6th CONGRESS OF THE
MEDITERRANEAN MULTIDISCIPLINARY ONCOLOGY FORUM
&
3rd INTERNATIONAL CONGRESS ON ONCOLOGICAL SCIENCES

28 November - 1 December 2019
Regnum Carya Convention Center
Antalya, Turkey

New horizons of treatment of bladder cancer

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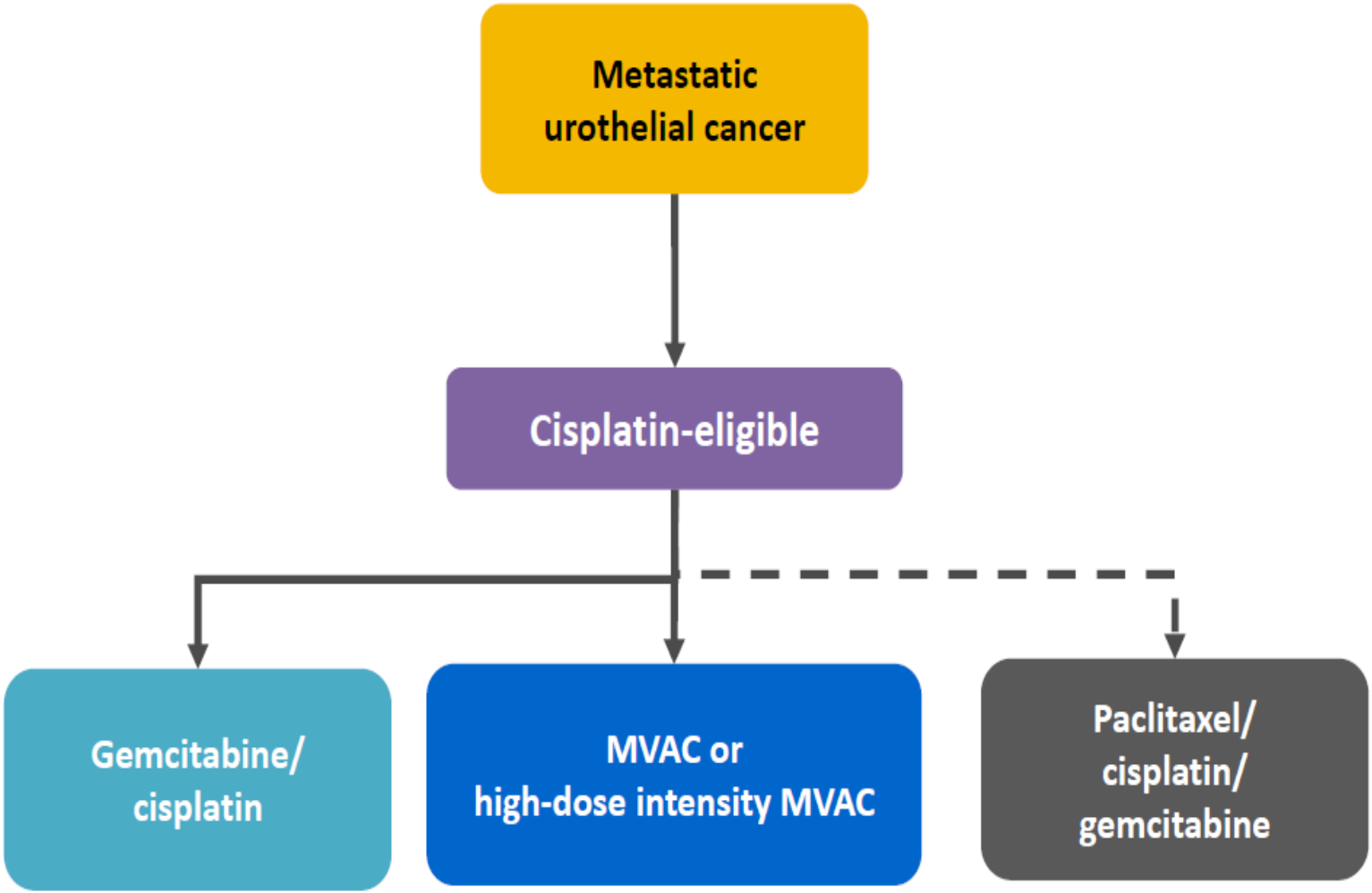
Antalya, 28/11/2019

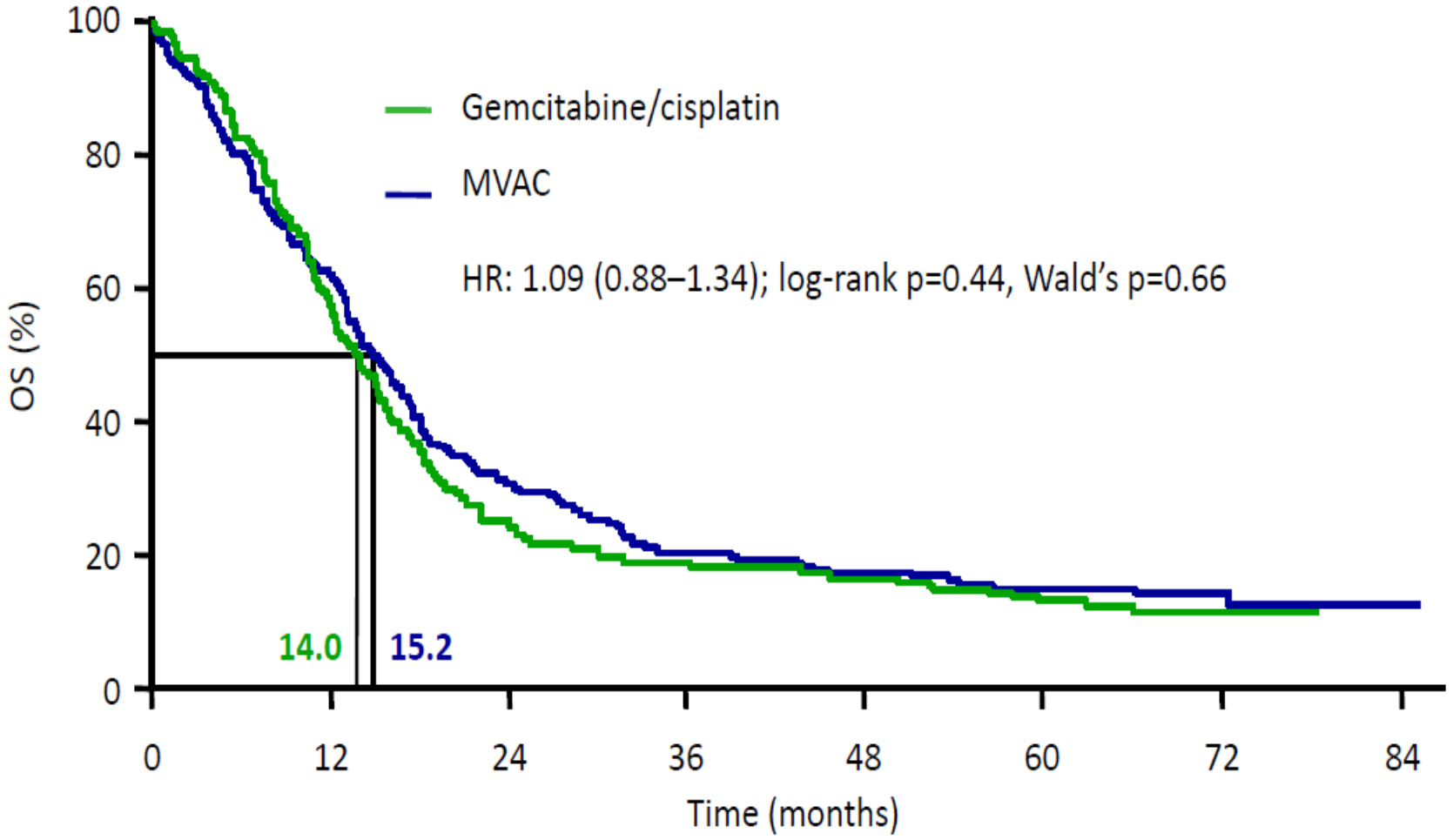
The Past

Options for first-line cisplatin-eligible patients



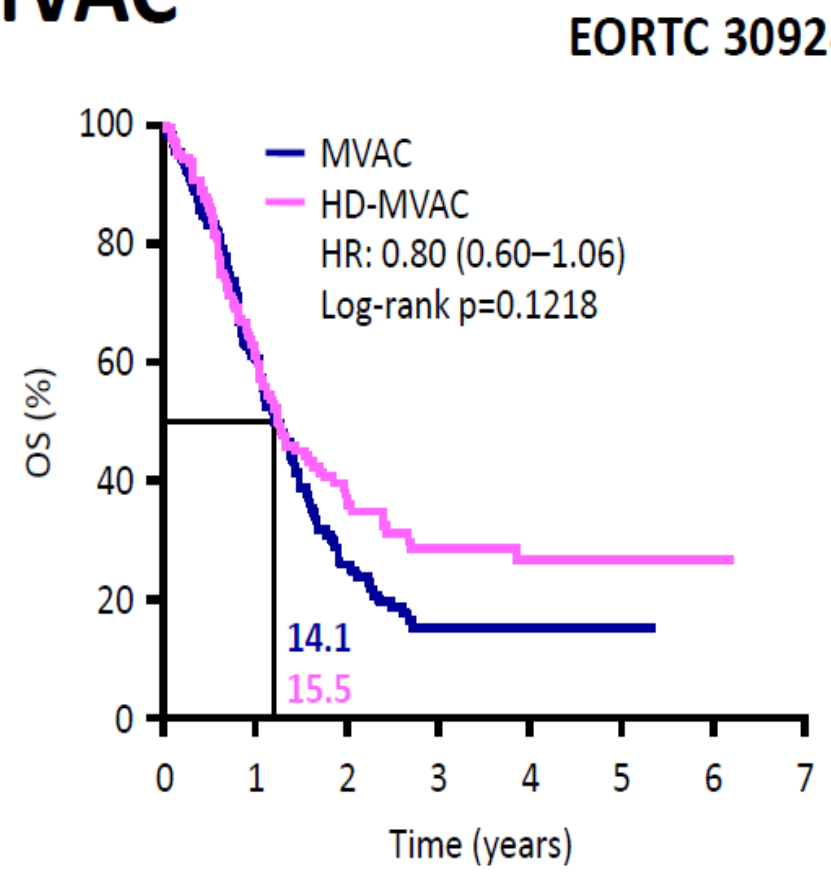
Bellmunt et al. Ann Oncol 2014

Median survival with gemcitabine/cisplatin and MVAC in 'fit' patients is 14–15 months



von der Maase et al. J Clin Oncol 2005

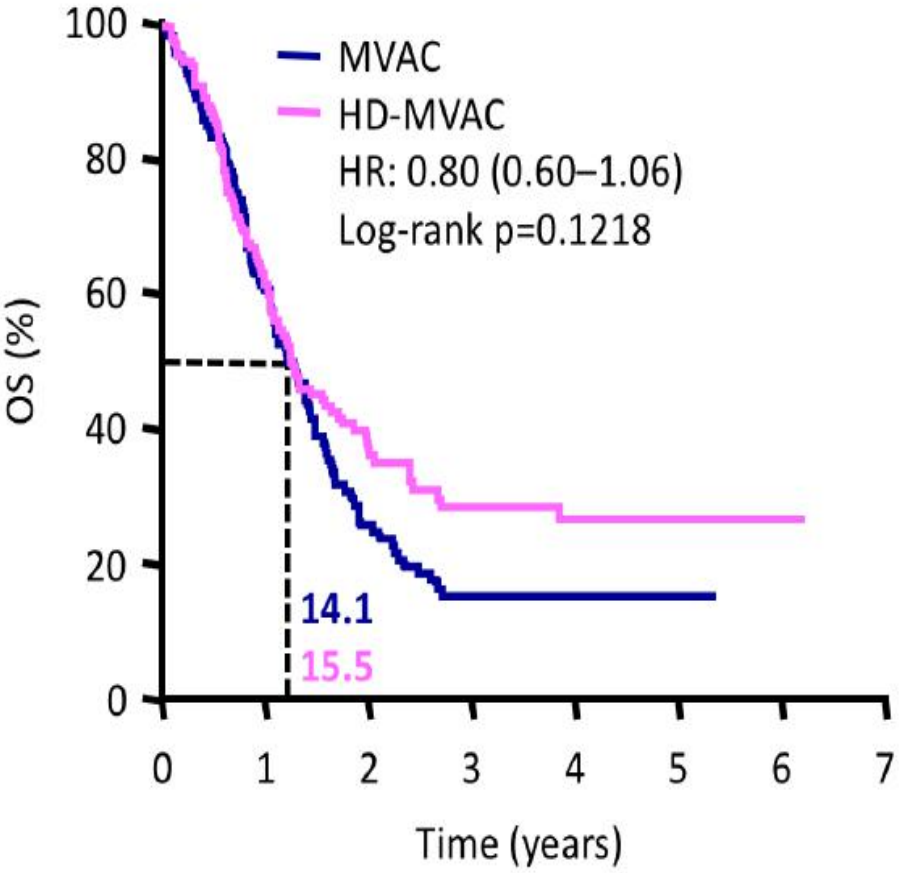
High-dose intensity MVAC is an alternative to MVAC

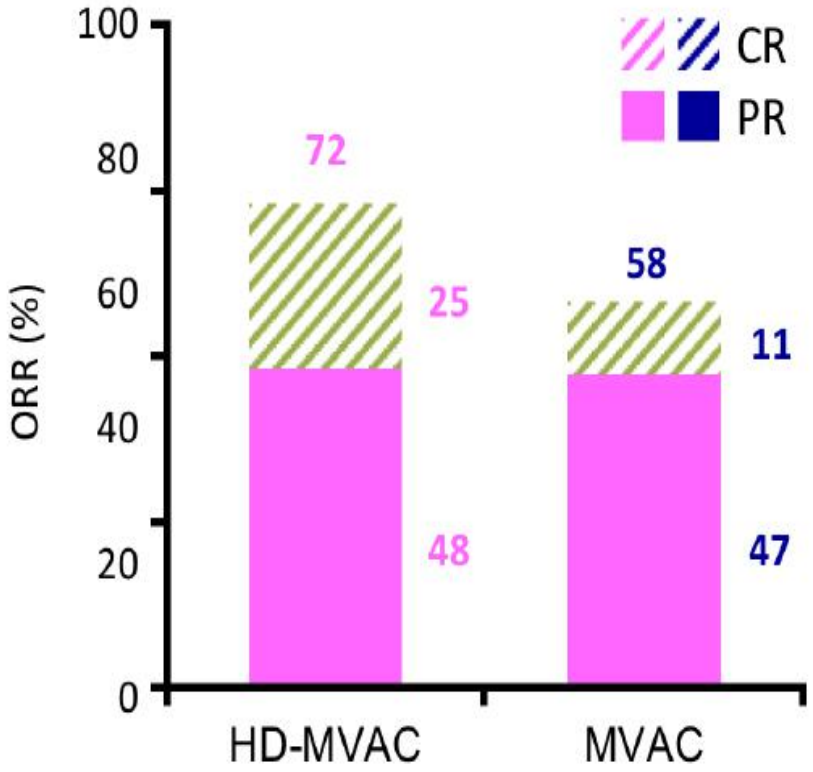


Sternberg et al. Eur J Cancer 2001

High-dose intensity MVAC is an alternative to MVAC

EORTC 30924 (3.2 years)

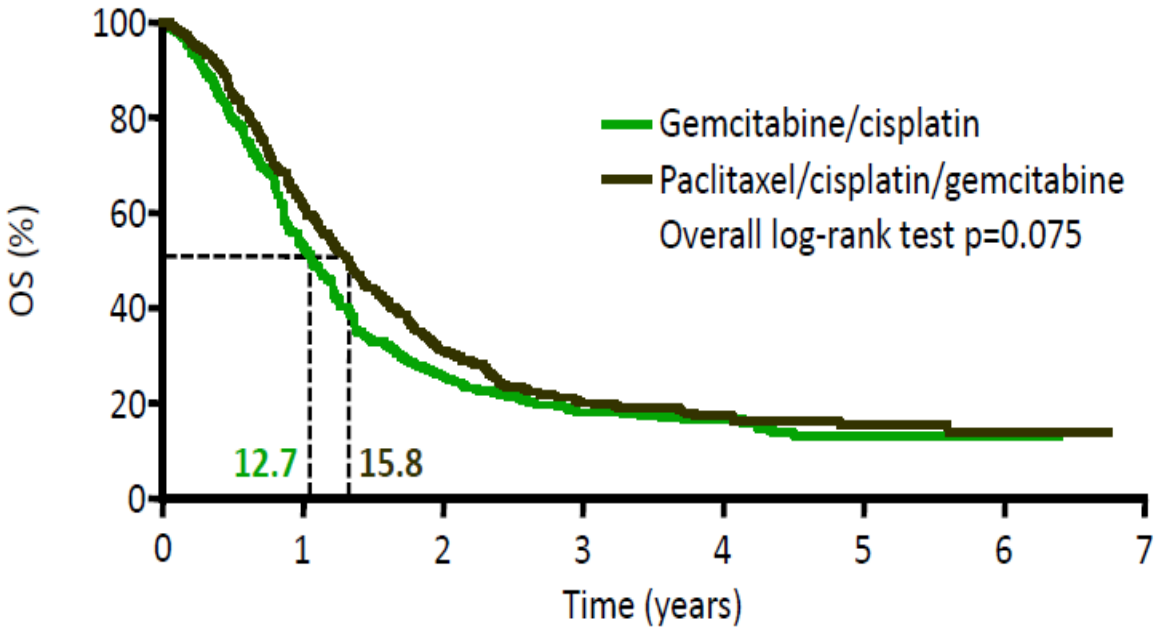




Sternberg et al. Eur J Cancer 2001

Paclitaxel/cisplatin/gemcitabine is an option for some 1L patients

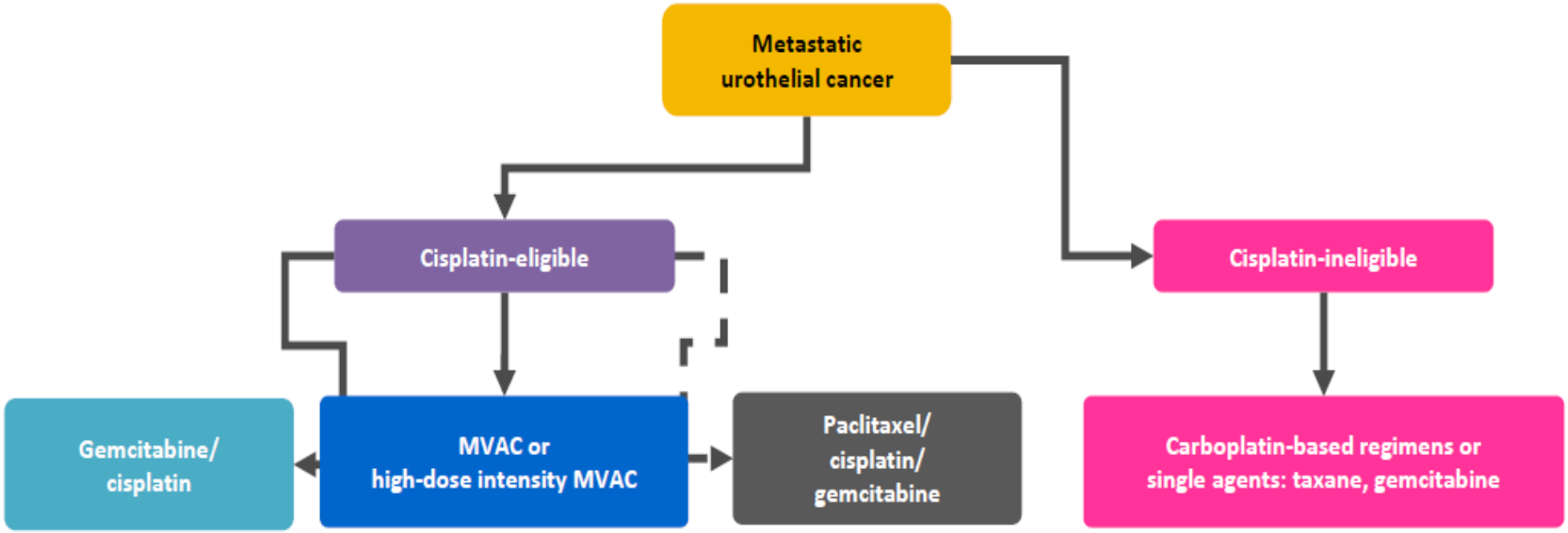
EORTC 30987



Exploratory analysis of patients with bladder as the primary tumour
Median OS was significantly longer after paclitaxel/cisplatin/gemcitabine:
15.9 vs 11.9 months; HR=0.80 (95% CI: 0.66–0.97), p=0.025

Bellmunt et al. J Clin Oncol 2012

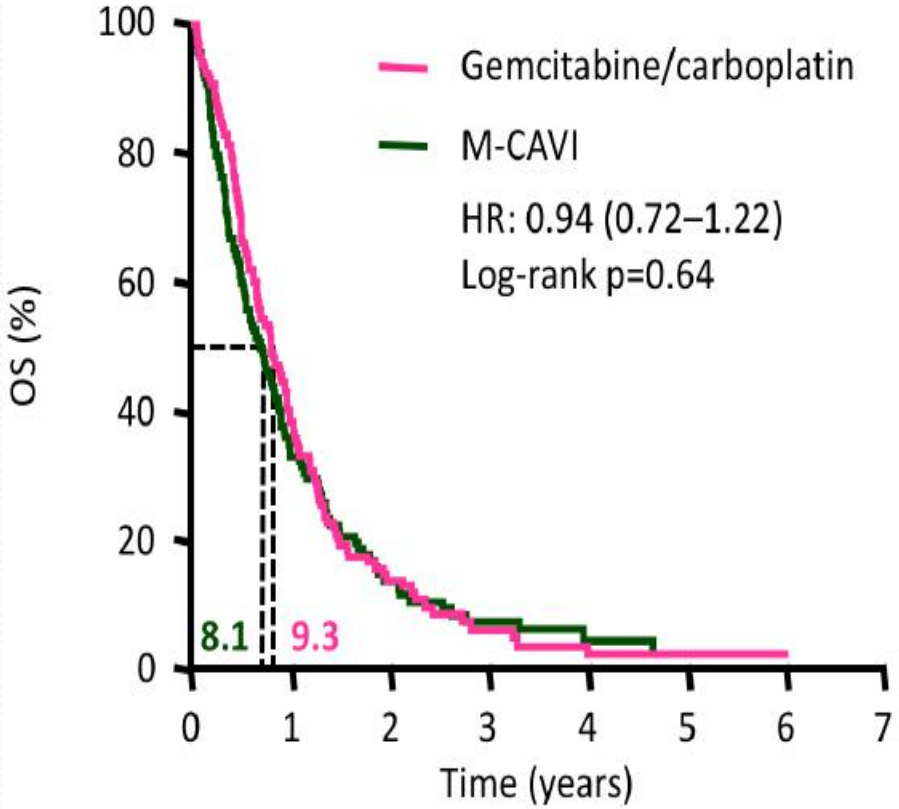
Options for first-line cisplatin-ineligible patients

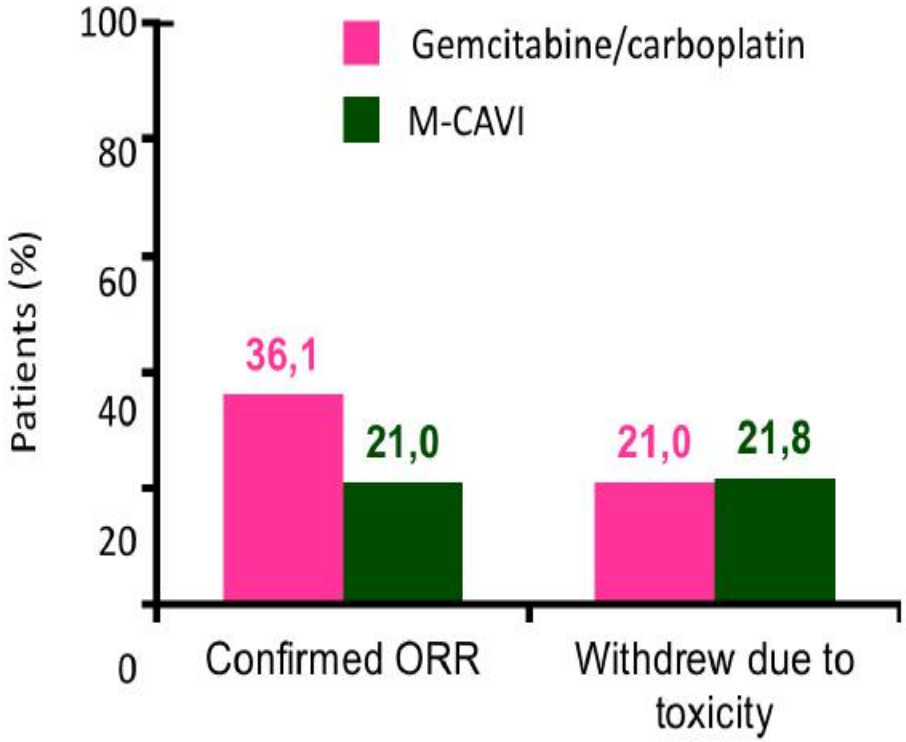


Bellmunt et al. Ann Oncol 2014

Median survival with gemcitabine/carboplatin and M-CAVI in 'unfit' patients is <10 months

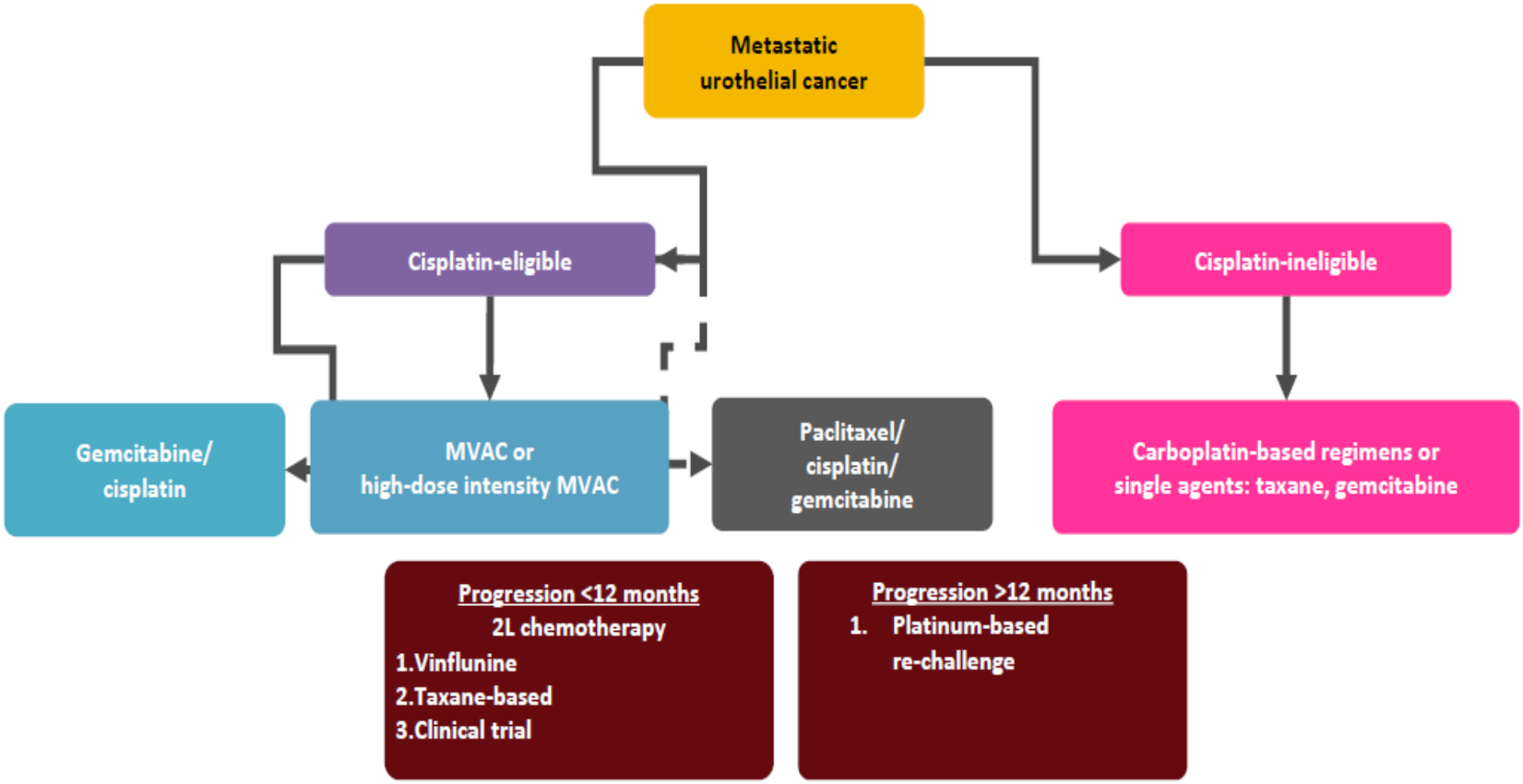
EORTC 30986





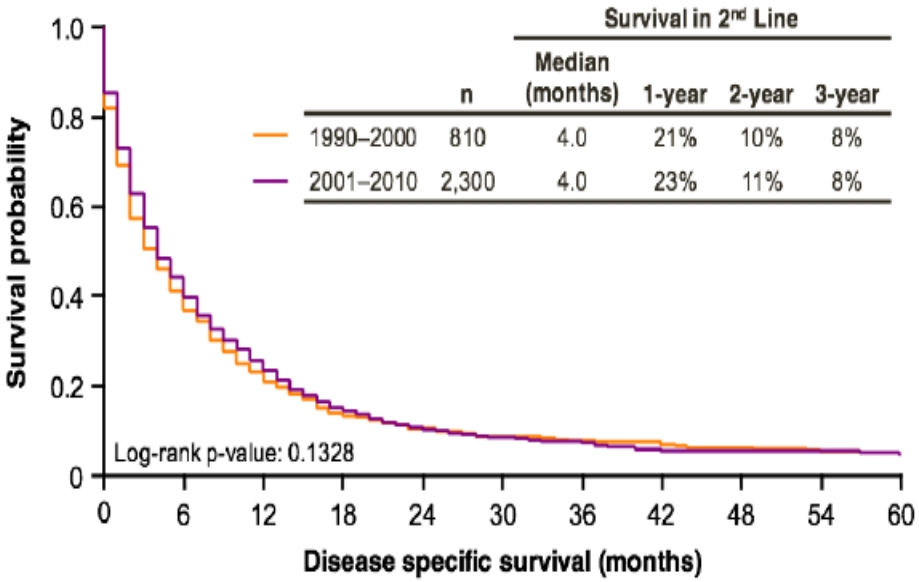
De Santis et al. J Clin Oncol 2012

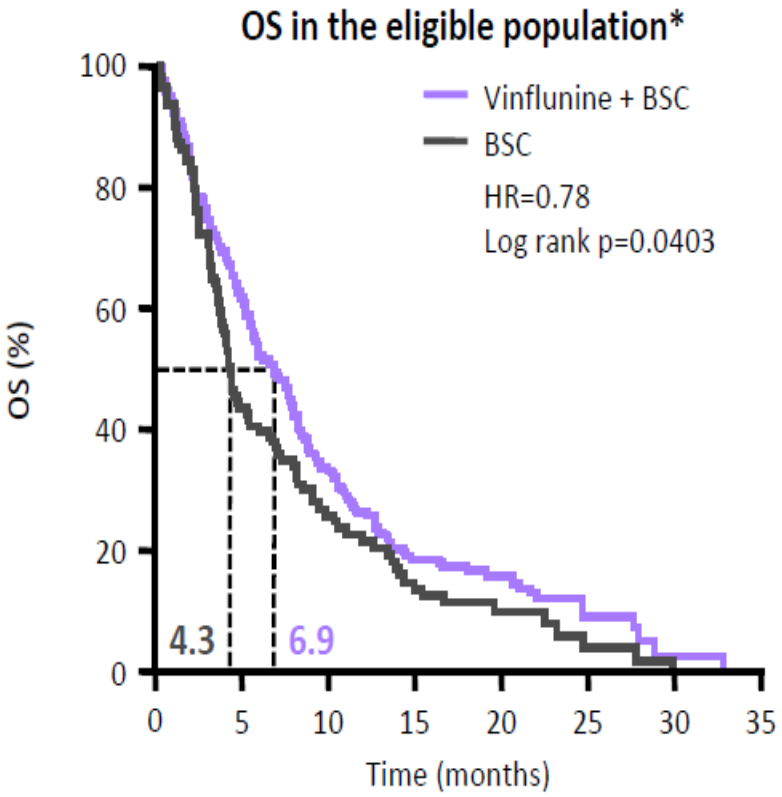
Options for second-line patients



Bellmunt et al. Ann Oncol 2014

Median survival with second-line was <7 months

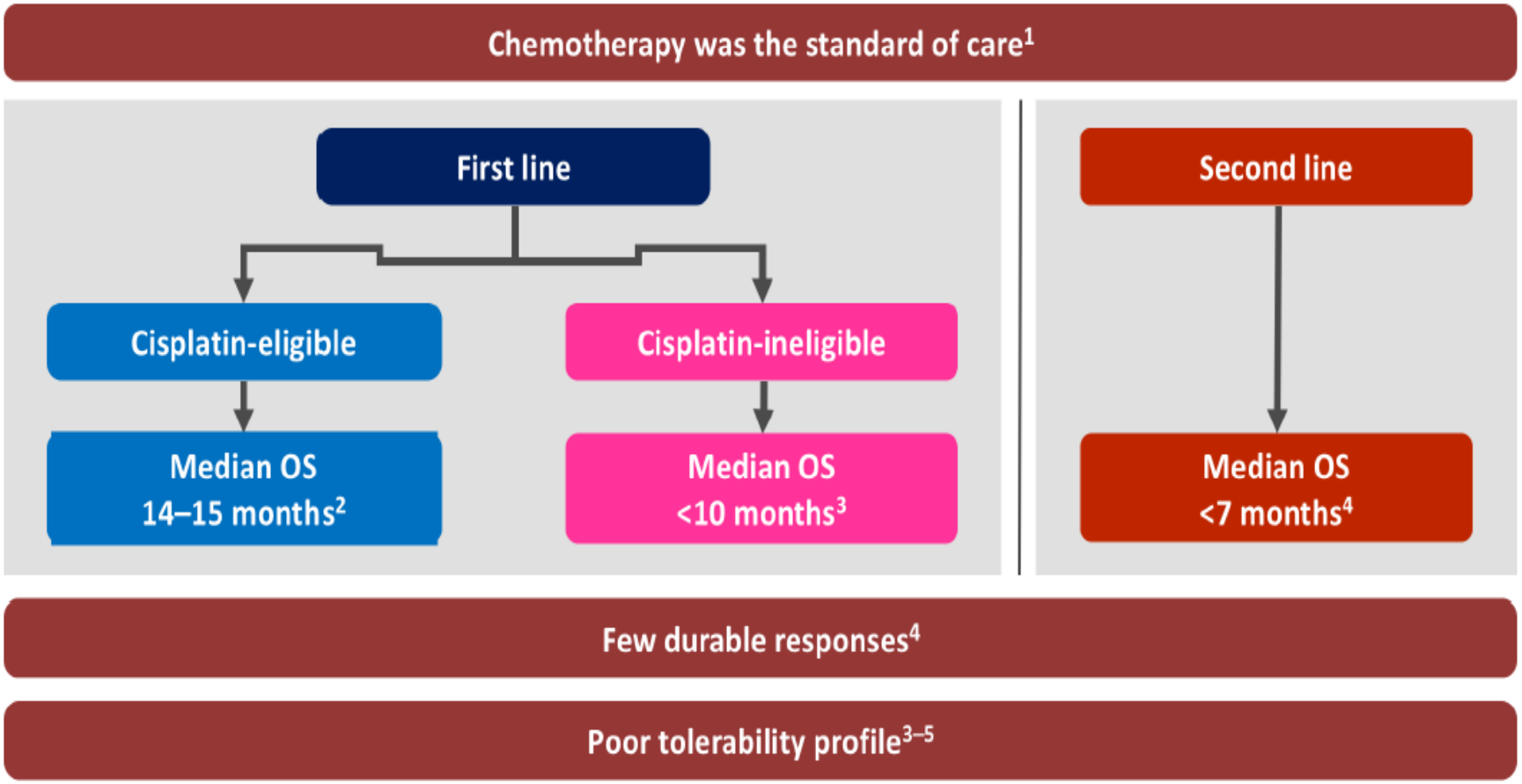




Pal SK, et al. Plos One 2015

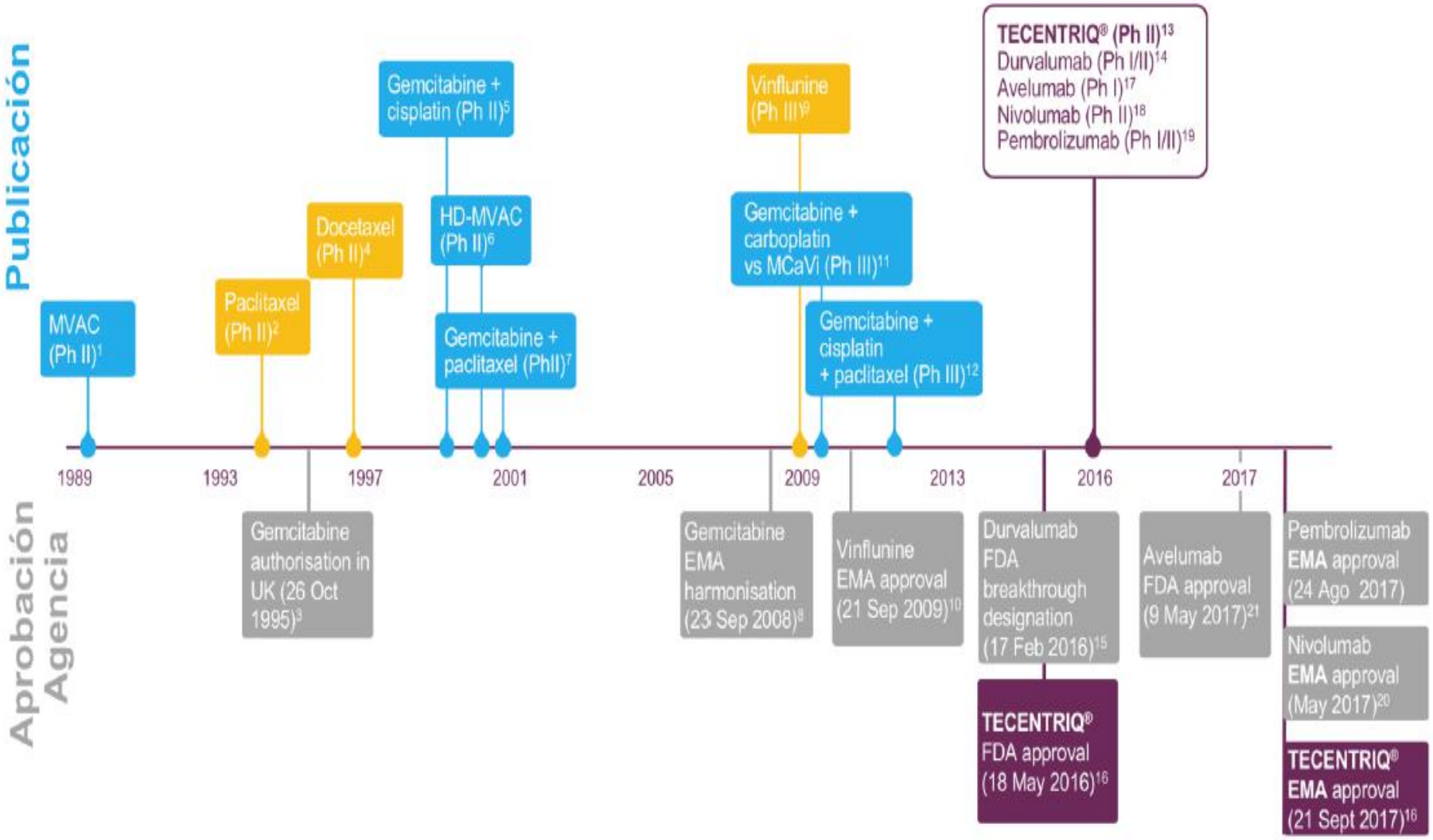
Bellmunt et al. J Clin Oncol 2009

Before 2016: substantial unmet medical need in the treatment of urothelial cancer



1. Bellmunt et al. Ann Oncol 2014; 2. von der Maase et al. J Clin Oncol 2005;
3. De Santis et al. J Clin Oncol 2012
4. Bellmunt et al. J Clin Oncol 2009; 5. von der Maase et al. J Clin Oncol 2000

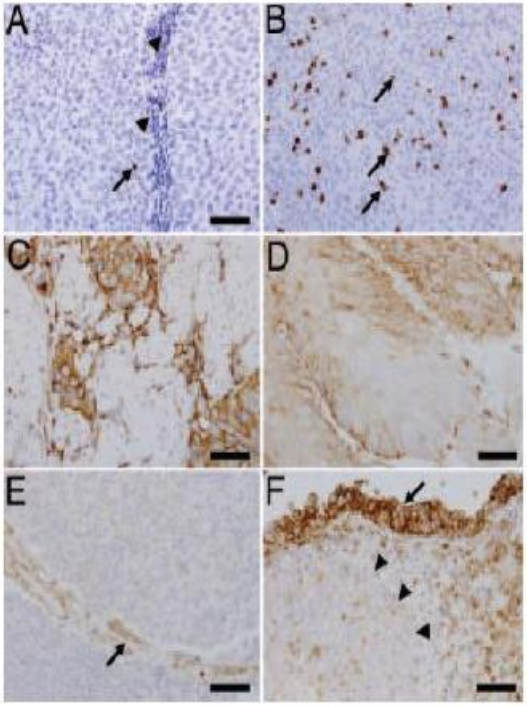
The Present

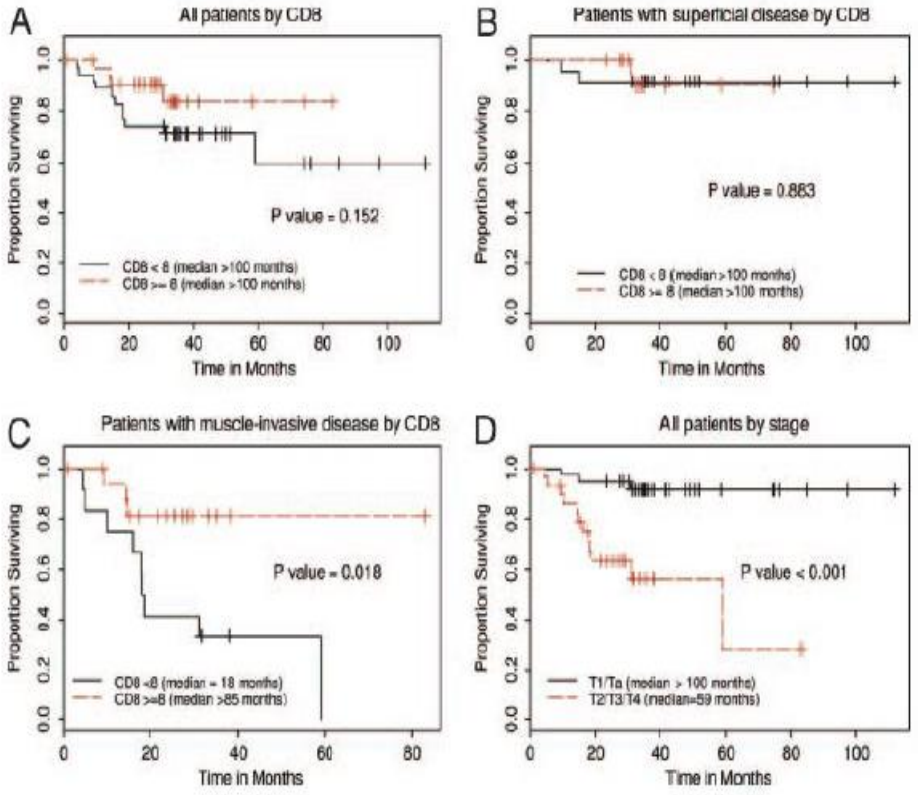


1. Sternberg CN et al. Cancer 1989;64:2448–2458; 2. Roth BJ et al. J Clin Oncol 1994;12:2264–2270; 3. Eli Lilly. SmPC Gemzar® 01 Jul 2014. Available at: http://www.medicines.org.uk; 4. McCaffrey JA et al. J Clin Oncol 1997;15:1853–1857; 5. Von der Maase H et al. J Clin Oncol 2000;18:3068–3077; 6. Sternberg 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. All links accessed Sept 2017.

Role of immunotherapy in bladder cancer

CD8 tumor-infiltrating lymphocytes are predictive of survival in MIUC



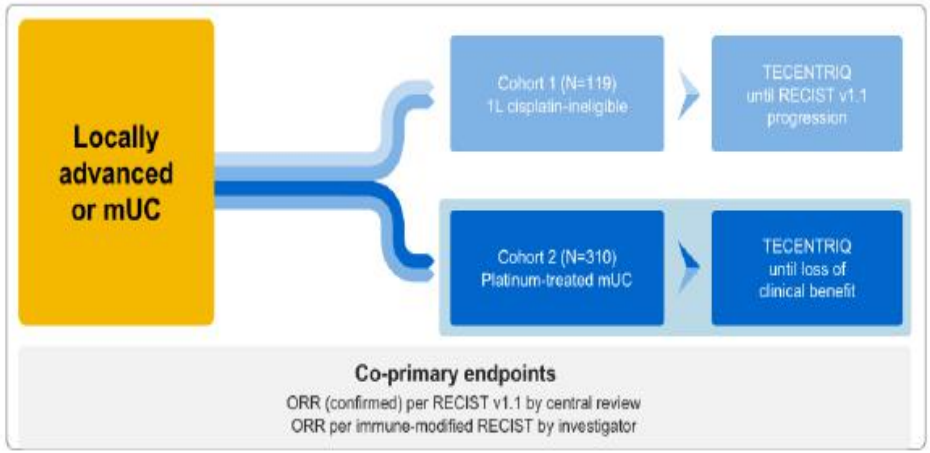


Sharma et al. PNAS 2007

Immune Checkpoints inhibitors in platinum-refractory setting

	Atezolizumab	Nivolumab	Pembrolizumab	Avelumab	Durvalumab
Phase	Phase II single arm & Phase III randomized	Phase II single arm	Phase III randomized	Phase Ib	Phase I/II
Number of patients	310 467	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% (IC 2/3 23%)**	**19.6%**	**21.1%**	**16.1%**	**17.8%**
Duration of response	84% ongoing at median fu 11.7 months	77% ongoing at median fu of 7 months	72% ongoing at median fu of 14.1 months	64% ongoing at data cut	NR 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 ¾ TRAEs	16% 20%	18%	13.5 % (15% G3)	10.8% G3-5	6.8%

IMvigor210 Cohort 2: study design

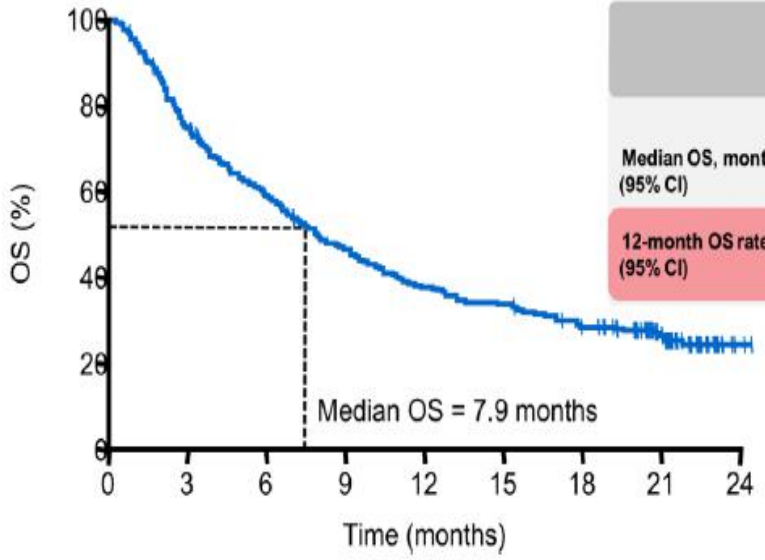


	All (N=310)
ORR 95% CI	16% (12, 20)
CR rate 95% CI	6% (4, 9)

Median DoR was not yet reached in all patients

Ongoing responses were recorded in **32 (65%) of 49 responders**

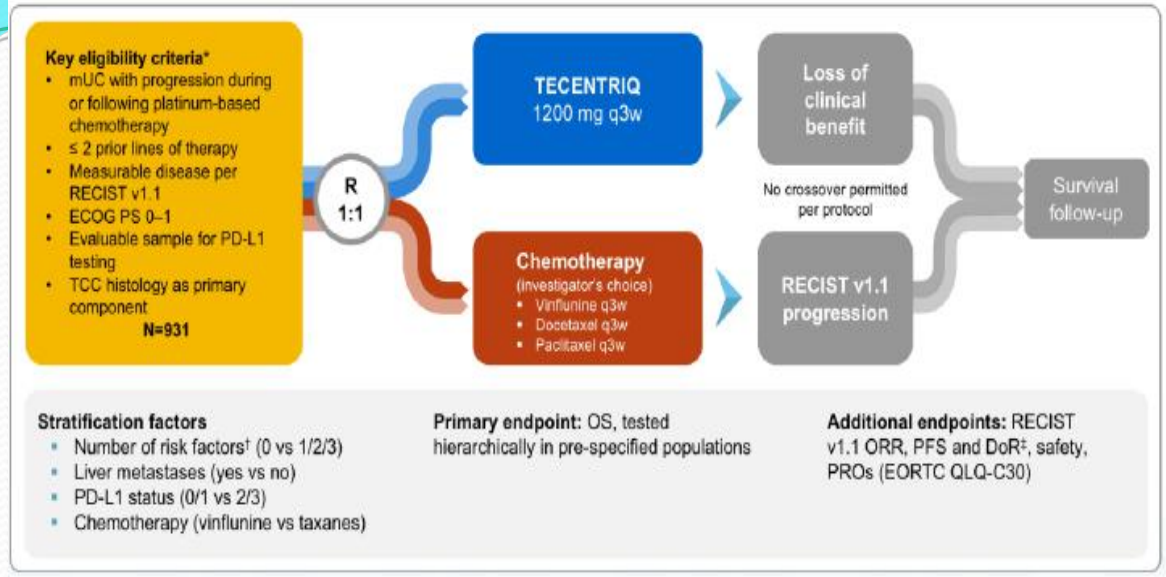
(median follow-up: 21.0 months)

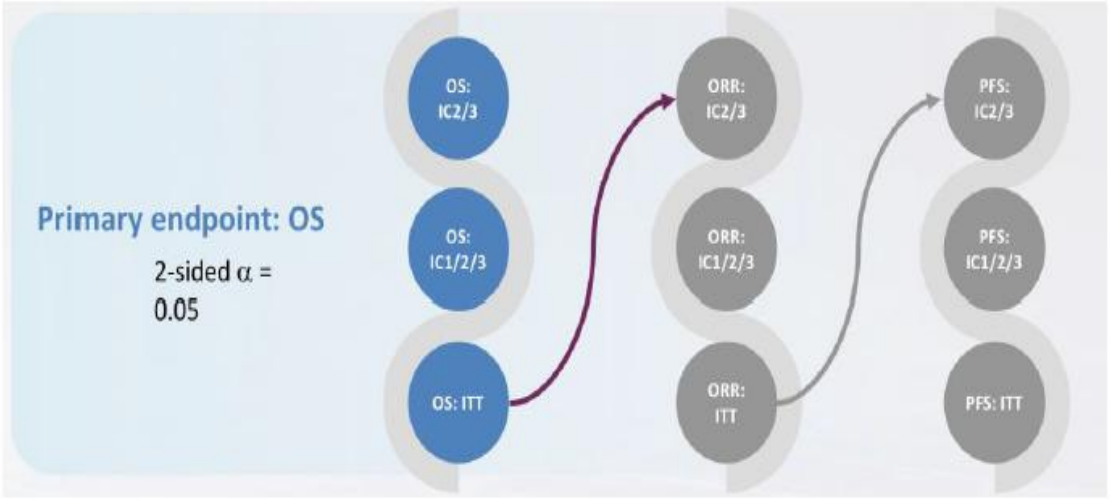


	IC0/1 (n=210)	IC2/3 (n=100)	All patients (N=310)
Median OS, months (95% CI)	6.7 (5.4–8.0)	11.9 (9.0–NE)	7.9 (6.7–9.3)
12-month OS rate, % (95% CI)	31 (24–37)	50 (40–60)	37 (31–42)

Rosenberg, et al. Lancet 2016

Atezolizumab in mUC: IMvigor 211 phase III

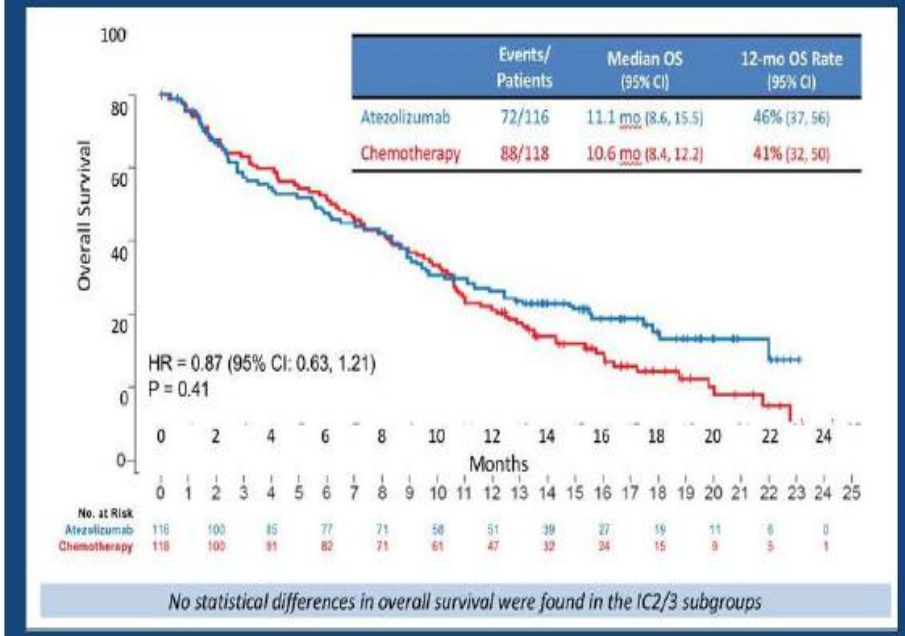




Powles T, et al. ASCO GU 2018

Atezolizumab in mUC: IMvigor 211 phase III

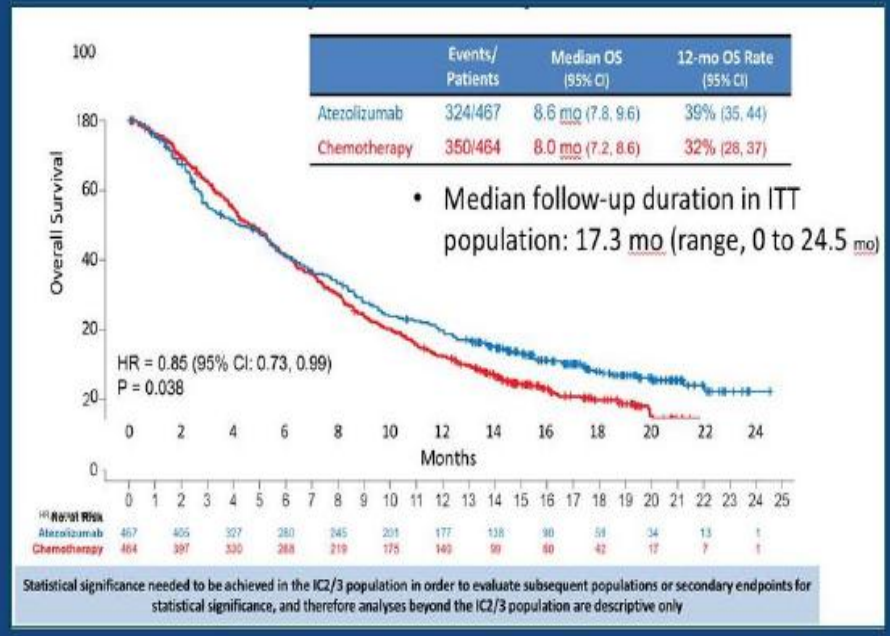
OS in IC 2/3



	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)

No statistical differences in overall survival were found in the IC2/3 subgroups

OS in ITT



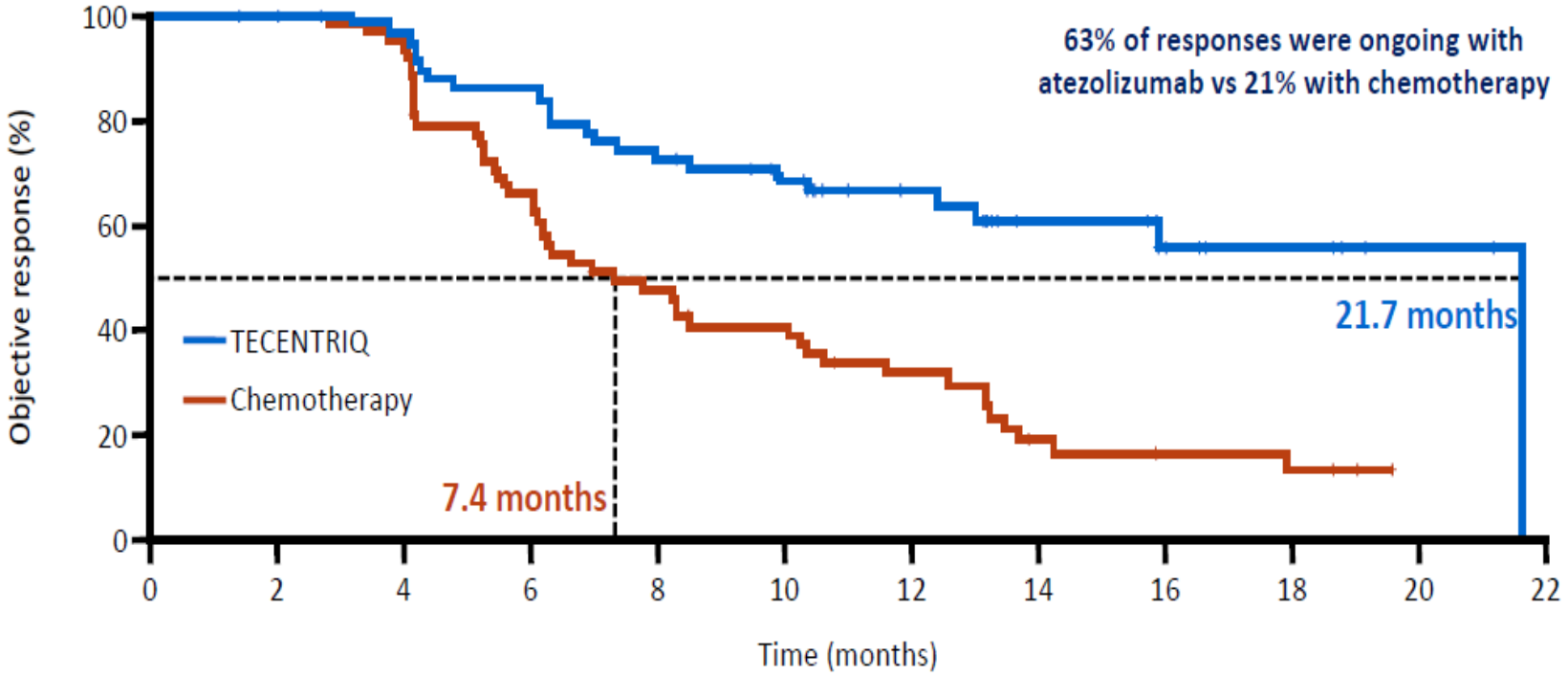
	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)

- Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

Statistical significance needed to be achieved in the IC2/3 population in order to evaluate subsequent populations or secondary endpoints for statistical significance, and therefore analyses beyond the IC2/3 population are descriptive only

Powles T, et al. ASCO GU 2018

Atezolizumab in mUC: IMvigor 211 phase III



Powles T, et al. ASCO GU 2018

Pembrolizumab in mUC: Keynote-045 phase III

Key Eligibility Criteria

- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1–2 lines of platinum-based chemotherapy or recurrence <12 months after perioperative platinum-based therapy
- ECOG performance status 0–2
- Provision of tumor sample for biomarker assessment

R (1:1)
N = 542

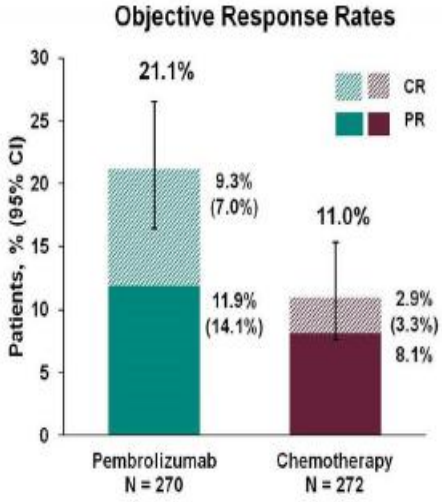
N = 270 → Pembrolizumab 200 mg IV Q3W

N = 272 → Paclitaxel 175 mg/m² Q3W OR Docetaxel 75 mg/m² Q3W OR Vinflunine 320 mg/m² Q3W

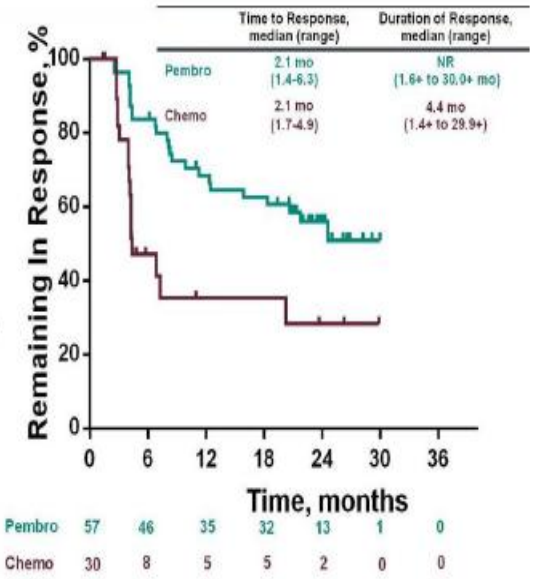
Stratification Factors

- ECOG performance status (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 months)

- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review
- Both unselected and biomarker-selected patients



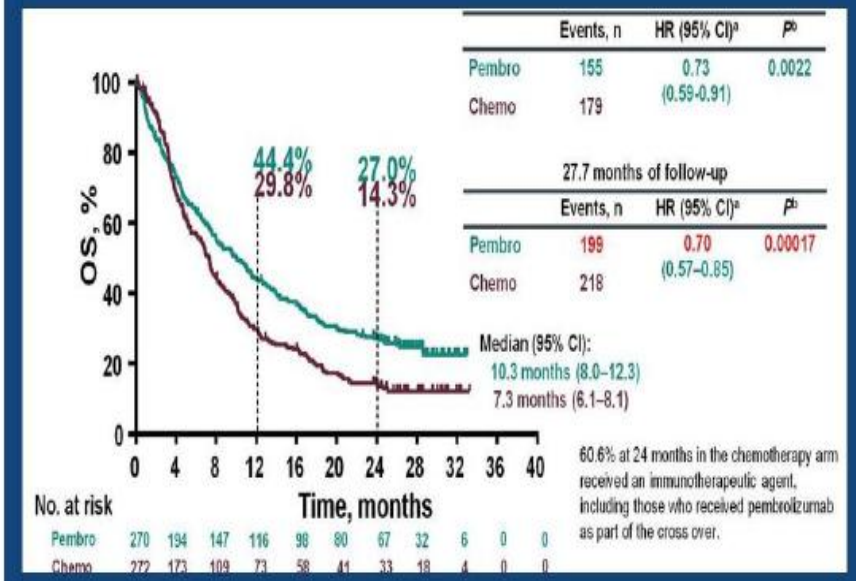
Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: October 26, 2017.



Bellmunt J, et al. ASCO GU 2018

Pembrolizumab in mUC: Keynote-045 phase III

OS



	Events, n	HR (95% CI)[a]	P[b]
Pembro	155	0.73 (0.59-0.91)	0.0022
Chemo	179		

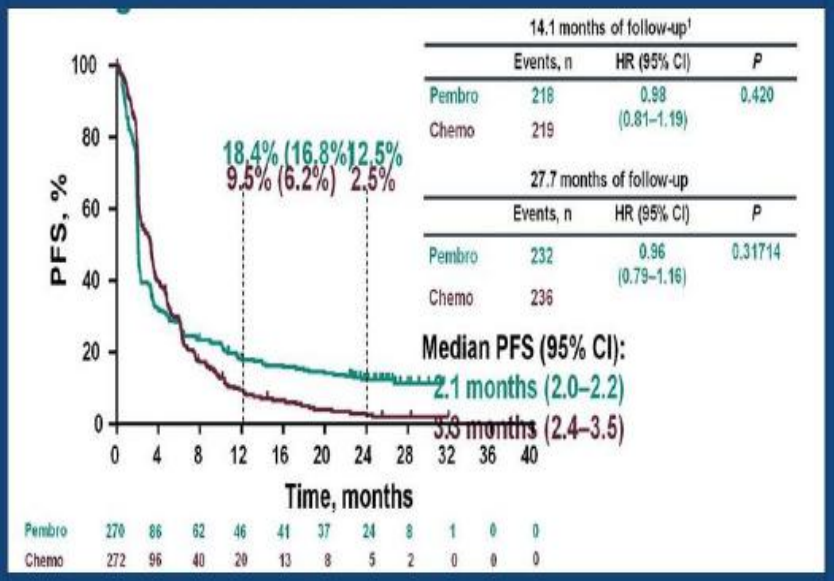
27.7 months of follow-up

	Events, n	HR (95% CI)[a]	P[b]
Pembro	199	0.70 (0.57–0.85)	0.00017
Chemo	218		

Median (95% CI):
10.3 months (8.0–12.3)
7.3 months (6.1–8.1)

60.6% at 24 months in the chemotherapy arm received an immunotherapeutic agent, including those who received pembrolizumab as part of the cross over.

PFS



14.1 months of follow-up[1]

	Events, n	HR (95% CI)	P
Pembro	218	0.98 (0.81–1.19)	0.420
Chemo	219		

27.7 months of follow-up

	Events, n	HR (95% CI)	P
Pembro	232	0.96 (0.79–1.16)	0.31714
Chemo	236		

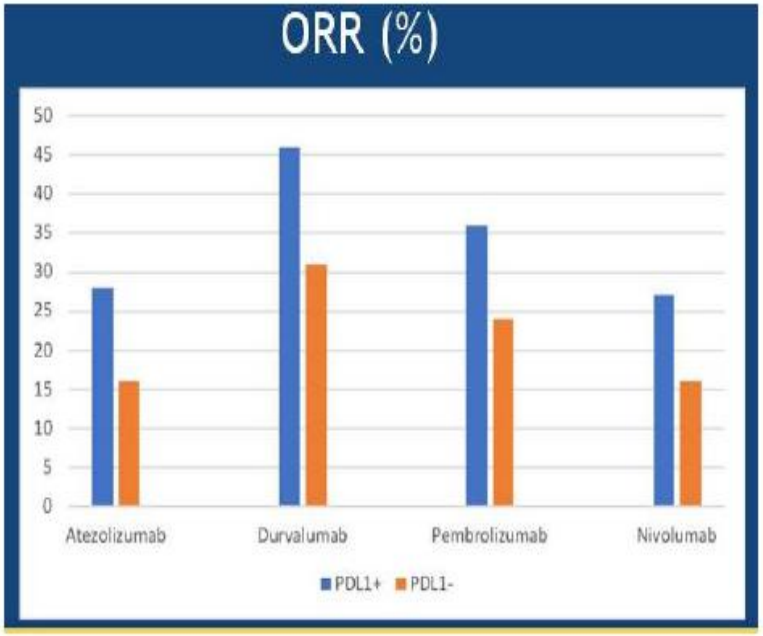
Median PFS (95% CI):
2.1 months (2.0–2.2)
3.3 months (2.4–3.5)

Bellmunt J, et al. ASCO GU 2018

PDL1 as a biomarker

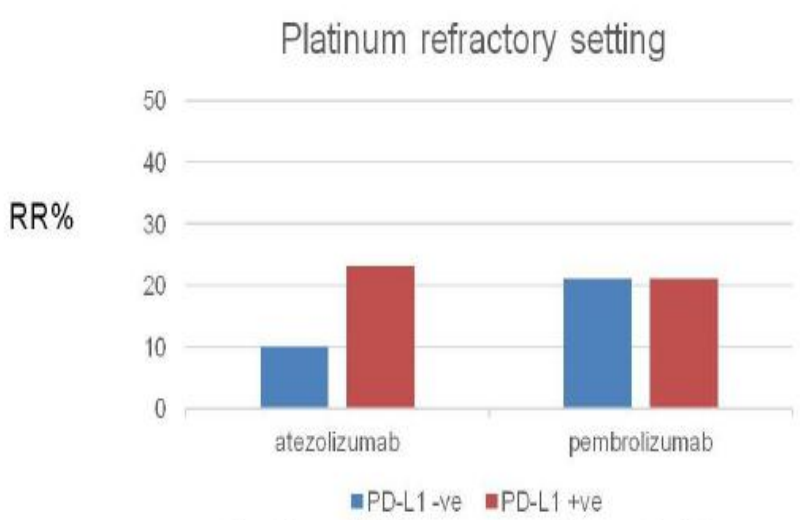
	Atezolizumab	Nivolumab	Pembrolizumab	Durvalumab	Avelumab
Antibody	SP142	28-8	22C3	SP263	73-10
IHC platform	Ventana	Dako	Dako	Ventana	Dako
Cell types	IC/TC	TC	TC	IC/TC	IC/TC
Definition for +	IHC2/3 >5%	>1%	>1%	>25%	>5%TC >10% IC

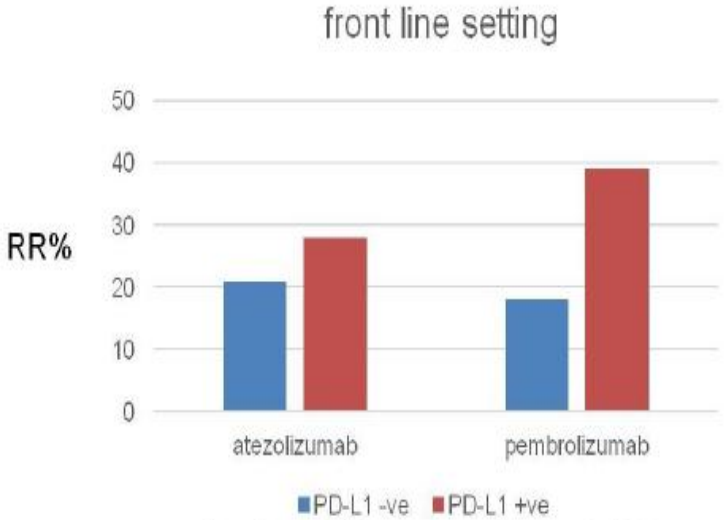
Issues with PDL1
Multiple assays
Primary vs met
Timing of testing
Patients with negative tests achieve CR
Cut off for positivity
Test on TC vs IC



Sandy Srinivas. ASCO 2018

Inconsistencies in the biomarkers with the same drug and asssay!!!

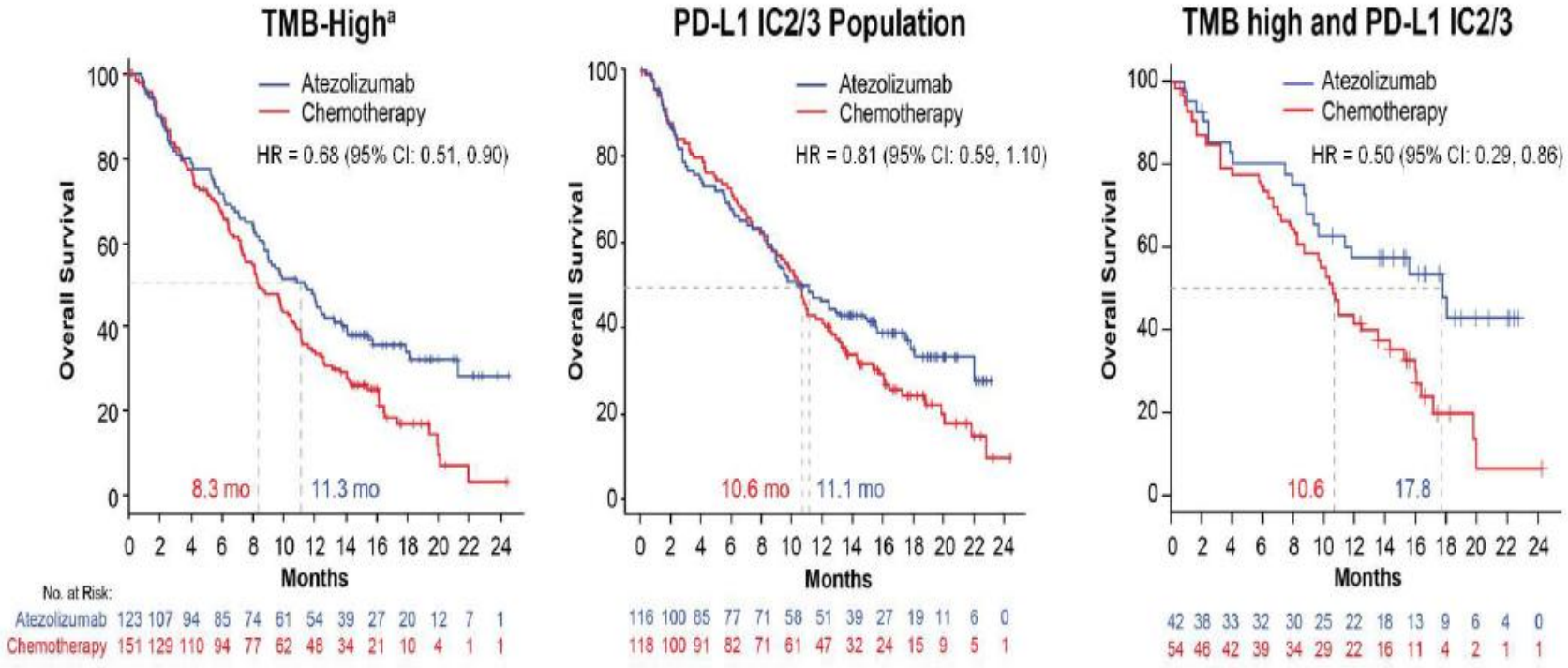




Conclusion:	Imvigor 211	Keynote45	Imvigor210	Keynote52
	good prognosis	not prognostic	not prognostic	good prognosis

Powles T et al. ASCO GU 2018

Atezolizumab in mUC: IMvigor 211 phase III



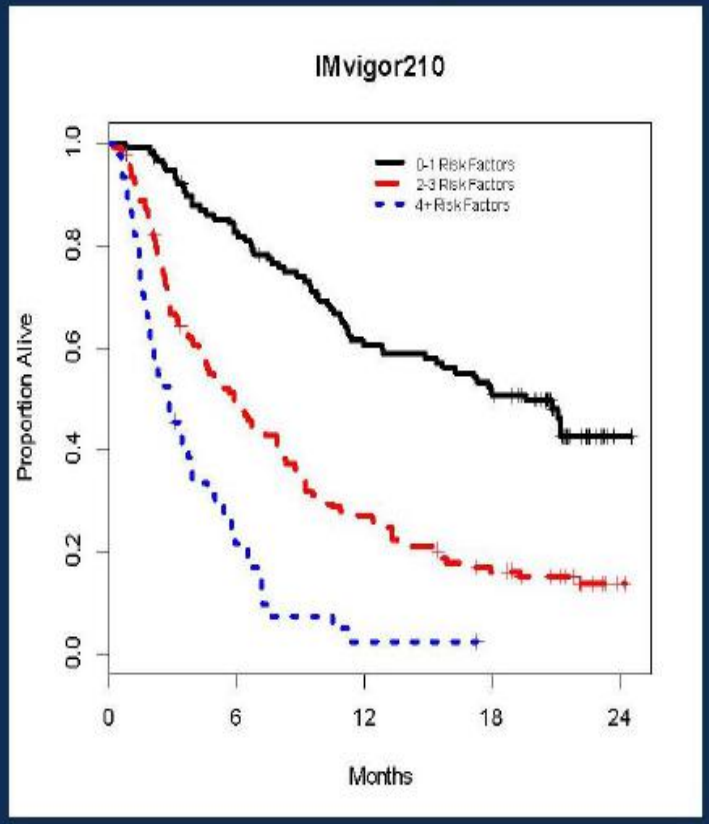
- Improved OS benefit was observed in patients with high TMB as well as high PD-L1 IC scores

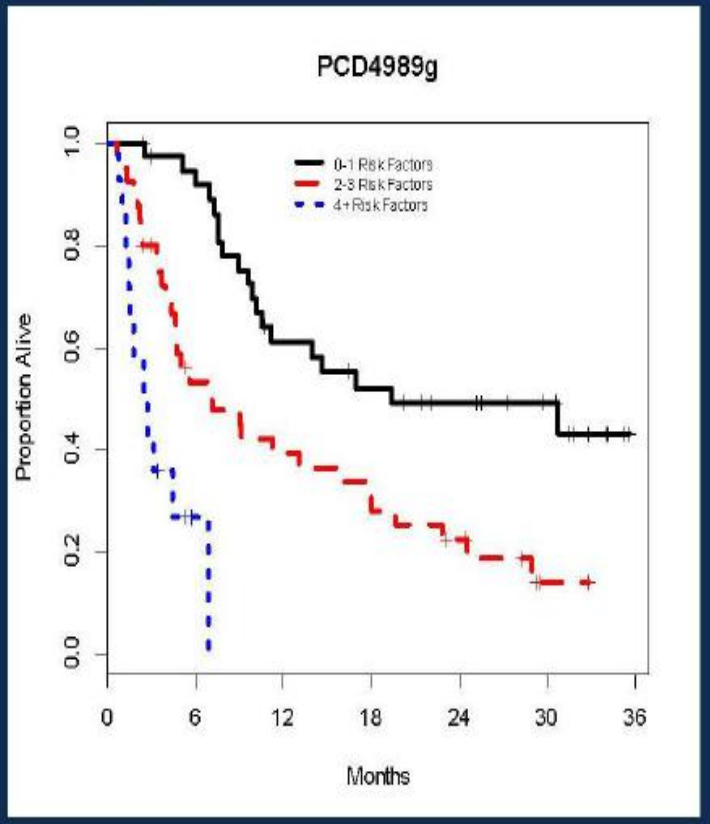
Unstratified HRs are displayed. Reprinted in part from *The Lancet*, Powles T, et al. 2017 Dec 18. [Epub], © 2017, with permission requested from Elsevier.

Powles T, et al. ASCO GU 2018

Prognostic factors with IO second-line

Characteristic	Comparison	N	Hazard Ratio (95% CI)	p-value
Data-Driven Model				
NLR	Log-transformed	294	1.84 (1.45, 2.34)	<0.001
ECOG-PS	1 vs 0		1.64 (1.20, 2.24)	0.002
Platelets	Log-transformed		1.73 (1.14, 2.61)	0.010
Hb <10 g/dL	Yes vs No		1.60 (1.17, 2.21)	0.004
LDH	Log-transformed		1.54 (1.19, 1.99)	0.001
Liver Mets	Yes vs No		1.45 (1.08, 1.94)	0.014





- Prognostic risk factors identified were NLR ≥5, ECOG PS≥1, platelets ≥400 10^9/L, hemoglobin <10 g/dL, LDH ≥280 U/L and the presence of liver metastasis.
- Median OS (months) for those with 0-1, 2-3 and 4+ factors was 19.6, 5.9 and 2.8 in Imvigor210 and 19.4, 7.2 and 2.6 in PCD4989g, respectively

Pond G, et al. ASCO GU 2018

ImVigor 210 (cohort 1)

Patients (N = 119)
- Advanced urothelial cancer
- No prior chemotherapy
- ECOG PS 0-2
- Ineligible for cisplatin:
  - CrCl <60 and >30 mL/min
  - ECOG PS 2
  - Grade ≥2 neuropathy or hearing loss
  - NYHA class III heart failure

→ Atezolizumab 1200 mg Q3W →

Continue until confirmed PD (RECIST 1.1)
- Intolerable toxicity
- Patient withdrawal

- **Primary end point: confirmed objective response rate**

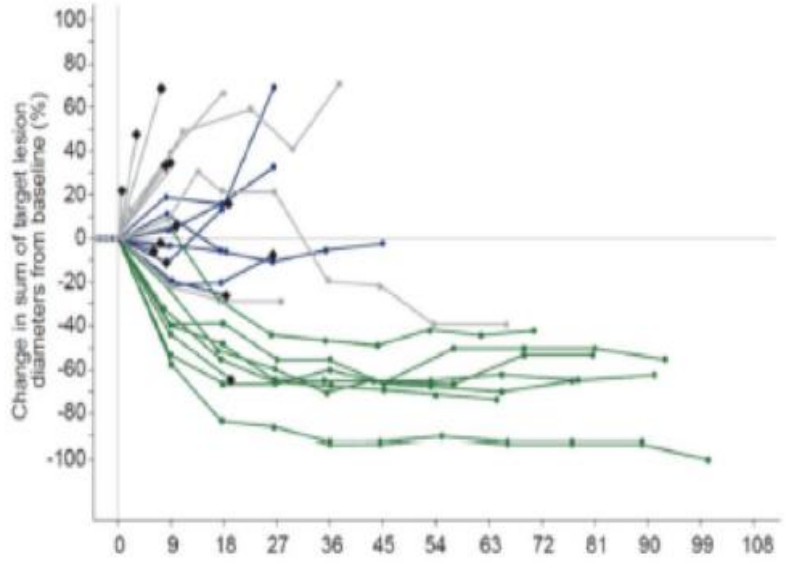
	N=119*
Median age, years (range)	73 (51–92)
≥80 years, %	21
Male / female, %	81 / 19
PD-L1 status on IC: IC2/3 / IC1 / IC0	27 / 40 / 33
Primary tumour site†: bladder or urethra / renal pelvis or ureter	71 / 28
Metastatic disease	92
Lymph node only	26
Visceral §	66
Liver sites	21
Prior therapy: radiotherapy / perioperative chemotherapy¶	10 / 18
Cisplatin ineligibility criteria:	
Renal impairment (GFR <60 and >30mL/min)	70
Hearing loss (25dB)	14
Peripheral neuropathy (Grade ≥2)	6
ECOG PS 2	20
Renal impairment and ECOG PS 2	7

Balar A, et al. Lancet 2017

ImVigor 210 (cohort 1)

Objective response rate by PD-L1 status on tumour-infiltrating immune cells

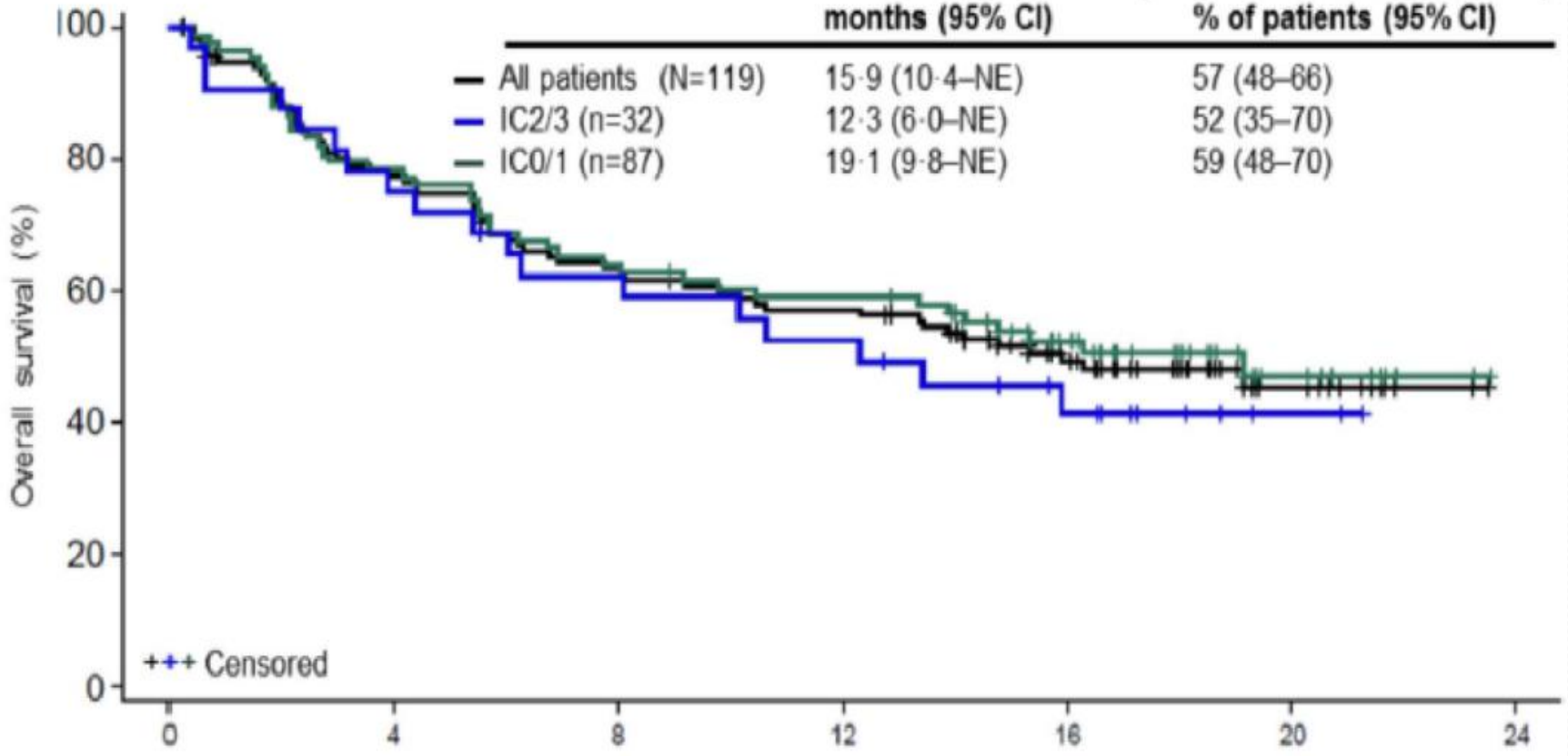
	Patients	Complete response	Partial response	Objective response rate, n (% [95% CI])*	Median duration of response (95% CI),
All patients	119	11	16	27 (23% (16–31)	NE (14·1–NE)
IC2/3	32	4	5	9 (28% (14–47])	NE (11·1–NE)
IC1/2/3	80	8	11	19 (24% [15–35])	NE (NE)
IC1	48	4	6	10 (21% ([11–35])	NE (NE)
IC0	39	3	5	8 (21% [9–37]))	NE (12·8–NE)



Subgroup	Patients	Objective response rate, n (% [95% CI])*
All patients	119	27 (23% [16–31])
Demographics and prior treatment		
Age ≥80 years	25	7 (28% [12–49])
Perioperative chemotherapy†	22	8 (36% [17–59])
Primary tumour sites‡		
Bladder/urethra	85	14 (17% [9–26])
Upper tract	33	13 (39% [23–58])
Metastatic sites at baseline		
Lymph node only	31	10 (32% [17–51])
Visceral§	78	11 (14% [7–24])
Liver	25	2 (8% [1–26])
Cisplatin ineligibility criteria		
Impaired renal function	83	21 (25% [16–36])
ECOG PS 2	24	6 (25% [10–47])
Hearing loss, 25 dB	17	2 (12% [2–36])
Peripheral neuropathy, grade ≥2	7	1 (14% [0–58])
Renal impairment and ECOG PS 2	8	2 (25% [3–65])
Bajorin risk factors¶		
0	35	12 (34% [19–52])
1	66	13 (20% [11–31])
2	18	2 (11% [1–35])

Balar A, et al. Lancet 2017

ImVigor 210 (cohort 1)



Number at risk

All Patients:	119	101	89	78	72	67	64	56	41	26	11	2	0
IC2/3	32	28	24	21	19	18	16	13	10	6	2	0	0
IC0/1	87	73	65	57	53	49	48	42	31	20	9	2	0

Balar A, et al. Lancet 2017

Keynote-052

Patients (N = 370)
- Advanced urothelial cancer
- No prior chemotherapy
- ECOG PS 0-2
- Ineligible for cisplatin:
  - CrCl <60 mL/min
  - ECOG PS 2
- Grade ≥2 neuropathy or hearing loss
- NYHA class III heart failure

→ Pembrolizumab 200 mg Q3W →

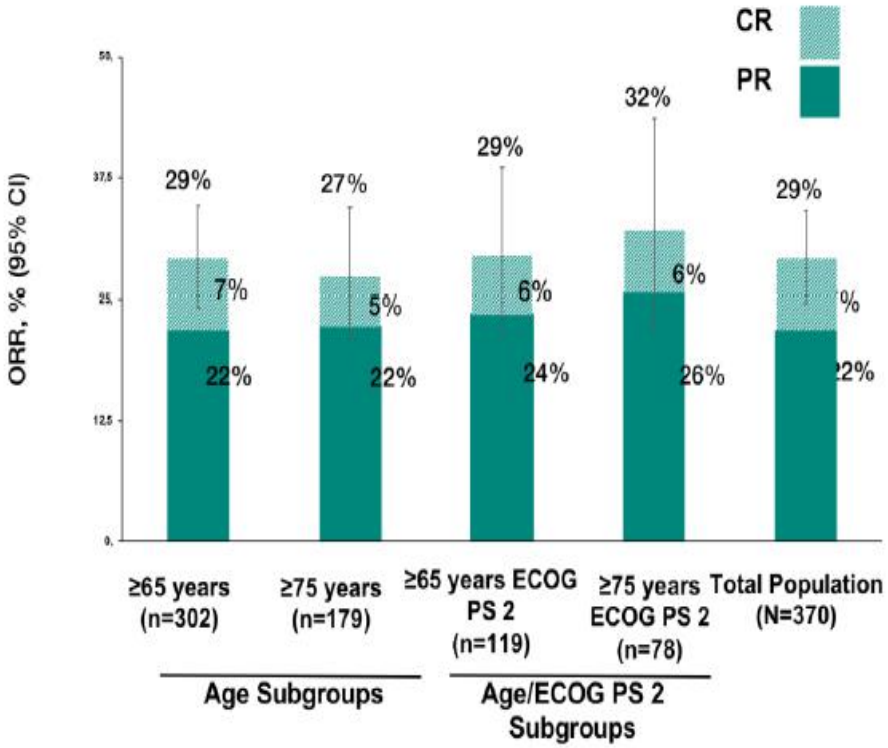
Continue until:
- 24 months of treatment
- Confirmed PD
- Intolerable toxicity
- Patient withdrawal

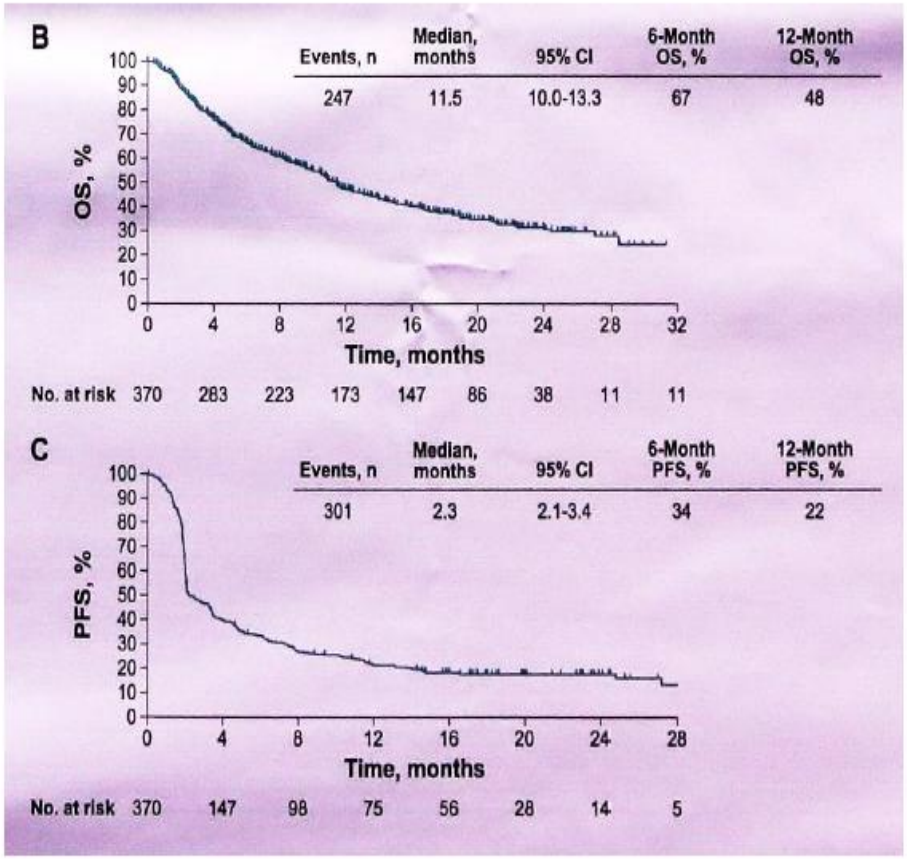
- Response assessed at W9, then Q6W for 1 y, Q12W thereafter
- Primary end point: confirmed objective response rate
- Analyses subgroups: ≥65 y, ≥75 y, ≥65 y ECOG PS 2, ≥75 y ECOG PS 2

Characteristic, n (%)	Total population (N=370)
Age, median (range), years	74 (34–94)
≥80 years	107 (29)
Male	286 (77)
ECOG PS*	
0 / 1 / 2	80 (22) / 134 (36) / 155 (42)
Primary tumour location‡	
Upper tract / lower tract	69 (19) / 300 (81)
Metastases location§	
Lymph node only / visceral / liver	51 (14) / 315 (85) / 77 (21)
Previous adjuvant / neoadjuvant platinum-based chemotherapy¶	37 (10)
Reasons for cisplatin ineligibility	
ECOG PS 2	120 (32)
Renal dysfunction†	183 (50)
ECOG PS 2 and renal dysfunction	34 (9)
Other reasons**	33 (9)

Castellano et al. EAU 2018

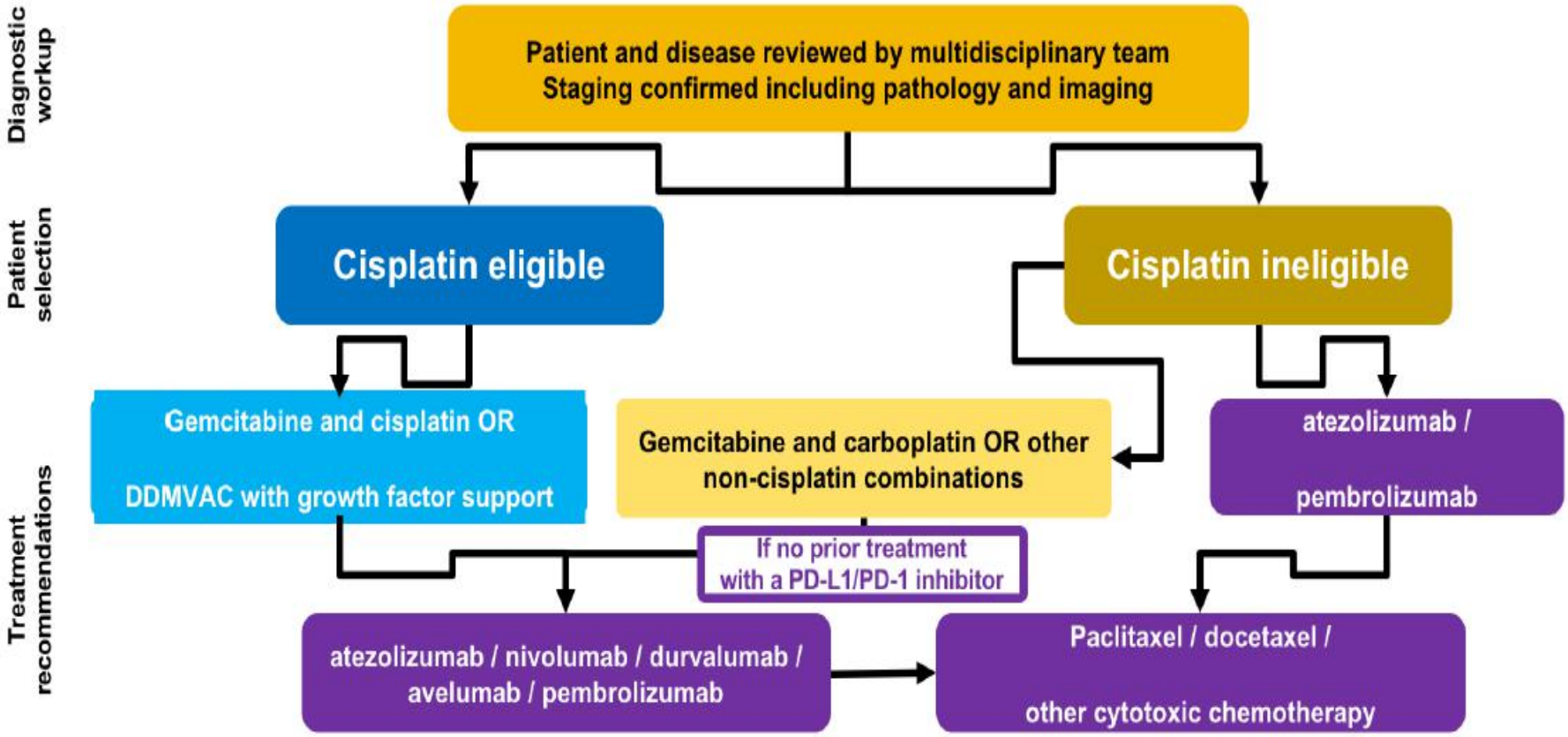
Keynote-052





Castellano et al. EAU 2018

What is the current paradigm?



Kamat et al .J Immunother Cancer 2017

The Future

IMvigor130 study design

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

→ **Arm A**
Atezo + plt/gem

→ **Arm B**
Atezo monotherapy

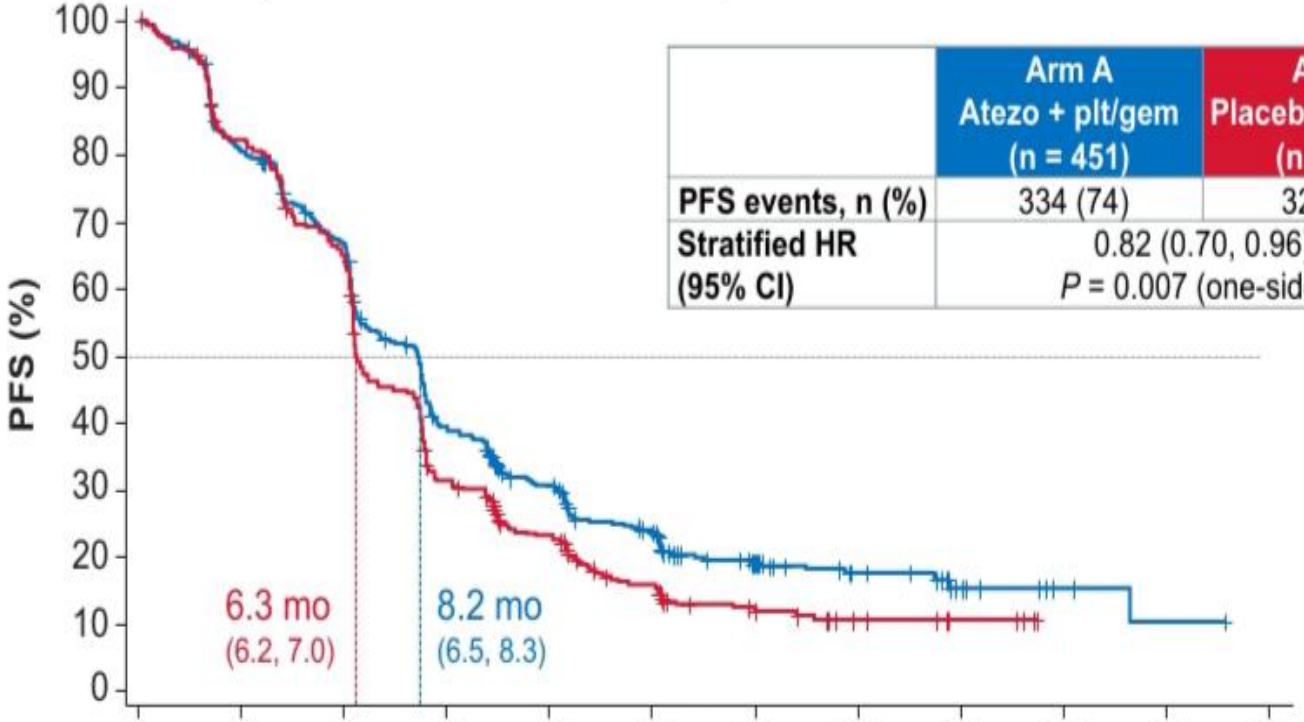
→ **Arm C**
Placebo + plt/gem

Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

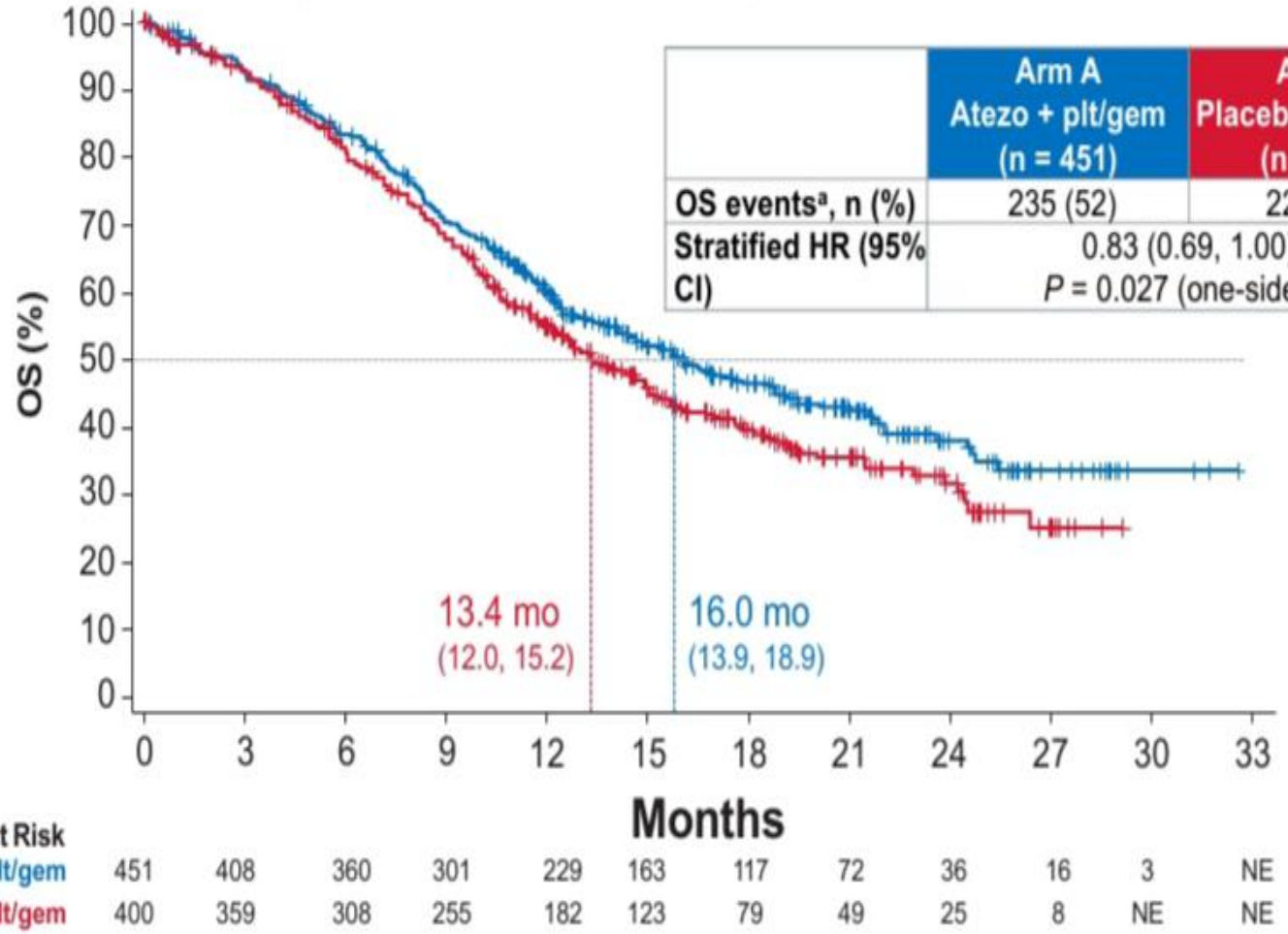
No. at Risk												
Atezo + plt/gem	451	345	282	160	111	74	42	22	10	4	2	NE
Placebo + plt/gem	400	317	246	116	73	40	18	11	4	NE	NE	NE

NE, not estimable. Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

IMvigor130—ESMO 2019 (LBA14): presented by Dr Enrique Grande

http://bit.ly/2Z1bPbD

Interim OS: ITT (Arm A vs Arm C)



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

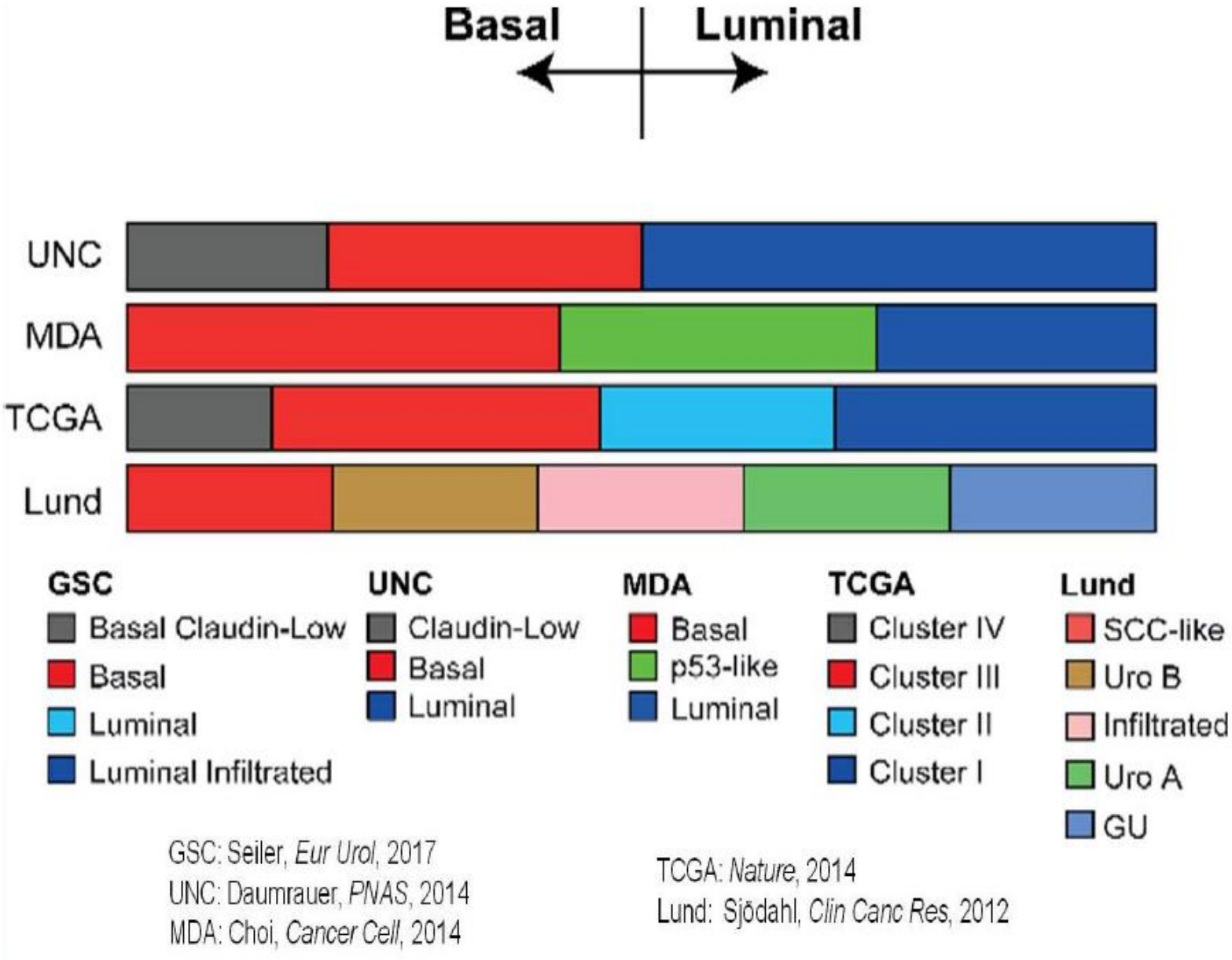
No. at Risk												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] 5% of patients from Arm A and 20% of patients from Arm C received non-protocol immunotherapy. [b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

IMvigor130—ESMO 2019 (LBA14): presented by Dr Enrique Grande

http://bit.ly/2Z1bPbD

Molecular subtypes



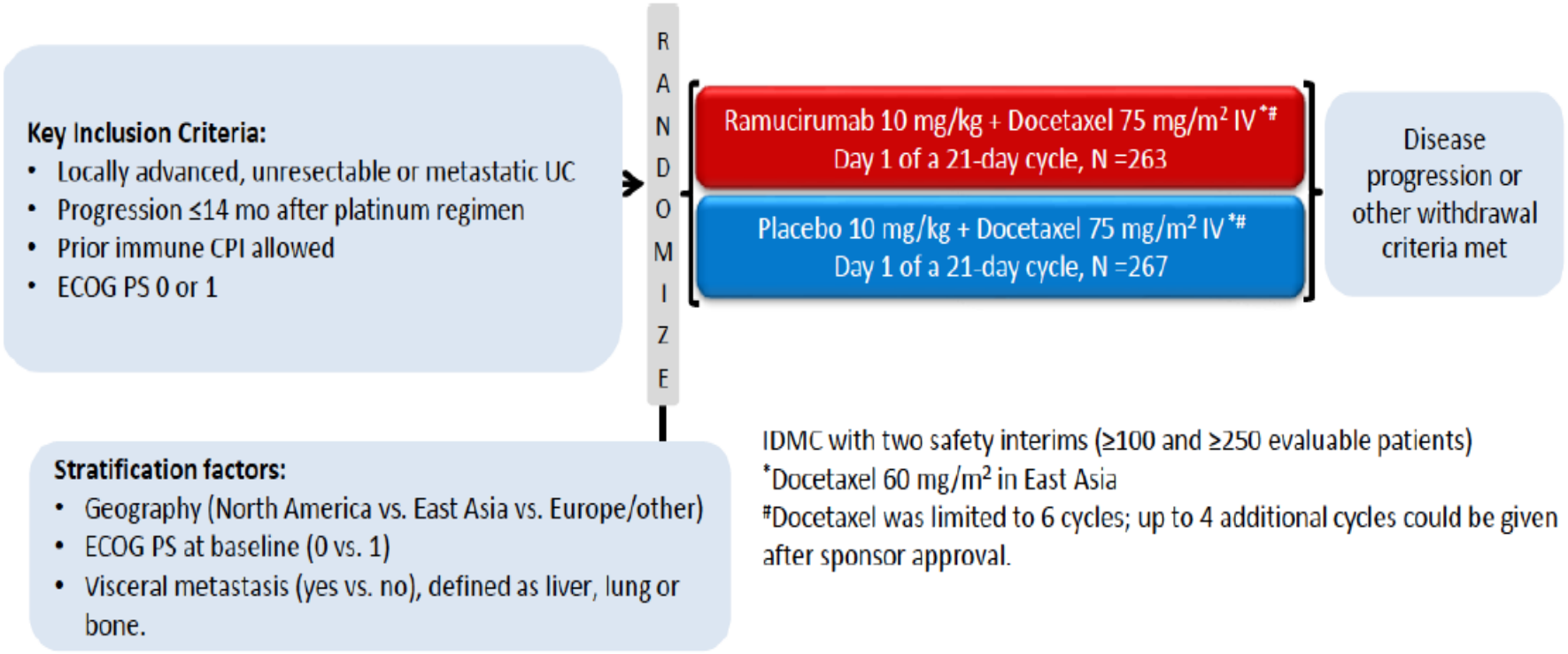
New drugs
New indications

New drugs:

Ramucirumab
Nab-paclitaxel
FGFR inhibitors
Enfortumab

New indications

Ramucirumab: RANGE phase III trial (PFS)



IDMC with two safety interims (≥100 and ≥250 evaluable patients)
*Docetaxel 60 mg/m² in East Asia
#Docetaxel was limited to 6 cycles; up to 4 additional cycles could be given after sponsor approval.

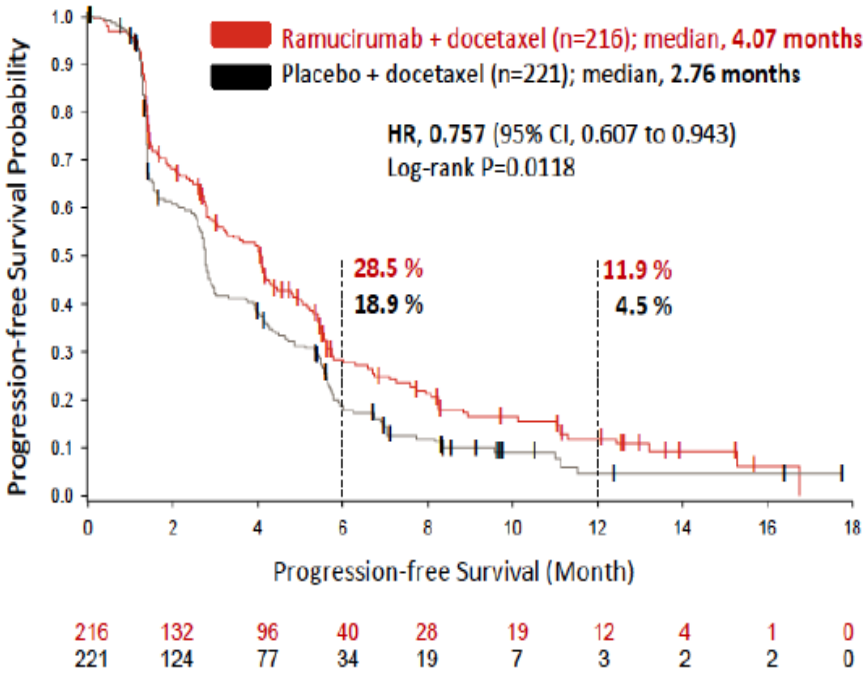
Primary Endpoint: Progression-free survival (investigator assessment)

Secondary Endpoints: OS, ORR, disease control rate, duration of response, safety, patient-reported outcomes, PK and immunogenicity

Petrylak D, et al. ESMO 2017

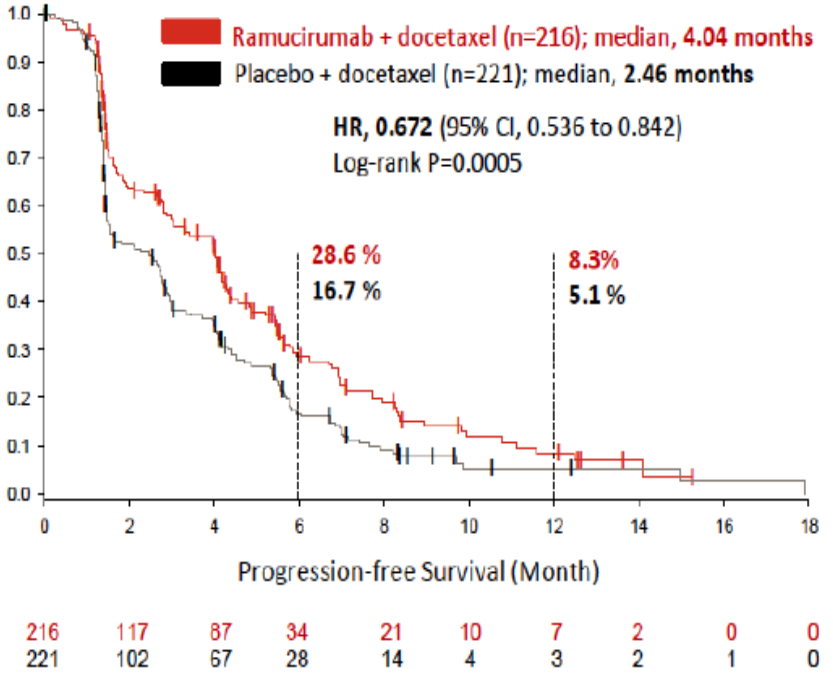
Ramucirumab: RANGE phase III trial (PFS)

Investigator assessment



216	132	96	40	28	19	12	4	1	0
221	124	77	34	19	7	3	2	2	0

Independent blinded assessment

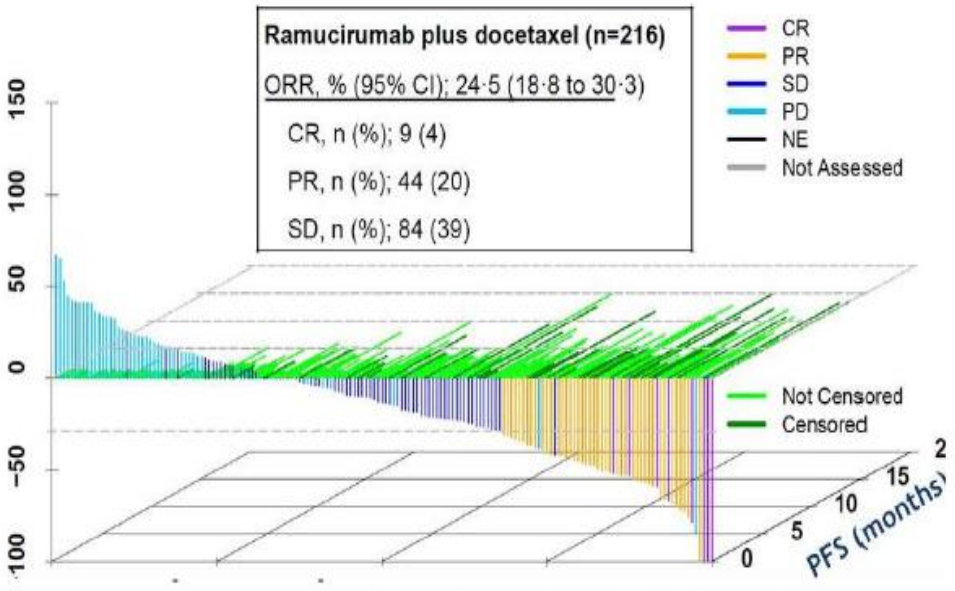


216	117	87	34	21	10	7	2	0	0
221	102	67	28	14	4	3	2	1	0

Median follow-up duration in the full ITT population was 5.0 months (interquartile range [IQR], 2.3–8.9)

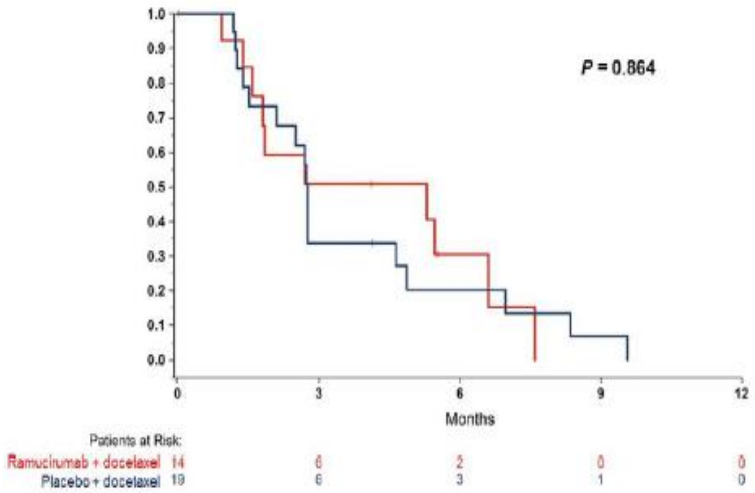
Petrylak D, et al. ESMO 2017

Ramucirumab: RANGE phase III trial (PFS)



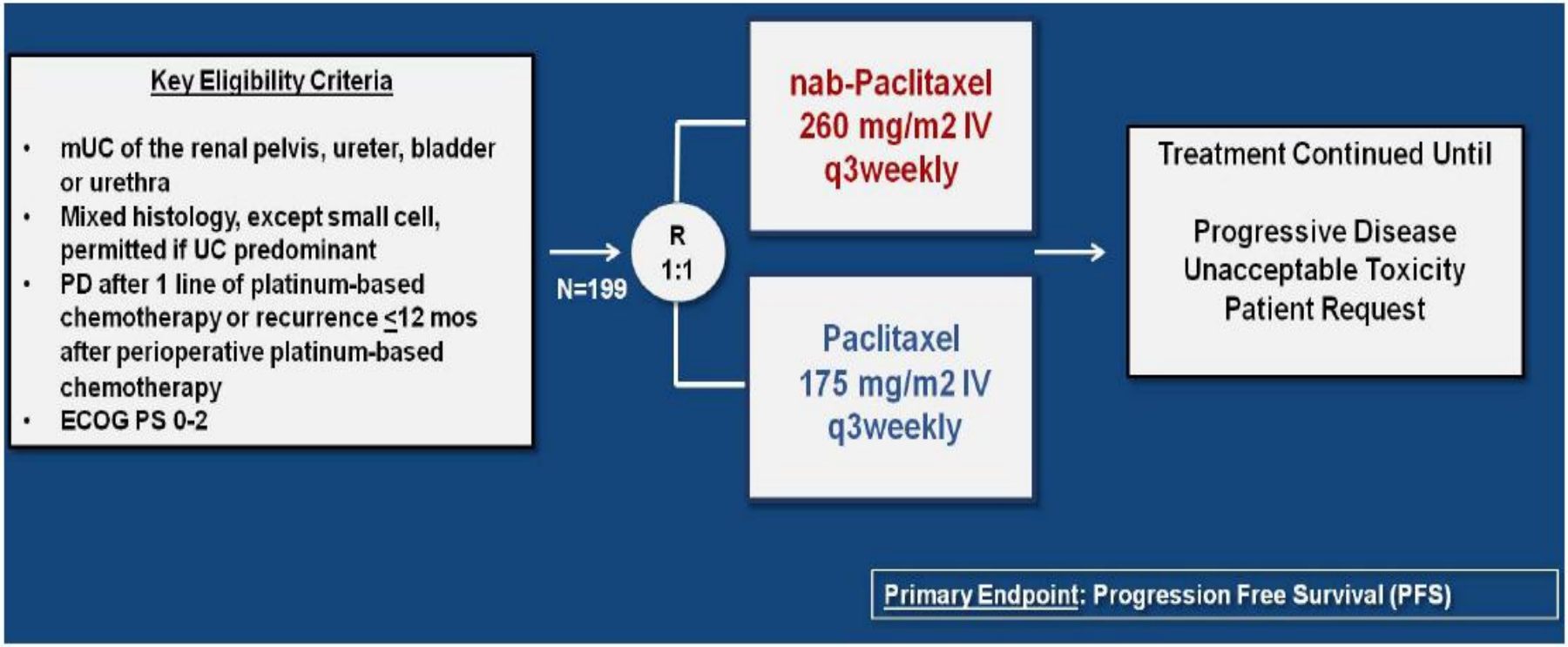
	Ramucirumab + docetaxel (n=14)	Placebo + docetaxel (n=19)
Prior ICI		
Atezolizumab	9 (64)	9 (47)
Pembrolizumab	4 (29)	8 (42)
BGBA317 (anti-PD-1)	1 (7)	0
Nivolumab	0	1 (5)
Durvalumab	0	1 (5)
ICI immediately prior to RANGE	13 (93)	17 (89)
Median duration of prior ICI, months (IQR)	2.9 (1.5-4.9)	3.5 (2.8-5.6)
Tumor response to ICI		
Complete Response	0	0
Partial Response	1 (7.1)	1 (5.3)
Stable Disease	3 (21.4)	6 (31.6)
Progressive Disease	10 (71.4)	12 (63.2)
Objective response, n (%)	1 (7.1)	1 (5.3)
Disease control (CR/PR/SD), n (%)	4 (28.6)	7 (36.8)

	Ramucirumab + docetaxel (n=14)	Placebo + docetaxel (n=19)
Progression-free survival		
Median, months (95% CI)	5.29 (1.61-6.60)	2.76 (1.54-4.63)
Hazard ratio (95% CI)	0.920 (0.409-2.067)	
3-month PFS rate, % (95% CI)	50.8 (21.4-74.2)	33.8 (13.9-55.1)
6-month PFS rate, % (95% CI)	30.5 (7.8-57.4)	20.3 (5.4-41.9)



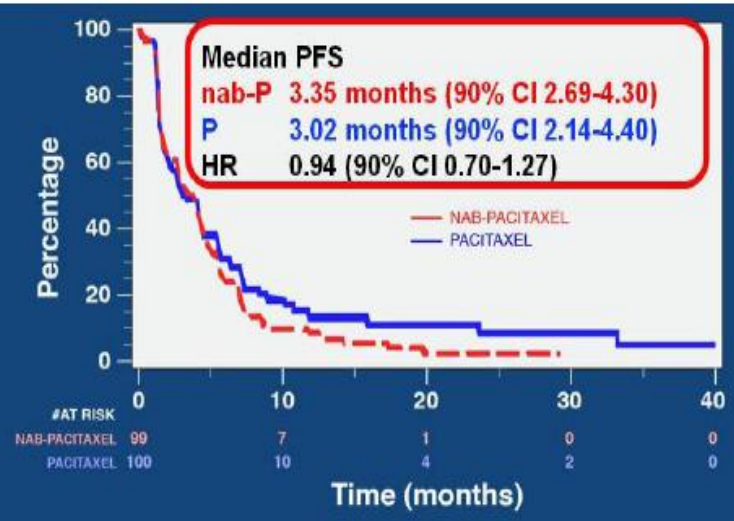
Petrylak D, et al. ESMO 2017

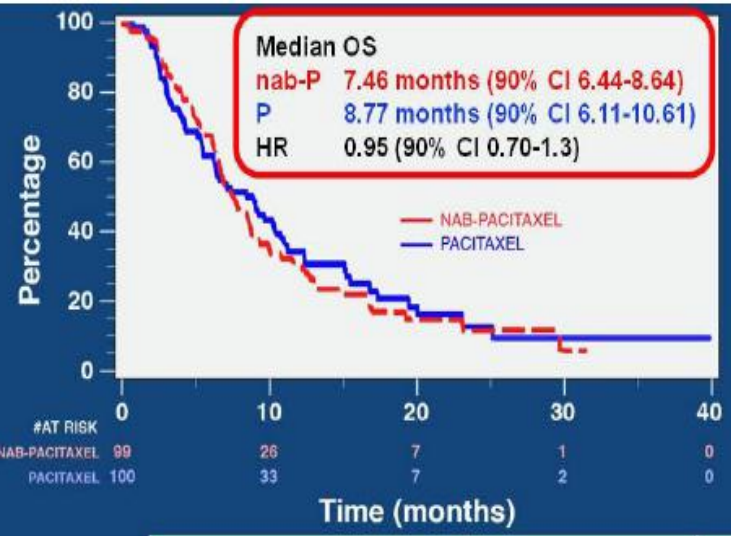
Nab-paclitaxel: phase II trial



Sridhar S, et al. ASCO 2018

Nab-paclitaxel: phase II trial





Abstract 4505	nab-Paclitaxel n=99	Paclitaxel n=100
Complete Response n (%)	3 (3)	2 (2)
Partial Response n (%)	18 (18)	21 (21)
Overall Response Rate n (%)	21 (21)	23 (23)

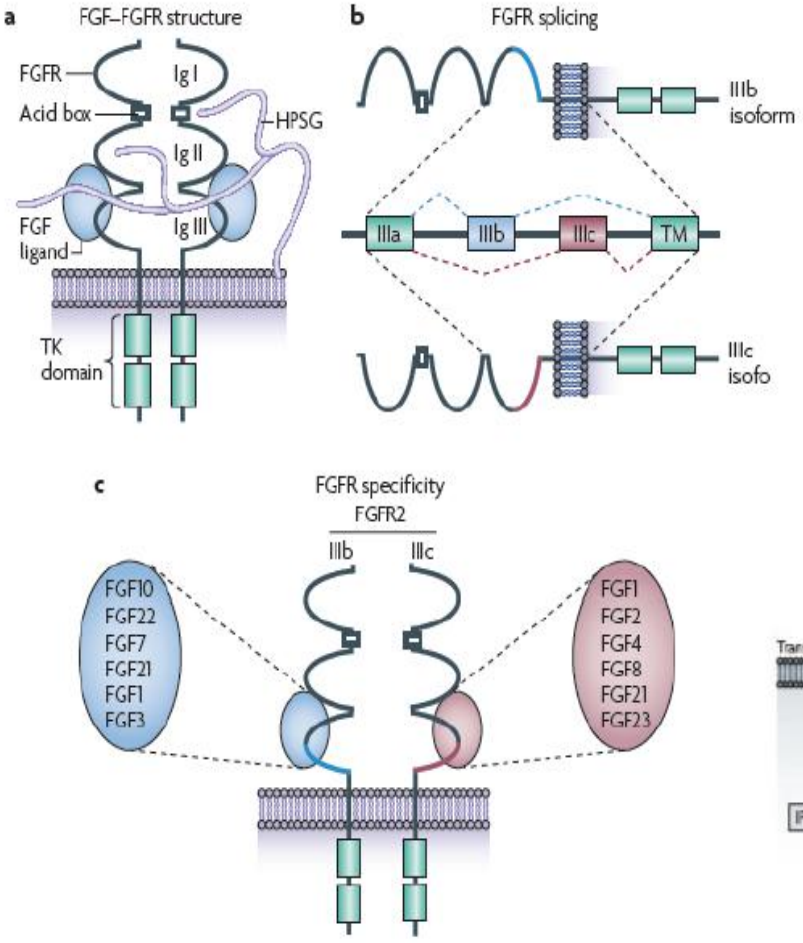
*Bellmunt J. et al. NEJM. 2017;376:1015-26.

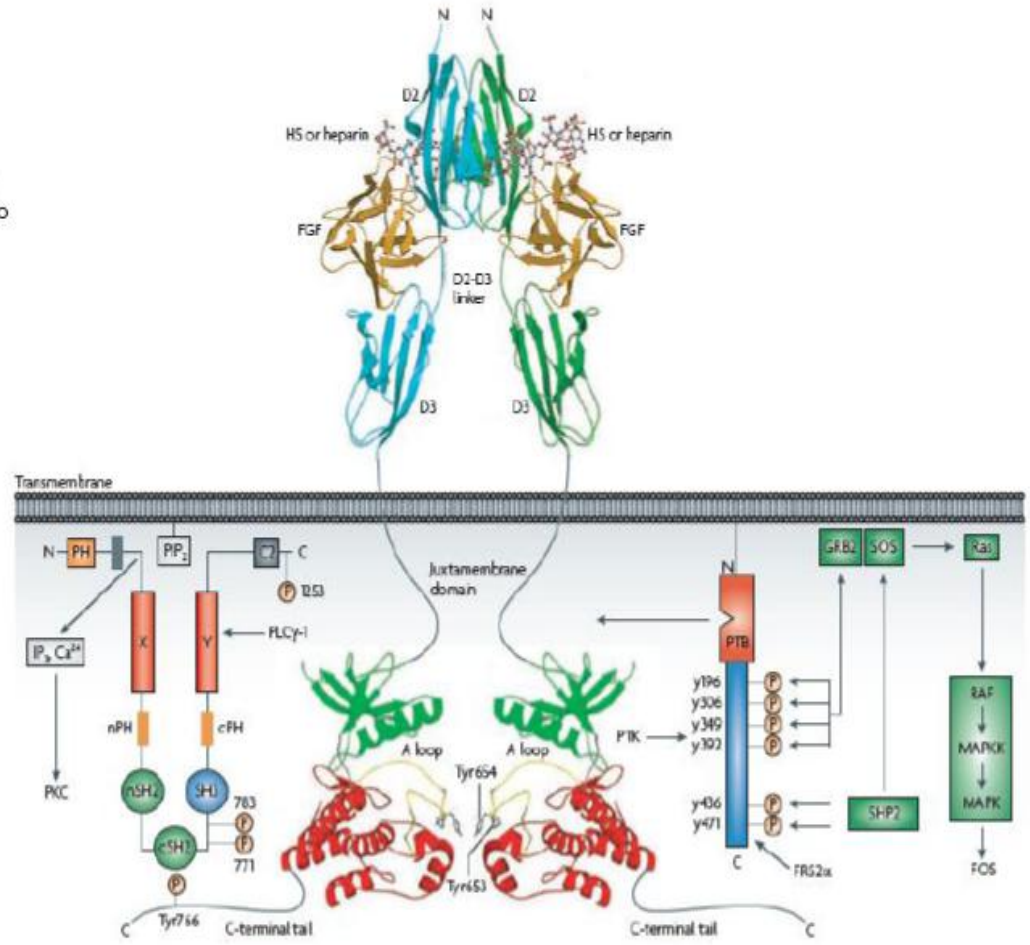
Phase III Trial KEYNOTE-045*	Pembrolizumab	Paclitaxel/ Docetaxel/ Vinflunine
ORR (%)	21	11
mPFS (months)	2.1	3.3
mOS (months)	10.3	7.4

Sridhar S, et al. ASCO 2018

FGFR biology

- FGFR3 most extensively described
  - Activating mutations are common (~86%) in low grade and early stage bladder tumors[1]
  - TCGA identified only 12% with mutations in muscle invasive bladder cancer[2]
  - Also more common in upper tract disease[3]
  - Oncogenic FGFR3 fusions more common in high grade, invasive tumors[4]





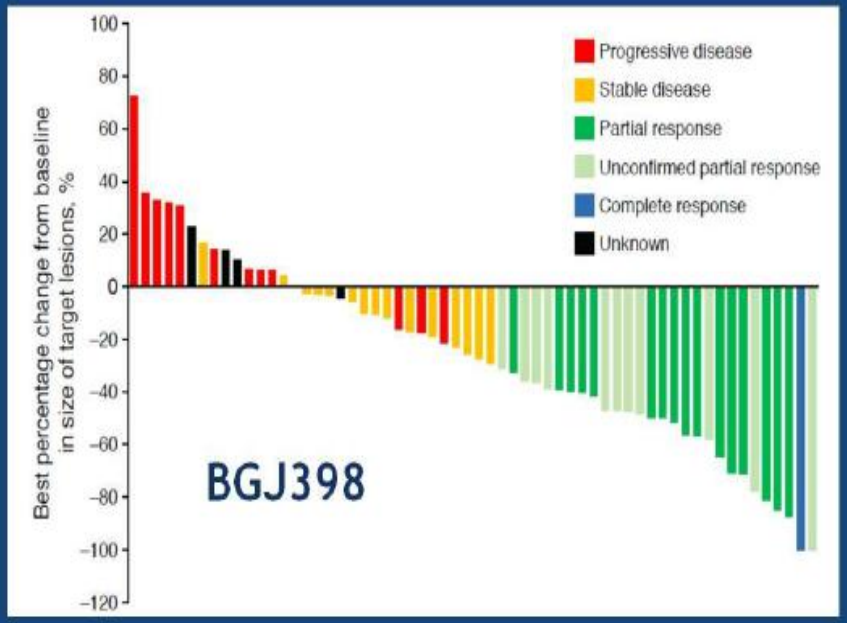
Nicholas Turner & Richard Grose. Nat Rev Cancer 2010; 10: 116-29

FGFR inhibitors in advanced urothelial carcinoma

Drug(s)	Phase	Clinicaltrials.gov	Other Details
AZD4547 (BISCAY)	1b	NCT02546661	Single agent or combined with durvalumab
BGJ398	2	NCT02160041	Fully accrued
Debio 1347	1	NCT01948297	Recruiting advanced solid tumors
INCB054828	2	NCT02872714	
LY3076226	1	NCT02529553	Urothelial cohort after dose escalation
Rogaratinib (BAY1163877)	1	NCT01976741	
Rogaratinib vs taxane (FORT-1)	2/3	NCT03410693	
Rogaratinib + Atezolizumab (FORT-2)	1b/2	NCT03473756	First-line cisplatin-ineligible
B-701 +/- Docetaxel (FIERCE 21)	1b/2	NCT02401542	FGFR3 specific monoclonal antibody; Phase 2 is docetaxel +/- B-701
B-701 + pembrolizumab (FIERCE 22)	1	NCT03123055	FGFR3 alteration not mandated

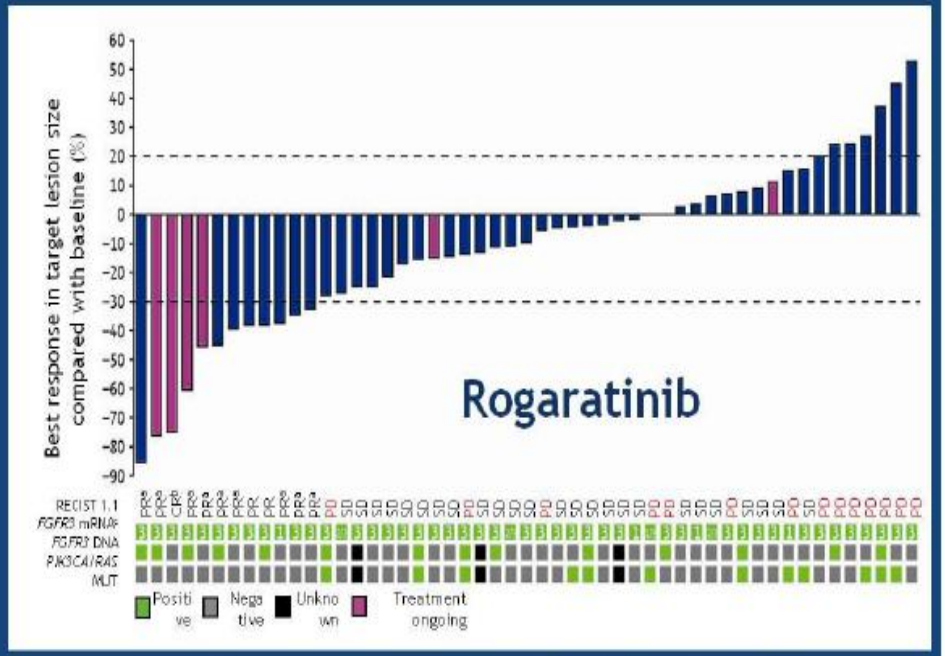
Apolo A, ASCO 2018

FGFR inhibitors in advanced urothelial carcinoma



- Metastatic urothelial carcinoma patients unable to receive platinum chemotherapy
- FGFR3 alteration through central or local testing mandated
- BGJ398 125 mg/d 3 weeks on:1 week off
- 70.1% had received 2 or more prior antineoplastic agents
- 17/67 (25.4%) ORR

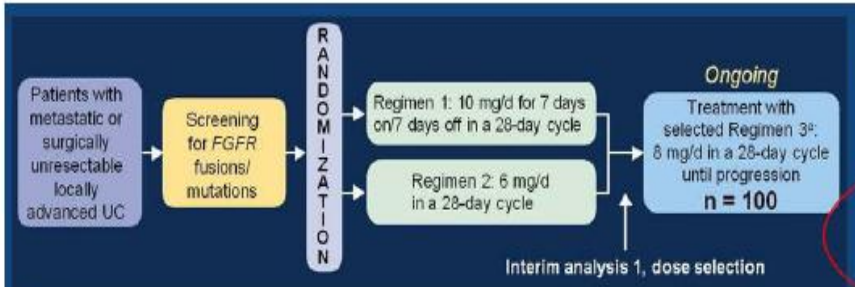
- Phase I expansion cohort of late-stage muscle-invasive UC
- FGFR1-3 mRNA-positive pts treated with rogaratinib 800 mg BID (continuous 21-day cycle)
- FFPE tumor tissue FGFR1-3 mRNA overexpression screened by RNA ISH and by NanoString® nCounter®
- Somatic mutations in FGFR downstream signaling genes detected by PCR



ORR 24% (1 CR, 11 PR); 49% SD, DCR 73%

Pal S, et al. Cancer Discov 2018; Joerger M, et al. ASCO GU 2018

Erdafatinib: BLC2001 phase II



Patients

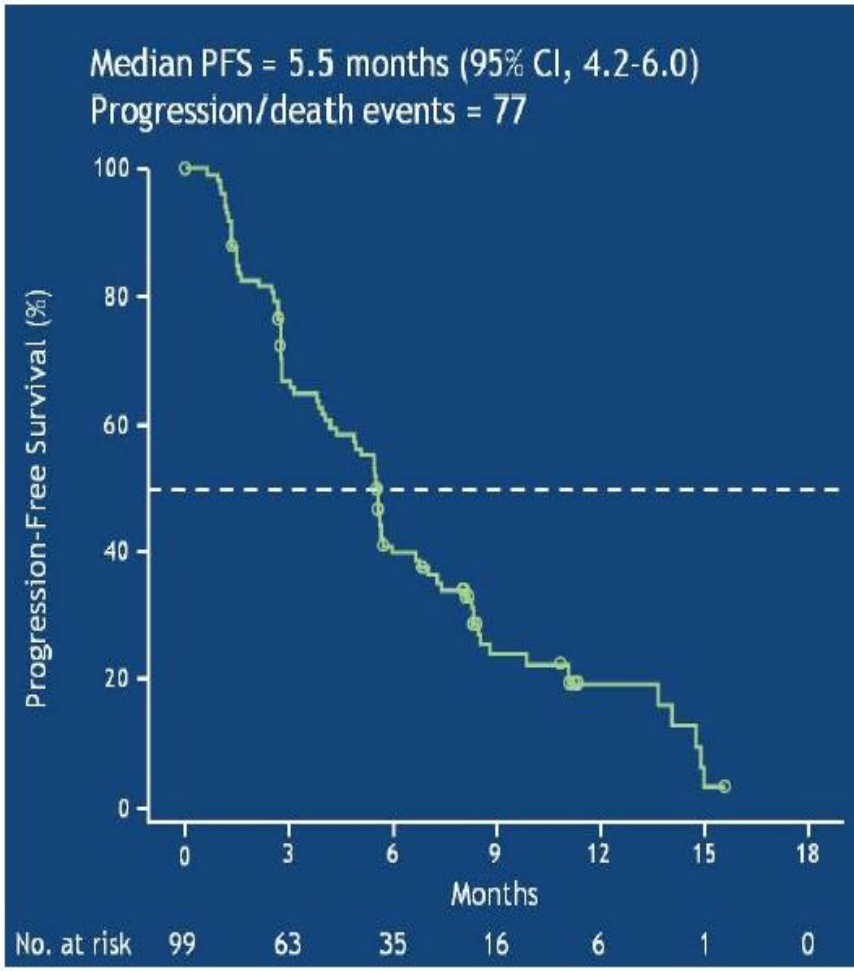
- **Chemo-refractory: progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo**
  OR
- **Chemo-naïve: cisplatin ineligible per protocol criteria[a]**
- **≥ 1 *FGFR2* or *FGFR3* fusion or *FGFR3* mutation per central lab testing with a custom assay**
- **No limit on prior lines of therapy**
- **Prior immunotherapy was allowed**
- **ECOG 0-2**

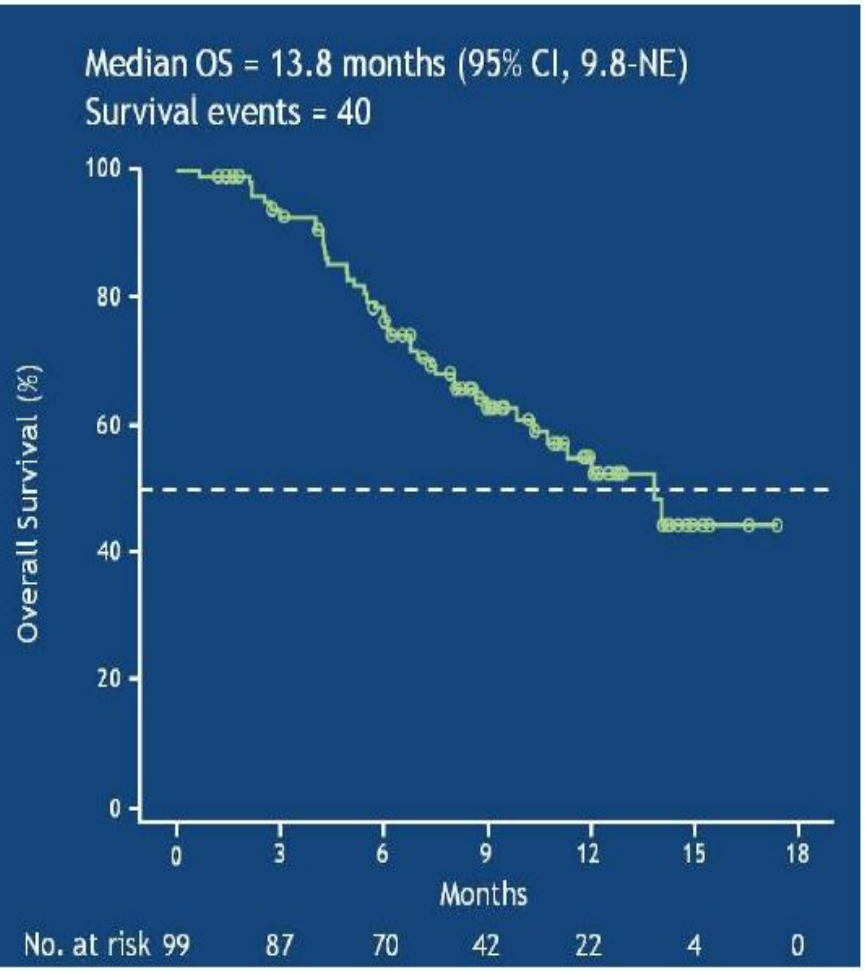
		[95% CI]
Patients, n	99	
Response per investigator assessment[a], n (%) ORR Complete response Partial response	40 (40.4) 3 (3.0) 37 (37.4)	[30.7-50.1]
Stable disease	39 (39.4)	
Progressive disease	18 (18.2)	
Unknown	2 (2.0)	
Median time to response	1.4 months	
Median duration of response	5.6 months	[4.2-7.2]
ORR among patient subgroups, n (%) Chemo-naïve Progressed or relapsed after chemo With visceral metastases Without visceral metastases	 5/12 (41.7) 35/87 (40.2) 30/78 (38.5) 10/21 (47.6)	

[a]Confirmed with second scan at least 6 weeks following the initial observation of response.

Siefker-Radtke et al. ASCO 2018

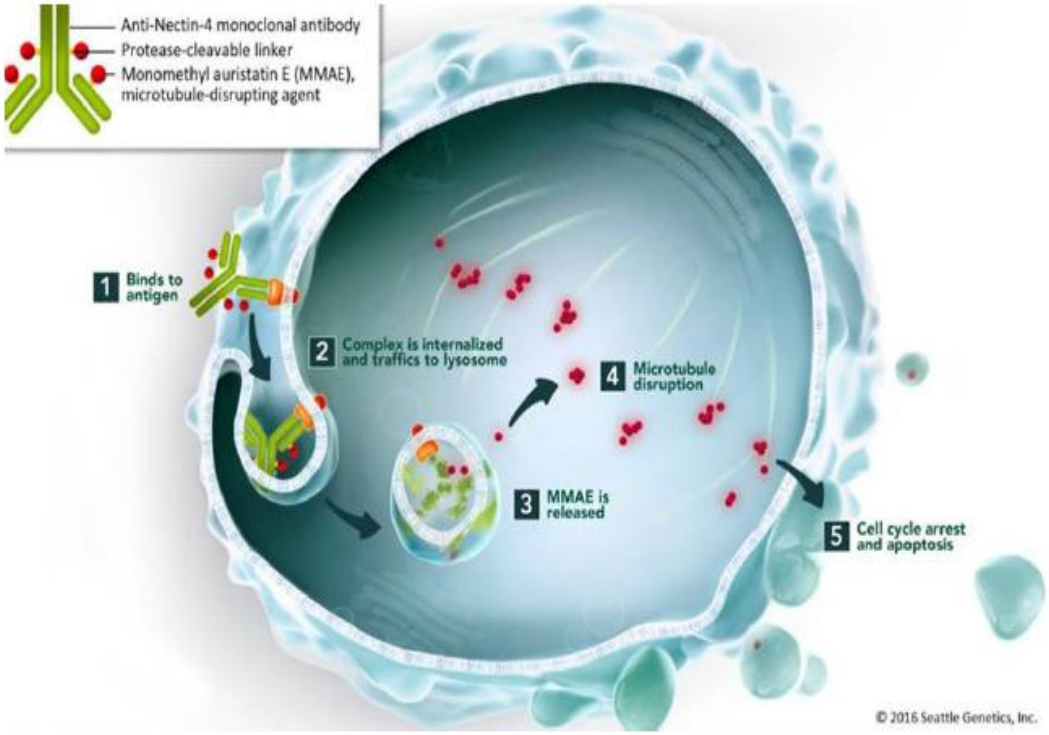
Erdafatinib: BLC2001 phase II

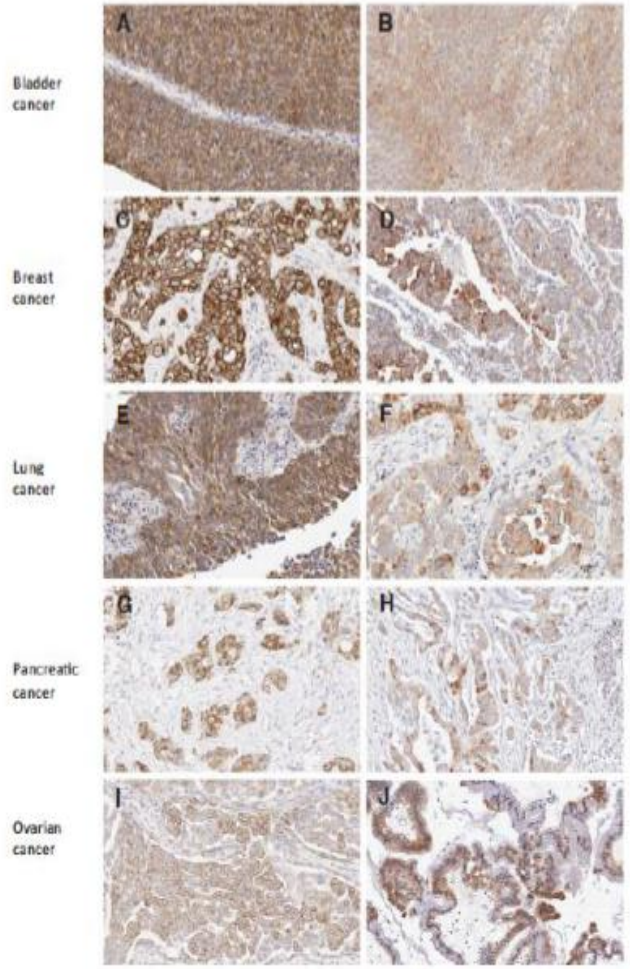




Siefker-Radtke et al. ASCO 2018

Enfortumab Vedotin

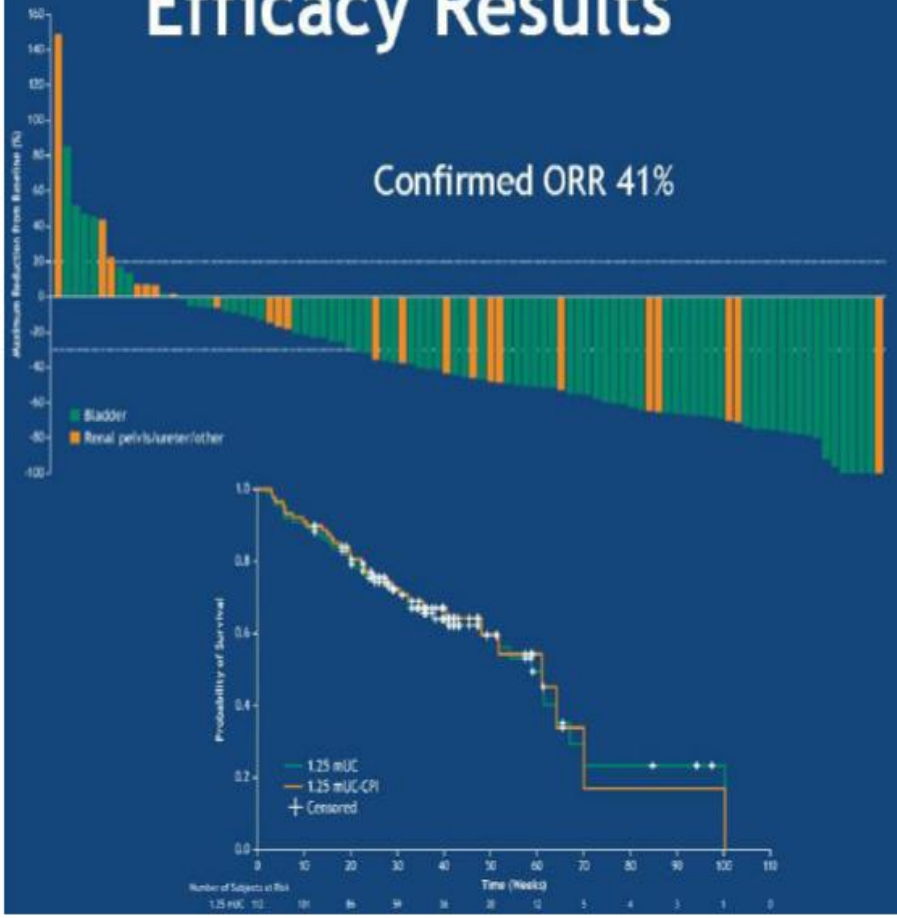




Rosenberg J, et al. ASCO 2018

Enfortumab Vedotin

Efficacy Results



	Prior CPI Treatment[a]	CPI-Naive[a]	Liver Metastases[a]
	1.25 mg/kg (n=89)	1.25 mg/kg (n=23)	1.25 mg/kg (n=33)
Confirmed complete response	3%	9%	0
Confirmed partial response	37%	35%	39%
Confirmed ORR[b] (95% CI)	40% (30.2, 51.4)	43% (23.2, 65.5)	39% (22.9, 57.9)
Stable disease	34%	17%	21%
DCR[c] (95% CI)	74% (63.8, 82.9)	61% (38.5, 80.3)	61% (42.1, 77.1)

Population	Median OS, Months (95% CI)
All patients	13.6 (11.0, 15.4)
Patients with prior CPI	14.0 (11.0, 16.1)

Rosenberg J, et al. ASCO 2018

New drugs:

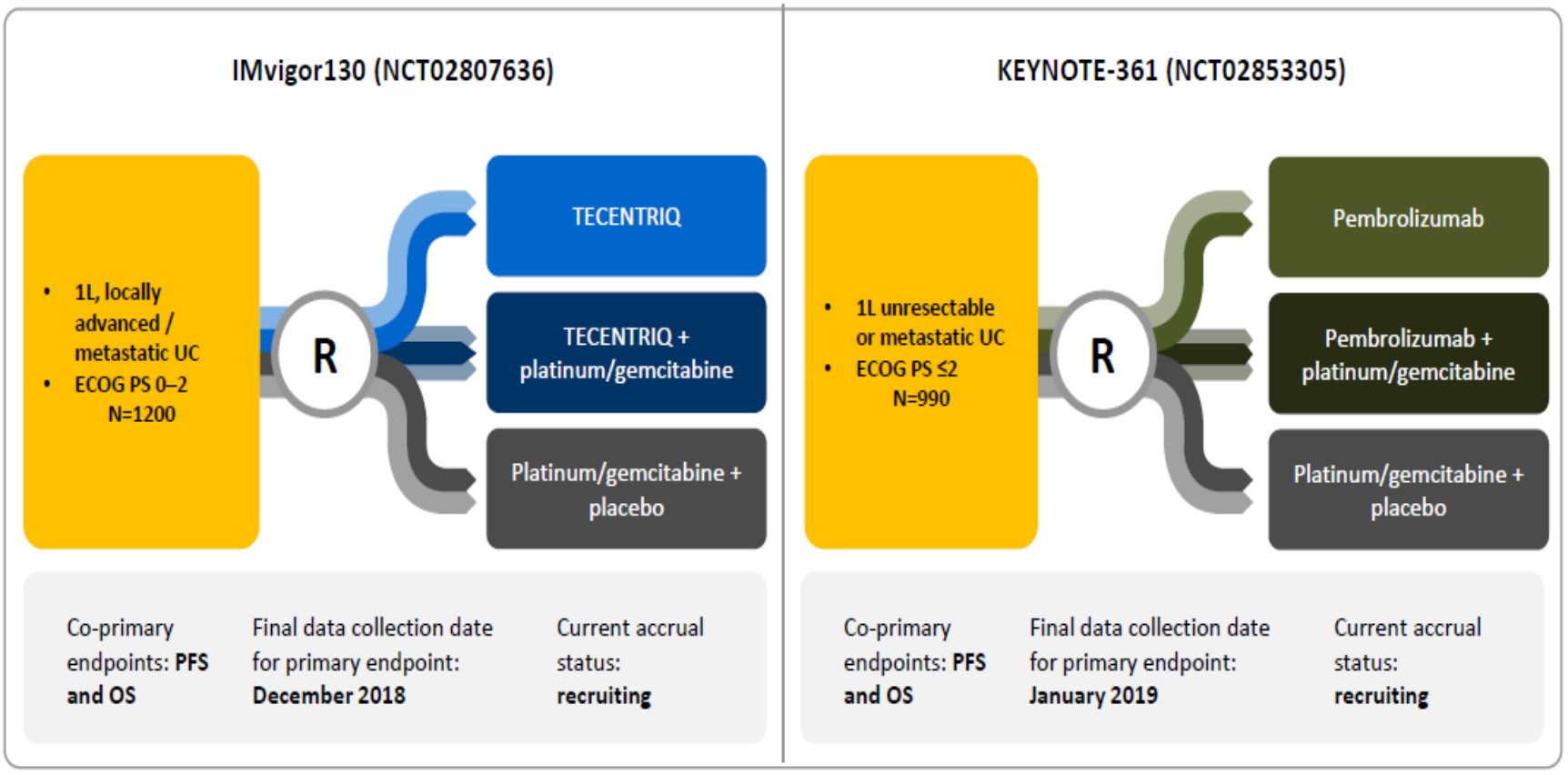
Ramucirumab
Nab-paclitaxel
FGFR inhibitors
Enfortumab

New indications

First-line setting
Neoadjuvant
Adjuvant

What's coming up next in 1L?

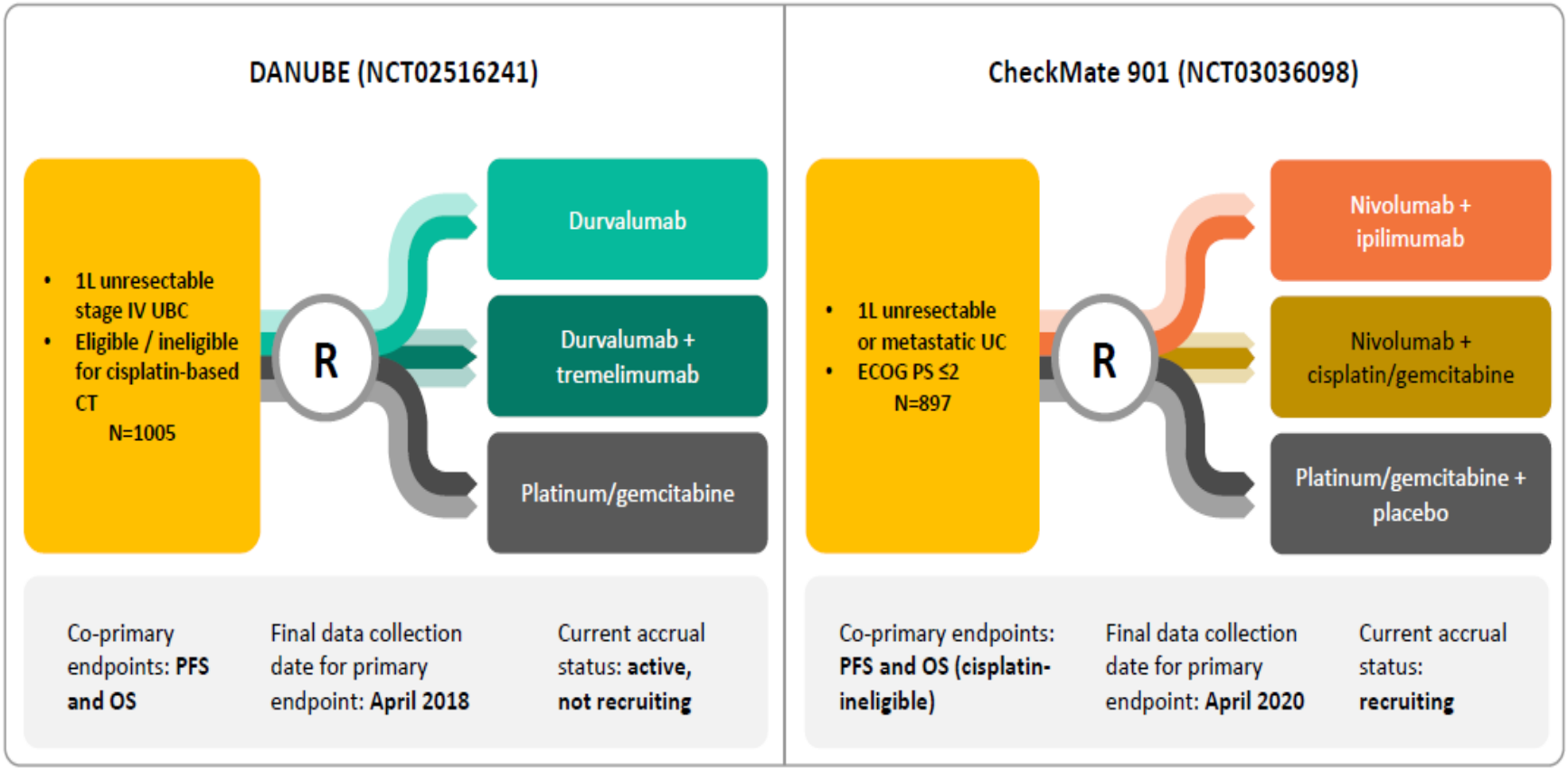
Phase III studies of immunotherapy ± chemotherapy



ClinicalTrials.gov (NCT02807636 and NCT02853305)

What's coming up next in 1L?

Phase III studies of PD-L1/PD-1 inhibitors + anti-CTLA4



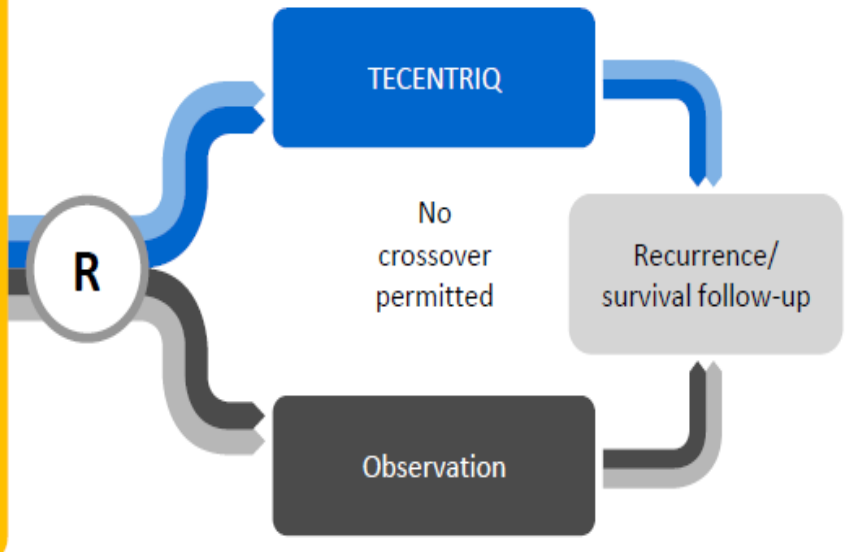
ClinicalTrials.gov (NCT02516241 and NCT03036098)

Ongoing phase III studies of adjuvant PD-L1 inhibitors

IMvigor010 (NCT02450331)

- Patients with high-risk bladder or upper tract muscle-invasive UC[a]
- Tumour stage
  - If prior neoadjuvant chemotherapy: ypT2-T4a or ypN+ (ypT2-4 or ypN+ for UTUC)
  - In no prior neoadjuvant chemotherapy: pT3-T4a or pN+ (pT3-4 or pN+ for UTUC)
    - If no prior neoadjuvant chemotherapy, patients must be ineligible for or have refused adjuvant cisplatin chemotherapy
- Radical surgical resection within previous 14 weeks with no residual disease
- No prior adjuvant therapy
- ECOG PS 0–2

N=700[b]



Primary endpoint: DFS

ClinicalTrials.gov (NCT02450331)

Ongoing phase III studies of adjuvant PD-L1 inhibitors

CheckMate 274 (NCT02632409)

- Invasive UC at high risk of recurrence originating in the bladder, ureter or renal pelvis
- Radical surgical resection (e.g. radical cystectomy)

N=640

R → Nivolumab
R → Placebo

Co-primary endpoints: DFS in patients with tumours expressing ≥1% PD-L1 and in all randomised patients

AMBASSADOR (NCT03244384)

- Histologically confirmed muscle-invasive UC of the bladder or upper tract
  - Neoadjuvant chemotherapy and pathologic stage at surgical resection is ≥ pT2 and/or N+ OR
  - Patients who are not cisplatin-eligible OR
  - Patients that decline adjuvant cisplatin-based or other systemic
- Radical surgical resection

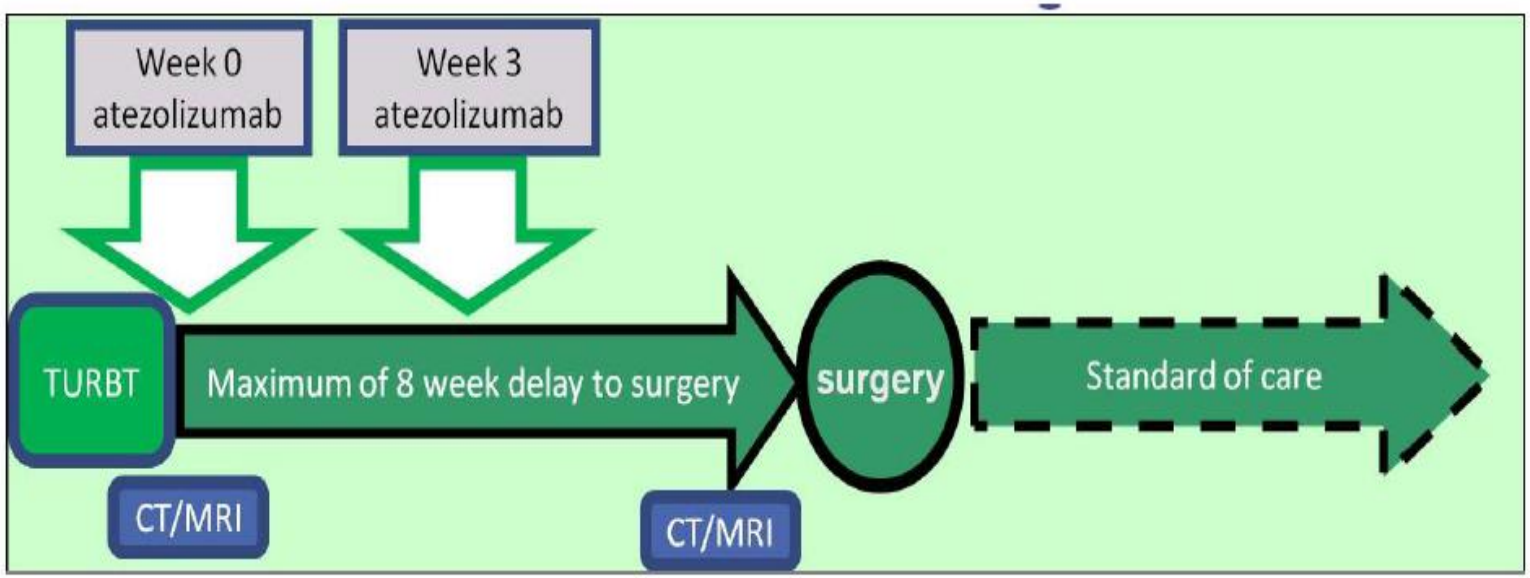
N=739

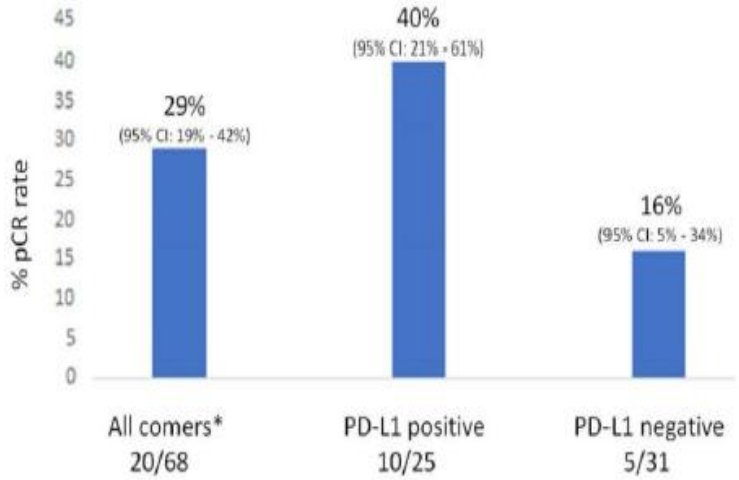
R → Pembrolizumab
R → Observation

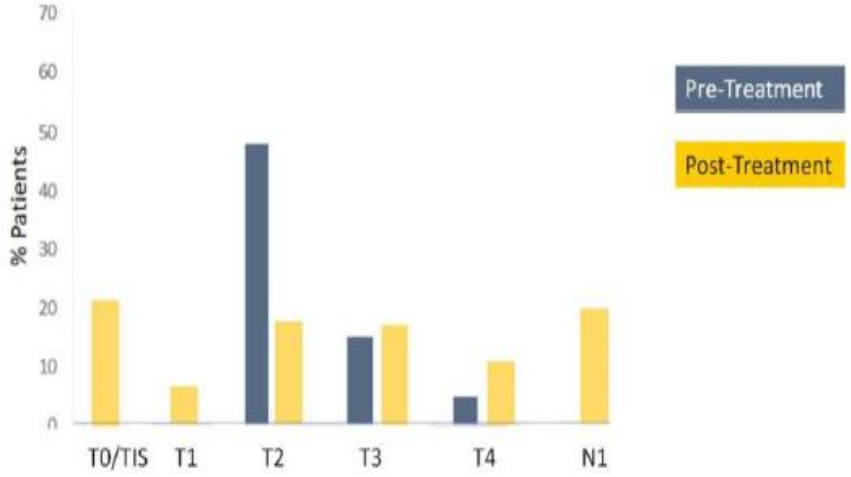
Co-primary endpoints: DFS and OS

ClinicalTrials.gov (NCT02632409 and NCT03244384)

Phase II neoadjuvant: ABACUS trial







Powles T, et al. ASCO 2018

Phase II neoadjuvant: PURE-01 trial

PURE-01 (NCT02736266): Neoadjuvant pembrolizumab before radical cystectomy for MIBC

- Fit and planned for cystectomy
- Predominant (i.e. 50% at least) UC histology
- cT≤3bN0 stage
- Residual disease after TURB (surgical opinion, cystoscopy or radiological presence)
- GFR ≥20 ml/min (Cockcroft – Gault formula)
- ECOG-PS 0-1

3×3 weekly cycles of pembrolizumab 200 mg IV

Additional DD-MVAC x 4 cycles in non-responding pts (investigator choice)

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

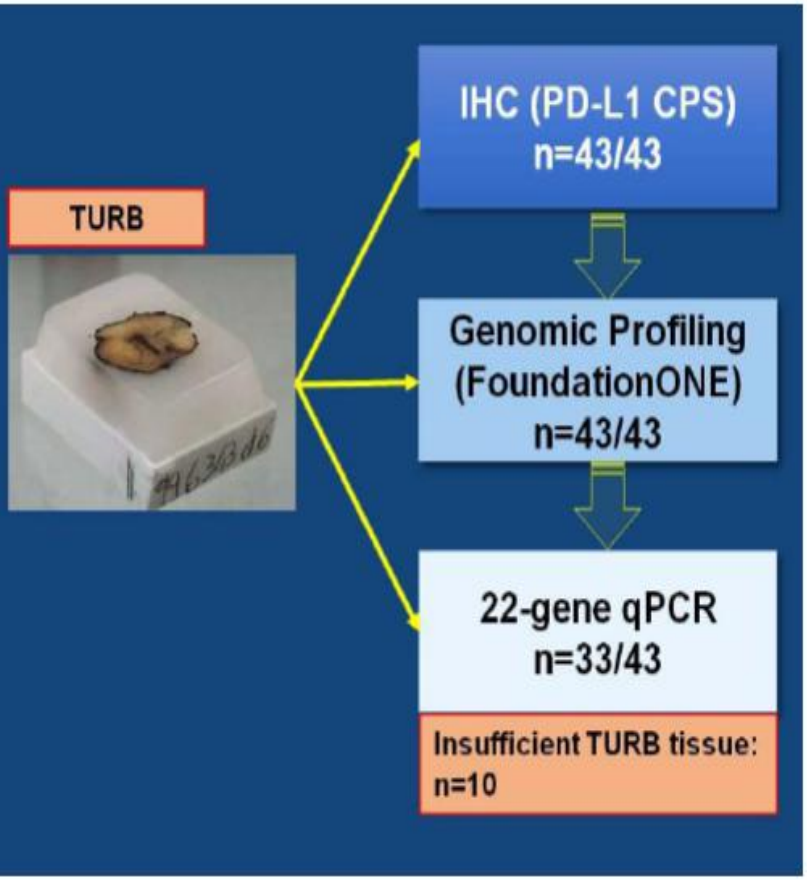
Pre-post treatment tissue/blood sample collection for biomarker analyses

Pre-post treatment imaging: multiparametric bladder MRI (mpMRI); ^{18}FDG-PET/CT scan, T/A CT scan

- Pathologic complete response (pT0) in ITT population is the primary endpoint
- The H_1 is pT0 ≥25% and H_0 pT0≤15%
- **71 pts** will be enrolled, with **43 pts** at first stage according to MinMax design
- pT0 limits for H0 rejection: **6 (1st stage); 14 (2nd stage)**
- 80% power and a one-sided test of significance at the 10% level
- Data cut-off: May 10th, 2018. Median Follow-up: 8 months

Pathologic response to pembrolizumab

	All treated patients N=43
Pathologic complete response, n (%), 95% CI	17 (39.5) 26.3–54.4
Secondary endpoint, n (%) Pathologic downstaging to pT<2	22 (51.2) (2 pTis; 2pTa; 1pT1)
Treatment failure, n (%)	
ypT2-4 ypN0	7 (16.3)
ypTany ypN+	9 (20.9)
"Clinical" failure (additional NAC*)	5 (11.6)
Clinical PD (RECIST v.1.1)	0 (-)



Powles T, et al. ASCO 2018

Current use of PD-L1/PD-1 inhibitors for metastatic urothelial cancer

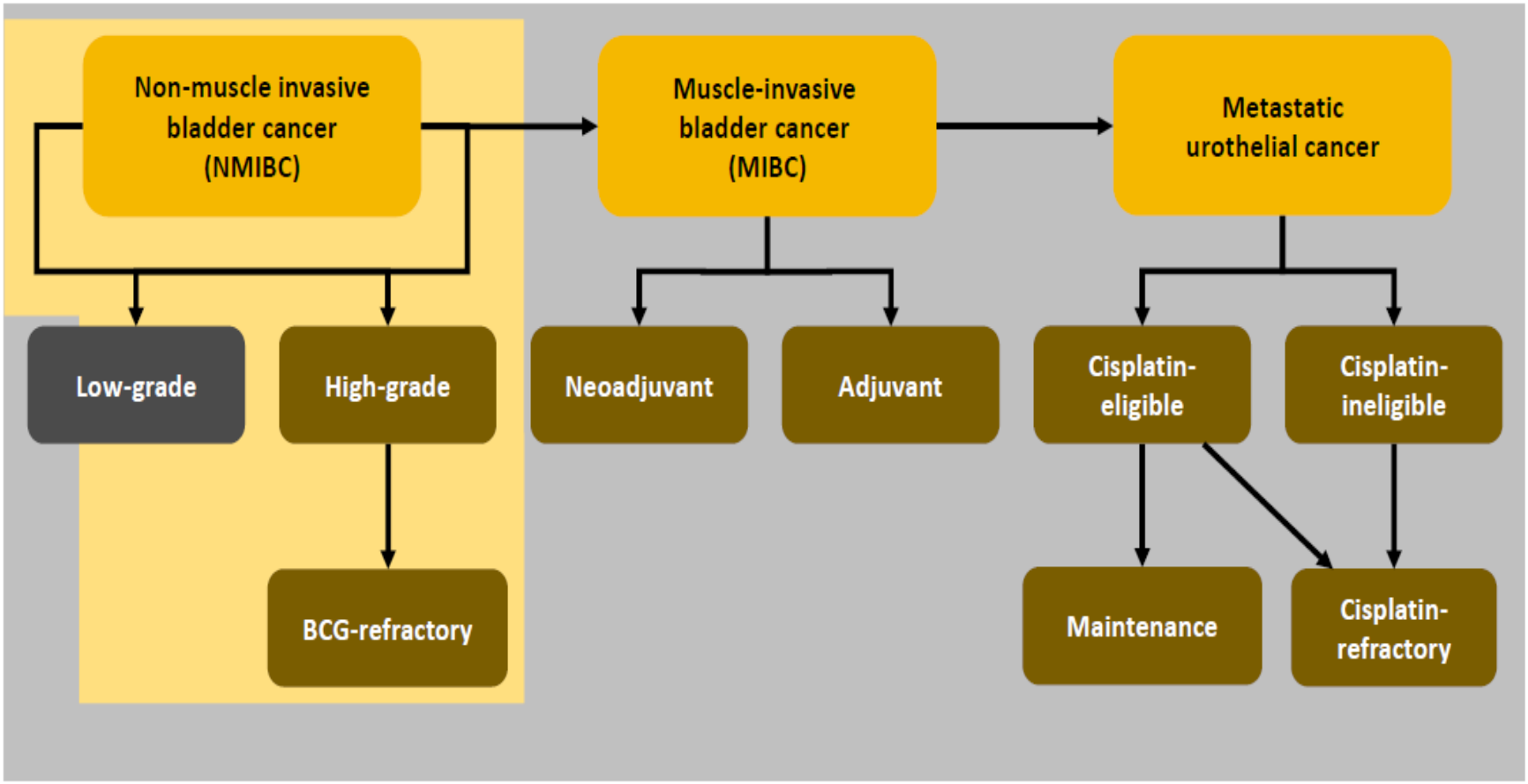


Figure adapted from Fakhrejahani et al. Curr Opin Urol 2015

Take home messages

- **Exciting times in the treatment of urothelial carcinoma**
- Immunotherapy is a well tolerated and active treatment for our patients
- However… **Only 15-20% of patients derive benefit** and many open questions remain with regards to understanding predicting factors
- Refining choices:
  - IO/IO
  - IO/Inmune based therapies (vaccines, APC; CAR-T cells, …)
  - IO + targeted agents (cabozantinib, FGFR inhibitors, …)
  - Combination/sequential use of chemo and XRT
  - Customized: biomarker/genomically driven design

Thank you for your attention