POR QUE ABIRATERONA NA DOENÇA METASTÁTICA HORMONIO SENSÍVEL

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Como revereter a injustiça

- Carlos Dzik – 15 minutos
- Fabio Kater – 12 minutos

- Carlos Dzik foi meu professor

E3805 – CHAARTED Treatment

STRATIFICATION

Extent of Mets
- High vs. Low

Age
≥70 vs < 70yo

ECOG PS
- 0-1 vs 2

CAB> 30 days
- Yes vs. No

SRE Prevention
- Yes vs. No

Prior Adjuvant ADT
≤12 vs. > 12 months

(N = 790)

RANDOMIZE

ARM A:
ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles

Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

ARM B:
ADT (androgen deprivation therapy alone)

Evaluate every 12 weeks

Follow for time to progression and overall survival

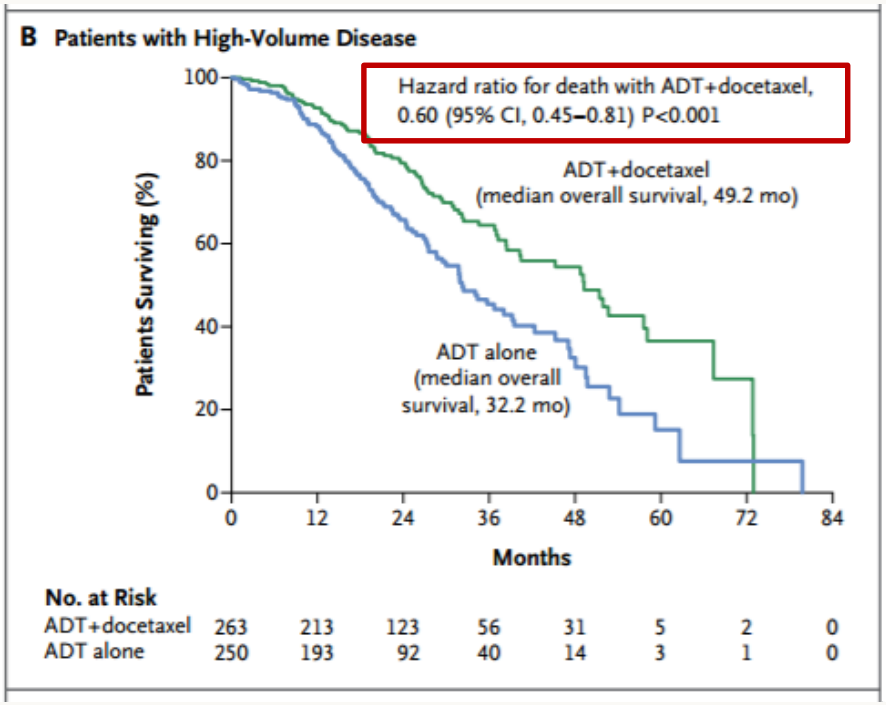
Chemotherapy at investigator's discretion at progression

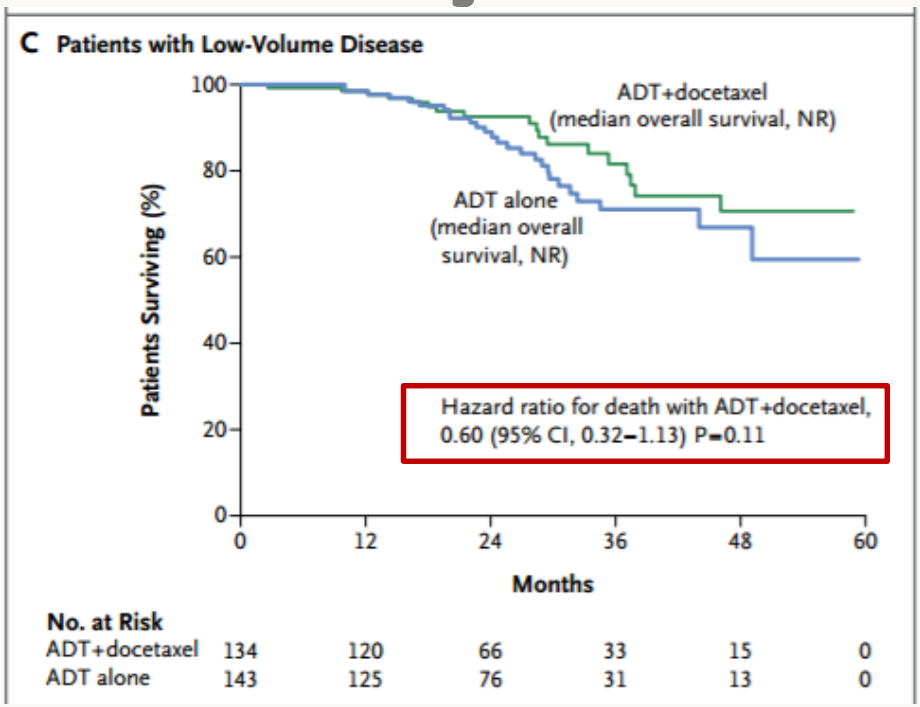
- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Estratificação em doença de alto e baixo volume

Alto volume: metas viscerais ou ≥ 4 metas ósseas sendo pelo menos 1 fora da vértebra e pelve

Curvas de sobrevida por volume de doença

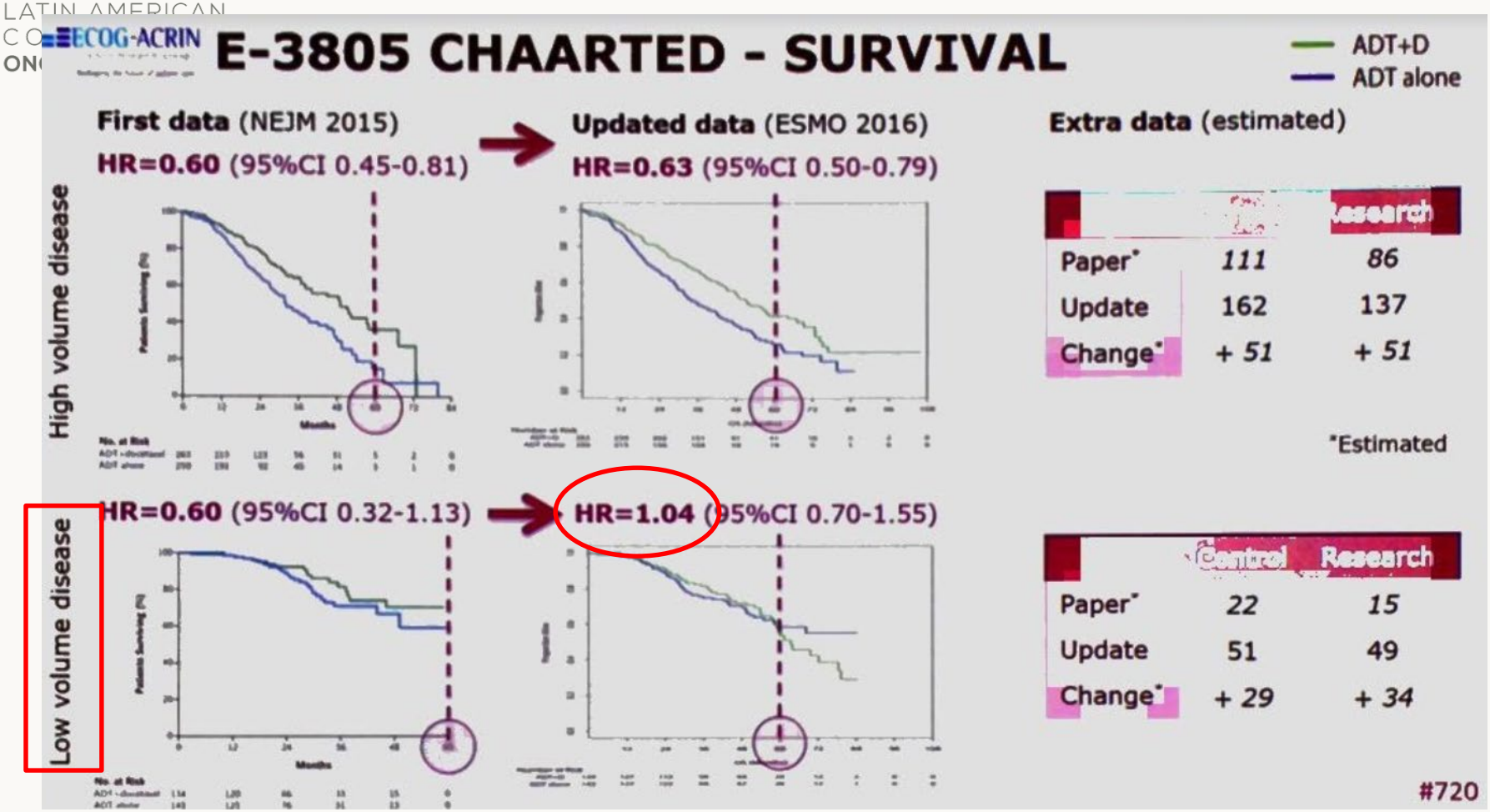




Sobrevida global alto volume: 49,2 vs 32,2 meses
Sobrevida global baixo volume: não alcançada

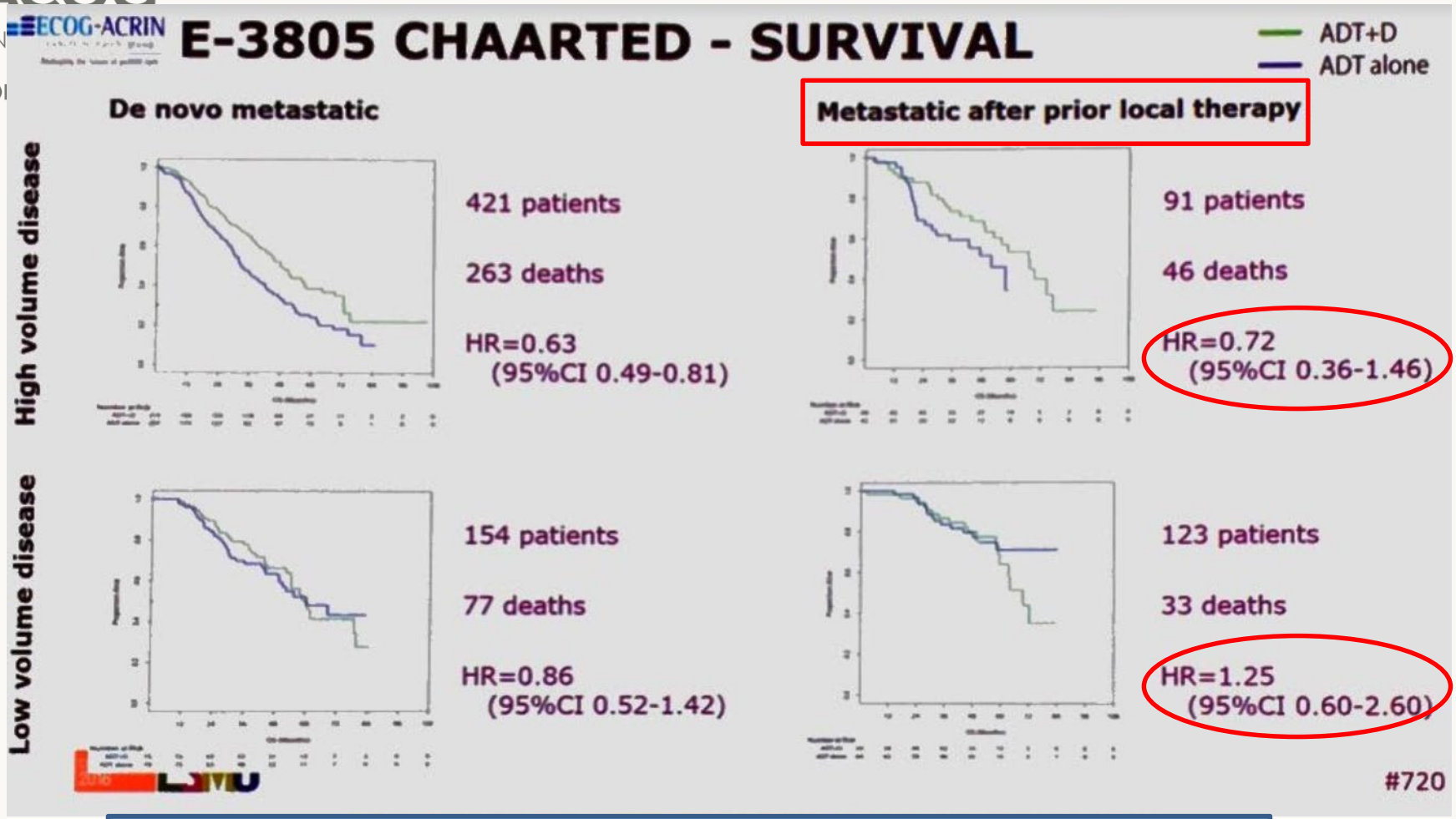
HR IGUAL – 0,6

Atualização de sobrevida por volume de doença – ESMO 2016



Perda do benefício no baixo volume

Avaliação de de novo e previamente tratado



Perda do benefício nos pacientes tratados previamente

Overall study design of LATITUDE

Patients
- Newly diagnosed adult men with high-risk mHNPC

Stratification factors
- Presence of visceral disease (yes/no)
- ECOG PS (0, 1 vs 2)

RANDOMIZED 1:1

ADT
+ Abiraterone acetate 1000 mg QD
+ Prednisone 5 mg QD
(n = 597)

ADT
+ placebos
(n = 602)

Efficacy end points

Co-primary:
- OS
- rPFS

Secondary: time to
- pain progression
- PSA progression
- next symptomatic skeletal event
- chemotherapy
- subsequent PC therapy

- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

Pelo menos dois de três fatores de risco:

Gleason ≥ 8

3 ou mais metástases ósseas

metástases viscerais mensuráveis

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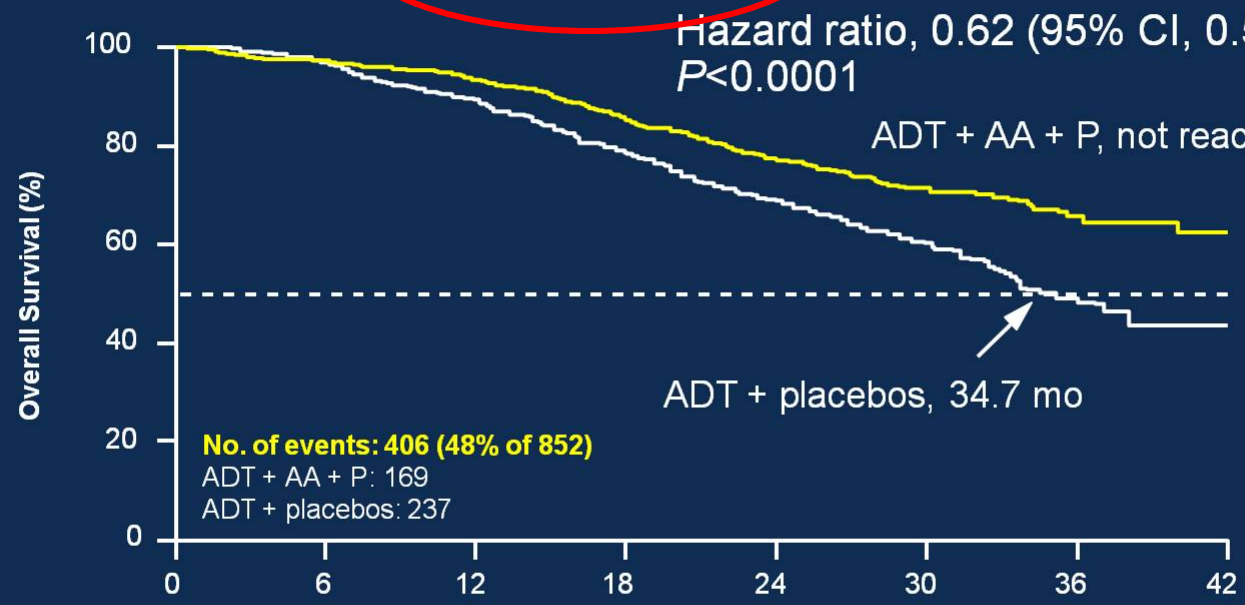
Statistically significant 38% risk reduction of death



OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

No. at risk								
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

Median follow-up: 30.4 months

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Inclusion criteria

Newly-diagnosed

Any of:

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

Relapsing after previous RP or RT with ≥1 of:

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/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.stampedetrial.org

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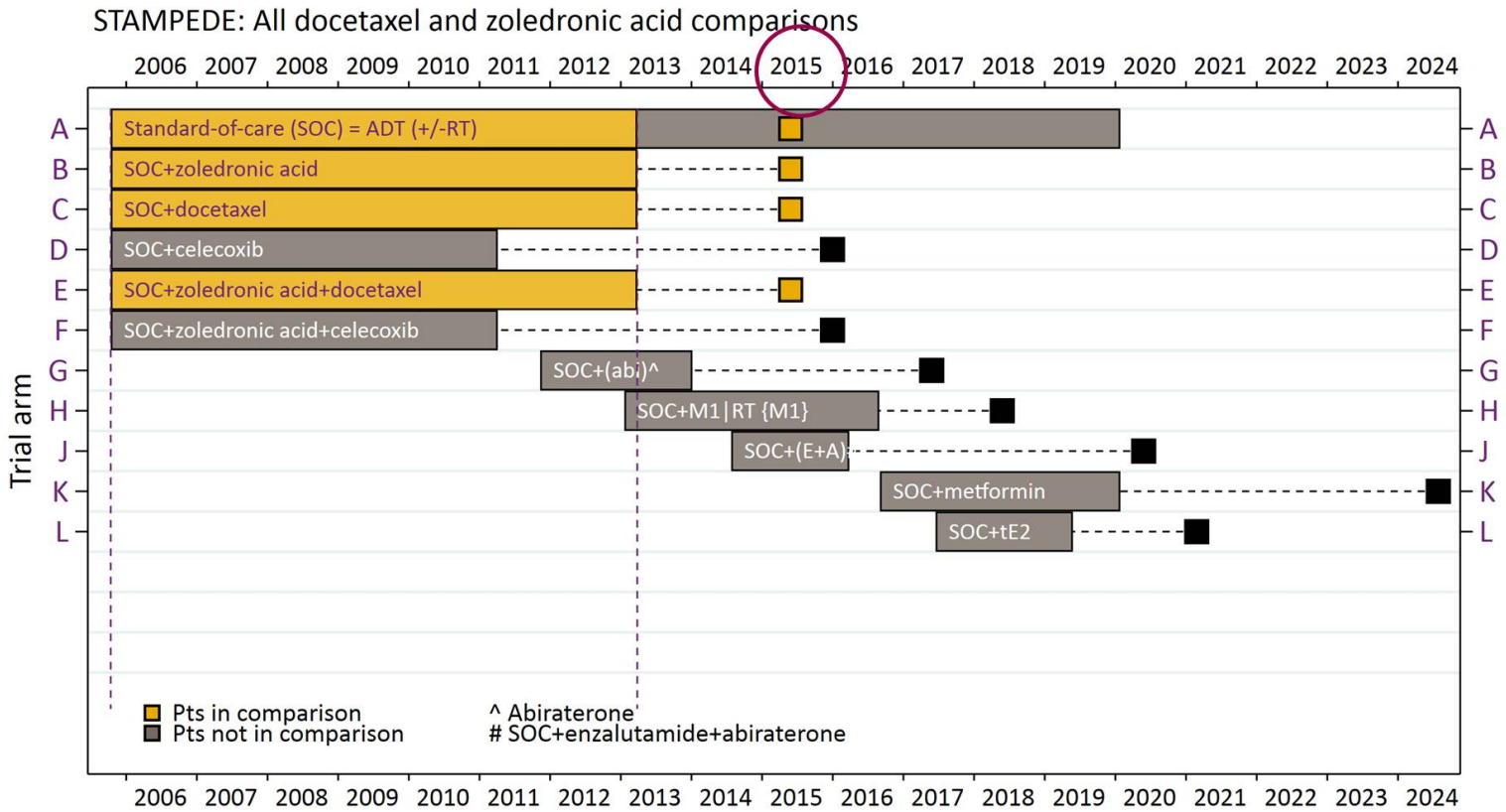
STAMPEDE: "original comparisons"



A = 1184/~1200 pts --> 415/~404 primary outcome measure events
B = 593/~600 pts, C = 592/~600 pts, E = 593~600 pts

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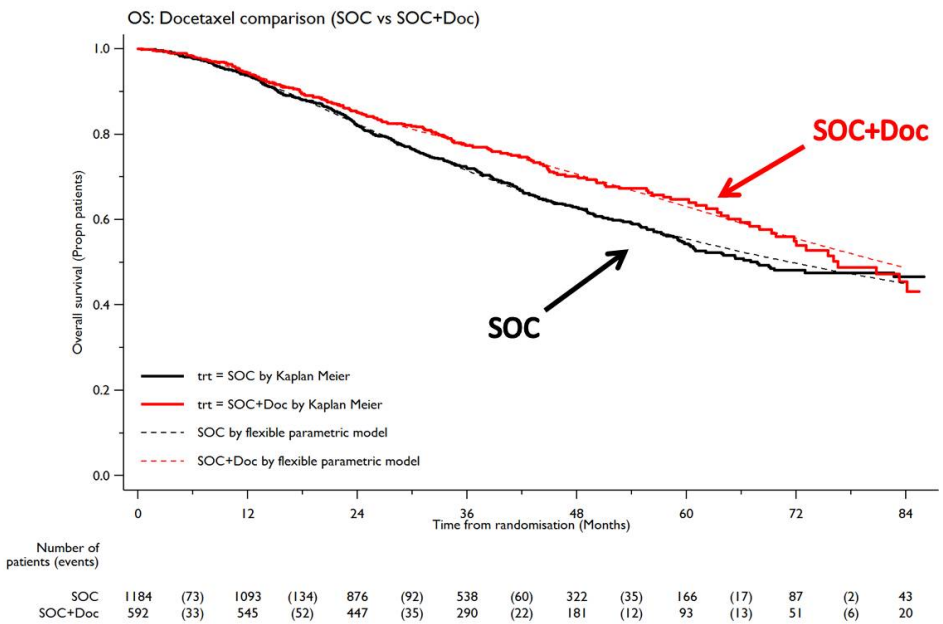
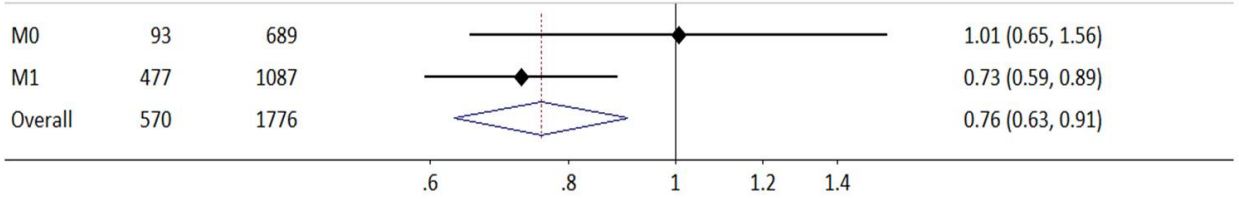
Docetaxel: Survival



HR (95%CI)	**0.78** (0.66, 0.93)
P-value	**0.006**

Non-PH p-value 0.87



STAMPEDE – ABIRATERONA (BRAÇO G) - Eficácia

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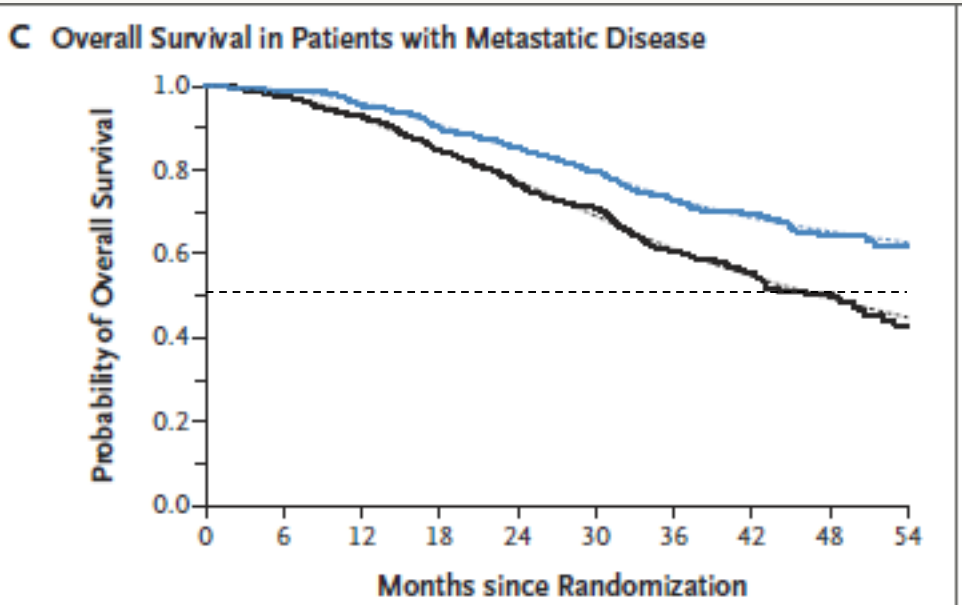
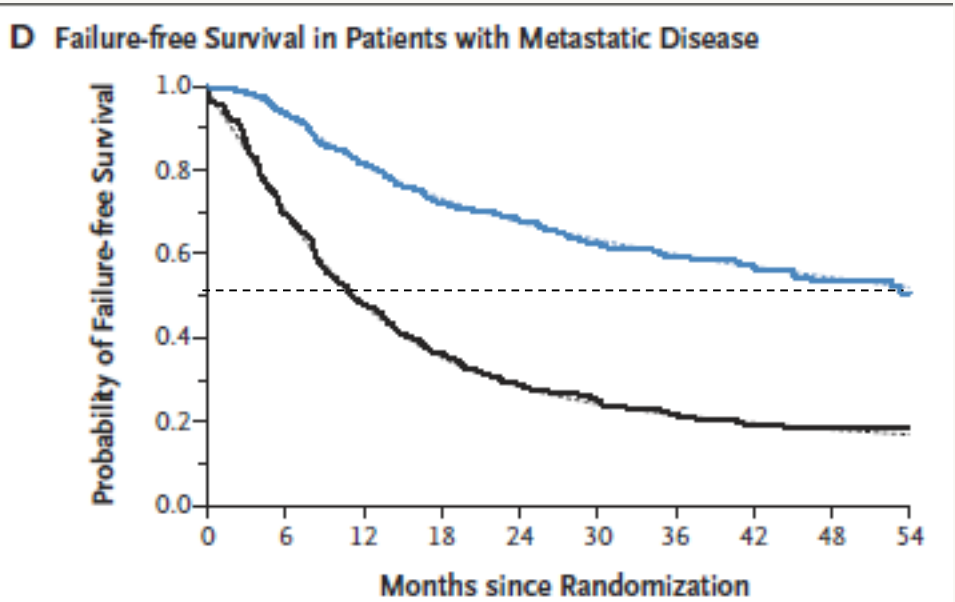
Sobrevida Global

Sobrevida Livre de Falha



No. of Patients (no. of deaths)

Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60



No. of Patients (no. of treatment-failure events)

Combination therapy	500	(92)	399	(65)	326	(40)	202	(11)	63
ADT alone	502	(258)	236	(93)	139	(33)	83	(9)	23

James ND et al. NEJM 2017

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The mCSPC landscape in 2018

Study	Agents	N	Indication	HR (95% CI)	ΔOS (mo)
CHAARTED[1]	DOC vs ADT	790	Metastatic hormone –sensitive PCa (mHSPC)	0.61 (0.47-0.80)	**+13.6**
STAMPEDE[2]	DOC/P vs ADT	1,086	mHSPC	0.73 (0.59-0.89)	**+22.0**
LATITUDE[3]	ABI/P vs ADT	1,199	High-risk mHSPC	0.62 (0.51-0.76)	Not reached
STAMPEDE[4]	ABI/P vs ADT	1,002	mHSPC	0.61 (0.49-0.75)	Not reached

ABI: abiraterone; ADT: androgen deprivation therapy; CABA: cabazitaxel; DOC: docetaxel; ENZA: enzalutamide; mito: mitoxantrone; OS: overall survival; pbo: placebo; P: prednisone

1. Sweeney, NEJM 2015;373:737-46; 2. James, Lancet 2016; 387:1163-77&ASCO2015 (abs 5001); 3. Fizazi, NEJM 2017;377:338-51; 4. James, NEJM 2017;377:338-51

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In mHSPC, for a patient who is fit to receive docetaxel chemotherapy

ADT + docetaxel

ADT + abiraterone

What would you choose?

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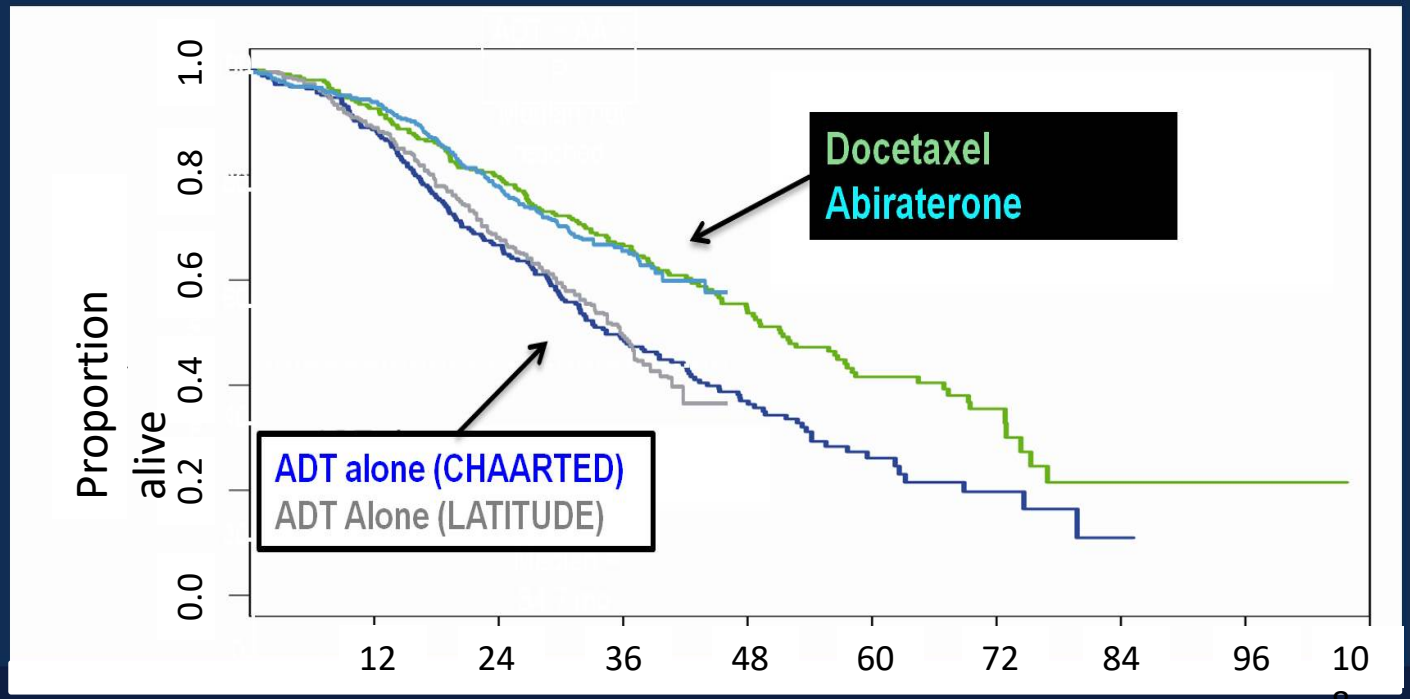

Overlay of LATITUDE KM Plot on CHAARTED (high volume) KM Plot

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Abi x Docetaxel

Nenhuma diferença estatisticamente diferente em nenhum subgrupo

		Doce-ADT vs ADT alone			Abi-ADT vs ADT alone			
		Studies	HR (95% CI)	I^2 (%)	Studies	HR (95% CI)	I^2 (%)	Abi-ADT vs Doce-ADT HR (95% CI)
Overall		3	0.75 (0.63–0.91)	51	2	0.63 (0.55–0.72)	0	0.84 (0.67–1.06)
Disease volume	High	2	0.68 (0.52–0.87)	25	1	0.60 (0.47–0.75)	NA	0.88 (0.62–1.25)
	Low	2	0.83 (0.50–1.37)	47	1	0.65 (0.45–0.96)	NA	0.78 (0.42–1.47)
Age	Younger	2	0.71 (0.60–0.85)	0	2	0.55 (0.45–0.66)	0	0.77 (0.60–1.004)
	Older	2	0.65 (0.32–1.33)	77	2	0.77 (0.53–1.12)	71	1.18 (0.53–2.65)
Performance Status	0	2	0.75 (0.63–0.91)	0	2	0.67 (0.56–0.80)	0	0.89 (0.69–1.15)
	1–2	2	0.59 (0.32–1.10)	78	2	0.57 (0.46–0.71)	0	0.97 (0.50–1.86)
Gleason Score	≤7	2	0.55 (0.35–0.89)	27	2	0.74 (0.48–1.15)	0	1.35 (0.71–2.55)
	≥8	2	0.70 (0.56–0.87)	29	2	0.61 (0.53–0.71)	0	0.87 (0.67–1.13)
Recurrent disease	Yes	3	0.74 (0.48–1.15)	0	1	0.94 (0.35–2.52)	NA	1.27 (0.43–3.74)
	No	3	0.78 (0.66–0.92)	24	1	0.61 (0.50–0.74)	NA	0.78 (0.60–1.01)
Visceral disease	Yes	1	0.52 (0.25–1.07)	n/a	1	0.51 (0.33–0.79)	NA	0.98 (0.42–2.29)
	No	1	0.64 (0.46–0.89)	n/a	1	0.66 (0.53–0.83)	NA	1.03 (0.69–1.54)

Abi = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; Doce = docetaxel; HR = hazard ratio; NA = not applicable.

Christopher J.D. Wallis EUROPEAN UROLOGY

Reclassificação pelo STAMPEDE - Abi

SUBGROUP RISK/VOLUME DISTRIBUTION

Population	Number	%
LATITUDE Low	428	47.5
LATITUDE High	473	52.5
CHAARTED Low	402	44.6
CHAARTED High	499	55.4

Individual	CHAARTED Low	CHAARTED High
LATITUDE Low	333 (37%)	**95 (10.5%)**
LATITUDE High	**69 (7.7)**	404 (44.8)

18.2%

ESMO 2018. LBA4

Abiraterona funciona independente do risco

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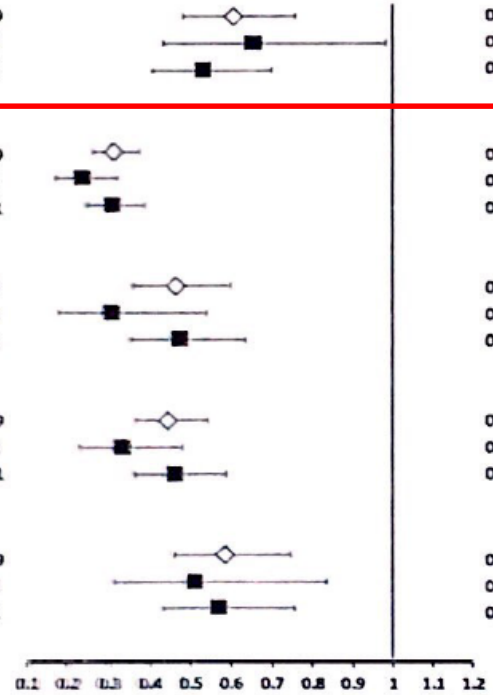
RESULTS: LATITUDE RISK STRATIFICATION

	ADT alone	AAP	Adjusted HR* (95%CI)	p-value	Interaction by metastatic volume p-value
	No. of events/No. of patients				
Overall survival					
All patients	195/452	135/449	0.609 (0.488-0.789)	<0.001	
Low risk	59/220	41/208	0.657 (0.438-0.983)	0.041	0.385
High risk	136/232	94/241	0.536 (0.411-0.699)	<0.001	
Failure free survival					
All patients	354/452	191/449	0.316 (0.264-0.378)	<0.001	
Low risk	152/220	56/208	0.238 (0.174-0.325)	<0.001	0.294
High risk	202/232	135/241	0.313 (0.250-0.392)	<0.001	
Skeletal related events					
All patients	164/452	93/449	0.467 (0.362-0.602)	<0.001	
Low risk	49/220	17/208	0.311 (0.179-0.543)	<0.001	0.207
High risk	115/232	76/241	0.477 (0.356-0.639)	<0.001	
Progression free survival					
All patients	267/452	158/449	0.446 (0.366-0.544)	<0.001	
Low risk	101/220	41/208	0.334 (0.232-0.482)	<0.001	0.159
High risk	166/232	117/241	0.463 (0.364-0.588)	<0.001	
Prostate cancer specific death*					
All patients	172/452	114/449	0.587 (0.462-0.746)	<0.001	
Low risk	49/220	27/208	0.511 (0.312-0.836)	0.008	0.728
High risk	123/232	87/241	0.570 (0.432-0.754)	<0.001	



ADT + Abiraterone + Prednisolone (AAP) ← → ADT alone

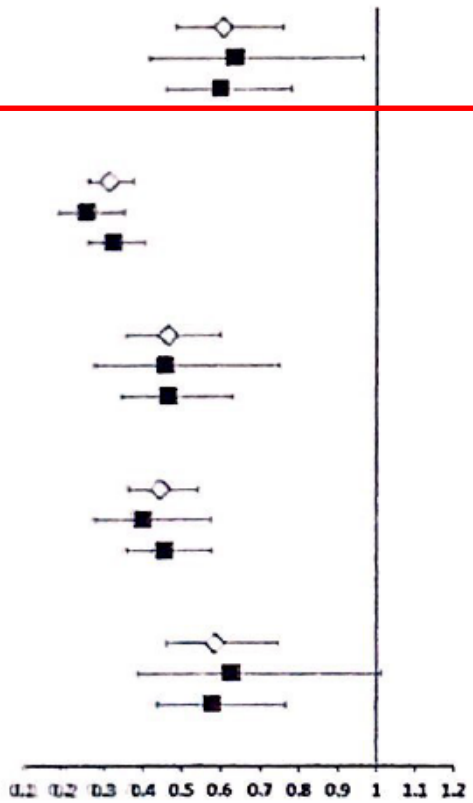
ESMO congress

ESMO 2018. LBA4

Abiraterona funciona inpendente do volume

CHAARTED VOLUME CRITERIA

	ADT alone	AAP	Adjusted HR* (95%CI)	p-value	Interaction by metastatic volume p-value
	No. of events/No. of patients				
Overall survival					
All patients	195/452	135/449	0.609 (0.488-0.789)	<0.001	
Low volume	53/196	39/206	0.637 (0.420-0.966)	0.034	0.771
High volume	142/256	96/243	0.601 (0.463-0.779)	<0.001	
Failure free survival					
All patients	354/452	191/449	0.316 (0.264-0.378)	<0.001	
Low volume	133/196	57/206	0.259 (0.189-0.356)	<0.001	0.472
High volume	221/256	134/243	0.327 (0.263-0.408)	<0.001	
Skeletal related events					
All patients	164/452	93/449	0.467 (0.362-0.602)	<0.001	
Low volume	46/196	25/206	0.459 (0.282-0.749)	0.002	0.981
High volume	118/256	68/243	0.468 (0.347-0.632)	<0.001	
Progression free survival					
All patients	267/452	158/449	0.446 (0.366-0.544)	<0.001	
Low volume	86/196	45/206	0.401 (0.279-0.577)	<0.001	0.670
High volume	181/256	113/243	0.457 (0.360-0.579)	<0.001	
Prostate cancer specific death*					
All patients	172/452	114/449	0.587 (0.462-0.746)	<0.001	
Low volume	43/196	31/206	0.627 (0.388-1.013)	0.057	0.740
High volume	129/256	83/243	0.579 (0.439-0.764)	<0.001	



ADT + Abiraterone + Prednisolone (AAP) better ← → ADT alone better

ESMO congress

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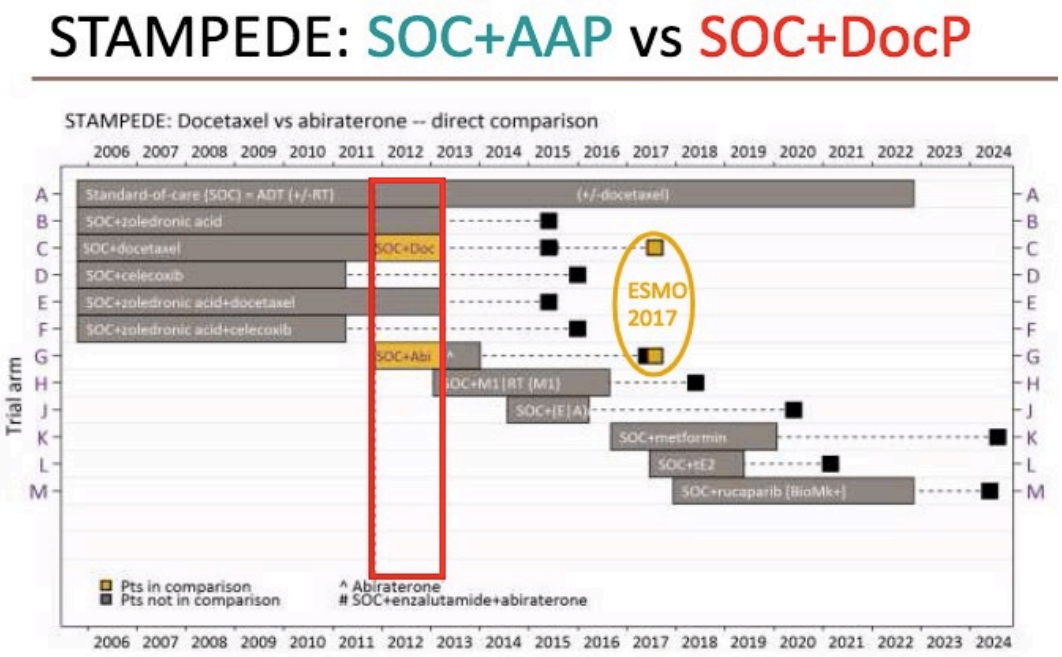
LBA31 - Abiraterona ou Docetaxel

Dados diretamente randomizados do STAMPEDE



- Pré-especificada
- Nenhum cálculo formal do tamanho da amostra
- Utilizados métodos padrões de análise de sobrevida
- Análise de eficácia: populáção ITT

Recruitment: Nov-2011 to Mar-2013

Reported: ESMO 2017
Published: (paper in development)

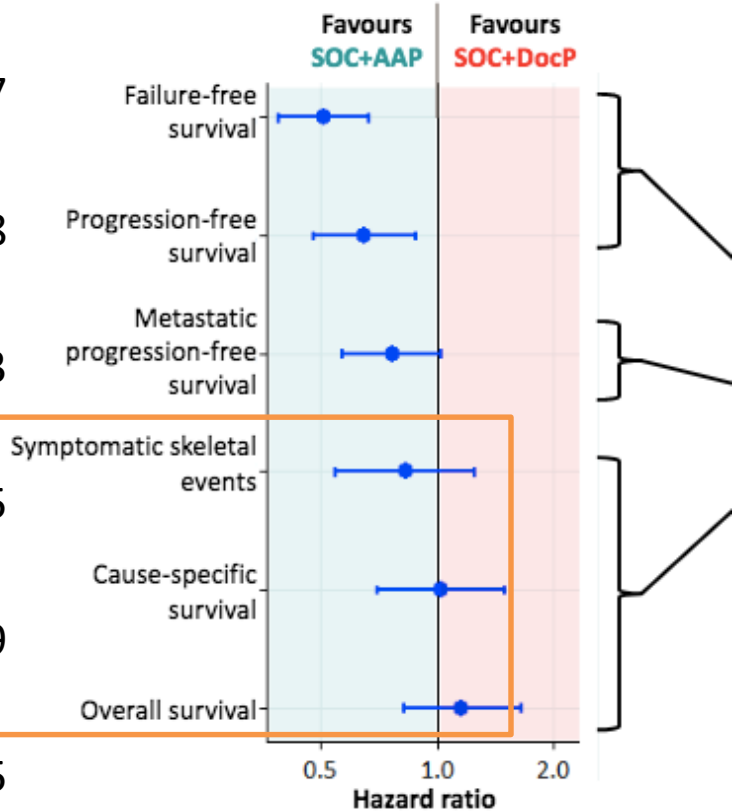
Patients: 189 SOC+DocP
377 SOC+AAP

566 pacientes randomizados contemporaneamente a cada braço da pesquisa

LBA31 - Abiraterona ou Docetaxel

Dados diretamente randomizados do STAMPEDE

HR	95% CI
0.51	0,39-0,67
0.65	0,48-0,88
0.77	0,57-1,03
0.83	0,55-1,25
1.02	0,79-1,49
1.16	0,82-1,65



Resumo

- Dados de 566 pacientes começando ADT de longa-duração para AdenoCa Próstata de Nov/2011 a Mar/2013
- Forte evidência favorecendo AAP em FFS, PFS
- Fraca evidência favorecendo AAP na MFS
- Ausência de boa evidência em sobrevida, CSS, SS
- Perfis de toxicidades muito diferentes, mas muito conhecidos

Sydes et al. ESMO 2017

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Adverse events – worst toxicity ever

Safety population	**SOC+DocP**	**SOC+AAP**
Patients included in adverse event analysis	172 (91%)	373 (>99%)
Grade 1+ AE	172 (100%)	370 (99%)
Grade 3+ AE	86 (50%)	180 (48%)
Grade 3+ AEs by category (*incl. expected AEs*)		
Endocrine disorder (*incl. hot flashes, impotence*)	15 (9%)	49 (13%)
Febrile neutropenia	29 (17%)	3 (1%)
Neutropenia	22 (13%)	4 (1%)
Musculoskeletal disorder:	9 (5%)	33 (9%)
Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*):	6 (3%)	32 (9%)
Gastrointestinal disorder:	9 (5%)	28 (8%)
Hepatic disorder (*incl. increased AST, increased ALT*):	1 (1%)	32 (9%)
General disorder (*incl. fatigue, oedema*):	18 (10%)	21 (6%)
Respiratory disorder (*incl. breathlessness*):	12 (7%)	11 (3%)
Renal disorder	5 (3%)	20 (5%)
Lab abnormalities (*incl. hypokalaemia*):	9 (5%)	11 (3%)

LATITUDE: PRO → Redução de 15% no risco de degradação da qualidade de vida

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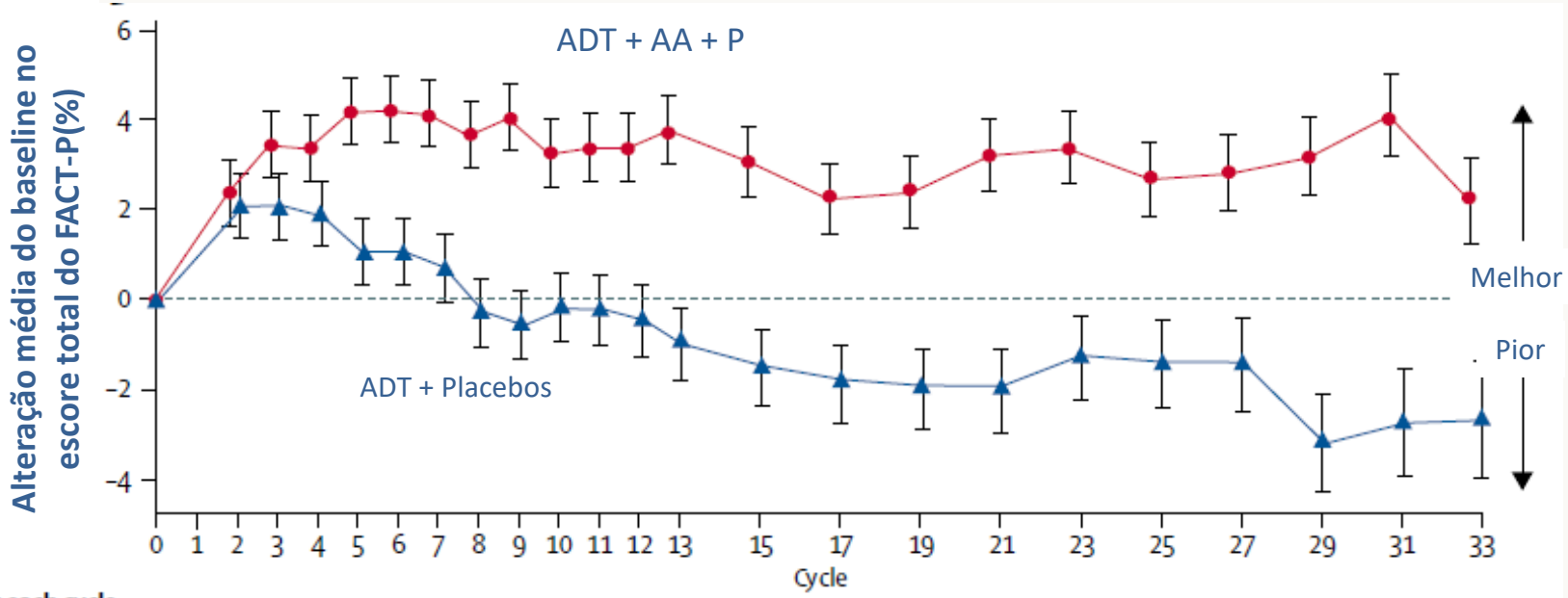
Abiraterona posterga significativamente a deteriorização da qualidade de vida (FACT-P)



Number of patients at each cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	15	17	19	21	23	25	27	29	31	33
ADT plus abiraterone acetate and prednisone	597	597	557	543	542	527	517	503	494	476	462	461	449	438	409	387	373	342	325	309	277	250	219	181
ADT plus placebos	602	602	569	555	542	526	488	479	451	431	394	370	357	345	303	270	237	209	185	168	142	124	100	76

Chi, K. Lancet Oncology. 2018. Jan 8. S1470-2045(17)30911-7

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Conclusão – 1

- Docetaxel (CHAARTED) perde benefício para doença de BAIXO VOLUME e NÃO de NOVO
  - Benefício na doença de novo de alto VOLUME
- Abiraterona: benefício de sobrevida global em alto RISCO (LATITUDE) e baixo RISCO (STAMPEDE- Abi)
- Abiraterona: benefício de SG em alto e baixo VOLUME (Stampede – Abi)

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Conclusão – 2

- Comparação entre Abi e Doce (STAMPEDE):
  - benefício de Abi para – Sobrevida livre de falência, Sobrevida livre de progressão e Sobrevida livre de metástases
  - Abi semelhante para Sobrevida câncer específica e sobrevida global
- Perfil de toxicidade mais conveniente para Abi
- Melhora de qualidade de vida a favor de Abi (LATITUDE)