Epidemiologia, Prevención, diagnostico y tratamiento del Cáncer de Prostata

Real Academia de Medicina
Valencia 17 de Junio de 2014

Avances en el tratamiento farmacológico del cáncer de próstata

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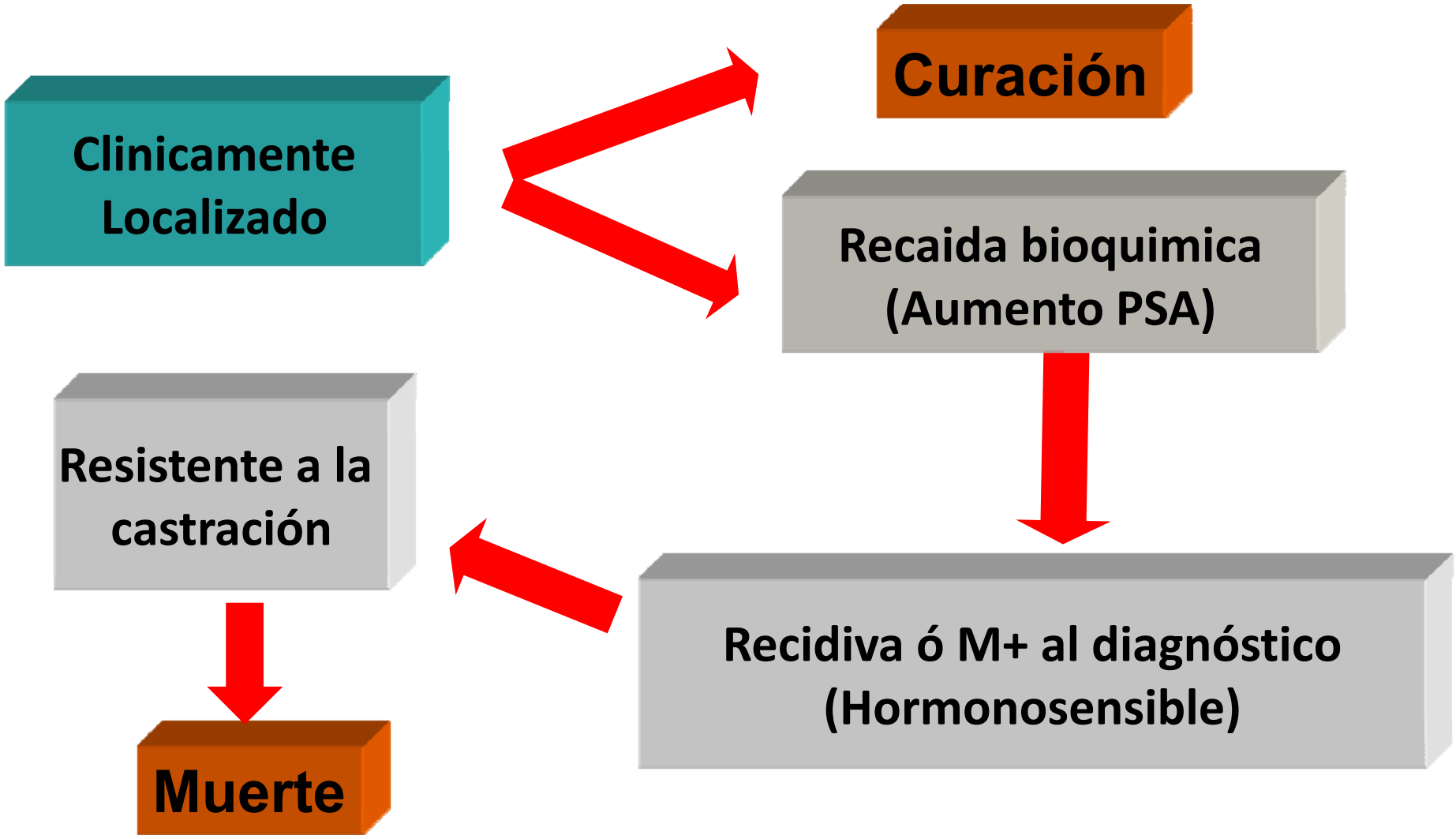
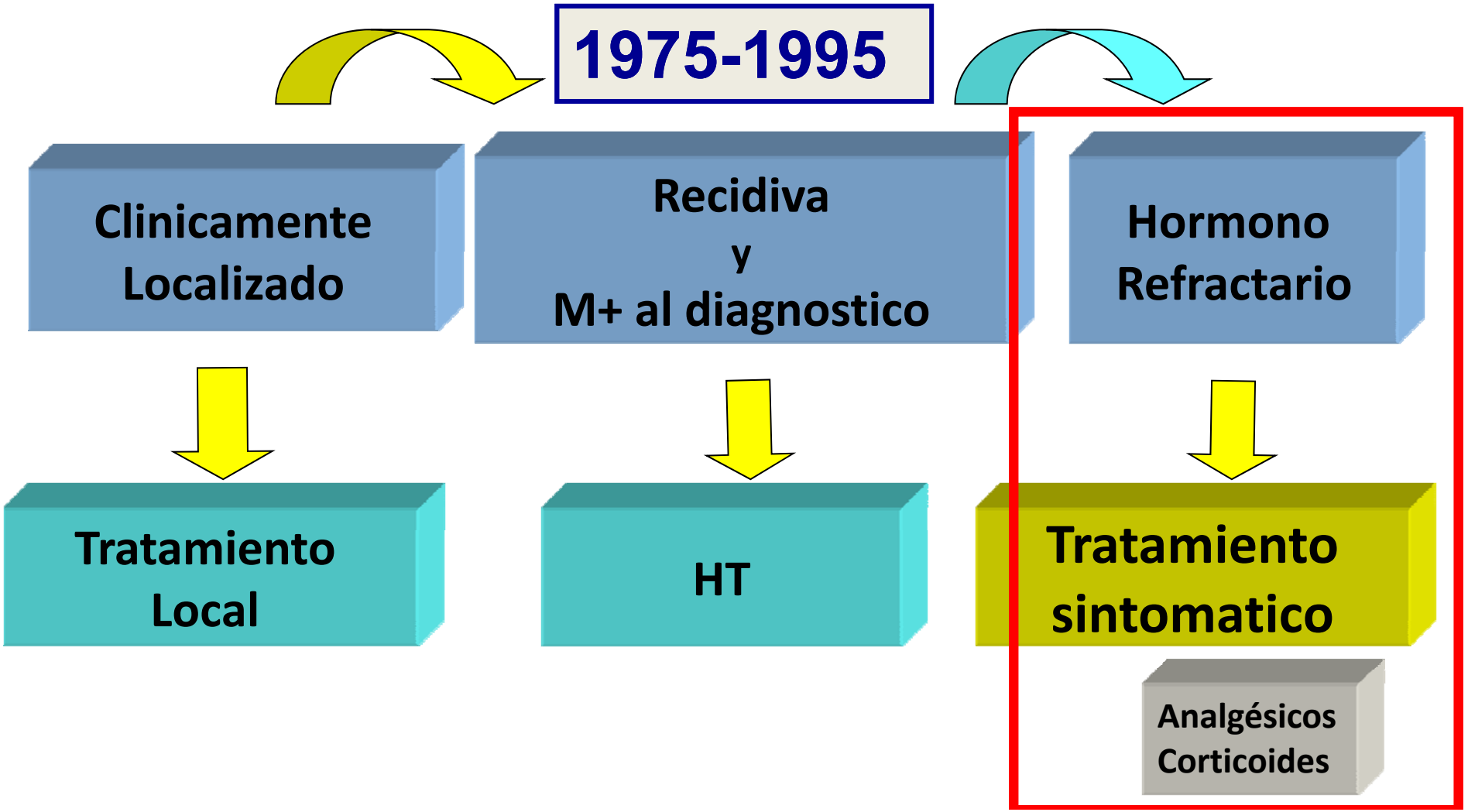
Fundación Instituto Valenciano de Oncologia

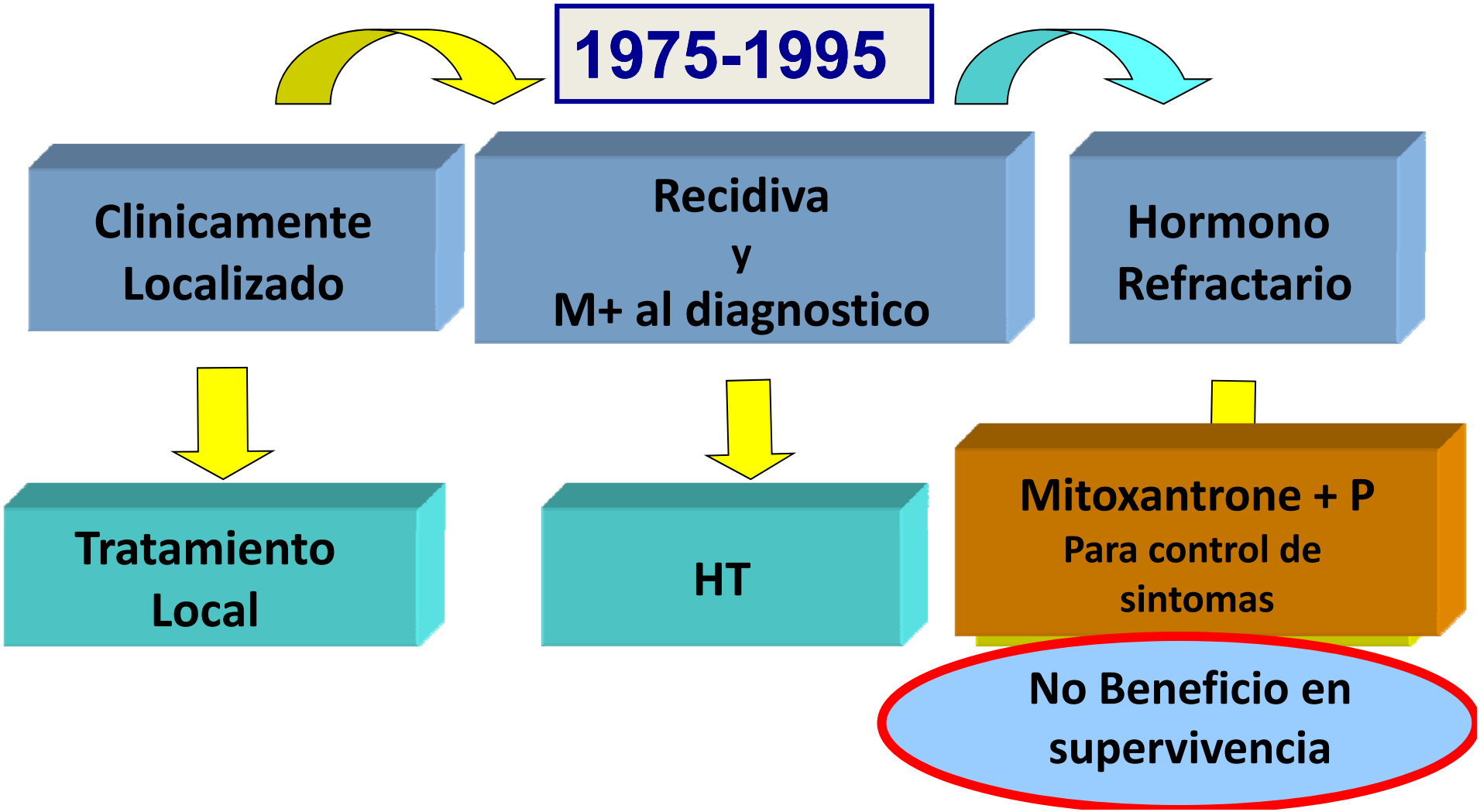
Cancer de Prostata
Historia Natural



Cancer de Prostata
Tratamiento



Cancer de Prostata
Tratamiento

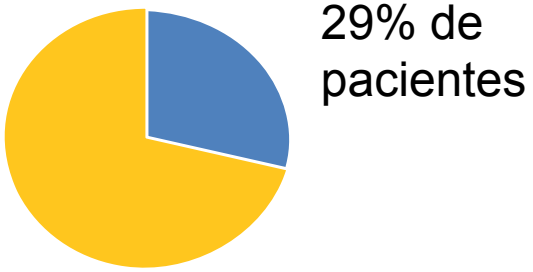


CPHR: QT con Mitoxantrone 1996

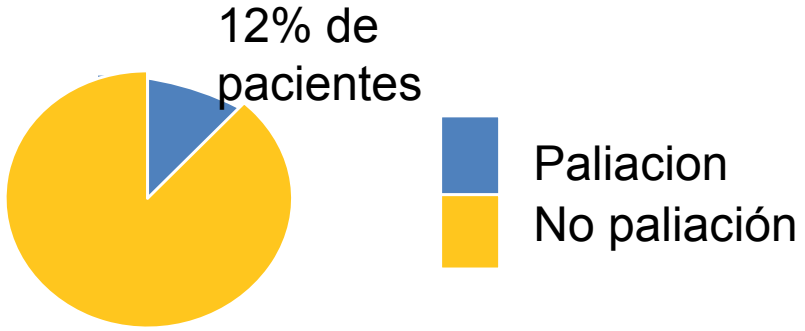
- Estudios Fase III de corticoides vs Mitoxantrone + corticoides demostraron:
  - Control de la sintomatología mejor y mas duradera (43 vs 18 semanas)
  - Mayor índice de respuestas de PSA (solo 7% de RO)
  - **No mejoría en la supervivencia**

(CANADA) Tannok IF JCO 14(6):1756,1996
(CALGB) Kantoff PW JCO 17(8):2506,1999

Mitoxantrone/prednisona



Prednisona



Tannock et al. J Clin Oncol 1996;14:1756–1764

Cancer de Próstata
Tratamiento

1996-2004

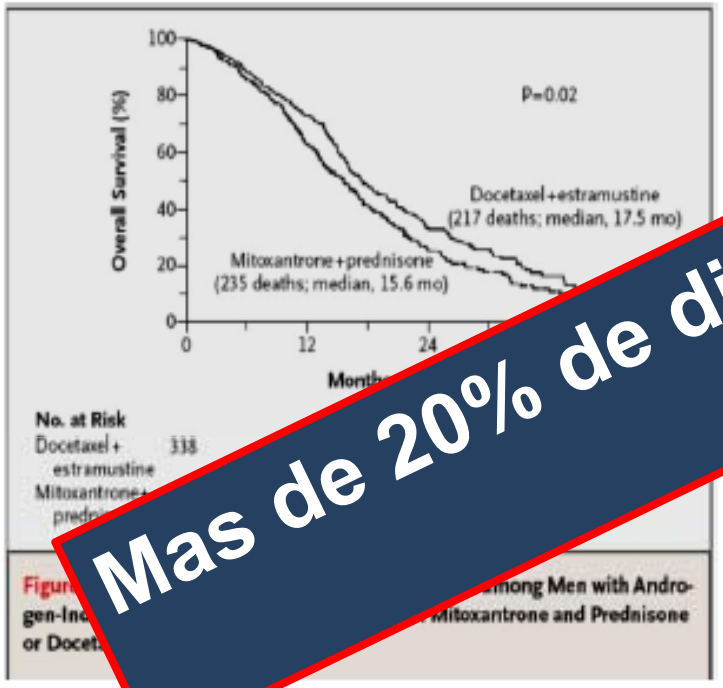
Clinicamente Localizado	Recidiva y M+ al diagnostico	Hormono Refractario
Tratamiento Local	HT	Mitoxantrone + P Para control de sintomas

No Beneficio en supervivencia

2004
Docetaxel

SWOG 99-16

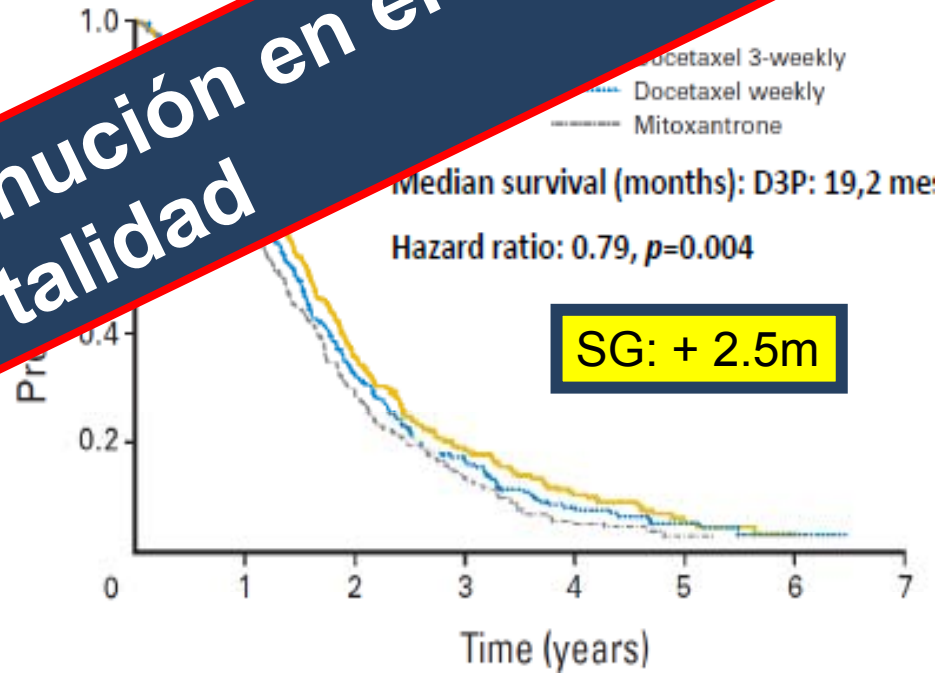
HR=0.80, p =0,002



Petrylak et al. New Eng J Med 2004; 351(15): 1513-1520

TAX-327

HR:

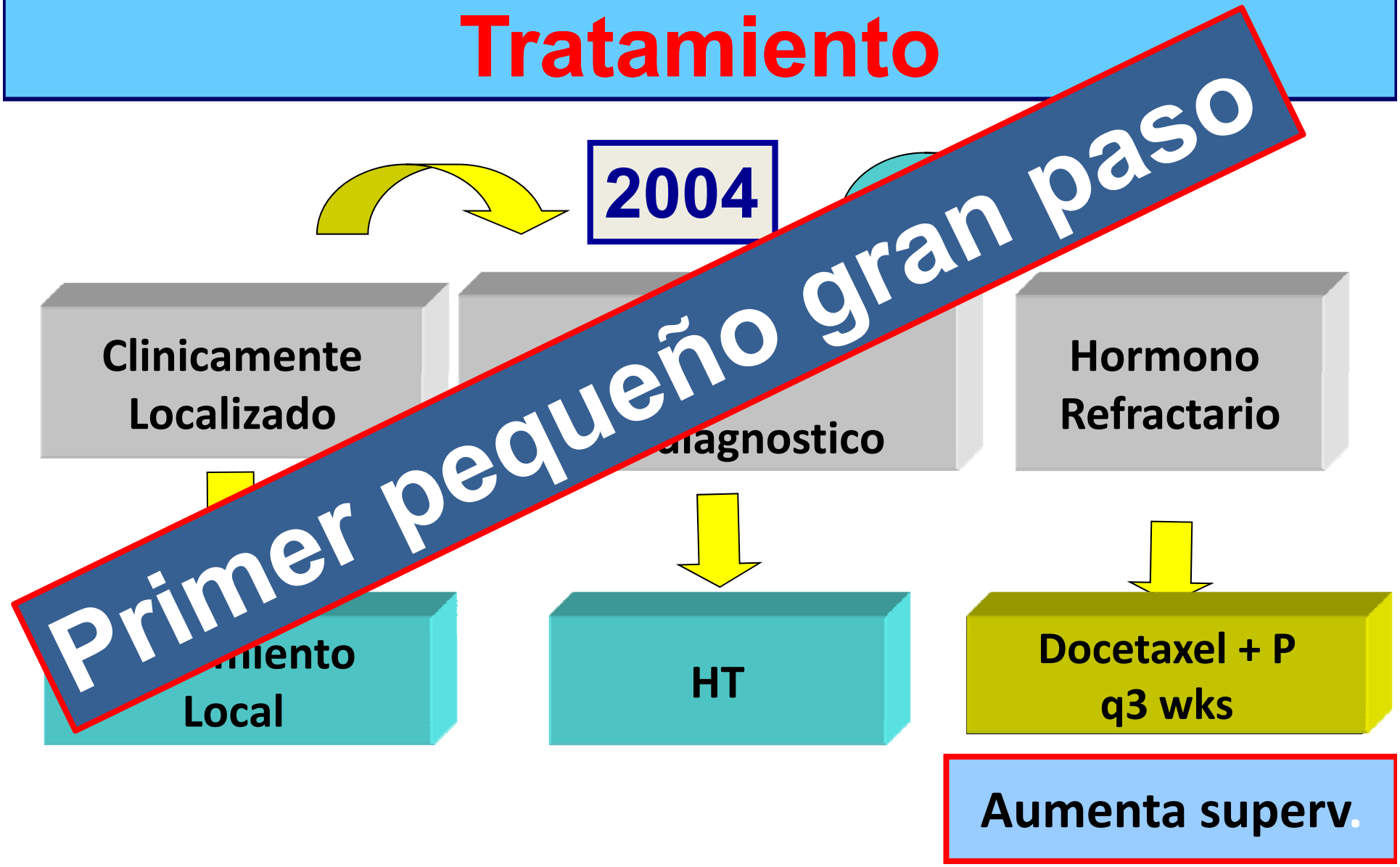


Tannok et al, NEJM; 2004
Berthold et al, Ann Oncol 2008

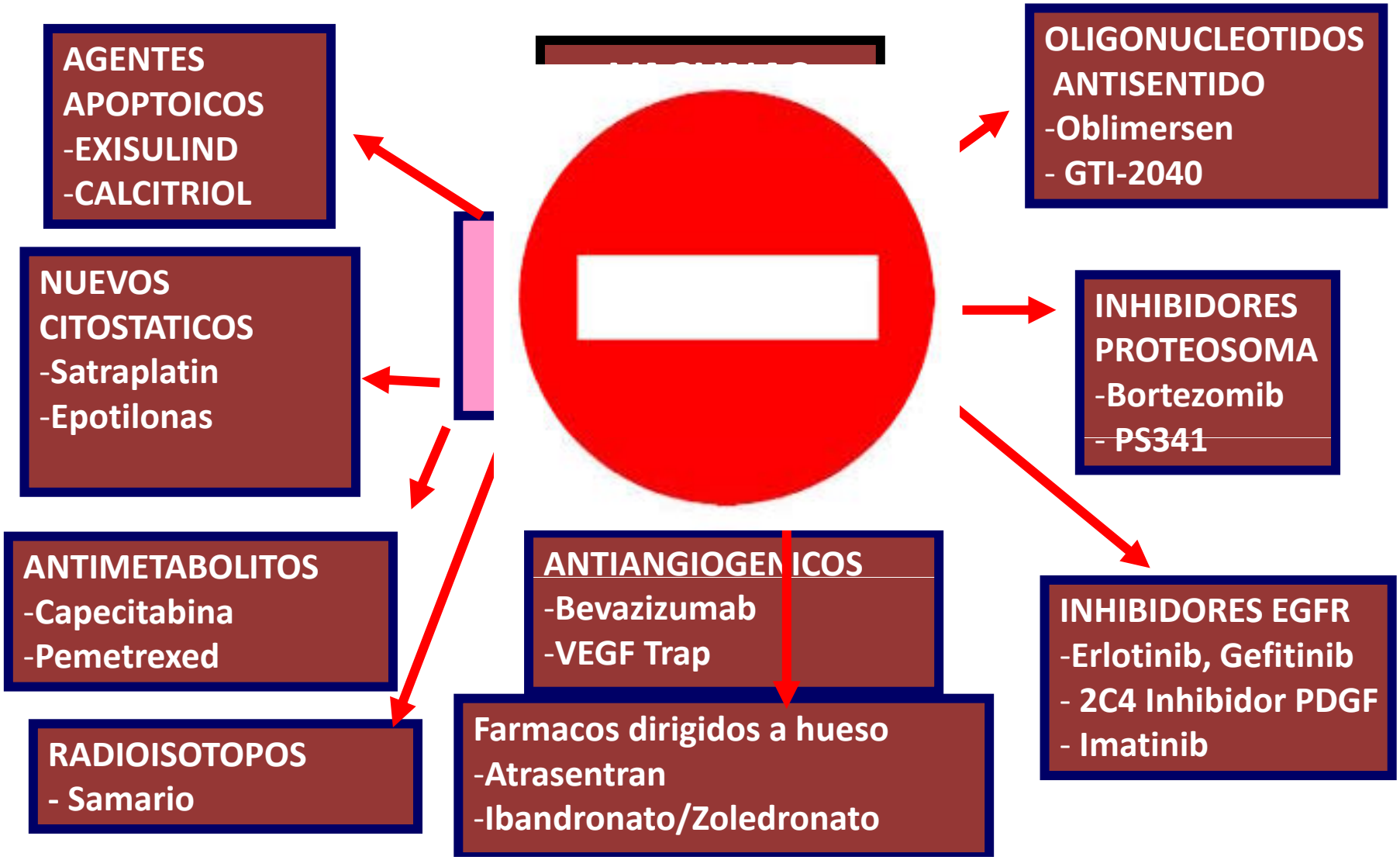
Mas de 20% de disminución en el riesgo de mortalidad

Cancer de Prostata

Tratamiento



Y despues de Docetaxel? 2006-2010



Fármacos aprobados por la FDA en los ultimos 7 años

Año de aprobacion	Riñon	Prostata	Vejiga
2006	Sunitinib		
2007	Sorafenib Temsirolimus		
2008		Degarelix	
2009	Everolimus	Sipuleucel T	
2010	Bevacizumab	Abiraterona Cabazitaxel	
2011	Pazopanib	Denosumab	
2012	Axitinib	Enzalutamida Alpharadin	

Cáncer de Próstata
Nuevos fármacos

- **Citostaticos**
  - Cabazitaxel
- **Hormonales**
  - Abiraterona
  - Enzalutamida
- **Radiofármacos**
  - Alfaradin

- **Inmunoterapia**
  - Sipuleucel T
- **Salud osea**
  - Acido Zoledronico
  - Denosumab

Tropic Study

Cabazitaxel

Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial

*Johann Sebastian de Bono, Stephane Oudard, Mustafa Ozguroglu, Steinbjørn Hansen, Jean-Pascal Machiels, Ivo Kocak, Gwenaëlle Gravis, Istvan Bodrogi, Mary J Mackenzie, Liji Shen, Martin Roessner, Sunil Gupta, A Oliver Sartor, for the TROPIC Investigators**

Summary

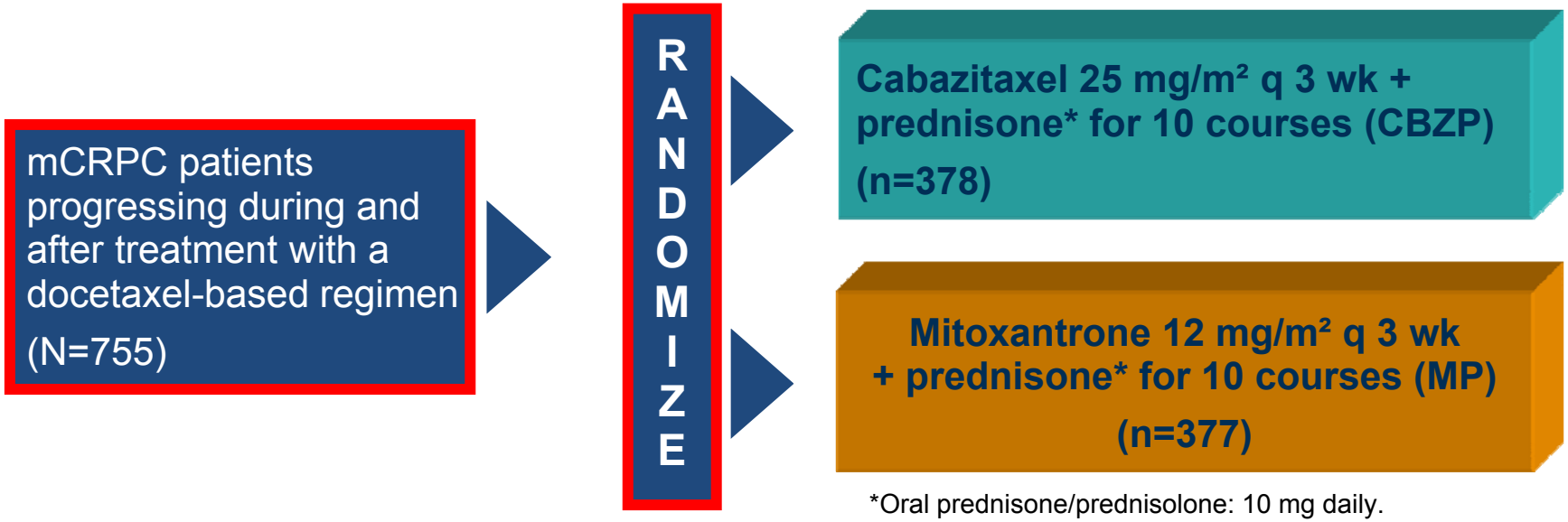
Background Cabazitaxel is a novel tubulin-binding taxane drug with antitumour activity in docetaxel-resistant cancers. We aimed to compare the efficacy and safety of cabazitaxel plus prednisone with those of mitoxantrone plus prednisone in men with metastatic castration-resistant prostate cancer with progressive disease after docetaxel-based treatment.

Lancet 2010; 376: 1147–54

This online publication has been corrected. The corrected version first appeared at thelancet.com on February 25, 2011

- New semi-synthetic taxane
  - Active in taxane-resistant cell lines and tumor models
  - Phase I studies suggested clinical activity after docetaxel

TROPIC:
Study Design—146 Centers in 26 Countries



*Oral prednisone/prednisolone: 10 mg daily.

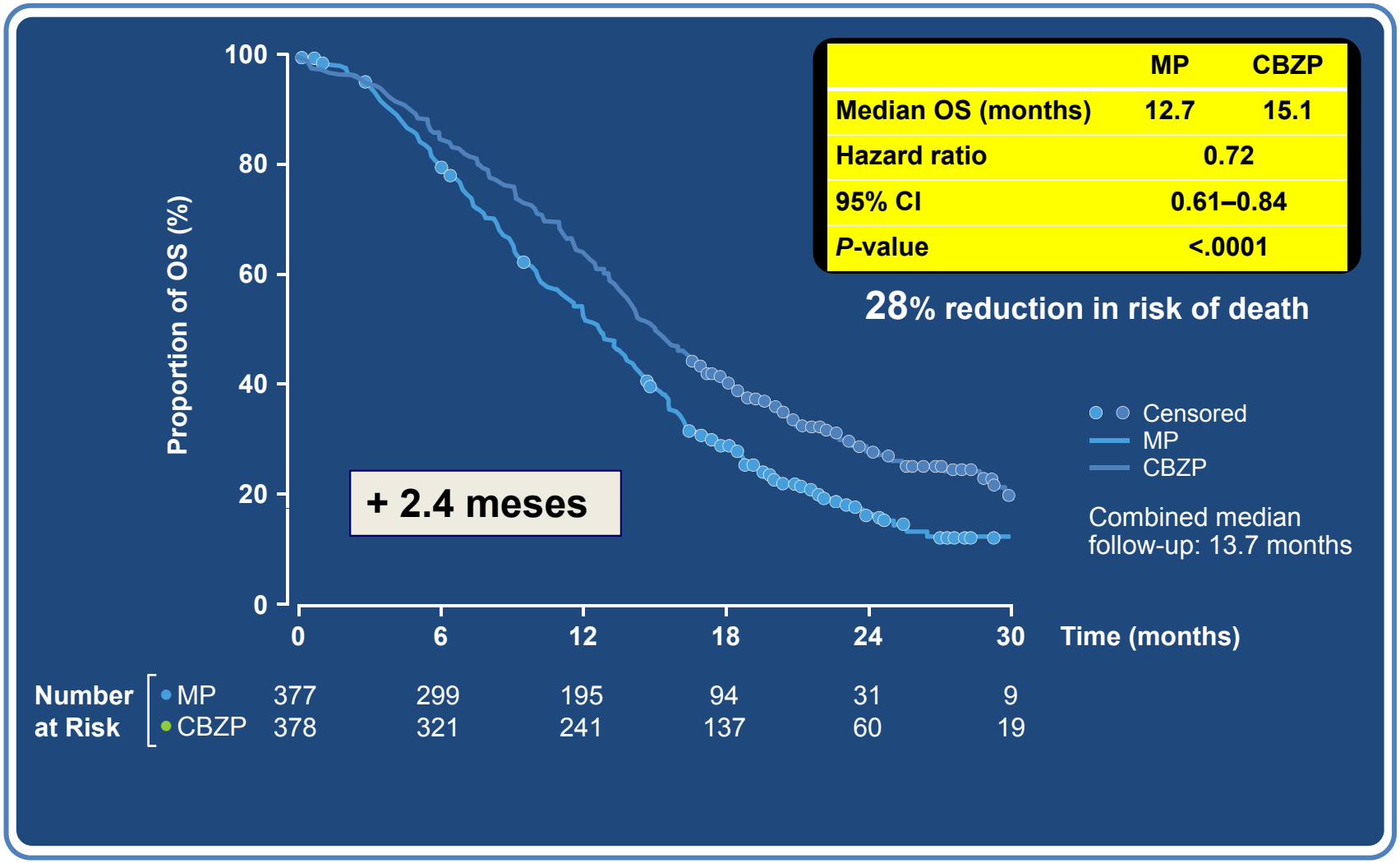
Stratification factors

- 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

TROPIC
Overall Survival



* Data cut-off 3/10/2010

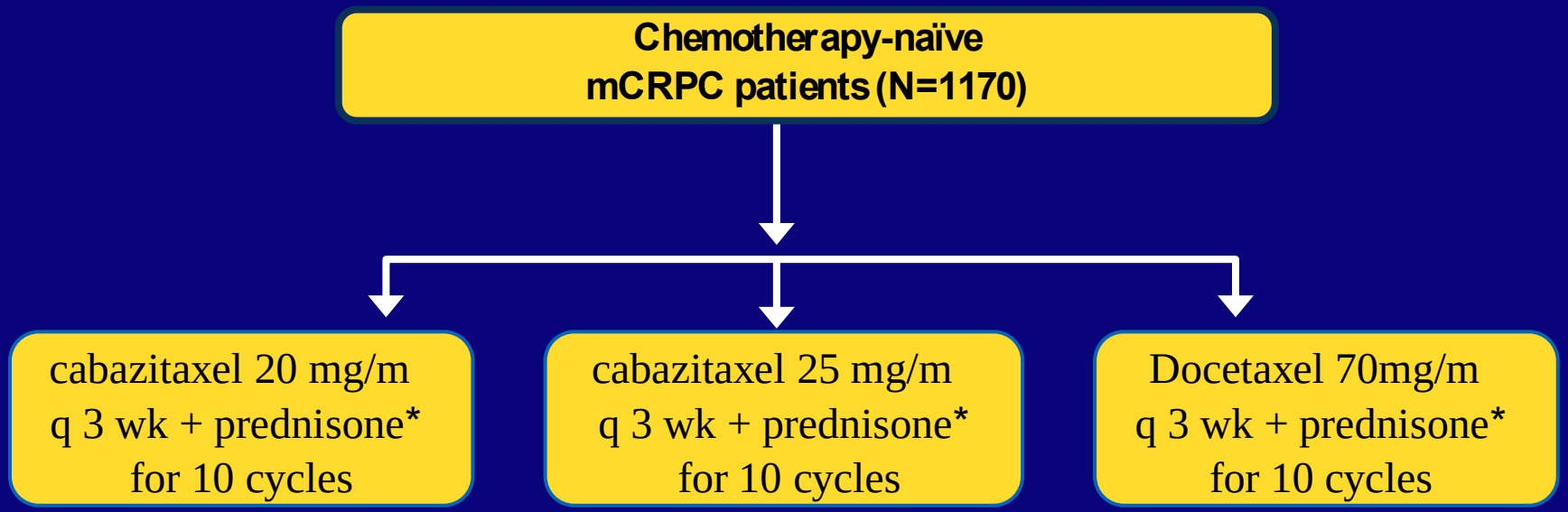
Cabazitaxel: Conclusiones

- **Cabazitaxel aumenta la supervivencia comparado con Mitoxantrone**
  - **15.1 vs 12.7 meses ($p<0.0001$)**

- **Toxicidad**
  - **Fiebre Neutropénica: 7.5% vs 1.7%**
  - **Aprobado en segunda línea tras Docetaxel**

- **En marcha, estudio comparativo con Docetaxel en primera línea**

FIRSTANA: First Line Chemo



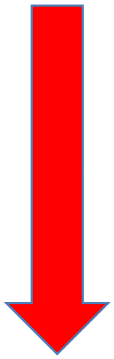
*Oral prednisone/prednisolone: 10 mg daily.

Primary endpoint: OS of cabazitaxel arms compared to docetaxel

Secondary endpoints: Progression-free survival (PFS), response rate, safety, HRQOL, PK/PD

Estándares para el CPRC -2011

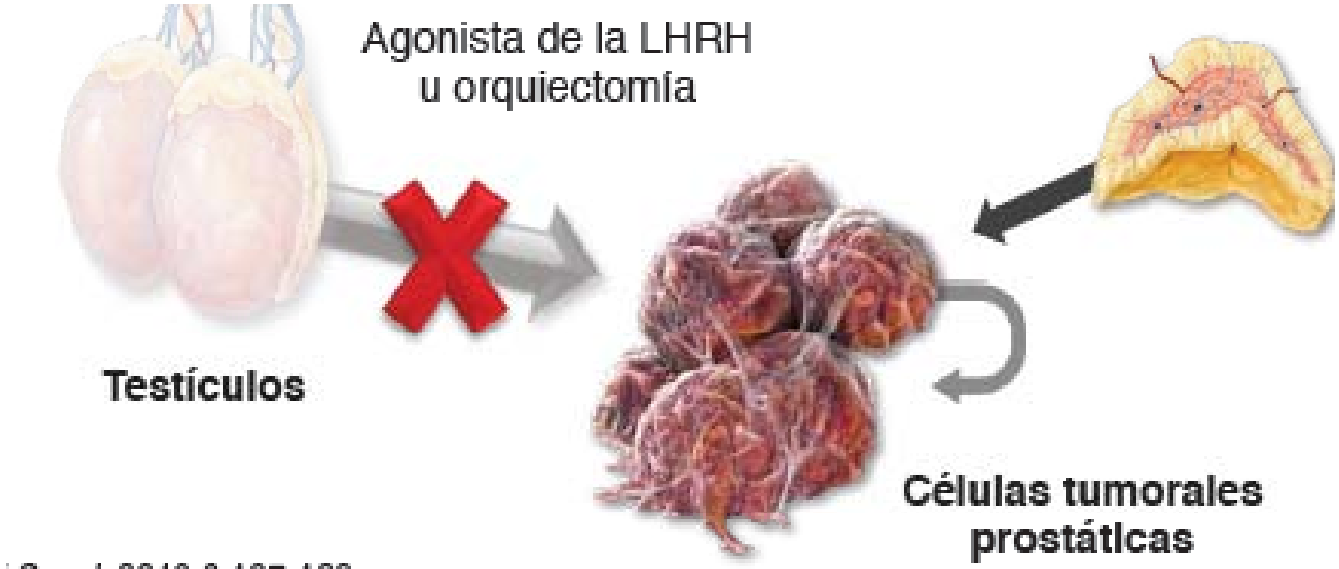
Los avances en el conocimiento biológico de la enfermedad y la aparición de nuevas novedades terapéuticas…



CAMBIO DE PARADIGMA EN EL TRATAMIENTO DEL CÁNCER DE PRÓSTATA RESISTENTE A CASTRACIÓN

Terapia de deprivación androgénica (TDA)

- Tras el BAM las glándulas adrenales pasan a ser la fuente principal de testosterona.
- Posteriormente y en fases más avanzadas de la enfermedad son las propias células tumorales las productoras de andrógenos que nutren su crecimiento.



Oncol. 2010;2:107-123.

Cambio de paradigma

- El BAM no elimina completamente los andrógenos (glándulas suprarrenales y el propio tumor)
- Por lo que cuando no responde a BAM ya no se describe el paso como de

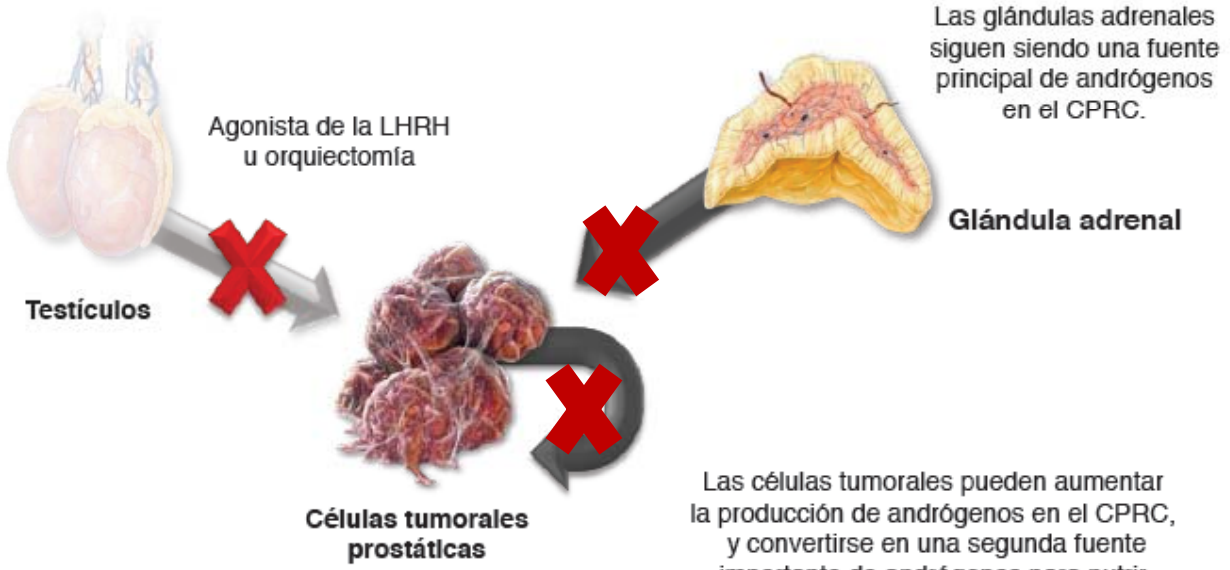
Hormonosensible a hormonorresistente

SINO

RESISTENTE A LA CASTRACIÓN (testosterona < 50ng/dl)

Necesidad médica en CPRCm

Reducir los niveles de andrógenos a indetectables



Fuentes:
Montgomery RB, y cols. *Cancer Res.* 2008;68:4447-4454.
Locke JA, y cols. *Cancer Res.* 2008;68:6407-6415.

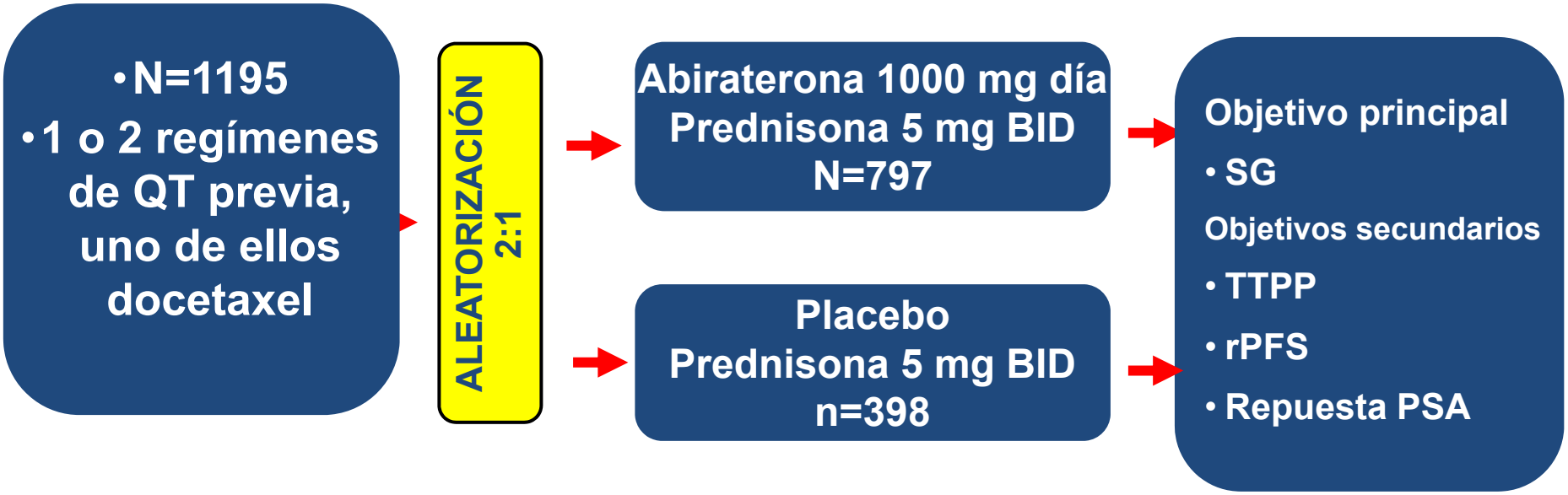
CPRCm
Opciones terapéuticas Hormonales tras Docetaxel

Hormonoterapia

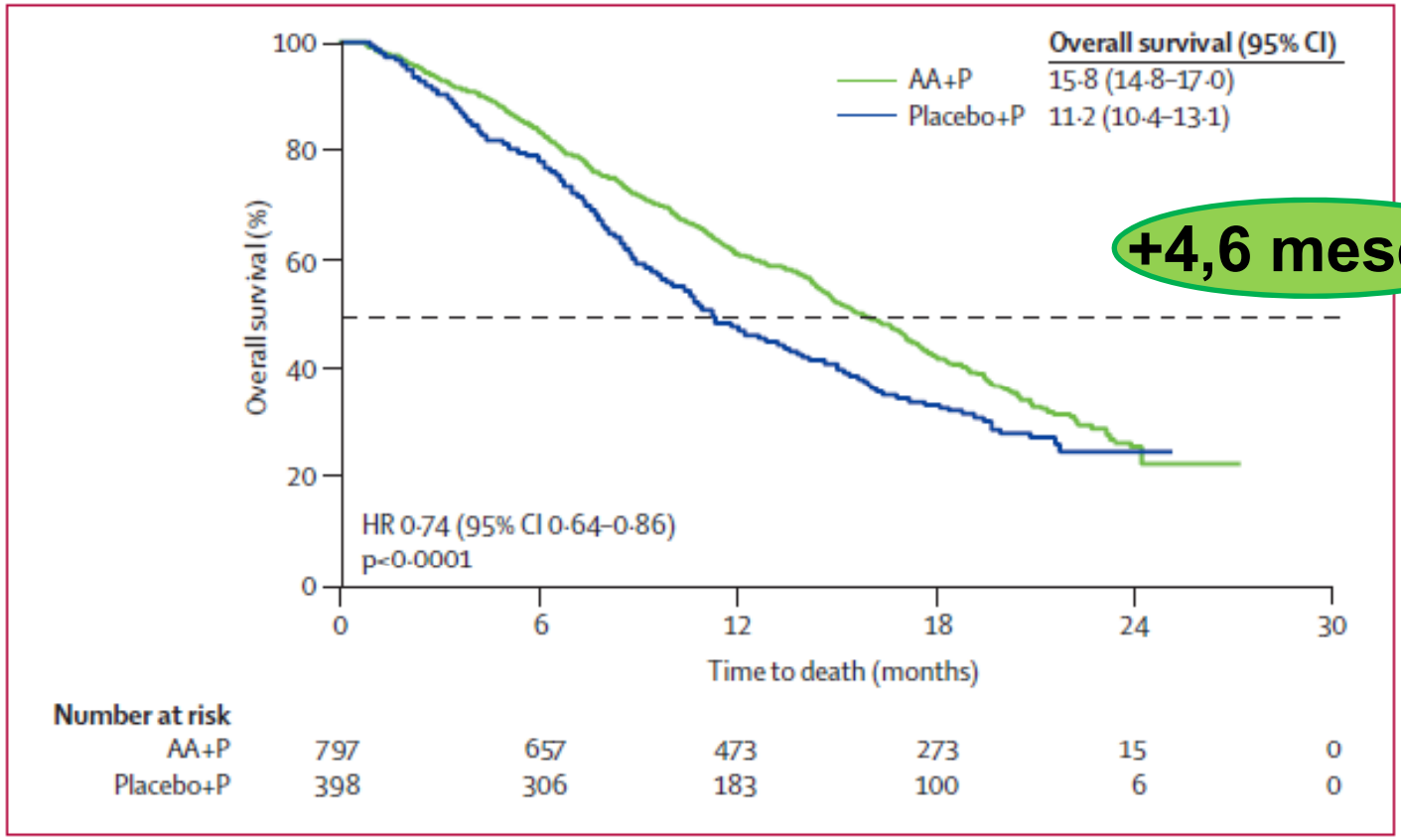
- **Abiraterona**
- **Enzalutamida**

Abiraterona

EC Fase III: COU-AA-301



COU-AA-301: Supervivencia

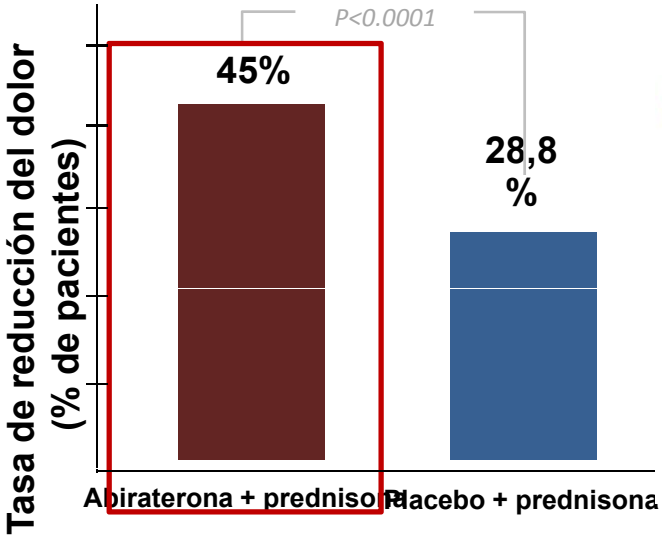


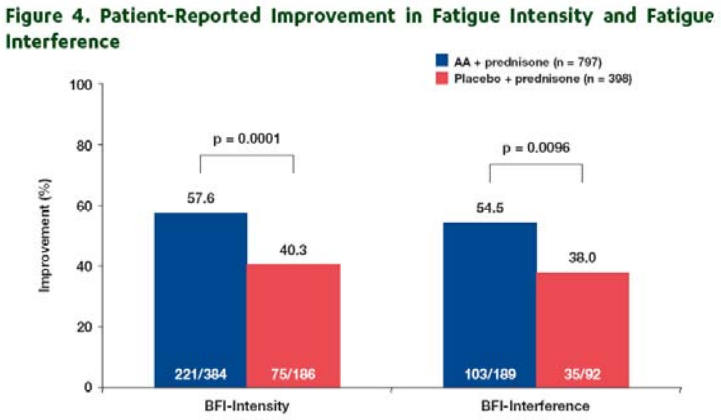
- **Mediana de seguimiento: 20.2 months**
- **Mediana de duración de tratamiento: 8 meses con AA vs. 4 meses con placebo**

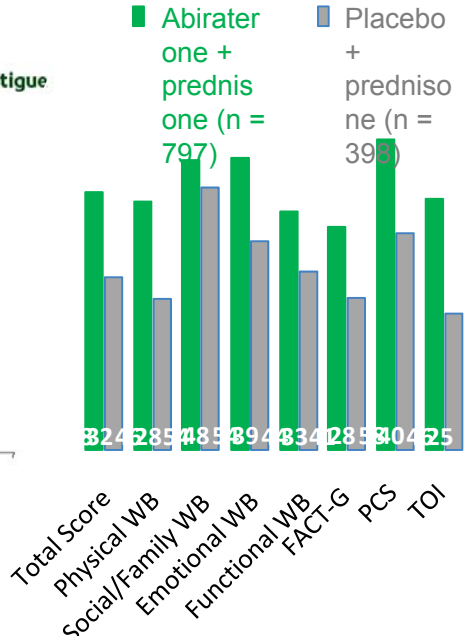
www.thelancet.com/oncology Published online September 18, 2012

COU-AA-301: Mejoría de Calidad de Vida

- El estudio **COU-AA-301** demostró:
  - Abiraterona aumenta de forma significativa la tasa de **reducción del dolor**.
  - Abiraterona **disminuye** la intensidad e interferencia de **la fatiga**.
  - Abiraterona **mejora el estado funcional** de los pacientes y aumenta el tiempo hasta el deterioro funcional.







Logothetis et al. J Clin Oncol 2011; 29 (Suppl): Abstract 4520 (oral presentation)

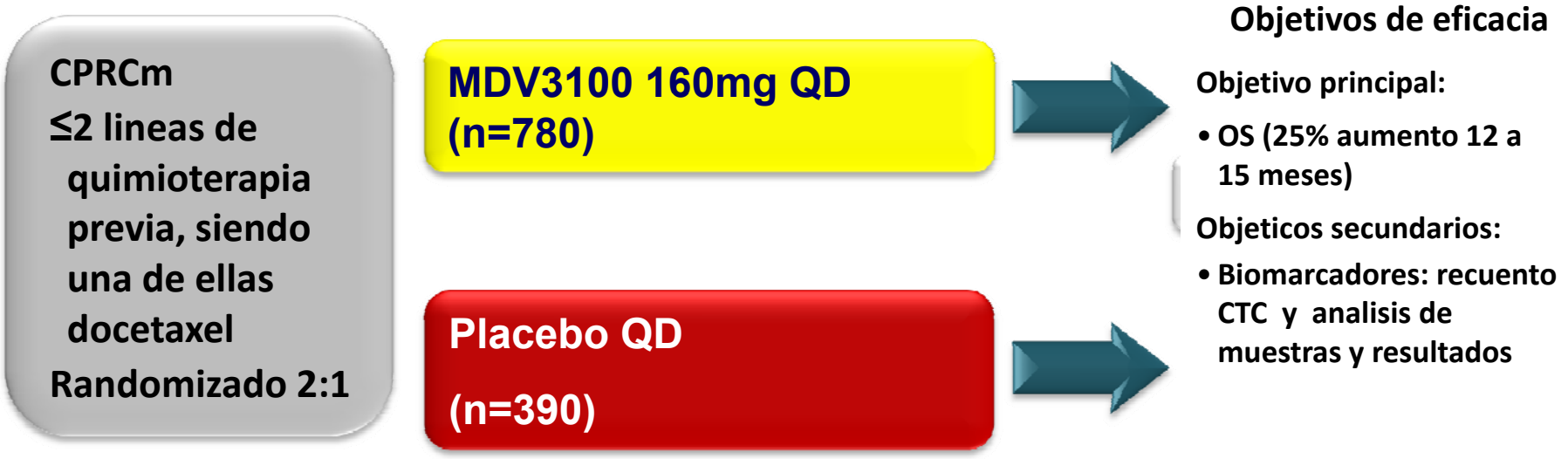
COU-AA-301: PERFIL TOLERANCIA

AE	AA (N = 791)			Placebo (N = 394)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
AEs of special interest						
Fluid retention/edema	31%	2%	< 1%	22%	1%	0%
Hypokalemia	17%	3%	< 1%	8%	1%	0%
Cardiac disorders[a]	13%	3%	1%	11%	2%	< 1%
LFT abnormalities	10%	3%	< 1%	8%	3%	< 1%
Hypertension	10%	1%	0%	8%	< 1%	0%

Enzalutamida (MDV-3100)

Enzalutamida: Estudio Fase III (AFFIRM)

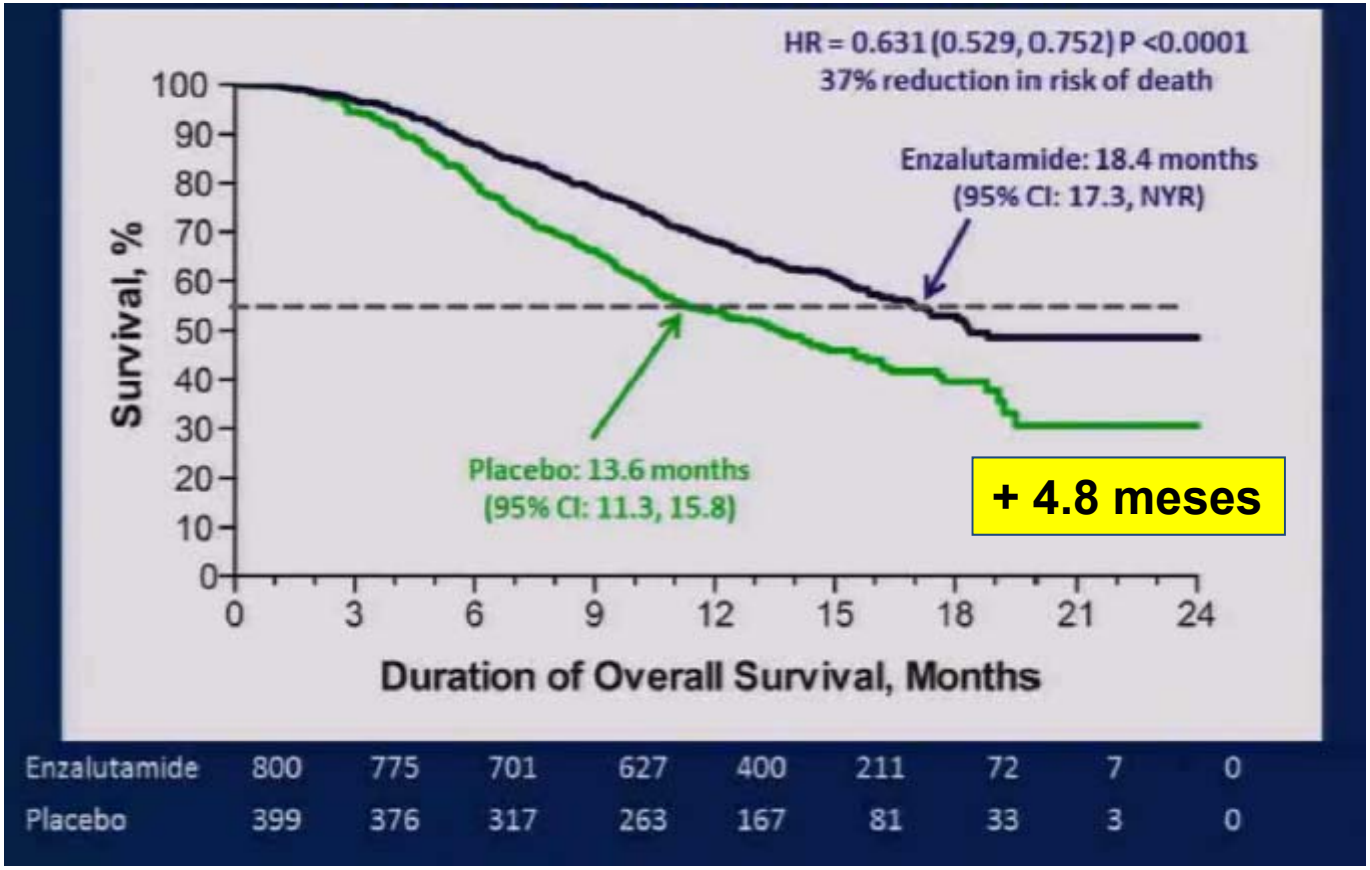
Fase 3, multinacional, multicentrico, randomizado, doble-ciego
(166 centros en 15 países; USA, Europa, Australia, Canada, Latino América)



Casi el 48% de los pacientes tomaron corticoides durante el ensayo

www.ClinicalTrials.gov identifier: NCT00974311

AFFIRM: Supervivencia Global



Radiofármacos

Alpharadin

- Radiofarmaco emisor de partículas alfa especificas de células óseas
- Combina una afinidad natural por las metástasis óseas y una potente actividad para eliminar células tumorales mediante la emisión de particulas alfa, con una afectación mínima de las células sanas

Fase III Alfaradin: ALSYMPCA

(149 centros en 19 países; USA, Europa, Australia, America Latina, Canada y Asia)

922 pacientes con CPRC y metastasis oseas (≥ 2 lesiones)

No metastasis viscerales conocidas

Post-docetaxel o no apto para docetaxel

Randomizado 2:1

Alpharadin 50 kBq/kg bw 6 IV doses

Best supportive care

Placebo 6 IV doses

Best supportive care

Objetivo principal:

- OS

Objetivos 2os:

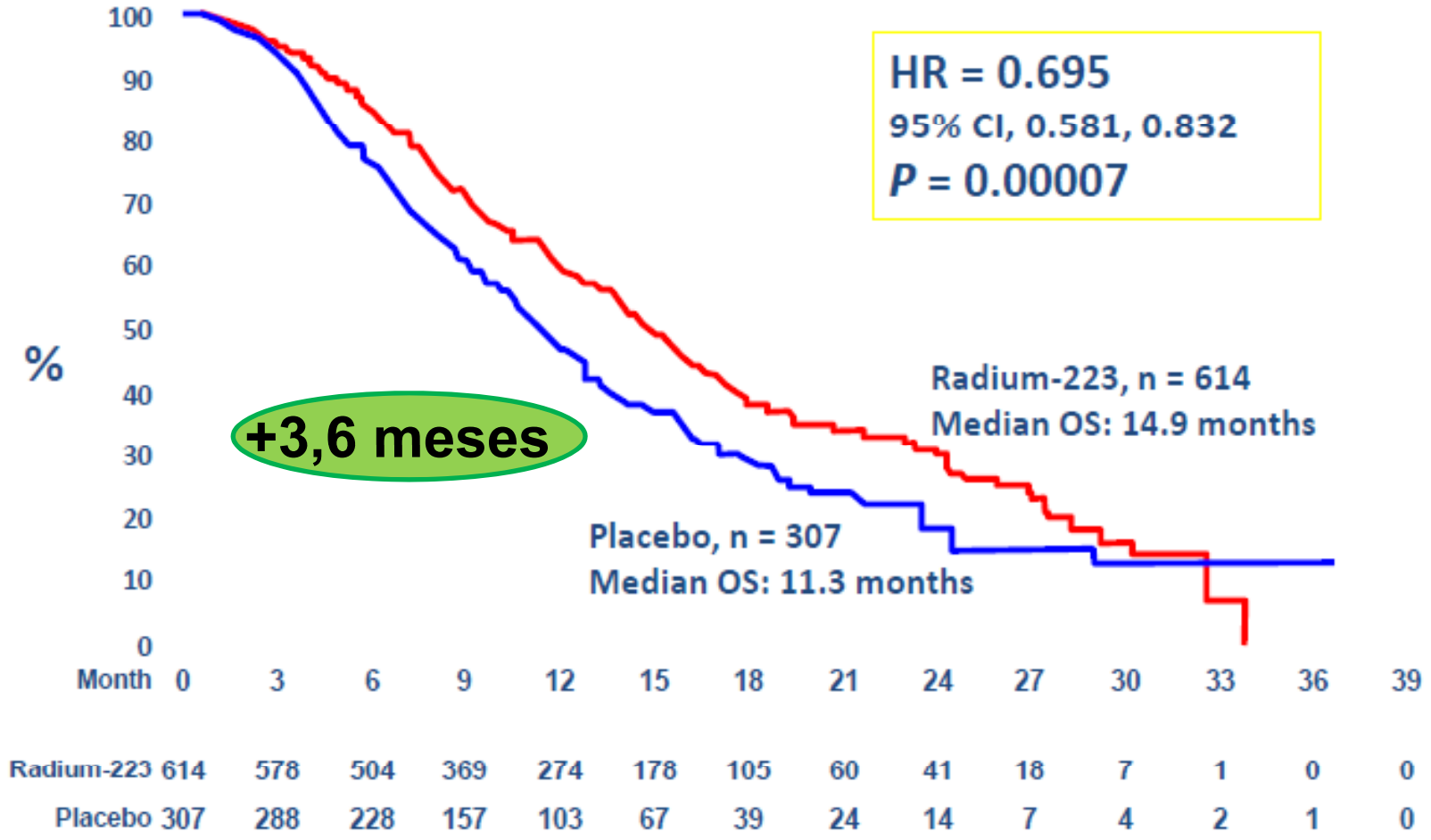
- TTPP
- TTP
- Safety
- HRQoL

Stratification by:

Total ALP:	**< 220 U/L vs.≥ 220 U/L**
Bisphosphonate use:	**Yes vs. No**
Prior docetaxel:	**Yes vs. No**

http://media01.smartcom.no/Microsite/start.aspx?eventid=6325. Accessed November 2011

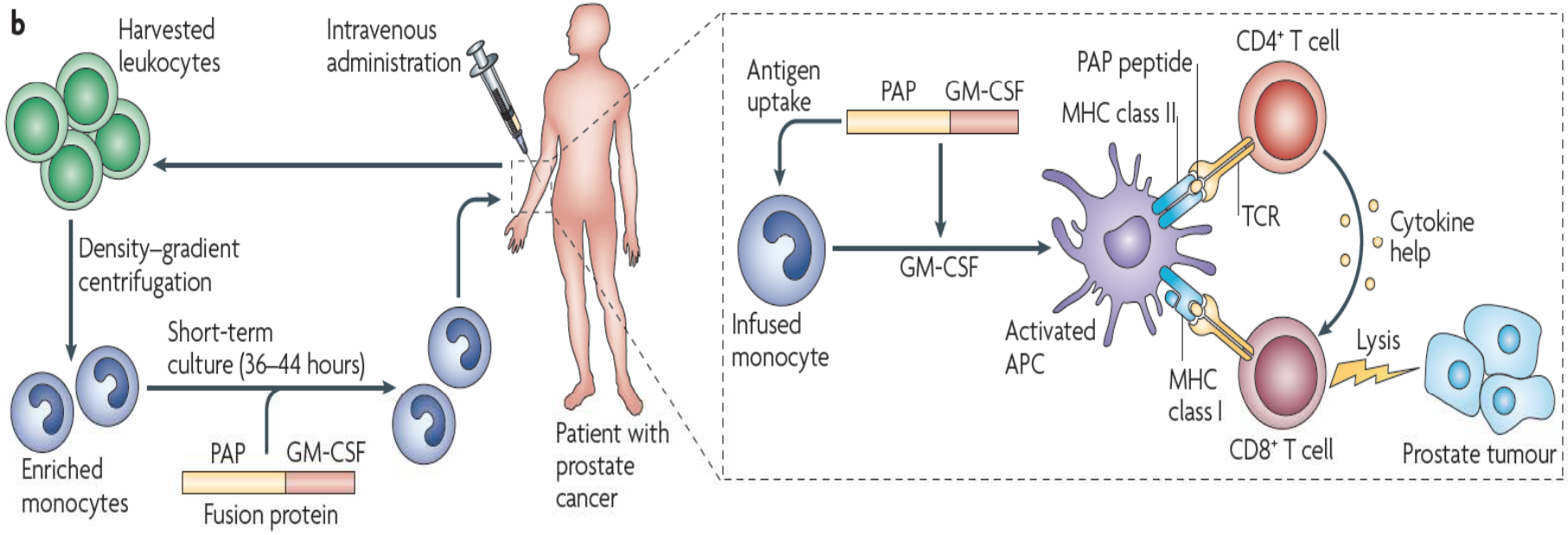
ALSYMPCA: Supervivencia Global



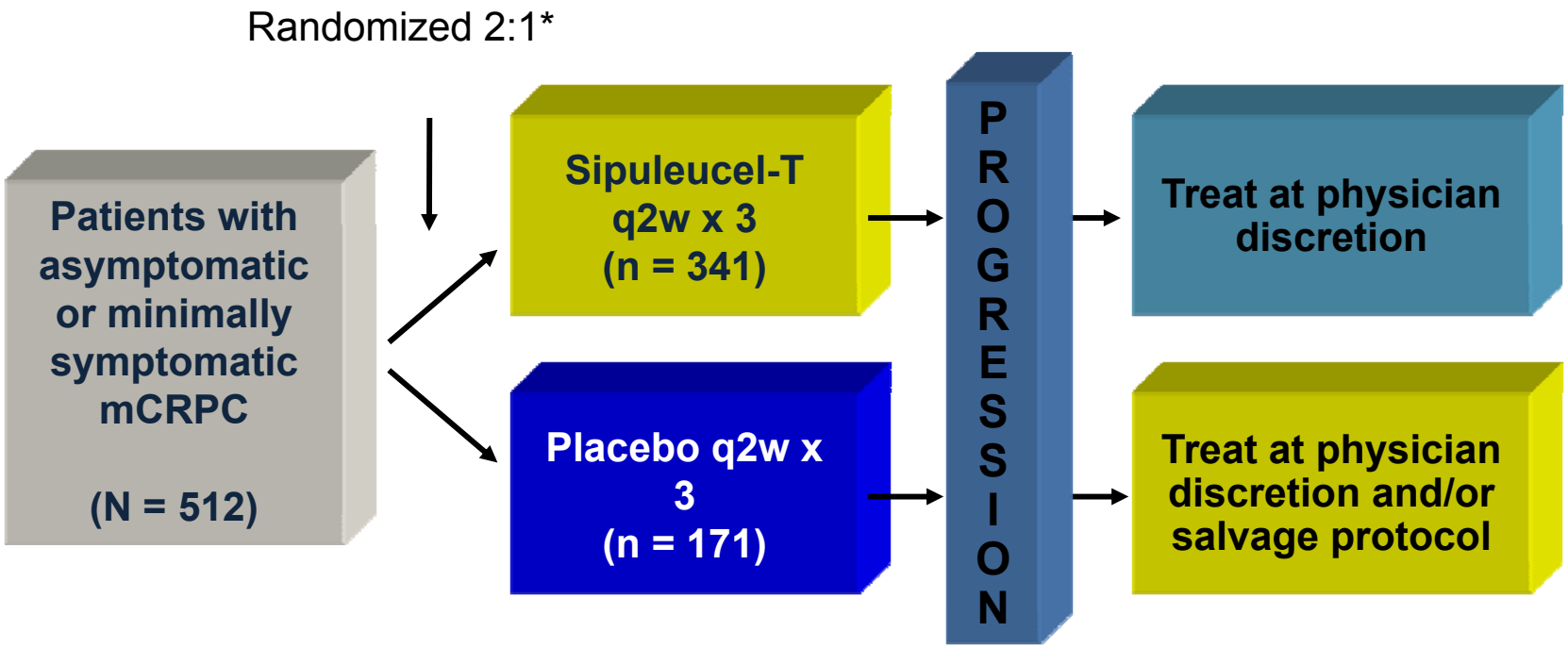
Inmunoterapia Vacunas

Sipuleucel-T

- **Inmunoterapia celular autologa (vacuna)**
- **Diseñado para utilizar el propio sistema inmune del paciente para atacar las células cancerígena**
- **Inmunoterapia celular producida por la exposición de los leucocitos del paciente a una proteina de fusion recombinante de Ag de Fosfatasa acida prostatica y GM-CSF**
- **No aprobada todavía en Europa**



IMPACT: Phase III Sipuleucel-T in mCRPC



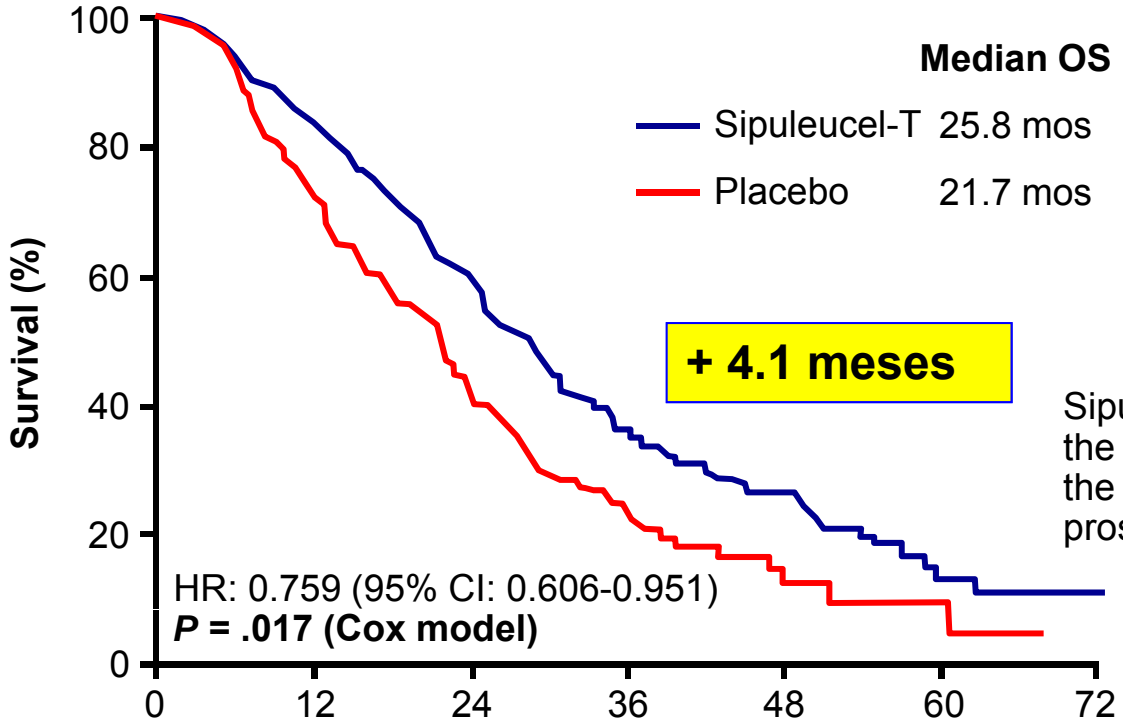
•Primary endpoint: OS

*Stratified by primary Gleason score, number of bone metastases, and bisphosphonate use

Kantoff P, et al.

IMPACT: Overall Survival

- Median follow-up: 36.5 mos (349 events)



Sipuleucel-T was approved by the FDA on April 30, 2010, for the treatment of metastatic prostate cancer

Pts at Risk, n						
Sipuleucel-T	341	274	142	56	18	3
Placebo	171	123	59	22	5	2

Kantoff P, et al. ASCO GU 2010. Abstract 8.

IMPACT: Safety

- Overall AEs more frequent with sipuleucel-T vs placebo
  - Incidence of any serious AE similar between arms: 24.3% vs 23.8%, respectively

AE,* %	Sipuleucel-T	Placebo
Chills	54.1	12.5
Pyrexia	29.3	13.7
Headache	16.0	4.8
Influenzalike illness	9.8	3.6
Myalgia	9.8	4.8
Hypertension	7.4	3.0
Hyperhidrosis	5.3	0.6
Groin pain	5.0	2.4

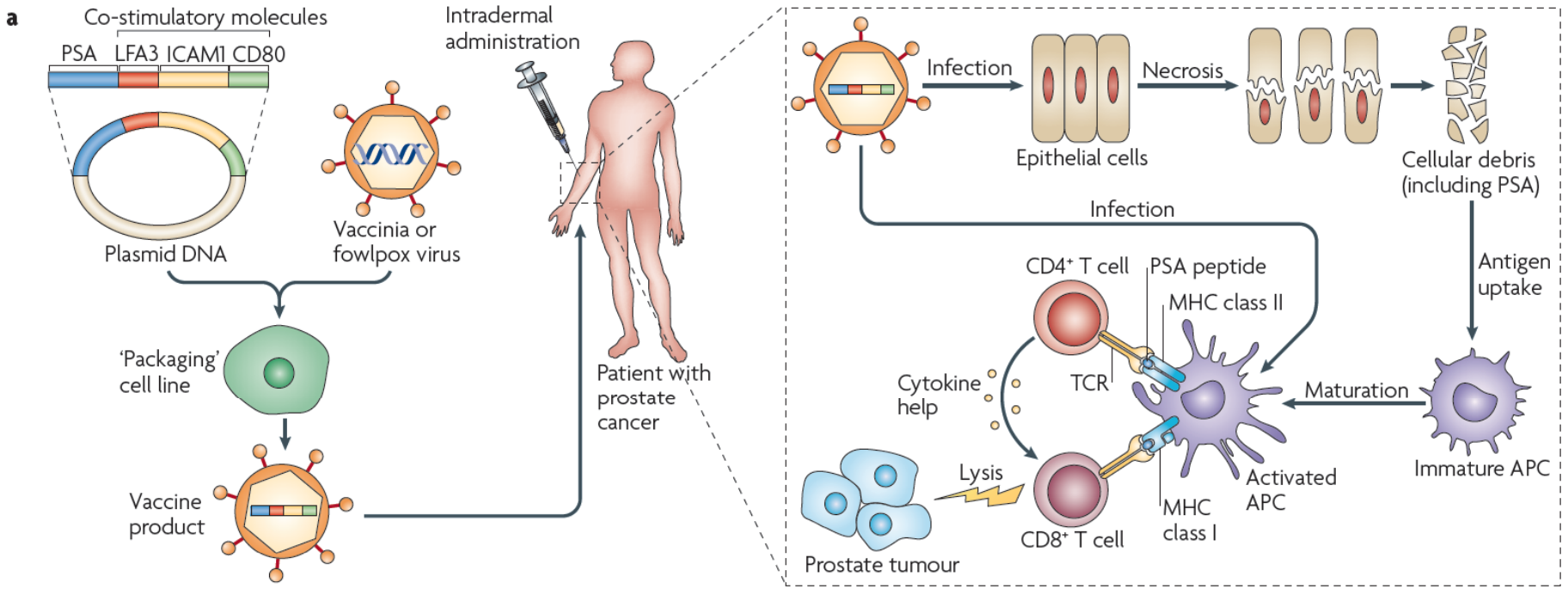
*Occurring in ≥ 5% of patients receiving sipuleucel-T with ≥ 2-fold increase in incidence relative to placebo.

Kantoff P

NUEVAS VACUNAS EN DESARROLLO

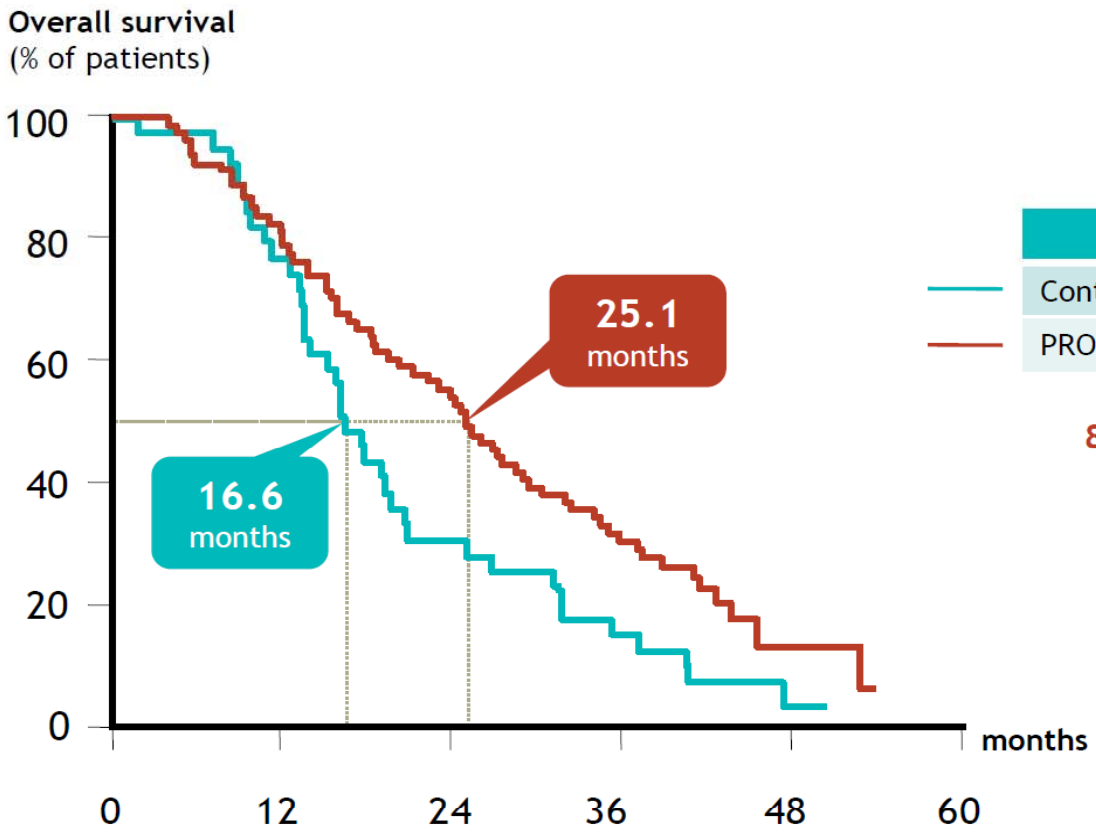
Vacunas células tumorales : ProstVac

Antígeno-> PSA



Drake, CG. Nat Rev Immunol Aug 2010; 10: 580-593

PROSTVAC PHASE II STUDY: Increased OS



	N	Deaths	Median
Control	40	37	16.6
PROSTVAC®	82	65	25.1

8.5 months improved survival

Hazard ratio
0.56 (95% CI 0.37–0.85)

p=0.0061

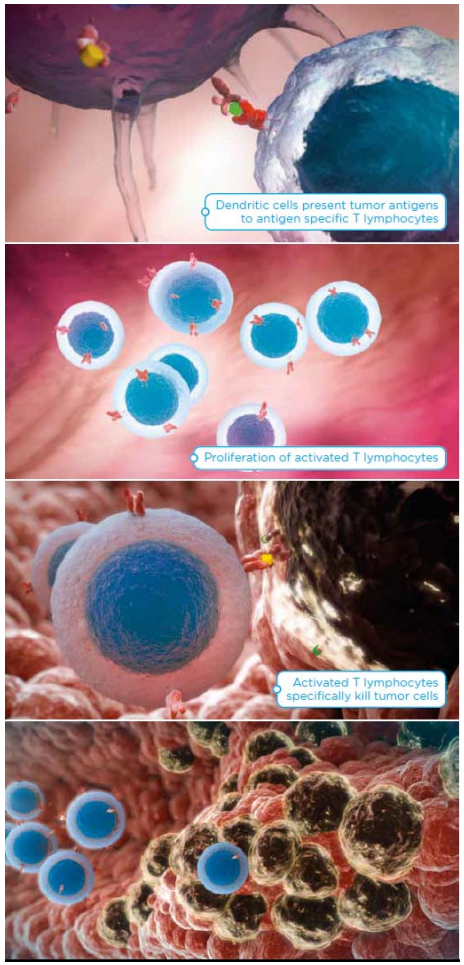
DCVAC/Pca

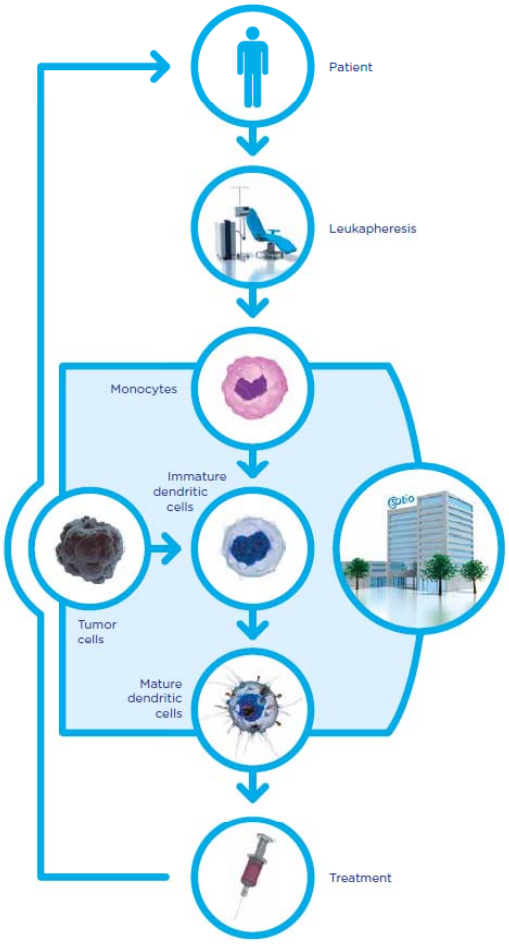
Active Cellular Immunotherapy

DCVAC/Pca for prostate cancer

DCVAC/OvCa, for epithelial ovarian cancer.

DCVAC/LuCa for lung cancer





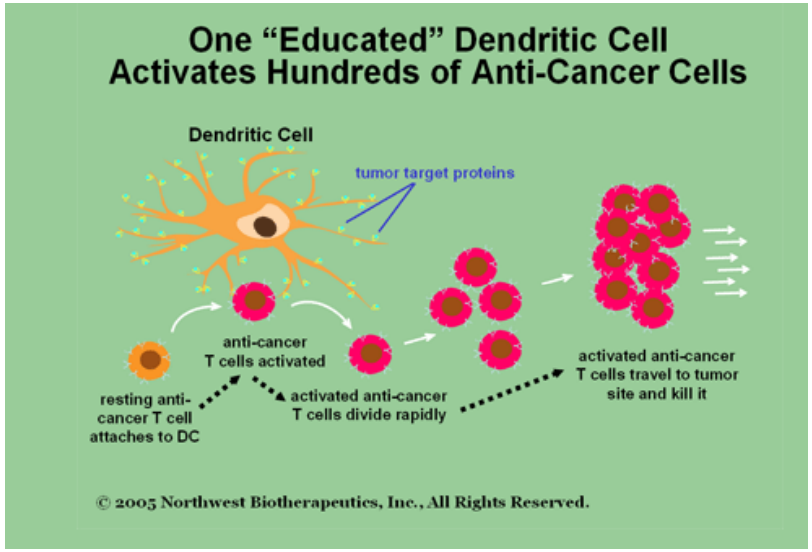
	Pre-clinical testing	Phase I	Phase I/II	Phase II	Phase III
Prostate cancer (DCVAC/PCa)	✓	✓	✓	✓	✓
Ovarian cancer (DCVAC/OvCa)	✓	✓		✓	
Lung cancer (DCVAC/LuCa)	✓	✓			

Legend: ✓ - In progress, ✓ - Planned for 2013

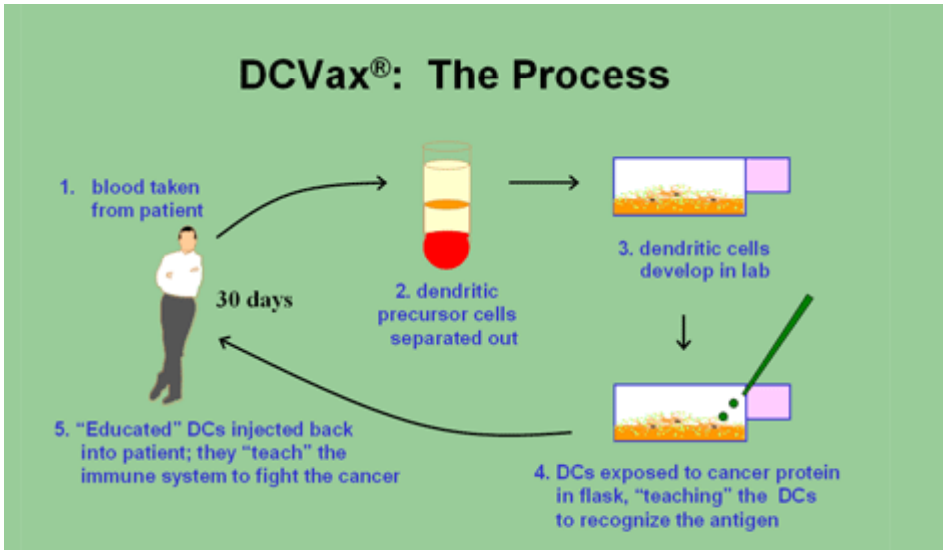
www.sotio.com

www.clinicaltrialregister.com

DC-Vax - Prostate



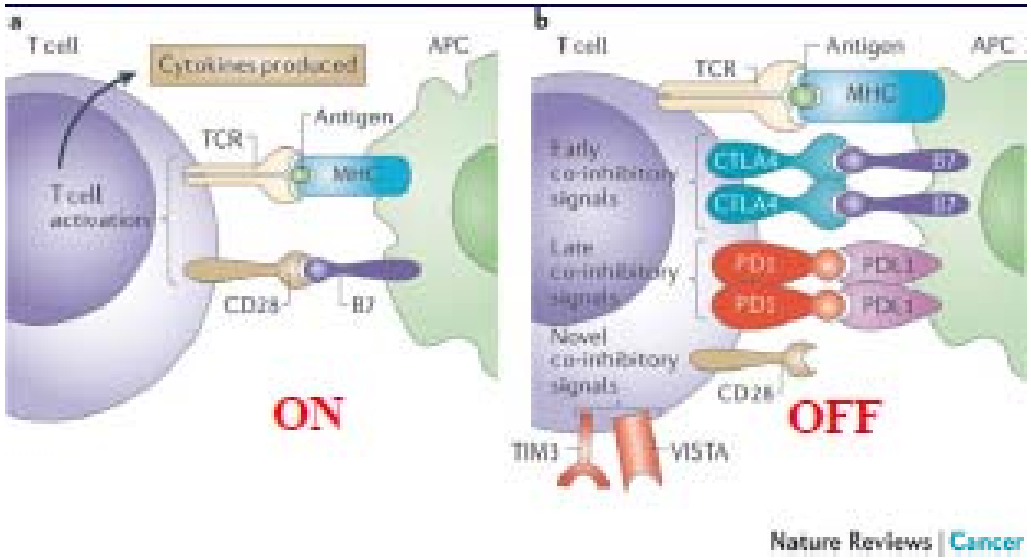
Anti PSMA

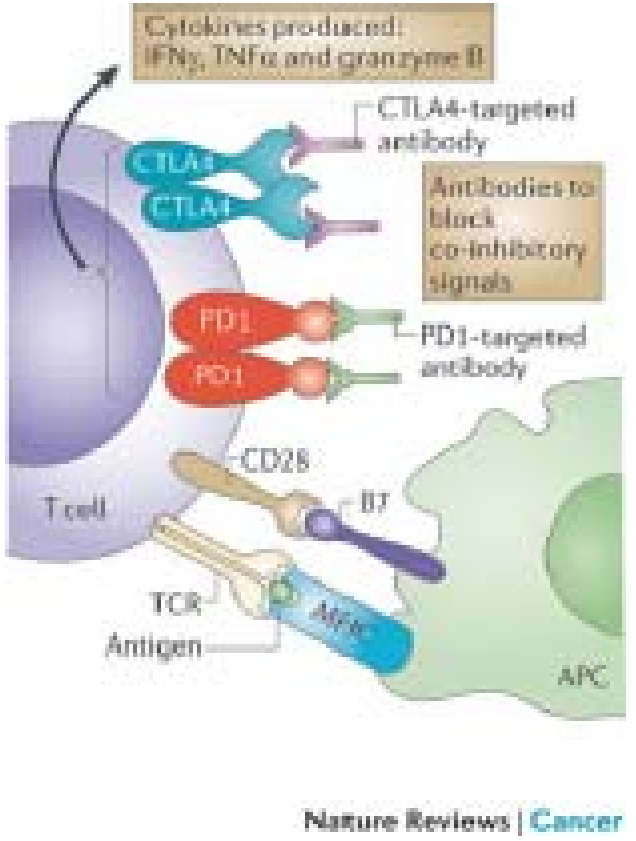


REGULADORES DE CHECK-POINTS INMUNOLÓGICOS

Ac Antimoduladores: Anti CTLA4 / PD1/PDL1

Estrategias para mantener los linfocitos T activados





Ac CTLA4: **Ipilumumab**
Tremelimumab

Ac PD-1: **MDX-1106**

CPRC: Aspectos clínicos tras Docetaxel

En muchas ocasiones nos encontramos

- ✓ **Paciente frágil**
- ✓ **Deterioro progresivo de la calidad de vida**
- ✓ **Aumento de complicaciones por las metástasis óseas**
- ✓ **Se suman las toxicidades de los tratamientos previos**

Docetaxel: Estándar 1ª línea

NO TODOS LOS PACIENTES LLEGAN O ESTÁN EN CONDICIONES DE RECIBIR DOCETAXEL

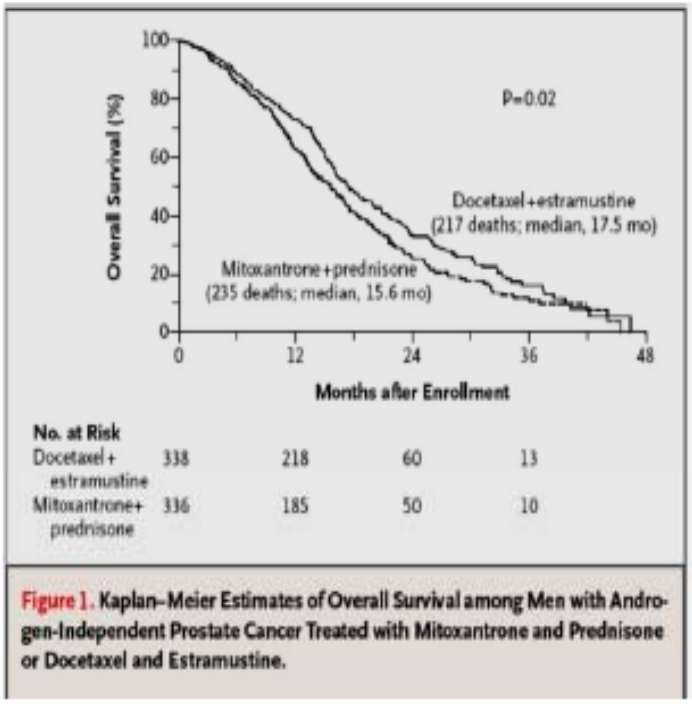
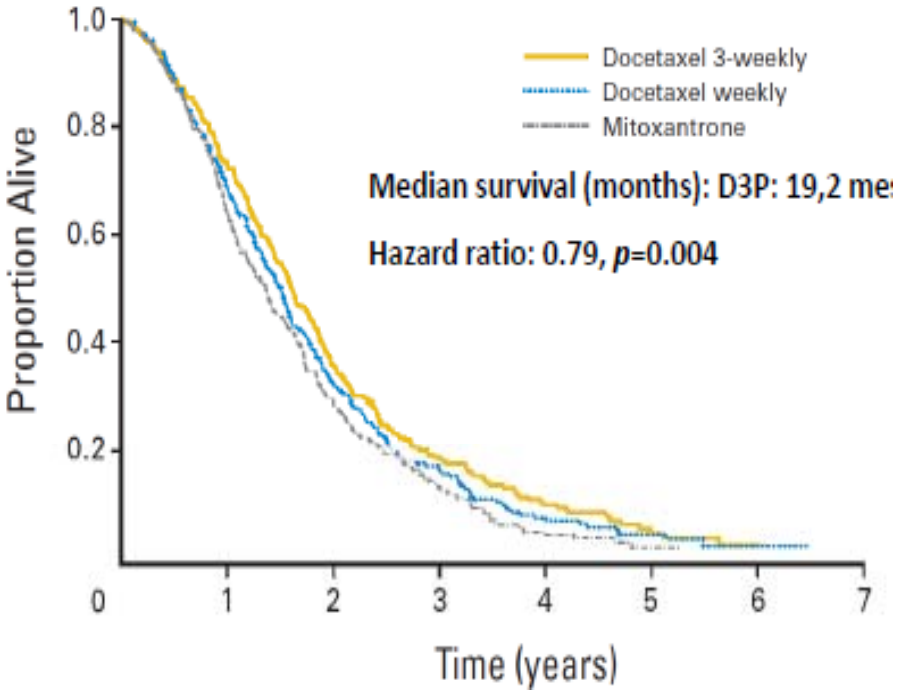


Figure 1. Kaplan–Meier Estimates of Overall Survival among Men with Androgen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine.

Petrylak et al. New Eng J Med 2004; 351(15): 1513-1520



Tannok et al, NEJM; 2004
Berthold et al, Ann Oncol 2008

Fármacos predocetaxel

- **Abiraterona**
- **Enzalutamida**
- **Docetaxel**

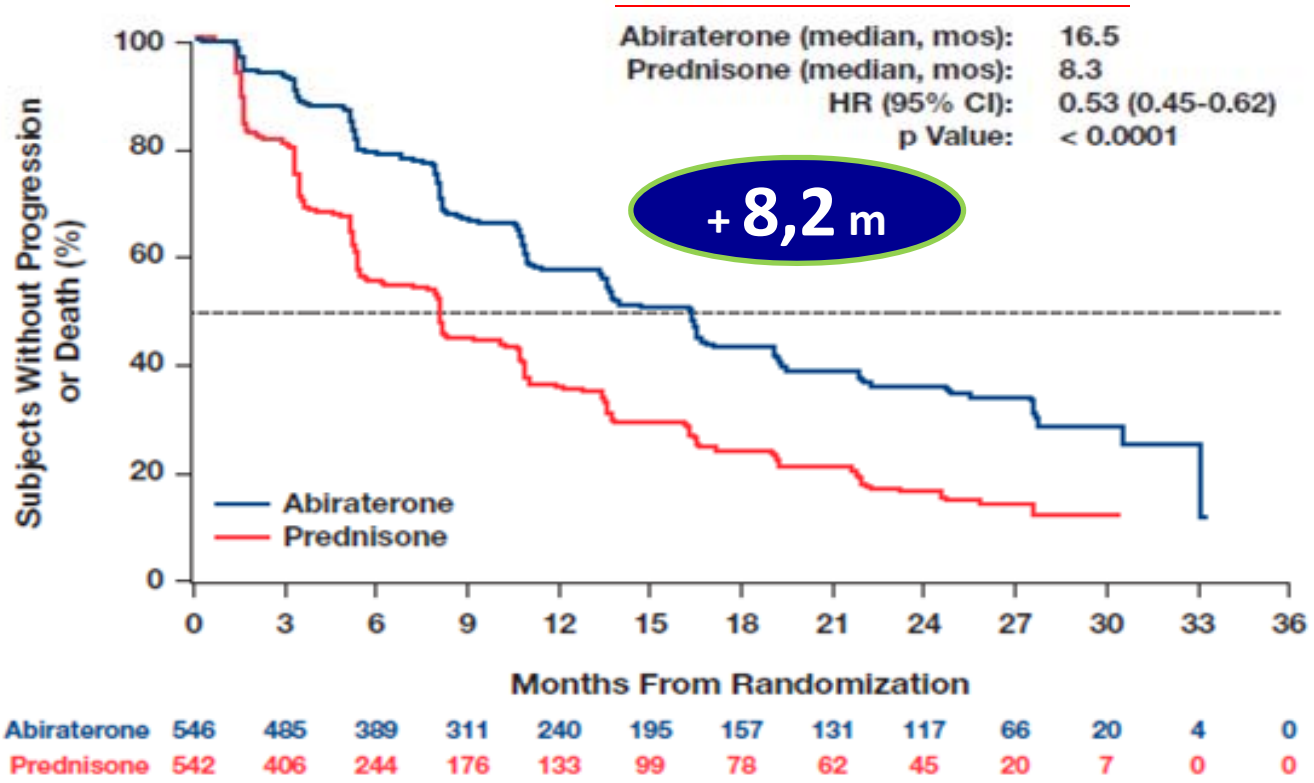
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

Charles J. Ryan, M.D., Matthew R. Smith, M.D., Ph.D., Johann S. de Bono, M.B., Ch.B., Ph.D., Arturo Molina, M.D., Christopher J. Logothetis, M.D., Paul de Souza, M.B., Ph.D., Karim Fizazi, M.D., Ph.D., Paul Mainwaring, M.D., Josep M. Piulats, M.D., Ph.D., Siobhan Ng, M.D., Joan Carles, M.D., Peter F.A. Mulders, M.D., Ph.D., Ethan Basch, M.D., Eric J. Small, M.D., Fred Saad, M.D., Dirk Schrijvers, M.D., Ph.D., Hendrik Van Poppel, M.D., Ph.D., Som D. Mukherjee, M.D., Henrik Suttmann, M.D., Winald R. Gerritsen, M.D., Ph.D., Thomas W. Flaig, M.D., Daniel J. George, M.D., Evan Y. Yu, M.D., Eleni Efstathiou, M.D., Ph.D., Allan Pantuck, M.D., Eric Winquist, M.D., Celestia S. Higano, M.D., Mary-Ellen Taplin, M.D., Youn Park, Ph.D., Thian Kheoh, Ph.D., Thomas Griffin, M.D., Howard I. Scher, M.D., and Dana E. Rathkopf, M.D., for the COU-AA-302 Investigators*

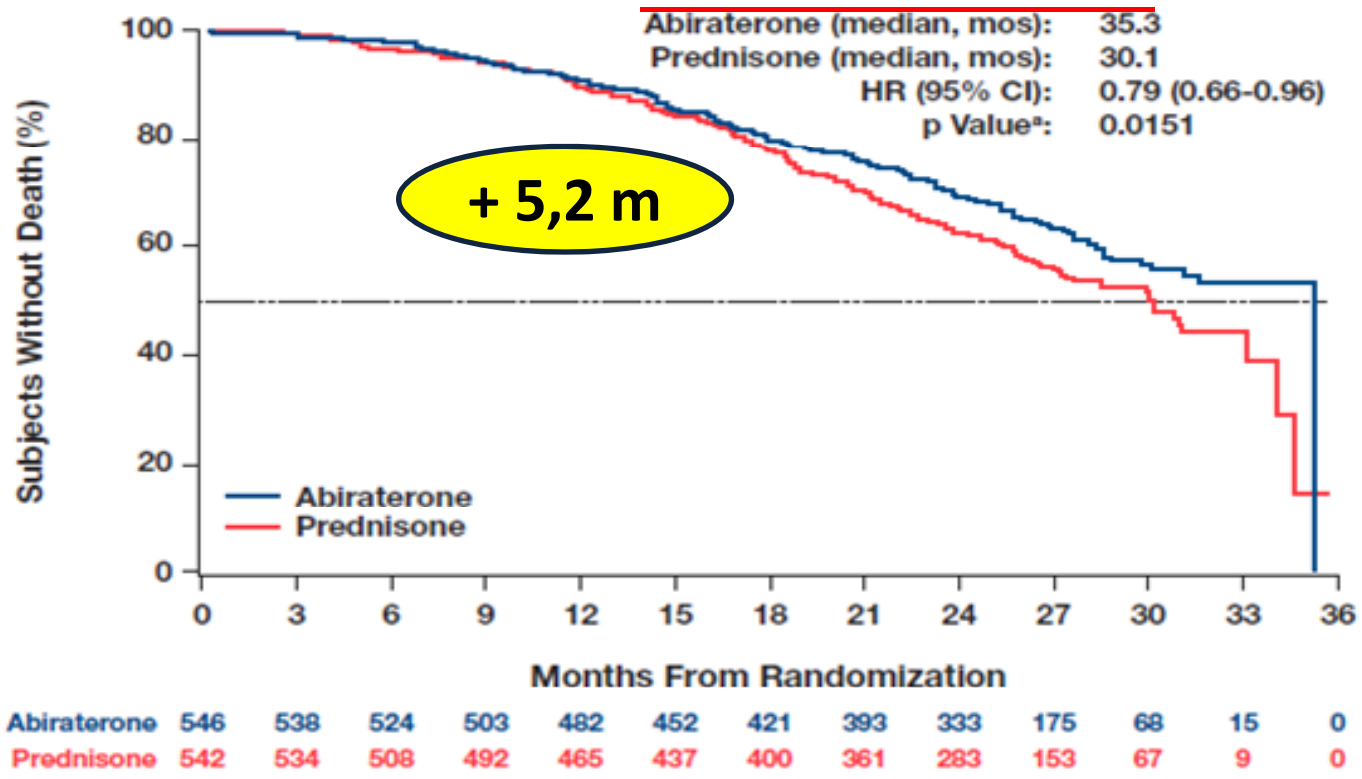
COU-AA-302
Abiraterona aumenta significativamente la rPFS



Reducción del riesgo de progresión radiológica o muerte del 47% en el grupo de pacientes tratados con Abiraterona

Poster presented at ASCO GU, February 14-16, 2013, Orlando, FL

COU-AA-302
Fuerte tendencia en incremento de SG con abiraterona



Reducción del riesgo de muerte del 21% en el grupo de pacientes tratados con Abiraterona

*el objetivo de SG se alcanzaba con una reducción del 20%

Poster presented at ASCO GU, February 14-16, 2013, Orlando, FL

Enzalutamida

ORIGINAL ARTICLE

Enzalutamide in Metastatic Prostate Cancer before Chemotherapy

T.M. Beer, A.J. Armstrong, D.E. Rathkopf, Y. Loriot, C.N. Sternberg, C.S. Higano, P. Iversen, S. Bhattacharya, J. Carles, S. Chowdhury, I.D. Davis, J.S. de Bono, C.P. Evans, K. Fizazi, A.M. Joshua, C.-S. Kim, G. Kimura, P. Mainwaring, H. Mansbach, K. Miller, S.B. Noonberg, F. Perabo, D. Phung, F. Saad, H.I. Scher, M.-E. Taplin, P.M. Venner, and B. Tombal, for the PREVAIL Investigators*

ABSTRACT

BACKGROUND

Enzalutamide is an oral androgen-receptor inhibitor that prolongs survival in men with metastatic castration-resistant prostate cancer in whom the disease has progressed after chemotherapy. New treatment options are needed for patients with metastatic prostate cancer who have not received chemotherapy, in whom the disease has progressed despite androgen-deprivation therapy.

METHODS

In this double-blind, phase 3 study, we randomly assigned 1717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily. The coprimary end points were radiographic progression-free survival and overall survival.

RESULTS

The study was stopped after a planned interim analysis, conducted when 540 deaths had been reported, showed a benefit of the active treatment. The rate of radiographic progression-free survival at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% confidence interval [CI], 0.15 to 0.23; P<0.001). A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data-cutoff date (29% reduction in the risk of death; hazard ratio, 0.71; 95% CI, 0.60 to 0.84; P<0.001). The benefit of enzalutamide was shown with respect to all secondary end points, including the time until the initiation of cytotoxic chemotherapy (hazard ratio, 0.35), the time until the first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs. 5%), the time until prostate-specific antigen (PSA) progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) (P<0.001 for all comparisons). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment.

CONCLUSIONS

Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer. (Funded by Medivation and Astellas Pharma; PREVAIL ClinicalTrials.gov number, NCT01212991.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Beer at OHSU Knight Cancer Institute, Oregon Health and Science University, 3303 SW Bond Ave., CH14R, Portland, OR 97239, or at beert@ohsu.edu.

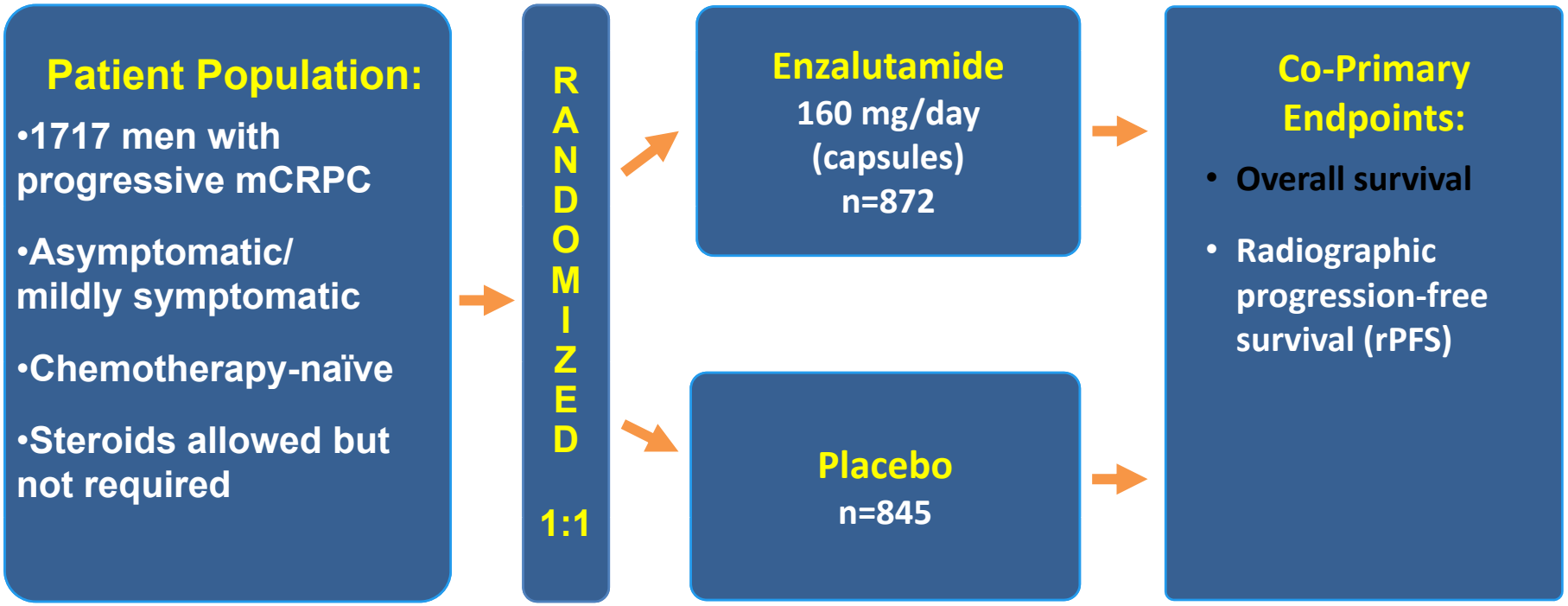
*Additional investigators in the PREVAIL study are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on June 1, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1405095

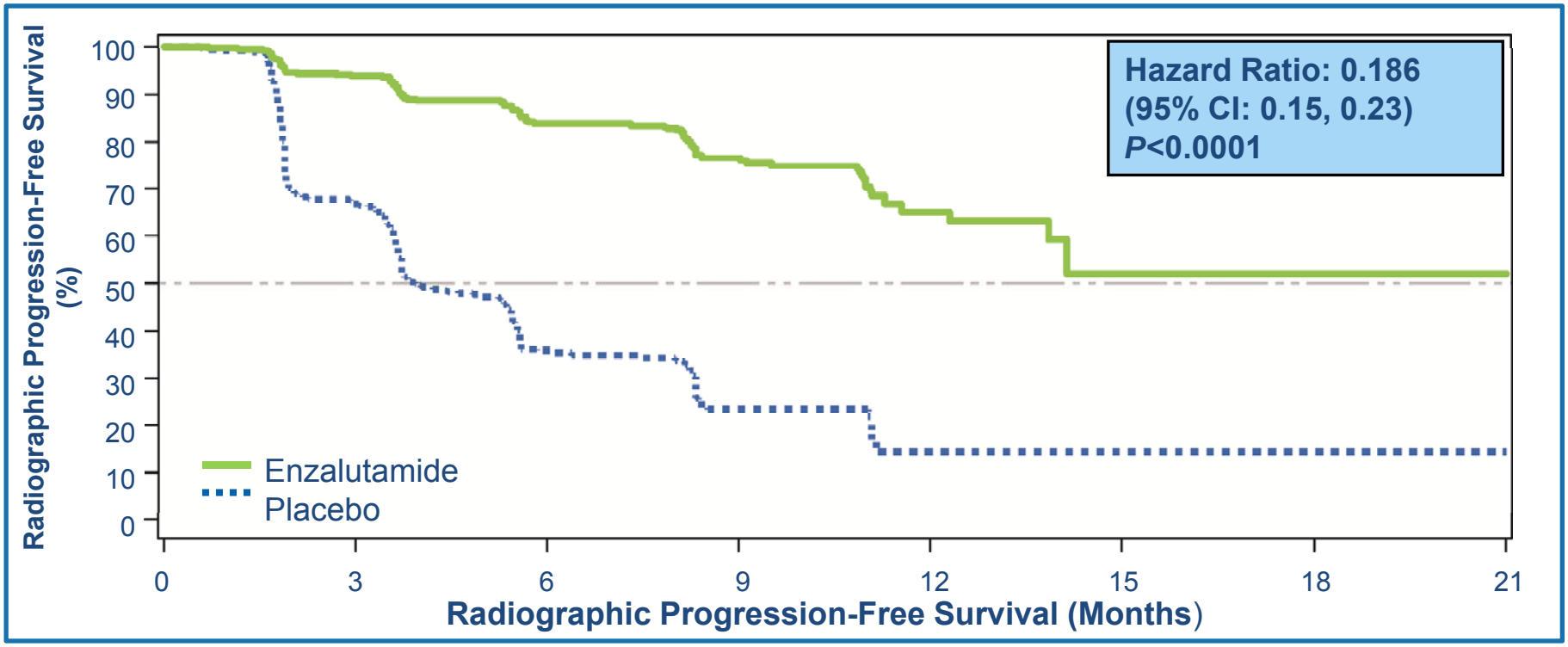
NEJM Junio 2014

PREVAIL Study



ClinicalTrials.gov identifier: NCT01212991.

Enzalutamide Prolonged Radiographic Progression-Free Survival

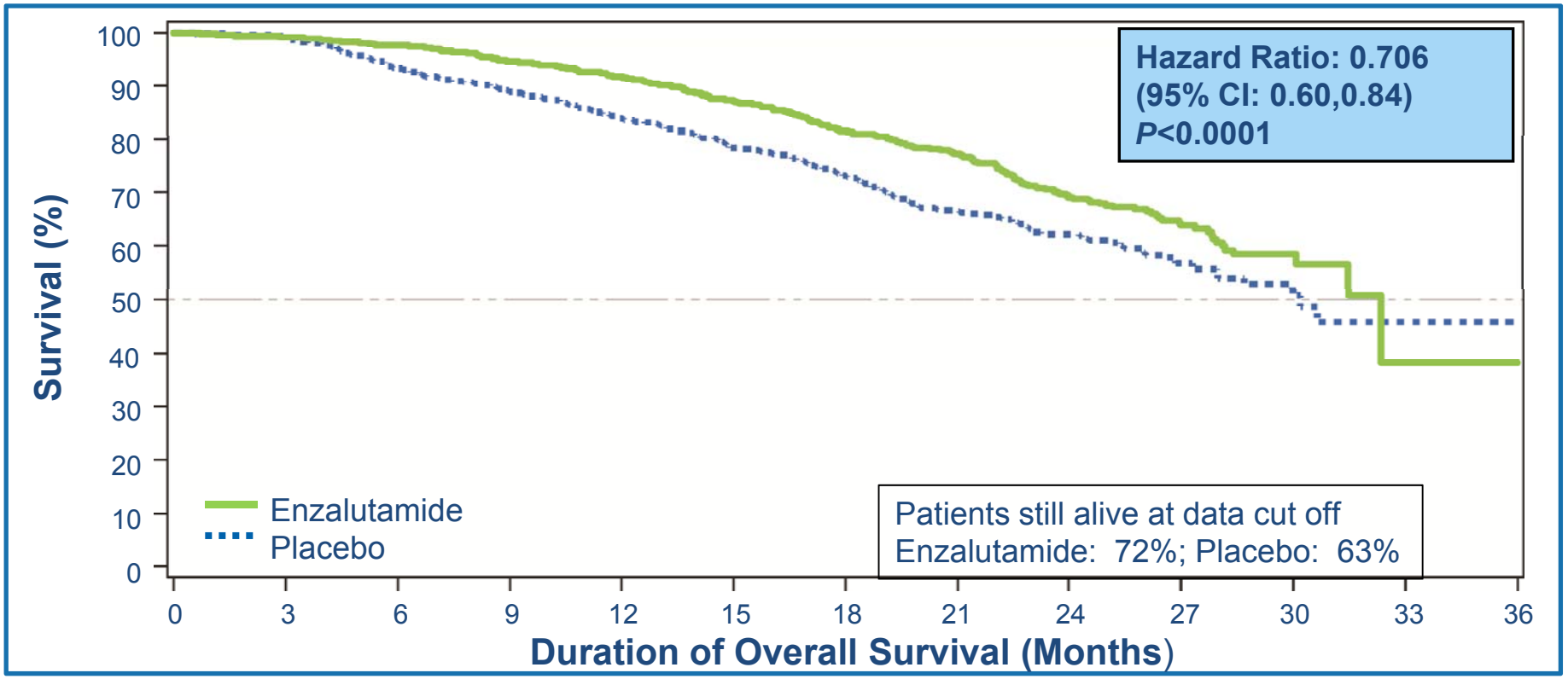


Patients at Risk								
Enzalutamide	832	514	256	128	34	5	1	0
Placebo	801	305	79	20	5	0	0	0

Estimated median rPFS, months (95% CI): Enzalutamide: NYR (13.8, NYR); Placebo: 3.9 (3.7, 5.4)

NYR = Not Yet Reached

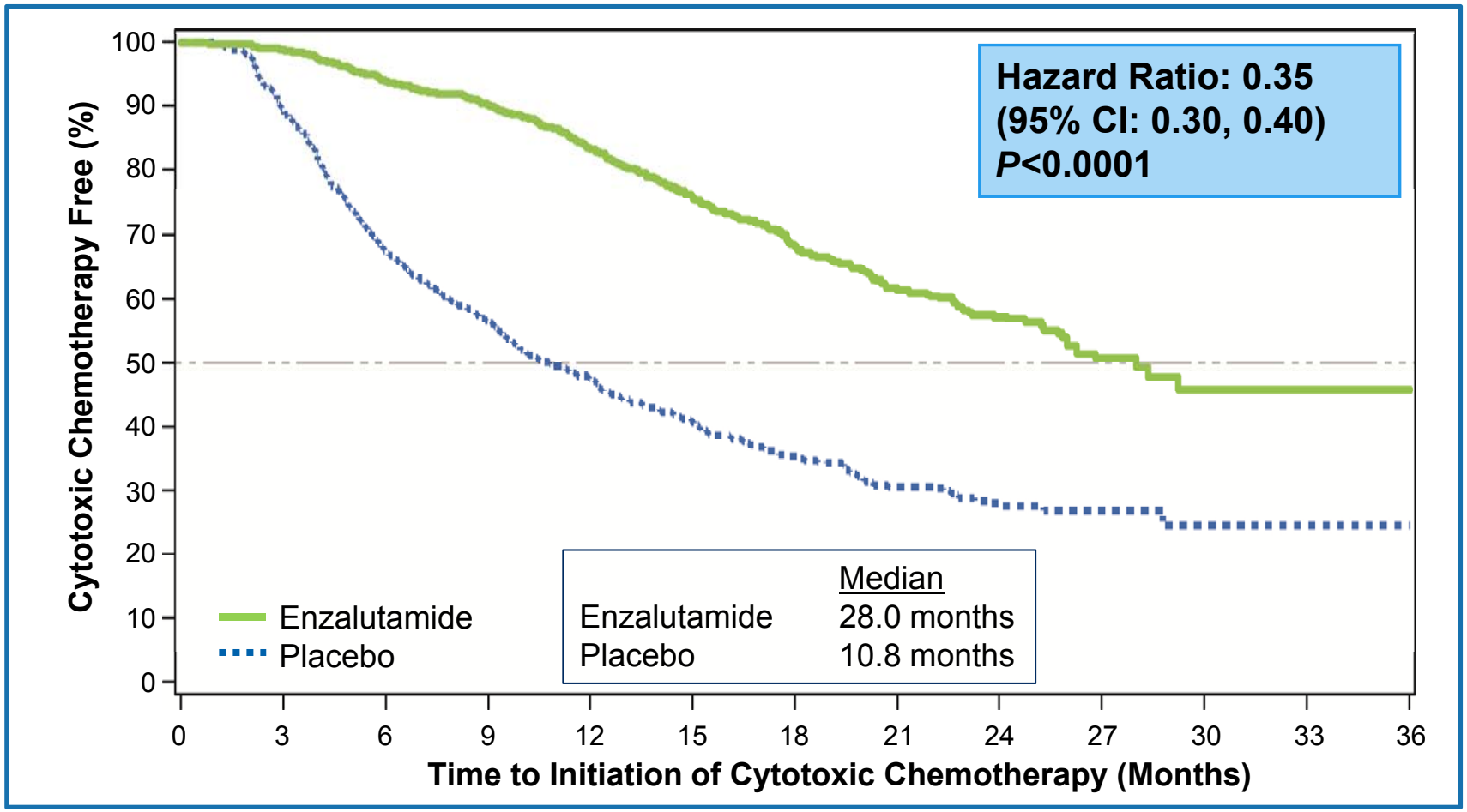
Enzalutamide Reduced Risk of Death by 29%



Patients at Risk													
Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo	845	835	781	744	701	644	484	328	213	102	27	2	0

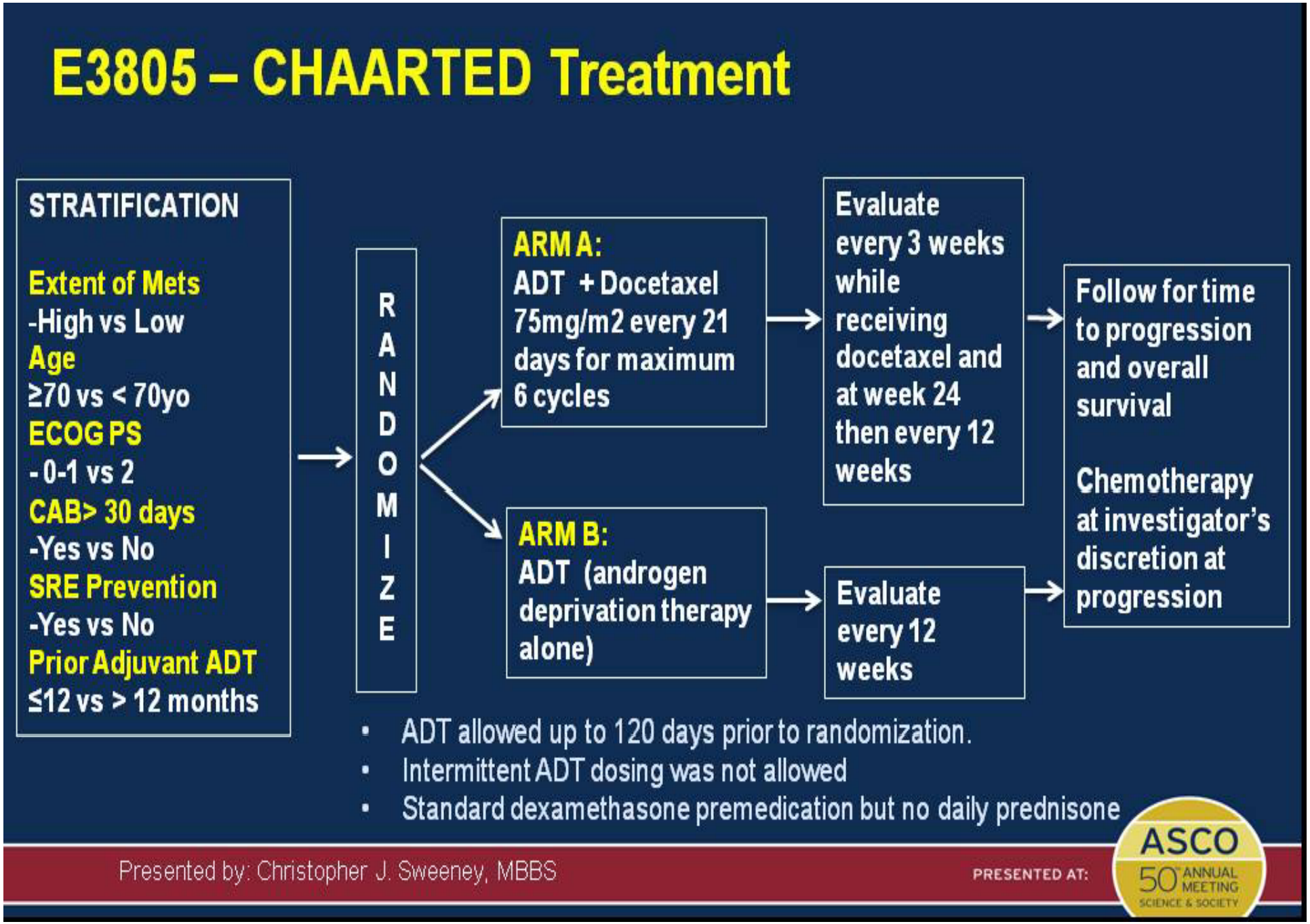
Estimated median OS, months (95% CI): Enzalutamide: 32.4 (30.1, NYR); Placebo: 30.2 (28.0, NYR) *NYR = Not Yet Reached*

Enzalutamide Delayed Median Time to Chemotherapy by 17 Months



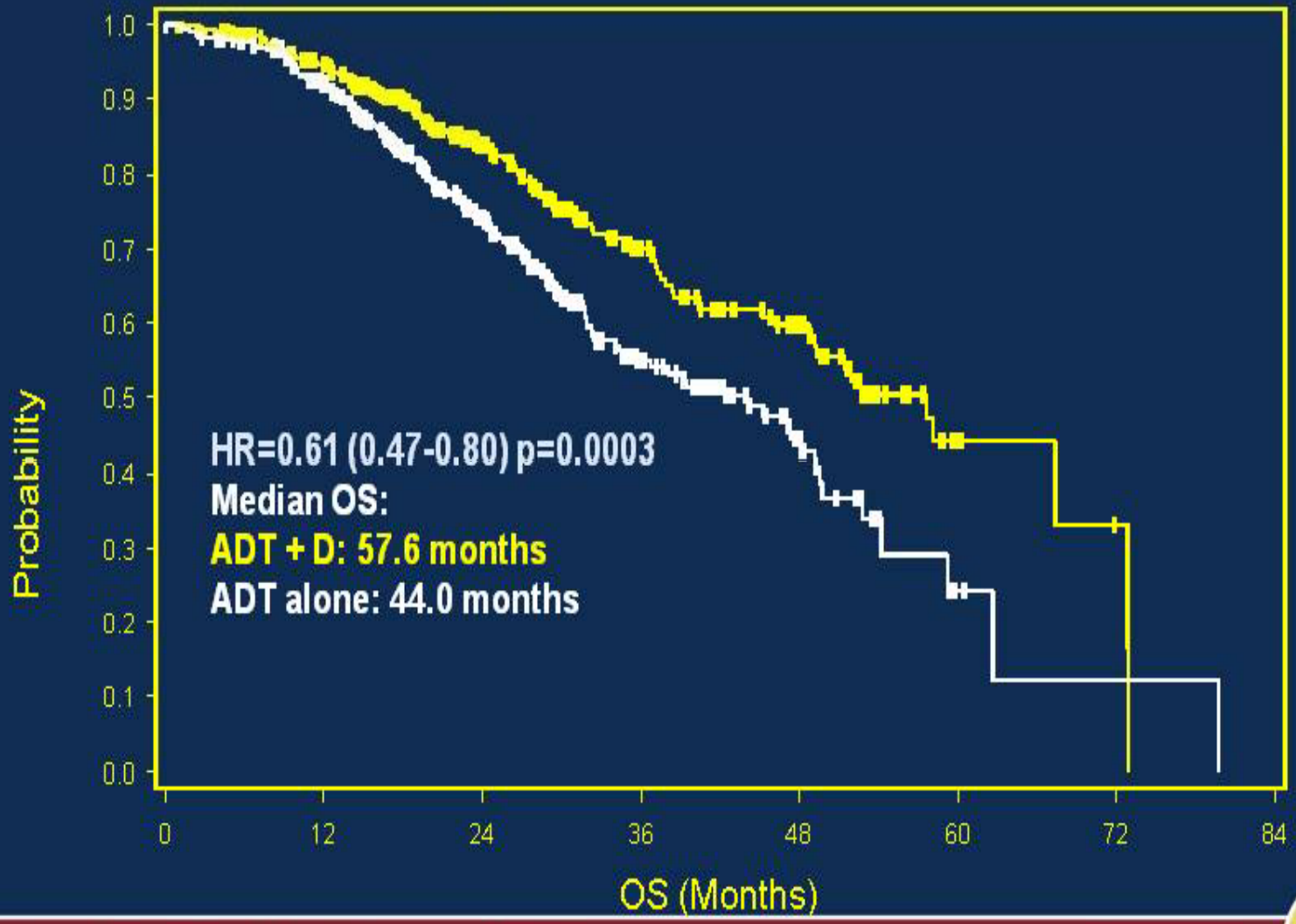
Patients at Risk

Enzalutamide	872	854	799	751	665	575	388	252	158	78	21	2	0
Placebo	845	734	518	415	324	257	165	103	64	25	9	0	0



Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

Primary endpoint: Overall survival



Presented by: Christopher J. Sweeney, MBBS

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

Conclusiones

- **En la actualidad, varios fármacos han demostrado un aumento de la supervivencia, en pacientes con cáncer de próstata metastásico, antes y después del tratamiento con Docetaxel.**
  - **Cabazitaxel** — **2.4 MESES**
  - **Abiraterona** — **4.6 MESES**
  - **Enzalutamida** — **4.8 MESES**
  - **Sipuleucel** — **4.1 MESES**
  - **Alfaradin** — **3.6 MESES**

- **Otros fármacos mejoran la calidad de vida retrasando los eventos óseos**
  - **Acido Zoledronico**
  - **Denosumab**

Cáncer de Próstata resistente a la castración

- Los avances en la biología molecular del cáncer de próstata están provocando el desarrollo de:
  - Nuevas vías de investigación
  - Nuevos fármacos

Que llevaran a una mayor supervivencia y una mejor calidad de vida de los pacientes con cáncer de próstata

MUCHAS GRACIAS POR SU ATENCION

Fármacos Fase II prometedores

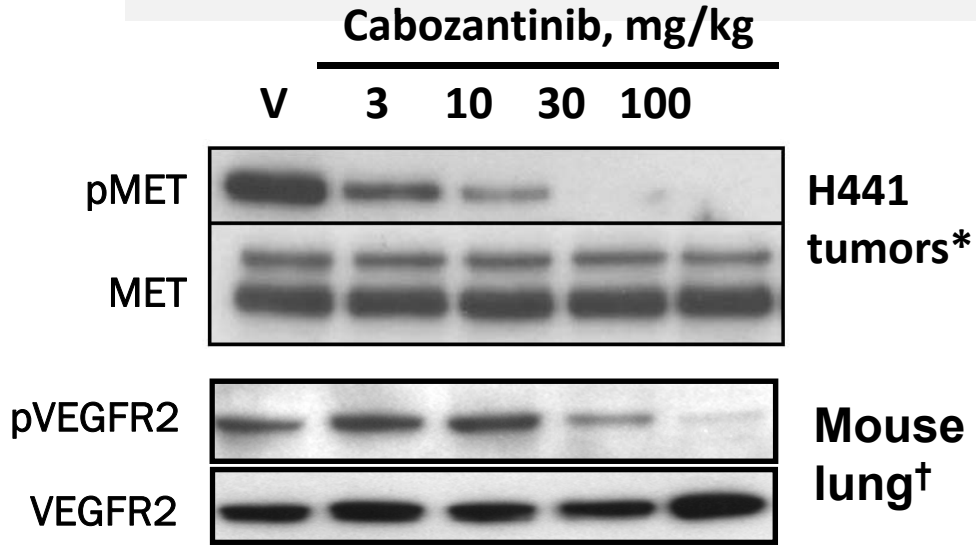
- **Cabozantinib**: Pacientes CPHR pre/post
  - QT. SLP 21 vs 6 semanas (HR 0.13),
  - RR 75%; EE 21%, Dolor RR 67%
- **Dasatinib:** CPHR con docetaxel.
  - RR 57%, Resorción ósea 87%
- **PROSTVAC-VF:** CPHR preQT.
  - SG 25.1 vs 16.6 meses, HR 0.56
- **Zibotentan:** CPHR OSS: SG HR, 0.76
- **Tasquinimod:** CPHR preQT: SLP 6m 69 vs 3

Cabozantinib (XL184): Target Profile

Kinase	IC_{50}, nM
MET	1.8
VEGFR2	0.035
RET	5.2
KIT	4.6
AXL	7.0
TIE2	14
FLT3	14
S/T Ks (47)	>200

ATP competitive, reversible

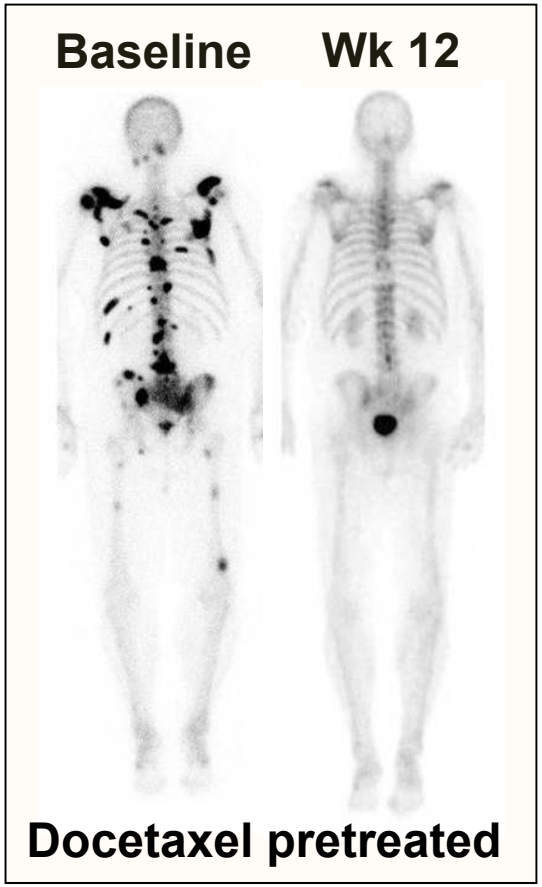
RTK	Cellular IC_{50}, nM, Autophosphorylation
MET	8
VEGFR2	4



*No growth factor stimulation.
†VEGF-A administered 30 min prior to harvest.

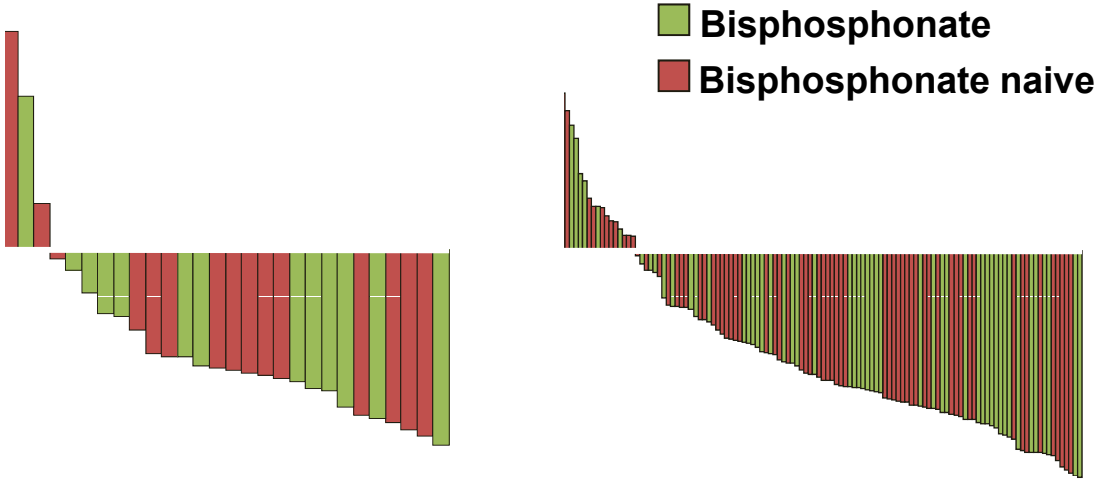
Data courtesy of Ron Weitzman and Dana Aftab.

Cabozantinib (cMET/VEGFR2 Inhibitor) Demonstrates Significant Bone Effects



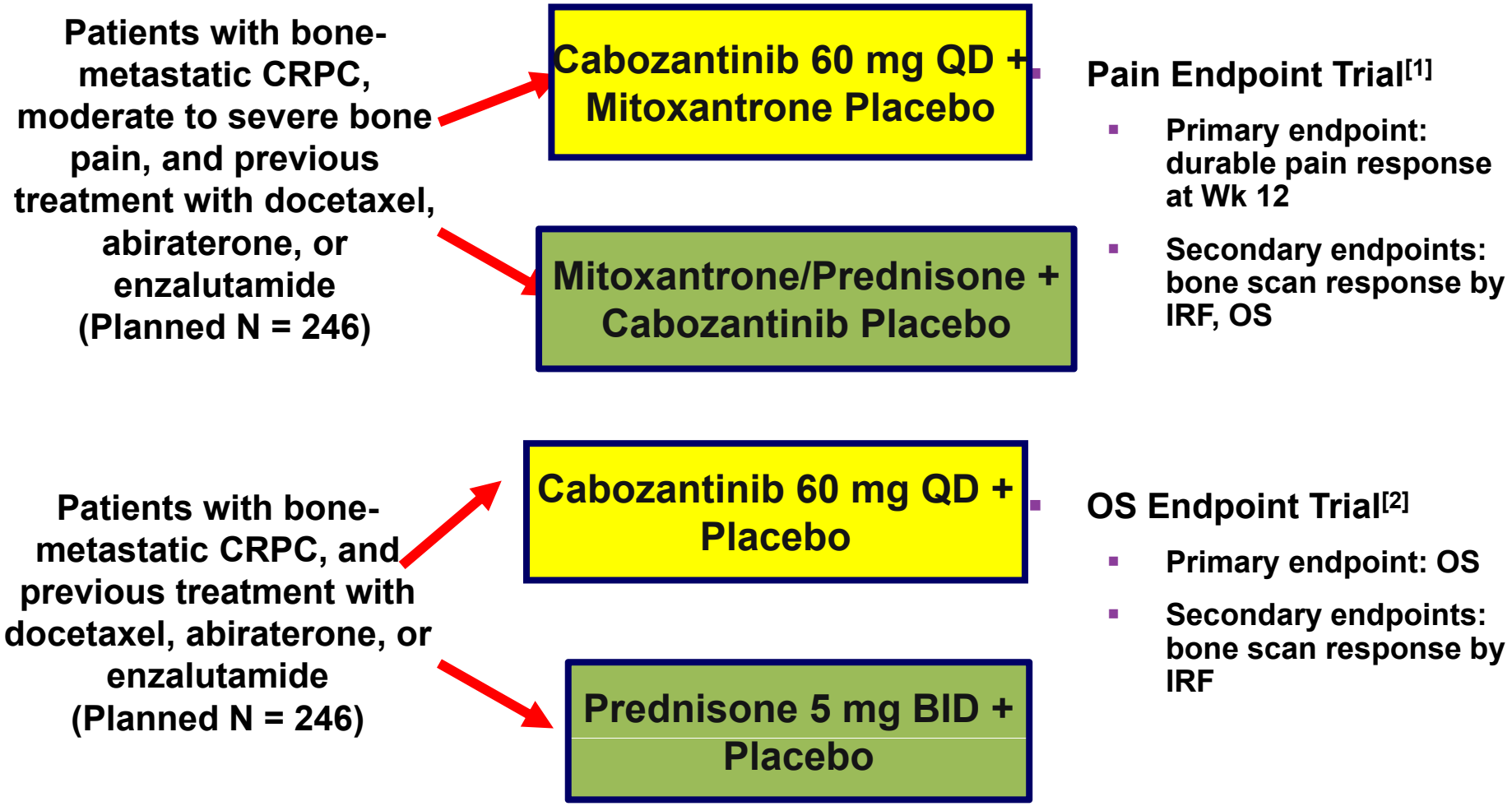
Hussain M, et al. ASCO 2011. Abstract 4516.

Bone Scan Evaluable (N = 108)	n (%)
Complete resolution	21 (19)
Partial resolution	61 (56)
Stable	23 (21)
Progressive disease	3 (3)



Effects on Osteoblast (t-ALP) and Osteoclast (CTx) Activity

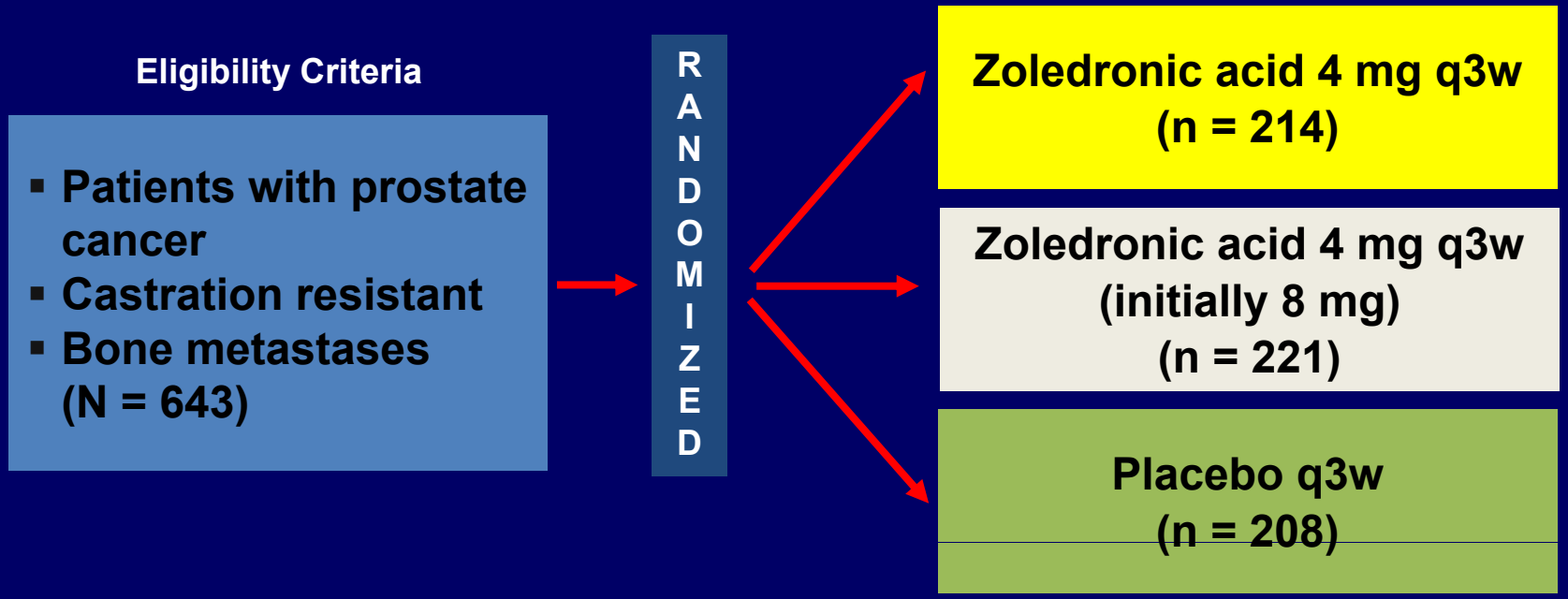
Cabozantinib: Randomized Phase III Trials



1. ClinicalTrials.gov. NCT01522443. 2. ClinicalTrials.gov. NCT01605227.

Treatment of Bone Metastases Secondary to Castration-Resistant Prostate Cancer

Zoledronic Acid in Castration-Resistant Prostate Cancer

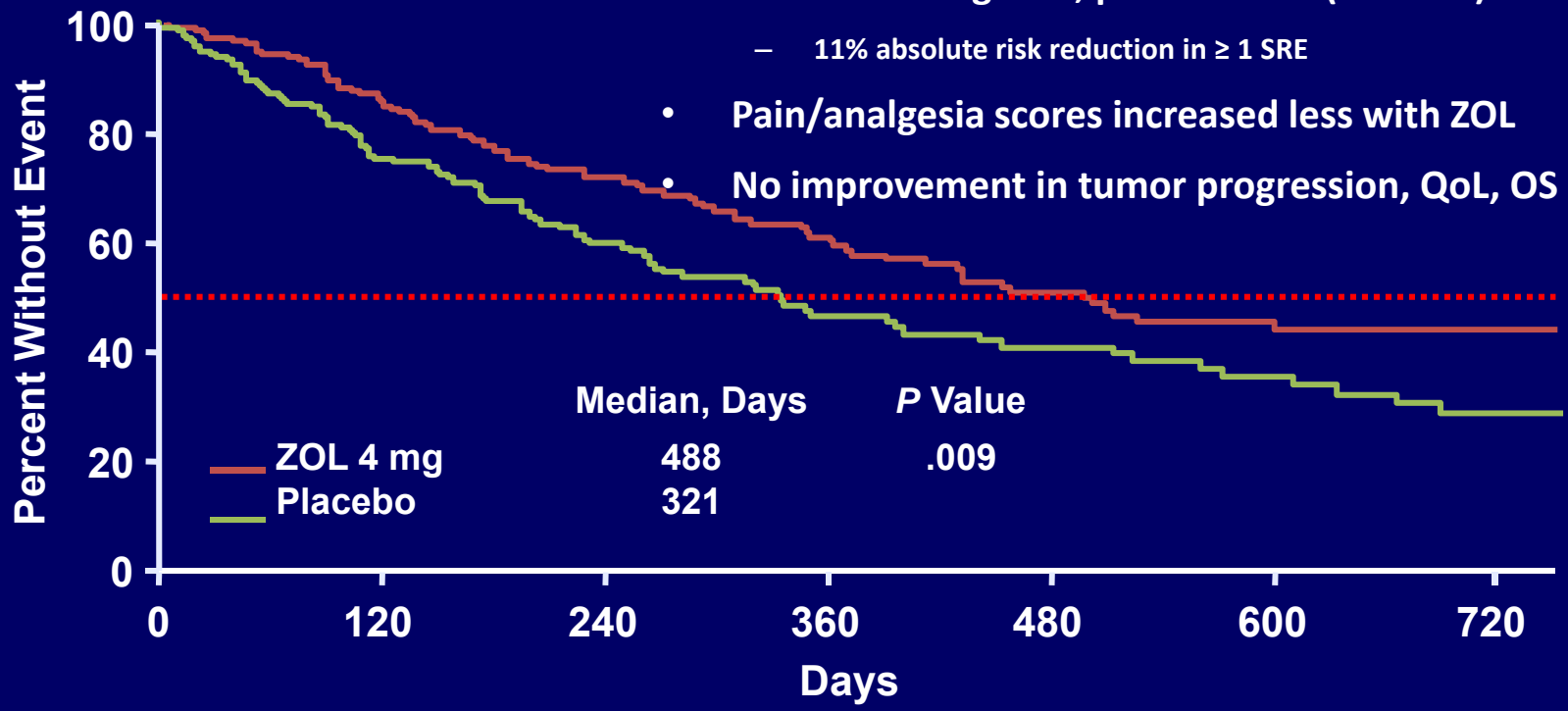


- Patients in 8-mg arm reduced to 4 mg because of renal toxicity
- Primary outcome: proportion of patients having ≥ 1 SRE
- Secondary outcomes: time to first on-study SRE, proportion of patients with SREs, and time to disease progression

Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468.

Time to First SRE: Zoledronic Acid vs Placebo

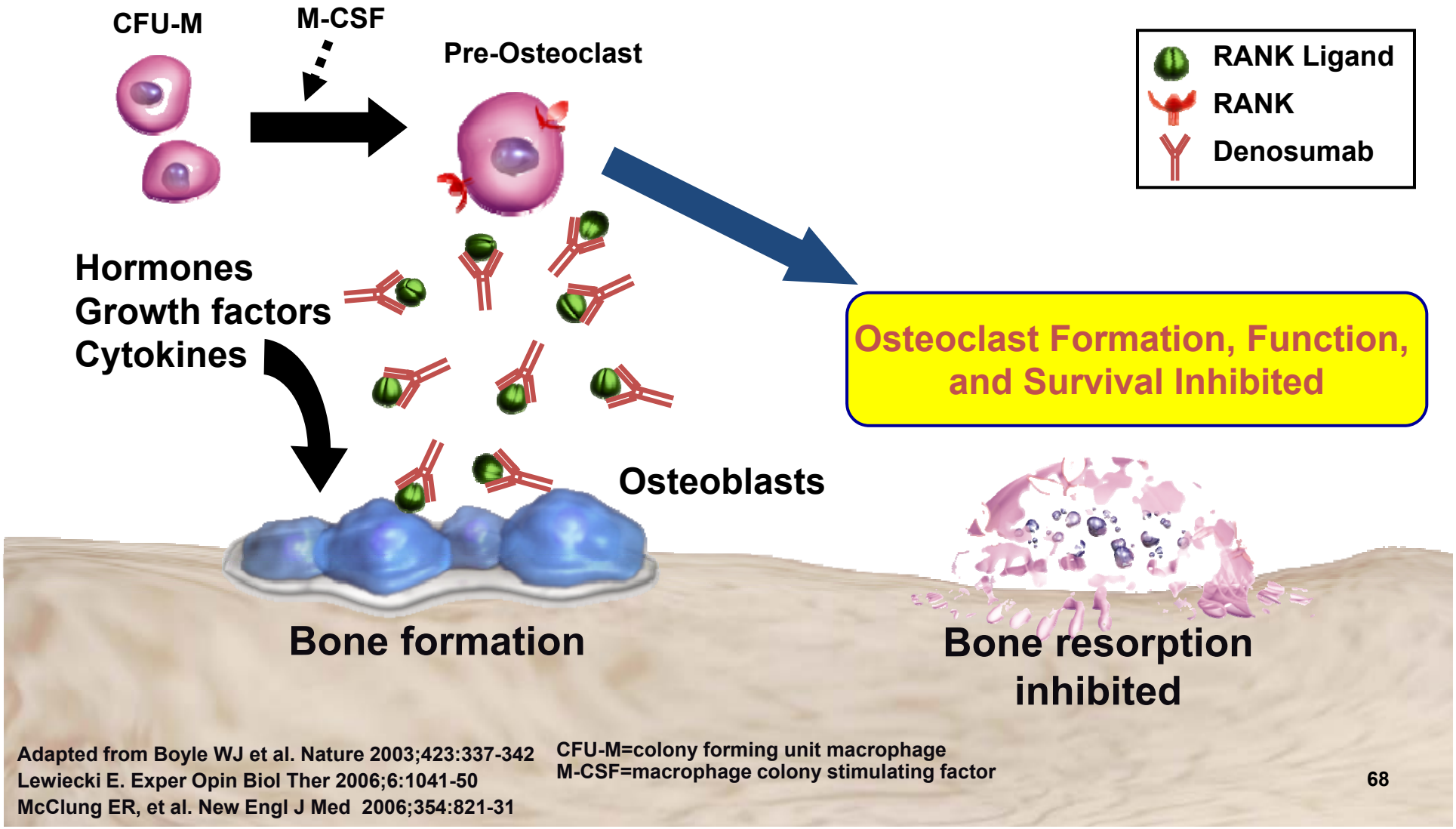
- SREs: ZOL 4 mg 38%; placebo 49% (*P* = .028)
  - 11% absolute risk reduction in ≥ 1 SRE
- Pain/analgesia scores increased less with ZOL
- No improvement in tumor progression, QoL, OS



ZOL 4 mg	214	149	97	70	47	35	3
Placebo	208	128	78	44	32	20	3

Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468. Saad F, et al. ASCO 2003. Abstract 1523. Saad F, et al. J Natl Cancer Inst. 2004;96:879-882.

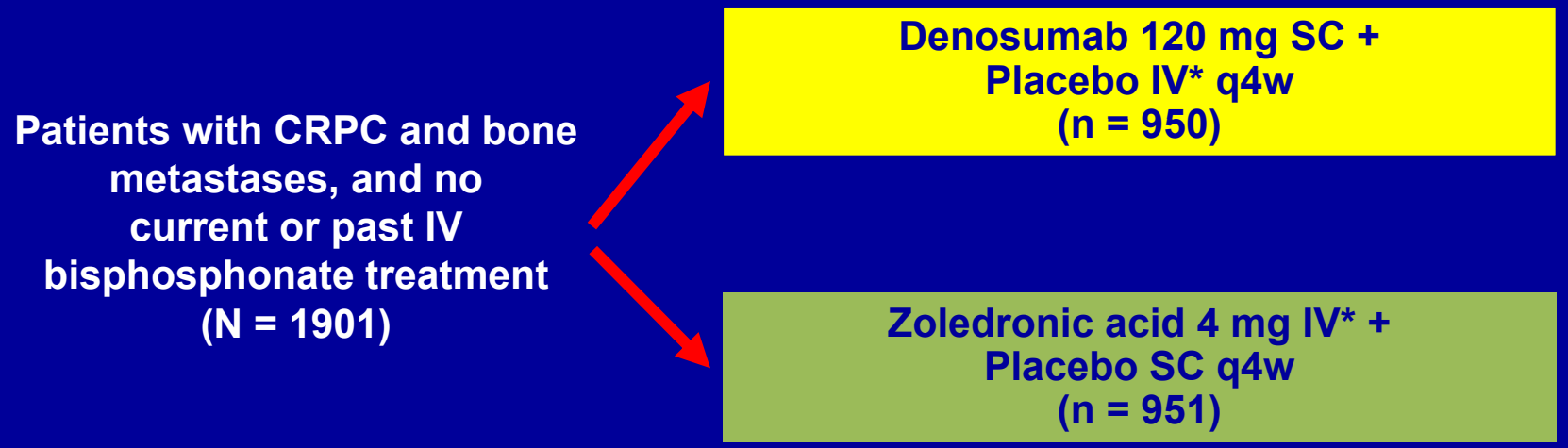
Denosumab antibody binds RANK Ligand and inhibits osteoclast-mediated bone destruction



Adapted from Boyle WJ et al. Nature 2003;423:337-342
Lewiecki E. Exper Opin Biol Ther 2006;6:1041-50
McClung ER, et al. New Engl J Med 2006;354:821-31

CFU-M=colony forming unit macrophage
M-CSF=macrophage colony stimulating factor

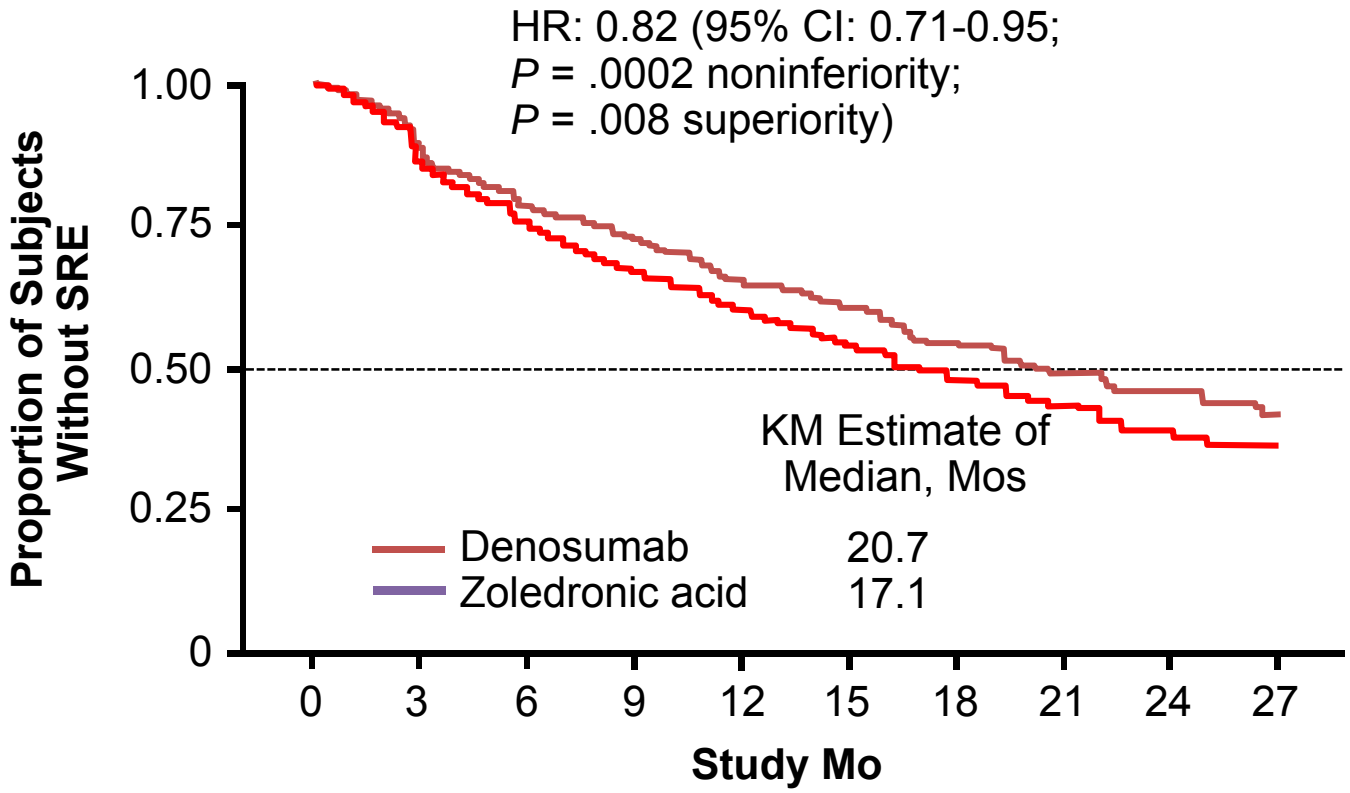
Denosumab vs Zoledronic Acid: Double-Blind, Placebo-Controlled Phase III Trial



- Calcium and vitamin D supplemented in both treatment groups
- Primary endpoint: time to first on-study SRE (fracture, radiation or surgery to bone, spinal cord compression)

Fizazi K, et al. Lancet. 2011;377:813-822.

Denosumab vs Ac. Zoledronico
Tiempo a primer ERE



Patients at Risk, n

Zoledronic acid	951	733	544	407	299	207	140	93	64	47
Denosumab	950	758	582	472	361	259	168	115	70	39

Fizazi K, et al. ASCO 2010. Abstract LBA4507. Reprinted with permission.

Resultados

- Denosumab fue superior a acido zoledronico
  - Retrasa tiempo a primer ERE
  - Reduce el indice de multiples EREs
- ONJ es poco frecuente, aunque mayor con Denosumab (p=NS)
- Hipocalcemia mas frecuente en denosumab

Fizazi K, et al. ASCO 2010. Abstract LBA4507.

CPRCm
Opciones terapeuticas en 2013…

- Hormonoterapia
  - Abiraterona
  - Enzalutamida
- Citostaticos
  - Cabazitaxel

- Radiofarmacos
  - Alpharadin
- Vacunas
  - Sipuleucel
  - Prost Vac
  - Ipilimumab
- Fármacos dirigidos al hueso
  - Acido Zoledronico
  - Denosumab
  - Atresantran

Cancer de Prostata

Otros fármacos en Investigación