FORJANDO ALIANZAS ENTRE FARMACIA Y ONCOLOGÍA

¿Por qué cada vez es más necesaria la implicación de FARMACIA en el Cáncer de Próstata?

RETOS
REDES
RESULTADOS

Actualización en cáncer de próstata

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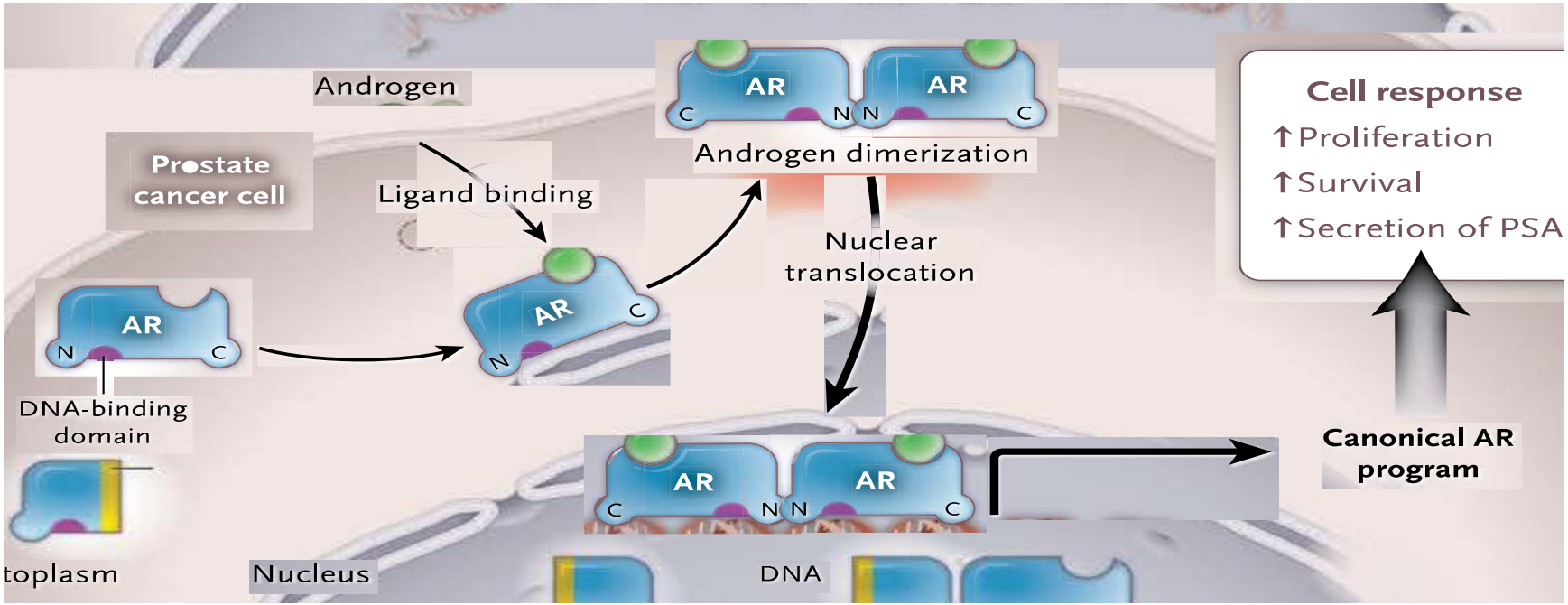
Palma de Mallorca

Madrid, 18 de octubre de 2017

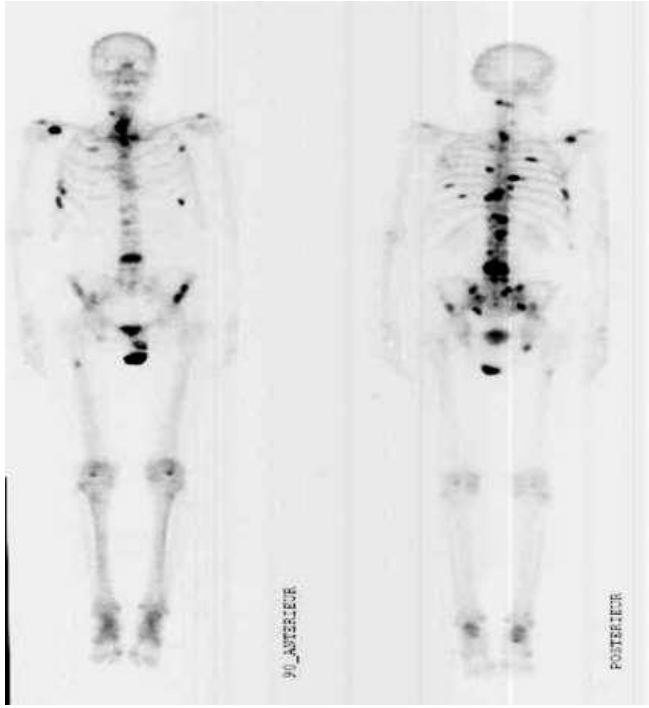
La vía de señal de AR es clave en la progresión del CPRC



Nelson, NEJM 7 sept 2014

PROSTATE CANCER IS HORMONE DEPENDENT

ADT HAS BEEN THE BACKBONE OF RX FOR METASTATIC PROSTATE CANCER SINCE THE 1940'S

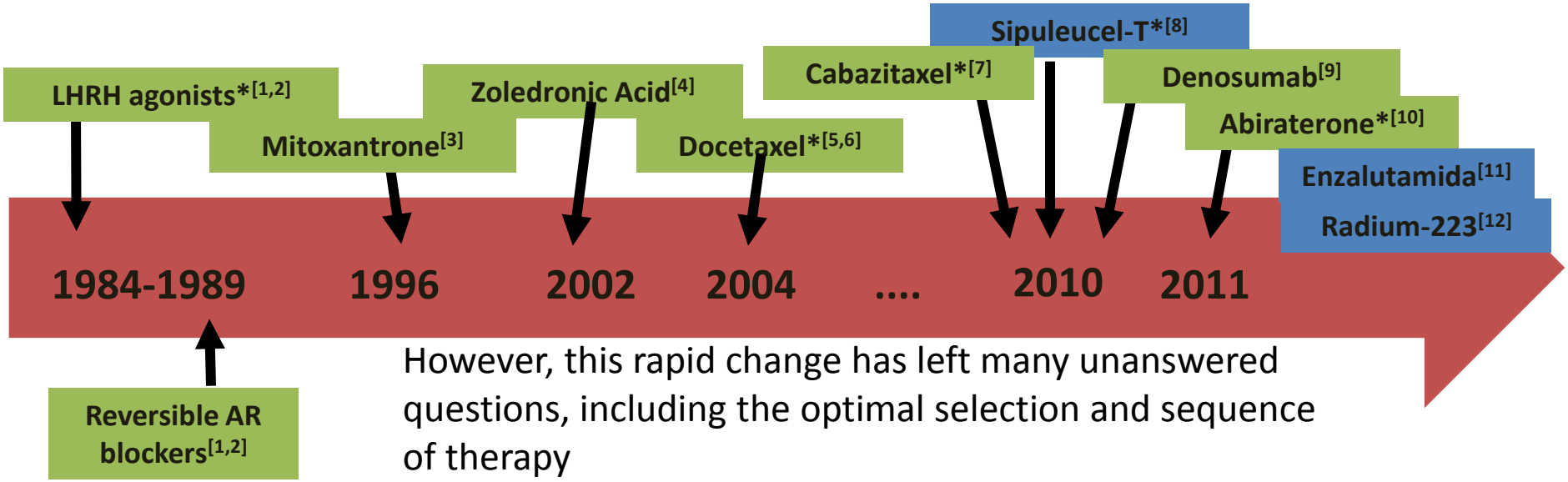


"Despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease"

Charles B. Huggins
Nobel Lecture
December 13, 1966

http://nobelprize.org/nobel_prizes/medicine/laureates/1966/huggins-lecture.html

Evolución histórica del tratamiento del cáncer de próstata avanzado



However, this rapid change has left many unanswered questions, including the optimal selection and sequence of therapy

1.The Leuprolide Study Group. N Engl J Med. 1984;311:1281-1286. 2. Crawford ED, et al. N Engl J Med. 1989;321:419-424. 3. Tannock IF, et al. J Clin Oncol. 1996;14:1756-1764. 4. Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468. 5. Petrylak DP, et al. N Engl J Med. 2004;351:1513-1520. 6. Tannock IF, et al. N Engl J Med. 2004;351:1502-1512. 7. de Bono JS, et al. Lancet. 2010;376:1147-1154. 8. Kantoff PW, et al. N Engl J Med. 2010;363:411-422. 9. Fizazi K, et al. Lancet. 2011;377:813-822. 10. de Bono JS, et al. N Engl J Med. 2011;364:1995-2005. 11. Scher HI, et al. ASCO GU 2012. Abstract LBA1. 12. Parker C, et al. ASCO GU 2012. Abstract 8.

RETOS REDES RESULTADOS

Cáncer de próstata resistente a castración metastásico (CPRCm)

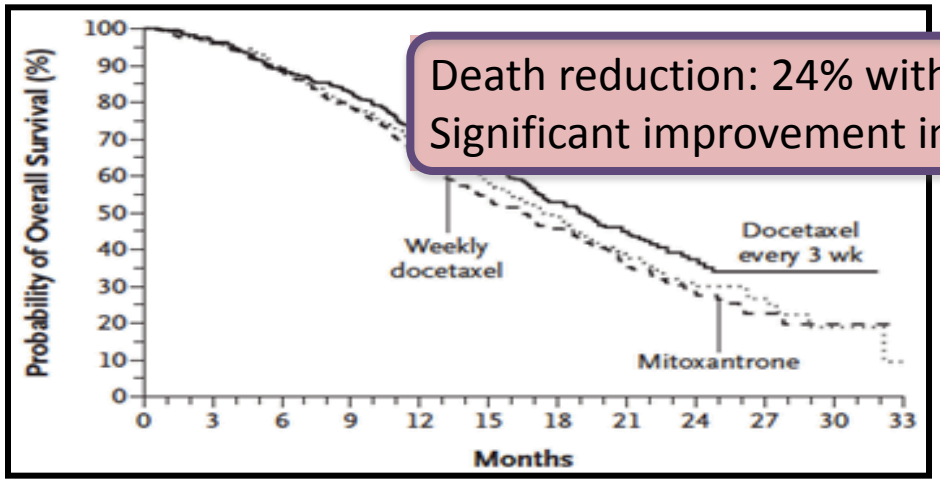
Definición de CPRC

- Denominamos **cáncer de próstata resistente a la castración (CPRC)** al cáncer de próstata que progresa a pesar de niveles séricos de castración (T <50 ng/ml)
- **Manifestaciones clínicas:**
  - Ascenso en niveles de PSA (90%)
  - Metástasis óseas (90%)
  - Dolor intenso (35%)
  - Metástasis partes blandas/ganglios linfáticos (20%)

Distintas situaciones clínicas en CPRC

ASINTOMATICO	MINIMAMENTE SINTOMATICO	SINTOMATICO
PROGRESION PSA	PROGRESION GGO	PROGRESION VISCERAL
BAJA CARGA TUMORAL		ALTA CARGA TUMORAL

2004: Docetaxel improves OS vs mitoxantrone



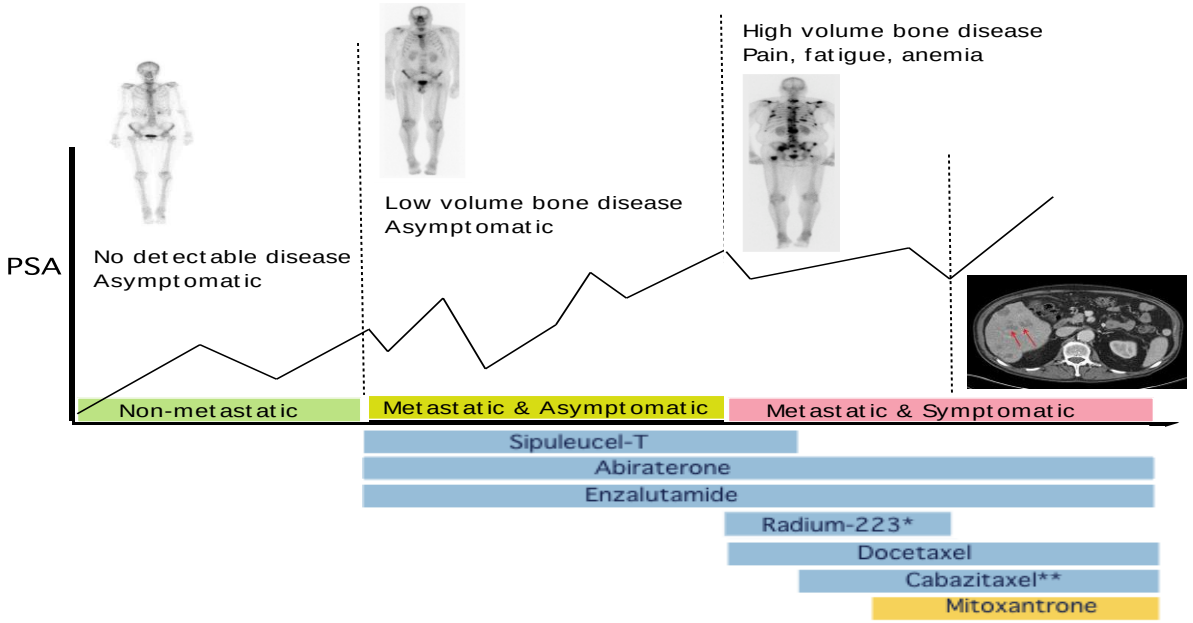
Death reduction: 24% with docetaxel q3w
Significant improvement in pain, QoL, PSA

	Median survival (months)	HR	P
Docetaxel q3w	18.9	0.76	0.009
Docetaxel q1w	17.3	0.93	0.3
Mitoxantrone q3w	16.4	-	-

	Docetaxel q3w (N=335)	Docetaxel q1w (N=334)	Mitoxantrone q3w (N=337)
3-year survival rate*	**18.6%**	16.8%	13.5%

Tannock IF et al. N Engl J Med 2004;351:1502-12.
Berthold D et al. J Clin Oncol 2008;26:242-5.
* Data 2006

Opciones terapéuticas en CPRC



	SG gr exp	SG gr control	ΔSG	HR
COU-302	35,3m	30,1m	4,8m	0,79
PREVAIL	32,4m	30m	2,4m	0,71

	SG gr exp	SG gr control	ΔSG	HR
TAX-327	18,9m	16,5m	2,4m	0,76
TROPIC	15,1m	12,7m	2,4m	0,70
COU-301	15,8m	11,2m	4,6m	0,74
AFFIRM	18,4m	13,6m	4,8m	0,63
ALSYMPCA	14m	11,2m	2,8m	0,70

David Lorente, curso SOGUG 2016

Ryan et al. NEJM 2013; Beer et al NEJM 2014; Tannock et al NEJM 2004; De Bono et al Lancet 2010; De Bono et al NEJM 2011; Scher et al NEJM 2012; Parker et al NEJM 2013

Factores pronósticos en CaP

Gleason
Niveles de PSA
Tiempo de doblaje del PSA (PSA-DT)
ECOG PS
Presencia de dolor
Tratamiento con opiáceos
Metástasis viscerales
Niveles basales de andrógenos
Respuesta y duración del tratamiento hormonal previo
Respuesta previa a docetaxel
Tipo de progresión (factores de progresión)
Niveles basales de albúmina, fosfatasas alcalinas, LDH, hemoglobina
Ratio neutrófilos/linfocitos

Perfil de Seguridad: Quimioterapia vs otros agentes

Docetaxel

TAX-327

Neutropenia: 32% vs 22%
Neutropenia febril: 3% vs 2%

Diarrea: 32% vs 10%

Neuropatía periférica: 32% vs 10%

Otros: astenia, alopecia (65%), toxicidad ungueal (30%), disgeusia (18%), mucositis (20%), edemas periféricos (19%)

Cabazitaxel

TROPIC

Neutropenia: 82% vs 58%
Neutropenia febril: 8% vs 1%

Diarrea: 47% vs 11%
(G3: 6% vs <1%)

Neuropatía periférica: 14% vs 3%

Abiraterona

COU-301

Neutropenia: 1% vs 1%
Anemia: 23% vs 26%

Diarrea: 18% vs 14%

Retención hídrica: 31% vs 22%

Hipopotasemia: 17% vs 8%
Hipertransaminasemia: 10% vs 8 %

Eventos cardíacos: 13% vs 11%

Enzalutamida

AFFIRM

Crisis comiciales (5 casos)

Diarrea: 21% vs 18%

Astenia: 34% vs 29%

Eventos cardíacos: 6% vs 8%

Ra-223

ALSYMPCA

Neutropenia febril: 1% vs 1%
Anemia: 31% vs 31%
(G3-4: 13% vs 13%)

Diarrea: 25% vs 15%
(G3: 2% vs 2%)

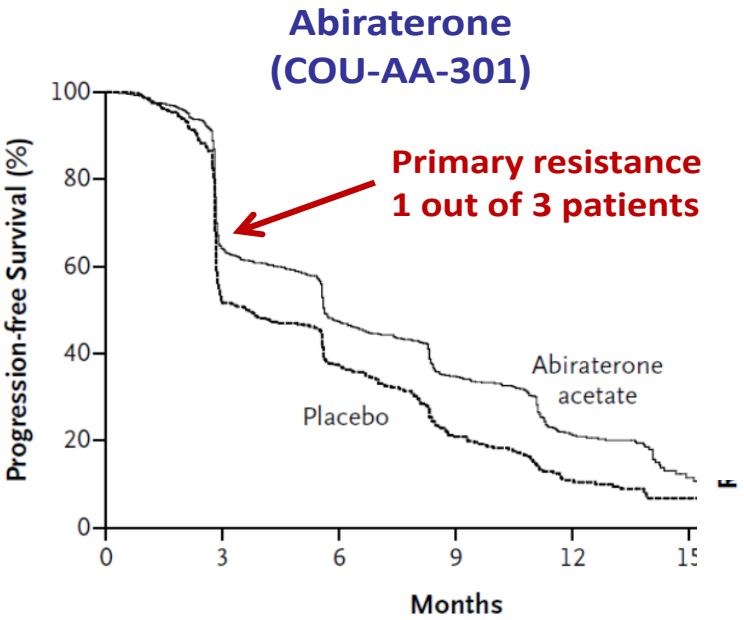
No aumento de neoplasias secundarias

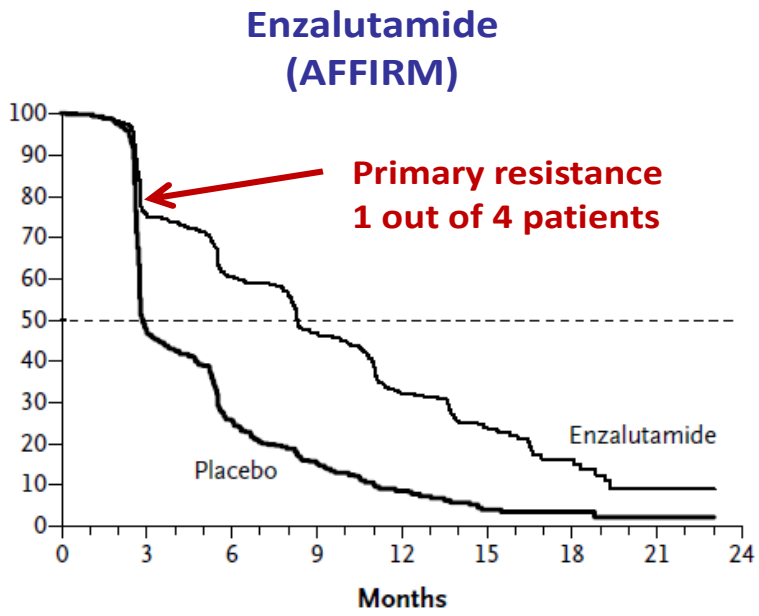
David Lorente, curso SOGUG 2016

¿ Como identificar la resistencia primaria a los nuevos agentes hormonales ?

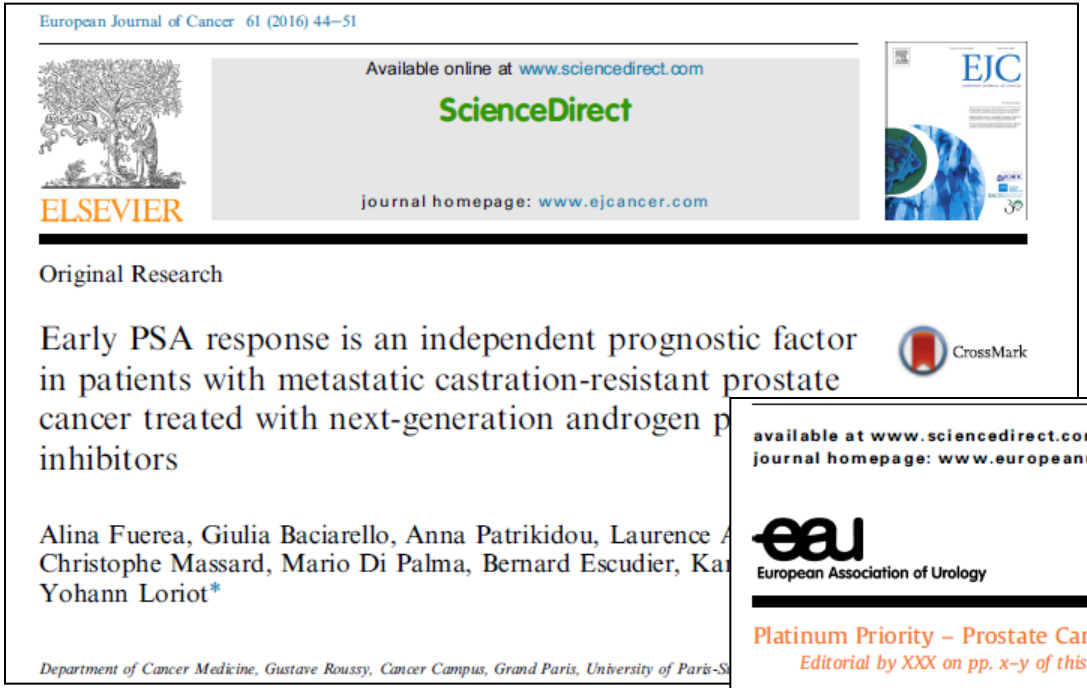
PRIMARY RESISTANCE TO AR-TARGETED AGENTS

rPFS





De Bono et al. N Engl J Med 2011;364:1995–2005
Scher H et al. N Engl J Med. 2012;367:1187-97



European Journal of Cancer 61 (2016) 44–51

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

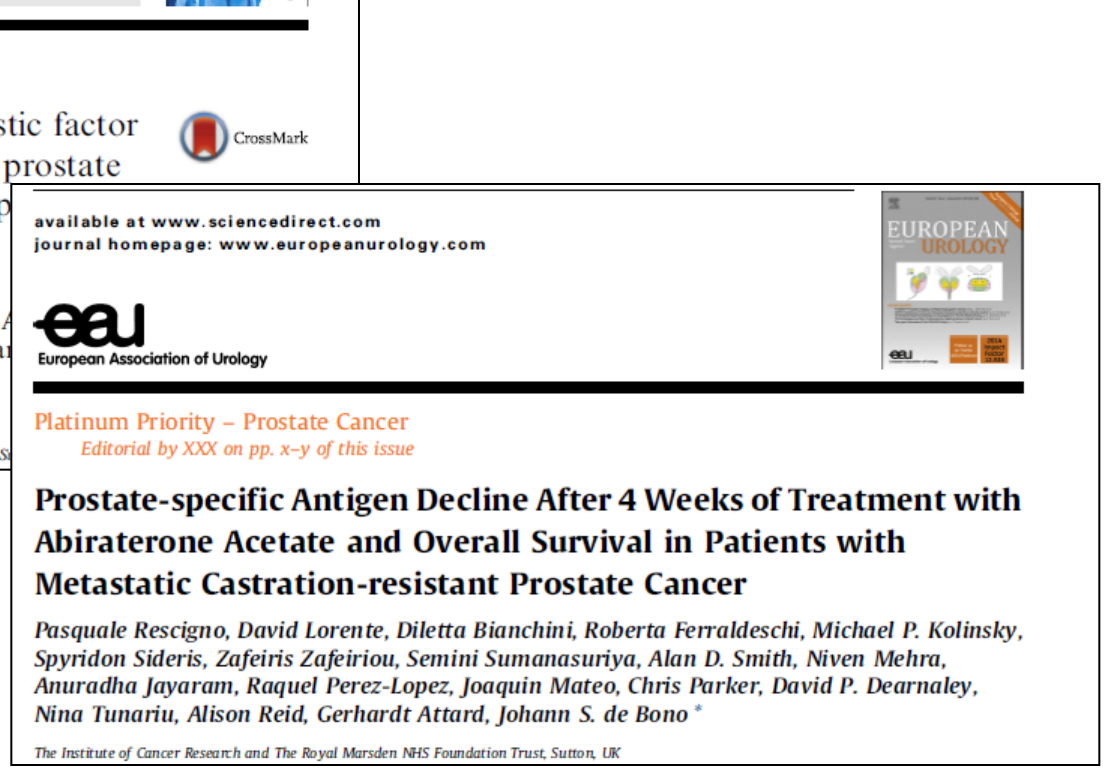
ELSEVIER

Original Research

Early PSA response is an independent prognostic factor in patients with metastatic castration-resistant prostate cancer treated with next-generation androgen p inhibitors

Alina Fuerea, Giulia Baciarello, Anna Patrikidou, Laurence A Christophe Massard, Mario Di Palma, Bernard Escudier, Ka Yohann Loriot*

Department of Cancer Medicine, Gustave Roussy, Cancer Campus, Grand Paris, University of Paris-S



available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

Prostate-specific Antigen Decline After 4 Weeks of Treatment with Abiraterone Acetate and Overall Survival in Patients with Metastatic Castration-resistant Prostate Cancer

*Pasquale Rescigno, David Lorente, Diletta Bianchini, Roberta Ferraldeschi, Michael P. Kolinsky, Spyridon Sideris, Zafeiris Zafeiriou, Semini Sumanasuriya, Alan D. Smith, Niven Mehra, Anuradha Jayaram, Raquel Perez-Lopez, Joaquin Mateo, Chris Parker, David P. Dearnaley, Nina Tunariu, Alison Reid, Gerhardt Attard, Johann S. de Bono **

The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, UK

PSA, prostate specific antigen

Rescigno P et al. Eur Urol 2017 (epub ahead of print); 2. Fuerera A et al. Eur J Cancer 2016; 61: 44-51

ORIGINAL ARTICLE

Radiographic progression with nonrising PSA in metastatic castration-resistant prostate cancer: *post hoc* analysis of PREVAIL

AH Bryce[1], JJ Alumkal[2], A Armstrong[3], CS Higano[4], P Iversen[5], CN Sternberg[6], D Rathkopf[7], Y Loriot[8], J de Bono[9], B Tombal[10], S Abhyankar[11,15], P Lin[12], A Krivoshik[13], D Phung[14] and TM Beer[2]

BACKGROUND: Advanced prostate cancer is a phenotypically diverse disease that evolves through multiple clinical courses. PSA level is the most widely used parameter for disease monitoring, but it has well-recognized limitations. Unlike in clinical trials, in practice, clinicians may rely on PSA monitoring alone to determine disease status on therapy. This approach has not been adequately tested.

METHODS: Chemotherapy-naive asymptomatic or mildly symptomatic men ($n = 872$) with metastatic castration-resistant prostate cancer (mCRPC) who were treated with the androgen receptor inhibitor enzalutamide in the PREVAIL study were analyzed *post hoc* for rising versus nonrising PSA (empirically defined as > 1.05 vs $\leqslant 1.05$ times the PSA level from 3 months earlier) at the time of radiographic progression. Clinical characteristics and disease outcomes were compared between the rising and nonrising PSA groups.

RESULTS: Of 265 PREVAIL patients with radiographic progression and evaluable PSA levels on the enzalutamide arm, nearly one-quarter had a nonrising PSA. Median progression-free survival in this cohort was 8.3 months versus 11.1 months in the rising PSA cohort (hazard ratio 1.68; 95% confidence interval 1.26–2.23); overall survival was similar between the two groups, although less than half of patients in either group were still at risk at 24 months. Baseline clinical characteristics of the two groups were similar.

CONCLUSIONS: Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients treated with enzalutamide. As restaging in advanced prostate cancer patients is often guided by increases in PSA levels, our results

Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients

Bryce AH et al. Prostate Cancer and Prostatic Dis 2017; 00: 1-7

Monitoring Treatment

- **Frequency and Modality**
  - Clinical: Every cycle
  - Biochemical: PSA every 4 weeks
  - Radiological: Every 3 months if other parameters stable otherwise earlier
- **Aim of Monitoring**
  - Ensure appropriate switching if not benefitting from current treatment
  - Prevent significant decline in performance status before offering subsequent treatment

Cross-Resistance Between AR-Targeted Agents

Table 3. Completed retrospective studies of sequencing abiraterone acetate and enzalutamide (Enza) in patients with metastatic castration-resistant prostate cancer in the post-chemotherapy setting.

Authors	Year published	Number of patients	Duration of second treatment	≥ 50% decline in PSA	Median PFS
Enza → AA					
Loriot *et al.* [51]	2013	38	3 months	3%	2.7 months
Noonan *et al.* [52]	2013	30	13 weeks	3%	3.8 months
AA → Enza					
Schrader *et al.* [53]	2013	35	4.9 months	29%	
Badrising *et al.* [54]	2014	61	3 months	21%	
Bianchini *et al.* [55]	2014	39	2.9 months	23%	
Schmid *et al.* [56]	2014	35	2.8 months	10%	
Brasso *et al.* [57]	2014	137	3.2 months	18%	

AA: Abiraterone acetate; PFS: Progression-free survival; PSA: Prostate-specific antigen.

Retrospective trials based on a small number of patients

Zhang T et al. *Expert Opin Pharmacother*. 2014;16:1–9.

Is Docetaxel Losing Activity After AR-Targeted Agents?

	FIRSTANA[1] DOC N=391
Therapy line	1
Visceral mets	YES
↓ PSA ≥50%	**68.5%**
Median PSA-PFS (mos)	8.3
OS, median	**24.3**

Other Trials*

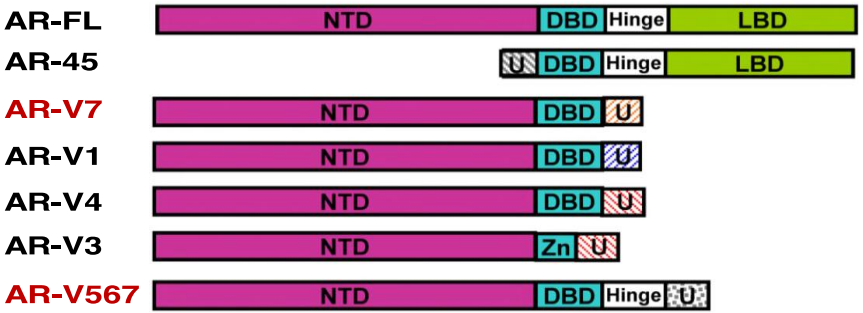
- **Mezynski**[2]: ABI→DOC (N=35); 2nd line therapy in pts with visceral mets:
  - PSA decline ≥50%= 26%
  - Median OS 12.5 mo
- **Schweizer**[3]: ABI→DOC (N=24); 2nd line therapy in pts with visceral mets:
  - PSA decline ≥50%= 38%
- **Azad**[4] : ABI→DOC (N=86); 2nd line therapy in pts with visceral mets:
  - PSA decline ≥50%= 35%
  - Median OS 11.7 mo
- **de Bono**[5]: ABI→DOC (N=100) 2nd line therapy in pts without visceral mets:
  - PSA decline ≥50%= 27%

**Retrospective studies in small number of patients.*

1. Oudard S, et al. *J Clin Oncol*. 2017. DOI: 10.1200/JCO.2016.72.1068; 2. Mezynski J et al. *Ann Oncol*. 2012;23:2943–7;
3. Schweizer MT et al. *Eur Urol*. 2014;66:646-52; 4. Azad AA et al. *Prostate*. 2014;74:1544–50; 5. de Bono J et al. *Eur Urol*. 2017;71:656–64.

SAGLB.CAB.17.06.0622(1)m (08/17)

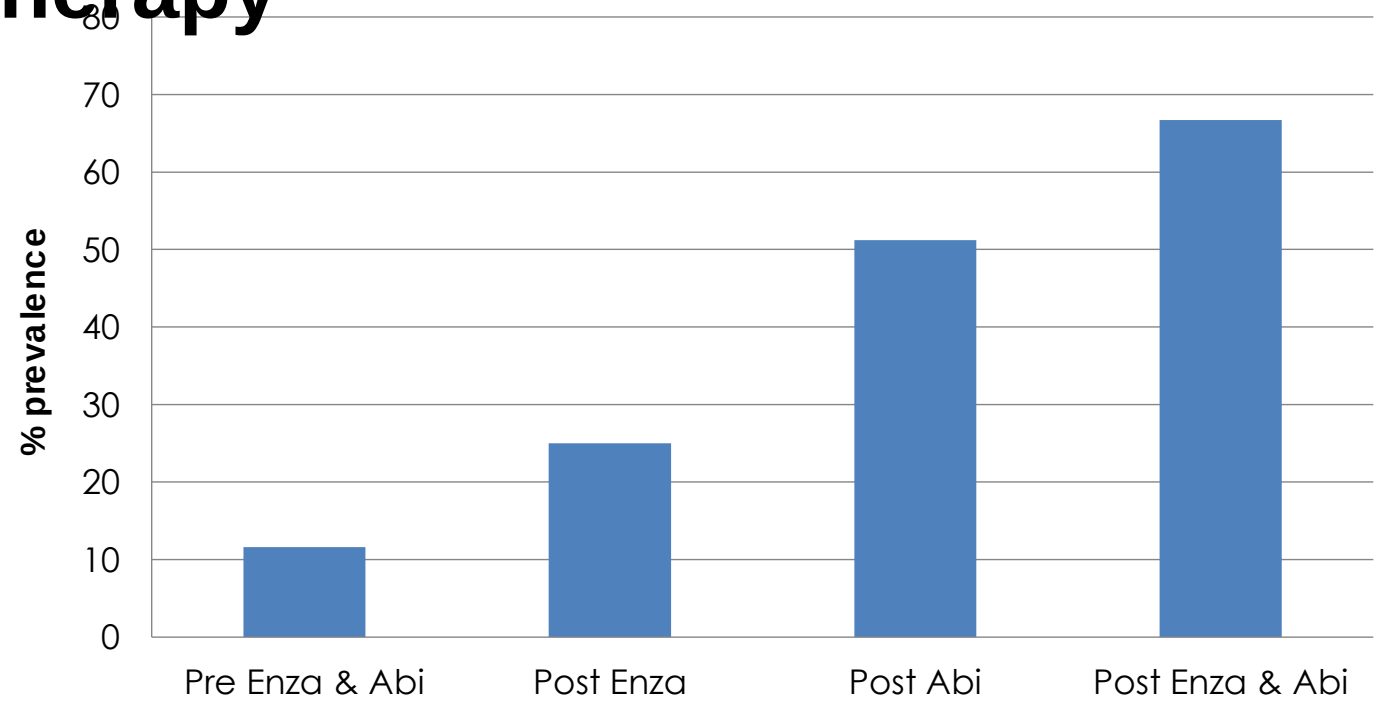
AR Splice Variants (ARv)



AR-FL: Full-Length Androgen Receptor
NTD: N-Terminal Domain
DBD: DNA-Binding Domain
LBD: Ligand-Binding Domain
U: Unique N- or C-terminal sequence

- ADT induces constitutively active splice variants which drive development of CRPC[1-2]
- ARv567 (43%) and ARv7 (24%) are the most prevalent[3]:
  - Both lack ligand-binding domain
  - AR-V7 also lacks Hinge domain
- Inhibition of ARv7 transcription by FOXO1 (potent AR suppressor)[4-5]

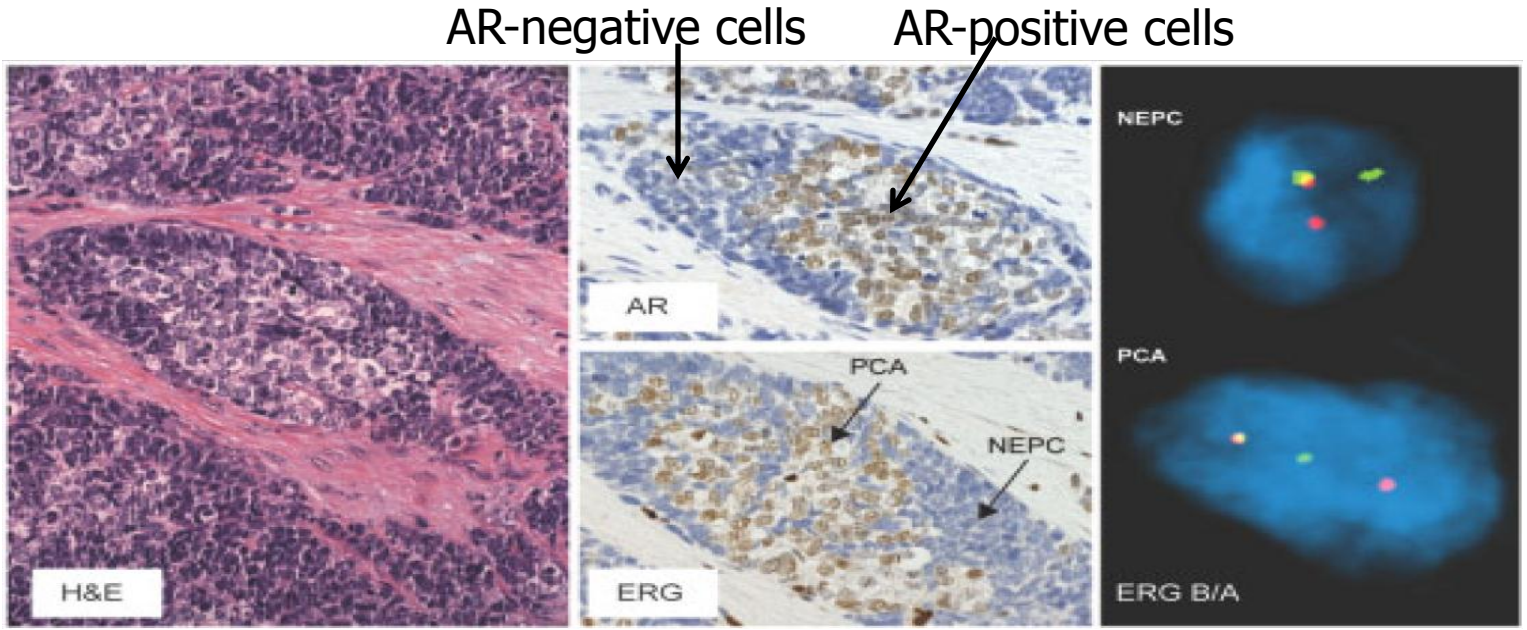
Prevalece of AR-V7 according to therapy



Antonarakis ES, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 5001)

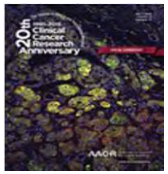
- **There are no prospective sequencing or head to head comparative studies to guide choice**
  - Limited number of patients
  - Mostly single institution experience
  - Retrospective data shortcoming

Co-Existence of AR-Positive and AR-Negative Tumor Cells in a Same Patient



Tumor with mixed features of neuroendocrine PCa and prostate adenocarcinoma

Beltran H et al. *Cancer Discov*. 2011;1:487-95



Platinum-based chemotherapy for variant castrate-resistant prostate cancer.
Aparicio AM. Clin Cancer Res. 2013;19:3621-30.

1. Small cell prostate carcinoma
2. Visceral metastases only
3. Lytic bone metastases
4. Bulky nodes or prostate mass
5. Low PSA relative to volume
6. NE markers & serum CEA or LDH
7. Primary castration-resistance

Cáncer de próstata hormonosensible (CPHS)

The Longitudinal Timeline of Systemic Therapy for Metastatic Hormone "Naïve" Prostate Cancer

1941: Charles Huggins publishes his observations that Androgen Deprivation Therapy is highly effective in controlling metastatic prostate cancer.

75 years!

2015: CHAARTED and STAMPEDE trials demonstrate that the addition of docetaxel to ADT prolongs life in men with (high volume) metastatic prostate cancer.

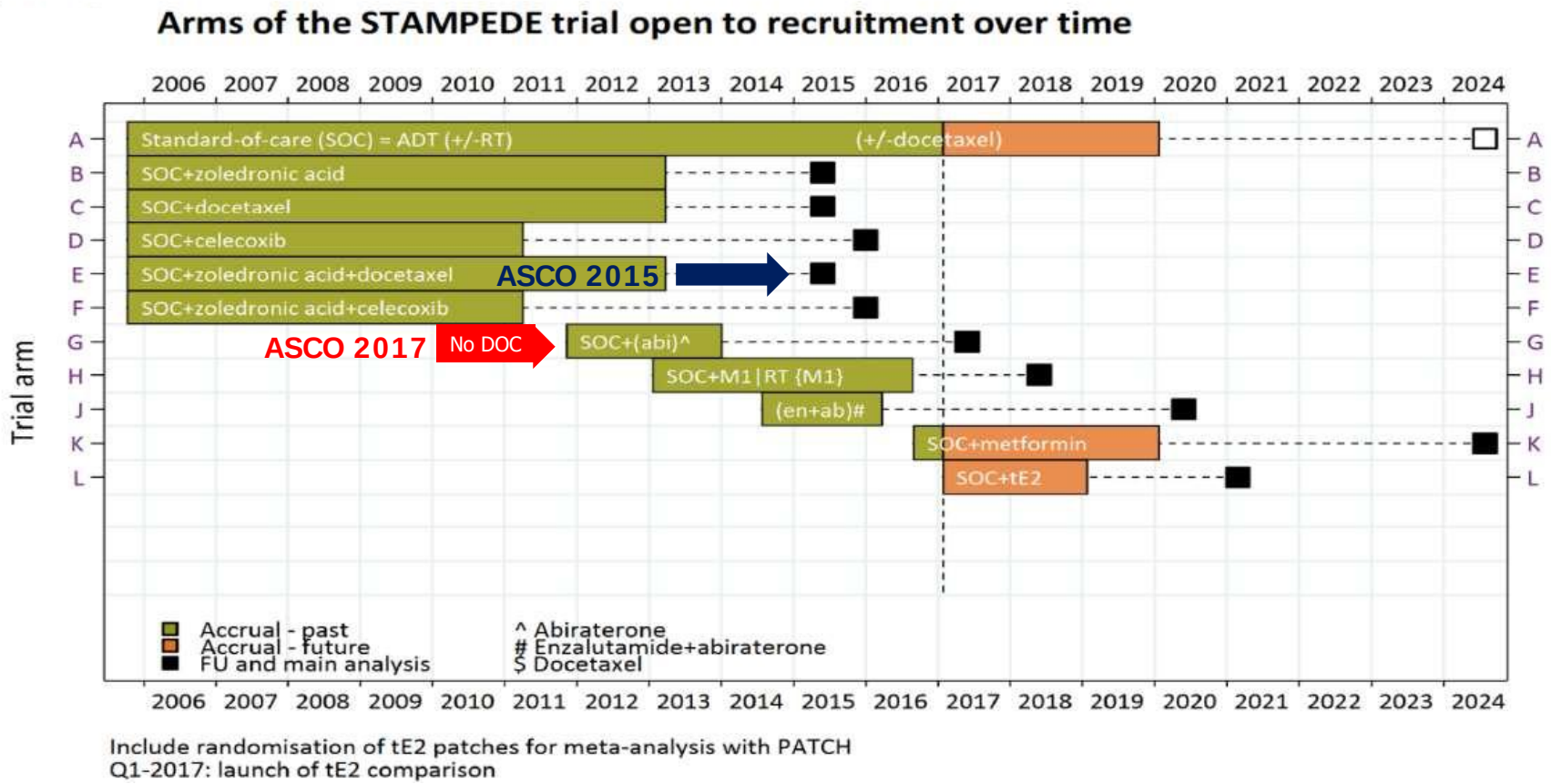
2 years

2017: LATITUDE and STAMPEDE: The addition of abiraterone to ADT prolongs life

??

Presented By Eric Small at 2017 ASCO Annual Meeting

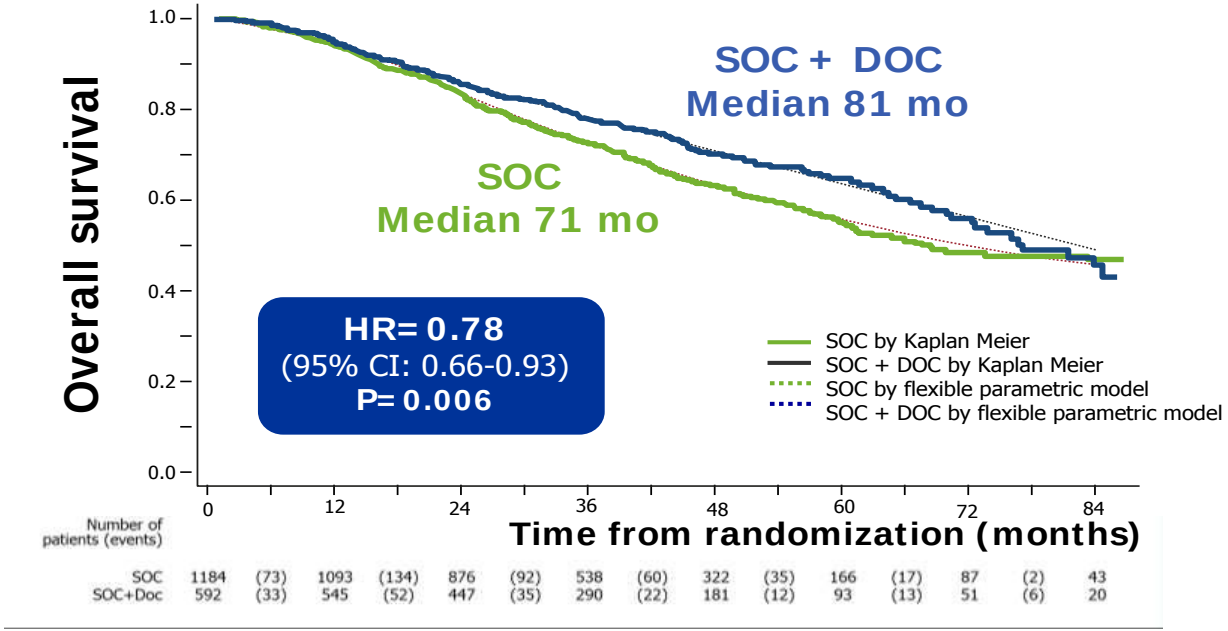
THE STAMPEDE TRIAL: A MULTI-ARM, MULTI-STAGE DESIGN



2:1 randomization against SOC= ADT +/-RT

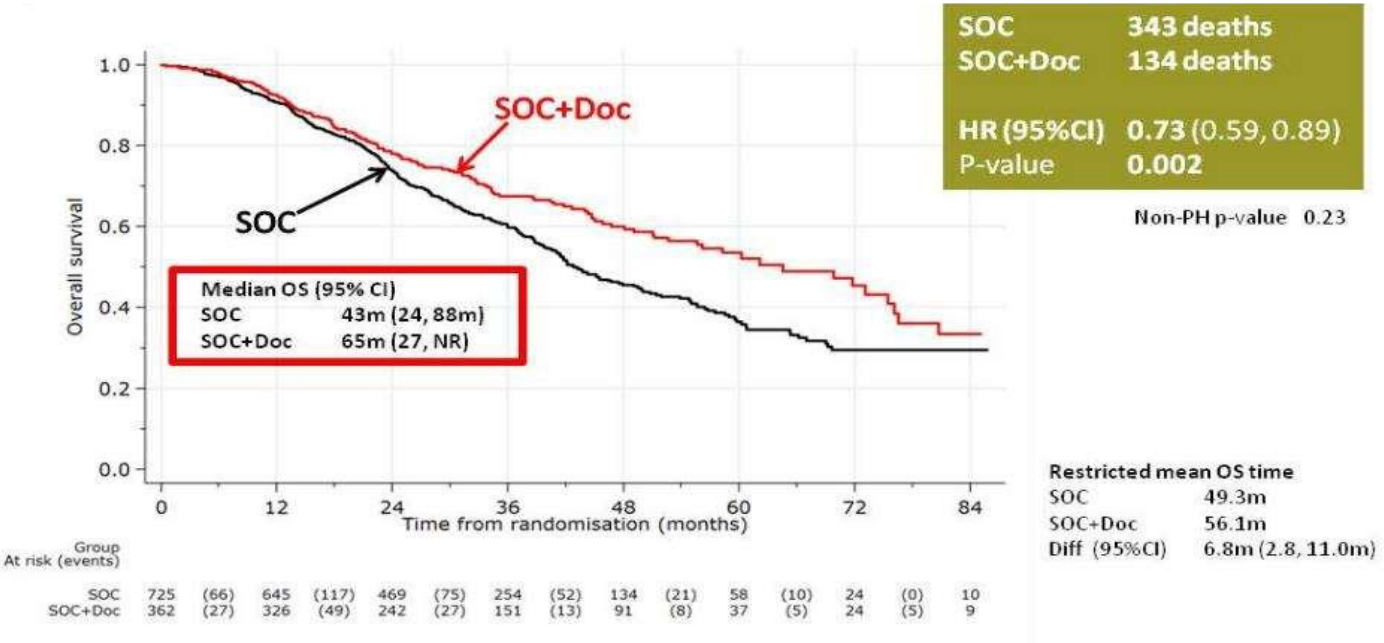
STAMPEDE – OS (primary endpoint) (n= 1,776)

- 61% M1; 15% N1M0; 24% N0M0; median follow-up: 43 mo



James, ND et al. Lancet. 2016;387:1163-77.

STAMPEDE – OS in M1 Patients Docetaxel

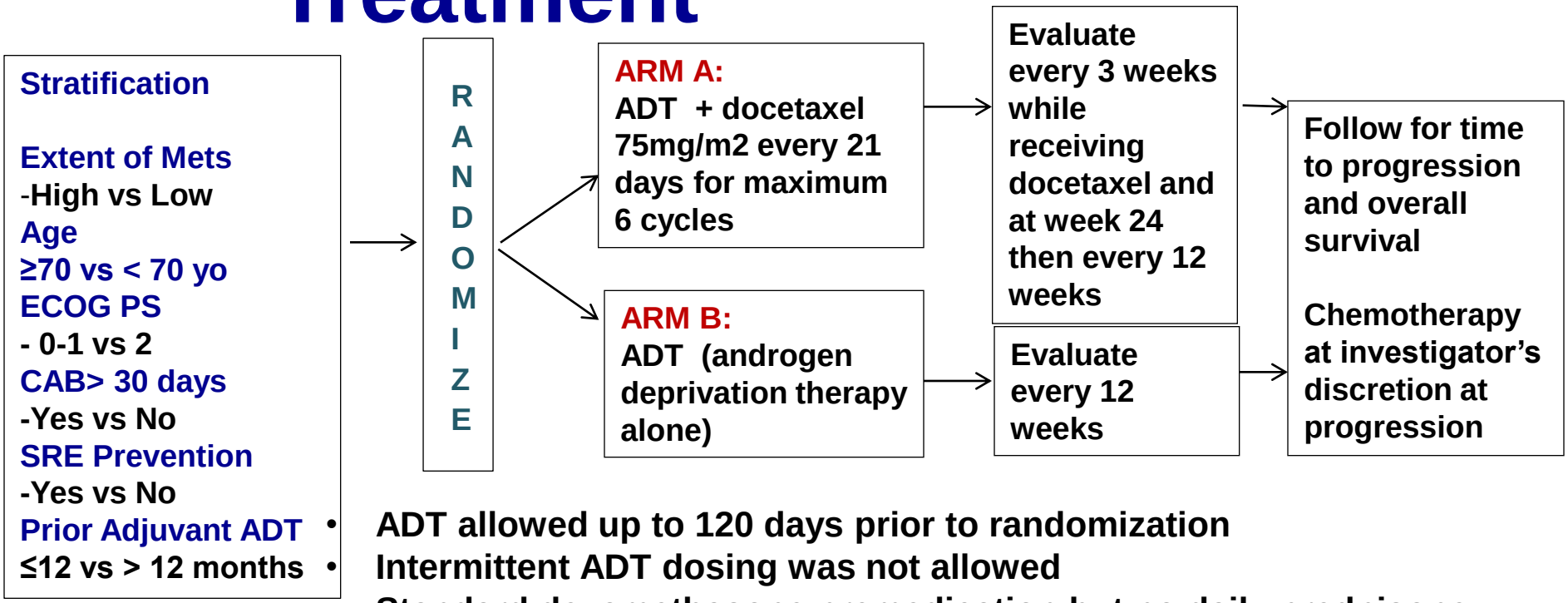


Phase III randomized trial in 2962 men with M0/M1 in 4 groups with zometa with hormone-naïve Pca; Primary endpoint: overall survival

OS: overall survival

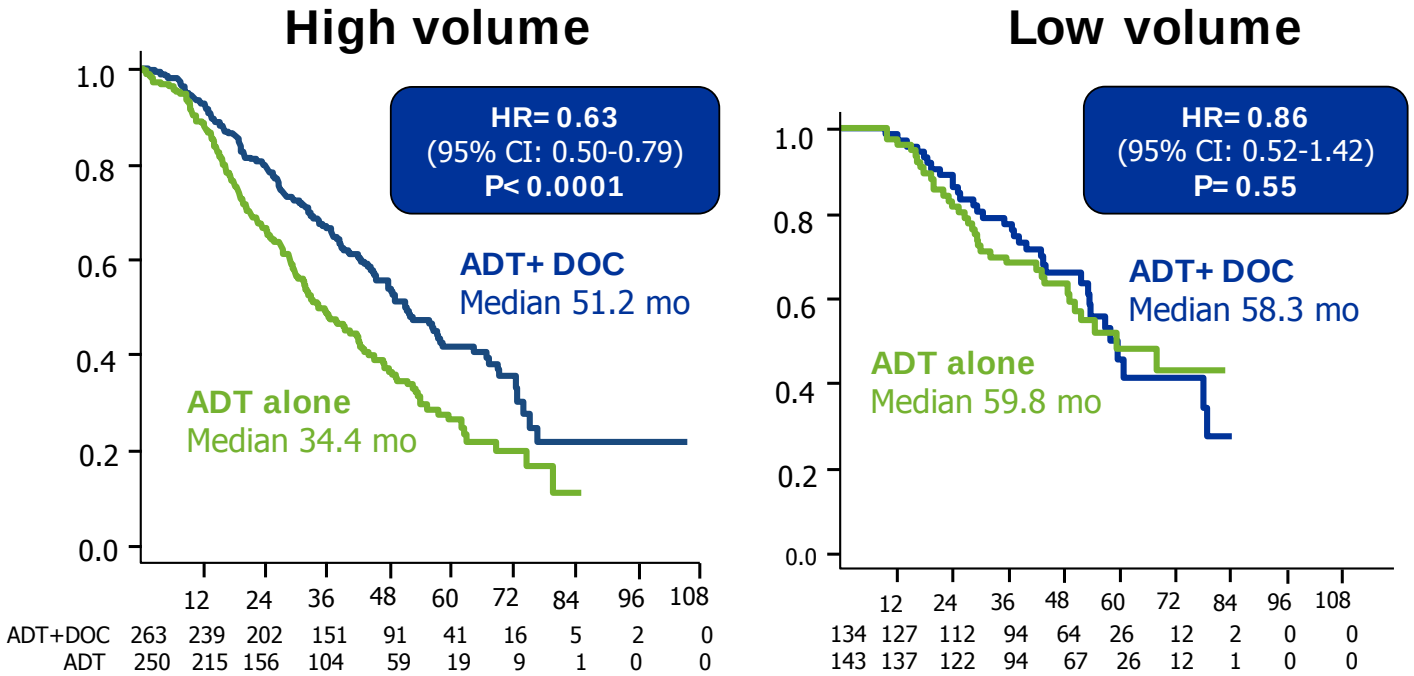
James, ND et al. Lancet. 2016;387:1163-77.

E3805 / CHAARTED Treatment



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

ECOG-ACRIN CHAARTED - OS by Tumor Volume (Update)

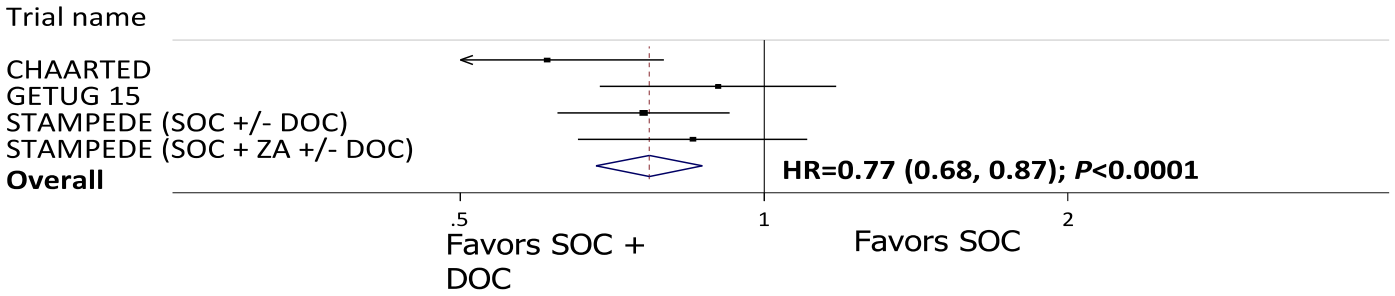


Phase III randomized trial in 790 men with metastastic hormone-naïve PCa
Primary endpoint: overall survival

Sweeney CJ et al. Ann Oncol 2016;27(suppl 6):abstract 720 and Sweeney CJ et al. N Engl J Med. 2015;373:737-46.

Upfront Docetaxel in M1
Systematic Review and Meta-Analysis

- Results based on 2,993 men / 1,254 deaths

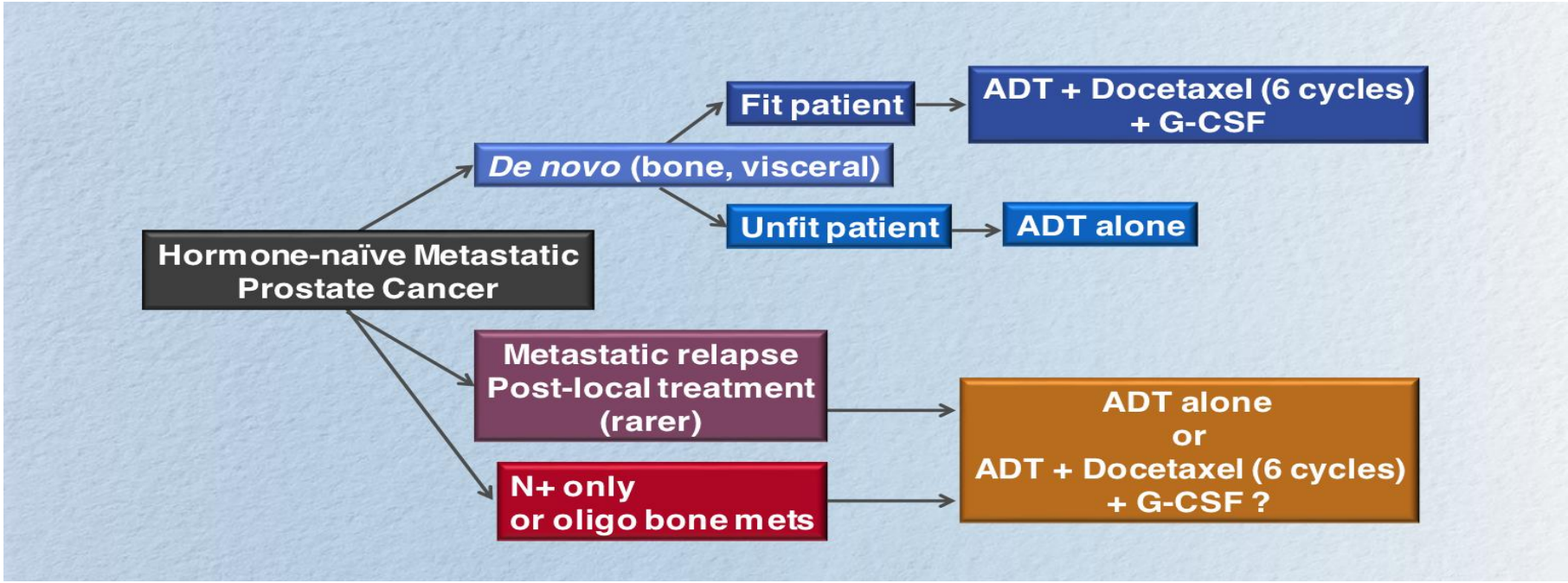


Heterogeneity: χ^2=4.80, df=3, *P*=0.187, I^2=37.5%

10% absolute improvement in survival (from 40% to 50%) at 4 years

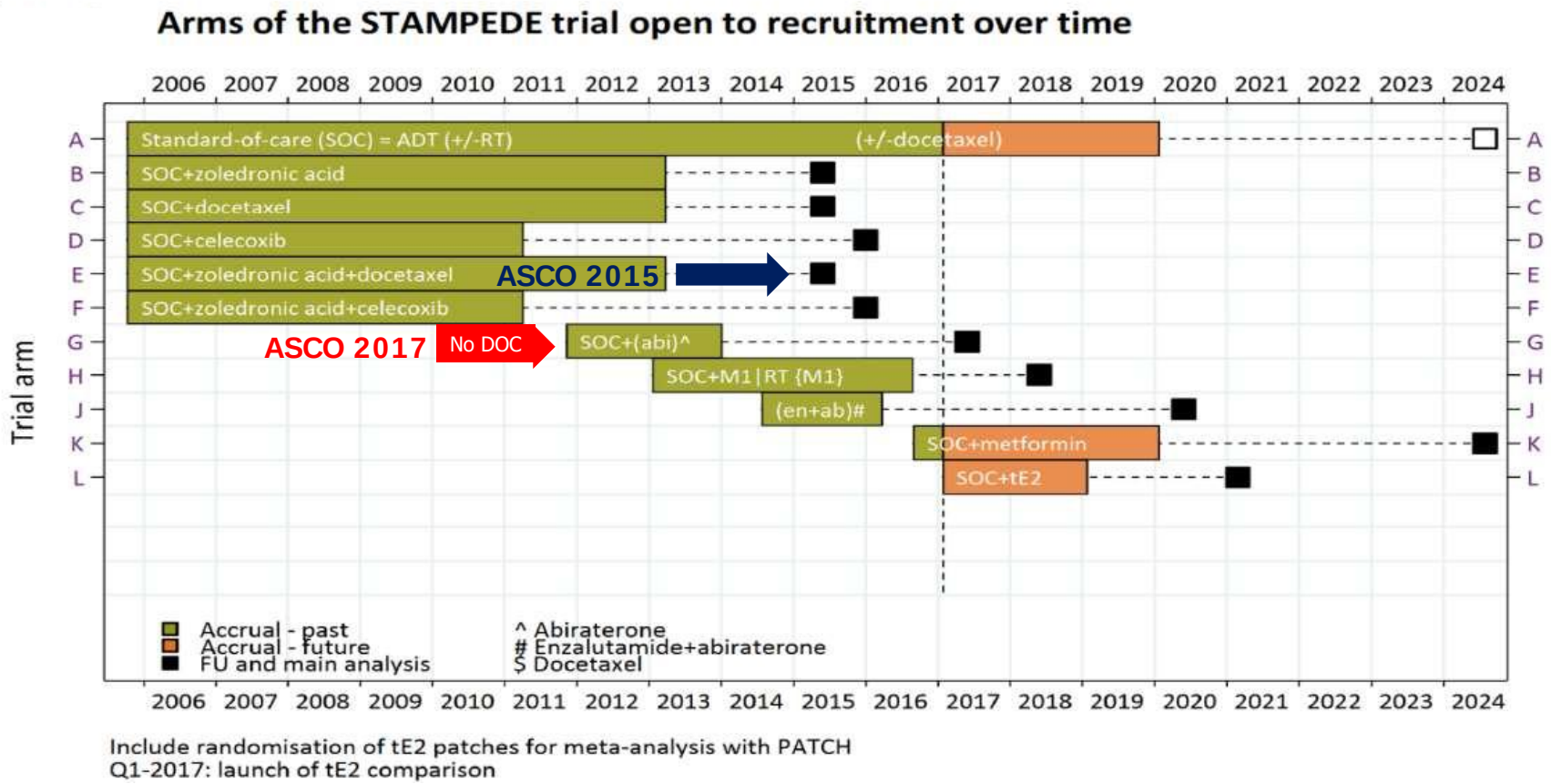
Vale CL et al. Lancet Oncol 2016;17:243-56.

Algoritmo de decisión CPHSm



Fizazi, Eur J Cancer 2016; 66: 125-30

THE STAMPEDE TRIAL: A MULTI-ARM, MULTI-STAGE DESIGN



2:1 randomization against SOC= ADT +/-RT

Patient characteristics [566 patients]

60%	Metastatic (87% inc bone)
22%	N+M0
17%	N0M0
56ng/ml	Median PSA (quartiles 22, 185)
66yr	Median age (quartiles 62, 70)
79%	WHO performance status 0
6%	Previous local therapy

Well balanced by allocated treatment

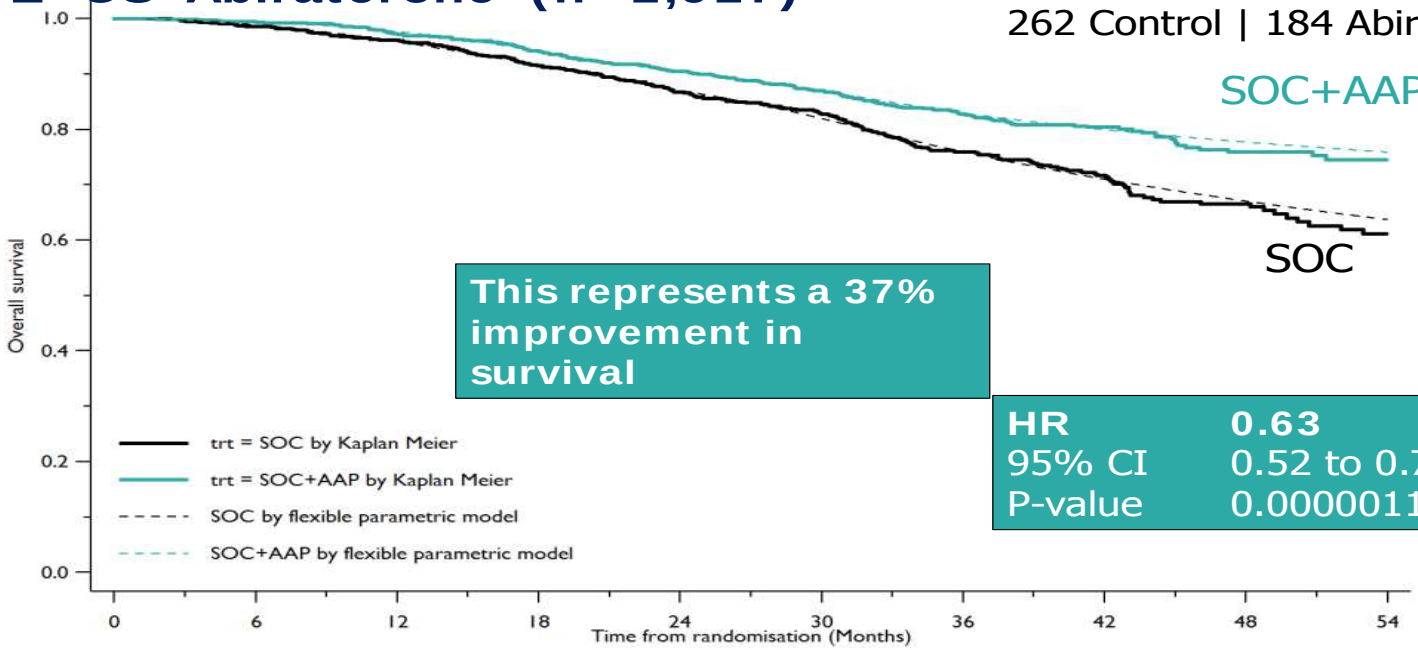
Stratification factors at randomisation:

:: Metastases
:: Nodal status
:: Choice of hormone therapy
:: Age
:: Hospital
:: Planned use of RT
:: NSAID/aspirin use
:: WHO performance status

STAMPEDE- OS Abiraterone (n=1,917)

Events
262 Control | 184 Abiraterone

mixed population of M1 and MO patients



This represents a 37% improvement in survival

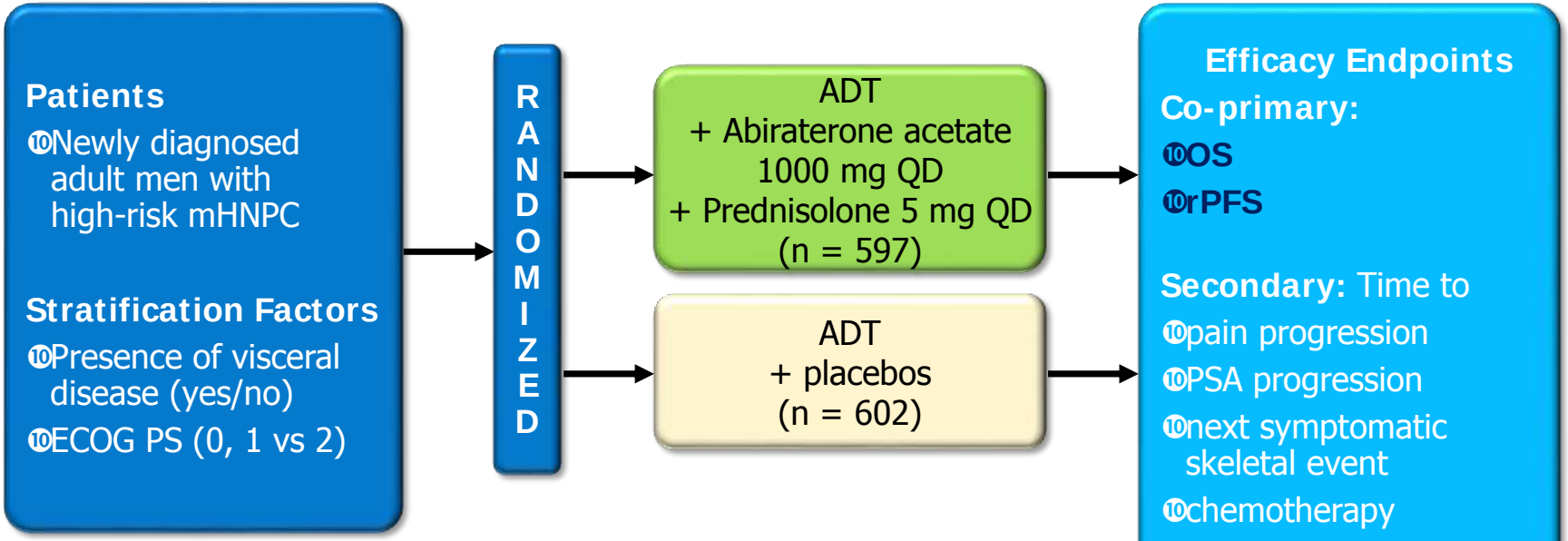
HR	**0.63**
95% CI	0.52 to 0.76
P-value	0.00000115

Number of patients (events)

SOC	957	(37)	909	(88)	806	(92)	491	(36)	123
SOC+AAP	960	(26)	917	(63)	840	(67)	541	(25)	161

James ND et al, N Engl J Med. 2017 Jul 27;377(4):338-351

LATITUDE: Phase III Trial of Abiraterone in patients with newly diagnosed metastatic prostate cancer (n=1,199)



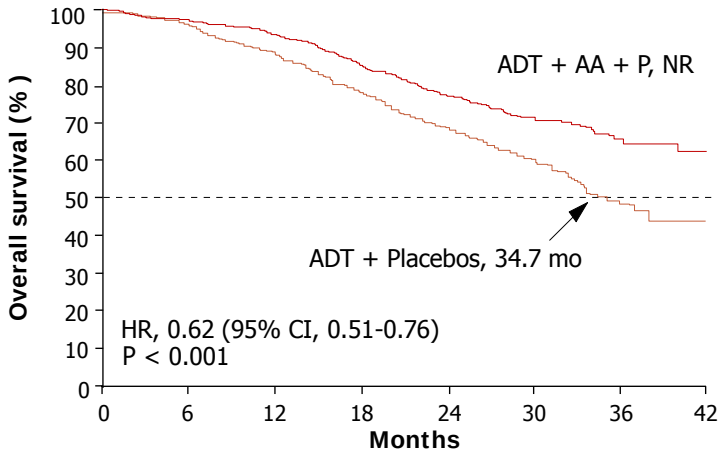
High-risk defined as meeting at least 2 of 3 high-risk criteria:

- [illegible]
- [illegible]
- Presence of measurable visceral lesion

Fizazi K et al. J Clin Oncol. 2017;35 (suppl; abstr LBA3); Fizazi K et al. N Engl J Med. 2017;377(4):352–60.

LATITUDE: Co-primary End Points

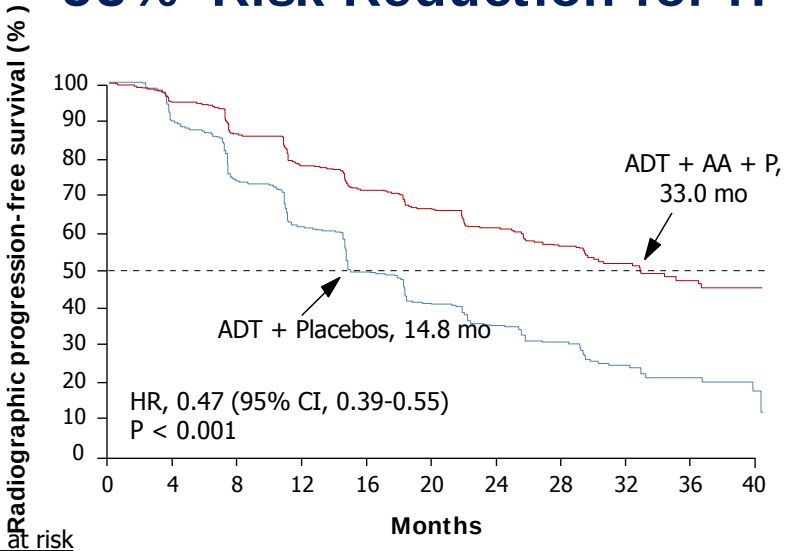
38% Risk Reduction for Death



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



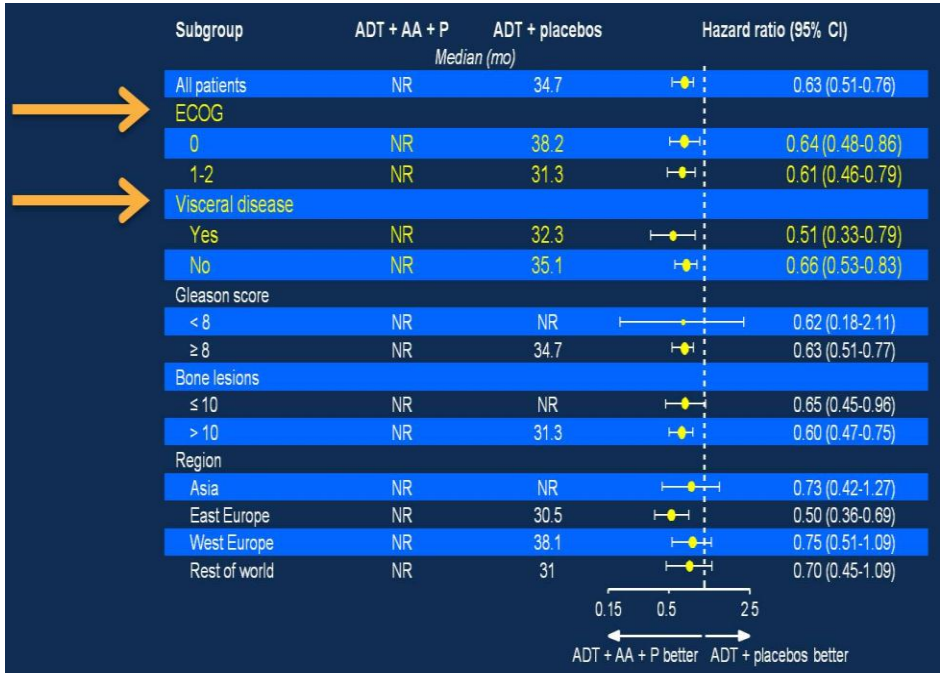
Patients at risk

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, et al. N Engl J Med. 2017;377:352-360. CI, confidence interval; HR, hazard ratio; NR, not reached.

LATITUDE: Características basales y subgrupos

	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 Liver Lungs Node	 97% 5% 12% 47%	 98% 5% 12% 48%
Baseline pain score (BPI-SF Item 3) 0-1 2-3 ≥ 4	 50% 22% 29%	 50% 24% 27%



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RETOS
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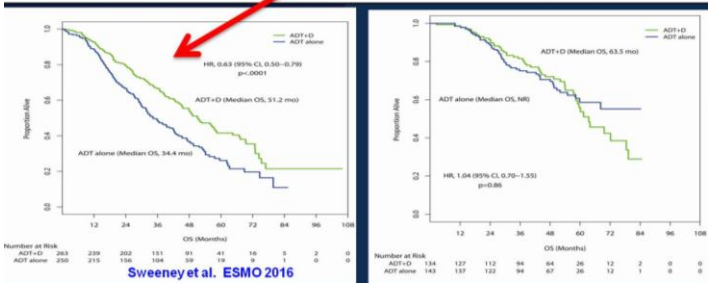
¿Docetaxel vs Abiraterona en CPHSm?

PRÓSTATA: Enfermedad metastásica HS

Abiraterona + prednisona

- **LATITUDE *vs* CHAARTED**

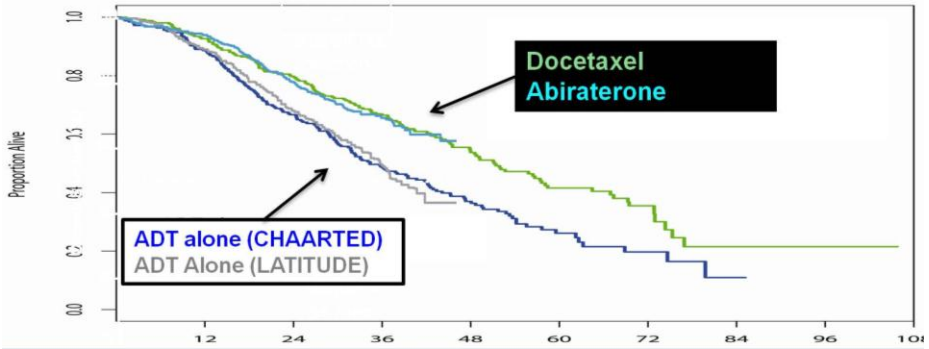
Evaluation of Rx by disease volume interaction using Cox proportional hazards model		
	HR (ADT+D/ADT)	95% CI
Overall	0.73	0.59 - 0.89
High volume	0.63	0.50 - 0.79
Low volume	1.04	0.70 - 1.55



Sweeney et al. ESMO 2016

	N	Patient Characteristics	
LATITUDE	1199	GS≥ 8 ≥3 bone mets Visceral mets Median Age	97.5% 97.5% 17% 67.5 yrs
CHAARTED	790	GS ≥ 8 "high vol" ≥4 bone mets Visceral mets Median Age	60% 65% na 24% 63.5 yrs

	Median OS			3 yr OS rate*	
	HR (95% CI)	Control (months)	Rx (months)	Control	Rx
LATITUDE	0.62 (0.51-0.76)	34.7 mo	NR	49%	66%
CHAARTED High Volume	0.63 (0.50-0.79)	34.4 mo	51.2 mo	~50%	~65%



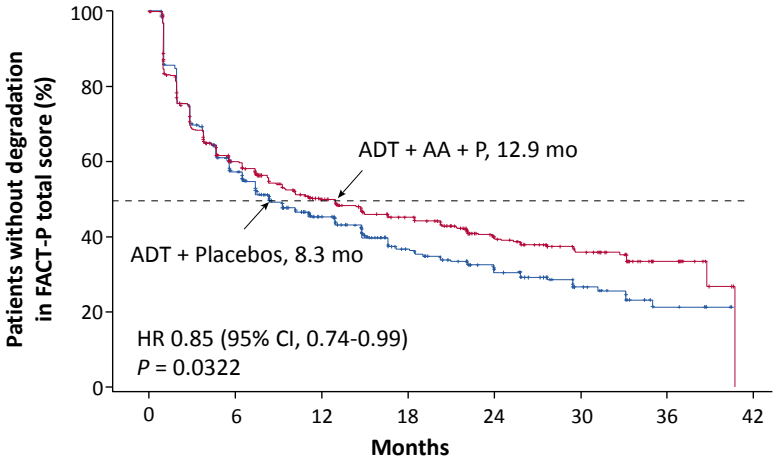
Small E, et al.Revisión Abstr LBA3.

Comparing Toxicity Across Studies

	Agent	Treatment-Associated Toxicity	Duration of experimental drug exposure
LATITUDE	Abi + Pred	**grade 3** / **grade 4** HTN: 20% / 0% ↓K: 10% / 0.8% ALT: 4% / 0.3%	On Rx until PD (median = 33 mos)
CHAARTED (entire cohort)	Docetaxel	Neutropenia: 12% Neutropenic fever: 6% Gr 3 or 4 infection with neutropenia: 2% 1 early death	6 cycles = 4.5 mos

ADT + AA + P Significantly Improved HRQoL per FACT-P

15% Risk Reduction for HRQoL Degradation

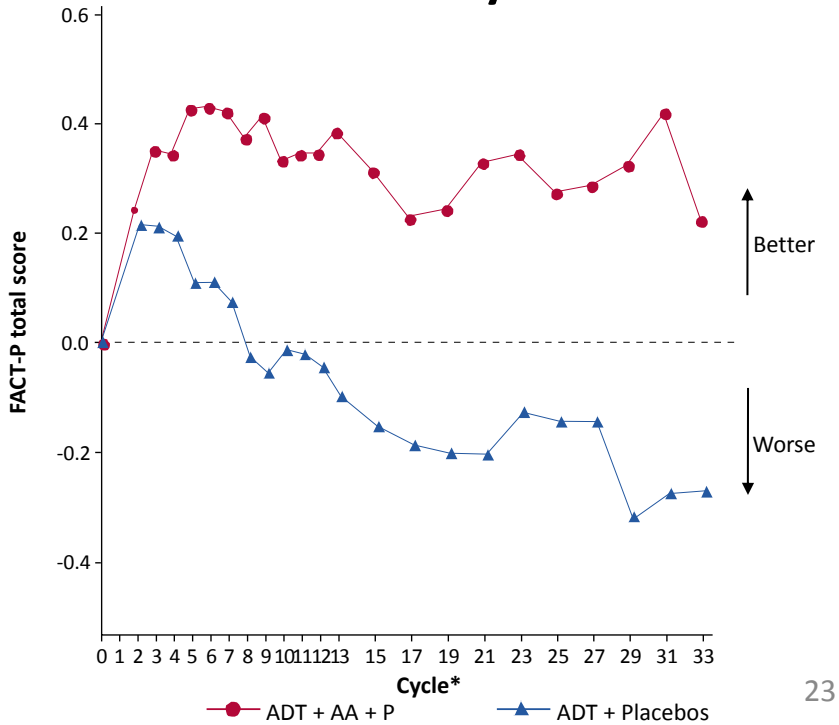


Patients at risk

ADT + AA + P	597	338	250	202	135	65	20	0
ADT + Placebos	602	309	192	119	77	33	7	0

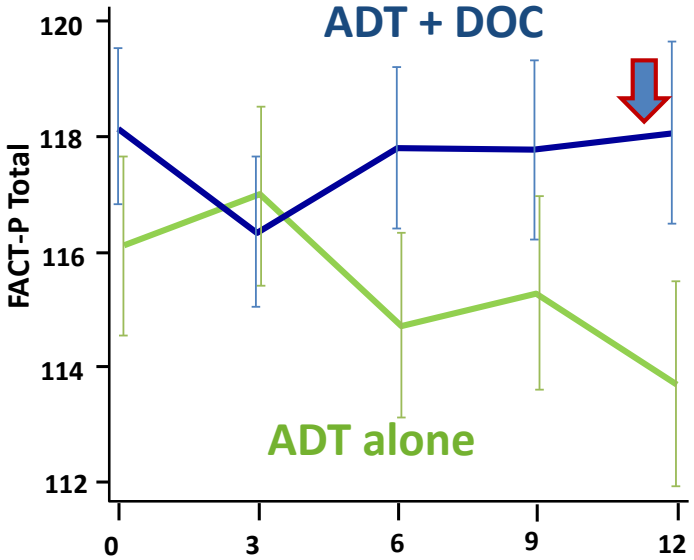
*1 cycle = 28 days.

Mean Change From Baseline Differed from Cycle 5 Onward



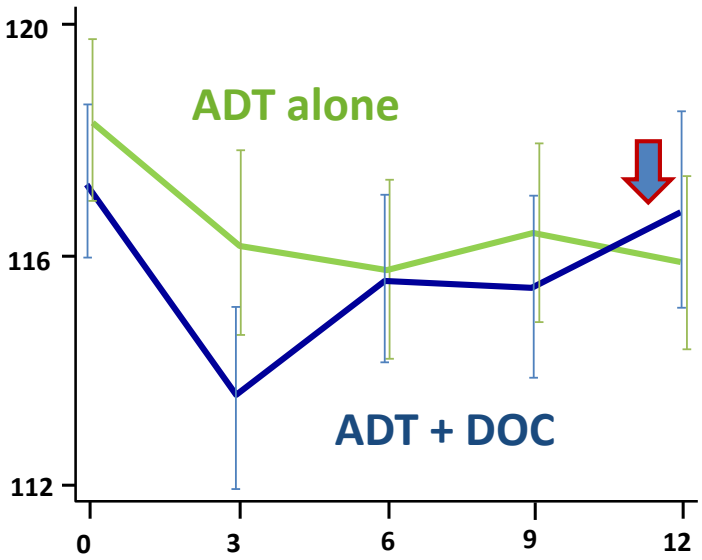
CHAARTED – Quality of Life (FACT-P)

High volume



Significant improvement in FACT-P at 1 year with ADT + DOC

Low volume



No significant difference at 1 year between both arms

FACT-P: Functional Assessment of Cancer Therapy – Prostate (higher values=improvement)

Sweeney CJ et al. Ann Oncol 2016;27(suppl 6):abstract 720

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%)

Adverse events – prevalence at 1 year and 2 years

1 year	SOC+DocP	SOC+AAP
Patients in safety dataset	136	323
Grade 3+ AE	15 (11%)	37 (11%)

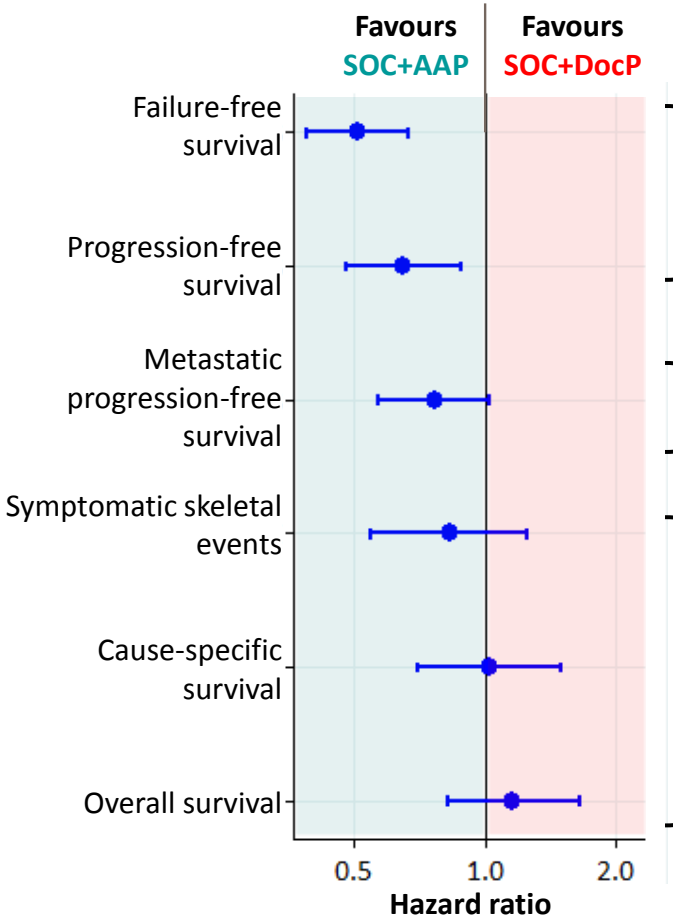
2 years	SOC+DocP	SOC+AAP
Patients in safety dataset	104	271
Grade 3+ AE	11 (11%)	30 (11%)

Safety dataset includes patients who:

:: started treatment

:: with assessment in toxicity window

:: without FFS event before window



Summary

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

Strong evidence favouring AAP

Weak evidence favouring AAP

No good evidence of a difference

→ Proportionately different time spent in each disease state

Toxicity profiles quite different and well known

Cuestiones pendientes

- **Coste-efectividad**
- Larga exposición a esteroides con Abiraterona
- Selección de clones AR-independientes tras Abi? Menos eficacia con docetaxel tras Abi?
- Perfil de paciente? Preferencias del paciente? Ancianos? Fragiles? Fit??
- Combinación de ambas estrategias vs secuenciación?

Phase III Trials With Life-Prolonging Therapies in Advanced Prostate Cancer

	Study	Agents	N	Indication	HR (95% CI)	ΔOS (mo)
2016	STAMPEDE[1]	DOC/SOC vs SOC	1,086	Metastatic hormone-naïve	0.73 (0.59-0.89)	+22.0
2017	STAMPEDE[2]	ABI/P/SOC vs SOC	1,917	Metastatic hormone-naïve	0.63 (0.52-0.76)	NR
2015	CHAARTED[3]	DOC/ADT vs ADT	790	Metastatic hormone-naïve	0.61 (0.47-0.80)	+13.6
2017	LATITUDE[4]	ABI/P/ADT vs ADT	1,199	Metastatic hormone-naïve	0.62 (0.51-0.76)	NR
2004	TAX-327[5]	DOC/P vs mito/P	1,006	mCRPC, symptomatic or not	0.76 (0.62-0.94)	+2.9
2010	IMPACT[6]	Sipuleucel-T vs pbo	512	mCRPC (pre-DOC) mild/no symptoms - No visceral mets	0.78 (0.61-0.98)	+4.1
2010	TROPIC[7]	CABA/P vs mito/P	755	mCRPC (post-DOC)	0.70 (0.59-0.83)	+2.4
2015	COU-AA-302[8]	ABI/P vs P	1,088	mCRPC (pre-DOC), mild/no symptoms - No visceral mets	0.81 (0.70-0.93)	+4.4
2012	COU-AA-301[9]	ABI/P vs P	1,195	mCRPC (post-DOC)	0.74 (0.64-0.86)	+4.6
2017	PREVAIL[10]	ENZA vs pbo	1,717	mCRPC (pre-DOC) mild/no symptoms , 11% visceral mets	0.71 (0.60-0.84)	+4.0
2012	AFFIRM[11]	ENZA vs pbo (or P)	1,199	mCRPC (post-DOC)	0.63 (0.53-0.75)	+4.8
2013	ALSYMPCA[12]	Radium-223 vs pbo	921	mCRPC (post-DOC or unfit for DOC)	0.70 (0.55-0.88)	+2.8

ABI, abiraterone; ADT, androgen deprivation therapy; CABA, cabazitaxel; DOC, docetaxel; ENZA, enzalutamide; mCRPC, metastatic castration resistant prostate cancer; mito, mitoxantrone; P, prednisone; Pbo, placebo; SOC, standard of care.

1. James ND. *Lancet*. 2016;387:1163–77; 2. James ND et al. N Engl J Med. 2017 Jun 3. doi: 10.1056/NEJMoa1702900; 3. Sweeney CJ. *N Engl J Med*. 2015;373:737–46;
4. Fizazi K, et al. *N Engl J Med*. 2017;377:352-360; 5. Tannock IF. *NEJM*. 2004;351:1502–12; 6. Kantoff PW. *NEJM*. 2010;363:411–22;
7. de Bono JS. *Lancet*. 2010;376:1147–54; 8. Ryan C. *Lancet Oncol*. 2015;16:152–60; 9. Fizazi K. *Lancet Oncol*. 2012;13:983–92;
10. Beer TM. *Eur Urol*. 2017 Feb;71(2):151–54; 11. Scher HI. *NEJM*. 2012;367:1187–97; 12. Parker C et al. *NEJM*. 2013;369:213–23.

Median OS in Advanced Prostate Cancer

1990s	Prednisone (P) alone (mCRPC):	**12.6** mo[1]
2004	TAX327 (DOC/P – mCRPC):	**18.9** mo[2]
2010	TROPIC (DOC/P → CAB/P – mCRPC)*:	**29.4** mo[3-4]
2011	COU-AA-301 (DOC/P → ABI/P – mCRPC)*:	**32.6** mo[5]
2013	COU-AA-302 (ABI/P pre-DOC – mCRPC):	**34.7** mo[6]
2014	PREVAIL (ENZA pre-DOC – mCRPC):	**35.3** mo[7]
2015	STAMPEDE – M1 (DOC/P + ADT – mHSPC):	**65.0** mo[8]

*Median OS calculated from first DOC cycle

1. Kantoff PW. *J Clin Oncol*. 1999;7:2506–13; 2. Tannock IF. *N Engl J Med*. 2004;351:1502–12; 3. de Bono JS et al. *Lancet*. 2010;376:1147–54;
4. Sartor O. *J Clin Oncol*. 2011;29(S15):abstract 4525 (podium presentation); 5. Fizazi K . *Lancet Oncol*. 2012;13:983–92 (supplementary appendix);
6. Ryan CJ. *Lancet Oncol*. 2015;16:152–60; 7. Beer TM. *Eur Urol*. 2017;71:151–54; 8. James ND et al. *Lancet*. 2016;387:1163–77.

SAGLB.CAB.17.06.0622(1)m (08/17)

Phase 3 Ongoing Combination Therapy Trials in HSPC

Study	Identifier	Study Drugs	Pts (N)	Primary End Point	Status/Read Out
LATITUDE	NCT01715285	ADT ± **AA**	1209	rPFS, OS	ASCO 2017
STAMPEDE (Arm G)	NCT00268476	ADT ± **AA**	1800	OS	LBA ASCO 2017
PEACE-1	NCT01957436	ADT ± DOC vs ADT + **AA** ± DOC (± local RT)	916	PFS, OS	Recruiting/2020
STAMPEDE (Arm J)	NCT00268476	ADT ± **AA + ENZ***	1800	OS	Closed-will report in 2-3 yrs
SWOG-1216	NCT01809691	ADT + **TAK-700** vs ADT + BIC	1304	OS	Recruiting/2027
ENZAMET	NCT02446405	ADT + **ENZ** vs ADT + antiandrogen	1100	OS	Recruiting/2020
TITAN	NCT02489318	ADT ± **APA (ARN 509)**	1000	rPFS, OS	Recruiting/ 2021
ARCHES	NCT02677896	ADT ± **ENZ**	1100	rPFS	Recruiting/ 2023
ARASENS	NCT02799602	ADT + DOC ± **ODM-201**	1300	OS	Recruiting/2022

*Includes upfront Doc

Modified from and courtesy of K. Fizazi

RETOS
REDES
RESULTADOS

La investigación en CaP

ENSAYO ABIDO-SOGUG

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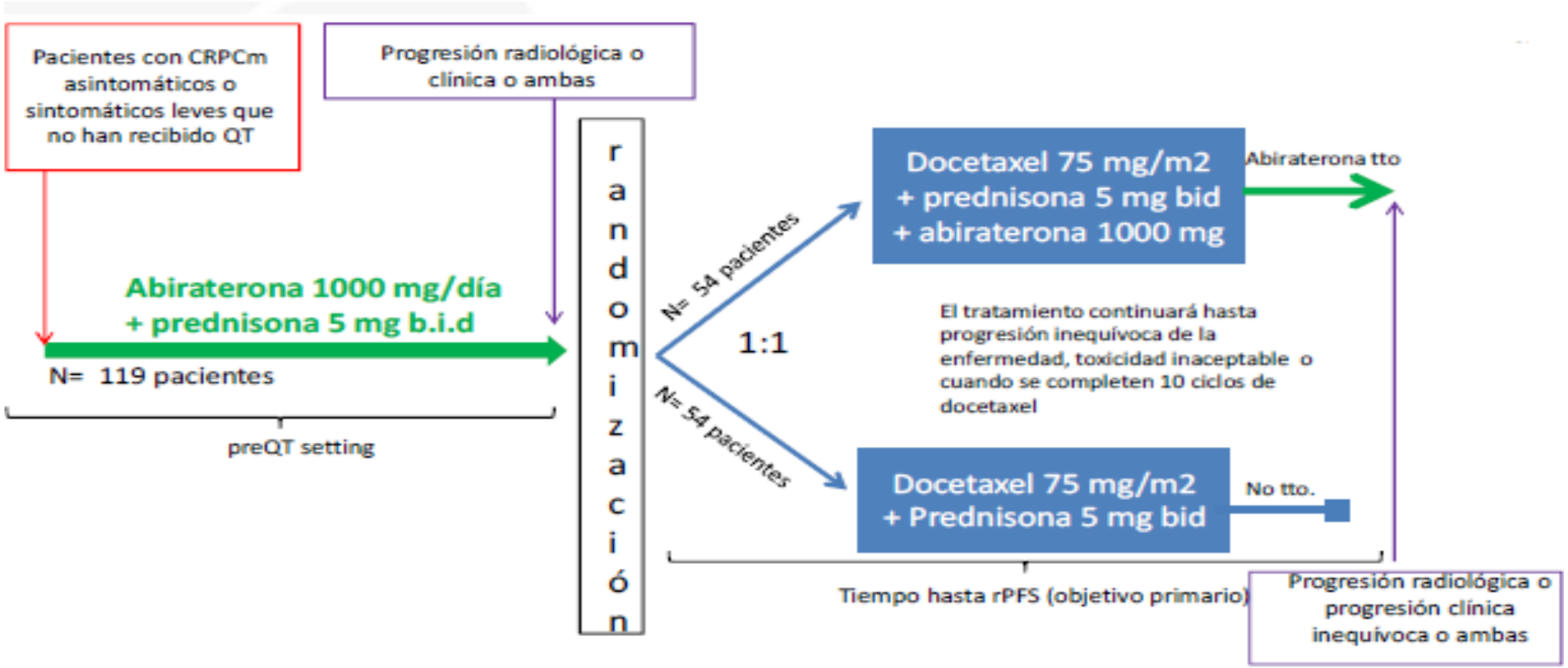

Conclusiones

- La vía de señalización de AR es clave en la progresión del cáncer de próstata
- En CPRCm cinco agentes han demostrado beneficio en SG aunque seguimos sin conocer la secuencia óptima
- La monitorización adecuada y la identificación temprana de resistencias permite optimizar los resultados
- En CPHSm Docetaxel y Abiraterona consiguen una ventaja similar en SG
- La inclusión de pacientes en ensayo clínico sigue siendo primordial: facilita el acceso a fármacos y responde a preguntas relevantes en nuestra práctica clínica.


GRACIAS