Metastatik Mesane Kanserinde Sistemik Tedavi

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Tıbbi Onkoloji

Ders Planı

- **Mesane Kanseri İnsidans ve Mortalite**

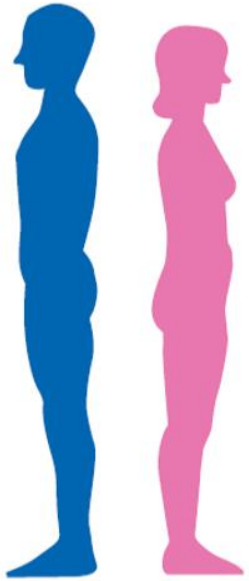
Metastatik Hastalık

- Sisplatine uygun hastada birinci basamak
- Sisplatine uygun olmayan hastada birinci basamak
- Platin sonrası, ikinci basamak tedavi
- İdame
- Gelecek Perspektif

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%**

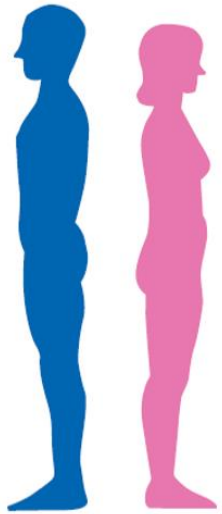


CA CANCER J CLIN 2019;69:7–34

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%**

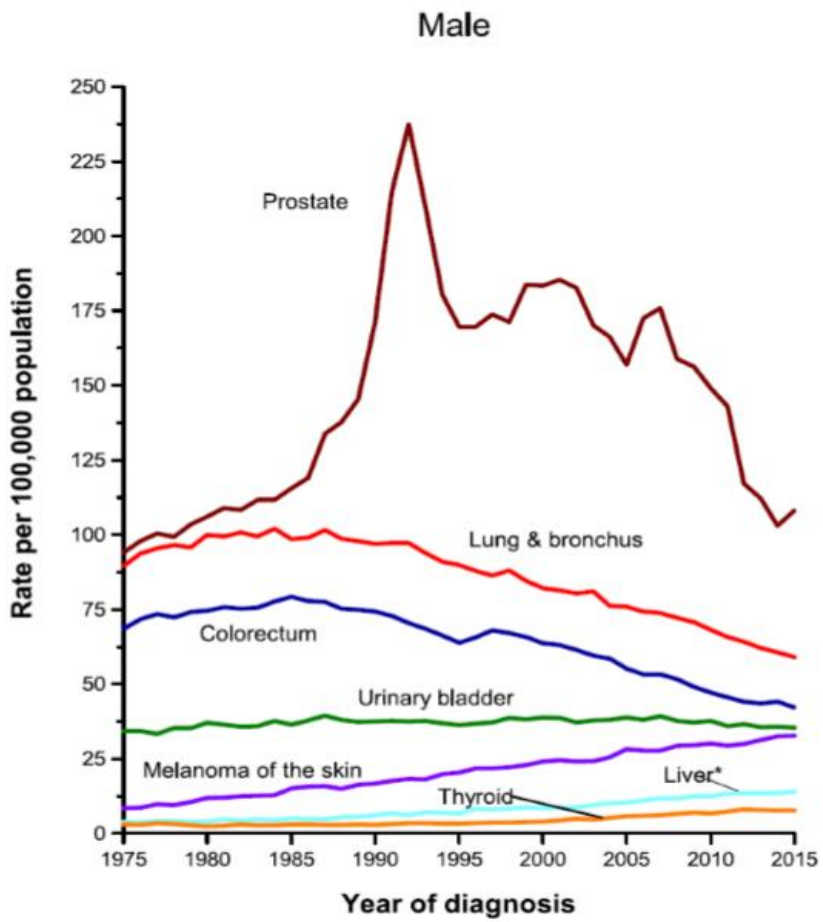


CA CANCER J CLIN 2019;69:7–34

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

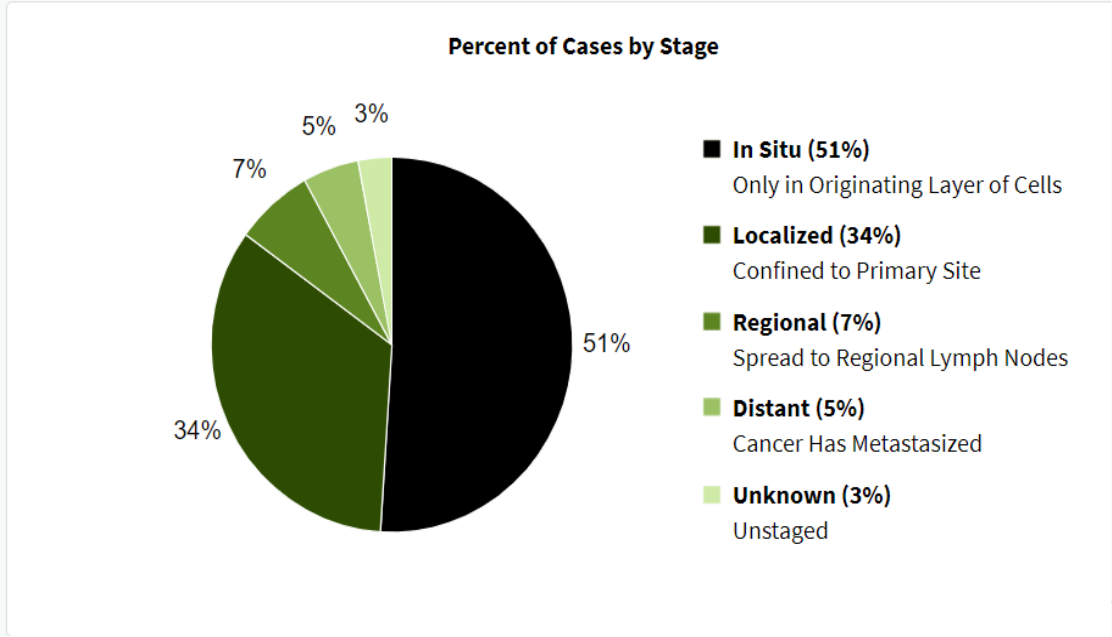
	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage IIIA	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
	T1-T4a	N1	M0
Stage IIIB	T1-T4a	N2,N3	M0
Stage IVA	T4b	Any N	M0
	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

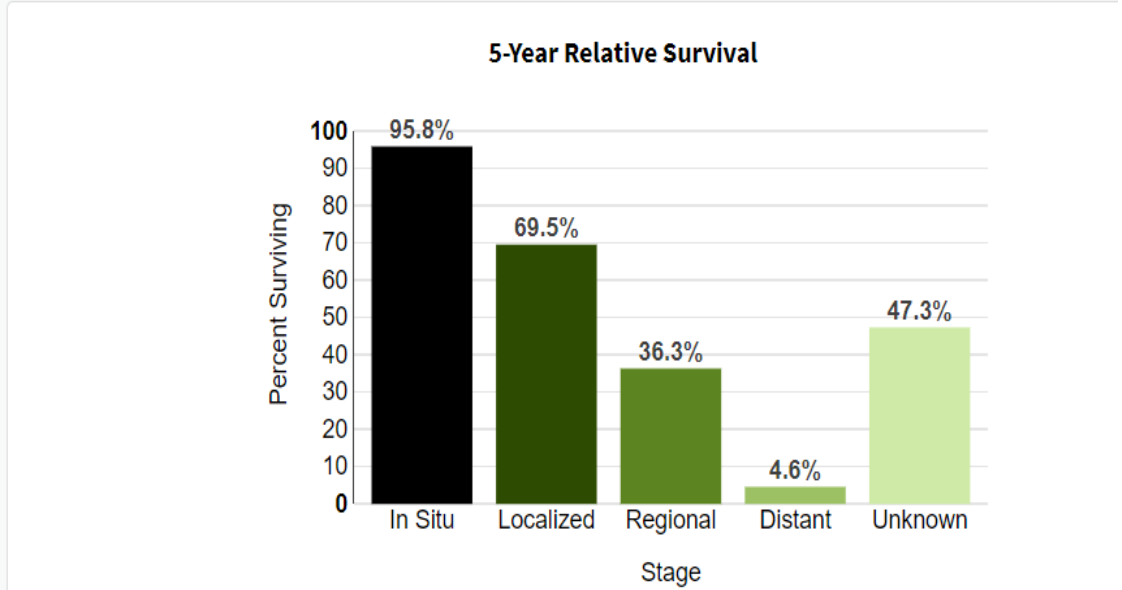
Continued

NCCN Guidelines® for Bladder Cancer (Version 1.2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: NCCN.org.

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

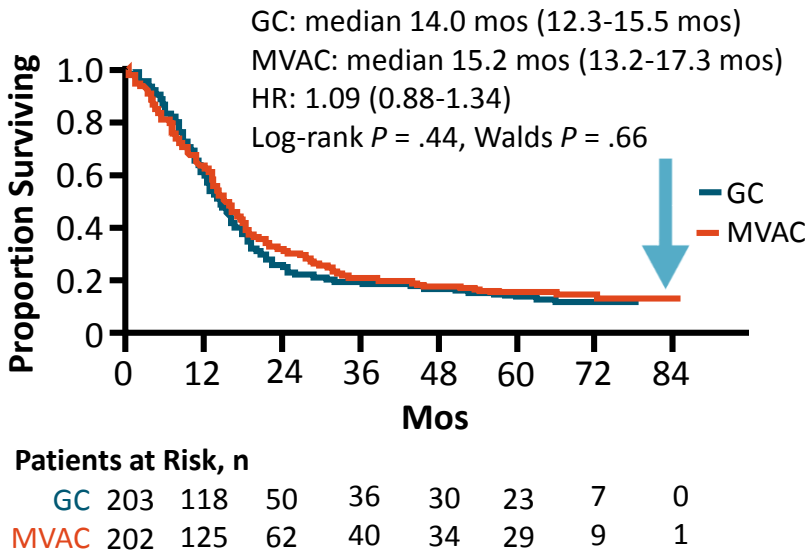
Sisplatin Uygun

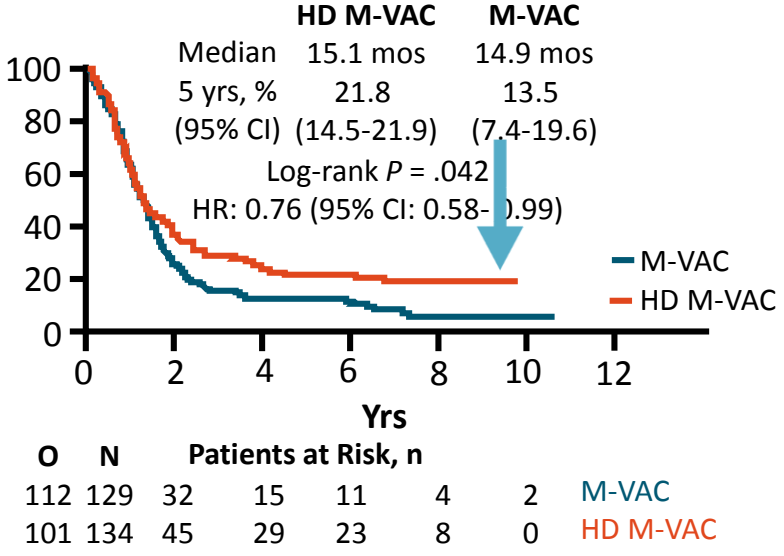
Gemcitabine + Cisplatin[1,2]
ORR: 49%
CR: 12%
Median OS: 14.0 mos

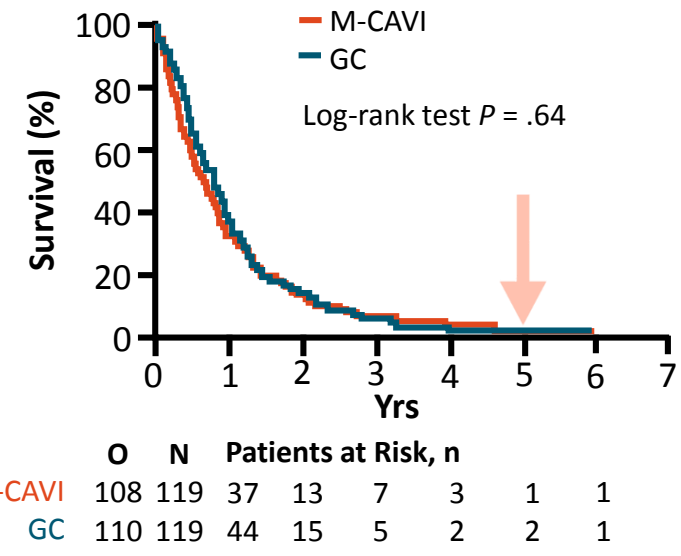
Dose Dense MVAC[3]
ORR: 72%
CR: 25%
Median OS: 15.1 mos

Sisplatin uygun değil

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







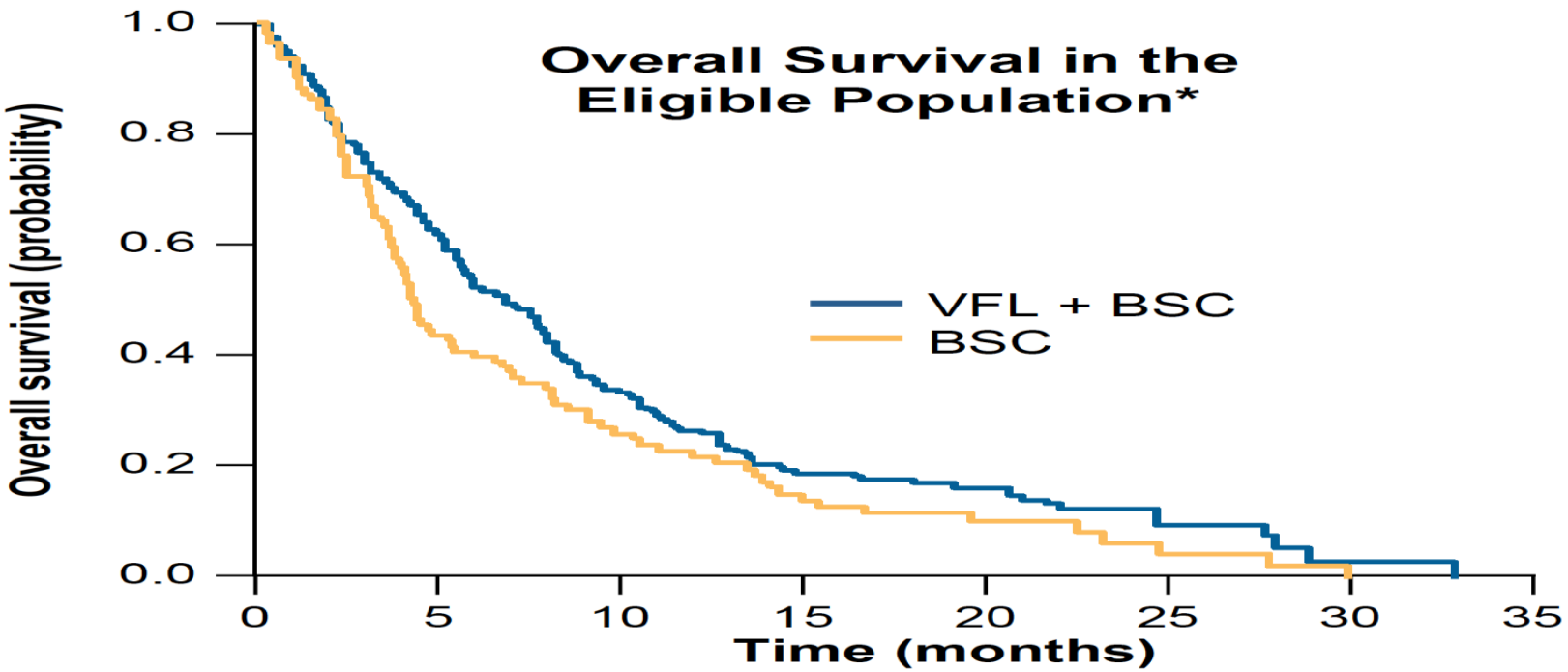
1. von der Maase H, et al. J Clin Oncol. 2005;23:4602-4608. 2. von der Maase H, et al. J Clin Oncol. 2000;18:3068-3077.
3. Sternberg CN, et al. Eur J Cancer. 2006;42:50-54. 4. De Santis M, et al. J Clin Oncol. 2012;30:191-199.

Metastatik Mesane Kanserinde İkinci basamak kemoterapi

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
İkinci Basamak Kemoterapi

	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
Birinci Basamak Tedavi Seçimi

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
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 cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[11] • Atezolizumab[12] (only for patients whose tumors express PD-L1[a] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[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) **Other recommended regimens** • Gemcitabine[14] • Gemcitabine and paclitaxel[15] **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[16] (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.[17]
- 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

İmmünoterapi

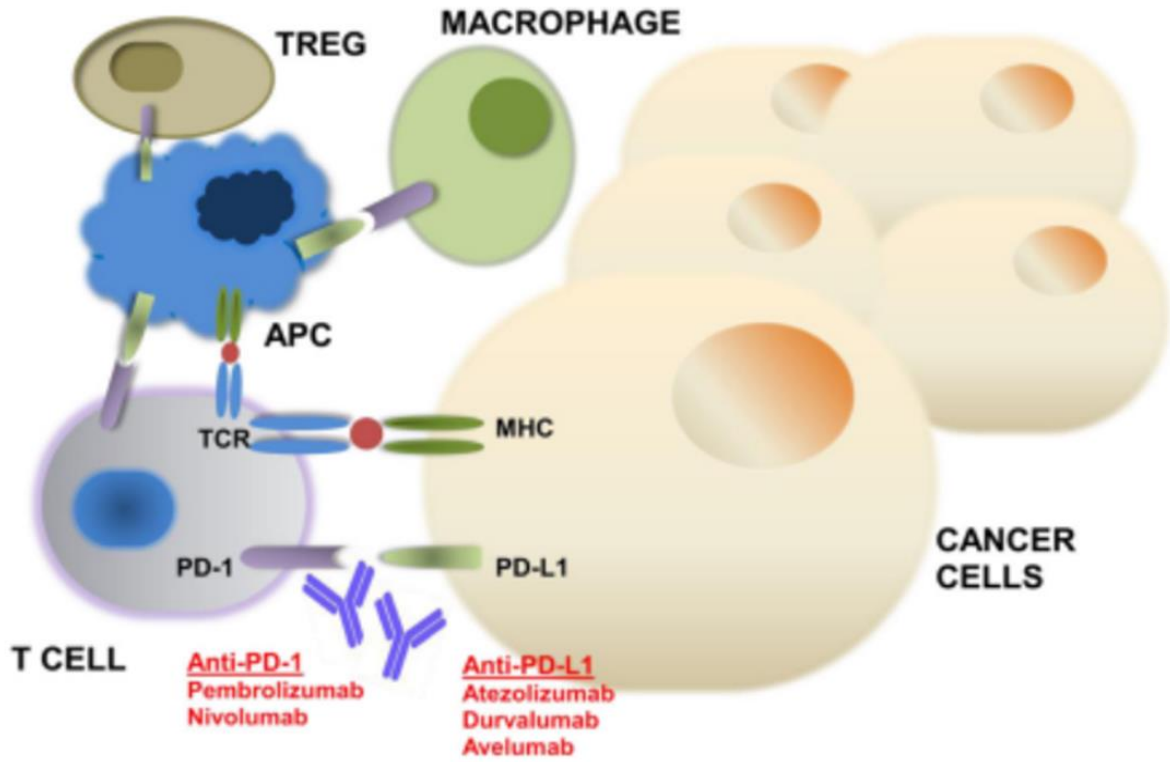


Fig. 1 Mechanism of action of PD-1 and PD-L1 inhibitors. The programmed cell death 1 (PD-1) receptor is expressed on activated T cells, B cells, macrophages, regulatory T cells (Tregs), and natural killer (NK) cells. Binding of PD-1 to its B7 family of ligands, programmed death ligand 1 (PD-L1 or B7-H1)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

İmmünoterapi

- immünoterapiyle ilgili ilk bilgiler New York da yaşayan cerrah William Coley 1891 yıllında veriyor. Dr coley enfeksiyon sonrası hastasının yüzünde ki kanserin (sarkom) gerilediğini belirtmiş.

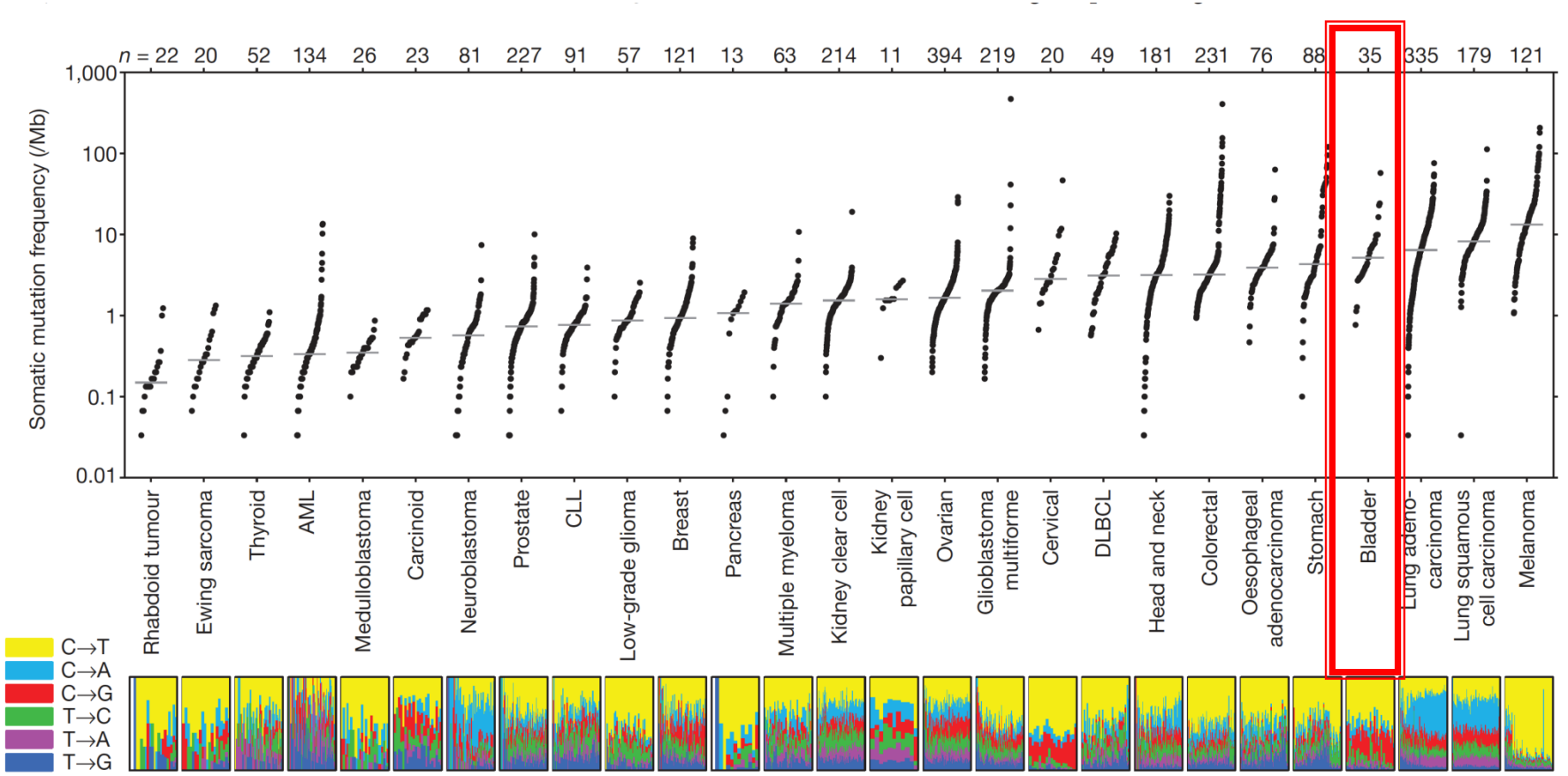
- İlerleyen zamanda bağışıklık sistemini aktive eden Streptococcus pyogenes and Serratia marcescens bakterilerinin antijenik yapılarının immün sistemi aktivite ettiği saptanıyor.

- Tübeküloz hastalığına karşı 1908 yılında Albert Calmette ve Camille Guerin BCG aşısını geliştiriyor.

- İlerleyen yıllarda tübeküloz olan hastalarda kanser oranın düşük olması bilim adamlarını araştırmalara yöneltiyor. Bu çalışmalar sonrası tüberküloz bakterilerinin antijenlerinde elde edilen BCG aşısı erken evre mesane kanserinde günümüze halen kullanılmaktadır.

- Modern immünoterapi 1985 yılında İnterleukin 2 metastatik melanomda kullanılmasıyla başlıyor.

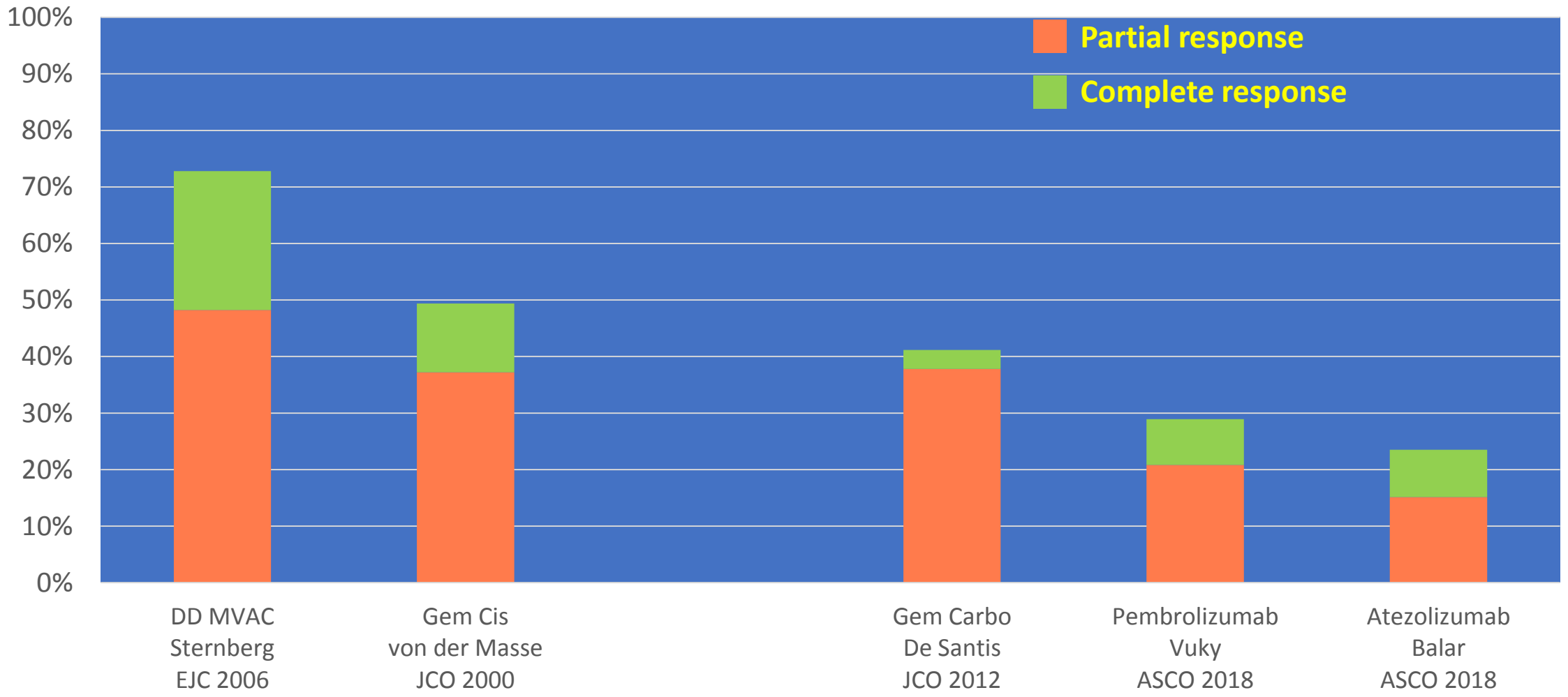
Mesane Kanserinde Tümör Mutasyon Yükü



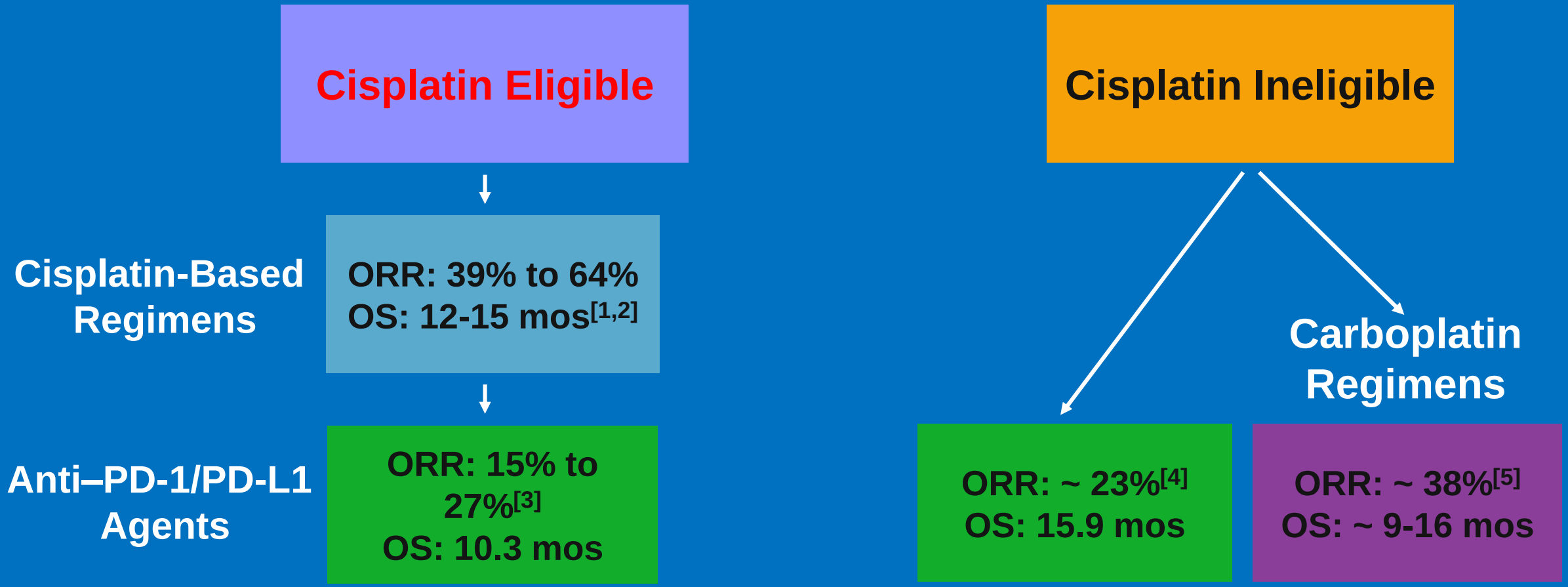
Lawrence et al. Nature 2013

- 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



Metastatik Mesane Kanseri Birinci Basamak Tedavi Seçenekleri



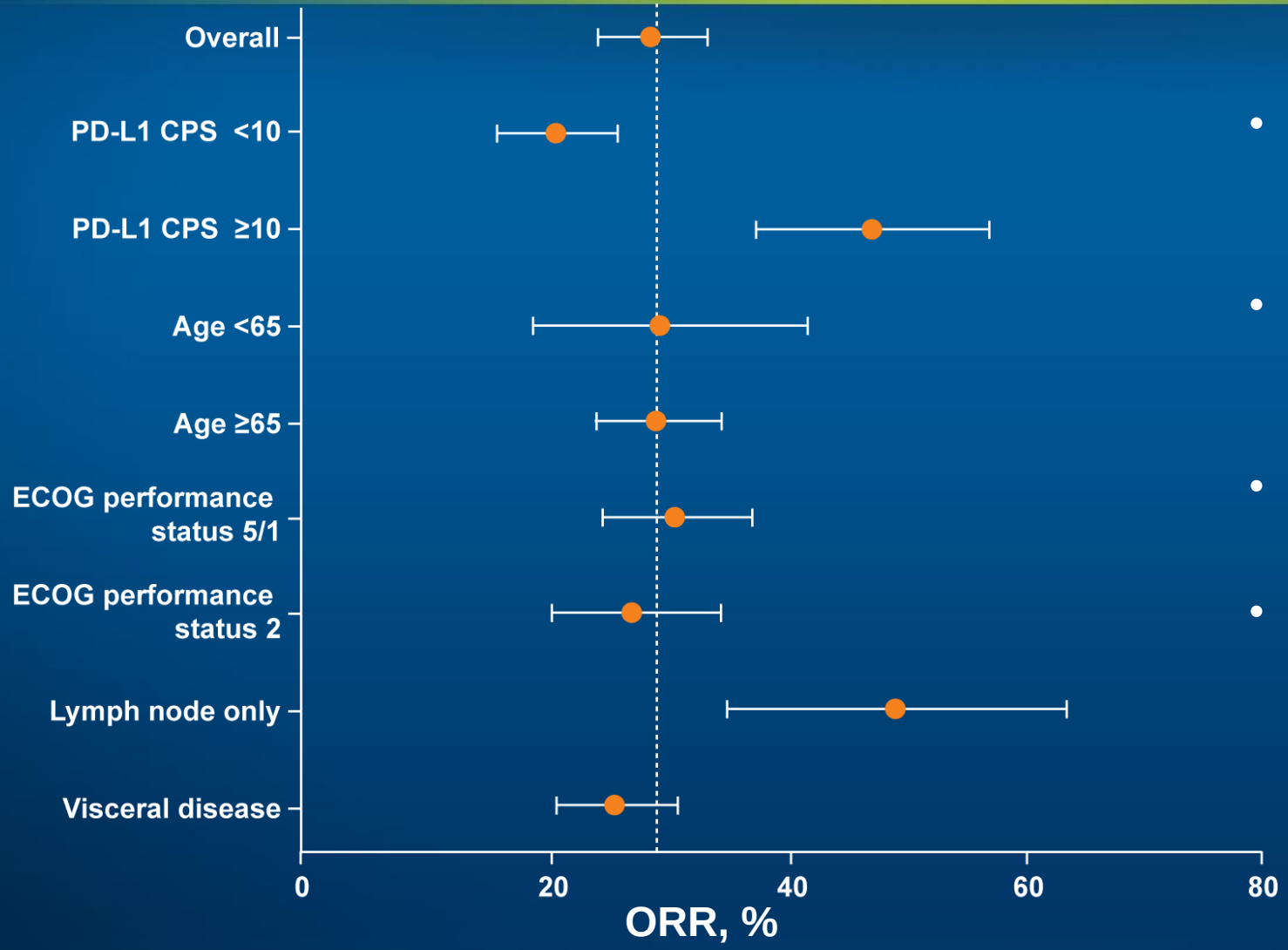
1. von Der Maase H, et al. J Clin Oncol. 2000;18:3068-3077. 2. Sternberg CN, et al. Eur J Cancer. 2006;42:50-54. 3. Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026. 4. Balar AV, et al. Lancet. 2017;389:67-76. 5. De Santis M, et al. J Clin Oncol. 2012;30:191-199.

Cisplatin-Ineligible Pts: Immunotherapy or Carboplatin-Based Chemotherapy?

Endpoint	Atezolizumab[1] Pembrolizumab[2] (Pivotal Phase II Trials)	Carboplatin + Gemcitabine[3] (Phase II Trial)	Carboplatin + Gemcitabine[4] (EORTC Phase II/III Trial)
ORR, %	~ 24 (up to 39% in selected pts)	38.3	36.1 confirmed
DCR, %	~ 30-45	63.3	74.0 unconfirmed
TTP/PFS, mos	~ 2-3	7.6	5.8
DoR, mos	NR	5.0	NR
OS, mos	15.9[1]	16.3	9.3
Toxicity	Fatigue Diarrhea Pruritus Rash irAEs Grade 3/4: 16%	Anemia Neutropenia Febrile neutropenia Nausea, emesis Grade 3: 18.3% Grade 4: 51.7%	9.3% with severe acute toxicities: Thrombocytopenia (grade 4) Renal toxicity (grade 3/4) Febrile neutropenia Mucositis (grade 3/4) 2 deaths

1. Balar AV, et al. Lancet. 2017;389:67-76. 2. Balar AV, et al. Lancet Oncol. 2017;18:1483-1492. 3. Bamias A, et al. Cancer. 2006;106:297-303. 4. Desantis M, et al. J Clin Oncol. 2012;30:191-199.

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.

Vuky J et al. *Proc ASCO* 2018;Abstract 4524.

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.

Cisplatin Uygun Olmayan Hastalarda Birinci Bamak Süren Çalışmalar

Trial	Phase	N	Opened	Estimated Completion
NCT03133390[1] ▪ Atezolizumab vs ▪ Atezolizumab + bevacizumab	II	118	September 2017	May 2019
NCT03361865[2] ▪ Pembrolizumab vs ▪ Pembrolizumab + epacadostat	III	650	December 2017	April 2021
NCT03240016[3] ▪ Pembrolizumab + nab-paclitaxel (single-arm)	II	36	December 2017	October 2021

1. ClinicalTrials.gov. NCT03133390. 2. ClinicalTrials.gov. NCT03133390. 3.ClinicalTrials.gov. NCT03240016.

Metastatik Mesane Kanseri İkinci Basamak Tedavi Seçenekleri

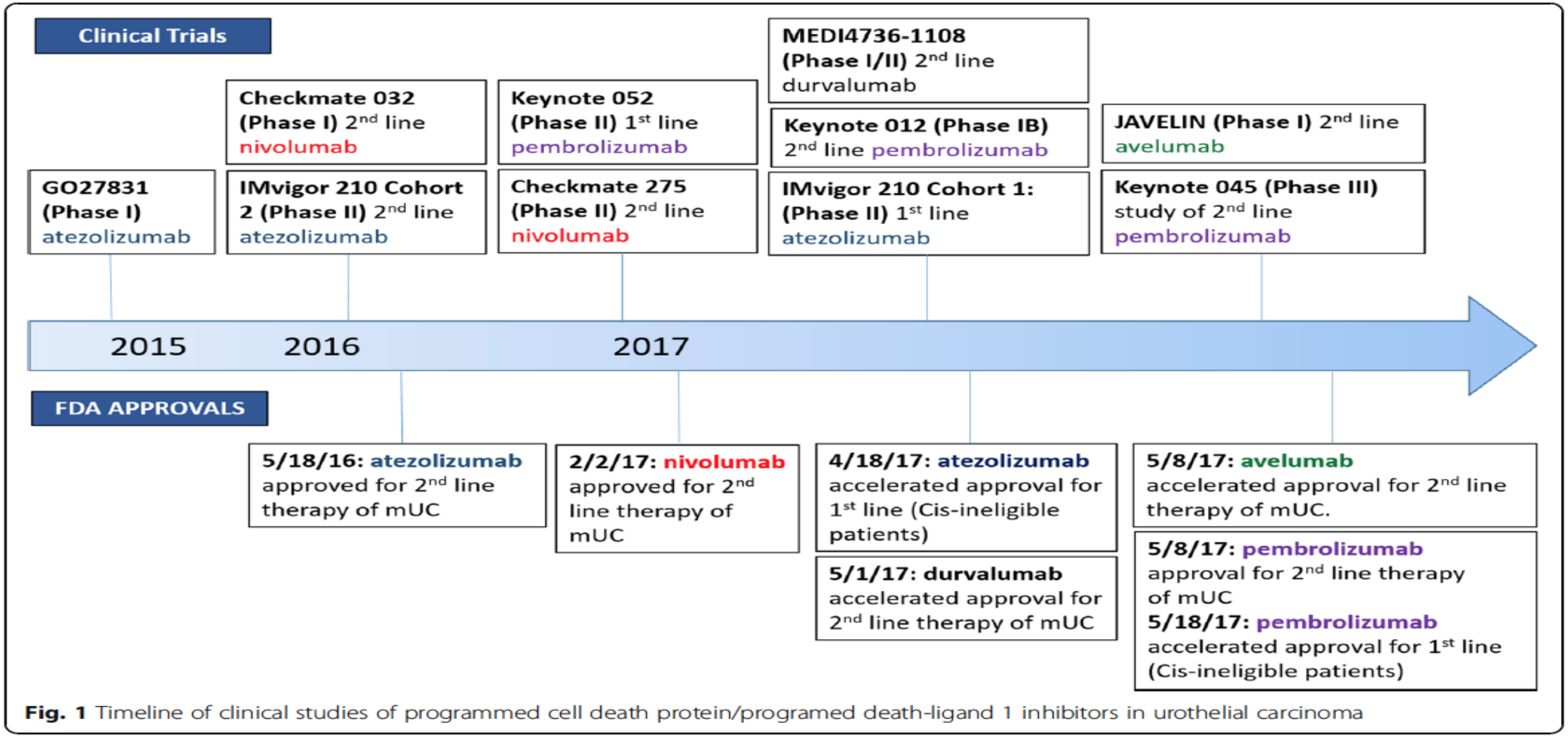


Fig. 1 Timeline of clinical studies of programmed cell death protein/programed death-ligand 1 inhibitors in urothelial carcinoma

Journal for ImmunoTherapy of Cancer (2017)

KEYNOTE-045: Çalışma dizaynı

- 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)

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)

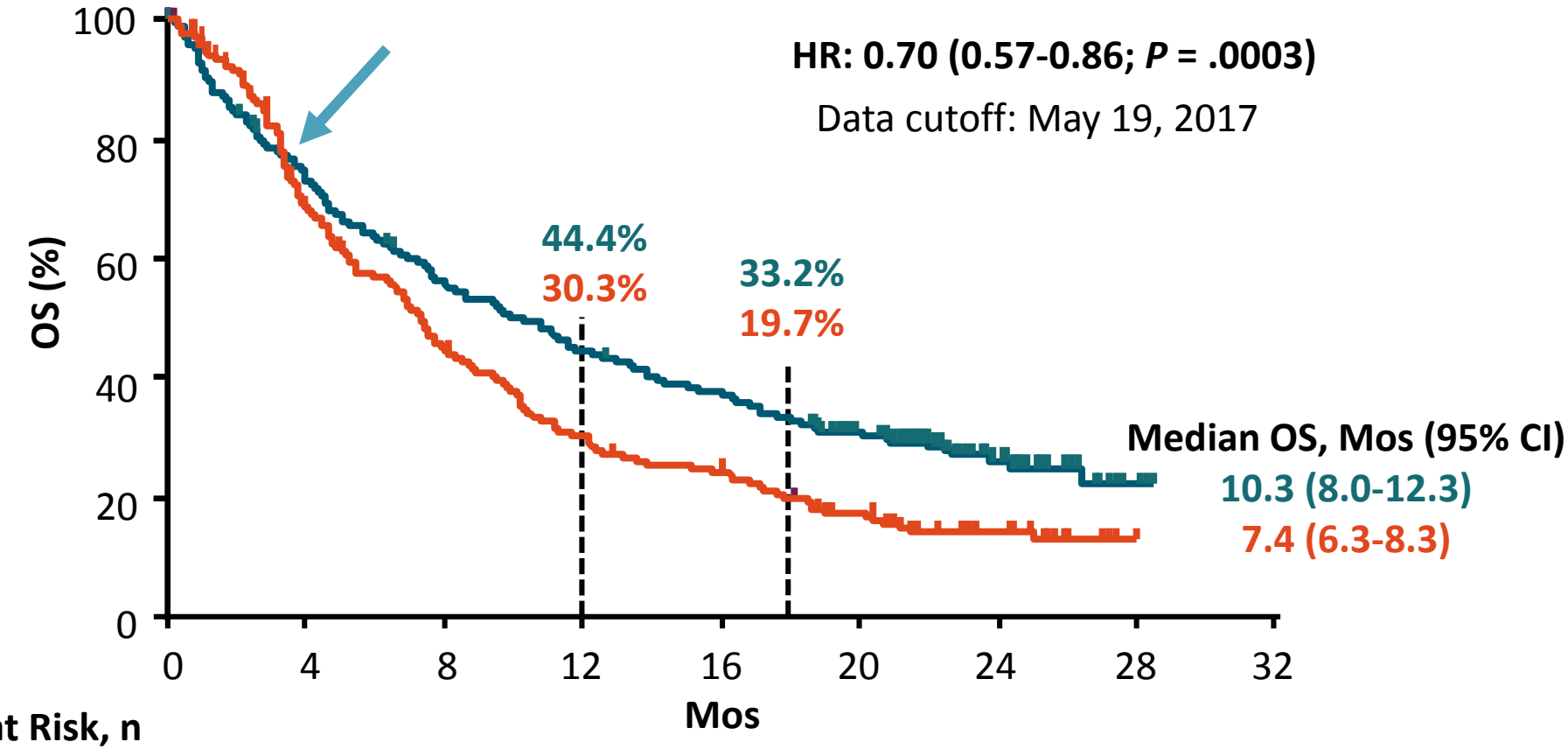
Paclitaxel 175 mg/m^2 IV Q3W or
Docetaxel 75 mg/m^2 IV Q3W or
Vinflunine 320 mg/m^2 IV Q3W
(n = 272)

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

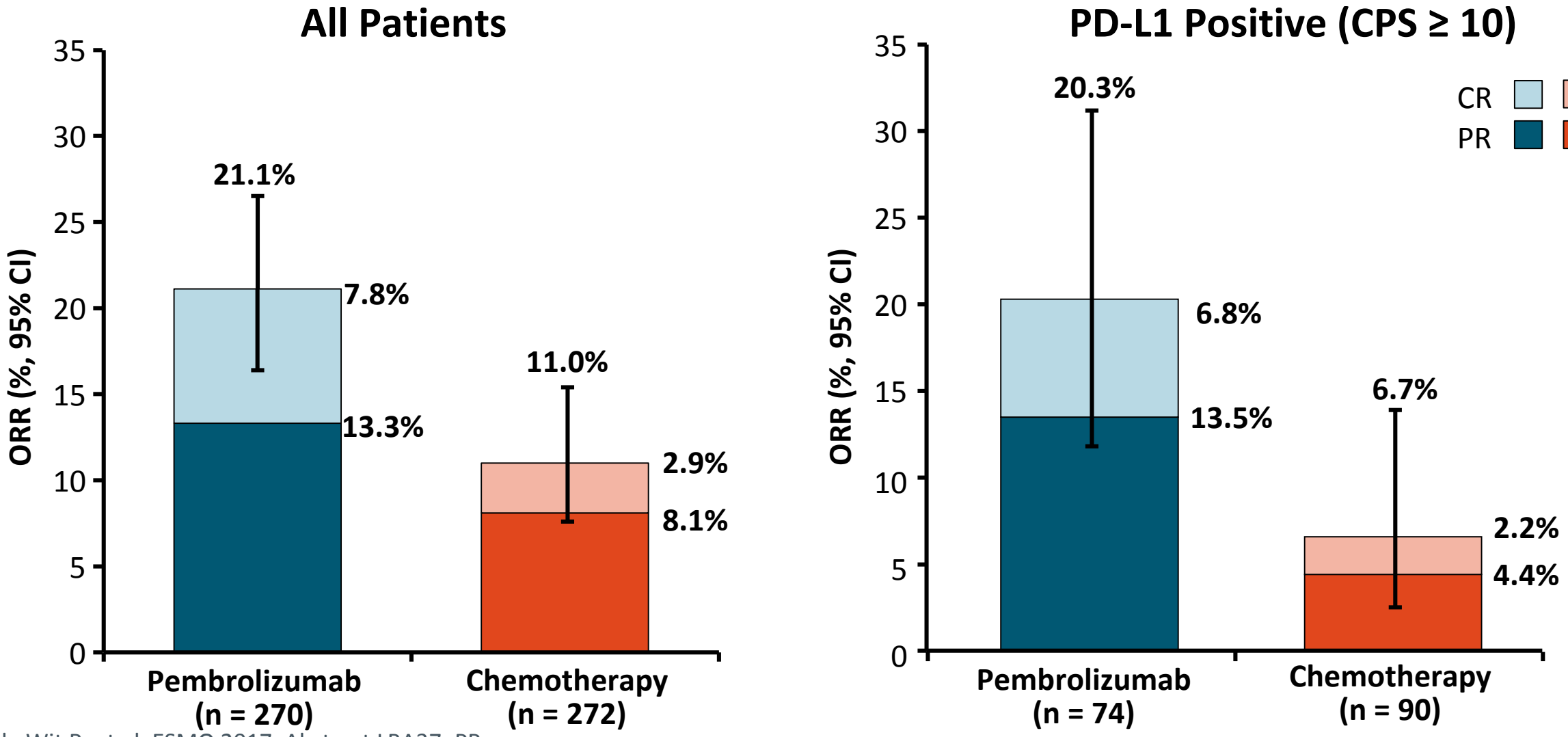


Patients at Risk, n

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: ORR



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

IMvigor211 Study Design

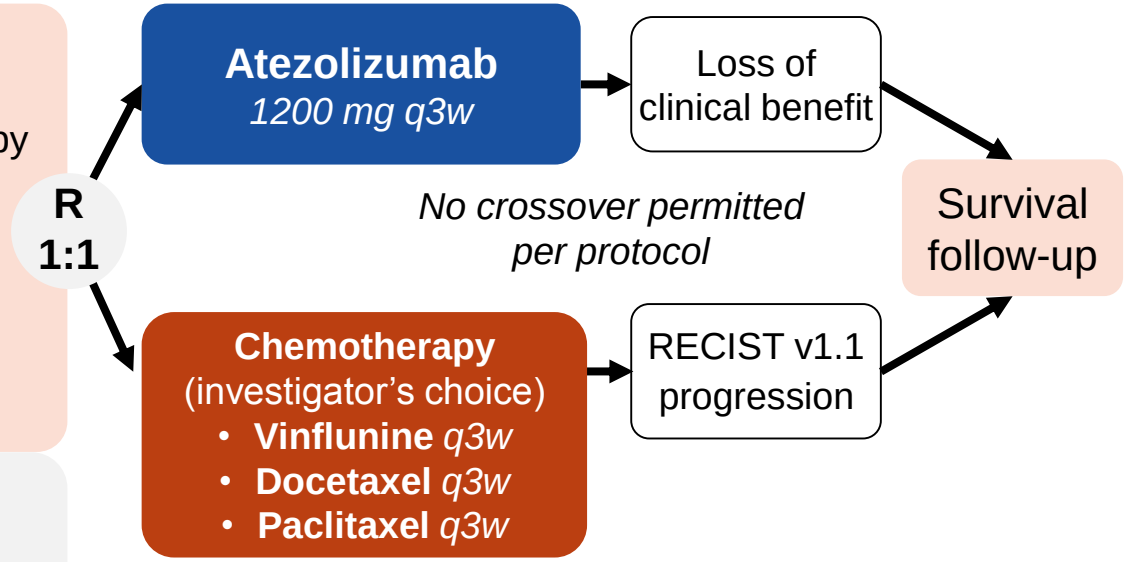
Key Eligibility Criteria[a]

- 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)

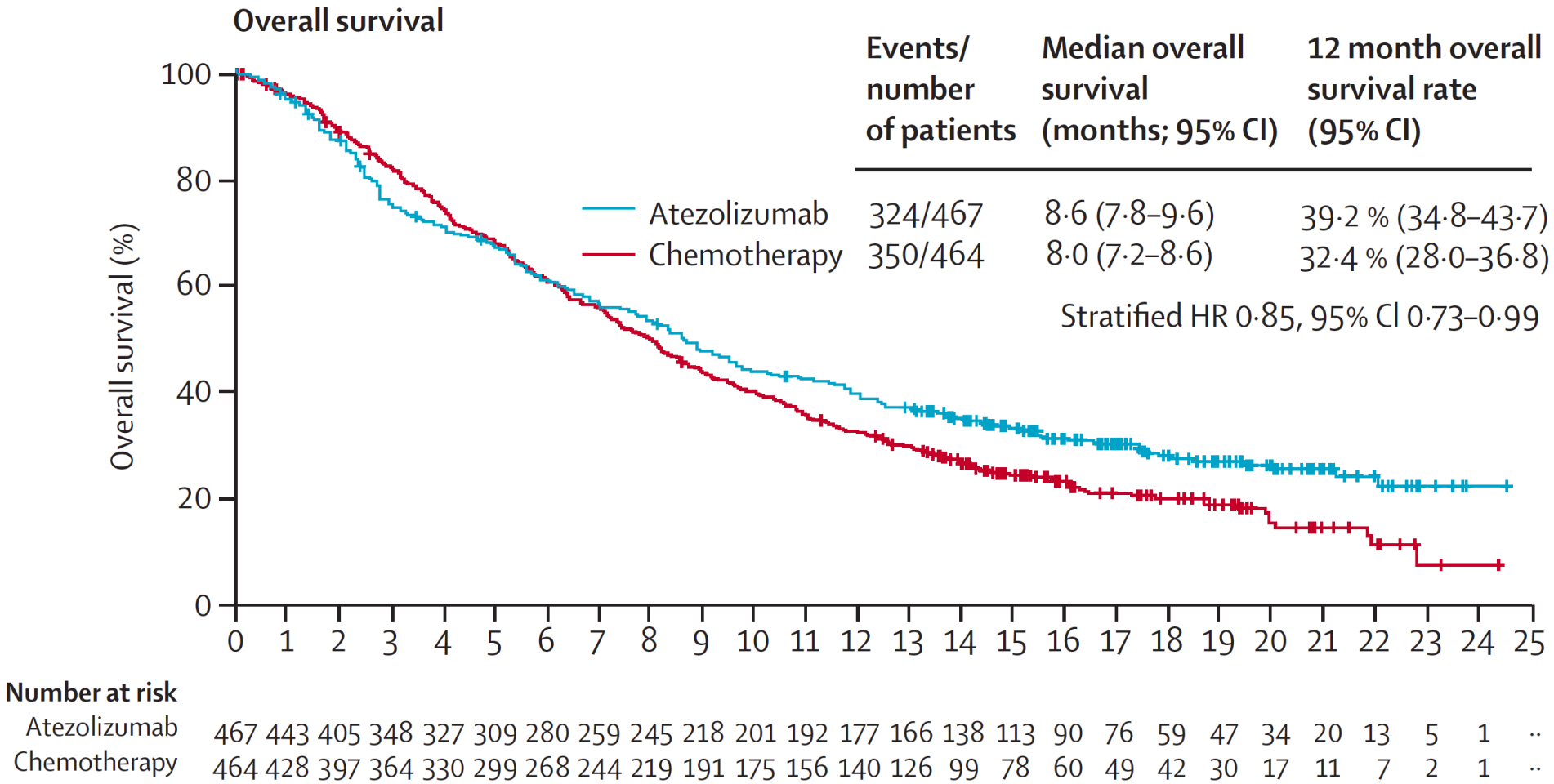


- **Primary endpoint**
  - OS, tested hierarchically in pre-specified populations
- **Additional endpoints**
  - Efficacy: RECIST v1.1 ORR, PFS and DOR[c]
  - Safety
  - PROs: EORTC QLQ-C30

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

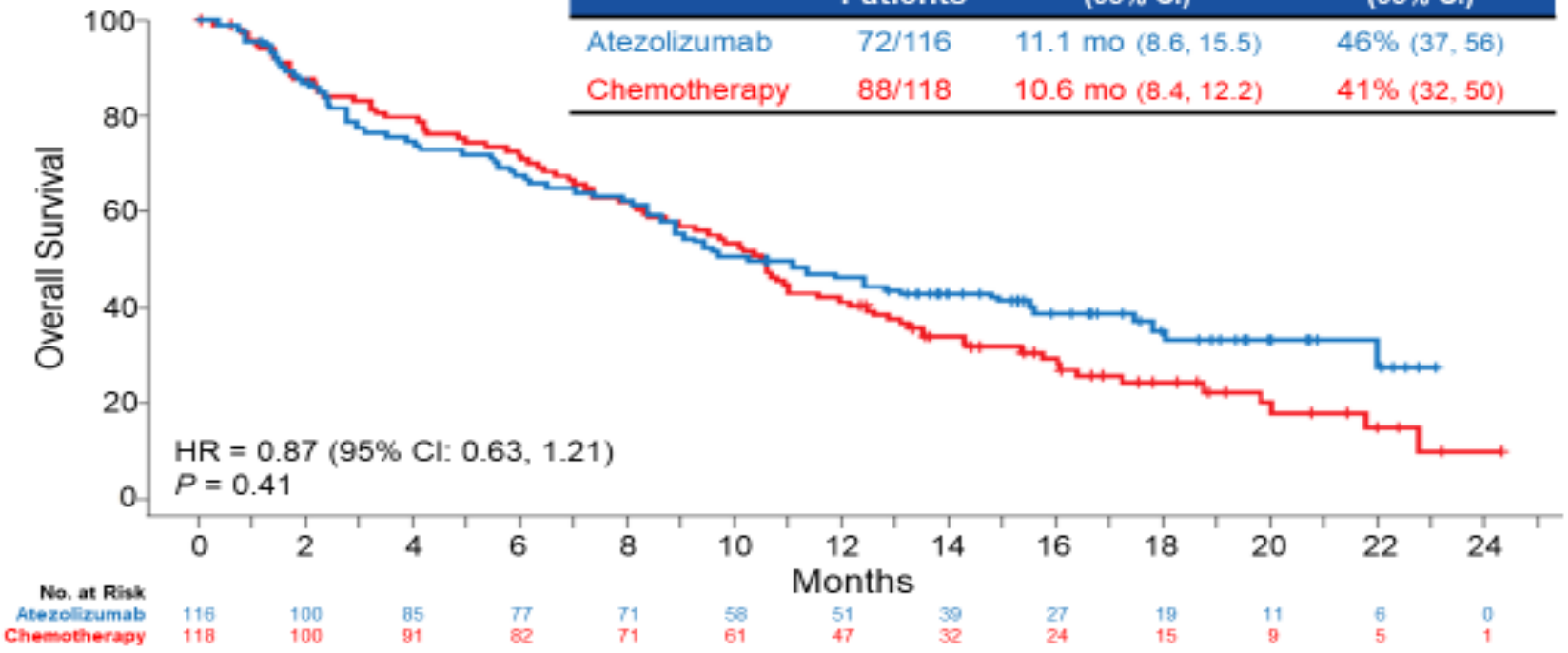


IMvigor211 Sonuçları

2nd Special Conference
EACR
AACR
SIC

OS Analysis: IC2/3 Population

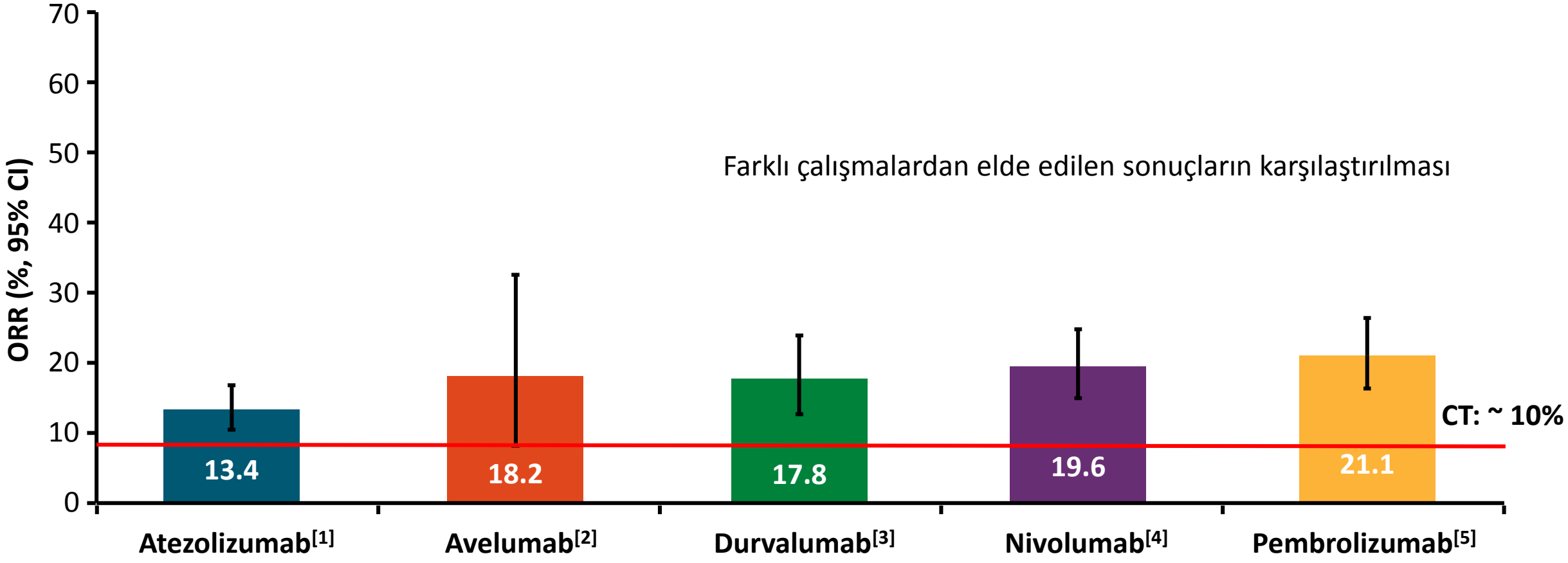
	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)



HR, hazard ratio.

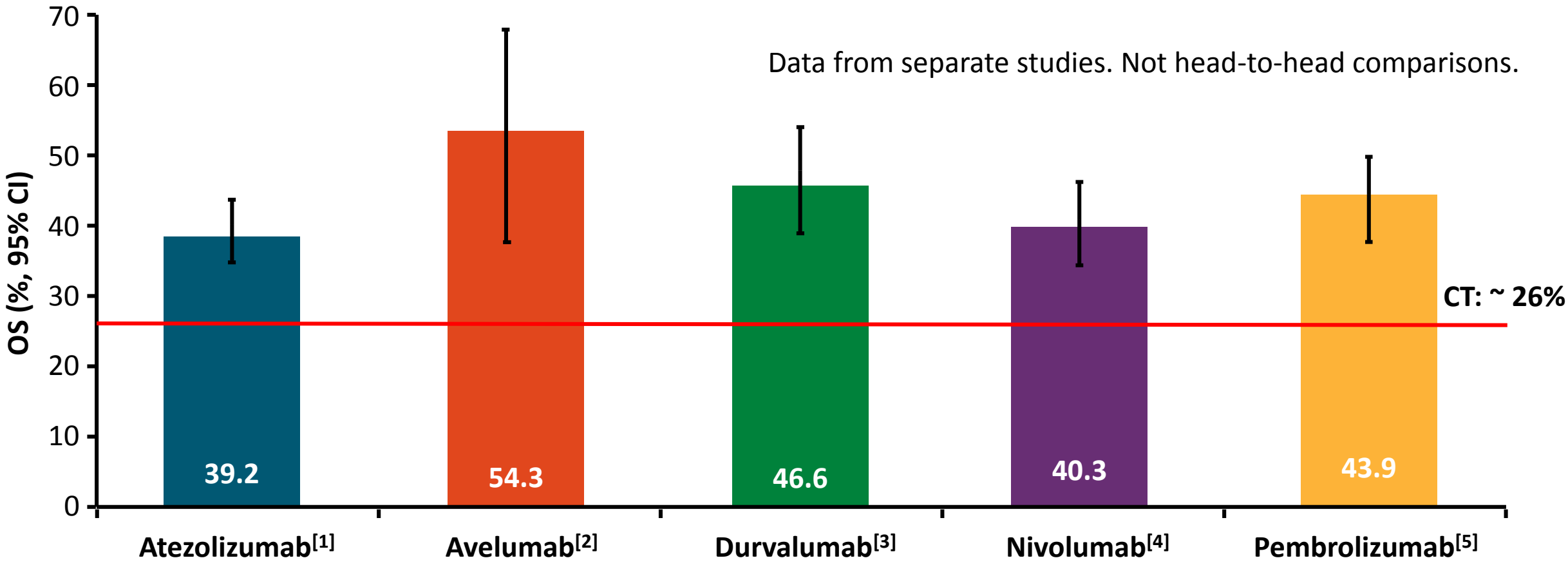
Powles T, et al. EAS 2017, IMvigor211.

Platin sonrası immünoterapi tedaviler: ORR



1. Powles T, et al. Lancet. 2018;391:748-757. 2. Apolo AB, et al. J Clin Oncol. 2017;35:2117-2124.
3. Powles T, et al. JAMA Oncol. 2017;3:e172411. 4. Sharma P, et al. Lancet Oncol. 2017;18:312-322.
5. Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

Platin sonrası immünoterapi : 12 ayda OS



1. Powles T, et al. Lancet. 2018;391:748-757. 2. Apolo AB, et al. J Clin Oncol. 2017;35:2117-2124.
3. O'Donnell P, et al. AACR 2018. Abstract CT031. 4. Sharma P, et al. AACR 2018. Abstract CT178.
5. Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

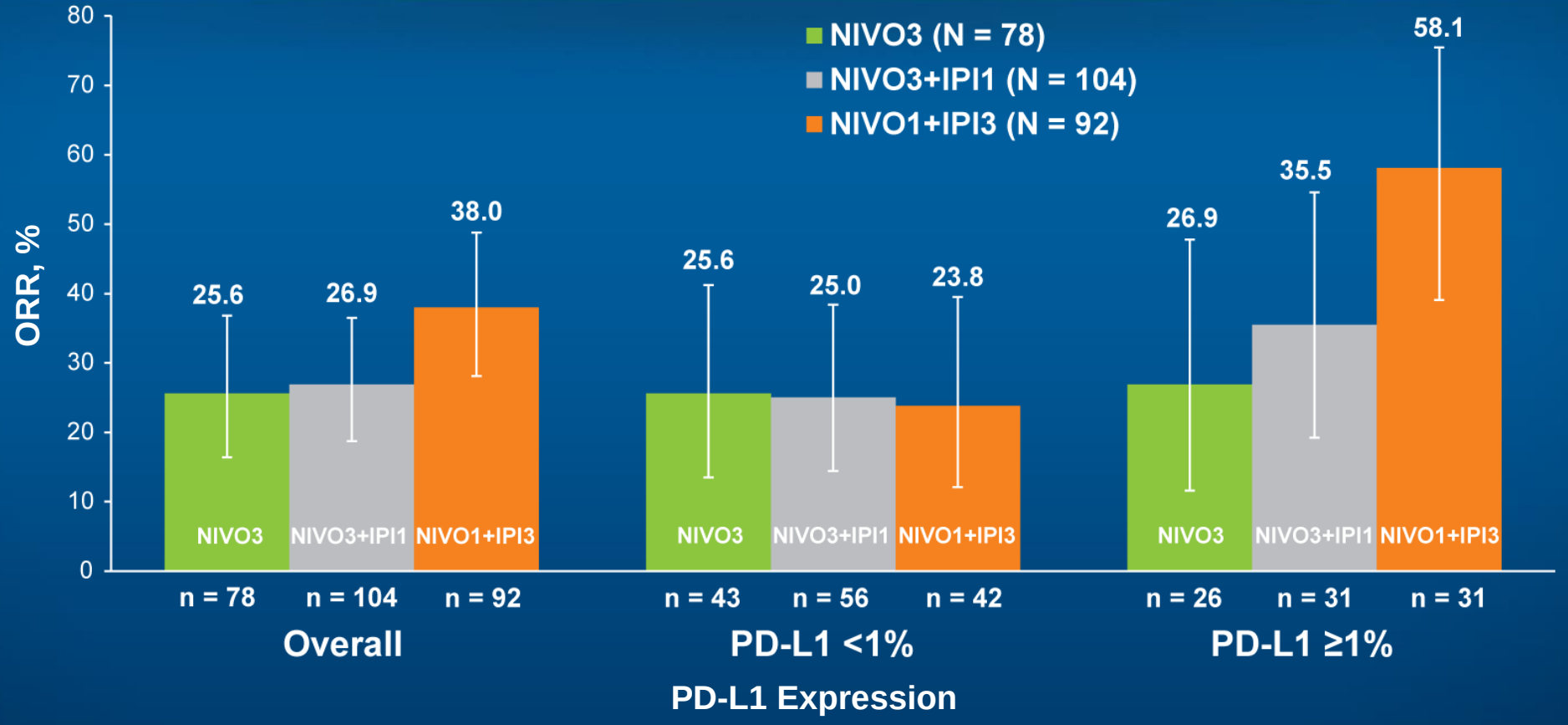
Platin sonrası: Güvenlik

Agent	Phase	Median F/U, Mos	Patients, n	Treatment-Related AEs, %			
				Any	Grade 3/4	Death	None
Atezolizumab[1]	III	17.3	459	70	20	< 1	30
Avelumab[2]	Ib	16.5	44	66	7	0	34
Durvalumab[3]	I/II	5.78	191	61	7	1	39
Nivolumab[4]	II	7.0	270	64	18	1	36
Pembrolizumab[5]	III	14.1	266	61	15*	2	39

*Reported as grade 3-5.

1. Powles T, et al. Lancet. 2018;391:748-757. 2. Apolo AB, et al. J Clin Oncol. 2017;35:2117-2124.
3. Powles T, et al. JAMA Oncol. 2017;3:e172411. 4. Sharma P, et al. Lancet Oncol. 2017;18:312-322.
5. Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

CheckMate 032: Response to Nivolumab Alone or in Combination with Ipilimumab in Platinum-Pretreated mUC by PD-L1 Expression



Overall cohort	NIVO3	NIVO3 + IPI1	NIVO1 + IPI3
Responders, N	20	28	35
Duration of response, median	30.5 mo	22.3 mo	22.9 mo

Rosenberg JE et al. *Proc ESMO* 2018;Abstract LBA32.

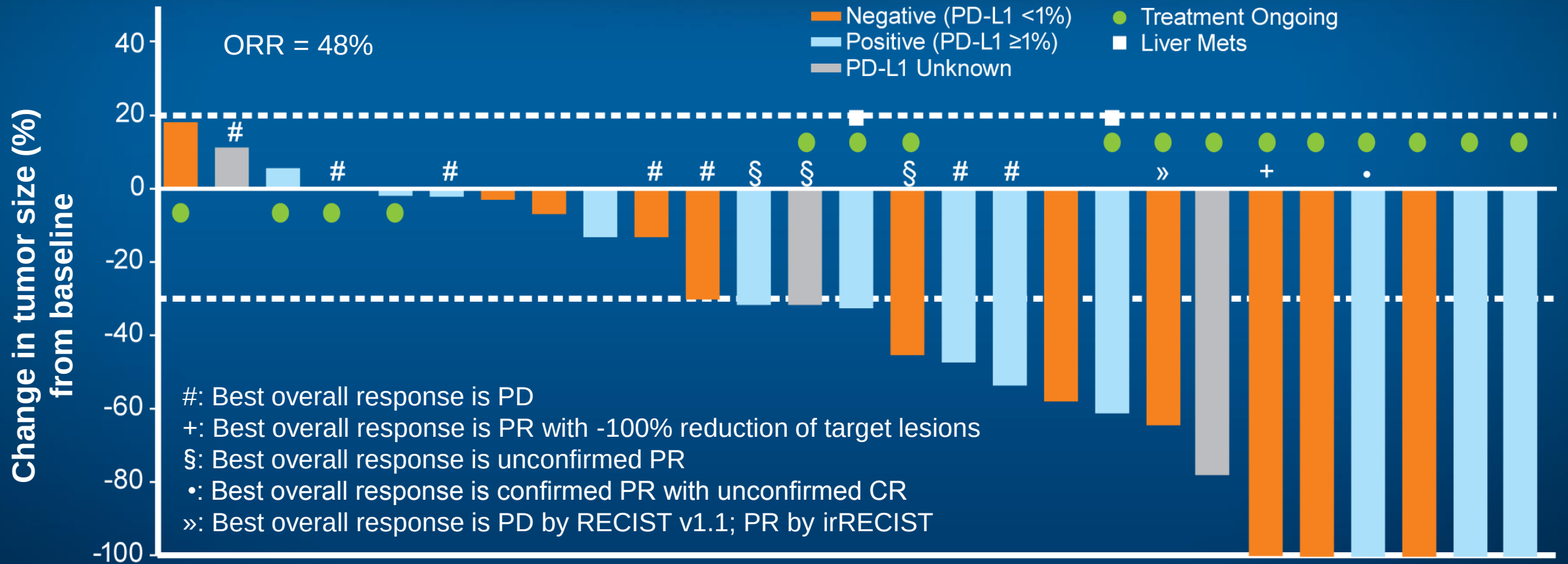
Activity and Tolerability of Durvalumab in Combination with Tremelimumab in Platinum-Refractory Metastatic UC

Response and survival	Overall (n = 168)	PD-L1 ≥ 25% (n = 68)	PD-L1 < 25% (n = 86)	PD-L1 unknown (n = 14)
Confirmed ORR	20.8%	29.4%	15.1%	14.3%
Ongoing ORR	74.3%	60.0%	92.3%	100%
Disease control rate	29.2%	32.4%	24.4%	42.9%
Median PFS	1.9 mo	3.5 mo	1.8 mo	4.9 mo
6-month PFS rate	25.4%	26.1%	22.6%	38.5%
Median OS	9.5 mo	18.9 mo	8.0 mo	16.4 mo
6-month OS rate	60.9%	66.4%	51.9%	91.7%

- Treatment-related AEs occurred in 75.6% of patients (Grade 3-4 = 28.6%).
- One patient died due to a treatment-related AE (pulmonary hemorrhage).
- Treatment-related AEs led to discontinuation of therapy in 11.9% of patients.

Balar AV et al. *Proc AACR* 2018;Abstract CT112.

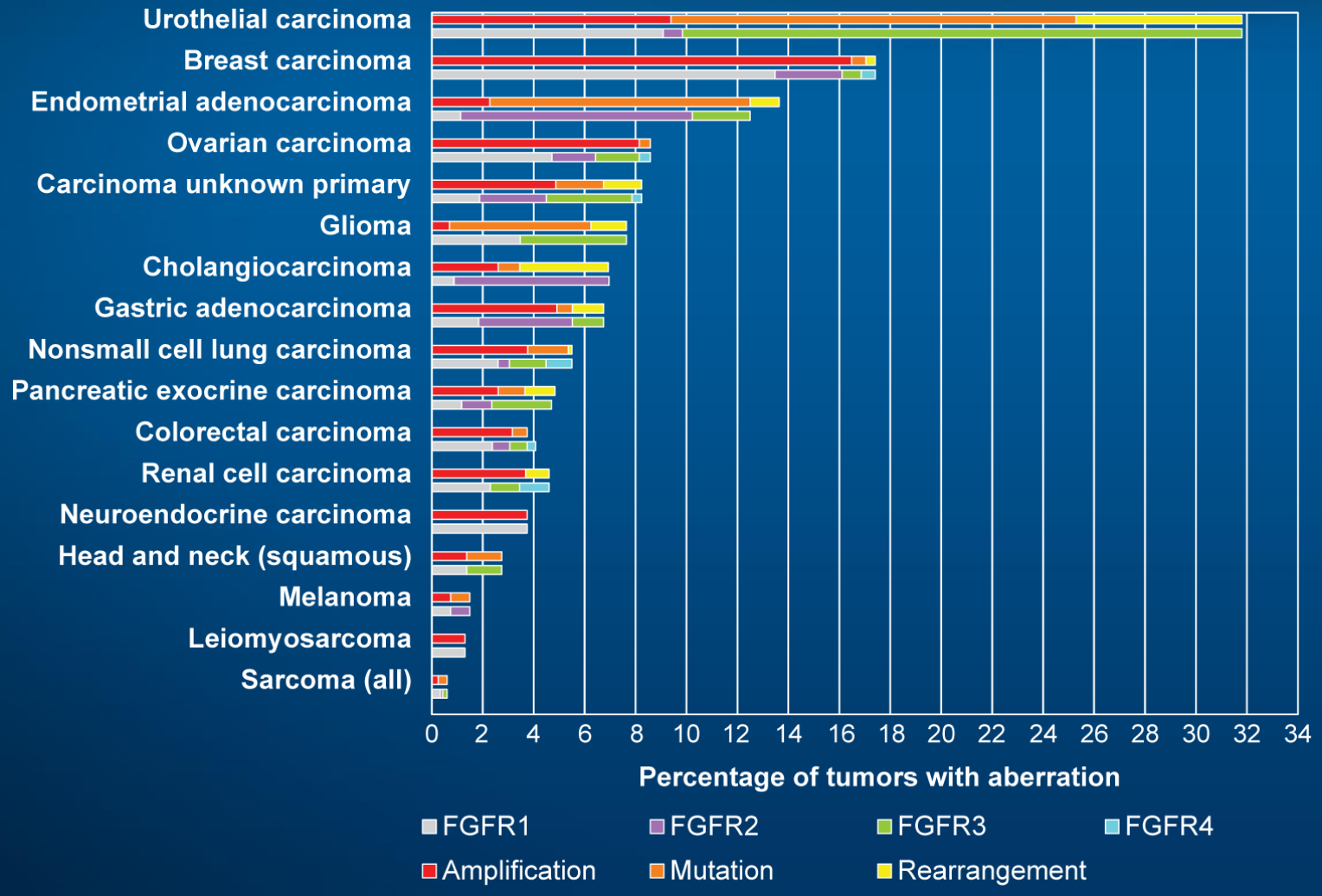
PIVOT-02: Updated Results of a Phase I/II Study of Bempegaldesleukin (NKTR-214) with Nivolumab as First-Line Therapy for Advanced UC



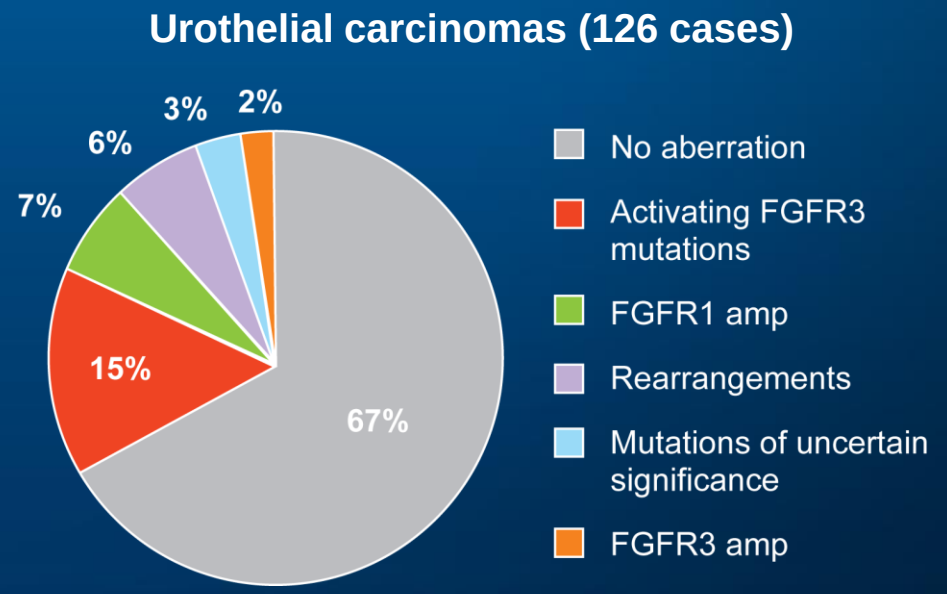
- Most common Grade 1 or 2 TRAEs occurring in >15% of the population (n = 41): flu-like symptoms (71%), fatigue (56%), rash (46%), pruritus (32%), decreased appetite (27%), nausea (22%)

Siefker-Radtke M et al. Genitourinary Cancers Symposium 2019;Abstract 388.

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

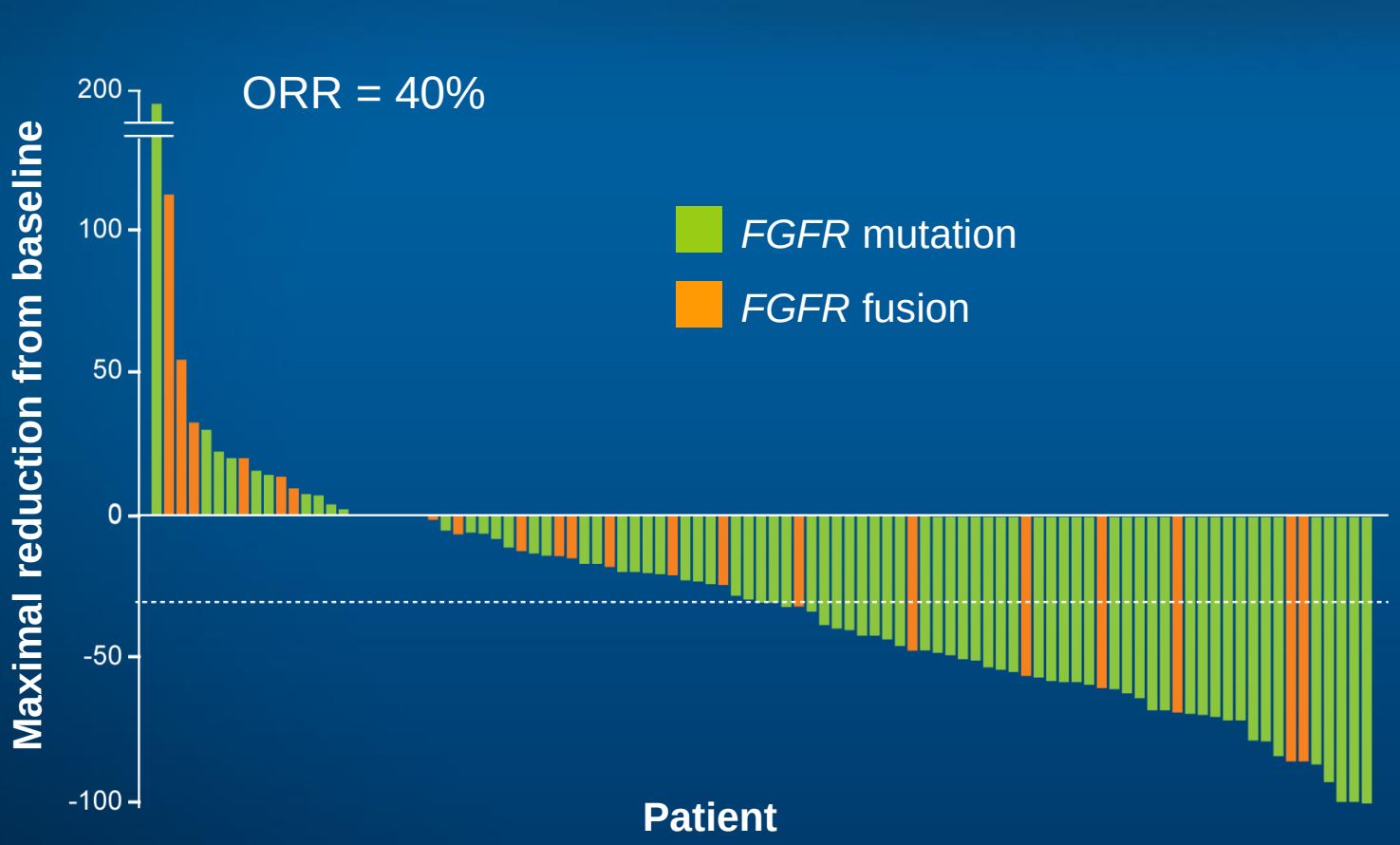


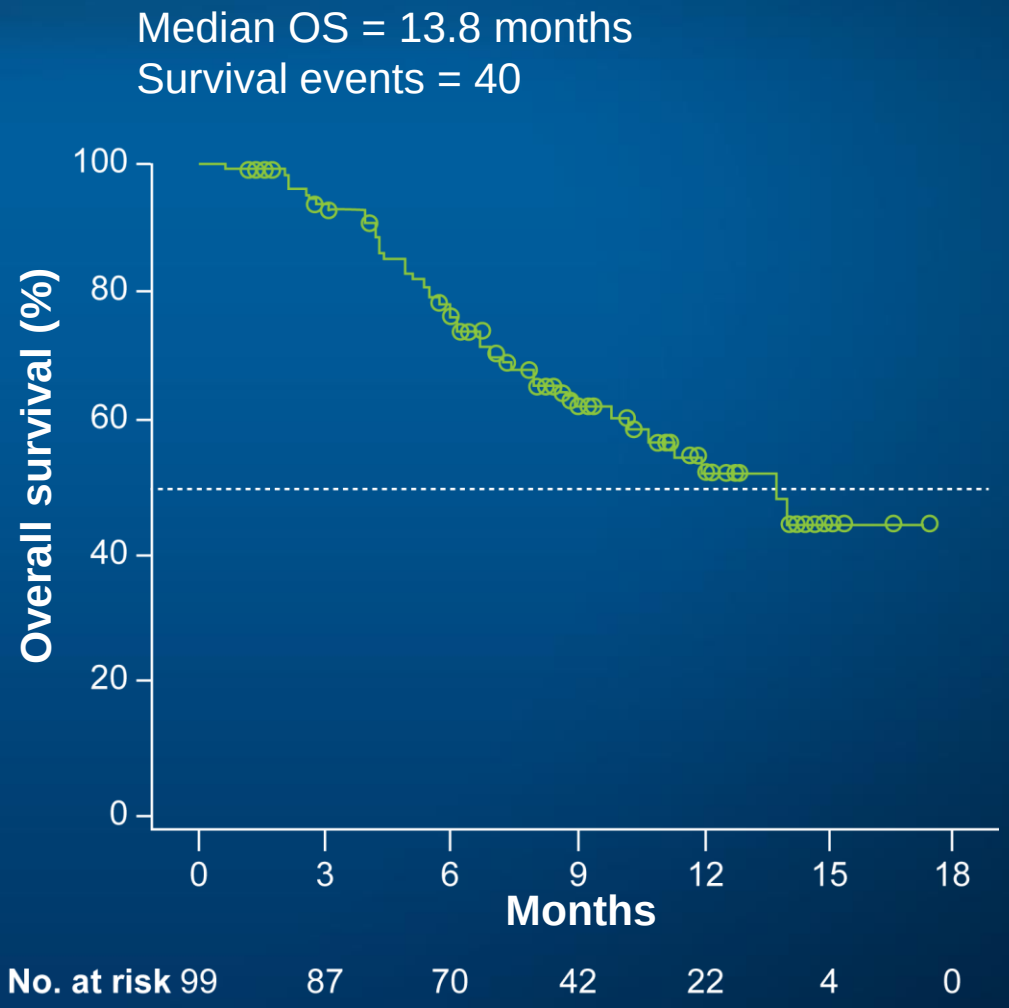
- The FGF/FGFR signalling axis comprises 18 ligands, which bind to 4 highly conserved trans-membrane tyrosine kinase receptors (FGFR1, 2, 3 and 4)



Helsten T et al. *Clin Cancer Res* 2016;22(1):259-67.

BLC2001: Response and Survival

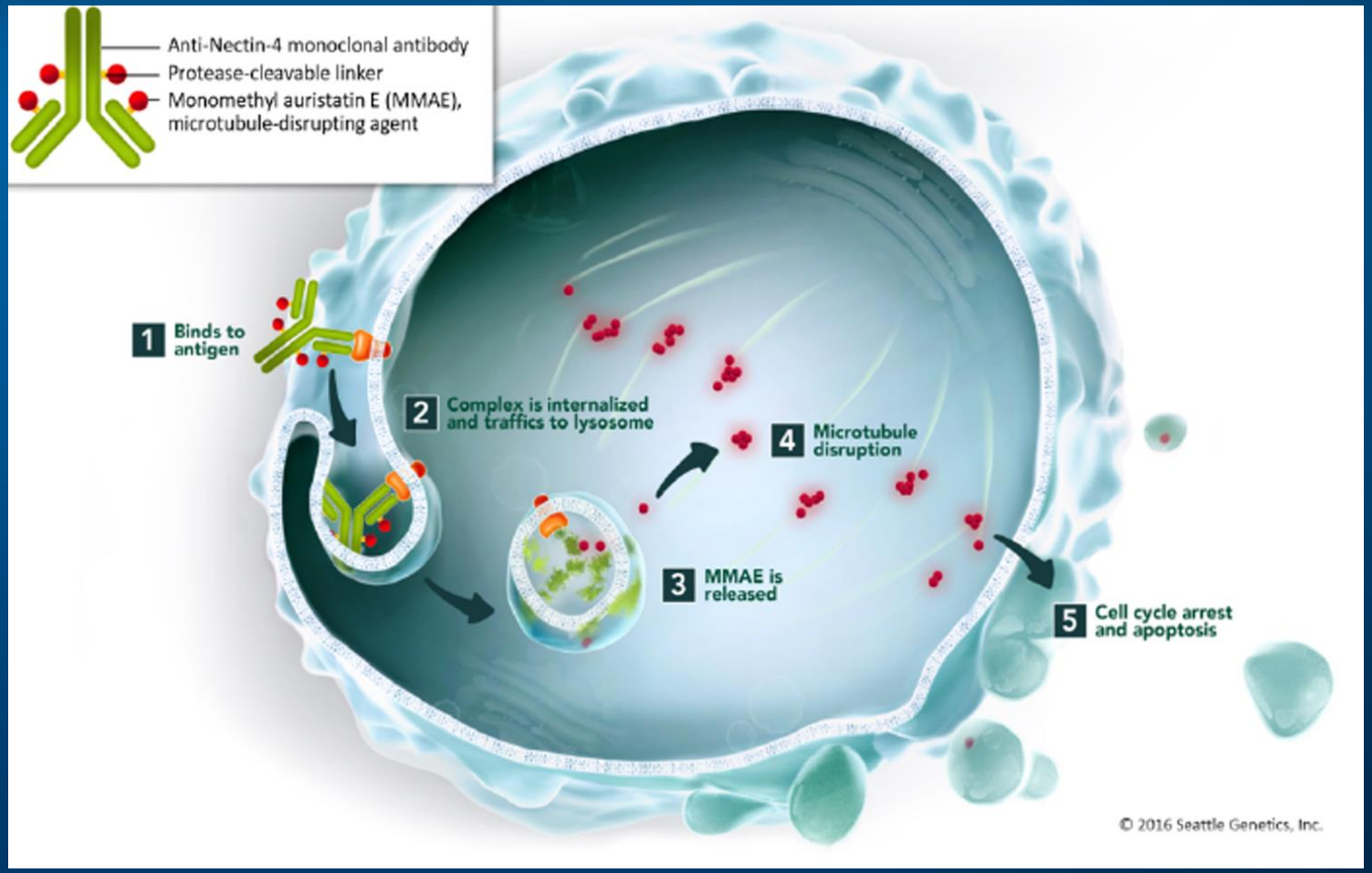




Siefker-Radtke AO et al. *Proc ASCO* 2018;Abstract 4503.

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

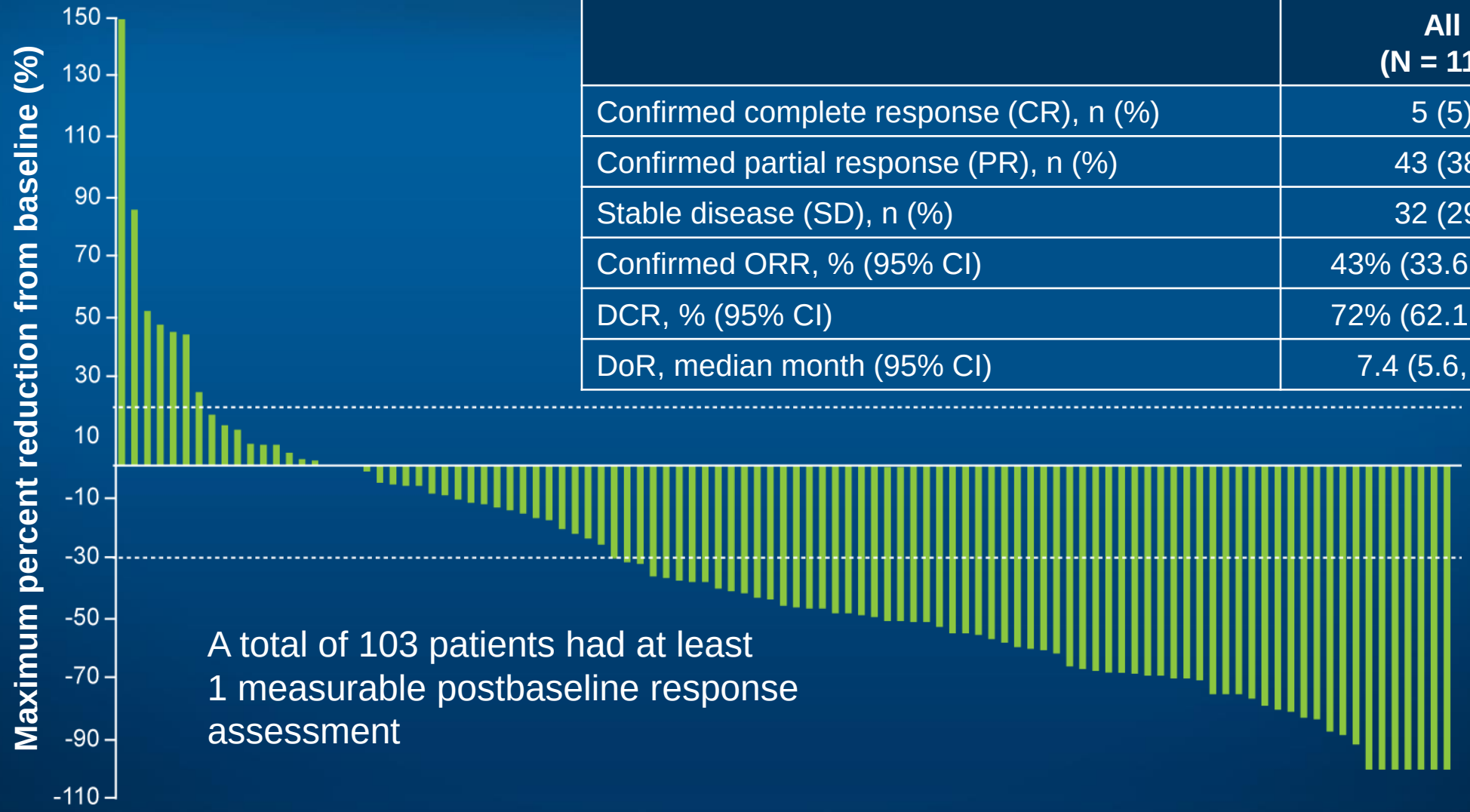
- Nectin-4, a transmembrane cell adhesion molecule,[1,2] was found to be highly expressed in 97% of mUC patient samples[3]
- Enfortumab vedotin (EV) is a fully humanized monoclonal antibody against Nectin-4 conjugated with the microtubule-disrupting agent monomethyl auristatin E by a protease-cleavable 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.

Phase I EV-101 Trial of Enfortumab Vedotin in Metastatic Urothelial Cancer: Response

	All (N = 112)
Confirmed complete response (CR), n (%)	5 (5)
Confirmed partial response (PR), n (%)	43 (38)
Stable disease (SD), n (%)	32 (29)
Confirmed ORR, % (95% CI)	43% (33.6, 52.6)
DCR, % (95% CI)	72% (62.1, 79.6)
DoR, median month (95% CI)	7.4 (5.6, 9.6)



Rosenberg JE et al. Genitourinary Cancers Symposium 2019;Abstract 377.

Select Ongoing Phase III Studies of PD-1/PD-L1 Checkpoint Inhibitors as First-Line Therapy

Study	Target accrual	Eligibility	Randomization	Primary endpoints
KEYNOTE-361 (NCT02853305)	990	• Advanced/unresectable or metastatic UC • No prior systemic therapy for advanced or metastatic UC, except neoadjuvant or adjuvant platinum-based chemo	• Pembrolizumab • Pembrolizumab + chemo* • Chemo*	PFS, OS
IMvigor130 (NCT02807636)	1,200	• Locally advanced or metastatic UC • No prior chemotherapy for advanced or metastatic UC, except neoadjuvant or adjuvant chemo with therapy-free interval of >12 mo from last treatment	• Atezolizumab • Atezolizumab + chemo* • Placebo + chemo*	PFS, OS, AEs

* Chemo = gemcitabine + cisplatin or carboplatin

www.clinicaltrials.gov. Accessed May 24, 2019.

Radyoterapi-immünoterapi çalışmaları

Study	Eligibility	Design	Intervention	Institution/Group
NCT02891161 (DUART)	MIBC Cis-ineligible	Phase Ib/II	RT + concurrent/adjuvant durvalumab	Big Ten Consortium
NCT03317158 (ADAPT-Bladder)	NMIBC	Phase I/II	Durvalumab alone, durvalumab + RT, durvalumab + BCG	Hoosier Cancer Research Network
NCT02662062 (PCR-MIB)	MIBC	Phase II	RT + concurrent cisplatin + concurrent/adjuvant pembrolizumab	ANZUP
NCT03171025 (NEXT)	MIBC/urethra/ ureter	Phase II	ChemoRT followed by adjuvant nivolumab	University of Utah
NCT03419130	MIBC No Chemo	Phase IIR	Concurrent pembrolizumab + either conventional RT vs. hypofractionated RT	UCSF
NCT02621151	MIBC	Phase II	RT + concurrent gemcitabine + pembrolizumab	NYU/Multi-institutional
NCT02560636 (PLUMMB)	MIBC, M0-M1	Phase I	RT + concurrent pembrolizumab	Royal Marsden

Metastatik Mesane Kanseri
İkinci Basamak Tedavi Seçimi

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Bladder Cancer

NCCN Guidelines Index
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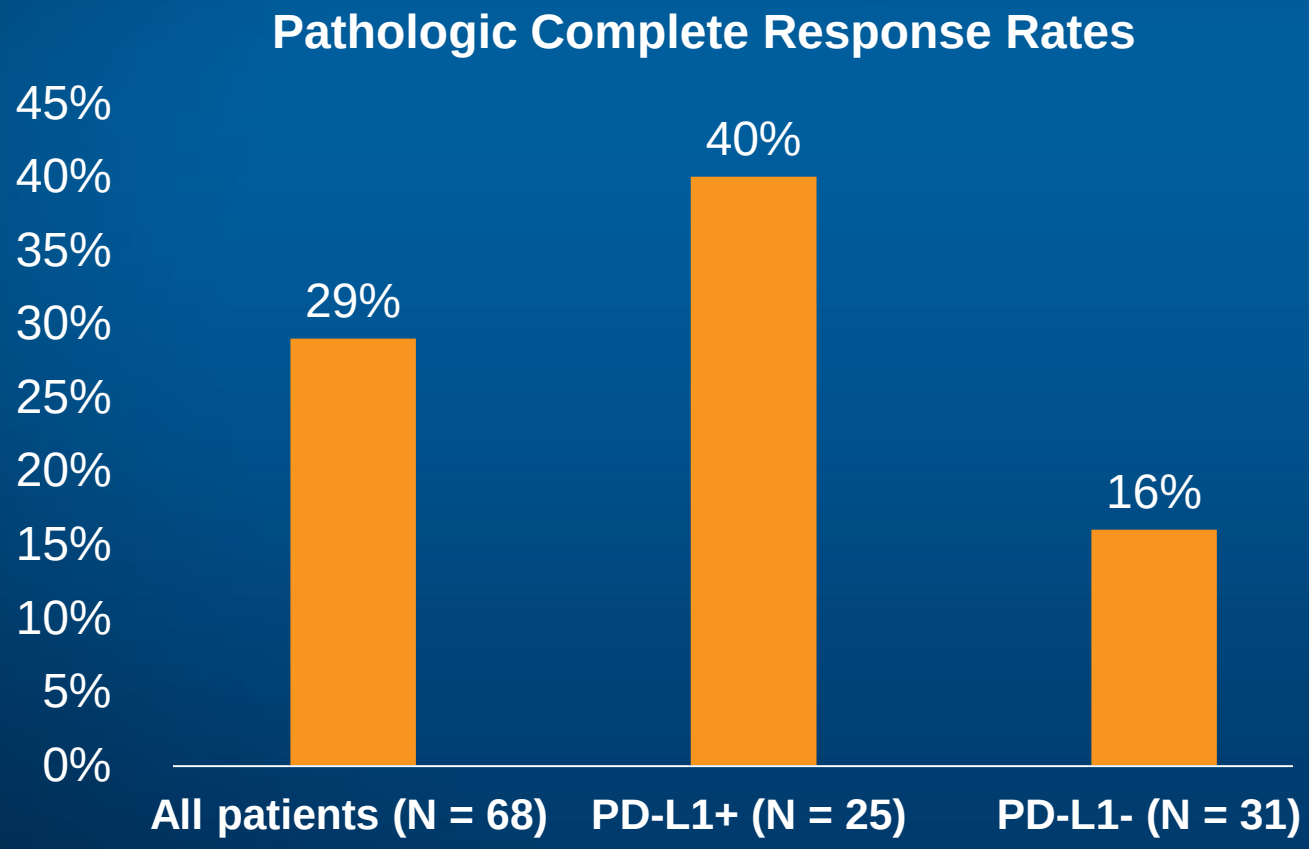
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1)[18]	Other recommended regimens • Albumin-bound paclitaxel[27] • Paclitaxel or docetaxel[25] • Gemcitabine[14] • Pemetrexed[26]
Alternative preferred regimens • Atezolizumab[19] • Nivolumab[20] • Durvalumab[21] • Avelumab[22,23] • Erdafitinib[d,24]	Useful in certain circumstances based on prior medical therapy • Ifosfamide[28] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

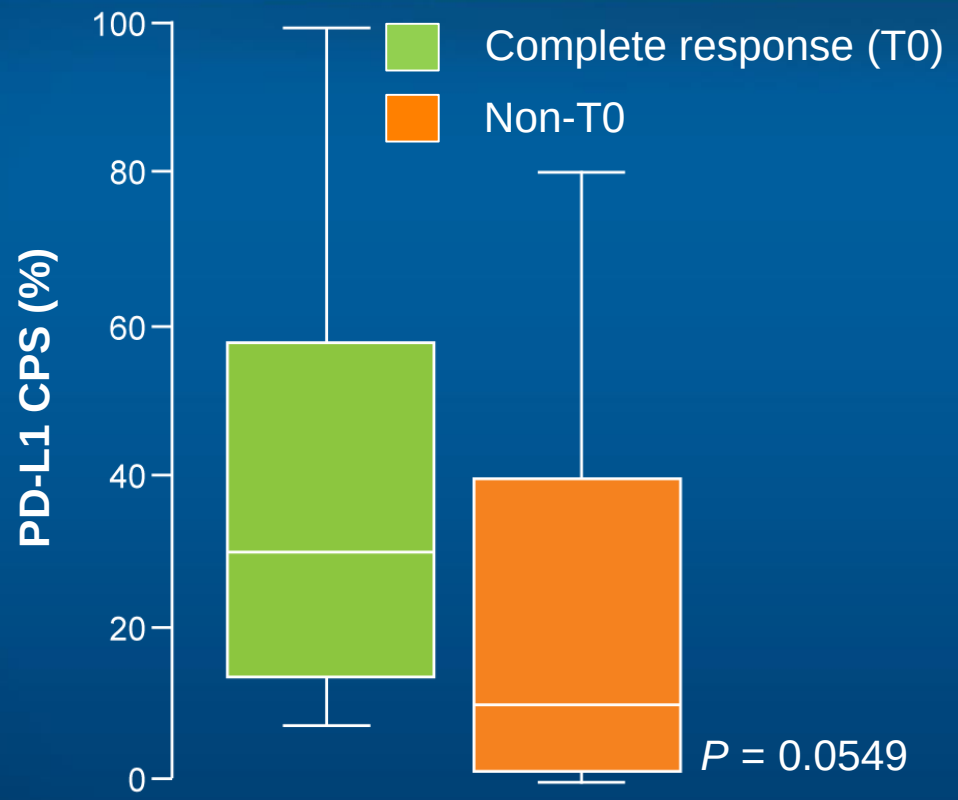
ABACUS: Safety and Efficacy of Neoadjuvant Atezolizumab in Muscle-Invasive Bladder Cancer

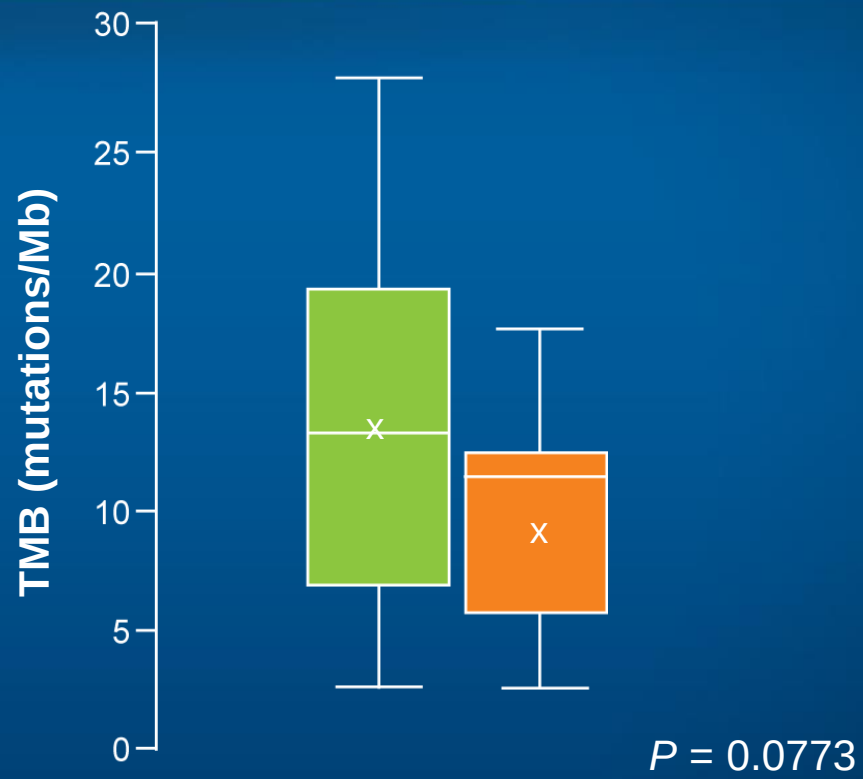


Adverse event	Grade 3-4	Total
Fatigue	3%	21%
Transaminitis	4%	7%
Anorexia	1%	8%
Rash	0%	7%
Pyrexia	1%	5%
Diarrhea	0%	5%
Pruritus	0%	5%

Powles T et al. *Proc ASCO* 2018;Abstract 4506.

PURE-01: Pathologic Complete Response by PD-L1 Combined Positive Score (CPS) and Tumor Mutational Burden (TMB)





	All patients (N = 50)	PD-L1 CPS ≥10% (n = 35)	PD-L1 CPS <10% (n = 15)
Pathologic complete response	42%	54%	13%
Pathologic downstaging to pT <2	54%	66%	27%

Necchi A et al. *J Clin Oncol* 2018;[Epub ahead of print]; Necchi A et al. *Proc ASCO* 2018;Abstract 4507.

Neoadjuvant İmmünoterapi Çalışmaları Faz II erken sonuçları

Characteristic	Pembrolizumab (n = 43)[1]	Atezolizumab (n = 68)[2]
Eligibility criteria	T2-T3b; N1 allowed	T2-T4a; N0 only
Cisplatin eligible, %	100	0
Received neoadjuvant CT, %	12	0
Duration of neoadjuvant checkpoint inhibition	3 cycles (9 wks)	2 cycles (6 wks)
Safe	Yes	Yes
Pathological CR (pT0), %	40	29
Available biomarker data	Yes	Yes

Kemoterapi sonrası pT0 oranları:

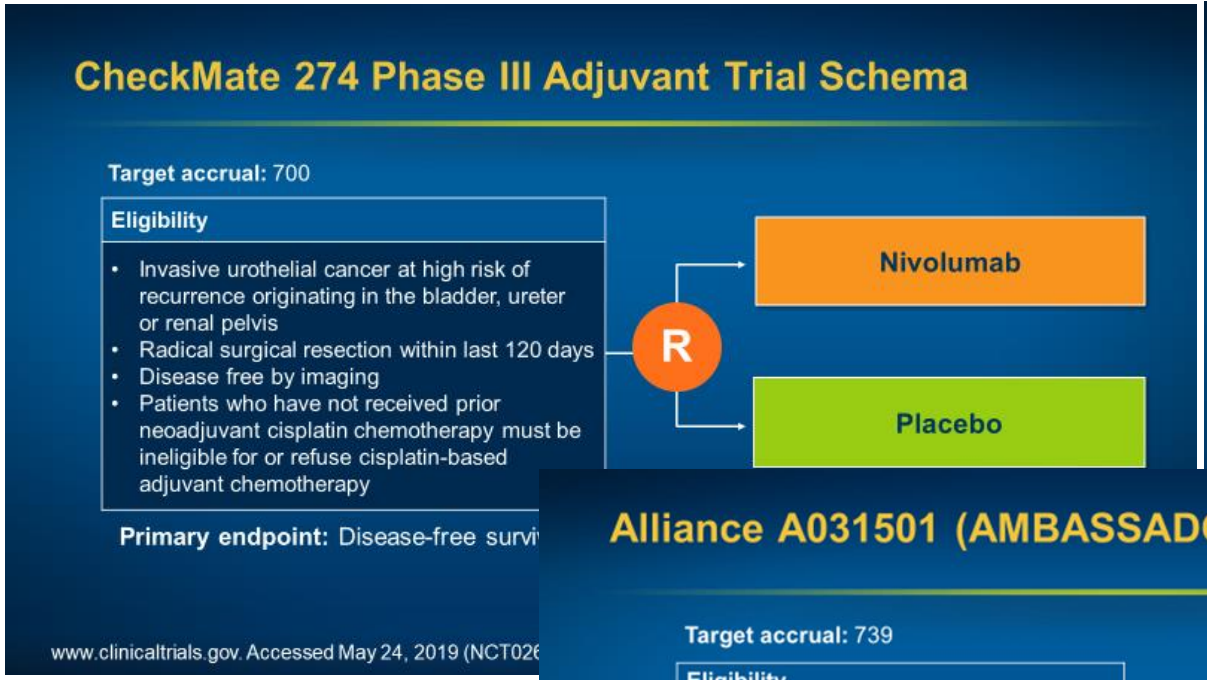
Gem/Cis, 15% to 32%

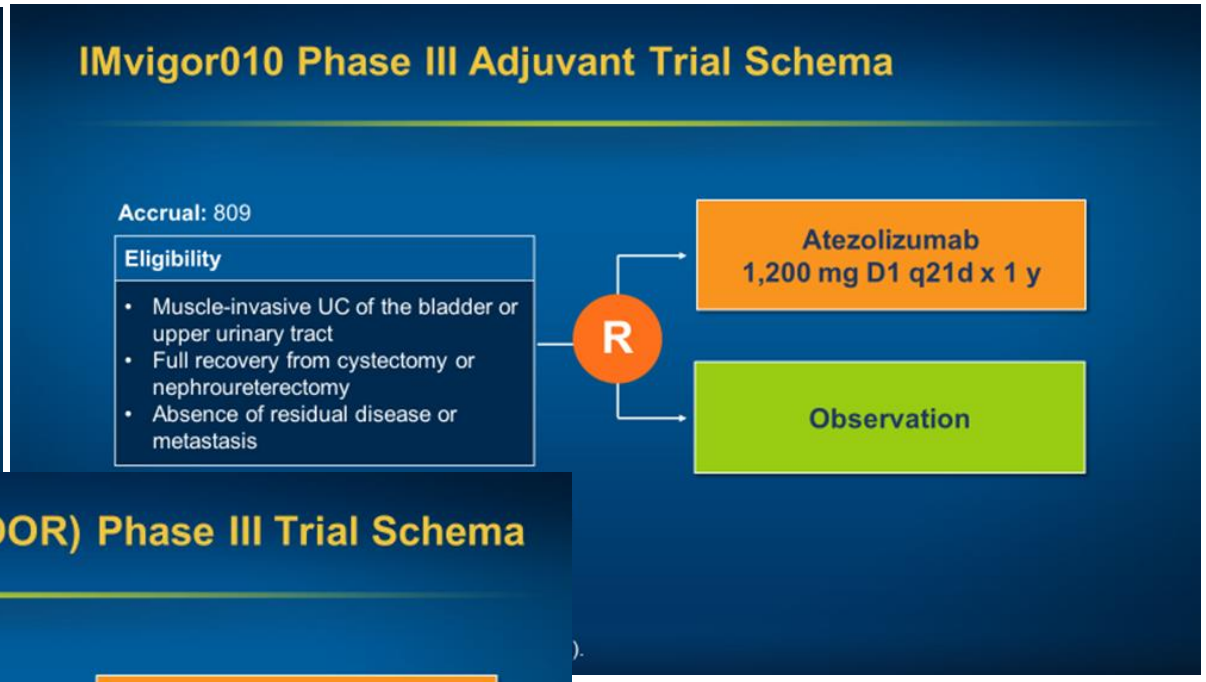
DD MVAC, 26% to 43%

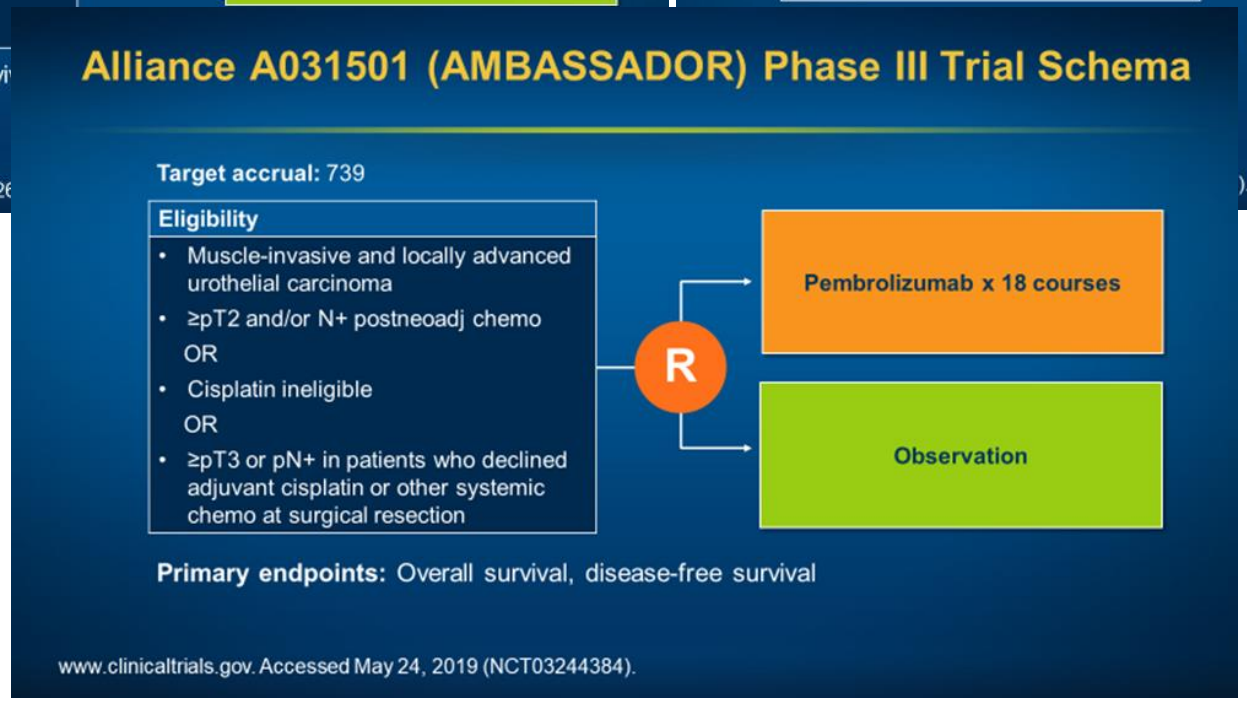
Ümit verici, uzun süreli sonuçları beklenmeli

1. Necchi A, et al. ASCO 2018. Abstract 4507. 2. Powles T, et al. ASCO 2018. Abstract 4506.

Mesane Kanserinde Devam Eden Adjuvan Tedavi Çalışmaları







Mesane Kanserinde Devam Eden İdame Tedavi Çalışmaları

Randomized Double-blind Phase II Study of Maintenance Pembrolizumab versus Placebo after First-line Chemotherapy in Patients (pts) with Metastatic Urothelial Cancer (mUC): HCRN GU14-182

Matt D Galsky et al.
ASCO 2019;Abstract 4504.

Genitourinary (Nonprostate) Cancers Oral Session
Monday, June 3rd, 9:12 AM - 9:24 AM, Arie Crown Theater

Research To Practice®

JAVELIN Bladder 100 Phase III Trial Schema: Maintenance Therapy

Target accrual: 668

Eligibility

- Unresectable locally advanced or metastatic transitional cell UC
- Stage IV disease at start of 1st-line chemo
- Prior 1st-line chemo: At least 4 cycles but no more than 6 cycles of gem/cis or gem/carbo
- No evidence of disease progression after completion of 1st-line therapy

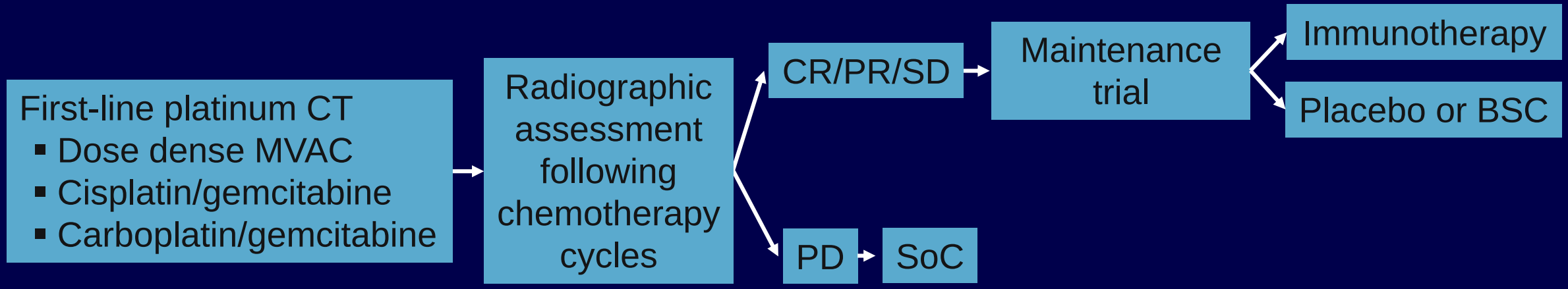
R

- Avelumab + best supportive care
- Best supportive care

Primary endpoint: Overall survival

www.clinicaltrials.gov. Accessed May 24, 2019 (NCT02603432).

Clinical Trials of Maintenance Immunotherapy Following First-line Platinum-Based CT

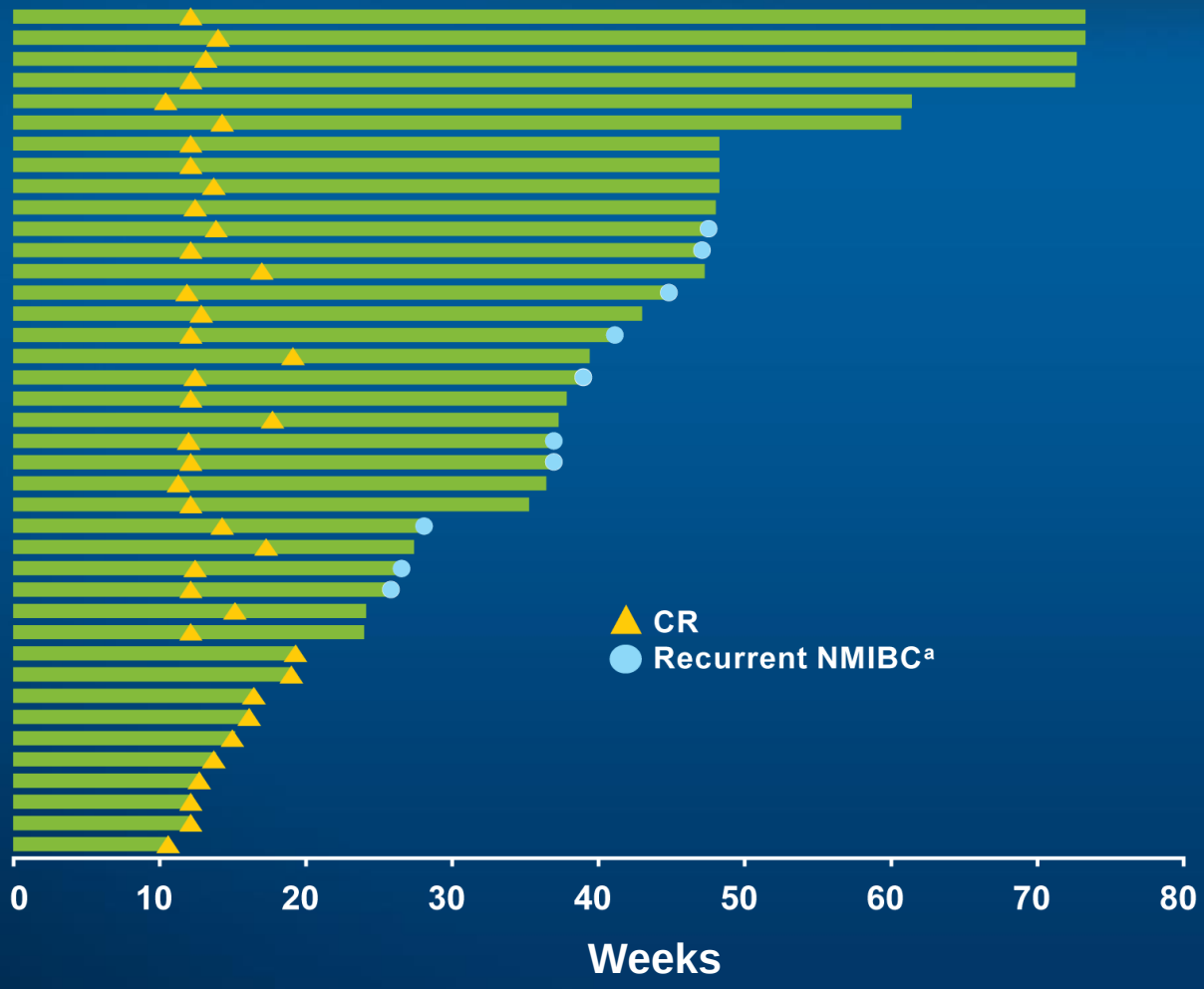


Trial	N	Chemotherapy Duration	Primary Endpoint	Opened	Estimated Completion
Phase II NCT02500121[1] ▪ Pembrolizumab vs ▪ Placebo (up to 24 mos)	200	Up to 8 cycles	6-mo PFS	November 2015	November 2019
Phase III JAVELIN Bladder 100[2] ▪ Avelumab vs ▪ BSC	668	4-6 cycles	OS	April 2016	July 2019

1. ClinicalTrials.gov. NCT02500121. 2. ClinicalTrials.gov. NCT02603432.

Slide credit: clinicaloptions.com

KEYNOTE-057: Response Rate at 3 Months, Time to CR and Development of Recurrent High-Risk NMIBC with Pembrolizumab



CR	**40/103**	**38.8%**
Non-CR	**57/103**	**55.3%**
Persistent		45.6%
NMIBC stage progression		8.7%
Extravesical disease		1%
Progression to T2		0
Median time to CR		**12.4 wk**
Ongoing response		**72.5%**

[a] Reappearance of HR NMIBC (CIS and/or high-grade Ta and/or T1 disease) after a disease-free interval (at each month or afterward)

De Wit R et al. *Proc ESMO* 2018;Abstract 864O.

Ongoing Phase III Studies of PD-1/PD-L1 Checkpoint Inhibitors in High-Risk, Non-Muscle Invasive Bladder Cancer (NMIBC)

Study	Target accrual	Randomization	Estimated primary completion
POTOMAC (NCT03528694)	975	• BCG (induction + maintenance) + durvalumab • BCG (induction only) + durvalumab • BCG	November 2021
KEYNOTE-676 (NCT03711032)	550	• BCG (induction and maintenance) + pembrolizumab x 2 y • BCG (induction and maintenance)	May 2022
ALBAN (NCT03799835)	614	• BCG (induction and maintenance) + atezolizumab x 1 y • BCG (induction and maintenance)	April 2022

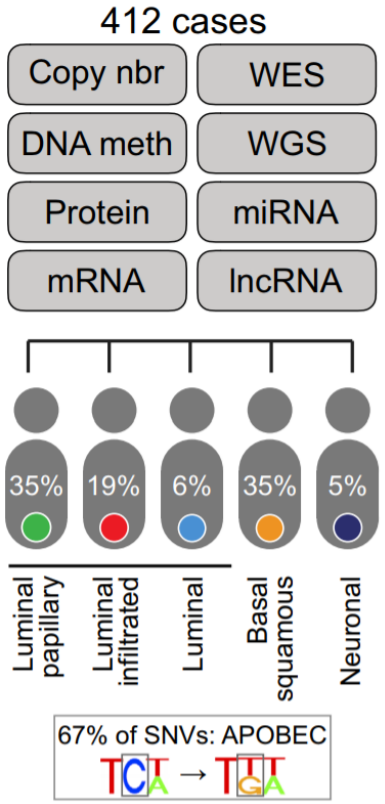
www.clinicaltrials.gov. Accessed May 24, 2019.

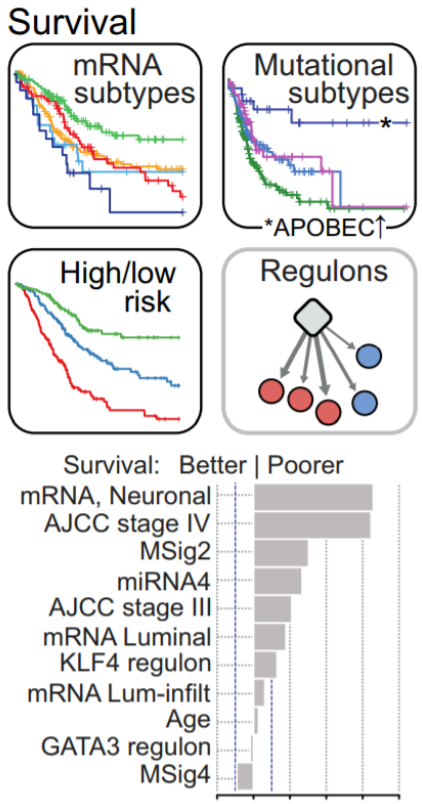
Mesane Kanserinin Moleküler Sınıflandırılması

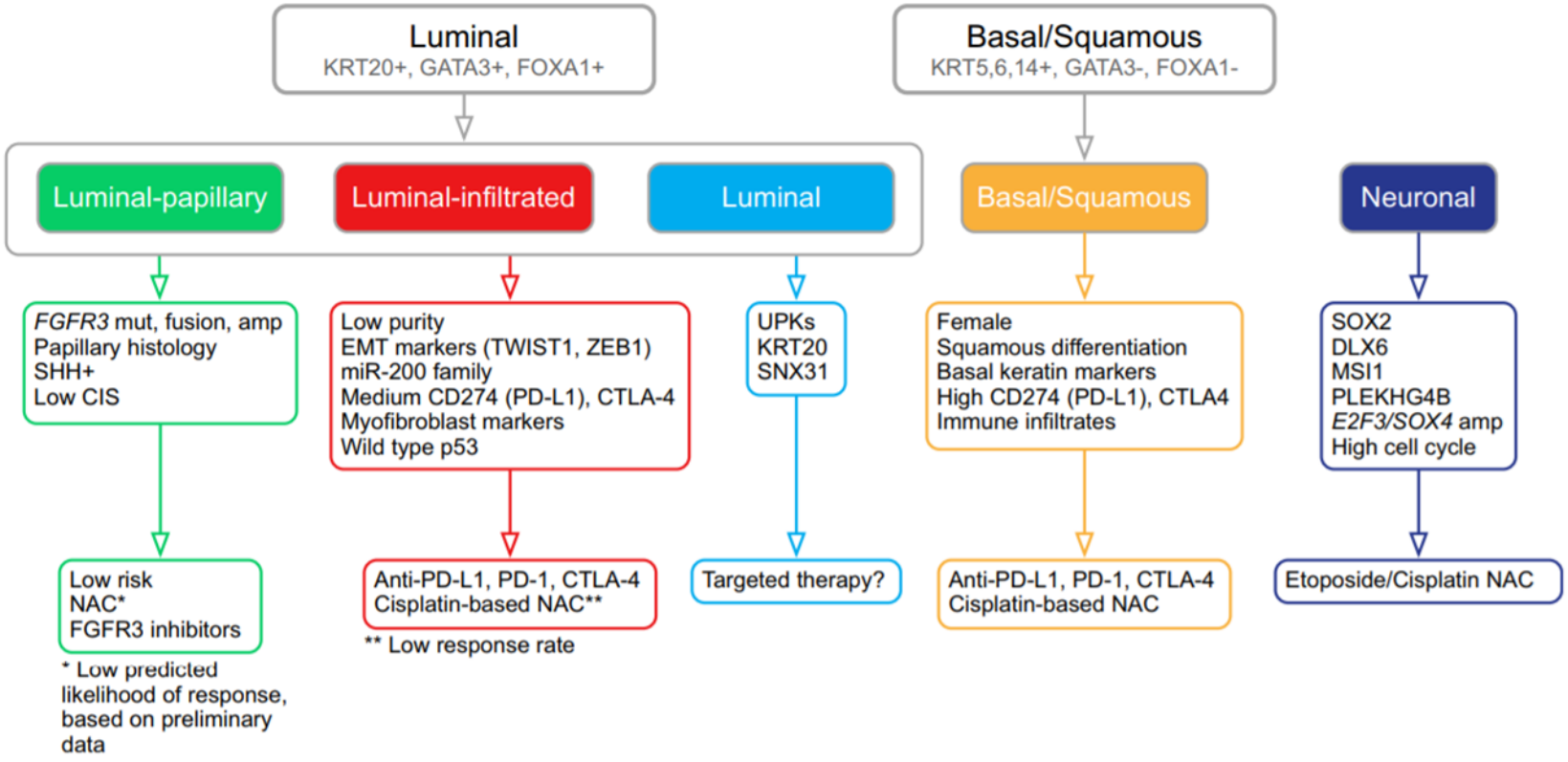
Article

Cell

Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer







Mesane Kanserinin Moleküler Sınıflandırılması

A

	CR	PR	SD	PD	CR+PR
TCGA2017 BS	11 (12%)	8 (9%)	16 (17%)	59 (63%)	19 (20%)
TCGA2017 Lum	3 (9%)	9 (28%)	4 (12%)	16 (50%)	12 (38%)
TCGA2017 Lum–Inf	6 (10%)	5 (8%)	21 (34%)	30 (48%)	11 (18%)
TCGA2017 Lum–Pap	3 (3%)	15 (15%)	22 (22%)	62 (61%)	18 (18%)
TCGA2017 Neuronal	2 (25%)	6 (75%)	0 (0%)	0 (0%)	8 (100%)

	CR	PR	SD	PD	CR+PR
Lund Basal/SCC	9 (16%)	3 (5%)	8 (14%)	36 (64%)	12 (21%)
Lund GU	6 (11%)	19 (36%)	9 (17%)	19 (36%)	25 (47%)
Lund Infiltrated	5 (6%)	7 (8%)	26 (31%)	46 (55%)	12 (14%)
Lund UroA	3 (3%)	13 (14%)	17 (19%)	57 (63%)	16 (18%)
Lund UroB	2 (13%)	1 (7%)	3 (20%)	9 (60%)	3 (20%)

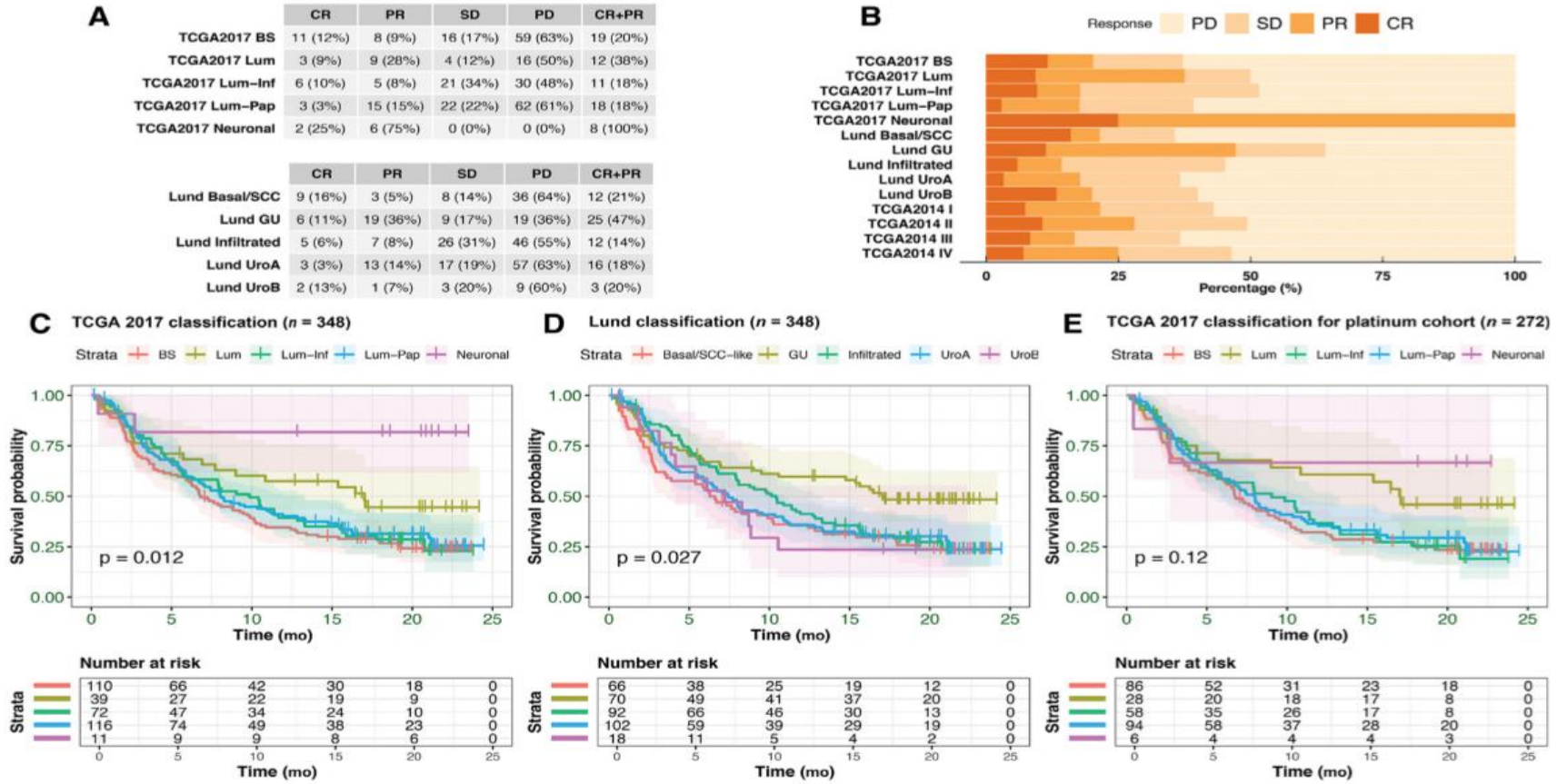


Fig. 2 – (A) Stratification of patients in the TCGA 2017 and Lund subtypes into response categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and CR + PR. (B) Objective response rate among IMvigor 210 patients to atezolizumab according to TCGA 2017, TCGA 2014, and Lund subtypes. Overall survival probabilities in the IMvigor 210 full cohort ($n = 348$) in (C) the TCGA 2017 and (D) Lund subtypes, and (E) the platinum-treated cohort ($n = 272$) in the TCGA 2017 subtypes. SCC = squamous cell carcinoma; GU = genitourinary; Lum = luminal; Inf = infiltrated; Pap = papillary; CIS = carcinoma in situ; BS = basal-squamous.

Sonuç

- Evre IV mesane kanserinde birinci basamak tedavide platin bazlı kemoterapi ilk seçenek
- Sisplatin alamayacak hastalarda PD-L1 pozitif olanlar immünoterapi alabilir
- Platin bazlı kemoterapi alamayacak hastalarda birinci basamak tedavide (ECOG PS≥2, komorbidite vs.) PD-L1 düzeyinden bağımsız İmmünoterapi düşünülebilir
- Mesane kanseri moleküler sınıflanmasına göre tedavi seçenekleri ileriki dönemde daha çok gündeme gelecek
- FGFR ve benzeri moleküler mutasyonlara yönelik hedefe yönelik tedaviler daha sık kullanılacak
- İmmünoterapi +/- kombinasyon tedaviler metastatik ve daha erken evrelerde tedavide kullanımı ile ilgili dataların olgunlaşmasını bekleyeceğiz