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2012 Genitourinary Cancers Symposium Presscast

January 31, 2012

Moderator:

Nicholas J. Vogelzang, MD

Presenters:

Ronald Chen, MD

Jay P. Ciezki, MD

Oliver Sartor, MD

June Chan, MD

Howard Scher, MD

Presented at the **Genitourinary Cancers Symposium**

Presented data is the property of the author.

Embargo Policy

- All abstracts presented at the 2012 Genitourinary Cancers Symposium, including abstracts highlighted in today's presscast, are embargoed until 6:00 PM EST today, January 31
- All 2012 Genitourinary Cancers Symposium abstracts will be posted on <http://www.gucasym.org/> today at 6:00 PM EST

About the Symposium

- Co-sponsored by:
 - The American Society of Clinical Oncology (ASCO)
 - The American Society of Radiation Oncology (ASTRO)
 - The Society of Urologic Oncology (SUO)
- Symposium will feature 470 abstracts on the detection and treatment of genitourinary cancers
- More than 2,300 surgical, medical and radiation oncologists from around the world will attend the meeting

About GU Cancers

- 482,000 people in the United States are expected to be diagnosed with genitourinary cancers this year and it is estimated 88,000 lives will be taken by these diseases
- Prostate cancer is expected to be diagnosed in 241,740 men in the United States in 2012 and claim more than 28,000 lives¹
- In 2008, nearly 900,000 men from around the world were diagnosed with prostate cancer and in the same year nearly 260,000 men died from prostate cancer²

¹ American Cancer Society, Cancer Facts and Figures 2012

² GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet].

Physical activity and prostate gene expression in men with low risk prostate cancer (PCa)

MJM Magbanua¹, EL Richman², EV Sosa¹, J Simko^{3,4}, LW Jones⁵,
K Shinohara³, CM Haqq³, PR Carroll³, JM Chan^{2,3}

Departments of ¹Hematology/Oncology, ²Epidemiology & Biostatistics, ³Urology, and ⁴Pathology, of the University of California, San Francisco & the Helen Diller Family Comprehensive Cancer Center (UCSF); ⁵Department of Surgery, Duke Cancer Care Research Program, Duke University Medical Center

Presented at the **Genitourinary Cancers Symposium**

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Acknowledgements: NCI/NIH, Prostate Cancer Foundation, all participants

Background

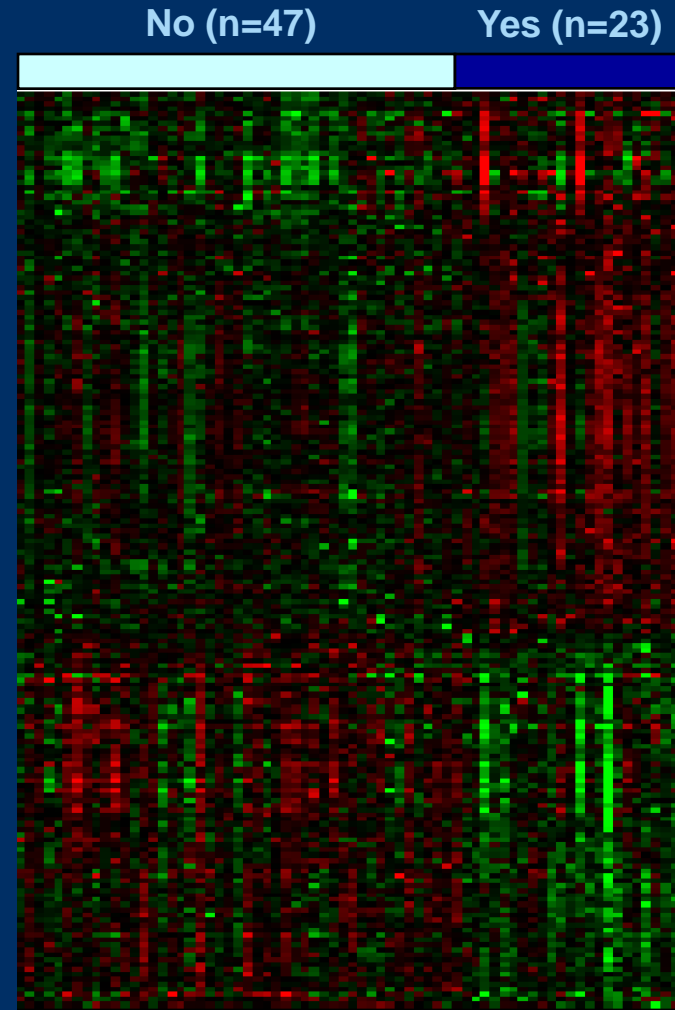
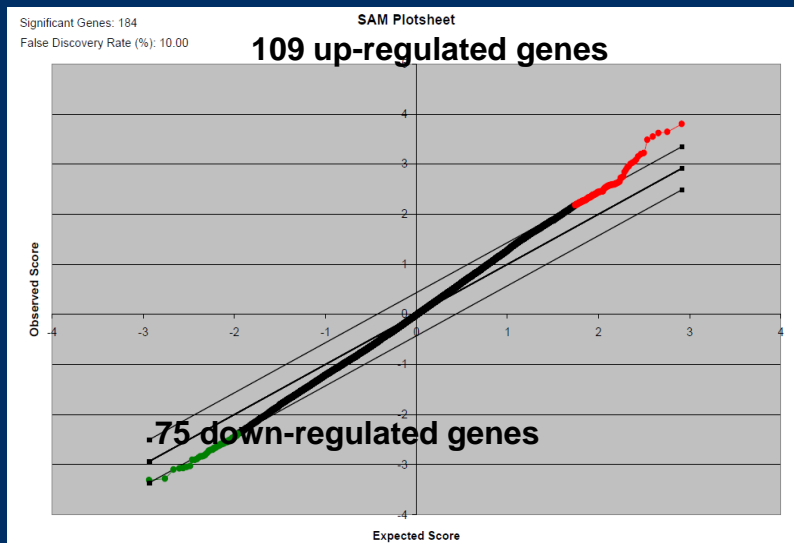
- Physical activity (PA) after diagnosis of prostate cancer (PCa) may reduce risk of PCa progression & PCa mortality
 - 3+h/wk vs. <1 h/wk **vigorous** PA (*Kenfield SA, JCO 2011*)
 - 49% lower risk All-Cause Mortality
 - 61% lower risk PCa Mortality
 - Vigorous PA: jogging, running, tennis, aerobics, swimming, etc...
 - Brisk vs. Easy walking pace (*Richman EL, CanRes 2011*)
 - 48% lower risk PCa progression (≥ 3 mph vs < 2 mph)
- Molecular mechanisms by which PA exerts its protective effect on prostate cancer remains unknown
- We sought to identify potential mechanisms by which PA influences the prostate gland
- **Hypothesis:** Vigorous PA is associated with distinct gene expression patterns in ***normal*** prostate tissue

Methods

- Study Population: 70 men, low-risk PCa, active surveillance
 - previously enrolled in clinical trial on nutritional supplements
 - provided biopsy tissue & survey data at baseline
 - Chan JM et al Cancer Causes Control 2011, Magbanua MJ PLoSOne 2011
- Exposure: Vigorous Physical Activity
 - 3+ h/wk vigorous PA (yes/no) and any vigorous PA (yes/no)
- Outcome: Individual Gene & Pathway (gene-set) Expression
 - RNA expression in **normal** tissue
- Methods: Significance Analysis of Microarrays
 - previously published microarray dataset #GSE27140
 - Genes and gene sets with a false discovery rate (FDR) ≤ 0.10 and 0.20 were considered significant, respectively.

RESULTS

- 184 genes were differentially expressed in men who self-reported vigorous PA for 3+ h/wk (n=23) vs. those who did not (n= 47)
- Up-regulated genes included known tumor suppressors, *BRCA1* & *BRCA2*



RESULTS cont' d

- Pathway (gene-set) analysis revealed that cell cycle and DNA repair pathways were positively modulated in men who self-reported participating in 3+h/wk vigorous PA vs. those who did less.
- There were no significant genes or pathways associated with PA when we compared men reporting engaging in any vigorous PA vs none
 - Suggests that a certain threshold of intensity or duration may be important

Conclusions

- Limitations:
 - Small sample, could be chance finding
 - Unable to consider potential confounding factors
- Further study warranted in larger population(s)
- If confirmed, results suggest longer duration of vigorous PA may offer protection against PCa progression through acting on DNA repair or cell cycle pathways
- Identifying mechanisms by which lifestyle factors influence normal prostate tissue may support the development of novel strategies to predict, monitor, or prevent PCa progression

THANK YOU

Comparative Effectiveness of Intensity Modulated Radiation Therapy (IMRT), Proton Therapy and Conformal Radiation Therapy in the Treatment of Localized Prostate Cancer

Ronald Chen, MD MPH

Nathan Sheets, Gregg Goldin, Anne-Marie Meyer, Yang Wu, YunKyung Chang, Til Sturmer, Jordan A Holmes, Bryce B Reeve, Paul A Godley, William R Carpenter

University of North Carolina Hospitals, Chapel Hill, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC

Presented at the **Genitourinary Cancers Symposium**

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Funded by the Agency for Healthcare
Research and Quality

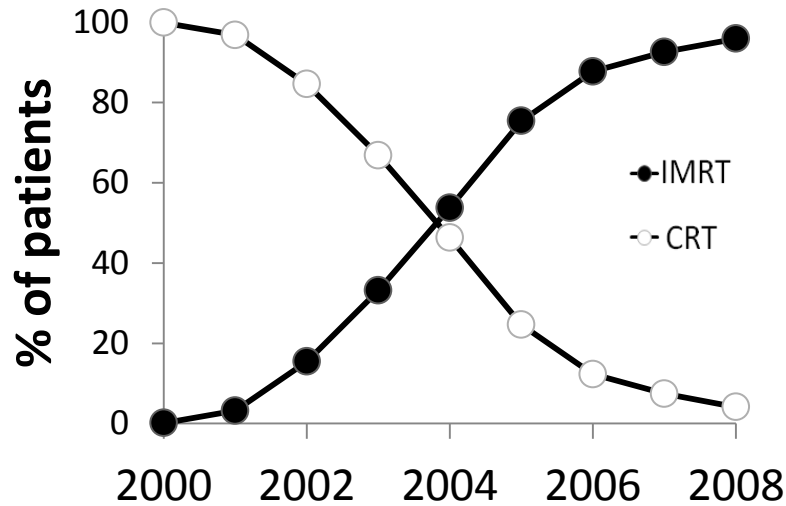


*Designated a Comprehensive Cancer Center by the
National Cancer Institute.*

Background

- >200,000 men are diagnosed with prostate cancer annually in the US
- Many receive radiation therapy
 - Older conformal radiation
 - Intensity-modulated radiation (IMRT, newer and costlier)
 - Proton radiation (even more costly)
- Unclear if newer treatments are better
- Comparative effectiveness research needed

Study Design



- Rapid increase in the use of IMRT for prostate cancer since 2000.
- Since 2006, there has been a rapid increase in the number of proton centers in US.
- Are newer radiation techniques better?

- SEER-Medicare database: Medicare patients with cancer
- Prostate cancer patients treated with radiation therapy from 2002-2007
- Compared results of patients treated with conformal radiation vs. IMRT vs. proton therapy
 - Side effects
 - Cancer control
- Used sophisticated statistical methods (propensity score) to minimize biases and confounding

Results: IMRT vs. CRT

Events per 100 person-years of follow up

	Propensity Adjusted			
	CRT	IMRT	Rate Ratio	P value
Morbidity				
Bowel	14.7	13.4	0.91	<0.001
Urinary non-incontinence	8.8	8.8		0.80
Urinary incontinence	3.7	3.5		0.22
Erectile dysfunction	5.3	5.9	1.12	0.006
Hip fracture	1.0	0.8	0.78	0.006
Cancer control				
Additional cancer treatments	3.1	2.5	0.81	<0.001

Results: IMRT vs. Proton

Events per 100 person-years of follow up

	Propensity Adjusted			
	IMRT	Proton	Rate Ratio	P value
Morbidity				
Bowel	12.2	17.8	0.66	<0.001
Urinary non-incontinence	7.5	6.3		0.06
Urinary incontinence	3.1	3.3		0.81
Erectile dysfunction	6.6	7.4		0.30
Hip fracture	0.8	0.7		----
Cancer control				
Additional cancer treatments	2.2	1.9		0.24

Conclusions

- This study supports use of IMRT as current standard radiation technique for prostate cancer
 - IMRT causes fewer side effects and achieves better cancer control compared to the older conformal radiation
- Currently, no clear evidence that proton therapy is better than IMRT
- Comparative effectiveness research needed:
 - North Carolina Prostate Cancer Comparative Effectiveness and Survivorship Study (NC ProCESS)
 - Randomized trial comparing IMRT to proton

Long-term Toxicity and Associated Cost of Initial and Subsequent Toxicity-related Intervention for Patients Treated with Prostatectomy, External Beam Radiotherapy, or Brachytherapy: A SEER/Medicare Database Study

Jay P. Ciezki, M.D.¹, Chandana A. Reddy, M.S.¹, Kenneth Angermeier, M.D.², James Ulchaker, M.D.², Kevin Stephans, M.D.¹, Rahul Tendulkar, M.D.¹, Andrew Altman, M.D.³, Nabil Chehade, M.D.³, Eric A. Klein, M.D.²,
¹Cleveland Clinic Department of Radiation Oncology; ²Cleveland Clinic Glickman Urological and Kidney Institute; and ³Kaiser Permanente-Ohio Department of Urology

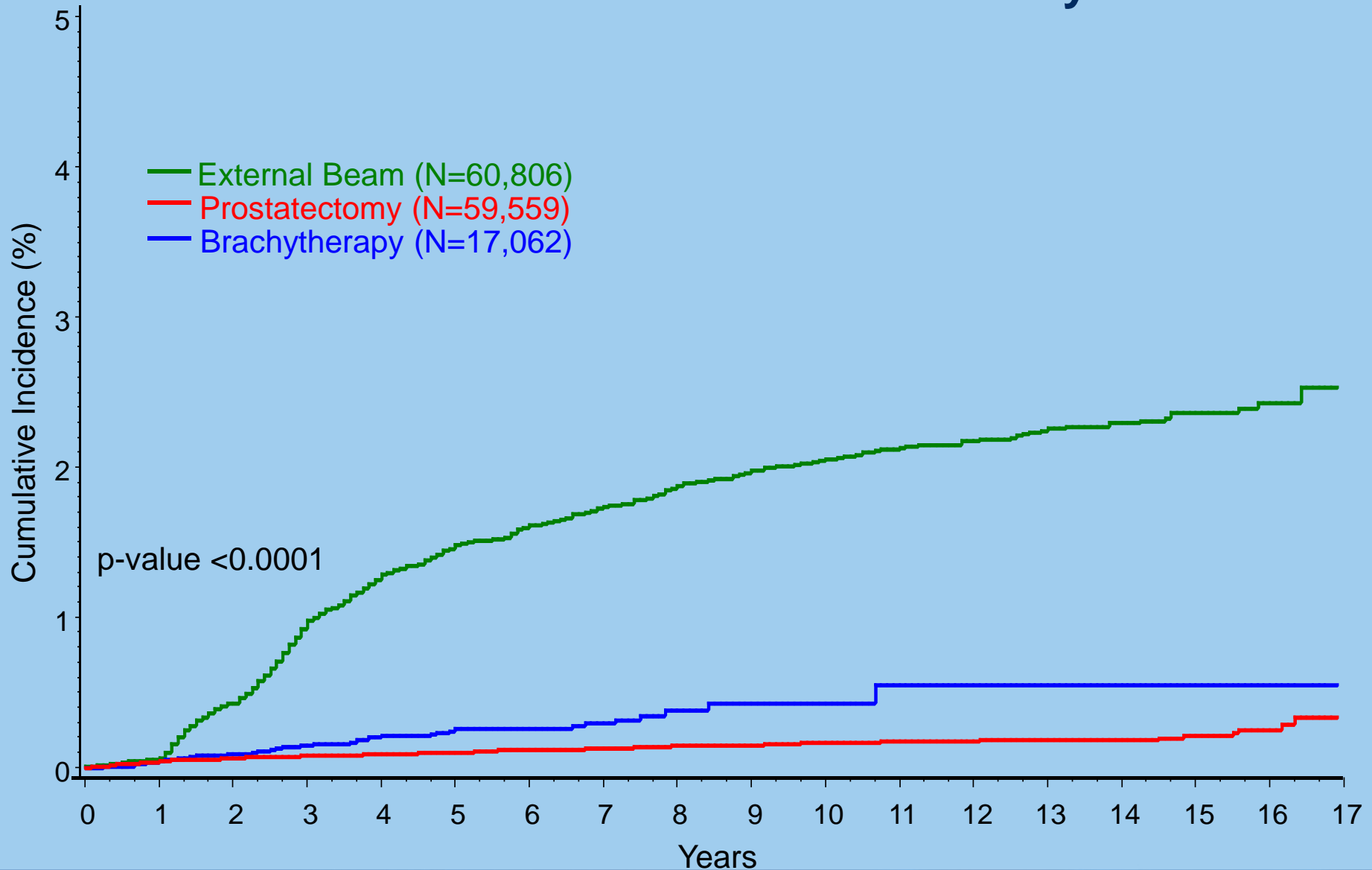
Presented at the **Genitourinary Cancers Symposium**

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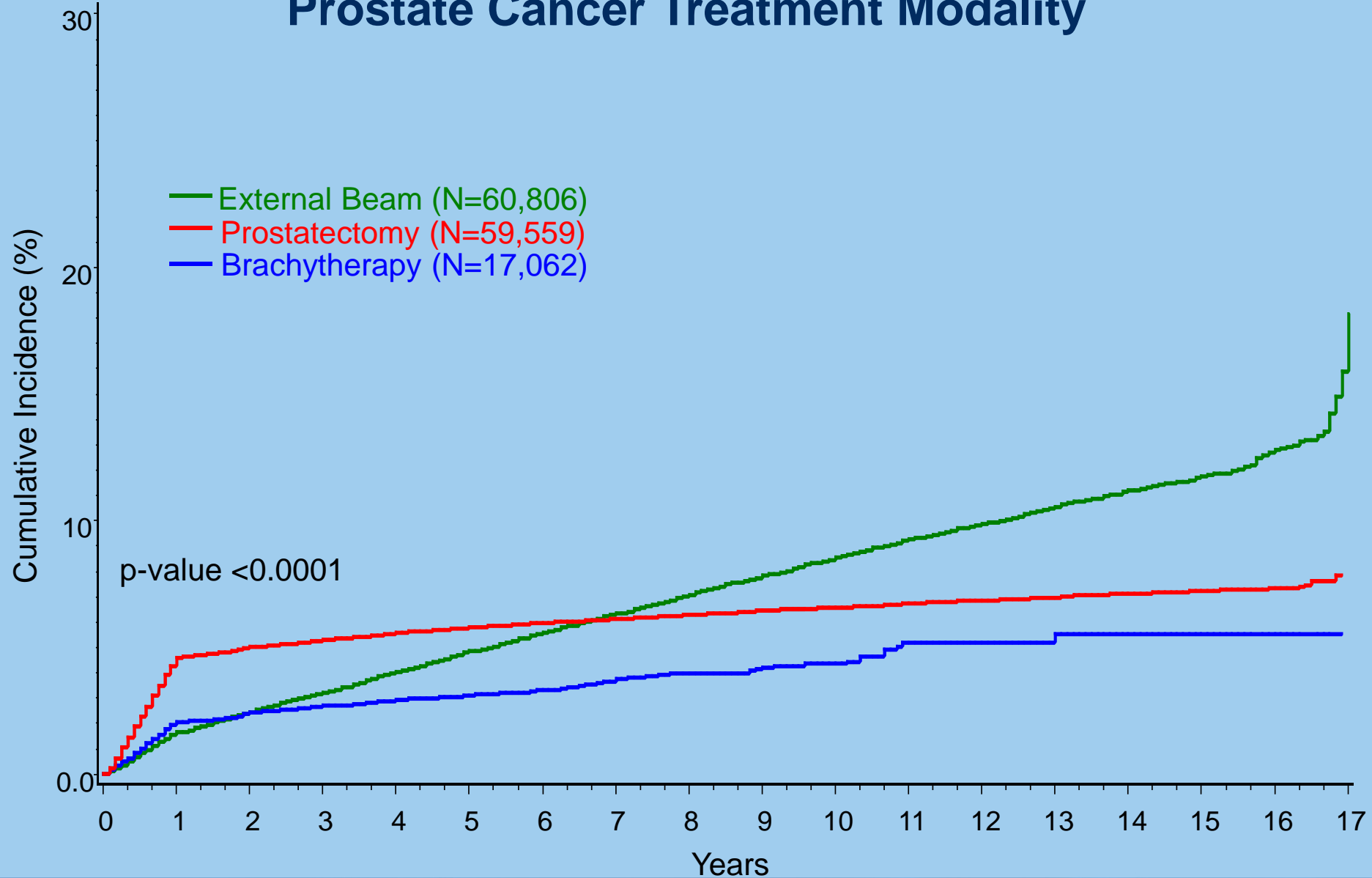
Summary

- The SEER-Medicare database was queried for prostate cancer (CaP) patients treated with prostatectomy (RP), external beam radiotherapy (EBRT), or brachytherapy (PI) between 1991-2007.
- We identified procedural billing codes associated with toxicity-related treatments.
- We obtained information on the Medicare reimbursement rates for the initial treatment and any toxicity-related interventions.
- We then computed the cost per patient-year within each treatment modality over time.
- A total of 137,427 patients who were 65 years or older at the time of CaP diagnosis and who had CaP as their only cancer diagnosis were retrieved from the SEER/Medicare database: 59,559 (43.3%) treated with RP, 60,806 (44.2%) treated with EBRT, and 17,062 (12.4%) treated with PI.
- No patient received combined therapy.
- The median follow-up is 71 months.

Cumulative Incidence for Gastrointestinal Toxicity by Prostate Cancer Treatment Modality



Cumulative Incidence for Genitourinary Toxicity by Prostate Cancer Treatment Modality



Cost Per Patient-Year Comparison among Modalities

Treatment Modality	Average Cost per Patient-Year (\$)	P-Value
External Beam	6,412.29	
Prostatectomy*	3,205.71	<0.0001
Brachytherapy	2,557.36	

*open procedure

Conclusion

The long-term toxicity and cost per patient-year of the major prostate cancer treatment modalities differ. EBRT is the most toxic and most costly.

Radium-223 chloride (Alpharadin) impact on skeletal-related events in patients with castration-resistant prostate cancer (CRPC) with bone metastases: A phase III randomized trial (ALSYMPCA)

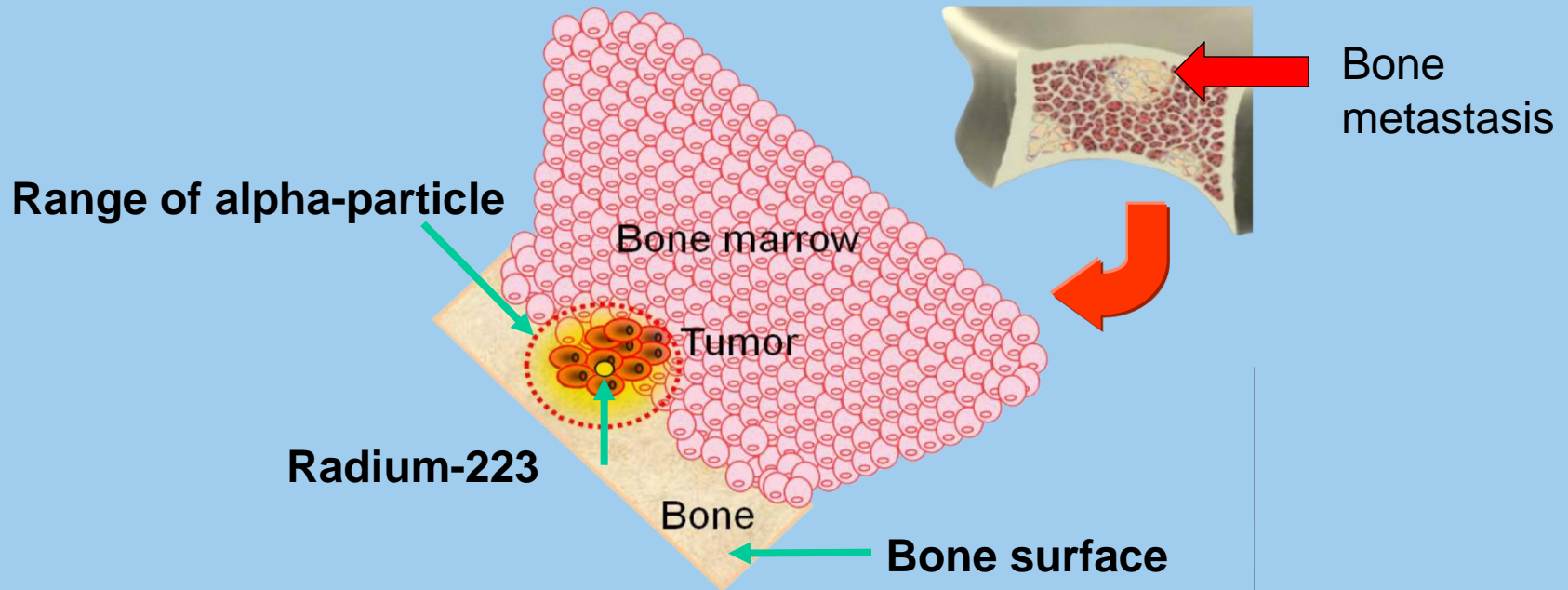
**O Sartor,¹ D Heinrich,² SI Helle,³ JM O'Sullivan,⁴ S Fosså,⁵ A Chodacki,⁶
T Demkow,⁷ J Logue,⁸ M Seke,⁹ A Widmark,¹⁰ DC Johannessen,¹¹
S Nilsson,¹² P Hoskin,¹³ A Solberg,¹⁴ ND James,¹⁵ I Syndikus,¹⁶
N Vogelzang,¹⁷ CG O'Bryan-Tear,¹⁸ M Shan,¹⁹ and C Parker²⁰**

Presented at the **Genitourinary Cancers Symposium**

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¹Tulane Cancer Center, New Orleans, LA, USA; ²Akershus University Hospital, Lørenskog, Norway; ³Haukeland University Hospital, Bergen, Norway; ⁴Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Northern Ireland; ⁵Radiumhospitalet, Oslo, Norway; ⁶Hospital Kochova, Chomutov, Czech Republic; ⁷Centrum Onkologii – Instytut im Skłodowskiej-Curie, Warsaw, Poland; ⁸Christie Hospital, Manchester, UK; ⁹Centrallasarettet Växjö, Växjö, Sweden; ¹⁰Norrlands University Hospital, Umeå, Sweden; ¹¹Ullevål University Hospital, Oslo, Norway; ¹²Karolinska Universitetssjukhuset, Stockholm, Sweden; ¹³Mount Vernon Hospital Cancer Centre, Middlesex, UK; ¹⁴St. Olavs Hospital, Trondheim, Norway; ¹⁵Cancer Research UK Clinical Trials Unit, Institute for Cancer Studies, Birmingham, UK; ¹⁶Clatterbridge Centre for Oncology, Wirral, UK; ¹⁷Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; ¹⁸Algeta ASA, Oslo Norway; ¹⁹Bayer Healthcare Pharmaceuticals, Montville, NJ, USA; ²⁰The Royal Marsden NHS Foundation Trust, Sutton, UK

Radium-223, An Alpha-Emitter, Binds to Stroma Adjacent to Bone Metastases

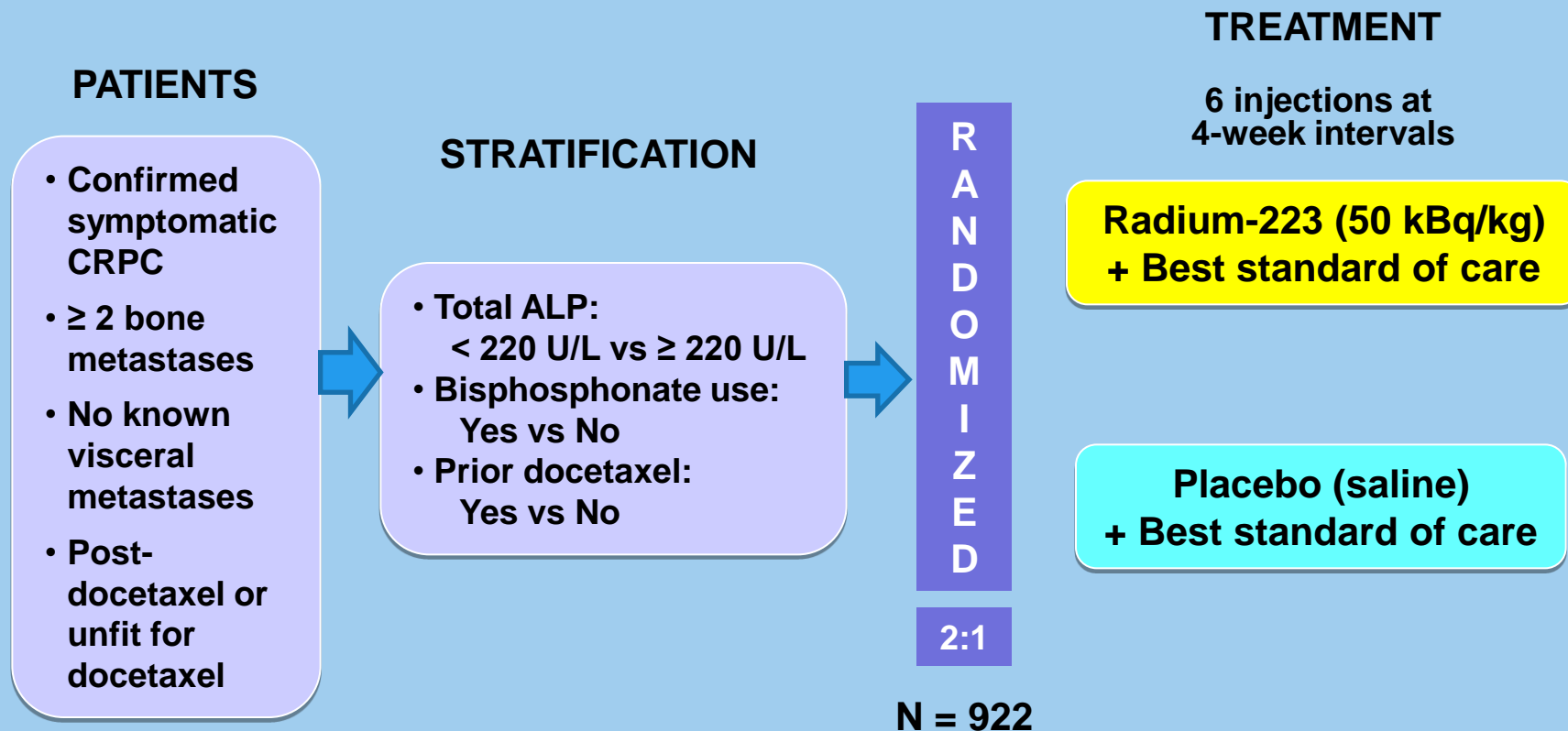


➤ Alpha-particles contain 2 protons and 2 neutrons and very effectively induce double-strand DNA breaks in adjacent cells¹

➤ Short penetration of alpha emitters (2-10 cell diameters) = highly localized tumor cell killing but minimal damage to surrounding normal tissue

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

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



Planned follow-up is 3 years

Radium-223 Improves Both Overall Survival And Skeletal Related Events (SRE)

- Overall Survival *P* value = 0.00185; HR = 0.695; medians 14.0 vs 11.2 months
- Time to first SRE *P* value = 0.00046; HR = 0.610; medians 13.6 vs 8.4 months

3 of 4 SRE components improved:

SRE Component	% of Events		Time to Event (Ra-223 vs Placebo)	
	Ra-223 N=541	Placebo N=268	<i>P</i> value	HR (95%CI)
Pathologic Bone Fracture	3.6%	6.7%	.013	.45
Spinal Cord Compression	3.1%	6.0%	.016	.44
External Beam Radiation	22.6%	26.9%	.0038	.65
Surgical Intervention	1.7%	1.9%	.69	.80

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 (%)
Hematologic				
Anemia	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-Hematologic				
Bone pain	217 (43)	147 (58)	89 (18)	59 (23)
Diarrhea	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)

Conclusions

In bone-metastatic CRPC patients radium-223 significantly prolongs:

- **Overall survival**
- **Time to first SRE**
- **Time to spinal cord compression**
- **Time to pathological bone fracture**
- **Time to external beam radiation**

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

MDV3100 Prolongs Life in Men with Late-Stage Prostate Cancer

Results from the Phase 3 AFFIRM Study

H. I. Scher, K. Fizazi, F. Saad, M. E. Taplin, C. N. Sternberg, K. Miller,
R. De Wit, P. Mulders, M. Hirmand, B. Selby, J. S. De Bono,
for the AFFIRM Investigators

Presented at the **Genitourinary Cancers Symposium**

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Memorial Sloan-Kettering Cancer Center, New York, NY; Institut Gustave Roussy, University of Paris Sud, Villejuif, France; University of Montreal Hospital Center, Montreal, QC; Dana-Farber Cancer Institute, Boston, MA; San Camillo and Forlanini Hospitals, Rome, Italy; Department of Urology, Charité Universitätsmedizin, Berlin, Germany; Erasmus University Medical Center, Rotterdam, Netherlands; Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; Medivation, San Francisco, CA; The Institute for Cancer Research and Royal Marsden Hospital, Sutton, United Kingdom

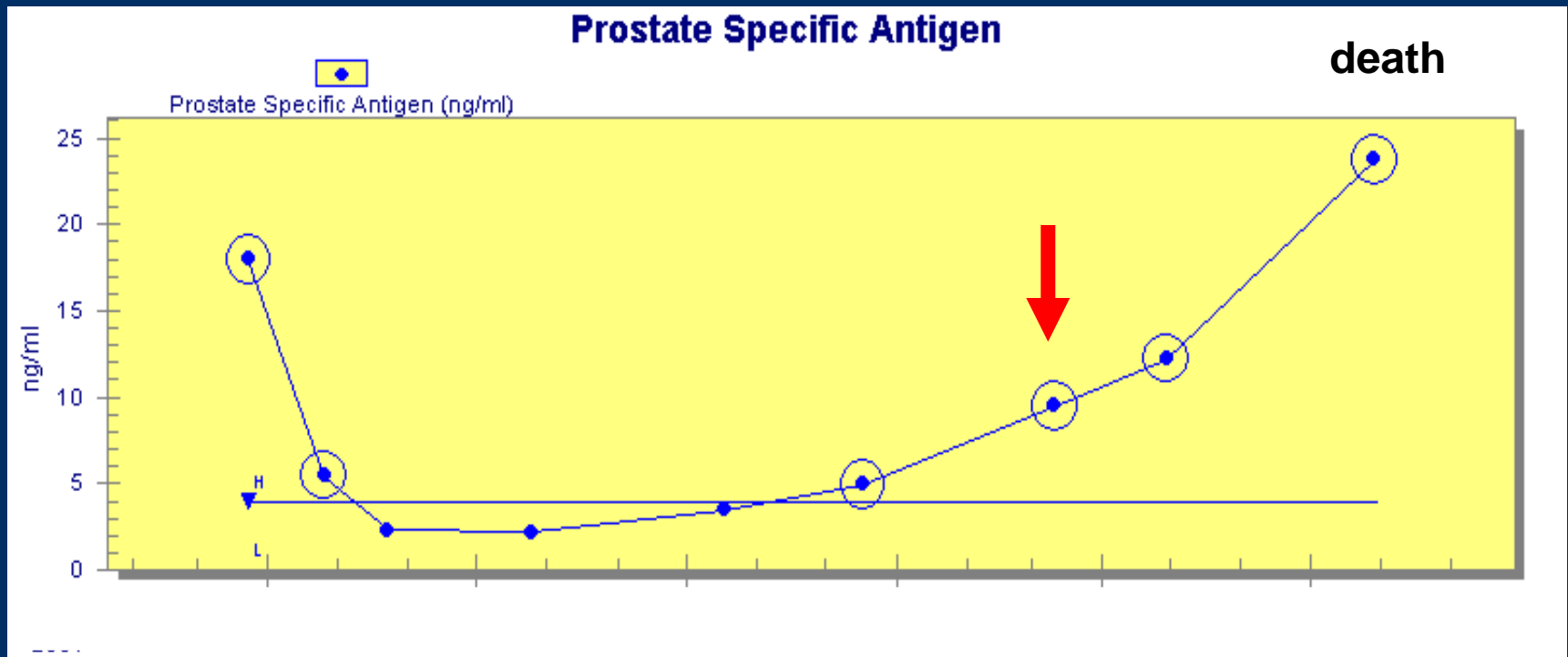
Prostate Cancer Disease Continuum

MDV3100
Phase 3 Trial

Hormone-Naive

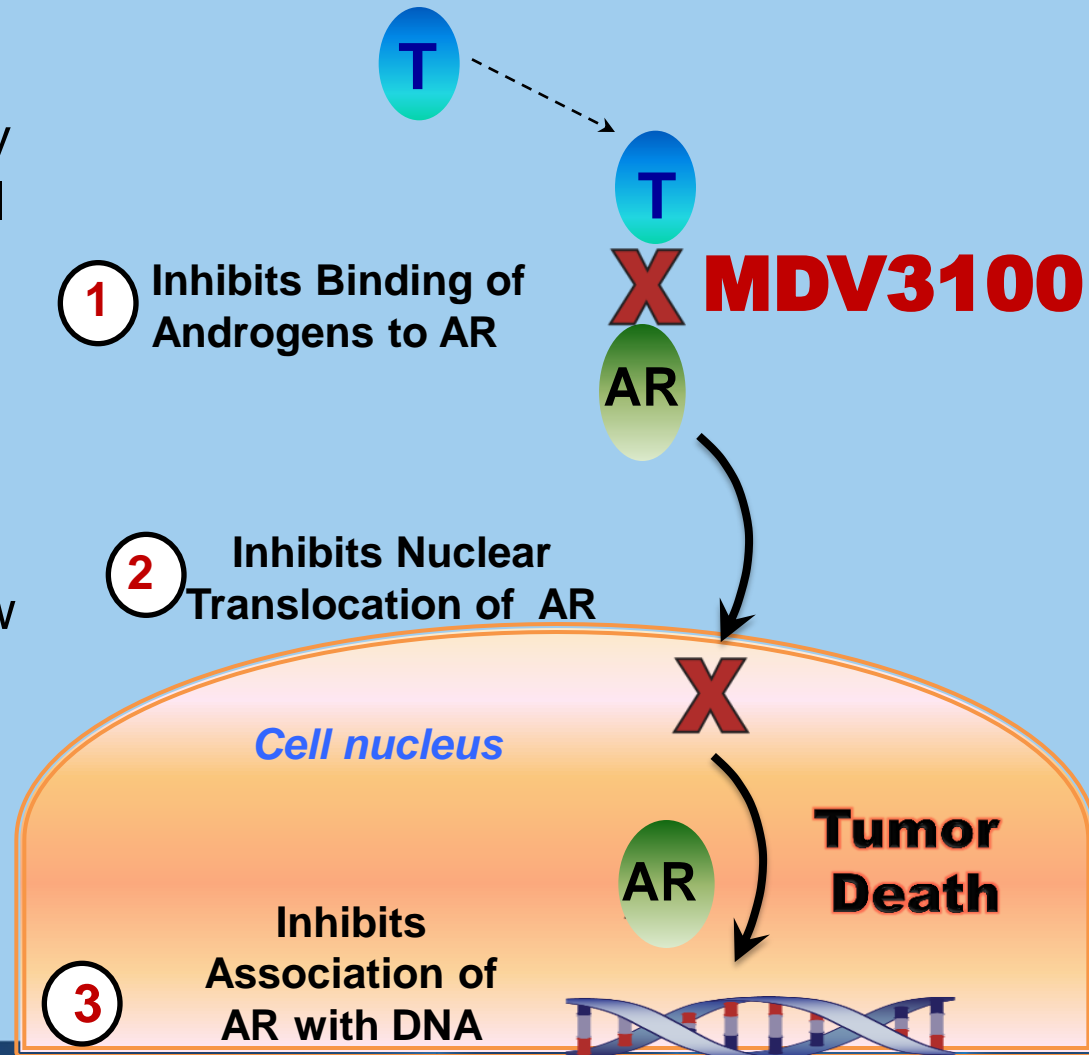
CRPC: pre-
docetaxel

CRPC: post-
docetaxel



MDV3100 for the Treatment of Prostate Cancer

1. MDV3100 is an oral investigational drug rationally designed as a new hormonal agent to target androgen receptor (AR) signaling, a key driver of prostate cancer growth.
2. MDV3100 is the first in a new class of Androgen Receptor Signaling Inhibitors that affects multiple steps in the androgen receptor signaling pathway.



AFFIRM: A Phase 3 Trial of MDV3100 vs. Placebo in Post-Chemotherapy Treated Castration-Resistant Prostate Cancer (CRPC)

Patient Population:

1199 patients with
progressive CRPC

Failed docetaxel
chemotherapy

R
A
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D
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D
2:1

MDV3100

160 mg daily
n = 800

Placebo

n = 399

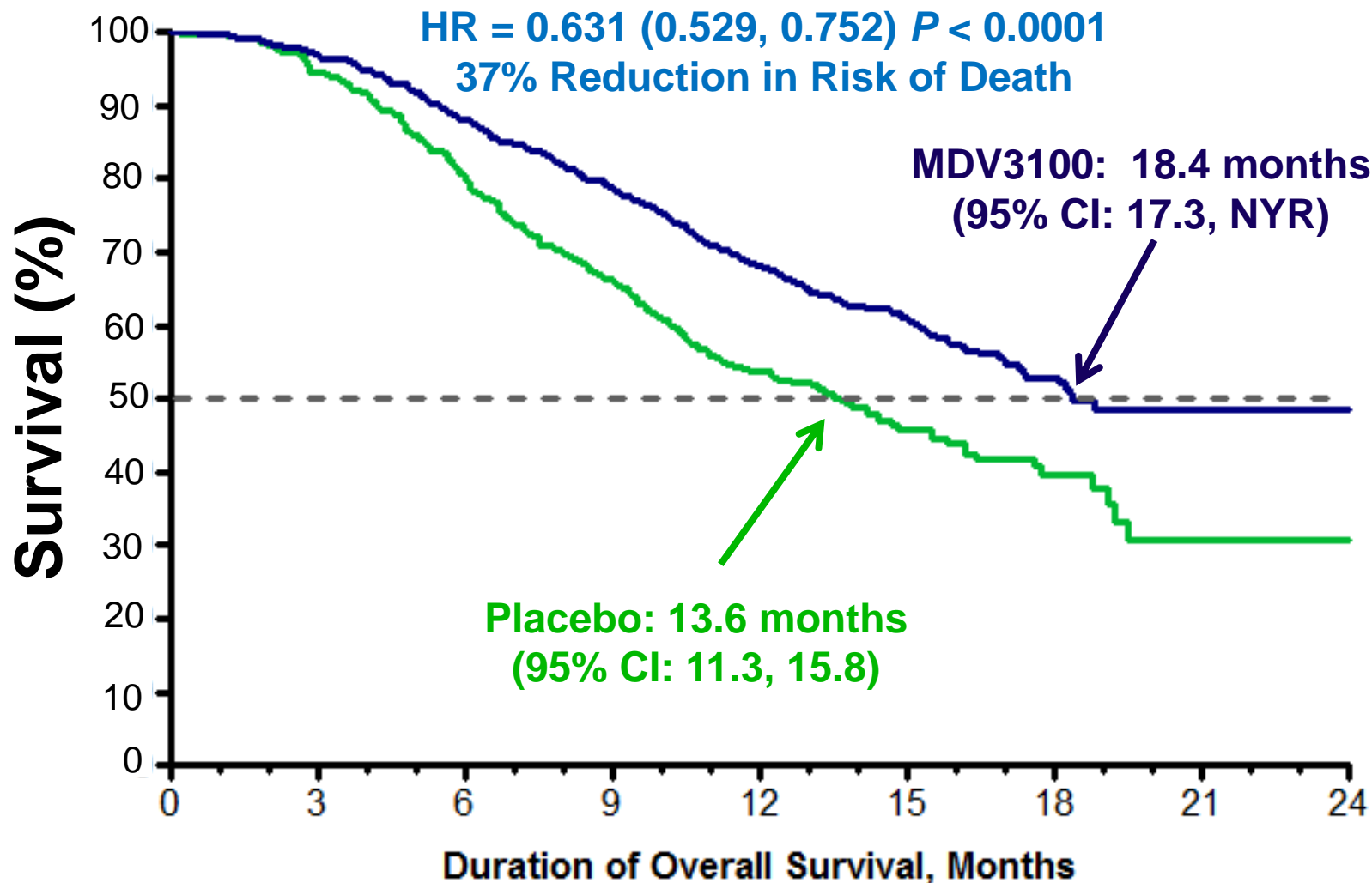
Primary Endpoint:
Overall Survival

Secondary Endpoints:
Radiographic and PSA
response and
progression

Co- Principal Investigators:
H. Scher & J. De Bono

Clinicaltrials.gov identifier: NCT00974311

MDV3100 Significantly Prolonged Survival by an Average of 4.8 months



MDV3100	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

The Benefits of MDV3100 Were Supported by Changes in the Secondary Outcomes

1. A significantly higher proportion of patients treated with MDV3100 showed tumor shrinkage by CT or MRI imaging and had a $\geq 50\%$ decline in PSA.
2. Time to disease progression assessed by imaging and PSA was longer on average by 5 months for MDV3100 vs. placebo patients.

The favorable changes are consistent with the survival benefit seen.

MDV3100 Produces Declines in PSA and Prolongs PSA Progression Times

Response	MDV3100	Placebo	P-value
Confirmed PSA Decline			
$\geq 50\%$ from Baseline	54.0%	1.5%	<0.0001
$\geq 90\%$ from Baseline	24.8%	0.9%	<0.0001

Progression	MDV3100	Placebo	Hazard Ratio (Confidence Interval) P-value
Median Time to Confirmed PSA Progression (months)	8.3	3.0	0.248 (0.204, 0.303) <0.0001

MDV3100 Produces Shrinkage of Soft Tissue Tumors and Prolongs the Time to Radiographic Progression

Response	MDV3100	Placebo	P-value
Soft Tissue Response by CT/MRI Imaging	28.9%	3.8%	<0.0001

Progression	MDV3100	Placebo	Hazard Ratio (Confidence Interval) P-value
Median Radiographic Progression-free Survival (months)	8.3	2.9	0.404 (0.350, 0.466) <0.0001

MDV3100 Was Well-Tolerated

	Total Events		Grades ≥ 3 Events*	
	MDV3100 (n = 800)	Placebo (n = 399)	MDV3100 (n = 800)	Placebo (n = 399)
Adverse Events	98.1%	97.7%	45.3%	53.1%
Serious Adverse Events	33.5%	38.6%	28.4%	33.6%
Discontinuations due to Adverse Events	7.6%	9.8%	4.6%	7.0%
Adverse Events Leading to Death	2.9%	3.5%	2.9%	3.5%

*Adverse events are graded for severity with Grades 1 and 2 milder and Grades 3-5 more severe

Conclusions

1. MDV3100, an oral Androgen Receptor Signaling Inhibitor given once a day, significantly and meaningfully prolonged survival by nearly 5 months in men with late-stage prostate cancer.
2. Secondary measures of response and time to progression were consistent with the survival benefit.
3. MDV3100 was well-tolerated, and the benefit:risk profile will likely position it as the front-line agent post-docetaxel therapy.
4. Trials of MDV3100 in earlier stages of prostate cancer are ongoing.

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QUESTION AND ANSWER SESSION

For More Information

- For oncologist-approved patient information resources, visit www.Cancer.Net, ASCO's patient Website
- For interview requests and additional information contact:
 - mediateam@asco.org