Metastatik Mesane ve Üst Üriner Sistem Kanserlerinde Klinik Pratiğimizi Değiştiren Çalışmalar

Dr. Deniz Tural
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

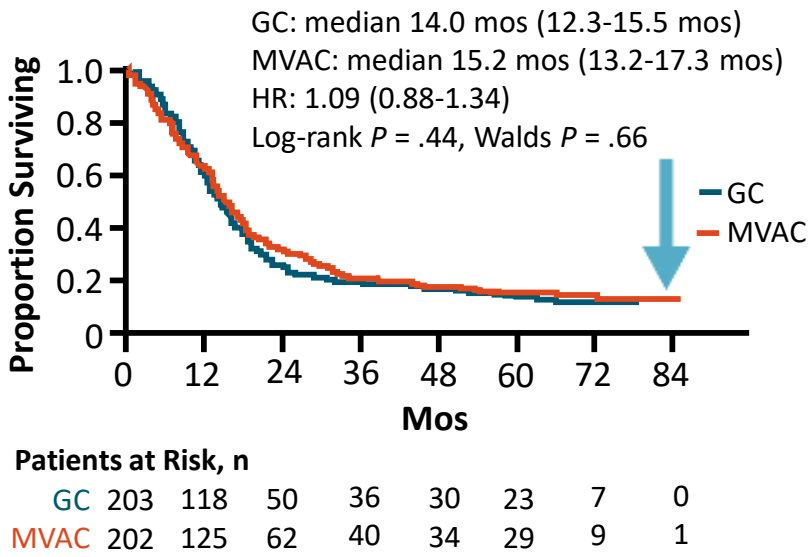
Study (year of publication)	*n*	Interventions	Response rate (%)	Median OS (months)	Toxicity
Logothetis *et al.*[36] (1990)	110	MVAC versus CISCA	65 versus 46; $P<0.05$	15.5 versus 10.1; $P=0.0003$	MVAC>CISCA
Loehrer *et al.*[37] (1992)	269	MVAC versus cisplatin	39 versus 12; $P<0.0001$	12.5 versus 8.2;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

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

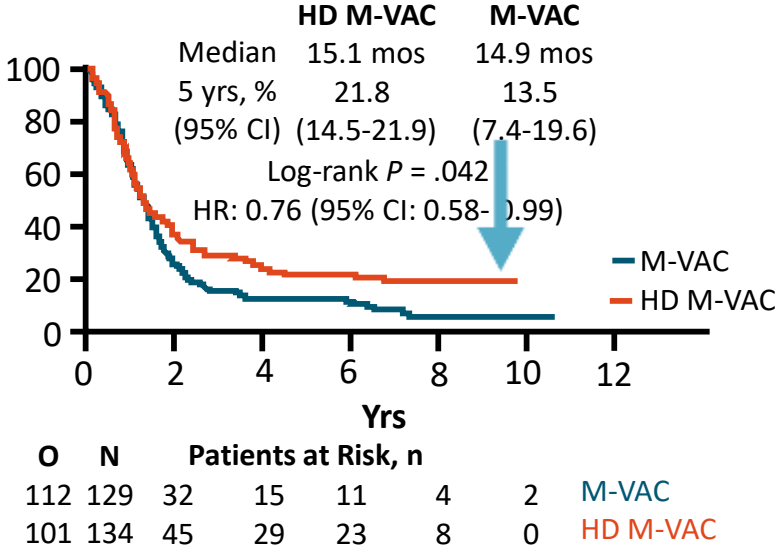
Metastatik Birinci Basamak Kemoterapi Sonuçları

Sisplatin Uygun

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

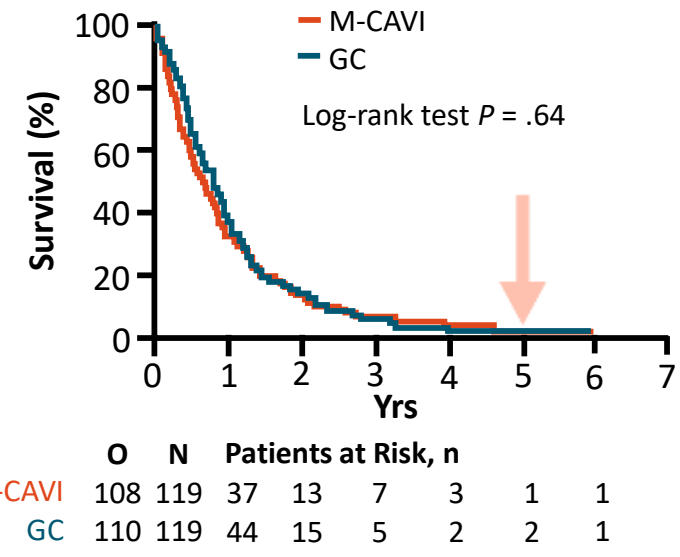


Dose Dense MVAC[3]
ORR: 72%
CR: 25%
Median OS: 15.1 mos



Sisplatin uygun değil

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



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

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

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: C Pfister - 5-y OS Vesper

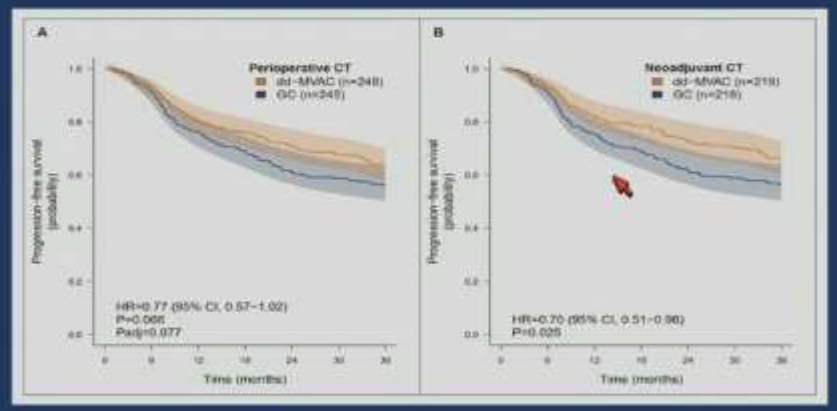
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

2023 ASCO ANNUAL MEETING

Hangi Kemoterapi Rejimi ? dd-MVAC/GC

PFS at 3 years

ESMO congress 16-21 September 2021



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

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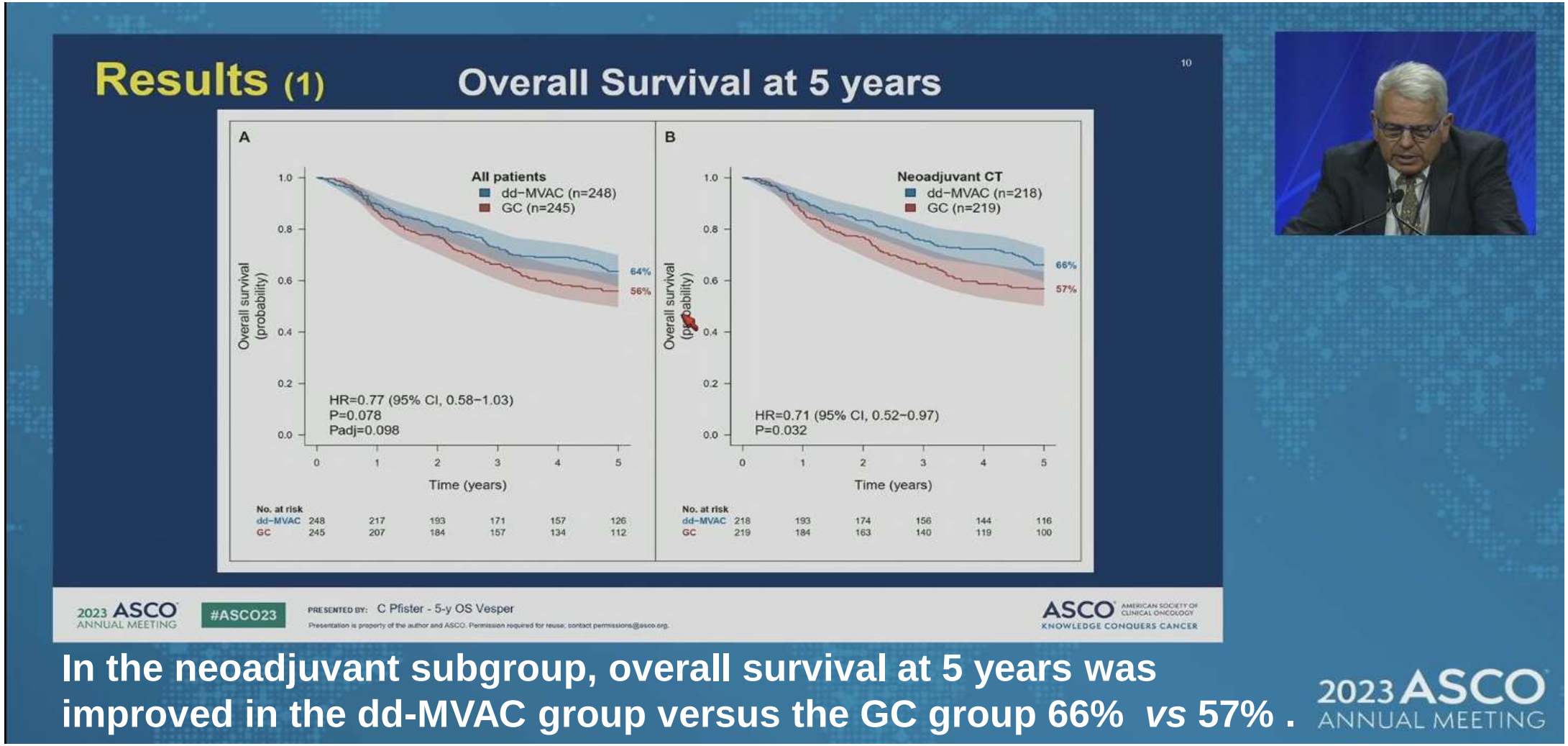
2023 ASCO ANNUAL MEETING

Hangi Kemoterapi Rejimi ? dd-MVAC/GC



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

Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçimi

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Bladder Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

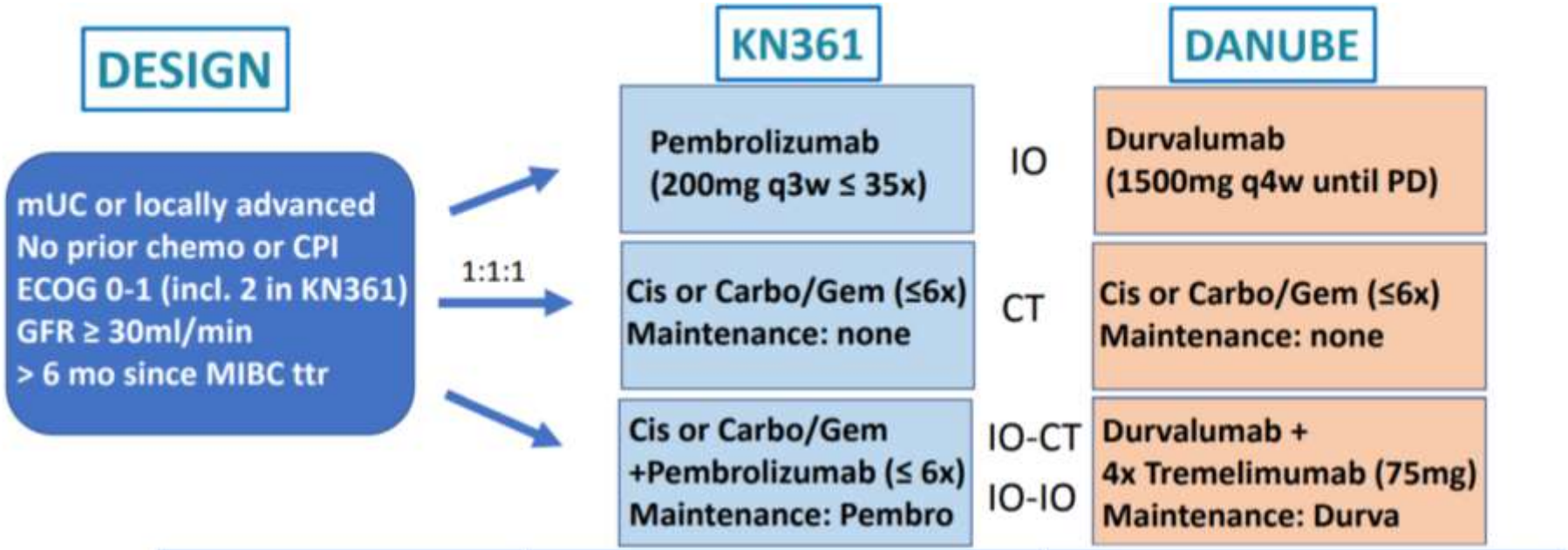
First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Pembrolizumab and enfortumab vedotin-ejfv[15] (category 1) **Other recommended regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy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

Sisplatin Kombinasyonlu Kemoterapiye Uygun Olmayan Hasta Grubu

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

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

Metastatik 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)

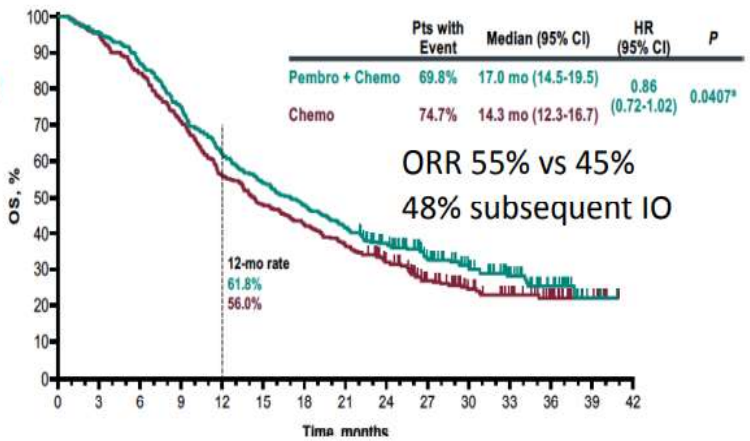
Metastatik Mesane Kanseri Birinci Basamak
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

Overall survival

Combination vs Chemo

TOTAL population (ITT)

KEYNOTE 361 –IO-CT vs CT (1˚EP)

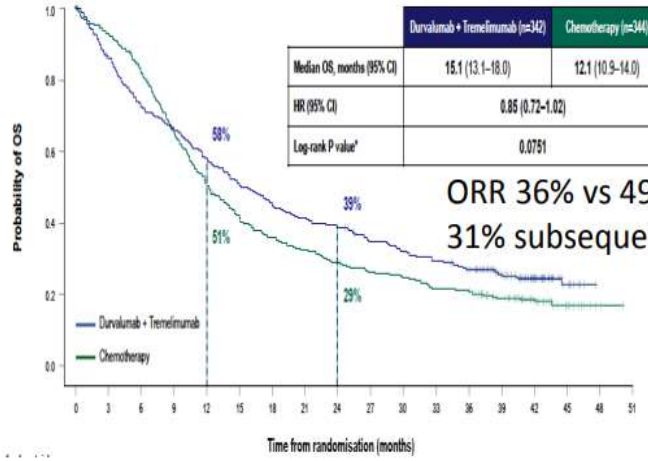


	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407*
Chemo	74.7%	14.3 mo (12.3-16.7)		

ORR 55% vs 45%

48% subsequent IO

DANUBE – IO-IO vs CT (1˚EP)



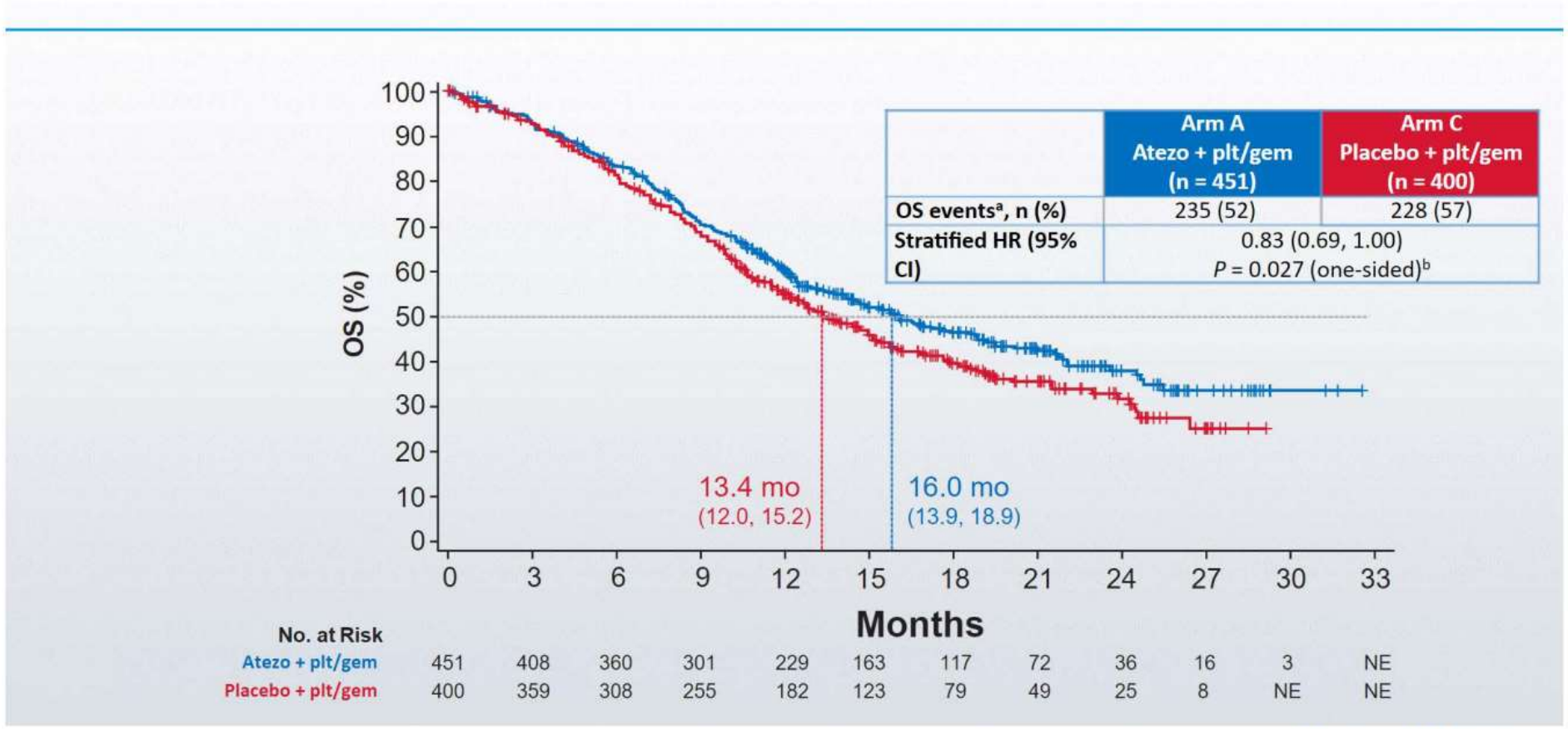
	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)
Median OS, months (95% CI)	15.1 (13.1–18.0)	12.1 (10.9–14.0)
HR (95% CI)	0.85 (0.72–1.02)	
Log-rank P value*	0.0751	

ORR 36% vs 49%

31% subsequent IO

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

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



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

Galsky et al, Lancet 2020 May; Grande ESMO 2019

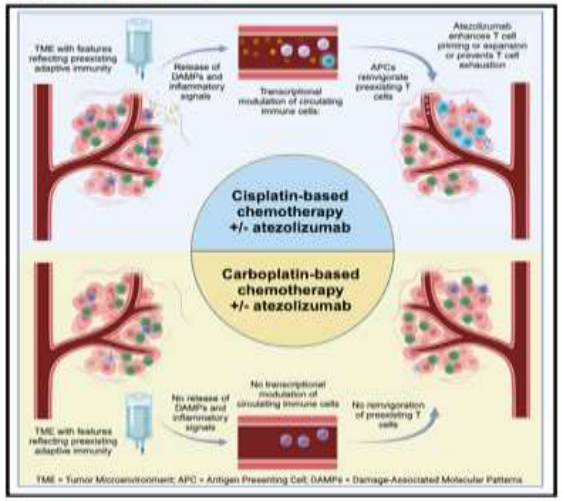
Sisplatin Ürotelyal Kanserlerde immünomodülatör

Cell Reports Medicine

Article

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

Graphical abstract



Authors

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

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

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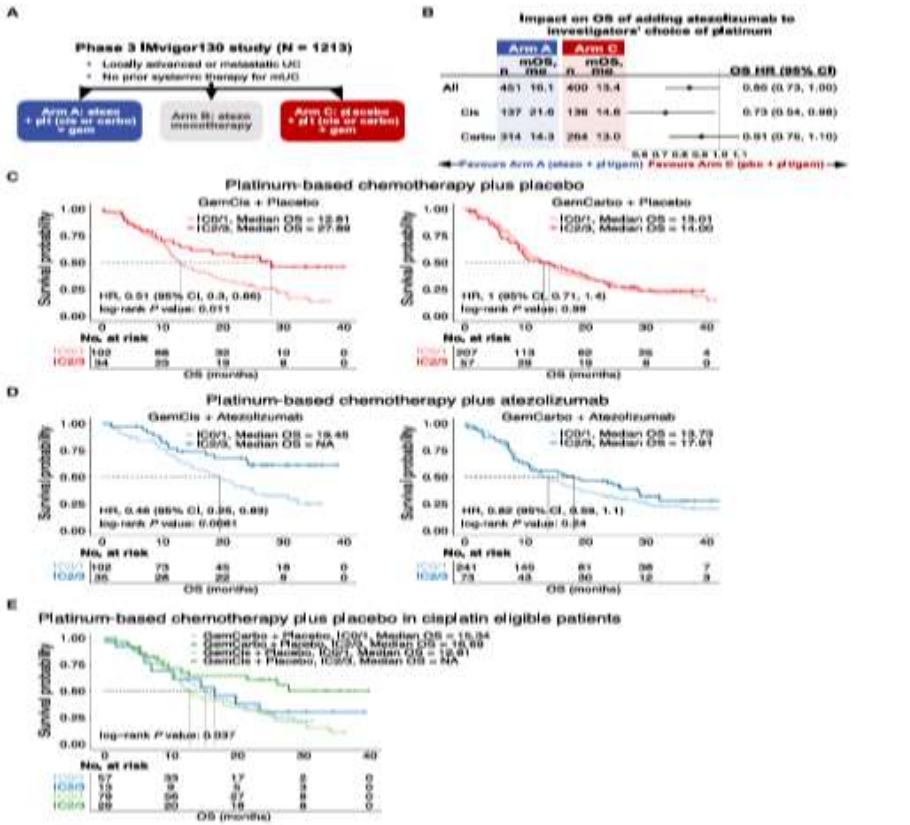
Cell Reports Medicine

Article



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Ürotelyal Kanserlerde Renal Yetmezlik ile İmmünoterapi Etkinliği Azalıyor

ASCO ABSTRACT #434954

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

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

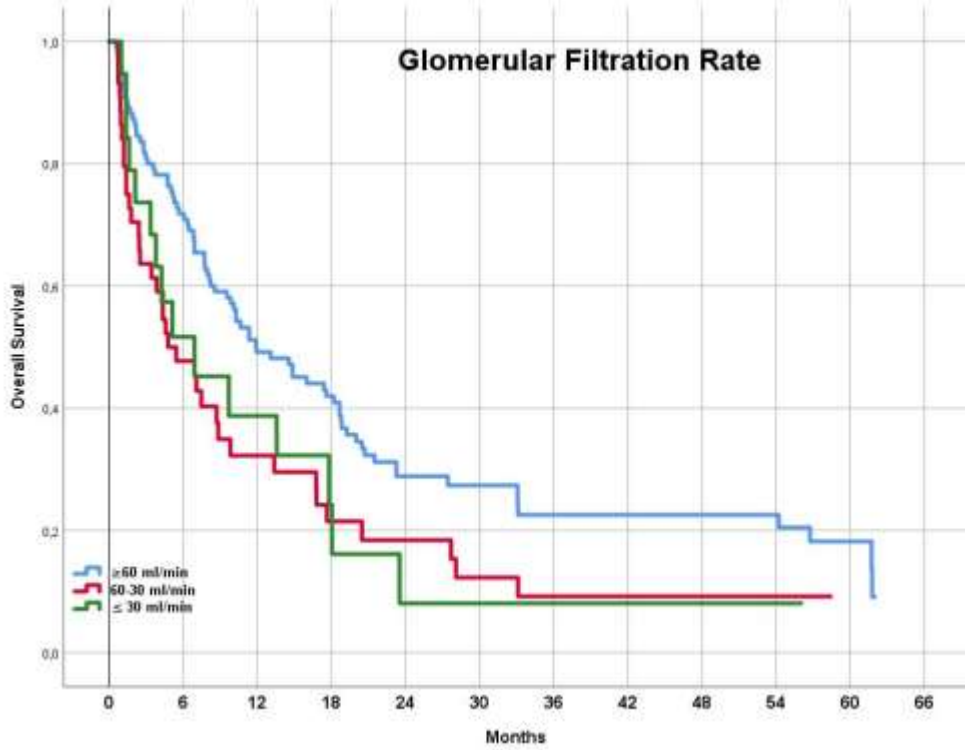
Background:

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

Methods:

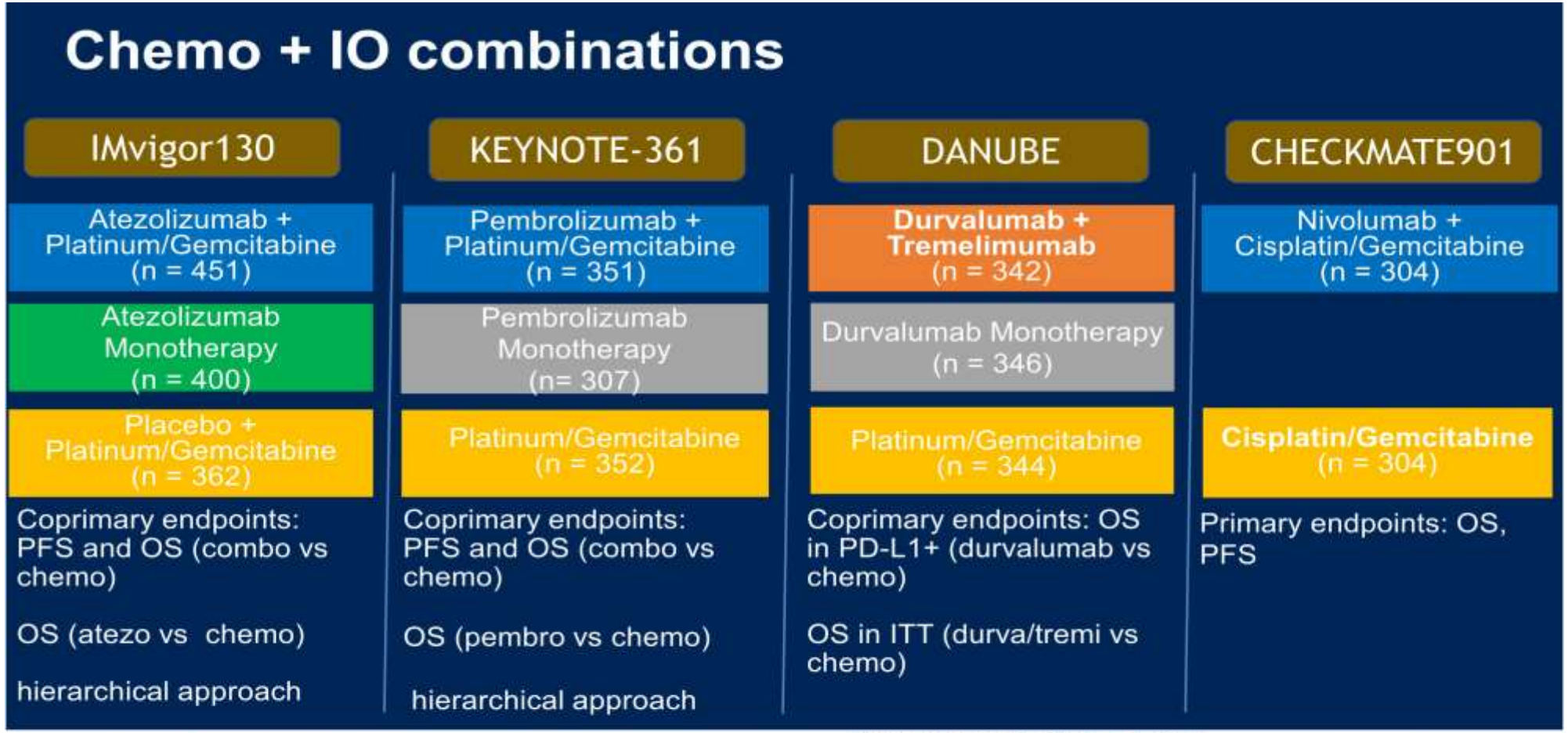
This study included metastatic urothelial carcinoma patients treated with at least one course of ICT. Impaired renal function was defined as a glomerular filtration rate [GFR] less than 60 mL/min. The patients were categorized into 3 different groups GFR≥60mL/min (normal), 60–30mL/min (low), and less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

Results:



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

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



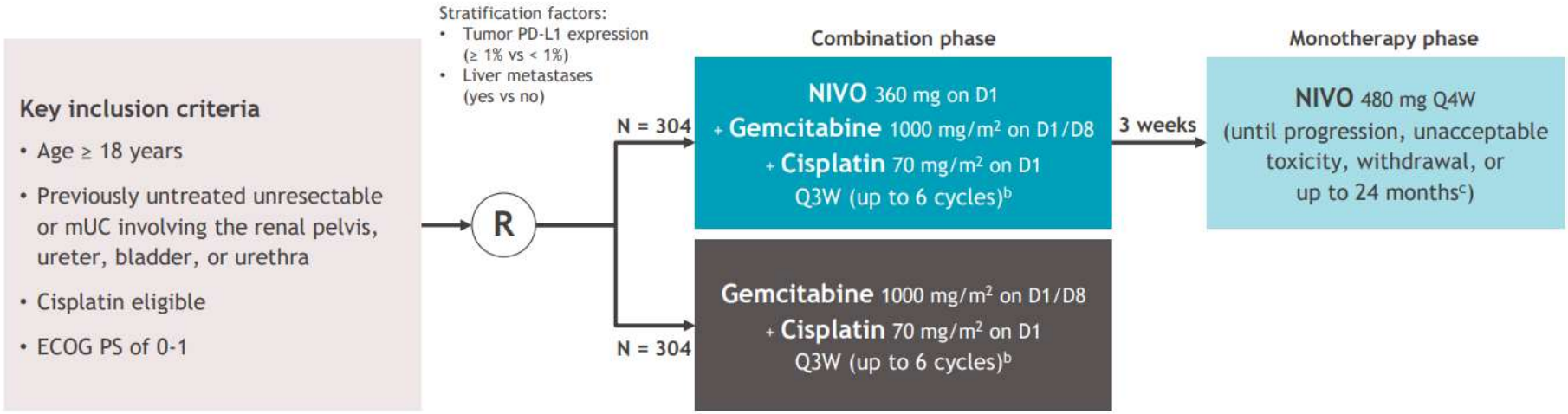
1.Grande et al. Lancet Onc 2024 PMID 38101433
2.Powles et al. Lancet Onc 2021 PMID 34051178
3.Powles et al. Lancet Onc 20201 PMID 32971005
4.Van der Heijden et al. NEJM 2023 PMID 37870949

Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

Study design

- NIVO + gemcitabine-cisplatin vs gemcitabine-cisplatin in cisplatin-eligible patients[a]



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

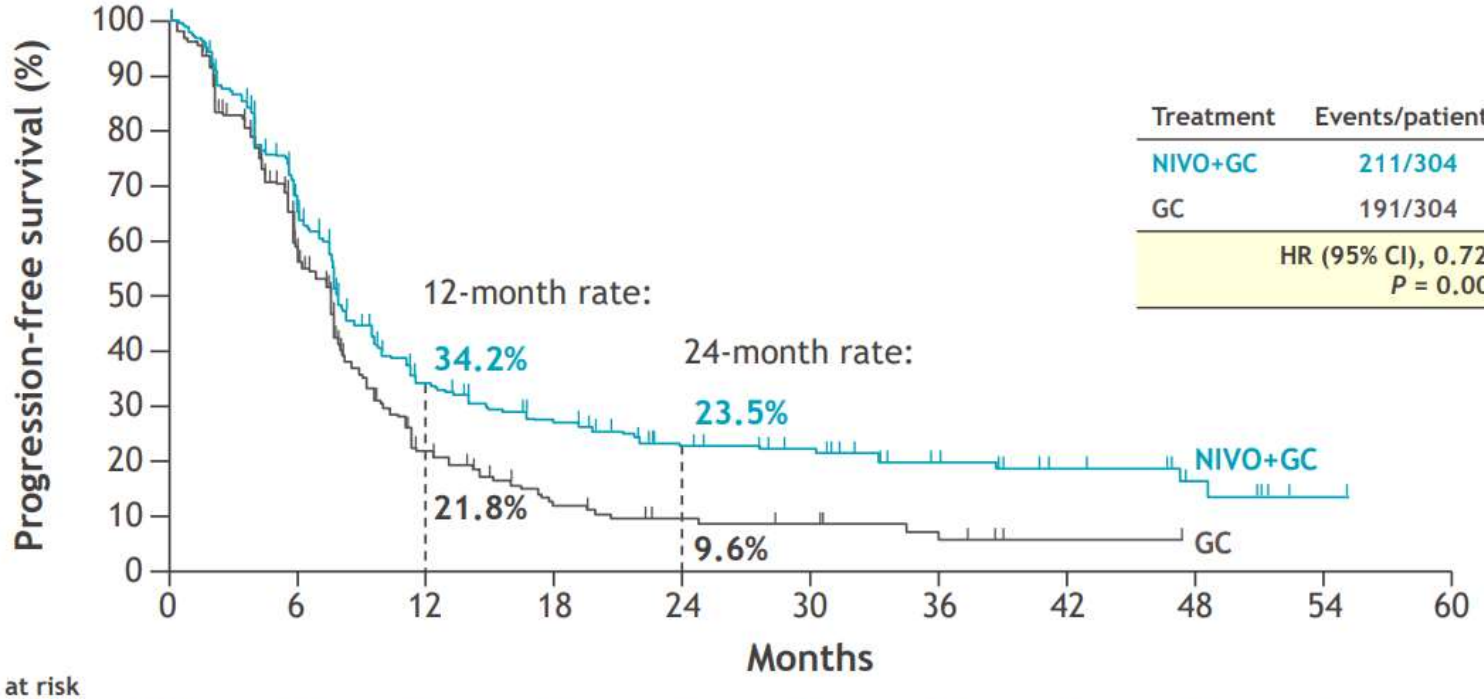
Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO + gemcitabine-cisplatin combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA, USA).
BICR, blinded independent central review; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q×W, every × weeks; R, randomization.

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

CheckMate 901

PFS per BICR (primary endpoint)



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

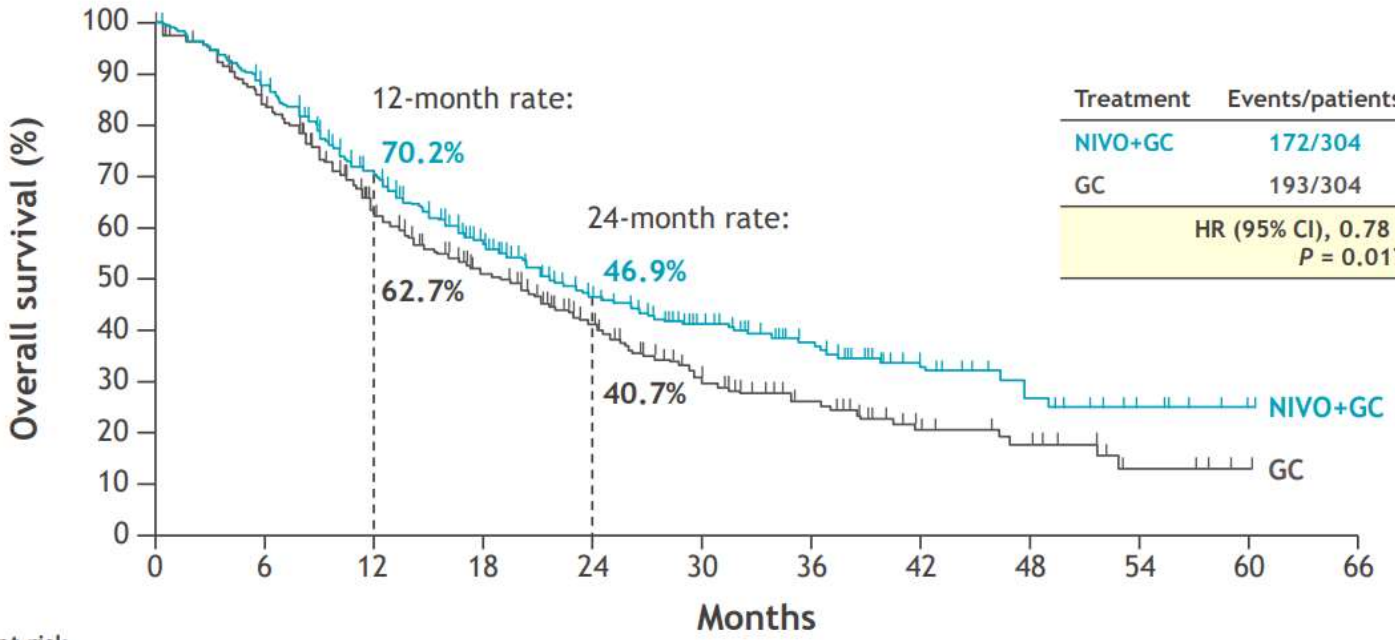
No. at risk											
NIVO+GC	304	179	82	57	41	31	19	11	6	1	0
GC	304	119	35	17	10	8	5	1	0	0	0

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

Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

OS (primary endpoint)



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

No. at risk												
NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

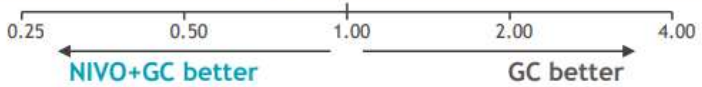
Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with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

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

CheckMate 901

OS in subgroups

Subgroup	No. of patients	NIVO+GC *No. of events/no. of patients*	GC *No. of events/no. of patients*	Unstratified HR for death (95% CI)
Overall (N = 608)		172/304	193/304	0.78 (0.63-0.95)
Age, years				
< 65	298	85/150	100/148	0.69 (0.51-0.92)
≥ 65 and < 75	236	65/120	66/116	0.89 (0.63-1.26)
≥ 75	74	22/34	27/40	0.86 (0.49-1.52)
Sex				
Male	470	133/236	147/234	0.76 (0.60-0.97)
Female	138	39/68	46/70	0.82 (0.54-1.26)
Race				
White	436	123/211	145/225	0.80 (0.63-1.02)
Asian	138	38/75	36/63	0.71 (0.45-1.12)
Other	32	11/18	10/14	0.84 (0.35-1.97)
Region				
US	40	18/19	15/21	1.92 (0.95-3.88)
Asia	133	36/72	34/61	0.73 (0.46-1.17)
Europe	276	72/134	90/142	0.73 (0.53-0.99)
Rest of the world	159	46/79	54/80	0.73 (0.49-1.08)
ECOG PS				
0	324	74/162	87/162	0.70 (0.51-0.95)
1	282	96/140	106/142	0.85 (0.64-1.11)
PD-L1 expression				
≥ 1%	221	64/111	67/110	0.75 (0.53-1.06)
< 1% or indeterminate	387	108/193	126/194	0.80 (0.62-1.04)
Liver metastases				
Yes	128	45/64	48/64	0.77 (0.51-1.16)
No	480	127/240	145/240	0.77 (0.61-0.98)
Previous systemic anticancer therapy				
Yes	156	44/88	41/68	0.90 (0.59-1.38)
No	452	128/216	152/236	0.76 (0.60-0.96)



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

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

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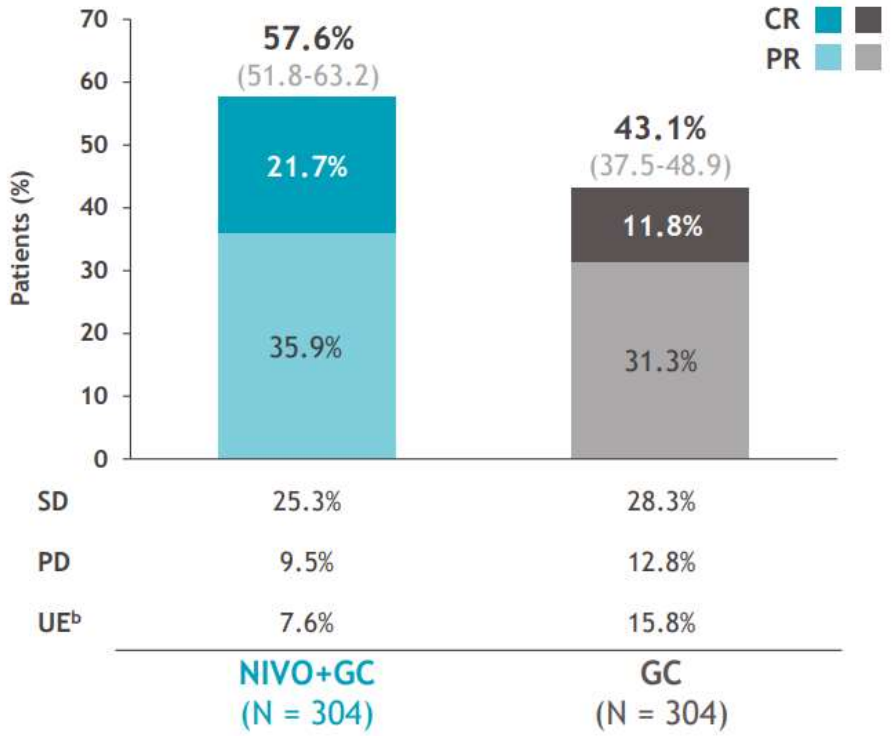
Objective response outcomes (exploratory endpoints)

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



Time to and duration of responses

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

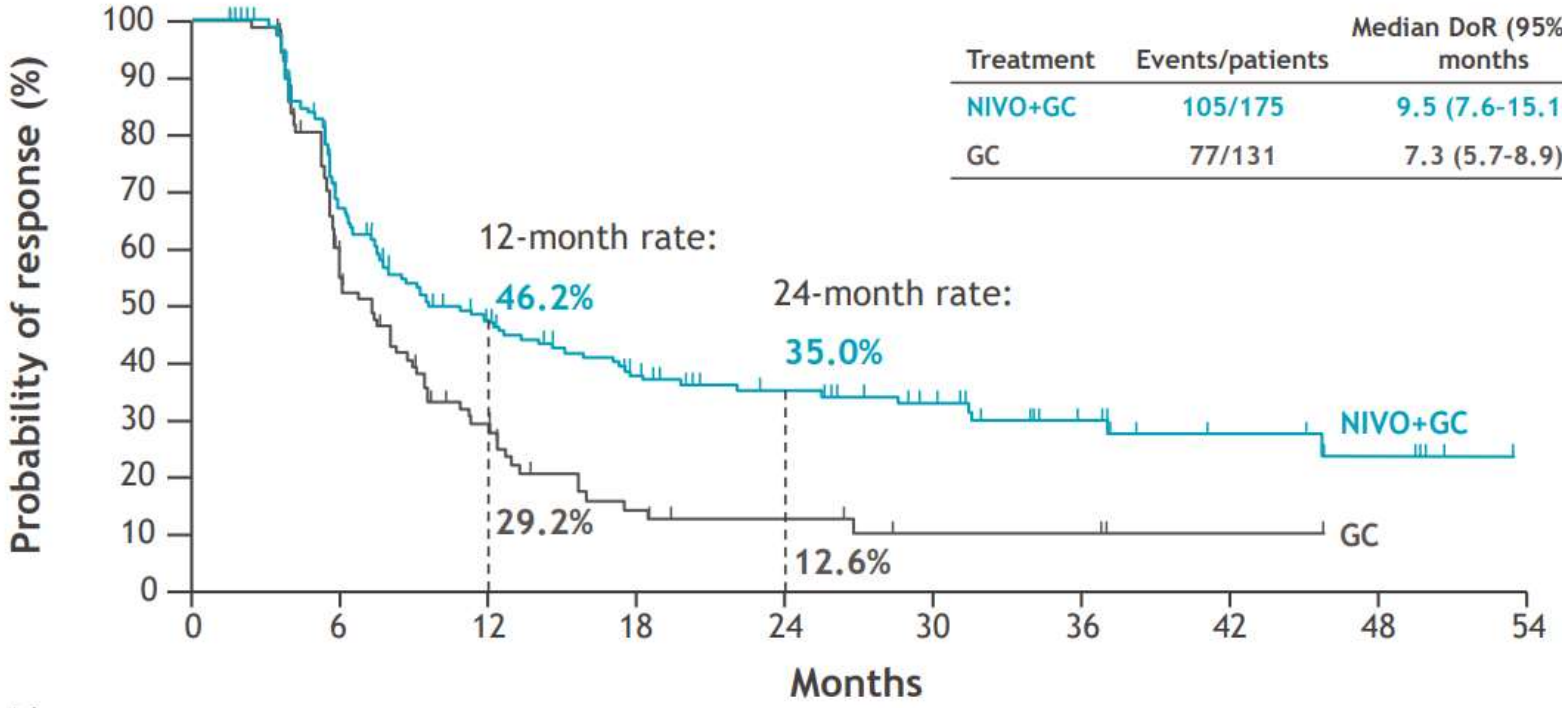
Complete response[d]	NIVO+GC (n = 66)	GC (n = 36)
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

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

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Nivolumab

CheckMate 901

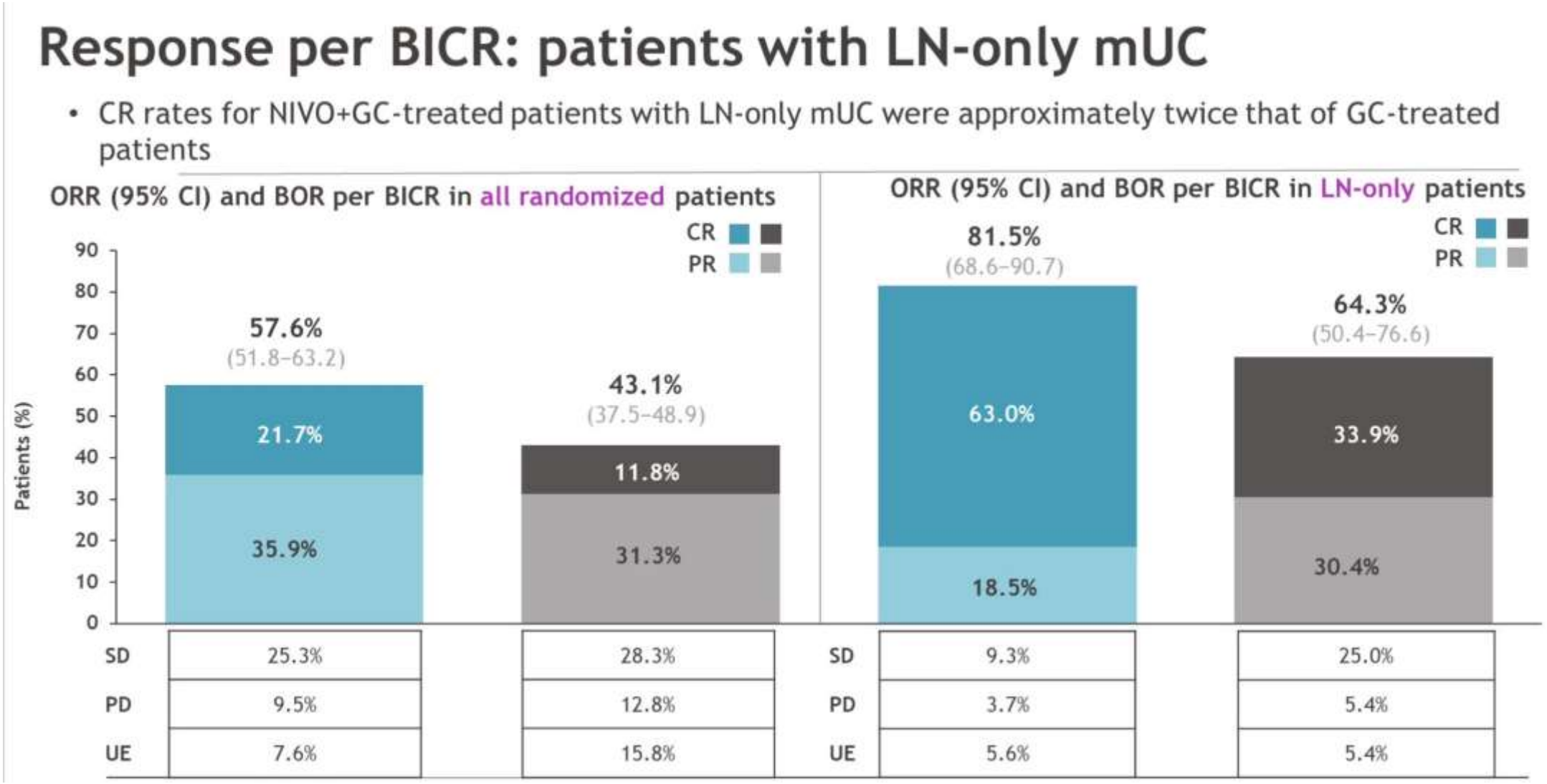
Duration of objective response per BICR



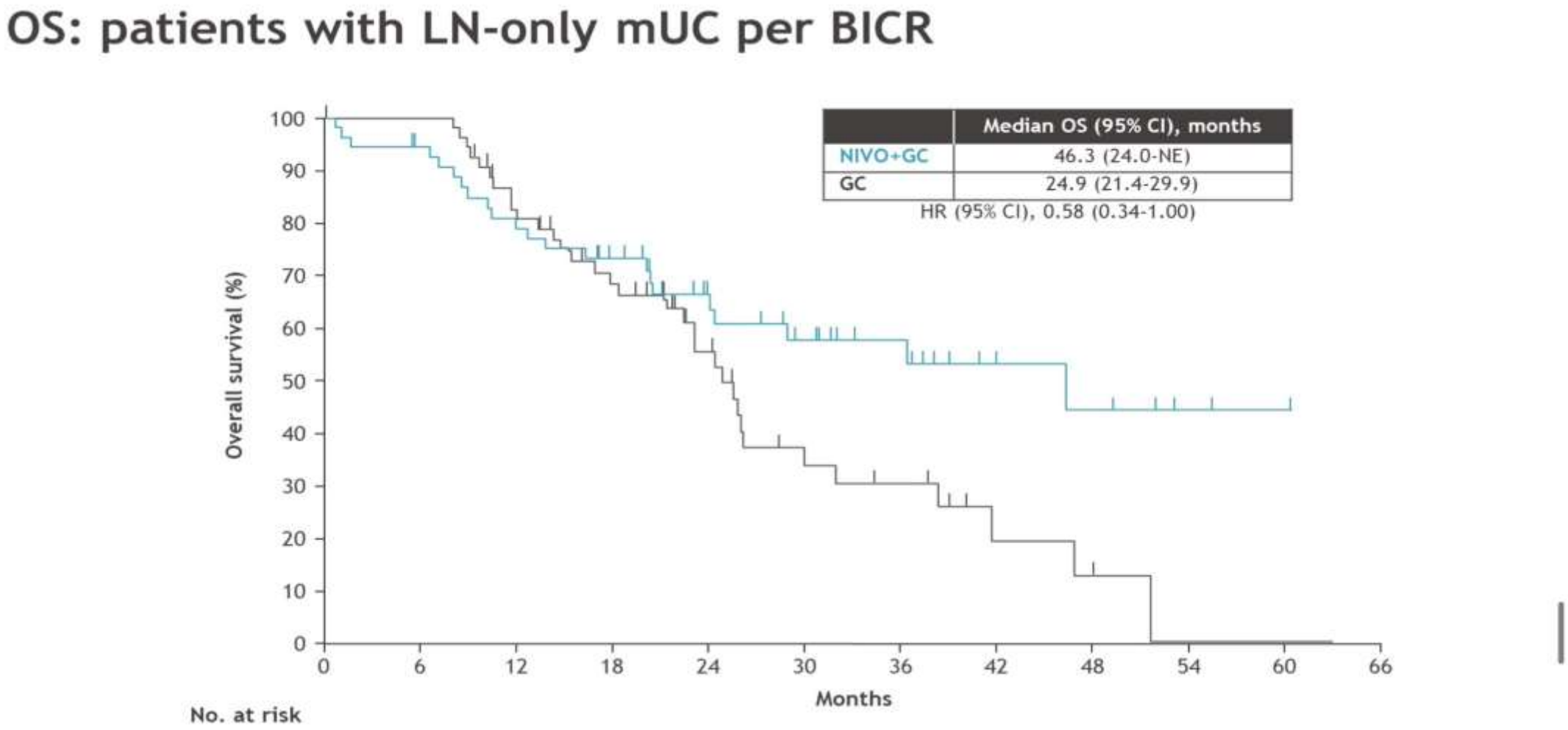
Treatment	Events/patients	Median DoR (95% CI), months
NIVO+GC	105/175	9.5 (7.6-15.1)
GC	77/131	7.3 (5.7-8.9)

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

Sisplatin+Gemsitabin+Nivolumab
Yalnız lenf nodu metastazı olanlarda yanıt



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

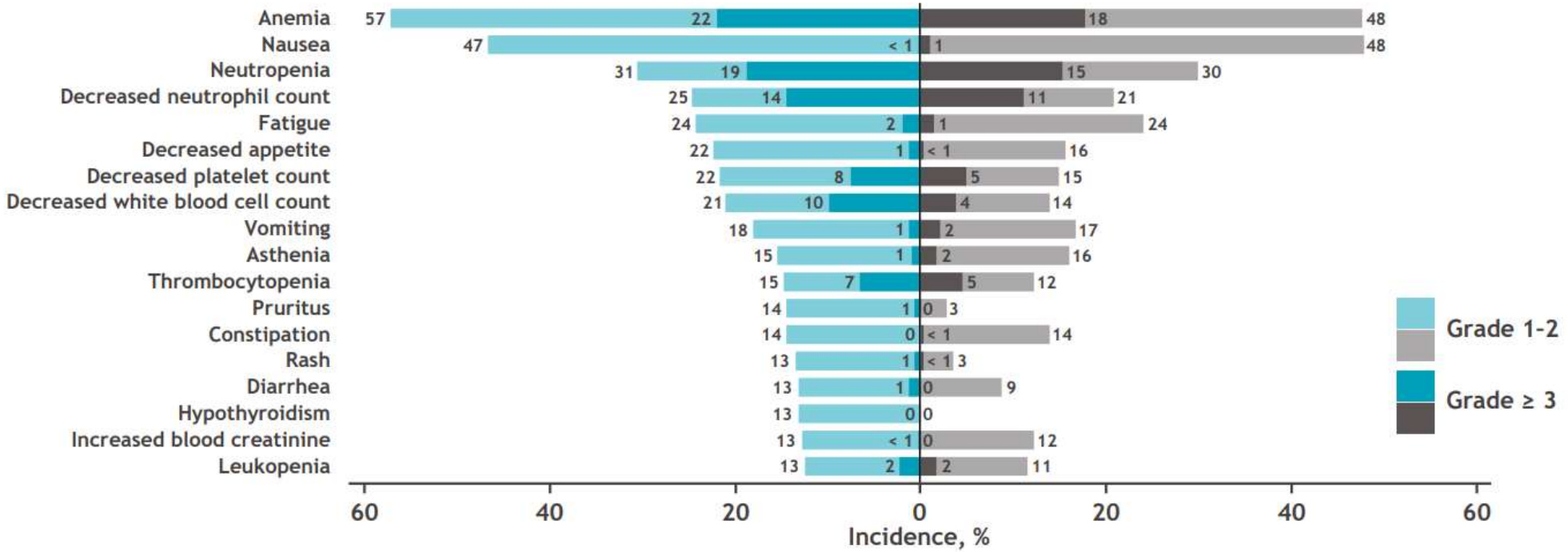


Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

Treatment-related AEs in all treated patients

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



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

Ürotelyal Kanserlerde Platin Direnci İmmünoterapi Direnci ile İlişkili

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

ORIGINAL ARTICLE

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

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

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

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

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

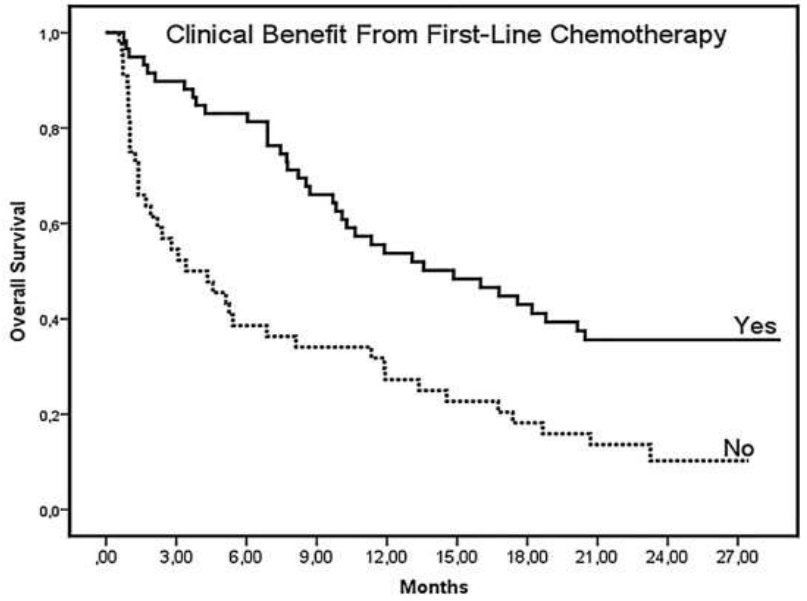
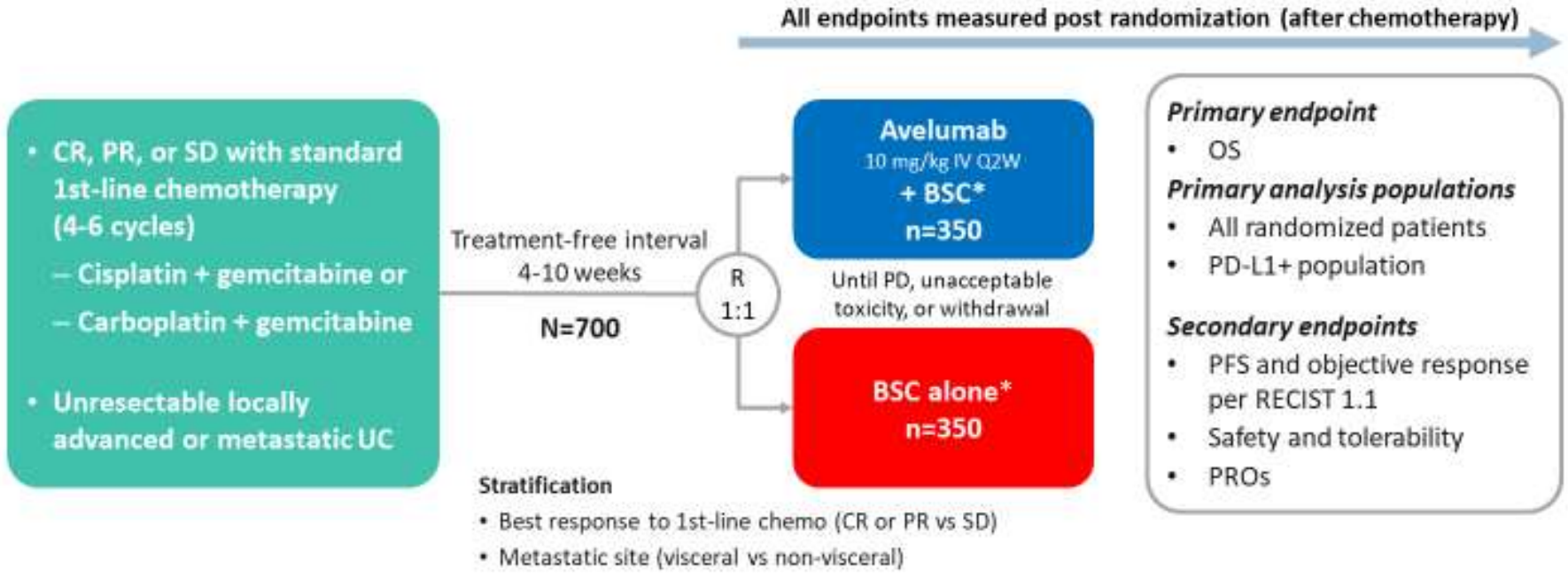


Fig. 2 Kaplan–Meier curves association of clinically benefited from the first-line treatment and overall survival

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

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

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

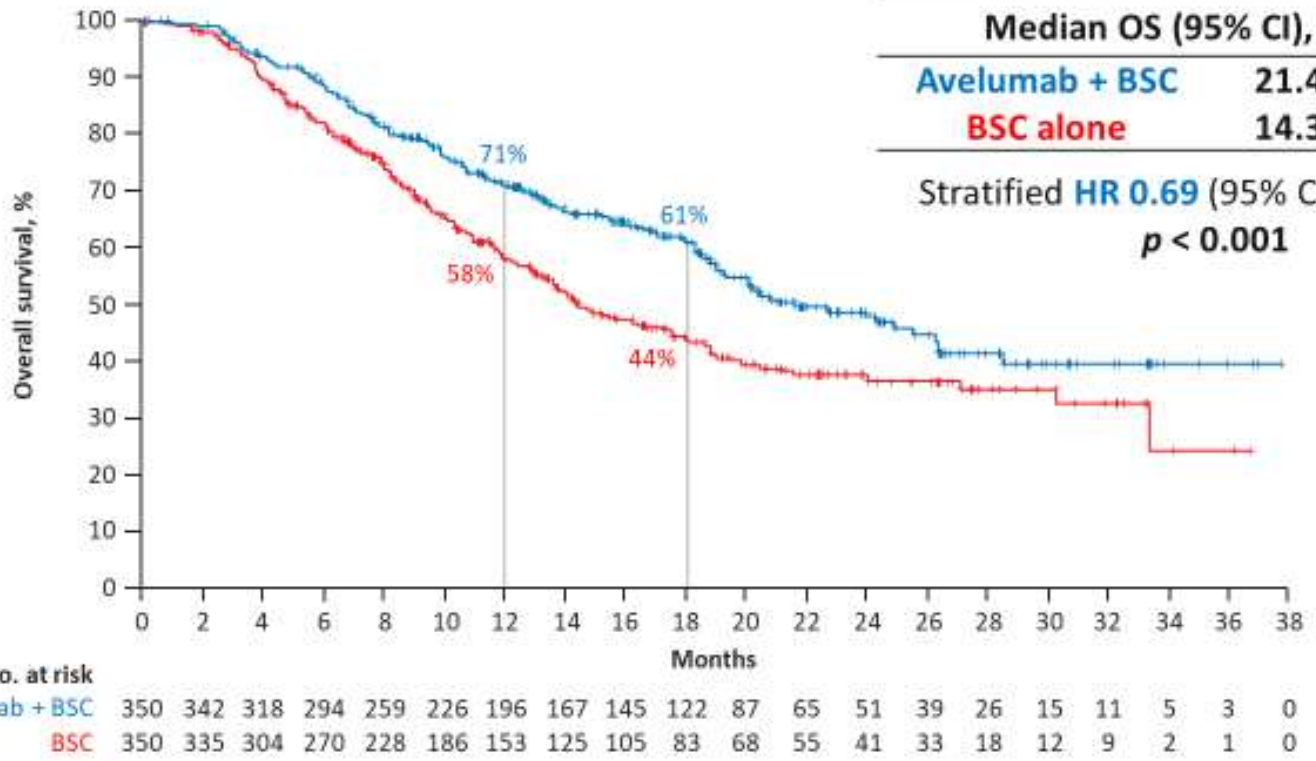
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Powles T et al. ASCO 2020;Abstract LBA1.

Courtesy of Arjun V. Balar, MD

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

OS in the overall population



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

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

***p* < 0.001**

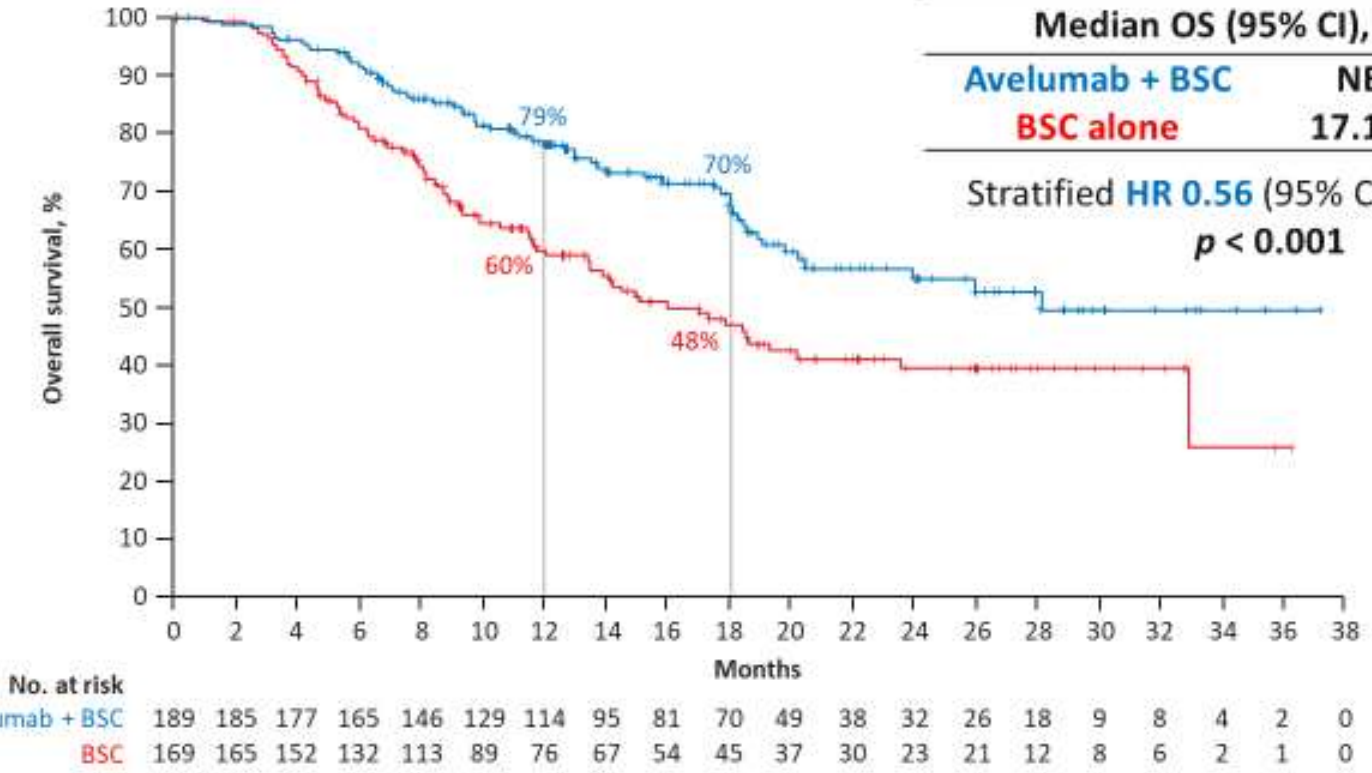
OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

Powles T et al. ASCO 2020;Abstract LBA1.

Courtesy of Arjun V. Balar, MD

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

OS in the PD-L1+ population



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

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

***p* < 0.001**

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

Powles T et al. ASCO 2020;Abstract LBA1.

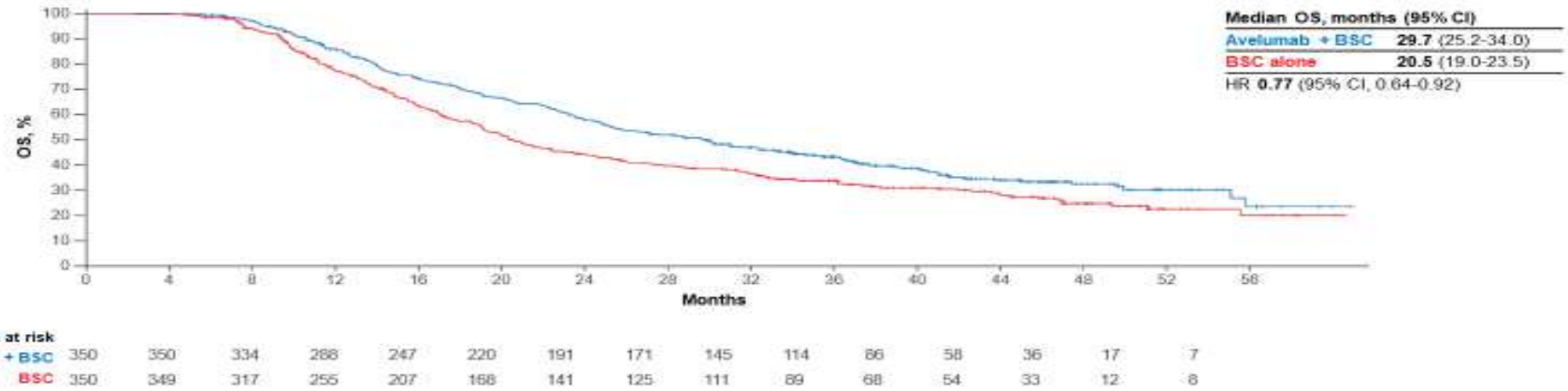
Courtesy of Arjun V. Balar, MD

Metastatik 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 Patients[1]

Post hoc analysis

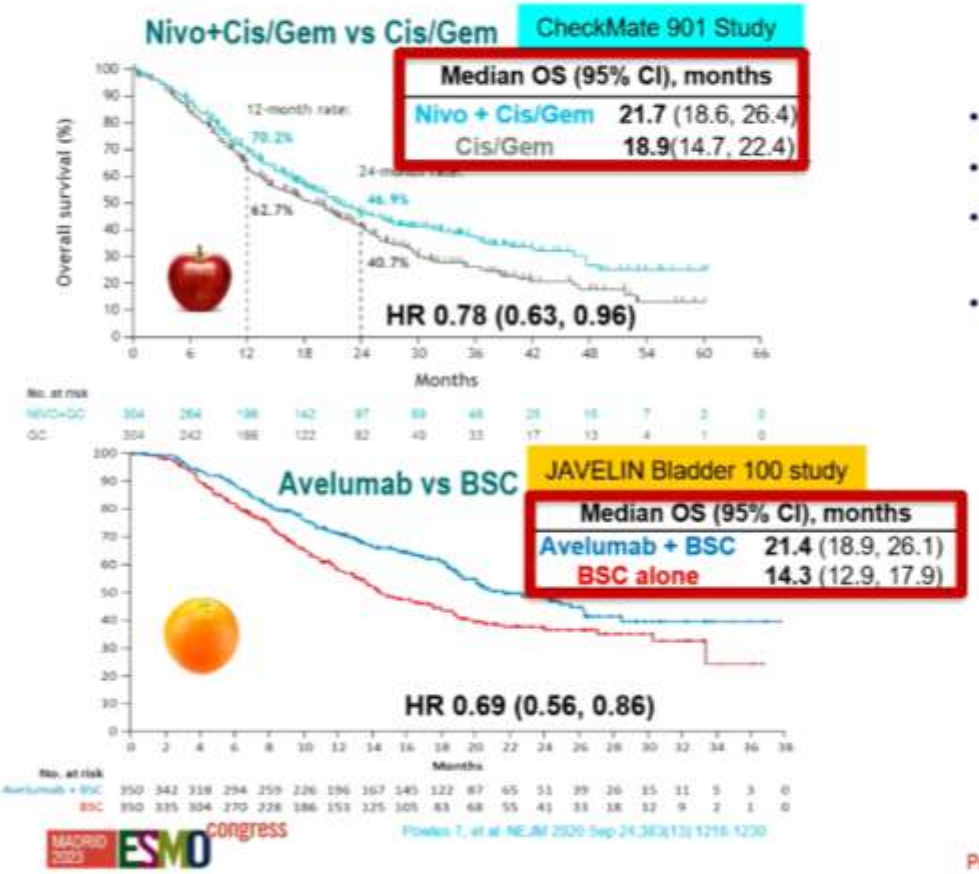


In the overall population, median OS measured from the start of 1L chemotherapy was 29.7 months (95% CI, 25.2-34.0) in the avelumab + BSC arm and 20.5 months (95% CI,19.0-23.5) in the BSC alone arm (HR, 0.77 [95% CI, 0.636-0.921])

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 Fransisco, CA.

Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçeneği
Sisplatin Gemsitabin Nivolumab vs. Platin bazlı kemoterapi sonrası Avelumab

Both sequential and combination chemo and CPI have efficacy



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

Andrea Apolo
Invited Discussant LBA6 and LBA7

Presented by Andrea B. Apolo, MD

Metastatik Mesane Kanseri Sisplatin Uygun Olmayanlarda Birinci Basamak Enfortumab+Pemrolizumab Sonuçları

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

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

N=149
R
1:1

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

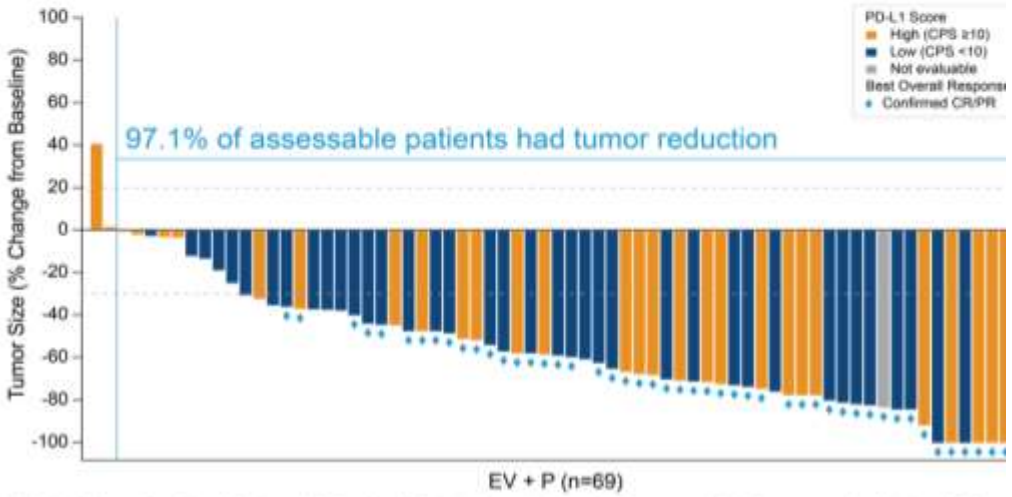
n=73
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle

Primary Endpoint
- ORR per BICR

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

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

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



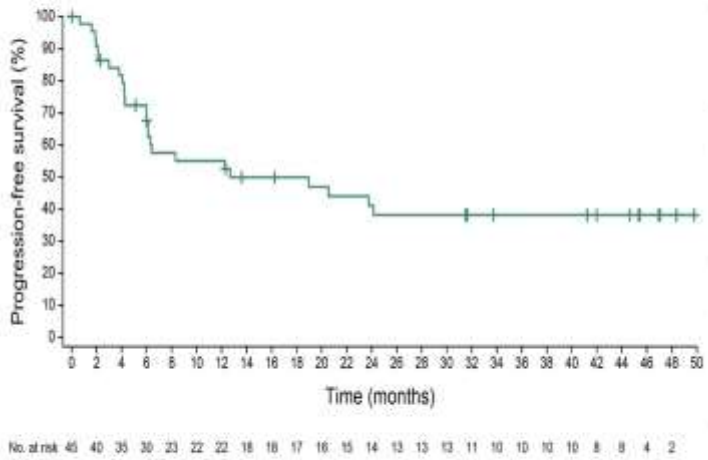
BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

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

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

Progression-Free Survival by BICR

41.1% of patients were progression-free at 24 months

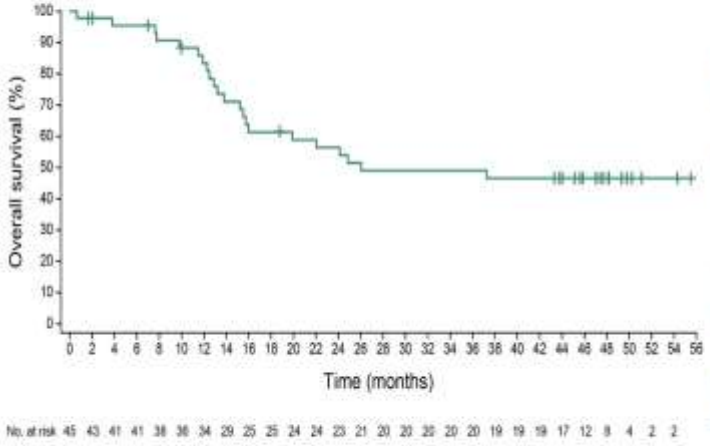


	Dose Escalation + Cohort A (N = 45)
PFS events, n	25
Median PFS (95% CI[a])	12.7 months (6.11-NE)
PFS rate[b] at:	
6 months, % (95% CI[a])	72.4 (56.47-83.26)
12 months, % (95% CI[a])	55.0 (38.84-68.58)
24 months, % (95% CI[a])	41.1 (25.69-55.88)

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

Overall Survival

Median survival exceeds 2 years



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

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

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

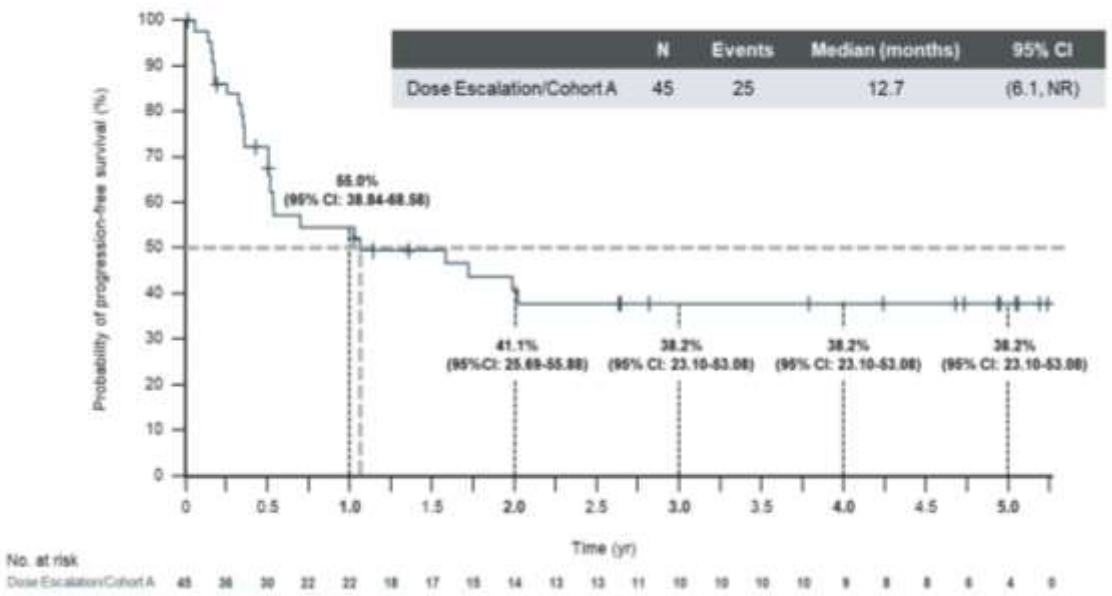
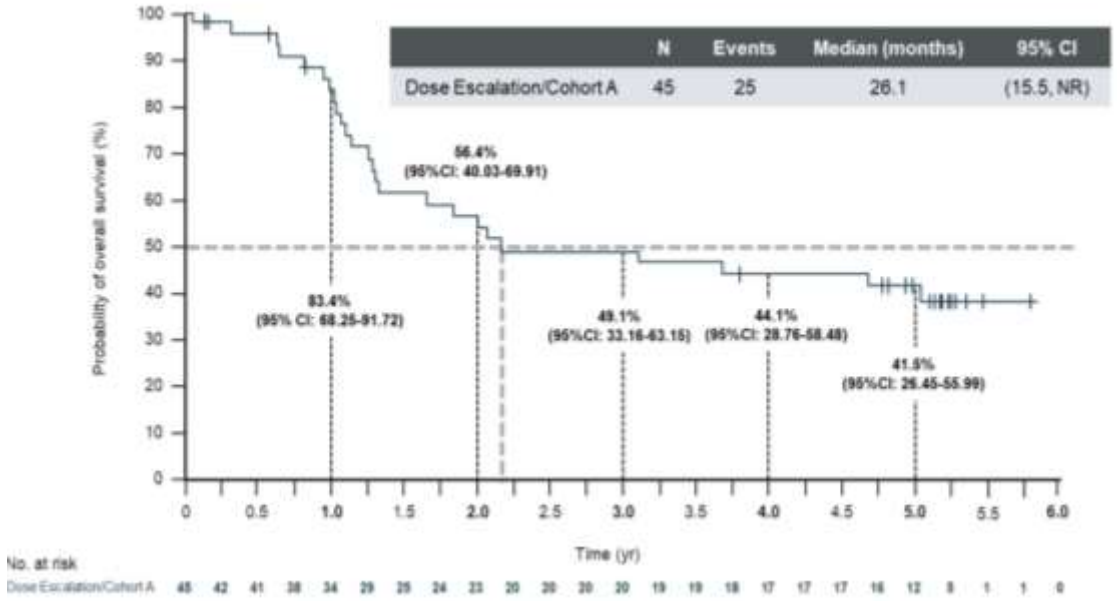
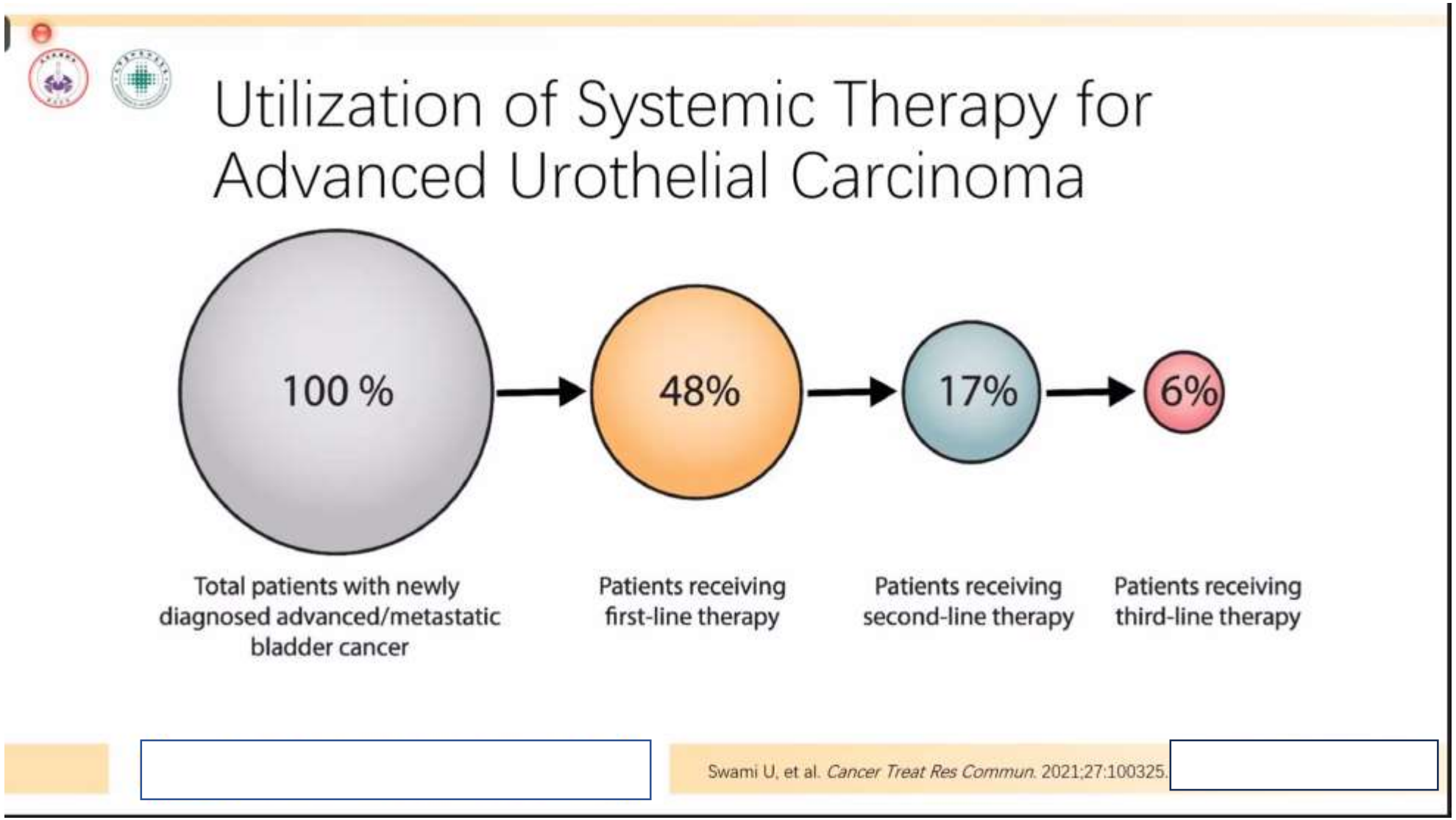


Figure 5. OS

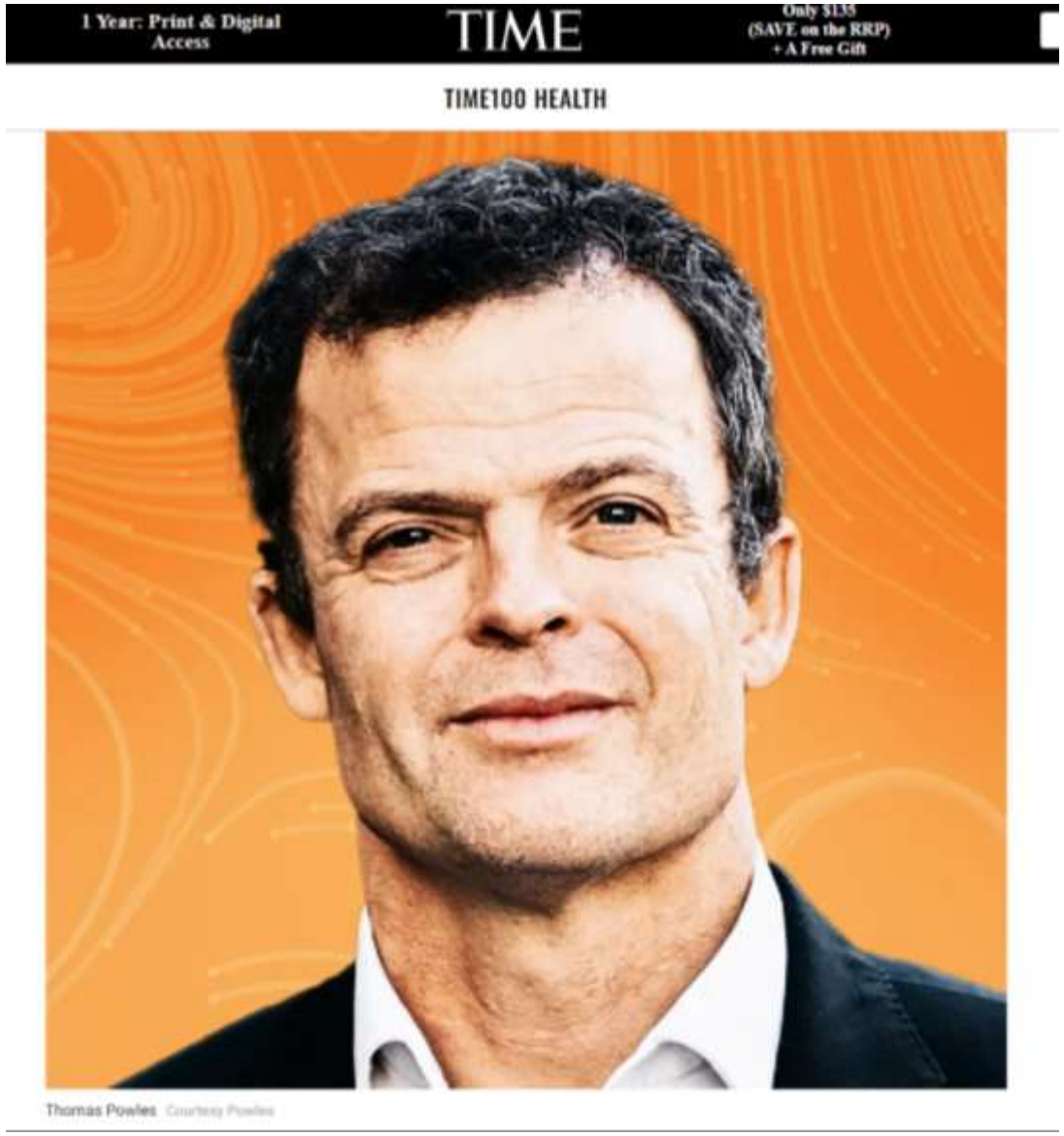


Enfortumab vedotin ve pembrolizumab kombinasyonu sisplatin uygun olmayan hastalarda 5-yılık sağkalım %40

En Etkili Tedavi En kısa Zamanda Vermek



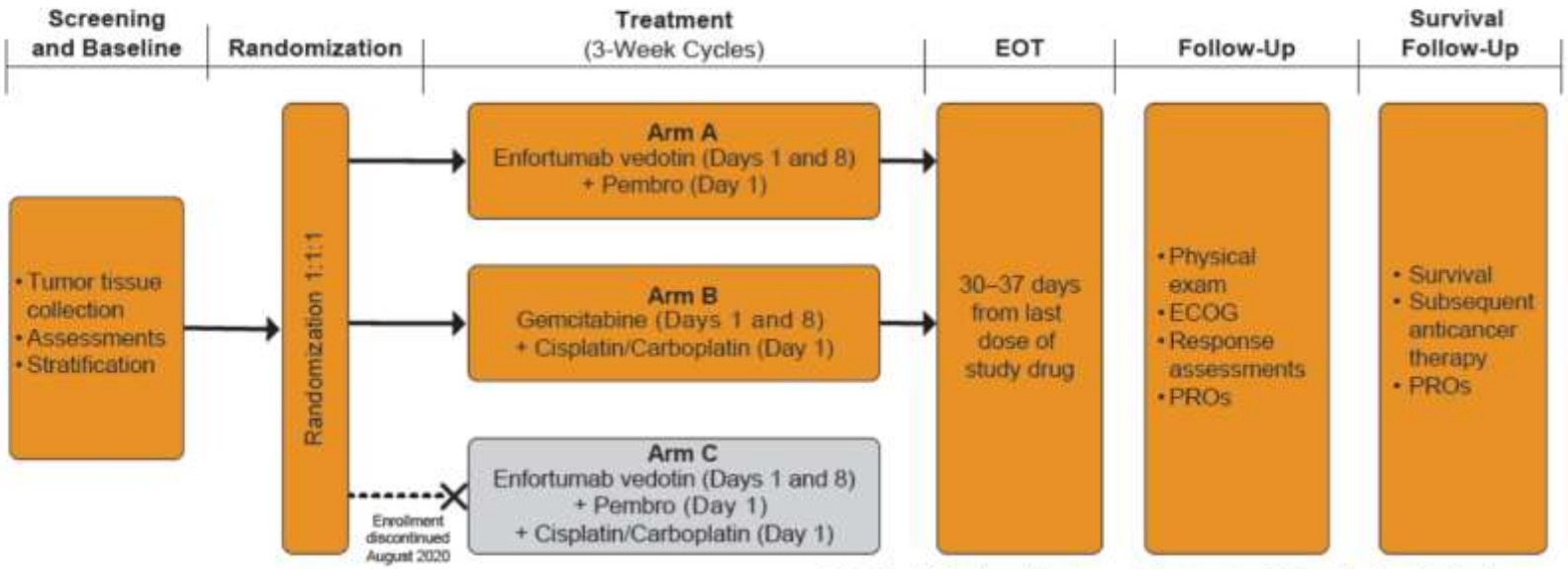
TIME Dergisine Kapak Olan Çalışmanın Sonuçları Açıklandı



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

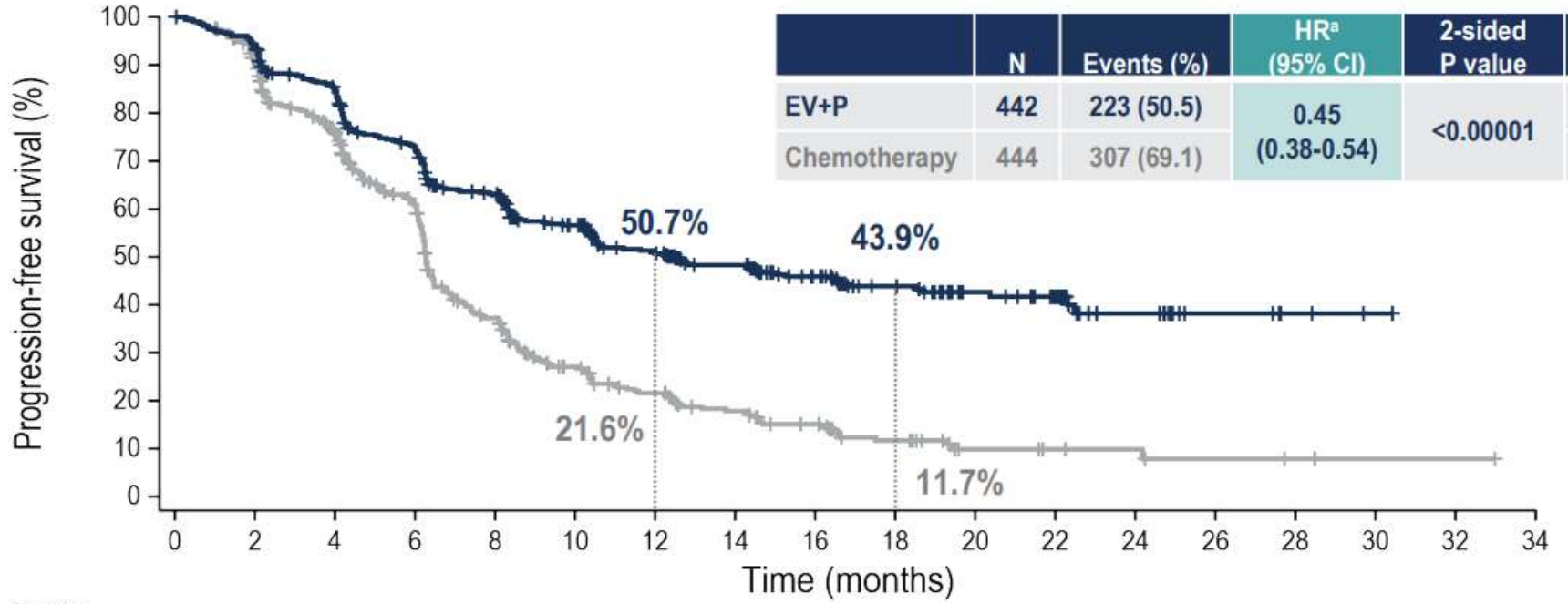
- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

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



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

N at risk

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

Data cutoff: 08 Aug 2023

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

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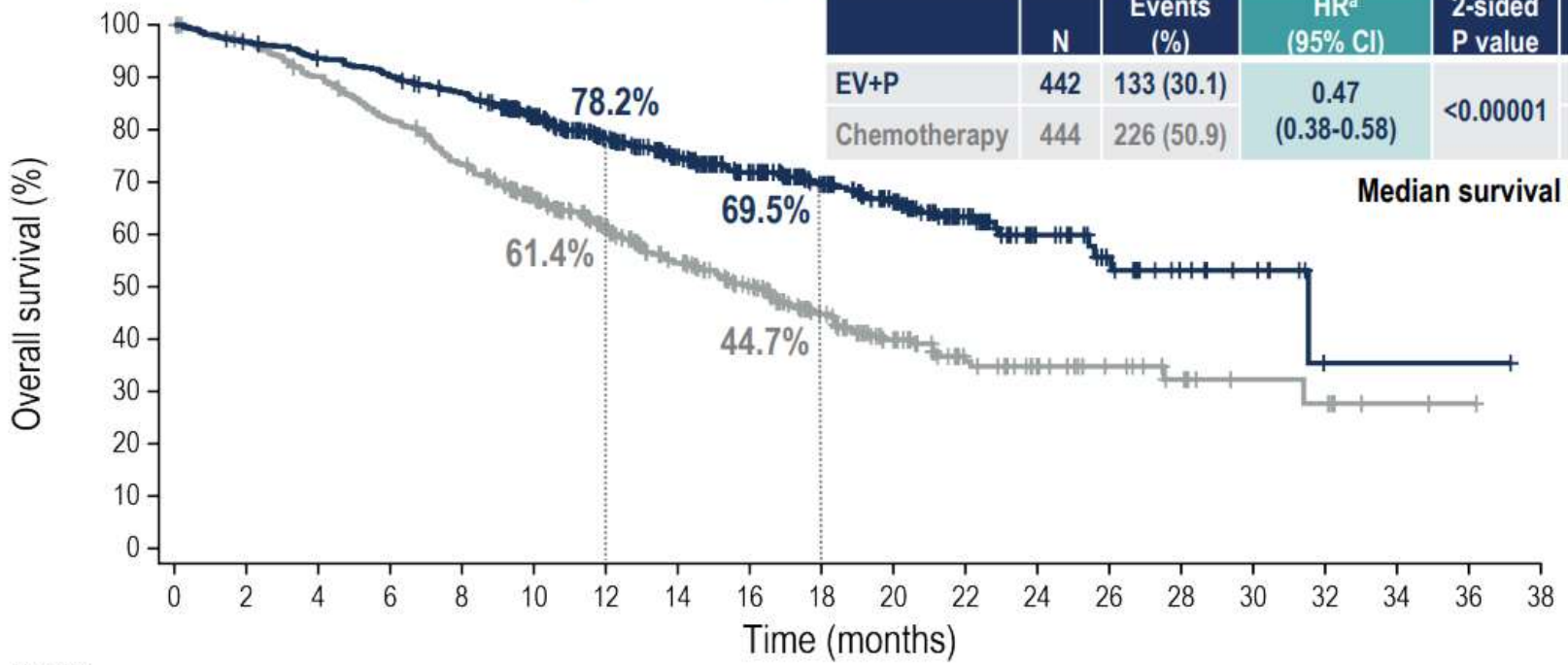
Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

Overall Survival

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

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

Median survival follow-up: 17.2 months



N at risk

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

Data cutoff: 08 Aug 2023

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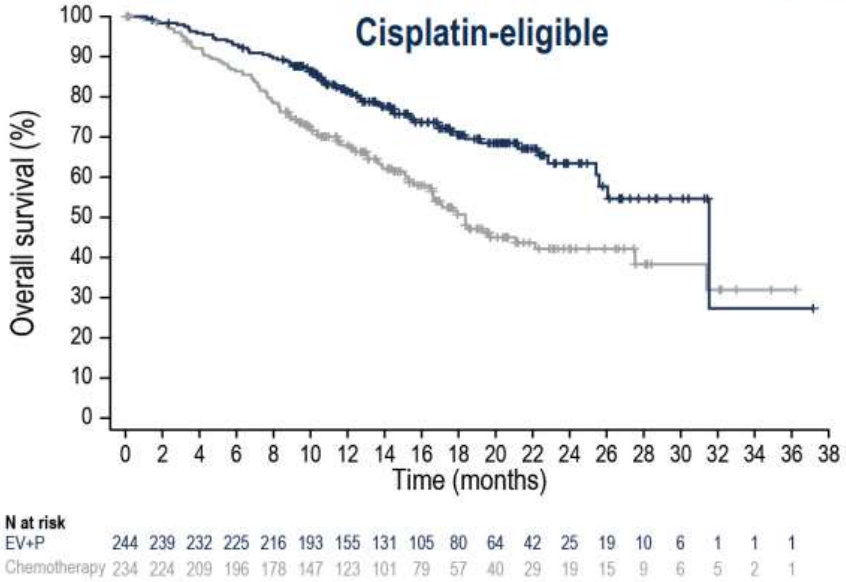
OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

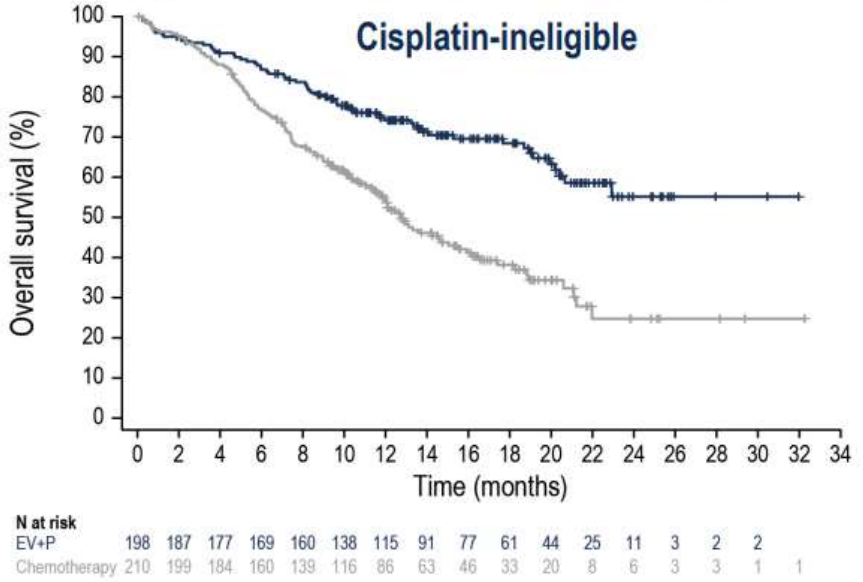
Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility



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



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

Data cutoff: 08 Aug 2023

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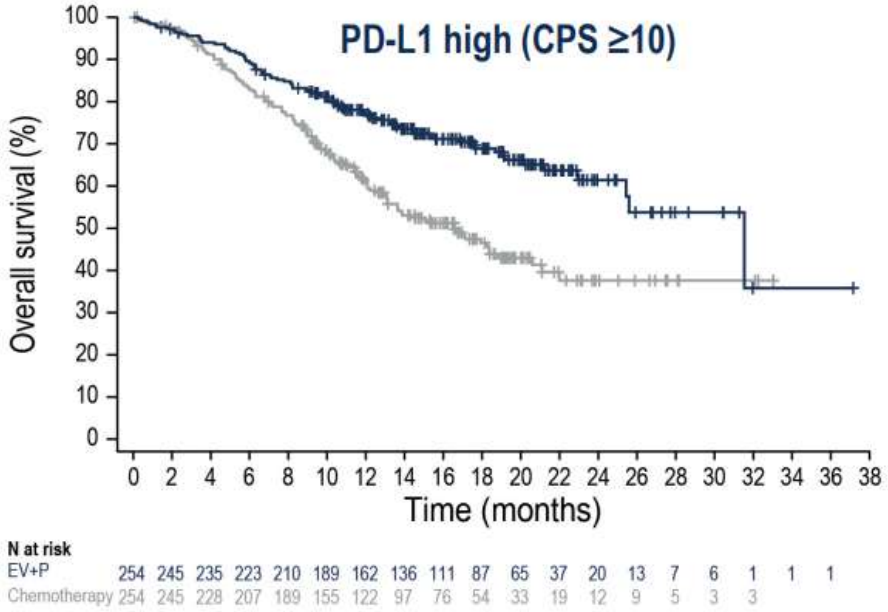
Powles et al.

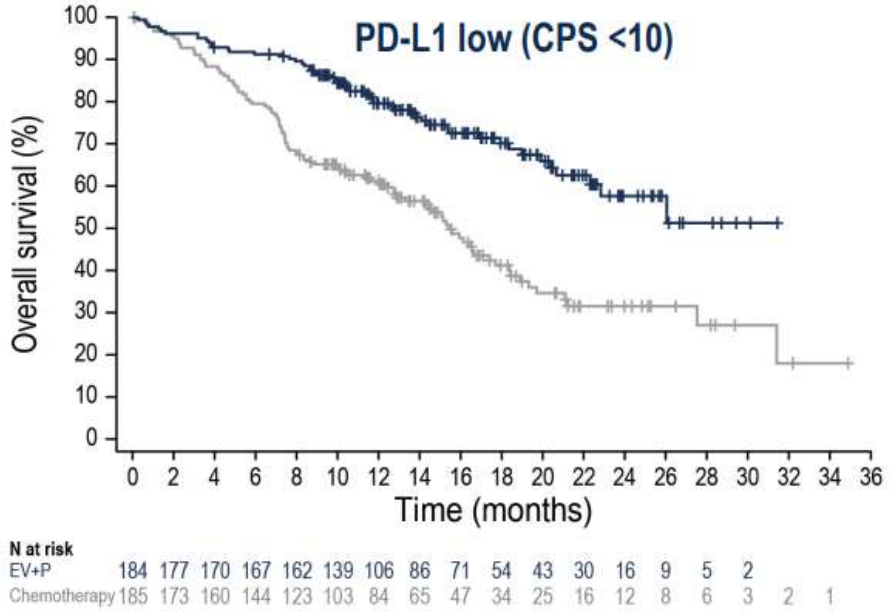
Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

OS Subgroup Analysis: PD-L1 Expression

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



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



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

Data cutoff: 08 Aug 2023

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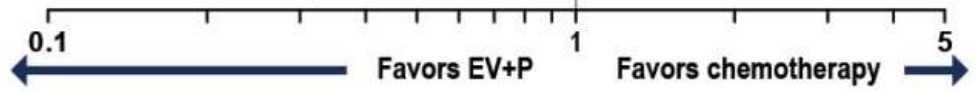
Metastatik Mesane Kanseri Birinci Basamak Tedavi
EV-302 -EV/pemrolizumab

Subgroup Analysis of OS

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

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



Data cutoff: 08 Aug 2023

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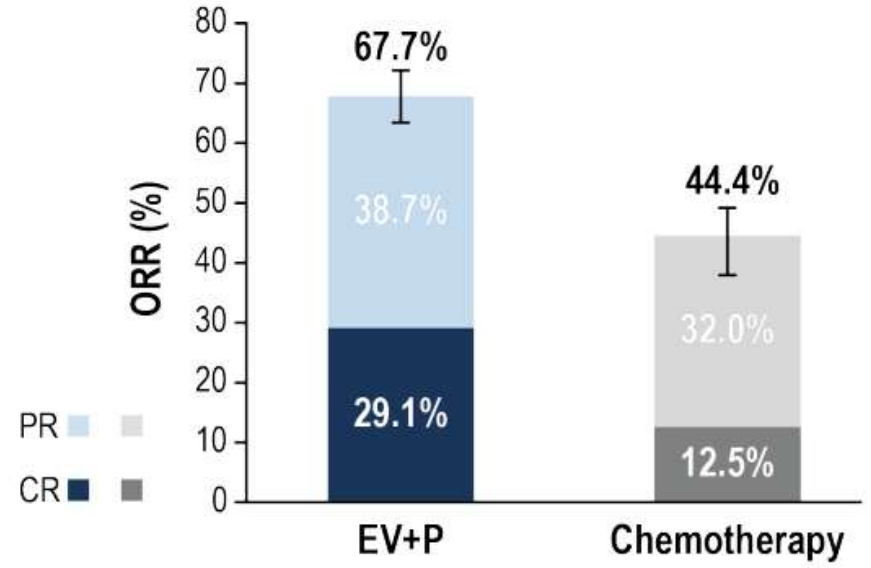
Powles et al.

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

Confirmed Overall Response per BICR

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



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

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

Data cutoff: 08 Aug 2023

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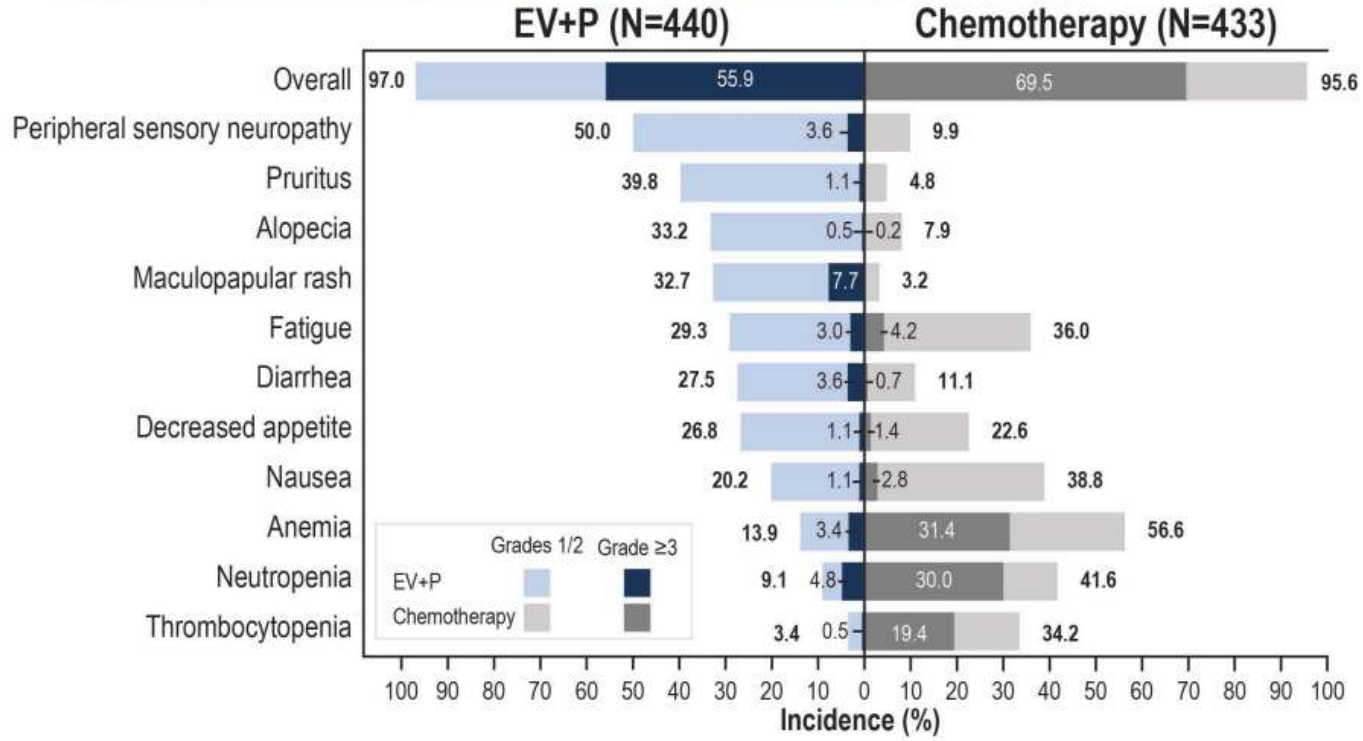
Powles et al.

CR, complete response; DOR, duration of response; PR, partial response
[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response
[b]Patients 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

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

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

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

EV Treatment-Related Adverse Events of Special Interest*

Majority of treatment-related AESIs were low grade

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

Data cutoff: 08 Aug 2023

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Powles et al.

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

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

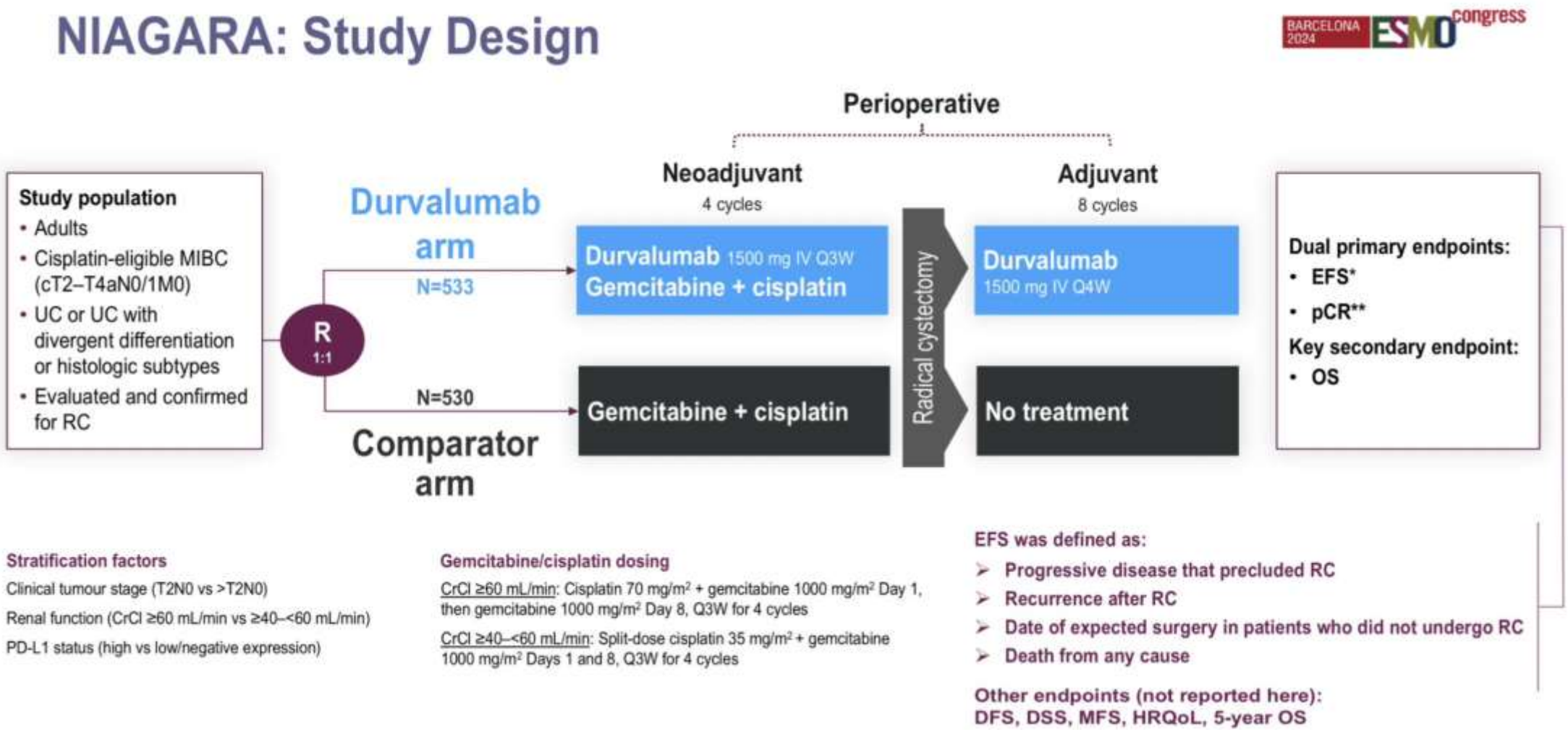
The NEW ENGLAND JOURNAL of MEDICINE

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. Roghmann, 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



Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan

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

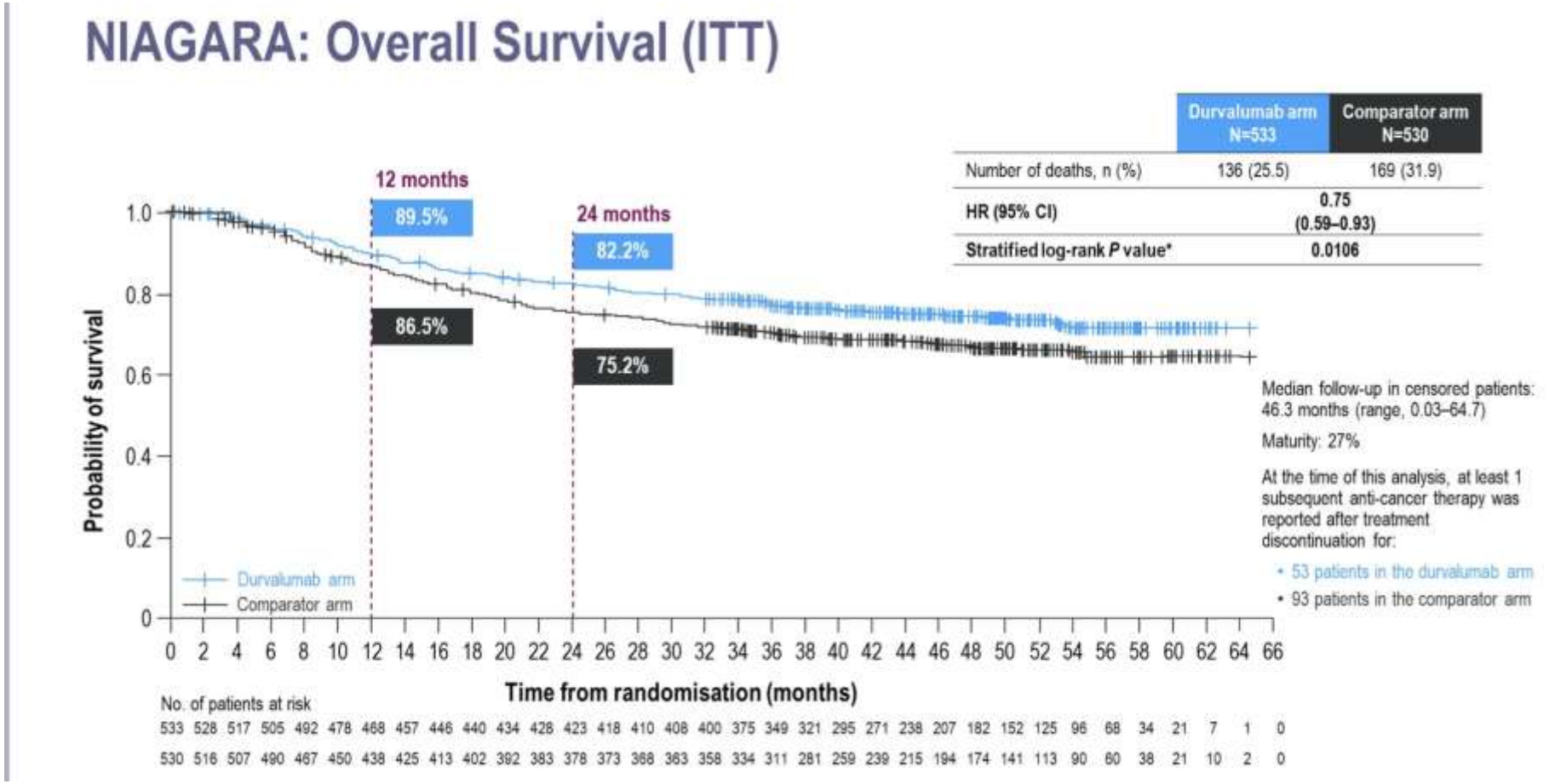
BARCELONA 2024 ESMO congress

	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	**0.68 (0.56–0.82)**	
Stratified log-rank *P* value*	**<0.0001**	

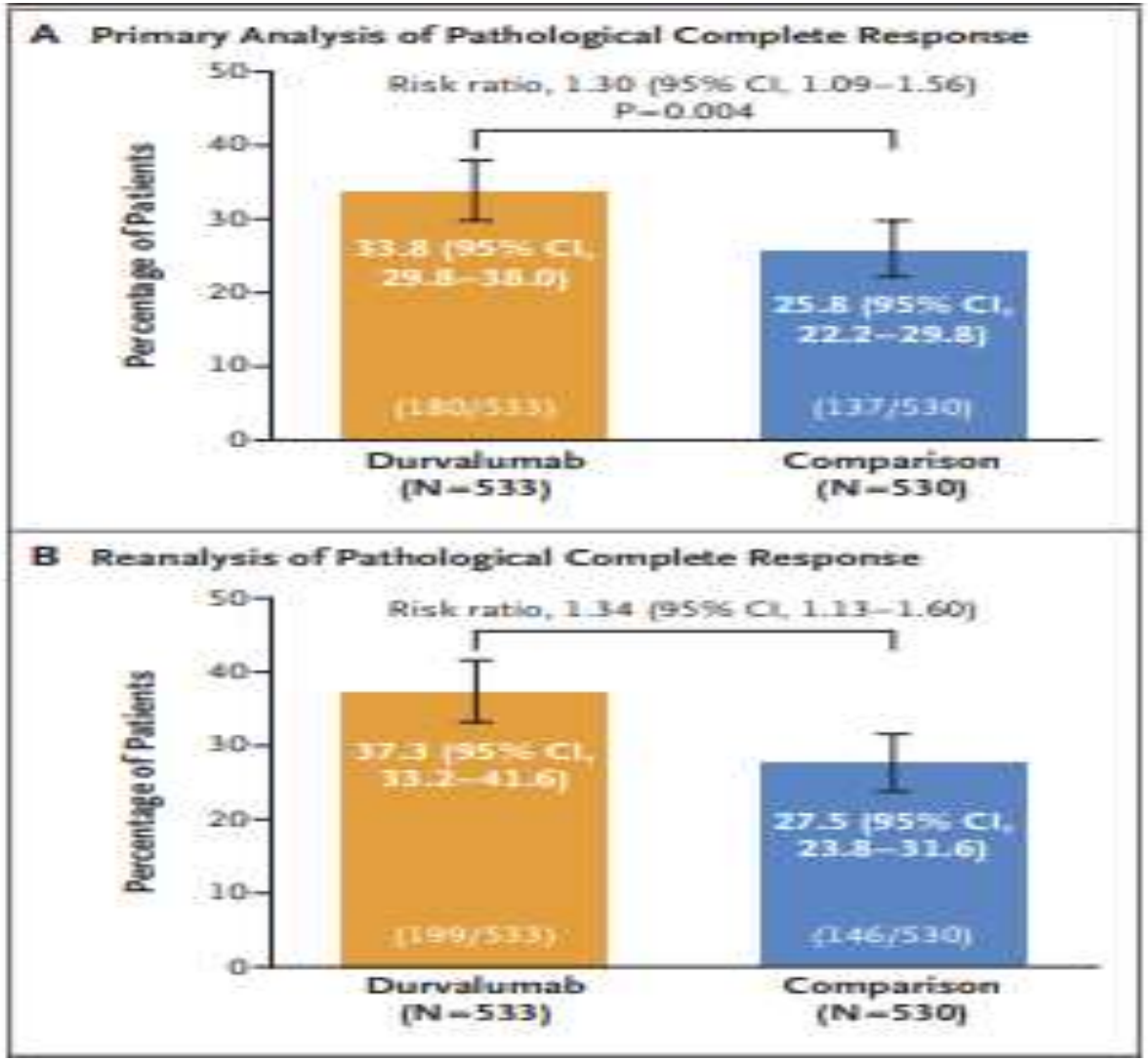
Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

Maturity: 39%

Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan



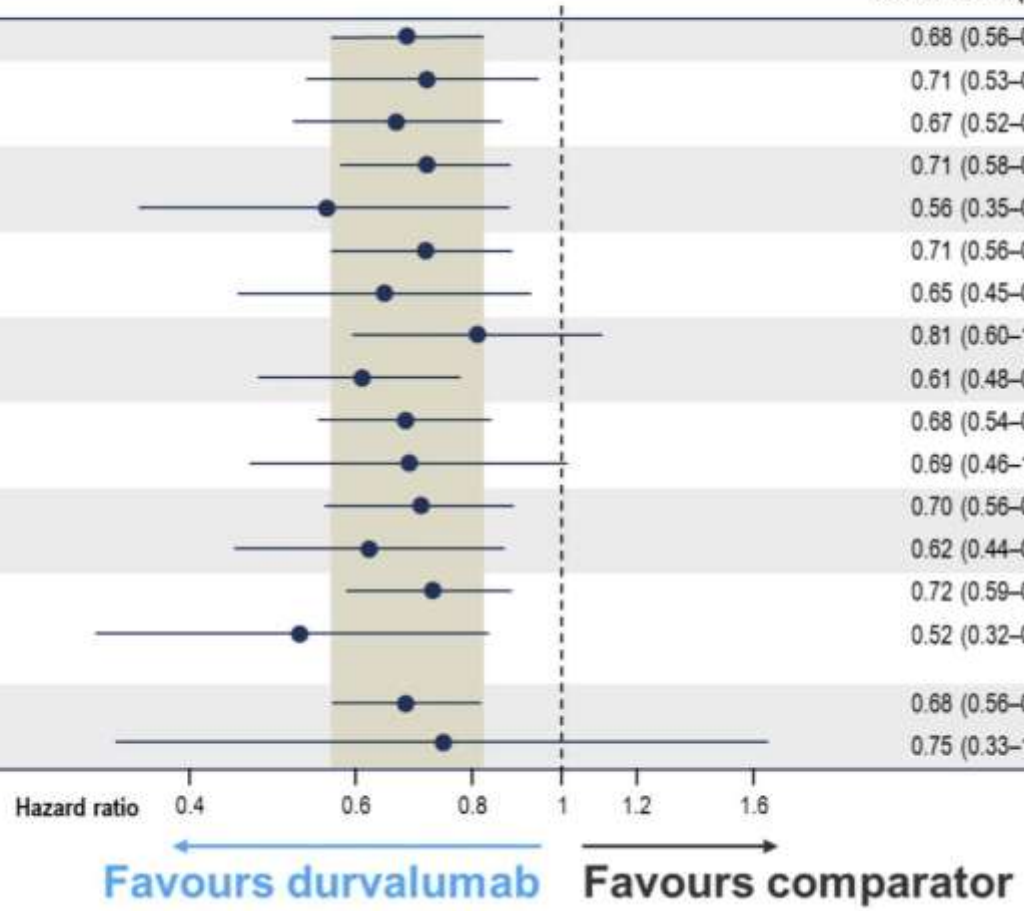
Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan



Sisplatine uygun hastalarda Sisplatin+Gemsitabin+Durvalumab Neoadjuvan

NIAGARA: Event-free Survival Subgroup Analyses

Subgroup	Category	N	Hazard ratio (95% CI)
All patients		1063	0.68 (0.56–0.82)
Age at randomisation	<65 years	499	0.71 (0.53–0.94)
	≥65 years	564	0.67 (0.52–0.86)
Sex	Male	870	0.71 (0.58–0.88)
	Female	193	0.56 (0.35–0.88)
Race	White	712	0.71 (0.56–0.89)
	Non-White	315	0.65 (0.45–0.92)
Tumour stage at baseline	T2N0	428	0.81 (0.60–1.10)
	>T2N0	635	0.61 (0.48–0.78)
Renal function at baseline	CrCl ≥60 mL/min	862	0.68 (0.54–0.84)
	CrCl ≥40–<60 mL/min	201	0.69 (0.46–1.01)
PD-L1 expression at baseline*	High	777	0.70 (0.56–0.88)
	Low/negative	286	0.62 (0.44–0.87)
Histology at baseline	UC	898	0.72 (0.59–0.89)
	UC with divergent differentiation or histologic subtypes	165	0.52 (0.32–0.84)
Lymph node positive at baseline	N0	1005	0.68 (0.56–0.83)
	N1	58	0.75 (0.33–1.64)



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)

Neoadjuvan TAR-200+immünoterapi kombinasyonu

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

Population:
- Aged ≥18 years
- Histologically confirmed cT2-T4a N0M0 MIBC (absence of nodal or metastatic disease at screening)
- Predominant UC histology
- ECOG PS of 0-1
- Ineligible or refusing NAC
- Scheduled for RC

Stratification:
- Visible residual disease at TURBT: complete vs incomplete (≤3 cm)
- Tumor stage at MIBC diagnosis: cT2 vs cT3-4a

R 5:3

4 CYCLES

TAR-200 + Cetrelimab *Cohort 1* (N=79) → **TAR-200** 225 mg gemcitabine Q3W (indwelling) 12 weeks **+ Cetrelimab IV** for 12 weeks

Cetrelimab Monotherapy *Cohort 2* (N=41) → **Cetrelimab IV alone** for 12 weeks

Radical cystectomy

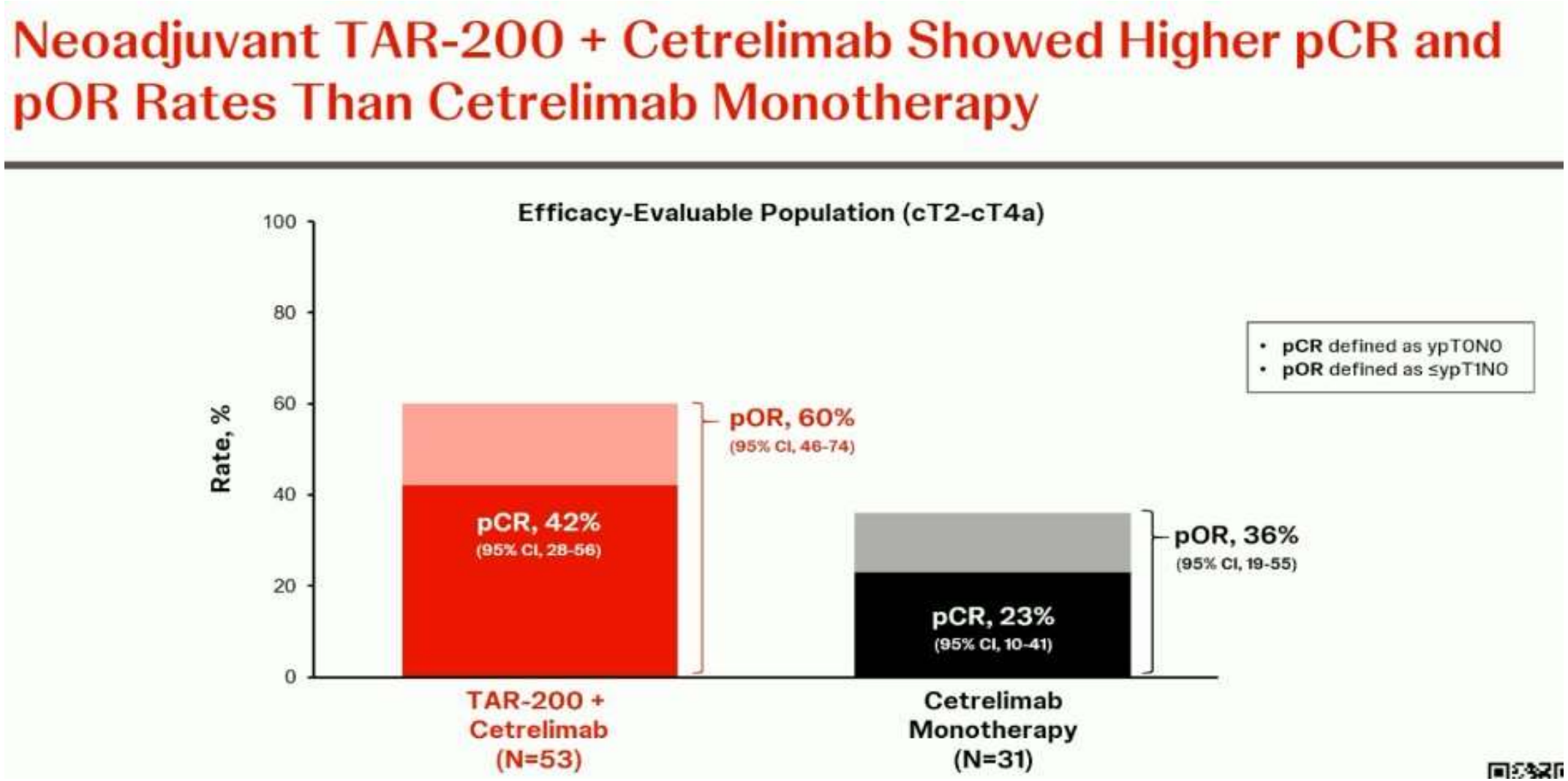
Follow-up Weeks 4-108
- Every 4 weeks until Week 12 post RC
- Every 12 weeks until Week 108 post RC (end of study)

Primary end point
- Pathologic CR rate (ypT0N0)

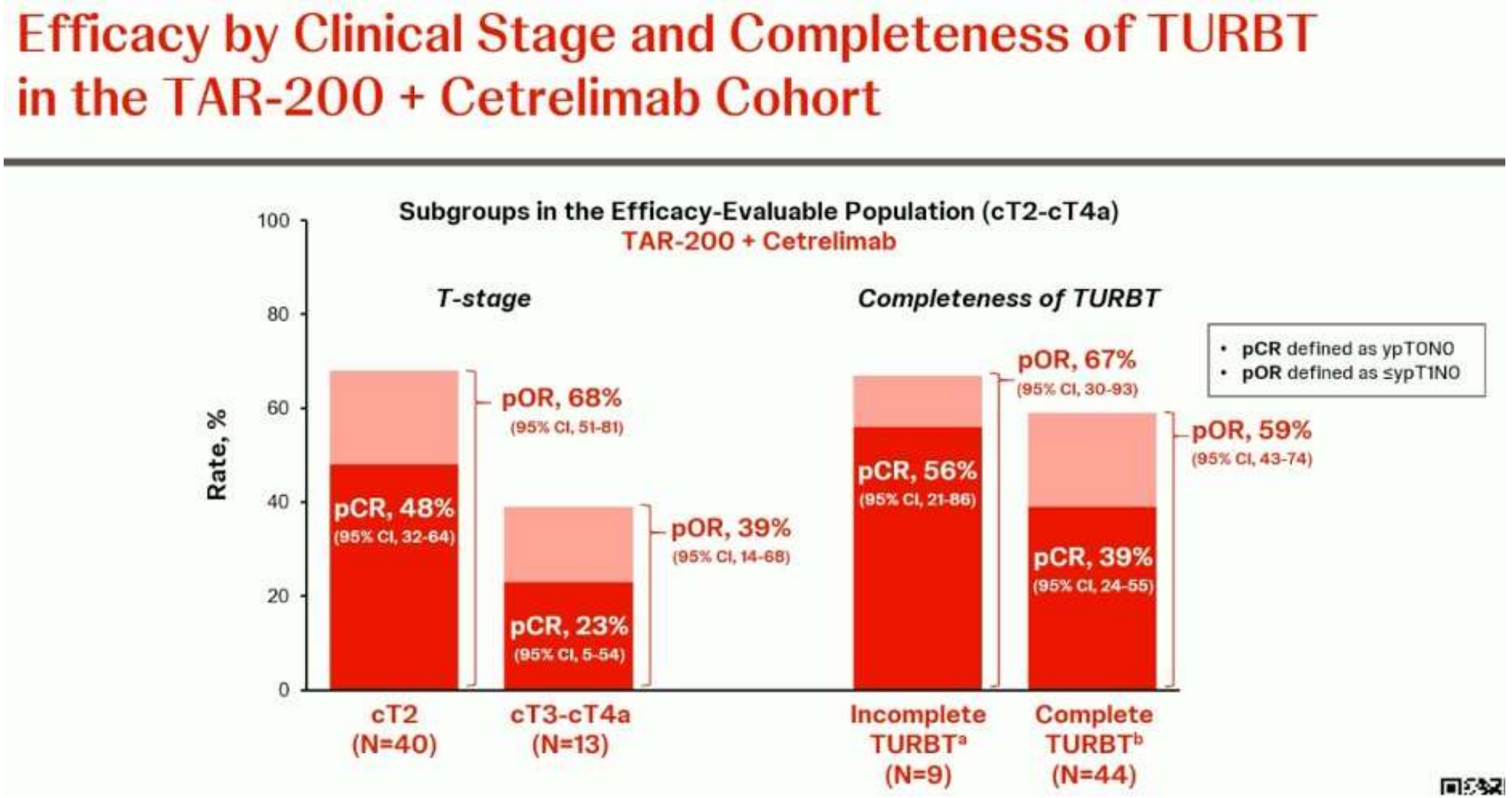
Secondary end points
- Recurrence-free survival
- Safety

Exploratory end points
- Pathologic OR rate (≤ypT1N0)
- Overall survival
- Time to symptomatic progression
- Quality of life according to FACT-BI
- Pharmacokinetics
- Biomarker analysis

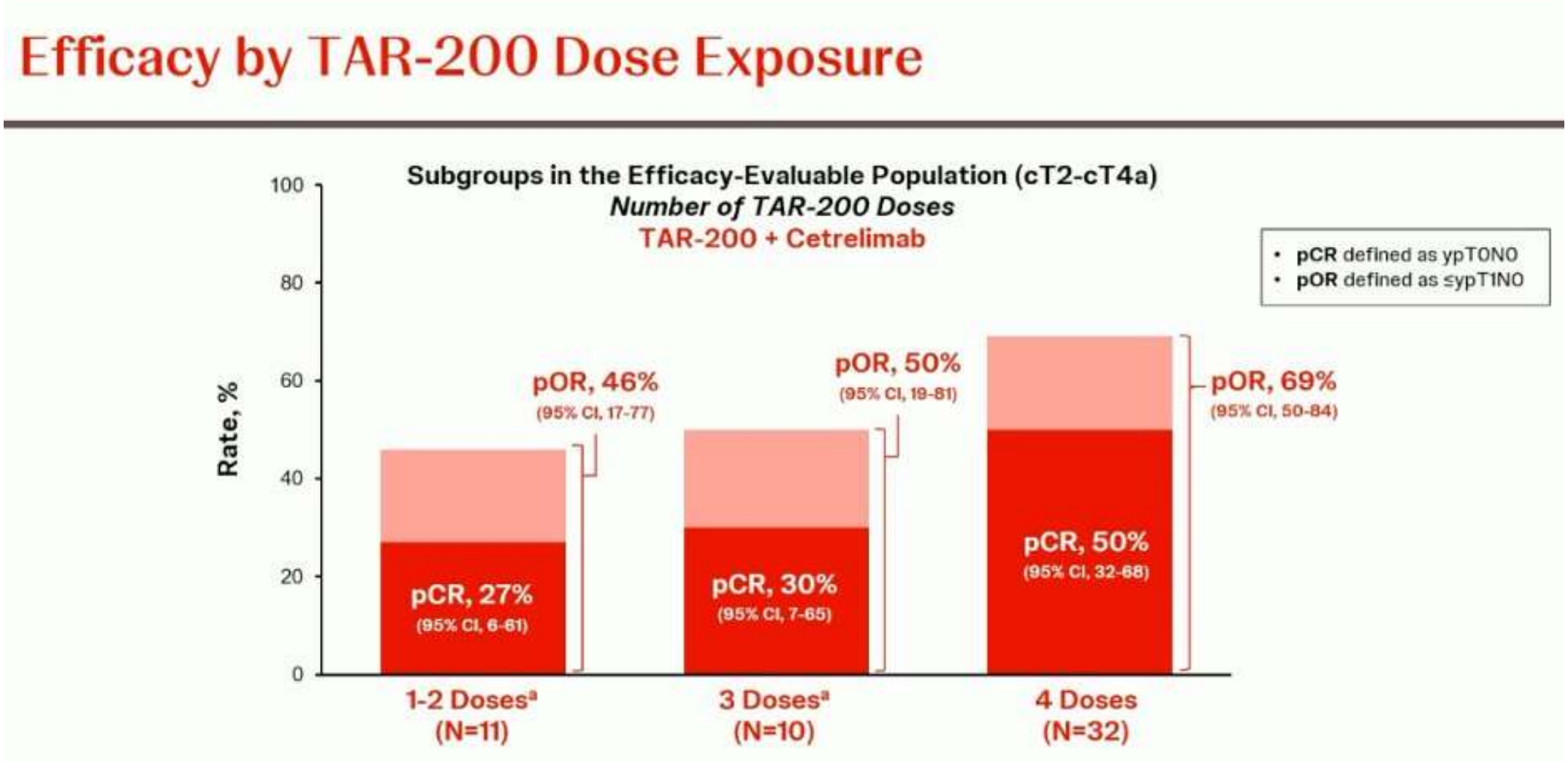
Neoadjuvan TAR-200+immünoterapi kombinasyonu



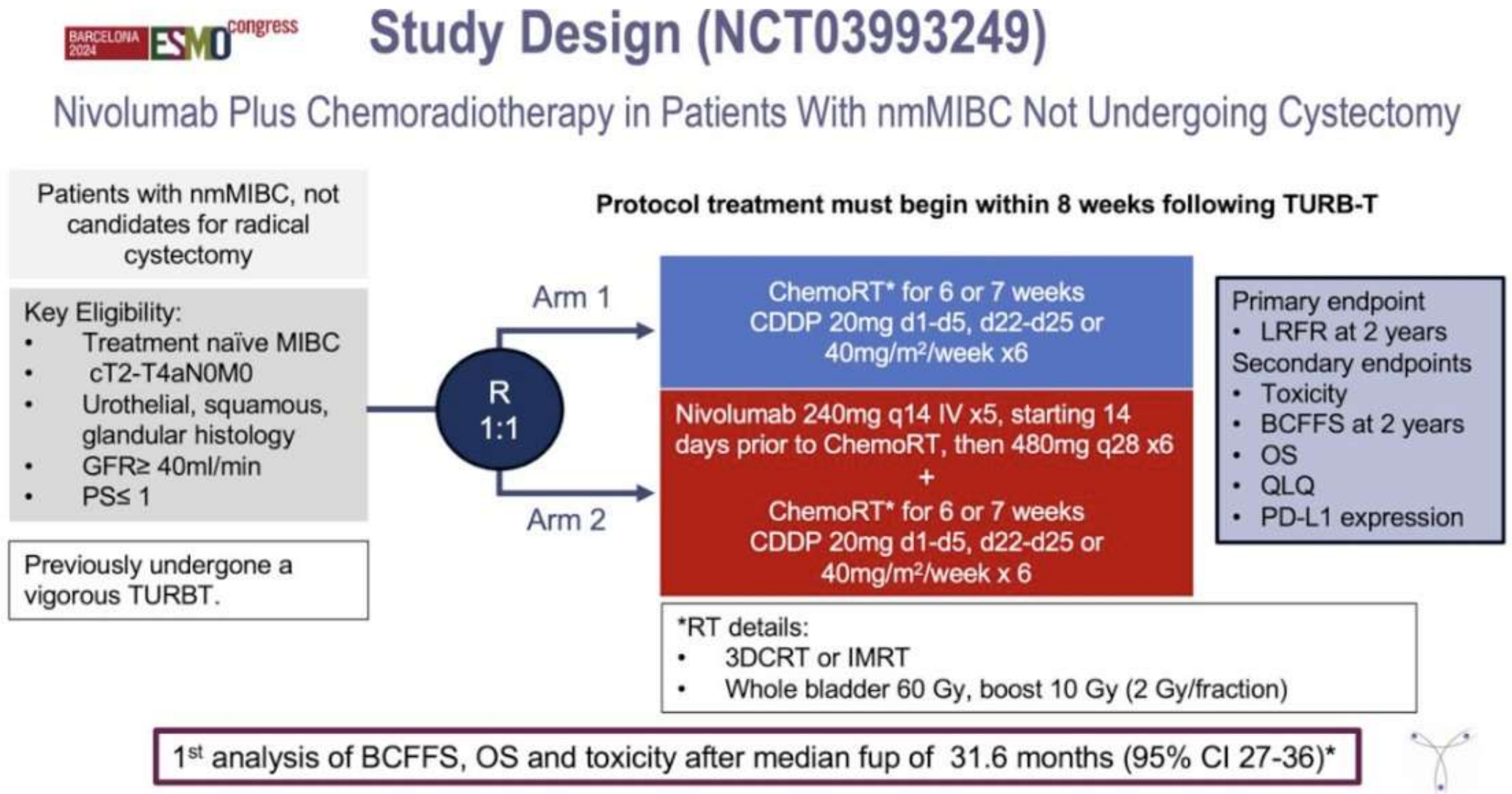
Neoadjuvan TAR-200+immünoterapi kombinasyonu



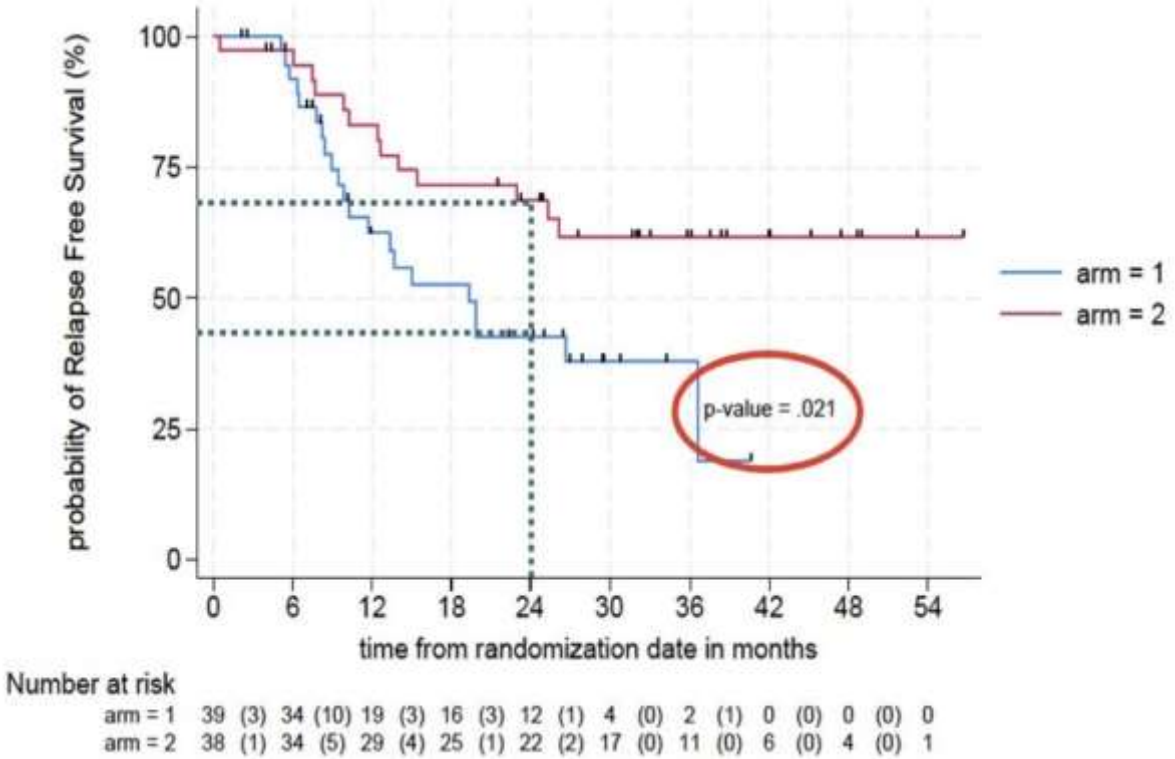
Neoadjuvan TAR-200+immünoterapi kombinasyonu

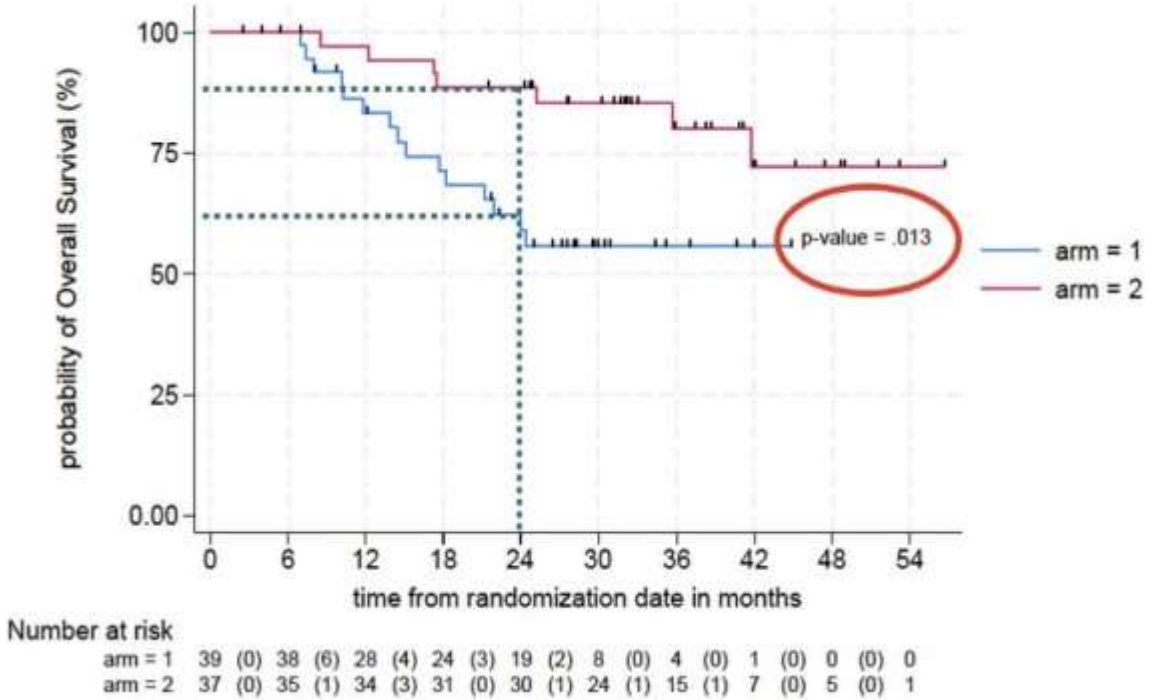


Definitif Radioterapi+kemoterapi+Nivolumab

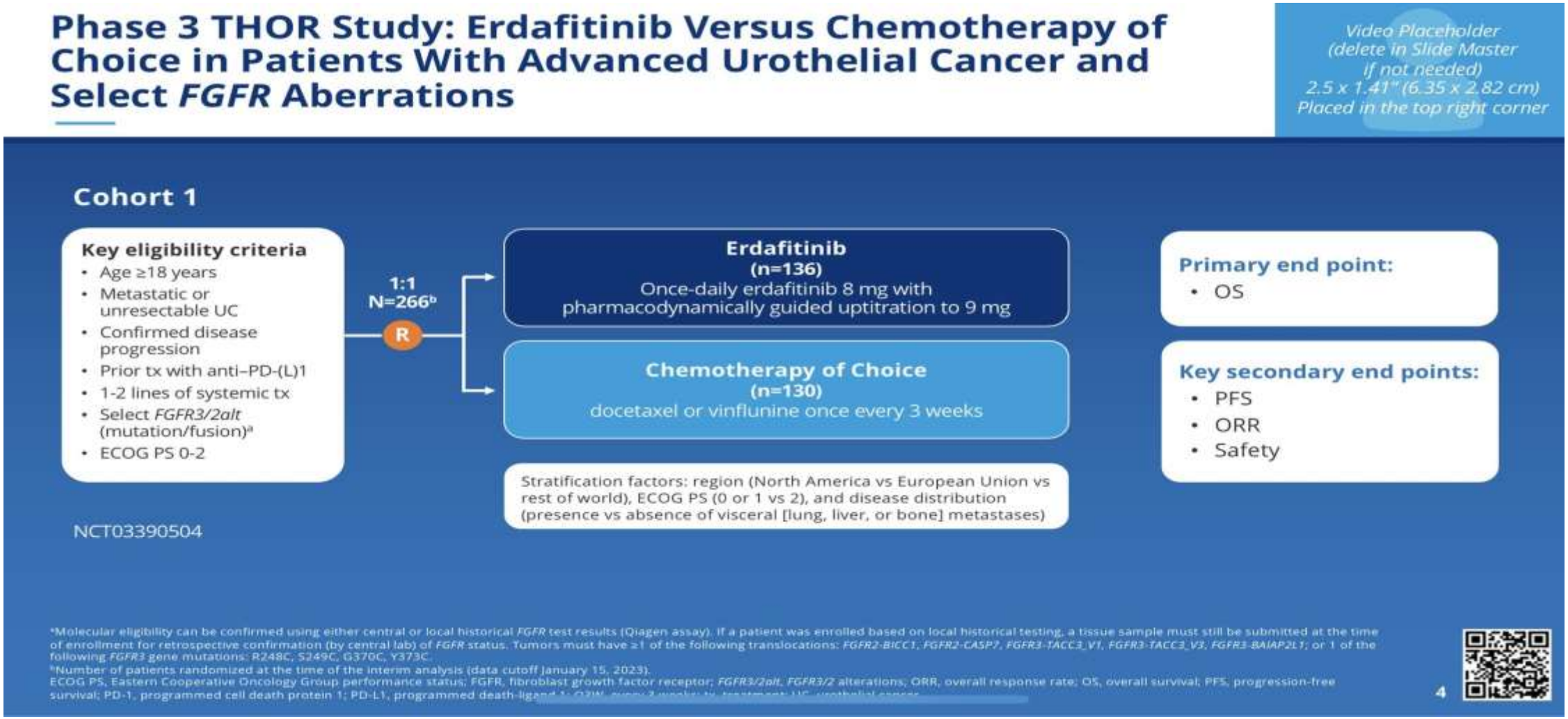


Definitif Radioterapi+kemoterapi+Nivolumab





Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi



Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

Table. Primary and Secondary Outcomes From the THOR Trial

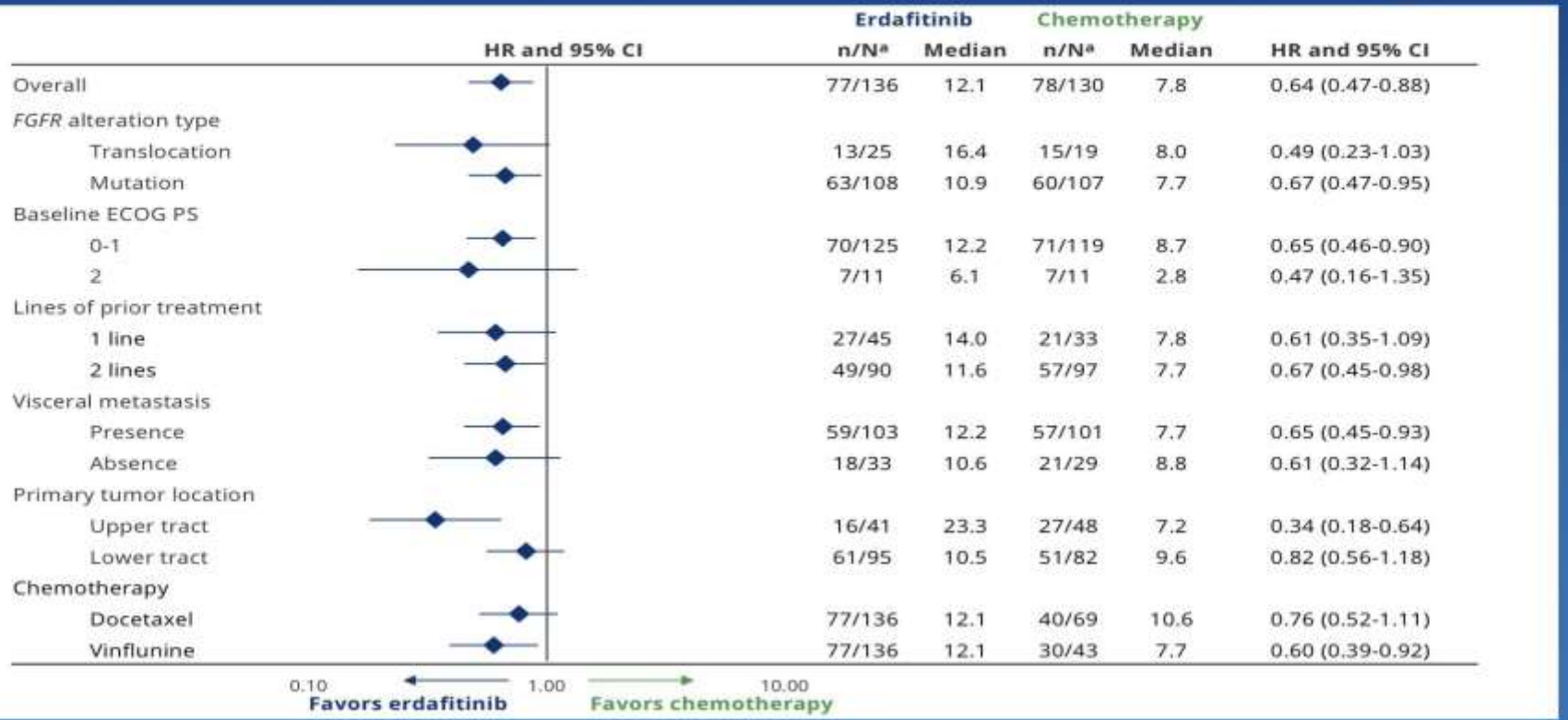
	Erdafitinib (136 patients)	Chemotherapy (130 patients)
OS, median (95% CI), mo	12.1	7.8
HR (95% CI)	0.64 [0.47, 0.88]; $P = .005$	
PFS, median (95% CI), mo	5.6	2.7
HR (95% CI)	0.58 [0.44, 0.78]; $P = .0002$	
ORR, %	45.6	11.5
RR (95% CI)	3.94 [2.37, 6.57]; $P < .001$	

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

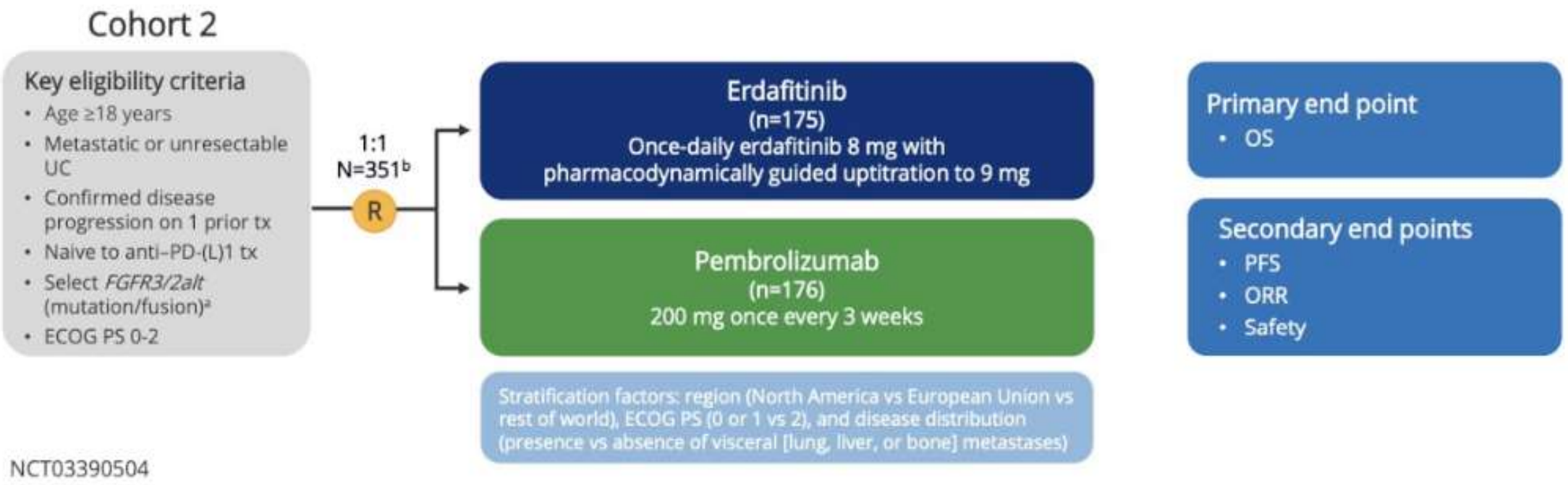
Video Placeholder (delete in Slide Master if not needed) 2.5 x 1.41" (6.35 x 2.82 cm) Placed in the top right corner



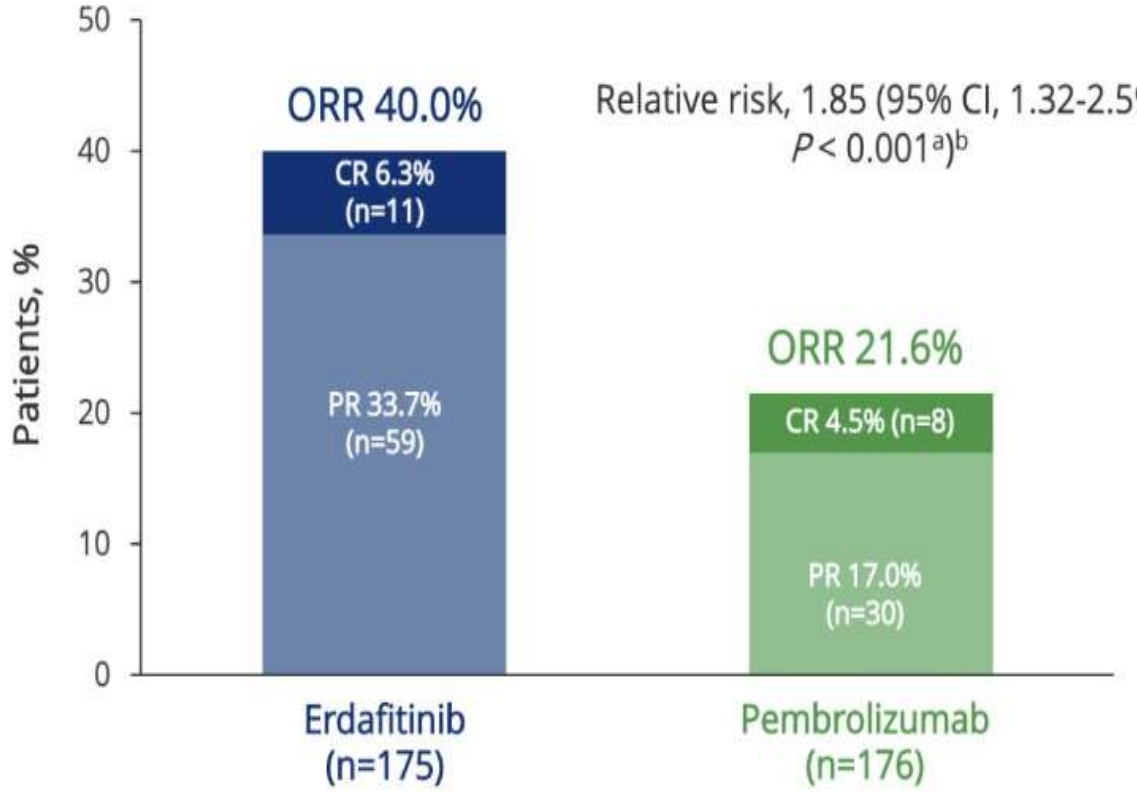
	HR and 95% CI	Erdafitinib n/N[a]	Erdafitinib Median	Chemotherapy n/N[a]	Chemotherapy Median	HR and 95% CI
Overall		77/136	12.1	78/130	7.8	0.64 (0.47-0.88)
FGFR alteration type						
Translocation		13/25	16.4	15/19	8.0	0.49 (0.23-1.03)
Mutation		63/108	10.9	60/107	7.7	0.67 (0.47-0.95)
Baseline ECOG PS						
0-1		70/125	12.2	71/119	8.7	0.65 (0.46-0.90)
2		7/11	6.1	7/11	2.8	0.47 (0.16-1.35)
Lines of prior treatment						
1 line		27/45	14.0	21/33	7.8	0.61 (0.35-1.09)
2 lines		49/90	11.6	57/97	7.7	0.67 (0.45-0.98)
Visceral metastasis						
Presence		59/103	12.2	57/101	7.7	0.65 (0.45-0.93)
Absence		18/33	10.6	21/29	8.8	0.61 (0.32-1.14)
Primary tumor location						
Upper tract		16/41	23.3	27/48	7.2	0.34 (0.18-0.64)
Lower tract		61/95	10.5	51/82	9.6	0.82 (0.56-1.18)
Chemotherapy						
Docetaxel		77/136	12.1	40/69	10.6	0.76 (0.52-1.11)
Vinflunine		77/136	12.1	30/43	7.7	0.60 (0.39-0.92)

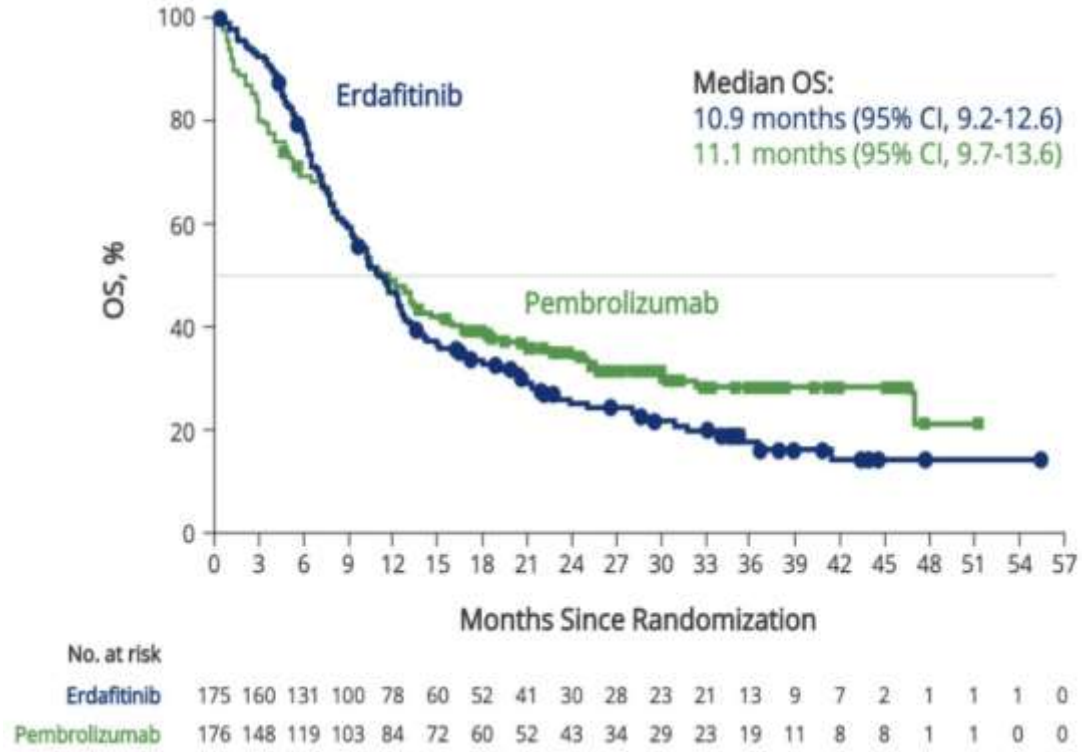
[a]n=number of events; N=number of patients in subgroup. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi



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
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

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

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

Adjuvan Seçenekler

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

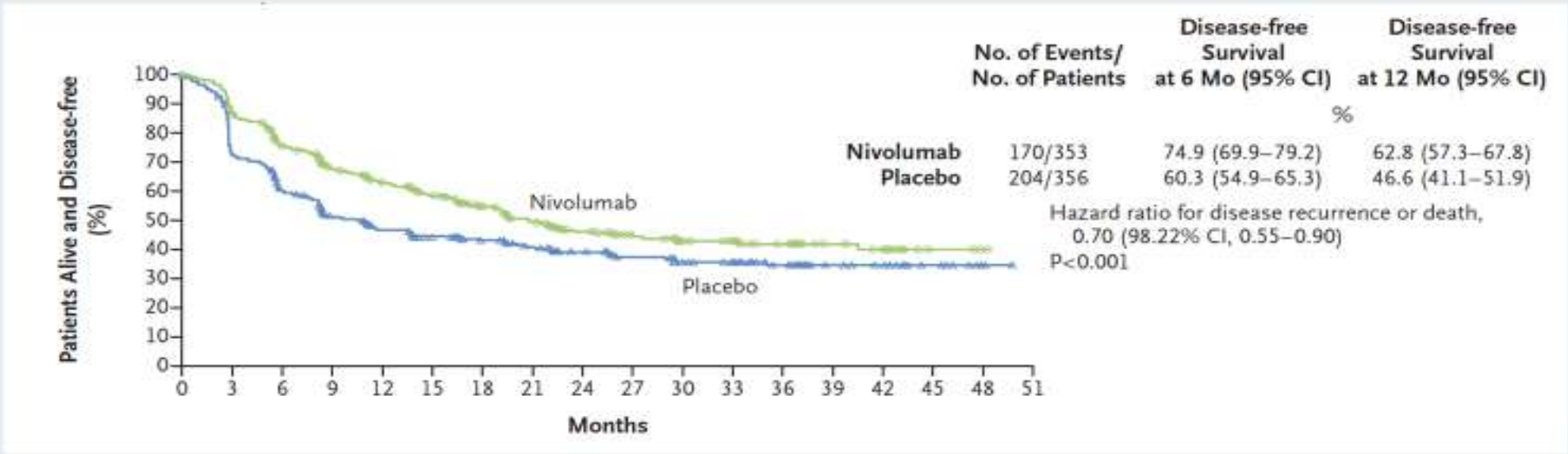
D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette,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

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

RTP RESEARCH TO PRACTICE

Adjuvan Seçenekler

CheckMate 274: Disease-Free Survival in the ITT Population



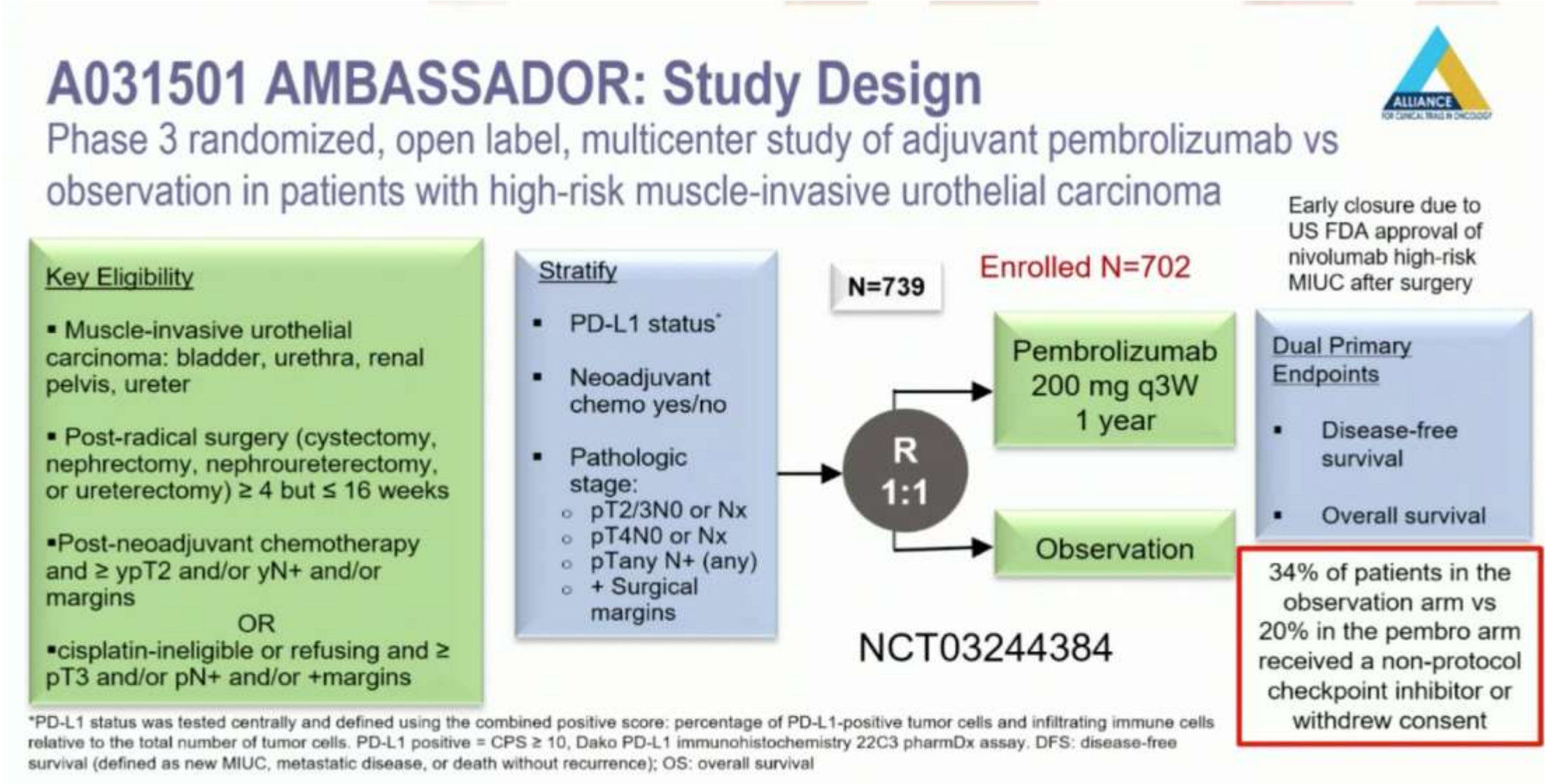
	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

Hazard ratio for disease recurrence or death, 0.70 (98.22% CI, 0.55–0.90)
P<0.001

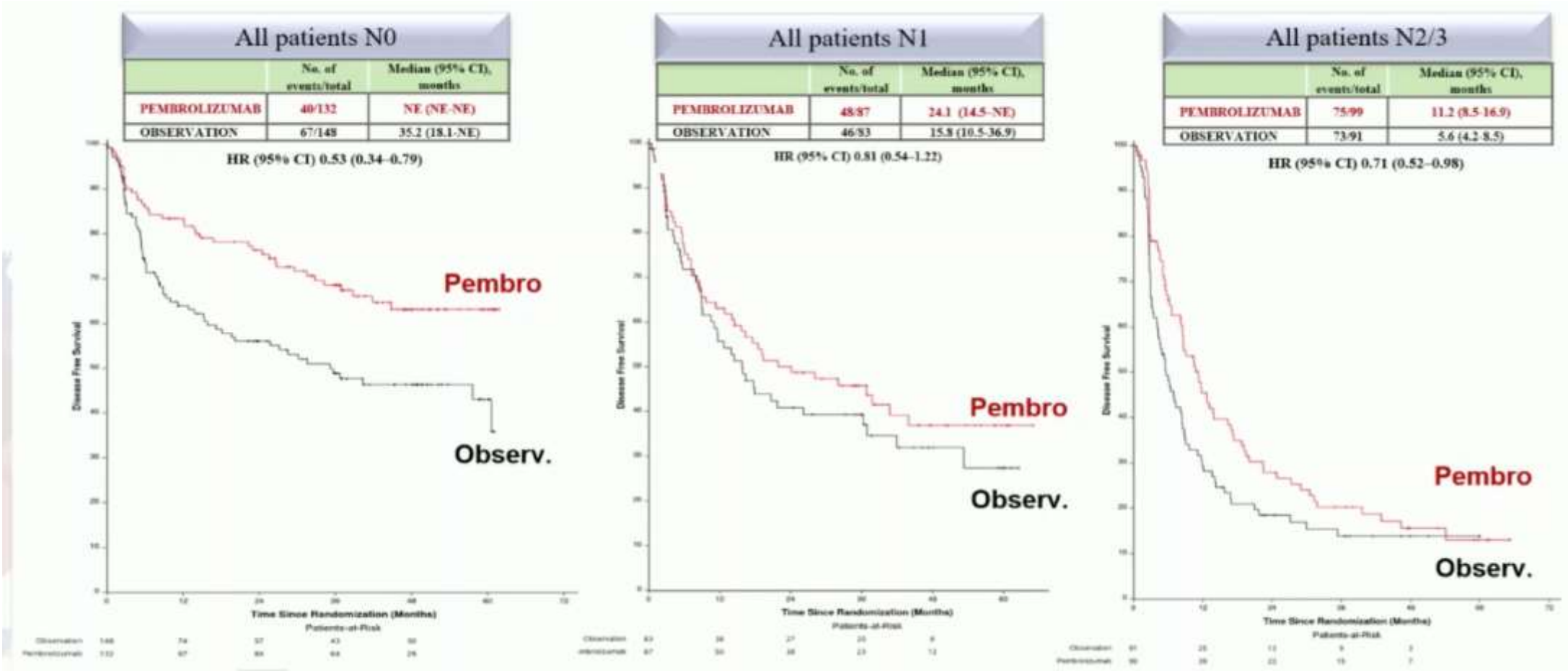
Bajorin DF et al. *N Engl J Med* 2021;384:2102-14.

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

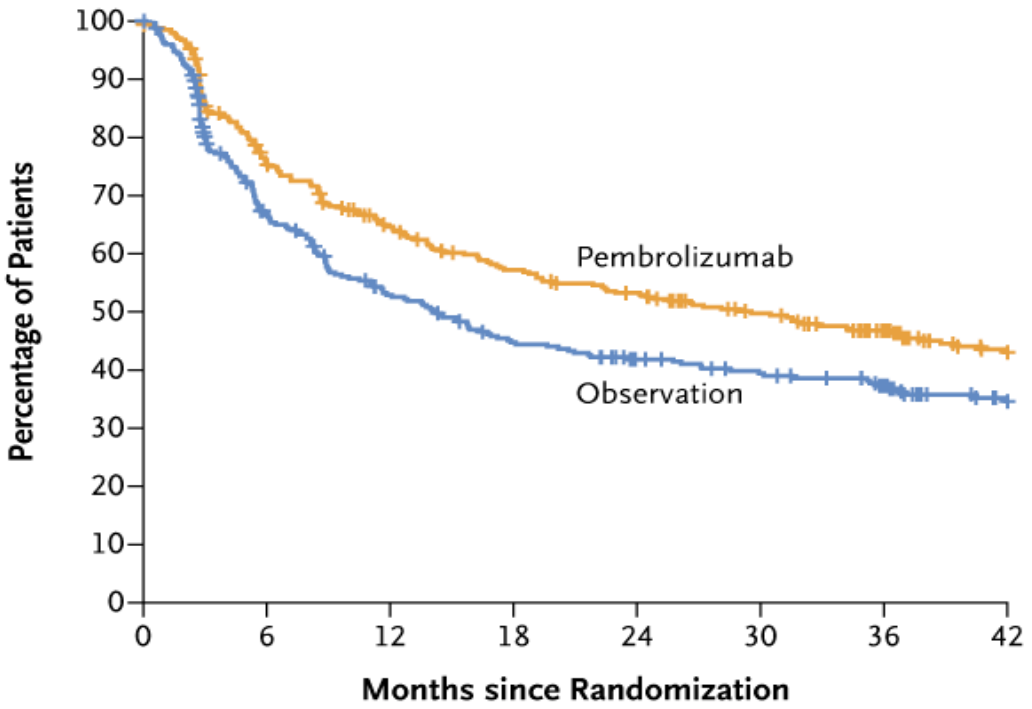
Adjuvan Seçenekler



Adjuvan Seçenekler



Adjuvan Seçenekler



No. at Risk								
Pembrolizumab	354	247	202	174	159	137	114	85
Observation	348	198	150	124	107	96	81	58

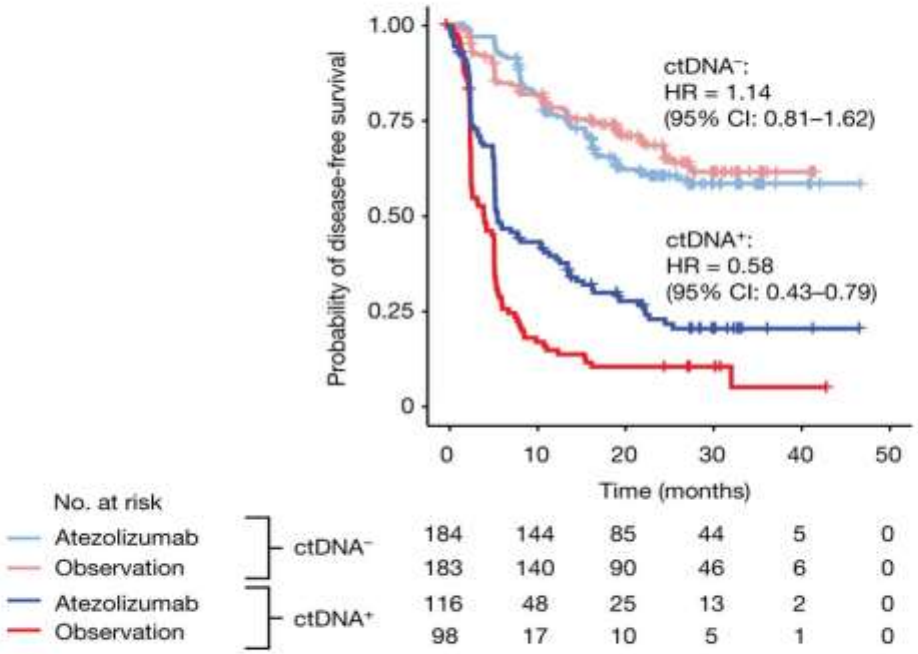
	No. of Events/ Total No. of Patients	Median Disease-free Survival (95% CI)
		mo
Pembrolizumab	185/354	29.6 (20.0–40.7)
Observation	194/348	14.2 (11.0–20.2)

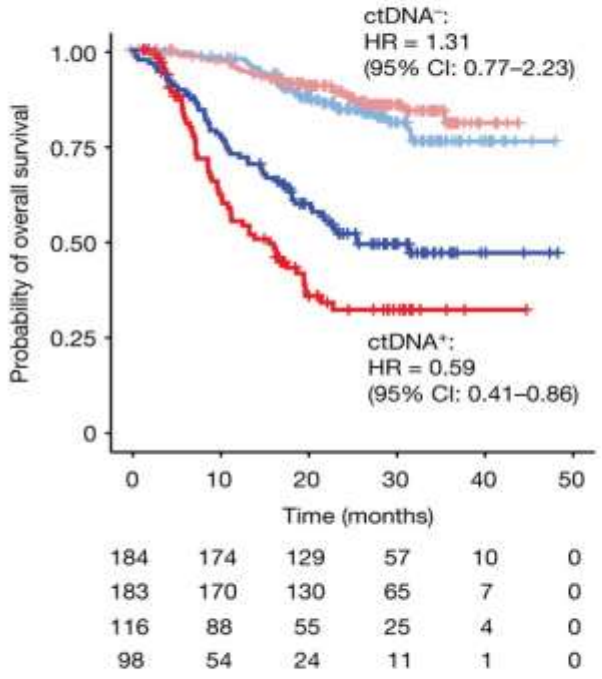
Hazard ratio for disease progression or death, 0.73 (95% CI, 0.59–0.90)
Stratified P=0.003 by log-rank test

Neoadjuvan tedavi sonrası ≥ pT2 ≥ +/- pN+ adjuvan pemrolizumab 12 ay kulanımı nüks riskini ortalama %30 düşürüyor

Gelecek Perspektif

Can ctDNA help Guide Adjuvant Therapy ?



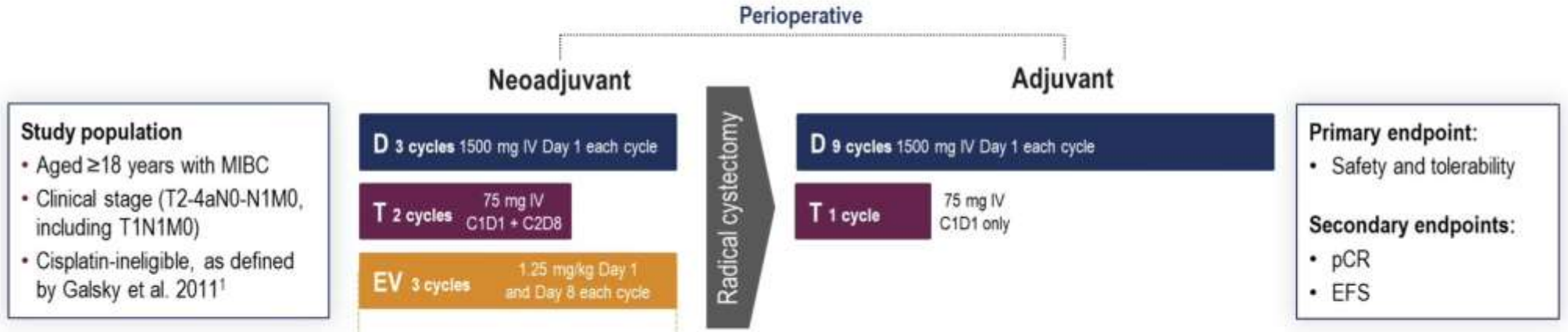


Powles, Nature, 2021

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



ctDNA analysis

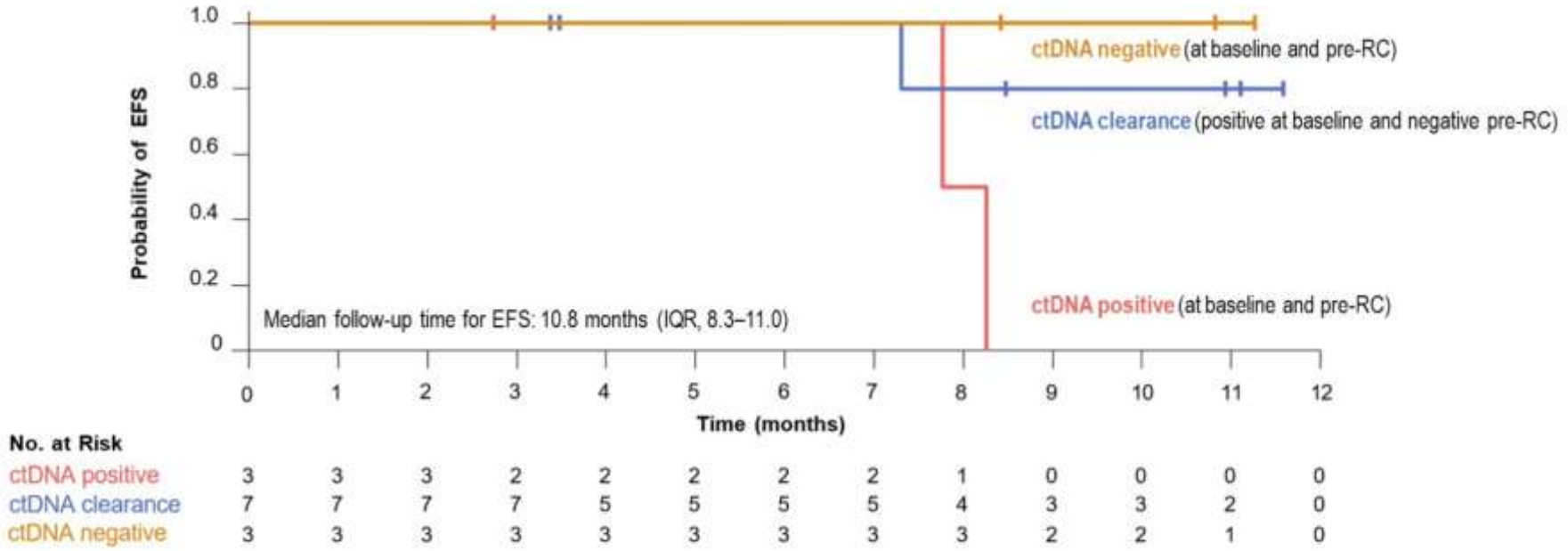
Baseline plasma sample

Pre-RC plasma sample (or Cycle 3, Day 1 sample)

- Cell-free DNA from plasma samples was assessed using GRAIL's Research Use Only (RUO) technology solution which detects methylation indicative of tumour DNA (GRAIL, Inc.)[2]
  - Cancer score cutoff: the exact choice of threshold is governed by the specificity parameter of GRAIL's algorithm; for this analysis, a specificity threshold of 98% was chosen, meaning 98% of non-cancer samples in a held-out calibration set would be correctly identified as negative for ctDNA[2]
- ctDNA detection at baseline and pre-RC were evaluated for association with pathologic assessment at RC and EFS

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**

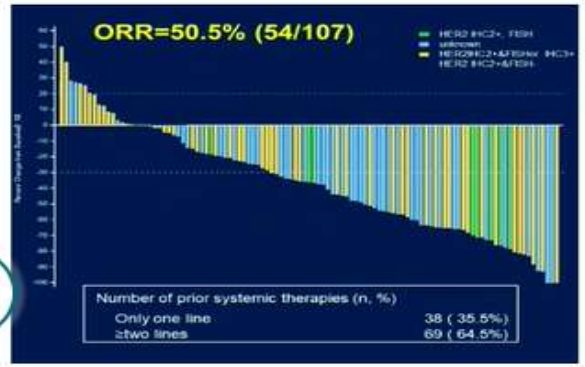
Gelecek Perspektif

Does CPI combine best with ADCs with MMAE payloads?

Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

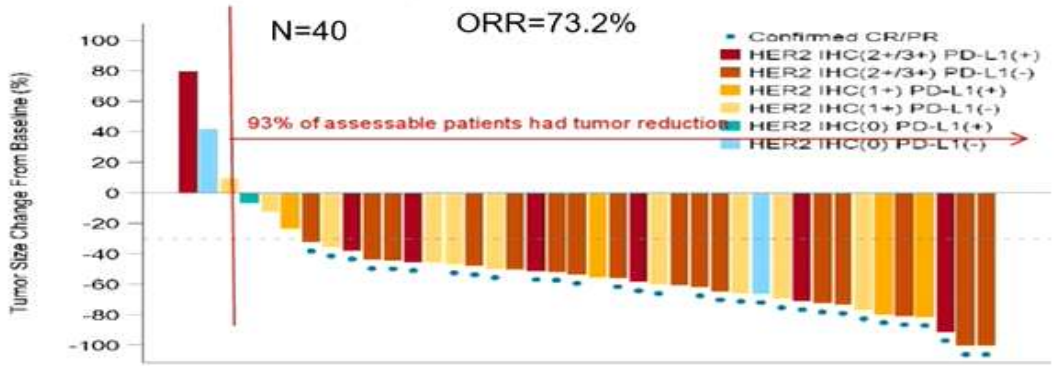
Disitamab vedotin

N=107 In the Second or Third-line setting



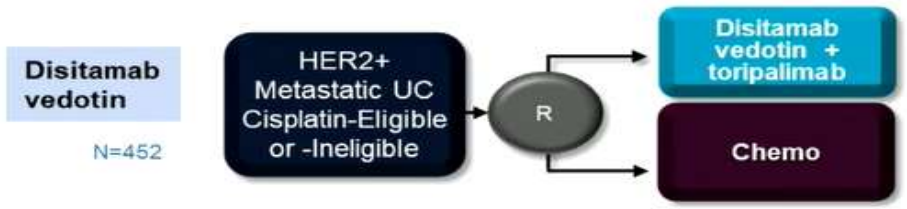
Sheng, et al. ASCO 2022 abstract 4518

Disitamab vedotin + toripalimab

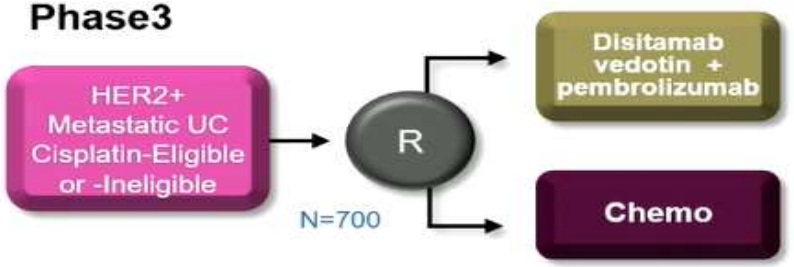


Sheng, X., et al. ASCO 2023

Phase 3



Phase3



Presented by Andrea B. Apolo, MD

@apolo_andrea

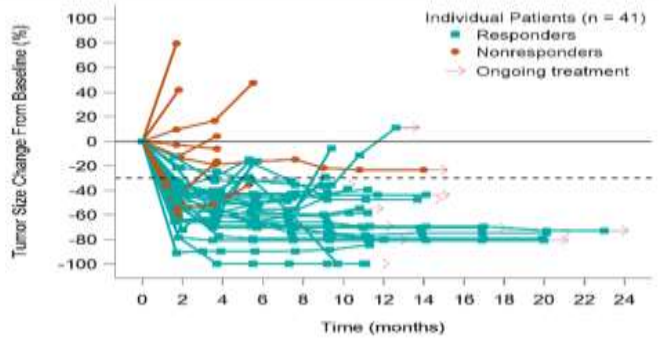
Gelecek Perspektif

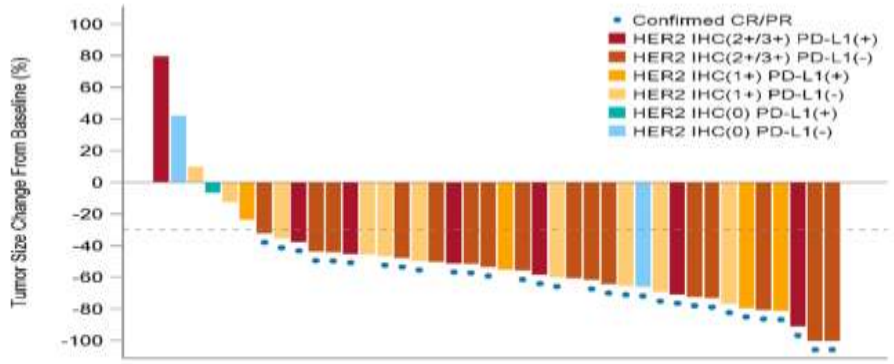
Phase 1b/2 Study C014: Disitamab vedotin + Toripalimab in Urothelial Cancer

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%**

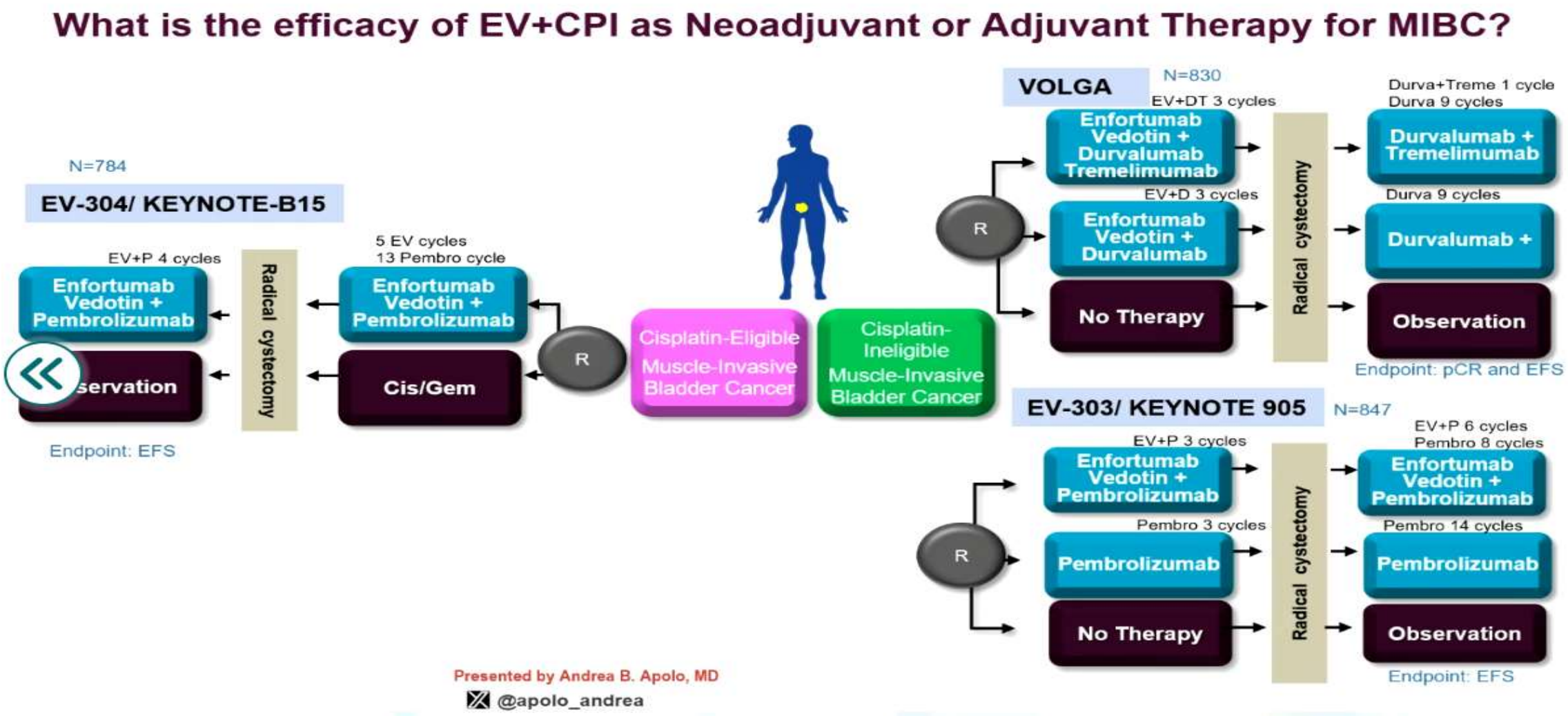
cORR by HER2 and PD-L1 Expression Status		
	PD-L1 (+)	**PD-L1 (-)**
HER2 IHC 2+, 3+	75% (n=8)	87.5% (n=16)
HER2 IHC 1+	50% (n=4)	70% (n=10)
HER2 IHC 0	0 (n=1)	50% (n=2)



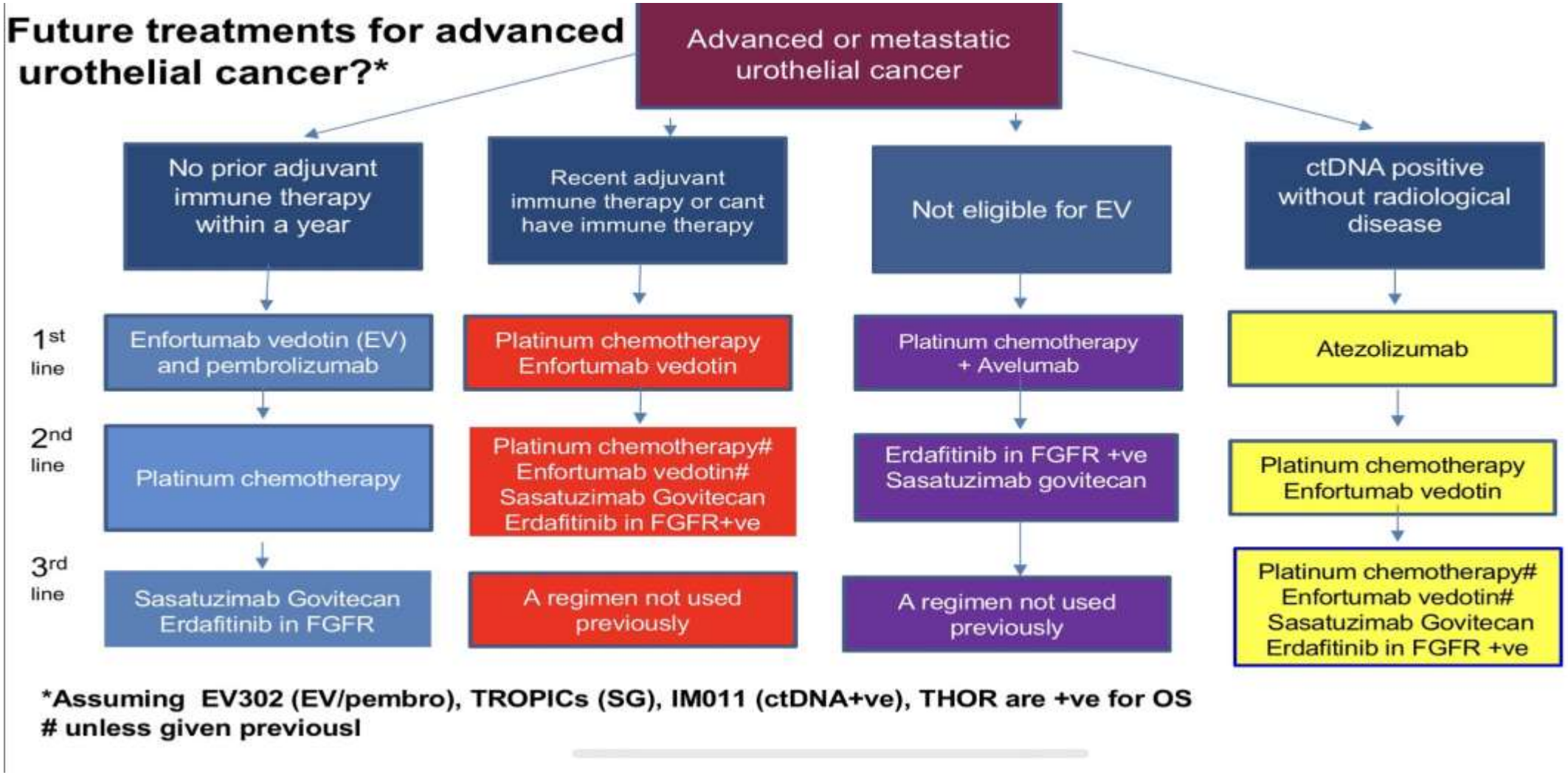


Sheng, et al. Abs 4566, ASCO 2023.

Gelecek Perspektif



Gelecek Perspektif



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≥2, komorbidite vs.) PD-L1 düzeyinden bağımsız Pemrolizumab önerilebilir