Metastatik Mesane ve Üst Üriner Sistem Kanserlerinde Sistemik Tedavi

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Tıbbi Onkoloji

Ders Planı

- Mesane Kanseri İnsidans ve Mortalite

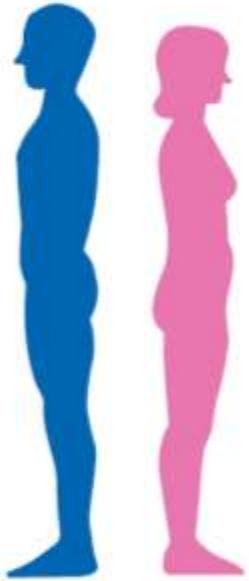
Metastatik Hastalık

- 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

Males			Females		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	8%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All Sites	**870,970**	**100%**	**All Sites**	**891,480**	**100%**

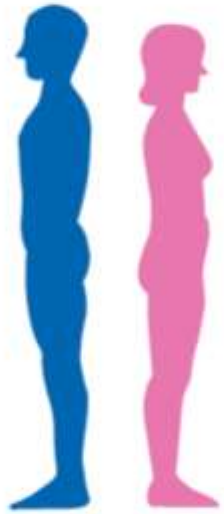


CA CANCER J CLIN 2019;69:7-34

Mesane Kanseri İnsidans ve Mortalite

2019 ESTIMATED CANCER DEATHS – US

Males			Females		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All Sites	**321,670**	**100%**	**All Sites**	**285,210**	**100%**

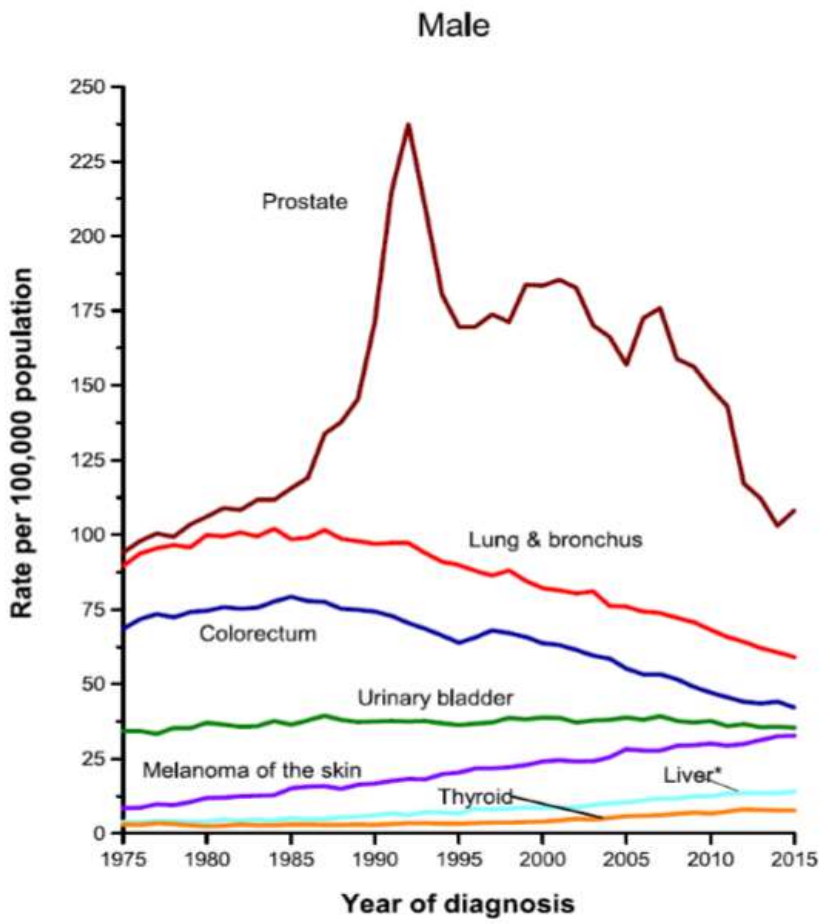


CA CANCER J CLIN 2019;69:7–34

Mesane Kanseri İnsidans ve Mortalite

TEMPORAL TRENDS IN THE INCIDENCE OF BLADDER CANCER

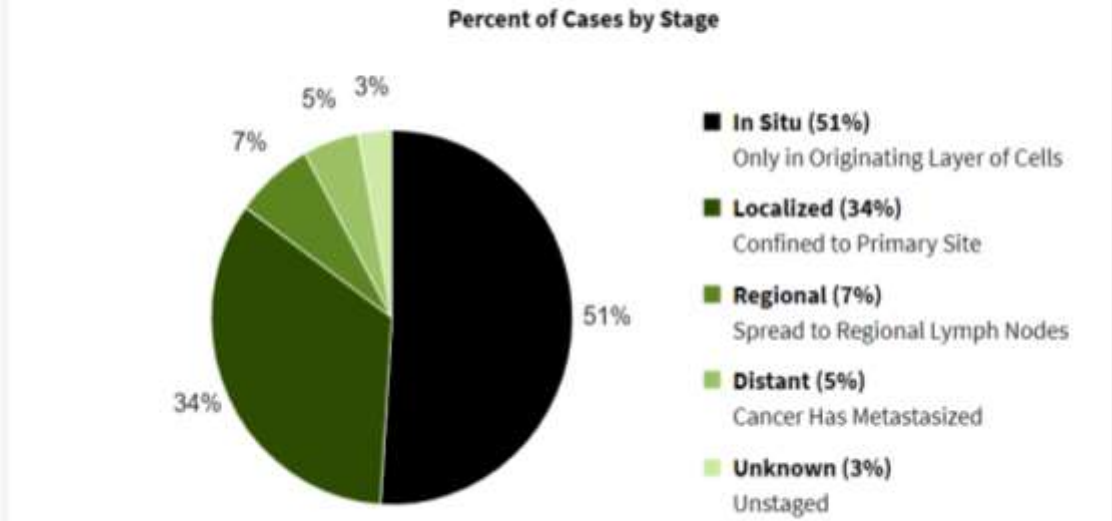
- The incidence of several major cancers has fallen over the last 40 years
  - There have been increased incidence in a few (melanoma and liver for example)
- No major changes in the incidence of bladder cancer in the last 40 years

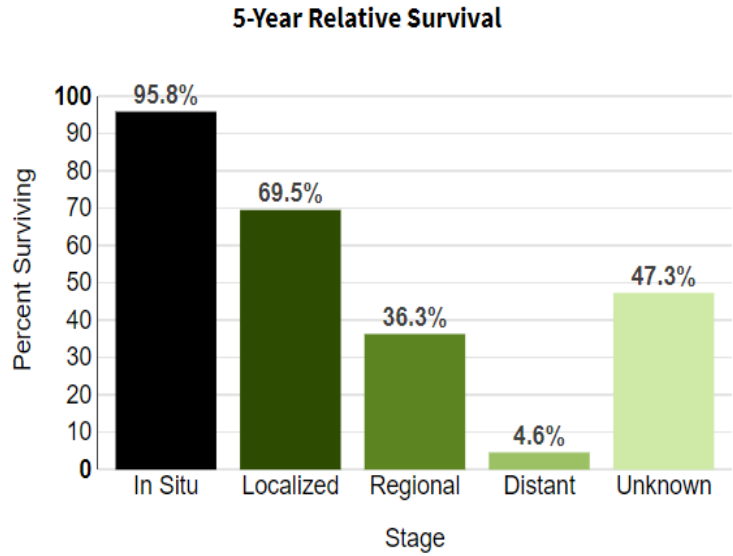


CA CANCER J CLIN 2019;69:7–34

Mesane Kanseri İnsidans ve Mortalite

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





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

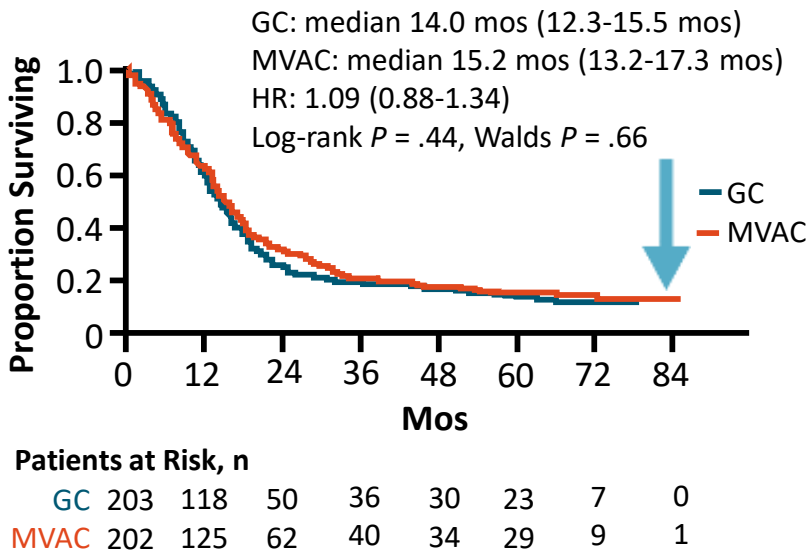
Study (year of publication)	*n*	Interventions	Response rate (%)	Median OS (months)	Toxicity
Logothetis *et al.*[36] (1990)	110	MVAC versus CISCA	65 versus 46; $P<0.05$	15.5 versus 10.1; $P=0.0003$	MVAC>CISCA
Loehrer *et al.*[37] (1992)	269	MVAC versus cisplatin	39 versus 12; $P<0.0001$	12.5 versus 8.2;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

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

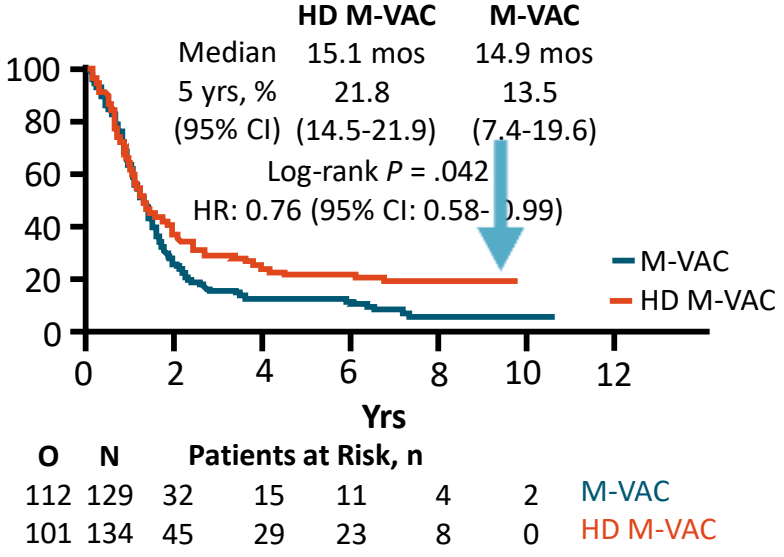
Metastatik Birinci Basamak Kemoterapi Sonuçları

Sisplatin Uygun

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

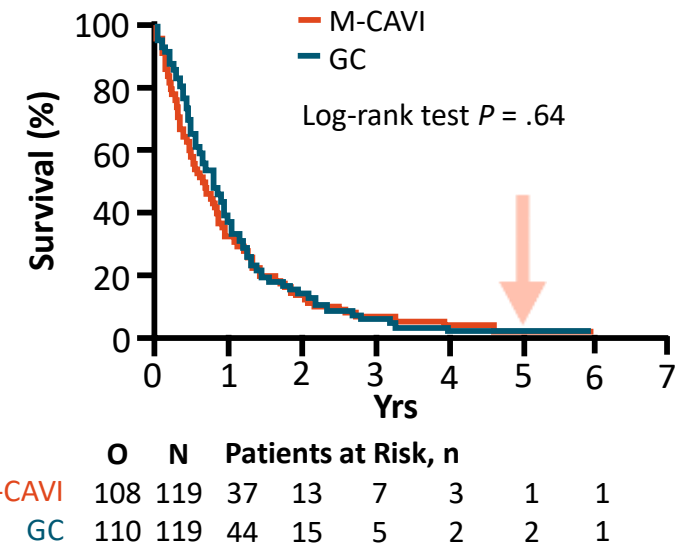


Dose Dense MVAC[3]
ORR: 72%
CR: 25%
Median OS: 15.1 mos



Sisplatin uygun değil

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



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

Metastatik 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

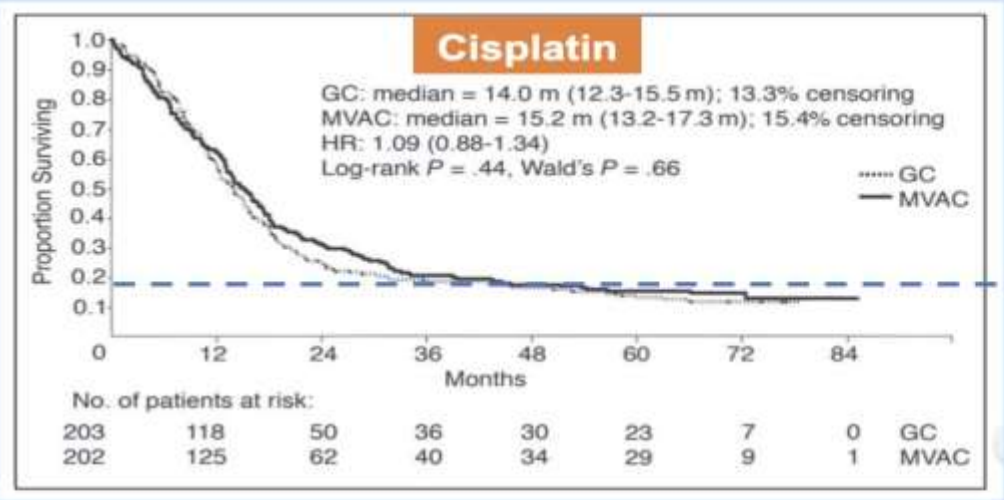
Source	Cisplatin-based		Carboplatin-based		Weight (%)	RR (95% CI)	*P* value
	Events	Total	Events	Total			
Petrioli et al. [15]	7	28	3	27	51.80	2.25 (0.65–7.18)	
Bellmunt et al. [13]	3	23	0	23	14.54	1.17 (0.07–18.58)	
Drecier et al. [2]	5	36	1	39	16.28	5.42 (0.66–44.12)	
Dogliotti et al. [14]	8	41	1	39	17.38	7.61 (0.96–58.06)	
Overall (Mantel–Haenszel method)	23	128	5	128		3.54 (1.48–8.49)	0.005

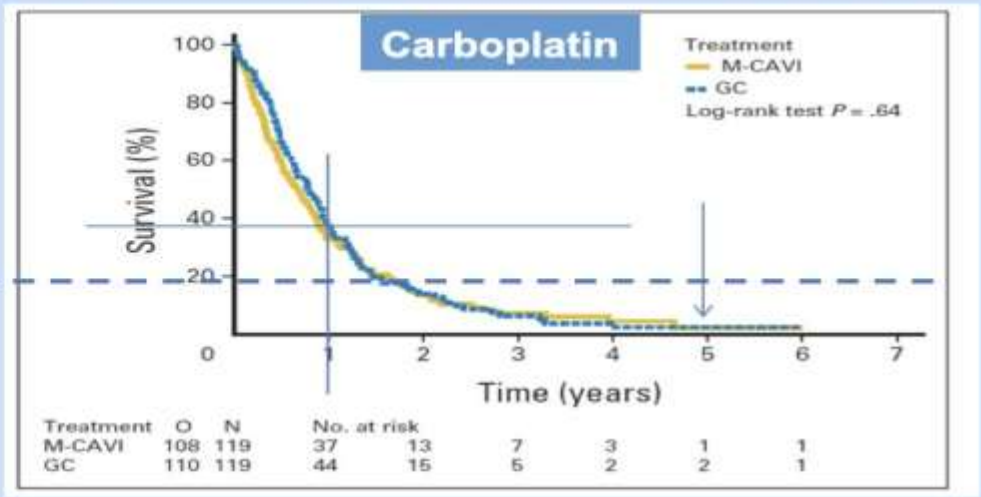
Heterogeneity chi-square test = 1.83 (d.f. = 3); $P = 0.609$; I-squared test (variation in RR attributable to heterogeneity) = 0.0%.
RR, risk ratio; CI, confidence interval.

Galsky et al, Ann Oncol, 2011

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

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

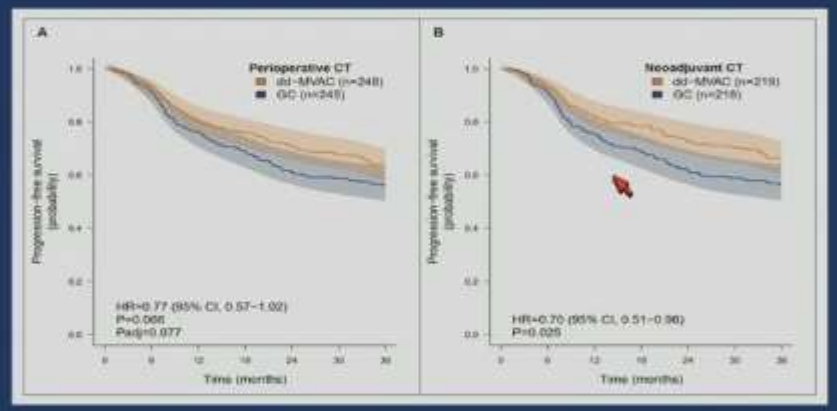
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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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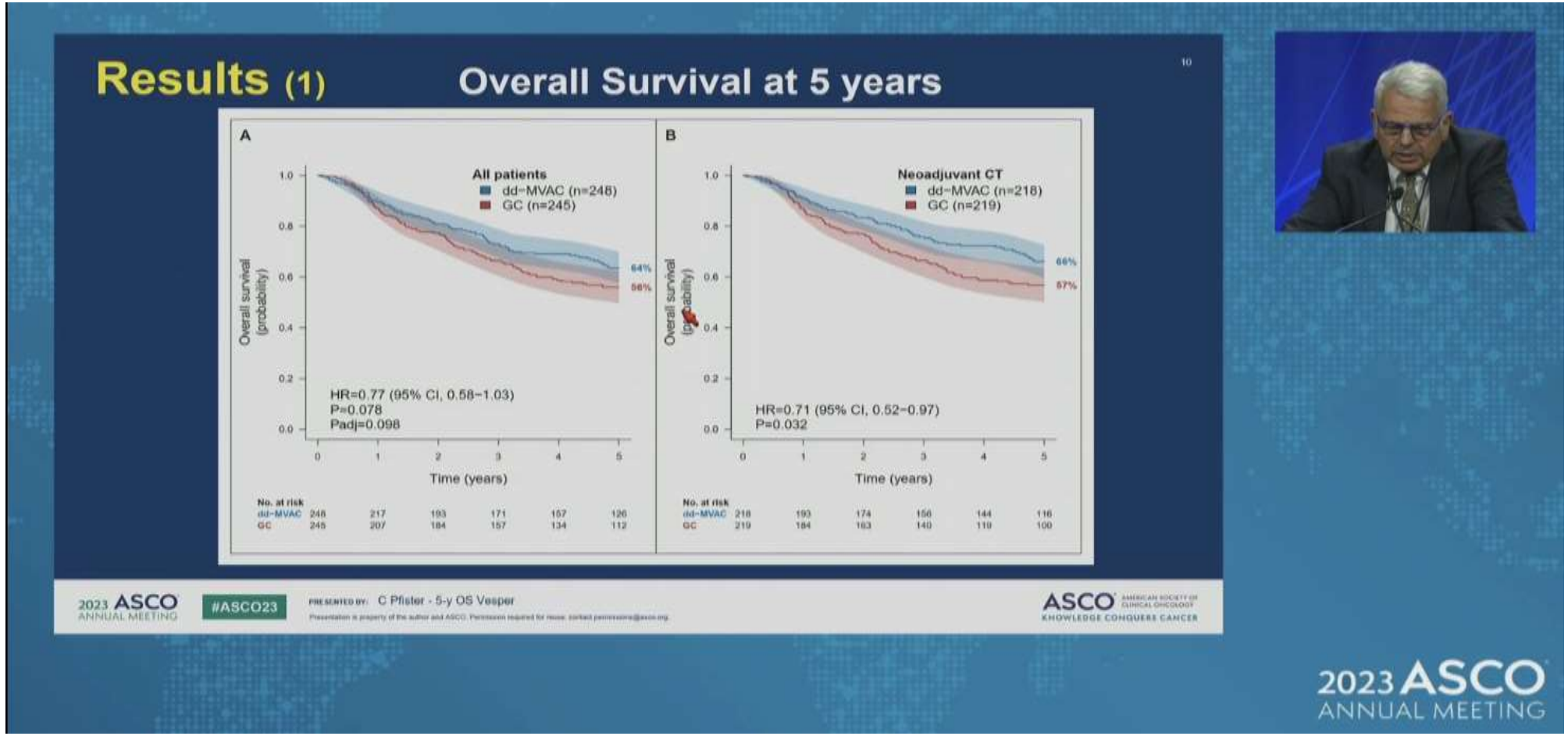
2023 ASCO ANNUAL MEETING

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

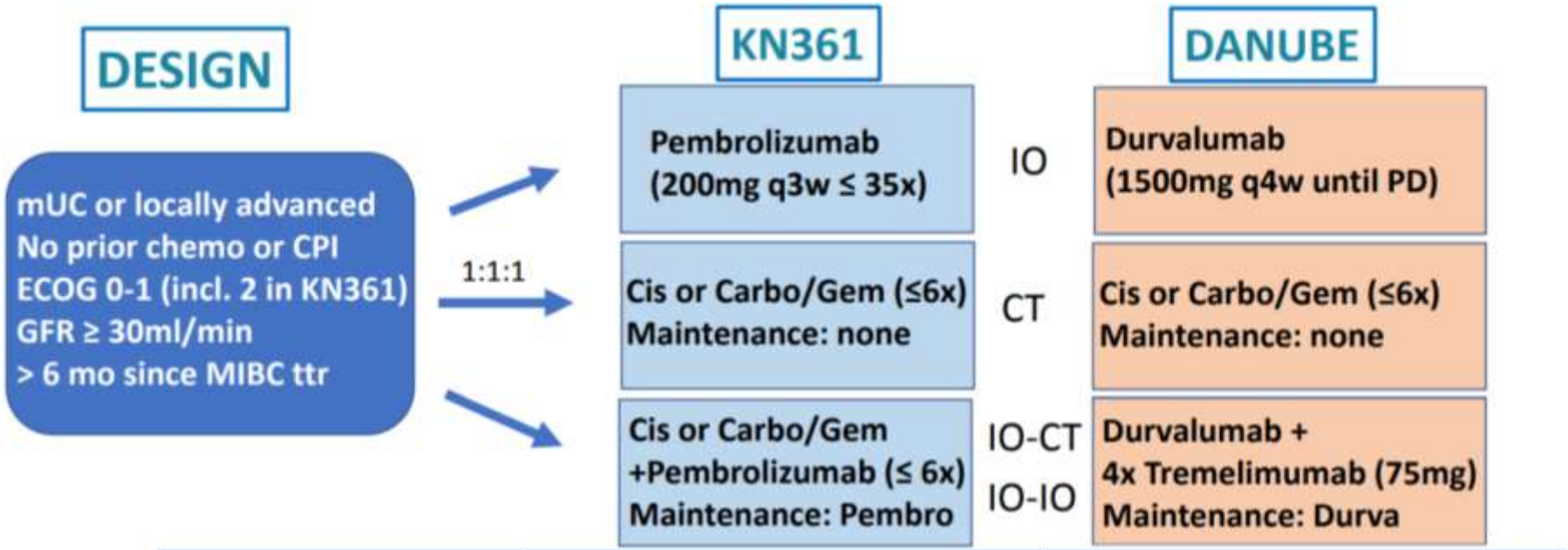
First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Pembrolizumab and enfortumab vedotin-ejfv[15] (category 1) **Other recommended regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (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)

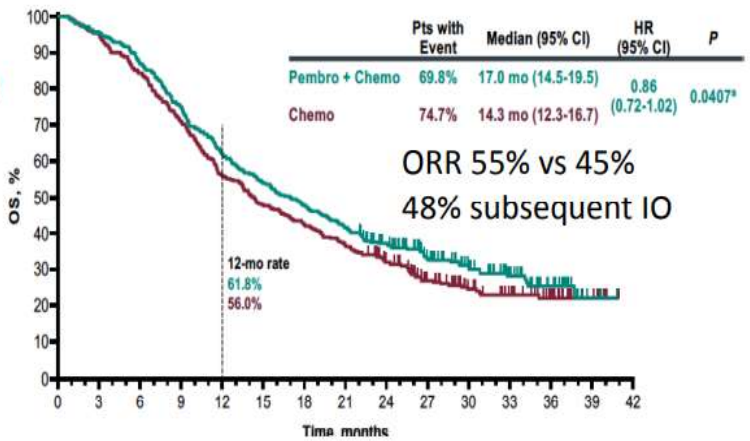
Metastatik Mesane Kanseri Birinci Basamak
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

Overall survival

Combination vs Chemo

TOTAL population (ITT)

KEYNOTE 361 –IO-CT vs CT (1˚EP)

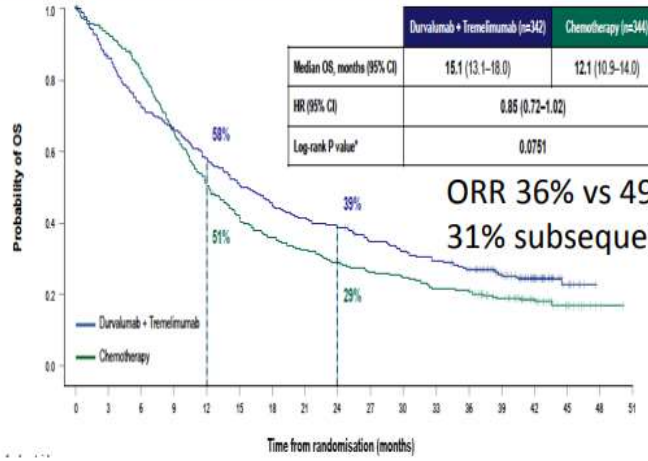


	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407*
Chemo	74.7%	14.3 mo (12.3-16.7)		

ORR 55% vs 45%

48% subsequent IO

DANUBE – IO-IO vs CT (1˚EP)



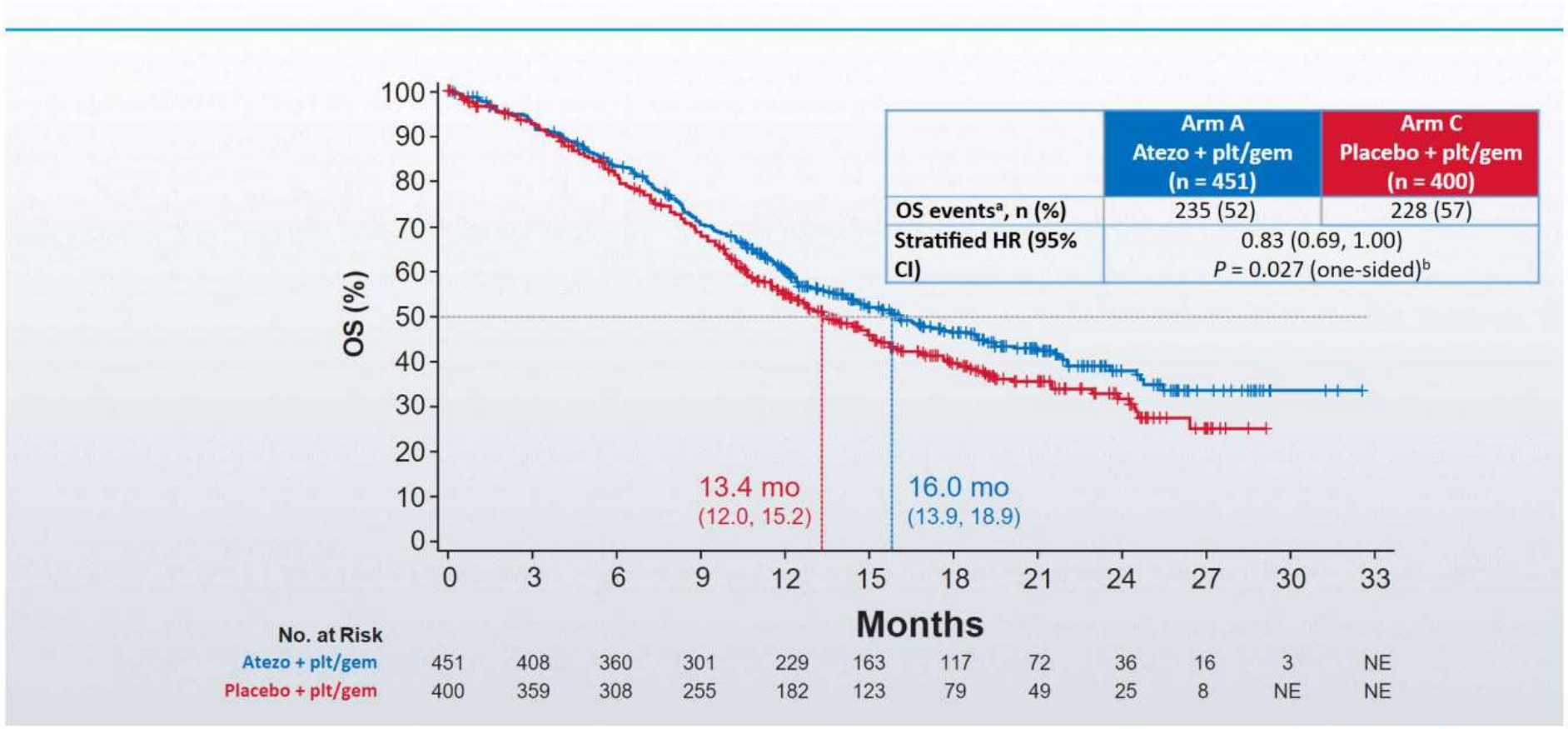
	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)
Median OS, months (95% CI)	15.1 (13.1–18.0)	12.1 (10.9–14.0)
HR (95% CI)	0.85 (0.72–1.02)	
Log-rank P value*	0.0751	

ORR 36% vs 49%

31% subsequent IO

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

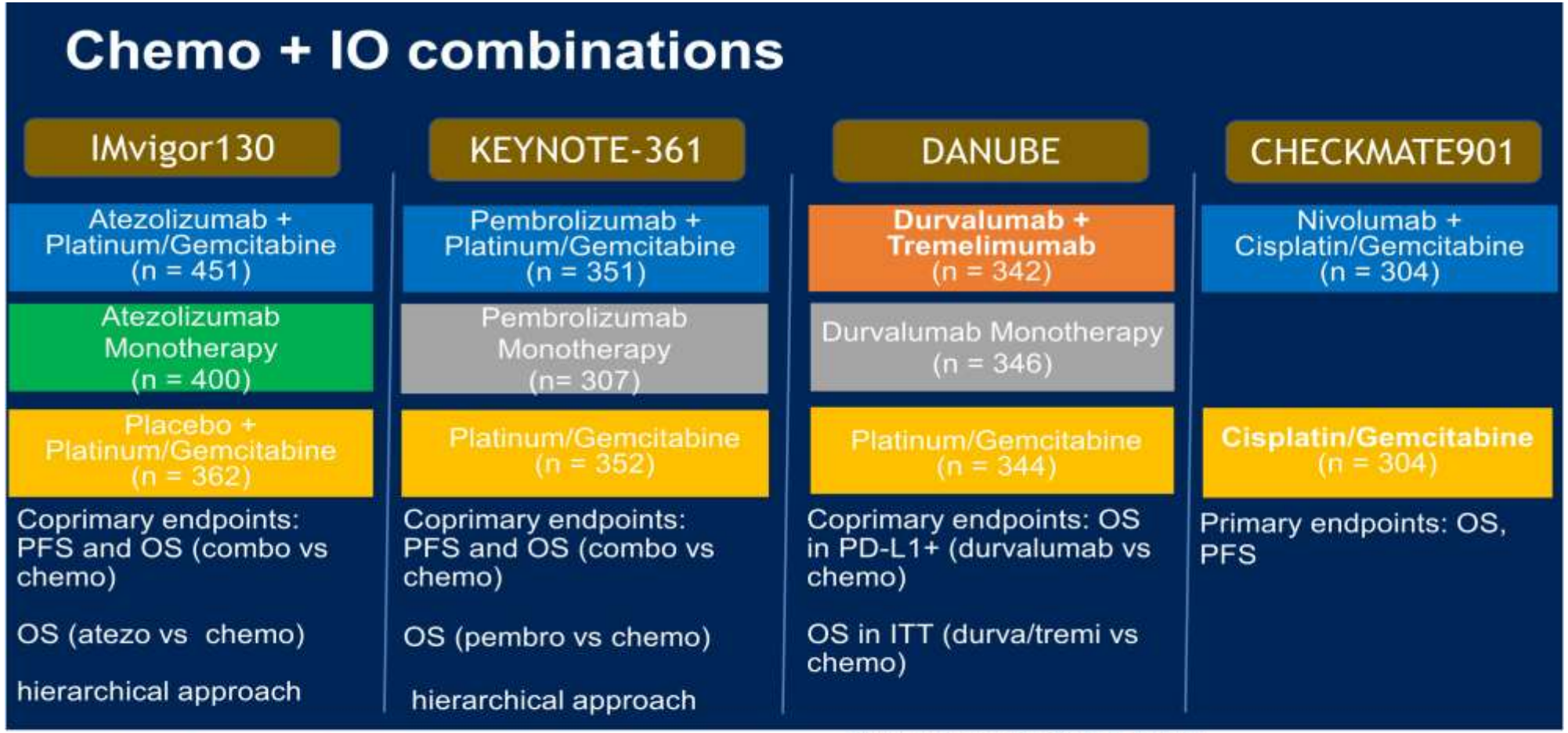
IMvigor130 Interim OS: ITT (Arm A vs Arm C)



	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

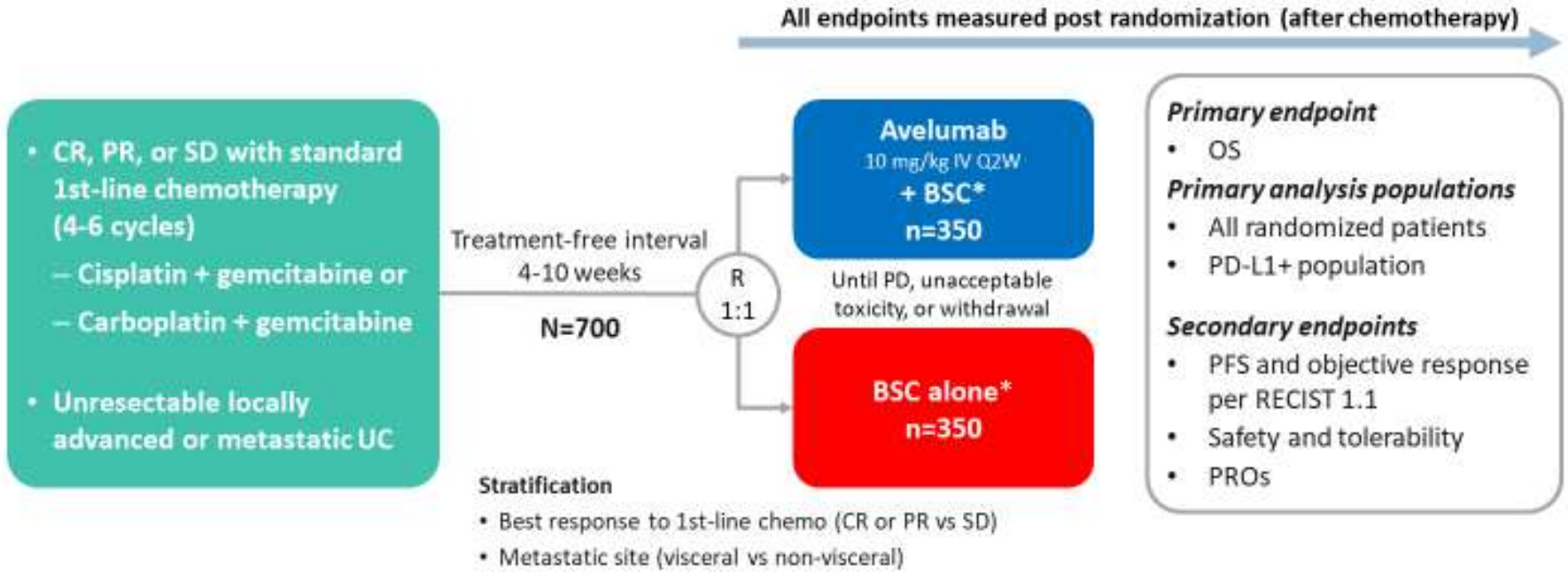
Metastatik Mesane Kanseri Birinci Basamak
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri



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

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

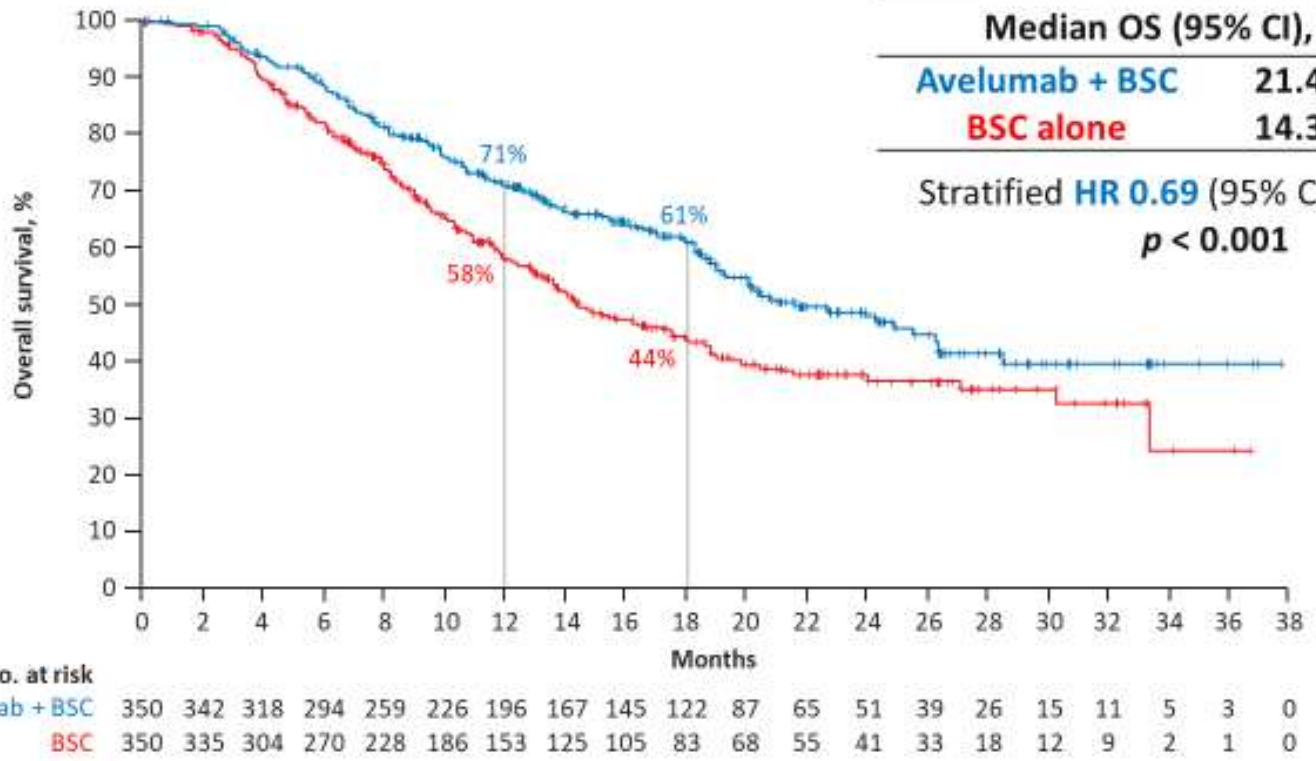
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

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**

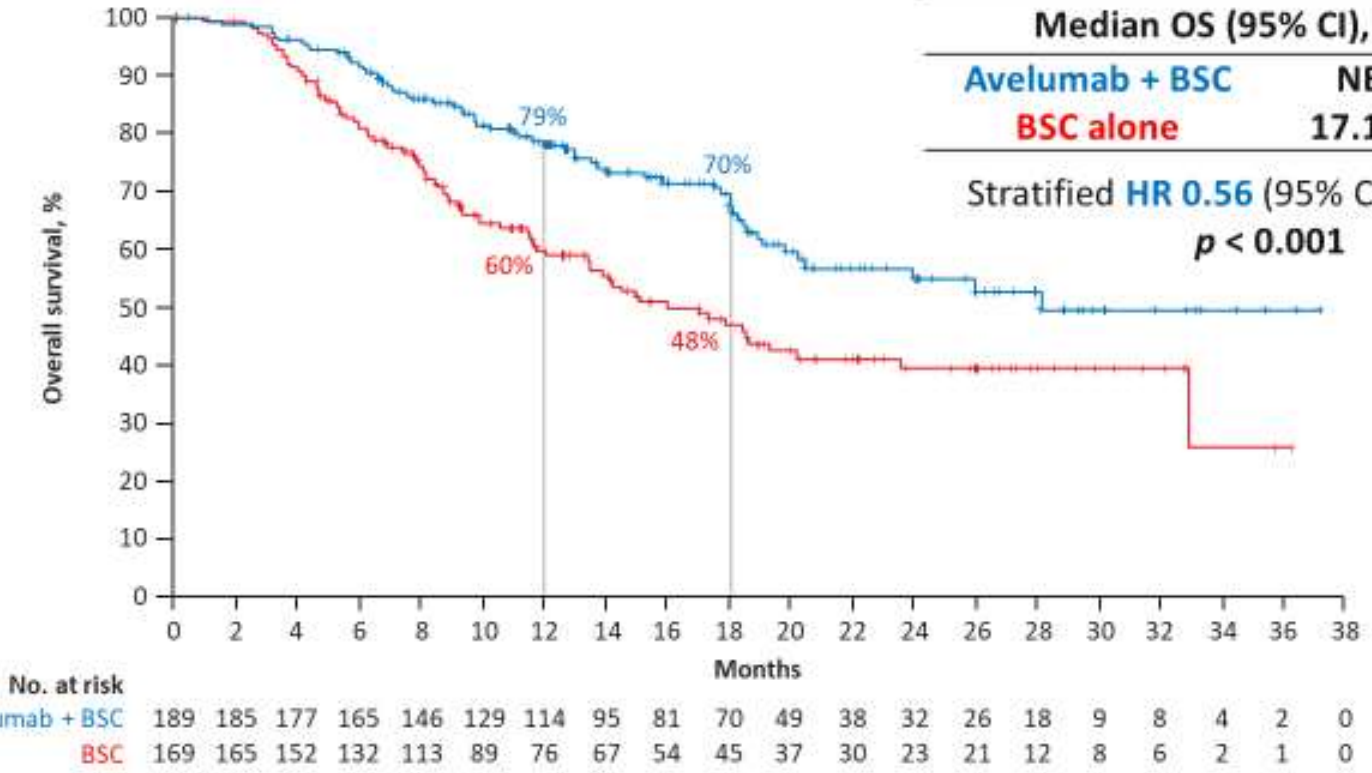
OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

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.

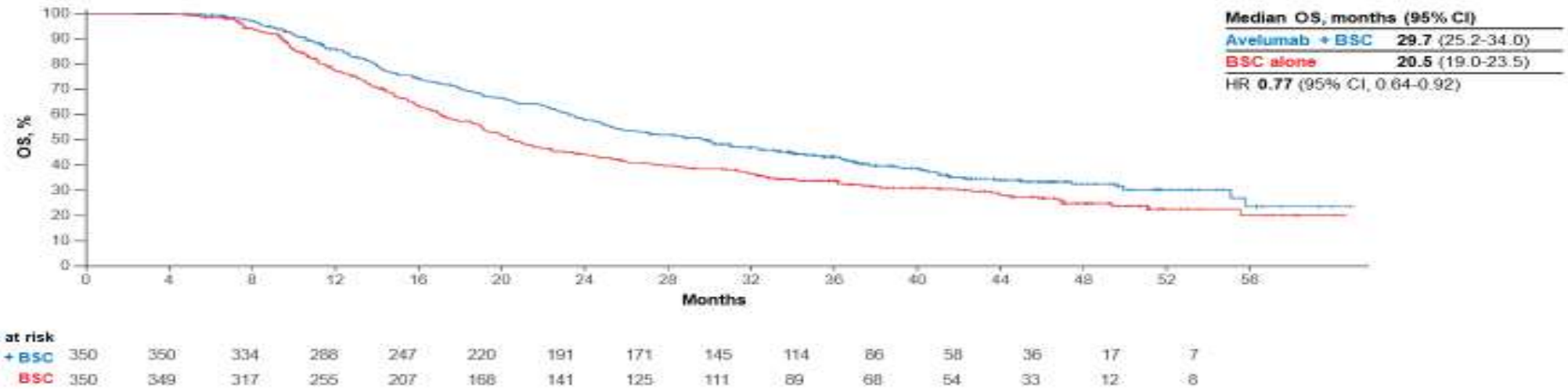
Courtesy of Arjun V. Balar, MD

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.

İmmün kontrol noktası inhibitörleri

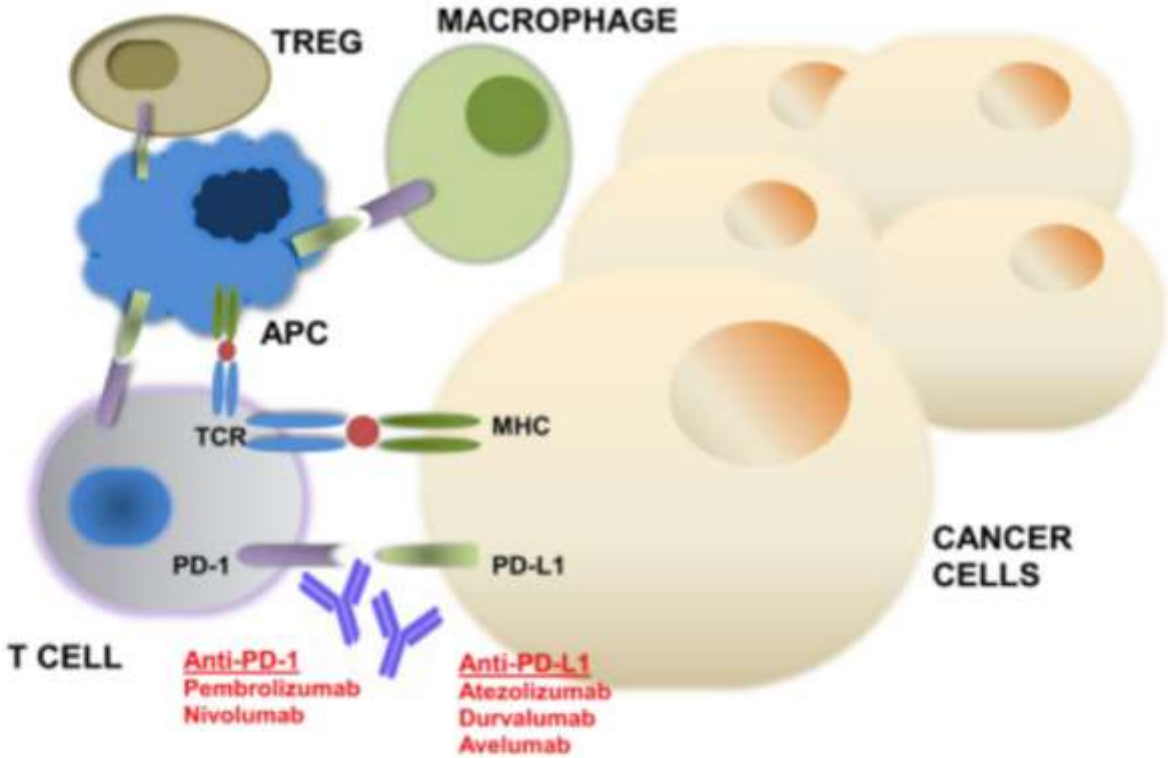
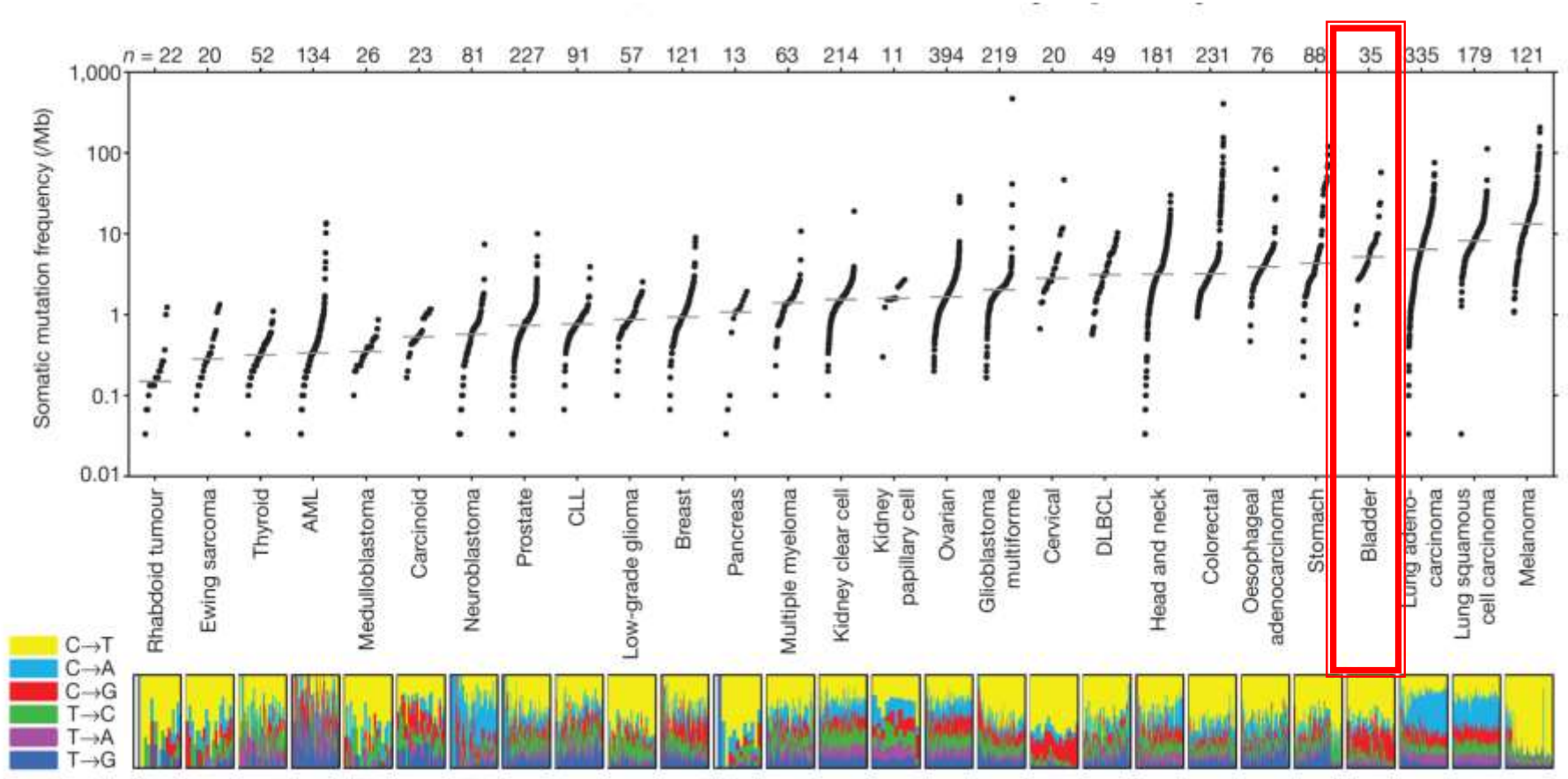


Fig. 1 Mechanism of action of PD-1 and PD-L1 inhibitors. The programmed cell death 1 (PD-1) receptor is expressed on activated T cells, B cells, macrophages, regulatory T cells (Tregs), and natural killer (NK) cells. Binding of PD-1 to its B7 family of ligands, programmed death ligand 1 (PD-L1 or B7-H1) 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

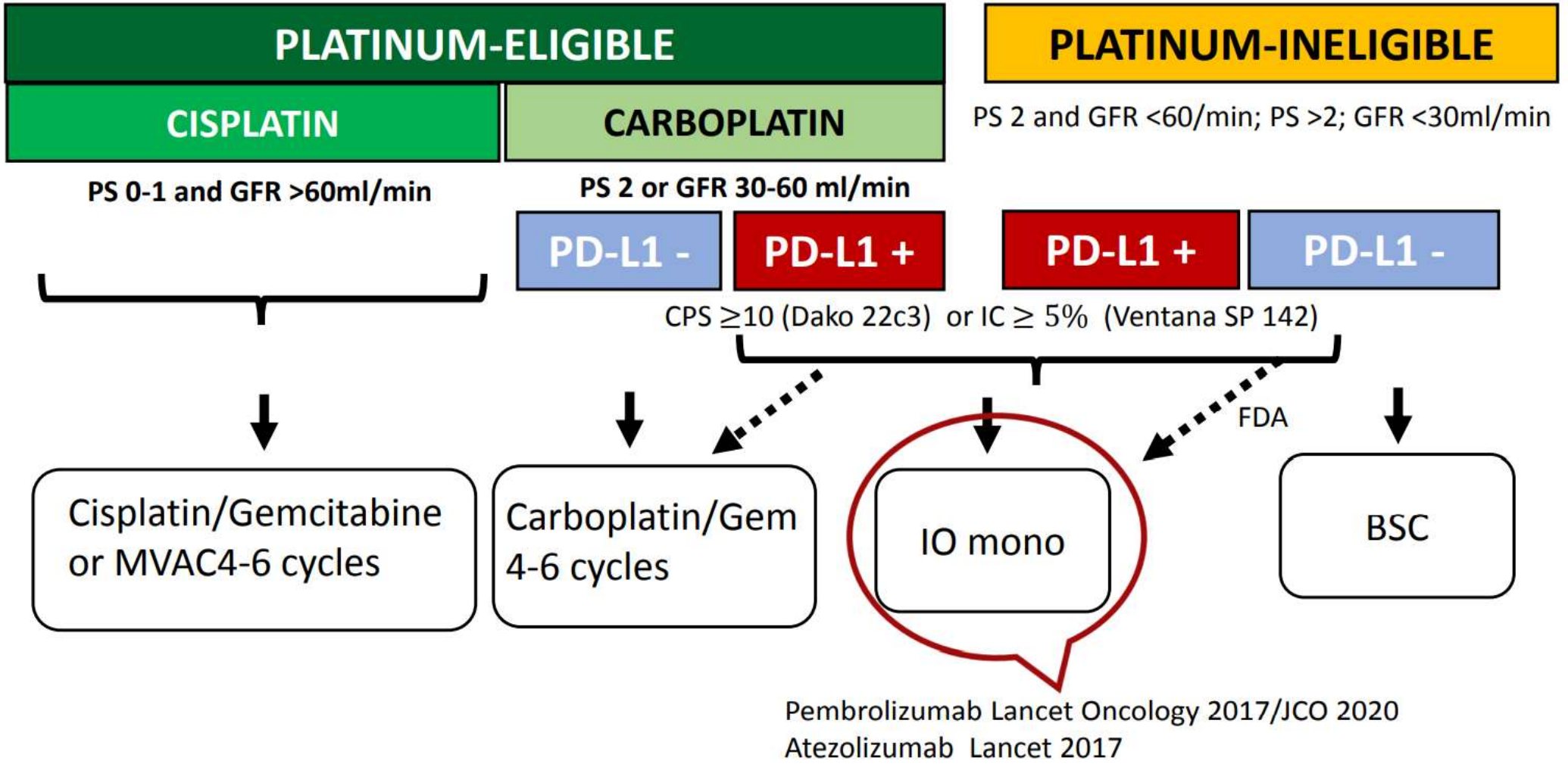
Mesane Kanserinde Tümör Mutasyon Yükü



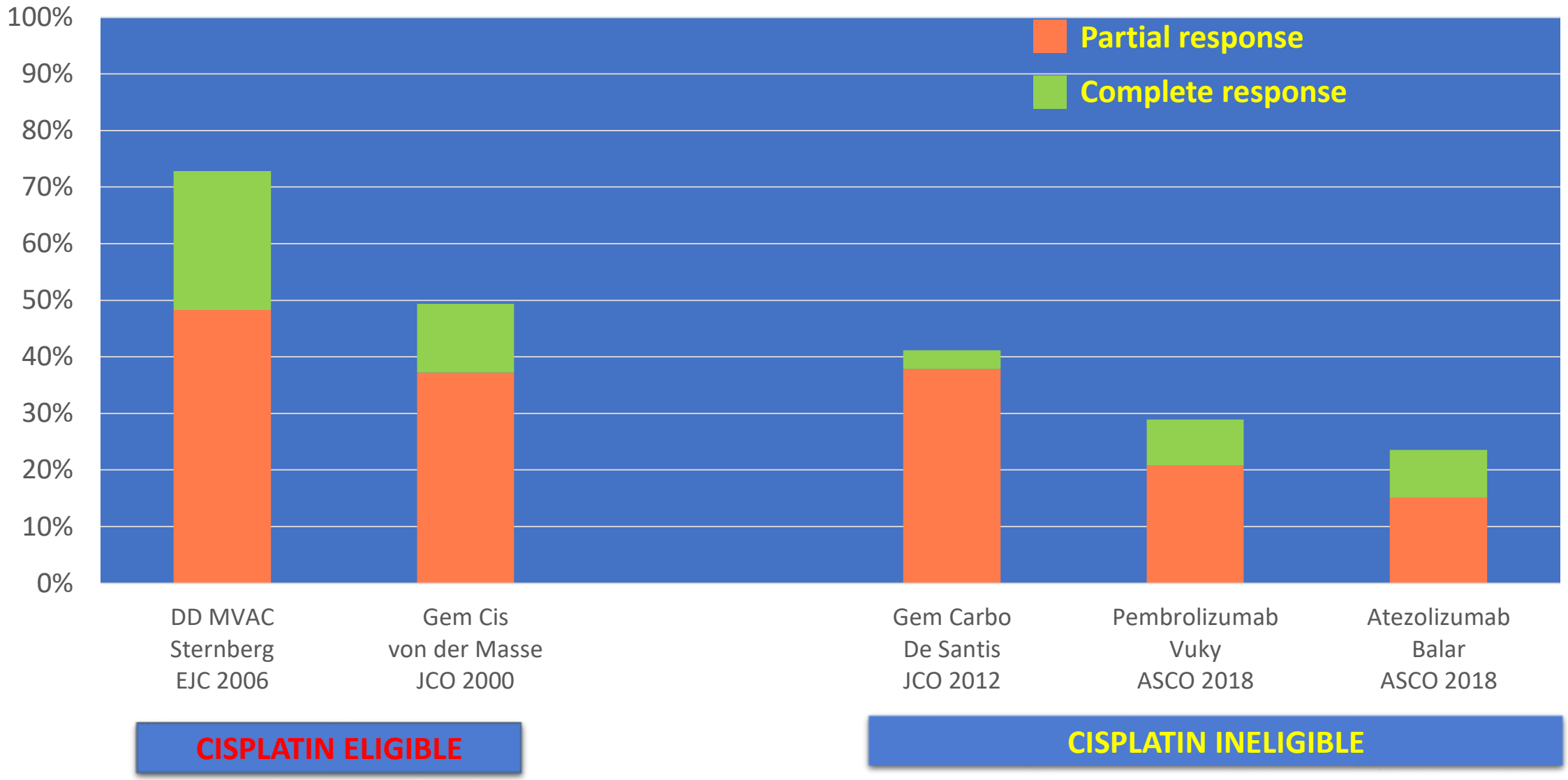
Lawrence et al. Nature 2013

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

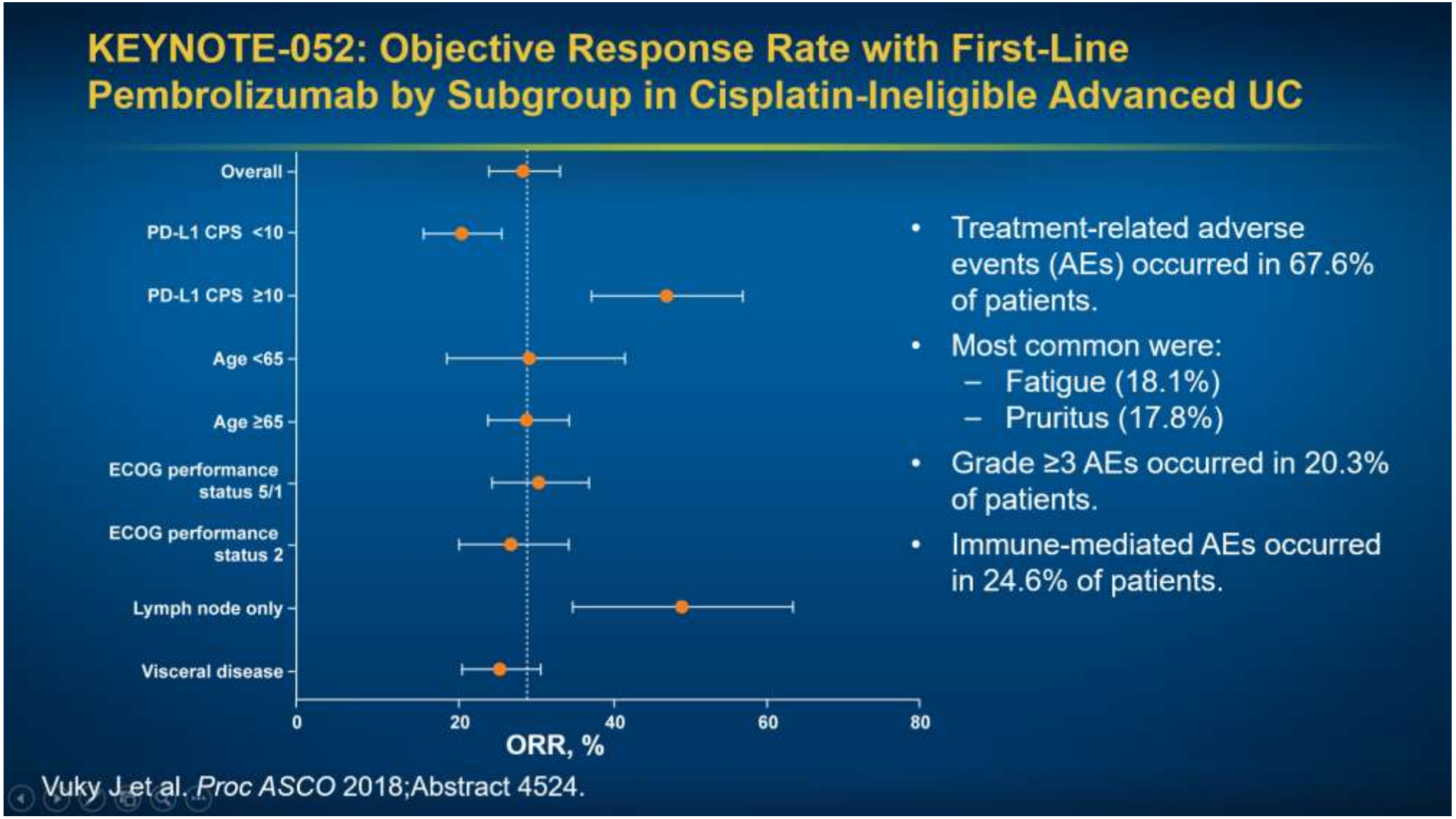
Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçimi
Herhangi Platinum bazlı kemoterapi alamayacak hastalarda



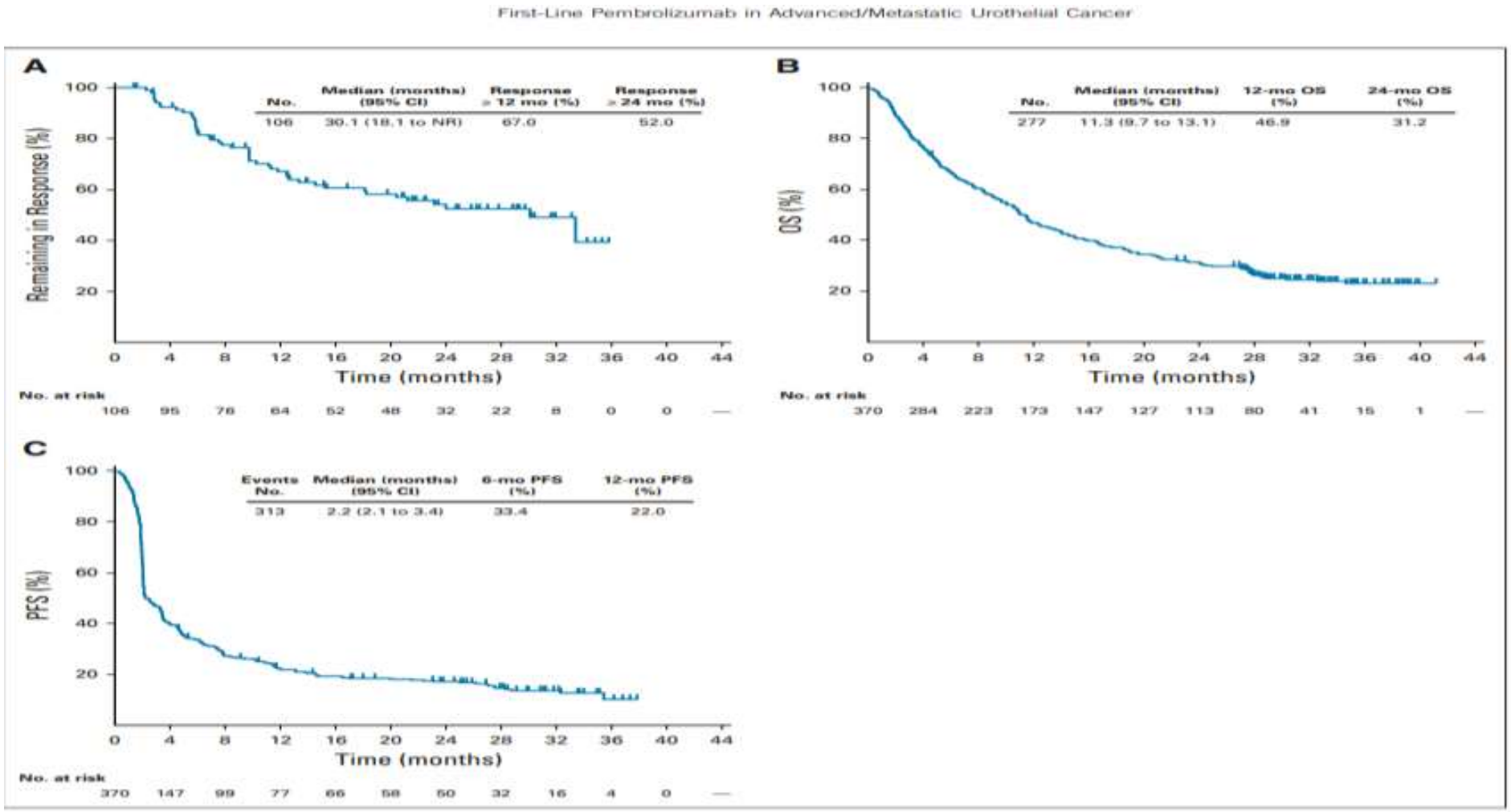
Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları



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



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



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%

Balar AV et al. *Proc ASCO* 2018;Abstract 4523.

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

Abstract 4262
Poster 699P

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)

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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,[4] with sustained responses observed with additional follow-up[5]
- 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 cisplatin[6,7]
- 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 design[4]

- Primary endpoint (Cohort 1) was objective response rate (ORR) per RECIST 1.1 as assessed by independent review facility (IRF)
- Key secondary endpoints reported here: duration of response (DOR) as assessed by IRF and overall survival (OS)
- In this poster, efficacy was descriptively evaluated in the all-comer patients and subgroups defined by PD-L1 status on IC (IC2/3 or PD-L1–expressing IC covering <5% of the tumour area [IC0/1])

RESULTS

Durable responses and long-term survival with 1L atezolizumab monotherapy were observed in this 5-year clinical update

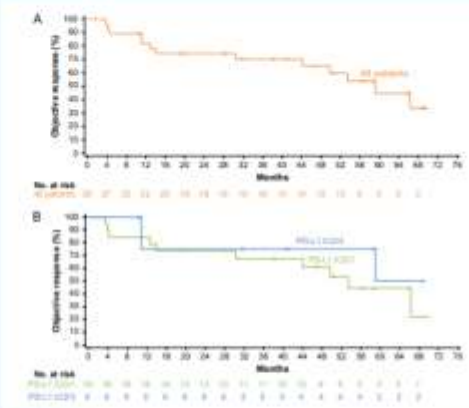
Table. Efficacy summary	All comers (N=119)	PD-L1 IC0/1 (n=87)	PD-L1 IC2/3 (n=32)
Objective response†			
ORR, n (%) [95% CI]	28 (23.5) [16.2, 32.2]	19 (21.8) [13.7, 32.0]	9 (28.1) [13.8, 46.8]
CR, n (%)	12 (10.1)	7 (8.0)	5 (15.6)
Ongoing responses, n/n (%)‡	15/28 (53.6)	9/19 (47.4)	6/9 (66.7)
Median DOR (95% CI), mo	55.1 (44.2, NE)	53.5 (30.4, NE)	NE (11.1, NE)
OS			
OS events, n (%)	92 (77.3)	69 (79.2)	24 (75.0)
Median OS (95% CI), mo	16.3 (13.4, 24.5)	16.1 (13.4, 25.2)	12.3 (8.3, 46.6)
24-mo OS (95% CI), %	41.1 (32.1, 50.2)	41.8 (31.1, 52.5)	39.3 (22.1, 56.6)
60-mo OS (95% CI), %	21.8 (13.7, 29.5)	19.8 (10.8, 28.3)	27.0 (10.3, 43.7)

Clinical cutoff, 31 January 2021
NE, not estimable
†Responses were per IRF in objective response evaluable patients
‡Defined as no death or progressive disease only in patients who continued on objective response

- As of the data cutoff, the median follow-up duration was 70.8 months (range, 0.2–77.5)
- There were no new responders since the 14 March 2016 data cutoff

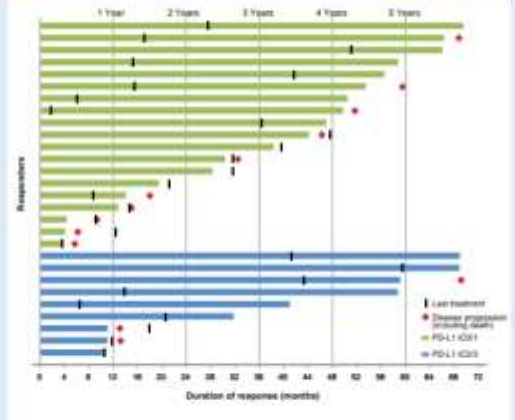
Median DOR has not been reached in the PD-L1 IC2/3 subgroup of patients

Figure 2. Kaplan-Meier curves for DOR (A) in all comers and (B) by PD-L1 status



Clinical cutoff, 31 January 2021

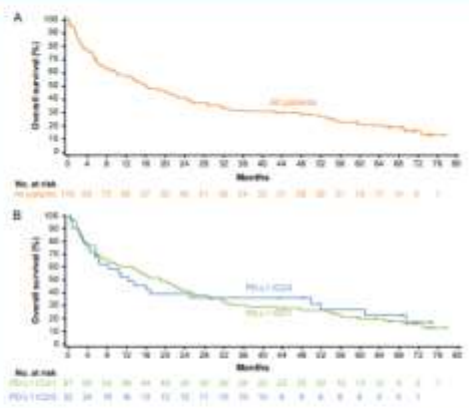
Figure 3. Duration of treatment and response by PD-L1 status



Clinical cutoff, 31 January 2021

Prolonged survival was seen in the all-comer population, including patients with PD-L1 IC0/1 and IC2/3 tumours

Figure 4. Kaplan-Meier curves for OS (A) in all comers and (B) by PD-L1 status



Clinical cutoff, 31 January 2021

CONCLUSIONS

Durable responses and long-term survival with 1L atezolizumab monotherapy in cisplatin-ineligible mUC were observed in this 5-year clinical update from the Phase II IMvigor210 study (Cohort 1)

Median DOR was not reached in patients with PD-L1 IC2/3 mUC

The 5-year OS rate seen in the overall all-comer population (≈22%) compares favourably with historic data,[8] including gemcitabine/carboplatin in cisplatin-ineligible patients[9]

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7. Davis I, et al. Oral presentation online at: AACR 2021. Abstract 5139.
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9. De Santis M, et al. J Clin Oncol 2012;30:191–9.

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- Sally Nelson of Genentech Inc for contributions to the statistical analysis
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DISCLOSURES

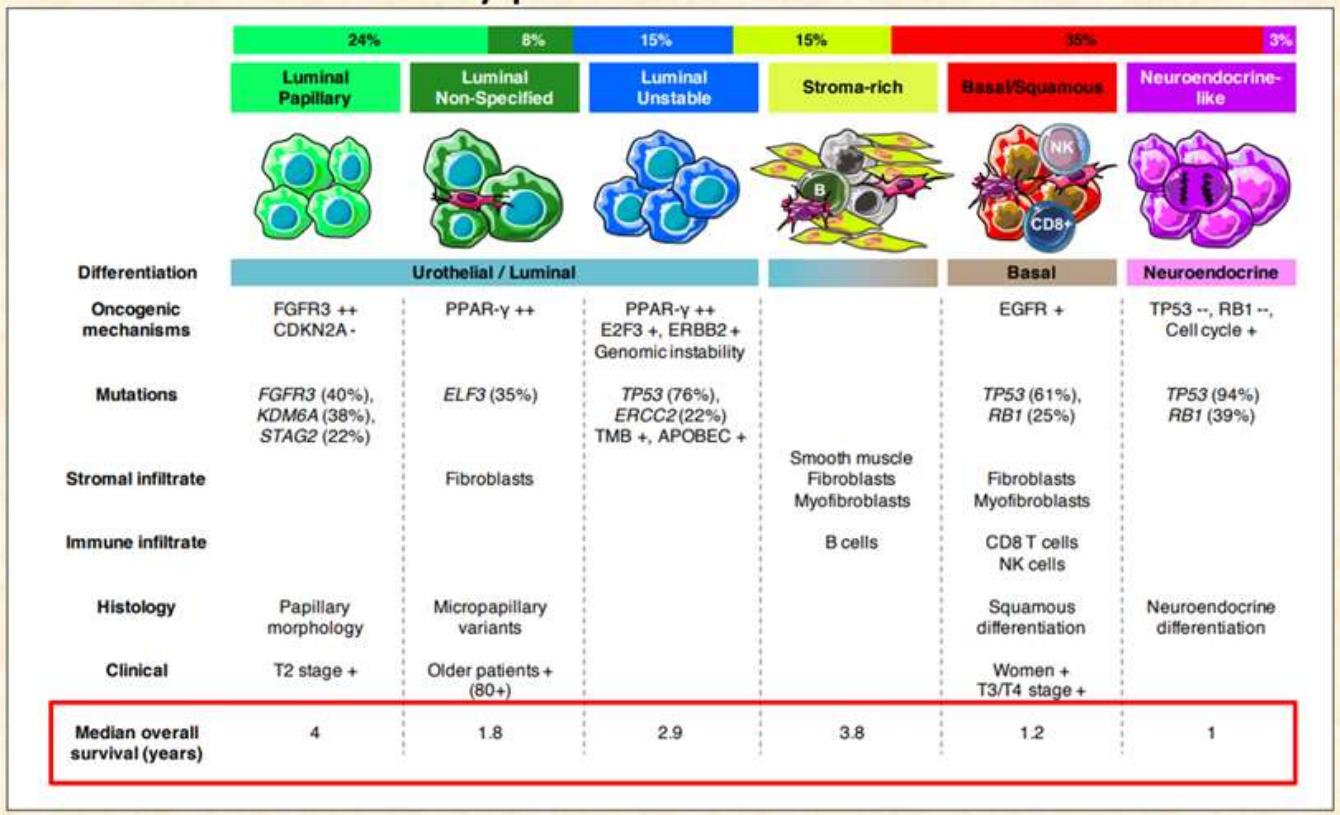
- Dr Rosenberg is an advisor to Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, EMD Serono, GlaxoSmithKline, QIAI, Janssen, Lilly, Merck, Merck, Pfizer, QED, Roche/Genentech, Seattle Genetics and Tyra Biosciences and received research funding support from Roche, Genentech, AstraZeneca, Zhaori, Seattle Genetics, Astellas and QED.
- For coauthor disclosures, please refer to published abstract

AUTHOR EMAIL

European Society for Medical Oncology (ESMO) Congress (Virtual). 17-21 September 2021.

Metastatik Mesane Kanseri
İkinci Basamak Tedavi Seçenekleri

Bladder cancer is composed of multiple tumors: Subtypes within subtypes



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	Dose expansion cohort A
EV + Pembro (n=5)	EV + Pembro (n=40)

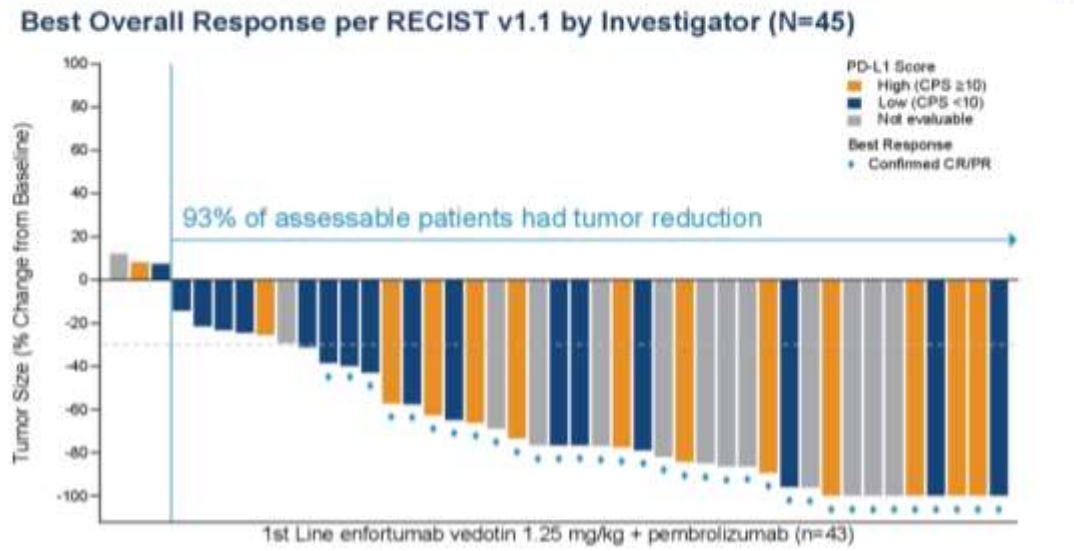
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembrolizumab 200 mg on day 1 of a 3-week cycle

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

Confirmed ORR 95% CI	73% (33/45) (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



Friedlander TW, et al. ASCO 2021. Abstract 4528.

Metastatik Mesane Kanseri Sisplatin Uygun Olmayanlarda Birinci Basamak Tedavi Yanıtları

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

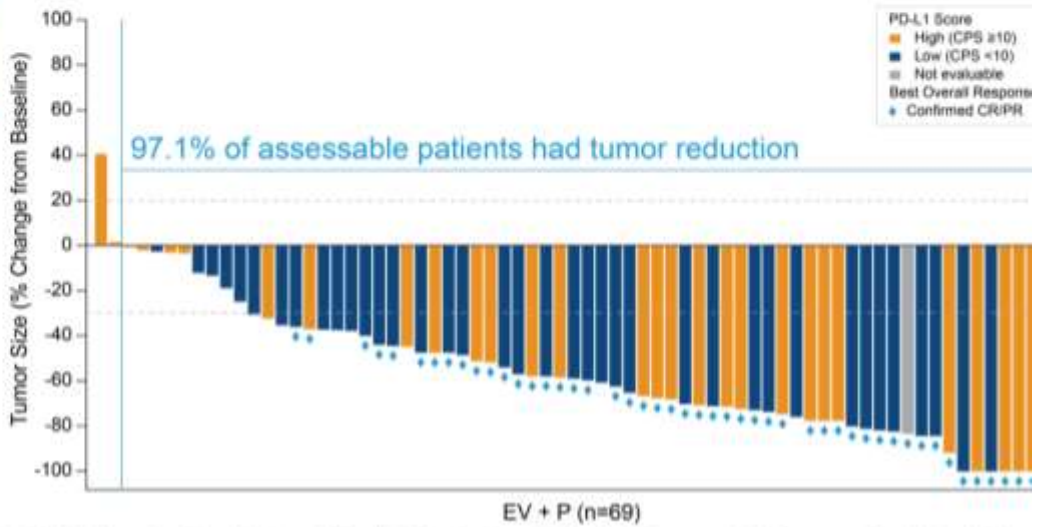
n=73
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle

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.

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

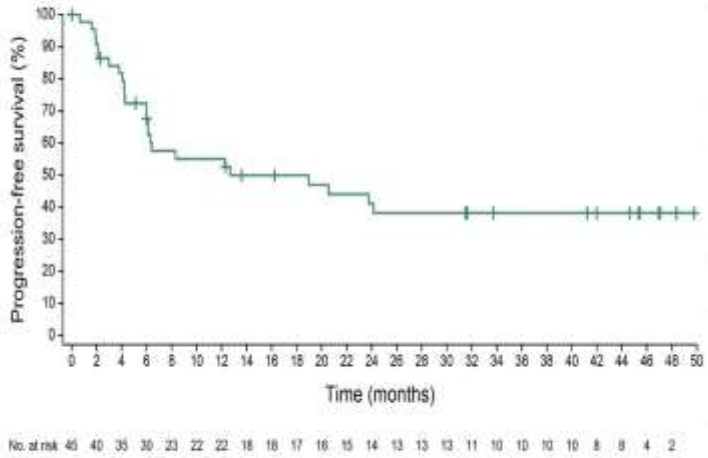
	Dose Escalation + Cohort A (N = 45)
Objective Response Rate, n (%)	33 (73.3)
95% CI[a] for ORR	58.1-85.4
Best Overall Response, n (%)	
Complete response	7 (15.6)
Partial response	26 (57.8)
Stable disease	5 (11.1)
Progressive disease	5 (11.1)
No assessment[b]	2 (4.4)
Disease Control Rate, n (%)	38 (84.4)
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
[a]CI was computed using the Clopper-Pearson method (Clopper 1934)
[b]Patients had no response assessment post-baseline
[c]ORR 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

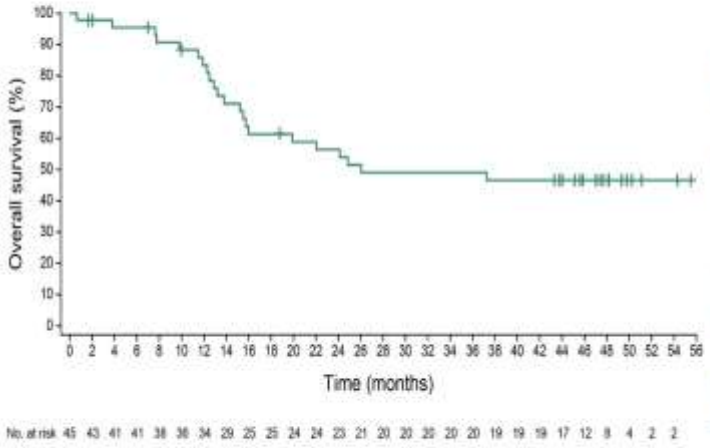


	Dose Escalation + Cohort A (N = 45)
PFS events, n	25
Median PFS (95% CI[a])	12.7 months (6.11-NE)
PFS rate[b] at:	
6 months, % (95% CI[a])	72.4 (56.47-83.26)
12 months, % (95% CI[a])	55.0 (38.84-68.58)
24 months, % (95% CI[a])	41.1 (25.69-55.88)

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

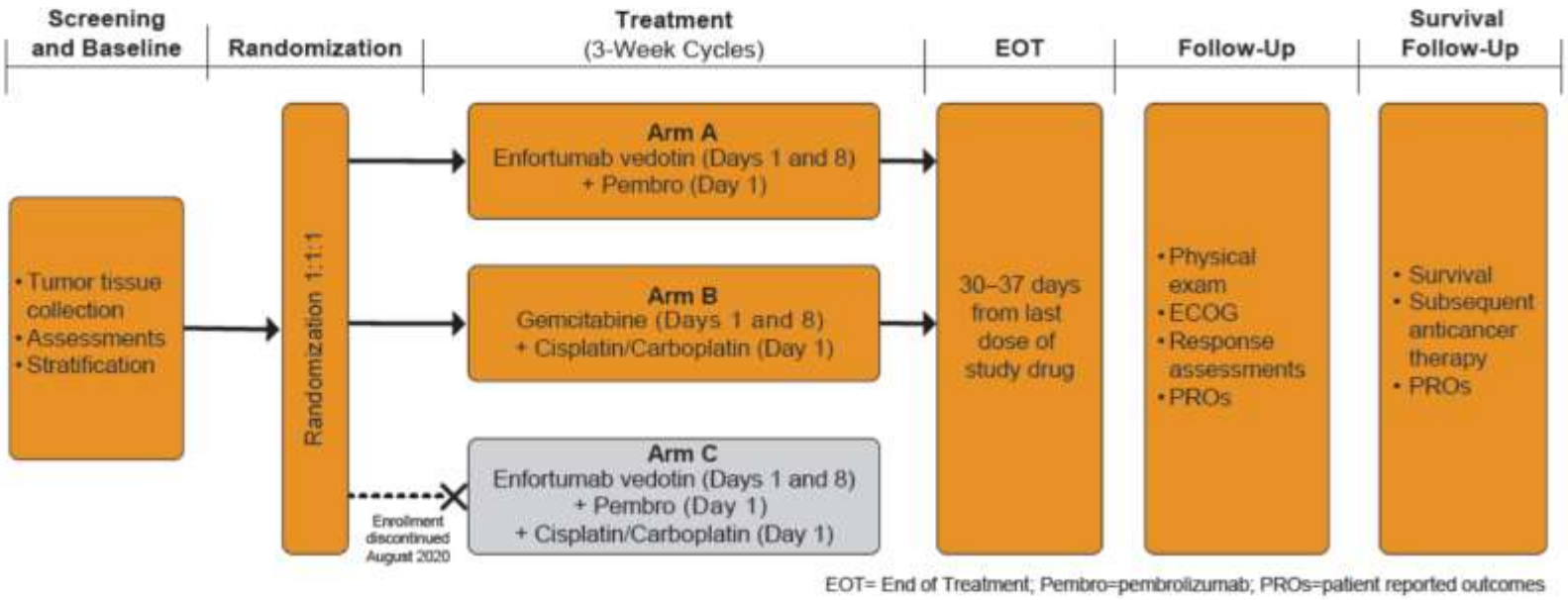
CI = confidence interval; NE = not estimable; OS = overall survival
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)
[b]As estimated using Kaplan-Meier method

Gelecek Perspektif

EV-302 Randomized Phase 3 Trial Schema

<u>Eligibility</u>

- 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

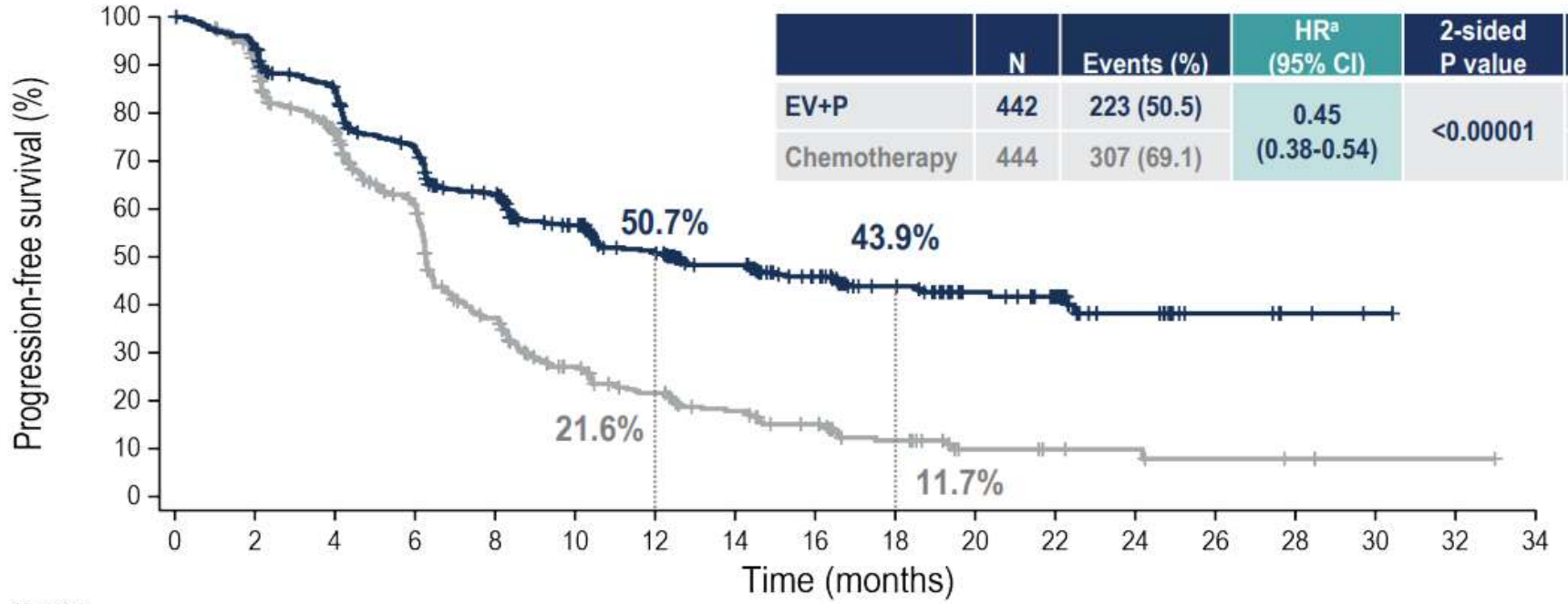
Primary Endpoints: PFS, OS
Secondary Endpoints: ORR, DOR, DCR, QOL, PRO, Safety

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

	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

MADRID 2023 ESMO congress

Powles et al.

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

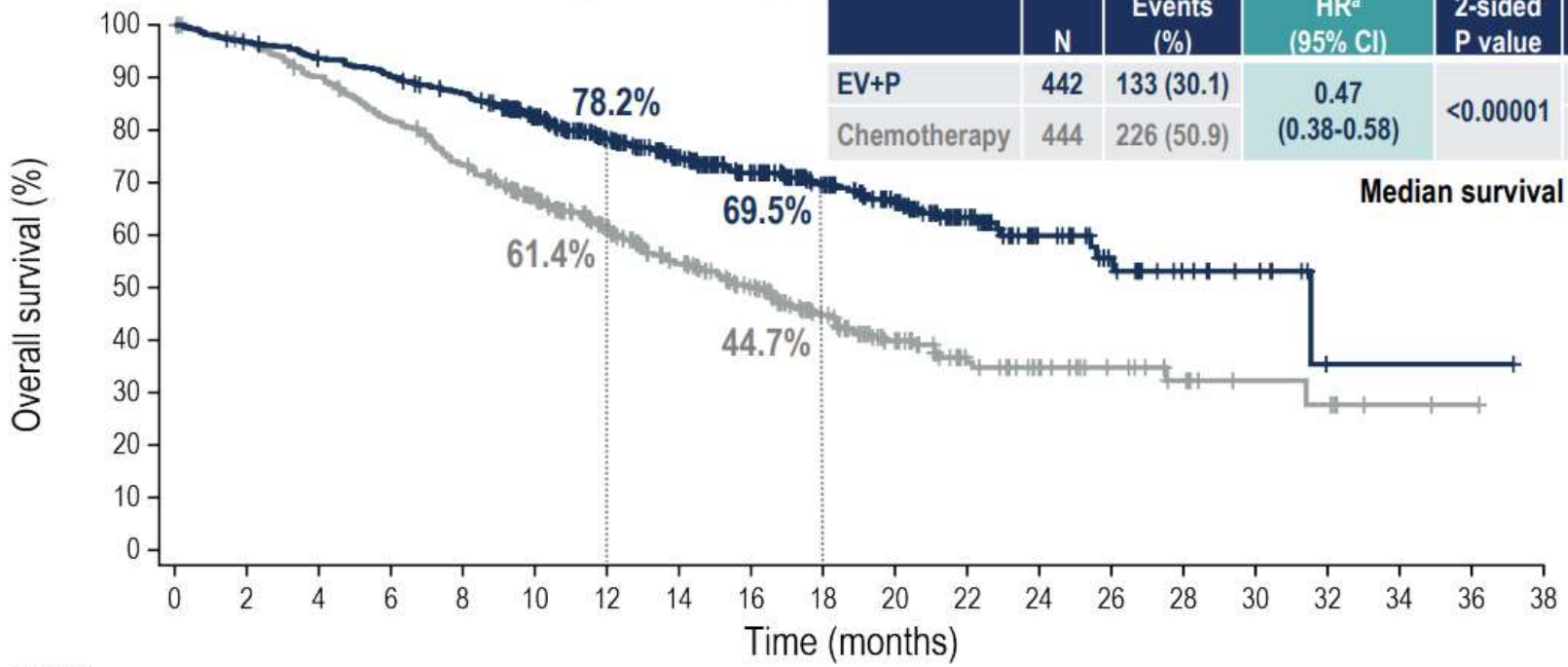
Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
EV103 -EV/pemrolizumab

Overall Survival

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

	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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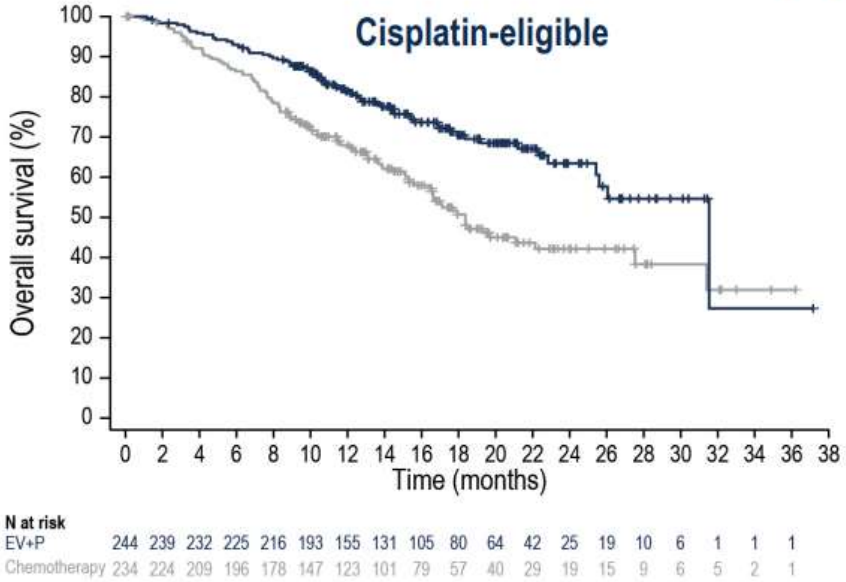
Powles et al.

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

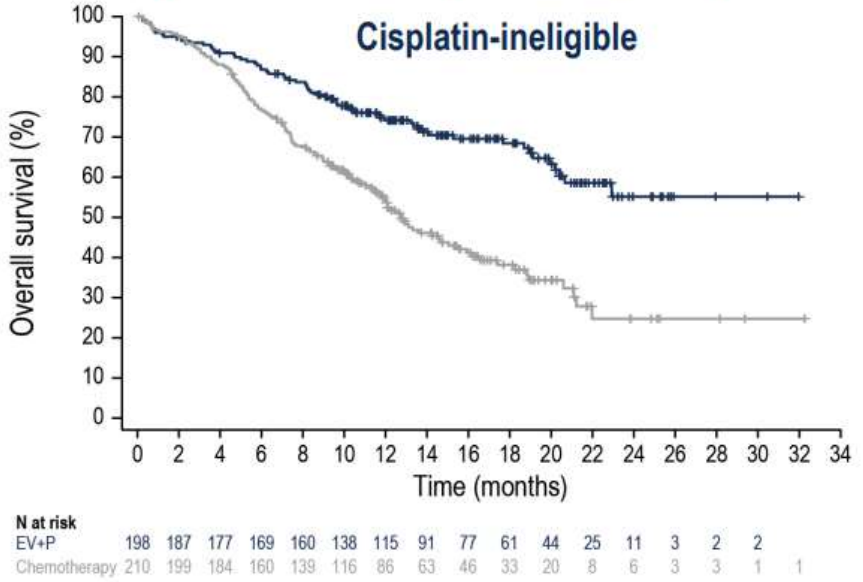
Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
EV103 -EV/pembrolizumab

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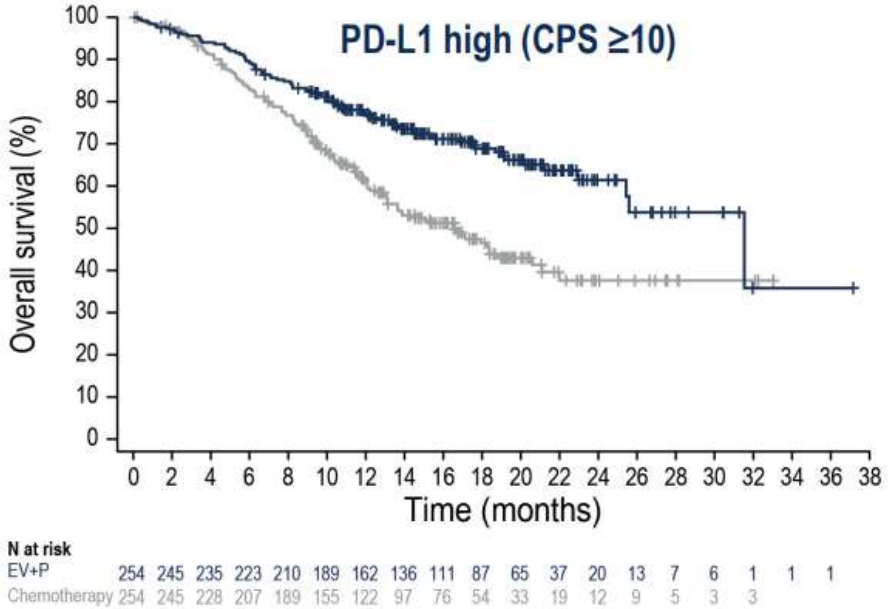
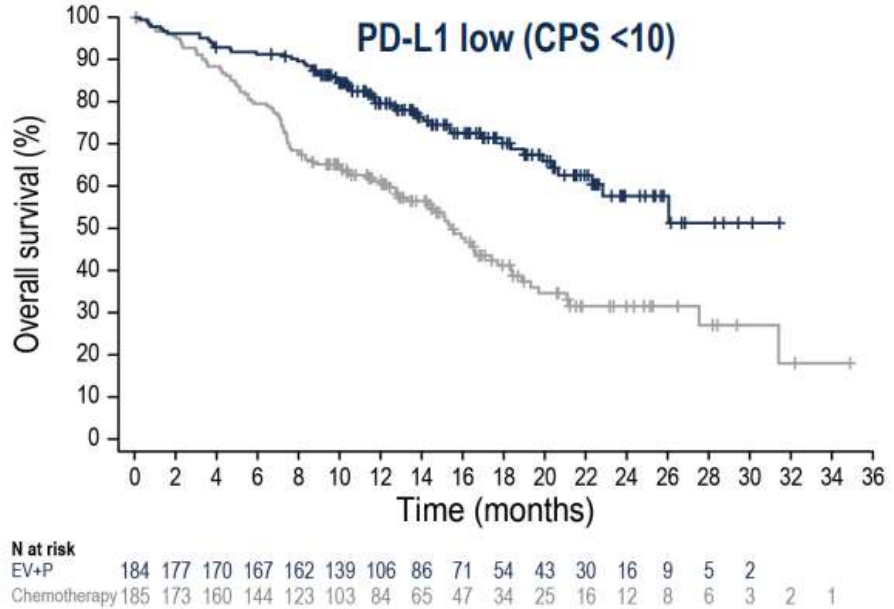
Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
EV103 -EV/pemrolizumab

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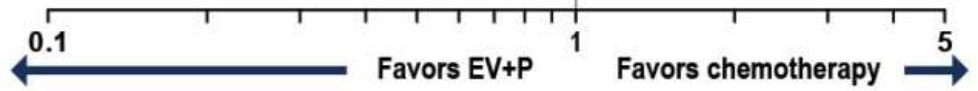
Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
EV103 -EV/pembrolizumab

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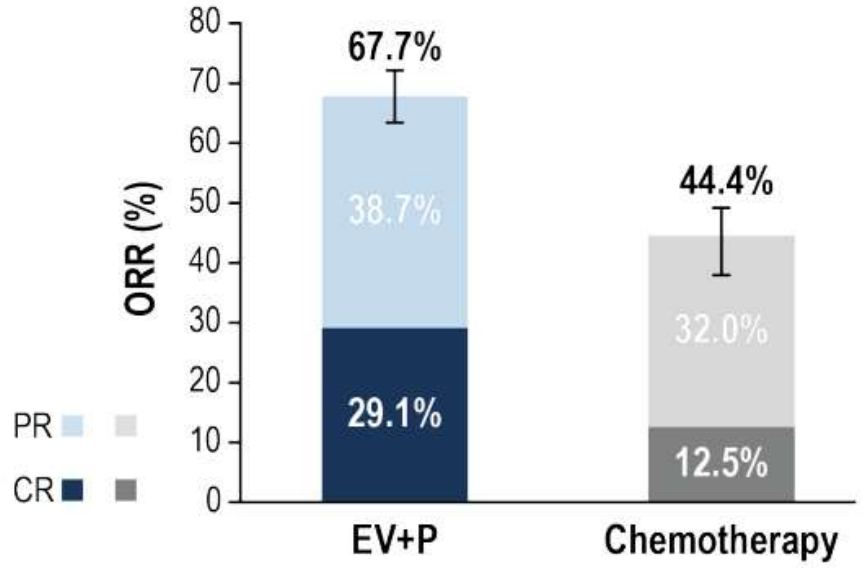
Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları EV103 -EV/pembrolizumab

Confirmed Overall Response per BICR

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



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

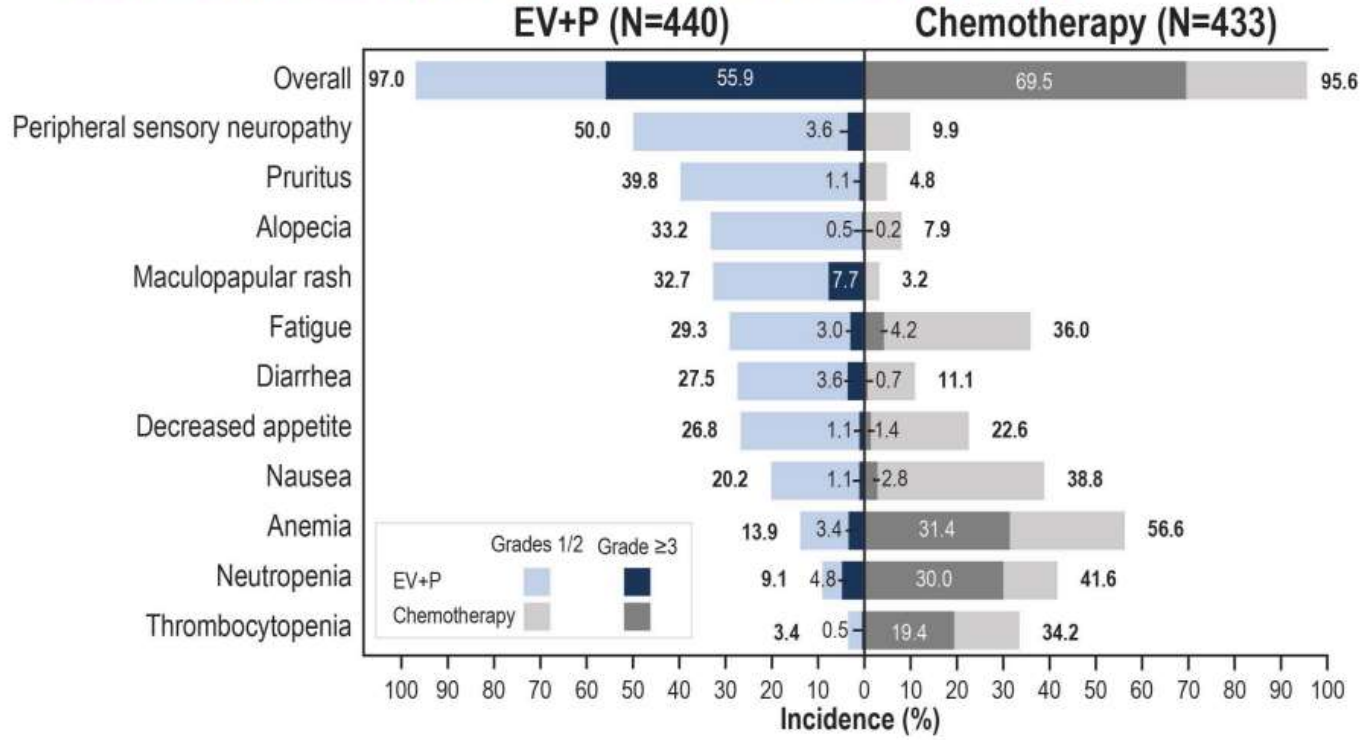
[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response

[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 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 ≥20% of patients for any grade in either arm
TRAEs, treatment-related adverse events

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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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

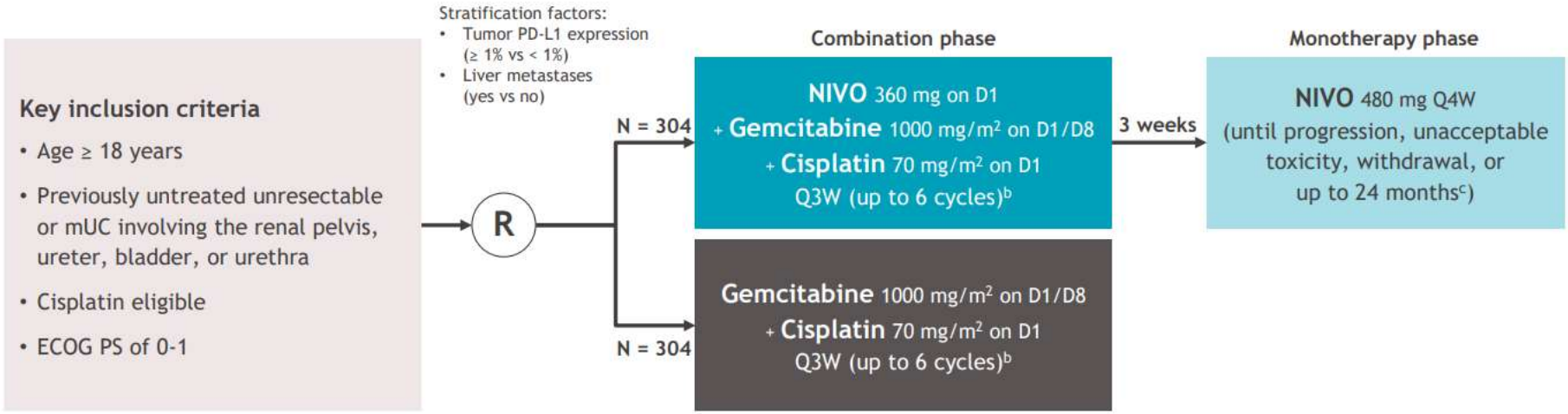
AESI, adverse event of special interest

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

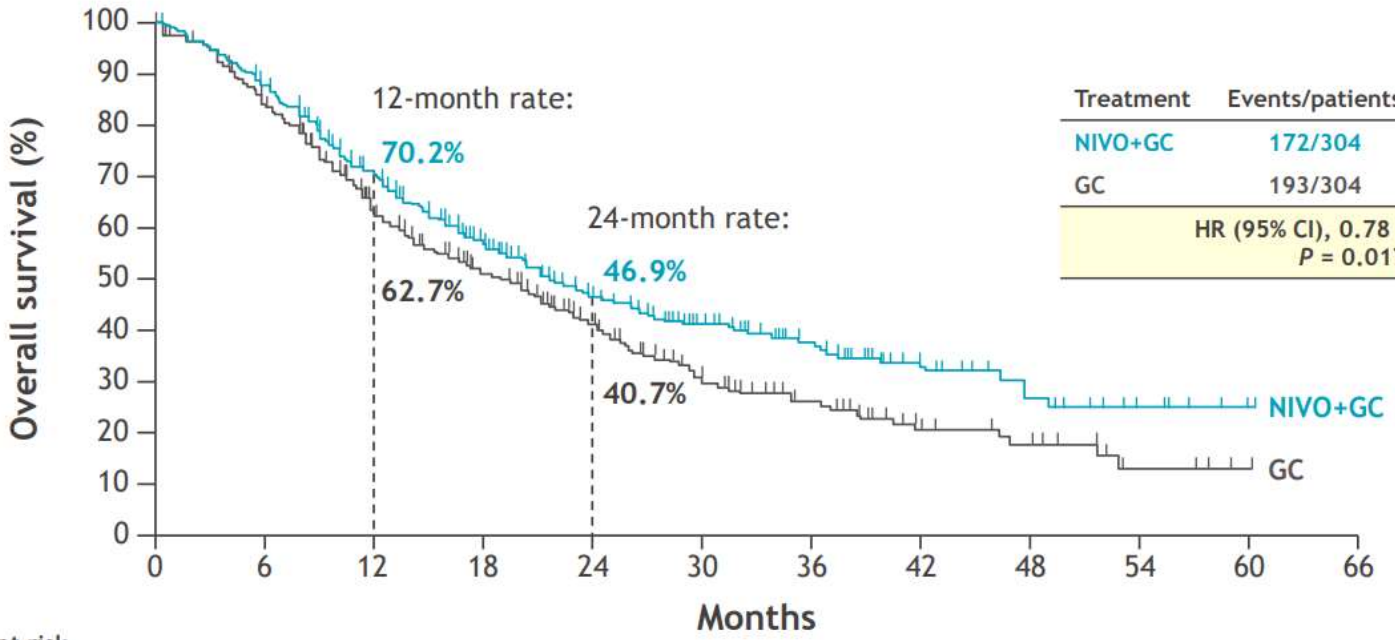
Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

[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 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

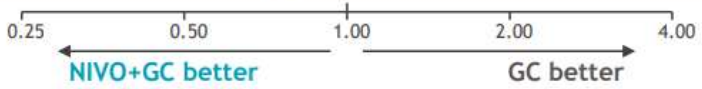
Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with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

Sisplatine uygun hastalarda KT+İmmünoterapi

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)

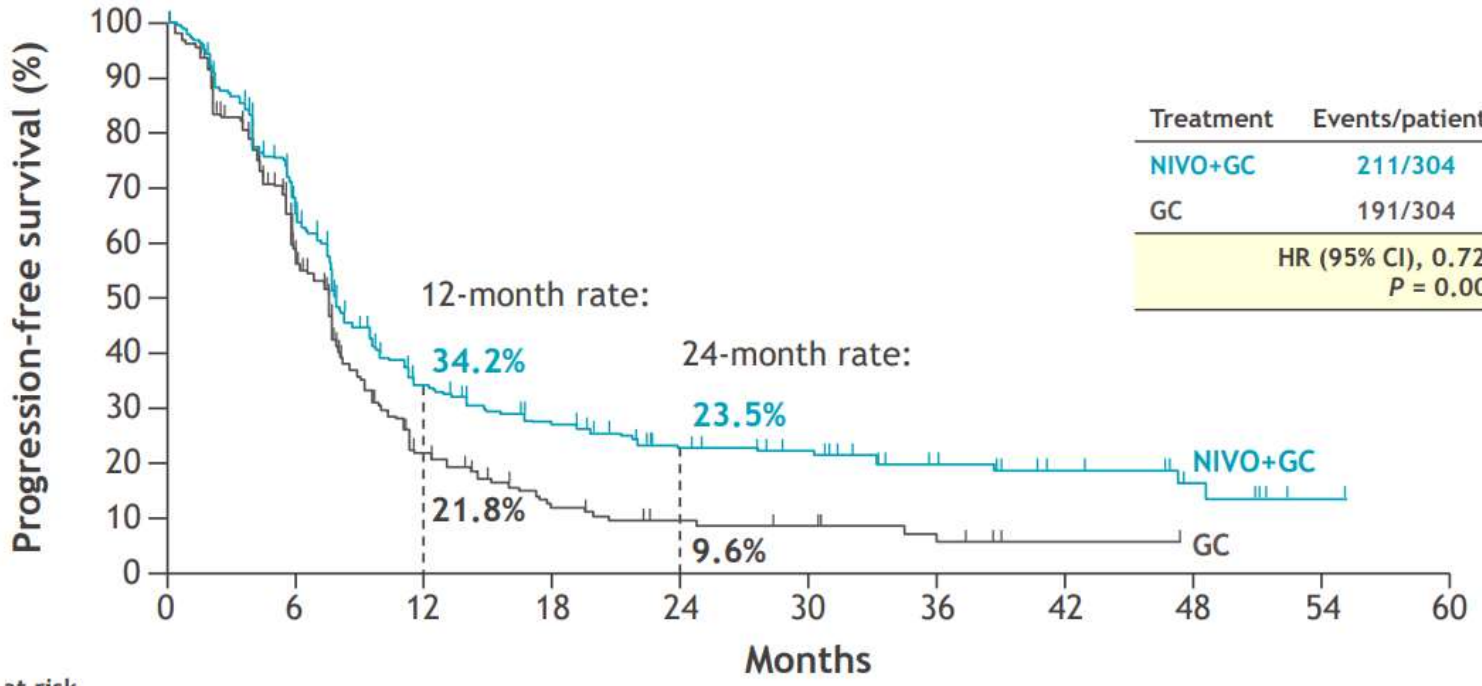


All randomized patients. HRs were not computed for subgroup categories (except for age, sex, race, and region) with < 10 patients per treatment group. Categories without a meaningful estimate of the HR are not shown. PD-L1 expression and liver metastases are per interactive response technology. There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

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

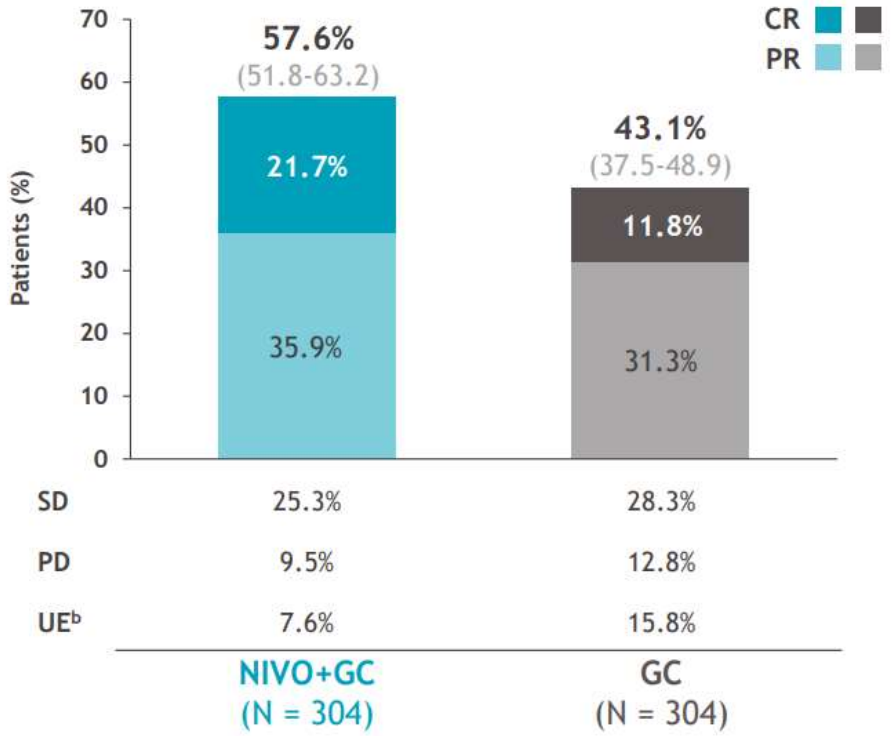
Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as time from randomization to first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who did not progress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

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)

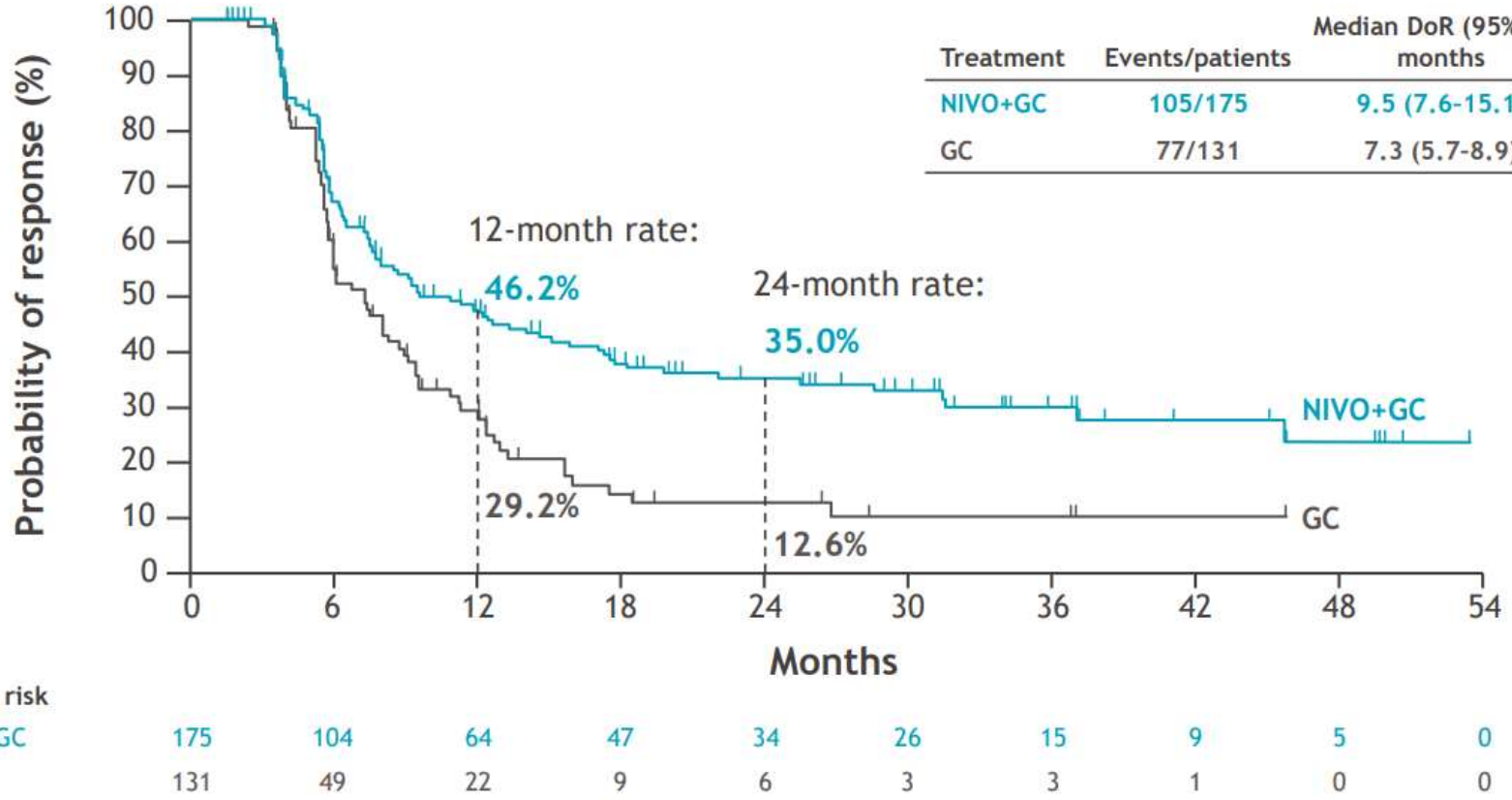
Complete response[d]	NIVO+GC (n = 66)	GC (n = 36)
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

[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 KT+İmmünoterapi

CheckMate 901

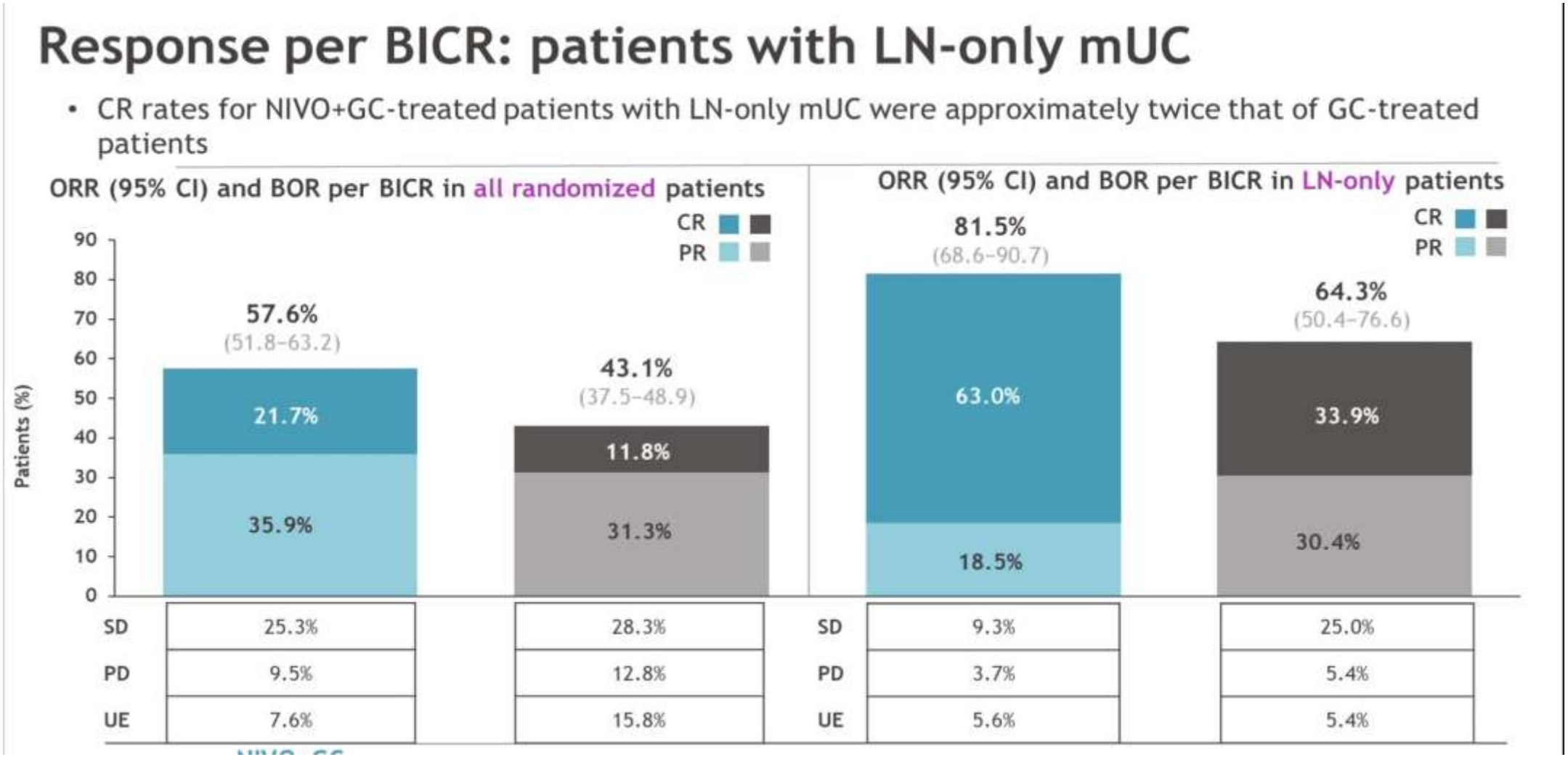
Duration of objective response per BICR



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)

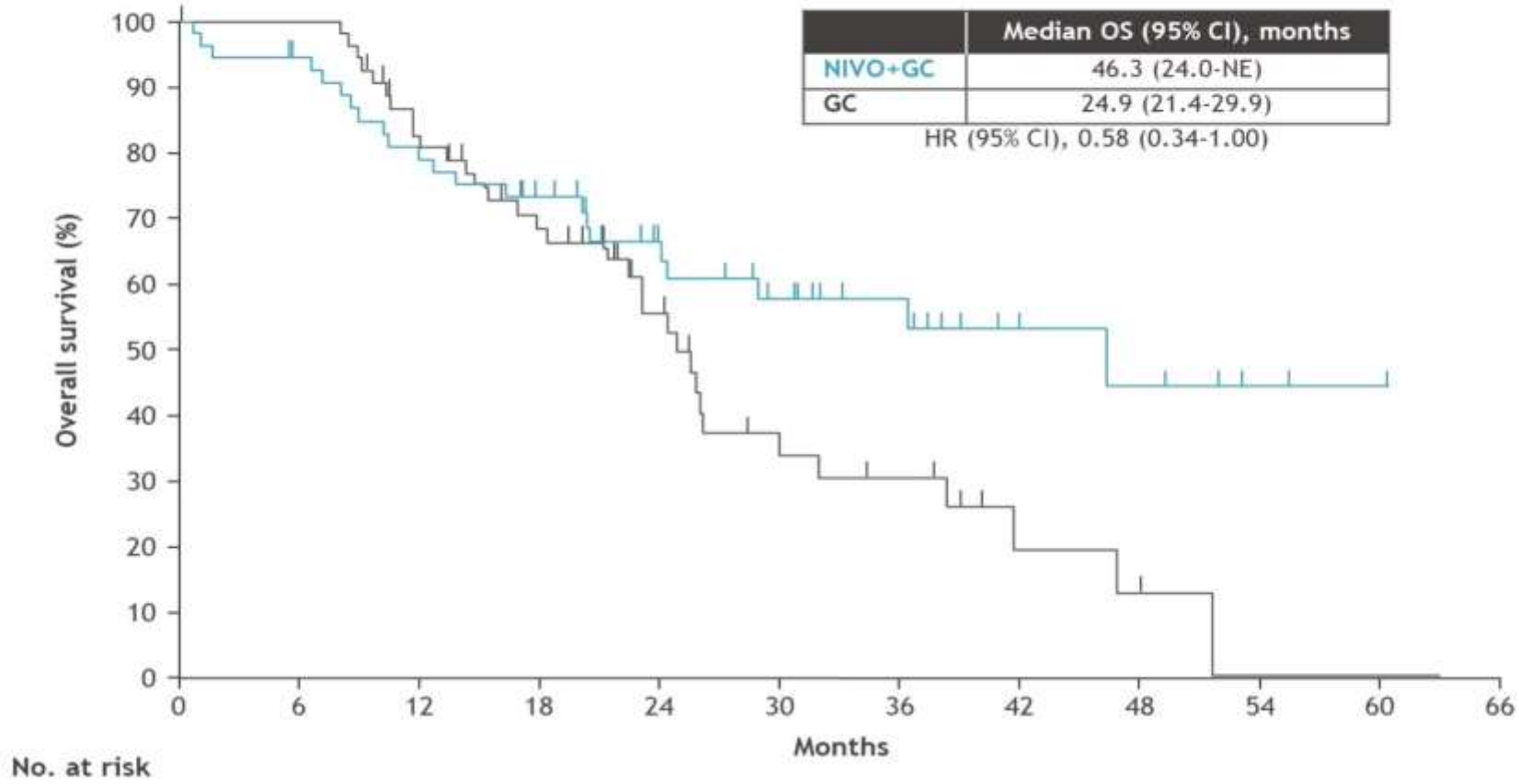
No. at risk										
NIVO+GC	175	104	64	47	34	26	15	9	5	0
GC	131	49	22	9	6	3	3	1	0	0

Sisplatine uygun hastalarda KT+İmmünoterapi



Sisplatine uygun hastalarda KT+İmmünoterapi

OS: patients with LN-only mUC per BICR

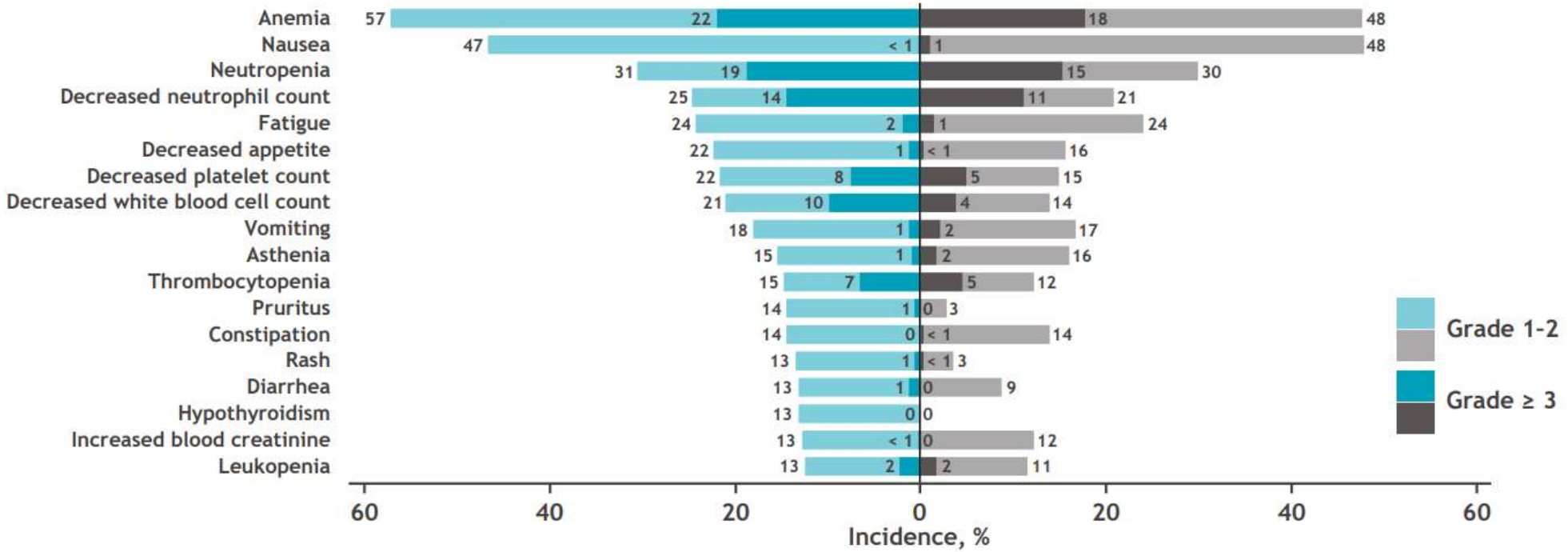


Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

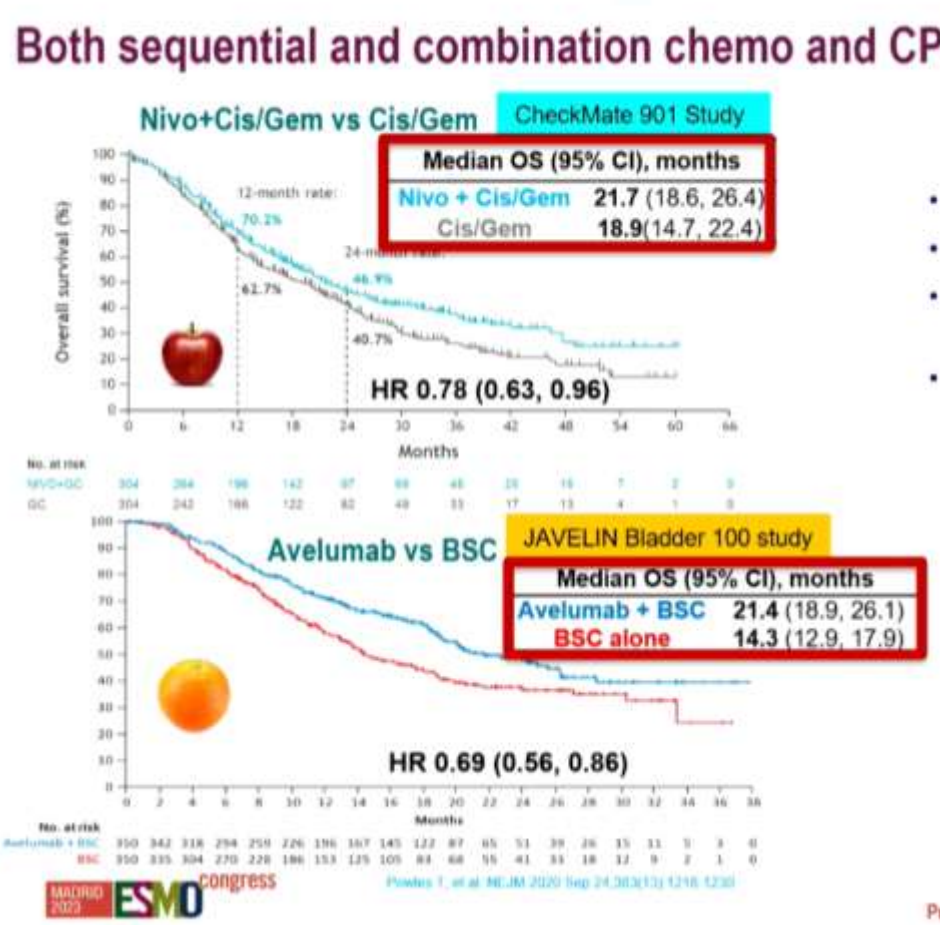
Treatment-related AEs in all treated patients

	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.

Evre IV mesane birinci basamak tedavi seçeneği

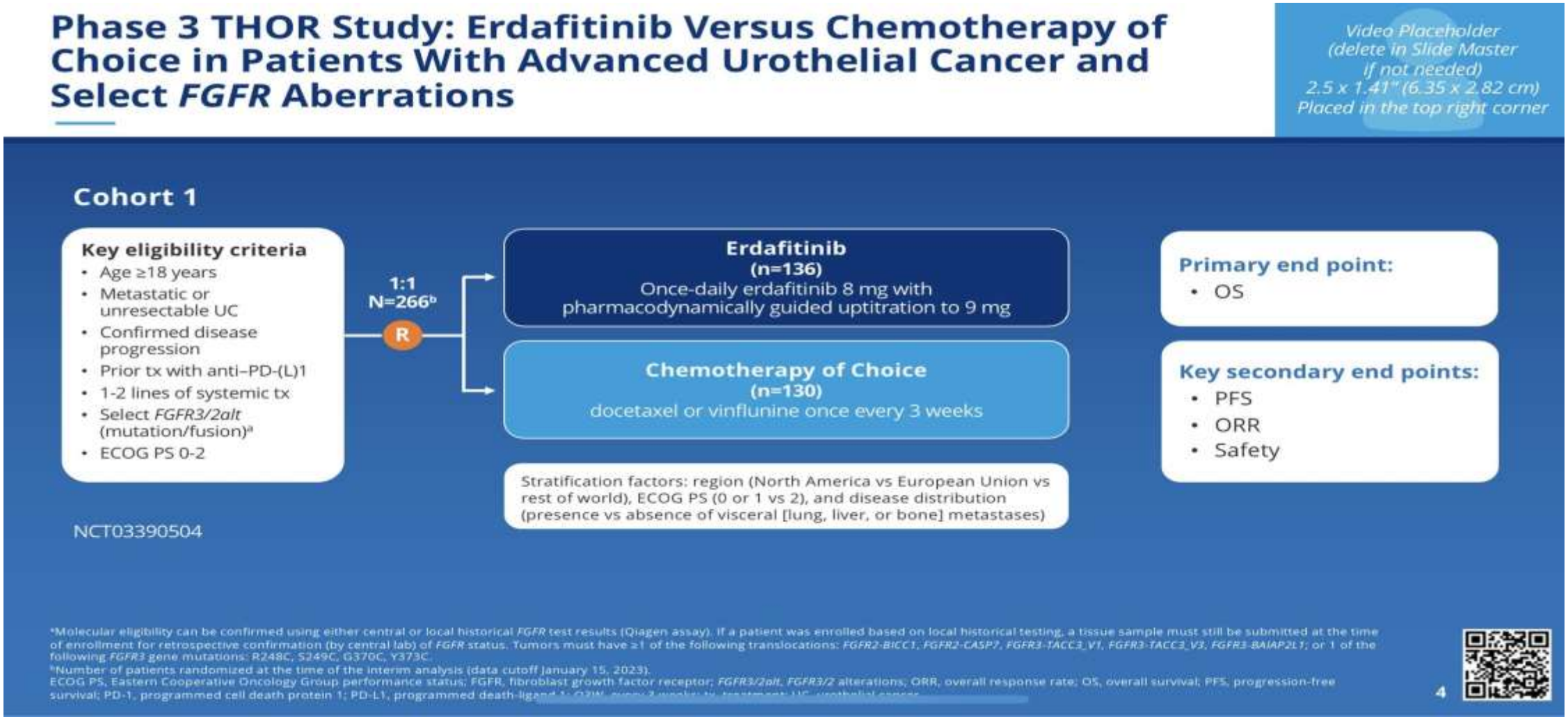


- We cannot directly compare these studies
- Different patient populations
- Avelumab maintenance study included only responders to 1L chemo
- Length of maintenance CPI therapy was similar: ~6 months for both

Andrea Apolo
Invited Discussant LBA6 and LBA7

Presented by Andrea B. Apolo, MD

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi



Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

Table. Primary and Secondary Outcomes From the THOR Trial

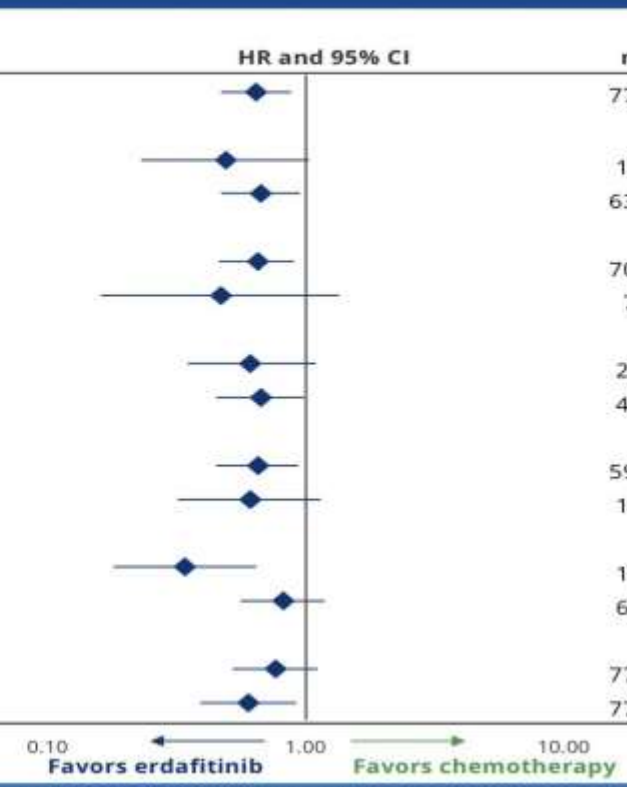
	Erdafitinib (136 patients)	Chemotherapy (130 patients)
OS, median (95% CI), mo	12.1	7.8
HR (95% CI)	0.64 [0.47, 0.88]; $P = .005$	
PFS, median (95% CI), mo	5.6	2.7
HR (95% CI)	0.58 [0.44, 0.78]; $P = .0002$	
ORR, %	45.6	11.5
RR (95% CI)	3.94 [2.37, 6.57]; $P < .001$	

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

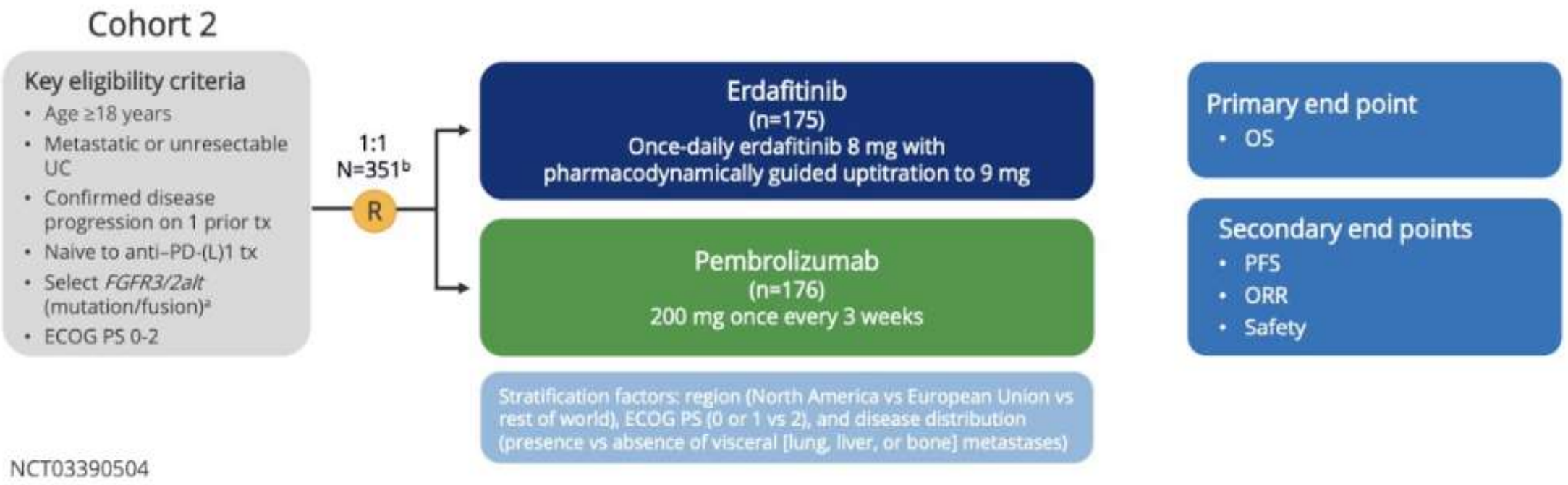
Video Placeholder (delete in Slide Master if not needed) 2.5 x 1.41" (6.35 x 2.82 cm) Placed in the top right corner



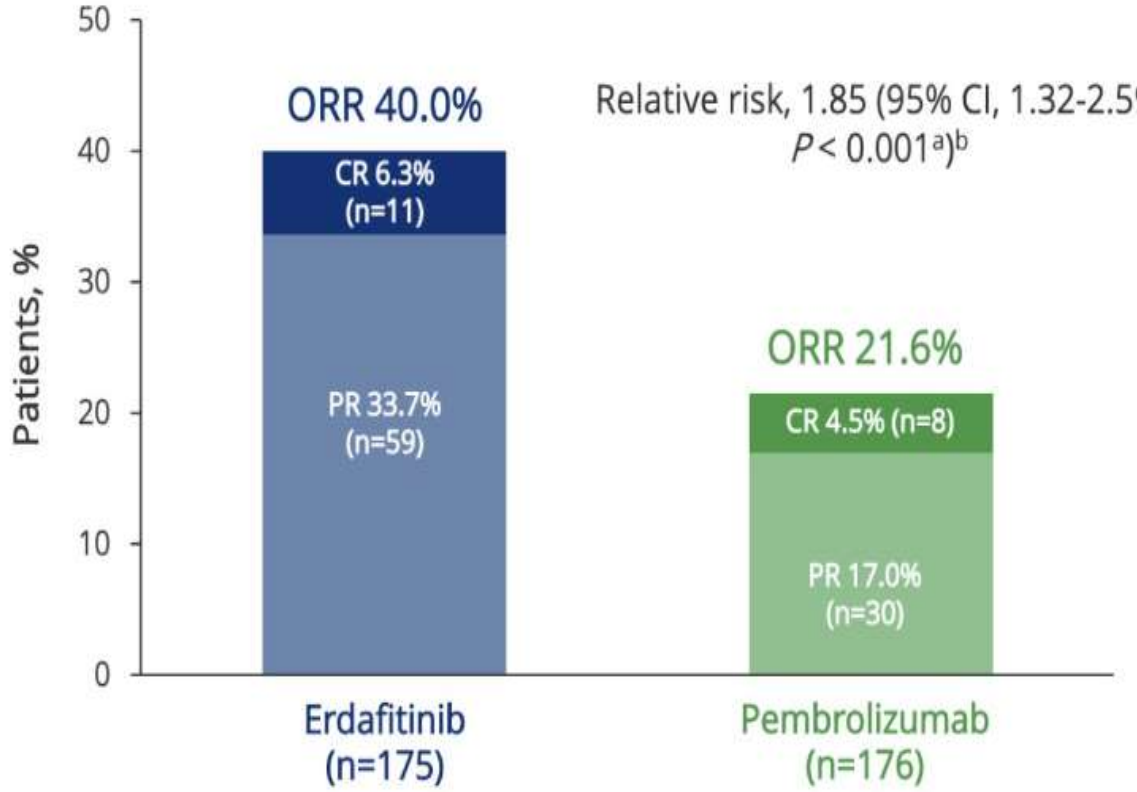
	Erdafitinib		Chemotherapy		
	n/N[a]	Median	n/N[a]	Median	HR and 95% CI
Overall	77/136	12.1	78/130	7.8	0.64 (0.47-0.88)
FGFR alteration type					
Translocation	13/25	16.4	15/19	8.0	0.49 (0.23-1.03)
Mutation	63/108	10.9	60/107	7.7	0.67 (0.47-0.95)
Baseline ECOG PS					
0-1	70/125	12.2	71/119	8.7	0.65 (0.46-0.90)
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)

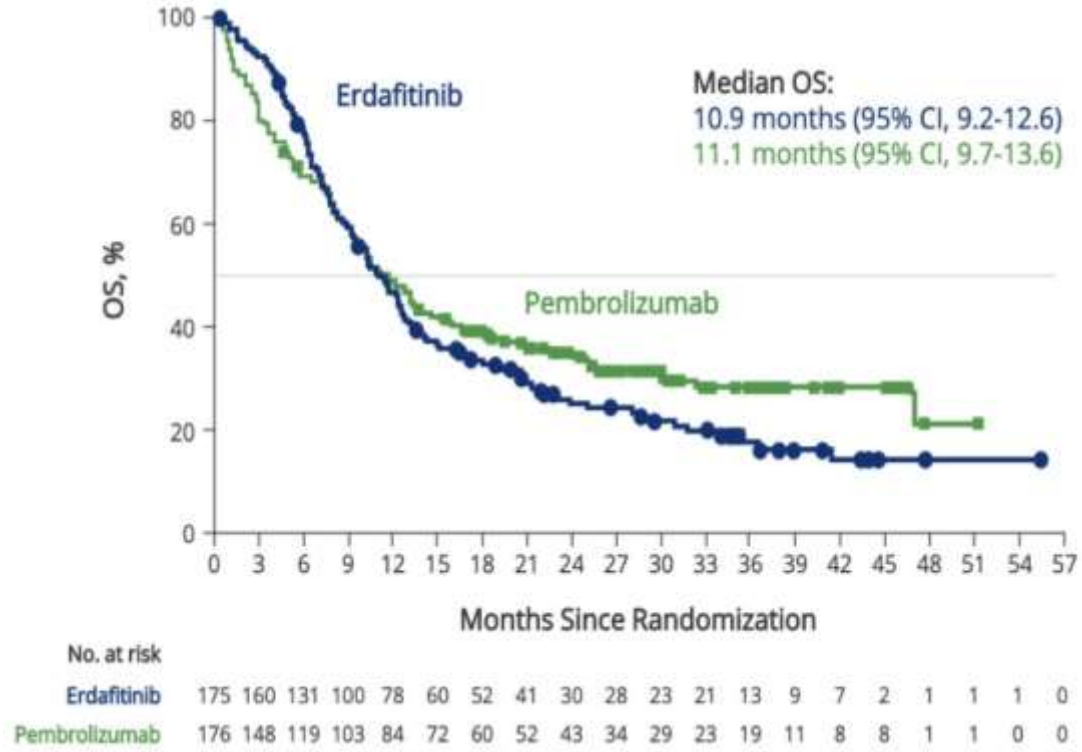
[a]=number of events; N=number of patients in subgroup. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

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

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

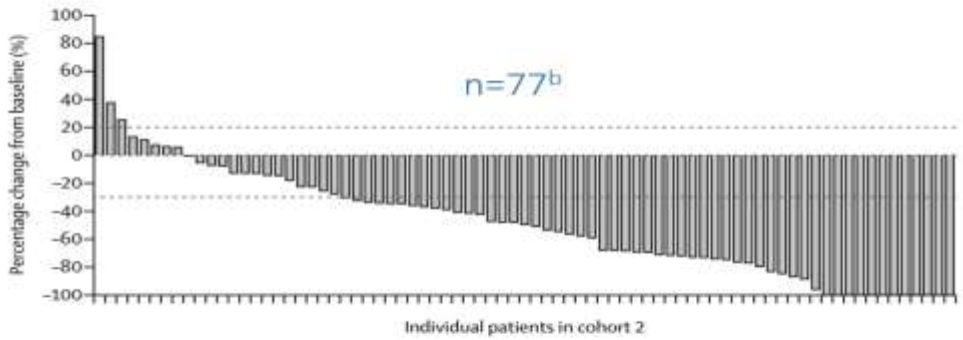
Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

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%)

Change in Target Lesions From Baseline



Median duration of treatment: 6 months

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

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

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

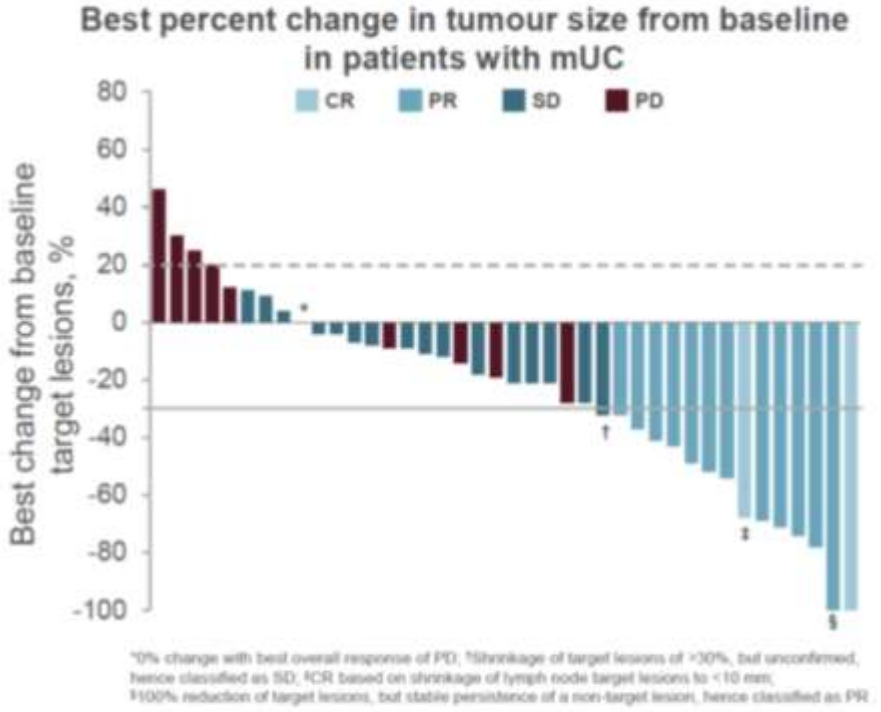
Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

Sacituzumab govitecan for mUC: Efficacy

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

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

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

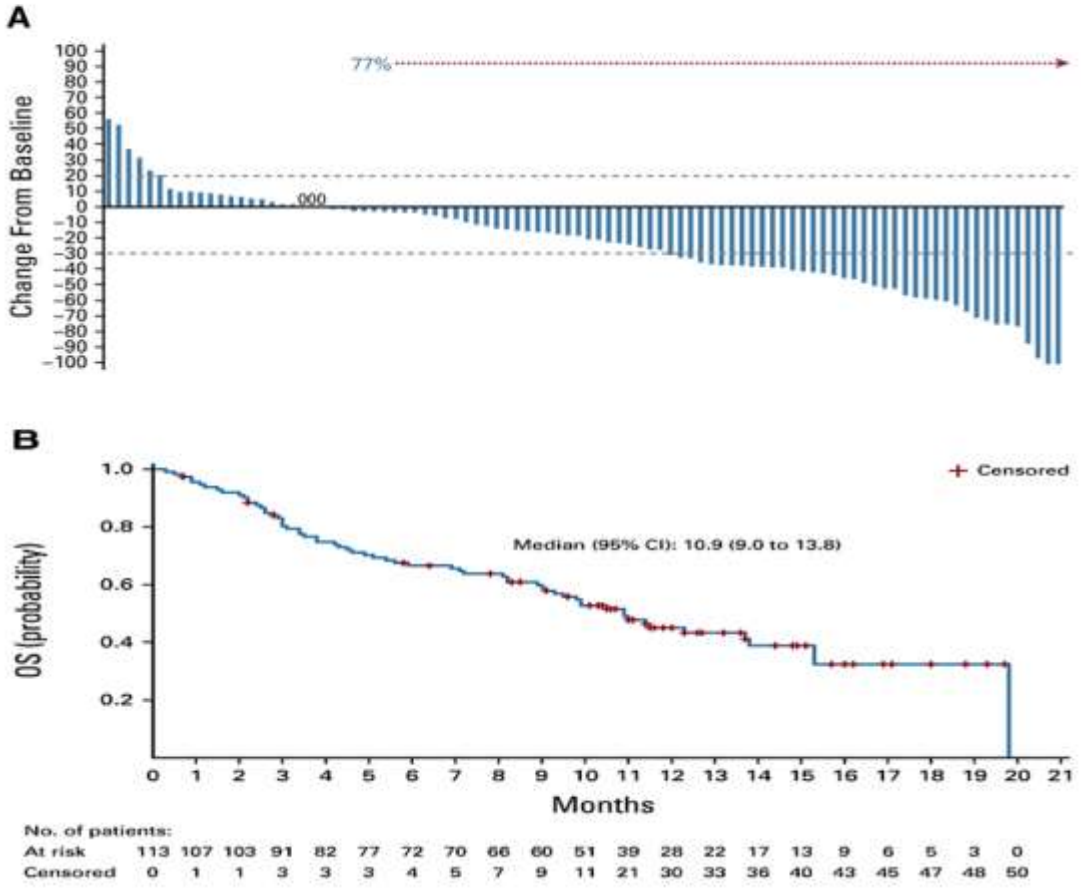


Tagawa ST et al. ASCO GU 2019;Abstract 354.

Courtesy of Thomas Powles, MBBS, MRCP, MD

Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

Sacituzumab Govitecan

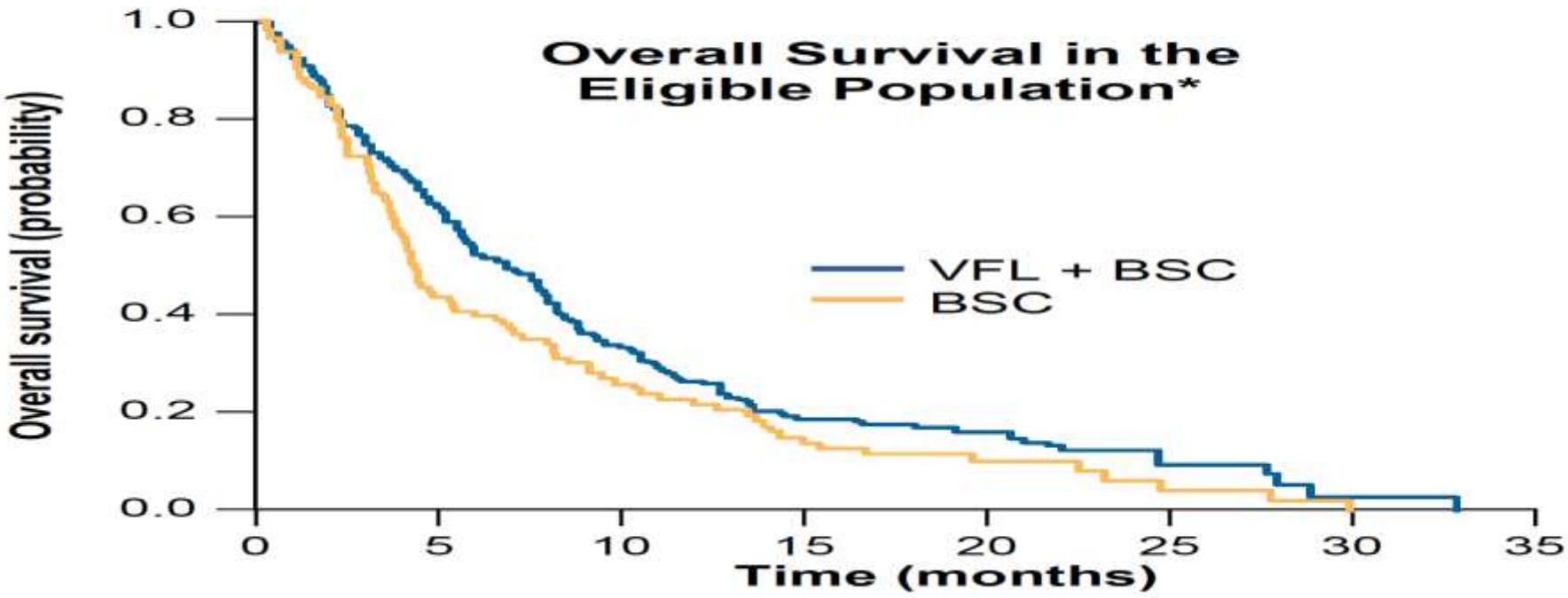


- N=113, post-platinum and post-IO
- SG 10 mg/kg d1, d8 q 3-wk
- GCSF as clinically indicated
- ORR 27%
- Med PFS: 5.4 mo
- Med OS: 10.9 mo
- Toxicity
  - Neutropenia ≥G3: 34%
  - Diarrhea ≥G3: 10%
- UGT1A homozygous/heterozygous
  - Potential increased risk neutropenia, pre-screening not required

Tagawa, et al. JCO 2021

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; *P*=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
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]

Gelecek Perspektif

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

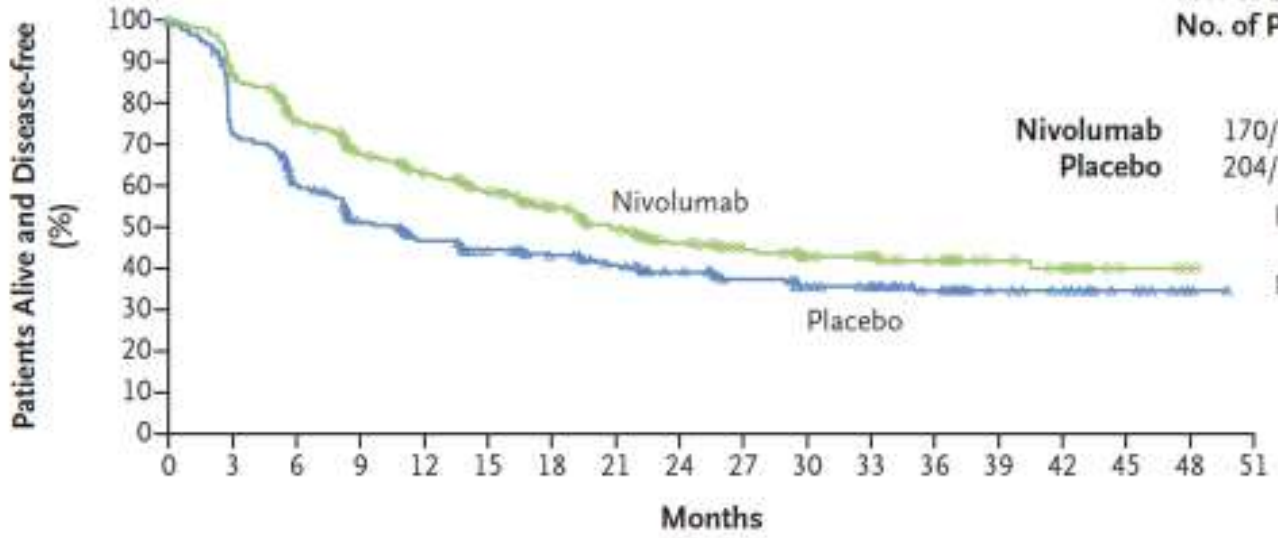
D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette,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

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

RTP RESEARCH TO PRACTICE

Gelecek Perspektif

CheckMate 274: Disease-Free Survival in the ITT Population



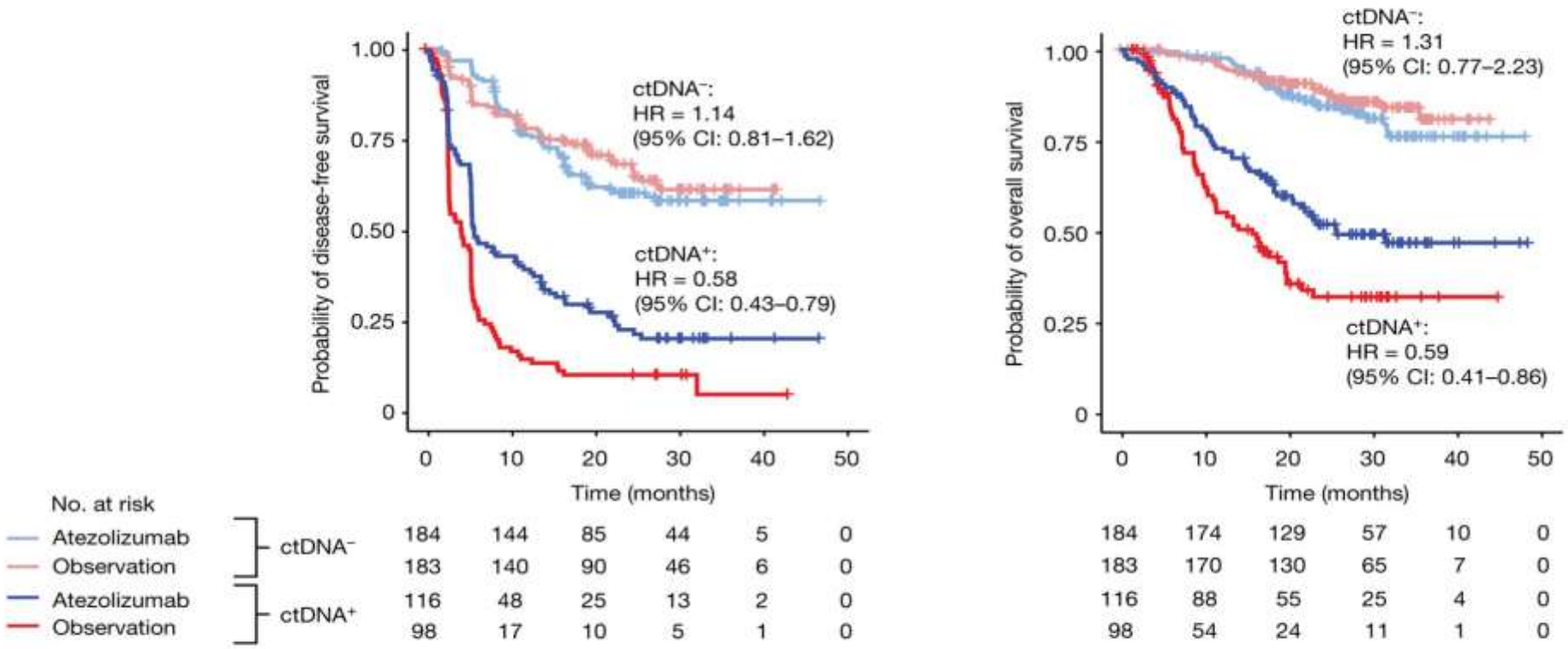
	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

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.

Gelecek Perspektif

Can ctDNA help Guide Adjuvant Therapy ?



Powles, Nature, 2021

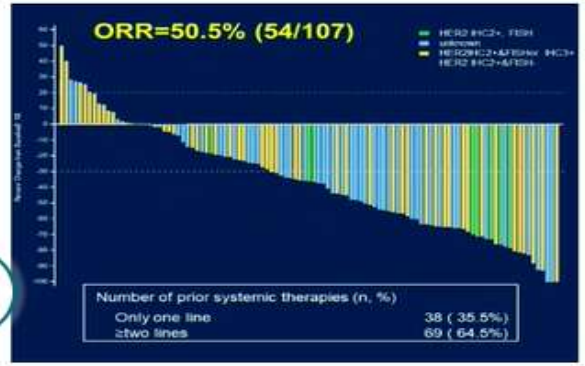
Gelecek Perspektif

Does CPI combine best with ADCs with MMAE payloads?

Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

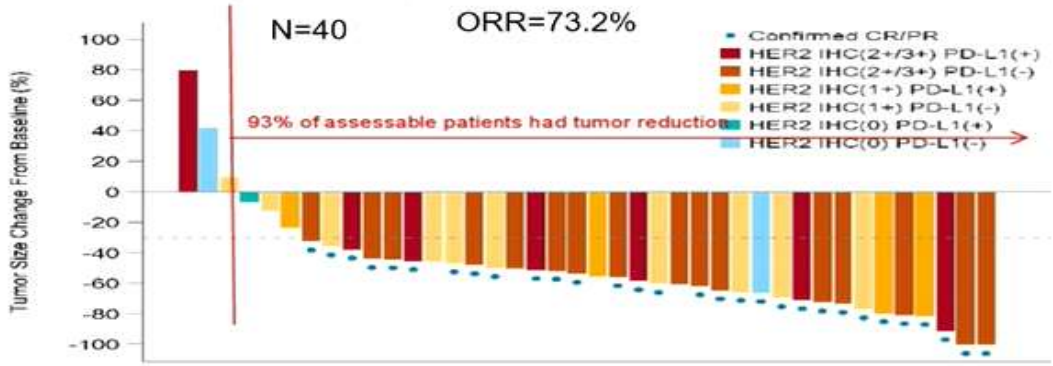
Disitamab vedotin

N=107 In the Second or Third-line setting



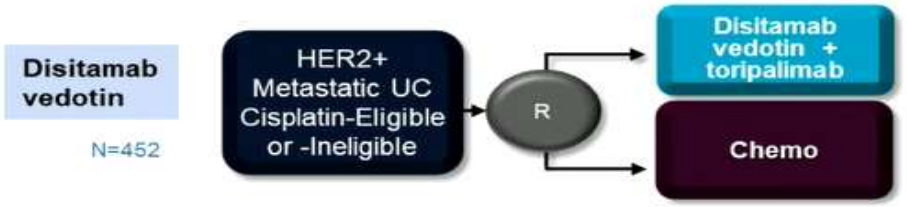
Sheng, et al. ASCO 2022 abstract 4518

Disitamab vedotin + toripalimab



Sheng, X., et al. ASCO 2023

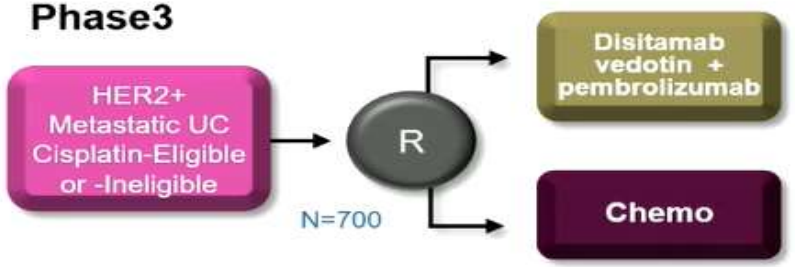
Phase 3



Presented by Andrea B. Apolo, MD

@apolo_andrea

Phase3



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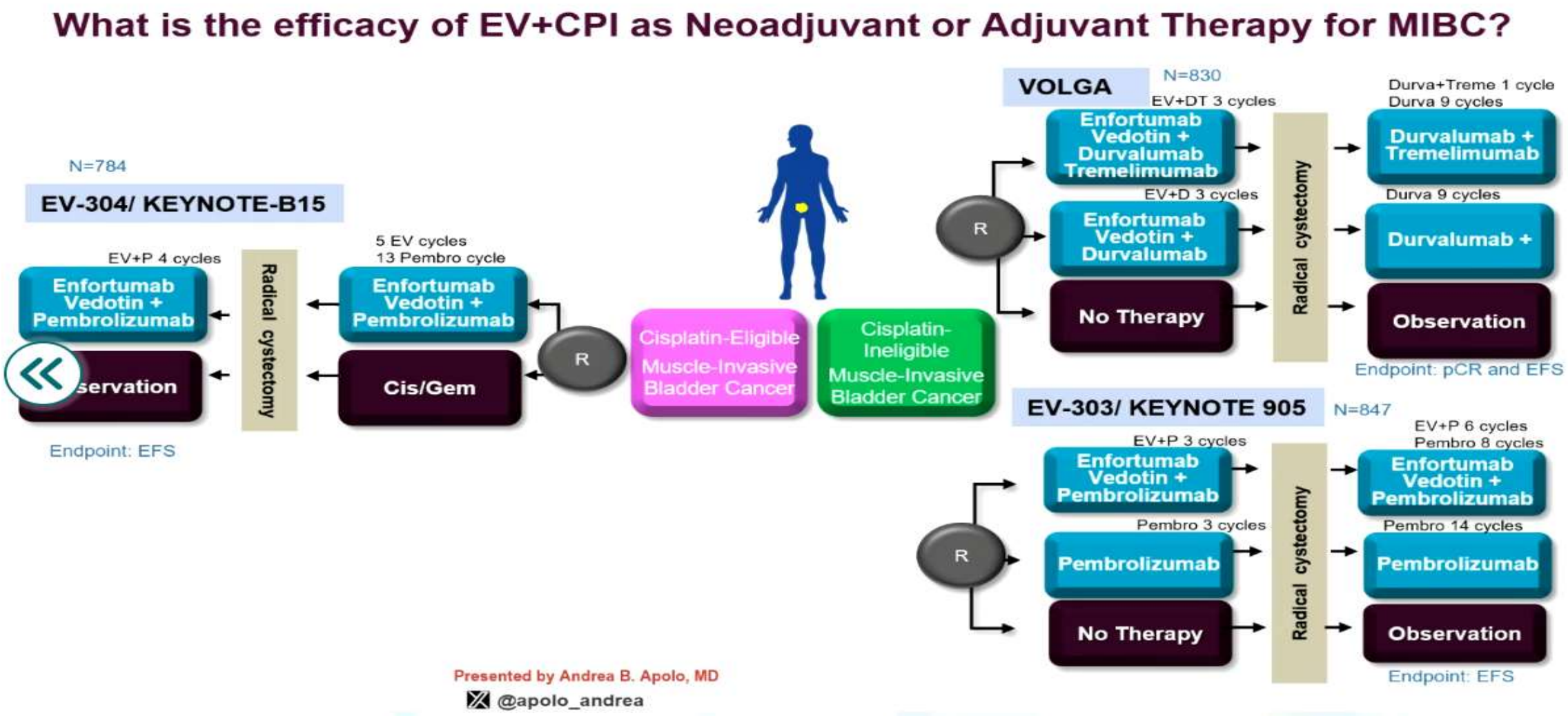
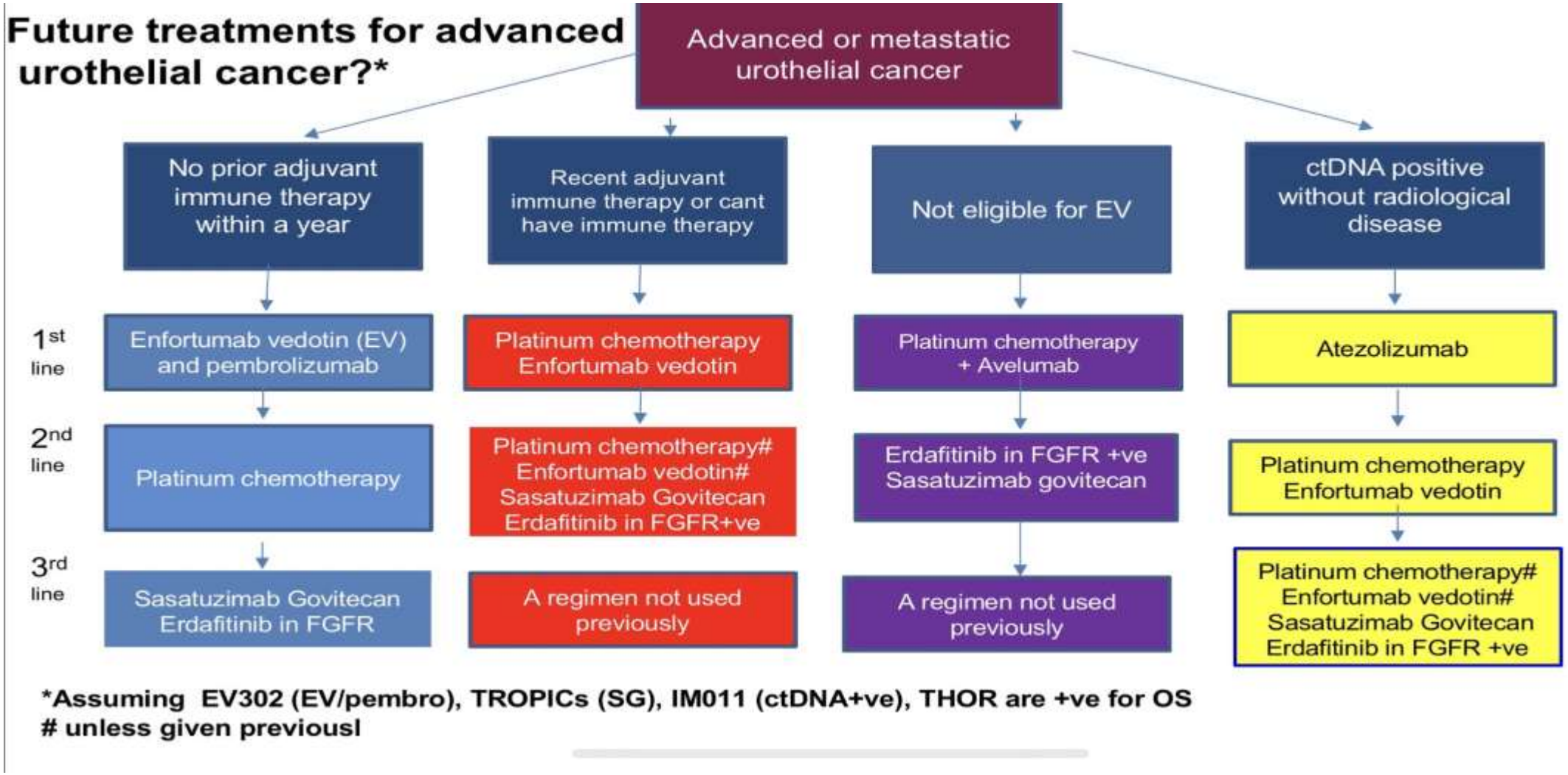


Gelecek Perspektif



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≥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**
- İmmün checkpoint ve enfortumab alanlarda sacituzumab govitecan
- Platin bazlı kemoterapi ve diğer seçenekleri almışsa Vinflunine