

**Radium 223 and SABR for
Bone metastases from Prostate Cancer**

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**Urology Rounds
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Dislosures

- Bayer
 - Makes Radium 223
 - Speakers fees
 - Ad Boards honoraria
- Varian
 - Make LINACs
 - Research grants

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Case 1

- 77 yr old, RP, pT2, iPSA 5.6, GS 4+5, R0
- Post op PSA 4.1 within 10 months
- Bone scan, progressive lesion in right iliac bone
- Mild pain
- CT confirmed sclerotic lesion at site of BS change
- No other lesions on CT or BS
- Otherwise healthy

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Standard Indications for External Beam irradiation to bone for bone mets

- Relieve pain
- Prevent impending fracture
- Prevent impending cord compression

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Solitary or Oligo (≤ 5) bone mets

-Does External beam RT to Asymptomatic bone mets(s) alter the natural history Survival for patients with metastatic prostate cancer?

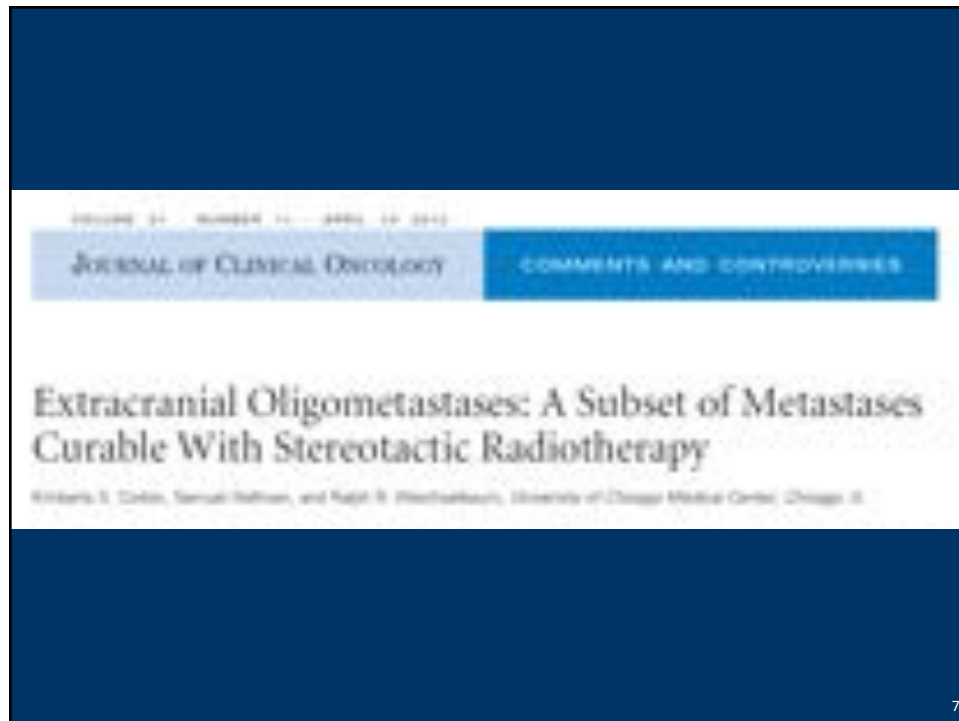
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Solitary or Oligo (≤ 5) bone mets

-Does External beam RT to Asymptomatic bone mets(s) alter the natural history Survival for patients with metastatic prostate cancer?

-Don't know

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Oligomets and SABR

-Arguments

- Surgery for mets,
 - tradition of increasing DFS
 - Liver mets with colon Ca
 - Renal Ca and lung mets

-Biology of Oligomets

- May be different from diffuse mets

-Detection of Oligomets

- Imaging

-SABR for oligomets

- Technical feasibility
- Retro and phase II data on local control

Oligomets and Prostate Ca

-Moreno. *Radiation Oncology* 2014, 9:258

(Table content is extremely faint and partially obscured by red boxes. Visible text includes '6 bone mets' in a red box.)

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Oligomets and Prostate Ca

-Moreno. *Radiation Oncology* 2014, 9:258

- Mix of sites*
- Very few, < 200 bone met patients*
- Mix of systemic therapy*
- Short follow-up*
- Impossible to tell if alters natural history/survival*

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SABR for Oligometes and Prostate Ca

-Muacevc. Urologic Oncology: Seminars and Original Investigations 31 (2013) 455–460

- 54 patients with bone mets, SABR, 19 with hormones
- MRI and PET/CT F-up
 - 12 mo local control 95%
- Mean F-up 14 months (3-48)
 - Only 8 patients at risk at >18 months

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High dose RT for Asx Solitary or oligo bone met:

- Confine to clinical trial?
- If outside of a trial, what dose and fractionation?
 - Occasionally in well informed patient willing to take the risk
 - 40/15 or 50/25, depends on tolerance of surrounding structures

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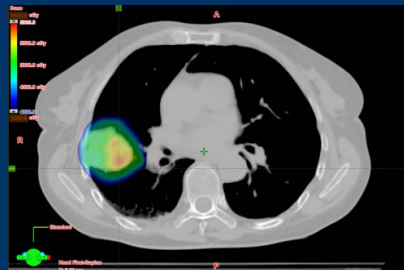
High dose RT for Asx Solitary or oligo bone met:

- If inside a trial do we have one open?
- Yes, SABR/COMET

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What is SABR? Stereotactic Ablative Radiotherapy

- SABR is high-precision, high-dose radiation therapy, based on two advances:
 - Improved targeting and planning
 - Improved treatment delivery
 - Usually also hypofractionated ($>7\text{Gy}/\#$)



Slide Courtesy of D Palma, National PI of SABR

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COMET Trial

Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET): A Randomized Phase II Trial

Principal Investigators

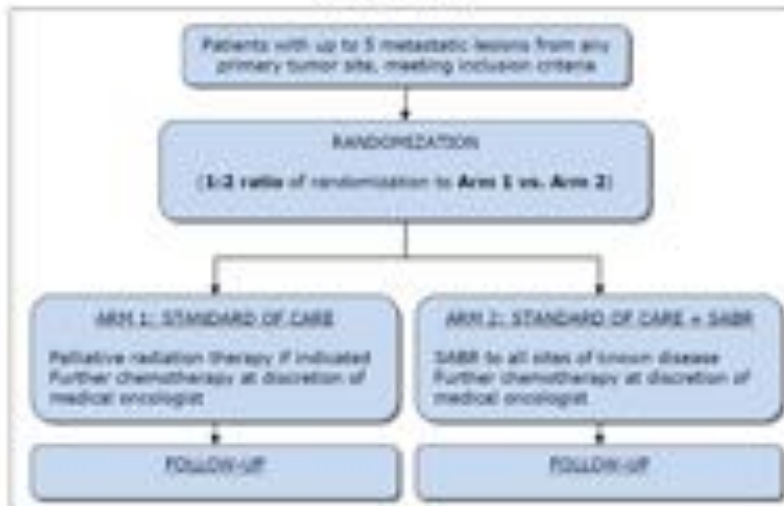
Dr. David Palma, MD, MSc, PhD, FRCP
 Radiation Oncologist
 OICR Clinical Scientist
 London Regional Cancer Program

Prof. Dr. Suresh Senan, MRCP, FRCR, PhD
 Professor of Clinical Experimental Radiotherapy
 Department of Radiation Oncology,
 VU University Medical Center

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Comet Trial

STEREOTACTIC ABLATIVE RADIOTHERAPY FOR COMPREHENSIVE TREATMENT OF OLIGOMETASTATIC TUMORS (SABR-COMET): A RANDOMIZED PHASE II TRIAL



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Doses:

-SABR arm of COMET:

- High doses, short course
 - Single Arc, VMAT, IGRT
 - Volumetric Modulated Arc, Image Guided RT
 - Eg 35 Gy/5#

-Conventional arm of COMET

- Anterior to posterior opposed fields,
- 20 Gy/5# or 8 Gy in 1# if Symptomatic

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COMET Trail Endpoints

Primary Endpoint

Overall Survival (two-sided $\alpha=0.2$; $\beta=0.2$)

Secondary Endpoints

- Quality of life
 - Functional Assessment of Cancer Therapy: General (FACT-G)
- Toxicity
 - NCI-CTC version 4
- Progression-free survival
 - Time from randomization to disease progression
- Number of cycles of further chemotherapy

REQUIRED SAMPLE SIZE = 99 patients

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COMET Inclusion Criteria

- Histologically confirmed malignancy with metastatic disease detected on imaging. Biopsy of metastasis is preferred,
- ECOG performance status 0-1, life expectancy > 6 months
- Controlled primary tumor
- All sites of disease can be safely treated
- Not a candidate for surgical resection at all sites
- No cytotoxic or targeted therapy 4 weeks prior to SABR or two weeks after
- Presentation of patient at MDT or QA rounds

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COMET consent

WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?

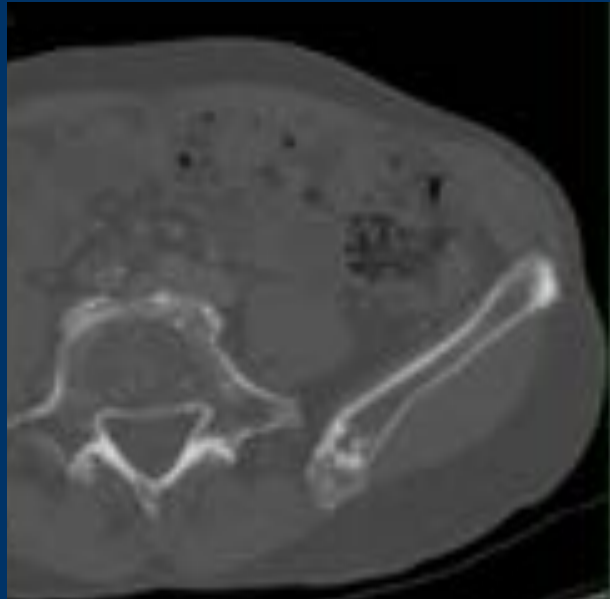
- No one knows whether or not you will benefit from this study. There may or may not be direct benefits to you.

Risks:

- Radiation treatments to bone can be associated with pain, ... and a risk of a broken bone.
- Spinal cord injury resulting in paraplegia
- these side effects may result in death.

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Case 1: CT image



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Conventional RT

Anterior to posterior
Parallel pair
20 Gy/5#



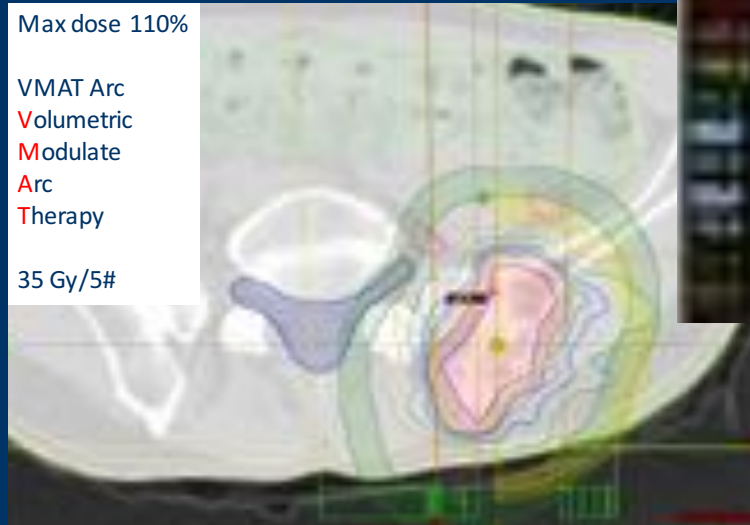
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SABR: Case 1

Max dose 110%

VMAT Arc
Volumetric
Modulate
Arc
Therapy

35 Gy/5#

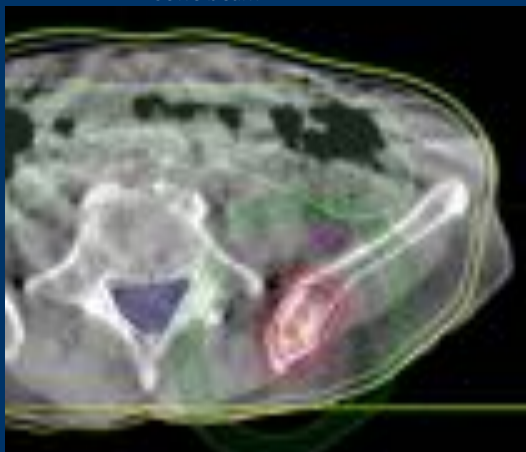


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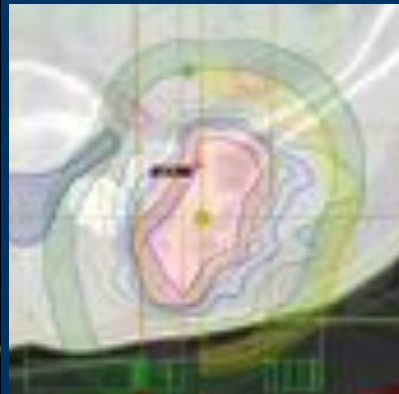
Case 1: immobilization and imaging

- Immobilization board with Vac Lock
- Kv bone match
- CT on LINAC to check match

Cone beam



Planning Scan



Case 1: Current status

- Randomized to SABR in Jan 2013, 35 Gy/5#
- 1 year AA with RT to bone lesion, last dose Feb 2013
- No side effects for RT (YET)
- June 2015: PSA 0.08, TTT 9.8 (since Jun 2014)
- Bone Scan and CT q3-6 months per protocol
 - no other lesions as yet
- ? Same effect with IAA

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Radioisotopes for CRPC with symptomatic bone mets

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Case 2:

- Prior RP for high risk prostate Ca
- Now 49 year old with pelvic (iliac) pain from metastatic CRPC

- History of bone pain Tx with RT to pelvis
- Previous treated with bicalutamide, nilutimide, Docetaxel,
 - Abiraterone, Enzalutamide,
- At referral, on denosumab x 3 months

- Rising PSA and iliac pain
- Bone scan – multiple mets,
- CTA and P – small pelvic nodes, no visceral mets
- Good marrow, renal and liver function

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Calcium, Radium and Strontium

Periodic Table of the Elements

Legend:

- Hydrogen
- alkali metals
- alkaline earth metals
- transition metals
- poor metals
- nonmetals
- noble gases
- rare earth metals

Highlighted elements:

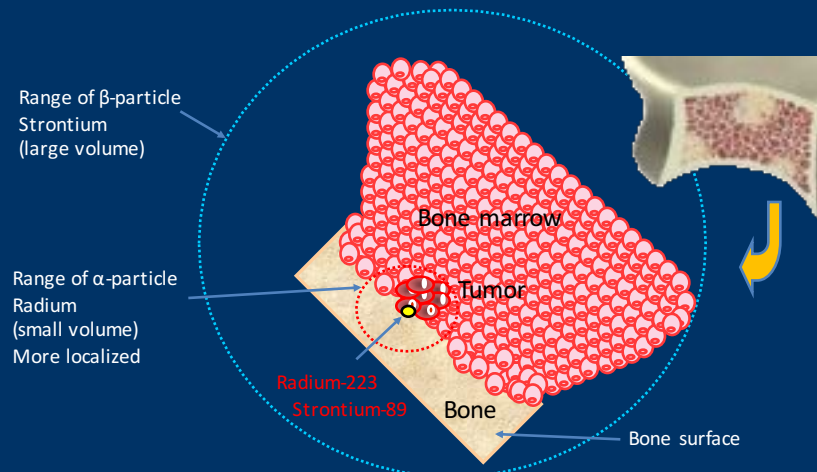
- Sr 38
- Ca 20
- Ra 88

- Radium: An alkaline earth metal
- A natural bone seeker because it is a 'calcium mimic' ¹
- Optimal for a radiopharmaceutical
- Physical half-life of 11.4 days ²

1. Bruland et al. Clin Cancer res 2006;12 (20 suppl)
 2. Henriksen et al. Can Res. 2002;62:3120.

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Radium and Strontium Mode of Action



1. Henriksen et al. *Cancer Res.* 2002;62:3120.
2. Brechbiel MW. *Dalton Trans.* 2007;43:4918–4928.
3. Vozelgang et al. Presented at: American Society for Clinical Oncology annual meeting 2013; poster 5068.

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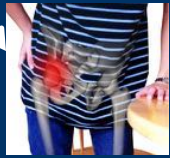
Characterizing events in bones

- Skeletal related events (SRE's)
- Symptomatic skeletal related events (SSE's)

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SRE'S: in CRPC

Pathologic Fracture



Spinal Cord Compression



Change in anticancer drugs



Radiotherapy to Bone



Surgery to Bone



SRE = skeletal-related event

Ibrahim A, et al. Clin Cancer Res 2003;9:2394-2399; ©iStockphoto.com/LesperElgaard. Image courtesy of Tel Aviv Sourasky Medical Center, Israel 1

Symptomatic SRE's in CRPC

Pathologic Fracture



Spinal Cord Compression



Radiotherapy to Bone



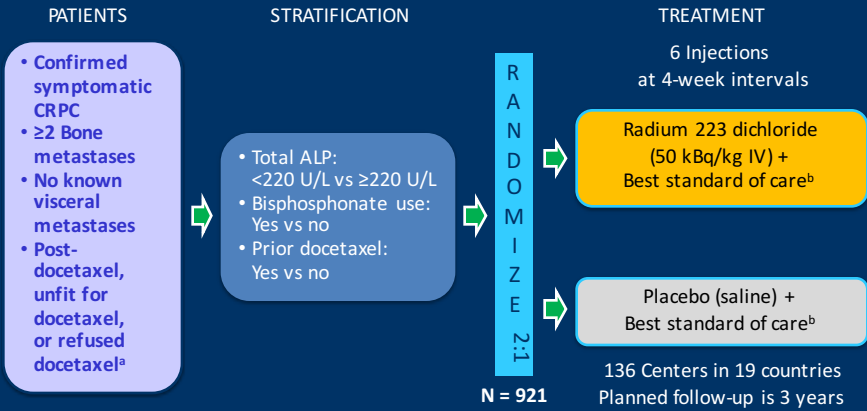
Surgery to Bone



SRE = skeletal-related event

Ibrahim A, et al. Clin Cancer Res 2003;9:2394-2399; ©iStockphoto.com/LesperElgaard. Image courtesy of Tel Aviv Sourasky Medical Center, Israel 2

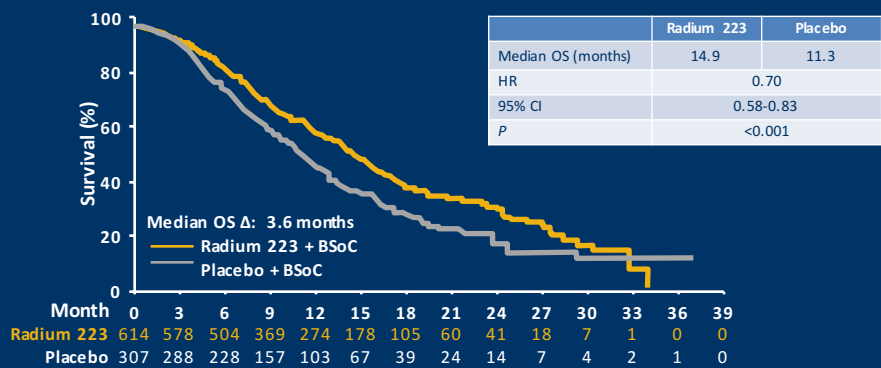
Radium 223: ALSYMPCA: Study Design



ALP, alkaline phosphatase; ALSYMPCA, ALpharadin in SYMptomatic Prostate CAncer; CRPC, castration-resistant prostate cancer; IV, intravenous.
^aUnfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable.
^bBest standard of care is defined as a routine standard of care at each center, eg, local external beam radiation therapy, corticosteroids, antiandrogens, estrogens (eg, stilbestrol), estramustine, or ketoconazole.
 From supplementary appendix. Parker C, et al. *N Engl J Med*. 2013;369:213-223

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ALSYMPCA: Updated Analysis Kaplan-Meier Estimates of Overall Survival

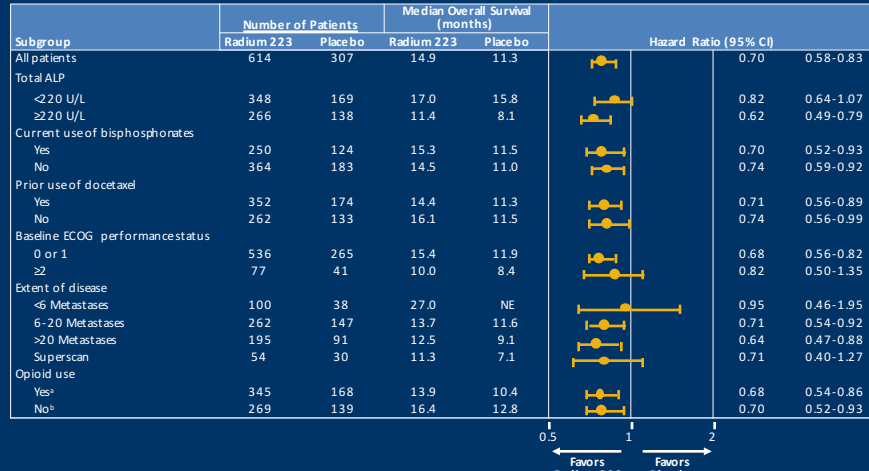


The updated analysis confirmed the interim analysis 30% reduction in risk of death for patients in the radium 223 group compared with placebo.

ALSYMPCA, ALpharadin in SYMptomatic Prostate CAncer; BSoC, Best standard of care; CI, confidence interval; HR, hazard ratio; OS, overall survival.
 Parker C, et al. *N Engl J Med*. 2013;369:213-223

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ALSYMPCA: Updated Analysis Overall Survival Benefit Across Patient Subgroups



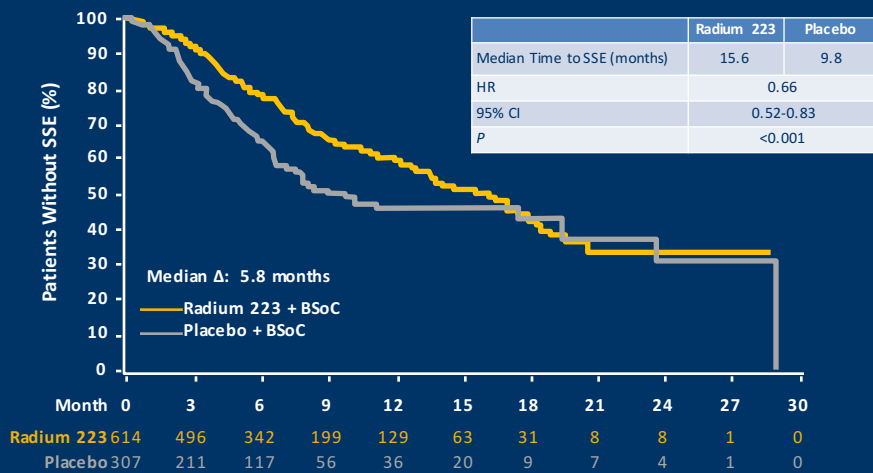
ALP, alkaline phosphatase; ALSYMPCA, ALpharadin in SYMptomatic Prostate Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

^aIncludes patients with a score of 2 or 3 on the World Health Organization (WHO) ladder for cancer pain.

^bIncludes patients without pain or opioid use at baseline and patients with a score of 1 on the WHO ladder for cancer pain.

Parker C, et al. *N Engl J Med.* 2013;369:213-223 35

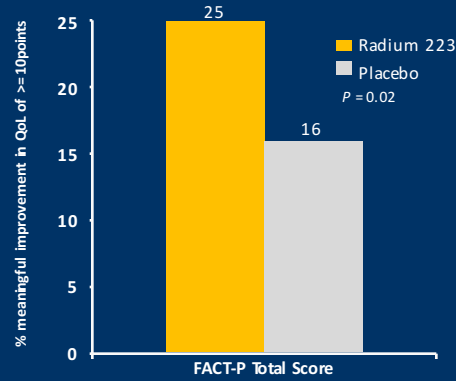
ALSYMPCA: Updated Analysis Kaplan-Meier Estimates of Time to First SSE



ALSYMPCA, ALpharadin in SYMptomatic Prostate Cancer; BSoC, Best standard of care; CI, confidence interval; HR, hazard ratio; SSE, symptomatic skeletal event.

Parker C, et al. *N Engl J Med.* 2013;369:213-223 36

ALSYMPCA Updated Analysis: Quality of Life FACT-P^a



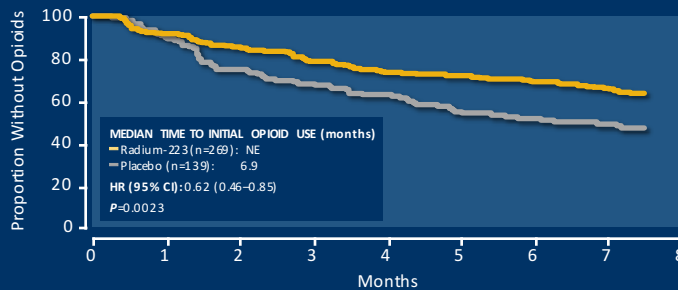
A significantly higher percentage of patients treated with radium 223, versus placebo, experienced a meaningful improvement in quality of life.

ALSYMPCA, ALpharadin in SYMptomatic Prostate Cancer; FACT-P, Functional Assessment of Cancer Therapy-Prostate.
^aTaken from page 219 (column 2, last paragraph)-page 220.

Parker C, et al. *N Engl J Med.* 2013;369:213-223 37

Time to Initial Opioid Significantly Longer with Radium-223

- 269/614 (44%) patients in the radium-223 group and 139/307 (45%) patients in the placebo group had no opioid use at baseline
- Of these, 96 (36%) in radium-223 group versus 70 (50%) in placebo group required opioid use for pain relief
- Median time to initial opioid use was significantly longer in the radium-223 group, compared with the placebo group



SOURCE: Nilsson S, et al. *J Clin Oncol.* 31, 2013 (suppl; abstr 5038).

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Adverse Reactions

- Most common clinical trial adverse drug reactions ($\geq 1\%$)

System Organ Class ^a	XOFIGO (n=600)		Placebo (n=301)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and lymphatic system disorders				
Leukopenia	4.2	1.3	0.3	0.3
Neutropenia	5.0	2.2	1.0	0.7
Pancytopenia	2.0	1.2	0.0	0.0
Thrombocytopenia	11.5	6.3	5.6	2.0
Gastrointestinal disorders				
Diarrhea	25.0	1.5 (grade 3 only)	15.0	1.7 (grade 3 only)
Nausea	35.5	1.7 (grade 3 only)	34.6	1.7 (grade 3 only)
Vomiting	18.5	1.7 (grade 3 only)	13.6	2.3 (grade 3 only)
General disorders and administration site conditions				
Injection site reactions (including erythema, pain and swelling)	1.2	0.0	0.0	0.0
Peripheral edema	13	2	10	1

^a Adverse reactions are identified using MedDRA version 14.1 and graded according to CTCAE version 3.0.

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How do you access

- Refer to Radiation Oncology
- Injections Done in nuclear medicine

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Where is Current access

- VCC- VGH
- CCSI-KGH
- VICC- RJH

- Future:
- FVCC-SMH, hopefully soon
- ACC-AH,
 - Likely to open in next 2 months
 - Further centres thereafter

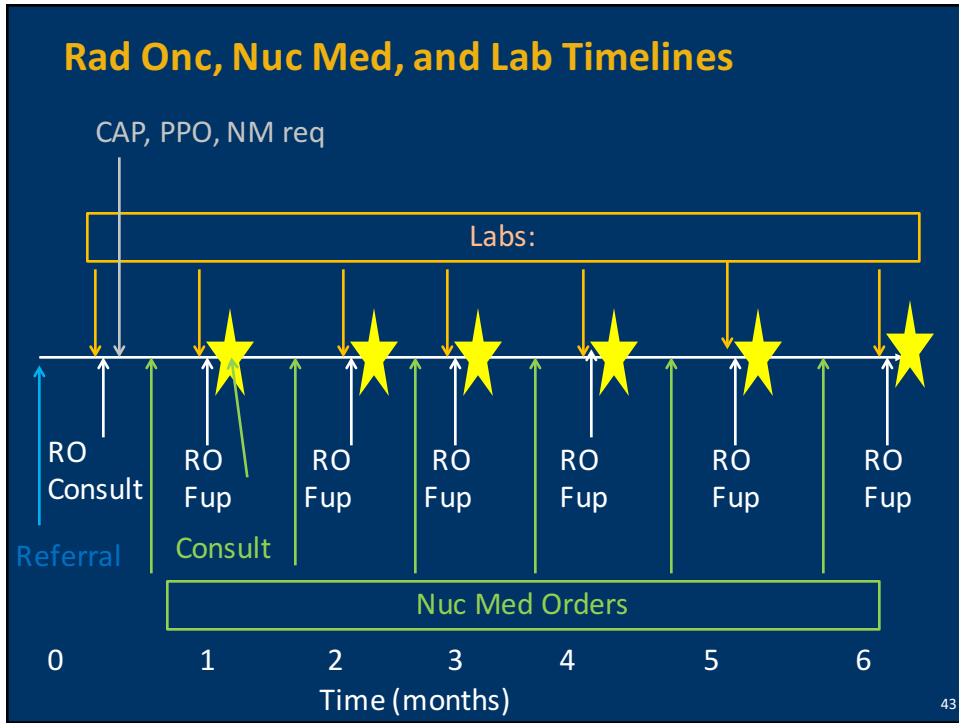
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Order and Delivery Timelines

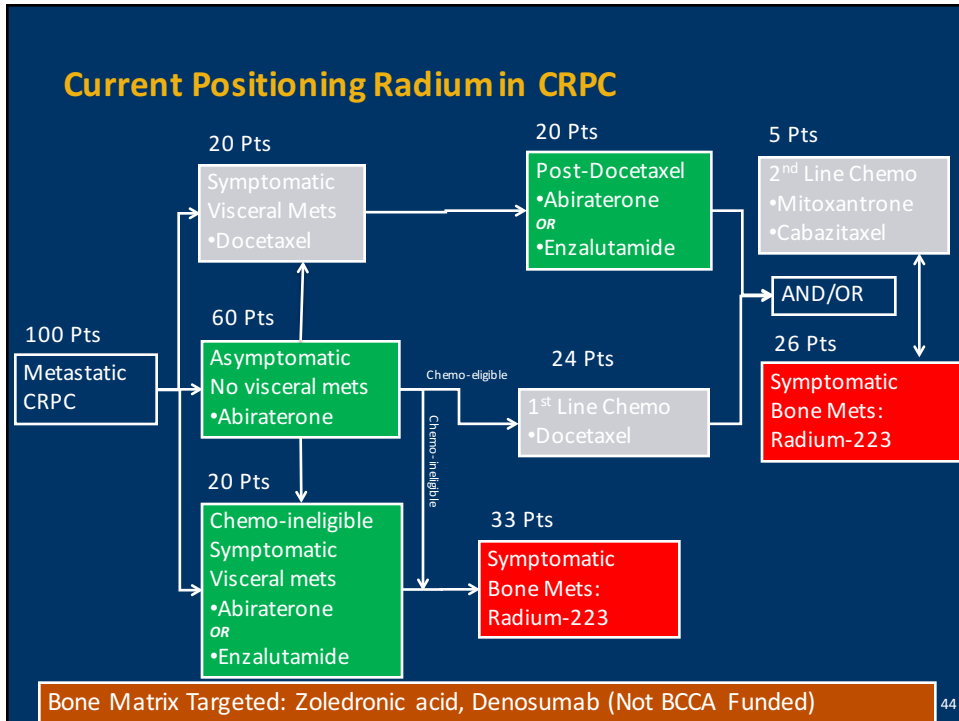
- Referral to rad onc consult: 1-7 days
- CAP: 1-2 days
- Nuc med rec to nuc med consult: 0-2 days
- Nuc med drug order to injection: 8 days

Site	Deadline for prescriber to order/injection begins	Deadline for order to be entered by Nuc Med	Earliest delivery	Guaranteed Delivery	Treatment Day
BCCA/renouveau General	Defined by Nuc Med	2:00 pm PST Tues	7:00 am PST Mon	5:00 pm PST Tues	Wed
Leadtime relative to Tx Day		-8	-2	-1	0

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Clinical Experience in BC as of April 2015

- 19 patients accrued on Access program
- 12 Patients in CAP since BCCA funding \
 - Feb to April 2015
- First 10 cases
 - 1st 4 cases accrued over 1 mo on study in Aug 2013.
 - 6 cases accrued in access program since May-June 2014.
 - In the Abi, Enza, Doce era

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Clinical Experience in BC: 1st 10 cases

- Prior therapies
 - Abiraterone: 10/10
 - EBRT to bone met: 10/10
 - Docetaxel: 9/10
 - Other Experimental agent: 8/10
 - Enzalutamide: 6/10
 - Mitoxantrone: 4/10
 - Carbazitaxel: 0/10
- Age at Radium 223
 - Median 73yr (50-88)

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Summary

- SABR, High dose RT for Asx oligometas
 - Experimental
 - Enrol in clinical trials
- Ra223 for Sx bone mets with CRPC:
 - Improves:
 - OS,
 - QoL,
 - Time to SSE,
 - Time to opioids in CRPC
 - Available: VCC, CCSI, VICC, FVCC soon
 - Refer to RO's