IMUNOTERAPIA NOS TUMORES UROLÓGICOS: ONDE ESTAMOS E PARA ONDE VAMOS?

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Declaração sobre Potenciais Conflitos de Interesse

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro que:

- *Apresentações*: como palestrante convidado, participo dos eventos de: Janssen, Pfizer, Bayer, Novartis, Astra Zeneca, Astellas, Pierre-Fabre, Merck-Serono, Sanofi, Roche.
- *Consultoria*: como membro de *advisory boards*, participo de reuniões com: Astellas, Janssen, Roche, Bayer, Lilly, Astra Zeneca, Novartis, MSD, BMS.

Não possuo ações de quaisquer destas companhias farmacêuticas.

Os meus pré-requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão, aspectos que esta empresa respeita.

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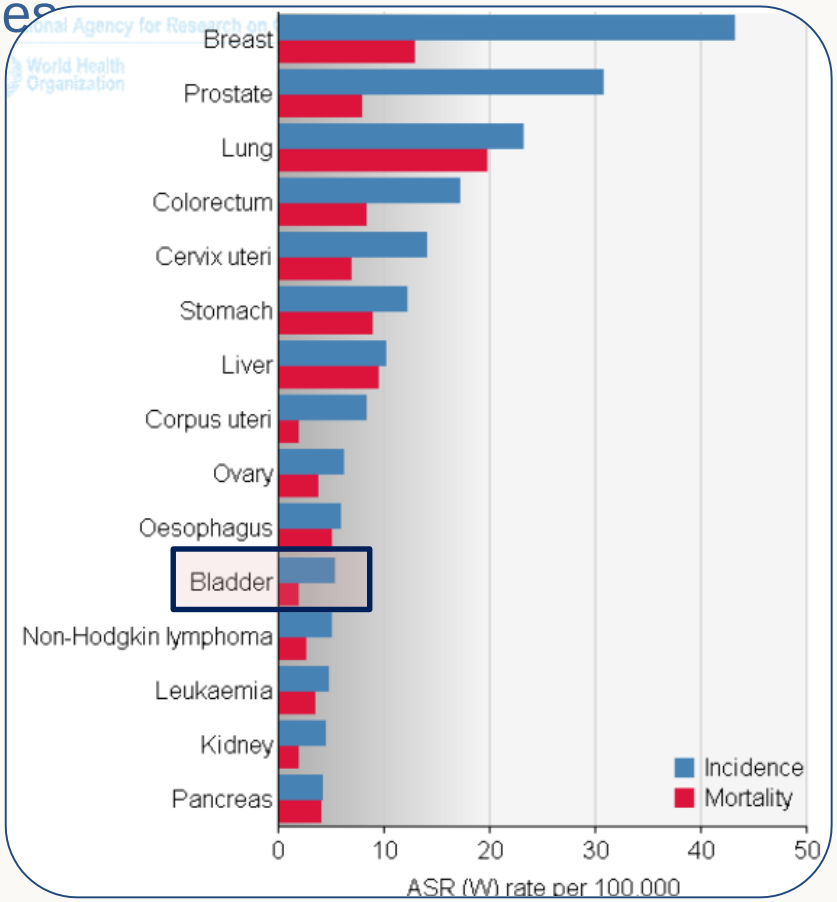
- Bladder cancer is the ninth most common cancer in the world, with 429,793 new cases diagnosed and 165,084 deaths in 2012
- About 59 per cent of bladder cancer cases occur in more developed countries
- It is four times more common in men compared with women
- Bladder cancer incidence is approximately 70% lower in Asia and South America compared with Western industrialized countries



Ferlay J, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet].

Epidemiology – Worldwide

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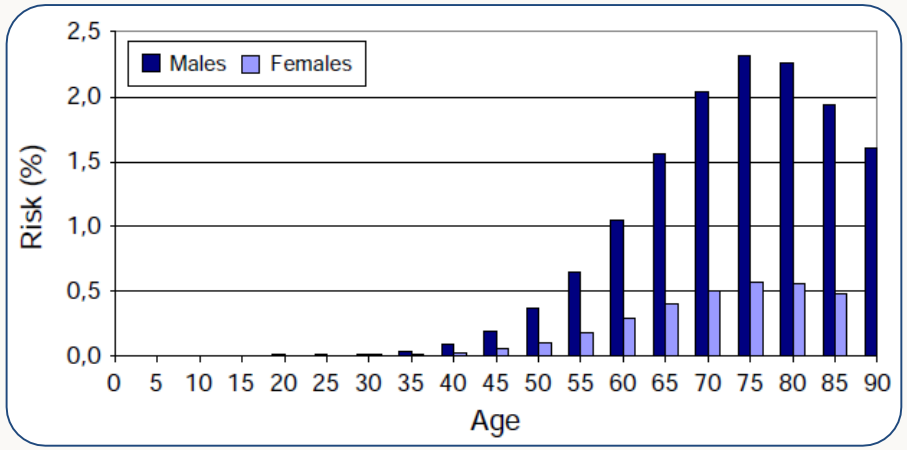
- Bladder cancer is the second most common urologic malignancy
- There has been a 50% increase in incidence over the past 40 years
- Urothelial cancer is a cancer of the environment and age
- The incidence and prevalence rates increase with age, especially in the sixth decade and peaking in the 8th decade of life



Ferlay J, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet].

Epidemiology – Brazil

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- There were an estimated 9,670 bladder cancer cases in 2016
- 6,2% of all malignant tumors in Brazil
- Bladder cancer is the second most common urologic malignancy

Localização Primária Neoplasia Maligna	Estimativa dos Casos Novos							
	Homens				Mulheres			
	Estados		Capitais		Estados		Capitais	
	Casos	Taxa Bruta	Casos	Taxa Bruta	Casos	Taxa Bruta	Casos	Taxa Bruta
Próstata	61.200	61,82	13.940	64,93	-	-	-	-
Mama Feminina	-	-	-	-	57.960	56,20	18.990	79,37
Colo do Útero	-	-	-	-	16.340	15,85	4.550	19,07
Traqueia, Brônquio e Pulmão	17.330	17,49	4.430	20,59	10.890	10,54	3.230	13,49
Cólon e Reto	16.660	16,84	5.560	25,80	17.620	17,10	6.210	25,95
Estômago	12.920	13,04	3.130	14,54	7.600	7,37	2.180	9,07
Cavidade Oral	11.140	11,27	2.780	12,95	4.350	4,21	1.230	5,04
Laringe	6.360	6,43	1.600	7,50	990	0,94	320	0,97
Bexiga	7.200	7,26	2.110	9,79	2.470	2,39	830	3,21
Esôfago	7.950	8,04	1.460	6,75	2.860	2,76	610	2,27
Ovário	-	-	-	-	6.150	5,95	2.170	8,92
Linfoma de Hodgkin	1.460	1,46	450	1,74	1.010	0,93	400	1,33
Linfoma não Hodgkin	5.210	5,27	1.550	7,15	5.030	4,88	1.670	7,02
Glândula Tireoide	1.090	1,08	350	1,27	5.870	5,70	1.800	7,46
Sistema Nervoso Central	5.440	5,50	1.290	5,86	4.830	4,68	1.250	5,20
Leucemias	5.540	5,63	1.370	6,38	4.530	4,38	1.180	4,88
Corpo do Útero	-	-	-	-	6.950	6,74	2.530	10,47
Pele Melanoma	3.000	3,03	840	3,86	2.670	2,59	740	2,96
Outras Localizações	51.850	52,38	11.890	55,45	47.840	46,36	11.820	49,33
Subtotal	214.350	216,48	52.750	245,63	205.960	199,57	61.710	257,55
Pele não Melanoma	80.850	81,66	17.370	80,90	94.910	91,98	21.910	91,65
Todas as Neoplasias	**295.200**	**298,13**	**70.120**	**326,51**	**300.870**	**291,54**	**83.620**	**348,99**

Estimativa 2016. Incidência de Câncer no Brasil. http://www.inca.gov.br/estimativa/2016/

Pontos chaves no tratamento atual do câncer de bexiga

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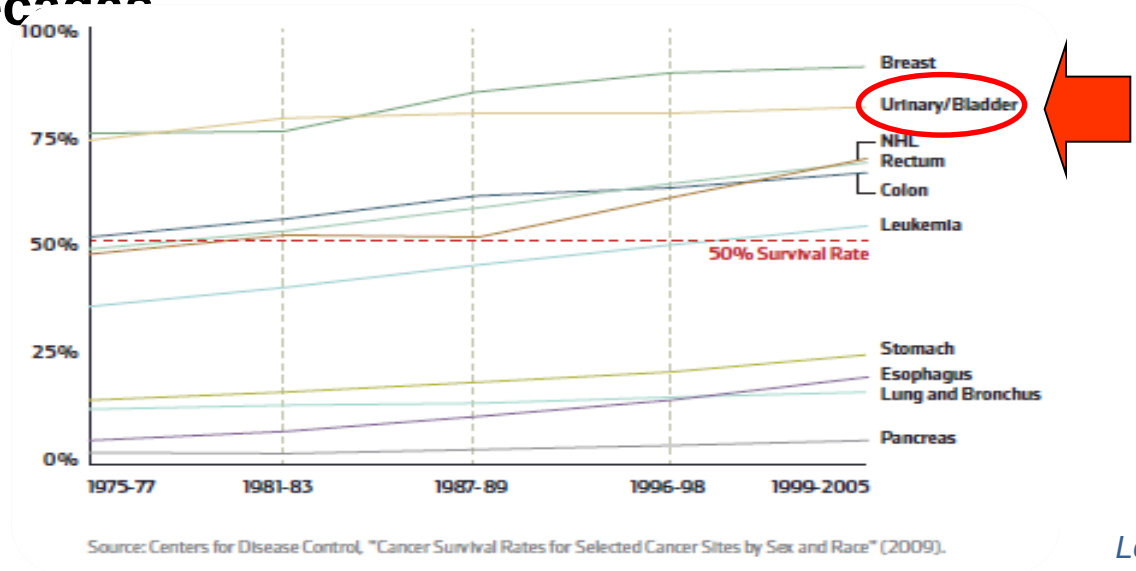
- **Recursos modestos & pesquisas limitadas**
  - Embora tenha havido melhora nas técnicas cirúrgicas e RT
  - Pouco progresso foi alcançado:
    - Introdução da BCG na década de 1970
    - M-VAC primeiro uso na década de 1980s

- **A sobrevida não aumentou na doença metastática por décadas**



Lotan Y, Cancer 2009
Stenzl A et al, Eur Urol

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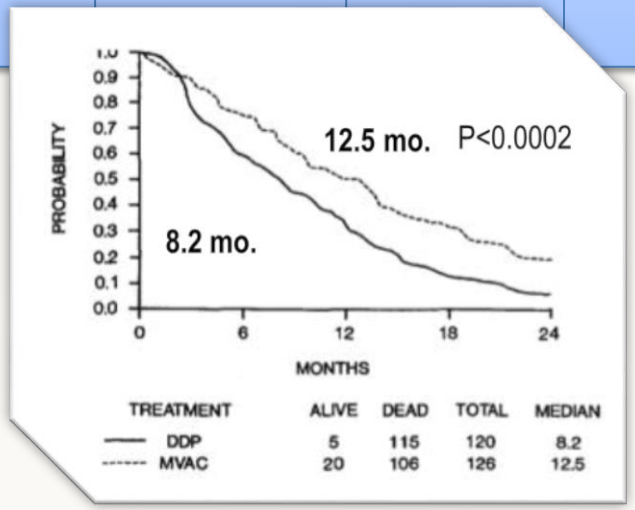
First Line Treatment

	Cisplatina[1]	MVAC[1]	MVAC[2]	HD-MVAC[2]	MVAC[3]	GC[3]	GC[4]	PCG[4]
TR	12%	39%	50%	64%	46%	49%	44%	56%
SLP	4 meses	10 meses	8,1 meses	9,5 meses	7 meses	7 meses	7,6 meses	8,3 meses
SG	8 meses	13 meses	14,9 meses	15,1 meses	15 meses	14 meses	13 meses	16 meses



1. Loehrer PJ Sr, et al. J Clin Oncol 1992; 10:1066.
2. Stenrberg CN, et al. Eur J Cancer. 2006 Jan;42(1):50-4. Epub 2005 Dec 5.
3. von der Maase H, et al. J Clin Oncol 2000; 18:3068.
4. Bellmunt J, et al. J Clin Oncol 2012; 30:1107.

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Progressão após 1° linha com platina

T4b N0 M0

ou

Qualquer T N2-3 M0

ou

Qualquer T Qualquer N M1

ECOG/WHO PS 0-1

Quimioterapia neo/ adjuvante não permitida

Vinflunina + Best Sup Care até PD (N=253)

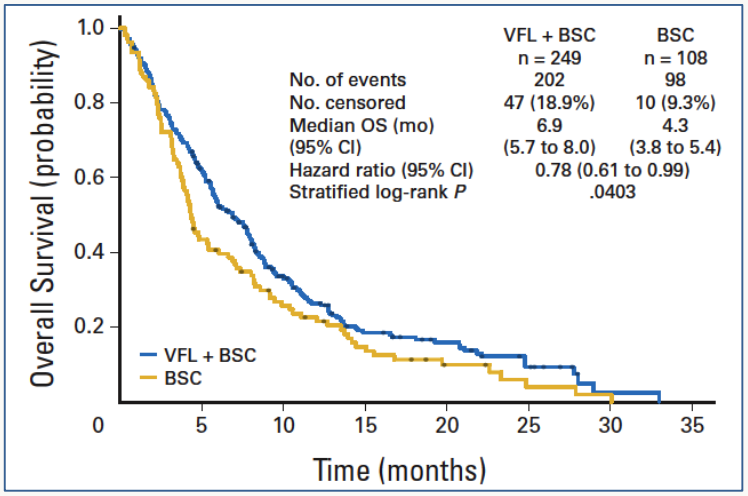
320 mg/m^2 ou 280 mg/m2 a cada 3 semanas

Randomização 2:1

Best Supportive Care até PD (N = 117)

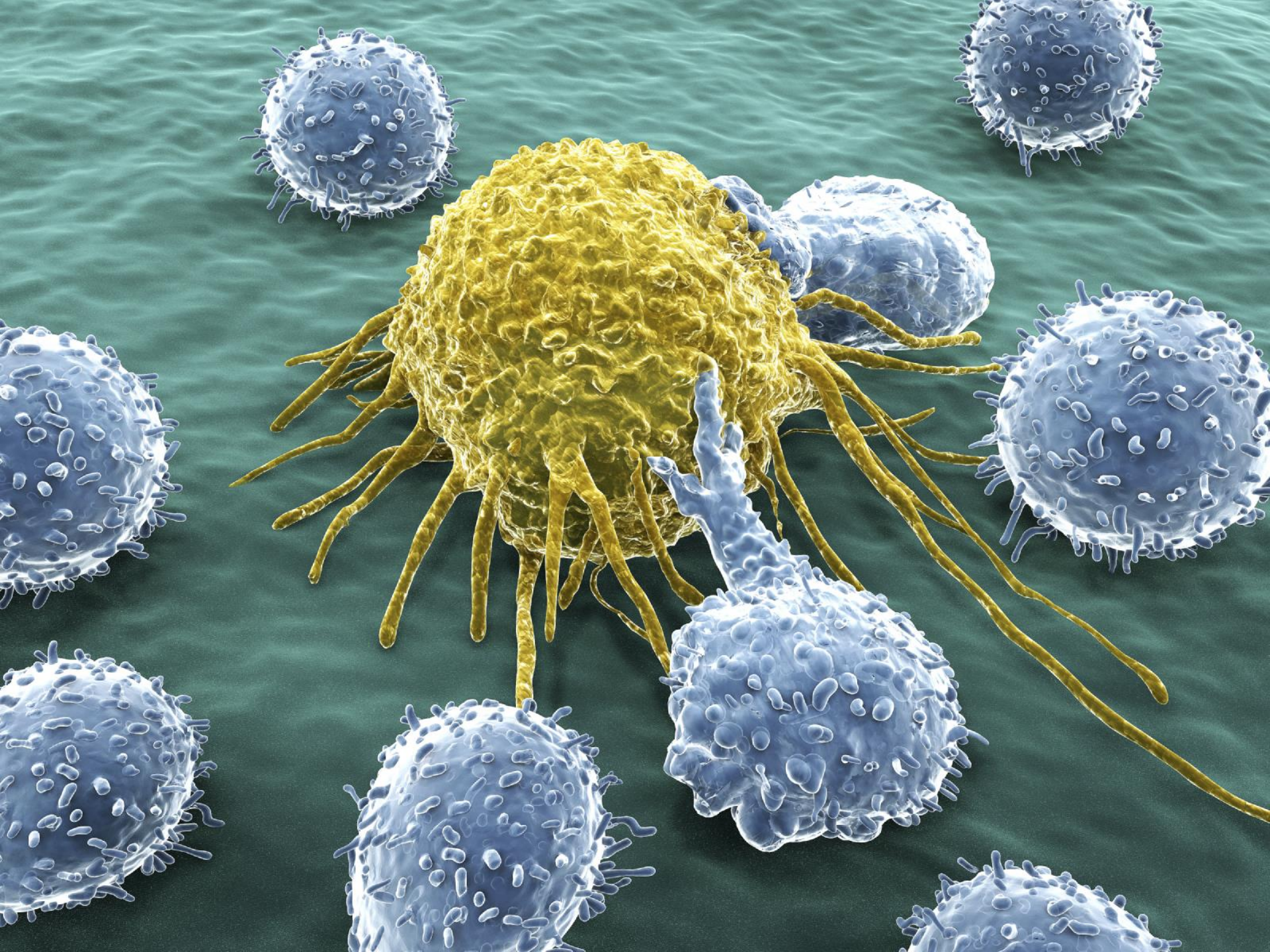
Endpoint primário: SG

Endpoints secundários: ORR, DCR, PFS, QoL, Segurança



- **Hipótese estatística: Sobrevida mediana= 6 meses Vs. 4 meses**; α= 5%, β= 10%
  - –Análise primária: População (ITT) “Intent-to-treat “
  - –Análise secundária: População Elegível
- **Análise de Cox multivariada pré –planejada em SG (ITT):** ajustada pelos fatores prognósticos

1. Bellmunt J, et al. J Clin Oncol 2009;27(27):4454-61. 2. Bellmunt J, et al. Ann Oncol 2013;24(6):1466-72



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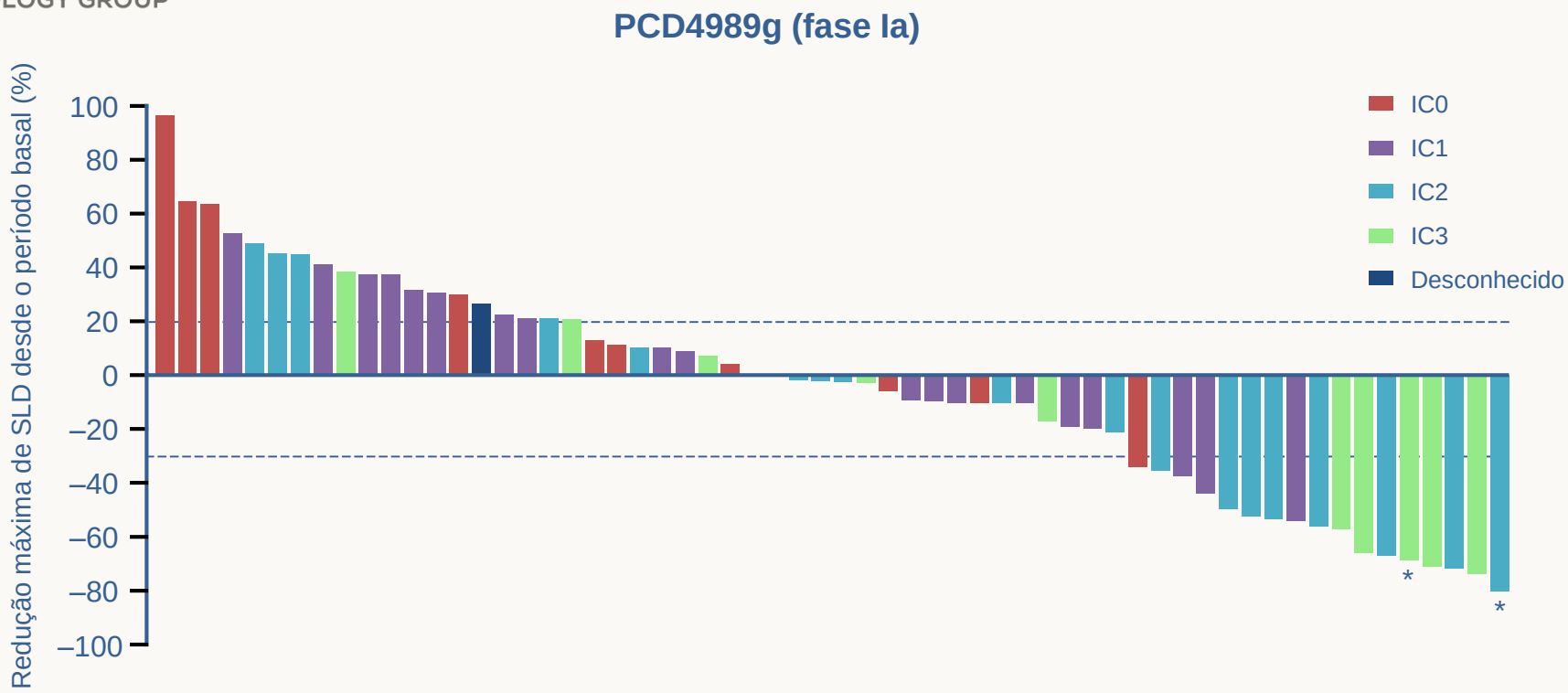
Atezolizumabe foi o primeiro inibidor de PDL1/PD-1 a demonstrar eficácia em câncer urotelial



*Pacientes com respostas completas que apresentaram ≤100% de redução das lesões alvo devido às lesões alvo nos linfonodos retornaram ao tamanho normal de acordo com RECIST v1.1.

Powles et al. Nature 2014

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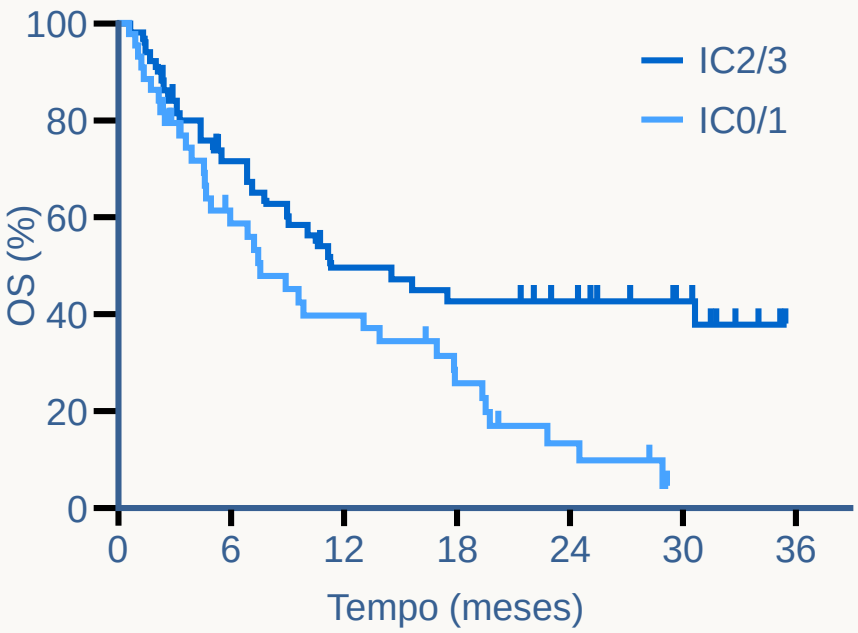
O acompanhamento prolongado >2 anos confirmou o benefício clínico de atezolizumabe

PCD4989g (acompanhamento mediano: 29,2 meses)



	IC0/1 n=43	IC2/3 n=51	ITT N=95*
ORR, %	12 (4–25)	39 (26–54)	27 (18–37)†
CR, %	2	16	10†
DoR mediana, meses (faixa)	26,3 (6,2–27,6)	18,0 (2,8 a 32,9+)	22,1 (2,8 to 32,9+)†
OS mediana, meses (IC de 95%)	7,6 (4,7–13,9)	11,3 (7,8–NE)	10,1* (7,3–17,0)
OS de 12 meses, % (IC de 95%)	40 (25–56)	50 (36–64)	46* (35–56)

*População de eficácia avaliável com ≥12 semanas de acompanhamento
†População com resposta objetiva avaliável (n=94). Inclui 9 pacientes com respostas ausentes/não avaliáveis
Petrylak et al. ASCO GU 2017

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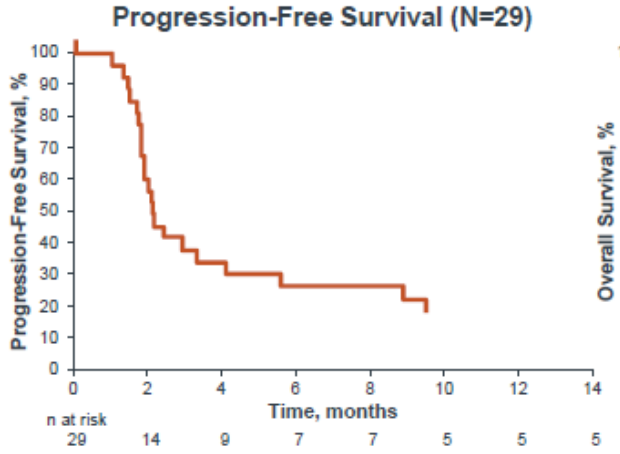
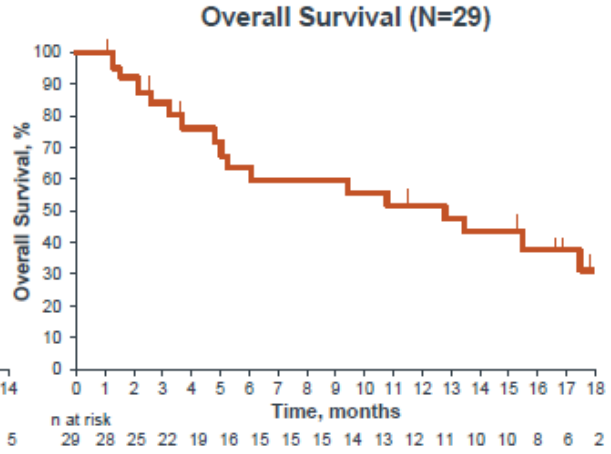
KN - 012

	Pembrolizumab 10 mg/kg Q2W N=33 (27 assessable). Median FU: 13 mo (1-26) N / % (95% CI)
ORR	7 / 26% (11, 46) p=0.0147
Best overall response	
Complete response	3 / 11% (2, 29)
Partial response	4 / 15% (4, 34)
Stable response	4 / 15% (4, 34)
Progressive Disease	14 / 52% (32, 7)
Unavailable	2/ 7%

- KEYNOTE-012: Results *(continued)*





- Median PFS: 2 months (95% CI, 1.7–4.0)
- PFS rate at 12 months: 19.1%
- Median OS: 12.7 months (95% CI, 5.0–NR)
- OS rate at 12 months: 52.9%

Analysis cutoff date: March 23, 2015

1. Pilmack ER, et al. *J Clin Oncol.* 2015;33:5s:Abstract 4502.

Lancet Oncol. 2017 Feb;18(2):212-220.

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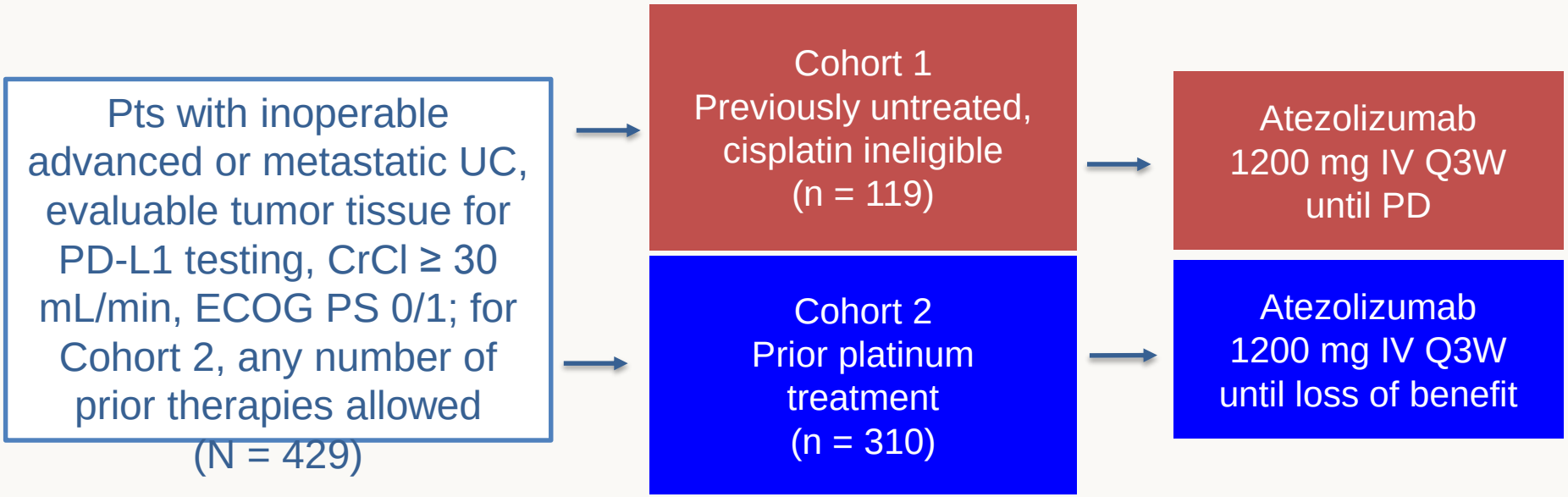
IMvigor 210: Atezolizumab for Advanced Urothelial Cancer

- ✓ Single-arm phase II study with 2 cohorts



- ✓ Primary endpoint: confirmed ORR by RECIST v1.1 (per central review)
- ✓ Secondary endpoints: DoR, PFS, OS, safety
- ✓ Exploratory endpoints: biomarkers

Lancet. 2017 January 07; 389(10064): 67–76

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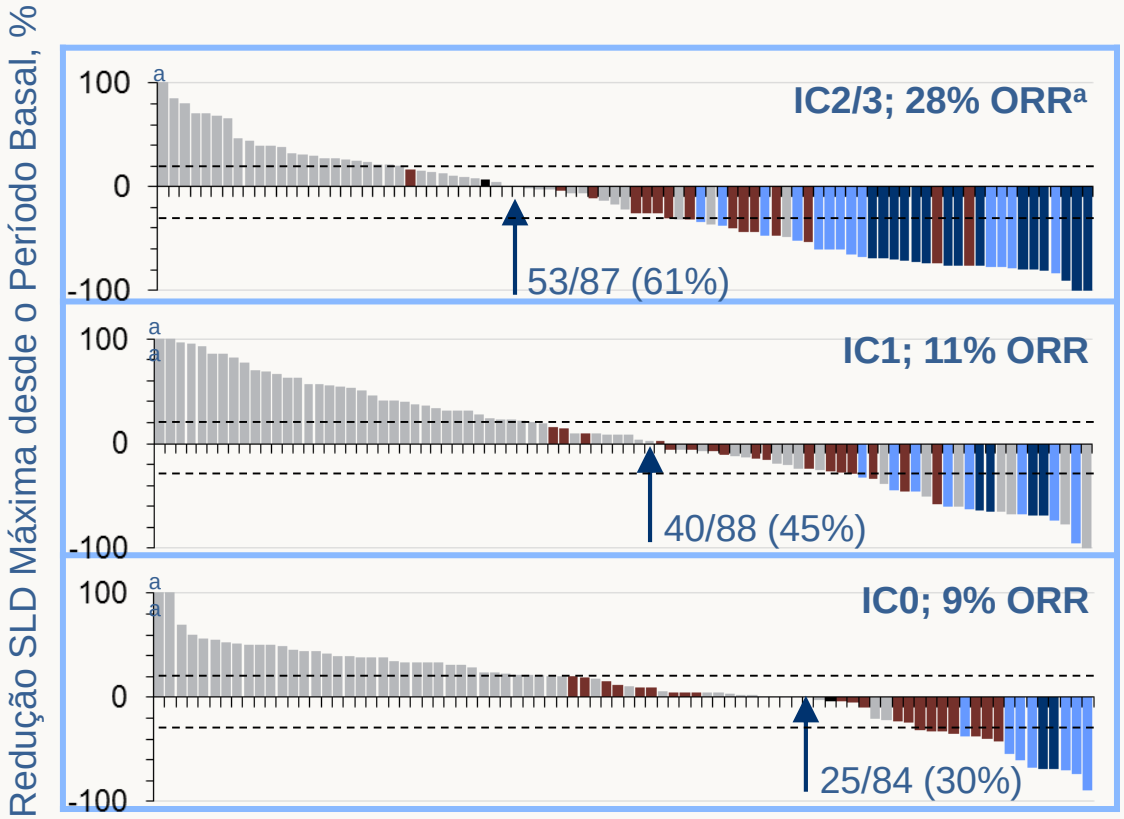
Eficácia

Redução da Carga Tumoral



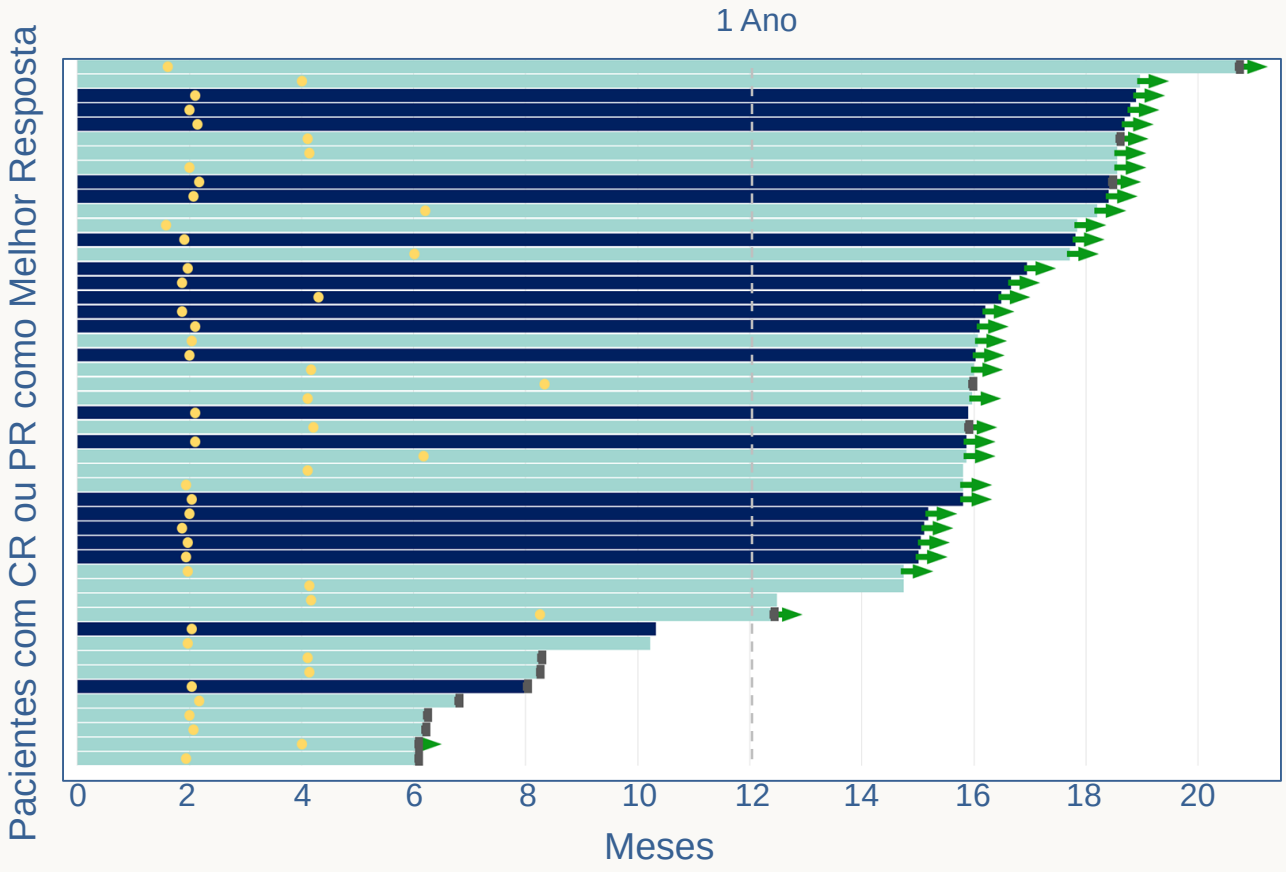
- ✓ 46% dos pacientes avaliáveis (118/259) apresentaram uma redução nas lesões alvo
  - ✓ Redução maior na carga tumoral vista com maior status PD-L1

Resposta RECIST v1.1
■ PD ■ SD ■ PR ■ CR ■ NE

Dreicer R, et al. IMvigor210: atezolizumab in platinum-treated mUC. ASCO 20

Eficácia

Duração do Tratamento e Resposta



- ✓ 71% das respostas (35/49) estavam em andamento
  - ✓ 86% das CRs estavam em andamento
- ✓ mDOR ainda não foi alcançada em qualquer subgrupo PD-L1 (faixa, 2,1+ a 19,2+ meses)[a]

- CR como melhor resposta
- PR como melhor resposta
- Primeira CR/PR
- Descontinuação do Tratamento[b]
- Resposta em andamento

[A] De acordo com IRF RECIST v1.1. [b] O símbolo da descontinuação não indica o horário. [c] Sem PD ou óbito somente. Corte de dados: 14 de março de 2016.

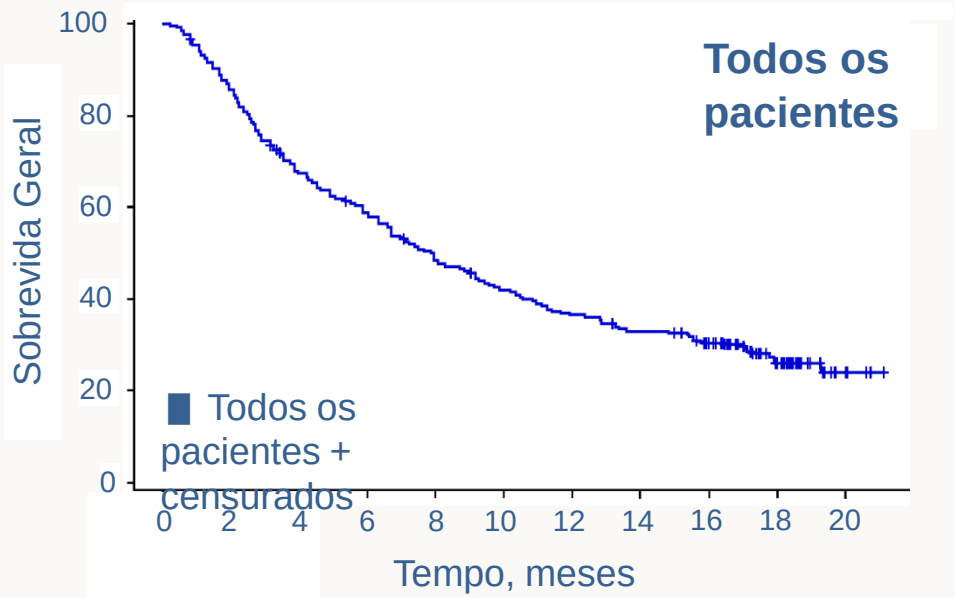
O tempo mediano até a primeira resposta[a] foi de 2,1 meses

Dreicer R, et al. IMvigor210: atezolizumab in platinum-treated mUC. ASCO

Eficácia

Sobrevida Geral

- ✓ OS mais linga observada em pacientes maior status de PD-L1 CI
- ✓ A OS de 12 meses se compara favoravelmente com estimativas históricas de ≈ 20%[1]



# em Risco:											
Todos os pacientes:	310	265	203	176	146	126	110	97	82	35	5

Subgrupo	OS Mediana (IC de 95%)		
	IC2/3	IC0/1	Todos
Todos os pacientes (N = 310)	11,9 meses (9,0, 17,9)	6,7 meses (5,4, 8,0)	7,9 meses (6,7, 9,3)
2L somente (n = 120)	NE (10,9, NE)	7,1 meses (5,0, 9,2)	9,0 meses (7,2, 11,3)

Subgrupo	OS de 12-meses (IC de 95%)		
	IC2/3	IC0/1	Todos
Todos os pacientes (N = 310)	50% (40, 60)	31% (24, 37)	37% (31, 42)
2L somente (n = 120)	61% (44, 77)	29% (19, 39)	38% (29, 47)

Acompanhamento mediano (faixa):
Todos os pacientes: 17,5 meses (0,2 a 21,1+ meses)
2L somente: 17,3 meses (0,5 a 21,1+ meses)

NE, não estimável. [A] Uma linha de terapia anterior para mUC e nenhuma terapia (neo)adjuvante. Corte de dados: 14 de março de 2016. 1. Agarwal *Clin Genitourin Cancer* 2014.

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Segurança
Resumo

- ✓ Atezolizumabe foi geralmente bem tolerado, sem óbitos relacionados ao tratamento
  - ✓ A duração mediana do tratamento foi de 12 semanas (faixa, 0-89) com uma mediana de 5 doses (faixa, 1-30)

EA (N = 310)	Todas as Causas	Relacionado ao Tratamento
Qualquer EA	97%	70%
EA Grave	46%	12%
EA Grau 3-4	57%	16%
EA Grau 5[a]	1%	0%
EA imunomediado[b]	10%	–
EA ocasionando a retirada do tratamento	3%	NA
EA ocasionando a interrupção da dose	31%	NA

[A] EAs de Grau 5 incluíam: hemorragia cerebral, sepse pulmonar e subíleo (oclusão intestinal). Corte de dados: 14 de março de 2016.

[B] EAs que exigem corticosteroides sem uma etiologia alternativa.

KEYNOTE-045 Study Design (NCT02256436)

Key Eligibility Criteria

- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1-2 lines of platinum-based chemo or recurrence within 12 mo of perioperative platinum-based therapy
- ECOG PS 0-2
- Provision of tumor sample for biomarker assessment

R (1:1)
N = 542

N = 270 → Pembrolizumab 200 mg IV Q3W for 2 years

N = 272 → Paclitaxel 175 mg/m^2 Q3W
OR
Docetaxel 75 mg/m^2 Q3W
OR
Vinflunine 320 mg/m^2 Q3W

Stratification Factors

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

Key End Points

Primary: OS and PFS in total and PD-L1 CPS ≥10% populations

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

Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

CPS = combined positive score.

KEYNOTE-045: Baseline Characteristics

Characteristic	Pembro (n = 270)	CT (n = 272)
Median age, yrs (range)	67 (29-88)	65 (26-84)
Male, n (%)	200 (74.1)	202 (74.3)
Upper tract disease, n (%)	38 (14.1)	37 (13.6)
ECOG PS, n (%) ▪ 0 ▪ 1 ▪ 2	 120 (44.4) 143 (53.0) 2 (0.7)	 106 (39.0) 158 (58.1) 4 (1.5)
Disease, n (%) ▪ Visceral ▪ Lymph node only ▪ Liver metastases	 241 (89.3) 28 (10.4) 91 (33.7)	 234 (86.0) 38 (14.0) 95 (34.9)
Setting of most recent tx, n (%) ▪ Neoadjuvant ▪ Adjuvant ▪ First line ▪ Second line ▪ Third line	 19 (7.0) 12 (4.4) 184 (68.1) 55 (20.4) 0	 22 (8.1) 31 (11.4) 158 (58.1) 59 (21.7) 2 (0.7)

Characteristic, n (%)	Pembro (n = 270)	CT (n = 272)
Hemoglobin < 10 g/dL	43 (15.9)	44 (16.2)
≥ 3 mos since last therapy	167 (61.9)	168 (61.8)
PD-L1 CPS ≥ 10%	74 (27.4)	90 (33.1)
Prior platinum therapy ▪Cisplatin ▪Carboplatin ▪Oxaliplatin or nedaplatin	 199 (73.7) 70 (25.9) 1 (0.4)	 214 (78.7) 56 (20.6) 2 (0.7)
Smoking status ▪Never ▪Former ▪Current	 104 (38.5) 136 (50.4) 29 (10.7)	 83 (30.5) 148 (54.4) 38 (14.0)
Risk factors* ▪0 ▪1 ▪2 ▪3-4	 54 (20.0) 96 (35.6) 66 (24.4) 45 (16.7)	 45 (16.5) 97 (35.7) 80 (29.4) 45 (16.5)

*ECOG PS > 0, Hb < 10 g/dL, liver mets, < 3 mos since CT.

Bajorin DF, et al. ASCO 2017. Abstract 4501.

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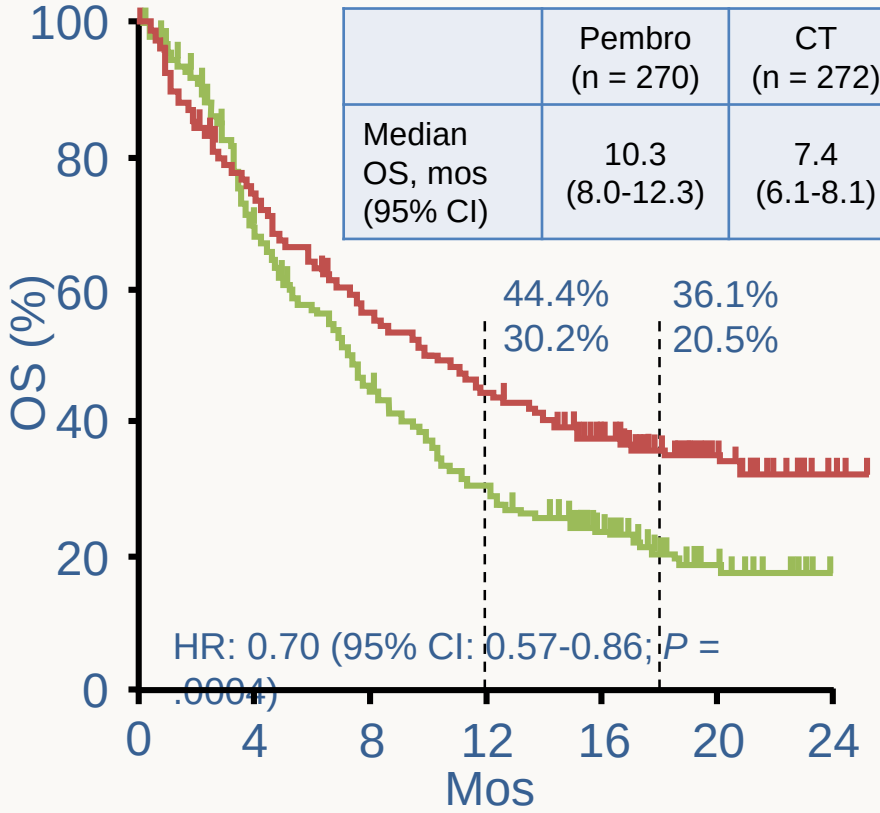
KEYNOTE-045: OS

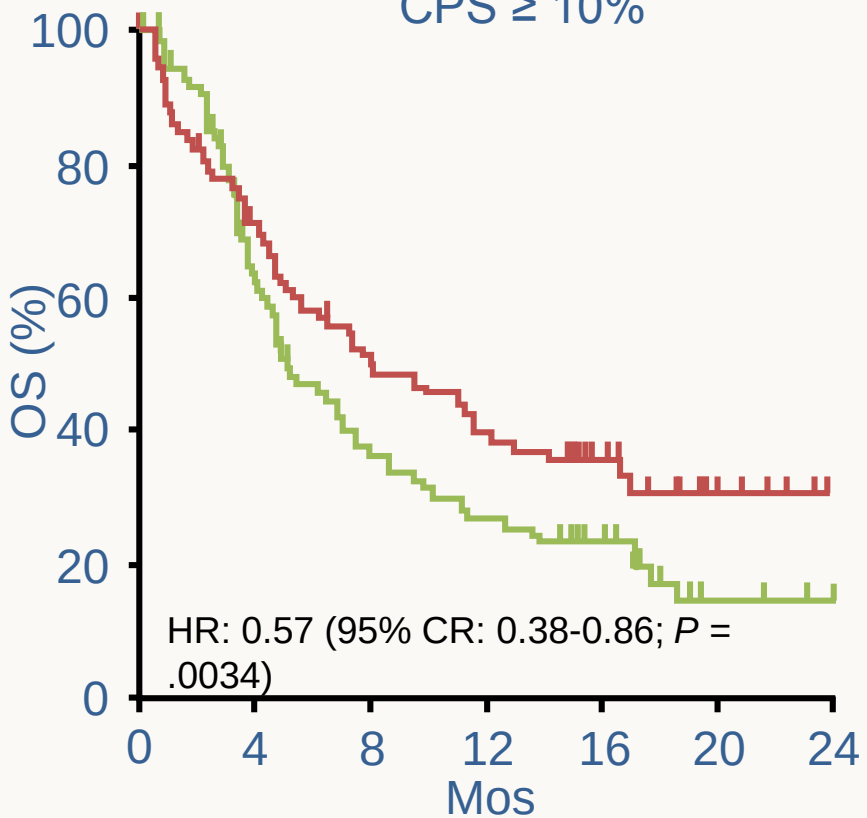
OS in All Pts

	Pembro (n = 270)	CT (n = 272)
Median OS, mos (95% CI)	10.3 (8.0-12.3)	7.4 (6.1-8.1)



Pembro	270	194	147	116	79	27	4
CT	272	171	109	73	46	15	1

OS in Pts With PD-L1* CPS ≥ 10%

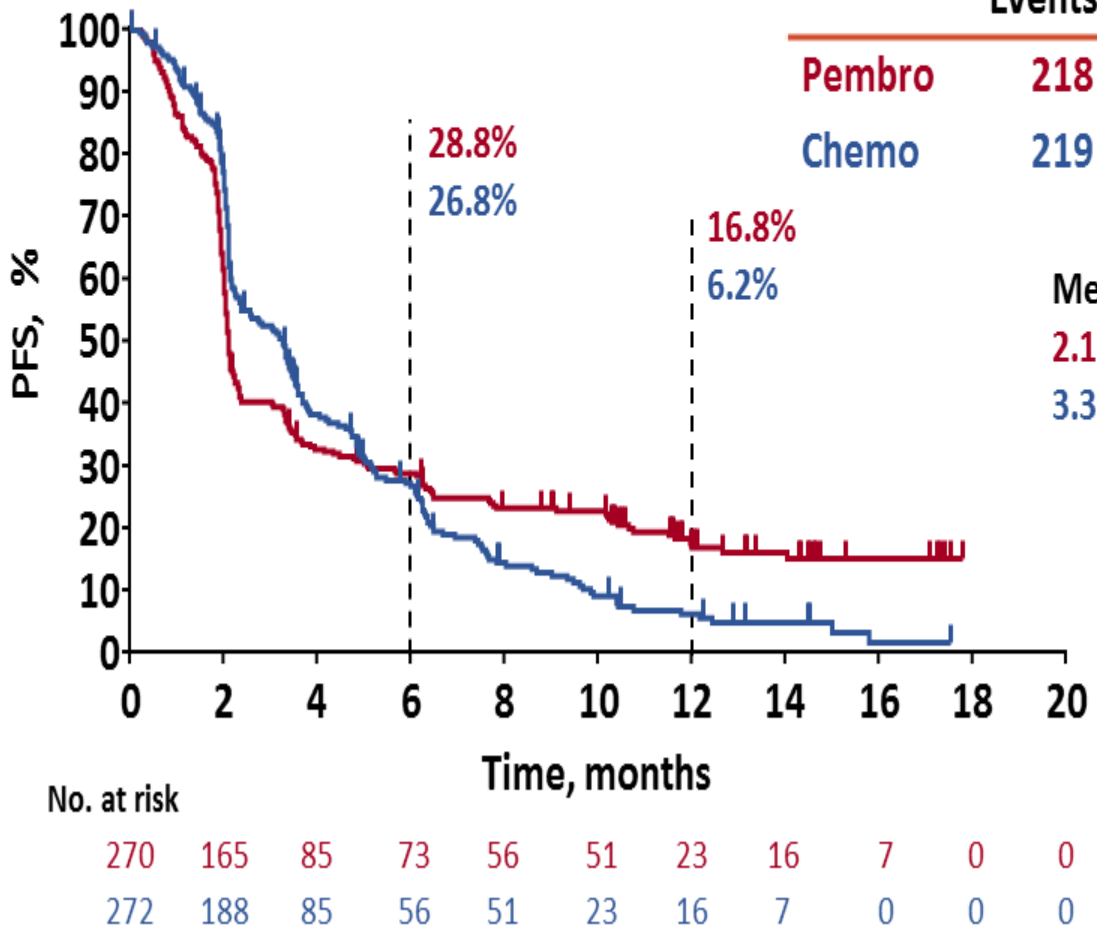


Pembro	74	51	35	28	17	7	0
CT	90	51	28	21	14	3	1

*Assayed with PD-L1 IHC 22C3 pharmDx.

Bajorin DF, et al. ASCO 2017. Abstract 4501.

Progression-Free Survival: Total



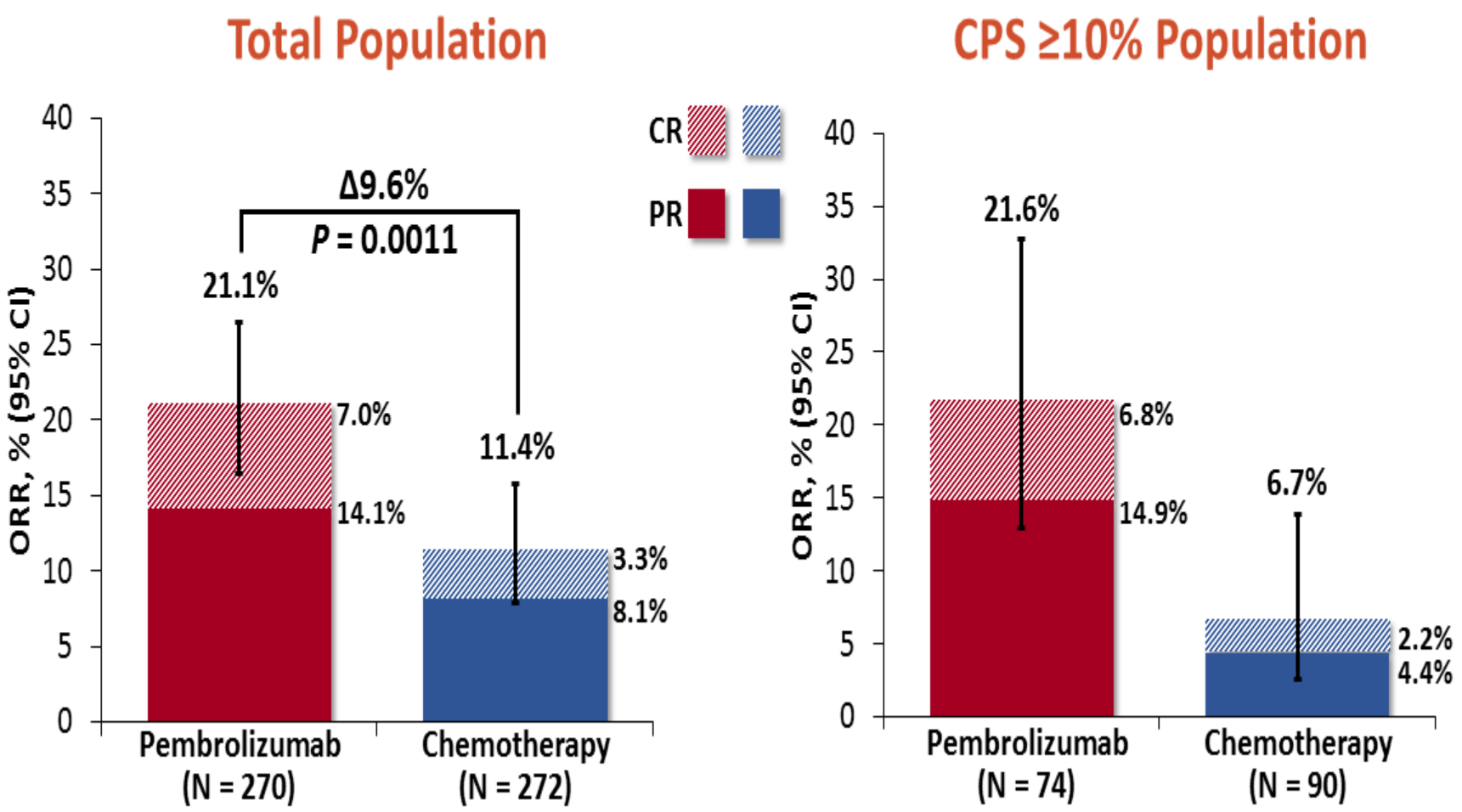
	Events, n	HR (95% CI)	*P*
Pembro	218	0.98 (0.81-1.19)	0.42
Chemo	219		

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.

Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026

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, et al. N Engl J Med. 2017;376:1015-1026

KEYNOTE-045: DoR, TTR

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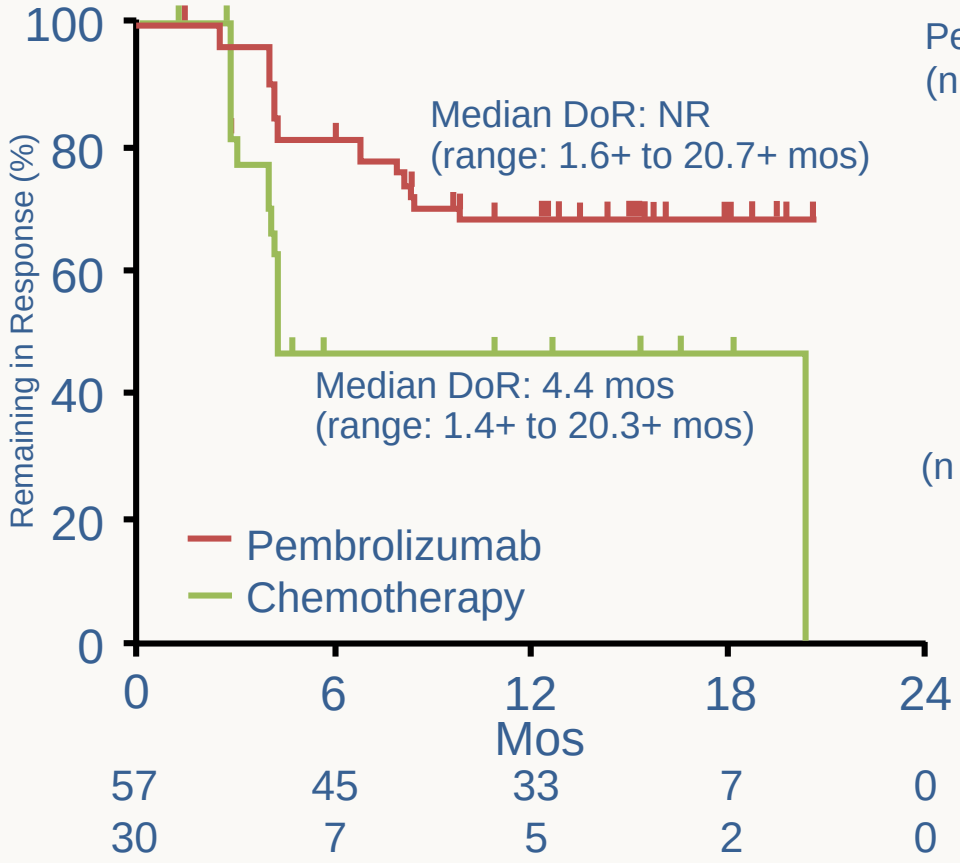
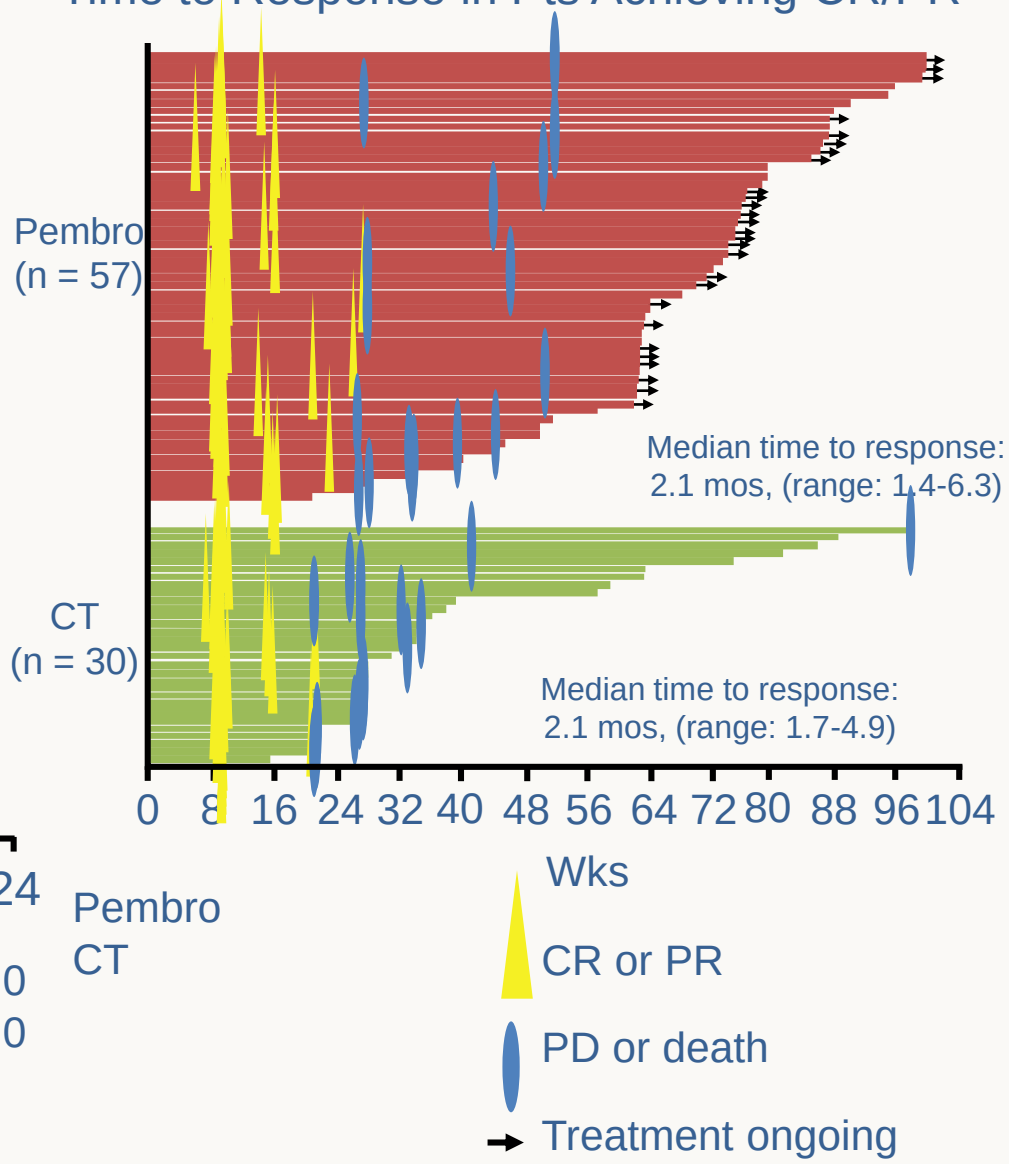
Duration of Response

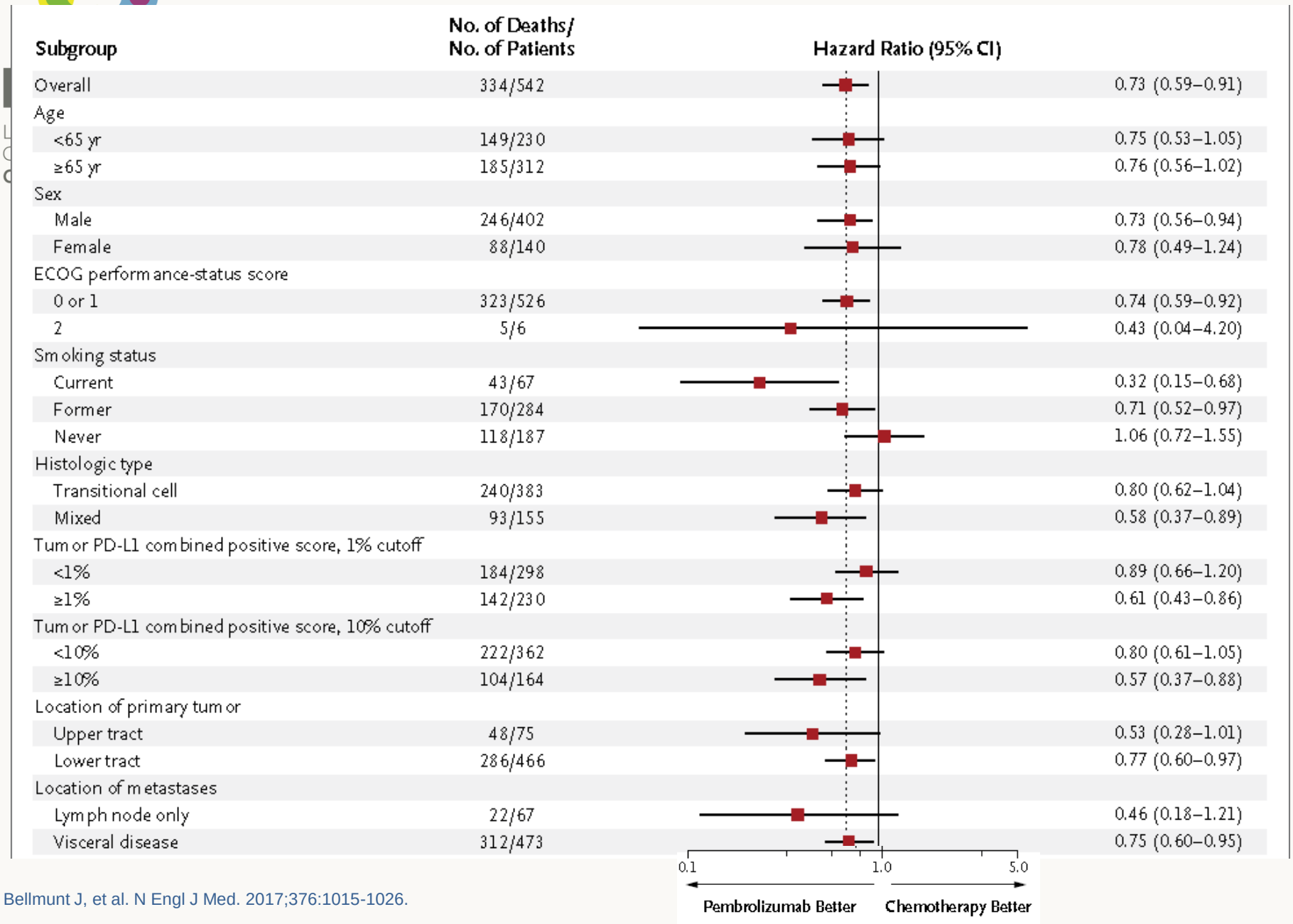


Time to Response in Pts Achieving CR/PR



Bajorin DF, et al. ASCO 2017. Abstract 4501.

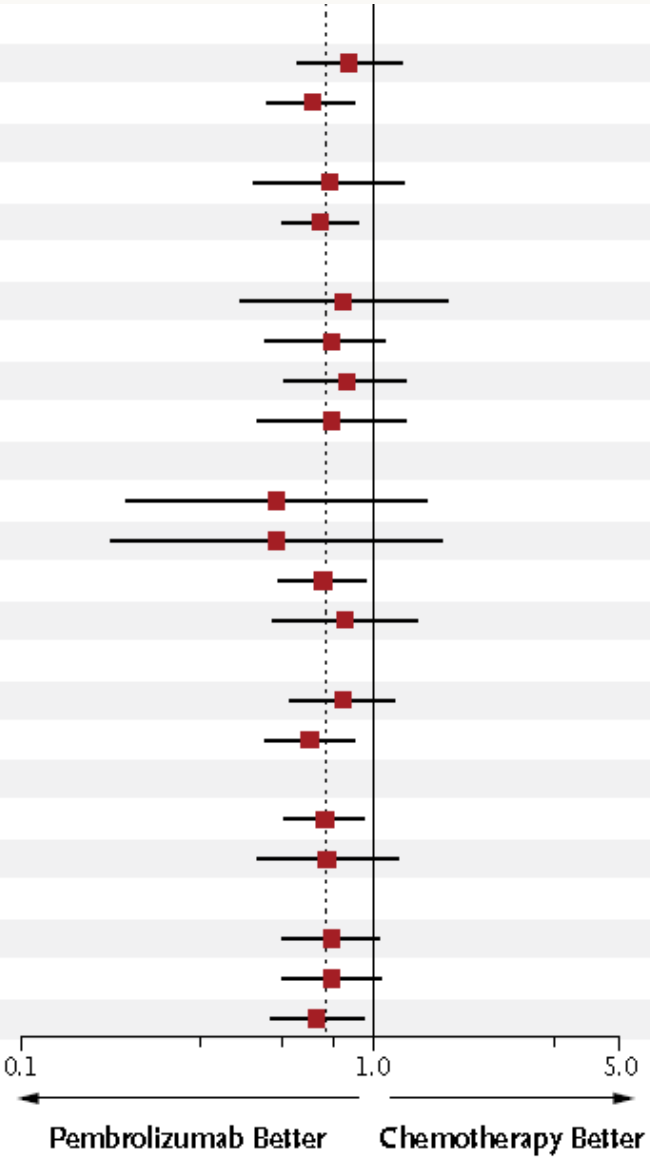
OS by subgroups



Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

OS by subgroups

Liver metastases		
Yes	145/186	0.85 (0.61–1.20)
No	189/355	0.67 (0.50–0.89)
Hemoglobin concentration		
<10 g/dl	71/87	0.75 (0.46–1.22)
≥10 g/dl	257/442	0.71 (0.55–0.91)
No. of risk factors		
0	35/98	0.82 (0.42–1.62)
1	104/193	0.73 (0.49–1.08)
2	111/146	0.84 (0.56–1.24)
3 or 4	76/90	0.76 (0.47–1.24)
Context of most recent therapy received		
Neoadjuvant therapy	22/41	0.53 (0.20–1.41)
Adjuvant therapy	27/43	0.53 (0.18–1.57)
First-line therapy for metastatic disease	203/340	0.72 (0.54–0.95)
Second-line therapy for metastatic disease	80/115	0.83 (0.52–1.33)
Time since most recent chemotherapy		
<3 mo	140/207	0.82 (0.58–1.15)
≥3 mo	193/333	0.66 (0.49–0.89)
Previous platinum therapy		
Cisplatin	248/411	0.73 (0.56–0.94)
Carboplatin	82/126	0.74 (0.47–1.18)
Investigator's choice of chemotherapy		
Paclitaxel	208/350	0.76 (0.55–1.04)
Docetaxel	203/350	0.76 (0.55–1.05)
Vinflunine	216/353	0.69 (0.51–0.94)



Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

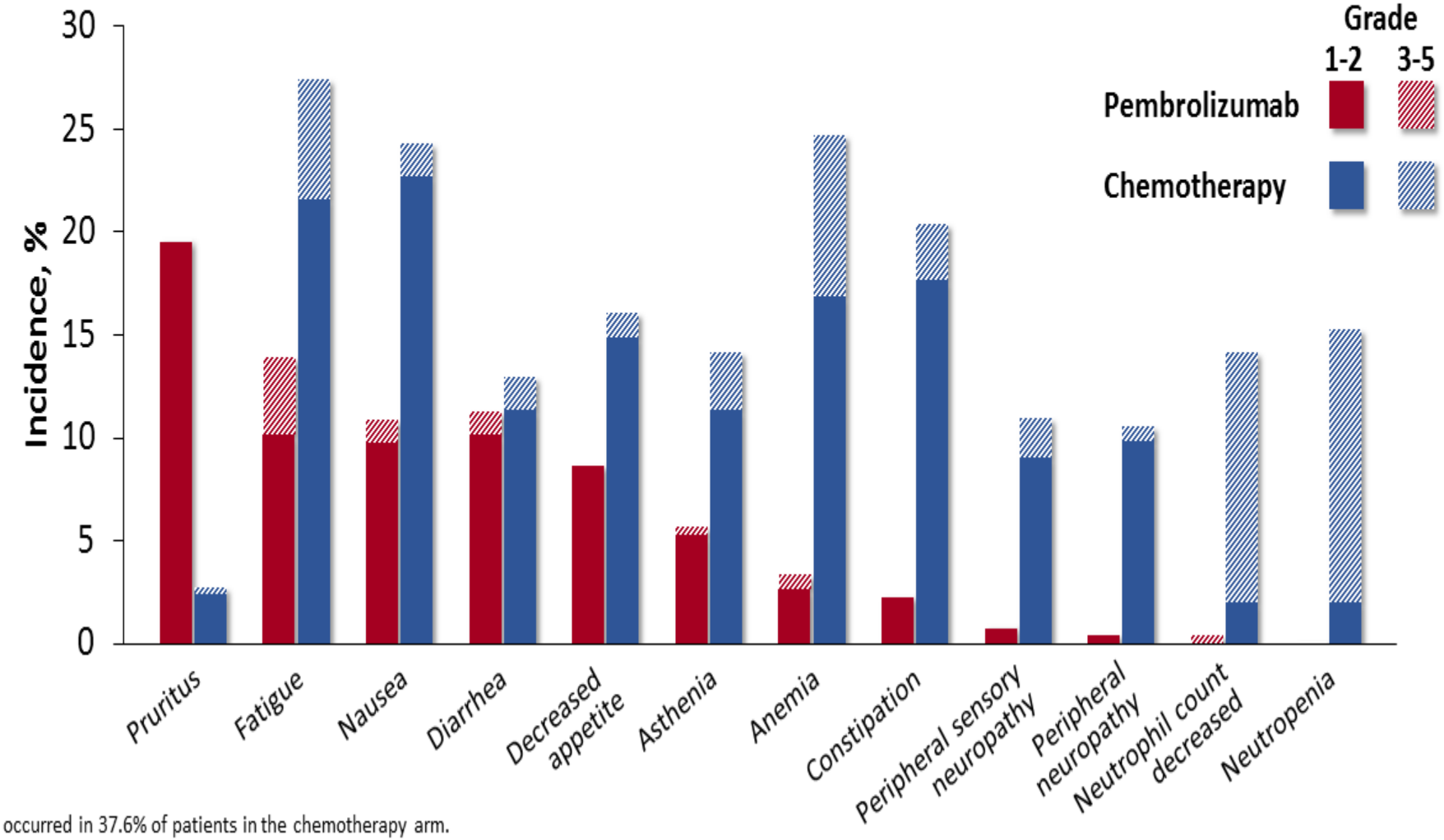
Exposure and AE Summary

	Pembrolizumab N = 266	Chemotherapy N = 255
Exposure, median (range)	3.5 mo (0.03-20.0)	1.5 mo (0.03-14.2)
Treatment-related AEs, n (%)	162 (60.9)	230 (90.2)
Grade 3-5	40 (15.0)	126 (49.4)
Serious	27 (10.2)	57 (22.4)
Discontinuation	15 (5.6)	28 (11.0)
Grade 5	4 (1.5)	4 (1.6)

Data cutoff date: Sep 7, 2016.

Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

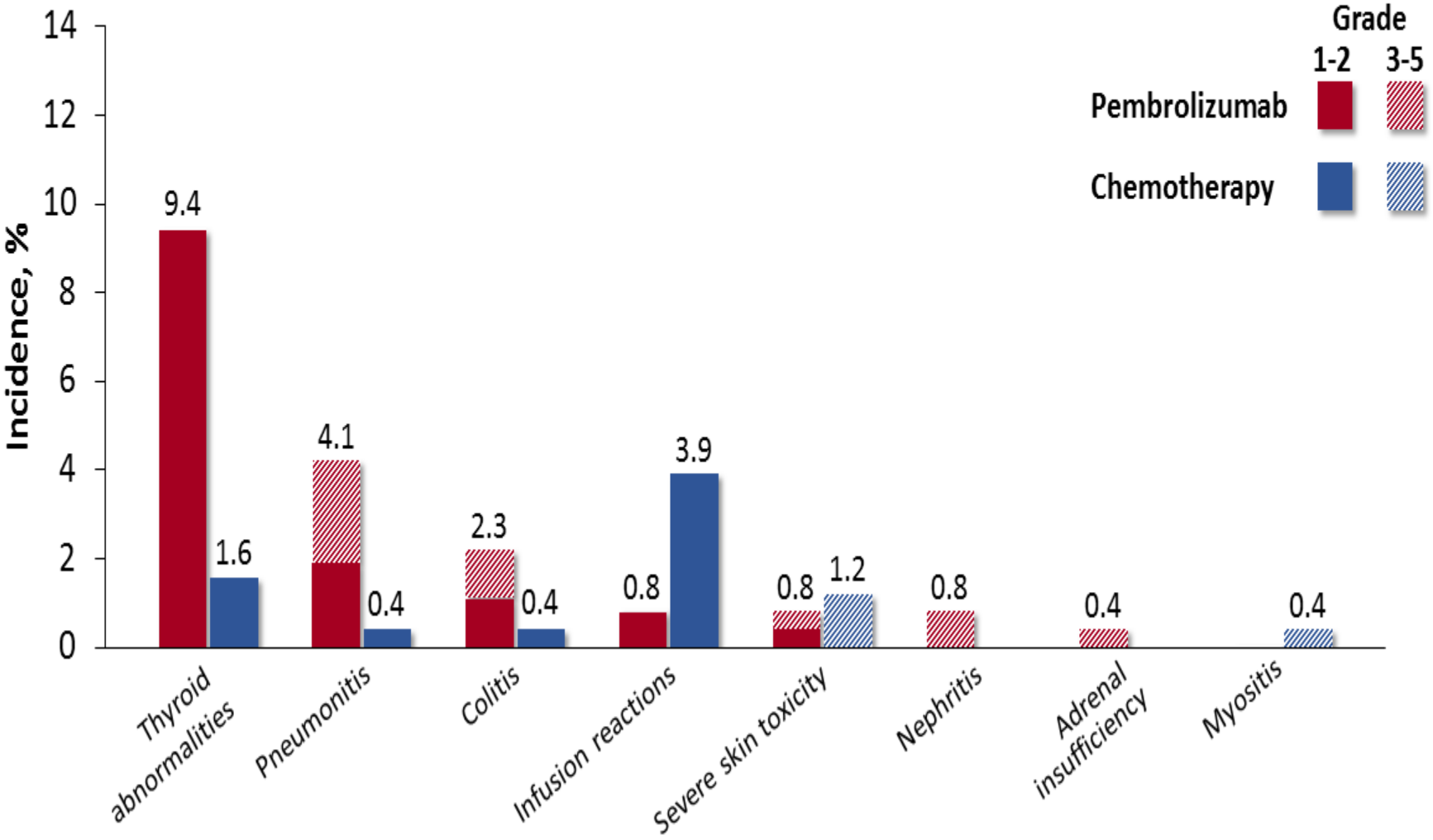
Treatment-Related AEs With Incidence ≥10%



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

Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

AEs of Interest



Data cutoff date: Sep 7, 2016.

Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

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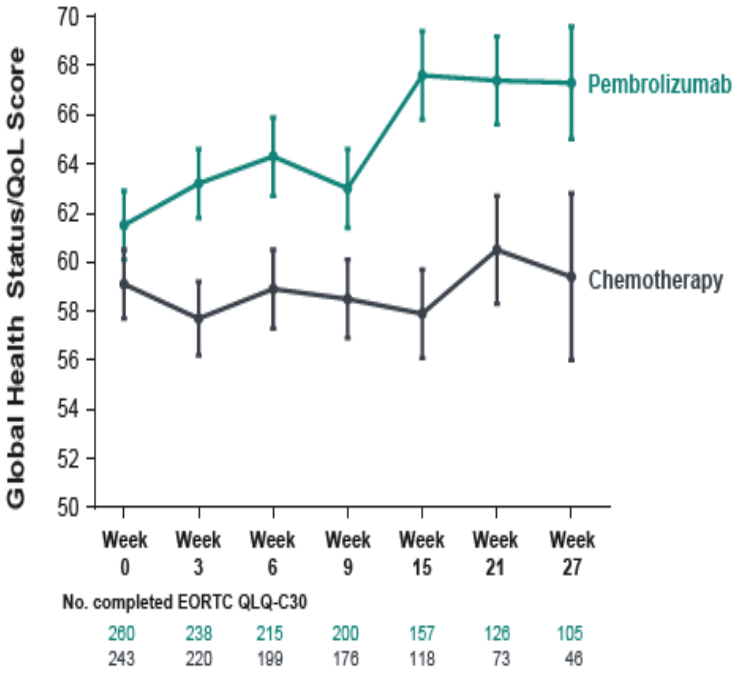
Key HRQoL Endpoints

✓ Global health status/QoL score was similar for the pembrolizumab and chemotherapy arms at baseline; starting at week 3, the score was better with pembrolizumab, a benefit maintained through week 27.

✓ Patients in the pembrolizumab arm had better HRQoL at week 15 compared with patients in the chemotherapy arm (difference in least squares [LS] means, 9.05; nominal 2-sided $P < 0.001$).

Figure 1. EORTC QLQ-C30 global health status/QoL score by visit.



Data are shown as mean ± standard error. The range of possible scores for the global health status/QoL score is 0 to 100.

Table 2. Change from Baseline to Week 15 in the EORTC QLQ-C30 Global Health Status/QoL Score

	Pembrolizumab	Chemotherapy
Baseline score, mean (SD)	n = 260[a] 61.1 (23.1)	n = 243[a] 59.1 (22.1)
Week 15 score, mean (SD)	n = 157[a] 67.6 (22.6)	n = 118[a] 57.9 (19.5)
Change from baseline to week 15, LS mean (95% CI)[c]	n = 266[b] +0.75 (–2.34 to +3.83)	n = 254[b] –8.30 (–11.76 to –4.83)
Difference in LS means (95% CI)	9.05 (4.61 to 13.48) $P < 0.001$	

[a]Number of patients in each arm who completed the EORTC QLQ-C30 at that timepoint.
[b]Number of patients in the total HRQoL analysis population.
[c]Based on a constrained longitudinal data analysis model with the global health status/QoL score as the response variable, treatment by study visit interaction, and stratification by the randomization stratification factors (ie, ECOG performance status 0/1 vs 2, presence vs absence of liver metastases, hemoglobin ≥10 g/dL vs <10 g/dL, and time from completion of most recent chemotherapy ≥3 months vs <3 months).

Vaughn et al. Presented at the 2017 Genitourinary Cancers Symposium (ASCO-GU) February 16-18, 2017 Orlando, Florida

IMvigor211 Study Design

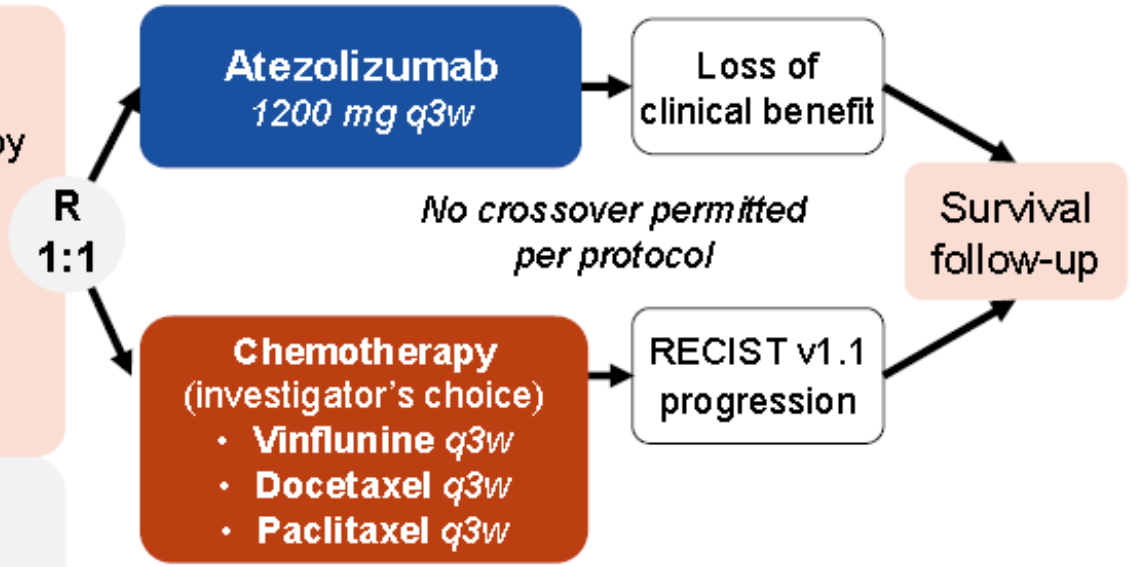
Key Eligibility Criteria[a]

- 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)

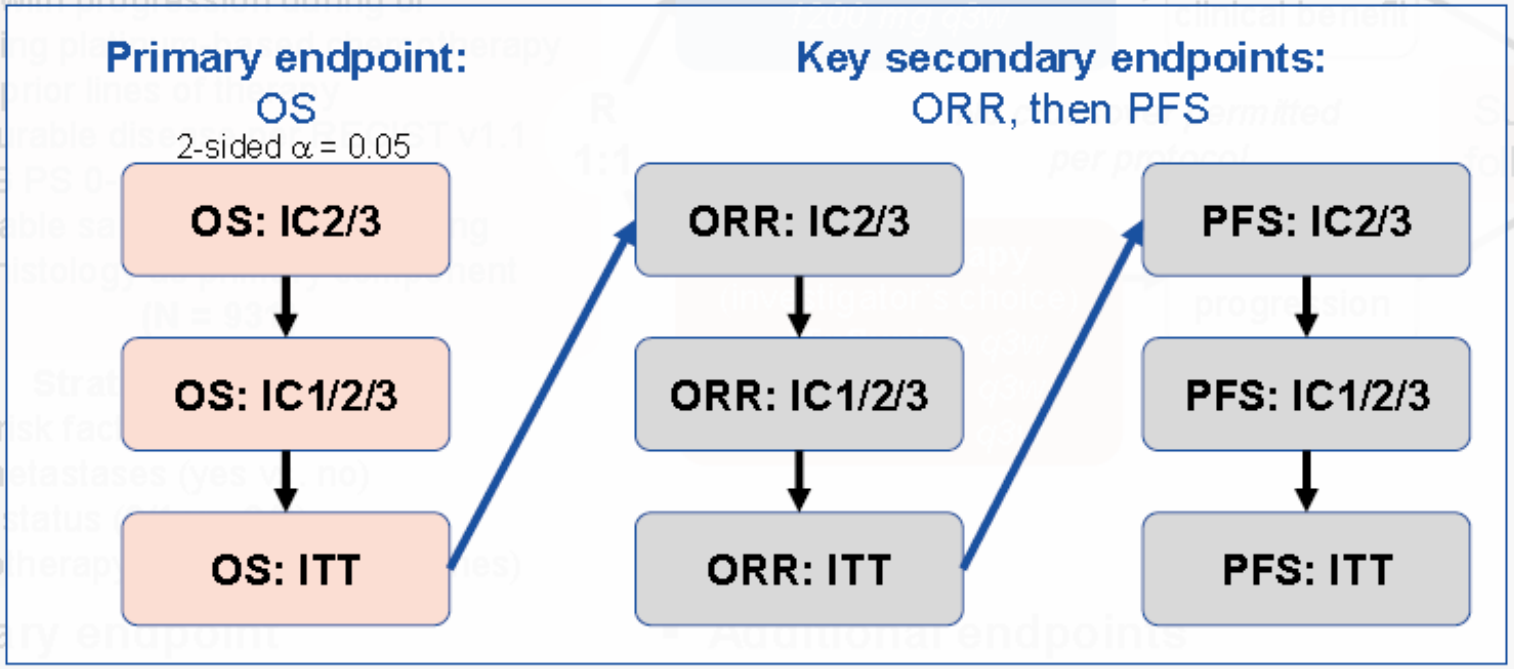


- **Primary endpoint**
  - OS, tested hierarchically in pre-specified populations
- **Additional endpoints**
  - Efficacy: RECIST v1.1 ORR, PFS and DOR[c]
  - Safety
  - PROs: EORTC QLQ-C30

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.

IMvigor211 Study Design



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.

Baseline Characteristics

Characteristic	ITT Population	
	Atezolizumab (n = 467)	Chemotherapy (n = 464)
Age, median (range)	67 y (33-88 y)	67 y (31-84 y)
Male	76%	78%
ECOG PS: 0 | 1	47% | 53%	45% | 55%
Tobacco use: Current | Former | Never	13% | 57% | 30%	13% | 61% | 26%
Hemoglobin < 10 g/dL	14%	16%
No. of risk factors:[1] 0 | 1 | 2 | 3	31% | 46% | 18% | 5%	30% | 45% | 21% | 4%
Primary tumor site:		
Lower Tract (bladder | urethra)	69% | 2%	73% | 2%
Upper Tract (renal pelvis | ureter | other)	14% | 13% | 2%	11% | 13% | 2%
Metastatic disease	91%	93%
Sites of metastases:		
Lymph node only | visceral[a] | liver	12% | 77% | 30%	14% | 77% | 28%
Prior cystectomy	43%	43%
Previous chemotherapy < 3 mo	34%	35%
Prior regimens (metastatic setting): 0 | 1 | 2 | ≥ 3[b]	28% | 53% | 17% | 2%	26% | 56% | 16% | 2%
PD-L1 status: IC2/3 | IC1 | IC0	25% | 43% | 32%	25% | 41% | 33%

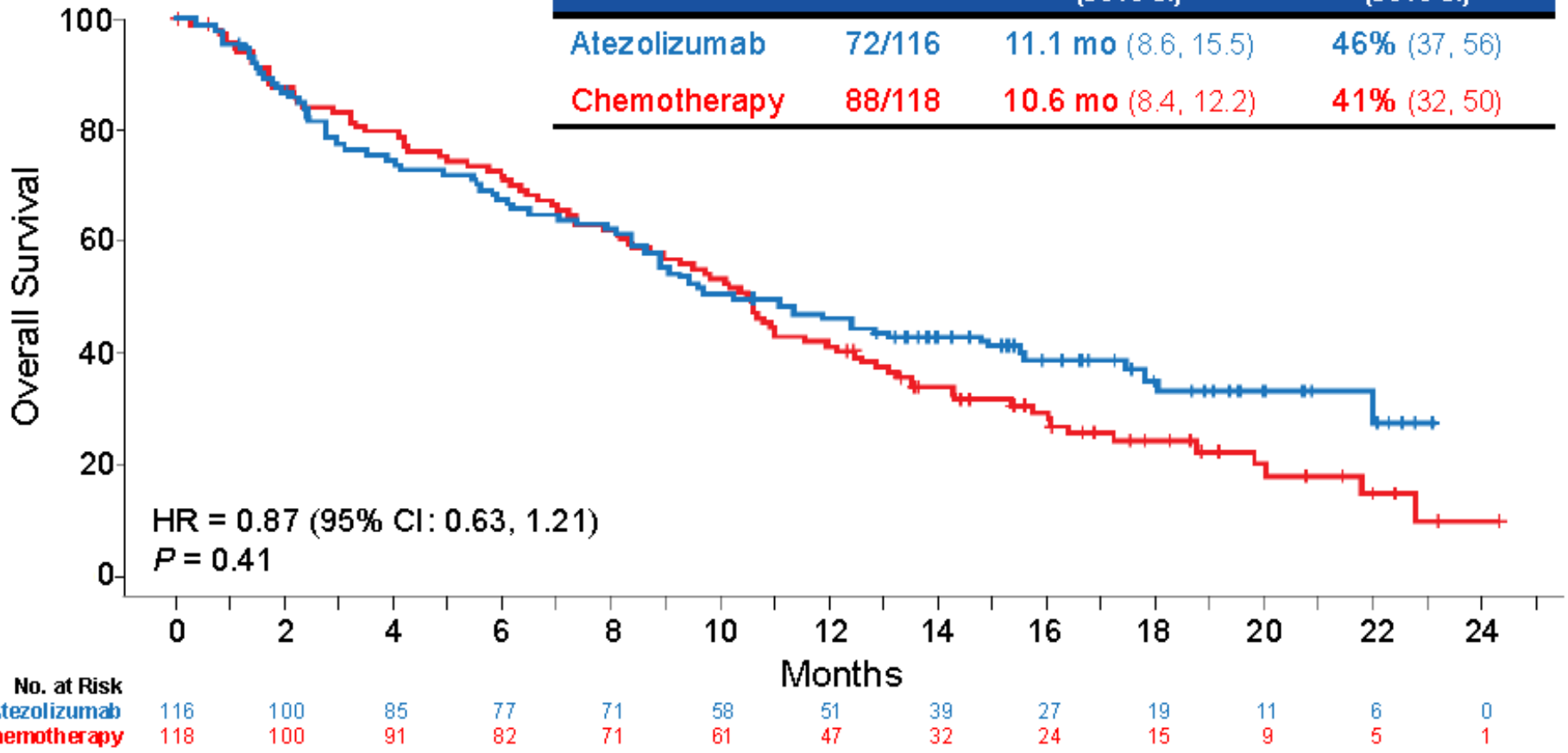
Data cutoff: March 13, 2017. [a] Visceral metastasis defined as liver, lung, bone, any non–lymph node or soft tissue metastasis. [b] 1 patient in the chemotherapy arm received 4 prior systemic regimens for mUC.

1. Bellmunt *J Clin Oncol* 2010.

Powles T, et al. EAS 2017, IMvigor211.

OS Analysis: IC2/3 Population

	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)

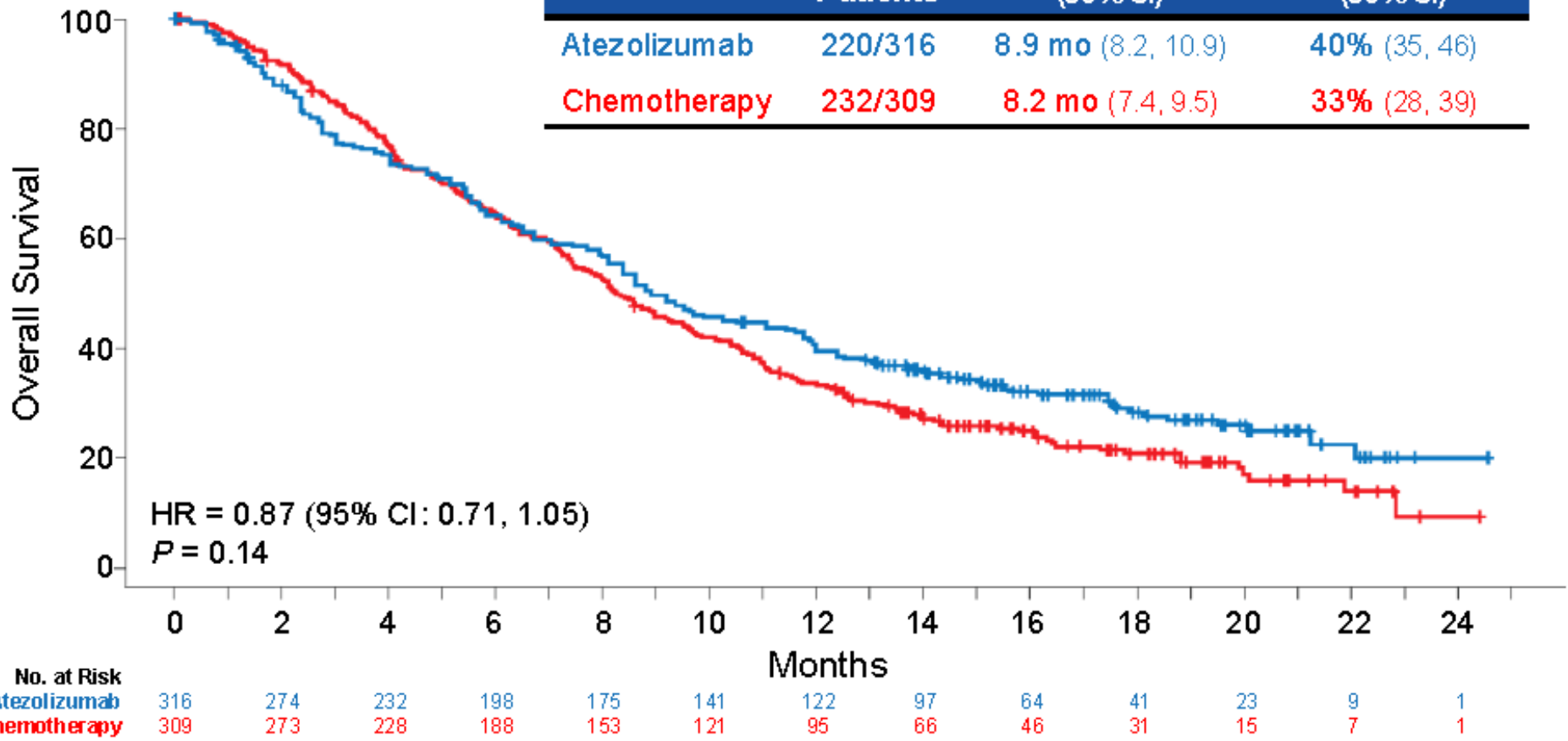


HR, hazard ratio.

Powles T, et al. EAS 2017, IMvigor211.

OS Analysis: IC1/2/3 Population

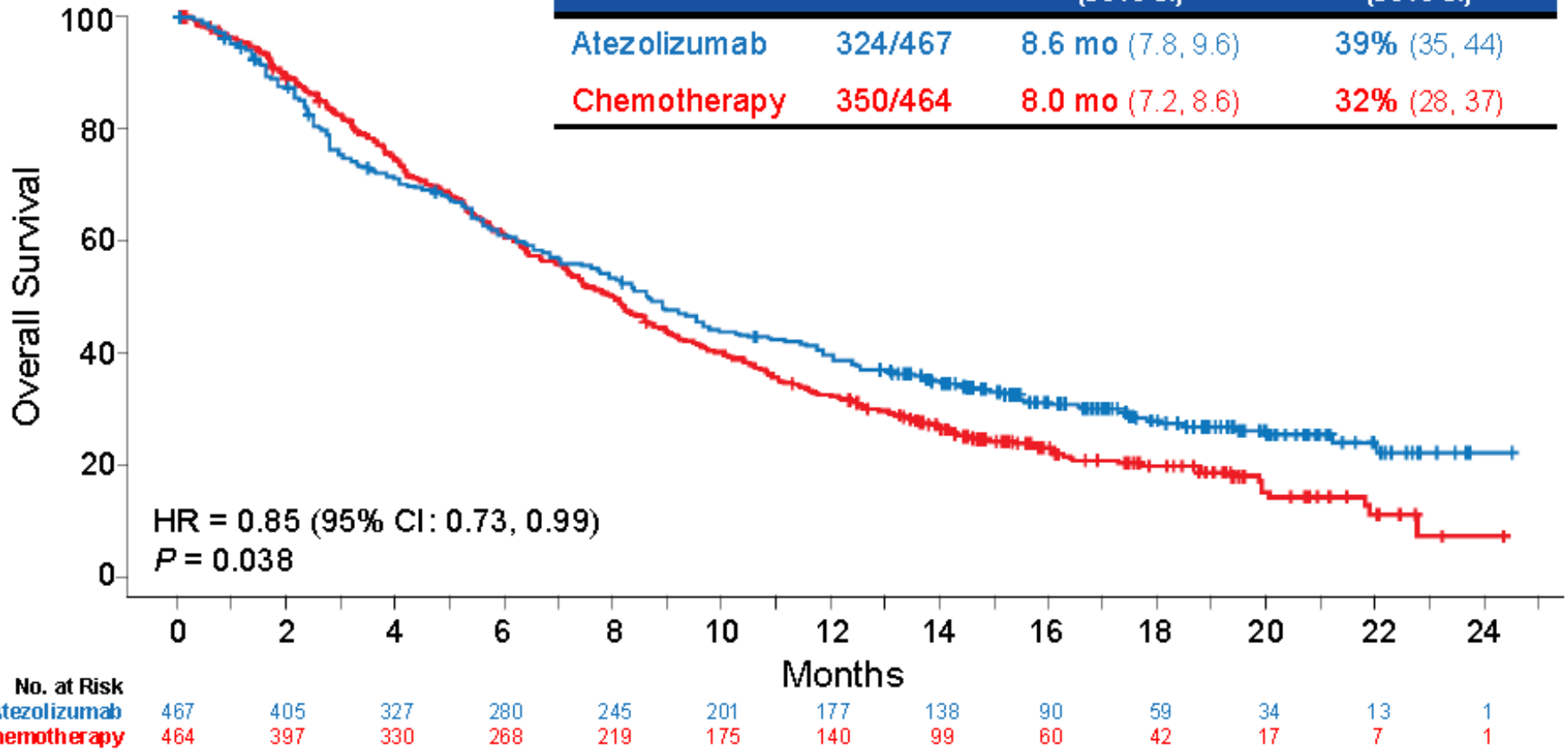
	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	220/316	8.9 mo (8.2, 10.9)	40% (35, 46)
Chemotherapy	232/309	8.2 mo (7.4, 9.5)	33% (28, 39)



Powles T, et al. EAS 2017, IMvigor211.

OS Analysis: ITT Population

	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)

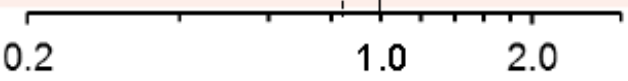


- Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

Powles T, et al. EAS 2017, IMvigor211.

OS in Clinical and Treatment Subgroups

Subgroup		Atezolizumab mOS	Chemotherapy mOS
PD-L1 status	IC2/3	11.1 mo	10.6 mo
	IC1/2/3	8.9 mo	8.2 mo
	ITT	8.6 mo	8.0 mo
Tobacco use history	Current	9.2 mo	6.7 mo
	Previous	8.4 mo	8.2 mo
	Never	10.4 mo	8.1 mo
ECOG PS	0	12.0 mo	10.1 mo
	1	6.1 mo	6.4 mo
Primary tumor site	Bladder	8.9 mo	7.7 mo
	Urethra	NE	12.5 mo
	Renal pelvis	5.9 mo	8.5 mo
	Ureter	8.9 mo	8.1 mo
Liver metastases	Yes	4.0 mo	5.2 mo
	No	10.1 mo	9.7 mo
Lymph node–only metastases	Yes	17.4 mo	12.2 mo
	No	8.1 mo	7.2 mo
Chemotherapy stratification	Taxane	8.3 mo	7.5 mo
	Vinflunine	9.2 mo	8.3 mo



Atezolizumab better ← → Chemotherapy better

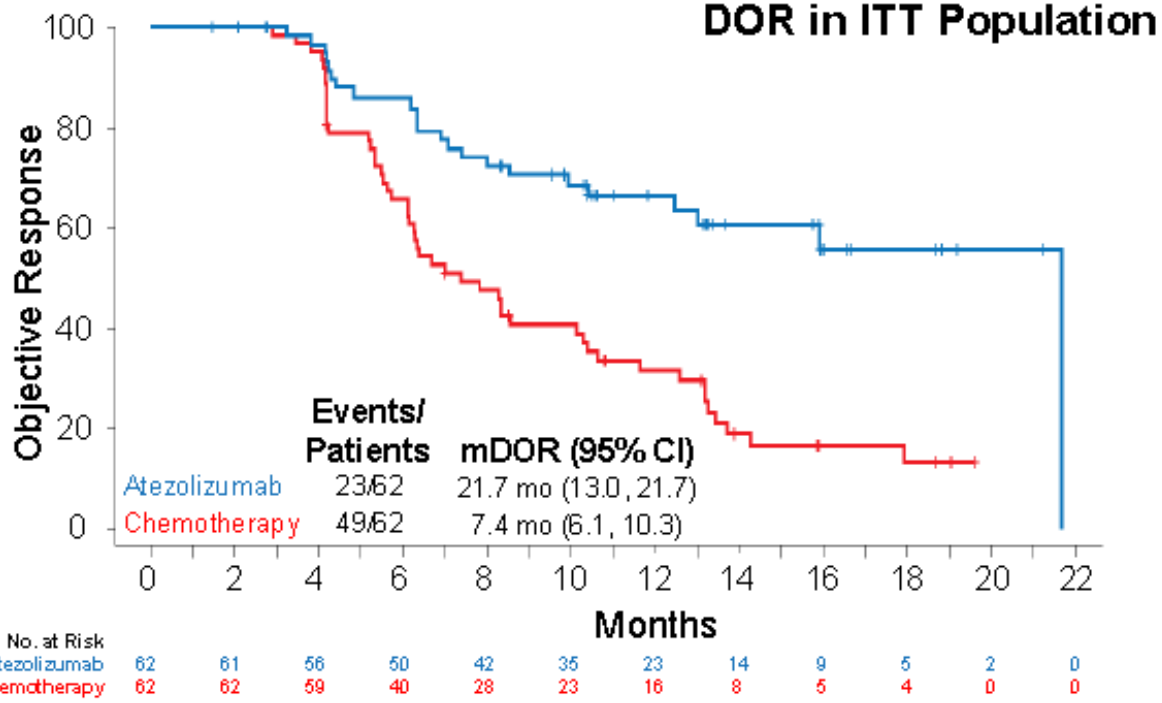
NE, not estimable. Unstratified hazard ratios are plotted. Dashed line refers to HR for ITT population.

Powles T, et al. EAS 2017, IMvigor211.

Response by PD-L1 Subgroup

Confirmed ORR[a]	IC2/3		IC1/2/3		ITT	
	Atezo (n = 113)	Chemo (n = 116)	Atezo (n = 312)	Chemo (n = 306)	Atezo (n = 462)	Chemo (n = 461)
Responders, n (%)	26 (23%)	25 (22%)	44 (14%)	45 (15%)	62 (13%)	62 (13%)
95% CI, %	16, 32	15, 30	10, 19	11, 19	11, 17	11, 17
CR, n (%)	8 (7%)	8 (7%)	11 (4%)	13 (4%)	16 (3%)	16 (3%)

- Objective response was similar between arms
- Responses to atezolizumab were durable regardless of PD-L1 status
  - 63% of patients in the atezolizumab arm and 21% in the chemotherapy arm had ongoing responses at data cutoff



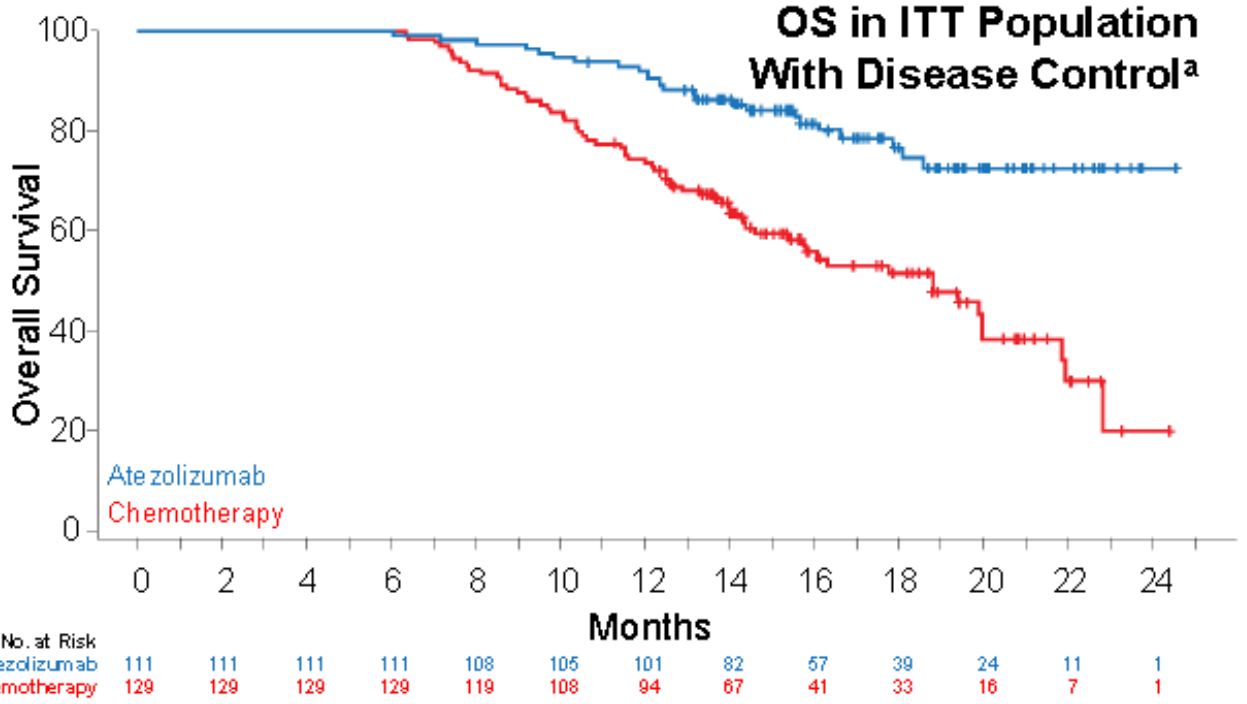
mDOR, median DOR.
[a] Confirmed RECIST v1.1 responses were assessed as an exploratory endpoint.

Powles T, et al. EAS 2017, IMvigor211.

Disease Control

Disease Control	IC2/3		IC1/2/3		ITT	
	Atezo (n = 113)	Chemo (n = 116)	Atezo (n = 312)	Chemo (n = 306)	Atezo (n = 462)	Chemo (n = 461)
DCR, %	**34%**	**33%**	**26%**	**28%**	**24%**	**28%**
95% CI, %	25, 43	24, 42	21, 31	23, 34	20, 28	24, 32

- Disease control was also observed across arms
  - DCR is defined by patients with confirmed CR/PR or SD ≥ 24 weeks per RECIST v1.1
- OS analysis suggests improved survival in patients with disease control in the atezolizumab arm



DCR, disease control rate; PD, progressive disease; SD, stable disease.
[a] Note: Analysis includes patients who survived long enough to be evaluated for disease control.

Powles T, et al. EAS 2017, IMvigor211.

Safety Summary

AE, n (%)	All Cause		Treatment Related	
	Atezo (N = 459)	Chemo (N = 443)	Atezo (N = 459)	Chemo (N = 443)
All-Grade AEs	438 (95%)	435 (98%)	319 (70%)	395 (89%)
Grade 3 or 4 AEs	233 (51%)	249 (56%)	91 (20%)	189 (43%)
Grade 5 AEs	17 (4%)	18 (4%)	3 (1%)	8 (2%)
All-Grade AESIs	139 (30%)	98 (22%)	-	-
Grade 3 or 4 AESIs	37 (8%)	13 (3%)	-	-
Grade 5 AESIs	0	1 (< 1%)	-	-
SAEs	188 (41%)	191 (43%)	72 (16%)	110 (25%)
AEs leading to treatment discontinuation	34 (7%)	78 (18%)	16 (3%)	63 (14%)
AEs leading to dose modification, delay or interruption	134 (29%)	210 (47%)	-	-

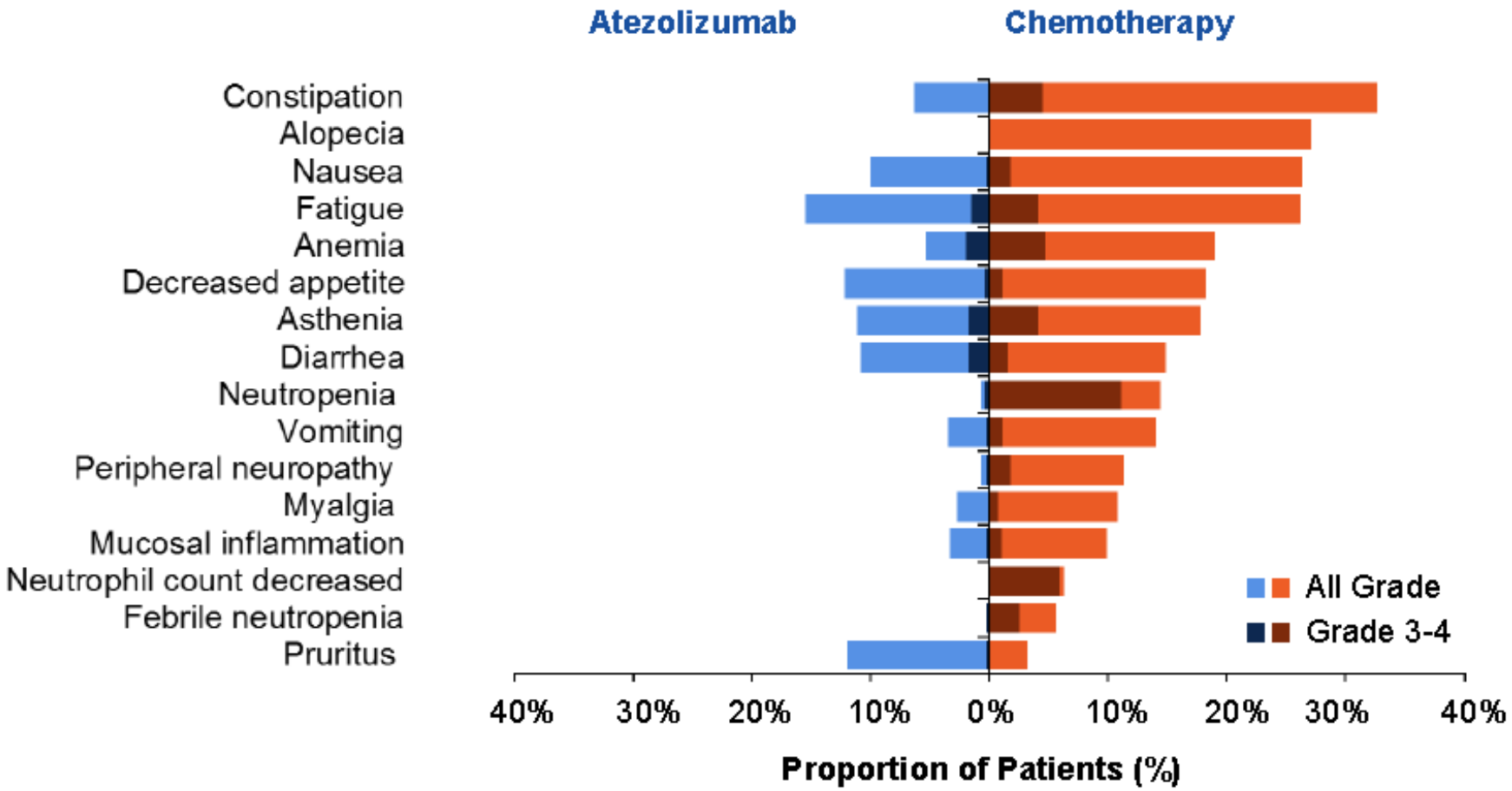
- Rates of treatment-related AEs and AEs leading to discontinuation (any cause) were numerically lower in the atezolizumab arm

AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.

Powles T, et al. EAS 2017, IMvigor211.

Treatment-Related AEs

Treatment-Related AEs in ≥ 10% (All Grade) or ≥ 4% (Grades 3-4) for Either Arm

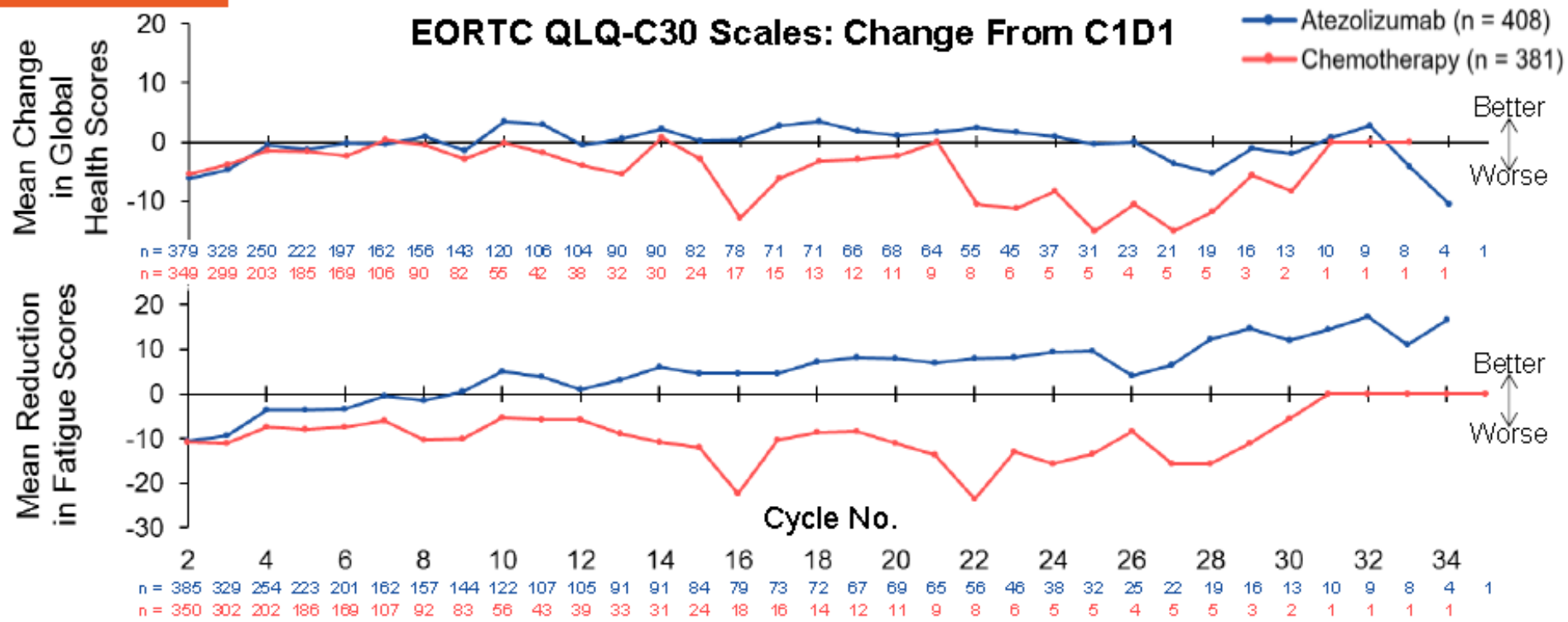


- The safety profile for atezolizumab was consistent with Phase I-II data[1,2]

1. Powles *Nature* 2014. 2. Rosenberg *Lancet* 2016.

Powles T, et al. EAS 2017, IMvigor211.

PROs: Change From Baseline



- 3 PROs (EORTC QLQ-C30 scales) were examined: global health status, physical functioning and fatigue
- In PRO-evaluable patients, an overall numerical trend toward better global health status and less fatigue was seen with atezolizumab
  - Mean global health status scores worsened initially but returned to baseline values more quickly with atezolizumab than with chemotherapy. Similar results were seen for physical functioning
  - Initial deterioration in fatigue levels was followed by rapid improvement with atezolizumab

C1D1, cycle 1, day 1.

Powles T, et al. EAS 2017, IMvigor211.

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Checkmate-275: Study Design

✓ A multicenter, single arm phase II trial

Pts with measurable metastatic or locally advanced urothelial carcinoma after recurrence or progression following ≥ 1 platinum-based chemotherapy; ECOG PS 0 or 1; evaluable tumor tissue for biomarker testing (N = 270)

→

Nivolumab
3 mg/kg Q2W
(N = 270)

→

*Treated PD and clinical deterioration, unacceptable AE, or protocol-defined decision**

Primary endpoints: ORR in all pts, ORR in pts with PD-L1 ≥ 5% or ≥ 1%

Secondary endpoints: PFS, OS, TTR, DoR, safety, QoL

*Pts allowed to continue treatment beyond initial radiographic progression if well tolerated and clinical benefit was noted.

Sharma P, et al. Lancet Oncol. 2017 Jan 25. [Epub ahead of pr

Checkmate-275: Efficacy

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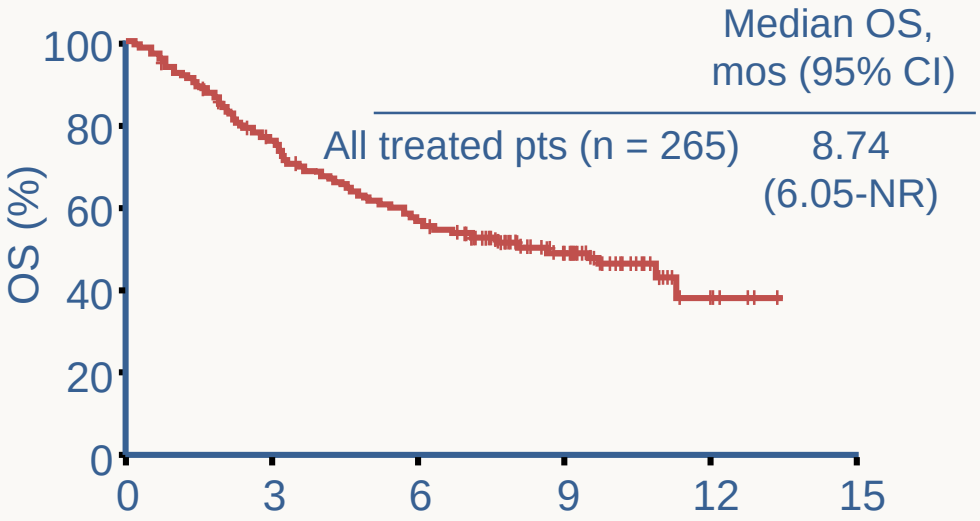
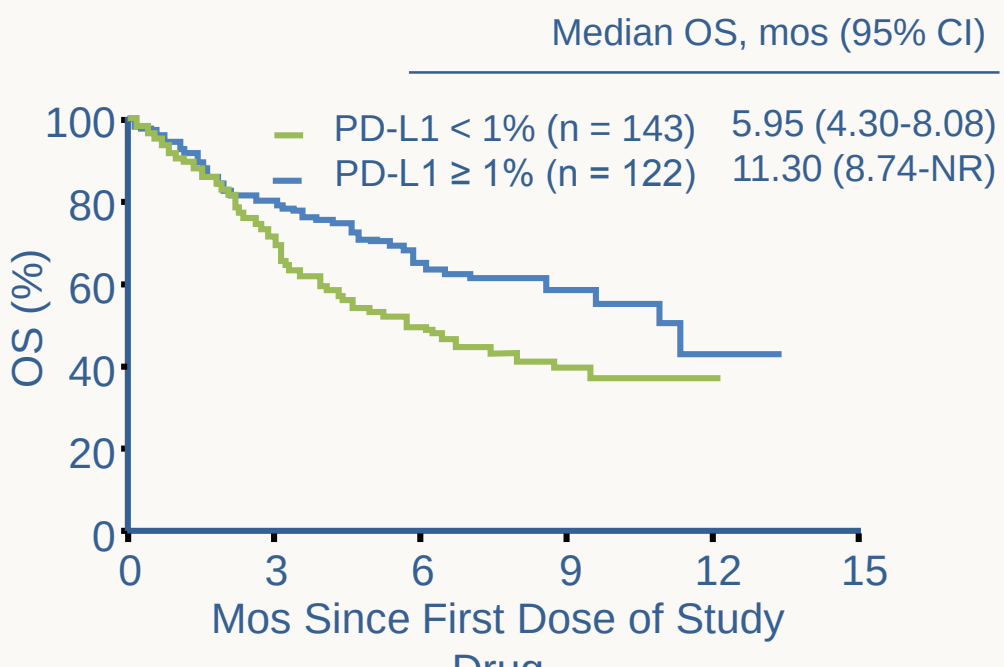
Parameter, %	Nivolumab (N = 265)
ORR ▪ CR ▪ PR ▪ SD	19.6 2 17 23
ORR by PD-L1 status ▪ < 1% ▪ ≥ 1% ▪ ≥ 5%	 16.1 23.8 28.4
TTR, mos (range)	1.87 (1.81-1.97)
DoR, mos (range)	NR (7.43-NR)





Sharma P, et al. Lancet Oncol. 2017 Jan 25. [Epub ahead of print].

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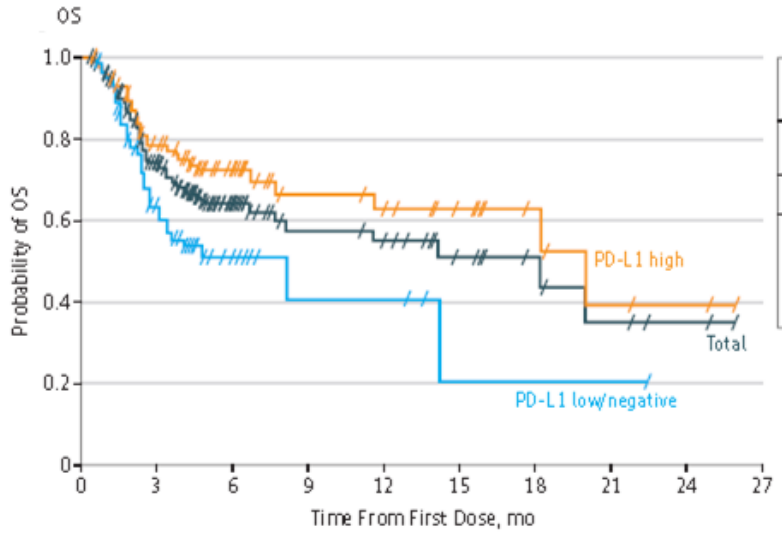
JAMA Oncology | Original Investigation

Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma
Updated Results From a Phase 1/2 Open-label Study

Thomas Powles, MD; Peter H. O'Donnell, MD; Christophe Massard, MD, PhD; Hendrik-Tobias Arkenau, MD, PhD; Terence W. Friedlander, MD; Christopher J. Hoimes, DO; Jae Lyun Lee, MD; Michael Ong, MD; Srikala S. Sridhar, MD; Nicholas J. Vogelzang, MD; Mayer N. Fishman, MD, PhD; Jingsong Zhang, MD, PhD; Sandy Srinivas, MD; Jigar Parikh, MD; Joyce Antal, MS; Xiaoping Jin, PhD; Ashok K. Gupta, MD, PhD; Yong Ben, MD; Noah M. Hahn, MD

Table 2. Antitumor Activity of Durvalumab per Blinded Independent Central Review in the UC Cohort, Including the ≥2L Postplatinum Subgroup

Parameter[a]	All UC			≥2L Postplatinum UC[b]		
	Total (n = 191)[c]	PD-L1 High (n = 98)[d]	PD-L1 Low or Negative (n = 79)[d]	Total (n = 182)	PD-L1 High (n = 95)[d]	PD-L1 Low or Negative (n = 73)[d]
Confirmed ORR, No. (%) [95% CI]	34 (17.8) [12.7 to 24.0]	27 (27.6) [19.0 to 37.5]	4 (5.1) [1.4 to 12.5]	32 (17.6) [12.3 to 23.9]	26 (27.4) [18.7 to 37.5]	3 (4.1) [0.9 to 11.5]
CR, No. (%)	7 (3.7)	4 (4.1)	2 (2.5)	6 (3.3)	4 (4.2)	1 (1.4)
PR, No. (%)	27 (14.1)	23 (23.5)	2 (2.5)	26 (14.3)	22 (23.2)	2 (2.7)
Nonevaluable, No. (%)[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, No. (%)	26 (76.5)	20 (74.1)	3 (75.0)	24 (75.0)	19 (73.1)	2 (66.7)
DoR, median (range), mo	NR (≥0.9 to ≥19.9)	NR (≥0.9 to ≥19.9)	12.25 (≥1.9 to ≥12.3)	NR (≥0.9 to ≥19.9)	NR (≥0.9 to ≥19.9)	12.25 (≥1.9 to 12.3)
≥6 mo, No. (%)	17 (50.0)	15 (55.6)	2 (50.0)	15 (46.9)	14 (53.8)	1 (33.3)
DCR, No. (%) [95% CI]	70 (36.6) [29.8 to 43.9]	44 (44.9) [34.8 to 55.3]	17 (21.5) [13.1 to 32.3]	66 (36.3) [29.3 to 43.7]	42 (44.2) [34.0 to 54.8]	15 (20.5) [12.0 to 31.6]



	PD-L1 High	PD-L1 Low/ Negative	Total
No. of patients (No. of events)	98 (30)	79 (35)	191 (68)
Median (95% CI), mo	20.0 (11.6, NE)	8.1 (3.1, NE)	18.2 (8.1, NE)
OS rate, % (95% CI)			
6 mo	72 (62-80)	51 (38-63)	64 (56-71)
9 mo	66 (53-77)	41 (21-60)	57 (47-66)
12 mo	63 (49-74)	41 (21-60)	55 (44-65)

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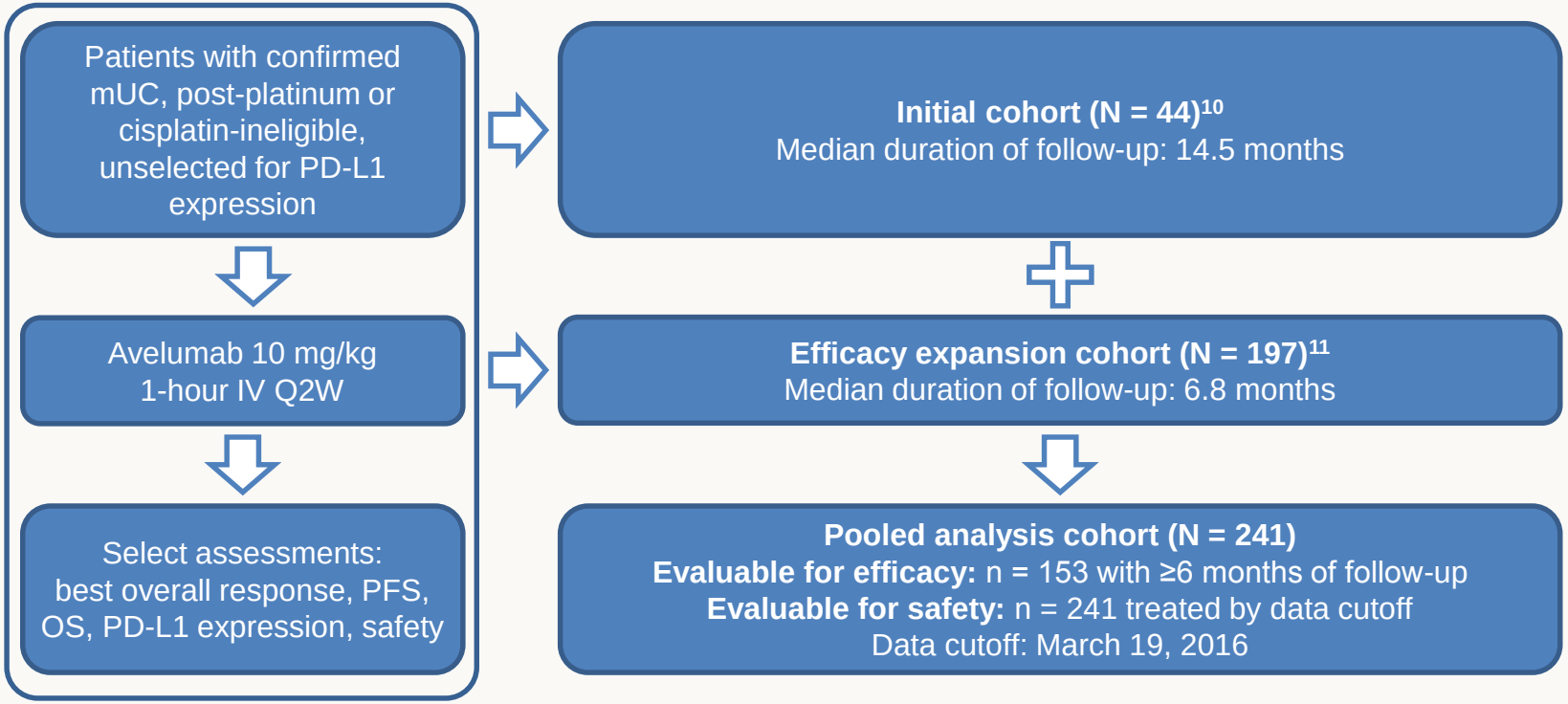
JAVELIN Solid Tumor Phase 1b Study: Study Design[1]



IV = intravenous; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; Q2W = every 2 weeks; mUC = metastatic urothelial carcinoma.

1. Patel M, et al. Presented at ASCO GU 2017; Abstract 330.

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JAVELIN: Summary of Clinical Activity in Patients With ≥6 Months of Follow-up[1]

Clinical activity end point by IERC	N = 153
Confirmed BOR, n (%)[a]	
Complete response	9 (5.9)
Partial response	18 (11.8)
Stable disease	36 (23.5)
Noncomplete response/nonprogressive disease[b]	1 (0.7)
Progressive disease	61 (39.9)
Nonevaluable[c]	28 (18.3)
Confirmed ORR, % (95% CI)	17.6 (12.0, 24.6)
Disease control rate, %[d]	41.2

1. Patel M, et al. Presented at ASCO GU 2017; Abstract 330.

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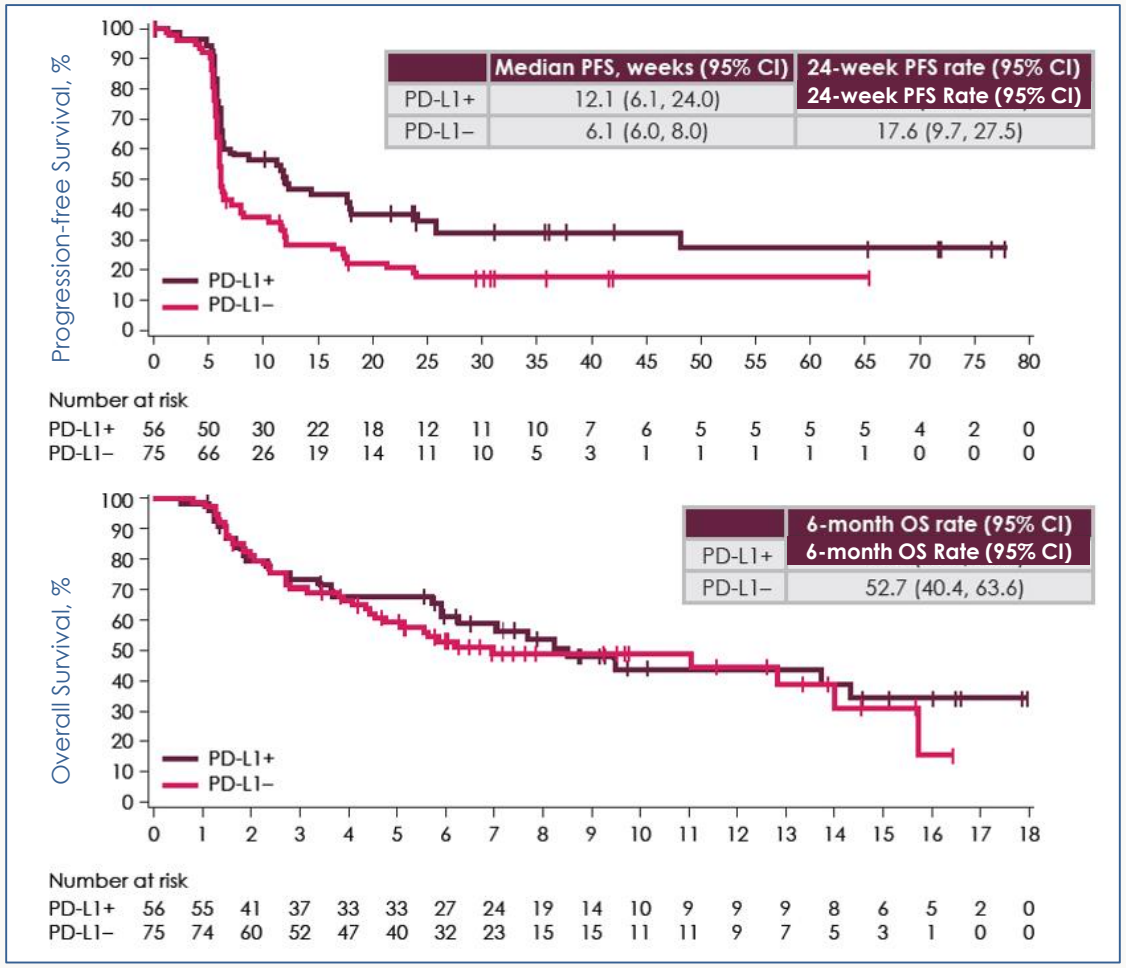
JAVELIN: PFS and OS by PD-L1 Expression in Patients With ≥6 Months of Follow-up



CI = confidence interval; OS = overall survival; PD-L1 = = programmed death ligand 1; PFS = progression-free survival.

1. Patel M, et al. Presented at ASCO GU 2017; Abstract 330.

Cisplatin ineligible

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Table 4. Proposed Working Group Eligibility Criteria for Clinical Trials Enrolling Patients With Metastatic Urothelial Carcinoma "Unfit" for Cisplatin-Based Chemotherapy

Eligibility Criteria (at least one of the following)
WHO or ECOG PS of 2 or Karnofsky PS of 60%-70%
Creatinine clearance (calculated or measured) < 60 mL/min
CTCAE v4 grade ≥ 2 audiometric hearing loss
CTCAE v4 grade ≥ 2 peripheral neuropathy
NYHA Class III heart failure

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status.

Source	Cisplatin-based		Carboplatin-based		Weight (%)	RR (95% CI)	*P* value
	Events	Total	Events	Total			
Petrioli et al. [15]	7	28	3	27	51.80	2.25 (0.65–7.18)	
Bellmunt et al. [13]	3	23	0	23	14.54	1.17 (0.07–18.58)	
Drecier et al. [2]	5	36	1	39	16.28	5.42 (0.66–44.12)	
Dogliotti et al. [14]	8	41	1	39	17.38	7.61 (0.10–58.06)	
Overall (Mantel–Haenszel method)	23	128	5	128		3.54 (1.48–8.49)	0.005

Heterogeneity chi-square test = 1.83 (d.f. = 3); $P = 0.609$; I-squared test (variation in RR attributable to heterogeneity) = 0.0%.
RR, risk ratio; CI, confidence interval.

J Clin Oncol. 2011 Jun 10;29(17):2432-8
Ann Oncol. 2012 Feb;23(2):406-10

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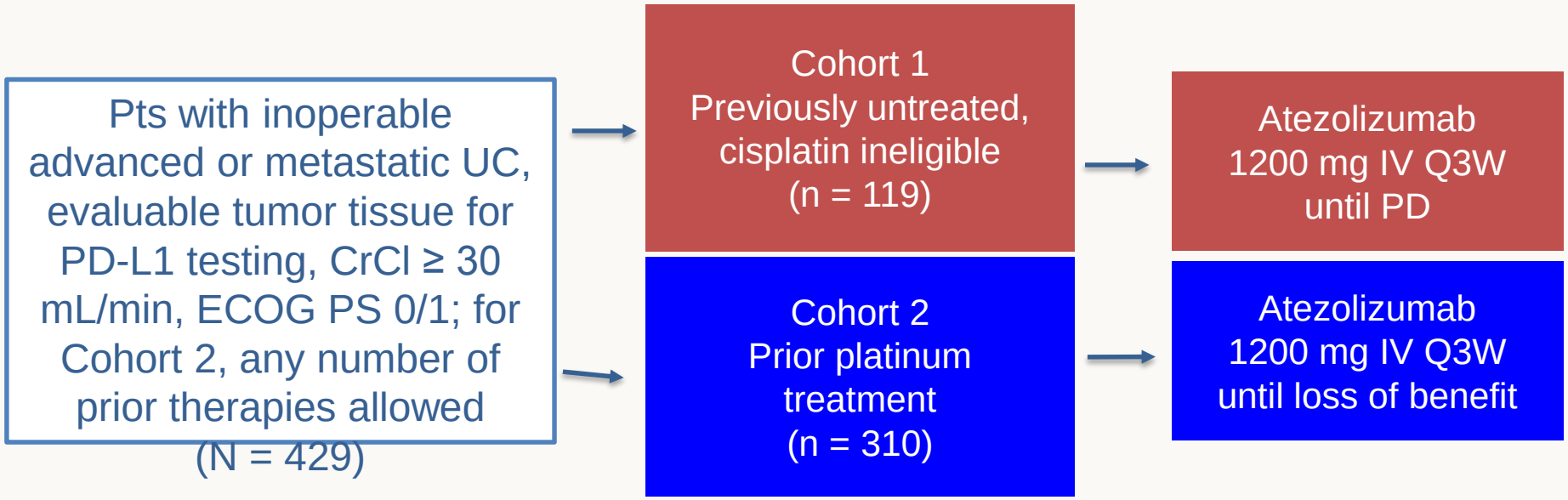
IMvigor 210: Atezolizumab for Advanced Urothelial Cancer

✓ Single-arm phase II study with 2 cohorts



- ✓ Primary endpoint: confirmed ORR by RECIST v1.1 (per central review)
- ✓ Secondary endpoints: DoR, PFS, OS, safety
- ✓ Exploratory endpoints: biomarkers

Lancet. 2017 January 07; 389(10064): 67–76

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Baseline Characteristics

Characteristic[a]	N = 119
Age, median (range)	73 (51-92)
≥ 80 years	21%
Male | female	81% | 19%
PD-L1 status on immune cells (IC)	
IC0 | IC1 | IC2/3	33% | 40% | 27%
Primary tumor site[b]	
Bladder/urethra	71%
Renal pelvis/ureter	28%
Metastatic disease	92%
Visceral sites[c]	66%
Prior therapy	
Radiotherapy	10%
Perioperative chemotherapy[d]	20%

Cisplatin Ineligibility Criteria[1]	N = 119
Renal impairment GFR < 60 and > 30 mL/min	70%
Hearing loss, 25 dB[e]	14%
Peripheral neuropathy, ≥ Grade 2	6%
ECOG PS 2	20%
Renal impairment **and** ECOG PS 2	7%

- Most patients were cisplatin ineligible due to renal impairment
  - Median GFR was 51 mL/min/1.73 m^2
- Baseline characteristics were generally consistent across PD-L1 IC subgroups

Lancet. 2017 January 07; 389(10064): 67–76

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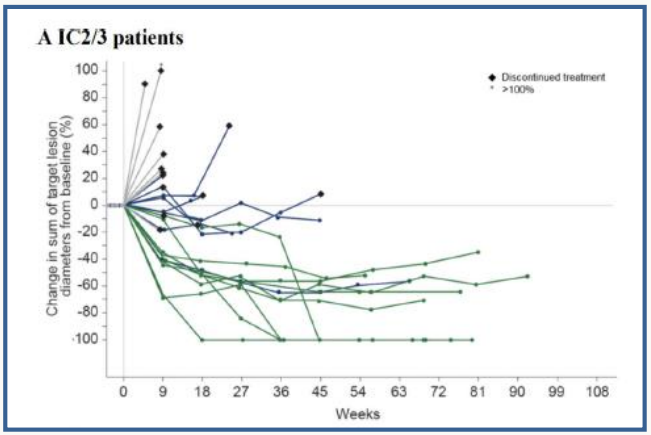
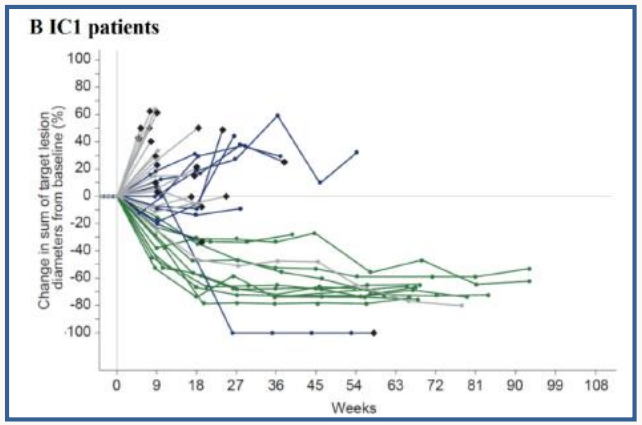
ORR

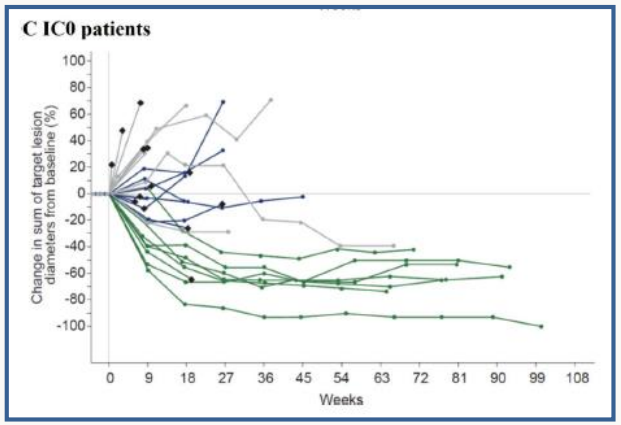
- ✓ Median follow up 17.2 months

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)







Lancet. 2017 January 07; 389(10064): 67–76

IMvigor 210: Duration of Atezolizumab Treatment and DoR

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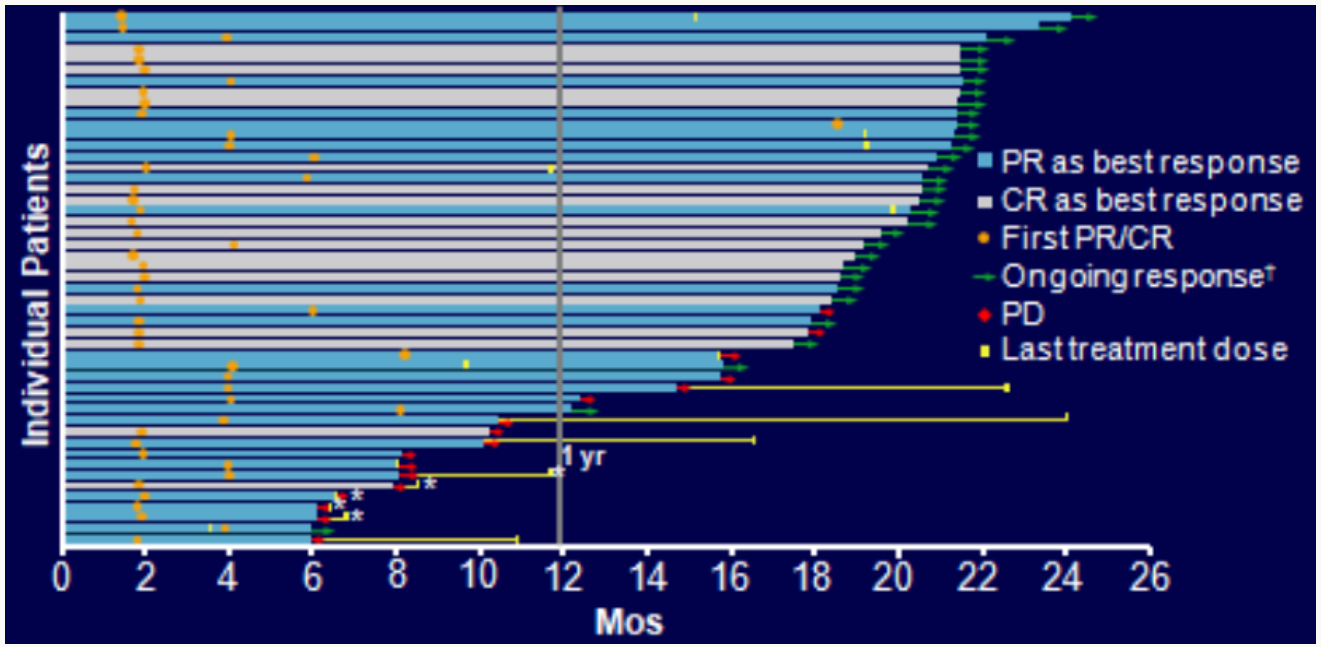
Patients With CR or PR as Best Response



*Pt deceased/timing not implied. †No PD or death.

- mTTR 2.1 mos (1.8-10.5)
- Median DoR not yet reached in all pts at median follow-up of 17.2 mos
- 70% (19 of 27 responding pts per IRF RECIST v1.1) with ongoing responses at data cutoff

Lancet. 2017 January 07; 389(10064): 67–76

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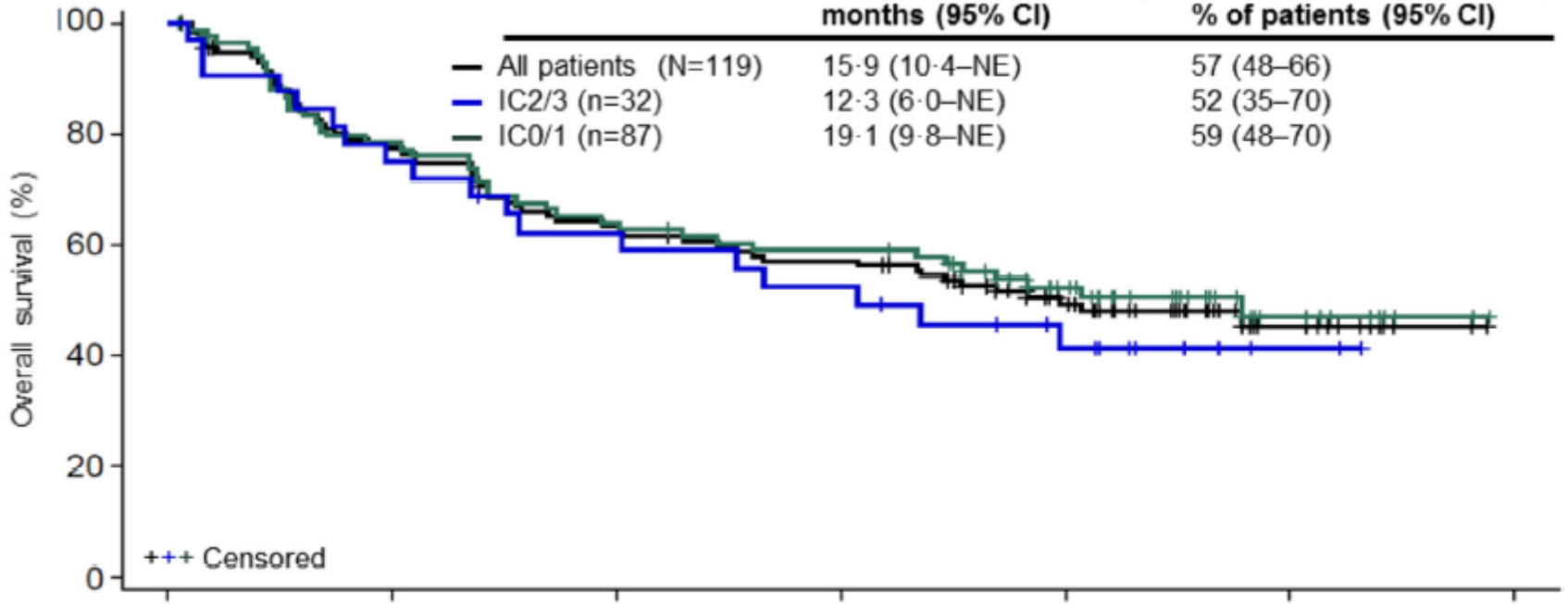
Overall Survival



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

Lancet. 2017 January 07; 389(10064): 67–76

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Pembrolizumab as First-Line Therapy in Cisplatin-Ineligible Advanced Urothelial Cancer: Results From the Total KEYNOTE-052 Study Population

✓KEYNOTE-052: Phase 2, advanced urothelial cancer, no prior chemotherapy for metastatic disease, ECOG 0-2, single-arm – pembro 200 mg Q3W

Baseline characteristics

✓ Of 541 patients screened, 370 were enrolled and received ≥1 dose of pembrolizumab

✓ 307 patients were enrolled for ≥4 months before the data cutoff, and, thus, had the opportunity for at least ✓2 postbaseline scans

✓ Overall, patients were representative of a cisplatin-ineligible population

Table 1. Baseline Demographics and Disease Characteristics (N = 370)

Characteristic, n (%)	Total Population
Age, median (range), years	74 (34-94)
≥80 years	107 (29)
Male	286 (77)
ECOG performance status†	
0	80 (22)
1	133 (36)
2	156 (42)
Primary tumor location‡	
Upper tract	69 (19)
Lower tract	300 (81)
Metastases location§	
Lymph node only	51 (14)
Visceral disease	315 (85)
Liver metastases	78 (21)
Previous adjuvant/neoadjuvant platinum-based chemotherapy‖	36 (10)
Reasons for cisplatin ineligibility	
ECOG performance status 2	120 (32)
Renal dysfunction††	182 (49)
ECOG performance status 2 and renal dysfunction	35 (10)
Other reasons‡‡	33 (9)

ECOG = Eastern Cooperative Oncology Group; NYHA = New York Heart Association.
†1 patient had an ECOG performance status of 3.
‡Primary tumor location unknown for 1 patient.
§Metastases location not reported for 4 patients.
‖Adjuvant platinum-based chemotherapy following radical cystectomy or neoadjuvant platinum-based chemotherapy with recurrence >12 months from completion of therapy was allowed.
††Renal dysfunction defined as creatinine clearance <60 mL/min.
‡‡Other reasons include NYHA Class III heart failure, grade ≥2 peripheral neuropathy, and grade ≥2 hearing loss.

Balar et al. Presented at the 2017 Genitourinary Cancers Symposium (ASCO-GU) February 16-18, 2017 Orlando, Florida

Efficacy

- ✓ Median follow-up duration was 5 months (range, 0.1-17 months) as of September 1, 2016
- ✓ ORR was 24% (95% CI, 20%-29%) among all patients and 27% (95% CI, 22%-32%) among those enrolled
- ✓≥4 months before the data cutoff

Figure 2. Treatment exposure and response duration in responders per RECIST v1.1 by central imaging vendor review (n = 89).

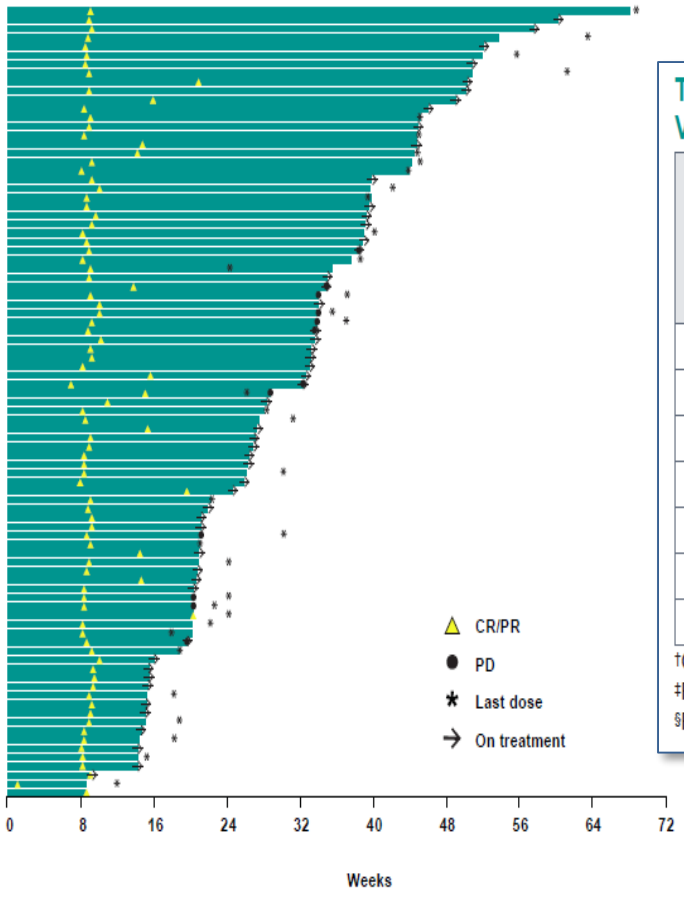

Table 2. Confirmed Objective Response Assessed per RECIST v1.1 by Central Imaging Vendor Review†

	Total Population N = 370		Patients Enrolled ≥4 Months Before Data Cutoff n = 307	
	n	% (95% CI)	n	% (95% CI)
Objective response rate	89	24 (20-29)	83	27 (22-32)
Complete response	17	5 (3-7)	17	6 (3-9)
Partial response	72	19 (16-24)	66	21 (17-27)
Stable disease	84	23 (19-27)	57	19 (14-23)
Progressive disease	156	42 (37-47)	130	42 (37-48)
No assessment‡	31	8 (6-12)	28	9 (6-13)
Not evaluable§	10	3 (1-5)	9	3 (1-6)

†Only confirmed responses are included.
‡Patient had no postbaseline imaging.
§Patient had postbaseline imaging, but images were not of sufficient quality to determine response.

Balar et al. Presented at the 2017 Genitourinary Cancers Symposium (ASCO-GU) February 16-18, 2017 Orlando, Florida

Ongoing immunotherapy trials in advanced urothelial cancer

Trial number	Investigational drug(s)	Setting	Trial design	Phase	Expected completion
NCT02335424	Pembrolizumab	First-line, platinum-ineligible	Single arm	II	June 2018
NCT02500121	Pembrolizumab	First-line maintenance if stable disease or better after chemotherapy	Randomized, double-blind, placebo-controlled	II	November 2018
NCT02256436	Pembrolizumab	Second- or third-line	Randomized to pembrolizumab or chemotherapy with either paclitaxel, docetaxel, or vinflunine	III	May 2017
NCT02387996	Nivolumab	Second-line and beyond, platinum-refractory	Single arm	II	April 2016
NCT02302807	Atezolizumab	Second-line and beyond, platinum-refractory	Randomized to atezolizumab or physician's choice chemotherapy	III	February 2017
NCT02478099	Atezolizumab	Second-line, platinum-refractory	Single arm with embedded imaging	II	August 2017
NCT01772004	Avelumab	Second-line and beyond	Single arm with expansion cohorts, multiple tumor types	I	May 2018
NCT02603432	Avelumab	First-line maintenance if stable disease or better after chemotherapy	Maintenance avelumab vs. best supportive care (no placebo)	III	July 2019
NCT02437370	Pembrolizumab + docetaxel OR gemcitabine	Second- or third-line metastatic	Arm 1: pembrolizumab + docetaxel Arm 2: pembrolizumab + gemcitabine Arms not compared. Patients receiving prior gemcitabine assigned to docetaxel arm	I	May 2017
NCT01524991	Ipilimumab + gemcitabine/cisplatin	First-line metastatic	Single arm	II	June 2016
NCT02807636	Atezolizumab + gemcitabine/carboplatin	First-line metastatic, cisplatin-ineligible	Randomized, double-blind, placebo-controlled	III	September 2019
NCT02581982	Pembrolizumab + paclitaxel	Second-ine, platinum-refractory	Single arm	II	March 2019
NCT02560636	Pembrolizumab + radiation therapy	Any line locally advanced or metastatic	Single-arm trial to receive pembrolizumab with 6 wk of radiation to the bladder	I	June 2019
NCT02443324	Pembrolizumab + ramucirumab	Second- to fourth-line metastatic	Single-arm study with parallel arms for other tumor types	I	December 2017
NCT02546661	Durvalumab alone or PLUS AZD4547 OR olaparib OR AZD1775	Second- or third-line metastatic	Multiarm, biomarker-directed, randomized study to durvalumab alone or various combinations	I	June 2018

Urol Oncol. 2016 Dec;34(12):538-547

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NCT02496208	Nivolumab + cabozantinib ± ipilimumab	Second-line and beyond	Arm 1: nivolumab + cabozantinib Arm 2: nivolumab + ipilimumab + cabozantinib	I	December 2017
NCT02527434	Durvalumab, tremelimumab	First-line metastatic	All patients begin tremelimumab, then at progression can switch to or add durvalumab	II	April 2018
NCT02516241	Durvalumab + tremelimumab	First-line metastatic	Arm 1: durvalumab alone Arm 2: durvalumab + tremelimumab Arm 3: chemotherapy with GC	III	November 2017
NCT02553642	Nivolumab ± ipilimumab	Second-line and beyond	Single-arm UC cohort (melanoma cohort). Nivolumab up to second progression, then may add ipilimumab	II	September 2017
NCT01928394	Nivolumab ± ipilimumab	Any line metastatic	Multiple tumor types randomized to nivolumab alone or various dose combinations	I/II	August 2017
NCT02619253	Pembrolizumab + vorinostat	Second-line and beyond	Dose escalation of vorinostat with fixed dose of pembrolizumab, followed by expansion cohorts	I/Ib	May 2018
NCT02636036	Pembrolizumab + enadenotucirev	Second- to fourth-line metastatic	Single-arm dose escalation followed by dose expansion	I	February 2017
NCT02351739	Pembrolizumab + acalabrutinib (ACP-196)	Second-line and beyond,	Arm 1: pembrolizumab alone Arm 2: pembrolizumab + acalabrutinib	II	May 2017
NCT02528357	Pembrolizumab, GSK3174998	Any line metastatic	Multiple tumor types Part 1: GSK3174998 alone Part 2: GSK3174998 + pembrolizumab	I	January 2020
NCT01968109	Nivolumab, BMS-980616	Any line metastatic	Multiple tumor types Part 1: BMS-980616 alone Part 2: BMS-980616 + nivolumab	I	May 2018

Urol Oncol. 2016 Dec;34(12):538-547

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NCT02655822	Atezolizumab, CPI-444	Any line metastatic	Multiple tumor types, dose selection study of CPI-444, 1 arm combining with atezolizumab	I	June 2018
NCT02318277	Durvalumab + epacadostat (INCB024360)	Second-line and beyond	Single arm	I/II	March 2017
NCT01730118	AdHER2 dendritic cell vaccine	Any line metastatic	Single arm in tumors with HER2 expression, includes multiple tumor types	I	November 2017
NCT02043665	Pembrolizumab, CVA21 oncolytic virus	Any line metastatic (part 2 NSCLC and bladder only)	Part 1: CVA21 Part 2: CVA21 + pembrolizumab	I	August 2019
NCT02643303	Poly-ICLC, durvalumab, tremelimumab	Any line metastatic	Multiple combinations of Poly-ICLC with durvalumab ± tremelimumab Includes multiple tumor types	I	August 2022
NCT02661100	Pembrolizumab + CDX-1401 + Poly-ICLC	Second-line and beyond	Single arm	I/II	July 2018
NCT02614456	Nivolumab + IFN-gamma	Second-line and beyond	Single arm for multiple tumors types, with expansion in UC and RCC	I	December 2017

Urol Oncol. 2016 Dec;34(12):538-547

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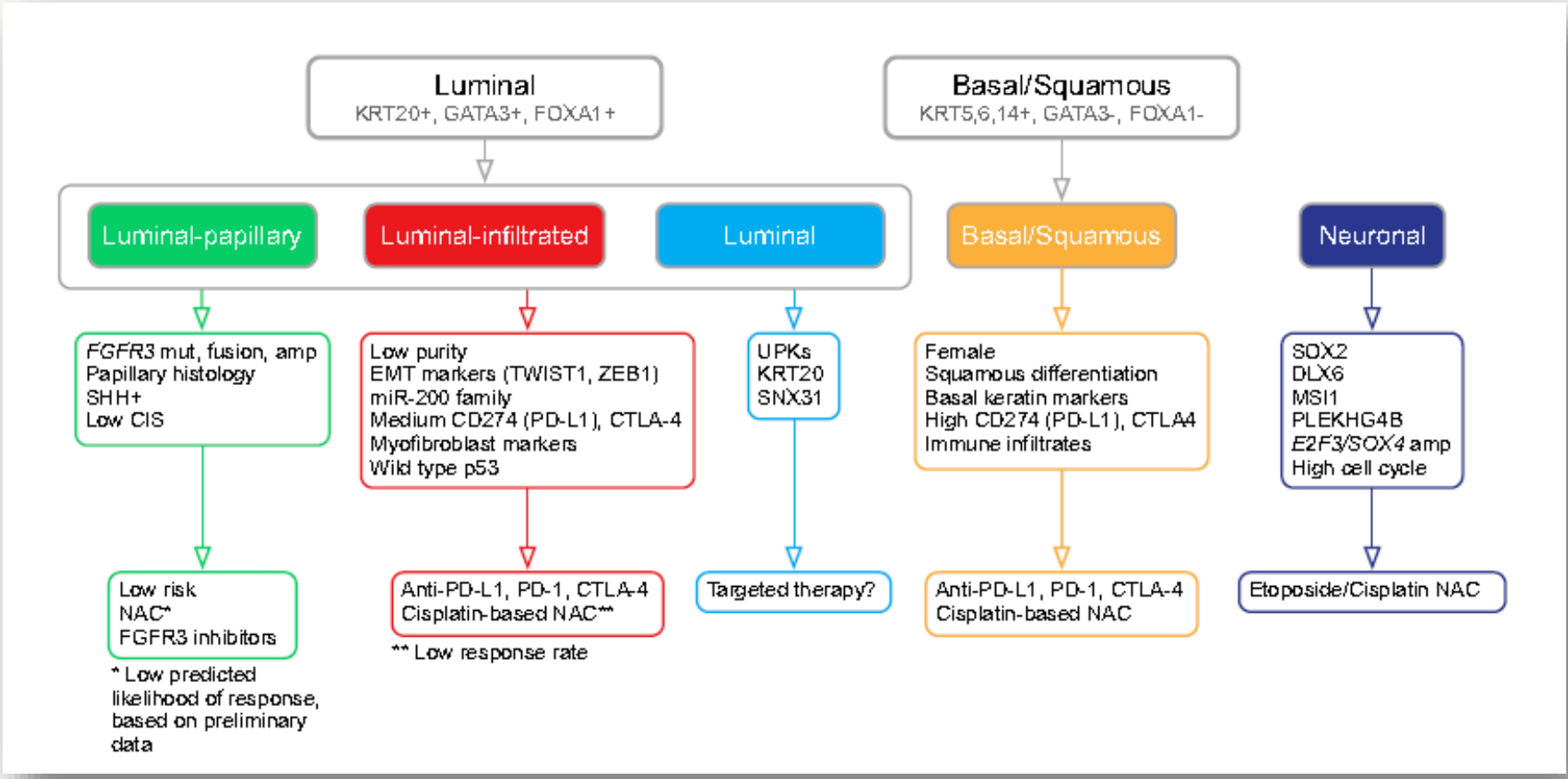
How to select patients?



Cell. 2017 Oct 19;171(3):540-556.e25

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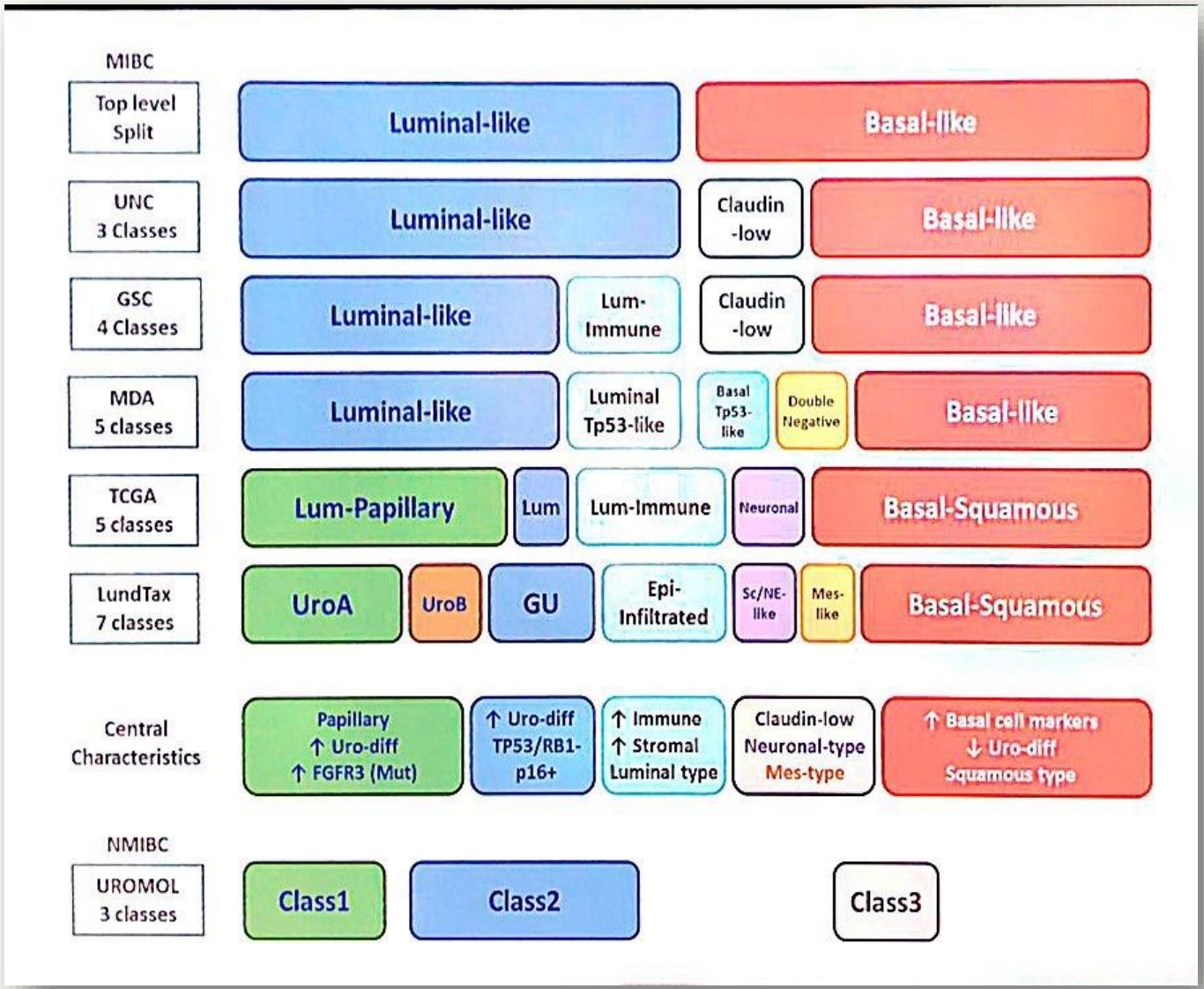
How to select patients?



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Carcinoma urotelial: Para aonde vamos?

Classificação	Estágio no diagnóstico	Proporção no diagnóstico		Taxa de sobrevida relativa de 5 anos[1]	Probabilidade de recorrência em 5 anos
Doença não musculo-invasiva	Não invasivo (Ta, Tis e T1)	51–75%[1–4]		96%	50–90%[2,4]
Doença musculo-invasiva	Localizado (T2–4, N0)	34%[1]	30%[4]	70%	≈50%[6]
	Regional (Tx, N1)	7%[1]		35%	
Doença metastática	Distante/metastático (Tx, Nx, M1)	4%[1,5]		5%	NA

1. Howlader N, et al. (eds). SEER Cancer Statistics Review, 1975–2013
2. NCCN Guidelines – Bladder cancer v2.2017; 3. Sharma S, et al. Am Fam Physician 2009
4. Kaufman DS, et al. Lancet 2009; 5. American Cancer Society 2014: Bladder Cancer
6. de Vos FY and de Wit R. Ther Adv Med Oncol 2010

THANK YOU

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