

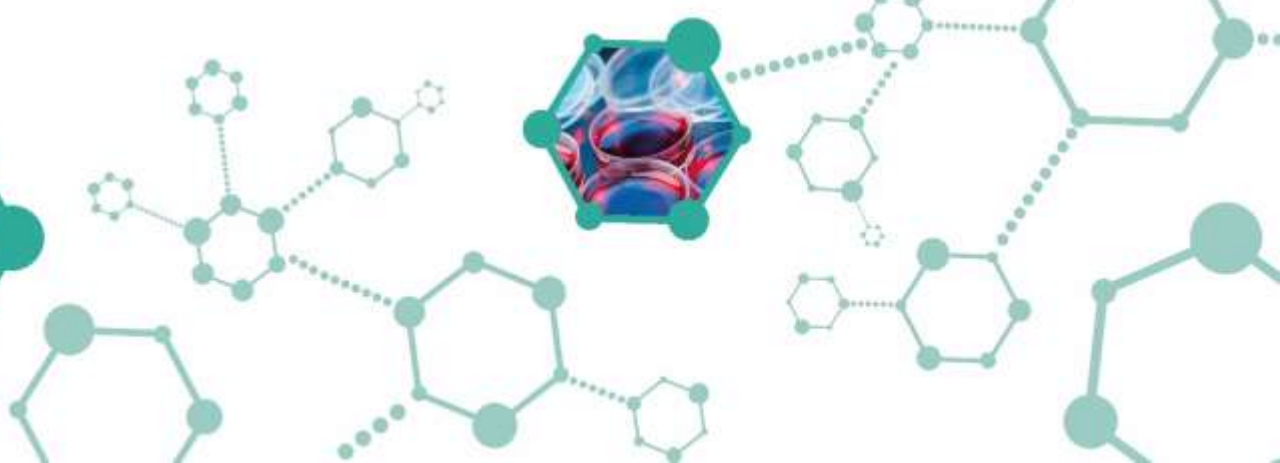


IV Simpósio Internacional de

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O FUTURO DA ONCOLOGIA

27 E 28 DE JULHO – HOTEL PULLMAN VILA OLÍMPIA





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Carcinoma de Células Renais - Biomarcadores

Fabio A. B. Schutz, MD

BP – A Beneficência Portuguesa de São Paulo



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, GSK
- ***Apresentações:*** como palestrante convidado, participei de eventos: Janssen, Sanofi, GSK, Bayer, Astellas
- ***Advisory Board:*** Bayer, Astellas, Janssen

Não possuo ações de quaisquer destas companhias farmacêuticas.

Tópicos

- **Estratificação de risco IMDC**
- **Subtipos moleculares e resposta a Sunitinibe**
- **Infiltrado tumoral de linfócitos T**
- **Carga mutacional e mutações tipo Indel (*Frameshift*)**
- **Microbioma fecal**
- **Expressão de PD-L1 por imunohistoquímica**

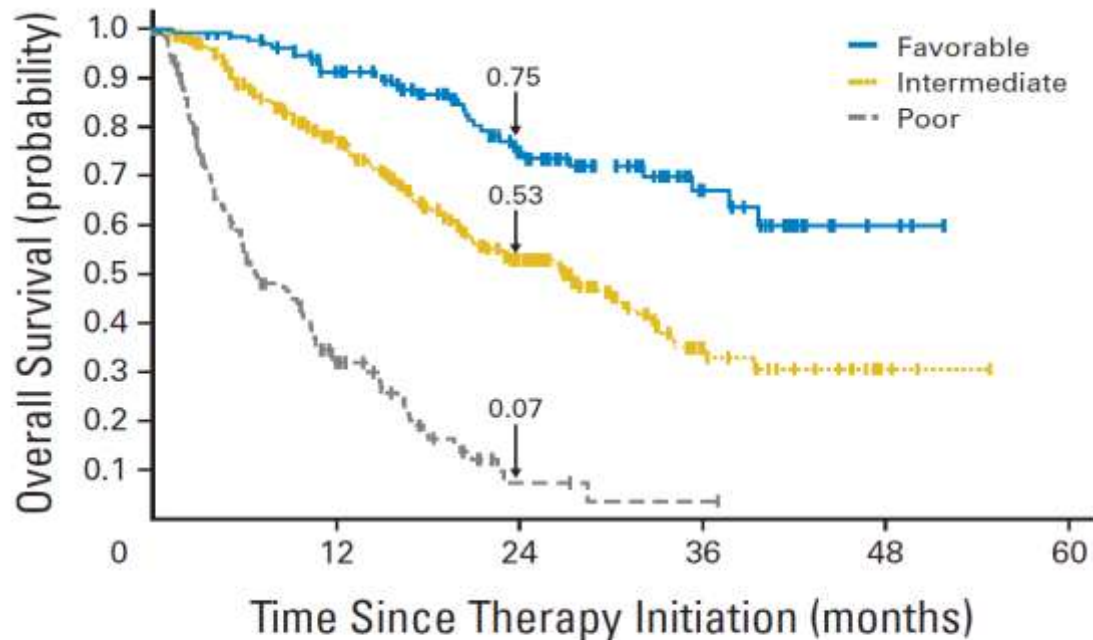


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ESTRATIFICAÇÃO RISCO IMDC



Grupos de risco IMDC



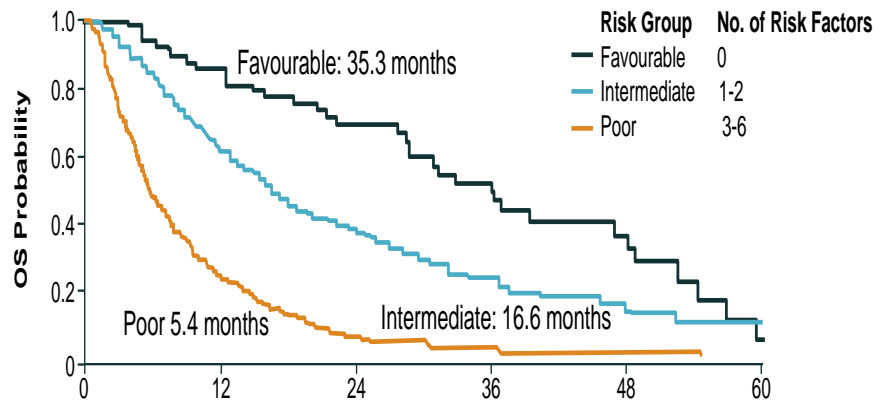
No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

Critérios:

- KPS < 80%
- Tempo do Dx ao Tx < 1ano
- Hb < Limite inf.
- Ca. > Limite sup.
- Neutrofilos > Limite sup.
- Plaquetas > Limite sup.

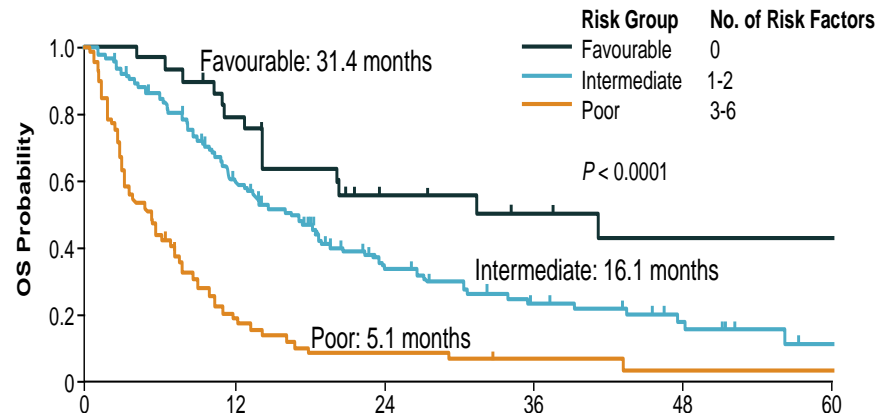
Grupos de risco IMDC

Segunda Linha de Tratamento



No. of patients at risk	Time Since Initiation of Second-line Therapy, months					
	0	12	24	36	48	60
Favourable	76	52	31	19	8	1
Intermediate	529	257	97	37	9	4
Poor	261	49	9	3	1	0

Não Células Claras



No. of patients at risk	Time Since Start of Treatment, months					
	0	12	24	36	48	60
Favourable	29	13	4	3	0	0
Intermediate	127	26	7	2	2	1
Poor	66	4	2	0	0	0



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SUBTIPOS MOLECULARES DE RCC



Subtipos moleculares com prognóstico distinto com Sunitinibe

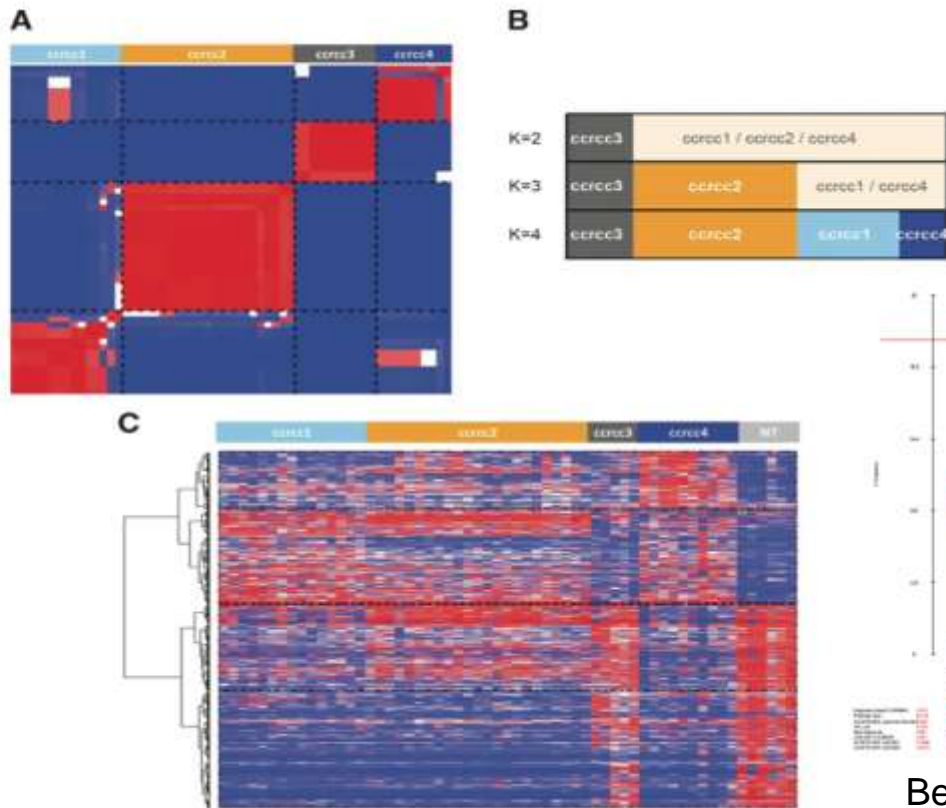
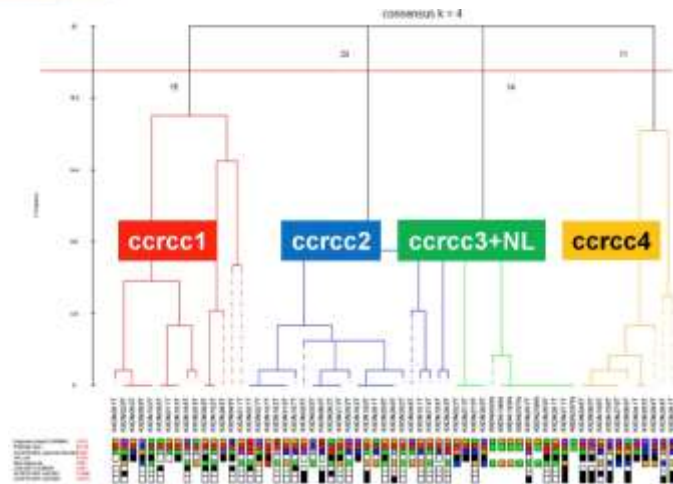
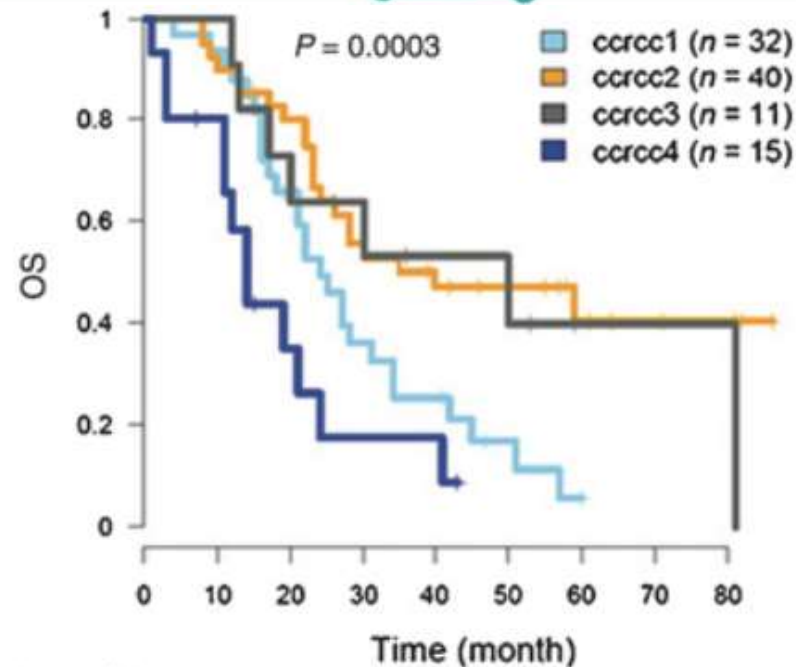
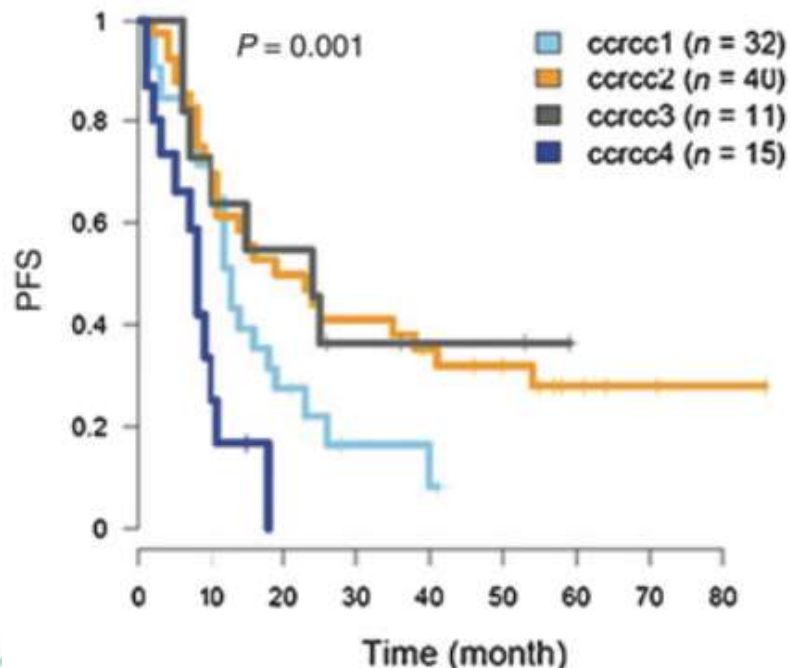


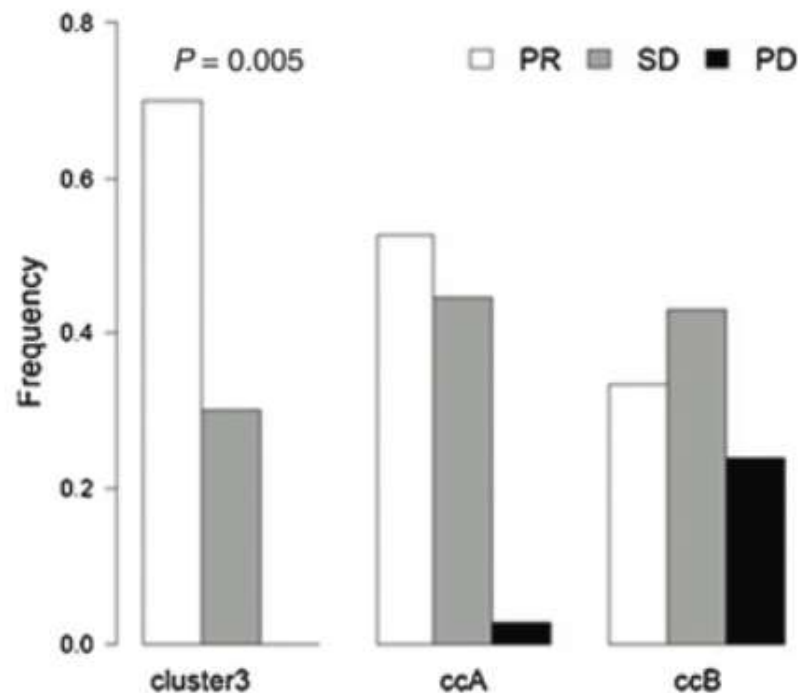
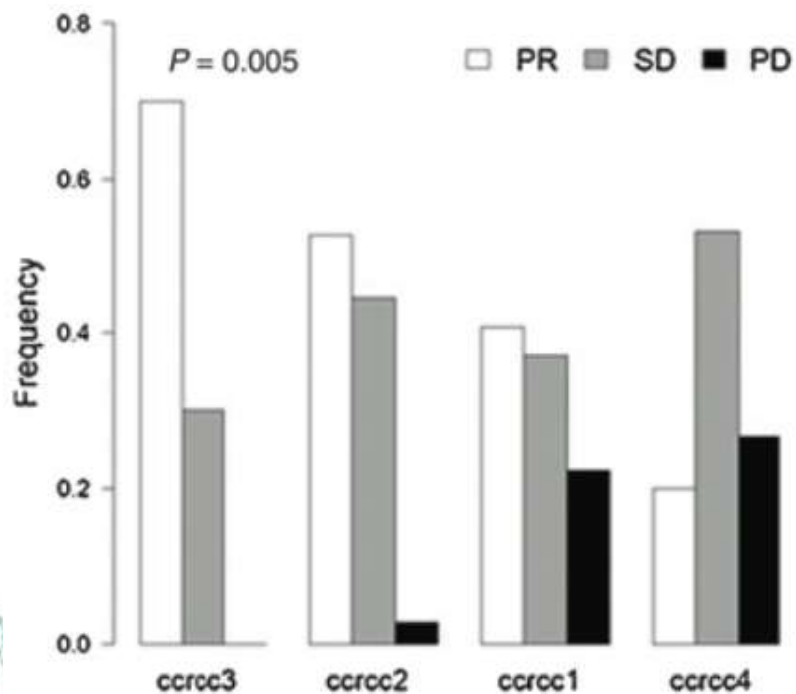
Figure 2. Identification of four robust subgroups through an unsupervised consensus clustering analysis of expression data. A, coclassification matrix of the 59 RCC samples. Blue = low coclassification and red = high coclassification. B, sample partition for K = 2 clusters to K = 4 clusters. C, gene expression profile heatmap of the most variant probe sets ordered by subtype. Blue = low expression level and red = high expression level.



Subtipos moleculares com prognóstico distinto com Sunitinibe



Subtipos moleculares com prognóstico distinto com Sunitinibe



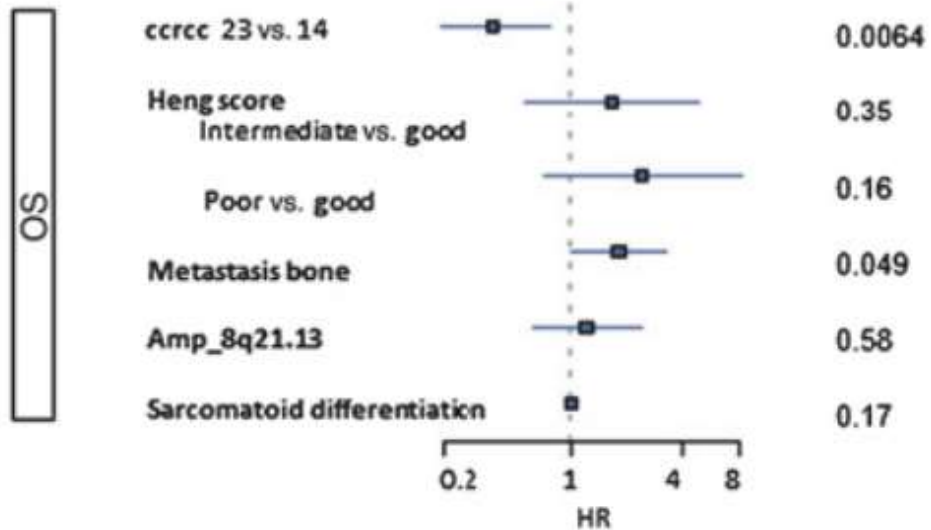
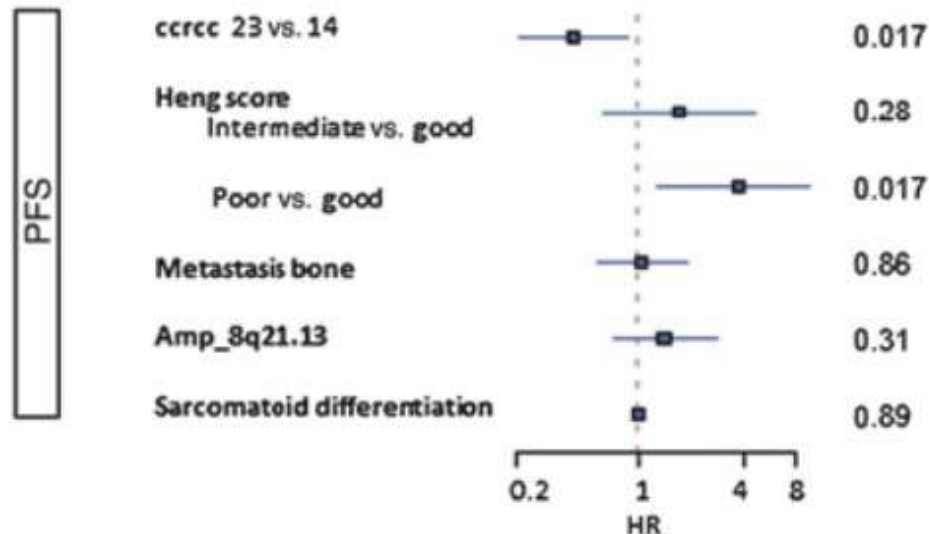
Subtipos moleculares com prognóstico distinto com Sunitinibe

Log-rank $P = 0.0001$

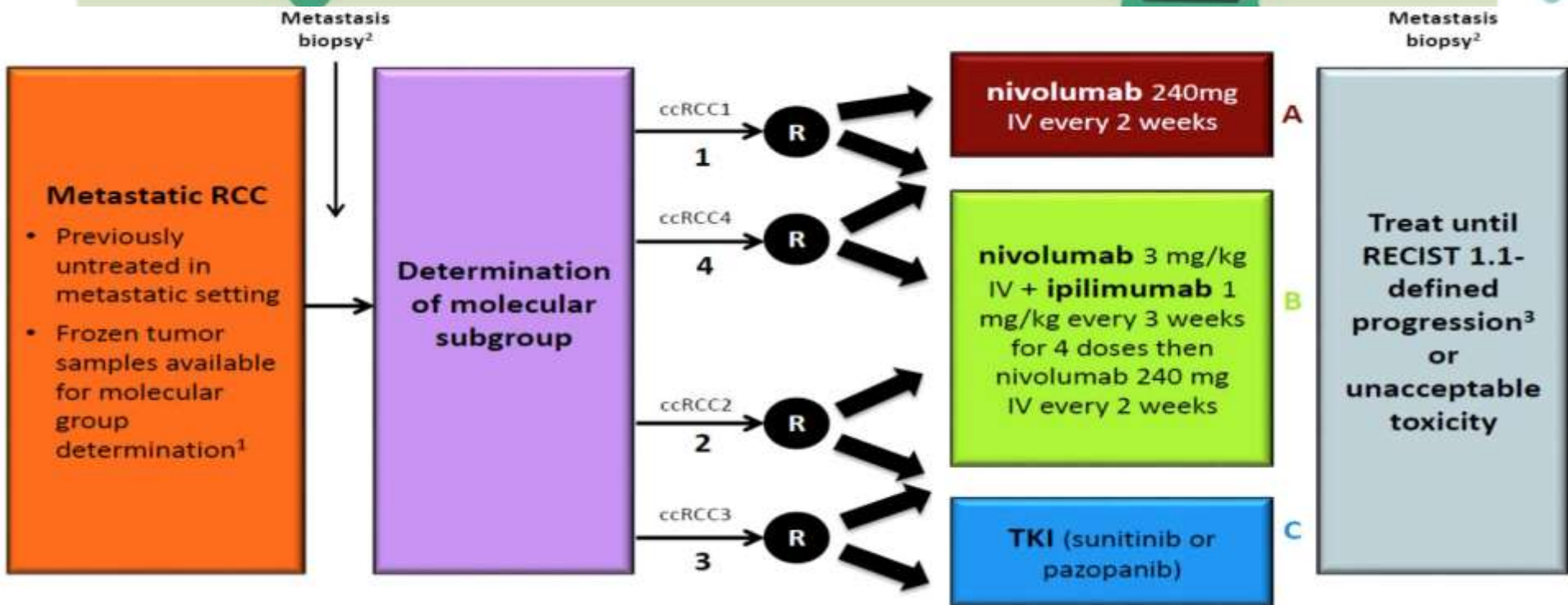
Wald P value

Log-rank $P = 0.00004$

Wald P value



BIONIKK Trial



Primary objective: objective response rate according to group (1 to 4) and treatment arm (A to C)



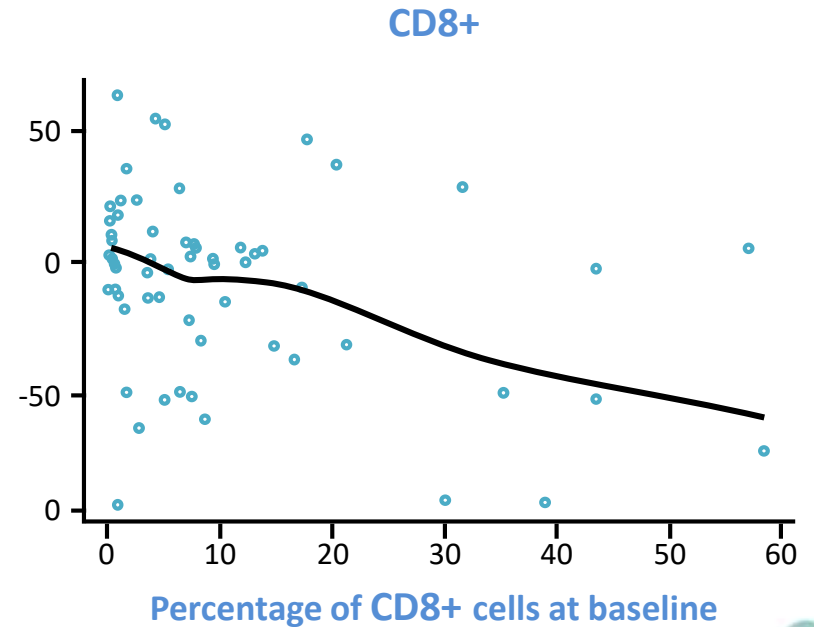
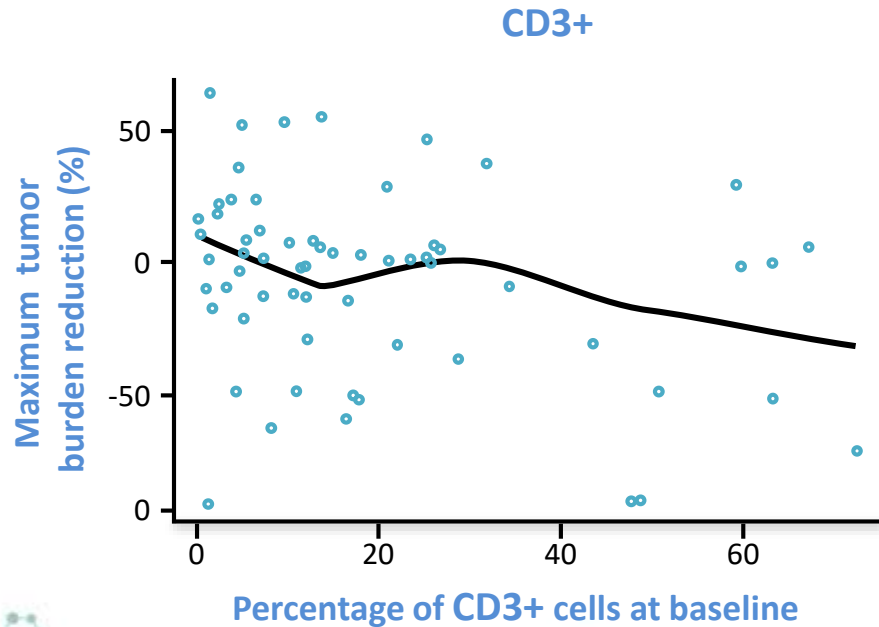
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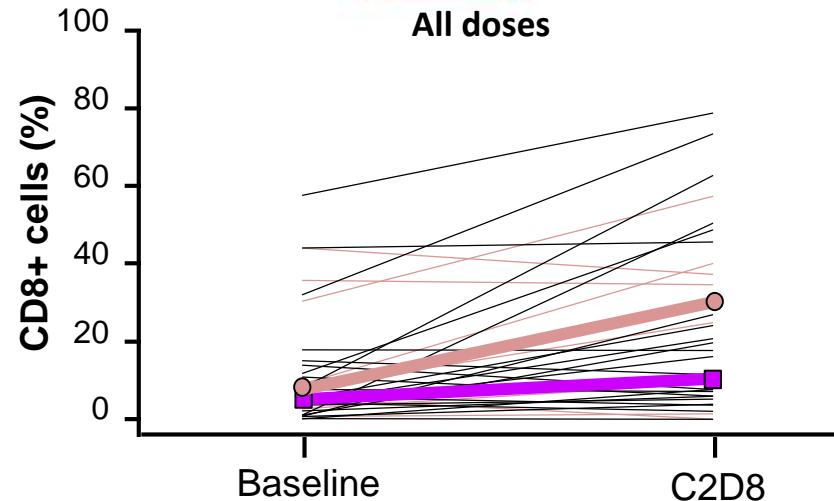
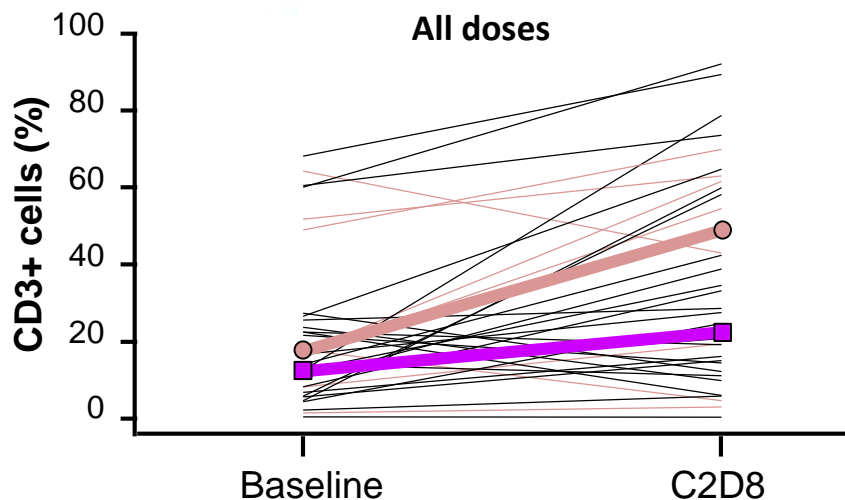
INFILTRADO TUMORAL DE LINFÓCITOS



Linfócito T tumoral se correlaciona com diminuição da carga tumoral



Linfócito T tumoral (CD3+ e CD8+) aumenta após tratamento com Nivolumabe



N=33

Individual responder — (red line)
Individual nonresponder — (black line)

Responder median — (red line with circles)
Nonresponder median — (purple line with squares)



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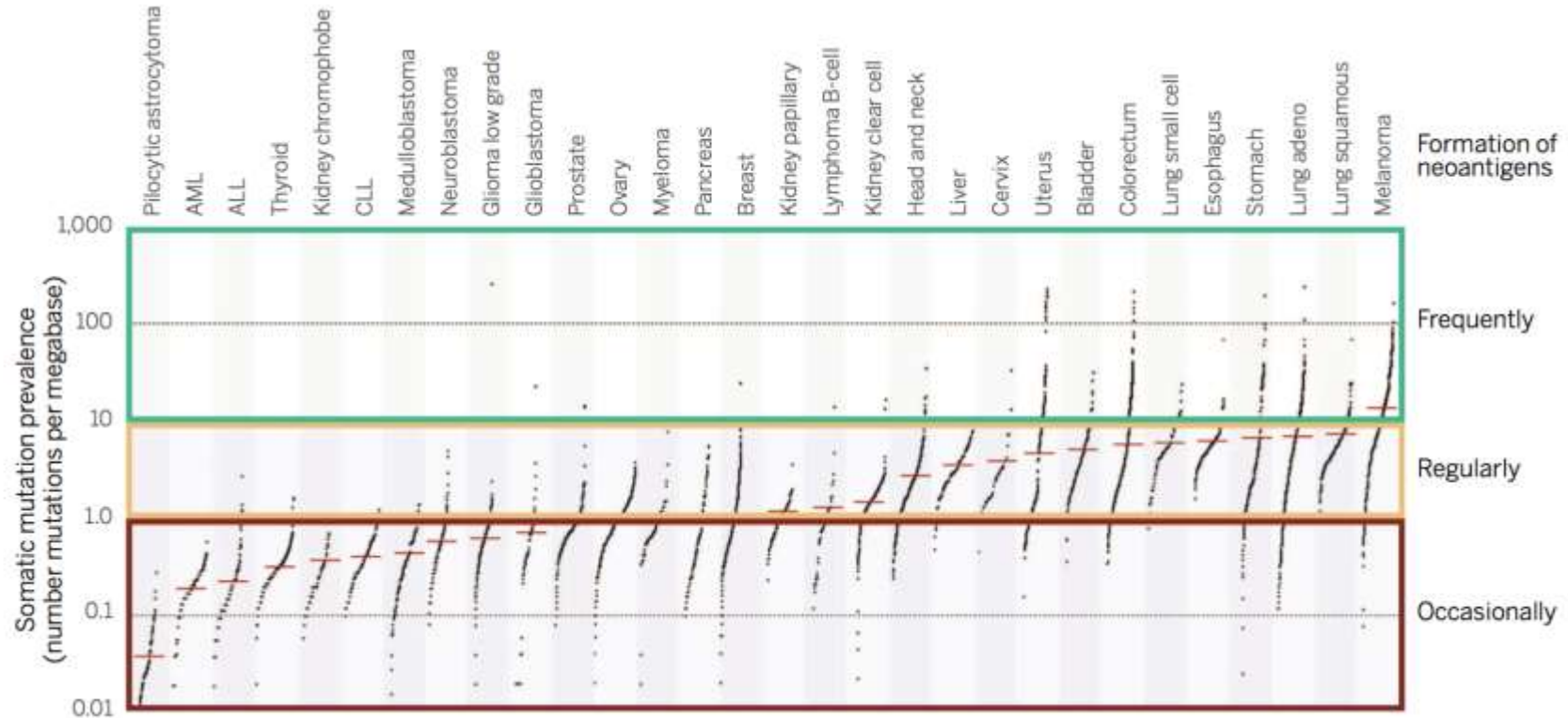


CARGA MUTACIONAL

MUTAÇÕES TIPO *INDEL* *FRAMESHIFT*



Carga Mutacional



Tipos de mutações

Missense mutation: changes an amino acid to another amino acid. This may or may not affect protein function, depending on whether the change is “conservative” or “nonconservative,” and what the amino acid actually does.

Nonsense mutation: changes an amino acid to a STOP codon, resulting in premature termination of translation.

“Silent” mutation: does not change an amino acid, but in some cases can still have a phenotypic effect, e.g., by speeding up or slowing down protein synthesis, or by affecting splicing.

Frameshift mutation: Deletion or insertion of a number of bases that is *not* a multiple of 3. Usually introduces premature STOP codons in addition to lots of amino acid changes.

Tipos de mutações

Frameshift (Insertion/Deletion)

Types of Point Mutations frameshift

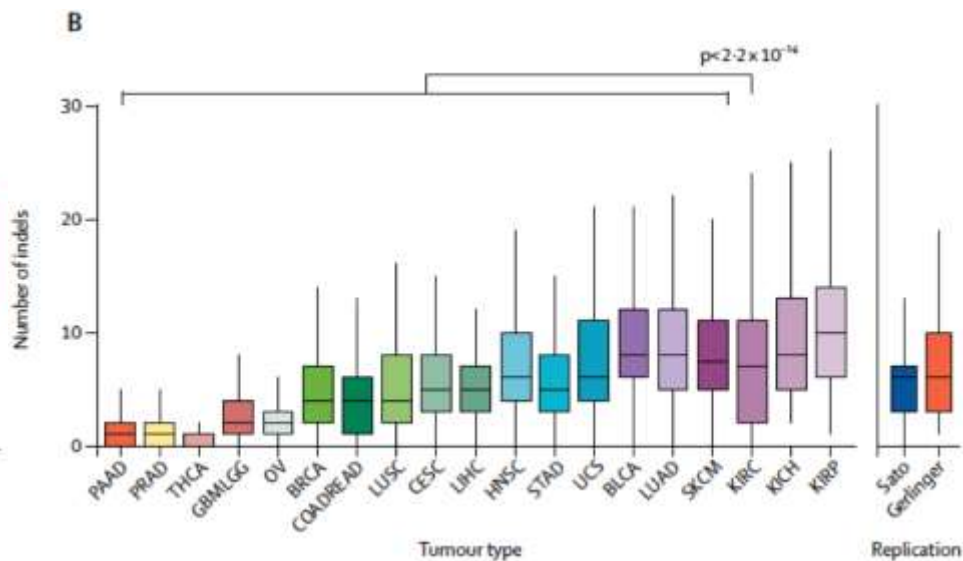
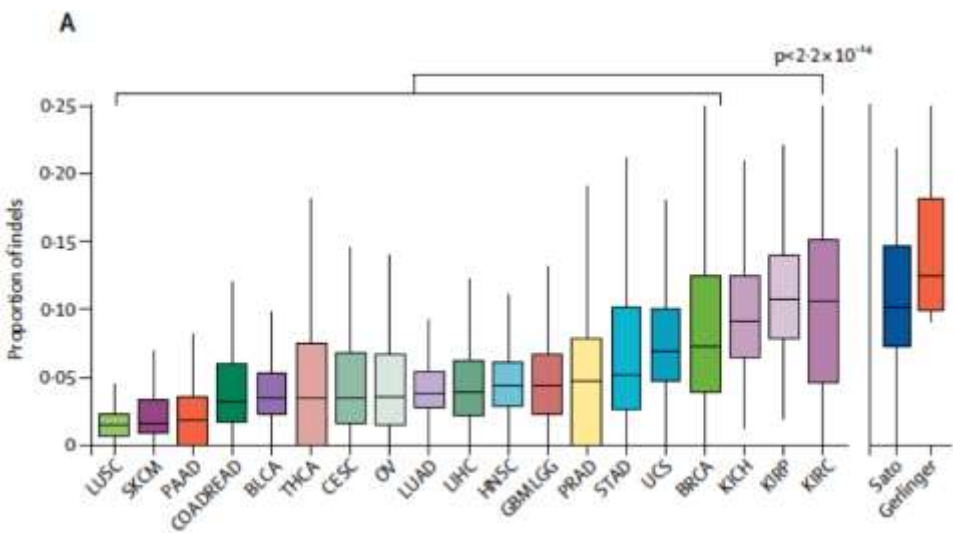
TAT TGG CTA GTA CAT

Tyr Trp Leu Val His

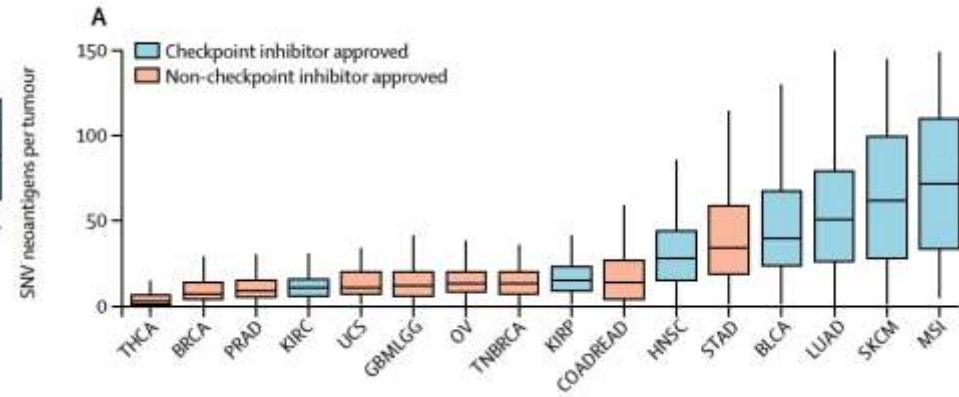
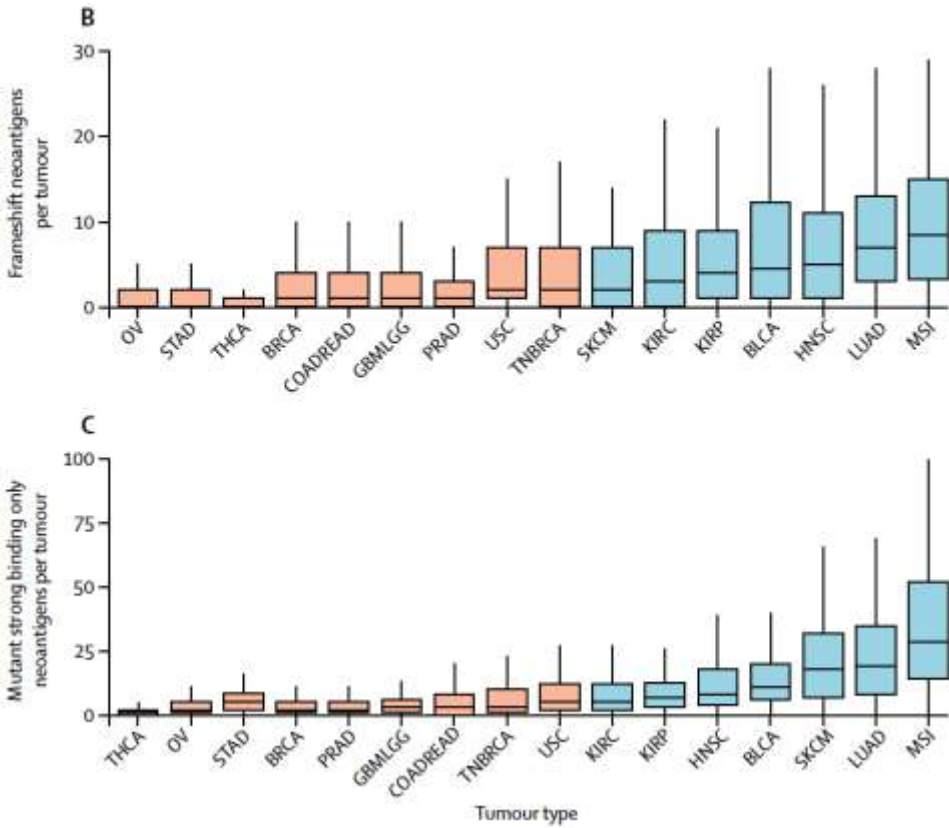
TAC TCG GCT AGT ACA T

Tyr Ser Ala Ser Thr

Número e proporção de mutação Indel tumorais



Neoantigenos específicos de mutações Indel frameshift estratifica melhor aprovações ICI



Carga mutacional de Indel's e correlação com resposta a Anti-PD(L)1 em mRCC

Patients/Cohorts

This analysis includes **tumors from 112 patients (pts) across three cohorts:**

- **Cohort "PD1-A":** 54 pts treated with single agent nivolumab on the phase II CheckMate 009 study.⁸
- **Cohort "PD1-B":** 23 pts treated with PD-1 directed regimens at three academic institutions (DFCI, JHU, MSKCC).
- PD1-A + PD1-B vary in regards to clinical setting (e.g. extent of prior treatment); the cohorts were analyzed separately, then jointly in a pooled, stratified analysis
- **Cohort "TKI":** 35 pts treated with first-line TKI therapy and with no prior exposure to CPI therapy; pts were treated across five academic institutions (DFCI, MDACC, MSKCC, UNC, UPMC); tumors were originally analyzed as part of the ccRCC TCGA.⁹

Carga mutacional de Indel e correlação com resposta a Anti-PD(L)1 em mRCC

Número de Indel's se correlaciona com SG em pacientes tratados com Anti-PD(L)1
Sem correlação com carga mutacional ou neoantígenos

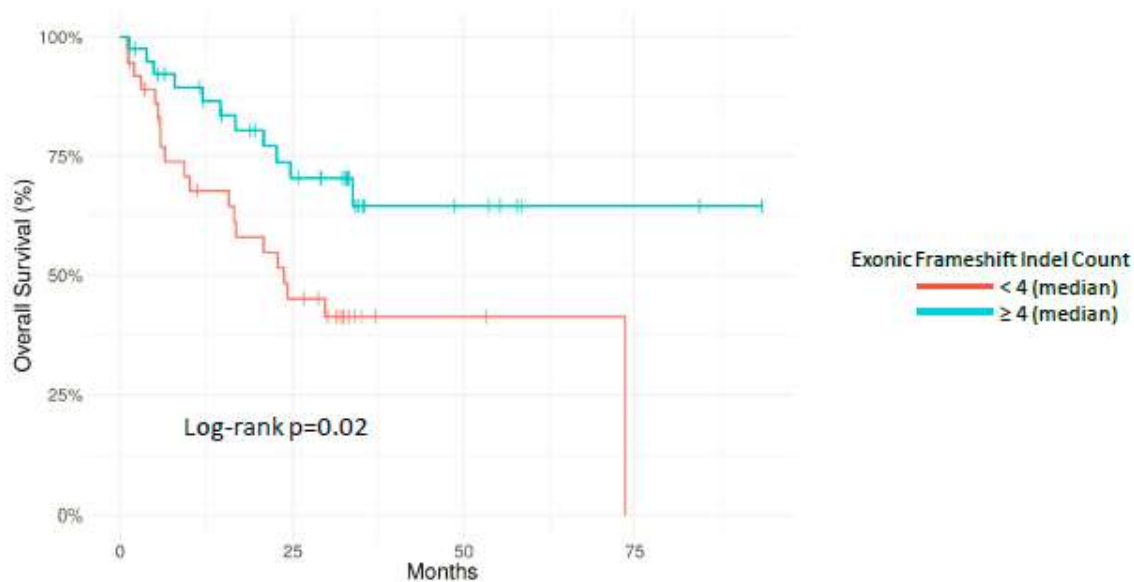
Overall mutation burden	n	HR per 10 variants	p-value (HR<>0)	p-value (log-rank test at median)
PD1-A	54	1.08 (1.00 - 1.16)	0.039	0.273
PD1-B	23	0.92 (0.79 - 1.06)	0.251	0.363
All PD1 cohorts (stratified analysis)	77	1.02 (0.95 - 1.09)	0.56	0.16

Predicted neoantigen burden	n	HR per neoantigen	p-value (HR<>0)	p-value (log-rank test at median)
PD1-A	54	1.00 (1.00 - 1.01)	0.081	0.678
PD1-B	23	0.99 (0.98 - 1.00)	0.056	0.174
All PD1 cohorts (stratified analysis)	77	1.00 (1.00 - 1.00)	0.688	0.741

Insertion/deletion burden	n	HR per indel	p-value (HR<>0)	p-value (log-rank test at median)
PD1-A	54	0.85 (0.74 - 0.98)	0.038	0.273
PD1-B	23	0.85 (0.71 - 1.03)	0.092	0.443
PD1-A+B (stratified analysis)	77	0.85 (0.76 - 0.95)	0.006	0.02

Carga mutacional de Indel e correlação com resposta a Anti-PD(L)1 em mRCC

WES analysis: Indel burden correlates with OS in PD1-treated cohorts.



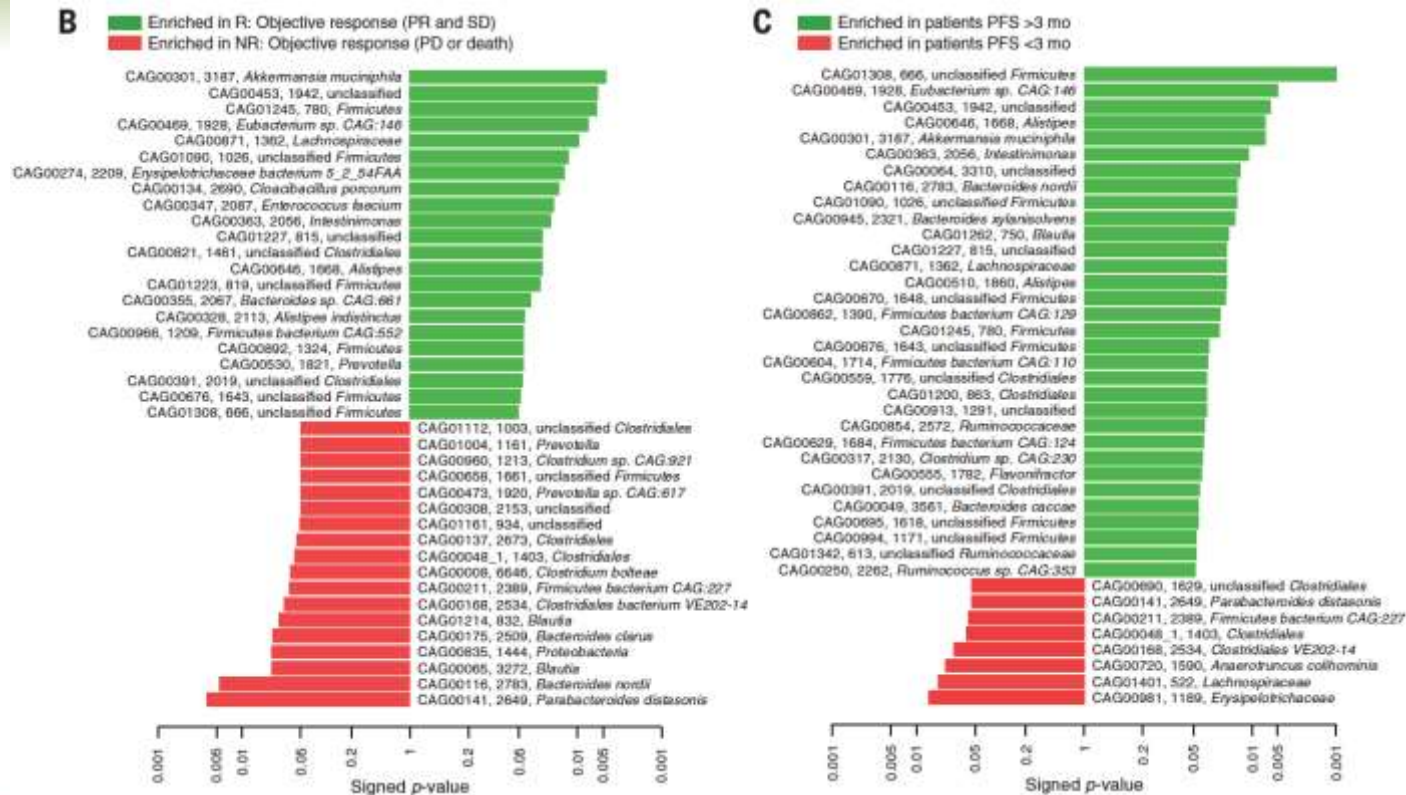


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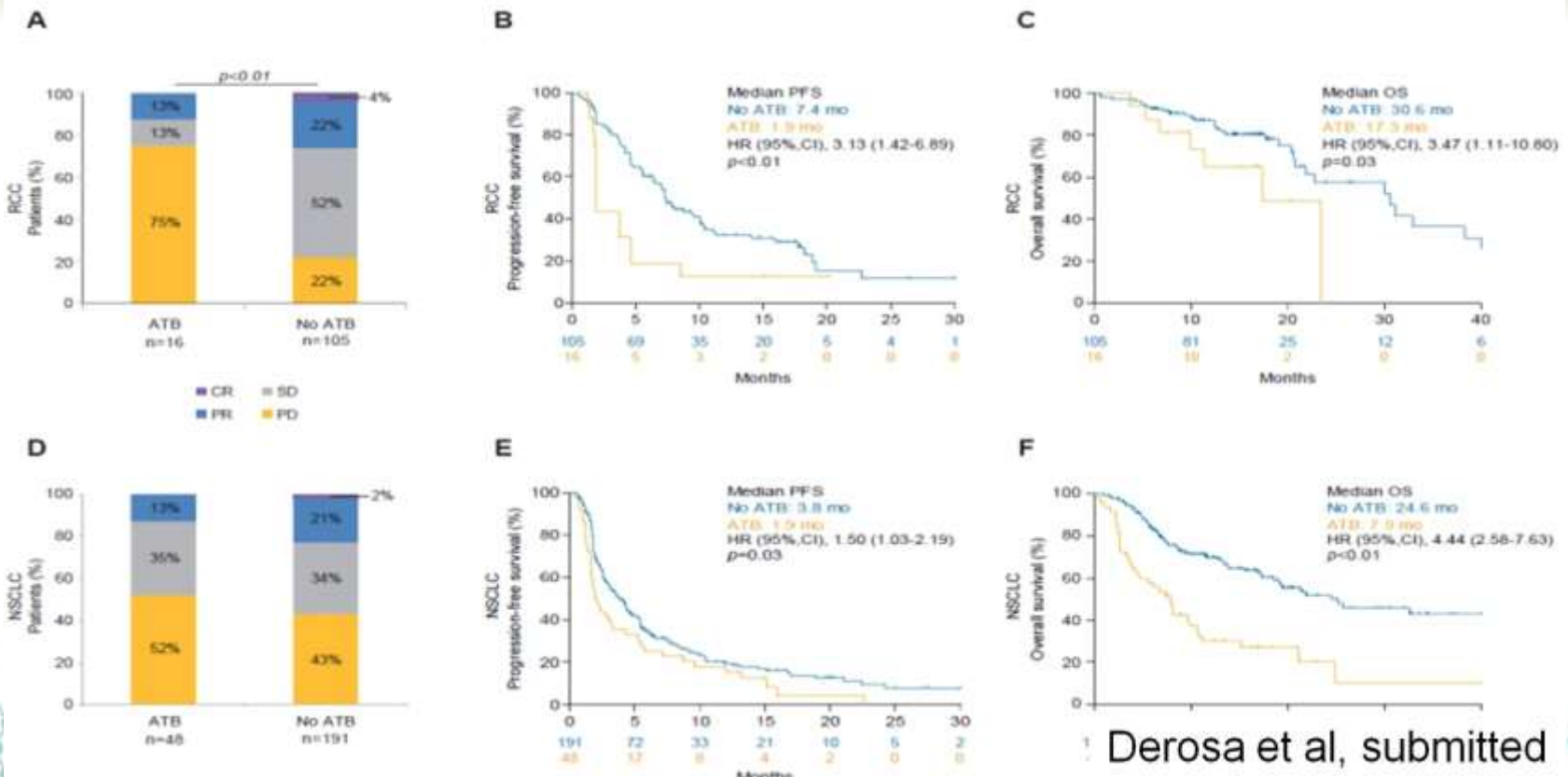
MICROBIOMA FECAL



Influência do Microbioma intestinal



Modificação de Microbioma Intestinal por antibióticos pode impactar eficácia de ICI





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EXPRESSÃO DE PD-L1



Expressão de PD-L1 – CheckMate 214

Resposta Objetiva

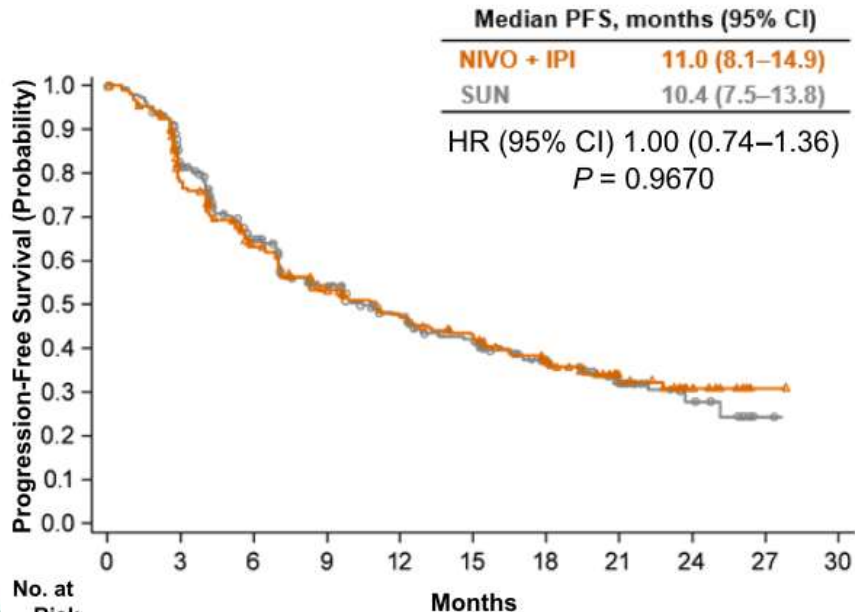
	IMDC intermediate/poor risk				Intention to treat			
	PD-L1 <1%		PD-L1 ≥1%		PD-L1 <1%		PD-L1 ≥1%	
Outcome	NIVO + IPI N = 284	SUN N = 278	NIVO + IPI N = 100	SUN N = 114	NIVO + IPI N = 386	SUN N = 376	NIVO + IPI N = 113	SUN N = 127
ORR,^a % (95% CI)	37 (32–43)	28 (23–34)	58 (48–68)	22 (15–31)	36 (31–41)	35 (31–40)	53 (44–63)	22 (15–30)
	<i>P</i> = 0.0252		<i>P</i> < 0.0001		<i>P</i> = 0.8799		<i>P</i> < 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

^aIRRC-assessed

Expressão de PD-L1 – CheckMate 214

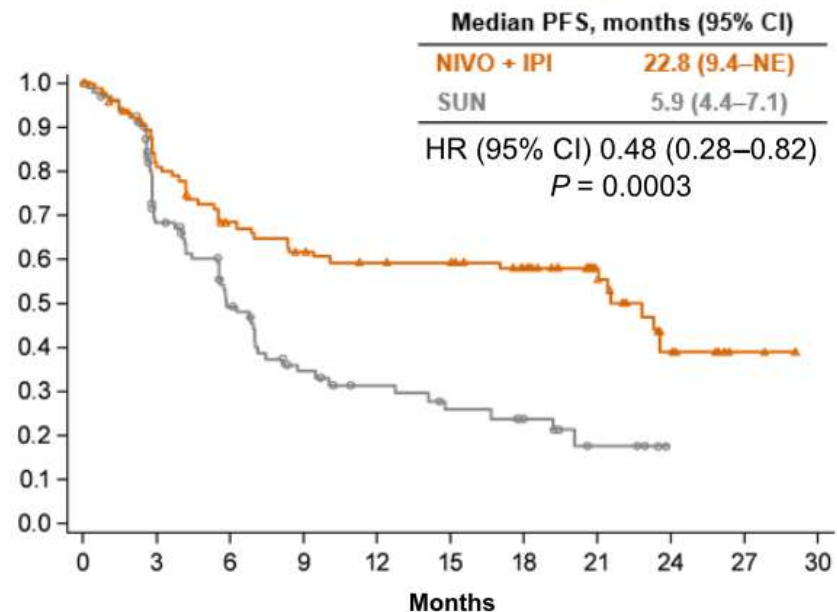
Sobrevida Livre de Progressão (Risco Intermediário/Alto)

PD-L1 <1% (n = 562)



No. at Risk	0	3	6	9	12	15	18	21	24	27	30
NIVO	284	202	155	119	102	90	70	23	9	1	0
SUN	278	200	138	105	83	67	43	25	11	1	

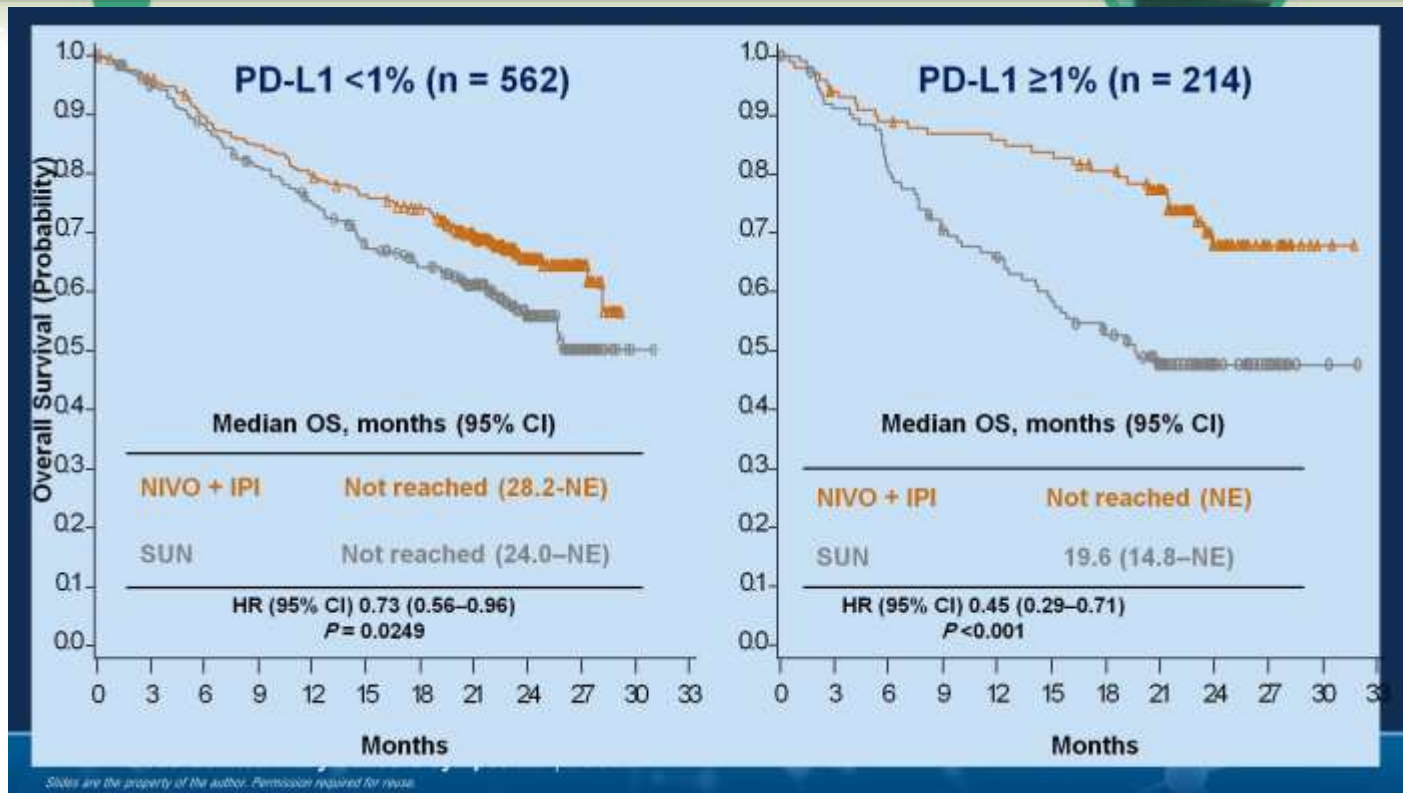
PD-L1 ≥1% (n = 214)



No. at Risk	0	3	6	9	12	15	18	21	24	27	30
NIVO	100	77	61	54	50	48	41	21	8	2	0
SUN	114	63	40	24	17	13	9	4	0	0	3

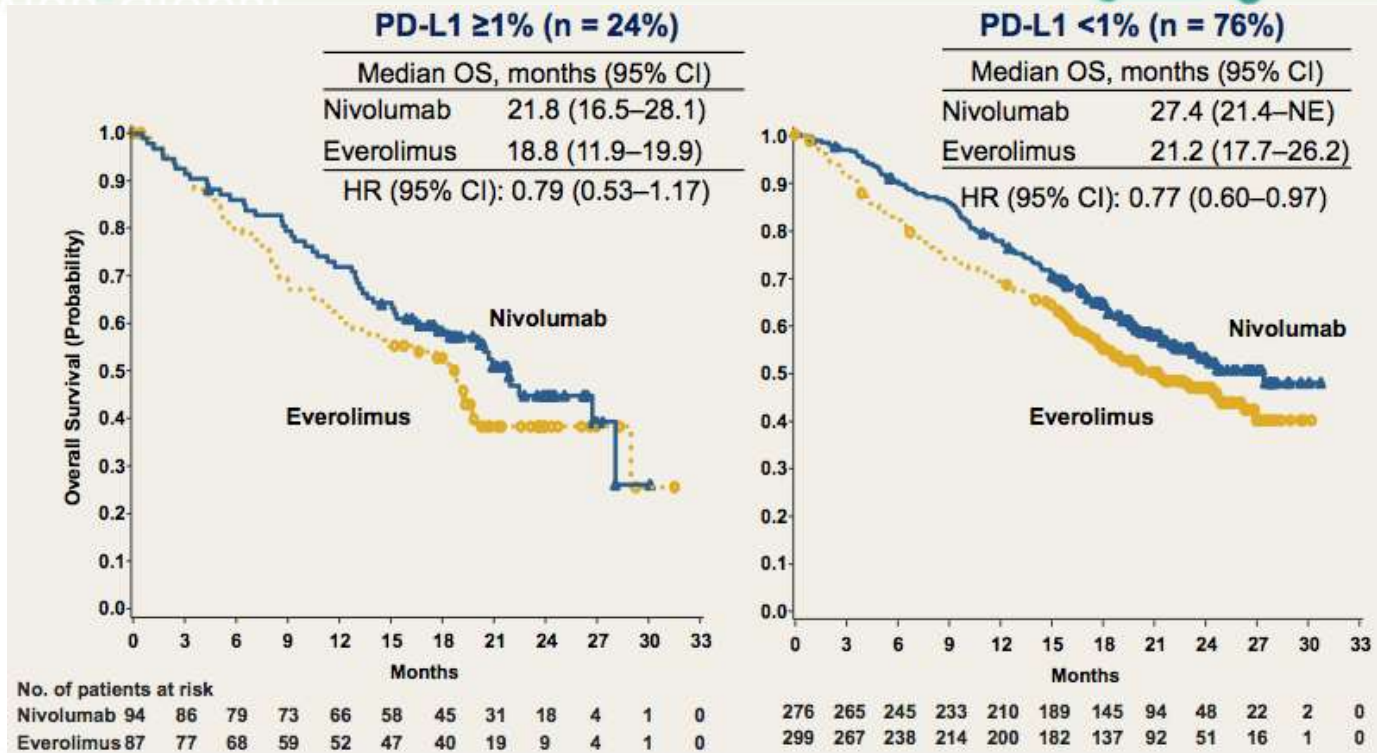
Expressão de PD-L1 – CheckMate 214

Sobrevida Global (Risco Intermediário/Alto)



Expressão de PD-L1 – CheckMate 025

Sobrevida Global



Expressão de PD-L1 – IMmotion151

Resposta Objetiva (investigador)

	PD-L1+		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 454	Sunitinib n = 460
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)	37% (32, 41)	33% (29, 38)
Complete response	9%	4%	5%	2%
Partial response	34%	30%	31%	31%
Stable disease	32%	35%	39%	39%
Progressive disease	19%	21%	18%	19%
Not evaluable ^a	7%	10%	7%	9%

Expressão de PD-L1 – IMmotion151

Resposta Objetiva e Sobrevida Livre de Progressão (IRC)

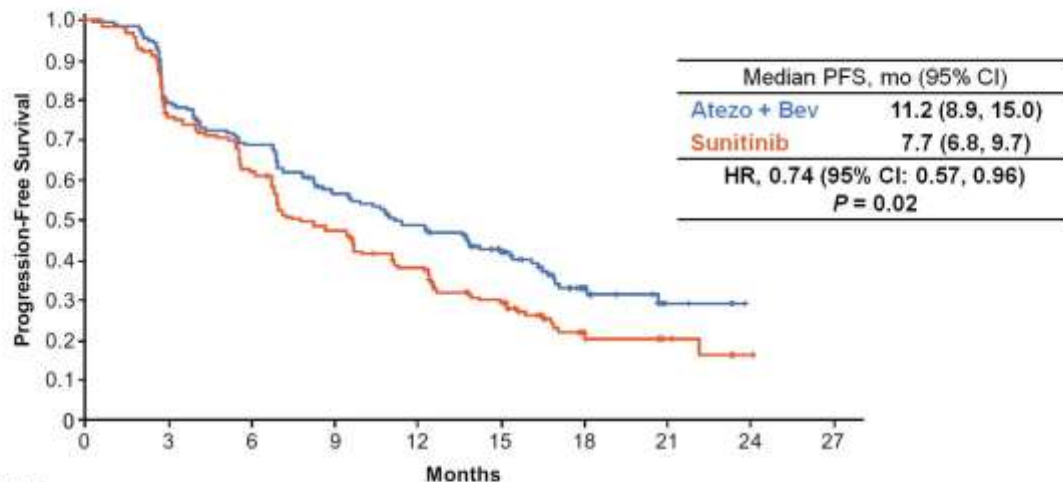
	PD-L1+		PD-L1 ^{-a}		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 276	Sunitinib n = 277 ^b	Atezo + Bev n = 454	Sunitinib n = 461
Median PFS, mo (95% CI)	8.9 (6.9, 12.5)	7.2 (6.1, 11.1)	11.0 (8.3, 13.3)	8.4 (7.4, 10.1)	9.6 (8.3, 11.5)	8.3 (7.0, 9.7)
Stratified HR (95% CI)	0.93 (0.72, 1.21)		0.84 (0.67, 1.04)		0.88 (0.74, 1.04)	
Confirmed ORR, % (95% CI)	36% (29, 44)	33% (26, 40)	32% (26, 37)	30% (25, 36)	33% (29, 38)	31% (27, 36)
CR rate	15%	8%	8%	6%	11%	7%

Expressão de PD-L1 – IMmotion151

Sobrevida Livre de Progressão em PD-L1 positivo

Co-Primary
Endpoint

Progression-Free Survival in PD-L1+

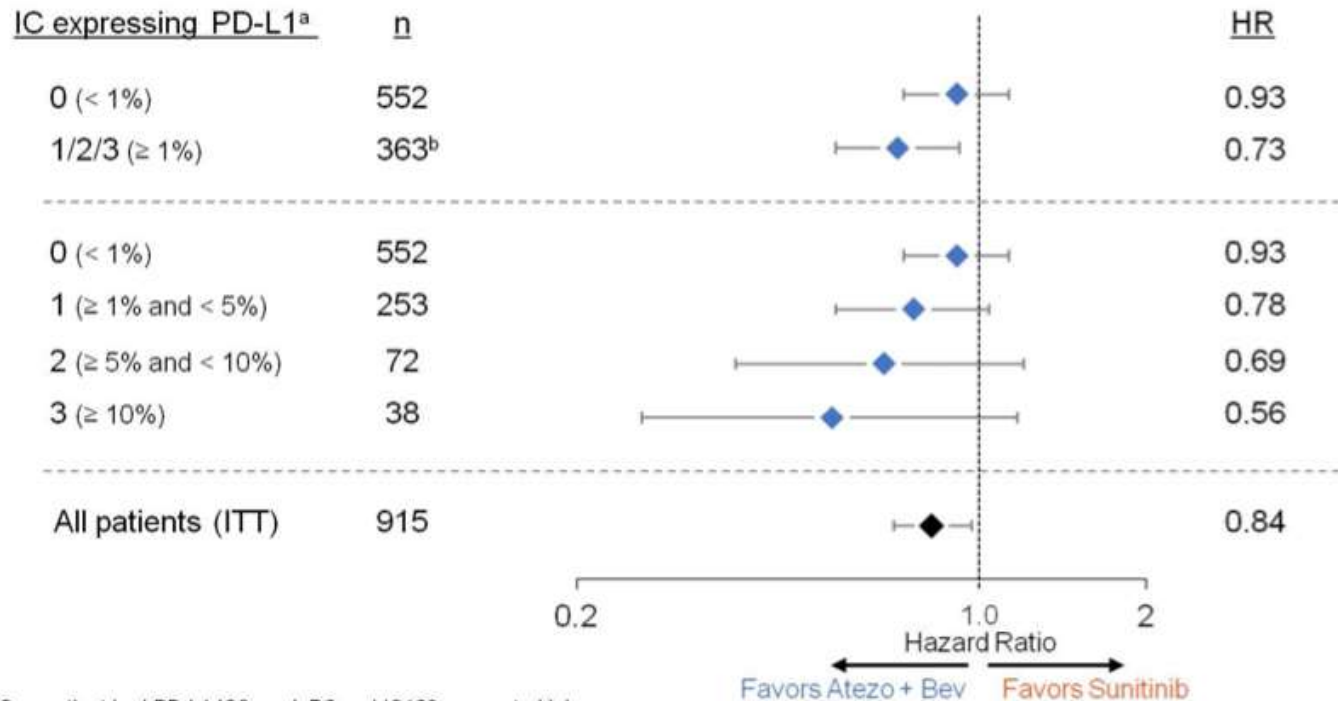


No. at Risk	0	3	6	9	12	15	18	21	24	27
Atezo + Bev	178	137	117	94	79	55	22	5		
Sunitinib	184	135	110	83	64	44	15	7	1	

PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.
The PFS analysis passed the pre-specified P value boundary of alpha = 0.04.

Expressão de PD-L1 – IMmotion151

Sobrevida Livre de Progressão em PD-L1 positivo

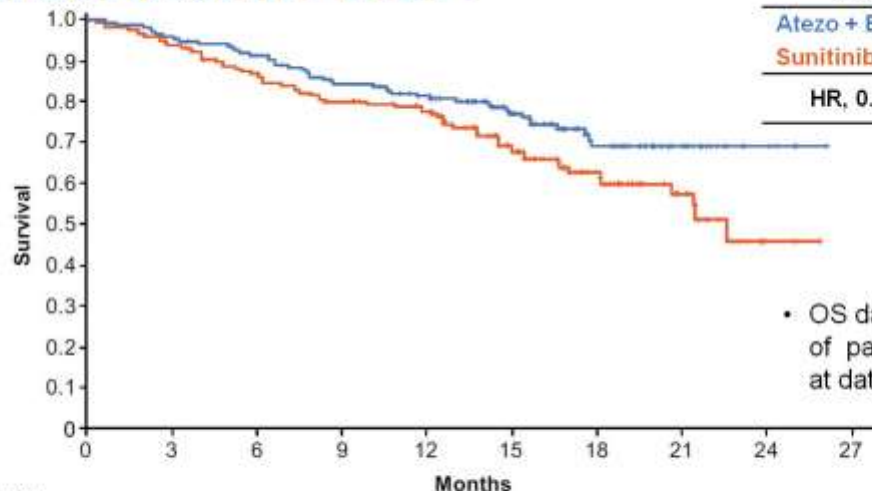


^a Per central lab. ^b One patient had PD-L1 IC0 per IxRS and IC123 per central lab. PFS assessed by investigators.

Expressão de PD-L1 – IMmotion151

Sobrevida Global em PD-L1 positivo

Overall Survival in PD-L1+



Secondary Endpoint

Median OS, mo (95% CI)

Atezo + Bev	Not reached
Sunitinib	23.3 (21.3, NR)

HR, 0.68 (95% CI: 0.46, 1.00)

No. at Risk	0	3	6	9	12	15	18	21	24	27
Atezo + Bev	178	169	160	147	139	109	55	26	6	
Sunitinib	184	169	154	141	134	96	51	27	6	

NR, not reached. Minimum follow-up, 12 mo. Median follow-up, 15 mo. Event/patient ratio: 25% for atezo + bev, 35% for sunitinib.

Expressão de PD-L1 – Nivo, Atezo e Ipi-Nivo

Resposta Objetiva

Table 2 Summary of assays and response rates in immune checkpoint inhibitor trials in metastatic renal cell carcinoma

Ref	CPI	Drug	Target	Antibody for PD-L1 IHC Assay	Definition of PD-L1 positivity	ORR (PD-L1+)	ORR (PD-L1-)	ORR All Patients
[14]	Single Agent	Nivolumab	PD-1	Rabbit 28–8 (Dako)	PD-L1 \geq 5% (TC)	45% (13/29)	18% (14/78)	25% (27/107)
[18]	Single Agent	Atezolizumab	PD-L1	Rabbit SP142 (Ventana)	IHC 1/2/3 IC ^a	18% (6/33)	9% (2/22)	15% (8/55)
[25]	Combination ^b	Nivolumab and Ipilimumab	PD-1 and CTLA-4	Rabbit 28–8 (Dako)	PD-L1 \geq 1% (TC)	58% (58/100)	37% (105/284)	42% (163/384)

TC tumor cells, IC percentage of PD-L1 positive immune cells in the tumor microenvironment, ORR overall response rate

^aIHC 1 is \geq 1%, IHC 2 is \geq 5%, IHC 3 is \geq 10%

^bIMDC Intermediate/poor risk

Conclusões - Biomarcadores

- Estratificação prognóstica IMDC ainda muito importante
- ccRCC apresenta perfis moleculares distintos
 - Estudos clínicos prospectivos avaliando tratamentos estratificados por perfil molecular (BIONIKK)
- Expressão de PD-L1 é o biomarcador para uso de ICI mais próximo da prática clínica
- Outros biomarcadores promissores
 - Microbioma fecal
 - Carga mutacional total e/ou tipo *frameshift Indel*



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Obrigado!



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