Focus sulla malattia metastatica ormonosensibile (mHSPC)

ADT e Terapia ormonale: quando e a chi?

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AGENDA

- **Literature data**
- **When ADT + 2nd generation HT?**
- **Who?**

Hormone Sensitive Prostate Cancer

LATITUDE STUDY

N Engl J Med. 2017 June 4

The NEW ENGLAND JOURNAL of MEDICINE

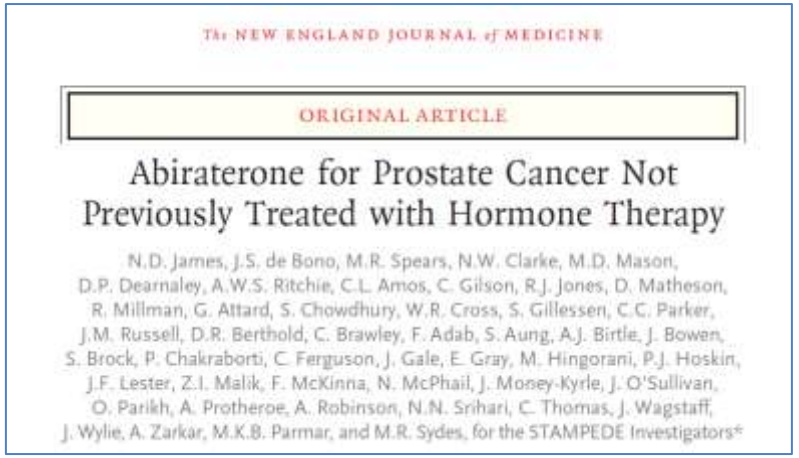
ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

STAMPEDE STUDY

N Engl J Med. 2017 June 3



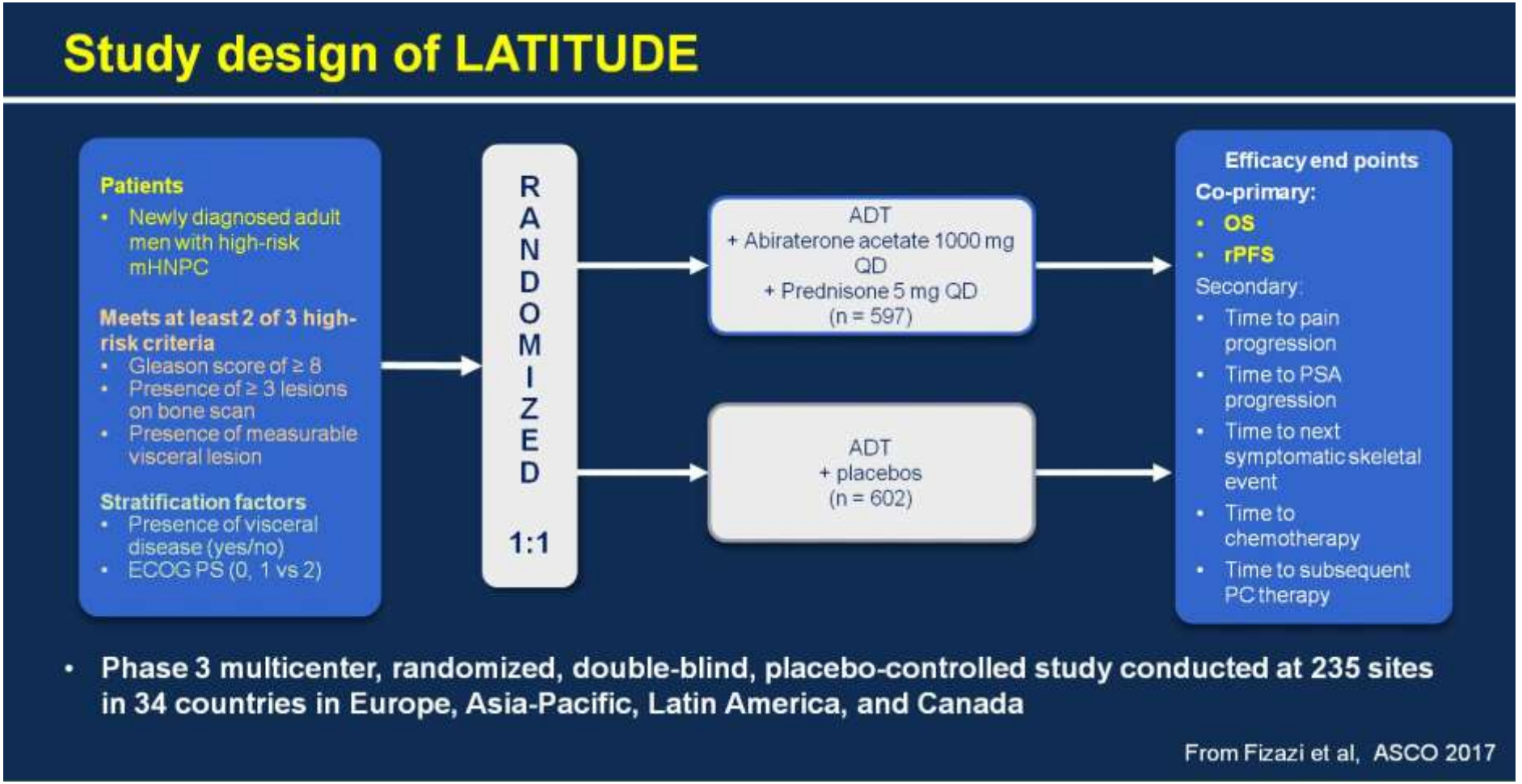
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

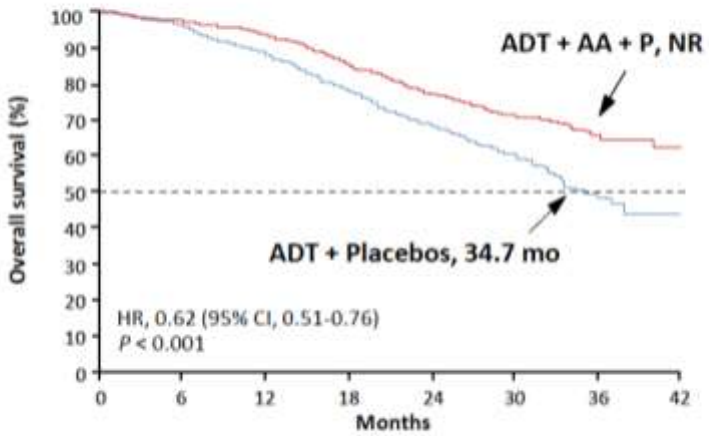
Hormone Sensitive Prostate Cancer



Fizazi K, NEJM 2017

Hormone Sensitive Prostate Cancer
LATITUDE

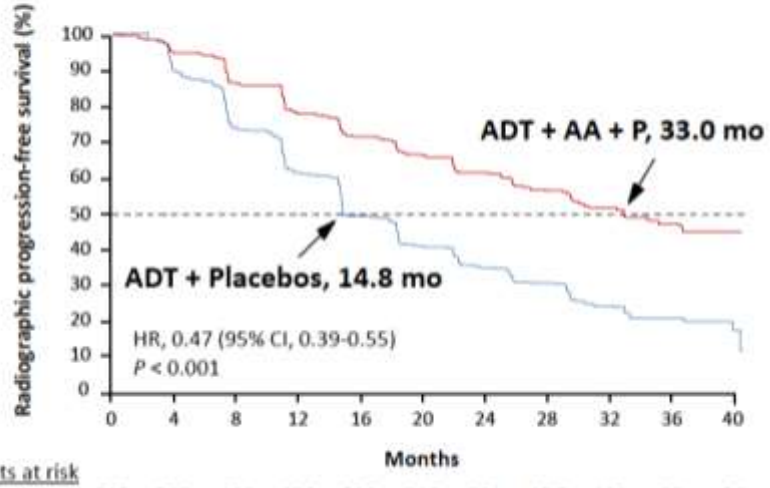
38% Risk Reduction for Death



Patients at risk

ADT + AA + P	597	565	529	479	388	233	93	9
ADT + Placebos	602	564	504	432	332	172	57	2

53% Risk Reduction for rPFS



Patients 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

Fizazi K, NEJM 2017

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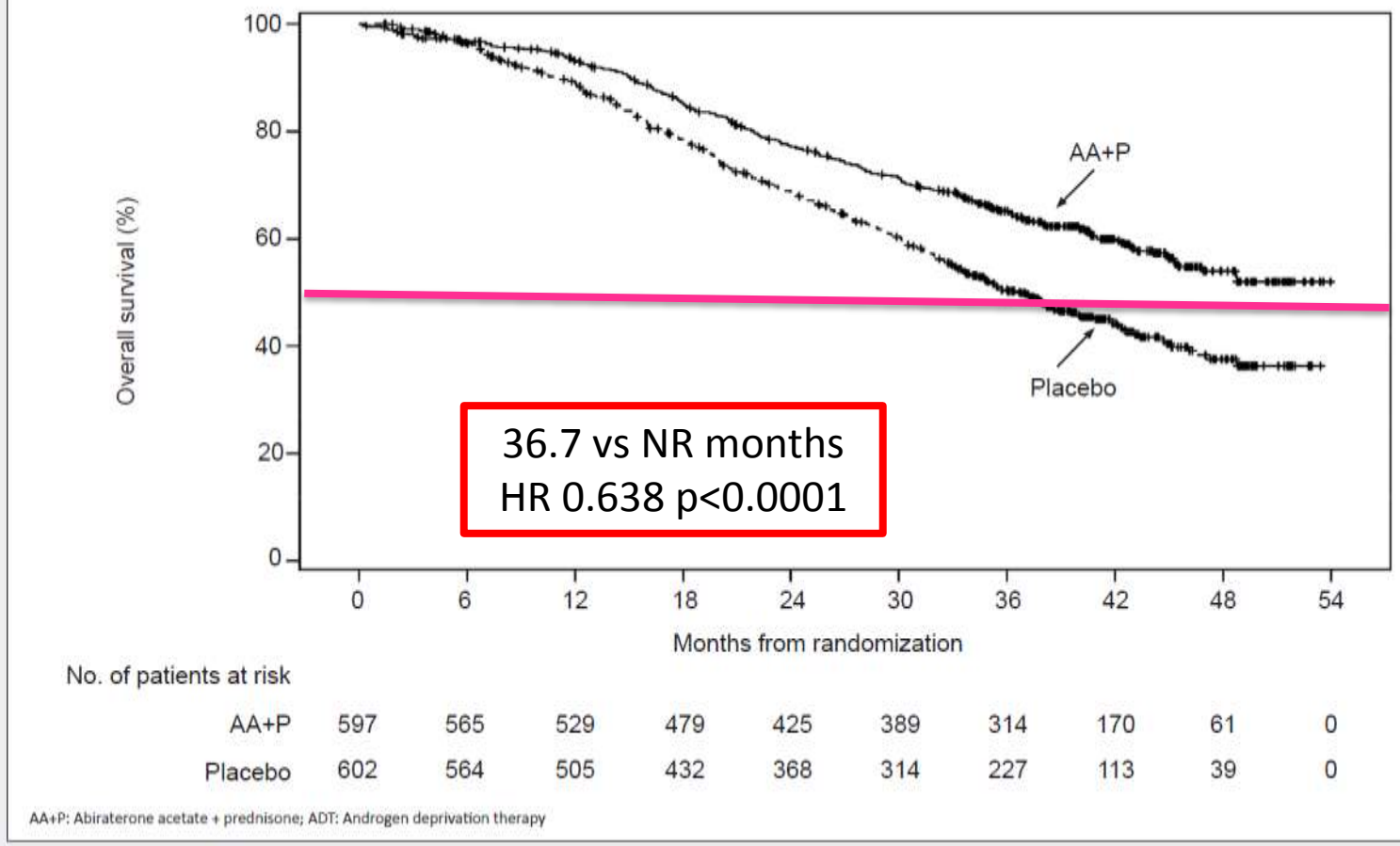
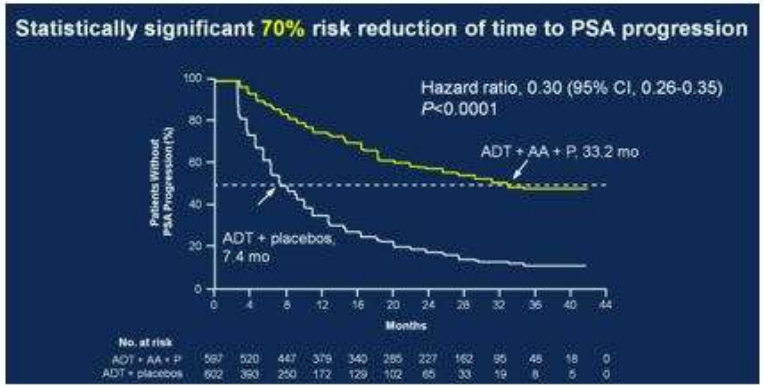
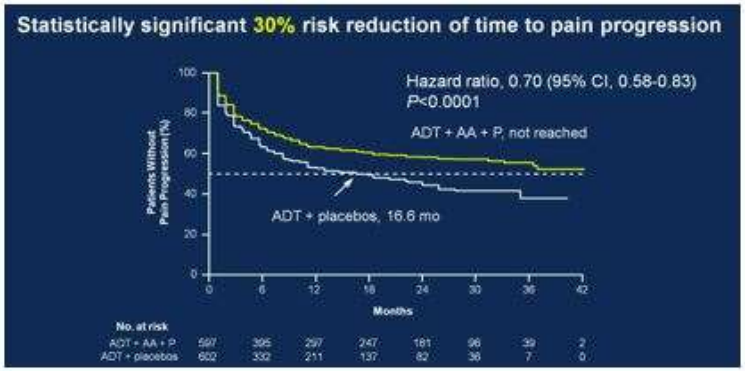
LATITUDE

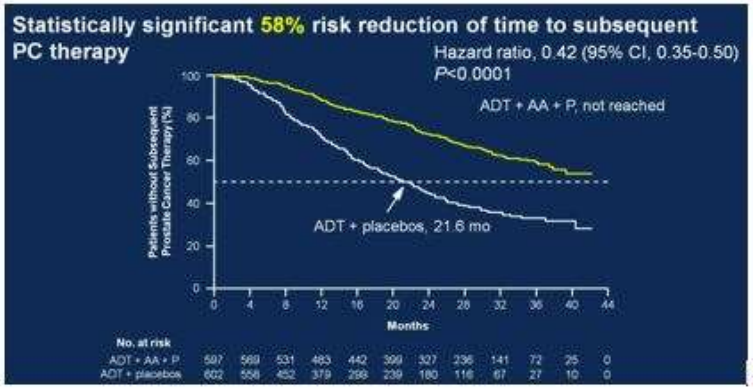
MEDIAN FOLLOW UP 41.4 MONTHS



Fizazi K, ASCO 2018







LATITUDE
Secondary Endpoints

Table 1. Prespecified Secondary and Exploratory Efficacy End Points.*

End Point	Abiraterone Group (N=597)	Placebo Group (N=602)	Hazard Ratio (95% CI)	P Value†
Secondary end points				
Median time to pain progression (mo)	NR	16.6	0.70 (0.58–0.83)	<0.001
Median time to PSA progression (mo)	33.2	7.4	0.30 (0.26–0.35)	<0.001
Median time to next symptomatic skeletal event (mo)	NR	NR	0.70 (0.54–0.92)	0.009
Median time to chemotherapy (mo)	NR	38.9	0.44 (0.35–0.56)	<0.001
Median time to subsequent prostate cancer therapy (mo)	NR	21.6	0.42 (0.35–0.50)	<0.001
Exploratory end point				
Patients with a PSA response (%)‡	91	67	1.36 (1.28–1.45)	<0.001

Fizazi K, NEJM 2017

LATITUDE
AEs 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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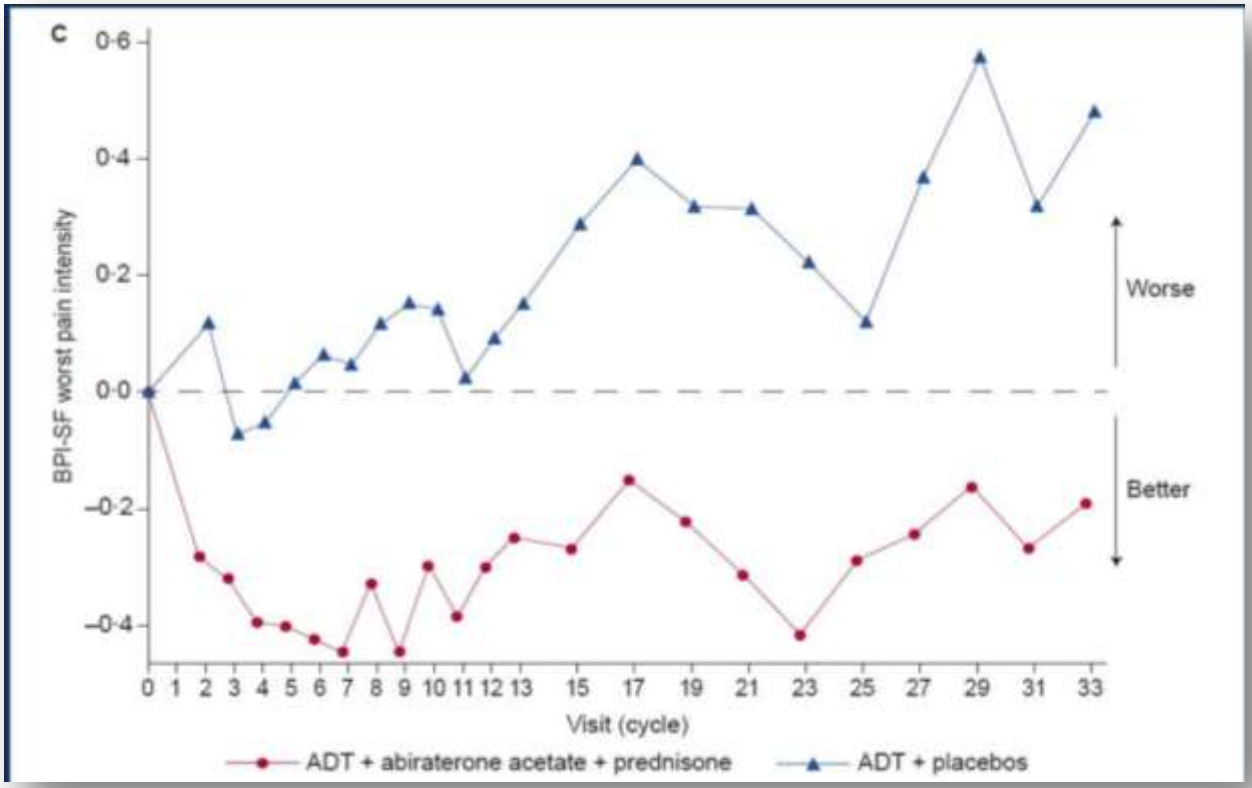
LATITUDE

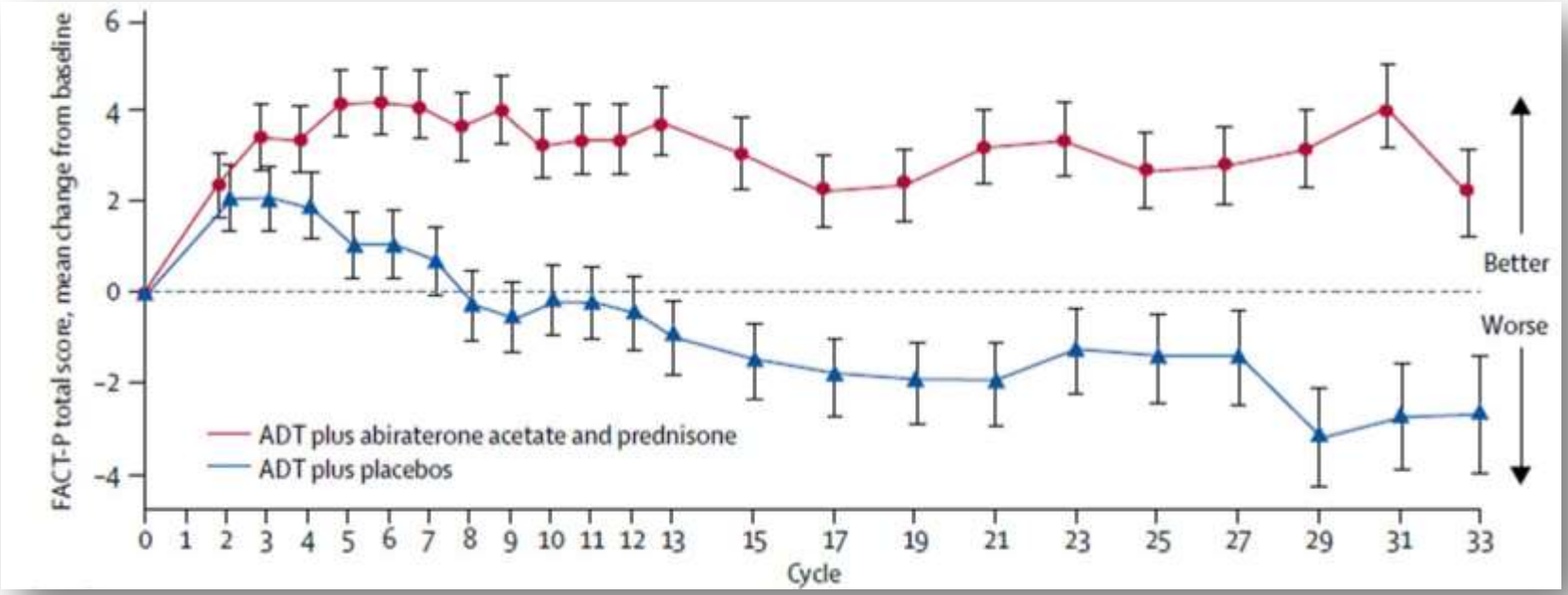
Mean change from baseline in worst pain score



Abiraterone arm = much better

Chi K, JCO 2018

LATITUDE
Quality of life: FACT-P



Abiraterone arm = much better

Chi K, JCO 2018

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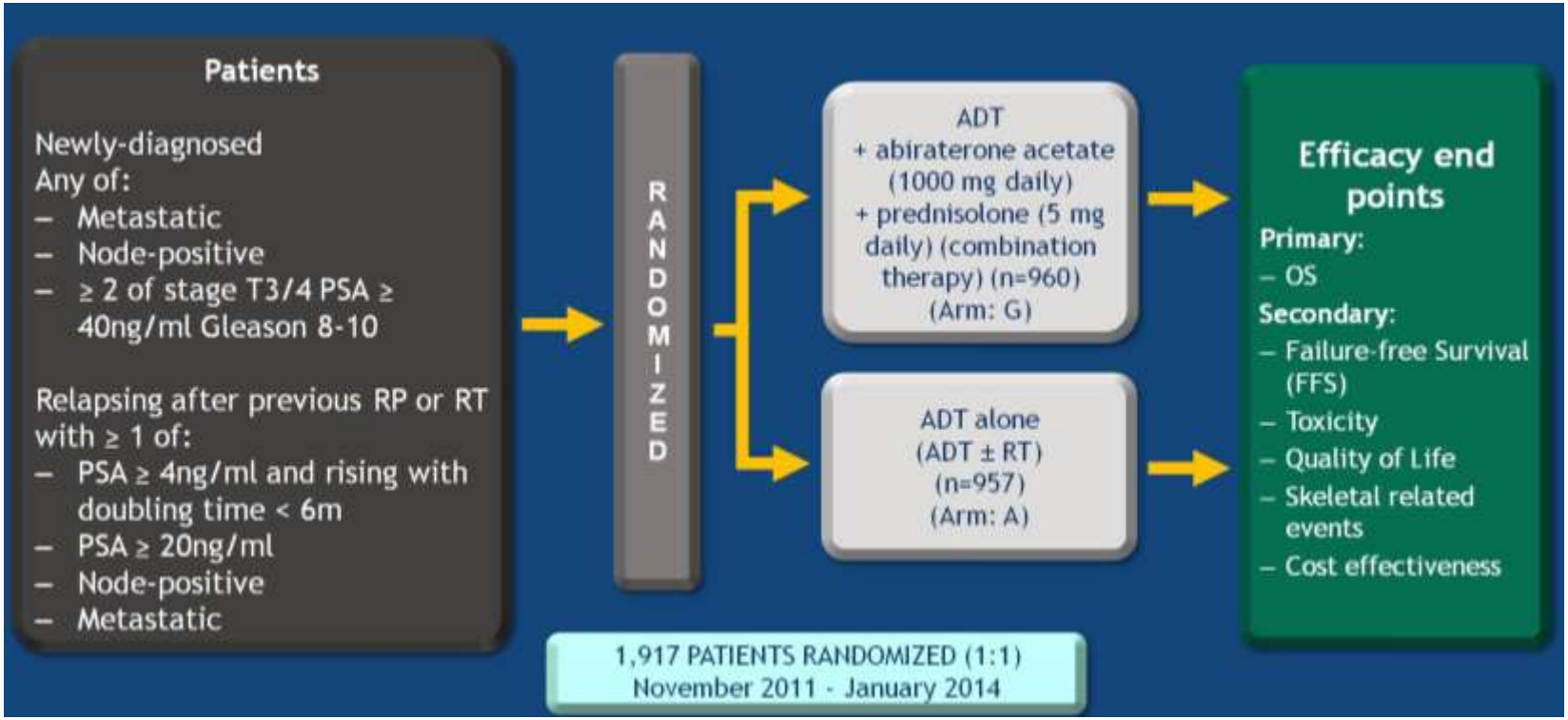
Hormone Sensitive Prostate Cancer

STAMPEDE. Multi-Arm Multi-Stage platform design



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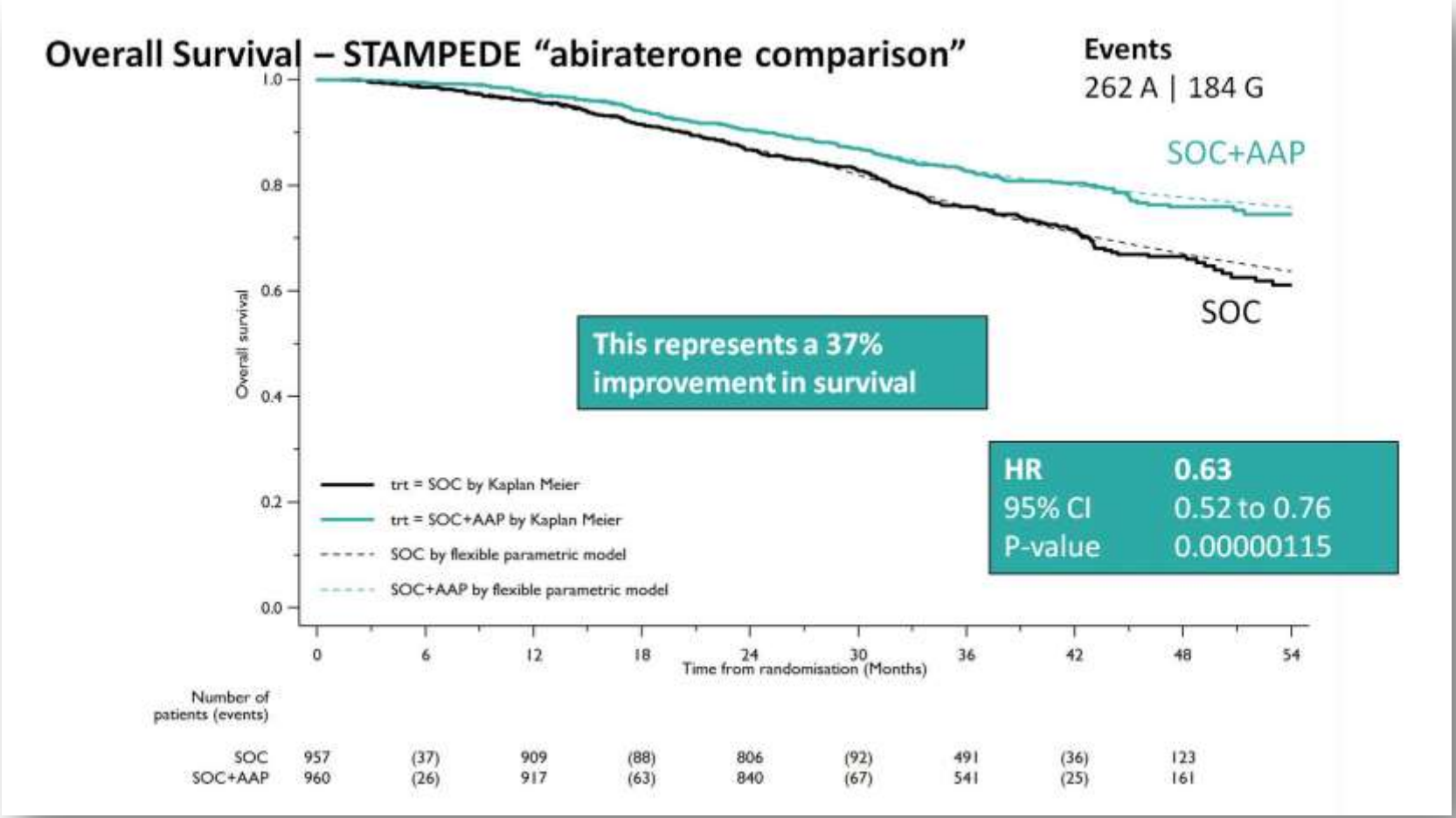
STAMPEDE



James N, NEJM 2017

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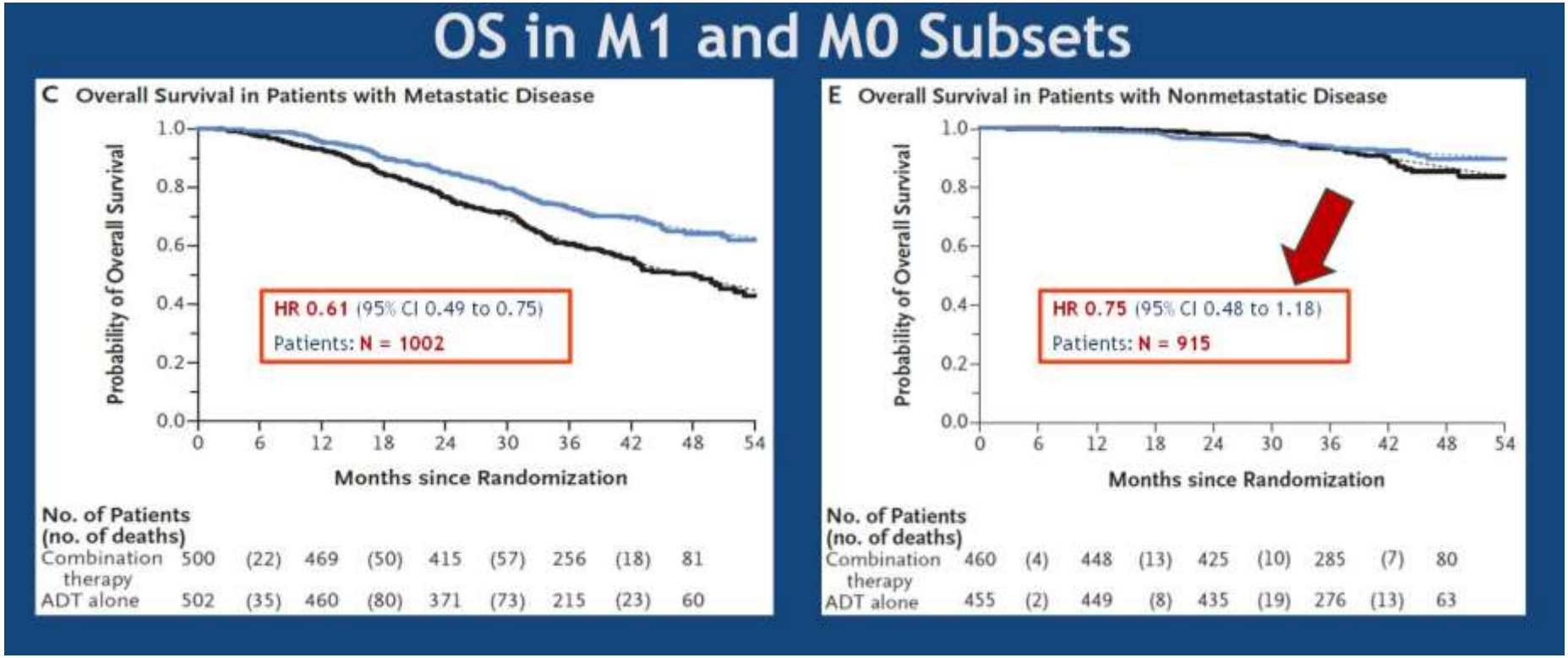
STAMPEDE



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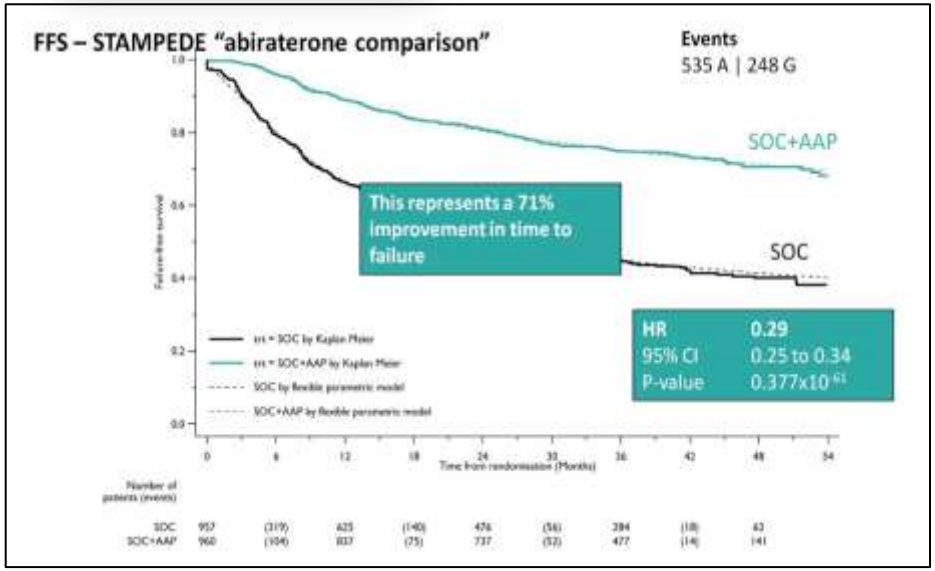

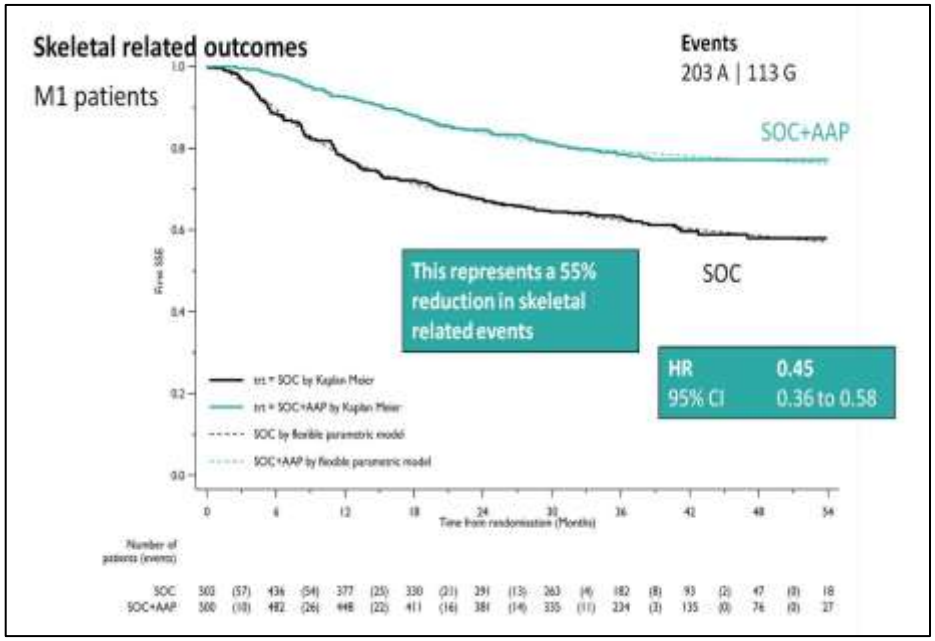

STAMPEDE
secondary end-points

Failure free survival: HR: 0.29

Skeletal related events: HR 0.45

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Table 2. Worst Adverse-Event Grade Reported during Entire Time in the Trial.*

Variable	ADT Alone	Combination Therapy
Safety population		
No. of patients	960	948
Patients with an adverse event — no. (%)		
Any grade	950 (99)	943 (99)
Grade 3–5	315 (33)	443 (47)
Grade 5 only†	3 (<1)	9 (1)
Grade 3–5 adverse events — no. (%)		
Endocrine disorders‡	133 (14)	129 (14)
Cardiovascular disorders	41 (4)	92 (10)
Hypertension	13 (1)	44 (5)
Myocardial infarction	9 (1)	10 (1)
Cardiac dysrhythmia	2 (<1)	14 (1)
Musculoskeletal disorders	46 (5)	68 (7)
Gastrointestinal disorders	40 (4)	49 (5)
Hepatic disorders	12 (1)	70 (7)
Increased ALT level	4 (<1)	53 (6)
Increased AST level	2 (<1)	10 (1)
General disorders	29 (3)	45 (5)
Fatigue	15 (2)	21 (2)
Edema	0	5 (1)
Respiratory disorders	23 (2)	44 (5)
Dyspnea	7 (1)	18 (2)
Laboratory abnormalities	21 (2)	34 (4)
Hypokalemia	3 (<1)	12 (1)
Intention-to-treat population		
Total no. of patients	957	960
No. of patients in safety analysis	953	955
Patients with an adverse event — no. (%)		
Any grade	943 (99)	950 (99)
Grade 3–5	312 (33)	446 (47)
Grade 5 only†	3 (<1)	9 (1)

STAMPEDE: AEs of special interest

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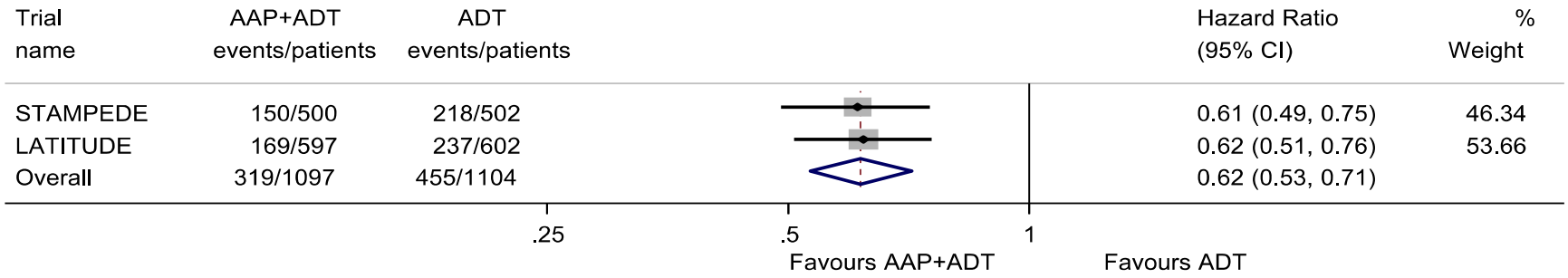
LATITUDE + STAMPEDE
A systematic review and meta-analysis

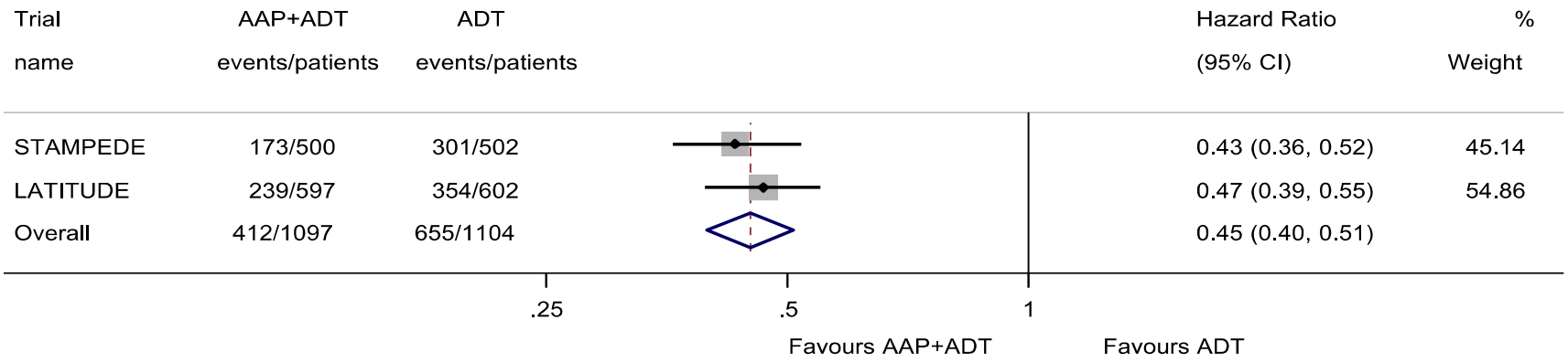
OVERALL SURVIVAL: data available for 2201 pts, 774 deaths recorded

HR = 0.62 → 38% reduction risk of death → **14%** absolute improvement in OS at 3 years with AAP



PROGRESSION-FREE SURVIVAL: data available for 2201 pts, 1067 events recorded

HR = 0.45 → 55% reduction risk of PFS → **28%** absolute improvement in PFS at 3 years with ABI



Rydzewska LHM, EJC 2017

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LATITUDE + STAMPEDE
A systematic review and meta-analysis

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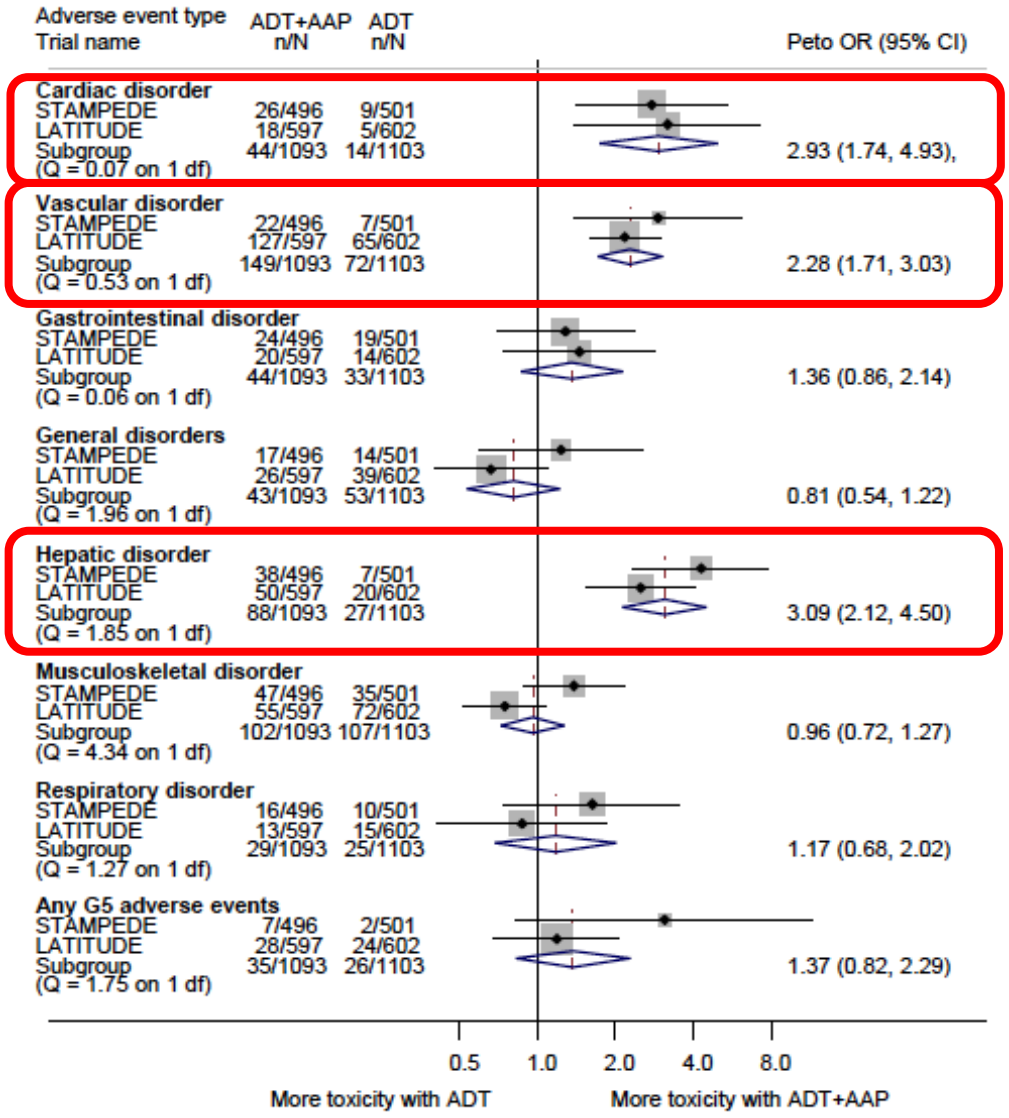

Rydzewska LHM, EJC 2017

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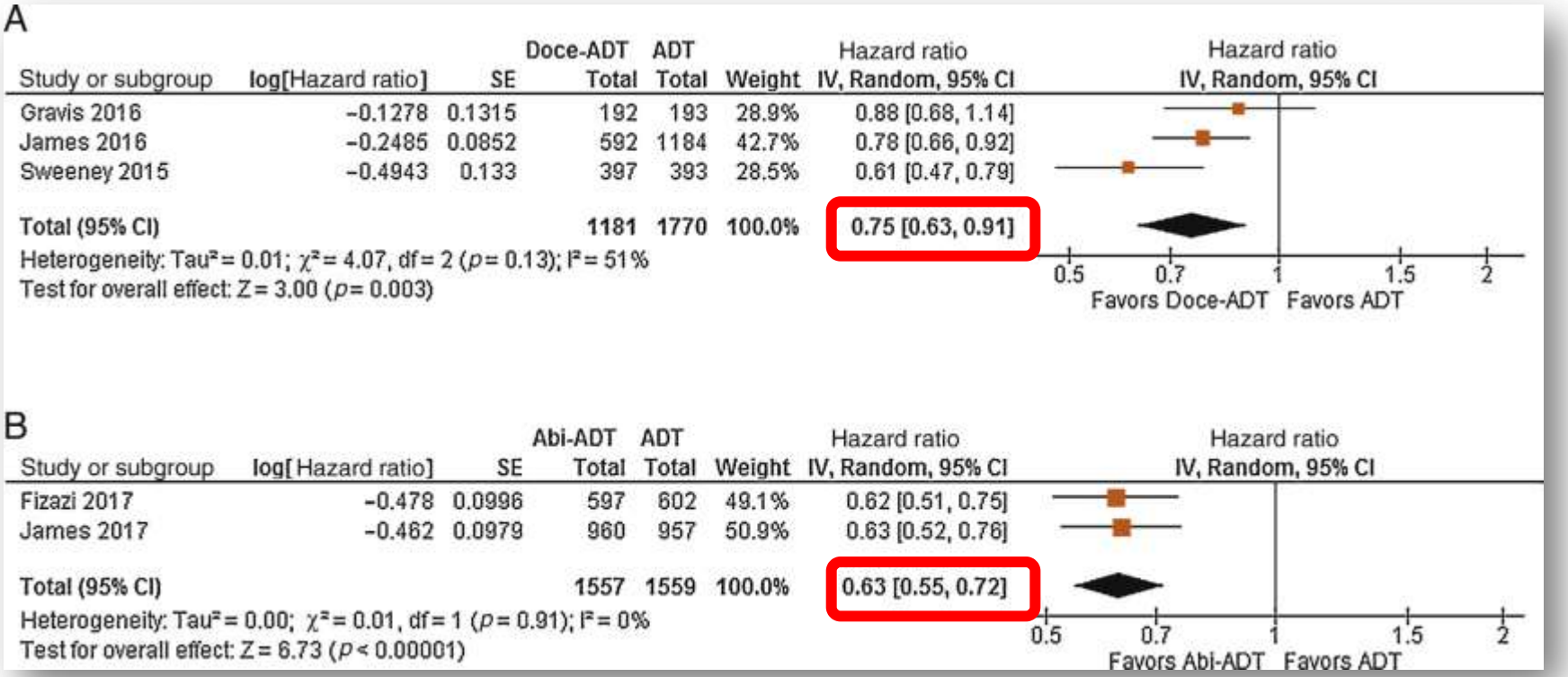
Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naïve Prostate Cancer: A Systematic Review and Network Meta-analysis

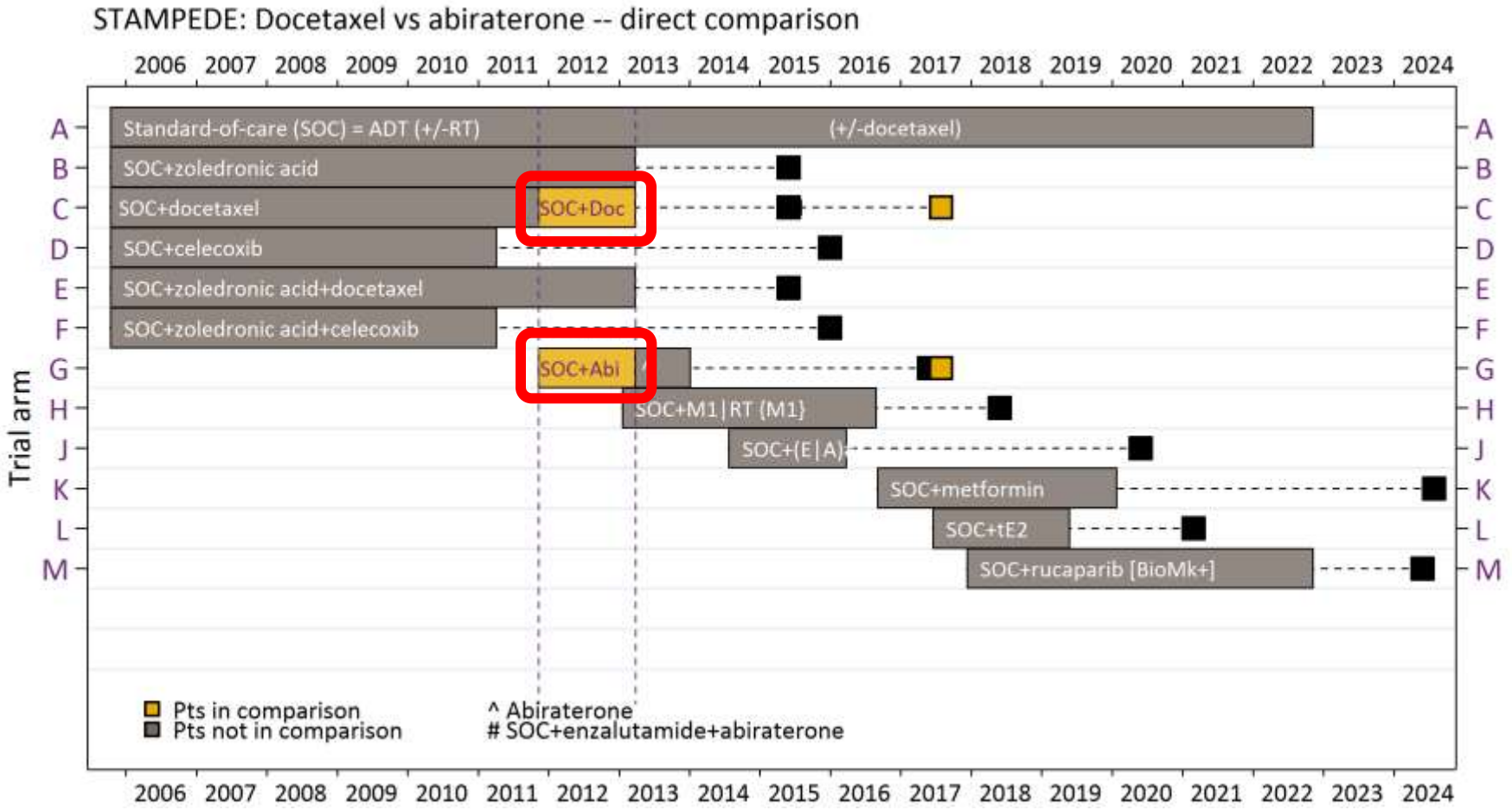
Christopher J.D. Wallis[a,†,*], *Zachary Klaassen*[a,b,†], *Bimal Bhindi*[c], *Hanan Goldberg*[a,b], *Thenappan Chandrasekar*[a,b], *Ann M. Farrell*[d], *Stephen A. Boorjian*[c], *Girish S. Kulkarni*[a,b], *Robert Jeffrey Karnes*[c], *Raj Satkunasivam*[a,e]



Wallis, Eur J Urol 2017

The role of CT or 2nd generation HT in mHSPC:

STAMPEDE: ADT+AA+P vs ADT+DOC (377 vs 189)



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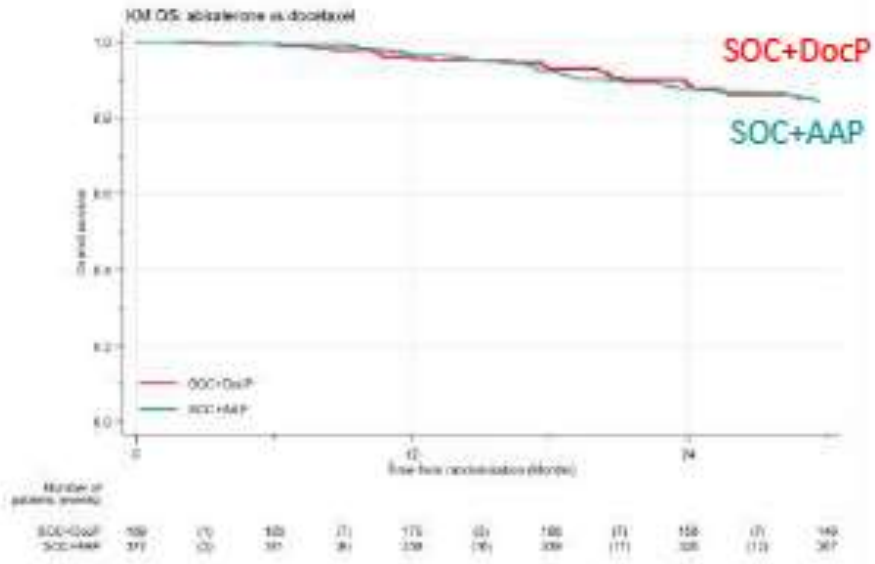
The role of CT or 2nd generation HT in mHSPC:

STAMPEDE

Overall survival [primary outcome measure]



	HR (95%CI)	P-val	Interact^n test
All	1.16 (0.82 to 1.65)	0.40	
M0	1.51 (0.58 to 3.93)	0.40	0.69
M1	1.13 (0.77 to 1.66)	0.53	

	SOC+DocP		SOC+AAP	
	Events	Pts	Events	Pts
All	44	189	105	377
M0	6	74	16	150
M1	38	115	89	227

Key:
HR<1 favours SOC+AAP
HR>1 favours SOC+DocP

Interact^n = test for interaction (heterogeneity of treatment effect)

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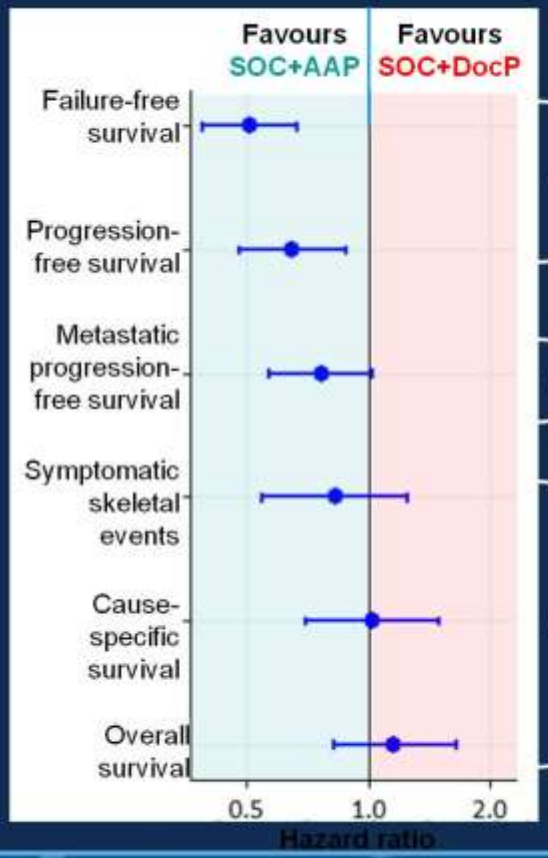
The role of CT or 2nd generation HT in mHSPC:



STAMPEDE
ADT + Doc vs ADT + Abi

Head-to-head data in 566 pts (Nov-2011 to Mar-2013)

Strong evidence favouring AAP to delay PSA rise

Weak evidence favouring AAP to delay radiol PD

No good evidence of a difference on major clinical outcomes

→ **"Proportionately different time spent in each disease state because targeting AR more intensely and longer with abiraterone"**

Sydes et al ESMO 2017
Slide courtesy of Matt Sydes

The role of CT or 2nd generation HT in mHSPC:

STAMPEDE

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%)

DocP

AAP

Sydes M, ESMO 2017

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CONCLUSIONS 1

- **Literature data:**

  upfront treatment with either abiraterone or docetaxel is the new standard of care of patients with mHSPC.

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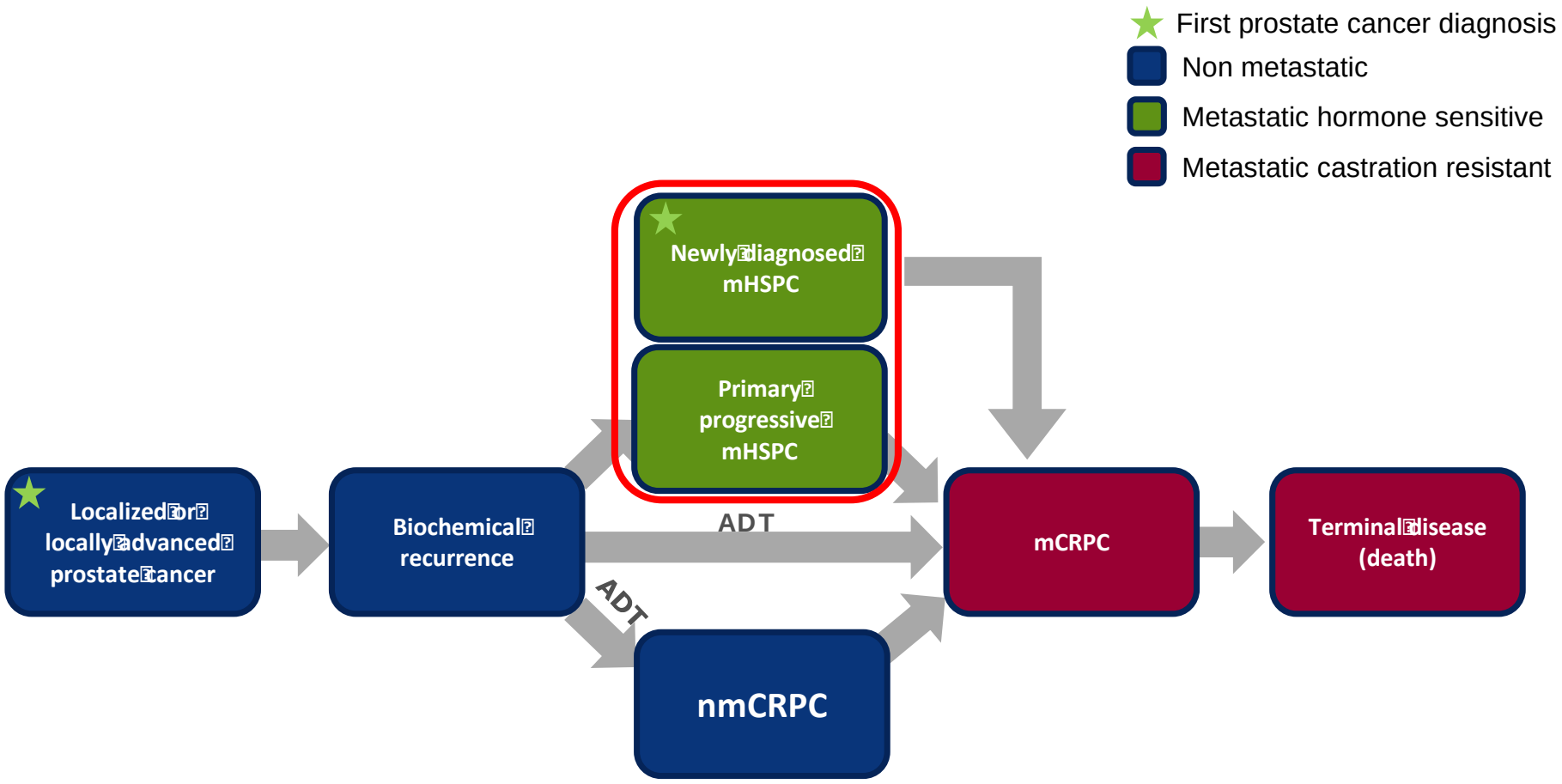
- **Literature data**
- **When ADT + 2nd generation HT?**
- **Who?**

The different stages of prostate cancer



Scher HI, et al. J Clin Oncol. 2016;34:1402-18.

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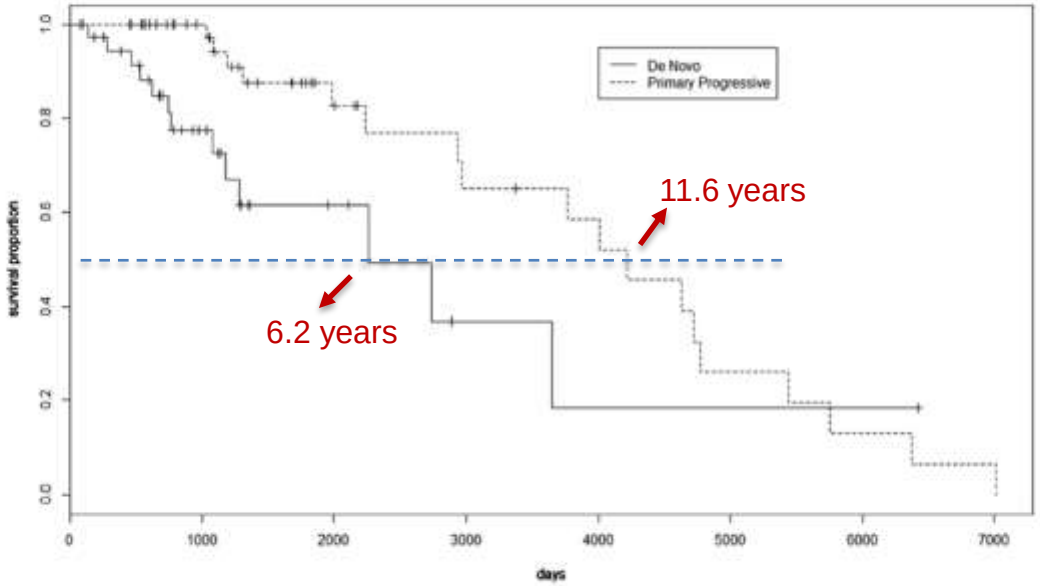
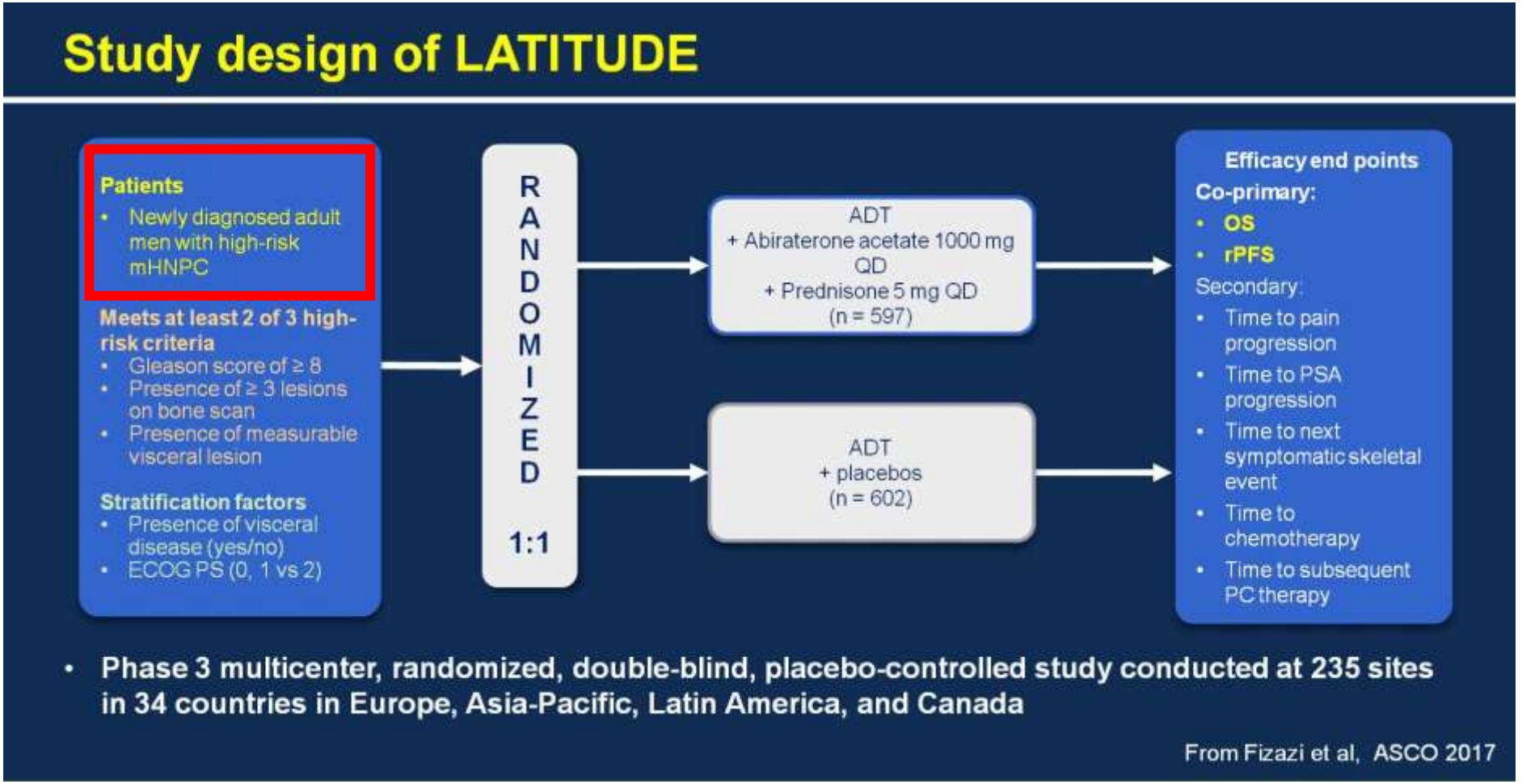
Characterization of Differences Between Prostate Cancer Patients Presenting With De Novo Versus Primary Progressive Metastatic Disease

Antoine Finianos,[1] Kanika Gupta,[1] Brandon Clark,[2] Samuel J. Simmens,[2] Jeanny B. Aragon-Ching[3]

Figure 1 Overall Survival for De Novo Versus Primary Progressive Disease From Time of Metastases



Hormone Sensitive Prostate Cancer



Fizazi K, NEJM 2017

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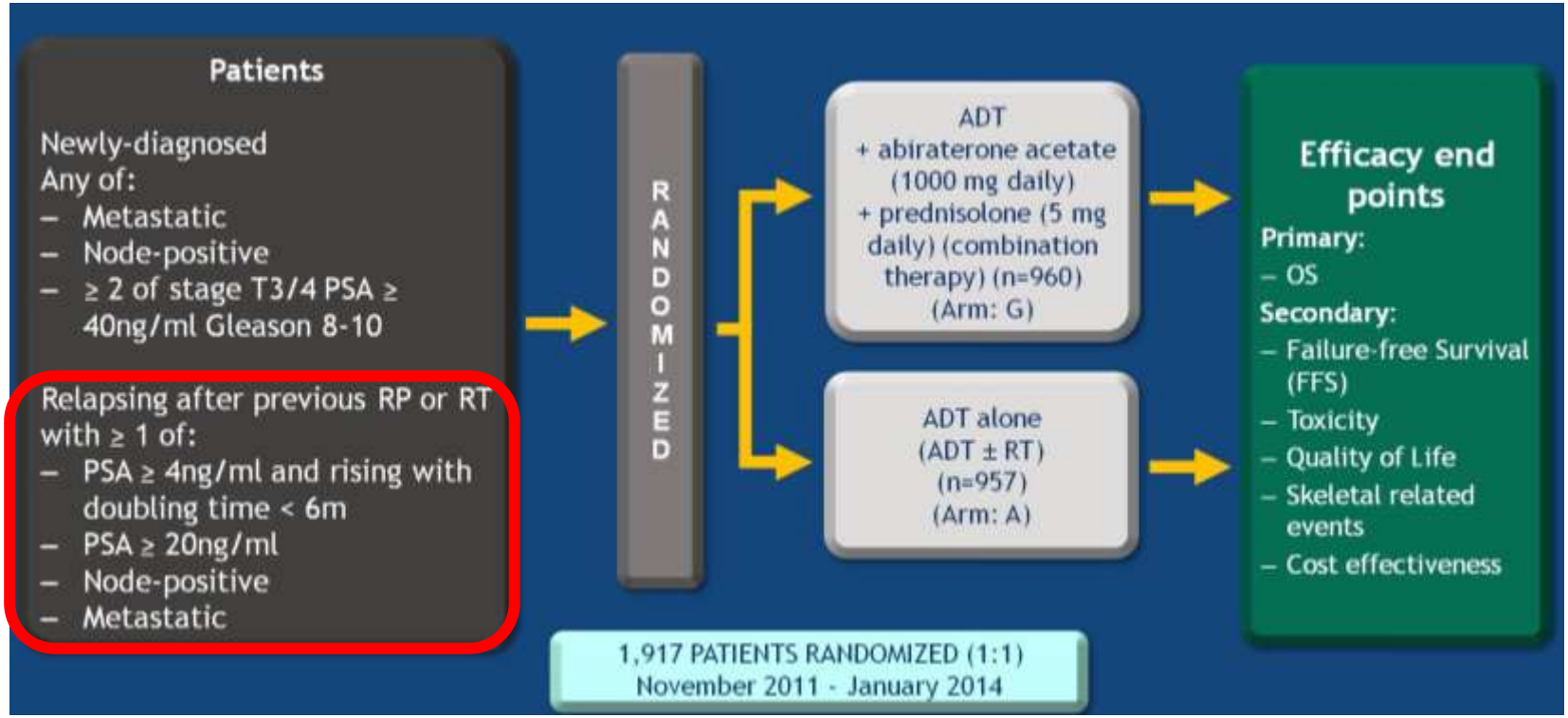
Hormone Sensitive Prostate Cancer

STAMPEDE. Multi-Arm Multi-Stage platform design



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Hormone Sensitive Prostate Cancer

STAMPEDE. Multi-Arm Multi-Stage platform design

Table 1. Characteristics of the Patients.*

Characteristic	ADT Alone (N=957)	Combination Therapy (N=960)
Age at randomization — yr		
Median (IQR)	67 (62 to 72)	67 (63 to 72)
Range	39 to 84	42 to 85
PSA level before ADT — ng/ml		
Median (IQR)	56 (19 to 165)	51 (19 to 158)
Range	0 to 10,530	0 to 21,460
WHO performance status — no. (%)†		
0	744 (78)	745 (78)
1 or 2	213 (22)	215 (22)
Disease group — no. (%)		
Newly diagnosed node-negative, nonmetastatic disease	256 (27)	253 (26)
Newly diagnosed node-positive, nonmetastatic disease	187 (20)	182 (19)
Newly diagnosed metastatic disease	476 (50)	465 (48)
Previously treated nonmetastatic disease	12 (1)	25 (3)
Previously treated metastatic disease	26 (3)	35 (4)

Patients with *de novo* M1

	ADT+ AA+ P vs ADT		ADT+ Doce vs ADT		
	LATITUDE* [1]	STAMPEDE (Arm G) [2,3]	GETUG-AFU 15 [4]	CHAARTED [5,6]	STAMPEDE (Arm C) [7]
Total sample size, n	1199	1917	385	790	1776
Patients with mHSPC	100%	52%	100%	100%	61%
Patients with high-risk/high volume mHSPC	100%	NE	47.5% (183)	65 % (513)	NE
Patients with *de novo* M1	100%	49%	71%	72.8%	58%
Patients with visceral metastasis	17.3%	3%	14.5%	15.6%	3.8%
Patients with Gleason Score ≥8	98%	74.9%	56.1%	61.3%	70.1%

* All LATITUDE patients had high-risk and newly diagnosed metastatic disease
NE, not evaluated

CONCLUSIONS 2

- Literature data:

  Upfront treatment with either abiraterone or docetaxel is the new standard of care of patients with mHSPC.

- **When ADT + 2nd generation HT?**

  In case of *de novo* mHSPC

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- **Literature data**
- **When ADT + 2nd generation HT?**
- **Who?**

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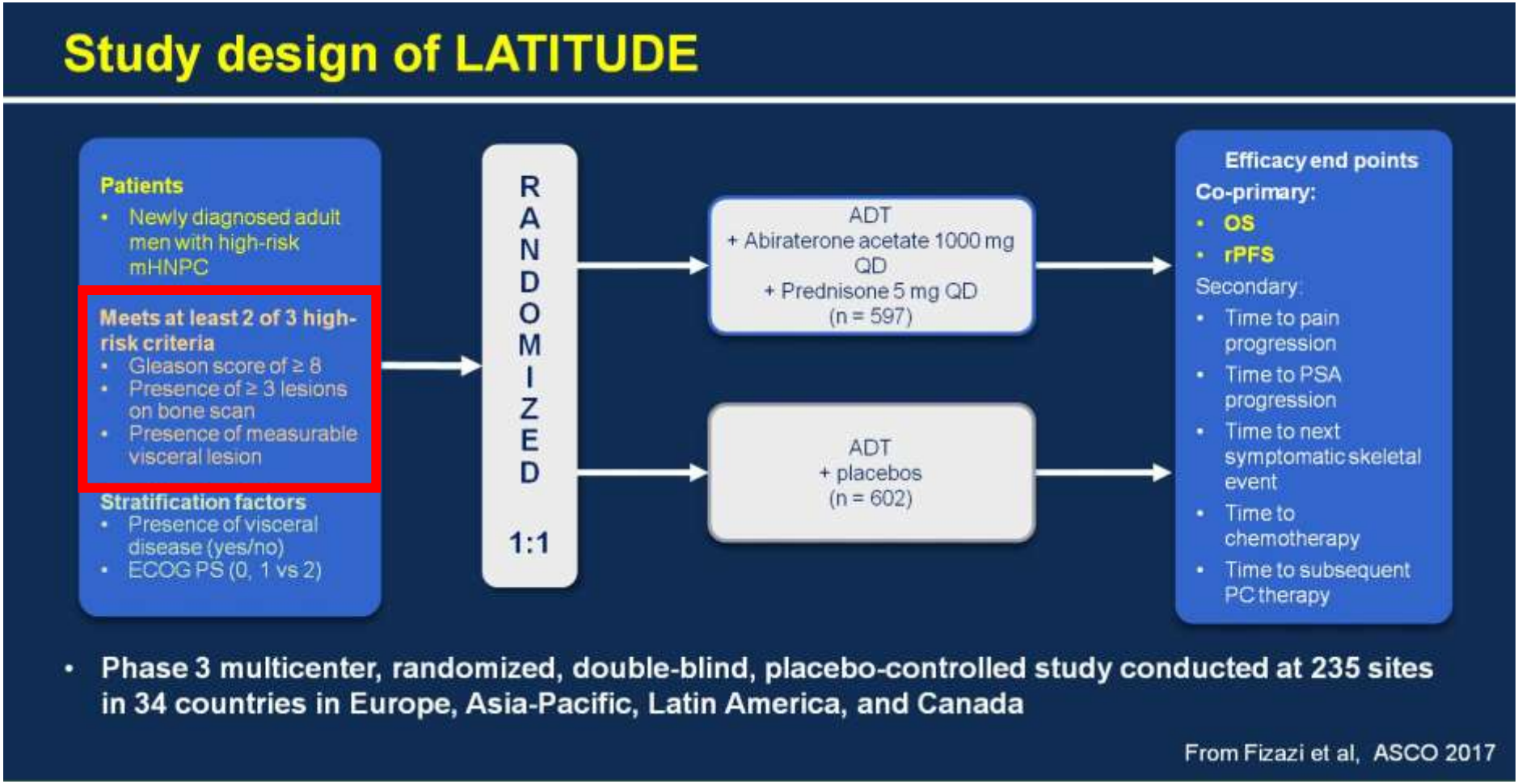

Fizazi K, NEJM 2017

Hormone Sensitive Prostate Cancer
LATITUDE

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%

Fizazi K, NEJM 2017

Hormone Sensitive Prostate Cancer

LATITUDE

Meets at least 2 of 3 high-risk criteria

- Gleason score of ≥ 8
- Presence of ≥ 3 lesions on bone scan
- Presence of measurable visceral lesion

CHARTEED

High-volume disease:

- Visceral M+ and/or
- ≥4 bone M+ with at least one M+ beyond the pelvis or vertebral column

Analyses From the LATITUDE Phase 3 Trial

The Majority of LATITUDE pts met the CHAARTED Definition for HV Disease

	AA + P + ADT	PBOs + ADT	Total
Overall population, n	597	602	1199
Patients with high-volume disease,[a] n (%)	487 (82)	468 (78)	955 (80)
Patients with low-volume disease, n (%)	110 (18)	133 (22)	243 (20)
Unknown,[b] n (%)	0	1 (<1)	1 (<1)

[a]Defined as the presence of visceral metastases and/or ≥ 4 bone lesions with ≥1 outside of the vertebral column and pelvis. [b]Due to missing baseline scan.

- Post hoc analisi:
- 80 % dei pazienti Latitude sono anche alto volume (HV) secondo I criteri Chaarted

Fizazi K, ASCO-GU2018

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Impact of prognostic features on outcome

Chaarted

Higano CS, ASCO 2018

Efficacy in mHS de novo high volume disease

Post hoc Latitude[1]

Clinical outcomes	Patients with high-volume disease		Patients with low-volume disease		Overall population	
	AA + P + ADT n = 487	PBOs + ADT n = 468	AA + P + ADT n = 110	PBOs + ADT n = 133	AA + P + ADT n = 597	PBOs + ADT n = 602[a]
Overall survival						
Median, months	NR	33.1	NR	NR	NR	34.7
HR (95% CI)	0.57 (0.46-0.71)[b]		0.81 (0.48-1.34)[c]		0.62 (0.51-0.76)[d]	
rPFS[e]						
Median, months	30.7	14.7	NR	22.4	33.0	14.8
HR (95% CI)	0.43 (0.36-0.52)[b]		0.53 (0.35-0.80)[f]		0.47 (0.39-0.55)[d]	

[a]Includes 1 patient with missing baseline scan. [b]p < 0.0001. [c]p = 0.4052. [d]p < 0.001. [e]Sequential radiographic imaging to assess rPFS (CT or MRI and bone scanning) was performed every 4 months, starting at Week 16. [f]p = 0.0024.
NR, not reached.

CHARTEED long term[2]

Overall survival	ADT + DOC	ADT alone	P value HR (95% CI)
Whole Study Population (mo.)	57.6	47.2	0.0017 0.73 (0.59 – 0.89)
High volume (mo.)	51.2	34.4	<0.001 **0.63** (0.50 – 0.79)
Low Volume (mo.)	63.5	NR	0.86 1.04 (0.70 – 1.55)
de novo metastatic prostate cancer			
High volume (mo.)	48.0	33.1	0.0004 **0.63** (0.49 - 0.81)
Low Volume (mo.)	58.3	59.8	0.55 0.86 (0.52 – 1.42)
Metastatic after prior local therapy*			
High volume (mo.)	66.9	51.7	0.37 0.72 (0.36 – 1.46)
Low Volume (mo.)	69.6	NR	0.55 1.25 (0.60 – 2.60)

mo: months, NR: not reached

1.Fizazi K, ASCO-GU 2018; 2.Kyriakopoulos CE, JCO 2018

Patients with *de novo* M1

	ADT+ AA+ P vs ADT		ADT+ Doce vs ADT		
	LATITUDE* [1]	STAMPEDE (Arm G) [2,3]	GETUG-AFU 15 [4]	CHAARTED [5,6]	STAMPEDE (Arm C) [7]
Total sample size, n	1199	1917	385	790	1776
Patients with mHSPC	100%	52%	100%	100%	61%
Patients with high-risk/high volume mHSPC	100%	NE	47.5% (183)	65 % (513)	NE
Patients with *de novo* M1	100%	49%	71%	72.8%	58%
Patients with visceral metastasis	17.3%	3%	14.5%	15.6%	3.8%
Patients with Gleason Score ≥8	98%	74.9%	56.1%	61.3%	70.1%

* All LATITUDE patients had high-risk and newly diagnosed metastatic disease
NE, not evaluated

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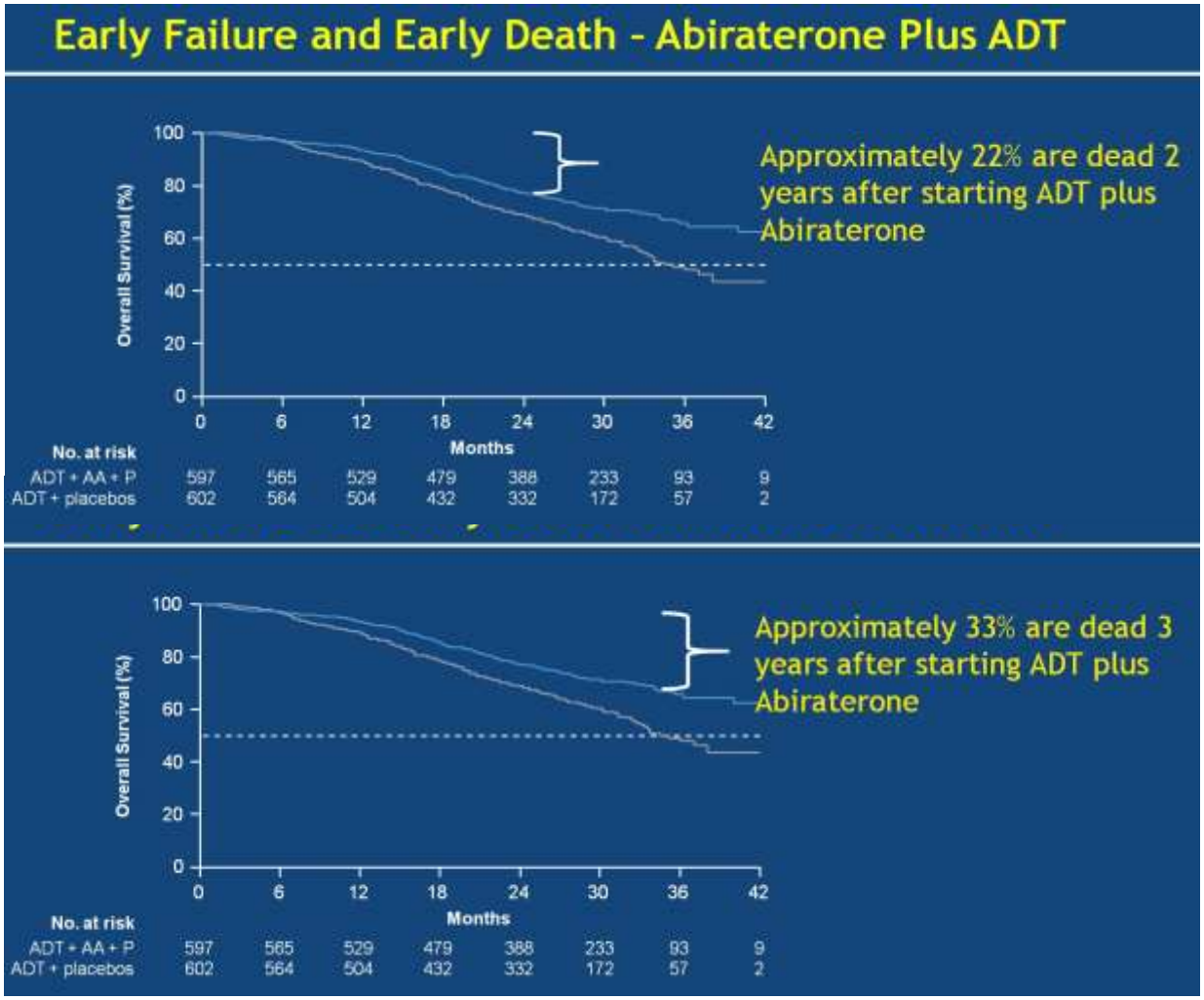
OPTIMAL PATIENT SELECTION

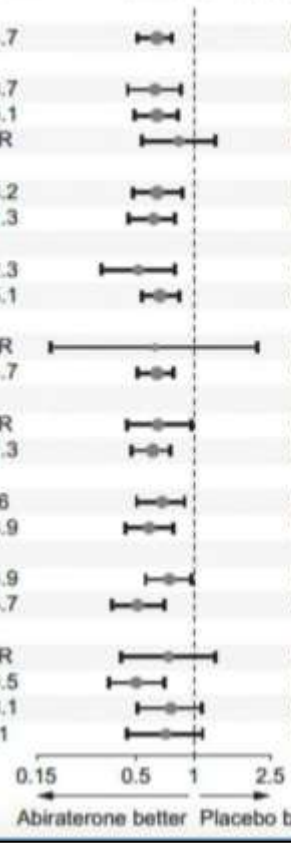


Ryan C, ASCO 2018

Should forest plots guide therapy?
LATITUDE

Supplementary Figure S2. Overall Survival Subgroup.

Subgroup	Abiraterone	Placebo	Hazard Ratio (95% CI)
		Median (mo)	
All patients	NR	34.7	0.63 (0.51–0.76)
Age			
<65 yr	NR	33.7	0.62 (0.45–0.84)
≥65 yr	NR	35.1	0.64 (0.49–0.82)
≥75 yr	NR	NR	0.82 (0.53–1.27)
ECOG			
0	NR	38.2	0.64 (0.48-0.86)
1-2	NR	31.3	0.61 (0.46-0.79)
Visceral disease			
Yes	NR	32.3	0.51 (0.33–0.79)
No	NR	35.1	0.66 (0.53–0.83)
Gleason score			
<8	NR	NR	0.62 (0.18–2.11)
≥8	NR	34.7	0.63 (0.51–0.77)
Bone lesions			
≤10	NR	NR	0.65 (0.45–0.96)
>10	NR	31.3	0.60 (0.47–0.75)
Above median PSA			
Yes	NR	36	0.68 (0.51–0.89)
No	NR	33.9	0.58 (0.44–0.77)
Above median LDH			
Yes	NR	33.9	0.74 (0.56–0.96)
No	NR	36.7	0.51 (0.38–0.69)
Region			
Asia	NR	NR	0.73 (0.42–1.27)
East Europe	NR	30.5	0.50 (0.36–0.69)
West Europe	NR	38.1	0.75 (0.51–1.09)
Rest of world	NR	31	0.70 (0.45–1.09)





Fizazi K, NEJM 2017

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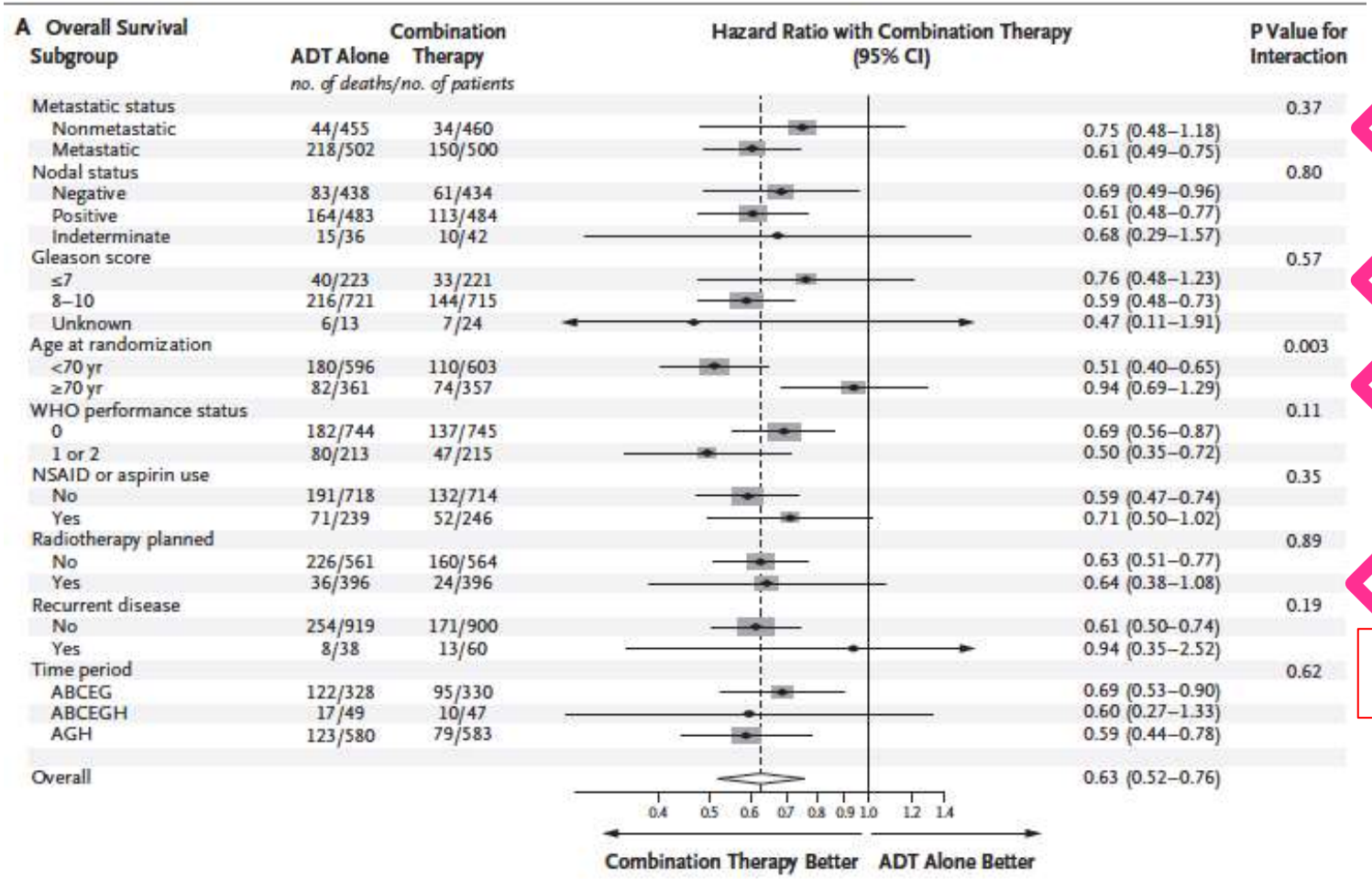
Should forest plots guide therapy?
STAMPEDE



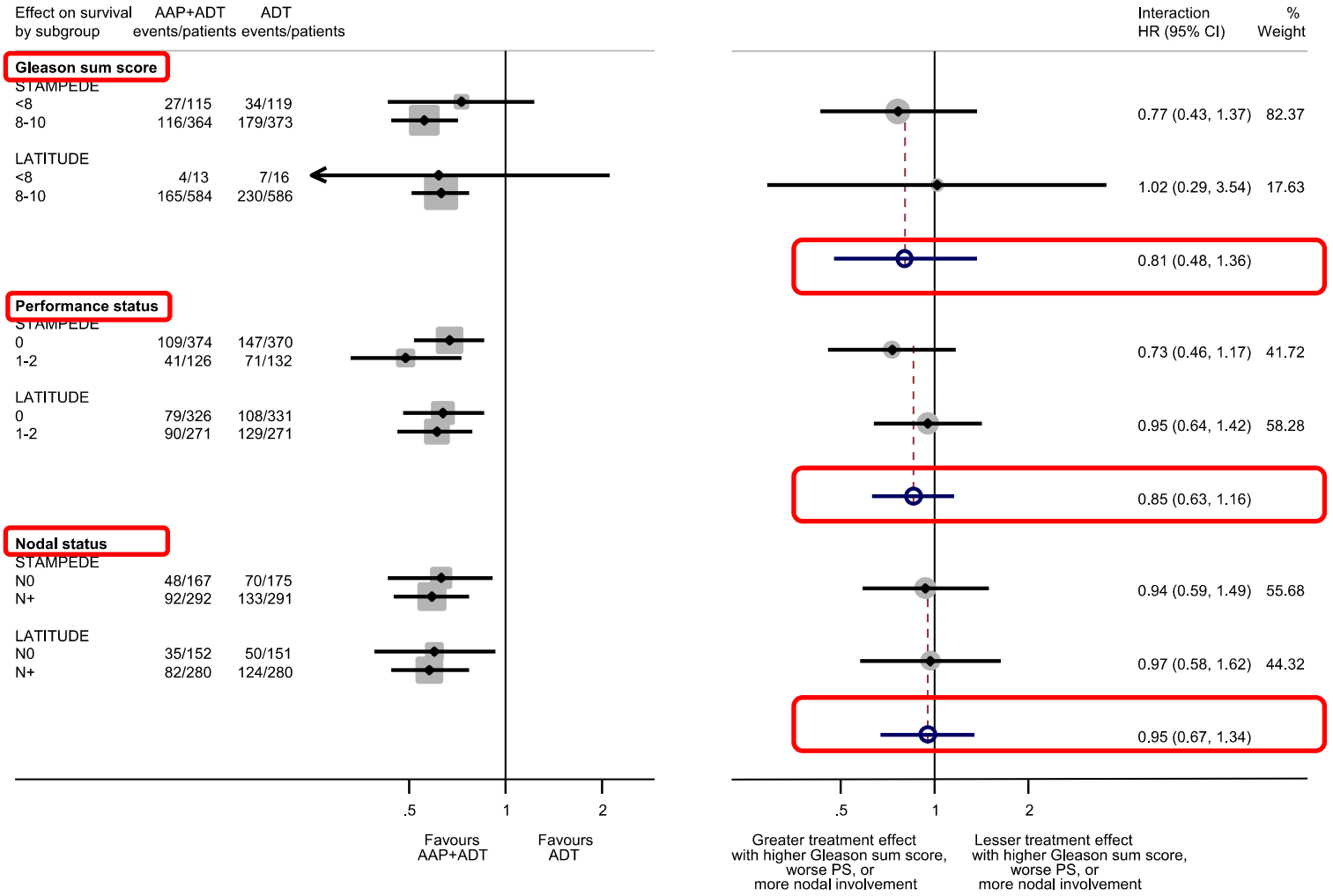
RT-planned and low extent of disease

James N, NEJM 2017

LATITUDE + STAMPEDE

A systematic review and meta-analysis

Effect of adding AAP to ADT on OS by:

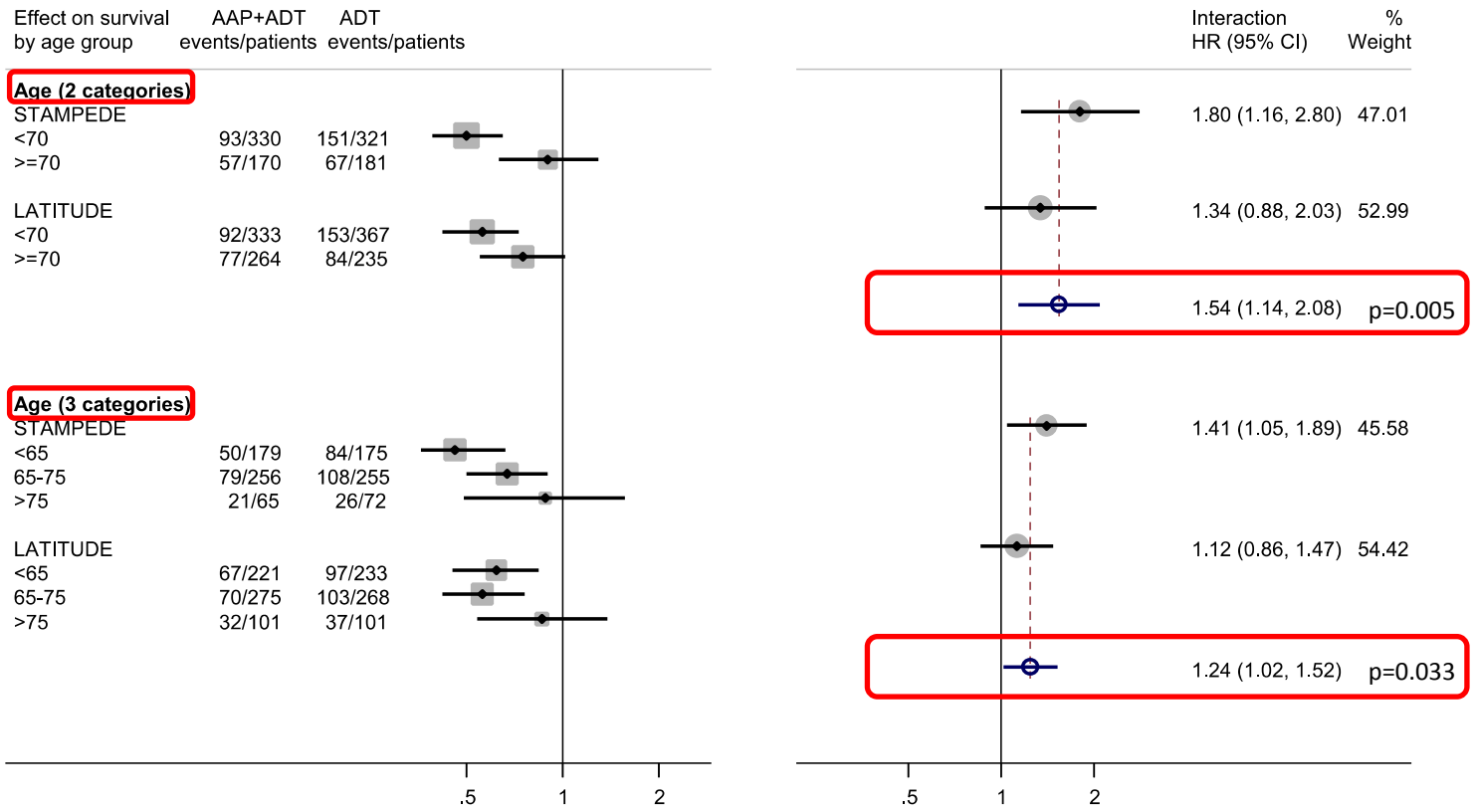


Rydzewska LHM, EJC 2017

LATITUDE + STAMPEDE

A systematic review and meta-analysis

Effect of adding AAP to ADT on OS by:



For **OS** there was evidence that the **size of benefit was greater in younger men** …. Older men are at higer risk of dying from other co-existing conditions or are less able to tolerate treatments

Rydzewska LHM, EJC 2017

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Conclusions 3

- **Literature data:**

  Upfront treatment with either abiraterone or docetaxel is the new standard of care of patients with mHSPC.

- **When ADT + 2nd generation HT?**

  In case of *de novo* mHSPC

- **Who?**

  Patients with high risk mHSPC (OS & rPFS high volume; rPFS low volume M+ disease).

  Patients unfit for chemotherapy or patients with a preference for oral therapy instead of IV.

Grazie per l'attenzione

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