Immunotherapy in urothelial cancer

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FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

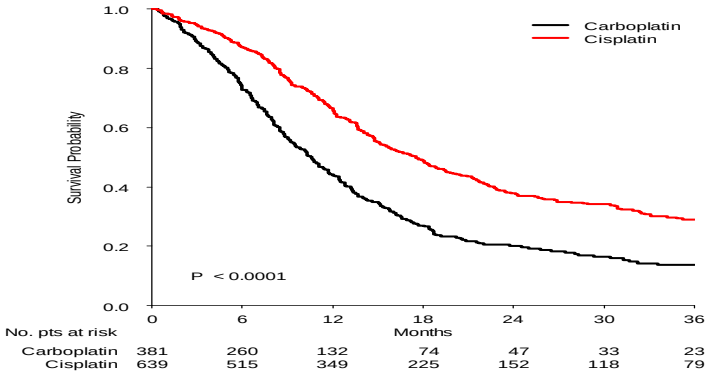
Advanced Urothelial Carcinoma Treatment

- First-line setting: standard is platinum-based chemotherapy, but long-term survival is poor
- Recurrent or progressive disease: no standard therapy
  - No therapies have demonstrated OS benefit over active comparator
  - Commonly used agents include taxanes, pemetrexed, and vinflunine
  - Clinical benefit is limited: the pooled median OS with single-agent chemotherapy was 6.9 months[1]
  - Significant toxicity profile

1. Raggi D et al. *Ann Oncol* 2016;27:49-61.

Outcome of different populations treated with different chemotherapy

(DD)MVAC or GEM-CIS +/- TXL	Vinflunine + GEM or CBDCA	GEM-CBDCA/MCaVI
PS 0-1, GFR: Good	**PS 0-1, GFR Poor**	**PS 2, GFR Poor**
ORR: 43-55%	ORR: 43-54%	ORR: 30-41%
mPFS: 7.6-8.3 months	mPFS: 5.9-6.1 months	mPFS: 4.2-5.8 months
mOS: 12.7-15.8 months	mOS: 12.8-14 months	mOS: 8.3-9.3 months



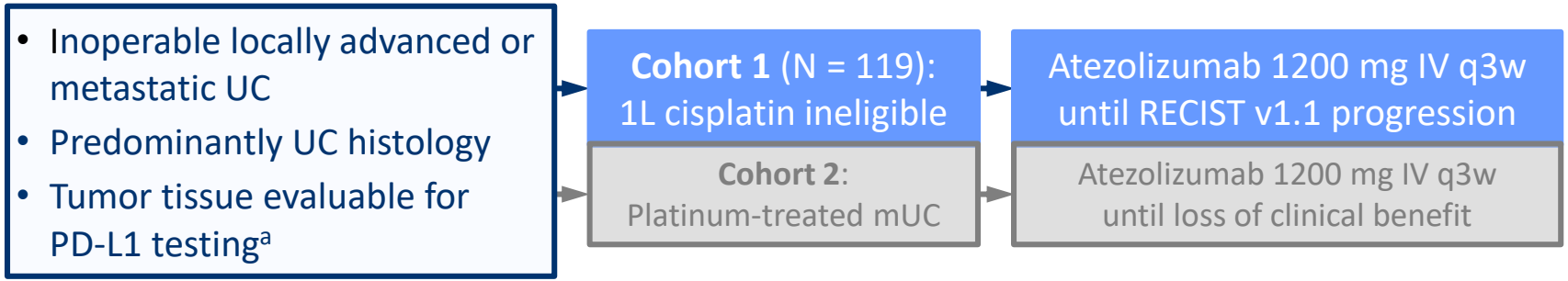
Necchi A et al, *Eur Urol* 2016

Immune checkpoint inhibitors in urothelial cancer

- Five checkpoint blockers have been approved in second line and first line CDDP ineligible:
  - Atezolizumab
  - Durvalumab (Europe)
  - Nivolumab (Europe)
  - Pembrolizumab (Europe)
  - Avelumab

- Approvals are not all based on randomized phase III trials. Indeed, they are based on large phase I trials in the US (Level III) .

Phase II IMvigor210 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

- Cohort 1–specific endpoints:
  - Primary: confirmed ORR per RECIST v1.1 (central IRF)
  - Key secondary: DOR, OS, safety

Balar AV et al, Lancet 2017

	Patients	Complete response	Partial response	Objective response, n (% [95% CI])*	Median duration of response (95% CI)
	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–NE)
IC1	48	4	6	10 (21% [10–35])	NE (NE–NE)
IC0	39	3	5	8 (21% [9–36])	NE (12·8–NE)

Data cutoff was July 4, 2016. PD-L1=programmed death-ligand 1. IC=tumour-infiltrating immune cell. NE=not estimable. *Includes objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (independent review facility).

***Table 2:* Objective response by PD-L1 status on tumour-infiltrating im**

N = 123 patients with previously untreated, CDDP UNFIT with inoperable advanced or metastatic UC
Median follow-up: 17.2 mos

ORR: 23%

- CR rate: 9%
- No difference by PD-L1 status

mOS: 15.9 mos

- Shorter in PD-L1 high vs low
- 57% alive at 12 mos

OS by PD-L1 Status

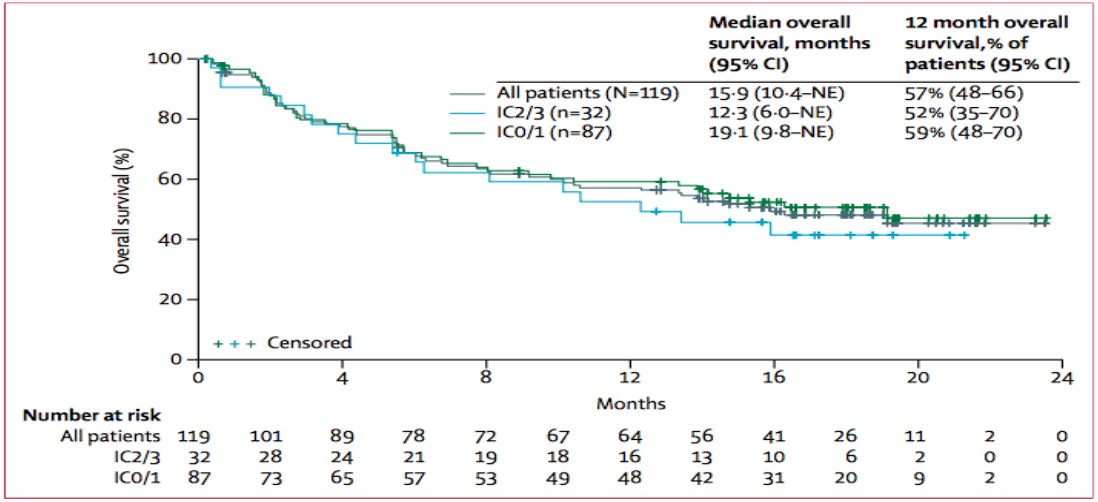
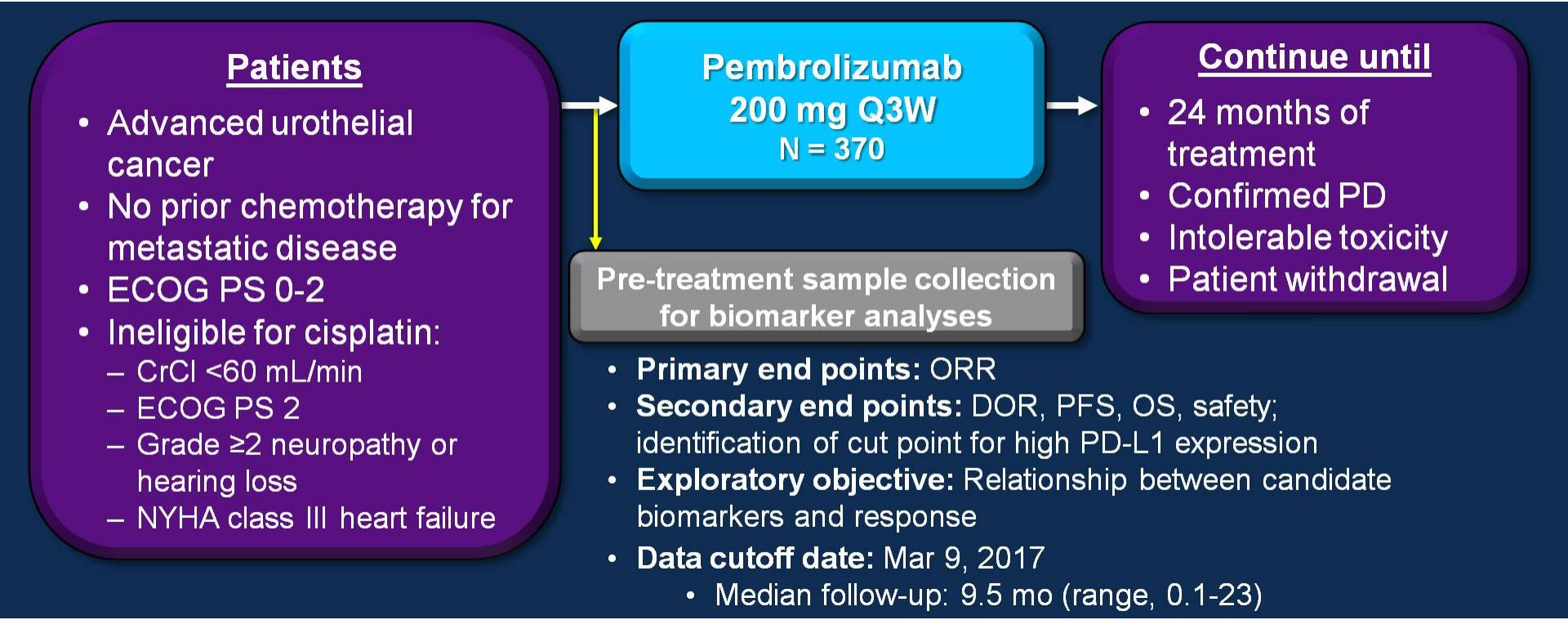


***Figure 3:* Overall survival in patients given atezolizumab according to PD-L1 status on immune cells**
A total of 59 events occurred in all patients by the data cutoff date (July 4, 2016; 18 in patients with IC2/3; 41 in patients with IC0/1). PD-L1=programmed death-ligand 1. NE=not estimable. IC=tumour-infiltrating immune cell.

Balar V., Lancet 2017; 389: 67–76

Phase 2 KEYNOTE-052 Study Design: Pembrolizumab as First-Line Therapy for Cisplatin-Ineligible Advanced/Metastatic Urothelial Cancer



Clinical Trials.gov NCT02335424

Confirmed Objective Response Rate

	Total Population N = 370		
	n	%	95% CI
Objective response rate	108	**29**	25-34
Complete response	27	7	5-10
Partial response	81	22	18-27
Stable disease	67	18	14-22
Progressive disease	155	42	37-47

With longer follow-up[a]:
- 5% increase in ORR
- 10 additional complete responses
- 9 additional partial responses

Data cutoff: March 9, 2017. Assessed per RECIST v1.1 by central imaging vendor review. An additional 31 patients had no pos... withdrawal of consent, loss to follow-up, or start of new anticancer therapy, and 9 patients had ≥1 postbaseline tu...

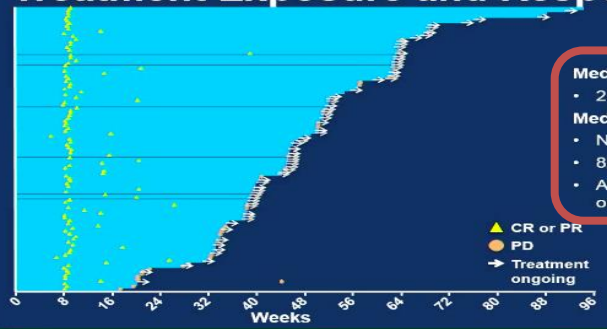
58% DECREASE IN TARGET LESIONS

Confirmed Objective Response Rate: Validation Set (CPS CUTPOINT PDL1 EXPRESSION)

	CPS <10% n = 185			CPS ≥10% n = 80		
	n	%	95% CI	n	%	95% CI
Objective response rate	42	**23**	17-29	41	**51**	40-63
Complete response	5	3	1-6	14	18	10-28
Partial response	37	20	15-27	27	34	24-45
Stable disease	35	19	14-25	15	19	11-29
Progressive disease	86	47	37-54	19	24	15-35

Data cutoff: March 9, 2017. ...patients had no postbaseline tumor assessment ...assessment, none of which were evaluable. For ...d not have a postbaseline imaging assessment.

Treatment Exposure and Response Duration[a]



Median time to response[a]
- 2 months (range, 1-9 months)

Median duration of response[a]
- Not reached (95% CI, 12 months-NR)[b]
- 82% of responses lasted ≥6 months[b]
- At data cutoff, 67% of responses were ongoing

Data cutoff: March 9, 2017. Median follow-up: 9.5 months (range, 0.1-23 months).
[a]Includes patients who achieved a confirmed PR or better per RECIST v1.1 by central imaging vendor review.
[b]Kaplan-Meier estimate.

Balar AV, et al. ASCO 2017.

Summary of the evidences with the use of ICI in first-line therapy

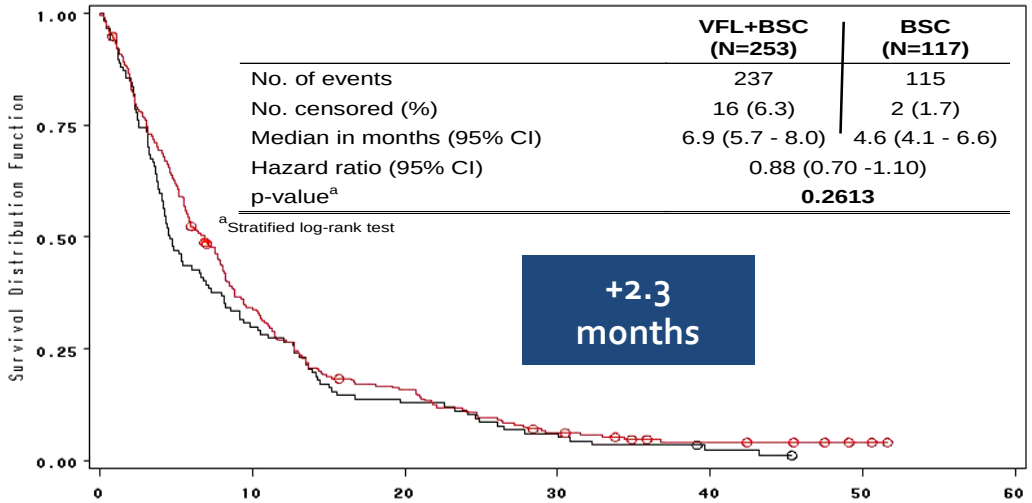
- Atezolizumab and pembrolizumab are well-tolerated and durable responses are seen in UC patients who are not eligible for cisplatin-based chemotherapy (**US-FDA & EMA Approved**). However randomised data on the benefit in this setting does not exist

- If clinical trials are not available and registration permits, treatment with atezolizumab or pembrolizumab could be considered for cisplatin-ineligible first-line patients

- In candidates for cisplatin-based therapy, there is currently no data to support use of checkpoint inhibitors as first-line treatment outside of clinical trials

- Currently, there is no evidence supporting the PD-L1 biomarker for selecting patients for ICI therapy in chemotherapy-naive patients

≥2L Immunotherapy options & The salvage therapy landscape



	VFL+BSC (N=253)	BSC (N=117)
No. of events	237	115
No. censored (%)	16 (6.3)	2 (1.7)
Median in months (95% CI)	6.9 (5.7 - 8.0)	4.6 (4.1 - 6.6)
Hazard ratio (95% CI)	0.88 (0.70 -1.10)	
p-value[a]	**0.2613**	

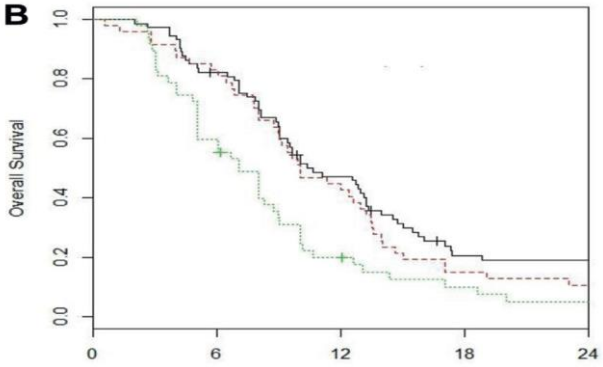
[a]Stratified log-rank test

+2.3 months

Bellmunt J et al, Ann Oncol 2013
Sonpavde G et al, J Urol 2015

Table 2. *Multivariate analysis of discovery set of 491 patients and validation set of 167*

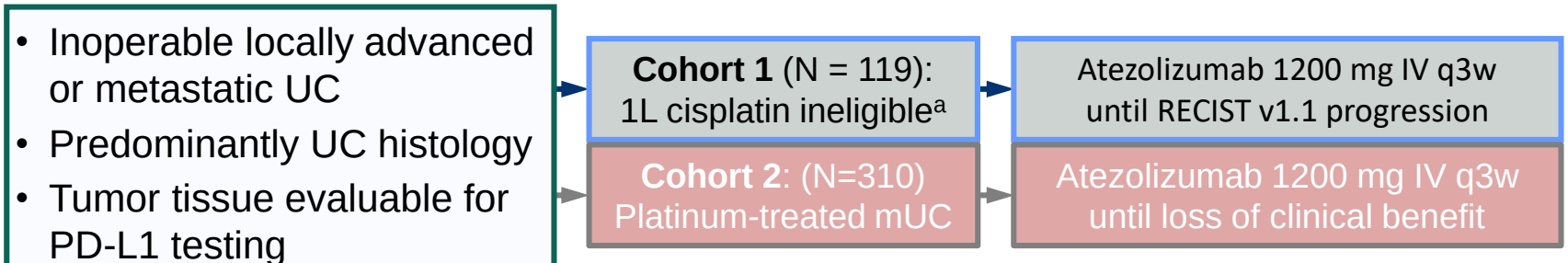
	Discovery*		Validation*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
TFPC less than 3 mos	1.49 (1.19—1.87)	<0.001	1.35 (0.87—2.08)	0.18
ECOG PS greater than 0	1.39 (1.16—1.67)	<0.001	1.58 (1.06—2.35)	0.023
LM	1.45 (1.16—1.81)	<0.001	1.26 (0.83—1.90)	0.27
Hb less than 10 gm/dl	1.73 (1.27—2.35)	<0.001	1.35 (0.94—1.96)	0.10
Albumin less than LLN	1.61 (1.20—2.15)	0.002	1.90 (1.27—2.85)	0.002



Mean c-index across bootstrap samples of 0.646

Phase 2 IMvigor210 Study Design: Atezolizumab for Advanced/Metastatic Urothelial Cancer (Second-Line)

- Single-arm phase II study with 2 cohorts[1,2]

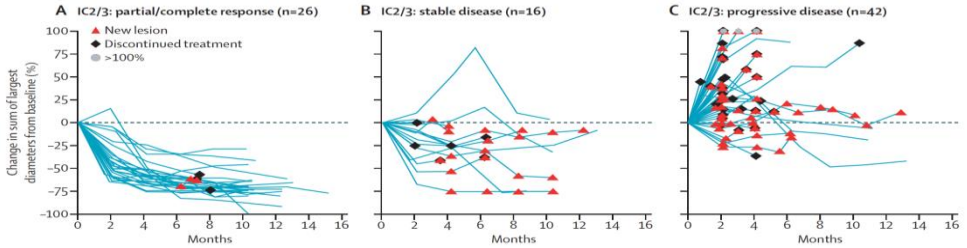


[a] ≥ 1 of the following: ECOG PS 2; grade ≥ 2 hearing loss or peripheral neuropathy; renal impairment ($eGFR_{CG}$: > 30, < 60 mL/min)

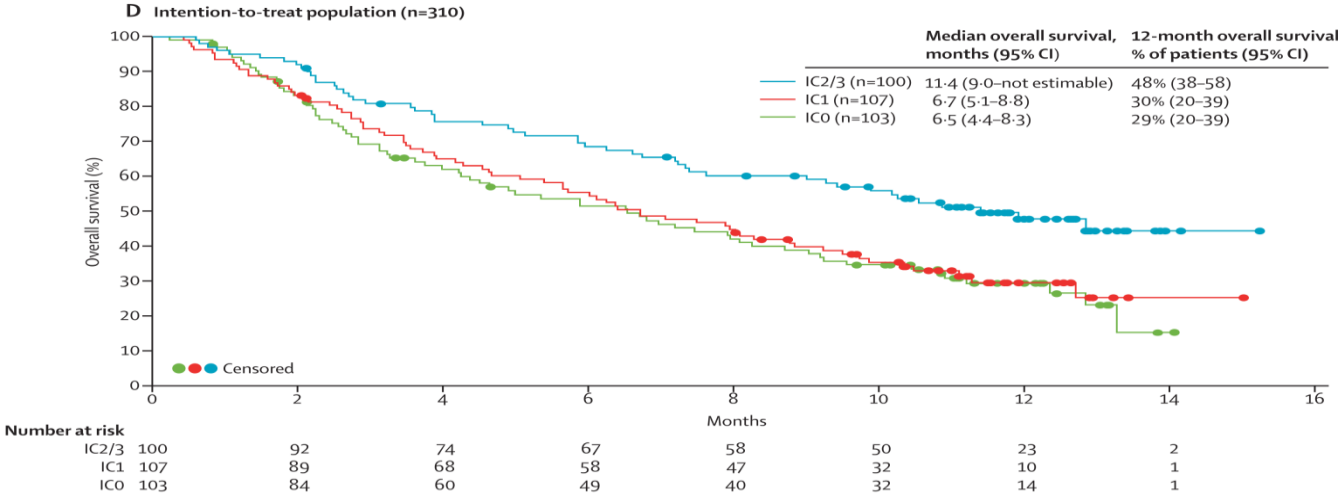
- **Cohort 2 study**
  - Co-primary endpoint: independent review facility-assessed ORR (RECIST v1.1) and the investigator-assessed ORR (immune-modified RECIST), analysed by ITT
  - Secondary endpoints included: DoR, PFS, OS, safety

1. Clinical Trials.gov NCT02951767
2. Clinical Trials.gov NCT02108652

Subgroup	n	Confirmed Responses Per IRF RECIST v1.1		
		ORR	95% CI	CR
IC2/3	100	26%	18, 36	11%
IC1/2/3	207	18%	13, 24	6%
IC1	107	10%	5, 18	2%
IC0	103	8%	3, 15	2%
All Patients	310	15%	11, 19	5%



mPFS (median follow up 11.7 mo)
2.1 mo (IC2/3, IC0/1, all) per IRF RECIST
4.0 mo (IC2/3), 2.2 mo (IC0/1), 2.7 mo (all) per mRECIST

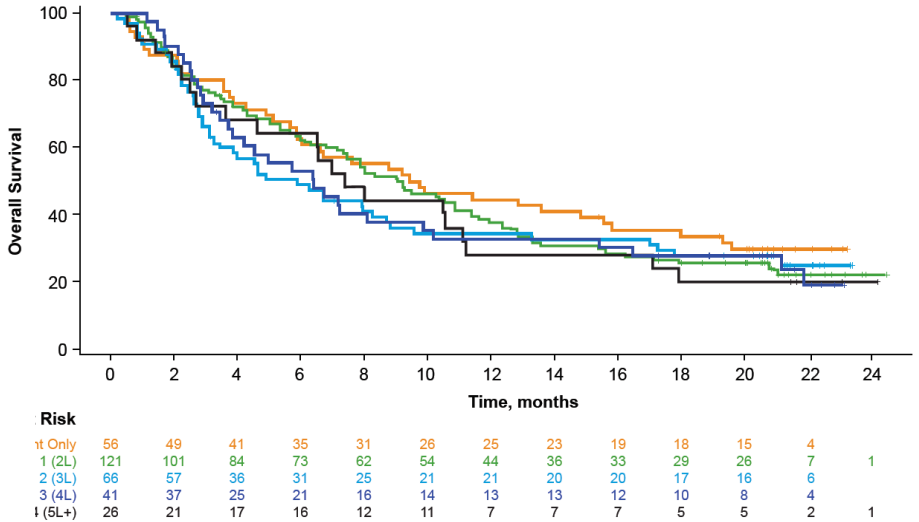


Rosenberg JE, et al. Lancet. 2016 May 7;387(10031):1909-20

IMvigor210: Atezolizumab in Platinum-Treated Locally Advanced or Metastatic Urothelial Carcinoma: Outcomes by Prior Number of Regimens

	Prior regimens for mUC					All Patients (*N* = 310) [a]
	0 (1L) (*n* = 56[f])	1 (2L) (*n* = 121)	2 (3L) (*n* = 66)	3 (4L) (*n* = 41)	≥4 (5L+) (*n* = 26)	
ORR, n(%) [a]	14 (25.0)	16 (13.2)	10 (15.2)	7 (17.1)	2 (7.7)	49 (15.8)
ORR 95% confidence interval	14.4–38.4	7.8–20.6	7.5–26.1	7.2–32.1	1.0–25.1	11.9–20.4
Response status, *n* (%) [b]						
CR	6 (10.7)	6 (5.0)	4 (6.1)	2 (4.9)	1 (3.8)	19 (6.1)
PR	8 (14.3)	10 (8.3)	6 (9.1)	5 (12.2)	1 (3.8)	30 (9.7)
SD	10 (17.9)	24 (19.8)	13 (19.7)	7 (17.1)	4 (15.4)	58 (18.7)
PD	26 (46.4)	63 (52.1)	32 (48.5)	20 (48.8)	16 (61.5)	157 (50.6)
Ongoing responses, *n* (%) [c]	7 (50.0)	9 (56.3)	8 (80.0)	6 (85.7)	2 (100.0)	32 (65.3)
Median DOR, mo [d]	16.0	not reached	not reached	not reached	not reached	not reached
DOR range [e]	2.9+–19.5+	4.2–19.4+	4.7–21.8+	2.1+–19.6+	17.6+– 22.6+	2.1+–22.6+

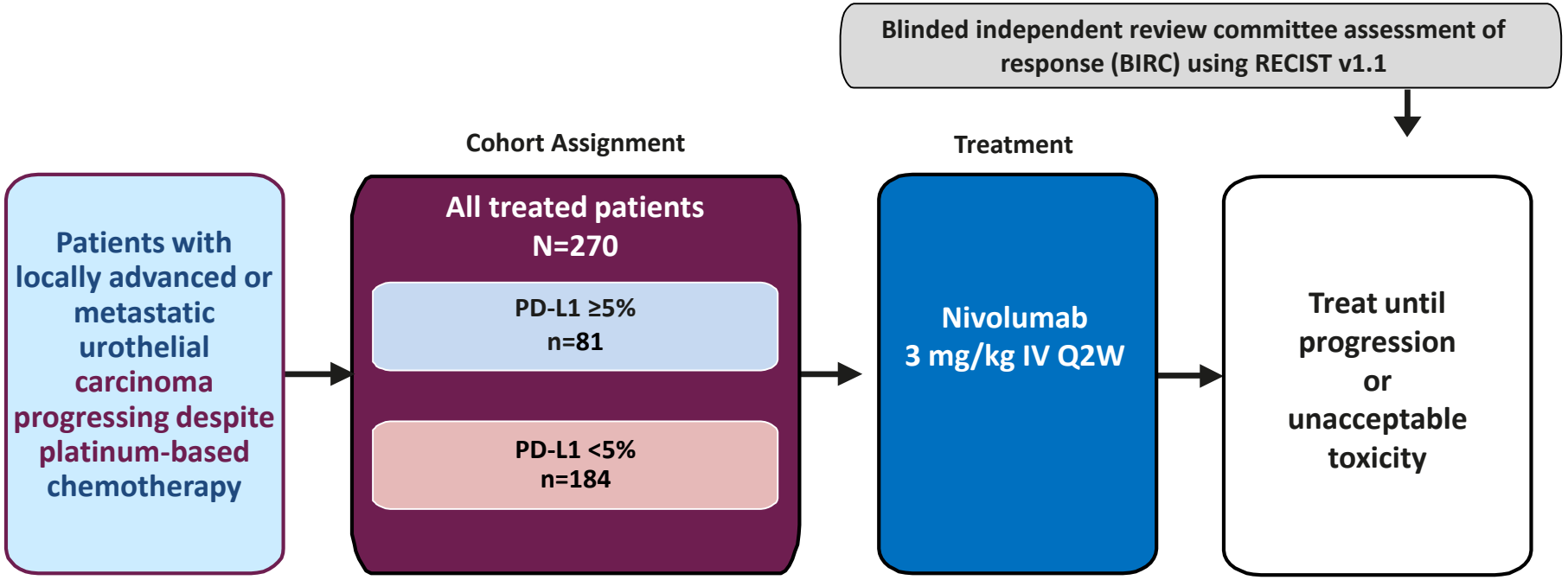
	Prior Regimens for mUC					All Patients (*N* = 310)
	0 (1L) (*n* = 56)	1 (2L) (*n* = 121)	2 (3L) (*n* = 66)	3 (4L) (*n* = 41)	≥4 (5L+) (*n* = 26)	
Median OS, mo	9.6	9.0	5.9	6.4	7.4	7.9
95% CI	5.9–15.8	7.3–11.3	3.3–8.7	3.8–10.2	4.6–11.2	6.7–9.3
12-mo OS rate, %	45	38	34	33	28	37
95% CI	32–58	29–47	23–46	18–47	10–46	31–42
18-mo OS rate, %	34	26	28	28	20	27
95% CI	21–46	18–34	17–39	14–42	4–36	22–32
OS events, n (%)	39 (70)	89 (74)	47 (71)	31 (76)	20 (77)	226 (73)



Perez-Gracia JL, et al. J Clin Oncol 35, 2017 (suppl 6S; abstract 323)

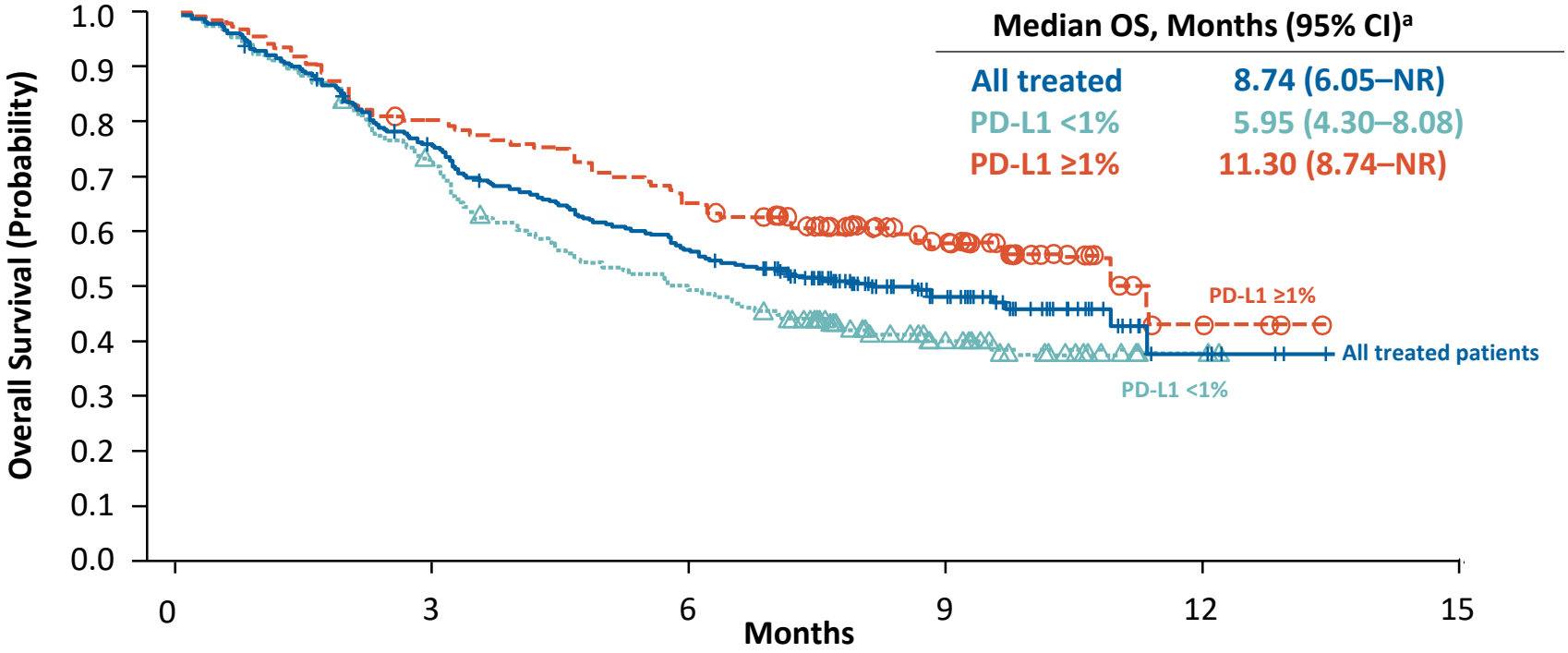
CheckMate 275: Study design

Open-label, single-arm, phase II study



Sharma P et al, Lancet Oncol. 2017 Mar;18(3):312-322

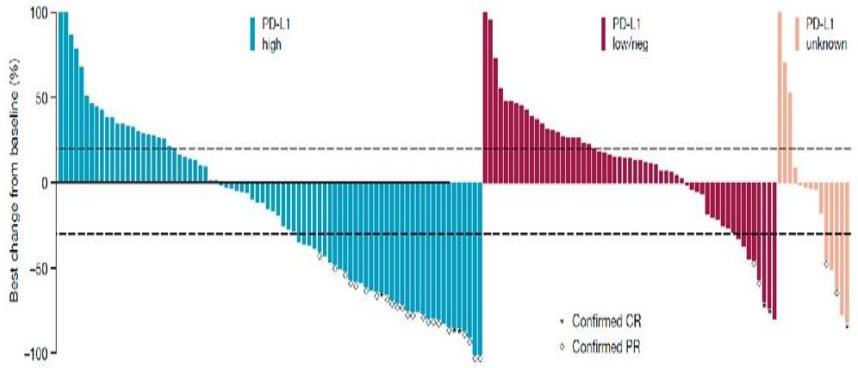
Overall survival

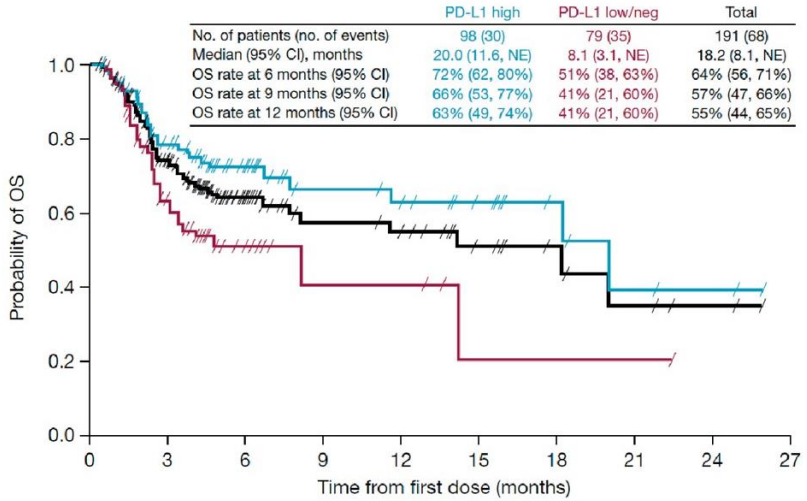


Sharma P et al, Lancet Oncol. 2017 Mar;18(3):312-322

Updated Durvalumab results from MEDI1108 trial

Parameter*	All UC			≥2L post-platinum UC§		
	Total†	PD-L1 high‡	PD-L1 low/ negative‡	Total	PD-L1 high‡	PD-L1 low/ negative‡
	N=191	N=98	N=79	N=182	N=95	N=73
Confirmed ORR, n (%) (95% CI)	34 (17.8) (12.7, 24.0)	27 (27.6) (19.0, 37.5)	4 (5.1) (1.4, 12.5)	32 (17.6) (12.3, 23.9)	26 (27.4) (18.7, 37.5)	3 (4.1) (0.9, 11.5)
CR	7 (3.7)	4 (4.1)	2 (2.5)	6 (3.3)	4 (4.2)	1 (1.4)
PR	27 (14.1)	23 (23.5)	2 (2.5)	26 (14.3)	22 (23.2)	2 (2.7)
Non-evaluable¶	33 (17.3)	11 (11.2)	22 (27.8)	31 (17.0)	11 (11.6)	20 (27.4)
Responses ongoing at time of DCO	26 (76.5)	20 (74.1)	3 (75.0)	24 (75.0)	19 (73.1)	2 (66.7)



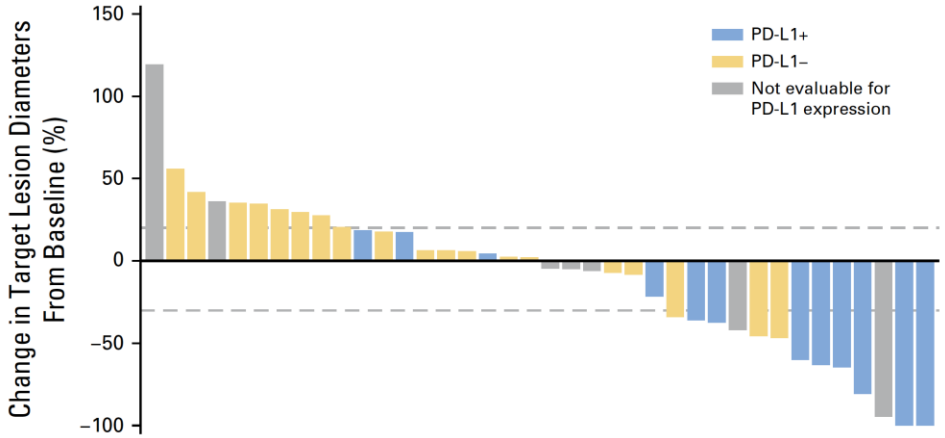


Hahn NM, et al. J Clin Oncol 35, 2017 (suppl; abstr 4525)

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

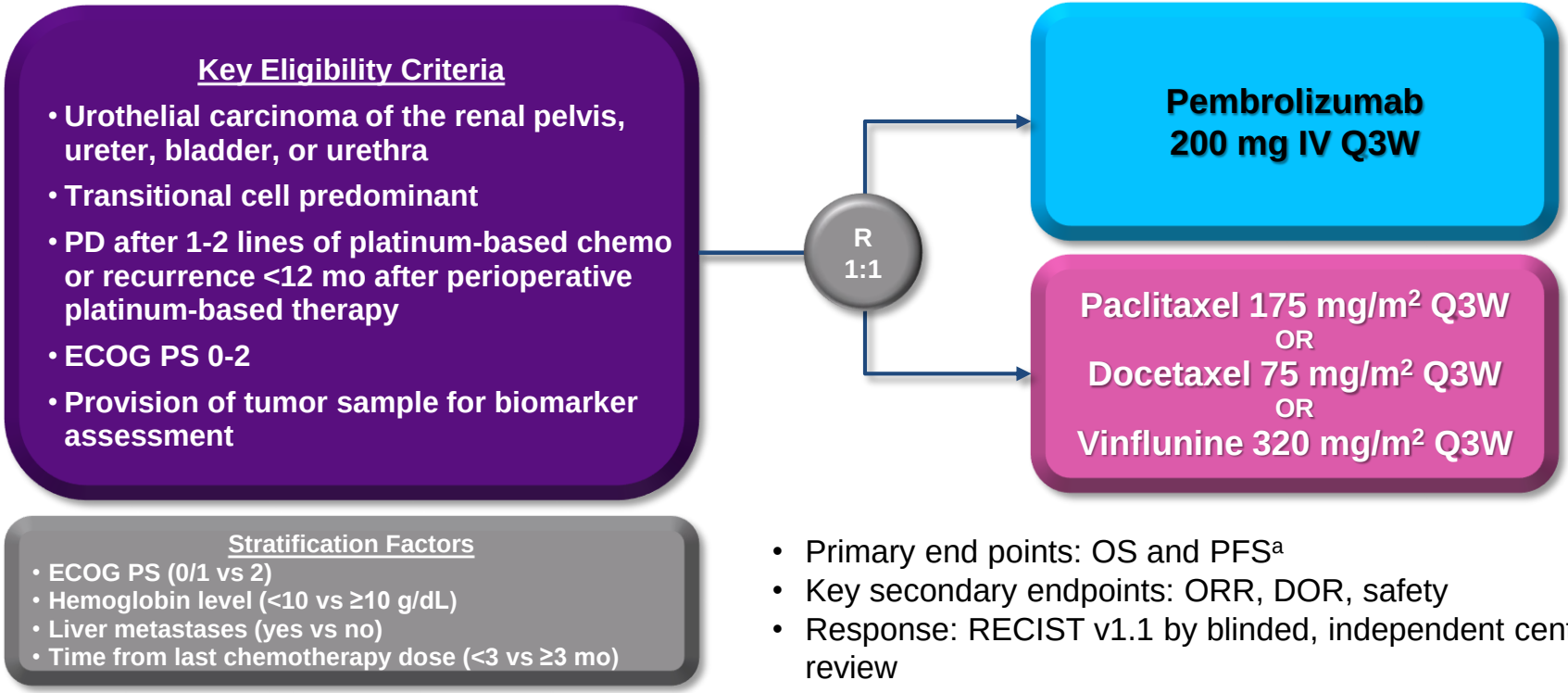
Avelumab, an Anti–Programmed Death-Ligand 1 Antibody, In Patients With Refractory Metastatic Urothelial Carcinoma: Results From a Multicenter, Phase Ib Study

Clinical Activity End Point	Avelumab (N = 44), No. (%)
Confirmed best response, no. (%)	
Complete response	5 (11.4)
Partial response	3 (6.8)
Stable disease	15 (34.1)
Progressive disease	15 (34.1)
Nonevaluable*	6 (13.6)
Confirmed ORR, % (95% CI)	18.2 (8.2 to 32.7)
Disease control rate, %	52.3
Median PFS, weeks (95% CI)	11.6 (6.1 to 17.4)
PFS rate at 48 weeks, % (95% CI)	19.1 (8.5 to 32.8)
Median OS, months (95% CI)	13.7 (8.5 to ne)
OS rate at 12 months, % (95% CI)	54.3 (37.9 to 68.1)



Apolo AB, J Clin Oncol 2017 (ePub ahead of print)

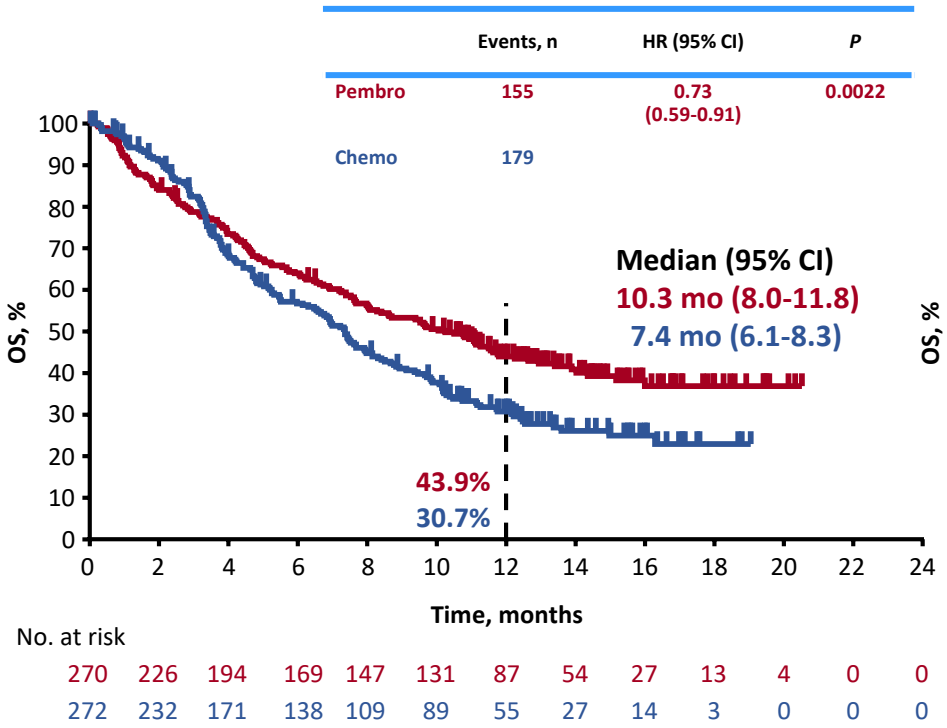
KEYNOTE-045 Study Design (NCT02256436)



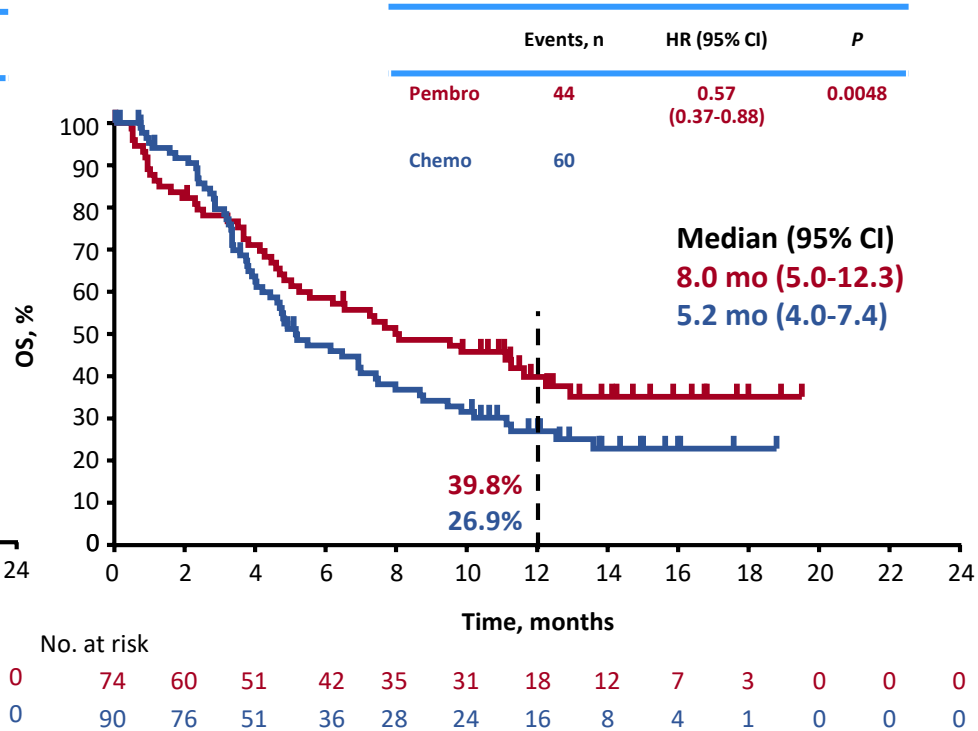
- Primary end points: OS and PFS[a]
- Key secondary endpoints: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review

[a]In total ITT population and in patients with CPS ≥10%.

Overall Survival



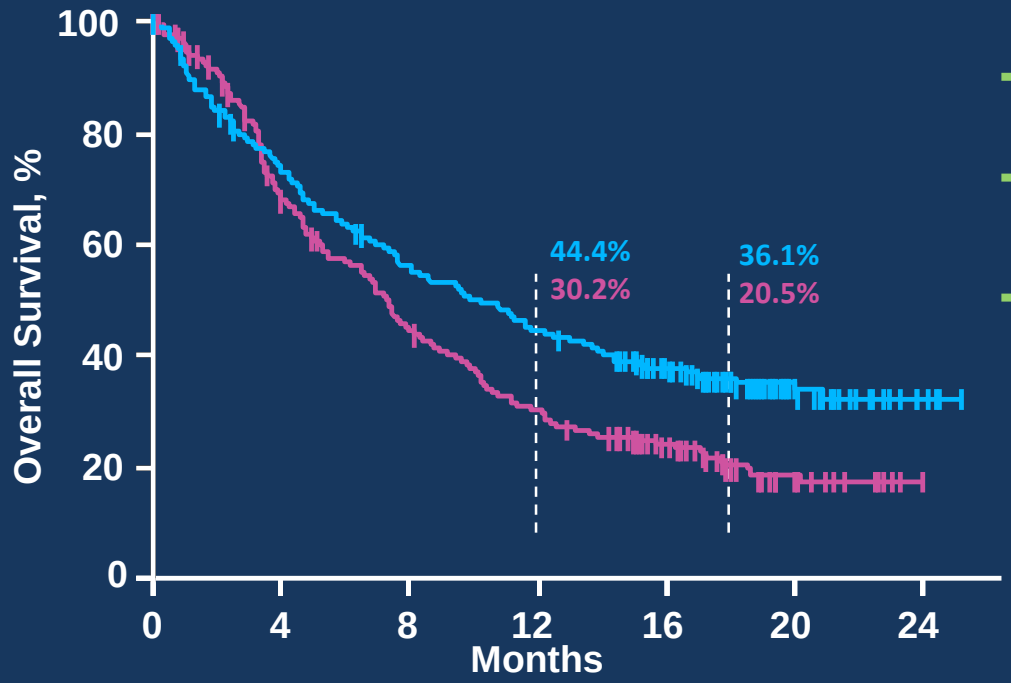
Total Population



CPS ≥10% Population

Data cutoff date: Sep 7, 2016.

Updated Overall Survival: Total



	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	170	0.70 (0.57-0.86)	0.0004
Chemo	196		

Median (95% CI):
10.3 mo (8.0-12.3)
7.4 mo (6.1-8.1)

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0/1 v 2), liver metastases (yes v no), hemoglobin (<10 v ≥10 g/dL), time from completion of chemotherapy (<3 v ≥3 mo).
[b]One-sided p-value based on stratified log-rank test.
Data cutoff date: Jan 18, 2017.

Bajorin DF, et al. J Clin Oncol 35, 2017 (suppl; abstr 4501)

Health-Related Quality of Life of Pembrolizumab vs Chemotherapy for Previously Treated Advanced Urothelial Cancer in KEYNOTE-045

R. de Wit[1]; D.F. Bajorin[2]; J. Bellmunt[3]; Y. Fradet[4]; J.L. Lee[5]; L. Fong[6]; N.J. Vogelzang[7]; M.A. Climent[8]; D.P. Petrylak[9]; T.K. Choueiri[3]; A. Necchi[10]; W. Gerritsen[11]; H. Gurney[12]; D.I. Quinn[13]; S. Culine[14]; C.N. Sternberg[15]; Y. Mai[16]; H. Li[16]; R.F. Perini[16]; D.J. Vaughn[17]

[1]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]CHU de Québec-Université Laval, Québec, QC, Canada; [5]Asan Medical Center and University of Ulsan College of Medicine, Seoul, South Korea; [6]University of California, San Francisco, San Francisco, CA, USA; [7]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [8]Fundación Instituto Valenciano de Oncología, Valencia, Spain; [9]Smilow Cancer Hospital at Yale University, New Haven, CT, USA; [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [11]Radboud University Medical Center, Nijmegen, Netherlands; [12]Westmead Hospital and Macquarie University, Sydney, NSW, Australia; [13]University of Southern California Norris Comprehensive Cancer Center and Hospital, Los Angeles, CA, USA; [14]Hôpital Saint-Louis, Paris, France; [15]San Camillo and Forlanini Hospitals, Rome, Italy; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA

Figure 2. Kaplan-Meier Sstimates of Time to Deterioration in the EORTC QLQ-C30 Global Health Status/QoL Score

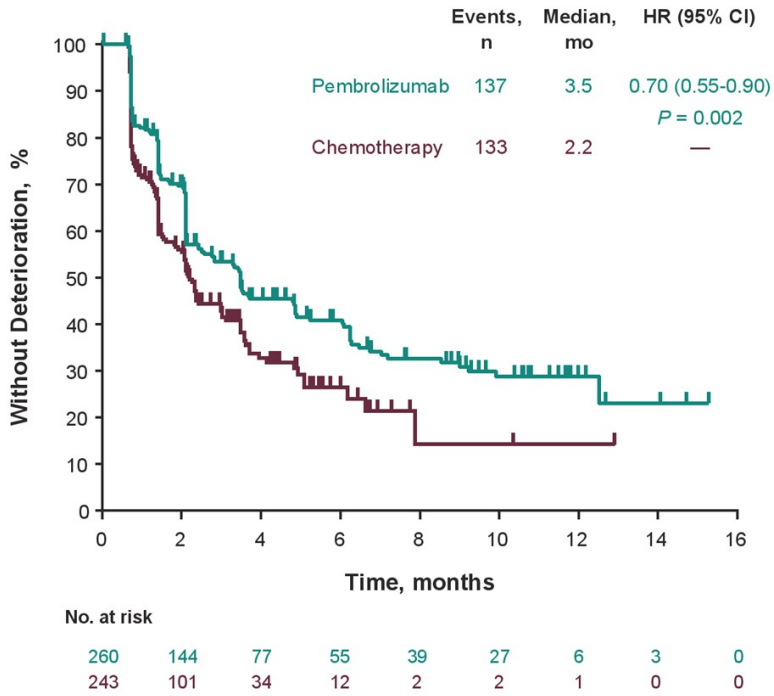
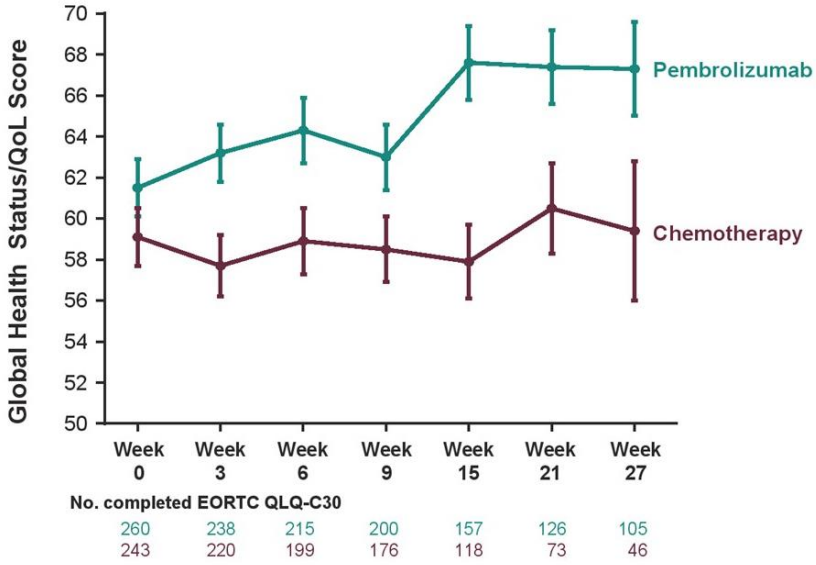
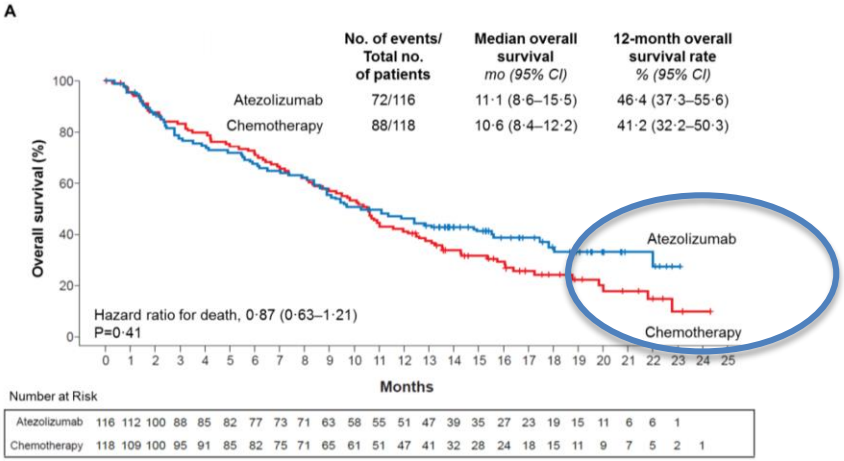


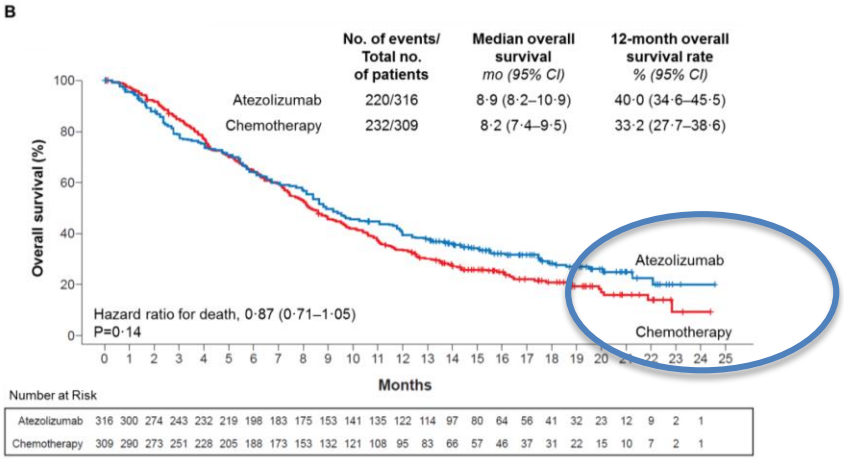
Figure 1. EORTC QLQ-C30 Global Health Status/QoL Score by Visit

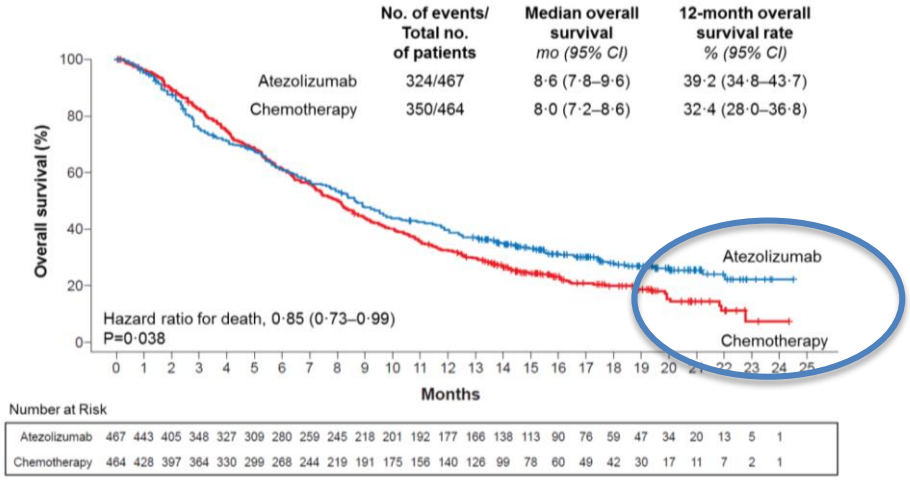


de Wit R, et al. J Clin Oncol 35, 2017 (suppl; abstr 4530)

Outcomes of IMvigor211 - Efficacy





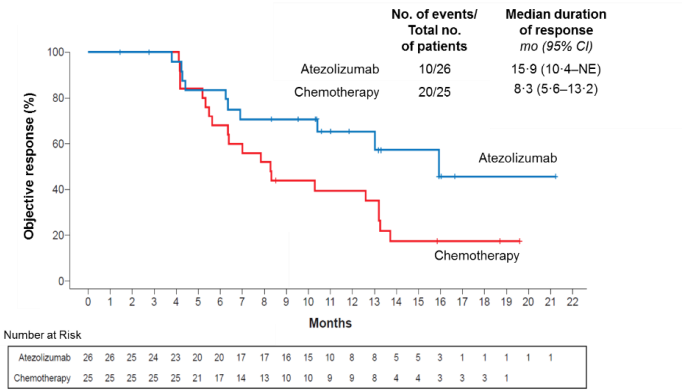


US FDA and EMA approval for platinum-treated, advanced UC

Powles T. et al, EACR/AACR/SIC 2017

Outcomes of IMvigor211 – Kaplan-Meier Analysis of Duration of Response

A



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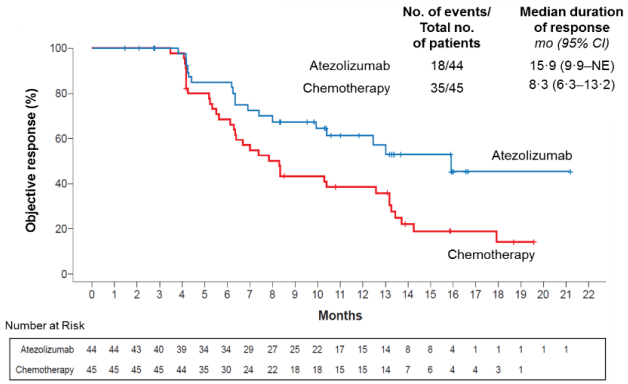

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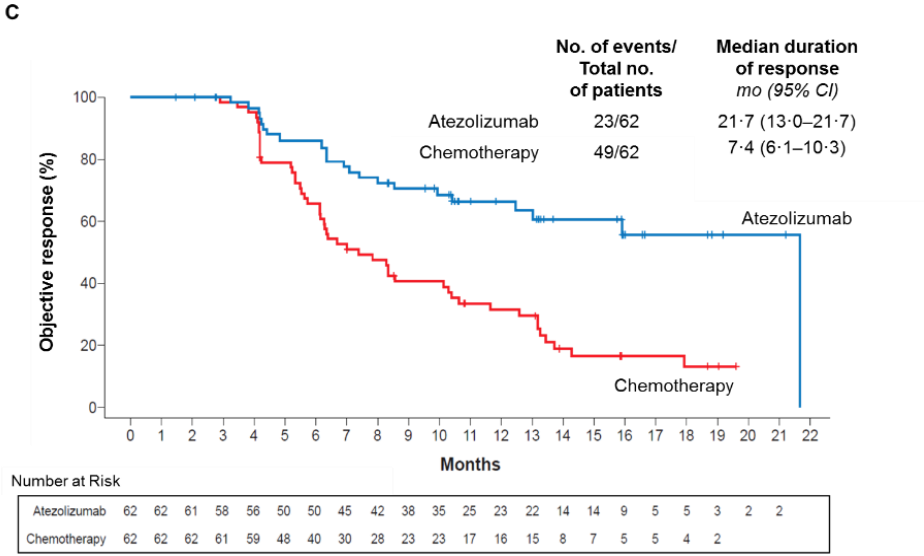


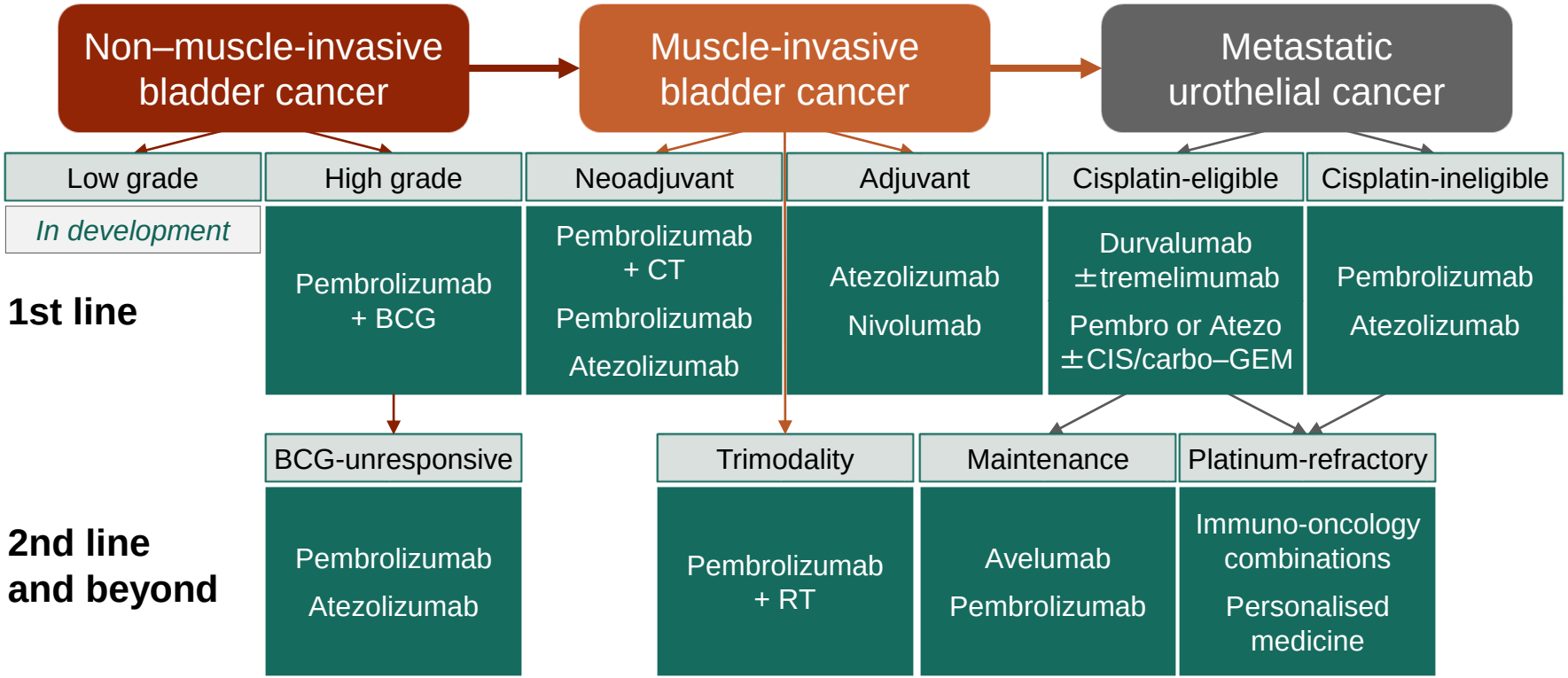
Median follow-up duration for ITT patients: 17.3 months

Powles T. et al, EACR/AACR/SIC 2017

Comparison of main outcomes from the Phase 3 trials

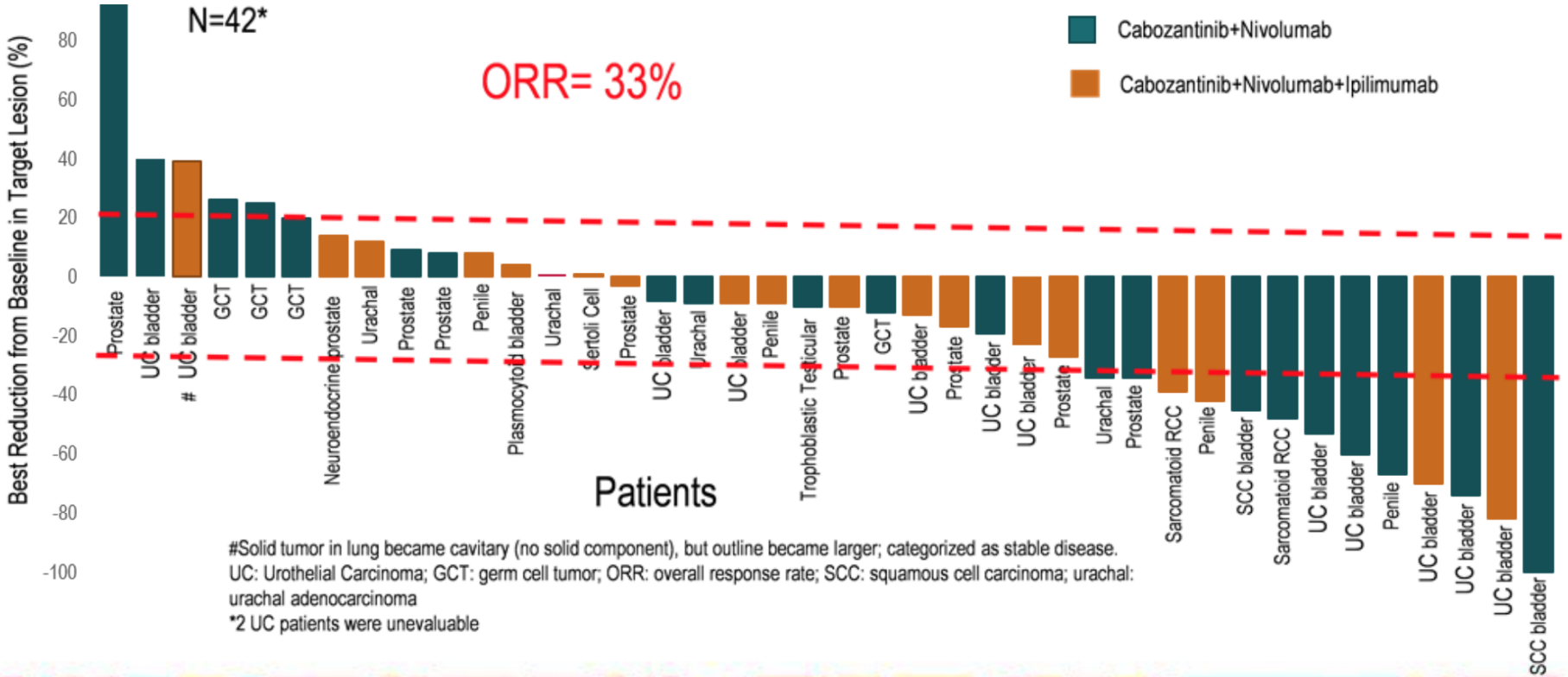
	IMVIGOR211	KEYNOTE45
Study drug	atezolizumab	pembrolizumab
Number of patients receiving study drug	467	270
PS 2	0	1%
Bladder primary	69%	86%
Liver metastasis	30%	34%
Patients with 2 or more risk factors	23%	41%
Visceral metastasis	77%	89%
2 or more previous lines of therapy	19%	20%
Vinflunine use in control arm	54%	34%
PD-L1 positive patients	25%	40%
Response rate in ITT	13%	21%
OS is PD-L1 positives	0.87 (95%CI: 0.63-1.21)	0.59 (95%CI: 0.37-0.88)
Response rates in PD-L1 positives	23%	22%
Overall survival in all comers	0.85 (95% CI: 0.73-0.99)	0.73 (95%CI: 0.59-0.91)
Median DOR (ITT, months, 95%CI)	21.7 (13.0-21.7)	NR (1.6-20.7)
Median Follow-up (ITT, months)	17.3	18.5

Future Development of PD-L1/PD-1 Inhibitors in Bladder Cancer



CT: chemotherapy; RT: radiotherapy.

Cabozantinib + Nivolumab +/- Ipilimumab
Best Target Lesions Reduction



#Solid tumor in lung became cavitary (no solid component), but outline became larger; categorized as stable disease.
UC: Urothelial Carcinoma; GCT: germ cell tumor; ORR: overall response rate; SCC: squamous cell carcinoma; urachal: urachal adenocarcinoma
*2 UC patients were unevaluable

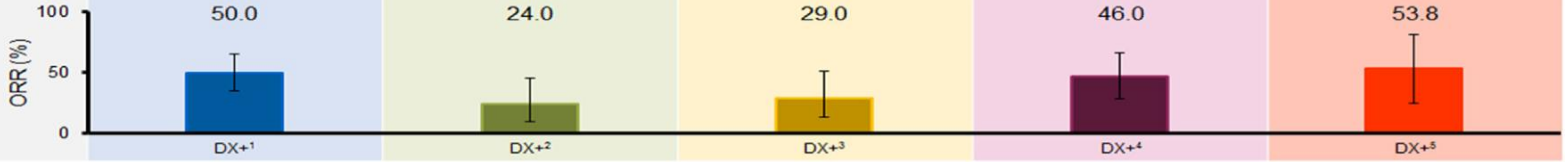
Nadal R. et al. ESMO 2017

Summary

- Studies with single-agent immunotherapy targeting the PD-1/PD-L1 axis have shown promise in patients with metastatic and chemotherapy-treated UBC
- Several agents now FDA-approved in UBC and nivolumab is EMA-approved
- Combination immunotherapy may result in further survival benefits over single-agent anti–PD-1/PD-L1, **but** toxicity is still a concern
- Biomarker (PD-L1) use for patient selection remains a matter of debate
- Clinical trials in early-stage disease may help to reinvigorate collaboration between urologists and medical oncologists

Biomarker Discovery for Immunotherapy and New Concepts for Clinical Management
The PD-L1 case

	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Durvalumab[4]	Avelumab[5]
Detection antibody	SP142	28-8	22C3	SP263	73-10
IHC platform	Ventana	Dako	Dako	Ventana	Dako
Cell types scored for urothelial cancer	IC and TC	TC	TC	IC and TC	IC and TC
Cut-off definitions for urothelial cancer	PD-L1+ (IHC 2/3) as ≥5% of ICs PD-L1+	PD-L1+ ≥1% TC expression	PD-L1+ ≥1% TC staining	PD-L1+ as ≥25% of ICs and TCs with membrane PD-L1 staining	PD-L1+ as ≥5% TC staining or ≥10% IC staining
Estimated PD-L1 prevalence in urothelial cancer trials	~32[1]	~37[2]	~62%[3]	~65%[4]	~36%[5]
PD-L1+ ORR (phase I trials)	50.0	24.0	29.0	46.0	53.8

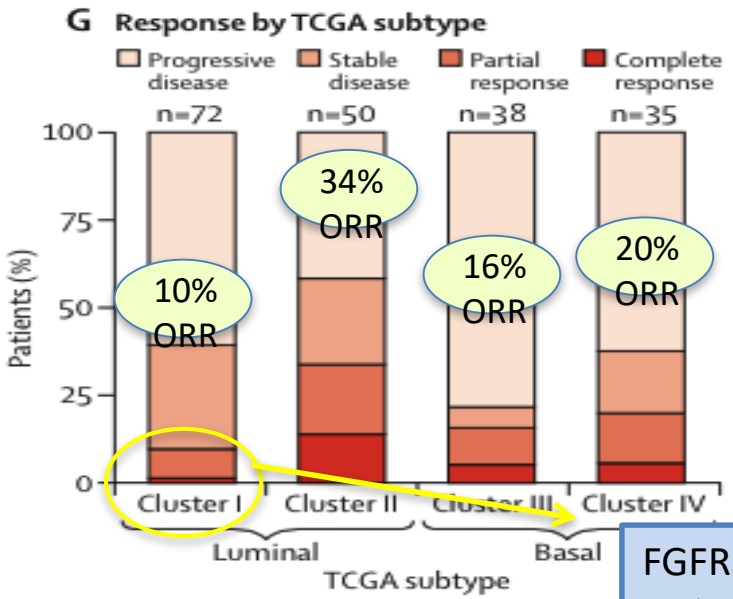


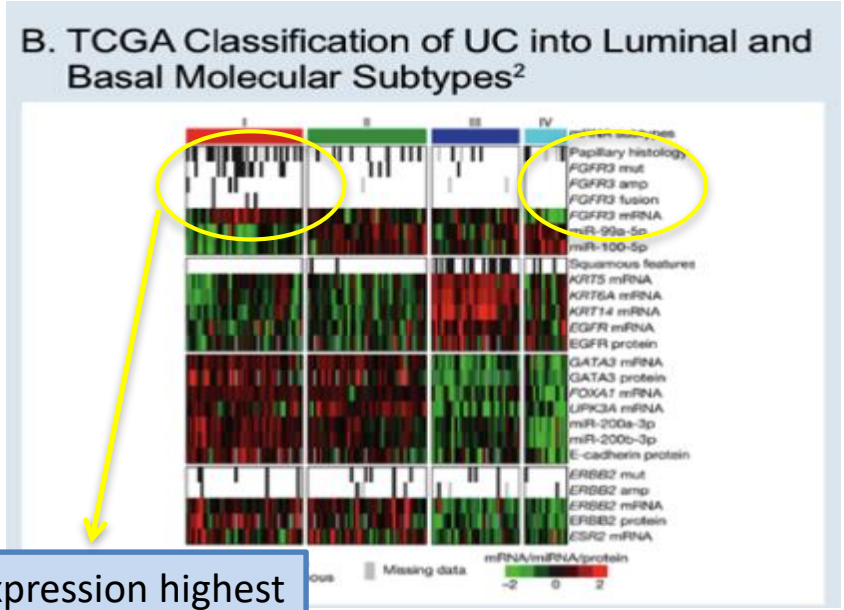
1. Loriot et al. ESMO 2016; 2. Sharma et al. ASCO 2016; 3. Plimack et al. ASCO 2015
4. Massard et al. ASCO 2016; 5. Apolo et al. ASCO 2016

Powles T, Smith K, Stenzl A, Bedke J. Eur Urol 2017 (in press)

Further Clinical Evidence that Combining B-701 and Checkpoint Inhibitor May Provide Benefit

Atezo Ph2 Data Shows Atezo Non-Responders in "Immune desert" with High FGFR3 Expressions



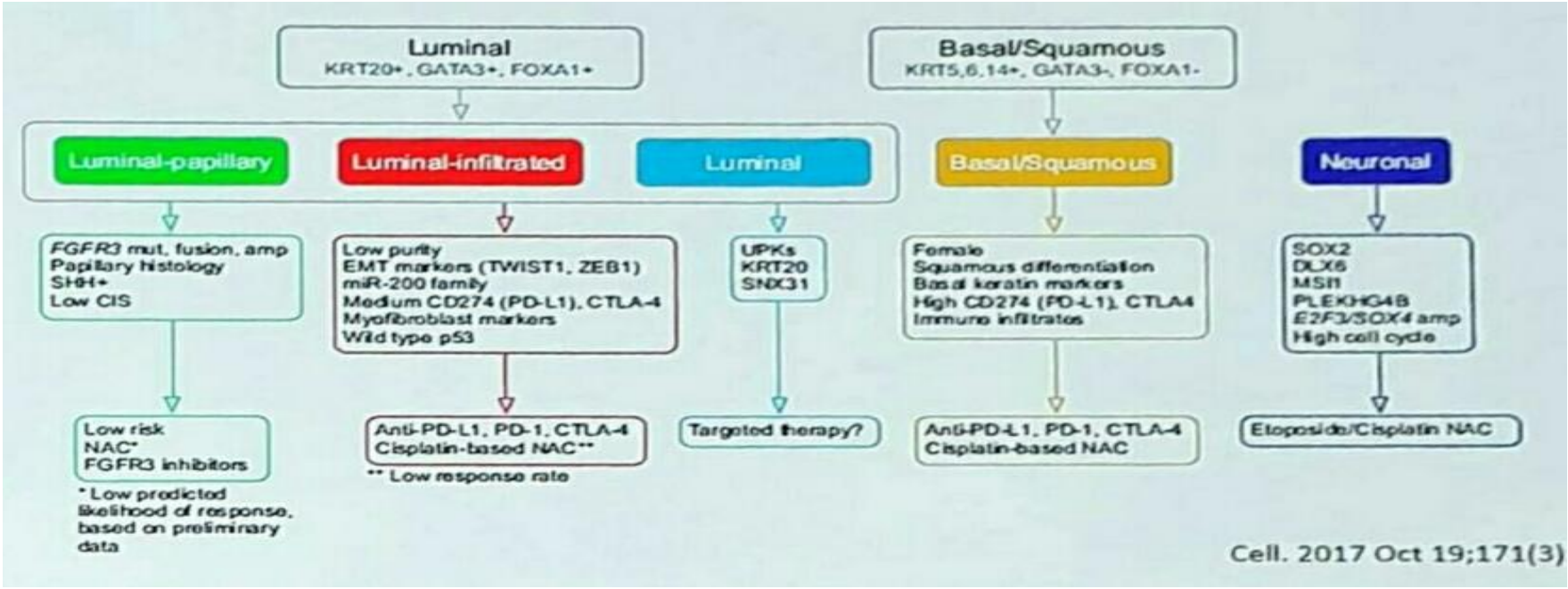


FGFR3 expression highest in Luminal Cluster I, where responses to Atezo is 10%

Rosenberg J et al. Lancet, 2016
Rosenberg J et al. ASCO 2016

J Powles, SITC 30th Annual Meeting 2015 Poster

Predictive biomarkers of response to anti-PD-1/PD-L1



Future Treatment Paradigm for MIBC?

Expression-Based, Subtype-Stratified Therapeutic Approach

- Required to facilitate appropriate patient selection for treatment.
- PD-L1 staining by immunohistochemistry cannot reliably predict outcomes in UC (Grade C): available data are conflicting (Level III).
- Bladder cancer has the third-highest mutational load among solid tumors.

Treatment algorithm (2017-18)

SCENARIO 1

Patient platinum unfit

IMMUNO CHECK POINT INHIBITOR (pembrolizumab, atezolizumab) → CBCDA/GEM → VINFLUVINA/TAXANO

SCENARIO 2

Patient fit

CIS/GEM MVAC → Atezolizumab Nivolumab Durvalumab Avelumab Pembrolizumab → VINFLUVINA/TAXANO

GU team INT Milan