MD Anderson Cancer Center
Madrid • España

Novedades en el tratamiento del Cáncer de Próstata Hormono Resistente

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Introducción

El tratamiento de pacientes con CP avanzado supone el uso secuencial de múltiples modalidades de tratamiento activo de reciente desarrollo junto con aproximaciones clásicas con la meta de prolongar supervivencia, minimizando complicaciones y manteniendo calidad de vida.

- El momento óptimo para iniciar la terapia sistémica no esta bien definido.
  - No es curativo
  - No se ha demostrado que el tratamiento inmediato mejore supervivencia global *(disminuye la mortalidad especifica)*
  - Los efectos secundarios afectan negativamente a la supervivencia.

Loblaw DA. ASCOJ Clin Oncol. 2007;25(12):1596.

Cáncer de próstata hormono-resistente (CPHR) engloba a los paciente que habiendo sido tratados con terapia de deprivación androgénica (TDA) tienen elevación de PSA, aparición de nuevas metástasis o progresión de las ya existentes.

La supervivencia varía entre los 12.2 y los 21.7 meses

La presencia de enfermedad hormono-resistente no supone que esta sea totalmente independiente de andrógenos y resistente a la terapia dirigida a la estimulación androgénica

El TDA debe continuarse cuando se inician otros tratamientos.

Tannock IF, et al. N Engl J Med 2004;351:1502-12.

Introducción

Las opciones de terapia sistémica para pacientes con elevación de PSA como única evidencia de enfermedad diseminada son las mismas que para aquellos con metástasis evidentes.

La enfermedad diseminada solo por elevación de PSA tiene una historia natural mas prolongada que la que se manifiesta con enfermedad ósea, ganglionar o visceral.

- Docetaxel, era la única terapia aprovada que mejoraba supervivencia con un beneficio de 2-3meses vs mitoxantrone + prednisona

- Mitoxantrone +prednisona había sido aprobado por su beneficio sintomático respecto a glucocorticoides sin beneficio en supervivencia.

Tannock IF, et al. N Engl J Med 2004;351:1502-12.
Petrylak DP, et al. N Engl J Med 2004;351:1513-20.

Approach	Indications, regulatory status	Route, schedule	Steroids	Symptoms, disease burden	Contraindications	PSA response to treatment	Median overal survival benefi
Abiraterone	Approved, metastatic CRPC	Oral, daily	Required	–	Severe liver dysfunction; hypokalemia; heart failure	Yes	Post docetaxel: 4.6 mos.[1] Chemotherapy naive:*[2]
Enzalutamide	Approved/post docetaxel	Oral, daily	Not required	–	Seizures	Yes	4.8 mos.[3]
Sipuleucel-T	Approved, pre/post docetaxel	IV, every 2 weeks x 3 doses	Possibly contraindicated	Asymptomatic or minimally symptomatic	Steroids; narcotics for cancer-related pain; GM-CSF; liver metastases	No	4.1 mos.[4]
Docetaxel	Approved, metastatic CRPC	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.5 mos.[5]
Cabazitaxel	Post docetaxel	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.4 mos.[6]
Radium-223	Approved, symptomatic bone metastases with no known visceral metastases	IV, every 4 weeks	Not required	Symptomatic bone metastases	Visceral metastases	Not reported	3.6 mos.[7]

Median survival not reached for abiraterone; hazard ratio 0.75.

1. *Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 stud Oncol 2012; 13: 983.*
2. *Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138.*
3. *Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367:1187.*
4. *Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411.*
5. *Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008; 26:242.*
6. *de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376:11*
7. *Parker C, Nilsson S, Heinrich D, et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSY Clin Oncol 30, 2012 (suppl; abst LBA4512).*

Agentes que mejoran supervivencia estudios fase III

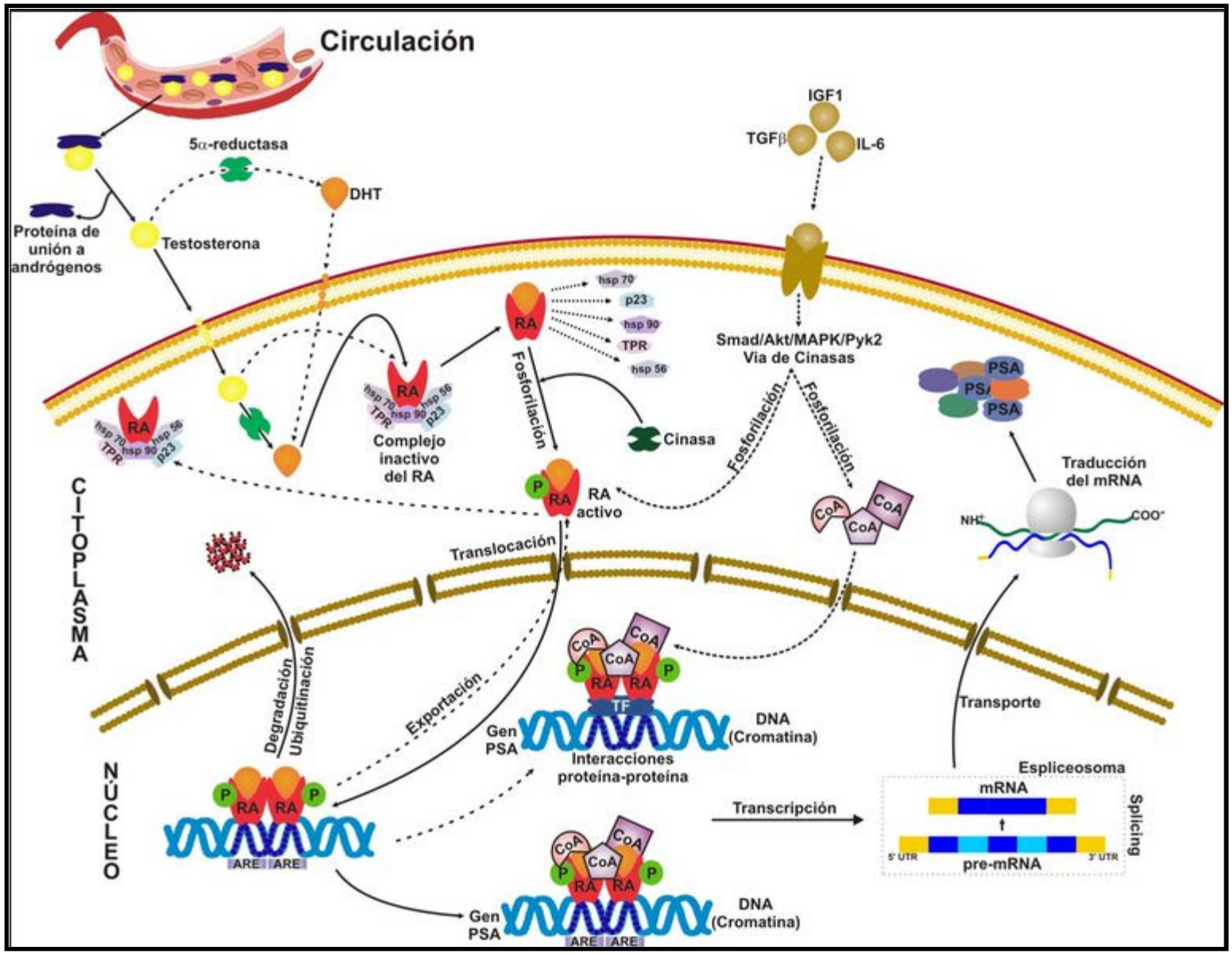
Agentes que interfieren con la estimulación androgénica: Abiraerona, Enzalutamida

Quimioterapia: Docetaxel y Cabacitaxel

Inmunoterapia: Sipoleucel-T

Radioisótopos: Radio 223

Antiguos tratamientos no bien estudiados en ensayos fase III que pueden mantener su utilidad?



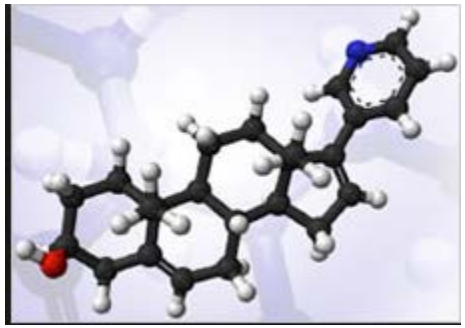
Adaptado de Luke y Coffey, 1994; Heinlein y Chang, 2004; Weigel y Moore, 2007.

Mecanismos de Resistencia Androgénica

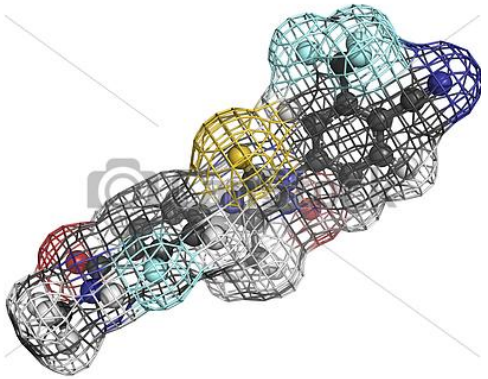
- Sobreestimulación de las enzimas que sintetizan andrógenos que aumentan su concentración a nivel intratumoral.
- Sobreexpreisón de receptores de andrógenos (RA).
- Mutaciones en el RA que pueden permitir la unión de ligandos adicionales que no estimularian el receptor natural.

Interferencia con la estimulación androgénica

Abiraterona

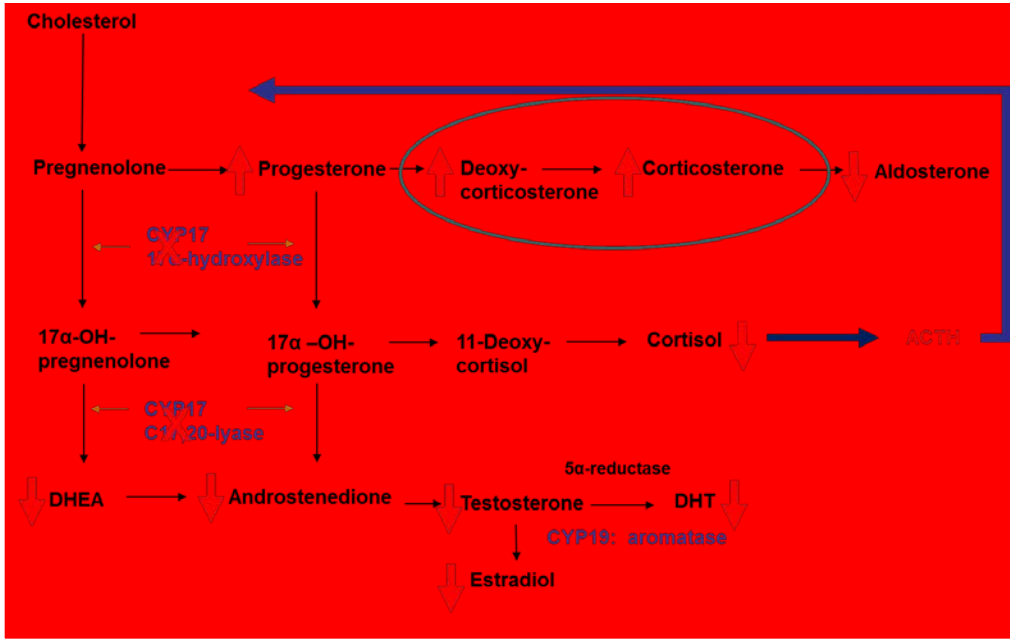


Enzalutamida



Abiraterona (Zytiga)

Pequeña molécula oral que inhibe irreversiblemente los productos del gen CYP17 citocromo p450 p17 (17,20-Lyasa y 17 alfa-hydroxilasa



Bloquea la síntesis de andrógenos en tumor, testículos y adrenales.

Los EA más frecuentes se asocian con incremento de niveles mineralocorticoides:

hipocaliemia, retención de liquidos, hipertensión que se controlan con la coadministración de bajas dosis de glucocorticoides

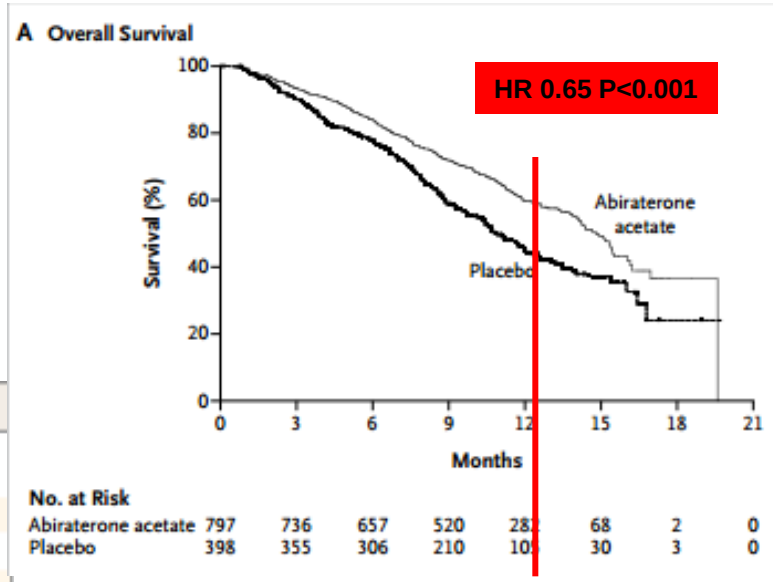
Abiraterona

Tras Docetaxel

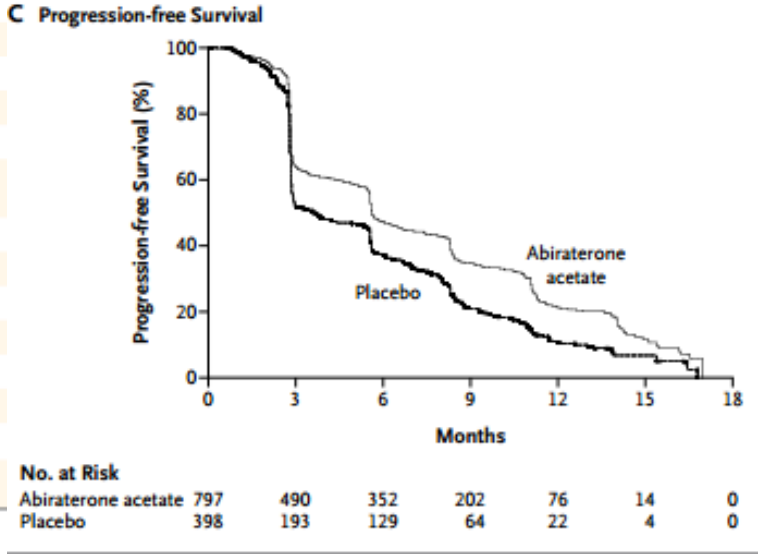
Abiraterona 1gr (250mgcx4) + Prednisona5mg/12 horas
2h despues o 1h antes de comida vs Placebo+Prednisona

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Abiraterone Acetate (N=797)	Placebo (N=398)
Age		
Median (range) — yr	69 (42–95)	69 (39–90)
≥75 yr — no. of patients/total no. (%)	220/797 (28)	111/397 (28)
Disease location — no. of patients/total no. (%)		
Bone	709/797 (89)	357/397 (90)
Node	361/797 (45)	164/397 (41)
Liver	90/797 (11)	30/397 (8)
BPI-SF score for pain†		
No. of patients	792	394
Median score (range)	3.0 (0–10)	3.0 (0–10)
No. of previous cytotoxic chemotherapy regimens — no. of patients/total no. (%)		
1	558/797 (70)	275/398 (69)
2	239/797 (30)	123/398 (31)
ECOG performance status — no. of patients/total no. (%)		
0 or 1	715/797 (90)	353/398 (89)
2	82/797 (10)	45/398 (11)
Prostate-specific antigen		
No. of patients	788	393
Median (range) — ng/ml	128.8 (0.4–9253.0)	137.7 (0.6–10114.0)



HR 0.74 a 20 meses



De Bono JS, et al. N Engl J Med. 2011;364(21):1995. Lancet Oncol. 2012;13(10):983.

Abiraterona

Table 4. Adverse Events.

Event	Abiraterone Acetate (N=791)			Placebo (N=394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
			number (percent)			
Nausea	233 (30)	12 (2)	1 (<1)	124 (32)	10 (3)	0
Vomiting	168 (21)	13 (2)	1 (<1)	97 (25)	11 (3)	0
Hematuria	65 (8)	11 (1)	0	31 (8)	9 (2)	0
Abdominal pain	95 (12)	16 (2)	0	44 (11)	6 (2)	0
Pain in arm or leg	134 (17)	18 (2)	1 (<1)	79 (20)	20 (5)	0
Dyspnea	102 (13)	8 (1)	2 (<1)	46 (12)	7 (2)	2 (<1)
Constipation	206 (26)	8 (1)	0	120 (31)	4 (1)	0
Pyrexia	71 (9)	3 (<1)	0	35 (9)	5 (1)	0
Arthralgia	215 (27)	33 (4)	0	89 (23)	16 (4)	0
Urinary tract infection	91 (12)	17 (2)	0	28 (7)	2 (<1)	0
Pain	13 (2)	5 (1)	0	19 (5)	6 (2)	1 (<1)
Bone pain	194 (25)	42 (5)	2 (<1)	110 (28)	25 (6)	4 (1)
Fluid retention and edema	241 (31)	16 (2)	2 (<1)	88 (22)	4 (1)	0
Hypokalemia	135 (17)	27 (3)	3 (<1)	33 (8)	3 (1)	0
Cardiac disorder*	106 (13)	26 (3)	7 (1)	42 (11)	7 (2)	2 (<1)
Liver-function test abnormalities	82 (10)	25 (3)	2 (<1)	32 (8)	10 (3)	2 (<1)
Hypertension	77 (10)	10 (1)	0	31 (8)	1 (<1)	0

* Cardiac disorders associated with abiraterone acetate treatment, as defined with the use of the standardized *Medical Dictionary for Regulatory Activities* (version 11.0) queries, included ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, cardiac failure, and possible arrhythmia-related tests, signs, and symptoms.

A 20 meses

Fatiga	7%	10%
Anemia	8%	8%
Dolor de espalda	7%	10%
Dolor óseo	6%	8%

12 meses

Taquicardia
FA

De Bono JS, et al. N Engl J Med. 2011;364(21):1995. Lancet Oncol. 2012;13(10):983.

ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

Charles J. Ryan, M.D., Matthew R. Smith, M.D., Ph.D.,

Randomizacion 1.1

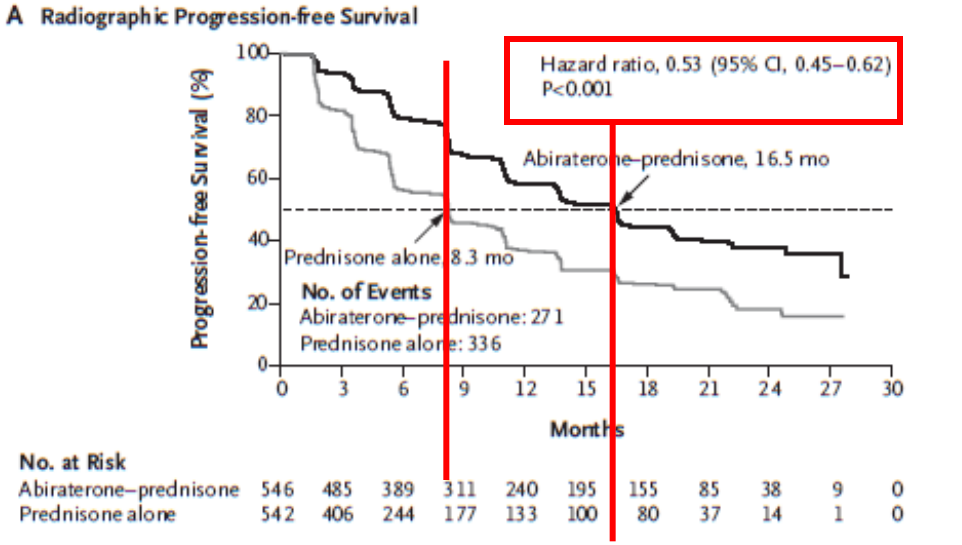
Excluye pacientes con **metástasis viscerales**, previamente tratados con quimioterapia o ketoconazol.

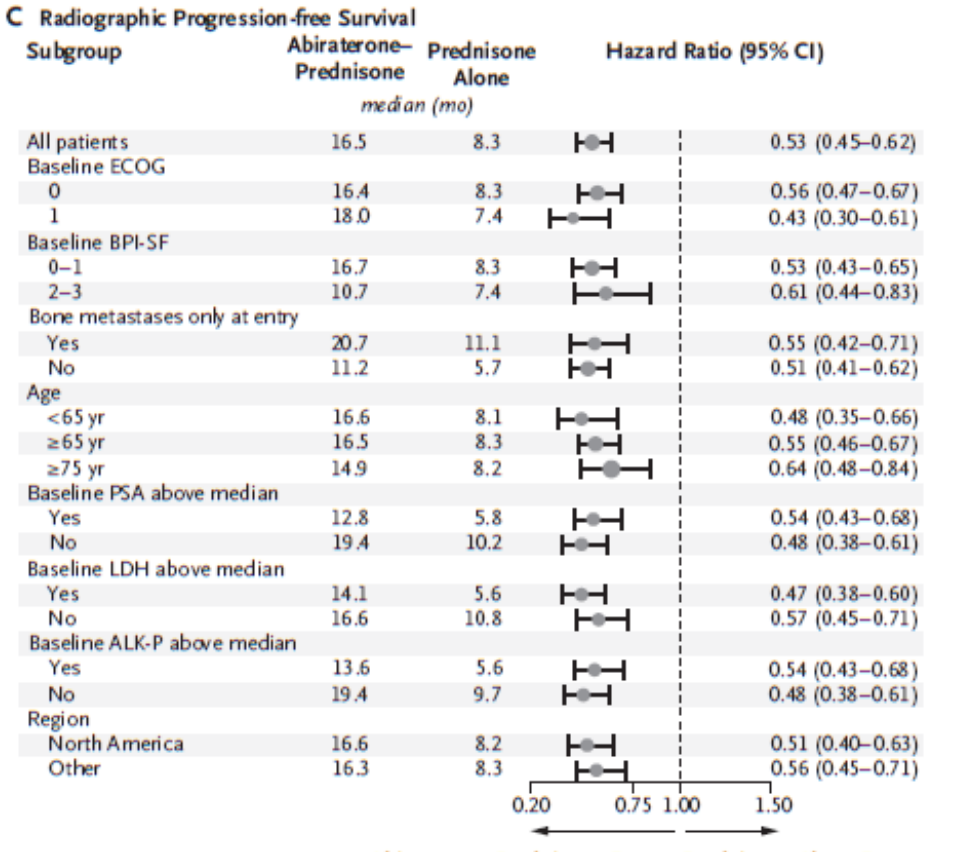
ECOG 0-1

No o poco sintomáticos

Estratifica por ECOG

Se abre el esnsayo en el segundo analisis interino con 43% de eventos por el beneficio en el brazo de abiraterona





Rayan C; et all. N Engl J Med 368;2 10, 2013 139

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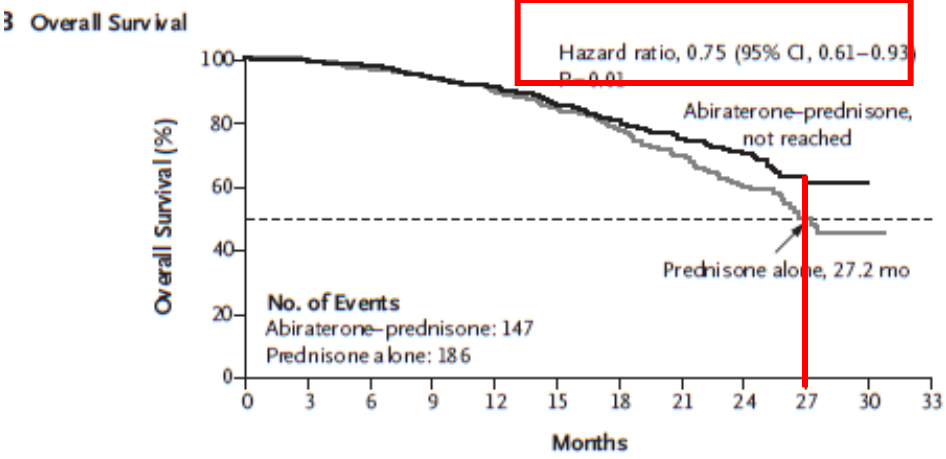

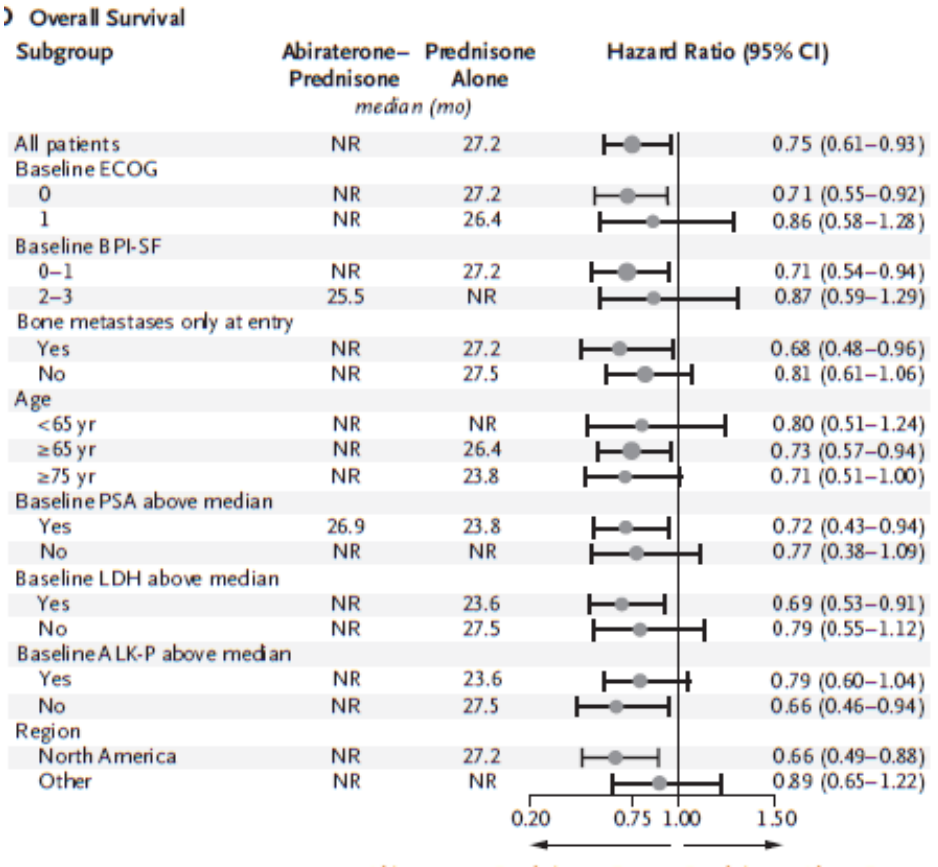

- Cross-over tras abrir el ciego.. Afectará a OS
- El 66% de pacientes en brazo experimental realizan segunda línea de tratamiento frente al 44%

Rayan C; et all. N Engl J Med 368;2 10, 2013 139

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

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Table 2. Adverse Events.*

Adverse Event	Abiraterone–Prednisone (N=542)	Prednisone Alone (N=540)
	no. of patients (%)	
Any adverse event	537 (99)	524 (97)
Grade 3 or 4 adverse event	258 (48)	225 (42)
Any serious adverse event	178 (33)	142 (26)
Adverse event leading to treatment discontinuation	55 (10)	49 (9)
Adverse event leading to death*	20 (4)	12 (2)
Adverse event of grade 1–4 in ≥15% of patients in either group		
Fatigue	212 (39)	185 (34)
Back pain	173 (32)	173 (32)
Arthralgia	154 (28)	129 (24)
Nausea	120 (22)	118 (22)
Constipation	125 (23)	103 (19)
Hot flush	121 (22)	98 (18)
Diarrhea	117 (22)	96 (18)
Bone pain	106 (20)	103 (19)
Muscle spasm	75 (14)	110 (20)
Pain in extremity	90 (17)	85 (16)
Cough	94 (17)	73 (14)

* The most common adverse events leading to death were general disorders, including disease progression, a decline in physical health, and infections including pneumonia and respiratory tract infection.

Table 3. Adverse Events of Special Interest.*

Adverse Event	Abiraterone–Prednisone (N=542)		Prednisone Alone (N=540)	
	Grade 1–4	Grade 3 or 4	Grade 1–4	Grade 3 or 4
Fluid retention or edema	150 (28)	4 (<1)	127 (24)	9 (2)
Hypokalemia	91 (17)	13 (2)	68 (13)	10 (2)
Hypertension	118 (22)	21 (4)	71 (13)	16 (3)
Cardiac disorder†	102 (19)	31 (6)	84 (16)	18 (3)
Atrial fibrillation	22 (4)	7 (1)	26 (5)	5 (<1)
ALT increased	63 (12)	29 (5)	27 (5)	4 (<1)
AST increased	58 (11)	16 (3)	26 (5)	5 (<1)

* Adverse events of special interest were selected on the basis of the safety profile of phase 2 and phase 3 studies of abiraterone. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† Cardiac disorders included ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, cardiac failure, and possible arrhythmia-related investigations, signs, and symptoms.

Enzalutamide (Xtandi)

Actúa uniéndose al RA en el lugar del andrógeno compitiendo con él inhibiendo su translocación al nucleo. No disminuye los niveles de andrógenos.

- Un 25% de los tumores podrían no expresar el receptor y podrían no ser sensibles. Tumores indiferenciados a small cells

- Atraviesa barrera hemato-encefálica.

Vogelzang N.J.N Engl J Med 2012; 367:1256-1257.
Tzelepi V, et all.Clin Cancer Res 2012;18:666-77

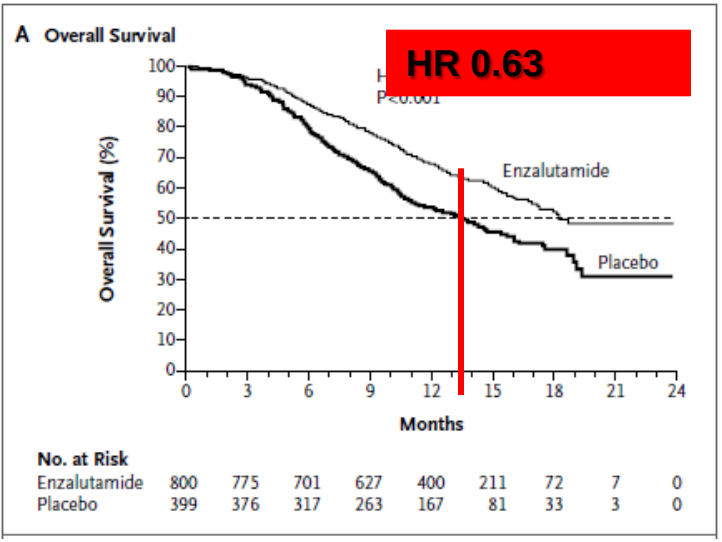
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 27, 2012 VOL. 367 NO. 13

Increased Survival with Enzalutamide in Prostate Canc after Chemotherapy

Howard I. Scher, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Mary-Ellen Taplin, M.D., Cora N. Sternb

Randomización 2:1
Enzalutamida 160 mg vo (4c de 40-mg)
End point: OS



Subgroup	No. of Patients	Enzalutamide	Placebo	Hazard Ratio (95% CI)
		median overall survival (mo)		
All patients	1199	18.4	13.6	0.63 (0.53–0.75)
Age				
<65 yr	362	—	12.4	0.63 (0.46–0.87)
≥65 yr	837	18.4	13.9	0.63 (0.51–0.78)
Baseline ECOG performance status score				
0–1	1097	—	14.2	0.62 (0.52–0.75)
2	102	10.5	7.2	0.65 (0.39–1.07)
Baseline mean pain score on BPI-SF (question no. 3)				
<4	858	—	16.2	0.59 (0.47–0.74)
≥4	341	12.4	9.1	0.71 (0.54–0.94)
Geographic region				
North America	395	17.4	12.3	0.63 (0.47–0.83)
Other	804	—	14.4	0.64 (0.51–0.80)
No. of previous hormonal treatments				
≤2	587	18.8	11.2	0.59 (0.46–0.75)
>2	605	18.3	14.7	0.68 (0.53–0.88)
No. of previous chemotherapy regimens				
1	875	—	14.2	0.59 (0.48–0.73)
≥2	324	15.9	12.3	0.74 (0.54–1.03)
Type of progression at study entry				
PSA progression only	490	—	19.5	0.62 (0.46–0.83)
Radiographic progression with or without PSA progression	704	17.3	13.0	0.64 (0.52–0.80)
No. of bone lesions				
≤20	746	—	16.2	0.59 (0.46–0.75)
>20	453	13.1	9.5	0.67 (0.52–0.87)
Visceral (liver or lung) disease at baseline				
No	921	—	14.2	0.56 (0.46–0.69)
Yes	278	13.4	9.5	0.78 (0.56–1.09)
Baseline PSA level				
≤Median	600	—	19.2	0.67 (0.50–0.89)
>Median	599	15.3	10.3	0.62 (0.50–0.78)
Baseline LDH level				
≤Median	603	—	19.2	0.63 (0.46–0.86)
>Median	594	12.4	8.5	0.61 (0.50–0.76)

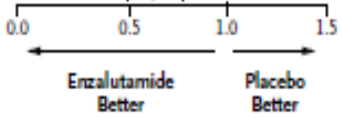


Figure 2. Subgroup Analyses of Hazard Ratios for Death in the Two Study Groups.

Scher H.I., et al.N Engl J Med 2012; 367:1187-1197

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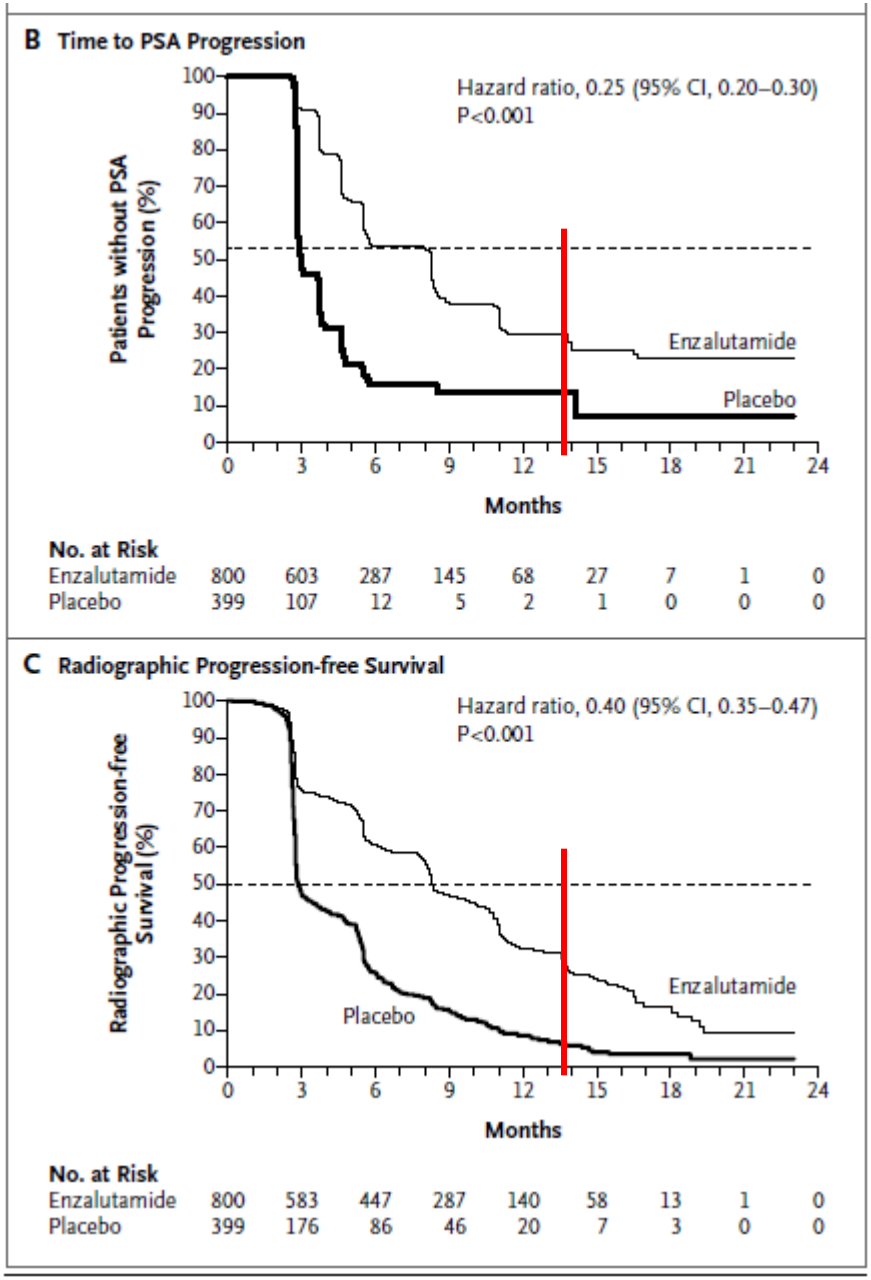
Table 2. Secondary End Points Related to Response and Disease Progression.*

End Point	Enzalutamide (N=800)	Placebo (N=399)	Hazard Ratio (95% CI)
Confirmed PSA decline†			
Patients with ≥1 postbaseline PSA assessment — no. (%)	731 (91)	330 (83)	
PSA response — no./total no. (%)			
Decline ≥50% from baseline	395/731 (54)	5/330 (2)	
Decline ≥90% from baseline	181/731 (25)	3/330 (1)	
Soft-tissue objective response			
Patients with measurable disease — no. (%)	446 (56)	208 (52)	
Complete or partial objective response — no./total no. (%)	129/446 (29)	8/208 (4)	
FACT-P quality-of-life response†			
Patients with ≥1 postbaseline assessment — no. (%)	651 (81)	257 (64)	
Quality-of-life response — no./total no. (%)‡	281/651 (43)	47/257 (18)	
Progression indicators			
Time to PSA progression — mo			0.25 (0.20–0.30
Median	8.3	3.0	
95% CI	5.8–8.3	2.9–3.7	
Radiographic progression-free survival — mo			0.40 (0.35–0.47
Median	8.3	2.9	
95% CI	8.2–9.4	2.8–3.4	
Time to first skeletal-related event — mo			0.69 (0.57–0.84
Median	16.7	13.3	
95% CI	14.6–19.1	9.9–NYR	



Scher H.I., et al.N Engl J Med 2012; 367:1187-1197

Enzalutamida: seguridad

Table 3. Adverse Events, According to Grade.

Adverse Event	Enzalutamide (N=800)		Placebo (N=399)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
≥1 Adverse event	785 (98)	362 (45)	390 (98)	212 (53)
Any serious adverse event	268 (34)	227 (28)	154 (39)	134 (34)
Discontinuation owing to adverse event	61 (8)	37 (5)	39 (10)	28 (7)
Adverse event leading to death	23 (3)	23 (3)	14 (4)	14 (4)
Frequent adverse events more common with enzalutamide*				
Fatigue	269 (34)	50 (6)	116 (29)	29 (7)
Diarrhea	171 (21)	9 (1)	70 (18)	1 (<1)
Hot flash	162 (20)	0	41 (10)	0
Musculoskeletal pain	109 (14)	8 (1)	40 (10)	1 (<1)
Headache	93 (12)	6 (<1)	22 (6)	0
Clinically significant adverse events				
Cardiac disorder				
Any	49 (6)	7 (1)	30 (8)	8 (2)
Myocardial infarction	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Abnormality on liver-function testing†	8 (1)	3 (<1)	6 (2)	3 (<1)
Seizure	5 (<1)	5 (<1)	0	0

* Included in this category are adverse events that occurred in more than 10% of patients in the enzalutamide group and that occurred in the enzalutamide group at a rate that was at least 2 percentage points higher than that in the placebo group.

† Abnormalities on liver-function testing included hyperbilirubinemia and increased levels of aspartate aminotransferase or alanine aminotransferase.

Periodo de observación de 8.3 vs 3 meses enzalutamida vs placebo

El tiempo para el primer EA es de 12.6 vs 4.2 meses.

Siguiente terapias sistémicas que pueden impactar en supervivencia alcanzan al 61% de los paciente en placebo vs 42%

Dosis dependiente.
Por inhibición de los canales de γ-aminobutyric acid–gated chloride

Scher H.I., et al.N Engl J Med 2012; 367:1187-1197

Agentes que mejoran supervivencia estudios fase III

MD Anderson Cancer Center Madrid · España

Agentes que interfieren con la estimulación androgénica: Abiraerona, Enzalutamida

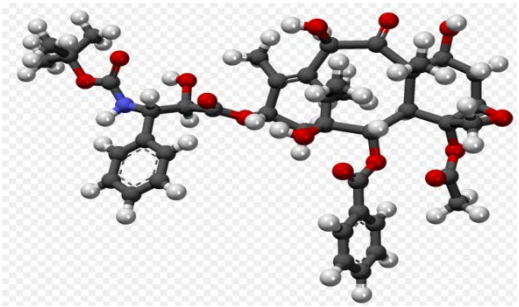
Quimioterapia: Docetaxel y Cabacitaxel

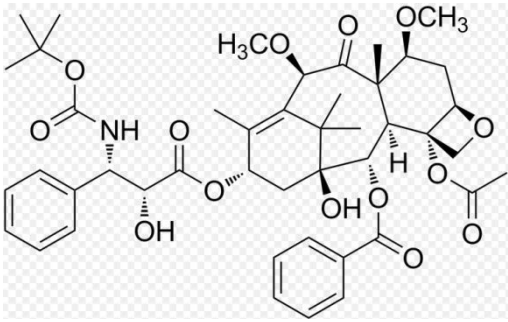
Inmunoterapia: Sipoleucel-T

Radioisótopos: Radio 223

Antiguos tratamientos no bien estudiados en ensayos fase III que pueden mantener su utilidad?

Taxanos





- Los taxanos son los únicos agentes de quimioterapia que en estudios fase III habían demostrado mejorías en supervivencia

- Docetaxel 75mg/m2 + Prednisona 5mg/12h TAX327.

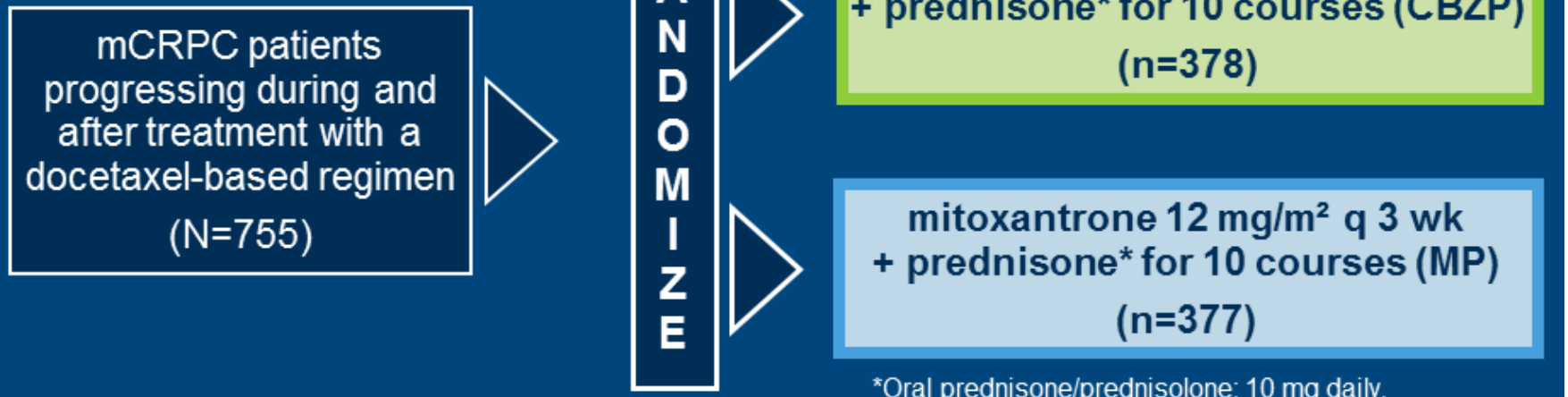
- Cabazitaxel taxano sintético desarrollado para ser activo en pacientes que han progresado a Docetaxel

Tannock IF, et al. N Engl J Med 2004;351:1502-12.
J Clin Oncol. 2008;26(2):242.

Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational Phase III trial (TROPIC)

J. S. de Bono, S. Oudard, M. Ozguroglu, S. Hansen, J. P. H. Machiels, L. Shen, P. Matthews, A. O. Sartor

Royal Marsden National Health Service Foundation Trust and Institute of Cancer Research, Sutton,



*Oral prednisone/prednisolone: 10 mg daily.

Stratification factors

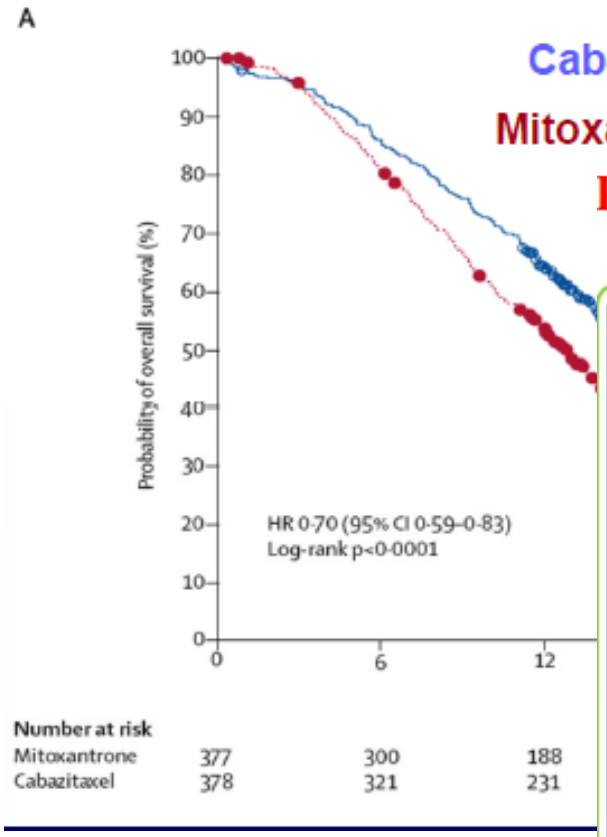
- ECOG PS (0, 1 vs 2)
- Measurable vs non-measurable disease

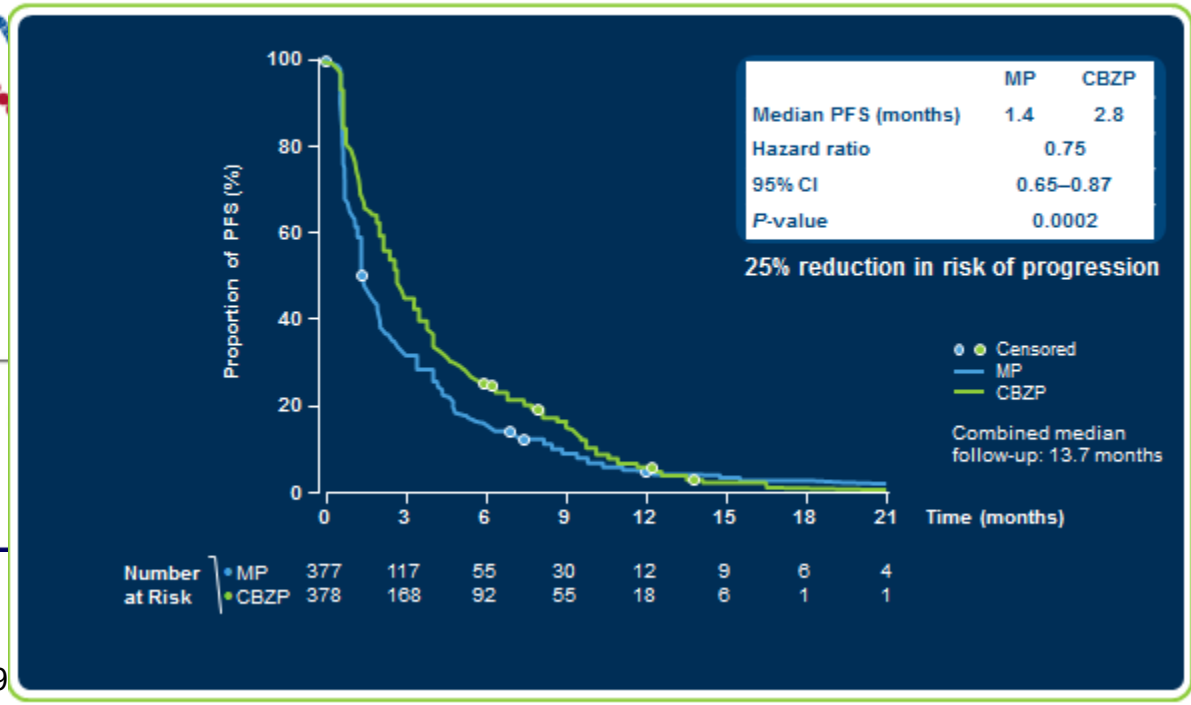
Premedication

- Premedication in the cabazitaxel group: antihistamine, steroid, and H_2 antagonist administered by IV infusion at least 30 minutes prior to each dose of cabazitaxel
- Antiemetic prophylaxis was administered when necessary

Cabazitaxel (Jevtana)

HR0.70
P<0.0001





de Bono JS, et all.TROPIC Lancet. 2010;376(9

Cabazitaxel

	Mitoxantrone (n = 371)		Cabazitaxel (n = 371)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hematologic				
Neutropenia	325 (88%)	215 (58%)	347 (94%)	303 (82%)
Febrile neutropenia	-	5 (1%)	-	28 (8%)
Leukopenia	343 (92%)	157 (42%)	355 (96%)	235 (68%)
Anemia	302 (81%)	18 (5%)	361 (97%)	39 (11%)
Thrombocytopenia	160 (43%)	6 (2%)	176 (47%)	15 (4%)
Nonhematologic				
Diarrhea	39 (11%)	1 (<1%)	173 (47%)	23 (6%)
Fatigue	102 (27%)	11 (3%)	136 (37%)	18 (5%)
Asthenia	46 (12%)	9 (2%)	76 (20%)	17 (5%)
Back pain	45 (12%)	11 (3%)	60 (16%)	14 (4%)
Nausea	85 (23%)	1 (<1%)	127 (34%)	7 (2%)
Vomiting	38 (10%)	0	84 (23%)	7 (2%)
Hematuria	14 (4%)	2 (1%)	62 (17%)	7 (2%)
Abdominal pain	13 (4%)	0	43 (12%)	7 (2%)
Pain in extremity	27 (7%)	4 (1%)	30 (8%)	6 (2%)
Dyspnea	17 (5%)	3 (1%)	44 (12%)	5 (1%)
Constipation	57 (15%)	2 (1%)	76 (20%)	4 (1%)
Pyrexia	23 (6%)	1 (<1%)	45 (12%)	4 (1%)
Arthralgia	31 (8%)	4 (1%)	39 (11%)	4 (1%)
Urinary-tract infection	11 (3%)	3 (1%)	27 (7%)	4 (1%)
Pain	18 (5%)	7 (2%)	20 (5%)	4 (1%)
Bone pain	19 (5%)	9 (2%)	19 (5%)	3 (1%)

de Bono JS, et all.TROPIC Lancet. 2010;376(9747):1147.

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Quimioterapia: Docetaxel y Cabacitaxel

Inmunoterapia: Sipoleucel-T

- Las células dendríticas: presentadoras de antígeno, son deficitarias en número y función en pacientes con cáncer.
- La presentación de antígenos es un método efectivo para mejorar la respuesta inmune mediada por células T

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 29, 2010 VOL. 363 NO. 5

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*

- Inmunoterapia celular activa tipo vacuna terapeutica.
- Células mononucleares de sangre periférica incluyendo células presentadoras de antígenos qe son activadas exvivo con una proteina de fusión recombinante (PA2024) consistente en el antigneo prostático PAP fusionada al factor estimulante de colonias de granulocíto macrófago.
- Selecciona pac con Gleason ≤ 7,asintomáticos. Tras el primer análisis ampliar a cualquier Gleason con enfermedad mínimamente sintomática. Esperanza de vida mayor a 6 meses.
- Excluyen:
  - ECOG >o igual a 2
  - Metástasis viscerales
  - Fracturas patológicas
  - Compresion medular
  - Tratamiento en los 28 días previos con glucocortivcoides, radioterapia, cirugía o terapia sistémica para CP. Excepto castracion.
  - Bifsofonatos en lso 28 días previso
  - Más de dos regimenes de quimioterapia en los 3 meses previos.

Sipoleucel T (Provenge)

Una infusión cada dos semanas x3 con tres leukaferesis a los 3 días de las infusiones.

Tras progresión se abría ciego y permitía cross-over.

OS end point. (fase II no beneficio en PFS)

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Sipuleucel-T (N=341)	Placebo (N=171)
Median age (range) — yr	72 (49–91)	70 (40–89)
Race — %†		
White	89.4	91.2
Black	6.7	4.1
Other	3.8	4.7
Median time since diagnosis (range) — yr	7.1 (0.8–24.5)	7.1 (0.9–21.5)
Median predicted survival — mo‡	20.3	21.2
ECOG performance status of 0 — %§	82.1	81.3
Gleason score ≤7 — %¶	75.4	75.4
Primary Gleason grade — %¶		
≤3	42.2	41.5
≥4	57.8	58.5
Disease location — %**		
Bone only	50.7	43.3
Soft tissue only	7.0	8.2
Bone and soft tissue	41.9	48.5
No. of bone metastases — %		
0–5	42.8	42.7
6–10	14.4	14.6
>10	42.8	42.7
Bisphosphonate use — %	48.1	48.0
Previous prostate-cancer therapy — %		
Androgen-deprivation therapy	100.0	100.0
Combined androgen blockade	81.8	82.5
Medical or surgical castration alone	18.2	17.5
Orchiectomy	9.4	7.6
Chemotherapy	19.6	15.2
Docetaxel	15.5	12.3
Radical prostatectomy	35.5	34.5
Radiation to prostate or prostate bed	54.3	53.2
Baseline pain score — %††		
0	51.5	52.6
≥0	48.5	47.4

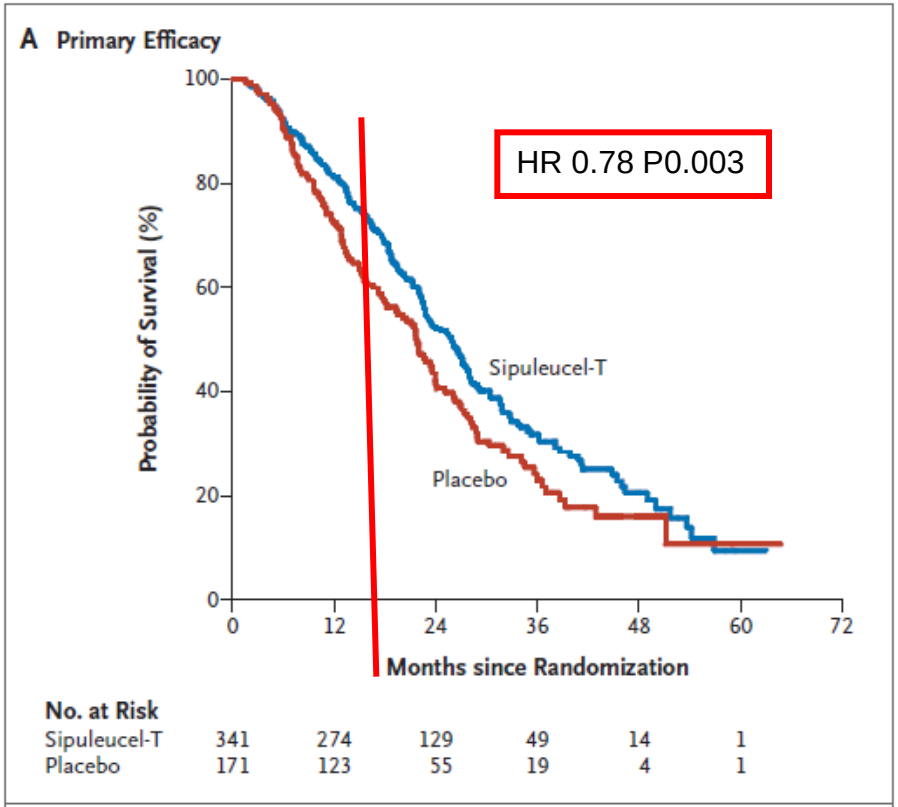

Table 2. Adverse Events.*

Event	Sipuleucel-T (N=338)		Placebo (N=168)	
	All Grades	Grade 3–5	All Grades	Grade 3–5
	number (percent)			
Any	334 (98.8)	107 (31.7)	162 (96.4)	59 (35.1)
Chills†	183 (54.1)	4 (1.2)	21 (12.5)	0
Fatigue	132 (39.1)	4 (1.2)	64 (38.1)	3 (1.8)
Back pain	116 (34.3)	12 (3.6)	61 (36.3)	8 (4.8)
Pyrexia†	99 (29.3)	1 (0.3)	23 (13.7)	3 (1.8)
Nausea	95 (28.1)	2 (0.6)	35 (20.8)	0
Arthralgia	70 (20.7)	7 (2.1)	40 (23.8)	5 (3.0)
Citrate toxicity‡	68 (20.1)	0	34 (20.2)	0
Vomiting	60 (17.8)	0	20 (11.9)	0
Headache†	54 (16.0)	1 (0.3)	8 (4.8)	0
Anemia	50 (14.8)	5 (1.5)	21 (12.5)	7 (4.2)
Limb pain	49 (14.5)	4 (1.2)	25 (14.9)	1 (0.6)
Dizziness	49 (14.5)	0	16 (9.5)	0
Paresthesia‡	45 (13.3)	0	26 (15.5)	0
Constipation	45 (13.3)	0	24 (14.3)	2 (1.2)
Musculoskeletal pain	44 (13.0)	3 (0.9)	20 (11.9)	3 (1.8)
Pain§	44 (13.0)	6 (1.8)	12 (7.1)	2 (1.2)
Paresthesia (oral)‡	41 (12.1)	0	21 (12.5)	0
Asthenia	37 (10.9)	6 (1.8)	13 (7.7)	2 (1.2)
Diarrhea	36 (10.7)	1 (0.3)	17 (10.1)	3 (1.8)
Musculoskeletal chest pain	33 (9.8)	2 (0.6)	19 (11.3)	2 (1.2)
Myalgia†	33 (9.8)	2 (0.6)	8 (4.8)	0
Influenza-like illness†	33 (9.8)	0	6 (3.6)	0
Bone pain	32 (9.5)	3 (0.9)	18 (10.7)	2 (1.2)
Hypertension†	25 (7.4)	2 (0.6)	5 (3.0)	0
Anorexia	24 (7.1)	1 (0.3)	27 (16.1)	3 (1.8)
Weight loss	20 (5.9)	2 (0.6)	18 (10.7)	1 (0.6)
Hyperhidrosis†	18 (5.3)	0	1 (0.6)	0
Groin pain†	17 (5.0)	0	4 (2.4)	0
Anxiety	13 (3.8)	0	14 (8.3)	0
Flank pain	9 (2.7)	0	10 (6.0)	0
Contusion	9 (2.7)	0	9 (5.4)	0
Depression	8 (2.4)	1 (0.3)	11 (6.5)	0

Sipoleucel T

Seguridad

-EA grado 1-2 practicamente el 70%

-Tras la infusión 1 a 3 días

-No hay un aumento de episodios cerebro-vasculares

No impacta en SLP o PSA

Kantoff PW, et all.IMPACT N Engl J Med. 2010;363(5):411.

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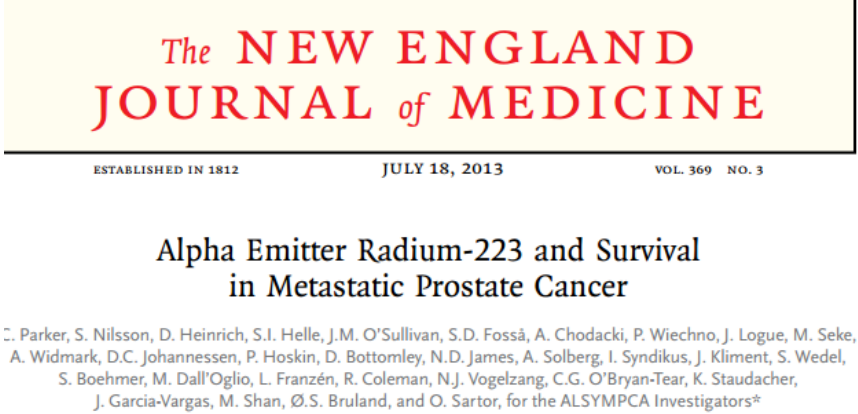
Radioisótopos: Radio 223

Antiguos tratamientos no bien estudiados en ensayos fase III que pueden mantener su utilidad?

Radium-223 (Xofigo)

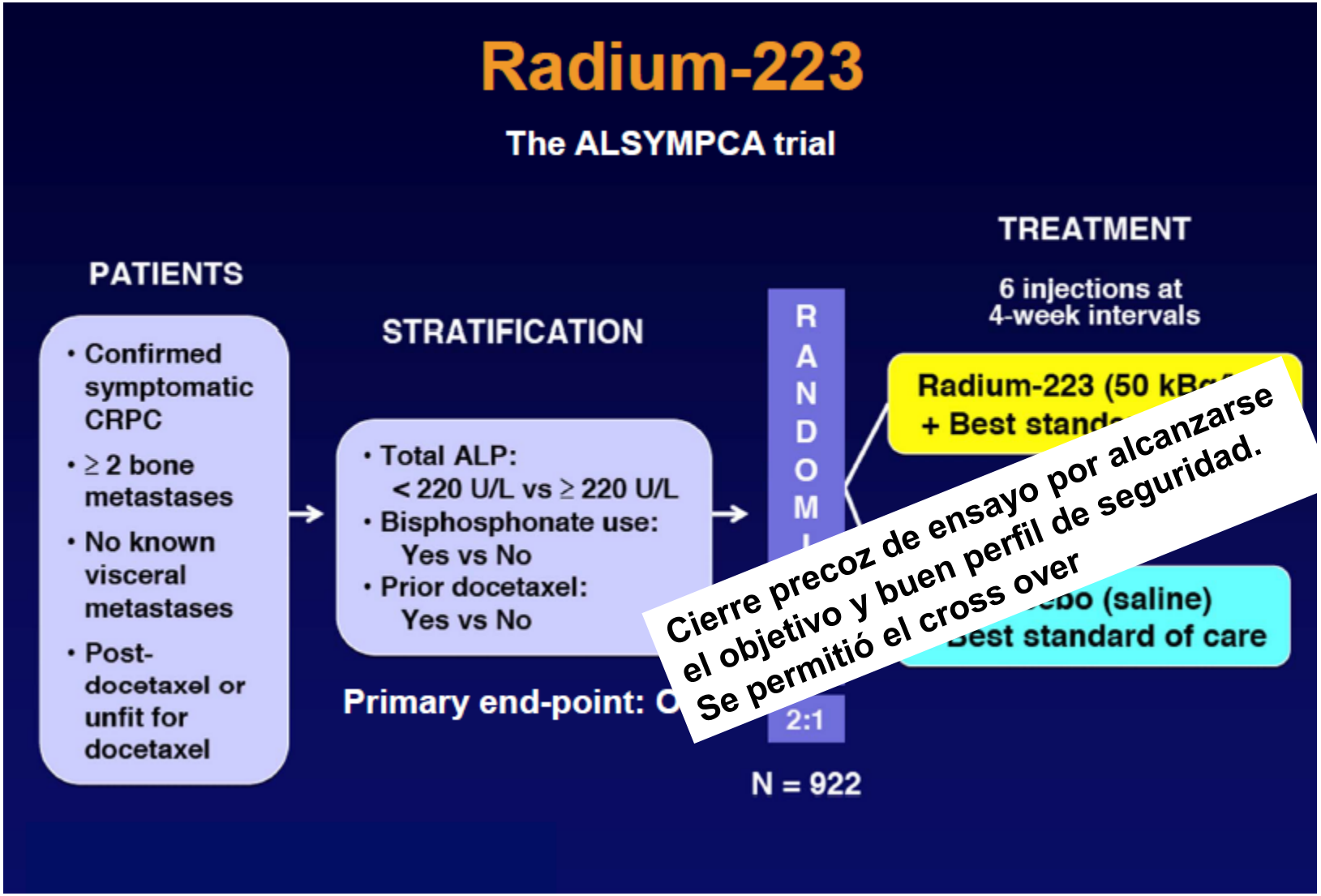


Radium-223 actua imitando al calcio , fijandose a hueso en áreas de aumento de su metabolismo. “bone-seeking”

Emite partículas alfa que inducen roturas en la doble cadena de DNA.

Su rango de actividad es extremadamente limitado (en orden de micras) permitiendo atacar células tumorales localizadas minimizando el daño en los tejidos circundantes.

Liepe K. *Curr Opin Investig Drugs* 2009;10(12):1346-1358.



Parker C, et al. *Eur J Cancer.* 2011;9(Suppl 2): Abstract LBA1.

Radium-223

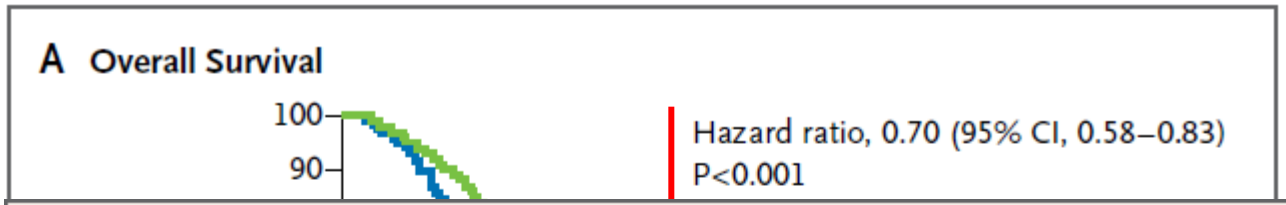


Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Radium-223 (N=614)	Placebo (N=307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Median time to increase in PSA level — mo	3.6	3.4	0.64 (0.54–0.77)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

Parker et all. N Engl J Med 2013;369:213-23.

Radium-223

Patients with Adverse Events (AEs), n (%)	Radium-223 (n = 509)	Placebo (n = 253)
All grade AEs	450 (88)	237 (94)
Grade 3 or 4 AEs	257 (51)	150 (59)
Serious AEs (SAEs)	220 (43)	139 (55)
Discontinuation due to AEs	68 (13)	51 (20)

Most common grade 3-4 AEs for Radium-223 were bone pain (18%), anemia (11%), and thrombocytopenia (4%), all less frequent than in the placebo arm

Parker C, et al. *Eur J Cancer.* 2011;9(Suppl 2): Abstract LBA1.

Conclusiones

Approach	Indications, regulatory status	Route, schedule	Steroids	Symptoms, disease burden	Contraindications	PSA response to treatment	Median overal survival benefi
Abiraterone	Approved, metastatic CRPC	Oral, daily	Required	–	Severe liver dysfunction; hypokalemia; heart failure	Yes	Post docetaxel: 4.6 mos.[1] Chemotherapy naive:*[2]
Enzalutamide	Approved/post docetaxel	Oral, daily	Not required	–	Seizures	Yes	4.8 mos.[3]
Sipuleucel-T	Approved, pre/post docetaxel	IV, every 2 weeks x 3 doses	Possibly contraindicated	Asymptomatic or minimally symptomatic	Steroids; narcotics for cancer-related pain; GM-CSF; liver metastases	No	4.1 mos.[4]
Docetaxel	Approved, metastatic CRPC	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.5 mos.[5]
Cabazitaxel	Post docetaxel	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.4 mos.[6]
Radium-223	Approved, symptomatic bone metastases with no known visceral metastases	IV, every 4 weeks	Not required	Symptomatic bone metastases	Visceral metastases	Not reported	3.6 mos.[7]

Median survival not reached for abiraterone; hazard ratio 0.75.

1. *Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 stud Oncol 2012; 13: 983.*
2. *Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138.*
3. *Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367:1187.*
4. *Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411.*
5. *Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008; 26:242.*
5. *de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376:11*
7. *Parker C, Nilsson S, Heinrich D, et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSY Clin Oncol 30, 2012 (suppl; abst LBA4512).*

PROXIMAMENTE

MD Anderson Cancer Center Madrid · España

Orteronel (TAK-700) inhibidor de CYP 17 en fase III en pacientes naive y tras docetaxel.

Custirsen (OGX-011) .

Tasquimimod

PROSVAC: Inmunoterapia

Cabozantinib inhibidor de MET y VEGF

Antiangiogénicos
- Bevacizumab
- Talidomida
- Lenalidomida

Inhibidores de src: Dasatinib

Table Agents for the Treatment of mCRPC That Are FDA-Approved or Soon Likely to Be

Agent	Study on Which Approval Was (or May Be) Based	Approximate Number of Patients Reviewed	Year of FDA Approval
Mitoxantrone	1999[3]	250	1999
Docetaxel	2003[4]	1,000	2004
Orteronel	2013[9]	1,400	unknown
Tasquinimod	2013[10]	1,200	unknown
Custirsen	2013[11]	600	unknown
Cabozantinib	2012[12]	600	unknown
PROSTVAC	2012[13]	1,200	unknown

GRACIAS