

Metastatik Mesane ve Üst Üriner Sistem Kanserlerinde İdeal Tedavi Algoritması

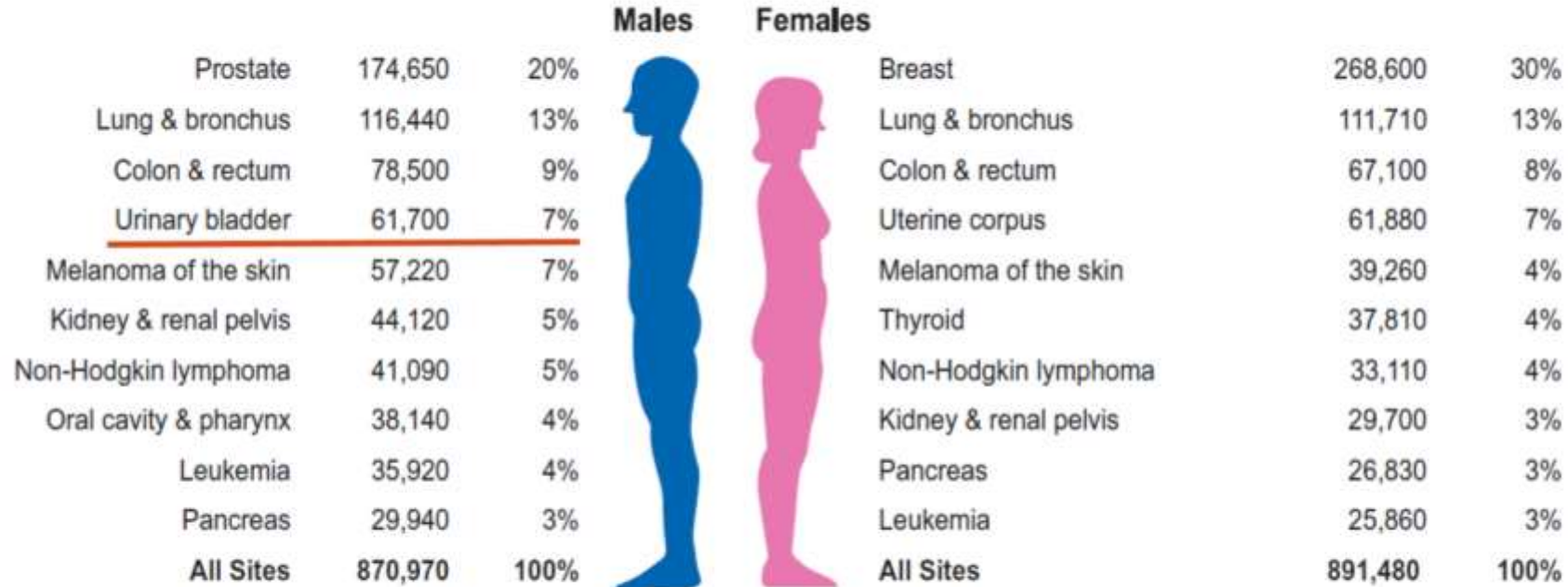
Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

Ders Planı

- ❑ Mesane Kanseri İnsidans ve Mortalite
- Metastatik Hastalık
- ❑ Sisplatine uygun hastada birinci basamak
- ❑ Sisplatine uygun olmayan hastada birinci basamak
- ❑ Platin sonrası, ikinci basamak tedavi
- ❑ İkinci basamak sonrası tedavi seçenekleri
- ❑ Özet

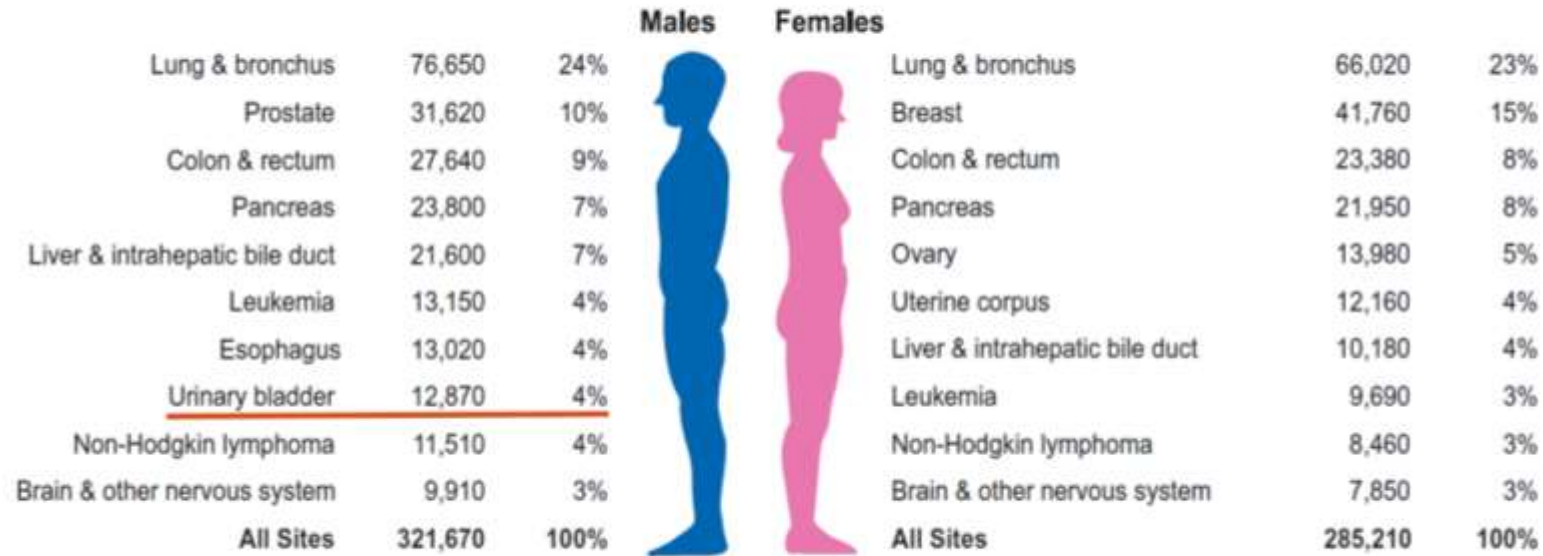
Mesane Kanseri İnsidans ve Mortalite

2019 ESTIMATED NEW CANCER CASES — US



Mesane Kanseri İnsidans ve Mortalite

2019 ESTIMATED CANCER DEATHS – US

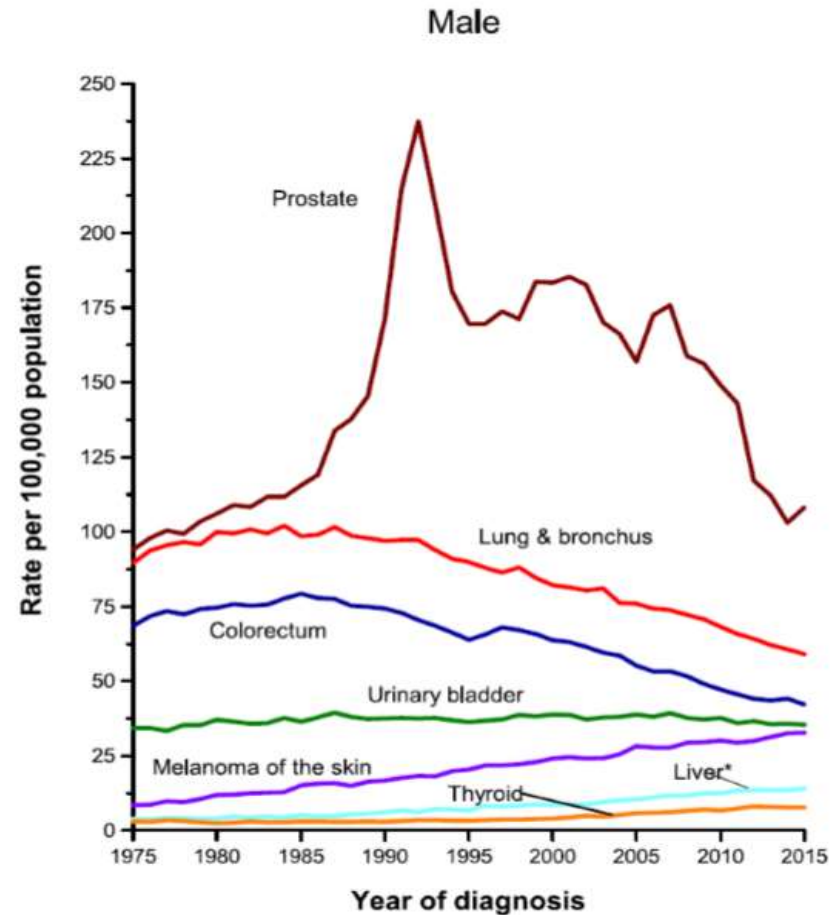


Mesane Kanseri İnsidans ve Mortalite

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 Kanserinde Sistemik Tedavi

T STAGE IN BLADDER CANCER

- Non muscle invasive disease includes:
 - Ta
 - Tis
 - T1
- Muscle invasive disease includes:
 - T2-T4
- When LN or metastatic deposits are also present, usually referred to regional or metastatic disease

Table 1. American Joint Committee on Cancer (AJCC) TNM Staging System for Bladder Cancer 8th ed., 2017)

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "flat tumor"
T1	<u>Tumor invades lamina propria (subepithelial connective tissue)</u>
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall

Tanı anında
%75 hasta

%25 hasta



Mesane Kanserinde Sistemik Tedavi

TUMOR STAGING, STAGE III DISEASE

- Changes were made in the AJCC staging manual the 8th edition (2017)
- N1 and N2 disease was previous characterized in the Stage IV prognostic group
- In the updated edition
 - N1 is in the Stage IIIA group
 - N1 = single regional LN in the true pelvis
 - N2 and N3 are in the Stage IIIB group
 - T4b moved from group IV to a new group of IVA

Table 2. AJCC Prognostic Groups

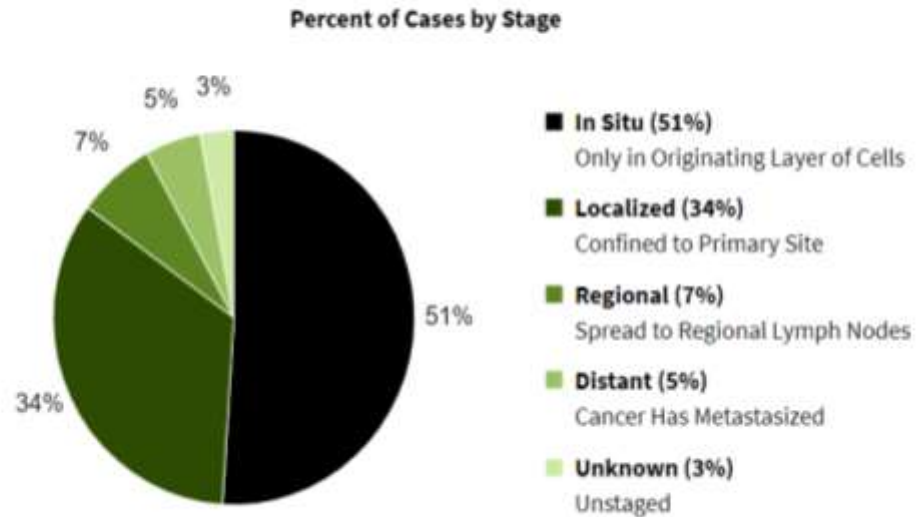
	T	N	M		T	N	M
Stage 0a	Ta	N0	M0	Stage IIIB	T1-T4a	N2,N3	M0
Stage 0is	Tis	N0	M0	Stage IVA	T4b	Any N	M0
Stage I	T1	N0	M0		Any T	Any N	M1a
Stage II	T2a	N0	M0	Stage IVB	Any T	Any N	M1b
	T2b	N0	M0				
Stage IIIA	T3a	N0	M0				
	T3b	N0	M0				
	T4a	N0	M0				
	T1-T4a	N1	M0				

[Continued](#)

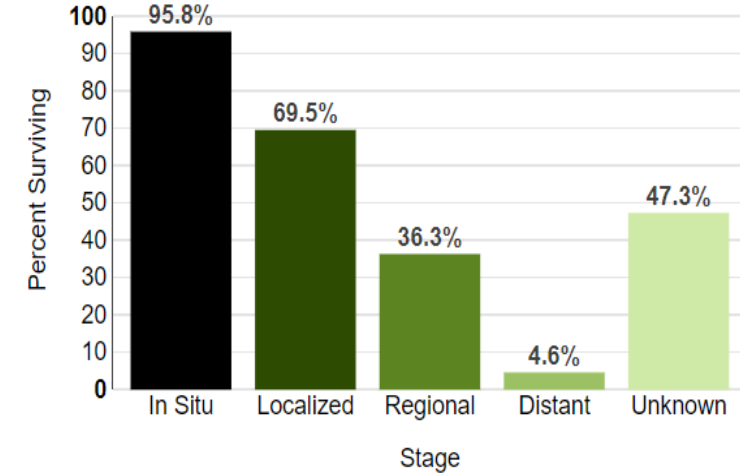


Mesane Kanseri İnsidans ve Mortalite

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

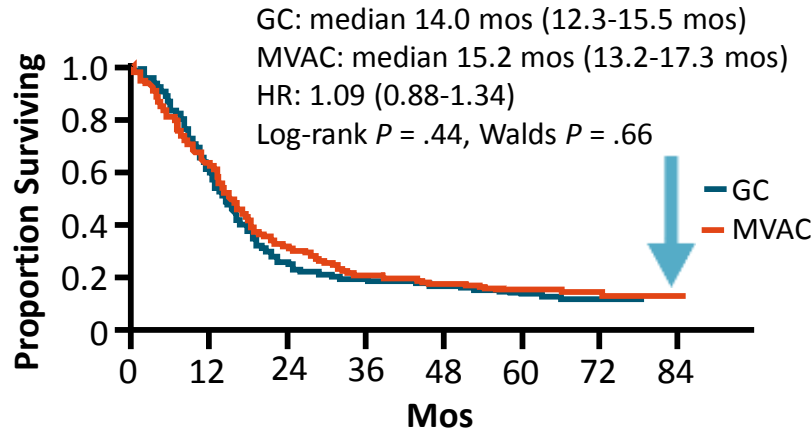
Sisplatin Uygun

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

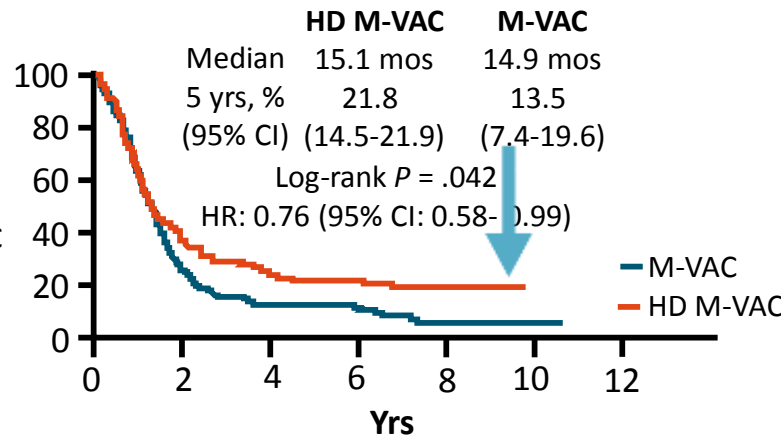
MVAC 202 125 62 40 34 29 9 1

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

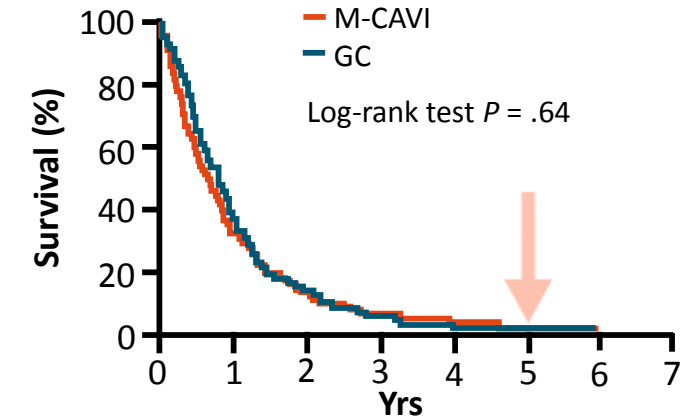
Sisplatin uygun değil

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 Mesane Kanseri Birinci Basamak Tedavi Seçimi



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021 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 • Gemcitabine and cisplatin⁴ (category 1) followed by avelumab maintenance therapy (category 1)^{a,11} • DDMVAC with growth factor support (category 1)^{2,8} followed by avelumab maintenance therapy (category 1)^{a,11}
Cisplatin ineligible	Preferred regimens • Gemcitabine and carboplatin¹² followed by avelumab maintenance therapy (category 1)^{a,11} • Atezolizumab¹³ (only for patients whose tumors express PD-L1^b or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab¹⁴ (only for patients whose tumors express PD-L1^c or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) Other recommended regimens • Gemcitabine¹⁵ • Gemcitabine and paclitaxel¹⁶ Useful under certain circumstances • Ifosfamide, doxorubicin, and gemcitabine¹⁷ (for patients with good kidney function and good PS)

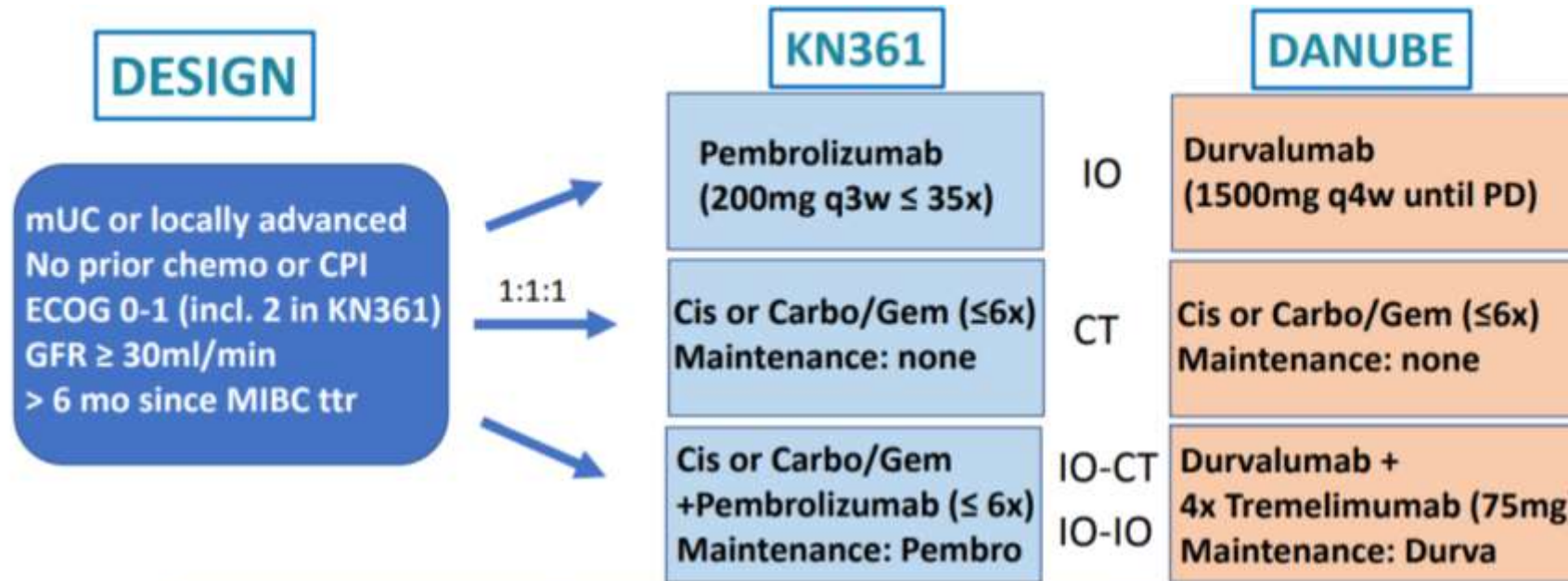
- The presence of both non-nodal metastases and ECOG performance score ≥ 2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.¹⁸
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
 - ▶ Participation in clinical trials of new or more tolerable therapy is recommended.

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

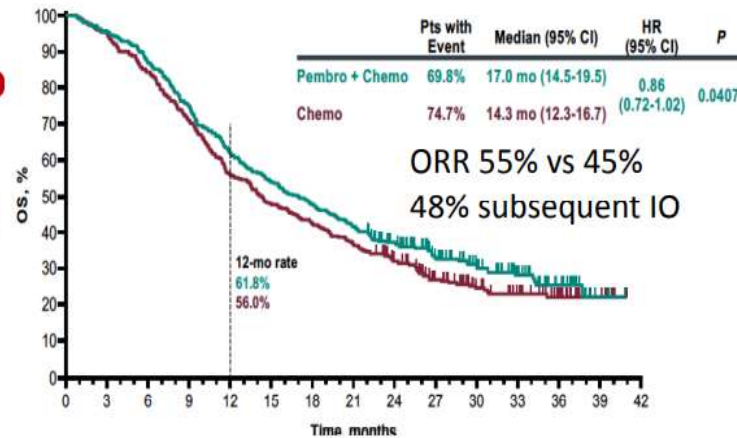
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

Overall survival

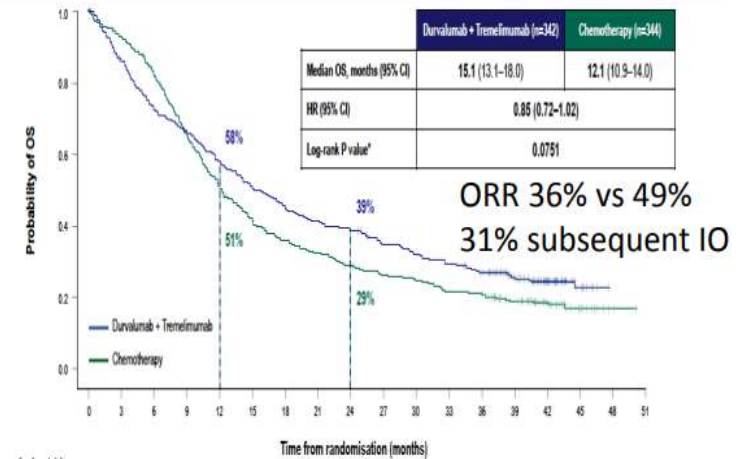
Combination vs Chemo

TOTAL population (ITT)

KEYNOTE 361 –IO-CT vs CT (1°EP)

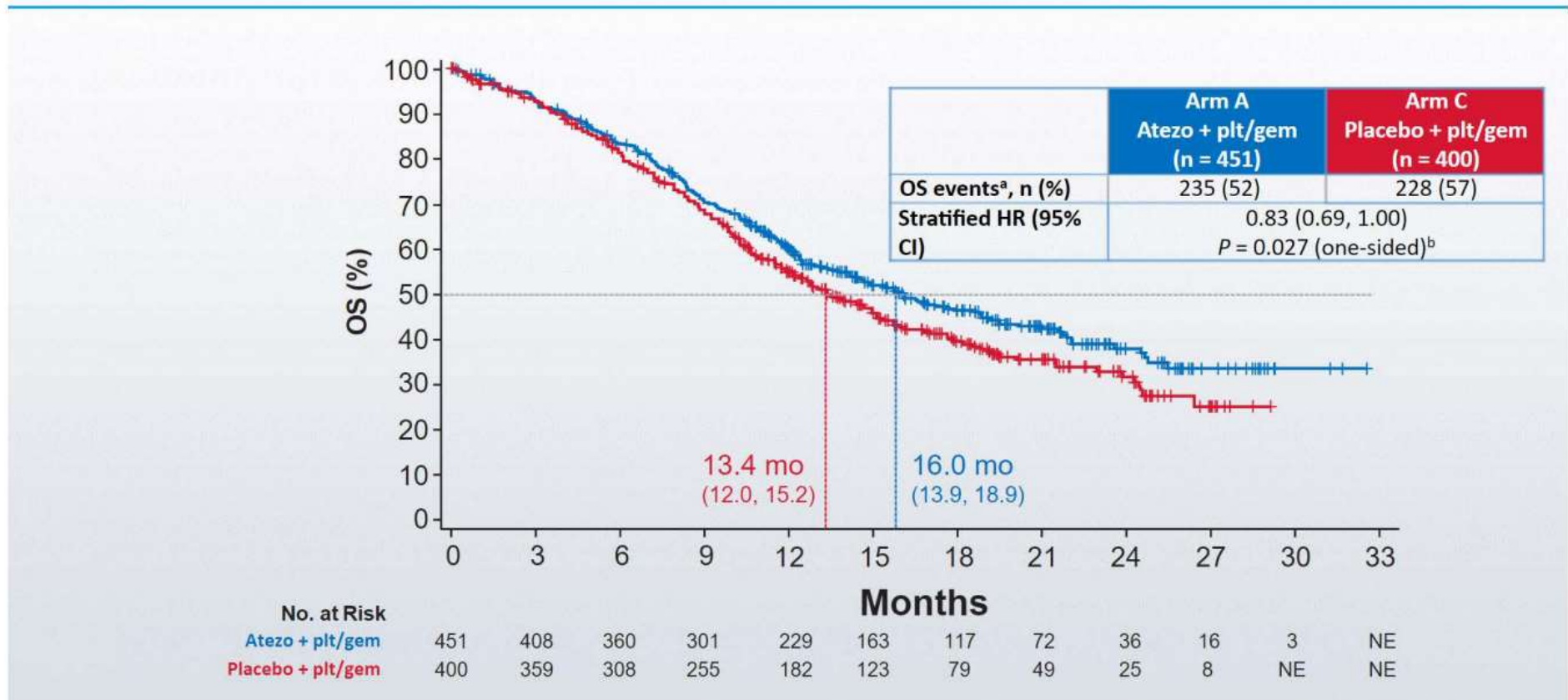


DANUBE – IO-IO vs CT (1°EP)

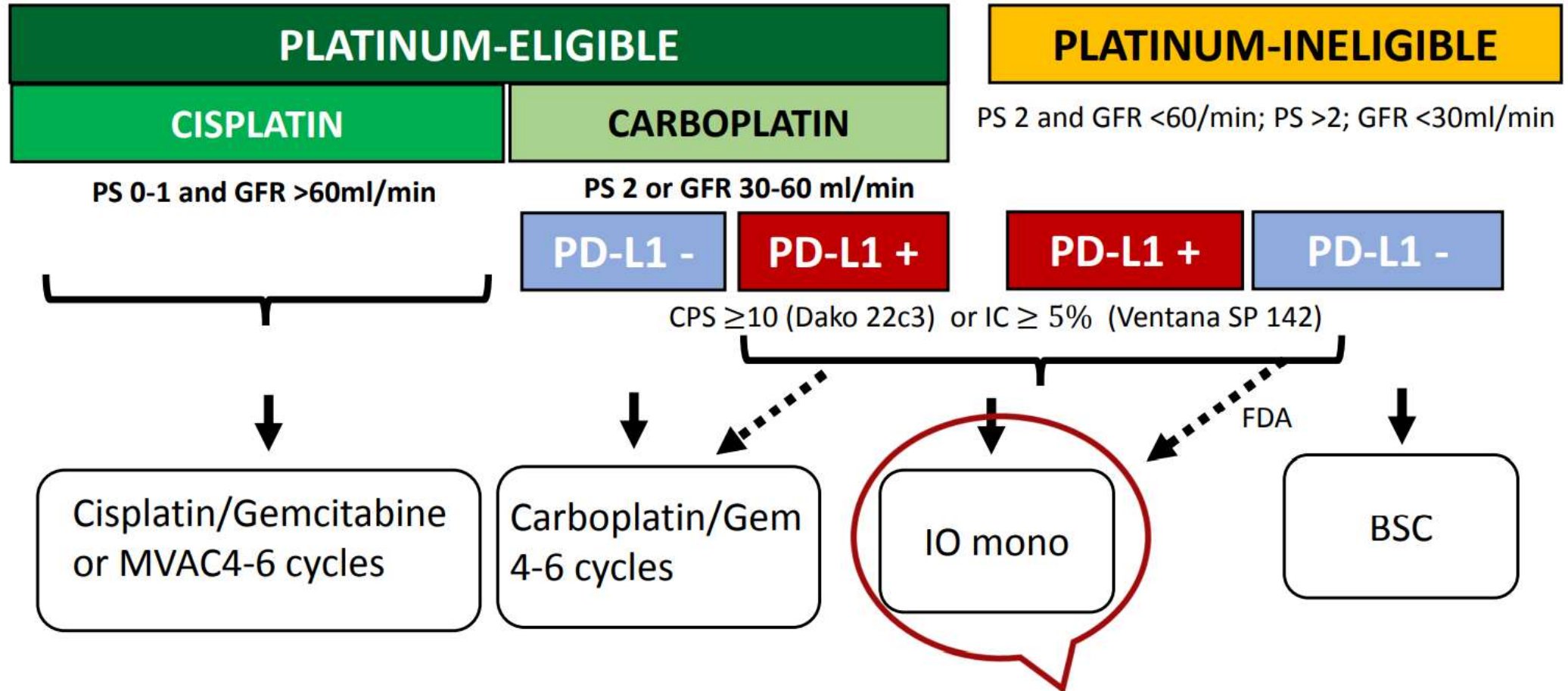


Metastatik Mesane Kanseri Birinci Basamak Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

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



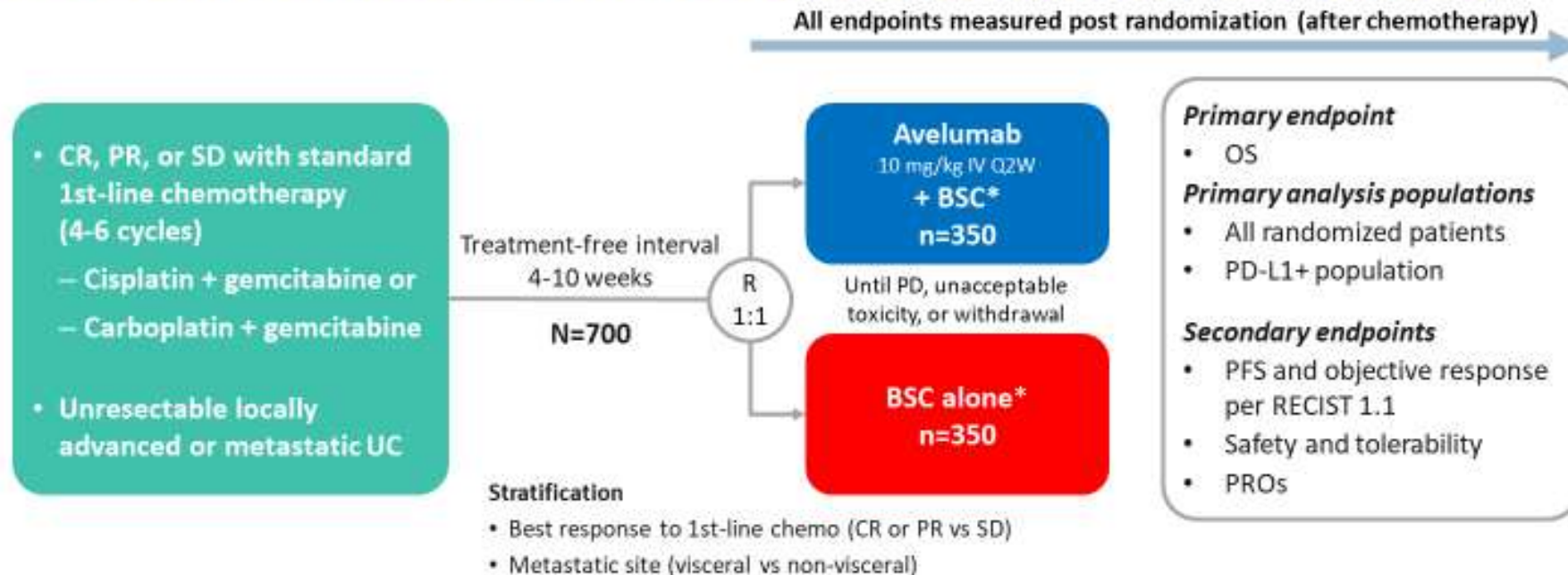
Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçimi



Pembrolizumab Lancet Oncology 2017/JCO 2020
Atezolizumab Lancet 2017

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

JAVELIN Bladder 100 study design (NCT02603432)



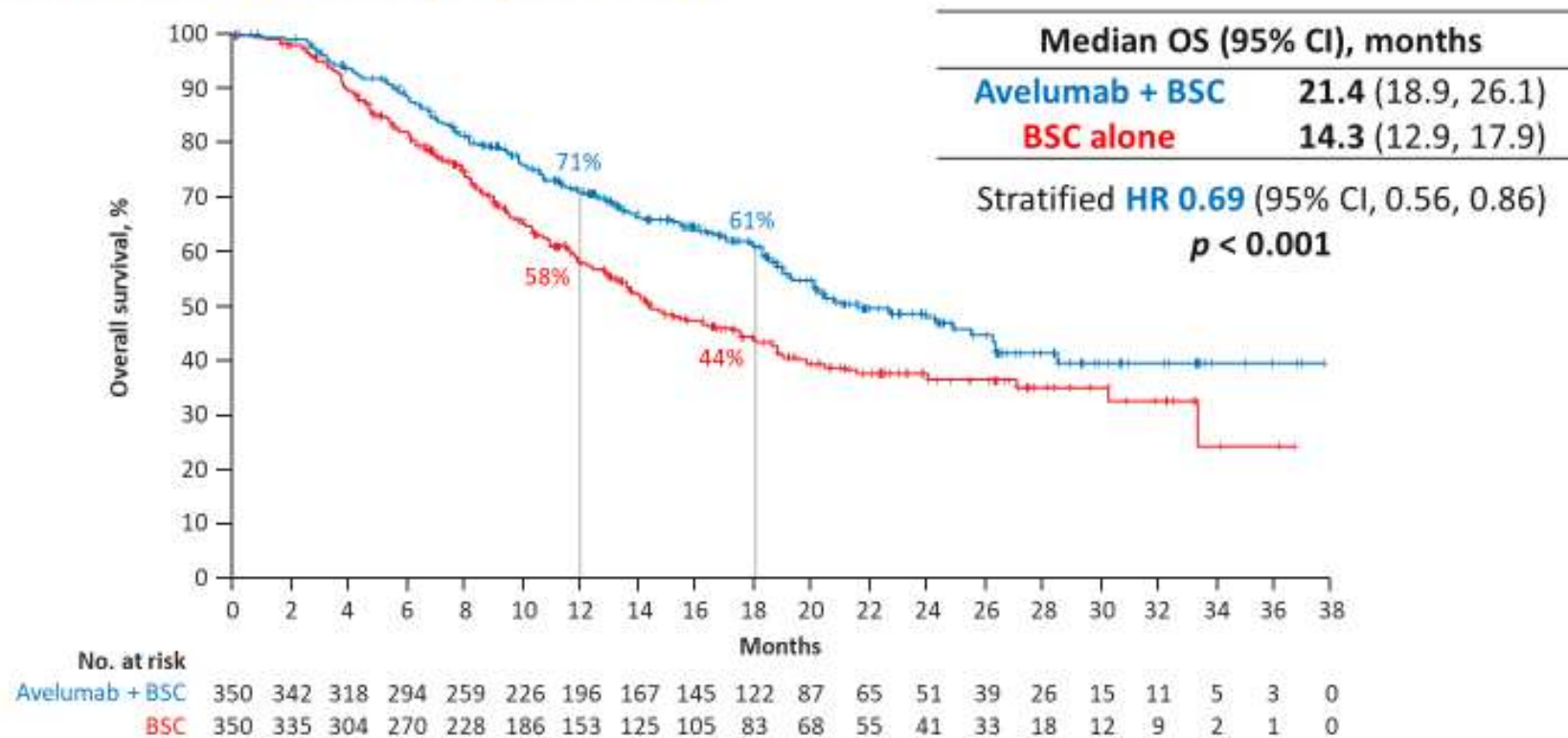
PD-L1+ status was defined as PD-L1 expression in $\geq 25\%$ of tumor cells or in $\geq 25\%$ or 100% of tumor-associated immune cells if the percentage of immune cells was $>1\%$ or $\leq 1\%$, respectively, using the SP263 assay; 358 patients (51%) had a PD-L1-positive tumor

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

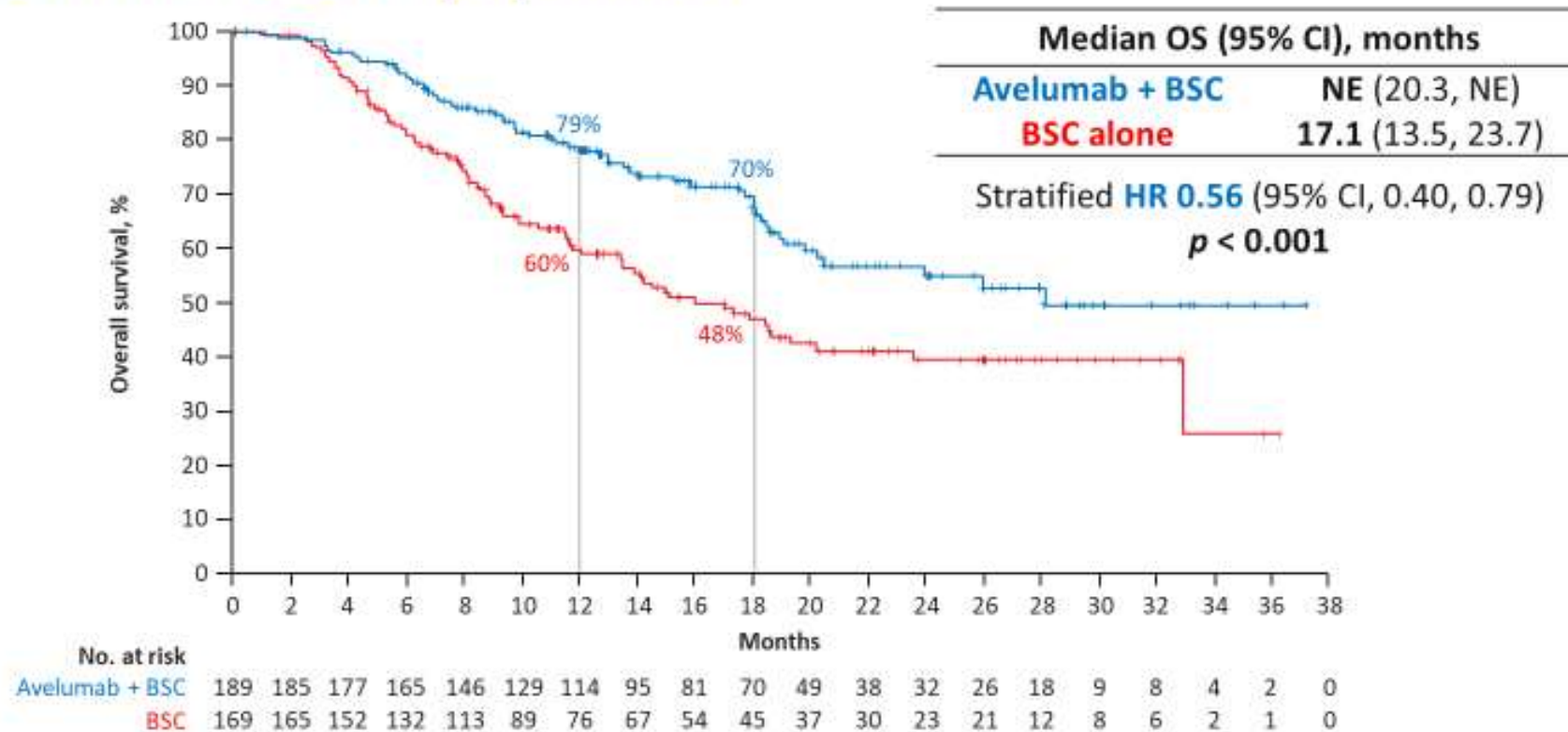
OS in the overall population



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

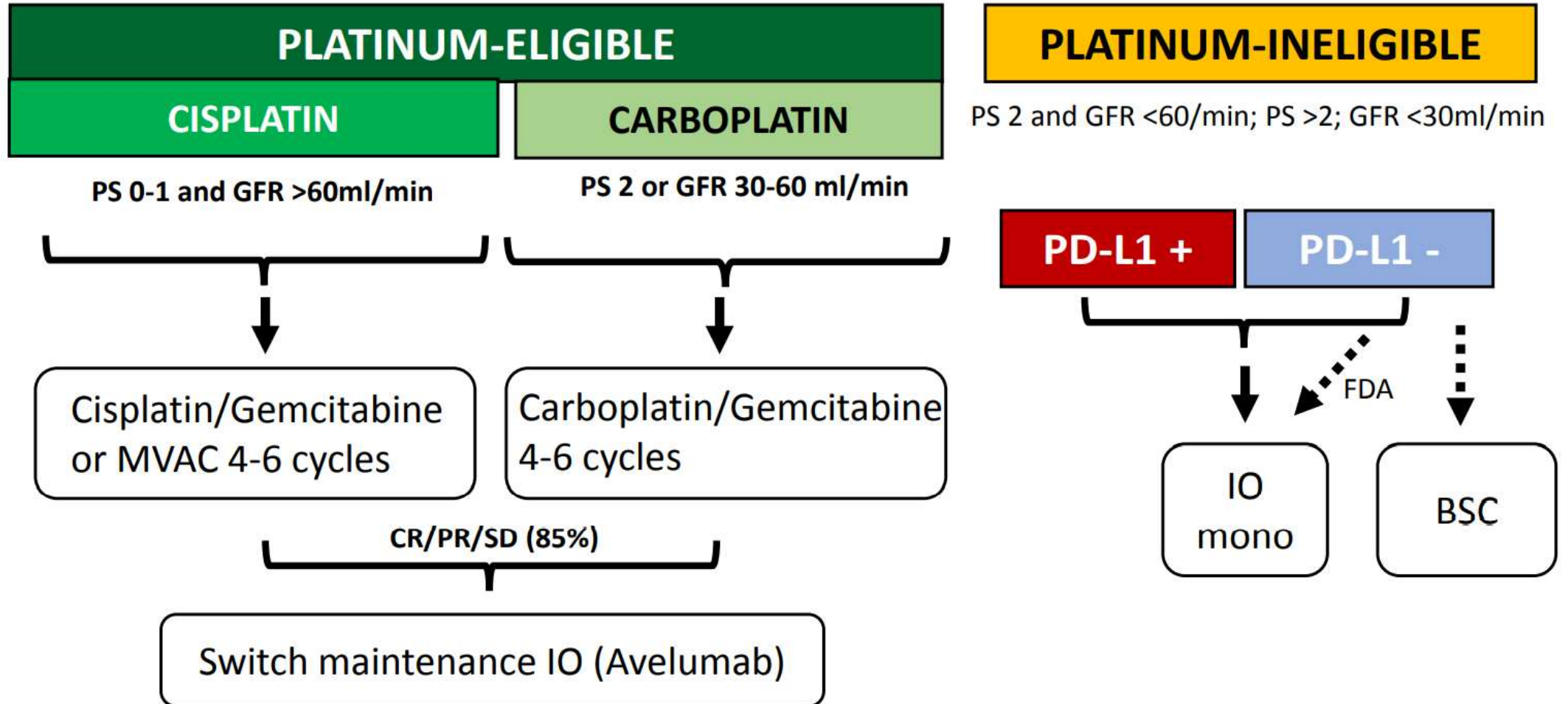
Metastatik Mesane Kanseri Birinci Basamak Tedavi Platin bazlı kemoterapi Sonrası İdame Avelumab

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 Seçimi



Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçimi



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021 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 • Gemcitabine and cisplatin⁴ (category 1) followed by avelumab maintenance therapy (category 1)^{a,11} • DDMVAC with growth factor support (category 1)^{2,8} followed by avelumab maintenance therapy (category 1)^{a,11}
Cisplatin ineligible	Preferred regimens • Gemcitabine and carboplatin¹² followed by avelumab maintenance therapy (category 1)^{a,11} • Atezolizumab¹³ (only for patients whose tumors express PD-L1^b or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab¹⁴ (only for patients whose tumors express PD-L1^c or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) Other recommended regimens • Gemcitabine¹⁵ • Gemcitabine and paclitaxel¹⁶ Useful under certain circumstances • Ifosfamide, doxorubicin, and gemcitabine¹⁷ (for patients with good kidney function and good PS)

- The presence of both non-nodal metastases and ECOG performance score ≥ 2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.¹⁸
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
 - ▶ Participation in clinical trials of new or more tolerable therapy is recommended.

İmmün kontrol noktası inhibitörleri

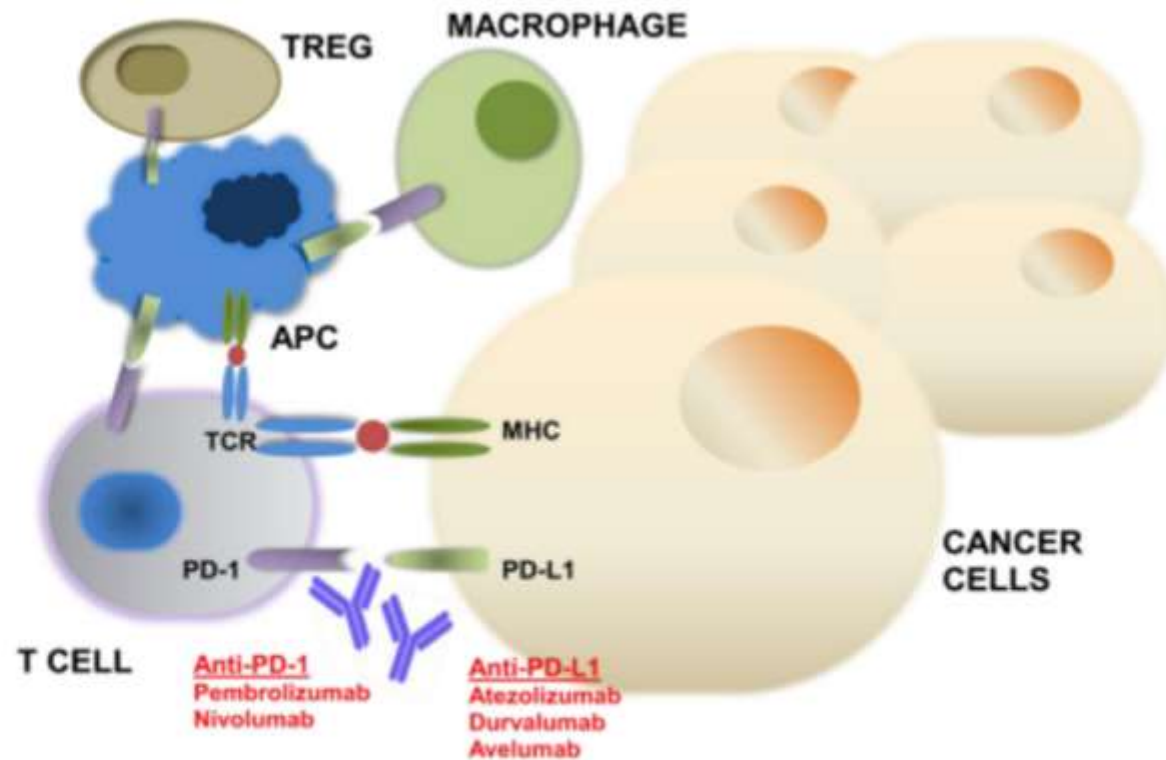
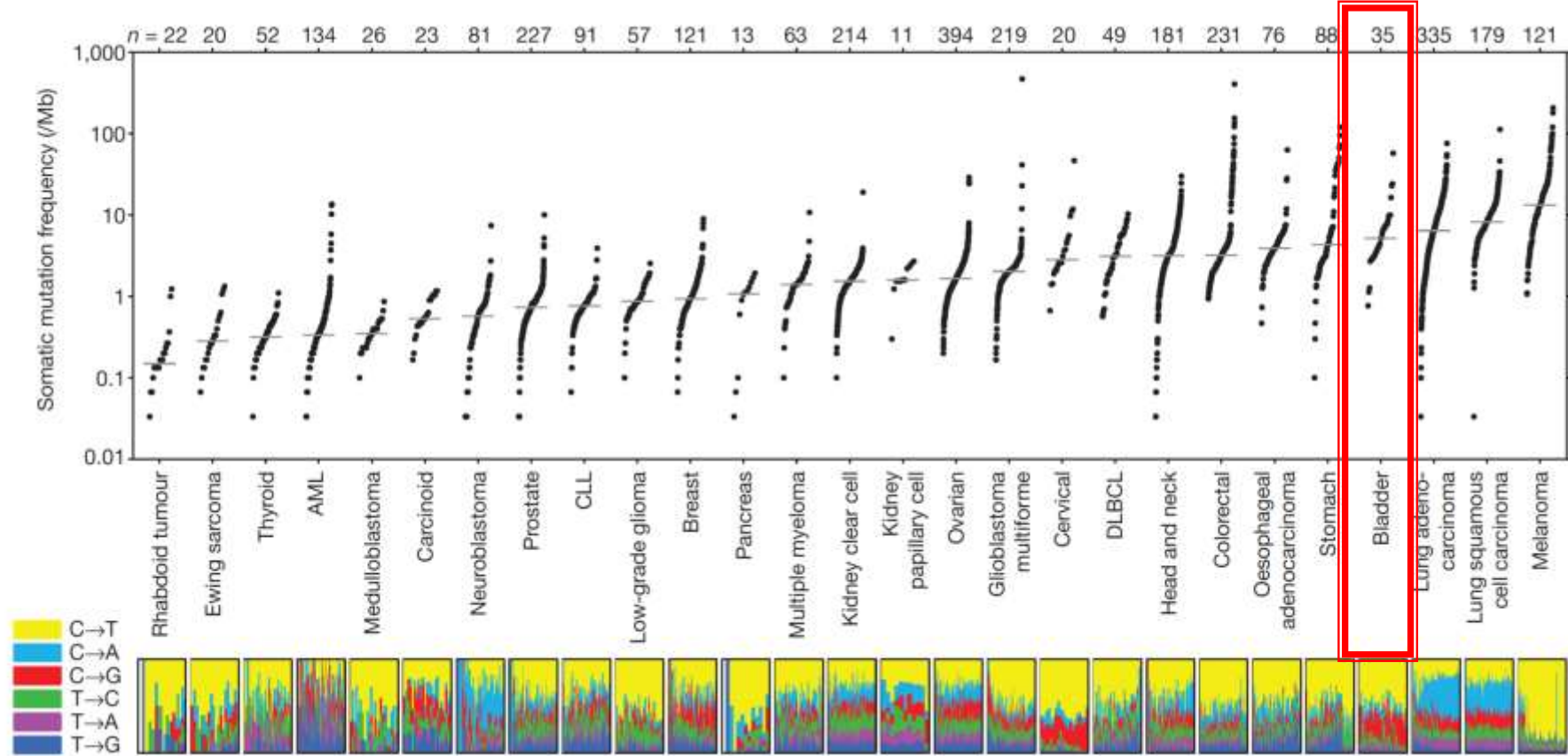


Fig. 1 Mechanism of action of PD-1 and PD-L1 inhibitors. The programmed cell death 1 (PD-1) receptor is expressed on activated T cells, B cells, macrophages, regulatory T cells (Tregs), and natural killer (NK) cells. Binding of PD-1 to its B7 family of ligands, programmed death ligand 1 (PD-L1 or B7-H1)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

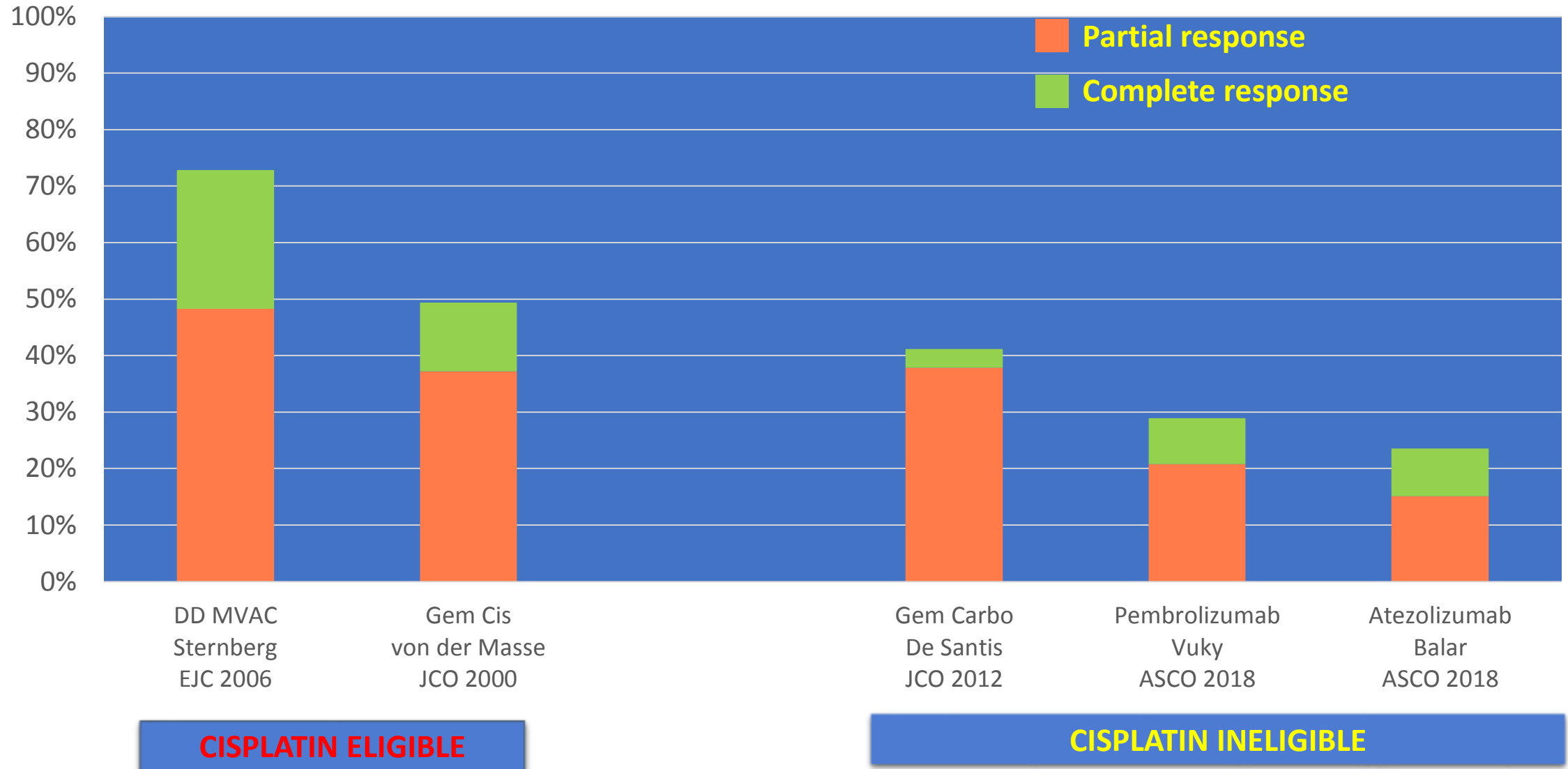
Mesane Kanserinde Tümör Mutasyon Yüğü



Lawrence et al. Nature 2013

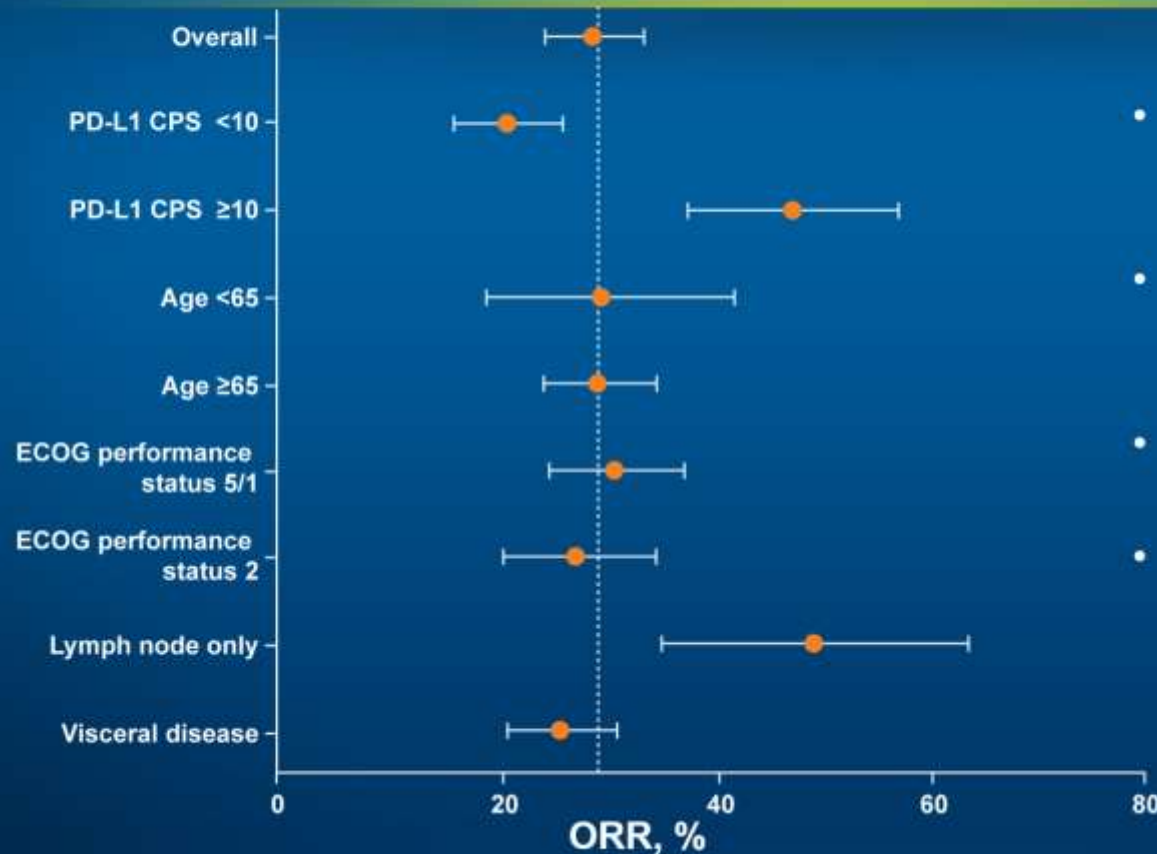
- ☐ Yüksek kompleks mutasyon durumu bütün ve diğer kanserojenlere maruz kalma ile benzer
- ☐ Bir çok neoantijen konakçı immün sistemi tarafından potansiyel olarak yabancı gibi görünür

Metastatik Mesane Kanseri Birinci Basamak Tedavi 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

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%

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.

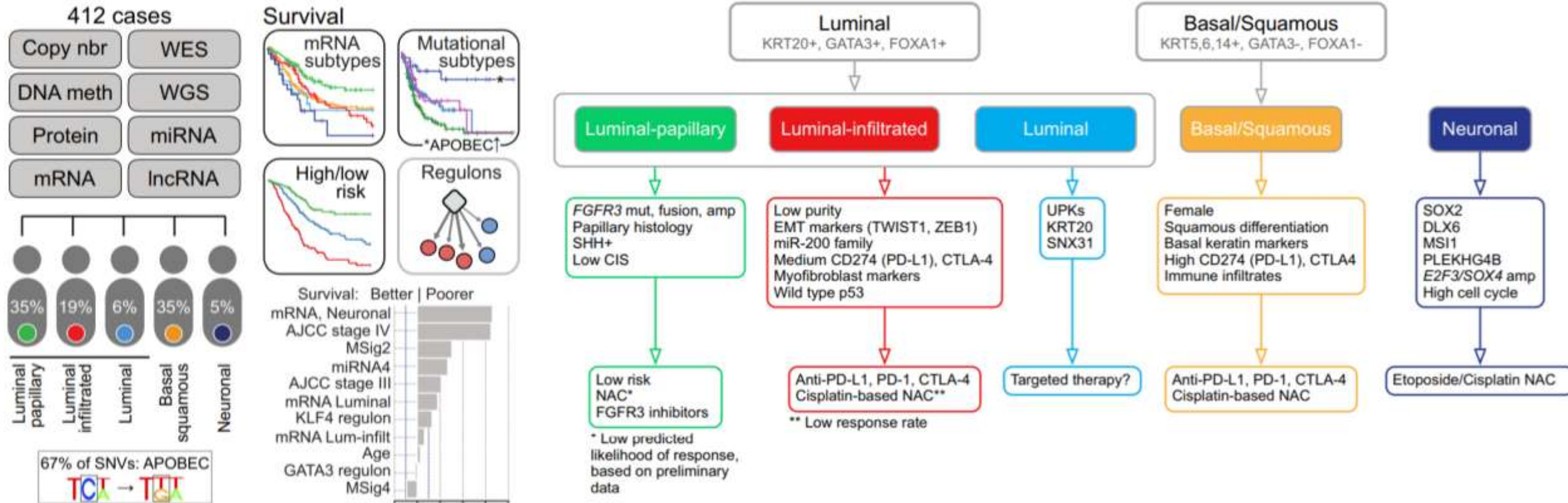
Courtesy of Arlene O. Siefker-Radtke, MD

Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

Cell

Article

Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer



Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçenekleri



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021 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)^{d,e}
Participation in clinical trials of new agents is recommended.

Preferred regimen

- Pembrolizumab (category 1)¹⁹

Other recommended regimens

- Paclitaxel²⁴ or docetaxel²⁵
- Gemcitabine¹⁵

Alternative preferred regimens

- Immune checkpoint inhibitor
 - ▶ Nivolumab²⁰
 - ▶ Avelumab^{21,22}
- Erdafitinib^{f,23}

Useful in certain circumstances based on prior medical therapy

- Ifosfamide, doxorubicin, and gemcitabine¹⁷
- Gemcitabine and paclitaxel¹⁶
- 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 regimen for cisplatin ineligible, chemotherapy naïve

- Gemcitabine/carboplatin

Other recommended regimens

- Erdafitinib^{f,23}
- Paclitaxel or docetaxel²⁵
- Gemcitabine¹⁵

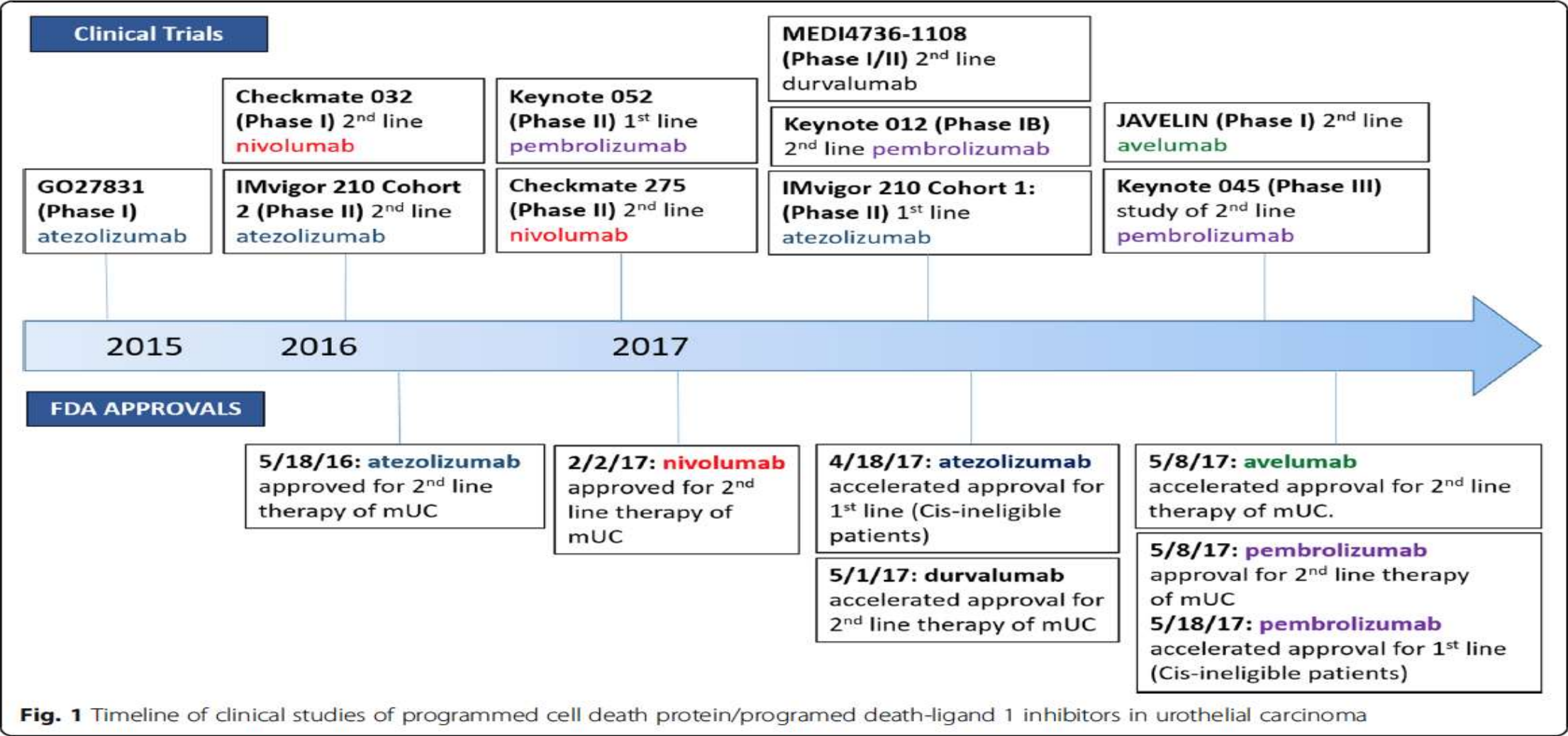
Preferred regimens for cisplatin eligible, chemotherapy naïve

- Gemcitabine and cisplatin⁴
- DDMVAC with growth factor support²

Useful in certain circumstances based on prior medical therapy

- Ifosfamide, doxorubicin, and gemcitabine¹⁷
- Gemcitabine and paclitaxel¹⁶

Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

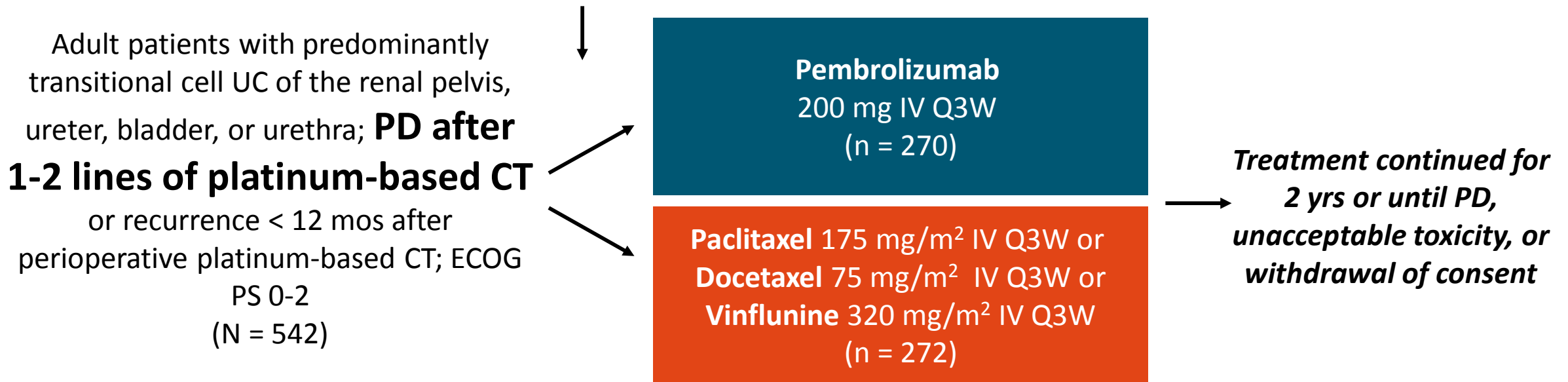


Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

- International, randomized, open-label phase III study

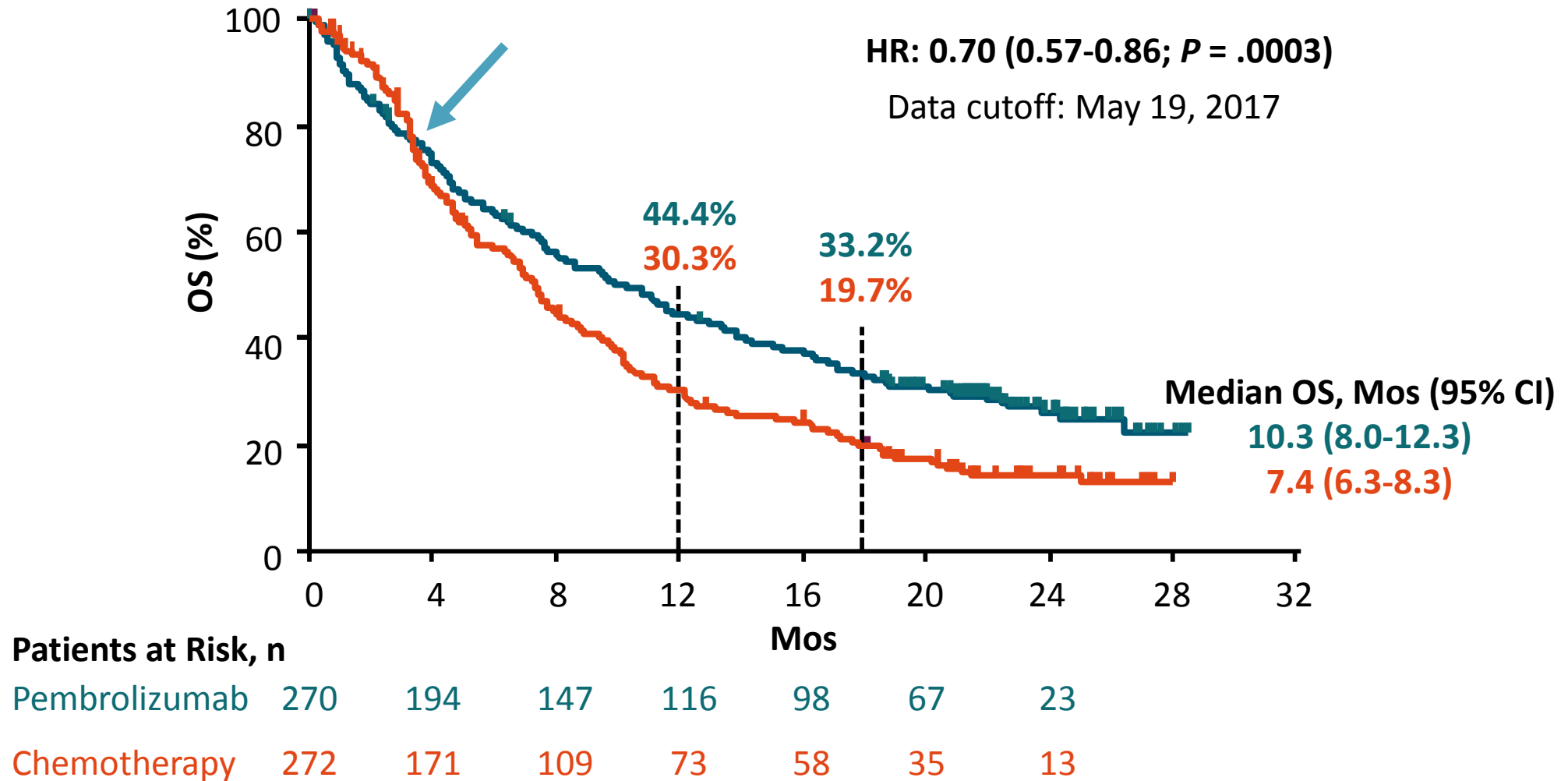
Stratified by ECOG PS (0/1 vs 2), Hg (< 10 vs ≥ 10 g/dL), liver mets (yes vs no), and time since last CT (< vs ≥ 3 mos)

KEYNOTE-045



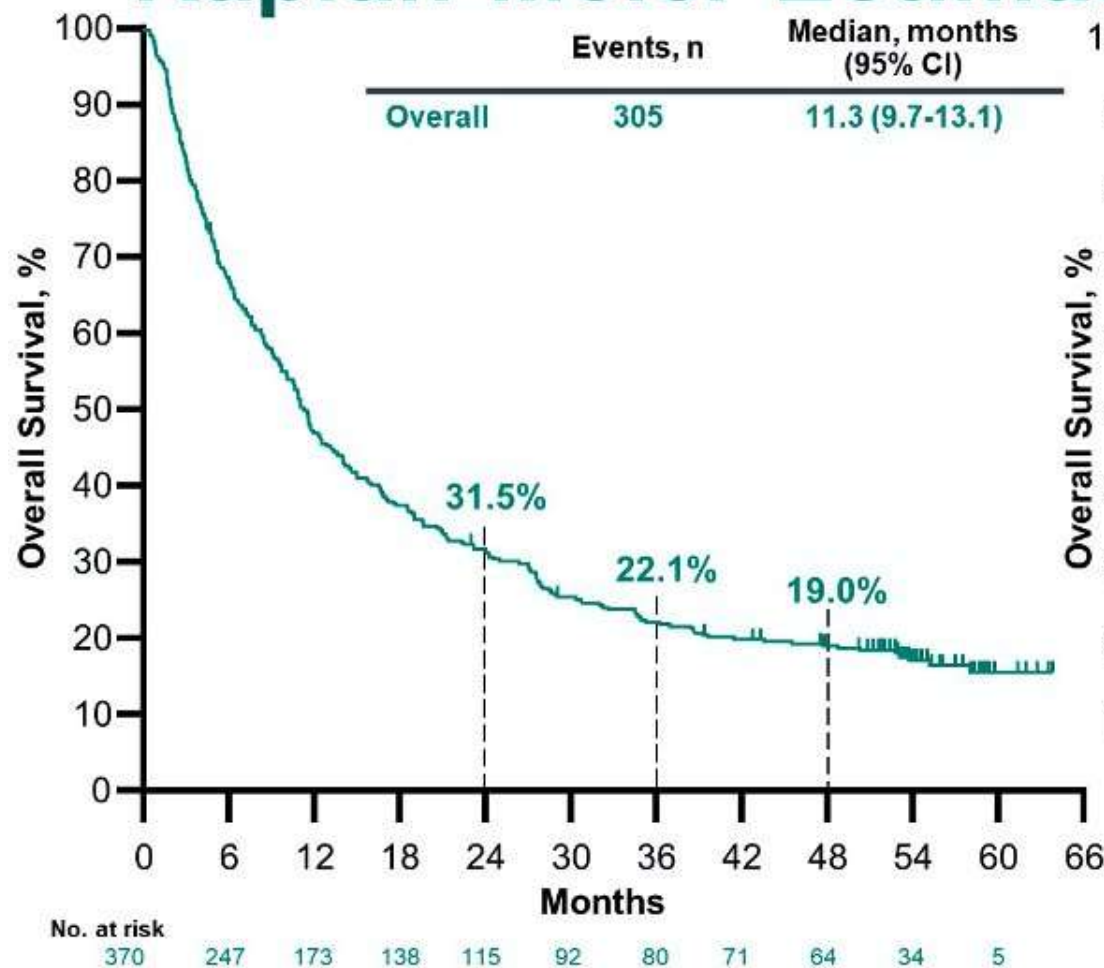
- Primary endpoints: OS, PFS
- Secondary endpoints: ORR, DoR, safety

KEYNOTE-045: OS

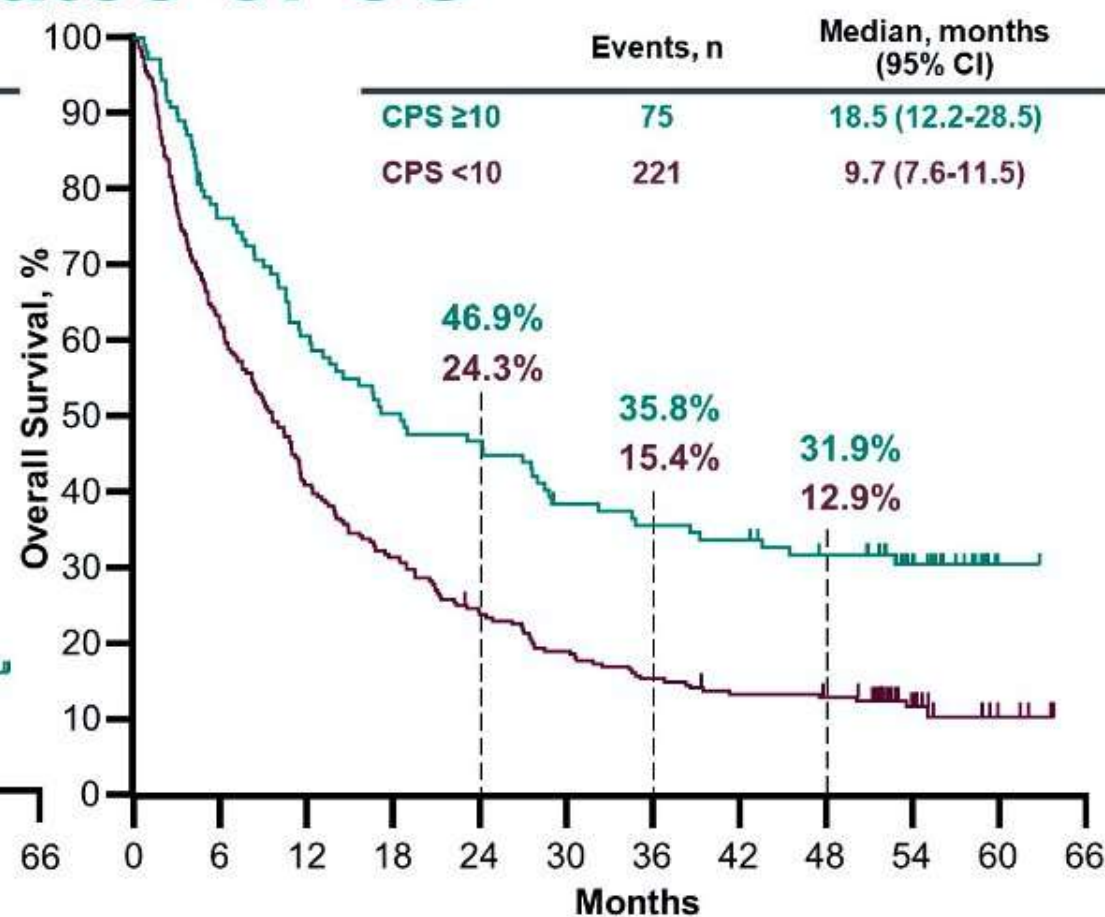


KEYNOTE-045: OS

Kaplan-Meier Estimates of OS

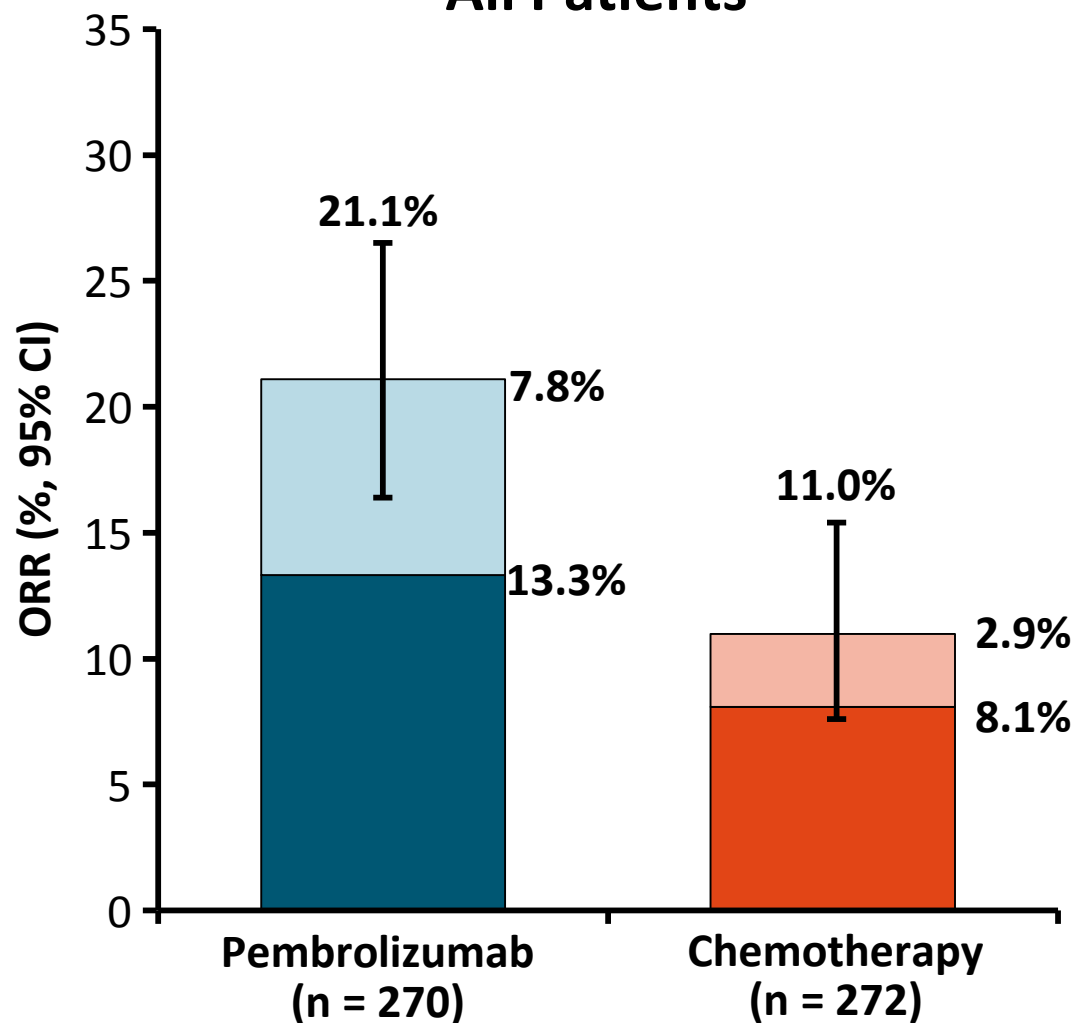


Data cutoff: September 26, 2020.

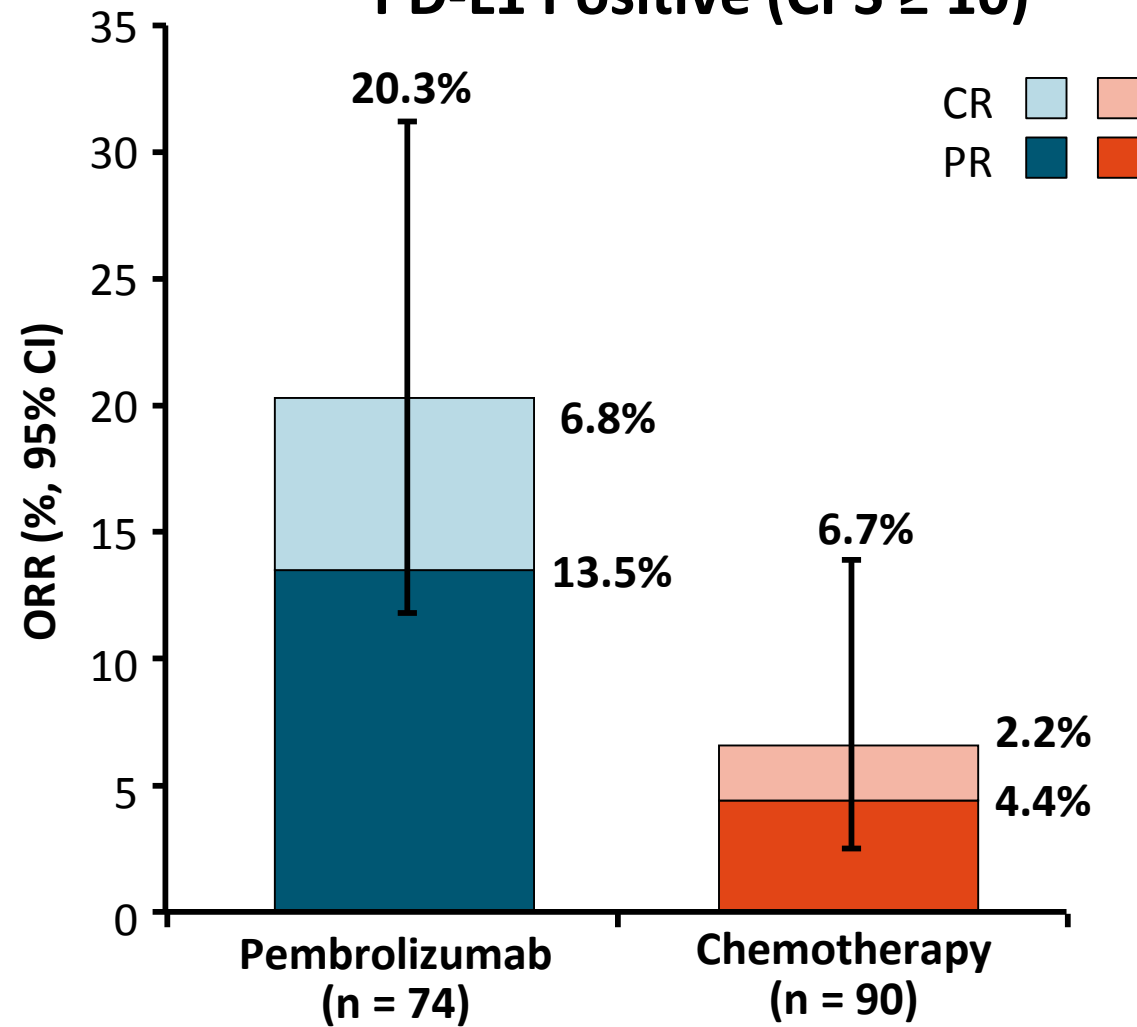


KEYNOTE-045: ORR

All Patients

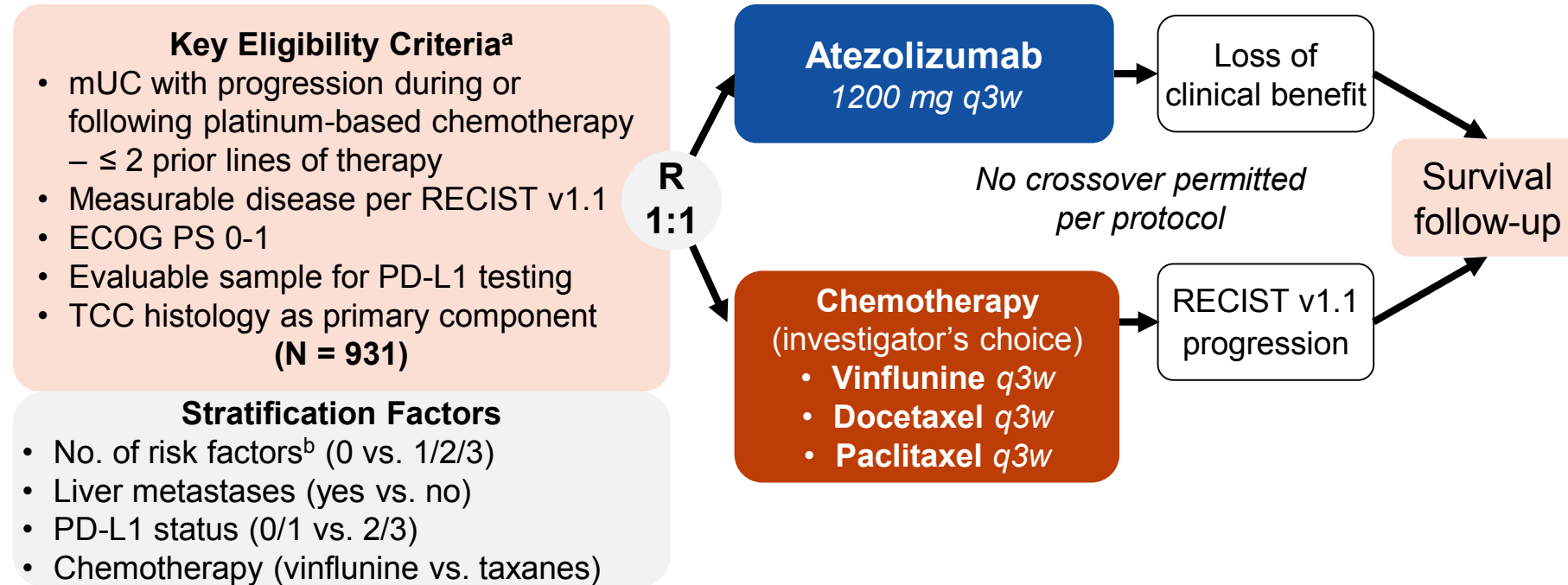


PD-L1 Positive (CPS ≥ 10)



Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

IMvigor211



▪ Primary endpoint

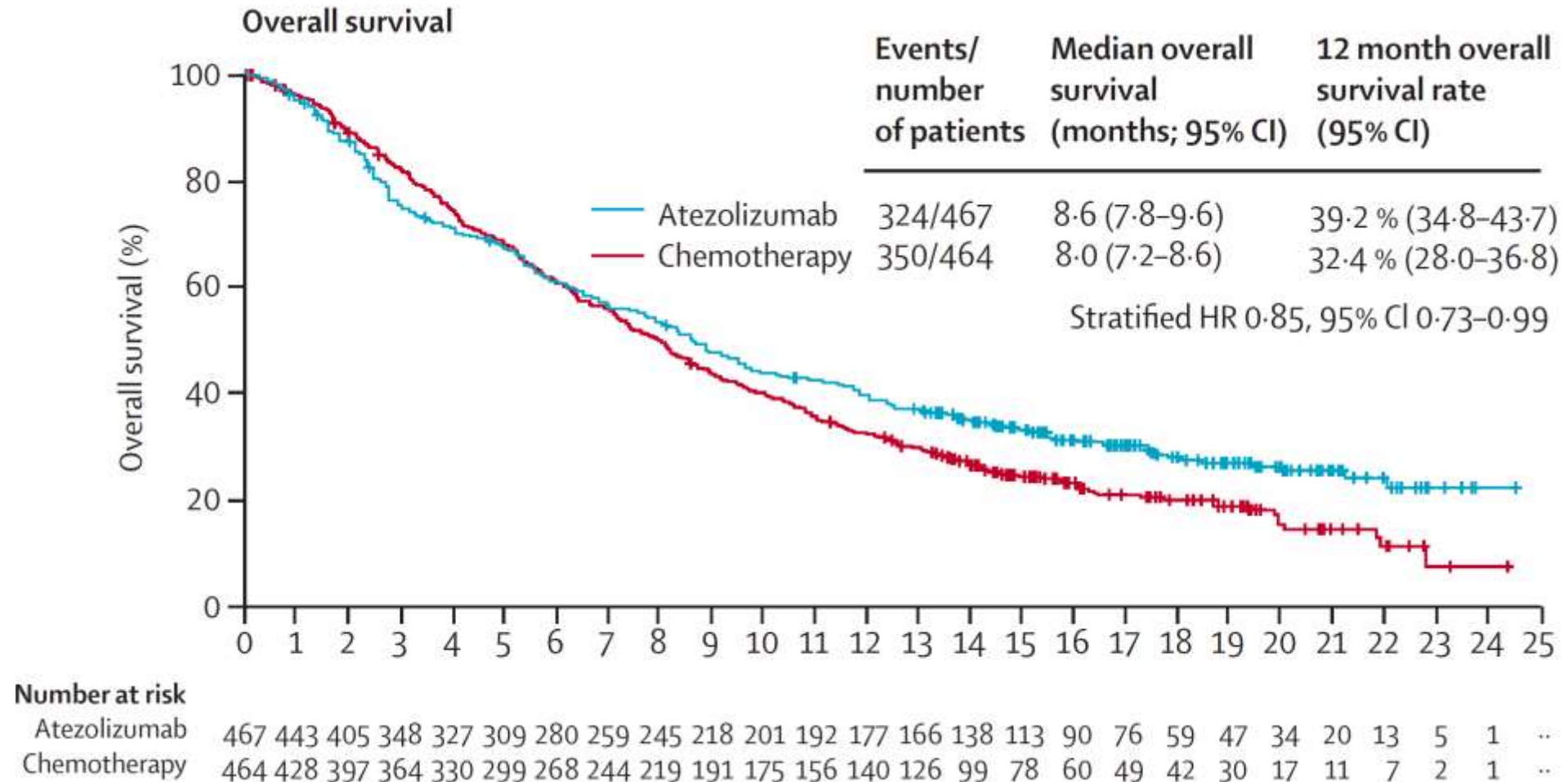
- OS, tested hierarchically in pre-specified populations

▪ Additional endpoints

- Efficacy: RECIST v1.1 ORR, PFS and DOR^c
- Safety
- PROs: EORTC QLQ-C30

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. ^a ClinicalTrials.gov, NCT02302807. ^b Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. ^c Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.

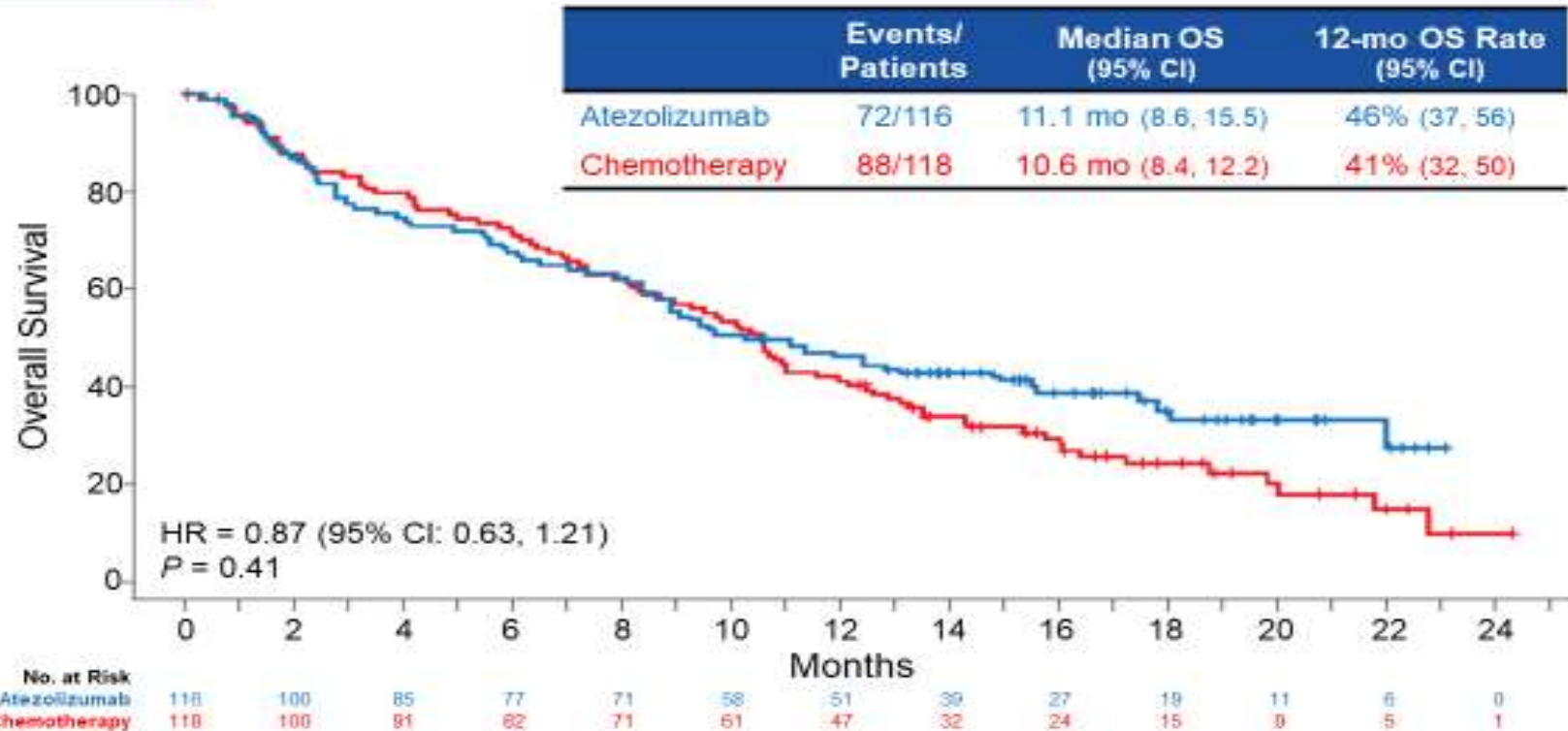
IMvigor211 Sonuçları



IMvigor211 Sonuçları



OS Analysis: IC2/3 Population



Evre IV Mesane Kanserinde Atezolizumab Tedavisi: Gerçek Yaşam Verileri

Deniz Tural¹, Ömer Fatih Ölmez², Ahmet Taner Sümbül³, Mehmet Artaç⁴, Nail Özhan⁵,
Emre Akar¹, Burcu Çakar⁶, Osman Köstek⁷, Nail Paksoy⁸, Mustafa Erman⁹, Hasan Şenol
Coşkun¹⁰, Fatih Selçukbiricik¹¹, Özge Keskin¹², Fatma Paksoy Türköz¹³, Kerem Oruç¹⁴,
Selami Bayram¹⁵, Uğur Yılmaz¹⁶, İrem Bilgetekin¹⁷, Birol Yıldız¹⁸, Mehmet Ali Nahit
Şendur¹⁹, Ahmet Dirican²⁰, Dilek Erdem²¹, Meltem Selam²², Özgür Tanrıverdi²³, Semra
Paydaş²⁴, Zuhut Urukçı²⁵, Elif Atağ²⁶, Sabri Güncan²⁷, Yüksel Ürün²⁸, Ali Alkan²⁹, Ali
Osman Kaya³⁰, Deniz Tataroğlu Özyükseler³¹, Halil Taşkaynatan³², Mustafa Yıldırım³³,
Müge Sönmez³⁴, Tuğba Başoğlu³⁵, Şeyda Gündüz³⁶, Saadettin Kılıçkap³⁷,

Türk Onkoloji Grubu

Türk Tıbbi Onkoloji Derneği 2020 Sanal Kongresi
13-15 Kasım 2020

available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus



Bladder Cancer

Atezolizumab in Patients with Metastatic Urothelial Carcinoma Who Have Progressed After First-line Chemotherapy: Results of Real-life Experiences

Deniz Tural^{a,*}, Ömer Fatih Ölmez^b, Ahmet Taner Sümbül^c, Mehmet Artaç^d, Nail Özhan^e, Emre Akar^a, Burcu Çakar^f, Osman Köstek^g, Meltem Ekenel^h, Mustafa Ermanⁱ, Hasan Şenol Coşkun^j, Fatih Selçukbiricik^k, Özge Keskin^l, Fatma Paksoy Türköz^m, Kerem Oruçⁿ, Selami Bayram^o, Uğur Yılmaz^p, İrem Bilgetekin^q, Birol Yıldızoğlu^r, Mehmet Ali Nahit Şendur^s, Nail Paksoy^h, Ahmet Dirican^t, Dilek Erdem^u, Meltem Selam^v, Özgür Tanrıverdi^w, Semra Paydaş^x, Zuhur Ural^y, Elif Atağ^z, Sabri Güncan^{aa}, Yüksel Ürün^{bb}, Ali Alkan^{cc}, Ali Osman Kaya^{dd}, Deniz Tataroğlu Özyükseler^{ee}, Halil Taşkaynatan^{ff}, Mustafa Yıldırım^{gg}, Müge Sönmez^{hh}, Tuğba Başoğluⁱⁱ, Şeyda Gündüz^{jj}, Saadettin Kölgöçkap^{kk}

^a Bakırköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey; ^b Medipol University Hospital, Istanbul, Turkey; ^c Medical Faculty, Baskent University, Adana, Turkey; ^d Medical Faculty, Necmettin Erbakan University Meram, Konya, Turkey; ^e Medical Faculty, Pamukkale University, Denizli, Turkey; ^f Medical Faculty, Ege University, Izmir, Turkey; ^g Medical Faculty, Trakya University, Edirne, Turkey; ^h Istanbul University Institute of Oncology, Istanbul, Turkey; ⁱ Medical Faculty, Hacettepe University, Ankara, Turkey; ^j Medical Faculty, Akdeniz University, Antalya, Turkey; ^k Medical Faculty, Koc University, Istanbul, Turkey; ^l Medical Faculty, Selçuk University, Konya, Turkey; ^m MedicalPark Goztepe Hospital, Istanbul, Turkey; ⁿ Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey; ^o Antalya Training and Research Hospital, Antalya, Turkey; ^p MedicalPark Izmir Hospital, Izmir, Turkey; ^q Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey; ^r Gulhane Training and Research Hospital, Ankara, Turkey; ^s Ankara Yıldırım Beyazıt University, Faculty of Medicine, Ankara, Turkey; ^t Medical Faculty, Celal Bayar University, Manisa, Turkey; ^u MedicalPark Samsun Hospital, Samsun, Turkey; ^v Liv Hospital, Istanbul, Turkey; ^w Medical Faculty, Sitki Kocman University, Mugla, Turkey; ^x Medical Faculty, Cukurova University, Adana, Turkey; ^y Medical Faculty, Dicle University, Diyarbakir, Turkey; ^z Medical Faculty, Dokuz Eylul University, Izmir, Turkey; ^{aa} Medical Faculty, Mersin University, Mersin, Turkey; ^{bb} Medical Faculty, Ankara University, Ankara, Turkey; ^{cc} Osmaniye State Hospital, Osmaniye, Turkey; ^{dd} Medicana Hospital, Istanbul, Turkey; ^{ee} Istanbul Kartal Dr. Lutfi Kırdar Training and Research Hospital, Istanbul, Turkey; ^{ff} Katip Celebi University Atatürk Training and Research Hospital, Izmir, Turkey; ^{gg} MedicalPark Gaziantep Hospital, Gaziantep, Turkey; ^{hh} Ordu State Hospital, Ordu, Turkey; ⁱⁱ Medical Faculty, Marmara University, Istanbul, Turkey; ^{jj} Antalya Memorial Hospital, Antalya, Turkey; ^{kk} Hacettepe University Institute of Oncology, Ankara, Turkey

Sonuçlar

Sağkalım

Ortalama PFS: 3.8 ay (95% CI, 2.25–5.49)

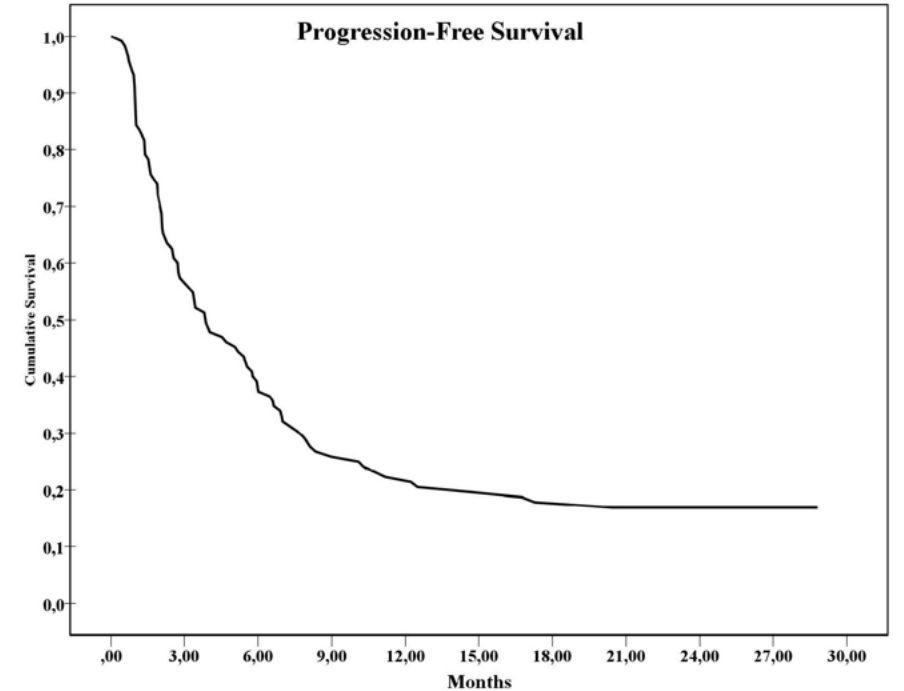
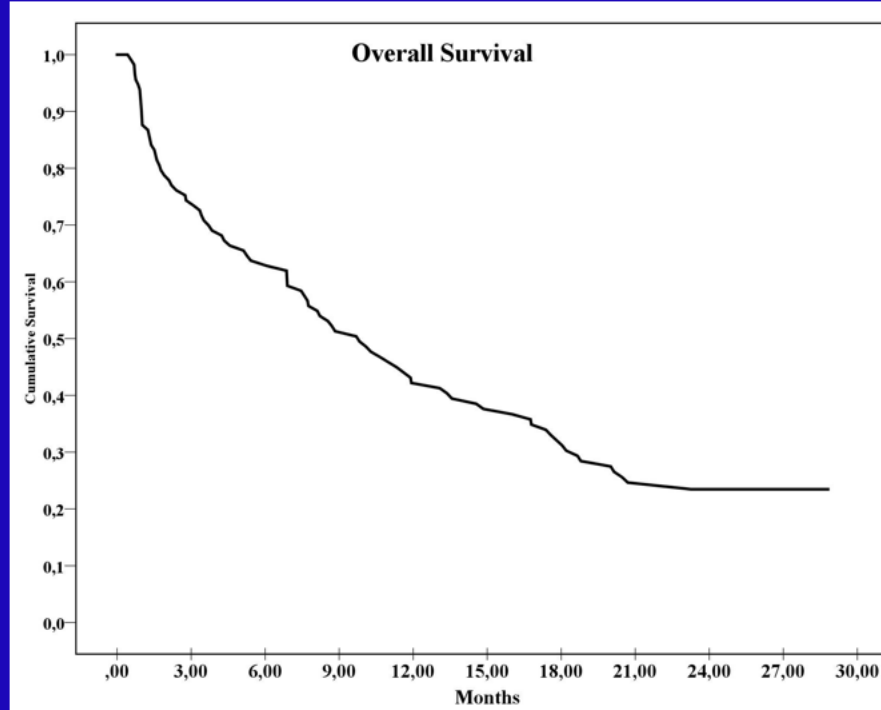
Ortalama OS: 9.8 ay (95% CI, 6.7–12.9)

12 ay PFS oranı: %22.3

24 ay PFS oranı: %16.9

12 ay OS oranı: %42.2

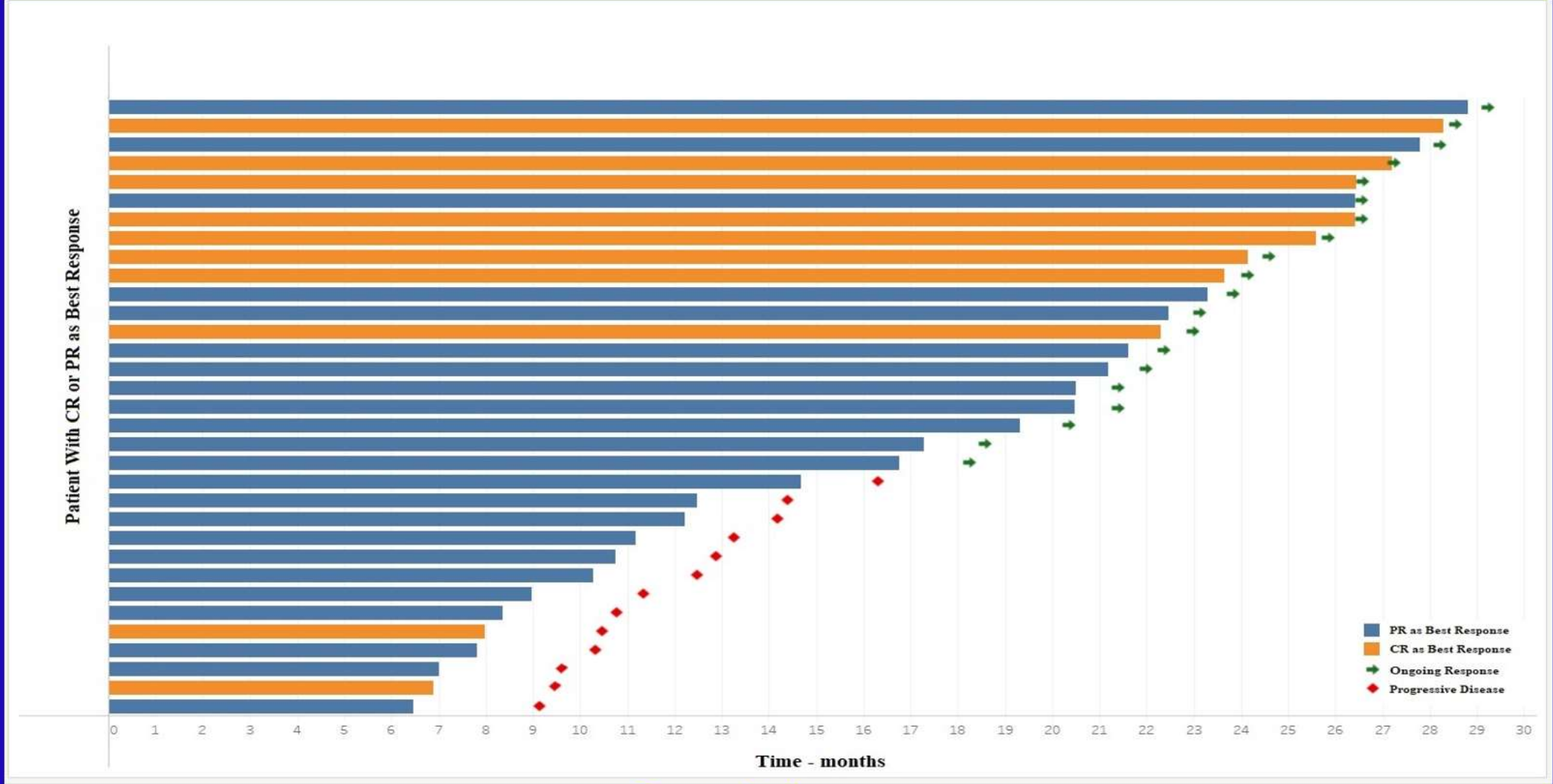
24 ay OS oranı: %23.5



Sonuçlar

Yanıt Süresi

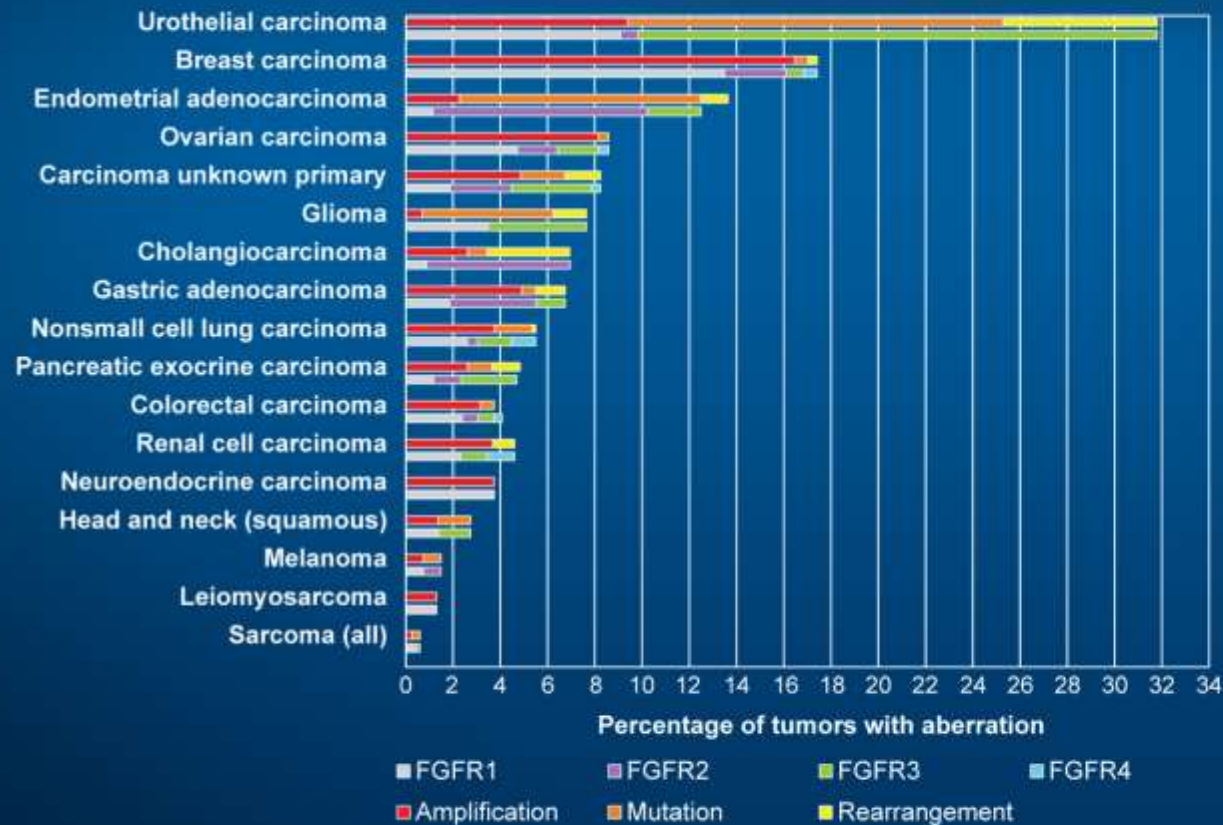
Yanıt alınan hastalar (CR veya PR)



Zaman (ay)

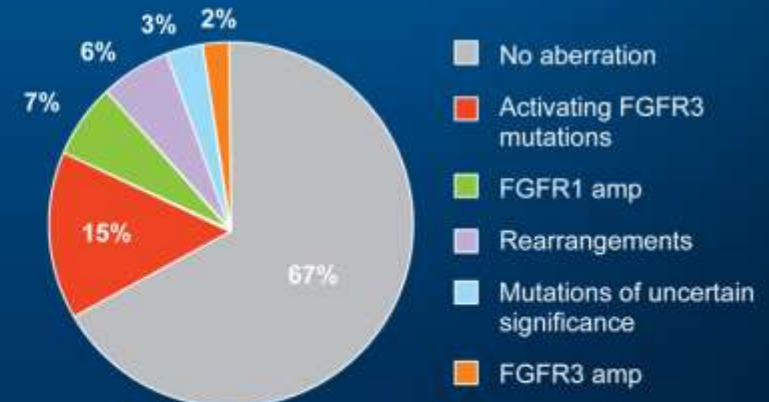
Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

The FGFR Mutation Landscape in Cancer: Analysis by Next-Generation Sequencing



- The FGF/FGFR signalling axis comprises 18 ligands, which bind to 4 highly conserved trans-membrane tyrosine kinase receptors (FGFR1, 2, 3 and 4)

Urothelial carcinomas (126 cases)



Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

Phase 2 BLC2001 Study Design



Patients

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

Primary hypothesis:

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

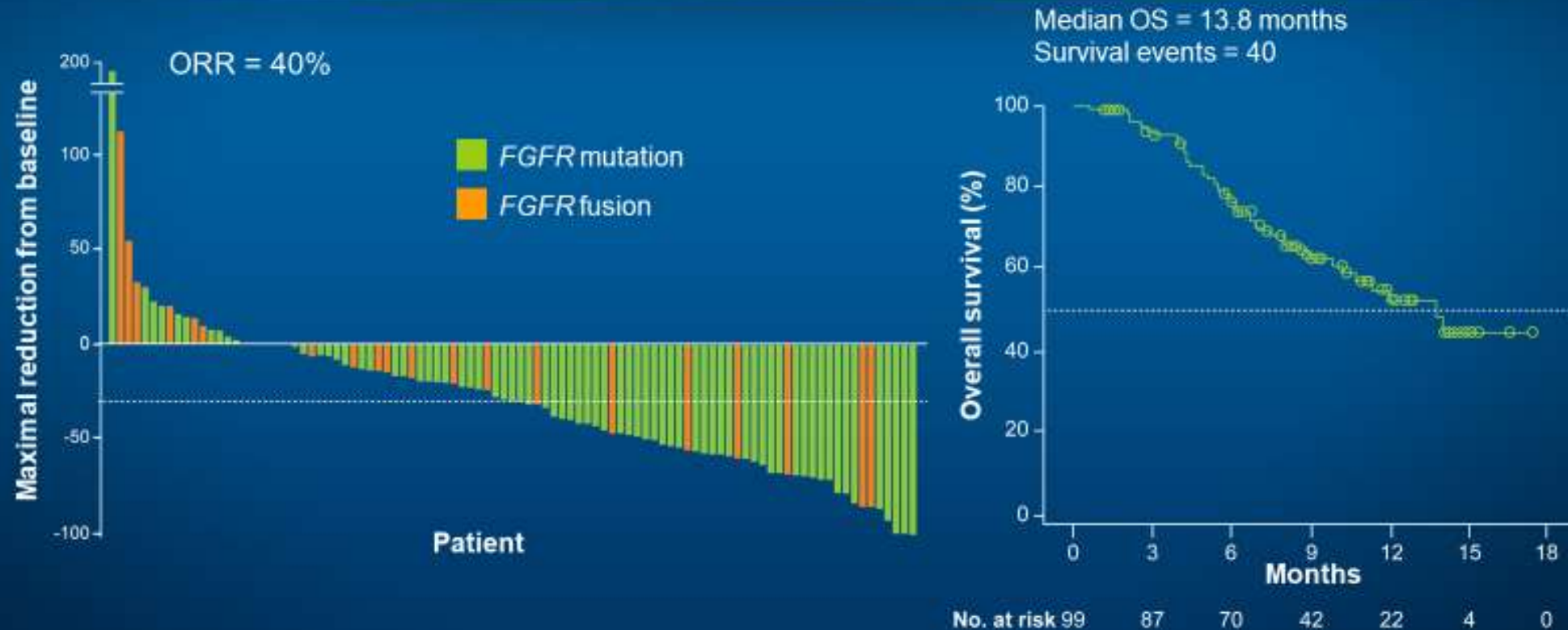
^aDose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.

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

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

Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

BLC2001: Response and Survival



Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

Phase III Trial Schema of Erdafitinib

Target accrual: 631

Eligibility

- Unresectable or metastatic urothelial cancer; transitional cell
- Cohort 1: Prior treatment with an anti-PD-(L) 1 agent as monotherapy or as combination therapy; no more than 2 prior lines of systemic treatment.
- Cohort 2: No prior treatment with an anti-PD-(L) 1 agent; only 1 line of prior systemic treatment

Primary endpoint: Overall survival



Cohort 1

Erdafitinib

Vinflunine or Docetaxel

Cohort 2

Erdafitinib

Pembrolizumab

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçenekleri



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2021 Bladder Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent-line systemic therapy for locally advanced or metastatic disease (Stage IV)^{g,h}
Participation in clinical trials of new agents is recommended.

Preferred regimens

- Enfortumab vedotin (category 1)^{26,27}
- Erdafitinib^f

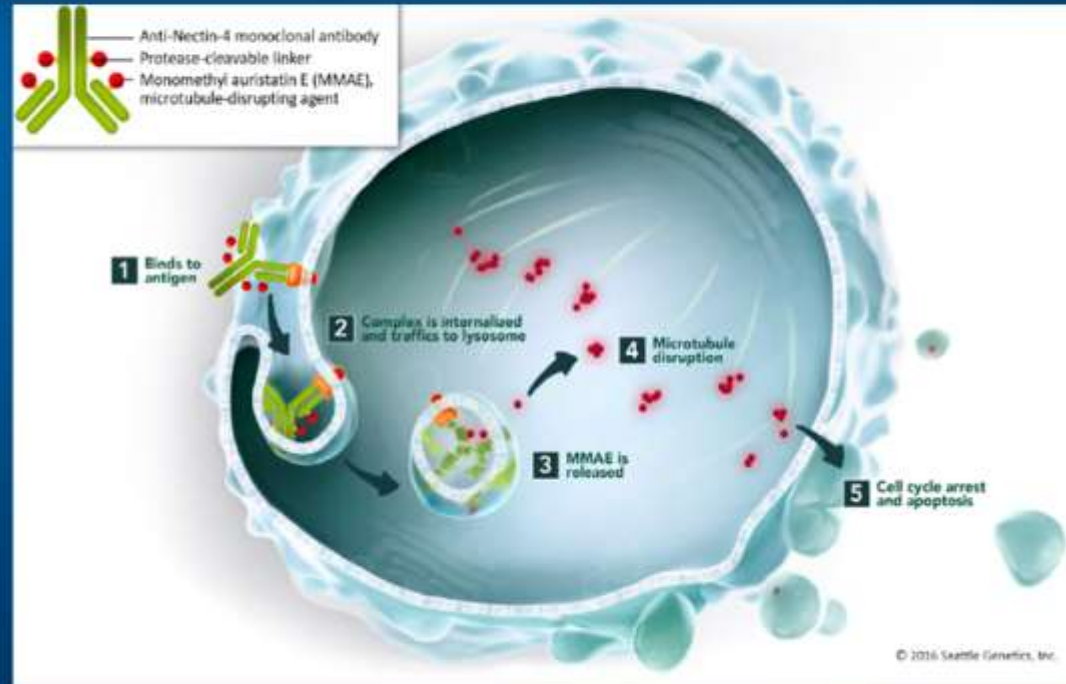
Other recommended regimens

- Gemcitabine¹⁵
- Paclitaxel²⁴ or docetaxel²⁵
- Ifosfamide, doxorubicin, and gemcitabine¹⁷
- Gemcitabine and paclitaxel¹⁶
- Gemcitabine and cisplatin⁴
- DDMVAC with growth factor support²

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçenekleri

Enfortumab Vedotin Is an Antibody-Drug Conjugate Targeting Nectin-4

- Nectin-4, a transmembrane cell adhesion molecule,^{1,2} was found to be highly expressed in 97% of mUC patient samples³
- Enfortumab vedotin (EV) is a fully humanized monoclonal antibody against Nectin-4 conjugated with the microtubule-disrupting agent monomethyl auristatin E by a protease-cleavable linker

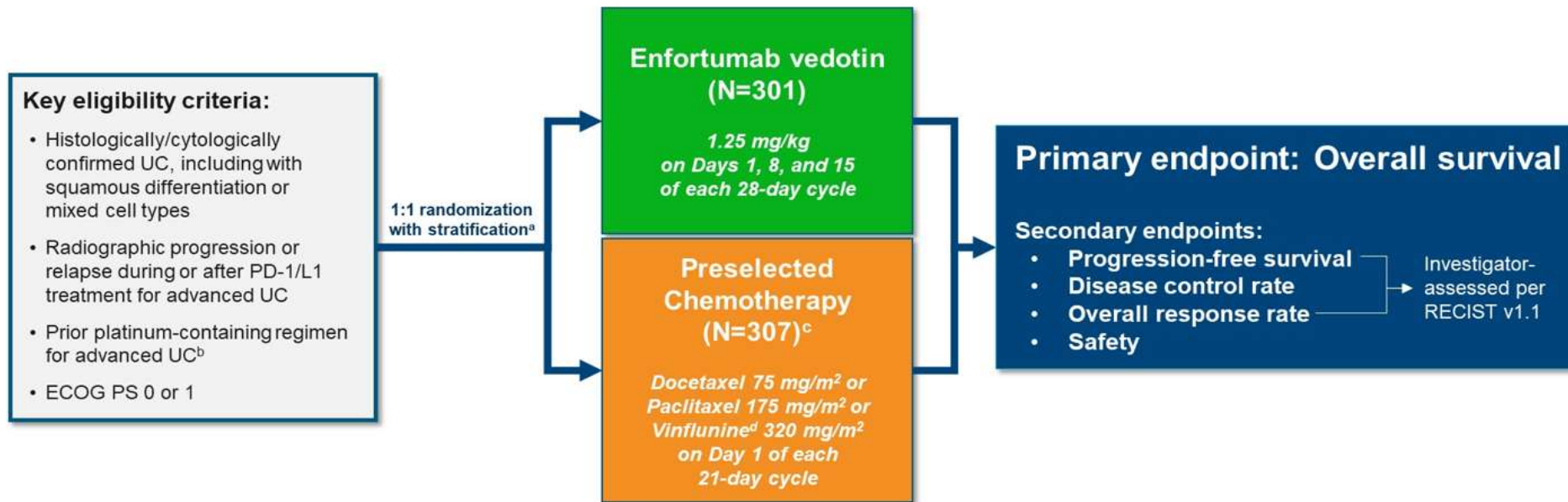


¹ Samanta D, Almo SC. *Cell Mol Life Sci* 2015;72:645-58; ² Challita-Eid PM et al. *Cancer Res* 2016;76:3003-13;

³ Petrylak DP et al. *J Clin Oncol* 2017;35:106.

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

EV-301 Open-Label Phase 3 Trial Design



^aStratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).

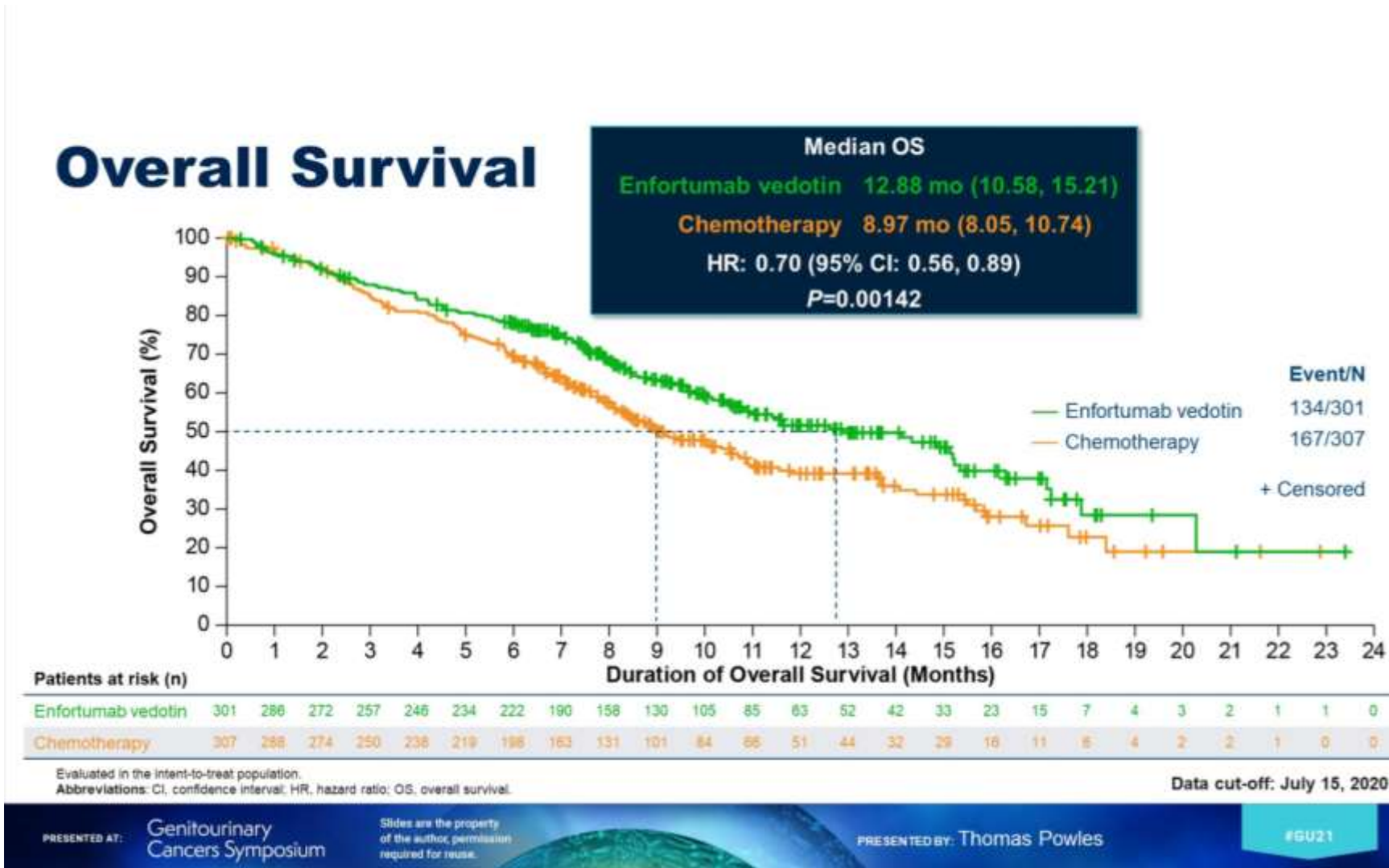
^bIf used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.

^cInvestigator selected prior to randomization.

^dIn countries where approved; overall proportion of patients receiving vinflunine capped at 35%.

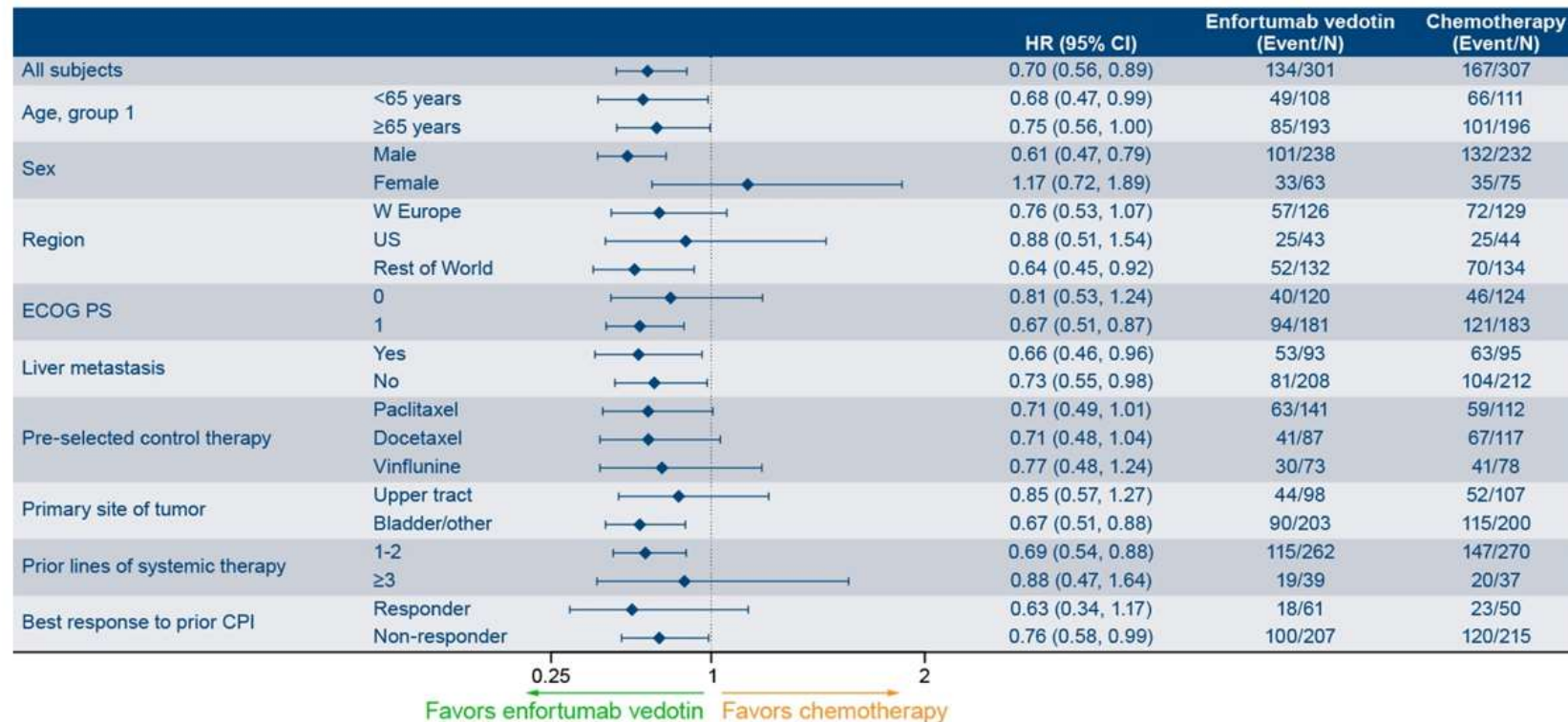
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi



Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

Overall Survival: Subgroup Analyses



Abbreviations: CI, confidence interval; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; US, United States; W, western.

Data cut-off: July 15, 2020

PRESENTED AT:

Genitourinary
Cancers Symposium

Slides are the property
of the author, permission
required for reuse.

PRESENTED BY: Thomas Powles

#GU21

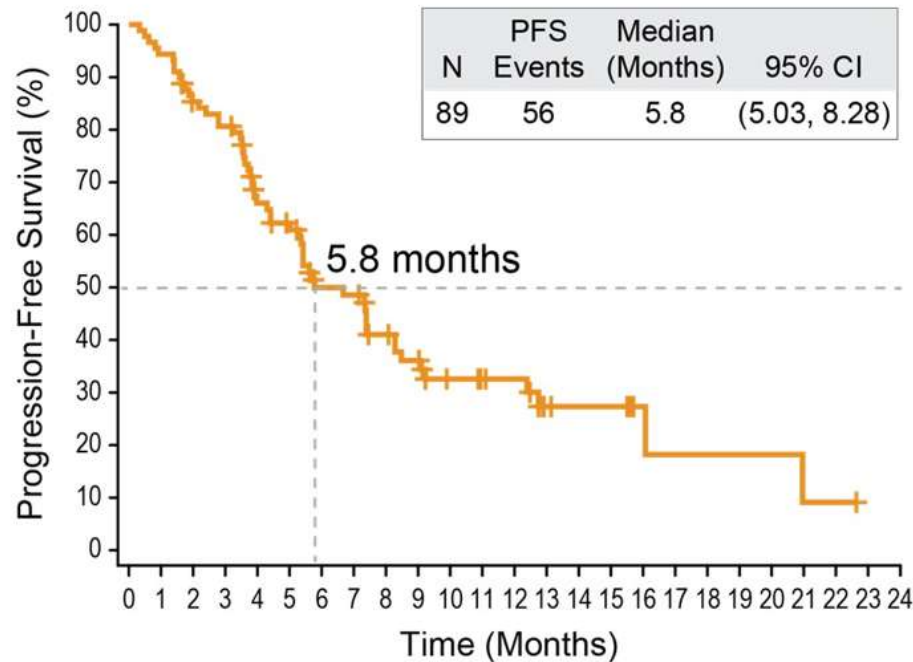
Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

**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)**

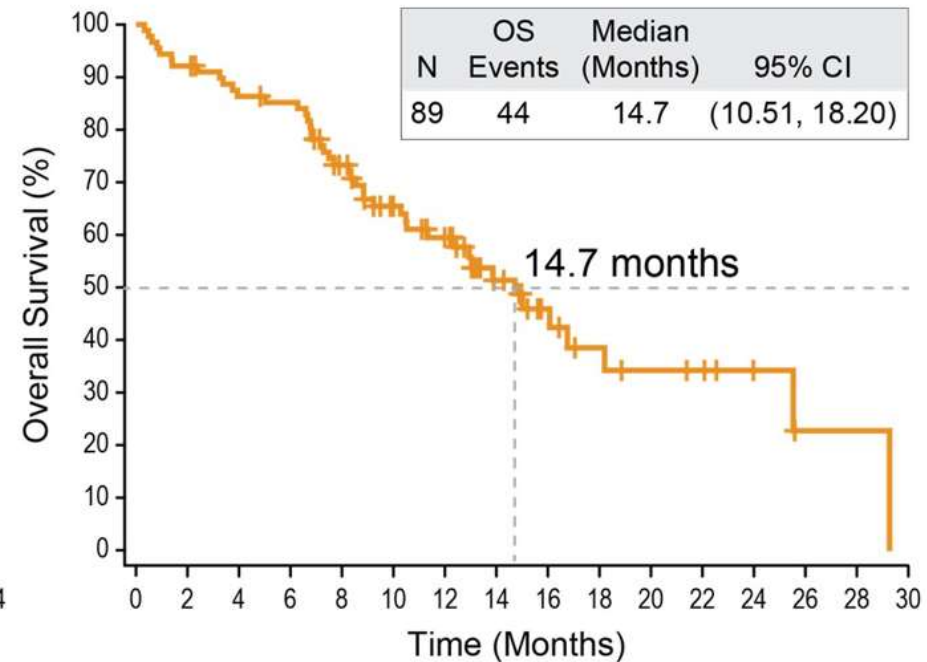
Arjun V. Balar, Bradley McGregor, Jonathan Rosenberg, Michiel S. van der Heijden, Se Hoon Park, Jae Lyun Lee, Michael R. Harrison, Elisabeth I. Heath, Mark N. Stein, Yohann Loriot, Andrea Necchi, Joyce Steinberg, Shang-Ying Liang, Eric Kim, Janet Trowbridge, Mary Campbell, Daniel P. Petrylak, and Evan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

Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

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



No. at Risk 89 84 73 69 52 47 35 34 26 22 16 14 13 7 6 6 3 2 2 2 2 1 1



No. at Risk 89 82 75 73 58 45 37 21 13 9 7 6 3 1 1

Median follow-up: 13.4 months

PRESENTED AT:

Genitourinary
Cancers Symposium

Slides are the property
of the author, permission
required for reuse.

PRESENTED BY: Arjun V. Balar

#GU21

Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC

TROPHY
U-01



Key Inclusion Criteria: Age ≥ 18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥ 30 mL/min,^{b,c} adequate hepatic function

Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

*Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor¹

^aExclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. ^bIn patients with CrCl ≥ 60 mL/min; ^cIn patients with creatinine clearance 50–60 mL/min. ^dFor patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days. CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan. 1. TRODELVY™ (sacituzumab govitecan-lzzy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

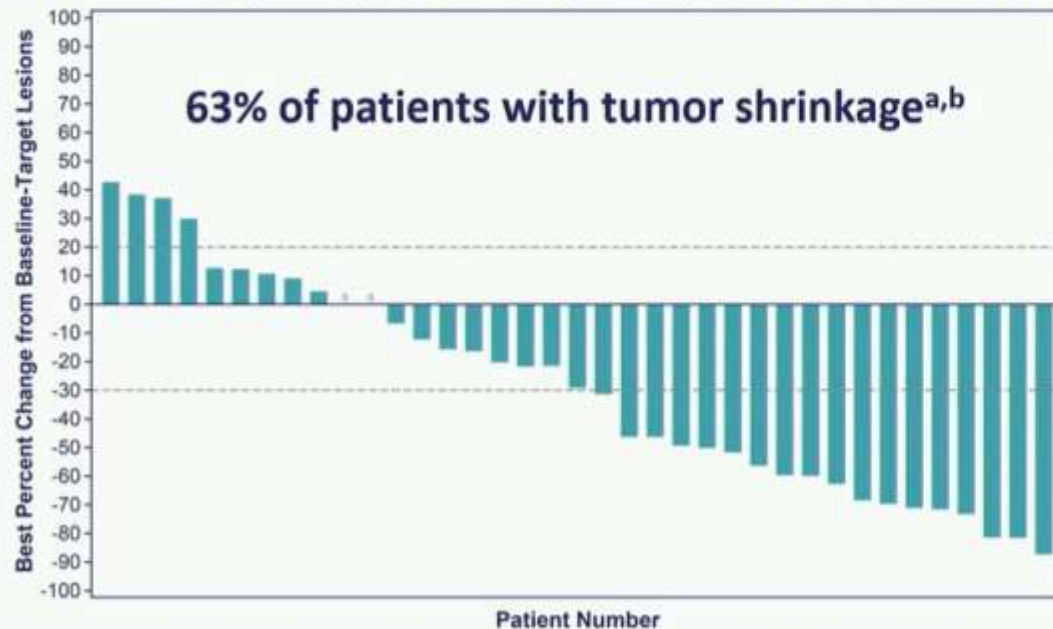
Abstract # 434. Content of this presentation is the property of the authors and licensed by ASCO. Permission required for reuse.

Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

Overall Response and Best % Change From Baseline in Tumor Size

†TROPHY
U-01

- Median follow-up: 5.8 months (data cutoff date: 2021-09-24)
- Median time to response: 2 months (1.3–2.8; n=14)
- Median DOR not yet reached: N/A (2.80-N/A)
- Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached



	Cohort 3 ^a (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	14 (34) [20.1-50.6]
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	4 (10)
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]	25 (61) [44.5-75.8]

^aResponses assessed by investigator in the intent-to-treat population. ^bPatients without post-baseline assessments are not shown here.
CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

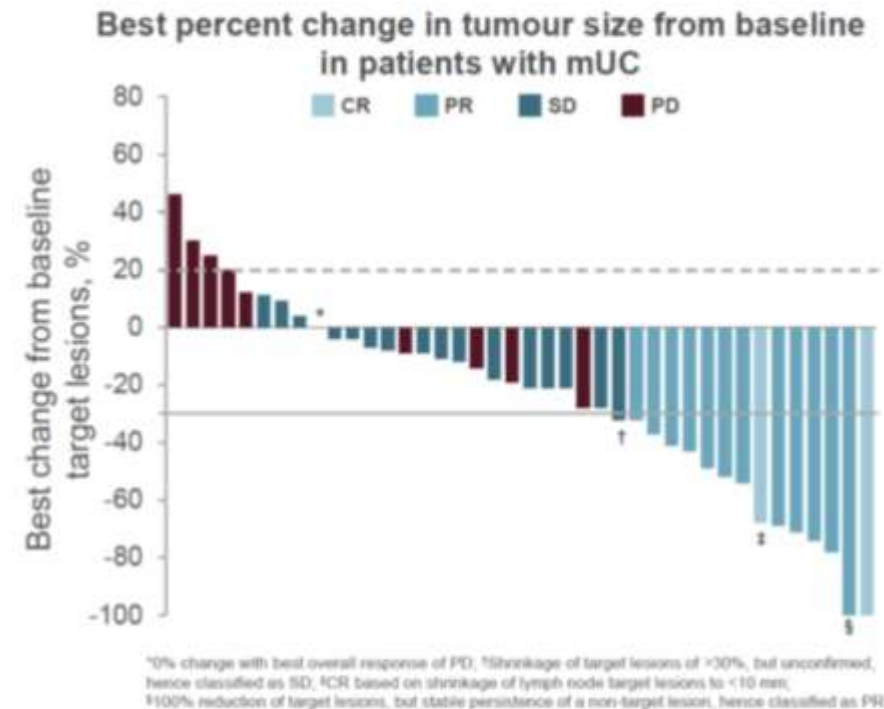
Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

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

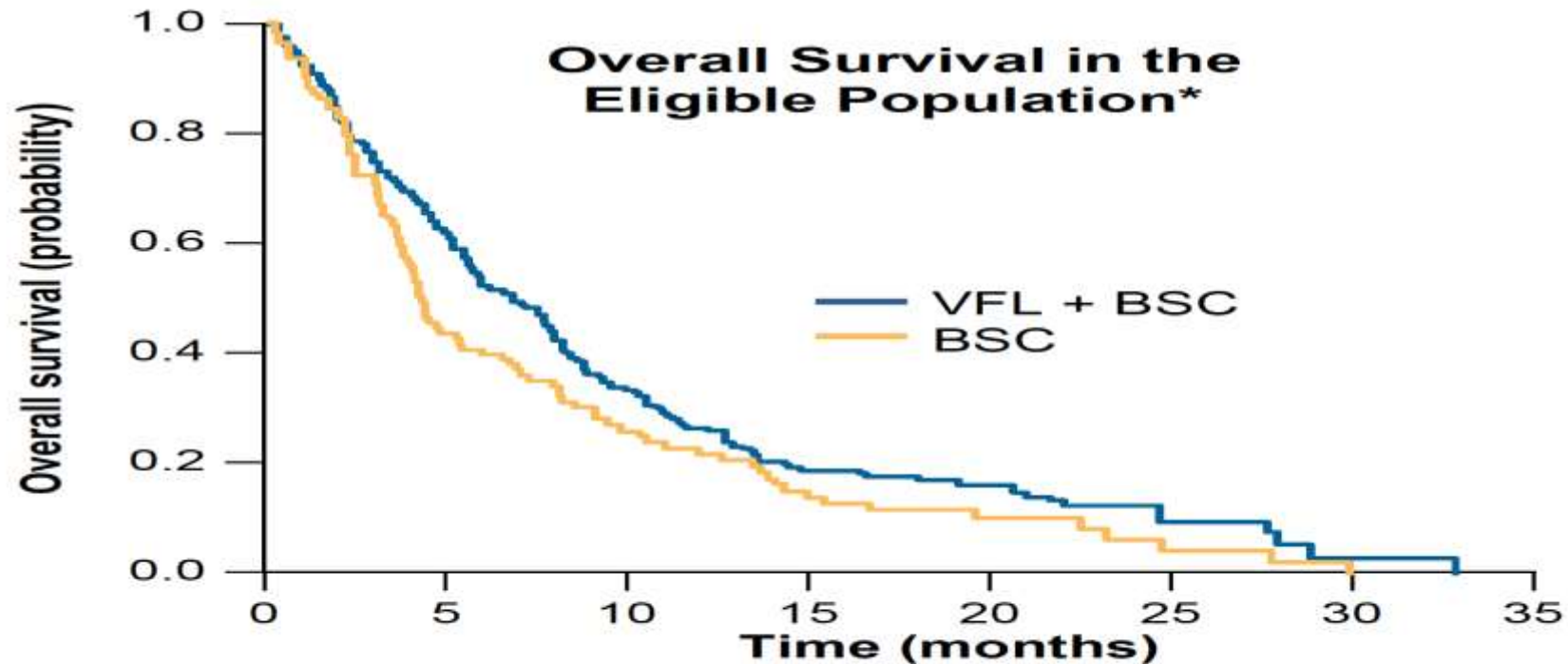


Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

Drug	Type of Study	Number of Patients	RR (%)	Time to Progression (mo)	Overall Survival (mo)
Paclitaxel ²³	Phase 2	31	10	2.2	7.2
Nanoparticle albumin-bound paclitaxel ²⁴	Phase 2	47	27.7	6	10.8
Pemetrexed ²⁵	Phase 2	13	8	—	—
Pemetrexed ²⁶	Phase 2	47	27.7	2.9	9.6
Docetaxel ²⁷	Phase 2	30	13.3	—	9
Gemcitabine ²⁸	Phase 2	28	11	4.9	8.7
Gemcitabine ²⁹	Phase 2	35	22.5	—	5
Vinflunine ³⁰	Phase 2	51	18	3	6.6
Vinflunine ³¹	Phase 2	151	15	2.8	8.2
Vinflunine ⁶	Phase 3	370	8.6	3	—
Oxaliplatin ³²	Phase 2	18	6	1.5	7
Irinotecan ³³	Phase 2	40	5	2.1	5.4
Ixabepilone ³⁴	Phase 2	42	11.9	2.7	8
Bortezomib ³⁵	Phase 2	25	0	1.4	5.7
Ifosfamide ³⁶	Phase 2	56	20	2.4	5.5
Lapatinib ³⁷	Phase 2	34	3	2	4.5
Topotecan ³⁸	Phase 2	44	9.1	1.5	6.3

Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

	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

Tedavi Seçenekleri

Standard Therapy in Advanced Urothelial Cancer *The Current Paradigm*

Setting		Regimen	Response Rate	Median Survival
First Line	Cisplatin-eligible	ddMVAC Gem/Cis PGC	40%–50%	12–15 months
	Cisplatin-ineligible	Gem/Carbo	36%–56%	7–9 months
	Platinum-ineligible or PD-L1 positive	Atezolizumab/Pembrolizumab	~24%	~15.9 months (atezolizumab)
Second Line		Atezolizumab, Nivolumab, Durvalumab, Avelumab, Pembrolizumab	15%–19%	7.9–10.3 months
		Single-agent chemo	~10%	5-8 months
Second/Third Line		Erdafitinib	40%	13.8 months
Third Line		Enfortumab Vedotin	44%	Median DOR 7.6 months

Loehrer PJ Sr, et al. *J Clin Oncol.* 1992; von der Maase H, et al. *J Clin Oncol.* 2000;
Bellmunt J, et al. *J Clin Oncol.* 2012; De Santis M, et al. *J Clin Oncol.* 2012; Linardou H, et al. *Urology.* 2004;
Nogué-Aliguer M, et al. *Cancer.* 2003; Rosenberg JE, et al. *Lancet.* 2016; Loriot Y, et al. *N Engl J Med.* 2019; Rosenberg J, et al. *J Clin Oncol.* 2019.

Sonuç

- ❑ Evre IV mesane kanserinde birinci basamak tedavide platin bazlı kemoterapi ilk seçenek
- ❑ Platin bazlı kemoterapi sonrası klinik yarar(CR/PR/SD) gören hastalarda idame tedavi olarak Avelumab
- ❑ Sisplatin alamayacak hastalarda carboplatin+ gemitabin kemoterapi kombinasyonu klinik yarar alanlarda Avelumab idame tedavi olarak önerilir
- ❑ Sisplatin alamayacak hastalarda PD-L1 pozitif olanlar(CPS $\geq$ 10 ya da PD-L1> 5) Pemrolizumab/Atezolizumab önerilebilir
- ❑ Platin bazlı kemoterapi alamayacak hastalarda birinci basamak tedavide (ECOG PS $\geq$ 2, komorbidite vs.) PD-L1 düzeyinden bağımsız Pemrolizumab/Atezolizumab önerilebilir
- ❑ Mesane kanseri ikinci basamak tedavi seçenekleri; immün kontrol noktası inhibitörleri birinci basamakta almamışsa verilebilir. FGFR mutasyonu olan hastalar için erdafitinib bir seçenektir
- ❑ Mesane kanseri ikinci basamak tedavi seçenekleri; platin bazlı kemoterapi alamayan immün kontrol noktası inhibitörleri alan hastalar için Enfortumab Vedotin bir seçenektir
- ❑ Mesane kanseri Enfortumab Vedotin sonrası tedavi seçenekleri; sacituzumab govitecan, vinflunine ve taksan vb. kemoterapi seçenekleri