



# Of people and trials against Bladder Cancer: A modern history

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IRCCS San Raffaele Hospital, Milan, Italy



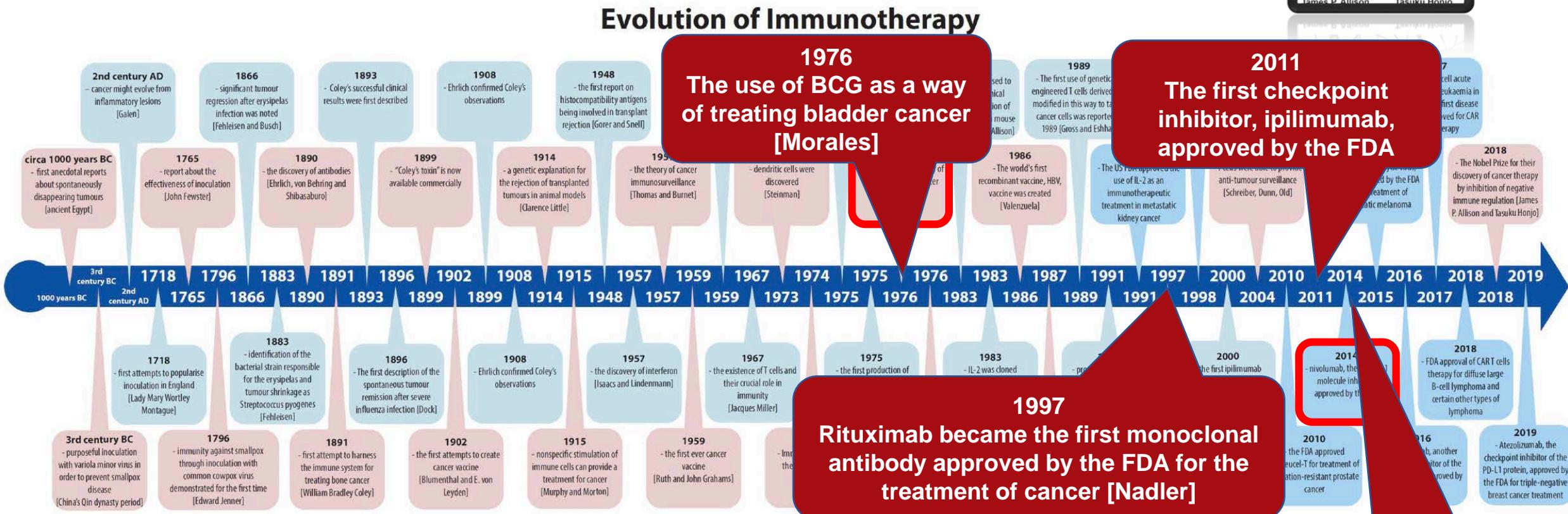
# Conflicts of interest

- Honoraria: Roche, MSD, AstraZeneca, Janssen, Foundation Medicine, , BMS, Astellas
- Consulting or Advisory role: MSD, Roche, Bayer, AstraZeneca, Clovis Oncology, Janssen, Incyte, Seattle Genetics/Astellas, Bristol-Myers Squibb, Rainier Therapeutics, Bycicle Therapeutics, GlaxoSmithKline, Basilea Pharmaceutica, Catalym
- Research Funding (Institution): MSD, AstraZeneca, Ipsen, Gilead
- Travel, Accommodations, Expenses: Roche, MSD, AstraZeneca, Janssen, Rainier Therapeutics, Pfizer
- Employment and Stock Ownership (spouse): Bayer

## Academic appointments:

- Vice-president of the Global Society of Rare GU Tumors (GSRGT)
- ASCO 2022 Annual Meeting Faculty
- ESMO 2023 Annual Meeting Planning Committee – GU Kidney and Bladder cancers track
- ESMO Faculty – Genitourinary tumors-Non prostate, 2021-2025
- Panel member of the ASCO/EAU penile cancer guidelines committee
- Board member – EAU Research Foundation (EAU-RF)

# Key advances in the history of cancer immunotherapy



- 1976: use of BCG for treating bladder cancer
- 1997: rituximab for treating NHL
- 2011: ipilimumab for treating metastatic melanoma
- 2014: nivolumab for treating metastatic melanoma



**2014**  
**Nivolumab, the first PD-1 molecule inhibitor, approved by the FDA**

# LETTER

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[doi:10.1038/nature13904](https://doi.org/10.1038/nature13904)

## MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

Thomas Powles<sup>1</sup>, Joseph Paul Eder<sup>2</sup>, Gregg D. Fine<sup>3</sup>, Fadi S. Braiteh<sup>4</sup>, Yohann Loriot<sup>5</sup>, Cristina Cruz<sup>6</sup>, Joaquim Bellmunt<sup>7</sup>, Howard A. Burris<sup>8</sup>, Daniel P. Petrylak<sup>2</sup>, Siew-leng Teng<sup>3</sup>, Xiaodong Shen<sup>3</sup>, Zachary Boyd<sup>3</sup>, Priti S. Hegde<sup>3</sup>, Daniel S. Chen<sup>3</sup> & Nicholas J. Vogelzang<sup>9</sup>

Powles T, et al. *Nature*. 2014 Nov 27;515(7528):558-62

# Pivotal IMvigor-210 Phase II Trial of Atezolizumab in Metastatic Urothelial Carcinoma



## Articles

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial



Jonathan E Rosenberg, Jean Hoffman-Censits, Tom Powles, Michiel S van der Heijden, Arjun V Balar, Andrea Necchi, Nancy Dawson, Peter H O'Donnell, Ani Balmanoukian, Yohann Loriot, Sandy Srinivas, Margitta M Retz, Petros Grivas, Richard W Joseph, Matthew D Galsky, Mark T Fleming, Daniel P Petrylak, Jose Luis Perez-Gracia, Howard A Burris, Daniel Castellano, Christina Canil, Joaquim Bellmunt, Dean Bajorin, Dorothee Nickles, Richard Bourgon, Garrett M Frampton, Na Cui, Sanjeev Mariathasan, Oyewale Abidoye, Gregg D Fine, Robert Dreicer



# Landmark Keynote-045 Phase III Trial of Pembrolizumab in Metastatic Urothelial Carcinoma



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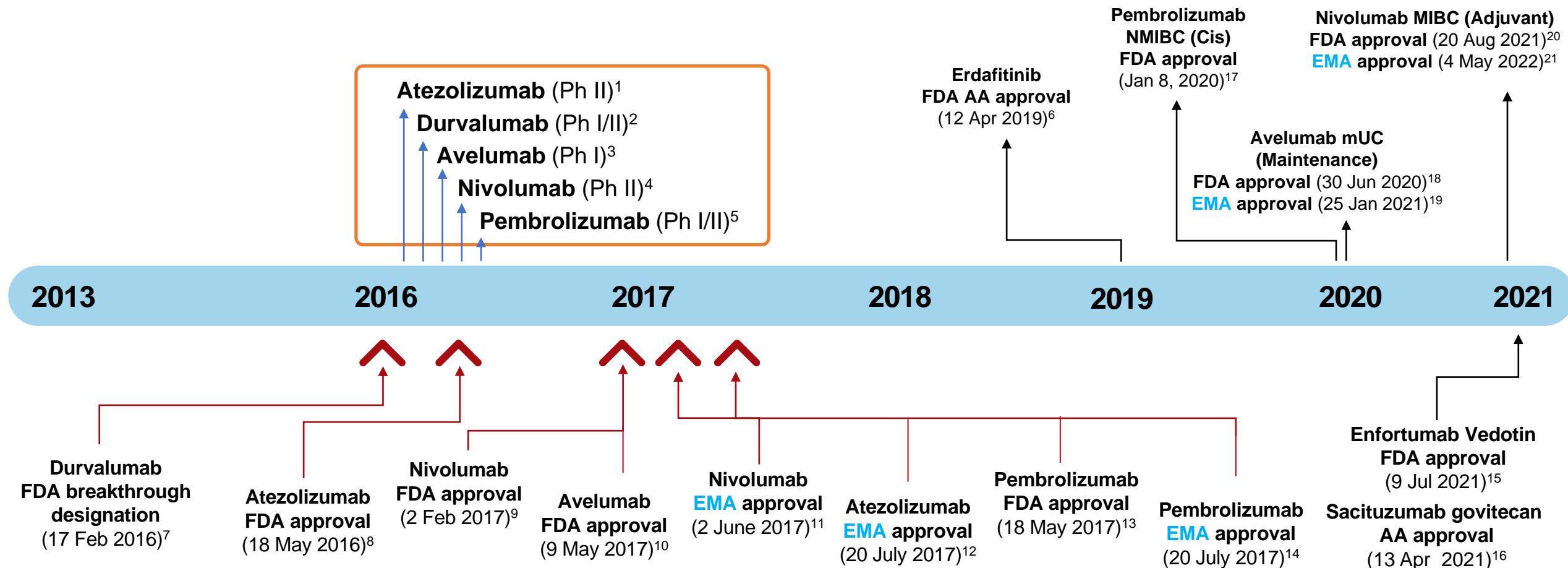
## Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators\*



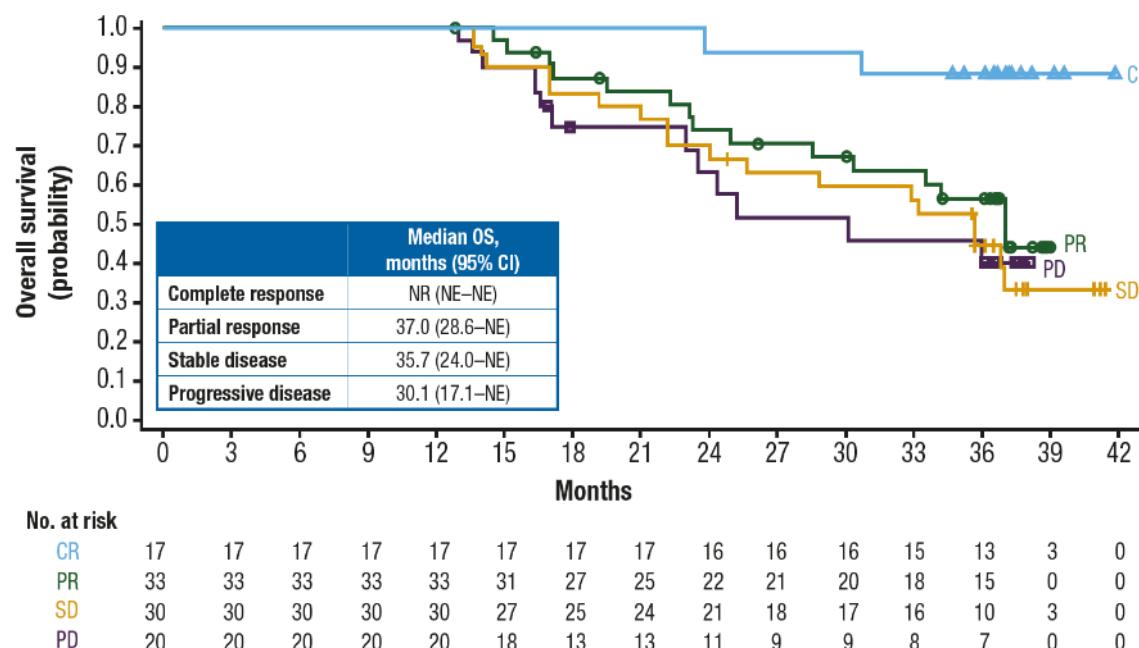


# In Urothelial Carcinoma we have 5 immunotherapeutic agents plus other agents in various clinical stages

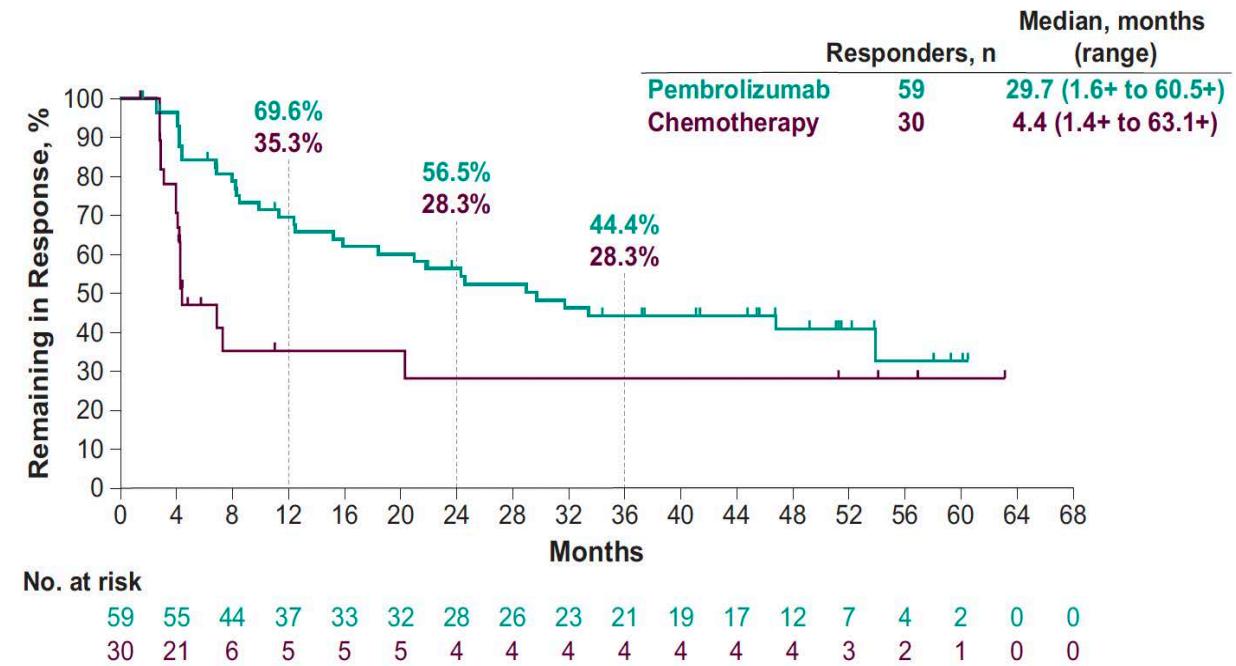


1. Rosenberg JE et al. Lancet 2016;387:1909–1920; 2. Powles T, et al. JAMA Oncol 2017;3(9):e172411; 3. Patel MR, et al. Lancet Oncol 2018;19:51–64; 4. Sharma P, et al. Lancet Oncol 2017;18:312–322; 5. Woodcock VK, et al. ASCO 2016 (Abstract No. 406); 6. Loriot Y, et al. N Engl J Med 2019;381:338–348; 7. AstraZeneca. Press release 17 Feb 2016. Available at: [www.astrazeneca.com](http://www.astrazeneca.com); 8. FDA. Press release 18 May 2016. Available at: [www.fda.gov](http://www.fda.gov); 9. FDA. Press release 2 Feb 2017. Available at: [www.fda.gov](http://www.fda.gov); 10. FDA. Press release 9 May 2017. Available at: [www.fda.gov](http://www.fda.gov); 11. EMA. [www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ii-0041-epar-assessment-report-variation\\_en.pdf](http://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ii-0041-epar-assessment-report-variation_en.pdf); 12. EMA. [https://www.ema.europa.eu/en/documents/assessment-report/tecentriq-epar-public-assessment-report\\_en.pdf](http://www.ema.europa.eu/en/documents/assessment-report/tecentriq-epar-public-assessment-report_en.pdf); 13. FDA. Press release 18 May 2017. Available at: [www.fda.gov](http://www.fda.gov); 14. EMA. [www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-keytruda\\_en.pdf](http://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-keytruda_en.pdf); 15. Press release 9 Jul 2021. Available at: [www.fda.gov](http://www.fda.gov). 16. Press release 13 Apr 2021. Available at: [www.fda.gov](http://www.fda.gov). 17. Press release 8 Jan 2020. Available at: [www.fda.gov](http://www.fda.gov). 18. Press release 30 Jun 2020. Available at: [www.fda.gov](http://www.fda.gov). 19. [https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information\\_en.pdf](http://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf). 20. Press release 20 Aug 2021. Available at: [www.fda.gov](http://www.fda.gov). 21. [https://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-003985-ii-0100-epar-assessment-report-variation\\_en.pdf](http://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-003985-ii-0100-epar-assessment-report-variation_en.pdf).

# Curative potential of immune-checkpoint inhibition from landmark 2L trials in advanced bladder cancer

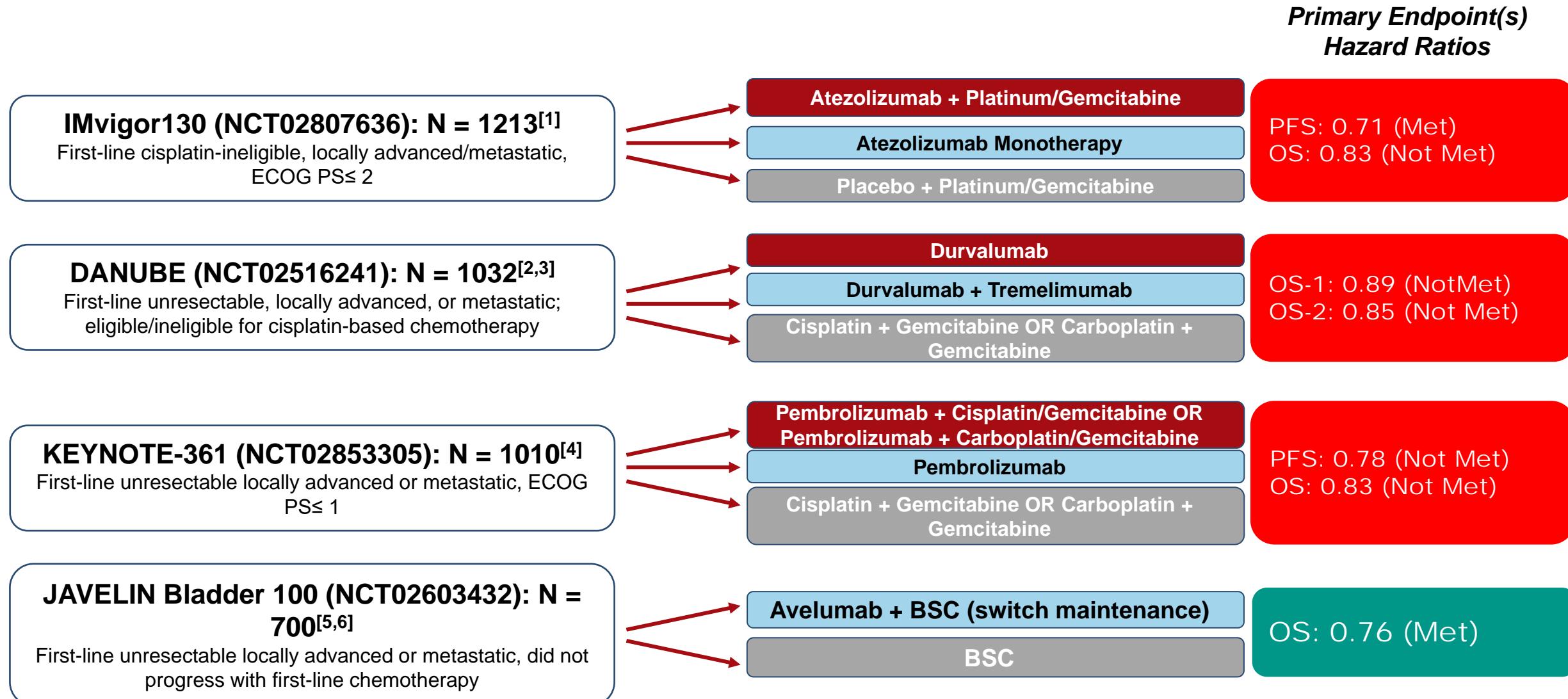


CheckMate-075: 3-y minimum follow-up

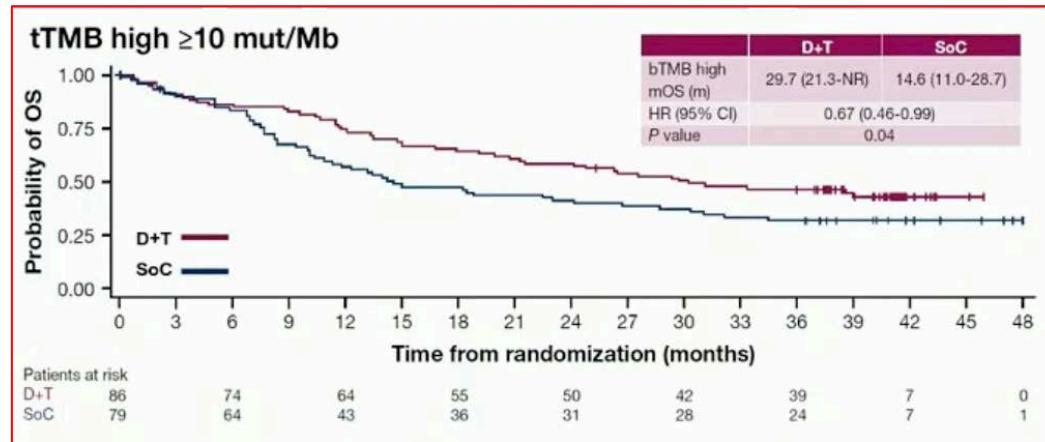


Keynote-045: 5-y minimum follow-up

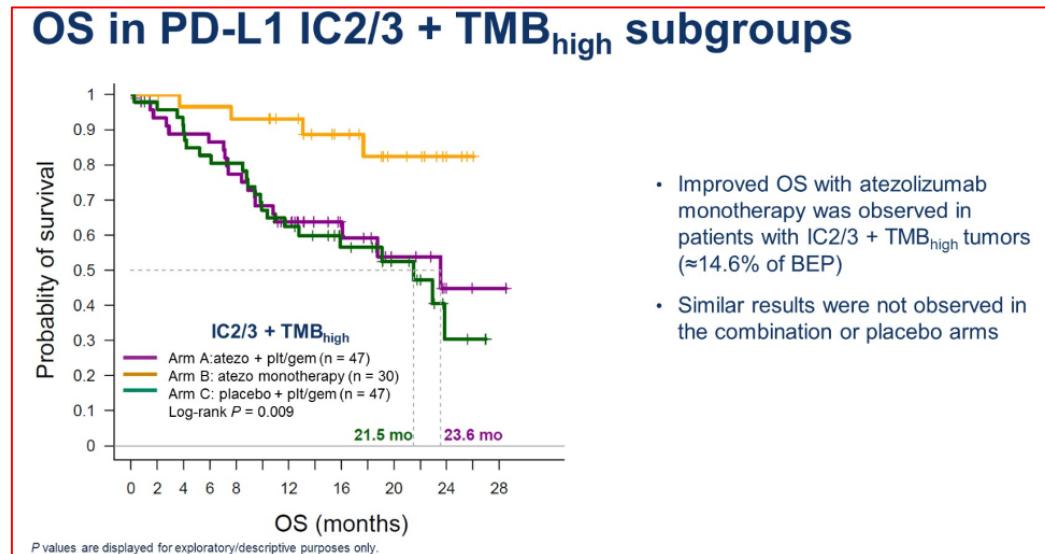
# Struggling against the First-line therapy: Results of Phase III Trials of Anti-PD-(L)1 in advanced UC



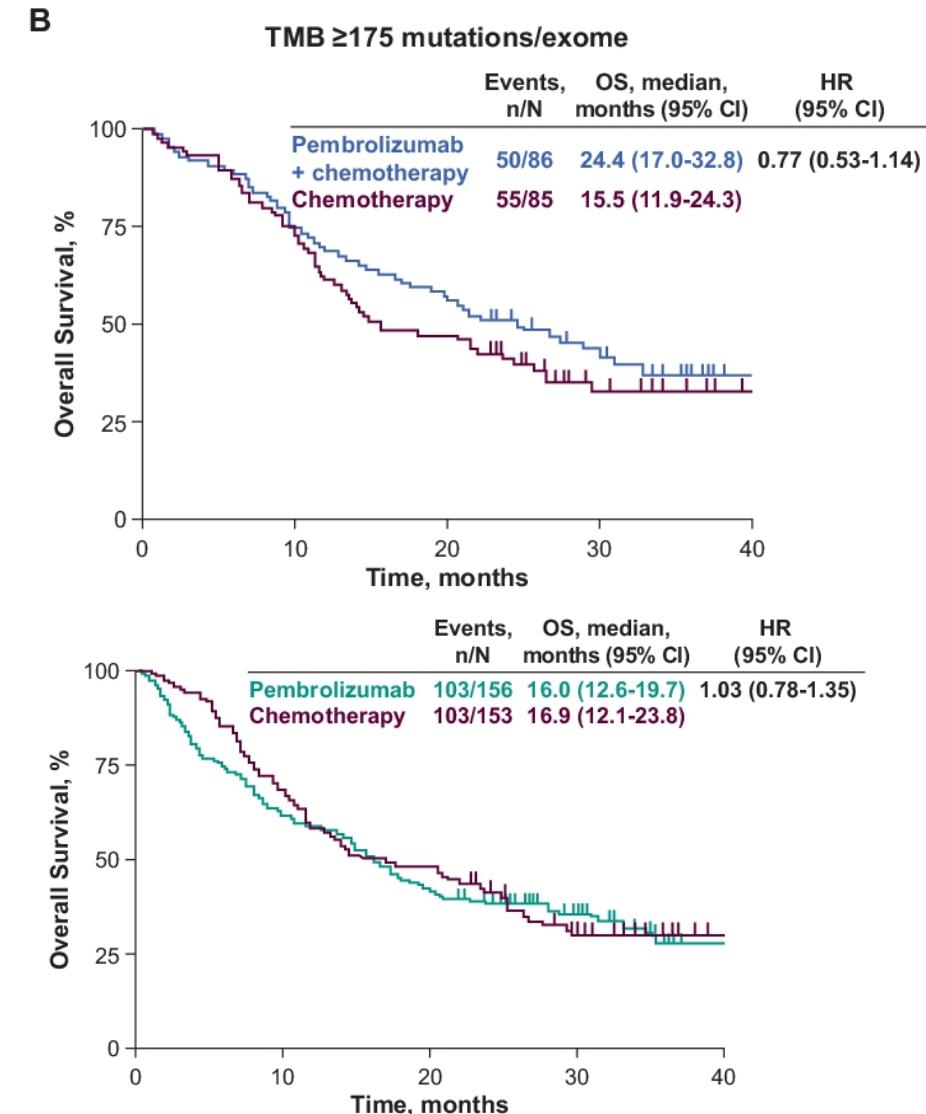
# Missing the biomarker: TMB and CPS remain largely inconsistent across studies



**DANUBE study:** Wildsmith S, et al. SITC 2020



**IMvigor130 study:** Galsky MD, et al. ASCO 2020



**KN-361:** Morales-Barrera R, et al. J Clin Oncol. 40, 2022 (suppl 6; abstr 540)

# Curative potential of immune-checkpoint inhibition from 1L trials in advanced bladder cancer

Figure 2. Kaplan-Meier estimates of OS from week 9 by objective response at week 9 for the primary analysis population

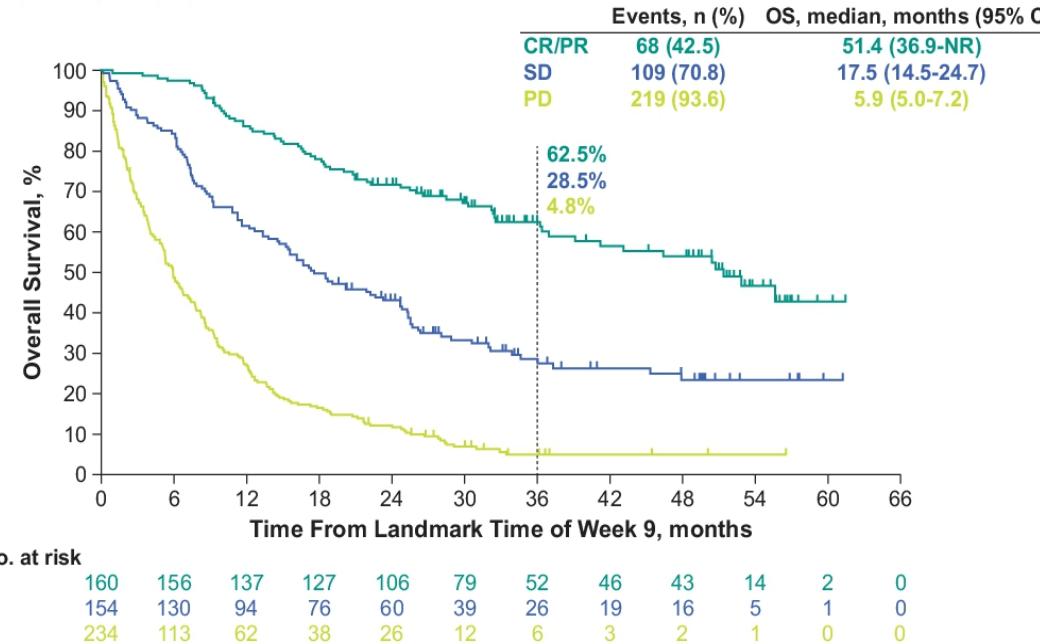
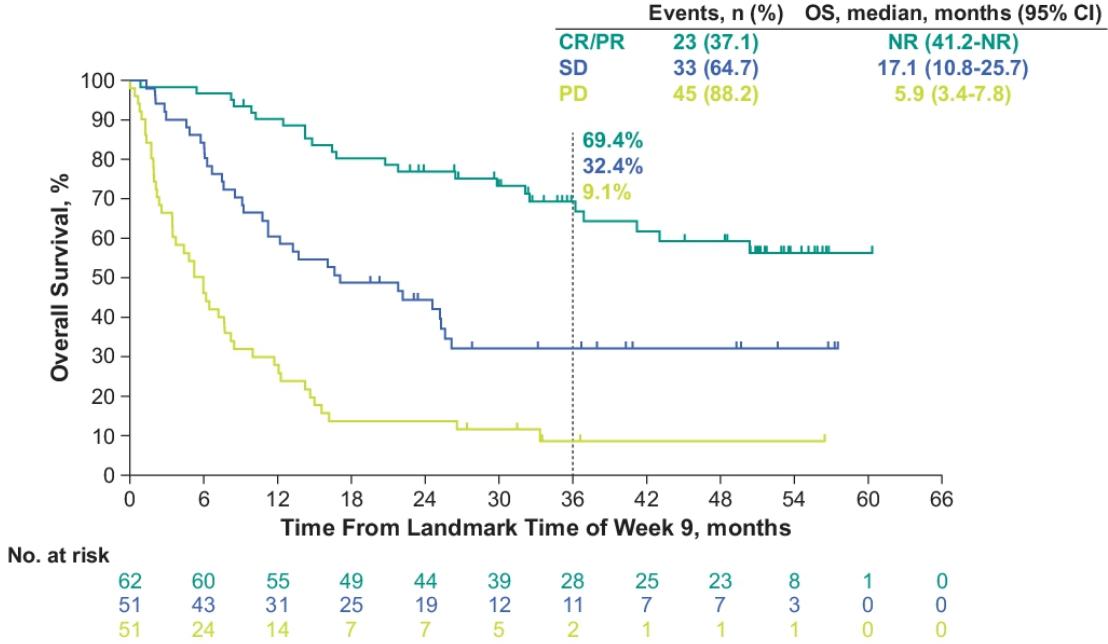


Figure 8. Kaplan-Meier estimates of OS from week 9 by objective response at week 9 for the sensitivity analysis population (PD-L1 CPS  $\geq 10$ )



- Response on Pembrolizumab at 9 weeks and OS from KN-052+KN-361 trials
- Marked clinical benefit in patients achieving a CR/PR at 9 weeks
- Potential surrogate of OS in next studies

# JAVELIN Bladder 100: “Switch Maintenance” Strategy After First-Line Chemotherapy<sup>1,2</sup>

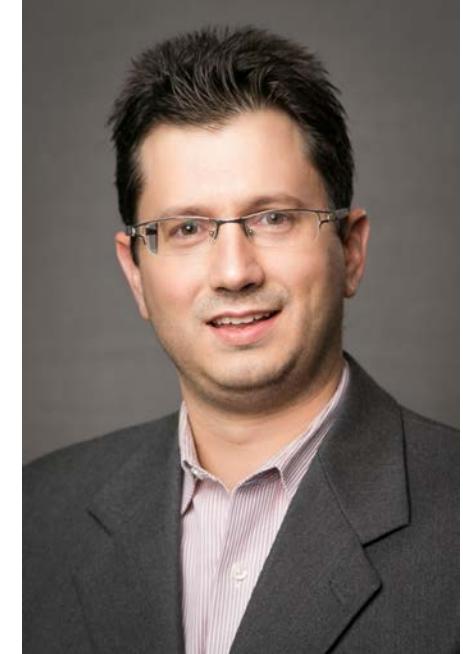


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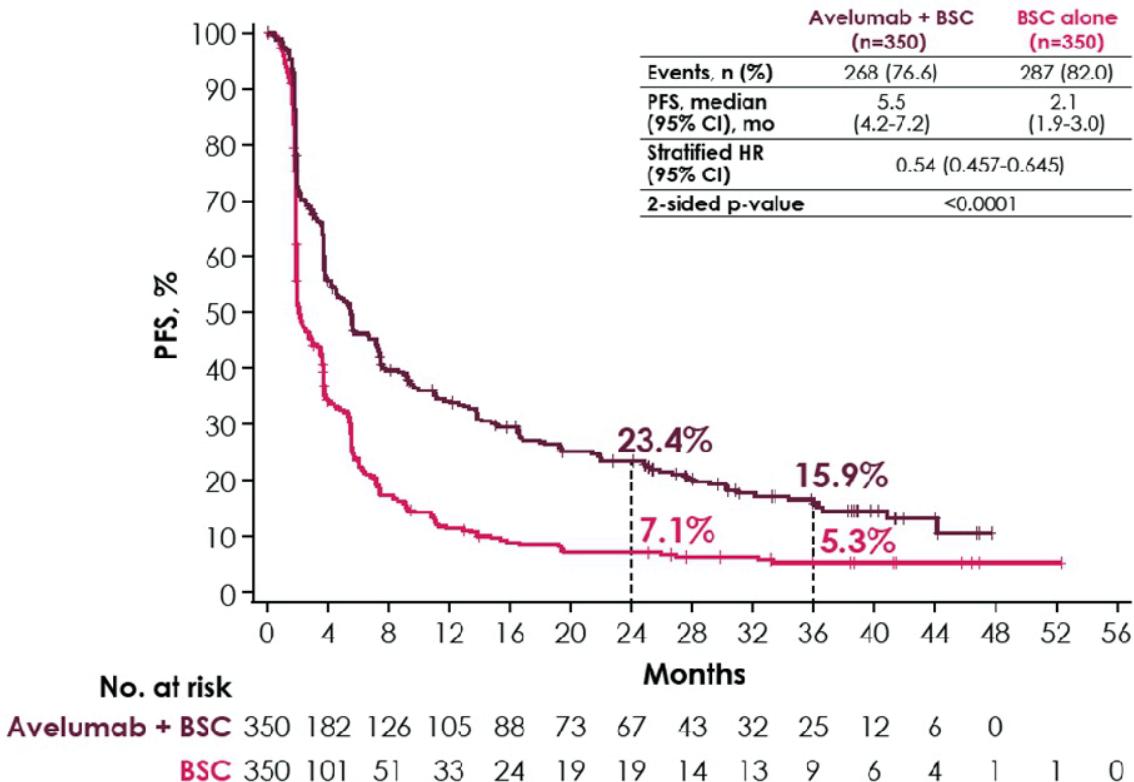
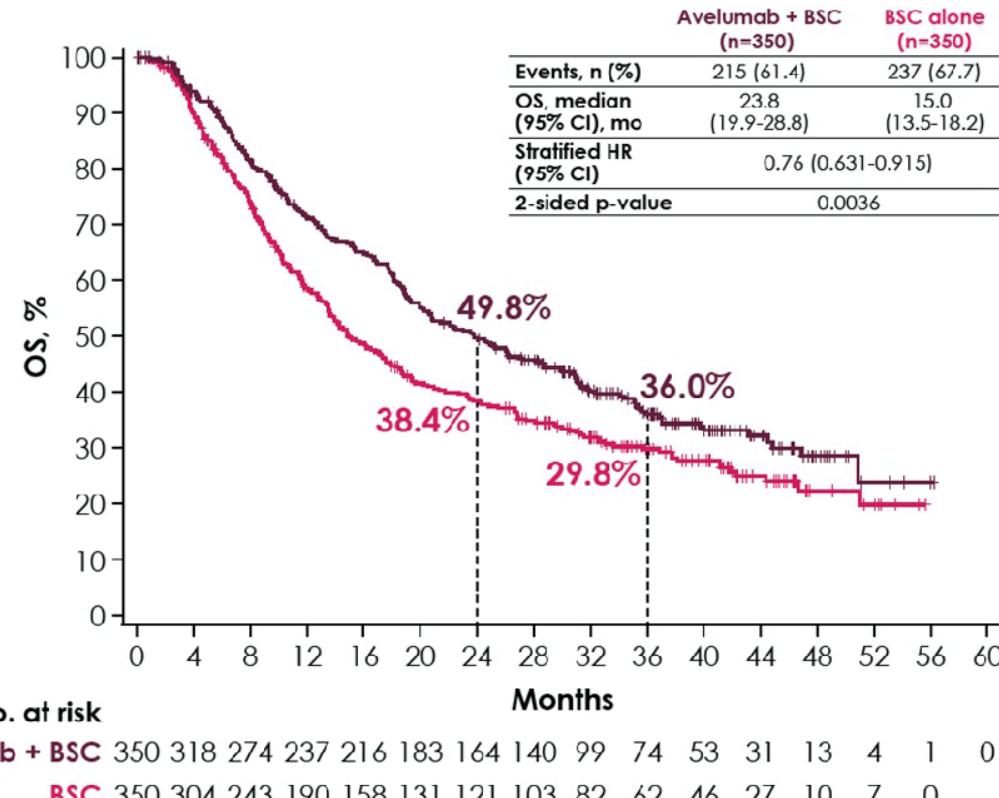
ORIGINAL ARTICLE

## Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

T. Powles, S.H. Park, E. Voog, C. Caserta, B.P. Valderrama, H. Gurney, H. Kalofonos, S. Radulović, W. Demey, A. Ullén, Y. Loriot, S.S. Sridhar, N. Tsuchiya, E. Kopyltssov, C.N. Sternberg, J. Bellmunt, J.B. Aragon-Ching, D.P. Petrylak, R. Laliberte, J. Wang, B. Huang, C. Davis, C. Fowst, N. Costa, J.A. Blake-Haskins, A. di Pietro, and P. Grivas



# JAVELIN Bladder-100 – Long-term follow-up results ( $\geq 2$ yr for all pts)



- No new safety signals were identified

# Therapeutic approaches in biomarker-selected patients

# Pivotal BLC2001 Phase 2 Trial of Erdafitinib in FGFR-Altered Metastatic or Unresectable UC



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ORIGINAL ARTICLE

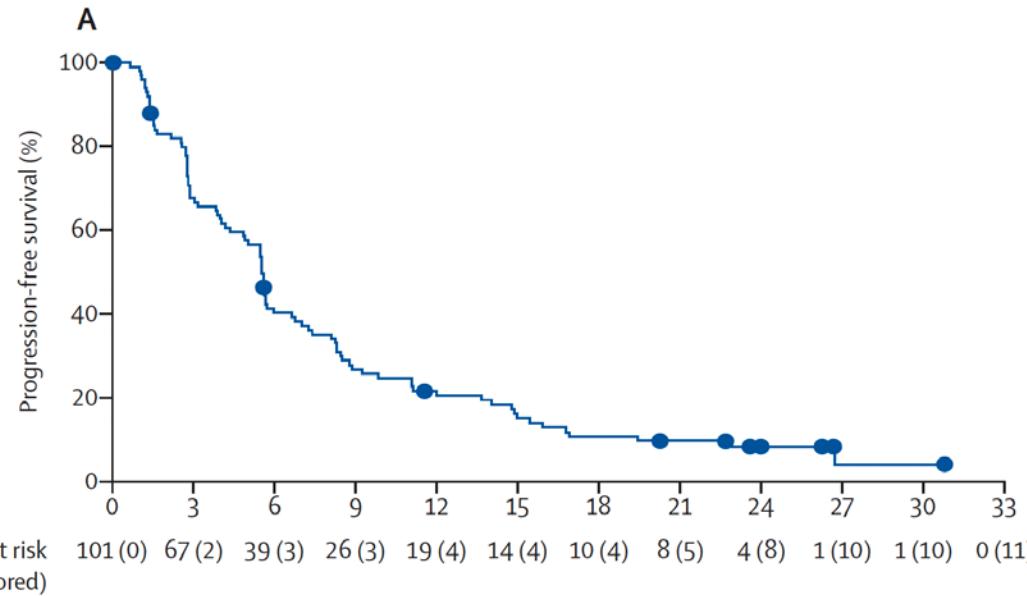
## Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Sieffker-Radtke,  
for the BLC2001 Study Group\*

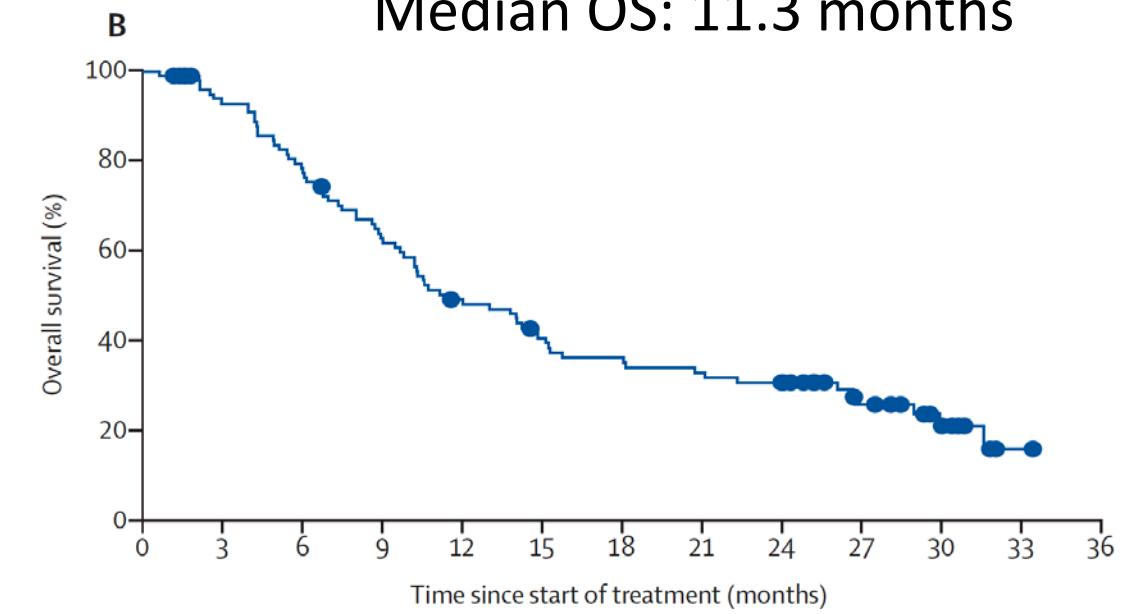


# BLC2001: PFS and OS<sup>1,2</sup>

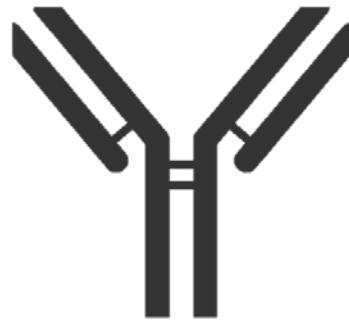
Median PFS: 5.5 months



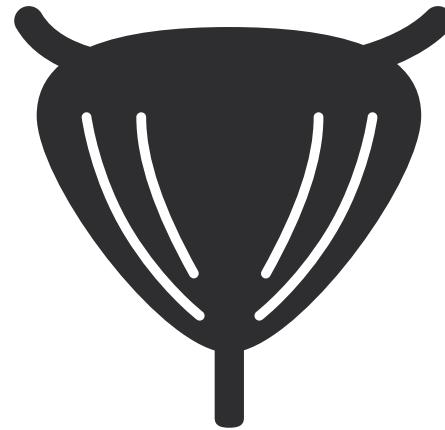
Median OS: 11.3 months



Results led to FDA approval of erdafitinib for locally advanced UC or mUC with *FGFR3* or *FGFR2* genomic alterations after progression on  $\geq 1$  line of prior platinum-containing chemotherapy

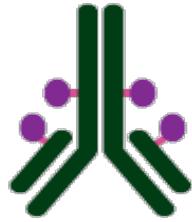


+ ??



*Is there a better partner ?*

# Antibody–Drug Conjugates in Bladder Cancer



## Enfortumab vedotin

**Target:** Nectin-4, a type 1 transmembrane cell adhesion molecule overexpressed in epithelial cancers  
**Linker:** Protease cleavable  
**Payload:** MMAE

**FDA approved:** post-PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy

### EV-201:<sup>1</sup>

- ORR: 44%; CR: 12%

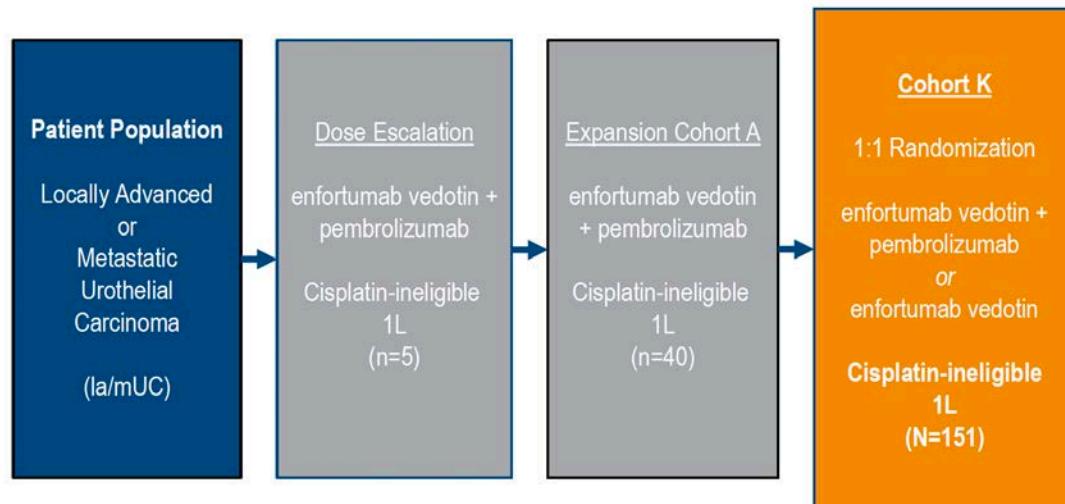
### EV-301:<sup>2</sup>

- OS (HR): 0.70;
- Median OS: 12.88 months



# Combination of ADC + ICI (EV + Pembro)

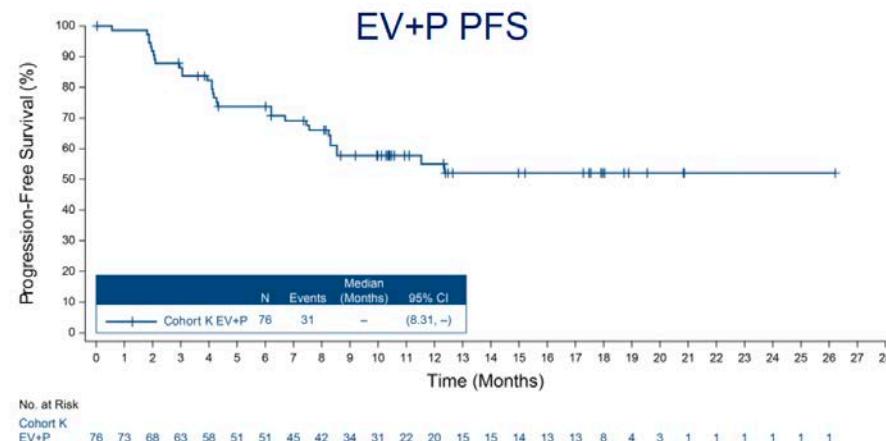
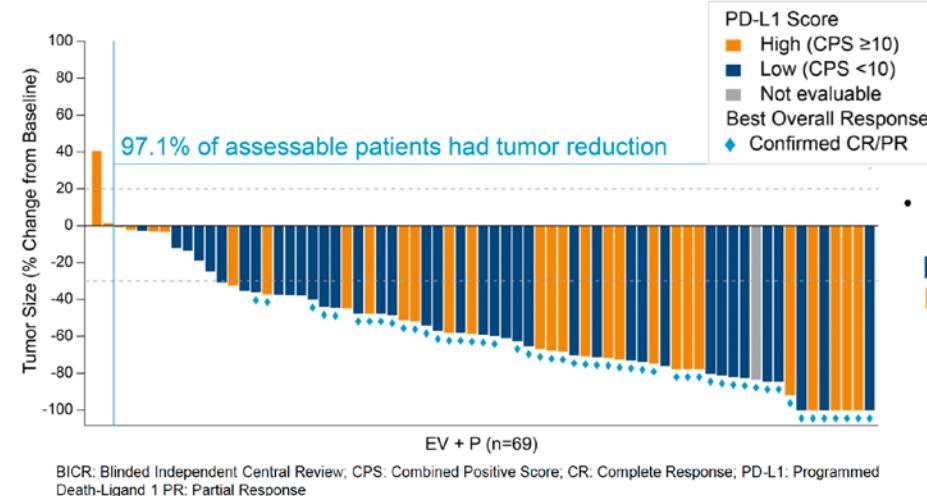
## EV-103 Cohort K



**Dosing:** EV 1.25 mg/kg IV on days 1 and 8, and P 200 mg IV on day 1 of every 3-week cycle

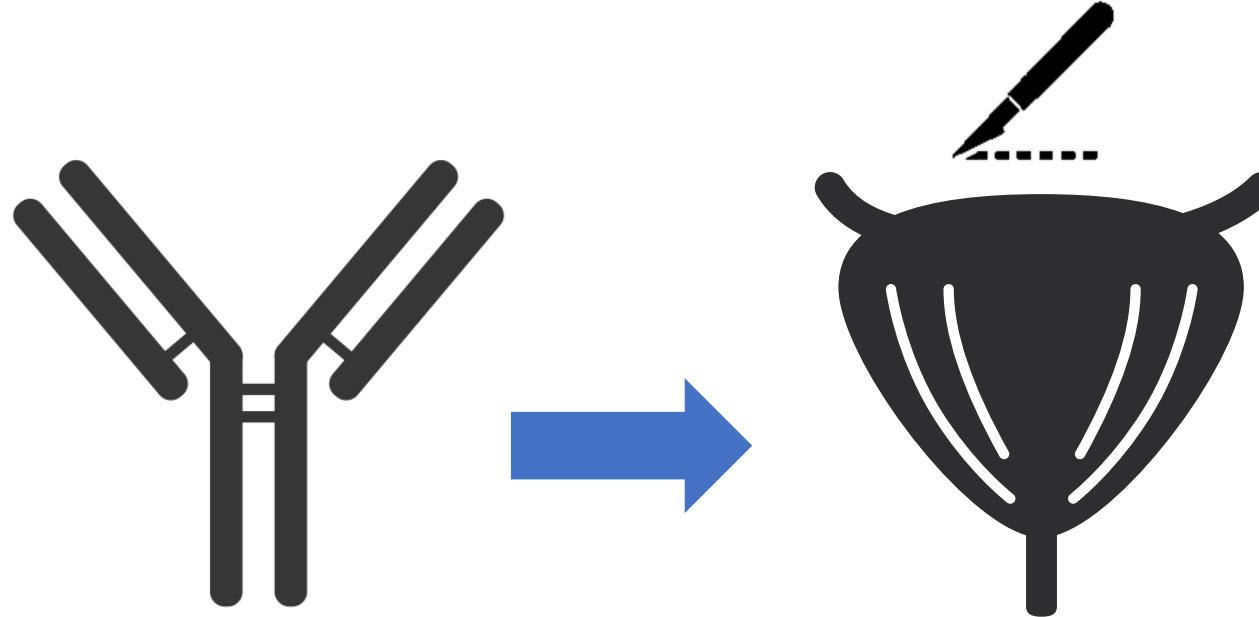
**Primary endpoint:** confirmed ORR by RECIST v1.1 per BICR

**ORR: 64.5% (EV-P) vs 45.2% (P)**



**1y-PFS: 55.1%**  
**1y-OS: 80.7%**

# Advancing the field in early-stage urothelial bladder carcinoma



# PURE-01 study design and achievements (2018-2022)<sup>1-10</sup>

- Fit and planned for cystectomy
- Predominant (i.e. 50% at least) UC histology OR pure/predominant variant histology (excluding small-cell tumors)
- cT≤4N0 stage
- GFR  $\geq 20$  ml/min (Cockcroft – Gault formula)
- ECOG-PS 0-1



**3x3 weekly cycles of pembrolizumab 200 mg IV**

Pre-post treatment tissue/blood sample collection for biomarker analyses

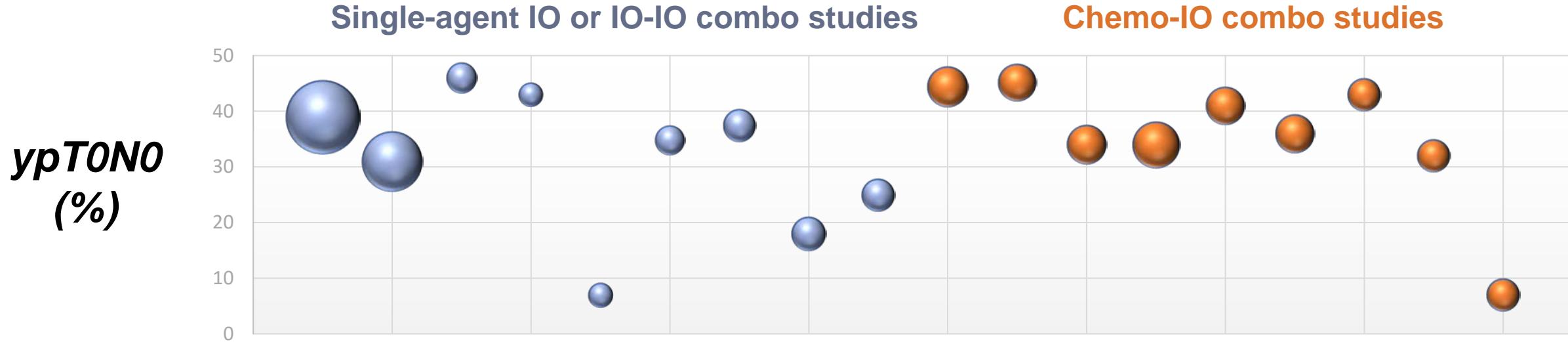
Pre-post treatment imaging: multiparametric bladder MRI (mpMRI); <sup>18</sup>FDG-PET/CT scan, T/A CT scan



- Cystectomy
- Post-cystectomy management according to EAU guidelines
- Survival data collected until 2-y post cystectomy

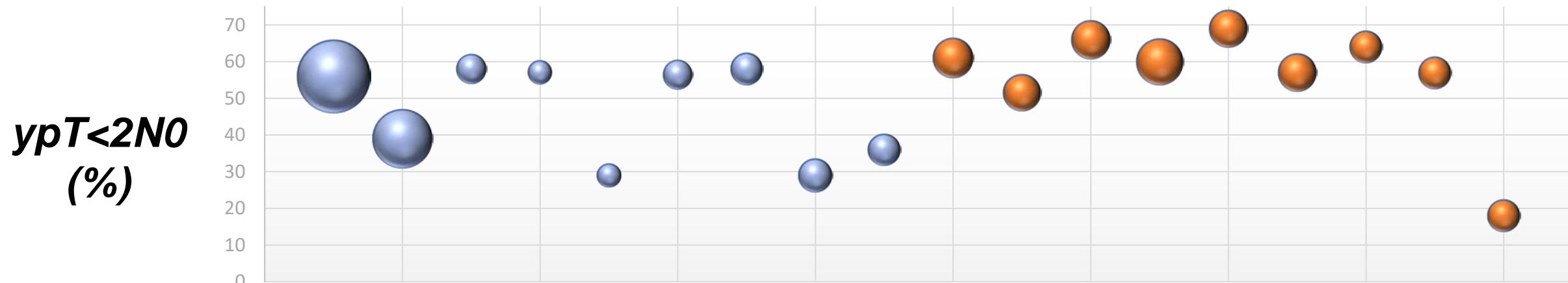
1. Necchi A, et al. *J Clin Oncol.* 2018;36:3353-3360; 2. Necchi A, et al. *Eur Urol.* 2020;77:439-446; 3. Briganti A, et al. *Eur Urol.* 2020;77:576-580; 4. Necchi A, et al. *Eur Urol.* 2021;80:149-159; 5. Necchi A, et al. *Eur Urol.* 2020;77:701-710; 6. Bandini M, et al. *Ann Oncol.* 2020;31:1755-1763; 7. Necchi A, et al. *Eur Urol.* 2020;77:636-643; 8. Bandini M, et al. *Eur Urol Oncol.* 2021;4:829-833; 9. Bandini M, et al. *J Natl Cancer Inst.* 2021;113:48-53; 10. Basile G, et al. *Clin Cancer Res.* 2022 Oct 3:CCR-22-2158. doi: 10.1158/1078-0432.CCR-22-2158. Online ahead of print.

# Uncertainties of pTN response in Neoadjuvant therapy trials: Chemo-free vs Chemo-IO studies

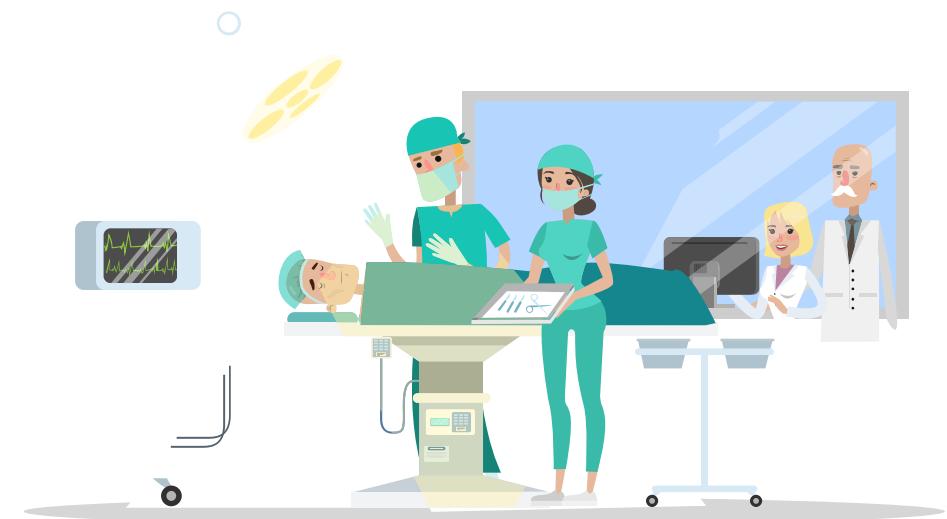


1. Bandini M et al. Ann Oncol. 2020;31:1755–1763. 2. Powles T et al. Nat Med. 2019;25:1706–1714. 3. Szabados B et al. Eur Urol. 2022;82:212–222. 4. van Dijk N et al. Nat Med. 2020;26:1839–1844.

5. van Dorp J et al. Ann Oncol. 2021;32(Suppl5):S1283–S1346. 6. Grande E et al. J Clin Oncol. 2020;38(Suppl15). Abstract 5012. 7. Gao J et al. Nat Med. 2020;26:1845–1851. 8. Grivas P et al. J Clin Oncol. 2021;39(Suppl15):4518. 9. Martinez Chanza N et al. J Clin Oncol. 2022;40(Suppl16):4517.



1. Hoimes CJ et al. J Clin Oncol. 2020; 38(Suppl15). Abstract 5543. 2. Kaimakliotis HZ et al. J Clin Oncol. 2020;38(Suppl15). Abstract 5019. 3. Urology Today. Accessed July 2022. <https://www.urotoday.com/conference-highlights/asco-2020/asco-2020-bladder-cancer/121911-asco-2020-phase-ii-neoadjuvant-n-gemcitabine-g-and-pembrolizumab-p-for-locally-advanced-urothelial-cancer-lauc-interim-results-from-the-cisplatin-c-ineligible-cohort-of-gu14-188.html> 4. Gupta S et al. J Clin Oncol. 2020;38(Suppl6). Abstract 439. 5. Cathomas R et al. J Clin Oncol. 2022;40(Suppl16). Abstract 4515. 6. Funt SA et al. J Clin Oncol. 2022;40:1312–1322. 7. Rose TL et al. J Clin Oncol. 2021;39:3140–3148. 8. Martinez Chanza N et al. Ann Oncol. 2021;32(Suppl5):S678–S724. 9. Martinez Chanza N et al. J Clin Oncol. 2022;40(Suppl16). Abstract 4517.



Are we able to improve the outcomes with adjuvant checkpoint inhibitors in high-risk MIBC?

# Landmark CheckMate-274 Phase III Trial of Adjuvant Nivolumab in High-Risk Urothelial Carcinoma



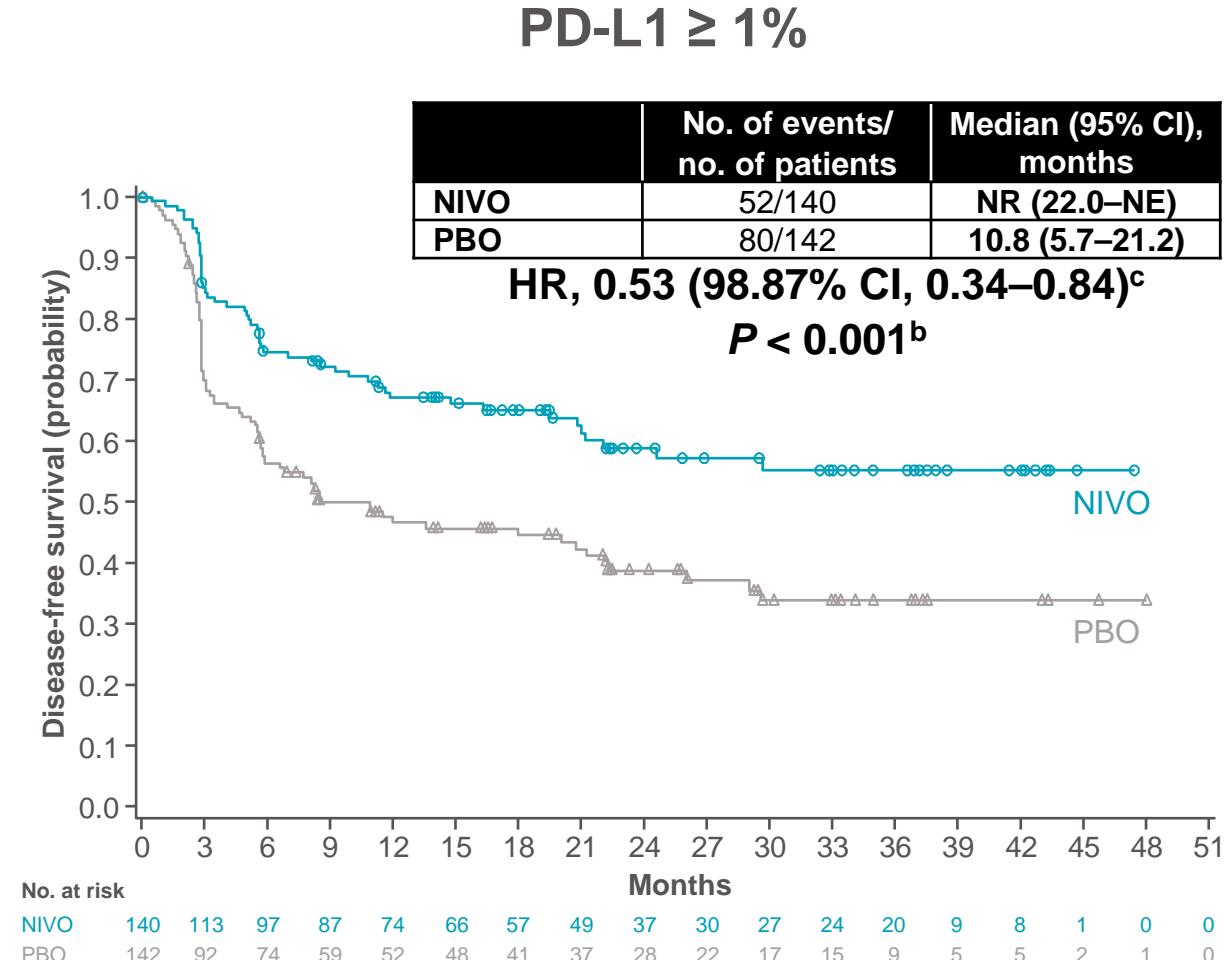
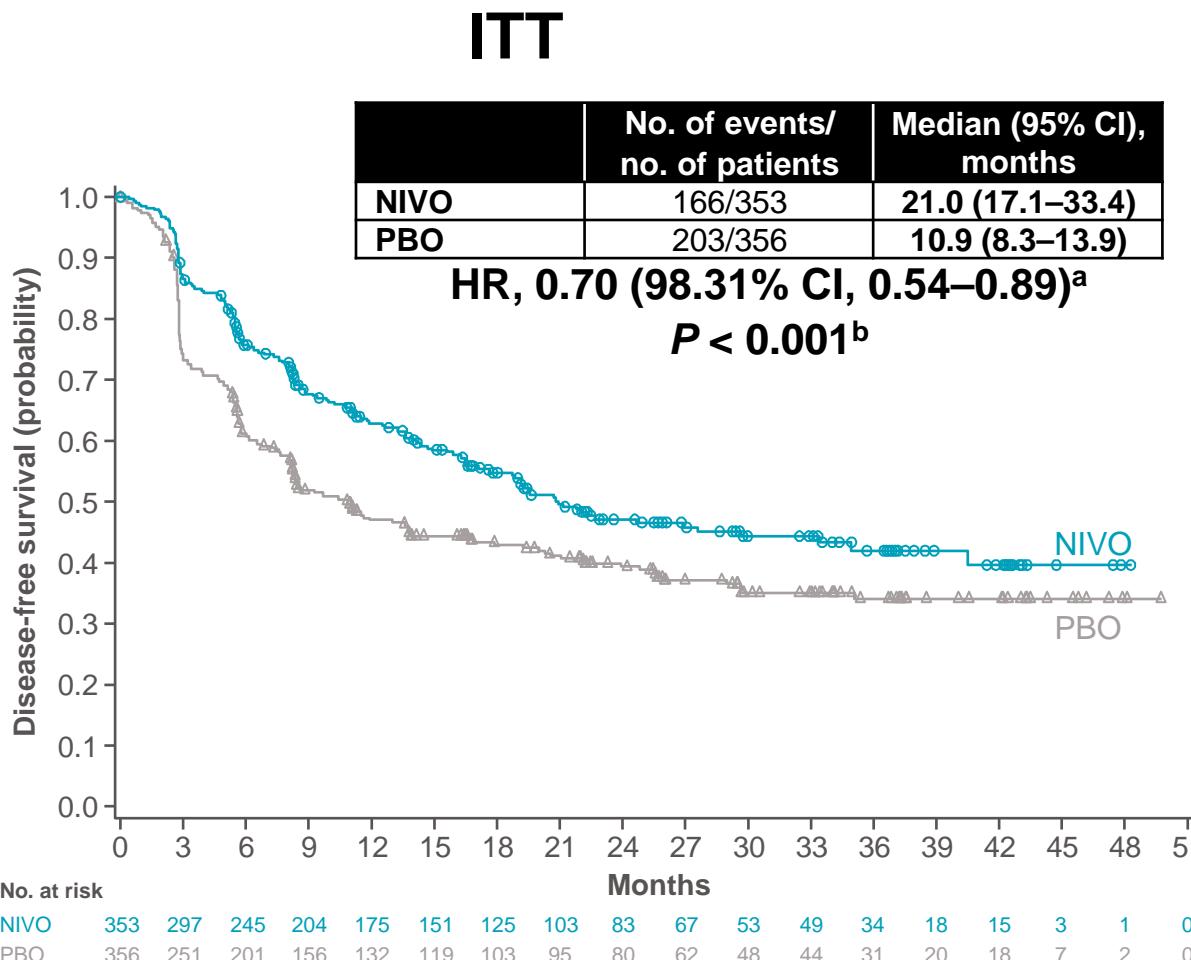
ORIGINAL ARTICLE

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

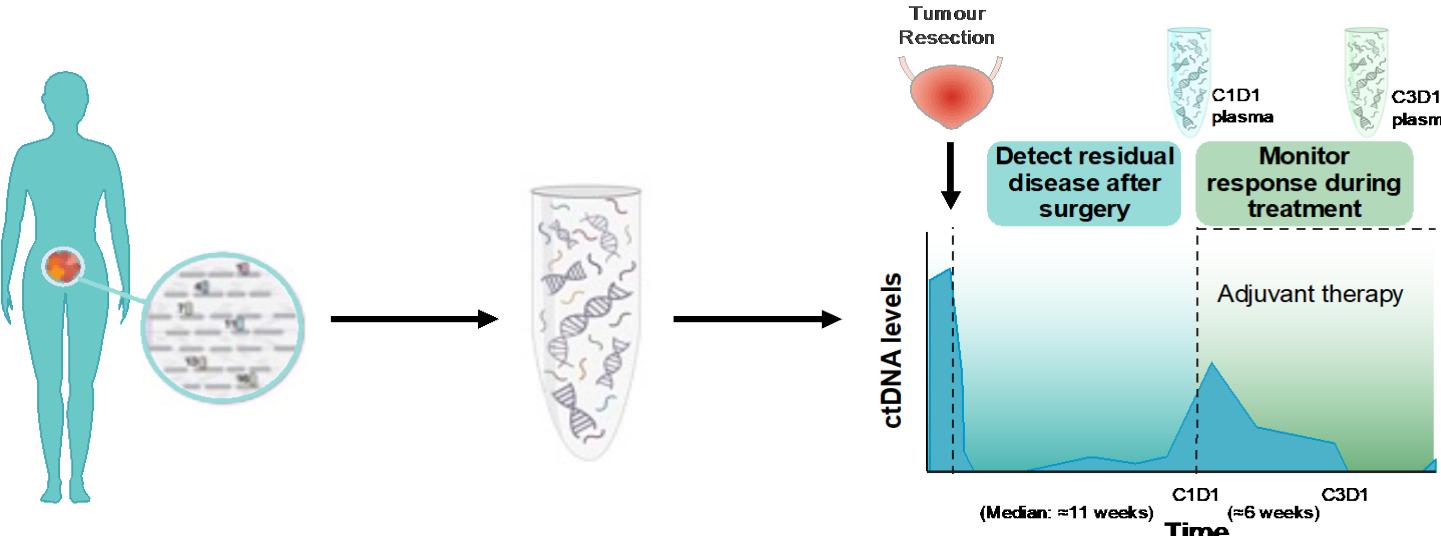
D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette,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



# Curative potential of immune-checkpoint inhibition in early bladder cancer



# Curative potential of Radical Cystectomy +/- immune-checkpoint inhibition in early bladder cancer



## *ctDNA- test post RC is prognostic*

Observation arm; ctDNA(-) (n=183); ctDNA(+) (n=98):

- ctDNA(-) (n=183); ctDNA(+) (n=98)
- DFS HR, 6.30 (95% CI: 4.45, 8.92)
- $p<0.0001$
- OS HR, 8.00 (95% CI: 4.92, 12.99)
- $p<0.0001$

## *ctDNA+ test post RC is predictive of adj IO benefit*

ctDNA(+): 37%

- DFS HR, 0.58 (95% CI: 0.43, 0.79)
- $p=0.0005$
- OS HR, 0.59 (95% CI: 0.41, 0.86)
- $p=0.0059$

## *ctDNA clearance is prognostic*

Atezolizumab arm:

Clearance+ (n=18) vs Clearance - (n=81):

- DFS HR, 0.26 (95% CI: 0.12, 0.56)
- OS HR, 0.41 (95% CI: 0.10, 1.70)
- $p=0.0059$

# Pivotal Keynote-057 Phase II Trial of Pembrolizumab in Non Muscle-Invasive Bladder Cancer



## Articles

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study



Arjun V Balar, Ashish M Kamat, Girish S Kulkarni, Edward M Uchio, Joost L Boormans, Mathieu Roumiguié, Laurence E M Krieger, Eric A Singer, Dean F Bajorin, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Badrinath R Konety, Haojie Li, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit





*Narrowing the gaps*



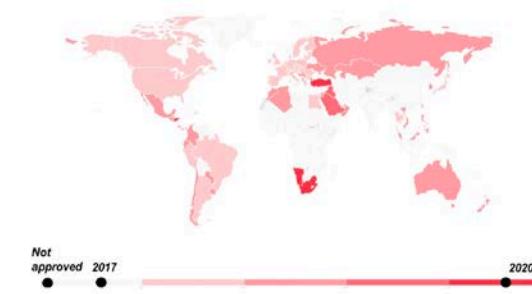
# Geography as a therapeutic destiny for patients with bladder cancer



Pembro 1L



Pembro 2L



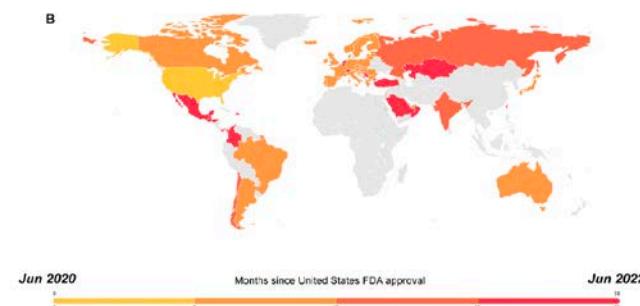
Sacituzumab govitecan



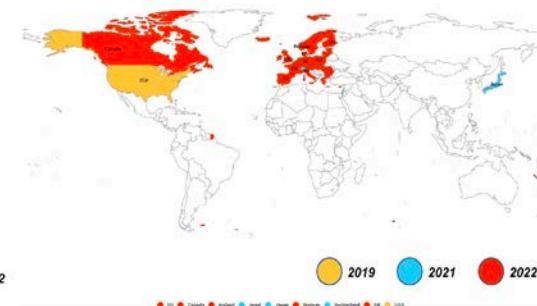
Adjuvant nivolumab



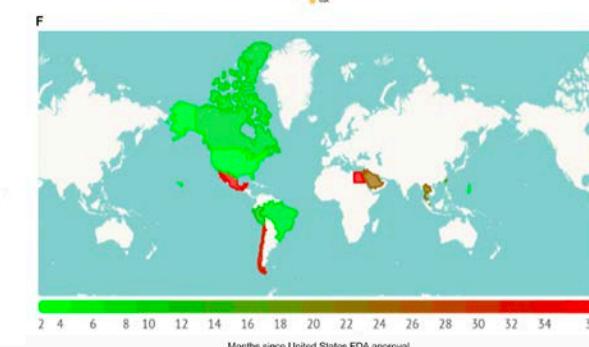
Avelumab maintenance



Enfortumab vedotin



Erdafitinib



Pembrolizumab NMIBC



# Bladder cancer treatment for the next decade: filling the management gaps



Safety remains a concern requiring continuous patient and physician's education. Safety/Efficacy threshold remains uncertain



Effective non-immunotherapy options are available but their optimal positioning is uncertain: the attrition rate from earlier-stage use may become critical



Most people are still far behind the forefront of such tremendous achievements



Shared decision-making still enables patients to engage and find the right treatment for them



Never forget the importance of offering patients enrolment in clinical trials



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