Educação
e Pesquisa

A Beneficência Portuguesa de São Paulo

Oncologia

Carcinoma de Rim e Carcinoma Urotelial - Imunoterapia

Dr. Fábio A. B. Schutz

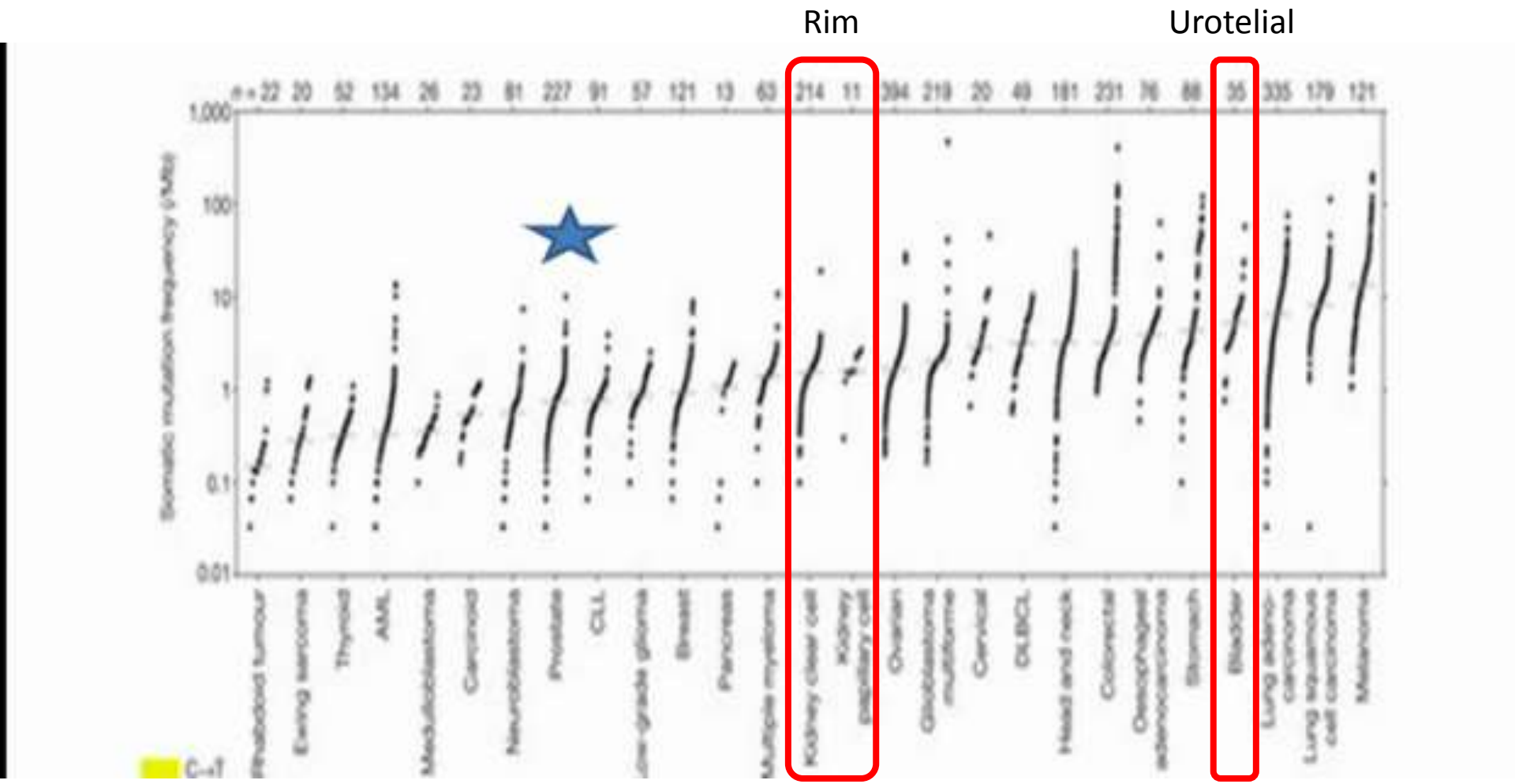
Oncologia Clínica

BP – A Beneficência Portuguesa de São Paulo

Declaração de Conflitos de Interesse

- De acordo com a Resolução 1595 / 2000 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro que:
  - Pesquisa Clínica: como médico investigador, participo de estudos patrocinados por: Roche, BMS, Novartis, Janssen, MSD
  - Apresentações: como palestrante convidado, participei de eventos: Sanofi, Novartis, Bayer, Janssen, Astellas, BMS, Pfizer
  - Advisory Board: Sanofi, Bayer, Janssen, Astellas, Novartis, Roche, MSD
  - Não possuo ações de quaisquer destas companhias farmacêuticas.

Carga Mutacional



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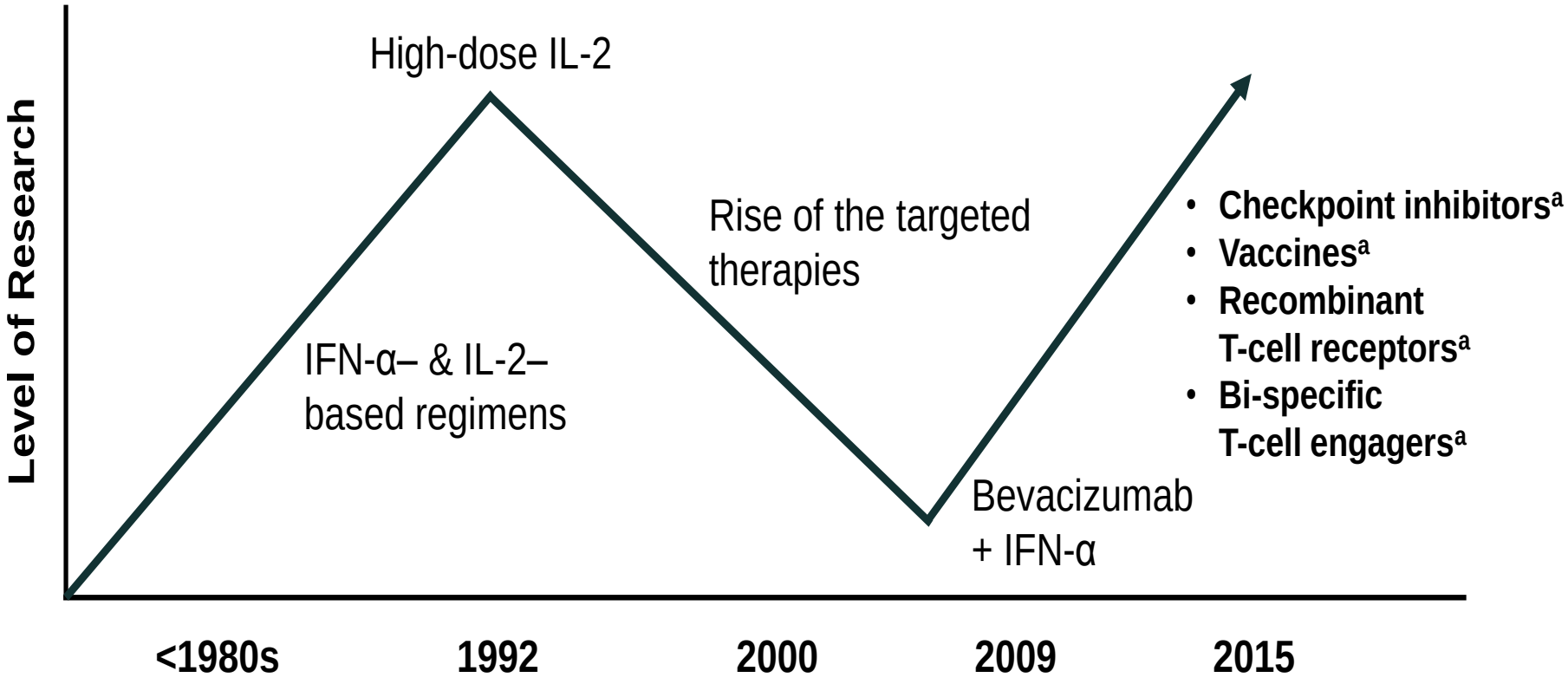
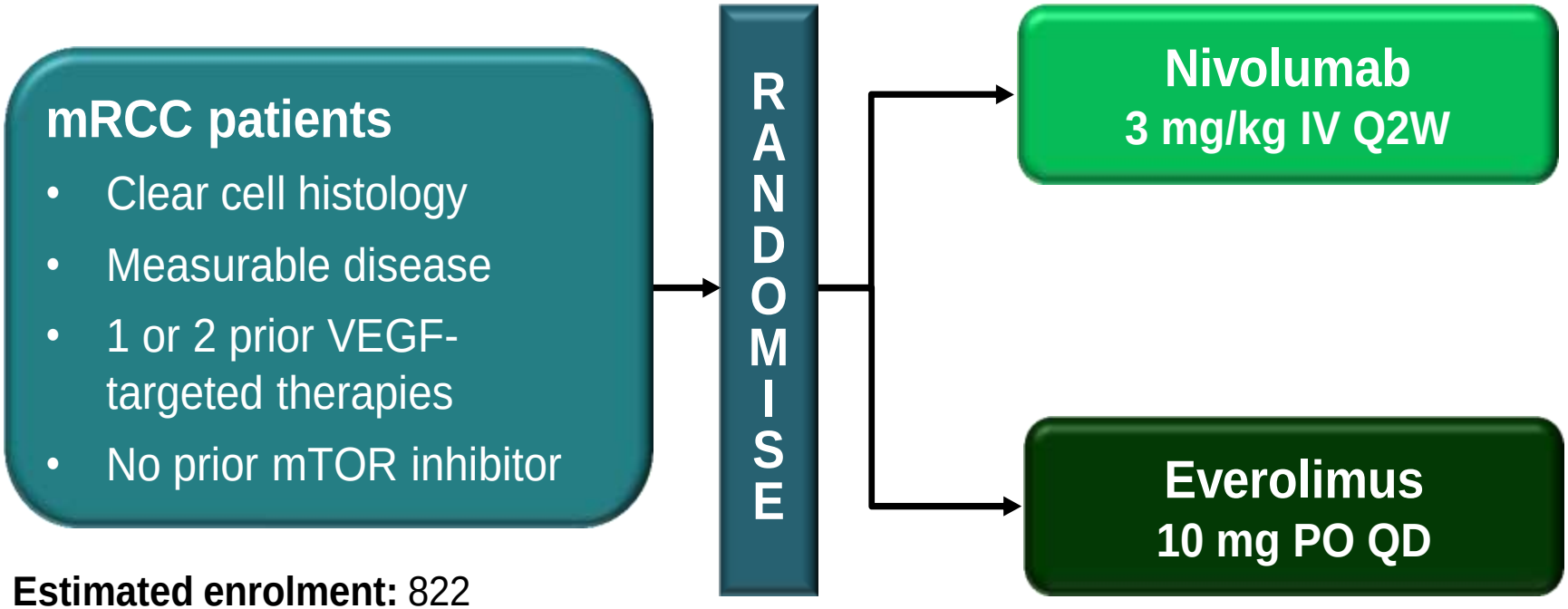
Carcinoma de Rim

Imunoterapia em câncer de rim – Interesse renovado



Plimack E, et al. ASCO 2015; abstract 4553.

CheckMate 025 – Fase 3

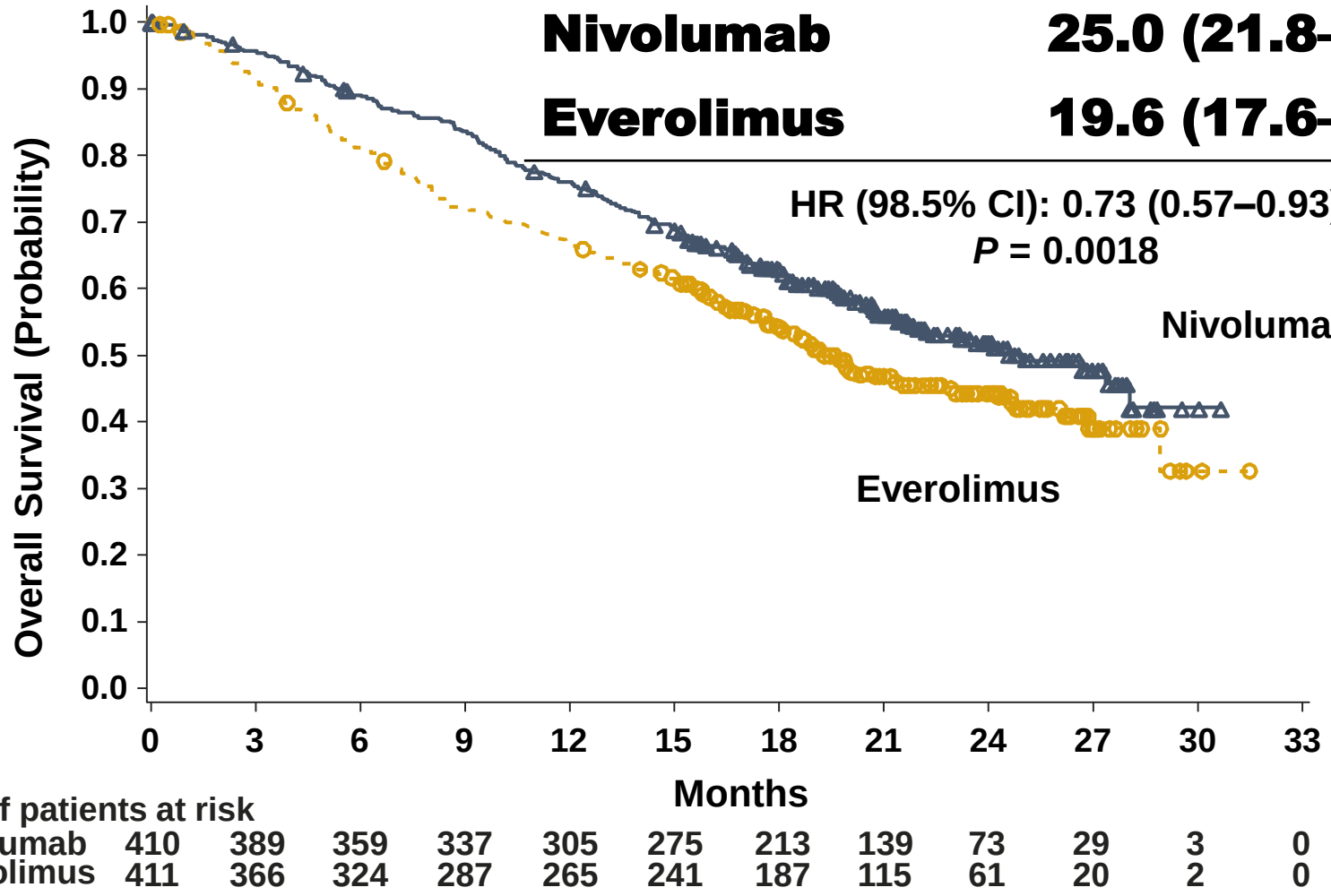


- **Estimated enrolment:** 822
- **Estimated completion date:** February 2016
- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, ORR, safety

Motzer RJ, et al. N Engl J Med 2015 Sep 25: Epub ahead of print.

CheckMate 025 – Fase 3

Median OS, months (95% CI)	
Nivolumab	**25.0 (21.8–NE)**
Everolimus	**19.6 (17.6–23.1)**



No. of patients at risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

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Motzer RJ, et al. N Engl J Med 2015 Sep 25: Epub ahead of print.

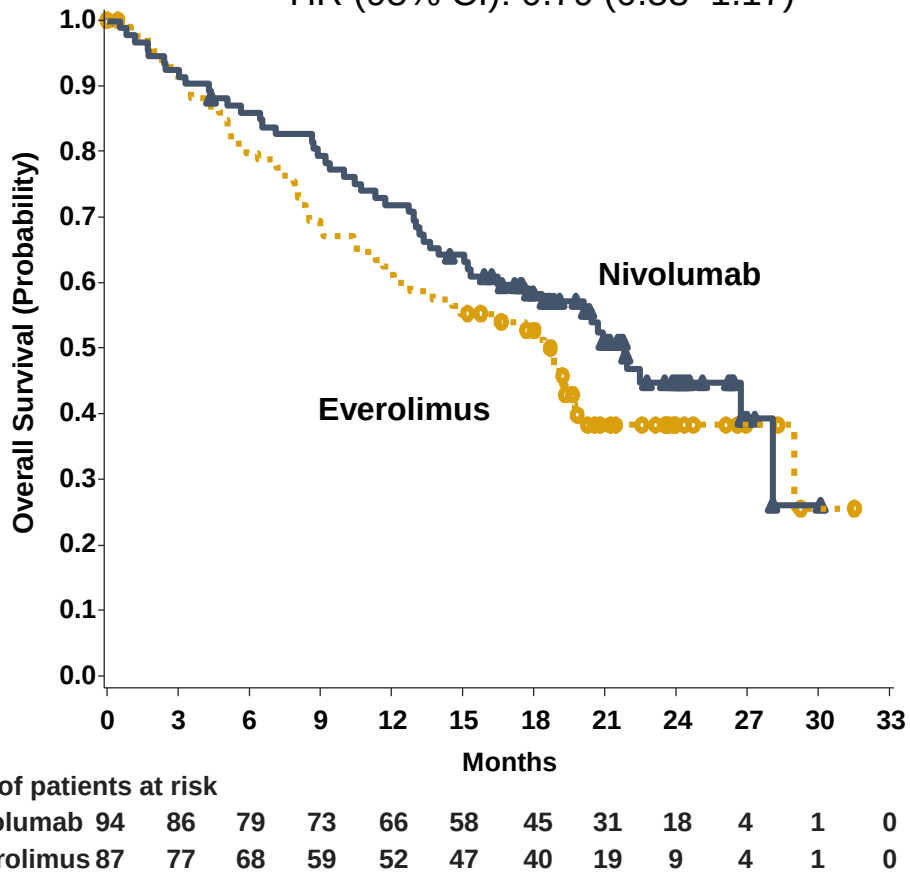
CheckMate 025 – Fase 3

SG e status PD-L1

PD-L1 ≥1% (n = 24%)

Median OS, months (95% CI)	
Nivolumab	21.8 (16.5–28.1)
Everolimus	18.8 (11.9–19.9)

HR (95% CI): 0.79 (0.53–1.17)



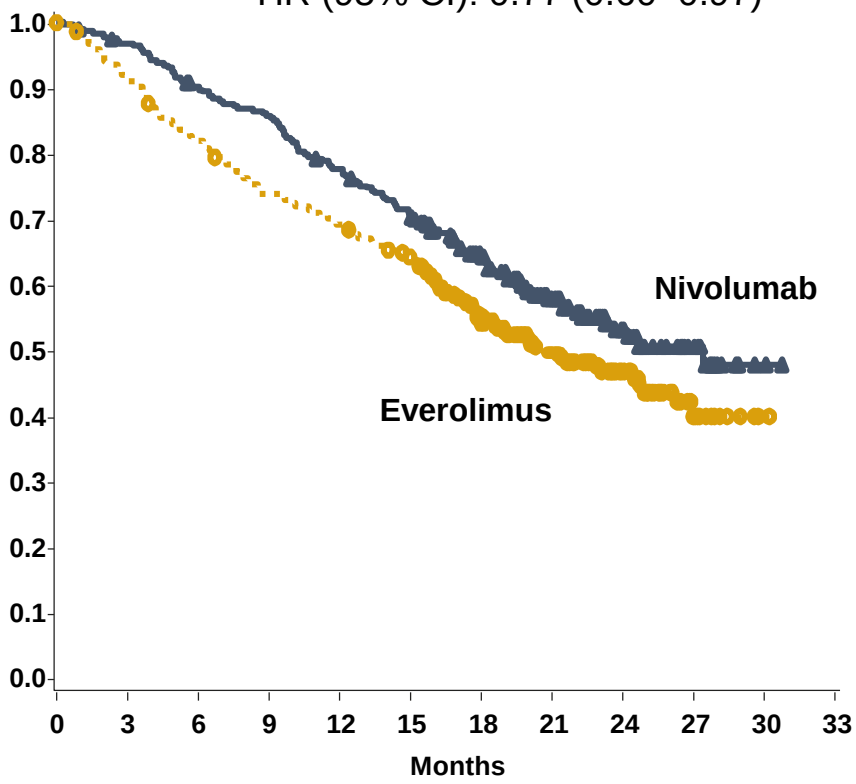
No. of patients at risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	87	77	68	59	52	47	40	19	9	4	1	0

PD-L1 <1% (n = 76%)

Median OS, months (95% CI)	
Nivolumab	27.4 (21.4–NE)
Everolimus	21.2 (17.7–26.2)

HR (95% CI): 0.77 (0.60–0.97)



Motzer RJ, et al. N Engl J Med 2015 Sep 25: Epub ahead of print.

CheckMate 025 – Fase 3

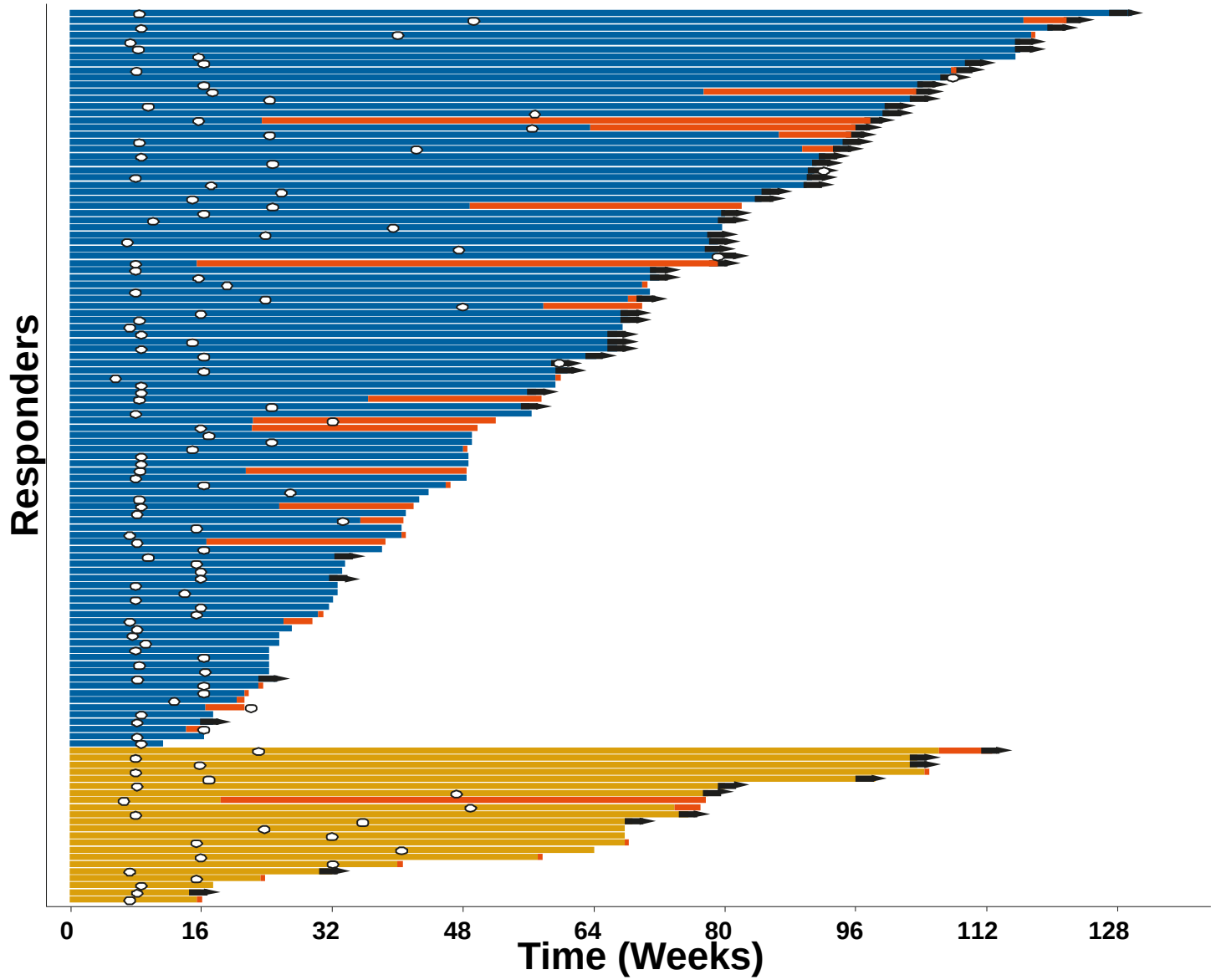
Resposta Objetiva

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
P value	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)*	12.0 (0–27.6)	12.0 (0–22.2)
Ongoing response, n/N (%)	49/103 (48)	10/22 (45)

Motzer RJ, et al. N Engl J Med 2015 Sep 25: Epub ahead of print.

CheckMate 025 – Fase 3

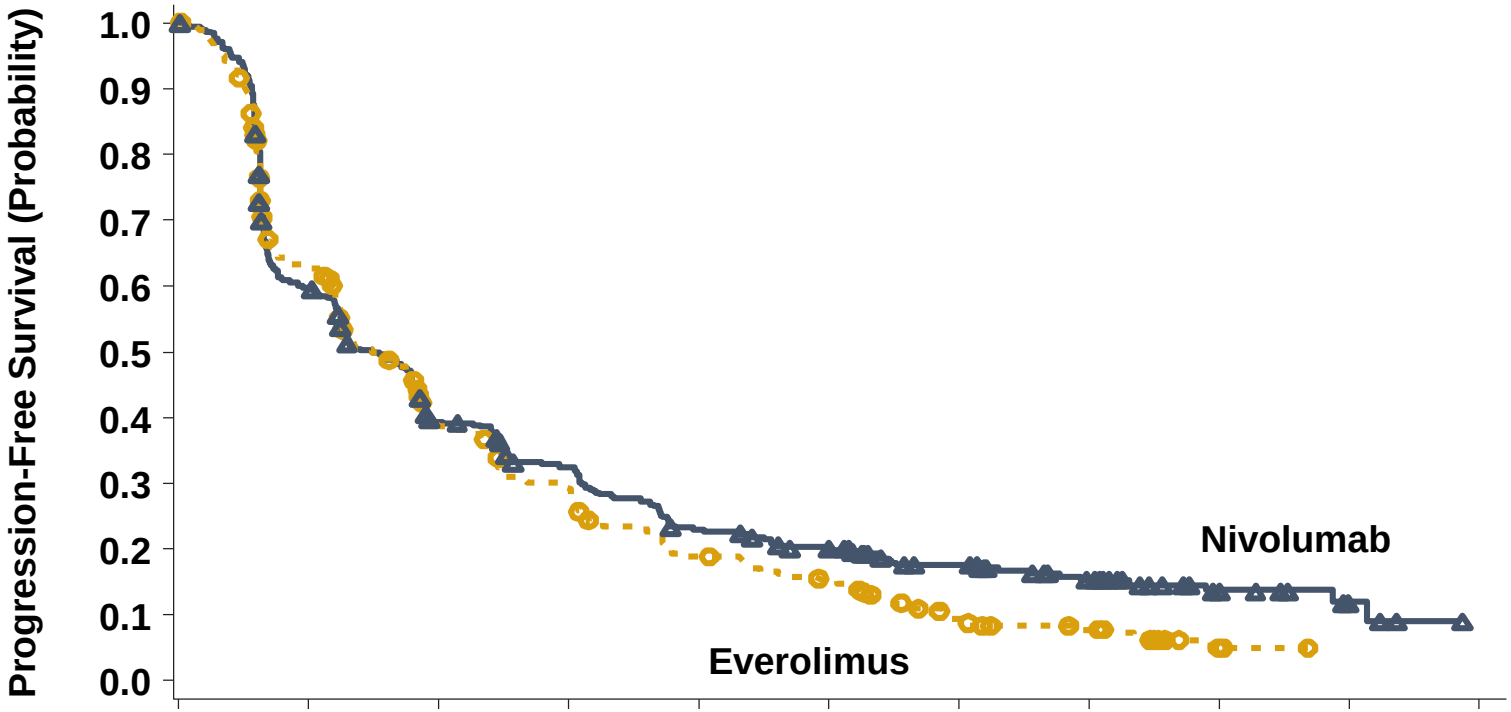
Resposta Objetiva



Motzer RJ, et al. N Engl J Med 2015 Sep 25: Epub ahead of print.

CheckMate 025 – Fase 3

Sobrevida Livre de Progressão



No. of patients at risk											
Nivolumab	410	230	145	116	81	66	48	29	11	4	0
Everolimus	411	227	129	97	61	47	25	16	3	0	0

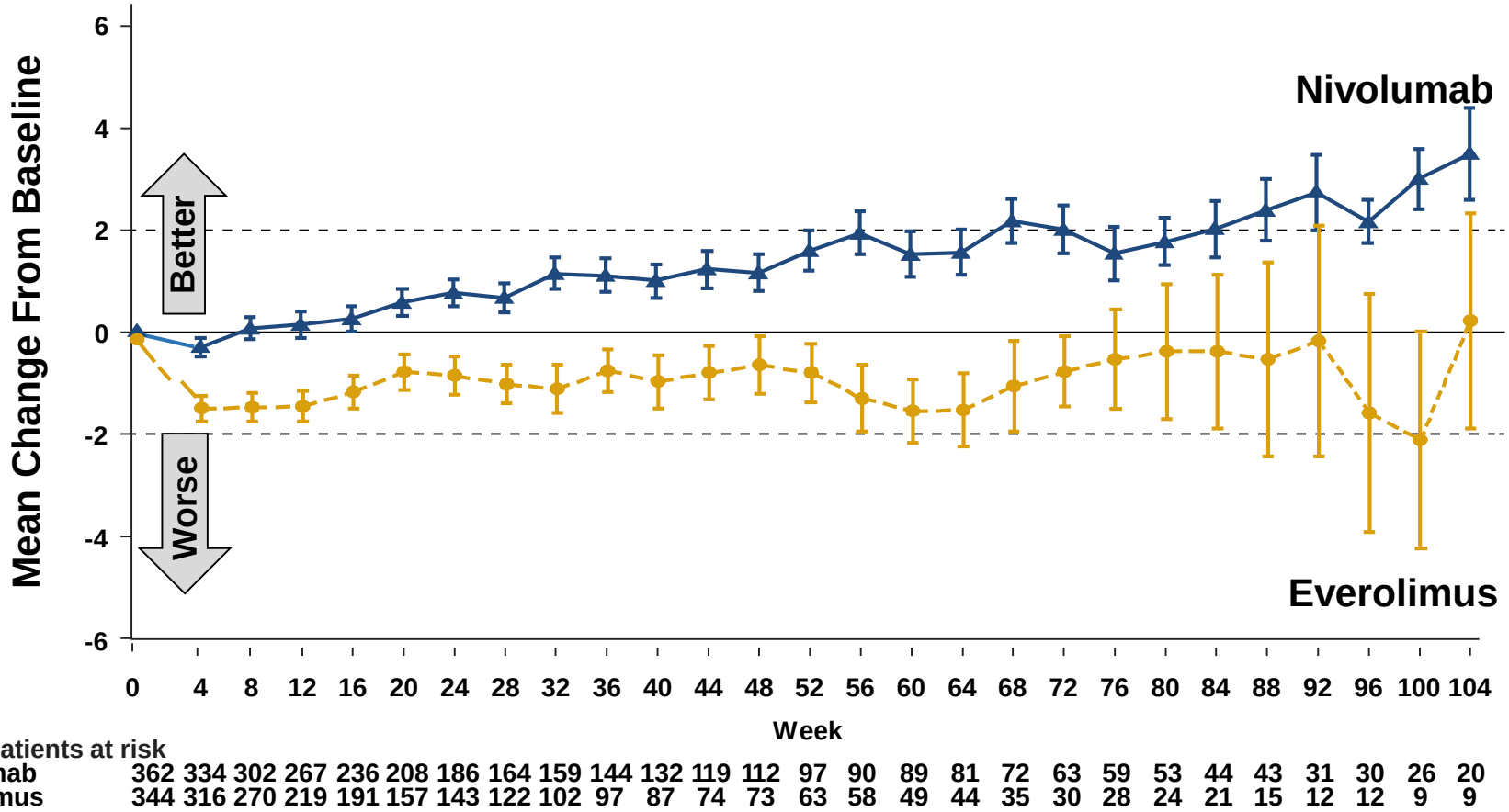
- In a post-hoc analysis of patients who had not progressed or died at 6 months, median PFS was 15.6 months for nivolumab vs 11.7 months for everolimus (HR (95% CI): 0.64 (0.47–0.88))

Motzer RJ, et al. N Engl J Med 2015 Sep 25: Epub ahead of print.

CheckMate 025 – Fase 3

Qualidade de Vida

- Mean change from baseline in the nivolumab group increased over time and differed significantly from the everolimus group at each assessment through week 76 (*P*<0.05)

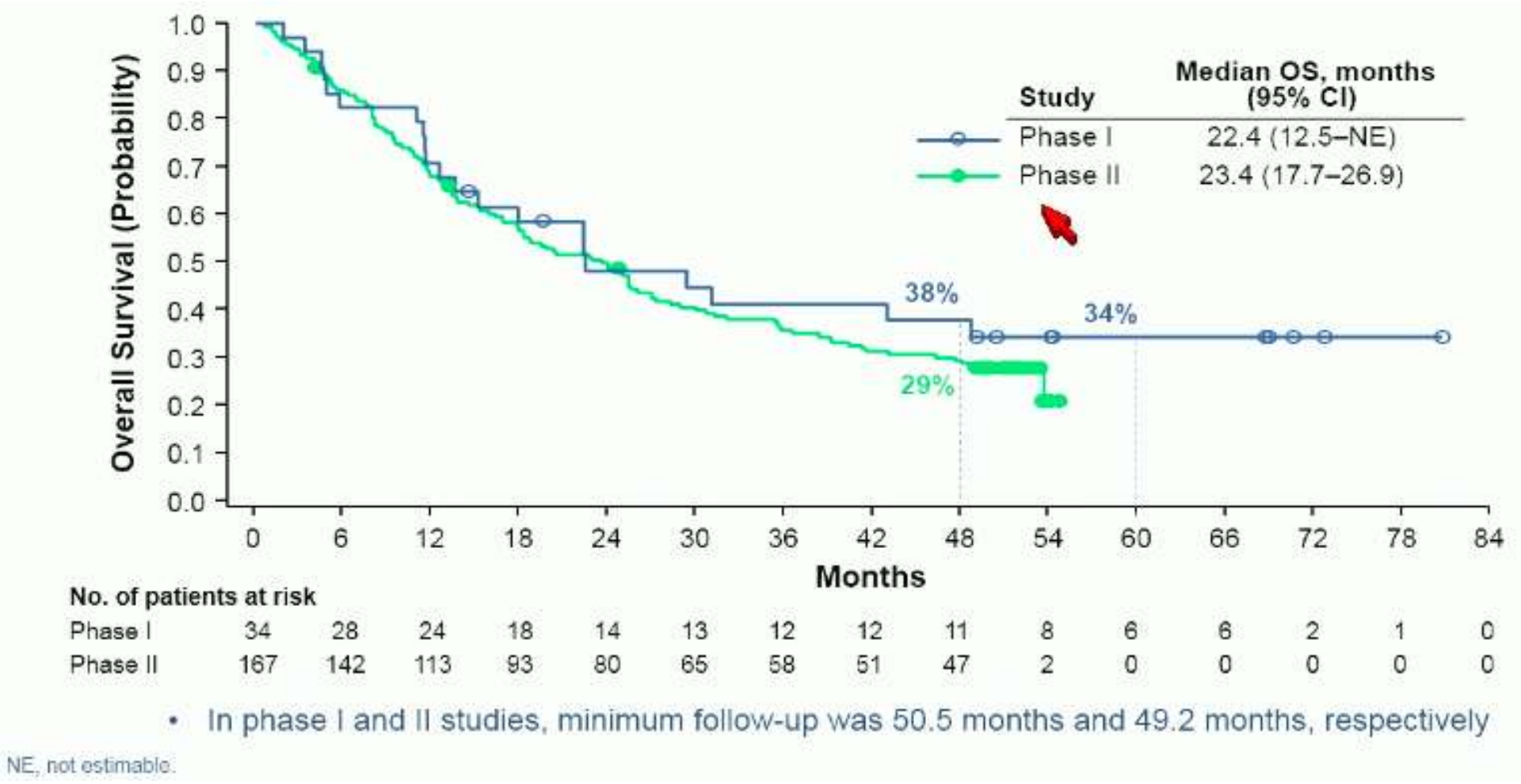


Motzer RJ, et al. N Engl J Med 2015 Sep 25: Epub ahead of print.

Nivolumabe Fase I e II

Seguimento de longo prazo

Sobrevida Global



- In phase I and II studies, minimum follow-up was 50.5 months and 49.2 months, respectively

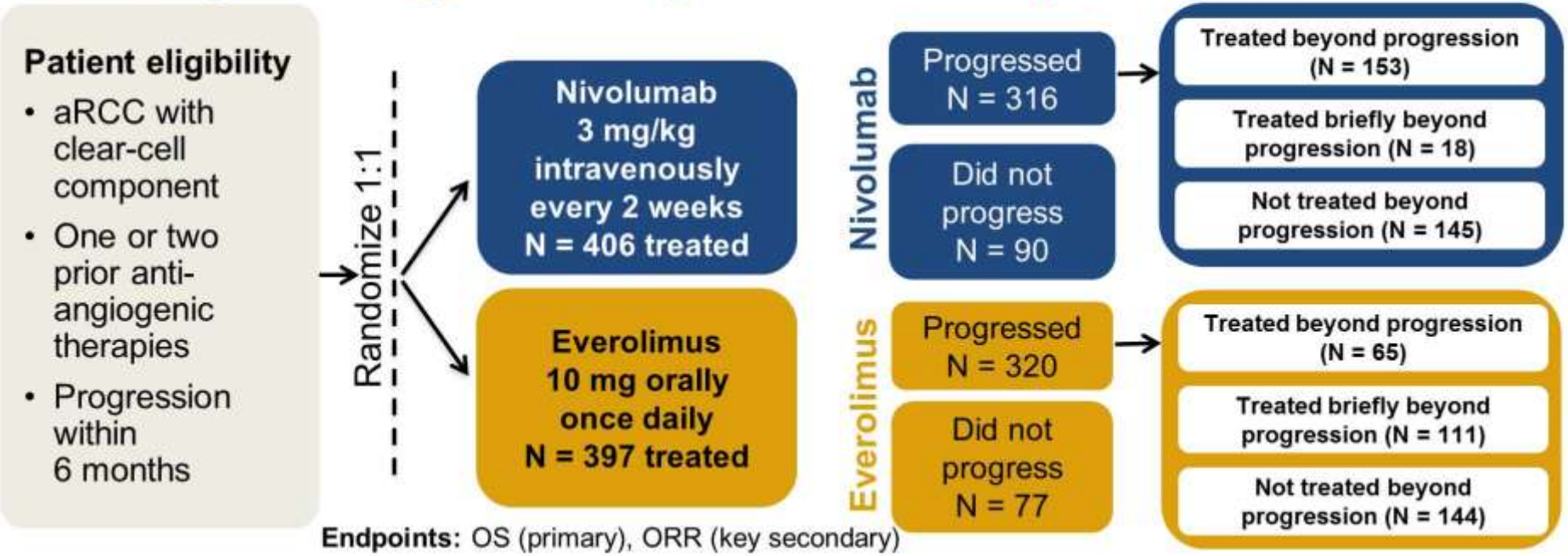
NE, not estimable.

McDermott DF, et al. ASCO Meeting 2016:abstract 4507.

Checkmate 025

Tratamento pós PD

Study design and patient disposition



- Treatment beyond progression was defined as treatment ≥4 weeks after first progression
- Treatment briefly beyond progression was defined as treatment <4 weeks after first progression

Escudier BJ, et al. ASCO Meeting 2016:abstract 4509.

Checkmate 025
Tratamento pós PD

Duration of treatment

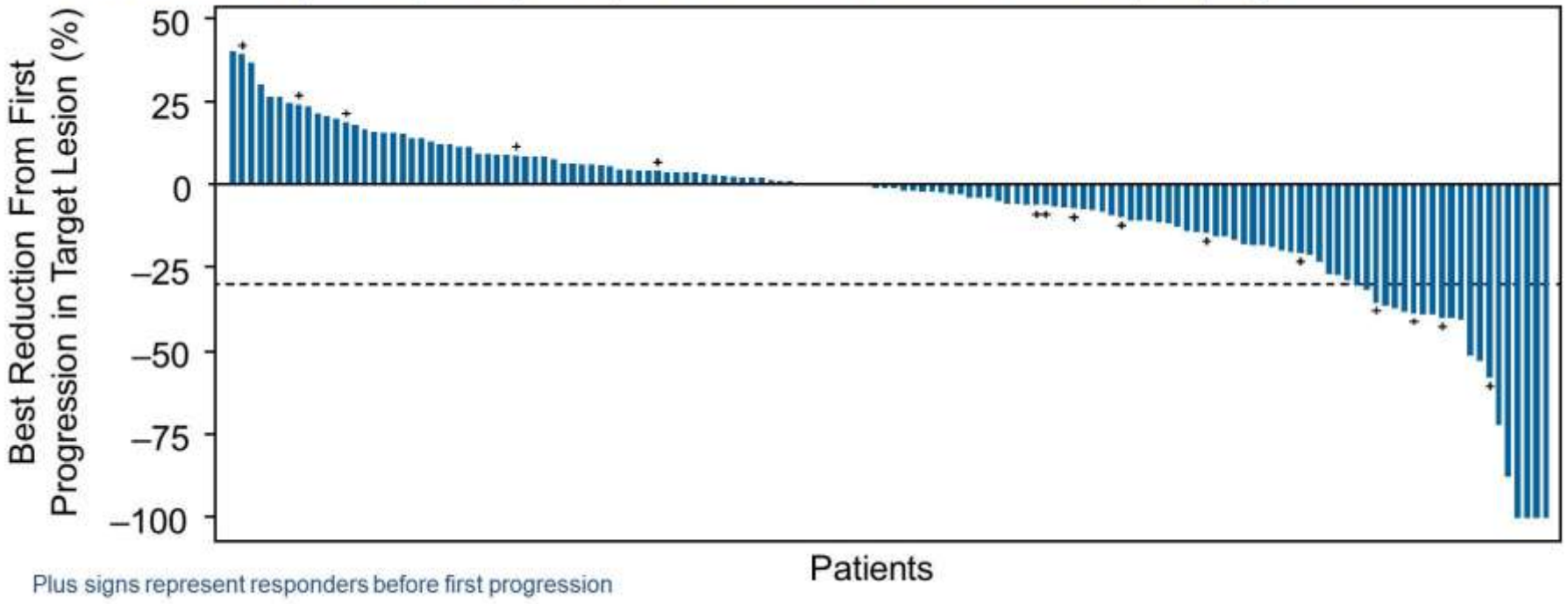
	Patients treated beyond progression (n = 153)	Patients not treated beyond progression (n = 145)
Median duration of treatment, months (95% CI)		
Overall	8.8 (7.4–10.2)	2.3 (1.7–3.3)
Randomization to first progression	2.7 (1.9–3.8)	2.3 (1.8–3.3)
Post-progression	3.4 (3.0–5.1)	Not applicable

Escudier BJ, et al. ASCO Meeting 2016:abstract 4509.

Checkmate 025
Tratamento pós PD

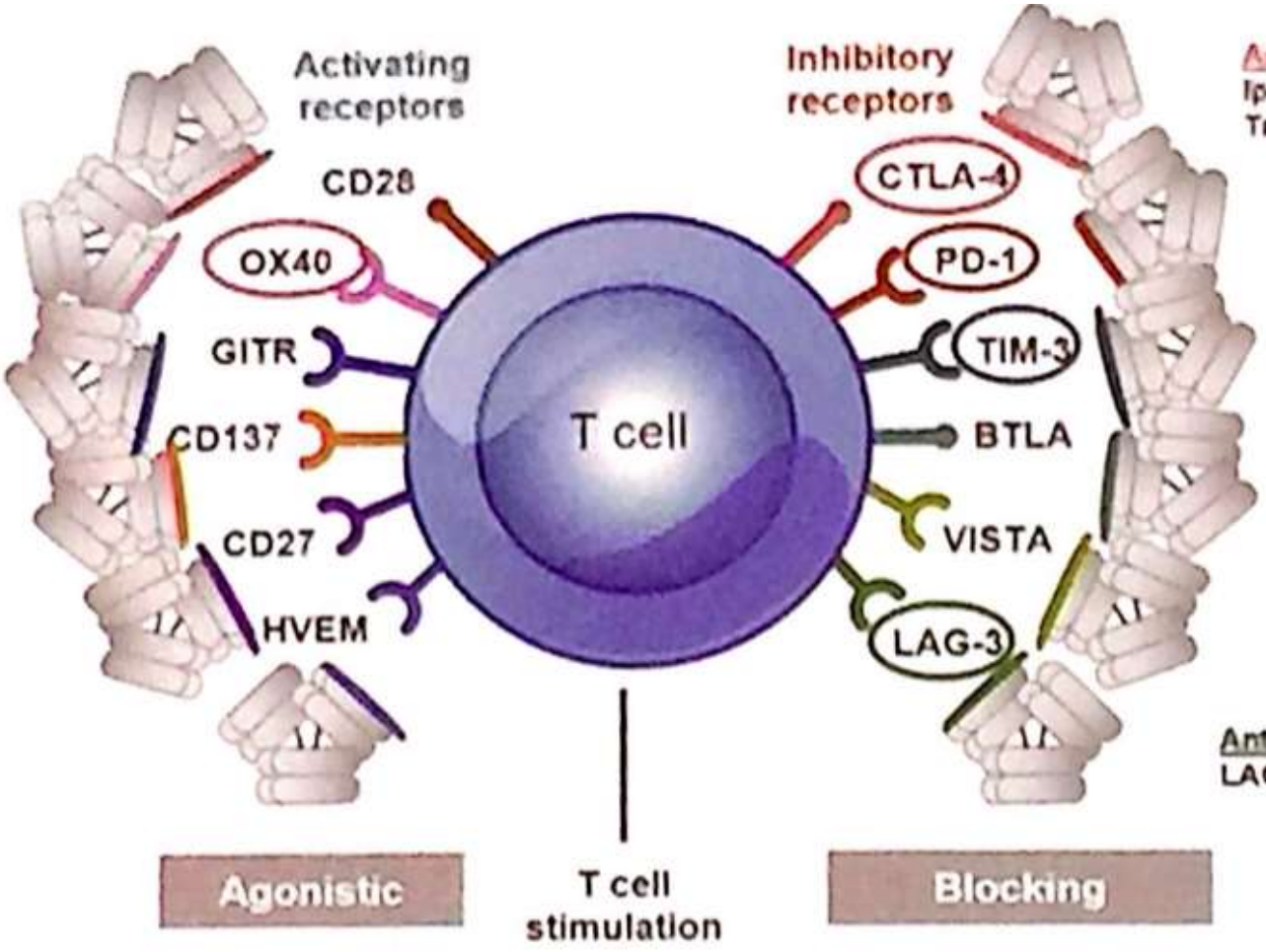
Tumor burden change post-progression in patients treated with nivolumab beyond progression

- A total of 142 of 153 patients treated with nivolumab beyond progression had tumor measurements pre- and post-progression
  - Of these 142 patients, 14% (n = 20) had ≥30% tumor burden reduction post-progression

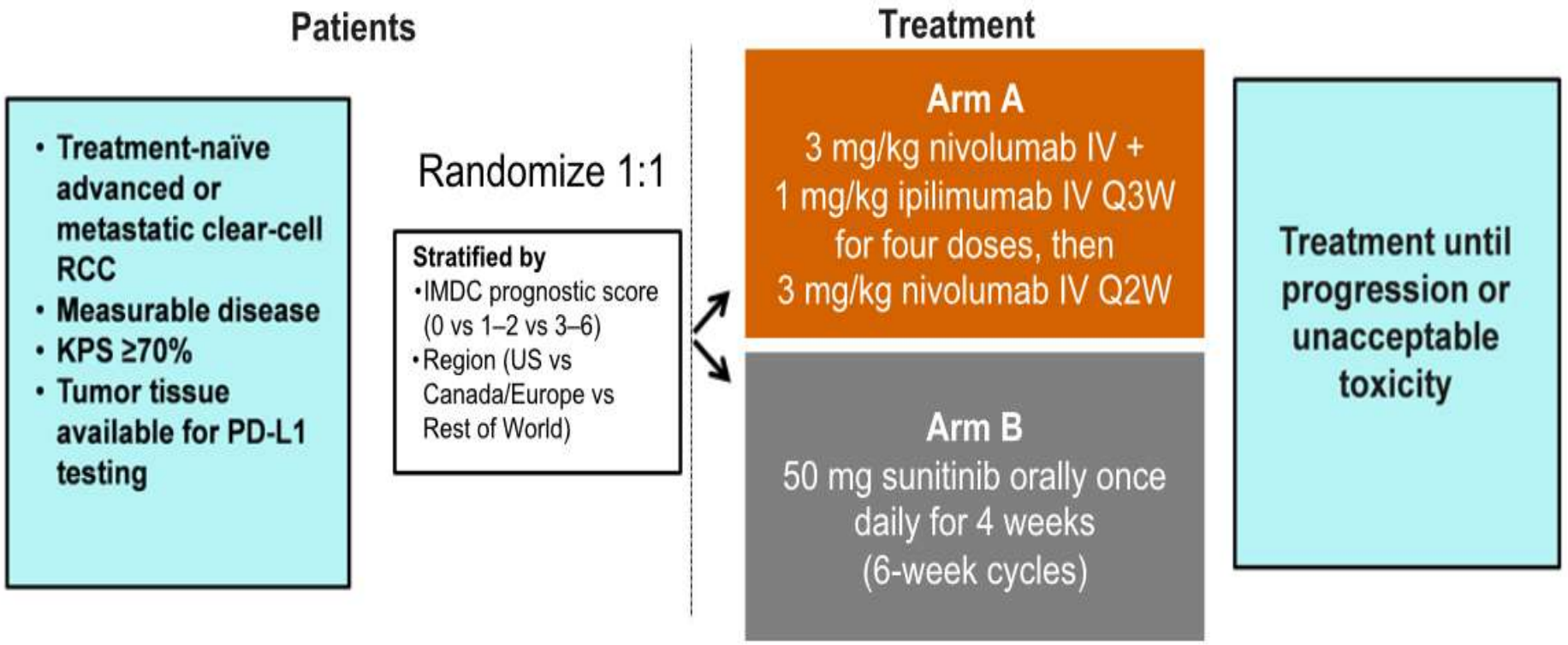


Escudier BJ, et al. ASCO Meeting 2016:abstract 4509.

Combinação de IO



Checkmate 214 – Ipi + Nivo (Fase III)



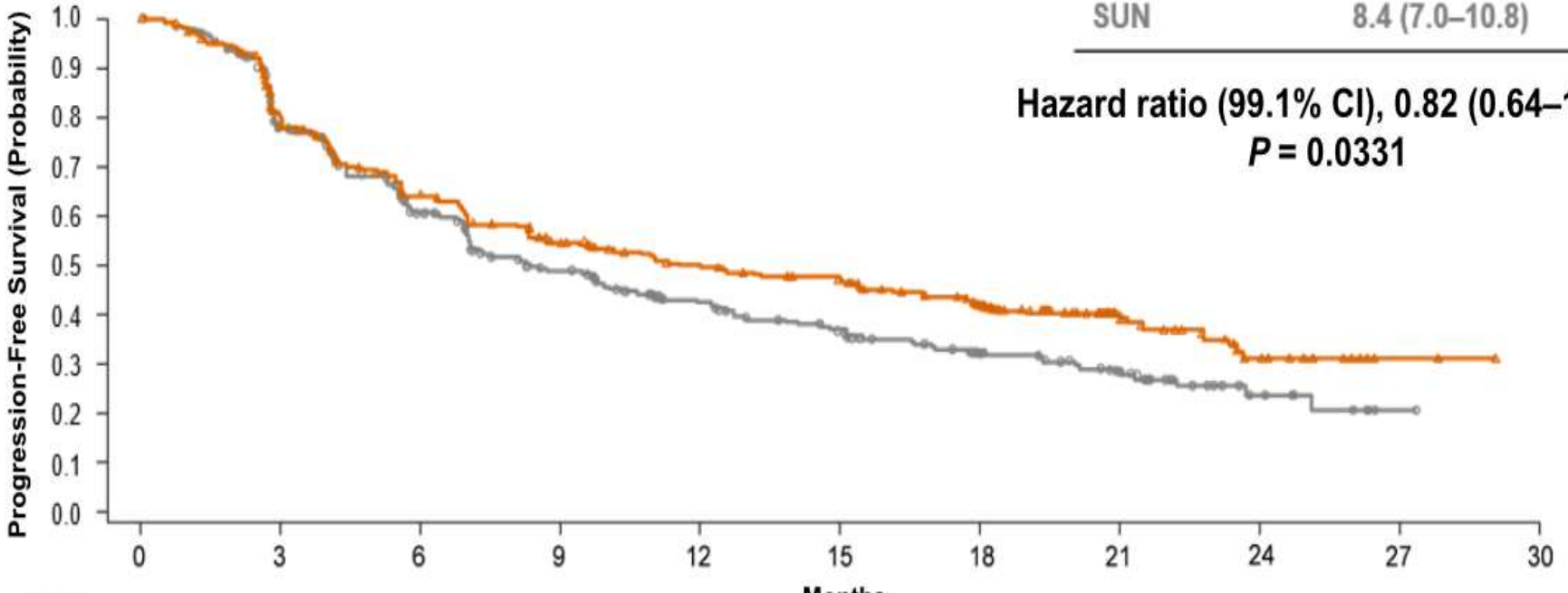
IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; Q3W, every 3 weeks

Escudier B, et al. ESMO 2017: abstract LBA5.

Checkmate 214 – Ipi + Nivo (Fase III)
SLP IMDC Risco Intermediário/Alto (Endpoint Primário)

Median PFS, months (95% CI)	
NIVO + IPI	11.6 (8.7–15.5)
SUN	8.4 (7.0–10.8)

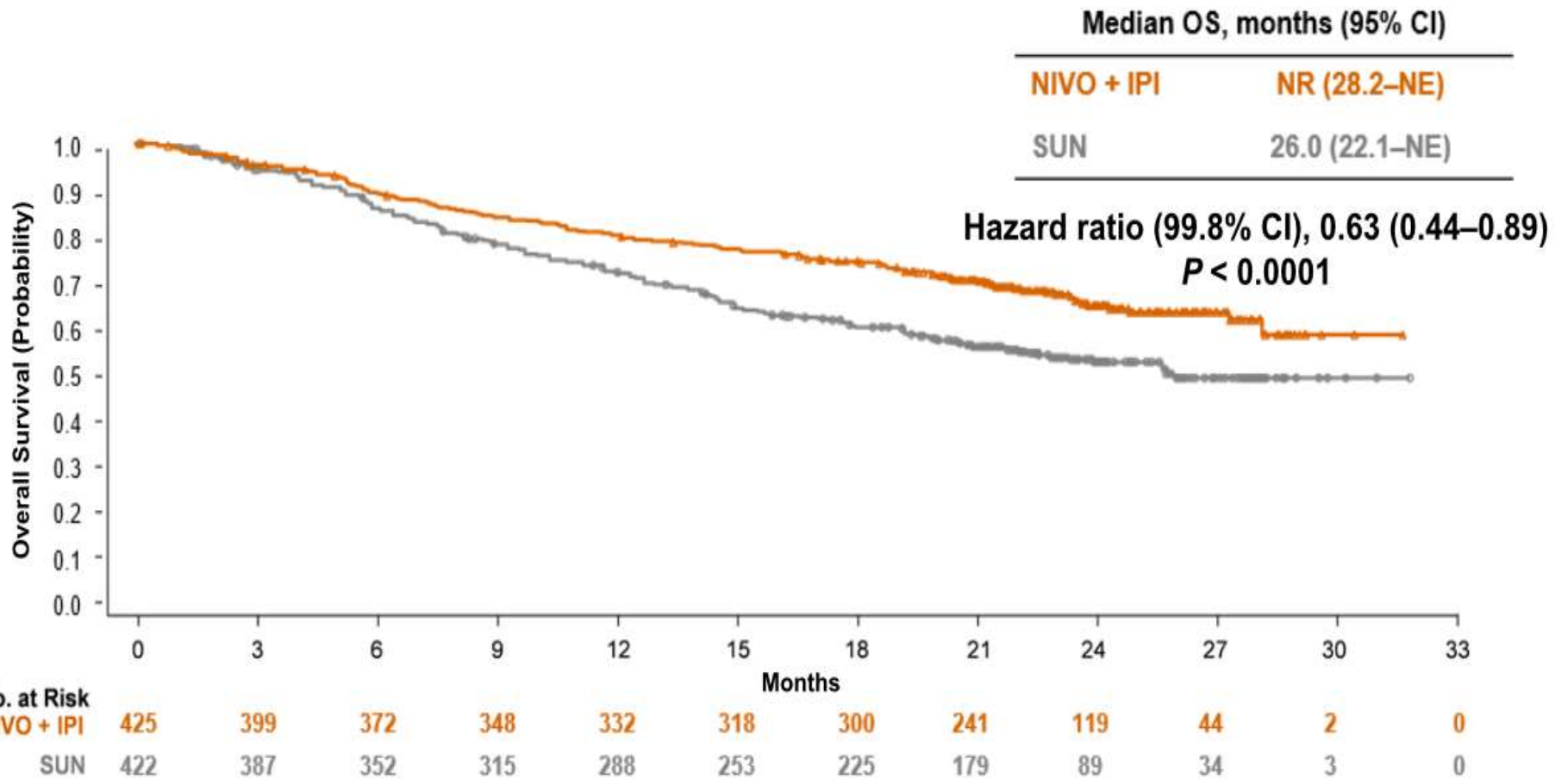
Hazard ratio (99.1% CI), 0.82 (0.64–1.05)
***P* = 0.0331**



No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

Escudier B, et al. ESMO 2017: abstract LBA5.

Checkmate 214 – Ipi + Nivo (Fase III)
SG IMDC Risco Intermediário/Alto (Endpoint Primário)



Escudier B, et al. ESMO 2017: abstract LBA5.

Checkmate 214 – Ipi + Nivo (Fase III)
RO e SLP – IMDC Risco Baixo (Endpoint Exploratório)

Outcome	N = 249[a]	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	29 (21–38)	52 (43–61)
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68)	
	P < 0.0001	

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[a]11% of patients in both arms had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed

Escudier B, et al. ESMO 2017: abstract LBA5.

Checkmate 214 – Ipi + Nivo (Fase III)

RO e status PD-L1 (Endpoint Exploratório)

	IMDC intermediate/poor risk				Intention to treat			
	PD-L1 <1%		PD-L1 ≥1%		PD-L1 <1%		PD-L1 ≥1%	
Outcome	NIVO + IPI N = 284	SUN N = 278	NIVO + IPI N = 100	SUN N = 114	NIVO + IPI N = 386	SUN N = 376	NIVO + IPI N = 113	SUN N = 127
ORR,[a] % (95% CI)	37 (32–43)	28 (23–34)	**58 (48–68)**	**22 (15–31)**	36 (31–41)	35 (31–40)	**53 (44–63)**	**22 (15–30)**
	P = 0.0252		*P* < 0.0001		*P* = 0.8799		*P* < 0.0001	
BOR,[a] %								
Complete response	7	1	16	1	9	2	14	1
Partial response	30	27	42	21	27	33	39	21
Stable disease	36	47	19	40	39	43	25	43
Progressive disease	20	13	14	25	18	11	14	23
NA	7	12	9	13	7	11	8	13

[a]IRRC-assessed

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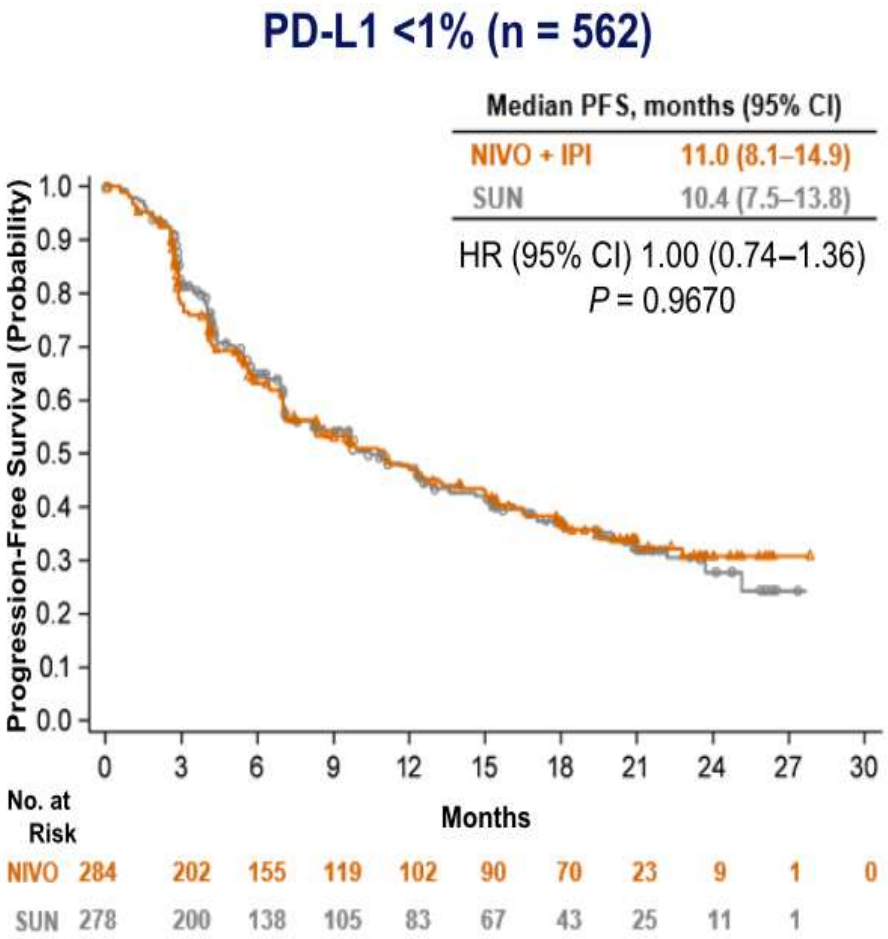
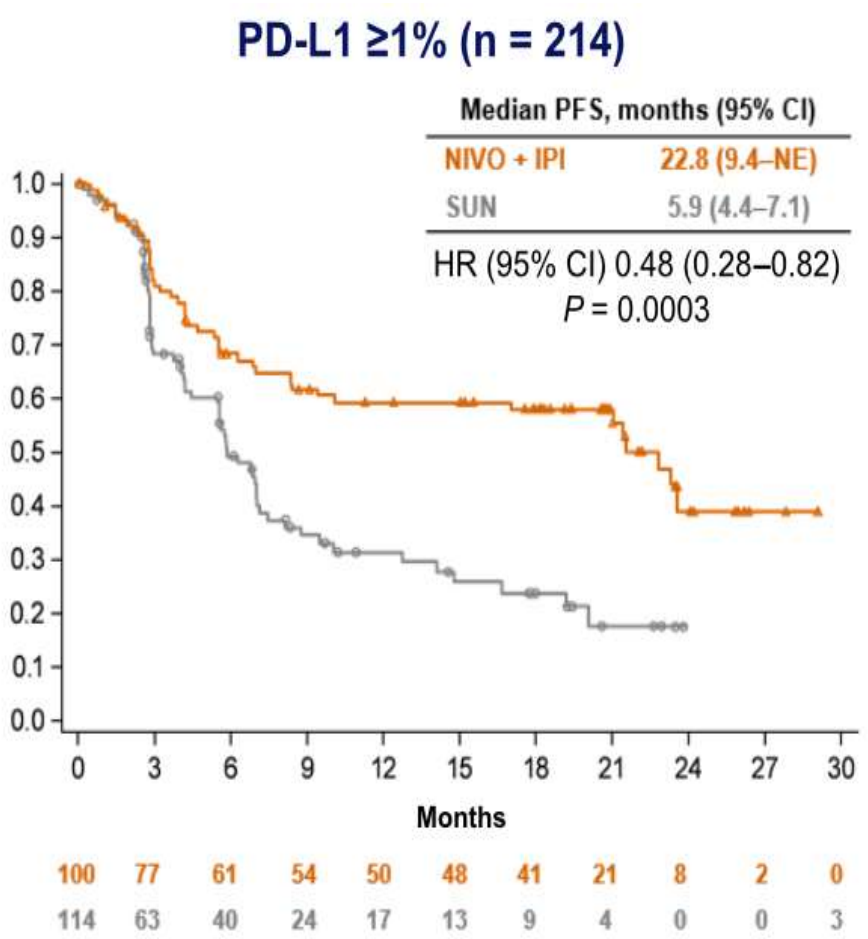
Escudier B, et al. ESMO 2017: abstract LBA5.

Checkmate 214 – Ipi + Nivo (Fase III)

SLP e status PD-L1 IMDC Risco Intermediário/Alto (Endpoint Exploratório)

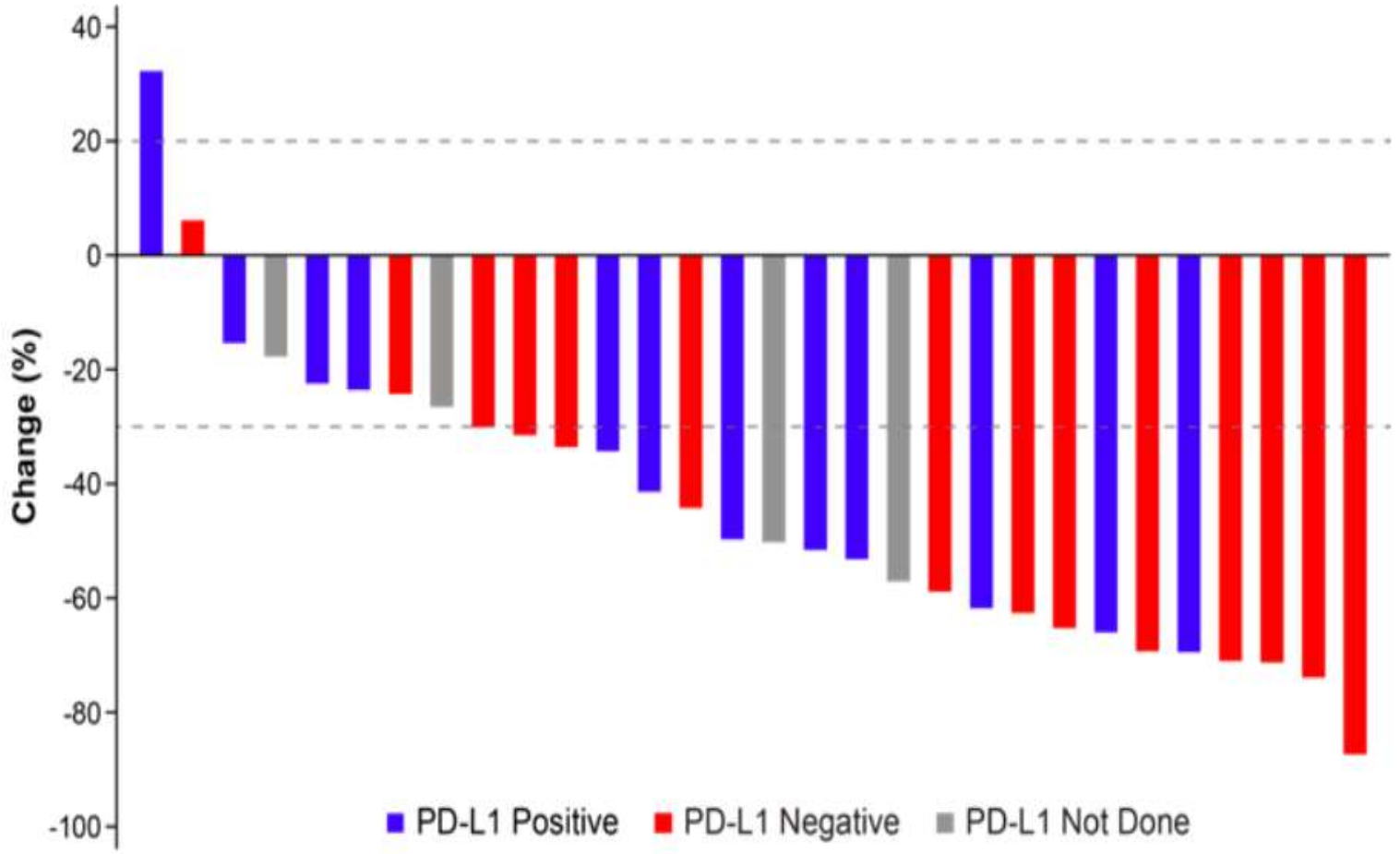




Escudier B, et al. ESMO 2017: abstract LBA5.

Lenvatinibe + Pembrolizumabe (Fase Ib/II)

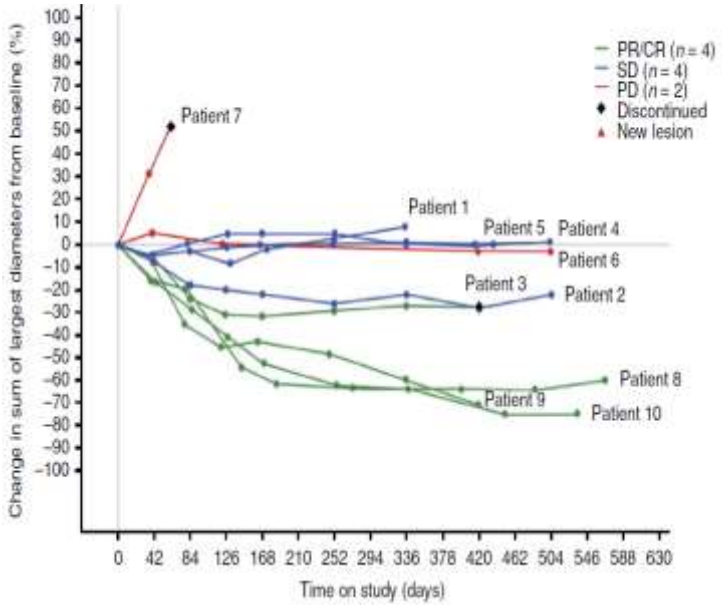
Resposta Objetiva e Status PD-L1

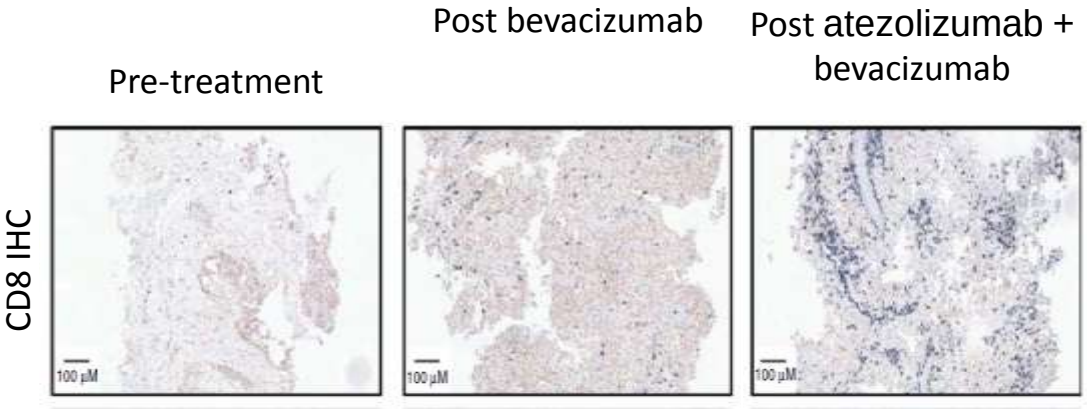


Escudier B, et al. ESMO 2017: abstract LBA5.

Atezolizumabe + Bevacizumabe (Fase Ib)

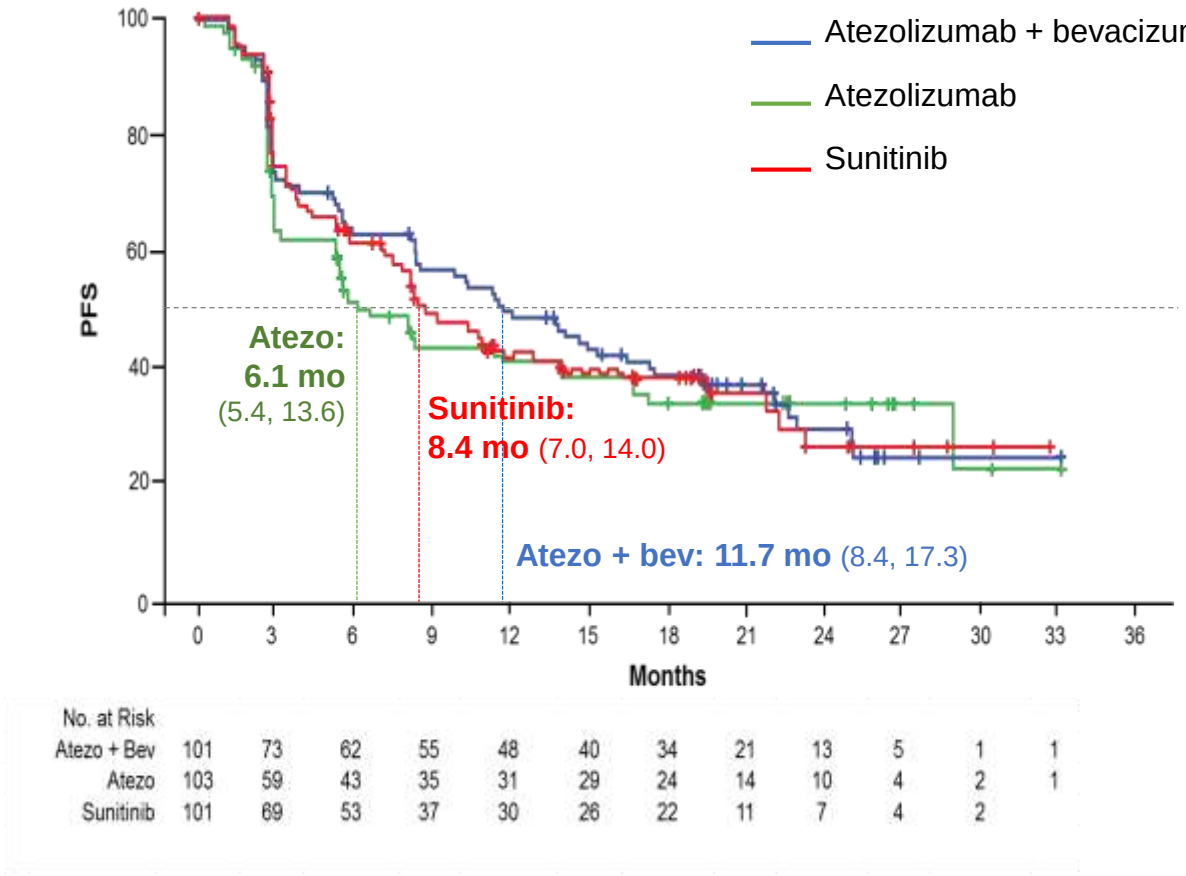
- A Phase Ib study in first-line mRCC showed anti-tumor activity and a tolerable safety profile for atezolizumab + bevacizumab[1,2]
- Sequential tumor biopsies provided preliminary evidence of enhanced anti-tumor immune responses following treatment with bevacizumab and atezolizumab + bevacizumab[2]





Presented by: Dr. Thomas Powles

IMmotion-150 – Atezo + Beva (Fase II)
Sobrevida Livre de Progressão (ITT)

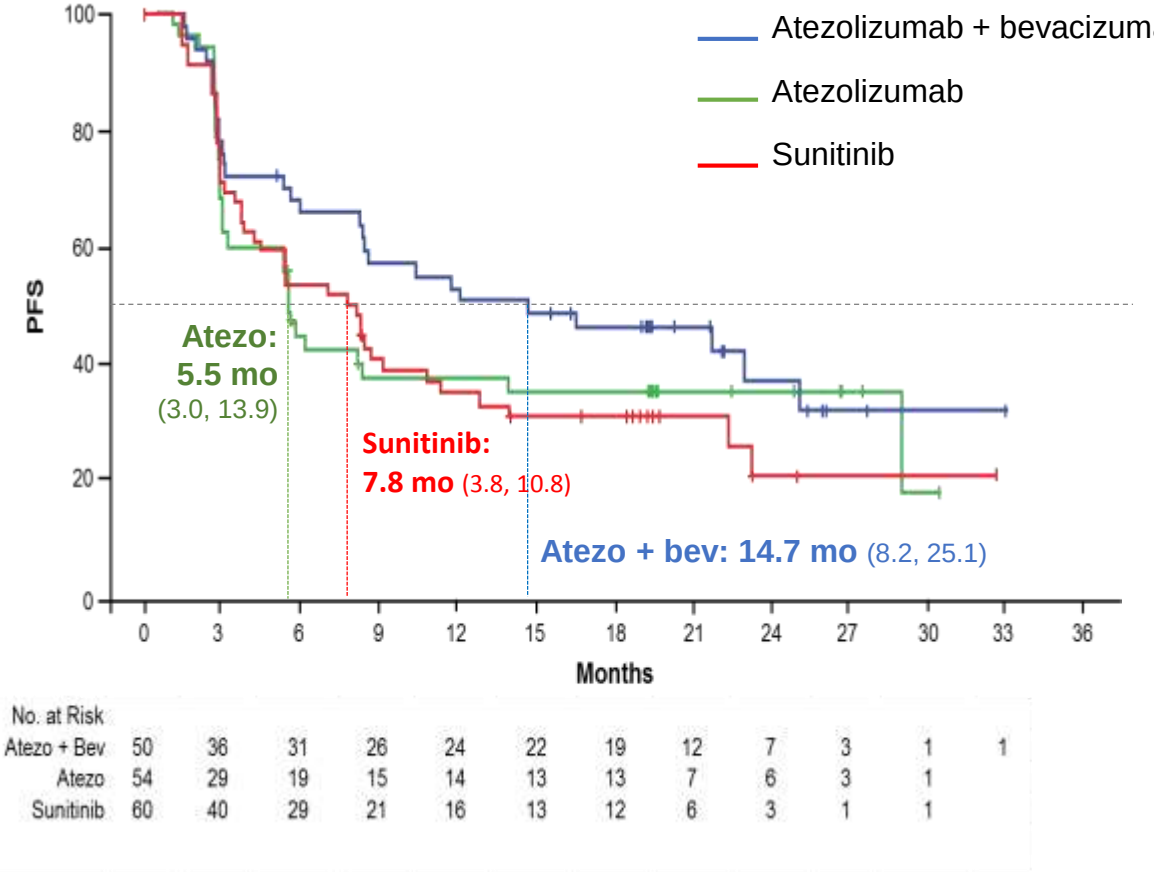


	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**1.00 (0.69, 1.45)**	0.982
Atezo vs sunitinib	**1.19 (0.82, 1.71)**	0.358

[a] *P* values are for descriptive purposes only and not adjusted for multiple comparisons.

Presented by: Dr. Thomas Powles

IMmotion-150 – Atezo + Beva (Fase II)
SLP e PD-L1 IC ≥1%



	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**0.64 (0.38, 1.08)**	0.095
Atezo vs sunitinib	**1.03 (0.63, 1.67)**	0.917

[a] *P* values are for descriptive purposes only and not adjusted for multiple comparisons.

Presented by: Dr. Thomas Powles

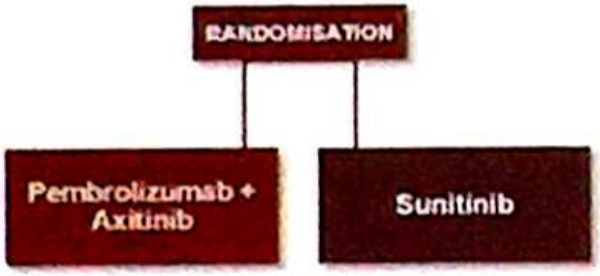
Combinação Anti-PD1/PD-L1 + Anti-VEGFR

	Nivolumab Sunitinib	Nivolumab Pazopanib	Avelumab Axitinib	Pembrolizumab Axitinib	Nivolumab Cabozantinib	Pembrolizumab Lenvatinib
n	33	20	6	52	23	13
ORR%	52	45	100	71.2	43	69.2
CR%	ne	ne	ne	5.8	4	0
PR%	ne	ne	ne	65.4	39	69.2

Combinação Anti-PD1/PD-L1 + Anti-VEGFR Estudos Fase III em andamento

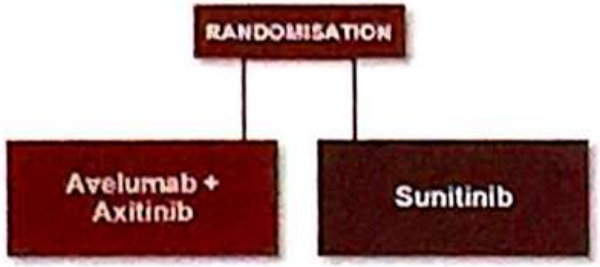
NCT02853331:
Combination PD-1 + VEGFR TKI[3]

Phase III N=840
Co-Primary endpoint: PFS, OS



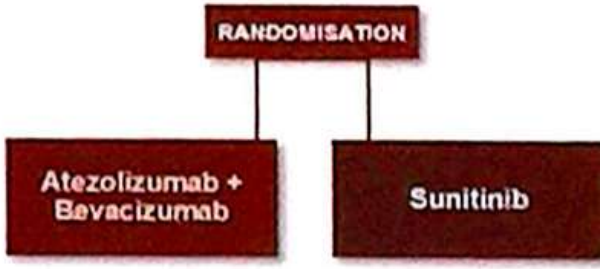
Javelin Renal 101 - NCT02684006:
Combination PD-L1 + VEGFR TKI[2]

Phase III N=583
Primary endpoint: PFS

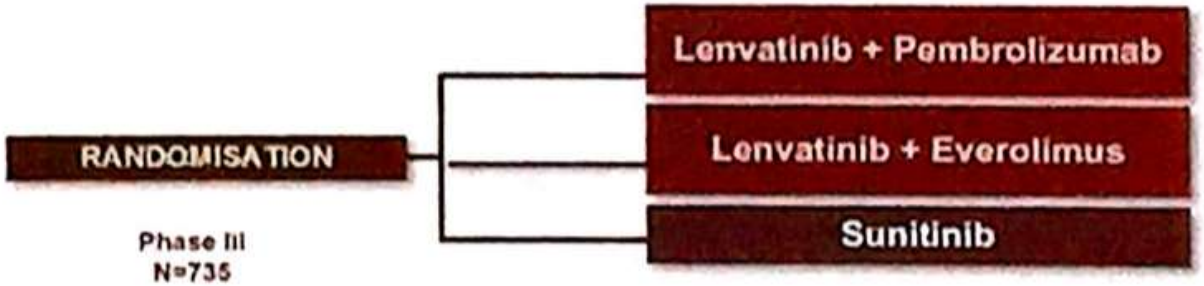


IMmotion151 - NCT02420821:
Combination PD-L1 + VEGF inhibition[4]

Phase III N=830
Co-Primary endpoint: PFS, OS



Lenvatinib + Everolimus or Pembrolizumab - NCT02811861:
Combination VEGFR + mTOR/PD-L1 inhibition[3]
Primary endpoint: PFS



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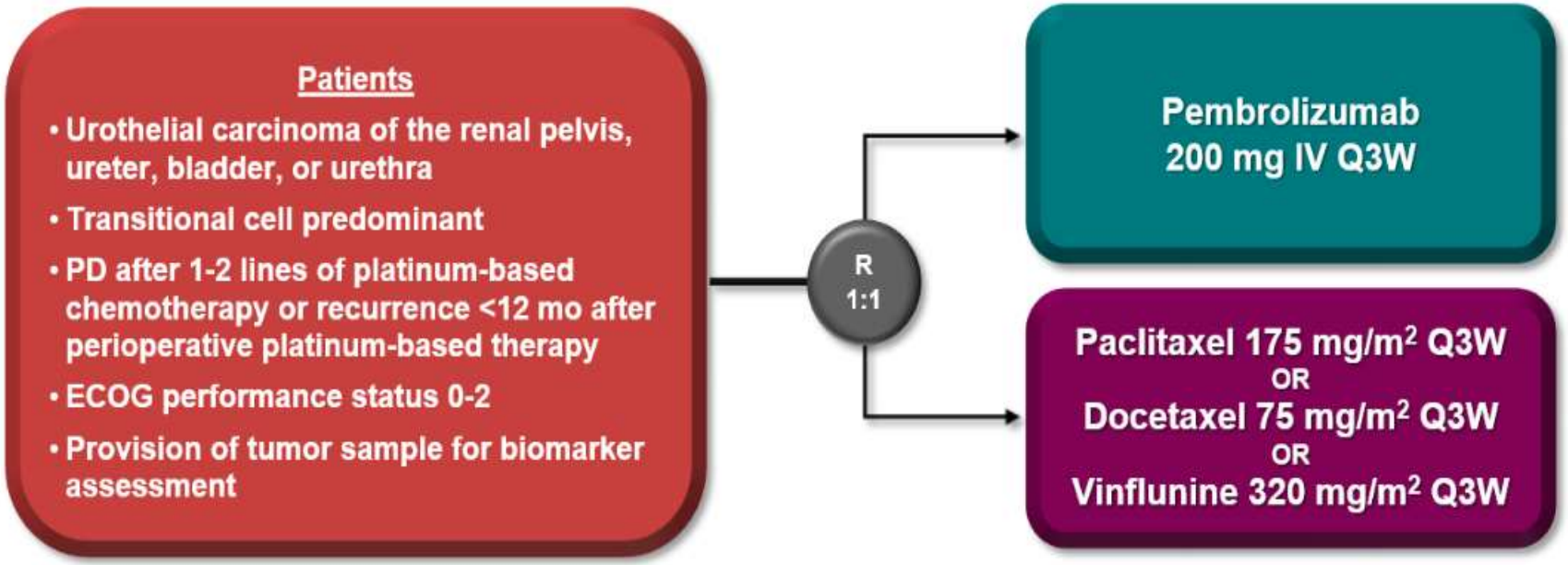
Carcinoma Urotelial

KeyNote-045 – Pembro vs. QT (Fase III)



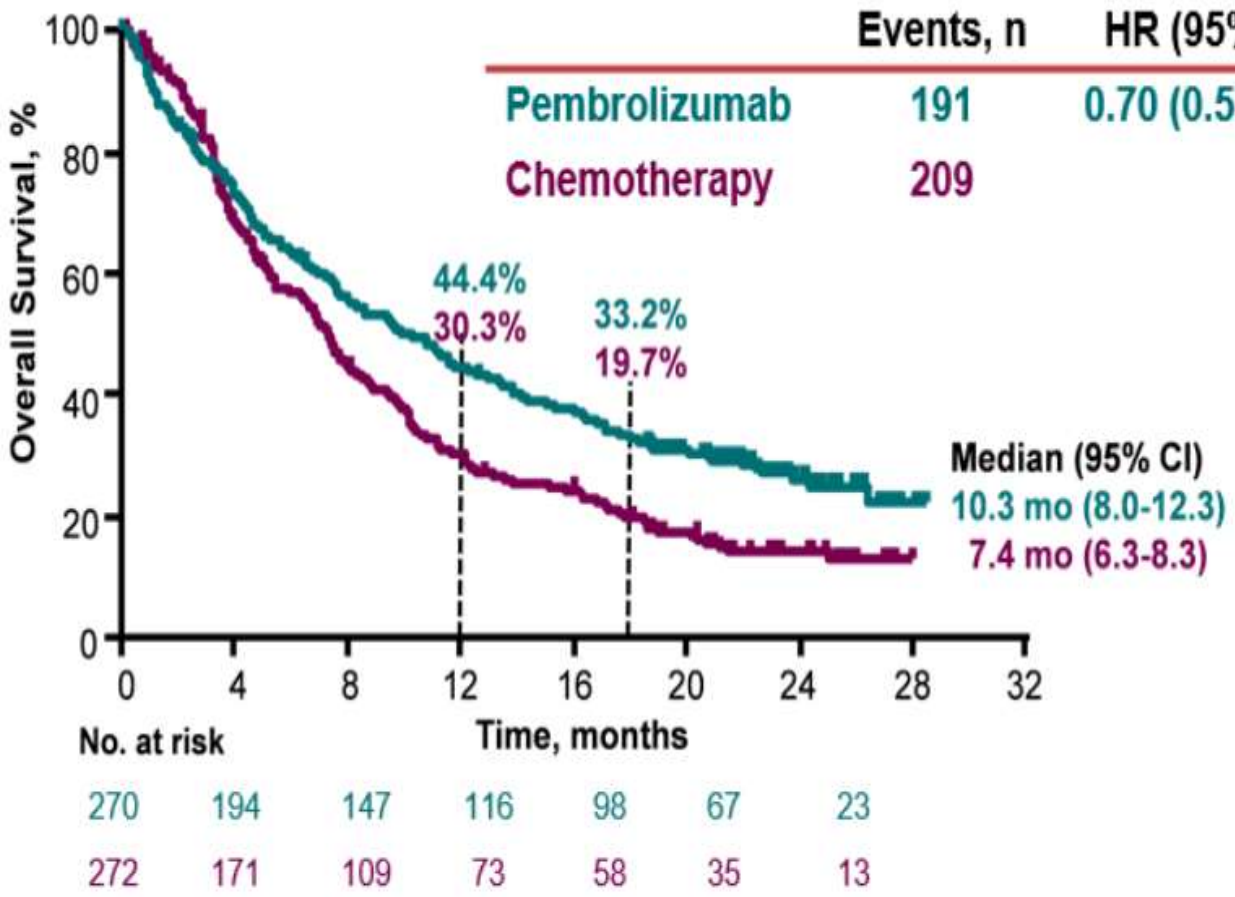
- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review
- Both unselected and biomarker-selected patients

[a]In total ITT population and in patients with combined positive score ≥10.

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

ESMO 2017: abstract LBA37.

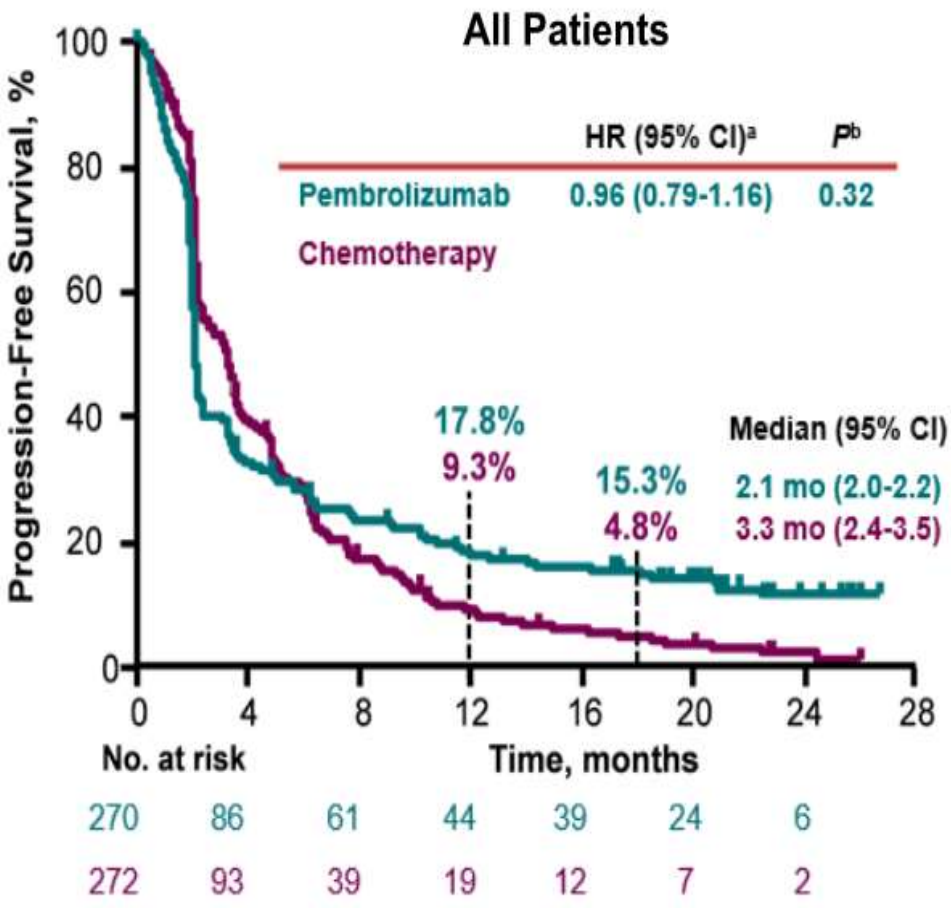
KeyNote-045 – Pembro vs. QT (Fase III)
SG atualizada (ESMO 2017)

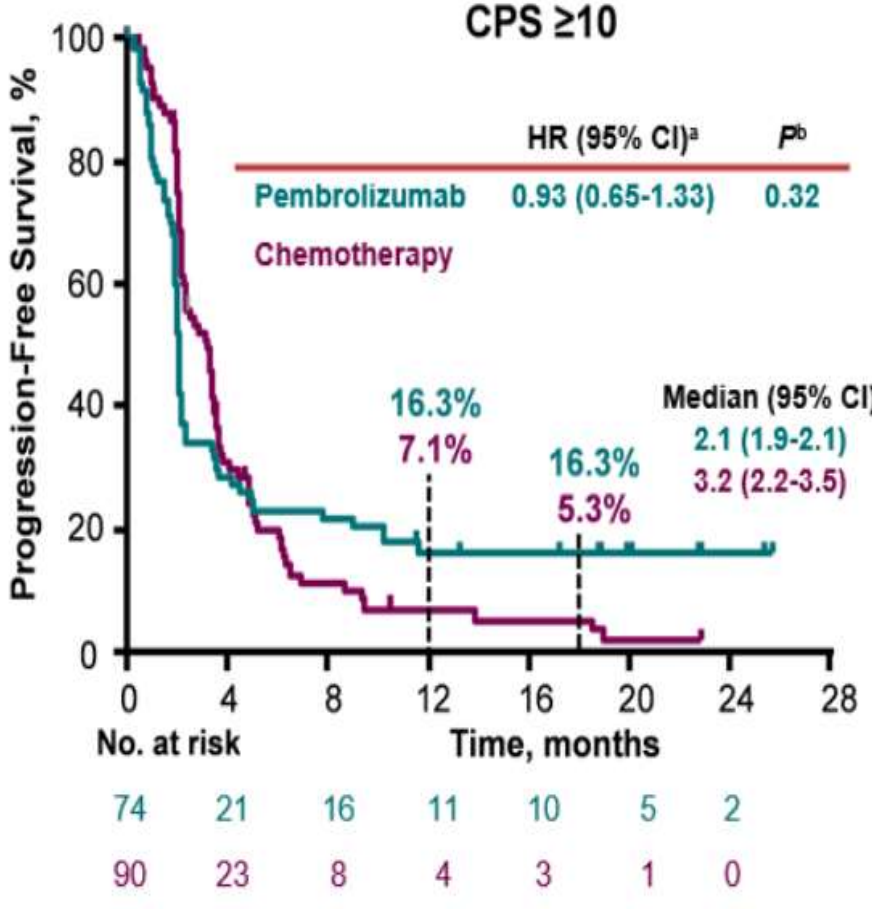


Data cutoff: May 19, 2017.
[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo).
[b]One-sided *P* value based on stratified log-rank test.

ESMO 2017: abstract LBA37.

KeyNote-045 – Pembro vs. QT (Fase III)
SLP atualizada (ESMO 2017)





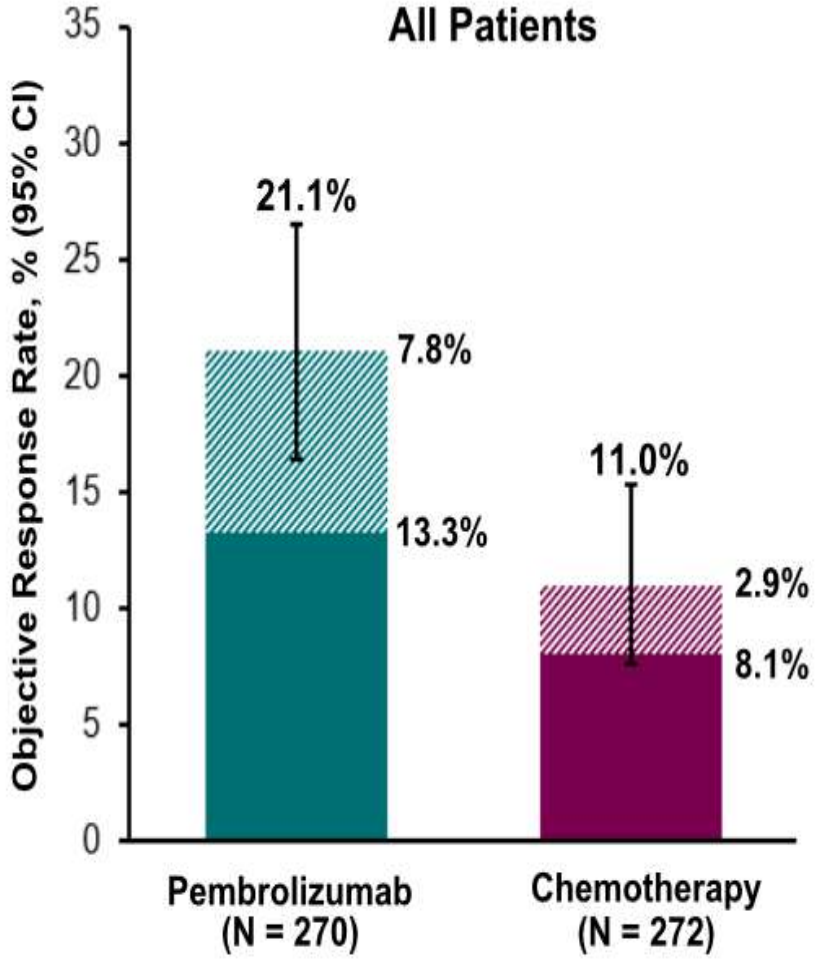
CPS, PD-L1 combined positive sore

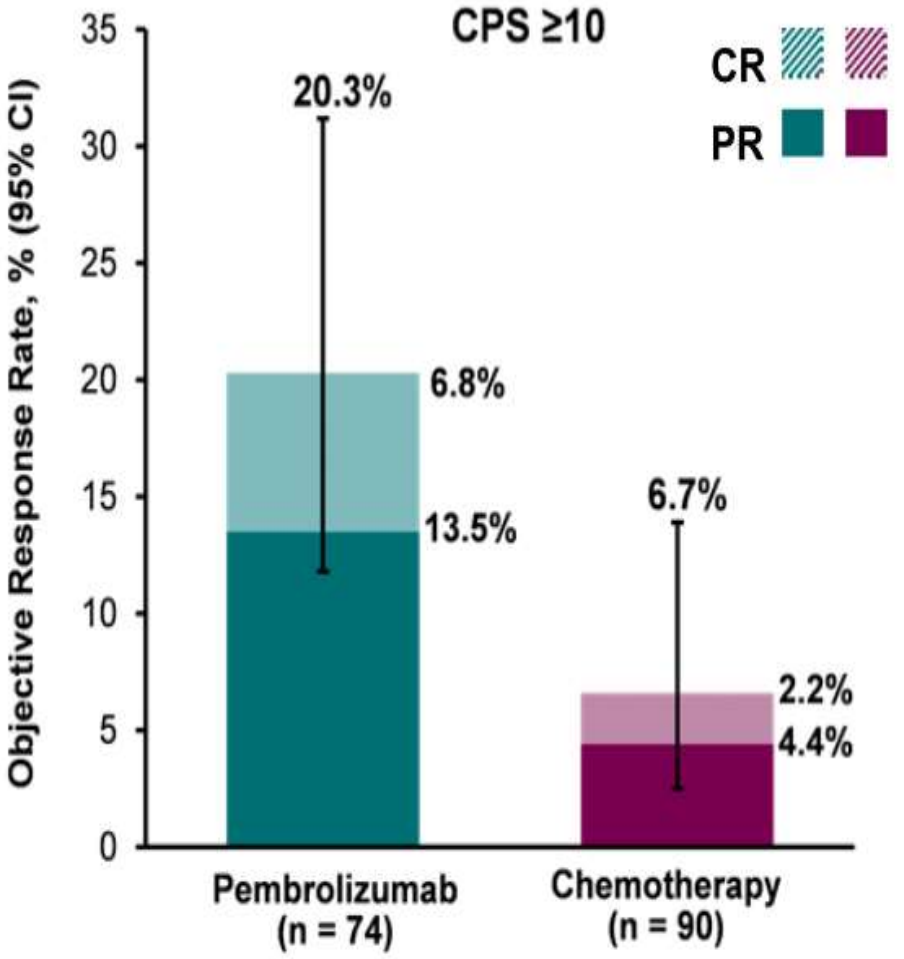
Data cutoff: May 19, 2017.
[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo).
[b]One-sided *P* value based on stratified log-rank test.

ESMO 2017: abstract LBA37.

KeyNote-045 – Pembro vs. QT (Fase III)

RO atualizada (ESMO 2017)





Data cutoff: May 19, 2017.

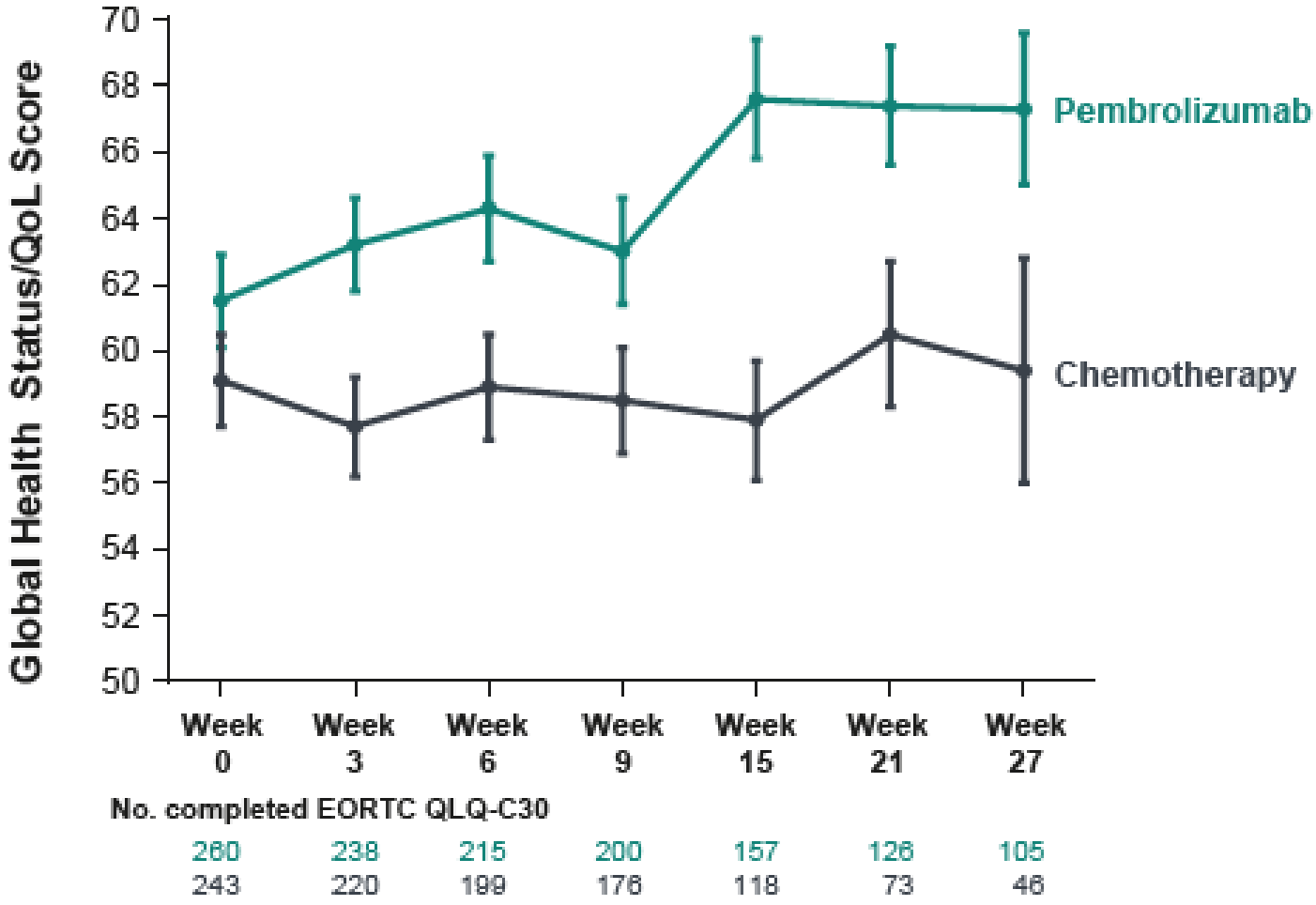
CPS, PD-L1 combined positive sore

ESMO 2017: abstract LBA37.

KeyNote-045 – Pembro vs. QT (Fase III)

Qualidade de Vida

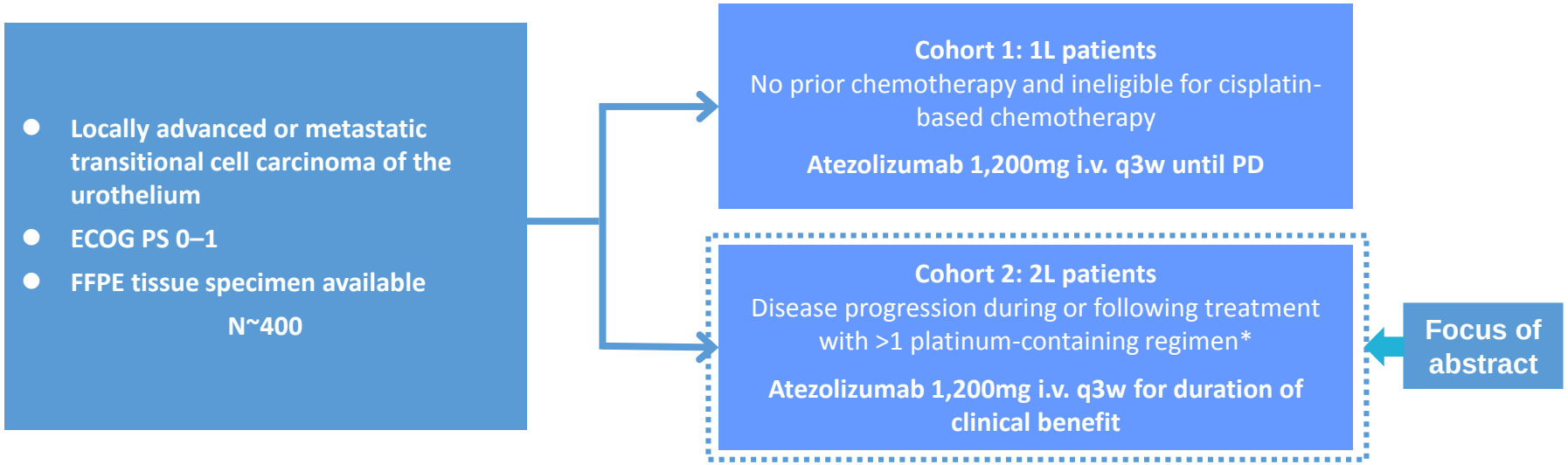
Figure 1. EORTC QLQ-C30 global health status/QoL score by visit.



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

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

IMvigor 210 – Atezolizumabe (Fase II)



1 Co-primary endpoints
- ORR (IRF-assessed by RECIST v1.1 and investigator-assessed by modified RECIST§)

2 Key secondary endpoints
- PFS
- DoR
- OS
- Safety

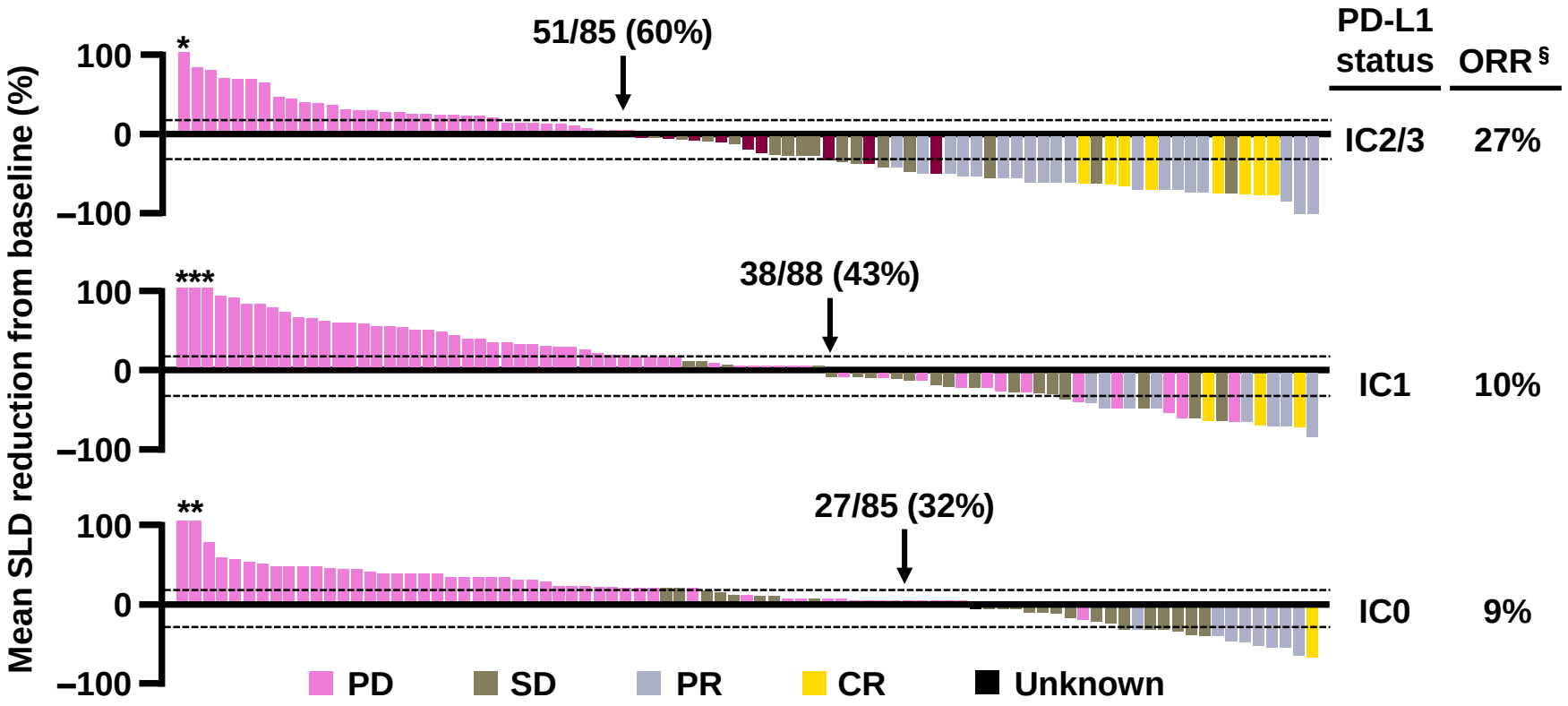
*Patients in Cohort 2 can receive atezolizumab for the duration of clinical benefit as assessed by the investigator (i.e. in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression); patients in Cohort 1 can receive atezolizumab until PD

§ Response assessed by RECIST v1.1 and modified RECIST; modified RECIST criteria account for possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment

DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status
FFPE = formalin-fixed paraffin embedded; IRF = independent review facility; ORR = overall response rate
OS = overall survival; PD = progressive disease; PFS = progression free survival; q3w = every 3 weeks
RECIST = Response Evaluation Criteria in Solid Tumors

Rosenberg, et al. ECC 2015

IMvigor 210 – Atezolizumabe (Fase II)
Coorte 2ª Linha (Pós Platina)

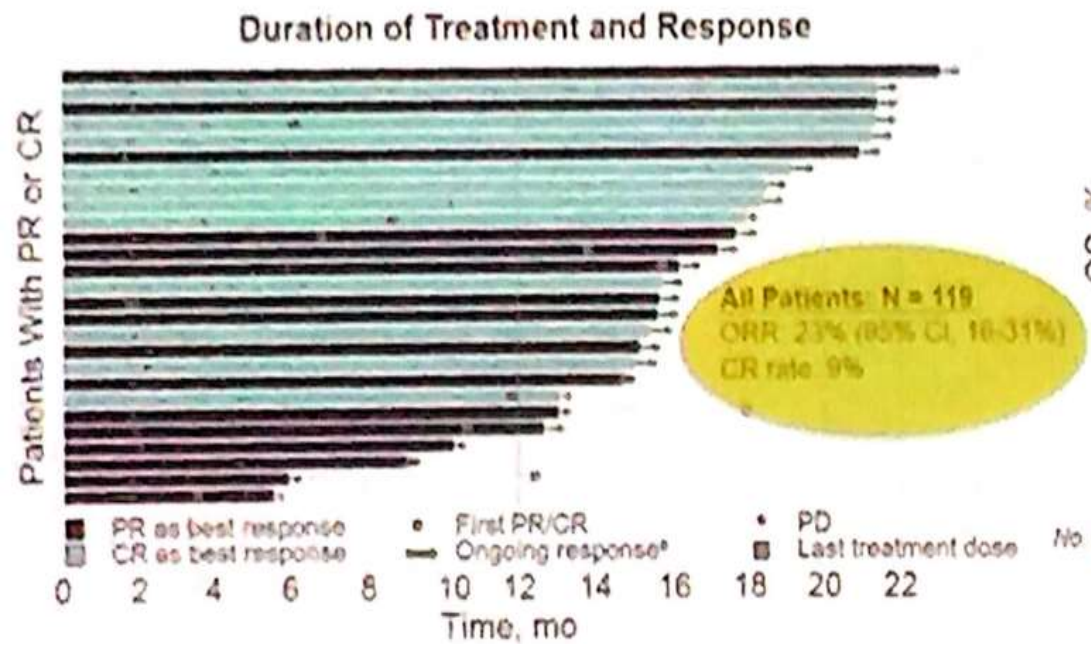


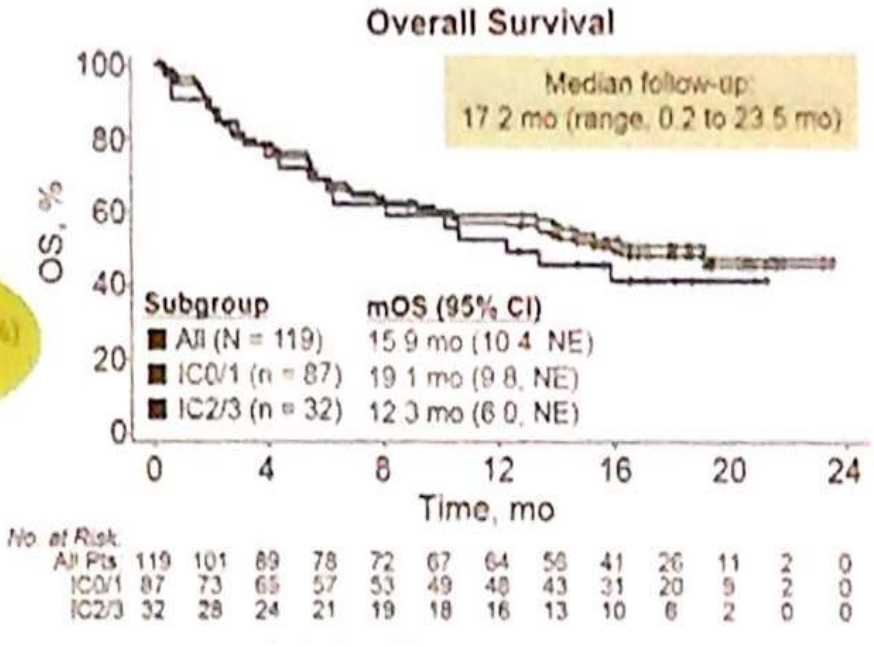
111/258 (43%) patients with tumour assessments had SLD reduction

*>100% increase. § Per confirmed RECIST v1.1 (independent review). Data cut-off May 5, 2015. Follow up ≥24 weeks. Patients without post-baseline tumour assessments not included. Several patients with CR had <100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1
Data cut-off May 5, 2015; follow-up ≥24 weeks
PR = partial response; SD = stable disease
SLD = sum of longest diameters

Rosenberg, et al. ECC 2015

IMvigor 210 – Atezolizumabe (Fase II)
Coorte 1ª Linha (Inelegível a Cisplatina)





Rosenberg, et al. ECC 2015

Atezo Vs. QT 1ª Linha (Inelegível a Cisplatina) – comparação indireta

Frontline Therapy for UC: Cis-Ineligible

Gem Carbo

Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy: EORTC Study 30986

Maria De Santis, Joaquim Bellmunt, Graham Mead, J. Martijn Kerst, Michael Leahy, Pablo Maroto, Thierry Gil, Sandrine Marreaud, Gedske Daugaard, Iwona Skoneczna, Sandra Collette, Julie Lorent, Ronald de Wit, and Richard Sylvester

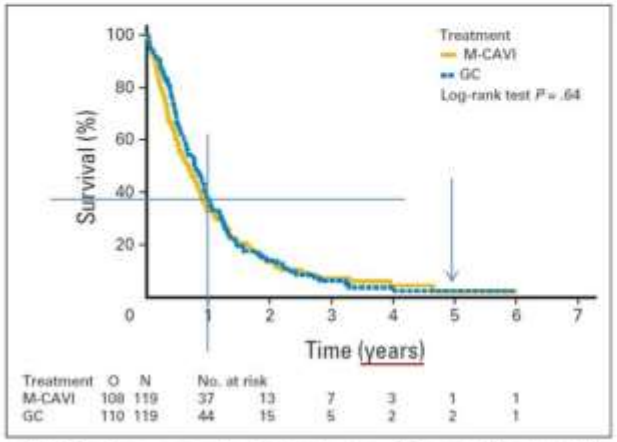
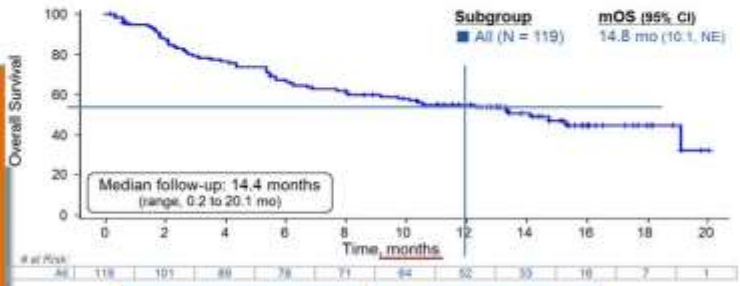


Fig 2. Duration of survival by treatment group. GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine; O, observed number of deaths.

ORR: 36%	ORR: 24%
mOS: 9.3 mo.	mOS: 14.8 mo.
1-year OS: 37%	1-year OS: 57%
5-year OS: ~ 0	5-year OS: ?

Atezolizumab

Cisplatin ineligibility criteria[1]	N = 119
Renal impairment GFR < 60 mL/min but > 30	70%
Hearing loss, 25 dB[e]	14%
Peripheral neuropathy, ≥ Grade 2	6%
ECOG PS2	20%
Renal impairment **and** ECOG PS2	7%



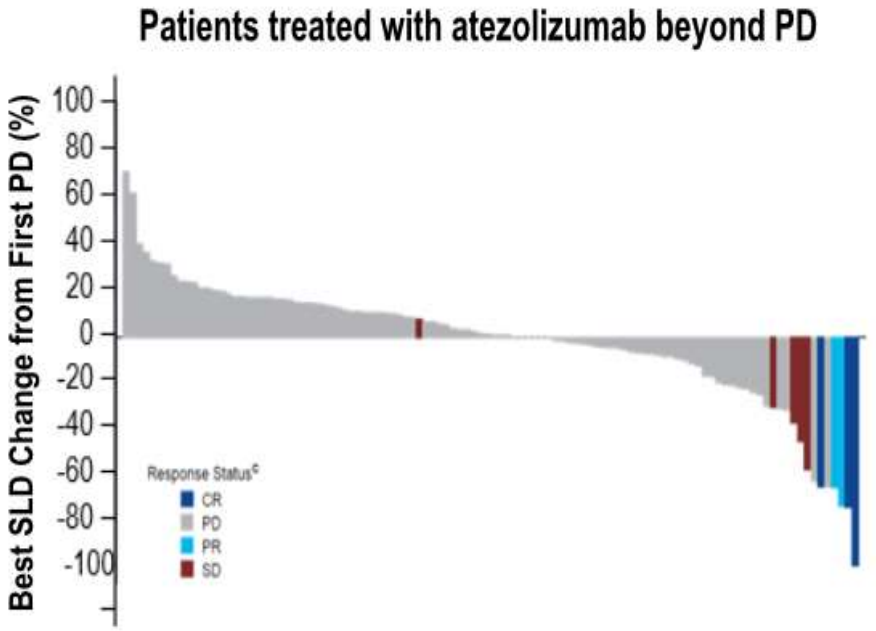
	All Patients (N = 119)
ORR[a] (95% CI)	24% (16, 32)
CR	7%
PR	17%

Balar A, et al. IMvigor210: 1L atezolizumab in cisplatin-ineligible mUC. ASCO 2016

Presented By Elizabeth Plimack at 2016 ASCO Annual Meeting

IMvigor 210 – Atezolizumabe (Fase II)
Tratamento pós PD

- Post-PD scans for 108/137 pts treated with atezolizumab beyond PD
  - 45 pts who continued atezolizumab (33%) experienced post-PD reductions in tumour burden
  - 5 new IRF confirmed RECIST v1.1 responses (3 CR; 2 PR) with respect to baseline were seen (3.6%)
  - None of these patients had previously had a response

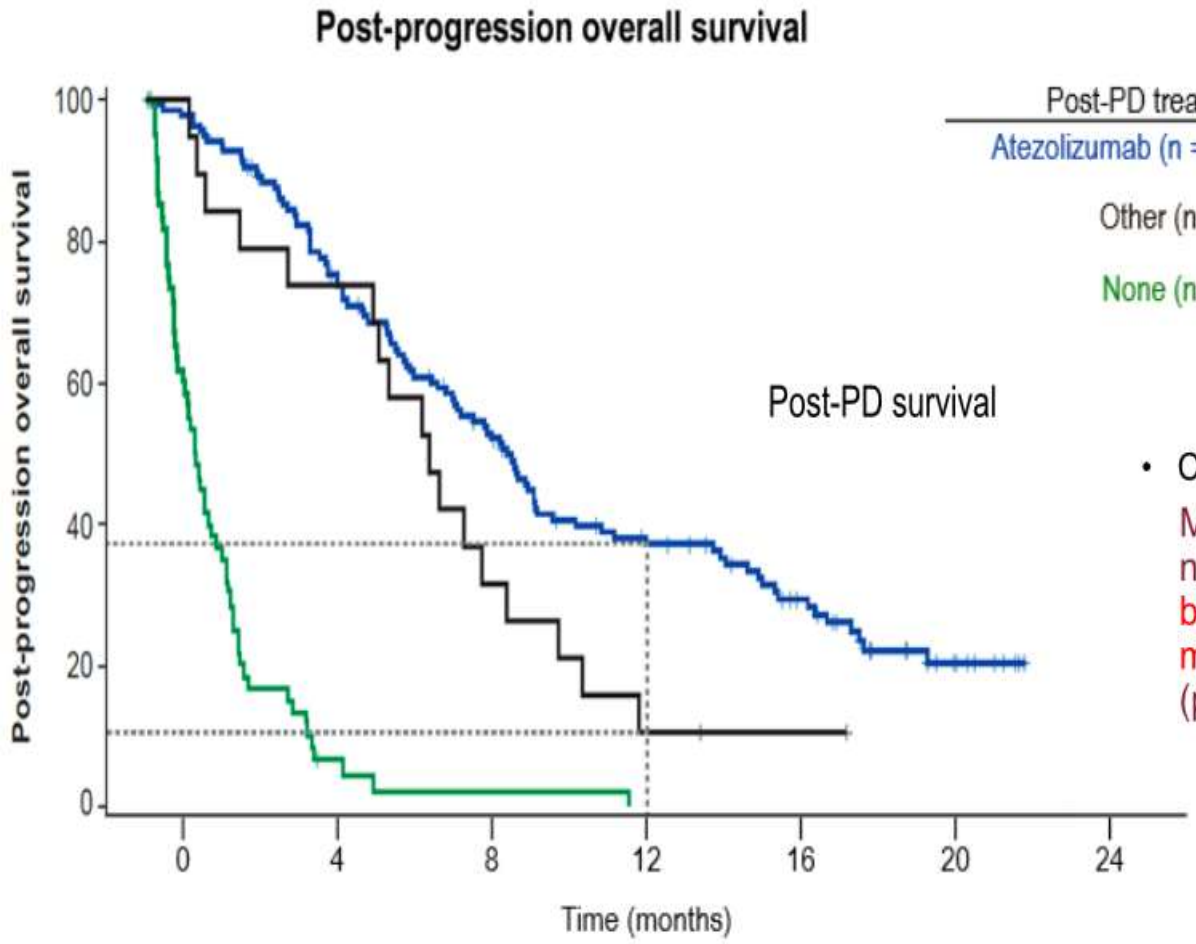


IC, tumor-infiltrating immune cells; NPT, subsequent non-protocol therapy; SLD, sum of target lesion diameters.
[a] ≥ 5% PD-L1 expression on IC. [b] Patients had ≥ 1 post-PD dose. Reference 1. Rosenberg *Lancet* 2016.

MADRID 2017 ESMO congress

ESMO 2017: abstract 852PD.

IMvigor 210 – Atezolizumabe (Fase II)
Tratamento pós PD



Post-PD treatment	Median (95% CI)	12-mo rate (95% CI)
Atezolizumab (n = 137)	8.6 mo (7.3, 9.3)	37.1% (28.6, 45.6)
Other (n = 19)	6.8 mo (5.4, 8.6)	10.5% (0.0, 24.3)
None (n = 64)	1.2 mo (0.8, 1.7)	0.0% (0.0, 0.0)

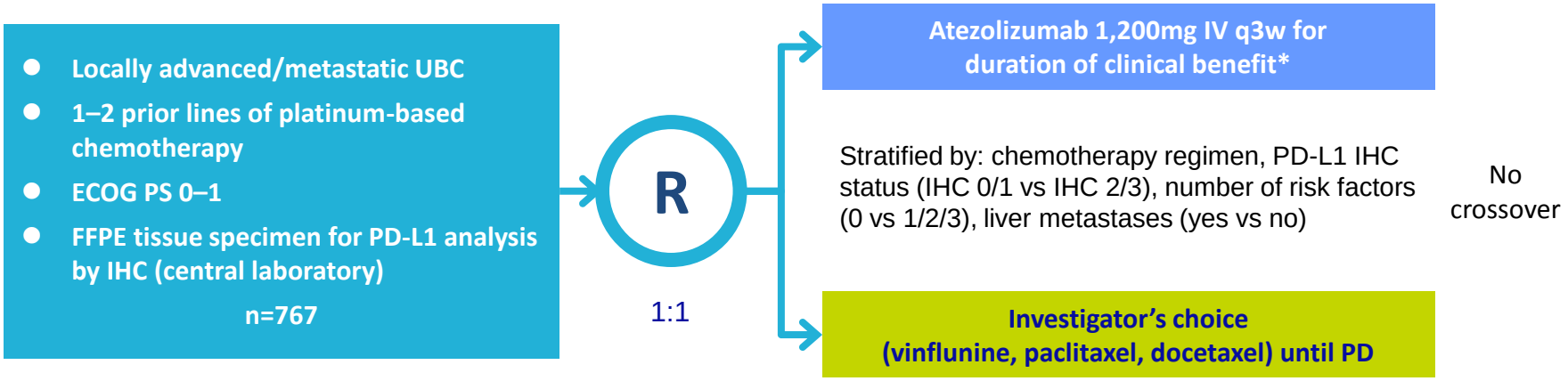
- Compared with the overall subgroup-

  Median post-PD OS with atezolizumab was numerically longer for subgroups with baseline ECOG PS 0, no visceral metastases or only lymph node disease (post-PD medians > 14 mos)

MADRID 2017 ESMO congress

ESMO 2017: abstract 852PD.

IMvigor 211 – Atezo Vs. QT (Fase III)



- Primary objective: OS
- Secondary objectives: ORR, PFS and DOR (RECIST v1.1); safety, tolerability and ATAs
- Other objectives: PK; patient-reported outcomes and health-related quality of life; PFS, ORR and DOR (modified RECIST §); DCR; potential biomarkers; predictive biomarkers

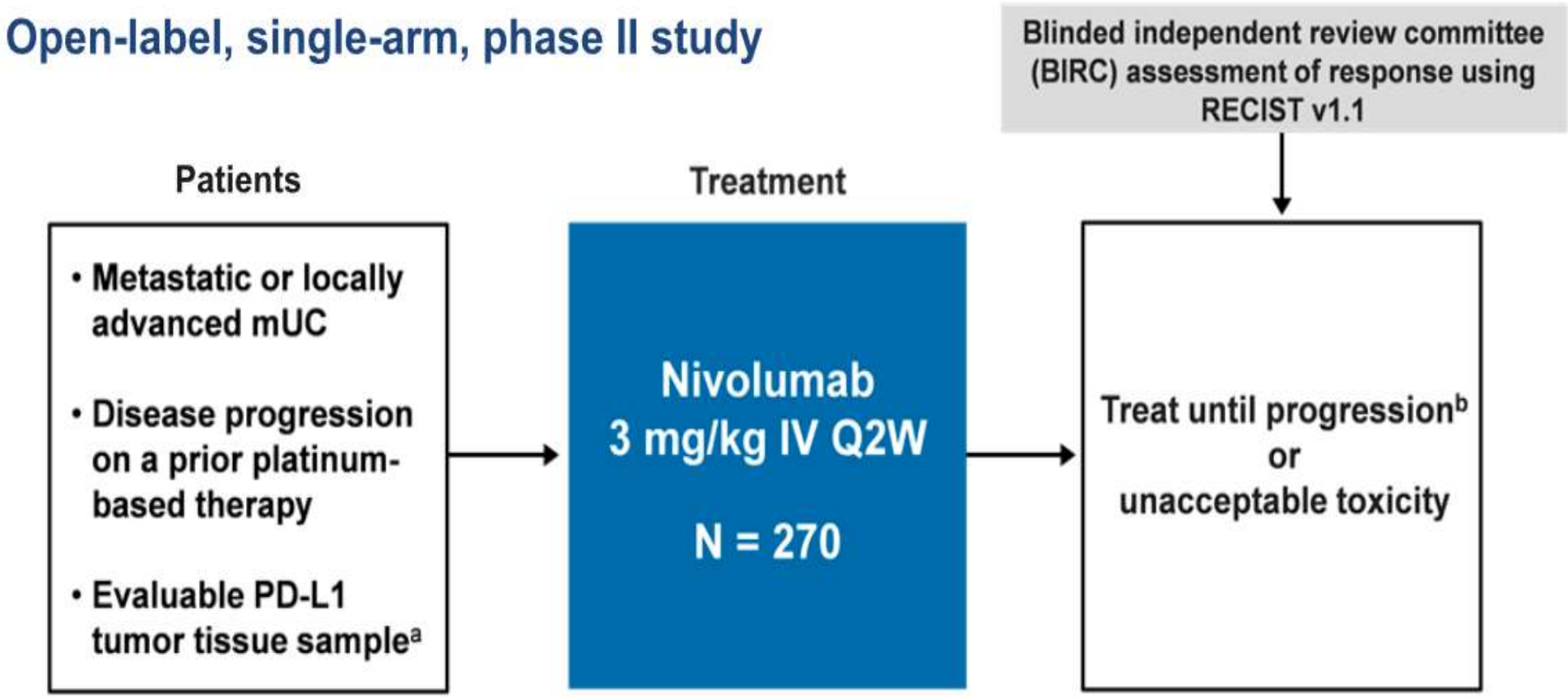
Patients with CR/PR/SD followed every 12 weeks; patients receiving atezolizumab followed up until disease progression per modified RECIST or treatment discontinuation; patients receiving chemotherapy followed up until disease progression per RECIST v1.1

*As assessed by the investigator (i.e. in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression); § Modified RECIST criteria account for possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment

ATAs = anti-therapeutic antibodies; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; FFPE = formalin-fixed paraffin embedded; IHC = immunohistochemistry; ORR = overall response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death ligand 1; PFS = progression free survival; PK = pharmacokinetics; q3w = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors

ESMO 2017: abstract 852PD.

CheckMate 275 – Nivolumabe (Fase II)



[a]Patients were required to have an evaluable tumor tissue sample for PD-L1 expression testing at screening, but were not excluded based on PD-L1 status

[b]Patients could have been treated beyond progression under protocol-defined circumstances

IV, intravenous; mUC, metastatic urothelial carcinoma; Q2W, every 2 weeks

ESMO 2017: abstract 848PD.

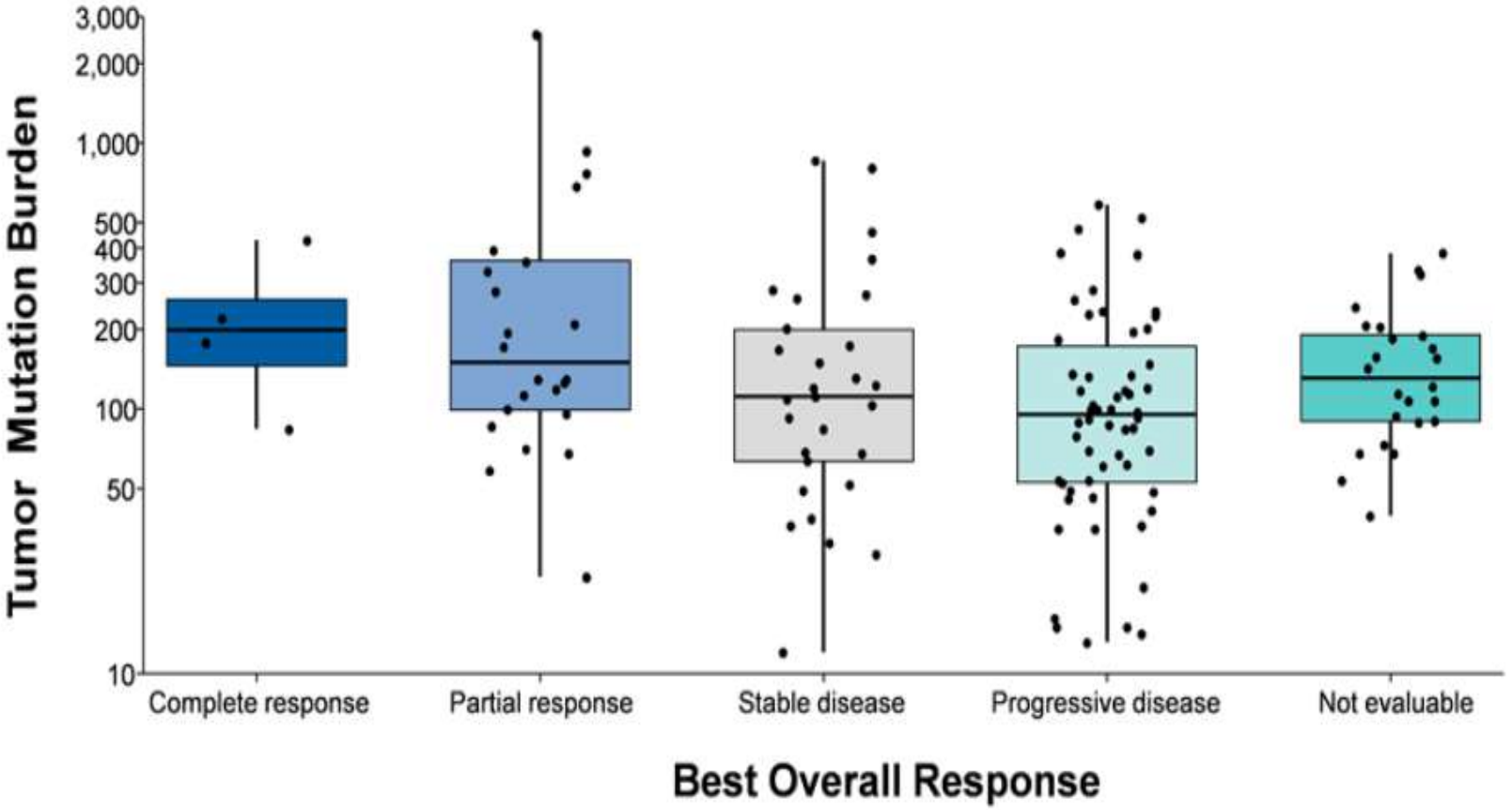
CheckMate 275 – Nivolumabe (Fase II)

Outcome, %	All N=265	PD-L1 <1% N=143	PD-L1 ≥1% N=122	PD-L1 <5% N=184	PD-L1 ≥5% N=81
Confirmed ORR by BIRC	19.6	16.1	23.8	15.8	28.4
95% CI	15.0-24.9	10.5-23.1	16.5-32.3	10.8-21.8	18.9-39.5
Median PFS (95% CI)	2.00 (1.87-2.63)	1.87 (1.77-2.04)	3.55 (1.94-3.71)		
Median OS (95% CI)	8.74 (6.05-NR)	5.95 (4.30-8.08)	11.30 (8.74-NR)		

Galsky MD, et al. ESMO 2016: Abstract LBA 31.

CheckMate 275 – Nivolumabe (Fase II)

Carga mutacional



- TMB was positively associated with ORR (P = 0.0006), PFS (P = 0.0001), and OS (P = 0.003), even when adjusted for baseline tumor PD-L1 expression, liver metastasis status, and serum hemoglobin

ESMO 2017: abstract 848PD.

JAVELIN – Avelumabe (Fase Ib)
Eficácia

Table 2. Clinical activity in patients with ≥6 months of follow-up

Clinical activity endpoint by independent review	n=153
Confirmed best overall response*	n (%)
Complete response	9 (5.9)
Partial response	18 (11.8)
Stable disease	36 (23.5)
Non–complete response/non–progressive disease†	1 (0.7)
Progressive disease	61 (39.9)
Non-evaluable‡	28 (18.3)
Confirmed ORR, % (95% CI)	17.6 (12.0, 24.6)
Disease control rate§, %	41.2

* Defined as best response obtained among all tumor assessments after the start of treatment with avelumab until documented disease progression; 27 patients had confirmed tumor shrinkage of ≥30% by independent review and met RECIST v1.1 criteria for a response

† Persistence of ≥1 non-target tumor and/or maintenance of tumor marker levels above normal

‡ Missing and/or not assessable information: 23 patients had no post-baseline tumor assessment (18 patients died within 6 weeks, 4 patients withdrew from the trial, and 1 patient was lost to follow-up); 1 patient had post-baseline assessments with an overall response of not evaluable; 3 patients started new anticancer therapy prior to the first post-baseline assessment; and 1 patient had stable disease of insufficient duration

§ Defined as rate of response or best overall response of stable disease or non-complete response/non-progressive disease

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

Durvalumabe (Study 1108) (Fase I/II)
Eficácia

Confirmed ORR and DCR by PD-L1 Expression

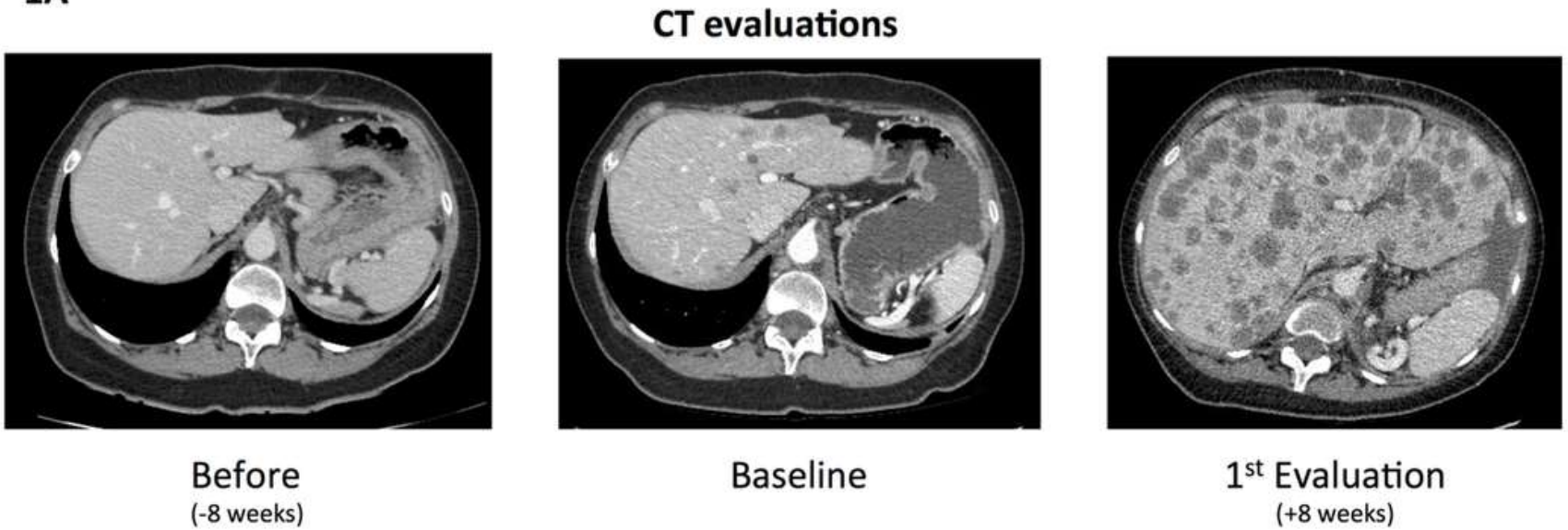
Parameter	All UC			≥2L post-platinum UC		
	Total[a]	PD-L1 high[b]	PD-L1 low/negative[b]	Total	PD-L1 high[b]	PD-L1 low/negative[b]
	N = 103	N = 61	N = 39	N = 94	N = 58	N = 33
Confirmed ORR, n (%)[c] (95% CI)	21 (20.4) (13.1, 29.5)	19 (31.1) (19.9, 44.3)	2 (5.1) (0.6, 17.3)	19 (20.2) (12.6, 29.8)	18 (31.0) (19.5, 44.5)	1 (3.0) (0.1, 15.8)
Best overall response, n (%)						
CR	4 (3.9)	2 (3.3)	2 (5.1)	3 (3.2)	2 (3.4)	1 (3.0)
PR	17 (16.5)	17 (27.9)	0	16 (17.0)	16 (27.6)	0
SD	23 (22.3)	12 (19.7)	8 (20.5)	21 (22.3)	11 (19.0)	7 (21.2)
Unconfirmed PR	3 (2.9)	2 (3.3)	1 (2.6)	3 (3.2)	2 (3.4)	1 (3.0)
PD	38 (36.9)	24 (39.3)	14 (35.9)	35 (37.2)	23 (39.7)	12 (36.4)
Non-evaluable	21 (20.4)	6 (9.8)	15 (38.5)	19 (20.2)	6 (10.3)	13 (39.4)
Responses ongoing at data cutoff	13 (61.9)	12 (63.2)	1 (50.0)	11 (57.9)	11 (61.1)	0
Disease Control Rate, n (%)[d] (95% CI)	44 (42.7) (33.0, 52.8)	31 (50.8) (37.7, 63.9)	10 (25.6) (13.0, 42.1)	40 (42.6) (32.4, 53.2)	29 (50.0) (36.6, 63.4)	8 (24.2) (11.1, 42.3)

[a]Includes 3 patients with unknown PD-L1 status due to biopsy samples with insufficient tumour who are not included in the PD-L1 high or low groups.
[b]PD-L1 high defined as ≥25% of tumour/immune cell staining; PD-L1 low/negative defined as <25% of tumour/immune cell staining.
[c]Objective response rate (ORR) defined as confirmed complete (CR) or partial response (PR) per RECIST v1.1 in response-evaluable patients.[2]
[d]Disease Control Rate (DCR) defined as confirmed CR or PR or stable disease (SD) for ≥6 weeks.

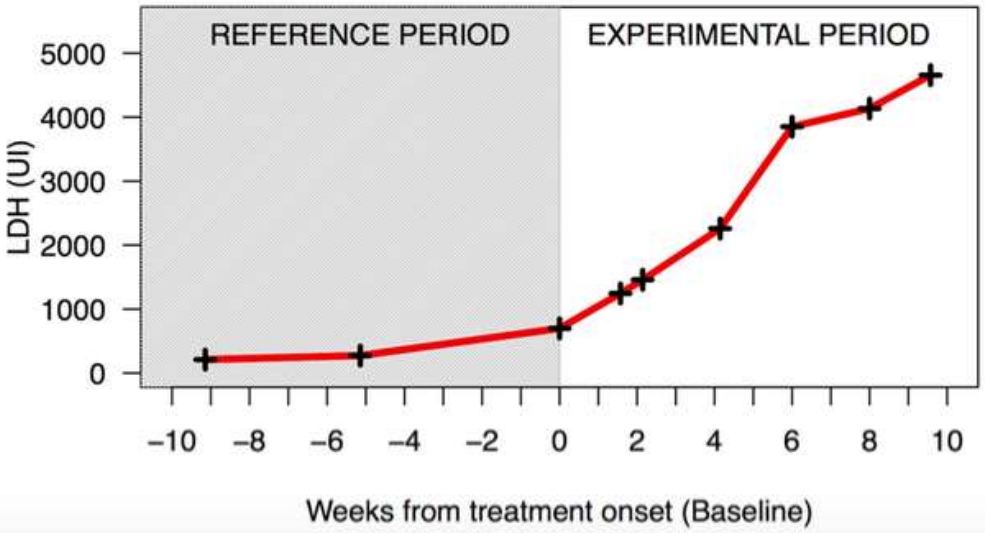
Powles et al. Presented at the 2017 Genitourinary Cancers Symposium (ASCO-GU) February 16-18, 2017 Orlando, Florida

Hiperprogressão

1A



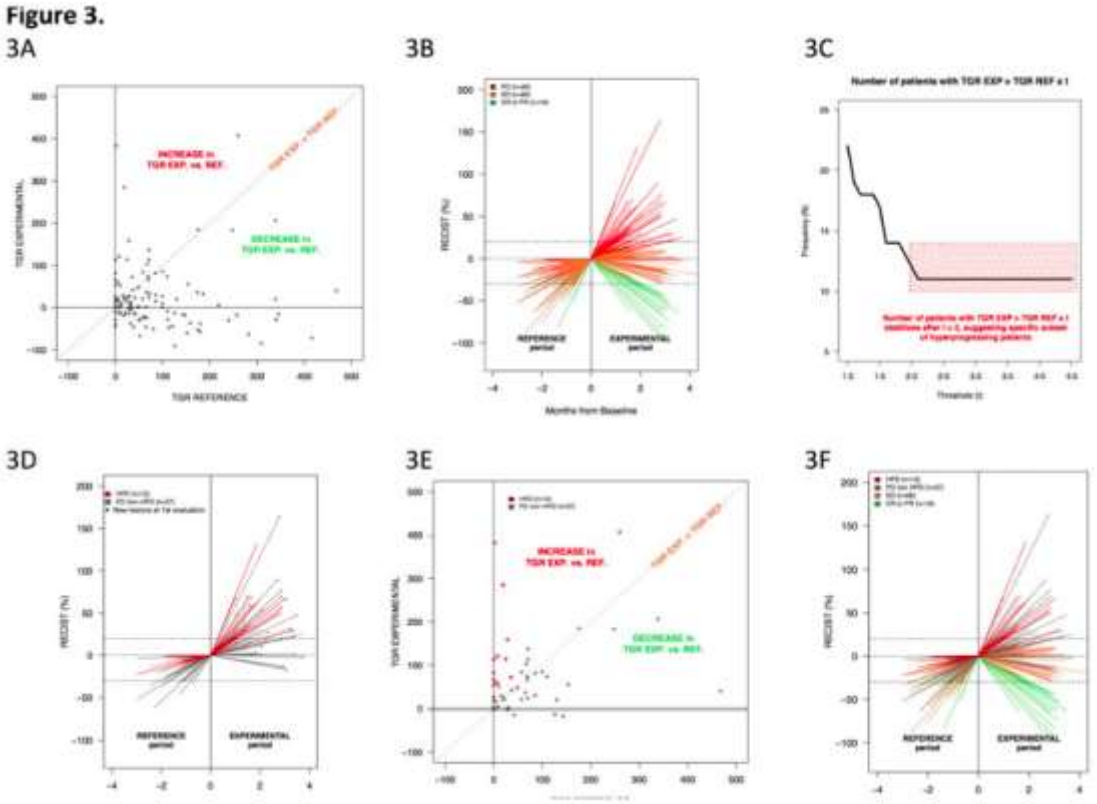
1B



Champiat S, et al. 2017.

Hiperprogressão

- N=131 pacientes tratados com inibidores de PD-1 / PD-L1 em estudos fase I/II (Gustave Roussy)
  - Comparada taxa de crescimento tumoral pré e pós inibidores de PD-1 / PD-L1
  - 12 pacientes (9%) considerados como tendo HPD



Champiat S, et al. 2017.

Conclusões

- Inibidores de checkpoint imunológicos vem avançando rapidamento no tratamento dos carcinomas de rim e urotelial
- Carcioma de rim tipo células claras:
  - Nivolumabe padrão no tratamento da 2ª linha (pós falha inibidores VEGFR)
  - Nivolumabe + Ipilimumabe (CheckMate 214) deve ser aprovado para o tratamento na primeira linha de pacientes de risco intermediário/alto
  - Diversas outras combinações em andamento (Fase 3):
    - Atezolizumabe + Bevacizumabe (IMmotion 151)
    - Pembrolizumabe + Axitinibe (KeyNote 426)
    - Pembrolizumabe + Lenvatinibe
    - Avelumabe + Axitinibe (Javelin Renal 101)

Conclusões

- Carcioma urotelial:
  - 5 inibidores de PD-1 / PD-L1 aprovados pelo FDA (atezolizumabe, nivolumabe, pembrolizumabe, avelumane e durvalumabe)
  - Pembrolizumabe (2ª linha) único com estudo Fase 3 positivo (KeyNote 045)
    - Aumento de RO, SG e QoL
  - Atezolizumabe (IMvigor 211) com endpoint primário de SG “estatisticamente” negativo, mas provavelmente “ainda” clinicamente significante
  - Diversos estudos Fase 3 em andamento na 1ª linha:
    - DANUBE: Durvalumabe + Tremelimumabe
    - KeyNote 361: Carbo/Cis + Gem + Pembrolizumabe
    - IMvigor 130: Carbo/Cis + Gem + Atezolizumabe

Conclusões

- Entretanto:
  - A minoria dos pacientes não selecionados apresentam benefício
  - Expressão de PD-L1 não parece muito útil
  - Biomarcadores de resposta necessitam desenvolvimento urgente para a melhor seleção e estratificação dos pacientes
  - Questões não bem compreendidas:
    - Pseudo-PD
    - Hiper-PD
    - Tratamento pós PD