荷爾蒙療法失敗之轉移性前列腺癌診療指引及最新治療方法簡介

Introduction of Guideline and Novel Treatment Modalities in The Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Date: March 29, 2014, AM 08:00 ~ 08:50
Venue：正心樓0211教室

2010年與2009年男性10大癌症發生率比較

發生序位	死亡序位 (2010年)	原發部位	2010年			2009年			2010年發生人數增減值	2010年發生率增減值
			個案數	標準化發生率	年齡中位數	個案數	標準化發生率	年齡中位數		
1	3	大腸	8,143	54.4	66	7,151	48.7	68	992	5.7
2	1	肝及肝內膽管	7,751	52.3	62	7,747	53.6	62	4	-1.3
3	2	肺、支氣管及氣管	6,697	43.7	71	6,737	45.1	72	-40	-1.4
4	4	口腔、口咽及下咽	6,028	40.6	53	5,927	40.8	52	101	-0.2
5	7	攝護腺	4,392	28.8	74	4,013	26.9	74	379	1.9
6	5	胃	2,415	15.4	71	2,404	15.9	72	11	-0.5
7	6	食道	2,091	13.8	56	1,898	13	57	193	0.8
8	18	皮膚	1,575	10.2	73	1,589	10.7	71	-14	-0.5
9	12	膀胱	1,427	9.2	72	1,419	9.4	72	8	-0.2
10	10	鼻咽	1,194	8.2	51	1,162	8.2	49	32	0
		全癌症	50,892	340.7	64	49,022	336.3	65	1,870	4.4

註：
1.序位係以標準化發生率（每10萬人口）排序。
2.年齡標準化發生率，係以西元2000年世界標準人口為標準人口計算。
3.2009年與2008年發生率增減值：2009年年齡標準化發生率-2008年年齡標準化發生率。
4.台灣癌症登記資料庫(不含原位癌)

中華民國 99 年

癌症登記報告

CANCER REGISTRY ANNUAL REPORT, 2010 TAIWAN

Age	<59	60~74	>75	Sum
New Dx	**281(7.5%)**	**1651(44.4%)**	**1787(48.1%)**	**3719**
Any ADT	**39.51%**	**48.15%**	**67.94%**	**57.01%**

放療 荷爾蒙治療		荷爾蒙治療 [6]		內分泌治療 [7]		緩和治療 [8]		拒絕治療 [9]		未治療 [10]		其它治療 [11]	
申報數	%	申報數	%	申報數	%	申報數	%	申報數	%	申報數	%	申報數	%
692	18.61	1013	27.24	44	1.18	20	0.54	149	4.01	24	0.65	7	0.19

Refine of Definition of Castration-Resistant Prostate Cancer

Patients with advanced prostate cancer treated with androgen deprivation therapy (ADT) will eventually experience disease progression.

Castration-resistant prostate cancer (CRPC) is defined as:

– Progressive prostate cancer (rising PSA, radiographic progression)

– With serum testosterone below castrate levels (< 0.50 ng/mL)

Evidence revealed 2nd hormonal agents, e.g. anti-androgens, ketoconazole, estrogens and several newer agents meet clinical response in patients who are 'refractory' to ADT.

- Receptor overexpression/amplification
- Androgen receptor (AR) mutations (e.g. receptor hypersensitivity)
- Increased AR ligand synthesis
- AR co-activators and chaperones
- Ligand-independent AR activation

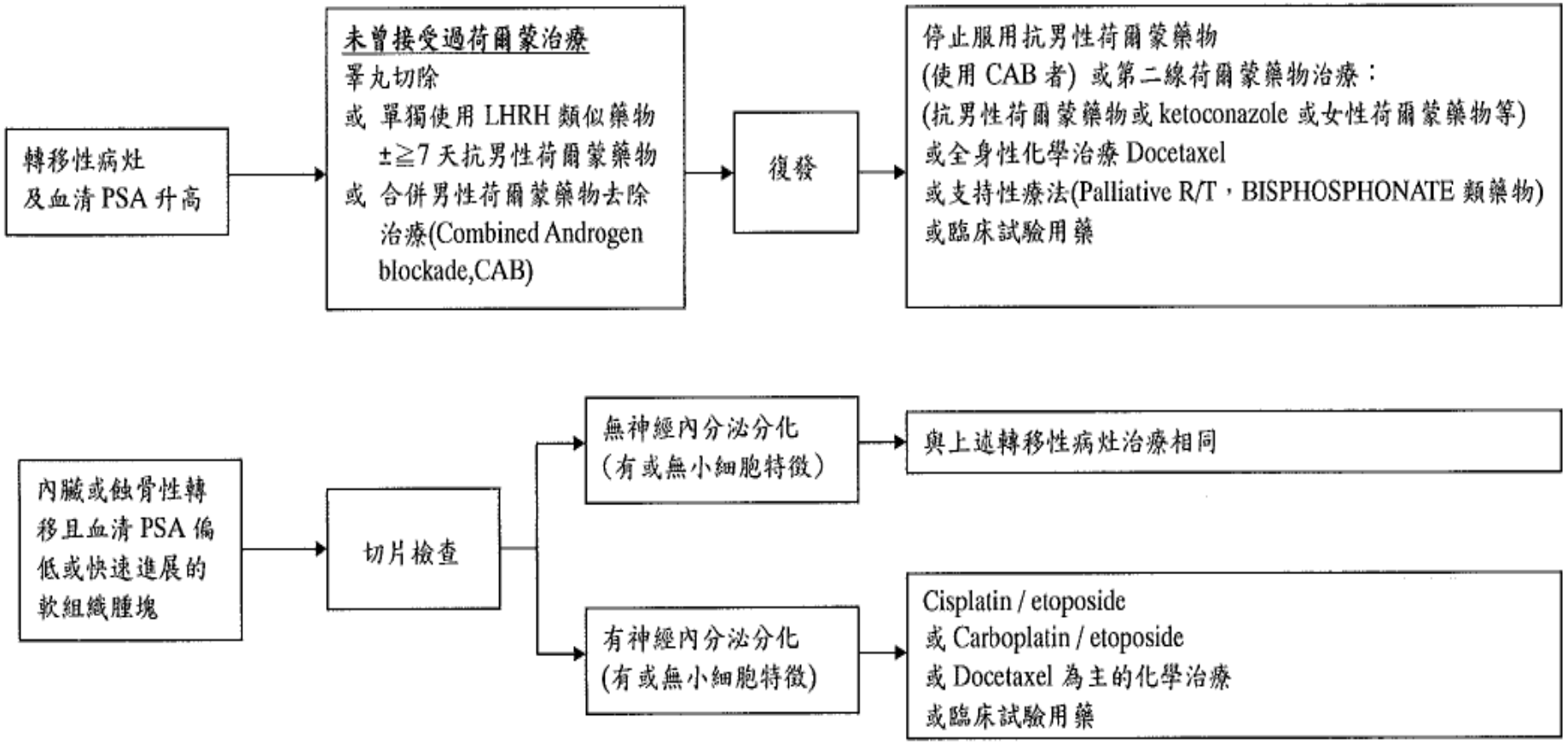
Garcia JA and Rini BI. *Cancer* 2012;118:2583–2593.

Scher HI, *et* al. *Endocr Relat Cancer* 2004;11:459–476;
Garcia JA and Rini BI. *Cancer* 2012;118:2583–2593
Taylor CD, *et al. J Clin Oncol* 1993;11:2167–2172.

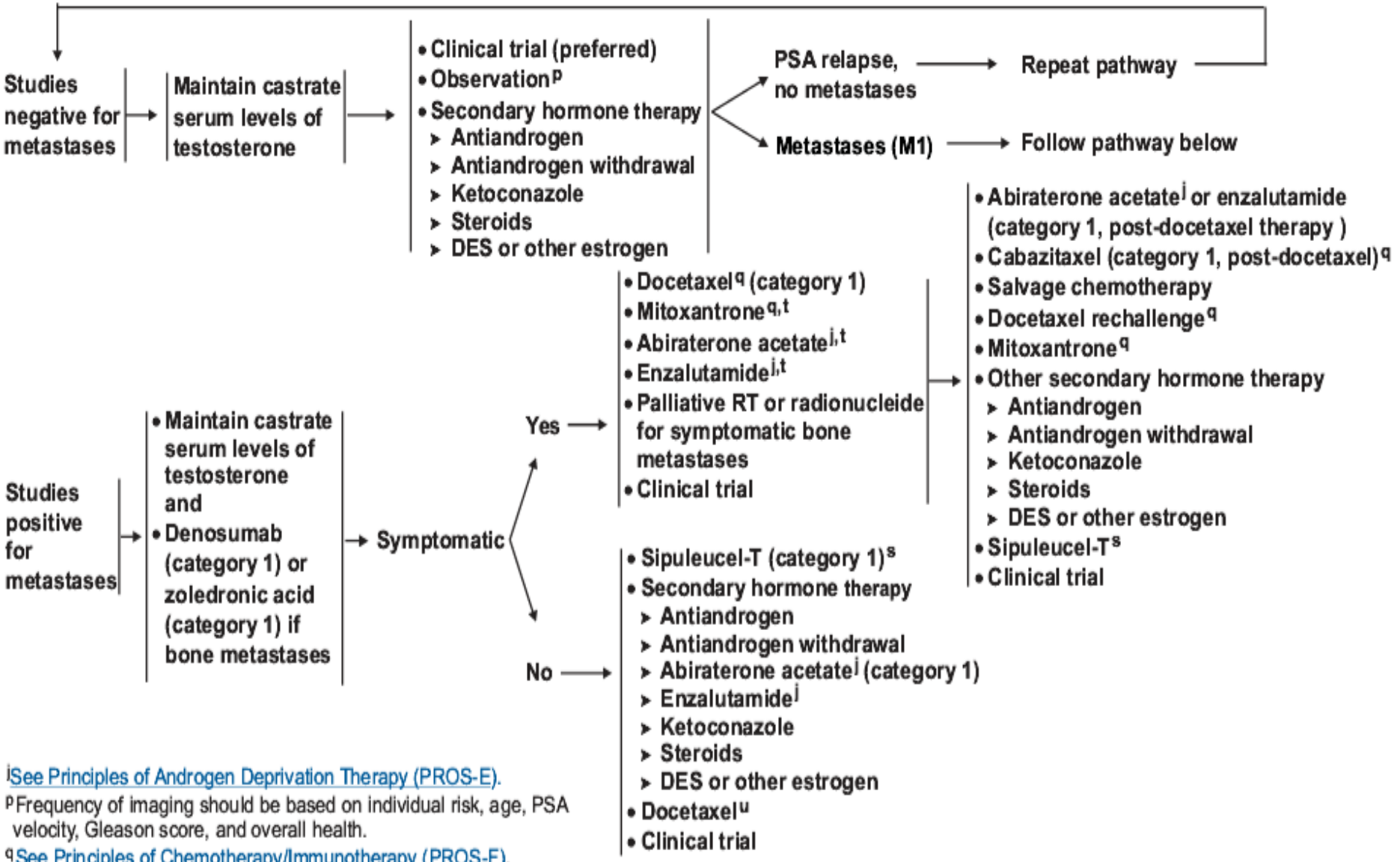
臨床期別（復發風險）	預期餘命	初步治療
臨床局限性腫瘤	非常低/低度復發風險 **T1-2a 期及** Gleason score 2-6 分 及 PSA＜10 ng/ml	＜10 年	積極監視(暫不予治療，定期 PSA 與 DRE 檢查)
		≧10 年	積極監視(暫不予治療，定期 PSA 與 DRE 檢查，視需要得重覆切片檢查) 或放射線治療±組織插腫近接治療 或根除性攝護腺切除手術＋骨盆腔淋巴結(切除)擴清術
	中度復發風險 **T2b-2c 期或** Gleason score 7 分 或 PSA10-20 g/ml	＜10 年	積極監視(暫不予治療，定期 PSA 與 DRE 檢查，視需要得重覆切片檢查) 或放射線治療±4-6 個月前置/伴隨/輔助性荷爾蒙治療±組織插腫近接治療
		≧10 年	根除性攝護腺切除手術＋骨盆腔淋巴結(切除)擴清術 或放射線治療±4-6 個月前置/伴隨/輔助性荷爾蒙治療±組織插腫近接治療
	非常高/高度復發風險 **T3a 期或** Gleason score 8-10 分 或 PSA＞20 ng/ml	放射線治療 ±2-3 年前置/伴隨/輔助性荷爾蒙治療 或根除性攝護腺切除手術+骨盆腔淋巴結(切除)擴清術(選擇性患者)
局部侵犯性腫瘤	T3b-4 期	放射線治療 ±2-3 年前置/伴隨/輔助性荷爾蒙治療 或根除性攝護腺切除手術+骨盆腔淋巴結(切除)擴清術(選擇性患者) 或(長期)荷爾蒙治療
轉移性腫瘤	任何 T 期,N1,M0	(長期)荷爾蒙治療或放射線治療+荷爾蒙治療
	任何 T 期, 任何 N 期,M1	(長期)荷爾蒙治療+緩解性放射治療

※2012 年預期餘命依據內政部的男性簡易生命表為 76.4 歲

擴散性疾病 全身性治療 全身性救援治療



ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER



[j] See Principles of Androgen Deprivation Therapy (PROS-E).

[p] Frequency of imaging should be based on individual risk, age, PSA velocity, Gleason score, and overall health.

[q] See Principles of Chemotherapy/Immunotherapy (PROS-F).

Content :
overview of the novel treatment for CRPC

Androgen deprivation therapy

Androgen Synthesis Inhibitors – Abiraterone

Androgen receptor antagonist - Enzalutamide

Immunotherapy

Sipuleucel-T

Chemotherapy

Docetaxel, Cabazitaxel, Mitoxantrone

Radiopharmaceutical

α- emitting agent: Radium-223

Abiraterone

“The androgen signaling pathway is still important in mCRPC.”

Philip W. Kantoff

MD, Director of The Lank Center for Genitourinary Oncology and Chief of Solid Tumor Oncology at the Dana-Farber Cancer Institute/ Brigham & Women’s Hospital, Boston

Abiraterone

a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450c17 (CYP17, 17-α-hydroxylase and C17, 20-lyase), a critical enzyme in testosterone synthesis in the adrenal glands, in the testes, and within the prostate tumor.

It is more potent and less toxic than ketoconazole.

FDA approved in April 2011 for mCRPC following docetaxel treatment.

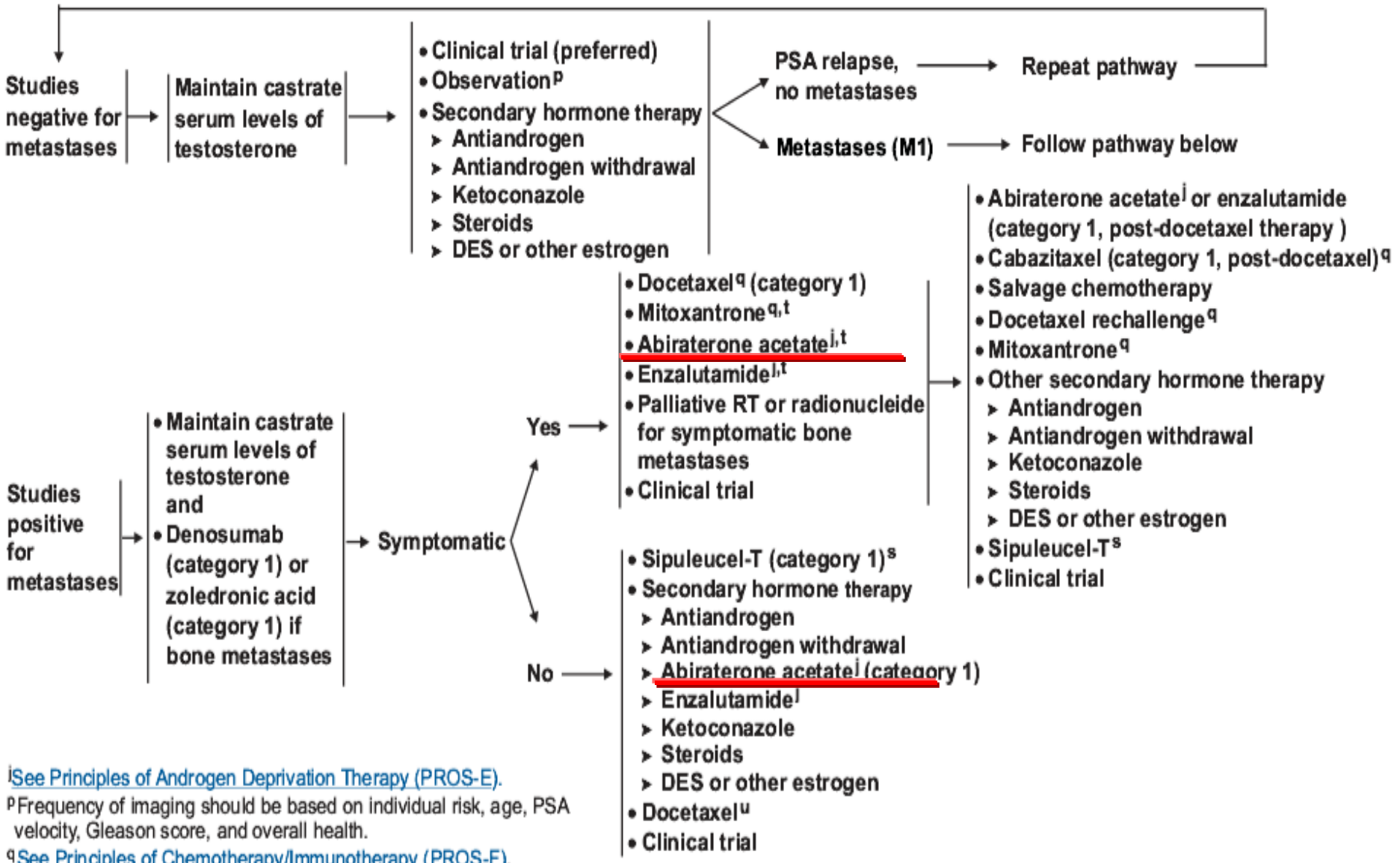
Trials

COUGAR 301 trial (N=1158):
- abiraterone plus prednisone in patients with mCRPC previously treated with docetaxel
- improve overall survival (OS) by almost 4 months (HR: 0.646; *P* <.0001)

COUGAR-302 trial (N = 1082):
- abiraterone was given before chemotherapy
- delayed the time to progression by 50%
- a trend toward improved OS

Data from 2013 Genitourinary Cancers Symposium:
- a near doubling in radiographic PFS, from 8.3 to 16.5 months (HR, 0.53; *P* <.0001)
- a trend toward improved OS, from 30.1 to 35.3 months with the combination (HR, 0.79; *P* =.0151)

ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER



[j] See Principles of Androgen Deprivation Therapy (PROS-E).

[p] Frequency of imaging should be based on individual risk, age, PSA velocity, Gleason score, and overall health.

[q] See Principles of Chemotherapy/Immunotherapy (PROS-F).

NCCN guidelines version 2.2013

principles of ADT: secondary hormonal manipulation

- Abiraterone (1000 mg daily on an empty stomach) and low dose prednisone (5 mg BID) improved radiographic progression-free survival (rPFS), time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration of performance status in a randomized controlled trial compared to prednisone alone. There was a trend toward improvement in overall survival. Use of abiraterone and prednisone in this setting is a category 1 recommendation. The side effects of abiraterone that require on-going monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.
- In uncontrolled studies of docetaxel-naive men, enzalutamide resulted in significant PSA declines, but the use of enzalutamide in the setting is category 2A until effects on overall survival or rPFS from the on-going randomized, controlled trial in this setting are reported. The side effects of enzalutamide that require long-term monitoring include fatigue, diarrhea, hot flashes, headache, and seizures (reported in 0.9% of men on enzalutamide).
- Both randomized trials of abiraterone and enzalutamide in the pre-docetaxel setting were conducted in men who had no or minimal symptoms due to metastatic CRPC. How these agents compare to docetaxel for pain palliation in this population of patients is not clear. However, both drugs have palliative effects in the post docetaxel setting and are suitable options for men who are not good candidates to receive docetaxel.
- In the post-docetaxel CRPC population, enzalutamide and abiraterone plus prednisone have been shown to extend survival in randomized, controlled trials. Therefore, each agent has a category 1 recommendation.
- Evidence-based guidance on the sequencing of these agents in either pre- or post-docetaxel remains unavailable.

Enzalutamide (MDV3100)

Androgen-receptor signaling is the key therapeutic target throughout the clinical spectrum of prostate cancer

Enzalutamide *vs* Current Antiandrogen Agents

Inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment.

greater affinity for the receptor.

Induces tumor shrinkage in xenograft models (in which conventional agents only retard growth).

No known agonistic effects.

Approved by FDA on 31 August 2012

Tran C, Ouk S, Clegg NJ, et al. . Science 2009;324:787-90.
Morris MJ, Basch EM, Wilding G, et al . Clin Genitourin Cancer 2009;7: 51-7.

AFFIRM

A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100

Patient Inclusion:
- histologically or cytologically confirmed
- Testosterone <50 ng per deciliter [1.7 nmol per liter]
- previous treatment with docetaxel
- progressive disease defined according to PCWG2 criteria three increasing values PSA or radiographically confirmed progression

2:1

- Enzalutamide (n=800) 160mg (4x40mg)
- Placebo (n=399)

The primary end point: **overall survival**

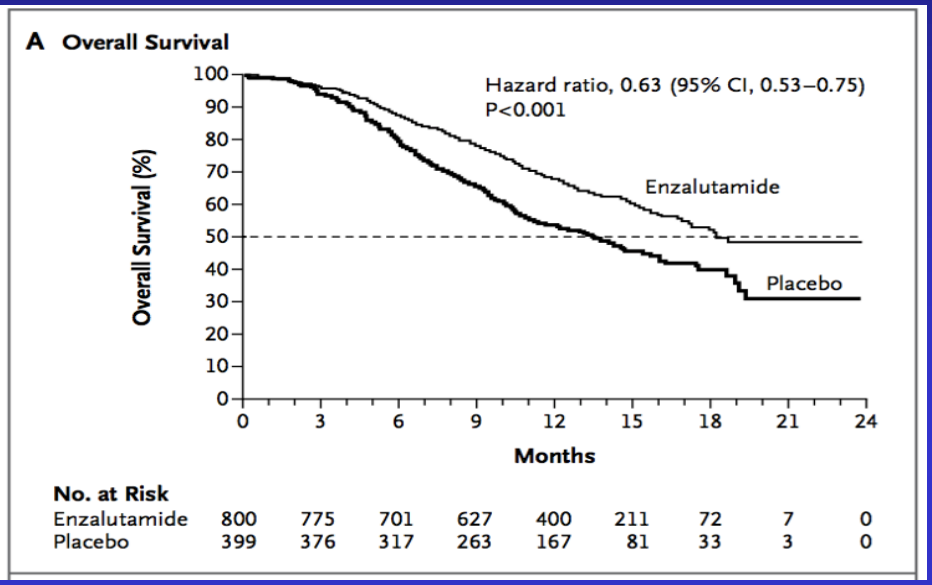
Secondary end points:

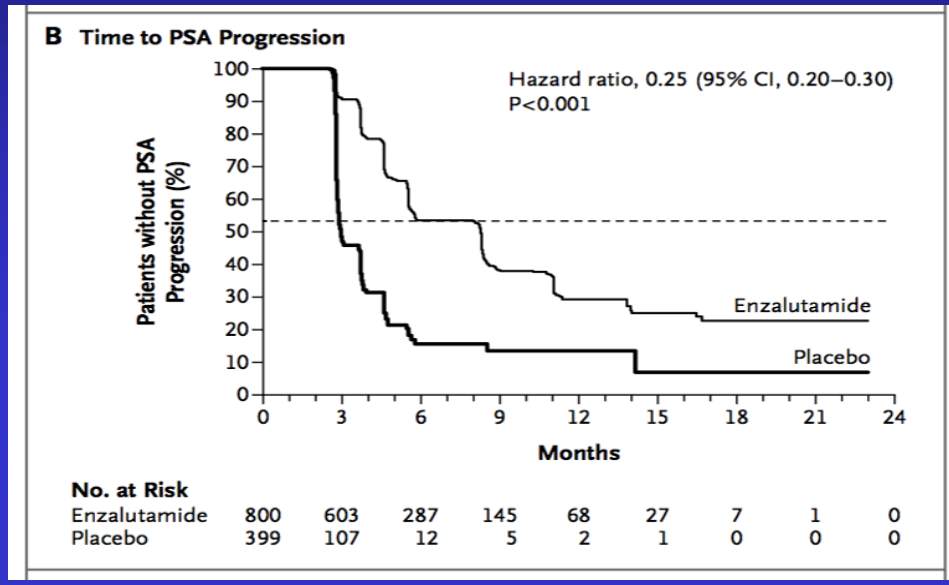
measures of response (in the PSA level, in soft tissue, and in the quality-of-life score)
.time to PSA progression
.radiographic progression-free survival
.time to the first skeletal-related event
.Safety

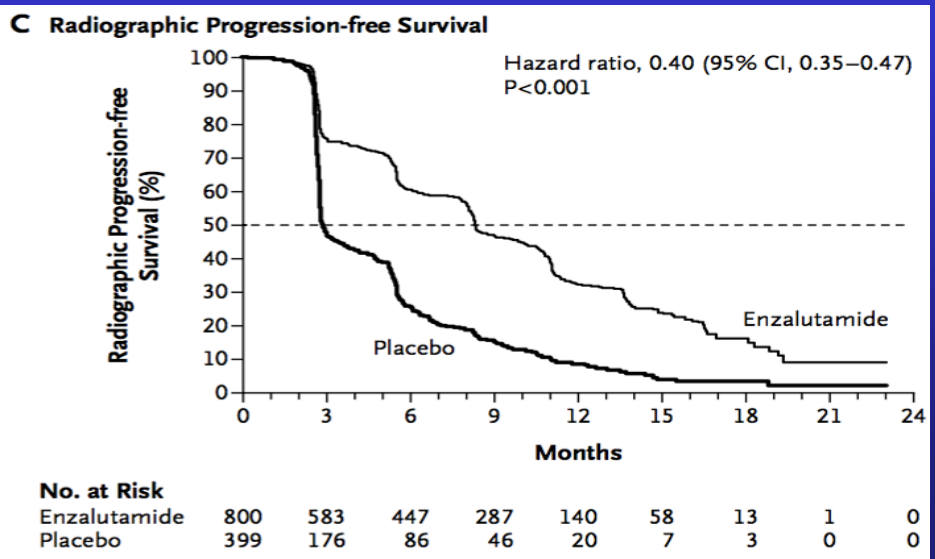
September 2009 through November 2010

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 27, 2012 VOL. 367 NO. 13

Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy







The OS endpoint was reached, for a difference of 4.8 months (HR, 0.63; *P* <.0001)

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

0.9% at FU

* 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.

PREVAIL Trial:
Enzalutamide for chemo-naïve CRPC

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail

Text Size

A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer (PREVAIL)

This study is ongoing, but not recruiting participants.

Sponsor:
Medivation, Inc.

Collaborator:
Astellas Pharma Inc

Information provided by (Responsible Party):
Medivation, Inc.

ClinicalTrials.gov Identifier:
NCT01212991

First received: September 29, 2010
Last updated: January 29, 2013
Last verified: January 2013
History of Changes

Descriptive Information

Brief Title ICMJE	A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer
Official Title ICMJE	A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy
Brief Summary	The purpose of this study is to determine the benefit of MDV3100 versus placebo as assessed by overall survival and progression-free survival in patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy but not yet received chemotherapy.

NCCN guidelines version 2.2013

principles of ADT: secondary hormonal manipulation

- Abiraterone (1000 mg daily on an empty stomach) and low dose prednisone (5 mg BID) improved radiographic progression-free survival (rPFS), time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration of performance status in a randomized controlled trial compared to prednisone alone. There was a trend toward improvement in overall survival. Use of abiraterone and prednisone in this setting is a category 1 recommendation. The side effects of abiraterone that require on-going monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.
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Sipuleucel-T

Rationale of Immunotherapy in CaP:

Prostate cancer provides a test system to determine the efficacy of vaccines

 # A Tumor that grows relatively slowly.

 # Recurrence is often diagnosed early and easy biochemical progression (PSA doubling time, PSA velosity, PSA> 02.ng/ml, PSA elevation > 2 excuative test...).

 # Various specific antigens have been identified and characterized (PAP...).

 # Vaccines can be used with a good safety profile combined with anti-androgen therapy, chemotherapy, or radiotherapy.

Cristina Suarez et al. Role of Immunotherapy in Castration-Resistant Prostate Cancer (CRPC). BJU International, 2013.

New studies based on immunotehrapy

Sipuleucel-T(APC 8015, Provenge)

GVAX

PROSTVAC-VF Vaccine(PSA-TRICOM)

Modified vaccinia Ankara(MVA)-MUC1-interleukin 2 (TG4010)

Ipilimumab (Anti-cytotoxic T-lymphocyte Antigen 4, MDX-010)

Prostate-specific Membrane Antigen (PSMA) and Antibodies (J5091)

Anti-programmed Death 1 (PD-1; MDX-1106/BMS-936558/ONO-4538)

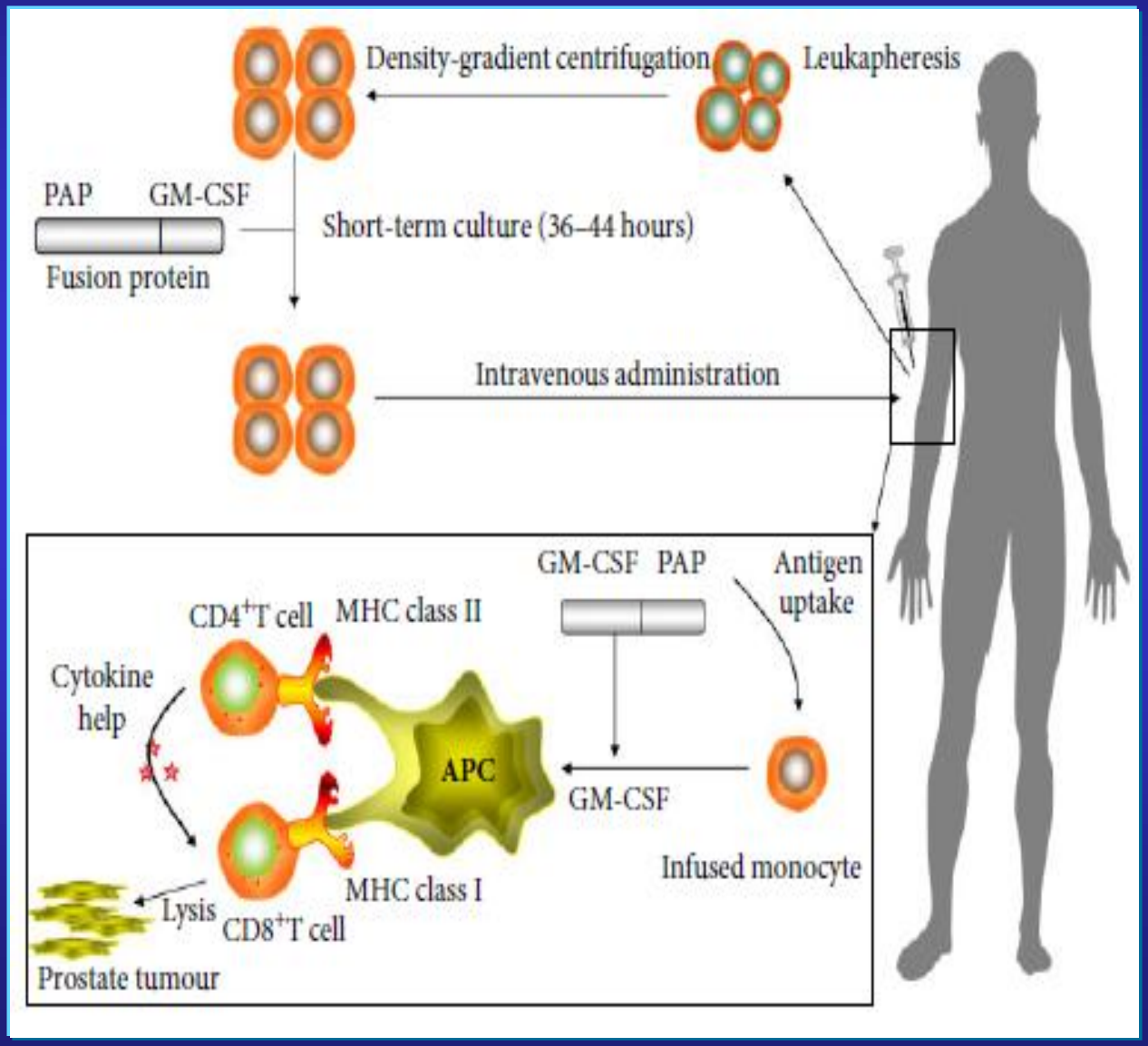
Table 1 Completed clinical trials of immunotherapy for patients with metastatic castration-resistant prostate cancer.

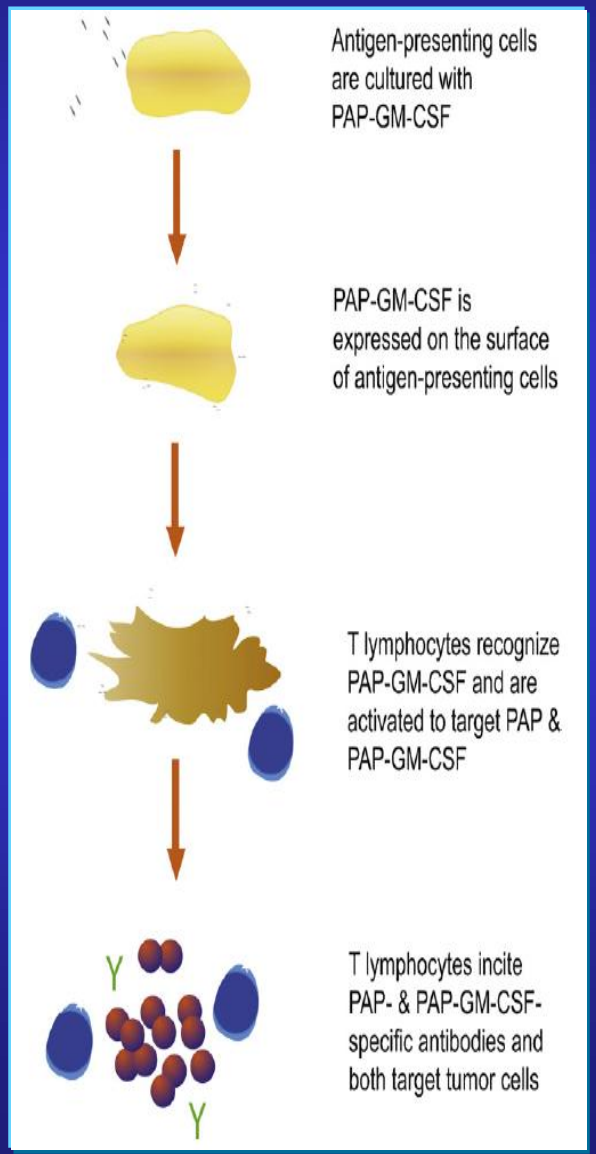
Agent	Phase	*n*	Setting	Target antigen	Platform	Comparison treatment	Time to progression	OS
Sipuleucel-T	III	127	Asymptomatic metastatic CRPC	PAP/GM-CSF fusion	Cultured autologous PMBCs	Placebo (autologous cells)	11.7 vs 10 weeks (HR 1.45, 95% CI 0.99–2.11; $P = 0.052$)	25.9 vs 21.4 months (HR 1.70, 95% CI 1.13–2.56; $P = 0.01$)
Sipuleucel-T	III	512	Asymptomatic metastatic CRPC	PAP/GM-CSF fusion	Cultured autologous PMBCs	Placebo (autologous cells)	HR 0.951, 95% CI 0.77–1.17; $P = 0.628$	25.8 vs 21.7 months (HR 0.775, 95% CI 0.614–0.974; $P =$ 0.032)
GVAX	III	626	Asymptomatic metastatic CRPC	Allogenic tumour lines	GM-CSF transduced cell lines	Docetaxel/ prednisone	–	20.7 vs 21.7 mo (HR 1.03, 95% CI 0.83–1.28; $P = 0.78$)
GVAX plus docetaxel	III	408	Symptomatic metastatic CRPC	Allogenic tumour lines	GM-CSF transduced cell lines	Docetaxel/ prednisone	–	12.2 vs 14.1 month (HR 1.70, 95% CI 1.15–2.53; $P = 0.008$)
PROSTVAC-VF	II	125	Minimally symptomatic metastatic CRPC	PSA	Vaccinia-fowl pox	Control Vector	3.8 vs 3.7 months (HR 0.884, 95% CI 0.568–1.375; $P = 0.6$)	25.1 vs 16.6 months (HR 0.56, 95% CI 0.37–0.85; $P = 0.006$)

PMBCs, peripheral blood mononuclear cells.

Mechnism of Sipuleucel-T

autologous APC loaded *ex vivo with a recombination fusion protein called PA2024 that consists of prostatic acid phosphatase linked to GM-CSF.*





Phase III Trial of Sipuleucel-T vs. Placebo in mCRPC

On 29 April 2010, approved by the FDA as the first immuno-thetapeutic agent for asymptomatic or minimally symptomatic mCRPC.

Integrated analysis of D9901 and D9902A:

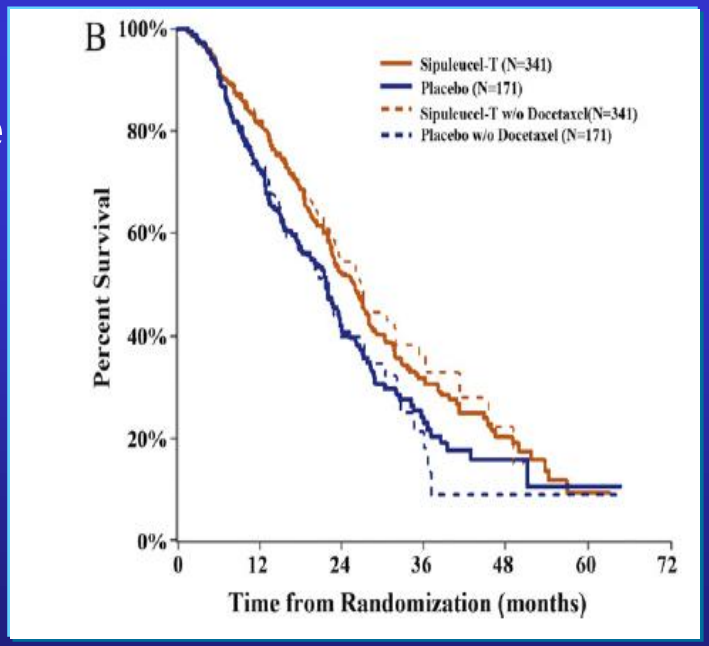
- 225(127+98) pts; sipuleucel-T (147 patients) or placebo (78); time to progression as primary endpoint
- a median benefit in OS of 4.3 months (23.2 vs 18.9 months)
- 33% reduction in the risk of death [HR: 1.50, *P* = 0.011]
- the vaccine was well tolerated
- the most common side-effects were flu-like symptoms

Cristina Suarez et al. Role of Immunotherapy in Castration-Resistant Prostate Cancer (CRPC). BJU International, 2013.

IMPACT trial (D9902B)

IMPACT trial (D9902B):

- randomly assigned 512 patients to sipuleucel-T (341 patients) or placebo (171) in a 2:1 ratio.
- OS was the primary endpoint.
- reduction of 22% in the risk of death as compared with the placebo group (HR 0.78; *P*=0.03)
- an increase of 4.1 month in the OS for the sipuleucel-T group (25.8 vs 21.7 months).
- 36-month survival probability was 31.7% and 23.0%
- no benefit in PFS, PSA
- AEs: chills, fever, and headache.



Guru Sonpavde et al. The Role of Sipuleucel-T in Therapy for Castration-Resistant Prostate Cancer: A Critical Analysis of the Literature. EUROPEAN UROLOGY 6 1 (2 0 1 2) 6 3 9 – 6 4 7

Issues reamins further studies

Optimal patient selection for sipuleucel-T and the development of tailored immunotherapy

Biochemically recurrent castration-sensitive disease

Immune response criteria as end points for evaluating immunotherapy

Sipuleucel-T in the context of need for cost-effective agents

The combination and proper sequencing of sipuleucel-T with other newly approved agents.

Cabazitaxel

Advanced Prostate Cancer Management

Metastatic hormone-sensitive prostate cancer

Metastatic castration-resistant 1st line

Palliative/supportive care
Rechallenge with docetaxel
Novel agents

LHRH analogues

Antiandrogens

LHRH antagonist

DOCETAXEL TAXOTERE®

Docetaxel Improves:

- Overall survival
- Quality of life
- Pain control
- PSA response

Survival benefit vs Mitoxantrone since 2004

Metastatic Castration-resistant 2nd line ?

Cabazitaxel

Oudard S, et al. *Eur J Cancer* 2011; 47(Suppl 1): Abst 7.049

Cabazitaxel: A Next Generation Taxane

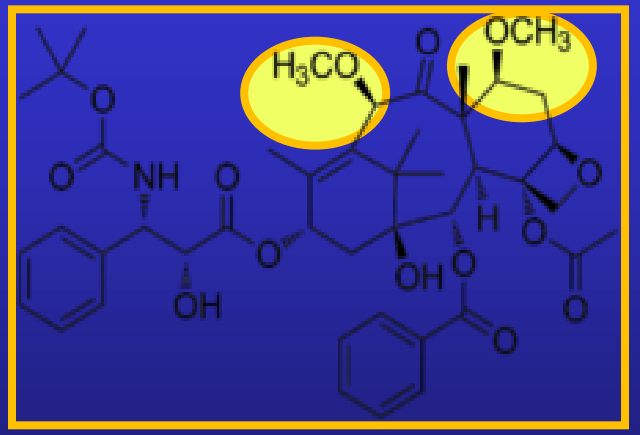
Selected from over 450 docetaxel analogues for its ability to overcome taxane resistance

a semi-synthetic taxane that is potent against taxane-sensitive and -resistant cell lines.

The first agent to be tested against an active control (mitoxantrone) in second line mCRPC

Docetaxel

Cabazitaxel



1. Sartor O, el al. *Clin Genitourin Cancer* 8(1):23-28, 2010.
2. Mita AC, et al. *Clin Can Res*. 15:723-730, 2009

Phase III TROPIC Study: 146 Sites in 26 Countries

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen
(n=755)

Stratification factors
ECOG PS (0, 1 vs 2) • Measurable versus non-measurable disease

Cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles
(n=378)

Mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles
(n=377)

*Oral prednisone/prednisolone: 10 mg daily.

Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

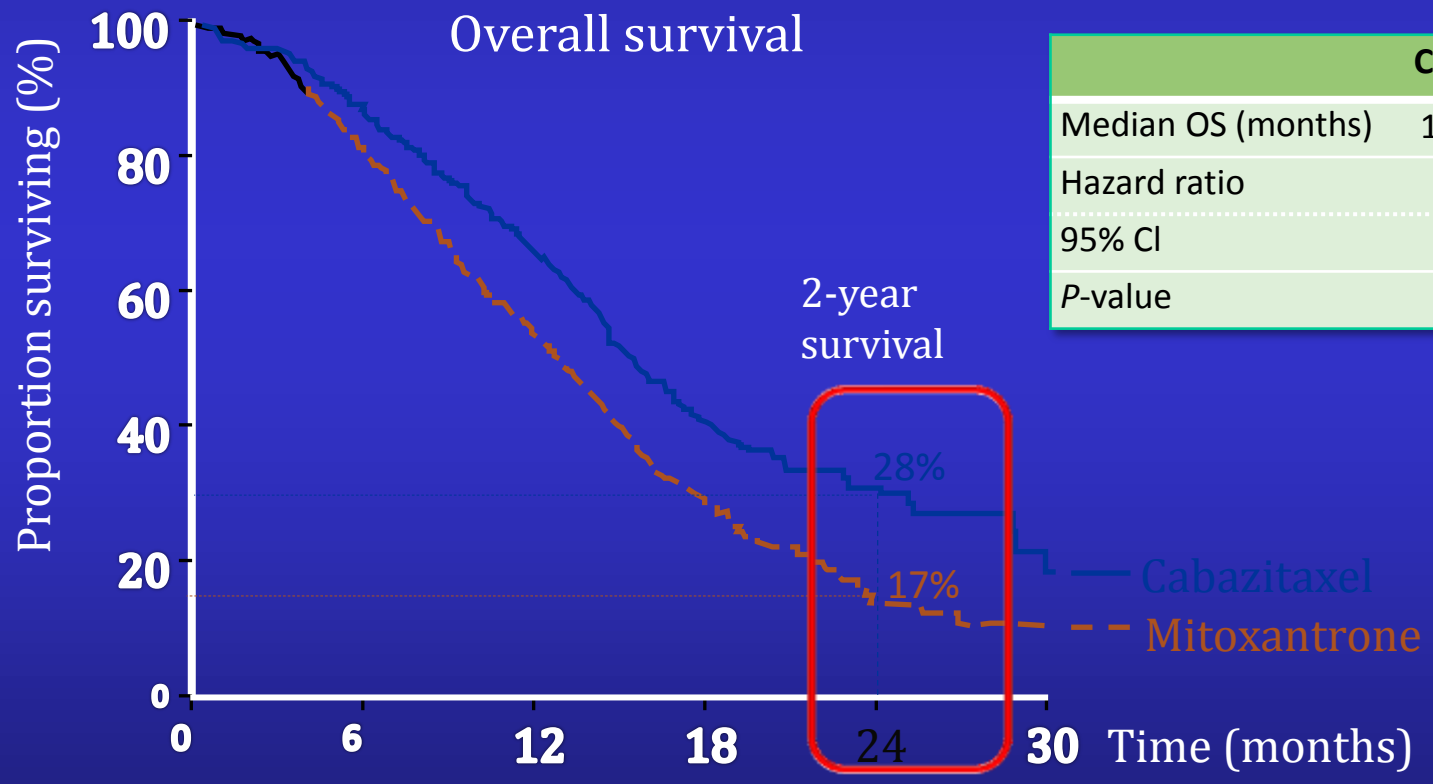
Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

N=720 patients (n=360 in each arm), maximum treatment duration 10 cycles,
511 events to detect 25% reduction in hazard ratio, 90% power, 2 sided 5% alpha level

Primary Endpoint: Overall Survival

JEVTANA® significantly extends overall survival vs an active comparator, mitoxantrone

Survival benefit sustained at 2 years with JEVTANA®



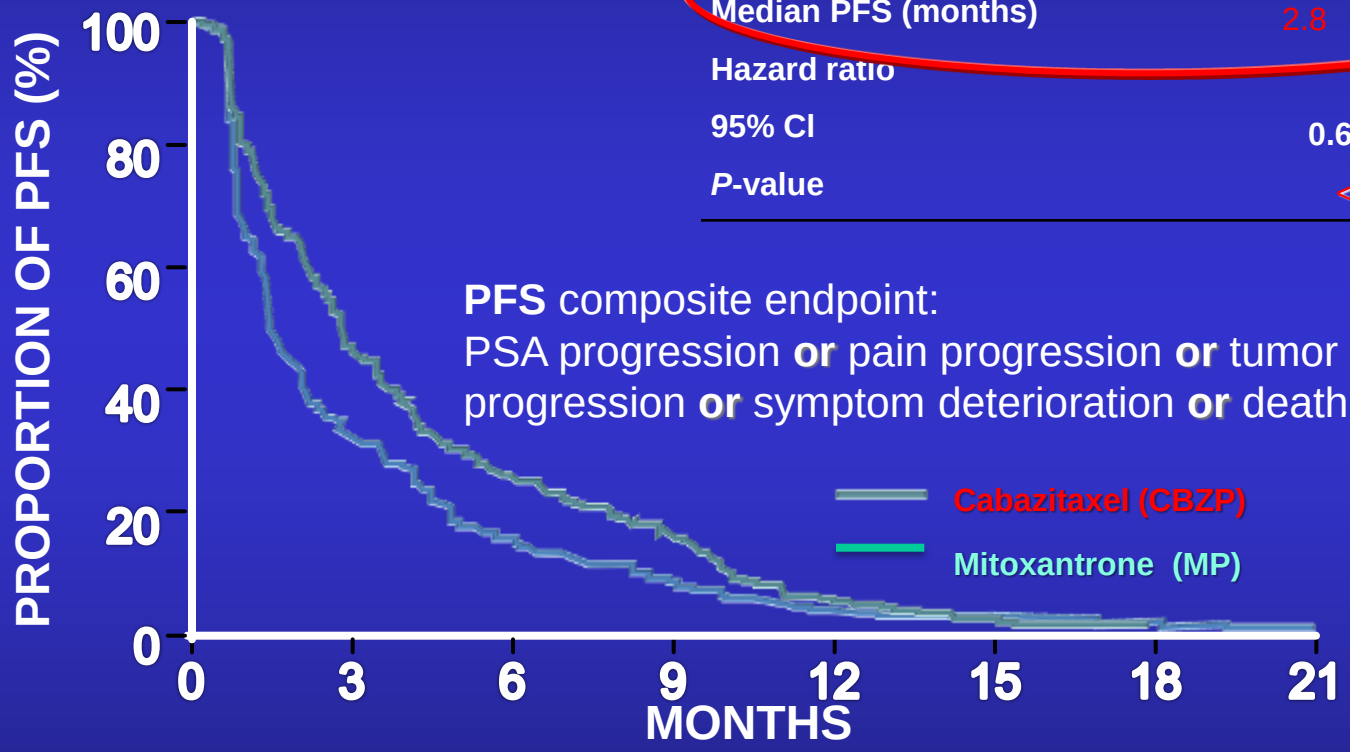
	CBZP	MP
Median OS (months)	15.1	12.7
Hazard ratio	0.70	
95% CI	0.59–0.83	
P-value	<.0001	

28% of patients alive at 2 years with cabazitaxel vs 17% with mitoxantrone

TROPIC: Progression Free Survival

25% Reduction in Risk of Progression

	CBZP	MP
Median PFS (months)	2.8	1.4
Hazard ratio	0.74	
95% CI	0.64 - 0.86	
P-value	<.0001	

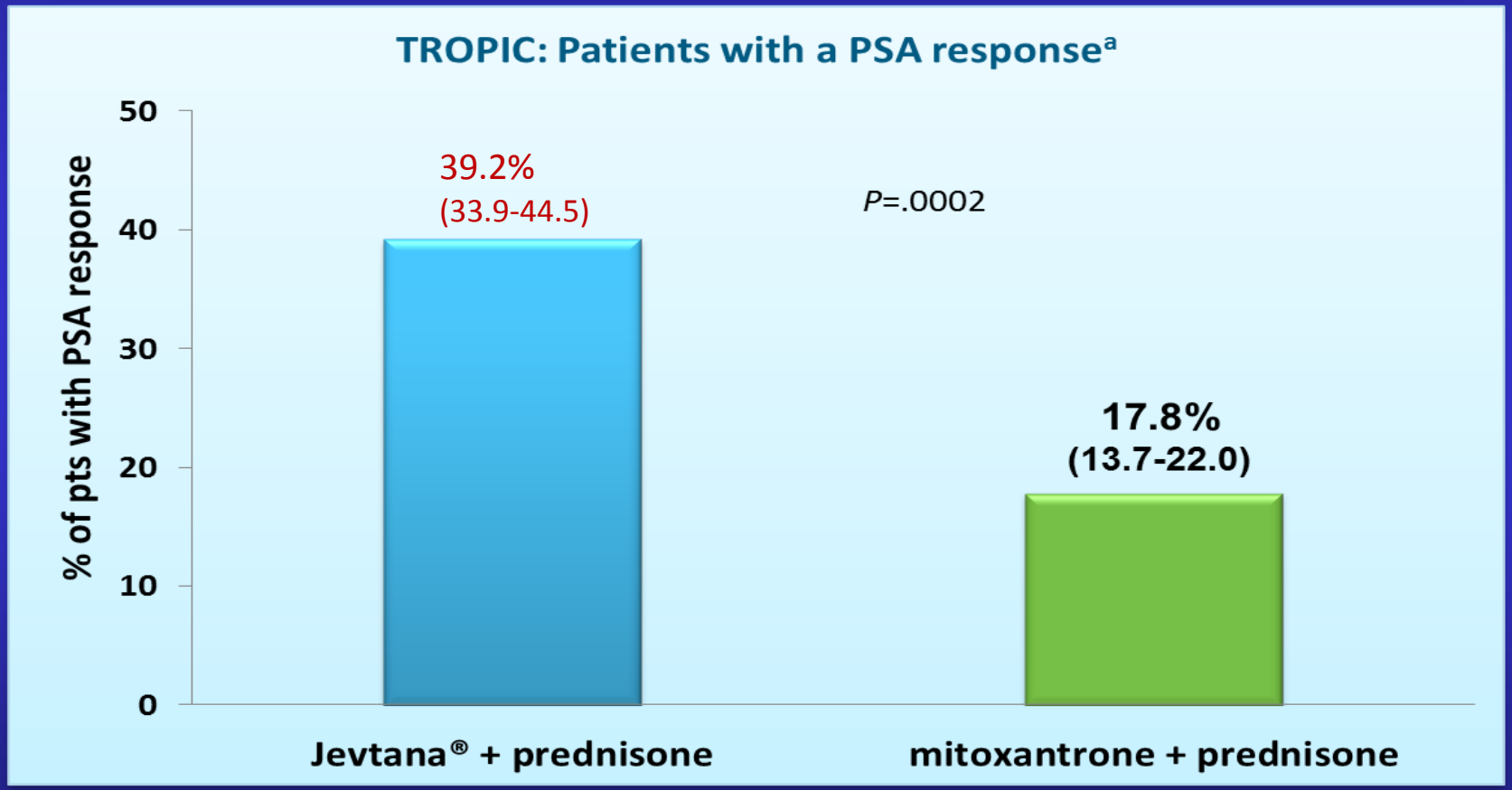


Number at risk								
CBZP	378	168	90	52	15	4	0	0
MP	377	115	52	27	9	6	4	2

de Bono JS et al. *Lancet* 376(9747):1147-1154, 2010

TROPIC: PSA Response Rates

The PSA response with JEVTANA® was more than double that seen with mitoxantrone



[a] Established only for pts with a serum PSA concentration of 20 ug/L or more at baseline, confirmed by a repeat PSA measurement after at least 3 weeks.

de Bono JS et al. Lancet 2010; 376: 1147-54.

Summary of Non-hematologic AEs

Nonhematologic AEs[a]	Cabazitaxel + prednisone (n=371)		Mitoxantrone + prednisone (n=371)	
	All Grades, n (%)	Grades 3/4, n (%)	All Grades, n (%)	Grades 3/4, n (%)
Diarrhea	**173 (47)**	**23 (6.2)**	39 (11)	1 (0.3)
Fatigue	**136 (37)**	**18 (5)**	102 (27)	11 (3)
Asthenia	**76 (21)**	**17 (5)**	46 (12)	9 (2)
Back pain	60 (16)	14 (4)	45 (12)	11 (3)
Nausea	127 (34)	7 (2)	85 (23)	1 (<1)
Vomiting	84 (23)	7 (2)	38 (10)	0
Hematuria	62 (17)	7 (2)	14 (4)	2 (1)
Abdominal pain	43 (12)	7 (2)	13 (4)	0
Pain in extremity	30 (8)	6 (2)	27 (7)	4 (1)
Dyspnea	44 (12)	5 (1)	17 (5)	3 (1)
Constipation	76 (20)	4 (1)	57 (15)	2 (1)
Pyrexia	45 (12)	4 (1)	23 (6)	1 (<1)
Arthralgia	39 (11)	4 (1)	31 (8)	4 (1)
Urinary tract infection	27 (7)	4 (1)	11 (3)	3 (1)
Pain	20 (5)	4 (1)	18 (5)	7 (2)
Bone pain	19 (5)	3 (1)	19 (5)	9 (2)

[a] Events ≥grade 3 severity in ≥1% of patients in either treatment group. Toxic effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

de Bono JS et al. *Lancet* 376(9747):1147-1154, 2010

Summary of Hematologic AEs

Hematologic AEs[a]	Cabazitaxel + prednisone (n=371)		Mitoxantrone + prednisone (n=371)	
	All Grades, n (%)	Grades 3/4, n (%)	All Grades, n (%)	Grades 3/4, n (%)
Neutropenia	347 (94)	303 (82)	325 (88)	215 (58)
Febrile neutropenia	–	28 (7.5)	–	5 (1.3)
Anemia	361 (97)	39 (11)	302 (81)	18 (5)
Leukopenia	355 (96)	253 (68)	343 (92)	157 (42)
Thrombocytopenia	176 (47)	15 (4)	160 (43)	6 (2)

[a] Events ≥grade 3 severity in ≥1% of patients in either treatment group. Toxic effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

 # side effect management recommendations

- Follow dose modifications

- Follow ASCO guidelines for prophylactic and therapeutic use of G-CSF

-Treat with rehydration and anti-diarrheal medications as needed

de Bono JS, Oudard S, Ozguroglu M, et al. *Lancet*. 376(9747):1147-1154, 2010
Smith TJ, Khatcheressian J, Lyman GH, et al. *J Clin Oncol*. 24(19):3187-3205, 2006
Cabazitaxel US Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC; June 2010

NCCN guidelines version 2.2013
principles of chemotherapy

- Men who have failed docetaxel-based chemotherapy should be encouraged to participate in clinical trials. However, cabazitaxel with prednisone has been shown in a randomized phase 3 study to prolong overall survival, progression-free survival, and PSA and radiologic responses when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second-line setting. Selection of patients without severe neuropathy and adequate liver, kidney, and bone marrow function is necessary, given the high risk of neutropenia and other side effects in this population, with consideration of prophylactic granulocyte growth factor injections.
- Mitoxantrone has not demonstrated a survival improvement in this post-docetaxel setting but remains a palliative therapeutic option, particularly in men who are not candidates for cabazitaxel therapy. No chemotherapy regimen to date has demonstrated improved survival or quality of life following cabazitaxel, and trial participation should be strongly encouraged. Outside of a clinical trial, several systemic agents have shown palliative benefits in single-arm studies. Treatment decisions should be individualized based on comorbidities and functional status. Finally, for patients who have not demonstrated definitive evidence of progression on prior docetaxel therapy, retreatment with this agent can be attempted.

EAU guidelines:

Cabazitaxel should be considered as an effective second-line treatment following docetaxel

-Level of evidence A-

Radium -223 dichloride (alpharadin)

發現人：皮耶居禮(Piere Curie)，瑪麗居禮(Maria Sklodowska Curie)

年代：1898年發現鐳元素(Radium)以及釙元素(Polonium)

性質：鐳元素放射能爲鈾的六十倍，釙元素放射能爲鈾的四百倍

價值：於1903年獲得諾貝爾物理獎，並於1911年再獲得諾貝爾化學獎

Background and Rationale

> 90% of patients with mCRPC have radiologic evidence of bone metastases

Skeletal-related events (SREs):

- spinal cord compression
- pathological fracture
- need for surgery
- radiotherapy

Bone metastases are a major cause of death, disability, decreased quality of life, and increased treatment cost

Current bone-targeted therapies have not been shown to improve survival

- Zoledronic acid (ZOMETA)
- Denazumab (XGEVA)

Radioisotopes for palliation of symptomatic bone pain

- β-emitting : strontium-89 , samarium-153 (FDA-approved)
- α-emitting agent: Radium-223

1. Tannock et al. *N Engl J Med.* 2004;351:1502-1512.
2. Lipton. *Semin Oncol.* 2010;37:S15-S29.
3. Lange and Vasella. *Cancer Metastasis Rev.* 1999;17:331-336.

Radium-223: mechanism

Radium-223 acts as a calcium mimic element.

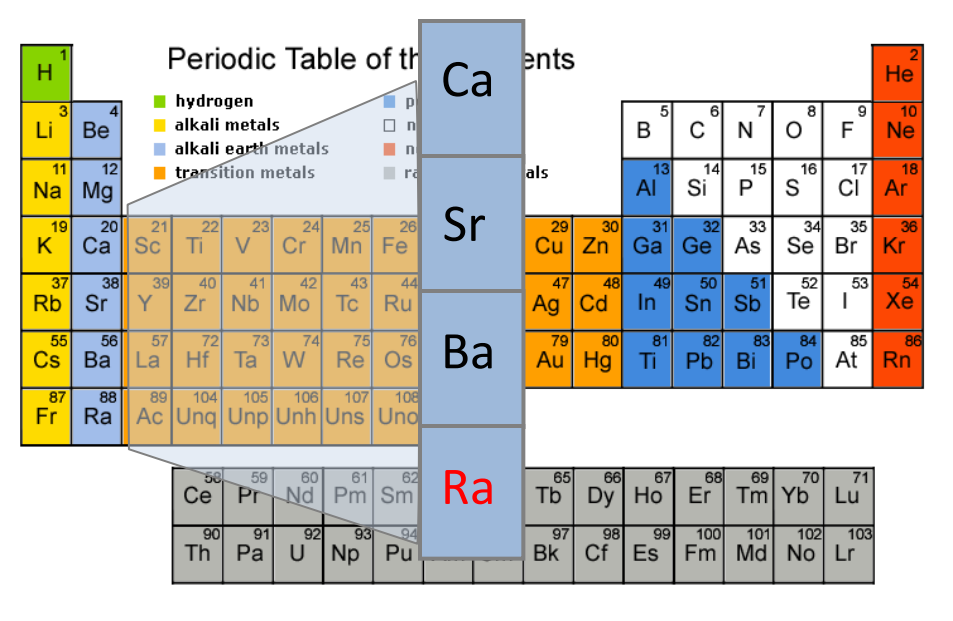
Naturally targets new bone growth in and around bone metastases.

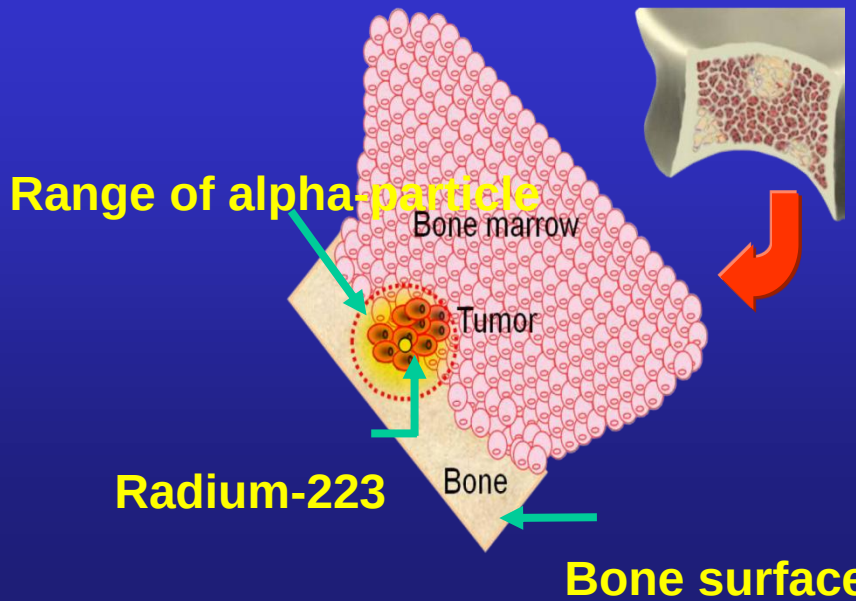
Radium-223 is excreted by the small intestine.

Alpha-particles induce double-strand DNA breaks in adjacent tumour cells[1]

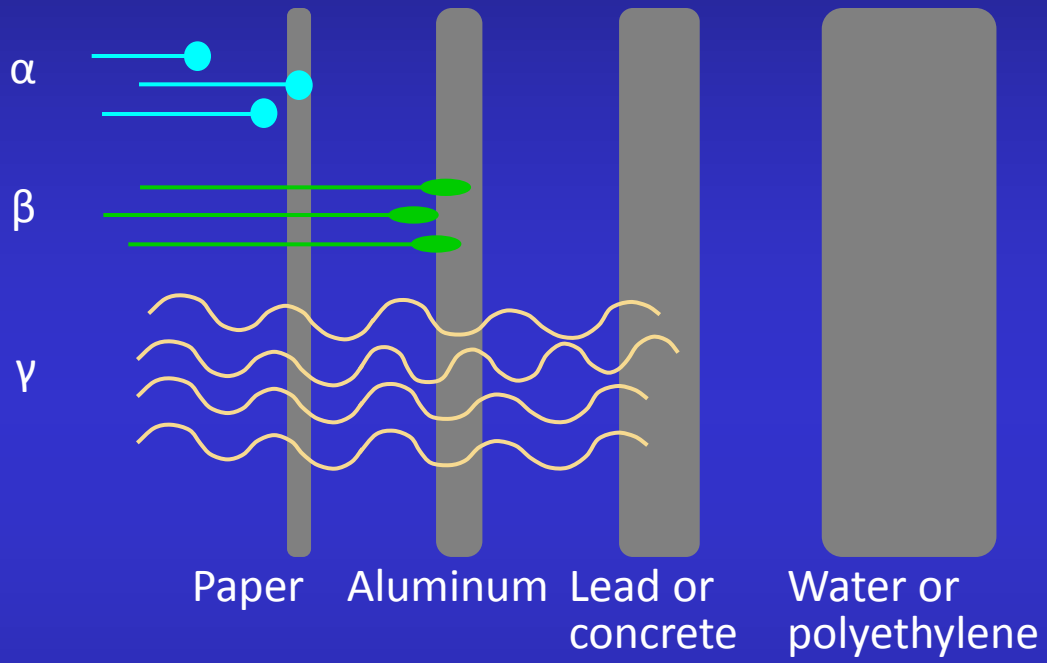
Short penetration of alpha emitters (2-10 cell diameters) = highly localised tumour cell killing and minimal damage to surrounding normal tissue

1. Perez et al. *Principles and Practice of Radiation Oncology.* 5th ed. Lippincott Williams & Wilkins; 2007:103.





Penetration of Ionizing Radiation Types

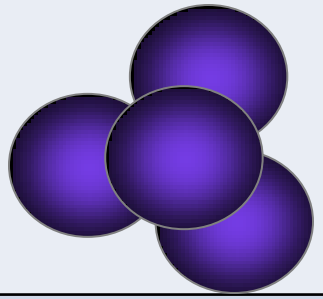


α radiation consists of helium (^{4}He) nuclei and is stopped by a sheet of paper or skin

β radiation, consisting of electrons, is halted by an aluminum plate or plastic

γ radiation, consisting of energetic photons, is attenuated by dense material

Differences Between α and β Particles

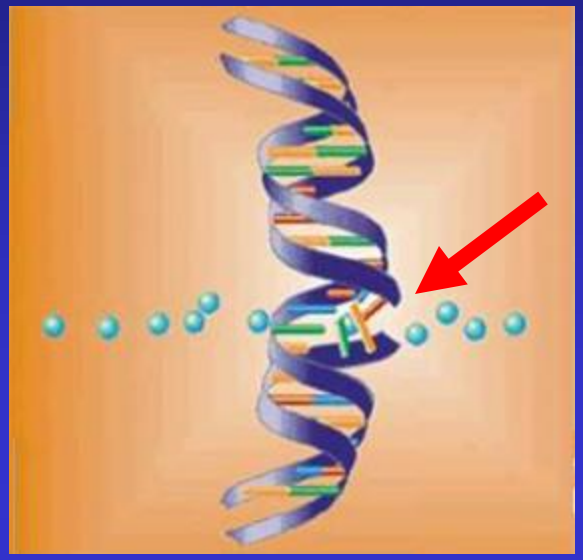
	α	β
Example emitters	Radium-223	Strontium-89, Samarium-153
Size		
Relative particle mass	**7000**	**1**
Initial energy (MeV)	**3–8**	**0.01–2.5**
Range in tissue (μm)	**40–90**	**50–5000**
LET (KeV/μm)	**60–230**	**0.015–0.4**
Charge	**+2**	**–1**
Ion pairs/μm	**2000–7000**	**5–20**
DNA hits to kill cell	**1–5**	**100–1000**

LET, linear energy transfer

Henriksen G, et al. J Nucl Med. 2003;44(2):252-9

Alpha-particles Cause Lethal Double-strand DNA Breaks

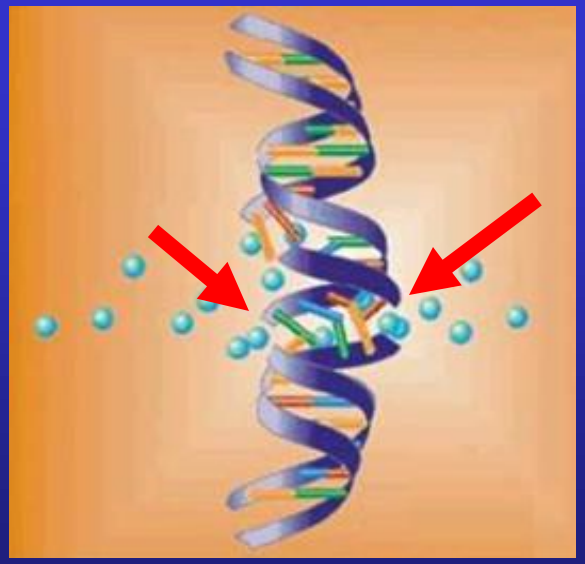
β-emitters:



- **Low-LET β radiation produces single-strand DNA breaks**
- Single-strand breaks are easily repaired using the opposite strand as a template
- Single-strand breaks are less likely to induce cell death

α-emitters:

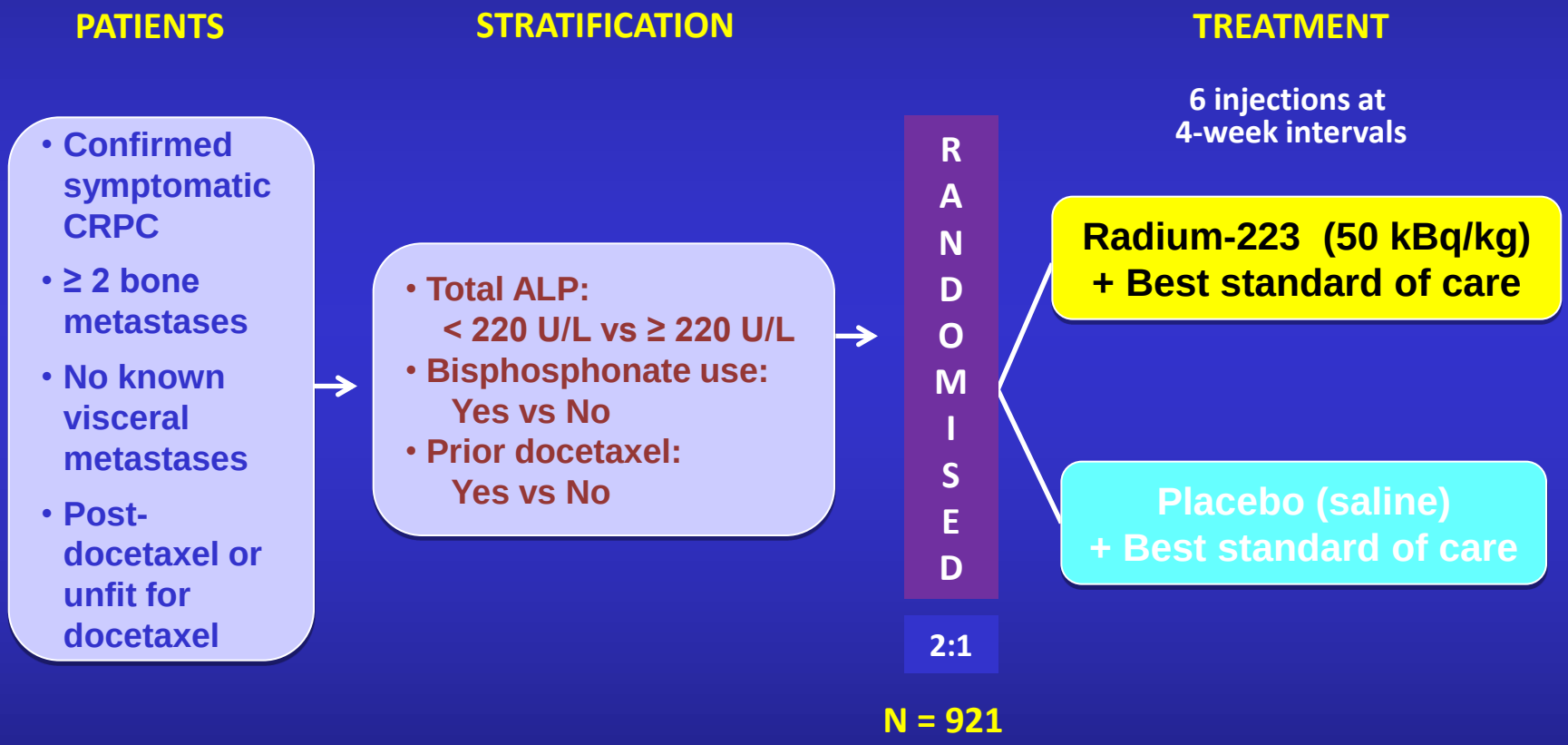
- **High-LET α particles produce double-strand DNA breaks**
- Double-strand breaks are difficult to repair
- Failure to repair double-strand breaks leads to apoptosis (programmed cell death)
- Mis-repaired double-strand breaks create chromosomal aberrations that result in mitotic cell death



LET, linear energy transfer

Bruland OS, et al. Clin Cancer Res. 2006;12(20):6250s–57s; Hall EJ and Giaccia AJ. Radiology for the Radiologist. 6th Ed. Philadelphia: J. B. Lippincott William & Wilkins 2006

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design



Planned follow-up is 3 years

Clinicaltrials.gov identifier: NCT00699751

ALSYMPCA

 # Primary Endpoint: Overall survival (OS)

 # Secondary Endpoints

Time to first SRE ; Time to total ALP progression ; Total ALP response
Total ALP normalization ; Time to PSA progression ; Safety; Quality of life

 # Planned interim analysis (IA)

314 events from 809 patients randomized at the time of the IA; Cut-off October 2010
June 3, 2011 the Independent Data Monitoring Committee (IDMC) recommended stopping the trial early due to evidence of a significant treatment benefit

 # Updated analysis

528 events from all 921 patients randomized to the study
Updated analysis conducted *prior to placebo patients crossing over to Radium-223 and when Radium-223 patients had completed treatment;* Cut-off July 2011

ALSYMPCA Updated Analysis

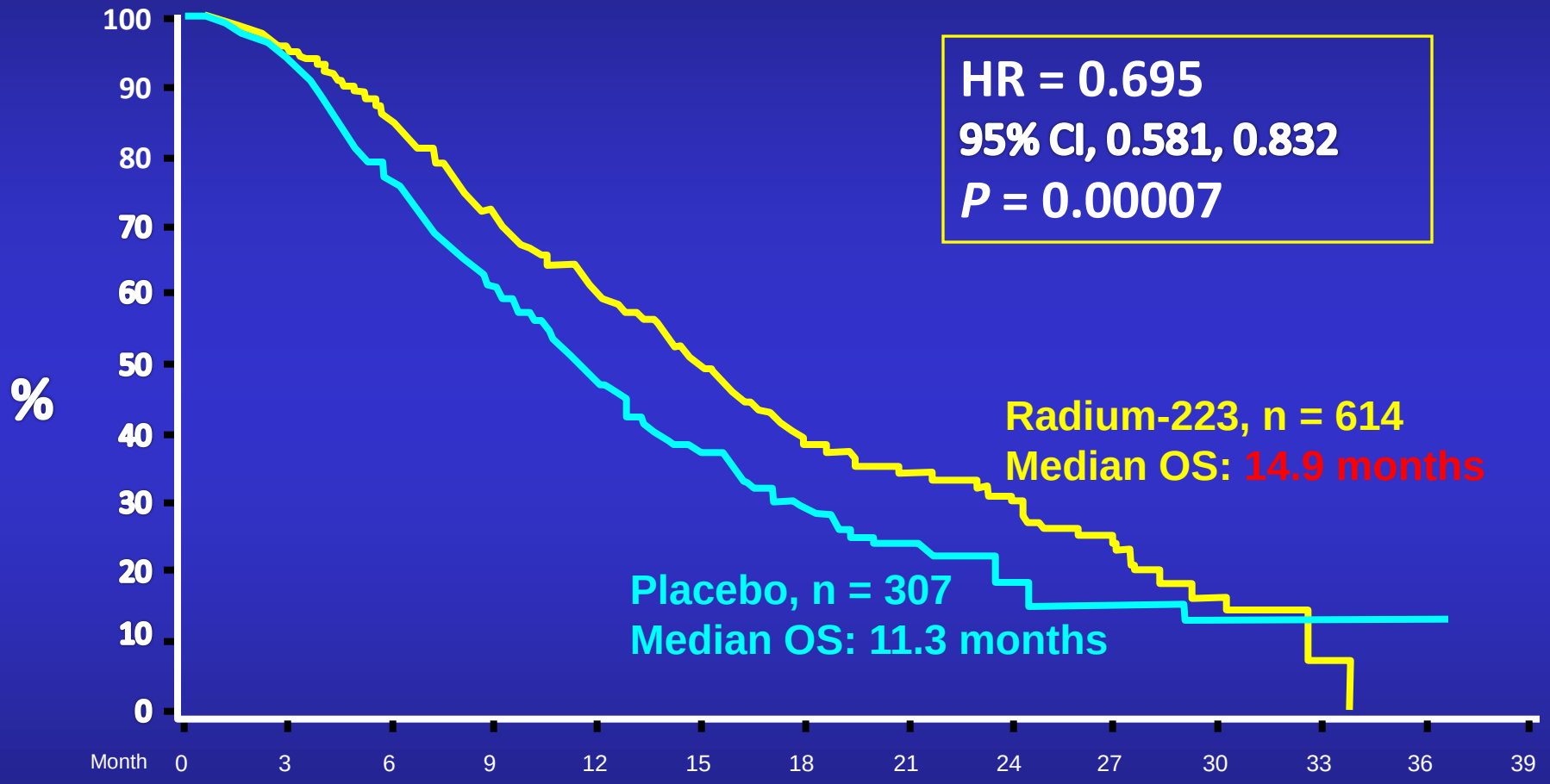
Patient Demographics and Baseline Characteristics (ITT N = 921)

Parameter	Radium-223 n = 614	Placebo n = 307
Age, yr		
Mean	**70.2**	**70.8**
Race, n (%)		
Caucasian	**575 (94)**	**290 (95)**
Baseline ECOG score, n (%)		
≤ 1	**536 (87)**	**265 (86)**
2	**76 (12)**	**40 (13)**
Extent of disease, n (%)		
< 6 metastases	**100 (16)**	**38 (12)**
6–20 metastases	**262 (43)**	**147 (48)**
> 20 metastases/superscan	**249 (41)**	**121 (40)**
WHO ladder, cancer pain index ≥ 2, n (%)	**345 (56)**	**168 (55)**

ALSYMPCA Updated Analysis
Patient Baseline Characteristics (ITT N = 921)

Parameter Median (min, max)	Radium-223 (n = 614)	Placebo (n = 307)
Haemoglobin, g/dL	**12.2 (8.5-15.7)**	**12.1 (8.5-16.4)**
Albumin, g/L	**40 (24-53)**	**40 (23-50)**
Total ALP, µg/L	**211 (32-6431)**	**223 (29-4805)**
LDH, U/L	**315 (76-2171)**	**336 (132-3856)**
PSA, µg/L	**146 (3.8-6026)**	**173 (1.5-14500)**
Current bisphosphonates **Yes, n (%)**	**250 (40.7)**	**124 (40.4)**
Prior docetaxel **Yes, n (%)**	**352 (57.3)**	**174 (56.7)**

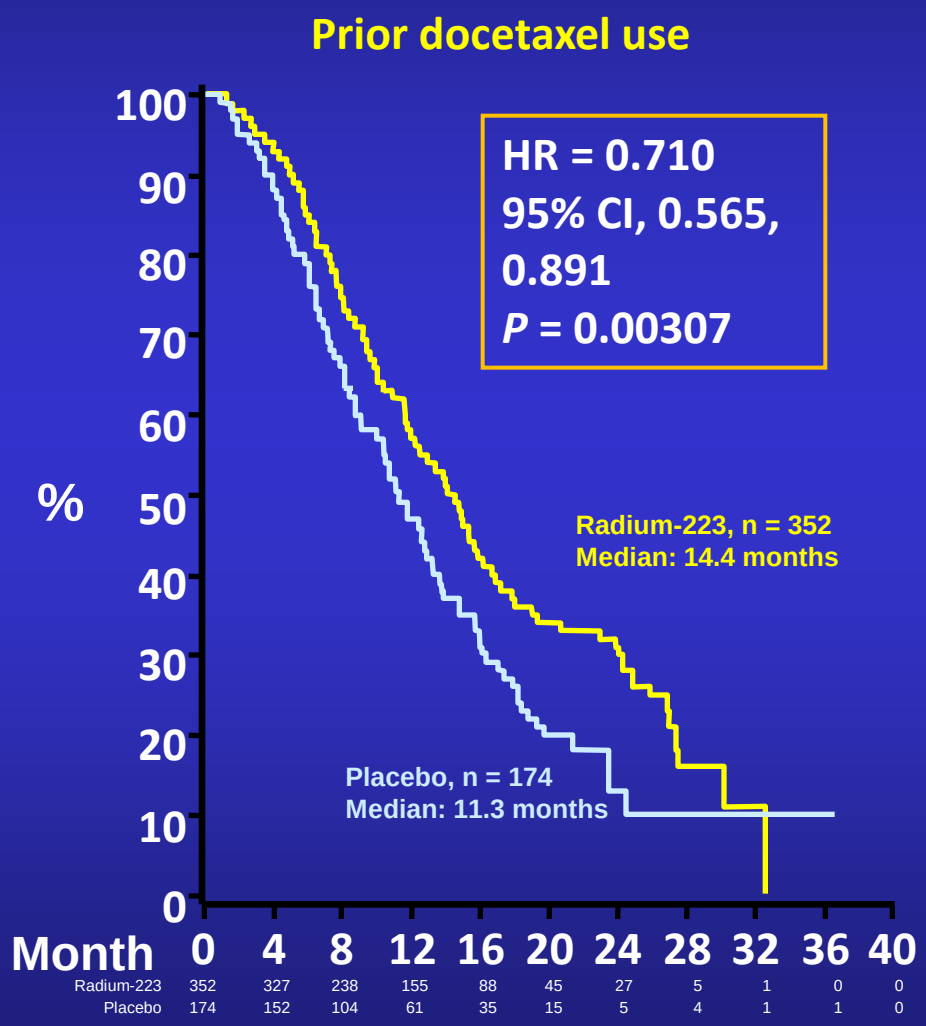
ALSYMPCA Updated Analysis
Overall Survival

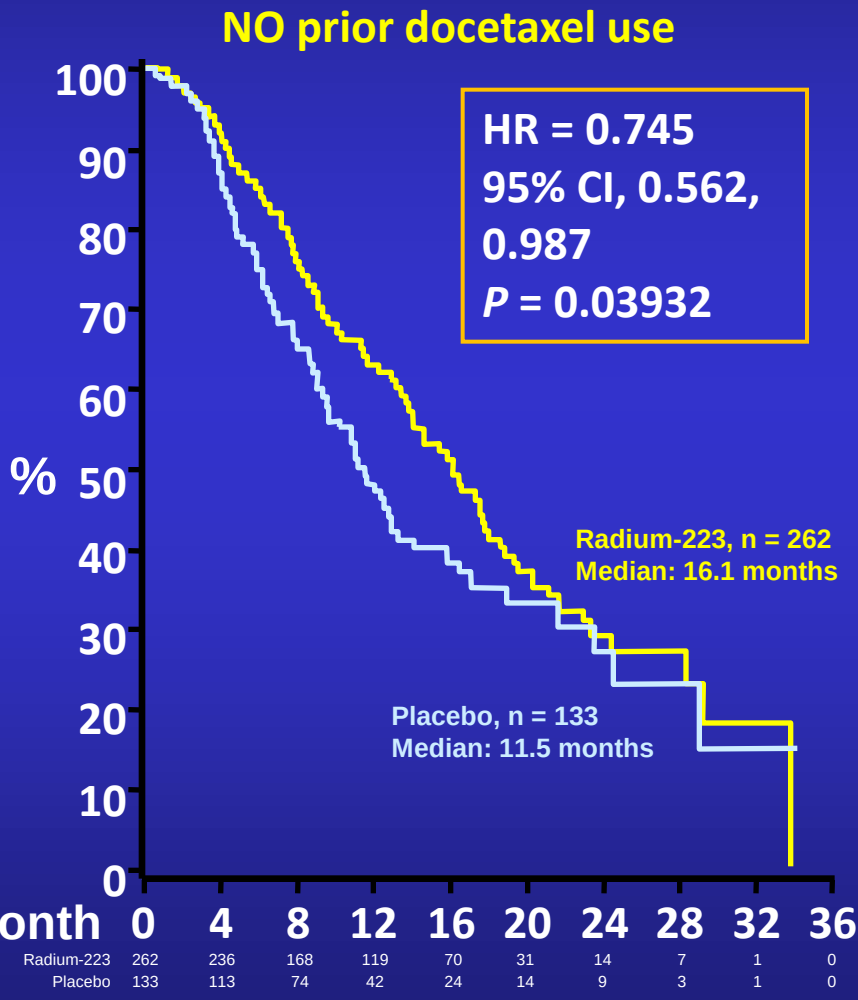


Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

ALSYMPCA Updated Analysis

OS by Stratification Variables: Prior Docetaxel Use

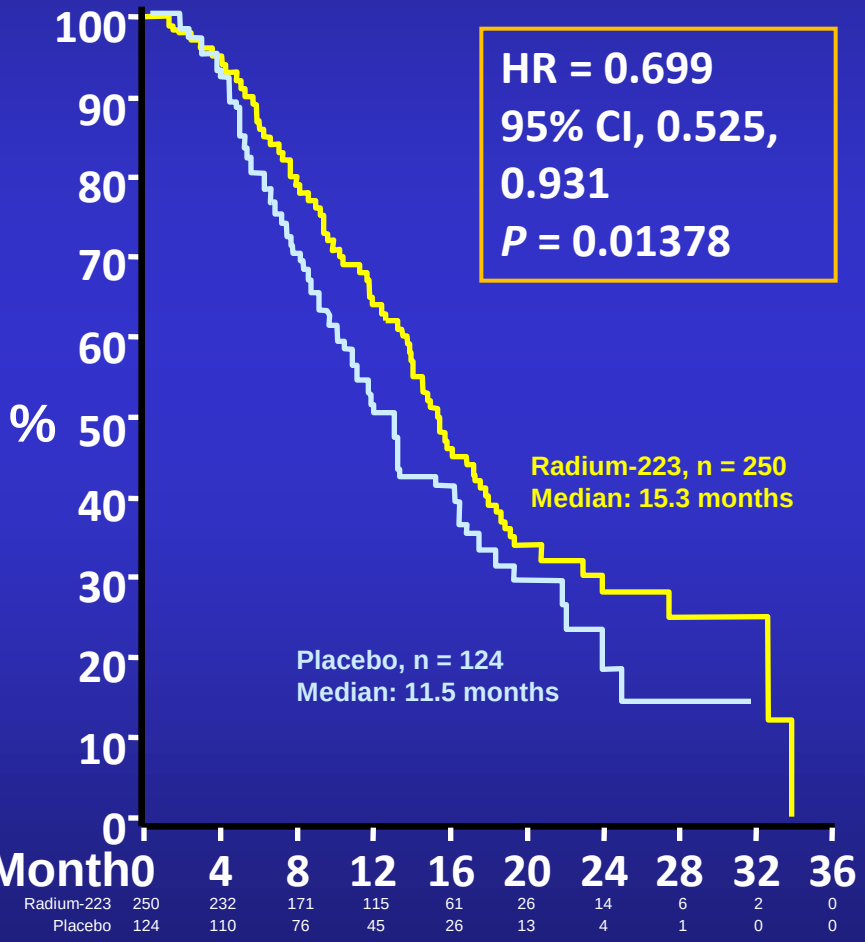




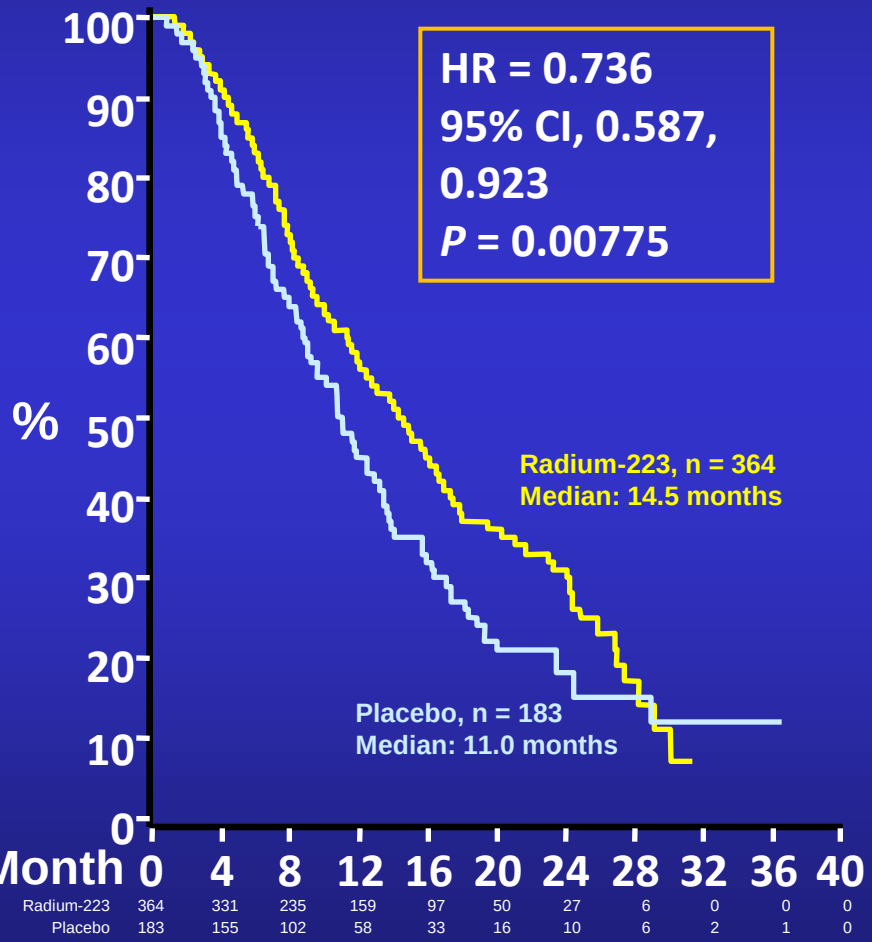
ALSYMPCA Updated Analysis

OS by Stratification Variables: Bisphosphonate Use

Current bisphosphonate use

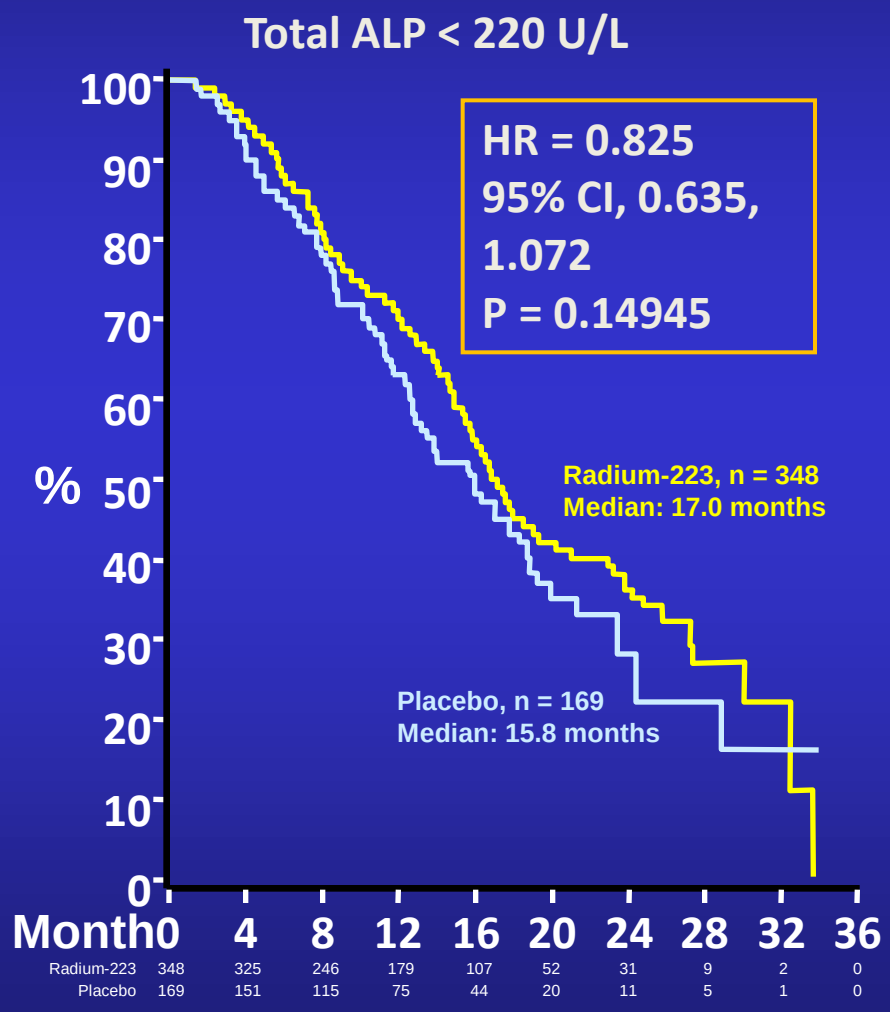


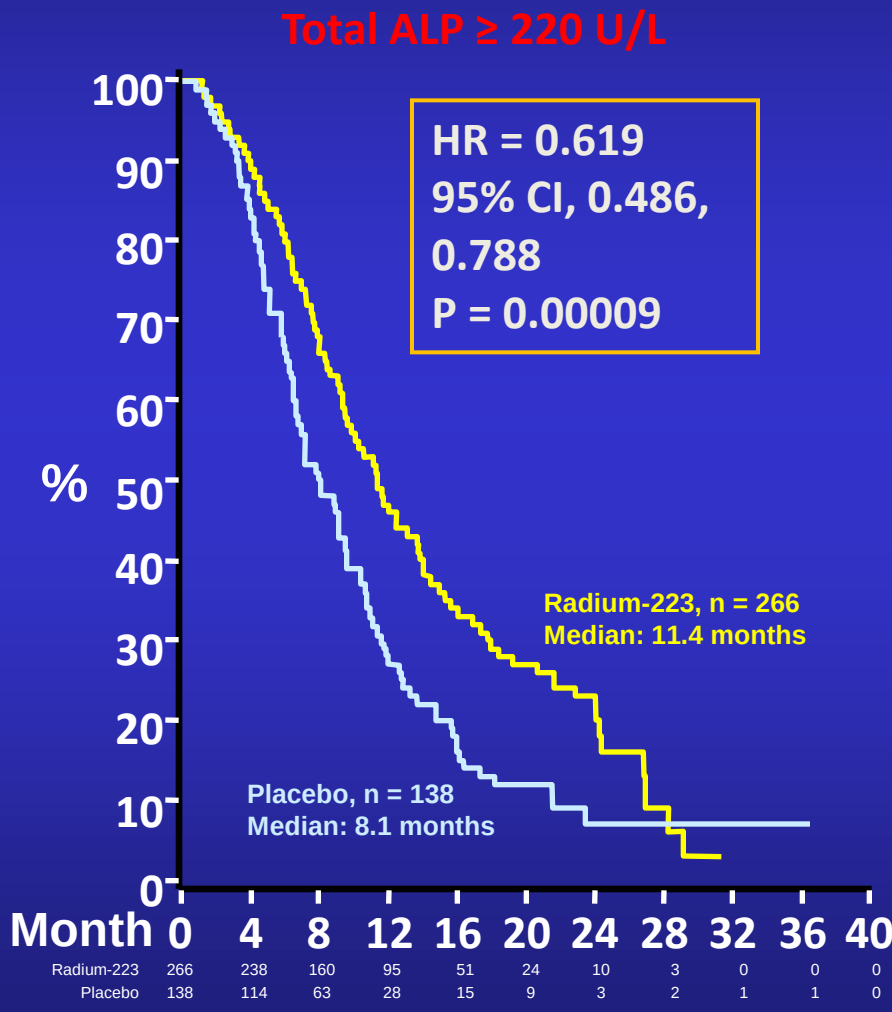
NO current bisphosphonate use



ALSYMPCA Updated Analysis

OS by Stratification Variables: Baseline ALP

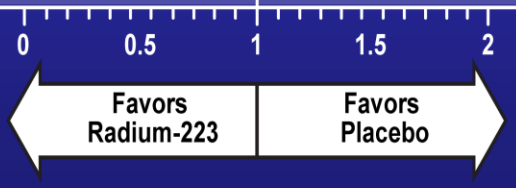




ALSYMPCA Updated Analysis

Survival Benefit Across Patient Subgroups

Variable	Subgroup	N	HR	95% CI
Overall Survival		921	0.695	0.581–0.832
Total ALP #	< 220 U/L	517	0.825	0.635–1.072
	>= 220 U/L	404	0.619	0.486–0.788
Current Use of Bisphosphonates #	Yes	374	0.699	0.525–0.931
	No	547	0.736	0.587–0.923
Prior Use of Docetaxel #	Yes	526	0.710	0.565–0.891
	No	395	0.745	0.562–0.987
Baseline ECOG Status	0 or 1	801	0.675	0.555–0.821
	2 or Higher	118	0.820	0.498–1.351



ALSYMPCA Updated Analysis

Secondary Endpoints: ALP and PSA

	Hazard ratio 95% CI	*P* value
Time to Total ALP progression	**0.167 (0.129, 0.217)**	**<0.00001**
Time to PSA progression	**0.643 (0.539, 0.768)**	**<0.00001**

	Radium-223 n (%)	Placebo n (%)	*P* value
Total ALP response	**233 (47)**	**7 (3)**	**<0.001**
30% reduction	**135 (27)**	**2 (<1)**	**<0.001**
50% reduction			
Total ALP normalization*	**109 (34)**	**2 (1)**	**< 0.001**

*In patients who had elevated total ALP at baseline.

ALSYMPCA Updated Analysis

Summary of Patients With Adverse Events: Safety Population*

Patients With Adverse Events (AEs), n (%)	Radium-223 n = 600	Placebo n = 301
All grade Aes	**558 (93)**	**290 (96)**
Grade 3 or 4 Aes	**339 (57)**	**188 (63)**
Serious AEs (SAEs)	**281 (47)**	**181 (60)**
Discontinuation due to Aes	**99 (17)**	**62 (21)**

*Safety population comprised patients who received at least 1 dose; 1 patient in the placebo group received one injection of Radium-223 (Week 0) and is included in the Radium-223 safety analysis.

ALSYMPCA Updated Analysis

AEs of Interest

	All Grades		Grades 3 or 4	
Patients with AEs n, (%)	Radium-223 n = 600	Placebo n = 301	Radium-223 n = 600	Placebo n= 301
Hematologic				
Anemia	**187 (31)**	**92 (31)**	**77 (13)**	**39 (13)**
Neutropenia	**30 (5)**	**3 (1)**	**13 (2)**	**2 (1)**
Thrombocytopenia	**69 (12)**	**17 (6)**	**38 (6)**	**6 (2)**
Non-Hematologic				
Bone pain	**300 (50)**	**187 (62)**	**125 (21)**	**77 (26)**
Diarrhea	**151 (25)**	**45 (15)**	**9 (2)**	**5 (2)**
Nausea	**213 (36)**	**104 (35)**	**10 (2)**	**5 (2)**
Vomiting	**111 (19)**	**41 (14)**	**10 (2)**	**7 (2)**
Constipation	**108 (18)**	**64 (21)**	**6 (1)**	**4 (1)**

ALSYMPCA Updated Analysis- QoL

At week 16, Ra-223 pts reported significantly greater well-being (physical, emotional, functional, prostate cancer score, and total score) (FACT-P) and significantly better QOL (EQ-5D) compared to Pbo pts.

Parameter	Ra-223 + BSC (n = 614)	Placebo + BSC (n = 307)	P value Hazard ratio (95% CI)
FACT-P*			
Physical well-being	-0.93	-1.65	0.047
Emotional well-being	-0.12	-1.27	<0.001
Functional well-being	-1.15	-2.23	0.011
Prostate cancer score	-0.10	-1.74	0.012
Trial outcome index score	-2.14	-5.16	0.011
FACT-P total score	-2.53	-6.88	0.006
EQ-5D*			
Single index utility	-0.0181	-0.0952	0.003

*Mean change from baseline at week 16.

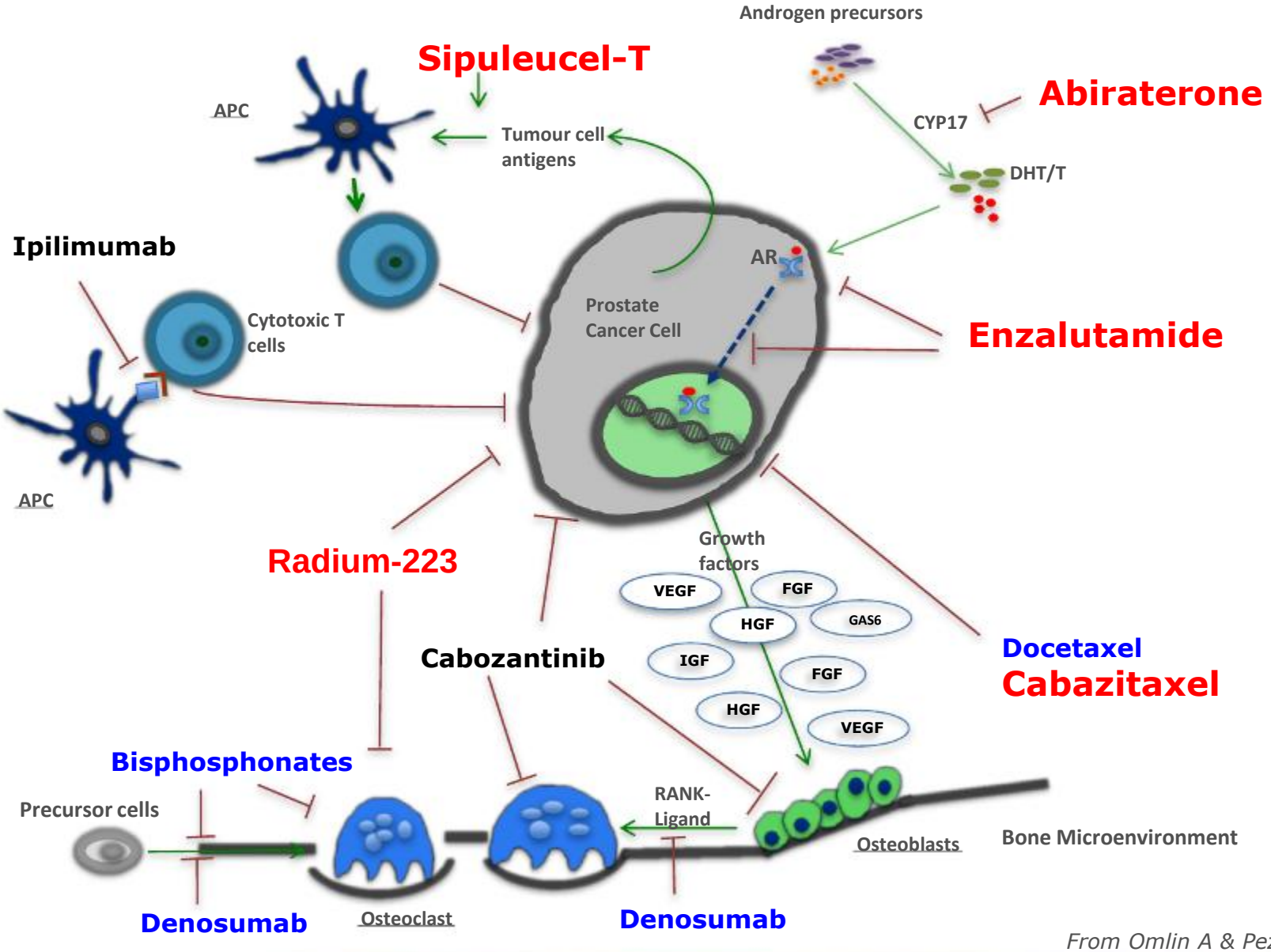
ALYSMPCA: Conclusions

Radium-223 compared with placebo in mCRPC patients with bone metastases:

- Significantly prolonged median OS by 3.6 months (*P* = 0.00007)
- 30.5% reduction in risk of death

Further follow-up in all randomized patients continues to show highly favorable safety profile.

Differing mechanisms of action



From Omlin A & Pezaro C.

Conclusions

Management of mCRPC is rapidly evolving

Multiple proven options in mCRPC:

Abiraterone: survival advantage vs placebo

Cabazitaxel: survival advantage vs mitoxantrone

Enzalutamide: survival advantage vs placebo

Rd-223 dichloride: survival advantage vs placebo

Sipuleucel-T: survival advantage vs placebo

The most appropriate sequencing of these new agents remains to be determined

New drugs in development: need to move to a tailored therapy

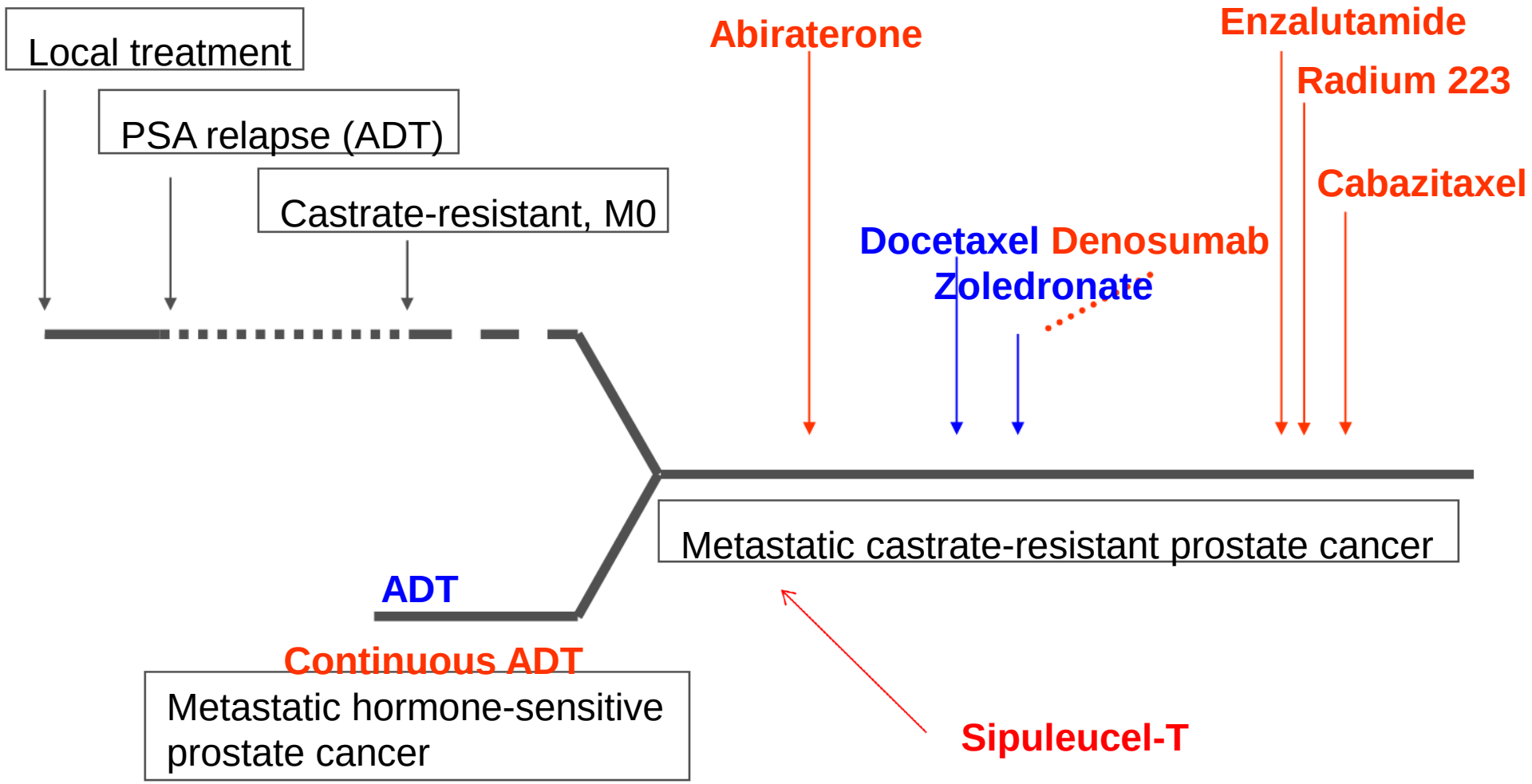
Agents with overall survival benefit in mCRPC

Trial (Agent) Approved	Disease State	Comparator	Median Benefit mo	Hazard Ratio	*P*-value
TAX327 (Docetaxel+ Prednisone) 2004	Pre-docetaxel CRPC	Mitoxantrone prednisone	2.5	0.76	.009
IMPACT (Sipuleucel-T) 2010	Pre-docetaxel mCRPC	Placebo	4.1	0.775	.032
COU 302 (Abiraterone+ Prednisone)	Pre-docetaxel mCRPC	Prednisone	5.2	0.75	.0097
AFFIRM (Enzalutimide)	Post-docetaxel CRPC	Placebo	4.8	0.63	<.0001
ALSYMPCA	Pre- and Post-docetaxel	Placebo	3.6	0.70	<.0001
TROPIC (Cabazitaxel)	Post-chemotherapy	Mitoxantrone prednisone	2.4	0.70	<.0001
COU 301 (Abiraterone+ Prednisone) 2011	Post-docetaxel CRPC	Prednisone	3.9	0.646	<.0001

Treatment landscape of CRPC in 2013

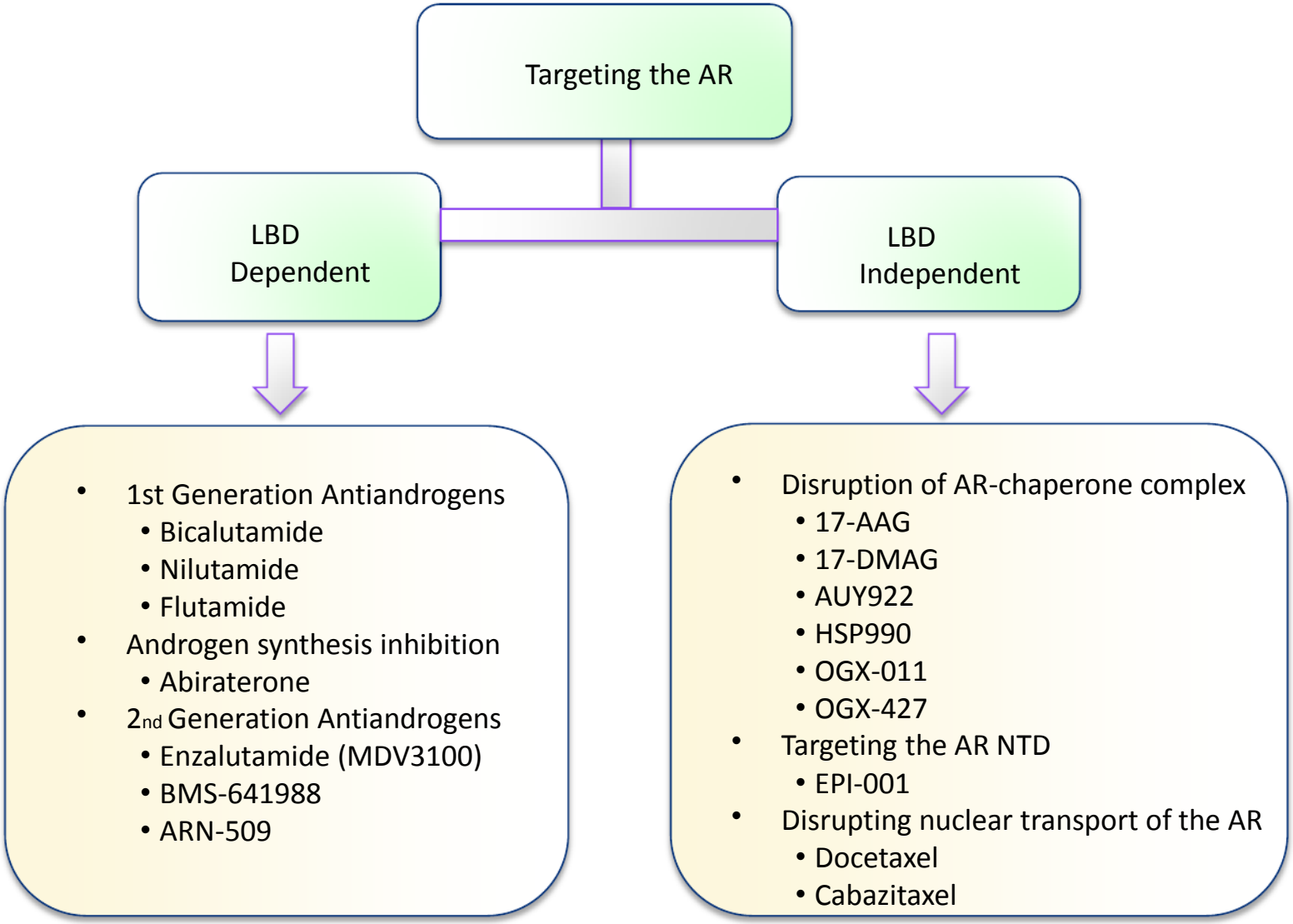
Non-metastatic	Metastatic, Chemotherapy-naïve Asymptomatic/MS	Metastatic, Chemotherapy-naïve Symptomatic	Metastatic-post docetaxel
No standard Second-line hormones	Sipuleucel-T Second-line hormones (Docetaxel) Zoledronic acid or Denosumab for skeletal-related events Abiraterone	Docetaxel Radium-223 (when approved)	Enzalutimide Abiraterone Cabazitaxel Radium-223 (when approved)

Systemic treatment for CRPC in 2012–2013



Thanks for your listening!

The androgen receptor (AR)



PROVENGE(sipuleucel T)的誕生

William Haseltine是一個科學家，生物技術企業家和慈善家，他在哈佛大學當教授時主要從事艾滋病和癌癥研究，如今是多家公司的創始人。

這個故事還得從上個世紀**80**年代，我在哈弗大學醫學院和**Dana – Farber**癌癥中心當教授研究 **HIV/AIDS**開始。那是已知**HIV**是男女之間的性傳播疾病。因爲這種病毒可以通過被血液污染的針頭傳播，因此性傳播在當時被認爲實際上也是和血液有關的，是通過性交過程中被撕裂的粘膜組織的小裂隙傳播。

當我看到一個報告稱**7**名婦女接受一名捐獻者的人工受精中被感染**HIV**，我開始懷疑這個解釋。我開始向所有我認識的科學家請教他們是否聽說過一種能穿過粘膜的細胞。我懷疑如果存在這種細胞，那么它可以攜帶病毒穿過粘膜進入體內。

最后我找到了洛克菲勒大學的**Ralph Steinman** ，**Ralph Steinman** 一直致力于對一種稱之爲樹突狀巨噬細胞（**dendretic macrophages**）的研究工作，他認爲這些細胞在免疫方面發揮關鍵作用，他們是對外來物質進行識別的第一種細胞，且在整個免疫系統中發揮著關鍵作 用。讓我感興趣的是樹突狀巨噬細胞被觀察到可以來回穿越子宮頸的粘膜。

后來，**Eric Langhoff**進入了我的實驗室，他是一個曾在 **Ralph Steinman** 的實驗室工作過的丹麥年輕醫生。很短的時間內，我們就證明了樹突狀巨噬細胞能高效率的攜帶**HIV**病毒。**HIV**病毒和樹突狀巨噬細胞緊密結合并被攜帶穿過粘膜到達淋巴結附近。樹突狀巨噬細胞通過它們的長牛透膜馴化其他的免疫細胞。這就是**HIV**接近易感免疫細胞**CDA**或**T**細胞的過程。病毒已經進入體內，開始感染。

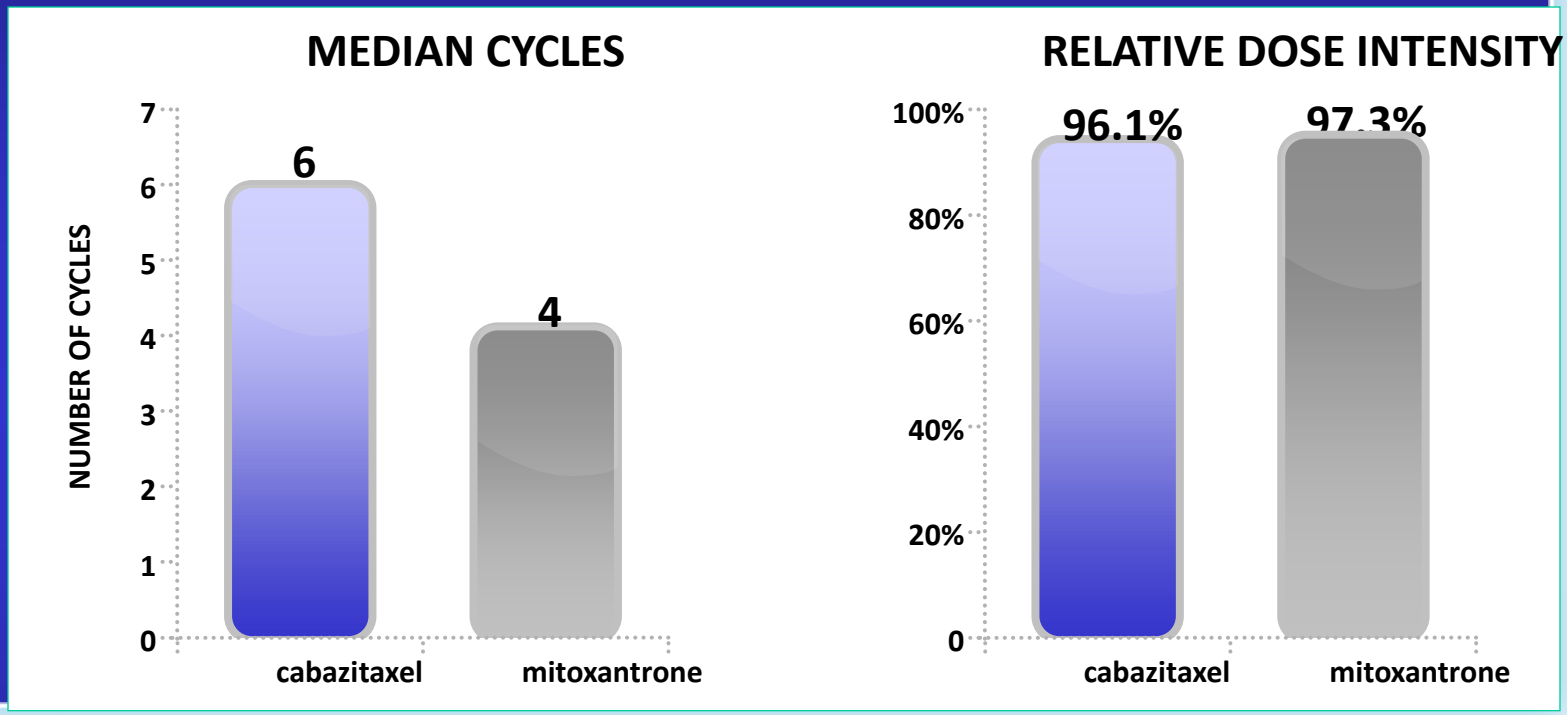
在這一研究過程中，我對這種細胞有了很深的認識。我發現離體樹突狀巨噬細胞可被用來馴化免疫系統，將純化樹突狀巨噬細胞暴露于外來物質，然后將這些細胞重新引入體內，結果其他的細胞也具有了對此物質的免疫力。

這個現象觸發了我的另一個想法，有沒有可能訓練純化樹突狀巨噬細胞識別腫瘤細胞，如果能這樣，那將這些細胞再導入體內訓練機體自身的免疫系統來攻擊自身的腫瘤。

我遇見了兩名來自斯坦福大學的科學家**Sam Strober** 和 **Ed Engelmann.**我們的想法不謀而合，而且均在建立公司的早期階段，因此我們聯合起來， **Activated Cell Therapy**公司誕生了。

種對晚期前列腺癌治療如今得到批復，癌癥治療中的這一小步給將來所有癌癥患者提供了新的希望。我們已經開始著手實現借助免疫系統的力量來對抗癌癥，這條道路雖然漫長曲折，但前途是光明的。

Greater Treatment Exposure With Cabazitaxel



- Completion of 10 cycles: cabazitaxel 28% vs mitoxantrone 12%
- Treatment discontinuations due to adverse drug reactions occurred in 67 (18%) patients receiving cabazitaxel vs 32 (8%) with mitoxantrone

de Bono J, et al. *Lancet* 2010;376:1147–54

ALSYMPCA Updated Analysis
Patient Disposition

	Radium-223 N = 614	Placebo N = 307
Patients treated, n	**599**	**302**
Median number of injections, range	**6 (1-6)**	**5 (1-6)**
Received all 6 injections, n (%)	**387 (63)**	**145 (47)**

Safety of Cytotoxic Chemotherapy Following Radium-223 Dichloride (Rd-223) Therapy

Parameter	Ra-223 + BSC (n = 90)	Placebo + BSC (n = 54)
Median time to Chemo; days (range)	79.0 (2–667)	64.5 (2–448)
Median duration Chemo; days (range)	117.5 (1–809)	112.5 (1–863)
Chemo = docetaxel; n (%)	63 (70.0)	39 (72.2)
Docetaxel daily dose (mg); n	22	17
Mean (SD)	97.8 (41.6)	102.7 (46.3)
Median (min-max)	92.5 (35-150)	120.0 (30-165)
Deaths on Chemo; n (%)	13 (14.4)	8 (14.8)
Cause: PC and skeletal mets (± other mets)	9 (10.0)	7 (13.0)
PC with other mets (or mets not specified)	3 (3.3)	0 (0)
Cerebral hemorrhage due to trauma Cardiopulmonary failure	1 (1.1) 0 (0)	0 (0) 1 (1.1)
Deaths within 30 days post Chemo; n (%)	5 (5.6)	2 (3.7)
Cause: PC and skeletal mets (± other mets)	3 (3.3)	2 (3.7)
Bronchopneumonia Respiratory failure + pulmonary edema	1 (1.1) 1 (1.1)	0 (0) 0 (0)
Neutrophils; (Absolute) (x10^9/L)	88 3.6 (0.9-26.0) 47	49 4.6 (1.9-16.4) 30
Baseline, n Median (min-max)	4.4 (0.5-24.4) 41	5.7 (1.6-13.1) 19
Month 2, n Median (min-max)	3.8 (1.3-10.8) 23	4.6 (1.1-8.9) 12
Month 4, n Median (min-max)	3.5 (0.5-6.3) 12	4.7 (1.5-12.2) 7
Month 6, n Median (min-max)	3.5 (1.9-9.4) 13	3.9 (3.0-6.4) 8 4.6
Month 8, n Median (min-max)	3.6 (1.1-8.9) 8	(3.0-8.5) 6 5.6
Month 10, n Median (min-max)	5.0 (2.5-7.1)	(2.8-8.9)
Month 12, n Median (min-max)		

- Number of deaths and causality during 30 days post Chemo and limited available hematologic data were similar in both groups

- The androgen receptor (AR) pathway remains a therapeutic target in patients with castration-resistant prostate cancer (CRPC)
- Abiraterone acetate, a selective *CYP17* inhibitor, has been approved by the FDA for the treatment of patients with metastatic CRPC (mCRPC) in prechemotherapy and postchemotherapy settings
- Enzalutamide (formerly known as MDV3100) is a multilevel AR inhibitor that has gained FDA approval for the treatment of patients with mCRPC who have already received docetaxel therapy
- Cabazitaxel, a taxane-based chemotherapeutic agent, is FDA-approved for patients who progress on, or after, docetaxel regimens
- Denosumab was the first osteoclast-targeted agent shown to significantly delay bone metastasis in patients with nonmetastatic CRPC
- Radium-223 was the first radiopharmaceutical agent shown to improve survival in patients with mCRPC