Università degli Studi di Genova

Società Italiana di Radiobiologia

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A.O. Spedali Civili di Brescia

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Associazione Italiana di Radioterapia Oncologica

EXPLOITING NEW EVIDENCES OF DRUG-RADIATION INTERACTIONS IN CLINICS

The role of "radioactive" drugs: from prostate cancer to lymphomas

Dr. G. Simontacchi
AOU Careggi - Firenze

…What if we could deliver radiation therapy in a way that…

- ✓Is tumor specific, with sparing of healthy tissue (low toxicity)
- ✓No limit to the absorbed dose
- ✓Radiation can be delivered to any numer of sites of disease
- ✓Radiation can be delivered to subclinical tumors and metastases that are too small to be imaged
- ✓ Radiation can be delivered to cells in the circulating blood including hematologic malignancy

→ **RADIOMETABOLIC THERAPY!!**

1896 - Henri Becquerel

Discovered radioactivity on 26 February 1896

"Some atoms give off energy in form of rays. Uranium gives off radiation."

Shared Nobel Prize in 1903 with P. Curie.

1913 - Frederick Proesher publishes the first study on the intravenous injection of radium for therapy of various diseases.

1936 - John H. Lawrence, the brother of Ernest, makes the first clinical therapeutic application of an artificial radionuclide when he uses phosphorus-32 to treat leukemia.

1938 John Livingood and Glenn Seaborg discover iodine-131 and cobalt-60 - all isotopes currently used in nuclear medicine. G. Seaborg shared Nobel Prize with MacMillan in 1951.

Characteristics of the Ideal Therapeutic Radiopharmaceutical

1. Prefer α or $\beta-$ particle emitters (high LET) to maximize tissue dose/mCi injected.
2. Prefer high energy (>1 MeV)
3. Minimal radiation exposure to personnel in contact with patient
4. High binding affinity to the intended target
5. High specificity with high target:non-target ratio to minimize radiation dose to non-target organ
6. High metabolic stability
7. Prefer rapid excretion of unbound material

- Radioisotopes:
  - -131I
  - -89Sr
  - -153Sm
  - -223Ra
- Radiopeptides:
  - -131I-mIBG
  - -90Y-DOTATOC
  - -177Lu-DOTATATE
- Radioimmunoconjugates:
  - -90Y-ibritumomab
  - -131I-tositumomab

- Radioisotopes: -131I
  -89Sr
  -186Re
  -223Ra
- Radiopeptides: -131I-mIBG
  -90Y-DOTATOC
  -177Lu-DOTATATE
- Radioimmunoconjugates: -90Y-ibritumomab
  -131I-tositumomab

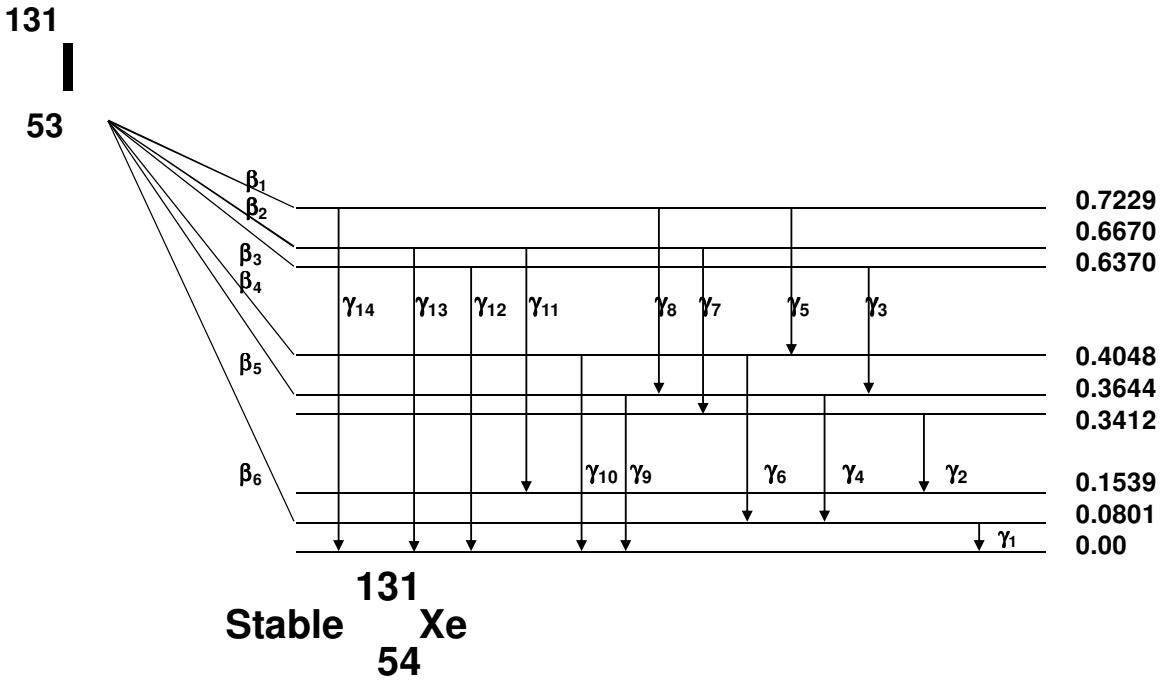
Tumor-seeking radiopharmaceuticals

- Radioisotopes: -131I
  -89Sr
  -153Sm
  -223Ra
- Radiopeptides: -131I-mIBG
  -90Y-DOTATOC
  -177Lu-DOTATATE
- Radioimmunoconjugates: -90Y-ibritumomab
  -131I-tositumomab

Bone-seeking radiopharmaceuticals

- Radioisotopes: -131I
  -89Sr
  -153Sm
  -223Ra
- Radiopeptides: -131I-mIBG
  -90Y-DOTATOC
  -177Lu-DOTATATE
- Radioimmunoconjugates: -90Y-ibritumomab
  -131I-tositumomab
- ‘’Local’’ therapy: -90Y microspheres
  -131I Lipiodol

Decay Scheme of I-131



^{131}I (53P, 78N) $\Rightarrow$ ^{131}Xe (54P, 77N)

$\Downarrow$

90% beta max 606 KeV, average 191 KeV

max tissue penetration 2mm $\rightarrow$ *therapy*

10% gamma 364 e 637 KeV

pass through body $\rightarrow$ *scintigraphy*

$^{131}I \rightarrow$ physical half-life *8.02 days*

Normal thyroid tissue: 1% uptake of I administred dose for 1g of tissue

- ✓ Effective half-life of about 8 days
- ✓ 3.7 GBq $\rightarrow$ Radioation dose of up to *500Gy*

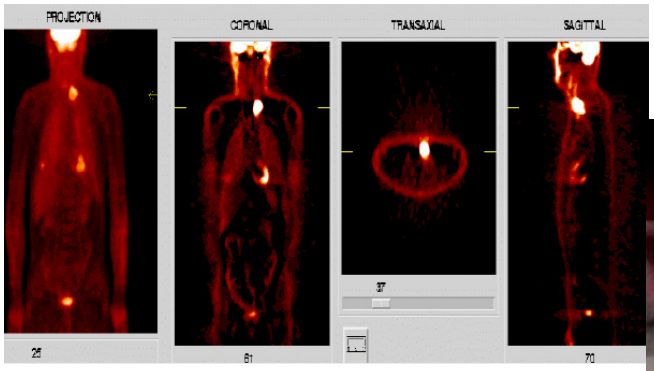
Neoplastic tissue: 0,5%-0,001% or less uptake for 1g of tissue

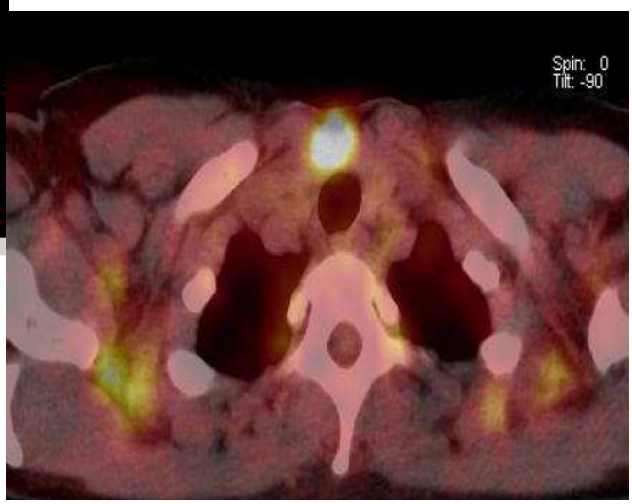
- ✓ Effective half-life of about 3 days or less
- ✓ If 0.1% uptake, with 3.7 GBq, absorbed dose will be
  - ◊about *30Gy* if HL 3 days
  - ◊about *15Gy* if HL 1.5 days

Site of metastasis	CR	PR	SD/PD
Lymponodes	68.2 %	18.8%	12.5%
Lung	45.9%	27.7%	24.5%
Bone	6.8%	35.6%	54.2%

Maxon III HR et al. End Metab North Am 19:685-718,1990

PET-positive patients





Resistance of [^{18}F]-Fluorodeoxyglucose–Avid Metastatic Thyroid Cancer Lesions to Treatment with High-Dose Radioactive Iodine

Weiping Wang, Steven M. Larson, R. Michael Tuttle, Hovanes Kalaigian, Katherine Kolbert, Martin Sonenberg, and Richard J. Robbins

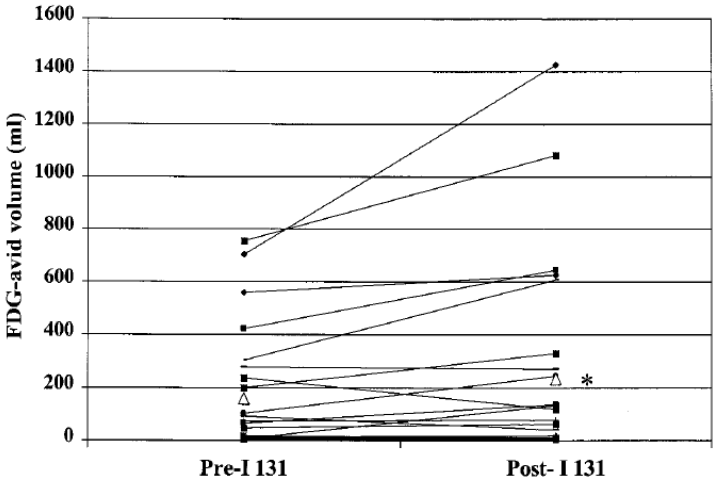


FIG. 2. Effect of ^{131}I on FDG volume. The total FDG-avid volume of all metastatic lesions in each patient is presented in ml. Pre-^{131}I, prior to radioiodine therapy; Post-^{131}I, after treatment with radioiodine. The open triangle represents the mean of all points for each group. *p = 0.036 compared to Pre-^{131}I.

Wang, Thyroid 2001

Effect of 131I on PET+ metastasis

	PD	SD or PR
PET + & 131I -	16 (70%)	7 (30%)
PET + & 131I +	5 (73%)	3 (27%)

Yoshio, Clin Nucl Med 2011

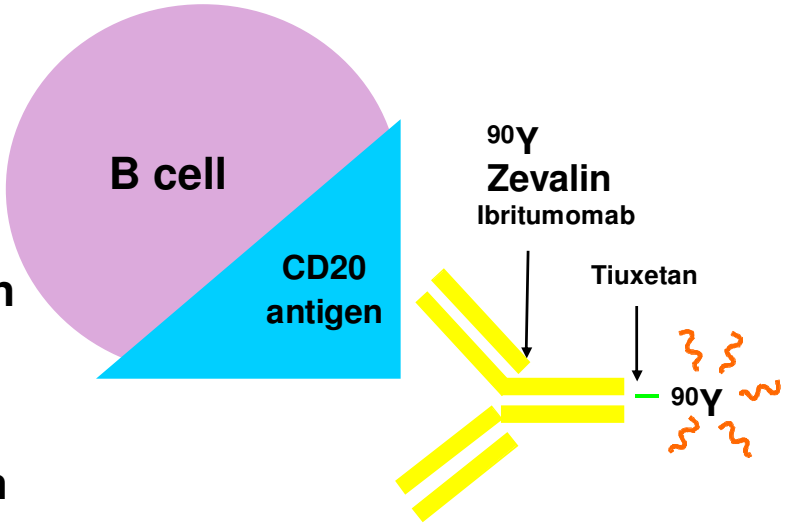
Radioimmunotherapy in lymphomas

The success of RIT in lymphoma can be attributed to the combination of:

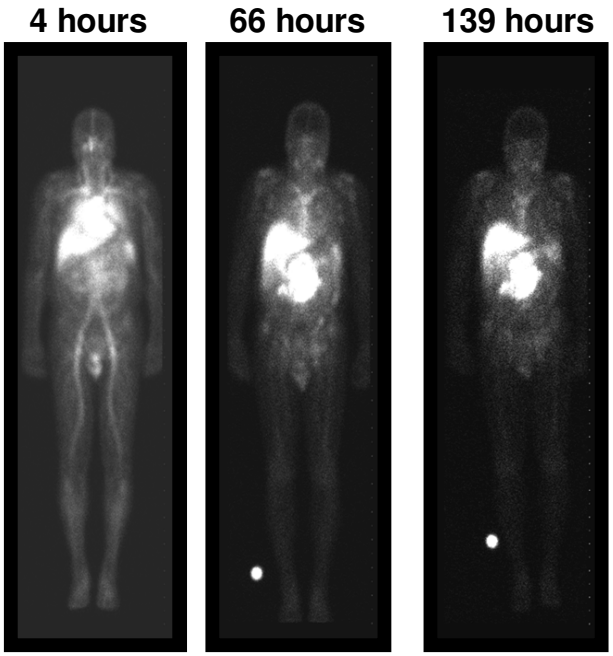
- Radiosensitivity of the disease
- The targeting of highly expressed antigens by signalling antibodies
- By antibodies that mediate other therapeutic effects in their own right
- RIT can kill both bound and neighboring tumor cells ("by-stander effect"), overcoming the problem of access in bulky or poorly vascularized tumors

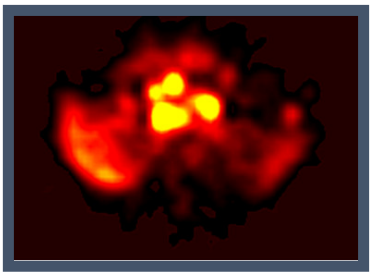
- Zevalin (ibritumomab tiuxetan)
  - Ibritumomab (murine parent of rituximab)
    - Binds CD20
  - Tiuxetan
    - Stable retention of ^{90}Y

- **CD20 antigen**
  - **Expressed only on B-lineage cells**
  - **Important for cell cycle initiation and differentiation**

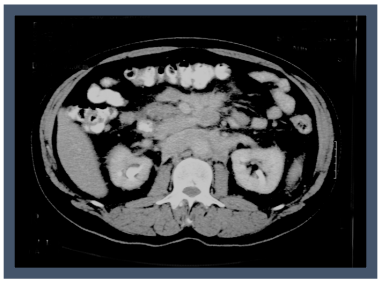


^{111}In-Labeled Zevalin Imaging



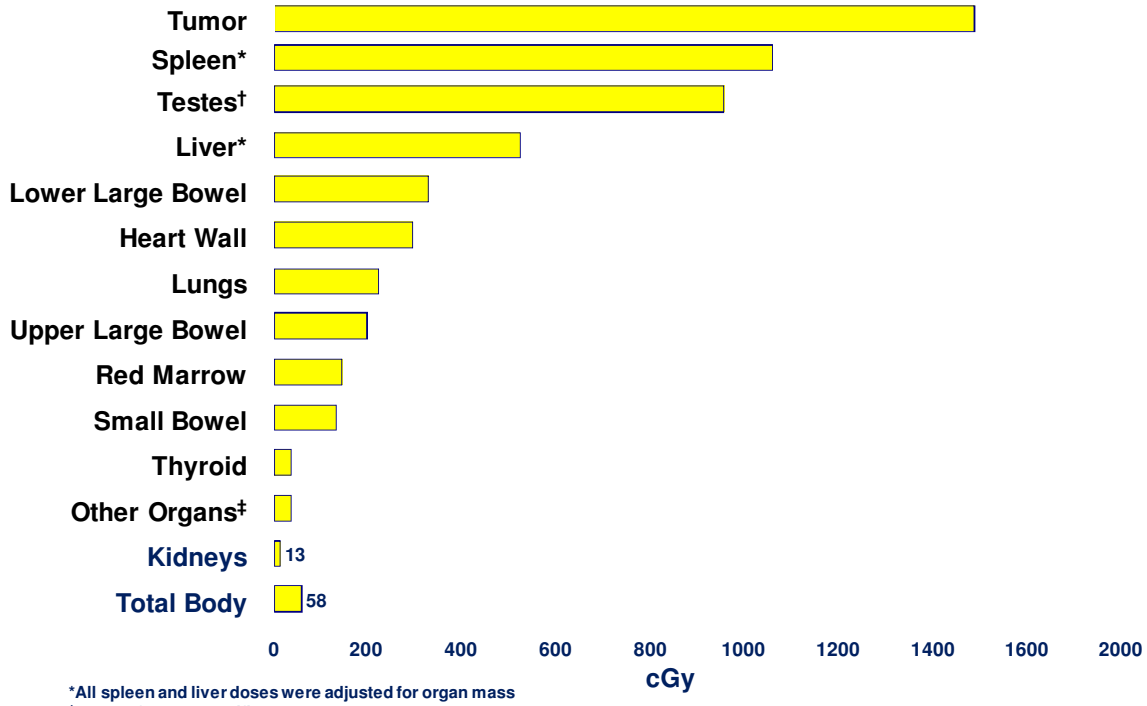


Abdominal SPECT



Abdominal CT

Median ^{90}Y Radiation Absorbed Dose

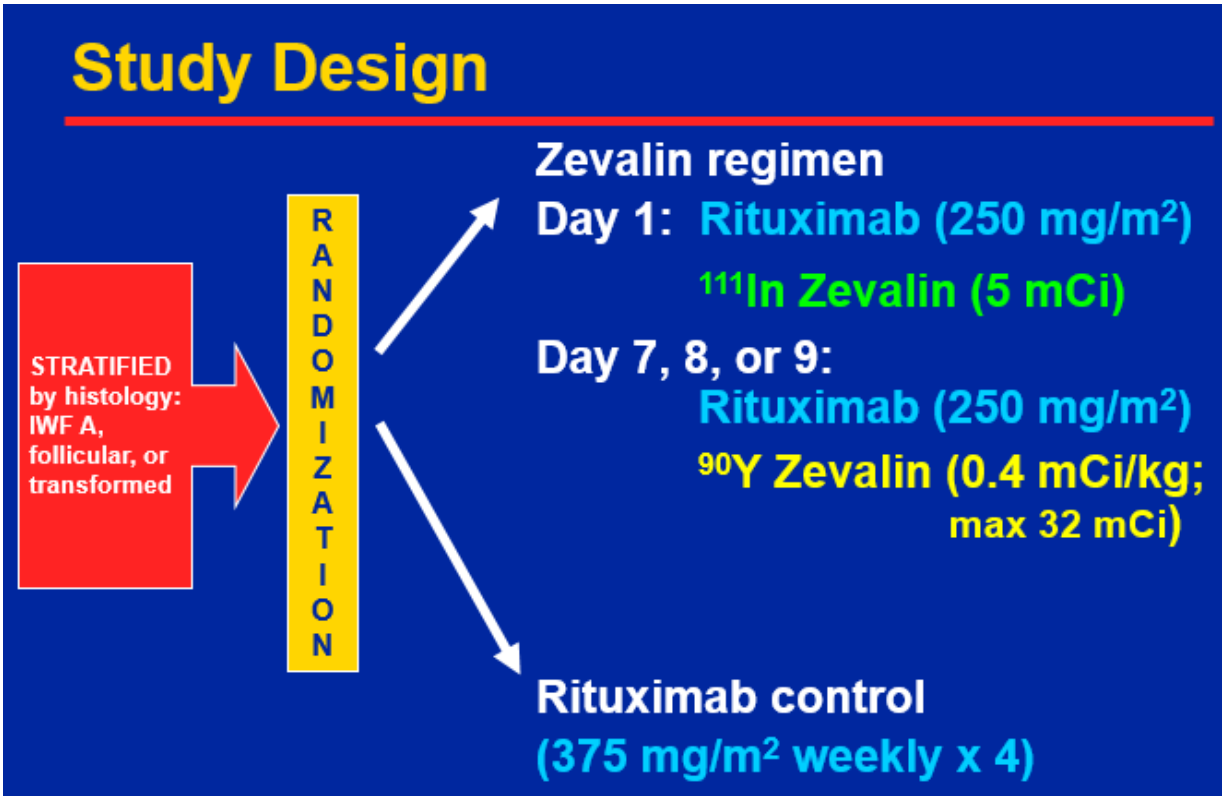


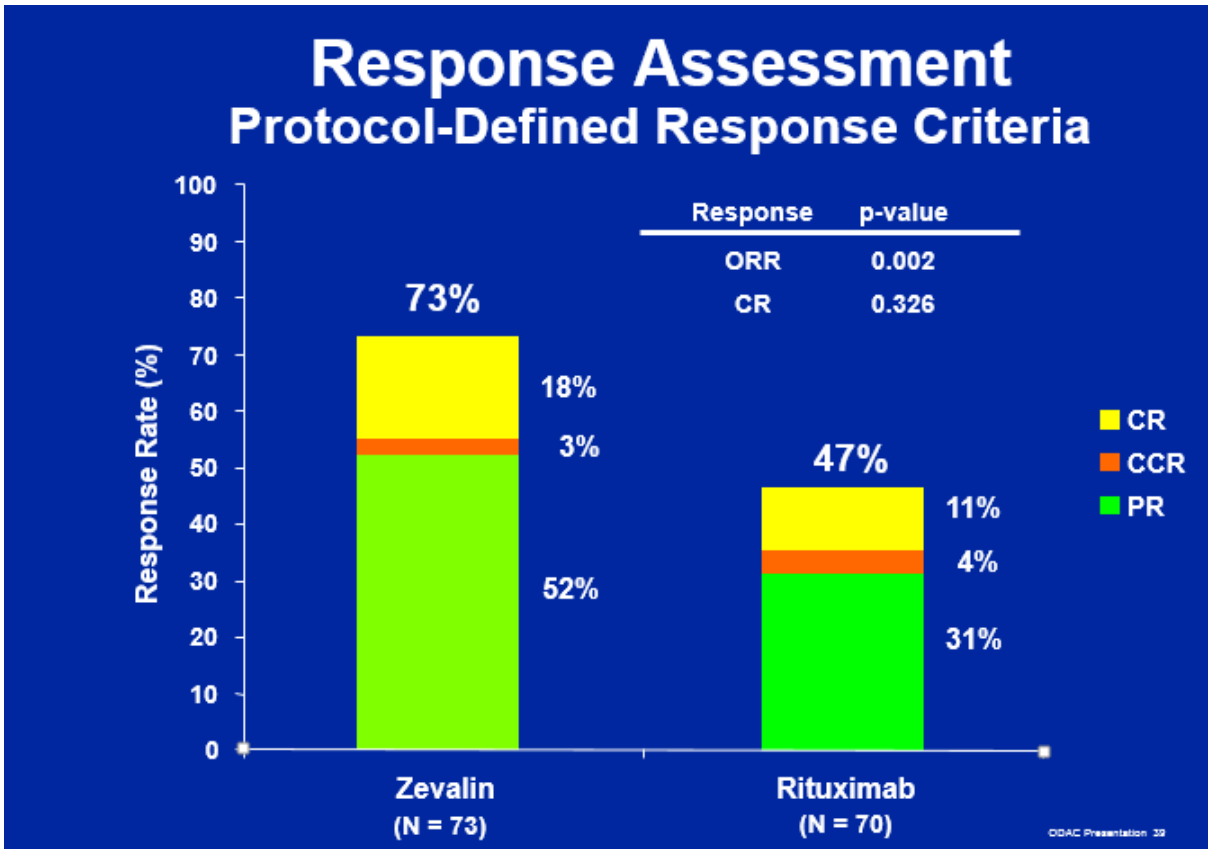
*All spleen and liver doses were adjusted for organ mass
†10 men for sex-specific organs
‡Adrenals, brain, breasts, gallbladder wall, muscle, pancreas, skin, thymus, stomach

Rituxan *vs* Zevalin for Non-Hodgkins for Lymphoma

- Relapsed or refractory follicular or transformed NHL
- 147 patients randomized to Rituxan or Zevalin

Witzig TE, Gordon LI, et al. *J Clin Oncol* 2002; 20:2453-63

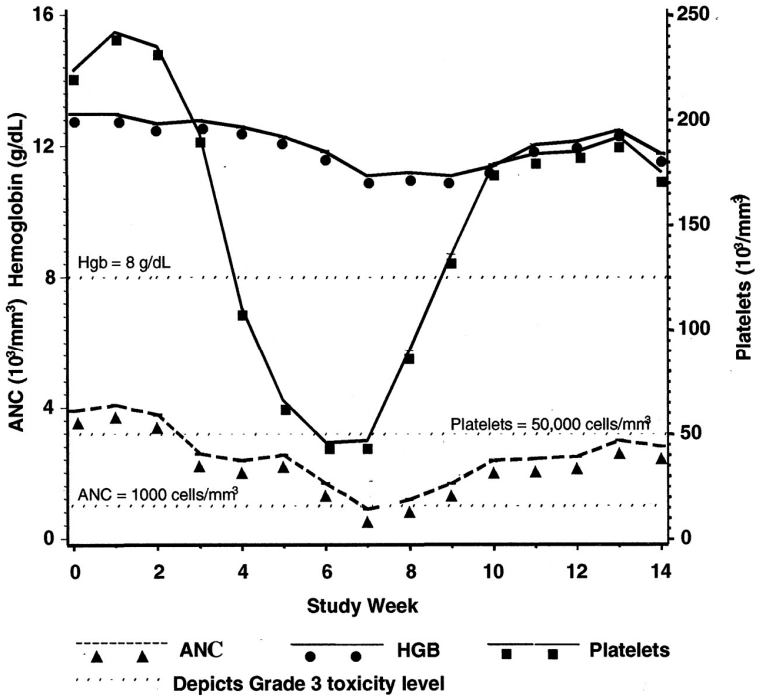




Phase III Randomized Summary

- **Efficacy objectives met**
  - **Primary**
    - **Significantly higher ORR as determined by independent, blinded LEXCOR panel**
  - **Secondary**
    - **Overall TTP comparable**
    - **Trend toward longer TTP in follicular and CR/CCR patients**
    - **Trend toward longer time to next therapy in all patients**
    - **Median TTP in responders: 15.4 months**

Rituxan *vs* Zevalin for non-Hodgkins for lymphoma



Witzig TE, Gordon LI, et al. J Clin Oncol 2002

Hematologic Toxicity: 0.4 mCi/kg dose (maximum 32 mCi)

	Median Nadir	Patients with Grade 3	Patients with Grade 4	Median Days Within Grade 3 or 4* (Only patients with Grade 3 or 4 Nadir)
ANC (cells/mm^3)	800	28%	30%	22
Platelets (/mm^3)	41,000	52%	10%	24
Hemoglobin (g/dL)	10.5	14%	3%	14

*ANC < 1000 cells/mm^3, platelets < 50,000/mm^3, and hemoglobin < 8.0 g/dL;

No difference in hematologic toxicity between patients < 65 years of age and patients ≥ 65

Integrated Safety: Hematologic Toxicity

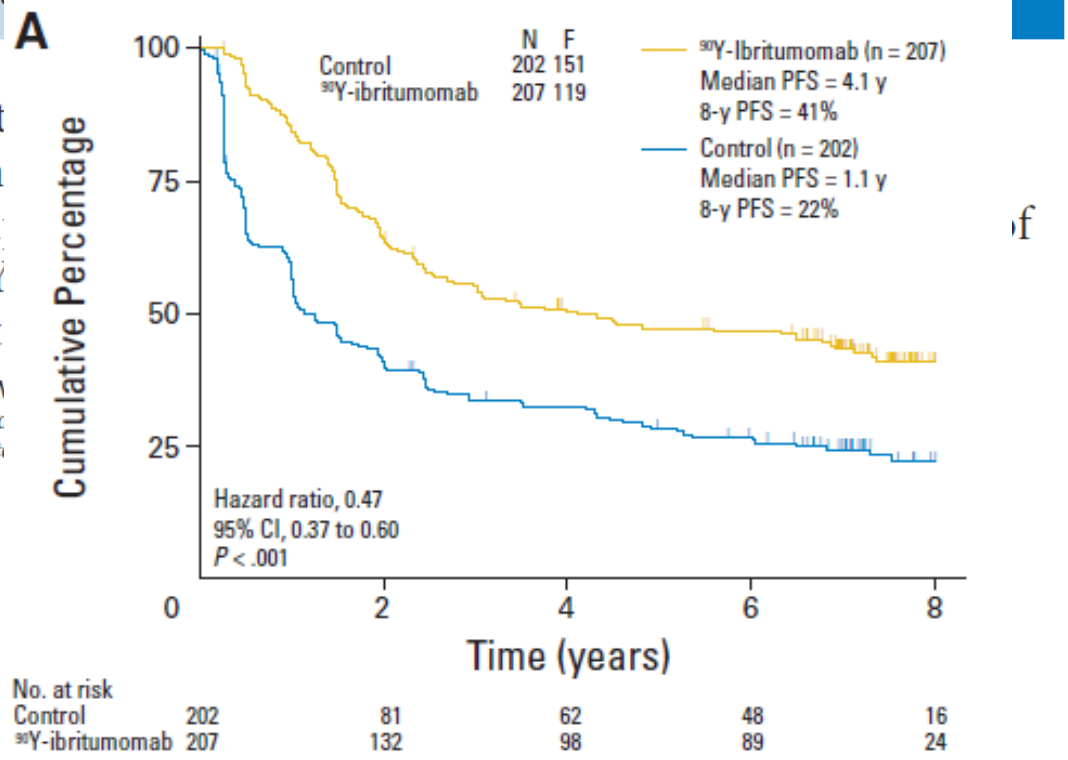
- Grade 3 and 4 toxicity correlates with:
  - % marrow involvement
  - Number of prior therapies/purine analogs
- Hematopoietic support
  - Growth factors 18% of patients
    - G-CSF 13%
    - Erythropoietin 8%
  - Red blood cell transfusion 20%
  - Platelet transfusion 22%
  - Grade 3 - 5 bleeding events 2%

VOLUME 31 · NUMBER 16 · JUNE 1 2013

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

^{90}Ytt
Rem
Lym
7.3 Y
First

Franck M
Pierre Sc
and Ant



Cancer Medicine

Open Access

ORIGINAL RESEARCH

Outcomes after ^{90}Yttrium-ibritumomab tiuxetan-BEAM in diffuse large B-cell lymphoma: a meta-analysis

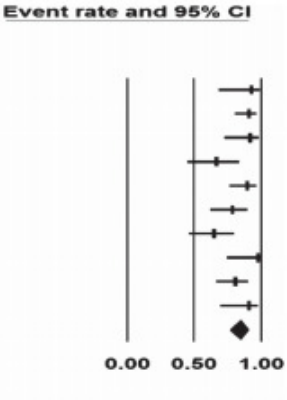
Sophie Auger-Quittet[1], Yohan Duny[2], Jean-Pierre Daures[2] & Philipe Quittet[3]

[1]Department of Internal Medicine, Mutualist Clinic Beausoleil, Montpellier, France
[2]Department of Biostatistical and Epidemiology, INSERM Unit EA, Montpellier, France
[3]Department of Hematology, University Hospital Saint-Eloi, Montpellier, France

(A)

First Author (year)	Total	Event rate	Lower limit	Upper limit
Nademanee AP. and al (2005)	17/18	0.930	0.685	0.988
Nademanee AP. and al (2006)	56/62	0.910	0.809	0.960
Alousi A. and al (2007)	23/25	0.920	0.731	0.980
Shimoni A. and al (2007)	15/22	0.670	0.455	0.832
Wondergem M. and al (2011)	39/43	0.900	0.769	0.961
Siddiqi T. and al (2012)	28/36	0.790	0.628	0.893
Briones J. and al (2012)	20/30	0.650	0.467	0.797
Wondergem M. and al (2012)	24/24	0.980	0.749	0.999
Krishnan A. and al (2012)	37/46	0.810	0.671	0.899
Shimoni A. and al (2012)	20/22	0.910	0.701	0.978
	279/328	0.845	0.766	0.901

Heterogeneity: Overall: $I^2 = 56.7\%$; $p = 0.014$



Historical Approach to Radionuclide Therapy

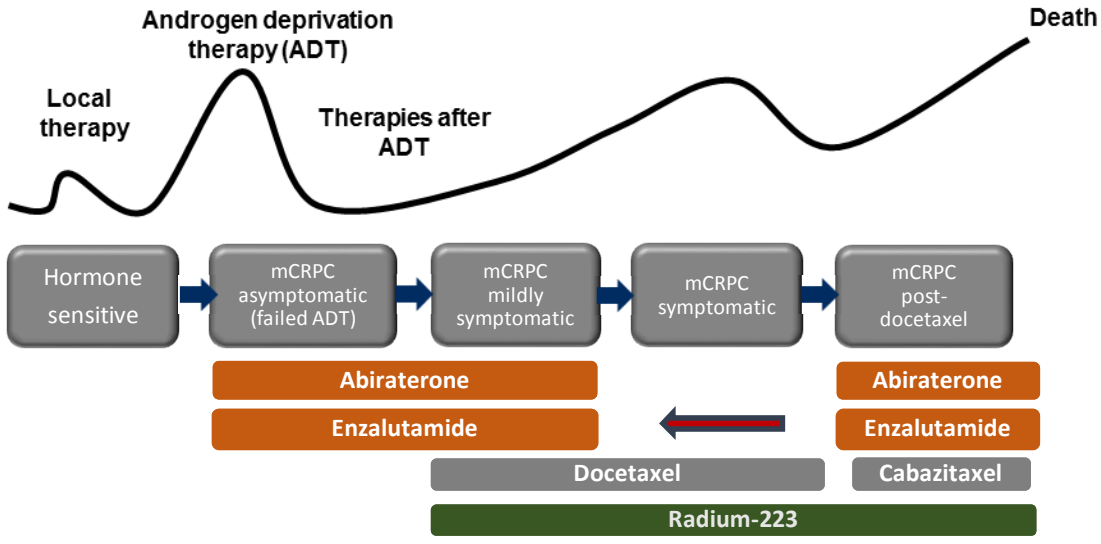
- ✓ $Na_3{}^{32}PO_4$ in 1940's
- ✓ $^{89}SrCl_2$ in late 1980's
- ✓ ^{153}Sm EDTMP in late 1990's

TABLE 1. PHYSICAL CHARACTERISTICS OF THE DIFFERENT RADIONUCLIDE

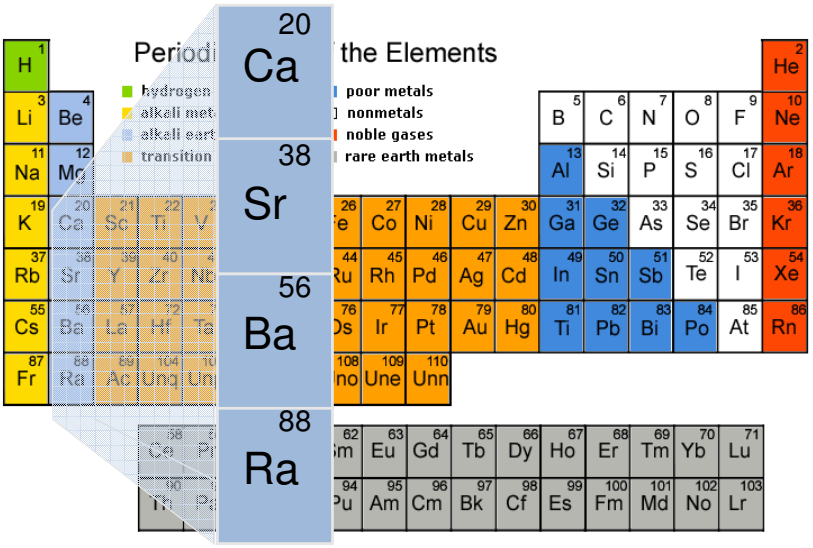
Radionuclide	*Physical half-life (days)*	*Emission*	*Maximum emission energy (Kev)*	*Recommended administered activity*	*Average tissue penetration (mm)*
Phosphorus-32	14.3	β	1710	185–370 MBq	2–3
Strontium-89	50.5	β	1470	1.48–2.22 MBq/Kg	2.4
Rhenium-186	3.7	β	1070	1295 MBq	1.1
Rhenium-188	0.7	β	2120	3300 MBq	3.1
Samarium-153	1.9	β	810	37 MBq/Kg	0.6
Radium-223	11.4	A	5850	0.05–0.25 MBq/Kg	0.05–0.08

Rubini 2013

Radium-223 in metastatic prostate cancer



- Radio-223 is a «bone-seeker drug»
- Increased uptake in sites with increased bone turnover

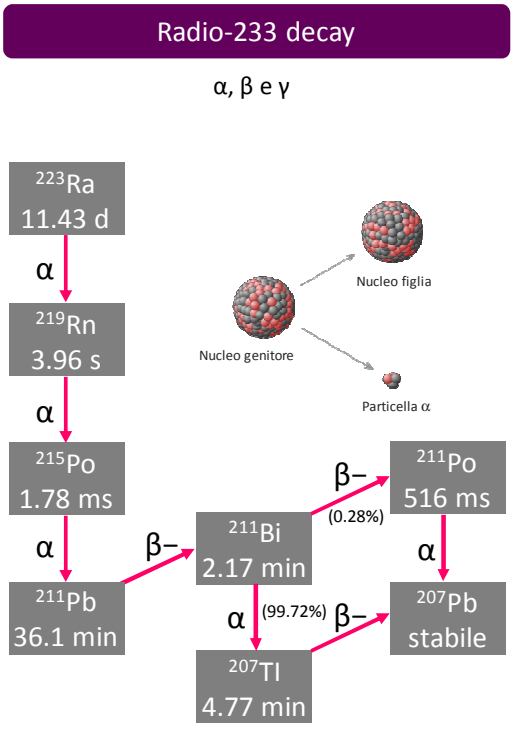


Hafeez S, et al. Expert Opin. Investig. Drugs (2013) 22(3):379-387

-93.5% α emission

< 4% β emission

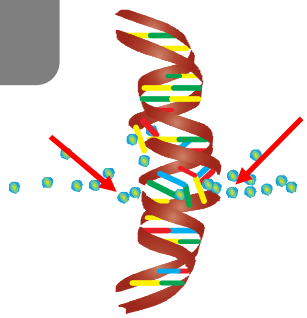
< 2% γ emission



β

- Low LET → single strand DNA break
- → more “hit” needed for cell killing

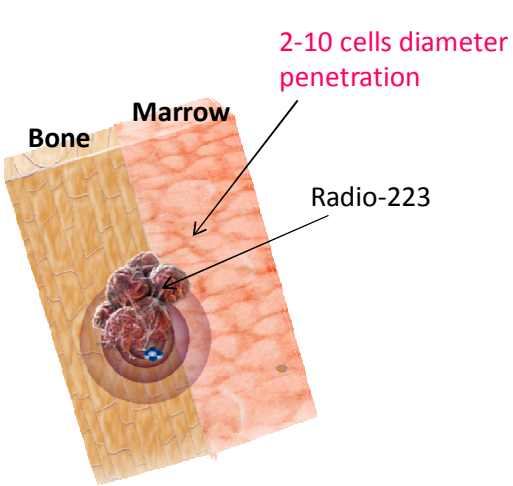
α

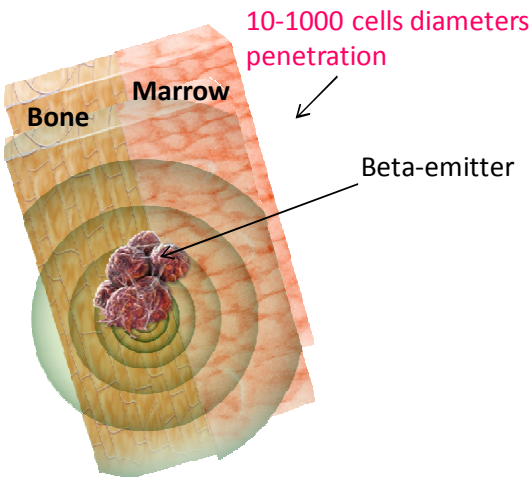


- Hi LET → double strand DNA break
- → reparation is less likely
- → higher chances of apoptosis or mititoc death

Modified form Bruland ØS et al. Clin Cancer Res 2006;12:6250s-7s; Henriksen G et al. Cancer Res 2002;62:3120-5

	Beta	Alfa
Tissue penetration (µm)	50–12 000	40–100
Particle relative mass	1	7000
DNA-hit for cell killing	>1000	1–4





Hobbs F, et al. Physics in medicine and biology 2012; 57: 3207

Radium-223 in metastatic prostate cancer

- Dose: 50kBq/Kg
- 6 administrations every 4weeks
- 15 minutes after injection only 20% still in blood and decreases to 4% at 4h and 1% at 24h
- Mainly intestinal excretion, 5% kidney excretion, no hepatobiliary excretion

Doses for a 73kg patients with a dose of 50 kBq/kg

	Gy per MBq	Rad per mCi	Gy	rad
Rectum	0.04645	171.88	0.1669	16.69
Ileum	0.00762	26.87	0.0265	2.65
Colon	0.03232	119.85	0.118	11.80
Red marrow	0.13879	513.51	0.5066	50.66
Ostheogenic cells	1.15206	4262.62	4.2050	420.50
Bladder wall	0.00403	14.90	0.0147	1.47
Kidneys	0.00320	11.86	0.0117	1.17
Liver	0.00298	11.01	0.0109	1.09

Lewington V, et al. Presented at ASCO GU2010. Abstract 216.

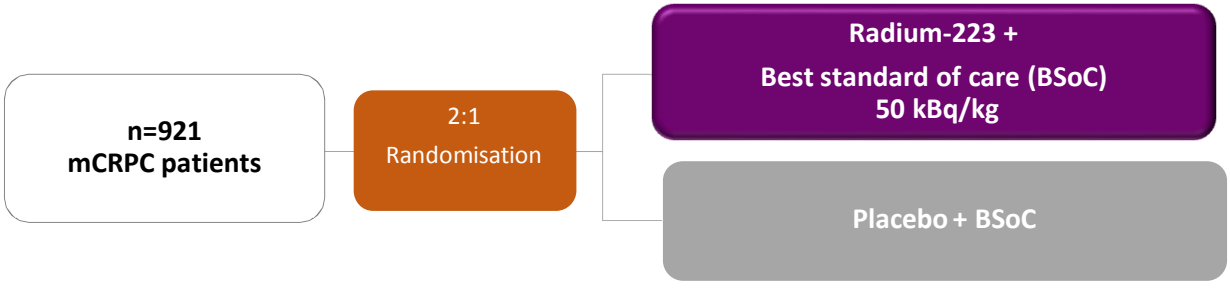
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

ALSYMPCA: Study Design



6 injections at 4 week intervals

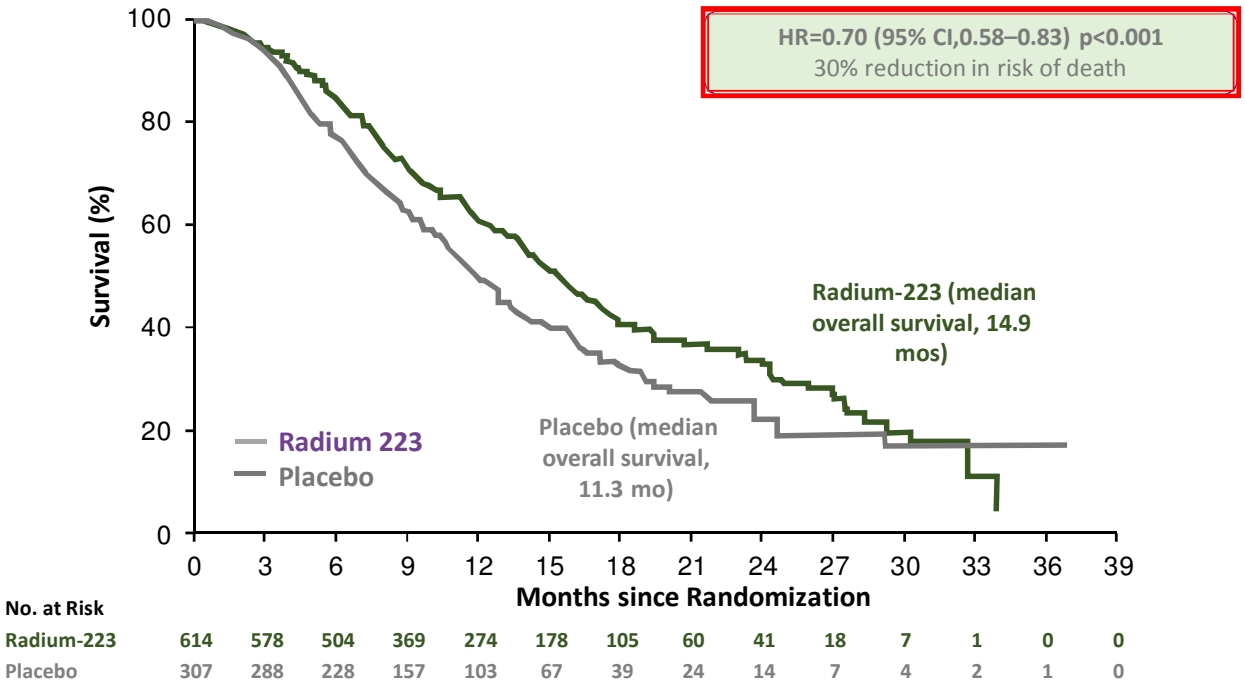
Key inclusion criteria
- Confirmed symptomatic CRPC
- ≥2 bone metastases
- No known visceral metastases
- Post docetaxel or unfit/unwilling for docetaxel

Stratification factors
- Total ALP: <220 U/L vs ≥220 U/L
- Bisphosphonate use: Yes vs no
- Prior docetaxel: Yes vs no

Parker C, et al. N Engl J Med. 2013;369:213-223.

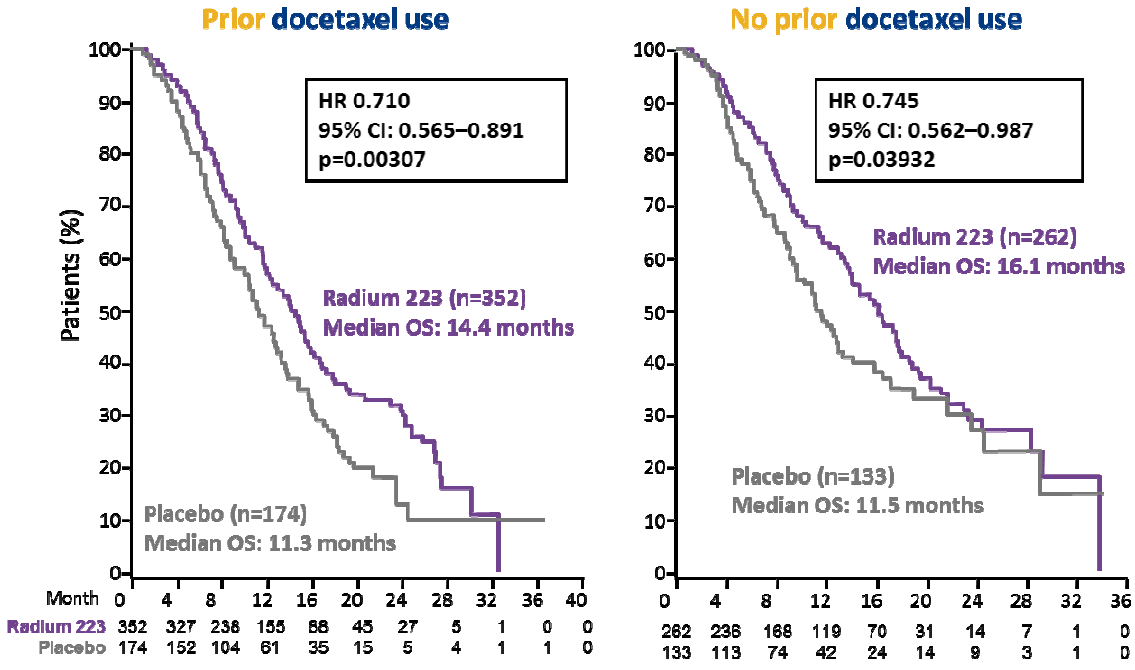
ALSYMPCA: Overall Survival

3.6 month improvement vs placebo



Parker et al. N Engl J Med. 2013; 18;369(3):213–223.

Phase 3 ALSYMPCA Overall Survival by prior docetaxel



Vogelzang NJ, et al. *J Clin Oncol.* 31, 2013 (suppl; abstr 5068).

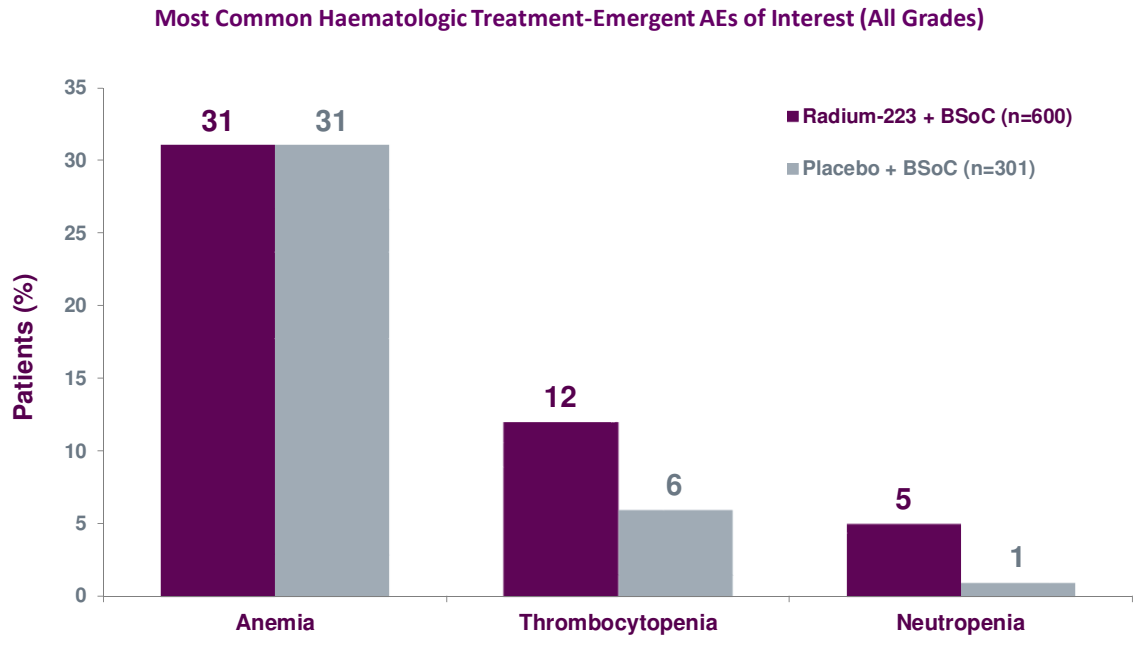
ALSYMPCA: Main Secondary Endpoints

Secondary Efficacy Endpoints	Radium-223 (n=614)	Placebo (n=307)	Hazard Ratio (95% CI)	P Value
Median time to first SSE (months)	15.6	9.8	0.66 (0.52-0.83)	<0.001
Median time to increase in total ALP level (months)	7.4	3.8	0.17 (0.13-0.22)	<0.001
Median time to increase in PSA level (months)	3.6	3.4	0.64 (0.54-0.77)	<0.001
Total ALP response (≥30% reduction) n/total n (%)	233/497 (47)	7/211 (3)	—	<0.001
Total ALP normalisation n/total n (%)	109/321 (34)	2/140 (1)	—	<0.001

All main secondary endpoints favour radium-223 (+ BSoC) compared with placebo (+ BSoC)

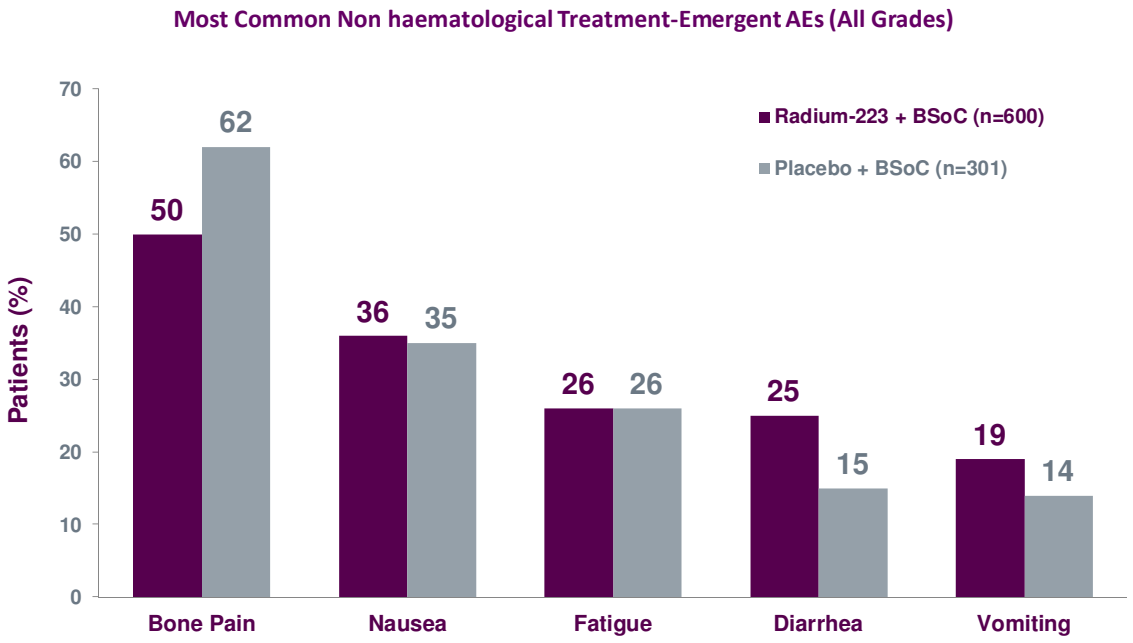
ALP, alkaline phosphatase; BSoC, best standard of care; PSA, prostate-specific antigen; SSE, symptomatic skeletal event

ALSYMPCA: Haematological Adverse Events



BSoC, best standard of care
Updated analysis.
Parker C, et al. N Engl J Med. 2013;369:213-223.

ALSYMPCA: Non Haematological Adverse Events



AE, adverse events; BSoC, best standard of care
Updated analysis.
Parker C, et al. N Engl J Med. 2013;369:213-223.

	All Grades		Grades 3 or 4	
	Radium 223 (n=600)	Placebo (n=301)	Radium 223 (n=600)	Placebo (n=301)
Hematological				
Anaemia	187 (31)	92 (31)	77 (13)	40 (13)
Neutropenia	**30 (5)**	**3 (1)**	**13 (2)**	**2 (1)**
Thrombocytopenia	**69 (12)**	**17 (6)**	**38 (6)**	**6 (2)**
Non-haematological				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhoea	**151 (25)**	**45 (15)**	**9 (2)**	**5 (2)**
Nausea	213 (36)	104 (35)	10 (2)	5 (2)
Vomiting	111 (18)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

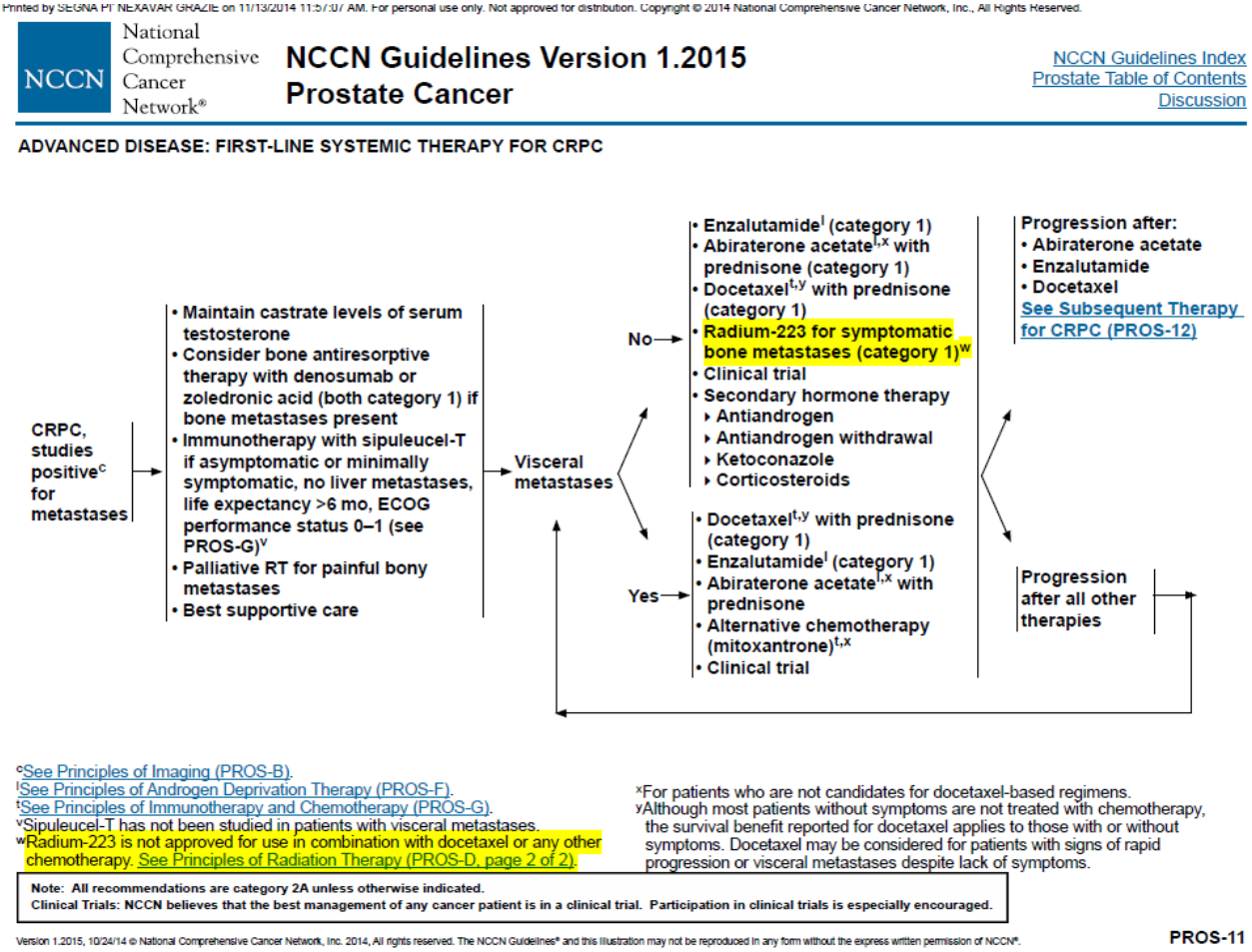
Data are n (%)

Parker C, et al. *N Engl J Med.* 2013;369:213-223

Front-line options that improve survival

Treatment	Trial	Visceral disease allowed	HR	Survival (mos)
Docetaxel/prednisone vs Mitoxantrone/prednisone	TAX 327[1]	Yes	0.79	18.9 vs 16.5
Sipuleucel-T vs control	IMPACT[2]	No	0.78	25.8 vs 21.7
Abiraterone/prednisone vs Placebo/prednisone	COU-302[3]	No	0.81	34.7 vs 30.3
Enzalutamide vs Placebo	PREVAIL[4]	Yes	0.70	32.4 vs 30.4
Radium 223 vs Placebo/BSC	ALSYMPCA[5]	No	0.70	14.9 vs 11.3

[1]Tannock et al. N Engl J Med 2004;351(15):1502-1512, [2]Kantoff et al. N Engl J Med 2010;363(5):411-422, [3]Ryan et al. N Eng J Med 2013;368:138–48, [4]Beer et al. N Engl J Med 2014, [5]Parker et al. NEJM 2013;369(2):213-223



ADVANCED DISEASE: SUBSEQUENT SYSTEMIC THERAPY FOR CRPC

No visceral metastases

Prior therapy enzalutamide/abiraterone:	Prior therapy docetaxel:
• Docetaxel with prednisone (category 1)[t] • Abiraterone acetate[l] or enzalutamide • Radium-223 (category 1) if bone-predominant disease • Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1 • Clinical trial • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care	• Enzalutamide (category 1) • Abiraterone acetate[l] with prednisone (category 1) • Radium-223 (category 1) if bone-predominant disease • Cabazitaxel with prednisone (category 1)[t] • Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1 • Clinical trial • Docetaxel rechallenge[t] • Alternative chemotherapy (mitoxantrone)[t] • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care

Visceral metastases

Prior therapy enzalutamide/abiraterone:	Prior therapy docetaxel:
• Docetaxel with prednisone (category 1)[t] • Clinical trial • Abiraterone acetate[l] or enzalutamide • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care	• Enzalutamide (category 1) • Abiraterone acetate[l] with prednisone (category 1) • Cabazitaxel with prednisone (category 1)[t] • Clinical trial • Docetaxel rechallenge[t] • Alternative chemotherapy (mitoxantrone)[t] • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care

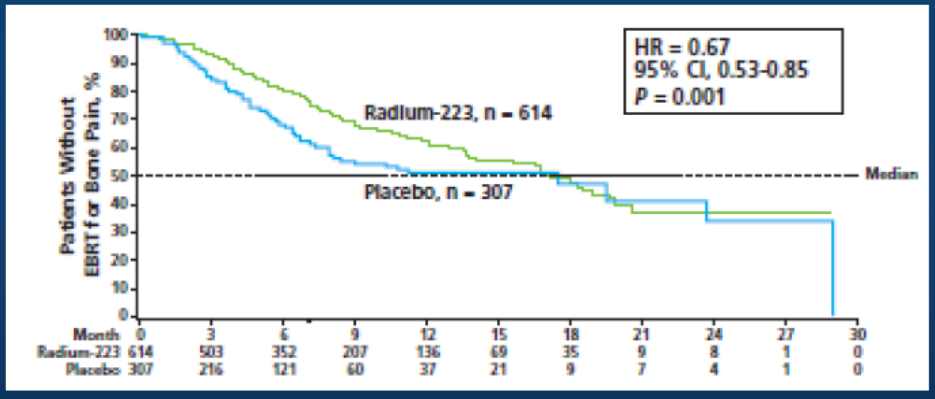
[l]See Principles of Androgen Deprivation Therapy (PROS-F). [t]See Principles of Immunotherapy and Chemotherapy (PROS-G).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

External beam radiation therapy (EBRT) use and safety with radium-223 dichloride (Ra-223) in patients (pts) with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (mets) from the ALSYMPCA trial. [Finkelstein et al. Abstract 182]

RESULTS: ON STUDY EBRT (RECOREDED AS A CONCOMITANT PROCEDURE)

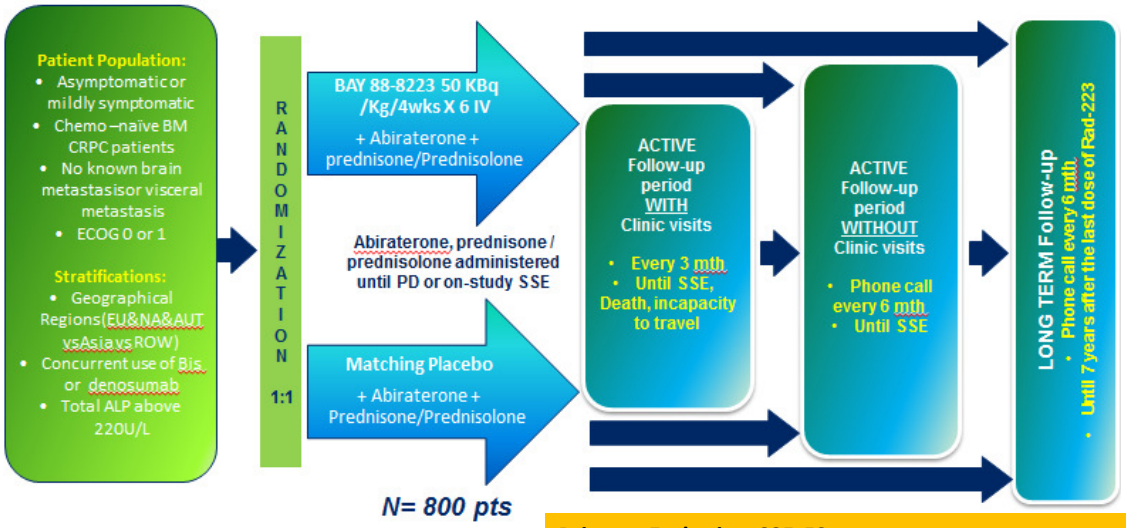
- 186/614 (30%) Ra-223 patients and 105/307 (34%) placebo patients received EBRT for bone pain and were included in the secondary endpoint analysis of time to first EBRT.
- Ra-223 significantly reduced the risk of EBRT for bone pain by 33% versus placebo (HR=0.67, P=0.001) (Figure).



- Treatment effect of Ra-223 on consistent across all analyzed subgroups, except patients with >20 mets (HR=1.06).
- Safety profile of Ra-223 was similar with or without concomitant EBRT.
  - Rates of myelosuppression were low regardless of concomitant EBRT use (with EBRT vs without EBRT, all grade): anemia 34% vs 30%; thrombocytopenia 12% vs 11%; neutropenia 6% vs 4%; and leukopenia 3% vs 5%).

Phase III Study ERA-223

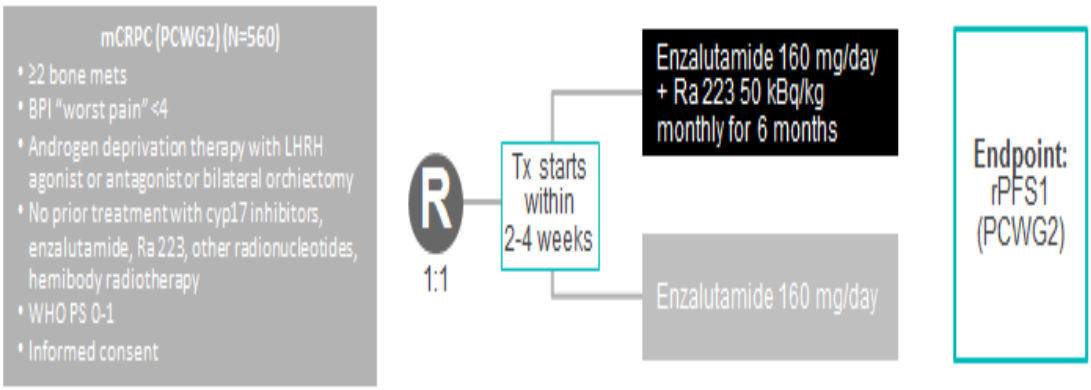
- Phase III; randomized, double blind, placebo-controlled
- Approximately 120 sites cross regions



Primary Endpoint: SSE-FS
Secondary Endpoints: OS; Time to opiate use for cancer pain;Time to pain progression; HRQoL ; rPFS; Safety

Attivo dal marzo 2014

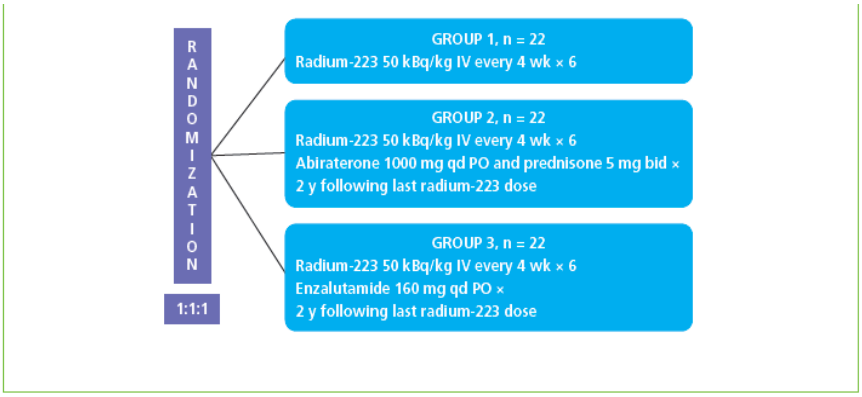
PCWG2 - Randomized Phase III Study



Phase II study

Criteri Inclusione: Gli stessi di ALSYMPCA

Arruolamento dovrebbe concludersi a fine 2015



OBJECTIVES

Primary Objective

- Test bone scan response at week 24 based on quantified BSLA for each regimen

Secondary Objectives

- Evaluate radium-223 safety alone and in combination with abiraterone or enzalutamide
- Describe radiologic progression-free survival (rPFS), symptomatic skeletal event–free survival (SSE-FS), OS, and time to radiologic bone progression
  - Symptomatic skeletal events (SSEs) include time to external beam radiation therapy use for bone pain or occurrence of new pathologic fracture (vertebral and nonvertebral), spinal cord compression, or tumor-related orthopedic surgery
  - SSE-FS calculated from time of randomization to date of first SSE or death

Select Exploratory Objectives

- Evaluate bone scan response by axial regions (pelvis, ribs, spine, and extremities)[14]
- Evaluate diffusion-weighted magnetic resonance imaging (DW-MRI) and sodium fluoride positron emission tomography–computed tomography (NaF PET-CT) imaging
- Evaluate alkaline phosphatase (ALP) and prostate-specific antigen (PSA)

Morris, MJ et al (Abstract 5012)
Effects of Radium-223 dichloride (Ra-223) with docetaxel on prostate-specific antigen (PSA) and bone metastases: A Phase 1/2A Clinical Trial

EFFECTS OF RADIUM-223 DICHLORIDE (RA-223) WITH DOCETAXEL (D) VS D ON PROSTATE-SPECIFIC ANTIGEN (PSA) AND BONE ALKALINE PHOSPHATASE (BALP) IN PATIENTS (PTS) WITH CASTRATION-RESISTANT PROSTATE CANCER (CRPC) AND BONE METASTASES (METS): A PHASE 1/2A CLINICAL TRIAL. (MORRIS ET AL. ABSTRACT 5012)

STUDY DESIGN AND RESULTS

- A follow-up presentation to Morris et al ASCO GU 2015 (Abstract 202) on the same endpoints.

PATIENTS N=46

- Progressive metastatic CRPC
- ≥2 bone metastases
- >2 lung and/or liver (>2 cm) metastases were not permitted
- No symptomatic nodal disease or other primary tumors

OBJECTIVES: Safety, PSA, and bALP dynamics

R 2:1

- Radium-223 50KBq/kg IV 6 week x 5 + docetaxel 60 mg/m² IV q 3 week x 10 + 5 mg prednisone bid **(n=33)**
- Docetaxel 75 mg/m² IV q 3 week x 10 (option of step down to docetaxel 60 mg/m² IV) + 5 mg prednisone bid **(n=13)**

RESULTS	PSA		bALP*	
	Ra-223 + DOC (n=33)	DOC (n=13)	Ra-223 + DOC (n=23)	DOC (n=11)
Any increase, n (%)	3 (9)	4 (31)	0	0
Decrease, n (%)				
<30%	4 912)	1 (8)	0	0
≥30%	26 (70)	8 (62)	23 (100)	11 (100)
>50%	20 (61)	7 (54)	22 (96)	9 (82)
>80%	10 (30)	4 (31)	9 (39)	2(18)
Normalization , n (%)	N/A	N/A	21 (91)	7 (64)
Median percentage change from baseline	-75	-55	-77	-59

- NOTE: Only 2/13 patients who received docetaxel alone completed the approved dose of 75 mg/m². A higher percentage of patients who received docetaxel alone (54%) compared with radium-223 + docetaxel (27%), discontinued treatment.

*Patients with baseline bALP > upper limit of normal (> 21 µg/L).

KEY TAKE AWAY: Radium-223 + docetaxel was well tolerated as confirmed by the preliminary safety findings in the phase 2a expansion cohort. PSA and bALP declines were seen in both treatment arms. A higher percentage of patients who received radium-223 + docetaxel ––versus docetaxel alone had normalized bALP levels.