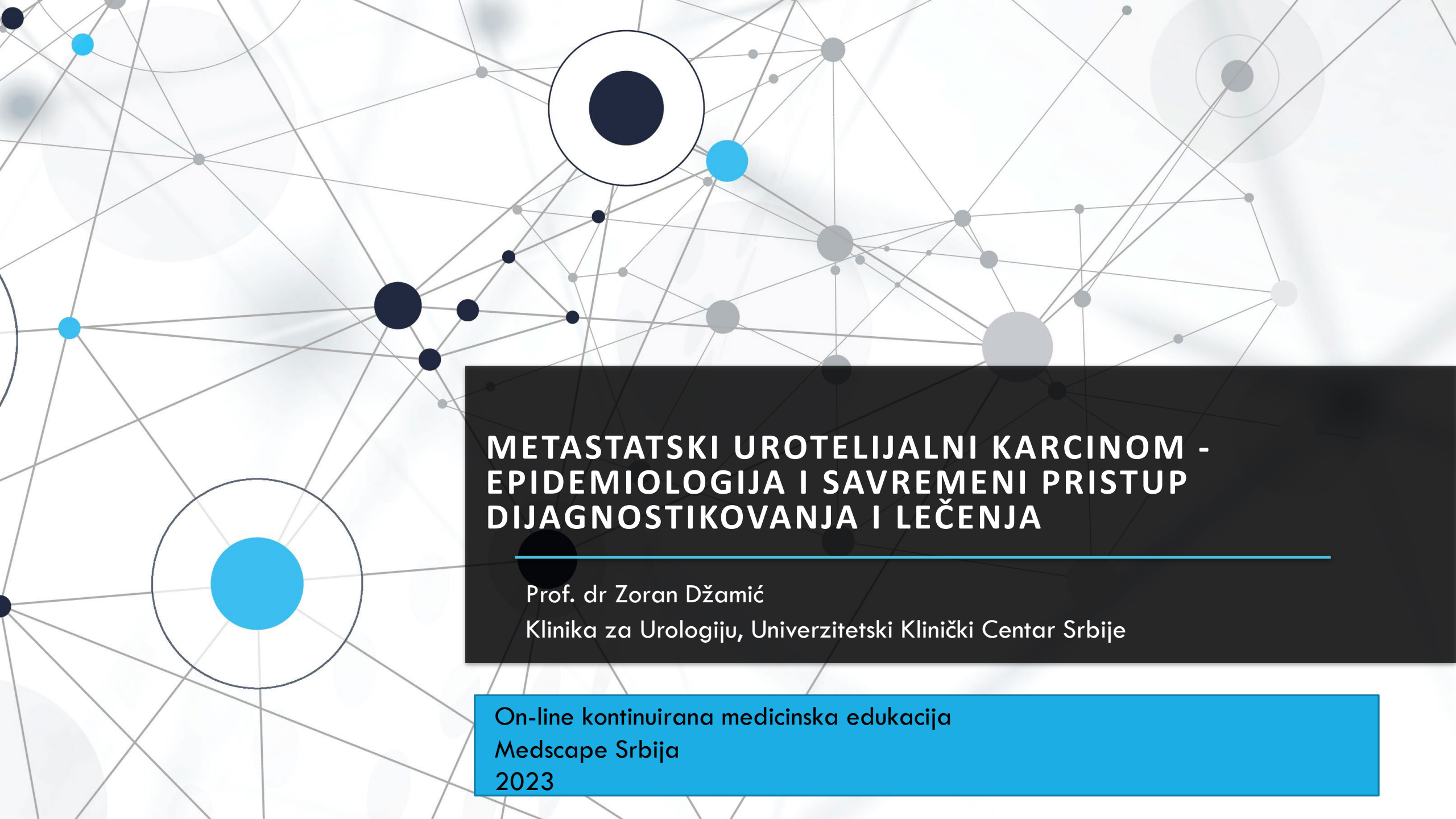




# **METASTATSKI UROTELIJALNI KARCINOM - EPIDEMIOLOGIJA I SAVREMENI PRISTUP DIJAGNOSTIKOVANJA I LEČENJA**

Prof. dr Zoran Džamić

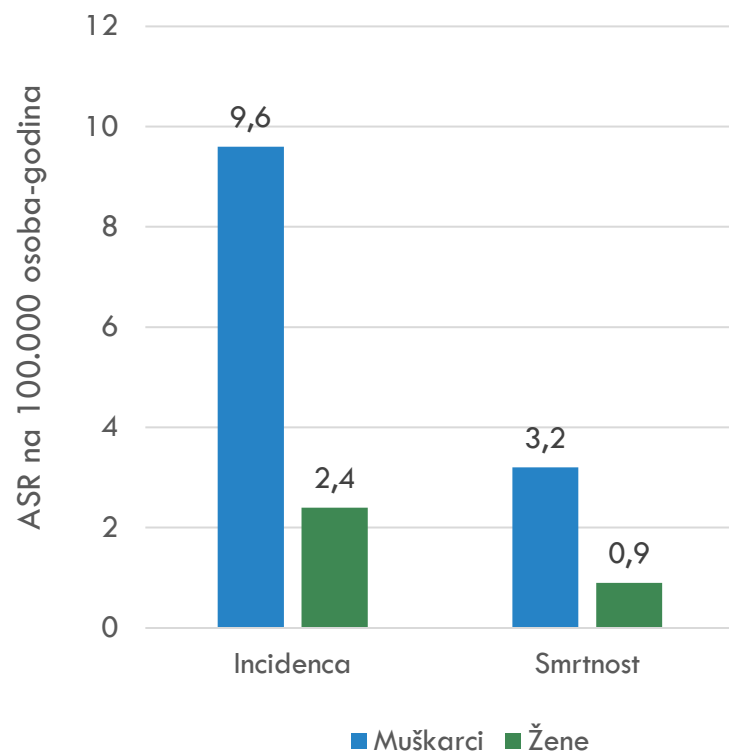
Klinika za Urologiju, Univerzitetski Klinički Centar Srbije

On-line kontinuirana medicinska edukacija  
Medscape Srbija  
2023

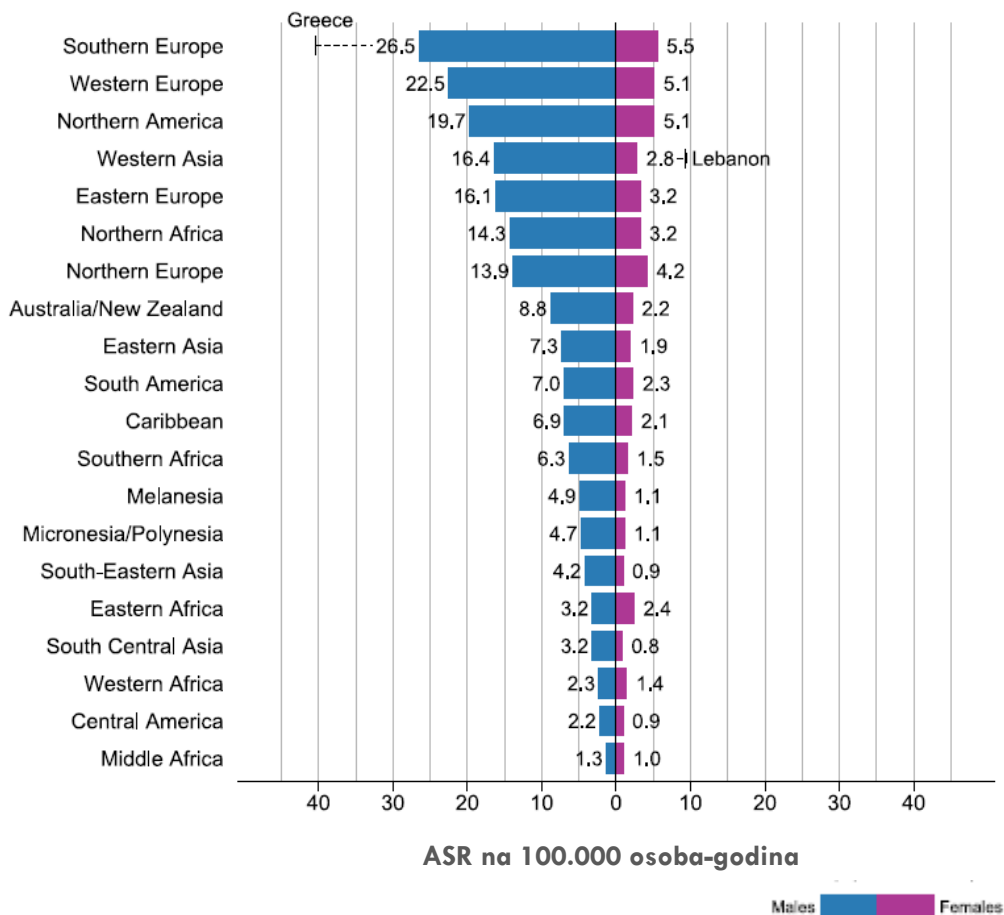
# KAKVA JE EPIDEMIOLOGIJA KARCINOMA MOKRAĆNE BEŠIKE?

Karcinom mokraćne beške je 10. najčešći oblik karcinoma u svetu

Svetska incidenca karcinoma mokraćne beške i povezani mortalitet (2018)



Incidenca karcinoma mokraćne beške u regionu (2018)



# INCIDENCA, MORTALITET I PREVALENCA NAJČEŠĆIH KARCINOMA U SRBIJI

Serbia

Source: Globocan

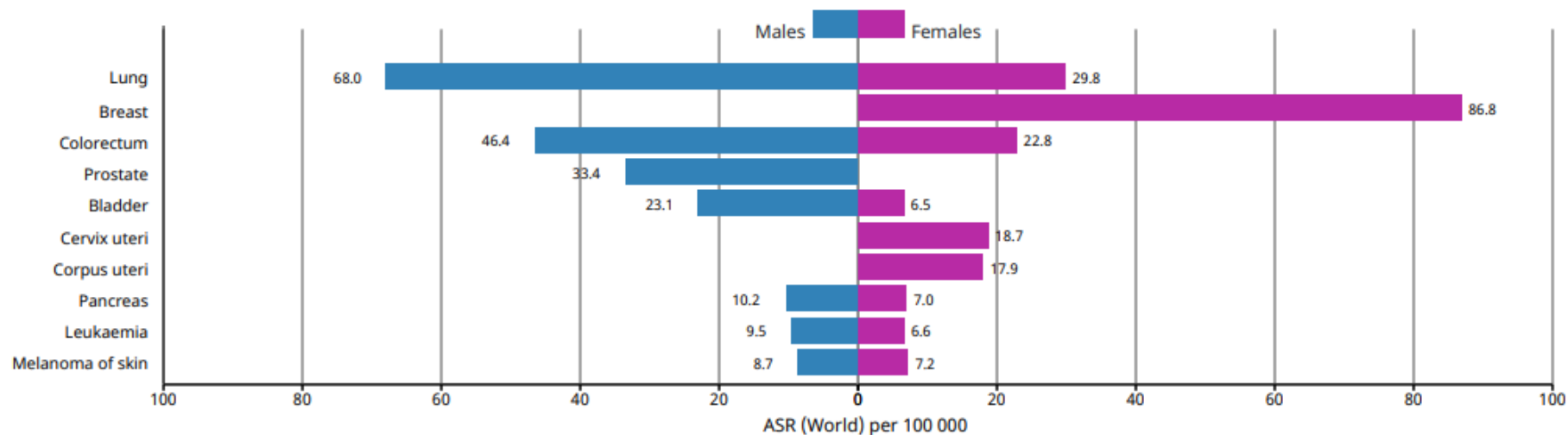


## Incidence, Mortality and Prevalence by cancer site

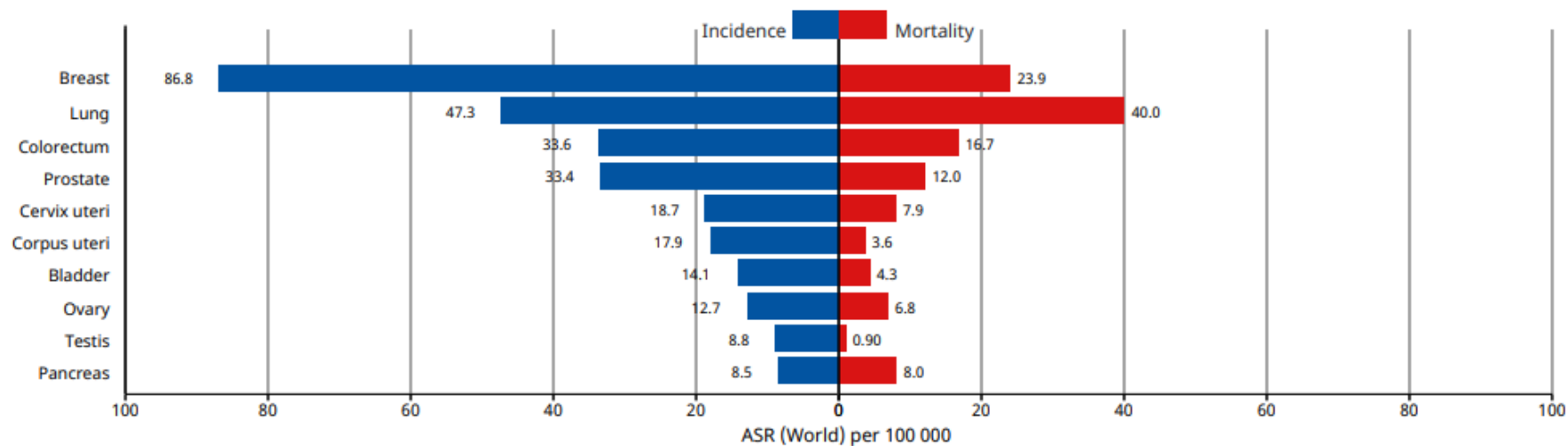
| Cancer       | New cases |      |      |          | Deaths |      |      |          | 5-year prevalence (all ages) |                     |
|--------------|-----------|------|------|----------|--------|------|------|----------|------------------------------|---------------------|
|              | Number    | Rank | (%)  | Cum.risk | Number | Rank | (%)  | Cum.risk | Number                       | Prop. (per 100 000) |
| Lung         | 8 048     | 1    | 16.4 | 6.02     | 7 084  | 1    | 25.2 | 5.24     | 9 281                        | 106.22              |
| Breast       | 6 724     | 2    | 13.7 | 9.26     | 2 342  | 2    | 8.3  | 2.70     | 24 487                       | 549.32              |
| Prostate     | 3 144     | 3    | 6.4  | 4.34     | 1 251  | 6    | 4.5  | 1.14     | 11 600                       | 271.05              |
| Rectum       | 2 956     | 4    | 6.0  | 2.09     | 1 493  | 5    | 5.3  | 0.89     | 8 407                        | 96.22               |
| Colon        | 2 947     | 5    | 6.0  | 1.99     | 1 819  | 3    | 6.5  | 1.06     | 7 595                        | 86.93               |
| Bladder      | 2 549     | 6    | 5.2  | 1.76     | 931    | 9    | 3.3  | 0.47     | 7 387                        | 84.54               |
| Pancreas     | 1 589     | 7    | 3.2  | 1.01     | 1 561  | 4    | 5.6  | 0.98     | 1 217                        | 13.93               |
| Corpus uteri | 1 539     | 8    | 3.1  | 2.24     | 383    | 19   | 1.4  | 0.44     | 5 276                        | 118.36              |
| Stomach      | 1 278     | 9    | 2.6  | 0.81     | 1 076  | 7    | 3.8  | 0.65     | 1 894                        | 21.68               |
| Cervix uteri | 1 205     | 10   | 2.5  | 1.86     | 634    | 12   | 2.3  | 0.88     | 3 393                        | 76.12               |
| Kidney       | 1 155     | 11   | 2.4  | 0.87     | 557    | 14   | 2.0  | 0.37     | 3 107                        | 35.56               |

# INCIDENCA I MORTALITET U SRBIJI

Age-standardized (World) incidence rates per sex, top 10 cancers



Age-standardized (World) incidence and mortality rates, top 10 cancers



## ODREĐIVANJE STADIJUMA KARCINOMA MOKRAĆNE BEŠIKE.

X

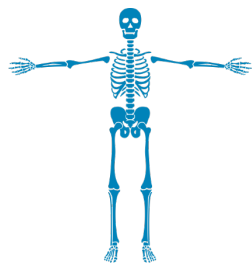
| Stadijum | T                | N           | M   |
|----------|------------------|-------------|-----|
| 0a       | Ta               | N0          | M0  |
| 0is      | Tis              | N0          | M0  |
| /        | T1               | N0          | M0  |
| II       | T2a              | N0          | M0  |
|          | T2b              | N0          | M0  |
| IIIa     | T3a, T3b ili T4a | N0          | M0  |
|          | T1–4a            | N1          | M0  |
| IIIb     | T1–4a            | N2–N3       | M0  |
| IVa      | T4b              | Bilo koji N | M0  |
|          | Bilo koji T      | Bilo koji N | M1a |
| IVb      | Bilo koji T      | Bilo koji N | M1b |

is, *in situ*; M, udaljena metastaza; N, regionalni limfni čvorovi; T, primarni tumor

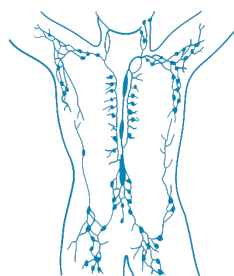
Američko udruženje za borbu protiv raka (eng. *American Cancer Society*). Stadijumi karcinoma mokraćne bešike. Dostupno na: [www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-staging](https://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-staging) (accessed june 2022).

## UOBIČAJENE METASTAZE OBUHVATAJU VISCERALNA (MEKA TKIVA) I NEVISCERALNA MESTA

### Najčešća mesta metastaza<sup>1</sup>



Kost



Udaljeni limfni čvorovi



Pluća

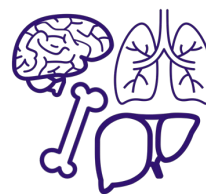


Jetra

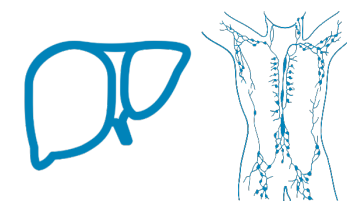
### Efekat stanja metastaza i mesta na ishode preživljavanja\*<sup>2</sup>



Pacijenti **bez metastaza** imaju znatno bolje ishode preživljavanja u odnosu na pacijente sa metastazama



Pacijenti bez metastaza na **kostima, mozgu, jetri i plućima** su nezavisni prognostičarski faktori ishoda



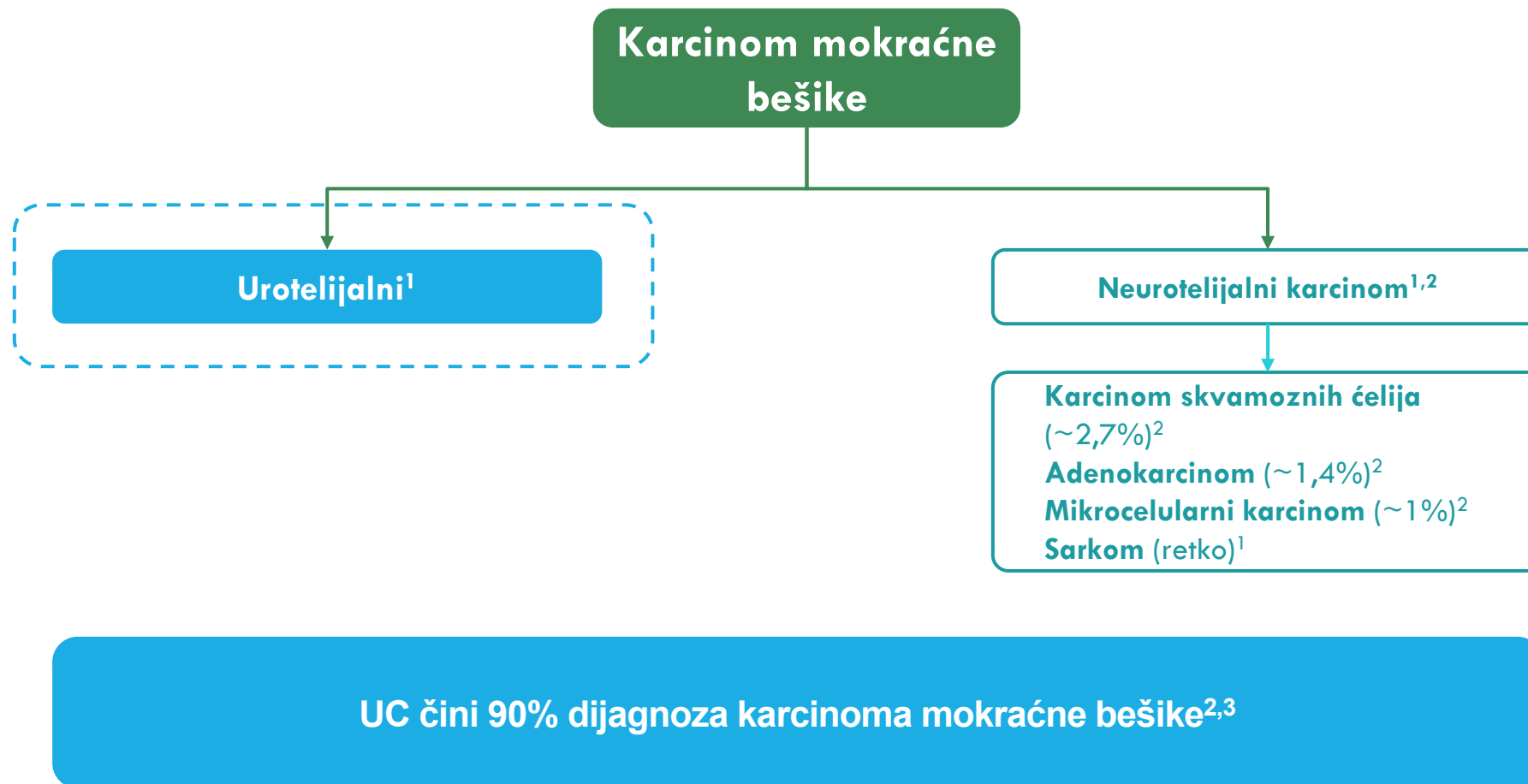
Pacijenti sa **udaljenim metastazama koje se javljaju samo na limfnim čvorovima i jetri** imaju najnepovoljnije ishode preživljavanja<sup>†</sup>

\*OS i CSS; <sup>†</sup>Testirana mesta van mesta metastaza: mozak, jetra, pluća, limfni čvorovi, kosti.

CSS, specifično preživljavanje u odnosu na karcinom (eng. *cancer-specific survival*); OS, ukupno preživljavanje (eng. *overall survival*).

1. Američko udruženje za borbu protiv raka (eng. *American Cancer Society*). What is bladder cancer? Dostupno na: <https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html> (accessed june 2022); 2. Dong et al. Cancer Manag Res 2017;9:611–26. Ikonice iz projekta „Noun“.

# HISTOLOGIJA KARCINOMA MOKRAĆNE BEŠIKE



UC, urotelijalni karcinom (eng. *urothelial cancer*).

1. Američko udruženje za borbu protiv raka (eng. *American Cancer Society*). What is bladder cancer? Dostupno na: <https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html> (accessed june 2022); 2. Chalasani V et al. Can Urol Assoc J 2009;3(6 Suppl. 4):S193–8; 3. Pasin E et al. Rev Urol 2008;10:31–43.

# ŠTA JE UROTELIJALNI KARCINOM?

UC potiče iz urotelijalnih ćelija i takođe se naziva i tranziciocelularni karcinom; odnosi se na grupu karcinoma mokraćne cevi, mokraćne bešike, mokraćovoda, bubrežne karlice i drugih organa<sup>1</sup>

**5–10%**

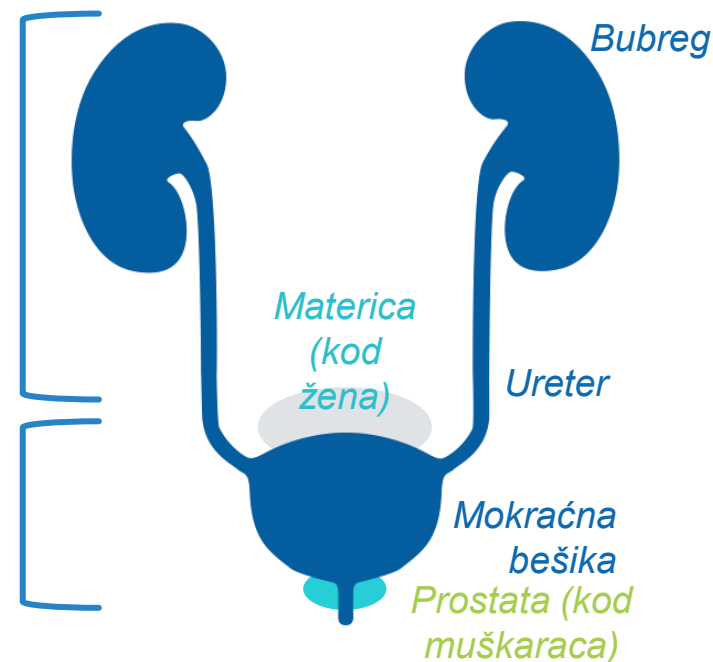
UC nastaje u gornjem traktu  
(bubrežna karlica, mokraćovod)<sup>2,3</sup>

**90–95%**

UC nastaje u donjem traktu  
(bubrežna karlica, mokraćovod)<sup>3</sup>

**UTUC**  
Karcinom  
gornjeg  
urotelijuma

**UCB**  
Urotelijalni  
karcinom  
mokraćne  
bešike



**Sve veći broj dokaza ukazuje na to da su UTUC i UCB različite bolesti koje zahtevaju različite terapijske strategije<sup>3</sup>**

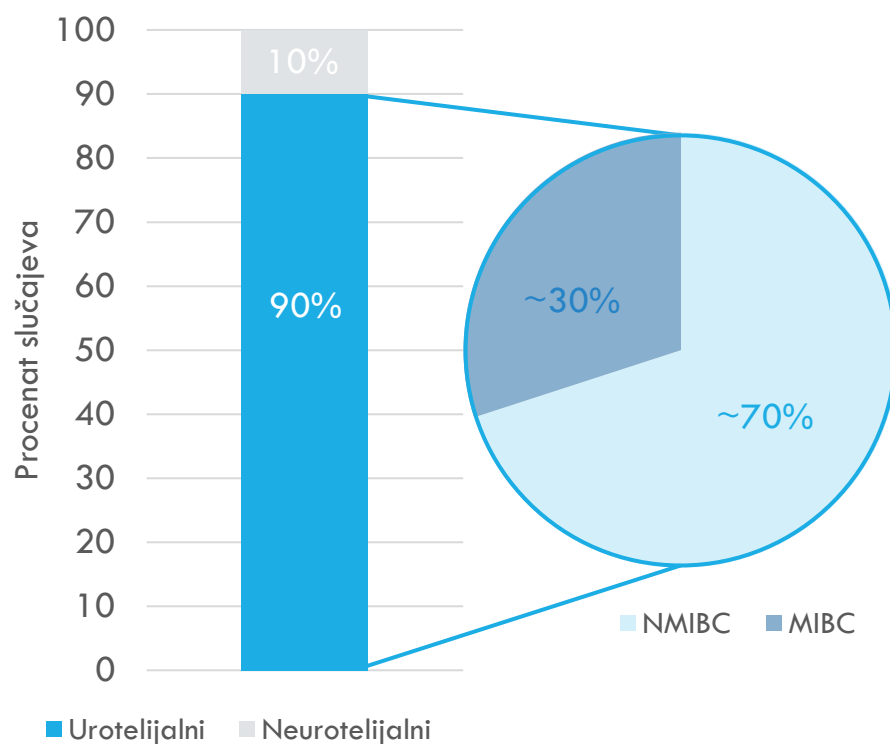
UC, urotelijalni karcinom (eng. *urothelial cancer*); UCB, urotelijalni karcinom mokraćne bešike (eng. *urothelial carcinoma of the urinary bladder*); UTUC, karcinom gornjeg urotelijuma (eng. *upper tract urothelial cancer*).

1. Američko udruženje za borbu protiv raka (eng. *American Cancer Society*). What is bladder cancer? Dostupno na: <https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html> (accessed june 2022); 2. Soria F et al. *World J Urol* 2017;35:379–87; 3. Leow JJ et al. *ESMO Open* 2017;1:e000126. Ikonice iz projekta „Noun“.

# KAKO SE KLASIFIKUJE KARCINOM MOKRAĆNE BEŠIKE?

Karcinom mokraćne bešike se klasifikuje ćelijskom karakterizacijom (UC/nonUC) primarnog tumora i invazijom na mišić zida mokraćne bešike

Oko 90% karcinoma mokraćne bešike su urotelijalni,<sup>1,2</sup> od kojih su oko 70% mišićno-neinvazivni<sup>1,3</sup>



## Mišićno-neinvazivni karcinom mokraćne bešike (NMIBC)

- Stadijum 0–I<sup>4</sup>
- Nema dokaza zahvatanju dubokih slojeva zida mokraćne bešike prilikom postavljanja dijagnoze<sup>5,6</sup>
- Kod većine pacijenata sa karcinomom mokraćne bešike neće se javljati invazija mišića<sup>6</sup>

## Mišićno-invazivni karcinom mokraćne bešike (MIBC)

- Stadijum II–IV<sup>4</sup>
- Tumor je zahvatio duboke slojeve zida mokraćne bešike prilikom postavljanja dijagnoze<sup>5</sup>

MIBC, mišićno-invazivni karcinom mokraćne bešike (eng. *muscle-invasive bladder cancer*); NMIBC, mišićno-neinvazivni karcinom mokraćne bešike (eng. *non-muscle-invasive bladder cancer*).

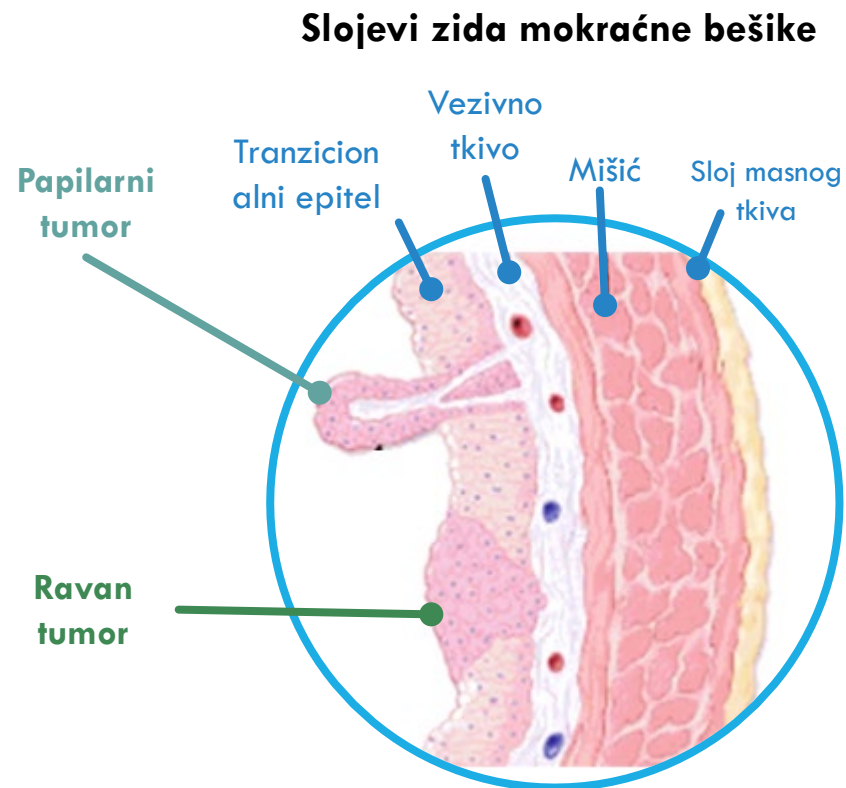
1. Gandhi NM, et al. In: Lerner SP et al. *Bladder Cancer: Diagnosis and Clinical Management*. Wiley-Blackwell. Oktobar 2015;  
2. Chalasani V et al. *Can Urol Assoc J* 2009;3(6 Suppl. 4):S193–8; 3. Cumberbatch MGK, Noon AP. *Transl Androl Urol*. 2019;8:5–11;  
4. NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. V2. 2021; 5. Američko udruženje za borbu protiv raka (eng. *American Cancer Society*). What is bladder cancer? Dostupno na: <https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html> (accessed june 2022); 6. Pasin E et al. *Rev Urol* 2008;10:31–43.

# KAKO NASTAJE NMIBC?

NMIBC se može klasifikovati prema načinu rasta

- Izrasline u obliku prsta koje se pružaju sa unutrašnje površine mokraćne bešike ka šupljem centru<sup>1</sup>
- Papilarni tumori mogu biti sporog rasta i neinvazivni<sup>1</sup>
  - Ovi tumori imaju tendenciju ka pozitivnom ishodu

- Pljosnate izrasline (CIS) nastaju unutar tranzicionalnog epitela<sup>1</sup>
  - Oni imaju tendenciju ka visokom gradusu i nose visoki rizik od ponovne pojave i metastaze<sup>2</sup>



Prilagođeno od: Američko udruženje za borbu protiv raka<sup>1</sup>

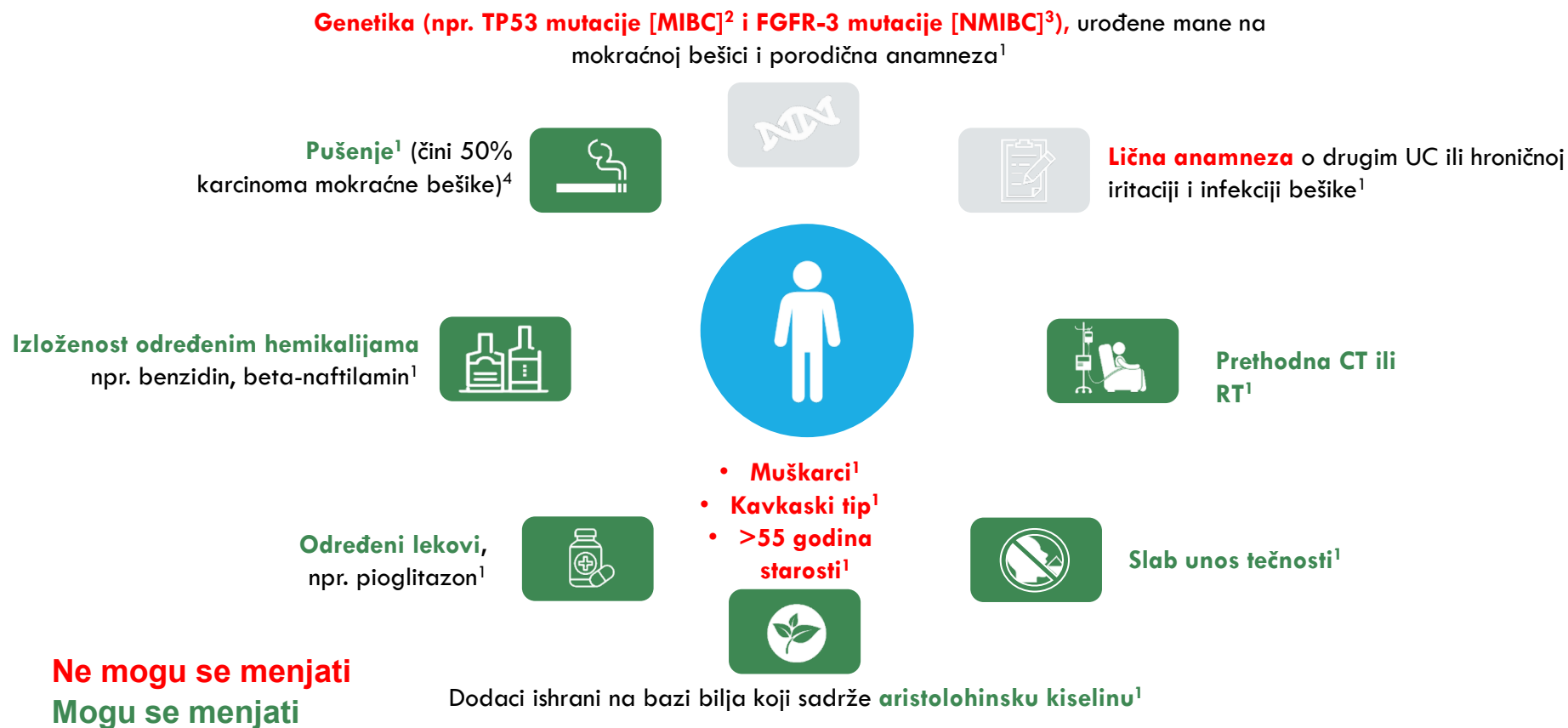
**Tumori mogu postati invazivni ako prođu van tranzicionalnog epitela<sup>1</sup>**

CIS, karcinom *in situ* (eng. *carcinoma in situ*); NMIBC, mišićno-neinvazivni karcinom mokraćne bešike (eng. *non-muscle-invasive bladder cancer*).

1. Američko udruženje za borbu protiv raka (eng. *American Cancer Society*). What is bladder cancer? Dostupno na: <https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html> (accessed june 2022); 2. Tang DH, Chang SS. *Ther Adv Urol* 2015;7:351–64.

# KOJI FAKTORI RIZIKA SU U VEZI SA KARCINOMOM MOKRAĆNE BEŠIKE?

**Pušenje je najvažniji faktor rizika;  
karcinom mokraćne beške je >3x češći kod pušača<sup>1</sup>**



CT, hemioterapija (eng. chemotherapy); MIBC, mišićno-invazivni karcinom mokraćne beške (eng. muscle-invasive bladder cancer); NMIBC, mišićno-neinvazivni karcinom mokraćne beške (eng. non-muscle-invasive bladder cancer); RT, radijaciona terapija (eng. radiation therapy);

TCGA, The Cancer Genome Atlas; UC, urotelijalni karcinom (eng. urothelial cancer). 1. American Cancer Society. Bladder cancer risk factors. Dostupno na: <https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html> (accessed june 2022); 2. Fujimoto K et al. Cancer Res 1992;52:1393–8; 3. Hernandez S et al. J Clin Oncol 2006;24:3664–71; 4. Cumberbatch MGK et al. Transl Androl Urol 2019;8:5–11. Ikone iz projekta „Noun“.

# KAKO SE DIJAGNOSTIKUJE KARCINOM MOKRAĆNE BEŠIKE?

Nekoliko znakova i simptoma mogu ukazati na karcinom mokraćne beške, a dijagnoza se potvrđuje kombinacijom biopsije i snimanja

## Znaci i simptomi

- Mikroskopska ili makroskopska hematurija<sup>1</sup> (sa ili bez drugih simptoma)<sup>2</sup>
- Povećana učestalost mokrenja (usled iritacije ili smanjenog kapaciteta mokraćne beške)<sup>1</sup>
- Infekcija urinarnog trakta<sup>1</sup>
- Opstrukcija ili bol u urinarnom traktu (uznapredovale lezije)<sup>1</sup>

## Potvrdni testovi<sup>1</sup>

1 Citoskopija

2 Transuretralna resekcija tumora mokraćne beške (TURBT) (da bi se potvrdila zahvaćenost bolešću)

3 Biopsija mišića (ako se sumnja na MIBC)

4 Kompjuterizovana tomografija urografija\* (preporučena metoda snimanja)

5 Snimanja kostiju i snimanje grudi

\*Pacijenti koji su u prošlosti imali reakcije na kontrastno sredstvo, pacijenti sa astmom, problemima sa bubrežima, dijabetesom ili pacijenti koji primaju metformin su pod većim rizikom od primene kontrasta u odnosu na druge pacijente.<sup>3</sup>

MIBC, mišićno-invazivni karcinom mokraćne beške (eng. *muscle-invasive bladder cancer*); TURBT, transuretralna resekcija tumora mokraćne beške (eng. *transurethral resection of bladder tumor*).

1. NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. V2. 2021; 2. Cha EK et al. World J Urol 2012;30:847–52; 3. Royal College of Radiologists. Standards for intravascular contrast administration to adult patients. Dostupno na: [https://www.rcr.ac.uk/sites/default/files/Intravasc\\_contrast\\_web.pdf](https://www.rcr.ac.uk/sites/default/files/Intravasc_contrast_web.pdf) (accessed june 2022).

# KAKO SE LEČI KARCINOM MOKRAĆNE BEŠIKE?

Odluke o terapiji zavise od klasifikaciji i stadijumu bolesti

## Lokalizovana bolest:

Ćelije tumora su potvrđene na primarnom mestu tumora



Lečenje vodi UROLOG

## Lokalno uznapredovala ili metastatska bolest:

Ćelije tumora proširile su se na okolno tkivo ili limfne čvorove (lokalno uznapredovala bolest) ili na udaljena mesta (metastatska bolest) u odnosu na mesto tumora



Lečenje vodi ONKOLOG

U donošenju odluka o terapiji može učestvovati multidisciplinarni tim urologa, radiologa onkologa i medicinskih onkologa

# FAKTORI KOJI UTIČU NA ODLUKU O TERAPIJI KOD PRVE LINIJE METASTATSKOG UC

**Kriterijumi po Galskom i Bajorin faktori rizika pomažu u vođenju terapije prve linije i prognozi kod metastatskog UC**

## Kriterijumi po Galskom za određivanje prikladnosti za terapiju cisplatinom<sup>1</sup>

**Pacijenti koji ispune najmanje jedan od sledećih kriterijuma smatraju se nepogodnim za hemioterapiju cisplatinom:**

- ECOG PS  $\geq 2$
- Klirens kreatinina  $< 60$  mL/min
- Gradus  $\geq 2$  gubitak sluha
- Gradus  $\geq 2$  neuropatija
- NYHA razred III srčane insuficijencije

## Bajorin faktori rizika za preživljavanje<sup>2</sup>

**Pacijenti su klasifikovani sa nula, jedan ili dva od sledećih faktora rizika:**

- Visceralne metastaze (kost, pluća, jetra)
- Karnofsky PS  $< 80\%$  (ECOG PS  $> 2$ )

**Broj faktora rizika prikazuje prognostički značaj za preživljavanje:**

| Broj faktora rizika | Medijana preživljavanja |
|---------------------|-------------------------|
| 0                   | 33 meseca               |
| 1                   | 13,4 meseca             |
| 2                   | 9,3 meseca              |

ECOG, Evropska kooperativna onkološka grupa (eng. *European Cooperative Oncology Group*); NYHA, Njujorško kardiološko udruženje (eng. *New York Heart Association*); PS, funkcionalni status (eng. *performance status*); UC, uroterijalni karcinom (eng. *urothelial cancer*).

1. Galsky MD et al. J Clin Oncol 2011;29:2432–8; 2. Bajorin DF et al. J Clin Oncol 1999;17:3173–81.

# TERAPIJA LOKALIZOVANE BOLESTI

Lokalizovana bolest se leči operacijom i intravezikalnom terapijom, u zavisnosti od stepena bolesti<sup>1-3</sup>

| NMIBC                          |                                                                                  |
|--------------------------------|----------------------------------------------------------------------------------|
| Lečenje                        | Primena                                                                          |
| <b>TURBT</b>                   | Standardna terapija za Ta (visoki gradus), T1 i Tis <sup>1,2</sup>               |
| <b>Intravezikalna terapija</b> | Neposredna i visokorizična bolest (BCG ili CT) <sup>1,2</sup>                    |
| <b>Cistektomija</b>            | Visokorizična bolest <sup>1</sup>                                                |
| <b>Održavanje BCG</b>          | Praćenje pacijenata koji su prethodno primili BCG (bilo koji rizik) <sup>1</sup> |

| MIBC                                                                 |                                                                                                                                 |
|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Lečenje                                                              | Primena                                                                                                                         |
| <b>Radikalna ili parcijalna cistektomija ± CT na bazi cisplatina</b> | Preporučuje se za kandidate za cistektomiju <sup>1</sup>                                                                        |
| <b>Istovremena hemioterapija</b>                                     | Preporučuje se za kandidate za cistektomiju radi očuvanja mokraćne bešike* ili kandidate koji nisu za cistektomiju <sup>1</sup> |
| <b>Radijaciona terapija</b>                                          | Alternativa za istovremenu hemioterapiju kod kandidata koji nisu za cistektomiju <sup>1</sup>                                   |
| <b>TURBT</b>                                                         | Alternativa za istovremenu hemioterapiju kod kandidata koji nisu za cistektomiju <sup>1,3</sup>                                 |

Lokalizovana bolest se leči operacijom i intravezikalnom terapijom, uključujući i hemioterapiju i BCG sa NCCN kategorijom dokaza br. 1, u zavisnosti od stadijuma tumora<sup>1-3</sup>

\*Optimalni kandidati za očuvanje mokraćne bešike sa hemioterapijom uključuju pacijente sa tumorima bez umerene/teške hidronefroze, bez istovremenih ekstenzivnih ili multifokalnih Tis i koji su <6 cm. U idealnom slučaju, tumori bi trebalo da omoguće kompletan ili maksimalan debulking TURBT-a.

BCG, Bacillus Calmette–Guérin; CT, hemioterapija (eng. chemotherapy); MIBC, mišićno-invazivni karcinom mokraćne bešike (eng. muscle-invasive bladder cancer); NCCN, Nacionalna sveobuhvatna mreža za borbu protiv raka (eng. National Comprehensive Cancer Network);

NMIBC, mišićno-neinvazivni karcinom mokraćne bešike (eng. non-muscle-invasive bladder cancer); T1, tumor je zahvatio sloj vezivnog tkiva; Ta, neinvazivni karcinom; Tis, ravan tumor *in situ*;

TURBT, Transuretralna resekcija tumora mokraćne bešike (eng. transurethral resection of bladder tumor). 1. NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. V1. 2022; 2. Babjuk M, et al. EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (TaT1 i CIS). 2021; 3. Witjes JA, et al. EAU Guidelines on Non-Muscle-Invasive Bladder Cancer. 2021.

## LOKALIZOVANA BOLEST: PROGRESIJA

Progresija bolesti je uobičajena

### NMIBC<sup>1</sup>

- Rizik zavisi od skorova progresije izračunatih na osnovu šest pondera:
  - Prethodna rekurenca (broj po godini)
  - Broj tumora (jedan, 2–7, ≥8)
  - Veličina tumora (<3 cm, ≥3 cm)
  - Kategorija T (Ta, T1)
  - Gradus (G1-3)
  - CIS (da, ne)
- Rizik od progresije u rasponu od 5 godina od **<1%** za najniže skorove progresije do **45%** za najviše

### MIBC<sup>2</sup>

- **Polovina svih pacijenata** ima relaps nakon radikalne cistektomije, u zavisnosti od:
  - Patološkog stadijuma primarnog tumora
  - Nodalnog statusa
- Lokalna rekurenca čini **30% relapsa**, dok su udaljene metastaze češće

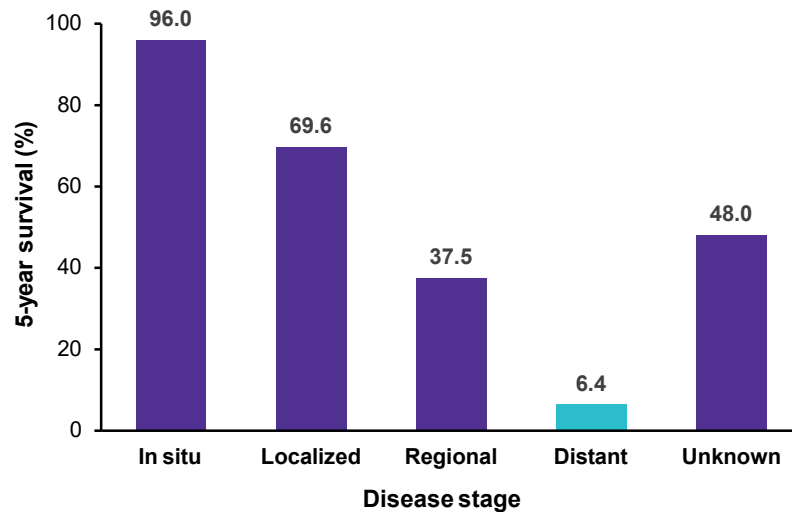
CIS, karcinom *in situ* (eng. *carcinoma in situ*), MIBC, mišićno-invazivni karcinom mokraćne bešike (eng. *muscle-invasive bladder cancer*); NMIBC, mišićno-neinvazivni karcinom mokraćne bešike (eng. *non-muscle-invasive bladder cancer*); Ta, neinvazivni karcinom (eng. *non-invasive carcinoma*);

1. Sylvester RJ et al. Eur Urol 2006;49:466–77; 2. Witjes JA, et al. EAU Guidelines on Non-Muscle-Invasive Bladder Cancer. 2021.

# PACIJENTI SA LOKALNO UZNAPREDOVALIM ILI METASTATSKIM KARCINOMOM MOKRAĆNE BEŠIKE

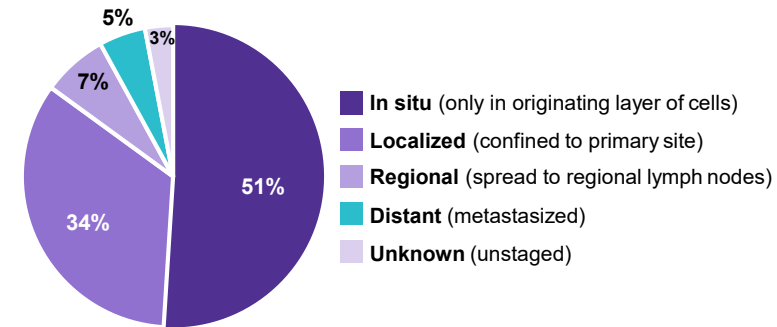
## IMAJU LOŠE ISHODE LEČENJA

5-godišnja stopa preživljavanja za IV stadijum karcinoma mokraćne bešike je <7%<sup>1</sup>



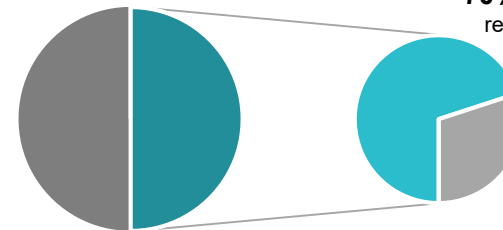
Stopa smrtnosti od karcinoma mokraćne bešike se nije promenila za >20 godina<sup>1</sup>

≈5% pacijenata ima metastatsku bolest prilikom postavljanja dijagnoze<sup>1</sup>



Metastaze nakon cistektomije su česte<sup>2</sup>

≈50% of patients have relapse after cystectomy



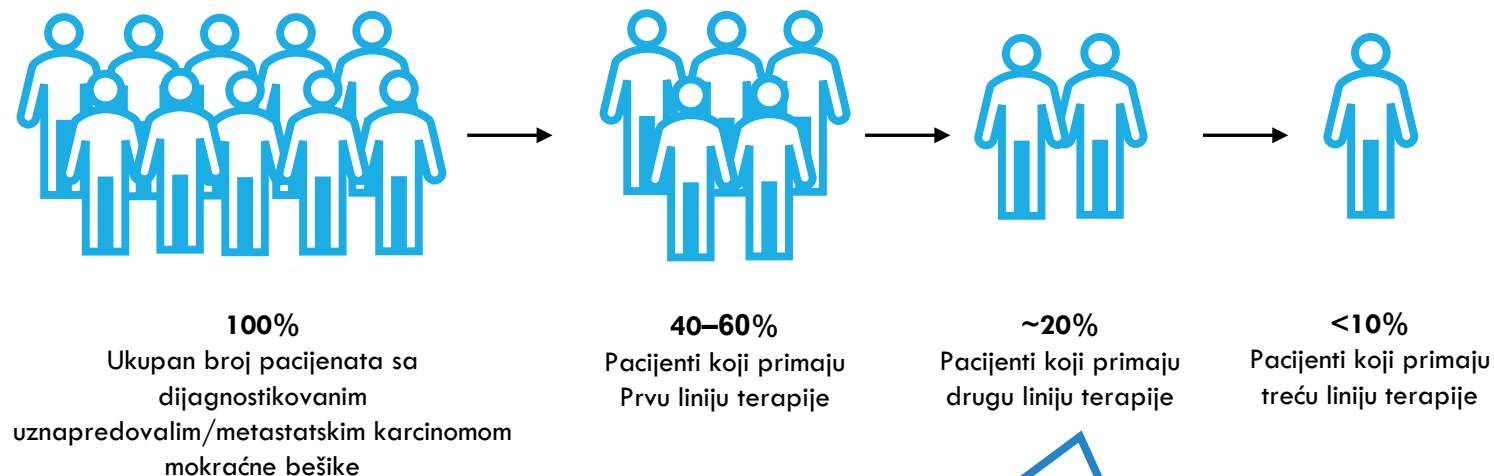
1L, first-line; OS, overall survival

1. SEER Cancer Stat Facts: Bladder Cancer. National Cancer Institute. Bethesda, MD, <https://seer.cancer.gov/statfacts/html/urinb.html>. Accessed March 2022, Reprinted from Swami U, et al. Cancer Treat Res Commun. 2021;27:100325. Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>); 2. NCCN Guidelines: Bladder Cancer, V4 2021. [https://www.nccn.org/professionals/physician\\_gls/PDF/bladder.pdf](https://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf). Accessed March 2022. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer, V4 2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 11, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

# POTREBA ZA OPTIMIZACIJOM PRVE LINIJE TERAPIJE

Broj pacijenata sa metastazama koji primaju prvu, drugu i treću liniju terapije u realnom životu je iznenađujuće nizak<sup>1-11</sup>

Pregled stvarnih baza podataka u SAD i van SAD\*

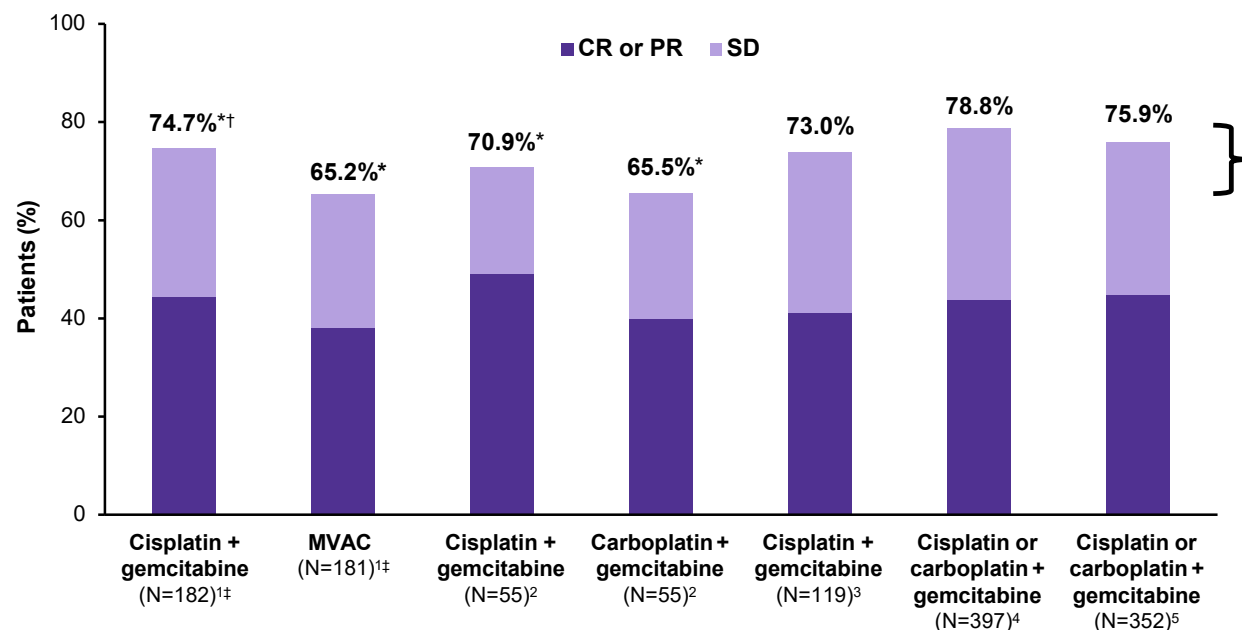


**25–50%** pacijenata koji primaju **prvu liniju hemioterapije** za uznapredovali UC **takođe je primilo drugu liniju terapije**<sup>\*1-11</sup>

\*Na osnovu nekoliko studija sprovedenih u realnom životu u više zemalja koje uključuju i SAD, UK, Holandiju, Dansku i Nemačku. UC, urotelijalni karcinom (eng. *urothelial carcinoma*).

1. Swami U, et al. Cancer Treat Res Commun 2021;27:100325; 2. Aly A, et al. J Med Econ 2019;22:662–70; 3. Galsky MD et al. Bladder cancer 2018;4:227–38; 4. Dinan MA, et al. J Geriatr Oncol 2021;12:298–304; 5. Fisher MD, et al. Clin Genitourin Cancer 2018;16:e1171–9; 6. Flannery K, et al. Future Oncol 2019;15:1323–34; 7. Jensen JB, et al. Ann Oncol. 2021;32:Abstract 707P (prezentacija); 8. Geynisman DM, et al. J Clin Oncol. 2021;39: Abstract 4538 (prezentacija); 9. Richters A, et al. Cancer Treat Res Commun 2020;25:100266; 10. Bilen M, et al. Ann Oncol. 2021;32:Abstract 701P (prezentacija); 11. Cheeseman S, et al. Front Oncol 2020;10:167.

# VEĆINA PACIJENATA SA UZNAPREDOVALIM UC KOJI DOBIJU 1L HEMIOTERAPIJE NA BAZI PLATINE IMAJU ODGOVOR ILI KONTROLU BOLESTI



U randomizovanim studijama, 65%-79% pacijenata sa lokalno uznapredovalim ili metastatskim UC su ostvarili kontrolu bolesti sa 1L hemioterapije na bazi platine

**Preporučeno maksimalno trajanje 1L hemioterapije na bazi platine je ≤6 ciklusa  
Duža primena nije preporučena zbog kumulativnih toksičnosti i nedostatka drugih benefita<sup>6</sup>**

1L, first-line; CR, complete response; DCR, disease control rate; ITT, intention-to-treat; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UC, urothelial carcinoma

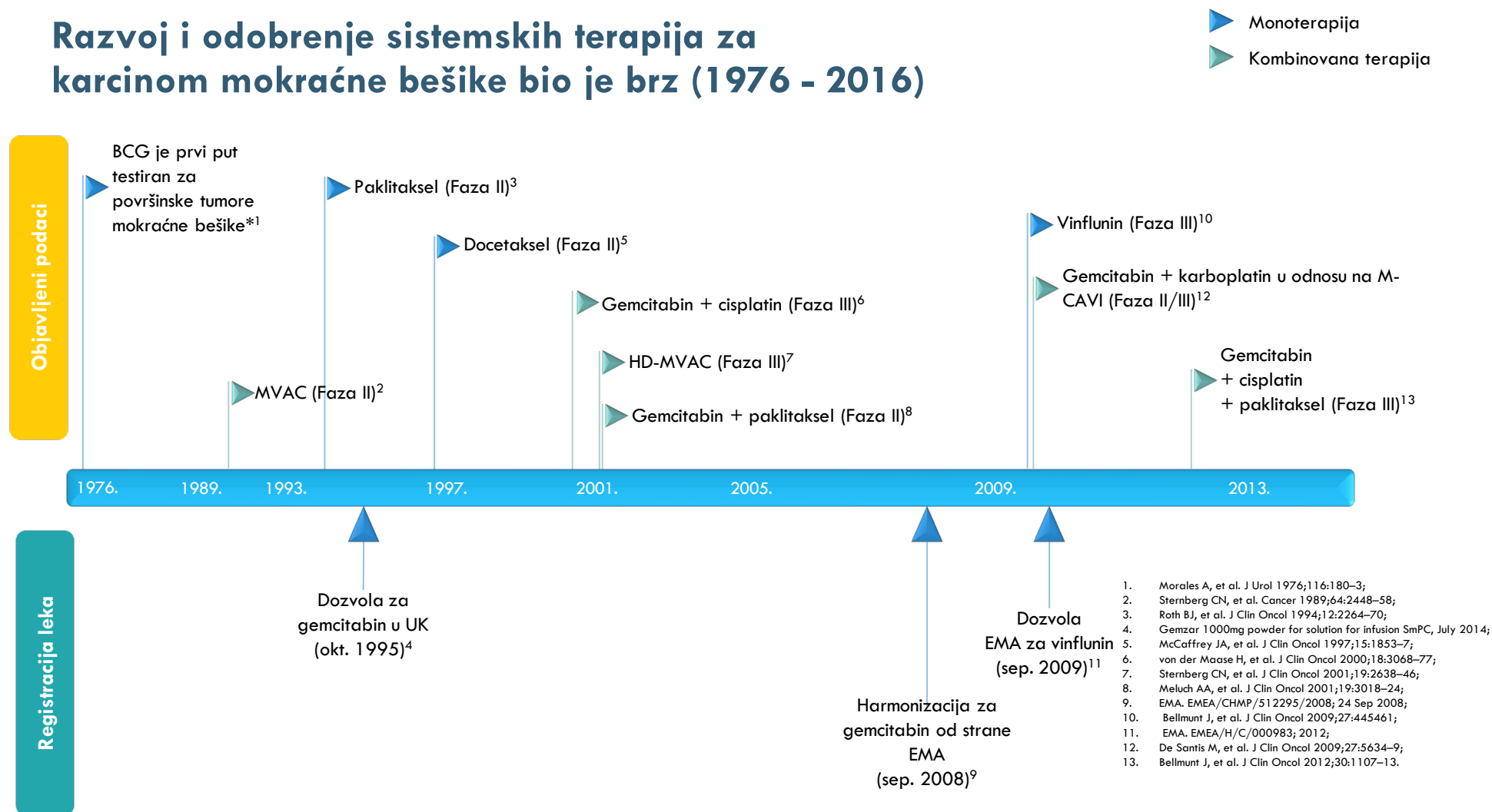
<sup>\*</sup>Derived disease control rates based on ITT analysis in all patients with measurable disease, consistent with RECIST 1.1 guidelines<sup>6</sup>; <sup>†</sup> Patient numbers with SD were derived from rates reported in evaluable patients in the publication (33.5% of 164, 32.5% of 151); <sup>‡</sup> Patients with measurable disease

1. von der Maase H, et al. J Clin Oncol. 2000;17:3068-77; 2. Dogliotti L, et al. Eur Urol. 2007;52:134-41; 3. De Santis M, et al. J Clin Oncol. 2012;30:191-9; 4. Galsky MD, et al. Lancet. 2020;395:1547-57; 5. Powles T, et al. Lancet Oncol. 2021;22:931-45; 6. Sonpavde G, et al. J Urol. 2018;200:1207-14; 7. NCCN Guidelines: Bladder Cancer, V4 2021. [https://www.nccn.org/professionals/physician\\_gls/PDF/bladder.pdf](https://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf). Accessed March 2022. Referenced with permission from the

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer, V4 2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 11, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 8. ESMO eUpdate – bladder cancer treatment recommendations, Dec 16, 2019 [https://www.annalsofoncology.org/article/S0923-7534\(21\)04827-4/fulltext](https://www.annalsofoncology.org/article/S0923-7534(21)04827-4/fulltext). Accessed March 2022

# RAZVOJ SISTEMSKE TERAPIJE ZA KARCINOM MOKRAĆNE BEŠIKE

## Razvoj i odobrenje sistemskih terapija za karcinom mokraćne bešike bio je brz (1976 - 2016)

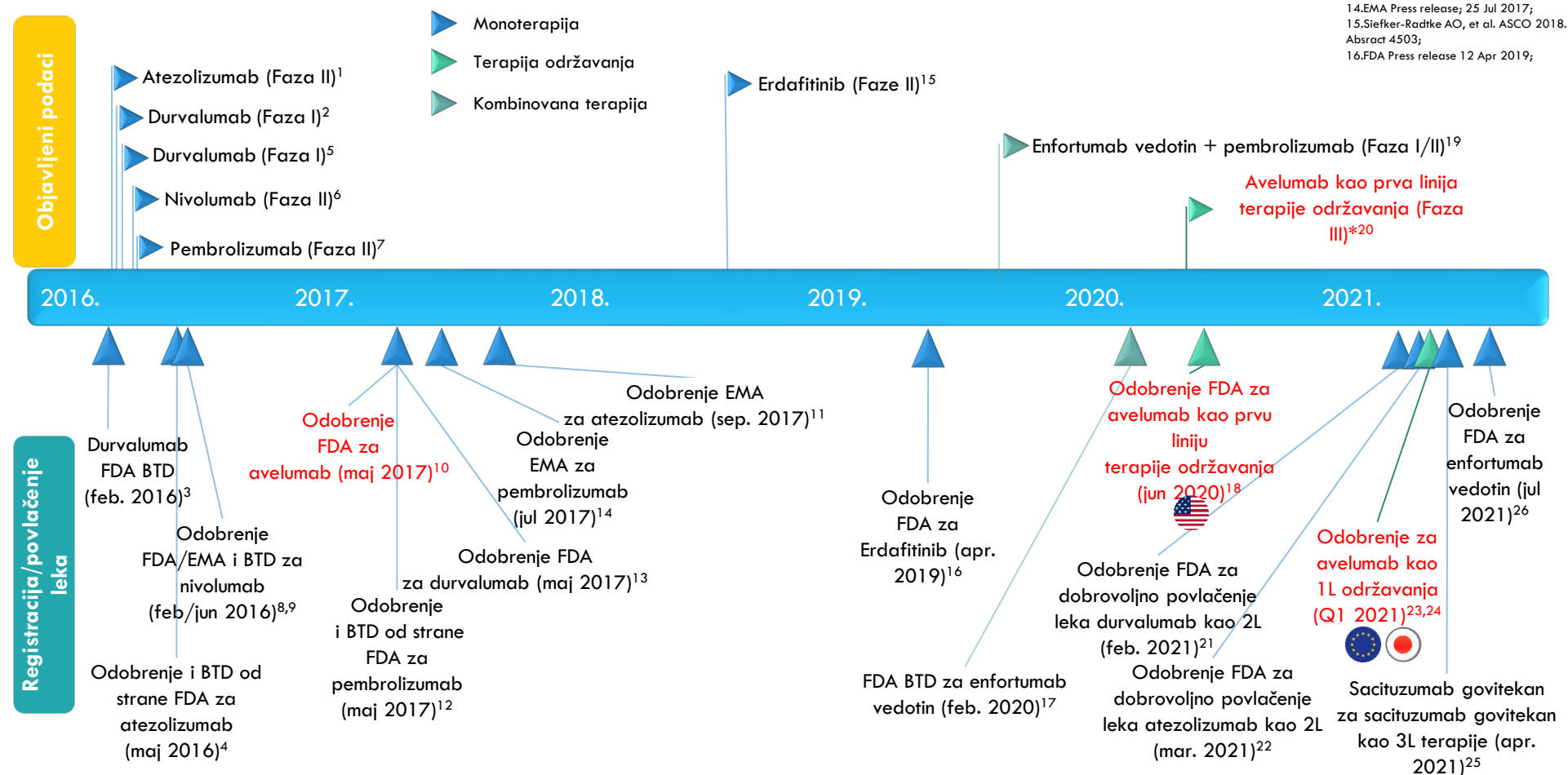


\*BCG je bila prva i tradicionalna intravezikalna terapija za karcinom mokraćne bešike.

BCG, *Bacillus Calmette-Guérin*; EMA, Evropska agencija za lekove (eng. *European Medicines Agency*); HD-MVAC, HD-MVAC, intenzivna terapija metotreksatom, vinblastinom, doksorubicinom i cisplatinom u visokoj dozi (eng. *high-dose intensity methotrexate, vinblastine, doxorubicin, cisplatin*); M-CAVI, metotreksat, karboplatin i vinblastin (eng. *methotrexate, carboplatin, and vinblastine*); MVAC, metotreksat, vinblastin, doksorubicin i cisplatin (eng. *methotrexate, vinblastine, doxorubicin, cisplatin*).

# RAZVOJ SISTEMSKE TERAPIJE ZA KARCINOM MOKRAĆNE BEŠIKE

## Razvoj i odobrenje sistemskih terapija za karcinom mokraćne bešike bio je brz (od 2016. do sada)

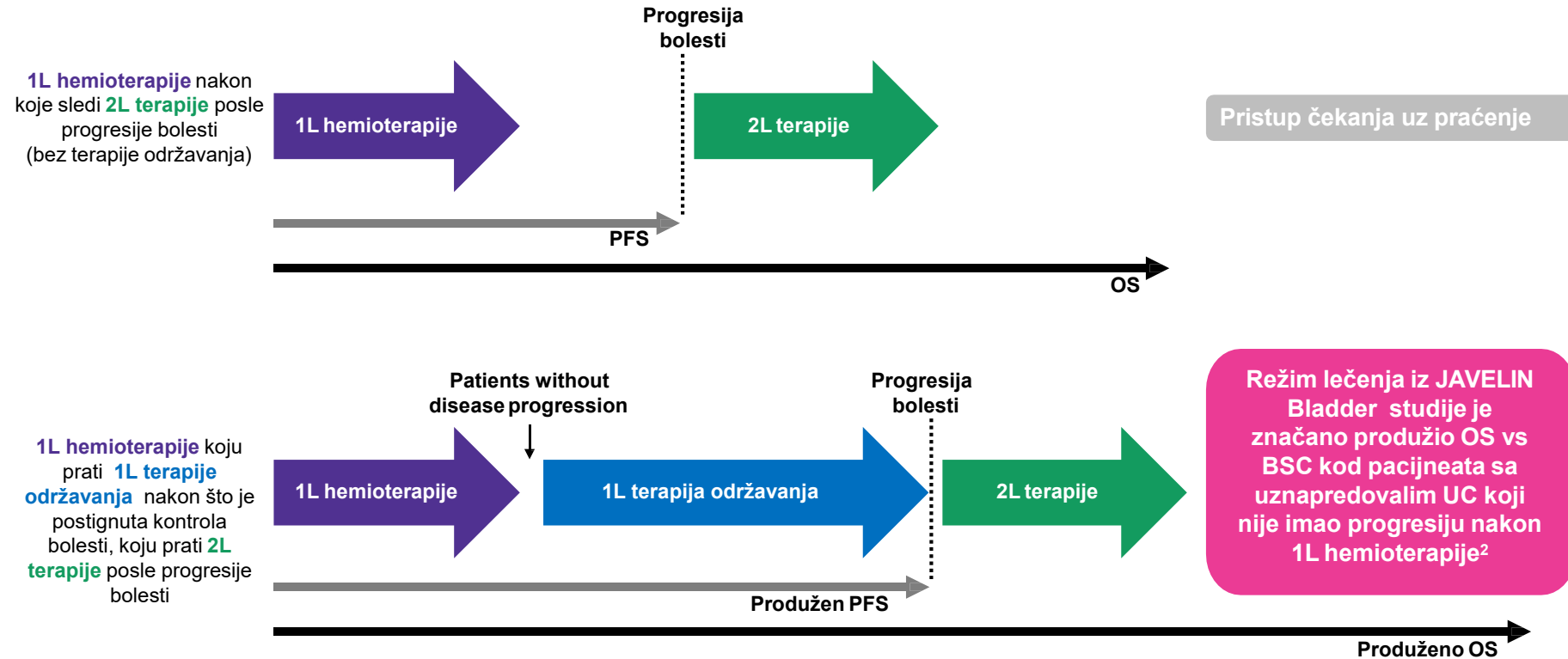


\*Avelumab kao terapija održavanja je bio prvenstveno odobren u SAD, a zatim u EU, Kanadi, Japanu, Australiji, Brazilu, Izraelu, Argentini, UAE i Libanu; avelumab kao terapija održavanja odobren je u 39 zemalja.

1L, prva linija terapije (eng. *first line*); 2L, druga linija terapije (eng. *second line*); 3L, treća linija terapije (eng. *third line*); BTĐ, inovativna terapija (eng. *breakthrough therapy designation*); EMA, Evropska agencija za lekove (eng. *European Medicines Agency*); FDA, Uprava za hranu i lekove (eng. *Food and Drug Administration*).

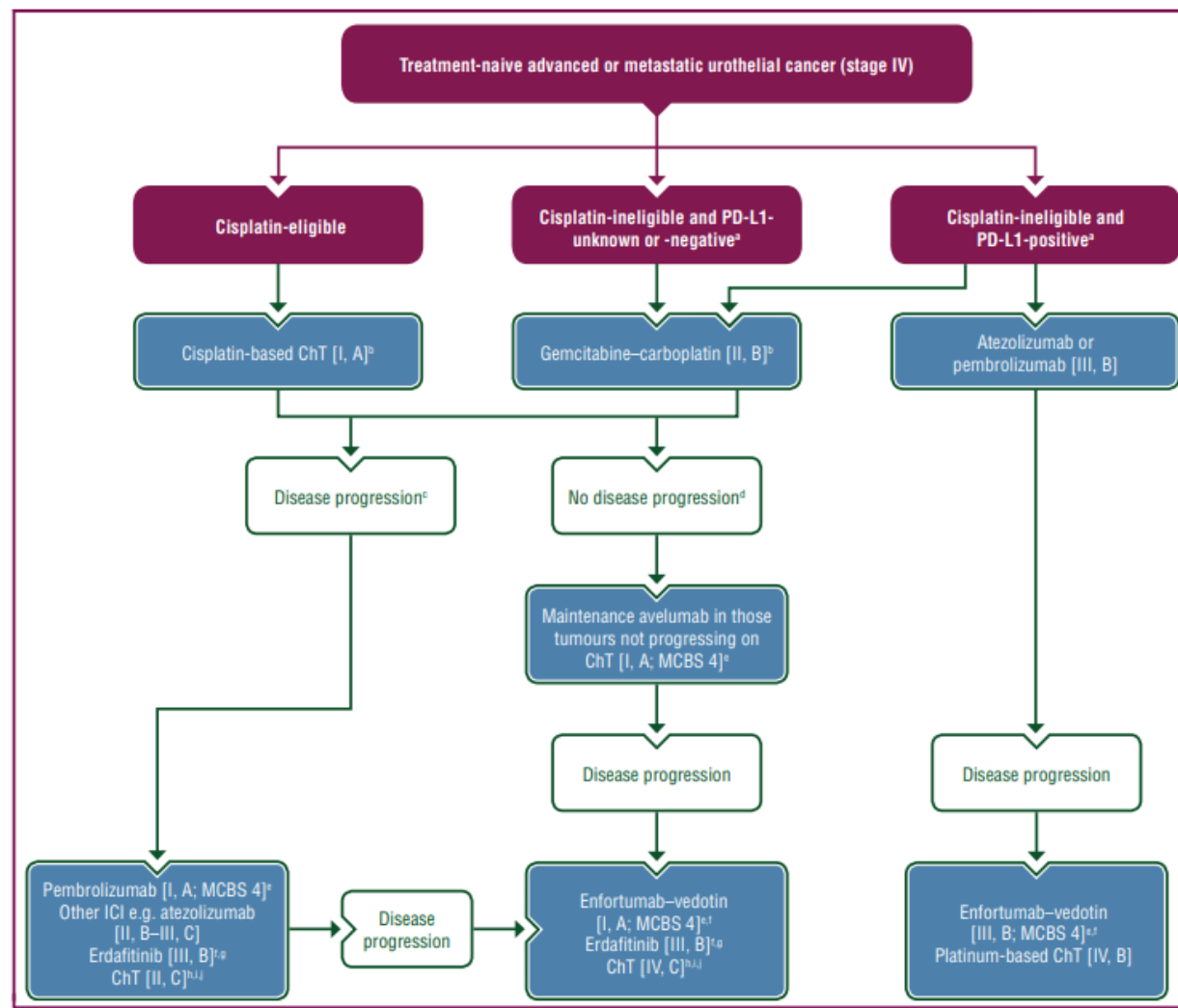
- Rosenberg JE, et al. Lancet 2016;387:1909–20;
- Massard C, et al. ASCO 2016. Abstract 4502 and oral presentation;
- AstraZeneca. Press release 17 Feb 2016;
- FDA. Press release 18 May 2016;
- Apolo AB, et al. ASCO 2016. Abstract 451421. AstraZeneca. Press release 22 Feb 2021; and poster;
- Sharma P, et al. Lancet Oncol 2017;18:312–22;
- Balar A, et al. ESMO 2016. Abstract #LBA32\_PR;
- FDA. Press release 2 Feb 2017;
- FDA. Press release 9 May 2017;
- EMA. EMA/584175/2020;
- FDA Press release 18 May 2017;
- FDA Press release 1 May 2017;
- EMA Press release; 25 Jul 2017;
- Sieffer-Radtke AO, et al. ASCO 2018. Abstract 4503;
- FDA Press release 12 Apr 2019;
- Astellas. Press release 20 Feb 2020;
- FDA Press release 1 July 2020;
- Hoimes CJ, et al. ESMO 2019. Abstract 901O;
- Powles T, et al. ASCO 2020. Abstract LBA1;
- AstraZeneca. Press release 22 Feb 2021;
- Roche. Press release 22 Feb 2021.

# TERAPIJE ODRŽAVANJA MOŽE DA PRODUŽI KONTROLU BOLESTI NAKON HEMIOTERAPIJE NA BAZI PLATINE KOD PACIJENATA KOD KOJI NEMAJU PROGRESIJU BOLESTI



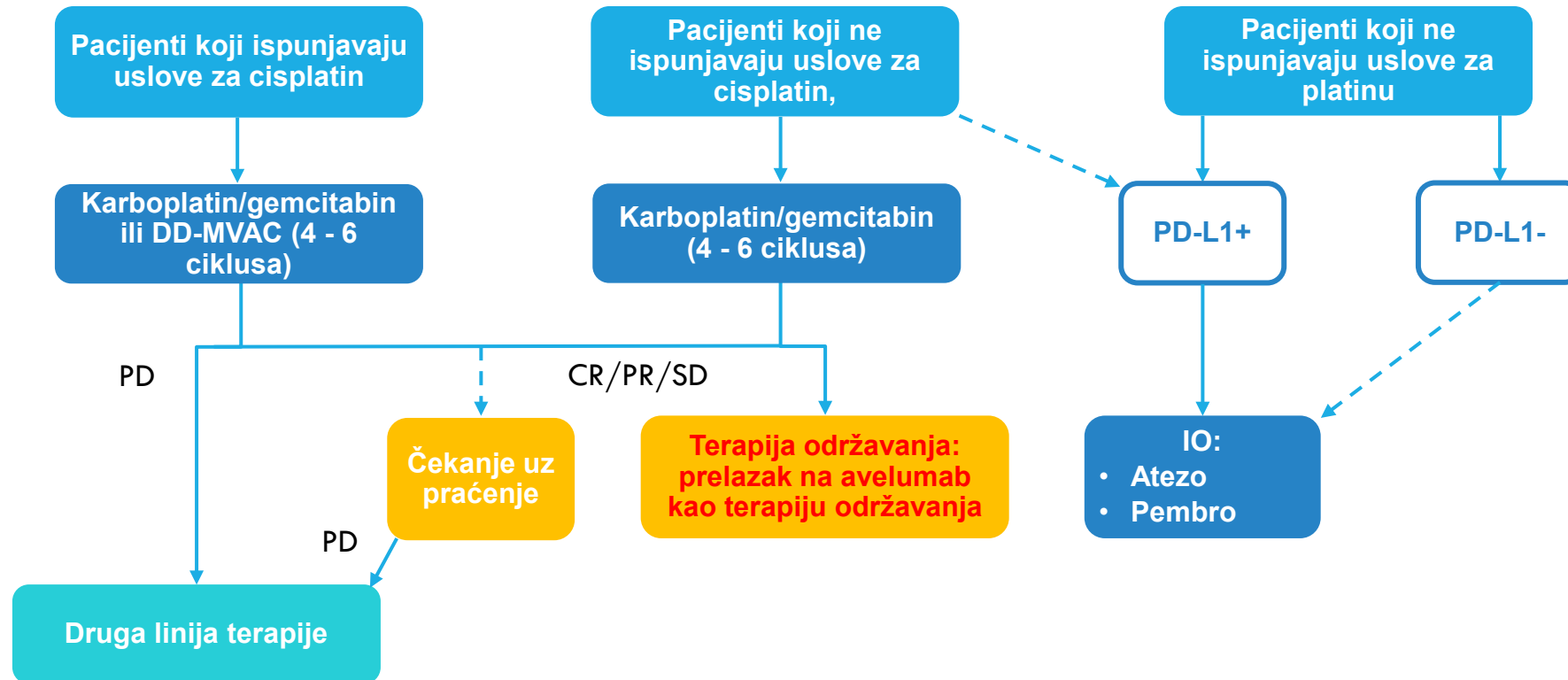
Dužina strelice je samo ilustrativna

# SMERNICE ESMO ZA LEČENJE MUC UKLJUČUJU TERAPIJU ODRŽAVANJA LEKOM AVELUMAB



# SMERNICE EAU: PRVA LINIJA TERAPIJE METASTAZA

Preporučena terapija je hemioterapija na bazi platine nakon koje sledi avelumab kao terapija održavanja



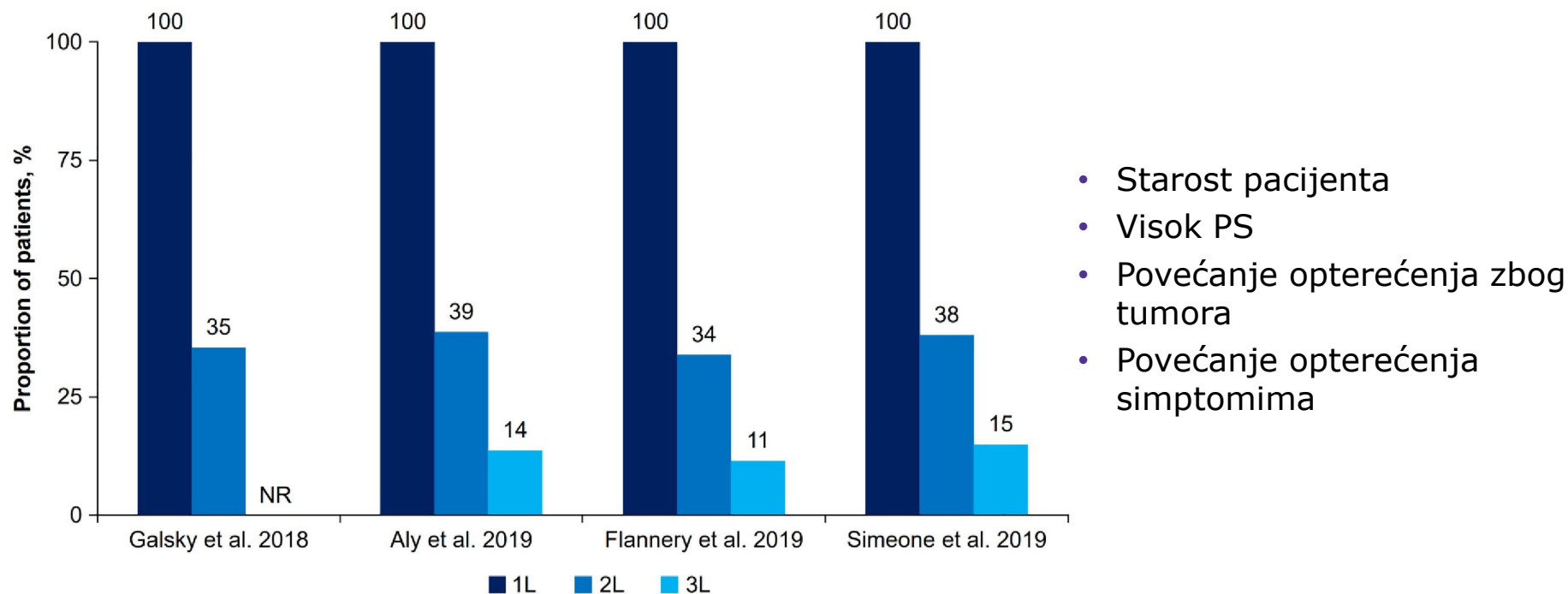
Atezo, atezolizumab; CR, potpuni odgovor (eng. complete response); CT, hemioterapija (eng. chemotherapy); DDMVAC, metotreksat, vinblastin, doksorubicin (Adriamycin) i cisplatin primenjeni u zgusnutim dozama (eng. dose-dense methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin); EAU, vropska urološka asocijacija (eng. European Association of Urology); IO, imunoterapija (eng. immunotherapy); PD, progresivna bolest (eng. progressive disease);

PD-L1, ligand 1 programirane smrti ćelije (eng. programmed death-ligand 1); pembro, pembrolizumab; PR, delimični odgovor (eng. partial response); SD, stabilna bolest (eng. stable disease).

Cathomas R, et al. The 2021 Updated European Association of Urology Guidelines on Metastatic Urothelial Carcinoma. 2021.

# ČEKANJE UZ PRAĆENJE, KAO ALTERNATIVA TERAPIJI ODRŽAVANJA LEKOM AVELUMAB, ZNAČAJNO SMANJUJE ŠANSE ZA IMUNOTERAPIJU U KASNIJIM LINIJAMA LEČENJA

~65% pacijenata sa mUC ne ispunjavaju kriterijume za 2L lečenja



# SAŽETAK SMERNICA NCCN, ESMO I EAU ZA METASTATSKI UC

## Preporuke za lečenje kod prve linije terapije

|                                                    | NCCN <sup>1</sup>                                                                                                                                                                                                                                                                                             | ESMO <sup>2</sup>                                                                                                                                                                                |                                                                                                                                                                                                                                                                                      | EAU <sup>3</sup>                                                                                                                                                                                                       |
|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pacijenti koji ispunjavaj u uslove za cisplatin    | <ul style="list-style-type: none"> <li>Gemcitabin/cisplatin (Kategorija 1) nakon kojih sledi terapija održavanja <b>avelumabom</b> (Kategorija 1)</li> <li>DDMVAC sa suportivnom terapijom sa faktorom rasta (Kategorija 1) nakon kojih sledi terapija održavanja <b>avelumabom</b> (Kategorija 1)</li> </ul> | CT na bazi cisplatina [I, A] nakon koje sledi <b>avelumab</b> kao terapija održavanja za tumore koji nisu uznapredovali za vreme CT [I, A]                                                       |                                                                                                                                                                                                                                                                                      | Gemcitabin/cisplatin ili DDMVAC, nakon koje sledi <b>avelumab</b> kao terapija održavanja za tumore koji nisu uznapredovali za vreme CT                                                                                |
| Pacijenti koji ne ispunjavaj u uslove za cisplatin | <ul style="list-style-type: none"> <li>Gemcitabin/karboplatin (Kategorija 2A) nakon kojih sledi terapija održavanja <b>avelumabom</b> (Kategorija 1)</li> <li>Atezolizumab (Kategorija 2A)</li> <li>Pembrolizumab (Kategorija 2A)</li> </ul>                                                                  | <b>sa PD-L1 nepoznatim ili negativnim tumorima</b><br>Gemcitabin/cisplatin [II, B] nakon koje sledi <b>avelumab</b> kao terapija održavanja za tumore koji nisu uznapredovali za vreme CT [I, A] | <b>sa PD-L1 pozitivnim tumorima</b><br><ul style="list-style-type: none"> <li>Gemcitabin/cisplatin [II, B] nakon koje sledi <b>avelumab</b> kao terapija održavanja za tumore koji nisu uznapredovali za vreme CT [I, A]</li> <li>Atezolizumab ili pembrolizumab [III, B]</li> </ul> | <ul style="list-style-type: none"> <li>Gemcitabin/cisplatin, nakon koje sledi <b>avelumab</b> kao terapija održavanja za tumore koji nisu uznapredovali za vreme CT</li> <li>Pembrolizumab ili atezolizumab</li> </ul> |

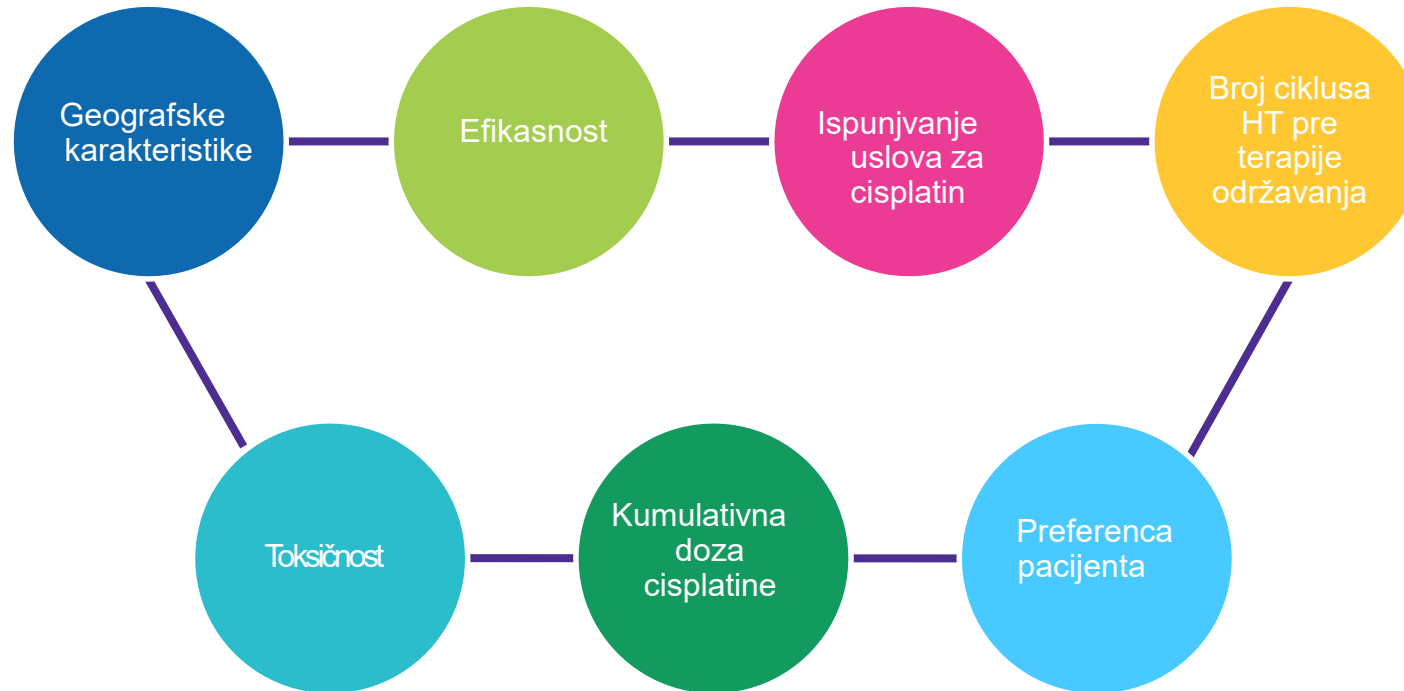
Monoterapija pembrolizumabom (Kategorija 2A) može se koristiti za lečenje pacijenata koji ne ispunjavaju uslove za bilo koju vrstu hemioterapije na bazi platine

CT, hemioterapija (eng. chemotherapy); DDMVAC, metotreksat, vinblastin, doksorubicin i cisplatin primenjeni u zgusnutim dozama (eng. dose-dense methotrexate, vinblastine, doxorubicin, cisplatin); EAU, Evropska urološka asocijacija (eng. European Association of Urology); ESMO, Evropsko udruženje za medicinsku onkologiju (eng. European Society for Medical Oncology); EV, enfortumab vedotin; FGFR, receptor fibroblastnog faktora rasta (eng. fibroblast growth factor receptor); ICI, inhibitor imunih kontrolnih tačaka (eng. immune checkpoint inhibitor); NCCN, Nacionalna sveobuhvatna mreža za borbu protiv raka (eng. National Comprehensive Cancer Network); PD-1, protein 1 programirane smrti ćelije (eng. programmed cell death protein 1); PD-L1, ligand 1 programirane smrti ćelije (eng. programmed death-ligand).

1. NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. V1. 2022; 2. Bladder cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol novembar 2021;33:244–258; 3. Cathomas R, et al. The 2021 Updated European Association of Urology Guidelines on Metastatic Urothelial Carcinoma. 2021.

# OPTIMIZACIJA LEČENJA METASTATSKOG KARCINOMA MOKRAĆNE BEŠIKE

## Šta treba uzeti u obzir



**Izbor sistemske terapije bi trebao da bude individualan za svakog pacijenta**



**Terapijski pristup i terapija  
održavanja u prvoj liniji lečenja  
lokalno uznapredovalog ili  
metastatskog urotelijalnog karcinoma  
lekom avelumab: rezultati pivotalne  
studije JAVELIN Bladder 100**

**Prim. Dr Suzana Matković, MD, PhD  
Institut za Onkologiju i Radiologiju Srbije**

# 1L hemioterapije je **Standard of Care** kod pacijenata sa lokalno uznapredovalim ili metastatskim UC

**Platinum-based chemotherapy (CT) remains the 1L SOC treatment in platinum-eligible patients with locally advanced or metastatic UC<sup>1,2</sup>**

Based on clinical trials, many patients with advanced UC have an objective response or disease control with 1L platinum-based CT<sup>3-5</sup>

- ORR of **~40-50%**
- Disease control rates of **~65-75%**

Platinum-based CT is typically administered for **4 to 6 cycles**, independent of regimen used, due to cumulative toxicity<sup>6,7</sup>

Patients who complete platinum-based CT without progressive disease are typically managed with **active surveillance or watchful waiting**, in consideration of further anticancer treatment upon progression<sup>6-9</sup>

- Active anticancer therapy is generally not given until disease progression occurs

1L, first line; CT, chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care; UC, urothelial carcinoma.

1. Guancial EA, et al. Clin Investig (Lond) 2011;1:546-55; 2. Grivas P, et al. Target Oncol 2019;14:505-25; 3. von der Maase H, et al. J Clin Oncol 2000;17:3068-77; 4. De Santis M, et al. J Clin Oncol 2012;30:191-199; 5. Dogliotti L, et al. Eur Urol 2007;52:134-141; 6. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. V3. 2020. NCCN guidelines. Bladder Cancer. Version 3, January 17, 2020. Available at: [https://www.nccn.org/professionals/physician\\_gls/default.aspx#site](https://www.nccn.org/professionals/physician_gls/default.aspx#site). Accessed 9 April 2020; 7. Sonpavde G, et al. J Urol 2018;200:1207-1214; 8. Gofrit ON, et al. Eur Urol. 2006;49(2):303-307; 9. Miyake M, et al. Investig Clin Urol. 2016; 57:S4-S13.

# 1L hemioterapije je **Standard of Care** kod pacijenata sa lokalno uznapredovalim ili metastatskim UC

Proportion of patients with durable responses is low, as most patients experience disease progression within **9 months** after initiation of treatment<sup>1,2,3</sup>

Median OS in trials of patients with locally advanced or metastatic UC<sup>1,2,3</sup>

**~14-15 months**

with 1L cisplatin plus gemcitabine or DDMVAC

**~8-9 months**

with 1L carboplatin plus gemcitabine

There is a limit to how much platinum an individual can receive in a lifetime<sup>4,5</sup>

- Patients undergoing prolonged platinum-based CT accumulate toxicity. This can have long-term effects, impair QoL and can require treatment discontinuation in patients with non-progressive disease<sup>4,5</sup>

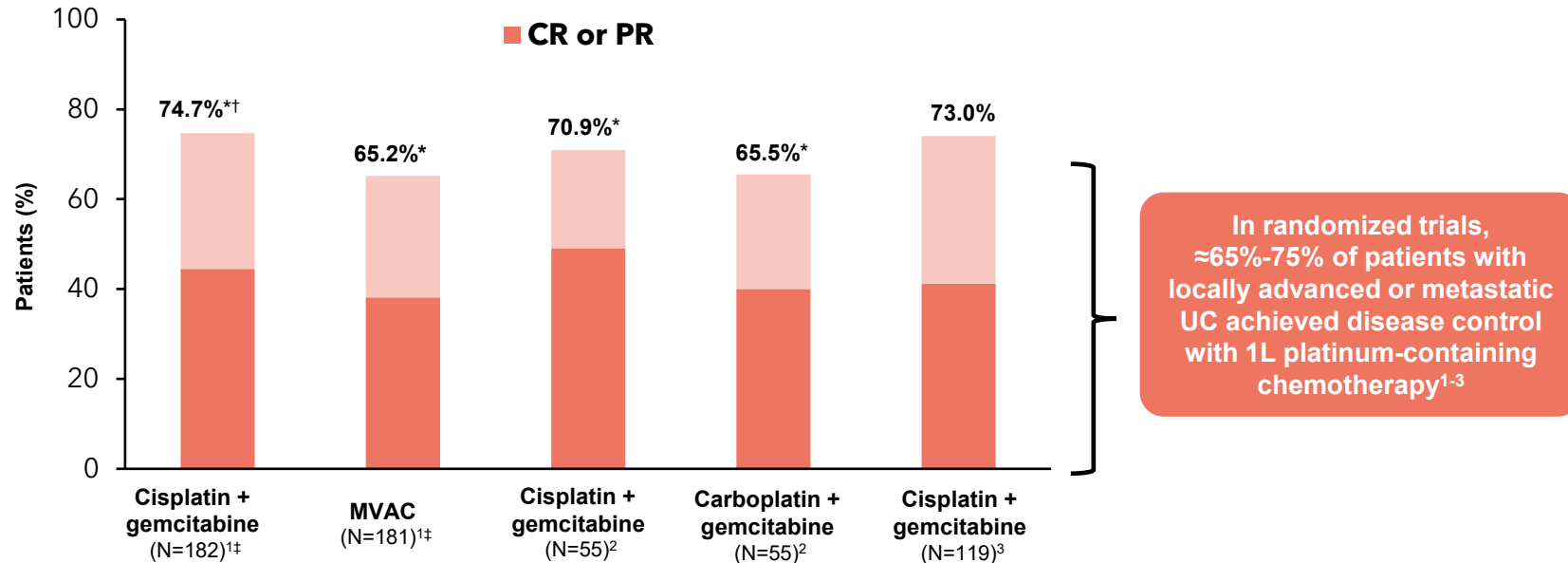
Cancers can be inherently resistant to platinum-based CT or can develop resistance over time<sup>4</sup>

**An unmet medical need exists to maintain or extend the benefits of 1L CT in order to delay the start of 2L treatment<sup>6</sup>**

1L, first line; 2L, second line; CT, chemotherapy; DDMVAC, dose-dense methotrexate vinblastine, adriamycin, cisplatin; OS, overall survival; QoL, quality of life; UC, urothelial cancer.

1. von der Maase H, et al. J Clin Oncol 2000;17:3068-77; 2. De Santis M, et al. J Clin Oncol 2012;30:191-199; 3. Sternberg C.N, et al. Euro J Cancer 2006;42:50-54; 4. Oun R, et al. Dalton Trans 2018;47:6645-53; 5. Sonpavde G, et al. J Urol 2018;200:1207-1214; 6. Grivas P, et al. Target Oncol 2019;14:505-25.

# Večina bolnikov s uznappedovalim UC odgovori na 1. liniju lečenja bazirano na platini<sup>1-3</sup>



**Recommended maximum duration of 1L platinum-based chemotherapy is ≤6 cycles**  
**Longer durations are not recommended because of cumulative toxicities and a lack of additional benefit<sup>4,5</sup>**

1L, first-line; CR, complete response; DCR, disease control rate; ITT, intention-to-treat; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UC, urothelial carcinoma

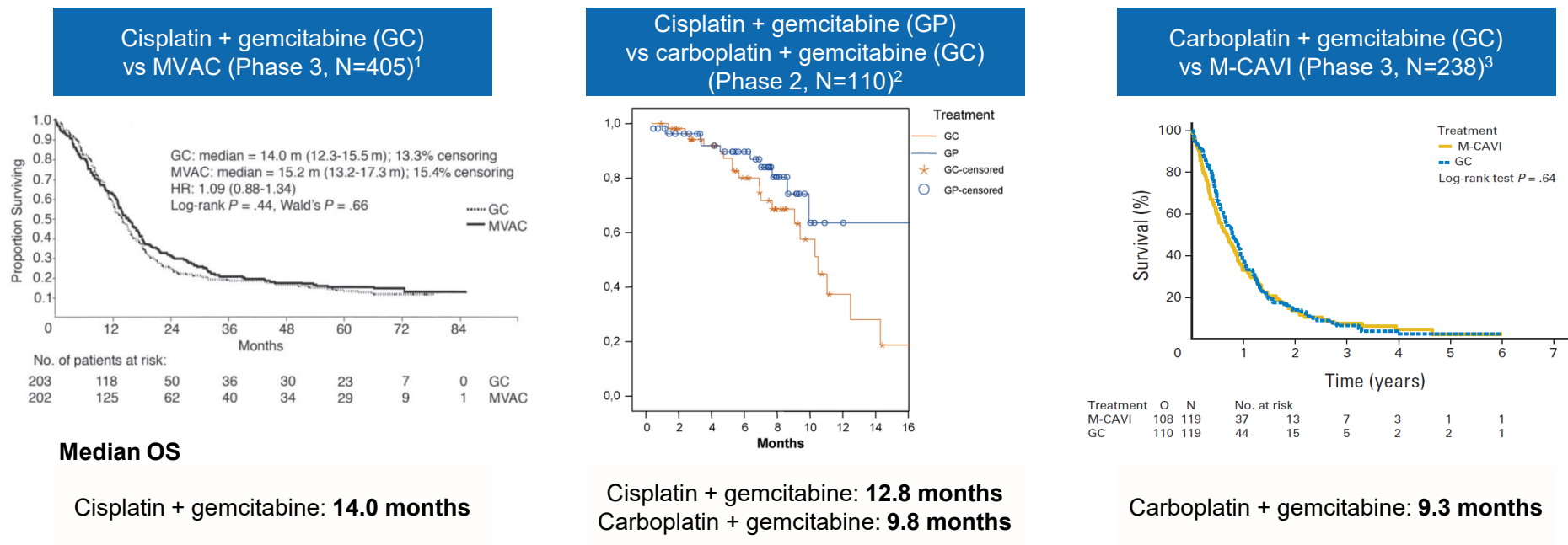
<sup>\*</sup> Derived disease control rates based on ITT analysis in all patients with measurable disease, consistent with RECIST 1.1 guidelines; <sup>†</sup> Patient numbers with SD were derived from rates reported in evaluable patients in the publication (33.5% of 164, 32.5% of 151); <sup>‡</sup> Patients with measurable disease

1. von der Maase H, et al. J Clin Oncol. 2000;17:3068-77; 2. Dogliotti L, et al. Eur Urol. 2007;52:134-41; 3. De Santis M, et al. J Clin Oncol. 2012;30:191-9; 4. Sonpavde G, et al. J Urol. 2018;200:1207-14; 5. NCCN Guidelines: Bladder Cancer, V6.2020. [https://www.nccn.org/professionals/physician\\_gls/PDF/bladder.pdf](https://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf).

# Medijana OS kod bolesnika s lokalno uznapredovalim i metastatskim karcinomom urotela

~14 mjeseci 1L cisplatin i gemcitabin i  
~9 mjeseci 1L karboplatin i gemcitabin<sup>1-3</sup>

## Randomized trials of 1L platinum-based chemotherapy for locally advanced or metastatic UC<sup>1-3</sup>



1. von der Maase H, et al. J Clin Oncol 2005;23:4602-4608.; 2. Dogliotti L, et al. Eur Urol 2007;52:134-141.; 3. De Santis M, et al. J Clin Oncol 2012;30:191-199.

# Racionala za istraživanje terapije održavanja imuno check-point inhibitorima kod lokalno uznapredovalog ili metastatskog UC

## Features that may be associated with increased response to ICIs in several tumor types, such as UC, include:

- A high tumor mutational burden and genomic instability<sup>2-4</sup>
- PD-L1 expression, which can downregulate antitumor immune responses by binding to PD-1 on T cells<sup>2,5</sup>

## Chemotherapy may help the immune system to<sup>1</sup>

- Restrain tumor growth (equilibrium)
- Decrease tumor burden (elimination)

However, **effects of chemotherapy may be temporary** until tumor cells acquire immune escape mechanisms<sup>1</sup>

Multiple ICIs have been approved in 2L locally advanced or metastatic UC, but<sup>1,6-8</sup>

- Earlier use of ICI may increase the likelihood that individual patients are exposed to a potentially active therapy
- Maintenance treatment approaches are established in other tumor types such as lung and ovarian cancers<sup>1,6</sup>

**The purpose of investigating maintenance therapy is to test whether it can maintain and extend the benefits of chemotherapy in patients with locally advanced or metastatic UC whose disease has not progressed<sup>1,6</sup>**

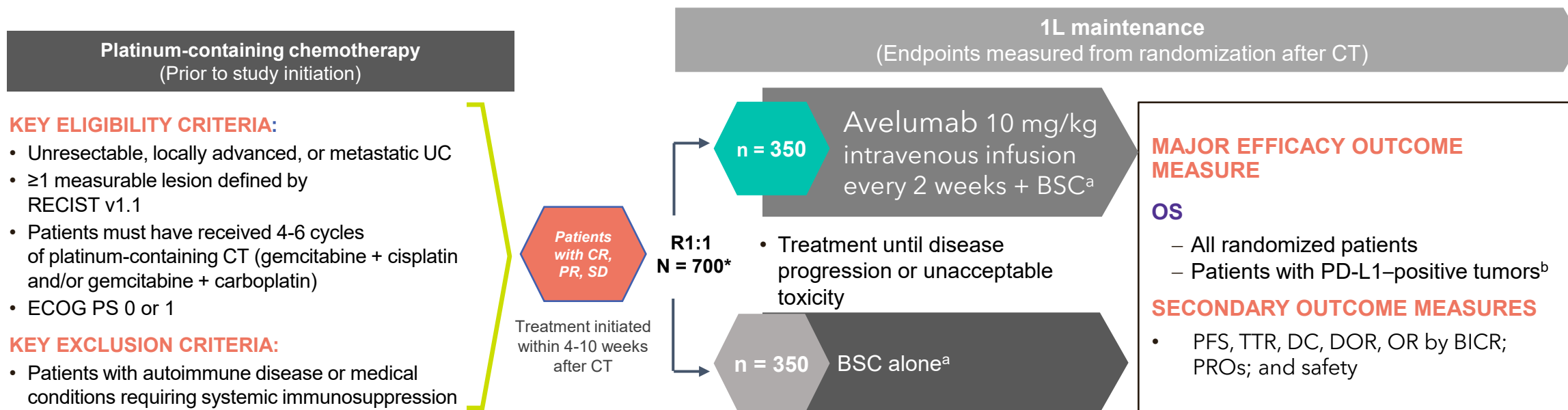
1L, first line; CT, chemotherapy; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; UC, urothelial cancer.

1. Grivas P, et al. Target Oncol 2019;14:505-25; 2. Kim JW, et al. Curr Opin Oncol 2015;27:191-200; 3. Mariathasan S, et al. Nature 2018;554:544-8; 4. Cheng W, et al. Oncogenesis 2018;7:2; 5. Pichler R, et al. Oncotarget 2017;8:66849-64; 6. Gerber DE, Schiller JH. J Clin Oncol. 2013;31(8):100-1020; 7. Flannery K, et al. Futur Oncol. 2019;15(12):1323-1334; 8. Galsky M, et al. J Clin Onc. 2020;38:1-11.

# JAVELIN Bladder 100 ([NCT02603432](https://clinicaltrials.gov/ct2/show/study/NCT02603432))

Phase III, randomized, open-label trial investigating 1L maintenance with avelumab in patients with locally advanced or metastatic UC that did not progress with platinum-containing CT<sup>1,2</sup>

## JAVELIN Bladder 100 regimen with avelumab as 1L maintenance treatment<sup>1,2</sup>



- Stratified by best response to CT (CR/PR vs SD per RECIST v1.1) and site of metastasis (visceral vs non-visceral [including bone metastasis]) assessed at the time of initiating 1L platinum-containing chemotherapy<sup>1,2</sup>
- Administration of avelumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator<sup>2</sup>
- Assessment of tumor status was performed at baseline, 8 weeks after randomization, then every 8 weeks up to 12 months after randomization, and every 12 weeks thereafter until documented confirmed disease progression based on BICR assessment per RECIST v1.1<sup>2</sup>

\* 1005 patients were screened with 305 deemed ineligible at screening; 267 screen failure, 21 no longer meet eligibility criteria, 11 withdrew consent, 3 deaths and 3 other reasons<sup>3</sup>. <sup>a</sup> BSC was administered as deemed appropriate by the treating physician, and could include treatment with antibiotics, nutritional support, and other patient management approaches with palliative intent (excludes systemic antitumor therapy). <sup>b</sup> PD-L1 expression was assessed in tumor samples using the VENTANA PD-L1 (SP263) assay.<sup>1</sup>

1L, first-line; BICR, blinded independent central review; BSC, best supportive care; CR, complete response; CT, chemotherapy; DC, disease control; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, overall response; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; PROs, patient-reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTR, time to response; UC, urothelial cancer.

1. Powles T, et al. N Engl J Med. 2020;383(13):1218-1230; 2. BAVENCIO [prescribing information]. Rockland, MA: EMD Serono, Inc; New York, NY: Pfizer Inc; 3. Powles T, et al. N Engl J Med. 2020;383(13):1218-1230 (suppl).

# JAVELIN Bladder 100 - Select Baseline Characteristics<sup>1</sup>

|                                        | All Randomized Patients  |                     | PD-L1–Positive Patients  |                     |
|----------------------------------------|--------------------------|---------------------|--------------------------|---------------------|
|                                        | Avelumab + BSC (n = 350) | BSC Alone (n = 350) | Avelumab + BSC (n = 189) | BSC Alone (n = 169) |
| <b>Median age, years (range)</b>       | 68 (37-90)               | 69 (32-89)          | 70 (37-90)               | 70 (32-84)          |
| <b>ECOG PS at randomization, n (%)</b> |                          |                     |                          |                     |
| 0                                      | 213 (60.9)               | 211 (60.3)          | 114 (60.3)               | 107 (63.3)          |
| 1                                      | 136 (38.9)               | 136 (38.9)          | 74 (39.2)                | 61 (36.1)           |
| 2                                      | 1 (0.3)                  | 0                   | 1 (0.5)                  | 0                   |
| 3                                      | 0                        | 3 (0.9)             | 0                        | 1 (0.6)             |
| <b>PD-L1 status, n (%)</b>             |                          |                     |                          |                     |
| Positive                               | 189 (54.0)               | 169 (48.3)          | 189 (100.0)              | 169 (100.0)         |
| Negative                               | 139 (39.7)               | 131 (37.4)          | 0                        | 0                   |

|                                                         | All Randomized Patients  |                     | PD-L1–Positive Patients  |                     |
|---------------------------------------------------------|--------------------------|---------------------|--------------------------|---------------------|
|                                                         | Avelumab + BSC (n = 350) | BSC Alone (n = 350) | Avelumab + BSC (n = 189) | BSC Alone (n = 169) |
| <b>Site of baseline metastasis (prior to CT), n (%)</b> |                          |                     |                          |                     |
| Visceral                                                | 191 (54.6)               | 191 (54.6)          | 88 (46.6)                | 79 (46.7)           |
| Non-visceral                                            | 159 (45.4)               | 159 (45.4)          | 101 (53.4)               | 90 (53.3)           |
| <b>1L CT regimen, n (%)</b>                             |                          |                     |                          |                     |
| Gem + cis                                               | 183 (52.3)               | 206 (58.9)          | 101 (53.4)               | 98 (58.0)           |
| Gem + carbo                                             | 147 (42.0)               | 122 (34.9)          | 74 (39.2)                | 54 (32.0)           |
| Gem + cis/carbo                                         | 20 (5.7)                 | 20 (5.7)            | 14 (7.4)                 | 15 (8.9)            |
| Not reported                                            | 0                        | 2 (0.6)             | 0                        | 2 (1.2)             |
| <b>Best response to 1L CT, n (%)</b>                    |                          |                     |                          |                     |
| CR                                                      | 90 (25.7)                | 89 (25.4)           | 60 (31.7)                | 53 (31.4)           |
| PR                                                      | 163 (46.6)               | 163 (46.6)          | 79 (41.8)                | 75 (44.4)           |
| SD                                                      | 97 (27.7)                | 98 (28.0)           | 50 (26.5)                | 41 (24.3)           |

**Baseline characteristics were balanced between the treatment arms, between all randomized and PD-L1–positive patient populations**

For full definitions please refer to Powles T, et al. N Engl J Med. 2020;383(13):1218-1230.

1L, first-line; BSC, best supportive care; carbo, carboplatin; cis, cisplatin; CT, chemotherapy; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; gem, gemcitabine; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

1. Powles T, et al. Poster E7. Presented at: ASCO GU Symposium; February 17-19, 2022; San Francisco, CA; 2. Powles T, et al. N Engl J Med. 2020;383(13):1218-1230 (suppl).

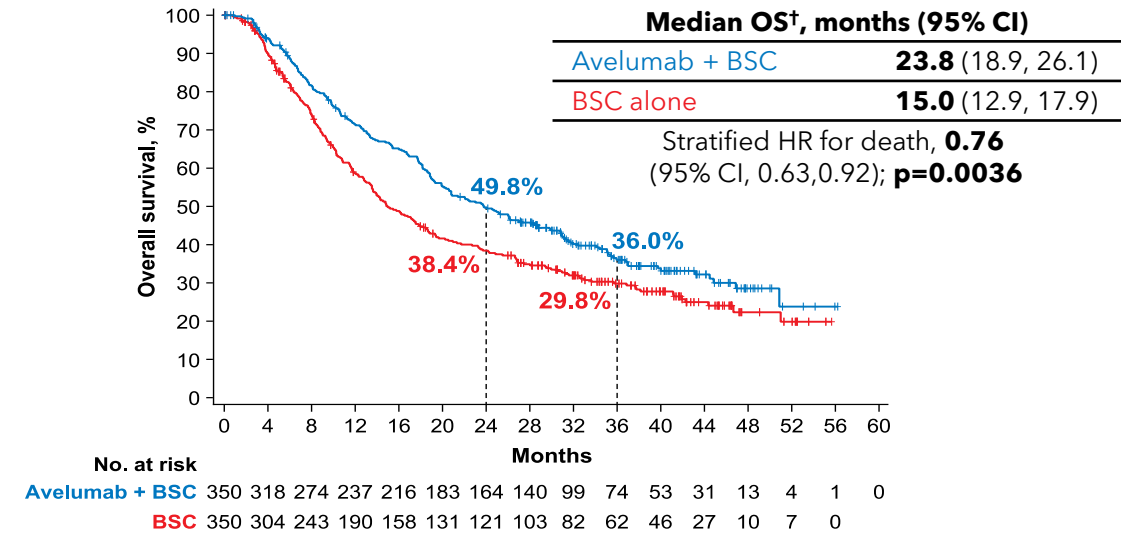
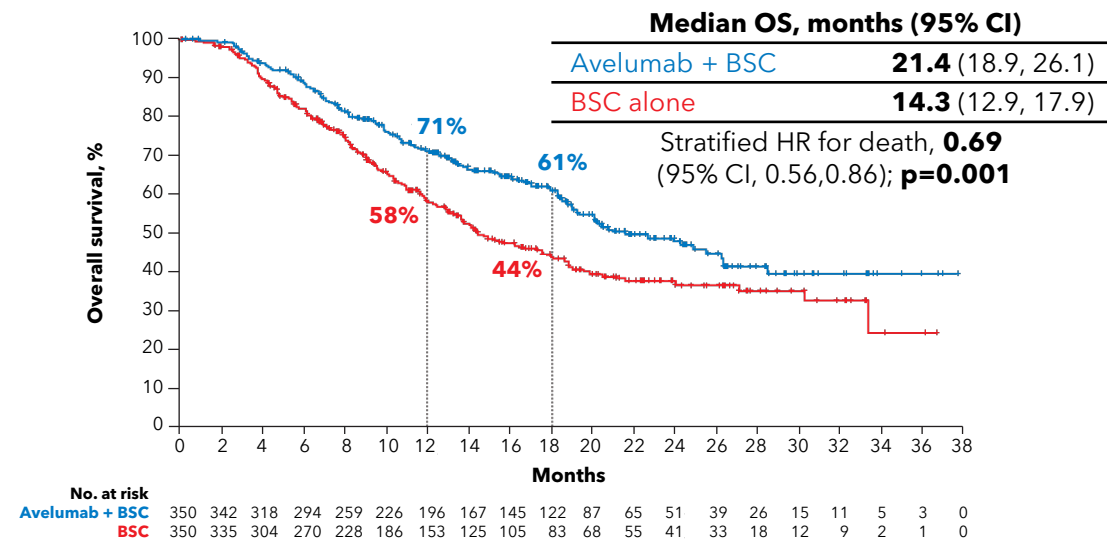
# JAVELIN Bladder 100 - Primary Endpoint: OS in All Randomized Patients<sup>1-3</sup>

## Primary Analysis

Data Cut-off: 21st October 2019  
mFU (95% CI), months:  
Avelumab + BSC: 19.6 (18.0, 20.6)  
BSC alone: 19.2 (17.4, 21.6)

## Long-term Analysis

Data Cut-off: 4th June 2021  
mFU (95% CI), months:  
Avelumab + BSC: 38.0 (36.1, 40.5)  
BSC alone: 39.6 (36.2, 41.7)



**In the primary analysis, patients receiving avelumab + BSC had a 31% decrease in the risk of death vs BSC alone**  
**A clinically meaningful improvement in OS is continued to be observed with longer follow-up**  
**At interim analysis (primary analysis), the primary endpoint of prolonging OS was met<sup>1,\*</sup>**

For full definitions please refer to Powles T, et al. N Engl J Med. 2020;383(13):1218-1230.

\*A pre-planned interim analysis (IA) occurred with a data cut-off of October 21, 2019. The IA was considered as the primary analysis of the trial since the primary endpoint was met<sup>1</sup>; median duration of treatment with avelumab + BSC in all randomized patients was 24.9 weeks (range, 2.0, 159.9)<sup>1</sup>; OS was measured post-randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (p<0.0053). <sup>†</sup>Long term follow-up OS analysis is investigator-assessed;

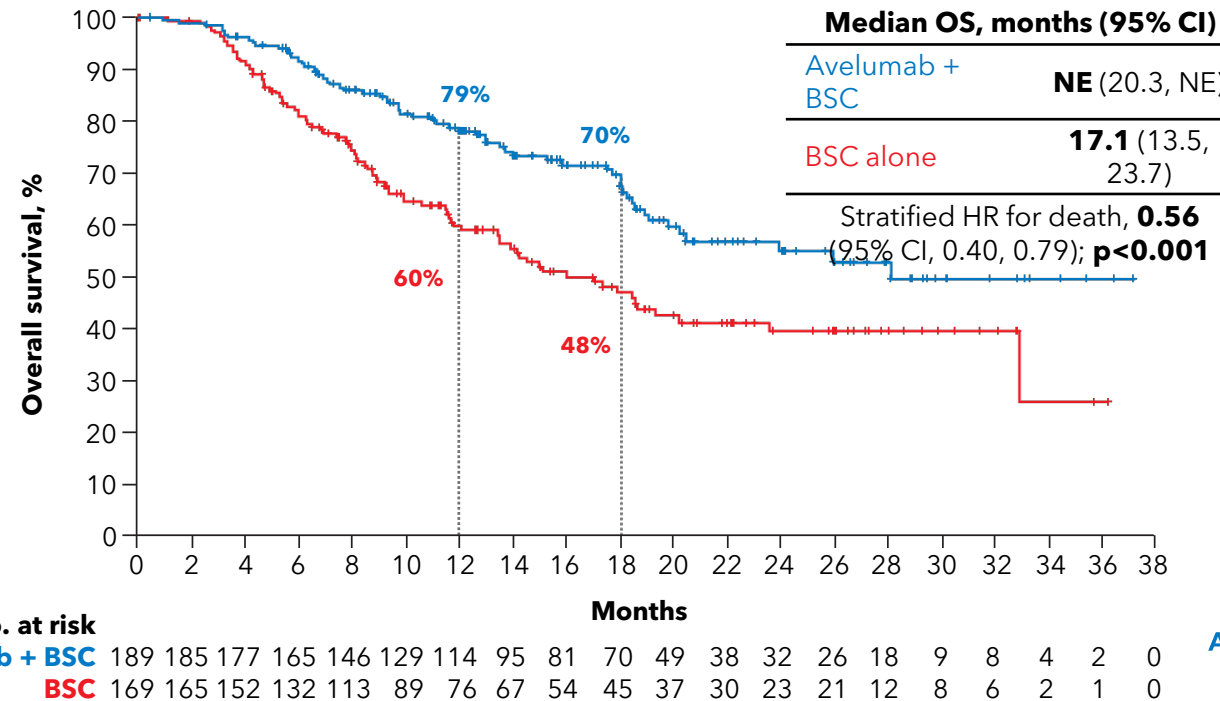
BSC, best supportive care; CI, confidence interval; HR, hazard ratio; mFU, median follow-up; OS, overall survival.

1. Powles T, et al. N Engl J Med. 2020;383(13):1218-1230; 2. Powles T, et al. Poster E7. Presented at: ASCO GU Symposium; February 17-19, 2022; San Francisco, CA; 3. Data on File B9991001; August 2, 2021.

# JAVELIN Bladder 100 - OS in PD-L1-Positive Population<sup>1-3</sup>

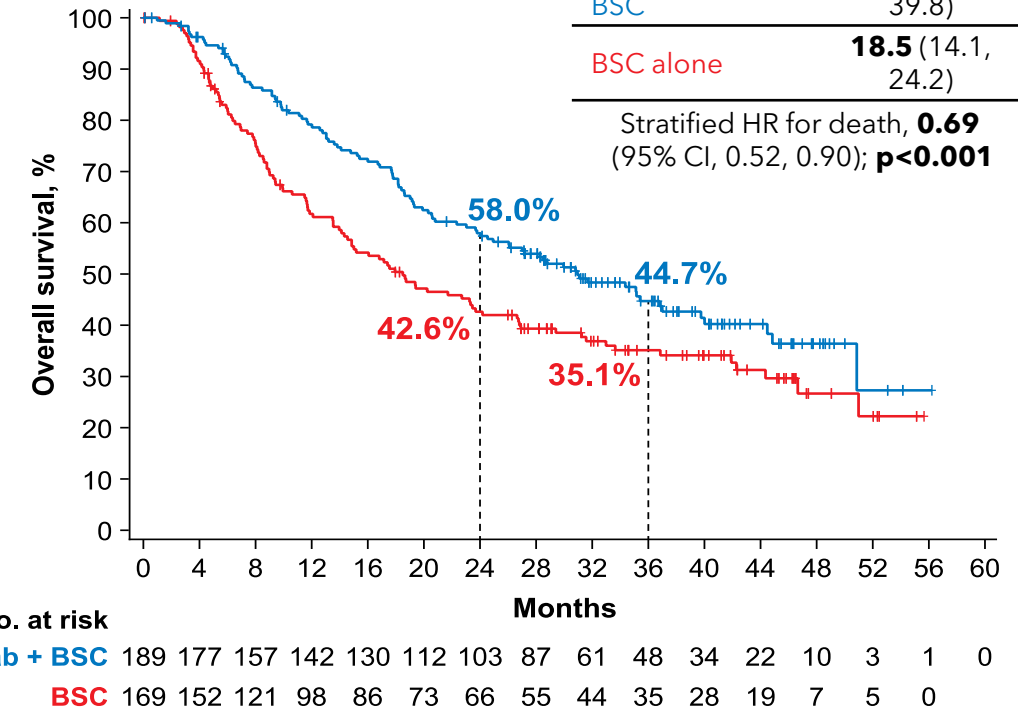
## Primary Analysis

Data Cut-off: 21st October 2019



## Long-term Analysis

Data Cut-off: 4th June 2021



**Avelumab + BSC significantly prolonged OS in patients with PD-L1-positive tumors compared with BSC alone<sup>1,\*</sup>**  
**The survival benefit with avelumab + BSC is prolonged based on long-term analysis with median follow-up of 38.0 months<sup>2</sup>**

For full definitions please refer to Powles T, et al. N Engl J Med. 2020;383(13):1218-1230.

\* OS was measured post-randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (p<0.0014).

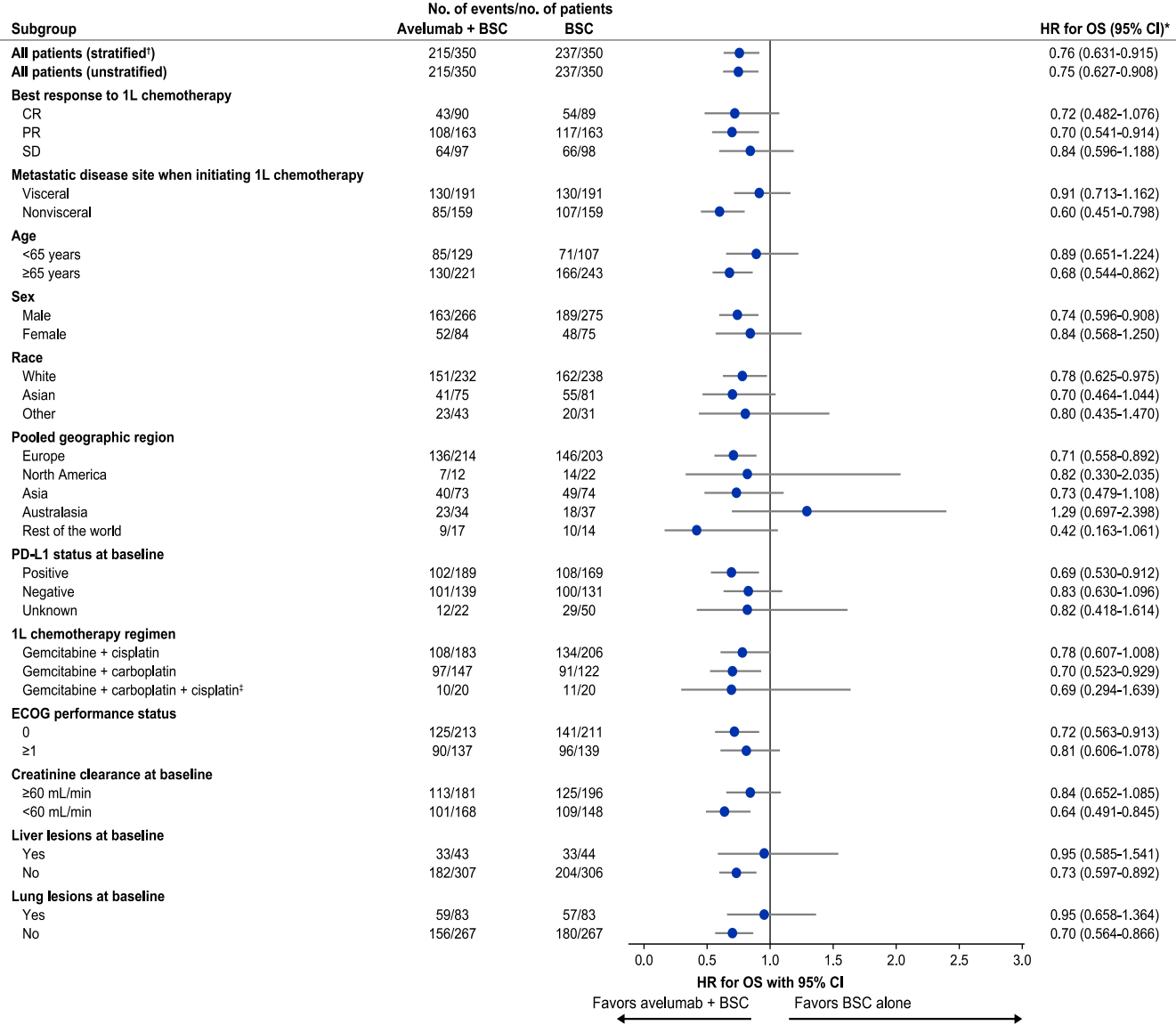
BSC, best supportive care; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1.

1. Powles T, et al. N Engl J Med. 2020;383(13):1218-1230; 2. Powles T, et al. Poster E7. Presented at: ASCO GU Symposium; February 17-19, 2022; San Francisco, CA; 3. Grivas P, et al. Abstract 704MO. Presented at: ESMO Virtual Congress; September 19-21, 2020.

# OS: Select Subgroup Analysis<sup>1</sup>

Protocol-specified subgroups in all randomized patients

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



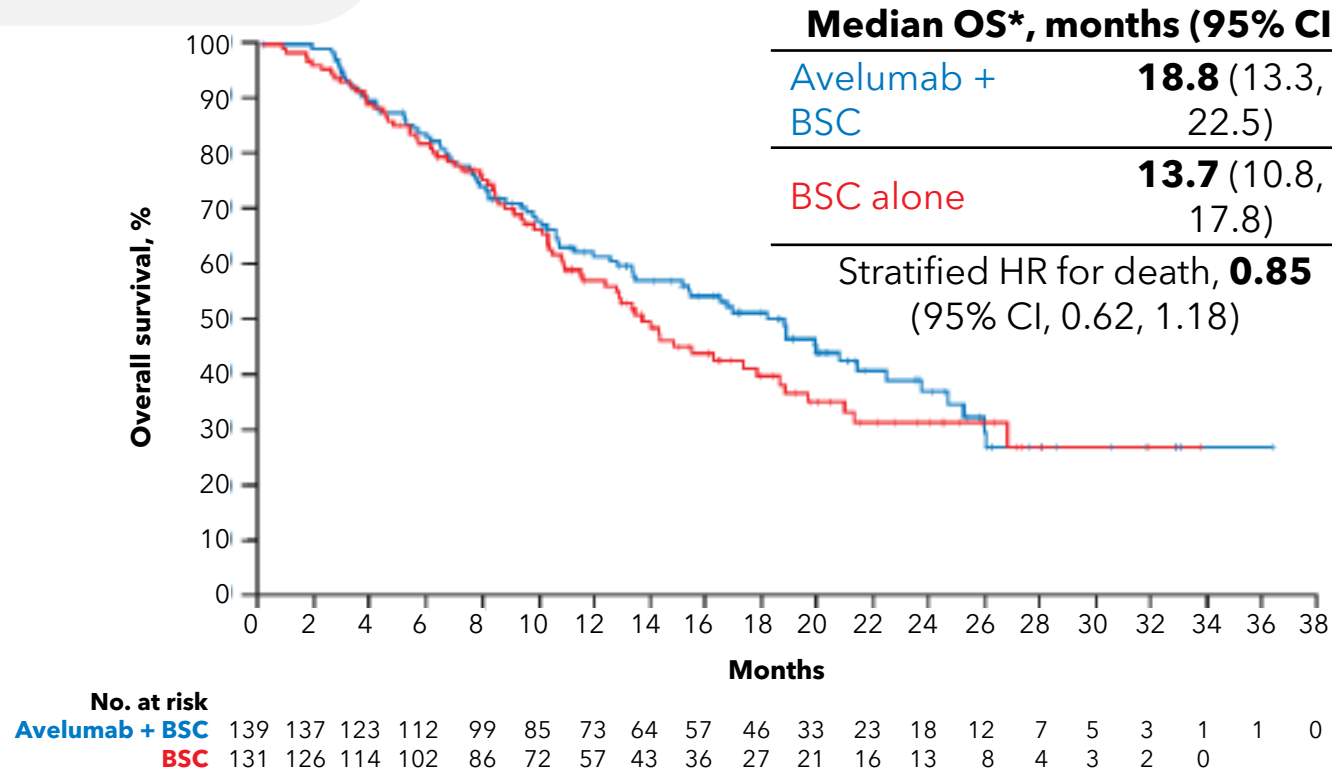
OS was longer with avelumab + BSC vs BSC alone across prespecified subgroups

\* HRs and CIs were calculated using a Cox proportional hazards model. <sup>†</sup> Patients were stratified by best response to 1L chemotherapy (CR or PR vs SD) and metastatic disease site when initiating 1L CT (visceral vs non-visceral). <sup>‡</sup> Includes patients who switched platinum regimens while receiving 1L CT. 1L, first-line; BSC, best supportive care; CI, confidence interval; CR, complete response; CT, chemotherapy; ECOG, eastern cooperative oncology group; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease. 1. Powles T, et al. Poster E7. Presented at: ASCO GU Symposium; February 17-19, 2022; San Francisco, CA.

# JAVELIN Bladder - OS in PD-L1—Negative Population<sup>1,2</sup>

## Primary Analysis

Data Cut-off: 21st  
October 2019



**Patients receiving avelumab + BSC had a 15% decrease in the risk of death vs BSC alone**

**Among patients with PD-L1-negative tumors, the stratified HR for OS was 0.85 (95% CI, 0.62-1.18); this exploratory subgroup was not part of the planned statistical analyses<sup>2</sup>**

For full definitions please refer to Powles T, et al. N Engl J Med. 2020;383(13):1218-1230.

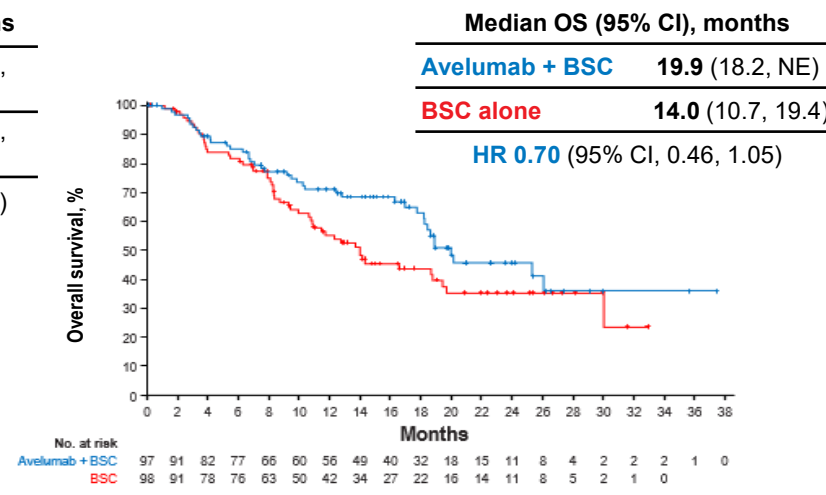
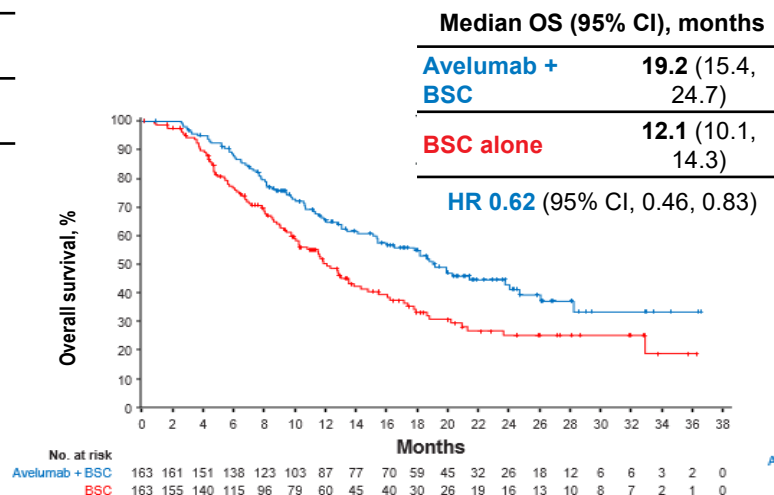
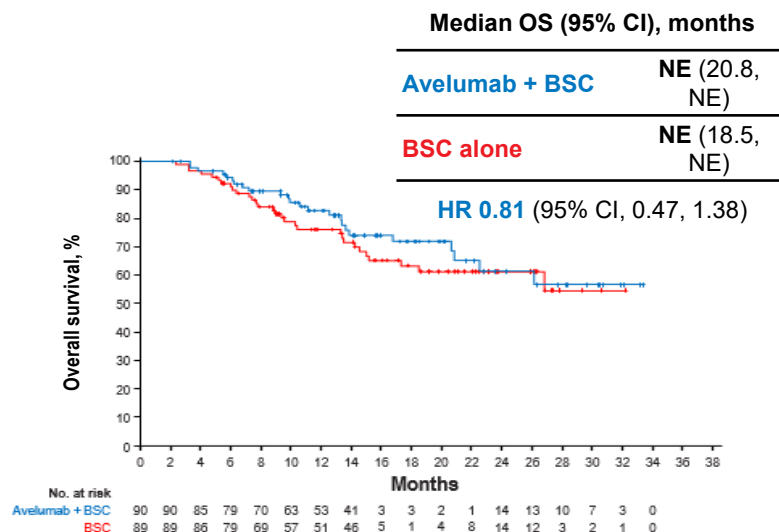
\* OS was measured post-randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function ( $p < 0.0014$ ).

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.

1. Powles T, et al. N Engl J Med. 2020;383(13):1218-1230 (suppl); 2. Powles T, et al. Abstract LBA1. Presented at: ASCO Virtual Annual Meeting; May 29-31, 2020

# Overall Survival by Best Response to 1L Platinum-Containing CT<sup>1,2</sup>

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



**OS was longer with avelumab + BSC vs BSC alone irrespective of best response to 1L platinum-containing CT regimen**

**CR**

| Median OS (95% CI), months          |                          |
|-------------------------------------|--------------------------|
| <b>Avelumab + BSC (n = 90)</b>      | <b>39.8</b> (28.5, NE)   |
| <b>BSC alone (n = 89)</b>           | <b>26.8</b> (18.5, 33.6) |
| <b>HR 0.72</b> (95% CI, 0.48, 1.38) |                          |

**PR**

| Median OS (95% CI), months          |                          |
|-------------------------------------|--------------------------|
| <b>Avelumab + BSC (n = 163)</b>     | <b>19.2</b> (16.0, 23.8) |
| <b>BSC alone (n = 163)</b>          | <b>12.8</b> (10.3, 14.8) |
| <b>HR 0.70</b> (95% CI, 0.54, 0.91) |                          |

**SD**

| Median OS (95% CI), months          |                          |
|-------------------------------------|--------------------------|
| <b>Avelumab + BSC (n = 97)</b>      | <b>22.3</b> (18.2, 28.8) |
| <b>BSC alone (n = 98)</b>           | <b>14.0</b> (10.6, 19.6) |
| <b>HR 0.84</b> (95% CI, 0.60, 1.19) |                          |

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

**In the long-term follow-up, longer OS with avelumab + BSC vs BSC alone irrespective of best response to 1L platinum-containing CT regimen was maintained**

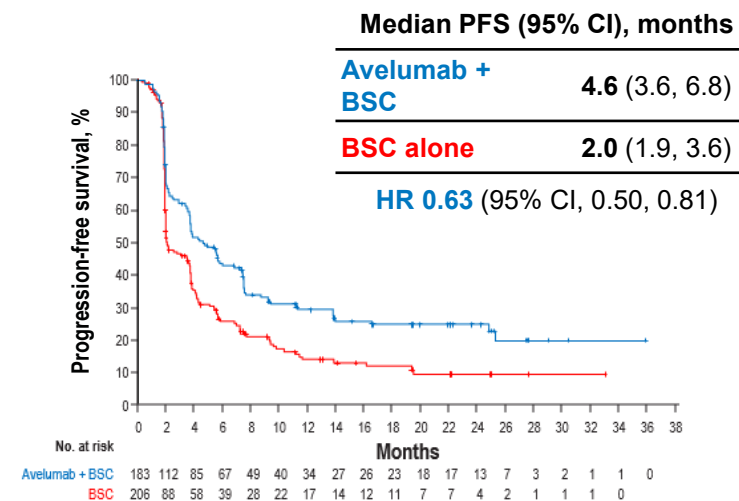
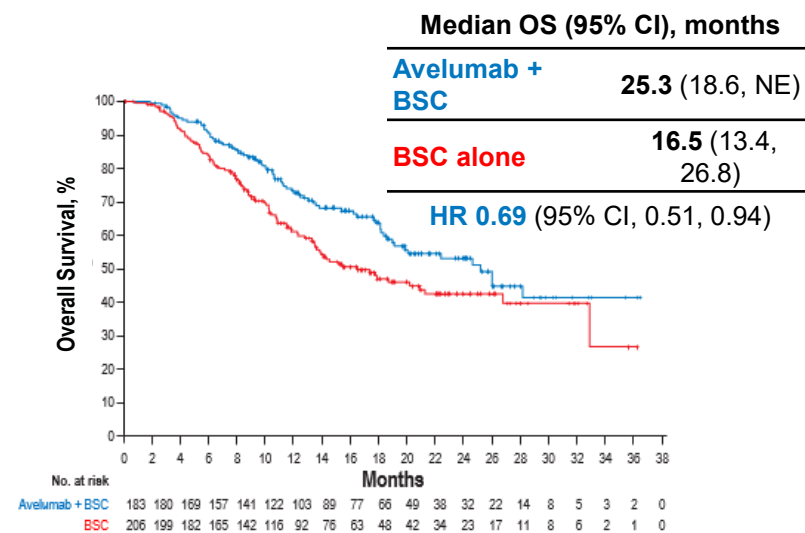
# Survival by 1L Platinum-Containing CT Regimen<sup>1</sup>

Protocol-specified subgroups in all randomized patients

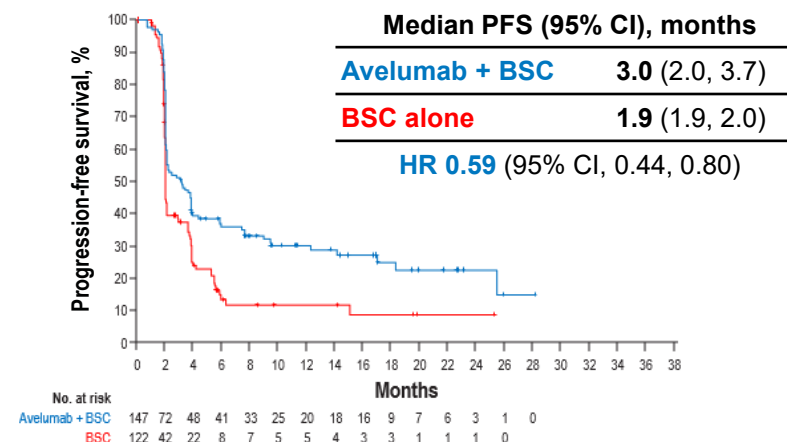
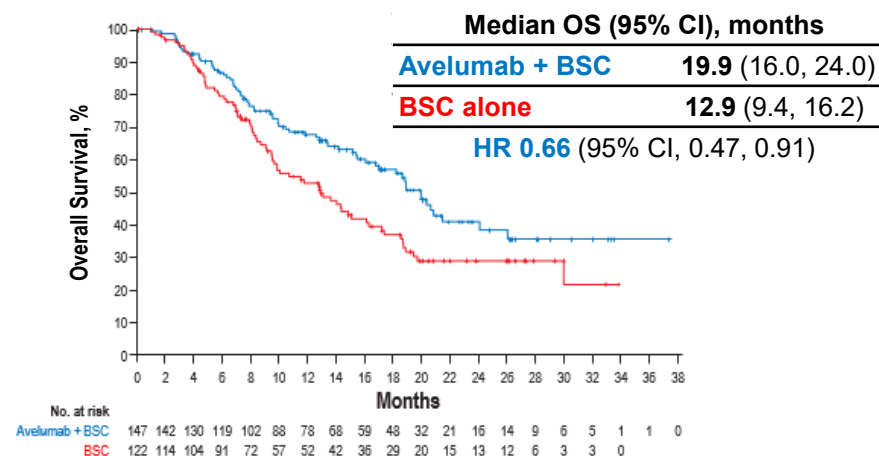
## Primary Analysis

Data Cut-off: 21st October 2019

**Gemcitabine + cisplatin  
(N = 389)**



**Gemcitabine + carboplatin (N = 269)**



**OS and PFS were prolonged with avelumab + BSC vs BSC alone irrespective of 1L CT regimen**

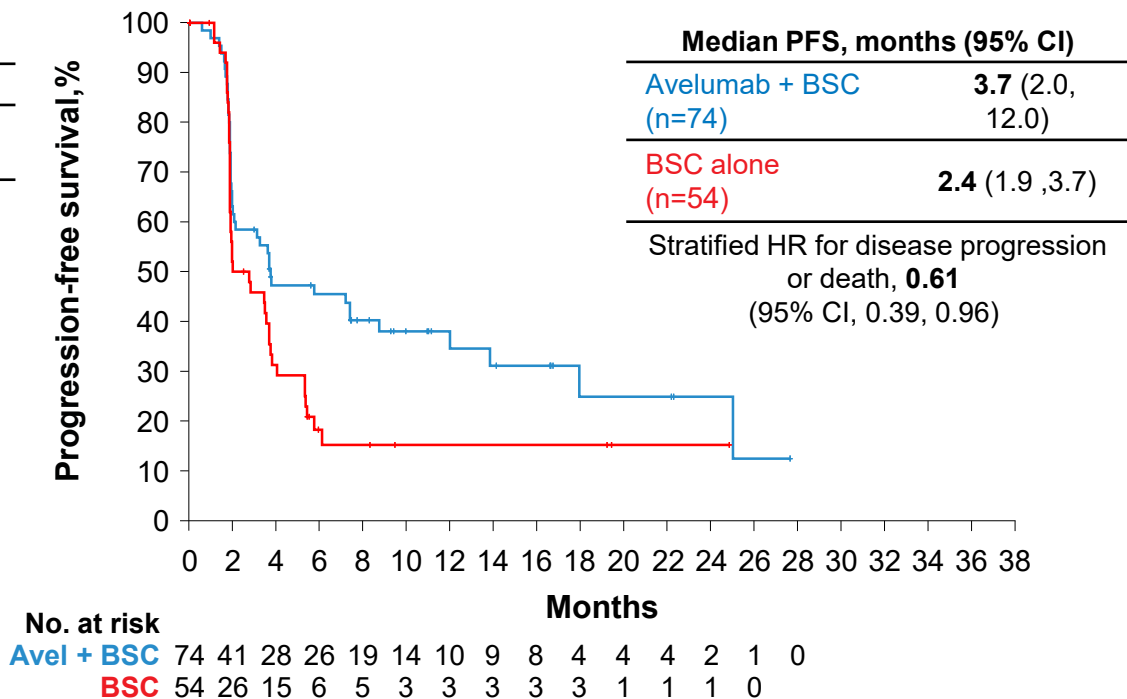
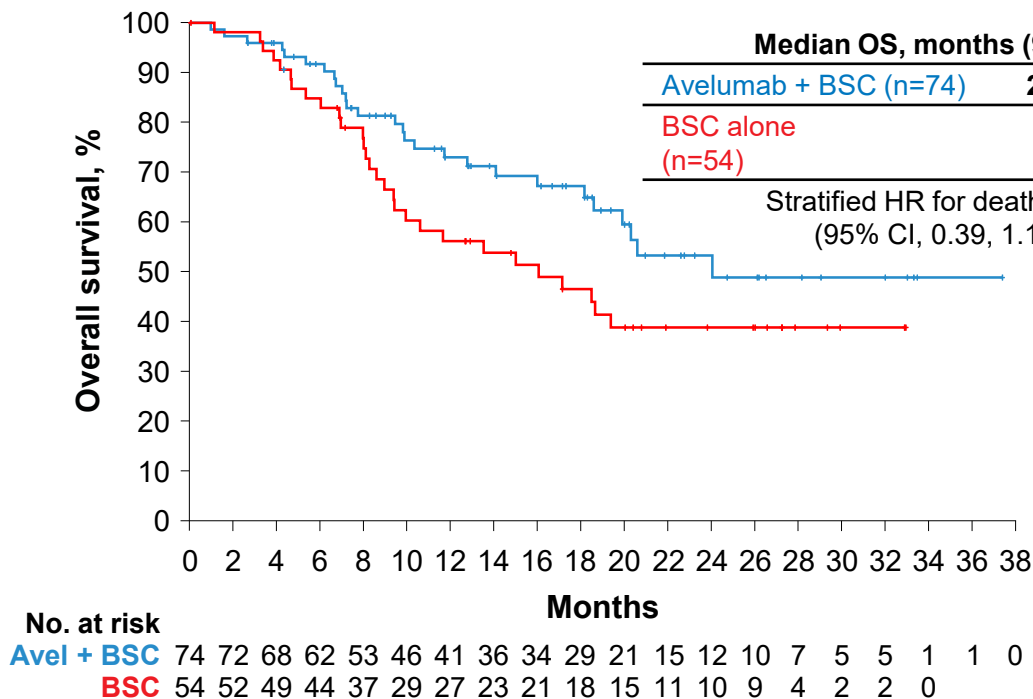
1L, first-line; BSC, best supportive care; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

1. Grivas P, et al. Abstract 704MO. Presented at: ESMO Virtual Congress; September 19-21, 2020.

# Survival Among Patients With PD-L1–Positive Tumors Who Received 1L Gemcitabine + Carboplatin<sup>1,2</sup>

## Primary Analysis

Data Cut-off: 21st October 2019



**Longer OS and PFS were observed with avelumab + BSC vs BSC alone in patients with PD-L1–positive tumors who received 1L gemcitabine + carboplatin and findings were consistent with the overall JAVELIN Bladder 100 trial population**

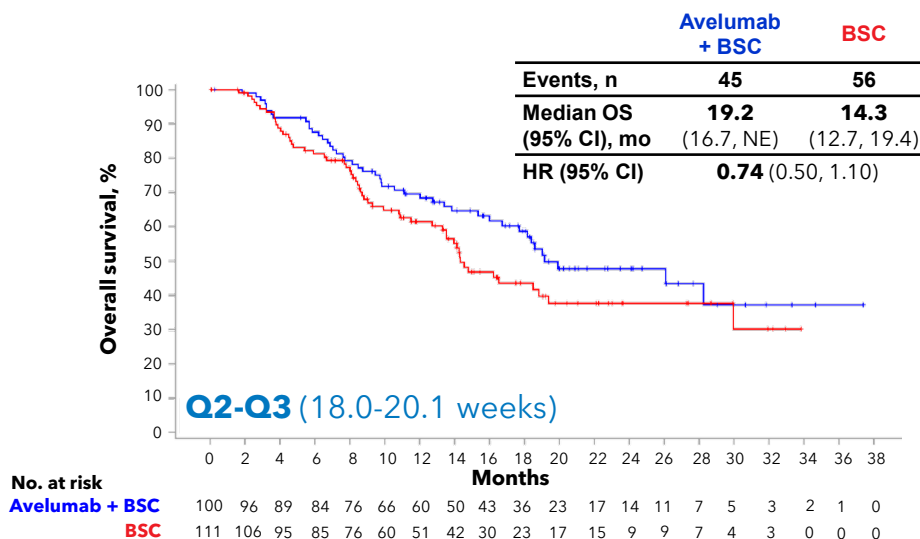
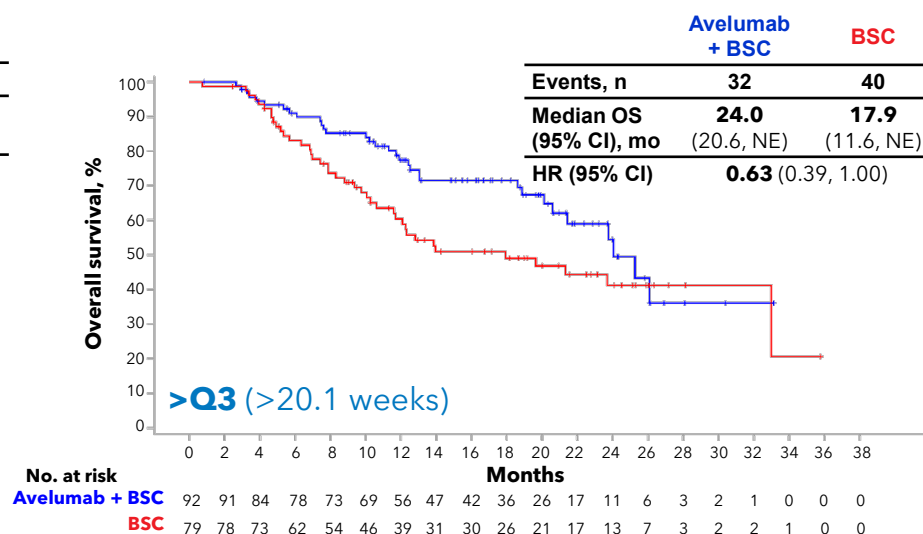
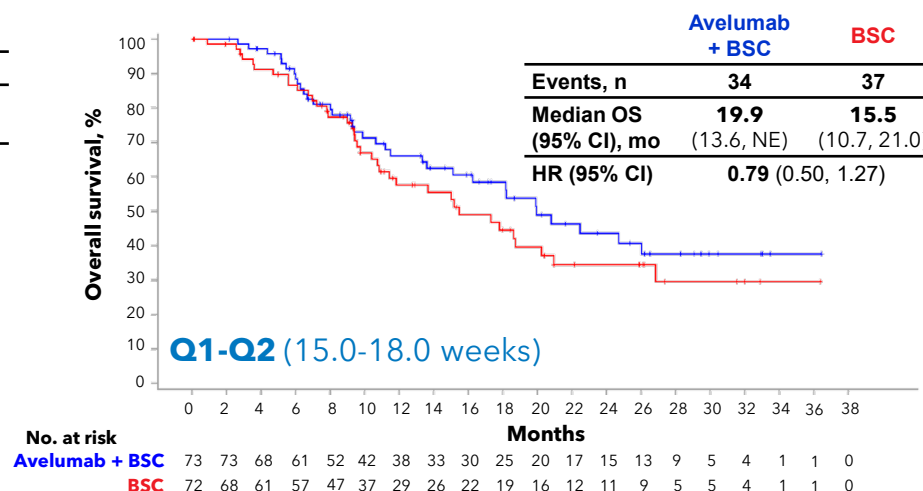
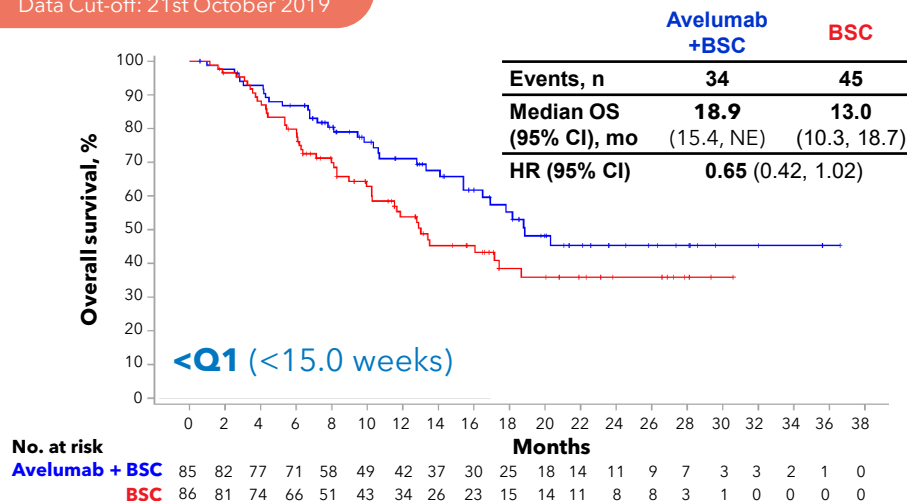
1L, first line; Avel, avelumab; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.  
1. Powles T, et al. Poster 4520. Presented at: ASCO Virtual Annual Meeting. June 4-8, 2021; 2 Powles T, et al. N Engl J Med. 2020;383(13):1218-1230.

# Survival by Duration of 1L Platinum-Containing CT<sup>1</sup>

## Post hoc analysis

### Primary Analysis

Data Cut-off: 21st October 2019



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

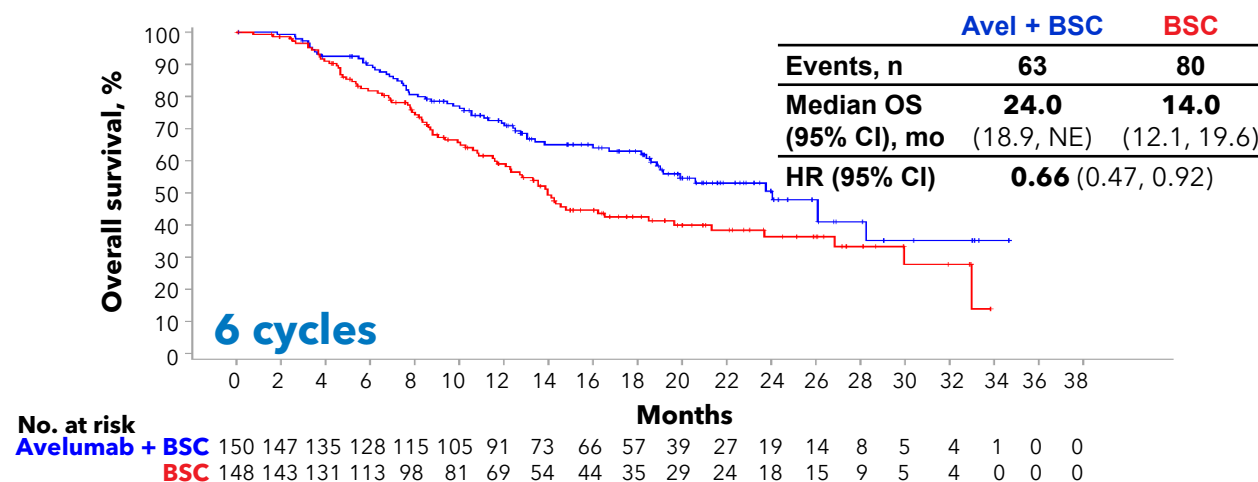
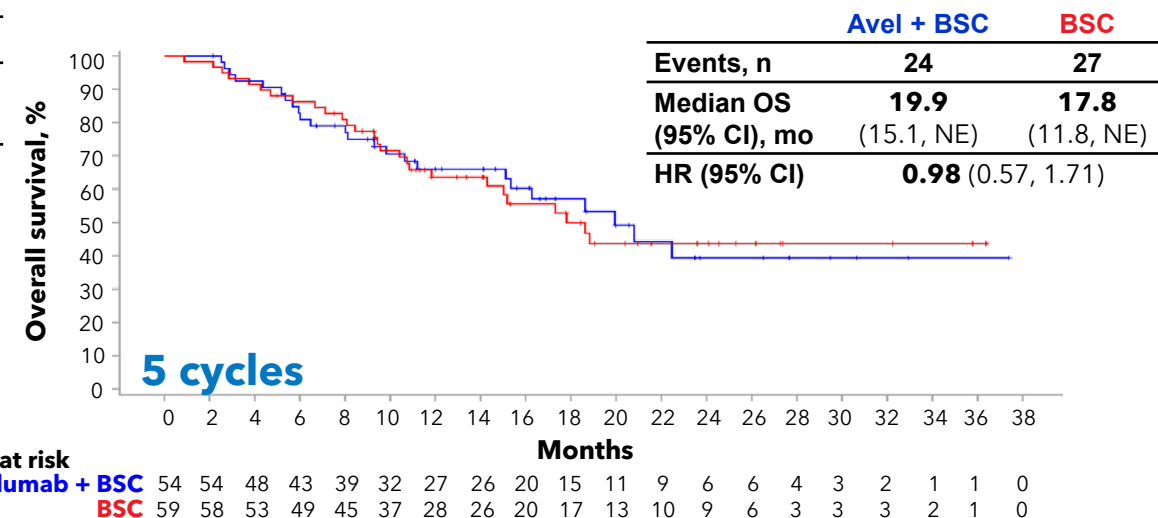
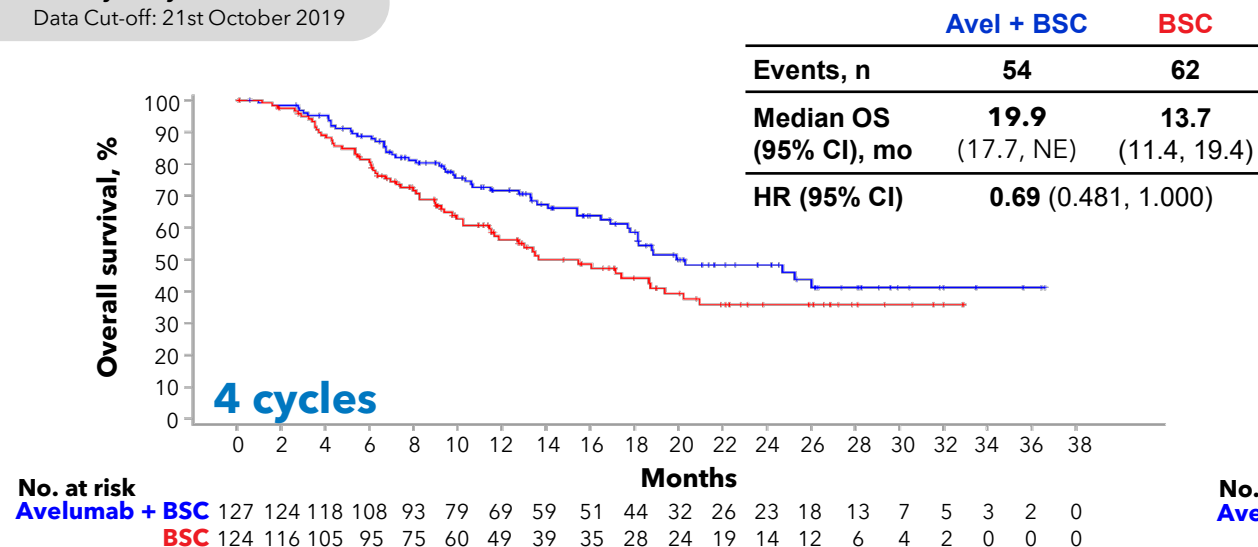
1L, first-line; Avel, avelumab; BSC, best supportive care; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; NE, not estimable; OS, overall survival; Q, quartile.  
1. Llorca Y, et al. Abstract 438. Presented at: ASCO GU Virtual Symposium; February 11-13, 2021.

# Survival by Number of 1L Platinum-Containing CT Cycles<sup>1</sup>

## Post hoc analysis

### Primary Analysis

Data Cut-off: 21st October 2019



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

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

1L, first-line; Avel, avelumab; BSC, best supportive care; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; NE, not estimable; OS, overall survival.  
1. Llorca Y, et al. Abstract 438. Presented at: ASCO GU Virtual Symposium; February 11-13, 2021.

# **Avelumab First-line (1L) Maintenance for Advanced Urothelial Carcinoma: Long-term Follow-up From the JAVELIN Bladder 100 Trial in Subgroups Defined by 1L Chemotherapy Regimen and Analysis of Overall Survival From Start of 1L Chemotherapy**

## **Prostate Cancer and Urothelial Carcinoma – Abstract No. 508 (Poster)**

S. S. Sridhar, T. Powles, S. Gupta, M. A. Climent Duran, J. B. Aragon-Ching, C. N. Sternberg, P. Cislo, N. Costa, A. di Pietro, J. Bellmunt, P. Grivas

## Avelumab First-line (1L) Maintenance for Advanced Urothelial Carcinoma: Long-term Follow-up From the JAVELIN Bladder 100 Trial in Subgroups Defined by 1L Chemotherapy Regimen and Analysis of Overall Survival From Start of 1L Chemotherapy

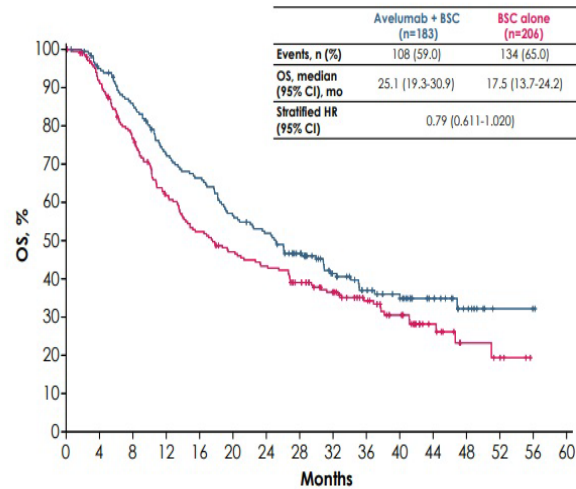
### Objective

- To report exploratory post hoc analyses of long-term outcomes from start of maintenance (randomization;  $\geq 2$  years of follow-up in all patients) in subgroups defined by 1L chemotherapy regimen from the JAVELIN Bladder 100 trial, which compared avelumab 1L maintenance + BSC in patients with advanced UC that had not progressed with 1L platinum-based chemotherapy. Additionally, OS from the start of 1L chemotherapy was analyzed in the overall population and by 1L chemotherapy regimen

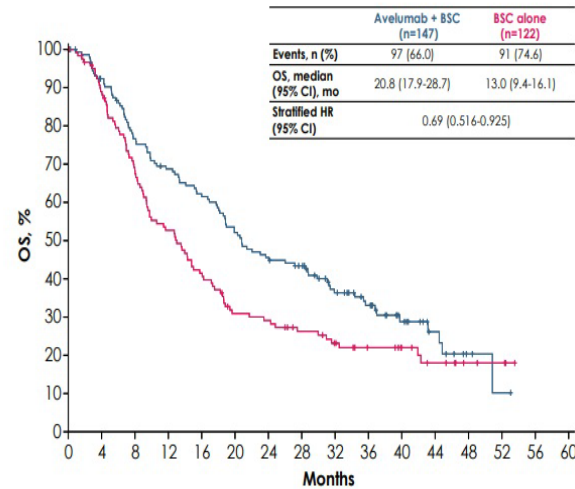
### Key Results

#### OS From the Start of Maintenance (Randomization) by 1L Chemotherapy Regimen (*Post hoc Exploratory Analyses*)

Cisplatin + gemcitabine

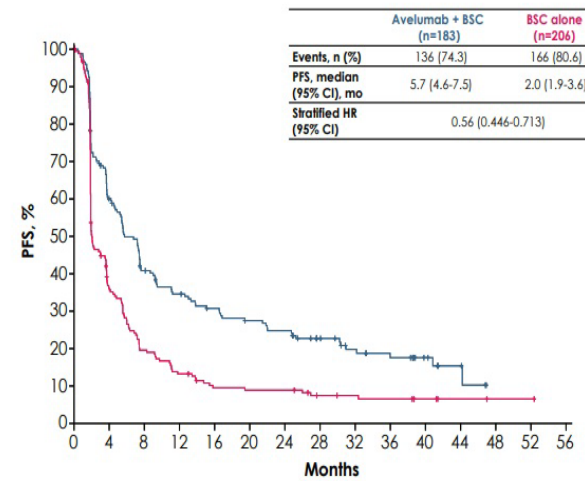


Carboplatin + gemcitabine

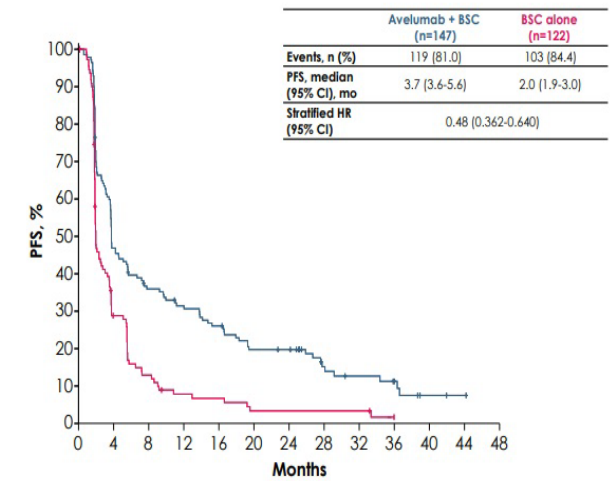


#### Investigator-assessed PFS From Start of Maintenance (Randomization) by 1L Chemotherapy Regimen (*Post hoc Exploratory Analyses*)

Cisplatin + gemcitabine



Carboplatin + gemcitabine



No. at risk

| Time (Months)  | 0   | 4   | 8   | 12  | 16  | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 |
|----------------|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|
| Avelumab + BSC | 183 | 169 | 151 | 126 | 115 | 98 | 89 | 73 | 51 | 39 | 32 | 19 | 9  | 2  | 1  |
| BSC alone      | 206 | 182 | 150 | 118 | 100 | 88 | 81 | 69 | 55 | 41 | 29 | 14 | 6  | 4  | 0  |

No. at risk

| Time (Months)  | 0   | 4   | 8   | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 |
|----------------|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|
| Avelumab + BSC | 147 | 130 | 107 | 95 | 86 | 72 | 63 | 56 | 39 | 30 | 17 | 9  | 3  | 1  | 0  |
| BSC alone      | 122 | 104 | 79  | 61 | 48 | 34 | 32 | 26 | 21 | 16 | 12 | 8  | 4  | 3  | 0  |

No. at risk

| Time (Months)  | 0   | 4   | 8  | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 |
|----------------|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Avelumab + BSC | 183 | 101 | 67 | 55 | 47 | 41 | 37 | 26 | 19 | 15 | 9  | 4  | 0  |    |    |
| BSC alone      | 206 | 63  | 34 | 23 | 15 | 14 | 14 | 9  | 8  | 7  | 4  | 2  | 1  | 1  | 0  |

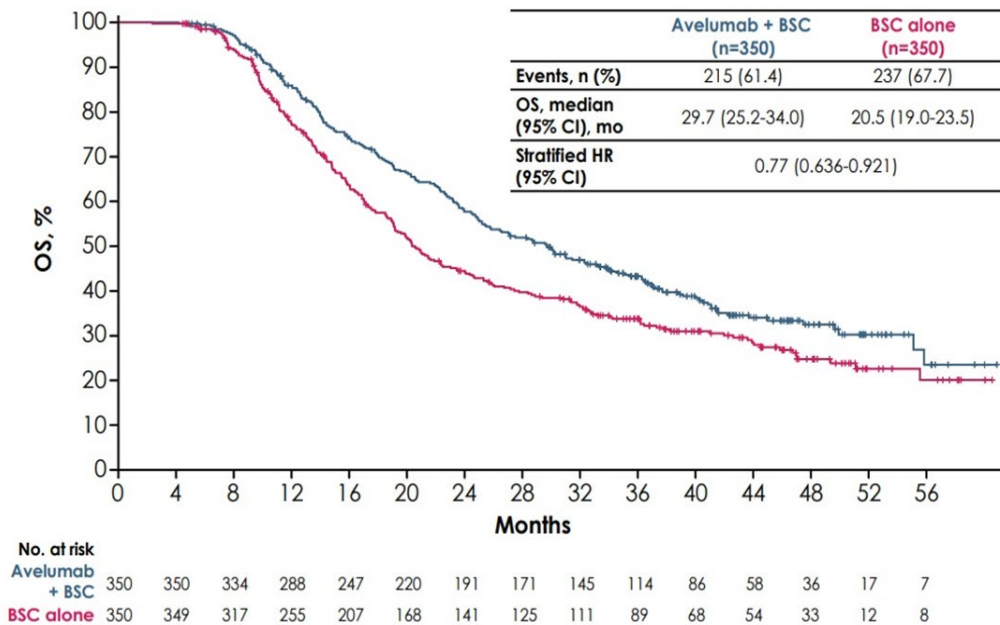
No. at risk

| Time (Months)  | 0   | 4  | 8  | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 |
|----------------|-----|----|----|----|----|----|----|----|----|----|----|----|----|
| Avelumab + BSC | 147 | 65 | 48 | 41 | 34 | 25 | 24 | 12 | 9  | 7  | 2  | 1  | 0  |
| BSC alone      | 122 | 29 | 13 | 7  | 6  | 3  | 3  | 3  | 3  | 3  | 0  |    |    |

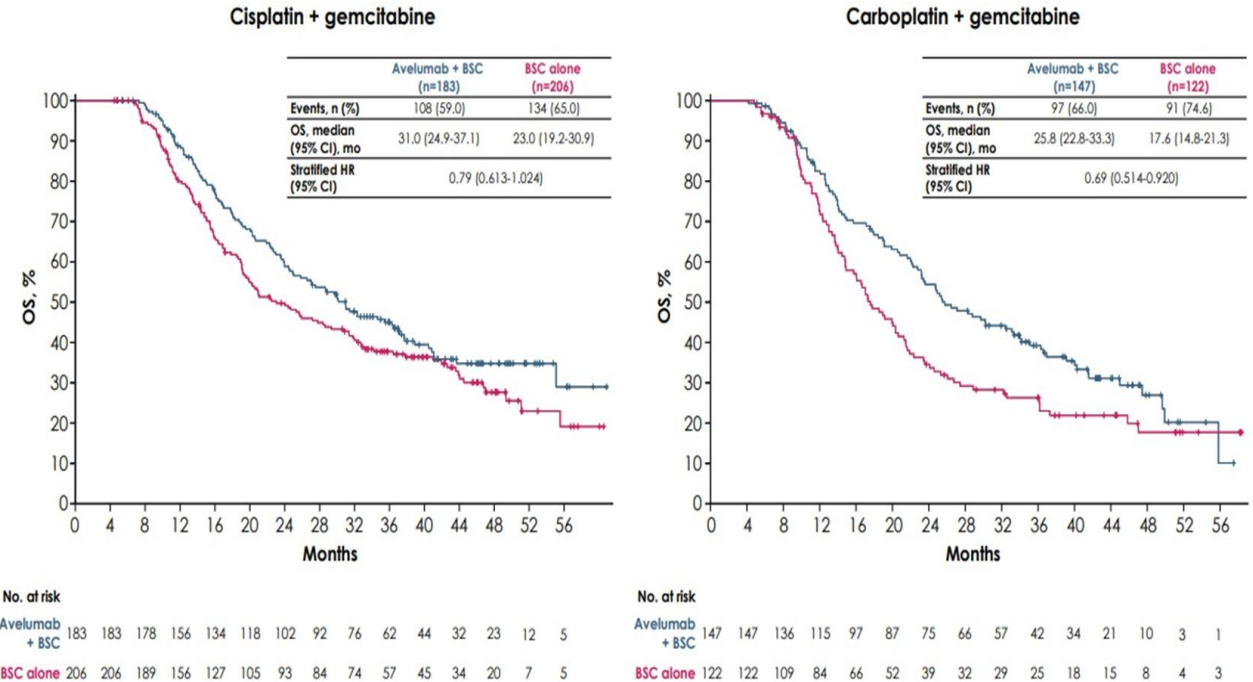
# Avelumab First-line (1L) Maintenance for Advanced Urothelial Carcinoma: Long-term Follow-up From the JAVELIN Bladder 100 Trial in Subgroups Defined by 1L Chemotherapy Regimen and Analysis of Overall Survival From Start of 1L Chemotherapy

## Key Results

### OS From the Start of 1L Chemotherapy (Post hoc Exploratory Analyses)\*,†



### OS From the Start of 1L Chemotherapy by 1L Chemotherapy Regimen (Post hoc Exploratory Analyses)\*,†



\*This analysis only includes patients who did not progress on first-line platinum-containing chemotherapy and subsequently enrolled in the JAVELIN Bladder 100 trial. Safety data are not available pre-randomization.

†This analysis is inclusive of platinum-containing chemotherapy, treatment-free interval, randomized study treatment with avelumab + BSC or BSC alone, and subsequent therapy. Therefore, no conclusions can be drawn from this OS analysis.

## Avelumab First-line (1L) Maintenance for Advanced Urothelial Carcinoma: Long-term Follow-up From the JAVELIN Bladder 100 Trial in Subgroups Defined by 1L Chemotherapy Regimen and Analysis of Overall Survival From Start of 1L Chemotherapy

### Key Results

#### Summary of Long-term Safety for Maintenance Treatment by Prior 1L Chemotherapy Regimen (Post hoc Exploratory Analyses)

| Events, n (%)                                 | Cisplatin + gemcitabine |                   | Carboplatin + gemcitabine |                   |
|-----------------------------------------------|-------------------------|-------------------|---------------------------|-------------------|
|                                               | Avelumab + BSC (n=182)  | BSC alone (n=204) | Avelumab + BSC (n=142)    | BSC alone (n=119) |
| <b>AE of any grade</b>                        | 182 (100)               | 160 (78.4)        | 136 (95.8)                | 90 (75.6)         |
| Grade ≥3 AE                                   | 92 (50.5)               | 51 (25.0)         | 82 (57.7)                 | 34 (28.6)         |
| <b>TRAE of any grade</b>                      | 147 (80.8)              | 5 (2.5)           | 107 (75.4)                | 1 (0.8)           |
| Grade ≥3 TRAE                                 | 30 (16.5)               | 0                 | 32 (22.5)                 | 0                 |
| <b>Serious AE</b>                             | 47 (25.8)               | 36 (17.6)         | 51 (35.9)                 | 31 (26.1)         |
| Serious TRAE                                  | 15 (8.2)                | 0                 | 15 (10.6)                 | 0                 |
| <b>AE leading to interruption of avelumab</b> | 80 (44.0)               | NA                | 69 (48.6)                 | NA                |
| <b>AE leading to discontinuation</b>          | 19 (10.4)               | 0                 | 27 (19.0)                 | 0                 |
| TRAE leading to discontinuation               | 16 (8.8)                | 0                 | 21 (14.8)                 | 0                 |
| <b>AE leading to death</b>                    | 3 (1.6)                 | 9 (4.4)           | 4 (2.8)                   | 12 (10.1)         |
| TRAE leading to death                         | 1 (0.5)                 | 0                 | 1 (0.7)                   | 0                 |
| <b>IRR of any grade</b>                       | 41 (22.5)               | 0                 | 27 (19.0)                 | 0                 |

- Long-term safety profile was similar in both the cisplatin + gemcitabine and carboplatin + gemcitabine subgroups
- Median duration of follow-up: ≥38.0 months

### Authors' Conclusions

- Long term follow-up from the JAVELIN Bladder 100 trial (median follow-up, ≥38.0 months) shows that avelumab 1L maintenance showed similar OS and PFS benefit in patients who received 1L cisplatin or carboplatin-based chemotherapy
  - Long-term safety of avelumab 1L maintenance was similar in patients who had received 1L cisplatin or carboplatin + gemcitabine
- In the overall population, median OS of the full JAVELIN Bladder regimen (1L cisplatin- or carboplatin-based chemotherapy followed by avelumab 1L maintenance) was 29.7 months vs 20.5 months for BSC
- These results further support avelumab 1L maintenance as standard of care in patients with aUC who are progression free following 1L platinum-based chemotherapy, and provide a benchmark for ongoing and future clinical trial outcomes

#### Limitations:

- This analysis only includes patients who did not progress on first-line platinum-containing chemotherapy and subsequently enrolled in the JAVELIN Bladder 100 trial. Safety data are not available pre-randomization
- This analysis is inclusive of platinum-containing chemotherapy, treatment-free interval, randomized study treatment with avelumab + BSC or BSC alone, and subsequent therapy. Therefore, no definitive conclusions can be drawn from this OS analysis

# JAVELIN Bladder 100: Updated Summary

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

1<sup>o</sup>

endpoint

**Long-term follow-up from JAVELIN Bladder 100 trial (≥2 years in all patients) continues to show prolongation of OS and PFS with avelumab + BSC vs BSC alone, both among all randomized patients and those with PD-L1–positive tumors<sup>1</sup>**



**OS rates at 2 years were 49.8% in the avelumab + BSC arm vs 38.4% in the BSC alone arm<sup>1</sup>  
2-year PFS rates were 23.4% vs 7.1%, respectively**



**OS was prolonged with avelumab 1L maintenance despite a high proportion of patients treated with BSC alone receiving a subsequent anticancer drug therapy (avelumab + BSC, 52.9%; BSC, 72.0%)**

Long-term OS by best response to 1L chemotherapy was prolonged in the avelumab + BSC arm vs BSC alone arm in all subgroups<sup>2</sup>:

- CR mOS: avelumab + BSC, 39.8 months; BSC, 26.8 months
- PR mOS: avelumab + BSC, 19.2 months; BSC, 12.8 months
- SD mOS: avelumab + BSC, 22.3 months; BSC, 14.0 months

2<sup>o</sup>

endpoint

**The long-term safety profile of avelumab was consistent with previous monotherapy studies<sup>3</sup> and no new safety signals were identified**



**These results further support the recommendation of avelumab 1L maintenance as standard of care for patients with advanced UC that has not progressed with 1L platinum-containing chemotherapy.<sup>1</sup> Long-term safety data and the high percentage of patients on treatment at 2 years indicate the good tolerability and feasibility of the regimen as treatment until progression**

1L, first-line; BSC, best supportive care; CR, complete response; mOS, median overall survival; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

1. Powles T, et al. Poster E7. Presented at: ASCO GU Symposium; February 17-19, 2022; San Francisco, CA; 2. Valderrama BP, et al. Poster 4559. Presented at: ASCO Hybrid Annual Meeting; June 3-7, 2022; Chicago, IL; 3. Kelly K, et al. Cancer 2018;124:2010-2017.

# Metastatski UC, ESMO PREPORUKE

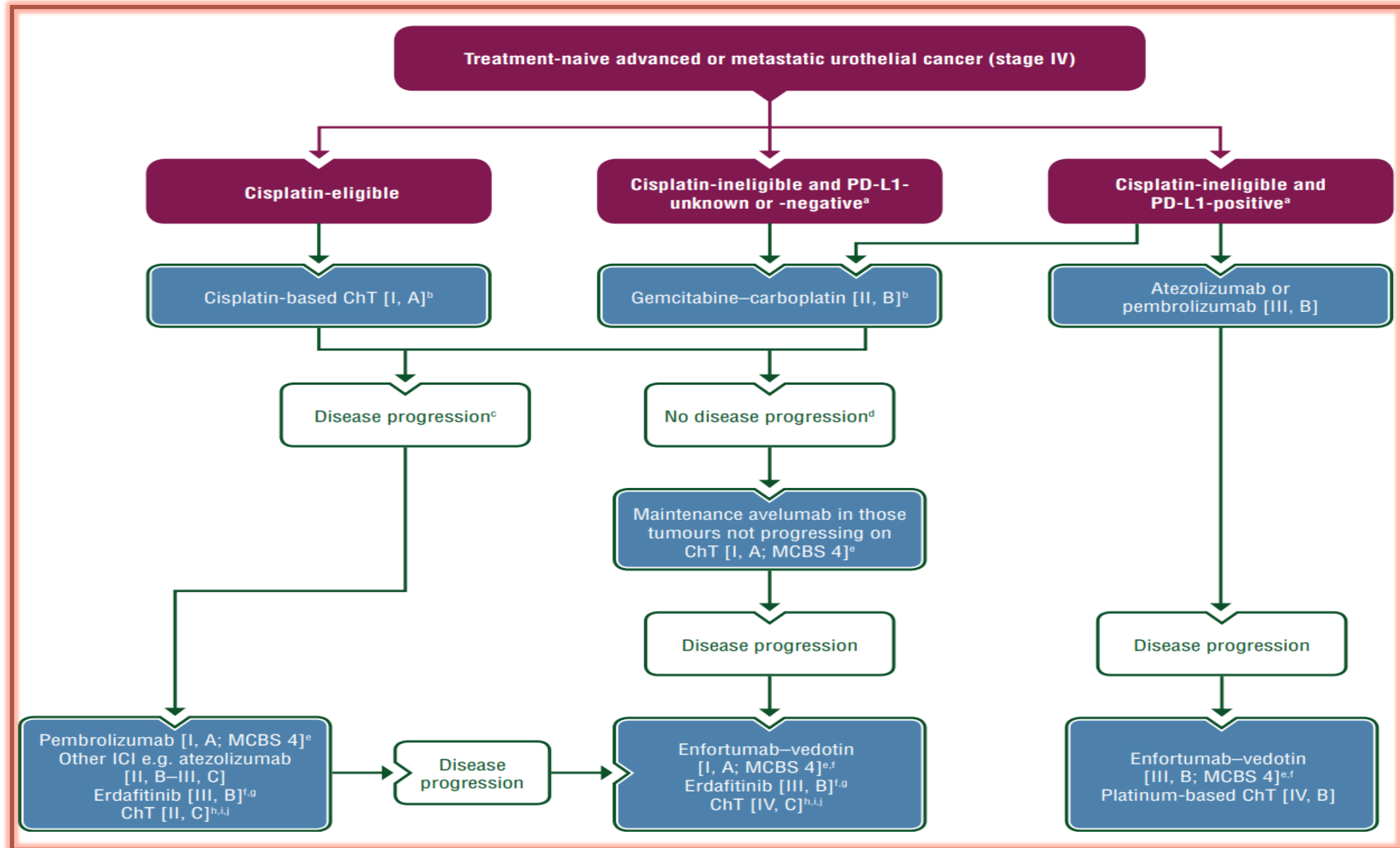
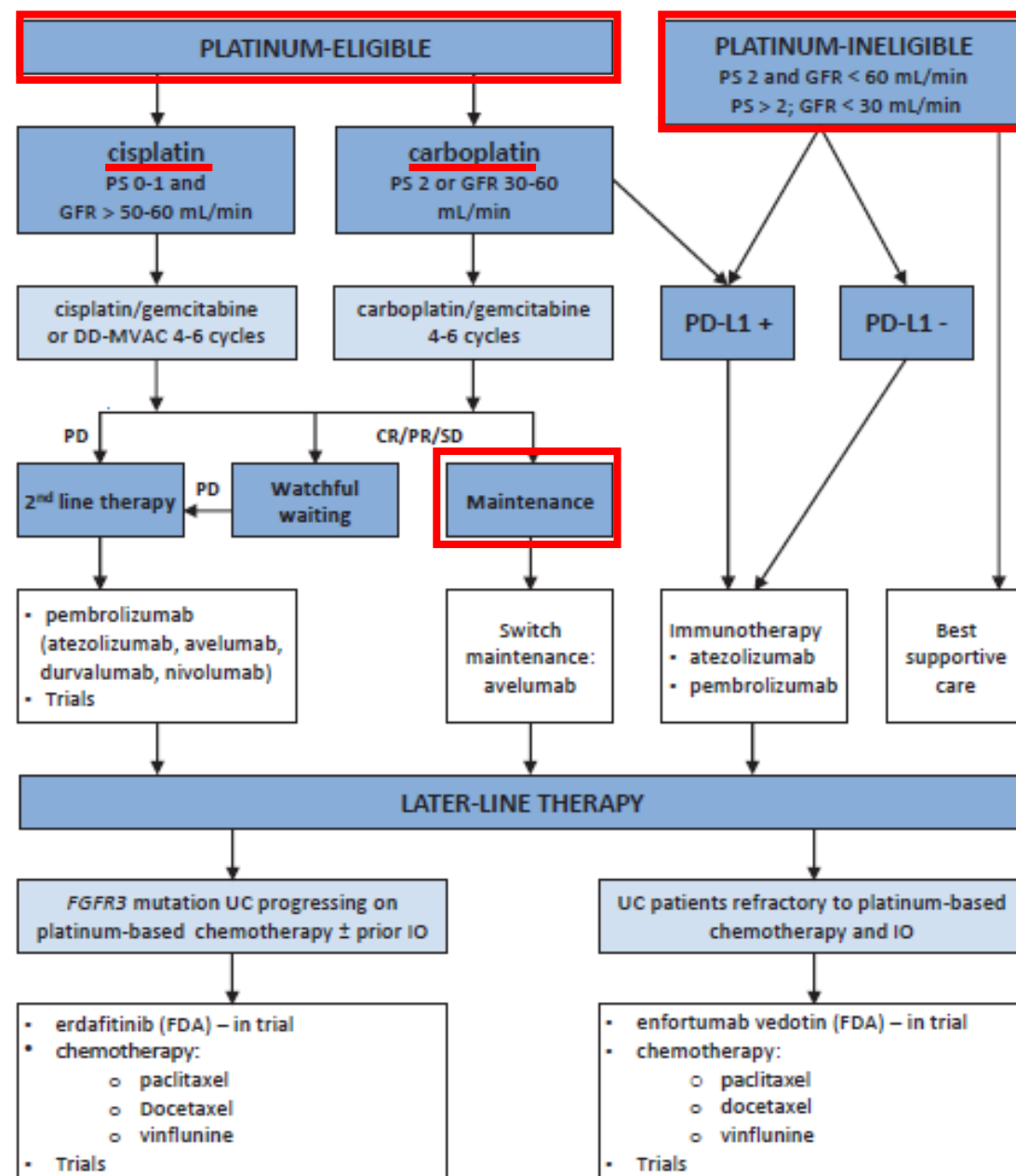


Figure 7.2: Flow chart for the management of metastatic urothelial cancer\*



# NCCN PREPORUKE

 **U.S. FOOD & DRUG**  
ADMINISTRATION

Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / FDA approves avelumab for urothelial carcinoma maintenance treatment

## FDA approves avelumab for urothelial carcinoma maintenance treatment

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Drug Approvals and Databases

Resources for Information | Approved Drugs

On June 30, 2020, the Food and Drug Administration approved avelumab (BAVENCIO, EMD Serono, Inc.) for maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

 National Comprehensive Cancer Network®

## NCCN Guidelines Version 2.2022

### Bladder Cancer

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

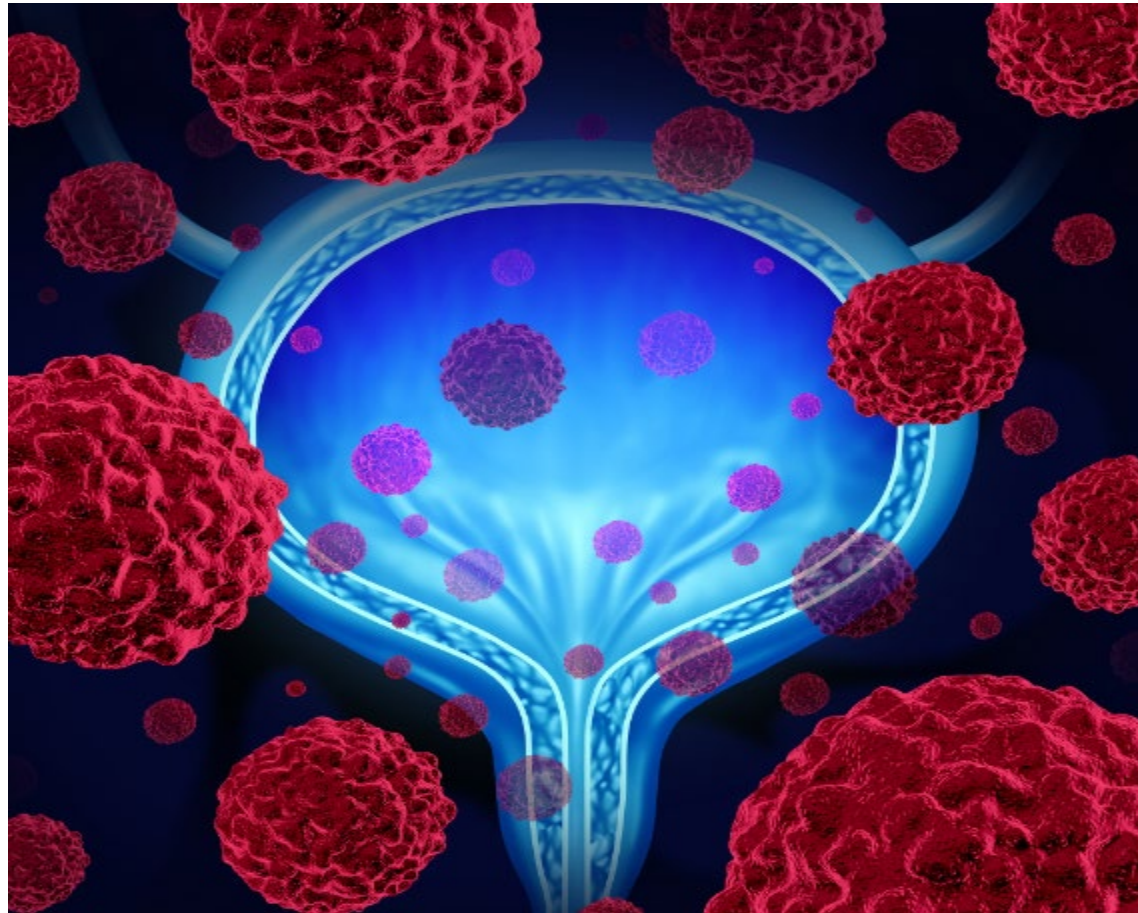
#### PRINCIPLES OF SYSTEMIC THERAPY

| First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cisplatin eligible                                                                | <b>Preferred regimens</b> <ul style="list-style-type: none"><li>Gemcitabine and cisplatin<sup>4</sup> (category 1) followed by avelumab maintenance therapy (category 1)<sup>a,11</sup></li><li>DDMVAC with growth factor support (category 1)<sup>2,8</sup> followed by avelumab maintenance therapy (category 1)<sup>a,11</sup></li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Cisplatin ineligible                                                              | <b>Preferred regimens</b> <ul style="list-style-type: none"><li>Gemcitabine and carboplatin<sup>12</sup> followed by avelumab maintenance therapy (category 1)<sup>a,11</sup></li><li>Atezolizumab<sup>13</sup> (only for patients whose tumors express PD-L1<sup>10</sup> or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)</li><li>Pembrolizumab<sup>14</sup> (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)</li></ul> <b>Other recommended regimens</b> <ul style="list-style-type: none"><li>Gemcitabine<sup>15</sup></li><li>Gemcitabine and paclitaxel<sup>16</sup></li></ul> <b>Useful under certain circumstances</b> <ul style="list-style-type: none"><li>Ifosfamide, doxorubicin, and gemcitabine<sup>17</sup> (for patients with good kidney function and good PS)</li></ul> |

<https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumab-urothelial-carcinoma-maintenance-treatment>

<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417>; accessed Novemb 2022

**Hvala na pažnji !**





# GU ASCO 2023: najnoviji naučni rezultati Real World Data studija o primeni IO terapije u lečenju metastatskog urotelijalnog karcinoma

PROF. DR LAZAR POPOVIĆ

INSTITUT ZA ONKOLOGIJU VOJVODINE

On-line KME „Najnovija saznanja o lečenju Urotelijalnog Karcinoma i preporuke“

## **Avelumab First-line (1L) Maintenance for Advanced Urothelial Carcinoma: Long-term Follow-up From the JAVELIN Bladder 100 Trial in Subgroups Defined by 1L Chemotherapy Regimen and Analysis of Overall Survival From Start of 1L Chemotherapy**

### **Prostate Cancer and Urothelial Carcinoma — Abstract No. 508 (Poster)**

S. S. Sridhar, T. Powles, S. Gupta, M. A. Climent Duran, J. B. Aragon-Ching, C. N. Sternberg, P. Cislo, N. Costa, A. di Pietro, J. Bellmunt, P. Grivas

# Avelumab First-line (1L) Maintenance for Advanced Urothelial Carcinoma: Long-term Follow-up From the JAVELIN Bladder 100 Trial in Subgroups Defined by 1L Chemotherapy Regimen and Analysis of Overall Survival From Start of 1L Chemotherapy

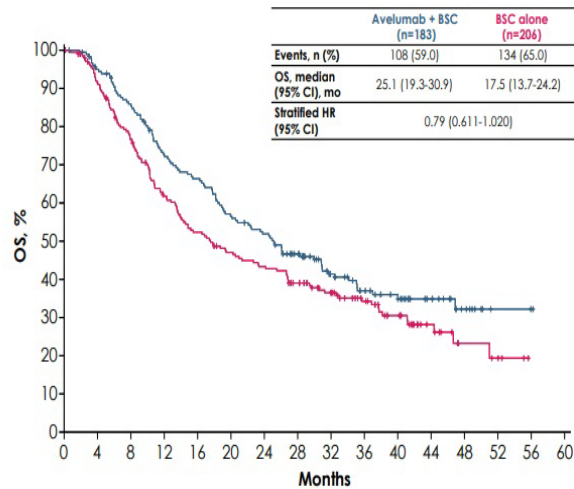
## Objective

- To report exploratory post hoc analyses of long-term outcomes from start of maintenance (randomization;  $\geq 2$  years of follow-up in all patients) in subgroups defined by 1L chemotherapy regimen from the JAVELIN Bladder 100 trial, which compared avelumab 1L maintenance + BSC in patients with advanced UC that had not progressed with 1L platinum-based chemotherapy. Additionally, OS from the start of 1L chemotherapy was analyzed in the overall population and by 1L chemotherapy regimen

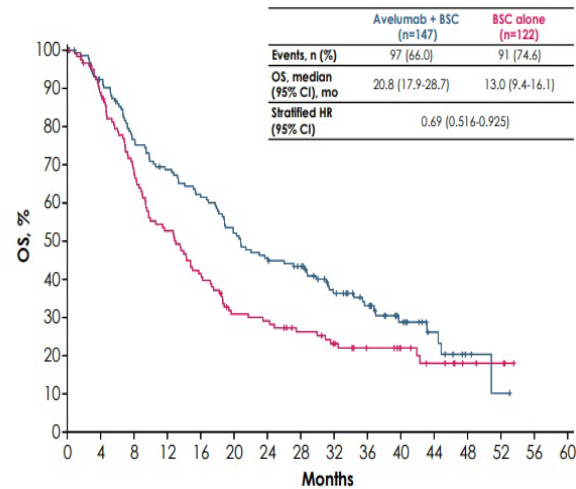
## Key Results

### OS From the Start of Maintenance (Randomization) by 1L Chemotherapy Regimen (Post hoc Exploratory Analyses)

Cisplatin + gemcitabine



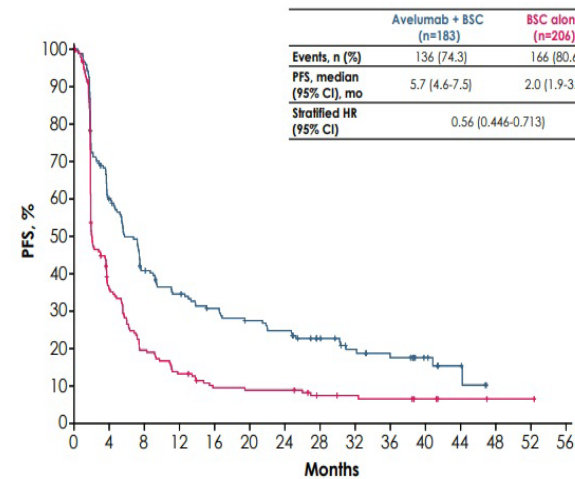
Carboplatin + gemcitabine



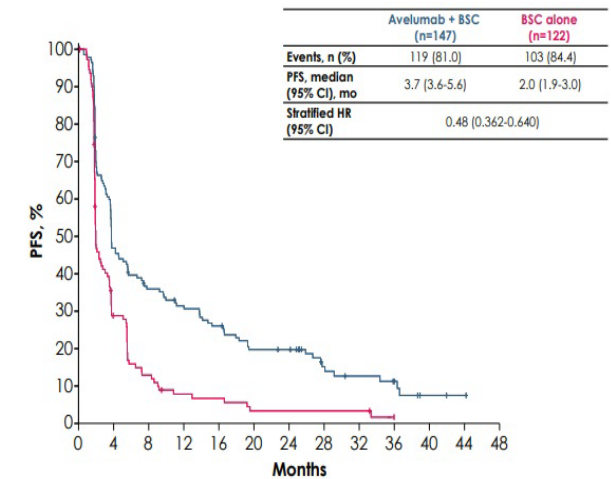
|                |  |     |     |     |     |     |    |    |    |    |    |    |    |   |   |   |   |  |  |
|----------------|--|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|---|---|---|---|--|--|
| No. at risk    |  |     |     |     |     |     |    |    |    |    |    |    |    |   |   |   |   |  |  |
| Avelumab + BSC |  | 183 | 169 | 151 | 126 | 115 | 98 | 89 | 73 | 51 | 39 | 32 | 19 | 9 | 2 | 1 | 0 |  |  |
| BSC alone      |  | 206 | 182 | 150 | 118 | 100 | 88 | 81 | 69 | 55 | 41 | 29 | 14 | 6 | 4 | 0 | 0 |  |  |

### Investigator-assessed PFS From Start of Maintenance (Randomization) by 1L Chemotherapy Regimen (Post hoc Exploratory Analyses)

Cisplatin + gemcitabine



Carboplatin + gemcitabine

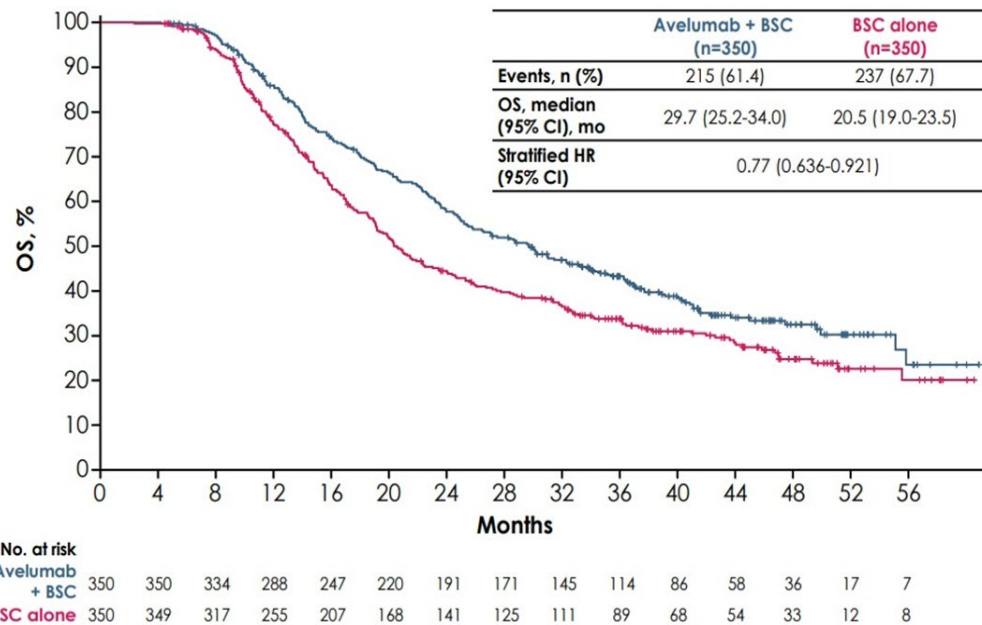


|                |  |     |     |    |    |    |    |    |    |    |    |   |   |   |   |   |  |  |  |
|----------------|--|-----|-----|----|----|----|----|----|----|----|----|---|---|---|---|---|--|--|--|
| No. at risk    |  |     |     |    |    |    |    |    |    |    |    |   |   |   |   |   |  |  |  |
| Avelumab + BSC |  | 183 | 101 | 67 | 55 | 47 | 41 | 37 | 26 | 19 | 15 | 9 | 4 | 0 |   |   |  |  |  |
| BSC alone      |  | 206 | 63  | 34 | 23 | 15 | 14 | 14 | 9  | 8  | 7  | 4 | 2 | 1 | 1 | 0 |  |  |  |

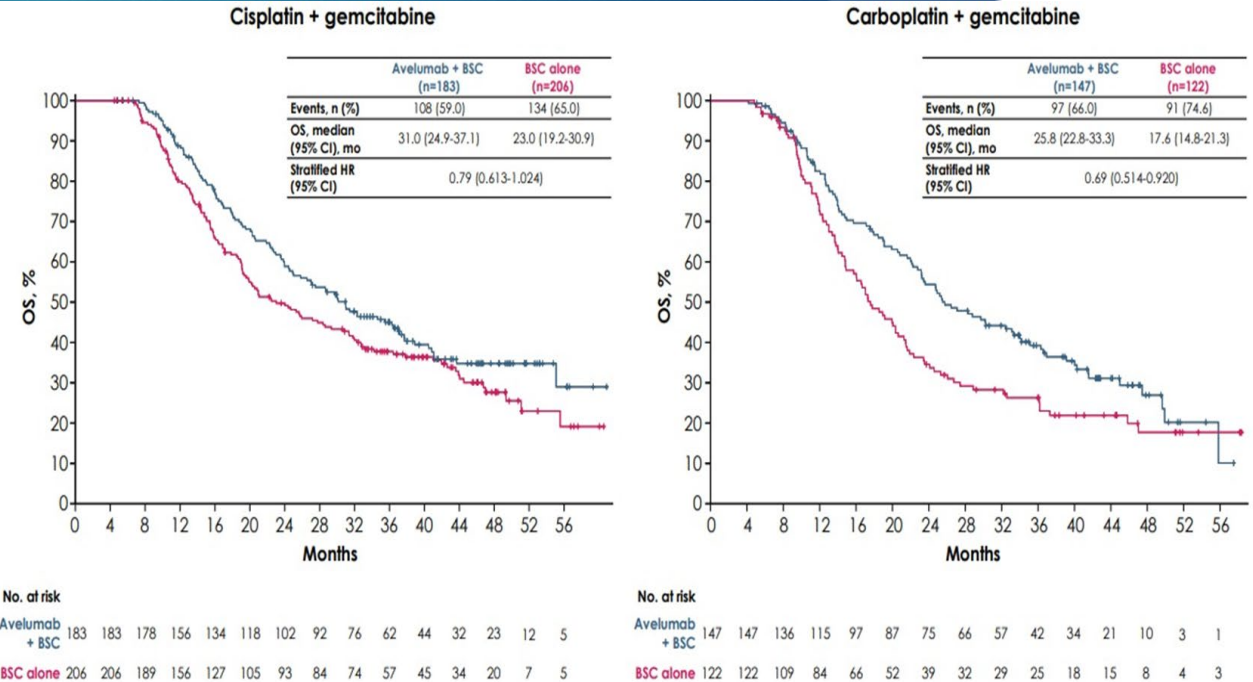
# Avelumab First-line (1L) Maintenance for Advanced Urothelial Carcinoma: Long-term Follow-up From the JAVELIN Bladder 100 Trial in Subgroups Defined by 1L Chemotherapy Regimen and Analysis of Overall Survival From Start of 1L Chemotherapy

## Key Results

### OS From the Start of 1L Chemotherapy (Post hoc Exploratory Analyses)\*,†



### OS From the Start of 1L Chemotherapy by 1L Chemotherapy Regimen (Post hoc Exploratory Analyses)\*,†



\*This analysis only includes patients who did not progress on first-line platinum-containing chemotherapy and subsequently enrolled in the JAVELIN Bladder 100 trial. Safety data are not available pre-randomization.

†This analysis is inclusive of platinum-containing chemotherapy, treatment-free interval, randomized study treatment with avelumab + BSC or BSC alone, and subsequent therapy. Therefore, no conclusions can be drawn from this OS analysis.

# Avelumab First-line (1L) Maintenance for Advanced Urothelial Carcinoma: Long-term Follow-up From the JAVELIN Bladder 100 Trial in Subgroups Defined by 1L Chemotherapy Regimen and Analysis of Overall Survival From Start of 1L Chemotherapy

## Key Results

### Summary of Long-term Safety for Maintenance Treatment by Prior 1L Chemotherapy Regimen (Post hoc Exploratory Analyses)

| Events, n (%)                                 | Cisplatin + gemcitabine |                   | Carboplatin + gemcitabine |                   |
|-----------------------------------------------|-------------------------|-------------------|---------------------------|-------------------|
|                                               | Avelumab + BSC (n=182)  | BSC alone (n=204) | Avelumab + BSC (n=142)    | BSC alone (n=119) |
| <b>AE of any grade</b>                        | 182 (100)               | 160 (78.4)        | 136 (95.8)                | 90 (75.6)         |
| Grade ≥3 AE                                   | 92 (50.5)               | 51 (25.0)         | 82 (57.7)                 | 34 (28.6)         |
| <b>TRAE of any grade</b>                      | 147 (80.8)              | 5 (2.5)           | 107 (75.4)                | 1 (0.8)           |
| Grade ≥3 TRAE                                 | 30 (16.5)               | 0                 | 32 (22.5)                 | 0                 |
| <b>Serious AE</b>                             | 47 (25.8)               | 36 (17.6)         | 51 (35.9)                 | 31 (26.1)         |
| Serious TRAE                                  | 15 (8.2)                | 0                 | 15 (10.6)                 | 0                 |
| <b>AE leading to interruption of avelumab</b> | 80 (44.0)               | NA                | 69 (48.6)                 | NA                |
| <b>AE leading to discontinuation</b>          | 19 (10.4)               | 0                 | 27 (19.0)                 | 0                 |
| TRAE leading to discontinuation               | 16 (8.8)                | 0                 | 21 (14.8)                 | 0                 |
| <b>AE leading to death</b>                    | 3 (1.6)                 | 9 (4.4)           | 4 (2.8)                   | 12 (10.1)         |
| TRAE leading to death                         | 1 (0.5)                 | 0                 | 1 (0.7)                   | 0                 |
| <b>IRR of any grade</b>                       | 41 (22.5)               | 0                 | 27 (19.0)                 | 0                 |

- ▶ Long-term safety profile was similar in both the cisplatin + gemcitabine and carboplatin + gemcitabine subgroups
- ▶ Median duration of follow-up: ≥38.0 months

## Authors' Conclusions

- Long term follow-up from the JAVELIN Bladder 100 trial (median follow-up, ≥38.0 months) shows that avelumab 1L maintenance showed similar OS and PFS benefit in patients who received 1L cisplatin or carboplatin-based chemotherapy
  - Long-term safety of avelumab 1L maintenance was similar in patients who had received 1L cisplatin or carboplatin + gemcitabine
- In the overall population, median OS of the full JAVELIN Bladder regimen (1L cisplatin- or carboplatin-based chemotherapy followed by avelumab 1L maintenance) was 29.7 months vs 20.5 months for BSC
- These results further support avelumab 1L maintenance as standard of care in patients with aUC who are progression free following 1L platinum-based chemotherapy, and provide a benchmark for ongoing and future clinical trial outcomes

### Limitations:

- This analysis only includes patients who did not progress on first-line platinum-containing chemotherapy and subsequently enrolled in the JAVELIN Bladder 100 trial. Safety data are not available pre-randomization
- This analysis is inclusive of platinum-containing chemotherapy, treatment-free interval, randomized study treatment with avelumab + BSC or BSC alone, and subsequent therapy. Therefore, no definitive conclusions can be drawn from this OS analysis

## **Baseline Characteristics From a Retrospective, Observational, US-based, Multicenter, Real-world Study of Avelumab First-line Maintenance in Locally Advanced/Metastatic Urothelial Carcinoma (la/mUC) (PATRIOT-II)**

### **Prostate Cancer and Urothelial Carcinoma — Abstract No. 465 (Poster)**

P. Grivas, P. Barata, H. Moon, T. Hutson, S. Gupta, C. N. Sternberg, V. Dave, C. Downey, A. C. Shillington, G. Devgan, M. Kirker, S. Thakkar, H. M. Katzenstein, A. Bhanegaonkar, F. X. Liu, J. Brown, G. P. Sonpavde

# Baseline Characteristics From a Retrospective, Observational, US-based, Multicenter, Real-world Study of Avelumab First-line Maintenance in Locally Advanced/Metastatic Urothelial Carcinoma (la/mUC) (PATRIOT-II)

## Objective

This study aims to examine real-world patient characteristics, treatment patterns and clinical outcomes in an observational cohort of patients with la/mUC that had not progressed on 1L PBC and who proceeded to receive avelumab as 1LM. This is an analysis of baseline data at the start of 1L PBC

## Key Results

### PBC Administered, Response, Discontinuations, and HCRU

|                                                                          | Patients (N=160) |
|--------------------------------------------------------------------------|------------------|
| No. of cycles, median (IQR)*                                             | 5 (3-6)          |
| Duration of PBC, median (IQR), weeks                                     | 13 (10-17)       |
| PBC administered, n (%)                                                  |                  |
| Cisplatin based                                                          | 100 (62.5)       |
| Carboplatin based                                                        | 60 (37.5)        |
| Best observed response, n (%)                                            |                  |
| Complete                                                                 | 21 (13)          |
| Partial                                                                  | 109 (68)         |
| Stable disease                                                           | 17 (11)          |
| Unknown                                                                  | 13 (8)           |
| Time to first imaging from treatment initiation, median (IQR), weeks     | 10 (5-14)        |
| PBC discontinued due to unacceptable adverse effects, n (%) <sup>†</sup> | 18 (11)          |
| Hospitalization during PBC treatment period, n (%)                       | 23 (14)          |
| Emergency department visit during PBC treatment period, n (%)            | 25 (16)          |

### ► Patient (N=160) baseline characteristics:

- 44 (28%) had positive PD-L1 tumors
- At PBC initiation, 119 patients (74%) had metastatic disease, with lymph nodes, bone, and lung being the most common metastatic sites
- 121 patients (76%) had an ECOG PS of 0-1

### ► 1L PBC: Cisplatin-based in 100 (63%) of patients and carboplatin-based in 60 (38%). Patients received a median of 5 PBC cycles (IQR, 3-6 cycles) for a median of 13 weeks (IQR, 10-17 weeks)

### ► Best observed response: Complete response in 21 patients (13%), partial response in 109 (68%), and stable disease in 17 (11%), with response unknown in 13 (8%). Median time to first imaging was 10 weeks (IQR, 5-14 weeks) after PBC initiation

### ► 23 patients (14%) were hospitalized while receiving PBC, and 25 (16%) were seen in the emergency department

### ► Patients proceeded to avelumab 1LM at a median of 4 weeks (IQR, 3-6 weeks) following PBC completion. Avelumab was administered every 2 weeks at 800 mg in 130 patients (81%), 10 mg/kg in 15 (9%), <800 mg in 8 (5%), and >800 mg in 7 (4%)

<sup>\*\*</sup>Carboplatin median, 5 cycles; cisplatin median, 4 cycles. <sup>†</sup>Despite discontinuing due to side effects, patients met response criteria to continue to 1LM. 31 PBC drugs were discontinued in 18 patients, 16 of which received either cisplatin or carboplatin. The median number of cycles prior to discontinuation was 4.

## Authors' Conclusions

- Baseline characteristics, treatment patterns, and response to PBC appeared consistent with responses to usual therapy paradigms in the 1L induction setting
- Future analyses of data are planned and include treatment patterns, clinical outcomes (real-world overall survival and progression-free survival), and HCRU at 6 and 12 months following inclusion in the study (baseline data collection)
- This analysis only includes patients who did not progress on first-line Limitations include the retrospective nature of the study, lack of central disease progression assessment, and potential selection and confounding biases

# Full Analysis From AVENANCE: A Real-world Study of Avelumab First-line Maintenance Treatment in Patients With Advanced Urothelial Carcinoma

## Prostate Cancer and Urothelial Carcinoma — Abstract No. 471 (Poster)

P. Barthélémy, Y. Loriot, E. Voog, J.C. Eymard, A. Ravaud, A. Fléchon, C. Abraham, M. Chasseray, V. Lorgis, W. Hilgers, A. Gobert, S. Le Moulec, C. Simon, E. Nicolas, A. Escande, D. Pouessel, C. Josse, M.-N. Solbes, P. Lambert, C. Thibault

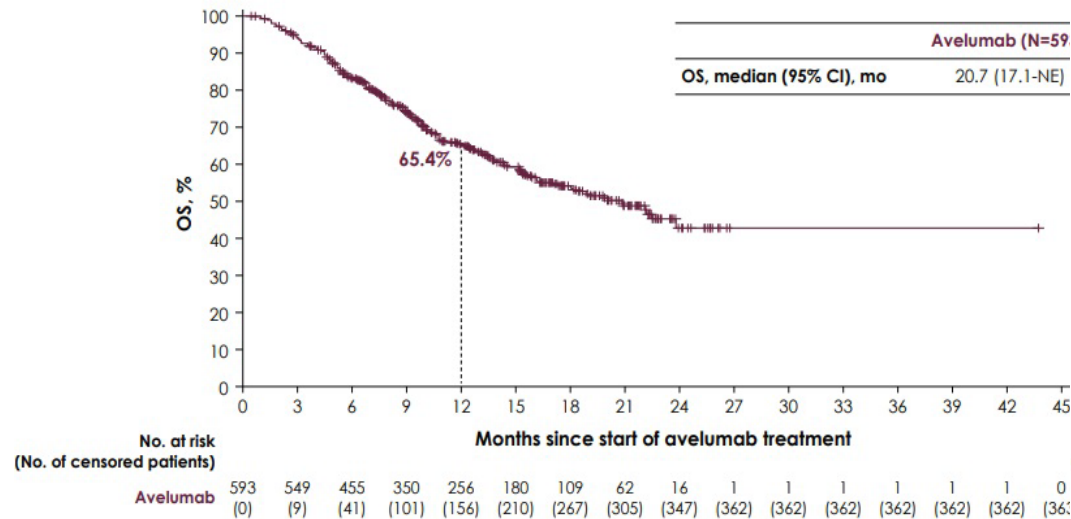
# Full Analysis From AVENANCE: A Real-world Study of Avelumab First-line Maintenance Treatment in Patients With Advanced Urothelial Carcinoma

## Objective

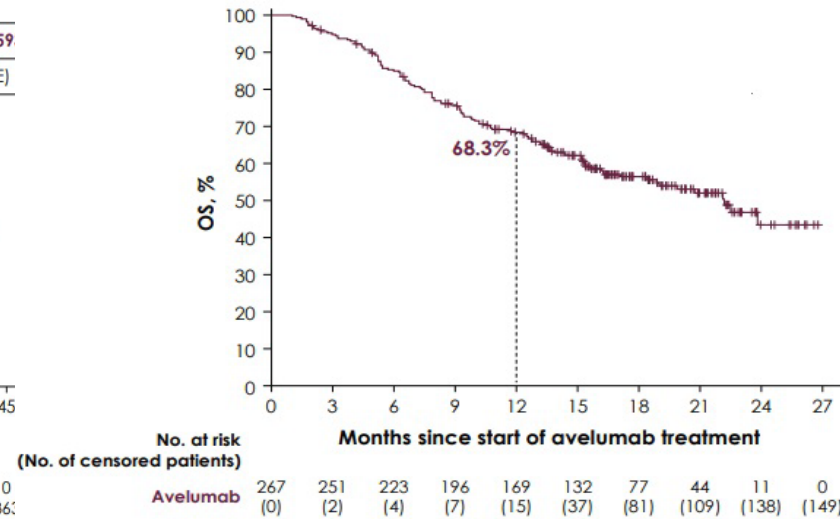
- To report the effectiveness and safety of avelumab 1L maintenance in patients with aUC in France from the full analysis set of AVENANCE, an ongoing, real-world, ambispective (retrospective and prospective) study

## Key Results

### OS From the Start of Avelumab Treatment (Primary Endpoint)



### Interim Analysis Population



- Data collection started on July 13, 2021, and data cutoff for this analysis was December 1, 2022
- Effectiveness and safety were analyzed in patients who had received  $\geq 1$  dose of avelumab
- Because follow-up in the full analysis set was relatively short, an additional analysis was conducted in the first 267 patients who were enrolled (interim analysis population)

- Median duration of treatment with avelumab was 5.8 months (95% CI, 5.1-7.1)
- Median OS from the start of avelumab treatment was 20.7 months (95% CI, 17.1-NE); the 12-month OS rate was 65.4% (95% CI, 61.0-69.4)
- In the interim analysis population, median OS was 22.2 months (95% CI, 17.1-NE)
- PFS from the start of avelumab treatment (secondary endpoint): 5.7 months (95% CI, 5.3-7.0)

## Full Analysis From AVENANCE: A Real-world Study of Avelumab First-line Maintenance Treatment in Patients With Advanced Urothelial Carcinoma

### Key Results

#### Most Common TEAEs of Any Grade

| Events, n (%)                         | N=593      |
|---------------------------------------|------------|
| <b>Any TEAE</b>                       | 428 (72.2) |
| Asthenia                              | 115 (19.4) |
| Pruritus                              | 59 (9.9)   |
| General physical health deterioration | 44 (7.4)   |
| Neoplasm progression                  | 44 (7.4)   |
| Intentional product misuse            | 43 (7.3)   |
| Diarrhea                              | 36 (6.1)   |
| Nausea                                | 34 (5.7)   |
| Arthralgia                            | 28 (4.7)   |
| Hematuria                             | 28 (4.7)   |
| Constipation                          | 27 (4.6)   |
| Urinary tract infection               | 27 (4.6)   |
| Rash                                  | 25 (4.2)   |
| Anemia                                | 24 (4.0)   |
| COVID-19                              | 23 (3.9)   |
| Fatigue                               | 20 (3.4)   |
| Neuropathy peripheral                 | 20 (3.4)   |
| Myalgia                               | 18 (3.0)   |
| Not coded                             | 24 (4.0)   |

- Any-grade TEAEs occurred in 428 patients (72.2%); the most common TEAE was asthenia (n=115, 19.4%)
- 5 patients (0.8%) had a TRAE that led to death (disease progression [n=3, 0.5%], hematuria [n=1, 0.2%], and lung disorder [n=1, 0.2%])
- In the interim analysis population (n=267), any-grade TEAEs occurred in 192 patients (71.9%), including serious TEAEs in 98 (36.7%)
  - In this subgroup, any-grade TRAEs occurred in 123 patients (46.1%), including serious TRAEs in 15 (5.6%)

Table shows TEAEs of any grade occurring in ≥3% of patients.

## Full Analysis From AVENANCE: A Real-world Study of Avelumab First-line Maintenance Treatment in Patients With Advanced Urothelial Carcinoma

### Key Results

#### Summary of AEs

| Events, n (%)                                       | N=593      |
|-----------------------------------------------------|------------|
| <b>TEAE*</b>                                        | 428 (72.2) |
| Serious TEAE                                        | 200 (33.7) |
| TEAE leading to temporary/permanent discontinuation | 171 (28.8) |
| TEAE leading to death                               | 99 (16.7)  |
| <b>TRAE</b>                                         | 254 (42.8) |
| Serious TRAE                                        | 31 (5.2)   |
| TRAE leading to temporary/permanent discontinuation | 78 (13.2)  |
| TRAE leading to death                               | 5 (0.8)    |

### Authors' Conclusions

- These data for avelumab 1L maintenance treatment in patients with aUC are the first to be reported from the full analysis set of the ongoing, real-world, AVENANCE study and support the findings of the JAVELIN Bladder 100 trial<sup>1,2</sup>
- Data from AVENANCE demonstrates the clinical activity and acceptable safety profile of avelumab 1L maintenance in a large cohort of patients (N=593) from a heterogeneous population outside of a clinical trial setting
  - The 12-month OS rate was 65.4%, and median OS was 20.7 months (95% CI, 17.1-NE)
  - Median PFS from the start of avelumab treatment was 5.7 months (95% CI, 5.3-7.0)
  - No new safety concerns were identified<sup>3</sup>
- These results support the recommendation of avelumab 1L maintenance as standard of care for patients with aUC that has not progressed with 1L platinum-based chemotherapy

\*AEs were considered "treatment emergent" if their start date was on or after avelumab initiation.

1. Powles T, et al. N Engl J Med. 2020;383(13):1218-30. 2. Powles T, et al. J Clin Oncol. 2022;40(Suppl 6). Abstract 487. 3. Kelly K, et al. Cancer. 2018;124(9):2010-17.

# **READY: REAL-world Data From an Italian Compassionate Use Program of Avelumab First-line Maintenance Treatment for Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)**

## **Prostate Cancer and Urothelial Carcinoma — Abstract No. 469 (Poster)**

L. Antonuzzo, M. Maruzzo, U. De Giorgi, D. Santini, R. Tambaro, S. Buti, F. Carrozza, F. Calabrò, G. Di Lorenzo, G. Fornarini, R. Iacovelli, D. Cullurà, C. Messina, C. Masi, A. Ciccia, G. Fazzi, F. Venturini, R. Colasanto, A. Necchi, S. Bracarda

# READY: REAL-world Data From an Italian Compassionate Use Program of Avelumab First-line Maintenance Treatment for Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

## Objective

To report baseline characteristics and outcomes in patients with la/mUC who received avelumab 1L maintenance in an Italian CUP before reimbursement from the Italian Medicines Agency was available

## Key Results

### Patient Characteristics at the Start of 1L Platinum-based Chemotherapy

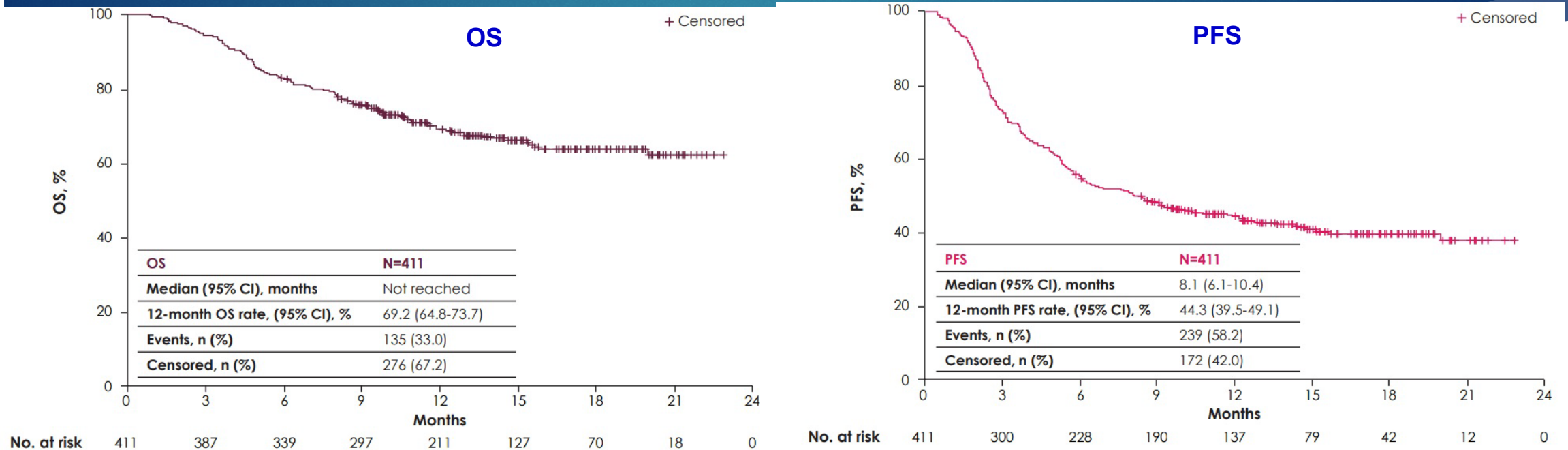
|                                     | Patients (N=464) |
|-------------------------------------|------------------|
| <b>Age, median (IQR), years</b>     | 70.0 (63-76)     |
| <b>Sex, n (%)</b>                   |                  |
| Male                                | 364 (78.5)       |
| Female                              | 100 (21.6)       |
| <b>ECOG PS, n (%)</b>               |                  |
| 0                                   | 321 (69.2)       |
| 1                                   | 140 (30.2)       |
| Not reported                        | 3 (0.7)          |
| <b>PD-L1 status, n (%)</b>          |                  |
| Positive                            | 14 (3.0)         |
| Negative                            | 10 (2.2)         |
| Not reported                        | 440 (94.8)       |
| <b>Disease stage, n (%)</b>         |                  |
| Metastatic                          | 346 (74.6)       |
| Locally advanced                    | 40 (8.6)         |
| Not reported                        | 78 (16.8)        |
| <b>Site of primary tumor, n (%)</b> |                  |
| Lower tract                         | 309 (66.6)       |
| Upper tract                         | 148 (31.9)       |
| Not reported                        | 7 (1.5)          |
| <b>Tumor histology, n (%)</b>       |                  |
| UC                                  | 333 (71.8)       |
| UC with squamous differentiation    | 26 (5.6)         |
| UC with glandular differentiation   | 2 (0.4)          |
| UC with variant differentiation     | 11 (2.4)         |
| Other                               | 7 (1.5)          |
| Not reported                        | 85 (18.3)        |

|                                                | Patients (N=464) |
|------------------------------------------------|------------------|
| <b>Creatinine clearance, n (%)</b>             |                  |
| >60 mL/min                                     | 231 (49.8)       |
| ≤60 mL/min                                     | 155 (33.4)       |
| Not reported                                   | 78 (16.8)        |
| <b>1L chemotherapy regimen, n (%)</b>          |                  |
| Carboplatin + gemcitabine                      | 241 (51.9)       |
| Cisplatin + gemcitabine                        | 214 (46.1)       |
| MVAC                                           | 1 (0.2)          |
| Other                                          | 8 (1.7)          |
| <b>No. of 1L chemotherapy cycles, n (%)</b>    |                  |
| 4                                              | 225 (48.5)       |
| 5                                              | 54 (11.6)        |
| 6                                              | 177 (38.2)       |
| 7-9                                            | 2 (0.4)          |
| Not reported                                   | 6 (1.3)          |
| <b>No. of chemotherapy cycles, median</b>      | 5                |
| <b>Best response to 1L chemotherapy, n (%)</b> |                  |
| Complete response                              | 51 (11.0)        |
| Partial response                               | 266 (57.3)       |
| Stable disease                                 | 147 (31.7)       |

- This prospective, noninterventional, multicenter CUP was open between January 18, 2021 and March 7, 2022
  - Median follow-up time was 14.6 months (95% CI, 13.9-15.2 months)
  - Median duration of avelumab treatment was 5.3 months (IQR, 2.4-9.1 months)
- In 66.6% of patients, the primary tumor was in the lower tract; in 31.9% of patients, the primary tumor was in the upper tract
- The 1L platinum-based chemotherapy regimen was carboplatin + gemcitabine in 51.9% of patients and cisplatin + gemcitabine in 46.1%
- 48.5% of patients had received 4 cycles of platinum-based chemotherapy, 11.6% had received 5 cycles, and 38.2% had received 6 cycles
- 11.0% of patients had a complete response to treatment, 57.3% had a partial response, and 31.7% had stable disease

# READY: REAL-world Data From an Italian Compassionate Use Program of Avelumab First-line Maintenance Treatment for Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

## Key Results



- ▶ At data cutoff, 411 patients were evaluable for OS and PFS
  - Median OS was not reached, with a 12-month OS rate of 69.2% (95% CI, 64.8%-73.7%)
  - Median PFS was 8.1 months (95% CI, 6.1-10.4 months), with a 12-month PFS rate of 44.3% (95% CI, 39.5%-49.1%)
- ▶ All-cause grade 3-4 adverse events occurred in 33 patients (7.1%)

## READY: REAL-world Data From an Italian Compassionate Use Program of Avelumab First-line Maintenance Treatment for Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

### Authors' Conclusions

- This CUP included a large patient population with la/mUC from 140 Italian oncology centers representative of daily clinical practice, and the results are consistent with previous studies<sup>1,2</sup>
- Avelumab 1L maintenance treatment showed clinical benefits and had a manageable safety profile in Italian patients with la/mUC, consistent with findings from the phase 3 JAVELIN Bladder 100 trial<sup>1,2</sup>
- Median OS was not reached, with a 12-month OS rate of 69.2% (95% CI, 64.8%-73.7%)
- Median PFS was 8.1 months (95% CI, 6.1-10.4 months)
- Clinical benefits were observed in a population that included high proportions of patients who had upper tract UC or received carboplatin-based chemotherapy
- Overall, these real-world data provide support for avelumab 1L maintenance as standard of care in eligible patients with la/mUC

### Limitations:

- Safety events may have been underreported because they were reported at the treating physician's discretion
- Short duration of follow-up

1. Powles T, et al. *N Engl J Med*. 2020;383(13):1218-30. 2. Powles T, et al. *J Clin Oncol*. 2022;40(Suppl 6): Abstract 487.

Antonuzzo L, et al. ASCO-GU Cancers Symposium 2023. Abstract No. 469.

# Economic Impact of Bladder Cancer in the United States

## **Prostate Cancer and Urothelial Carcinoma — Abstract No. 479 (Poster)**

O. Clark, T. Sarmento, A. Eccleston, J. Brinkmann, R. Picoli, V. Daliparthi, J. Voss, S. Chandrasekar, A. Thompson, J. Chang

# Economic Impact of Bladder Cancer in the United States

## Objective

- To estimate and understand the direct costs associated with the treatment of bladder cancer from the payer's perspective in the US, in the year of 2021, including costs for both newly diagnosed bladder cancer (stages 0a – IV) and recurrent patients

## Key Results

### Number of Patients and Costs by Stage for Bladder Cancer in the US, 2021

|             |                    |                      |                   |          |            | Tx cost break-down |           |            |           |
|-------------|--------------------|----------------------|-------------------|----------|------------|--------------------|-----------|------------|-----------|
| Stage       | Number of patients | Average cost pp(USD) | Total costs (USD) | DS %cost | Tx % costs | DR % cost          | AE % cost | SUR % cost | RT % cost |
| Incidence   |                    |                      |                   |          |            |                    |           |            |           |
| Stage 0a    | 39,833             | 19,521               | 777,585,028       | 67.3     | 32.7       | 10.8               | 3.4       | 18.5       | 0         |
| Stage 0is   | 3,700              | 21,819               | 80,735,231        | 60.1     | 39.9       | 19.2               | 3         | 17.7       | 0         |
| Stage I     | 19,251             | 23,577               | 453,872,499       | 55.7     | 44.3       | 17.8               | 2.8       | 23.7       | 0         |
| Stage II    | 10,266             | 35,545               | 364,908,905       | 36.9     | 63.1       | 16.7               | 4.7       | 30         | 11.7      |
| Stage III   | 3,354              | 37,204               | 124,781,180       | 35.3     | 64.8       | 20.4               | 4.2       | 26.8       | 13.4      |
| Stage IV M0 | 3,200              | 36,550               | 116,977,967       | 35.9     | 64.1       | 24.4               | 8.7       | 19.9       | 11.1      |
| Stage IV M1 | 3,928              | 169,553              | 665,922,919       | 7.8      | 92.2       | 74.6               | 9.3       | 6.9        | 1.4       |
| Total       | 83,532             | 30,944               | 2,584,783,729     | -        |            | -                  | -         | -          | -         |
| Recurrent   |                    |                      |                   |          |            |                    |           |            |           |
| NMIBC       | 46,906             | 31,375               | 1,471,712,344     | 37.5     | 62.5       | 29.6               | 2.8       | 30.1       | 0         |
| MIBC        | 21,278             | 56,247               | 1,196,810,439     | 19.1     | 80.9       | 46.1               | 2.1       | 27.1       | 5.6       |
| Metastatic  | 7,576              | 169,558              | 1,284,573,532     | 7.7      | 92.3       | 74.6               | 9.3       | 6.9        | 1.5       |
| Total       | 75,760             | 52,179               | 3,953,096,316     | -        |            | -                  | -         | -          | -         |

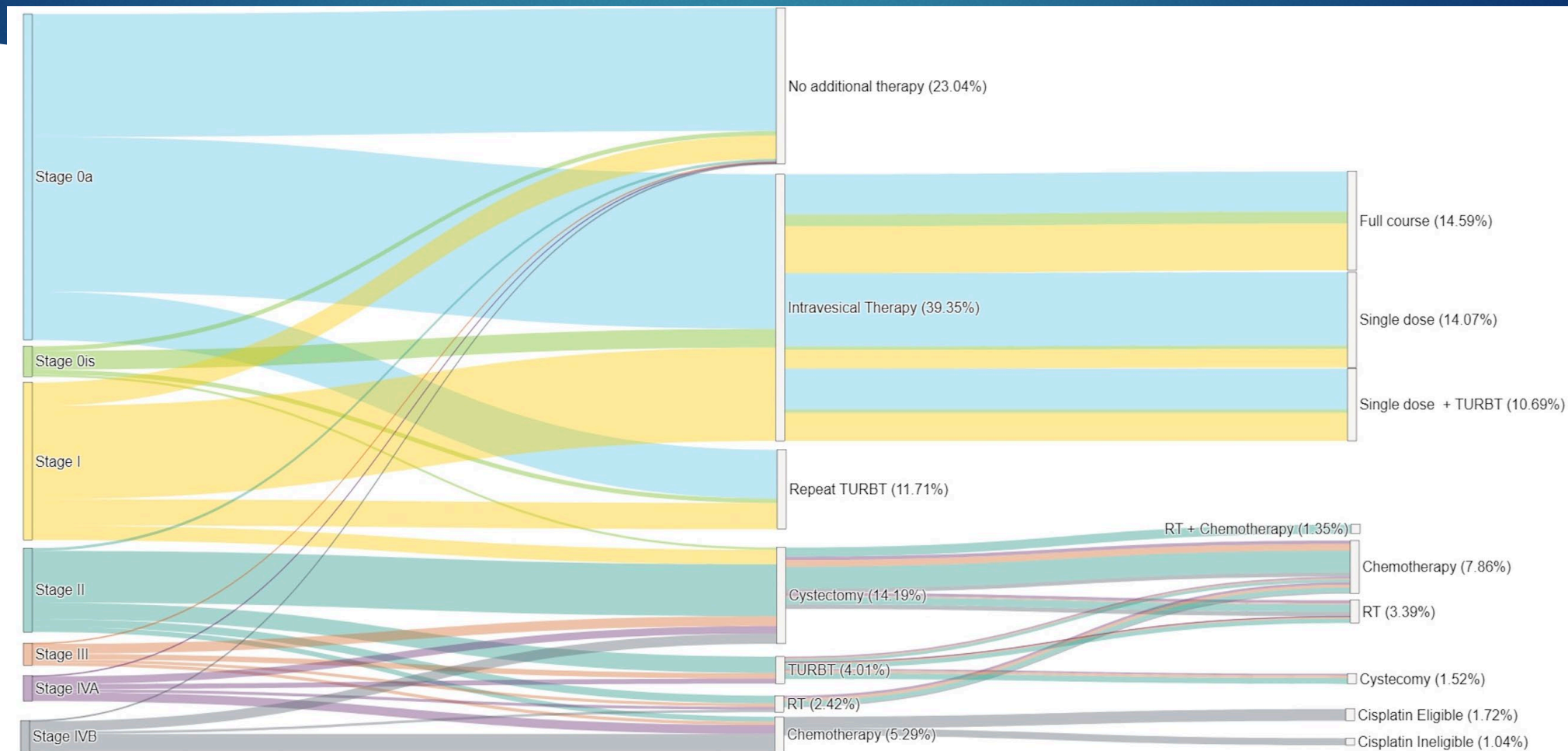
This table was generated using the decision tree model to estimate the cost of treating bladder cancer. The decision model inputs include epidemiological data, data about treatment patterns from the CMP database, resource utilization, and costs from published literature and the VA database.

- ▶ A total of 83,532 patients were estimated to have been newly diagnosed with bladder cancer in the US in 2021 and an additional 75,760 were diagnosed with a bladder cancer recurrence or progression
- ▶ The total cost to treat newly diagnosed patients was USD 2.6 billion while the total cost to treat patients with recurrent bladder cancer was almost USD 4 billion
- ▶ Average cost per patient differed among the stages, with higher costs for later stages
- ▶ For earlier stages, diagnostic and surveillance procedures accounted for more than half of the cost
- ▶ For patients with intermediate stages of disease, treatment costs accounted for more than 60% of total costs. This percentage was even higher for metastatic patients (92.2%)
- ▶ For patients with disease recurrence, costs associated with treatment procedures were higher than diagnosis and surveillance costs across all stages

# Economic Impact of Bladder Cancer in the United States

## Key Results

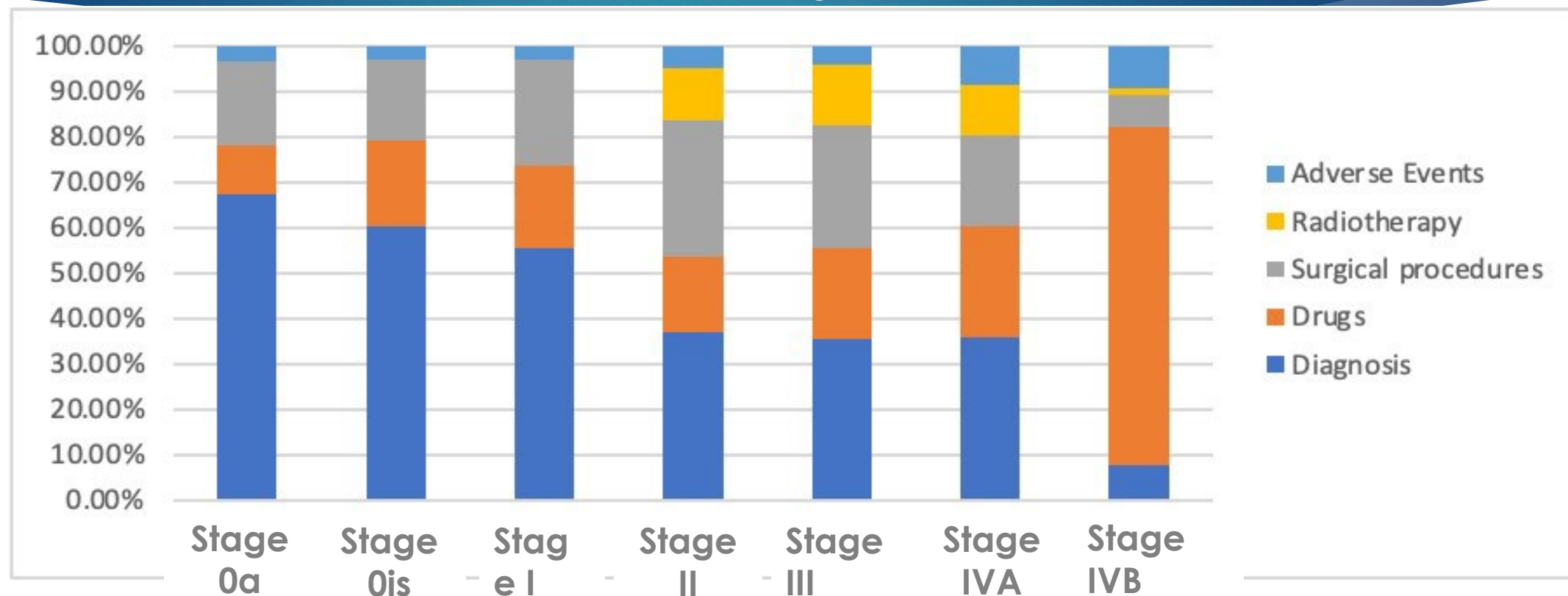
Sankey Diagram of Real-World Treatment Patterns in Patients with Bladder Cancer



# Economic Impact of Bladder Cancer in the United States

## Key Results

### Cost Composition to Treat Patients With Bladder Cancer in the US, 2021, by Stage\*



- Average cost per patient differed among the stages, with higher costs for later stages

\*These values represent the cost share for each treatment within a given stage. It is defined as the unit cost for a given treatment, weighted by the volume of patients undergoing such treatment.

# Economic Impact of Bladder Cancer in the United States

## Authors' Conclusions

- This analysis estimated that in 2021, more than USD 6.5 billion were spent in treating patients with bladder cancer in the US
- This model was built to represent the total cost of treating patients with bladder cancer in 2021 and does not incorporate possible impact of future therapies
- The model showed that the cost profile varied based on the stage of disease
- Treatment of patients with metastatic disease had a much higher total average cost of treatment than those with early or intermediate stage disease. This was true for both newly diagnosed patients as well as those patients experiencing a recurrence or progression of their disease
- On average, costs to treat patients with earlier stages of the disease are 85% to 87% smaller than those with late-stage disease
- Although there were fewer patients with recurrent disease than those who were newly diagnosed, disease recurrence disproportionately drives up the costs of bladder cancer for the healthcare system
- New treatment strategies that prevent or delay recurrence or progression for patients with early-stage bladder cancer may lower the total costs of the disease

### Limitations:

- Most of the information used to build the clinical evolution, patterns of care, and outcomes of the model were informed by physician surveys, a method with known limitations, in particular recall bias<sup>1</sup>
- The use of the VA as the major source of costs, while it is reliable and public information, it also lacks national representativeness as the VA prices may differ from other commercial providers and networks

1. Cerner Enviza. CMP: CancerMPact®, Patient Metrics® 2022 [cited April, 23rd, 2022]. Available from: [www.cancermpact.com](http://www.cancermpact.com)

## Time-to-Event Following Bacillus Calmette-Guerin Therapy Initiation in Medicare Beneficiaries With Intermediate- to High-Risk Non-Muscle Invasive Bladder Cancer, 2010-2019 (Petrilla, et al)

| Product | Company | Indication/Patient Population    | Phase and Trial ID | Abstract    |
|---------|---------|----------------------------------|--------------------|-------------|
| BCG     | NA      | Intermediate- to High-risk NMIBC | NA                 | 473, poster |

### Key Results

**Objective:** To identify intermediate- to high-risk NMIBC patients among Medicare beneficiaries to understand patient characteristics, BCG treatment patterns, and outcomes

#### Select Patient Characteristics and Time to Event Outcomes<sup>a</sup>

| Patient Characteristics and Outcomes                                | Subgroup 1: Adequate BCG Therapy (N= 19,859) | Subgroup 2: Inadequate BCG Therapy (N= 26,193) |
|---------------------------------------------------------------------|----------------------------------------------|------------------------------------------------|
| Patient Age (mean years, SD)                                        | 76.0 (7.3)                                   | 76.7 (7.7)                                     |
| Male sex (%)                                                        | 77.3%                                        | 76.8%                                          |
| Non-Hispanic White (%)                                              | 93.1%                                        | 92.2%                                          |
| Charlson Comorbidity Index Score (mean, SD)                         | 4.5 (2.4)                                    | 4.7 (2.5)                                      |
| Duration of follow up (mean months, SD)                             | 53.0 (29.5)                                  | 52.0 (30.1)                                    |
| Number of BCG instillations during follow up (median, IQR)          | 12.0 (8.0)                                   | 6.0 (1.0)                                      |
| BCG initiation to discontinuation <sup>b</sup> (median months, IQR) | 13.3 (16.8)                                  | 1.3 (8.6)                                      |
| BCG initiation to radical cystectomy (median months, IQR)           | 20.2 (21.7)                                  | 12.4 (19.8)                                    |
| BCG initiation to systemic chemotherapy (median months, IQR)        | 23.7 (27.1)                                  | 18.9 (29.2)                                    |
| BCG initiation to radiation (median months, IQR)                    | 24.9 (33.6)                                  | 23.9 (35.9)                                    |
| BCG initiation to metastasis (median months, IQR)                   | 25.1 (30.2)                                  | 21.8 (30.4)                                    |

<sup>a</sup>All TTE outcomes were calculated across patients who experience such events.

<sup>b</sup>Discontinuation of treatment is observed and not part of the TTE analysis.

- Retrospective cohort study using 100% sample of Medicare Fee-for-Service medical and pharmacy claims and enrollment data (N=46,052)
  - 43.1% received adequate BCG; 56.9% received inadequate BCG
  - Mean duration of follow-up was approximately 4 years
  - Median (IQR) time from NMIBC diagnosis to BCG initiation was 2.8 (8.2) months for adequate and 3.6 (14.4) months for inadequate BCG subgroups, respectively
  - Patients with inadequate BCG therapy had numerically shorter time to radical cystectomy, systemic therapy, radiation, and metastatic disease diagnosis vs those with adequate BCG therapy

### Analysis/Implications

- Between 2010 and 2019, 57% of Medicare patients who initiated BCG following diagnosis of NMIBC and TURBT may not have received adequate BCG therapy
- The proportion of patients who had radical cystectomy, systemic therapy, radiation, and metastatic diagnosis were similar between the BCG adequate and inadequate groups, but TTE were numerically shorter in the BCG inadequate group
- Real-world adherence to BCG therapy is inadequate for the majority of patients; this study provides supporting evidence that adhering to BCG treatment duration recommended by clinical guidelines will likely improve patient outcomes

# **Treatment Patterns, Indicators of Receiving Systemic Treatment, and Clinical Outcomes in Metastatic Urothelial Carcinoma: A Retrospective Analysis of Real-world Data in Germany**

**Prostate Cancer and Urothelial Carcinoma — Abstract No. 464 (Poster)**

G. Niegisch, M.-O. Grimm, F. Hardtstock, J. Krieger, A. Starry, U. Osowski, S. Guenther, B. Deiters, U. Maywald, T. Wilke, M. Kearney

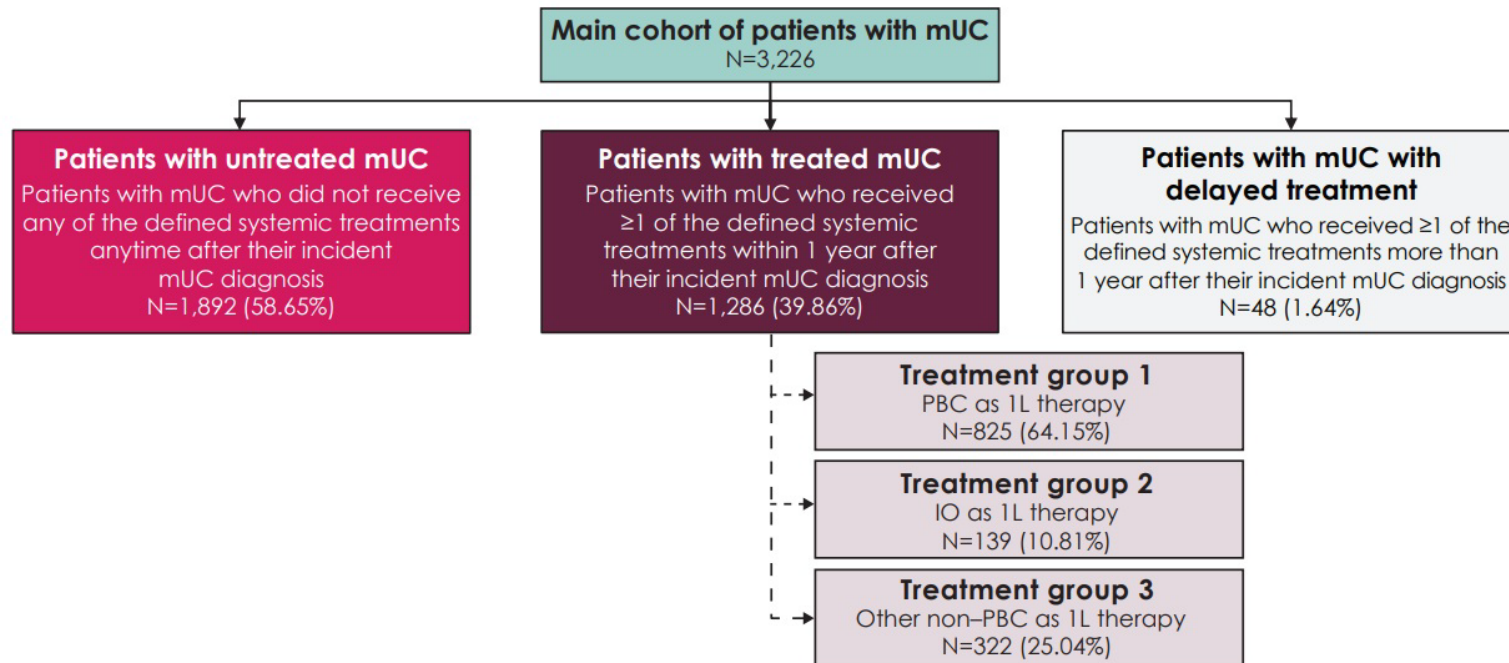
# Treatment Patterns, Indicators of Receiving Systemic Treatment, and Clinical Outcomes in Metastatic Urothelial Carcinoma: A Retrospective Analysis of Real-world Data in Germany

## Objective

This retrospective claims data study characterized real-world treatment patterns, treatment rates, and clinical outcomes in patients with mUC in Germany, and assessed factors associated with receiving treatment

## Key Results

### Study Population



- ▶ Using 2 statutory health insurance (AOK PLUS and GWQ) claims databases in Germany (2013-2020), adults with an incident mUC diagnosis from 2015-2019 were identified
- ▶ Patients were observed for ≥12 months after the incident mUC diagnosis (index) or until death. Treated patients were delineated into 3 groups based on 1L treatment received: PBC, non-PBC, and IO
- ▶ The study included 3,226 patients with mUC, with a mean (SD) follow-up of 13.8 (16.1) months
- The mean (SD) age was 73.8 (10.8) years, 70.8% were male, and the mean (SD) Elixhauser Comorbidity score was 17.6 (11.4)

## Treatment Patterns, Indicators of Receiving Systemic Treatment, and Clinical Outcomes in Metastatic Urothelial Carcinoma: A Retrospective Analysis of Real-world Data in Germany

### Key Results

#### OS Outcomes by Types of 1L Systemic Treatment

|                                                               |          | Main cohort<br>N=3,226 | Untreated cohort<br>N=1,892 | Treated cohort<br>N=1,286 | PBC cohort<br>N=825   | IO cohort<br>N=139   | Non-PBC cohort<br>N=322 |
|---------------------------------------------------------------|----------|------------------------|-----------------------------|---------------------------|-----------------------|----------------------|-------------------------|
| Median OS from mUC index (IQR), months                        | AOK PLUS | 5.92<br>(1.84-19.13)   | 3.02<br>(1.18-10.78)        | 13.74<br>(6.81-32.91)     | –                     | –                    | –                       |
|                                                               | GWQ      | 9.07<br>(2.53-31.23)   | 3.55<br>(1.18-18.84)        | 13.81<br>(7.07-41.69)     |                       |                      |                         |
| Median OS from 1L systemic treatment initiation (IQR), months | AOK PLUS | –                      | –                           | 11.61<br>(4.90-31.53)     | 12.89<br>(6.21-33.11) | 4.11<br>(1.78-14.14) | 11.18<br>(4.41-36.00)   |
|                                                               | GWQ      |                        |                             | 11.67<br>(5.06-37.55)     | 13.8<br>(7.43-49.35)  | 8.19<br>(2.76-NE)    | 6.54<br>(2.60-15.48)    |

- ▶ Median OS from index diagnosis was 13.7 months (AOK PLUS) and 13.8 months (GWQ) in the treated cohort vs 3.0 months (AOK PLUS) and 3.6 months (GWQ) in the untreated cohort
- ▶ Median OS after 1L initiation was as follows:
  - ▶ 12.9 months (AOK PLUS) and 13.8 months (GWQ) in the PBC subcohort
  - ▶ 11.2 months (AOK PLUS) and 6.5 months (GWQ) in the non-PBC subcohort
  - ▶ 4.1 months (AOK PLUS) and 8.2 months (GWQ) in the IO subcohort

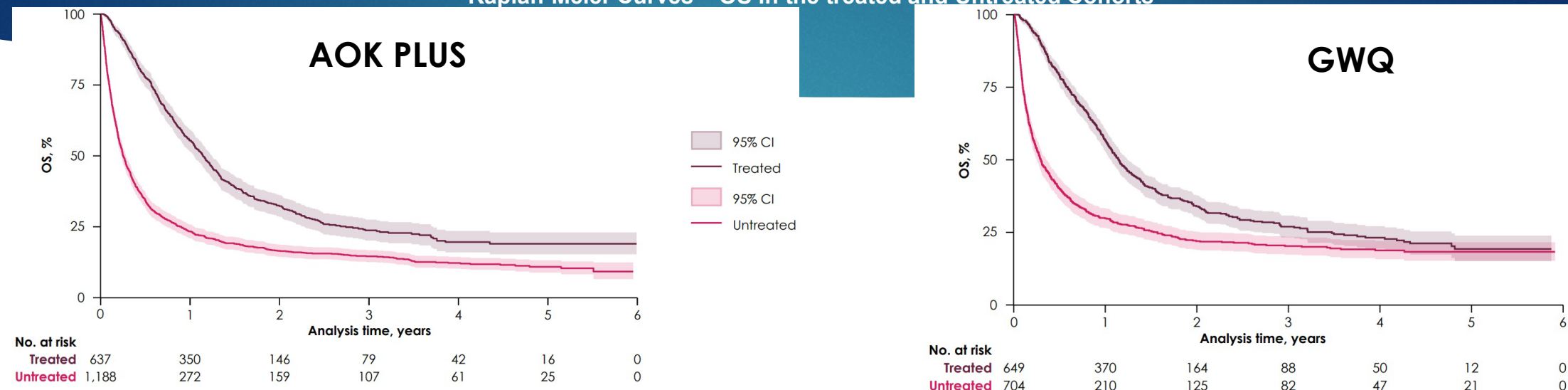
- Multiple factors were associated with a higher likelihood of receiving 1L treatment:
  - Younger age (odds ratio, 0.93)
  - Male sex (odds ratio, 0.83)
  - Lower comorbidity score (odds ratio, 0.97)
  - Previous UC-related interventions (odds ratio, 1.65)
  - Lower number of previous hospitalization visits (odds ratio, 0.97)
  - Inpatient diagnosis of mUC (odds ratio, 1.28)
  - More recent mUC diagnosis (odds ratio, 1.11)

Immortal time bias may slightly confound the results but not the general trend. Data for patients with mUC with delayed treatment are not shown due to the small number of patients in this subgroup.

# Treatment Patterns, Indicators of Receiving Systemic Treatment, and Clinical Outcomes in Metastatic Urothelial Carcinoma: A Retrospective Analysis of Real-world Data in Germany

## Key Results

### Kaplan-Meier Curves – OS in the treated and Untreated Cohorts



- ▶ Median OS from index diagnosis was 10.2-10.7 months longer in the treated vs untreated cohort (treated: AOK PLUS, 13.7 months and GWQ, 13.8; untreated: AOK PLUS, 3.0 and GWQ, 3.6)
- ▶ Median OS after 1L initiation was longest in the PBC subcohort (AOK PLUS, 12.9 months and GWQ, 13.8), followed by the non-PBC subcohort (AOK PLUS, 11.2 months and GWQ, 6.5) and the IO subcohort (AOK PLUS, 4.1 months and GWQ, 8.2)

## Authors' Conclusions

- This study describes real-world treatment patterns, treatment rates, and clinical outcomes in German patients with mUC from 2015-2020 and highlights that the majority received no systemic treatment within the first 12 months, despite a trend in 1L treatment utilization rates over time
- Treated patients were more likely to be younger and male and to have fewer comorbidities than untreated patients
- Receiving systemic treatment was associated with longer OS; among treated patients, OS was longer in those receiving 1L PBC (12.9 months) than in those receiving other 1L treatment (11.2 months)
- Future research should explore the unmet need in untreated patients to confirm alignment with updated treatment guidelines and newer standards of care

# **Real-world Treatment Patterns and Sequencing in Patients With Locally Advanced or Metastatic Urothelial Cancer (la/mUC) in the US**

**Prostate Cancer and Urothelial Carcinoma — Abstract No. 572 (Poster)**

M. Kearney, S. H. Mahmoudpour, C. Ike, A. Modh, S. Monzon, S. Fragkogianni, K. Carson

# Real-world Treatment Patterns and Sequencing in Patients With Locally Advanced or Metastatic Urothelial Cancer (la/mUC) in the US

## Objective

To describe baseline demographic and clinical characteristics, real-world treatment patterns, and treatment sequencing in patients with la/mUC in the US

## Key Results

### Baseline Demographics and Clinical Characteristics in Patients in the Overall La/muC Cohort

| Characteristic                                         | N=821             | Characteristic (cont)               | N=821 (cont) |
|--------------------------------------------------------|-------------------|-------------------------------------|--------------|
| <b>Systemic treatment, n (%)</b>                       |                   | <b>Smoking status, n (%)</b>        |              |
| Treated, curated                                       | 634 (77)          | History of smoking                  | 361 (63)     |
| Untreated                                              | 187 (23)          | Never                               | 212 (37)     |
| <b>Follow-up from la/mUC diagnosis, median, months</b> | 9.20 (3.71-18.80) | Unknown                             | 248          |
| <b>Age at la/mUC diagnosis, median (IQR), years</b>    | 69 (62, 76)       | <b>Histology type, n (%)</b>        |              |
| <b>Year of la/mUC diagnosis, n (%)</b>                 |                   | Ambiguous carcinoma                 | 131 (16)     |
| 2016                                                   | 90 (11)           | Other                               | 30 (3.7)     |
| 2017                                                   | 95 (12)           | Squamous                            | 2 (0.2)      |
| 2018                                                   | 110 (13)          | Transitional                        | 658 (80)     |
| 2019                                                   | 182 (22)          | <b>Histopathology grade, n (%)</b>  |              |
| 2020                                                   | 207 (25)          | Grade 2 (moderately differentiated) | 8 (1.6)      |
| 2021                                                   | 129 (16)          | Grade 3 (poorly differentiated)     | 67 (14)      |
| 2022                                                   | 8 (1)             | Grade 4 (undifferentiated)          | 1 (0.2)      |
| <b>Sex, n (%)</b>                                      |                   | High                                | 416 (84)     |
| Female                                                 | 221 (27)          | Low                                 | 1 (0.2)      |
| Male                                                   | 600 (73)          | Unknown                             | 328          |
| <b>Race, n (%)</b>                                     |                   | <b>Comorbidities, n (%)</b>         |              |
| American Indian or Alaska Native                       | 1 (0.1)           | 1                                   | 147 (37)     |
| Black or African American                              | 53 (6.5)          | 2                                   | 86 (22)      |
| Other                                                  | 48 (5.8)          | 3                                   | 54 (14)      |
| Unknown                                                | 200 (24)          | 4+                                  | 106 (27)     |
| White                                                  | 519 (63)          | Unknown                             | 428          |
| <b>Region, n (%)</b>                                   |                   | <b>Death records, n (%)</b>         | 305 (37)     |
| Midwest                                                | 214 (46)          | <b>PD-L1 status, n (%)</b>          |              |
| Northeast                                              | 33 (7)            | Negative                            | 123 (64)     |
| South                                                  | 108 (23)          | Positive                            | 70 (36)      |
| West                                                   | 115 (24)          | Unknown                             | 628          |
| Unknown                                                | 351               |                                     |              |
| <b>Data source, n (%)</b>                              |                   |                                     |              |
| Academic centers                                       | 221 (27)          |                                     |              |
| Community centers                                      | 169 (21)          |                                     |              |
| Other                                                  | 426 (52)          |                                     |              |
| Unknown                                                | 5                 |                                     |              |

- ▶ This retrospective observational study used the Tempus database, a nationwide longitudinal EHR database<sup>1</sup>
- ▶ Patients aged ≥18 years and diagnosed with la/mUC (T4b, N2/3, and/or M1 or overall cancer stage 3/4) (index date) between January 1, 2016, and February 23, 2022, were included
- ▶ Patients who completed 1L PBC and then received an IO therapy were categorized as 1LM or 2L. These patients were further split into pre- and post-groups based on when they completed their 1L PBC treatment in relation to avelumab's 1LM US approval<sup>2</sup> on June 30, 2020
- ▶ A total of 821 patients were included from community centers (21%), academic centers (27%), and ASCO CancerLinQ network sites (52%)
- ▶ Median age at diagnosis was 69 years (IQR, 62-76 years), 73% of patients were male, 63% were White, and 80% had transitional cell carcinoma

1. Tempus. Data-driven precision medicine. <https://www.tempus.com/>. Accessed January 2023. 2. Bavencio (avelumab). Prescribing information. EMD Serono, Rockland, MA, USA; 2020. Kearney M, et al. ASCO-GU Cancers Symposium 2023. Abstract No. 572.

# Real-world Treatment Patterns and Sequencing in Patients With Locally Advanced or Metastatic Urothelial Cancer (la/mUC) in the US

## Key Results

### Treatment Patterns Across Lines of Treatment

|           | All patients (N=821)    | Most common tx                                                                                                                                                                                                              |
|-----------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Untreated | 187 (22.8%)             | N/A                                                                                                                                                                                                                         |
| Treated   |                         |                                                                                                                                                                                                                             |
| 1L tx     | 634 (77.2%)             | <b>Cisplatin + gemcitabine:</b> 175 (27.6%)<br><b>Carboplatin + gemcitabine:</b> 124 (19.6%)<br><b>Pembrolizumab:</b> 108 (17.0%)<br><b>MVAC:</b> 45 (7.1%)<br><b>Atezolizumab*:</b> 35 (5.5%)<br><b>Other:</b> 147 (23.2%) |
| 1LM tx    | 97 (24.6%) <sup>†</sup> | <b>Avelumab:</b> 63 (64.9%)<br><b>Other IO therapy:</b> 34 (35.1%)                                                                                                                                                          |
| 2L tx     | 210 (33.1%)             | <b>Pembrolizumab:</b> 57 (27.1%)<br><b>Enfortumab vedotin:</b> 35 (16.7%)<br><b>Carboplatin + gemcitabine:</b> 19 (9.0%)<br><b>Atezolizumab*:</b> 12 (5.7%)<br><b>Avelumab:</b> 14 (6.7%)<br><b>Other:</b> 73 (34.8%)       |
| 3L tx     | 65 (31.0%)              | <b>Enfortumab vedotin:</b> 14 (21.5%)<br><b>Pembrolizumab:</b> 13 (20.0%)<br><b>Avelumab:</b> 8 (12.3%)<br><b>Atezolizumab*:</b> 7 (10.8%)<br><b>Carboplatin + gemcitabine:</b> 4 (6.2%)<br><b>Other:</b> 19 (29.2%)        |

- A total of 634 patients (77%) received 1L systemic treatment; of those, 62% (395/634) received PBC, 24% (155/634) received IO monotherapy, 7% (45/634) received non-PBC, and 6% (39/634) received other regimens<sup>†</sup>
- Among all patients who received 1L PBC, the majority received cisplatin (63.8%; n=252/395), and most of the remaining patients received carboplatin (35.7%; n=141/395)
- Among all patients who received 1L treatment, 33.1% (210/634) had evidence of receiving a 2L treatment. The most common 2L therapies included pembrolizumab (27.1%), enfortumab vedotin (16.7%), and carboplatin plus gemcitabine (9.0%)
- Among all patients who received 2L treatment, 31.0% (65/210) had evidence of receiving a 3L treatment. The most common 3L therapies included enfortumab vedotin (21.5%), pembrolizumab (20.0%), and atezolizumab<sup>‡</sup> (10.8%)

\*Atezolizumab is no longer approved in the US to treat patients with locally advanced or metastatic urothelial carcinoma following the manufacturer's decision to withdraw its indication after consulting with the FDA. The withdrawal was made in accordance with the FDA's Accelerated Approval Program after results from the phase 3 IMvigor130 trial (NCT02807636) failed to meet the postmarketing requirement necessary to convert the accelerated approval for atezolizumab into regular approval.<sup>1</sup> †Percentage calculated from patients that received 1L platinum-based chemotherapy (n=395).

<sup>‡</sup>Other regimens included: ADCs, ADC combinations with IO therapy, chemotherapy or IO therapy + chemotherapy, IO therapy combinations, hormone + targeted therapy, tyrosine kinase inhibitors, and unlabeled investigational new drugs. <sup>‡</sup>Atezolizumab is no longer approved in the US to treat patients with la/mUC following the manufacturer's decision to withdraw its indication after consulting with the FDA. The withdrawal was made in accordance with the FDA's Accelerated Approval Program after results from the phase 3 IMvigor130 trial (NCT02807636) failed to meet the postmarketing requirement necessary to convert the accelerated approval for atezolizumab into regular approval.<sup>1</sup>

1. Cancer network. Atezolizumab No Longer Available in US for a Certain Type of Bladder Cancer. <https://www.cancernetwork.com/view/atezolizumab-no-longer-available-in-us-for-a-certain-type-of-bladder-cancer>. Accessed January 2023.

Kearney M, et al. ASCO-GU Cancers Symposium 2023. Abstract No. 572.

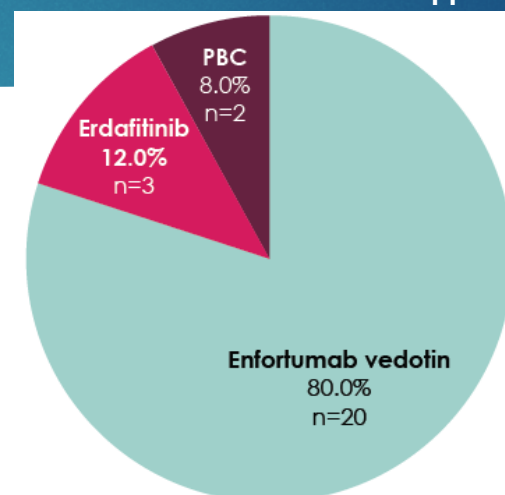
# Real-world Treatment Patterns and Sequencing in Patients With Locally Advanced or Metastatic Urothelial Cancer (la/mUC) in the US

## Key Results

### Treatment Sequencing

|                                                                        | 1L PBC end date<br>pre-avelumab 1LM<br>approval (n=243) n/N (%)             | 1L PBC end date<br>post-avelumab 1LM<br>approval (n=152) n/N (%)                                                                                                          |
|------------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Received IO therapy as 2L or 1LM<br>following 1L PBC                   | 87/243 (36)                                                                 | 84/152 (55)                                                                                                                                                               |
| Received IO therapy as 2L                                              | 59/87 (68)                                                                  | 17/84 (20)                                                                                                                                                                |
| Received IO therapy as 1LM                                             | 28/87 (32)                                                                  | 67/84 (80)<br><b>Avelumab:</b> 56/67 (84)<br>(18/56 patients (32%)<br>were still receiving<br>avelumab at the end of<br>the follow-up period)<br><b>Other:</b> 11/67 (16) |
| Received 2L tx after progression<br>on IO 1LM                          | 9/28 (32)<br><b>Enfortumab vedotin:</b><br>4/9 (44)<br><b>PBC:</b> 5/9 (56) | 25/67 (37)<br><b>Enfortumab vedotin:</b><br>20/25 (80)<br><b>Erdafitinib:</b> 3/25 (12)<br><b>PBC:</b> 2/25 (8)                                                           |
| Did not receive IO therapy after<br>1L PBC but received 2L or later tx | 110/243 (45)                                                                | 34/152 (22)                                                                                                                                                               |

### Breakdown of 2L Treatments After Progression on IO 1LM Post-avelumab Approval



- Of those receiving IO therapy (n=84) as subsequent treatment post-avelumab approval, 80% (67/84) received an IO therapy as 1LM, of which 84% (56/67) received avelumab 1LM
- Of the 25 patients who received 2L treatment after progression on IO 1LM post-avelumab approval, enfortumab vedotin was the most commonly used 2L agent (80%; 20/25)

## Authors' Conclusions

- The treatment patterns observed are consistent with known and evolving treatment paradigms in la/mUC; 77% of patients received systemic anticancer treatment following la/mUC diagnosis; among them, most patients (62%) received guideline-recommended 1L PBC
- Use of PBC has increased and the use of IO and non-PBC has decreased in the 1L setting from 2020 through February 2022 following updated clinical guidelines and FDA label changes for IO monotherapy in 1L setting
- Post-avelumab approval, in patients receiving IO as subsequent treatment to PBC, 80% received IO as 1LM, of which 84% received avelumab 1LM
- High attrition rates beyond 1L were observed with only 33% of patients receiving 2L therapy, indicating the persistence of high unmet treatment needs
- Enfortumab vedotin was the most commonly used 2L agent in patients who discontinued 1LM during the study period

# **Assessment of Treatment Patterns and Real-world Outcomes Following Changes in the Treatment Paradigm for Locally Advanced/Metastatic Urothelial Carcinoma (la/mUC) in the US**

## **Prostate Cancer and Urothelial Carcinoma — Abstract No. 468 (Poster)**

M. Kirker, A. Abraham, A. Vlahiotis, A. Bhanegaonkar, D. Benjumea, C. Kim, H. Sun, M. Kearney, S. Chandrasekar, B. Li, S. Thakkar, H. H. Moon

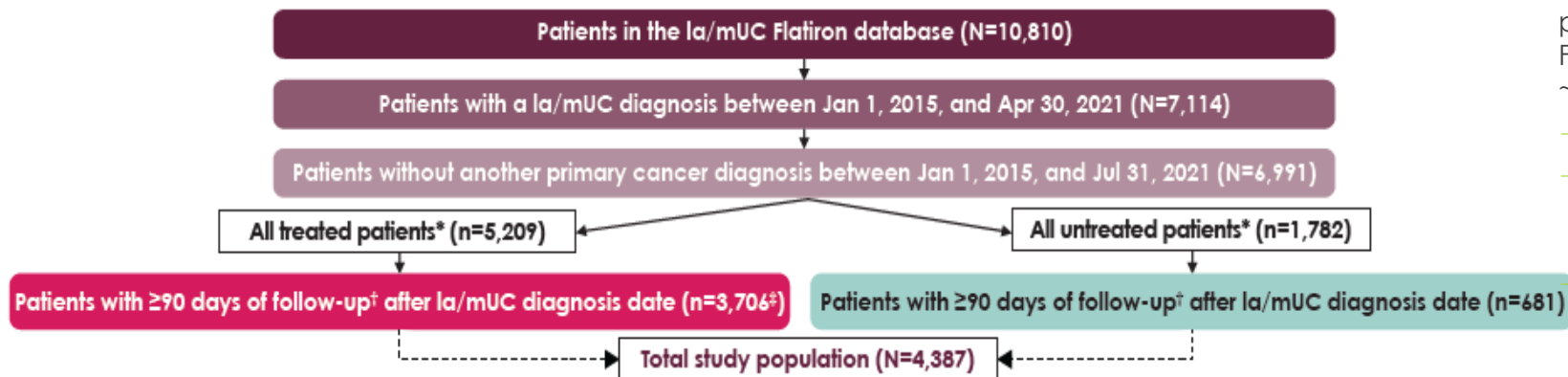
# Assessment of Treatment Patterns and Real-world Outcomes Following Changes in the Treatment Paradigm for Locally Advanced/Metastatic Urothelial Carcinoma (la/mUC) in the US

## Objective

To understand treatment patterns and real-world outcomes in patients with la/mUC in the US, including the early implementation of avelumab 1LM since its US Food and Drug Administration approval in June 2020

## Key Results

### Study Design



► Non-interventional, retrospective cohort study of patients with la/mUC in the US using data from the Flatiron Health database with data originating from ~280 cancer clinics<sup>1</sup>

- Study period: January 1, 2015 to July 31, 2021
- Identification period: January 1, 2015 to April 30, 2021 (to ensure ≥3-month follow-up unless the patient died)

Index date: la/mUC diagnosis date in the identification period

- Of 4,387 patients included in this study, 3,706 (84.5%) received systemic anticancer treatments
- Cisplatin-based therapy was the most common 1L therapy (33.3%), followed by carboplatin-based therapy (30.9%), then IO therapies (28.0%)
- Since July 2020, 89 received 1LM avelumab; median follow-up from the start of avelumab 1LM was 6.0 months and clinical outcomes data were immature
- Bladder was the most common site of disease (76.2%), with most patients having a high disease grade at la/mUC diagnosis (grade ≥2 in 85.9%)
- Mean follow-up from la/mUC diagnosis was similar for treated and untreated patients (16.7 and 16.8 months, respectively)

\*All patients were aged ≥18 years; †Unless in the case of death; ‡To reach this patient number, additional eligibility criteria were met: (1) no systemic treatment for la/mUC in the baseline period (n=5,118); (2) <180 days between la/mUC diagnosis date and administration of 1L treatment (n=4,634); (3) no clinical study drug during the study period (n=4,532).

1. Flatiron. Real-World Data. 2022. <https://flatiron.com/real-world-evidence/>.

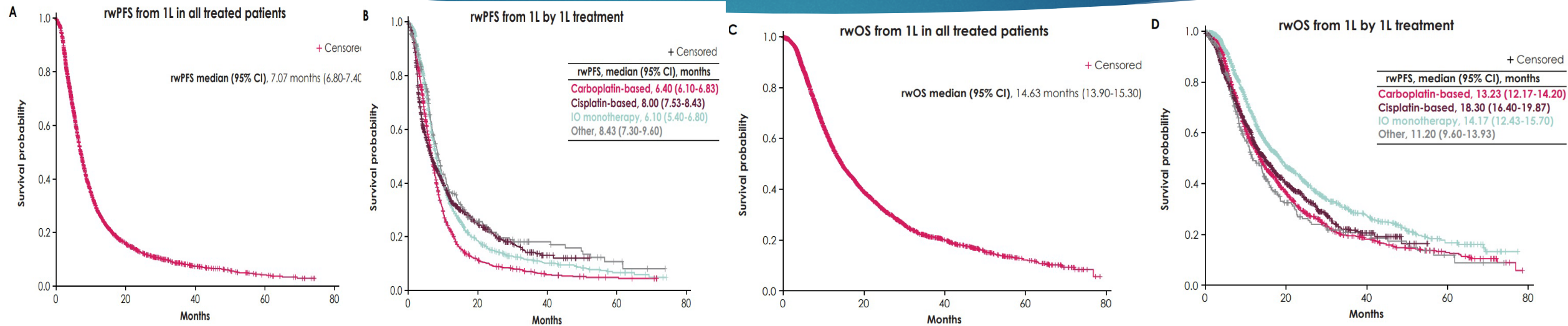
Kirker M, et al. ASCO-GU Cancers Symposium 2023. Abstract No. 468.

# Assessment of Treatment Patterns and Real-world Outcomes Following Changes in the Treatment Paradigm for Locally Advanced/Metastatic Urothelial Carcinoma (la/mUC) in the US

## Key Results

### Kaplan-Meier Estimates of PFS

### Kaplan-Meier Estimates of OS



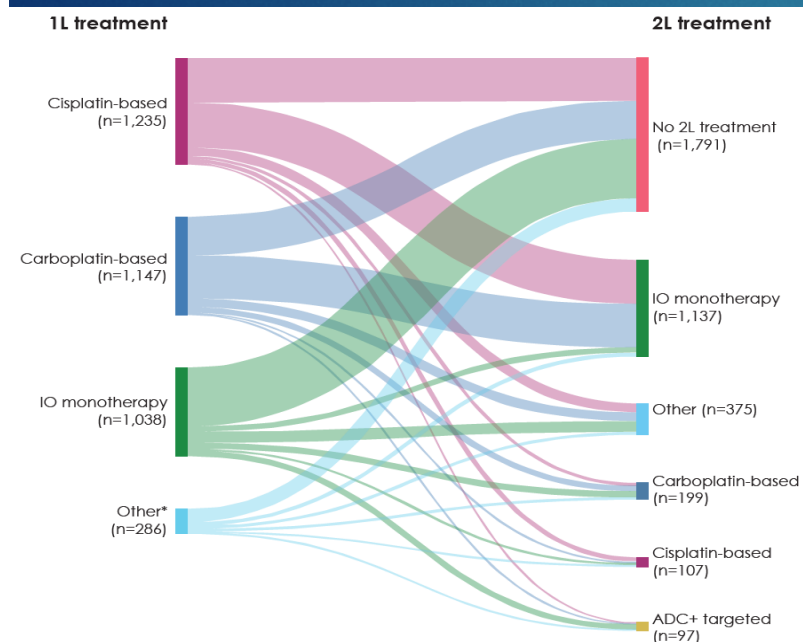
- Median PFS was 8.0 months in patients treated with 1L cisplatin-based therapies (95% CI, 7.5-8.4), 6.4 months for 1L carboplatin-based therapies (95% CI, 6.1-6.8), and 6.1 months for IO therapies (95% CI, 5.4-6.8)

- Median OS in the treated cohort was 14.6 months (95% CI, 13.9-15.3) from the initiation of 1L therapy
- Median OS was 18.3 months in patients treated with 1L cisplatin-based therapies (95% CI, 16.4-19.9), 14.2 months for 1L IO therapies (95% CI, 12.4-15.7), and 13.2 months for 1L carboplatin-based therapies (95% CI, 12.2-14.2)

# Assessment of Treatment Patterns and Real-world Outcomes Following Changes in the Treatment Paradigm for Locally Advanced/Metastatic Urothelial Carcinoma (la/mUC) in the US

## Key Results

### Treatment Sequence from 1L to 2L



|                 |                   | 2L treatment    |                   |                |               |            |                  |
|-----------------|-------------------|-----------------|-------------------|----------------|---------------|------------|------------------|
| Patients, n (%) |                   | Cisplatin-based | Carboplatin-based | IO monotherapy | ADC+ targeted | Other      | No 2L treatment† |
| 1L treatment    | Cisplatin-based   | 50 (4.0)        | 35 (2.8)          | 522 (42.3)     | 18 (1.5)      | 110 (8.9)  | 500 (40.5)       |
|                 | Carboplatin-based | 17 (1.5)        | 66 (5.8)          | 508 (44.3)     | 10 (0.9)      | 103 (9.0)  | 443 (38.6)       |
|                 | IO monotherapy    | 22 (2.1)        | 69 (6.6)          | 63 (6.1)       | 65 (6.3)      | 128 (12.3) | 691 (66.6)       |
|                 | Other*            | 18 (6.3)        | 29 (10.1)         | 44 (15.4)      | 4 (1.4)       | 34 (11.9)  | 157 (54.9)       |

\*Inclusive of ADC+ targeted. †Inclusive of patients still receiving 1L at end of follow-up: cisplatin-based therapy (48.6%); carboplatin-based therapy (62.3%); IO monotherapy (79.9%); other (61.1%).

Of 1L-treated patients, 50.6% moved on to 2L therapy during the study period

with carboplatin-based therapy des other platinum-based

## Authors' Conclusions

- In this real-world cohort, most treated patients received standard-of-care PBC in the 1L (64.3%), with those receiving 1L cisplatin-based therapy demonstrating favorable outcomes
- Of patients who received 1L therapy, only half (50.6%) received 2L therapy during the study period
- Early uptake of avelumab as 1LM was observed in accordance with treatment guidelines
- As longer follow-up becomes available, future analyses should examine clinical outcomes of patients who received avelumab 1LM following 1L PBC

# **SPADE: Design of a Real-world Observational Study of Avelumab First-line Maintenance in Advanced Urothelial Carcinoma in the Asia-Pacific Region**

**Trials in Progress: Urothelial Carcinoma — Abstract No. TPS577 (Poster)**

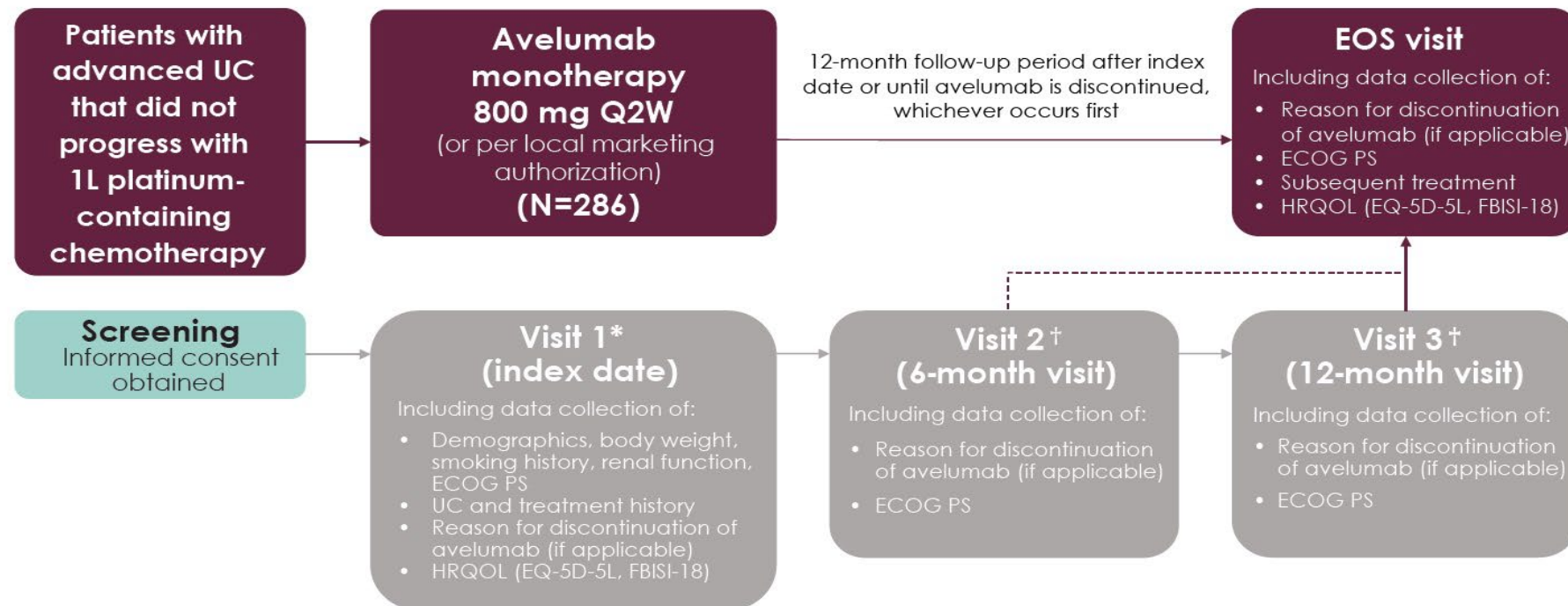
P.-J. Su, S.-H. Park, Y.-C. Tsai, M. Kim, W.-J. Wu, S. Gao, S.-J. Shin

# SPADE: Design of a Real-world Observational Study of Avelumab First-line Maintenance in Advanced Urothelial Carcinoma in the Asia-Pacific Region

## Objective

Noninterventional study to examine real-world outcomes in patients with advanced UC without disease progression after 1L platinum-containing chemotherapy who received avelumab 1L maintenance in the APAC region

## Study Design



\*Index date is defined as the date of initiation of avelumab 1L maintenance therapy. Screening and visit 1 can be performed on the same day. †Visits 2 and 3 will only be performed if the patient is still receiving avelumab treatment. If a patient discontinues avelumab before visit 2, EOS visit will be performed instead of visit 2. If a patient discontinues avelumab between visit 2 and visit 3, EOS visit will be performed instead of visit 3. If a patient is still receiving avelumab at visit 3, EOS visit will be performed at the same time as visit 3. A patient will be considered "lost to follow-up" after 2 documented failed attempts to contact the patient during the treatment period; the reason for discontinuation should be determined, if obtainable.

# SPADE: Design of a Real-world Observational Study of Avelumab First-line Maintenance in Advanced Urothelial Carcinoma in the Asia-Pacific Region

## Data Collection and Planned Analyses

### Patient demographics and clinical characteristics

- Patient demographics at index date (year of birth, country of residence, ethnicity, sex, weight, and smoking history)
- History of UC at index date (age at initial diagnosis, date of initial diagnosis, and TNM stage)
- ECOG PS at index date (visit 1), at 6 months (visit 2)/EOS, and at 12 months (visit 3)/EOS visits post index date
- Primary tumor location (upper or lower urinary tract)
- Location of metastases (bone or visceral)
- Prior cancer-related surgeries, cancer therapies or procedures
- Renal function at index date (normal or chronic kidney disease [mild/moderate/severe])

### Treatment patterns

- 1L platinum-containing chemotherapy details (type, number of cycles, and response per RECIST criteria [CR/PR/SD])
- Interval between end of 1L platinum-containing chemotherapy and avelumab 1L maintenance therapy
- Duration of avelumab 1L maintenance therapy (and reason for discontinuation, if applicable)
- Proportion of patients still receiving avelumab 1L maintenance at 12 months post index date
- Subsequent treatment plan (type and time to initiation of 2L therapy)

### Treatment outcomes

- OS rate at 6 months and at 12 months post index date
- HRQoL assessment per the EQ-5D-5L and NCCN/FACT FBIS-18 questionnaires at index date (visit 1) and EOS visit

- ▶ All planned analyses will be descriptive; no formal statistical comparisons will be performed
- ▶ 6- and 12-month OS rates will be analyzed using the Kaplan-Meier method
- ▶ HRQoL will be measured on the index date and at the end of study visit using the EQ-5D-5L and the NCCN/FACT FBIS-18 questionnaires
- ▶ An interim analysis is planned after ~30% of patients have been enrolled

## Authors' Conclusions

- The ongoing SPADE study will facilitate the understanding of real-world patient characteristics, treatment patterns, patient-reported outcomes (PROs), and treatment outcomes in patients with advanced UC receiving avelumab 1L maintenance in the APAC region
- Study enrollment began in December 2022 and is currently ongoing in South Korea, and expected to expand to Australia, Hong Kong, India, Malaysia, Singapore, and Taiwan in 2023

Su P-J, et al. ASCO-GU Cancers Symposium 2023. Abstract No. TPS577

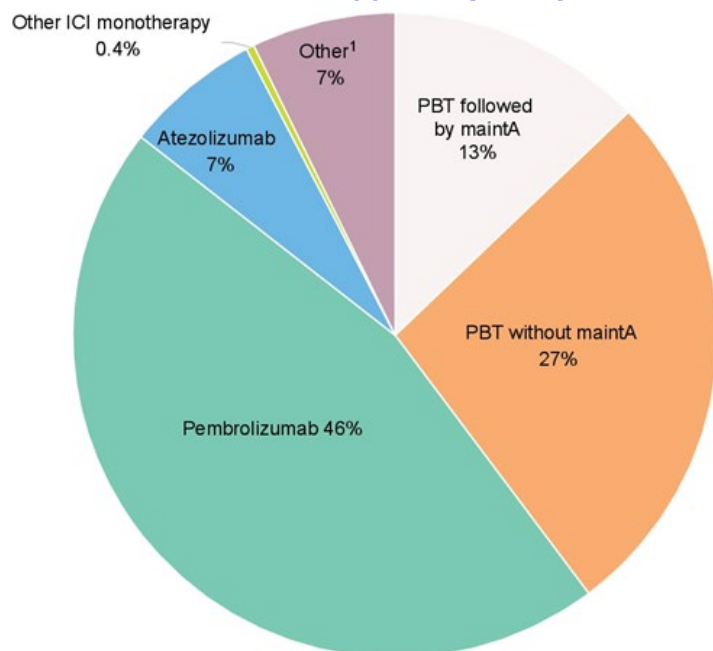
# US Real-World First-Line (1L) Treatment Patterns and Outcomes for Patients With Metastatic Urothelial Carcinoma Following Maintenance Avelumab Approval. (Li)

| Product  | Company | Indication/Patient Population | Phase and Trial ID                            | Abstract |
|----------|---------|-------------------------------|-----------------------------------------------|----------|
| Avelumab | Merck   | mUC                           | RWE, retrospective observational cohort study | 483      |

## Key Results

**Objective:** To describe: 1) Baseline patient characteristics, 2) Real-world 1L treatment patterns (including maintA use) following maintA approval, and 3) Real-world clinical outcomes by 1L treatment group for mUC patients who initiated 1L treatment in a US community oncology setting

**1L Treatment Pattern For Patients With mUC Following MaintA Approval (n=249)\***



### Patient characteristics at baseline (N=249)

- Median follow-up duration: 14.5 months
- Compared with mUC patients receiving 1L PBT:
  - 1L ICI monotherapy-treated mUC patients were older (73.5 vs 69.8 years)
  - Lower proportion of the 1L ICI monotherapy-treated patients had de novo disease (27% vs 54%)
  - Higher proportion of 1L ICI monotherapy-treated had visceral disease at baseline (56% vs 48%), Modified Charlson Comorbidity Index 3+ (21% vs 11%), and ECOG 2+ (21% vs 11%)

### Real-world 1L treatment patterns

- Of the 249 1L-treated mUC patients:
  - 53% received ICI monotherapy
  - 40% received PBT
  - 7% received other treatments (chemo, ICI-chemo, nonchemo/non-ICI)
- ~13% of received 1L PBT followed by maintA
- The most common ICI received in 1L was pembrolizumab (46%), followed by atezolizumab (7%)
- 1L ICI monotherapy use constituted the majority of systemic treatments used for patients ≥ 75 year and those with Modified Charlson Comorbidity Index ≥ 3
- Median duration of 1L treatment was 12 weeks for ICI monotherapy and 11 weeks for PBT

\*This includes patients diagnosed April 2020-June 2021, with follow-up until December 2021, last patient record, or death, whichever occurred first.

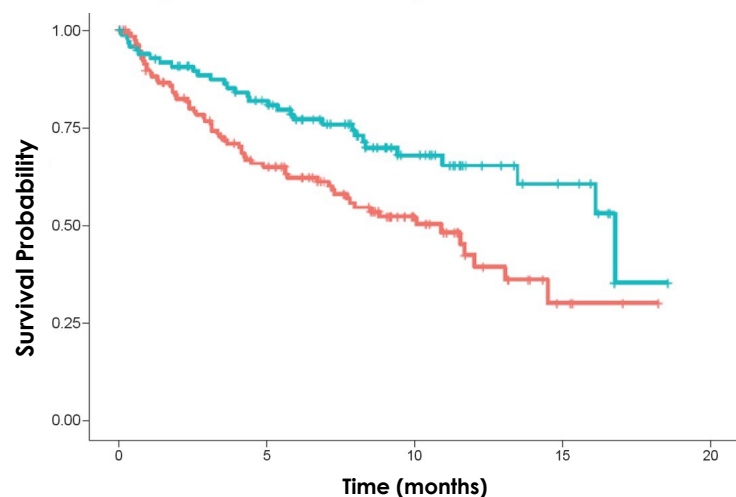
# US Real-World First-Line (1L) Treatment Patterns and Outcomes for Patients With Metastatic Urothelial Carcinoma Following Maintenance Avelumab Approval. (cont.) (Li)

| Product  | Company | Indication/Patient Population | Phase and Trial ID                            | Abstract |
|----------|---------|-------------------------------|-----------------------------------------------|----------|
| Avelumab | Merck   | mUC                           | RWE, retrospective observational cohort study | 483      |

## Key Results

### KM Estimates of OS For Patients With mUC Who Received 1L ICI monotherapy or PBT (+/- MaintA) Following MaintA Approval

Strata ICI monotherapy Platinum-based chemotherapy (+/- maintenance avelumab)



| OS                       | 1L ICI monotherapy | 1L PBT (+/- maintA) |
|--------------------------|--------------------|---------------------|
| Number of patients       | 132                | 99                  |
| Deaths, n (%)            | 62 (47.0%)         | 31 (31.3%)          |
| Median (95% CI) (months) | 10.9 (7.2, 13.0)   | 16.8 (13.5, NR)     |
| Survival probability     |                    |                     |
| 6 months                 | 62.3% (53.0, 70.3) | 77.3% (67.2, 84.6)  |
| 12 months                | 42.6% (30.8, 53.8) | 65.4% (53.1, 75.3)  |
| 18 months                | 30.2% (16.2, 45.6) | 35.4% (9.1, 63.9)   |

### Real-world OS

- Two-fifths (n=101) of 1L-treated mUC patients died during follow-up
- Median OS (95% CI) for patients receiving 1L ICI monotherapy was 10.9 (7.2, 13.0) months
- Median OS (95% CI) for patients receiving 1L PBT (+/- maintA) was 16.8 (13.5, NR) months

\*This includes patients diagnosed April 2020-June 2021, with follow-up until December 2021, last patient record, or death, whichever occurred first.

## Analysis/Implications

- The uptake of maintA in this US community oncology dataset was modest during the 18-month period following maintA approval
- ICI monotherapy was the most utilized 1L treatment for mUC patients, particularly the elderly and those with poorer health status
- Real-world median OA for 1L PBT (+/- maintA) during the post-mainA era was similar to that during the pre-mainA era, demonstrating a relatively small impact of maintA approval on OS and continued unmet need in 1L PBT-treated mUC patients
- Future studies are warranted to track changes in treatment patterns and outcomes with larger sample size and longer follow-up in the real-world setting

# Cell-free Urinary Tumor DNA to Detect Minimal Residual Disease Prior to Repeat Transurethral Resection of Bladder Tumor in Non-muscle Invasive Bladder Cancer: A Prospective Study (Rose)

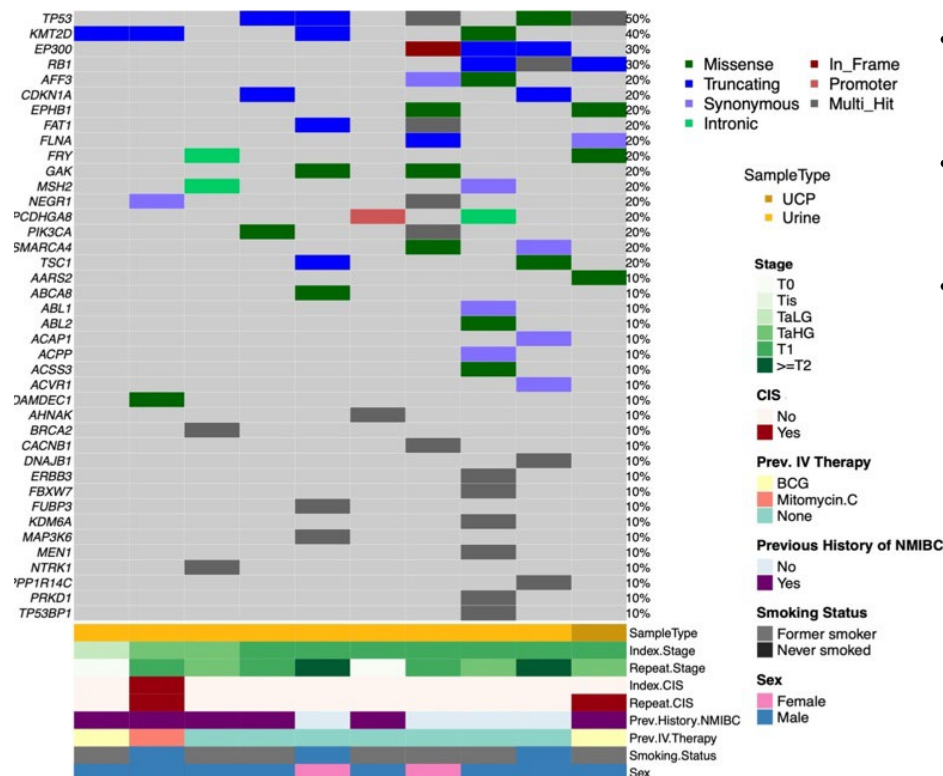
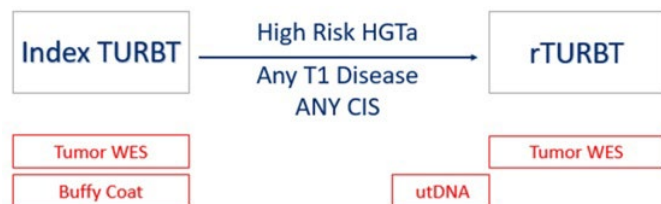
| Product | Company | Indication/patientPopulation | Phase and Trial ID | Abstract       |
|---------|---------|------------------------------|--------------------|----------------|
| NA      | NA      | NMIBC                        | NA                 | LBA445, poster |

## Key Results

**Objective:** To assess cell-free urinary tumor DNA (utDNA)'s ability to measure MRD at the time of standard-of-care rTURBT in NMIBC

- 11 patients underwent rTURBT for high-risk NMIBC

### Schema

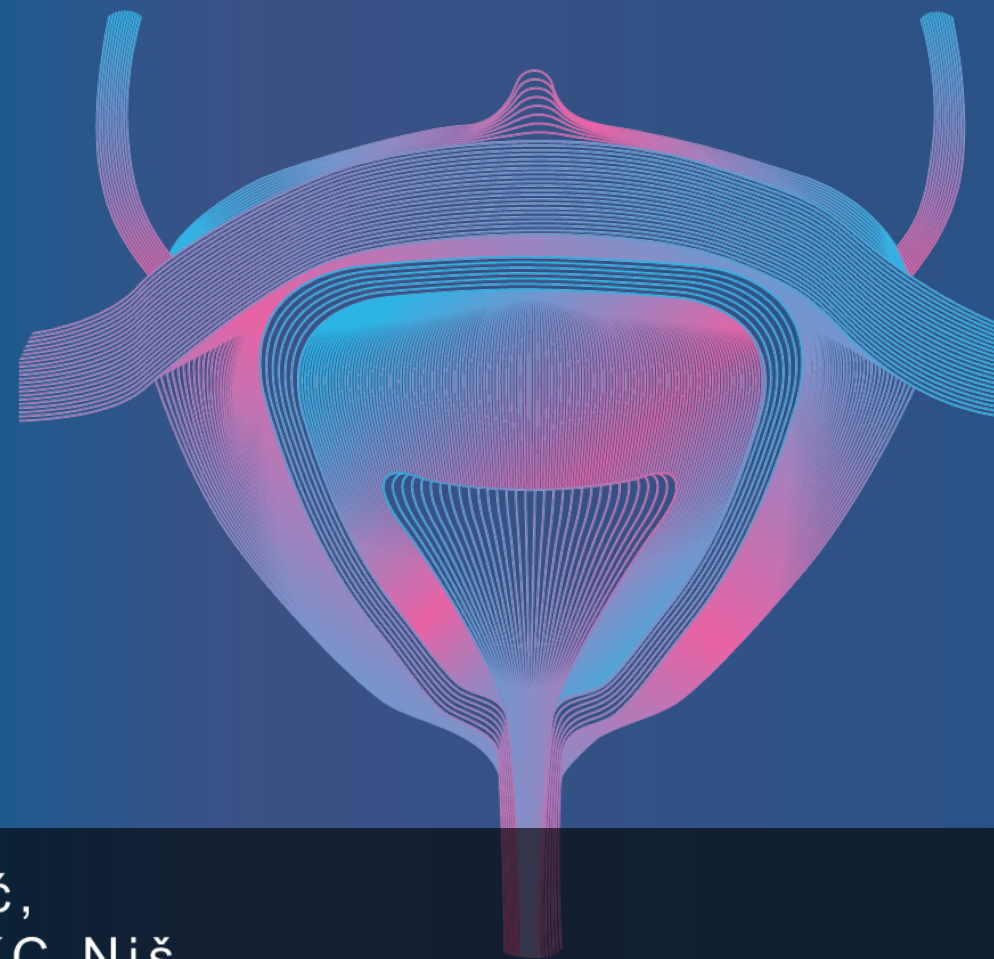


- 50 genes with NS mutations found in at least 2 samples were identified including TP53, PIK3CA, RB1, MYC, CDKN1A and ARID1A
- Concordance rates were 83% on average between primary and rTURBT, highest for patients upstaged to T2 disease and lowest for patients harboring CIS
- The tumor fraction of utDNA was higher in patients with residual disease (mean 2.5% vs 0.2%,  $P=0.10$ )

### Analysis/implications

- Cell-free urinary tumor DNA can be a potential liquid biomarker to detect minimal residual disease in NMIBC. However, due to the small sample size, further studies are needed to determine if it can be used for risk-stratify patients prior to TURBT

# Terapijski menadžment pacijenata sa urotelijalnim karcinomom lečenih inovativnom imunoterapijom check-point inhibitorima



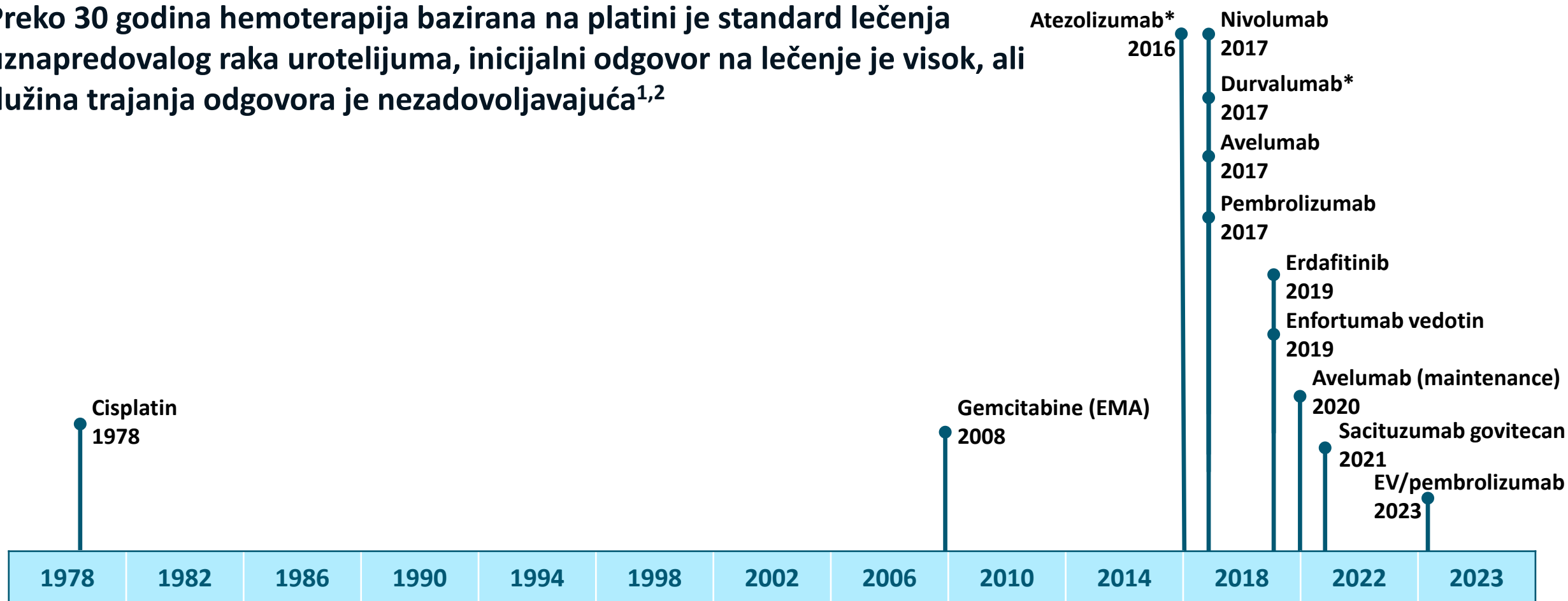
Dr Vesna Stojanović,  
Klinika za onkologiju UKC Niš

Akreditovano predavanje, Medscape Srbija 2023



# The Treatment Landscape for Locally Advanced/ Metastatic Urothelial Carcinoma

Preko 30 godina hemoterapija bazirana na platini je standard lečenja uznapredovalog raka urotelijuma, inicijalni odgovor na lečenje je visok, ali dužina trajanja odgovora je nezadovoljavajuća<sup>1,2</sup>



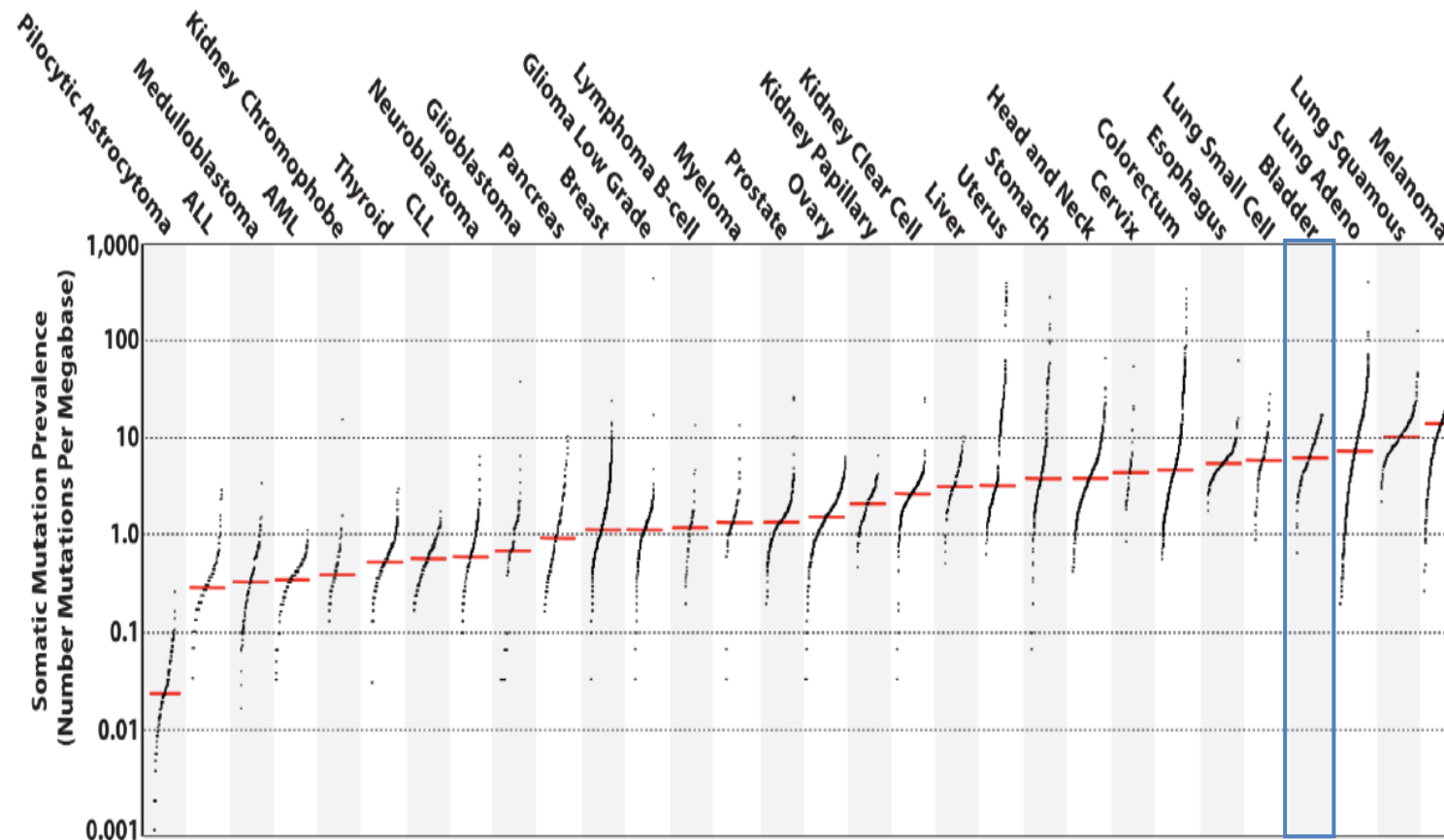
1.Simeon JC et al. Cancer Epidemiol 2019;60:121-127.; 2. Niegisch G, et al. J Cancer. 2018;9 (8 ):1337-1348

Cisplatin PI. [ema.europa.eu/en/medicines/human/referrals/gemzar](https://www.ema.europa.eu/en/medicines/human/referrals/gemzar). Rhea. Clin Med Insights Oncol. 2021;15:11795549211044963.

Nivolumab PI. Avelumab PI. Pembrolizumab PI. Erdafitinib PI. Enfortumab vedotin PI. Avelumab PI. Sacituzumab govitecan PI.

# UC is an immunogenic tumour with a high mutational burden<sup>1</sup>

## Prevalence of somatic mutations in different tumour types<sup>1</sup>



### UC immunogenicity<sup>1-4</sup>

#### Gene level

- High PD-L1 expression
- DNA damage response mutations
- 4<sup>th</sup> highest median tumour mutational burden, after melanoma and two NSCLC subtypes

...leading to the formation of immunogenic neoantigens

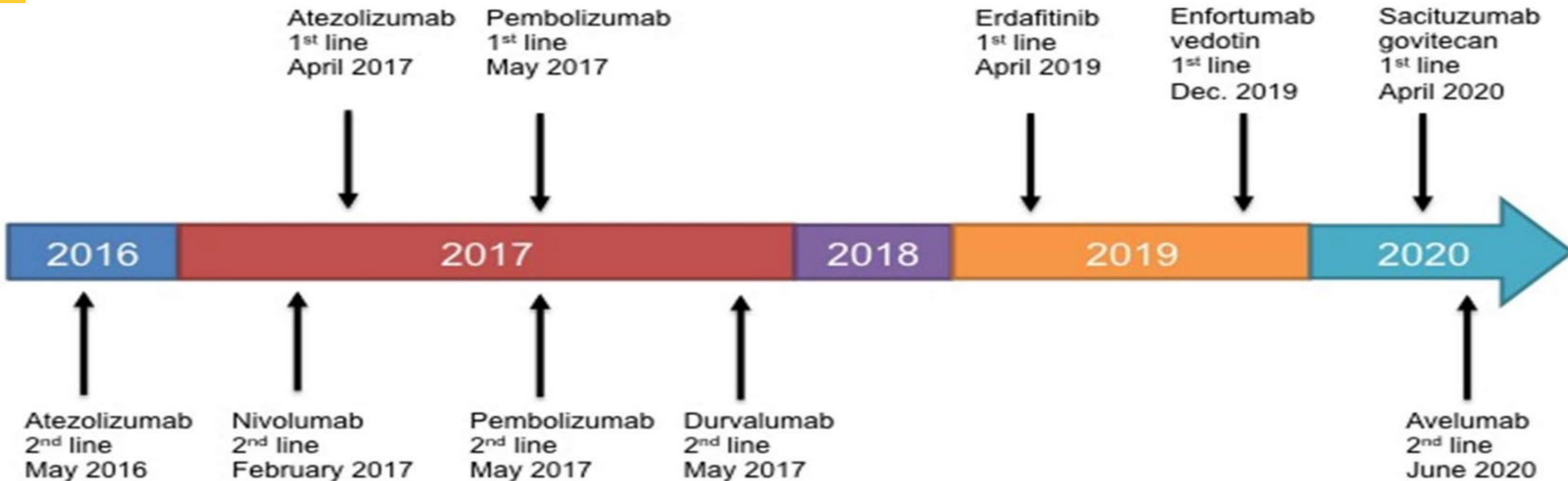
#### Protein level

- Relatively high PD-L1 surface expression

**Cancers with higher rates of somatic mutations have been shown to respond better to IO checkpoint inhibitors<sup>2</sup>**

CPI, checkpoint inhibitor; CT, chemotherapy; DNA, deoxyribonucleic acid; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.

# Systemic Therapy for Urothelial Carcinoma:



There were 10 US Food and Drug Administration approvals of novel therapies from 2016 to 2020

**Atezolizumab, nivolumab, avelumab, durvalumab, and pembrolizumab** were approved for patients who progressed on platinum-based chemotherapy (CT) in the advanced setting or within 12 months of neoadjuvant or adjuvant (NA/A) treatment

**Atezolizumab and pembrolizumab** are approved for treatment-naïve, cisplatin-ineligible patients who have tumors with high PD-L1 expression, as defined below.

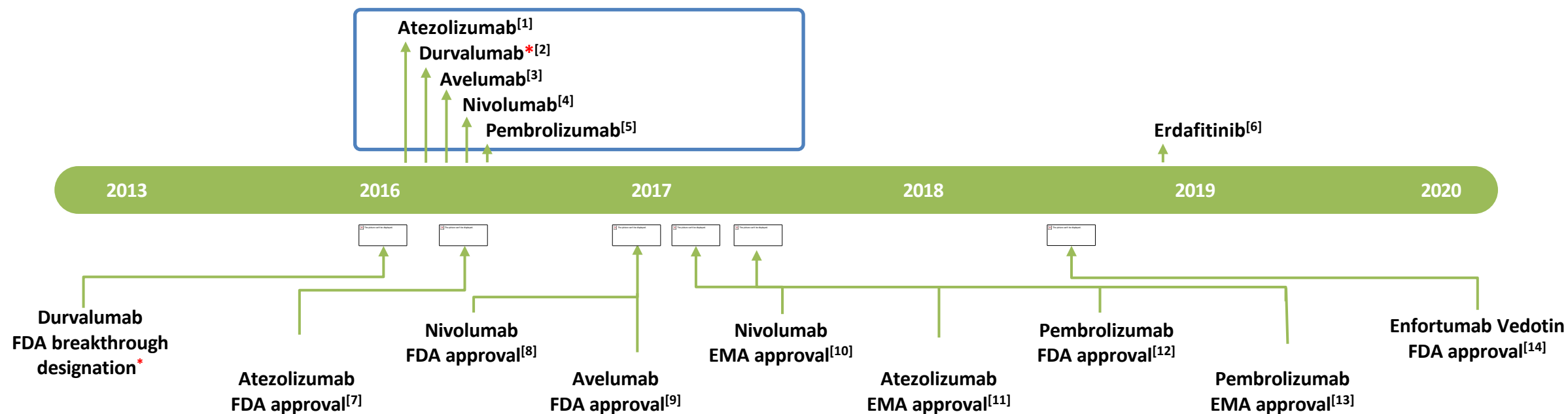
**Erdatifinib**, a fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor (TKI), was approved for patients who have tumors with FGFR2 or FGFR3 alterations and progressed on platinum-based CT.

**Enfortumab vedotin**, an antibody-drug conjugate (ADC), is approved for patients who progressed on platinum-based CT.

Maintenance IO with **avelumab** is a standard of care for all patients with disease stabilisation on first-line platinum-based chemotherapy.

**Sacituzumab** govitecan has received accelerated FDA approval for metastatic UC with prior platinum and IO pre-treatment.

# Systemic Therapy for Urothelial Carcinoma: 5 New Immunotherapeutic Agents

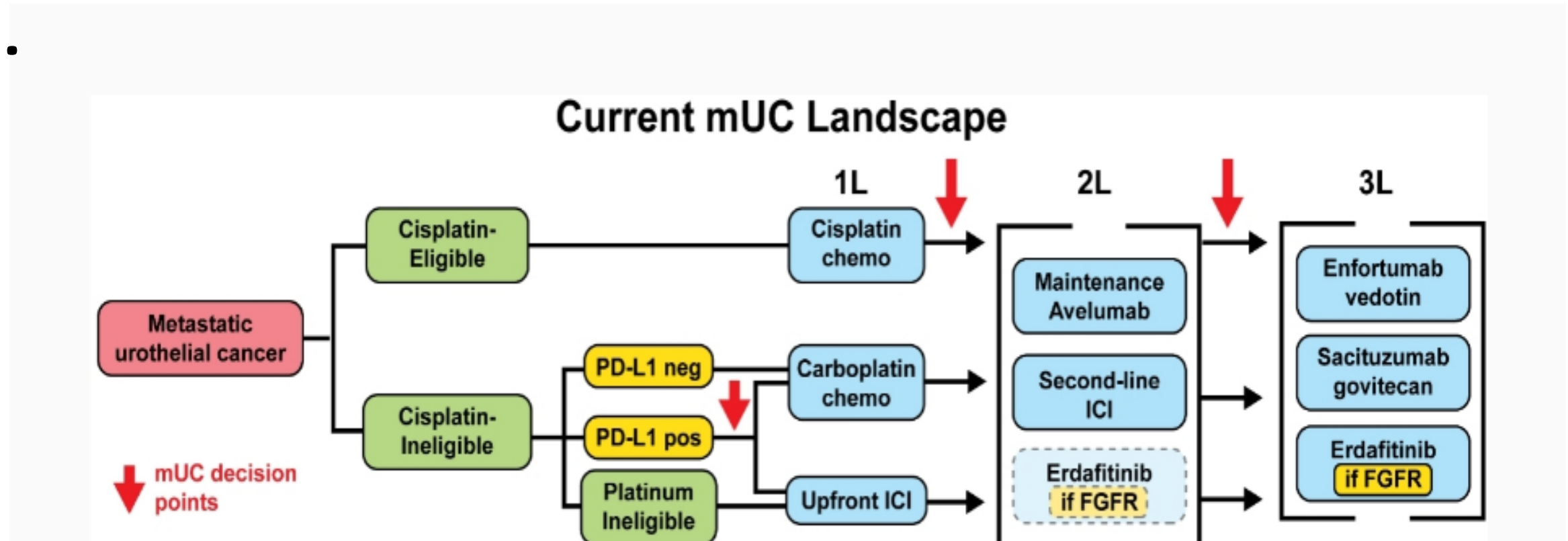


1. Atezolizumab PI. 2. Durvalumab PI. 3. Avelumab PI. 4. Nivolumab PI. 5. Pembrolizumab PI. 6. Erdafitinib PI. 7. FDA. Atezolizumab for urothelial carcinoma. May 19, 2016. 8. FDA. Nivolumab for treatment of urothelial carcinoma. Feb 2, 2017. 9. FDA. FDA grants accelerated approval to avelumab for urothelial carcinoma. May 9, 2017. 10. EMA. Nivolumab assessment report. June 28, 2018. 11. EMA. Atezolizumab assessment report. July 20, 2017. 12. FDA. Pembrolizumab: advanced or metastatic urothelial carcinoma. May 18, 2017. 13. EMA. Pembrolizumab assessment report. July 20, 2017. 14. FDA. FDA grants accelerated approval to enfortumab vedotin-ejfv for metastatic urothelial cancer. Dec 19, 2019.

\*FDA indication withdrawn in February 2021.

# What is the current state of the field regarding the treatment of patients with advanced bladder cancer?

•



**enfortumab vedotin with pembrolizumab (EV/P) enfortumab vedotin (EV )**

PD-L1: Programmed death-ligand 1; ICI: immune checkpoint inhibitor; 1L: first-line; 2L: second-line; 3L: third-line.

# First line mUC: status september 2020

## PLATINUM-ELIGIBLE

### CISPLATIN

PS 0-1 and GFR >60ml/min

### CARBOPLATIN

PS 2 or GFR 30-60 ml/min

Cisplatin/Gemcitabine  
or MVAC 4-6 cycles

Carboplatin/Gemcitabine  
4-6 cycles

CR/PR/SD (85%)

Switch maintenance IO (Avelumab)

## PLATINUM-INELIGIBLE

PS 2 and GFR <60/min; PS >2; GFR <30ml/min

### PD-L1 +

### PD-L1 -

IO  
mono

BSC

FDA

## Cisplatin Ineligible

### Preferred

- Gemcitabine + carboplatin → avelumab maintenance
- Atezolizumab (PD-L1 + or pts not eligible for platinum chemo regardless of PD-L1)
- Pembrolizumab (for pts not eligible for platinum chemo)

### Other recommended

- Gemcitabine ± paclitaxel

# Therapy: A New Standard of Care for Cisplatin-Ineligible Metastatic Urothelial Carcinoma

**IMvigor210  
(cohort 1)<sup>1,2</sup>  
Atezolizumab**



- ORR: 23%; CR: 9%
- mOS: 16.3 mo
- 1-yr OS: 58%; 2-yr OS: 41%
- FDA approved in February 2017

**KEYNOTE-052<sup>3</sup>  
Pembrolizumab**



- ORR: 29%; CR: 9%
- mOS: 11.3 mo
- PD-L1 CPS  $\geq 10\%$  ORR
- FDA approved in May 2017



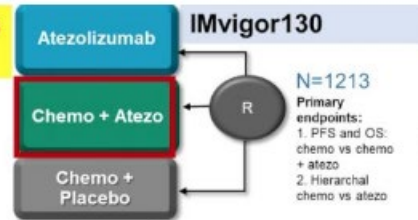
## Regulatory Updates for PD-1/PD-L1 Therapy in Advanced Cisplatin-Ineligible UC

Requires the use of an FDA-approved companion diagnostic test to determine PD-L1 levels in tumor tissue

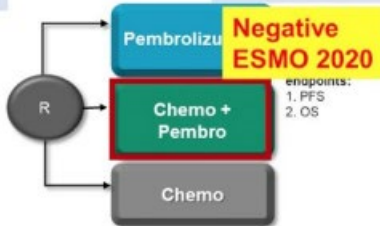
- **Pembrolizumab** is indicated for treating patients with locally advanced or metastatic UC not eligible for cisplatin-containing chemotherapy and whose tumors express **PD-L1 (CPS  $\geq 10$ )** as determined by an FDA-approved test, or in patients not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status
- **Atezolizumab** is indicated for treating patients with locally advanced or metastatic UC not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1–stained tumor-infiltrating immune cells covering  **$\geq 5\%$  of the tumor area**), as determined by an FDA-approved test, or in patients not eligible for any platinum-containing therapy, regardless of PD-L1 status

# Is there a role for chemo + IO?

**Positive for PFS  
ESMO 2019**



**KEYNOTE-361**

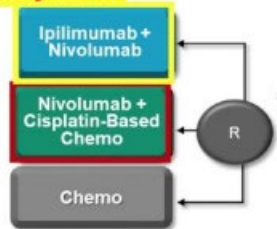


**Negative, PD-L1+  
Press Release May 2022**

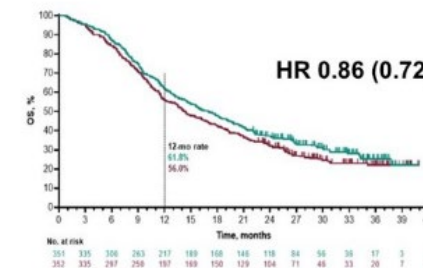
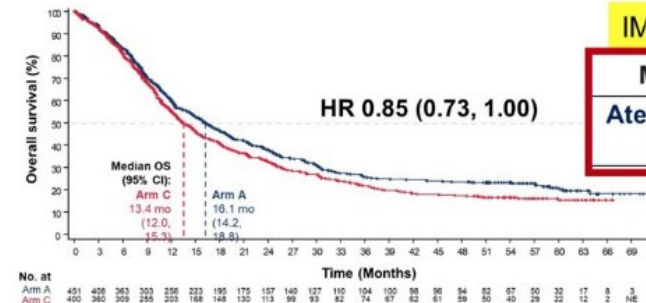
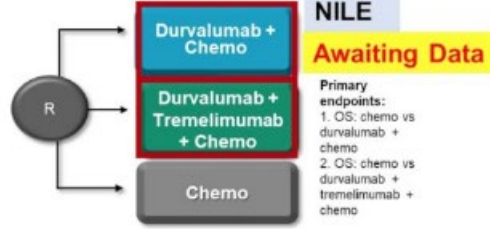
**CheckMate-901**

N=690

Primary endpoints:  
1. OS in cis-ineligible  
2. OS in PD-L1+  
3. PFS in cis-eligible  
4. OS in cis-eligible



**Metastatic UC  
Cisplatin-Eligible  
or -Ineligible**



# Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line chemotherapy in advanced urothelial carcinoma: JAVELIN Bladder 100 phase III results

Thomas Powles,<sup>1</sup> Se Hoon Park,<sup>2</sup> Eric Voog,<sup>3</sup> Claudia Caserta,<sup>4</sup> Begoña P. Valderrama,<sup>5</sup> Howard Gurney,<sup>6</sup> Haralabos Kalofonos,<sup>7</sup> Sinisa Radulovic,<sup>8</sup> Wim Demey,<sup>9</sup> Anders Ullén,<sup>10</sup> Yohann Lorient,<sup>11</sup> Srikala S. Sridhar,<sup>12</sup> Norihiko Tsuchiya,<sup>13</sup> Evgeny Kopyltsov,<sup>14</sup> Cora N. Sternberg,<sup>15</sup> Joaquim Bellmunt,<sup>16</sup> Jeanny B Aragon-Ching,<sup>17</sup> Daniel P. Petrylak,<sup>18</sup> Alessandra di Pietro,<sup>19</sup> Petros Grivas<sup>20</sup>

<sup>1</sup>Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, UK; <sup>2</sup>Sungkyunkwan University Samsung Medical Center, Seoul, Korea; <sup>3</sup>Centre Jean Bernard Clinique Victor Hugo, Le Mans, France; <sup>4</sup>Medical Oncology Unit, Azienda Ospedaliera S. Maria, Terni, Italy; <sup>5</sup>Department of Medical Oncology, Hospital Universitario Virgen del Rocío, Sevilla, Spain; <sup>6</sup>Department of Clinical Medicine, Macquarie University, Sydney, New South Wales, Australia; <sup>7</sup>Medical Oncology, University General Hospital of Patras, Patras, Greece; <sup>8</sup>Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; <sup>9</sup>Department of Medical Oncology, AZ KLINA, Brasschaat, Belgium; <sup>10</sup>Patient Area Pelvic Cancer, Theme Cancer, Karolinska University Hospital and Department of Oncology-Pathology, Karolinska Institute, Solna, Sweden; <sup>11</sup>Gustave Roussy, INSERMU981, Université Paris-Saclay Villejuif, France; <sup>12</sup>Princess Margaret Cancer Center, University Health Network, Toronto, Ontario, Canada; <sup>13</sup>Department of Urology, Yamagata University Faculty of Medicine, Yamagata, Japan; <sup>14</sup>State Institution of Healthcare Regional Clinical Oncology Dispensary, Omsk, Russia; <sup>15</sup>Weill Cornell Medicine, Hematology/Oncology, New York, New York, USA; <sup>16</sup>Department of Medical Oncology, Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, Massachusetts, USA; <sup>17</sup>Inova Schar Cancer Institute, Fairfax, Virginia, USA; <sup>18</sup>Yale Cancer Center, New Haven, Connecticut, USA; <sup>19</sup>Pfizer srl, Milano, Italy; <sup>20</sup>Department of Medicine, Division of Oncology, University of Washington; Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

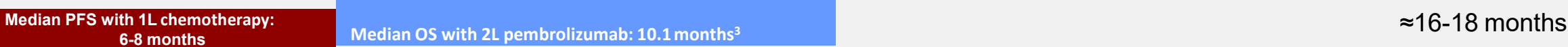
# Režim JAVELIN Bladder 100 je pokazao najdužu medijanu OS od svih ispitivanja faze 3 kod pacijenata sa lokalno uznapredovalim ili metastatskim UC<sup>1</sup>

**JAVELIN Bladder 100:** 1L platinum-containing chemotherapy avelumab 1L maintenance in patients without PD

Estimated median OS from start of 1L therapy



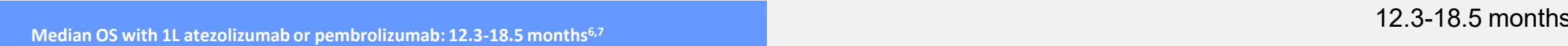
**ICI as 2L therapy after 1L platinum-containing chemotherapy**



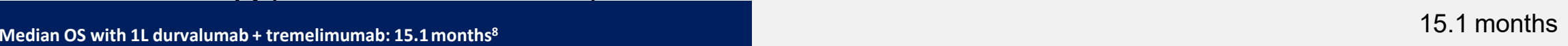
**ICI in combination with 1L platinum-containing chemotherapy**



**ICI as 1L monotherapy (for cisplatin-ineligible patients with a PD-L1+ tumor only)**



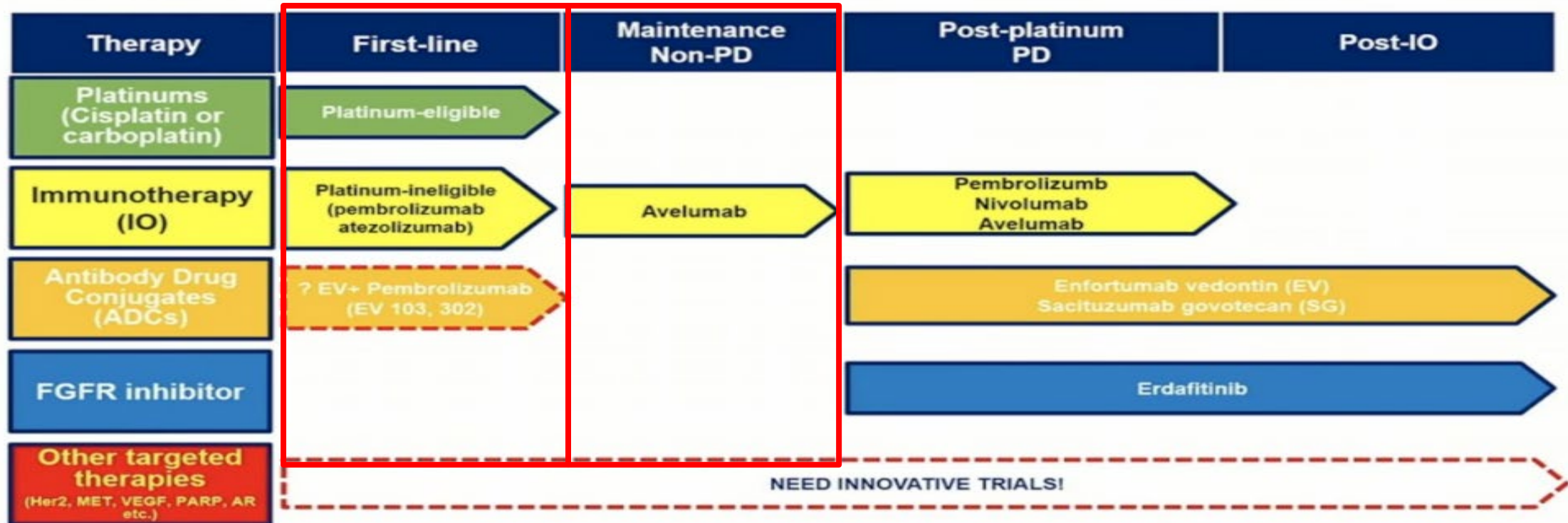
**ICI + ICI as 1L therapy (anti-PD-L1 + anti-CTLA-4)**



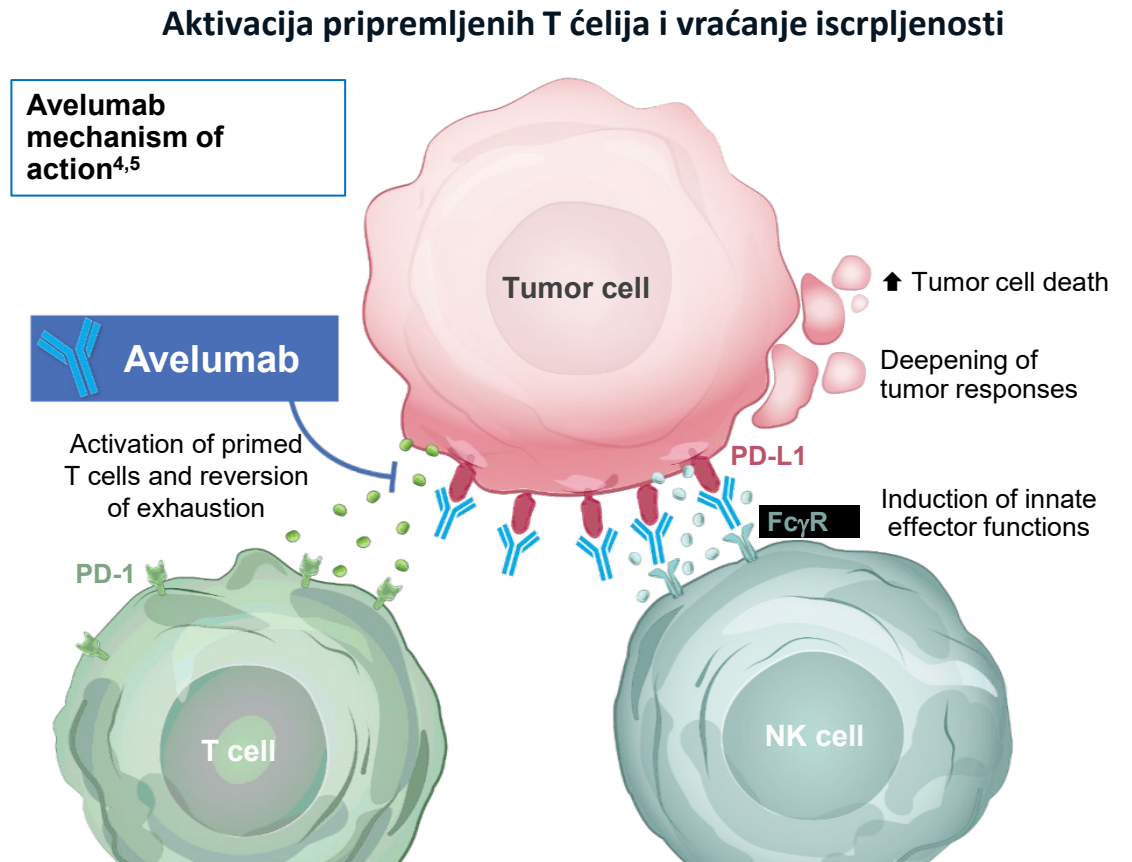
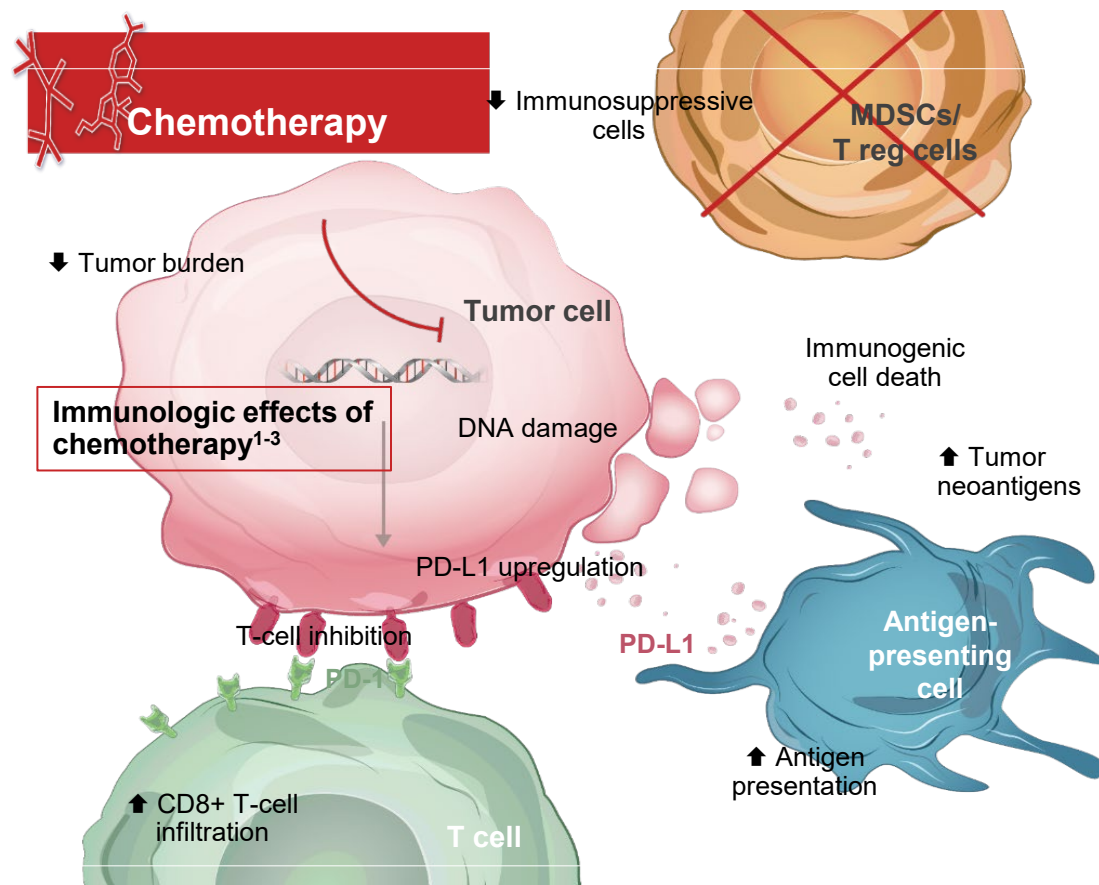
\* lekovi durvalumab, tremelimumab nisu registrovani u Srbiji za lečenje mUC

Reprinted from Grivas P, et al. Cancer Treat Rev. 2021;97:102187, Copyright 2021, with permission from Elsevier.  
1L, first-line; 2L, second-line; ICI, immune checkpoint inhibitor; OS, overall survival; PD, progressive disease; TFI, treatment-free interval  
1. Grivas P, et al. Cancer Treat Rev. 2021;97:102187; 2. Powles T, et al. N Engl J Med. 2020;383:1218-30; 3. Fradet Y, et al. Ann Oncol. 2019;30:970-6; 4. Galsky MD, et al. Lancet. 2020;395:1547-1557; 5. Powles T, et al. Lancet Oncol. 2021;22:931-945; 6. Balar AV, et al. Lancet. 2017;389:67-76; 7. Vuky J, et al. J Clin Oncol. 2020;38:2658-66; 8. Powles T, et al. Lancet Oncol. 2020;21:1574-88.

# Current Treatment Options for Metastatic Urothelial Cancer (mUC) June 2022



# Preclinical studies suggest that maintenance therapy could allow additive or synergistic antitumor activity between agents with different mechanisms of action<sup>1</sup>



**In addition to direct cytotoxic activity, chemotherapy has immunogenic effects, which may result in enhanced antitumor activity with immune checkpoint inhibitor unapređeni maintenance therapy<sup>1</sup>**

FcγR, Fc gamma receptor; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Treg, T regulatory

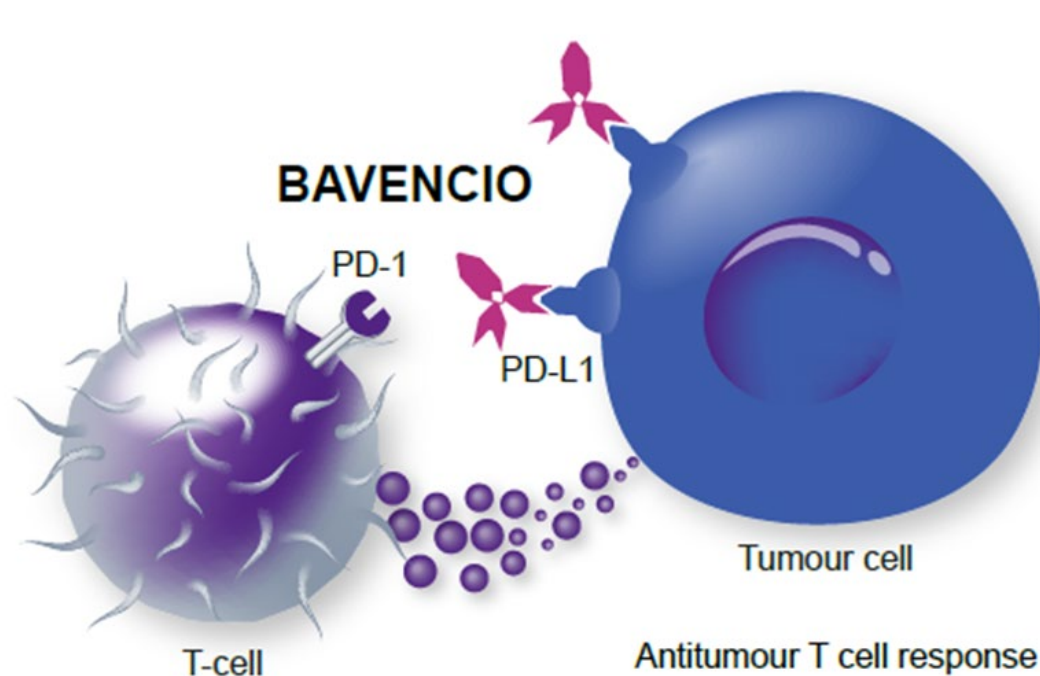
1. Grivas P, et al. Target Oncol. 2019;14:505-25; 2. Galluzzi L, et al. Cancer Cell. 2015;28:690-714; 3. De Biasi AR, et al. Clin Cancer Res. 2014;20:5384-91; 4. Collins JM, Gulley JL. Hum Vaccin Immunother. 2019;15:891-908; 5. Joseph J, et al. Ann Pharmacother. 2018;52:928-35.

# Mehanizam delovanja Avelumaba-Bavencio

Avelumab je humani imunoglobulin, monoklonsko At usmereno na ligand 1 programirane smrti ć-je (PD-L1).

Avelumab se veže na PD-L1 i blokira interakciju PD-L1 i receptora 1 programirane smrti ćelije (PD-1) i receptora B7.1. To sprečava supresivne učinke PD-L1 na citotoksične CD8+ T-celije, što dovodi do obnove antitumorskih odgovora T-ć-ja

Avelumab indukuje lizu tumorskih c-ja posredovanu celijama prirodnim ubojicama (engl. Natural Killer, NK) putem ćelijske citotoksičnosti zavisne od At (engl. antibody-dependent cell-mediated cytotoxicity, ADCC).



\*Preclinical model *in vitro* data.

ADCC, antibody-dependent cellular cytotoxicity; IgG1, immunoglobulin G1; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

1. BAVENCIO® (avelumab) Sažetak karakteristika leka, Decembar 2021

2. Boyerinas B et al. *Cancer Immunol Res* 2015;3:1148–1157.

## **AVELUMAB (BAVENCIO)**

### **Terapijske indikacije**

- Lek Bavencio je indikovano kao monoterapija u prvoj liniji terapije održavanja kod odraslih pacijenata sa lokalno uznapređovalim ili metastatskim urotelijalnim karcinomom kod kojih nije došlo do progresije nakon hemioterapije na bazi platine.
- Lek Bavencio u kombinaciji sa aksitinibom indikovano je kao prva linija terapije kod odraslih pacijenata sa uznapređovalim karcinomom bubrežnih ćelija, RCC
- Lek Bavencio je indikovano kao monoterapija za lečenje odraslih pacijenata sa metastatskim karcinomom Merkelovih ćelija.

# Ko su kandidati za terapiju održavanja Avelumabom?

## JAVELIN Bladder 100 regimen with BAVENCIO® (avelumab) as first-line maintenance treatment

### Platinum-containing chemotherapy

(Prior to study initiation)

#### KEY ELIGIBILITY CRITERIA<sup>1</sup>

- Unresectable, locally advanced or metastatic UC
- ≥1 measurable lesion defined by RECIST v1.1
- Patients must have received 4-6 cycles of platinum-containing chemotherapy (gemcitabine + cisplatin and/or gemcitabine + carboplatin)
- ECOG PS 0 or 1

#### KEY EXCLUSION CRITERIA

- Patients with autoimmune diseases or medical conditions requiring systemic immunosuppression

Patients with  
CR, PR, or SD

Treatment  
initiated within  
4-10 weeks after  
chemotherapy

1:1 randomization  
N=700

n=350

BAVENCIO 10 mg/kg  
intravenous infusion every  
2 weeks + best supportive  
care (BSC)\*

- Treatment until  
disease progression or  
unacceptable toxicity

n=350

BSC alone\*

### First-line maintenance

(Endpoints measured from randomization after chemotherapy)

#### MAJOR EFFICACY OUTCOME MEASURE

- **Overall survival (OS)**
  - All randomized patients
  - Patients with PD-L1-positive tumors<sup>†</sup>

Recommended dose of BAVENCIO® (avelumab)

800 MG IV INFUSION



OVER 60 MINUTES



EVERY 2 WEEKS



Injection: 200 mg/10 mL (20 mg/mL) solution for infusion in a single-dose vial.

Prior to BAVENCIO administration      PREMEDICATION



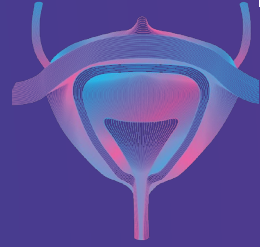
First 4 infusions

**Premedicate patients** with an antihistamine and with acetaminophen prior to the first 4 infusions

After 4th infusion

**Administer premedication** for subsequent BAVENCIO doses based on clinical judgement and presence and severity of prior infusion reactions

- **No dose reduction for BAVENCIO is recommended**
- In general, **withhold** BAVENCIO for severe (Grade 3) immune-mediated adverse reactions
- **Permanently discontinue** BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids



# Treatment schedule (premedication and dose adjustment)<sup>1</sup>

In the JAVELIN Bladder 100 trial, patients who had not progressed on 4–6 cycles of 1L platinum-based CT\* were initiated on BAVENCIO 4–10 weeks following cessation of treatment with platinum-based CT.<sup>2</sup> Baseline radiological tumour assessment was performed during this treatment interval.<sup>2</sup> In this trial, the post-CT confirmatory scan was performed within 28 days prior to randomisation.<sup>3†</sup>

**Platinum-based CT regimen**

BAVENCIO can only be administered to adult patients who are progression-free following 1L platinum-based CT<sup>1</sup>

After cessation of 1L platinum-based CT<sup>1</sup>

Avelumab

2 weeks

BAVENCIO

2 weeks

Mandatory premedication should be administered before each of the first 4 infusions with an antihistamine and paracetamol; If the fourth infusion is completed without an infusion-related reaction, premedication for subsequent doses should be administered at the discretion of the physician.<sup>1‡</sup>

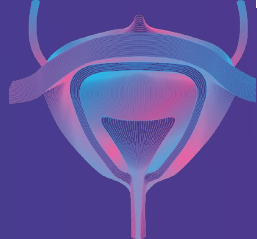
BAVENCIO should continue to be administered every 2 weeks until disease progression or unacceptable toxicity.<sup>1</sup> Treatment cessation may also be due to patient choice.

\*Cisplatin + gemcitabine or carboplatin + gemcitabine; † Randomisation occurred at least 4 weeks but no more than 10 weeks after the date of administration of the last dose of CT. Patients initiated study treatment (Cycle 1 Day 1) within 3 days after randomisation; ‡Patients should be monitored for the signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain and urticaria.

1L, first-line; CT, chemotherapy.

1. BAVENCIO® (avelumab) Sažetak karakteristika leka, Decembar 2021

2. Powles T et al. *N Engl J Med* 2020;383:1218–1220; 3 . Powles T et al. *N Engl J Med* 2020;383:1218–1220\_protocol.



# BEZBEDOSNI PROFIL AVELUMABA : 1

Only 9.0% (31 patients) of patients treated with avelumab required high-dose corticosteroids ( $\geq 40$  mg total daily prednisone or equivalent) following immune-related AEs<sup>1</sup>

| Adverse events, n (%) <sup>1</sup> | avelumab + BSC (n=344) |                  | BSC alone (n=345) |                |
|------------------------------------|------------------------|------------------|-------------------|----------------|
|                                    | All grades             | Grade $\geq 3$   | All grades        | Grade $\geq 3$ |
| <b>Patients with any event</b>     | <b>266 (77.3)</b>      | <b>57 (16.6)</b> | <b>4 (1.2)</b>    | <b>0</b>       |
| Pruritus                           | 47 (13.7)              | 1 (0.3)          | 0                 | 0              |
| Hypothyroidism                     | 36 (10.5)              | 1 (0.3)          | 0                 | 0              |
| Diarrhoea                          | 35 (10.2)              | 0                | 0                 | 0              |
| Infusion-related reaction          | 35 (10.2)              | 3 (0.9)          | 0                 | 0              |
| Asthenia                           | 34 (9.9)               | 0                | 0                 | 0              |
| Fatigue                            | 33 (9.6)               | 1 (0.3)          | 0                 | 0              |
| Rash                               | 25 (7.3)               | 1 (0.3)          | 0                 | 0              |
| Chills                             | 24 (7.0)               | 0                | 0                 | 0              |
| Nausea                             | 24 (7.0)               | 1 (0.3)          | 0                 | 0              |
| Arthralgia                         | 23 (6.7)               | 1 (0.3)          | 0                 | 0              |
| Pyrexia                            | 23 (6.7)               | 0                | 0                 | 0              |
| Hyperthyroidism                    | 21 (6.1)               | 0                | 0                 | 0              |
| Dry skin                           | 18 (5.2)               | 0                | 0                 | 0              |
| Increased amylase                  | 15 (4.4)               | 7 (2.0)          | 0                 | 0              |
| Increased lipase                   | 13 (3.8)               | 10 (2.9)         | 0                 | 0              |

**No new safety signals were identified for avelumab during the JAVELIN Bladder 100 study<sup>2</sup>**

**TRAEs led to discontinuation of avelumab in 9.6% of cases (n=33)<sup>1</sup>**

Safety was assessed in all patients who received  $\geq 1$  dose of BAVENCIO in the BAVENCIO arm, or who completed the Cycle 1 Day 1 visit in the BSC arm (N=689). Data cut-off date: 21 October 2019. Median duration of treatment in the BAVENCIO + BSC group was 24.9 weeks (range: 2.0–159.9); in the BSC alone group, it was 13.1 weeks (range: 0.1–155.6). Median follow-up for each group was more than 19 months.

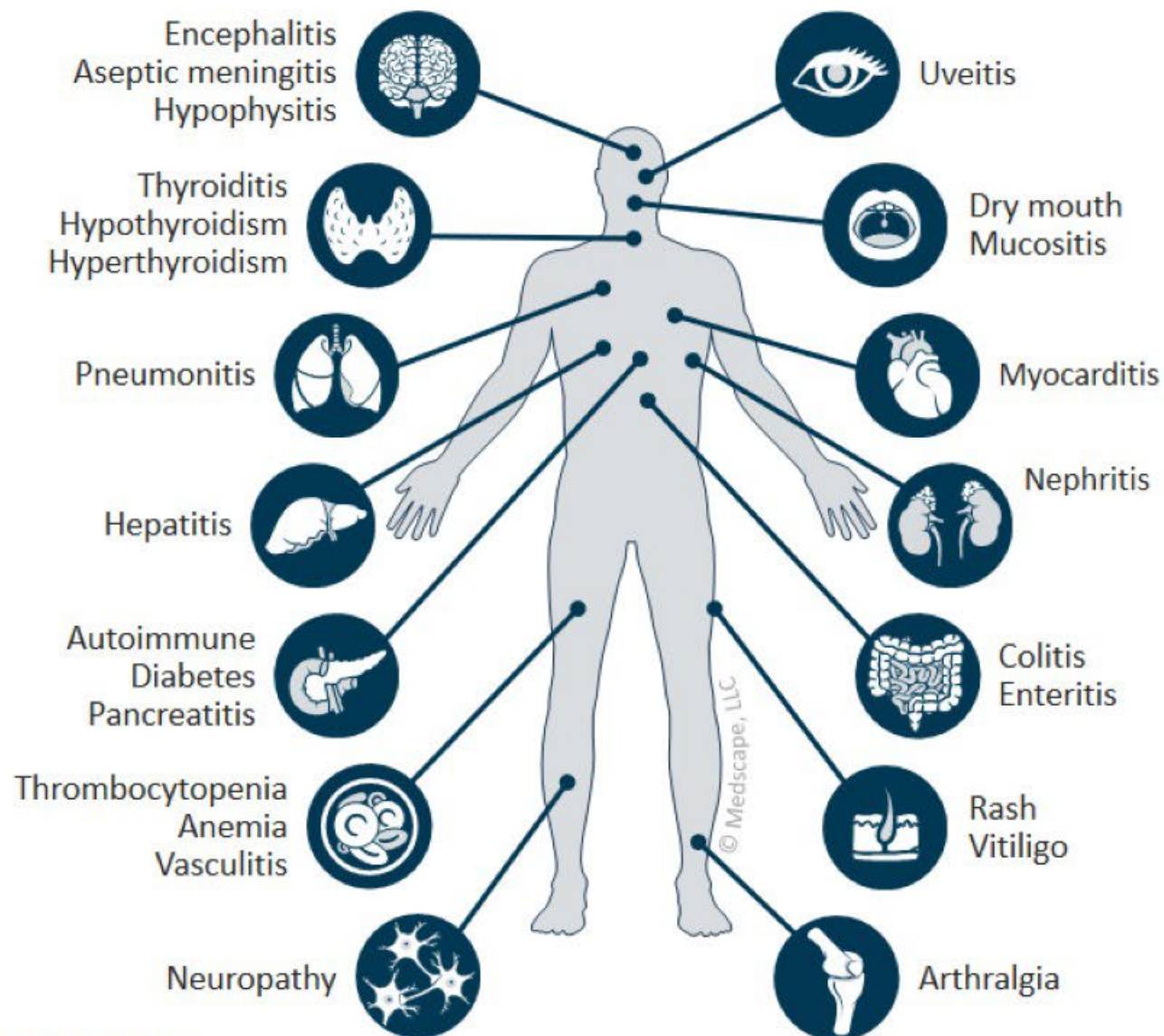
AE, adverse event; BSC, best supportive care; IRR, infusion-related reaction; TRAE, treatment-related adverse event.

Median duration of study treatment: 24.9 weeks in BAVENCIO + BSC group vs 13.1 weeks in the BSC alone group.<sup>2</sup>

1. Powles T et al. *N Eng J Med* 2020;383:1218–1230. Supplementary appendix; 2. Powles T et al. *N Eng J Med* 2020;383:1218–1230.

# The Spectrum of irAEs

- Common irAEs affect the skin, gut, endocrine organs, liver, musculoskeletal system, and lungs
- Most irAEs occur early, within weeks to a few months after treatment initiation
- First onset has been documented as long as 1 to 2 years after the start of therapy



irAE, immune-related adverse event.

Haanen JB, et al. Ann Oncol. 2017;28(suppl 4):iv119-iv142; Postow MA, et al. N Engl J Med. 2018;378:158-168.

# Organs affected by and manifestations of immune-related adverse events.

## Skin

- Dermatitis, erythroderma
- Erythema multiforme
- Stevens–Johnson syndrome
- Toxic epidermal necrolysis
- Psoriasis
- Vitiligo
- Alopecia

## Eyes

- Conjunctivitis
- Uveitis, iritis, retinitis
- Scleritis, episcleritis
- Blepharitis

## Endocrine system

- Hypo- or hyperthyroidism
- Hypophysitis, hypopituitarism
- Adrenal insufficiency
- Type 1 diabetes

## Cardiovascular system

- Myocarditis
- Pericarditis
- Vasculitis

## Liver

- Hepatitis

## Kidneys

- Nephritis
- Lupus-like glomerulonephritis

## Neurologic system

- Neuropathy
- Myelopathy
- Guillain–Barré syndrome
- Myasthenia gravis–like syndrome
- Encephalitis, meningitis

## Lungs

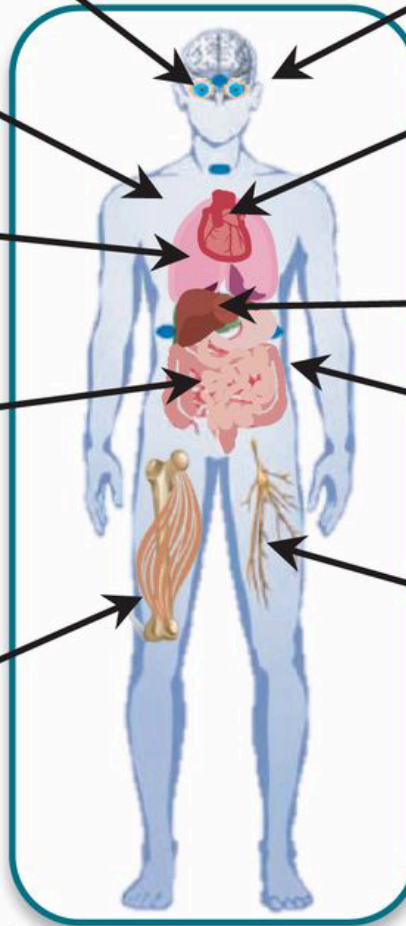
- Pneumonitis
- Pleuritis
- Interstitial lung disease

## Gastrointestinal tract

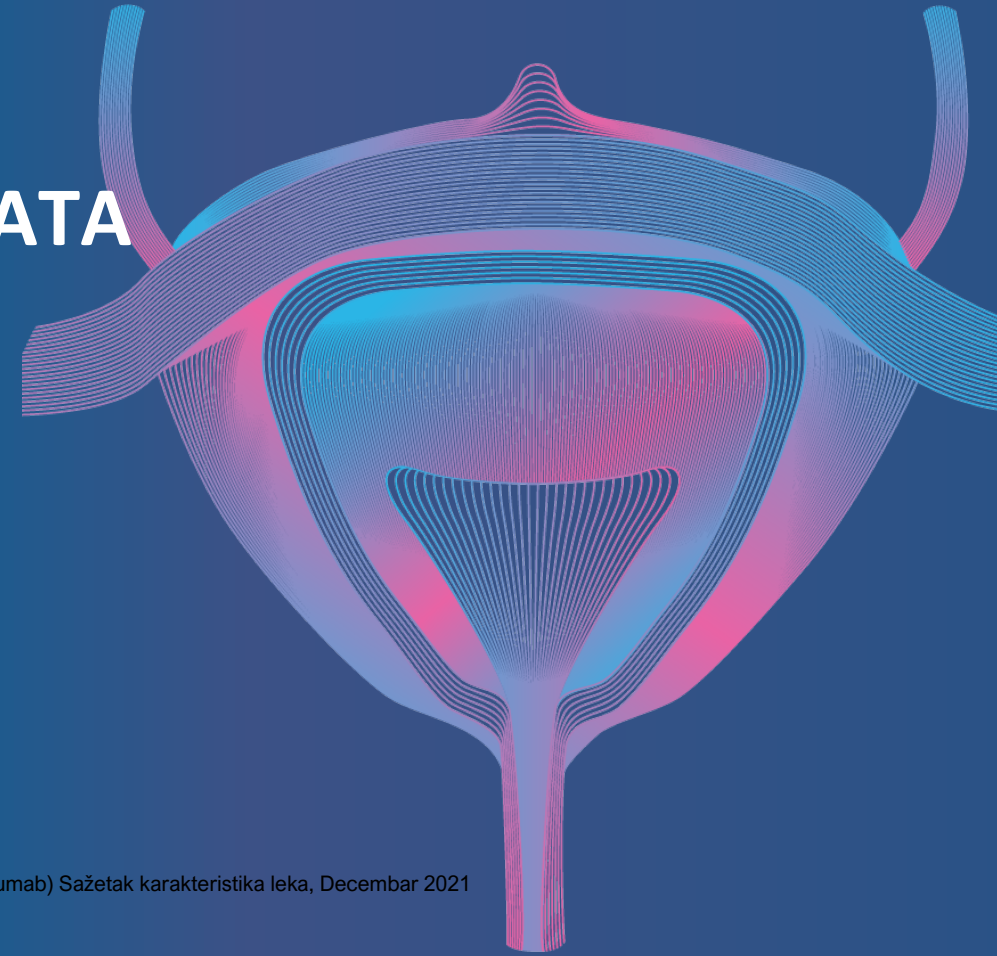
- Colitis
- Ileitis
- Pancreatitis
- Gastritis
- Perforation

## Musculoskeletal system

- Arthralgias, arthritis
- Myalgias, myositis
- Enthesitis



# KAKO SPREČITI POJAVU NEŽELJENIH EFEKATA TOKOM TERAPIJE BAVENCIO?



\*Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ).

BAVENCIO® (avelumab) Sažetak karakteristika leka, Decembar 2021

# Quick reference guide for managing immune-related adverse events when using BAVENCIO 1L maintenance therapy for mUC

Non immune-related and immune-related adverse events that are not attributed to the use of BAVENCIO are not listed. In general, dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.<sup>1</sup>

| Adverse events                                                                      |                                                  | Grade 1                                                                                         | Grade 2                                                                                                                                                                                     | Adverse events                                                                        |                                                  | Grade 3                                                                           | Grade 4                                                              |
|-------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------|
|    | <b>Infusion-related reactions<sup>1</sup></b>    | Mild transient reaction <sup>2,†</sup>                                                          | Shortness of breath or wheezing, chills or shaking, bumpy rash or skin wheals, flushing, low blood pressure (dizziness, fatigue, nausea), fever, back pain, abdominal pain <sup>1,3,†</sup> |    | <b>Infusion-related reactions<sup>1</sup></b>    | Prolonged; recurrence of symptoms following initial improvement <sup>2</sup>      | Life-threatening consequences <sup>2</sup>                           |
|    | <b>Pneumonitis<sup>1</sup></b>                   | Asymptomatic; clinical or diagnostic observations only <sup>2</sup>                             | Symptomatic; ↓ instrumental activity <sup>2,†</sup>                                                                                                                                         |    | <b>Pneumonitis<sup>1</sup></b>                   | Severely symptomatic; ↓ basic activity <sup>2</sup>                               | Life-threatening respiratory compromise <sup>2</sup>                 |
|    | <b>Hepatitis<sup>1</sup></b>                     | ASAT/ALAT up to 3 x ULN<br>Bilirubin up to 1.5 x ULN <sup>2</sup>                               | ASAT/ALAT 3-5 x ULN<br>Bilirubin 1.5-3 x ULN <sup>2</sup>                                                                                                                                   |    | <b>Hepatitis<sup>1</sup></b>                     | ASAT/ALAT 5-20 x ULN<br>Bilirubin 3-5 x ULN <sup>2</sup>                          | ASAT/ALAT > 20 x ULN<br>Bilirubin > 5 x ULN <sup>2</sup>             |
|    | <b>Colitis<sup>1</sup></b>                       | Asymptomatic; clinical or diagnostic observations only <sup>2</sup>                             | Abdominal pain; blood or mucus in stool <sup>2</sup>                                                                                                                                        |    | <b>Colitis<sup>1</sup></b>                       | Severe abdominal pain; stool irregularities; peritoneal irritation <sup>2,†</sup> | Life-threatening consequences <sup>2</sup>                           |
|    | <b>Pancreatitis<sup>1</sup></b>                  | Pancreatitis <sup>2, *</sup>                                                                    | Elevated enzymes; radiological findings only <sup>2</sup>                                                                                                                                   |    | <b>Pancreatitis<sup>1</sup></b>                  | Severe pain; vomiting <sup>2</sup>                                                | Life-threatening consequences <sup>2</sup>                           |
|    | <b>Myocarditis<sup>1</sup></b>                   | Asymptomatic with laboratory or cardiac imaging abnormalities <sup>2, †</sup>                   | Symptoms with moderate activity <sup>2,§</sup>                                                                                                                                              |    | <b>Myocarditis<sup>1</sup></b>                   | Severely symptomatic; symptoms at rest / with minimal activity <sup>2,§</sup>     | Life-threatening consequences <sup>2,§</sup>                         |
|    | <b>Adrenal insufficiency<sup>1</sup></b>         | Asymptomatic; clinical or diagnostic observations only <sup>2</sup>                             | Moderately symptomatic <sup>2</sup>                                                                                                                                                         |    | <b>Adrenal insufficiency<sup>1</sup></b>         | Severely symptomatic <sup>2</sup>                                                 | Life-threatening consequences <sup>2</sup>                           |
|    | <b>Hypothyroidism<sup>1</sup></b>                | Asymptomatic; clinical or diagnostic observations only <sup>2</sup>                             | Moderately symptomatic; Thyroid replacement therapy indicated; ↓ instrumental activity <sup>2</sup>                                                                                         |    | <b>Hypothyroidism<sup>1</sup></b>                | Severely symptomatic; ↓ Basic activity <sup>2</sup>                               | Life-threatening consequences <sup>2</sup>                           |
|   | <b>Hyperthyroidism<sup>1</sup></b>               | Asymptomatic; clinical or diagnostic observations only <sup>2</sup>                             | Moderately symptomatic; Thyroid suppression therapy indicated; ↓ instrumental activity <sup>2</sup>                                                                                         |   | <b>Hyperthyroidism<sup>1</sup></b>               | Severely symptomatic; ↓ Basic activity <sup>2</sup>                               | Life-threatening consequences <sup>2</sup>                           |
|  | <b>Hyperglycemia<sup>1</sup></b>                 | Fasting glucose value >ULN - 160 mg/dL;<br>Fasting glucose value >ULN - 8.9 mmol/L <sup>1</sup> | Fasting glucose value >160 - 250 mg/dL;<br>Fasting glucose value >8.9 - 13.9 mmol/L <sup>1</sup>                                                                                            |  | <b>Hyperglycemia<sup>1</sup></b>                 | >250 - 500 mg/dL; >13.9 - 27.8 mmol/L <sup>1</sup>                                | >500 mg/dL; >27.8 mmol/L; life-threatening consequences <sup>1</sup> |
|  | <b>Nephritis / renal dysfunction<sup>1</sup></b> | Creatinine > 1-1.5 x baseline value <sup>1</sup>                                                | Creatinine > 1.5-3.0 x baseline value <sup>2</sup>                                                                                                                                          |  | <b>Nephritis / renal dysfunction<sup>1</sup></b> | Creatinine >3.0 x baseline value <sup>2</sup>                                     | Creatinine > 6.0 x ULN <sup>2</sup>                                  |

 **Continue therapy, monitor symptoms**  
 **Withhold therapy until symptoms have decreased to grade 0-1**

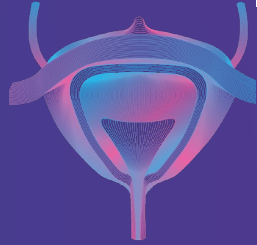
 **Permanently discontinue therapy, symptom-oriented diagnostics and therapy**  
 **1-2 mg/kg/day corticosteroids (e.g., prednisone) subsequent tapering**

Toxicity grades are in accordance with the US National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.03).

\* Reduce infusion rate by 50%; † Resume infusion at 50% lower rate; ‡ Permanently discontinue therapy if recurrent; § If no improvement after 24 hours of corticosteroid therapy, consider administration of additional immunosuppressants (e.g., mycophenolate, infliximab, antithymocyte globulin); ALAT: Alanine aminotransferase; ASAT: Aspartate aminotransferase; ULN: upper limit of normal; \* Suspected pancreatitis: avelumab should be withheld and should be permanently discontinued if confirmed. † Suspected myocarditis avelumab should be withheld and permanently discontinued if confirmed.

**References:** 1. BAVENCIO Summary of Product Characteristics. 2. U.S. Department of Health and Human Services, National Institute of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). V4.03: June 14, 2010. Available at: [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Accessed October 2022. 3. BAVENCIO Patient Information Leaflet.

# Immune-related adverse events<sup>1</sup>



Patient  
self-  
monitoring

**Adverse events may occur weeks or months after receiving the last dose of BAVENCIO.<sup>1</sup>**

Patients are advised to carry a BAVENCIO Patient Alert Card for at least 3 months after their last treatment with BAVENCIO<sup>2</sup>

Evaluation and  
management

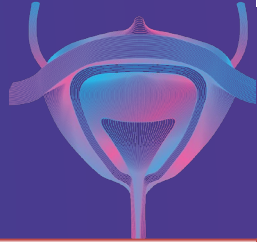
For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, BAVENCIO should be withheld and corticosteroids administered. If corticosteroids are used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement<sup>3</sup>

In patients, whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants may be considered<sup>3</sup>

Discontinuation

Some immune-related adverse reactions warrant permanent discontinuation regardless of grade<sup>3</sup>

**Most immune-related adverse reactions with avelumab were reversible and managed with temporary or permanent discontinuation of avelumab administration of corticosteroids and/or supportive care<sup>3</sup>**



# Infusion-related adverse reactions

**Monitor patients for signs and symptoms in other organs, including:<sup>1</sup>**

- Pyrexia
- Chills
- Flushing
- Hypotension
- Dyspnoea
- Wheezing
- Abdominal pain
- Back pain
- Urticaria

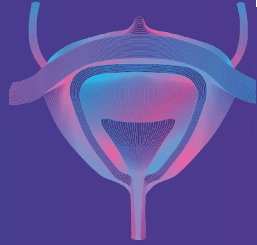
## **Premedication<sup>1</sup>**

Patients have to be premedicated with an antihistamine and with paracetamol prior to the first 4 infusions of BAVENCIO

If the 4<sup>th</sup> infusion is completed without an infusion-related reaction, premedication for subsequent doses should be administered at the discretion of the clinician

Patients should be monitored for the signs and symptoms of infusion-related adverse reactions<sup>3</sup>

Infusion-related reactions of Grade  $\geq 3$  were experienced in 0.9% of patients in the BAVENCIO arm of the JAVELIN Bladder 100 trial<sup>2,3</sup>

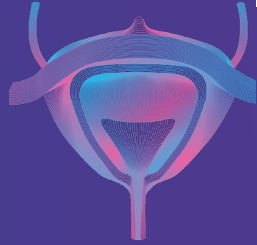


# Management of infusion-related adverse reactions

Depending on the severity of an infusion-related adverse event, it may be necessary to reduce the rate of infusion, suspend treatment or permanently discontinue treatment with avelumab<sup>1</sup>

| Grade 1 or 2 <sup>1*</sup>                                                                                                                                                                                                                                                                                                                          | Grade 3 or 4 <sup>1*</sup>                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• For Grade 1 infusion-related reactions, the infusion rate should be slowed by 50% for the current infusion</li><li>• For Grade 2 infusion-related reactions, the infusion should be temporarily discontinued until Grade 1 or resolved, then restart the infusion with a 50% slower infusion rate</li></ul> | <ul style="list-style-type: none"><li>• Stop the infusion and permanently discontinue BAVENCIO for severe or life-threatening infusion-related reactions</li></ul> |

# Fatigue



## **Very common ( $\geq 1/10$ ) with avelumab<sup>1</sup>**

Fatigue is a very common adverse reaction experienced by patients treated with avelumab. Patients should be advised to use caution when driving or operating machinery until they are certain that avelumab does not adversely affect them<sup>1</sup>

### **Management of fatigue<sup>2</sup>**

-  **Keeping active can boost your appetite, give you more energy and improve sleep.  
It is best to start slowly and balance with rest**
-  **Eating well can help you keep or regain your strength and give you more energy**
-  **Keep to a normal sleep routine: good-quality sleep may help with fatigue, as well as reduce your need to sleep during the day**
-  **Try complementary therapies including relaxation, massage therapy and yoga.  
Before you use a complementary therapy, talk to your specialist doctor or nurse**

1. BAVENCIO® (avelumab) Sažetak karakteristika leka, Decembar 2021;

2. Macmillan Cancer Support. Tiredness (fatigue). <https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/tiredness> (accessed November 2021).

## Immune related gastrointestinal toxicities

GI toxicity of ICPIs (most commonly observed with anti-CTLA-4 alone or anti-CTLA-4 + anti-PD-1/PD-L1)

### Summary of recommendations

|                                           |                                                                                                                                                                                                           |
|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Most common symptoms                      | Diarrhoea, abdominal pain, hematochezia, weight loss, fever and vomiting, mouth ulcers, anal lesions and extra-intestinal manifestations<br>(Upper GI symptoms and endoscopic lesions have been reported) |
| Main biological abnormalities             | Anaemia, increased serum CRP and low serum albumin levels                                                                                                                                                 |
| Ruling out infection and cancer as causes | Bacterial enteropathogens and <i>Clostridium difficile</i> toxin content of stools and investigation of GI metastases                                                                                     |
| Further investigations                    | Flexible endoscopy can confirm the diagnosis of enterocolitis                                                                                                                                             |

# CLINICAL PRACTICE GUIDELINES

## Immune related gastrointestinal toxicities

ICPi-related toxicity: Management of diarrhoea and colitis

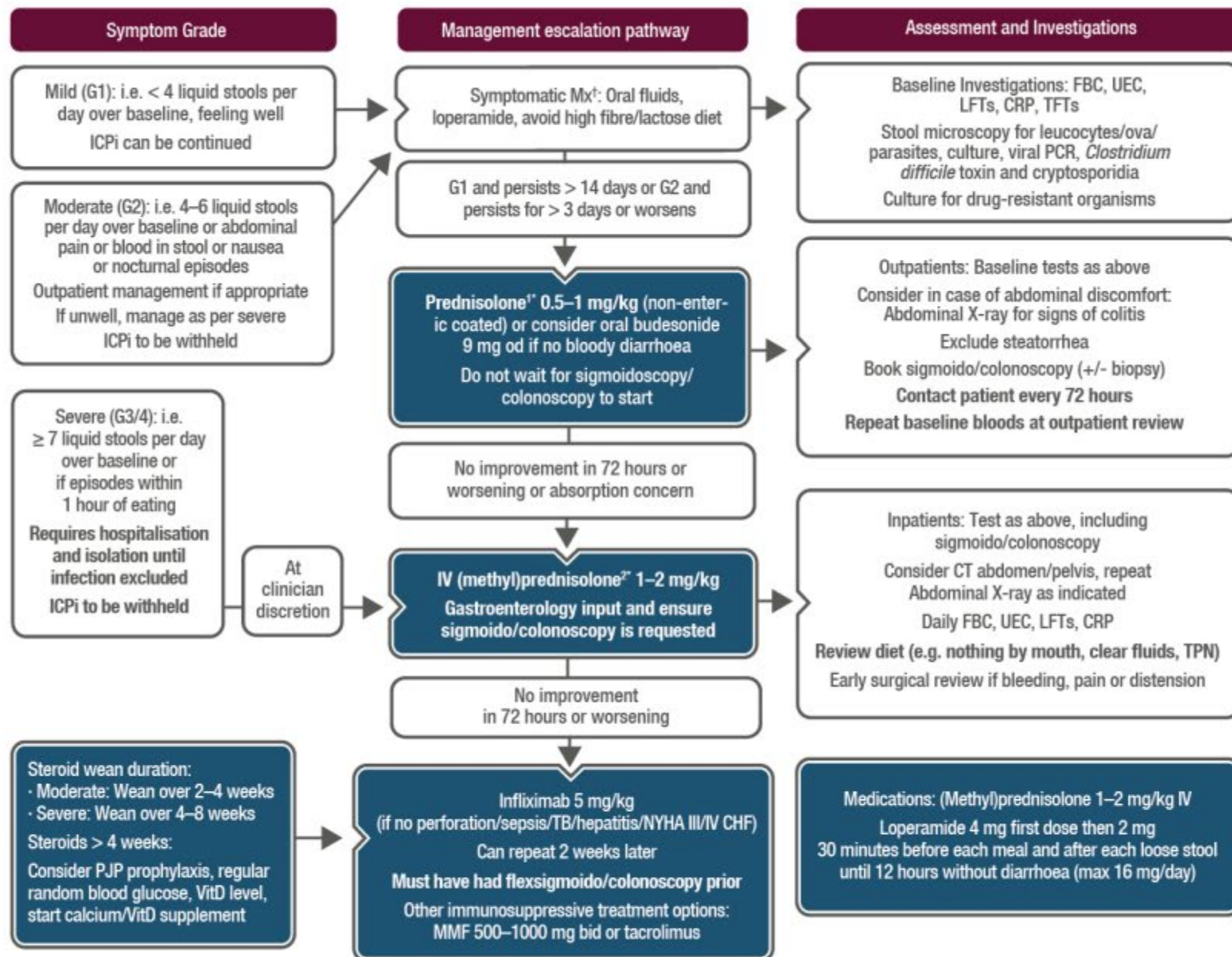
<sup>†</sup>Loperamide 4 mg first dose then 2 mg 30 minutes before each meal and after each loose stool until 12 hours without diarrhoea (max 16 mg/day)

Steroid wean duration:

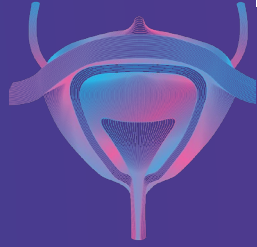
<sup>1</sup>Moderate: wean over 2–4 weeks

<sup>2</sup>Severe: wean over 4–8 weeks

\*Steroids > 4 weeks: Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement



# Diarrhoea



**Very common ( $\geq 1/10$ ) with avelumab<sup>1</sup>**

**Diarrhoea is one of the most common adverse reactions with avelumab.**

Patients should also be monitored for the signs and symptoms of immune-related colitis, and causes other than immune-related colitis should be ruled out<sup>1</sup>

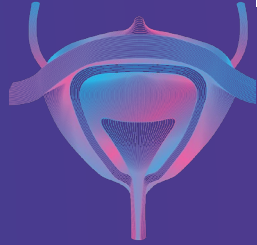
## Management of diarrhoea<sup>2</sup>

- ✓ Drink at least 2 litres (3½ pints) of fluids each day. This will replace the fluid lost from diarrhoea
- ✓ Eat less fibre, such as cereals, raw fruits and vegetables, until the diarrhoea improves
- ✓ Avoid drinking alcohol and coffee
- ✓ Take anti-diarrhoea medicines as directed by your doctor
- ✓ Eat small, frequent meals made from light foods. This could be white fish, poultry, well-cooked eggs, white bread, pasta or rice
- ✓ Avoid greasy, fatty foods such as chips and beef burgers, and spicy foods like chilli peppers
- ✓ Eat your meals slowly

**If a patient experiences Grade  $\geq 2$  diarrhoea, please refer to the Summary of Product Characteristics for more information on withholding or discontinuing avelumab**

1. BAVENCIO® (avelumab) Sažetak karakteristika leka, Decembar 2021; 2. Macmillan Cancer Support. Tips for managing eating problems. <https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/eating-problems/tips-for-managing-eating-problems> (accessed November 2021).

# Nausea



**Very common ( $\geq 1/10$ ) with avelumab<sup>1</sup>**

**Nausea is one of the most common adverse reactions with avelumab<sup>1</sup>**

## Management of nausea<sup>2</sup>

- |                                                                                                                                                                                     |                                                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <b>Avoid fried foods or foods with a strong smell</b>                                             |  <b>Try eating ginger biscuits or drinking ginger beer</b>                                                                        |
|  <b>Prepare small meals and eat little and often</b>                                               |  <b>Sipping a fizzy drink is a popular remedy to stop feeling sick</b>                                                            |
|  <b>Eat cold or warm food if the smell of hot food makes you feel sick</b>                         |  <b>You could try wearing sea bands (available from chemists) around your wrists. They use acupressure to help relieve nausea</b> |
|  <b>Peppermints or peppermint tea may help some people</b>                                        |  <b>Using relaxation tapes or taking part in activities that you find relaxing may help you cope with nausea</b>                 |
|  <b>Try sitting by an open window while you eat, so there is plenty of fresh air in the room</b> |  <b>There is some evidence that acupuncture may help to control nausea, but more research is needed</b>                         |
|  <b>Try not to drink a lot just before you eat</b>                                               |                                                                                                                                                                                                                      |

1. BAVENCIO® (avelumab) Sažetak karakteristika leka, Decembar 2021;

2. Support. Nausea and vomiting. <https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/nausea-and-vomiting> (accessed November 2021).

## Immune related hepatotoxicity

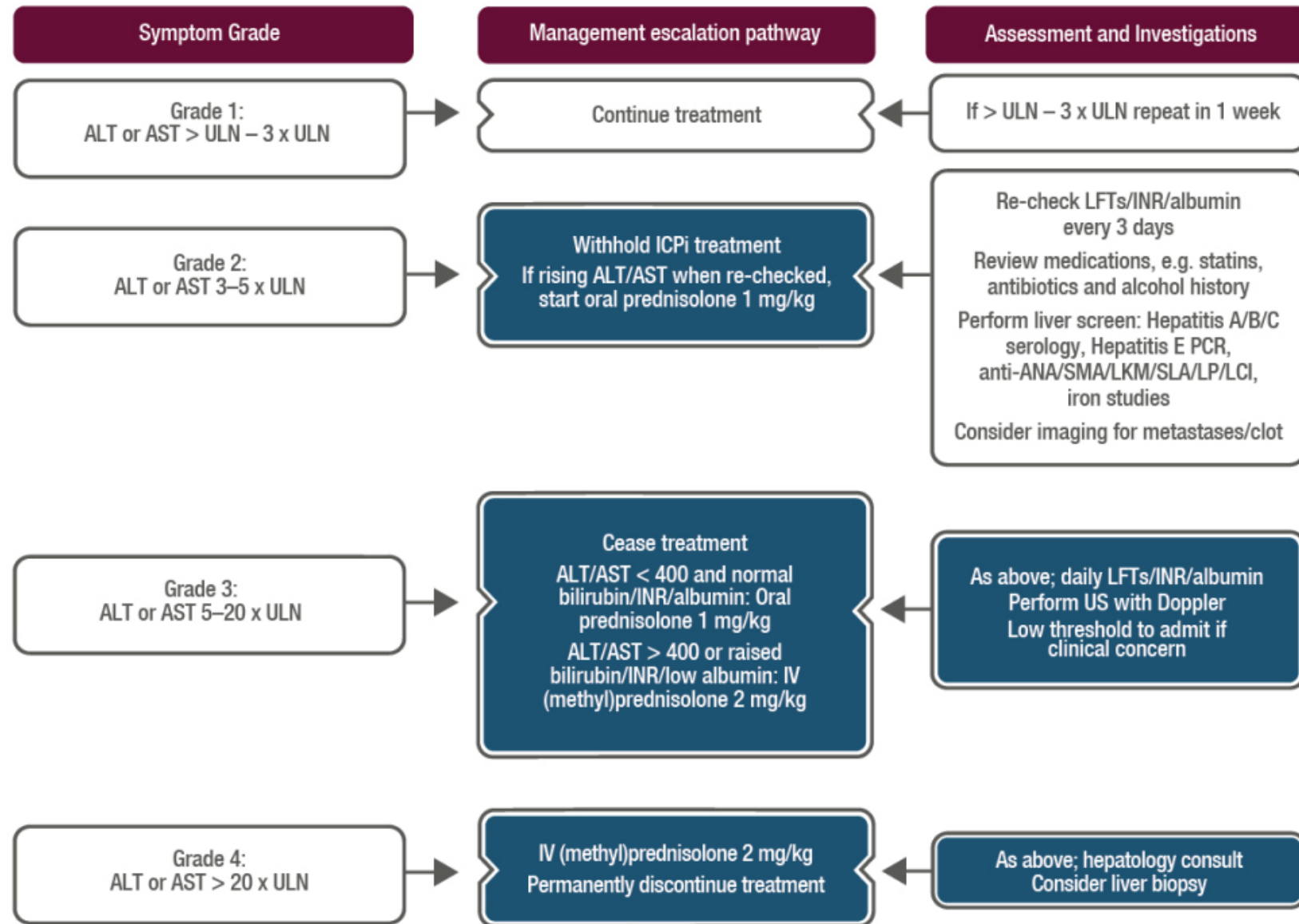
ICPi-related toxicity: Management of hepatitis

### Steroid wean:

- Grade 2: Once grade 1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone  $\leq 10$  mg
- Grade 3/4: Once improved to grade 2, can change to oral prednisolone and wean over 4 weeks; for grade 3, re-challenge only at consultant discretion

### Worsening despite steroids:

- If on oral change to IV (methyl)prednisolone
- If on IV add MMF 500–1000 mg bid
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis



## Immune related pneumonitis toxicities

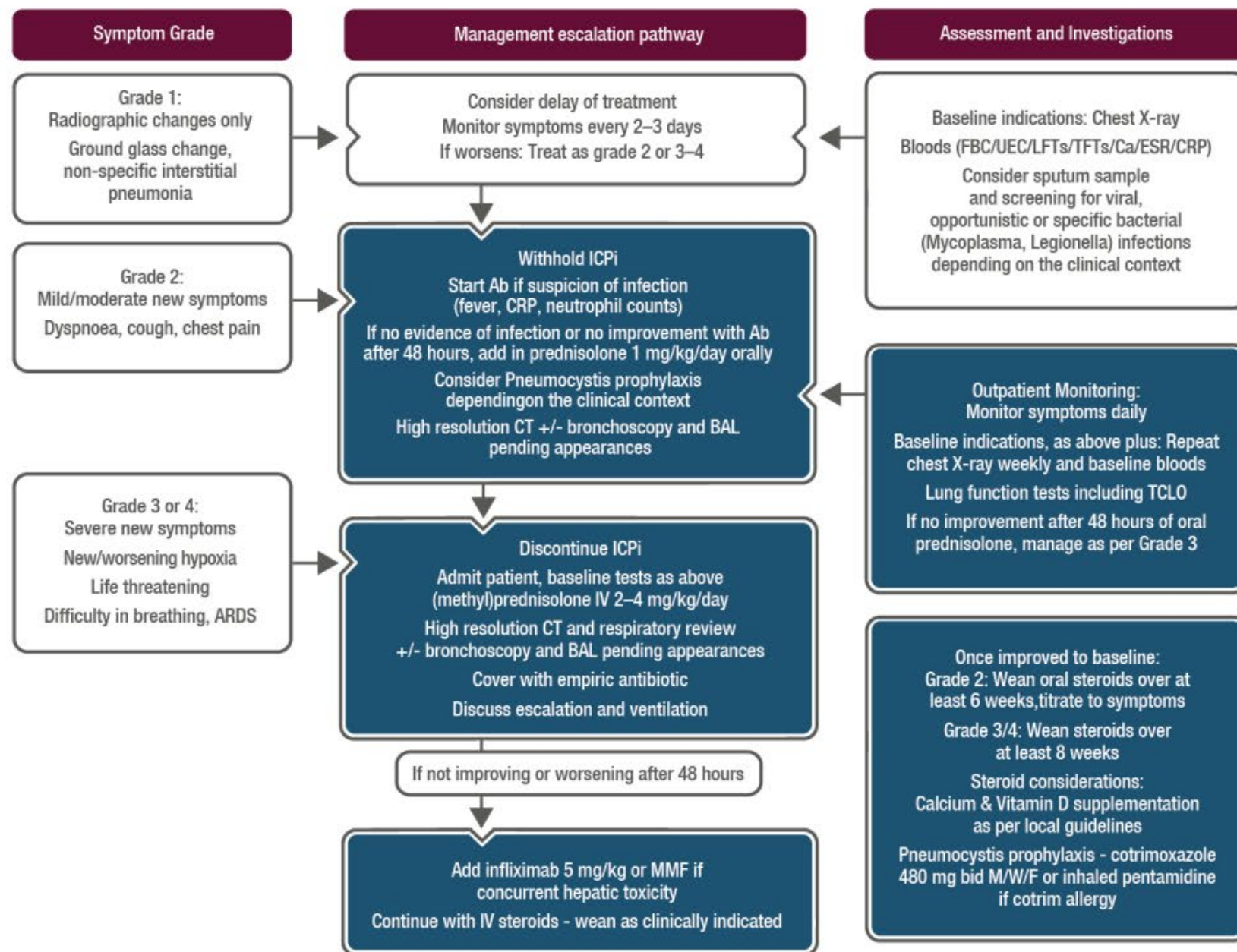
ICPi-related toxicity: Management of pneumonitis

### History:

Pulmonary hypertension/respiratory; disease/connective tissue disease; Influenza/Mycobacterium; tuberculosis exposure; Smoking history; Travel history; Allergy history including exposure to home/occupational aeroallergens

### Differential Diagnosis:

Pneumonia (including atypical, pneumocystis, tuberculosis); Lymphangitis; Usual interstitial pneumonias; Pulmonary oedema; Pulmonary emboli; Sarcoidosis



## Immune related toxicities - endocrinopathies

ICPi monitoring and management:  
Thyroid function

Baseline Endocrine Panel:  
TSH, FT4, T3\* TFTs

Baseline abnormal values do not  
preclude treatment; discuss with  
endocrinologist if uncertain  
\*when indicated

Monitoring during treatment:

Anti-CTLA-4 (including combination with anti-PD-1)

- TFTs every cycle
  - TFTs 4-6 weeks after cycle 4 (i.e. with restaging CT)
- Late endocrine dysfunction can occur

Anti-PD-1/Anti-PD-L1

- TFTs every cycle for first 3 months, every second cycle thereafter (in case of 2-weekly schedule)
- Cortisol as indicated by symptoms/falling TSH

A falling TSH across two measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements should be performed

If TSH is abnormal, refer to algorithm below. Iodine from CT scans may impact TFTs

Hypothyroidism: Low FT4 with  
elevated TSH or TSH  
> 10 with normal FT4

Treatment: Thyroxine  
0.5–1.5 µg/kg (start low in  
elderly, if cardiac history)

Continue ICPi

Thyrotoxicosis (DDx thyroiditis, Grave's disease):

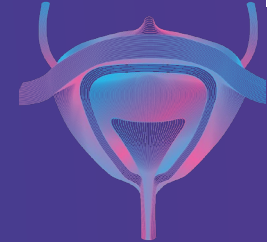
Investigations: Anti-TSH receptor Ab, anti-TPO Ab,  
nuclear medicine thyroid uptake scan

Treatment: Propranolol or atenolol for symptoms; consider  
carbimazole if anti-TSH receptor Ab-positive

Painful thyroiditis – consider prednisolone  
0.5 mg/kg and taper

If unwell, withhold ICPi and consider restarting  
when symptoms controlled

# Hypothyroidism – immune-related endocrinopathy



**Common ( $\geq 1/100$  to  $< 1/10$ ) with avelumab<sup>1</sup>**

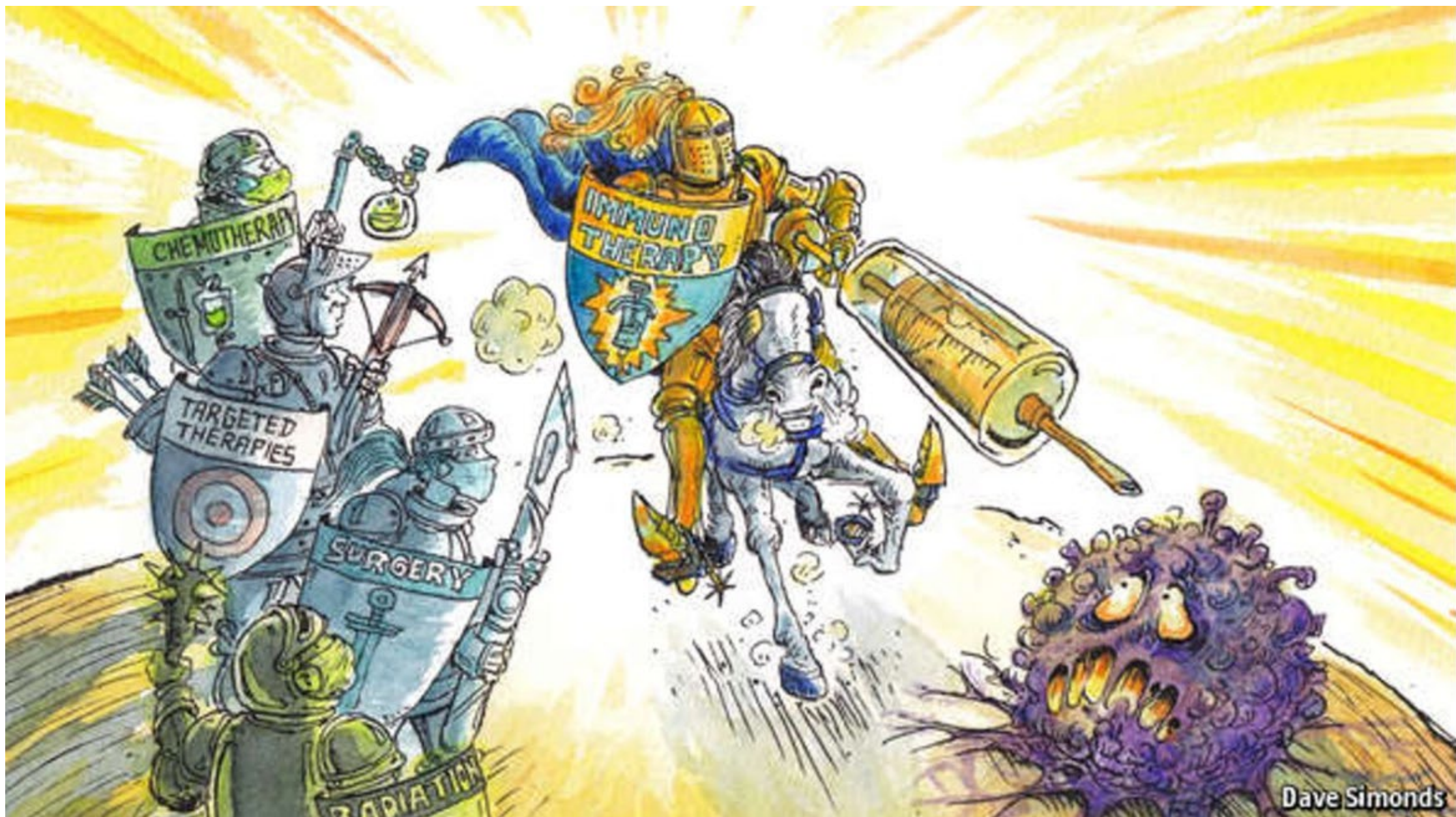
Thyroid disorders can occur at any time during treatment, and patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Hypothyroidism should be managed with replacement therapy, as needed

## Management of hypothyroidism<sup>2</sup>

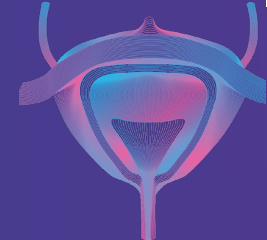


**Take treatment to manage underactive thyroid, which may include thyroid hormone replacement therapy, as directed by your doctor**

**BAVENCIO should be withheld for Grade 3 or 4 thyroid disorders until recovery to Grade 1 or 0<sup>1</sup>**



# Zaključak



- ASCO GU 2023 JAVELIN Bladder 100 study: Potvrđen bezbedonosni profil avelumaba <sup>1</sup>
- Dostupno je više vodiča /EMO, NCCN/ za prevenciju i terapiju neželjenih efekata imunoterapije <sup>2-3</sup>
- Edukacija pacijenta i porodice i zdravstvenih radnika da na vreme prepoznaju neželjena dejstva imunoterapije i da se pacijent što pre javi onkologu radi sprovođenja adekvatne suportivne terapija je od velikog značaja <sup>4-5</sup>

1. <https://dailynews.ascopubs.org/doi/long-term-javelin-bladder-100-findings-solidify-first-line-avelumab-maintenance>

2. J Natl Compr Canc Netw. 2022 Apr;20(4):387-405. doi: 10.6004/jnccn.2022.0020.

3. <https://doi.org/10.1016/j.annonc.2022.10.001>

4. Wood LS et al. J Adv Pract Oncol 2019;10(Suppl 1):47-62;

5. . BAVENCIO® (avelumab) Sažetak karakteristika leka, Decembar 2021;

**HVALA NA PAŽNJI**