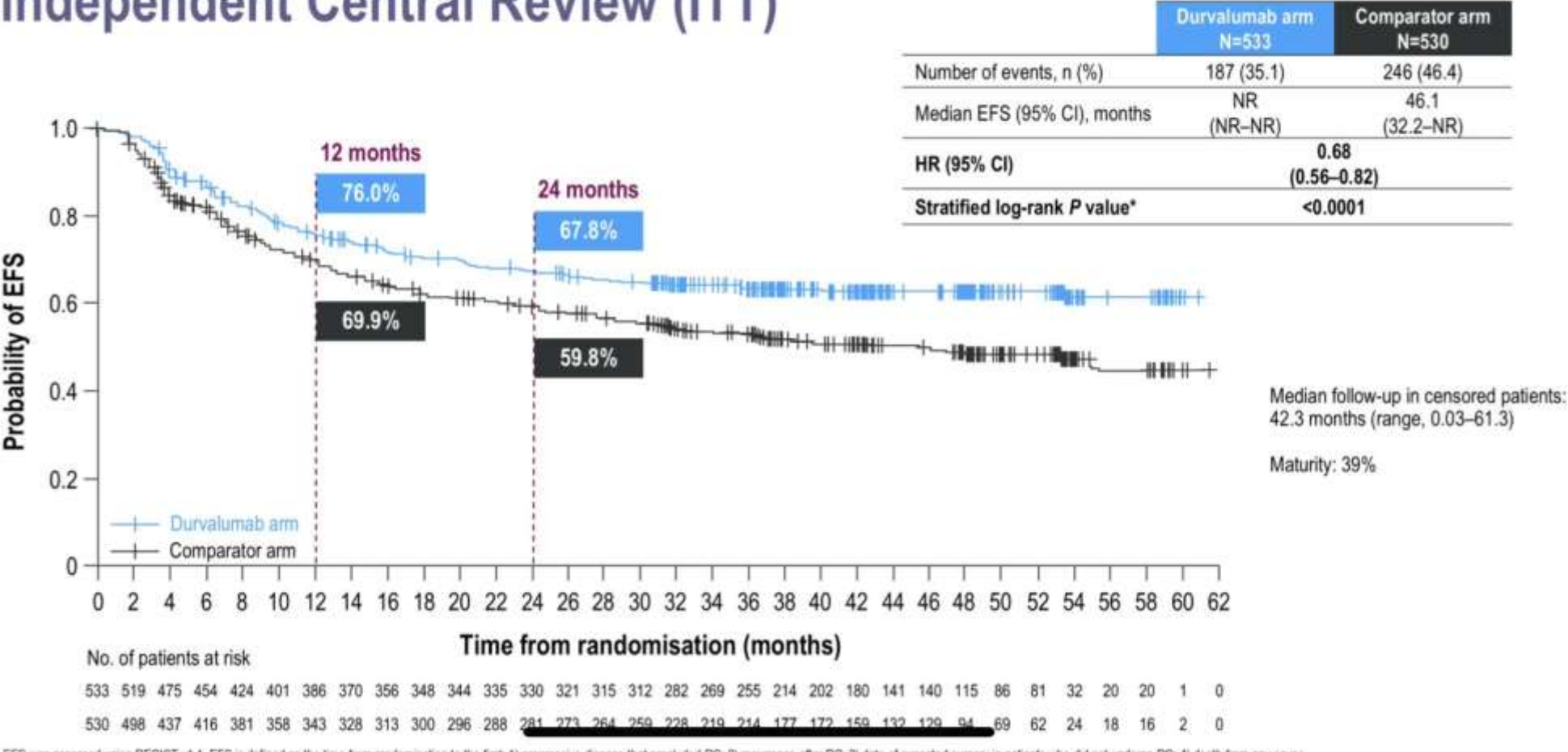
- Progressive disease that precluded RC
- Recurrence after RC
- Date of expected surgery in patients who did not undergo RC
- Death from any cause

Other endpoints (not reported here):
DFS, DSS, MFS, HRQoL, 5-year OS

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan

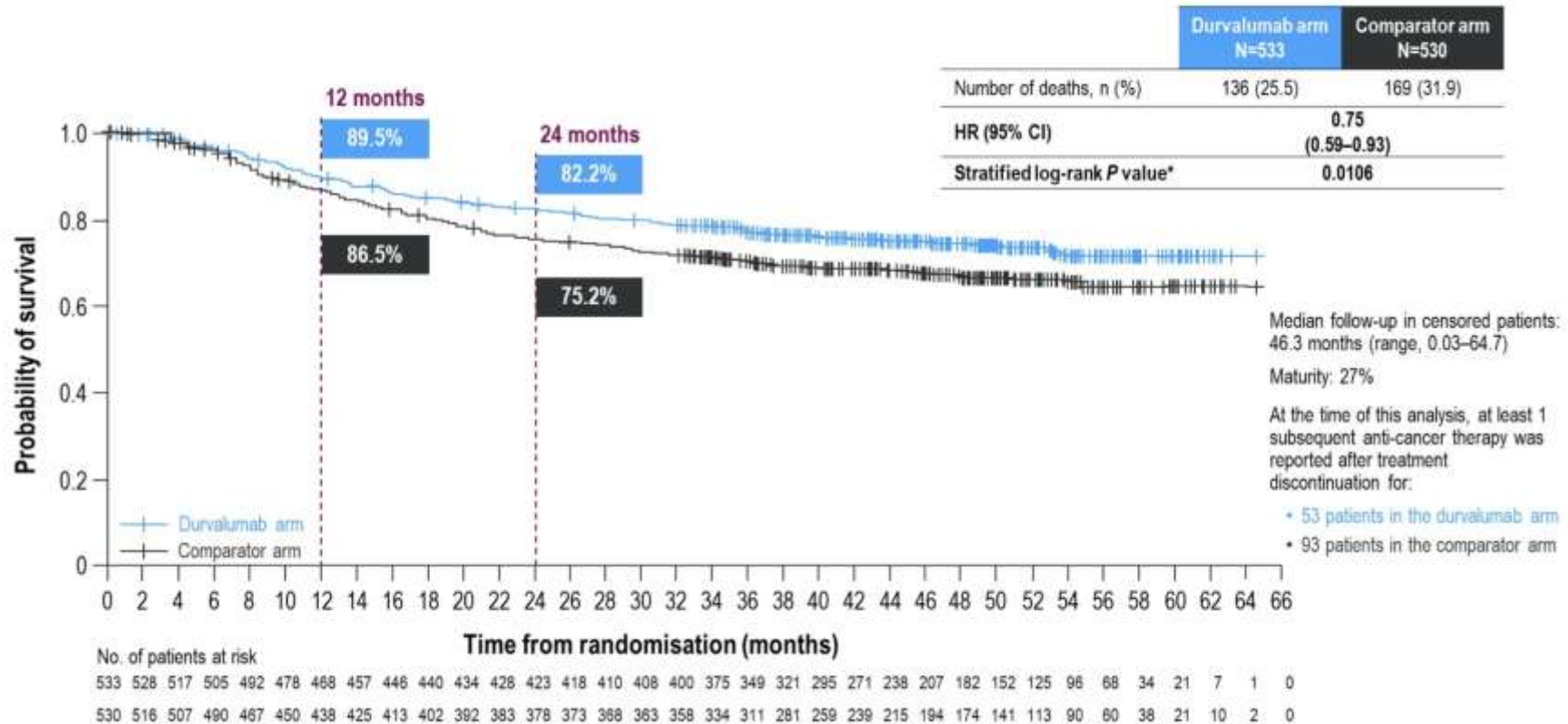
NIAGARA: Event-free Survival by Blinded Independent Central Review (ITT)

BARCELONA 2024 ESMO congress

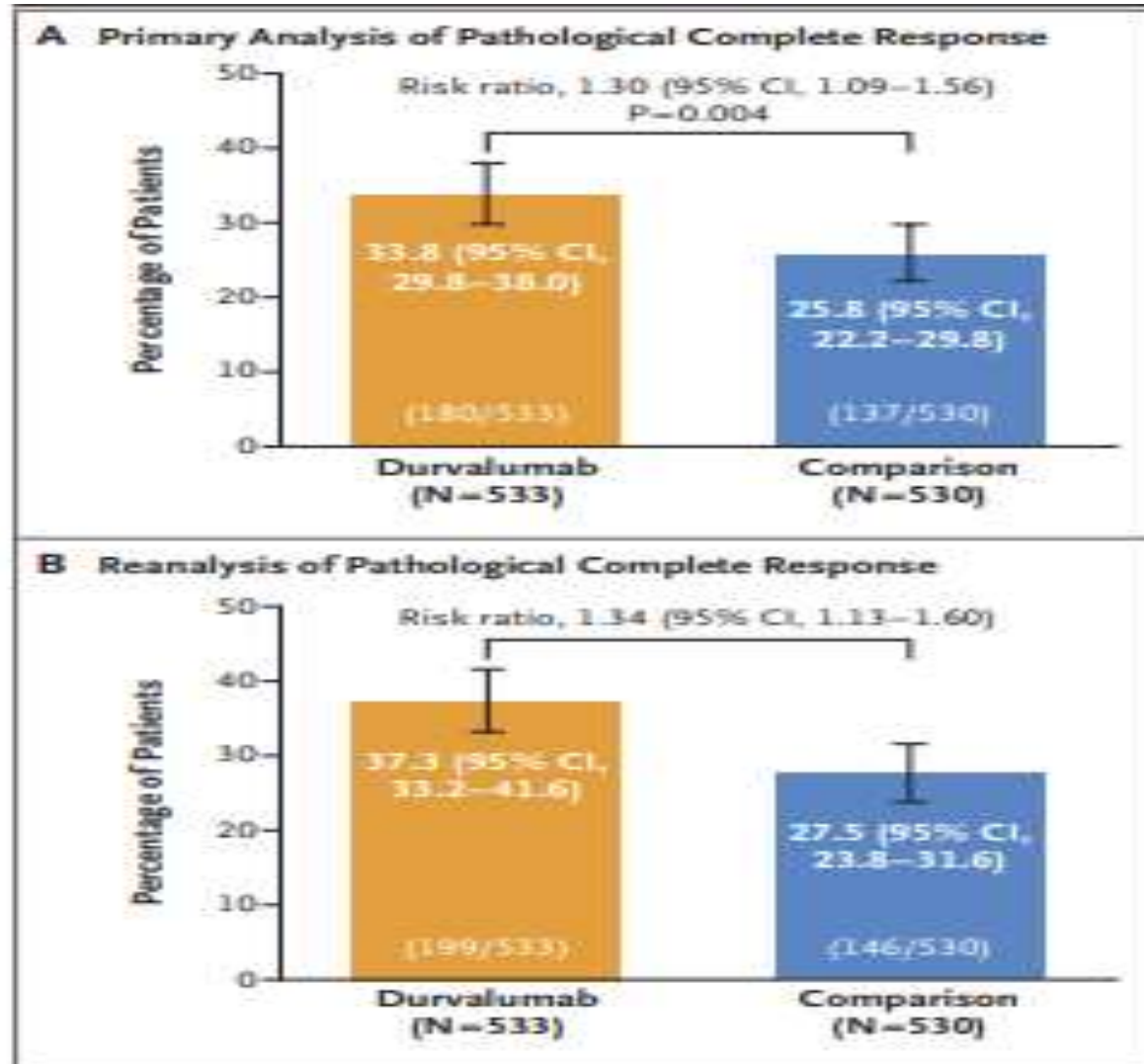


Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan

NIAGARA: Overall Survival (ITT)

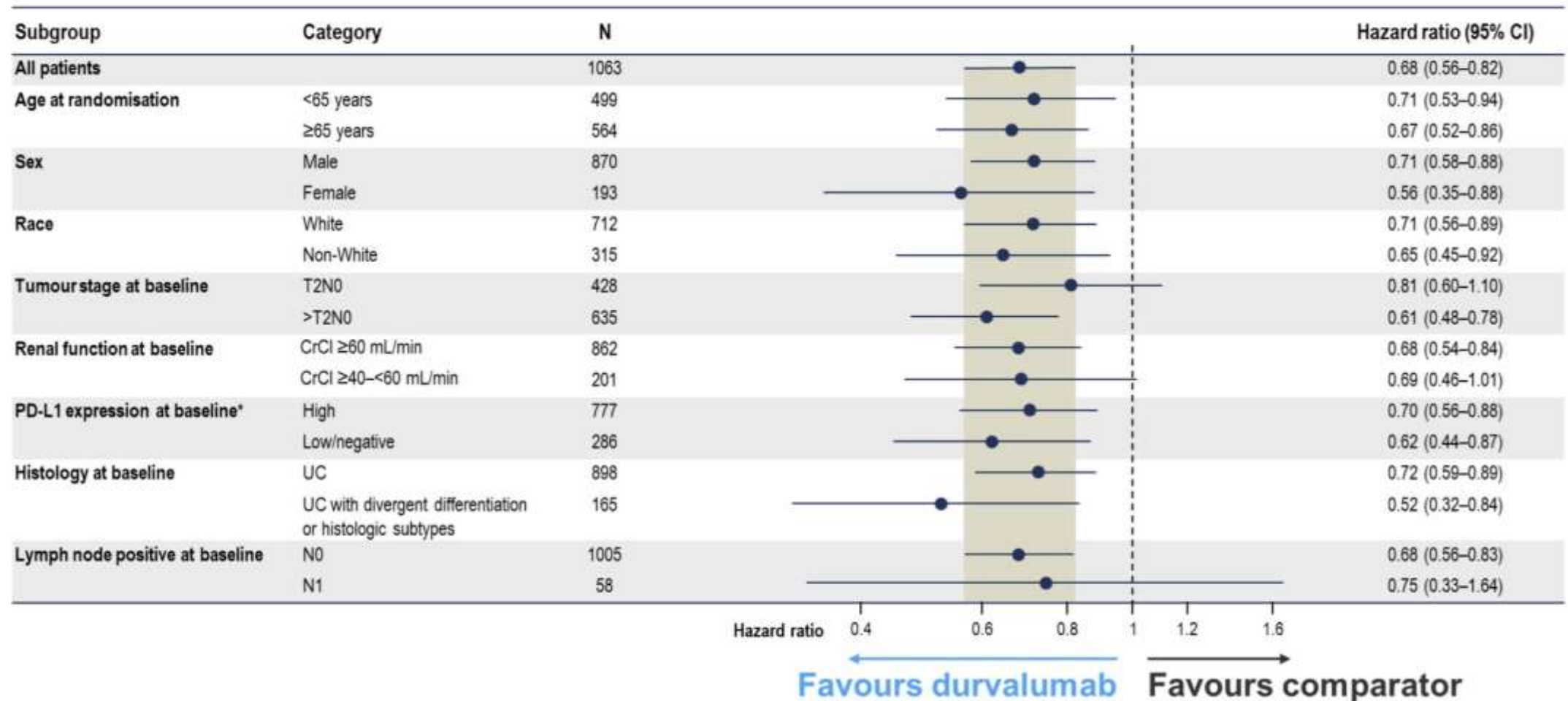


Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan



Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan

NIAGARA: Event-free Survival Subgroup Analyses



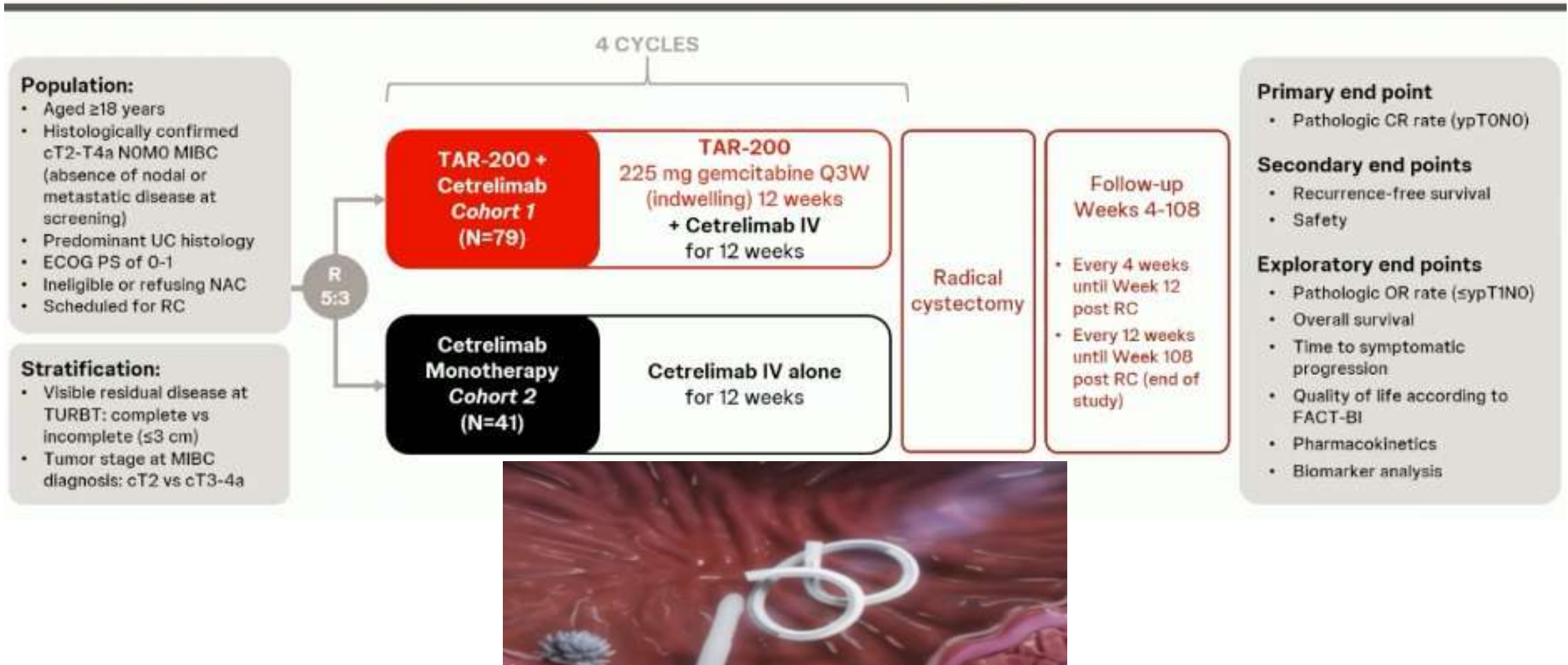
Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan

NIAGARA: AE Summary (Safety Population)

Overall study period (unless otherwise stated)	Durvalumab arm N=530	Comparator arm N=526
AEs of any cause, n (%)	527 (99)	525 (100)
Maximum grade 3 or 4	368 (69)	355 (68)
Serious AEs	326 (62)	287 (55)
Outcome of death	27 (5)	29 (6)
Leading to discontinuation of study treatment	112 (21)	80 (15)
Leading to discontinuation of neoadjuvant durvalumab	50 (9)	---
Leading to discontinuation of NAC	72 (14)	80 (15)
Leading to patient not undergoing RC	6 (1)	7 (1)
Leading to delay in surgery*	9 (2)	6 (1)
Leading to discontinuation of adjuvant durvalumab	30/383† (8)	---
AEs possibly related to any treatment, n (%)[‡]	502 (95)	487 (93)
Maximum grade 3 or 4 (treatment related)	215 (41)	215 (41)
Outcome of death (treatment related)	3 (0.6)	3 (0.6)
Any-grade immune-mediated AEs	111 (21)	16 (3)

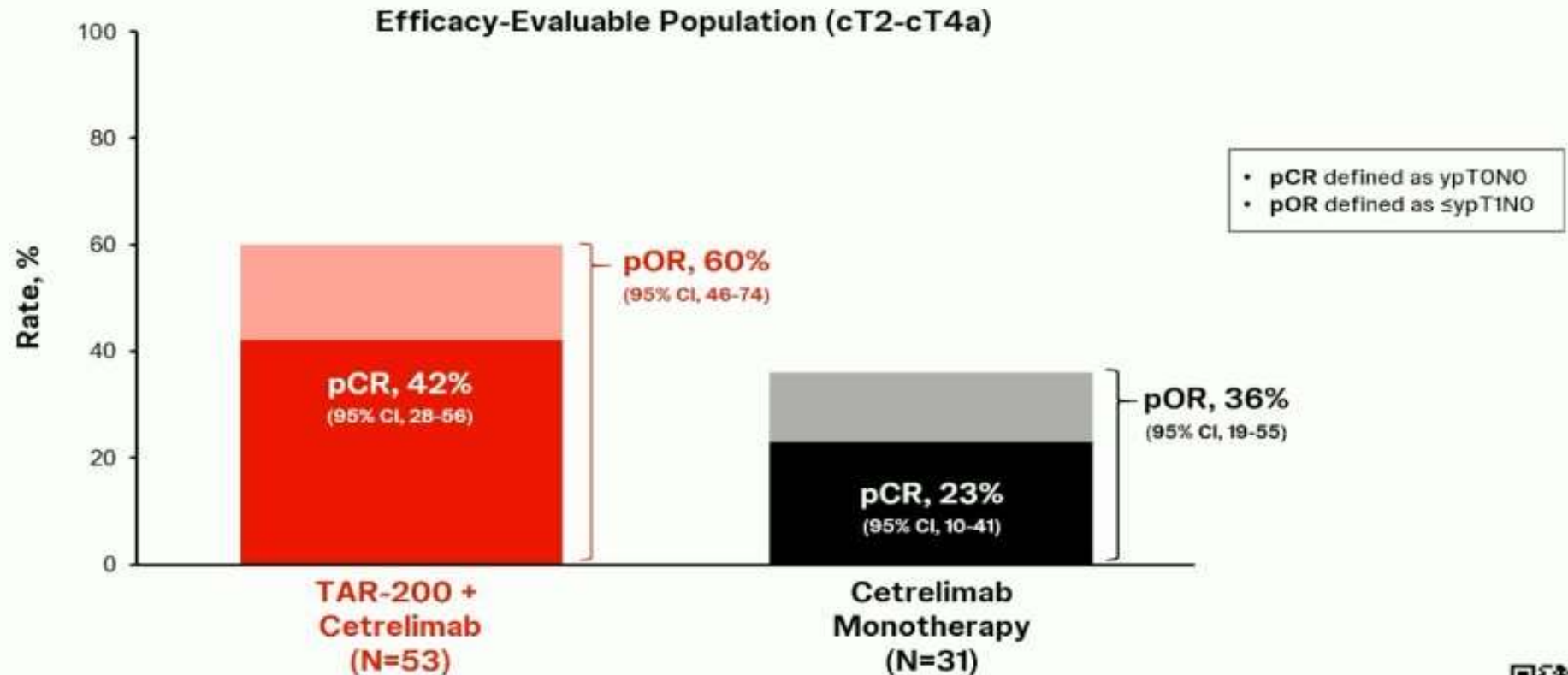
Neoadjuvant TAR-200+immünoterapi kombinasyonu

SunRISe-4: Phase 2b Study of Neoadjuvant TAR-200 + Cetrelimab in Patients With MIBC (cT2-T4a N0M0)



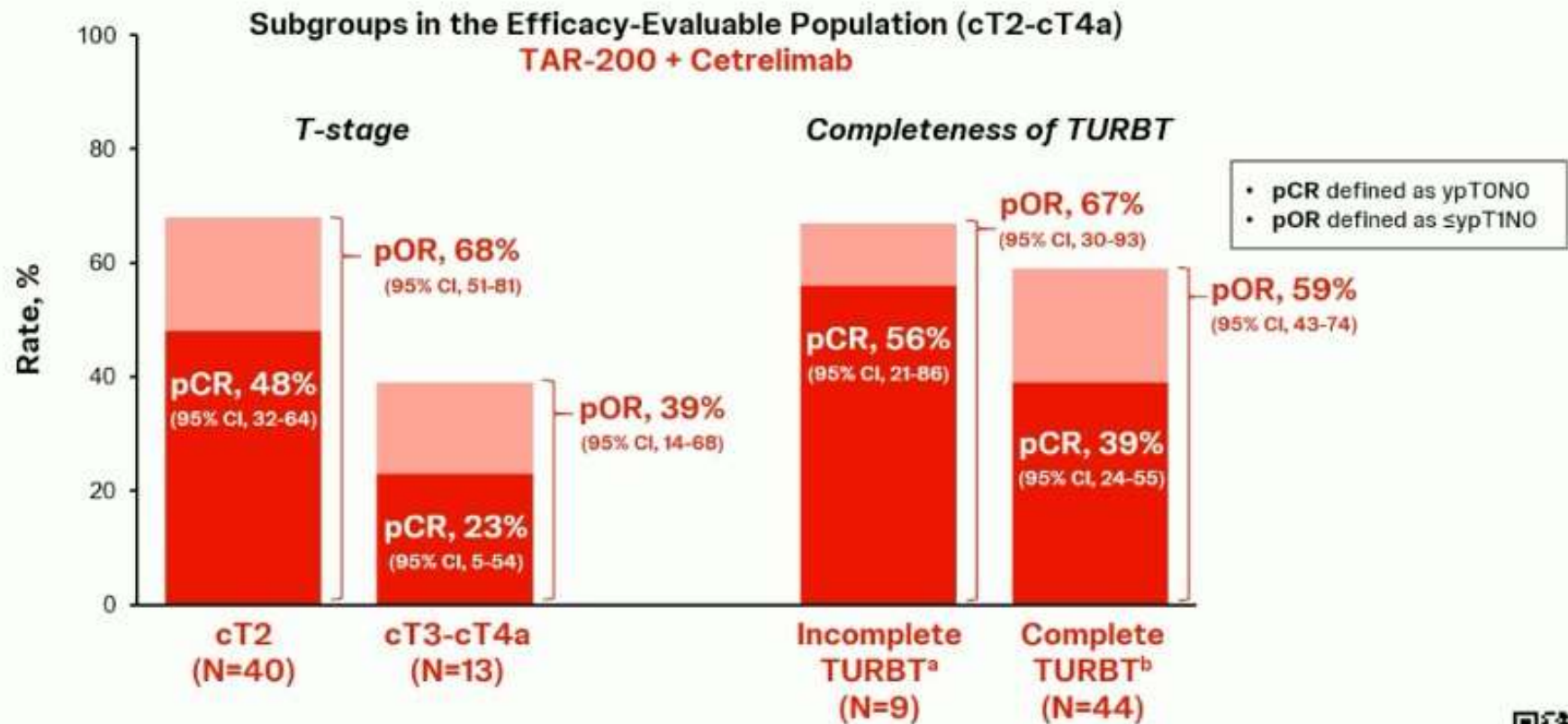
Neoadjuvant TAR-200+immünoterapi kombinasyonu

Neoadjuvant TAR-200 + Cetrelimab Showed Higher pCR and pOR Rates Than Cetrelimab Monotherapy



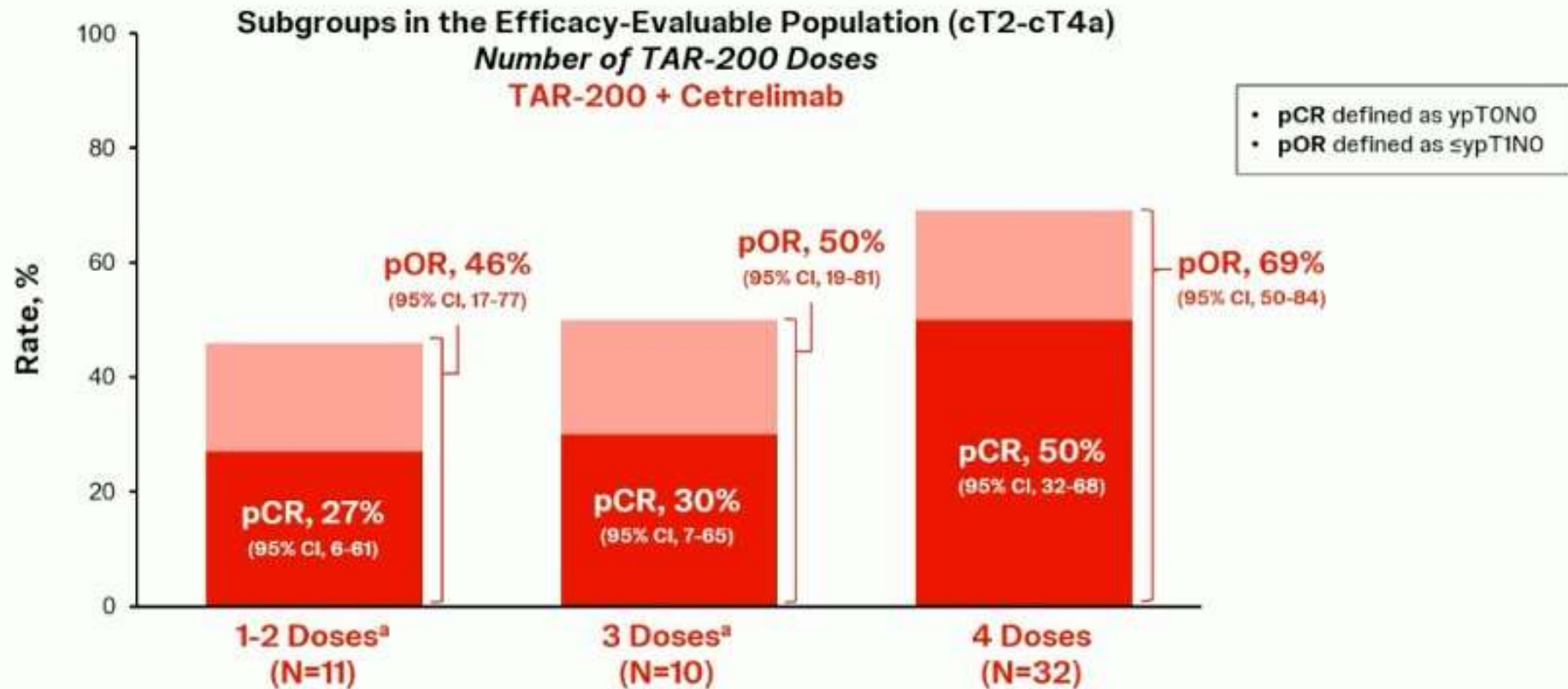
Neoadjuvan TAR-200+immünoterapi kombinasyonu

Efficacy by Clinical Stage and Completeness of TURBT in the TAR-200 + Cetrelimab Cohort



Neoadjuvan TAR-200+immünoterapi kombinasyonu

Efficacy by TAR-200 Dose Exposure

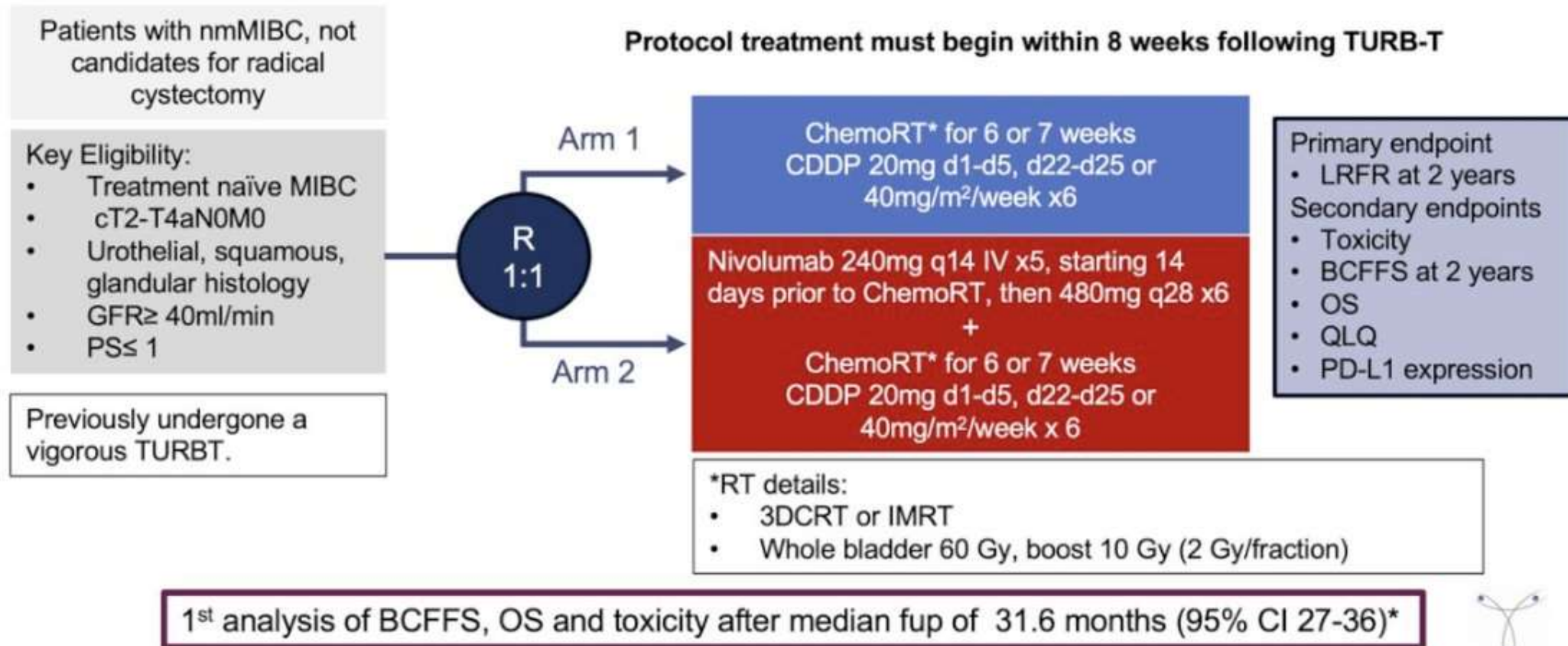


Definitif Radioterapi+kemoterapi+Nivolumab

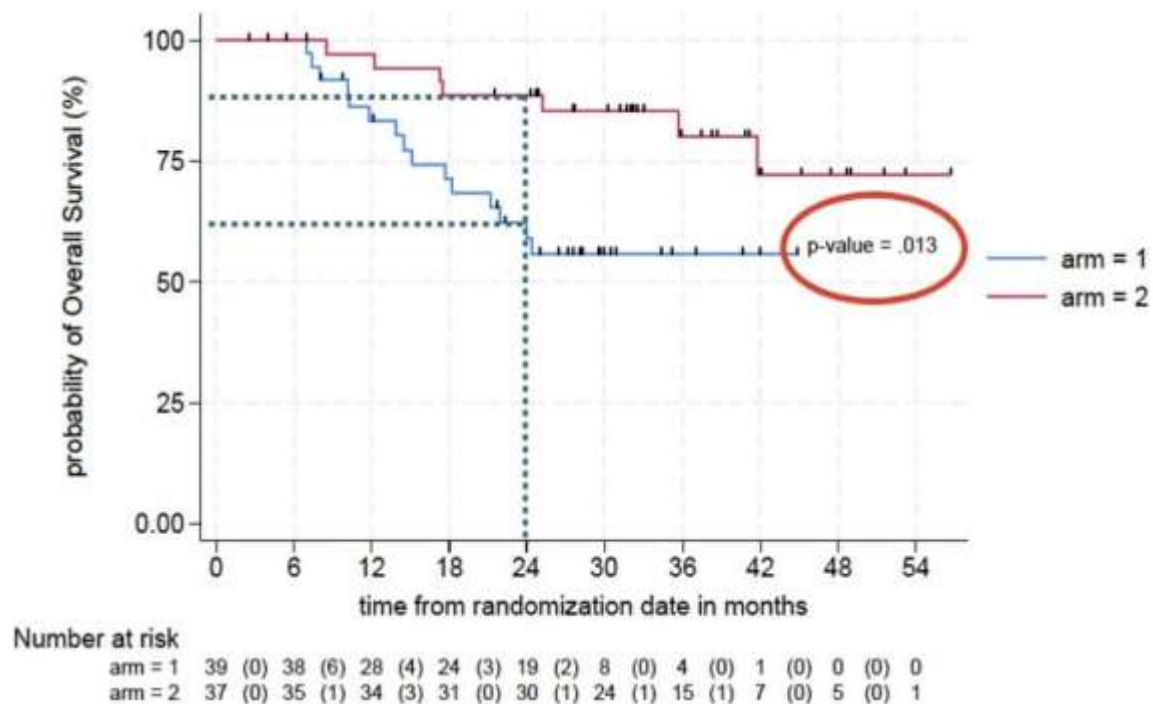
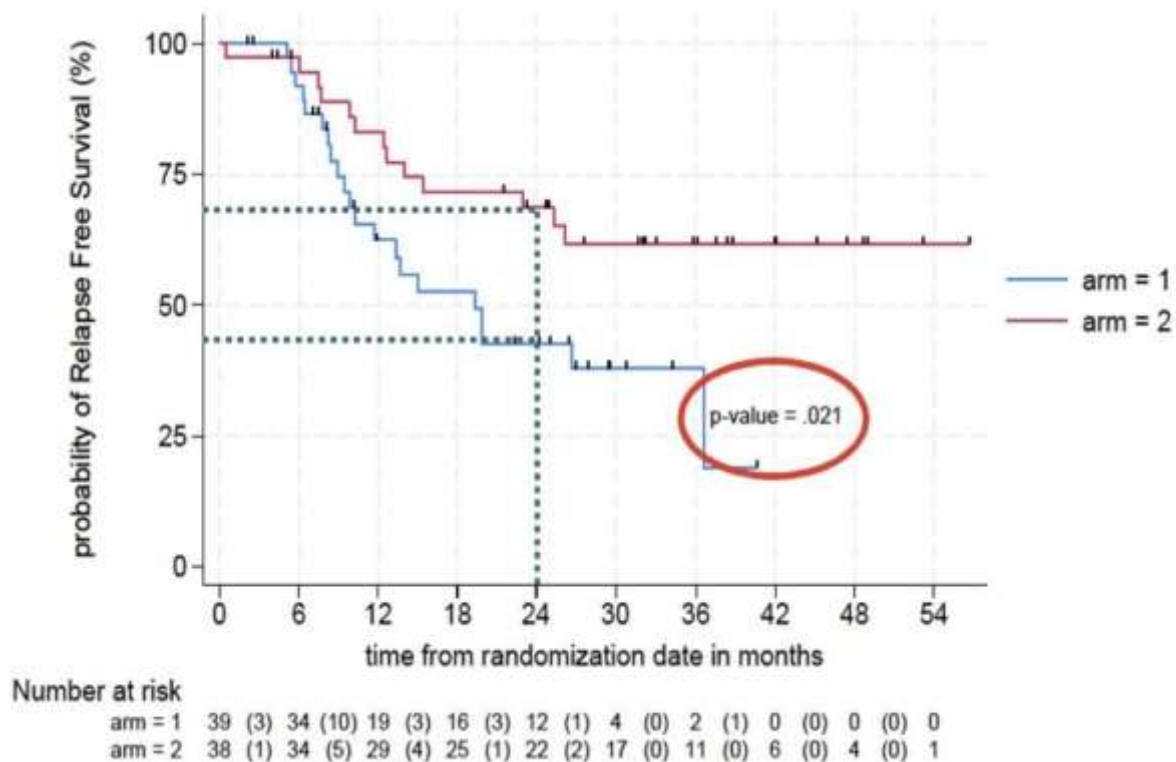


Study Design (NCT03993249)

Nivolumab Plus Chemoradiotherapy in Patients With nmMIBC Not Undergoing Cystectomy



Definitif Radioterapi+kemoterapi+Nivolumab



Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Select *FGFR* Aberrations

Video Placeholder
(delete in Slide Master
if not needed)
2.5 x 1.41" (6.35 x 2.82 cm)
Placed in the top right corner

Cohort 1

Key eligibility criteria

- Age ≥ 18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- Prior tx with anti-PD-(L)1
- 1-2 lines of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)^a
- ECOG PS 0-2

1:1
N=266^b

R

Erdafitinib (n=136)

Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

Chemotherapy of Choice (n=130)

docetaxel or vinflunine once every 3 weeks

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

Primary end point:

- OS

Key secondary end points:

- PFS
- ORR
- Safety

NCT03390504

^aMolecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥ 1 of the following translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C.

^bNumber of patients randomized at the time of the interim analysis (data cutoff January 15, 2023).

ECOG PS, Eastern Cooperative Oncology Group performance status; *FGFR*, fibroblast growth factor receptor; *FGFR3/2alt*, *FGFR3/2* alterations; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.



Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

Table. Primary and Secondary Outcomes From the THOR Trial

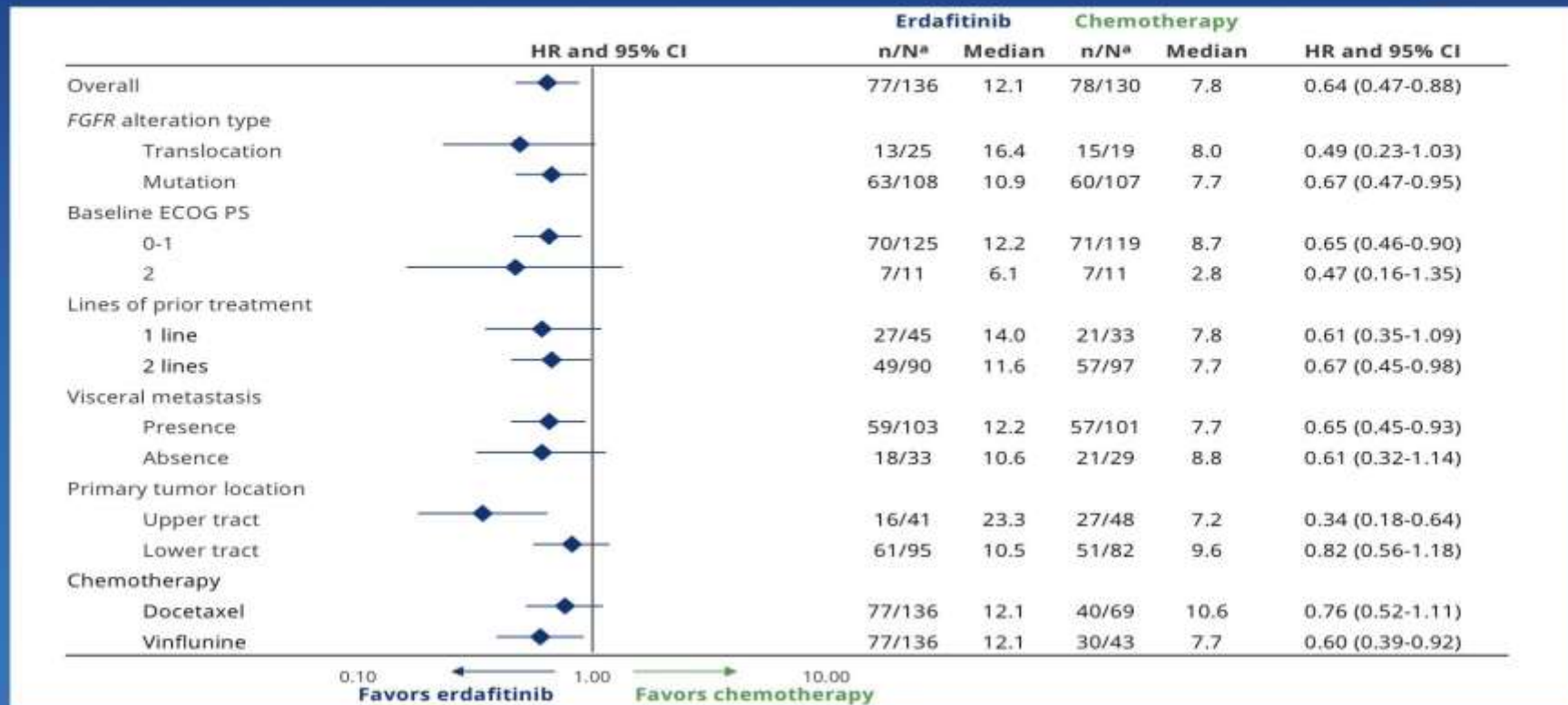
	Erdafitinib (136 patients)	Chemotherapy (130 patients)
OS, median (95% CI), mo	12.1	7.8
HR (95% CI)	0.64 [0.47, 0.88]; <i>P</i> = .005	
PFS, median (95% CI), mo	5.6	2.7
HR (95% CI)	0.58 [0.44, 0.78]; <i>P</i> = .0002	
ORR, %	45.6	11.5
RR (95% CI)	3.94 [2.37, 6.57]; <i>P</i> < .001	

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RR, relative risk.[View larger](#)

Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

Overall Survival Benefit With Erdafitinib Versus Chemotherapy Was Consistently Observed Across Subgroups

Video Placeholder
(delete in Slide Master
if not needed)
2.5 x 1.41" (6.35 x 2.82 cm)
Placed in the top right corner

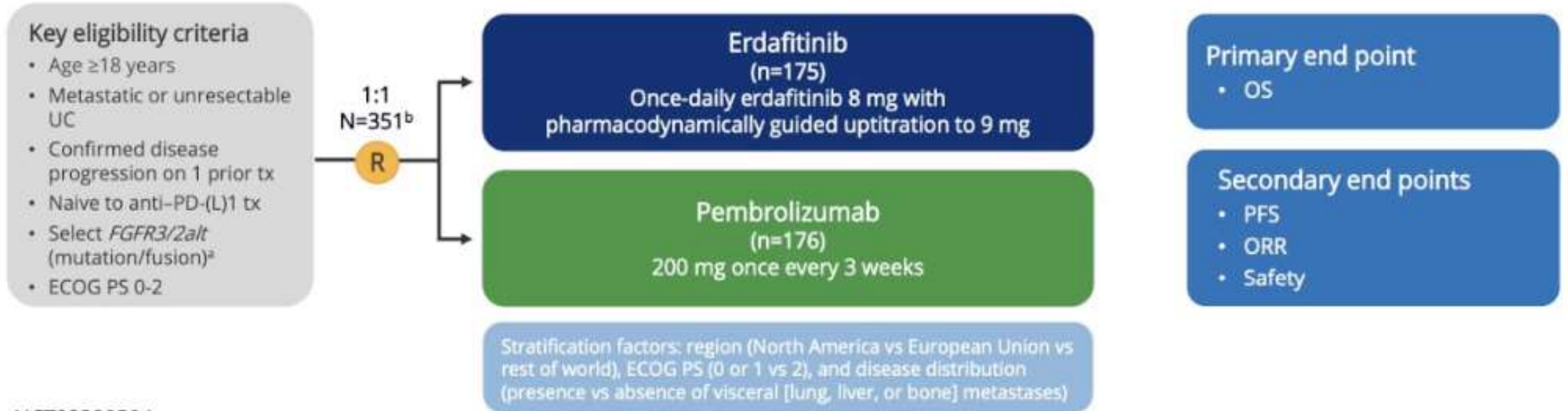


*n=number of events; N=number of patients in subgroup. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.



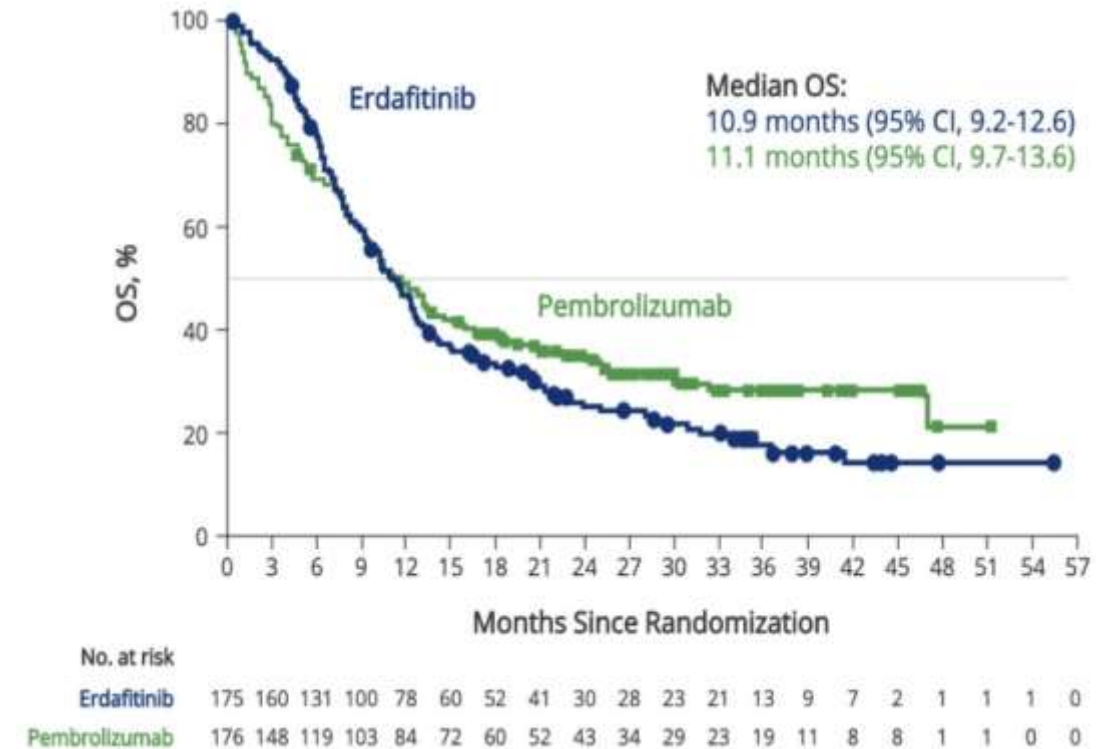
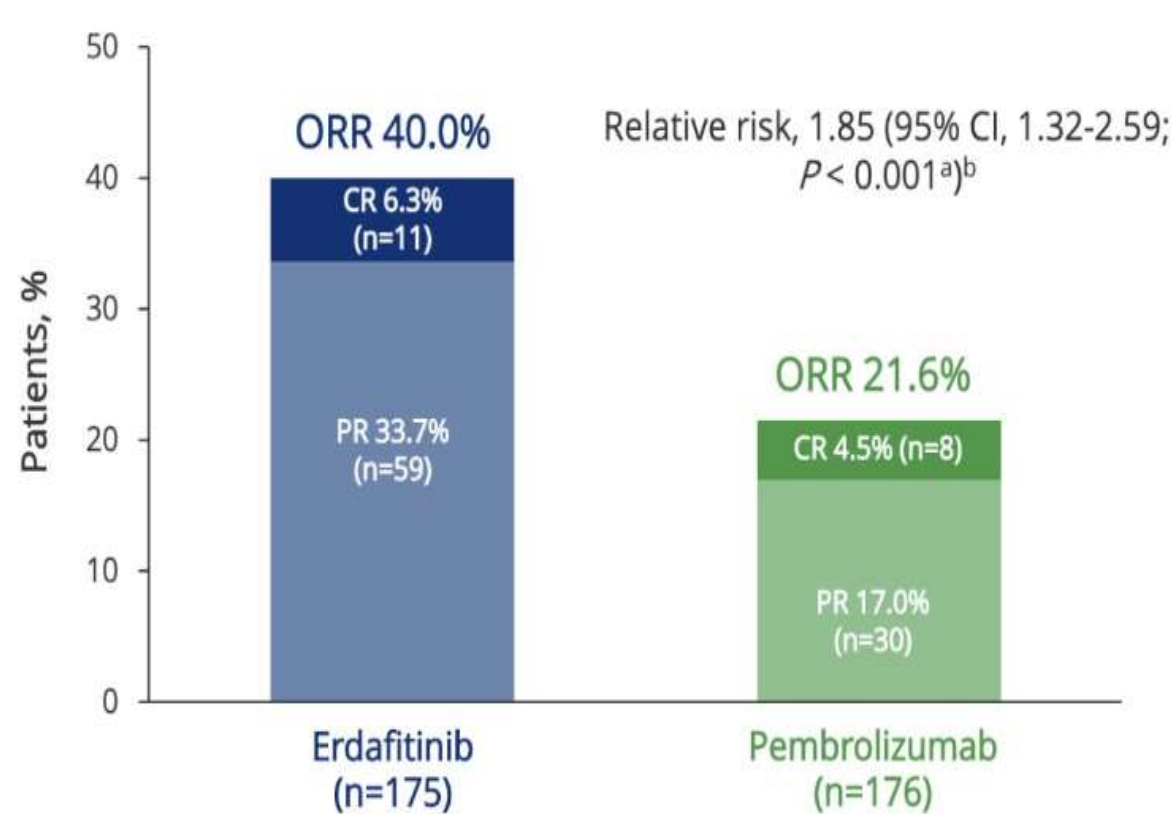
Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

Cohort 2



NCT03390504

Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi



Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 4.2024 Bladder Cancer

[NCCN Guidelines Index](#)
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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 • 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

Adjuvan Seçenekler

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

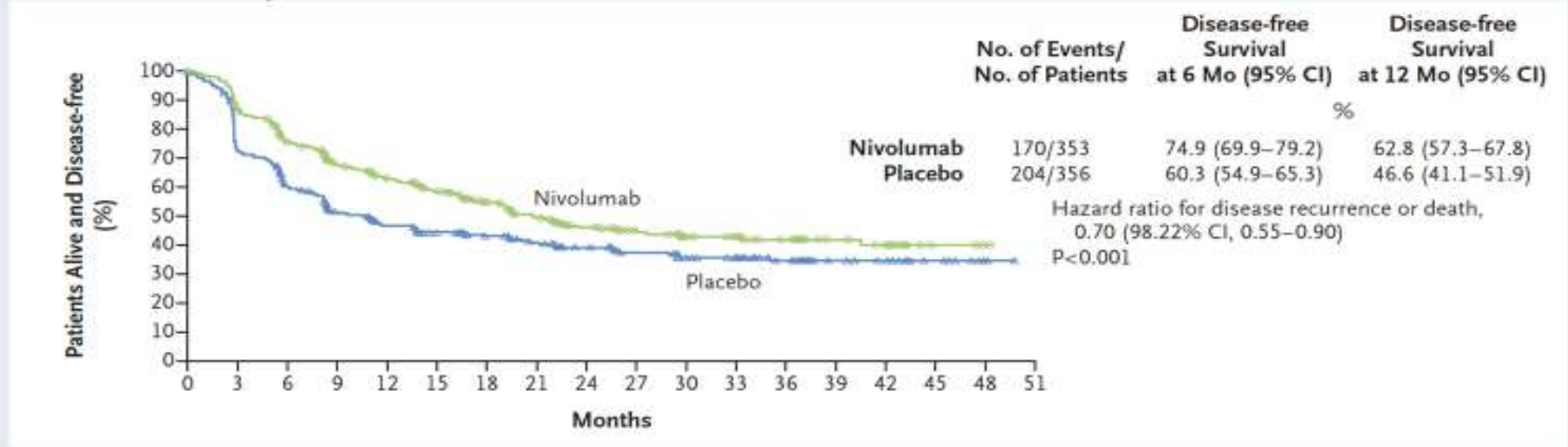
Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebrecht, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette, K. Unsal-Kacmaz, E. Broughton, D. Zardavas, H.B. Koon, and M.D. Galsky

***N Engl J Med* 2021 June 3;384:2102-14.**

Adjuvan Seçenekler

CheckMate 274: Disease-Free Survival in the ITT Population



Bajorin DF et al. *N Engl J Med* 2021;384:2102-14.



Neoadjuvan tedavi sonrası $\geq pT2+/- \geq pN+$ adjuvan nivolumab 12 ay kullanımı nüks riskini ortalama %30 düşürüyor

Adjuvan Seçenekler

A031501 AMBASSADOR: Study Design

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



Key Eligibility

- Muscle-invasive urothelial carcinoma: bladder, urethra, renal pelvis, ureter
 - Post-radical surgery (cystectomy, nephrectomy, nephroureterectomy, or ureterectomy) ≥ 4 but ≤ 16 weeks
 - Post-neoadjuvant chemotherapy and $\geq$ ypT2 and/or yN+ and/or margins
- OR
- cisplatin-ineligible or refusing and $\geq$ pT3 and/or pN+ and/or +margins

Stratify

- PD-L1 status*
- Neoadjuvant chemo yes/no
- Pathologic stage:
 - pT2/3N0 or Nx
 - pT4N0 or Nx
 - pTany N+ (any)
 - + Surgical margins

N=739

Enrolled N=702

R
1:1

Pembrolizumab
200 mg q3W
1 year

Observation

NCT03244384

Early closure due to US FDA approval of nivolumab high-risk MIUC after surgery

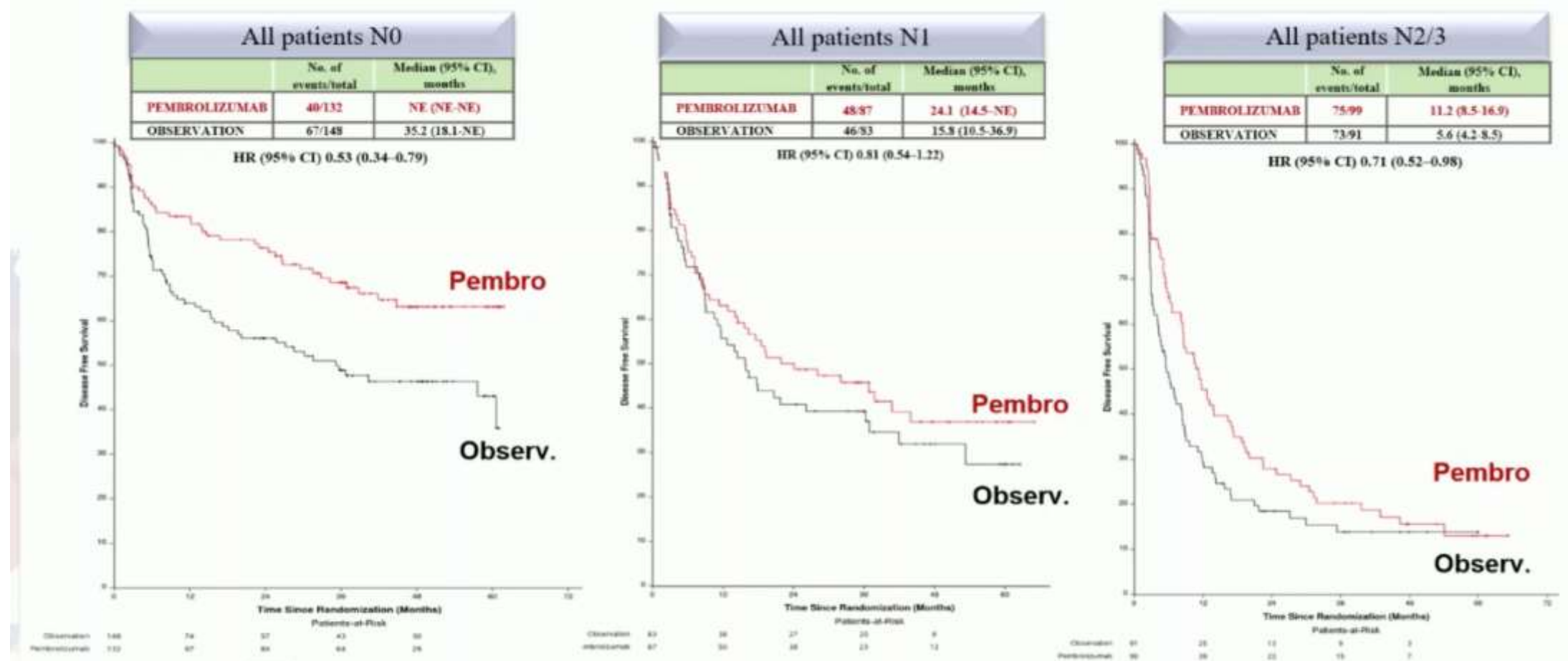
Dual Primary Endpoints

- Disease-free survival
- Overall survival

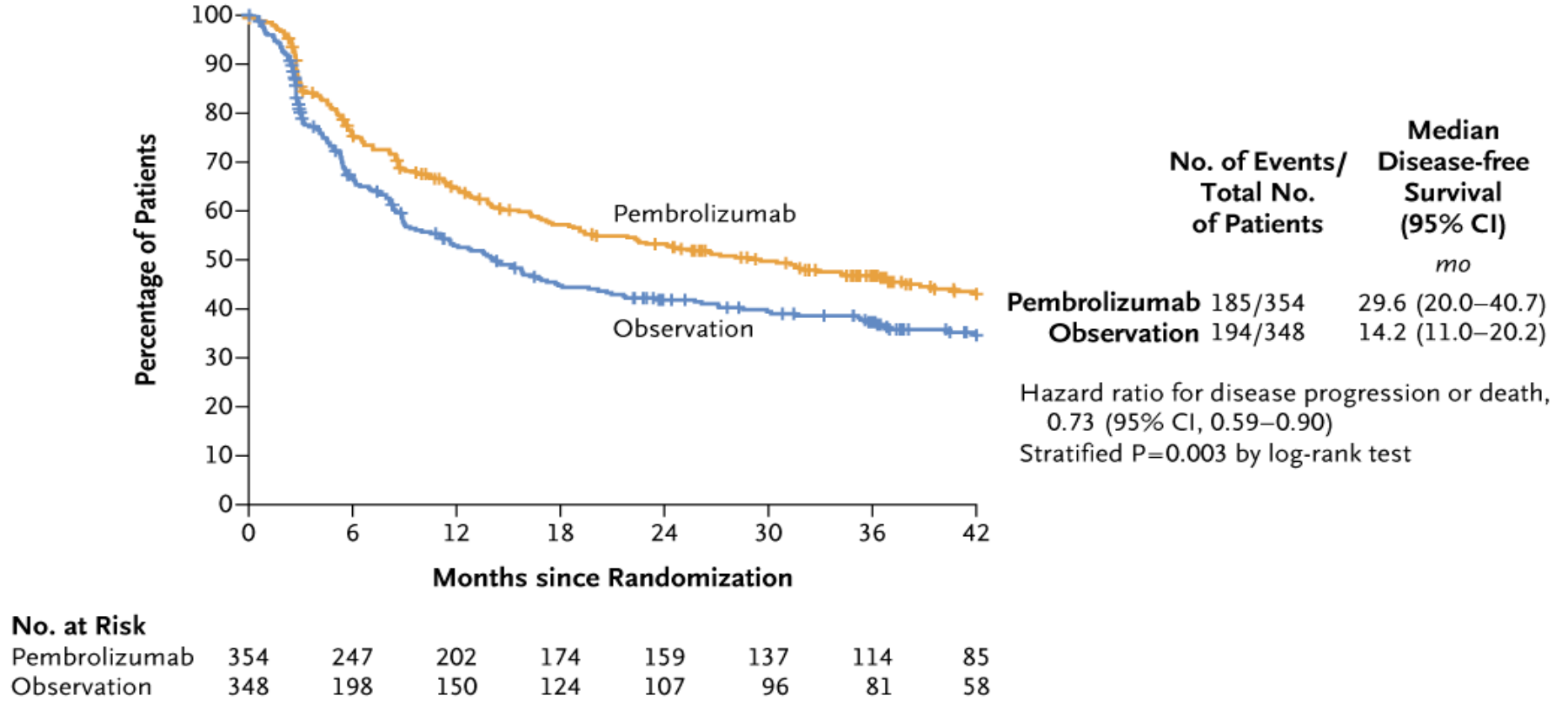
34% of patients in the observation arm vs 20% in the pembro arm received a non-protocol checkpoint inhibitor or withdrew consent

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

Adjuvan Seçenekler



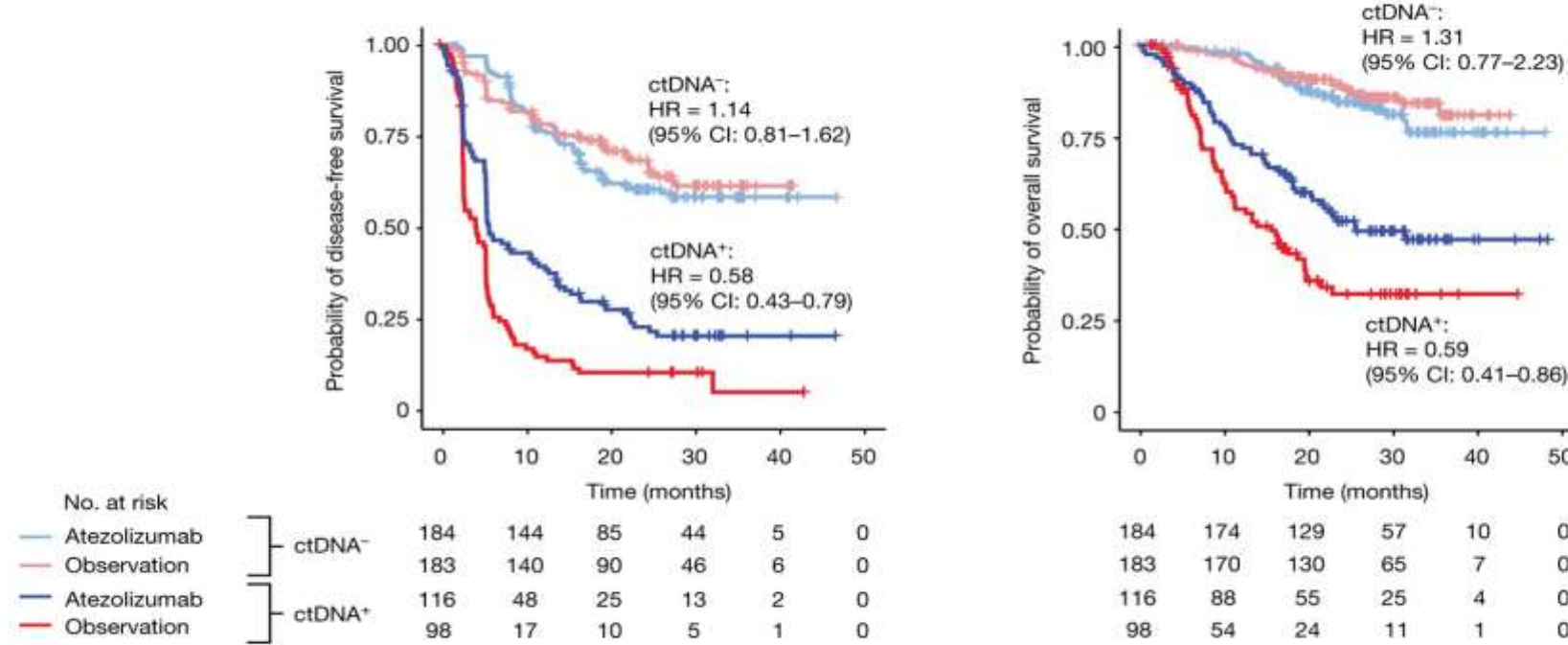
Adjuvan Seçenekler



Neoadjuvan tedavi sonrası $\geq pT2 \geq +/- pN+$ adjuvan pemrolizumab 12 ay kullanımı nüks riskini ortalama %30 düşürüyor

Gelecek Perspektif

Can ctDNA help Guide Adjuvant Therapy ?

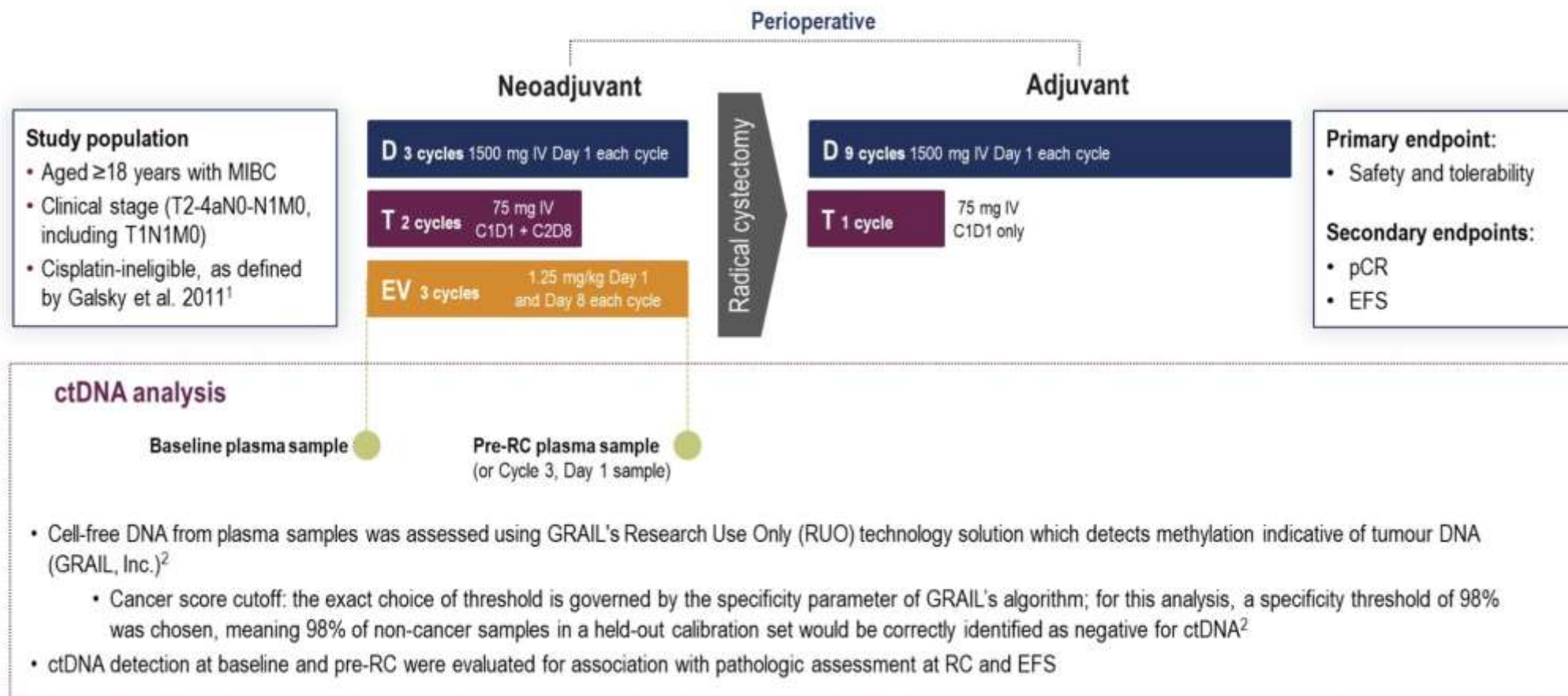


Powles, Nature, 2021

IMvigor010 çalışmasının alt analizi, neoadjuvan sonrası ctDNA pozitif olan hastalarda Atezolizumab nüks ve ölüm oranını yaklaşık %40 azaltıyor

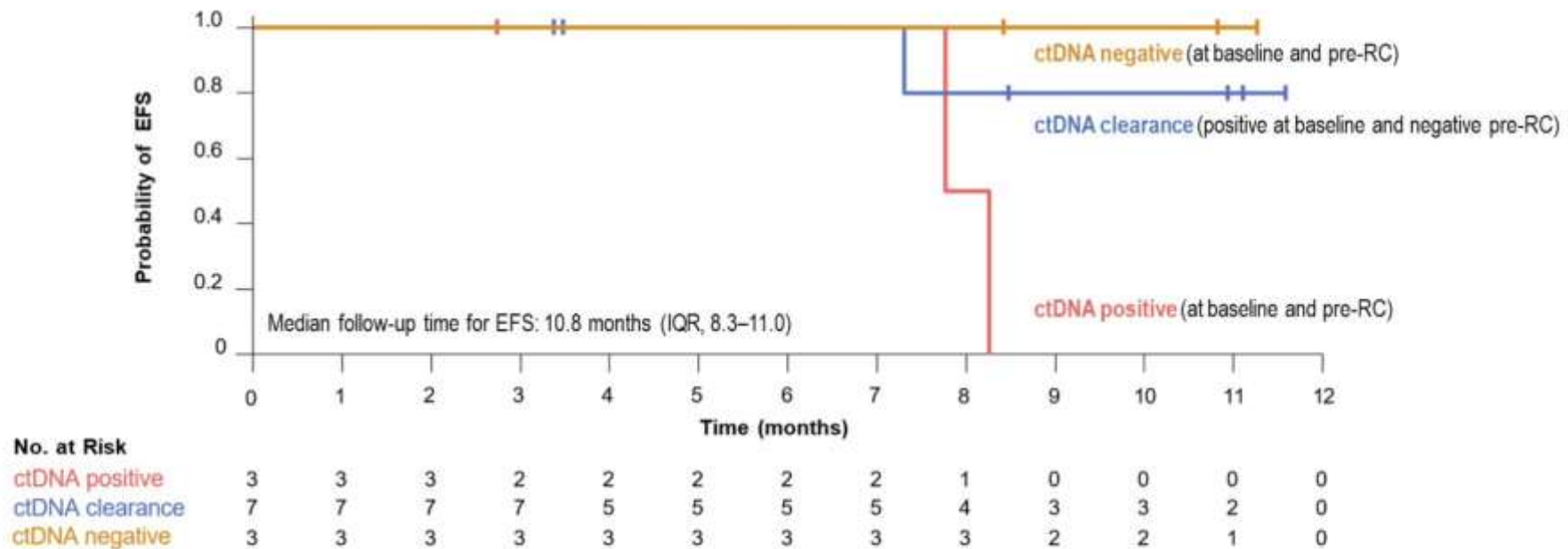
Gelecek Perspektif

VOLGA safety run-in design and ctDNA analysis



Gelecek Perspektif

ctDNA clearance and its association with EFS



- EFS was assessed in 13 patients who completed RC; 10 were ctDNA-positive at baseline, and 3 were ctDNA-negative at baseline
- Longer EFS was observed in the **ctDNA clearance** and **ctDNA negative** groups compared with the **ctDNA positive** group

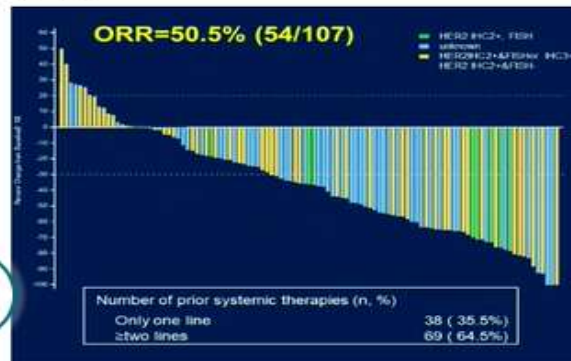
Gelecek Perspektif

Does CPI combine best with ADCs with MMAE payloads?

Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

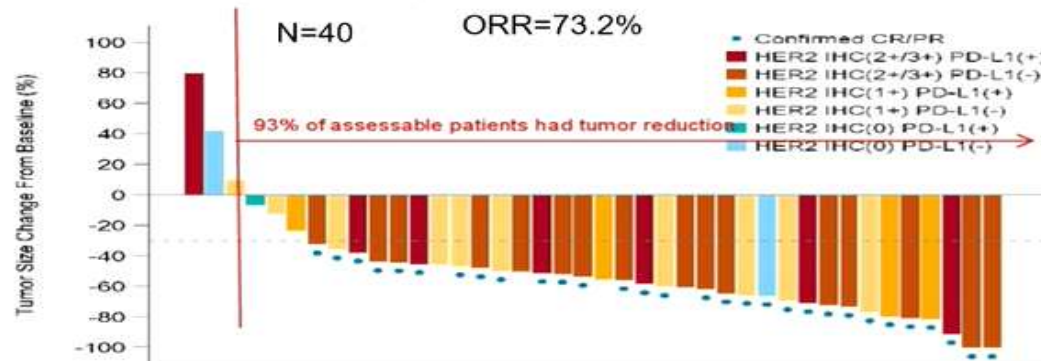
Disitamab vedotin

N=107 In the Second or Third-line setting



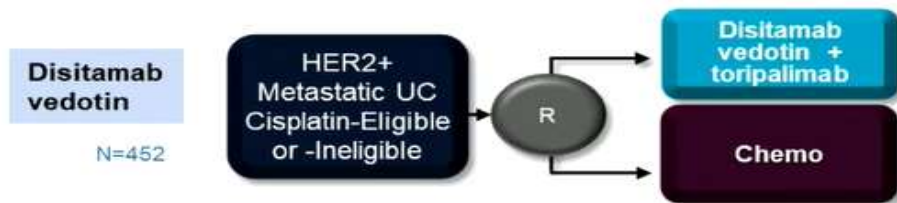
Sheng, et al. ASCO 2022 abstract 4518

Disitamab vedotin + toripalimab



Sheng, X., et al. ASCO 2023

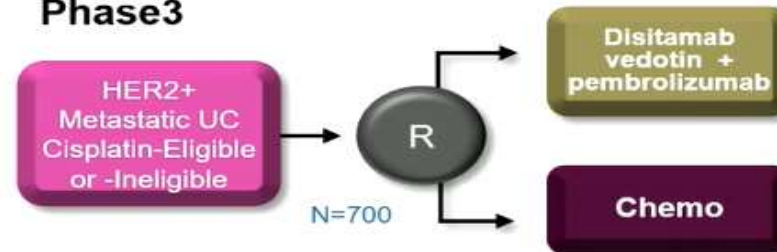
Phase 3



Presented by Andrea B. Apolo, MD

@apolo_andrea

Phase3



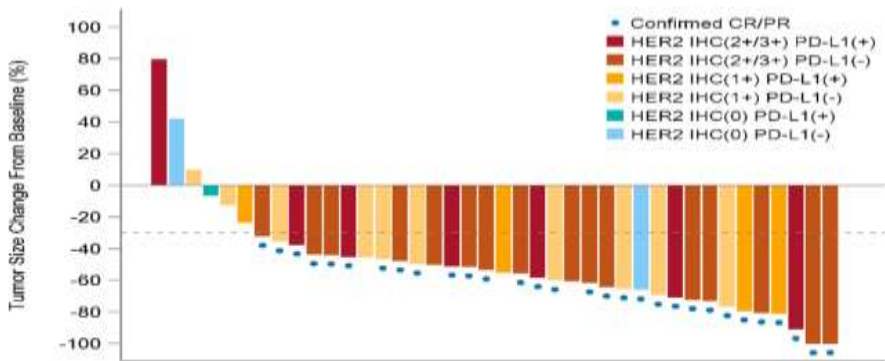
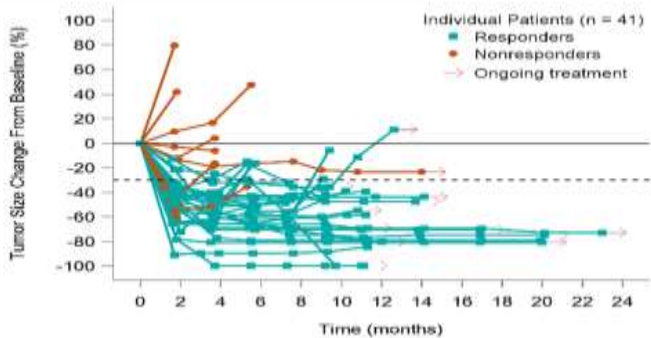
Gelecek Perspektif

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%

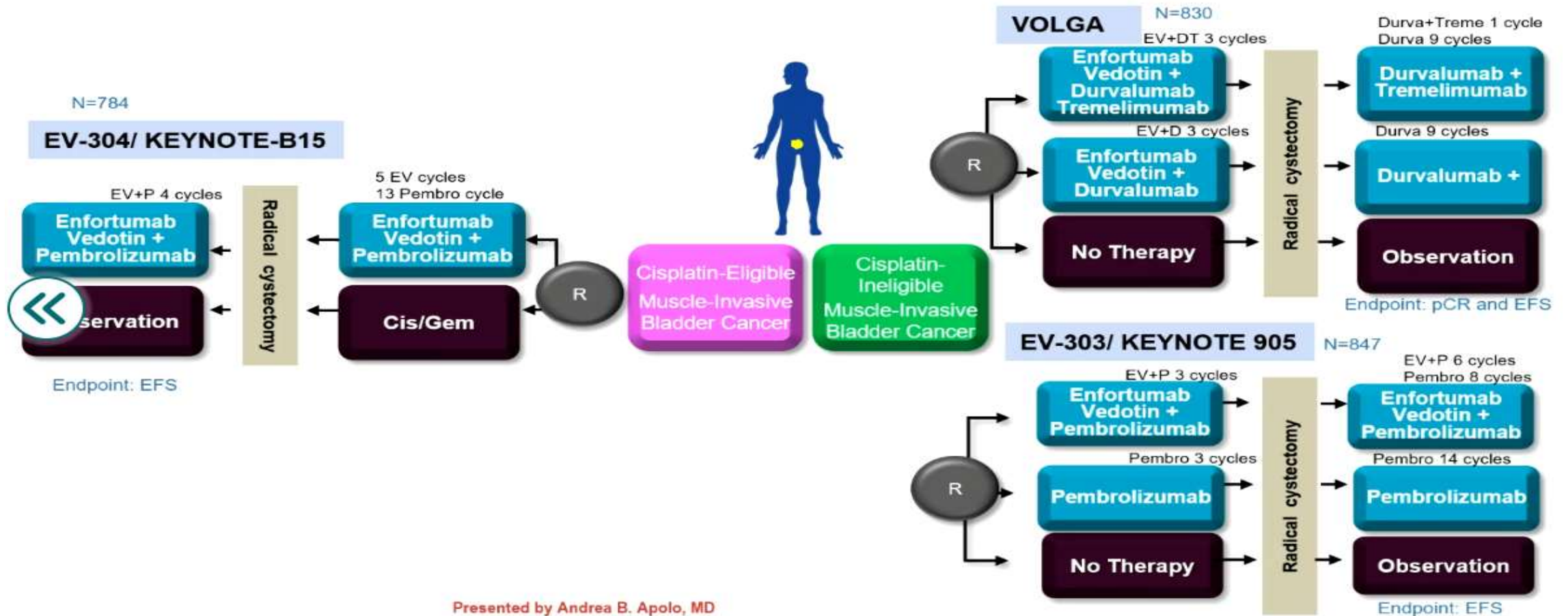
cORR by HER2 and PD-L1 Expression Status		
	PD-L1 (+)	PD-L1 (-)
HER2 IHC 2+, 3+	75% (n=8)	87.5% (n=16)
HER2 IHC 1+	50% (n=4)	70% (n=10)
HER2 IHC 0	0 (n=1)	50% (n=2)



Sheng, et al. Abs 4566, ASCO 2023.

Gelecek Perspektif

What is the efficacy of EV+CPI as Neoadjuvant or Adjuvant Therapy for MIBC?

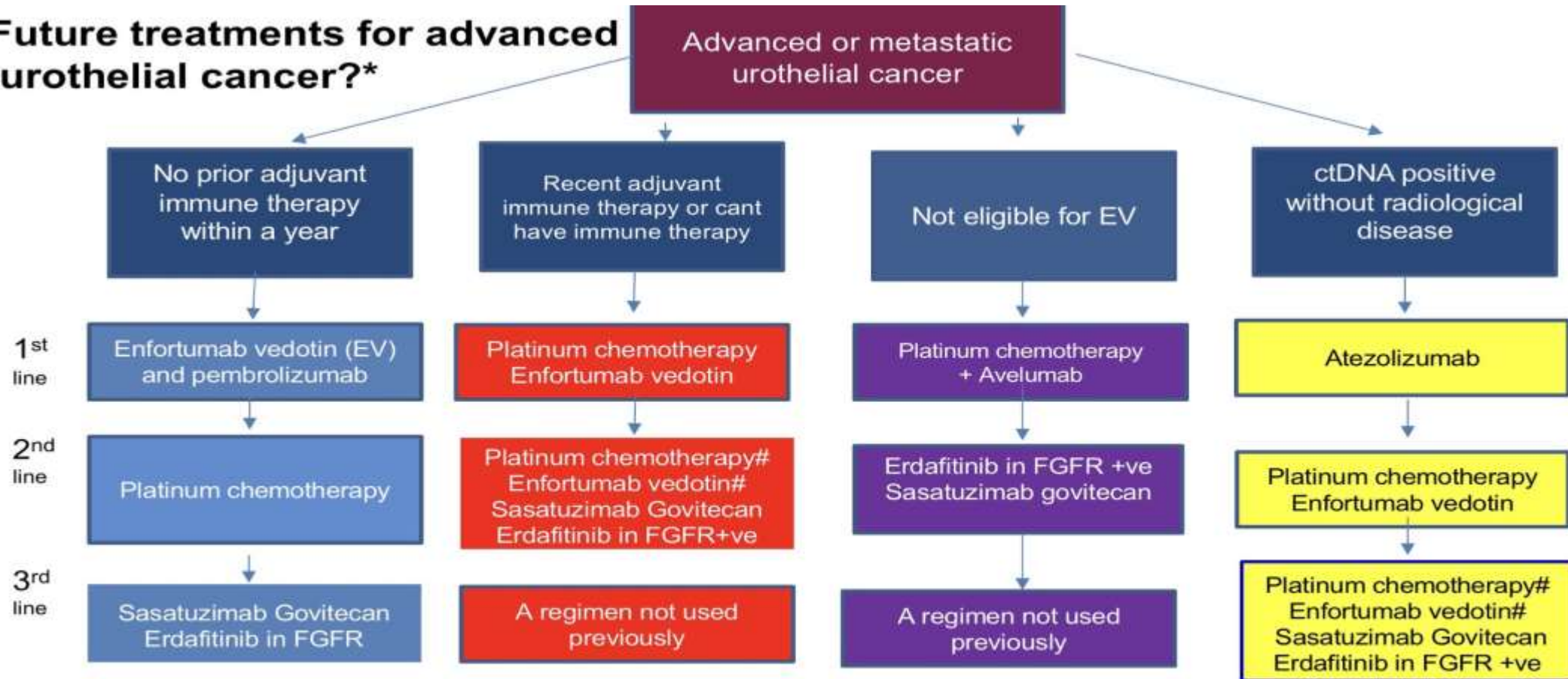


Presented by Andrea B. Apolo, MD

✉ @apolo_andrea

Gelecek Perspektif

Future treatments for advanced urothelial cancer?*



*Assuming EV302 (EV/pembro), TROPICs (SG), IM011 (ctDNA+ve), THOR are +ve for OS
unless given previousl

Sonuç

- ❑ Enfortumab vedotin +pembrolizumab sisplatin uygunluğundan bağımsız standart tedavi
- ❑ Evre IV mesane kanserinde birinci basamak tedavide sisplatin+gemsitabin+nivolumab bir seçenek
- ❑ Platin bazlı kemoterapi sonrası klinik yarar(CR/PR/SD) gören hastalarda idame tedavi olarak Avelumab bir seçenek
- ❑ Sisplatin alamayacak hastalarda carboplatin+ gemsitabin kemoterapi kombinasyonu klinik yarar alanlarda Avelumab idame tedavi olarak bir seçenek
- ❑ Platin bazlı kemoterapi alamayacak hastalarda birinci basamak tedavide (ECOG PS $\geq$ 2, komorbidite vs.) PD-L1 düzeyinden bağımsız Pemrolizumab önerilebilir