

Sessão de fuzilamento:

Bloqueio Hormonal + Abiraterona melhor terapia inicial
mHSPC

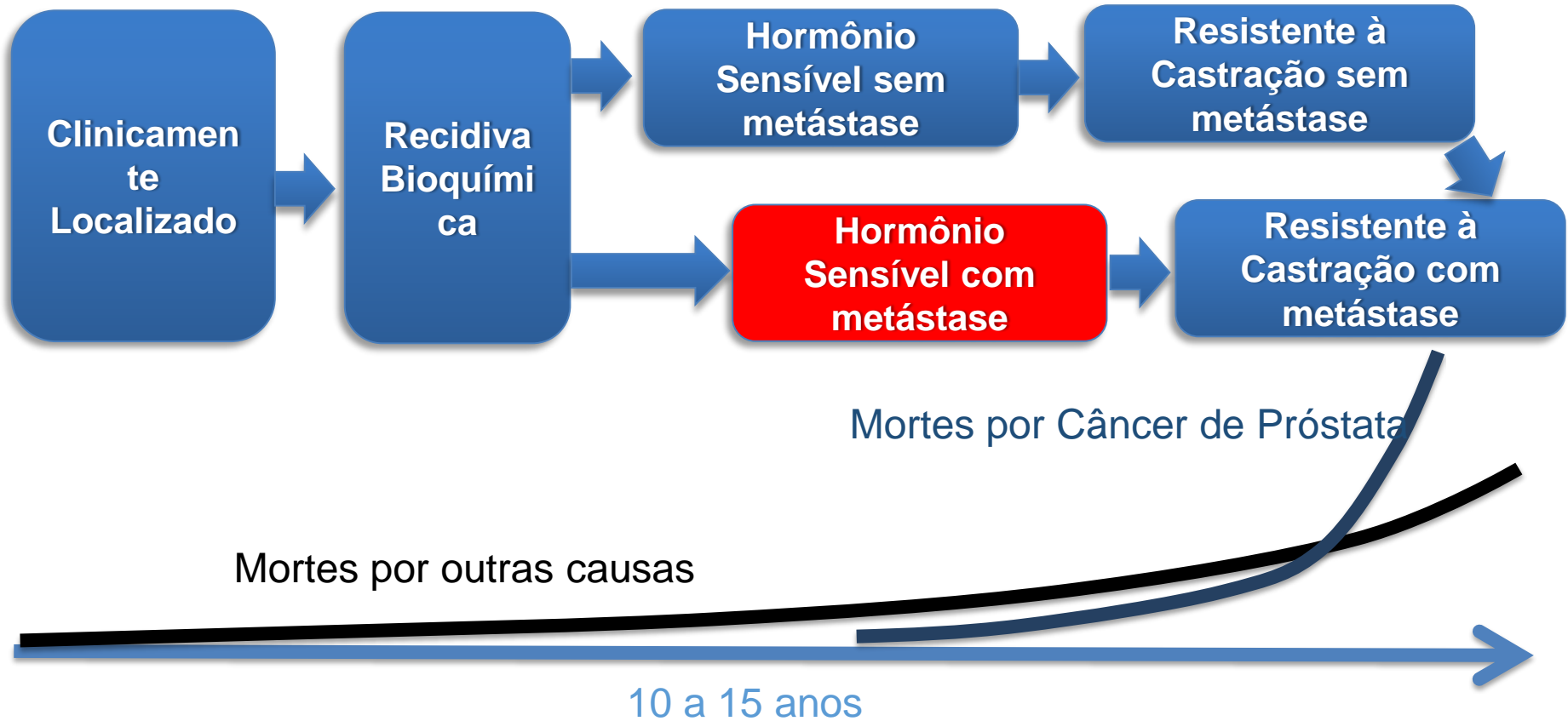


Daniel Herchenhorn

Coordenador Científico

Coordenador do Programa de Residência em Oncologia Clínica

Grupo de Oncologia D`Or



Sobre os fatos:

- Estudos de fase III demonstraram, com nível I de evidência, na população de interesse:
 - A adição de quimioterapia – Docetaxel, foi superior ao bloqueio hormonal isolado
 - Estudos Chaarted, Stampede, Meta-análises
 - A adição de Abiraterona, foi superior ao bloqueio hormonal isolado
 - Estudos Latitude, Stampede
- A comparação entre as 2 abordagens:
 - Indireta entre os estudos
 - Única comparação dentro do mesmo estudo, Stampede (diversos braços em paralelo)

Updated Guidelines for Metastatic Hormone-sensitive Prostate Cancer: Abiraterone Acetate Combined with Castration Is Another Standard[☆]

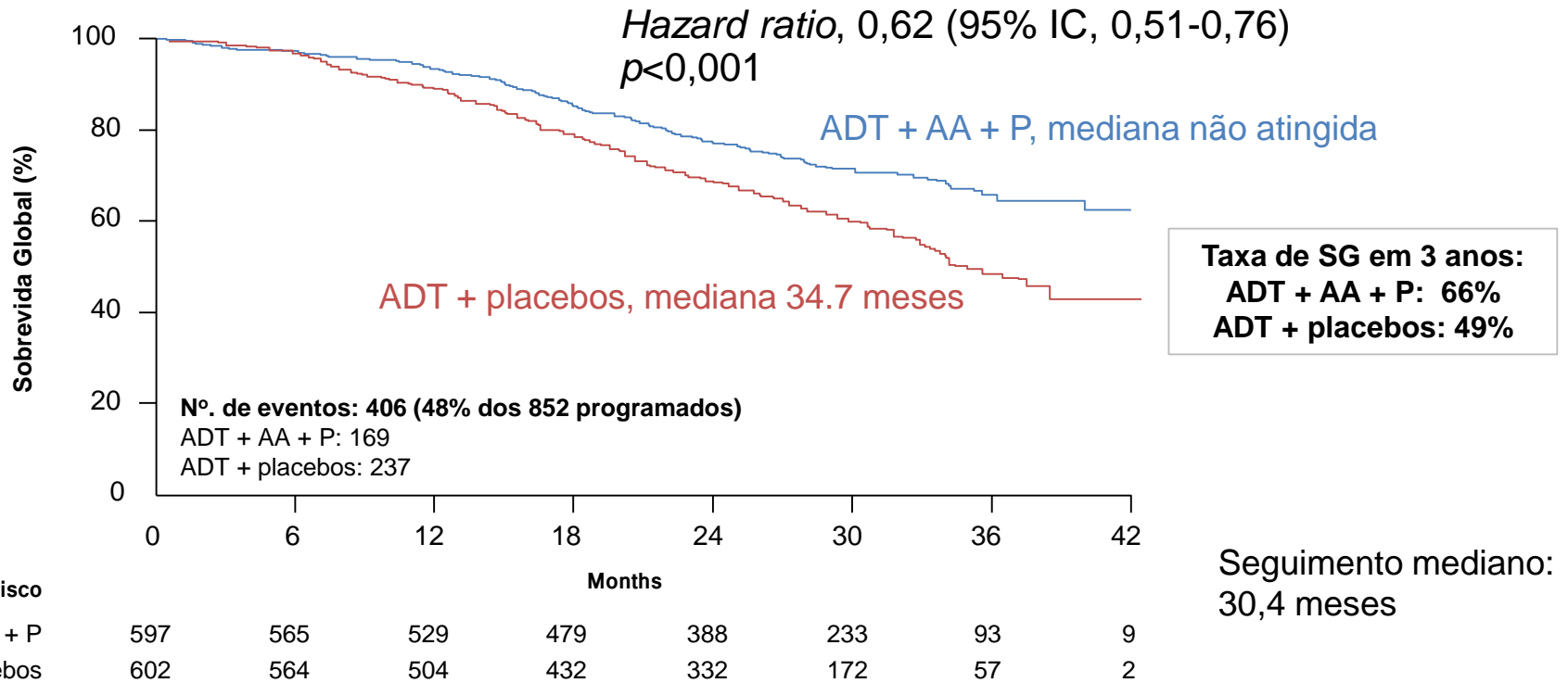
Nicolas Mottet^{a,*}, Maria De Santis^{b,c}, Erik Briers^k, Silke Gillessen^{d,m},
Jeremy P. Grummet^e, Thomas B. Lam^{f,g}, Henk G. van der Poel^h, Olivier Rouvière^{i,j},
Roderick C. Van den Bergh^h, Philip Cornford^j

^aDepartment of Urology, University Hospital, St. Etienne, France; ^bClinical Trials Unit, University of Warwick, UK; ^cDepartment of Urology, Medical University of Vienna, Austria; ^dDepartment of Oncology/Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; ^eDepartment of Surgery, Central Clinical School, Monash University, Melbourne, Australia; ^fAcademic Urology Unit, University of Aberdeen, Aberdeen, UK; ^gDepartment of Urology, Aberdeen Royal Infirmary, Aberdeen, UK; ^hDepartment of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands; ⁱHospices Civils de Lyon, Radiology Department, Edouard Herriot Hospital, Lyon, France; ^jRoyal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool, UK; ^kPatient Advocate, Hasselt, Belgium; ^lUniversité de Lyon; Université Lyon 1, Faculté de médecine Lyon Est, France; ^mUniversity of Bern, Switzerland

Table 6 – New guidelines to consider now for metastatic hormone-sensitive prostate cancer

	Recommendation
Offer surgical or medical castration (luteinizing-hormone-releasing hormone agonist or antagonist) as androgen deprivation therapy	Strong
Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy	Strong
Offer castration combined with abiraterone acetate + prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen	Strong
Offer castration, with or without an antiandrogen, to patients unfit for a combination with docetaxel or abiraterone acetate + prednisone, or who are unwilling to consider it	Strong

REDUÇÃO NO RISCO DE MORTE DE **38%**



Siglas: ADT = Terapia de Deprivação Androgênica; AA = acetato de abiraterona; P = prednisona; SG = sobrevida global

LATITUDE: *Endpoints* secundários e exploratórios

<i>End Points</i> Secundários	AA + P + ADT n = 597 Mediana (meses)	P+ADT n =602 Mediana (meses)	HR (IC 95%)	Valor de p
Tempo para Progressão de PSA	33,2	7,4	↓ 70%	<0,001
Tempo para progressão de DOR	NR	16,6	↓ 30%	<0,001
Tempo para próximo EVENTO ESQUELÉTICO sintomático	NR	NR	↓ 30%	0,009
Tempo para QUIMIOTERAPIA	NR	38,9	↓ 56%	<0,001
Tempo para TERAPIA SUBSEQUENTE	NR	21,6	↓ 58%	<0,001
			0,42 (0,35-0,50)	<0,001

<i>End Point</i> Exploratório	ADT + AA + P n = 597 Mediana (m)	ADT + P n =602 Mediana (m)	HR (IC 95%)	Valor de p
Pacientes com resposta no PSA (50% do <i>baseline</i>) - %	91	67	↑ 36%	<0,001
			1,58 (1,43-1,75)	

HR = *hazard ratio*

ADT = Terapia de Deprivação Androgênica

AA = acetato de abiraterona

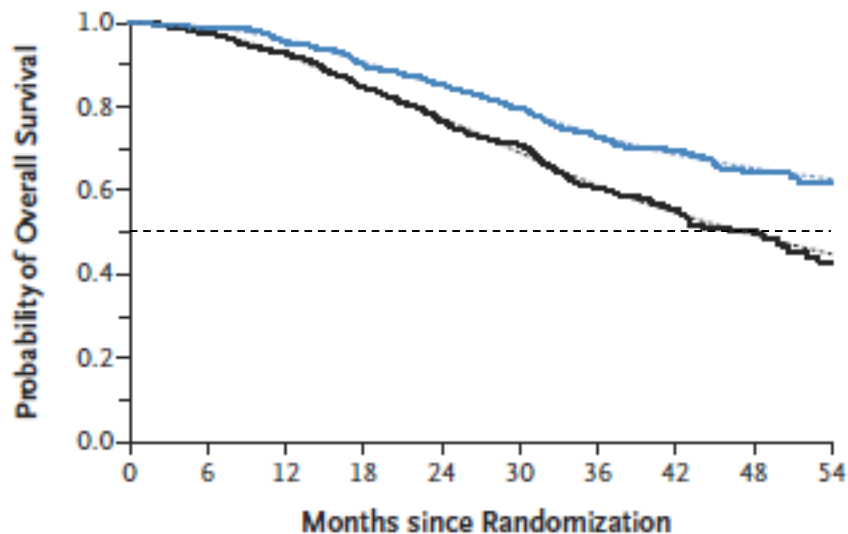
P = prednisona

Adaptado de Fizazi, 2017

STAMPEDE – ABIRATERONA (BRAÇO G) - Eficácia

Sobrevida Global

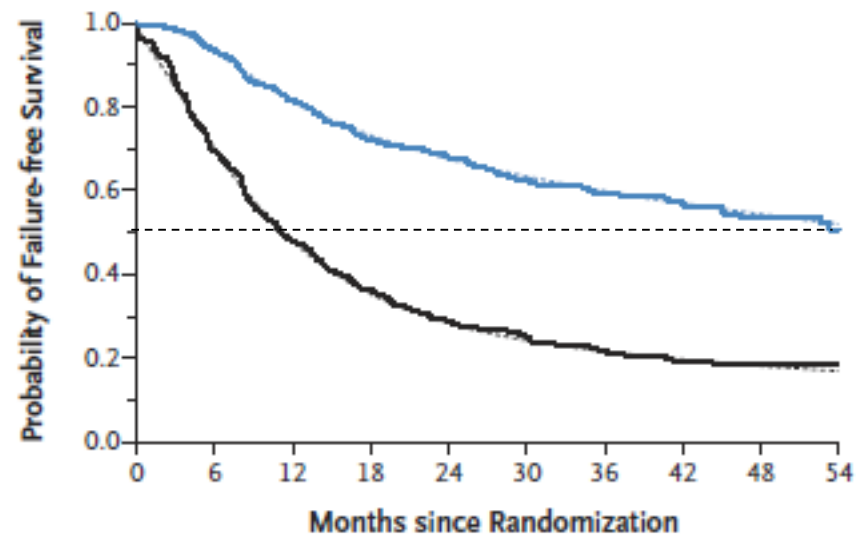
C Overall Survival in Patients with Metastatic Disease



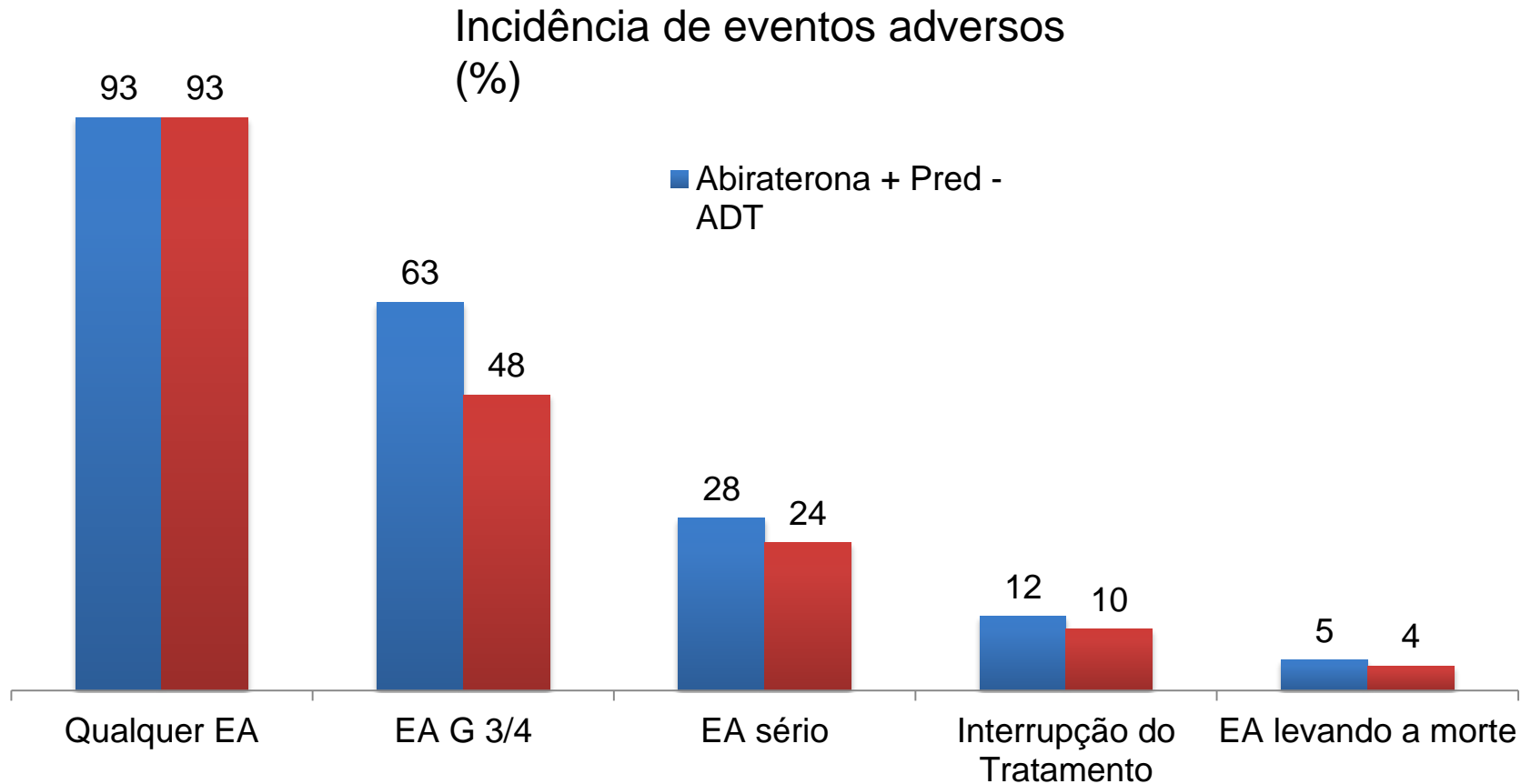
No. of Patients (no. of deaths)		0	6	12	18	24	30	36	42	48	54
Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81		
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60		

Sobrevida Livre de Falha

D Failure-free Survival in Patients with Metastatic Disease



No. of Patients (no. of treatment-failure events)		0	6	12	18	24	30	36	42	48	54
Combination therapy	500	(92)	399	(65)	326	(40)	202	(11)	63		
ADT alone	502	(258)	236	(93)	139	(33)	83	(9)	23		



EA = evento adverso
G 3/4 = graus 3 e 4
ADT = Terapia de deprivação androgênica

Gráfico elaborado a partir de Fizazi, NEJM 2017

Grade 3–5 AEs in $\geq 2\%$ of patients

AE, %	CHAARTED ¹			LATITUDE ²		STAMPEDE ARM G ³
	ADT + Docetaxel (n=390)			ADT + Abiraterone (n=597)		ADT + Abiraterone (n=948)
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 3–5
Allergic reaction	1.8	0.3	0	–	–	–
Fatigue	4.1	0	0	2	0	2
Neutropenia	3.1	9.0	0	–	–	–
Febrile neutropenia	3.8	2.3	0	–	–	–
Pulmonary disorder	–	–	0.3	–	–	–
Hypertension	–	–	–	20	0	1
Hypokalaemia	–	–	–	10	1	<1
ALT increased	–	–	–	5	<1	<1
Hyperglycaemia	–	–	–	4	<1	–
AST increased	–	–	–	4	<1	<1
Bone pain	–	–	–	3	0	–
Cardiac disorder	–	–	–	3	1	10
Endocrine disorder	–	–	–	–	–	14
Gastrointestinal disorder	–	–	–	–	–	5
General disorder	–	–	–	–	–	5

Carlo Messina,^{a,b} Marco Messina,^c Francesco Boccardo,^{a,b}

Tratamento sob Investigação	Abi + ADT <i>versus</i> ADT	Doc + ADT <i>versus</i> ADT	Abi/Doc + ADT vs ADT
Estudos incluídos	LATITUDE STAMPEDE	CHAARTED STAMPEDE GETUG-AFU15	LATITUDE STAMPEDE CHAARTED STAMPEDE GETUG-AFU15
Número de Pacientes	2.201 (1.097 vs 1.104)	2.951 (1.181 vs 1.770)	5.152 (2.278 vs 2.874)
HR agrupada para SG	0,62 (IC 95%: 0,53 – 0,71, <i>p</i> <0,001)	0,73 (IC 95%: 0,60 – 0,90, <i>p</i> = 0,02)	0,67 (IC 95%: 0,59 – 0,77, <i>p</i> <0,01)
HR agrupada para SLP	0,38 (IC 95%: 0,25 – 0,57, <i>p</i> <0,001)	0,63 (IC 95%: 0,57 – 0,70, <i>p</i> <0,001)	0,51 (IC 95%: 0,39 – 0,68, <i>p</i> <0,001)

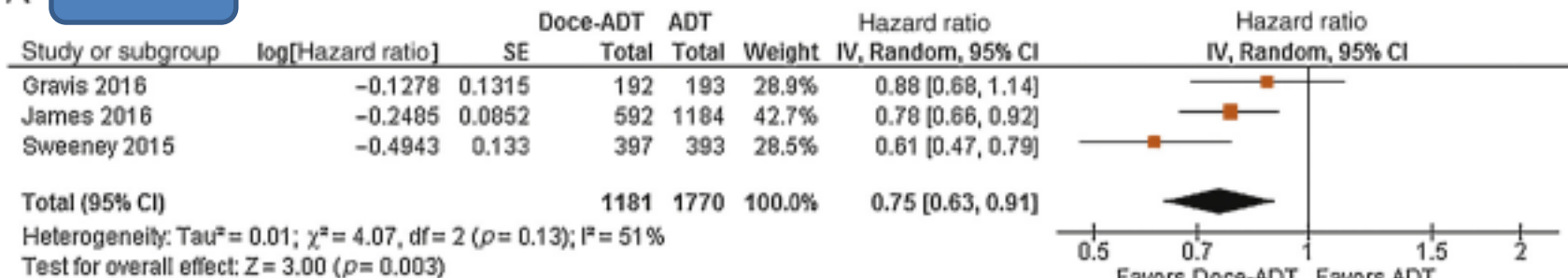
SG – sobrevida global, SLP – sobrevida livre de progressão, Abi – abiraterona, Doc – docetaxel, IC – intervalo de confiança

Abi + ADT vs Doc + ADT

Tratamento sob Investigação	Abi + ADT versus Doc + ADT
Estudos incluídos	LATITUDE + STAMPEDE GETUG+CHAARTED+STAMPEDE
Número de Pacientes	5.152 (2.278 vs 2.874)
HR agrupada para SG	↓ 33% (IC 95%: 0,50 – 0,77, p <0,01)
HR agrupada para SLP	↓ 49% (IC 95%: 0,39 – 0,68, p <0,001)

Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naïve Prostate Cancer: A Systematic Review and Network Meta-analysis

A Docetaxel



B Abirateron
a

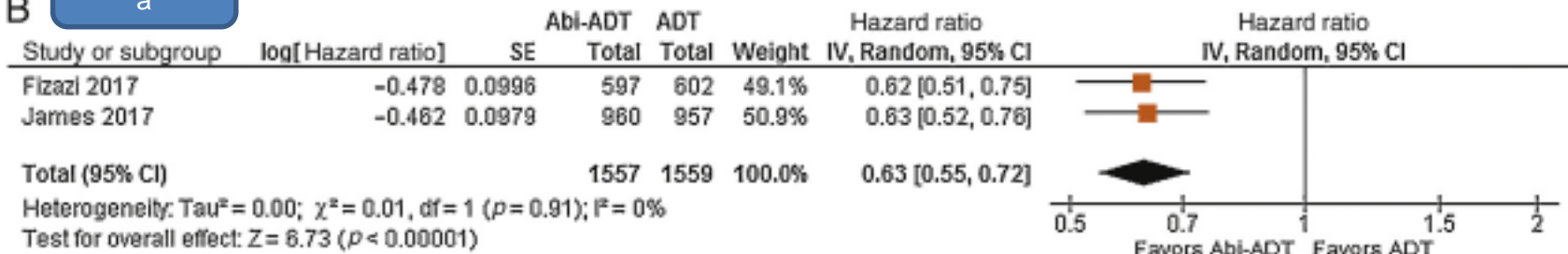


Fig. 1 – Forest plot for meta-analysis of combination therapy compared to androgen deprivation therapy (ADT) alone: (A) docetaxel plus ADT versus ADT alone and (B) abiraterone plus ADT versus ADT alone.

Abi = abiraterone acetate; CI = confidence interval; df = degrees of freedom; Doce = docetaxel; HR = hazard ratio; IV = instrumental variables; SE = standard error.

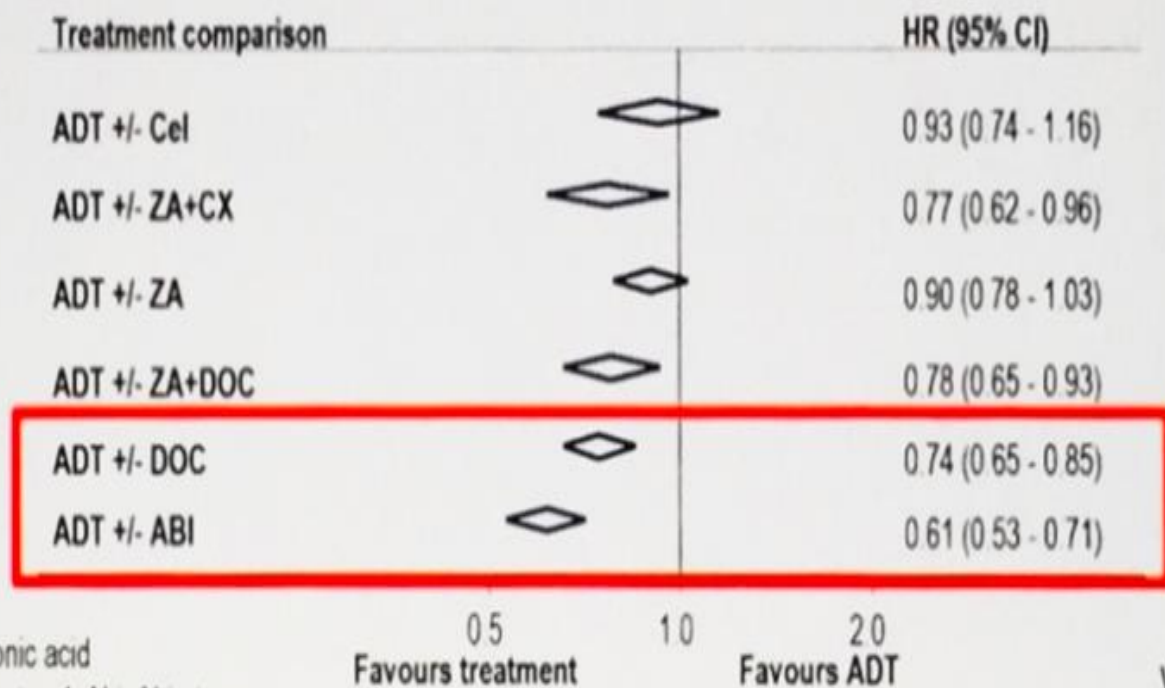
- Docetaxel + ADT como Abiraterona + Prednisona + ADT são opções *standard of care* para o manejo de pacientes com mHNPC de alto volume ou alto risco
- Abiraterona pode ser preferida por melhor perfil de toxicidade.
- Pacientes com baixo volume de doença tiveram pouco benefício de quimioterapia
 - Comparações indiretas e direta (Stampede) demonstram resultado superior para Abi vs Docetaxel
 - O manejo deve ser individualizado baseado na preferência do médico e do paciente levando em consideração acesso, prognóstico, perfil de efeitos colaterais e duração do tratamento.
- Desenvolvimento de novos biomarcadores são essenciais para selecionar os pacientes entre quimioterapia *versus* terapia hormonal.



SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Results: Overall survival

- Results from the network meta-analysis are consistent with reported comparisons of treatments versus ADT:

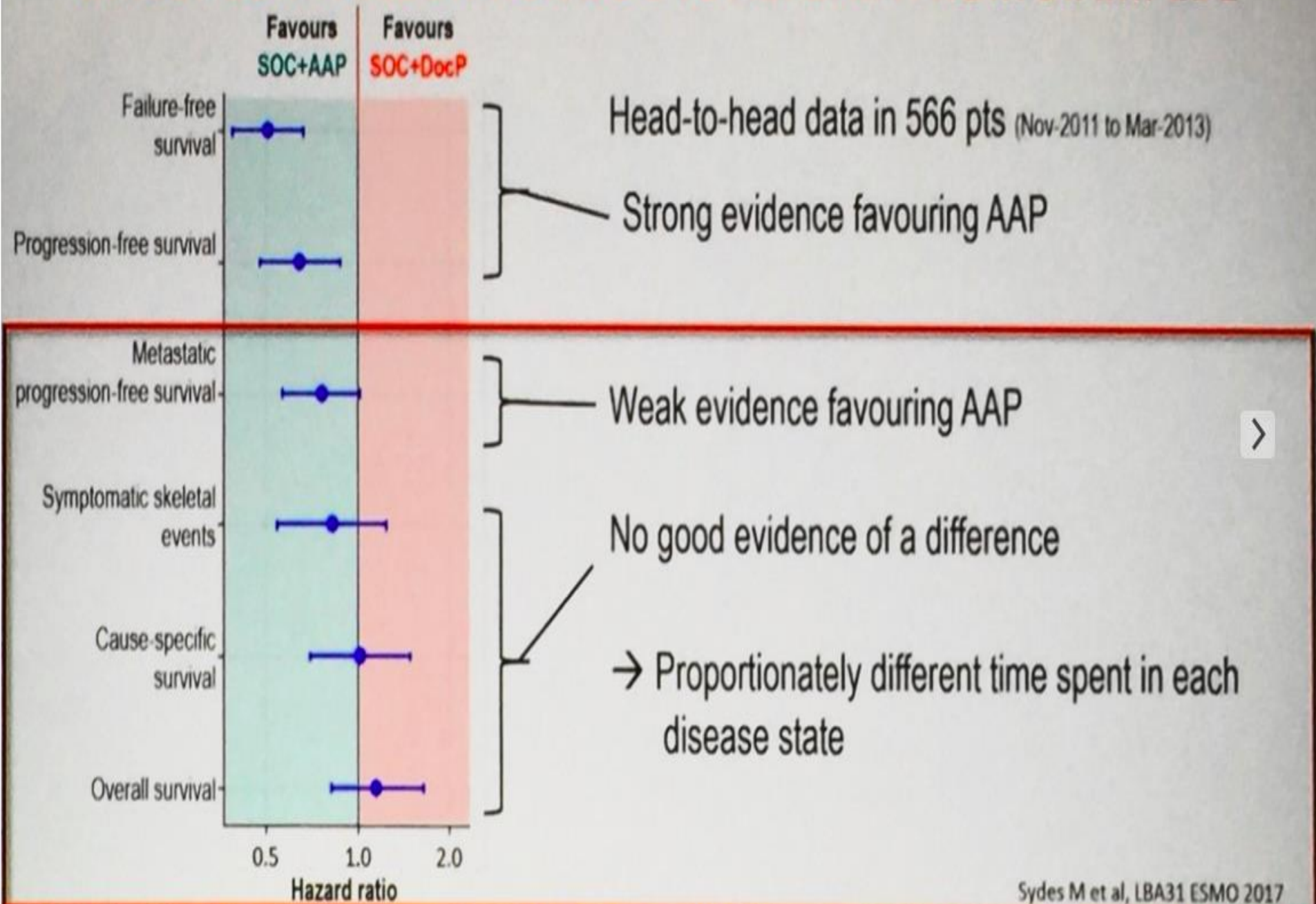


SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

- Ranking of the **OS results** from the network suggest that:
 - ADT + AAP** is likely to be the optimal treatment (**93% probability**)
 - ADT + DOC** is most likely to be the second-best (**43% probability**)

	AAP	DOC	ZA+ DOC	ZA+ Cel	ZA	Cel	ADT
Best	92.5	2.1	1.5	3.9	0.0	0.0	0.0
2 nd best	6.6	43.4	20.8	28.4	0.0	0.8	0.0
3 rd best	0.7	34.8	31.3	28.6	2.1	2.5	0.0
4 th best	0.1	17.9	34.5	26.9	10.9	9.7	0.0
5 th best	0.1	1.7	9.3	9.2	49.6	28.2	1.9
6 th best	0.0	0.1	2.5	2.6	33.0	35.0	26.8
Worst	0.0	0.0	0.1	0.4	4.4	23.8	71.3

DIRECT COMPARISON RCT: DOC VS ABI DATA FROM STAMPEDE



Clin Ther. 2017 Apr;39(4):723-737

Patients' Preferences for the Treatment of Metastatic Castrate-resistant Prostate Cancer: A Discrete Choice Experiment.

FINDINGS:

Within each attribute category and with all other factors being equal, participants (N = 285) indicated a **strong preference for treatments that fully control bone pain (OR = 12.069 [95% CI, 10.555-13.800]) and for treatments that delay chemotherapy (OR, 1.727 [95% CI, 1.548-1.927]).**

They also preferred treatments that were associated with the lowest risk of foginess (OR, 2.115 [95% CI, 1.849-2.420]), a lower risk of fatigue (OR, 1.365 [95% CI 1.219-1.528]), and fewer additional hospital visits (OR, 1.245 [95% CI 1.111-1.397]) than the respective reference categories.

- Quem prefere quimioterapia???
- O que vc faria para um paciente idoso, com comorbidades? **ABI**
- O que vc faria para um jovem, hígido e com doença anaplásica e visceral? **DOC**
- O que vc faria para doença de baixo volume???

