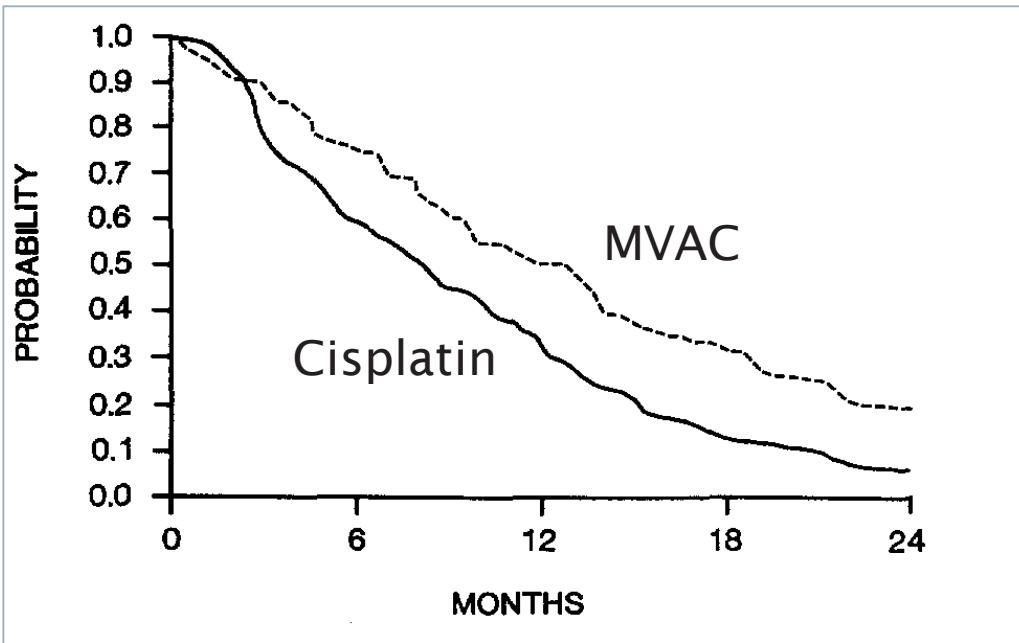


# **Treatment Of Metastatic Urothelial Carcinoma: State Of The Art in 2018 (cisplatin eligible and ineligible)**

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# Combination chemotherapy for bladder cancer



Cisplatin 70 mg/m<sup>2</sup>, day

Methotrexate 30 mg/m<sup>2</sup>, day 1, 15, 22,

Vinblastine 3 mg/m<sup>2</sup>, day 2 15, 22,

Doxorubicin 30 mg/m<sup>2</sup>, day 2

q28d

	C	MVAC	p
OS (months)*	8.2	12.5	0.0002
Response (%)*	12	39	<0.0001
Leukocytes < 1000/mm <sup>3</sup> (%)	1	24	<0.0001
Sepsis (%)	1	6	0.04
Nausea/vomiting (%)	1	12	0.0004

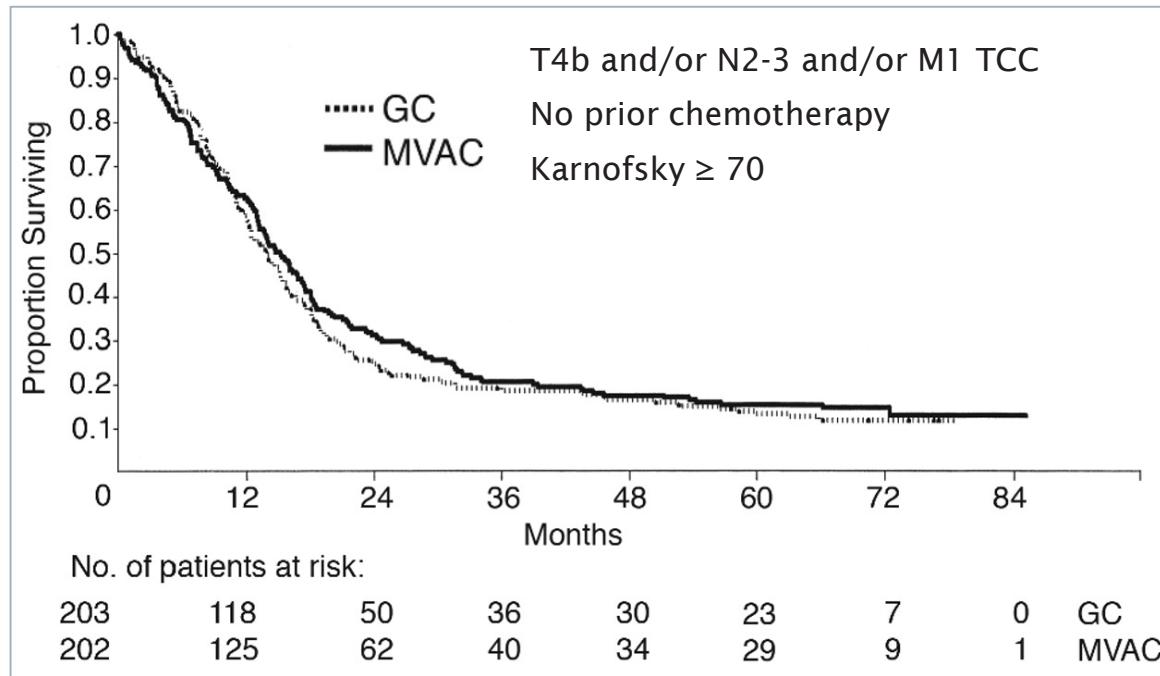
\* Primary endpoint

5 (4%) toxic death rate with MVAC (versus none)

Survival predicted by

- Performance status
- Visceral metastases
- Histology (TCC > SCC/adeno)

# Cisplatin/Gemcitabine versus MVAC



	GC	MVAC	p
OS (months)*	13.8	14.8	0.75
ORR (%)	49.4	45.7	0.51
PFS (months)	7.4	7.4	0.66
Toxic death (%)	1	3	NS
G3/4 neutropenia	71.1	82.3	
G3/4 mucositis	1.0	21.9	
G3/4 infection	2.5	15.1	

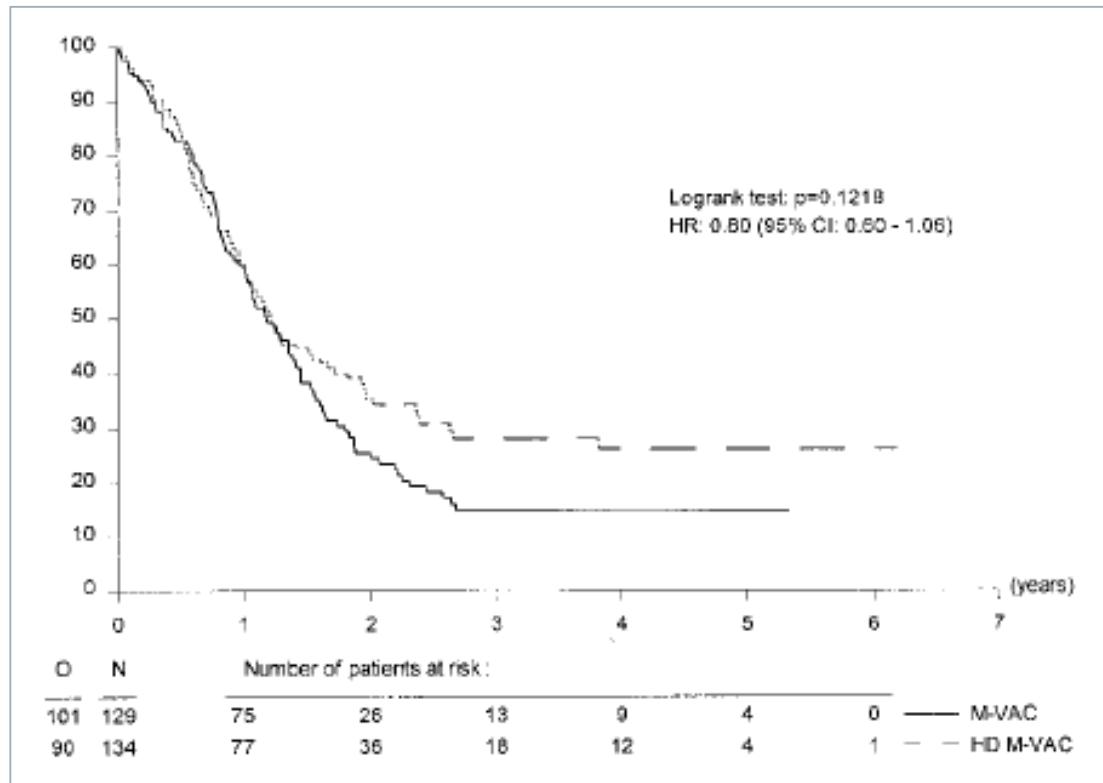
\* Primary endpoint

Cisplatin 70 mg/m<sup>2</sup>, day 2 +  
Gemcitabine 1000 mg/m<sup>2</sup>, day 1, 8, 15  
q28d

Survival predicted by

- Performance status
- M stage
- ALP
- >3 metastatic sites
- Visceral metastases

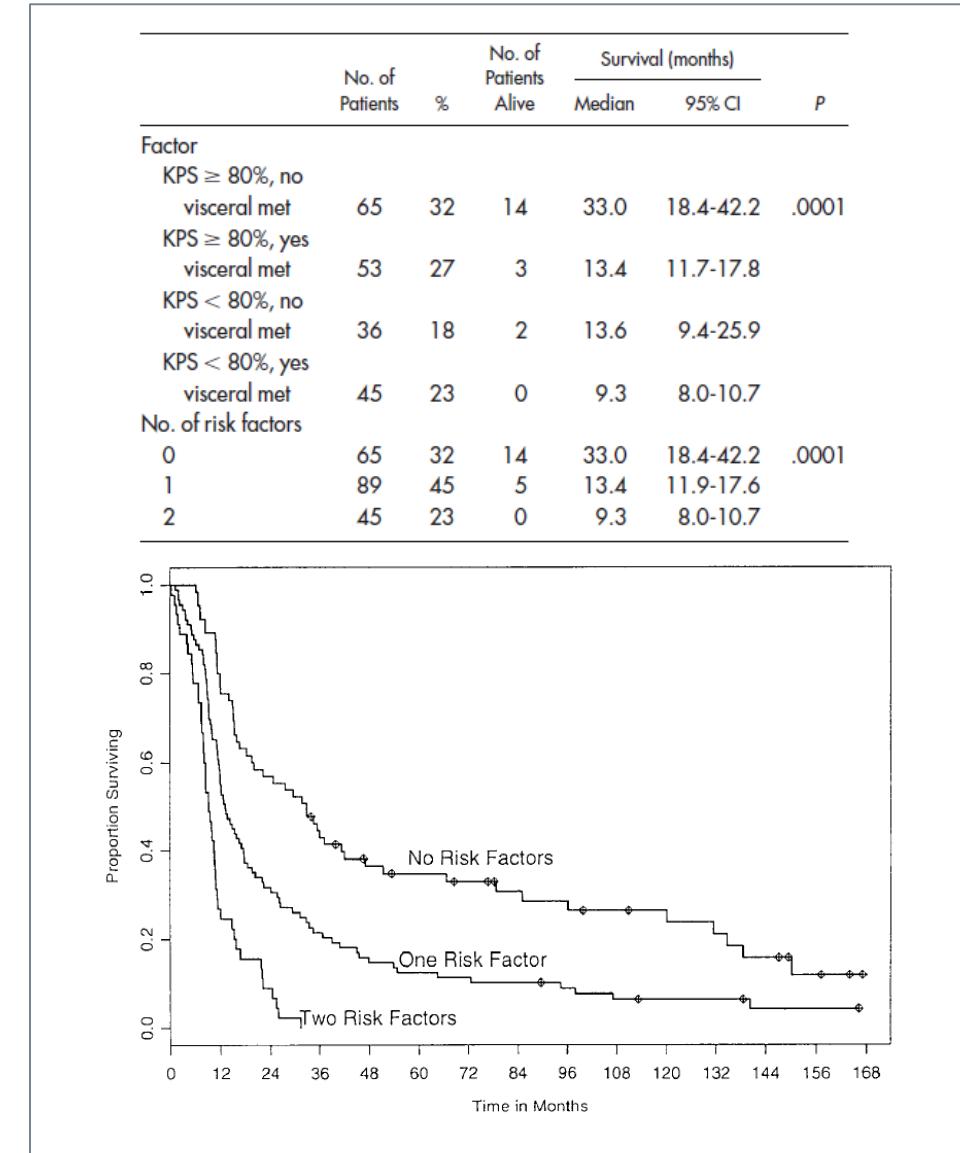
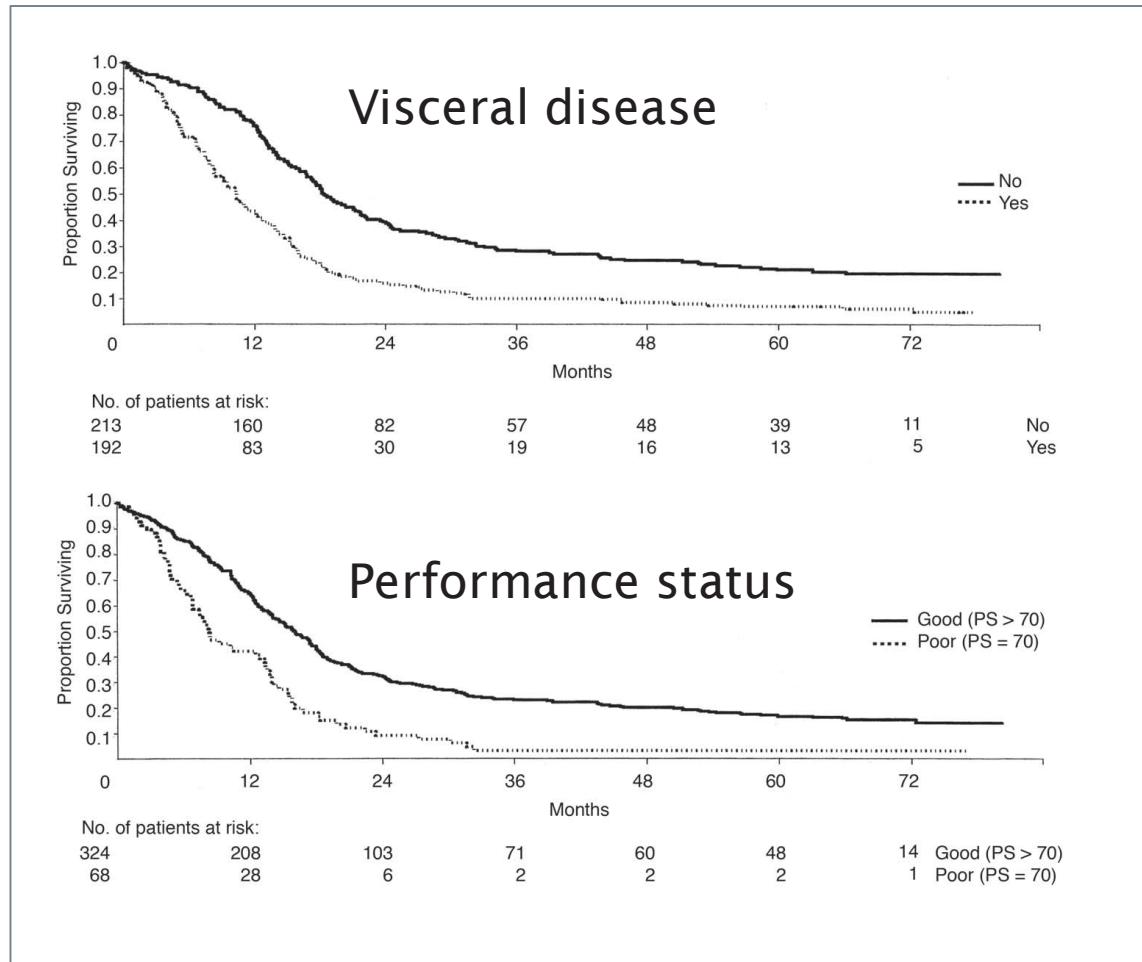
# Accelerated MVAC versus MVAC



	MVAC	HD-MVAC	p
OS (months)*	14.1	15.5	.122
Objective response rate (%)	50	62	.06
Complete response rate (%)	9	21	.009
PFS (months)	8.2	9.1	.037
Toxic death (%)	4	3	NS
Febrile neutropenia	26	10	.001
G3/4 mucositis	17	10	.034

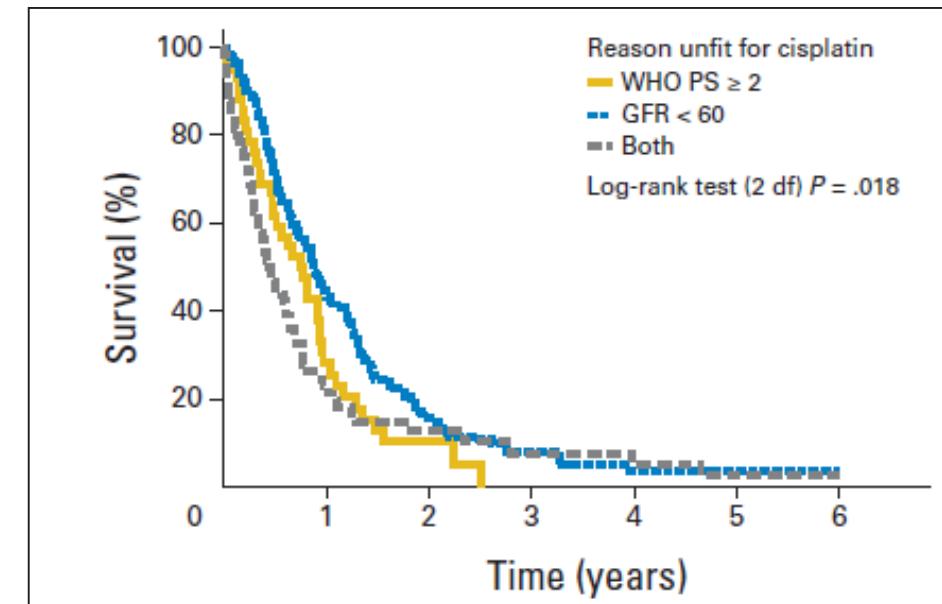
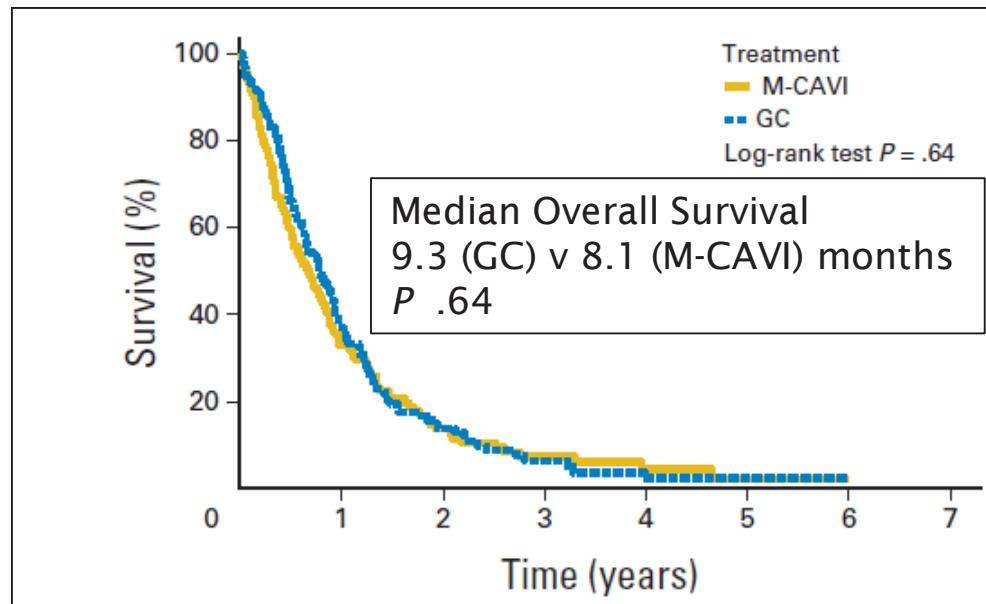
\* Primary endpoint

# Prognostic factors for first line treatment



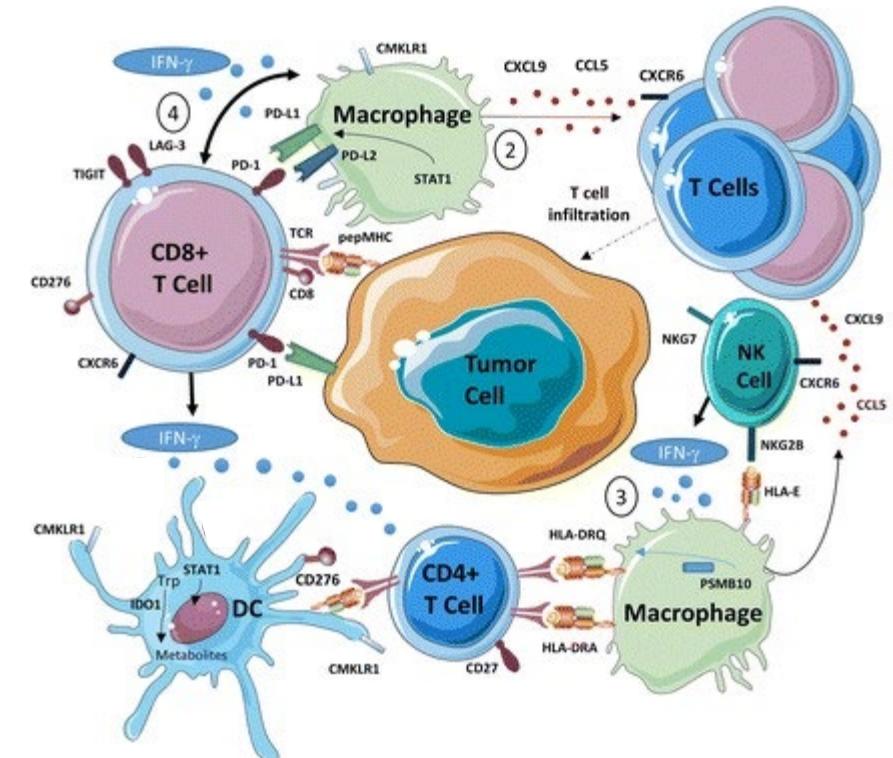
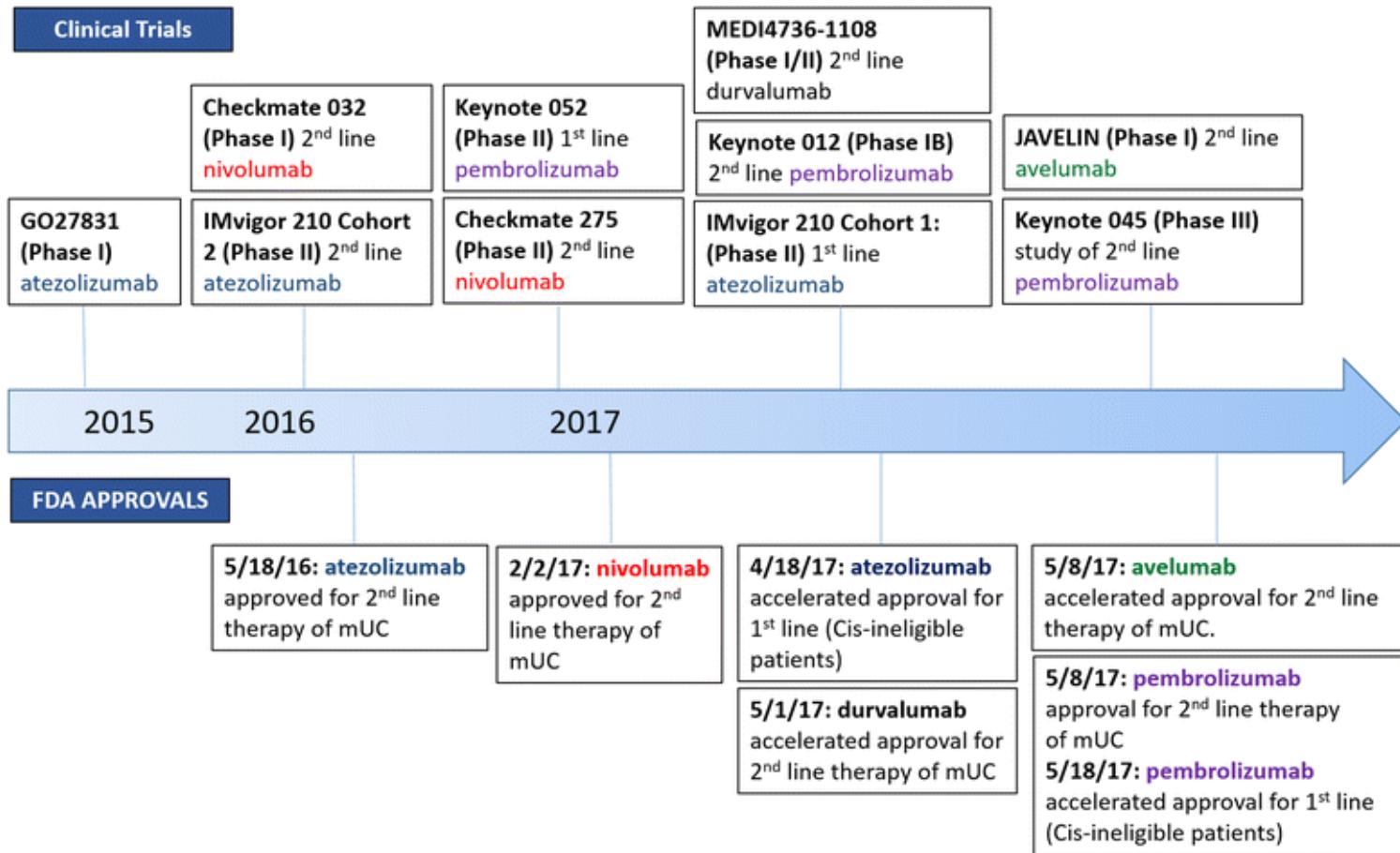
# First line chemotherapy if ‘cisplatin ineligible’

- Carboplatin AUC 4.5 / Gemcitabine 1g/m<sup>2</sup> d1+8 v Methotrexate/Carboplatin/Vinblastine
- Cisplatin unfit: PS2 and/or GFR 30-60 mL/min



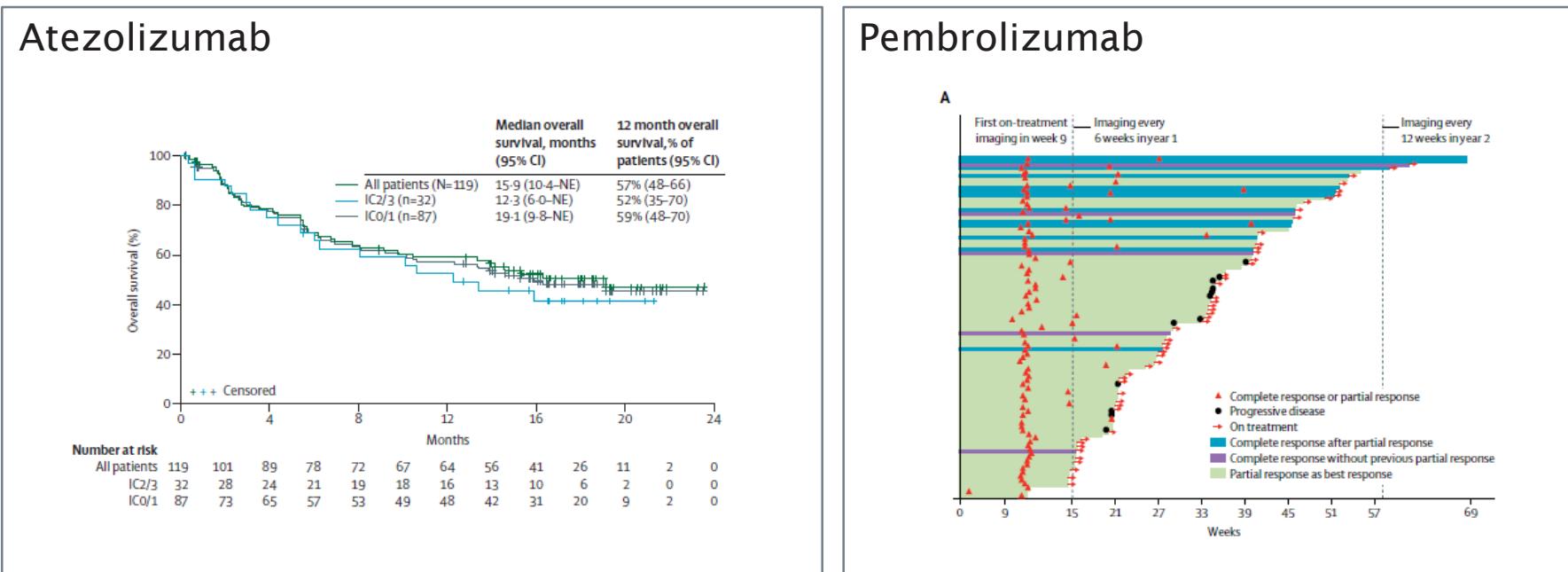
- Severe Acute Toxicity: 9.3 with GCarbo versus 21.2 % with M-CAVI
  - G3/4 mucositis, G4 plt and bleeding, G3/4 neutropenic fever, G3/4 renal toxicity, death

# PD1/PD-L1 inhibitor approvals in urothelial cancer

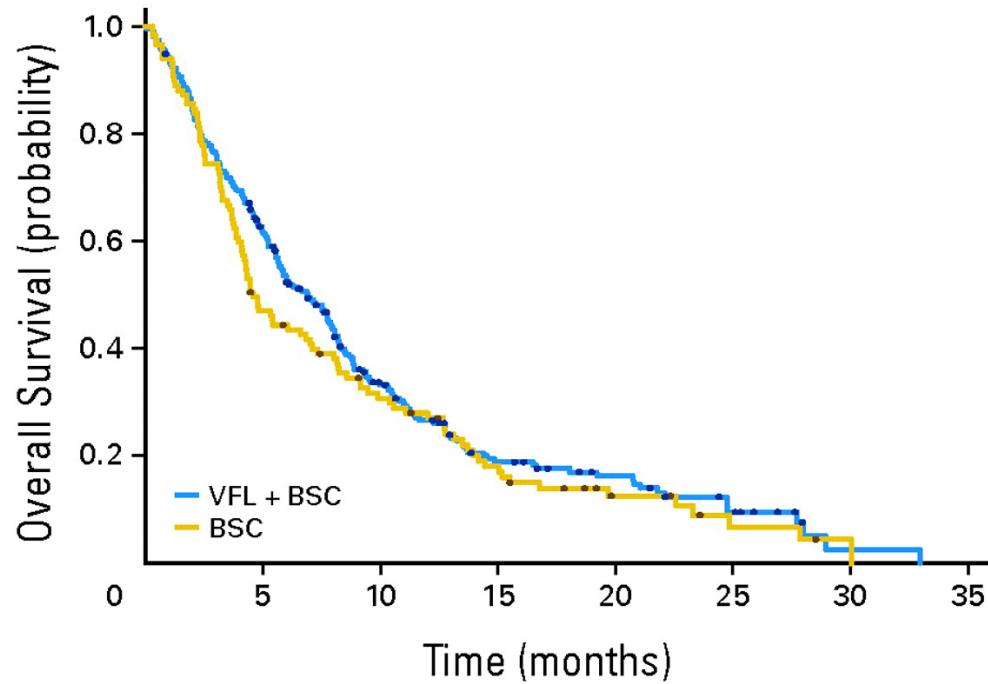


# First line immunotherapy if ‘cisplatin ineligible’

	Atezolizumab	Pembrolizumab	Carboplatin/gemcitabine
n	123	374	119
ORR	23% (95% CI 16 to 31)	24% (95% CI 20 to 29)	41.2% (36.1% confirmed)
Complete response	9%	5%	3.4%
Median PFS	2.7 months (2.1 to 4.2)	2 months (2-3)	5.8 months
Median OS	15.9 months (10.4 to NR)		9.3
6 month OS		67% (95% CI 62-73)	
12 month OS	57% (95% CI 48-66)		



# Second line treatment options



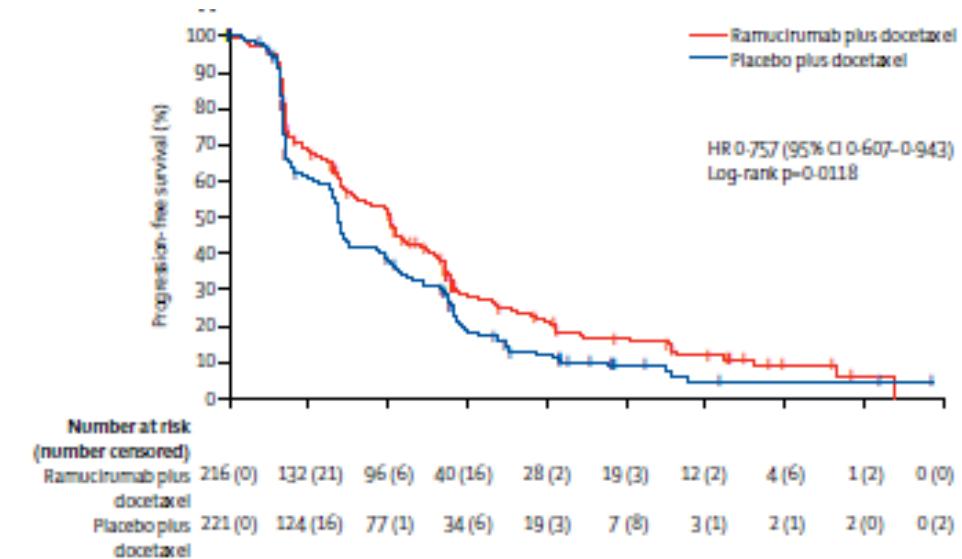
	BSC	V+BSC	p
Overall survival (months)*	4.6	6.9	.287
Objective response rate (%)	0	8.6	.006
Progression free survival (months)	1.5	3.0	.037
G3/4 neutropenia (%)	1	50	
Febrile neutropenia (%)	0	6	
G3/4 constipation (%)	1	16	

\* Primary endpoint

- Progression after platinum based chemo
- PS 0 or 1

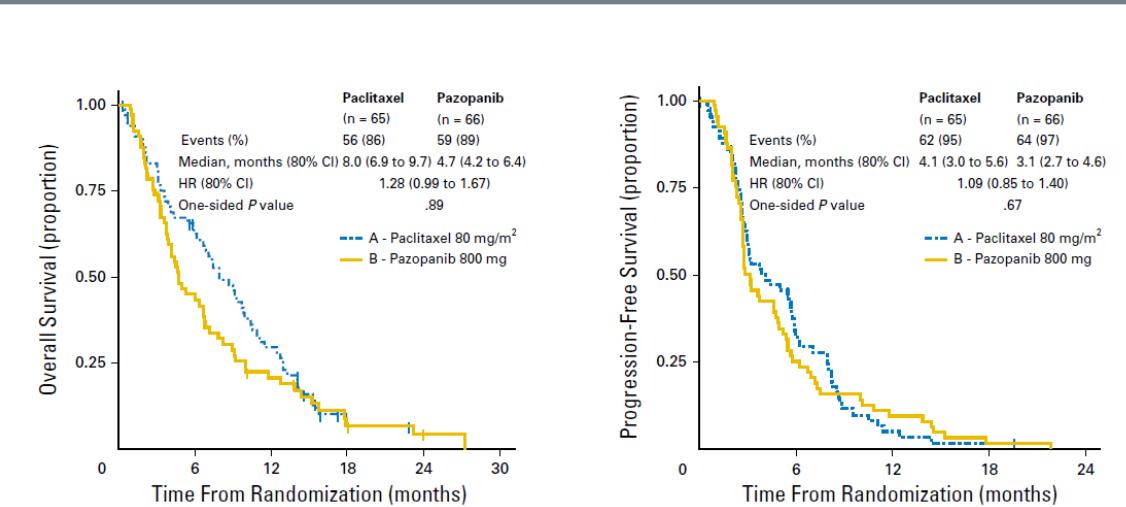
	BSC	V+BSC	p
Eligible population	107	244	
Overall survival (months)	4.3	6.9	.04

# Other chemotherapy options



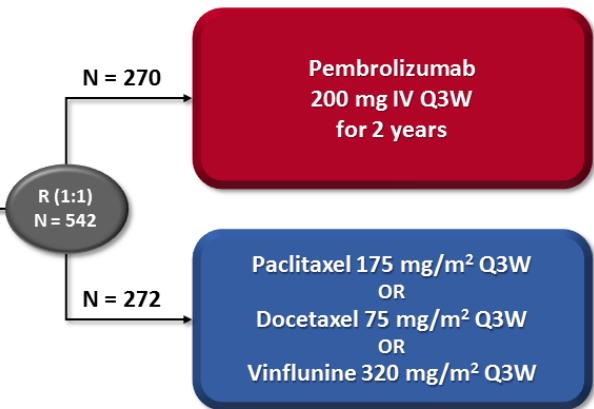
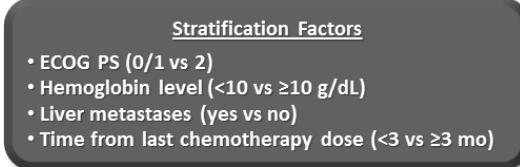
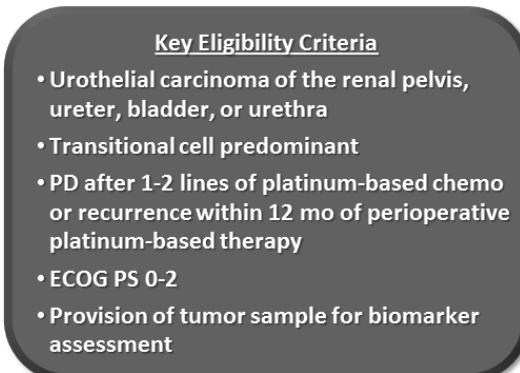
	PFS	OS*
Ramucirumab/Docetaxel	4.07	9.40
Placebo/Docetaxel	2.76	7.85
Hazard ratio	0.757	0.887
p	0.0118	0.2461

\*update at ESMO2018



	PFS	OS
Paclitaxel	4.1	8.0
Pazopanib	3.1	4.7
Hazard ratio	1.09	1.28
p	0.67	0.89

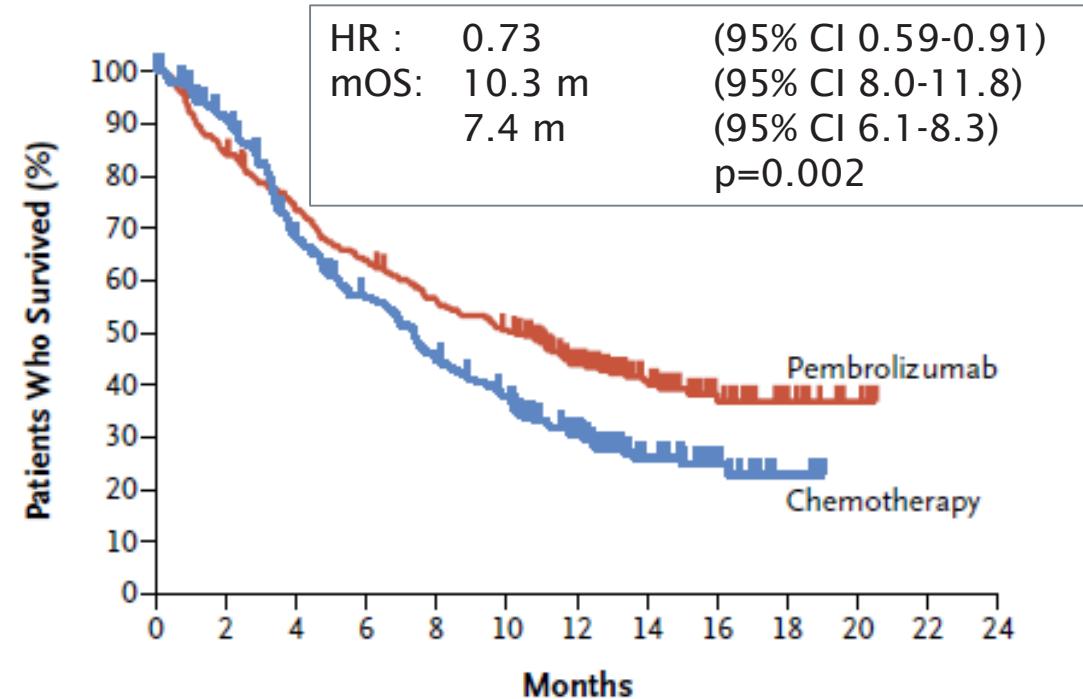
# KEYNOTE-045



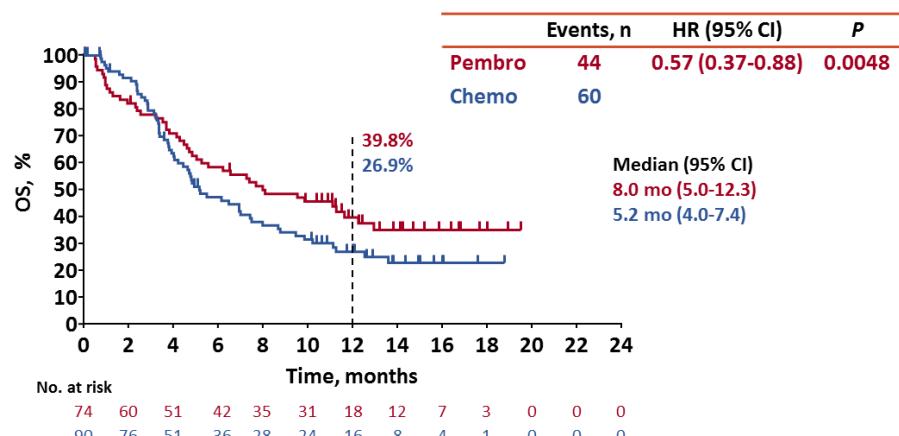
### Key End Points

Primary: OS and PFS in total and PD-L1 CPS ≥10% populations  
 Secondary: ORR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

CPS = combined positive score.

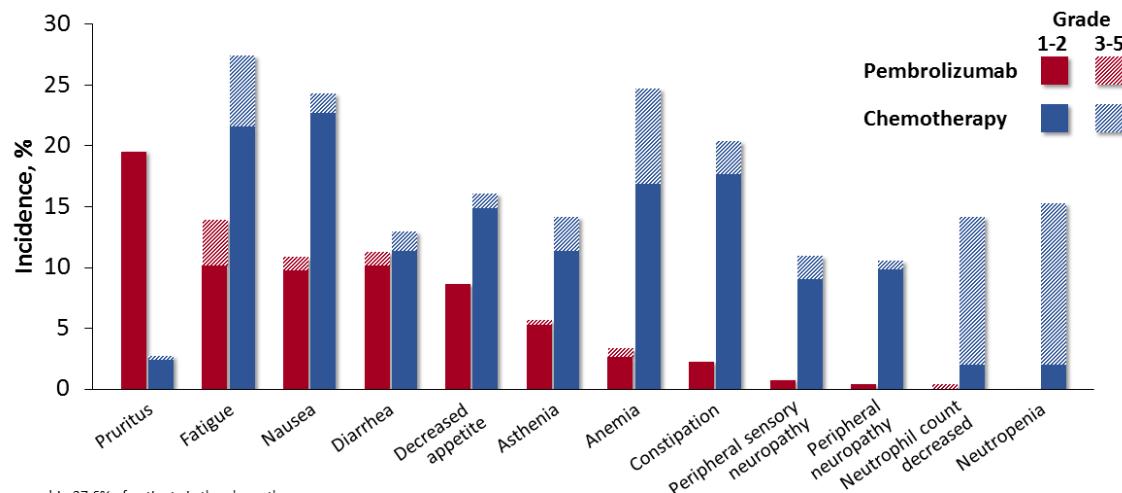


### Overall Survival: CPS ≥10%

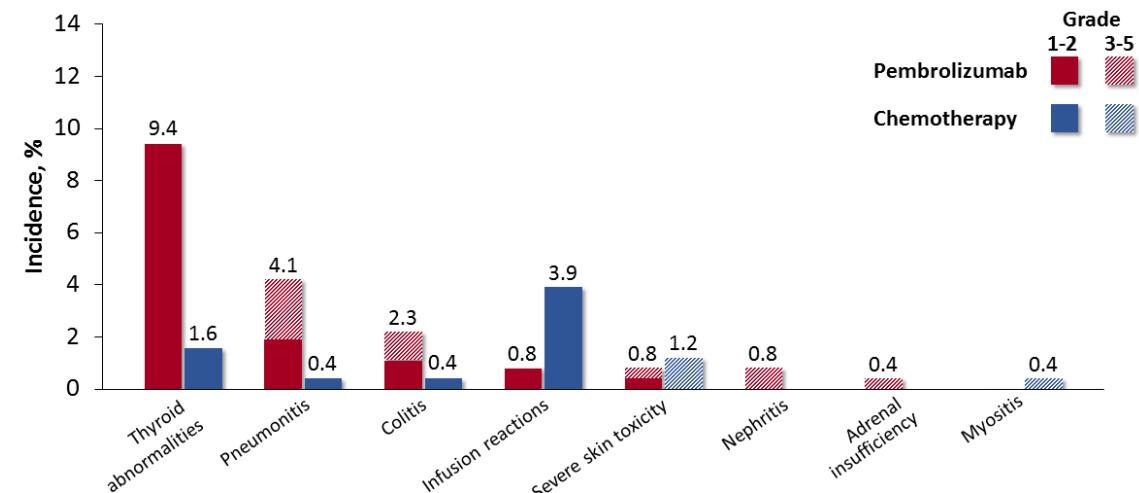


# KEYNOTE-045 safety data

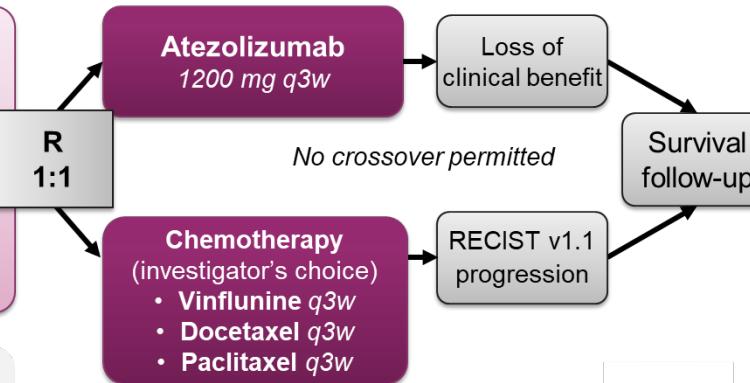
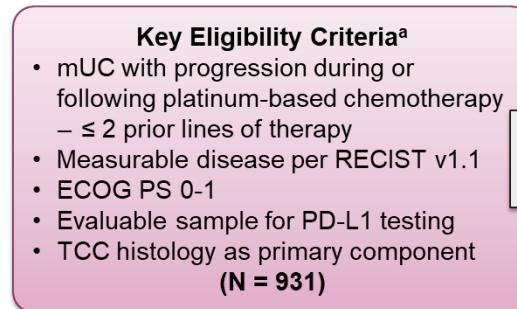
## Treatment-Related AEs With Incidence $\geq 10\%$



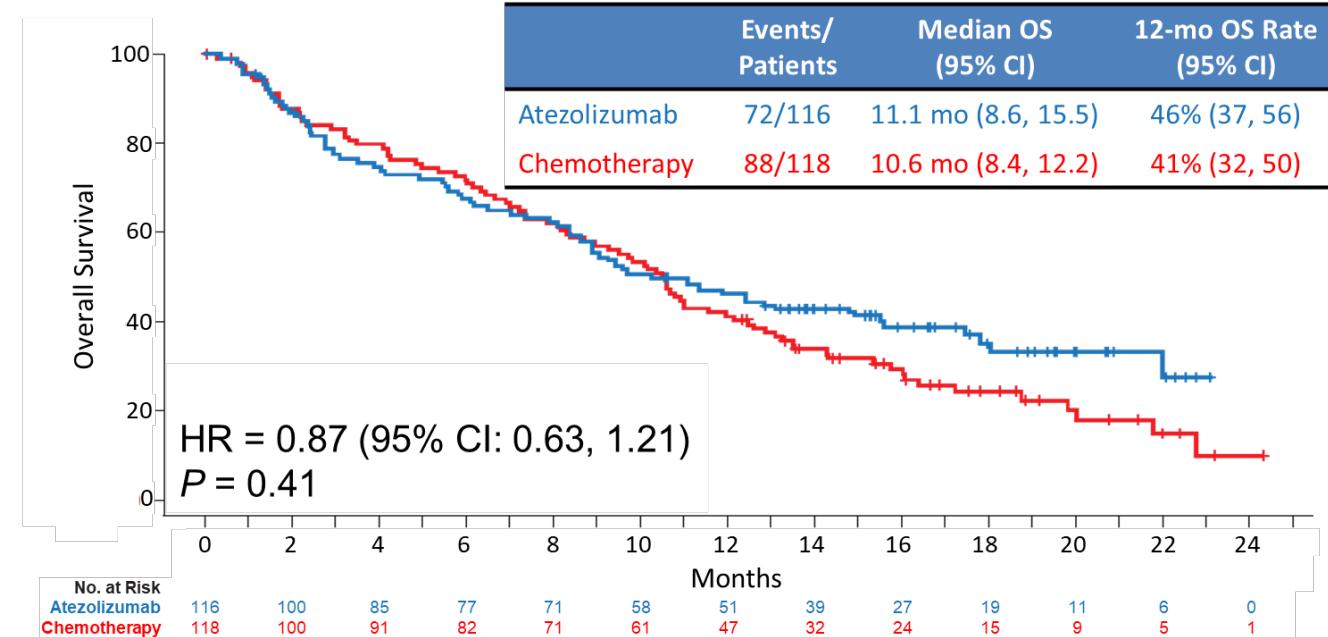
## AEs of Interest



# IMvigor211

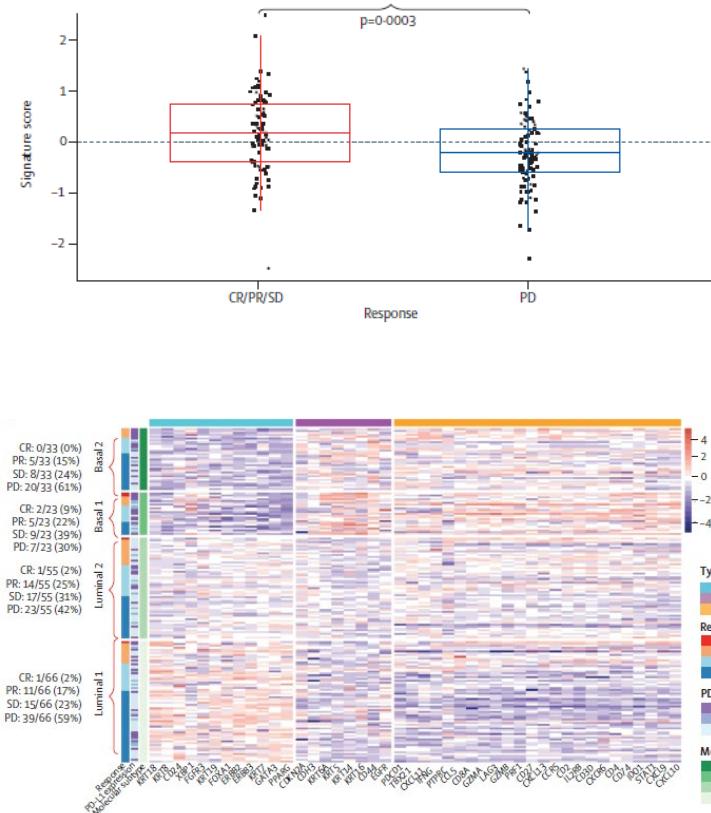


- Primary endpoint**
  - OS, tested hierarchically in pre-specified populations

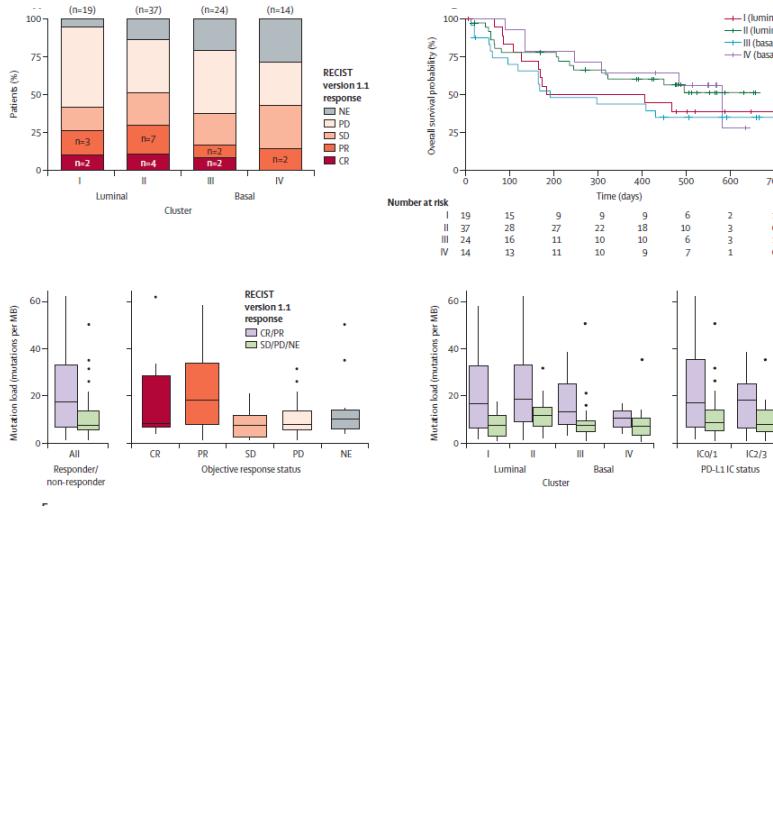


# Options for immunotherapy predictive biomarkers

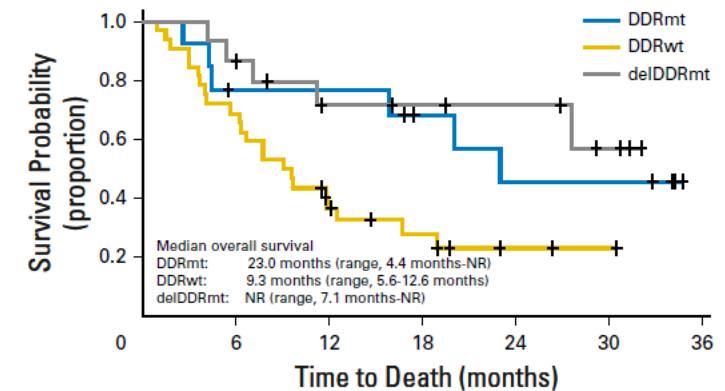
Nivolumab (2<sup>nd</sup> line):  
IFN $\gamma$  signature and TCGA subtype



Atezolizumab (1<sup>st</sup> or 2<sup>nd</sup> line):  
Mutational burden and TCGA subtype



Various PD1/PD-L1 inhibitors:  
DNA repair genes



# Is PD-L1 a predictive factor first line?

 **EUROPEAN MEDICINES AGENCY**  
SCIENCE MEDICINES HEALTH

1 June 2018  
EMA/364553/2018

**EMA restricts use of Keytruda and Tecentriq in bladder cancer**

Data show lower survival in some patients with low levels of cancer protein PD-L1.

Early data from two clinical trials<sup>1</sup> show reduced survival with Keytruda (pembrolizumab) and Tecentriq (atezolizumab) when used as first-line treatments for urothelial cancer (cancer of the bladder and urinary tract) in patients with low levels of a protein called PD-L1. The data indicate that Keytruda and Tecentriq may not work as well as chemotherapy medicines in this group of patients.

As a result, the European Medicines Agency (EMA) has recommended restricting the use of these medicines as first line-treatments for urothelial cancer.

Keytruda and Tecentriq should now only be used for first-line treatment of urothelial cancer in patients with high levels of PD-L1 (see full indications below).

There are no changes to how these medicines should be used in patients with urothelial cancer who have had chemotherapy or in patients with other cancers for which these medicines are approved.

The two clinical trials are continuing but no new patients with low levels of PD-L1 will be given only Keytruda or Tecentriq. Patients in the trials who have any questions should speak to the doctor treating them.

The review of data on Keytruda and Tecentriq was carried out by EMA's Committee for Medicinal Products for Human Use (CHMP).

**Information for patients**

 U.S. Department of Health and Human Services

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**FDA Alerts Health Care Professionals and Oncology Clinical Investigators about an Efficacy Issue Identified in Clinical Trials for Some Patients Taking Keytruda (pembrolizumab) or Tecentriq (atezolizumab) as Monotherapy to Treat Urothelial Cancer with Low Expression of PD-L1**

**Update [8/16/2018]:** The FDA has updated the prescribing information for Keytruda (pembrolizumab) and Tecentriq (atezolizumab) to require the use of an FDA-approved companion diagnostic test to determine PD-L1 levels in tumor tissue from patients with locally advanced or metastatic urothelial cancer who are cisplatin-ineligible. Two different companion diagnostic tests were approved by the FDA, one for use with Keytruda and one for use with Tecentriq, as described below.

On August 16, 2018, the FDA approved the Dako PD-L1 IHC 22C3 PharmDx Assay (Dako North America, Inc.) as

# Conclusions

- Cisplatin based chemotherapy is the standard of care for patients fit to receive it. It provides a modest survival advantage but survival outcomes remain poor
- Optimal treatment options for cisplatin ineligible patients are not fully defined and a survival advantage is not yet established for any option
- Carboplatin/gemcitabine, or PD1/PD-L1 directed immunotherapy in ‘PD-L1 high’ tumours, are appropriate options
- Pembrolizumab is the new standard of care second line treatment following prior platinum based chemotherapy (including within 12 months of neoadjuvant treatment)
- We lack any properly validated predictive biomarkers for response to either immunotherapy or chemotherapy (although chemotherapy rather than immunotherapy first line if ‘PD-L1 low’ is appropriate)
- There remains an unmet need for improved treatment options in this setting