

Grupo
ONCOCLÍNICAS
Sua vida. Nossa vida.



**DESTAQUES
ASCO TUMORES
UROLÓGICOS**

○ Apresentação

A Sociedade Americana de Oncologia Clínica (ASCO) foi fundada em 1964 e, desde então, tornou-se a principal organização voltada para profissionais que lidam diariamente com o câncer em todo o mundo.

Sua missão é promover o combate à doença, habilitando seus membros a oferecer o que existe de melhor em termos de tratamento para os seus pacientes. Para isso, investe maciçamente em pesquisa e é reconhecida por promover educação continuada de alto nível.

Todos os anos, a ASCO organiza seu Congresso, reunindo os mais renomados profissionais do mundo em todas as áreas da Oncologia. O contato direto com profissionais de destaque, o intenso compartilhamento de informações, assim como a troca de experiências cotidianas criam um ambiente favorável para o aprendizado.

O Grupo Oncoclínicas não poderia deixar de estar presente nesse evento, trazendo para seus pacientes e parceiros todas as novidades apresentadas. Em linha com nosso objetivo de nos transformar no melhor grupo de Oncologia do país, estivemos presentes com mais de 80 Oncologistas em Chicago, coletando os principais e mais atualizados dados científicos.

E por meio do Instituto Oncoclínicas conseguimos compilar as informações mais relevantes, transformando-as em um *slide kit* didático, versátil e inovador. É com prazer que disponibilizamos a vocês, nossos parceiros, o “Melhor da ASCO 2017”.

Instituto Oncoclínicas



CONFLITOS DE INTERESSE

Esses slides estão isentos de conflitos de interesses e possuem finalidade essencialmente educacional.

ROTEIRO

1. CÂNCER DE PROSTATA

Primeira linha tumores alto risco: LATITUDE E STAMPEDE

Tempo de Hormoniterapia: 18 x 36 meses

2. CÂNCER RENAL

Tratamento adjuvante: PROTECT

3. CÂNCER DE BEXIGA

Imunoterapia: KEYNOTE-045



DESTAQUES ASCO 2017

CÂNCER DE PRÓSTATA



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LATITUDE: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

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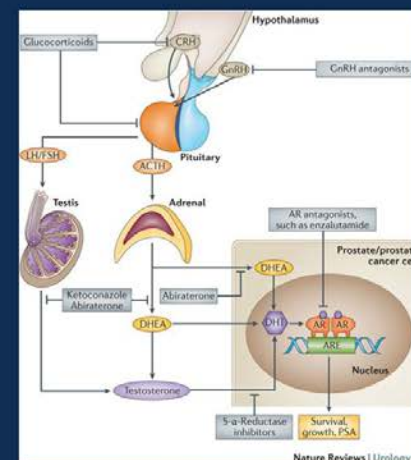
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De novo metastatic prostate cancer

- Metastatic castration-naïve prostate cancer (mCNPC) incidence is¹⁻⁵:
 - ~3% in US and rising;
 - ~6% across Europe
 - ~4-10% in Latin America
 - ~60% in Asia-Pacific
- Historically, androgen deprivation therapy (ADT) has been the standard of care⁶
- Most men with metastases progress to mCRPC largely driven by reactivation of AR signaling⁶



Narayanan S, et al. *Nat Rev Urol*. 2016;13:47-60, with permission from Nature Publishing Group.

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1. Weiner AB, et al. *Prostate Cancer Prostatic Dis*. 2016;19:395-397. 2. Buzzoni C, et al. *Eur Urol*. 2015;68:885-890. 3. Chen R, et al. *Asian J Urol*. 2014;1:15-29. 4. Ito K. *Nat Rev Urol*. 2014;11:15-29. 5. Nardi AC. *Int Braz J Urol*. 2012;38:155-166. 6. Yamaoka M, et al. *Clin Cancer Res*. 2010;16:4319-4324.

2

- Pacientes com câncer de próstata metastático ao diagnóstico são pacientes não tão comuns, mas com prognóstico mais reservado.

ADT + docetaxel: a new standard of care for men with mCNPC and high metastatic burden (2015)

Overall Survival	ADT + DOC	ADT	HR (95% CI)	P Value
	Median (mos)	Median (mos)		
GETUG-15 ¹	62.1	48.6	0.88 (0.68-1.14)	0.3
CHAARTED ²	57.6	47.2	0.73 (0.59-0.89)	0.0018
STAMPEDE ³	60	45	0.76 (0.62-0.92)	0.005

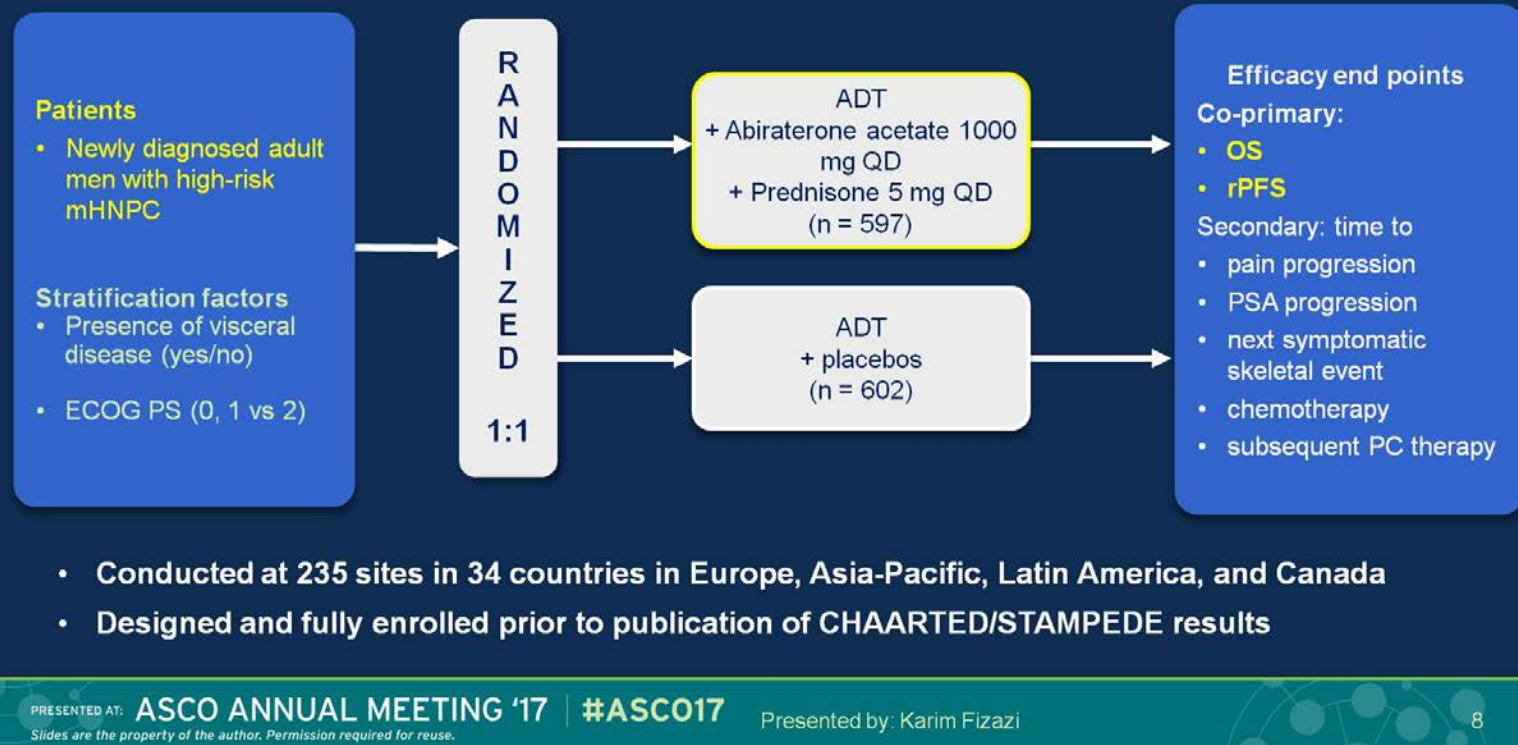


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1. Gravis G, et al. *Eur Urol*. 2016;70:256-262. 2. Sweeney C, et al. *N Engl J Med*. 2015;373:737-748; Sweeney C, et al. *Ann Oncol*. 2016;27(Suppl 6):243-265. 3. James N, et al. *Lancet*. 2016;387:1163-1177. 3 and Vale C, et al. *Lancet Oncol* 2016;17:243-256.

- Há 2 anos já é estabelecido que a quimioterapia com docetaxel associada a terapia de deprivação hormonal é o tratamento padrão para este perfil de pacientes

Overall study design of LATITUDE



- LATITUDE buscou a abordagem destes pacientes de alto risco, usando a abiraterona ao invés de docetaxel.

Treatment arms were well balanced

	ADT + AA + P (n = 597)	ADT + Placebos (n = 602)
Median age, years (range)	68.0 (38-89)	67.0 (33-92)
Gleason score ≥ 8 at initial diagnosis	98%	97%
Patients with ≥ 3 bone metastases at screening	98%	97%
Extent of disease		
Bone	97%	98%
Liver	5%	5%
Lungs	12%	12%
Node	47%	48%
Baseline pain score (BPI-SF Item 3)		
0-1	50%	50%
2-3	22%	24%
≥ 4	29%	27%

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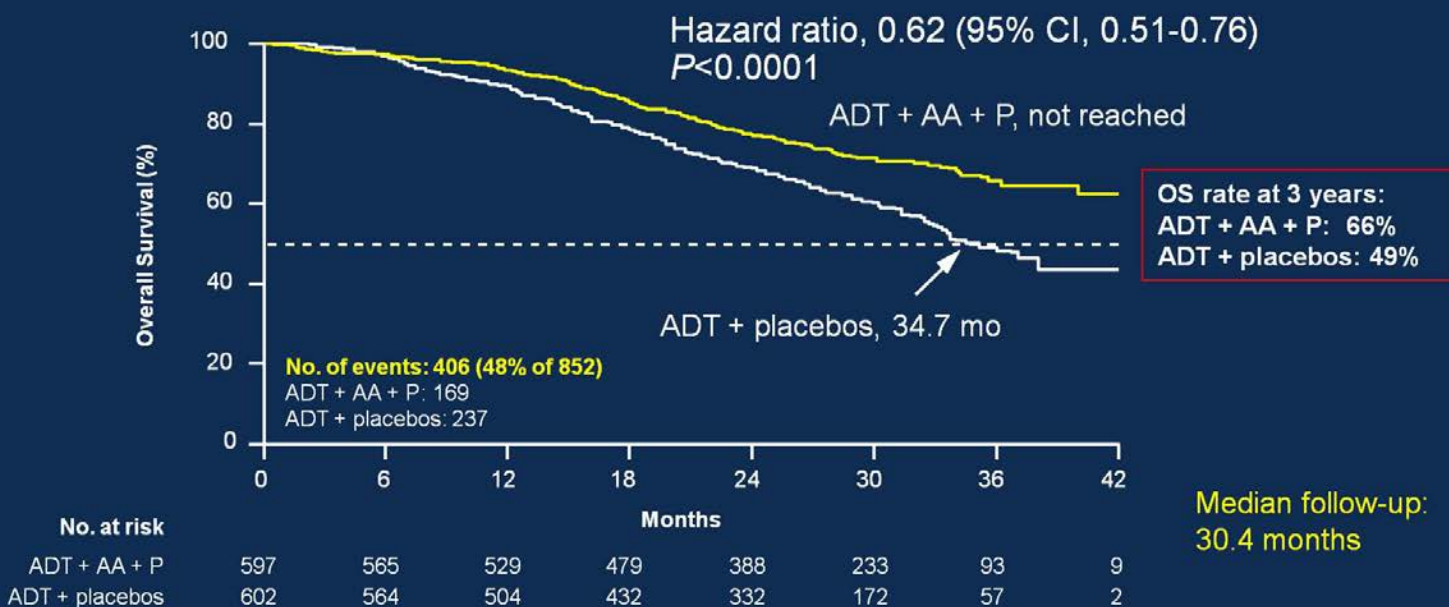
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10

- Pacientes de alto risco, e diferentemente do CHAARTED praticamente todos os pacientes eram gleason 8 ou mais.

Statistically significant **38%** risk reduction of death



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11

- Estudo francamente positivo para sobrevida global!

OS benefit consistently favorable across subgroups



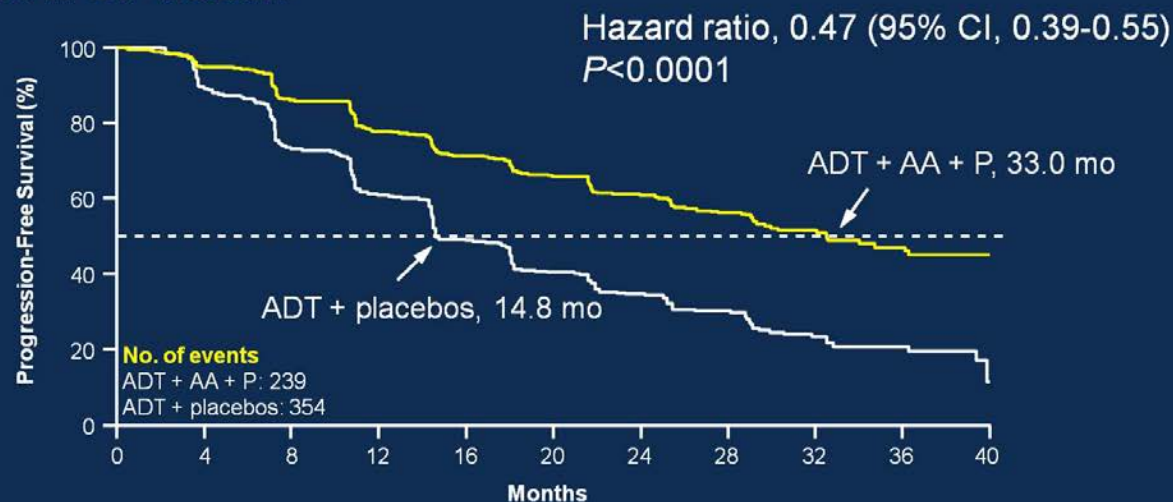
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12

- Estudo positivo em todos os subgrupos, inclusive nos pacientes com doença visceral.

Statistically significant **53%** risk reduction of radiographic progression or death



No. at risk											
ADT + AA + P	597	533	464	400	353	316	251	177	102	51	21
ADT + placebos	602	488	367	289	214	168	127	81	41	17	7

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- Estudo positivo em todos os desfechos, primários e secundários.

Statistically significant improvement in all secondary end points

Secondary End Points	ADT + AA + P (n = 597)	ADT + placebos (n = 602)	HR (95% CI)	P Value
	Median (months)	Median (months)		
Time to PSA progression	33.2	7.4	0.30 (0.26-0.35)	<0.0001
Time to pain progression	NR	16.6	0.70 (0.58-0.83)	<0.0001
Time to next symptomatic skeletal event	NR	NR	0.70 (0.54-0.92)	0.0086
Time to chemotherapy	NR	38.9	0.44 (0.35-0.56)	<0.0001
Time to subsequent prostate cancer therapy	NR	21.6	0.42 (0.35-0.50)	<0.0001

NR = not reached.

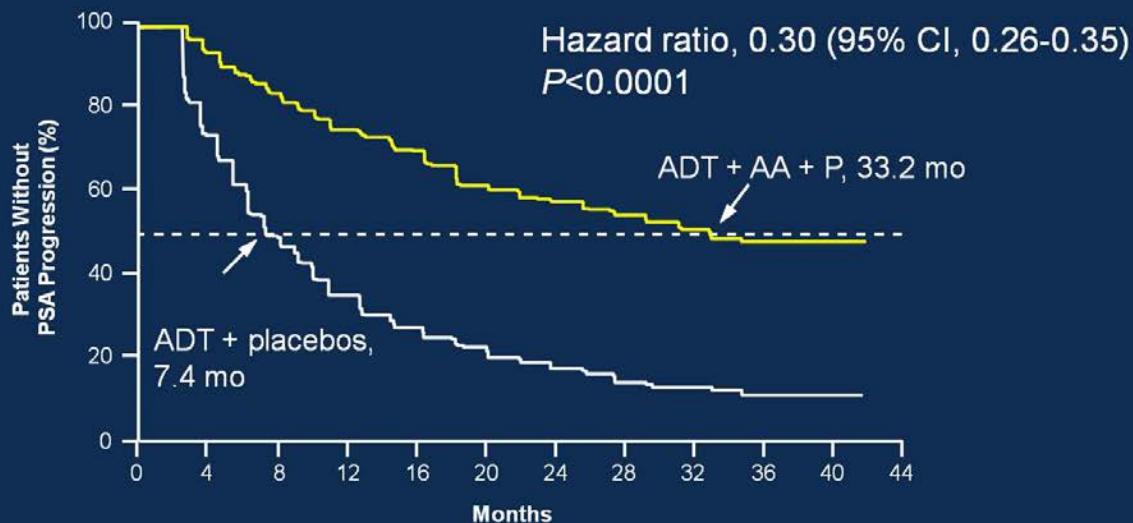
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14

Statistically significant **70%** risk reduction of time to PSA progression



No. at risk												
ADT + AA + P	597	520	447	379	340	285	227	162	95	48	18	0
ADT + placebos	602	393	250	172	129	102	65	33	19	8	5	0

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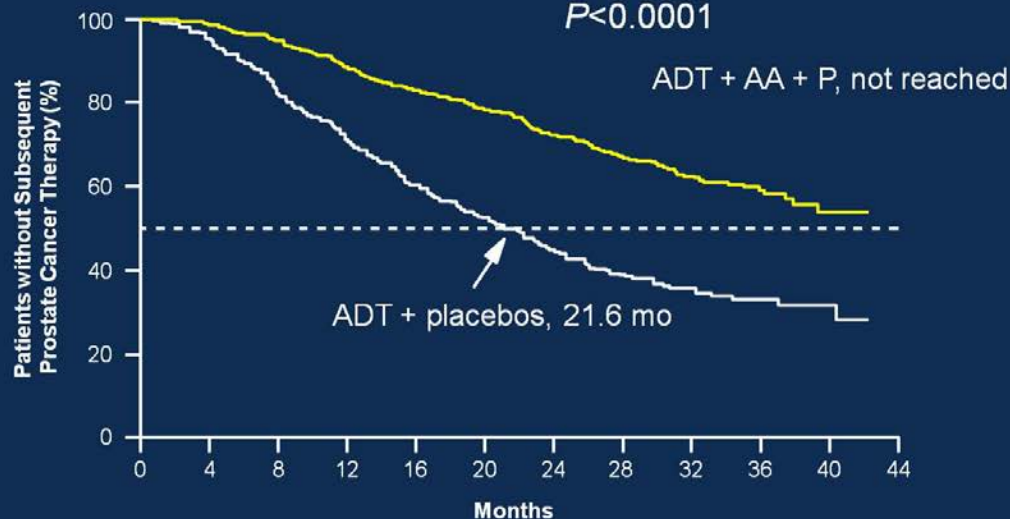
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15

- Melhor controle do PSA.

Statistically significant **58%** risk reduction of time to subsequent PC therapy

Hazard ratio, 0.42 (95% CI, 0.35-0.50)
 $P < 0.0001$



No. at risk

ADT + AA + P	597	569	531	483	442	399	327	236	141	72	25	0
ADT + placebos	602	558	452	379	299	239	180	116	67	27	10	0

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17

Subsequent life-prolonging therapy for prostate cancer

	ADT + AA + P (n = 597)	ADT + placebos (n = 602)
	n (%)	n (%)
Patients eligible*	n = 314 (53%)	n = 469 (78%)
Patients who received life-prolonging therapy	125 (40)	246 (52)
Docetaxel	106 (34)	187 (40)
Enzalutamide	30 (10)	76 (16)
AA-P	10 (3)	53 (11)
Cabazitaxel	11 (4)	30 (6)
Radium-223	11 (4)	27 (6)

*Patients who discontinued treatment and were eligible for subsequent therapy.

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18

- Como terapia subsequente, poucos pacientes no grupo do placebo receberam abiraterona.
- Se o grupo placebo tivesse recebido abiraterona na progressão do PSA desfecho teria sido tão positivo?

Adverse events of special interest

Adverse Events	ADT + AA + P (n = 597)		ADT + placebos (n = 602)	
	Grade 3	Grade 4	Grade 3	Grade 4
	%		%	
Hypertension	20	0	10	0.2
Hypokalemia	10	0.8	1	0.2
ALT increased	5	0.3	1	0
AST increased	4	0.2	1	0
Hyperglycemia	4	0.2	3	0
Bone pain	3	0	3	0
Cardiac disorder	3	0.8	1	0
Anemia	2	0.5	4	0.2
Back pain	2	0	3	0
Fatigue	2	0	2	0
Spinal cord compression	2	0	1	0.5

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20

- Aumento da incidência de efeitos colaterais, especialmente hepáticos e cardiovasculares

Safety

- Hypertension
 - Only rarely required treatment discontinuation
- Hypokalemia
 - Only 2 patients discontinued treatment due to hypokalemia
 - No hypokalemia-related deaths
- Cardiovascular events
 - 2 patients in each group died of cerebrovascular events;
 - 10 (ADT + AA + P) versus 6 (ADT + placebos) died of cardiac disorders

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21

Conclusions

- In the phase 3 LATITUDE, addition of AA + P to ADT led to:
 - Significantly improved OS with a 38% reduction in the risk of death
 - Significantly prolonged rPFS (53% reduction) and all secondary end points
- The overall safety profile of ADT + AA + P was consistent with prior studies in patients with mCRPC

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- Um novo “standart of care” para este perfil de pacientes.

Conclusions

- These findings indicate that the addition of AA + P to ADT can potentially be considered a new standard of care for patients with high-risk, newly diagnosed mCNPC

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23

Adding abiraterone for men with high-risk prostate cancer starting long-term androgen deprivation therapy: Survival results from STAMPEDE

Nicholas James

University of Birmingham and Queen Elizabeth Hospital Birmingham
on behalf of

Johann De Bono, Melissa R Spears, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Silke Gillesen, David Matheson, San Aung, Alison Birtle, Simon Chowdhury, Joanna Gale, Zafar Malik, Joe O'Sullivan, Anjali Zarkar, Mahesh KB Parmar, Matthew R Sydes and the STAMPEDE Investigators

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Setting and hypothesis

- Setting

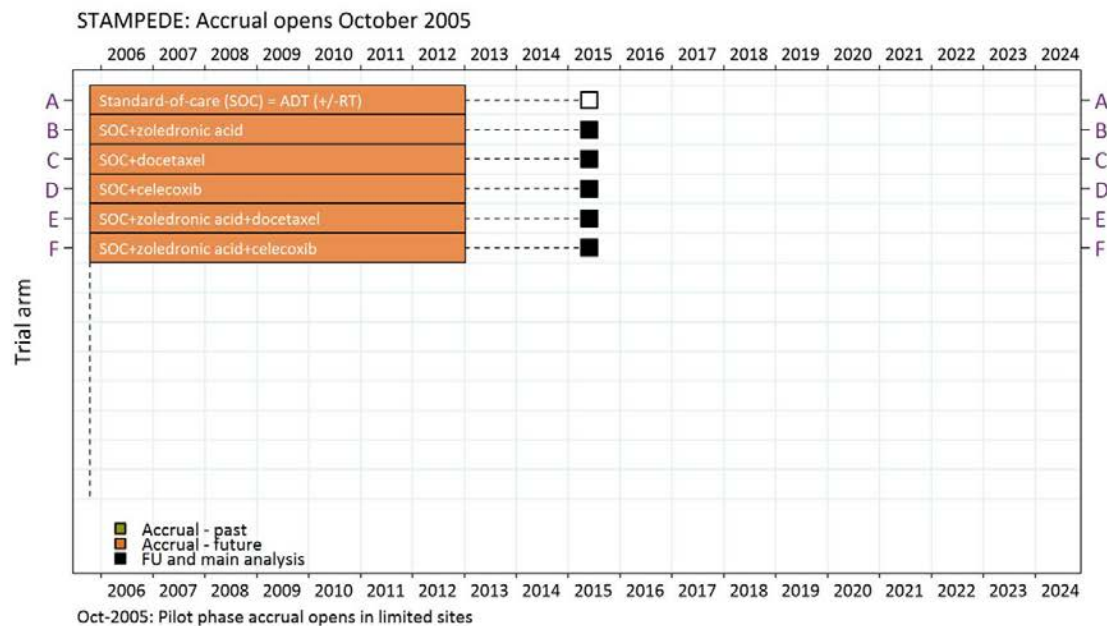
- Hormone therapy the mainstay of treatment since 1940s
- Addition of radiotherapy to N0M0 disease improves outcomes
- Docetaxel became part of standard of care 2014-5
 - Recruitment to the abiraterone comparison completed prior to this

- Hypothesis

- Early use of therapies may give a larger absolute benefit in overall survival

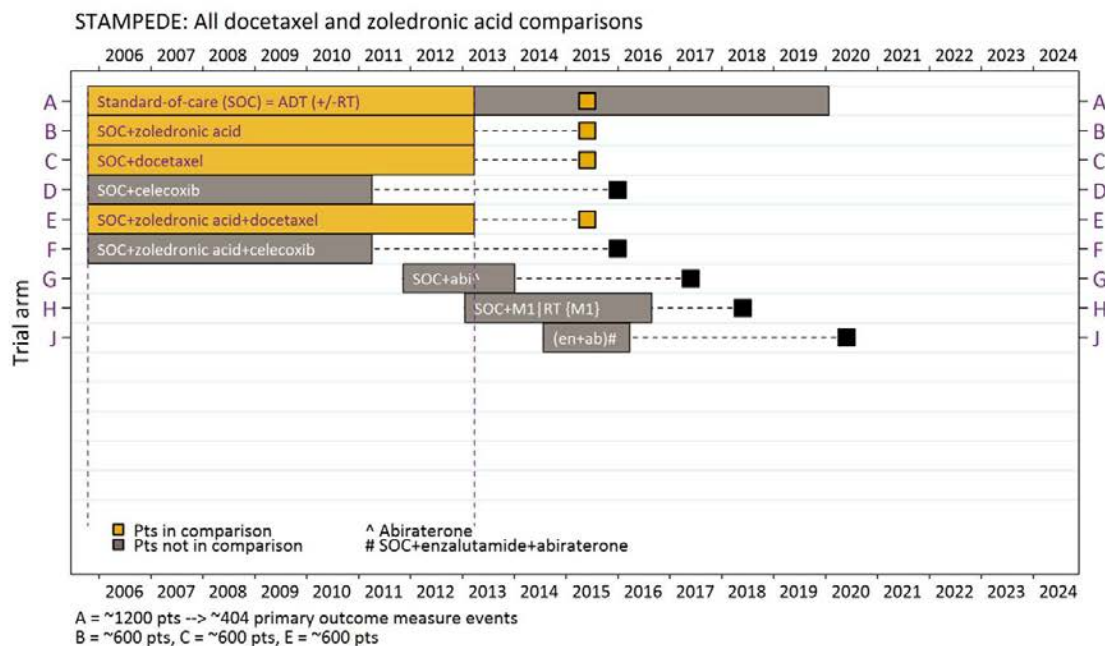
- Um estudo que procurou analisar várias alternativas de tratamento na abordagem dos pacientes de alto risco.

Trial activity: original research arms



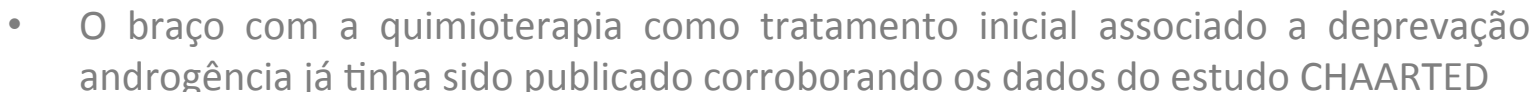
- Pacientes foram inicialmente randomizados para 6 braços diferentes

Docetaxel & ZA comparisons: patients



- Braços com antiinflamatórios foram descontinuados e posteriormente foram acrescentados o braço com a abiraterona e a combinação abi+enza

A vertical strip of a hexagonal lattice structure, showing a repeating pattern of hexagons and rhombi. The lattice is composed of black lines forming a series of interconnected hexagons and rhombi. The pattern is periodic and extends vertically across the entire height of the image.



Inclusion criteria

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥ 2 of: Stage T3/4
PSA ≥ 40 ng/ml
Gleason 8-10

Relapsing after previous RP or RT with ≥ 1 of:

- PSA ≥ 4 ng/ml and rising with doubling time < 6 m
- PSA ≥ 20 ng/ml
- Node-positive
- Metastatic

All patients

- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Full criteria

www.stampededtrial.org

- População de alto risco, submetida ou não a tratamento definitivo com radio ou cirurgia.

Outcome measures

Primary outcome measure

- Overall survival

Secondary outcome measures

- Failure-free survival (FFS)
- Toxicity
- Quality of life
- Skeletal-related events
- Cost effectiveness

FFS definition

First of:

PSA failure
Local failure
Lymph node failure
Distant metastases
Prostate cancer death

PSA failure definition

PSA fall $\geq 50\%$

→ 24wk nadir + 50% **and**
→ $>4\text{ng/ml}$

PSA fall of $<50\%$

→ failure at $t=0$

- População de “menor risco” do que o LATITUDE, com os mesmos desfechos

Patient characteristics

1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
67yr	Median age (min 39, max 85)	[s]
52%	Metastatic (88% Bony mets)	[s]
20%	N+M0	
28%	N0M0	
99%	LHRH analogues	[s]
41%	Planned for RT (96% of N0M0 pts; 62% of N+M0 pts)	[s]
5%	Previous local therapy	

Balanced by arm

[s] = Stratification factors

Also stratified on

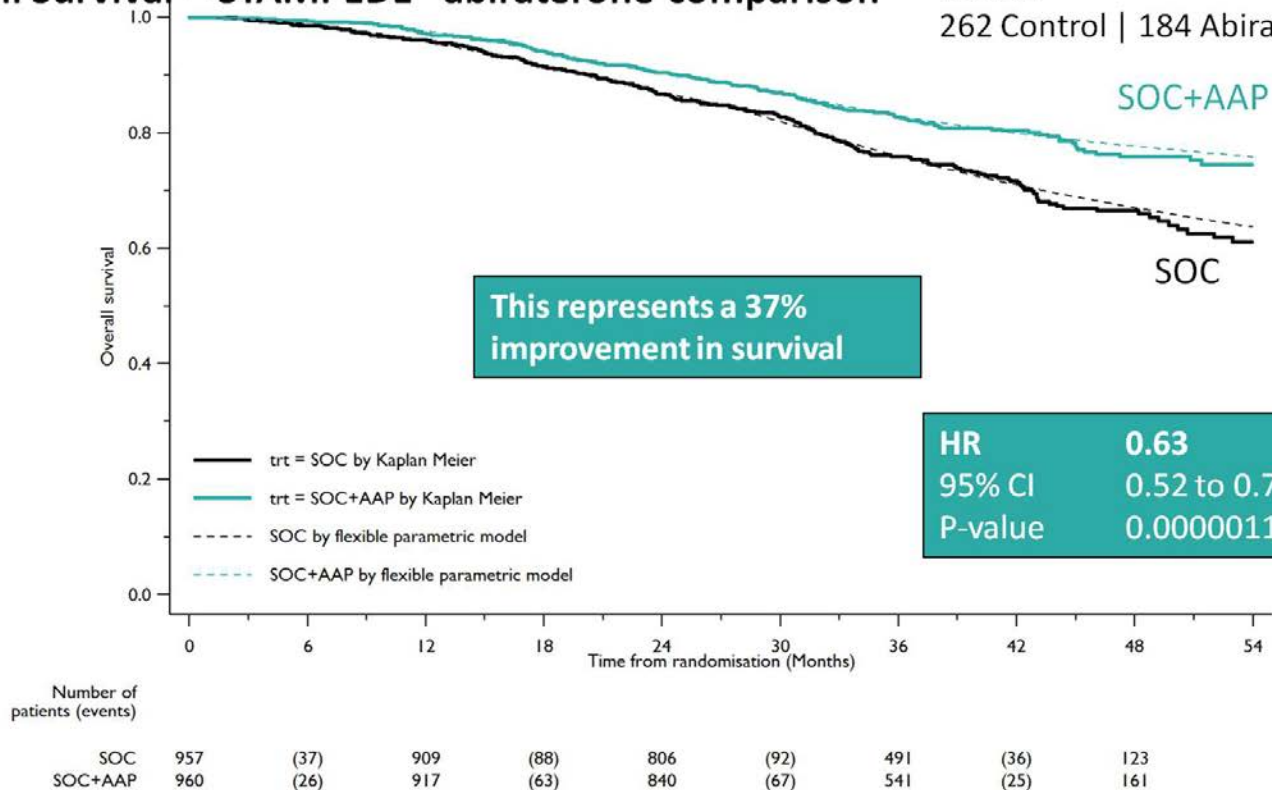
:: hospital

:: NSAID/aspirin

Overall Survival – STAMPEDE “abiraterone comparison”

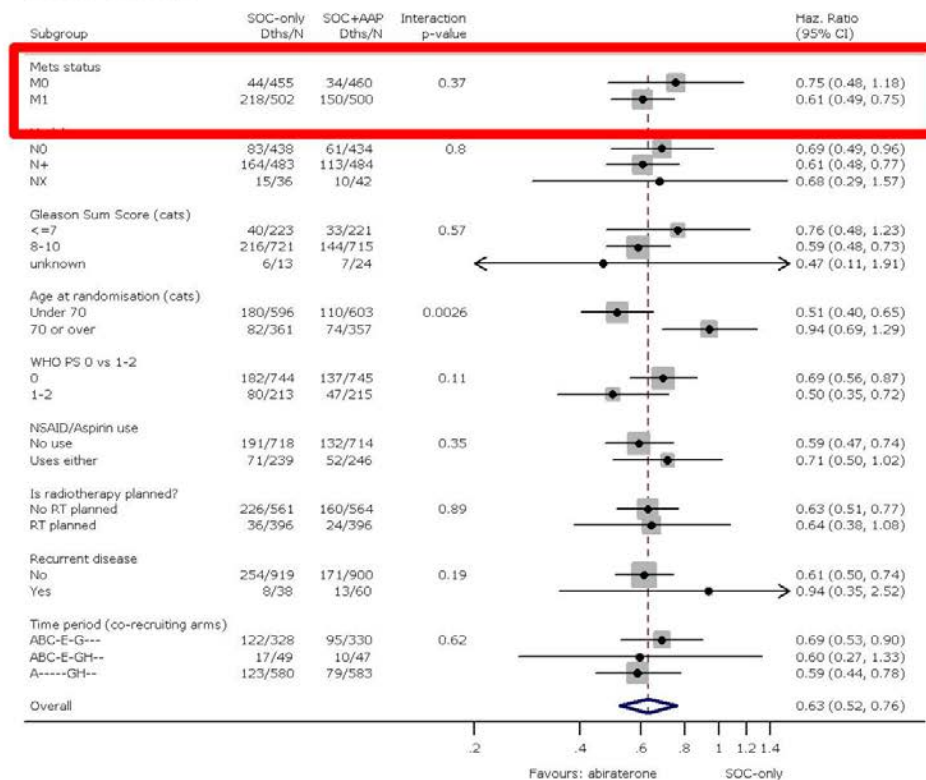
Events

262 Control | 184 Abiraterone



- A análise mostra benefício semelhante ao estudo LATITUDE

SOC vs SOC+AAP



Overall Survival – STAMPEDE “abiraterone comparison”

**No good
evidence of
heterogeneity by
stratification
factors**

- Benefício parece se estender aos pacientes que são M0.

STAMPEDE “abiraterone comparison”

Overall Survival by metastatic status – pre-planned analysis

SOC vs SOC+AAP

Mets status	SOC-only Dths/N	SOC+AAP Dths/N
-------------	--------------------	-------------------

M0	44/455	34/460
----	--------	--------

M1	218/502	150/500
----	---------	---------

Overall		
---------	--	--

Mets * treatment interaction
P-value = 0.37

Haz. Ratio
(95% CI)

0.75 (0.48, 1.18)

0.61 (0.49, 0.75)

0.63 (0.52, 0.76)

0.2 0.4 0.6 0.8 1.0 1.2 1.4
Favours: abiraterone SOC-only
0.63

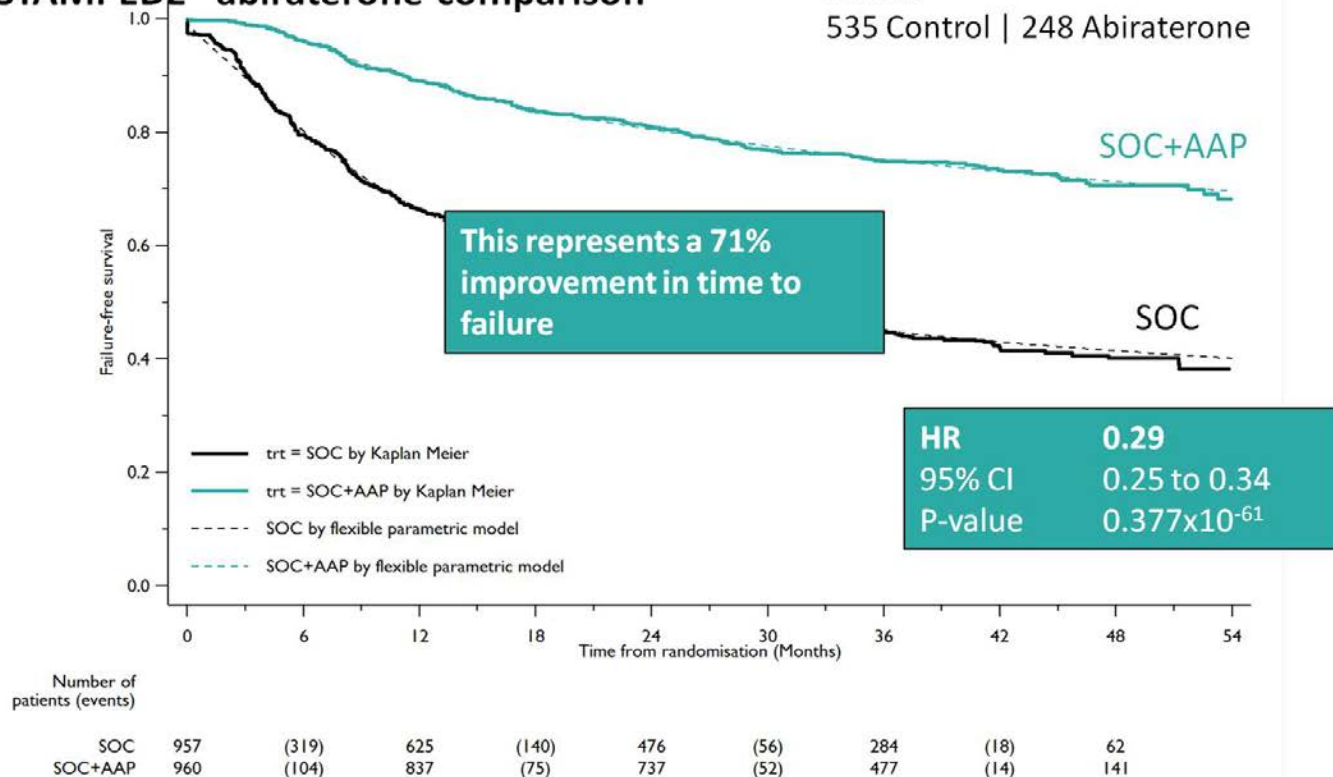
No good evidence of heterogeneity by metastatic status

- Mas este benefício é menos evidente

FFS – STAMPEDE “abiraterone comparison”

Events

535 Control | 248 Abiraterone



- Desfechos secundários também positivos.

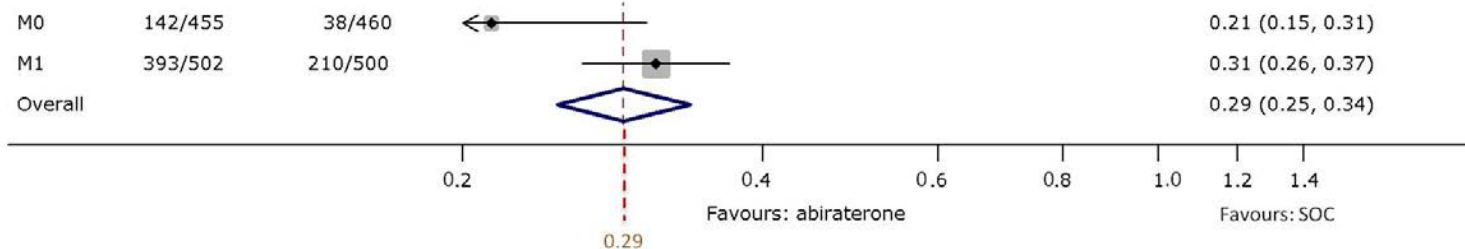
STAMPEDE “abiraterone comparison” FFS by metastatic status – pre-planned analysis

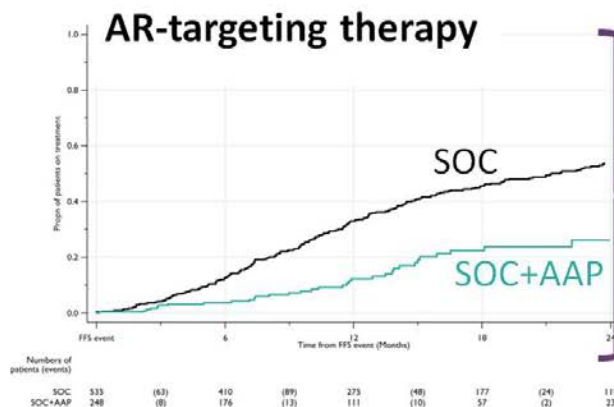
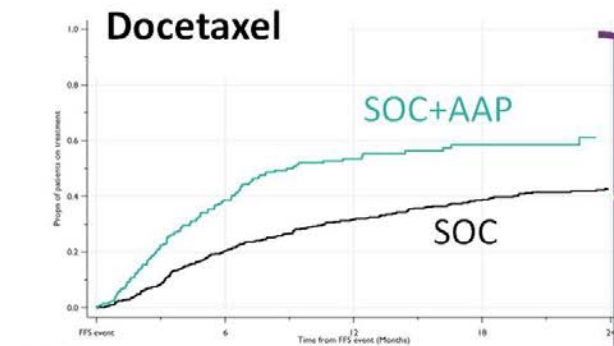
SOC vs SOC+AAP

Mets status	SOC-only FFS/N	SOC+AAP FFS/N
-------------	-------------------	------------------

Mets * treatment interaction
P-value = 0.085

Haz. Ratio
(95% CI)





Treatment started since first progression	A SOC	G SOC+abi
Patients randomised	957	960
Patients with progression	535 (56%)	248 (26%)
Reported new treatment	477 (89%)	196 (79%)
Reported "life-prolonging" treatment	310 (58%)	131 (53%)
Docetaxel	200 (37%)	115 (46%)
Enzalutamide	138 (26%)	25 (10%)
Abiraterone	120 (22%)	8 (3%)
Radium-223	24 (5%)	19 (8%)
Cabazitaxel	28 (5%)	15 (6%)

Graph timed from first FFS event

- Também no estudo STAMPEDE os pacientes do grupo controle foram poucos expostos ao uso da abiraterona

Safety population

Patients included in adverse event analysis

Grade 1-5 AE

Grade 3-5 AE

Grade 5 AE

SOC-only

SOC+AAP

960

948

950 (99%)

943 (99%)

315 (33%)

443 (47%)

3

9

Grade 3-5 AEs by category (*incl. expected AEs*)

Endocrine disorder (*incl. hot flashes, impotence*)

133 (14%)

129 (14%)

Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*):

41 (4%)

92 (10%)

Musculoskeletal disorder:

46 (5%)

68 (7%)

Gastrointestinal disorder:

40 (4%)

49 (5%)

Hepatic disorder (*incl. increased AST, increased ALT*):

12 (1%)

70 (7%)

General disorder (*incl. fatigue, oedema*):

29 (3%)

45 (5%)

Respiratory disorder (*incl. breathlessness*):

23 (2%)

44 (5%)

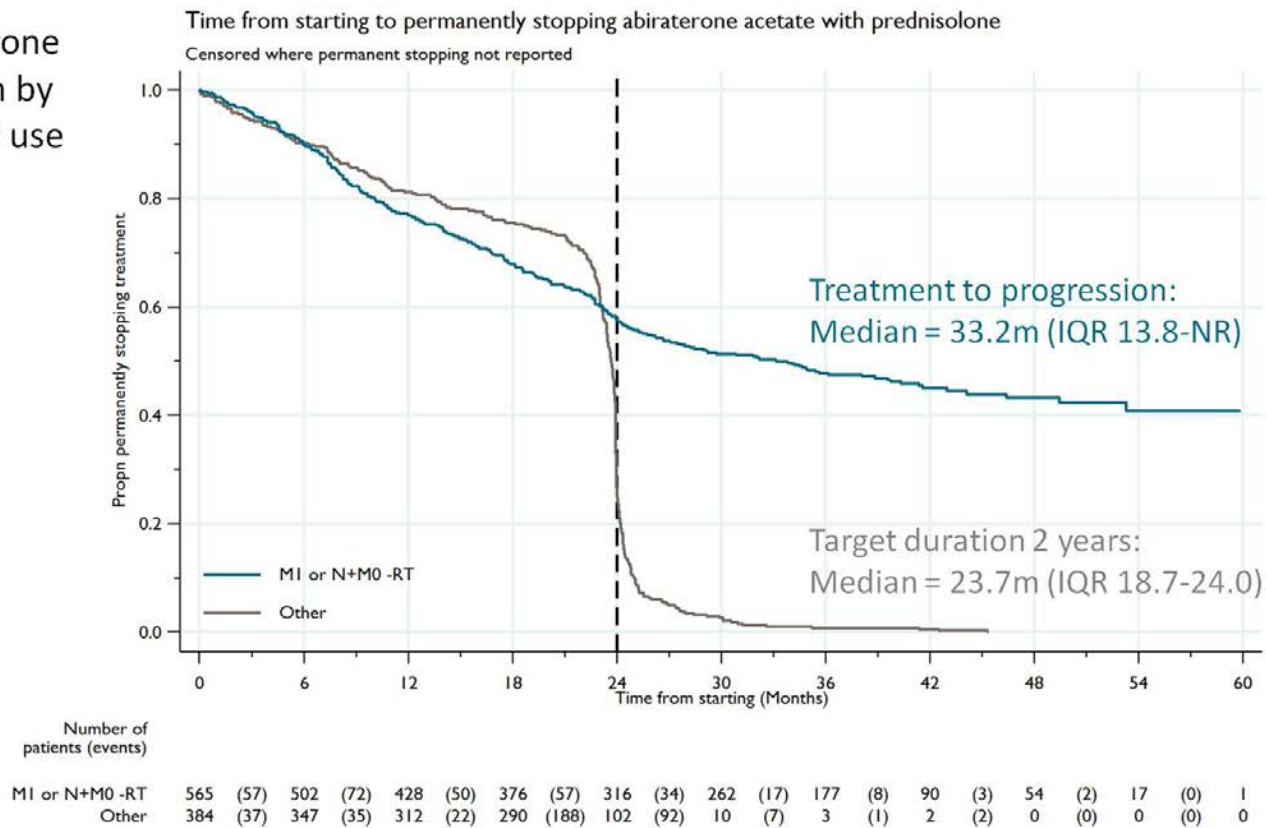
Lab abnormalities (*incl. hypokalaemia*):

21 (2%)

34 (4%)

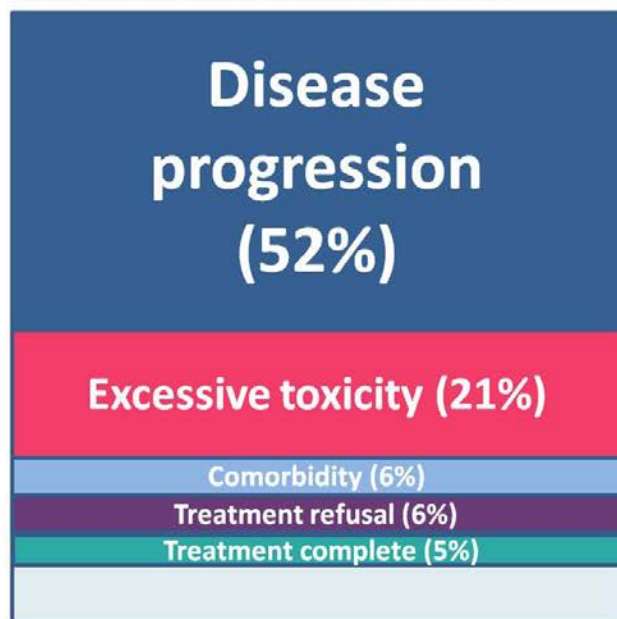
- Perfil de toxicidade conhecido, com alterações hepáticas e cardiovasculares

Abiraterone duration by planned use

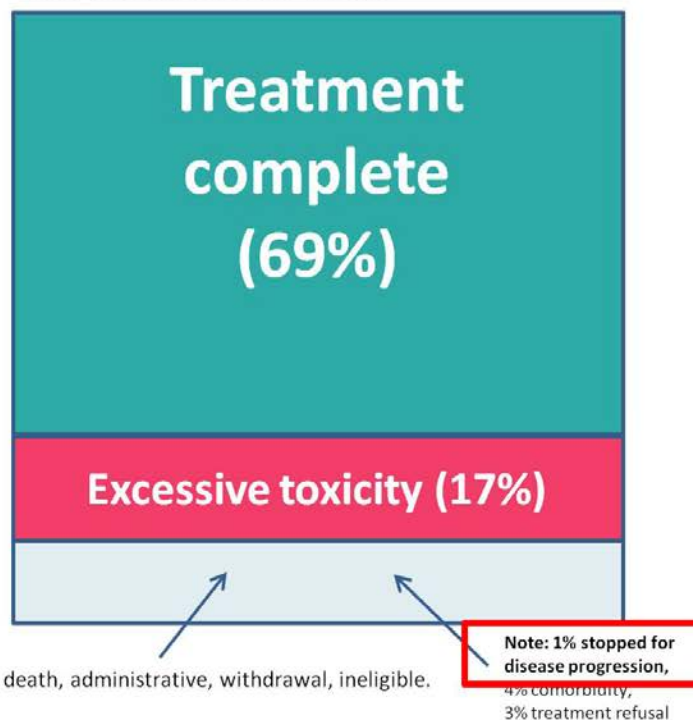


Reasons for permanently stopping research abiraterone acetate + prednisolone

Target duration to progression



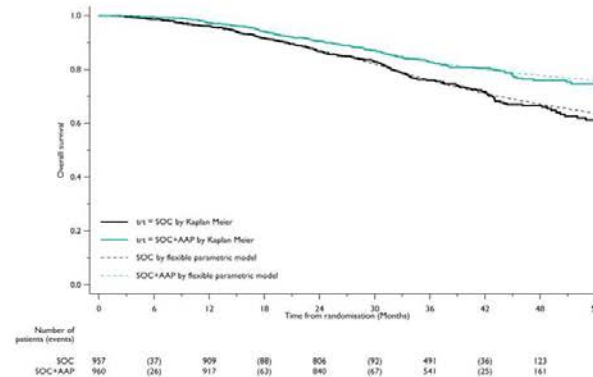
Target duration 2 years



Other reasons <5%: Patient choice, clinician decision, intercurrent illness, death, administrative, withdrawal, ineligible.

Conclusions

- In hormone naïve prostate cancer abiraterone acetate + prednisolone improves
 - **Overall survival by 37%**
 - Failure free survival by 71%
 - Symptomatic skeletal events by 55%
- Treatment was well tolerated
- Abiraterone acetate + prednisolone should be part of the standard of care for men starting long term androgen deprivation therapy



DISCUSSÃO

Qual o melhor desenho para este tipo de estudo?

Este não é um estudo de uma droga nova, mas sim, de um posicionamento de droga. O braço placebo deveria ter sido mais exposto a abiraterona...

CHAARTED ou LATITUDE?

Duas possibilidades de abordagem para este paciente de alto risco. Não há escolha melhor, mas é certo que este perfil de pacientes deve ser inicialmente tratado de forma mais agressiva, seja com abiraterona ou quimioterapia...

Toxicidade financeira?

6 ciclos de docetaxel será realmente bem mais barato do que 3 anos de abiraterona...

Seleção de pacientes

Faremos o tratamento apenas pacientes de muito alto risco?

Doença M0



Duration of Androgen Deprivation Therapy in High Risk Prostate Cancer: Final Results of a Randomized Phase III Trial

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Abstract ID 5008 (186877)

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Inclusion Criteria

T3-T4, PSA >20 ng/ml, Gleason score >7
Age ≤80 years, Zubrod 0-1
Normal hepatic function
No regional disease
No distant metastases

Exclusion Criteria

Pre-existing medical conditions precluding use of
androgen deprivation therapy (ADT) or radiotherapy (RT)

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- Qual o melhor tempo de hormonioterapia concomitante a radio?

Randomization 10/2000 to 01/2008

630 Patients Arm 1 (310) : ADT* 36 months + RT**
Arm 2 (320) : ADT* 18 months + RT**

*ADT: Bicalutamide 50 mg id x 1 month + Goserelin 10.8 mg q 3 months

**RT: pelvis 44 Gy - 4 ½ weeks, prostate 70 Gy - 7 weeks

Median Follow-up 9.4 years

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- Estudo com follow-up adequado para câncer de próstata!

Risk Factors

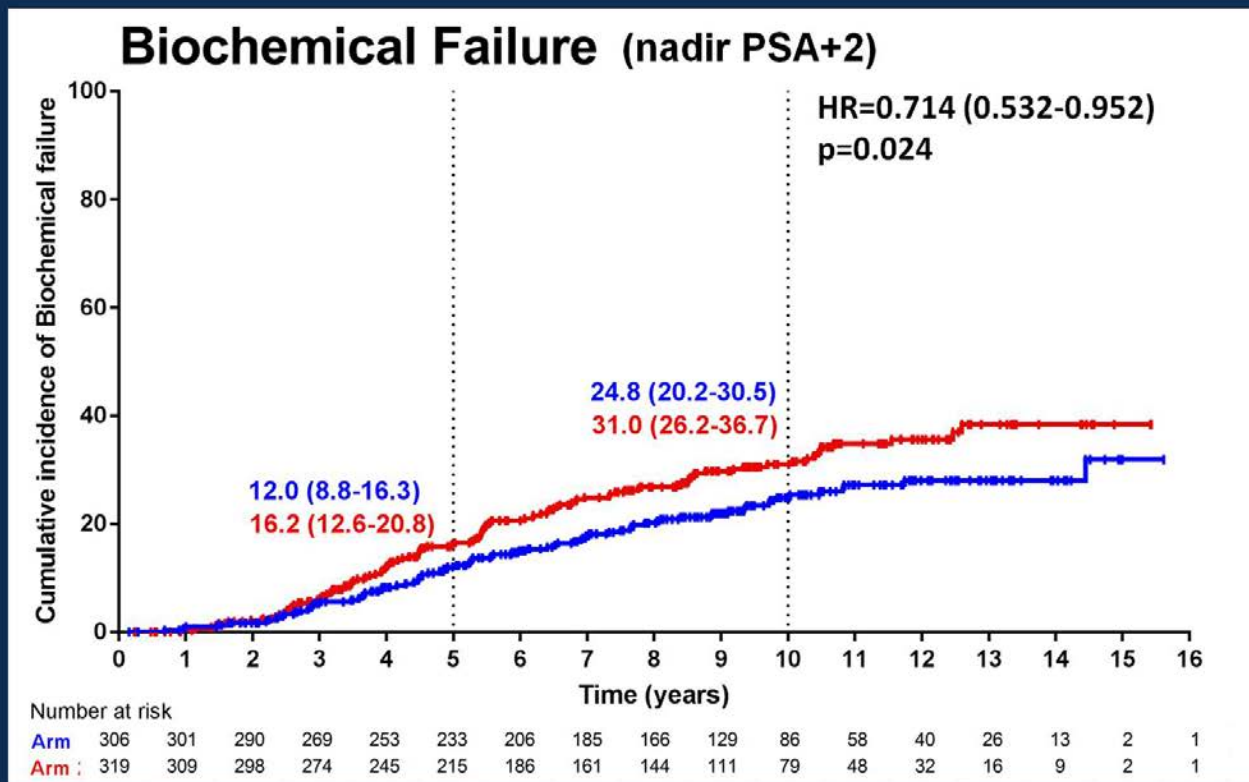
	36 months n=310	18 months n=320	Total n=630
T3 – T4	80 (25.8)	72 (22.5)	152 (24.1)
PSA >20	142 (45.8)	137 (42.8)	279 (44.3)
Gleason score >7	183 (59.0)	193 (60.3)	376 (59.7)

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- População com critérios de alto risco de D'Amico comparáveis entre os dois grupos



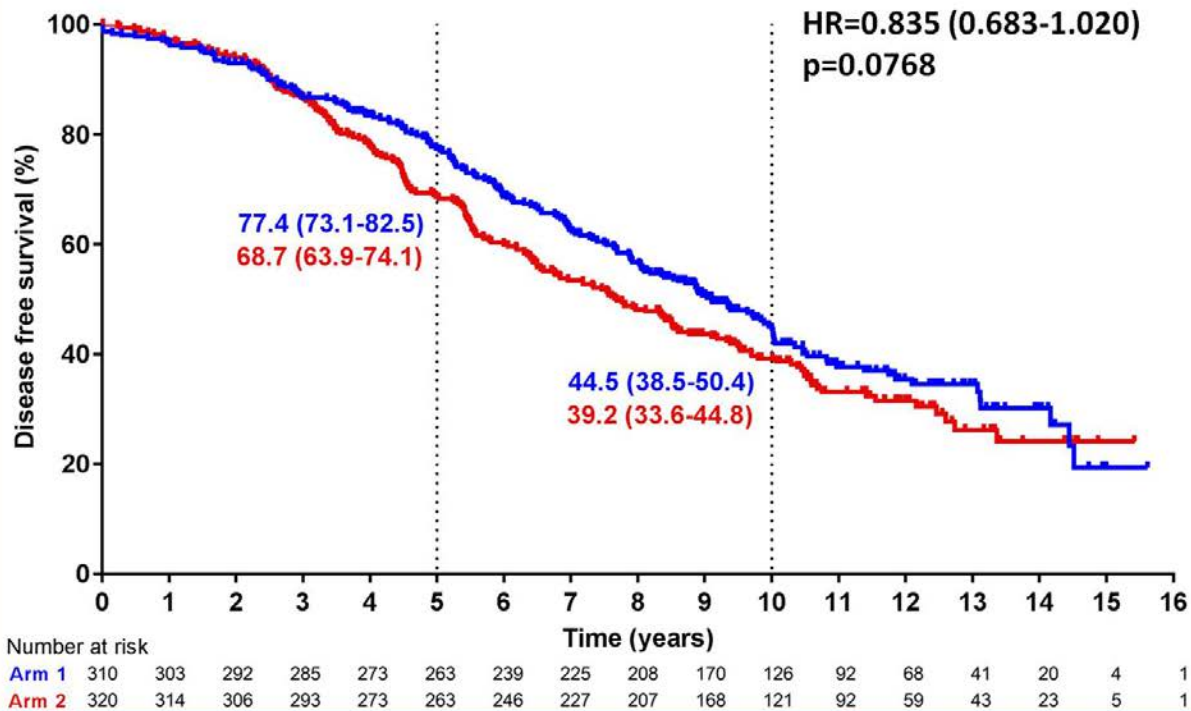
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- Como esperado melhor desfecho sobre a recidiva do PSA para o maior tempo de hormonioterapia

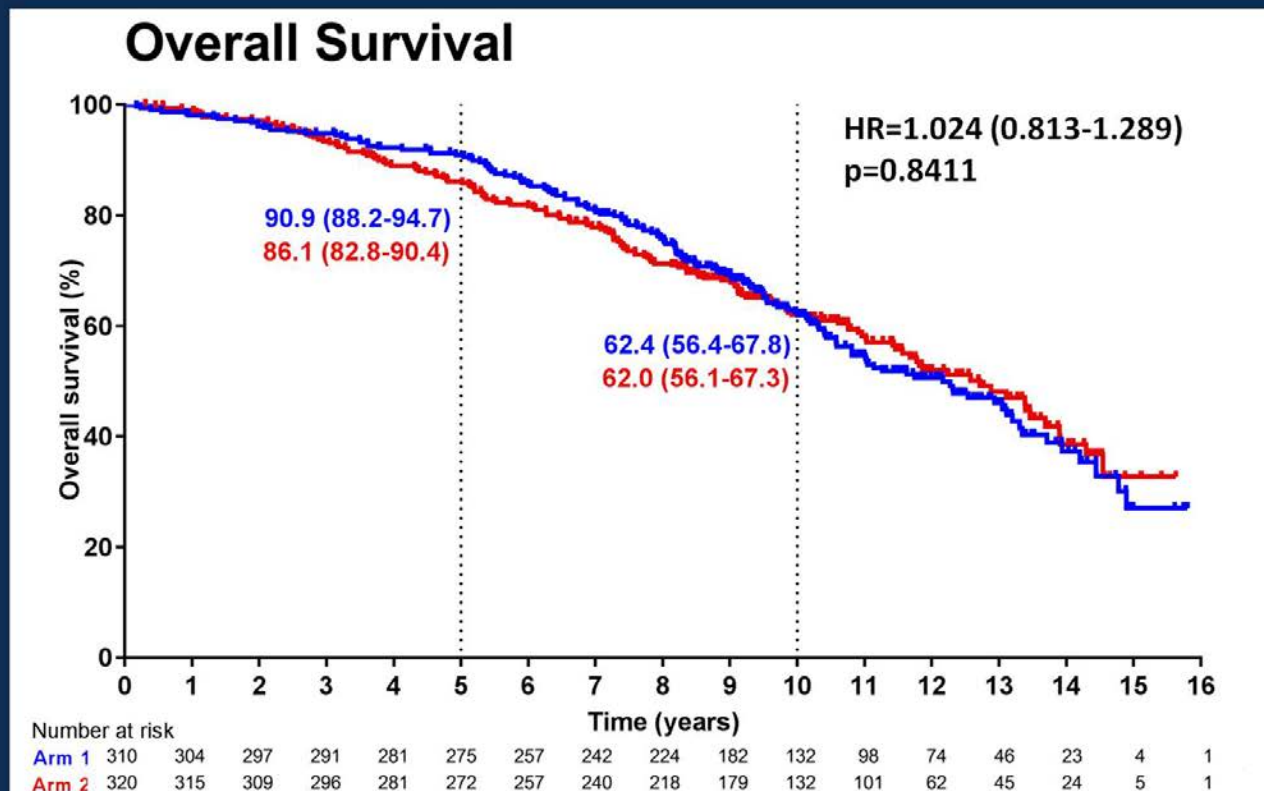
Disease Free Survival



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Sem diferença de sobrevida global

Causes of Death

Events	36 months	18 months
Second cancer	35 (23.8%)	40 (28.0%)
Prostate cancer	31 (21.1%)	33 (23.1%)
Cardiovascular	25 (17.0%)	25 (17.5%)
Pulmonary	22 (15.0%)	17 (11.9%)
Digestive	4 (2.7%)	5 (3.5%)
Other causes	20 (13.6%)	15 (10.5%)
Unknown	10 (6.8%)	8 (5.6%)
Total 290/630	147/310 (47.4%)	143/320 (44.6%)

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- Inclusive, sem diferença de sobrevida CÂNCER ESPECÍFICA

Quality of Life

In favor of 18 months of ADT:

- 13/55 items, 6/21 scales

Clinically significant: $p < 0.01$

-2 items (Hot flushes, enjoyable sex)

Clinically Relevant:
difference in mean scores ≥ 10 points

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Conclusion

In localised HRPC treated with RT and ADT:
ADT duration can be safely reduced from 36 to 18 months
18 months could represent a threshold effect in ADT duration
Side effects and treatment costs can be reduced
18 months of ADT represents a new standard of care

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- 18 meses de hormonioterapia é o padrão de tratamento.

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Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT)

Robert Motzer, Naomi Haas, Frede Donskov, Marine Gross-Goupil, Sergei Varlamov, Evgeny Kopyltsov, Jae-Lyun Lee, Bohuslav Melichar, Brian Rini, Toni Choueiri, Milada Zemanova, Lori Wood, Dirk Fahlenkamp, Martin Reaume, Arnulf Stenzl, Weichao Bao, Paola Aimone, Christian Doehn, Paul Russo, Cora Sternberg for the PROTECT investigators

Abstract 4507

PROTECT, Pazopanib as adjuvant therapy in localized/locally advanced RCC after nephrectomy (VEG113387).

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Presented by: Robert Motzer, MD

Introduction

- About 75% of patients with RCC have localized disease and 30% to 40% with high-risk localized RCC relapse following nephrectomy
- Adjuvant VEGFR-TKI therapy is being investigated to improve disease-free survival (DFS)
- ASSURE trial did not meet the primary end point; S-TRAC met the primary end point for sunitinib^{1,2}

TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

1. Haas NB, et al. *Lancet*. 2016;387:2008. 2. Ravaud A, et al. *N Engl J Med*. 2016;375:2246-2254.

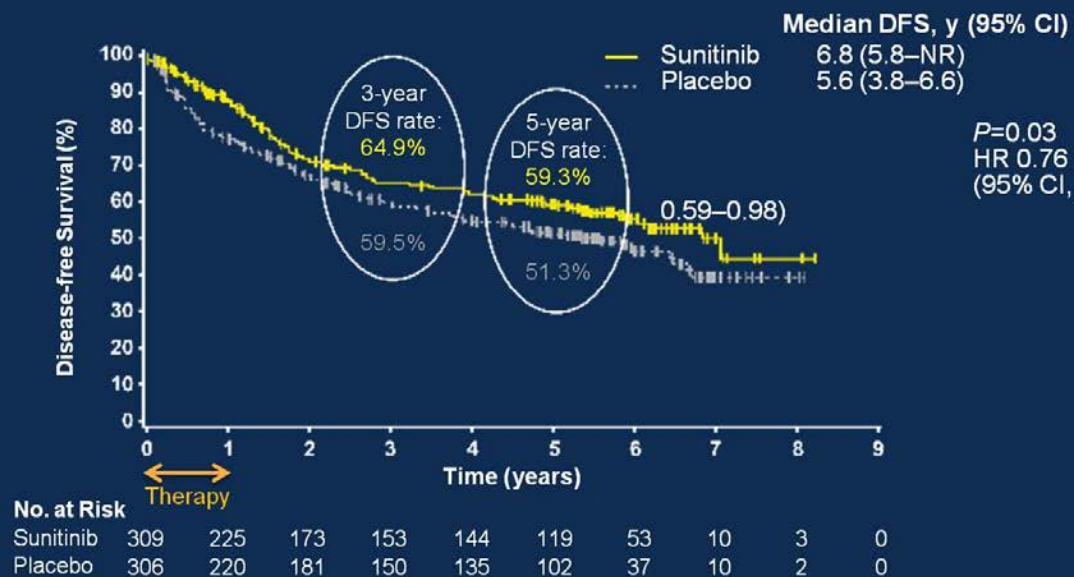
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- Será o câncer de rim o único tumor em que um agente anti VEGF tem eficácia no tratamento adjuvante?

Background (II)



Ravaud A, et al. N Engl J Med 2016;375:2246-54. Copyright © 2016. Reprinted with permission from Massachusetts Medical Society.
 CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; NR=not reached

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- Benefício do STRAC visto mesmo antes do tempo de uso do sunitinibe...

Study Design

Key eligibility criteria

- Resected non-metastatic clear-cell RCC histology and pathologic staging*
 - pT2, G3 or G4, N0
 - pT3, G_{any}, N0
 - pT4, G_{any}, N0
 - pT_{any}, G_{any}, N1
- Baseline imaging assessment by independent radiologist review that excluded metastasis
- Adequate PS and organ function

Randomized
1:1

Pazopanib
daily for 52
weeks**

Placebo
daily for 52 weeks

Stratification: partial vs radical nephrectomy; pathologic staging

**Starting dose 600 mg assessed for safety at 8-12 weeks and could be escalated to 800 mg or maintained at 600 mg based on patient's tolerability

*Staging based on TNM classification per the American Joint Committee on Cancer (AJCC) 2010 version and Fuhrman nuclear grades

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- Pacientes foram inicialmente tratados com 600mg/dia.
- Menor parte da amostra foi levada a dose de 800mg/dia

Study Assessments

- Tumor imaging at baseline, weeks 20, 36, and 52 during year 1, every 6 months during years 2-5, and yearly thereafter
 - Baseline imaging assessment by independent radiologist and investigator; all subsequent imaging studies assessed by investigator only
- Safety evaluations at regular intervals
- Quality of life using FKSI-19

FKSI-19, Functional Assessment of Cancer Therapy-Kidney Symptom Index-19.

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- Seguimento adequado para detectar recidivas.

Baseline Characteristics (n=1538)

	ITT _{600mg} (n=1135)		ITT _{800mg} (n=403)	
	Pazopanib n = 571	Placebo n = 564	Pazopanib n = 198	Placebo n = 205
Age, years, median (range)	58 (22–83)	58 (21–82)	56 (29–80)	60 (30–79)
Gender, %				
• Male	70	71	70	75
• Female	30	29	30	25
KPS,* %				
• 100	67	69	66	72
• 80 or 90	33	31	34	28
Nephrectomy, %				
• Partial	7	7	4	5
• Radical	93	93	96	95
Fuhrman grade,** %				
• High (Grade 3 or 4)	69	63	71	63
• Low (Grade 1 or 2)	31	37	29	37

*KPS was unknown for one patient in the ITT_{600mg} placebo group; **Fuhrman grade was missing for two patients in the ITT_{600mg} placebo group.

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- Sem diferenças significativas dos fatores prognósticos entre os grupos.

Baseline Characteristics

	ITT _{600mg}		ITT _{800mg}	
	Pazopanib n = 571	Placebo n = 564	Pazopanib n = 198	Placebo n = 205
Primary tumor stage, %				
• T1	<1	<1	1	<1
• T2	15	15	14	15
• T3	82	82	83	82
• T4	2	3	3	3
Regional lymph node status, %				
• N0	94	95	93	95
• N1	6	5	7	5
Tumor staging and grade, %				
• pT2G3–G4N0	14	14	14	14
• pT3G _{any} N0	78	78	77	79
• pT4G _{any} N0 and pT _{any} G _{any} N1	8	8	9	7

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DFS Results at Primary and Follow Up Analysis

	ITT _{600mg}		ITT _{800mg}	
	Pazopanib n = 571	Placebo n = 564	Pazopanib n = 198	Placebo n = 205
DFS—Primary analysis,* HR (95% CI)	0.86 (0.70, 1.06)		0.69 (0.51, 0.94)	
DFS—Follow up analysis,** HR (95% CI)	0.94 (0.77, 1.14)		0.66 (0.49, 0.90)	
DFS rate, % (95% CI)				
• 1 year	85 (81, 88)	76 (72, 79)	84 (78, 88)	73 (66, 78)
• 2 years	71 (67, 75)	68 (64, 72)	72 (65, 78)	62 (55, 69)
• 3 years	67 (62, 71)	64 (60, 68)	66 (58, 72)	56 (48, 62)

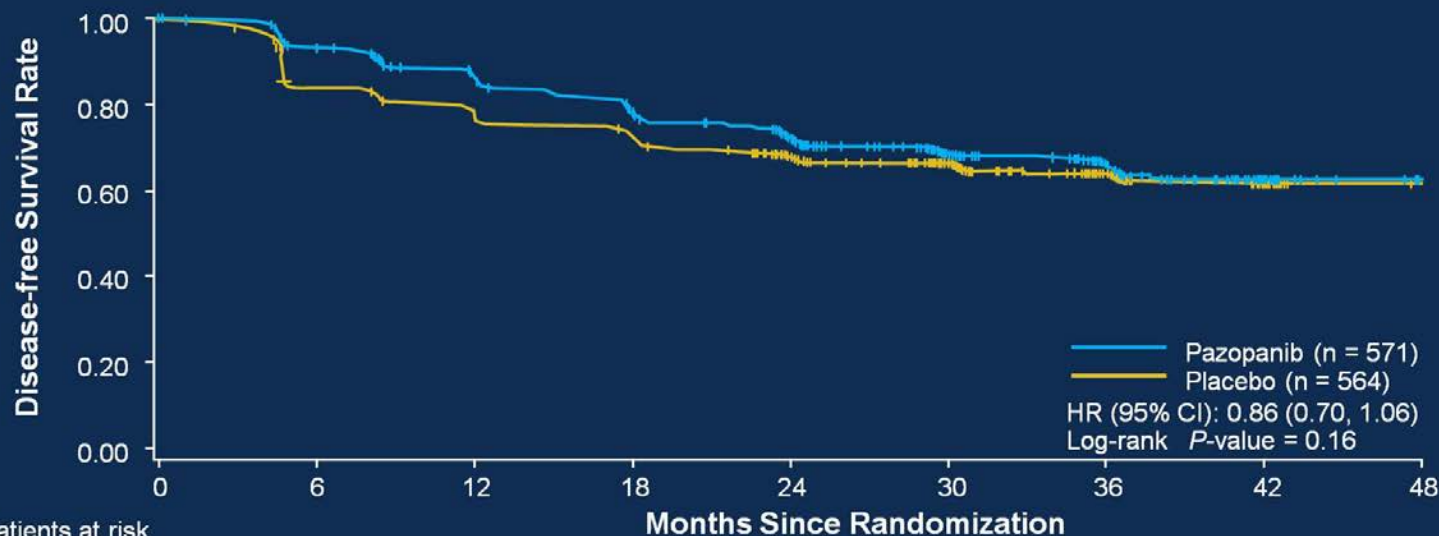
*Primary analysis data cut-off: October 2015; **Follow-up data analysis cut-off: October 2016.

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- Existiram diferenças de desfecho nos grupos de 600mg/dia e 800mg/dia.
- Mas o grupo de 800mg com número de pacientes insuficiente

Primary Analysis of DFS in ITT_{600mg}



Patients at risk

Pazopanib	571	482	423	382	308	209	118	29	0
Placebo	564	443	394	372	300	213	118	37	0

The median duration of follow up was 30.4 months and 30.7 months for the pazopanib and placebo arms, respectively.

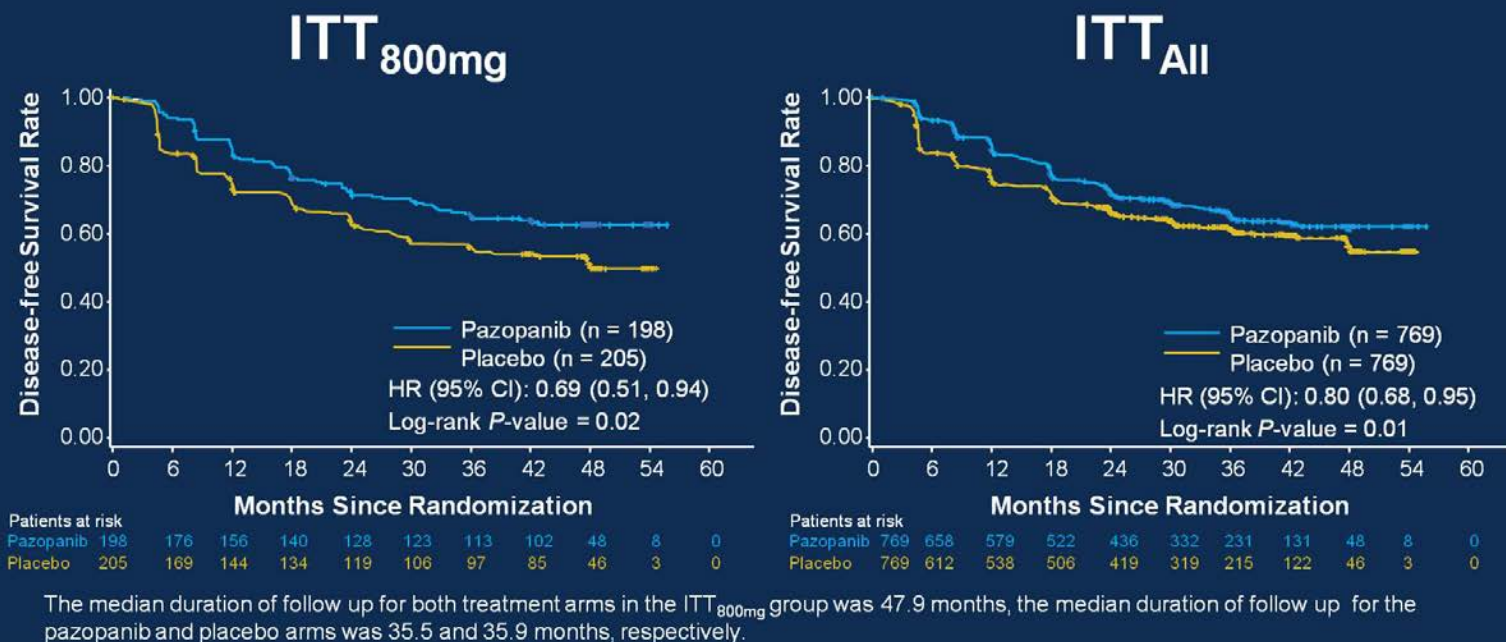
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- Estudo francamente negativo no corte de pacientes com 600mg

Secondary Analyses of DFS



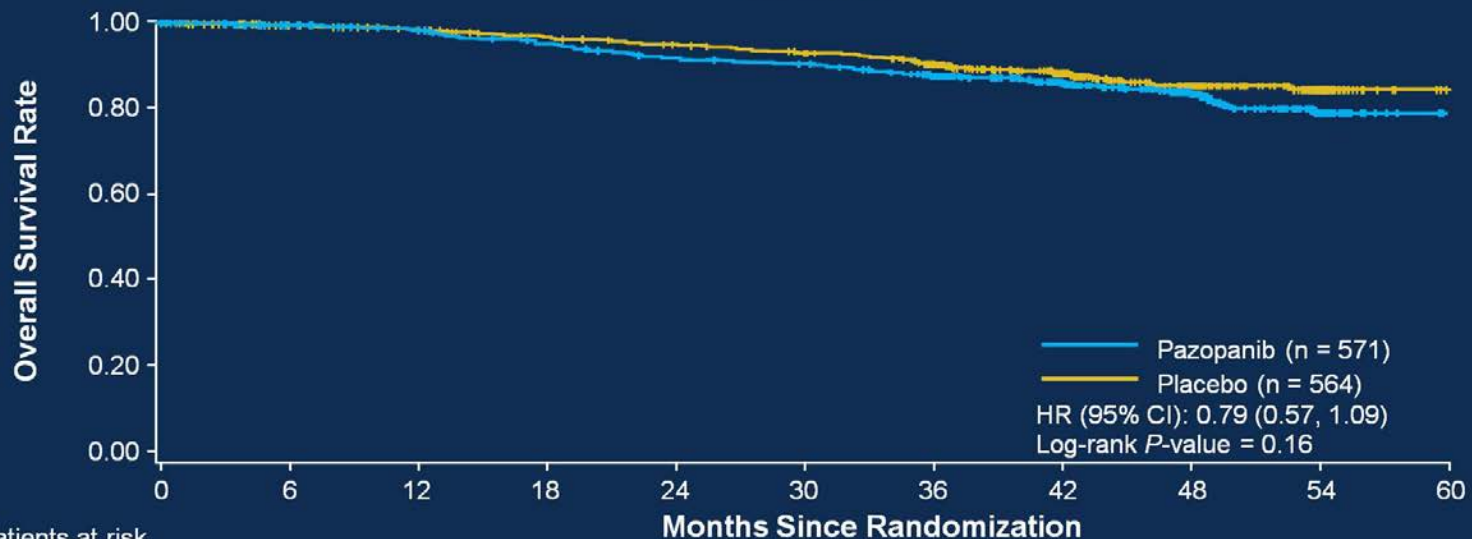
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- Dados positivos para a menor população que foi escalada a dose até 800mg/dia N insuficiente para conclusões no estudo.

Overall Survival in ITT_{600mg}



Patients at risk

Pazopanib	571	529	517	498	484	468	428	315	178	58	0
Placebo	564	539	525	504	484	476	427	310	176	63	0

Interim analysis was based on 65 and 83 events in the pazopanib and placebo arms, respectively and performed on data cut-off October 15, 2016 as part of DFS follow-up.

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- Desfecho de sobrevida francamente negativo no corte de 600mg

Quality-of-Life Assessment by FKSI-19 for ITT_{600mg} vs Placebo



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Conclusions

- Pazopanib 600 mg daily dose as adjuvant therapy did not prolong DFS
- Pazopanib 800 mg starting dose resulted in a 31% decrease in the risk of recurrence or death, but this was a secondary objective of the study
- The safety profile was similar between 600 mg and 800 mg dose cohorts, and consistent with prior experience in advanced RCC
- Pazopanib is not recommended for adjuvant therapy following resection of locally advanced RCC

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- Há ainda espaço para algum tratamento adjuvante em câncer de rim hoje?
- Em algum perfil específico?

Phase III trial of adjuvant sunitinib in patients with high-risk renal cell carcinoma: validation of the 16-gene recurrence score in stage III patients

Bernard Escudier¹, Brian Rini², Jean-Francois Martini³, Yen-Hwa Chang⁴, Jan Breza⁵, Ahmed Magheli⁶, Christer Svedman⁷, Margarita Lopatin⁷, Dejan Knezevic⁷, Audrey Goddard⁷, Patricia English³, Rachel Li⁸, Xun Lin³, Olga Valota⁹, Giacomo Carteni¹⁰, Michael Staehler¹¹, Robert Motzer¹², Alain Ravaud¹³

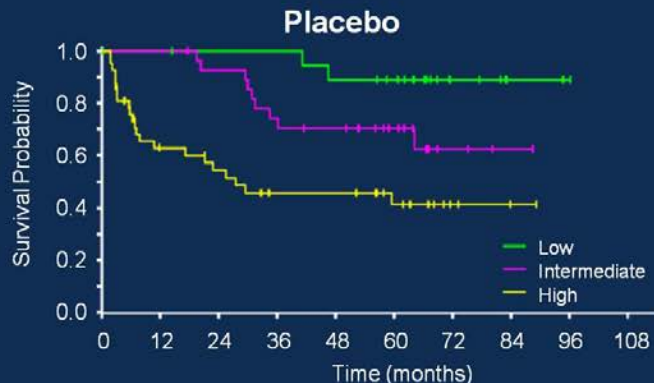
¹Institut Gustave Roussy (IGR), Department of Medical Oncology, Villejuif, France; ²Cleveland Clinic, Cleveland, OH, USA; ³Pfizer Inc, La Jolla, CA, USA; ⁴Department of Urology, Taipei Veterans General Hospital, Taipei, Taiwan; ⁵Department of Urology, Slovak Medical University in Bratislava, Bratislava, Slovakia; ⁶Department of Urology, Charité Universitätsmedizin Berlin, Berlin, Germany; ⁷Genomic Health Inc, Redwood City, CA, USA; ⁸Pfizer Inc, San Francisco, CA, USA; ⁹Pfizer S.r.l., Milan, Italy; ¹⁰Division of Oncology and Division of Urology, Azienda Ospedaliera di Rilievo Nazionale A. Cardarelli, Naples, Italy; ¹¹Department of Urology, Hospital of Munich, Munich, Germany; ¹²Department of Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; ¹³Department of Medical Oncology, Bordeaux University Hospital, Bordeaux, France

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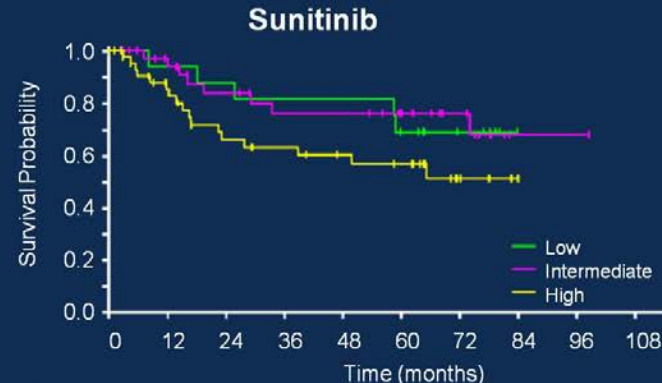
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- Este estudo tentou validar um teste biomolecular (“tipo Oncotype”) para validar o tratamento adjuvante em câncer renal.

Secondary objective: Recurrence risk by RS groups



No. at Risk										
Low	20	19	18	18	16	14	6	2	1	0
Int	28	28	25	20	18	13	3	1	0	0
High	42	23	19	14	14	9	3	1	0	0



No. at Risk										
Low	16	15	14	13	13	9	5	0	0	0
Int	39	30	24	20	20	16	11	1	1	0
High	48	32	23	21	18	16	5	0	0	0

High vs Low RS group, HR (95% CI)

Placebo (n=90)
9.18 (2.15–39.24) $P<0.001$

Sunitinib (n=103)
1.86 (0.68–5.06) $P=0.20$

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- Teste conseguiu ser prognóstico...
- MAS NÃO PREDITIVO!

Conclusions

- RS was associated with TTR, DFS, and RCSS in both arms, with the strongest associations observed in the placebo arm, thus confirming **the overall prognostic value** of the 16-gene assay
- **The predictive value** of RS to select patients for adjuvant sunitinib therapy has not been demonstrated, but would warrant further investigation in adequately powered and prospectively designed adjuvant trials
- RS results may help identify patients with clear-cell, stage III high-risk RCC who could derive higher absolute benefit from adjuvant therapy

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19

DISCUSSÃO

Qual a diferença entre o PROTECT e o STRAC?

Estudos são bem parecidos com populações parecidas.

Protect fez um escalonamento de dose não realizado no STRAC.

Há papel para adjuvância com TKI? Em quais pacientes?

O tratamento adjuvante em câncer de rim ainda pede por uma novidade mais eficaz.

Tratamento hoje deve ser individualizado e amplamente discutido com o paciente

Trials em andamento

A maior esperança ainda continua sendo a imunoterapia...



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Updated Survival Analysis From KEYNOTE-045: Phase 3, Open-Label Study of Pembrolizumab Versus Paclitaxel, Docetaxel, or Vinflunine in Recurrent, Advanced Urothelial Cancer

Dean F. Bajorin,¹ Ronald de Wit,² David J. Vaughn,³ Yves Fradet,⁴ Jae Lyun Lee,⁵ Lawrence Fong,⁶ Nicholas J. Vogelzang,⁷ Miguel A. Climent,⁸ Daniel P. Petrylak,⁹ Toni K. Choueiri,¹⁰ Andrea Necchi,¹¹ Winald Gerritsen,¹² Howard Gurney,¹³ David I. Quinn,¹⁴ Stéphane Culine,¹⁵ Cora N. Sternberg,¹⁶ Yabing Mai,¹⁷ Markus Puhlmann,¹⁷ Rodolfo F. Perini,¹⁷ Joaquim Bellmunt¹⁰

¹Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²Erasmus MC Cancer Institute, Rotterdam, Netherlands; ³Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; ⁴CHU de Québec-Université Laval, Québec City, QC, Canada; ⁵Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea; ⁶University of California, San Francisco, San Francisco, CA, USA; ⁷Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; ⁸Fundación Instituto Valenciano de Oncología, Valencia, Spain; ⁹Smilow Cancer Hospital at Yale University, New Haven, CT, USA; ¹⁰Dana-Farber Cancer Institute, Boston, MA, USA; ¹¹Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ¹²Radboud University Medical Center, Nijmegen, Netherlands; ¹³Westmead Hospital and Macquarie University, Sydney, NSW, Australia; ¹⁴University of Southern California Norris Comprehensive Cancer Center and Hospital, Los Angeles, CA, USA; ¹⁵Hôpital Saint-Louis, Paris, France; ¹⁶San Camillo Forlanini Hospital, Rome, Italy; ¹⁷Merck & Co., Inc., Kenilworth, NJ, USA

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Challenges of Treating Recurrent Urothelial Carcinoma After Platinum Therapy

- Currently no universally accepted second-line therapy
 - Vinflunine: approved, commonly used in European Union¹
 - Taxanes: supported by consensus guidelines²
 - Checkpoint inhibitors (atezolizumab, nivolumab, durvalumab, avelumab) received accelerated approvals in United States based on response rates
- Level 1 evidence for enhanced survival and safety over chemotherapy is of critical importance in advancing the treatment of urothelial cancer

1. Houede N et al. *BMC Cancer*. 2016;16:752.
2. NCCN Guidelines. Bladder cancer. 2017:version 1.2017.

- Este estudo evidenciou os dados de sobrevida de pembrolizumabe em câncer de bexiga de segunda linha.

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 chemotherapy or recurrence <12 mo after perioperative platinum-based therapy
- ECOG performance status 0-2
- Provision of tumor sample for biomarker assessment

Stratification Factors

- ECOG performance status (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)

R
1:1

Pembrolizumab
200 mg IV Q3W

Paclitaxel 175 mg/m² Q3W
OR
Docetaxel 75 mg/m² Q3W
OR
Vinflunine 320 mg/m² Q3W

- 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

^aIn total ITT population and in patients with combined positive score ≥10%.

- Podemos observar que a segunda linha padrão em vários locais pode ser tanto um taxane com a vinflunina...

Baseline Characteristics

n (%)	Pembro (n = 270)	Chemo (n = 272)
Age, median (range), y	67 (29-88)	65 (26-84)
Men	200 (74.1)	202 (74.3)
Upper tract disease	38 (14.1)	37 (13.6)
Lower tract disease	232 (85.9)	235 (86.4)
ECOG PS ^a		
0	120 (44.4)	106 (39.0)
1	143 (53.0)	158 (58.1)
2	2 (0.7)	4 (1.5)
Visceral disease	241 (89.3)	234 (86.0)
Disease in lymph node only	28 (10.4)	38 (14.0)

n (%)	Pembro (n = 270)	Chemo (n = 272)
Liver metastases	91 (33.7)	95 (34.9)
Hemoglobin <10 g/dL ^b	43 (15.9)	44 (16.2)
Time since completion of most recent prior therapy		
≥3 months	167 (61.9)	168 (61.8)
<3 months	103 (38.1)	104 (38.2)
Setting of most recent prior therapy ^c		
Neoadjuvant	19 (7.0)	22 (8.1)
Adjuvant	12 (4.4)	31 (11.4)
First line	184 (68.1)	158 (58.1)
Second line	55 (20.4)	59 (21.7)
Third line	0	2 (0.7)

^aMissing for 5 patients in the pembro arm and 4 patients in the chemo arm. ^bMissing for 8 patients in the pembro arm and 4 patients in the chemo arm. ^cSetting and time from completion were missing for 1 patient in each arm. Data cutoff date: January 18, 2017.

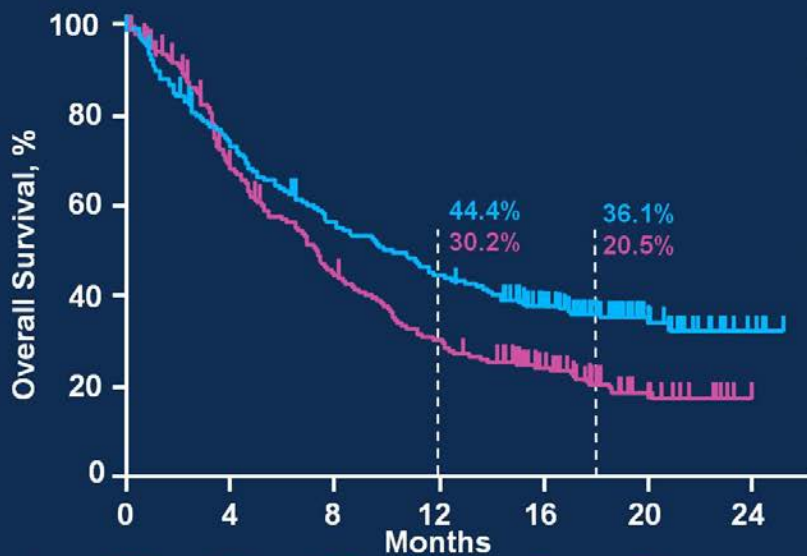
Baseline Characteristics

n (%)	Pembro (n = 270)	Chemo (n = 272)
Prior platinum therapy		
Cisplatin	199 (73.7)	214 (78.7)
Carboplatin	70 (25.9)	56 (20.6)
Other ^a	1 (0.4)	2 (0.7)
Smoking status ^b		
Never	104 (38.5)	83 (30.5)
Former	136 (50.4)	148 (54.4)
Current	29 (10.7)	38 (14.0)
PD-L1 CPS ≥10%	74 (27.4)	90 (33.1)

n (%)	Pembro (n = 270)	Chemo (n = 272)
Risk Factors ^c		
0	54 (20.0)	45 (16.5)
1	96 (35.6)	97 (35.7)
2	66 (24.4)	80 (29.4)
3-4	45 (16.7)	45 (16.5)

^aOxaliplatin, nedaplatin. ^bMissing for 1 patient in the pembro arm and 3 patients in the chemo arm. ^cIncludes Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL, and liver metastases (J Clin Oncol 2010;27:1850-1855) + time from prior chemotherapy <3 mo (Eur Urol 2013;63:717-723). Missing for 9 patients in the pembro arm and 5 patients in the chemo arm. Data cutoff date: January 18, 2017.

Overall Survival: Total



	Events, n	HR (95% CI) ^a	P ^b
Pembro	170	0.70 (0.57-0.86)	0.0004
Chemo	196		

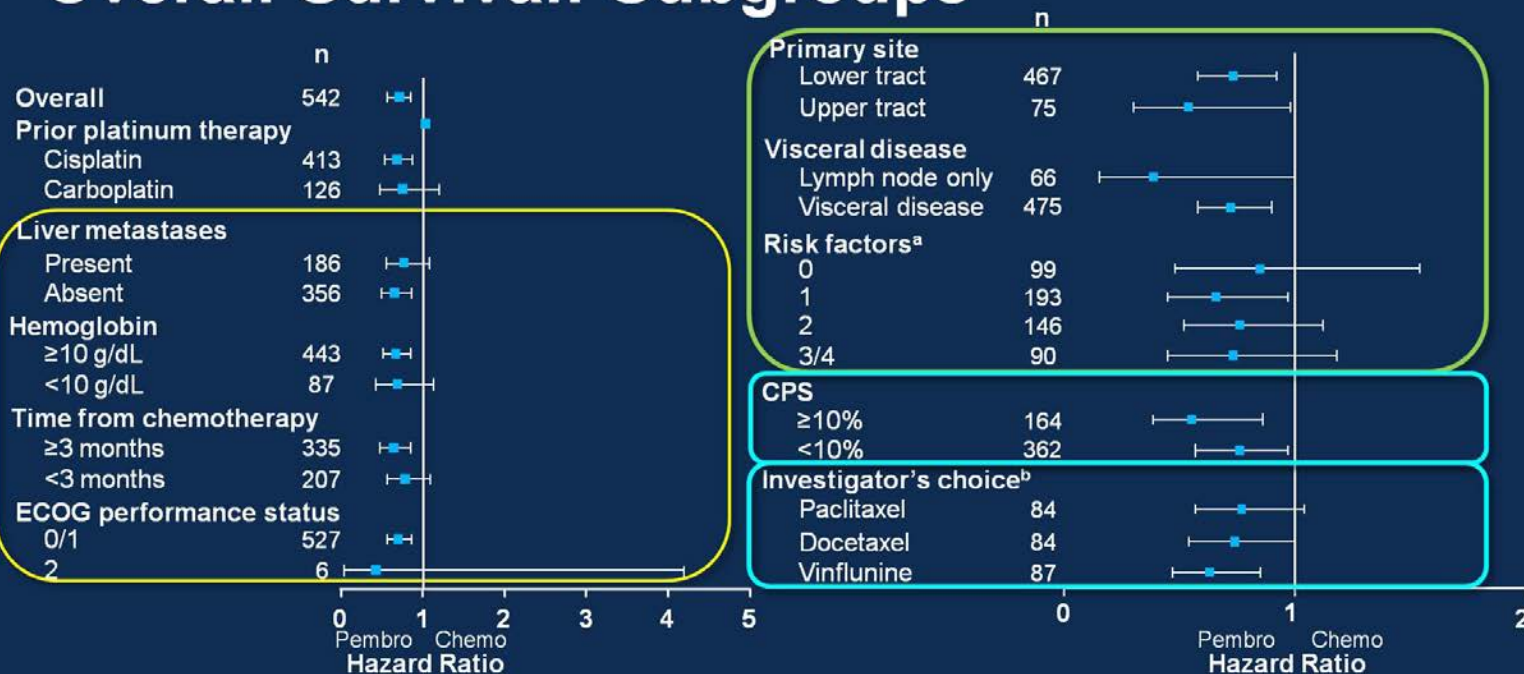
Median (95% CI):
10.3 mo (8.0-12.3)
7.4 mo (6.1-8.1)

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

^aBased 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). ^bOne-sided P value based on stratified log-rank test. Data cutoff date: January 18, 2017.

- Ganho inequívoco de sobrevida global em favor da imunoterapia

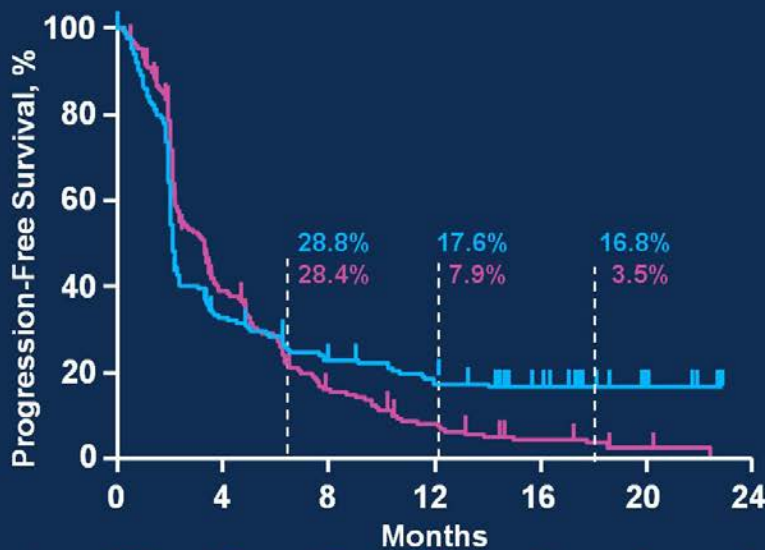
Overall Survival: Subgroups



^aIncludes Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL, and liver metastases (*J Clin Oncol.* 2010;27:1850-1855) + time from prior chemotherapy <3 mo (*Eur Urol.* 2013;63:717-723). ^bN is shown for the chemotherapy arm only. All comparisons were to all patients in the pembrolizumab arm. Data cutoff date: January 18, 2017.

- Ganho mais acentuado no subgrupo com expressão do PDL1 acima de 10%

Progression-Free Survival: Total



	Events, n	HR (95% CI)	P
Pembro	270	0.96 (0.79-1.16)	0.32
Chemo	272		

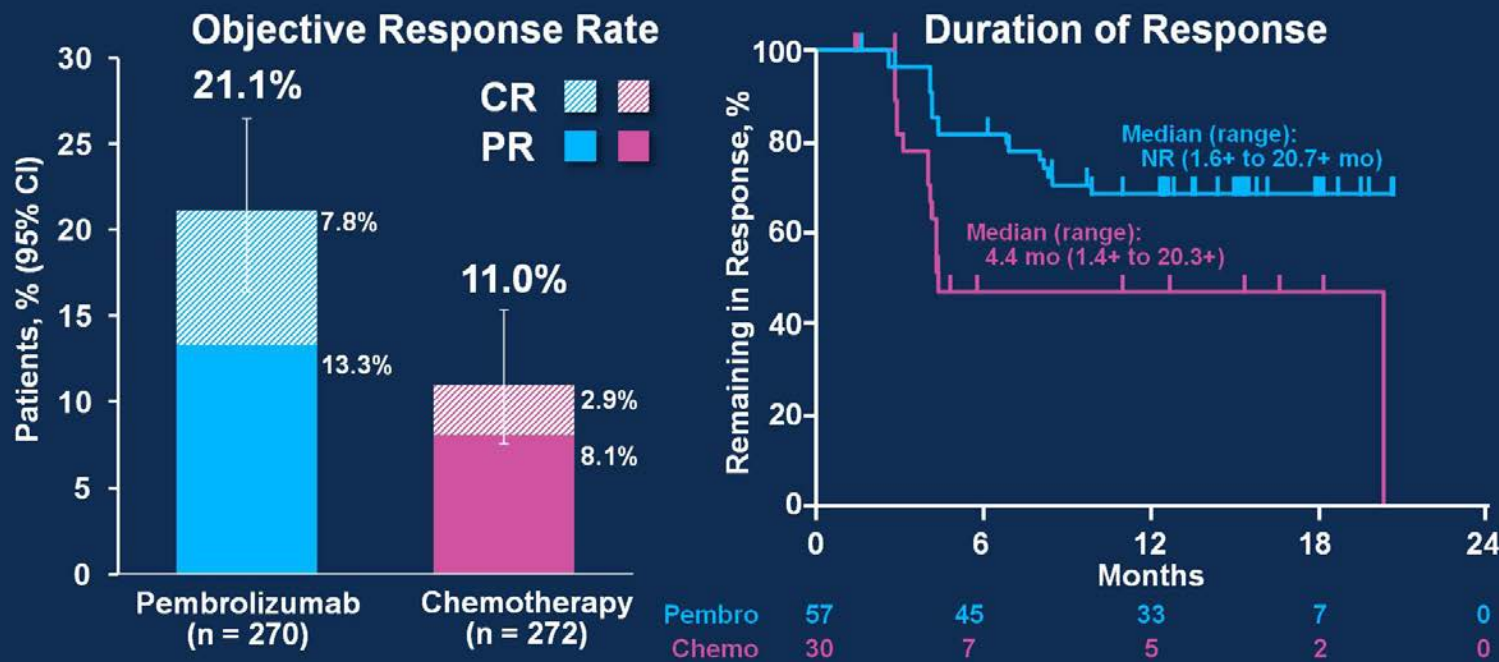
Median (95% CI):
2.1 mo (2.0-2.2)
3.3 mo (2.4-3.5)

Pembro	270	85	56	41	24	8	0
Chemo	272	91	34	15	6	2	0

Assessed per RECIST v1.1 by blinded, independent central review.
 Data cutoff date: January 18, 2017.

- Devido as dificuldades de se avaliar resposta pelo RECIST, o SLP pode ser inferior no braço da imunoterapia mesmo com ganho de sobrevida global...

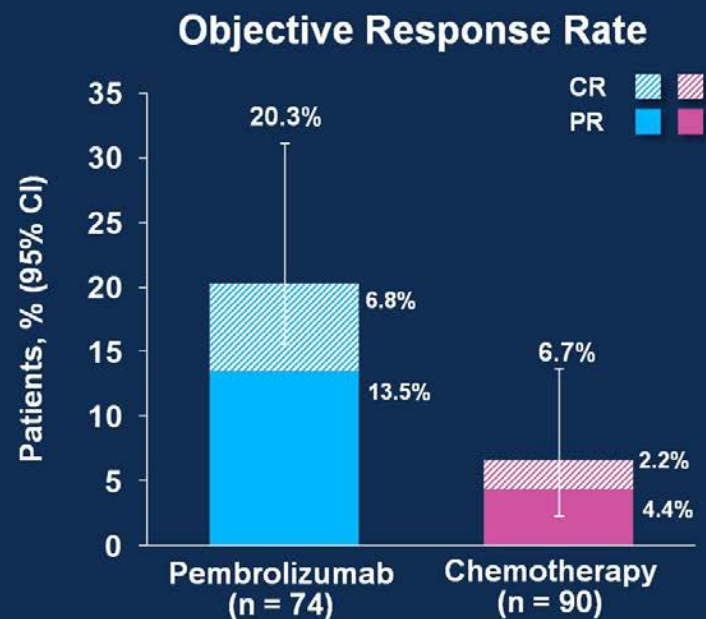
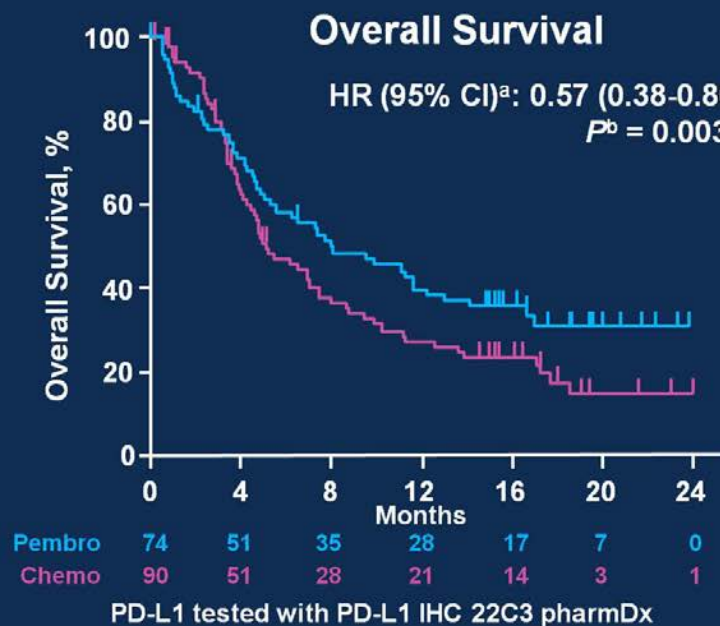
Objective Response and Response Duration



Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: January 18, 2017.

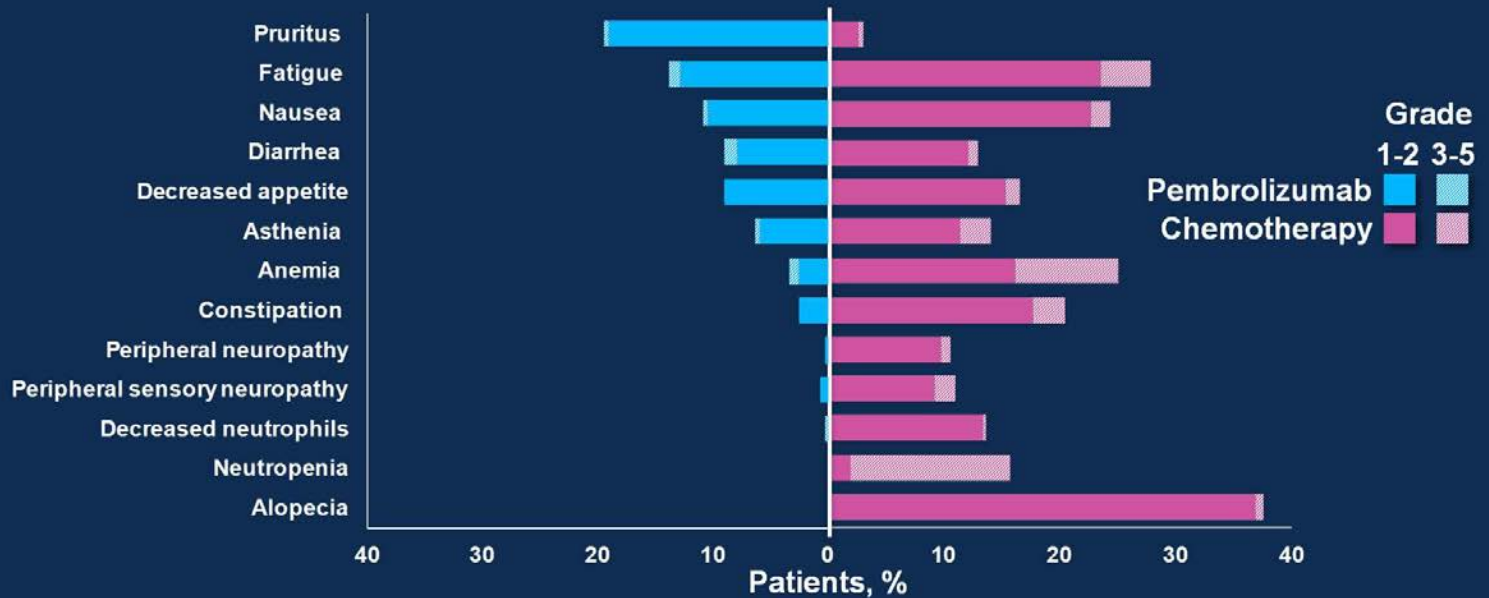
- Melhor resposta objetiva para a imunoterapia...
- Boa parte do benefício da QT é doença estável...

Efficacy: PD-L1 CPS $\geq 10\%$



^aBased 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). ^bOne-sided P value based on stratified log-rank test. Data cutoff date: January 18, 2017.

Treatment-Related AEs Occurring in $\geq 10\%$ Patients^a



^aOf patients in either treatment arm.
7.5% febrile neutropenia in the chemotherapy arm.
Data cutoff date: January 18, 2017.

- Efeitos colaterais esperados para a imunoterapia...

Summary

- Pembrolizumab survival benefit maintained with longer follow-up
 - Median OS, 10.3 versus 7.4 mo; HR, 0.70; $P = 0.0004$; median follow-up, 18.5 mo
 - OS at 12 months (44.4% vs 30.2%) and 18 months (36.1% vs 20.5%)
- Continued higher ORR with pembrolizumab versus chemotherapy
- Responses more durable with pembrolizumab versus chemotherapy
 - Median duration of response: Not reached versus 4.4 mo
 - Responses lasting ≥ 12 months: 69% versus 36%
- Better safety profile with pembrolizumab versus chemotherapy
 - Treatment-related AEs: 61.3% versus 90.2%
 - Grade ≥ 3 treatment-related AEs: 16.5% versus 49.8%

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Conclusions

- Pembrolizumab is the first immunotherapy to demonstrate superior survival over chemotherapy in patients with advanced urothelial carcinoma after failure of platinum-based therapy
- Pembrolizumab should be considered a standard of care for these patients, supported by level 1 evidence
- Based on these data, the FDA provided full approval of pembrolizumab for the treatment of advanced urothelial carcinoma after failure of platinum-based therapy without the need for PD-L1 staining

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- Pembrolizumabe é o novo padrão para segunda linha de tratamento para tumores uroteliais avançados

DISCUSSÃO

Só a imunoterapia vale?

Hoje a imunoterapia é o tratamento padrão para tumores uroteliais em segunda linha e para tumores não elegíveis a tratamento com platina na primeira linha.



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