

Metastatik Mesane ve Üst Üriner Sistem Kanserlerinde Sistemik Tedavi

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Tıbbi Onkoloji

Ders Planı

- ❑ Mesane Kanseri İnsidans ve Mortalite

Metastatik Hastalık

- ❑ Sisplatine uygun hastada birinci basamak

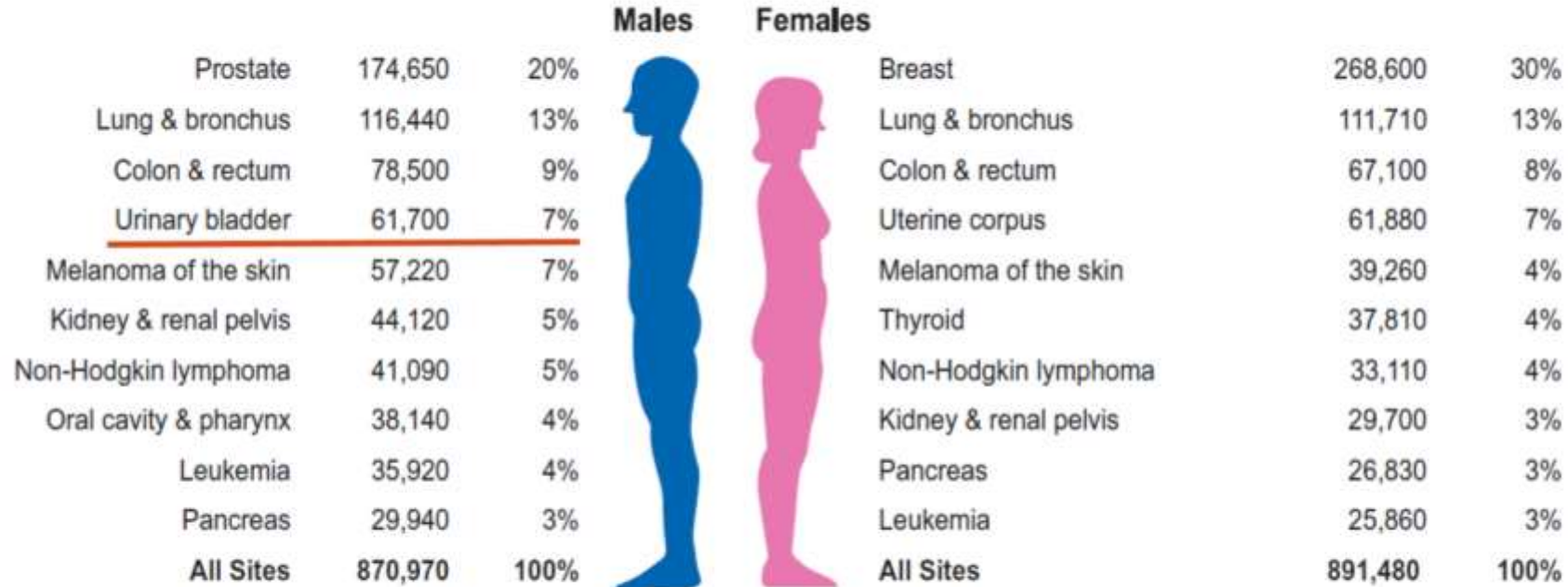
- ❑ Sisplatine uygun olmayan hastada birinci basamak

- ❑ İkinci basamak ve sonrası tedavi seçenekleri

- ❑ Özet

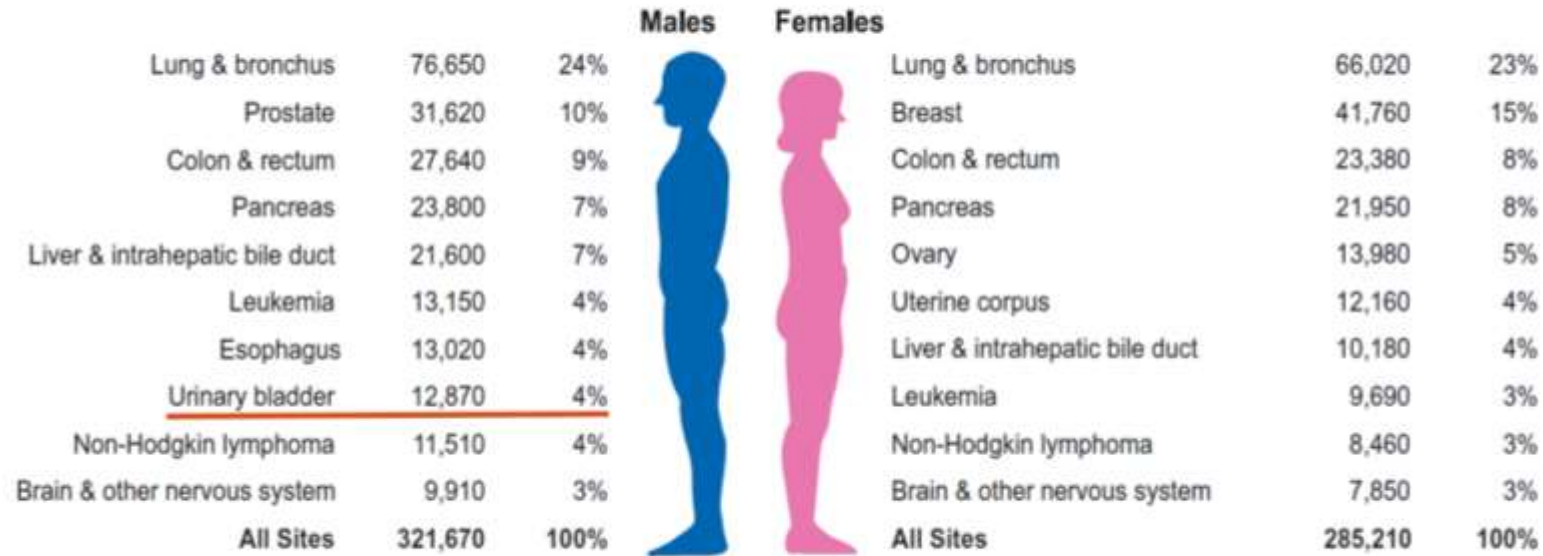
Mesane Kanseri İnsidans ve Mortalite

2019 ESTIMATED NEW CANCER CASES — US



Mesane Kanseri İnsidans ve Mortalite

2019 ESTIMATED CANCER DEATHS – US

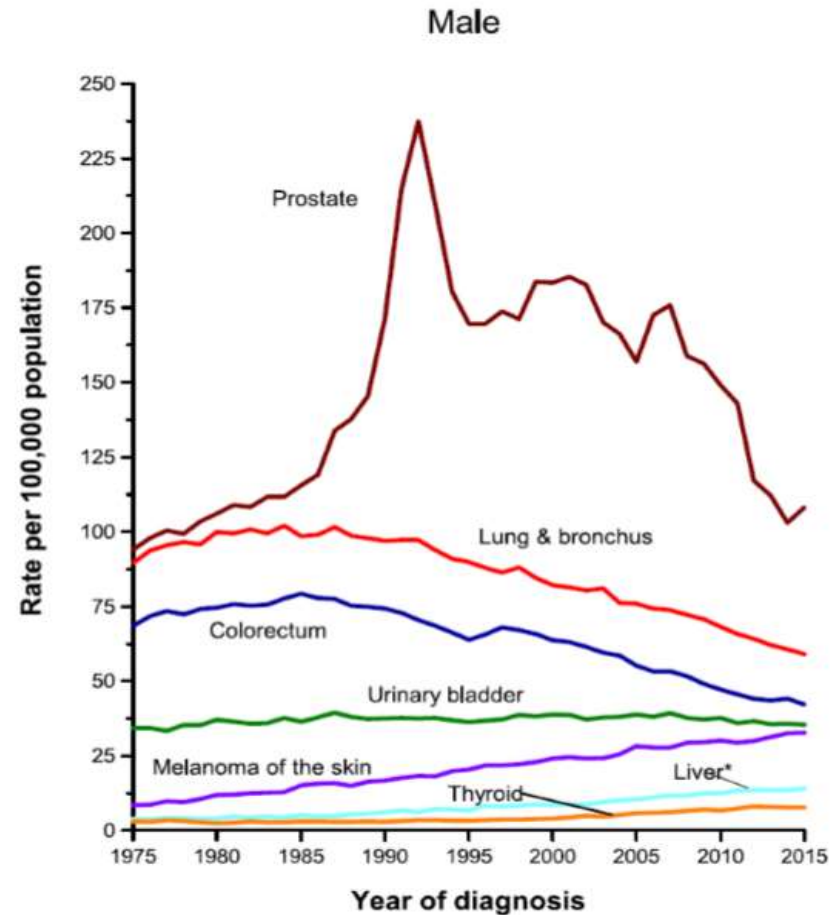


Mesane Kanseri İnsidans ve Mortalite

TEMPORAL TRENDS IN THE INCIDENCE OF BLADDER CANCER

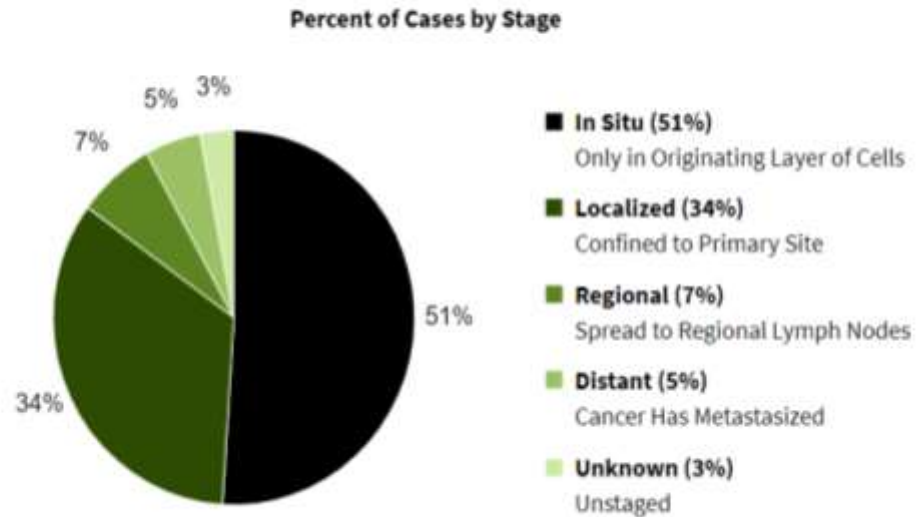
- The incidence of several major cancers has fallen over the last 40 years
 - There have been increased incidence in a few (melanoma and liver for example)
- No major changes in the incidence of bladder cancer in the last 40 years

CA CANCER J CLIN 2019;69:7-34

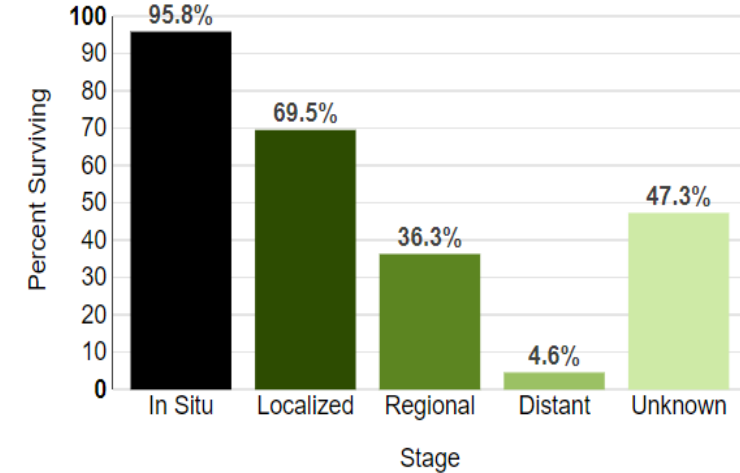


Mesane Kanseri İnsidans ve Mortalite

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



5-Year Relative Survival



SEER 18 2009-2015, All Races, Both Sexes by SEER Summary Stage 2000

Metastatik Mesane Kanseri

Birinci Basamak Kemoterapi

Selected randomized clinical trial comparisons of chemotherapy for metastatic bladder cancer

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

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

Metastatik Birinci Basamak Kemoterapi Sonuçları

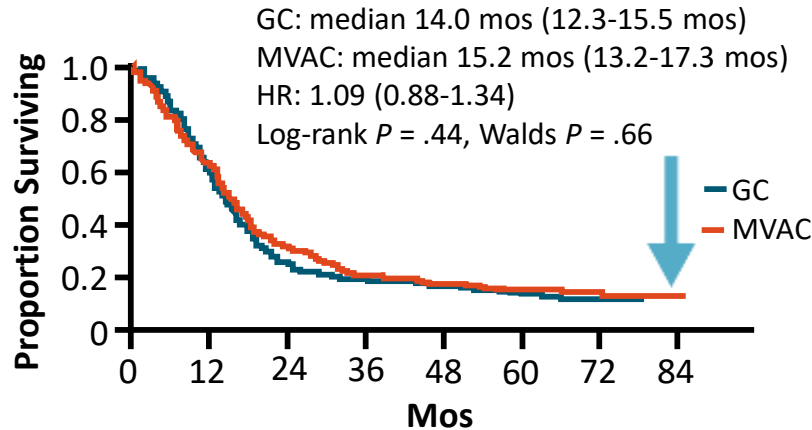
Sisplatin Uygun

Gemcitabine + Cisplatin^[1,2]

ORR: 49%

CR: 12%

Median OS: 14.0 mos



Patients at Risk, n

GC 203 118 50 36 30 23 7 0

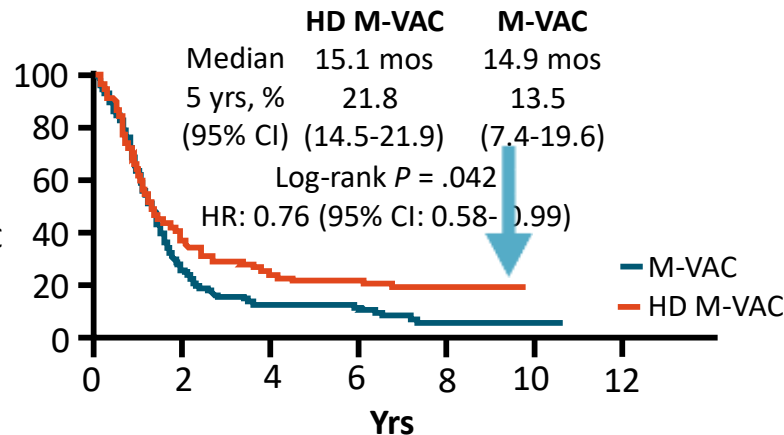
MVAC 202 125 62 40 34 29 9 1

Dose Dense MVAC^[3]

ORR: 72%

CR: 25%

Median OS: 15.1 mos



O N Patients at Risk, n

112 129 32 15 11 4 2 M-VAC

101 134 45 29 23 8 0 HD M-VAC

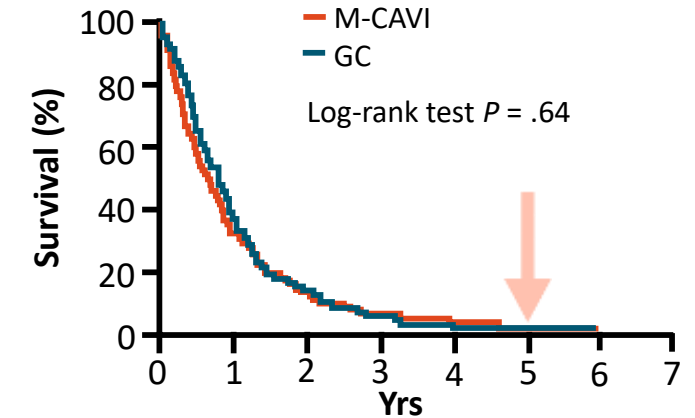
Sisplatin uygun değil

Gemcitabine + Carboplatin^[4]

ORR: 36%

CR: 3%

Median OS: 9.3 mos



O N Patients at Risk, n

M-CAVI 108 119 37 13 7 3 1 1

GC 110 119 44 15 5 2 2 1

1. von der Maase H, et al. J Clin Oncol. 2005;23:4602-4608. 2. von der Maase H, et al. J Clin Oncol. 2000;18:3068-3077.

3. Sternberg CN, et al. Eur J Cancer. 2006;42:50-54. 4. De Santis M, et al. J Clin Oncol. 2012;30:191-199.

Metastatik Birinci Basamak Kemoterapi Sonuçları

Cisplatin-based yields higher CR rates than carboplatin-based therapy in UC

Objective response

Source	Cisplatin-based		Carboplatin-based		Weight (%)	RR (95% CI)	P value
	Events	Total	Events	Total			
Petrioli et al. [15]	12	23	9	23	20.64	1.75 (1.05–2.93)	
Bellmunt et al. [13]	20	28	11	27	16.58	1.33 (0.70–2.54)	
Drecier et al. [2]	14	36	12	39	21.23	1.26 (0.68– 2.36)	
Dogliotti et al. [14]	27	41	22	39	41.55	1.17 (0.82–1.66)	
Overall (Mantel–Haenszel method)	73	128	54	128		1.34 (1.04–1.71)	0.02

Heterogeneity chi-square test = 1.68 (d.f. = 3); $P = 0.642$; I-squared test (variation in RR attributable to heterogeneity) = 0.0%.

RR, risk ratio; CI, confidence interval.

Complete response

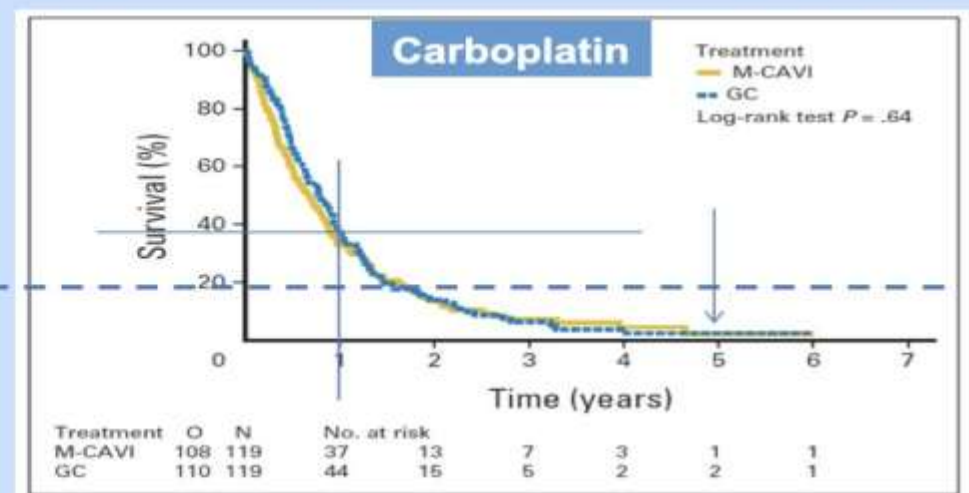
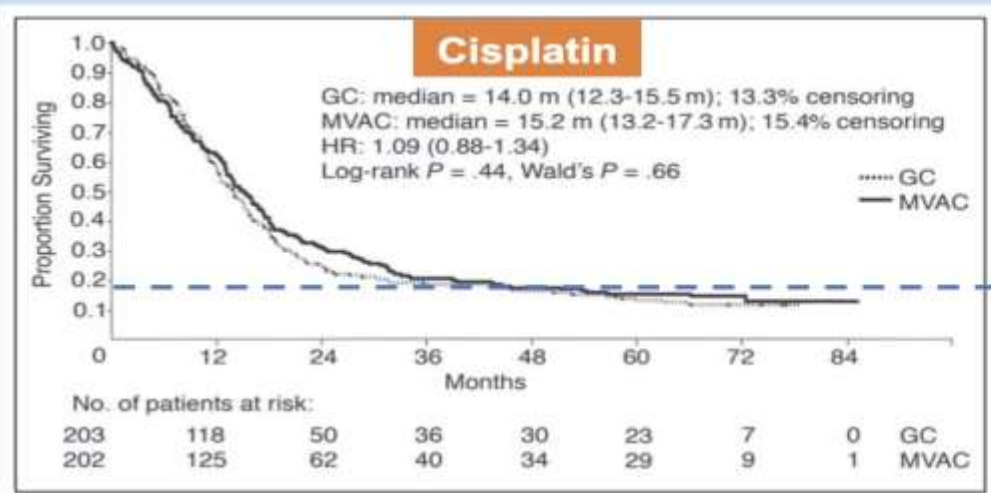
Source	Cisplatin-based		Carboplatin-based		Weight (%)	RR (95% CI)	P value
	Events	Total	Events	Total			
Petrioli et al. [15]	7	28	3	27	51.80	2.25 (0.65–7.18)	
Bellmunt et al. [13]	3	23	0	23	14.54	1.17 (0.07–18.58)	
Drecier et al. [2]	5	36	1	39	16.28	5.42 (0.66–44.12)	
Dogliotti et al. [14]	8	41	1	39	17.38	7.61 (0.10–58.06)	
Overall (Mantel–Haenszel method)	23	128	5	128		3.54 (1.48–8.49)	0.005

Heterogeneity chi-square test = 1.83 (d.f. = 3); $P = 0.609$; I-squared test (variation in RR attributable to heterogeneity) = 0.0%.

RR, risk ratio; CI, confidence interval.

Metastatik Birinci Basamak Kemoterapi Sonuçları

Where is the tail of the curve with carboplatin-based chemotherapy?



1. von der Maase H, et al. J Clin Oncol. 2005. PMID: 16034041
2. De Santis M, et al. EORTC 30986. J Clin Oncol. 2011. PMID: 19786668

Hangi Kemoterapi Rejimi ? dd-MVAC/GC

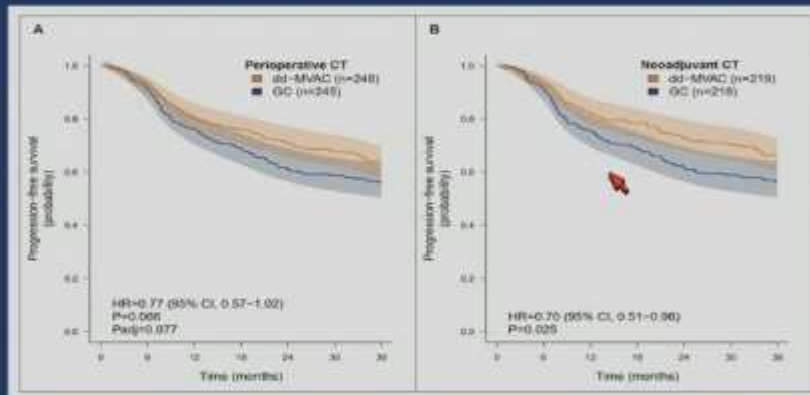
Trial design (3)

- 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

#ASCO23

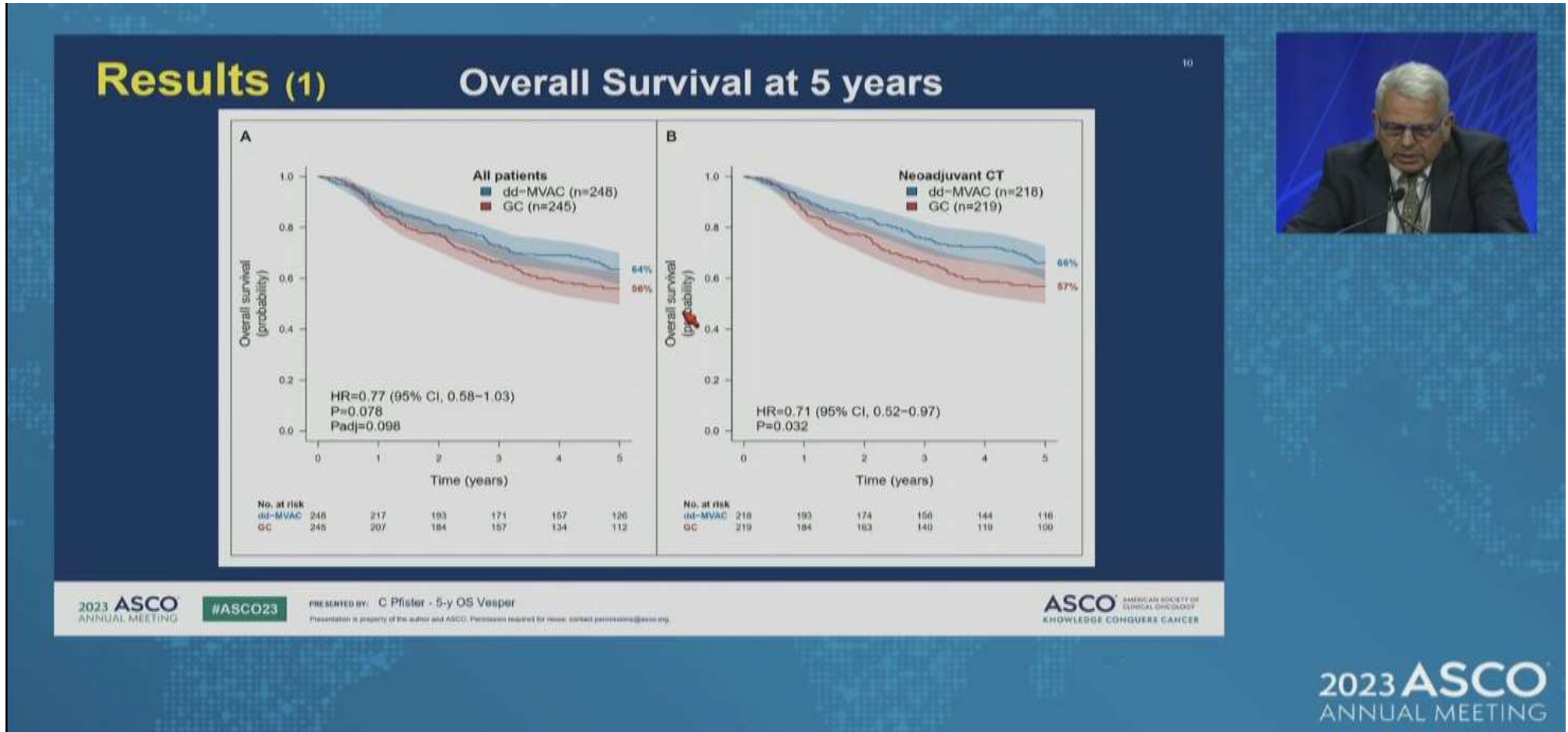
PRESENTED BY: C Pfister - 5-y OS Vespel

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KNOWLEDGE CONQUERS CANCER

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](#)

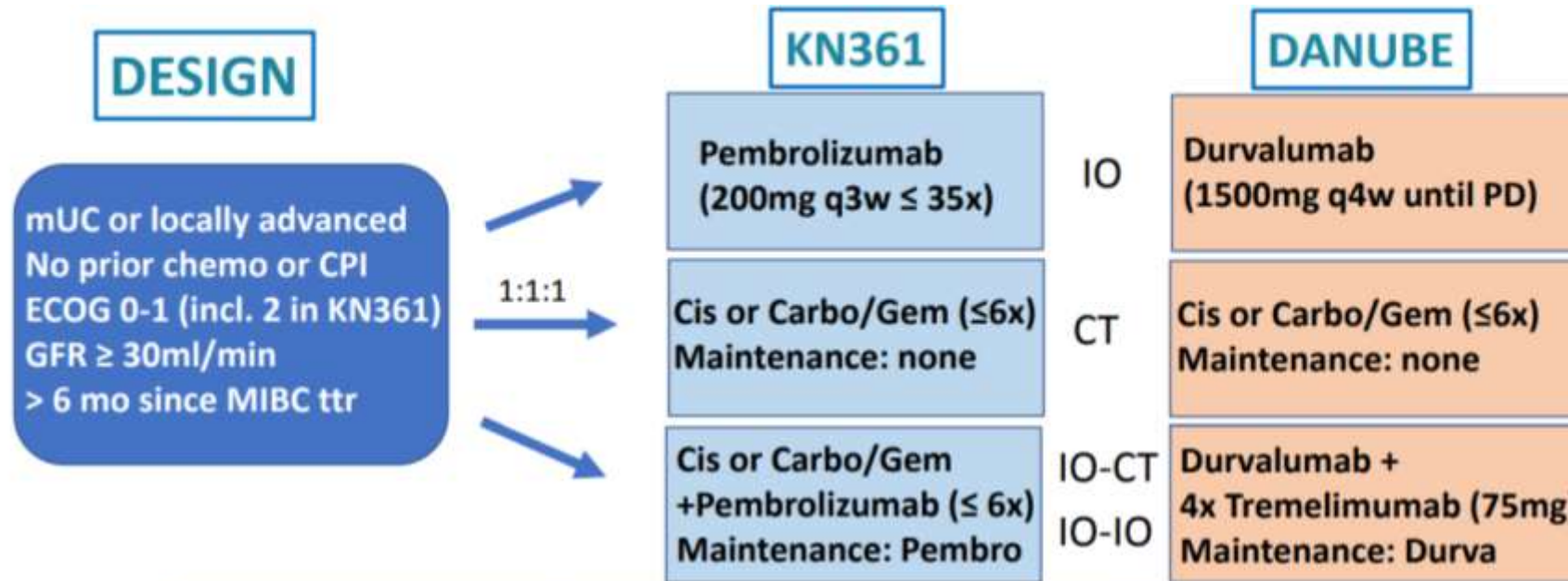
PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	Preferred regimens • Pembrolizumab and enfortumab vedotin-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

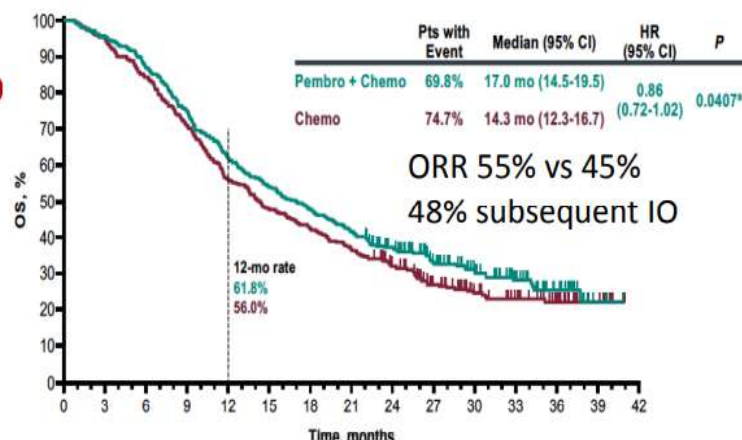
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

Overall survival

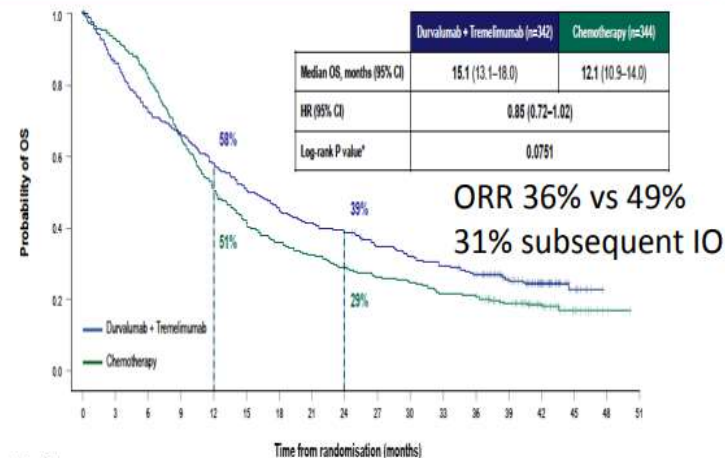
Combination vs Chemo

TOTAL population (ITT)

KEYNOTE 361 –IO-CT vs CT (1°EP)

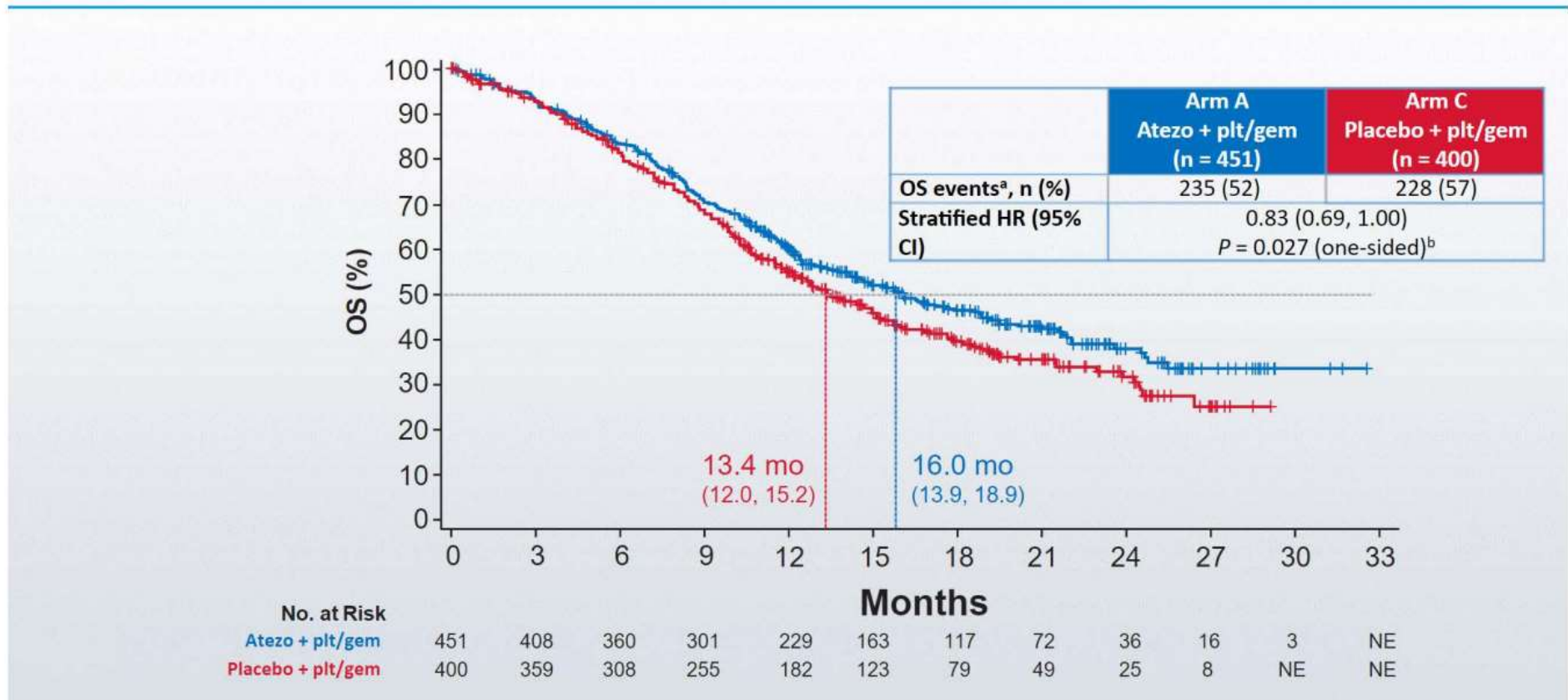


DANUBE – IO-IO vs CT (1°EP)



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

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

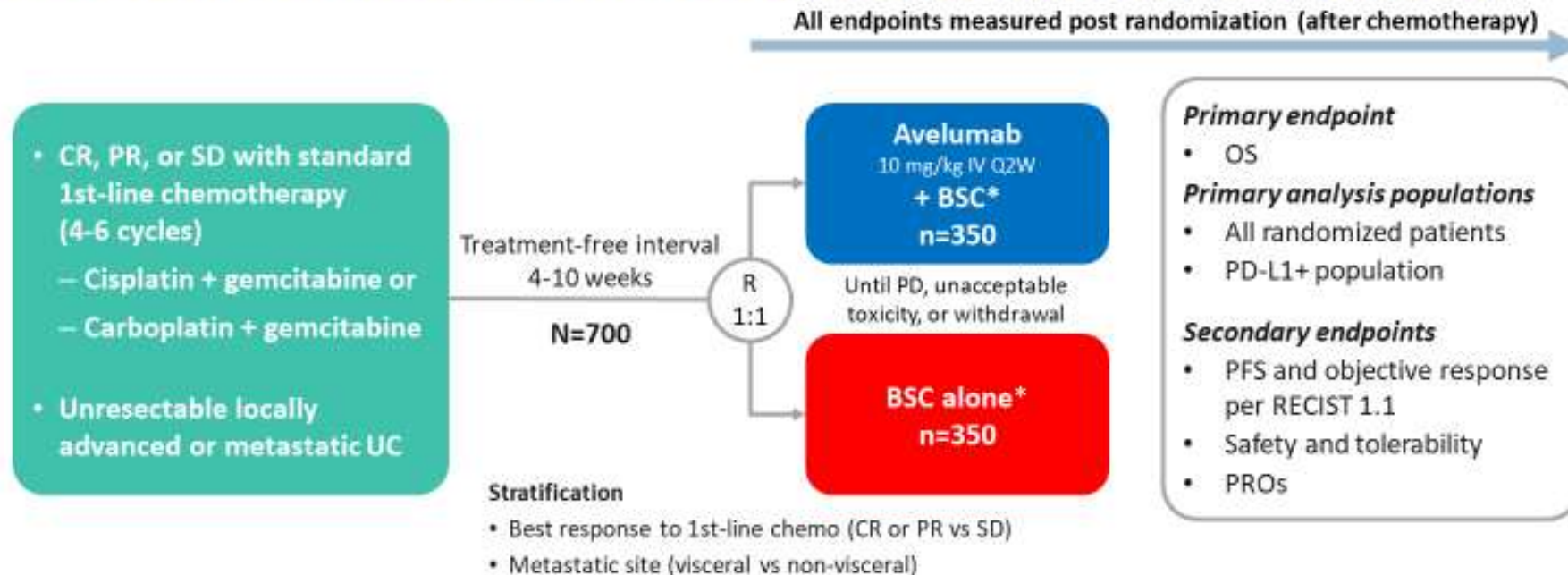


Metastatik Mesane Kanseri Birinci Basamak Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

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		

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

JAVELIN Bladder 100 study design (NCT02603432)



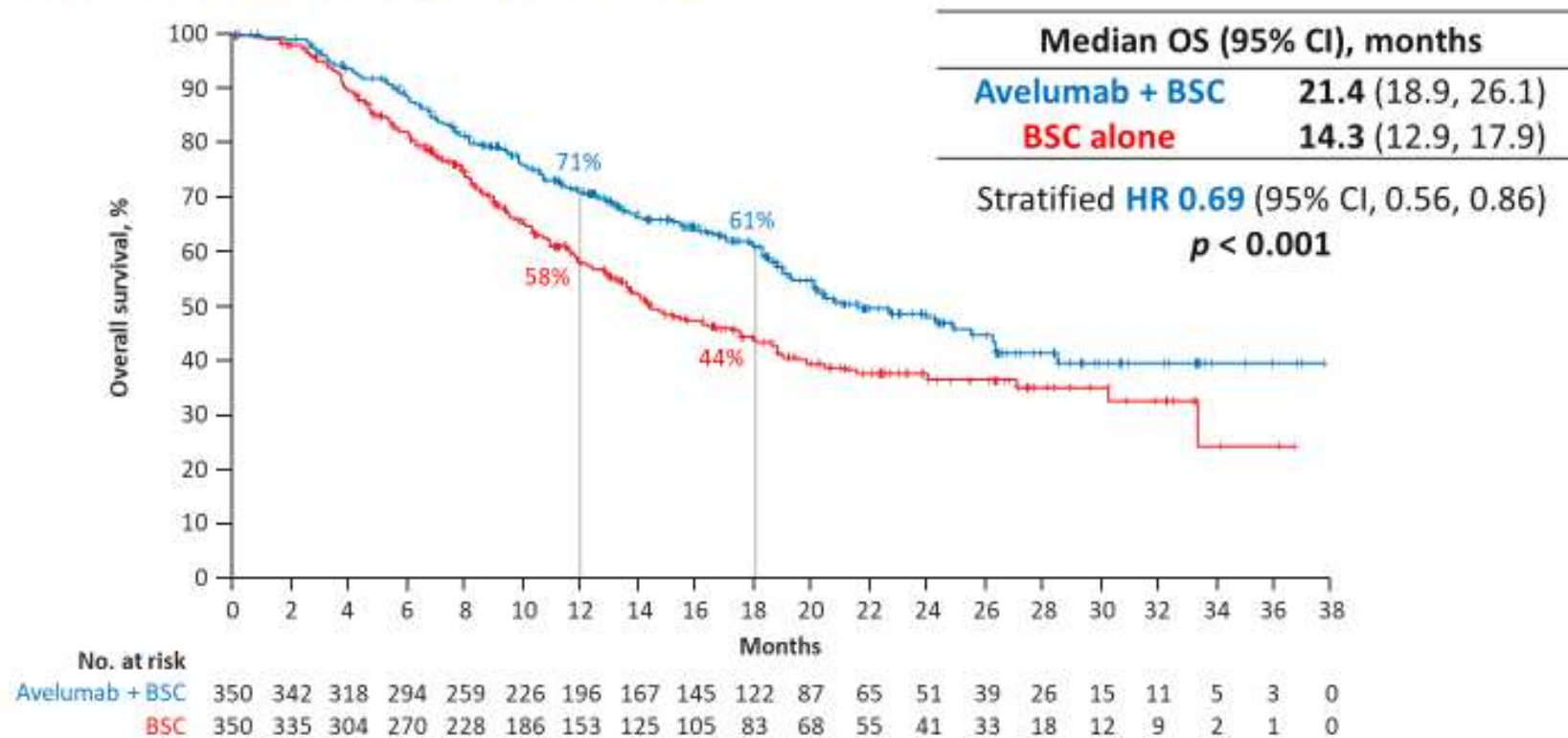
PD-L1+ status was defined as PD-L1 expression in $\geq 25\%$ of tumor cells or in $\geq 25\%$ or 100% of tumor-associated immune cells if the percentage of immune cells was $>1\%$ or $\leq 1\%$, respectively, using the SP263 assay; 358 patients (51%) had a PD-L1-positive tumor

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

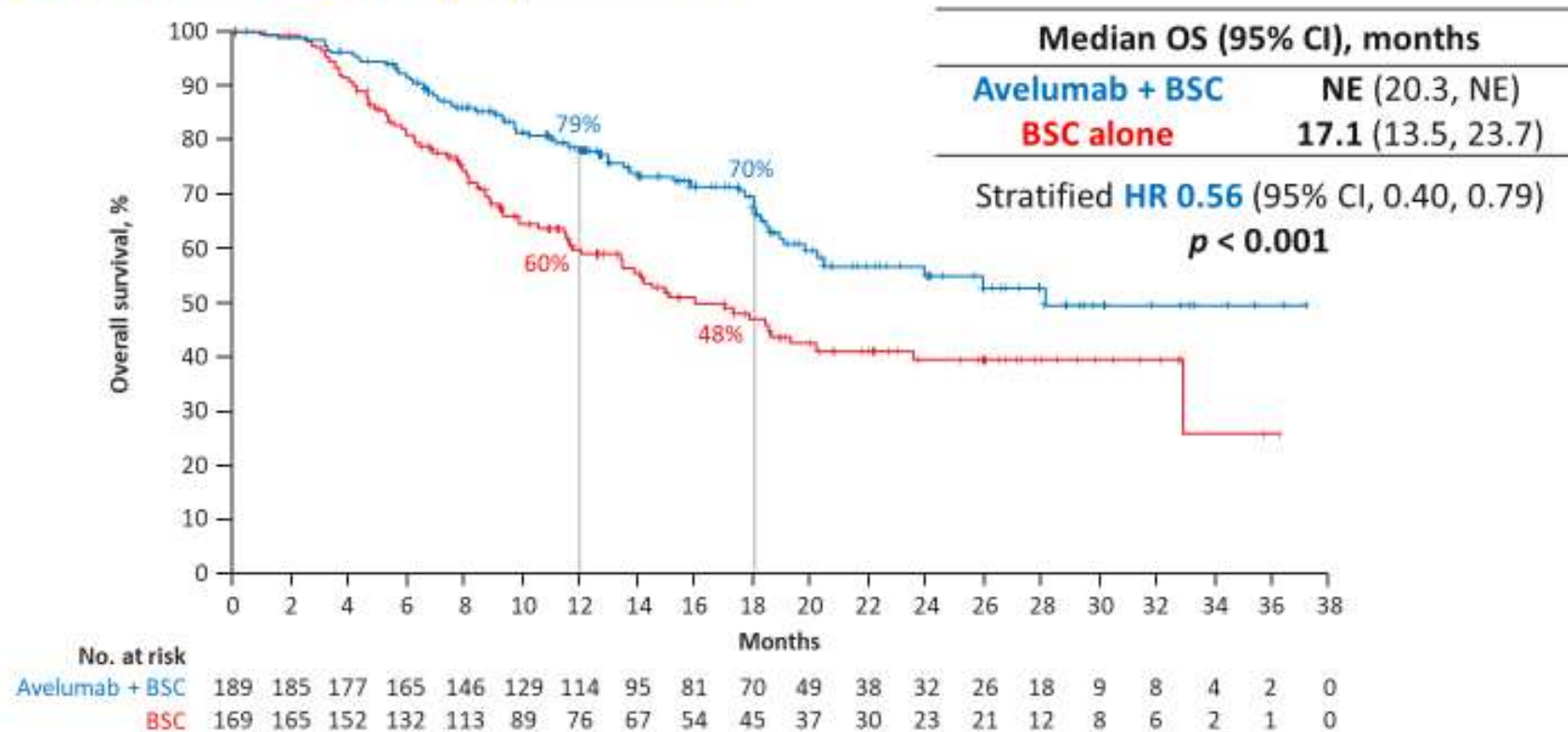
OS in the overall population



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



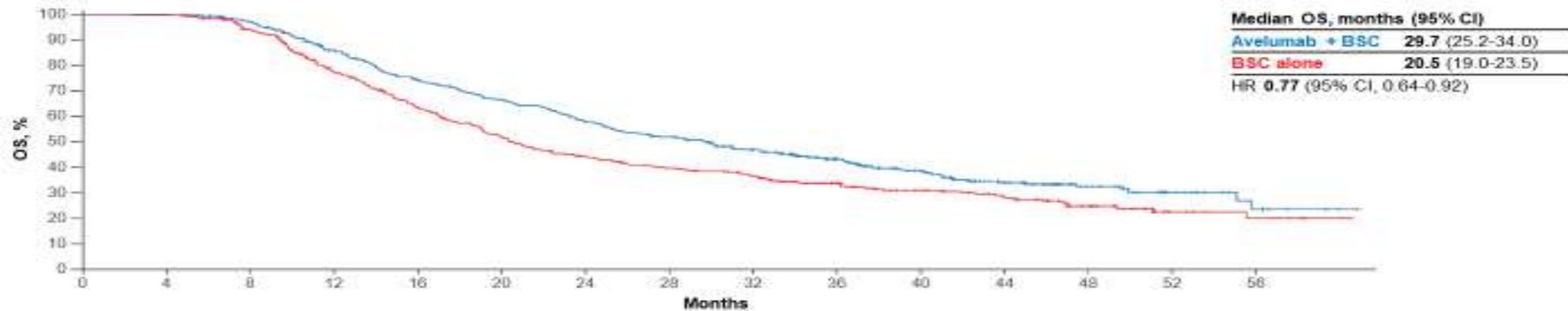
OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function ($P < 0.0014$). NE, not estimable

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])

İmmün kontrol noktası inhibitörleri

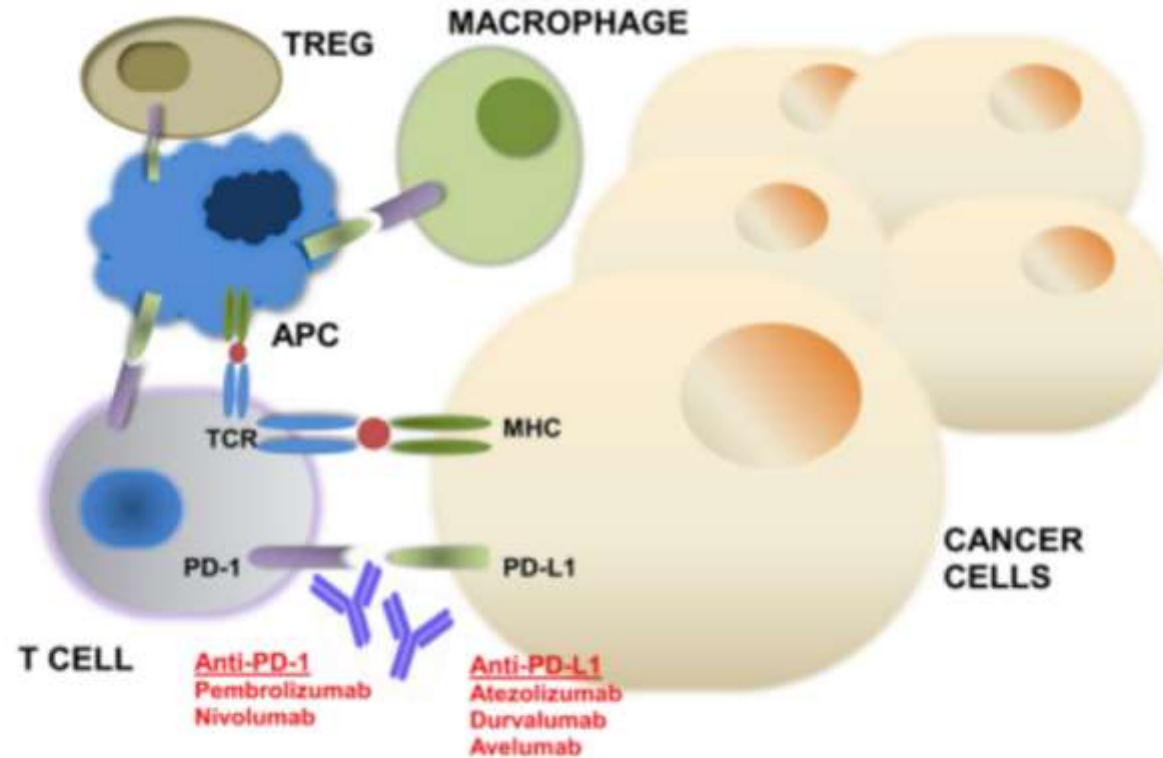
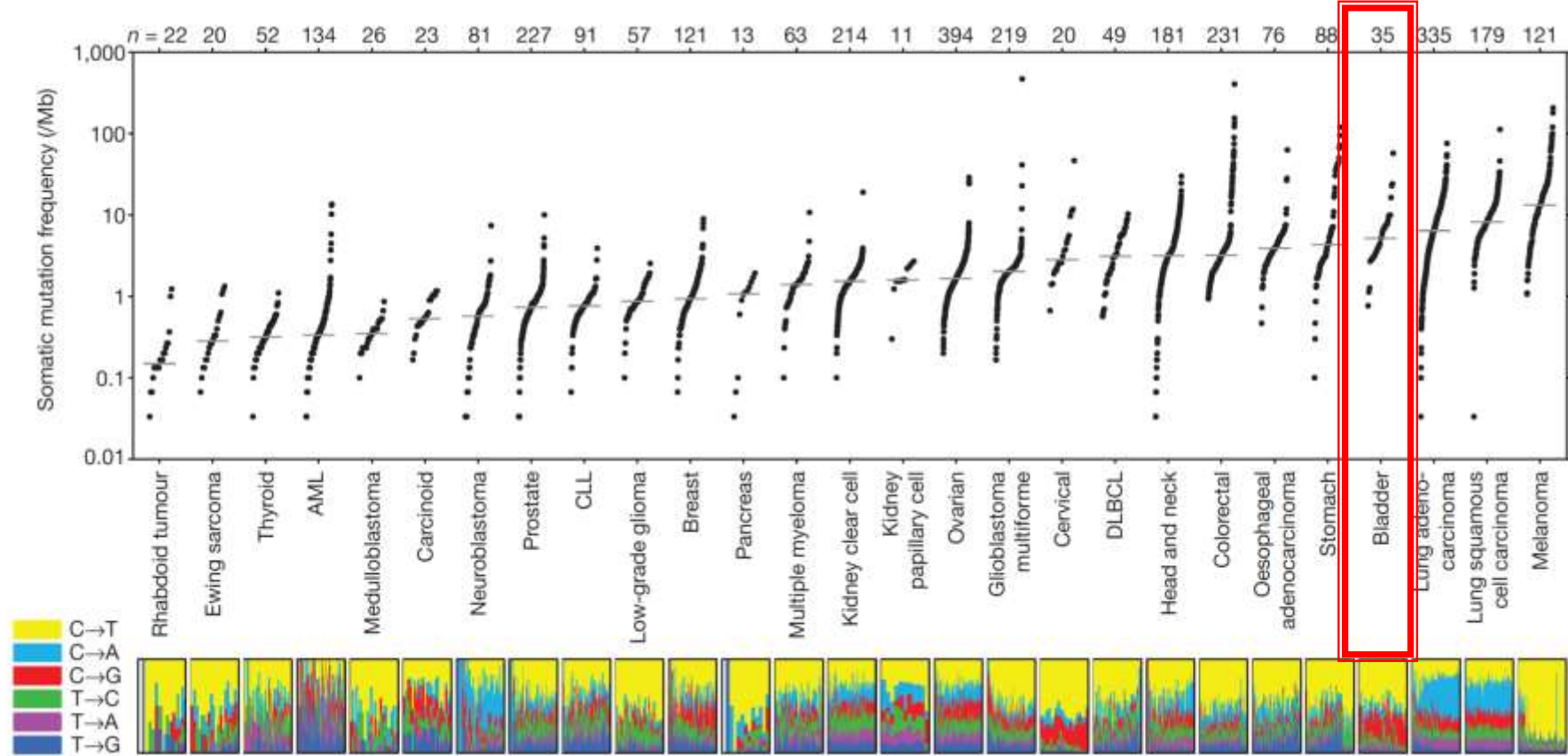


Fig. 1 Mechanism of action of PD-1 and PD-L1 inhibitors. The programmed cell death 1 (PD-1) receptor is expressed on activated T cells, B cells, macrophages, regulatory T cells (Tregs), and natural killer (NK) cells. Binding of PD-1 to its B7 family of ligands, programmed death ligand 1 (PD-L1 or B7-H1) or PD-L2 (B7-DC) results in suppression of proliferation and immune response of T cells. Activation of PD-1/PD-L1 signaling serves as a principal mechanism by which tumors evade antigen-specific T-cell immunologic responses. Antibody blockade of PD-1 or PD-L1 reverses this process and enhances antitumor immune activity. TCR, T-cell receptor; MHC, major histocompatibility complex; APC, antigen-presenting cell

Mesane Kanserinde Tümör Mutasyon Yüğü

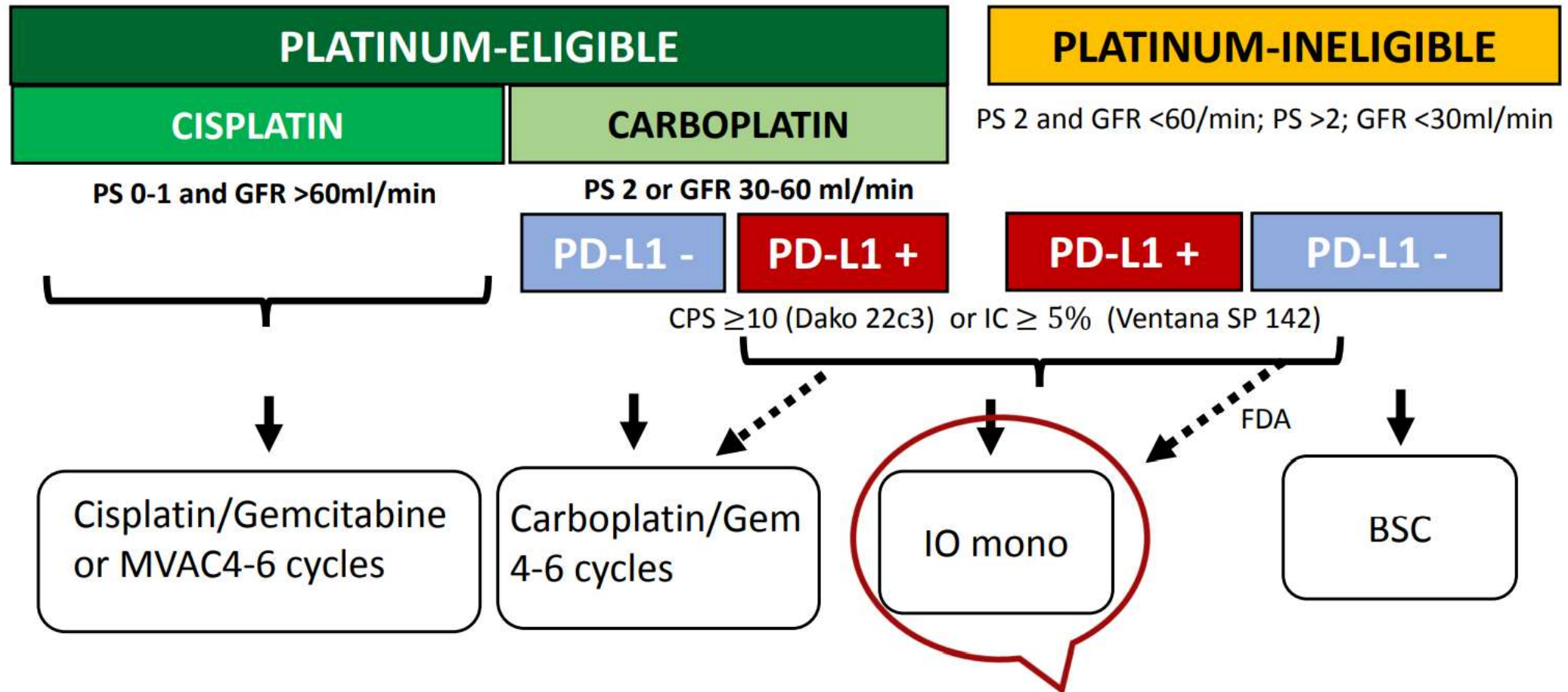


Lawrence et al. Nature 2013

- ☐ Yüksek kompleks mutasyon durumu bütün ve diğer kanserojenlere maruz kalma ile benzer
- ☐ Bir çok neoantijen konakçı immün sistemi tarafından potansiyel olarak yabancı gibi görünür

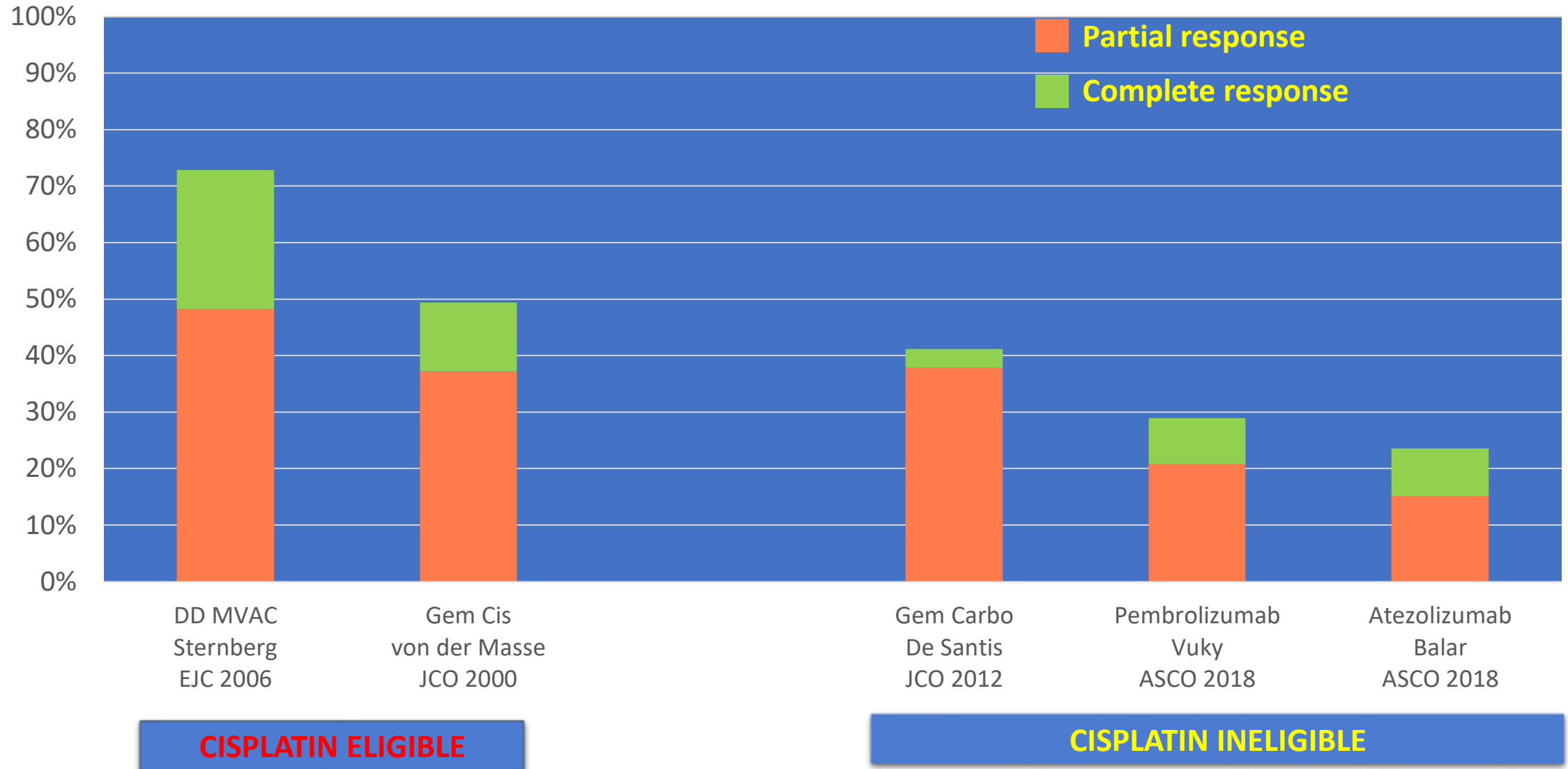
Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçimi

Herhangi Platinum bazlı kemoterapi alamayacak hastalarda



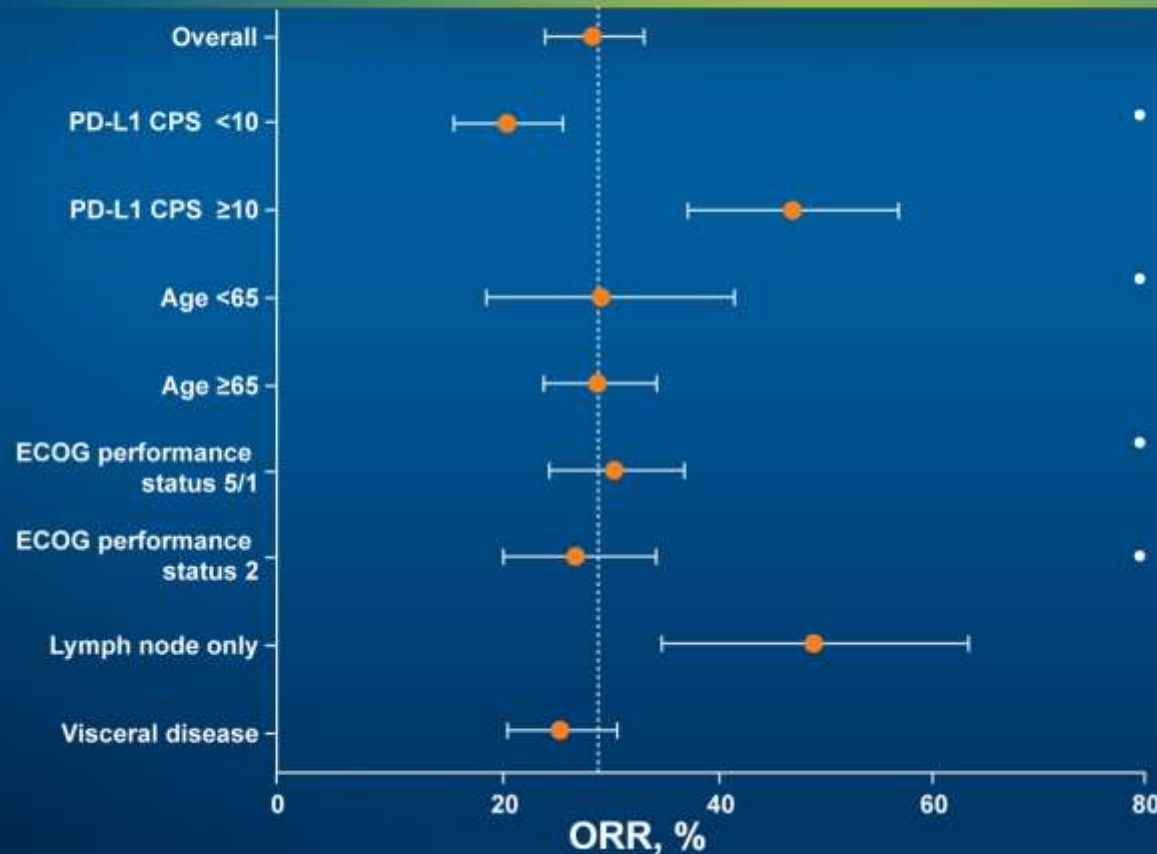
Pembrolizumab Lancet Oncology 2017/JCO 2020
Atezolizumab Lancet 2017

Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları



Sisplatin Tedavisine Uygun Olmayan Grupta Birinci Basamak Tedavi İmmün kontrol noktası inhibitörleri

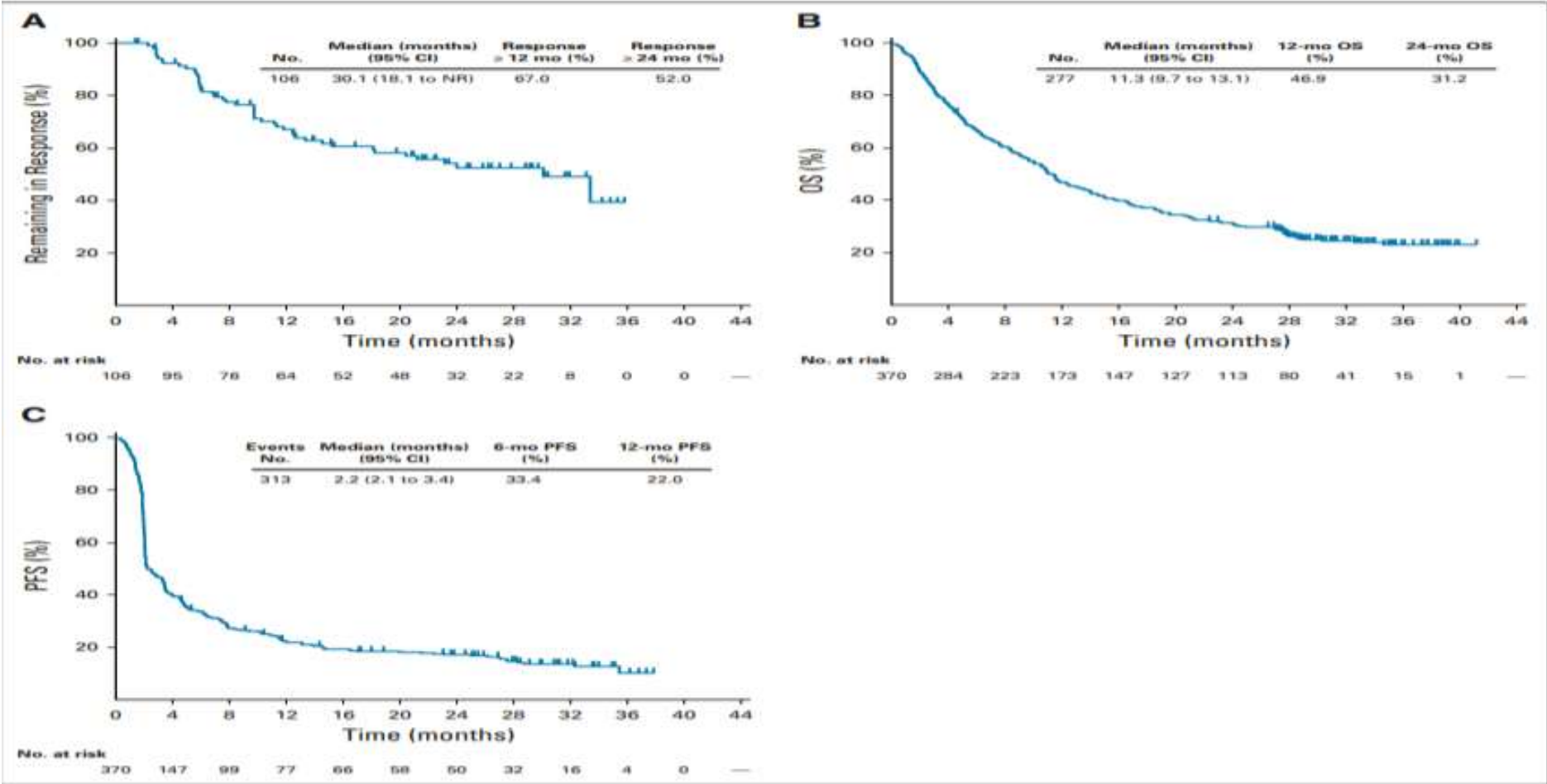
KEYNOTE-052: Objective Response Rate with First-Line Pembrolizumab by Subgroup in Cisplatin-Ineligible Advanced UC



- Treatment-related adverse events (AEs) occurred in 67.6% of patients.
- Most common were:
 - Fatigue (18.1%)
 - Pruritus (17.8%)
- Grade ≥3 AEs occurred in 20.3% of patients.
- Immune-mediated AEs occurred in 24.6% of patients.

Sisplatin Tedavisine Uygun Olmayan Grupta Birinci Basamak Tedavi İmmün kontrol noktası inhibitörleri

First-Line Pembrolizumab in Advanced/Metastatic Urothelial Cancer



Sisplatin Tedavisine Uygun Olmayan Grupta Birinci Basamak Tedavi İmmün kontrol noktası inhibitörleri

IMvigor210: Efficacy of Atezolizumab in First-Line Cisplatin-Ineligible or Platinum-Treated Locally Advanced or Metastatic UC

	Cohort 1 (cisplatin ineligible)	Cohort 2 (platinum treated)
Median follow-up, months	29.3	32.9
Response		
ORR	24%	16%
CR	8%	7%
Median DOR (range), months	NR (30.4-NE)	24.8 (13.8-30.4)
Survival		
Median OS, months	16.3	7.9
1-year OS	58%	37%
2-year OS	41%	23%

Sisplatin Tedavisine Uygun Olmayan Grupta Birinci Basamak Tedavi İmmün kontrol noktası inhibitörleri

Atezolizumab Monotherapy in Cisplatin-Ineligible Patients With Previously Untreated Metastatic Urothelial Carcinoma: 5-Year Response and Survival Analysis From the Phase II IMvigor210 Study (Cohort 1)

Jonathan E. Rosenberg,¹ Matthew D. Galsky,² Arjun V. Balar,¹
Yohann Loriot,⁴ Andrea Necchi,⁵ Jean Hoffman-Censits,⁶
Sandy Srinivas,⁷ Alexandra Drakaki,⁸ Apurva Javery,⁹
Yi Shi,¹⁰ Hannah (Xinhui) Huang,¹¹ Xiaodong Shen,¹²
Michiel S. van der Heijden¹³

¹ Memorial Sloan Kettering Cancer Center, New York, NY, USA; ² Kaplan School of Medicine at Mount Sinai/Tisch Cancer Institute, New York, NY, USA; ³ Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; ⁴ Université Paris-Saclay, Université Paris-Saclay, Gustave Roussy, Villejuif, France; ⁵ Vita-Salute San Raffaele University and IRCCS San Raffaele Hospital, Milan, Italy; ⁶ Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; ⁷ Stanford University Medical Center, Stanford, CA, USA; ⁸ University of California, Los Angeles, Los Angeles, CA, USA; ⁹ Symptom Health, Raleigh, NC, USA; ¹⁰ Genentech Inc., South San Francisco, CA, USA; ¹¹ Janssen-Cilag Cancer Institute, Amsterdam, the Netherlands

BACKGROUND

- Cisplatin-based chemotherapy is the standard of care for first-line (1L) treatment of metastatic urothelial carcinoma (mUC), although many patients are ineligible for cisplatin
- Atezolizumab (anti-PD-L1) is recommended for the treatment of several types of locally advanced or mUC, including cisplatin-ineligible patients whose tumours express PD-L1 (PD-L1-expressing immune cells [IC] covering ≥5% of the tumour area [IC2/3])¹⁻⁴
- Cohort 1 of the pivotal, single-arm, Phase II, IMvigor210 study demonstrated the tolerability of and durable responses to 1L atezolizumab in patients with cisplatin-ineligible mUC, with sustained responses observed with additional follow-up⁵
- The ongoing Phase III IMvigor130 study has also demonstrated prolonged efficacy with 1L atezolizumab monotherapy vs platinum-based chemotherapy in exploratory analyses in patients with PD-L1 IC2/3 tumours, including those ineligible for cisplatin⁶
- To evaluate the long-term efficacy of atezolizumab in patients with cisplatin-ineligible previously untreated mUC, here, we report updated data from IMvigor210 Cohort 1, based on over 5 years of follow-up



METHODS

IMvigor210 is an ongoing, global, single-arm, Phase II trial investigating the efficacy and safety of atezolizumab monotherapy in 1L cisplatin-ineligible mUC and previously platinum-treated mUC

Figure 1. IMvigor210 study design⁵



Checkpoints for OS: IMvigor210 Cohort 1, MET02/0000 Cohort 2; Cohort 1, Cohort 2, Cohort 3, Cohort 4, Cohort 5, Cohort 6, Cohort 7, Cohort 8, Cohort 9, Cohort 10, Cohort 11, Cohort 12, Cohort 13, Cohort 14, Cohort 15, Cohort 16, Cohort 17, Cohort 18, Cohort 19, Cohort 20, Cohort 21, Cohort 22, Cohort 23, Cohort 24, Cohort 25, Cohort 26, Cohort 27, Cohort 28, Cohort 29, Cohort 30, Cohort 31, Cohort 32, Cohort 33, Cohort 34, Cohort 35, Cohort 36, Cohort 37, Cohort 38, Cohort 39, Cohort 40, Cohort 41, Cohort 42, Cohort 43, Cohort 44, Cohort 45, Cohort 46, Cohort 47, Cohort 48, Cohort 49, Cohort 50, Cohort 51, Cohort 52, Cohort 53, Cohort 54, Cohort 55, Cohort 56, Cohort 57, Cohort 58, Cohort 59, Cohort 60, Cohort 61, Cohort 62, Cohort 63, Cohort 64, Cohort 65, Cohort 66, Cohort 67, Cohort 68, Cohort 69, Cohort 70, Cohort 71, Cohort 72, Cohort 73, Cohort 74, Cohort 75, Cohort 76, Cohort 77, Cohort 78, Cohort 79, Cohort 80, Cohort 81, Cohort 82, Cohort 83, Cohort 84, Cohort 85, Cohort 86, 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Metastatik Mesane Kanseri

İkinci Basamak Tedavi Seçenekleri

Bladder cancer is composed of multiple tumors:
Subtypes within subtypes

	24%	8%	15%	15%	35%	3%
	Luminal Papillary	Luminal Non-Specified	Luminal Unstable	Stroma-rich	Basal/Squamous	Neuroendocrine-like
						
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 ++ CDKN2A-	PPAR-γ ++	PPAR-γ ++ E2F3 +, ERBB2 + Genomic instability		EGFR +	TP53 --, RB1 --, Cell cycle +
Mutations	FGFR3 (40%), KDM6A (38%), STAG2 (22%)	ELF3 (35%)	TP53 (76%), ERCC2 (22%) TMB +, APOBEC +		TP53 (61%), RB1 (25%)	TP53 (94%) RB1 (39%)
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology	Micropapillary variants			Squamous differentiation	Neuroendocrine differentiation
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

APOBEC, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like; CDKN2A, cyclin-dependent kinase Inhibitor 2A; E2F3, E2F transcription factor 3; NK, natural killer; TMB, tumour mutation burden.

Kamoun A, et al. 2019. Epub ahead of print date.

Courtesy of Arlene O. Siefker-Radtke, MD

Metastatik Mesane Kanseri Sisplatin Uygun Olmayanlarda Birinci Basamak Tedavi Yanıtları

EV-103: Phase 1b/2 Trial of Enfortumab + Pembrolizumab

Patients With 1L Cisplatin-Ineligible
la/mUC (N=45)

Dose escalation

EV + Pembro
(n=5)

Dose expansion cohort A

EV + Pembro
(n=40)

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

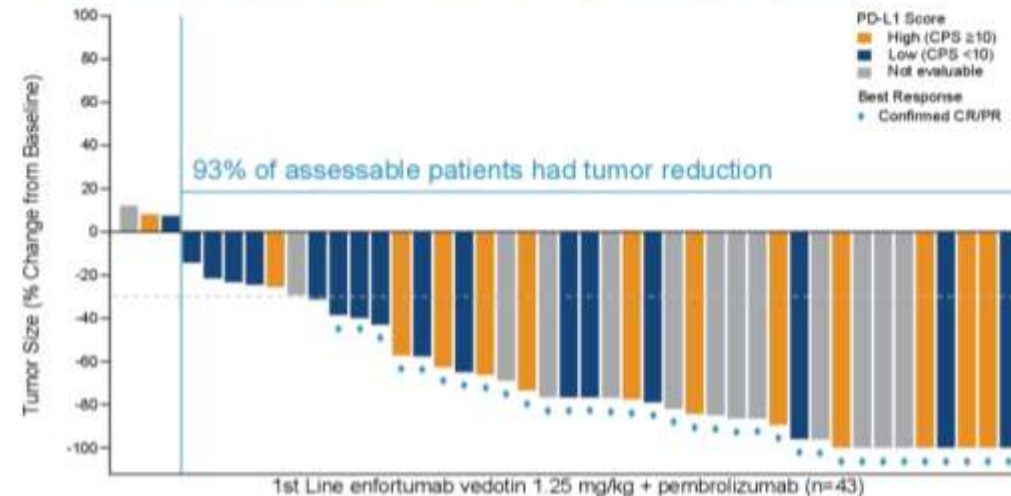
- 84% of patients had visceral disease and 31% had liver metastasis
- 31% of patients had PD-L1 CPS ≥ 10

Confirmed ORR	73% (33/45)
95% CI	(58.1, 85.4)
Complete response	16% (7/45)
Partial response	58% (26/45)

- 57% confirmed ORR in patients with liver metastases

Maximum Target Lesion Reduction From Baseline by PD-L1 Status

Best Overall Response per RECIST v1.1 by Investigator (N=45)



Metastatik Mesane Kanseri Sisplatin Uygun Olmayanlarda Birinci Basamak Tedavi Yanıtları

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

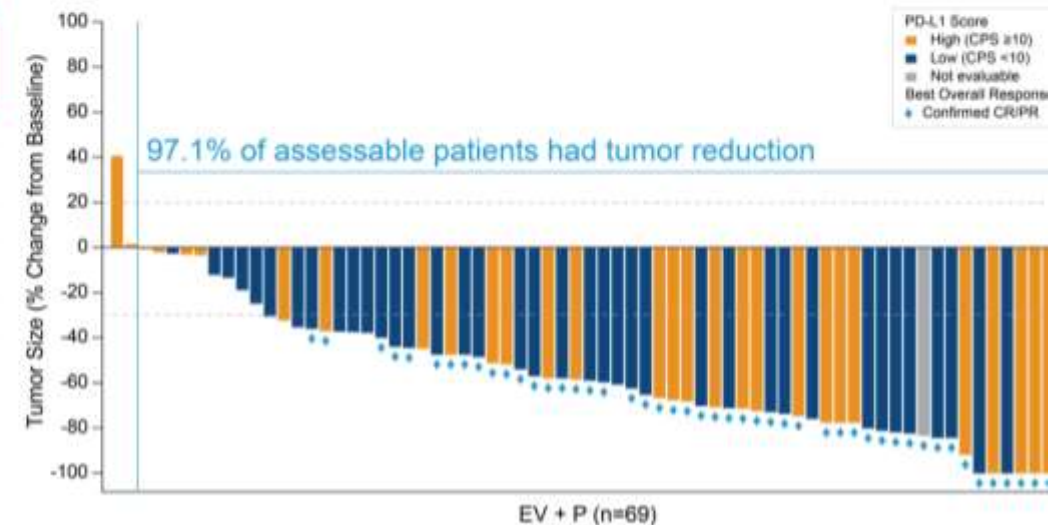
Primary Endpoint

- 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.

Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları EV103 -EV/pembrolizumab

Overall Objective Response Rates by BICR

High confirmed ORR (73.3%) with high concordance rate between BICR and INV assessments

	Dose Escalation + Cohort A (N = 45)
Objective Response Rate, n (%)	33 (73.3)
95% CI ^a for ORR	58.1-85.4
Best Overall Response, n (%)	
Complete response	7 (15.6)
Partial response	26 (57.8)
Stable disease	5 (11.1)
Progressive disease	5 (11.1)
No assessment ^b	2 (4.4)
Disease Control Rate, n (%)	38 (84.4)
95% CI ^a for DCR	70.5-93.5
Concordance rate of BOR between BICR and INV^c assessment	95.3%

BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; DCR = disease control rate; INV = investigator; ORR = objective response rate

^aCI was computed using the Clopper-Pearson method (Clopper 1934)

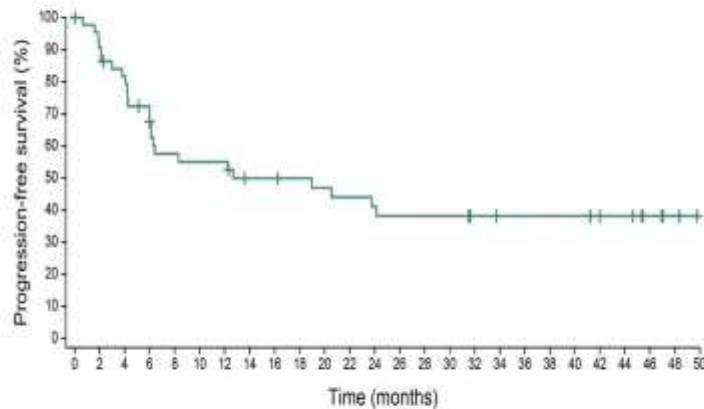
^bPatients had no response assessment post-baseline

^cORR per INV assessment was 33/45 (73.3%)

Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları EV103 -EV/pemrolizumab

Progression-Free Survival by BICR

41.1% of patients were progression-free at 24 months



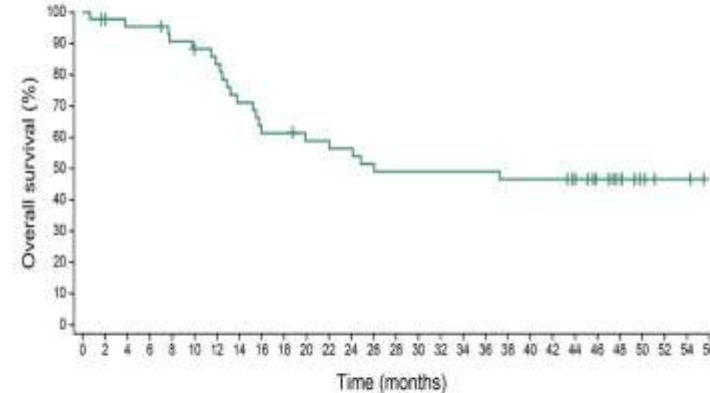
No. at risk 45 40 35 30 23 22 18 17 16 15 13 13 11 10 10 10 8 8 4 2

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 23 21 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

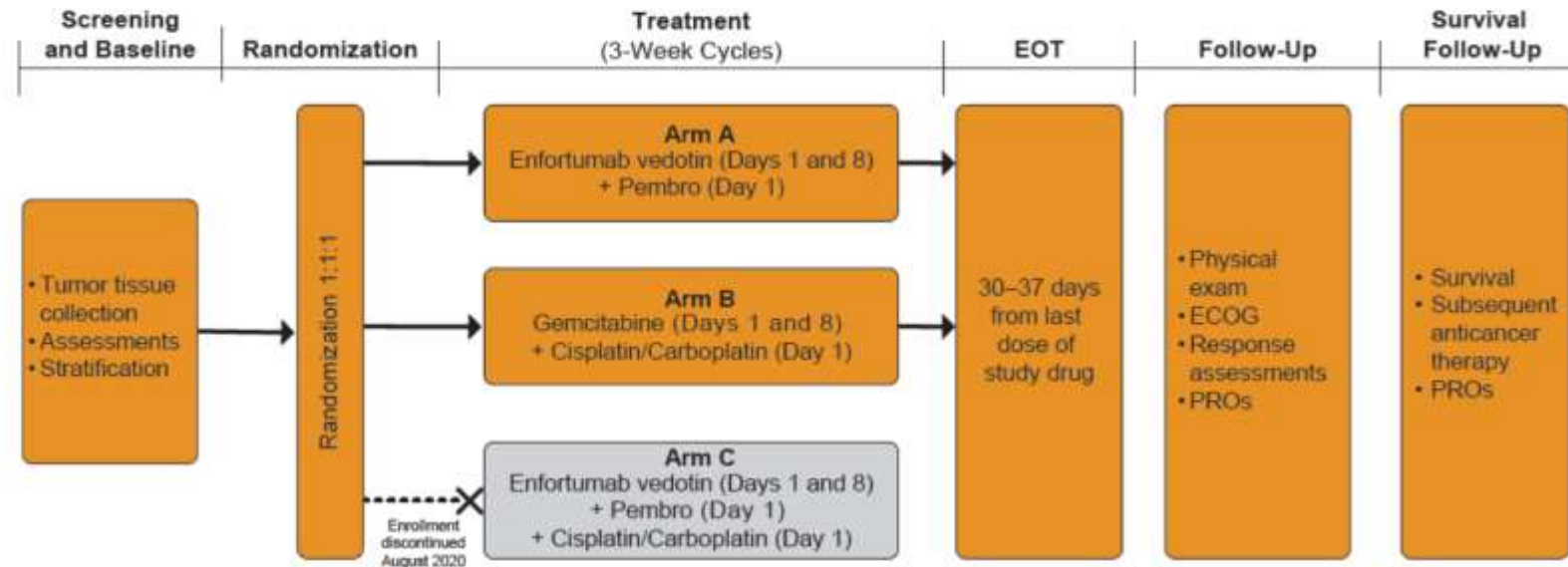
CI = confidence interval; NE = not estimable; OS = overall survival.
^aCI was calculated using the complementary log-log transformation method (Collett, 1994).
^bNot estimated using Kaplan-Meier method.

Gelecek Perspektif

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

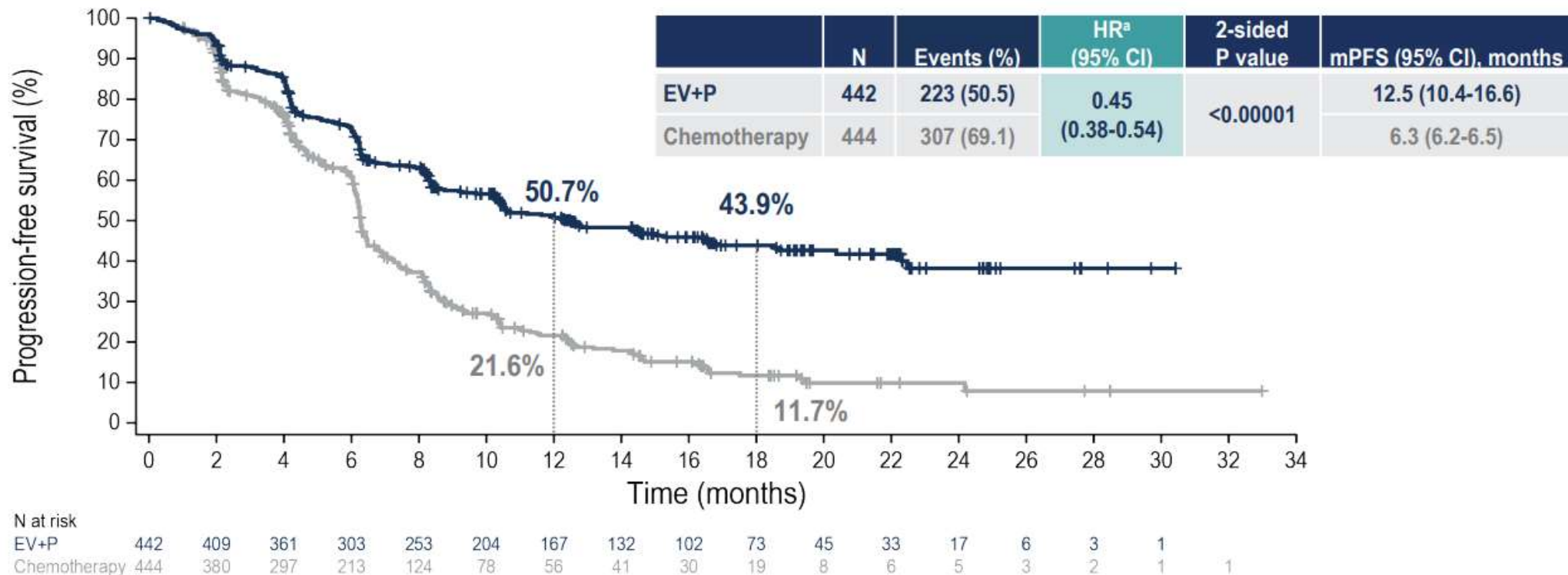
Primary Endpoints: PFS, OS
Secondary Endpoints: ORR, DOR, DCR, QOL, PRO, Safety

Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları

EV103 -EV/pembrolizumab

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

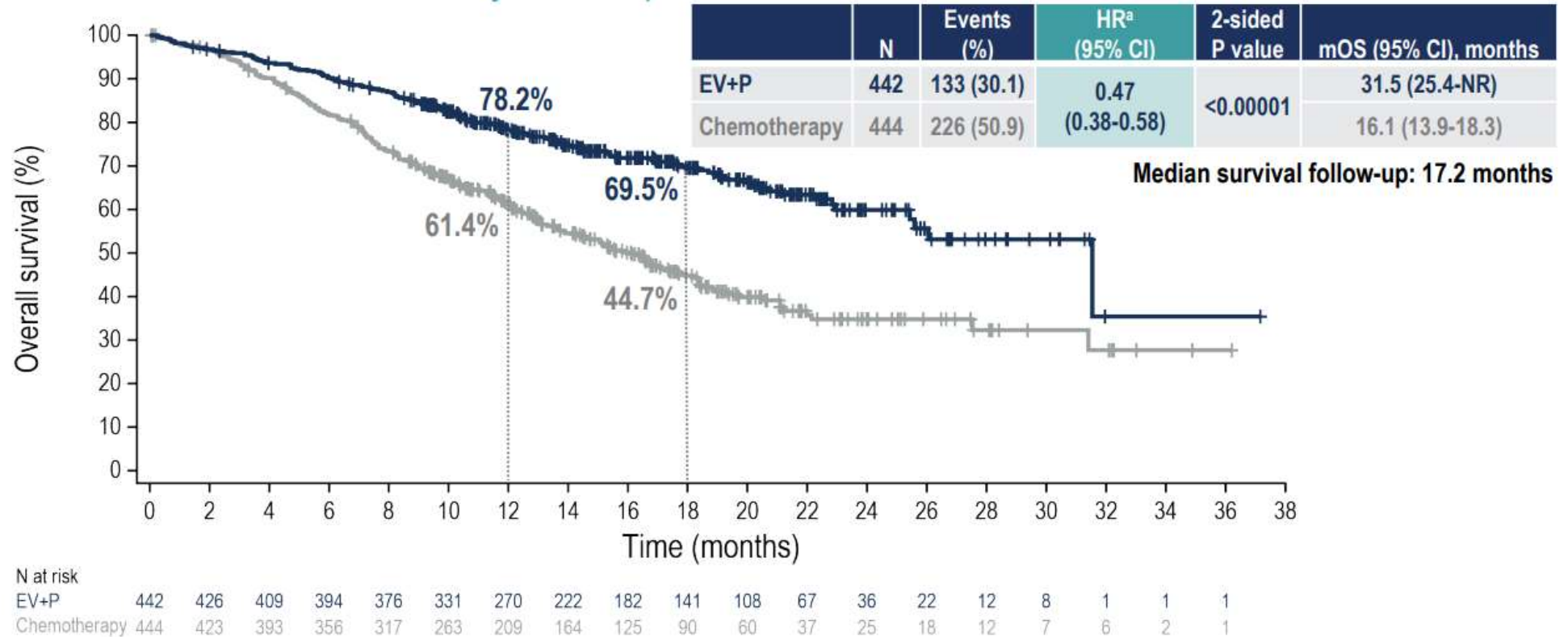
^aCalculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

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Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları EV103 -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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OS Subgroup Analysis: Cisplatin Eligibility

Cisplatin-eligible

Overall survival (%)

Time (months)

Time (months)	Survival (%) - Dark Blue Group	Survival (%) - Grey Group
0	100	100
2	98	95
4	95	88
6	92	80
8	90	72
10	88	65
12	85	60
14	82	58
16	78	55
18	75	50
20	72	48
22	70	45
24	68	42
26	65	40
28	65	38
30	65	38
32	55	32
34	55	32
36	55	32
38	28	32

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

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Cisplatin-ineligible

Overall survival (%)

Time (months)

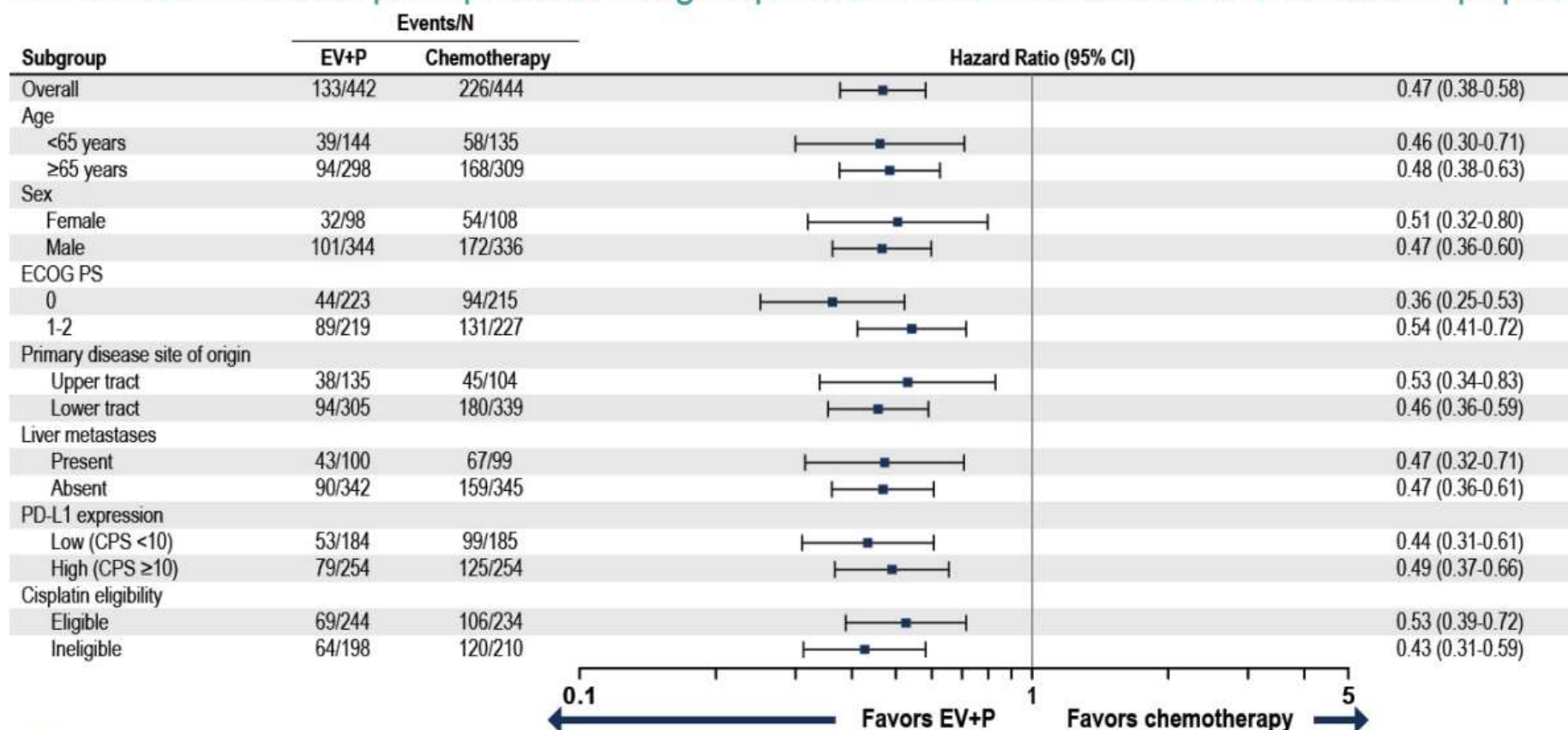
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43	NR (20.7-NR)
Chemotherapy	120	(0.31-0.59)	12.7 (11.4-15.5)

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Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları EV103 -EV/pembrolizumab

Subgroup Analysis of OS

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

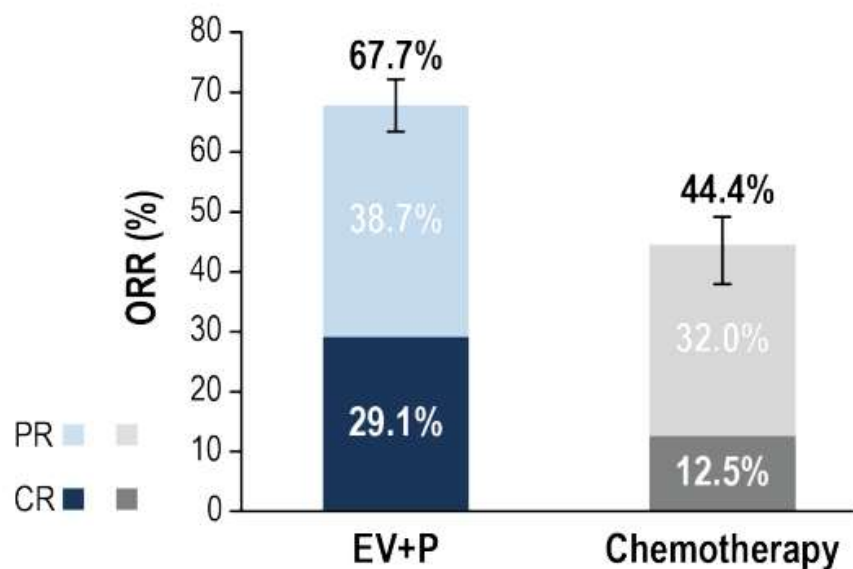


Data cutoff: 08 Aug 2023

Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları EV103 -EV/pembrolizumab

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



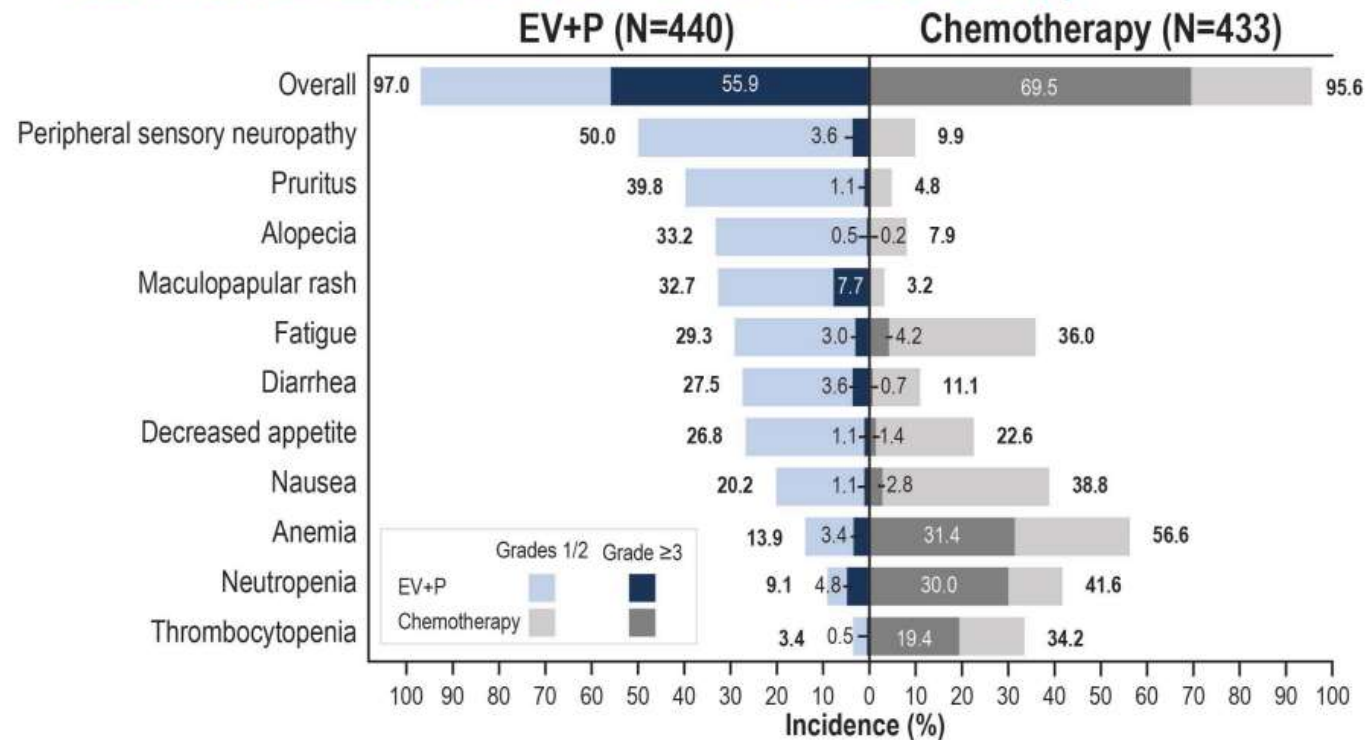
Powles et al.

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Metastatik Mesane Kanseri Birinci Basamak Tedavi Yan etki EV103 -EV/pembrolizumab

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 $\geq 20\%$ of patients for any grade in either arm TRAEs, treatment-related adverse events

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Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları EV103 -EV/pembrolizumab

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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*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.

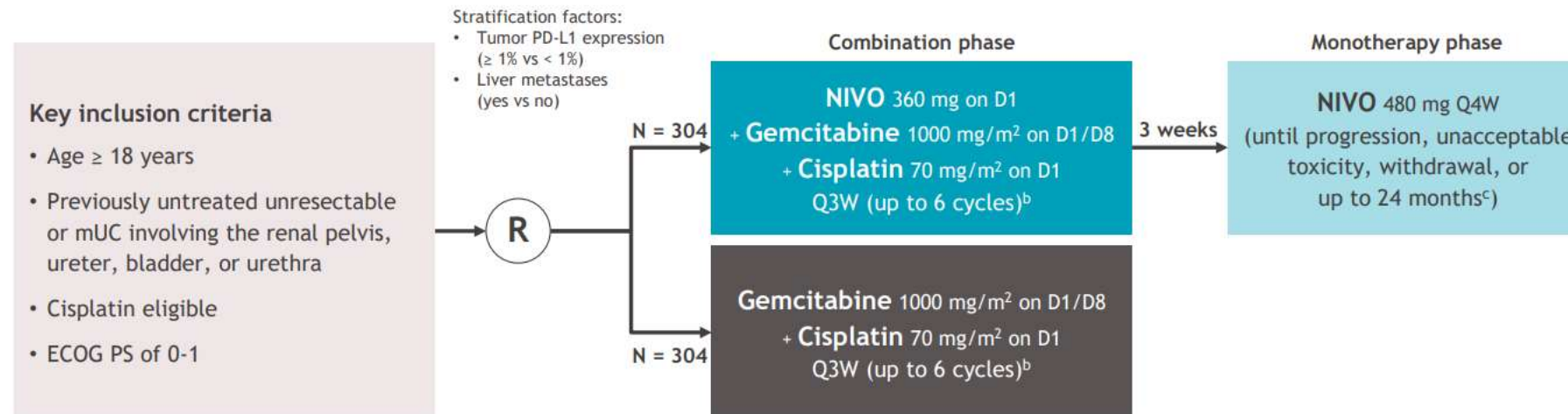
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Sisplatine uygun hastalarda KT+İmmünoterapi

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 $\geq 1\%$,^d HRQoL

Key exploratory endpoints: ORR per BICR, safety

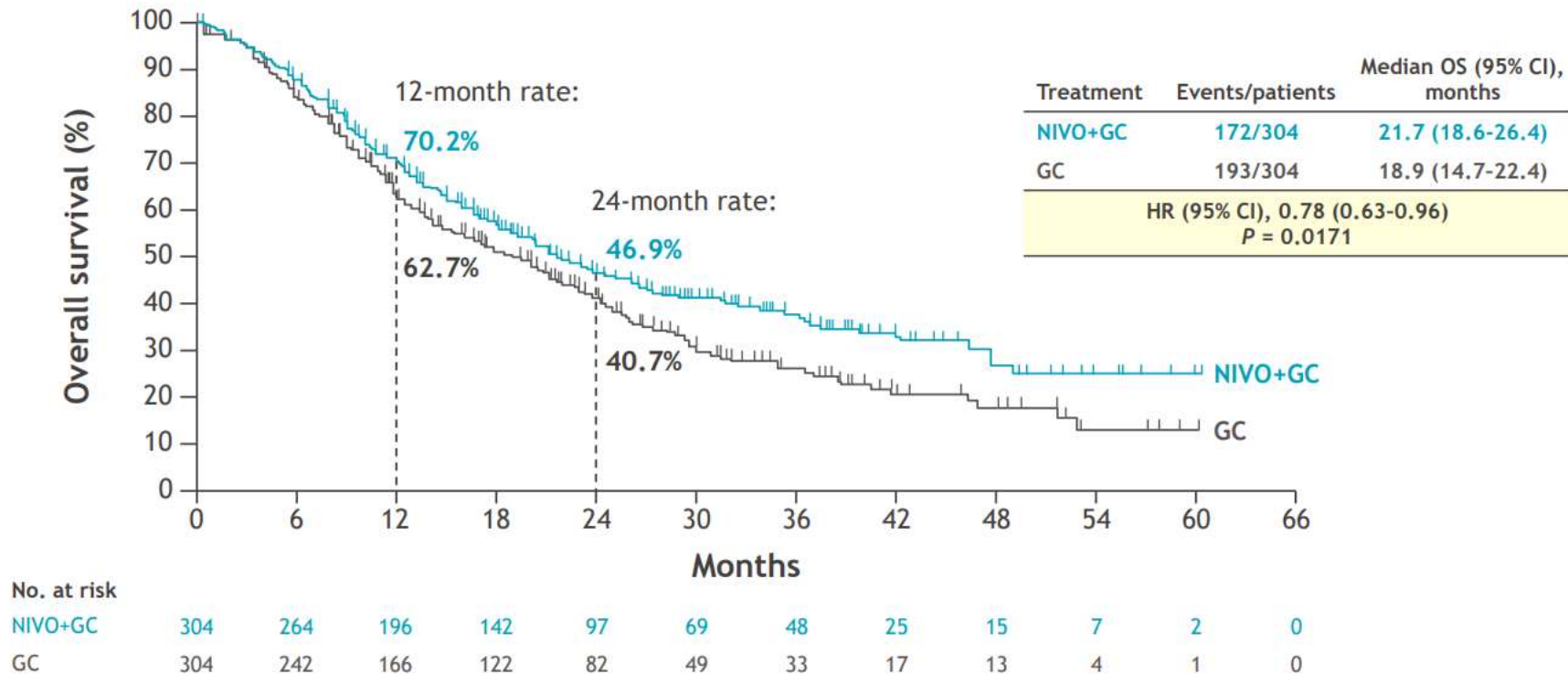
^aFurther CheckMate 901 trial design details are available at <https://clinicaltrials.gov/ct2/show/NCT03036098>. ^bPatients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). ^cA maximum of 24 months from first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

CheckMate 901

OS (primary endpoint)

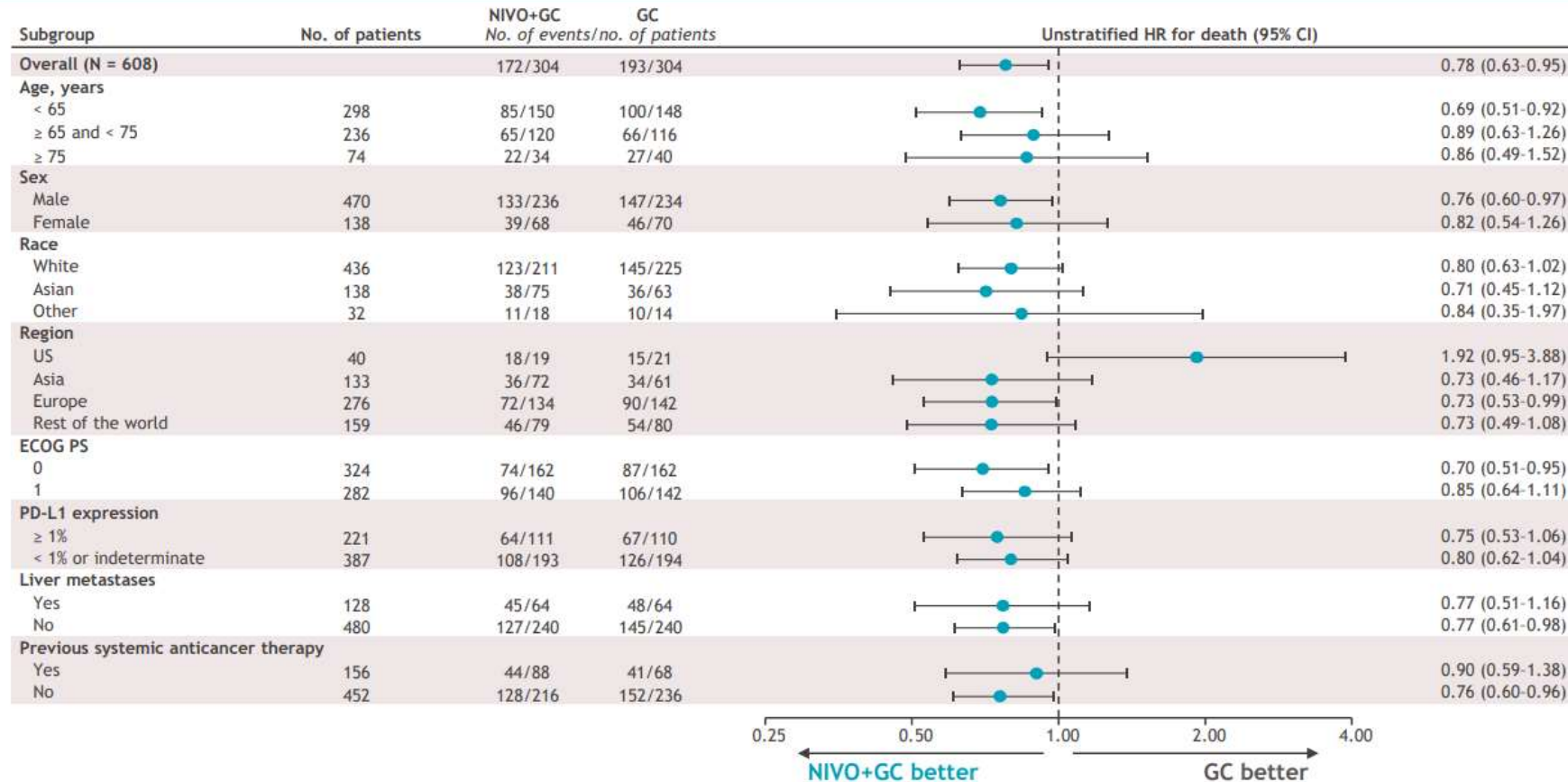


Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with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

Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

OS in subgroups

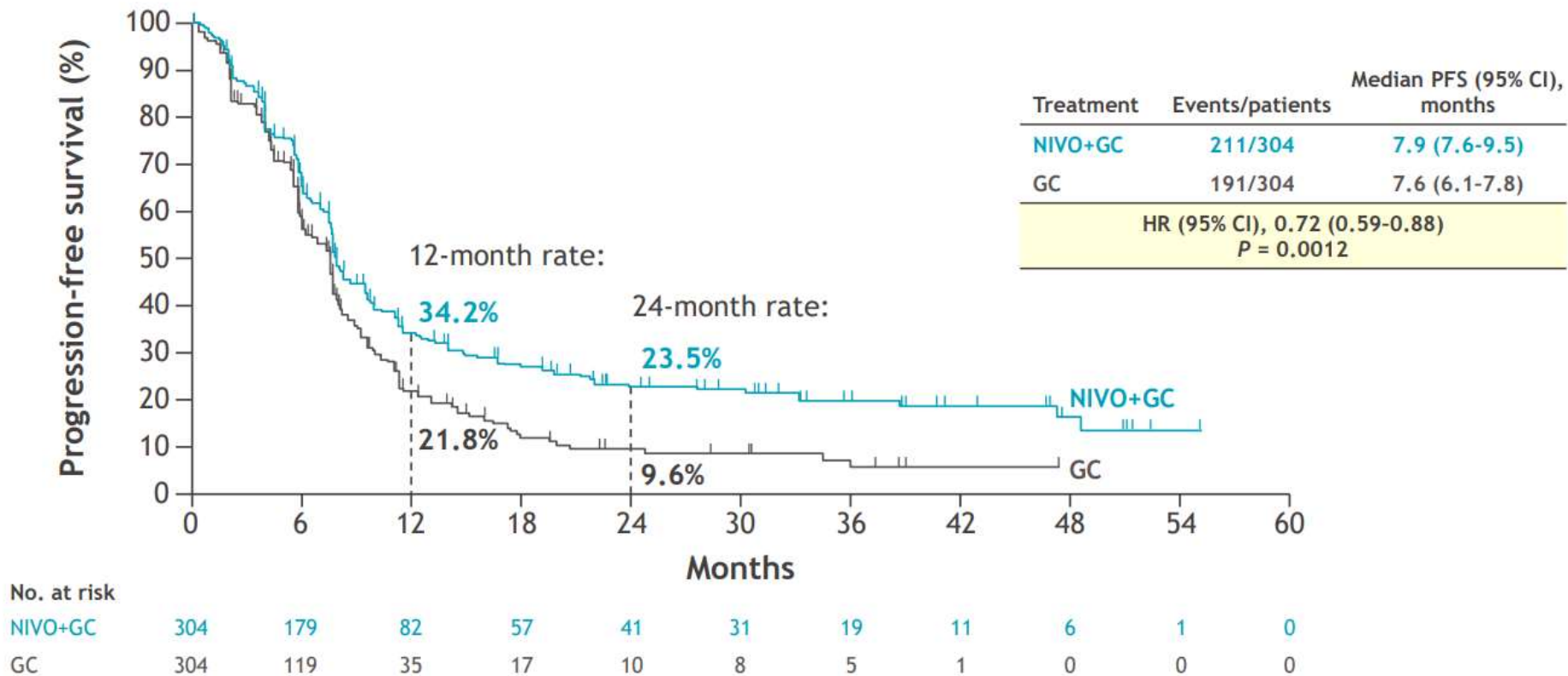


All randomized patients. HRs were not computed for subgroup categories (except for age, sex, race, and region) with < 10 patients per treatment group. Categories without a meaningful estimate of the HR are not shown. PD-L1 expression and liver metastases are per interactive response technology. There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

Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

PFS per BICR (primary endpoint)

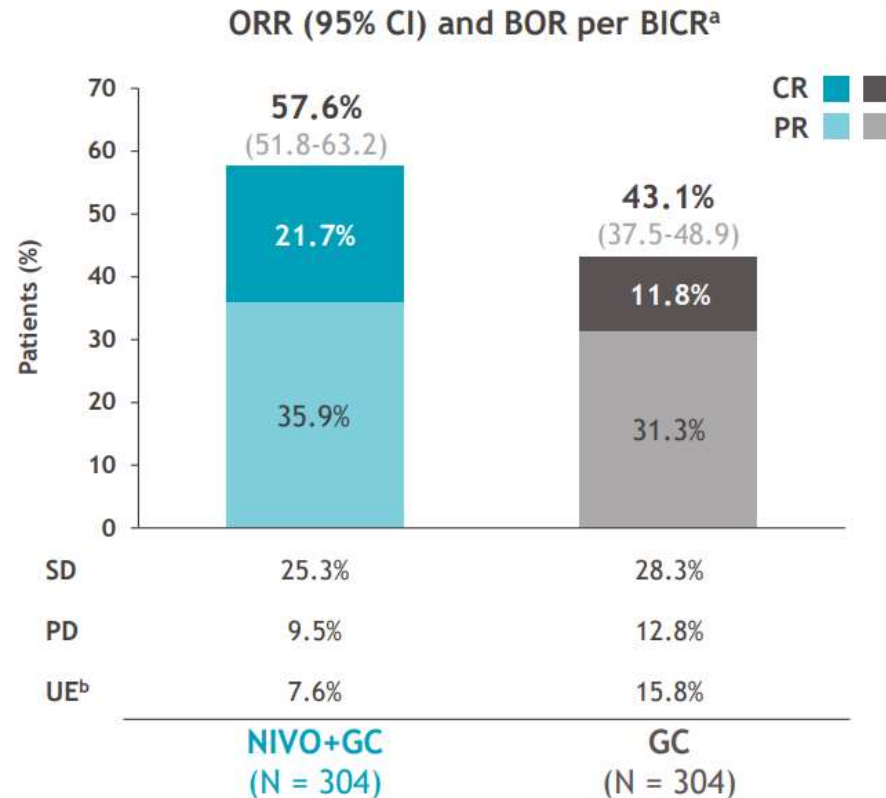


Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as time from randomization to first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who did not progress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

Sisplatine uygun hastalarda KT+İmmünoterapi

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)

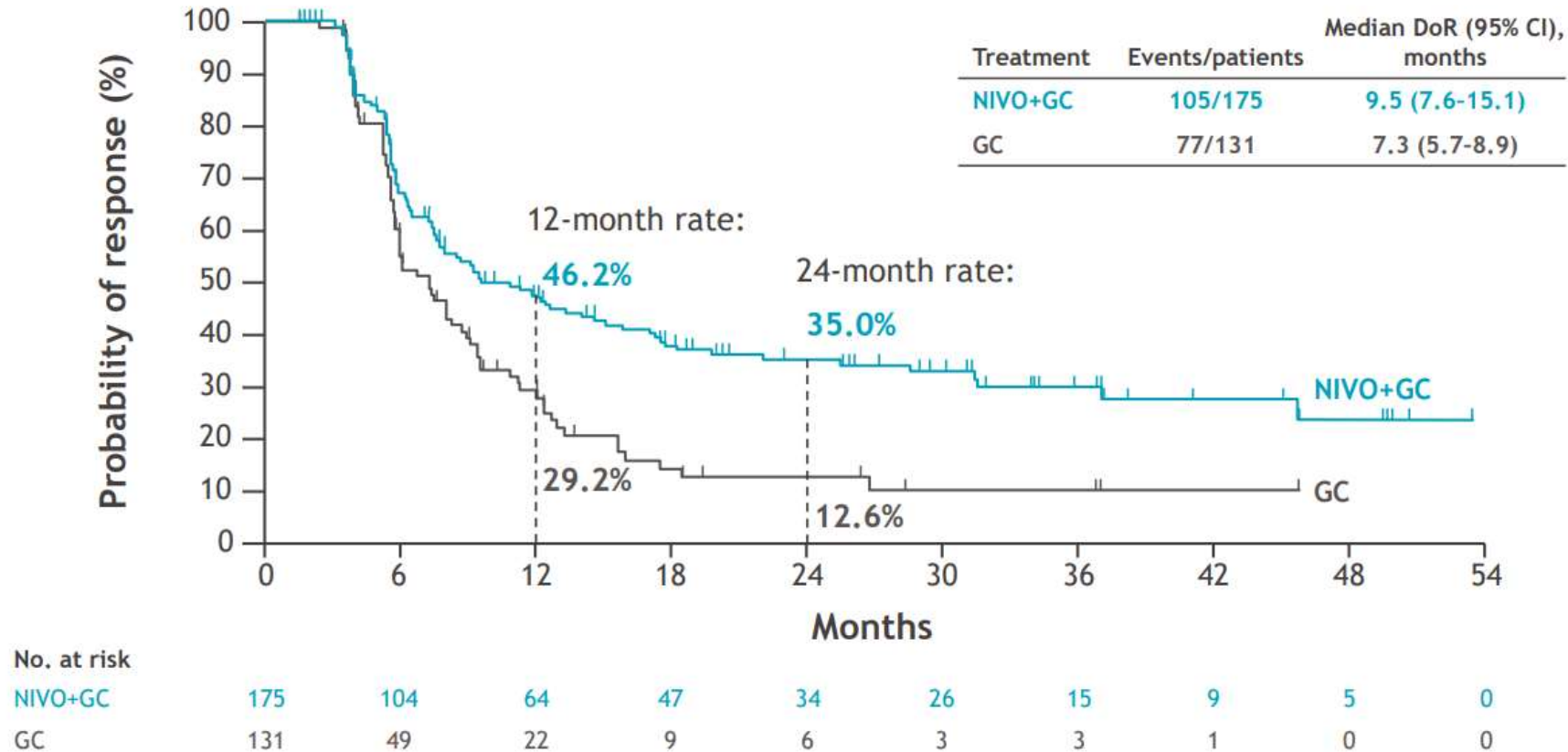
	NIVO+GC (n = 66)	GC (n = 36)
Complete response ^d		
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

^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 KT+İmmünoterapi

CheckMate 901

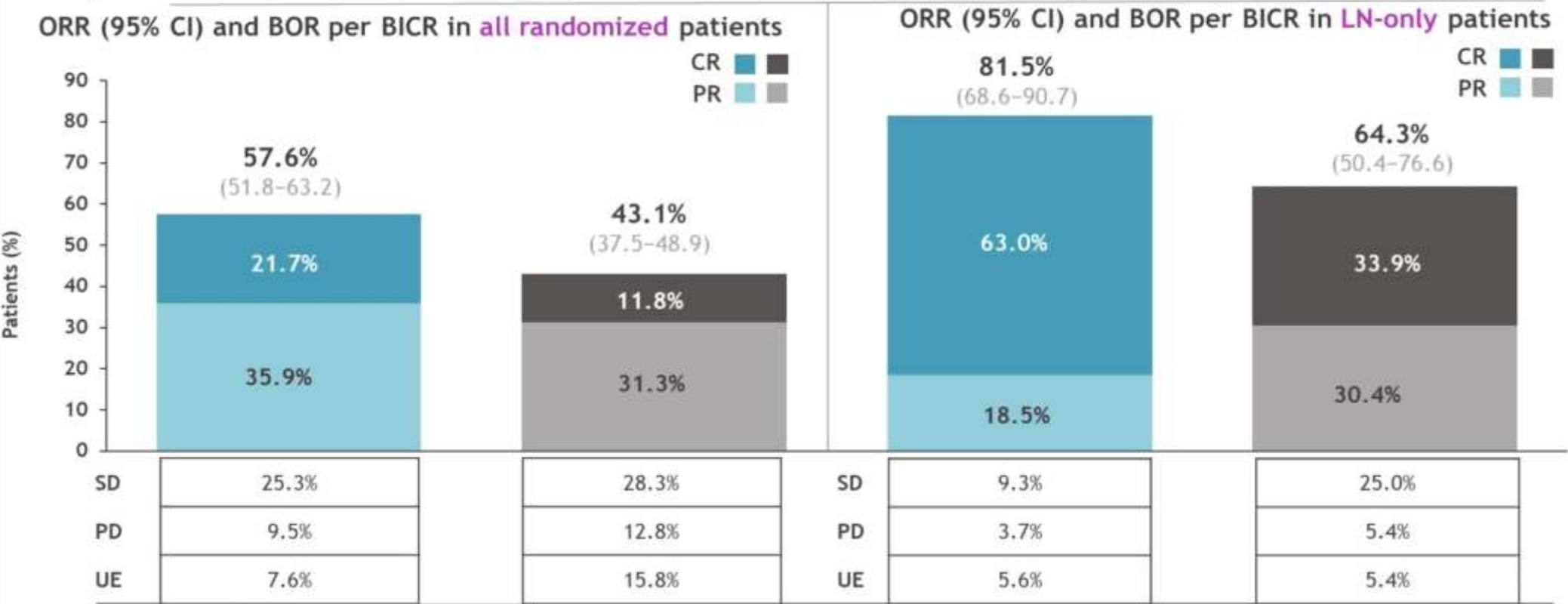
Duration of objective response per BICR



Sisplatin uygun hastalarda KT+İmmünoterapi

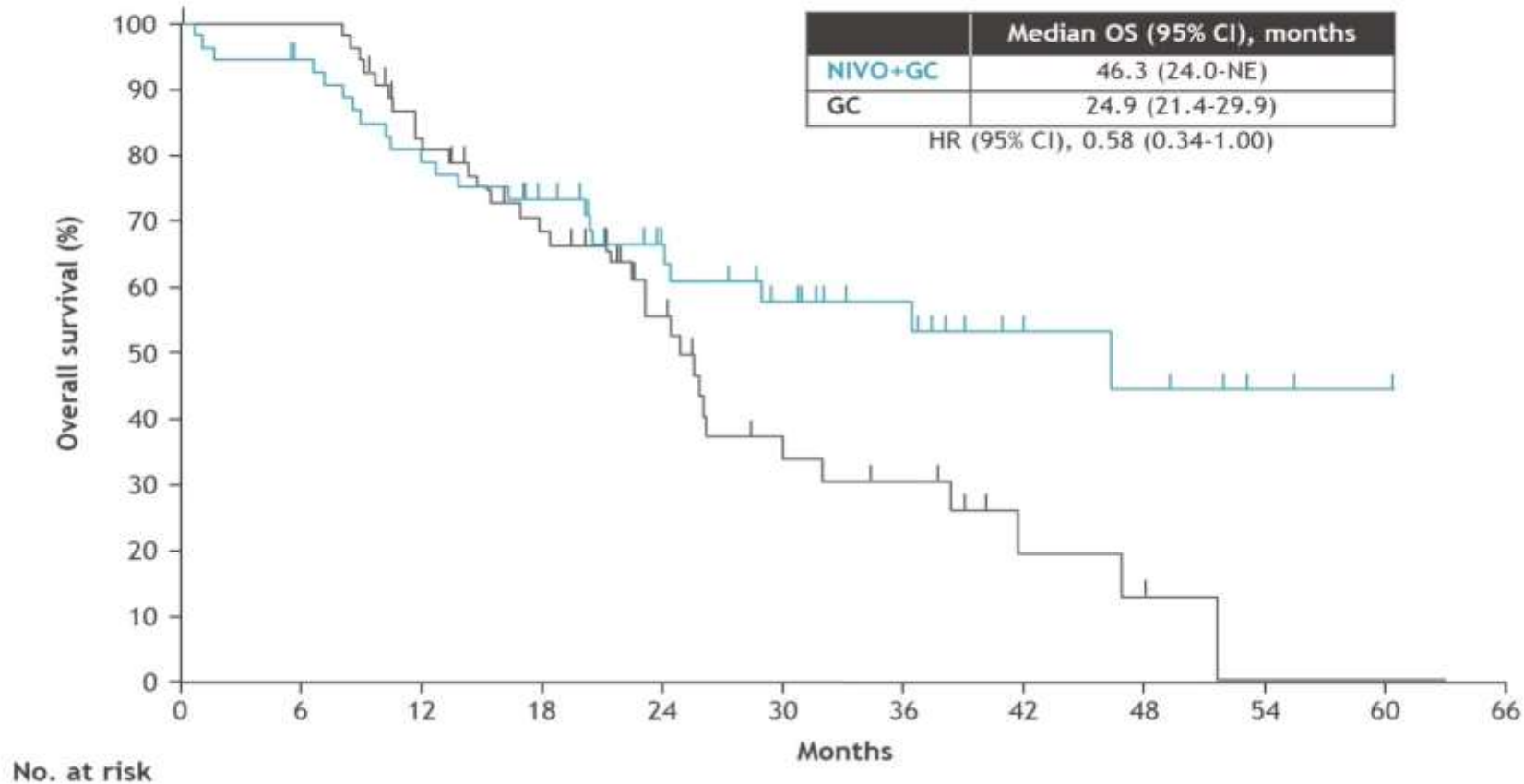
Response per BICR: patients with LN-only mUC

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



Sisplatine uygun hastalarda KT+İmmünoterapi

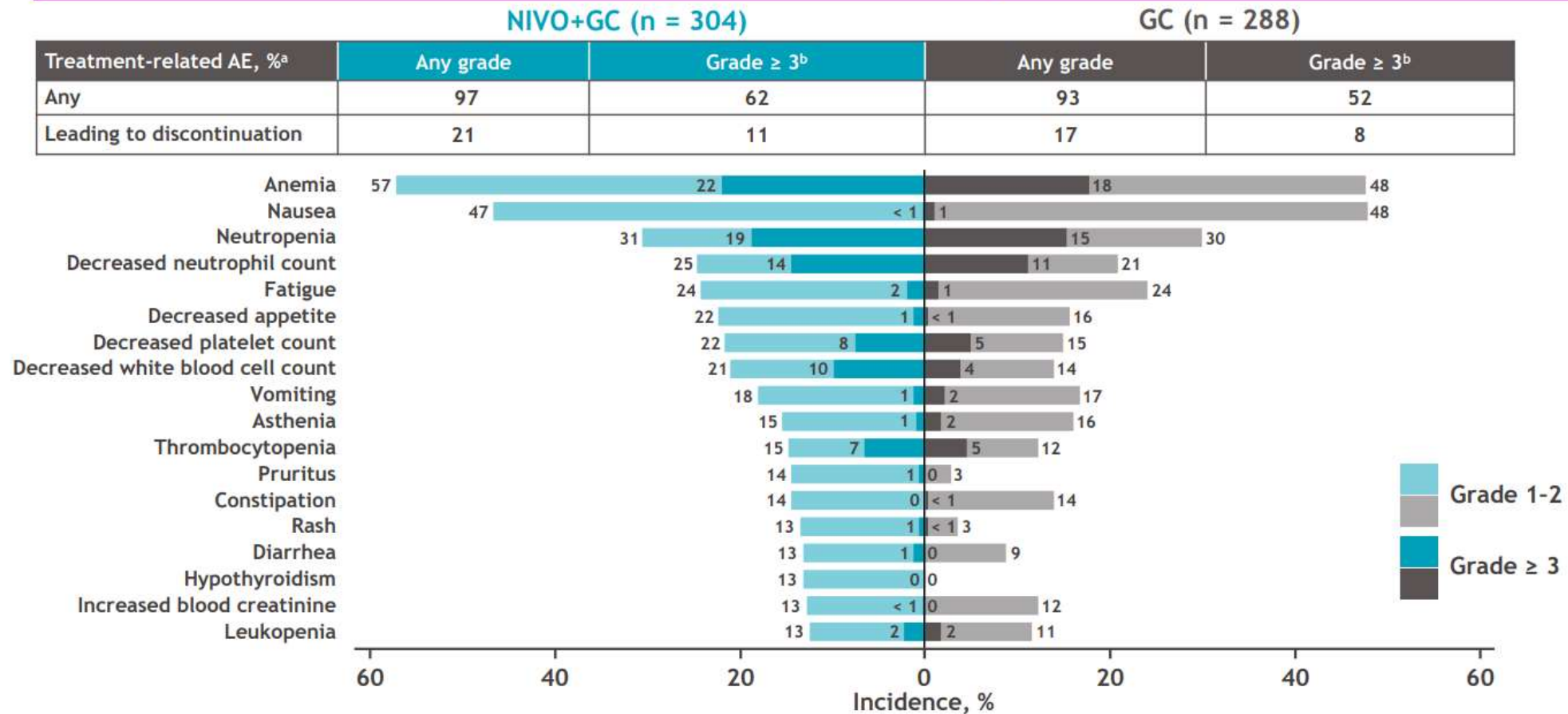
OS: patients with LN-only mUC per BICR



Sisplatin uygun hastalarda KT+İmmünoterapi

CheckMate 901

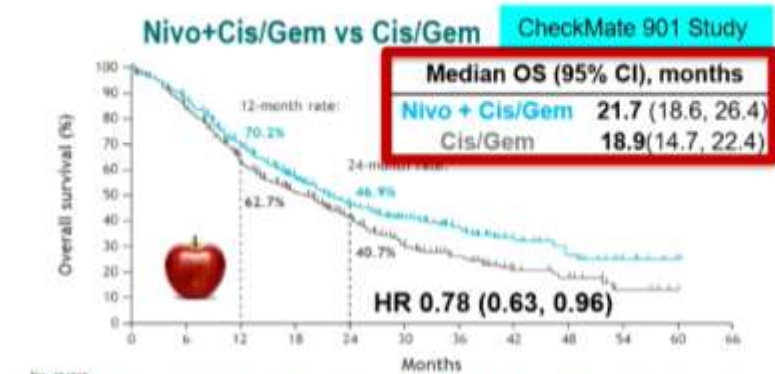
Treatment-related AEs in all treated patients



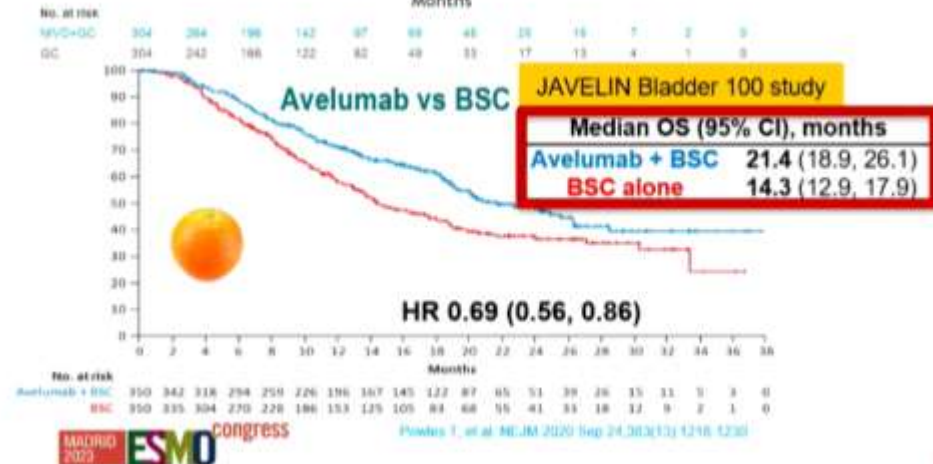
^aIncludes events that occurred in treated patients between first dose and 30 days after last dose of study therapy. Tornado plot displays individual treatment-related AEs occurring at any grade in ≥ 10% of treated patients in either arm. ^bOne grade 5 event occurred in each arm (sepsis in the NIVO+GC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

Evre IV mesane birinci basamak tedavi seçeneği

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 İkinci Basamak Sonrası Tedavi Seçimi

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

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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

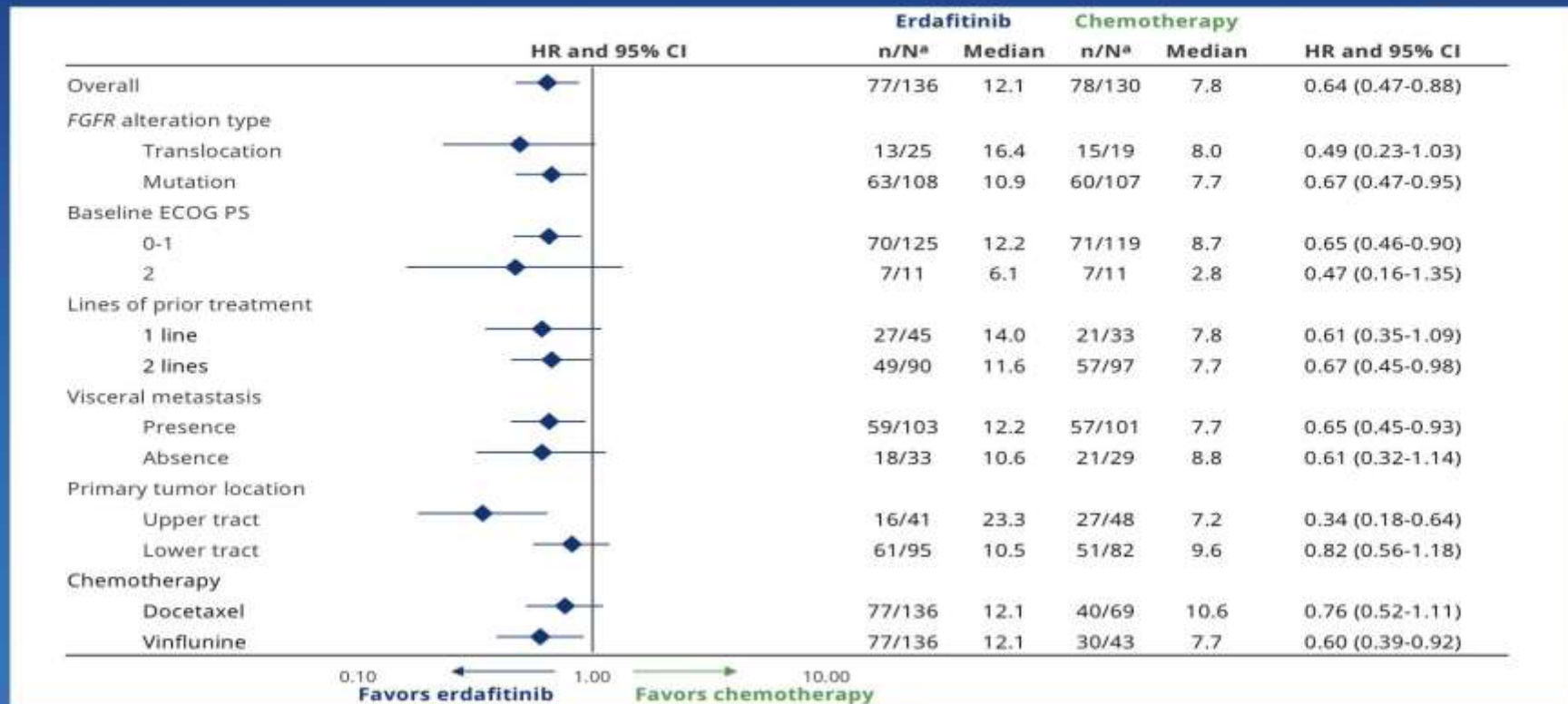
	Erdafitinib (136 patients)	Chemotherapy (130 patients)
OS, median (95% CI), mo	12.1	7.8
HR (95% CI)	0.64 [0.47, 0.88]; <i>P</i> = .005	
PFS, median (95% CI), mo	5.6	2.7
HR (95% CI)	0.58 [0.44, 0.78]; <i>P</i> = .0002	
ORR, %	45.6	11.5
RR (95% CI)	3.94 [2.37, 6.57]; <i>P</i> < .001	

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

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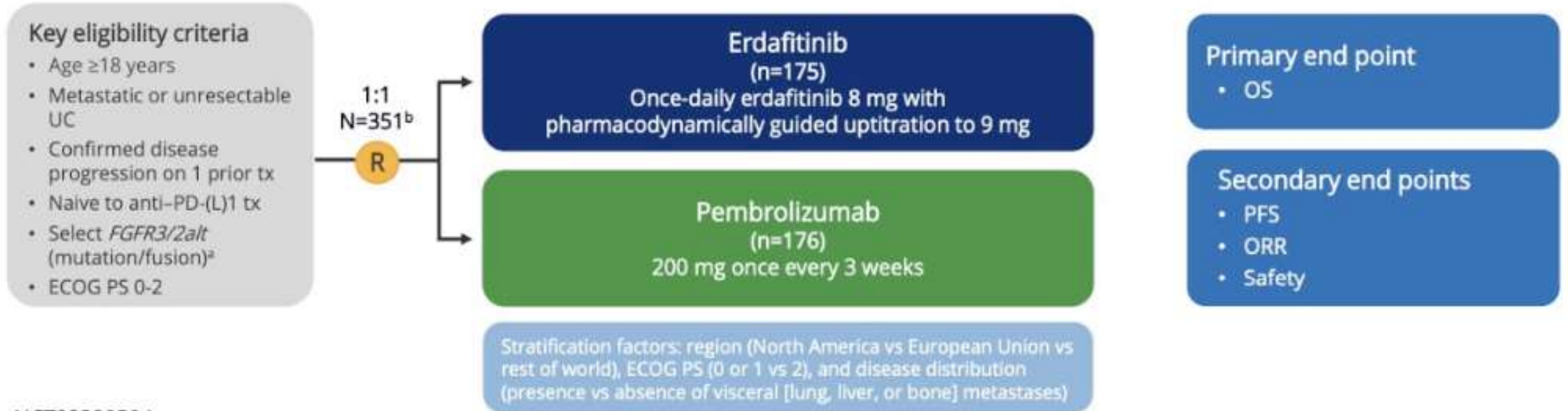


*n=number of events; N=number of patients in subgroup. CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.



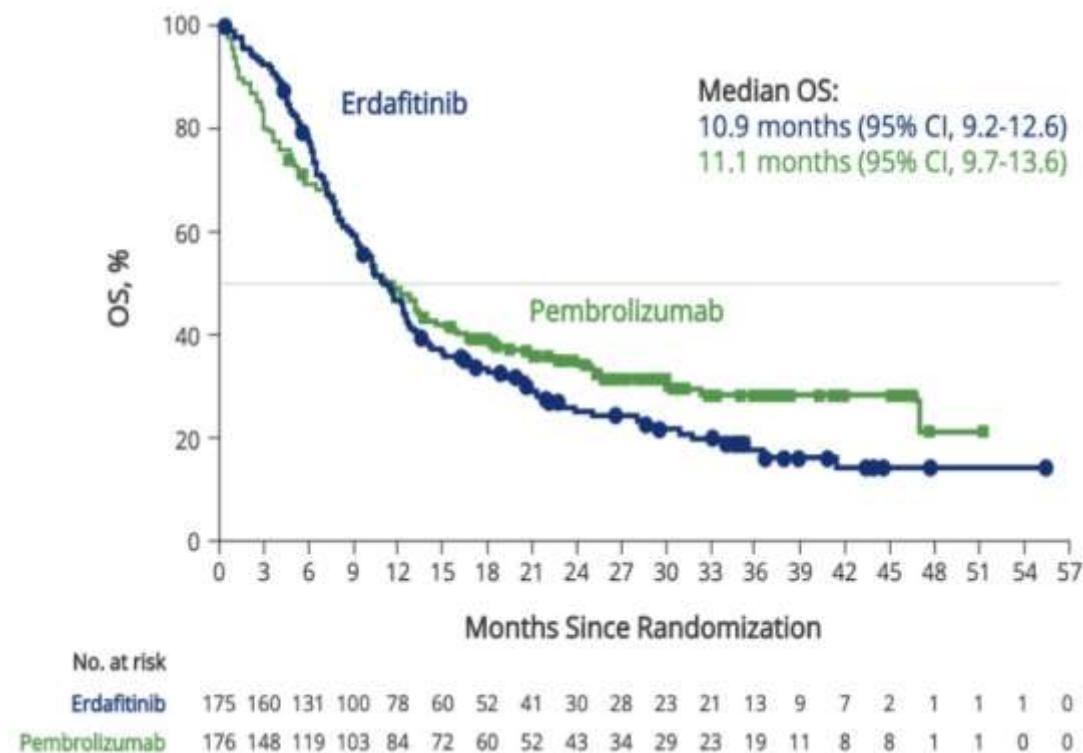
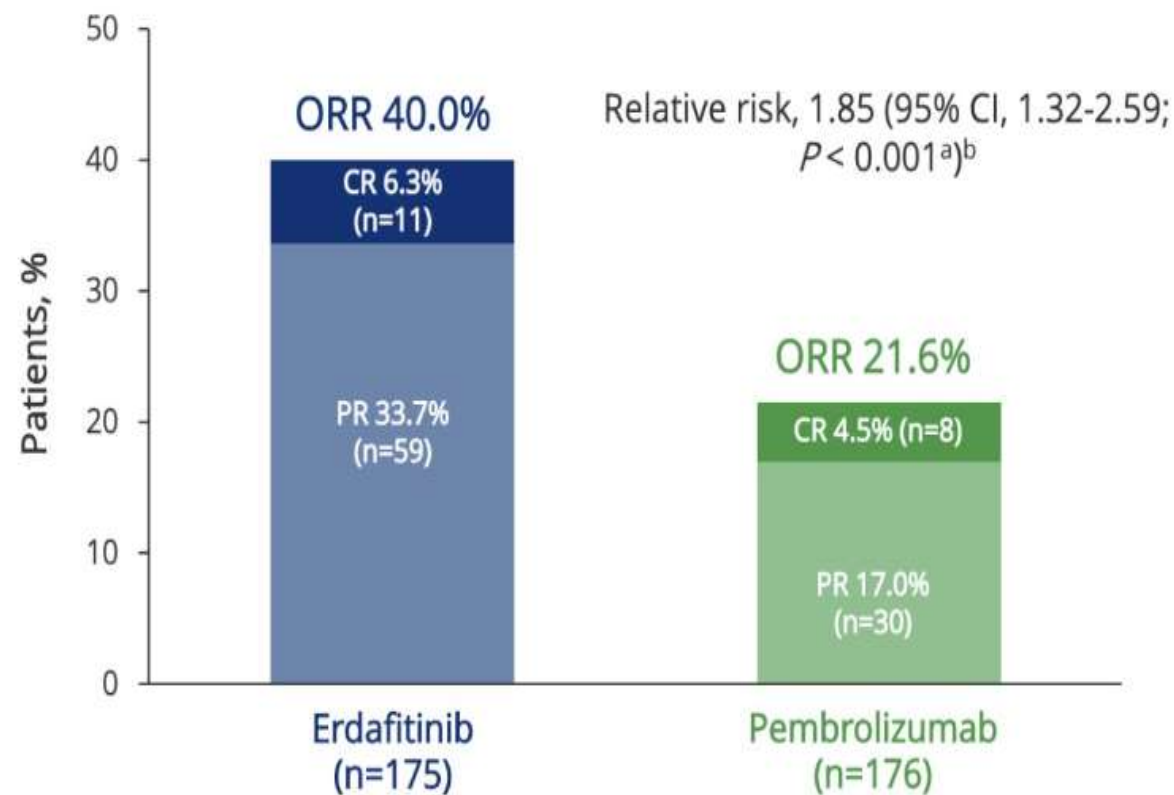
Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

Cohort 2



NCT03390504

Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi



Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

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

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

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

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

Confirmed Best Overall Response per BICR

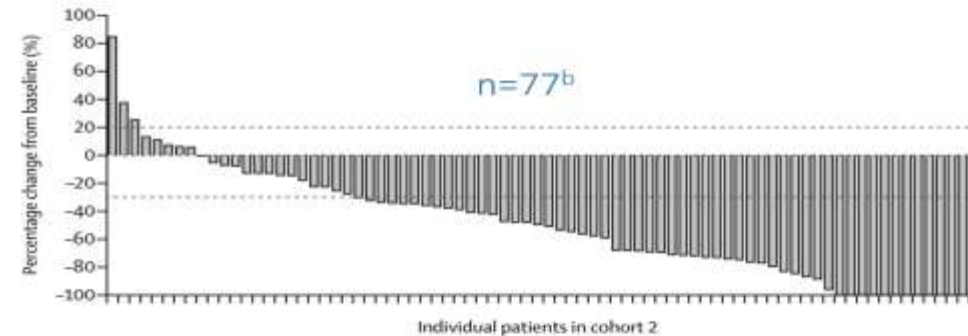
	Cohort 2 (n=89)
Objective response rate	46 (52%)
95% CI	41-62
Best overall response	
Complete response	18 (20%)
Partial response	28 (31%)
Stable disease	27 (30%)
Progressive disease	8 (9%)
Not evaluable ^a	8 (9%)

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

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

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

Change in Target Lesions From Baseline



Median duration of treatment: 6 months

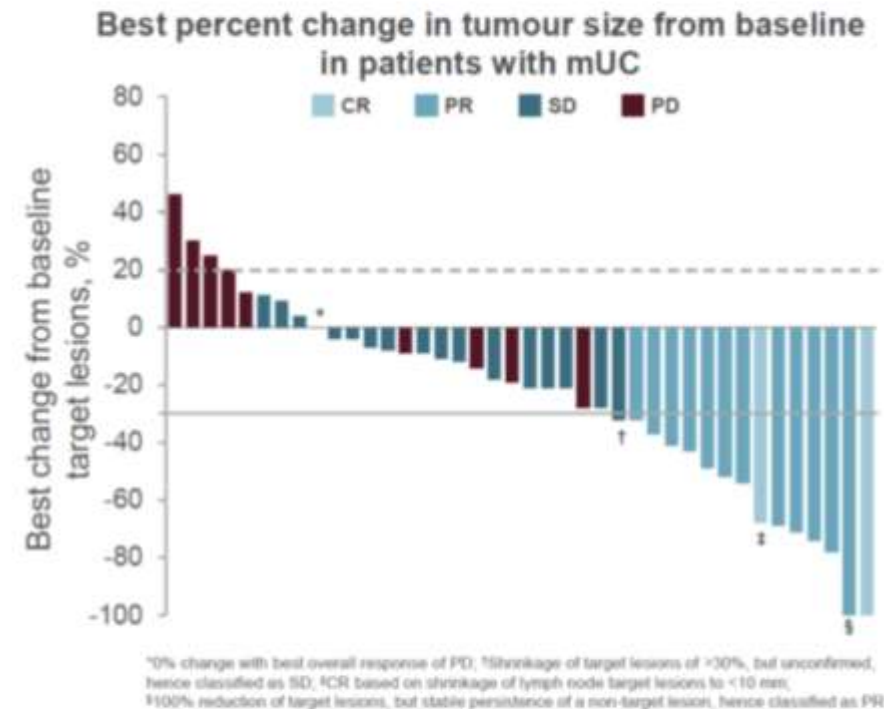
Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

Sacituzumab govitecan for mUC: Efficacy

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

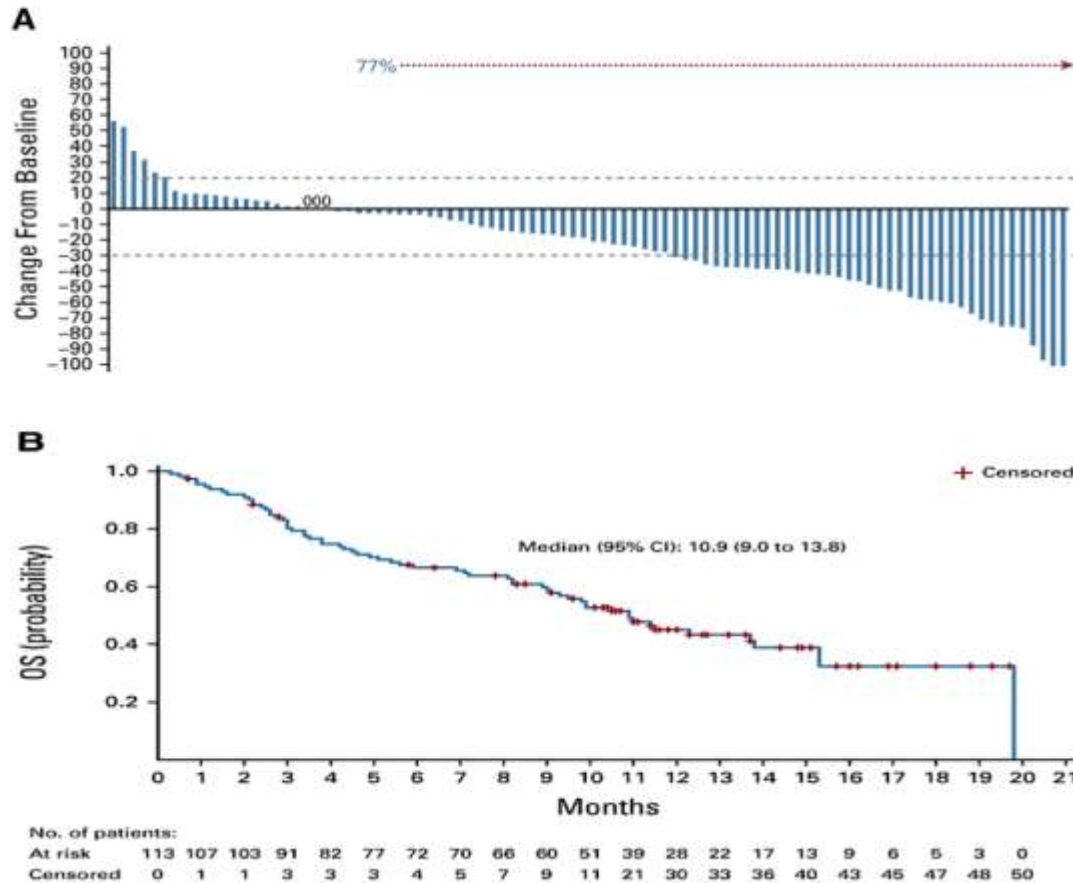
NCT01631552: Phase I/II study of SG in patients with epithelial cancers (PS 0–1)

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



Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

Sacituzumab Govitecan

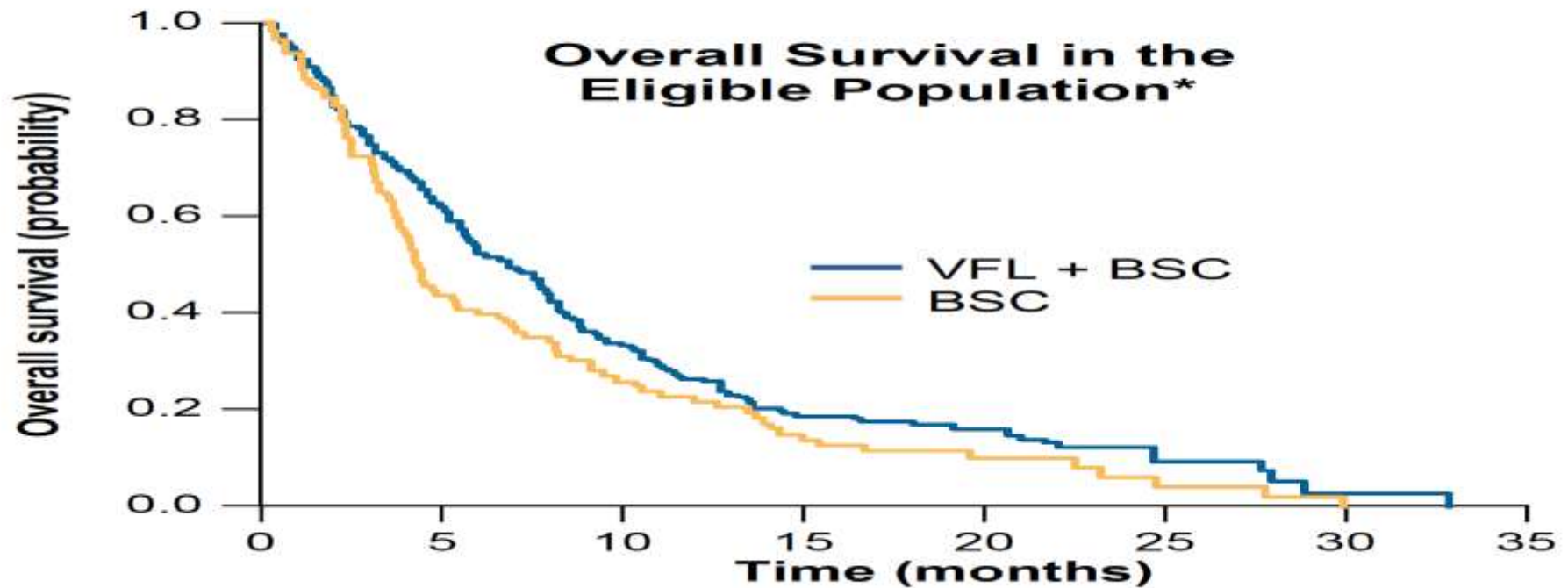


- N=113, post-platinum and post-IO
- SG 10 mg/kg d1, d8 q 3-wk
- GCSF as clinically indicated
- ORR 27%
- Med PFS: 5.4 mo
- Med OS: 10.9 mo
- Toxicity
 - Neutropenia $\geq$ G3: 34%
 - Diarrhea $\geq$ G3: 10%
- UGT1A homozygous/heterozygous
 - Potential increased risk neutropenia, pre-screening not required

Metastatik Mesane Kanseri

Platin bazlı Kemoterapi sonrası tedavi seçeneği

	Vinflunine + BSC (n=249)	BSC (n=108)
mOS, mos (95% CI)	6.9 (5.7–8.0)	4.3 (3.8–5.4)
HR: 0.78; 95% CI, 0.61–0.99; <i>P</i> =0.0403		



Adapted from Bellmunt et al, 2009.

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

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimens for cisplatin ineligible, chemotherapy naïve • Enfortumab vedotin-ejfv²⁹ • Gemcitabine and carboplatin • Erdafitinib^{d,28}	Other recommended regimens • Paclitaxel or docetaxel³¹ • Gemcitabine¹⁸
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin⁴ • DDMVAC with growth factor support² • Erdafitinib^{d,28}	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine²² • Gemcitabine and paclitaxel¹⁹

Gelecek Perspektif

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

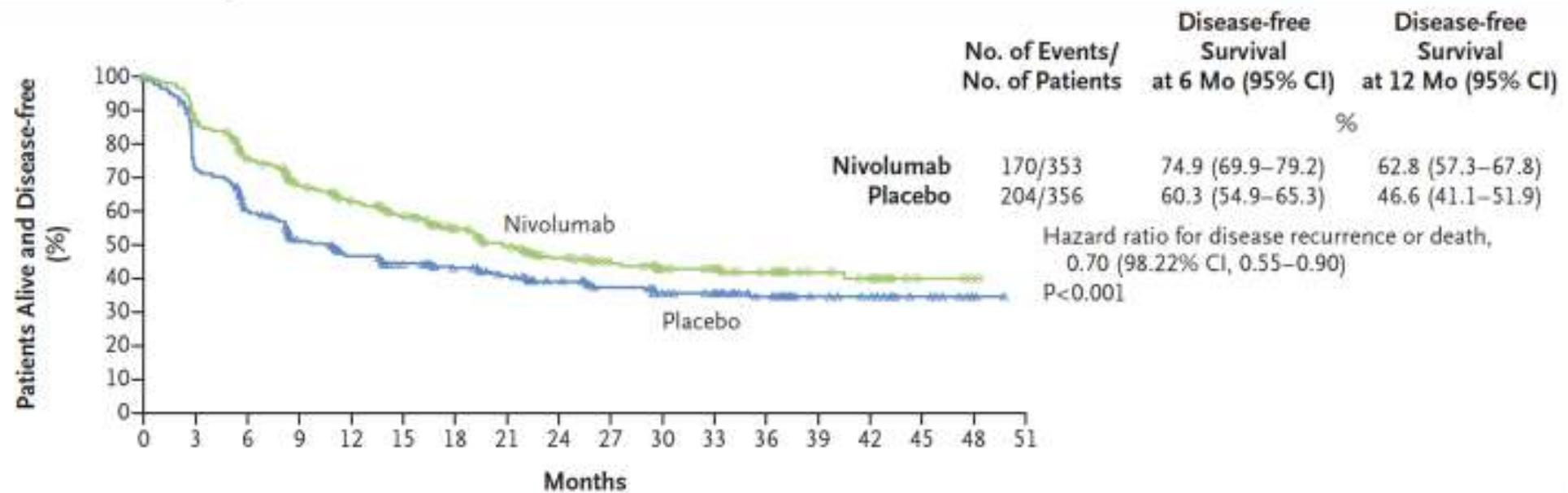
Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

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.

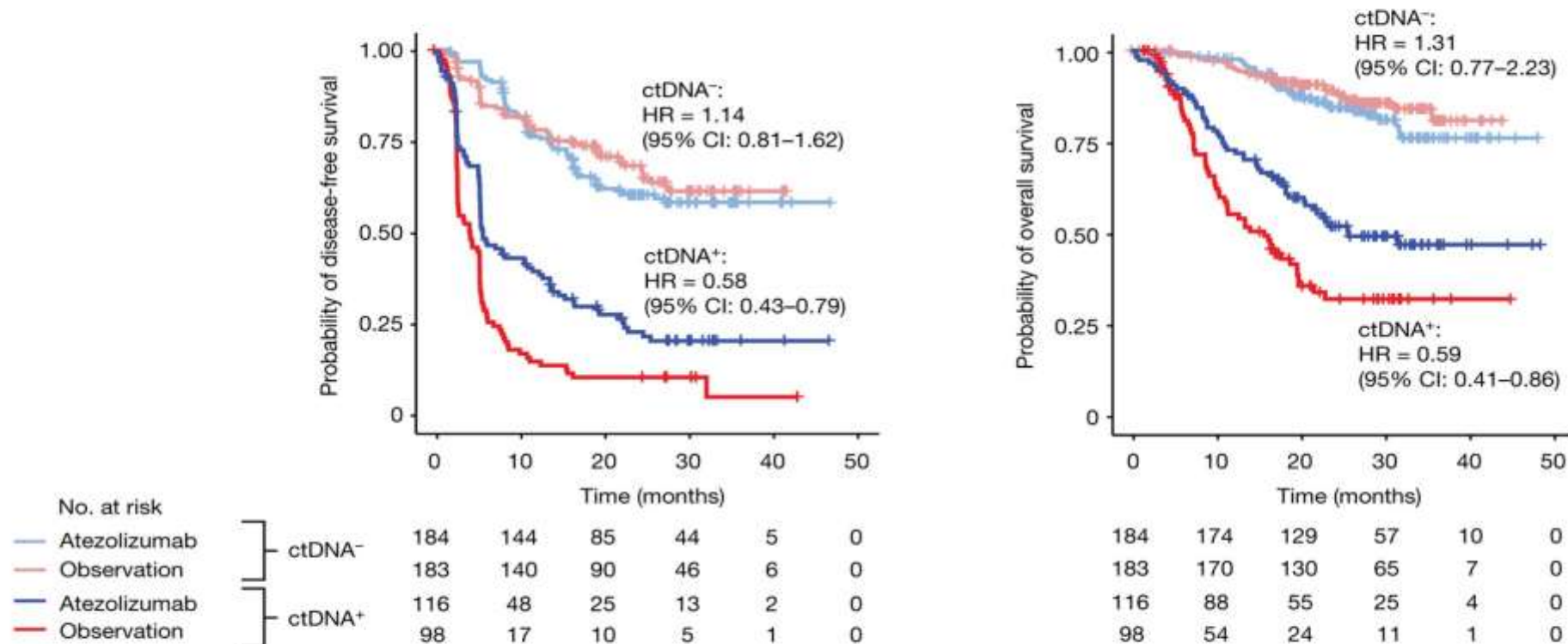
Gelecek Perspektif

CheckMate 274: Disease-Free Survival in the ITT Population



Gelecek Perspektif

Can ctDNA help Guide Adjuvant Therapy ?



Powles, Nature, 2021

Gelecek Perspektif

Does CPI combine best with ADCs with MMAE payloads?

Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

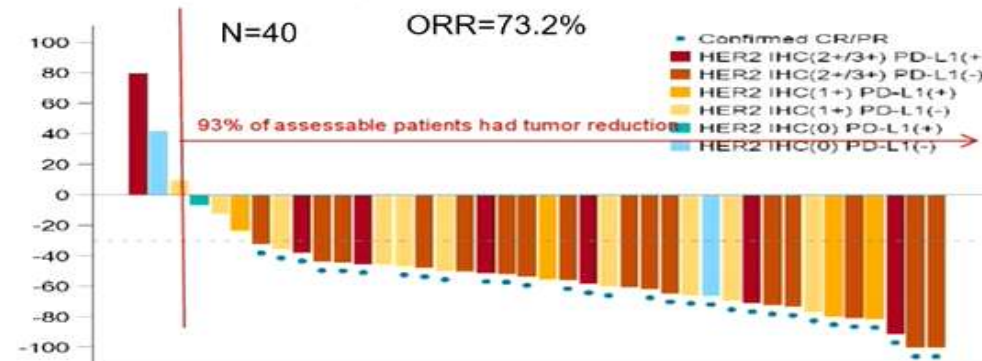
Disitamab vedotin

N=107 In the Second or Third-line setting



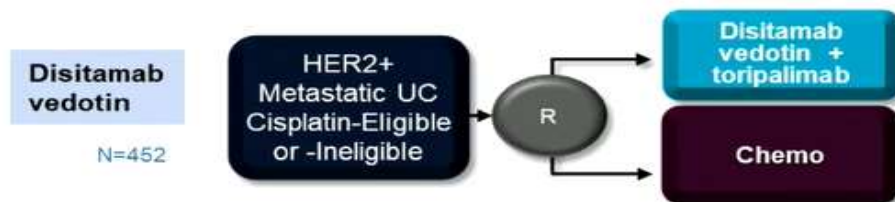
Sheng, et al. ASCO 2022 abstract 4518

Disitamab vedotin + toripalimab



Sheng, X., et al. ASCO 2023

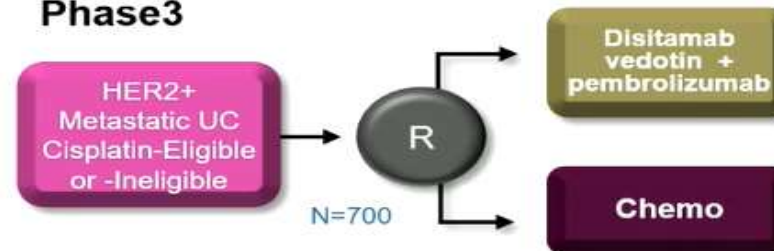
Phase 3



Presented by Andrea B. Apolo, MD

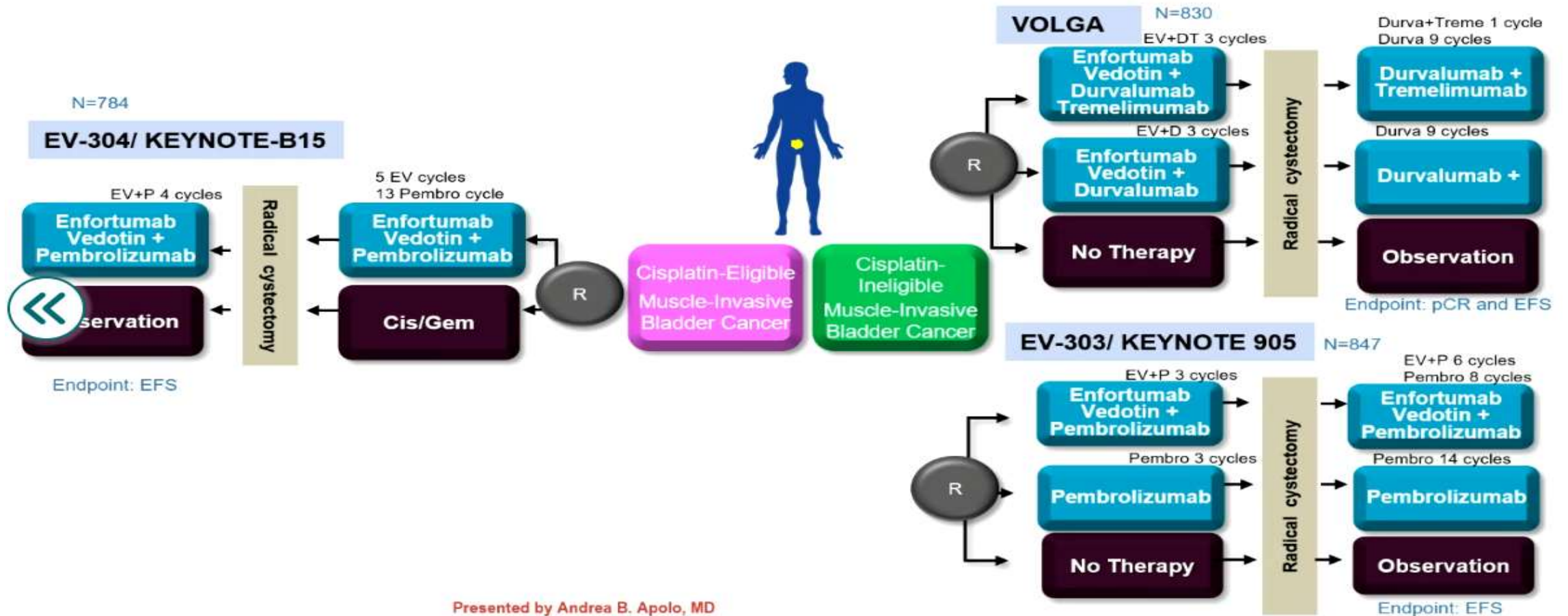
@apolo_andrea

Phase3



Gelecek Perspektif

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

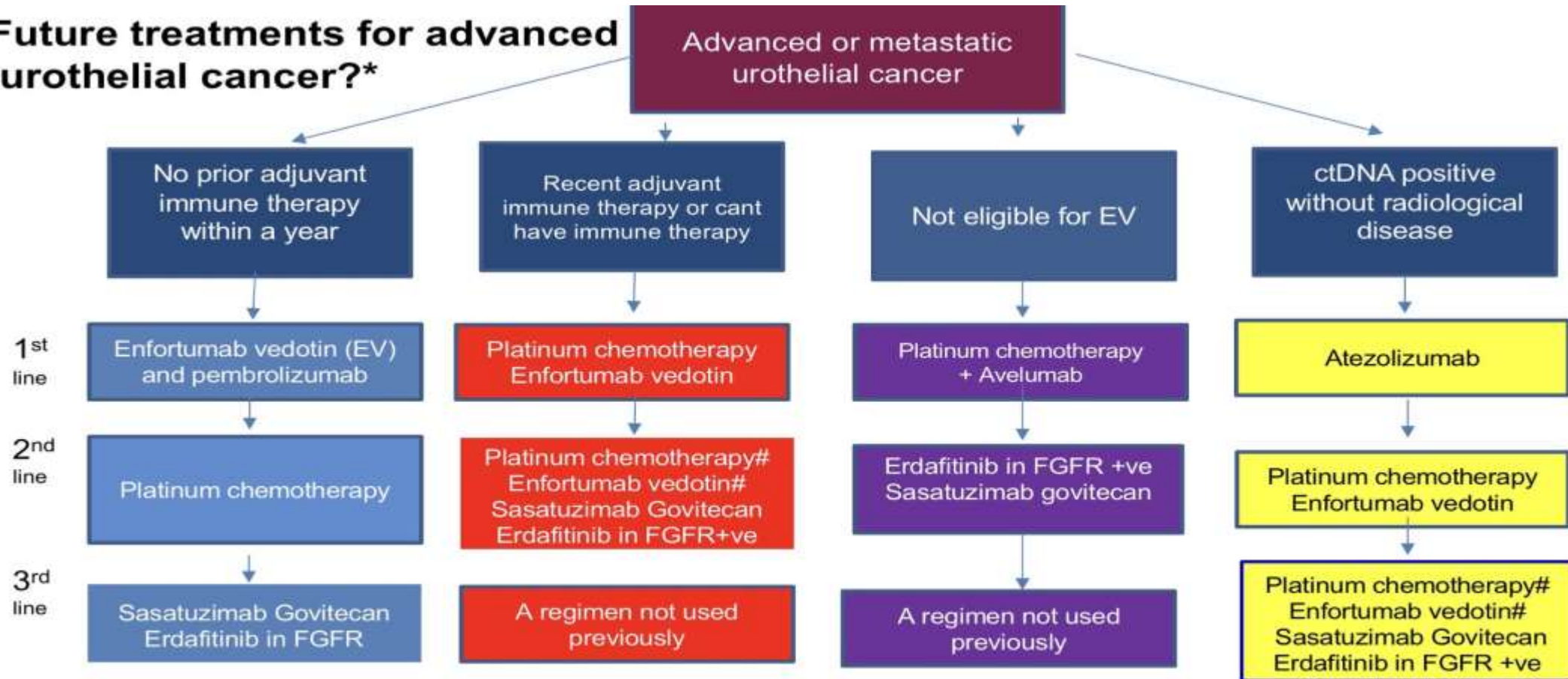


Presented by Andrea B. Apolo, MD

✉ @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 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

Sonuç

- ❑ İkinci basamak ve sonrası tedavileri hastanın kliniğine bağlı olarak ilk seride aldığı tedaviye bağlı olarak değişir
- ❑ Daha önce immün checkpoint inhibitörü almamışsa pembrolizumab vb.
- ❑ FGFR mutasyonu olanlarda **Erdafitinib**
- ❑ Immün checkpoint ve enfortumab alanlarda sacituzumab govitecan
- ❑ Platin bazlı kemoterapi ve diğer seçenekleri almışsa Vinflunine