ALSYMPCA Phase III Data

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Overall Survival Benefit of Radium-223 Chloride (Alpharadin) in the Treatment of Patients With Symptomatic Bone Metastases in Castration-Resistant Prostate Cancer (CRPC): A Phase III Randomized Trial (ALSYMPCA)

C. Parker,[1] D. Heinrich,[2] J.M. O'Sullivan,[3] S. Fossås,[4] A. Chodacki,[5]
T. Demkow,[6] A. Cross,[7] B. Bolstad,[8] J. Garcia-Vargas,[9] and O. Sartor,[10] on behalf of the ALSYMPCA Investigators

[1]The Royal Marsden Hospital, Surrey, UK; [2]Haukeland Univ Hospital, Bergen, Norway; [3]Centre for Cancer Research and Cell Biology, Queen's Univ, Belfast, Northern Ireland; [4]Radiumhospitalet, Oslo, Norway; [5]Hospital Kochova, Chomutov, Czech Republic; [6]Centrum Onkologii – Instytut im Sklodowskiej-Curie, Warsaw, Poland; [7]PharmaNet, Hemel Hempstead, UK; [8]Algeta ASA, Oslo Norway; [9]Bayer HealthCare Pharmaceuticals, Montville, NJ, USA; [10]Tulane Cancer Center, New Orleans, LA, USA

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- C. Parker has served in a consultant or advisory role for Algeta ASA (uncompensated) and Bayer
- D. Heinrich and O. Sartor have served in consultant or advisory roles for Algeta ASA
- B. Bolstad has an ownership interest in and was employed by Algeta ASA until December 2010
- J. Garcia-Vargas is an employee of Bayer HealthCare Pharmaceuticals
- J.M. O'Sullivan, S. Fosså, A. Chodacki, T. Demkow, and A. Cross have nothing to disclose

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Investigators from 19 countries:

Massimo Aglietta
Dino Amadori
Enrique Aranda
Javier Arbizu
Amit Bahl
Vladimir Balaz
Pilar Bello
Rami Ben-Yosef
Ignace Billiet
David Bottomley
Jan Breza
Michael Brown
Walter Cabral
Micheal Cano
Joan Carles
Prabir Chakraborti
Piotr Chlosta
Ales Chodacki
Rob Coleman
Marian Cvik
David Dalley
Marcos Dall'Oglio
Ronaldo Damiao
Marinus de Goeij
Graeme Dickie
Sanjay Dixit
Jesus Garcia Donas
Anthony Dowling
Ygael Dror
Lionel Duck
Monstserrat Estorch
Ursula Falkmer
David Feltl
Sophie Dorothea Fosså
Ann-Sofie Fransson
Lars Franzen
Stephanie Gibbs
John Graham
Alexander Haese
Christian Hampel
Rosemary Harrup
Catherine Heath
Daniel Heinrich
Svein Inge Helle
Milan Hora
Peter Hoskin
Gary Hudes
Michael Jackson
Nick D James
Barbara Jarzab
Piotr Jarzemski
Dag Clement Johannessen
Walter José Koff
Unn-Miriam Kasti
Christian Keil
Jon Kindblom
Olbjorn Klepp
Robert Klijer
Jan Kliment
Laurence Klotz
Ivo Kocak
Andrzej Kolodziejczyk
Markus Kuczyk
Philip Kwong
Magnus Lagerlund
Kari Margrethe Larsen
Angus Leung
Eugene Leung
Roberto Llarena
John Logue
Rafael López
Jarad Martin
Gavin M Marx
Begoña Mellado
Wilmosh Mermershtain
Caterina Messina
Jeff Michalski
Andrew Miller
Ivan Mincik
Julian Money-Kyrle
Alain Monnier
Andre Moraes
Andre Murad
Chee Kwan Ng
Carsten Nieder
Sten Nilsson
Joe O'Sullivan
Christopher Parker
Sarah Pascoe
Samir Patel
Alain Pecking
Jaroslav Pernicka
Ken Pittman
Frank Priou
Prakash Ramachandra
Robert Reid
Angus Robinson
Ton Roeleveld
Claudio Rossetti
Alberto Sáenz-Cusí
Diana Salvo
Carlos Sampaio
Howard Sandler
Alton Oliver Sartor
Andres Jan Schrader
Jan Schraml
Christopher Scrase
Mihalj Seke
Avishay Sella
Sergio Vicente Serrano
Mark Sidhom
Arne Solberg
Anna Sowa-Staszczak
John Staffurth
Andrew Stockdale
Arne Strauss
Santhanam Sundar
Peter Swift
Isabel Syndikus
Miah Hiang Tay
Michael Tomblyn
Michel Toubeau
Michael Carsten Truss
Penny Vande Streek
Subramaniam Vasanthan
Henk Vergunst
Paul Verhagen
Nicholas Vogelzang
Wolfgang von Pokrzywnitzki
Steffen Alexander Wedel
Anders Widmark
Pawel Jan Wiechno
Sibylle Böhmer
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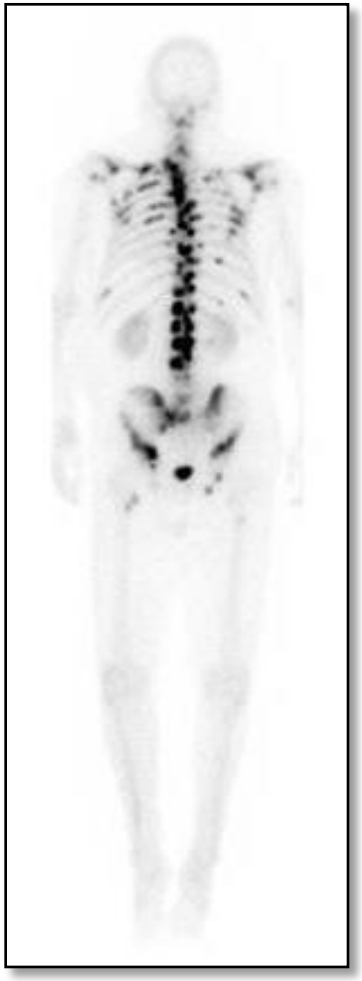
Background and Rationale

- > 90% of patients with metastatic CRPC have radiologic evidence of bone metastases[1]
- Skeletal-related events (SREs) include spinal cord compression, pathological fracture, and need for surgery or EBRT[2]
- Bone metastases are a major cause of death, disability, decreased quality of life, and increased treatment cost[3]
- Current bone-targeted therapies have not been shown to improve survival

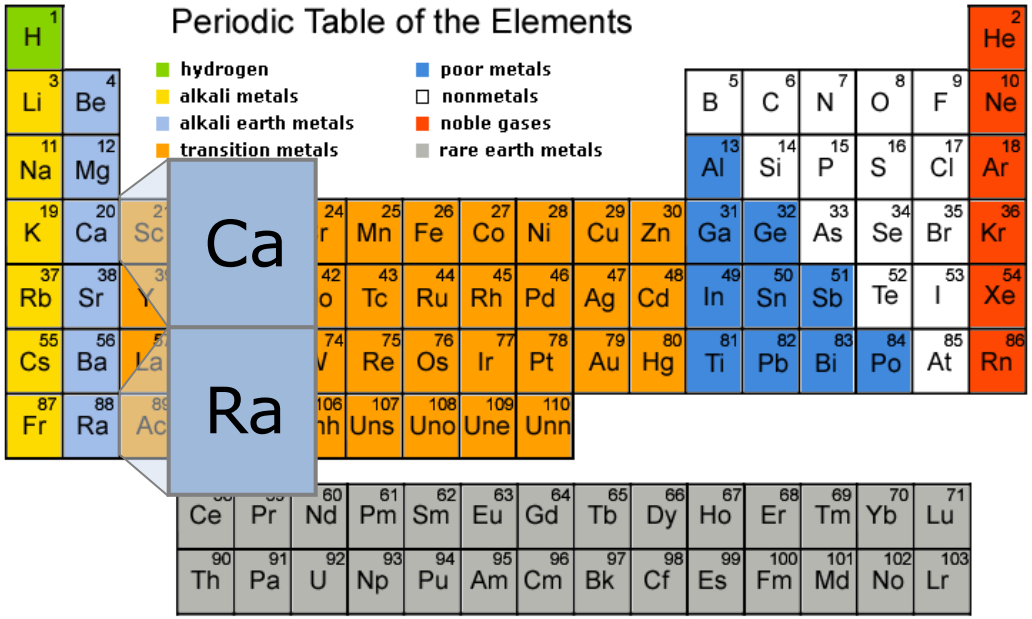


1. Tannock et al. *N Engl J Med.* 2004;351:1502-1512.
2. Lipton. *Semin Oncol.* 2010;37:S15-S29.
3. Lange and Vasella. *Cancer Metastasis Rev.* 1999;17:331-336.

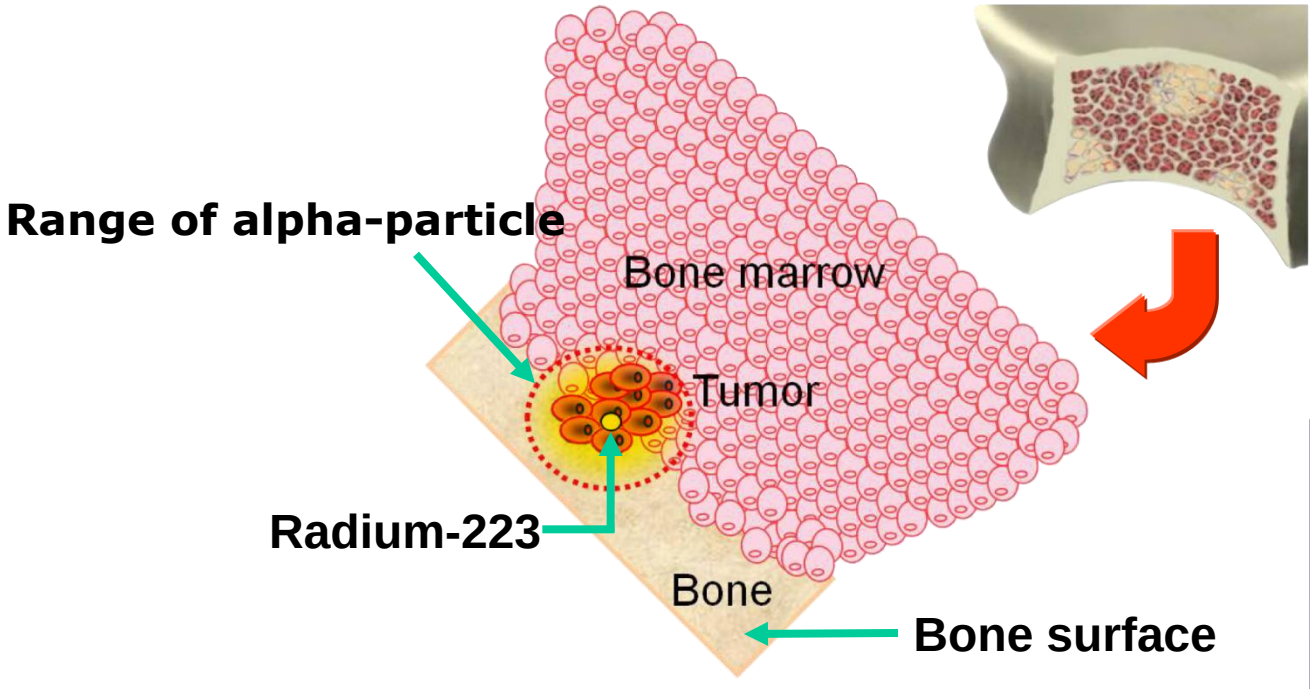
ALGETA

Radium-223 Targets Bone Metastases

- Radium-223 acts as a calcium mimic
- Naturally targets new bone growth in and around bone metastases
- Radium-223 is excreted by the small intestine



Radium-223 Targets Bone Metastases



- 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.

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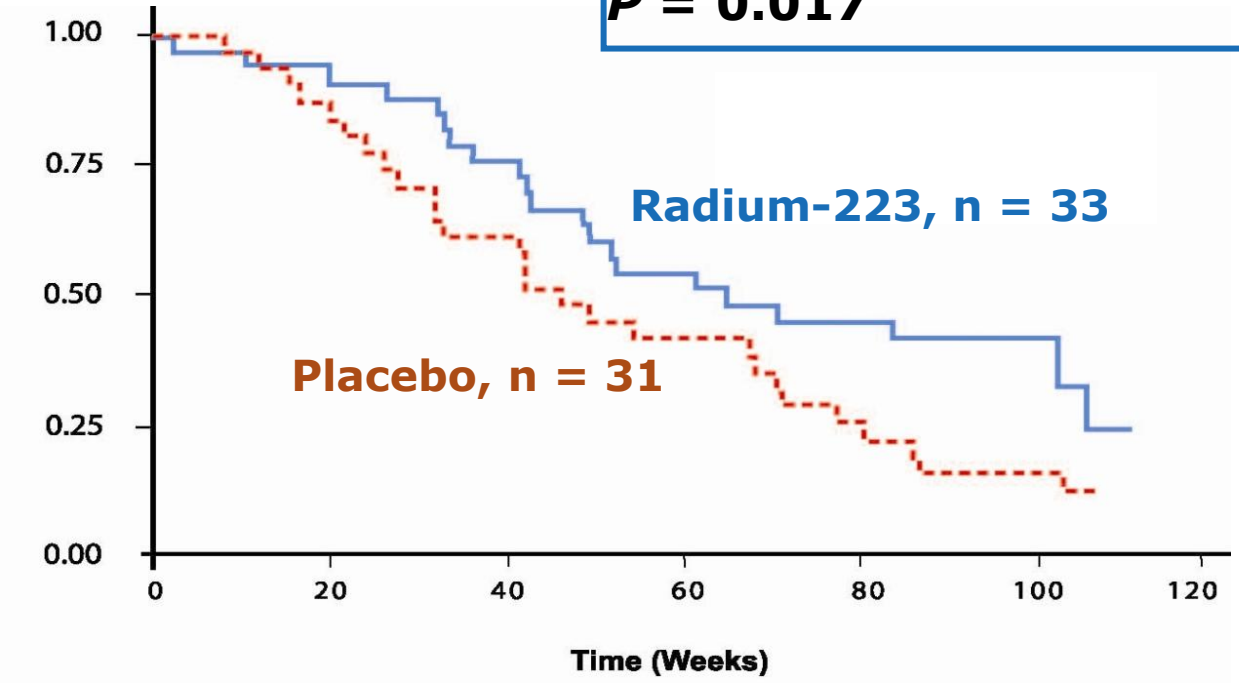
Phase II: Improved Overall Survival

HR: 0.48; 95% CI: 0.26-0.88
***P* = 0.017**



	Radium-223	Placebo	*P* Value
PSA	–24%	+45%	0.003
Total ALP	–46%	+31%	< 0.0001
PINP	–63%	+38%	< 0.0001

	Radium-223	Placebo
AEs	155	174
SAEs	12	19

Nilsson. *Lancet Oncol*. 2007;8:587-594.

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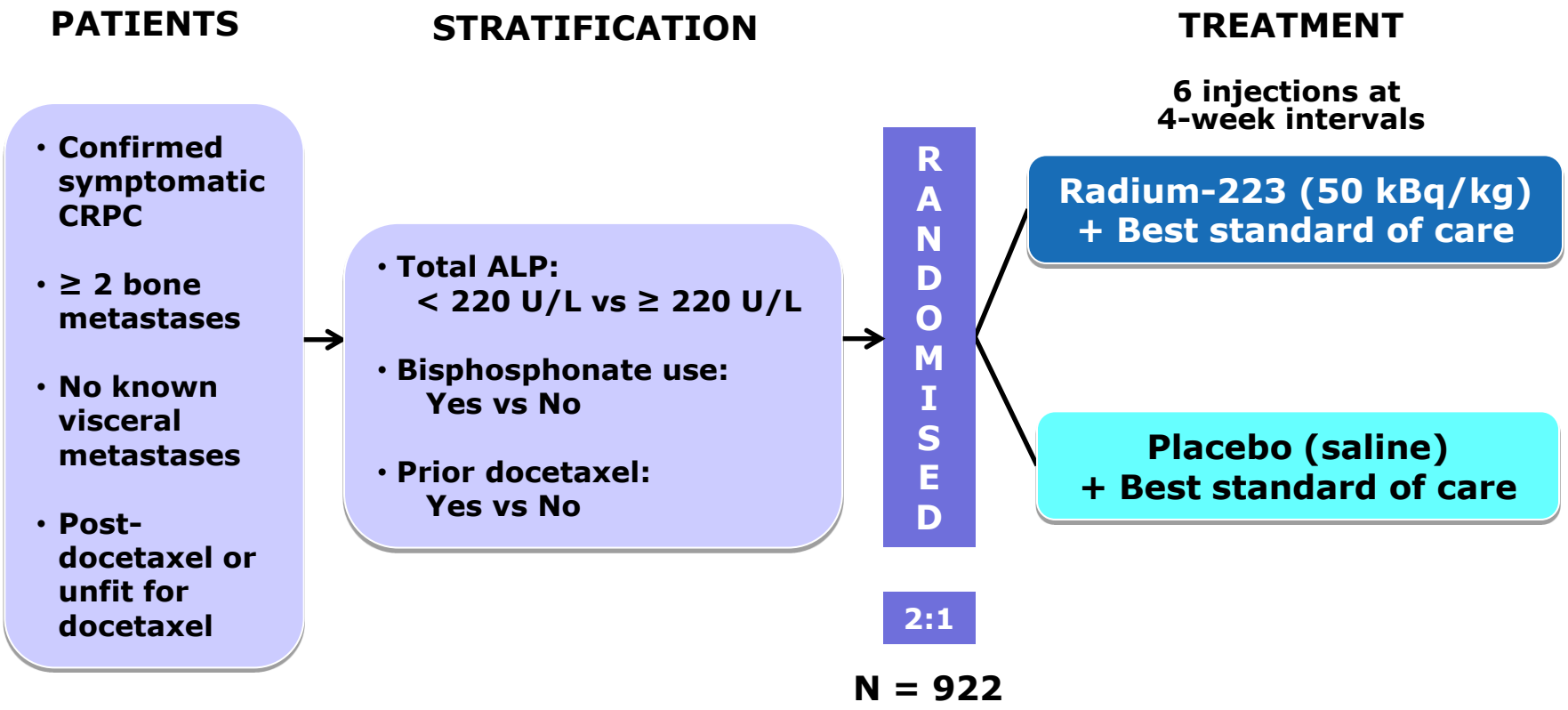
ALSYMPCA* Phase III Study Design



Planned follow-up is 3 years

*ALYMPCA – ALpharadin in SYMptomatic Prostate CAncer
Clinicaltrials.gov identifier: NCT00699751.

ALSYMPCA Study Endpoints

- Primary Endpoint
  - Overall survival

- 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

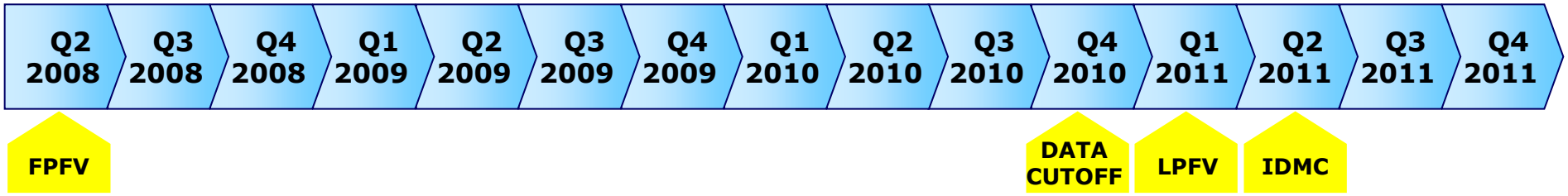
ALSYMPCA Statistical Design

- Statistical assumption
  - 90% power
  - HR = 0.76
  - 0.05 two-sided alpha

	Planned Interim Analysis	Final Analysis
Events	320	640
Alpha	0.00306	0.05

ALSYMPCA Planned Interim Analysis

- 314 events from 809 patients randomized at the time of the interim analysis
- Improvement in OS met the predetermined boundary for stopping the trial
- On June 3, 2011, the Independent Data Monitoring Committee (IDMC) recommended stopping the trial early due to evidence of a significant treatment benefit



ALSYMPCA Patient Demographics & Baseline Characteristics

(ITT; N = 809)

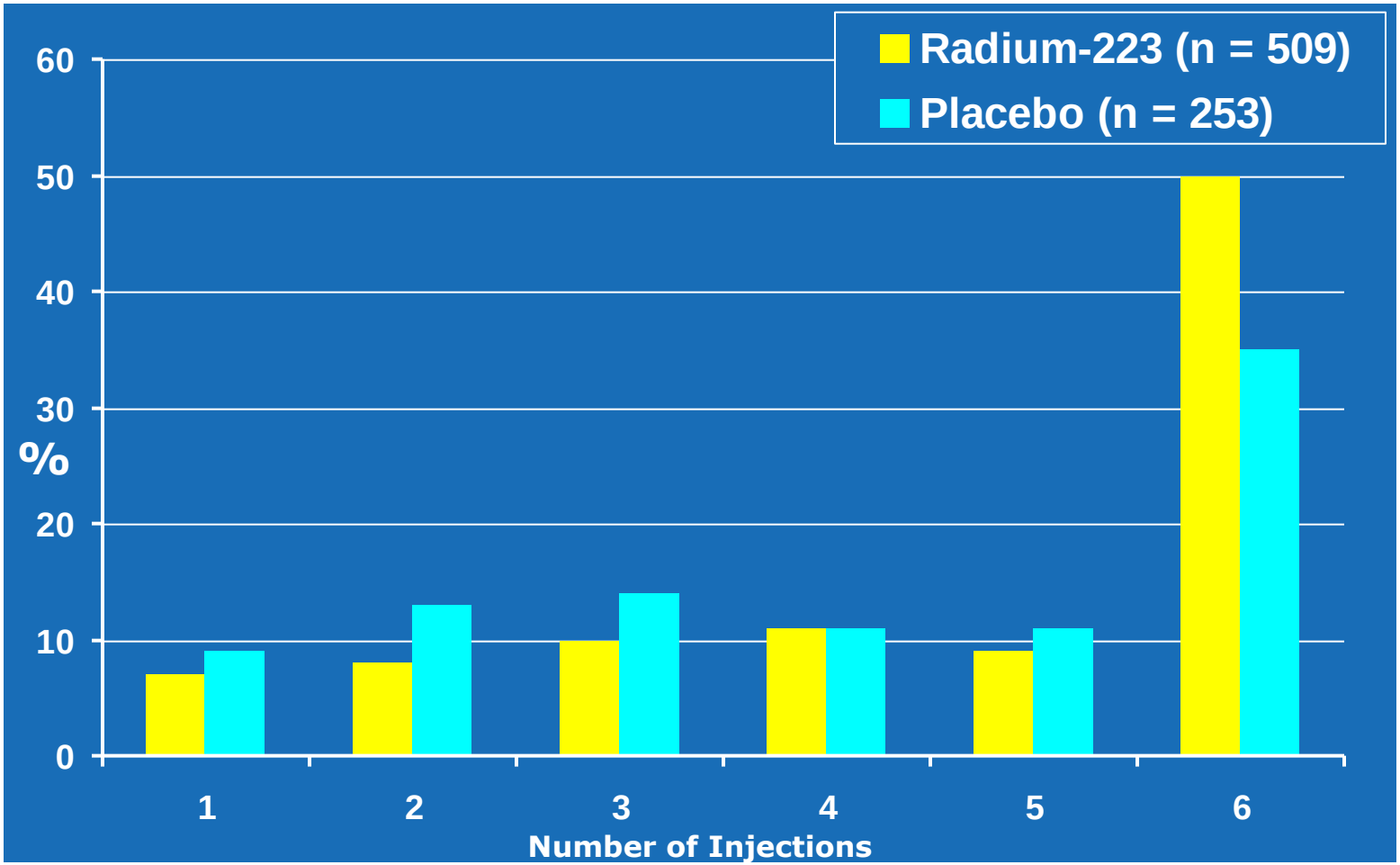
Parameter	Radium-223 (n = 541)	Placebo (n = 268)
Age, y Mean	70.2	70.7
Race, n (%) Caucasian	507 (94)	252 (94)
Baseline ECOG score, n (%) ≤ 1 2	467 (86) 71 (13)	229 (85) 37 (14)
Extent of disease, n (%) < 6 metastases 6-20 metastases > 20 metastases/superscan	88 (16) 235 (44) 217 (40)	33 (12) 129 (48) 106 (40)
WHO ladder, cancer pain index ≥ 2, n (%)	294 (54)	142 (53)

ALSYMPCA Patient Baseline Characteristics, continue

(ITT; N = 809)

Parameter Median (min, max)	Radium-223 (n = 541)	Placebo (n = 268)
Haemoglobin, g/dL	12.2 (8.5-15.7)	12.1 (8.4-16.4)
Albumin, g/L	40 (24-53)	40 (23-50)
Total ALP, µg/L	213 (32-4661)	224 (29-3225)
LDH, U/L	317 (76-2171)	328 (132-3856)
PSA, µg/L	159 (3.78-6026)	195 (1.5-14500)

ALSYMPCA Study Drug Treatment Received*



*Based on the number of injections patients had received at the time of the interim analysis.
Treatment ongoing in 107 (21%) patients on radium-223 and 49 (19%) on placebo.

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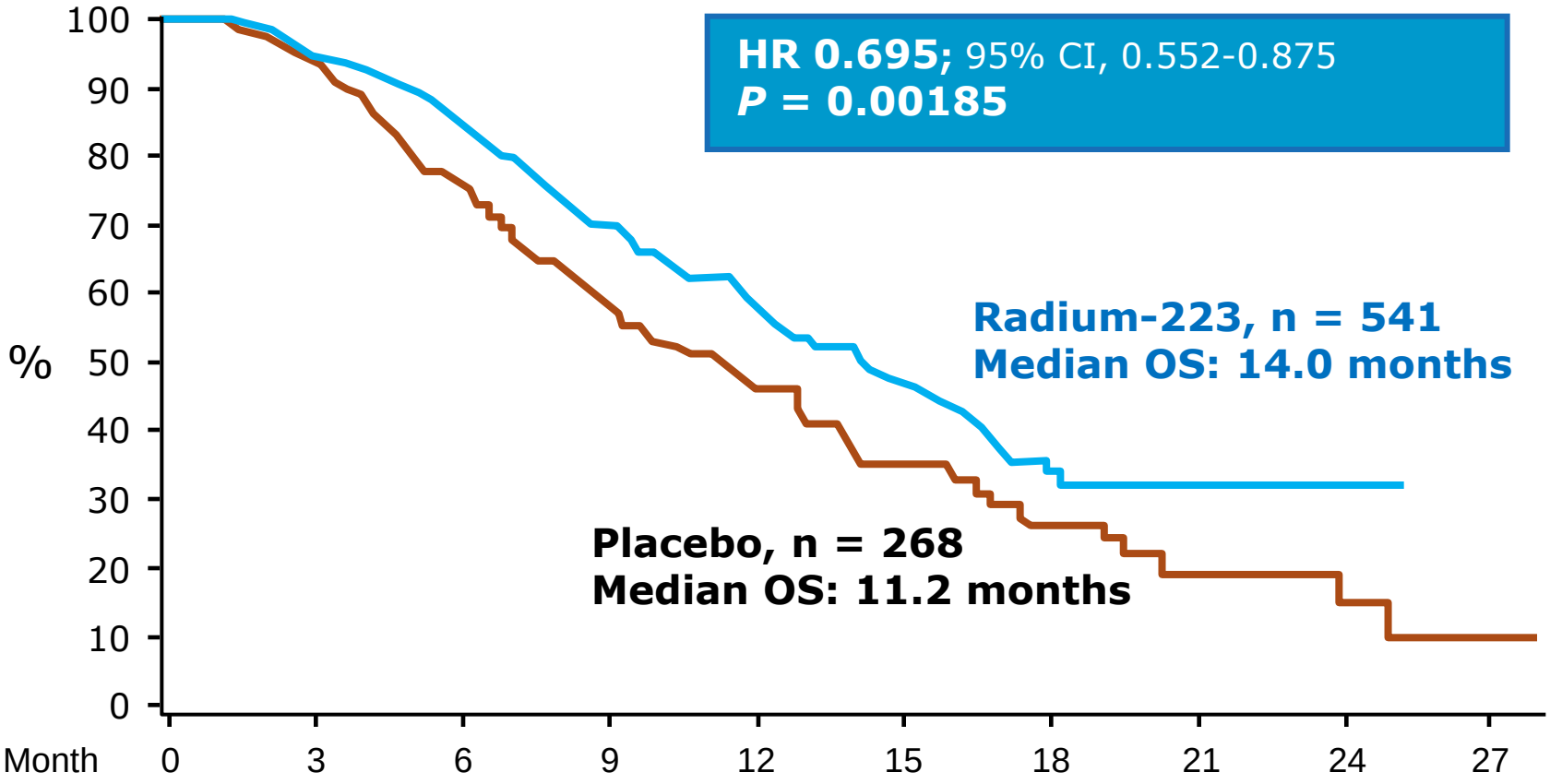
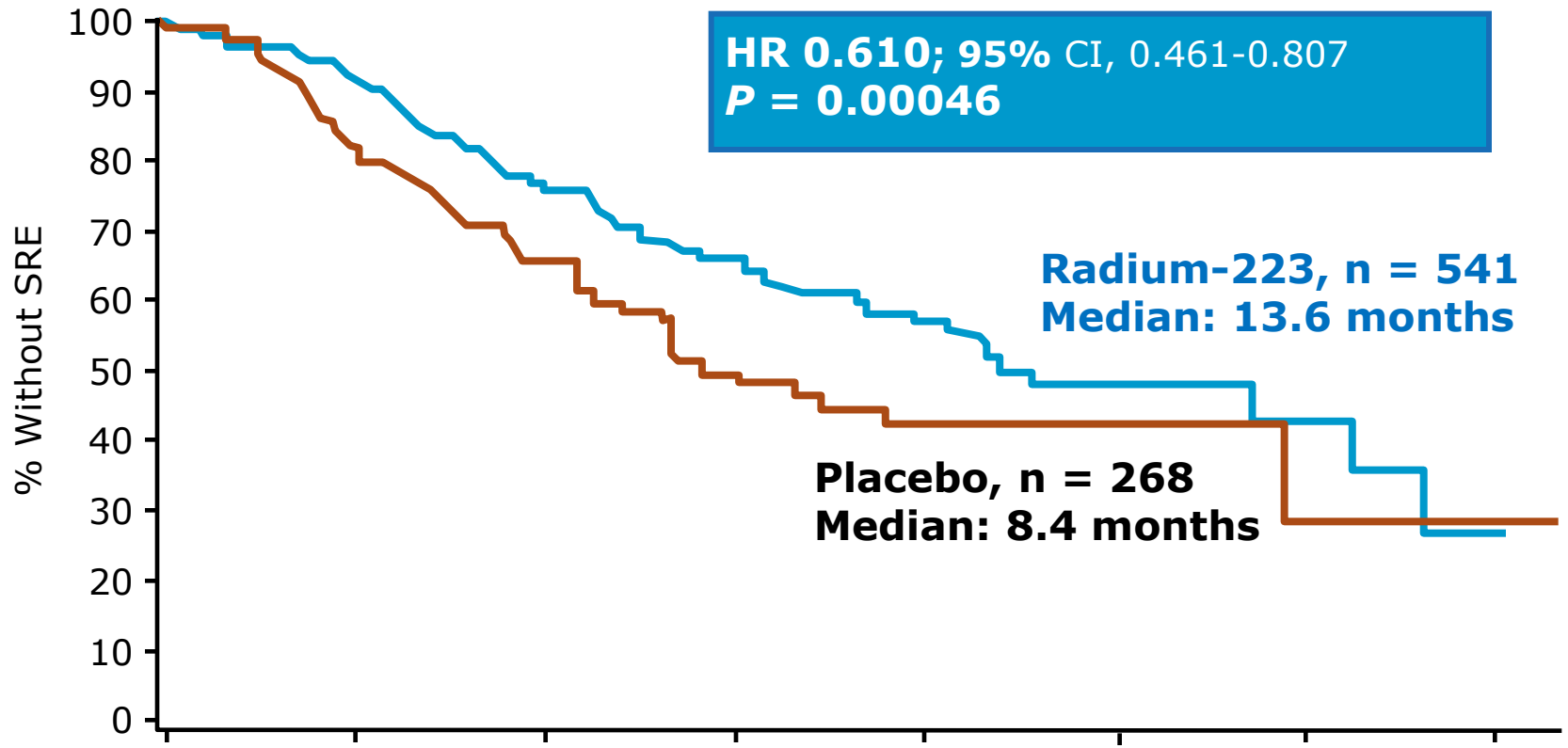
ALSYMPCA Overall Survival



Radium- 223	**541**	**450**	**330**	**213**	**120**	**72**	**30**	**15**	**3**	**0**
Placebo	**268**	**218**	**147**	**89**	**49**	**28**	**15**	**7**	**3**	**0**

ALSYMPCA Time to First Skeletal-Related Event



Month	0	3	6	9	12	15	18	21
Radium-223	**541**	**379**	**214**	**111**	**51**	**22**	**6**	**0**
Placebo	**268**	**159**	**74**	**30**	**15**	**7**	**2**	**0**

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ALSYMPCA Secondary Endpoints: ALP and PSA

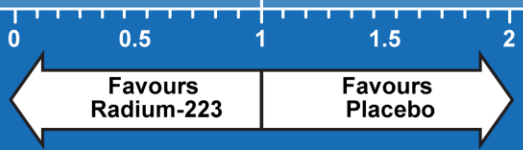
	Hazard ratio 95% CI	P-value
Time to Total ALP progression	0.163 (0.121 – 0.221)	< 0.00001
Time to PSA progression	0.671 (0.546 – 0.826)	0.00015

	Radium-223 n (%)	Placebo n (%)	P-value
Total ALP response (30% reduction)	165 (43)	4 (3)	< 0.001
Total ALP normalization*	83 (33)	1 (1)	< 0.001

*In patients who had elevated total ALP at baseline.

Survival Benefit Across Patient Subgroups

Variable	Subgroup	N	HR	95% CI
All Patients		809	0.695	0.552–0.875
Total ALP	< 220 U/L	452	0.691	0.497–0.962
	≥ 220 U/L	357	0.689	0.504–0.941
Current Use of Bisphosphonates	Yes	331	0.582	0.397–0.854
	No	478	0.752	0.567–0.999
Prior Use of Docetaxel	Yes	470	0.755	0.565–1.009
	No	339	0.611	0.423–0.883
Baseline ECOG Status	0 or 1	696	0.691	0.535–0.892
	2 or Higher	110	0.731	0.398–1.343



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Summary of Patients With Adverse Events: Safety Population*

(N = 762)

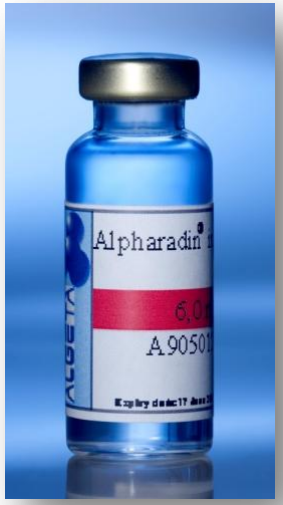
Patients With Adverse Events (AEs), n (%)	Radium-223 (n = 509)	Placebo (n = 253)
All grade AEs	450 (88)	237 (94)
Grade 3 or 4 AEs	257 (51)	150 (59)
Serious AEs (SAEs)	220 (43)	139 (55)
Discontinuation due to AEs	68 (13)	51 (20)

*Patients who received at least 1 injection.

ALSYMPCA Adverse Events of Interest

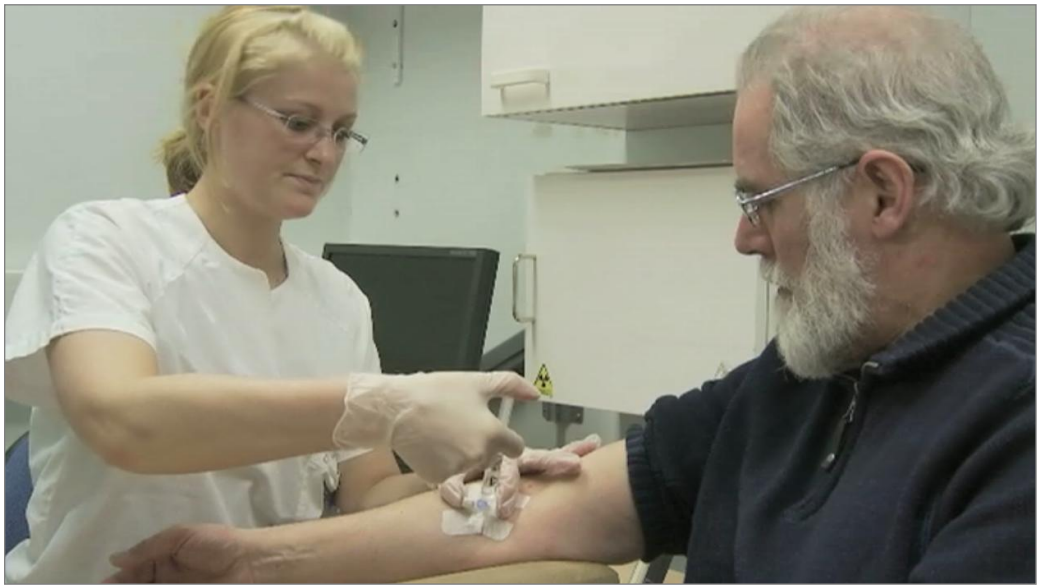
	All Grades		Grades 3 or 4	
	Radium-223 (n = 509) n (%)	**Placebo (n = 253) n (%)**	**Radium-223 (n = 509) n (%)**	**Placebo (n = 253) n (%)**
Haematologic:				
Anaemia	136 (27)	69 (27)	54 (11)	29 (12)
Neutropenia	20 (4)	2 (1)	9 (2)	2 (1)
Thrombocytopenia	42 (8)	14 (6)	22 (4)	4 (2)
Non-Haematologic:				
Bone pain	217 (43)	147 (58)	89 (18)	59 (23)
Diarrhoea	112 (22)	34 (13)	6 (1)	3 (1)
Nausea	174 (34)	80 (32)	8 (2)	4 (2)
Vomiting	88 (17)	32 (13)	10 (2)	6 (2)
Constipation	89 (18)	46 (18)	6 (1)	2 (1)

Alpharadin: Easy and Convenient to Administer



- Ready to use vials
- Long shelf life (4 wks)
- Easy to handle

- Total 6 i.v. injections
- One injection every 4 weeks
- Out-patient treatment



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Conclusions

In CRPC patients with bone metastases:

- **Radium-223 significantly prolonged OS**
  - P value = 0.00185; HR = 0.695; 95% CI, 0.552-0.875
- **Radium-223 significantly prolonged time to first SRE**
  - P value = 0.00046; HR = 0.610; 95% CI, 0.461-0.807
- **Radium-223 was very well tolerated**

Radium-223, a novel Alpha-pharmaceutical, may provide a new standard of care for the treatment of CRPC patients with bone metastases

For further information, please contact:

Andrew Kay, CEO	+47 2300 7990 / +47 4840 1360
Øystein Soug, CFO	+47 2300 7990 / +47 9065 6525
	post@algeta.com
International media enquiries:	+44 207 638 9571
Mark Swallow / Sita Shah / David Dible	mark.swallow@citigatedr.co.uk
Citigate Dewe Rogerson	
US investor enquiries:	+1 646 378 2928
Jessica Lloyd	jlloyd@troutgroup.com
The Trout Group	

Presentation backups

Overall Survival Benefit in Recent CRPC Trials

Agent (trial, year)	Disease State	Comparator	Hazard Ratio	*P* value
Radium-223/Alpharadin (ALSYMPCA 2011)	Bone metastases CRPC	Placebo + best standard of care	0.695	0.00185
Docetaxel/Taxotere[1] (TAX327 2004)	Chemo-naive CRPC	Mitoxantrone Prednisone	0.76	0.009
Cabazitaxel/Jevtana[2] (TROPIC 2010)	Post-docetaxel CRPC	Mitoxantrone Prednisone	0.70	<0.0001
Sipuleucel-T/Provenge[3] (IMPACT 2010)	Chemo-naive CRPC	Placebo	0.775	0.032
Abiraterone/Zytiga[4] (COU-AA-301 2010)	Post-docetaxel CRPC	Placebo Prednisone	0.65	<0.001

1. Tannock et al. *N Engl J Med.* 2004;351:1502-1512.
2. de Bono. *Lancet.* 2010;376:1147-1154.
3. Kantoff et al. *N Engl J Med.* 2010;363:411-422.
4. de Bono. *N Engl J Med.* 2011:364:1995-2005.