Imunoterapia em Câncer de Próstata, Pênis e Testículo

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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, Novartis, Janssen**

***Apresentações*: como palestrante convidado, participei de eventos: Sanofi, Novartis, Bayer, Janssen, Astellas, BMS, Pfizer**

***Advisory Board*: Sanofi, Bayer, Janssen, Astellas, Novartis, Roche**

Não possuo ações de quaisquer destas companhias farmacêuticas.

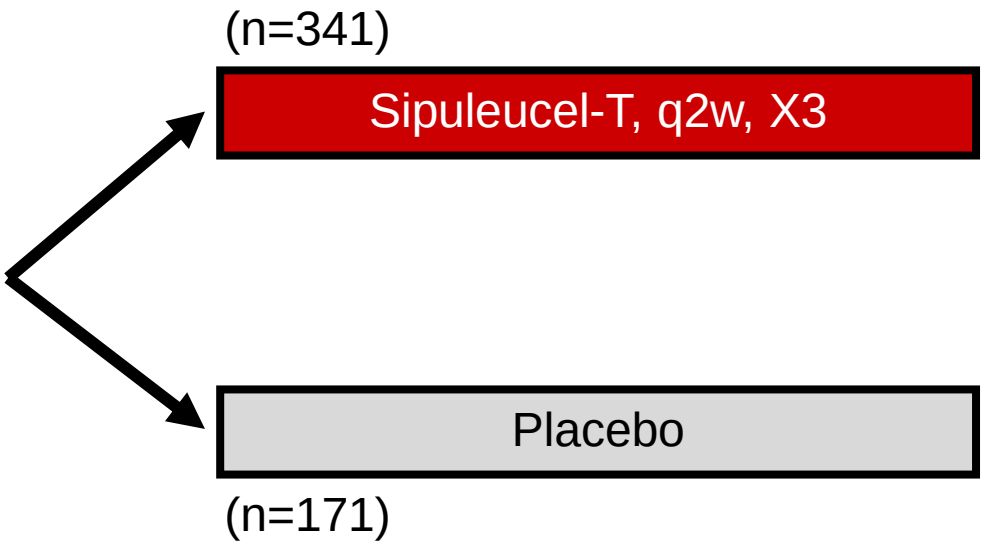
IMUNOTERAPIA SIPULEUCEL-T

Figure 1. Sipuleucel-T (Provenge) Manufacturing Process

SIPULEUCEL-T FASE III

mCRPC (PD por imagem ou PSA), assintomático ou minimamente sintomático

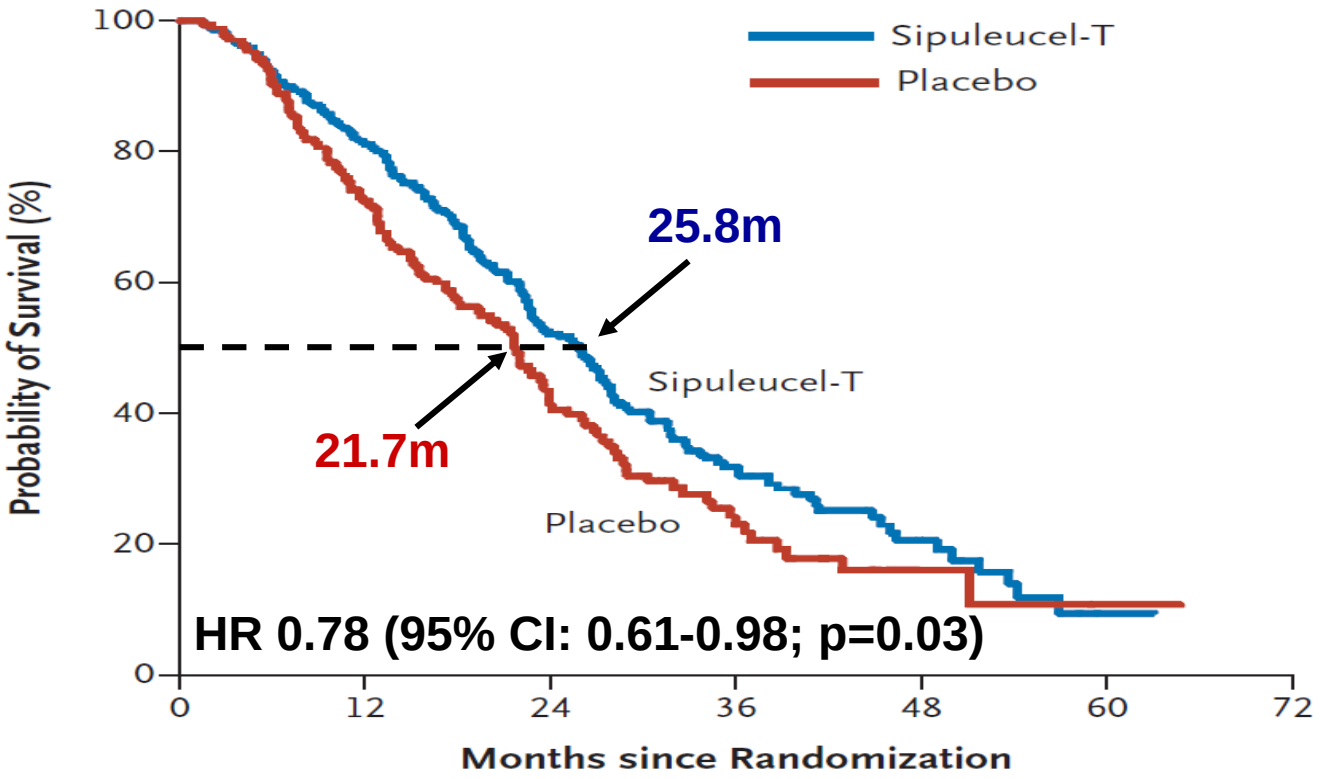
(n=512)



Objetivo primário: SG

Kantoff PW, *N Engl J Med* 2010:411

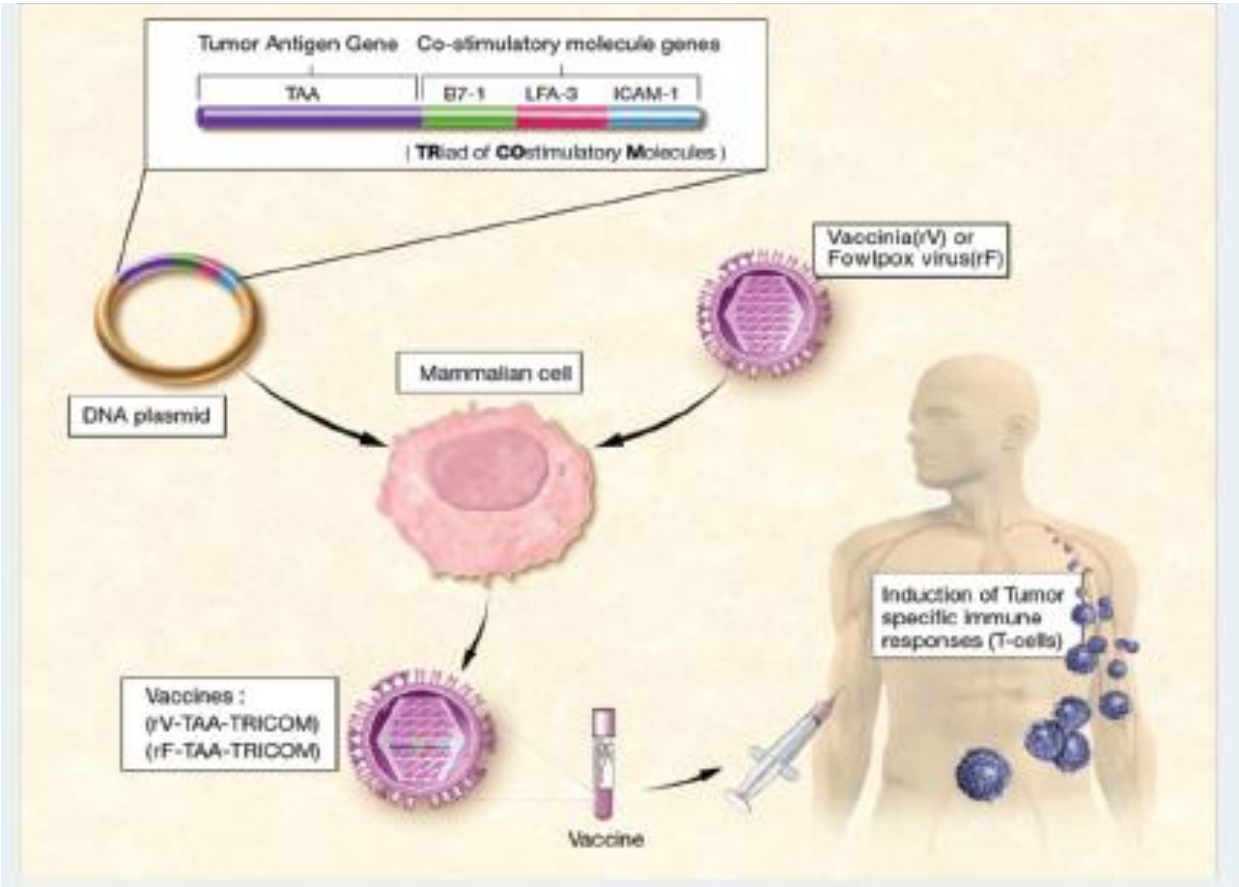
SIPULEUCEL-T
SOBREVIDA GLOBAL



No. at Risk						
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

Kantoff PW, *N Engl J Med* 2010:411

Imunoterapia PROSTVAC®

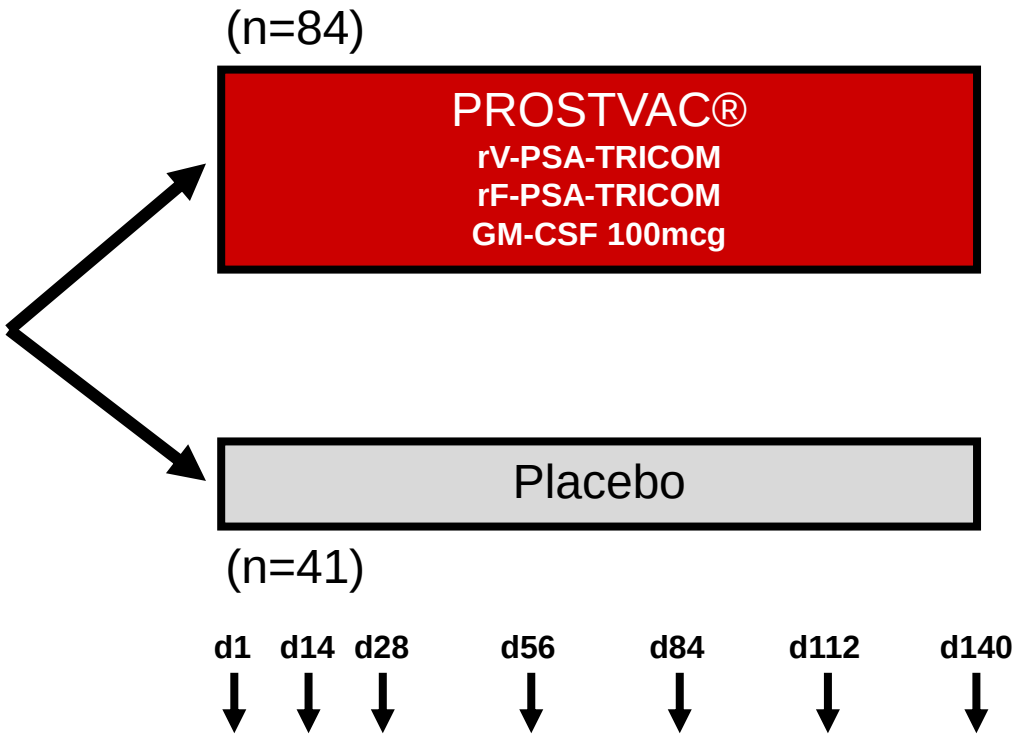


PROSTVAC®
Fase II randomizado

mCRPC, minimamente sintomático (com metastases ósseas e sem metástases viscerais)

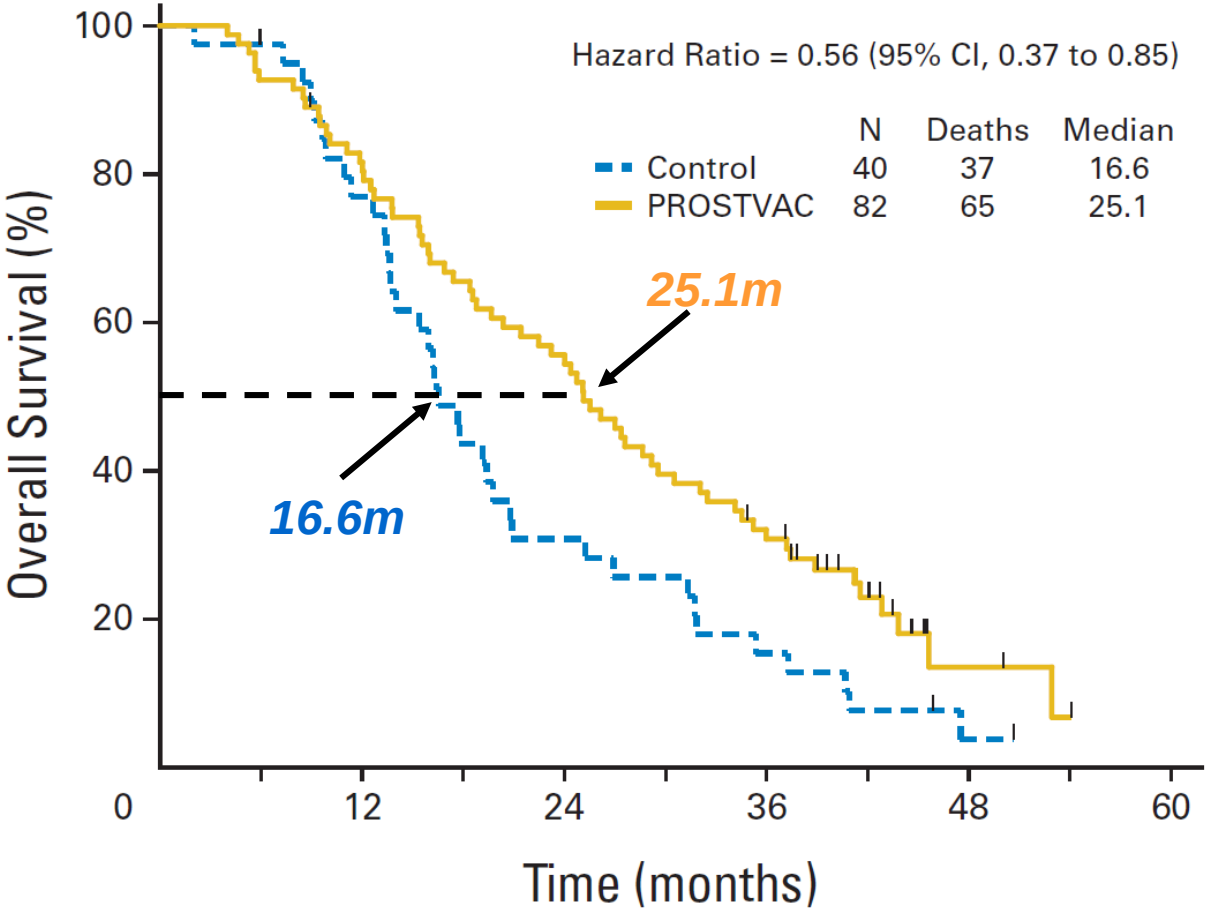
(n=125)

Objetivo primário: SG



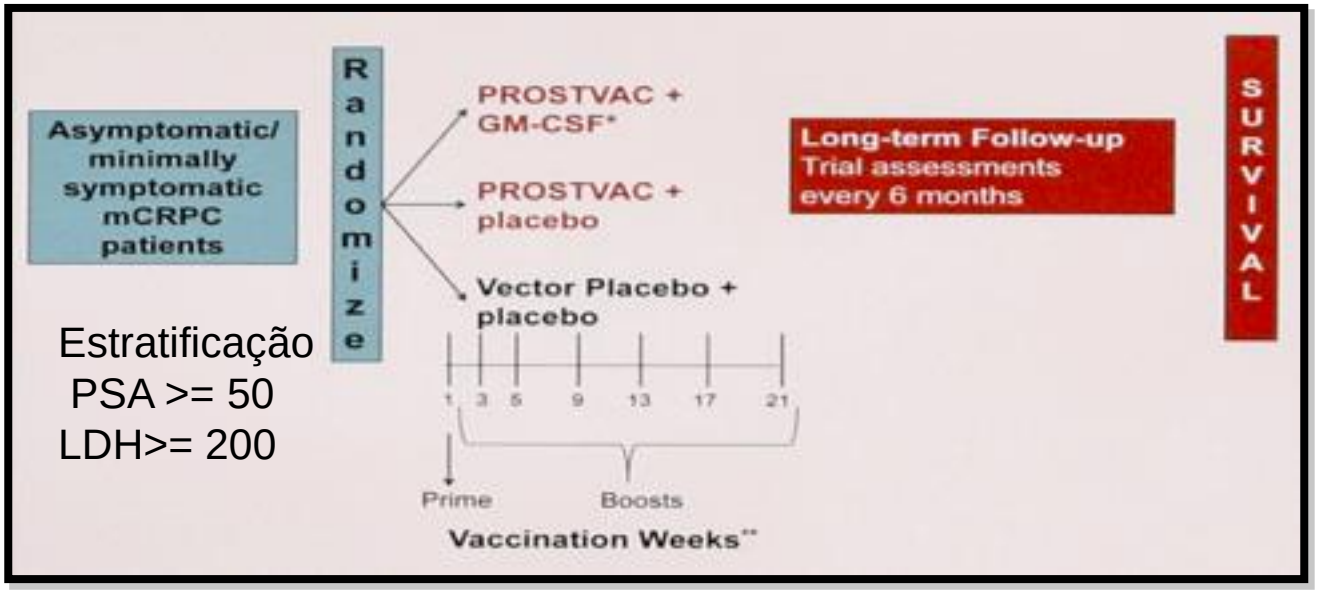
Kantoff PW, *J Clin Oncol* 2010:1099

PROSTVAC® - FASE II RANDOMIZADO
Sobrevida Global



Kantoff PW, *J Clin Oncol* 2010:1099

ESTUDO PROSPECT



- Fase III, duplo-cego
- QT naive, meta visceral excluído
- Desfecho primário: SG
- Resultados: inclusão terminada em 12-2014 (1200 pacientes)

J Clin Oncol 33, 2015 (suppl; abstr TPS5081

ESTUDO PROSPECT

Search

ABOUT US PIPELINE INVESTORS CAREERS

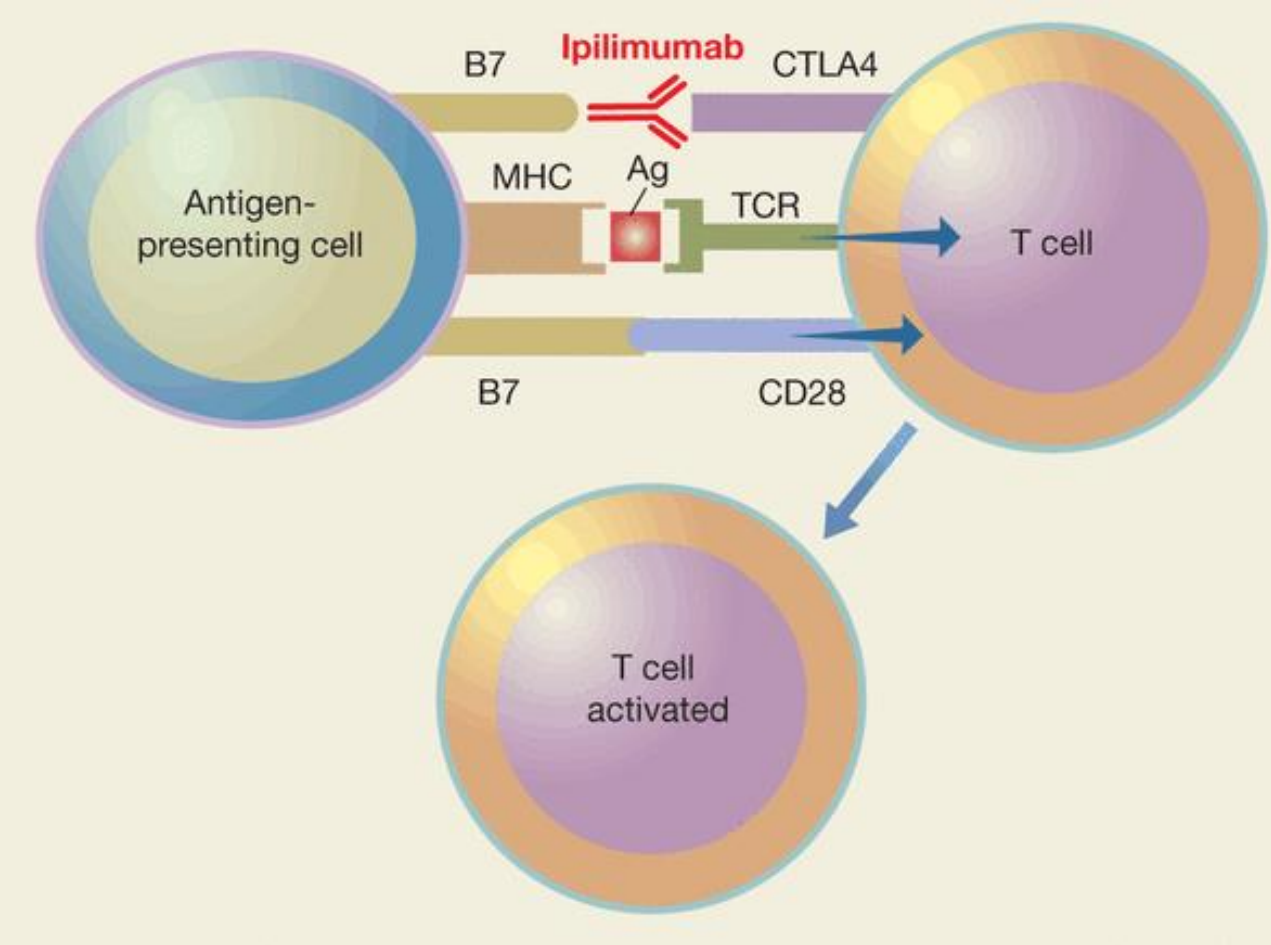
INDEPENDENT DATA MONITORING COMMITTEE RECOMMENDS DISCONTINUATION OF BAVARIAN NORDIC'S PHASE 3 STUDY OF PROSTVAC IN METASTATIC PROSTATE CANCER

- Conference call scheduled for 2:00 PM CEST / 8:00 AM EDT tomorrow, Friday, September

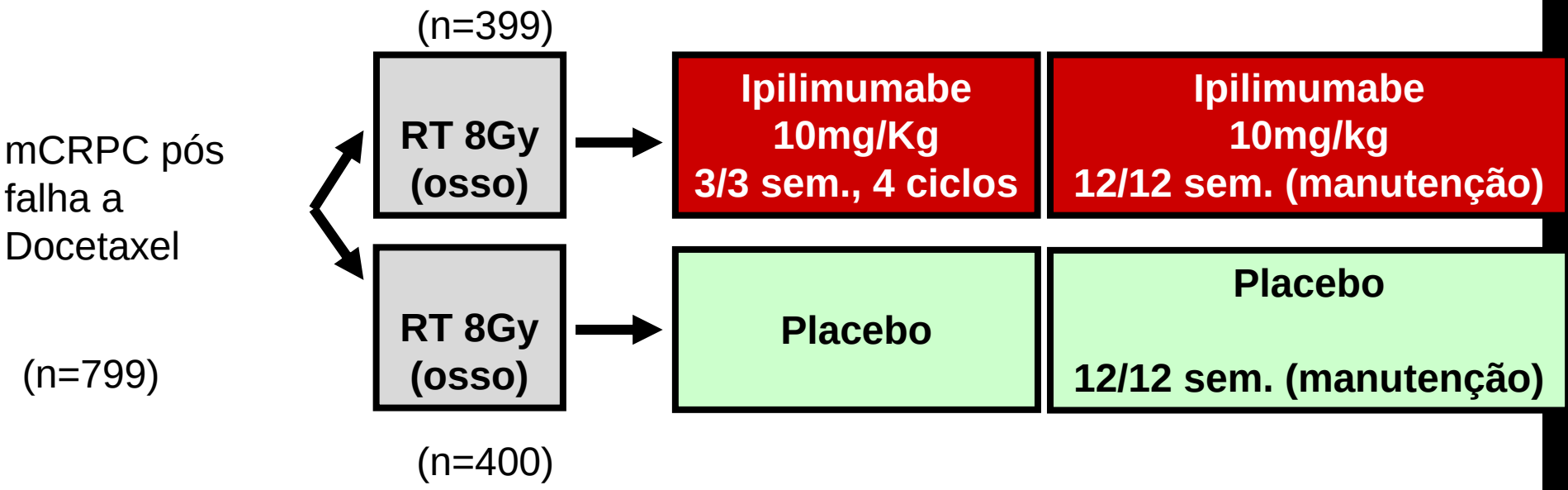
THIRD QUARTERLY REPORT 2017

J Clin Oncol 33, 2015 (suppl; abstr TPS5081

Ipilimumabe



mCRPC pós docetaxel
Ipilimumabe Vs. Placebo (Fase 3)

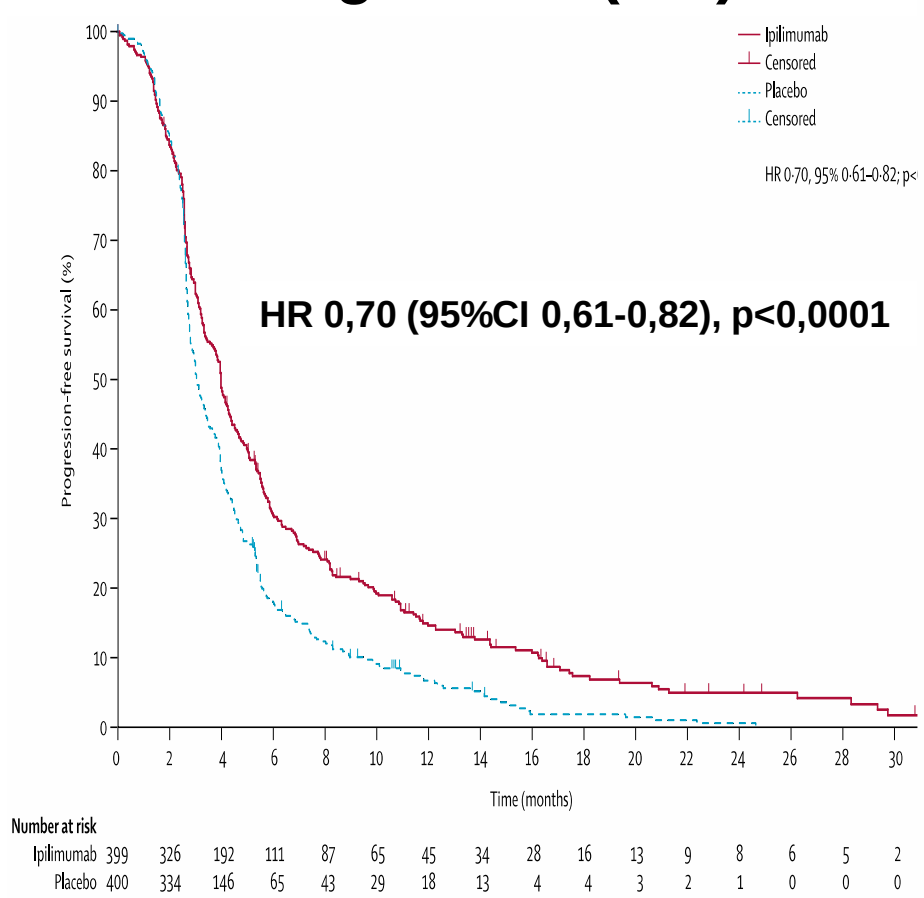


191 centros em 26 países

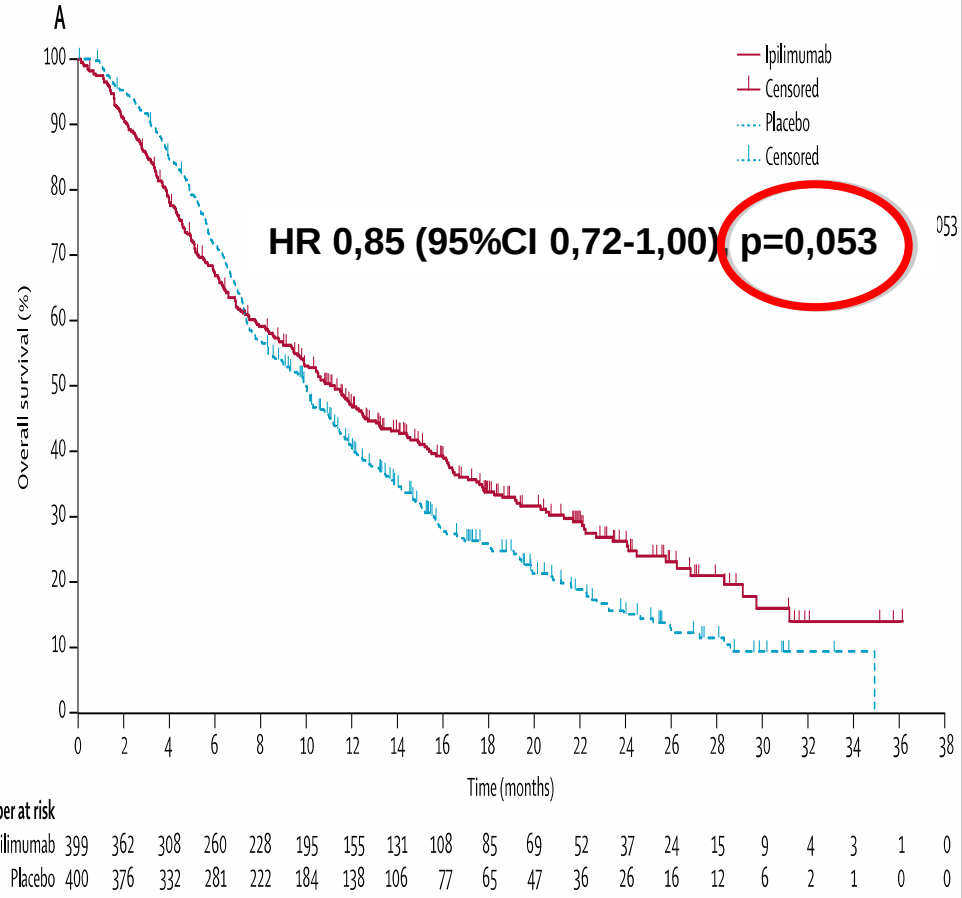
Kwon ED, et al. Lancet Oncol 15:700, 2014

mCRPC pós docetaxel Ipilimumabe Vs. Placebo (Fase 3)

Sobrevida Livre de Progressão (ITT)



Sobrevida Global (ITT)

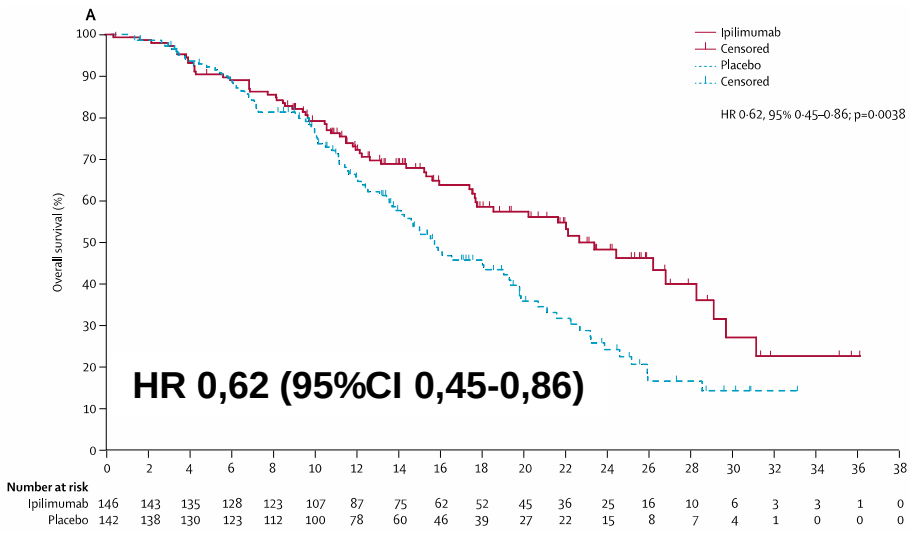


Kwon ED, et al. Lancet Oncol 15:700, 2014

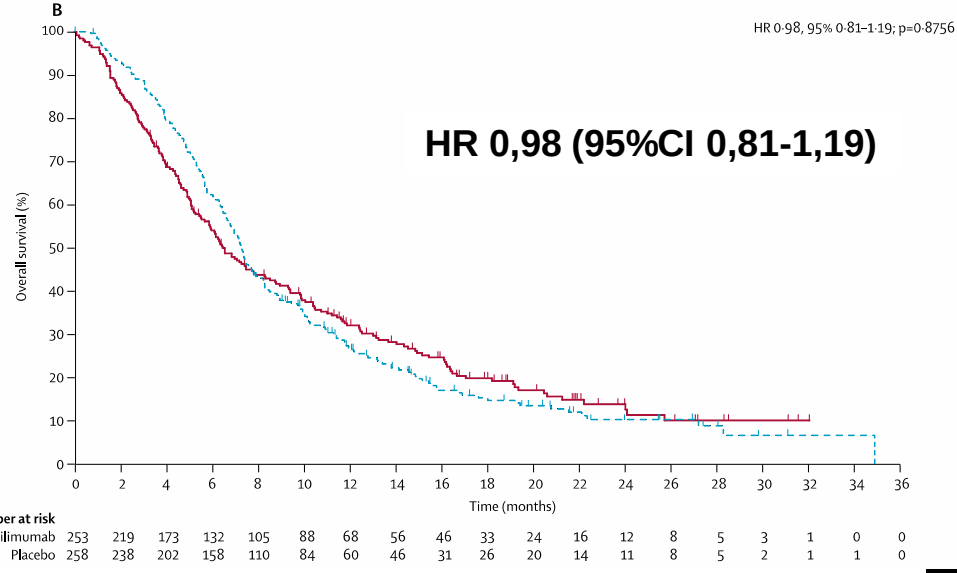
mCRPC pós docetaxel
Ipilimumabe Vs. Placebo (Fase 3)

SG de acordo com grupo prognóstico

Hb>11g/dL, FA<1,5x e sem M visceral



Hb<11g/dL OU FA>1,5x OU M visceral



Kwon ED, et al. Lancet Oncol 15:700, 2014

mCRPC pré docetaxel
Ipilimumabe Vs. Placebo (Fase 3)

JOURNAL OF CLINICAL ONCOLOGY

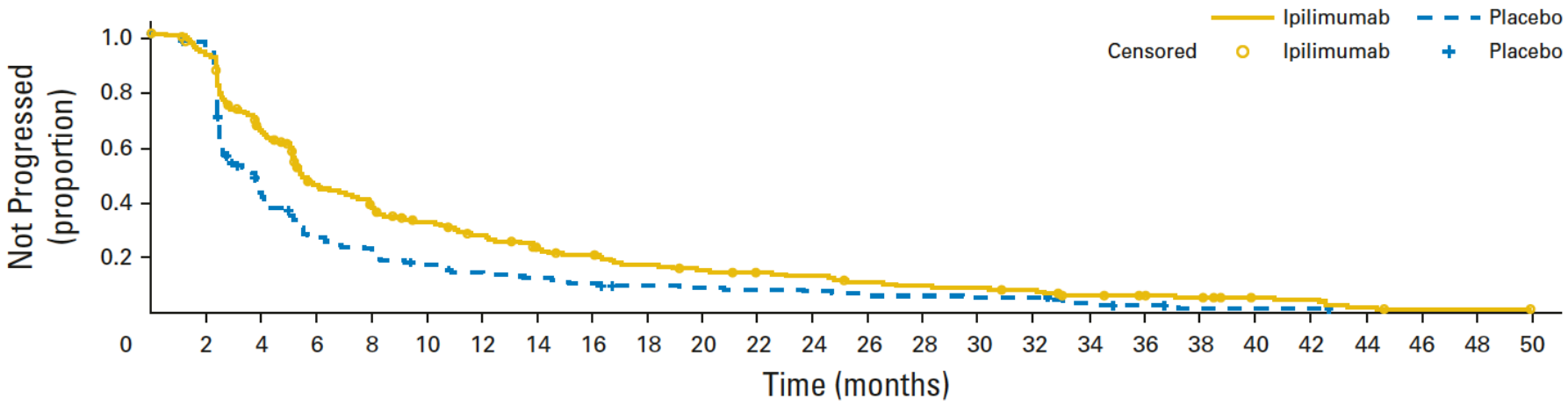
ORIGINAL REPORT

Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer

Tomasz M. Beer, Eugene D. Kwon, Charles G. Drake, Karim Fizazi, Christopher Logothetis, Gwenaelle Gravis, Vinod Ganju, Jonathan Polikoff, Fred Saad, Piotr Humanski, Josep M. Piulats, Pablo Gonzalez Mella, Siobhan S. Ng, Dirk Jaeger, Francis X. Parnis, Fabio A. Franke, Javier Puente, Roman Carvajal, Lisa Sengeløv, M. Brent McHenry, Arvind Varma, Alfonsus J. van den Eertwegh, and Winald Gerritsen

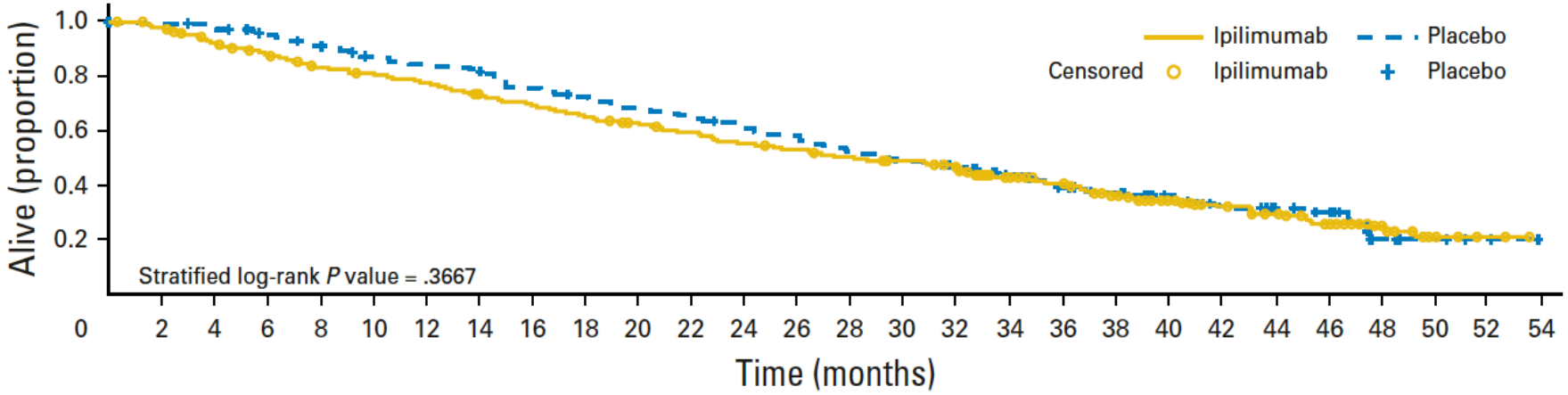
Beer TM, et al. J Clin Oncol 35:40, 2017

mCRPC pré docetaxel
Ipilimumabe Vs. Placebo (Fase 3)



No. at risk

Ipilimumab	400	371	258	173	149	118	97	80	71	56	49	44	41	33	29	27	24	17	13	12	7	6	3	1	1	0
Placebo	202	192	85	50	40	31	26	22	19	16	15	13	12	10	10	9	9	5	3	1	1	1	0			



No. at risk

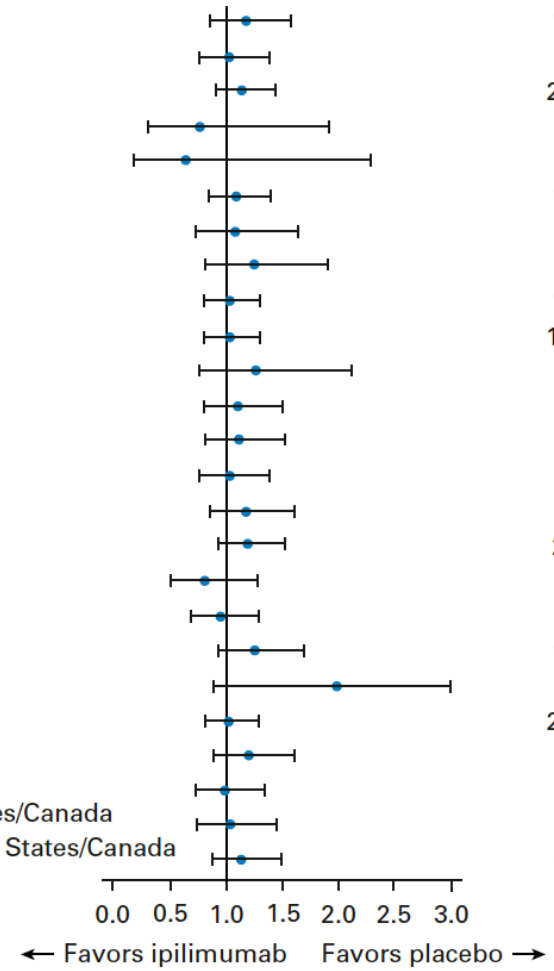
Ipilimumab	400	389	364	342	320	310	298	279	265	250	236	223	208	197	186	179	166	136	116	94	78	64	46	32	18	7	3	0
Placebo	202	198	195	186	175	166	161	155	142	136	128	122	113	108	98	92	85	74	59	53	41	33	25	19	6	4	2	0

Beer TM, et al. J Clin Oncol 35:40, 2017

mCRPC pré docetaxel Ipilimumabe Vs. Placebo (Fase 3)

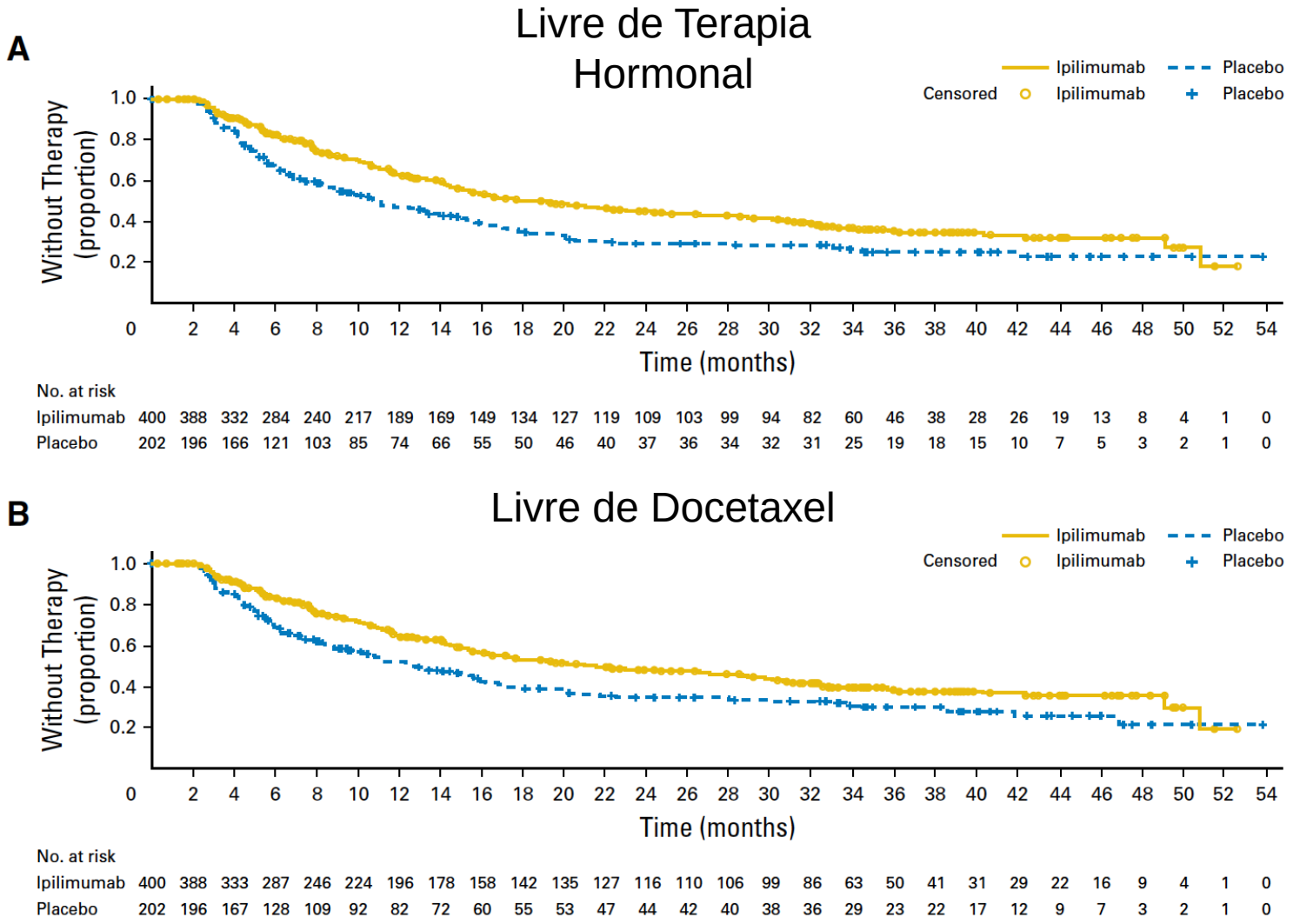
Sobrevida Global – Forrest Plot

Subgroup		Events/Randomly Assigned Patients (Ipilimumab *v* Placebo)	HR (95% CI)
Age	< 70 years	125/200 *v* 62/104	1.16 (0.85 to 1.57)
	≥ 70 years	129/200 *v* 64/98	1.02 (0.75 to 1.37)
Race	White	232/361 *v* 115/185	1.14 (0.91 to 1.42)
	Black	11/20 *v* 8/11	0.76 (0.31 to 1.91)
	Other	11/19 *v* 3/6	0.62 (0.17 to 2.28)
ECOG performance status	0	187/305 *v* 91/152	1.09 (0.85 to 1.40)
	1	67/95 *v* 35/50	1.08 (0.72 to 1.62)
Bisphosphonate use	Yes	60/99 *v* 34/62	1.25 (0.82 to 1.90)
	No	194/301 *v* 92/140	1.02 (0.79 to 1.30)
Alkaline phosphatase	< 1.5 x ULN	195/327 *v* 107/176	1.01 (0.80 to 1.28)
	≥ 1.5 x ULN	59/72 *v* 19/26	1.26 (0.75 to 2.12)
Gleason score	≤ 7	115/189 *v* 60/103	1.09 (0.80 to 1.49)
	> 7	128/192 *v* 60/91	1.12 (0.82 to 1.52)
LDH	< 200 IU/L	135/237 *v* 69/118	1.02 (0.76 to 1.36)
	≥ 200 IU/L	119/163 *v* 57/84	1.17 (0.86 to 1.61)
Presence of bone metastases	Yes	204/312 *v* 98/159	1.19 (0.94 to 1.52)
	No	49/85 *v* 27/39	0.80 (0.50 to 1.28)
Presence of measurable disease	Yes	108/169 *v* 64/96	0.94 (0.69 to 1.28)
	No	145/228 *v* 61/102	1.25 (0.92 to 1.68)
Hemoglobin	< 11 g/dL	25/31 *v* 9/14	1.98 (0.88 to 4.43)
	≥ 11 g/dL	227/364 *v* 116/183	1.02 (0.82 to 1.28)
Pain	None	144/225 *v* 63/113	1.20 (0.89 to 1.61)
	Minimal	110/175 *v* 63/89	0.98 (0.72 to 1.34)
Region	United States/Canada	89/136 *v* 49/70	1.02 (0.72 to 1.45)
	Non–United States/Canada	165/264 *v* 77/132	1.13 (0.86 to 1.48)



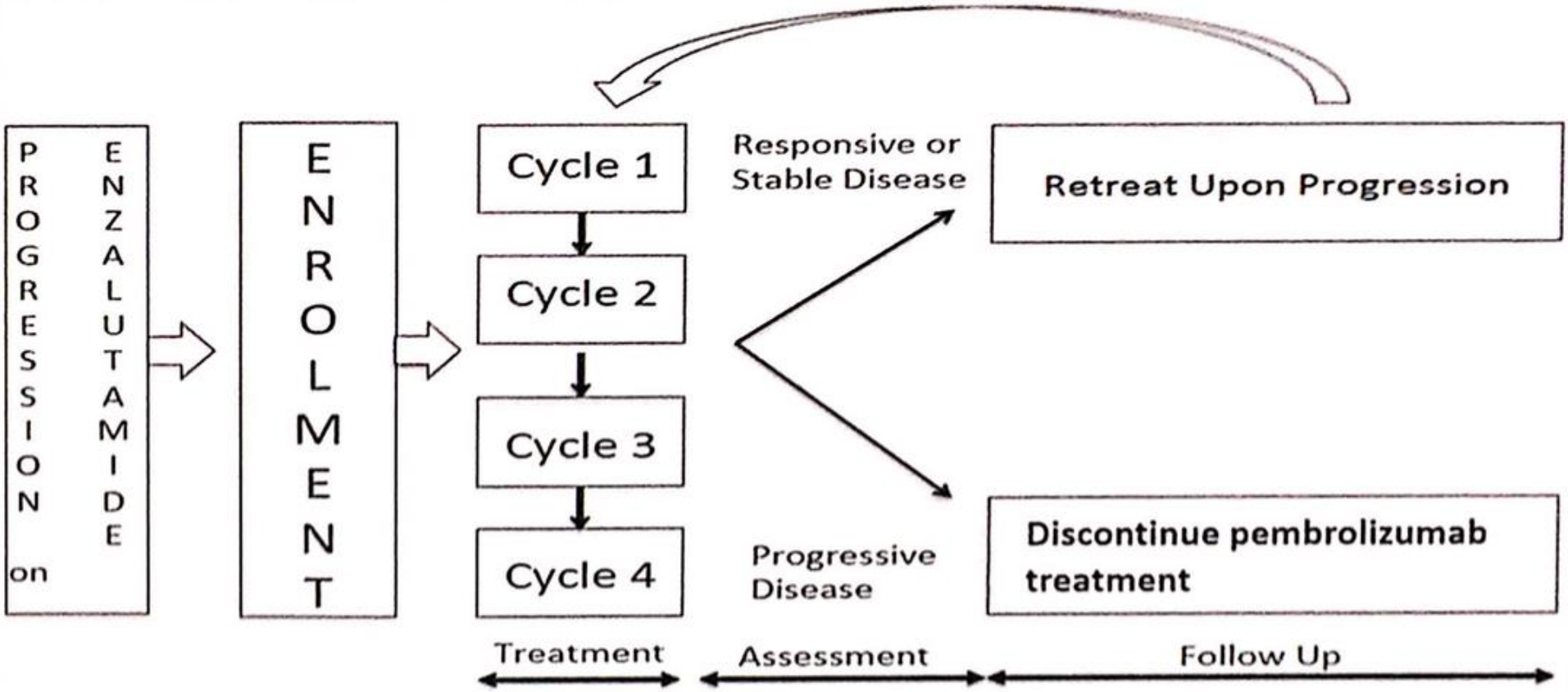
Beer TM, et al. J Clin Oncol 35:40, 2017

mCRPC pré docetaxel Ipilimumabe Vs. Placebo (Fase 3)



Beer TM, et al. J Clin Oncol 35:40, 2017

Adição de Pembrolizumabe em mCRPC pós falha de Enzalutamida



Pembrolizumabe 200mg EV a cada 3 semanas (4 doses) com retratamento
Enzalutamida continuada pós progressão

Graff JN, et al. ESMO 2016: Abstract 719O.

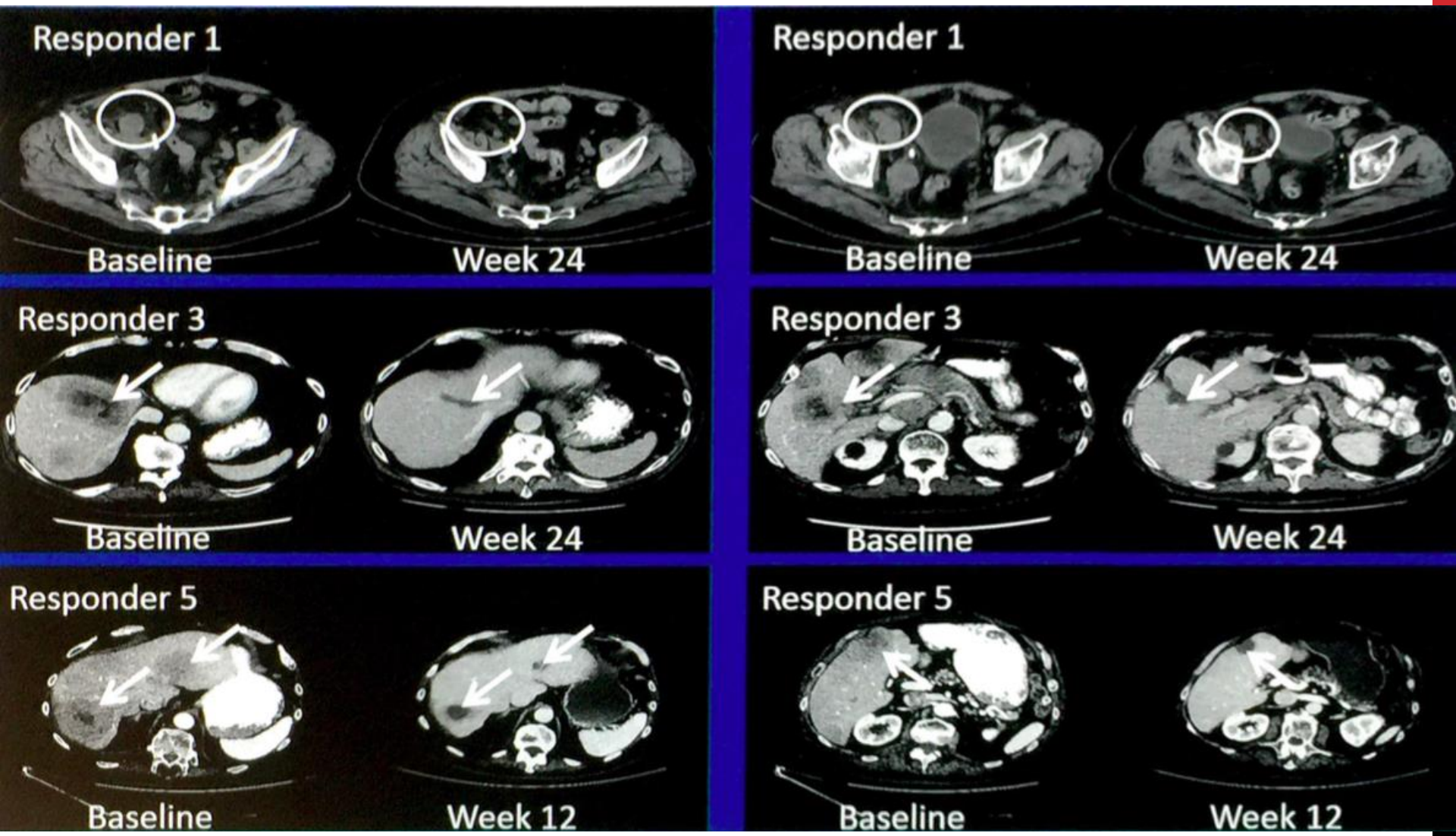
Adição de Pembrolizumabe em mCRPC pós falha de Enzalutamida

Responder	Cycle 1	PSA (ng/ml) every 3-weeks and nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI
1	April 2015	**70.65** → 11.11 → 1.18 → 0.11 → **0.08**	Yes (lymph)	PR	present
2	October 2015	**46.09** → 41.22 → 12.99 → 9.89 → **0.02**	No	n/a	n/a
3	January 2016	**2502.75** → 1.26 → 0.07 →0.01 → **<0.01**	Yes (liver)	PR	absent
4	March 2016	**82.43** → 17.34 → 0.3 → **0.01**	No	n/a	n/a
5	June 2016	**250** → 88.69 → 5.1 → 0.43 → **0.18***	Yes (liver)	PR	pending

5 de 27 pacientes (19%) com queda confirmada de PSA
4 de 19 pacientes (21%) com DE >6meses sem resposta de PSA

Graff JN, et al. ESMO 2016: Abstract 719O.

Adição de Pembrolizumabe em mCRPC pós falha de Enzalutamida



Graff JN, et al. ESMO 2016: Abstract 719O.

Durvalumab + Olaparib em mCRPC

Olaparib + Durvalumab in mCRPC

- Multi-cohort study (*NCT02484404*)
- mCRPC patients that have been treated with enzalutamide and/or abiraterone
  - olaparib 300 mg tablets by mouth every 12 hours
  - durvalumab (anti-PD-L1 inhibitor) 1500 mg IV every 28 days

PI: Dr. Jung-Min Lee

Karzai F, et al. ASCO GU 2018

Durvalumab + Olaparib em mCRPC

Protocol Mandated On-Study Biopsy Results

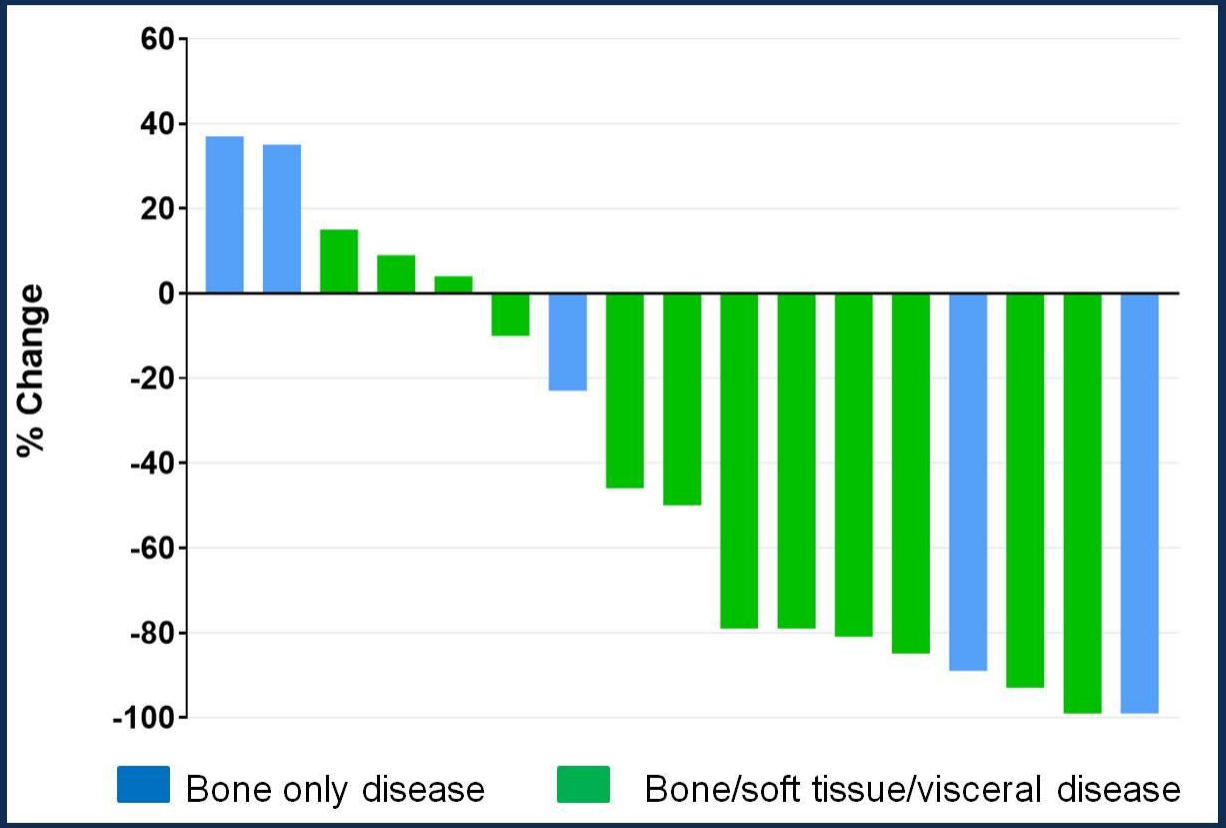
Patient Number	DNA Damage Repair (DDR) Pathway Mutation(s)	Other Genomic Aberration(s)	Maximum % PSA Decline
1	BRCA2	None	-79%
2	BRCA2	ASXL1	-99%
3	None	TP53, RB1	15%
4	None	AR amplification	35%
5	None	MYD88, CCND3, BIRC3	-79%
6	BRCA2 (germline)	SPOP, 13q deletion, AR amplification	-89%
7	Insufficient specimen	Insufficient specimen	-99%
8	BRCA2 (germline)	13q deletion, PKP2	-93%
9	Insufficient specimen	Insufficient specimen	-23%
10	BRCA2	TP53, KAT6A	-85%
11	BRCA2 (germline)	Copy number loss and allelic imbalance on 13q	-50%
12	None	RYR2, PIK3CA	37%
13	Insufficient specimen	Insufficient specimen	9%
14	BRCA2	HRAS	-80%
15	None	PIK3CA, ADGRB3, TP53	4%
16	None	TP53, STAG1	-46%
17	None	BRAF, AR amplification, ASXL1, MYH11	-10%

- OncoVar DNA sequencing analysis of 500+ genes done by Dr. Paul Meltzer's Lab (Genetics Branch, NCI)
- All mutations are somatic unless otherwise noted

Karzai F, et al. ASCO GU 2018

Durvalumab + Olaparib em mCRPC

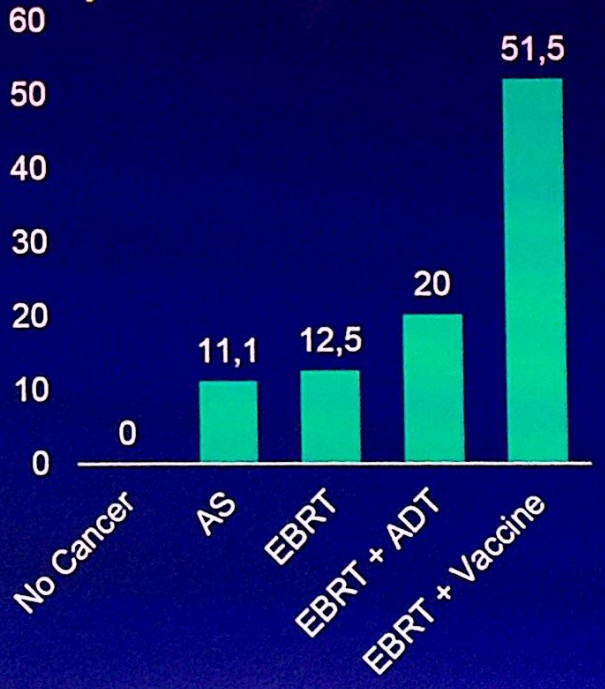
Maximum Decline in PSA (n=17)



Karzai F, et al. ASCO GU 2018

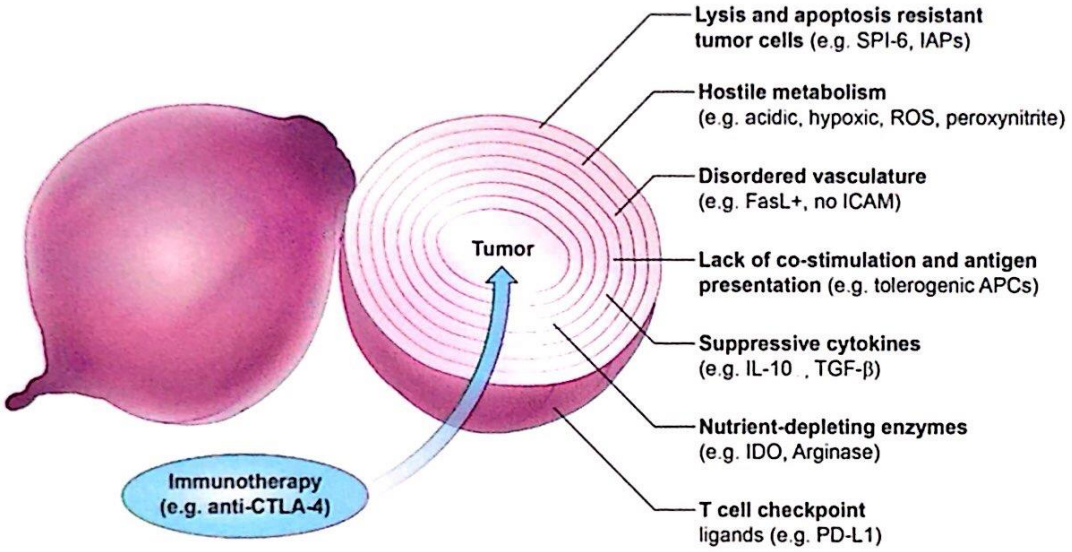
Anti-tumor Immune Response More Efficient with Vaccine (Prostvac) vs. SOC

	Cancer-free controls (n = 15)	AS (n = 9)	EBRT (no vaccine; n = 8)	EBRT + ADT (n = 15)	EBRT+ Vaccine (n = 33)
Western blot	0 (0%)	1 (11.1%)	1 (12.5%)	3 (20.0%)	15 (45.5%)
Antigen array	0 (0%)	1 (11.1%)	0 (0%)	2 (13.3%)	7 (21.2%)
Overall	0 (0%)	1 (11.1%)	1 (12.5%)	3 (20.0%)	17 (51.5%)



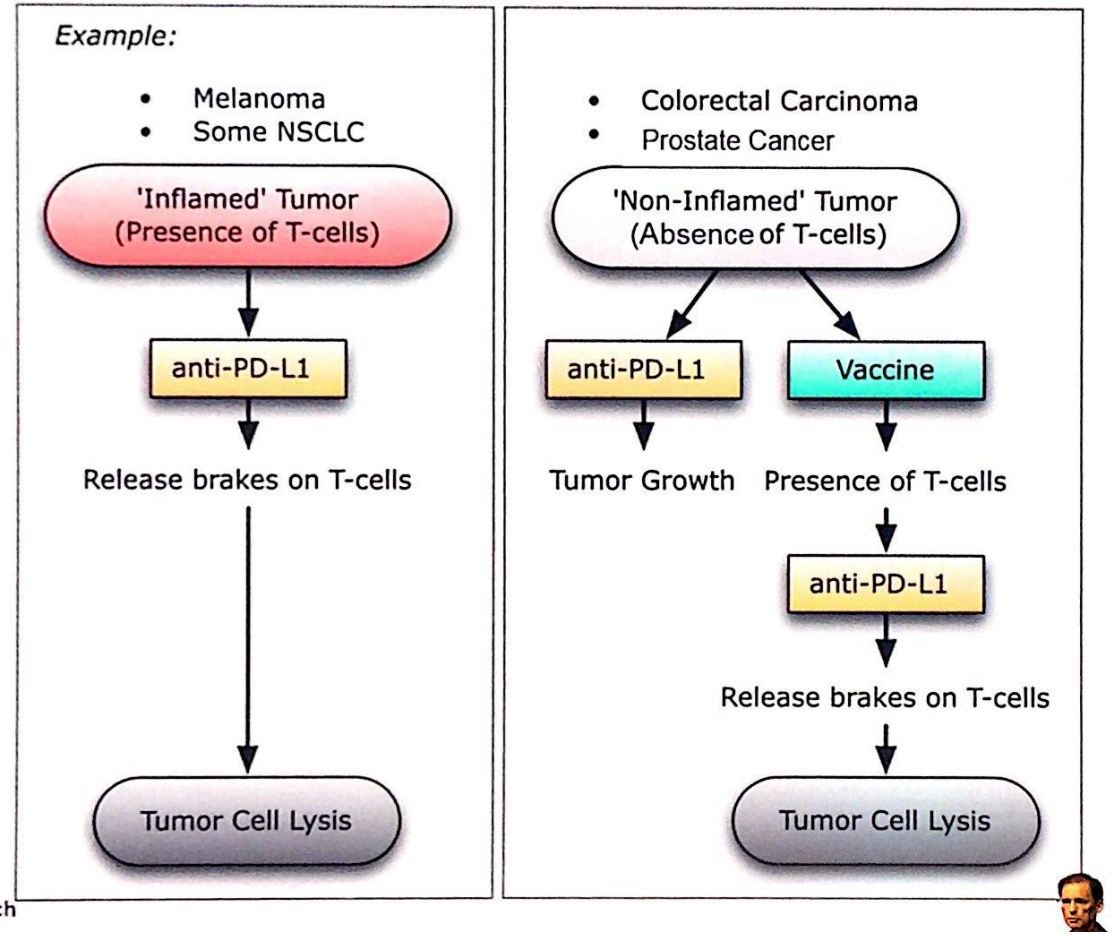
Nesslinger... Schlom, Gul... et al, *Clin Ca Res*, 2010

Multi-layered immunosuppression



- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can "peel back" the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor

Working Model for T-cell infiltration and Immunotherapy Implications



Expressão de PD-L1 em câncer de pênis

Total n=37
62,2% PD-L1 + (n=23)

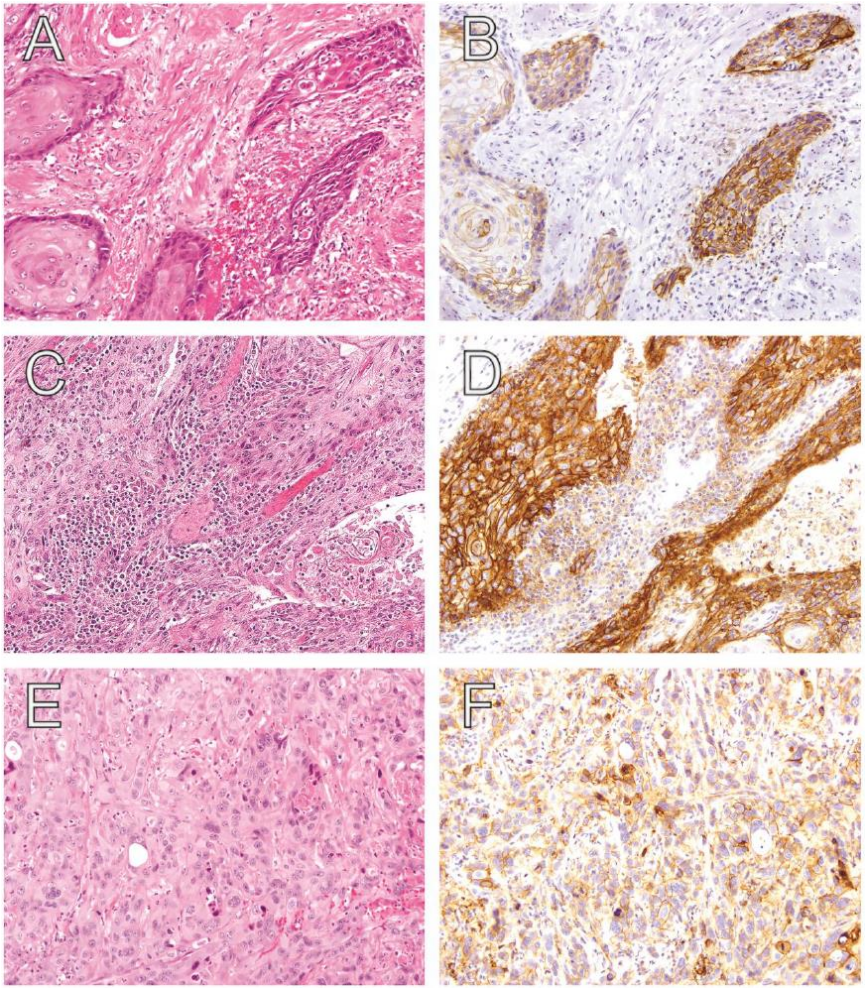


Table 1. Association of primary tumor PD-L1 expression with clinicopathologic parameters.

Parameter		PD-L1-positive (N = 23)	PD-L1-negative (N = 14)	*P*-value
Age	≤65 years	11 (47.8%)	9 (64.3%)	0.498
	>65 years	12 (52.2%)	5 (35.7%)	
Circumcision status	Yes	4 (22.2%)	2 (18.2%)	1.000
	No	14 (77.8%)	9 (81.8%)	
Histologic subtype	Usual	18 (78.3%)	6 (42.9%)	**0.040**
	Other[1]	5 (21.7%)	8 (57.1%)	
Histologic grade	Well	4 (17.4%)	6 (42.9%)	0.197
	Moderate	11 (47.8%)	6 (42.9%)	
	Poor	8 (34.8%)	2 (14.2%)	
HPV status	Positive	2 (10.5%)	3 (21.4%)	0.629
	Negative	17 (89.5 %)	11 (78.6%)	
p16 expression	Positive	5 (22.7%)	5 (38.5%)	0.444
	Negative	17 (77.3%)	8 (61.5%)	
Pathologic stage	pT1	4 (19.0%)	6 (46.2%)	0.130
	pT2-4	17 (81.0%)	7 (53.8%)	
Lymph node status	pN0/NX	11 (52.4%)	12 (92.3%)	**0.024**
	pN1-3	10 (47.6%)	1 (7.7%)	
Clinical stage	I	4 (19.0%)	7 (50.0%)	0.073
	II-IV	17 (81.0%)	7 (50.0%)	
Local recurrence	Yes	2 (10.0%)	0 (0.0%)	0.501
	No	18 (90.0%)	14 (100.0%)	
Distant progression	Yes	5 (25.0%)	0 (0.0%)	0.063
	No	15 (75.5%)	14 (100.0%)	
Cancer-specific mortality	Yes	7 (31.8%)	0 (0.0%)	**0.029**
	No	15 (68.2%)	14 (100.0%)	

Udager AM, et al. Ann Oncol 27:1706, 2016.

Cabozantinibe-Nivolumabe-Ipilimumabe Carcinoma Geniturinários

MADRID 2017 ESMO congress

Study design (NCT02496208)

Key Eligibility Criteria:

- Histologically confirmed diagnostic of genitourinary (GU) malignancy
- Patients with metastatic GU malignancy who had disease progression on at least one standard therapy or there must be no standard treatment that prolongs survival
- Karnofsky performance status ≥ 70%
- One evaluable site of disease or bone disease by NaF PET/CT

Treatment

Part 1: 28 day cycle

Cabozantinib PO daily
+
Nivolumab IV every 2 weeks

→

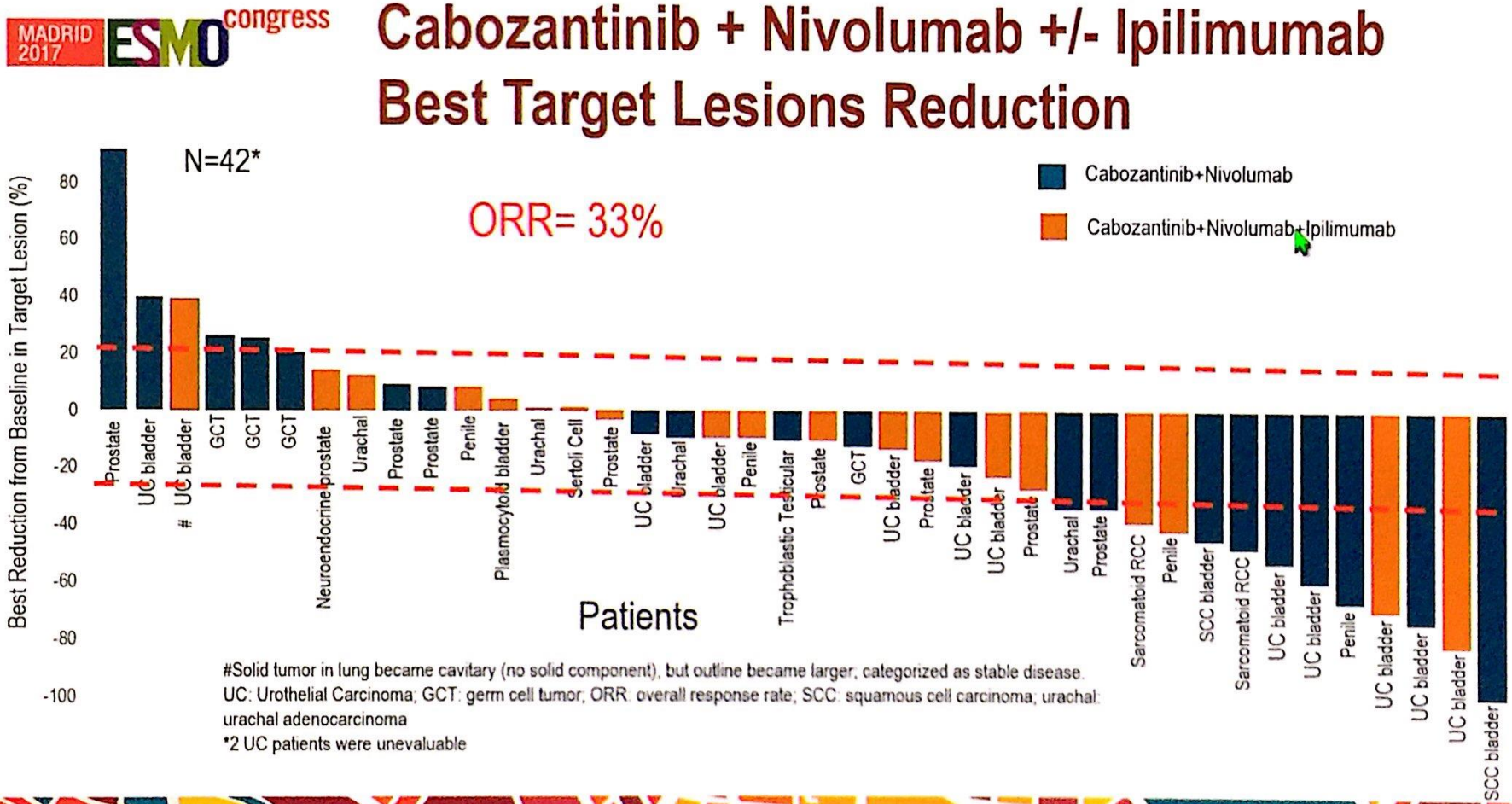
Part 2: 21 day cycle

Cabozantinib PO daily
+
Nivolumab IV every 2 weeks
+
Ipilimumab IV every 3 weeks
x 4 doses only

7

Nadal RM, et al. ASCO GU 2018: Abstr. 515.

Cabozantinibe-Nivolumabe-Ipilimumabe Carcinoma Geniturinários



Nadal RM, et al. ASCO GU 2018: Abstr. 515.

Cabozantinibe-Nivolumabe-Ipilimumabe Carcinoma Geniturinários

MADRID 2017 ESMO congress

Response by tumor type and regimen

*Two urothelial carcinoma patients were no evaluable by RECIST v 1.1

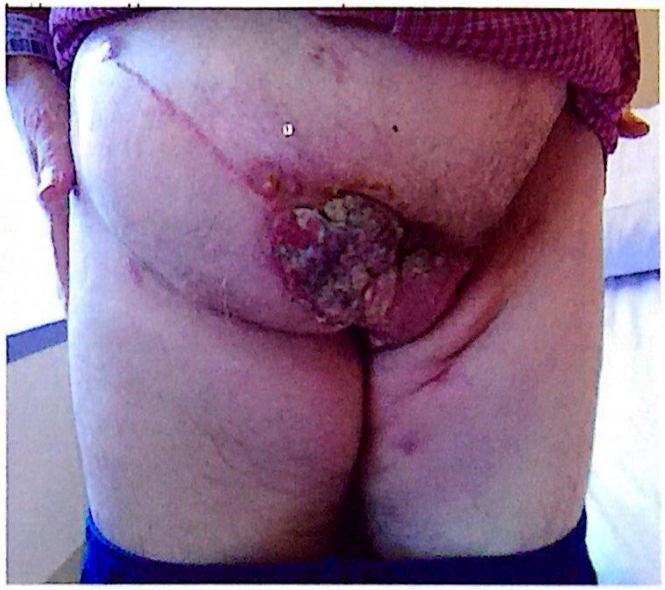
	Total N	Stable Disease % (N)	Partial Response % (N)	Complete Response % (N)	ORR* (%, N)
Tumor Type	**42***	**50 (20)**	**25 (10)**	**8 (3)**	**33 (13)**
Urothelial carcinoma	15*	38 (5)	23 (3)	15 (2)	38 (5)
Urachal adenocarcinoma	4	75 (3)	25 (1)	-	25 (1)
Squamous cell carcinoma of the bladder	2	-	50 (1)	50 (1)	100 (2)
Castration-resistant prostate cancer (1 pts small cell PC)	9	67 (6)	11 (1)	-	11 (1)
Renal cell carcinoma—sarcomatoid	2		100 (2)		100 (2)
Penile cancer	4	50 (2)	50 (2)	-	50 (2)
Trophoblastic	1	100 (1)	-	-	-
Germ cell tumor	4	25 (1)	-		-
Sertoli	1	100 (1)	-	-	-
Combination					
CaboNivo	24	43 (10)	30 (7)	8 (2)	38 (9)
CaboNivolpi	18	59 (10)	17 (3)	6 (1)	22 (4)

Nadal RM, et al. ASCO GU 2018: Abstr. 515.

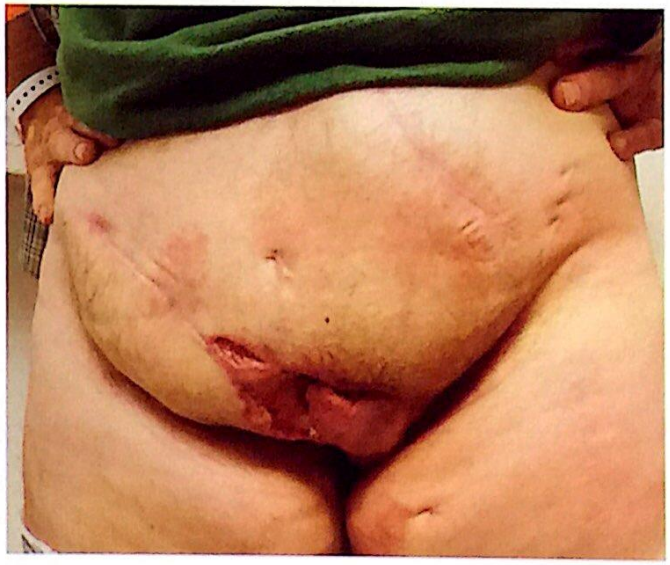
Cabozantinibe-Nivolumabe-Ipilimumabe Carcinoma Geniturinários

MADRID 2017 ESMO congress

Penile cancer-# 3 (part 2-CaboNivolpi)



08JUL2016 Cycle 1 Day 1



12SEP2016 Cycle 4 Day 1

Courtesy of Dr. Amir Mortazavi, OSU

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Nadal RM, et al. ASCO GU 2018: Abstr. 515.

CONCLUSÕES

- **ADENOCARCINOMA DE PRÓSTATA**
  - Vacinas: Sipuleucel-T (aprovado FDA)
  - Resultados preliminares com anti-PD1 promissores
  - Algum papel para Ipilimumabe, mas ainda preliminar
    - Biomarcadores?

- **CÂNCER DE PÊNIS**
  - Maioria dos tumores expressão PD-L1
  - Resultados preliminares promissores, com alta taxa de RO

- **TUMOR GERMINATIVO**
  - ?!?!