# Metastatik Mesane ve Üst Üriner Sistem Kanserlerinde Birinci Basamak Tedavi

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**Tıbbi Onkoloji**

# Ders Planı

- Mesane Kanseri İnsidans ve Mortalite

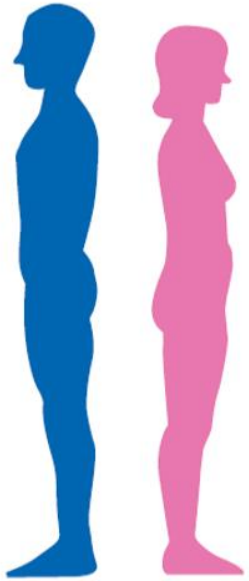
Metastatik Hastalık

- Sisplatine uygun hastada birinci basamak
- Sisplatine uygun olmayan hastada birinci basamak
- Özet

# Mesane Kanseri İnsidans ve Mortalite

## 2019 ESTIMATED NEW CANCER CASES – US

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

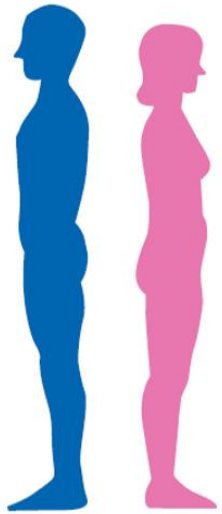


CA CANCER J CLIN 2019;69:7–34

# Mesane Kanseri İnsidans ve Mortalite

## 2019 ESTIMATED CANCER DEATHS – US

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

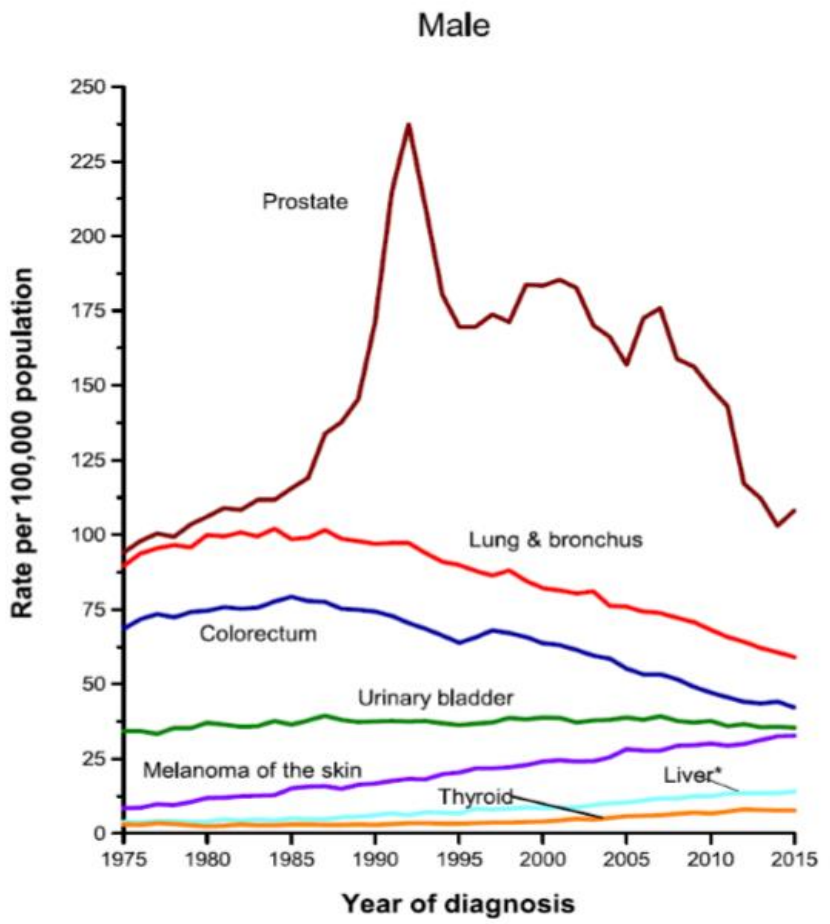


CA CANCER J CLIN 2019;69:7-34

# Mesane Kanseri İnsidans ve Mortalite

## TEMPORAL TRENDS IN THE INCIDENCE OF BLADDER CANCER

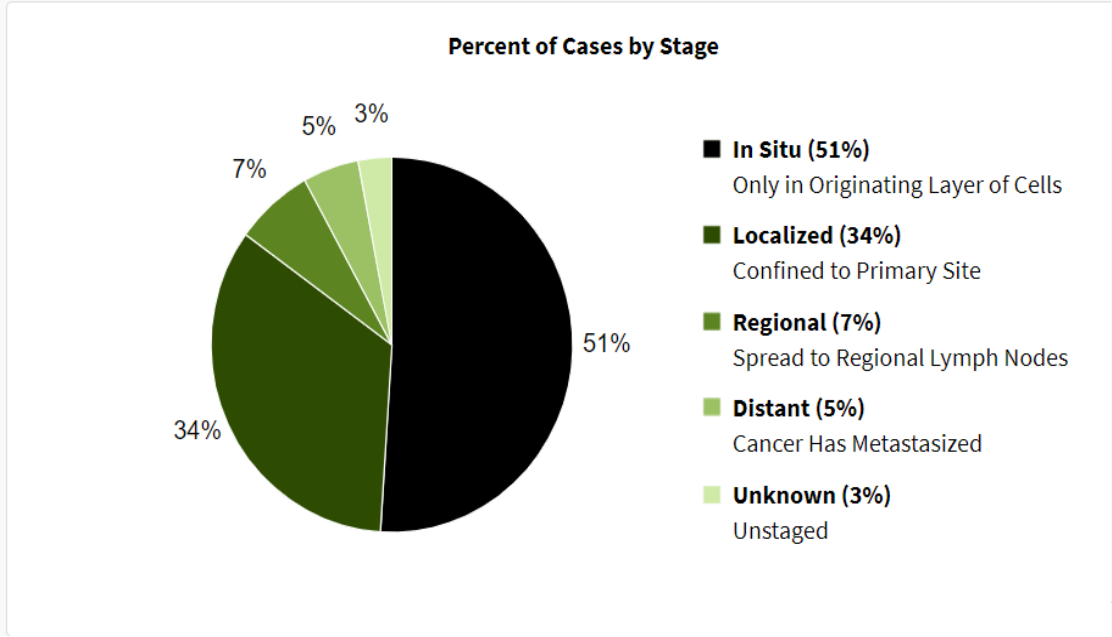
- The incidence of several major cancers has fallen over the last 40 years
  - There have been increased incidence in a few (melanoma and liver for example)
- No major changes in the incidence of bladder cancer in the last 40 years

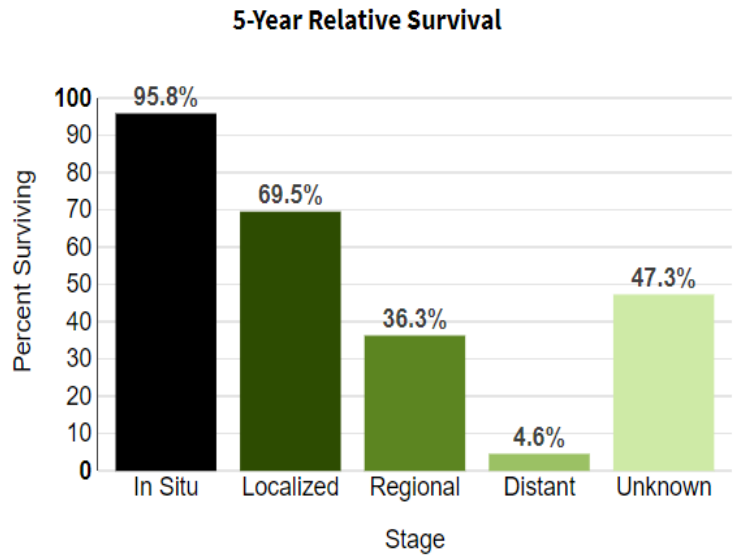



CA CANCER J CLIN 2019;69:7–34

# Mesane Kanseri İnsidans ve Mortalite

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




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

# Metastatik Mesane Kanseri
# Birinci Basamak Kemoterapi

Selected randomized clinical trial comparisons of chemotherapy for metastatic bladder cancer

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

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

# Metastatik Birinci Basamak Kemoterapi Sonuçları

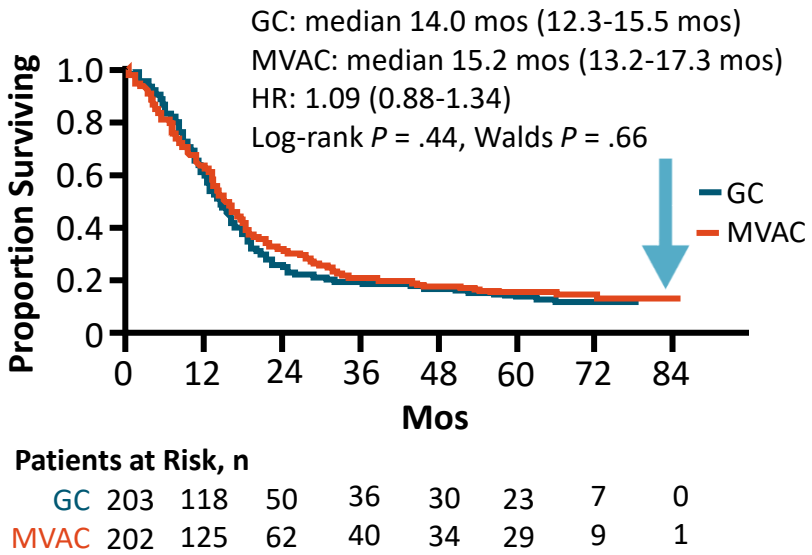
## Sisplatin Uygun

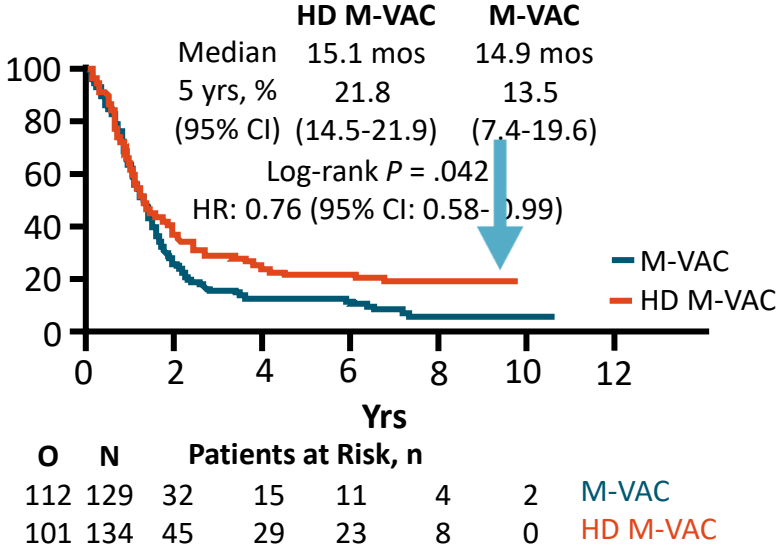
### Gemcitabine + Cisplatin[1,2]
ORR: 49%
CR: 12%
Median OS: 14.0 mos

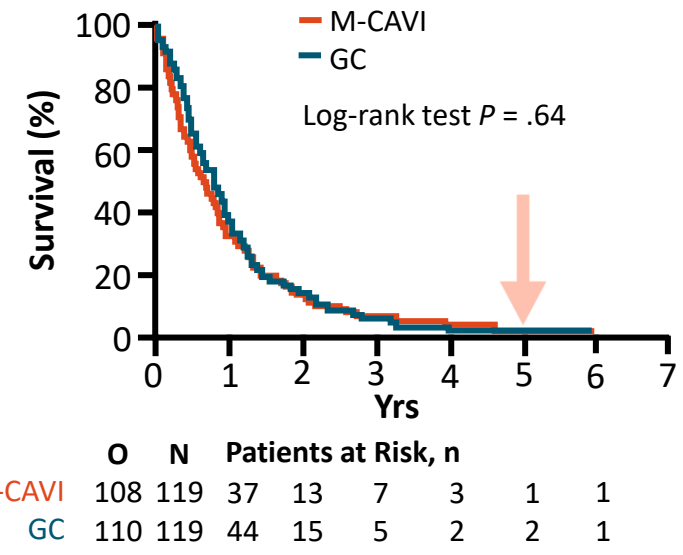
### Dose Dense MVAC[3]
ORR: 72%
CR: 25%
Median OS: 15.1 mos

## Sisplatin uygun değil

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




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

# Metastatik Birinci Basamak Kemoterapi Sonuçları

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

### Objective response

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

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

### Complete response

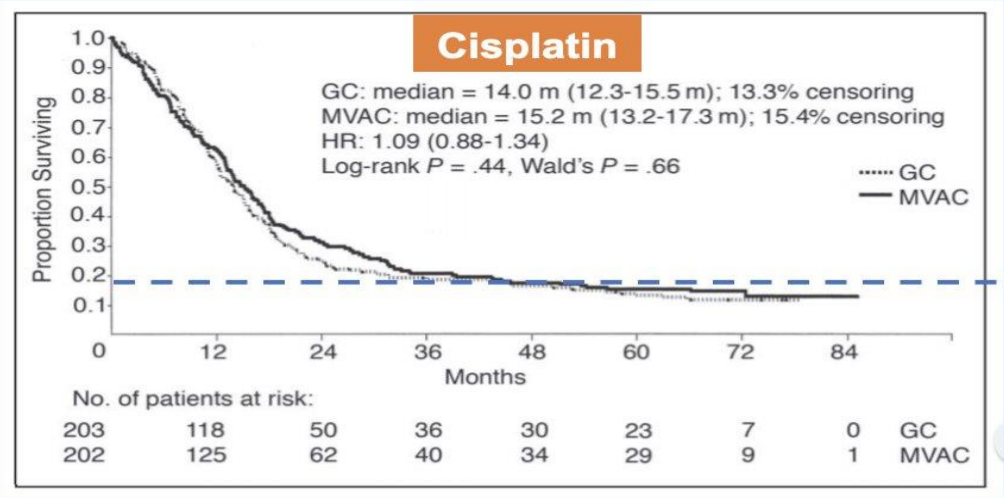
| Source | Cisplatin-based | | Carboplatin-based | | Weight (%) | RR (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | | |
| Petrioli et al. [15] | 7 | 28 | 3 | 27 | 51.80 | 2.25 (0.65–7.18) | |
| Bellmunt et al. [13] | 3 | 23 | 0 | 23 | 14.54 | 1.17 (0.07–18.58) | |
| Drecier et al. [2] | 5 | 36 | 1 | 39 | 16.28 | 5.42 (0.66–44.12) | |
| Dogliotti et al. [14] | 8 | 41 | 1 | 39 | 17.38 | 7.61 (0.10–38.06) | |
| Overall (Mantel–Haenszel method) | 23 | 128 | 5 | 128 | | 3.54 (1.48–8.49) | 0.005 |

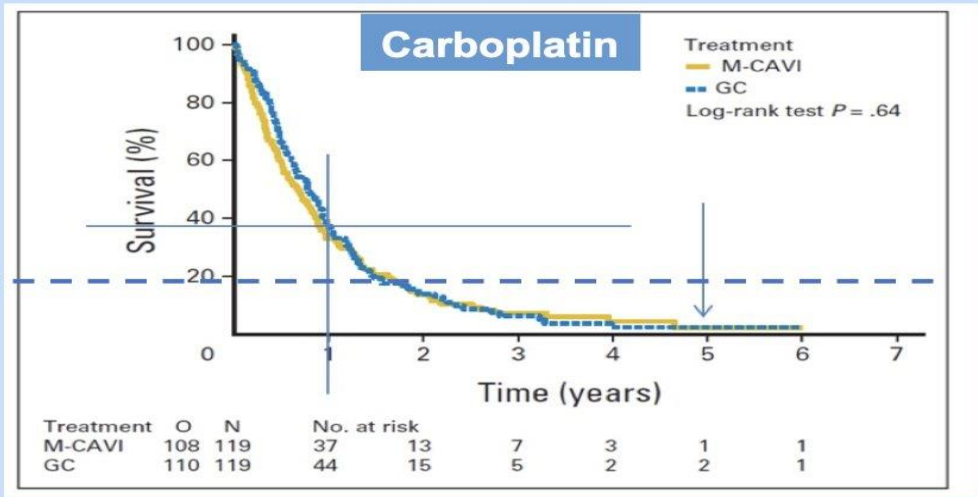
Heterogeneity chi-square test = 1.83 (d.f. = 3); $P = 0.609$; I-squared test (variation in RR attributable to heterogeneity) = 0.0%.
RR, risk ratio; CI, confidence interval.

Galsky et al, Ann Oncol, 2011

# Metastatik Birinci Basamak Kemoterapi Sonuçları

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





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

# Metastatik Birinci Basamak Kemoterapi Sonuçları

**Supplementary Table S3. Multivariate Cox Regression Analysis for Overall Survival in the Overall Population.**

| Variable* | Levels | Parameter Estimate | Standard Error | Wald Chi-Square Statistic | P-Value (2-sided) | HR (95% CI) |
|---|---|---|---|---|---|---|
| **Treatment group** | Avelumab plus BSC | −0.370 | 0.1143 | 10.46 | 0.0012 | 0.69 (0.552-0.865) |
| | BSC alone | | | | | |
| **Best response to first-line chemotherapy** | Stable disease | | | | | |
| | Complete or partial response | −0.079 | 0.1241 | 0.41 | 0.5242 | 0.92 (0.724-1.179) |
| **Site of baseline metastasis** | Nonvisceral | | | | | |
| | Visceral | 0.188 | 0.1221 | 2.36 | 0.1244 | 1.21 (0.950-1.533) |
| **Age** | <65 years | | | | | |
| | ≥65 years | −0.215 | 0.1225 | 3.07 | 0.0796 | 0.81 (0.635-1.026) |
| **Race** | White | | | | | |
| | Asian | −0.252 | 0.1466 | 2.95 | 0.0857 | 0.78 (0.583-1.036) |
| | Other | −0.589 | 0.2207 | 7.11 | 0.0076 | 0.56 (0.360-0.855) |
| **PD-L1 status** | Positive | | | | | |
| | Negative | 0.294 | 0.1212 | 5.87 | 0.0154 | 1.34 (1.058-1.701) |
| | Unknown | 0.256 | 0.1981 | 1.68 | 0.1956 | 1.29 (0.876-1.905) |
| **First-line chemotherapy regimen** | Gemcitabine plus cisplatin | | | | | |
| | Gemcitabine plus carboplatin | 0.262 | 0.1218 | 4.64 | 0.0312 | 1.30 (1.024-1.651) |
| | Gemcitabine plus cisplatin/carboplatin | −0.314 | 0.2927 | 1.15 | 0.2840 | 0.73 (0.412-1.297) |
| **ECOG performance status** | 0 | | | | | |
| | ≥1 | 0.462 | 0.1149 | 16.18 | <0.0001 | 1.59 (1.267-1.988) |
| **Liver metastasis** | Yes | | | | | |
| | No | −0.421 | 0.1621 | 6.73 | 0.0095 | 0.66 (0.478-0.902) |

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1.

* Explanatory variables were selected using a stepwise selection procedure. The level of significance for a variable to enter the model was 0.15 and the significance level for removal was 0.04.

# Hangi Kemoterapi Rejimi ?

## Trial design (3)

- **500 patients included in 28 centers from 2013 to 2018**

  *(493 patients available for intent-to-treat analysis)*

- **Adjuvant** (n=56) **and Neoadjuvant** (n=437) (88%)
- **Primary end-point :** Progression Free Survival at 3 years
- **Final analysis :** Overall and Specific Survival at 5 years

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



ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

2023 ASCO ANNUAL MEETING

# Hangi Kemoterapi Rejimi ?

## PFS at 3 years

2021 ESMO congress 16-21 September 2021

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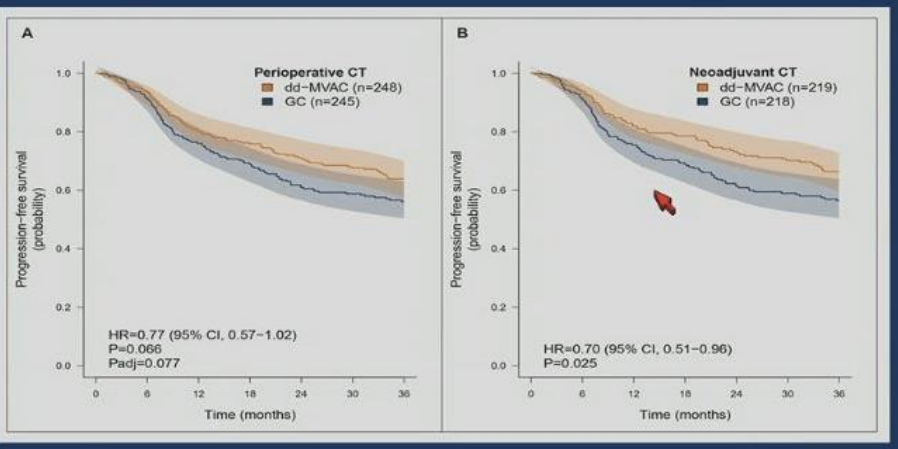


Perioperative dd-MVAC improved 3-y PFS over GC

In the neoadjuvant group, better bladder tumor local control with a significant improvement on 3-y PFS in the dd-MVAC arm

*Pfister et al. J Clin Oncol 2022*

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PRESENTED BY: C Pfister - 5-y OS Vesper



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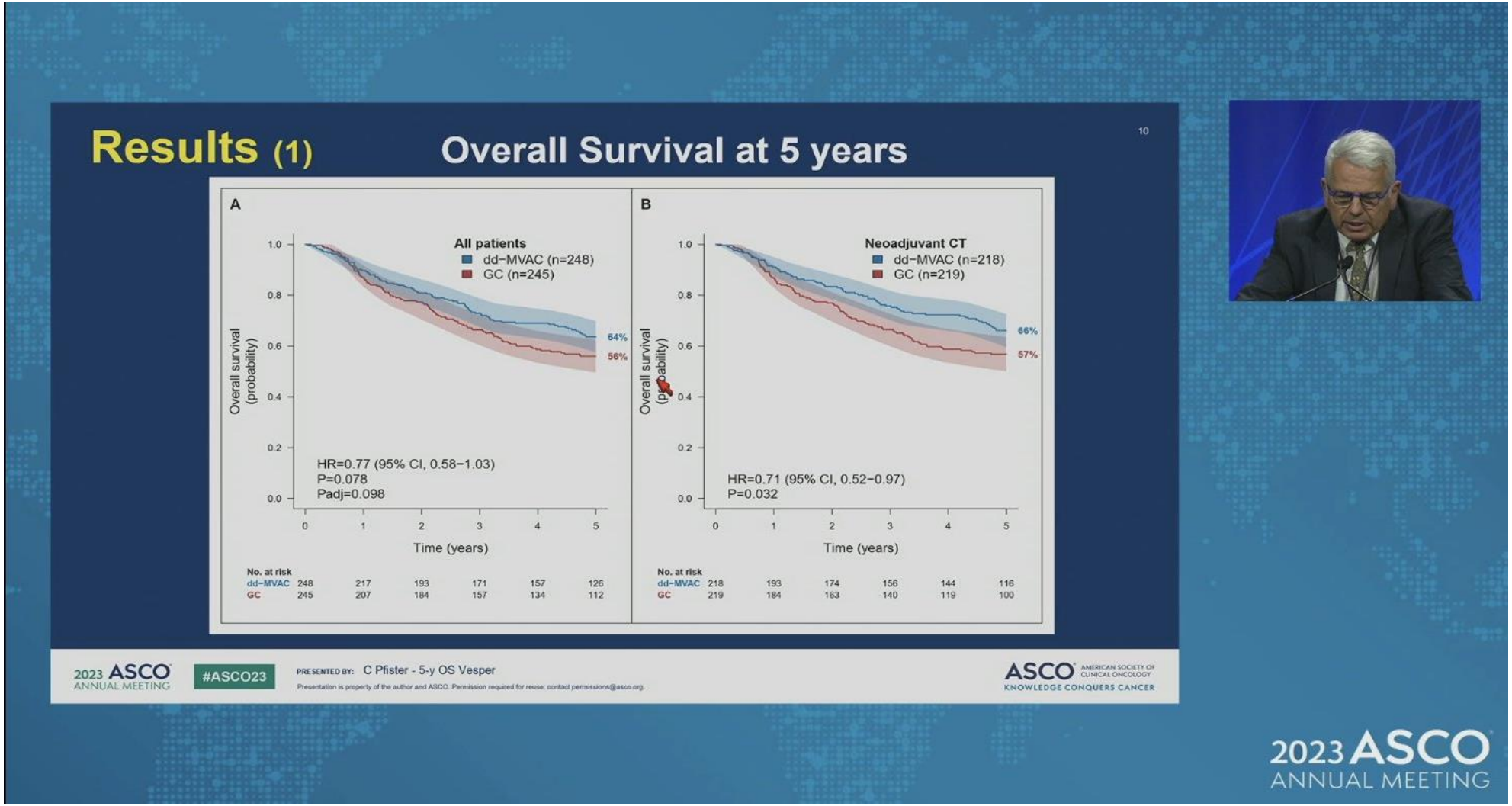
2023 ASCO ANNUAL MEETING

# Hangi Kemoterapi Rejimi ?



# Metastatik Mesane Kanseri  Birinci Basamak Tedavi Seçimi

National Comprehensive Cancer Network®

## NCCN Guidelines Version 3.2023
## Bladder Cancer

NCCN Guidelines Index
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Discussion

### PRINCIPLES OF SYSTEMIC THERAPY

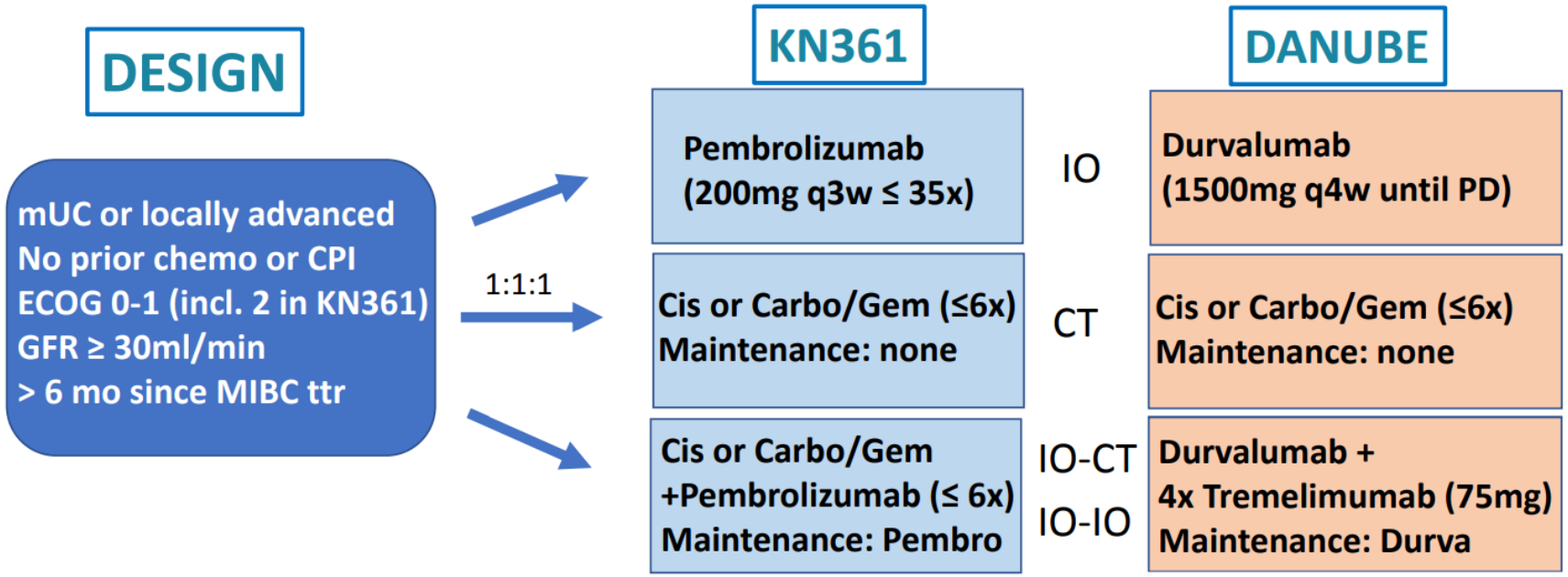
| First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) | |
|---|---|
| **Cisplatin eligible** | **Preferred regimens**<br>• Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,11]<br>• DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,11] |
| **Cisplatin ineligible** | **Preferred regimens**<br>• Gemcitabine and carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11]<br>• Pembrolizumab[14] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)<br>• Pembrolizumab and enfortumab vedotin-ejfv[17]<br><br>**Other recommended regimens**<br>• Gemcitabine[15]<br>• Gemcitabine and paclitaxel[16]<br>• Atezolizumab[13] (only for patients whose tumors express PD-L1[b]) (category 2B)<br><br>**Useful under certain circumstances**<br>• Ifosfamide, doxorubicin, and gemcitabine[18] (for patients with good kidney function and good performance status)<br>• Atezolizumab[13] (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 3) |

# 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<br>PD-L1: CPS ≥10 | Cisplatin eligibilty<br>PD-L1: ≥25% IC and/or TC positive<br>Liver and/or lung  metastases |
| **Primary endpoints** | PFS and OS: IO-CT vs CT (total)<br>OS: IO vs CT (total and PD-L1 +)<br>**Sequential testing!** | OS: IO-IO vs CT (ITT)<br>OS: IO vs CT (PD-L1 +) |
| **Minimum follow up** | 22 months (median 31.7) | 34 months (median 41.2) |

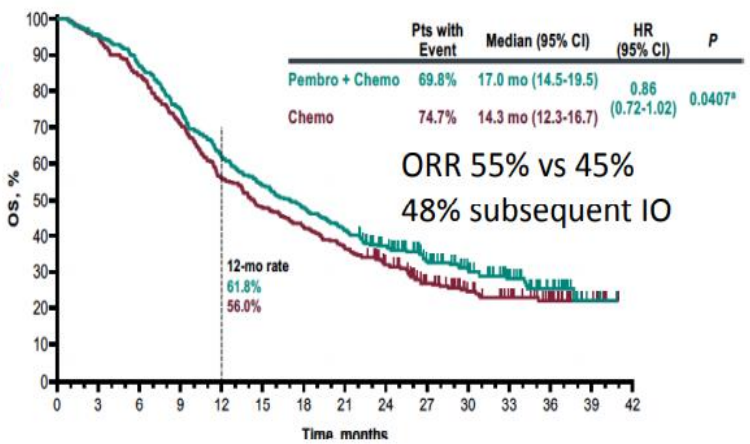
# Metastatik Mesane Kanseri  Birinci Basamak
# Platin bazlı kemoterapi+ İmmün kontrol noktası inhibitörleri

**Overall survival**

**Combination vs Chemo**

**TOTAL population (ITT)**

## KEYNOTE 361 –IO-CT vs CT (1˚EP)

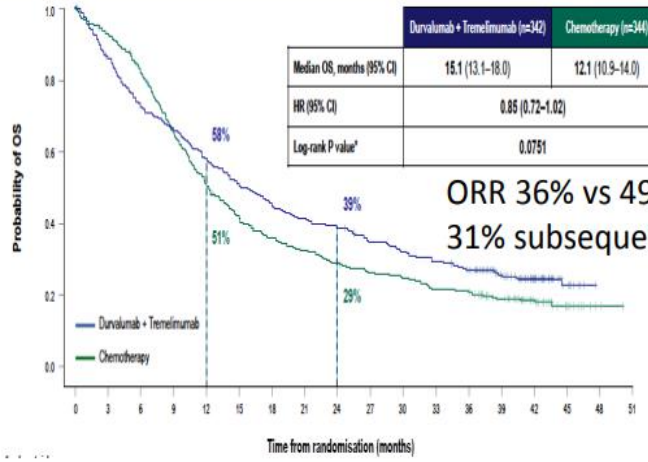



| | Pts with Event | Median (95% CI) | HR (95% CI) | P |
|---|---|---|---|---|
| Pembro + Chemo | 69.8% | 17.0 mo (14.5-19.5) | 0.86 (0.72-1.02) | 0.0407[a] |
| Chemo | 74.7% | 14.3 mo (12.3-16.7) | | |

ORR 55% vs 45%

48% subsequent IO

## DANUBE – IO-IO vs CT (1˚EP)



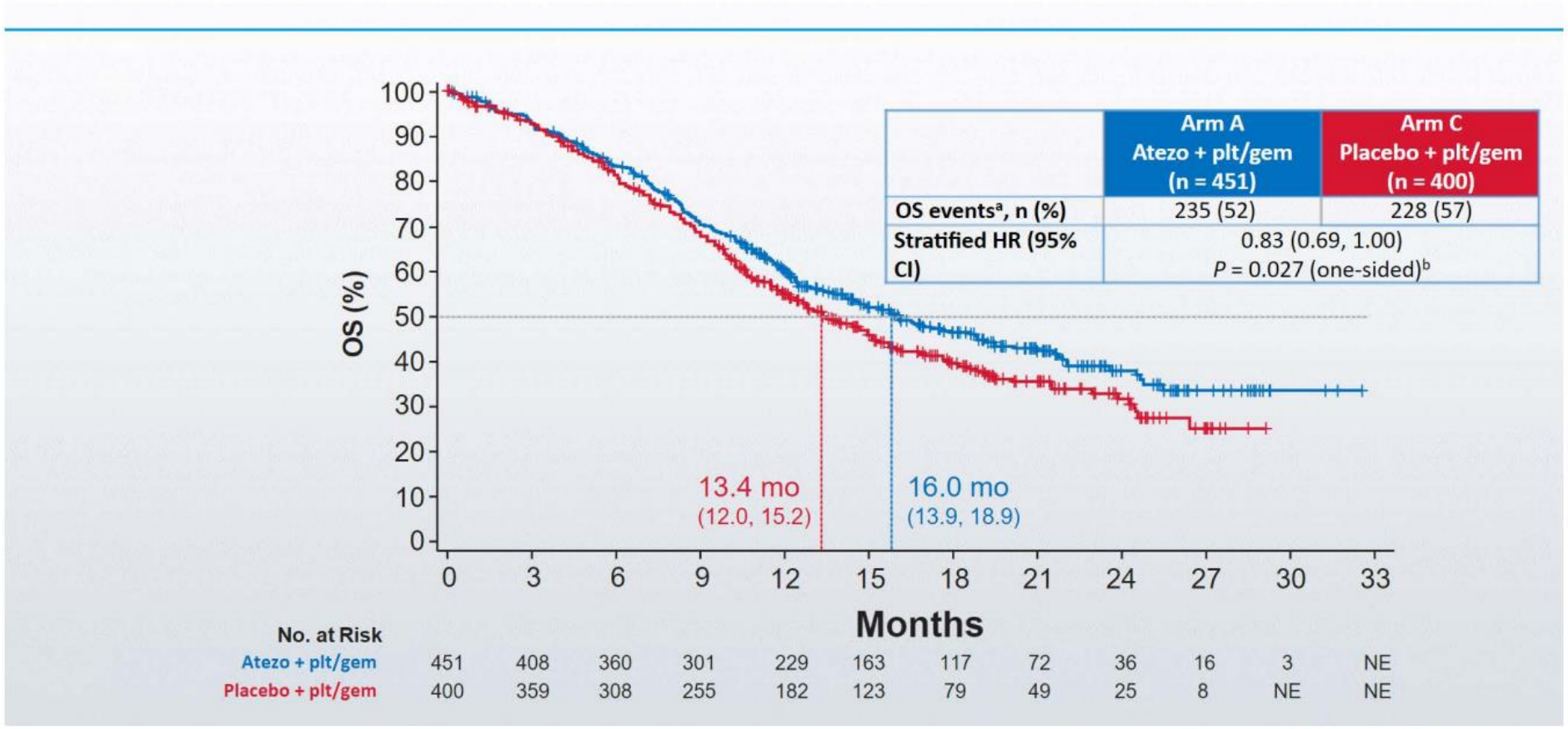

| | Durvalumab + Tremelimumab (n=342) | Chemotherapy (n=344) |
|---|---|---|
| Median OS, months (95% CI) | 15.1 (13.1–18.0) | 12.1 (10.9–14.0) |
| HR (95% CI) | 0.85 (0.72–1.02) | |
| Log-rank P value[a] | 0.0751 | |

ORR 36% vs 49%

31% subsequent IO

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

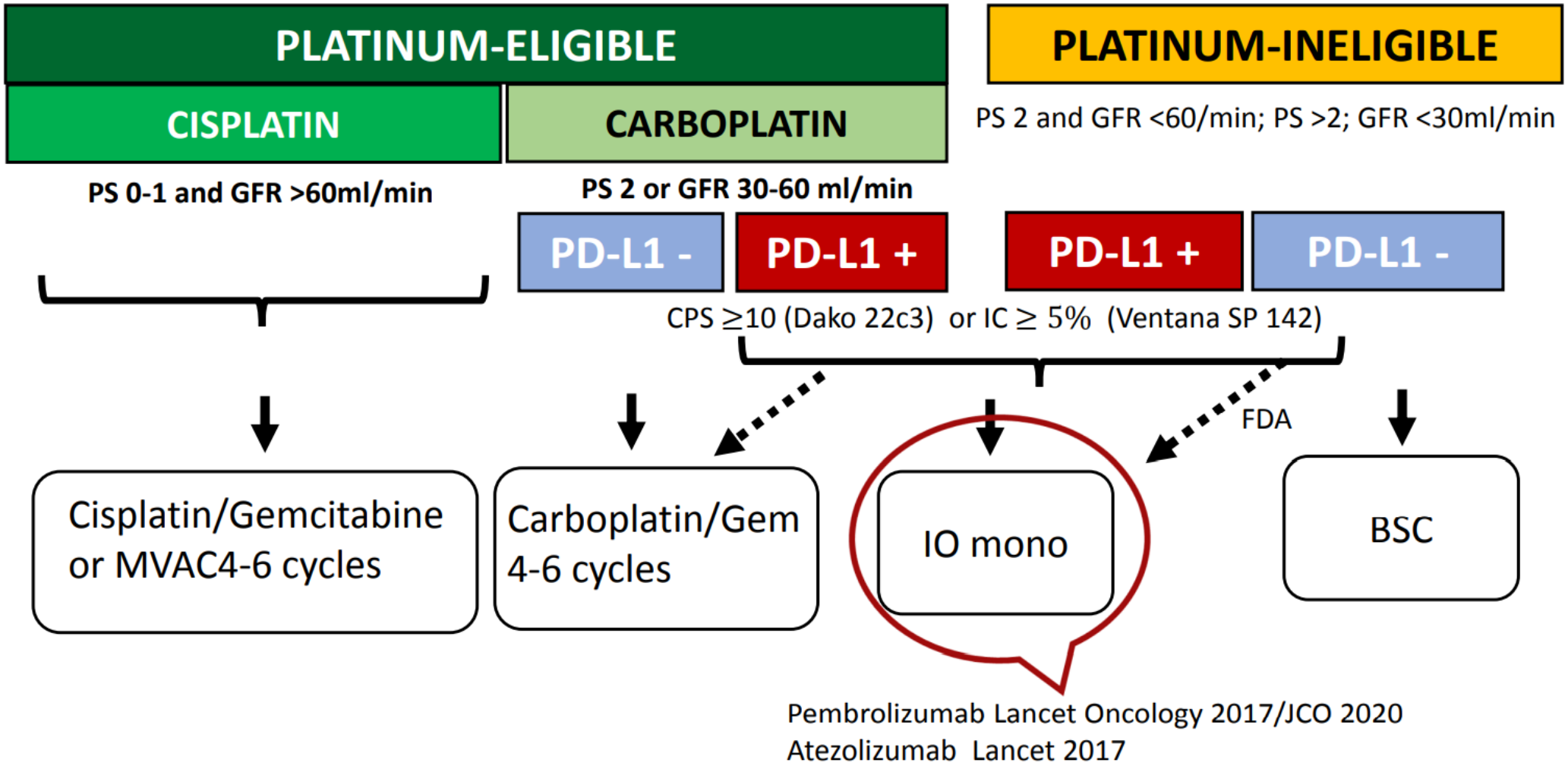
## IMvigor130 Interim OS: ITT (Arm A vs Arm C)




| | Arm A Atezo + plt/gem (n = 451) | Arm C Placebo + plt/gem (n = 400) |
|---|---|---|
| OS events[a], n (%) | 235 (52) | 228 (57) |
| Stratified HR (95% CI) | 0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b] | |

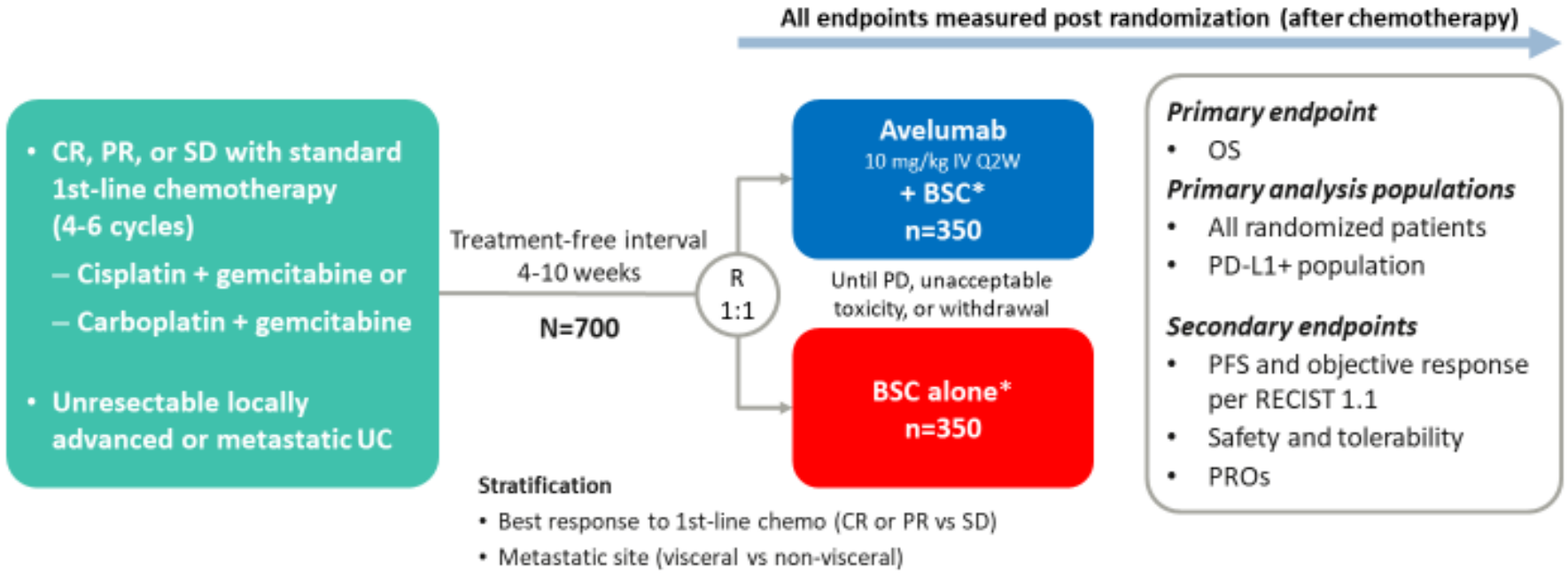
Galsky et al, Lancet 2020 May; Grande ESMO 2019

# Metastatik Mesane Kanseri  Birinci Basamak 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

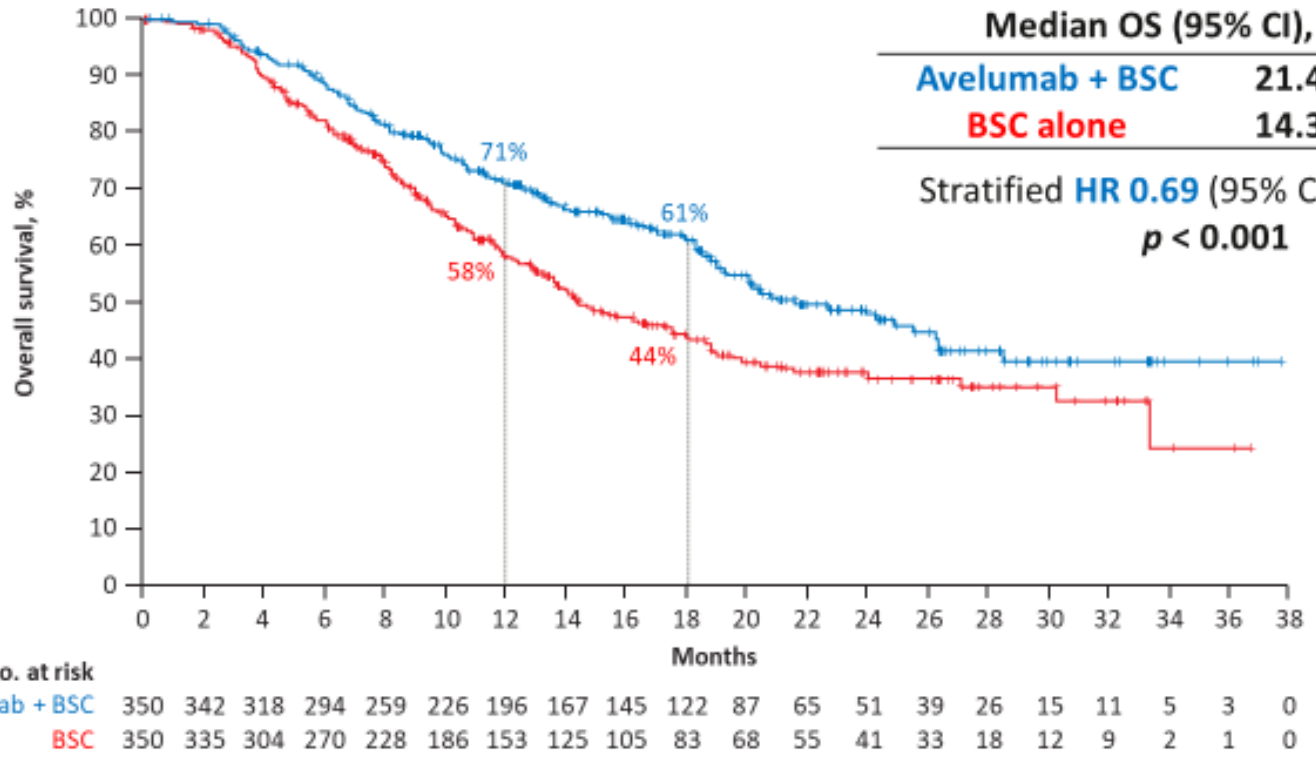
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

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**

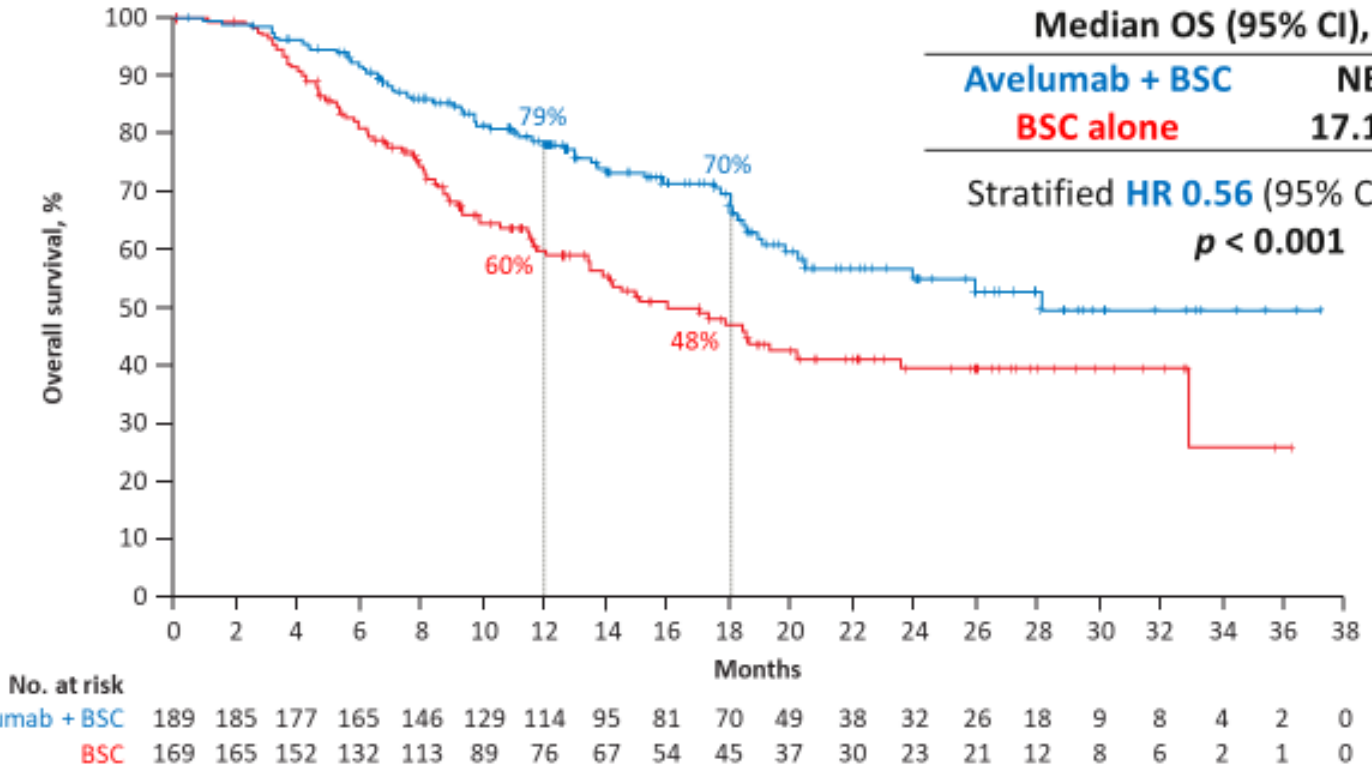
OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

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.

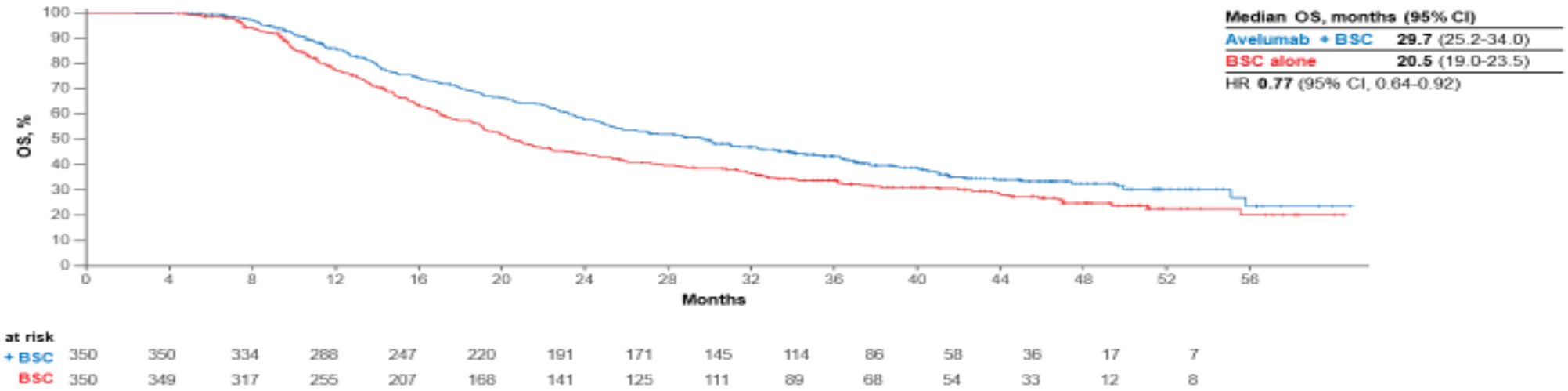
Courtesy of Arjun V. Balar, MD

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

Long-term Analysis | Data Cut-off: 4th June 2021

## OS From the Start of 1L CT in All Randomized Patients[1]

Post hoc analysis




**In the overall population, median OS measured from the start of 1L chemotherapy was 29.7 months (95% CI, 25.2-34.0) in the avelumab + BSC arm and 20.5 months (95% CI,19.0-23.5) in the BSC alone arm (HR, 0.77 [95% CI, 0.636-0.921])**

1L, first-line; BSC, best supportive care; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival.
1. Sridhar SS, et al. Poster 508. Presented at: ASCO GU Symposium; February 16-18, 2023; San Fransisco, CA.

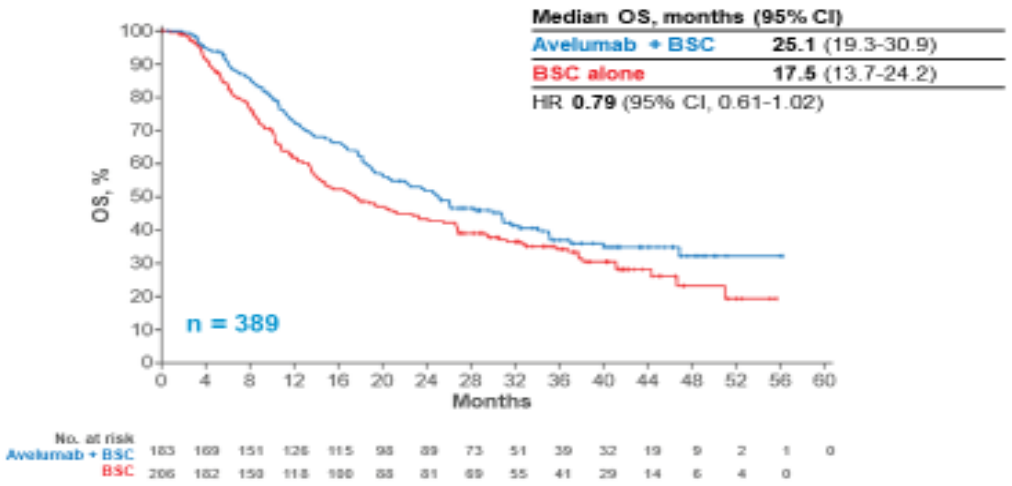
# Metastatik Mesane Kanseri  Birinci Basamak Tedavi
# Platin bazlı kemoterapi Sonrası  İdame Avelumab

Long-term Analysis | Data Cut-off: 4th June 2021

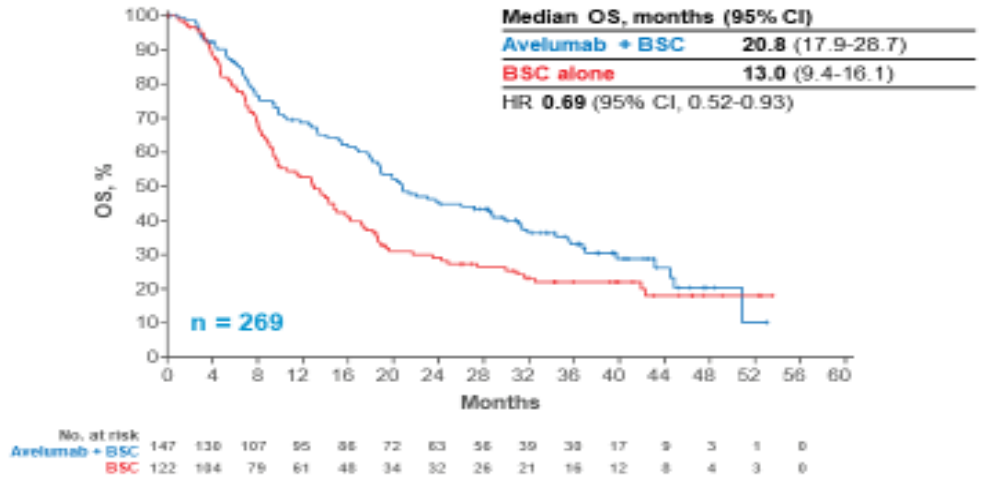
## OS From the Start of Randomization by 1L CT Regimen[1]

Post hoc analysis

### Gemcitabine + cisplatin




### Gemcitabine + carboplatin




**OS was longer with avelumab + BSC vs BSC alone in patients irrespective of 1L chemotherapy regimen received**

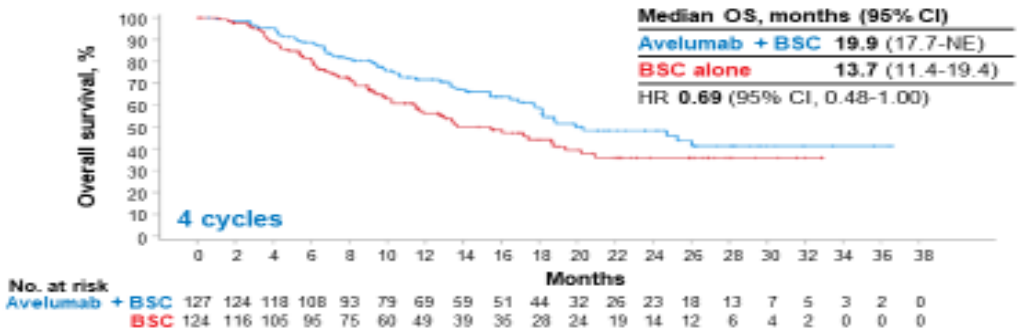
1L, first-line; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival.
1. Sridhar SS, et al. Poster 508. Presented at: ASCO GU Symposium; February 16-18, 2023; San Fransisco, CA.

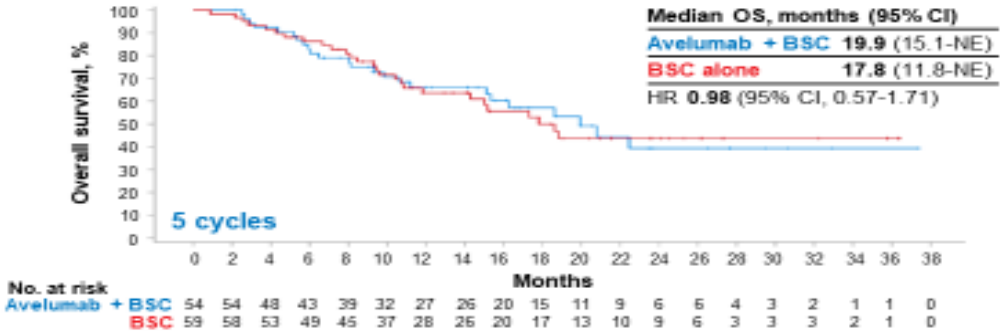
# Metastatik Mesane Kanseri Birinci Basamak Tedavi
# Platin bazlı kemoterapi Sonrası İdame Avelumab

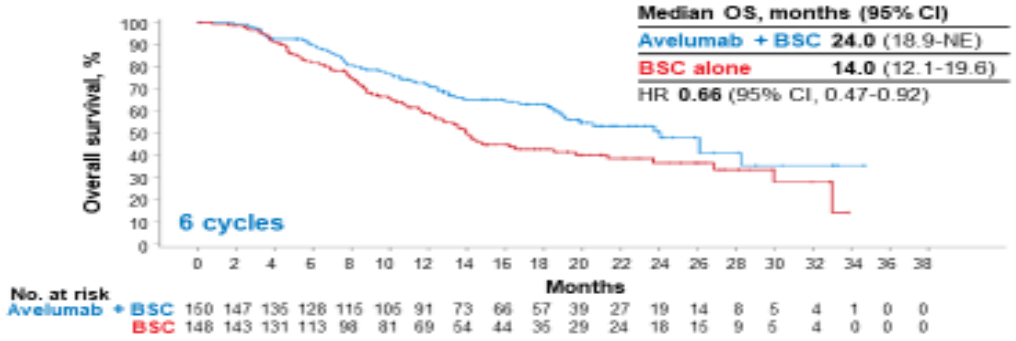
Primary Analysis | Data Cut-off: 21st October 2019

## Survival by Number of 1L Platinum-Containing CT Cycles[1]

Post hoc analysis



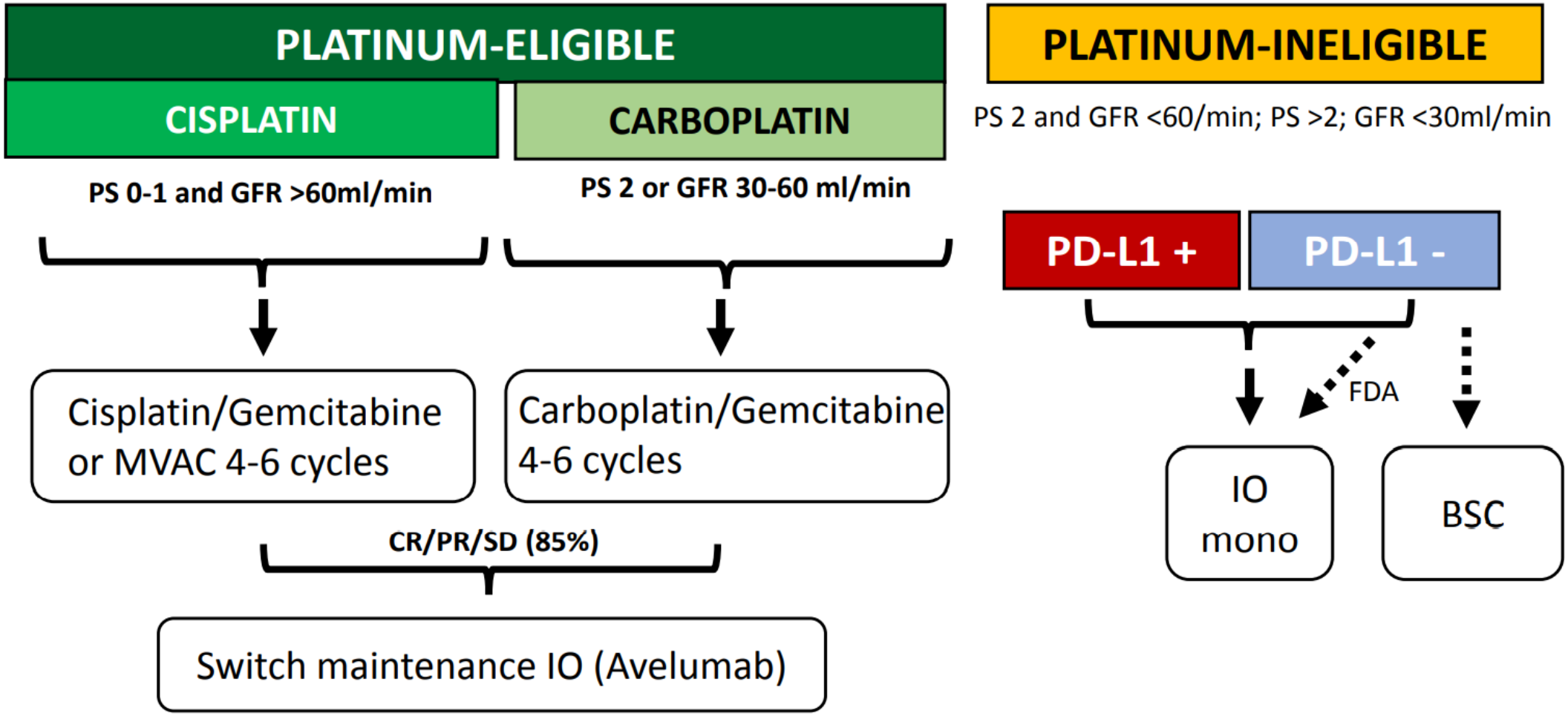

**OS was prolonged with avelumab + BSC vs BSC alone across subgroups with differing cycles of 1L CT**

No significant treatment-by-cycle interaction (at $p<0.05$ level) was observed

1L, first line; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

1. Powles T, et al. Poster 4520. Presented at: ASCO Virtual Annual Meeting. June 4-8, 2021.

# Metastatik Mesane Kanseri  Birinci Basamak Tedavi Seçimi



# Metastatik Mesane Kanseri  Birinci Basamak Tedavi Seçimi

National Comprehensive Cancer Network®

## NCCN Guidelines Version 2.2022
## Bladder Cancer

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### PRINCIPLES OF SYSTEMIC THERAPY

| First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) | |
|---|---|
| Cisplatin eligible | **Preferred regimens**<br>• Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,11]<br>• DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,11] |
| Cisplatin ineligible | **Preferred regimens**<br>• Gemcitabine and carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11]<br>• 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)<br>• Pembrolizumab[14] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)<br><br>**Other recommended regimens**<br>• Gemcitabine[15]<br>• Gemcitabine and paclitaxel[16]<br><br>**Useful under certain circumstances**<br>• Ifosfamide, doxorubicin, and gemcitabine[17] (for patients with good kidney function and good PS) |

# Metastatik Mesane Kanseri  Birinci Basamak Tedavi Seçimi

National Comprehensive Cancer Network®

## NCCN Guidelines Version 3.2023
## Bladder Cancer

NCCN Guidelines Index
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Discussion

### PRINCIPLES OF SYSTEMIC THERAPY

| First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) | |
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| **Cisplatin ineligible** | **Preferred regimens**<br>• Gemcitabine and carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11]<br>• Pembrolizumab[14] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)<br>• Pembrolizumab and enfortumab vedotin-ejfv[17]<br><br>**Other recommended regimens**<br>• Gemcitabine[15]<br>• Gemcitabine and paclitaxel[16]<br>• Atezolizumab[13] (only for patients whose tumors express PD-L1[b]) (category 2B)<br><br>**Useful under certain circumstances**<br>• Ifosfamide, doxorubicin, and gemcitabine[18] (for patients with good kidney function and good performance status)<br>• Atezolizumab[13] (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 3) |

# İmmün kontrol noktası inhibitörleri

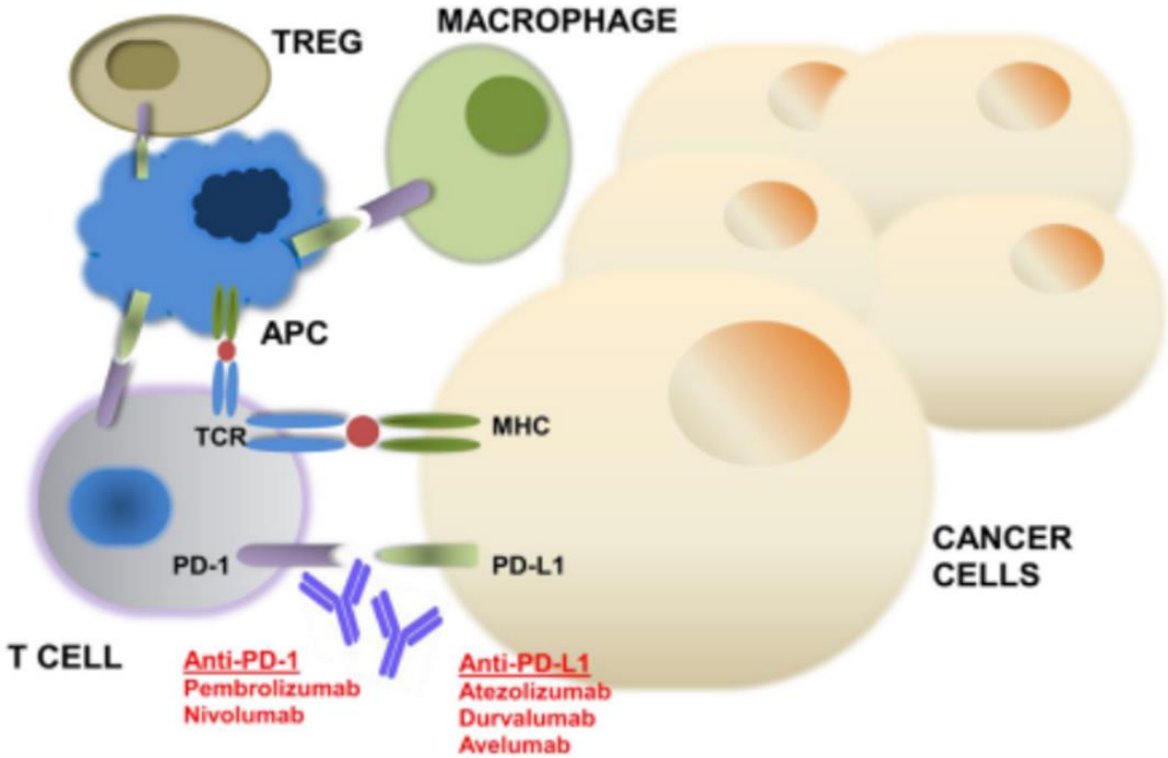
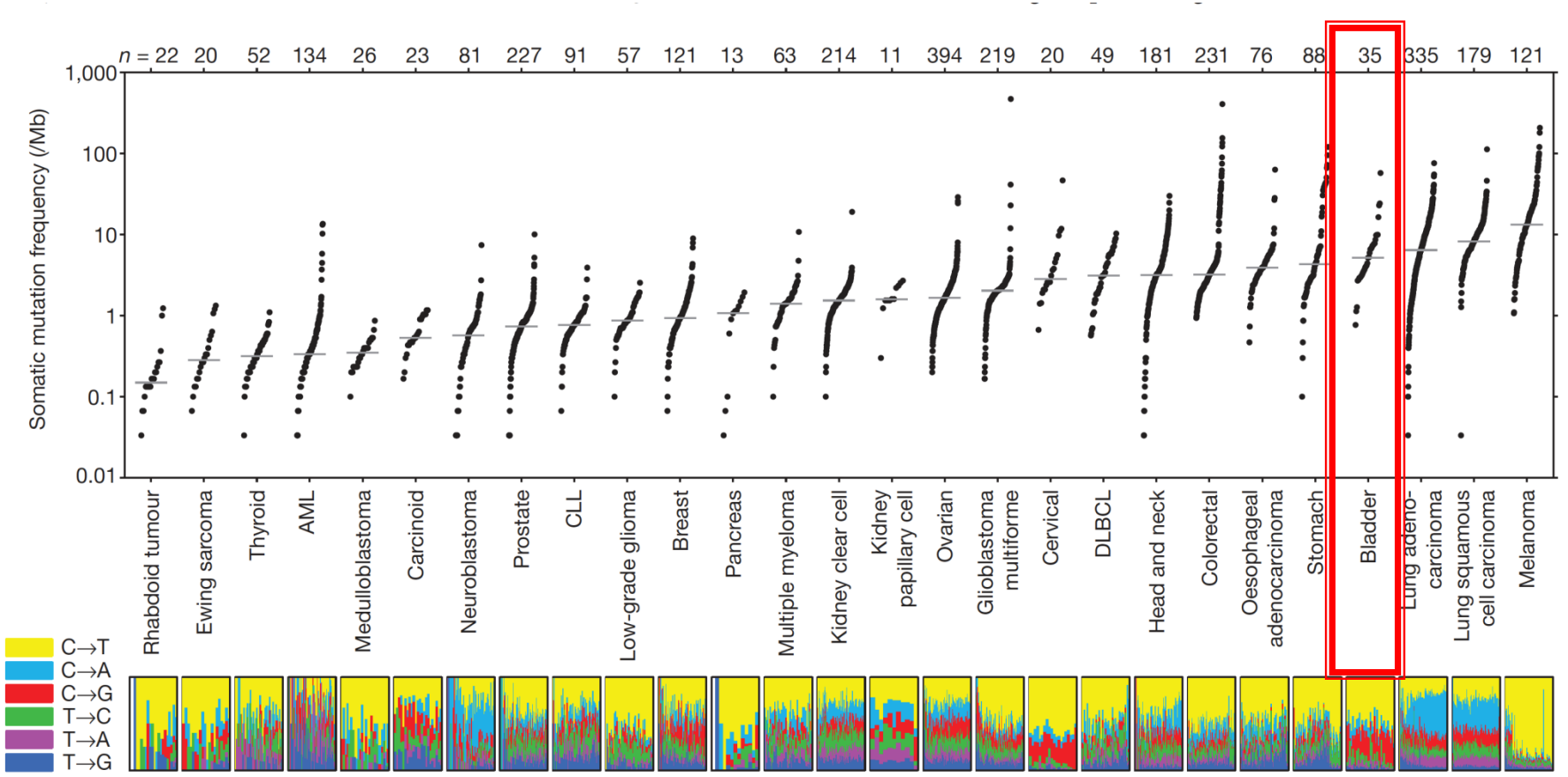



**Fig. 1** Mechanism of action of PD-1 and PD-L1 inhibitors. The programmed cell death 1 (PD-1) receptor is expressed on activated T cells, B cells, macrophages, regulatory T cells (Tregs), and natural killer (NK) cells. Binding of PD-1 to its B7 family of ligands, programmed death ligand 1 (PD-L1 or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

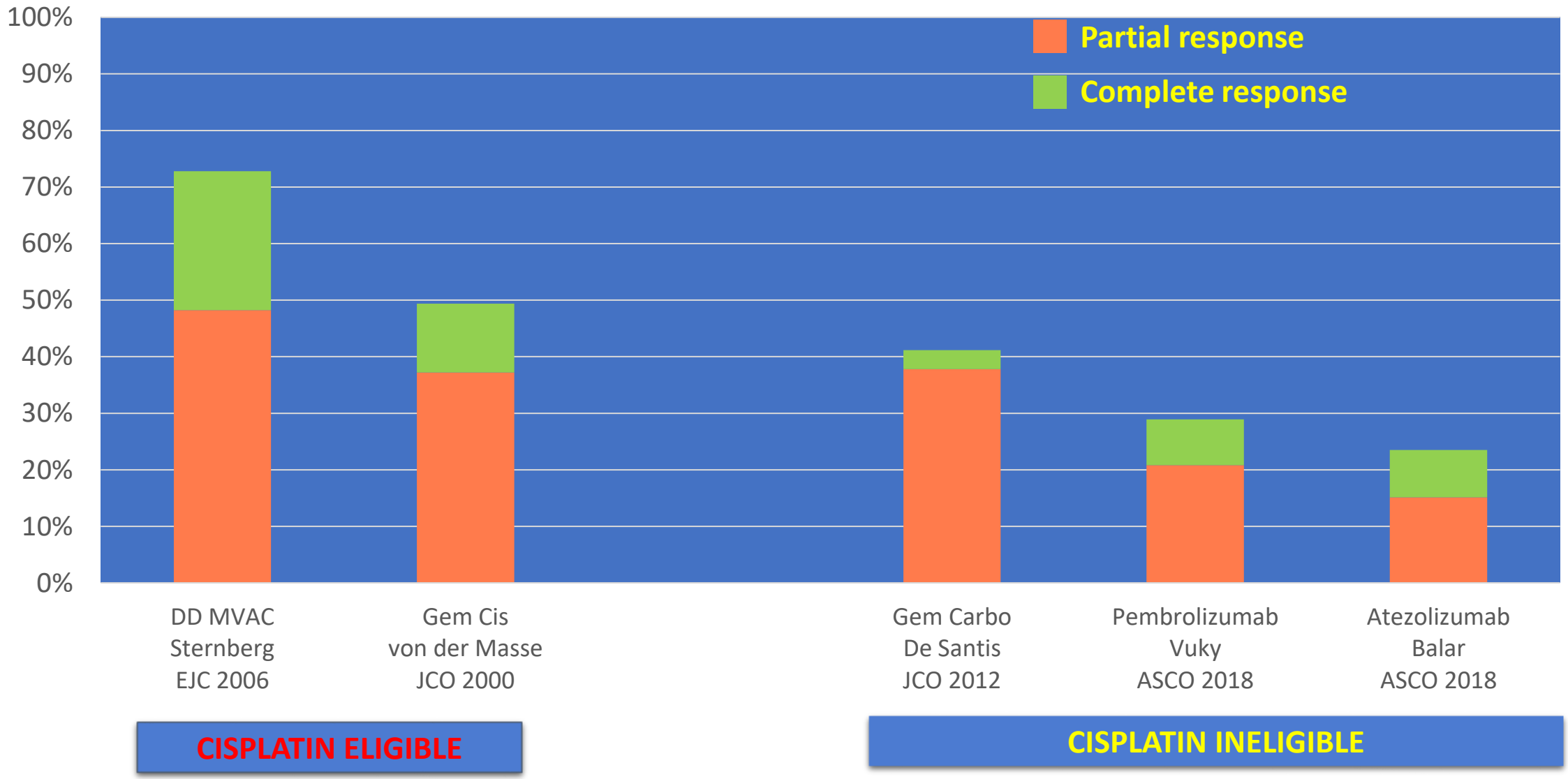
# Mesane Kanserinde Tümör Mutasyon Yükü




Lawrence et al. Nature 2013

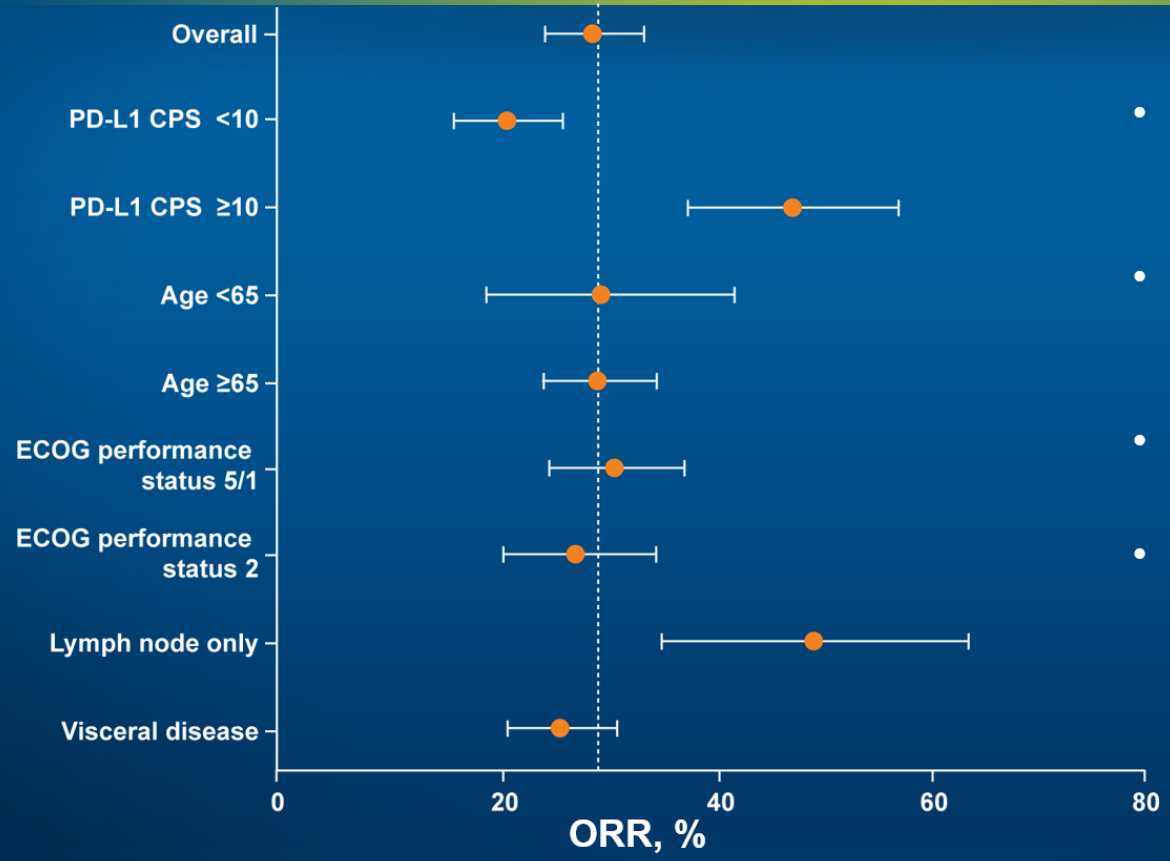
- Yüksek komleks mutasyon durumu tütün ve diğer kanserojenlere maruz kalma ile benzer
- Bir çok neoantijen konakçı immün sistemi tarafından potansiyel olarak yabancı gibi görünür

# Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları



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

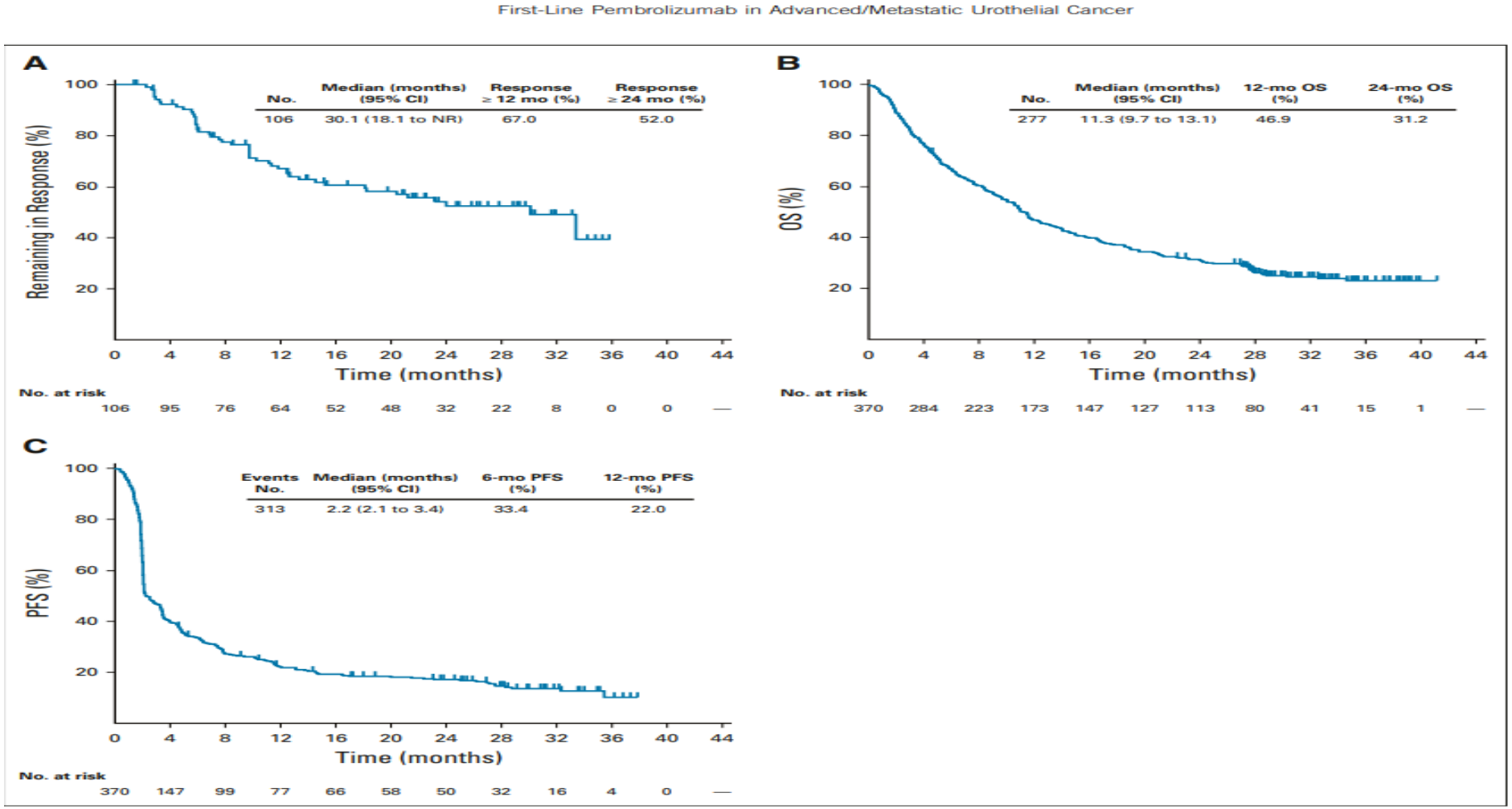
## KEYNOTE-052: Objective Response Rate with First-Line Pembrolizumab by Subgroup in Cisplatin-Ineligible Advanced UC




- 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.

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



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

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

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

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

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

Abstract 4262
Poster 699P

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


Jonathan E. Rosenberg,[1] Matthew D. Galsky,[2] Arjun V. Balar,[3] Yohann Loriot,[4] Andrea Necchi,[5] Jean Hoffman-Censits,[6] Sandy Srinivas,[7] Alexandra Drakaki,[8] Apurva Javery,[9] Yi Shi,[10] Hannah (Xinhui) Huang,[10] Xiaodong Shen,[10] Michiel S. van der Heijden[11]

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


## BACKGROUND

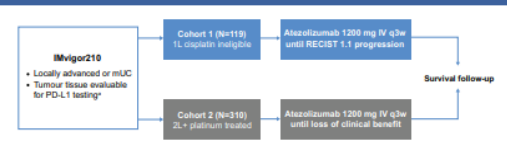
- Cisplatin-based chemotherapy is the standard of care for first-line (1L) treatment of metastatic urothelial carcinoma (mUC), although many patients are ineligible for cisplatin
- Atezolizumab (anti–PD-L1) is recommended for the treatment of several types of locally advanced or mUC, including cisplatin-ineligible patients whose tumours express PD-L1 (PD-L1–expressing immune cells [IC] covering ≥5% of the tumour area [IC2/3])[1-3]
- Cohort 1 of the pivotal, single-arm, Phase II, IMvigor210 study demonstrated the tolerability of and durable responses to 1L atezolizumab in patients with cisplatin-ineligible mUC,[4] with sustained responses observed with additional follow-up[5]
- The ongoing Phase III IMvigor130 study has also demonstrated prolonged efficacy with 1L atezolizumab monotherapy vs platinum-based chemotherapy in exploratory analyses in patients with PD-L1 IC2/3 tumours, including those ineligible for cisplatin[6,7]
- To evaluate the long-term efficacy of atezolizumab in patients with cisplatin-ineligible previously untreated mUC, here, we report updated data from IMvigor210 Cohort 1, based on over 5 years of follow-up


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


## METHODS

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

**Figure 1. IMvigor210 study design[4]**




ClinicalTrials.gov IDs: NCT02951767 (Cohort 1), NCT02108652 (Cohort 2).
2L, second line; q3w, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours 1.1.
* PD-L1 status was prospectively and centrally evaluated using the VENTANA SP142 IHC assay. The study enrolled an all-comer population (patients were eligible regardless of PD-L1 status).

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

## RESULTS

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

**Table. Efficacy summary**

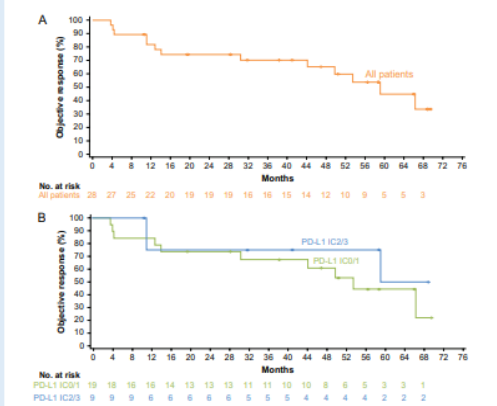
| | All comers (N=119) | PD-L1 IC0/1 (n=87) | PD-L1 IC2/3 (n=32) |
|---|---|---|---|
| **Objective response*** | | | |
| ORR, n (%) [95% CI] | 28 (23.5) [16.2, 32.2] | 19 (21.8) [13.7, 32.0] | 9 (28.1) [13.8, 46.8] |
| CR, n (%) | 12 (10.1) | 7 (8.0) | 5 (15.6) |
| Ongoing responses, n/n (%)† | 15/28 (53.6) | 9/19 (47.4) | 6/9 (66.7) |
| Median DOR (95% CI), mo | 59.1 (44.2, NE) | 53.5 (30.4, NE) | NE (11.1, NE) |
| **OS** | | | |
| OS events, n (%) | 92 (77.3) | 68 (78.2) | 24 (75.0) |
| Median OS (95% CI), mo | 16.3 (10.4, 24.5) | 19.1 (10.4, 25.2) | 12.3 (6.0, 49.8) |
| 24-mo OS (95% CI), % | 41.1 (32.1, 50.2) | 41.8 (31.1, 52.5) | 39.3 (22.1, 56.5) |
| 60-mo OS (95% CI), % | 21.6 (13.7, 29.5) | 19.6 (10.8, 28.5) | 27.0 (10.3, 43.7) |

Clinical cutoff, 31 January 2021.
NE, not estimable.
*Response was per IRF in objective response–evaluable patients.
†Refers to no death or progressive disease only in patients who achieved an objective response.

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

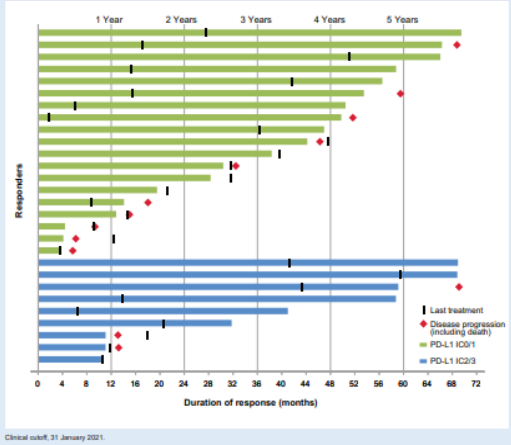
***Median DOR has not been reached in the PD-L1 IC2/3 subgroup of patients***

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




Clinical cutoff, 31 January 2021

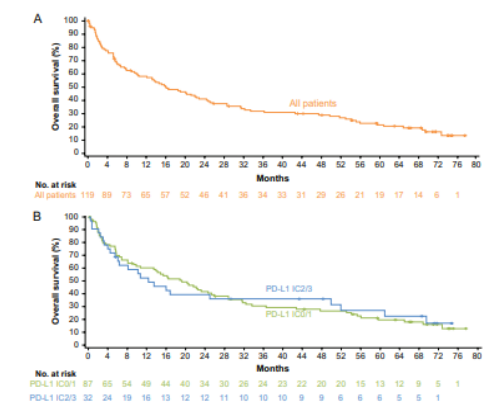
**Figure 3. Duration of treatment and response by PD-L1 status**




Clinical cutoff, 31 January 2021.

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

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




Clinical cutoff, 31 January 2021

## CONCLUSIONS

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

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

The 5-year OS rate seen in the overall all-comer population (≈22%) compares favourably with historic data,[8] including gemcitabine/carboplatin in cisplatin-ineligible patients[9]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9. De Santis M, et al. J Clin Oncol 2012;30:191-9.



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- Betty Nelson of Genentech Inc for contributions to the statistical analyses
- Medical writing assistance for this poster was provided Priscilla Hong, PharmD, of Health Interactions and funded by F. Hoffmann-La Roche Ltd


**DISCLOSURES**

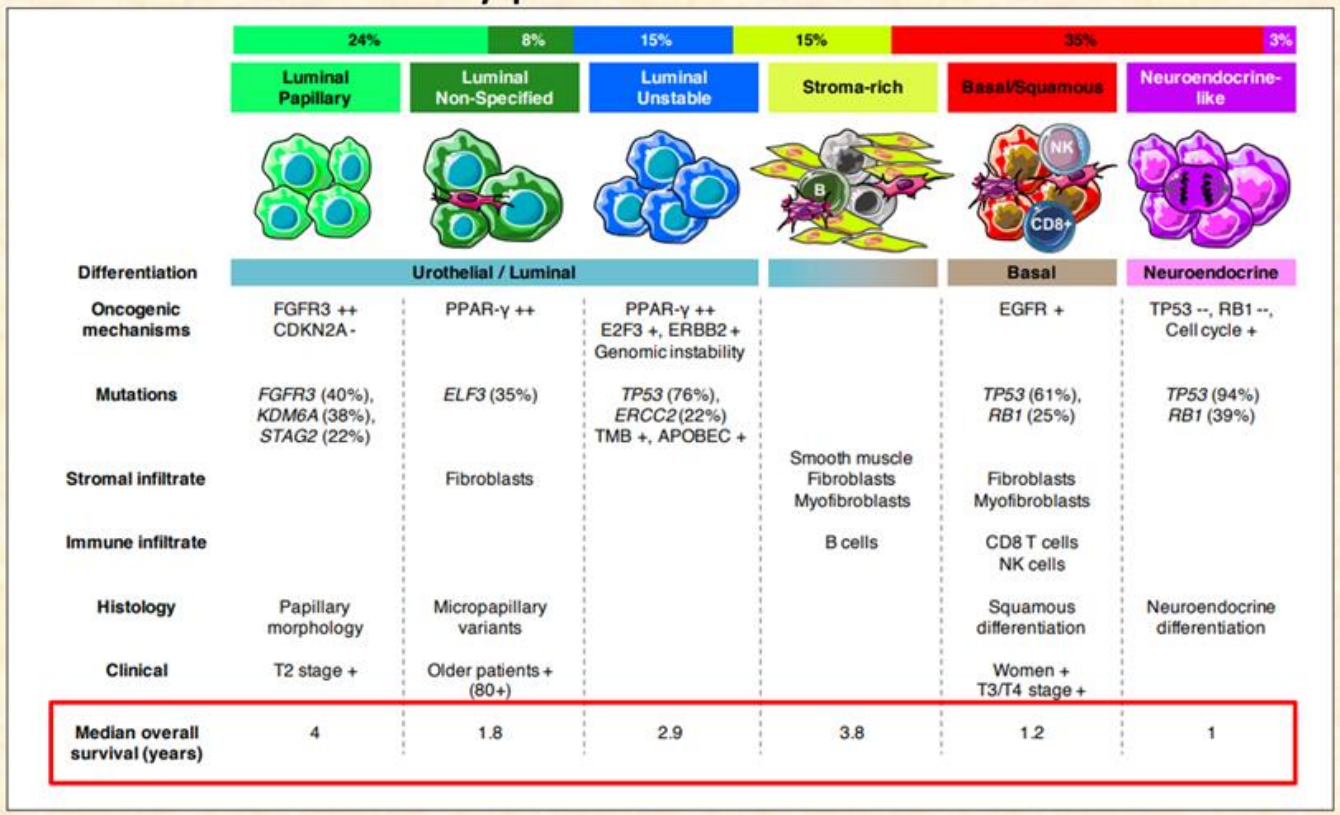
- Dr Rosenberg is an advisor to Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, EMD Serono, Gilead/Immunomedics, GSK, Janssen, Lilly, Merck, Mirati, Pfizer, QED, Roche/Genentech, Seattle Genetics and Tyra Biosciences and received research funding support from Roche, Genentech, AstraZeneca, Zbayer,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


**AUTHOR EMAIL**

For questions or comments on this poster, please contact Dr Jonathan E. Rosenberg at rosenbj1@mskcc.org

# 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 Sisplatin Uygun Olmayanlarda Birinci Basamak Tedavi Yanıtları

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

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

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

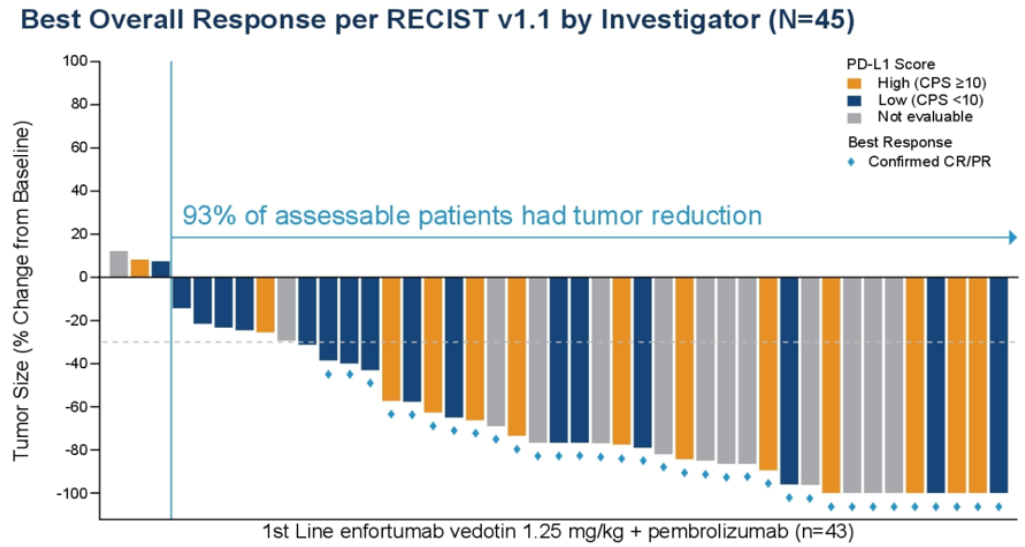
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembrolizumab 200 mg on day 1 of a 3-week cycle

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

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

- 57% confirmed ORR in patients with liver metastases

Maximum Target Lesion Reduction From Baseline by PD-L1 Status




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

# Metastatik Mesane Kanseri Sisplatin Uygun Olmayanlarda Birinci Basamak Tedavi Yanıtları

## EV-103 Cohort K: Phase 1b/2 Trial

**Cohort K**
- Unresectable la/mUC
- Cisplatin ineligible
- No prior treatment for la/mUC

N=149
R 1:1

n=76
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembrolizumab 200 mg on day 1 of a 3-week cycle

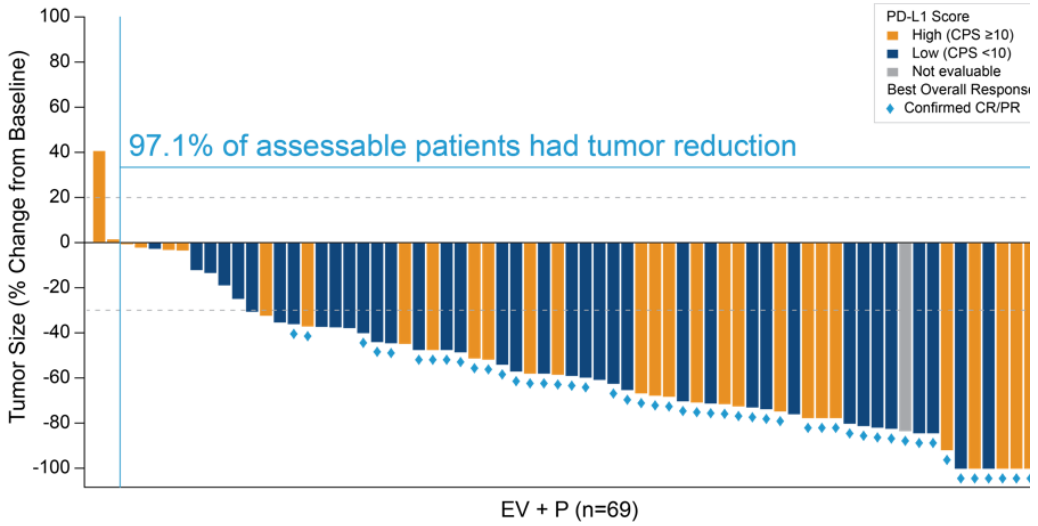
n=73
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle

**Primary Endpoint**
- ORR per BICR

**Secondary Endpoints**
- ORR per investigator assessment
- DOR
- Disease control rate
- PFS
- OS
- Safety

| | EV+P (N=76) | EV Mono (N=73) |
|---|---|---|
| **Confirmed ORR, n (% ) (95% CI)** | 49 (64.5) (52.7, 75.1) | 33 (45.2) (33.5, 57.3) |
| **Best overall response, n (%)** | | |
| Complete Response | 8 (10.5) | 3 (4.1) |
| Partial Response | 41 (53.9) | 30 (41.1) |
| Stable Disease | 17 (22.4) | 25 (34.2) |
| Progressive Disease | 6 (7.9) | 7 (9.6) |
| Not Evaluable | 3 (3.9) | 5 (6.8) |
| No Assessment | 1 (1.3) | 3 (4.1) |
| **Median time to objective response (range), mos** | 2.07 (1.1, 6.6) | 2.07 (1.9, 15.4) |
| **Median number of treatment cycles (range)** | 11.0 (1, 29) | 8.0 (1, 33) |

Data cutoff: 10Jun2022
BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached




BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

Rosenberg JE, et al. ESMO 2022. Abstract 2895/LBA73.

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

## Overall Objective Response Rates by BICR

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

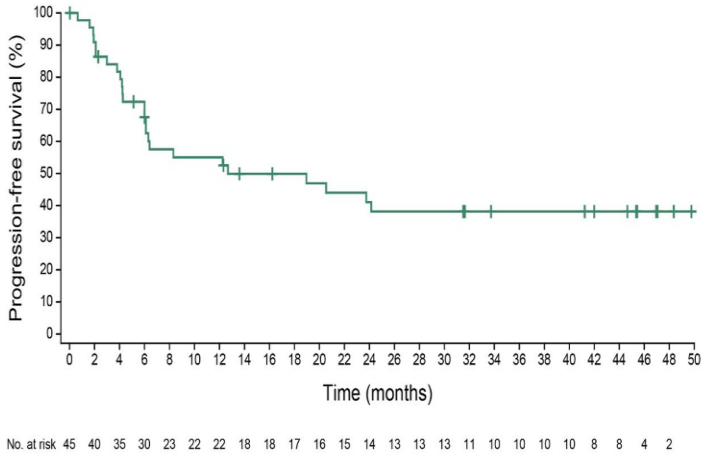
| | Dose Escalation + Cohort A (N = 45) |
|---|---|
| **Objective Response Rate, n (%)** | 33 (73.3) |
| 95% CI[a] for ORR | 58.1-85.4 |
| **Best Overall Response, n (%)** | |
| Complete response | 7 (15.6) |
| Partial response | 26 (57.8) |
| Stable disease | 5 (11.1) |
| Progressive disease | 5 (11.1)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

BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; DCR = disease control rate; INV = investigator; ORR = objective response rate
[a]CI was computed using the Clopper-Pearson method (Clopper 1934)
[b]Patients had no response assessment post-baseline
[c]ORR per INV assessment was 33/45 (73.3%)

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

## Progression-Free Survival by BICR

41.1% of patients were progression-free at 24 months



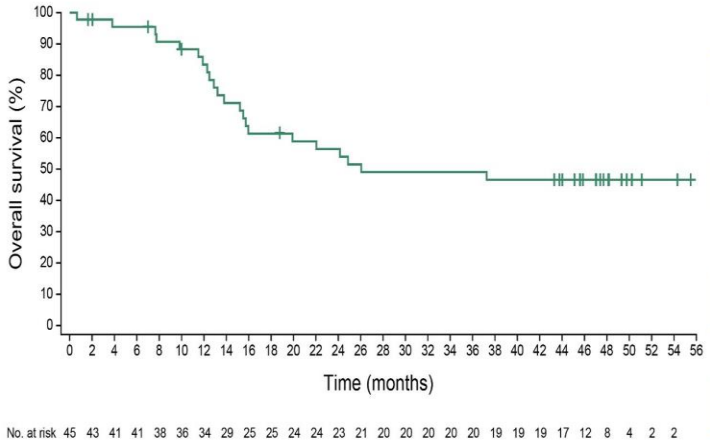

| | Dose Escalation + Cohort A (N = 45) |
|---|---|
| **PFS events, n** | 25 |
| **Median PFS (95% CI[a])** | 12.7 months (6.11-NE) |
| **PFS rate[b] at:** | |
| 6 months, % (95% CI[a]) | 72.4 (56.47-83.26) |
| 12 months, % (95% CI[a]) | 55.0 (38.84-68.58) |
| 24 months, % (95% CI[a]) | 41.1 (25.69-55.88)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

BICR = blinded independent central review; CI = confidence interval; NE = not estimable; PFS = progression-free survival
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)
[b]As estimated using Kaplan-Meier method



## Overall Survival

Median survival exceeds 2 years




| | Dose Escalation + Cohort A (N = 45) |
|---|---|
| **OS events, n** | 22 |
| **Median OS (95% CI[a])** | 26.1 months (15.51-NE) |
| **OS rate[b] at:** | |
| 6 months, % (95% CI[a]) | 95.4 (83.00-98.84) |
| 12 months, % (95% CI[a]) | 83.4 (68.25-91.72) |
| 24 months, % (95% CI[a]) | 56.4 (40.03-69.91) |
| **Median follow-up time** | 47.0 months |

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

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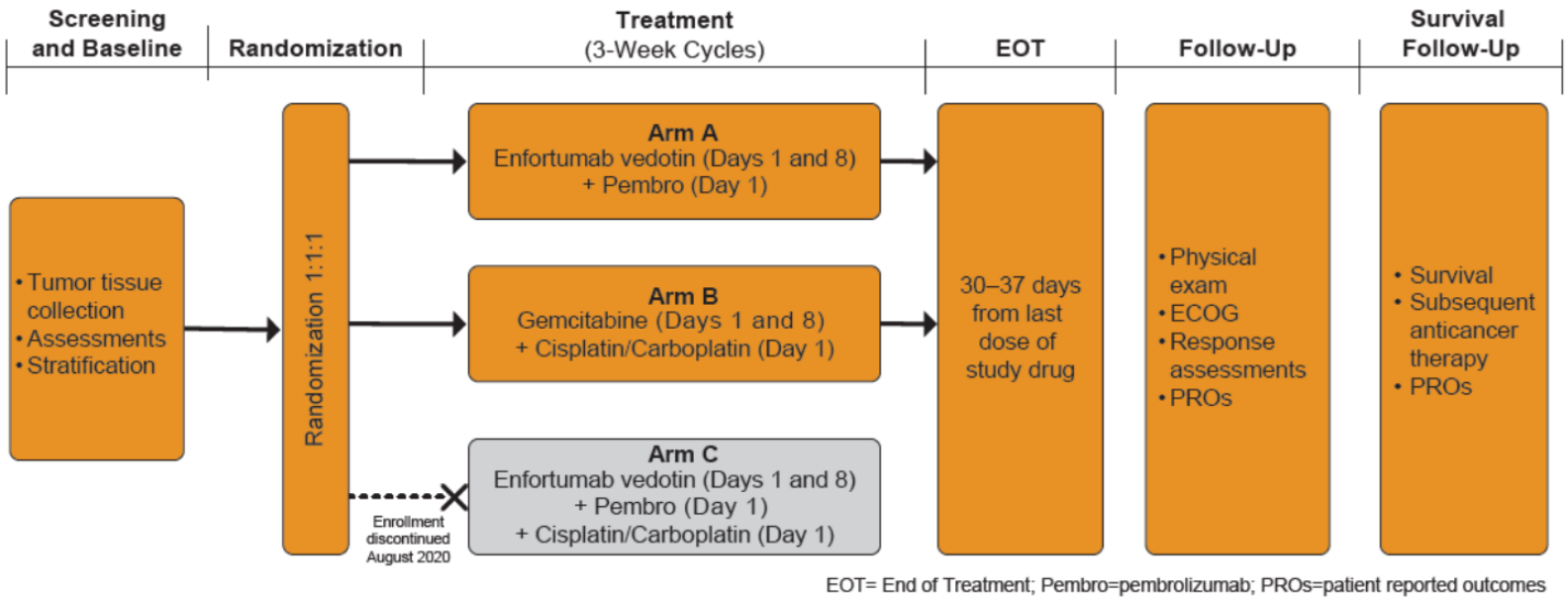
# Gelecek Perspektif

## EV-302 Randomized Phase 3 Trial Schema

Eligibility

- Locally advanced or metastatic urothelial carcinoma
- 1st line systemic therapy
- Platinum-eligible




EOT= End of Treatment; Pembro=pembrolizumab; PROs=patient reported outcomes

- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

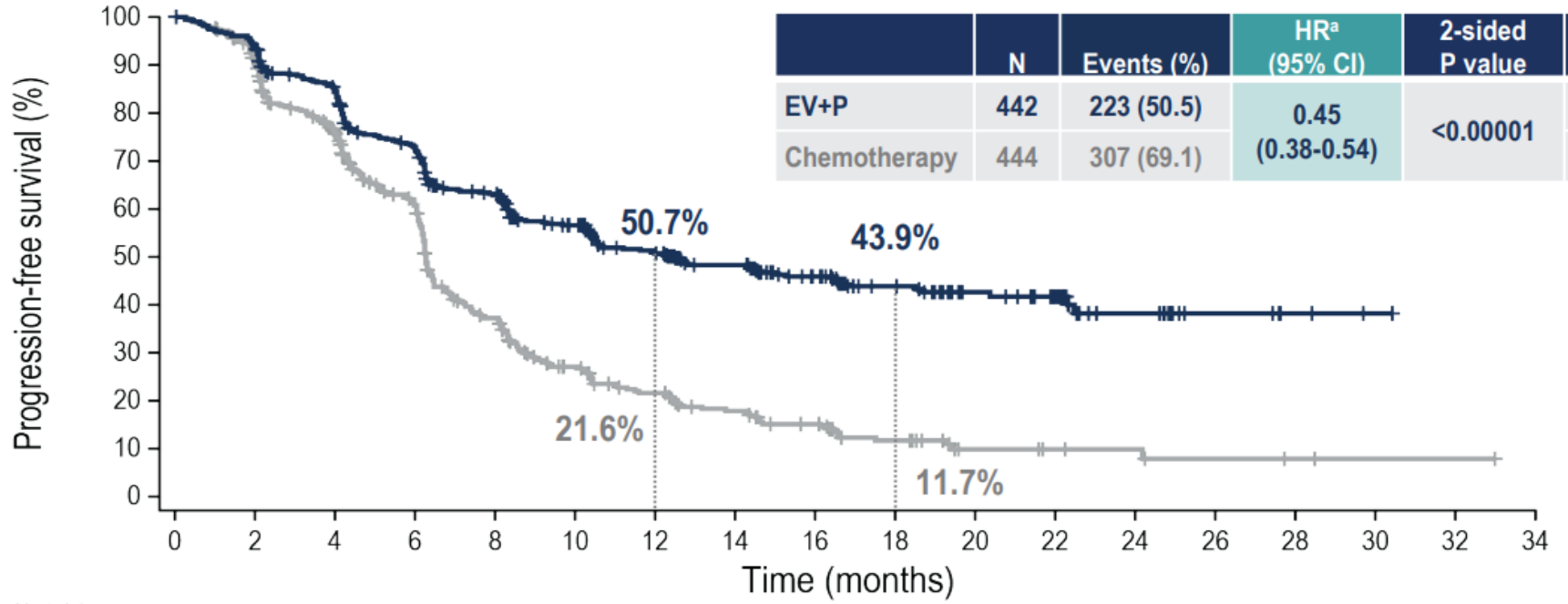
**Primary Endpoints: PFS, OS**
**Secondary Endpoints: ORR, DOR, DCR, QOL, PRO, Safety**

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

## Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

| | N | Events (%) | HR[a] (95% CI) | 2-sided P value | mPFS (95% CI), months |
|---|---|---|---|---|---|
| EV+P | 442 | 223 (50.5) | 0.45 (0.38-0.54) | <0.00001 | 12.5 (10.4-16.6) |
| Chemotherapy | 444 | 307 (69.1) | | | 6.3 (6.2-6.5) |




N at risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 442 | 409 | 361 | 303 | 253 | 204 | 167 | 132 | 102 | 73 | 45 | 33 | 17 | 6 | 3 | 1 |
| Chemotherapy | 444 | 380 | 297 | 213 | 124 | 78 | 56 | 41 | 30 | 19 | 8 | 6 | 5 | 3 | 2 | 1 | 1 |

Data cutoff: 08 Aug 2023

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Powles et al.

PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

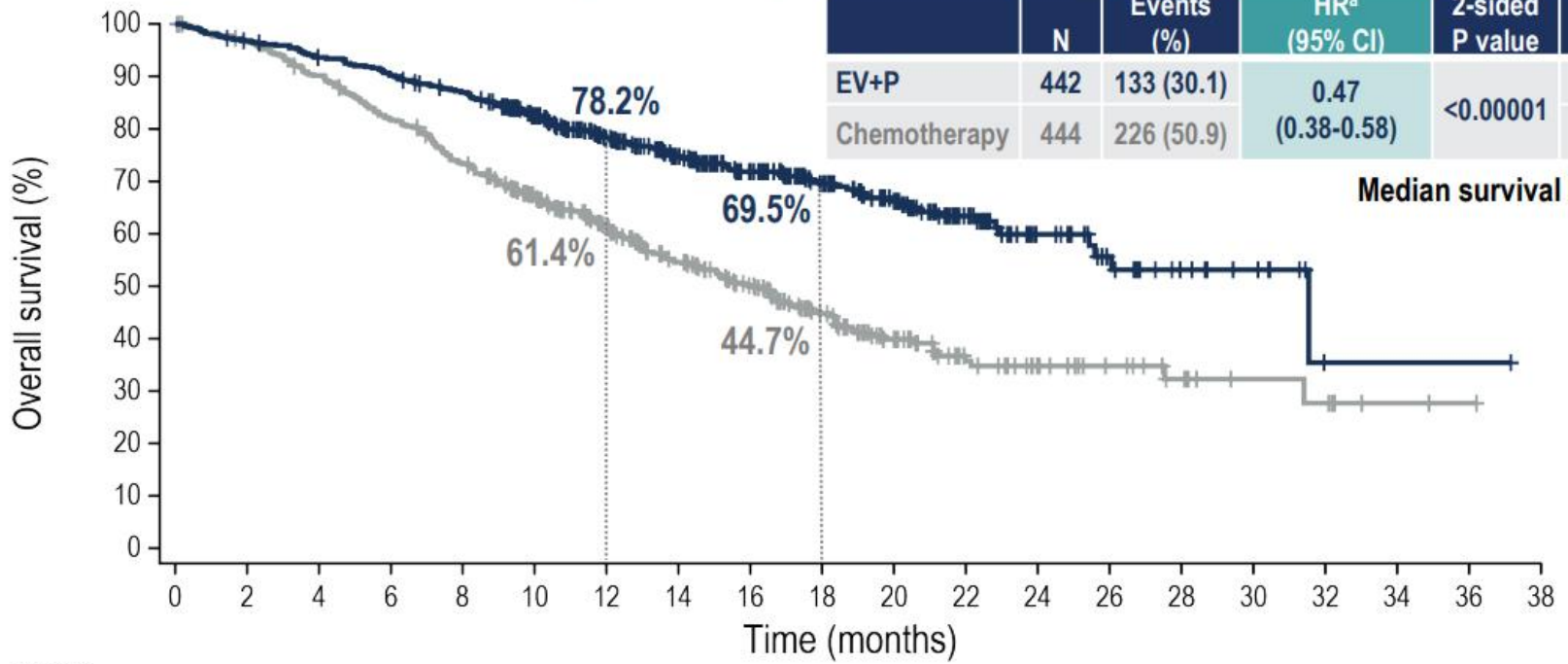
# Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
# EV103 -EV/pemrolizumab

## Overall Survival

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

| | N | Events (%) | HR[a] (95% CI) | 2-sided P value | mOS (95% CI), months |
|---|---|---|---|---|---|
| EV+P | 442 | 133 (30.1) | 0.47 (0.38-0.58) | <0.00001 | 31.5 (25.4-NR) |
| Chemotherapy | 444 | 226 (50.9) | | | 16.1 (13.9-18.3) |

Median survival follow-up: 17.2 months




N at risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 442 | 426 | 409 | 394 | 376 | 331 | 270 | 222 | 182 | 141 | 108 | 67 | 36 | 22 | 12 | 8 | 1 | 1 | 1 |
| Chemotherapy | 444 | 423 | 393 | 356 | 317 | 263 | 209 | 164 | 125 | 90 | 60 | 37 | 25 | 18 | 12 | 7 | 6 | 2 | 1 |

Data cutoff: 08 Aug 2023

OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

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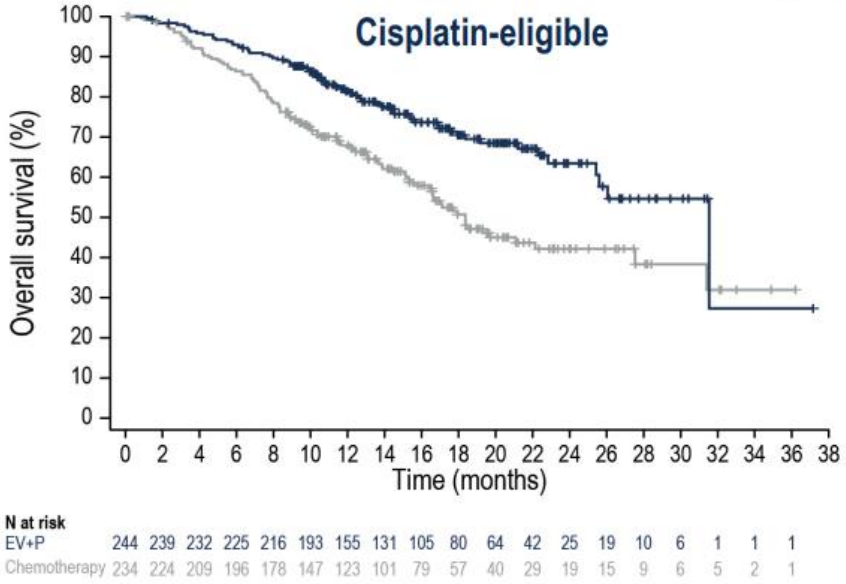
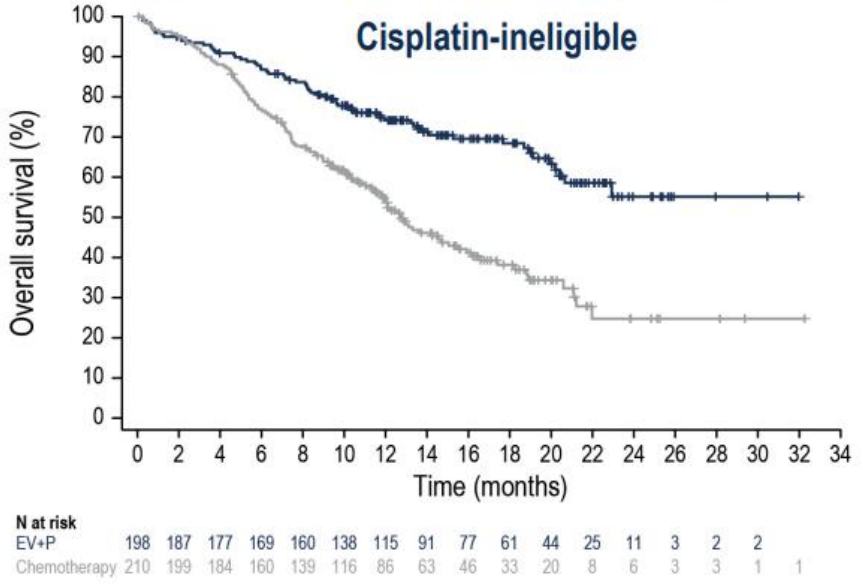
# Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
# EV103 -EV/pembrolizumab

## OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility




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




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

Data cutoff: 08 Aug 2023

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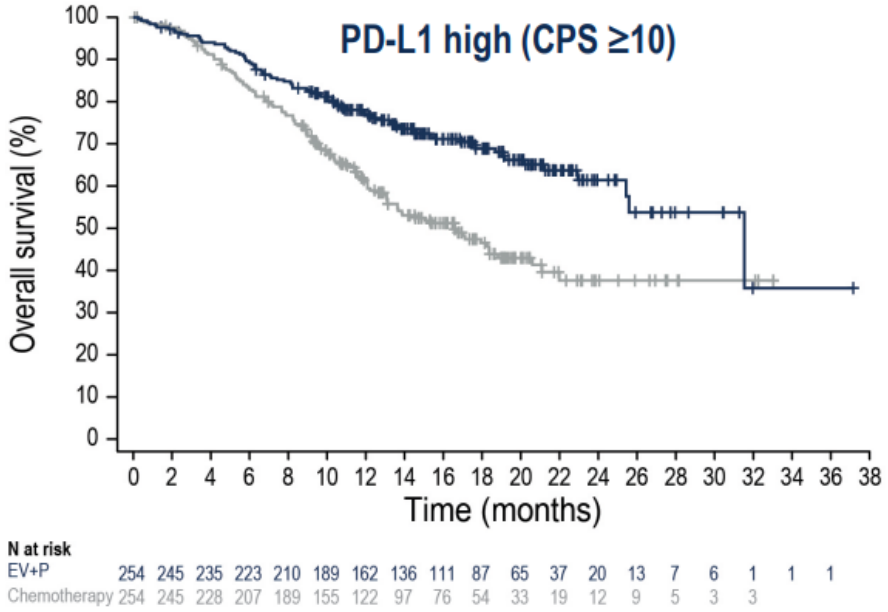
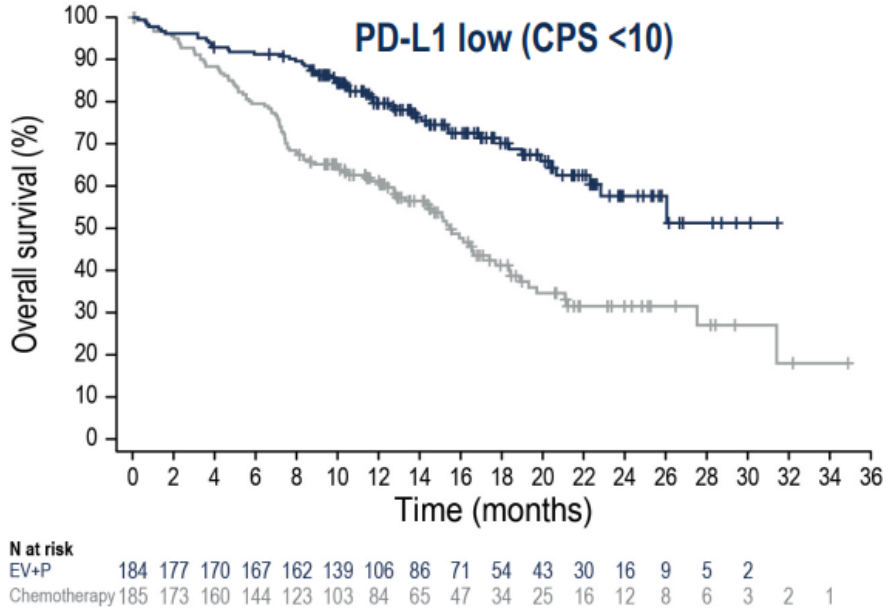
# Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
# EV103 -EV/pemrolizumab

## OS Subgroup Analysis: PD-L1 Expression

OS benefit was consistent with overall population regardless of PD-L1 expression status




| | Events, n | HR (95% CI) | mOS (95% CI), months |
|---|---|---|---|
| EV+P | 79 | 0.49 (0.37-0.66) | 31.5 (25.4-NR) |
| Chemotherapy | 125 | | 16.6 (13.1-20.6) |




| | Events, n | HR (95% CI) | mOS (95% CI), months |
|---|---|---|---|
| EV+P | 53 | 0.44 (0.31-0.61) | NR (22.3-NR) |
| Chemotherapy | 99 | | 15.5 (12.9-17.7) |

Data cutoff: 08 Aug 2023

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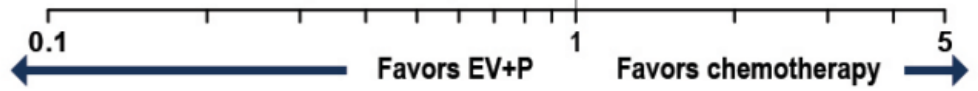
# Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
# EV103 -EV/pembrolizumab

## Subgroup Analysis of OS

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

| Subgroup | Events/N EV+P | Events/N Chemotherapy | Hazard Ratio (95% CI) |
|---|---|---|---|
| Overall | 133/442 | 226/444 | 0.47 (0.38-0.58) |
| Age | | | |
| <65 years | 39/144 | 58/135 | 0.46 (0.30-0.71) |
| ≥65 years | 94/298 | 168/309 | 0.48 (0.38-0.63) |
| Sex | | | |
| Female | 32/98 | 54/108 | 0.51 (0.32-0.80) |
| Male | 101/344 | 172/336 | 0.47 (0.36-0.60) |
| ECOG PS | | | |
| 0 | 44/223 | 94/215 | 0.36 (0.25-0.53) |
| 1-2 | 89/219 | 131/227 | 0.54 (0.41-0.72) |
| Primary disease site of origin | | | |
| Upper tract | 38/135 | 45/104 | 0.53 (0.34-0.83) |
| Lower tract | 94/305 | 180/339 | 0.46 (0.36-0.59) |
| Liver metastases | | | |
| Present | 43/100 | 67/99 | 0.47 (0.32-0.71) |
| Absent | 90/342 | 159/345 | 0.47 (0.36-0.61) |
| PD-L1 expression | | | |
| Low (CPS <10) | 53/184 | 99/185 | 0.44 (0.31-0.61) |
| High (CPS ≥10) | 79/254 | 125/254 | 0.49 (0.37-0.66) |
| Cisplatin eligibility | | | |
| Eligible | 69/244 | 106/234 | 0.53 (0.39-0.72) |
| Ineligible | 64/198 | 120/210 | 0.43 (0.31-0.59) |




Data cutoff: 08 Aug 2023

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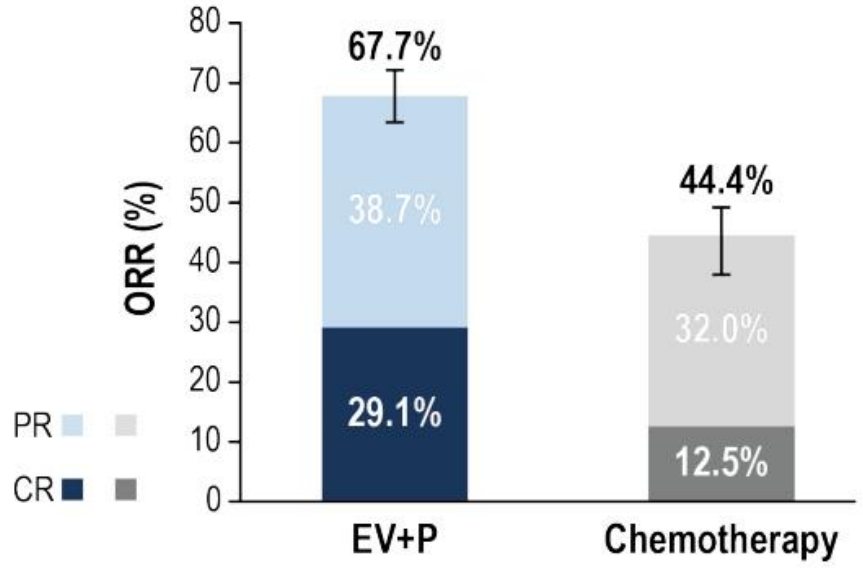
# Metastatik Mesane Kanseri Birinci Basamak Tedavi Yanıtları
# EV103 -EV/pembrolizumab

## Confirmed Overall Response per BICR

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




| | EV+P (N=437) | Chemotherapy (N=441) |
|---|---|---|
| **Confirmed ORR, n (%) (95% CI)** | **296 (67.7) (63.1-72.1)** | **196 (44.4) (39.7-49.2)** |
| **2-sided P value** | <0.00001 | |
| **Best overall response[a], n (%)** | | |
| Complete response | 127 (29.1) | 55 (12.5) |
| Partial response | 169 (38.7) | 141 (32.0) |
| Stable disease | 82 (18.8) | 149 (33.8) |
| Progressive disease | 38 (8.7) | 60 (13.6) |
| Not evaluable/No assessment[b] | 21 (4.8) | 36 (8.2) |

| | | |
|---|---|---|
| **Median DOR (95% CI)** | NR (20.2, NR) | 7.0 (6.2, 10.2) |

Data cutoff: 08 Aug 2023

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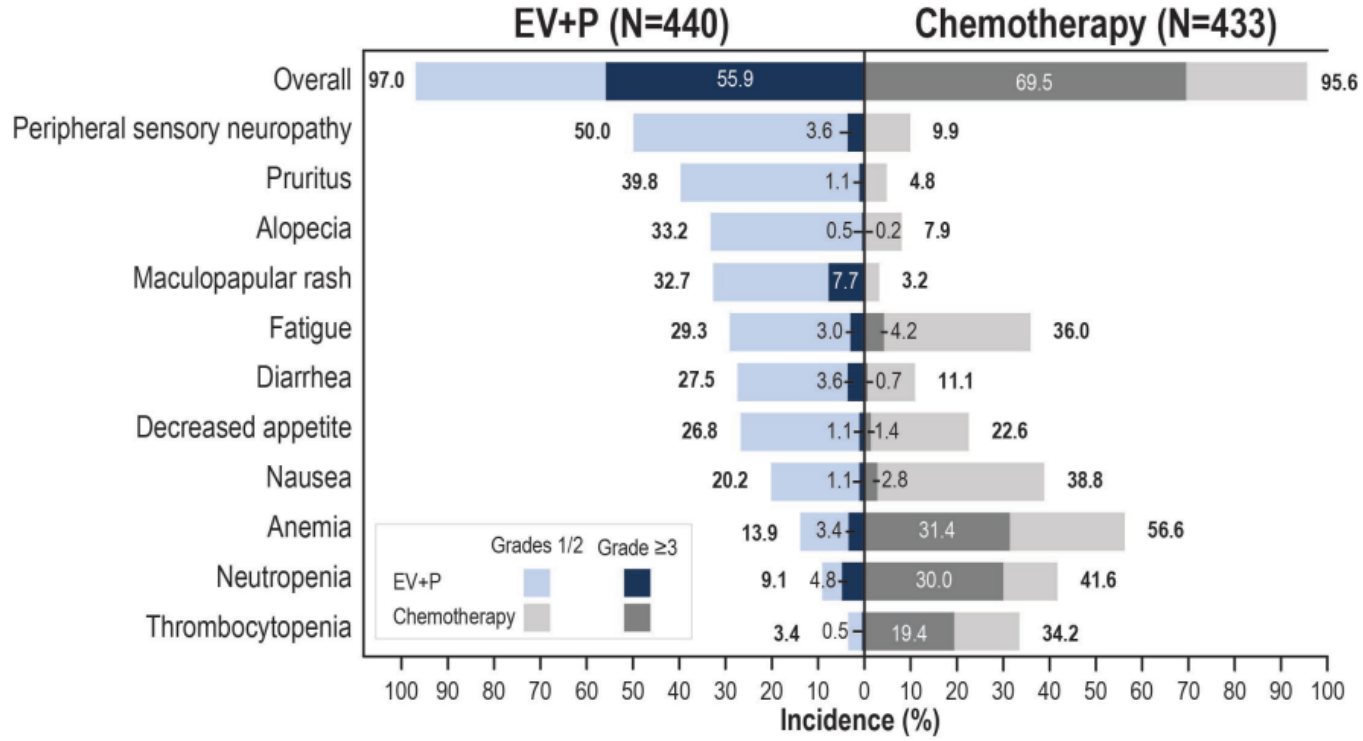
CR, complete response; DOR, duration of response; PR, partial response
[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response
[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline

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

## Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy




Serious TRAEs:
- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):
EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

Data cutoff: 08 Aug 2023

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TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm
TRAEs, treatment-related adverse events

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

## EV Treatment-Related Adverse Events of Special Interest*

### Majority of treatment-related AESIs were low grade

| | EV+P (N=440) n (%) | | Chemotherapy (N=433) n (%) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Skin reactions | 294 (66.8) | 68 (15.5) | 60 (13.9) | 1 (0.2) |
| Peripheral neuropathy | 278 (63.2) | 30 (6.8) | 53 (12.2) | 0 (0.0) |
| Sensory events | 260 (59.1) | 19 (4.3) | 51 (11.8) | 0 (0.0) |
| Motor events | 44 (10.0) | 12 (2.7) | 5 (1.2) | 0 (0.0) |
| Ocular disorders | 94 (21.4) | 0 (0.0) | 12 (2.8) | 0 (0.0) |
| Dry eye | 82 (18.6) | 0 (0.0) | 8 (1.8) | 0 (0.0) |
| Hyperglycemia | 57 (13.0) | 27 (6.1) | 3 (0.7) | 0 (0.0) |
| Infusion-related reactions | 9 (2.0) | 0 (0.0) | 9 (2.1) | 0 (0.0) |

Data cutoff: 08 Aug 2023

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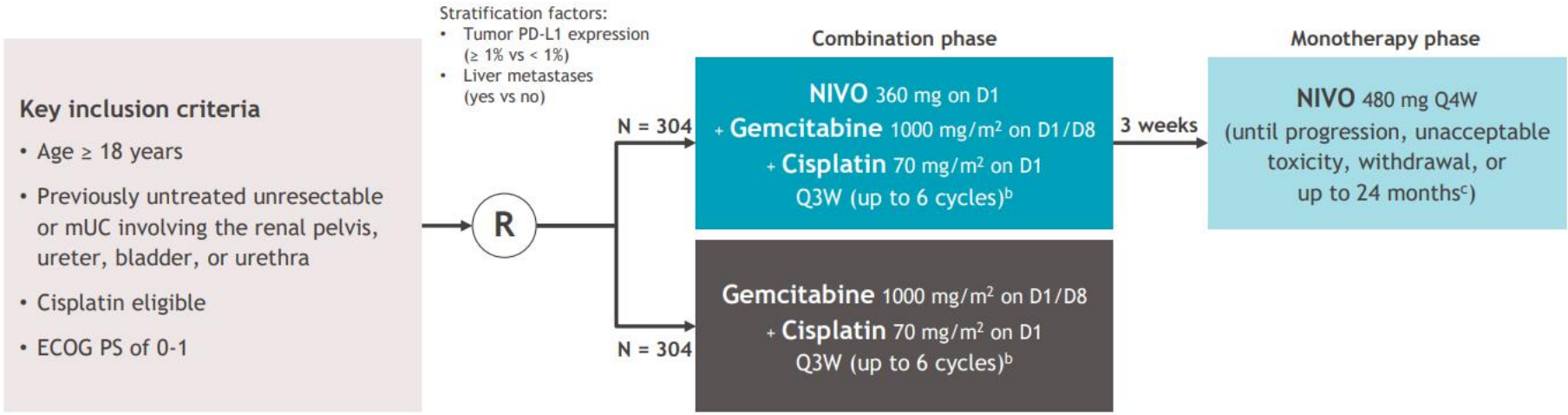
*There are differences in the rates of skin reactions reported for EV treatment-related AESIs and P TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and P monotherapies, respectively
AESI, adverse event of special interest

# Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

## Study design

- NIVO + gemcitabine-cisplatin vs gemcitabine-cisplatin in cisplatin-eligible patients[a]




**Median (range) study follow-up,** 33.6 (7.4-62.4) months

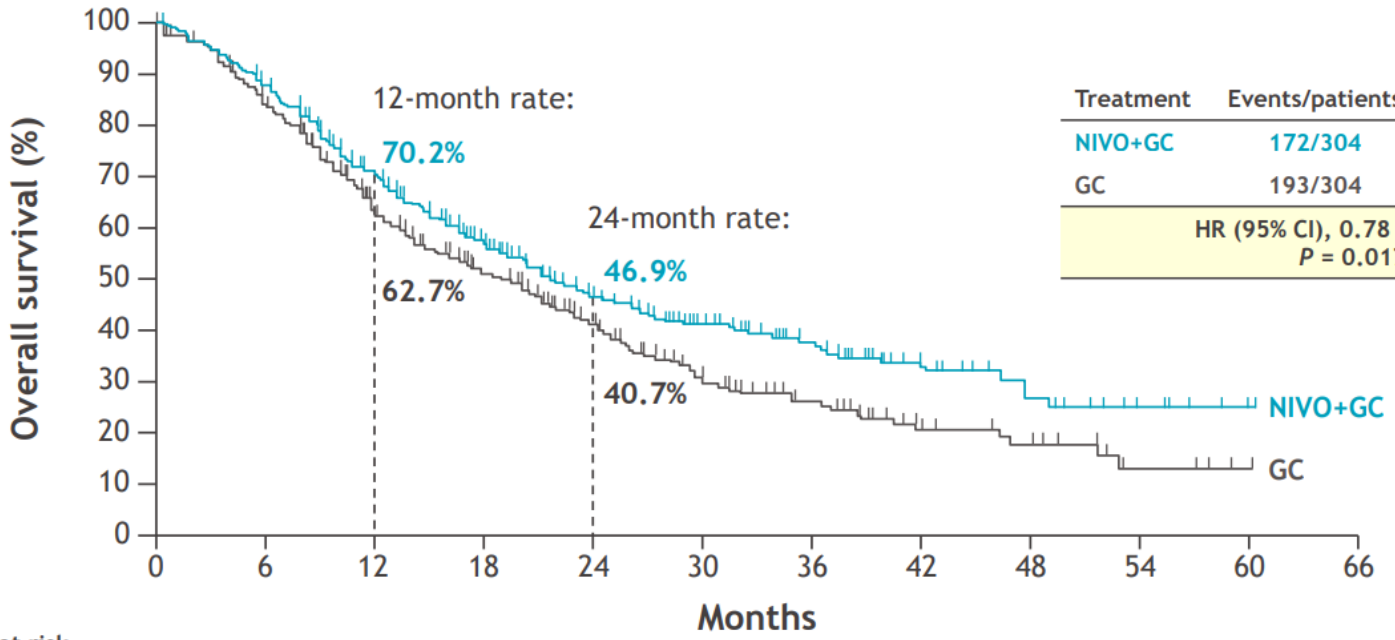
**Primary endpoints:** OS, PFS per BICR
**Key secondary endpoints:** OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
**Key exploratory endpoints:** ORR per BICR, safety

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO + gemcitabine-cisplatin combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA, USA).
BICR, blinded independent central review; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q×W, every × weeks; R, randomization.

# Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

## OS (primary endpoint)




| Treatment | Events/patients | Median OS (95% CI), months |
|---|---|---|
| NIVO+GC | 172/304 | 21.7 (18.6-26.4) |
| GC | 193/304 | 18.9 (14.7-22.4) |
| HR (95% CI), 0.78 (0.63-0.96) *P* = 0.0171 | | |

| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+GC | 304 | 264 | 196 | 142 | 97 | 69 | 48 | 25 | 15 | 7 | 2 | 0 |
| GC | 304 | 242 | 166 | 122 | 82 | 49 | 33 | 17 | 13 | 4 | 1 | 0 |

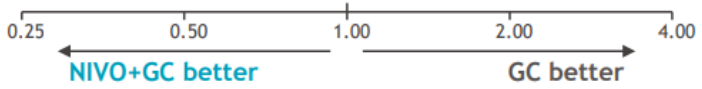
Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with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

# Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

## OS in subgroups

| Subgroup | No. of patients | NIVO+GC *No. of events/no. of patients* | GC *No. of events/no. of patients* | Unstratified HR for death (95% CI) |
|---|---|---|---|---|
| **Overall (N = 608)** | | 172/304 | 193/304 | 0.78 (0.63-0.95) |
| **Age, years** | | | | |
| < 65 | 298 | 85/150 | 100/148 | 0.69 (0.51-0.92) |
| ≥ 65 and < 75 | 236 | 65/120 | 66/116 | 0.89 (0.63-1.26) |
| ≥ 75 | 74 | 22/34 | 27/40 | 0.86 (0.49-1.52) |
| **Sex** | | | | |
| Male | 470 | 133/236 | 147/234 | 0.76 (0.60-0.97) |
| Female | 138 | 39/68 | 46/70 | 0.82 (0.54-1.26) |
| **Race** | | | | |
| White | 436 | 123/211 | 145/225 | 0.80 (0.63-1.02) |
| Asian | 138 | 38/75 | 36/63 | 0.71 (0.45-1.12) |
| Other | 32 | 11/18 | 10/14 | 0.84 (0.35-1.97) |
| **Region** | | | | |
| US | 40 | 18/19 | 15/21 | 1.92 (0.95-3.88) |
| Asia | 133 | 36/72 | 34/61 | 0.73 (0.46-1.17) |
| Europe | 276 | 72/134 | 90/142 | 0.73 (0.53-0.99) |
| Rest of the world | 159 | 46/79 | 54/80 | 0.73 (0.49-1.08) |
| **ECOG PS** | | | | |
| 0 | 324 | 74/162 | 87/162 | 0.70 (0.51-0.95) |
| 1 | 282 | 96/140 | 106/142 | 0.85 (0.64-1.11) |
| **PD-L1 expression** | | | | |
| ≥ 1% | 221 | 64/111 | 67/110 | 0.75 (0.53-1.06) |
| < 1% or indeterminate | 387 | 108/193 | 126/194 | 0.80 (0.62-1.04) |
| **Liver metastases** | | | | |
| Yes | 128 | 45/64 | 48/64 | 0.77 (0.51-1.16) |
| No | 480 | 127/240 | 145/240 | 0.77 (0.61-0.98) |
| **Previous systemic anticancer therapy** | | | | |
| Yes | 156 | 44/88 | 41/68 | 0.90 (0.59-1.38) |
| No | 452 | 128/216 | 152/236 | 0.76 (0.60-0.96) |

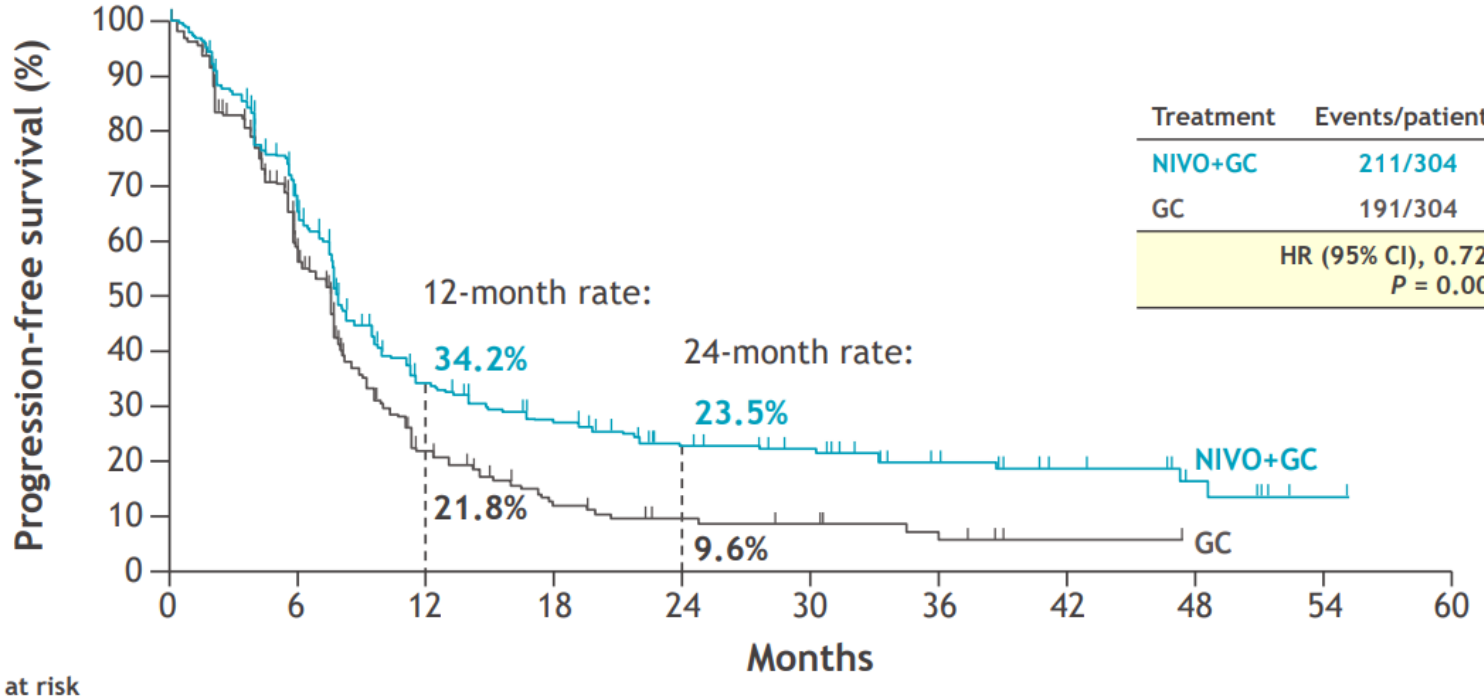



All randomized patients. HRs were not computed for subgroup categories (except for age, sex, race, and region) with < 10 patients per treatment group. Categories without a meaningful estimate of the HR are not shown. PD-L1 expression and liver metastases are per interactive response technology. There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

# Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

## PFS per BICR (primary endpoint)




| Treatment | Events/patients | Median PFS (95% CI), months |
|---|---|---|
| NIVO+GC | 211/304 | 7.9 (7.6-9.5) |
| GC | 191/304 | 7.6 (6.1-7.8) |
| HR (95% CI), 0.72 (0.59-0.88) *P* = 0.0012 | | |

| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+GC | 304 | 179 | 82 | 57 | 41 | 31 | 19 | 11 | 6 | 1 | 0 |
| GC | 304 | 119 | 35 | 17 | 10 | 8 | 5 | 1 | 0 | 0 | 0 |

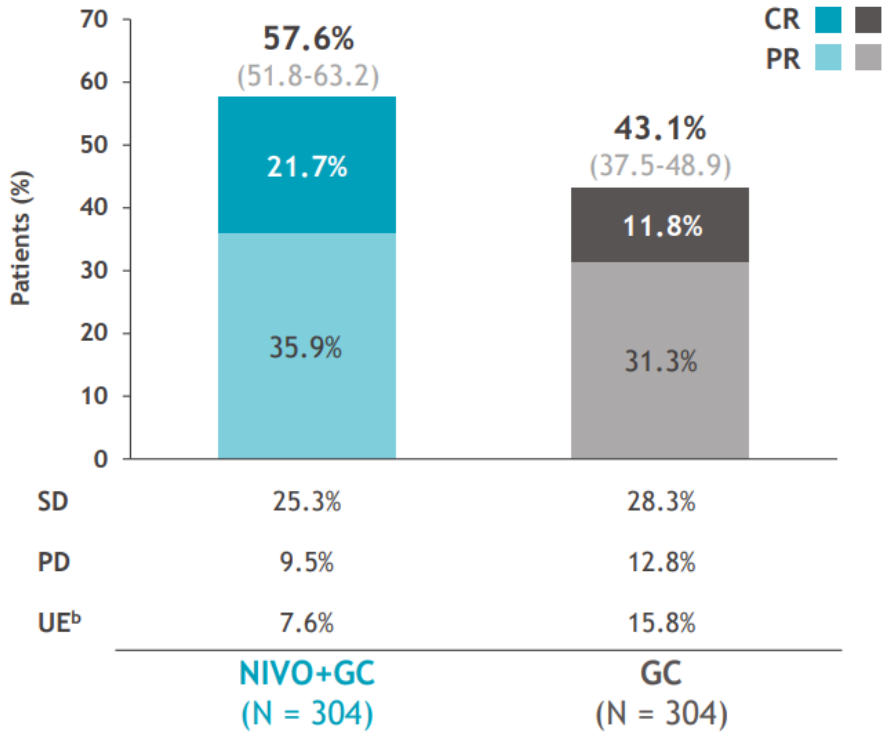
Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as time from randomization to first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who did not progress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

# Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

## Objective response outcomes (exploratory endpoints)

### ORR (95% CI) and BOR per BICR[a]




### Time to and duration of responses

| Any objective response[c] | NIVO+GC (n = 175) | GC (n = 131) |
|---|---|---|
| Median TTR (Q1-Q3), months | 2.1 (2.0-2.3) | 2.1 (2.0-2.2) |
| Median DoR (95% CI), months | 9.5 (7.6-15.1) | 7.3 (5.7-8.9) |

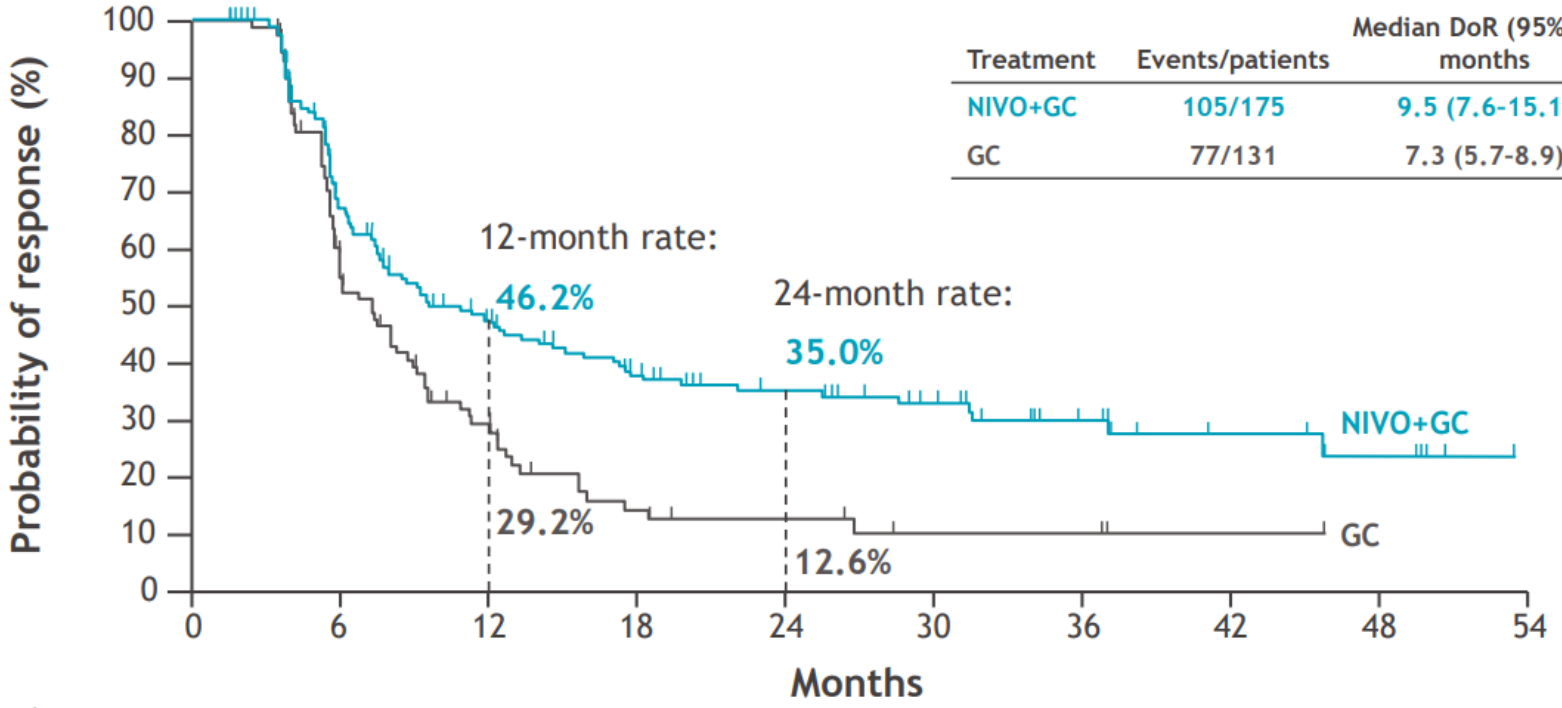
| Complete response[d] | NIVO+GC (n = 66) | GC (n = 36) |
|---|---|---|
| Median TTCR (Q1-Q3), months | 2.1 (1.9-2.2) | 2.1 (1.9-2.2) |
| Median DoCR (95% CI), months | 37.1 (18.1-NE) | 13.2 (7.3-18.4) |

[a]In all randomized patients. [b]The most common reasons for UE response included death before first tumor assessment, withdrawal of consent, treatment stopped due to toxicity, patient never treated, and receipt of subsequent anticancer therapy before first tumor assessment. [c]Based on patients with an objective response per BICR (PR or CR as BOR). [d]Based on patients with a CR per BICR.
BOR, best overall response; CR, complete response; DoCR, duration of complete response; DoR, duration of objective response; NE, not estimable; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease; TTCR, time to complete response; TTR, time to objective response; UE, unevaluable.

# Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

## Duration of objective response per BICR




| Treatment | Events/patients | Median DoR (95% CI), months |
|---|---|---|
| NIVO+GC | 105/175 | 9.5 (7.6-15.1) |
| GC | 77/131 | 7.3 (5.7-8.9) |

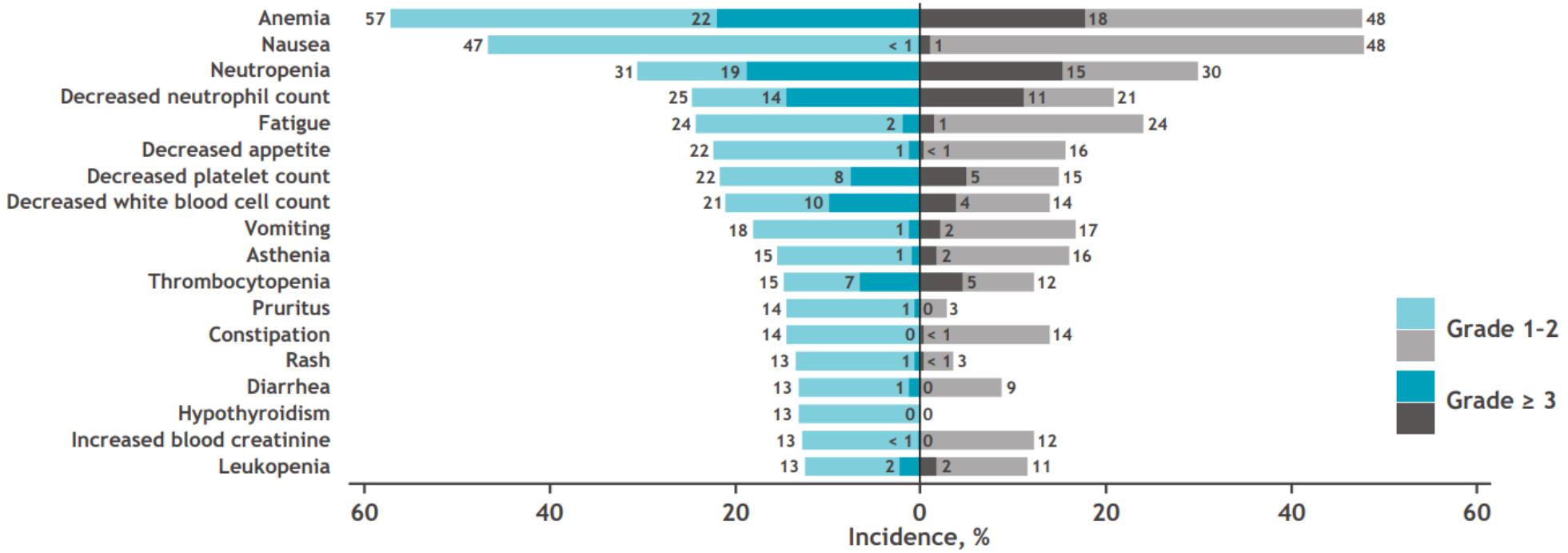
| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+GC | 175 | 104 | 64 | 47 | 34 | 26 | 15 | 9 | 5 | 0 |
| GC | 131 | 49 | 22 | 9 | 6 | 3 | 3 | 1 | 0 | 0 |

# Sisplatine uygun hastalarda KT+İmmünoterapi

CheckMate 901

## Treatment-related AEs in all treated patients

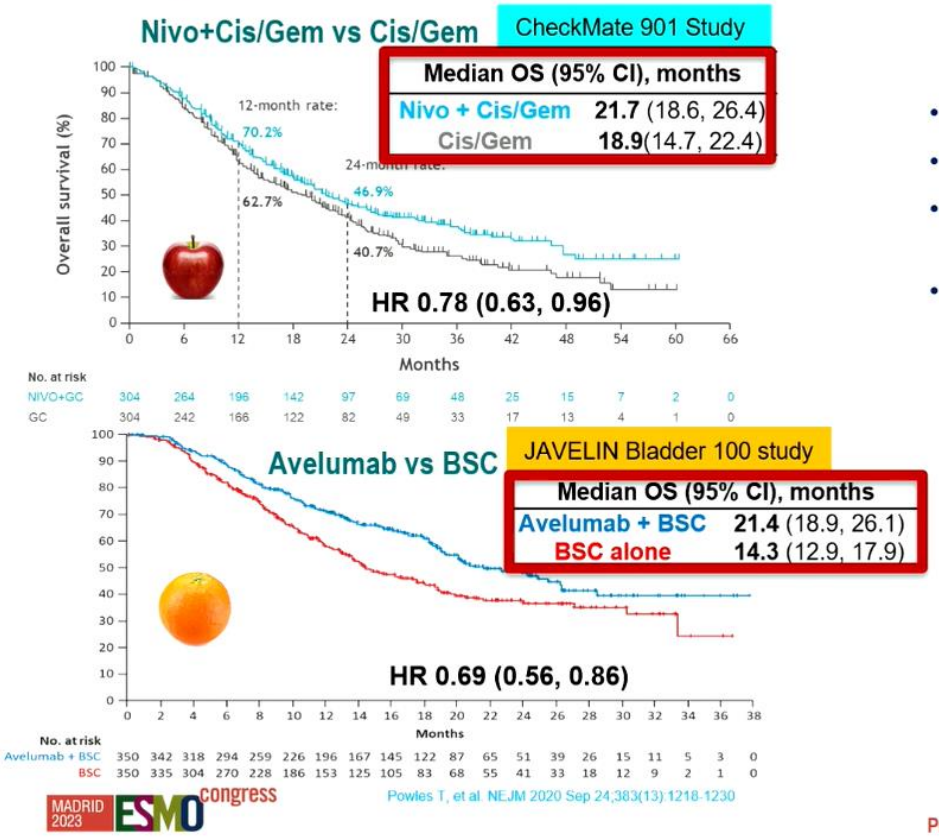
| | NIVO+GC (n = 304) | | GC (n = 288) | |
|---|---|---|---|---|
| Treatment-related AE, %[a] | Any grade | Grade ≥ 3[b] | Any grade | Grade ≥ 3[b] |
| Any | 97 | 62 | 93 | 52 |
| Leading to discontinuation | 21 | 11 | 17 | 8 |




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

# Evre IV mesane birinci basamak tedavi seçeneği

## Both sequential and combination chemo and CPI have efficacy




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

**Andrea Apolo**
Invited Discussant LBA6 and LBA7

Presented by Andrea B. Apolo, MD

# Gelecek Perspektif

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

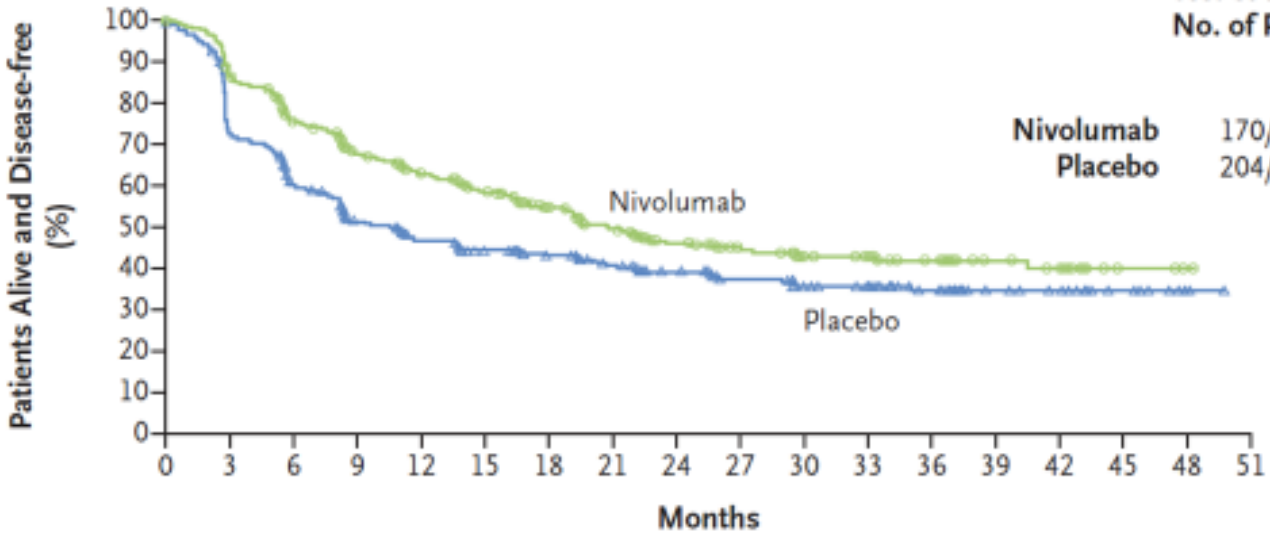
D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette,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

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

RTP RESEARCH TO PRACTICE

# Gelecek Perspektif

## CheckMate 274: Disease-Free Survival in the ITT Population




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

Hazard ratio for disease recurrence or death, 0.70 (98.22% CI, 0.55–0.90)
P<0.001

Bajorin DF et al. *N Engl J Med* 2021;384:2102-14.

RTP RESEARCH TO PRACTICE

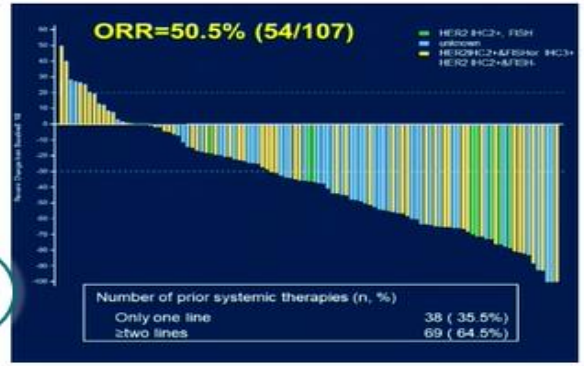
# Gelecek Perspektif

## Does CPI combine best with ADCs with MMAE payloads?

### Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

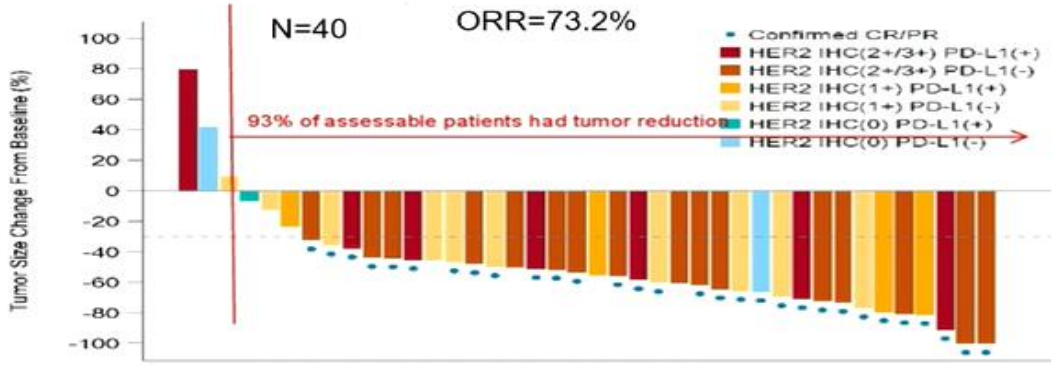
**Disitamab vedotin**

N=107 In the Second or Third-line setting



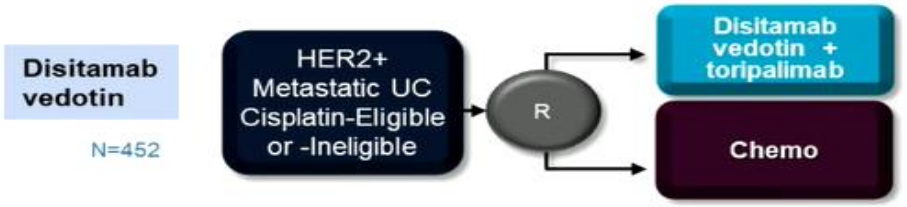

Sheng, et al. ASCO 2022 abstract 4518

**Disitamab vedotin + toripalimab**




Sheng, X., et al. ASCO 2023

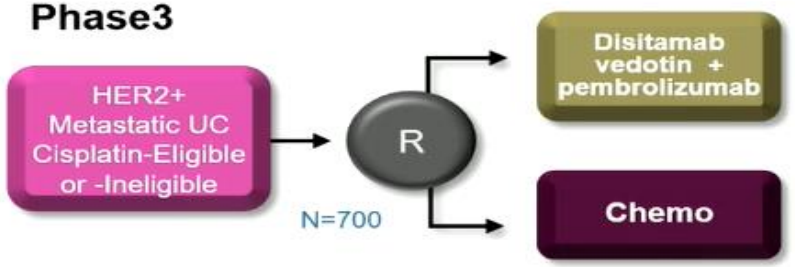
**Phase 3**



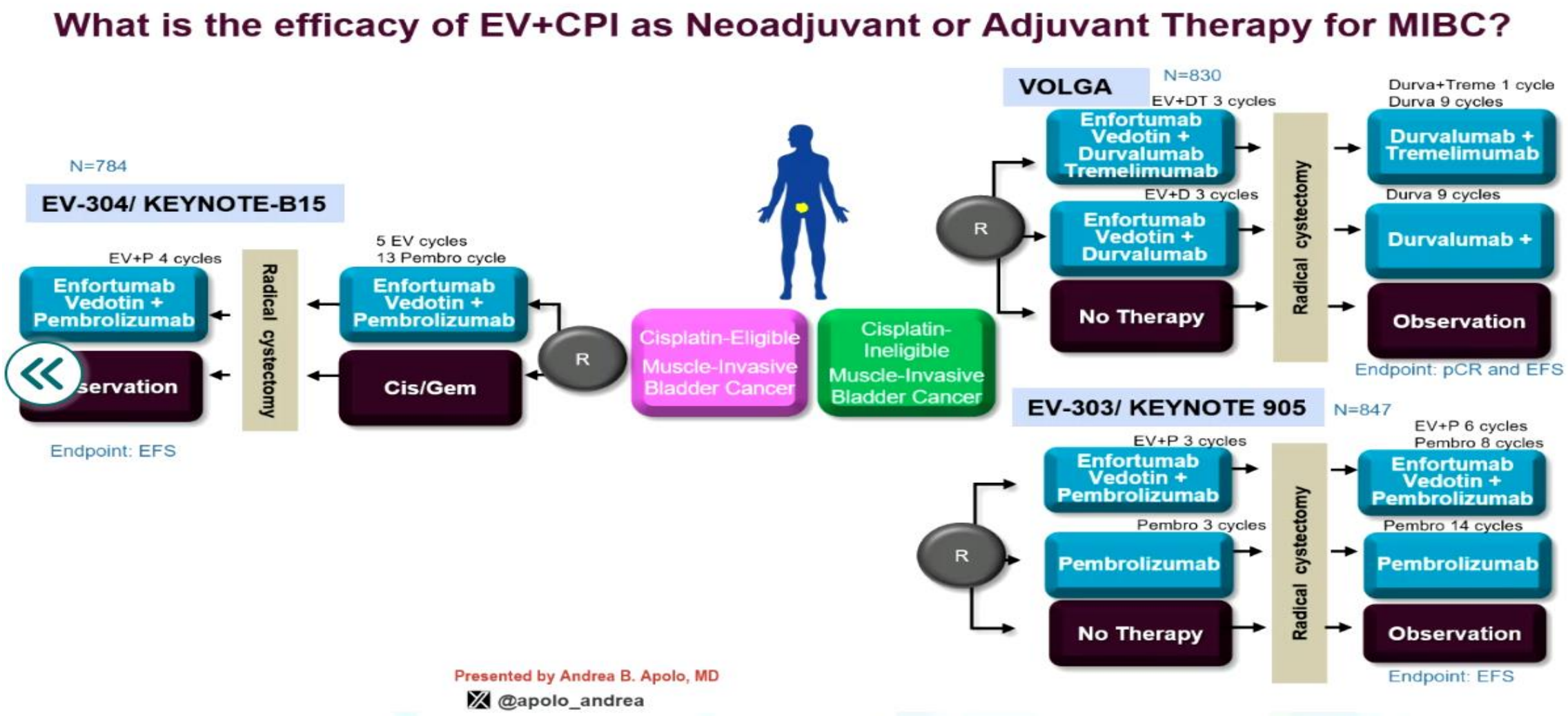

Presented by Andrea B. Apolo, MD

@apolo_andrea

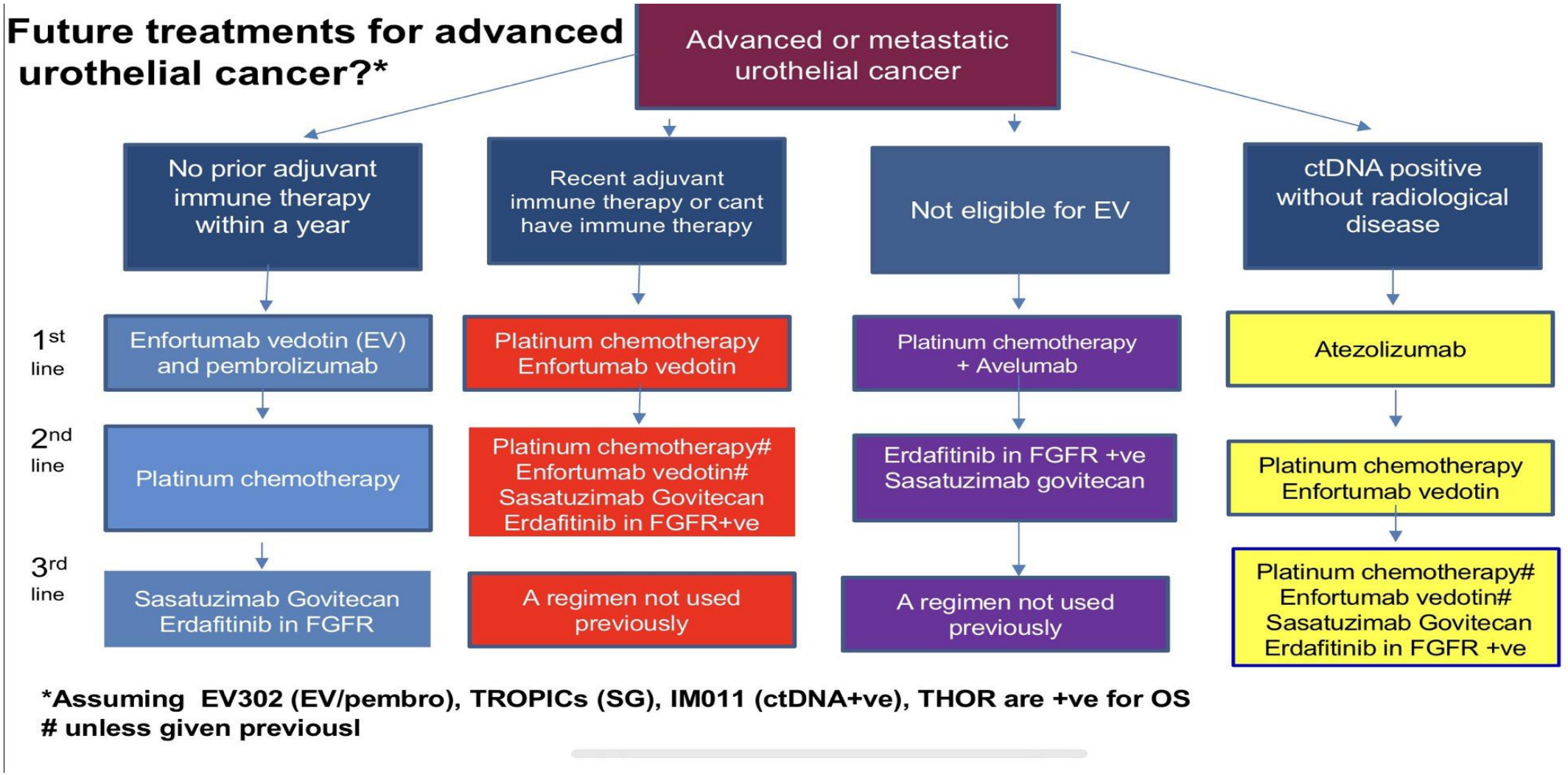
**Phase3**



# Gelecek Perspektif



# Gelecek Perspektif




***Assuming EV302 (EV/pembro), TROPICs (SG), IM011 (ctDNA+ve), THOR are +ve for OS**
**# unless given previousl**

# Sonuç

- Enfortumab vedotin +pembrolizumab standart tedavi
- Evre IV mesane kanserinde birinci basamak tedavide  sisplatin+gemsitabin+nivolumab  bir seçenek
- Platin bazlı kemoterapi sonrası klinik yarar(CR/PR/SD) gören hastalarda idame tedavi olarak Avelumab bir seçenek
- Sisplatin alamayacak hastalarda carboplatin+ gemsitabin kemoterapi kombinasyonu klinik yarar alanlarda Avelumab

  idame tedavi olarak bir seçenek
- Platin bazlı kemoterapi alamayacak hastalarda birinci basamak tedavide ( ECOG PS≥2, komorbidite vs.)  PD-L1 düzeyinden bağımsız Pemrolizumab önerilebilir