Immunoterapia nella malattia avanzata

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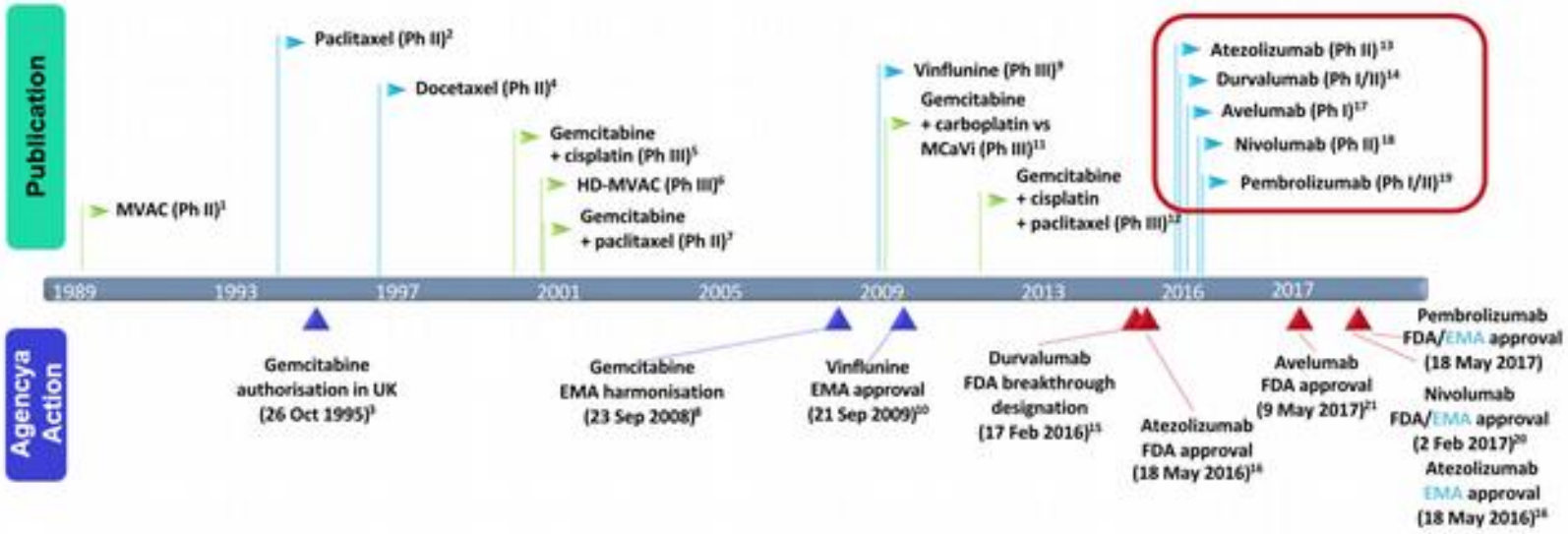
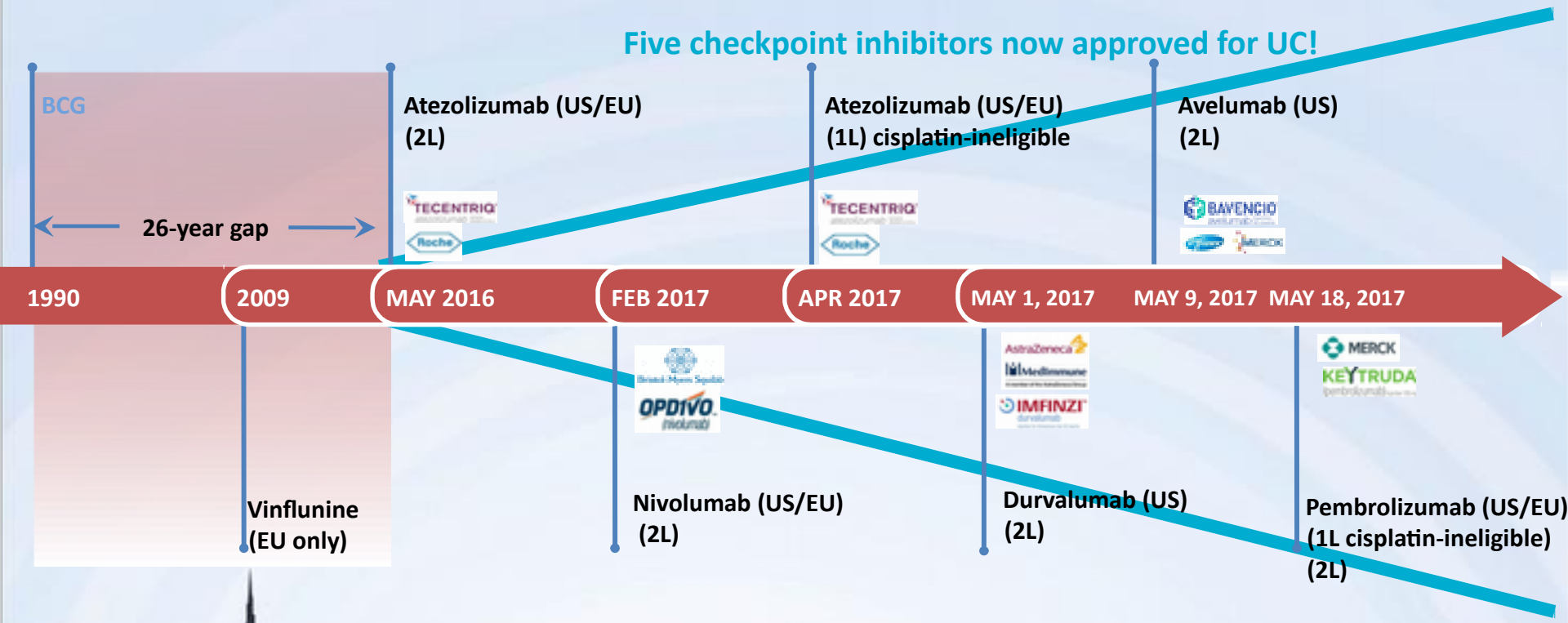
Systemic therapy for urothelial cancer - 5 new immunotherapeutic agents



1. Sternberg CN et al. Cancer 1989;64:2448–2458; 2. Roth BJ et al. J Clin Oncol 1994;12:2264–2270; 3. Eli Lilly. SmPC Gemzar® 01 Jul 2014. Available at: http:// www.medicines.org.uk; 4. McCaffrey JA et al. J Clin Oncol 1997;15:1853–1857; 5. Von der Maase H et al. J Clin Oncol 2000;18:3068–3077; 6. Sternberg CN et al. J Clin Oncol 2001;19:2638–2646; 7. Meluch AA et al. J Clin Oncol 2001;19:3018–3024; 8. EMA. EMEA/CHMP/512295/2008; 24 Sep 2008. Available at: http:// www.ema.europa.eu; 9. Bellmunt J et al. J Clin Oncol 2009;27:4454–4461; 10. EMA. EMEA/H/C/000983; 2012. Available at: http:// www.ema.europa.eu; 11. De Santis M et al. J Clin Oncol 2009;27:5634–5639; 12. Bellmunt J et al. J Clin Oncol 2012;30:1107–1113; 13. Rosenberg JE et al. Lancet 2016;387:1909–1920; 14. Massard C et al. ASCO 2016. Abstract #4502 and oral presentation; 15. AstraZeneca. Press release 17 Feb 2016. Available at: http:// www.astrazeneca.com; 16. FDA. Press release 18 May 2016. Available at: http:// www.fda.gov); 17. Apolo AB et al. ASCO 2016. Abstract #4514 and poster; 18. Galsky MD et al. ESMO 2016. Abstract #LBA31_PR; 19. Balar A et al. ESMO 2016. Abstract #LBA32_PR; 20. FDA. Press release 2 Feb 2017. Available at http://www.fda.gov; 21. FDA. Press release 9 May 2017. Available at http://www.fda.gov.

Five checkpoint inhibitors now approved for UC!



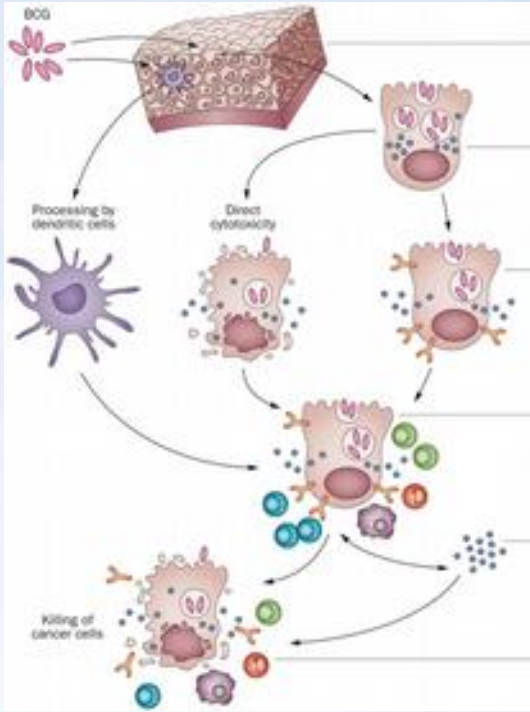
1. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm501762.htm; 2. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm539646.htm;
3. https://www.roche.com/media/store/releases/med-cor-2017-04-18.htm; 4. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm555930.htm;
5. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm557162.htm; 6. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm559300.htm.

1L, first-line; 2L, second-line;
BCG, Bacillus Calmette–Guérin vaccine; UC, urothelial carcinoma.

Rationale for immune checkpoint inhibitors in UC

BCG was the first immunotherapy to receive approval from the FDA for cancer treatment and remains the gold standard for NMIBC[1,2]

- BCG is an attenuated form of *Mycobacterium bovis,* the bacterium that causes bovine tuberculosis[1]
- The MOA of BCG is not yet completely understood, despite its long history of use in bladder cancer[1,3]



Attachment to urothelial cells

Internalisation by bladder cancer cells

Antigen presentation and cytokine release by bladder cancer cells

Immune cell recruitment

Cytokine production

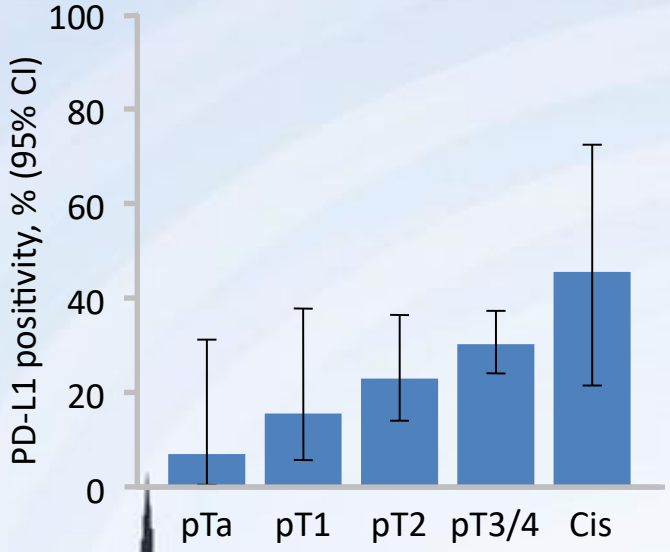
Immune-mediated cytotoxicity

1. Ghasemzadeh A, et al. *Clin Cancer Res* 2016;22:793–801; 2. Necchi A, et al. *Curr Opin Urol* 2017;27 [Epub ahead of print]; 3. Redelman-Sidi G, et al. *Nat Rev Urol* 2014;11:153–162.

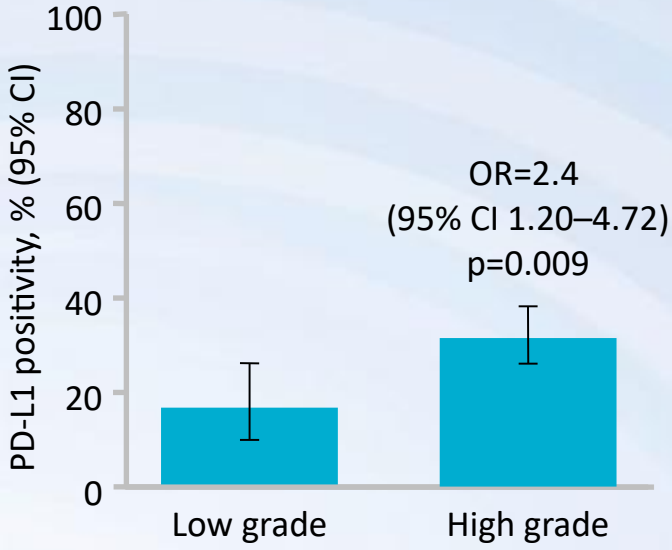
BCG, Bacillus Calmette–Guérin vaccine; FDA, Food and Drug Administration; MOA, mechanism of action; NMIBC, non-muscle-invasive bladder cancer.

PD-L1 expression is associated with grade and stage in UC

PD-L1 positivity increases with advancing local tumour stage in UC

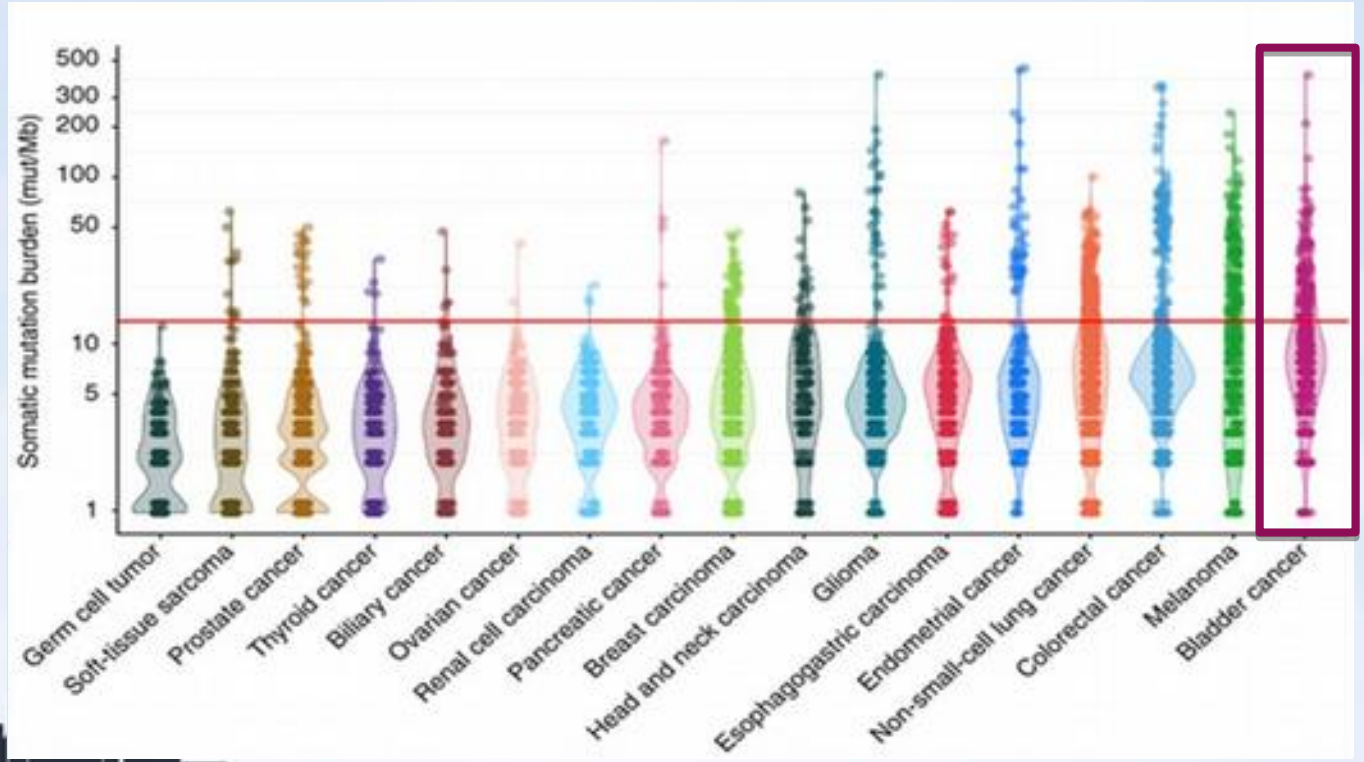


PD-L1 positivity is significantly associated with high tumour grade in UC



CI, confidence interval; OR, odds ratio; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.

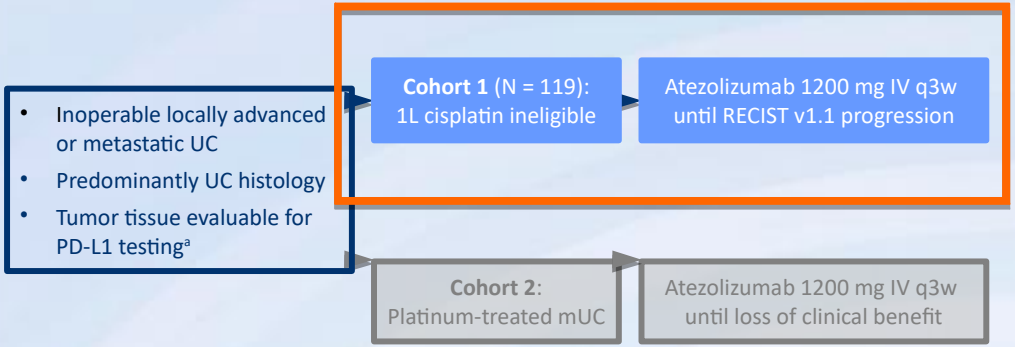
Bladder cancer is considered to be a highly immunogenic tumour[1]

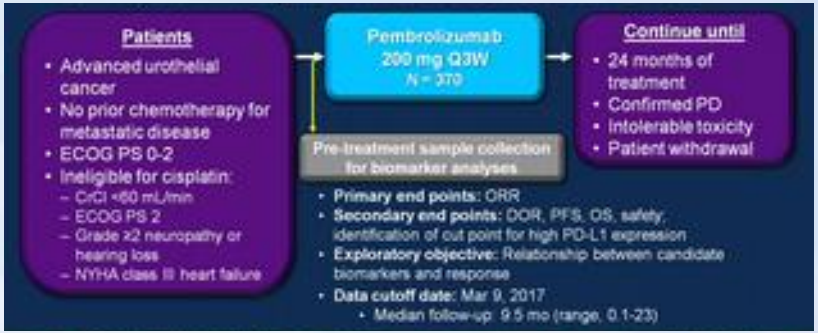


1. Zehir A, et al. *Nat Med* 2017;23:703–713

1L metastatic setting

Phase II IMvigor210 & KN052 Study Design and Objectives





- Key cohort 1 inclusion criteria:
  - No prior treatment for mUC (> 12 months since perioperative chemotherapy)
  - ECOG PS 0-2
  - Cisplatin ineligibility based on ≥ 1 of the following:[1] GFR < 60 and > 30 mL/min (Cockcroft-Gault), Grade ≥ 2 hearing loss (25 dB at 2 contiguous frequencies) or peripheral neuropathy, ECOG PS 2
- Endpoints:
  - Primary: confirmed ORR per RECIST v1.1 (central IRF)
  - Key secondary: DOR, OS, safety

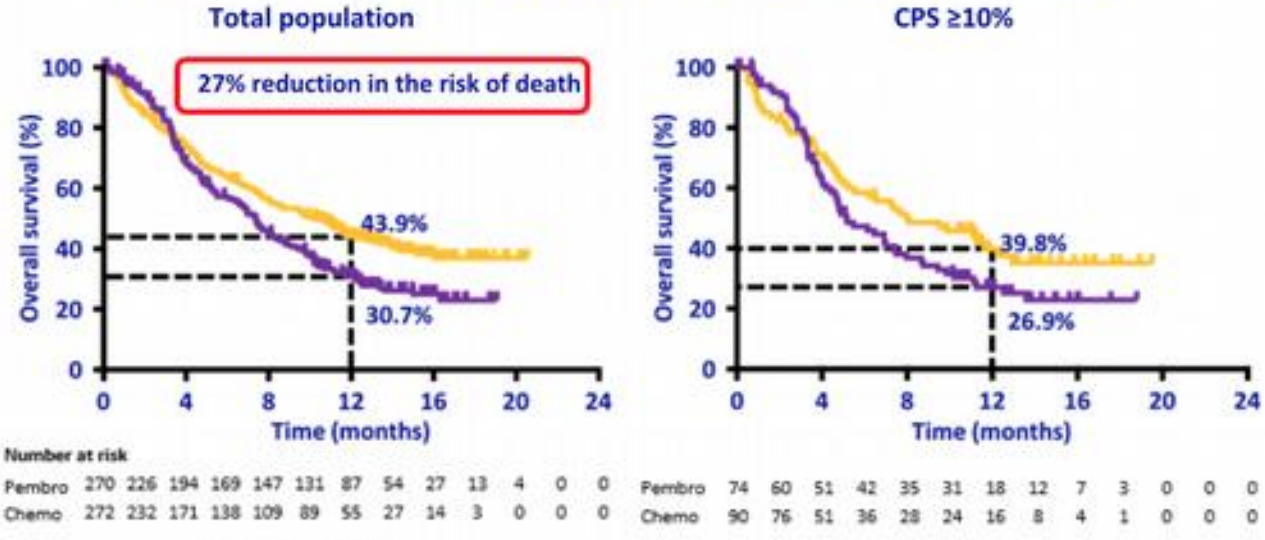
Balar AV et al, Lancet. 2017 Jan 7;389(10064):67-76
Balar AV, et al. Lancet Oncol 2017; 10.1016/S1470-2045(17)30602-2

Recruiting Clinical Trials: First-Line Metastatic Bladder Cancer

Study	Agent	Phase and Type	Primary Endpoint
MK3475-361/ KEYNOTE-361[1]	Pembrolizumab ± chemotherapy[a] vs chemotherapy	3 Randomised, controlled	PFS, OS
IMvigor130[2]	Atezolizumab ± chemotherapy[a] vs chemotherapy	3 Randomised, controlled	PFS, OS, % with AEs
DANUBE[3]	Durvalumab ± tremelimumab vs SOC chemotherapy	3 Randomised, open label	PFS, OS
CheckMate901[4] *Galsky MD et al. TPS 539*	Nivolumab+Ipilimumab vs chemotherapy	3 Randomised, open label	PFS, OS

≥2L metastatic setting

KEYNOTE-045: Phase III Pembrolizumab study in platinum refractory patients (n=542)

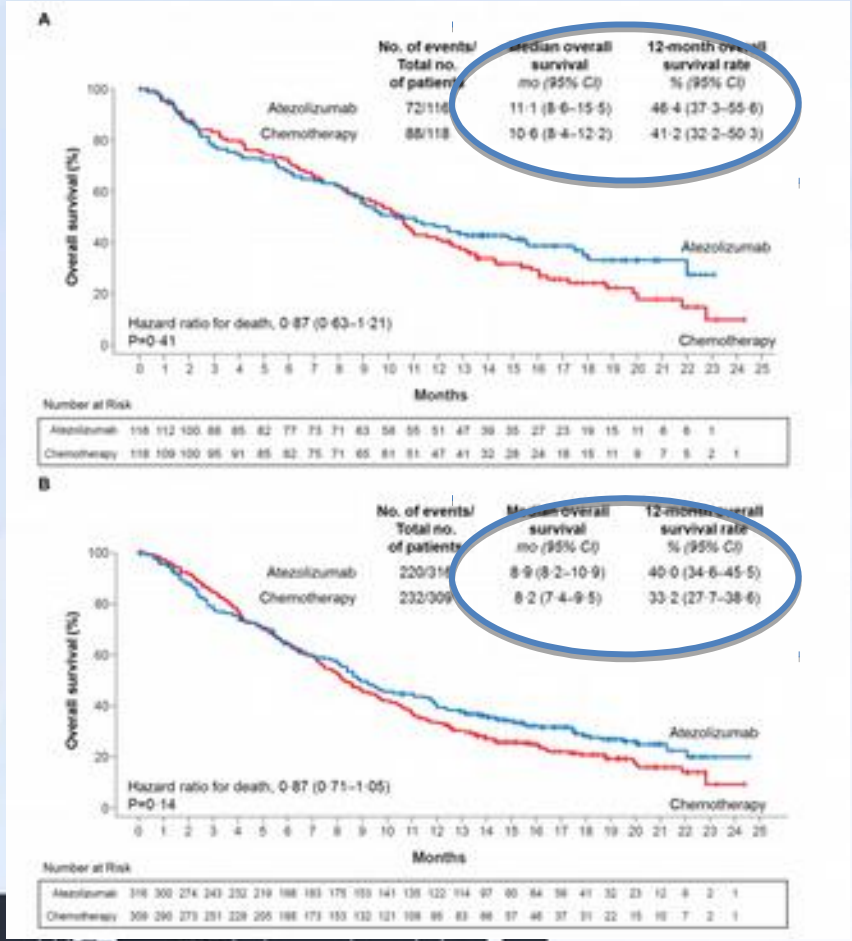


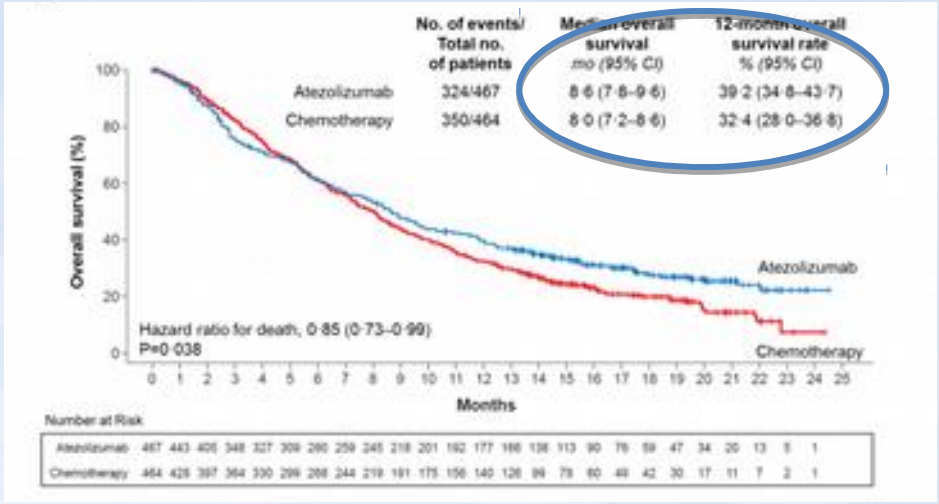
	Median OS months (95% CI)	HR (95% CI)	*P*
Pembrolizumab	**10.3** (8.0–11.8)	0.73 (0.59–0.91)	**0.0022**
Chemotherapy	**7.4** (6.1–8.3)		

Median OS months (95% CI)	HR (95% CI)	*P*
8.0 (5.0–12.3)	0.57 (0.37–0.88)	**0.0048**
5.2 (4.0–7.4)		

CPS, combined positive score (defined as percentage of PD-L1+ tumor cells (TC) and infiltrating immune cells (IC) relative to the total number of TCHigh PD-L1 expression was defined as CPS ≥10%
Data cut-off date: September 7, 2016

Bellmunt J et al. N Engl J Med 2017 Mar 16;376(11):1015-1026





Outcomes of IMvigor211 - Efficacy

US FDA and EMA approval for platinum-treated, advanced UC

Powles T. et al, Lancet 2017 & GU-ASCO 2018

Immune checkpoint inhibitors in the platinum-refractory setting (no Head to Head comparisons)

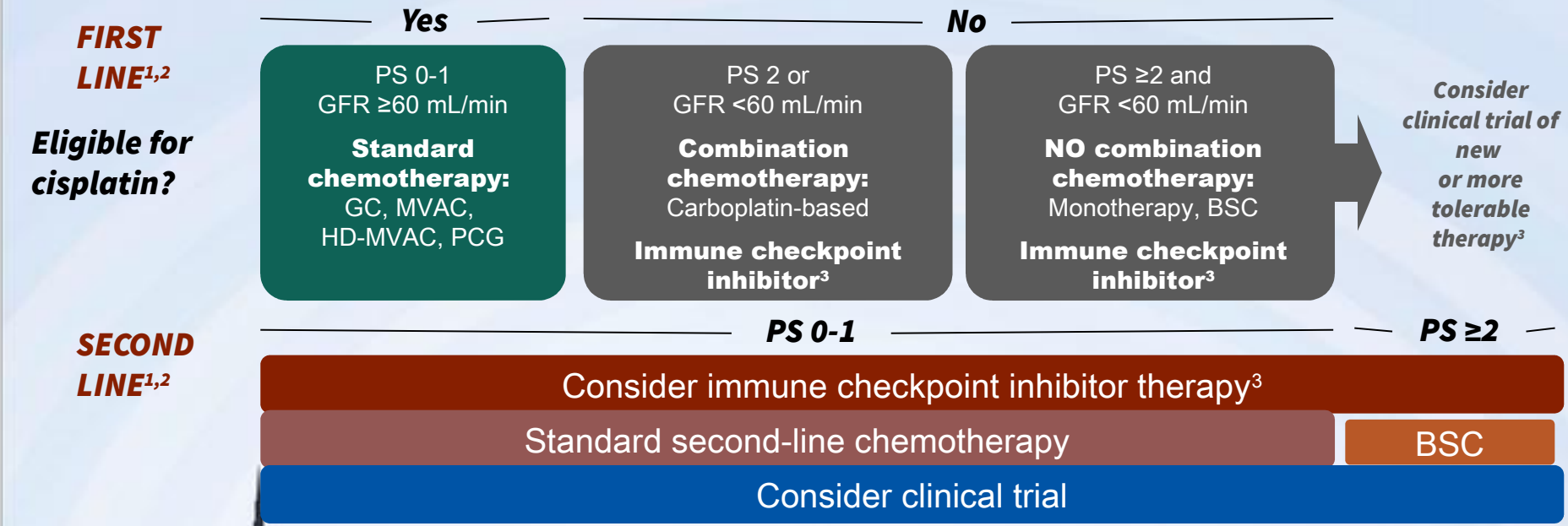
	Atezolizumab[1,6]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase II single arm Phase III randomized	Phase II single arm	Phase III randomized	Phase Ib	Phase I/II
Number of patients	310[1] 467[6]	265	270	249	191
Dosing	1200 mg q3w	3 mg/kg q3w	200 mg q3w	10 mg/kg q2w	10 mg/kg q2w
ORR	15%; IC2/3 23%	19.6%	21.1%	17%	17.8%
Duration of response	84% ongoing at median follow-up of 11.7 months/15.9months[6]	77% ongoing at median follow-up of 7.0 months	72% ongoing at median follow-up of 14.1 months	64% ongoing at data cut	Not reached at data cut
Median OS	7.9/11.1 months	8.7 months	10.3 months	7.7 months	18.2 months
Median PFS	2.1 months	2.0 months	2.1 months	1.5 months	1.5 months
Grade 3/4 TRAEs	16%[1]/20%[6]	18%	15% G3–5	10.8% G3–5	6.8%

1. Rosenberg JE et al. Lancet 2016;387:1909–1920; 2. Sharma P et al. Lancet Oncol 2017;18:312–322 ; 3. Bellmunt J et al. N Engl J Med 2017 2017;376:1015–1026; 4. . Patel MR et al, Lancet Oncol 2018 Jan 19 (1): 51-64 and Apolo AB et al. J Clin Oncol 2017 Jul 1;35(19):2117-2124 5. Powles T et al. JAMA Oncol. doi:10.1001/jamaoncol.2017.2411. 6. Powles T et al The Lancet 2018

Summary ≥2L

- **Updated results confirm that clinical benefit with ICI use is maintained at long term**
- Clinical prognostic factor models derived from non-comparative trials did support the benefit from ICI therapy compared to standard chemotherapy
- Results from translational studies will likely provide the basis for understanding patient outcome in this setting

How Emerging Clinical Data Will Impact the European/US Treatment Algorithm for Metastatic Urothelial Cancer



BSC: best supportive care; GFR: glomerular filtration rate; (HD-)MVAC: (high-dose) methotrexate, vinblastine, doxorubicin, cisplatin; PCG: paclitaxel, cisplatin, gemcitabine.

1. Witjes JA et al. *Eur Urol*. 2017;71:462-475. 2. Witjes JA et al. https://uroweb.org/wp-content/uploads/EAU-Guidelines-Muscle-invasive-and-Metastatic-Bladder-Cancer-Guidelines-2016.pdf. Published 2016. Accessed March 3, 2017.
3. National Comprehensive Cancer Network (NCCN). Bladder Cancer (Version 1.2017). https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed February 9, 2017.

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