Metastatik Mesane ve Üst Üriner Sistem Kanserlerinde İdeal Tedavi Algoritması

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Tıbbi Onkoloji

Ders Planı

- Mesane Kanseri İnsidans ve Mortalite

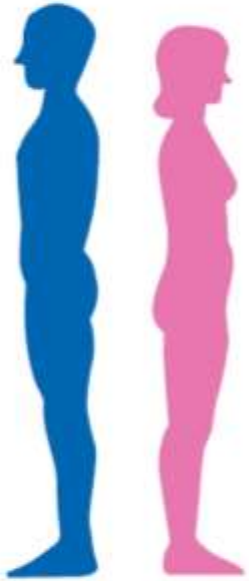
Metastatik Hastalık

- Sisplatine uygun hastada birinci basamak
- Sisplatine uygun olmayan hastada birinci basamak
- Platin sonrası, ikinci basamak tedavi
- İkinci basamak 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%**

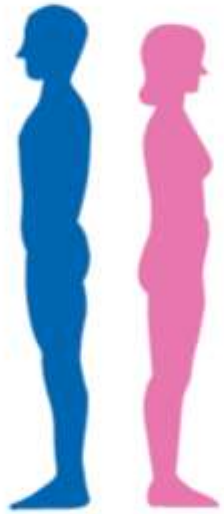


CA CANCER J CLIN 2019;69:7-34

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%**

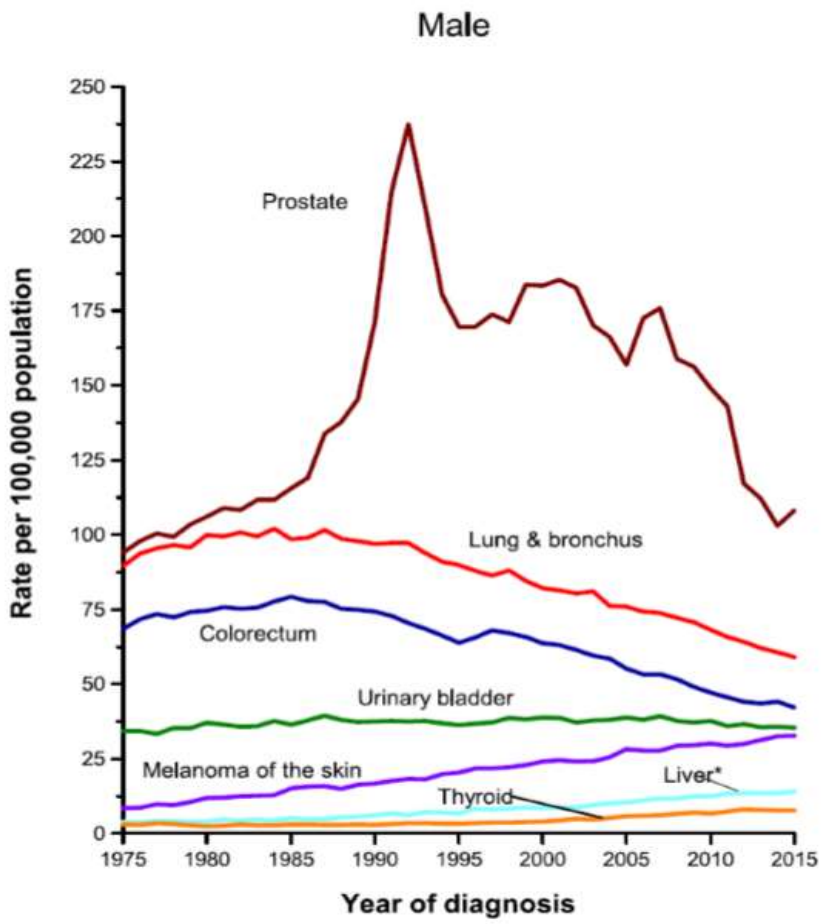


CA CANCER J CLIN 2019;69:7–34

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 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	Tumor invades lamina propria (subepithelial connective tissue)
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

LN = lymph node

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Bladder Cancer (Version 1.2019).

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

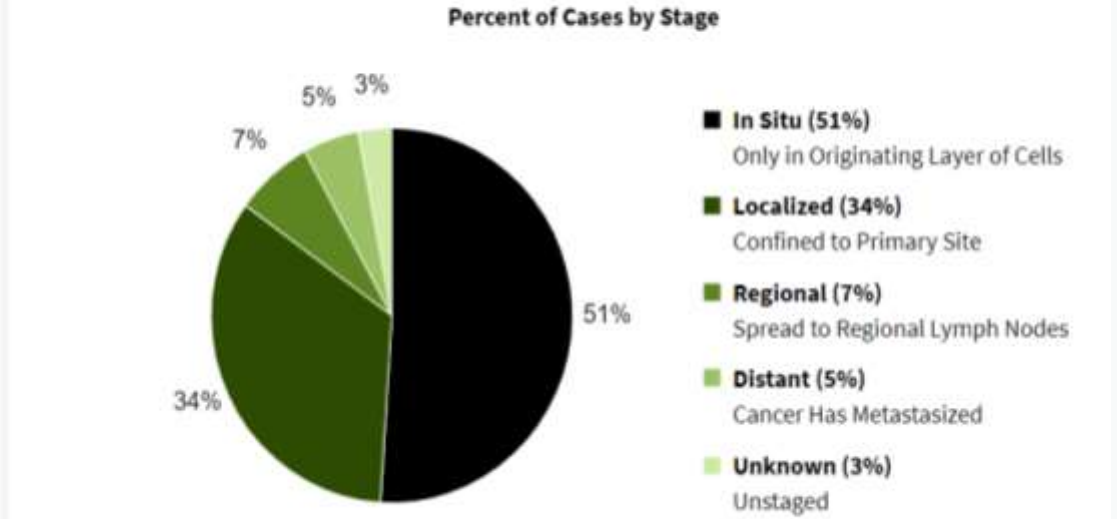
Table 2. AJCC Prognostic Groups

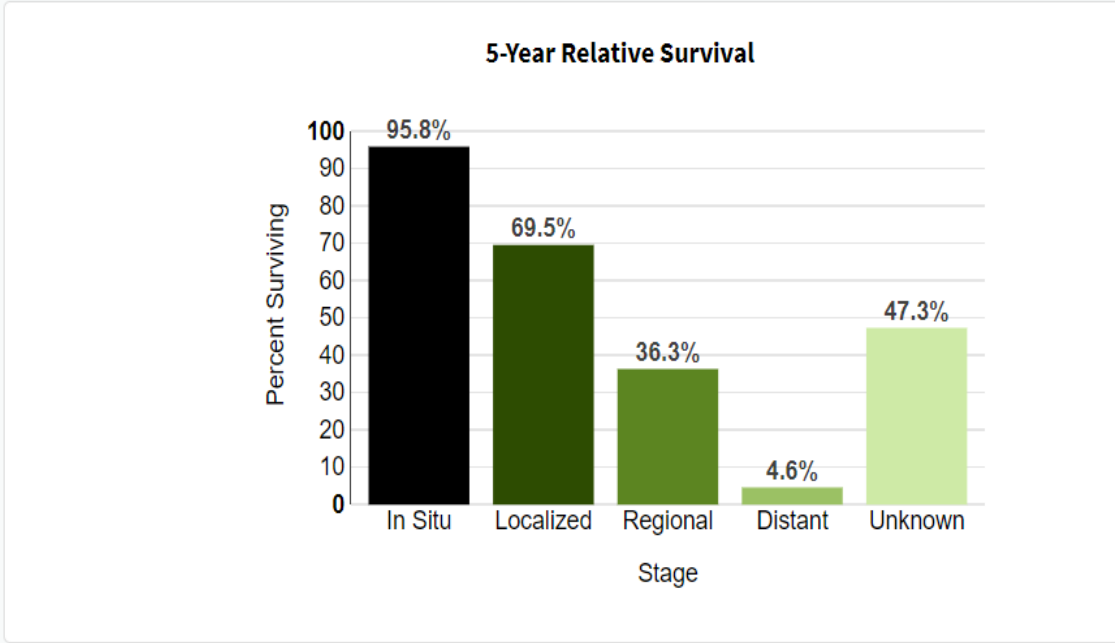
	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage IIIA	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
	T1-T4a	N1	M0
Stage IIIB	T1-T4a	N2,N3	M0
Stage IVA	T4b	Any N	M0
	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Continued

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

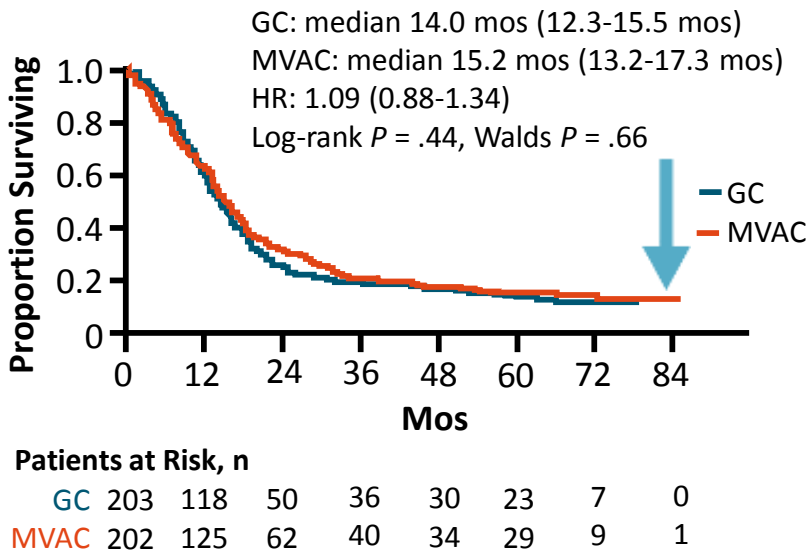
Sisplatin Uygun

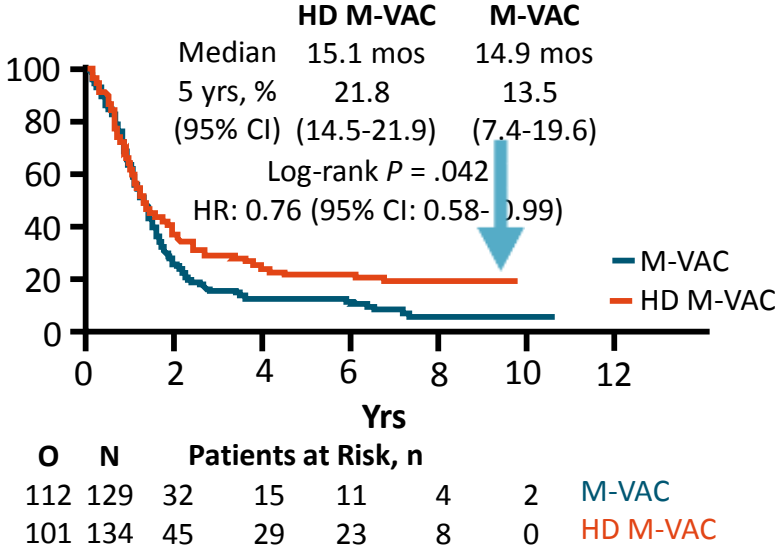
Gemcitabine + Cisplatin[1,2]
ORR: 49%
CR: 12%
Median OS: 14.0 mos

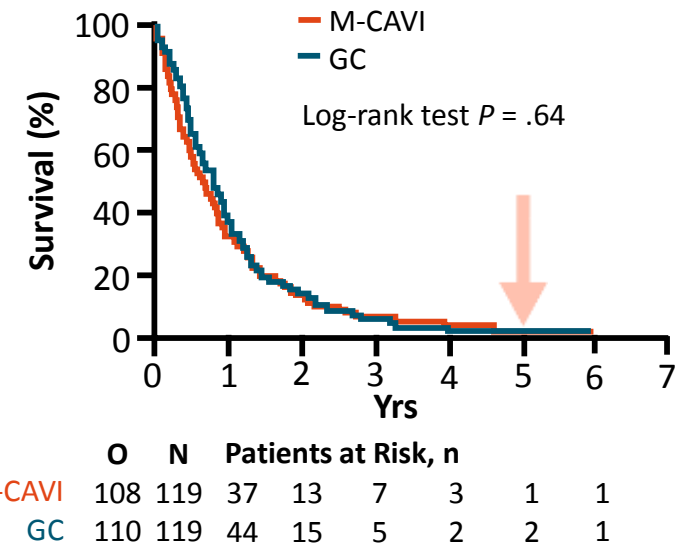
Dose Dense MVAC[3]
ORR: 72%
CR: 25%
Median OS: 15.1 mos

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 Mesane Kanseri Birinci Basamak Tedavi Seçimi

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PRINCIPLES OF SYSTEMIC THERAPY

First-line systemic therapy for locally advanced or metastatic disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cisplatin[4] (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 carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11] • Atezolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[14] (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** • Gemcitabine[15] • Gemcitabine and paclitaxel[16] **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[17] (for patients with good kidney function and good PS)

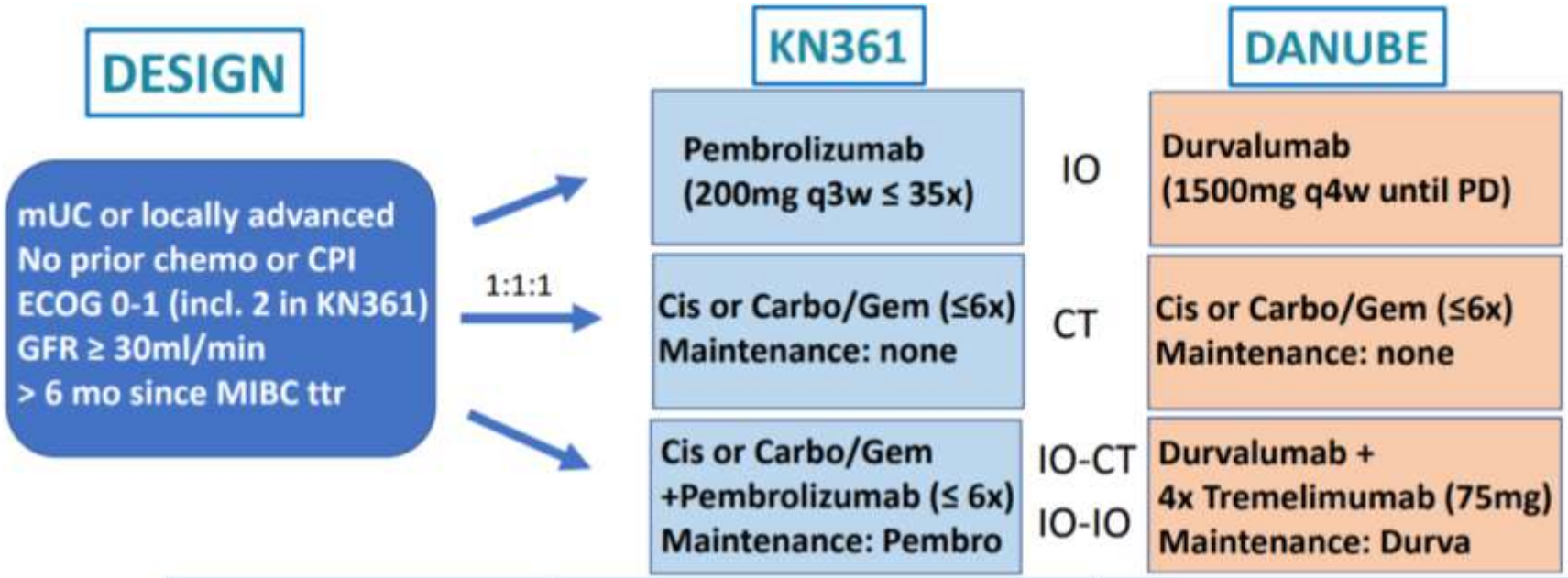
- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully 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 < 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)

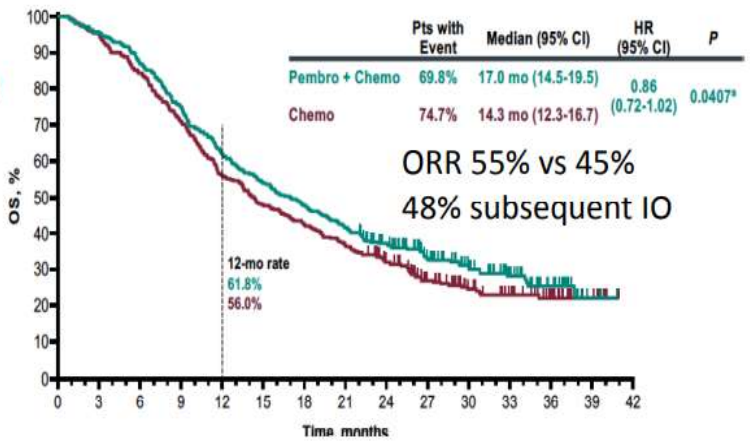
Metastatik Mesane Kanseri Birinci Basamak
Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

Overall survival

Combination vs Chemo

TOTAL population (ITT)

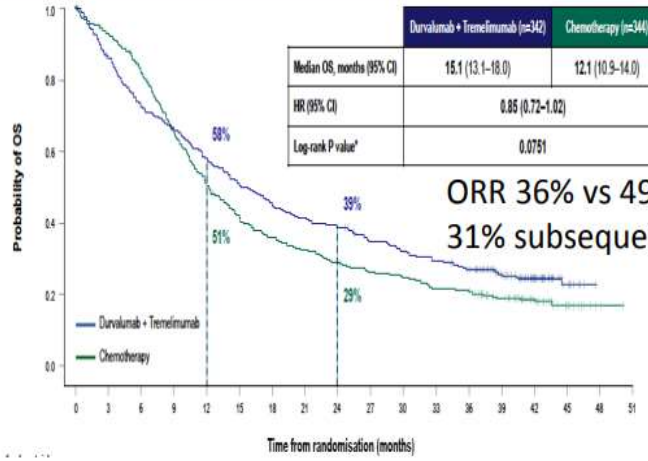
KEYNOTE 361 –IO-CT vs CT (1˚EP)



ORR 55% vs 45%

48% subsequent IO

DANUBE – IO-IO vs CT (1˚EP)

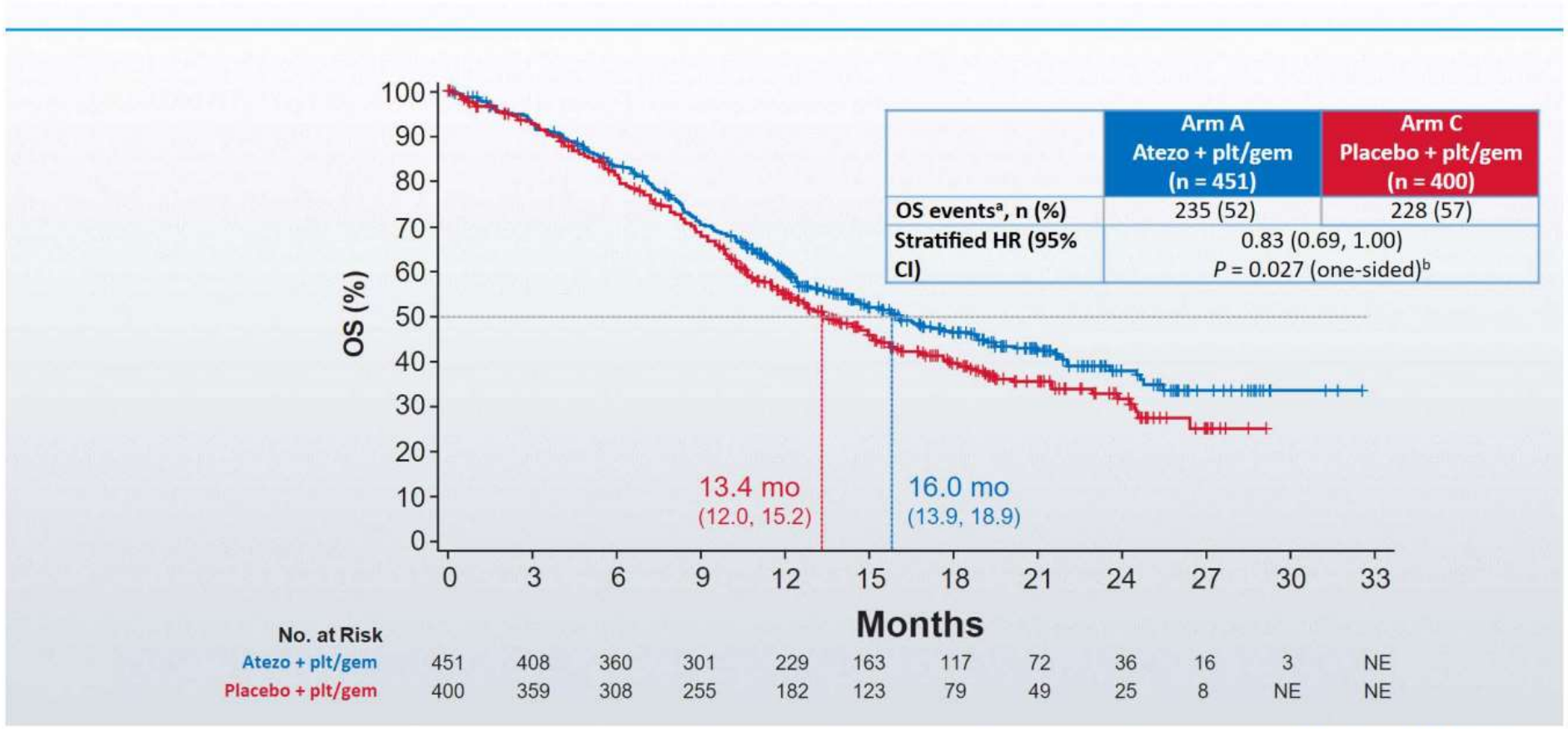


ORR 36% vs 49%

31% subsequent IO

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

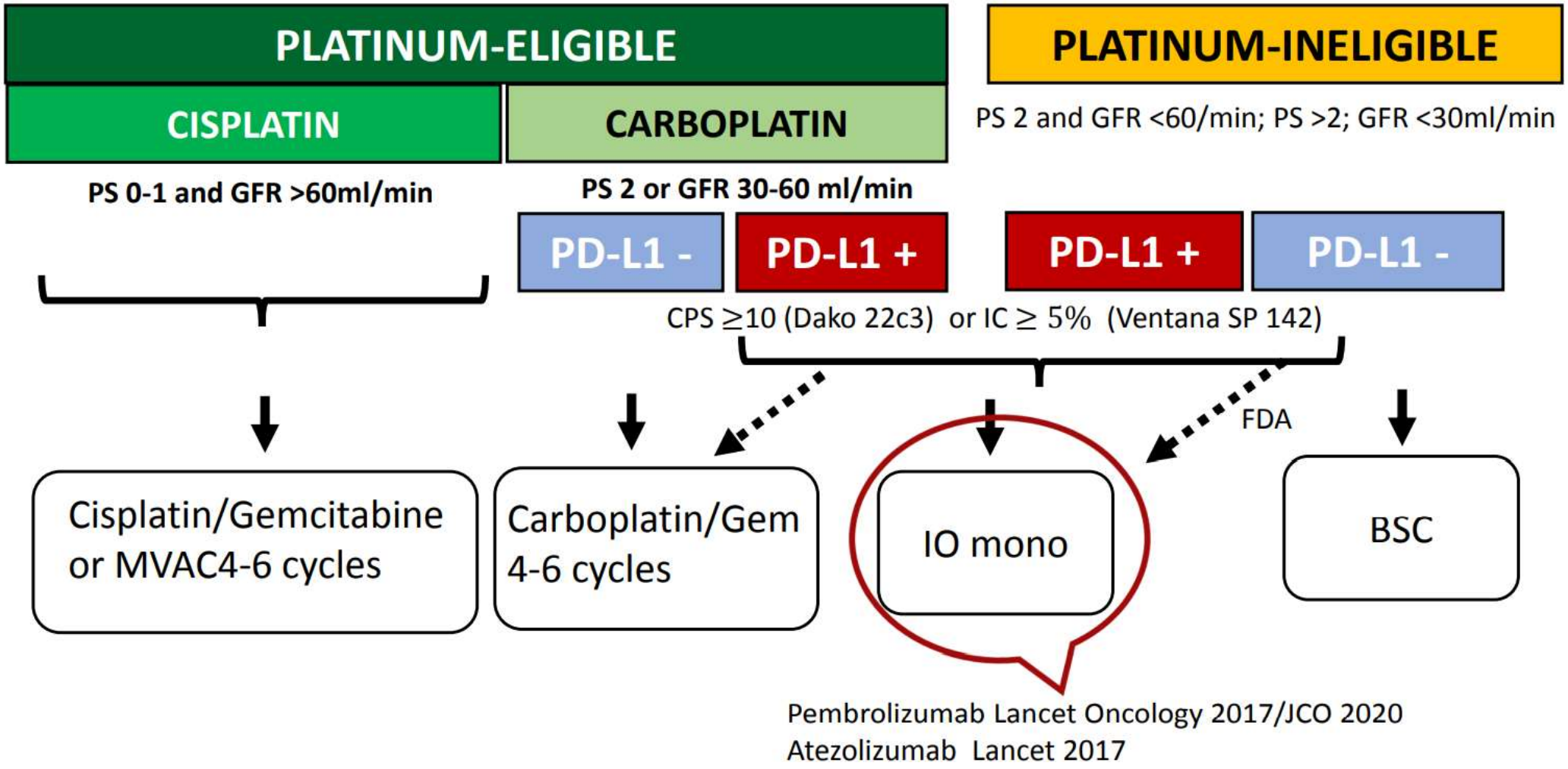
IMvigor130 Interim OS: ITT (Arm A vs Arm C)



	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]	

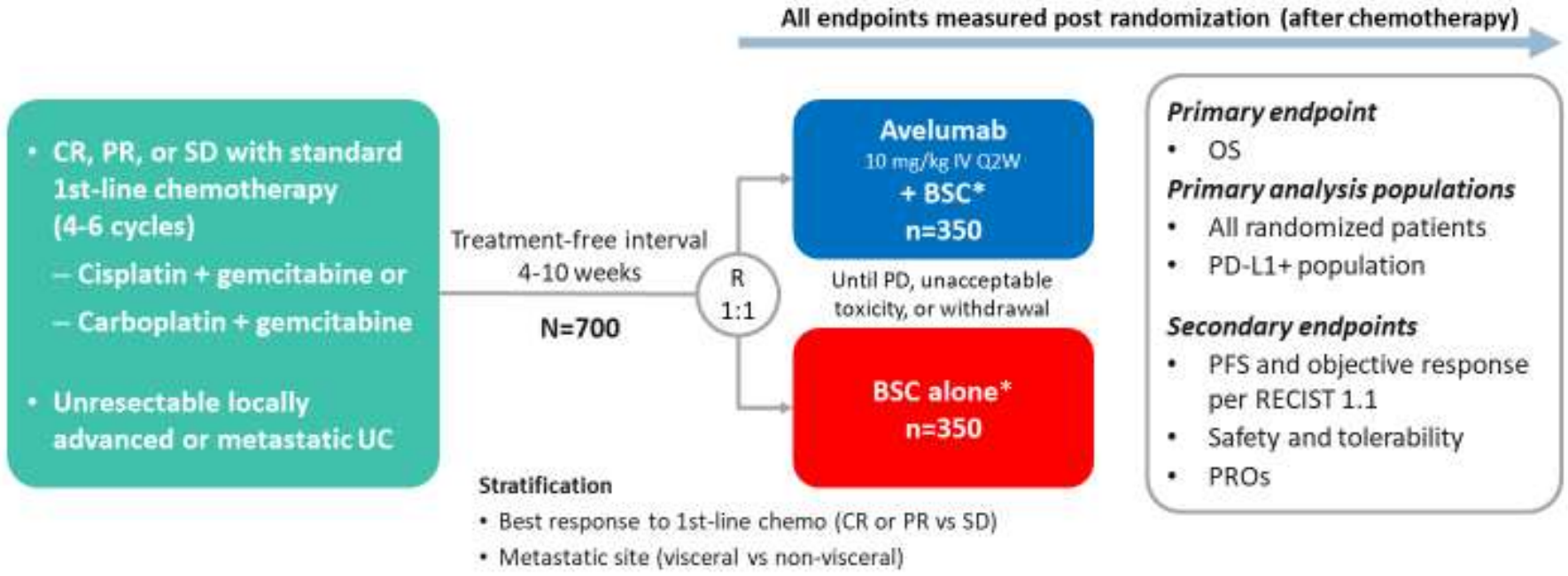
Galsky et al, Lancet 2020 May; Grande ESMO 2019

Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçimi



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

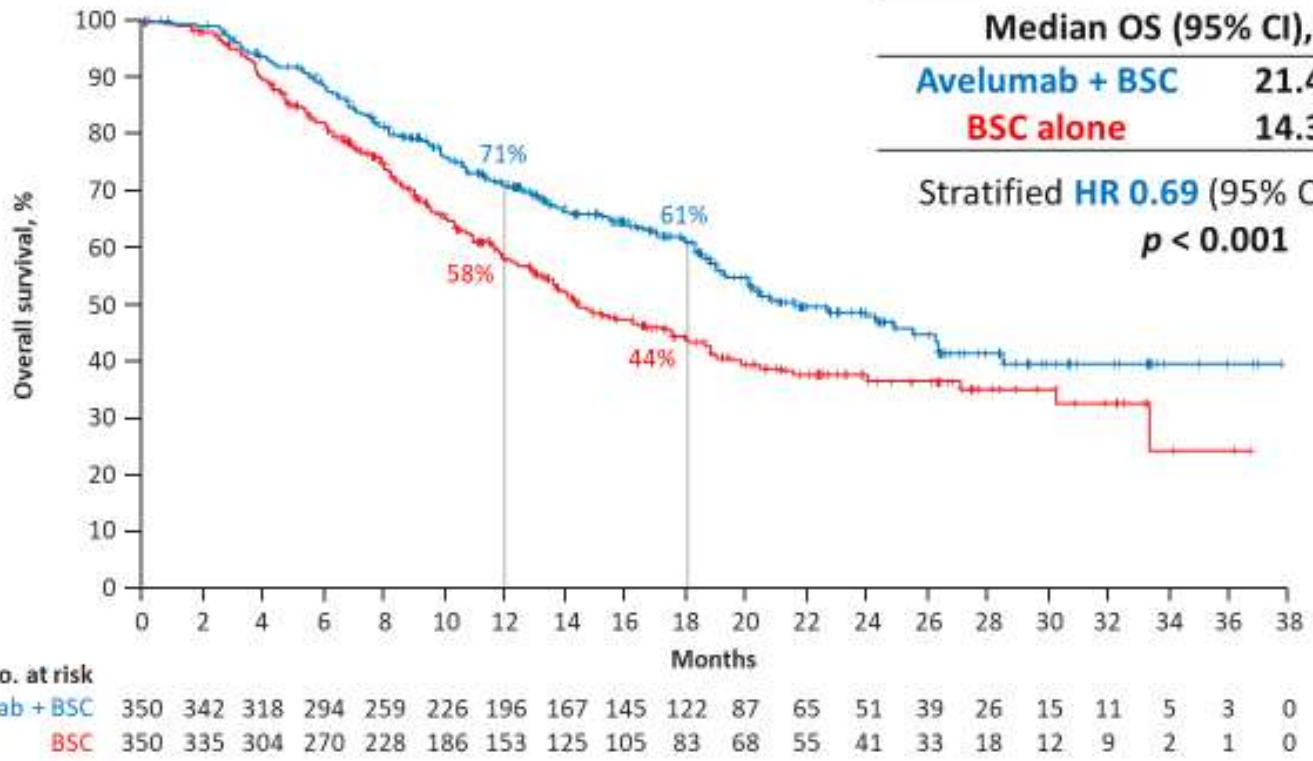
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

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**

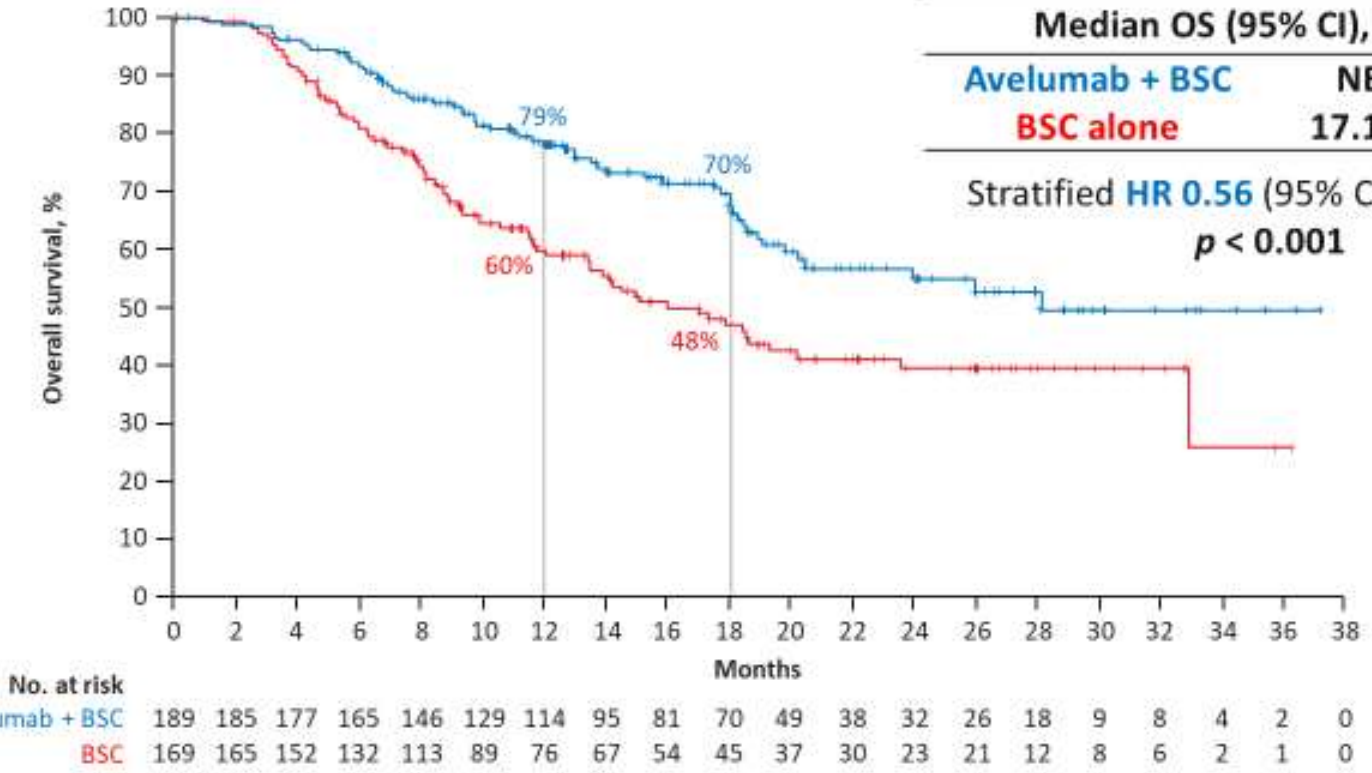
OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

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)

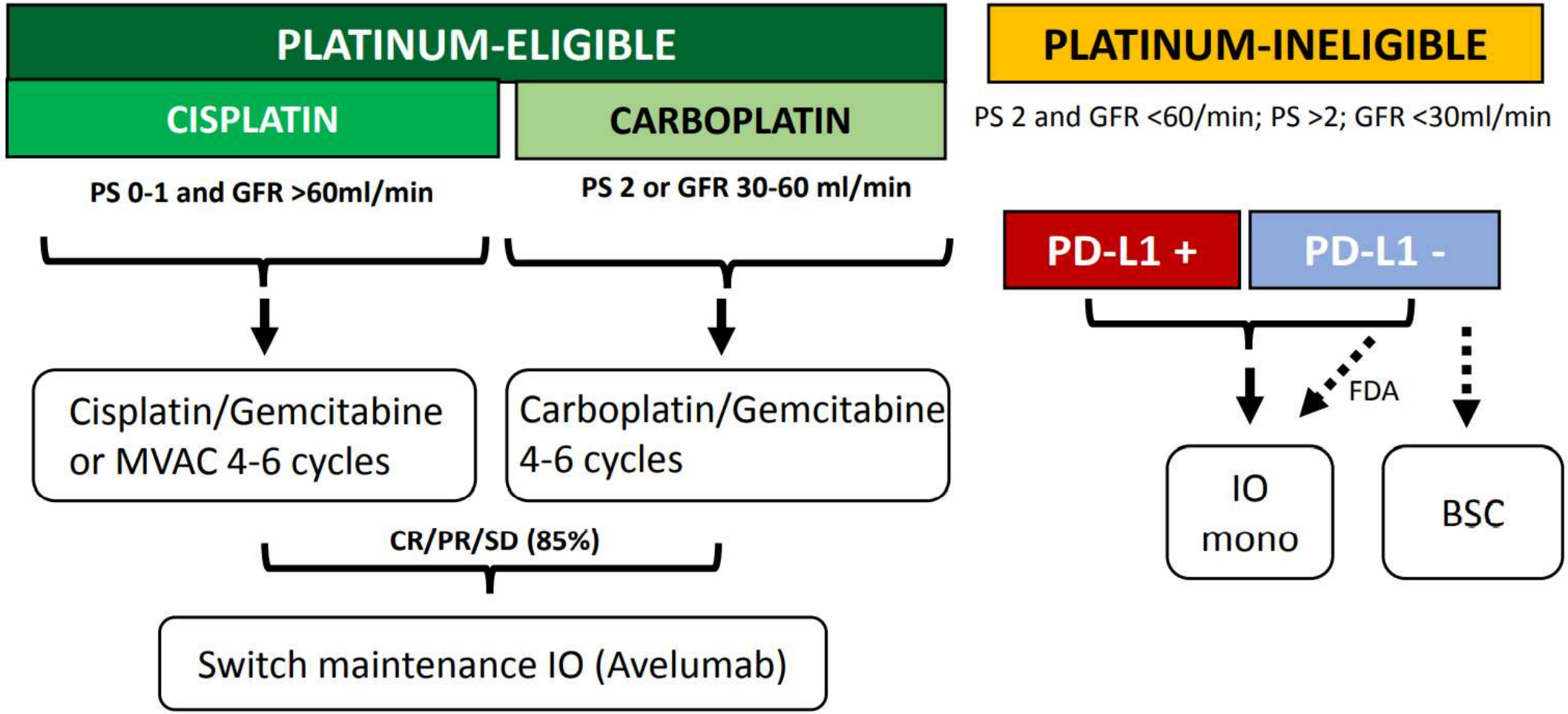
***p* < 0.001**

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 Seçimi



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İmmün kontrol noktası inhibitörleri

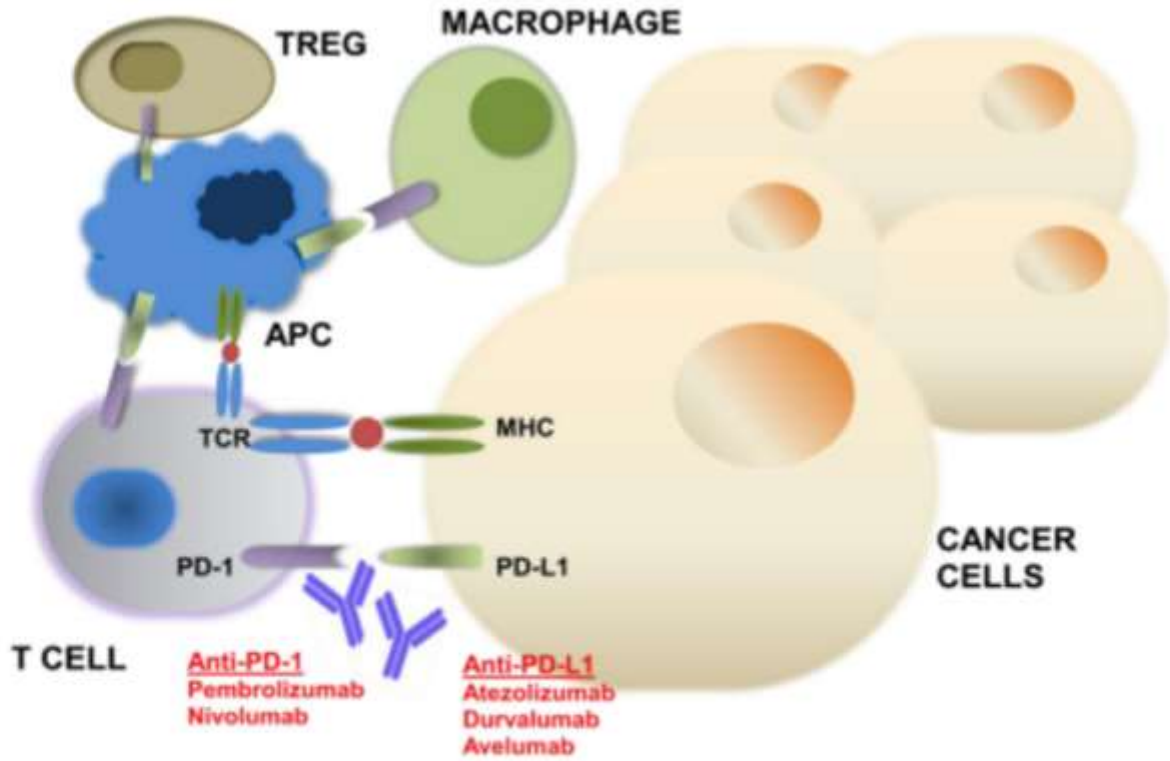
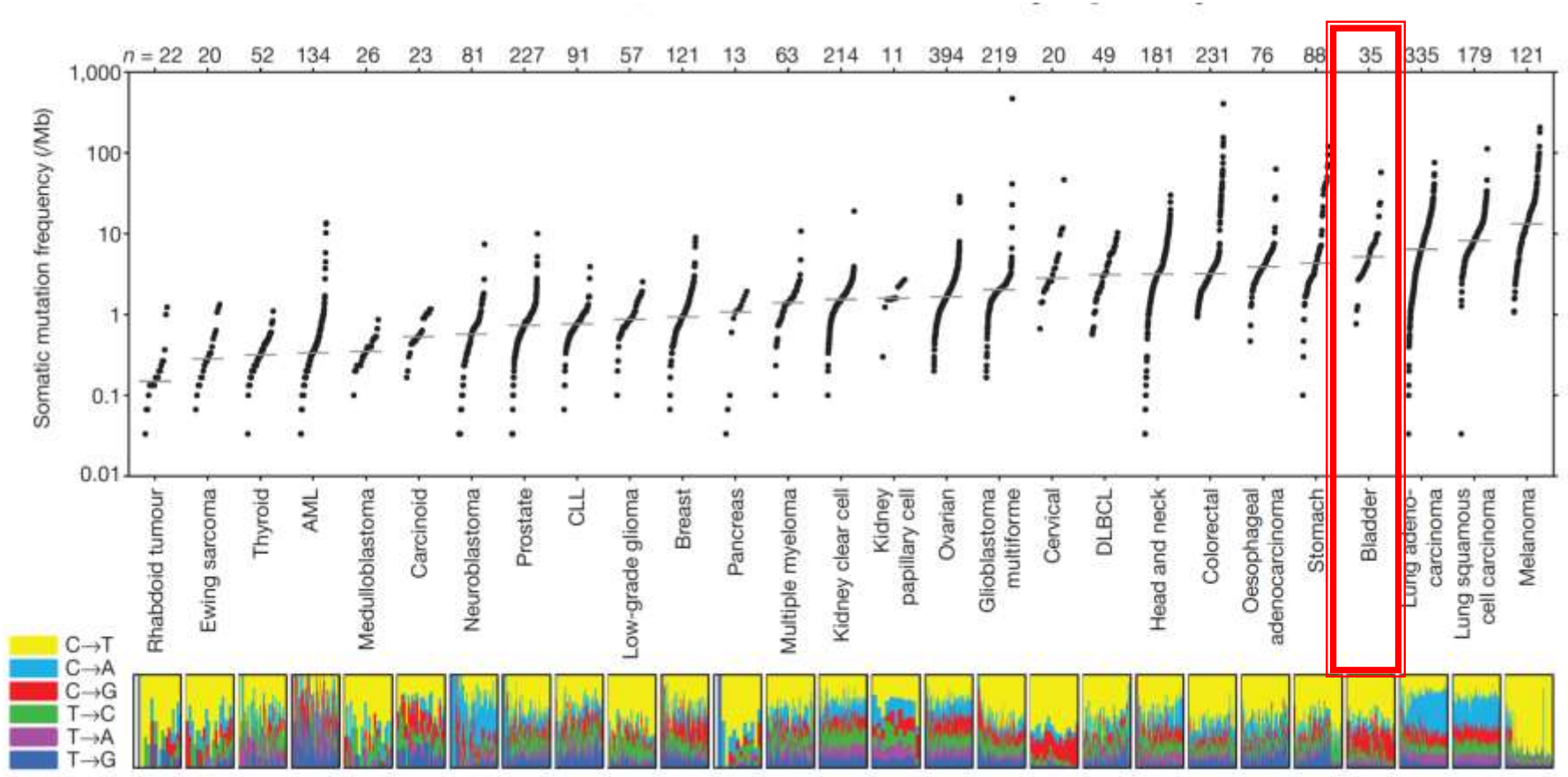


Fig. 1 Mechanism of action of PD-1 and PD-L1 inhibitors. The programmed cell death 1 (PD-1) receptor is expressed on activated T cells, B cells, macrophages, regulatory T cells (Tregs), and natural killer (NK) cells. Binding of PD-1 to its B7 family of ligands, programmed death ligand 1 (PD-L1 or B7-H1)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

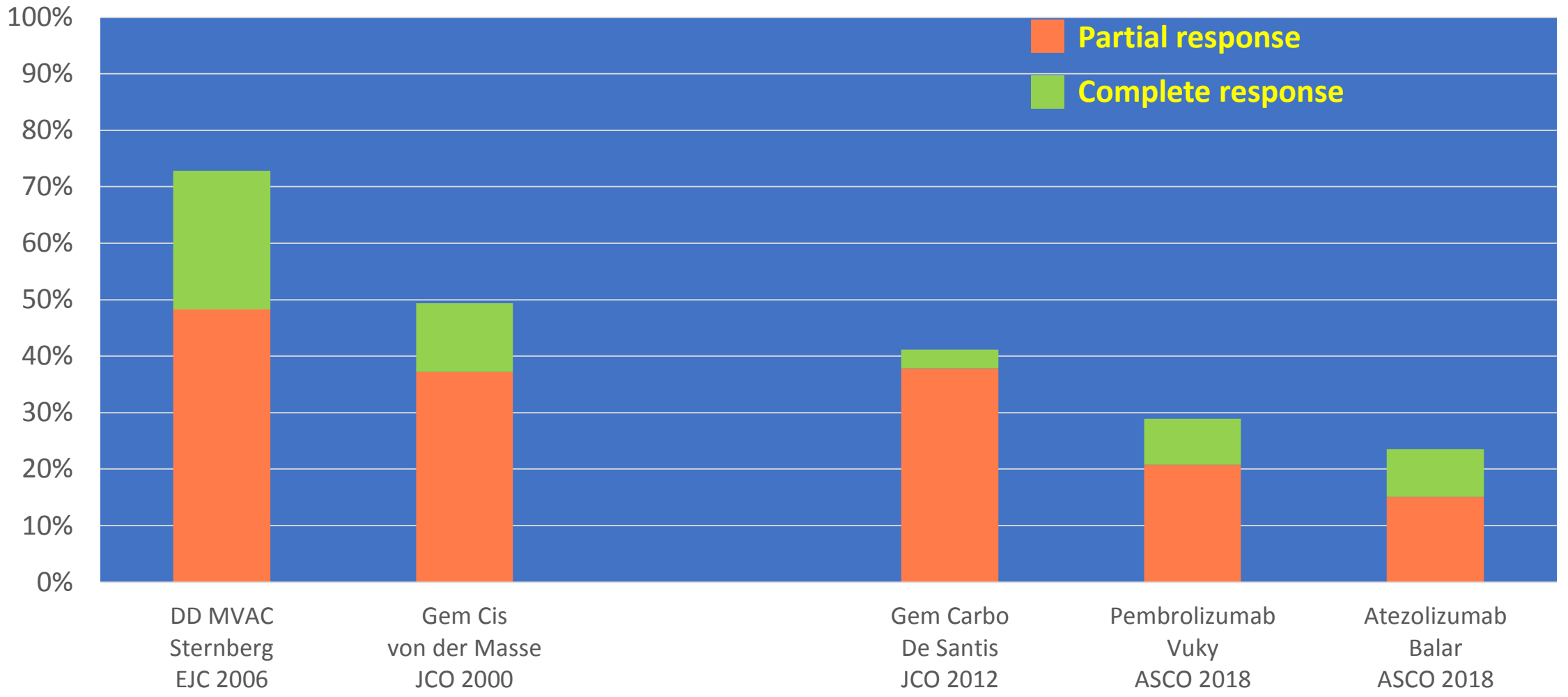
Mesane Kanserinde Tümör Mutasyon Yükü



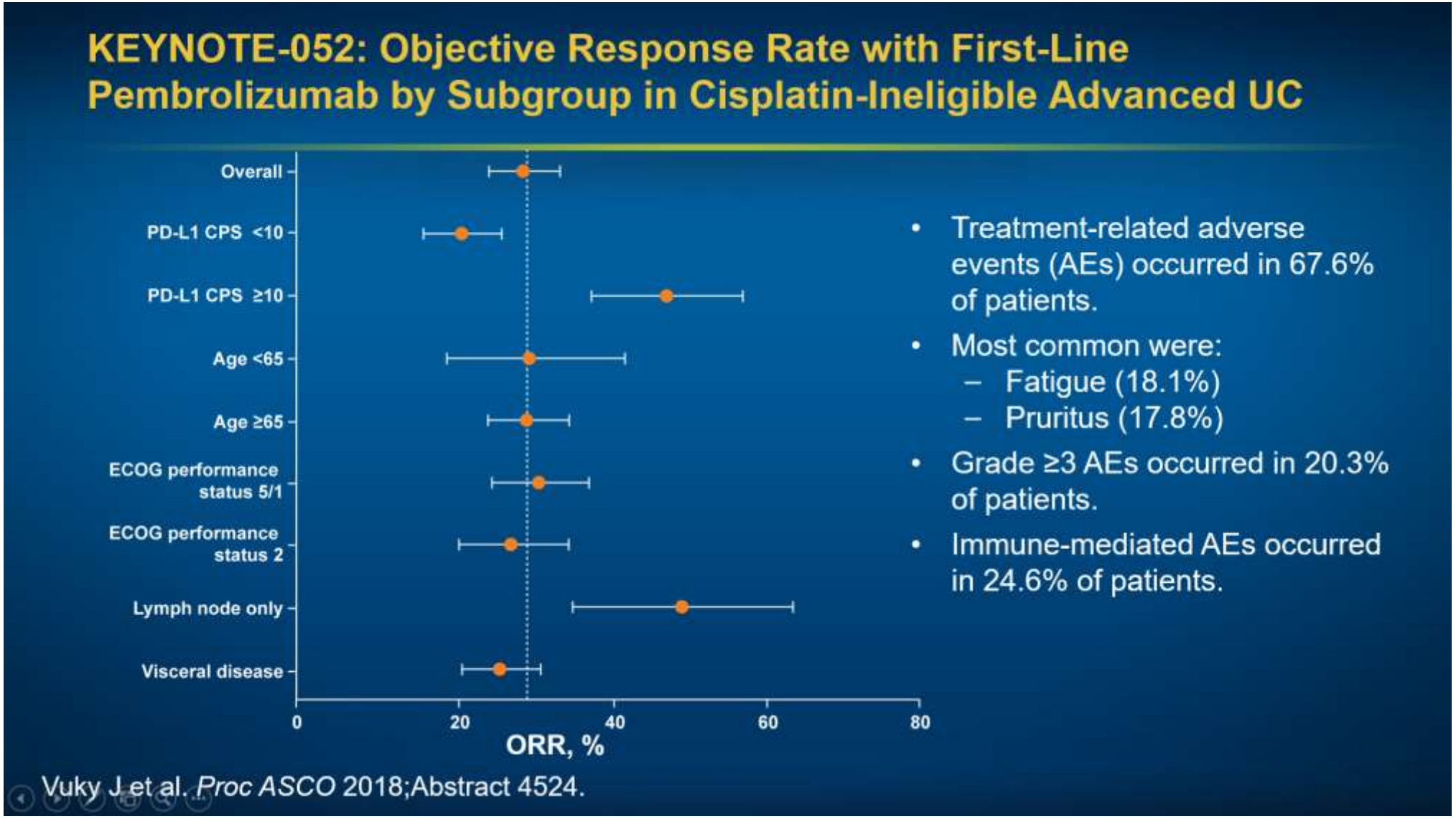
Lawrence et al. Nature 2013

- 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 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

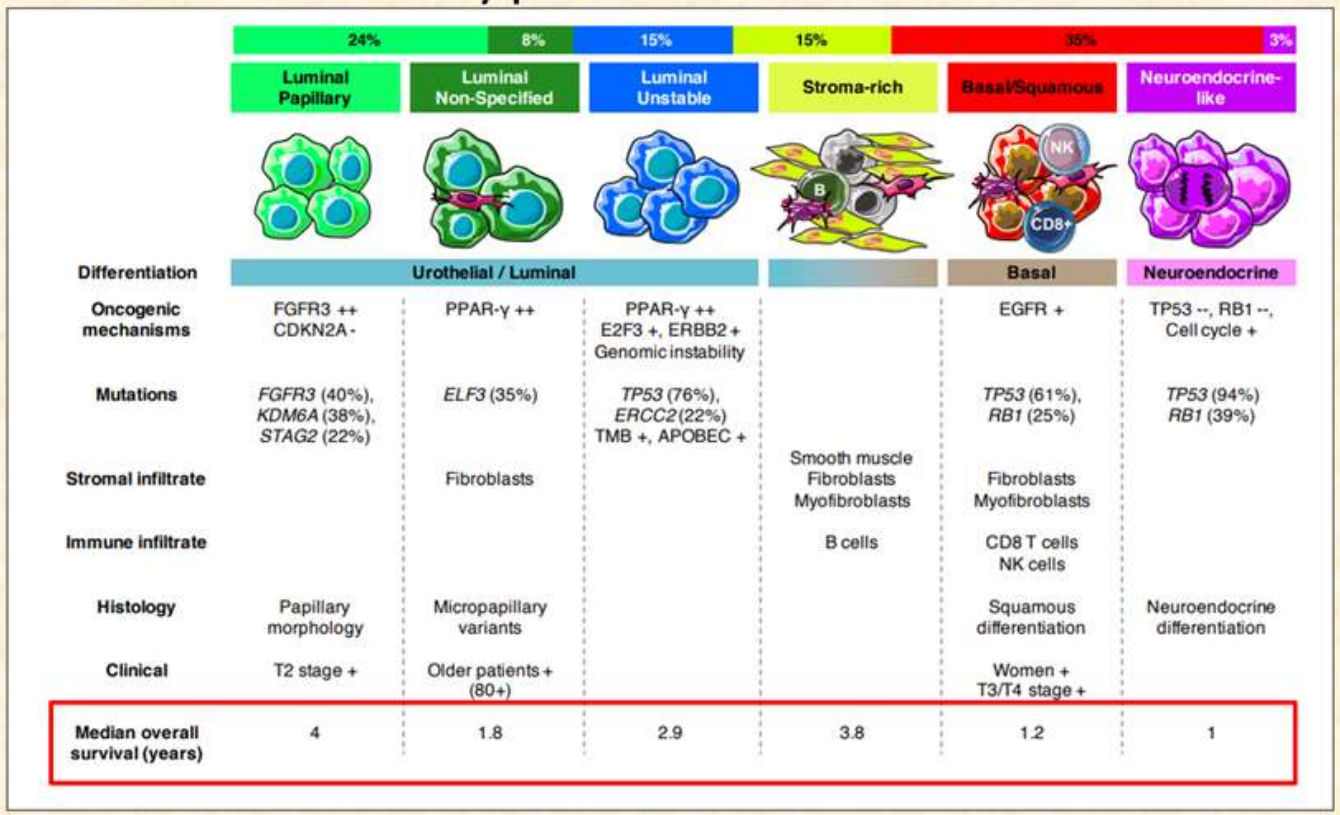
IMvigor210: Efficacy of Atezolizumab in First-Line Cisplatin-Ineligible or Platinum-Treated Locally Advanced or Metastatic UC

	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.

Metastatik Mesane Kanseri
İkinci Basamak Tedavi Seçenekleri

Bladder cancer is composed of multiple tumors: Subtypes within subtypes



	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.

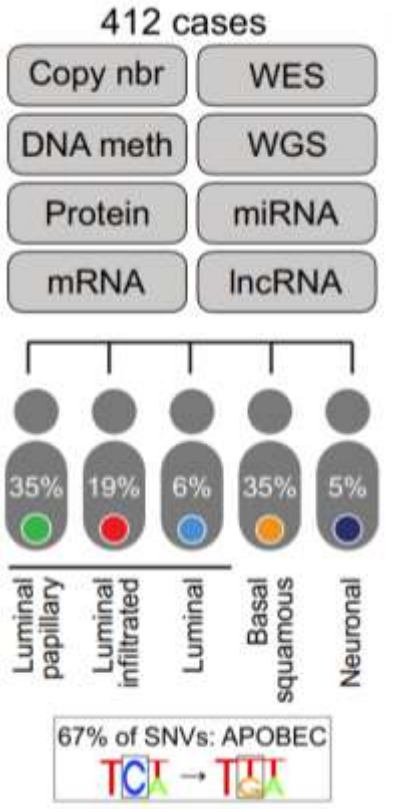
Courtesy of Arlene O. Siefker-Radtke, MD

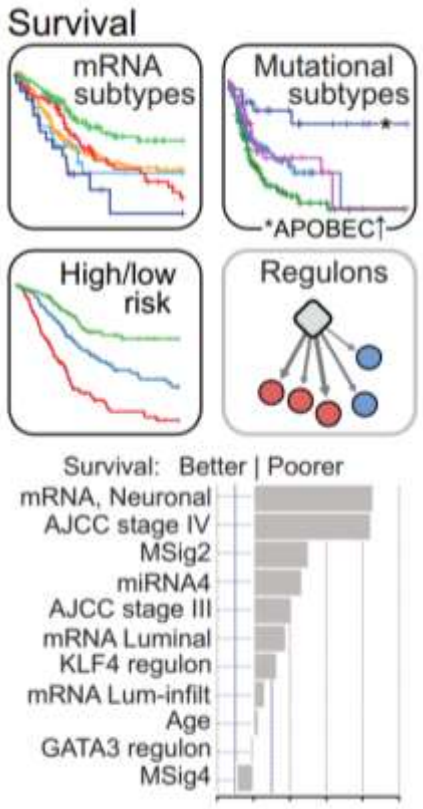
Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

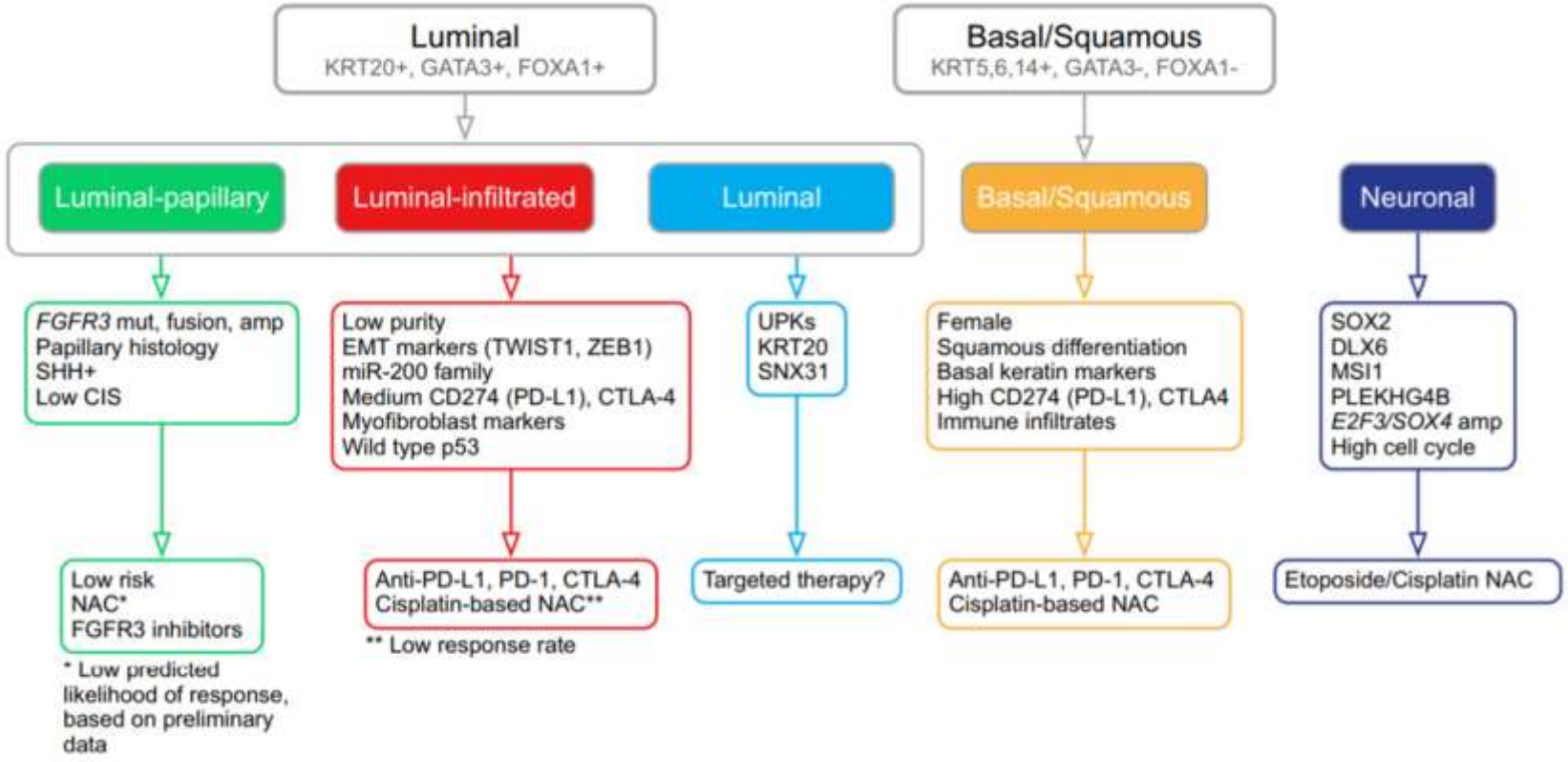
Article

Cell

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

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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** • Paclitaxel[24] or docetaxel[25] • Gemcitabine[15]
Alternative preferred regimens • Immune checkpoint inhibitor ▸ Nivolumab[20] ▸ Avelumab[21,22] • Erdafitinib[f,23]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16] • 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 regimen for cisplatin ineligible, chemotherapy naïve • Gemcitabine/carboplatin	**Other recommended regimens** • Erdafitinib[f,23] • Paclitaxel or docetaxel[25] • Gemcitabine[15]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16]

Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

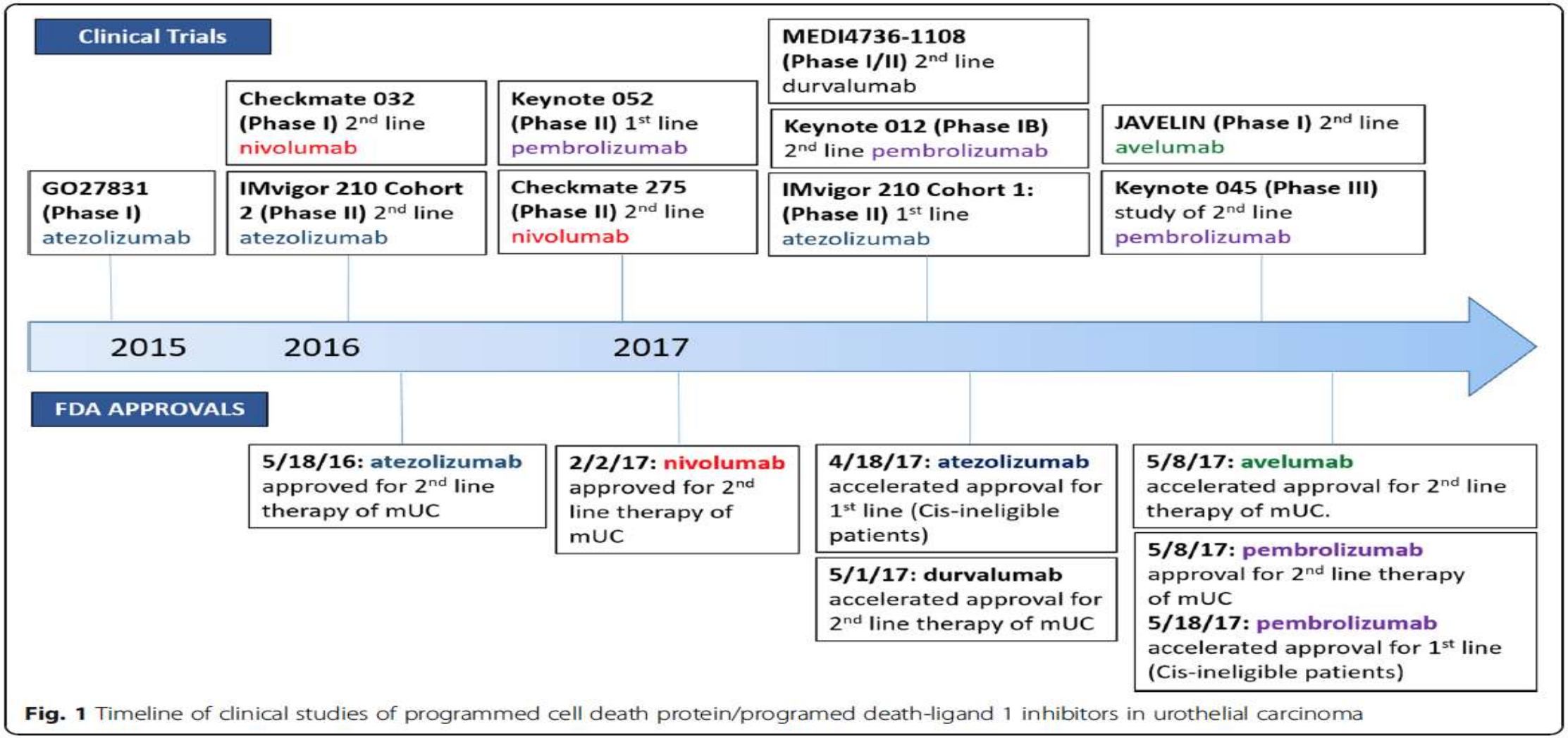


Fig. 1 Timeline of clinical studies of programmed cell death protein/programed death-ligand 1 inhibitors in urothelial carcinoma

Journal for ImmunoTherapy of Cancer (2017)

Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

- International, randomized, open-label phase III study **KEYNOTE-045**

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)

Adult patients with predominantly transitional cell UC of the renal pelvis, ureter, bladder, or urethra; **PD after 1-2 lines of platinum-based CT** or recurrence < 12 mos after perioperative platinum-based CT; ECOG PS 0-2
(N = 542)

Pembrolizumab
200 mg IV Q3W
(n = 270)

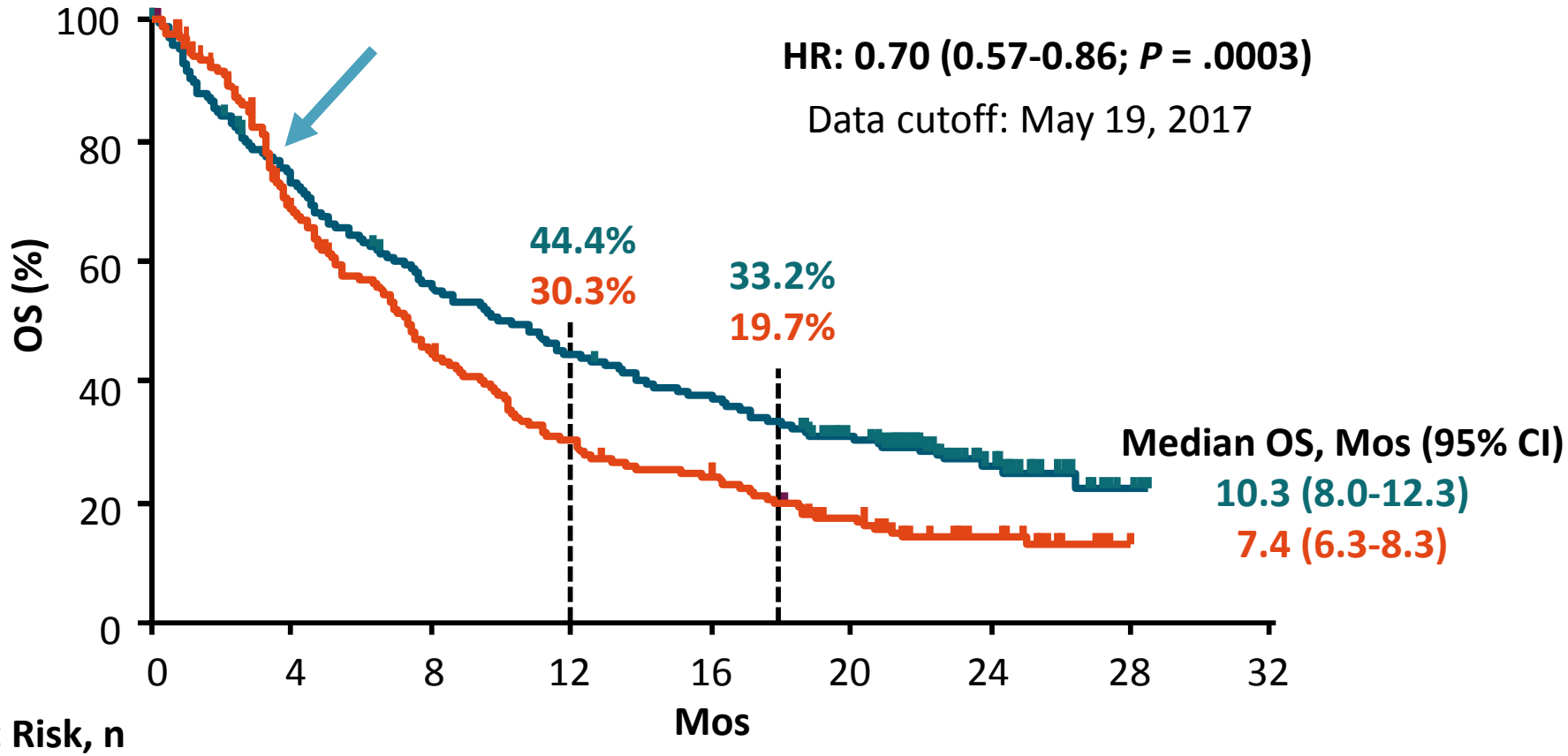
Paclitaxel 175 mg/m^2 IV Q3W or
Docetaxel 75 mg/m^2 IV Q3W or
Vinflunine 320 mg/m^2 IV Q3W
(n = 272)

Treatment continued for 2 yrs or until PD, unacceptable toxicity, or withdrawal of consent

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

Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

KEYNOTE-045: OS

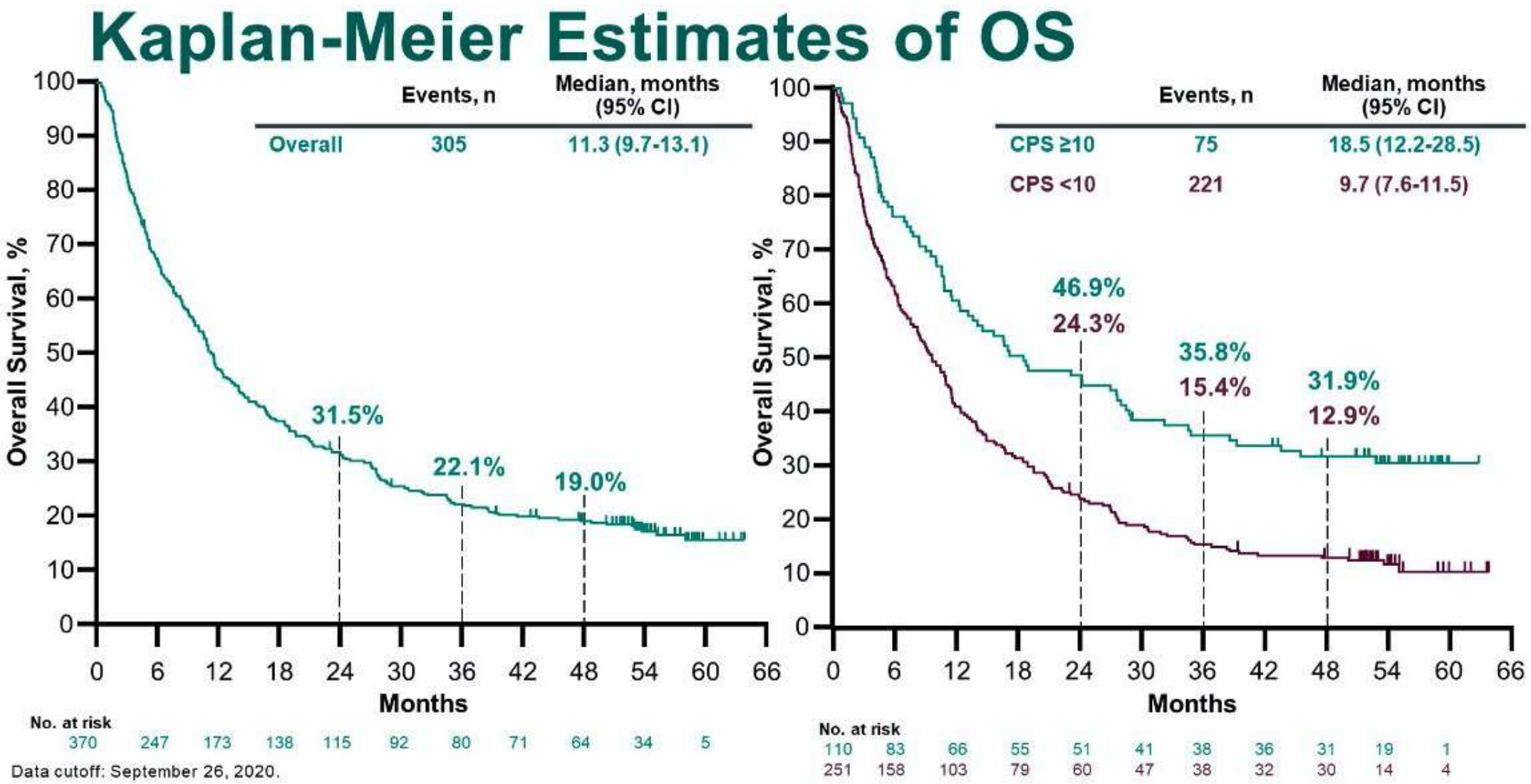


Patients at Risk, n

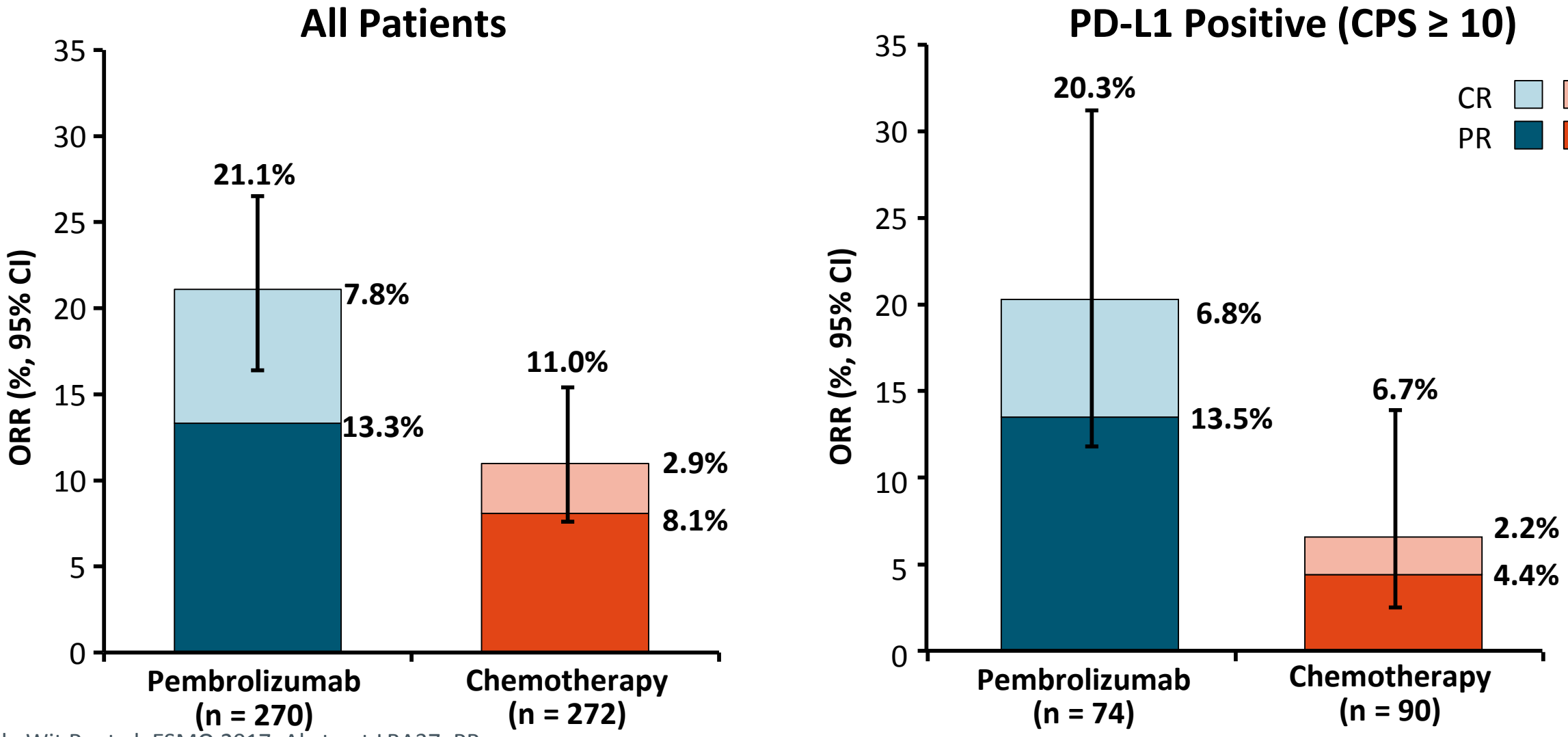
Pembrolizumab	270	194	147	116	98	67	23
Chemotherapy	272	171	109	73	58	35	13

de Wit R, et al. ESMO 2017. Abstract LBA37_PR.

KEYNOTE-045: OS



KEYNOTE-045: ORR



de Wit R, et al. ESMO 2017. Abstract LBA37_PR.

Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi

IMvigor211

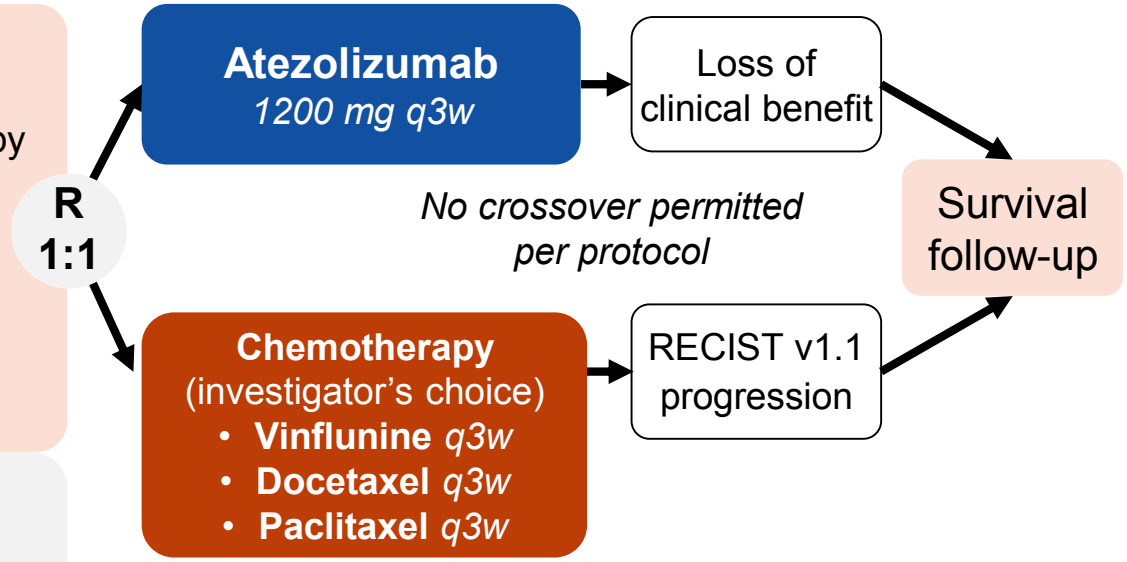
Key Eligibility Criteria[a]

- mUC with progression during or following platinum-based chemotherapy – ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component

(N = 931)

Stratification Factors

- No. of risk factors[b] (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)

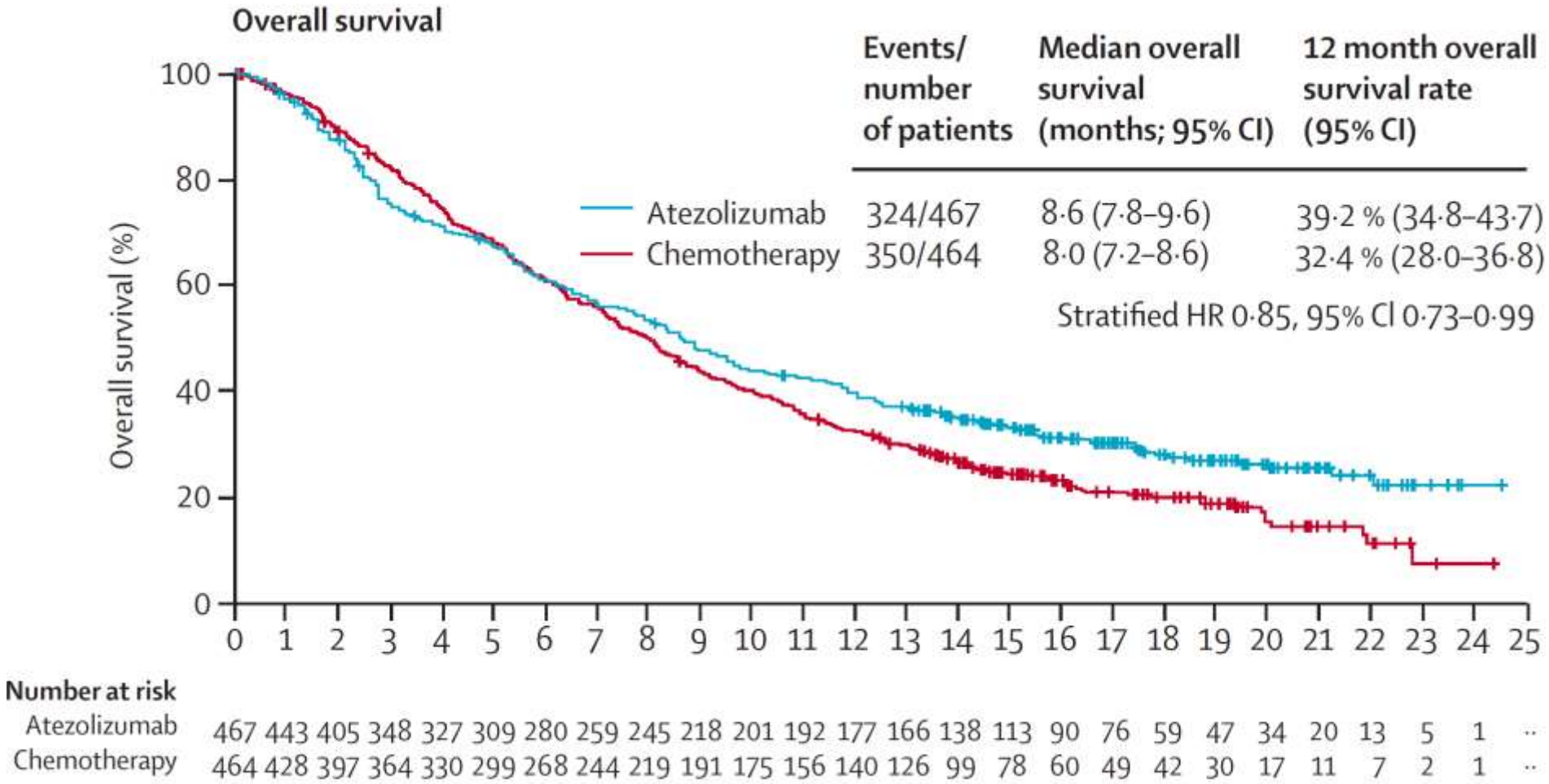


- **Primary endpoint**
  - OS, tested hierarchically in pre-specified populations
- **Additional endpoints**
  - Efficacy: RECIST v1.1 ORR, PFS and DOR[c]
  - Safety
  - PROs: EORTC QLQ-C30

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.

Powles T, et al. EAS 2017, IMvigor211.

IMvigor211 Sonuçları

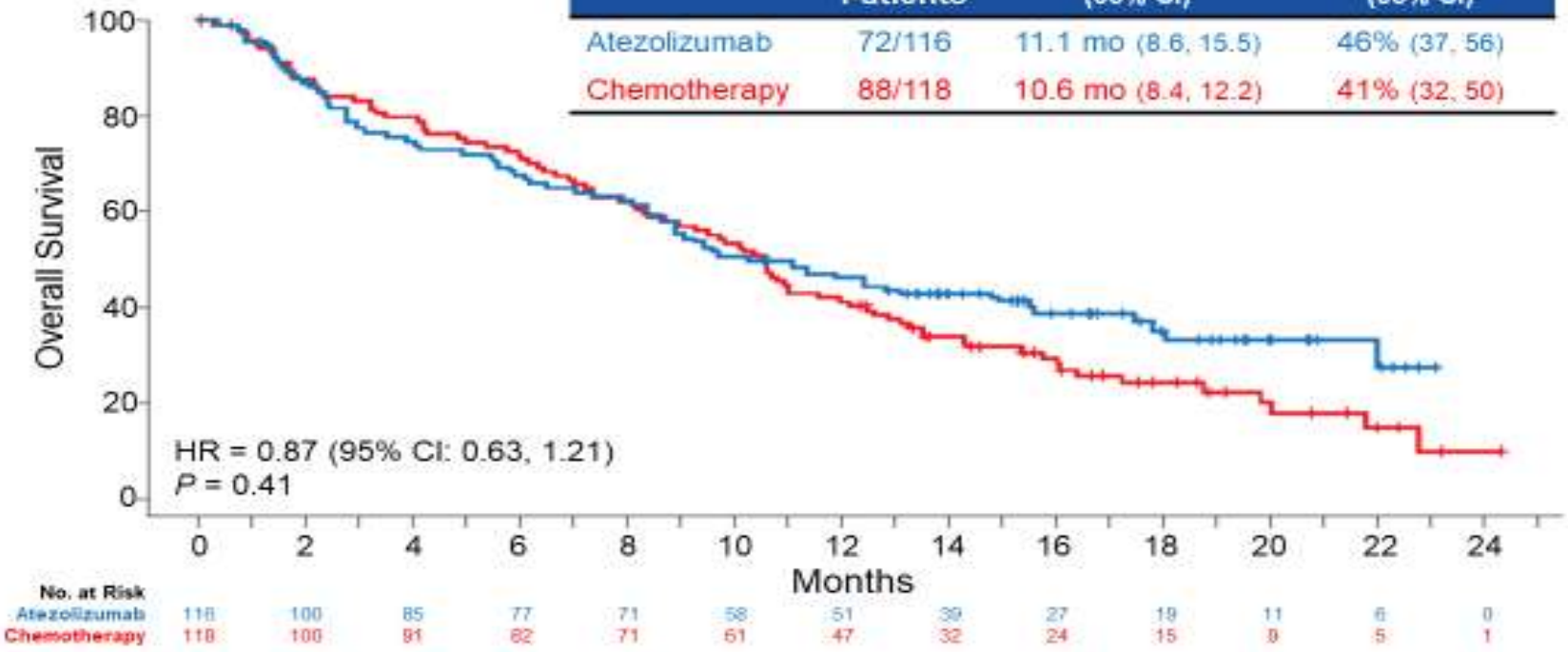


IMvigor211 Sonuçları

3rd Special Conference
EACR
AACR
SIC

OS Analysis: IC2/3 Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)



HR, hazard ratio.

Powles T, et al. EAS 2017, IMvigor211.

Evre IV Mesane Kanserinde Atezolizumab Tedavisi: Gerçek Yaşam Verileri

Deniz Tural[1], Ömer Fatih Ölmez[2], Ahmet Taner Sümbül[3], Mehmet Artaç[4], Nail Özhan[5], Emre Akar[1], Burcu Çakar[6], Osman Köstek[7], Nail Paksoy[8], Mustafa Erman[9], Hasan Şenol Coşkun[10], Fatih Selçukbiricik[11], Özge Keskin[12], Fatma Paksoy Türköz[13], Kerem Oruç[14], Selami Bayram[15], Uğur Yılmaz[16], İrem Bilgetekin[17], Birol Yıldız[18], Mehmet Ali Nahit Şendur[19], Ahmet Dirican[20], Dilek Erdem[21], Meltem Selam[22], Özgür Tanrıverdi[23], Semra Paydaş[24], Zuhat Urakçı[25], Elif Atağ[26], Sabri Güncan[27], Yüksel Ürün[28], Ali Alkan[29], Ali Osman Kaya[30], Deniz Tataroğlu Özyükseler[31], Halil Taşkaynatan[32], Mustafa Yıldırım[33], Müge Sönmez[34], Tuğba Başoğlu[35], Şeyda Gündüz[36], Saadettin Kılıçkap[37],
Türk Onkoloji Grubu

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

EUROPEAN UROLOGY FOCUS XXX (2019) XXX–XXX

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 Erman*[i], *Hasan Şenol Coşkun*[j], *Fatih Selçukbiricik*[k], *Özge Keskin*[l], *Fatma Paksoy Türköz*[m], *Kerem Oruç*[n], *Selami Bayram*[o], *Uğur Yılmaz*[p], *İrem Bilgetekin*[q], *Birol Yıldız*[r], *Mehmet Ali Nahit Şendur*[s], *Nail Paksoy*[h], *Ahmet Dirican*[t], *Dilek Erdem*[u], *Meltem Selam*[v], *Özgür Tanrıverdi*[w], *Semra Paydaş*[x], *Zuhat Urakçı*[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 Başoğlu*[ii], *Şeyda Gündüz*[jj], *Saadettin Kılıçkap*[kk]

[a] *Bakirköy 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, Selcuk 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 OncologyTraining 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 Kirdar 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)

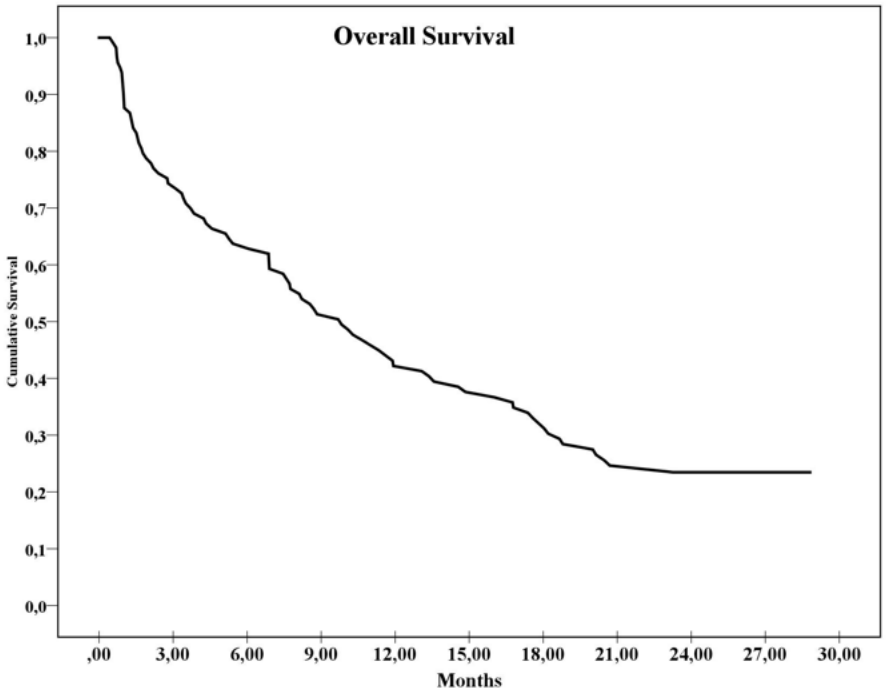
Ortalama OS: 9.8 ay (95% CI,6.7–12.9)

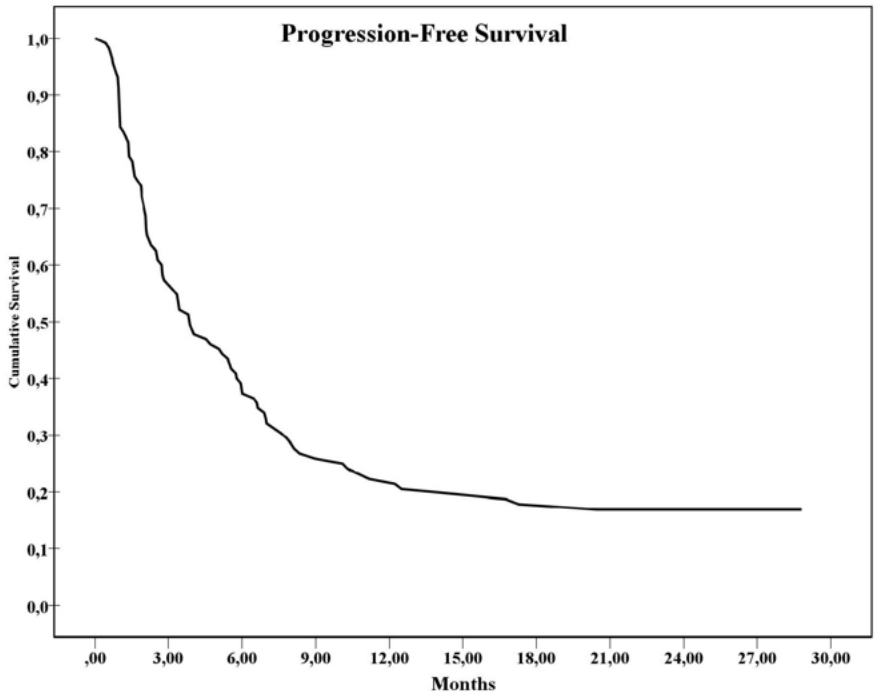
12 ay PFS oranı: %22.3

24 ay PFS oranı: %16.9

12 ay OS oranı: %42.2

24 ay OS oranı: %23.5

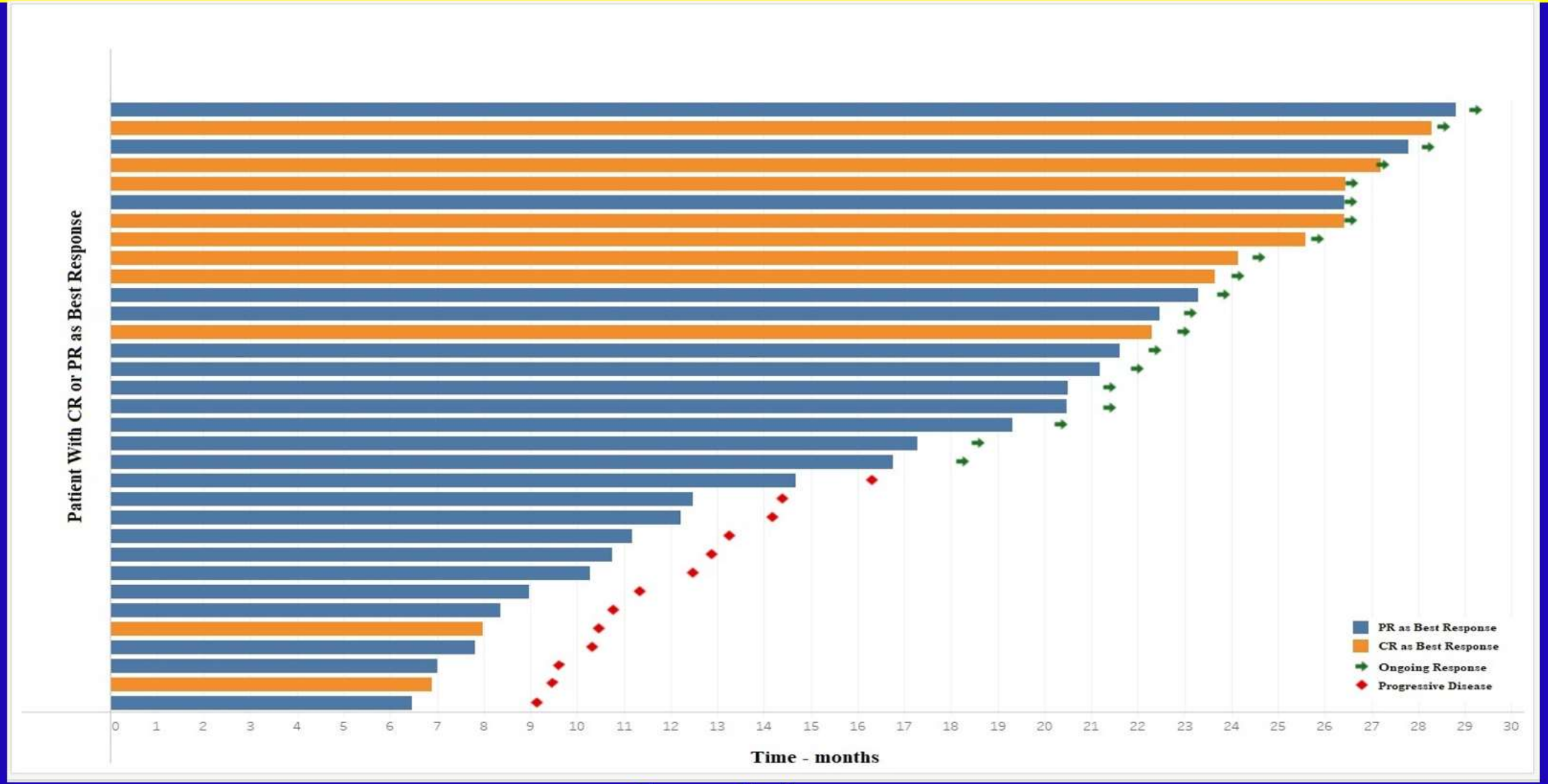




Sonuçlar

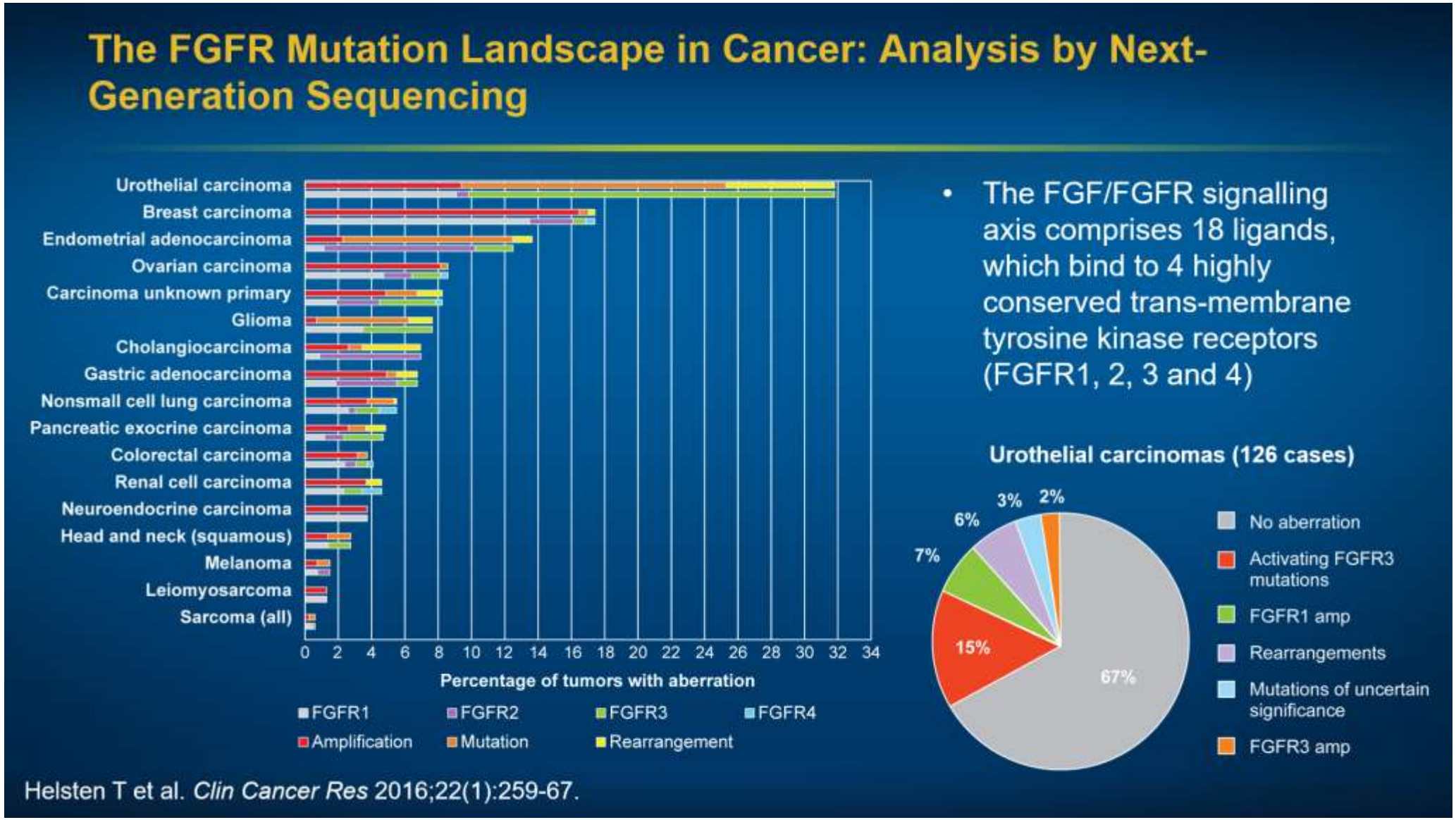
Yanıt Süresi

Yanıt alınan hastalar (CR veya PR)

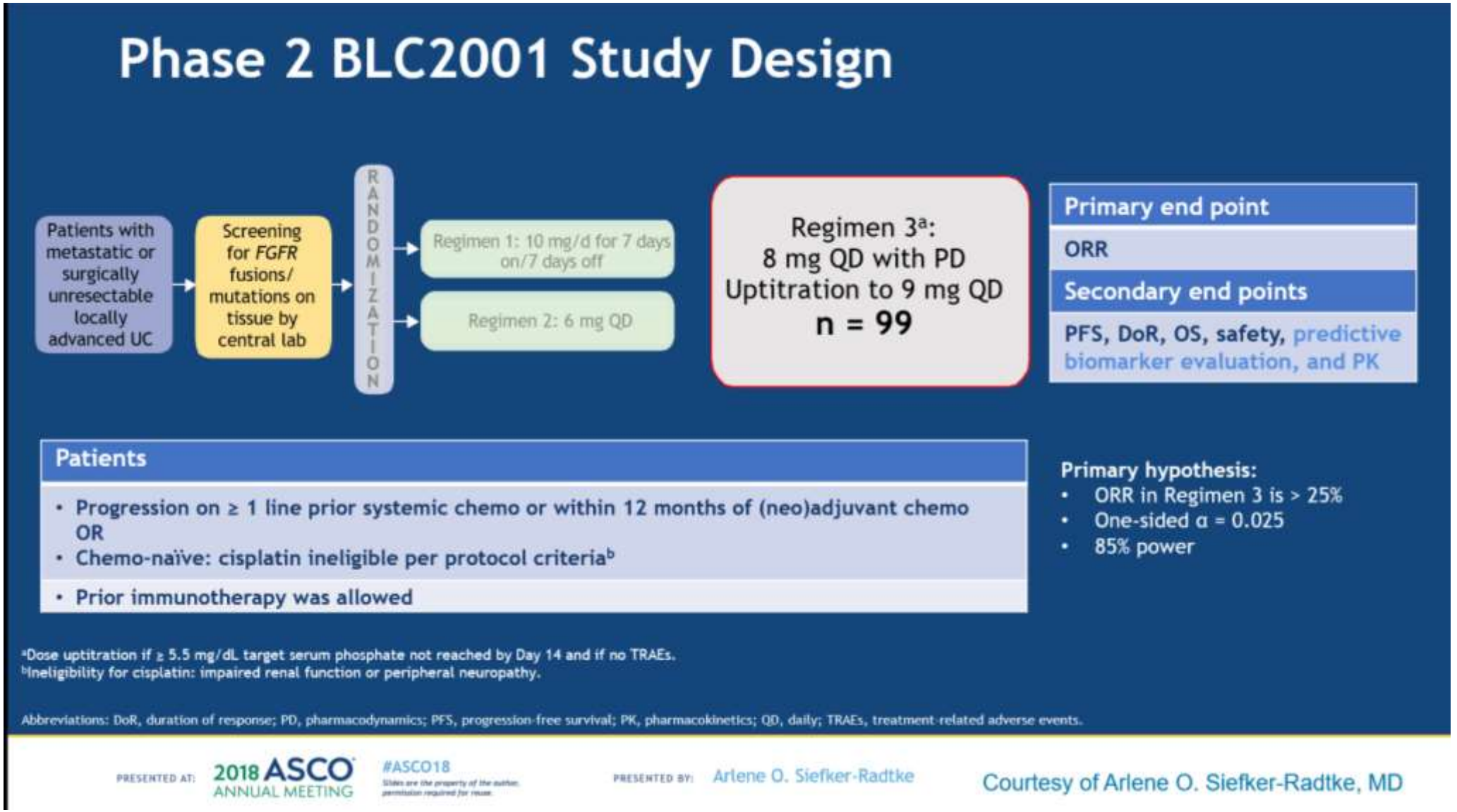


Zaman (ay)

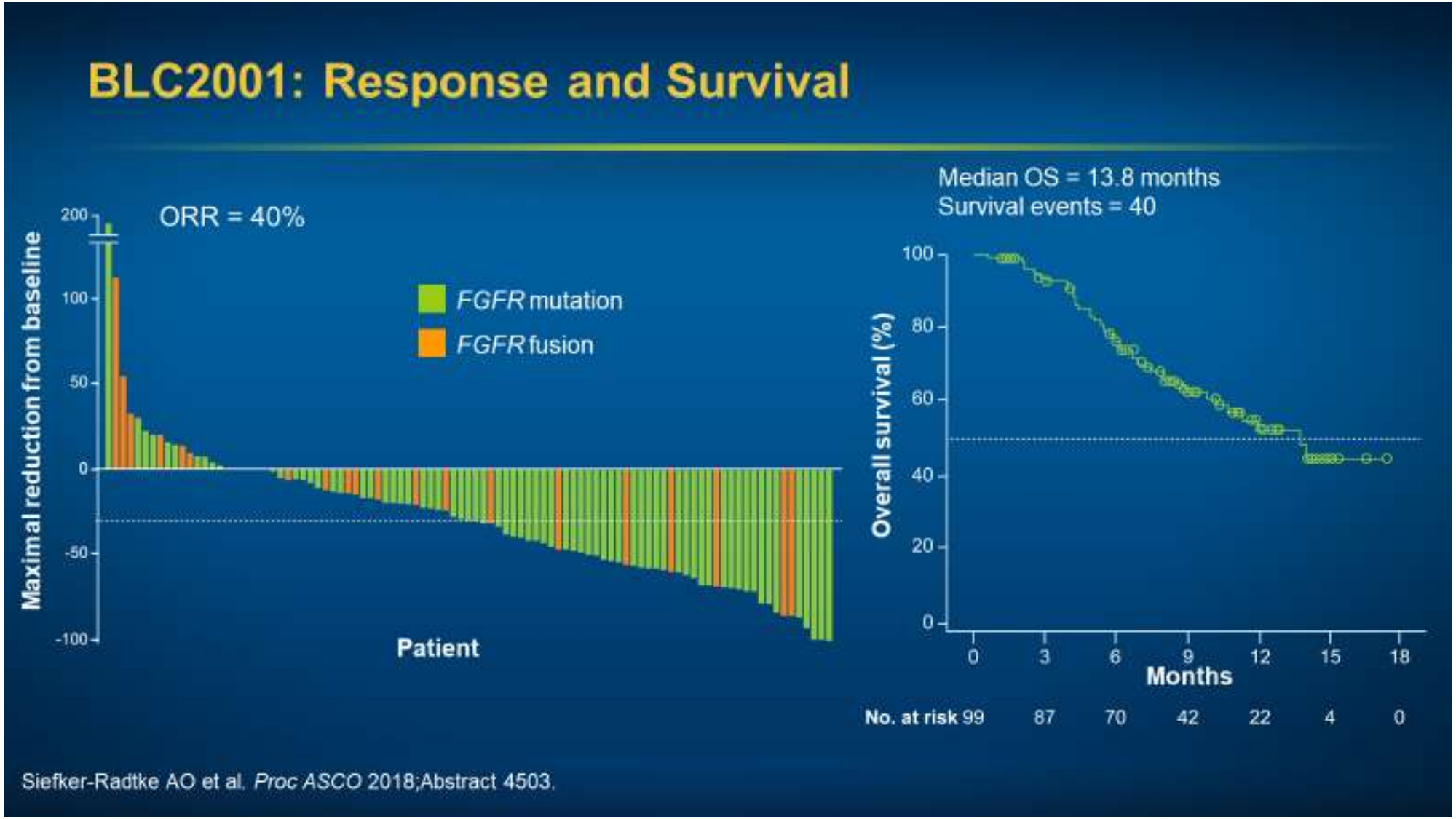
Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi



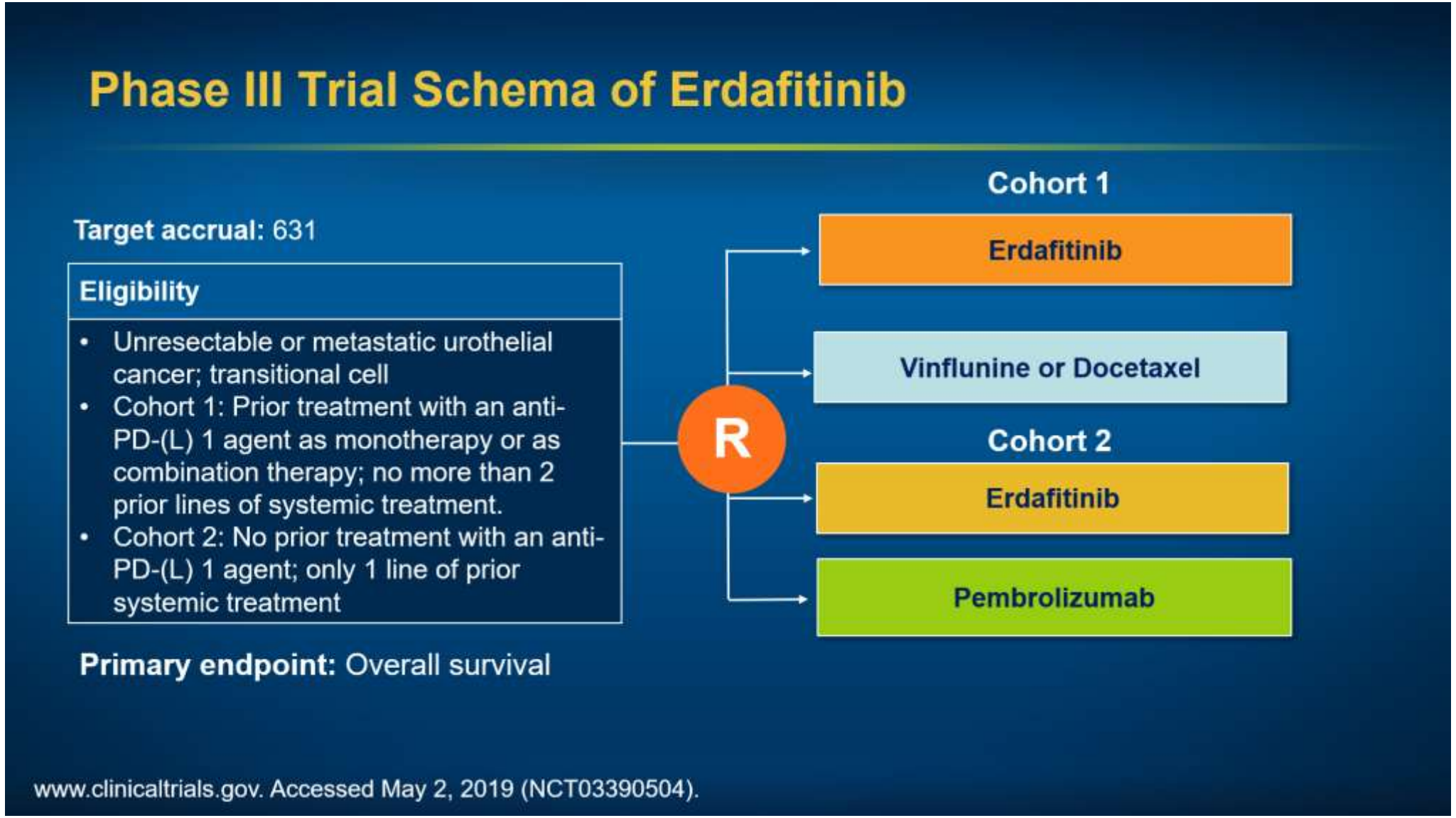
Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi



Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi



Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçimi



Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçenekleri

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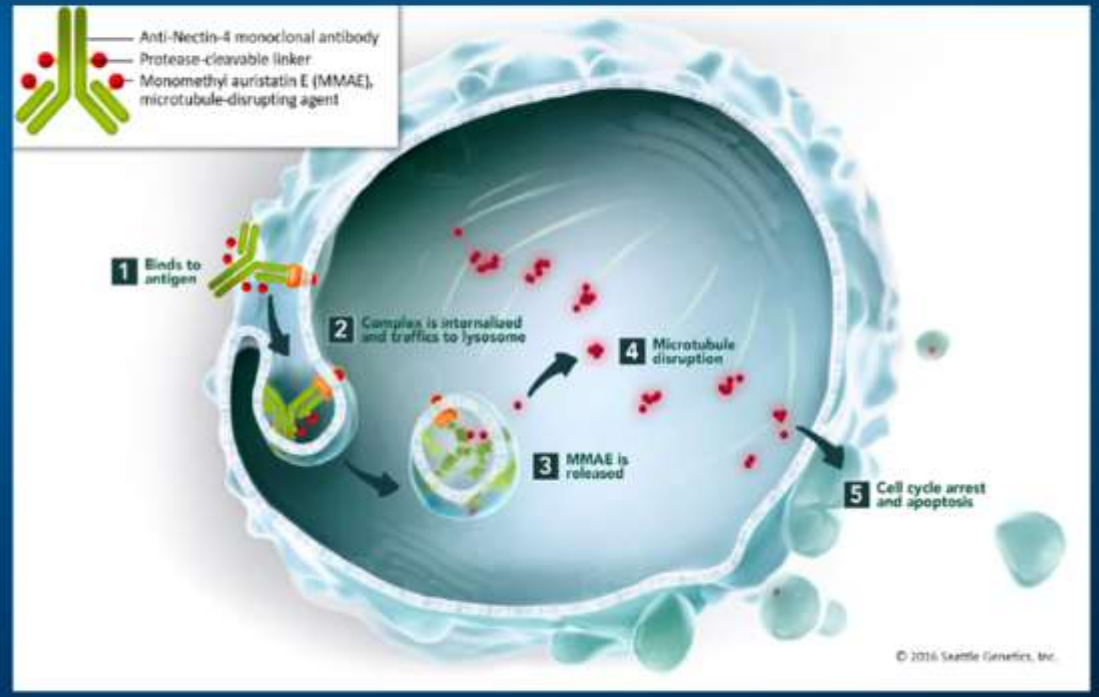
PRINCIPLES OF SYSTEMIC THERAPY

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** • Gemcitabine[15] • Paclitaxel[24] or docetaxel[25] • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

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 samples[3]
- 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

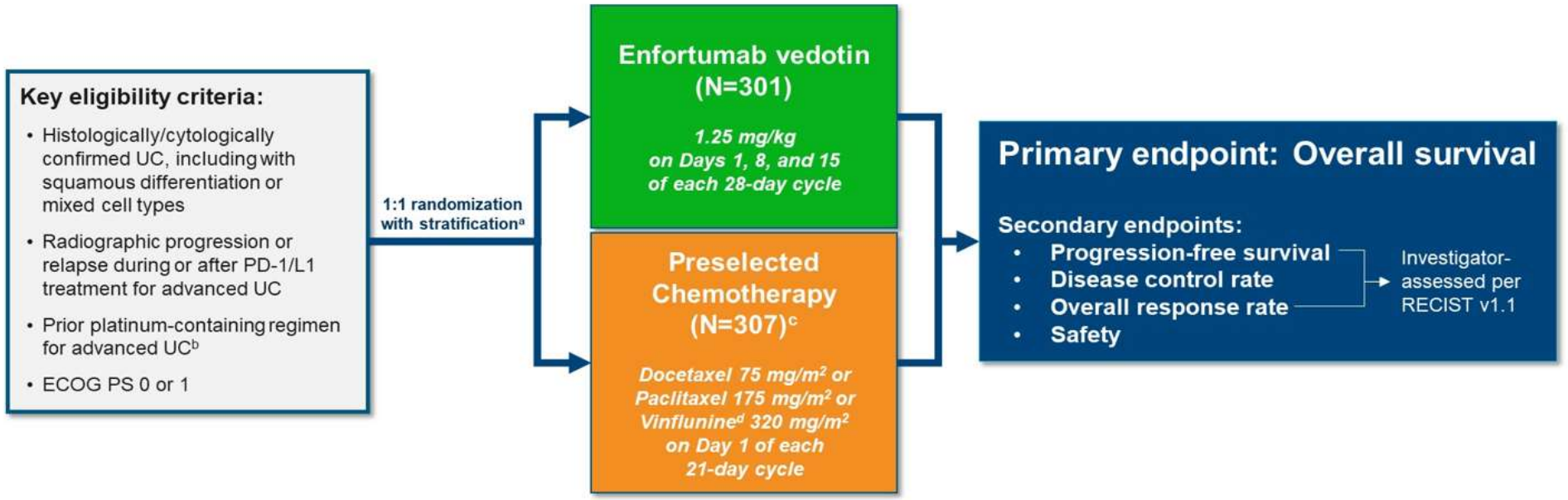


[1] Samanta D, Almo SC. *Cell Mol Life Sci* 2015;72:645-58; [2] Challita-Eid PM et al. *Cancer Res* 2016;76:3003-13;
[3] Petrylak DP et al. *J Clin Oncol* 2017;35:106.

Rosenberg ASCO 2018

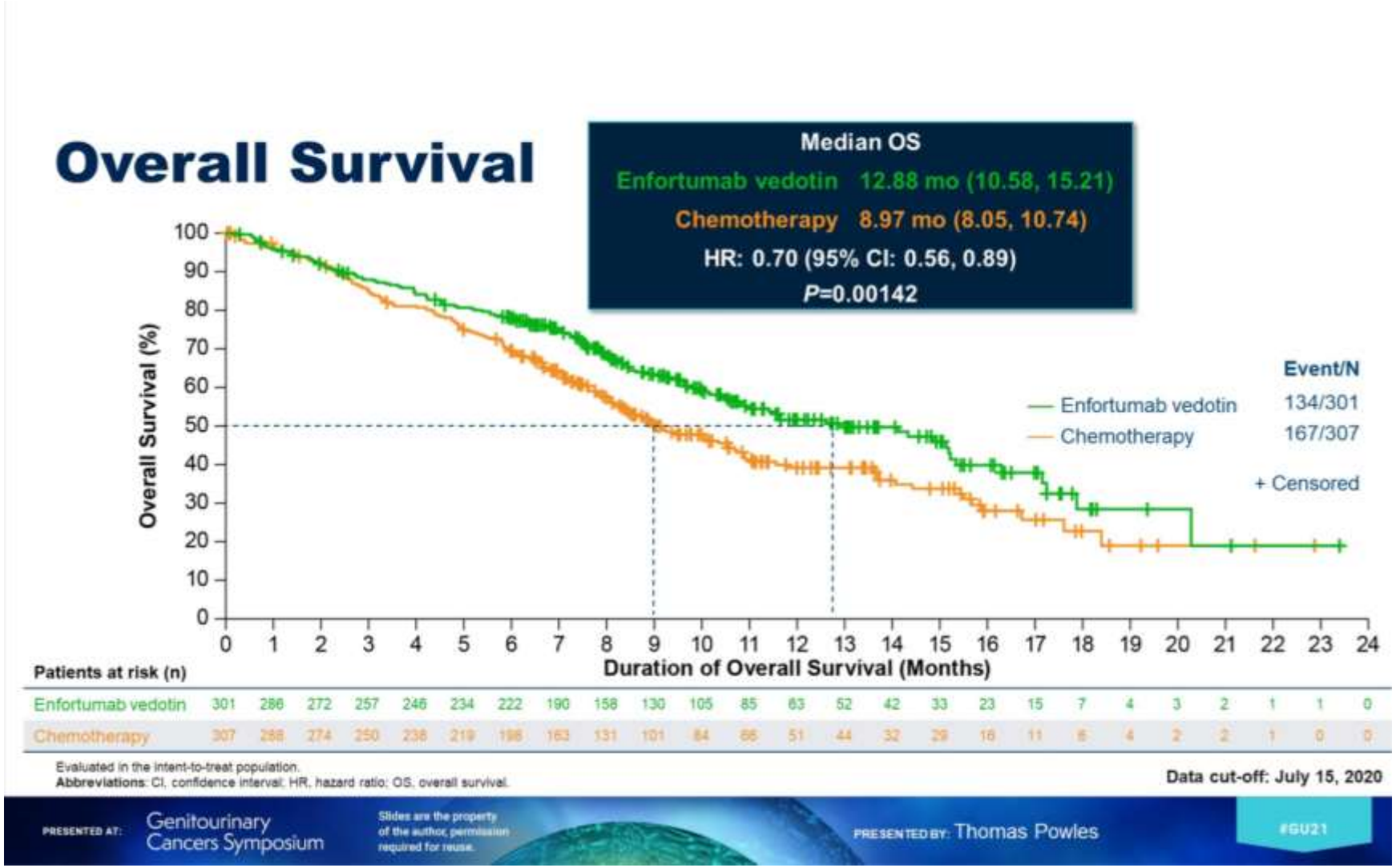
Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

EV-301 Open-Label Phase 3 Trial Design



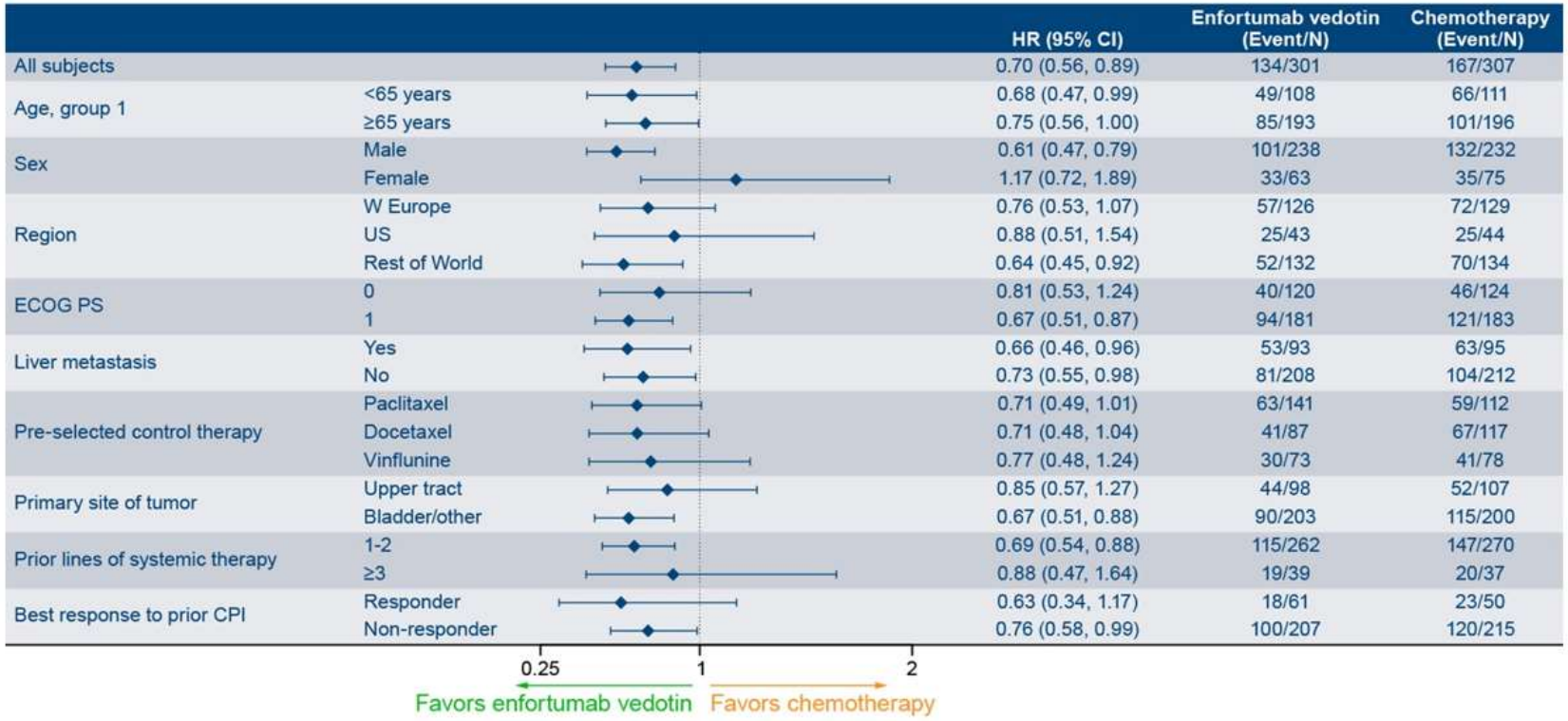
[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In 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



		HR (95% CI)	Enfortumab vedotin (Event/N)	Chemotherapy (Event/N)
All subjects		0.70 (0.56, 0.89)	134/301	167/307
Age, group 1	<65 years	0.68 (0.47, 0.99)	49/108	66/111
	≥65 years	0.75 (0.56, 1.00)	85/193	101/196
Sex	Male	0.61 (0.47, 0.79)	101/238	132/232
	Female	1.17 (0.72, 1.89)	33/63	35/75
Region	W Europe	0.76 (0.53, 1.07)	57/126	72/129
	US	0.88 (0.51, 1.54)	25/43	25/44
	Rest of World	0.64 (0.45, 0.92)	52/132	70/134
ECOG PS	0	0.81 (0.53, 1.24)	40/120	46/124
	1	0.67 (0.51, 0.87)	94/181	121/183
Liver metastasis	Yes	0.66 (0.46, 0.96)	53/93	63/95
	No	0.73 (0.55, 0.98)	81/208	104/212
Pre-selected control therapy	Paclitaxel	0.71 (0.49, 1.01)	63/141	59/112
	Docetaxel	0.71 (0.48, 1.04)	41/87	67/117
	Vinflunine	0.77 (0.48, 1.24)	30/73	41/78
Primary site of tumor	Upper tract	0.85 (0.57, 1.27)	44/98	52/107
	Bladder/other	0.67 (0.51, 0.88)	90/203	115/200
Prior lines of systemic therapy	1-2	0.69 (0.54, 0.88)	115/262	147/270
	≥3	0.88 (0.47, 1.64)	19/39	20/37
Best response to prior CPI	Responder	0.63 (0.34, 1.17)	18/61	23/50
	Non-responder	0.76 (0.58, 0.99)	100/207	120/215

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, 20

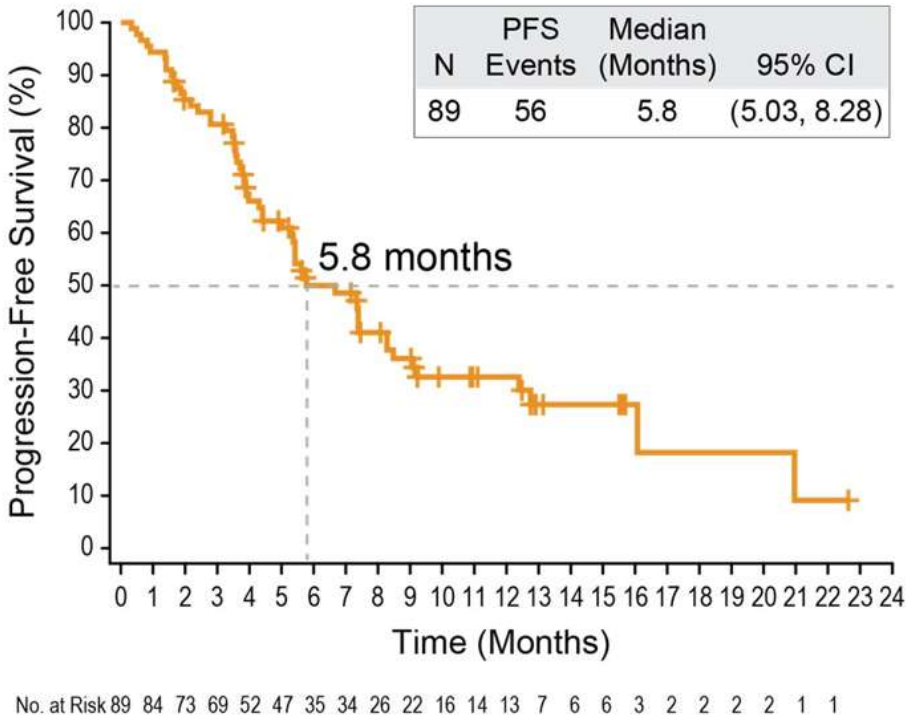
Metastatik Mesane Kanseri İkinci Basamak Sonrası Tedavi Seçimi

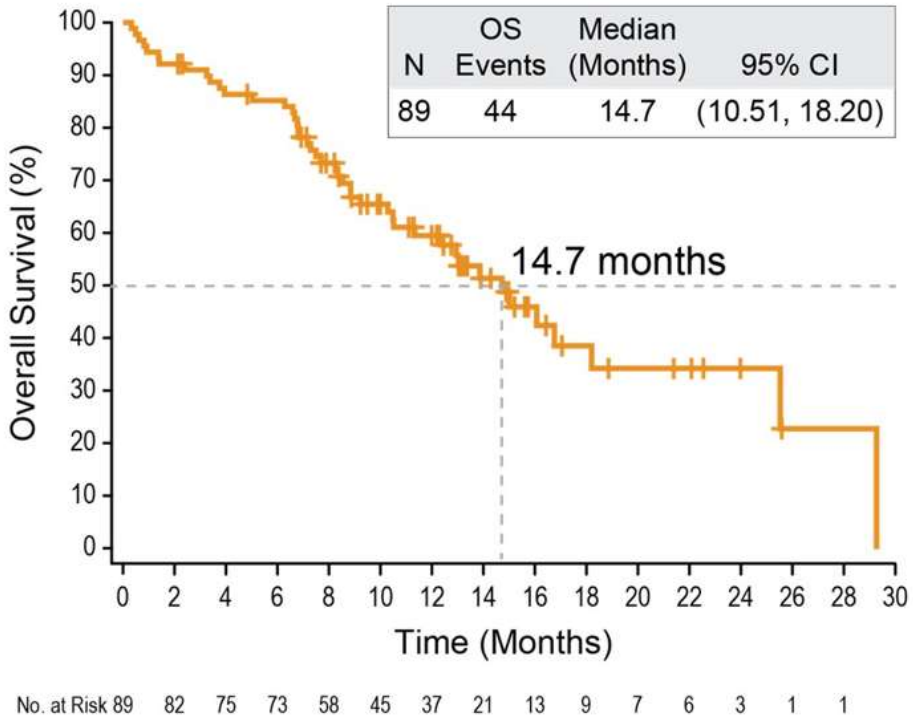
EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors (NCT03219333)

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

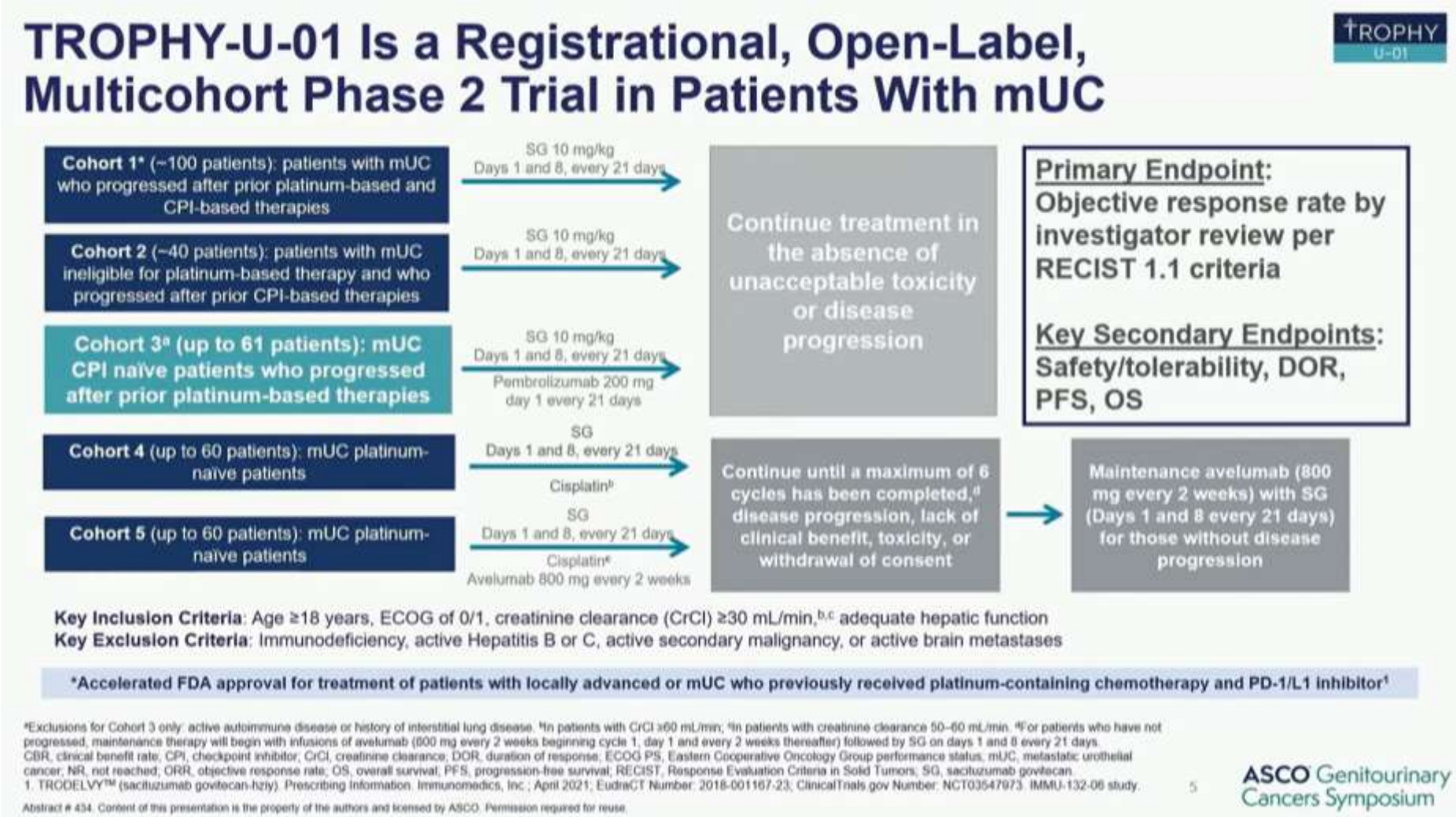
EV-201 Cohort 2: Progression-Free Survival and Overall Survival





Median follow-up: 13.4 months

Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

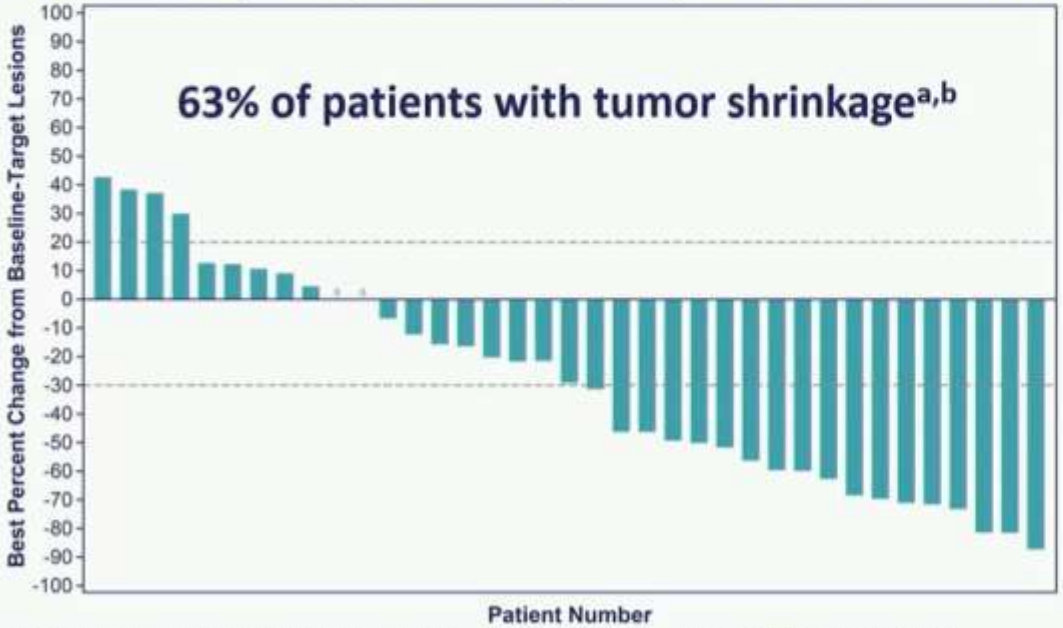


Metastatik Mesane Kanseri İkinci Basamak ve Sonrası Tedavi Seçimi

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]

[a]Responses assessed by investigator in the intent-to-treat population. [b]Patients 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

ASCO Genitourinary Cancers Symposium

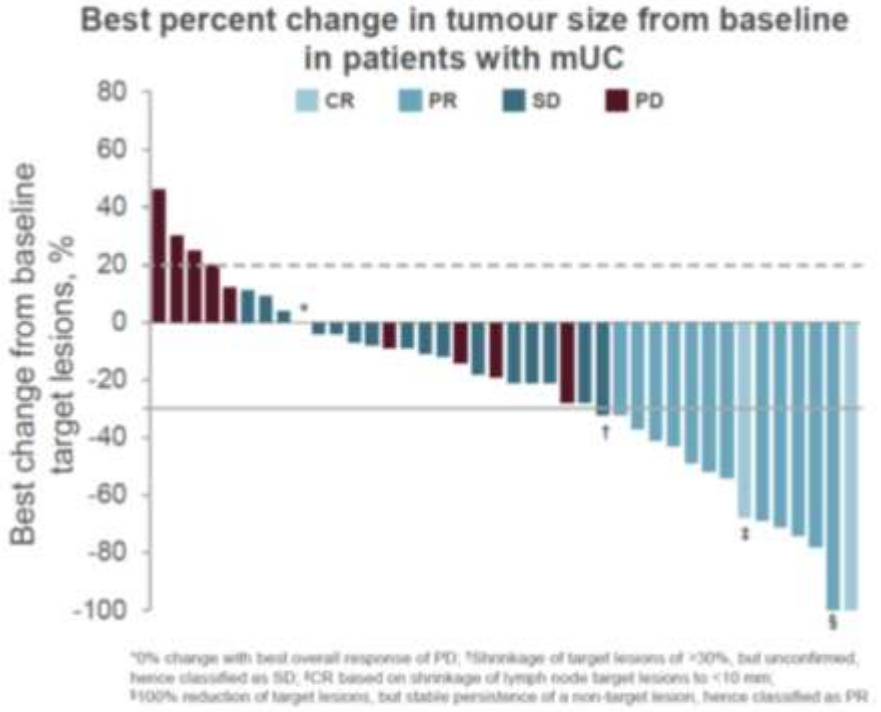
Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

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.

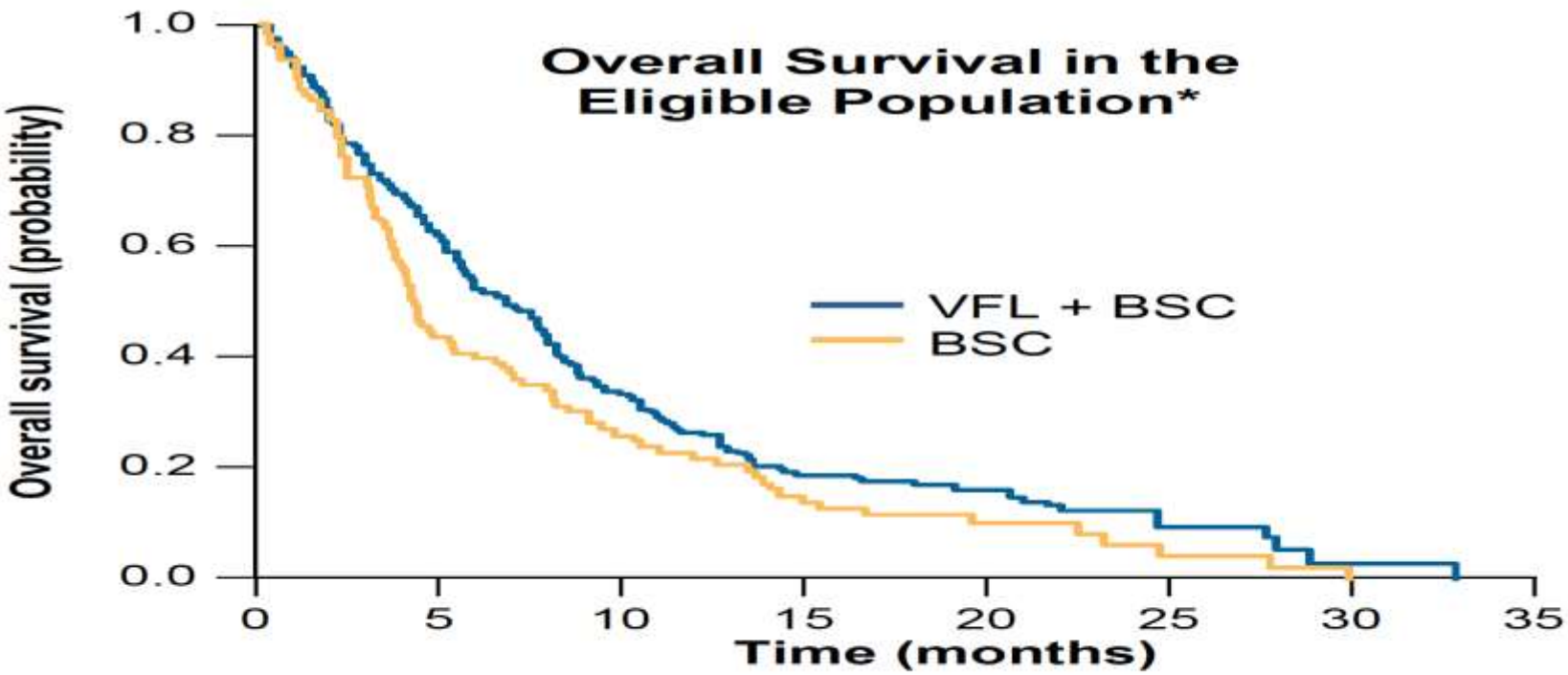
Courtesy of Thomas Powles, MBBS, MRCP, MD

Metastatik Mesane Kanseri Enfortumab Vedotin Sonrası Tedavi Seçimi

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; *P*=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+ gemsitabin kemoterapi kombinasyonu klinik yarar alanlarda Avelumab idame tedavi olarak önerilir
- Sisplatin alamayacak hastalarda PD-L1 pozitif olanlar(CPS≥10 ya da PD-L1> 5) Pemrolizumab/Atezolizumab önerilebilir
- Platin bazlı kemoterapi alamayacak hastalarda birinci basamak tedavide (ECOG PS≥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