Metastatic Bladder Cancer: Immunotherapy

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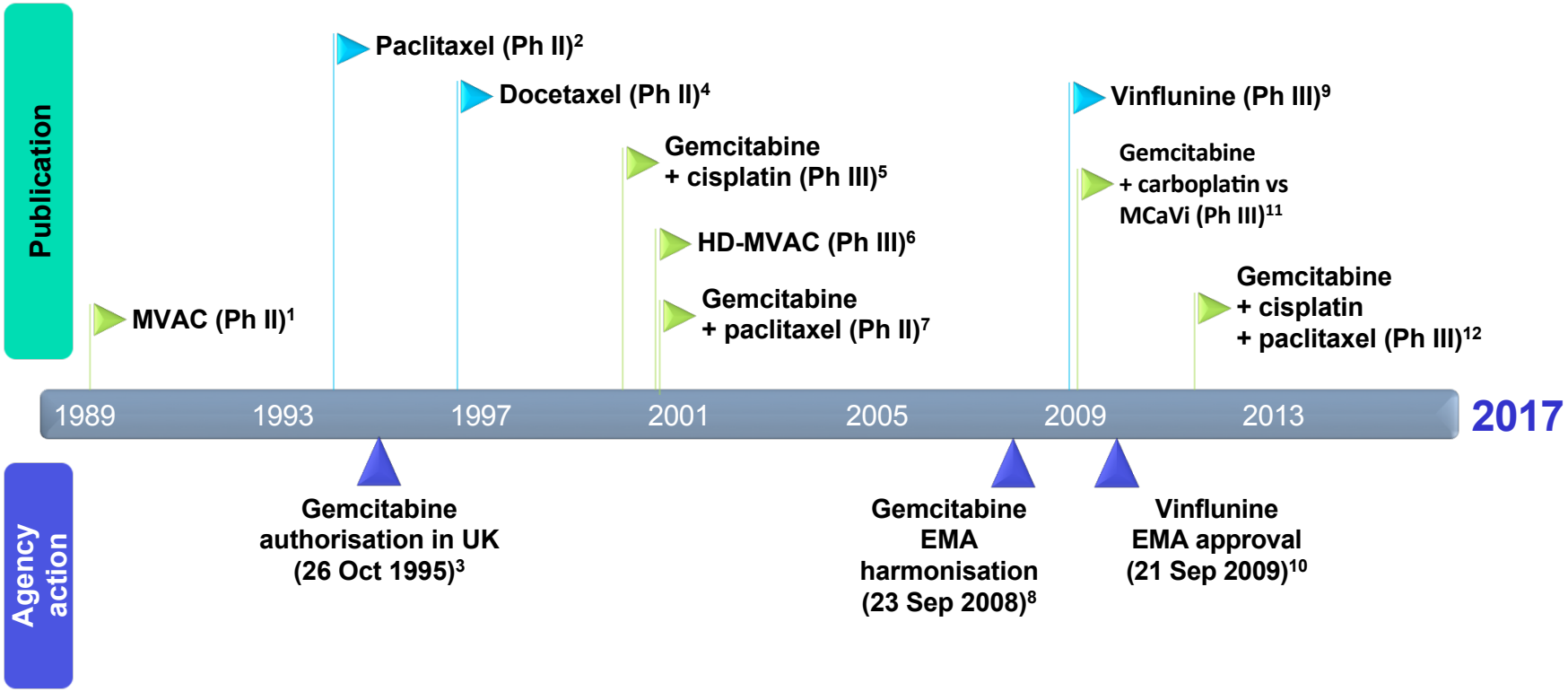
Disclosures

- Advisory role:
  - Genentech, Merck, Pfizer, GSK, BMS, Pierre-Fabre, Sanofi Aventis, Astellas, OncoGenex, Janssen
- Speaker role:
  - Pfizer, Merck, GSK, Novartis, Pierre-Fabre, Astellas
- Research funding:
  - Takeda, Pfizer, Novartis, Sanofi Aventis

Objectives

- Review present standard of care in first- and second-line management of advanced bladder cancer
- Emerging role of immunotherapy in treatment of urological malignancies
- Recent results of Phase II and III trials with PD-1/PD-L1 inhibitors
- Future directions with immunotherapy in urothelial cancer

Evolution of systemic therapy for urothelial cancer



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 Sept 2008. Available at: http://www.ema.europa.eu;
9. Bellmunt J et al. J Clin Oncol 2009;2:4454–4461; 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. All links accessed Sept 2017.

Treatment options following platinum failure

Second-line Therapy? Confusing Activity with Progress!

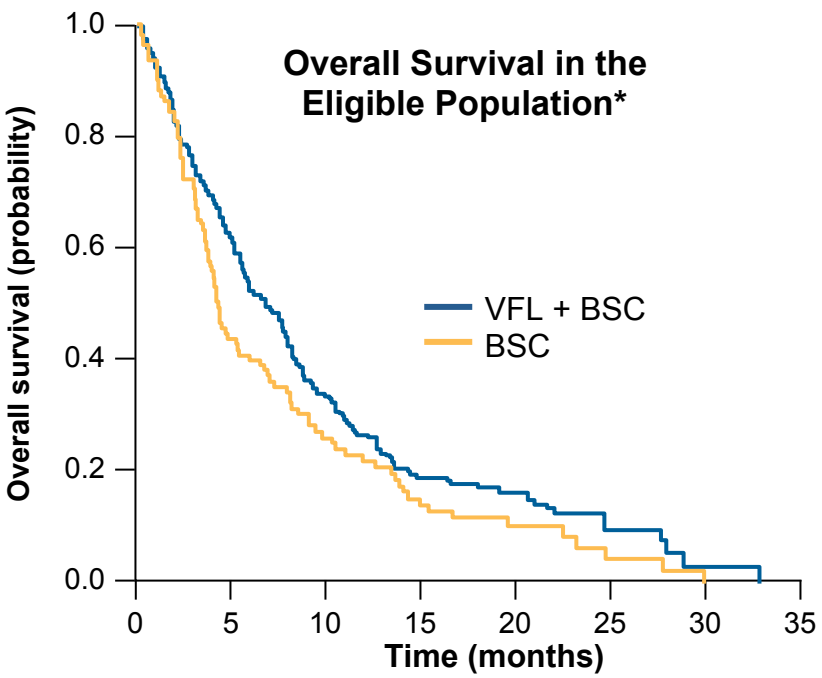
Setting	Agent	Dose	Response rate (%)	No.	Visceral metastases (%)	Median Survival (months)	Reference
Second line	Ifosfamide		20%		NA	NR	(Roth 1996)
	Gallium nitrate		18%		NA	NR	(Petrylak 2002)
	Ifosfamide	every 3 weeks					Rembrink et al. 2001)

* Note: patients had not received gemcitabine as part of first line therapy.

No second-line chemotherapy definitively improves survival!

Efficacy and safety in vinflunine + BSC vs BSC: advanced/metastatic urothelial carcinoma

	Vinflunine + BSC (n=249)	BSC (n=108)
mOS, mos (95% CI)	6.9 (5.7–8.0)	4.3 (3.8–5.4)
HR: 0.78; 95% CI, 0.61–0.99; *P*=0.0403		



Adapted from Bellmunt et al, 2009.

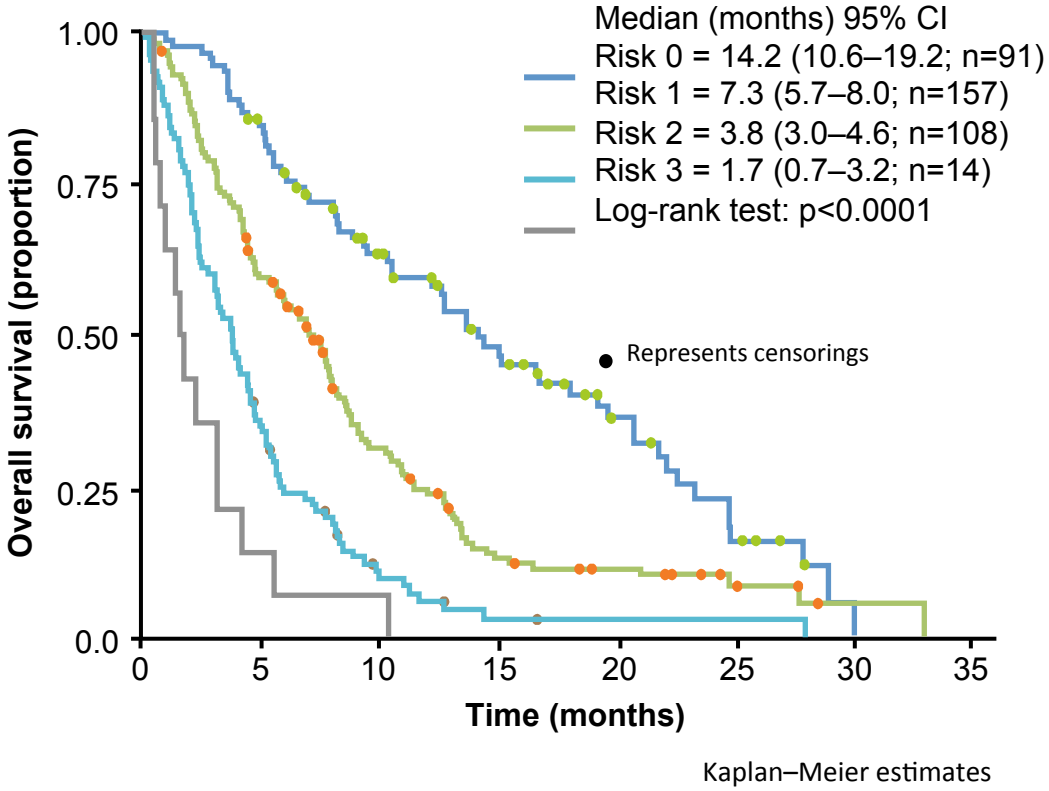
	Vinflunine + BSC (n=248)		BSC (n=117)	
Adverse event, %	**All grade AEs**	**Grade 3–4 AEs**	**All grade AEs**	**Grade 3–4 AEs**
Anaemia	93	**19**	61	**8**
Neutropenia	77	**50**	3	**<1**
Thrombocytopenia	51	**6**	16	**<1**
Fatigue/asthenia	50	**19**	61	**18**
Constipation	48	**16**	25	**<1**
Nausea	39	**2**	21	**<1**
Stomatitis/ mucositis	29	**2**	2	**0**
Alopecia	29	**0**	2	**0**
Vomiting	29	**3**	15	**0**
Infusion/ injection site	27	**<1**	0	**0**
Abdominal pain	16	**4**	18	**6**
Myalgia	16	**3**	7	**0**
Neuropathy sensory	12	**1**	11	**0**
Febrile neutropenia	6	**6**	0	**0**

* The eligible population excludes 13 patients who presented at least one major protocol violation at baseline.

1. Bellmunt J et al. J Clin Oncol. 2009;27:4454–4461.

Prognostic factors in urothelial carcinoma after treatment failure with platinum-containing regimen

- Haemoglobin level >10 g/dL
- ECOG performance status <1
- Absence of liver metastases



Life expectancy up to **14.2** months

Bellmunt J et al. J Clin Oncol 2010;28:1850–1855.

Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial

Daniel P Petrylak, Ronald de Wit, Kim N Chi, Alexandra Drakaki, Cora N Sternberg, Hiroyuki Nishiyama, Daniel Castellano, Syed Hussain, Aude Fléchon, Aristotelis Bamias, Evan Y Yu, Michiel S van der Heijden, Nobuaki Matsubara, Boris Alekseev, Andrea Necchi, Lajos Géczi, Yen-Chuan Ou, Hasan Senol Coskun, Wen-Pin Su, Miriam Hegemann, Ivor J Percent, Jae-Lyun Lee, Marcello Tucci, Andrey Semenov, Fredrik Laestadius, Avivit Peer, Giampaolo Tortora, Sofia Safina, Xavier Garcia del Muro, Alejo Rodriguez-Vida, Irfan Cicin, Hakan Harputluoglu, Ryan C Widau, Astra M Liepa, Richard A Walgren, Oday Hamid, Annamaria H Zimmermann, Katherine M Bell-McGuinn, Thomas Powles, for the RANGE study investigators*

Summary

Background Few treatments with a distinct mechanism of action are available for patients with platinum-refractory advanced or metastatic urothelial carcinoma. We assessed the efficacy and safety of treatment with docetaxel plus either ramucirumab—a human IgG1 VEGFR-2 antagonist—or placebo in this patient population.

Published Online September 12, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32365-6

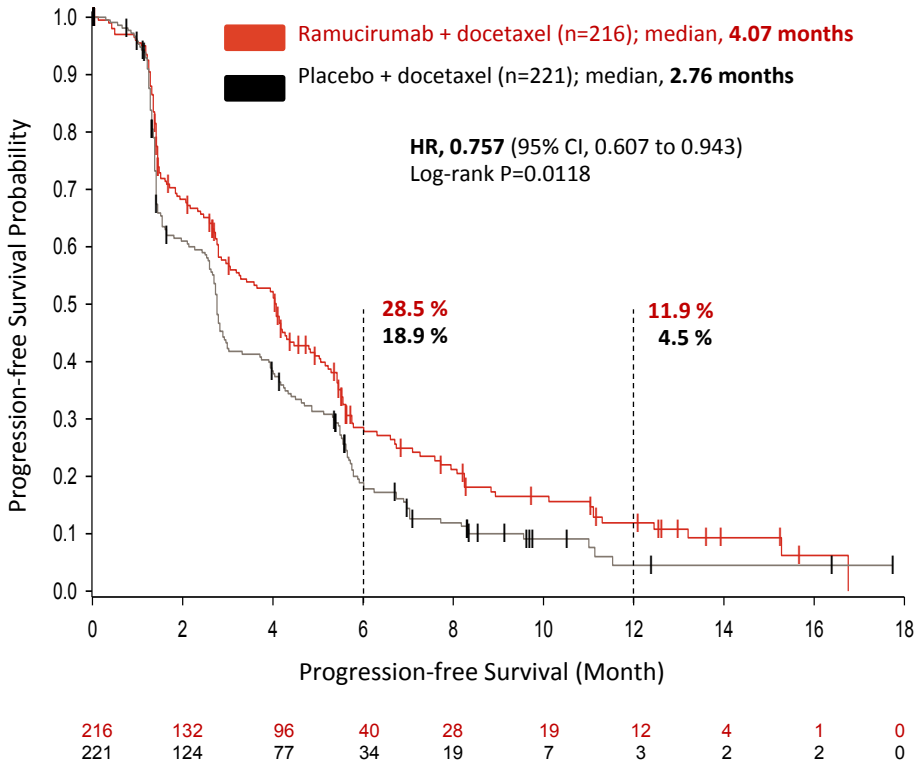
Lancet. 2017 Sep 12. pii: S0140-6736(17)32388-7. doi: 10.1016/S0140-6736(17)32388-7.

Antiangiogenesis to curb urothelial cancer.

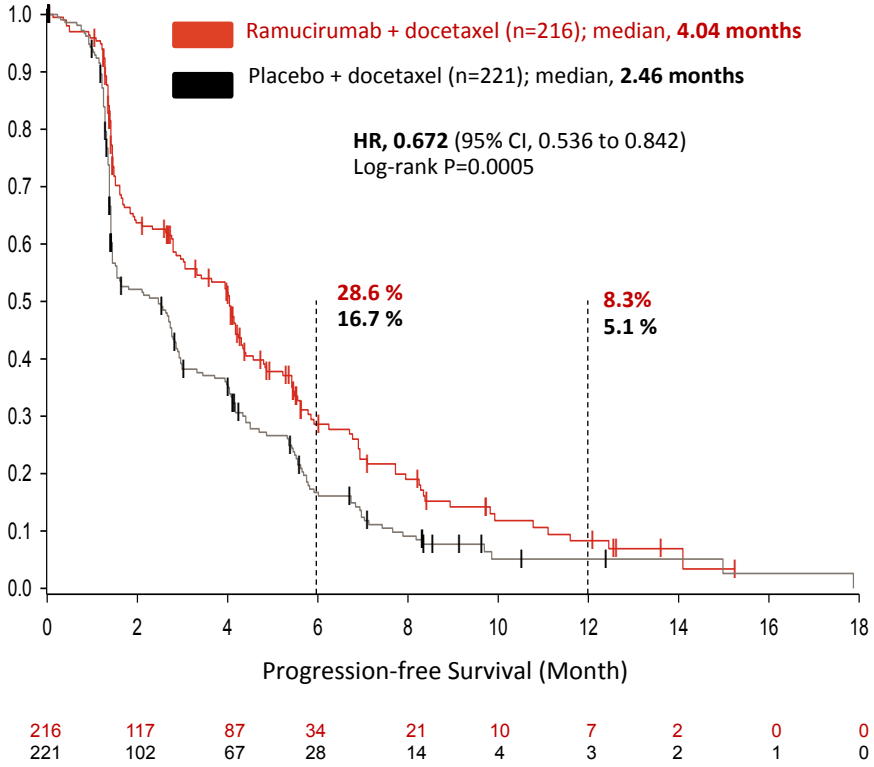
Bellmunt J[1].

Progression-free Survival

Investigator assessment



Independent blinded assessment



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

Emerging Treatment Options in mUC: Immunotherapy with Check-point Inhibitors

Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma

7 US FDA Approvals May 2016-May 2017

Setting	Antibody	Approval Status
1st line (cisplatin-ineligible)	Atezolizumab	• Accelerated approval granted in April 2017
	Pembrolizumab	• Accelerated approval granted in May 2017
Platinum-pretreated	Atezolizumab	• Accelerated approval granted in May 2016. • In May 2017, the subsequent phase 3 IMvigor211 trial did not meet primary endpoint of overall survival
	Nivolumab	• Accelerated approval granted in February 2017
	Durvalumab	• Accelerated approval granted in May 2017
	Avelumab	• Accelerated approval granted in May 2017
	Pembrolizumab	• Full approval granted in May 2017

Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma

7 US FDA Approvals May 2016-May 2017
5 EAU approvals

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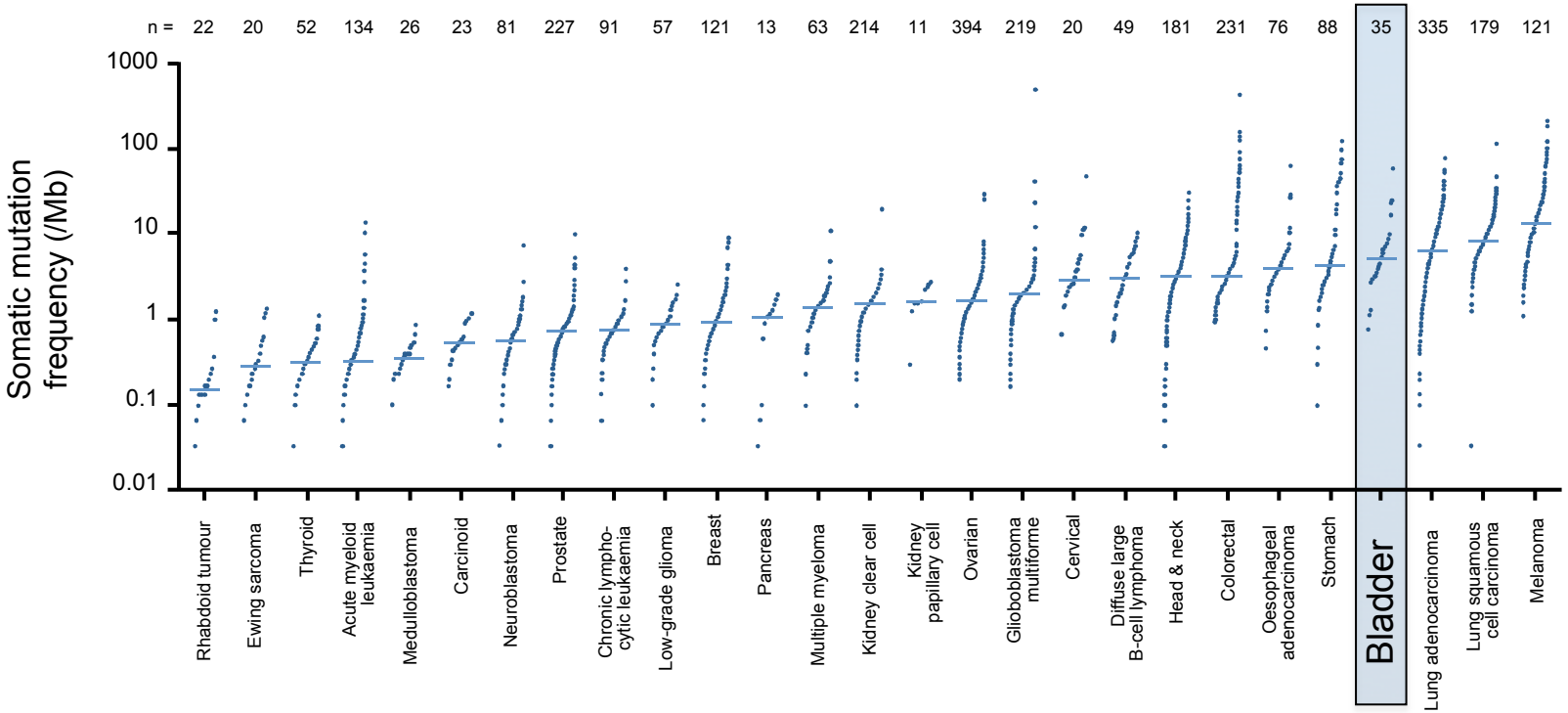
Mutational burden



Somatic mutation frequencies observed in exomes from 3,083 tumour-normal pairs, with frequencies increasing from left to right

Bladder tumours, along with other malignancies such as lung and melanoma, display a high number of somatic mutations, rendering these tumours more immunogenic

Modified from: Lawrence MS et al. Nature 2013;499:214–248.

OVERVIEW OF LATEST DATA FOR CHECKPOINT INHIBITORS IN BLADDER CANCER

Atezolizumab in Patients with Metastatic Urothelial Carcinoma: a 2-Year Clinical Update From a Phase Ia Study

Daniel P. Petrylak,[1] Thomas Powles,[2] Joaquim Bellmunt,[3] Fadi Braiteh,[4] Yohann Loriot,[5] Rafael Morales,[6] Howard A. Burris,[7] Joseph W. Kim,[1] Beiying Ding,[8] Dannis Chang,[8] Marcella Fassò,[8] Carol O'Hear,[8] Nicholas Vogelzang[4]

[1]Yale Cancer Center, New Haven, CT; [2]Barts Cancer Institute, Queen Mary University of London, London, UK; [3]Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA; [4]University of Nevada School of Medicine, Las Vegas, NV, and US Oncology/Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [5]Gustave Roussy, Villejuif, France; [6]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona, Barcelona, Spain; [7]Sarah Cannon Research Institute, Nashville, TN; [8]Genentech, Inc., South San Francisco, CA

LETTER

doi:10.1038/nature13904

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

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

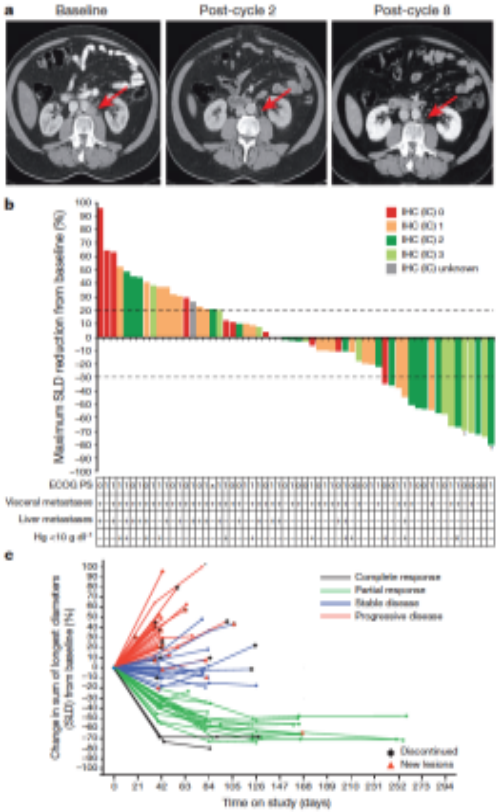
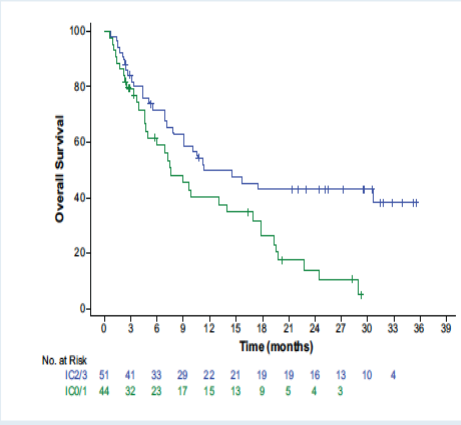


Table 6. Median and Landmark OS by PD-L1 Status

	IC0/1 (n = 44)	IC2/3 (n = 51)	All Patients[a] (N = 95)
Median OS (95% CI)	7.6 mo (4.7, 13.9)	11.3 mo (7.8, NE)	10.1 mo (7.3, 17.0)
1-year OS rate (95% CI)	40% (25, 56)	50% (36, 64)	46% (35, 56)
2-year OS rate (95% CI)	14% (2, 26)	43% (29, 57)	30% (20, 40)

NE, not estimable.
[a] Efficacy-evaluable population with ≥ 12-week follow-up.

Figure 3. Kaplan-Meier Plot of OS by PD-L1 Status

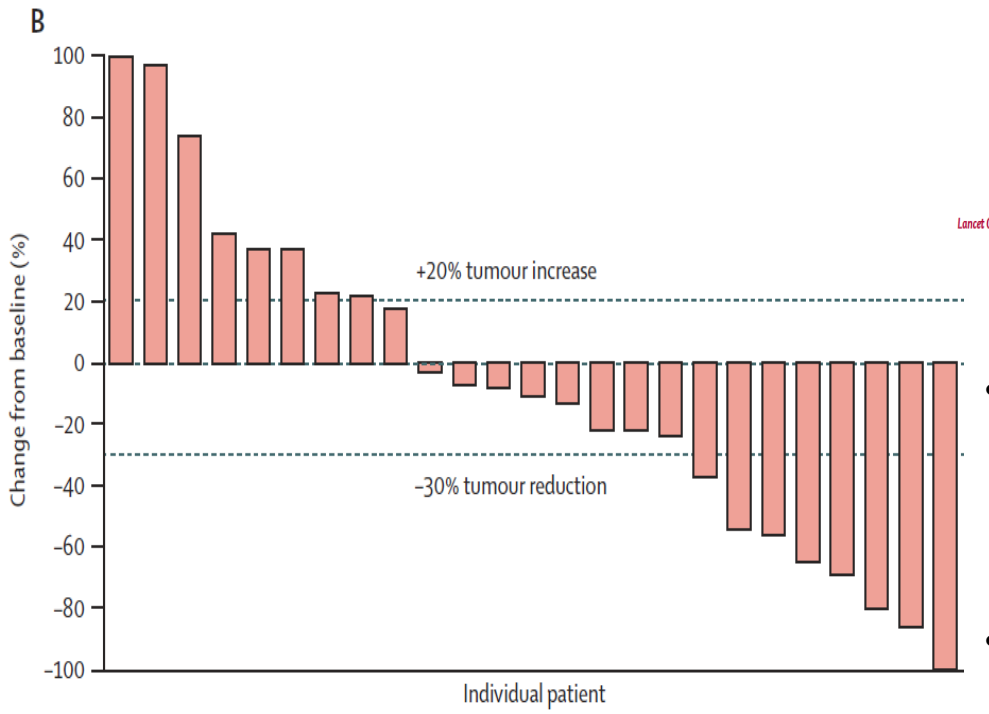


Censored values are indicated with a plus (+) symbol.

- A trend toward longer survival in patients with higher PD-L1 status was observed
- OS was assessed in key clinical subgroups (Figure 4)

1. PowlesT et al. Nature 2014;515:558–562; Petrylak D.P et al. ASCO GU 2017

Pembrolizumab activity in locally advanced or metastatic UC: Phase 1b study (KEYNOTE-012)



Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study

Elizabeth R Plimack, Joaquim Bellmunt, Shilpa Gupta, Raanan Berger, Laura Q M Chow, Jonathan Juco, Jared Lunceford, Sanatan Saraf, Rodolfo F Perini, Peter H O'Donnell

Lancet Oncol 2017; 18: 212–20
Published Online January 9, 2017

Summary

Background PD-1 and its ligands are expressed in urothelial cancer, and findings have shown that inhibition of the PD-1 pathway has clinical benefit. We aimed to assess the safety and activity of an anti-PD-1 antibody pembrolizumab in patients with locally advanced or metastatic urothelial cancer.

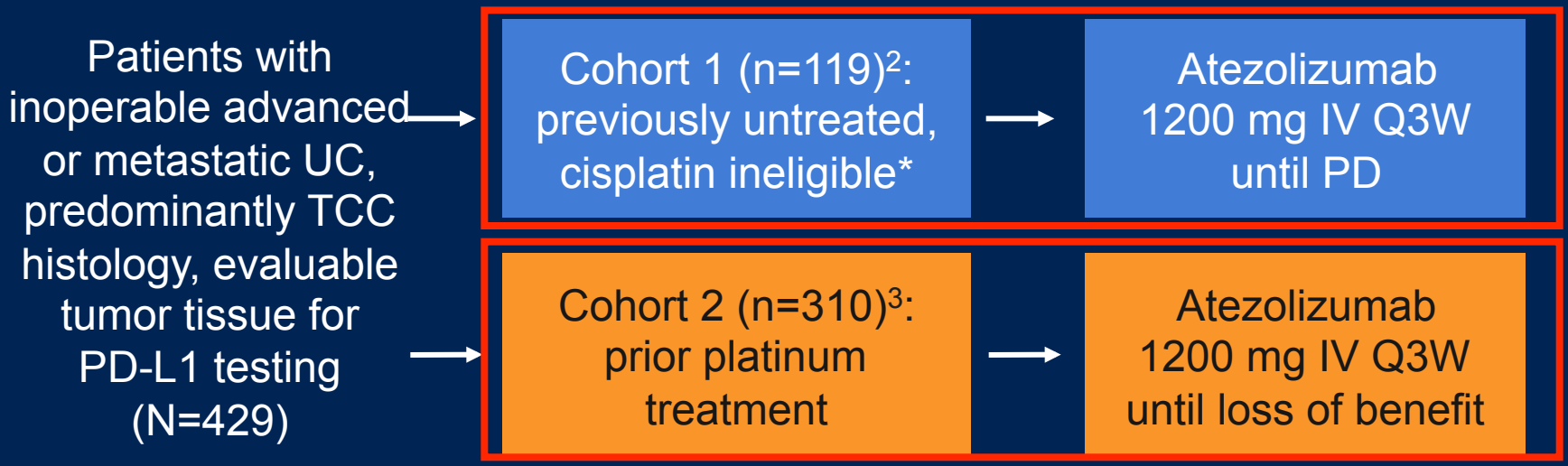
- Overall response rate: 26%
  (7/27 assessable patients [95% CI 11–46])
  - 3 CR (11% [2–29])
  - 4 PR (15% [4–34])
- Median overall survival: 13 months
  (95% CI 5.0–20)
- Overall survival at 12 months: 50%

Median follow-up of 13 months (range 1–26, IQR 5–23)

Plimack ER et al. Lancet Oncol 2017;18:212–220.

IMvigor 210: Study Design

- Single-arm Phase II study with 2 cohorts[1]



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

- Cohort 1 study
  - Primary endpoint: confirmed ORR by RECIST v1.1 (per central, independent review)
  - Secondary endpoints: DoR, PFS, OS, safety

1. ClinicalTrials.gov. NCT02108652.
2. Balar AV, et al. Presented at ASCO 2016. Jun 3 -7, 2016. Chicago, IL. Abstract LBA4500.
3. Dreicer R, et al Presented at ASCO 2016. Jun 3 -7, 2016. Chicago, IL. Abstract 4515.

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

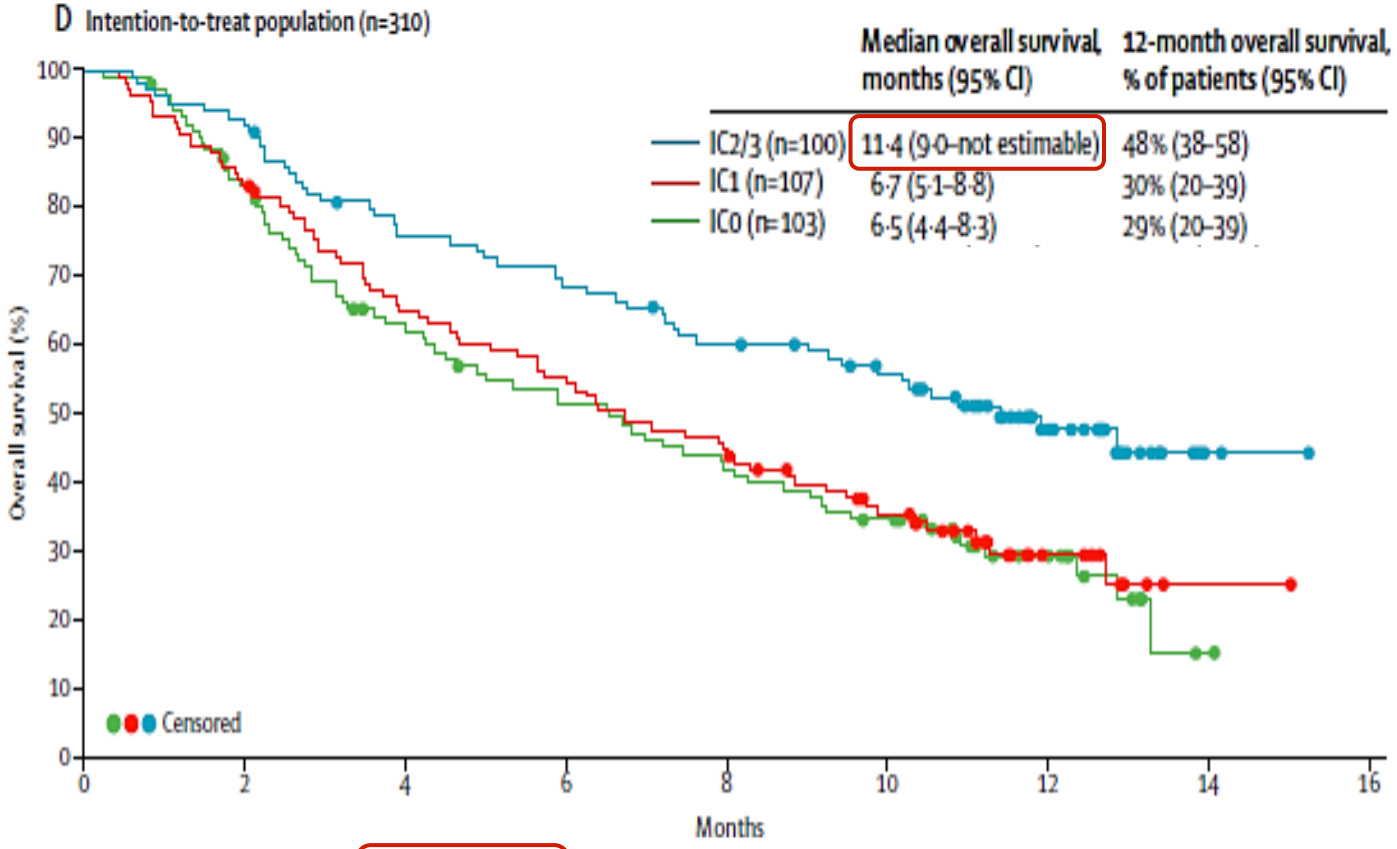
Objective response rate by IC scope

PD-L1 subgroup	n	CR (%)	ORR (%)	95% CI	*P* value[b]
IC2/3	100	8%	27%	19–37	<0·0001
IC1/2/3	208	5%	18%	13–24	0·0004
All	311	4%	15%	11–20	0·0058
IC1	108	3%	10%	5–18	N/A[c]
IC0	103	1%	9%	4–16	N/A[c]

RECIST v1.1 criteria by independent reviewa (pre-planned primary analysis. Data cut off: May 5, 2015)
[a]Objective response evaluable population: all treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1.
[b]P-value for Ho: ORR=10% versus Ha: ORR≠10%, where 10% ORR is historical control, α=0.05.
[c]No formal hypothesis testing conducted.

Rosenberg JE et al. Lancet 2016;387:1909–1920

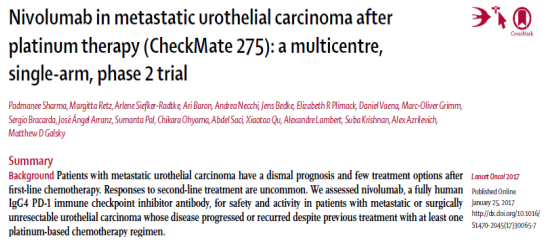
Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial



Median overall survival was 7.9 months (95% CI 6.6–9.3) for the entire cohort of patients

Rosenberg JE et al. Lancet 2016;387:1909–1920

CheckMate 275: Antitumor Activity to Nivolumab



Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial

Padmanee Sharma, Margitta Retz, Arlene Siefker-Radtke, Ari Baron, Andrea Necchi, Jens Bedke, Elizabeth R Plimack, Daniel Vaena, Marc-Oliver Grimm, Sergio Bracarda, José Ángel Arranz, Sumanta Pal, Chikara Ohyama, Abdel Saci, Xiaotao Qu, Alexandre Lambert, Suba Krishnan, Alex Azrilevich, Matthew D Galsky

Summary

Background Patients with metastatic urothelial carcinoma have a dismal prognosis and few treatment options after first-line chemotherapy. Responses to second-line treatment are uncommon. We assessed nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, for safety and activity in patients with metastatic or surgically unresectable urothelial carcinoma whose disease progressed or recurred despite previous treatment with at least one platinum-based chemotherapy regimen.

Lancet Oncol 2017
Published Online
January 25, 2017
http://dx.doi.org/10.1016/S1470-2045(17)30065-7

- Median follow-up was 7 months (minimum of 6 months)

Outcome	All (N=265[a])	PD-L1 <1% (n=143)	PD-L1 ≥1% (n=122)	PD-L1 ≥5% (n=81)
Confirmed ORR by BIRC[b]	19.6	16.1	23.8	28.4
95% CI	15.0 to 24.9	10.5 to 23.1	16.5 to 32.3	18.9 to 39.5
Best overall response				
Complete response	2.3	<1	4.1	4.9
Partial response	17.4	15.4	19.7	23.5
Stable disease	22.6	17.5	28.7	28.4
Progressive disease	39.2	46.9	30.3	25.9
Unable to determine	18.5	19.6	17.2	17.3

- Confirmed ORR in patients with PD-L1 <5% was 15.8 % (95% CI, 10.8-21.8)

[a]265 of 270 patients were evaluated for efficacy, as 5 patients had insufficient follow-up. [b]By RECIST v1.1.
RECIST=Response Evaluation Criteria in Solid Tumors.

Galsky, et al. Presented at ESMO 2016. 07-11 October 2016. Copenhagen, Denmark. Abstract LBA31.

JAMA Oncology | Original Investigation

Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma

Updated Results From a Phase 1/2 Open-label Study

Parameter[b]	All UC			≥2L post-platinum UC[a]		
	Total[c]	PD-L1 high[d]	PD-L1 low/ negative[d]	Total	PD-L1 high[d]	PD-L1 low/ negative[d]
	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[e]	33 (17.3)	11 (11.2)	22 (27.8)	31 (17.0)	11 (11.6)	20 (27.4)
Responses ongoing at time of DCO[f]	26 (76.5)	20 (74.1)	3 (75.0)	24 (75.0)	19 (73.1)	2 (66.7)
DoR, months						
Median	NR	NR	12.25	NR	NR	12.25
(min, max)	≥0.9, ≥19.9	≥0.9, ≥19.9	≥1.9, ≥12.3	≥0.9, ≥19.9	≥0.9, ≥19.9	≥1.9, 12.3
≥6 months, n (%)	17 (50.0)	15 (55.6)	2 (50.0)	15 (46.9)	14 (53.8)	1 (33.3)
DCR, n (%) (95% CI)	70 (36.6) (29.8, 43.9)	44 (44.9) (34.8, 55.3)	17 (21.5) (13.1, 32.3)	66 (36.3) (29.3, 43.7)	42 (44.2) (34.0, 54.8)	15 (20.5) (12.0, 31.6)

[a]The ≥2L post-platinum subgroup includes patients who had progressed while on or after a platinum-based therapy, including those patients whose disease progressed within 12 months of receiving therapy in a neoadjuvant/adjuvant setting. [b]Based on RECIST 1.1. [c]Includes 14 patients who had unknown/unavailable PD-L1 status and who are not included in either the PD-L1 high or PD-L1 low/negative subgroups. [d]PD-L1 expression status was unknown (due to insufficient tumor in biopsy) or unavailable (as testing had not been processed at data cutoff) for 14 patients. [e]Non-evaluable patients were those without post-baseline scans due to death, PD, or withdrawal of consent prior to the first on-treatment disease assessment or had a post-baseline scan that did not meet the minimum required interval for SD. [f]Data cutoff October 24, 2016. ≥2L = second-line or greater; BICR = blinded independent central review; CI = confidence interval;

Adapted from Powles T et al. Online ahead of print. *JAMA Onc*. 2017. Published online August 17, 2017.

Avelumab (Phase Ib)

Clinical activity endpoint by IR	n=242
Confirmed BOR, n (%)	
Complete response (CR)	12 (5.0)
Partial response	27 (11.2)
Stable disease	67 (27.7)
Non-CR/non-PD*	1 (0.4)
Progressive disease (PD)	93 (38.4)
Non-evaluable†	42 (17.4)
Confirmed ORR, % (95% CI)	16.1 (11.7–21.4)
Disease control rate, %	43.8

THE LANCET Oncology
Volume 19, Issue 1, January 2018, Pages 51-64

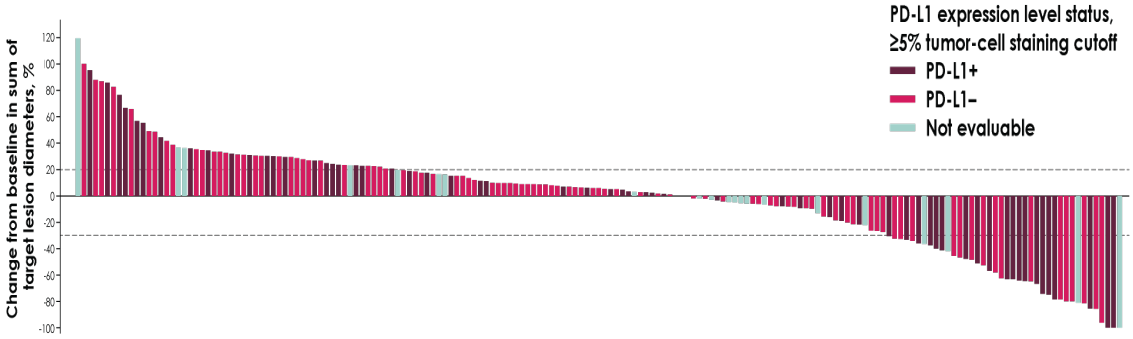
Articles

Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial

Manish R Patel MD [a], John Ellerton MD [b], Jeffrey R Infante MD [c], Manish Agrawal MD [d], Michael Gordon MD [e], Raid Aljumaily MD [f], Carolyn D Britten MD [g], Luc Dirix MD [h], Keun-Wook Lee MD [i], Mathew Taylor MD [j], Prof Patrick Schöffski MD [k], Ding Wang MD [l], Prof Alain Ravaud MD [m], Arnold B Gelb MD [n], Junyuan Xiong MS [n], Galit Rosen MD [n], James L Gulley MD [o, p], Andrea B Apolo MD [q]

Pooled analysis of 242 patients with ≥12 months FU evaluated for efficacy (N=197 included); all comers welcome (PD-L1 ≥5% = 34%):

- 124 patients (49.8%) had received ≥2 lines of prior therapy for advanced disease
- ORR in PD-L1+ and PD-L1– patients was 23.8% (15.2–34.3) and 11.5% (6.6–18.3) respectively
- mPFS = 1.5 months (95% CI 1.4–2.7) median OS = 7.7 months (95% CI 6.2–10.3)



*One patient did not have data reported for target lesion size, and a BOR of non-CR/non-PD in a non-target lesion was assigned.
†Missing and/or not assessable information: 35 patients had no postbaseline tumor assessment (28 died within 8 weeks, 6 withdrew from the trial, and 1 was lost to follow-up); 2 patients had post-baseline assessments with an overall response of not evaluable; and 5 patients had stable disease of insufficient duration

Agent has not yet received EMA approval for treatment of indication listed
Apolo A et al. ESMO 2017. Abstract No. 856P(Poster).

Immune checkpoint inhibitors in platinum-refractory setting

	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 (242 pts ≥12 months follow-up)	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%	16.1%	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%	13.5% (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. Apolo AB et al. ESMO 2017. Abst 856P; 5. Powles T et al. JAMA Oncol. doi:10.1001/jamaoncol.2017.2411. 6. Powles T et al The Lancet 2018 Table adapted from Grivas P. ASCO 2017.

Immune checkpoint inhibitors as first-line in cisplatin-ineligible patients

	Atezolizumab[1]	Pembrolizumab[2]
Phase	Phase II (IMvigor Cohort 1)	Phase II (Keynote-052)
Number of patients	119	370
Dosing	1200 mg every 3 weeks	200 mg every 3 weeks
ORR	23% (9% CR)	29% (7% CR)
Duration of response	70% of responses ongoing at 17.2 months	82% of responses ongoing at ≥ 6 months
Median OS	15.9 months	11.5 months
Median PFS	2.7 months	2.0 months
Rate of Grade 3/4 treatment-related AEs	16%	19%

1. Balar AV et al. Lancet 2017; 389:67–76; 2. O'Donnell, ASCO 2017. Abstract No. 4502. Table reproduced from Grivas P. ASCO 2017.

Opposite results in the cis-ineligible 1st line single arm trials

Vuky # 4524

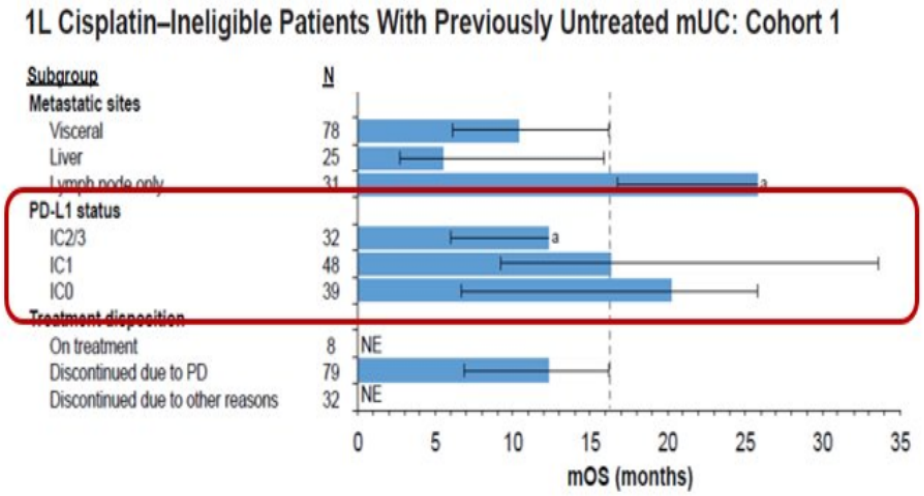
In KN052 – Cisplatin ineligible front line **pembrolizumab**, low PDL1 (CPS <10) patients were 74% of the study population and had worse median OS.

Table 3. Overall Survival by Subgroups

Response	N	Events, n (%)	Median OS (95% CI), mo
PD-L1 subgroup			
PD-L1 CPS <10	251	186 (74)	10.0 (7.8-11.6)
PD-L1 CPS ≥10	110	57 (52)	18.5 (12.2 to NR)

Balar # 4523

In contrast, in IMvigor210 – Cisplatin ineligible front line **atezolizumab** - low PDL1 (IC0/1) patients were 70% of the study population and had similar to slightly better median OS.

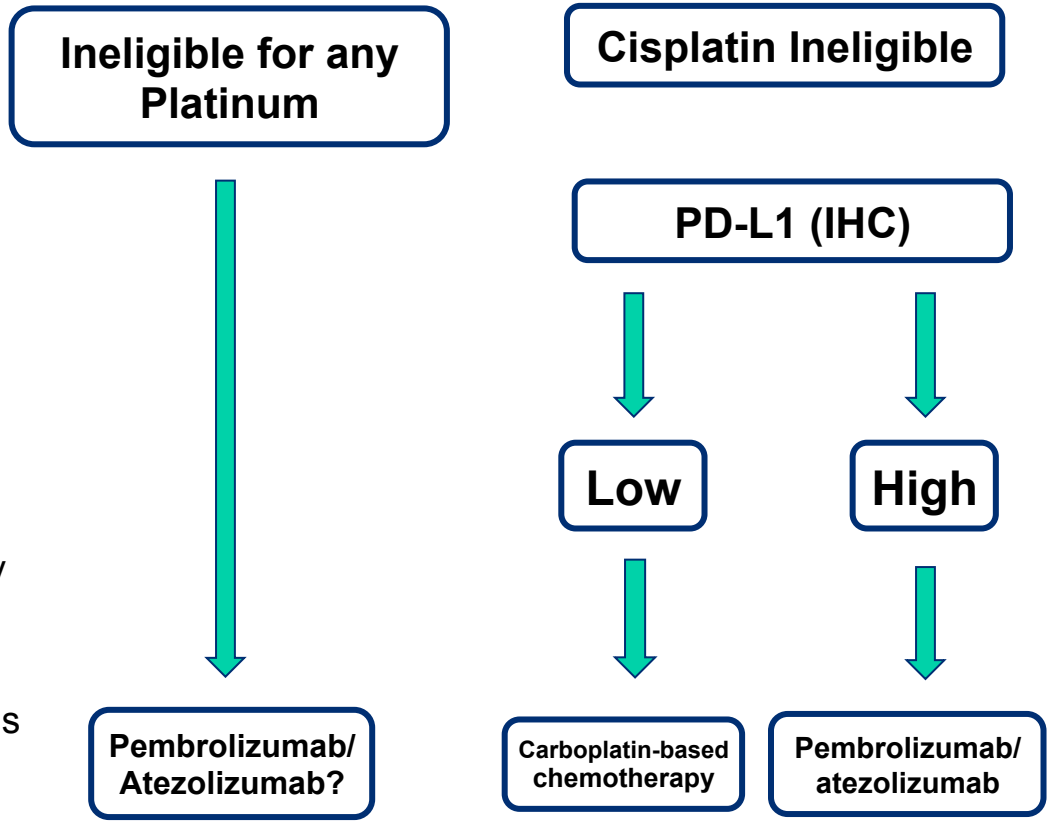


Vuky J, et al. J Clin Oncol 36, 2018 (suppl; abstr 4524)
Balar AV, et al. J Clin Oncol 36, 2018 (suppl; abstr 4523)

Use PD-L1 Expression To Select Therapy For Cisplatin-ineligible Patients? (US)

5/18/2018 - FDA Alert

- In 2 ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130), the Data Monitoring Committees' (DMC) found patients in the **monotherapy (pembrolizumab/ atezolizumab) arms of both trials with PD-L1 low status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy**
- Both trials have stopped enrolling patients whose tumors have PD-L1 low status to the pembrolizumab or atezolizumab monotherapy arms
- The monotherapy arms remain open only to patients whose tumors have PD-L1 high status



FDA. https://www.fda.gov/Drugs/DrugSafety/ucm608075.htm. May 18, 2018.

J. Bellmunt 2018

SECOND LINE Phase III

KEYNOTE-045 Study Design (NCT02256436)[1]

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.
- No more than 2 prior lines of systemic chemotherapy.

Randomization
N = 542 patients

Estimated timelines
Estimated completion: Sept 2016 (Early termination)

Pembrolizumab

SOC: Paclitaxel, Docetaxel or Vinflunine

Primary end points
OS & PFS

Secondary end points
- ORR
- Safety

IMvigor211 Study Design (NCT02302807)[2]

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.

Randomization
N = 932 patients

Estimated timelines
Estimated completion: Nov 2017

Atezolizumab

SOC: Docetaxel, Paclitaxel or Vinflunine

Primary end points
OS

Secondary end points
- ORR
- PFS
- DOR
- Safety

[1]Bellmunt J, et al. *N Engl J Med.* 2017; [2]Clinicaltrials.gov.

The NEW ENGLAND JOURNAL of MEDICINE

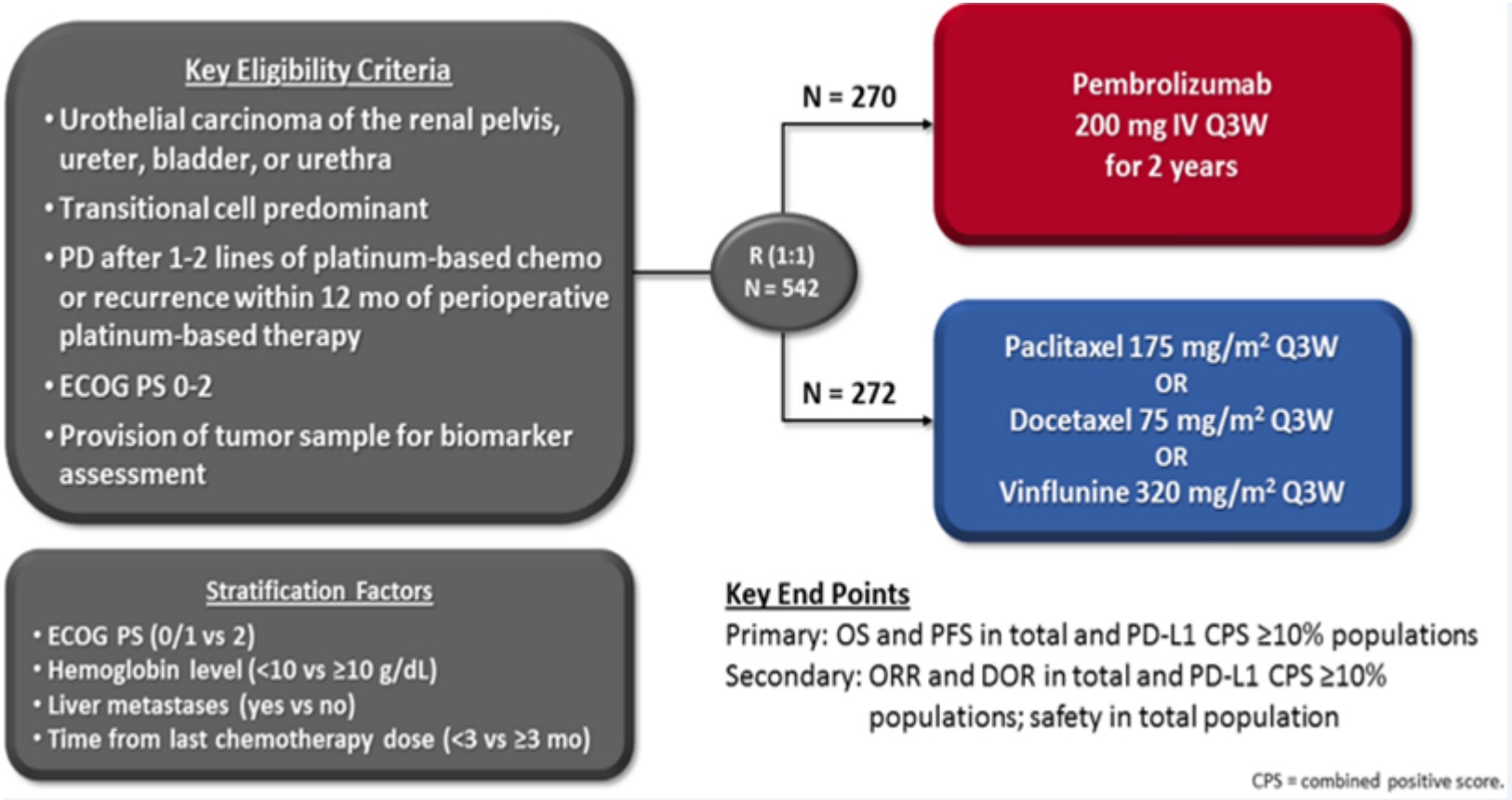
ESTABLISHED IN 1812 MARCH 16, 2017 VOL. 376 NO. 11

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

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

KEYNOTE-045: Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

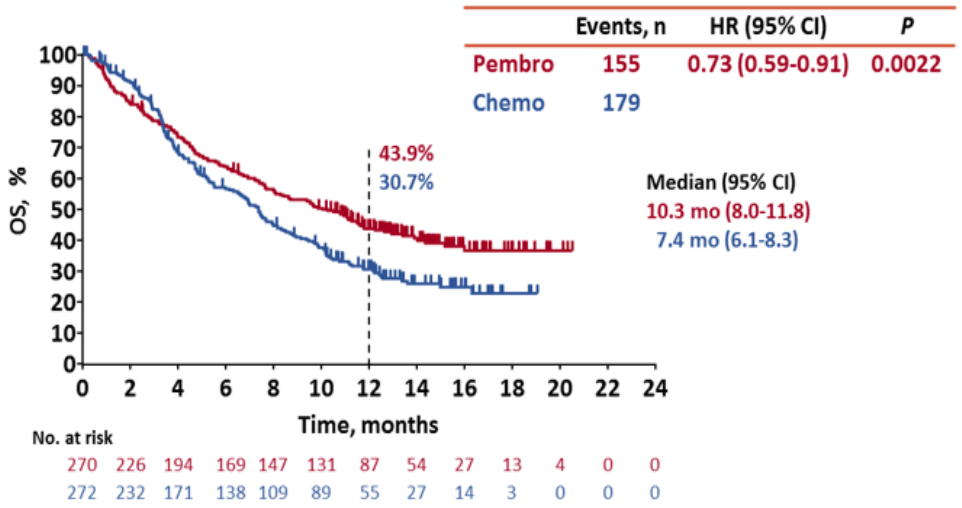
Open-label 2-arm, multi-centre, international, randomised (1:1) Phase III trial



Bellmunt, J.; De Wit, R.; Vaughn, D.J.; Fradet, Y.; Lee, J.L.; Fong, L.; Vogelzang, N.J.; Climent, M.A.; Petrylak, D.P.; Choueiri, T.K.; et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.

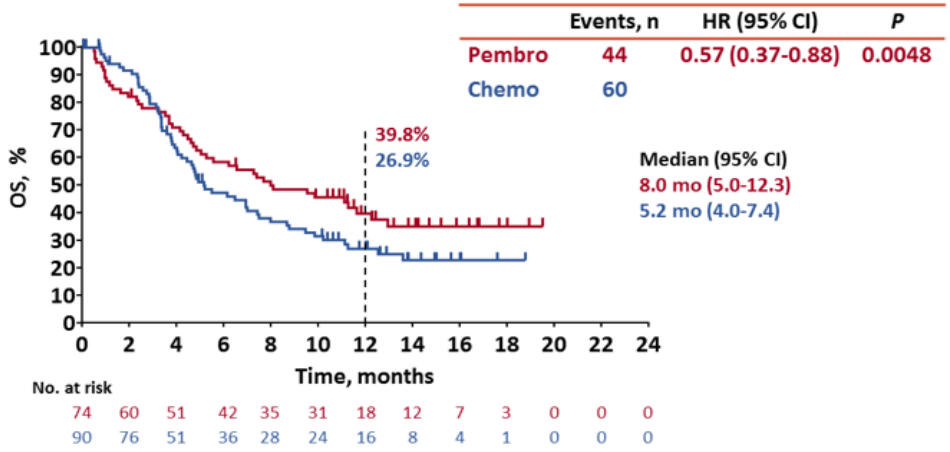
KEYNOTE-045: OVERALL SURVIVAL

Overall Survival: Total



Data cutoff date: Sep 7, 2016.

Overall Survival: CPS ≥10%

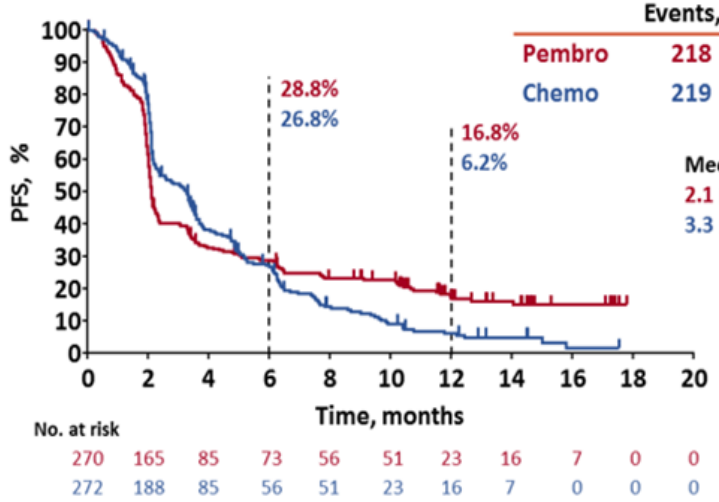


Data cutoff date: Sep 7, 2016.

Bellmunt, J.; De Wit, R.; Vaughn, D.J.; Fradet, Y.; Lee, J.L.; Fong, L.; Vogelzang, N.J.; Climent, M.A.; Petrylak, D.P.; Choueiri, T.K.; et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.

KEYNOTE-045: PFS , ORR

Progression-Free Survival: Total

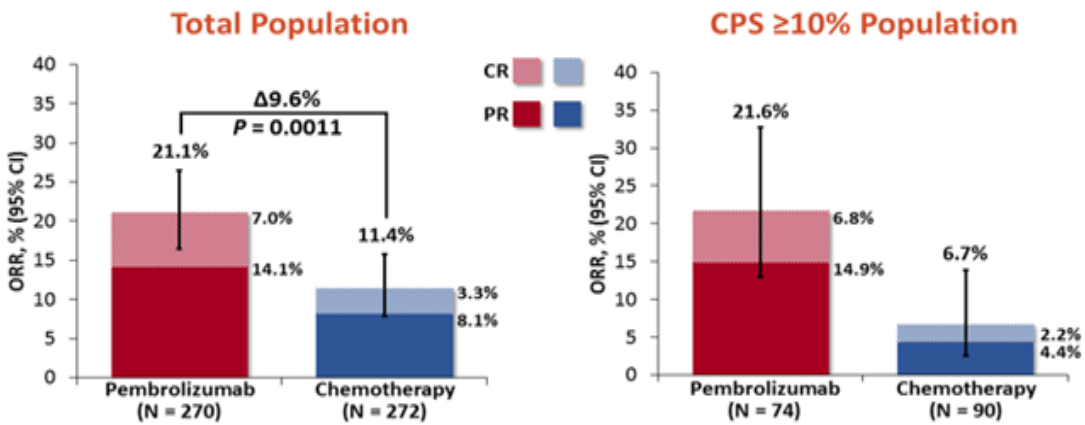


	Events, n	HR (95% CI)	*P*
Pembro	218	0.98 (0.81-1.19)	0.42
Chemo	219		

Median (95% CI)
2.1 mo (2.0-2.2)
3.3 mo (2.3-3.5)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: Sep 7, 2016.

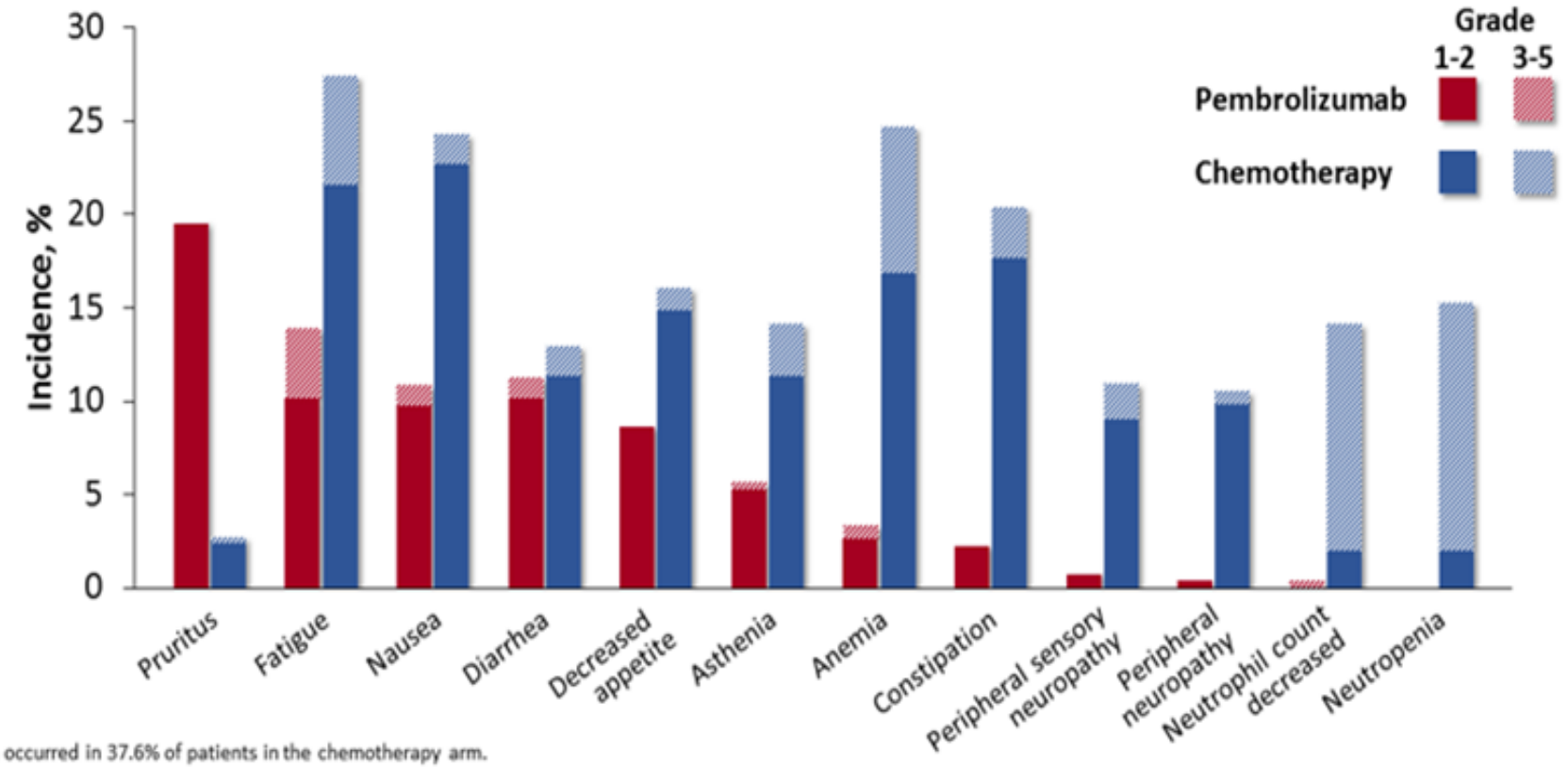
Confirmed Objective Response Rate



No alpha allocated to the comparison of ORR in the CPS ≥10% population.
Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: Sep 7, 2016.

Bellmunt, J.; De Wit, R.; Vaughn, D.J.; Fradet, Y.; Lee, J.L.; Fong, L.; Vogelzang, N.J.; Climent, M.A.; Petrylak, D.P.; Choueiri, T.K.; et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.

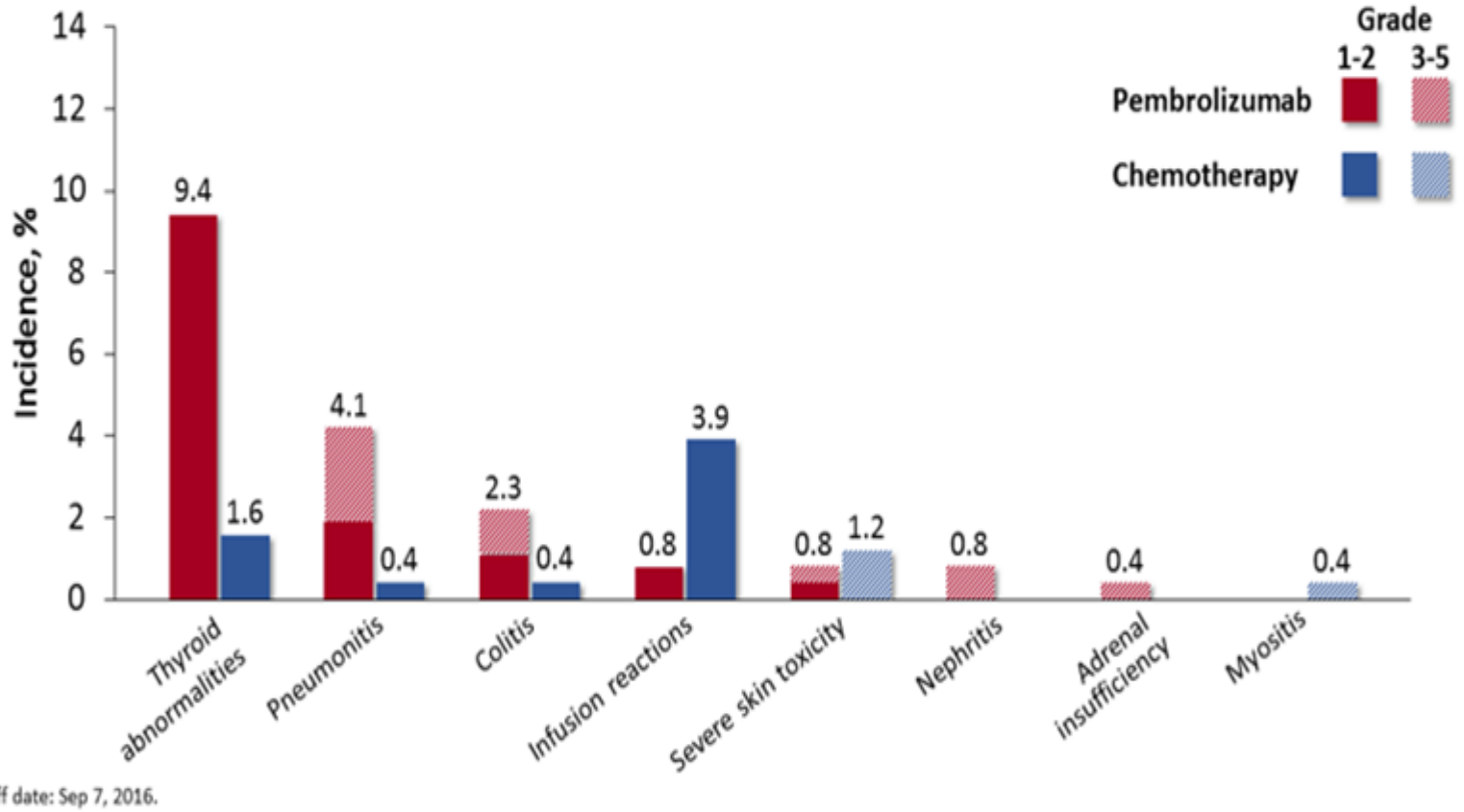
KEYNOTE-045
Treatment-Related AEs with Incidence ≥ 10 %



Alopecia occurred in 37.6% of patients in the chemotherapy arm.
Data cutoff date: Sep 7, 2016.

Bellmunt, J.; De Wit, R.; Vaughn, D.J.; Fradet, Y.; Lee, J.L.; Fong, L.; Vogelzang, N.J.; Climent, M.A.; Petrylak, D.P.; Choueiri, T.K.; et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.

KEYNOTE-045: AEs of interest



Data cutoff date: Sep 7, 2016.

Bellmunt, J.; De Wit, R.; Vaughn, D.J.; Fradet, Y.; Lee, J.L.; Fong, L.; Vogelzang, N.J.; Climent, M.A.; Petrylak, D.P.; Choueiri, T.K.; et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.

SECOND LINE Phase III

KEYNOTE-045 Study Design (NCT02256436)[1]

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.
- No more than 2 prior lines of systemic chemotherapy.

Randomization
N = 542 patients

Estimated timelines
Estimated completion: Sept 2016 (Early termination)

- Pembrolizumab
- SOC: Paclitaxel, Docetaxel or Vinflunine

Primary end points
OS & PFS

Secondary end points
- ORR
- Safety

IMvigor211 Study Design (NCT02302807)[2]

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.

Randomization
N = 932 patients

Estimated timelines
Estimated completion: Nov 2017

- Atezolizumab
- SOC: Docetaxel, Paclitaxel or Vinflunine

Primary end points
OS

Secondary end points
- ORR
- PFS
- DOR
- Safety

[1]Bellmunt J, et al. *N Engl J Med.* 2017; [2]Clinicaltrials.gov.

IMvigor211 Study Design

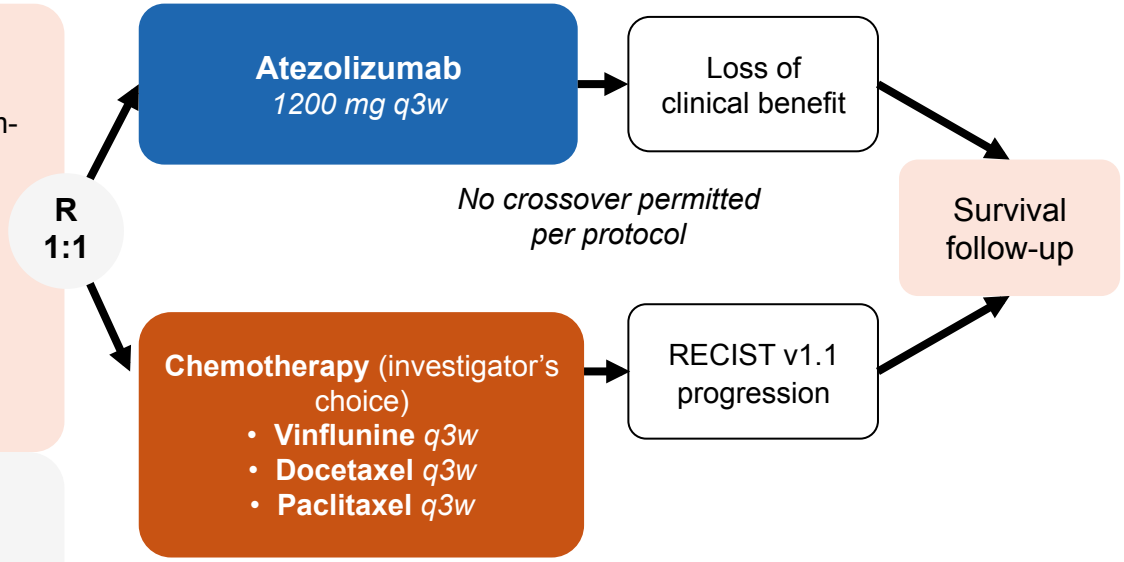
Key Eligibility Criteria[a]

- mUC with progression during or following platinum-based chemotherapy
  - ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component

(N = 931)

Stratification Factors

- No. of risk factors[b] (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)



- **Primary endpoint**
  - OS, tested hierarchically in pre-specified populations
- **Additional endpoints**
  - Efficacy: RECIST v1.1 ORR, PFS and DOR[c]
  - Safety
  - PROs: EORTC QLQ-C30

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. [a] ClinicalTrials.gov, NCT02302807. [b] Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. [c] Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.

Powles T, et al. EAS 2017, IMvigor211.

Atezolizumab

❑ IMvigor 211: fase III.

Key Eligibility Criteria[a]
- mUC with progression during or following platinum-based chemotherapy – ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
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- No. of risk factors[b] (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)

R 1:1

Atezolizumab *1200 mg q3w* → Loss of clinical benefit

Chemotherapy (investigator's choice)
- **Vinflunine** *q3w*
- **Docetaxel** *q3w*
- **Paclitaxel** *q3w*

→ RECIST v1.1 progression

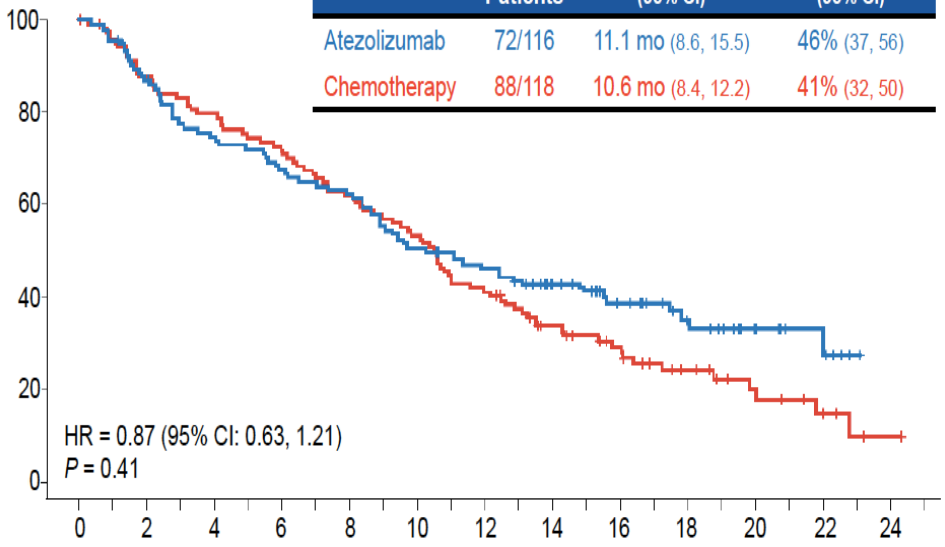
No crossover permitted per protocol

→ Survival follow-up

Media F/U: 17.3 mo

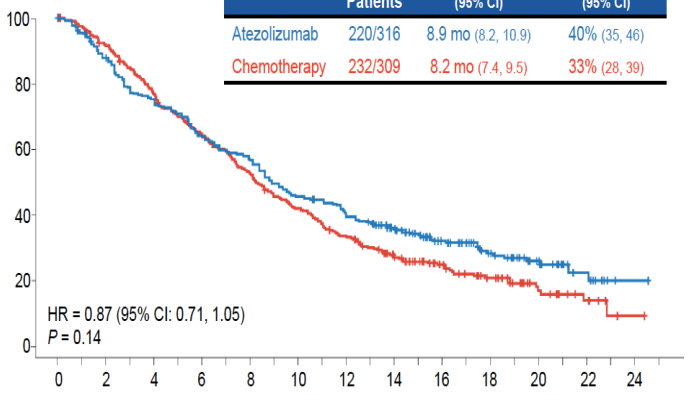
OS in PD-L1 IC2/3.

	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)



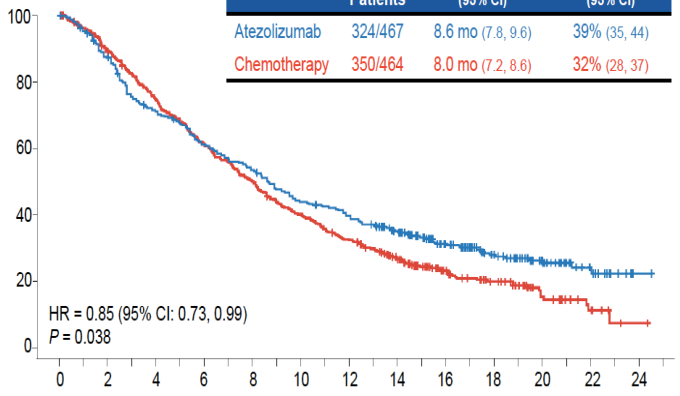
OS in patirents PD-L1 IC 1/2/3.

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	220/316	8.9 mo (8.2, 10.9)	40% (35, 46)
Chemotherapy	232/309	8.2 mo (7.4, 9.5)	33% (28, 39)



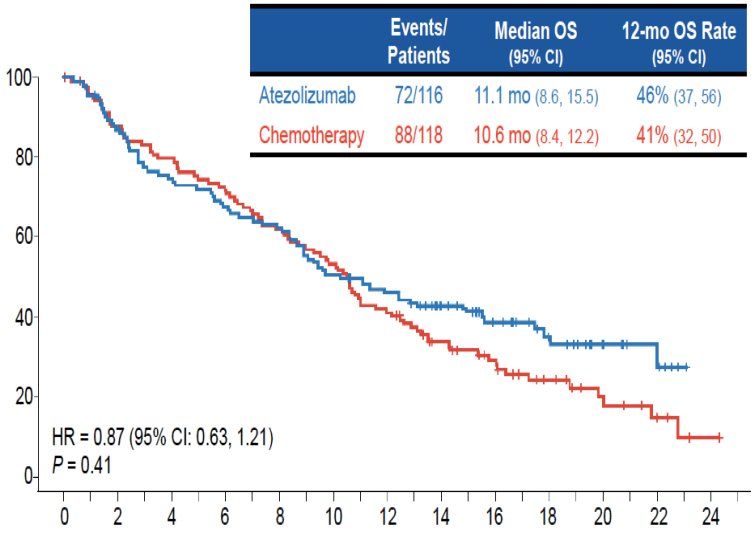
OS in ITT

	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)



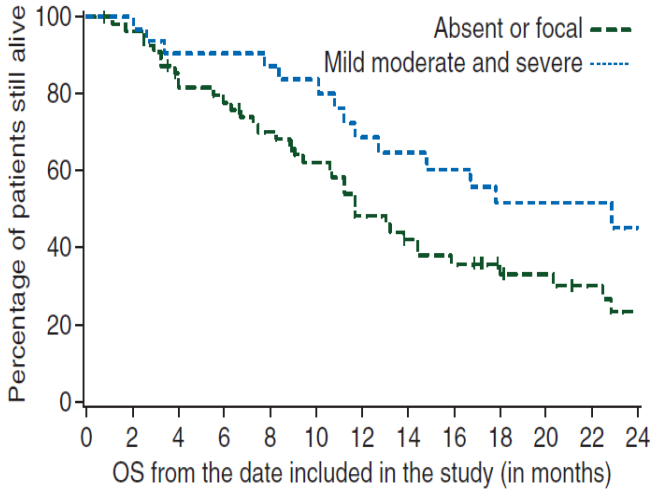
Powles T, et al. Lancet 2017 Dec 18 [epub ahead of print].

Why no differences in survival.
Chemo outperforming ?



Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma

J. Bellmunt[1,2,3,4], S. A. Mullane[1,4,†], L. Werner[1,†], A. P. Fay[1,4], M. Callea[5], J. J. Leow[1], M. E. Taplin[1,2,3,4], T. K. Choueiri[1,2,3,4], F. S. Hodi[3,4,6], G. J. Freeman[3,4] & S. Signoretti[1,3,5]



- Positive PD-L1 expression (score of 2–4) in TIMCs was significantly associated with longer OS (12 versus 23 months) in both univariate (P = 0.04) and multivariable analysis (P = 0.0007) (adjusting for ECOG status and visceral disease)
- PD-L1 expression in tumor cell membrane was not associated with survival (P = 0.45)

Bellmunt J, et al Ann Oncol. 2015 Apr;26(4):812-7.

Long term follow-up data

- Phase I Atezolizumab
- Phase II Nivolumab
- Phase III Pembrolizumab

JAMA Oncology | Original Investigation

Atezolizumab (MPDL3280A) Monotherapy for Patients With Metastatic Urothelial Cancer

Long-term Outcomes From a Phase 1 Study

Daniel P. Petrylak, MD; Thomas Powles, MBBS, MRCP, MD; Joaquim Bellmunt, MD, PhD; Fadi Braiteh, MD; Yohann Loriot, MD, PhD; Rafael Morales-Barrera, MD; Howard A. Burris, MD; Joseph W. Kim, MD; Beiying Ding, PhD; Constanze Kaiser, PhD; Marcella Fassò, PhD; Carol O'Hear, MD, PhD; Nicholas J. Vogelzang, MD

Figure 2. Overall Survival (OS) by Programmed Death Ligand 1 (PD-L1) Status and Key Clinical Subgroups

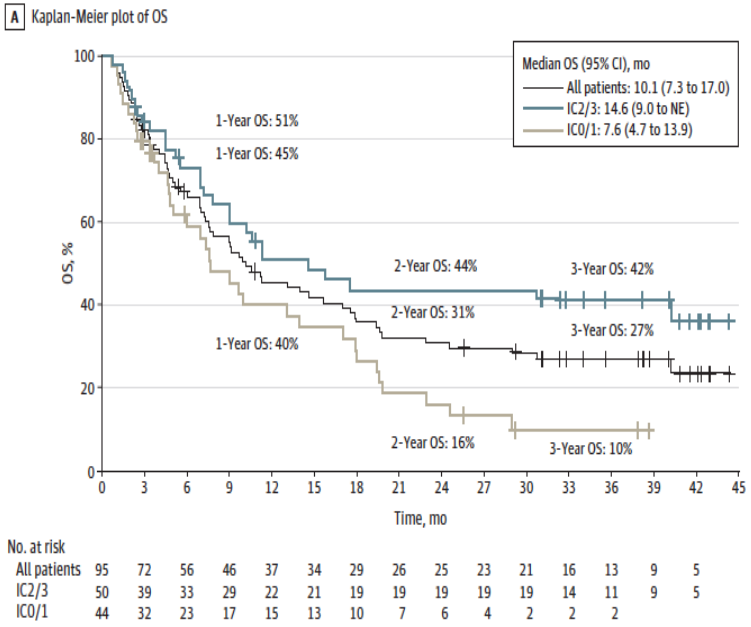


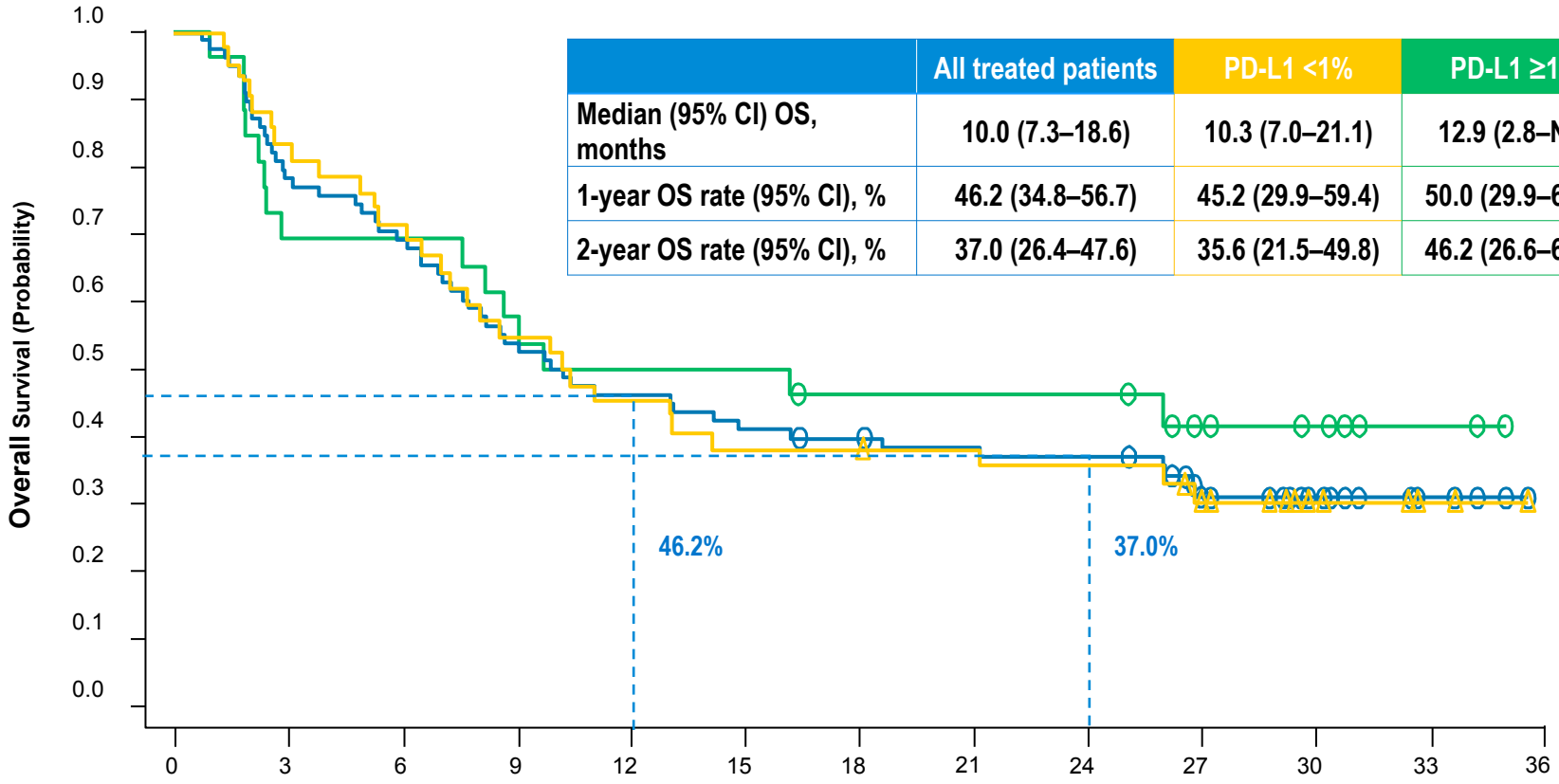
Table 3. Objective Response Rates to Atezolizumab Treatment and Duration of Response by Programmed Death Ligand 1 Immunohistochemical Status

Parameter	IC0/1 (n = 44)	IC2/3 (n = 50)	All Patients (N = 95)[a]
Objective response rate (95% CI)[b]	11 (4 to 25)	40 (26 to 55)	26 (18 to 36)
Best overall response, No. (%)			
Complete response	1 (2)	8 (16)	9 (10)
Partial response	4 (9)	12 (24)	16 (17)
Stable disease	9 (21)	9 (18)	18 (19)
Progressive disease	24 (55)	17 (34)	42 (44)
No assessment[c]	6 (14)	4 (8)	10 (11)
Duration of response, mo (range)	27.6 (6.2 to >34.3)	18.0 (2.8 to >41.0)	22.1 (2.8 to >41.0)

JAMA Oncol. doi:10.1001/jamaoncol.2017.5440 Published online February 8, 2018.

Overall Survival

	All treated patients	PD-L1 <1%	PD-L1 ≥1%
Median (95% CI) OS, months	10.0 (7.3–18.6)	10.3 (7.0–21.1)	12.9 (2.8–NR)
1-year OS rate (95% CI), %	46.2 (34.8–56.7)	45.2 (29.9–59.4)	50.0 (29.9–67.2)
2-year OS rate (95% CI), %	37.0 (26.4–47.6)	35.6 (21.5–49.8)	46.2 (26.6–63.6)



No. at Risk													
All treated patients	78	61	54	42	36	32	30	28	27	18	10	4	0
PD-L1 ≥1%	26	18	18	15	13	13	11	11	11	7	5	2	0
PD-L1 <1%	42	35	30	23	19	16	16	15	14	10	5	2	0

Sharma P, et al. *J Clin Oncol.* 2018;36:(suppl 6S; abstract 414). ASCO GU 2018

- Highlight of new data presentation:
- ASCO 2018
  - Abstract 4523 (Long term phase II Imvigor 210. Both cohorts)
  - Abstracts 4524 (Keynote-052 Pembro first line unfit)

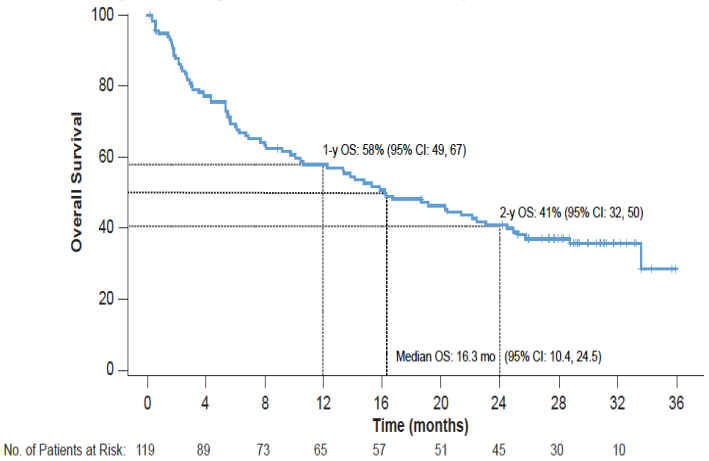
Atezolizumab in First-Line Cisplatin–Ineligible or Platinum-Treated Locally Advanced or Metastatic Urothelial Cancer: Long-Term Efficacy From Phase II Study IMvigor210

Abstract #4523
Poster #349

Arjun V. Balar,[1] Robert Dreicer,[2] Yohann Loriot,[3] Jose Luis Perez-Gracia,[4] Jean H. Hoffman-Censits,[5] Daniel P. Petrylak,[6] Michiel S. van der Heijden,[7] Beiying Ding,[8] Xiaodong Shen,[8] Jonathan E. Rosenberg[9]

[1]Perlmutter Cancer Center, NYU Langone Health, New York, NY; [2]Division of Hematology/Oncology, University of Virginia, Charlottesville, VA; [3]Gustave Roussy, Villejuif, France; [4]Department of Medical Oncology, Clínica Universidad de Navarra, Pamplona, Spain; [5]Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [6]Yale Cancer Center, New Haven, CT; [7]Netherlands Cancer Institute, Amsterdam, the Netherlands; [8]Oncology, Genentech, Inc., South San Francisco, CA; [9]Memorial Sloan Kettering Cancer Center, New York, NY

A 1L Cisplatin–Ineligible Patients With Previously Untreated mUC: Cohort 1[a]



B Patients With mUC Previously Treated With Platinum: Cohort 2[b]

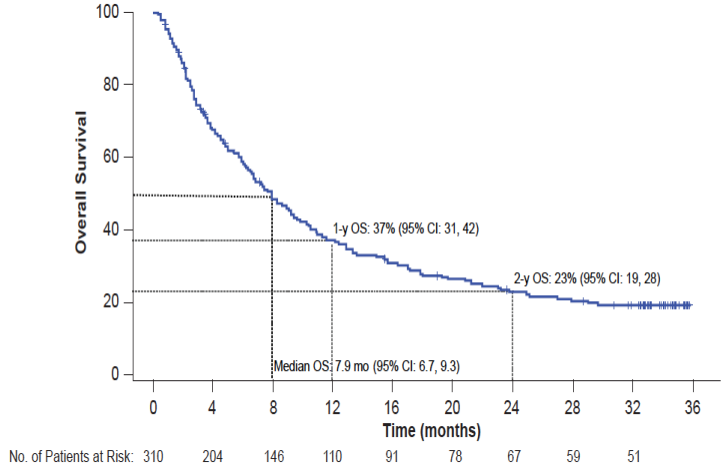


Table 2. Confirmed IRF-Assessed RECIST v1.1 ORR and DOR

Variable	Cohort 1 (N = 119)	Cohort 2 (N = 310)
ORR (95% CI)	24% (16, 32)[a]	16% (13, 21)[b]
CR rate	8%	7%
DOR, median (95% CI)	NE (30.4 mo, NE)	24.8 mo (13.8, 30.4)
Patients with ongoing response[c]	19 of 28	21 of 51

CR, complete response; NE, not estimable.
Patients with missing or unevaluable response status: [a] 19 in Cohort 1 and [b] 46 in Cohort 2. [c] No death or IRF-assessed RECIST v1.1 PD event.

Table 3. Outcomes in Elderly Patients (age ≥ 80 years): Cohort 1

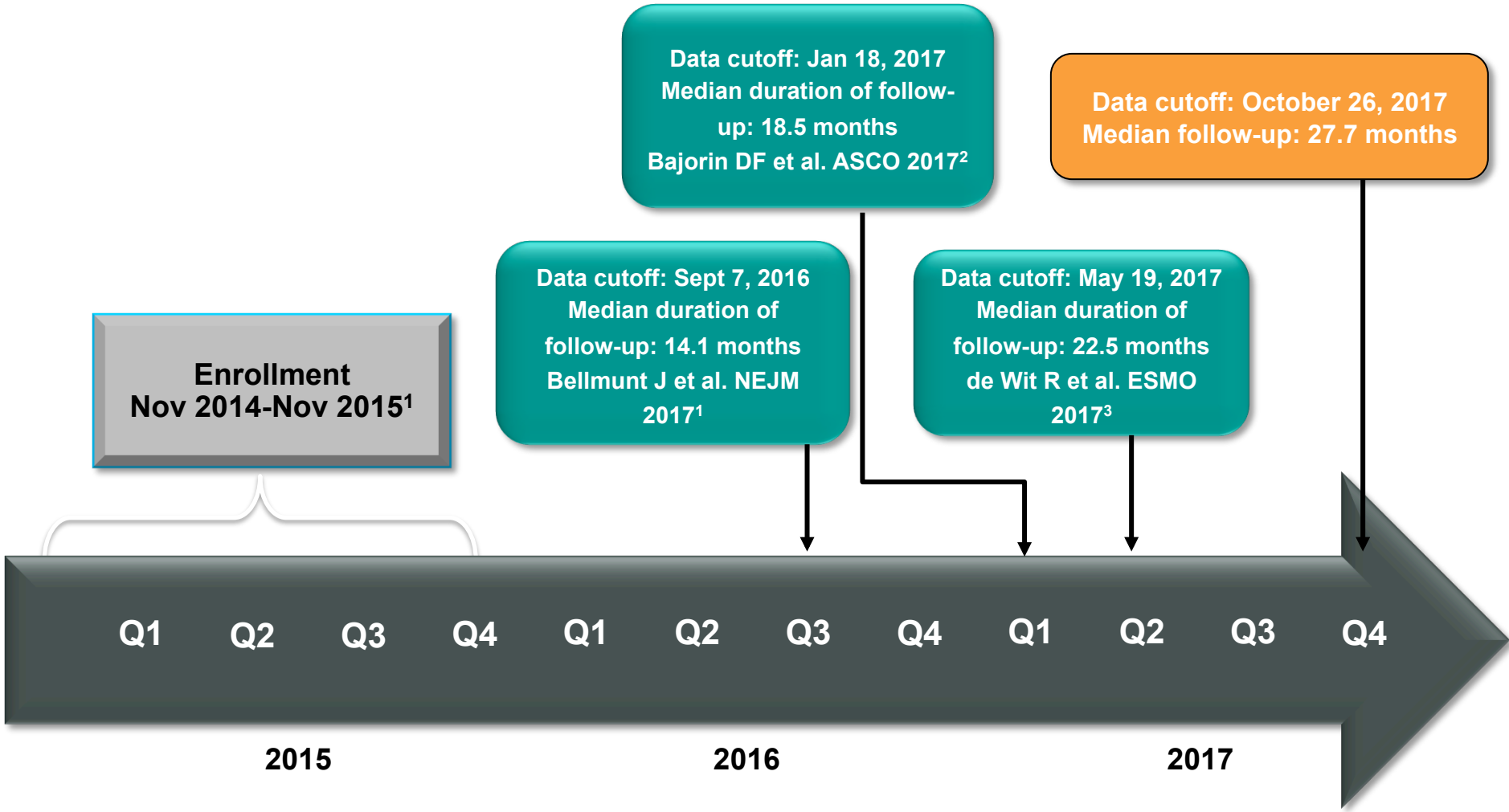
Variable	Cohort 1 (n = 25)
ORR (95% CI)	28% (12, 49)
CR rate	12%
DOR (95% CI)	NE (20.2 mo, NE)
OS, median (95% CI)	21.4 mo (6.3, NE)

- Patients aged ≥ 80 years in Cohort 1 had a noteworthy CR rate and median OS

CONCLUSIONS

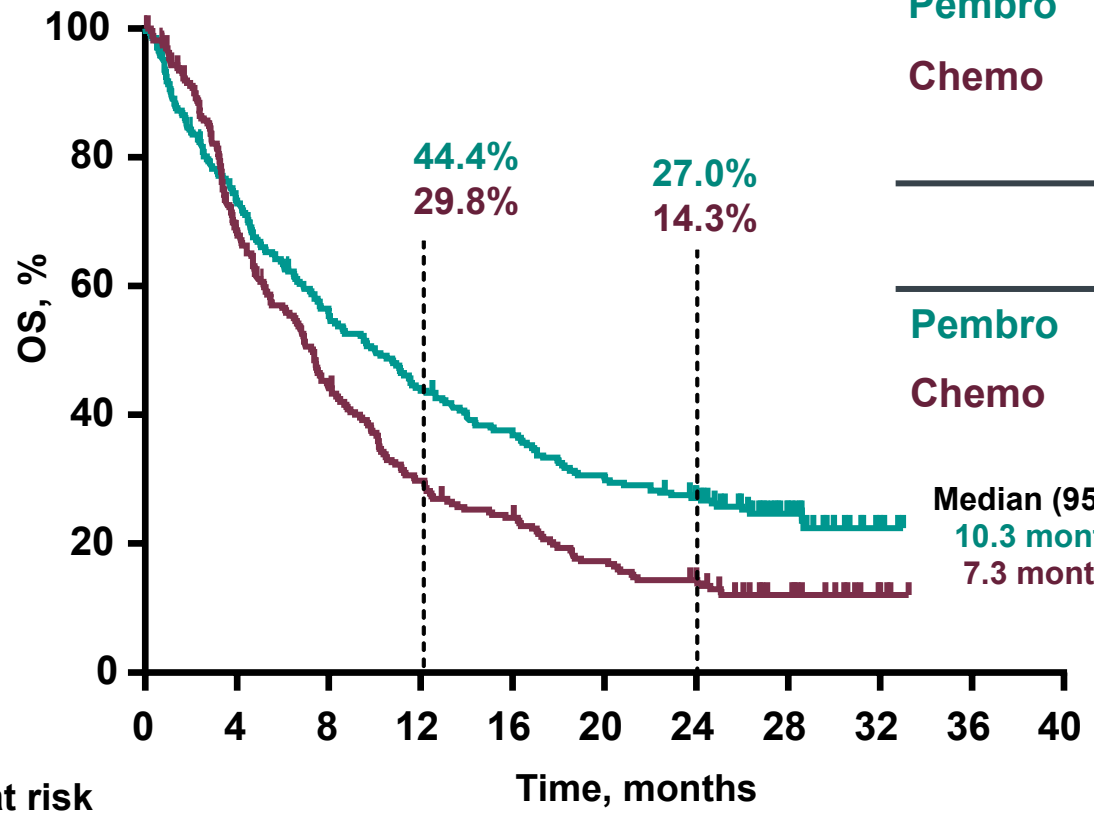
- With > 2.5 years of median follow-up, ORR and OS in previously treated patients (Cohort 2) were in line with prior data
  - Taken together with median DOR, which is now estimable for this cohort, data were consistent with Phase III results (IMvigor211)[18]
- With > 2 years of median follow-up, responses to 1L atezolizumab in cisplatin-ineligible patients with mUC (Cohort 1) appeared durable (median DOR not yet reached), resulting in continued improvement in OS since the primary analysis
- In Cohort 1, patients aged ≥ 80 years experienced a clinically meaningful benefit with atezolizumab, with median DOR also not yet reached in this subgroup
- These data warrant further investigation in a broader population of patients with mUC in the 1L setting. The randomized Phase III trial, IMvigor130, is ongoing (ClinicalTrials.gov identifier, NCT02807636)

KEYNOTE-045 Trial Follow-Up



1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.
2. Bajorin DF et al. *J Clin Oncol*. 2017;35(suppl 15):4501.
3. de Wit R et al. *Ann Oncol*. 2017;28(suppl 5):v605-v649.

Overall Survival: Total



No. at risk

Pembro	270	194	147	116	98	80	67	32	6	0	0
Chemo	272	173	109	73	58	41	33	18	4	0	0

14.1 months of follow-up[1]

	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

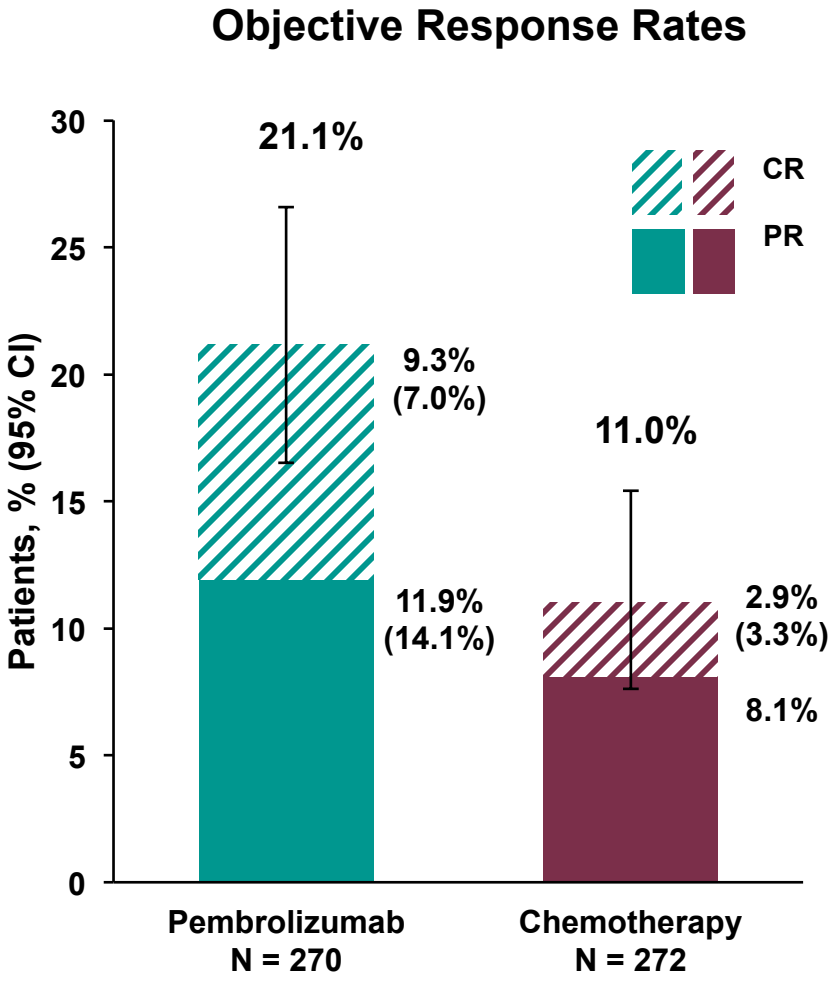
	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	199	0.70 (0.57–0.85)	0.00017
Chemo	218		

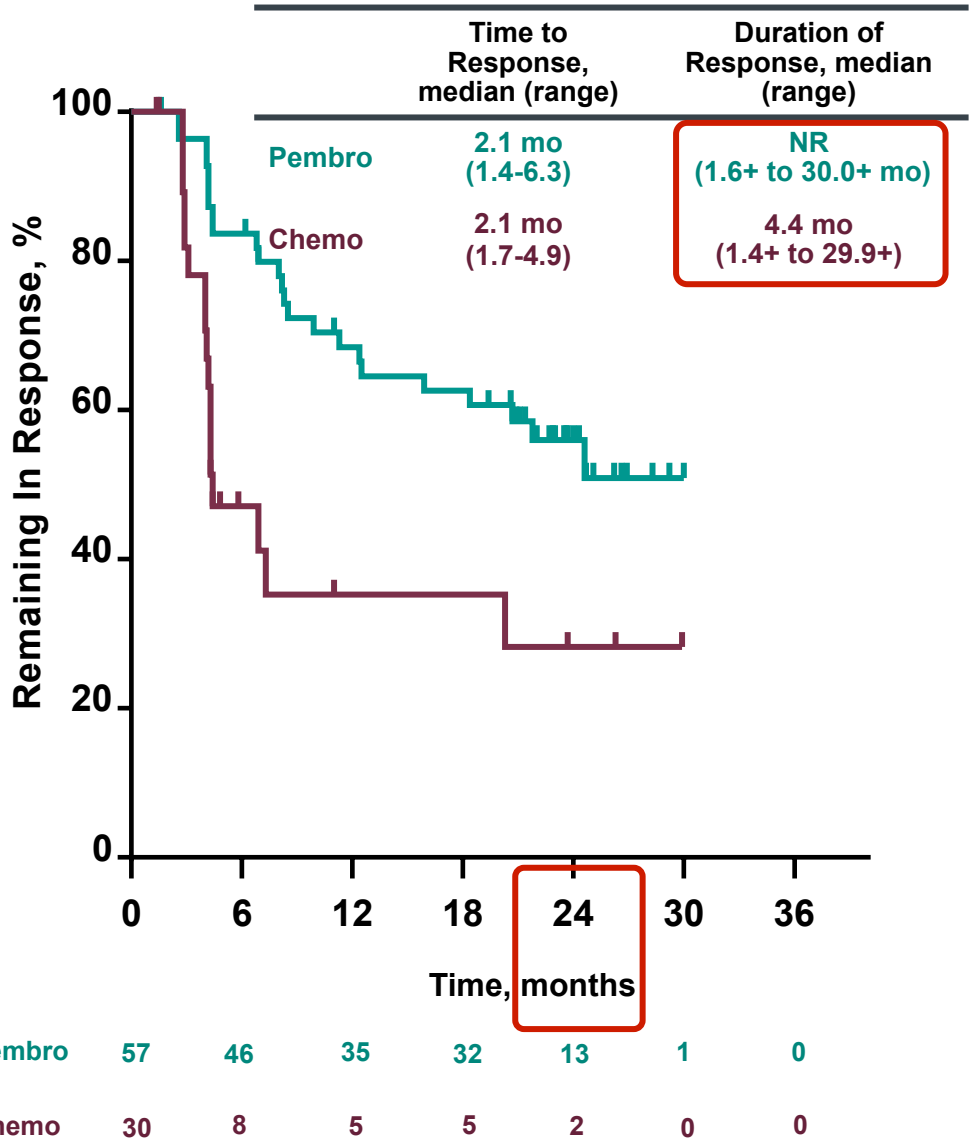
Median (95% CI):
10.3 months (8.0–12.3)
7.3 months (6.1–8.1)

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

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.
1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

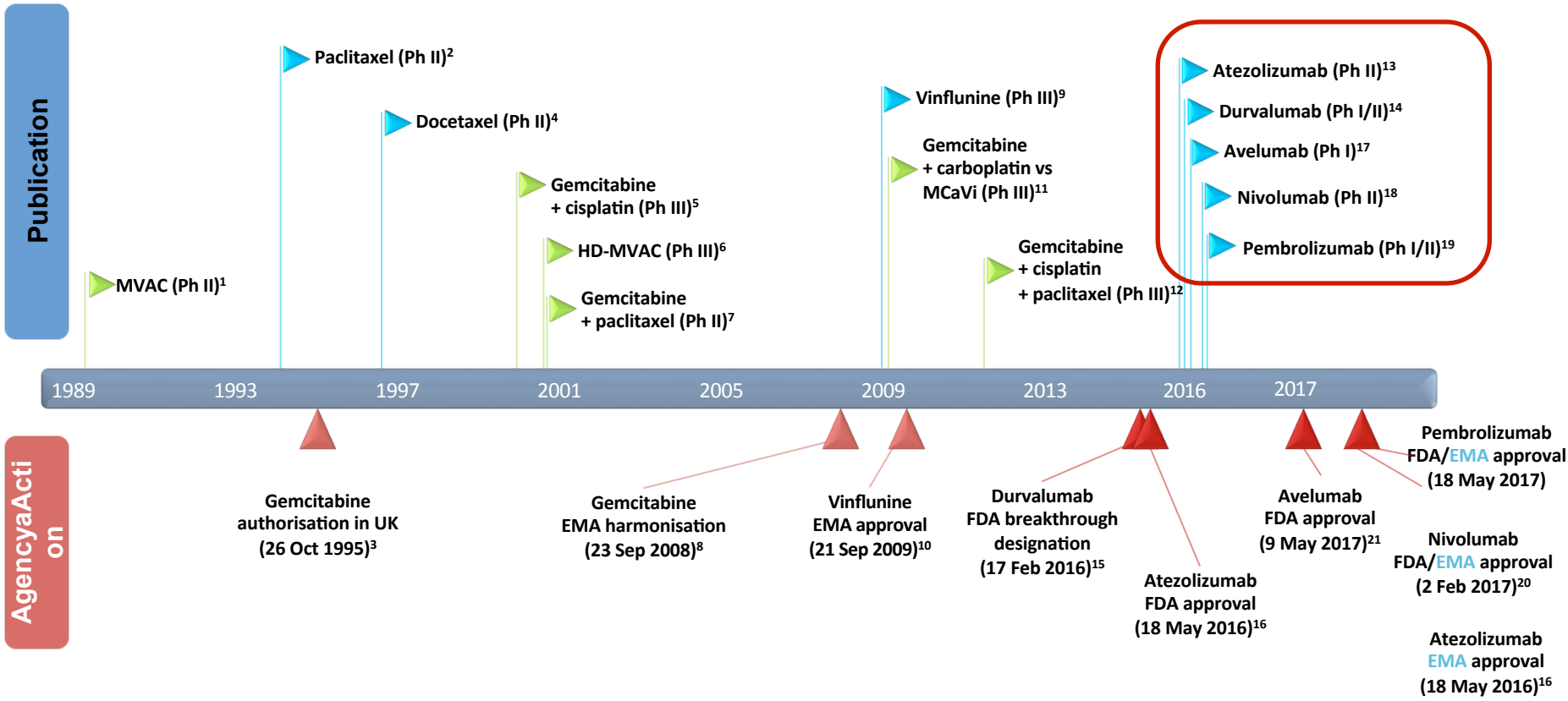
Objective Response and Response Duration





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

Evolution of systemic therapy for urothelial cancer to 2018



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.

Advanced Urothelial Cancer Treatment Algorithm: September 2018…

	Disease state	Context	Level 1 evidence	Standard Options
1st line	Metastatic, no prior chemotherapy	Cisplatin-eligible	Cisplatin-based combination chemotherapy	
1st line	Metastatic, no prior chemotherapy	Cisplatin-ineligible		Atezolizumab Pembrolizumab Nivolumab Gemcitabine/ carboplatin Single agent chemoth
2nd line	Metastatic, prior platinum chemotherapy or relapse within 1 year of perioperative cisplatin-based therapy		Pembrolizumab	Atezolizumab Nivolumab Durvalumab Avelumab
2nd line	Metastatic, prior immunotherapy			Taxane Vinflunine (EU)

Clinical trial enrollment very important throughout disease spectrum

Keynote 045 trial data interpretation

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)Version 2. 2018 Bladder Cancer

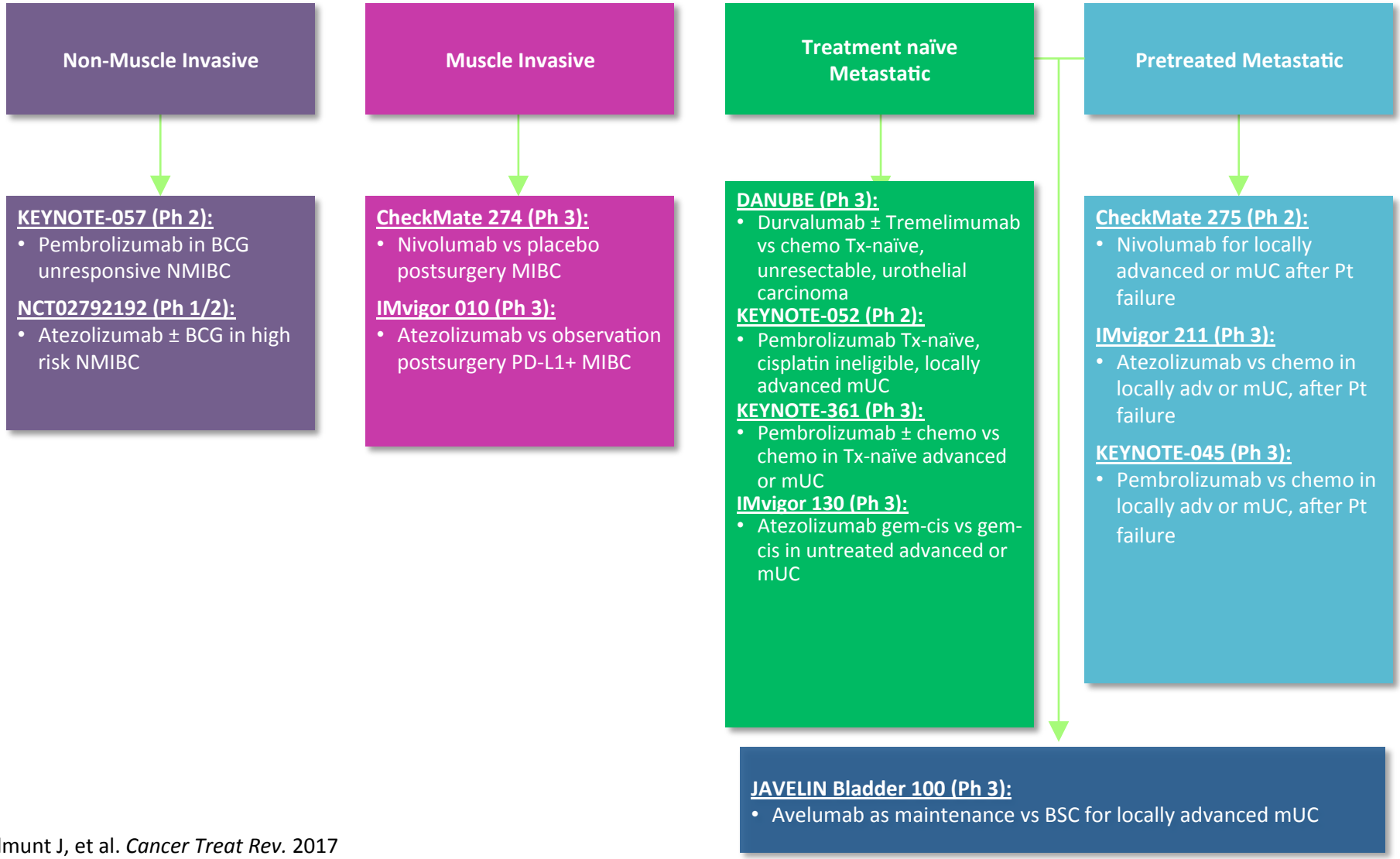
PRINCIPLES OF SYSTEMIC THERAPY

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[a] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1)[18]	Other recommended regimens • Nab-paclitaxel[26] • Paclitaxel or docetaxel[24] • Gemcitabine[14] • Pemetrexed[25]
Alternative preferred regimens • Atezolizumab[19] • Nivolumab[20] • Durvalumab[21] • Avelumab[22,23]	Useful in certain circumstances based on prior medical therapy • Ifosfamide[27] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

[a]If platinum (eg, cisplatin or carboplatin) more than 12 months ago, consider re-treatment with platinum if the patient is still platinum eligible.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Where Do We Go from Here?
Select Ongoing Trials in Bladder Cancer

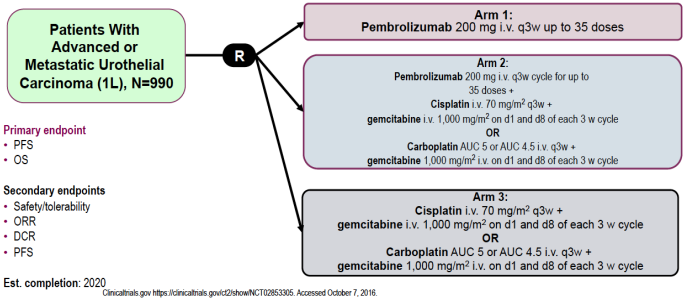


Bellmunt J, et al. *Cancer Treat Rev.* 2017

First line trials exploring IO/IO or chemo Immunotherapy given concurrently

KEYNOTE-361 (ongoing): Study Design

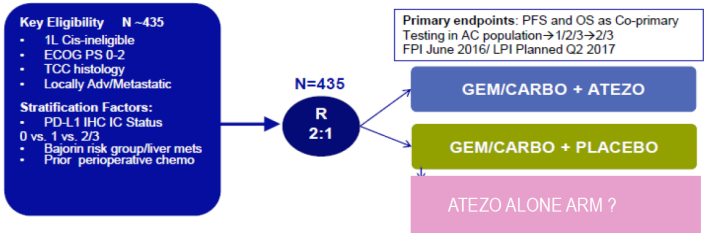
- A phase 3 randomized, controlled clinical trial of pembrolizumab +/- platinum-based combination chemotherapy vs chemotherapy in subjects with advanced or metastatic urothelial carcinoma



Clinicaltrials.gov https://clinicaltrials.gov/ct2/show/NCT02853305. Accessed October 7, 2016.

Chemotherapy + Immunotherapy in 1st- line "unfit"?

ImVigor 130



FIRST LINE PHASE III

DANUBE Study Design (NCT02516241)

Durvalumab ± Tremelimumab vs SOC in the first-Line Advanced UBC

Randomization Stratification Factors
1. Cisplatin eligibility (eligible vs. ineligible)
2. PD-L1 status (positive vs. negative)
3. Visceral metastasis (presence or absence; i.e., bone, lung or liver)

- TCC of the urothelium (renal pelvis, ureters, urinary bladder and urethra)
- Treatment-naïve patients
- Unresectable/ stage IV

Randomization
N = 650 patients

- Durvalumab + tremelimumab N = 217
- Durvalumab monotherapy N = 217
- SoC N = 217

Primary end points
PFS & OS (combo vs. SoC)

Secondary end points
- PFS (single agent vs SOC)
- PFS (PD-L1+ and PD-L1-)
- OS (combo vs. SoC)
- ORR (combo vs. SoC)
- FACT-BL
- Immunogenicity

Estimated timelines
Estimated completion: September 2019
Estimated primary data: March 2018

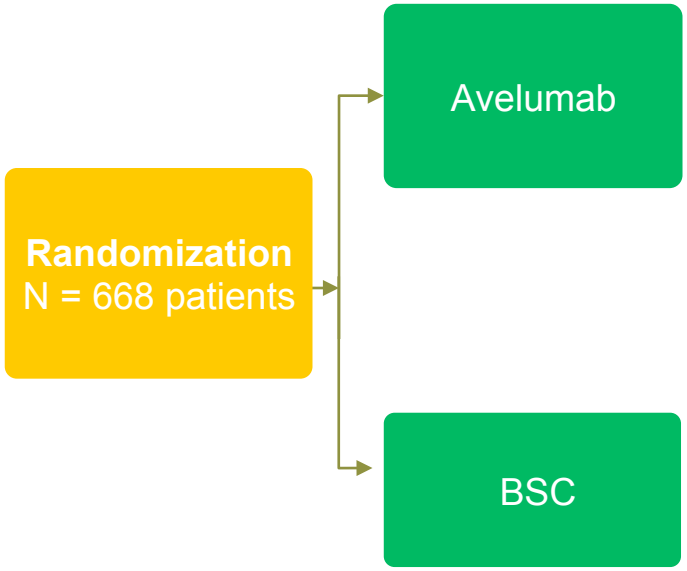
Study of Nivolumab in Combination With Ipilimumab Compared to the Standard of Care Chemotherapy in Treatment of Patients With Untreated Inoperable or Metastatic Urothelial Cancer (CheckMate901)

MAINTENANCE PHASE III

JAVELIN Bladder 100 Study Design (NCT02603432)

Maintenance treatment in patients with metastatic urothelial cancer after first-line platinum-based chemotherapy

- Advanced or metastatic transitional cell carcinoma of the urothelium
- Prior first-line chemotherapy (4 cycles- 6 cycles of gemcitabine + cisplatin and/or gemcitabine + carboplatin)
- No evidence of progressive disease following completion of first-line chemotherapy



Primary end point

OS

Secondary end points

- PFS
- ORR
- Duration of response
- Pk
- QOL

Estimated timelines
Estimated completion: July 2019

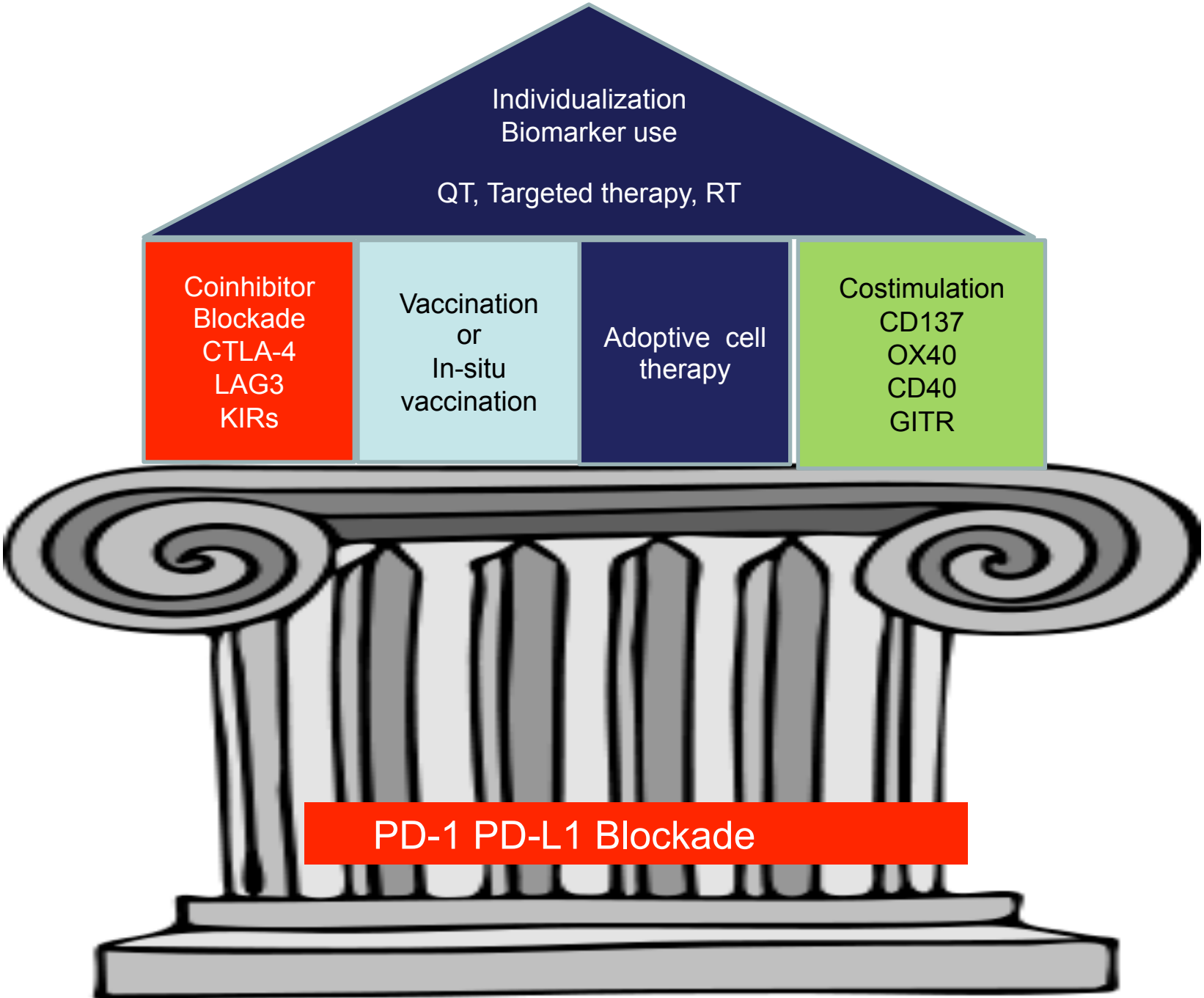
Immunotherapy in UC

- **Exciting times in the treatment of urothelial carcinoma**

- Immunotherapy is a well tolerated and active treatment for our patients
- → **But only 15-20% of patients derive benefit** and many open questions remain

  with regards to understanding predicting factors

- Refining choices
  - Combinations ? Sequential therapy ?
    - IO/IO
    - IO/Immune based therapies (vaccines, ADC, Bispecific antibodies, CAR-T cells…)
    - IO + Targeted agents (cabozantinib, FGFr3 inh..)
    - Combination/ Sequential use of chemo and XRT
    - Customized: Biomarker/Genomically driven designs


Individualization
Biomarker use
QT, Targeted therapy, RT
Coinhibitor Blockade
CTLA-4
LAG3
KIRs
Vaccination or In-situ vaccination
Adoptive cell therapy
Costimulation
CD137
OX40
CD40
GITR
PD-1 PD-L1 Blockade