

Bone Targeted Therapy Across the PC Continuum

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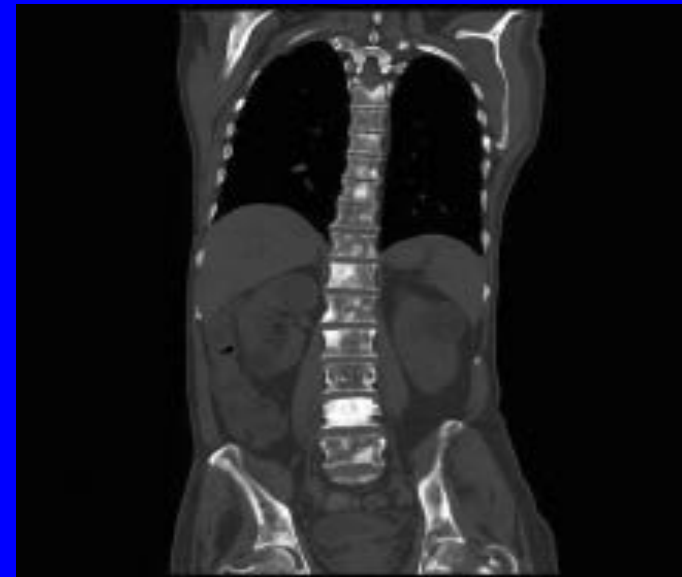
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Disclosures

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| Consulting Agreements | AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bellicum Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Dendreon Pharmaceuticals Inc, EMD Serono Inc, Johnson & Johnson Pharmaceuticals, Medivation Inc, a Pfizer Company, OncoGenex Pharmaceuticals Inc, Sanofi Genzyme, Tokai Pharmaceuticals Inc; Contracted Research: Bayer HealthCare Pharmaceuticals, Endocyte Inc, Innocrin, Johnson & Johnson Pharmaceuticals, Sanofi Genzyme |
|------------------------------|--|

What Bone Targeted Agents Are FDA Approved in Prostate Cancer

- To increase bone mass for men with osteoporosis secondary to androgen deprivation
 - Denosumab at 60 mg q 6 months
 - Four other drugs approved for osteoporosis in men
- Prevention of skeletal related events for those with bone metastatic CRPC
 - Zoledronic acid, denosumab
- Relief of pain for those with CRPC
 - Strontium-89, samarium-153 lexidronam
 - External beam radiation too!
- Prolong survival for those with bone-metastatic CRPC
 - Radium-223

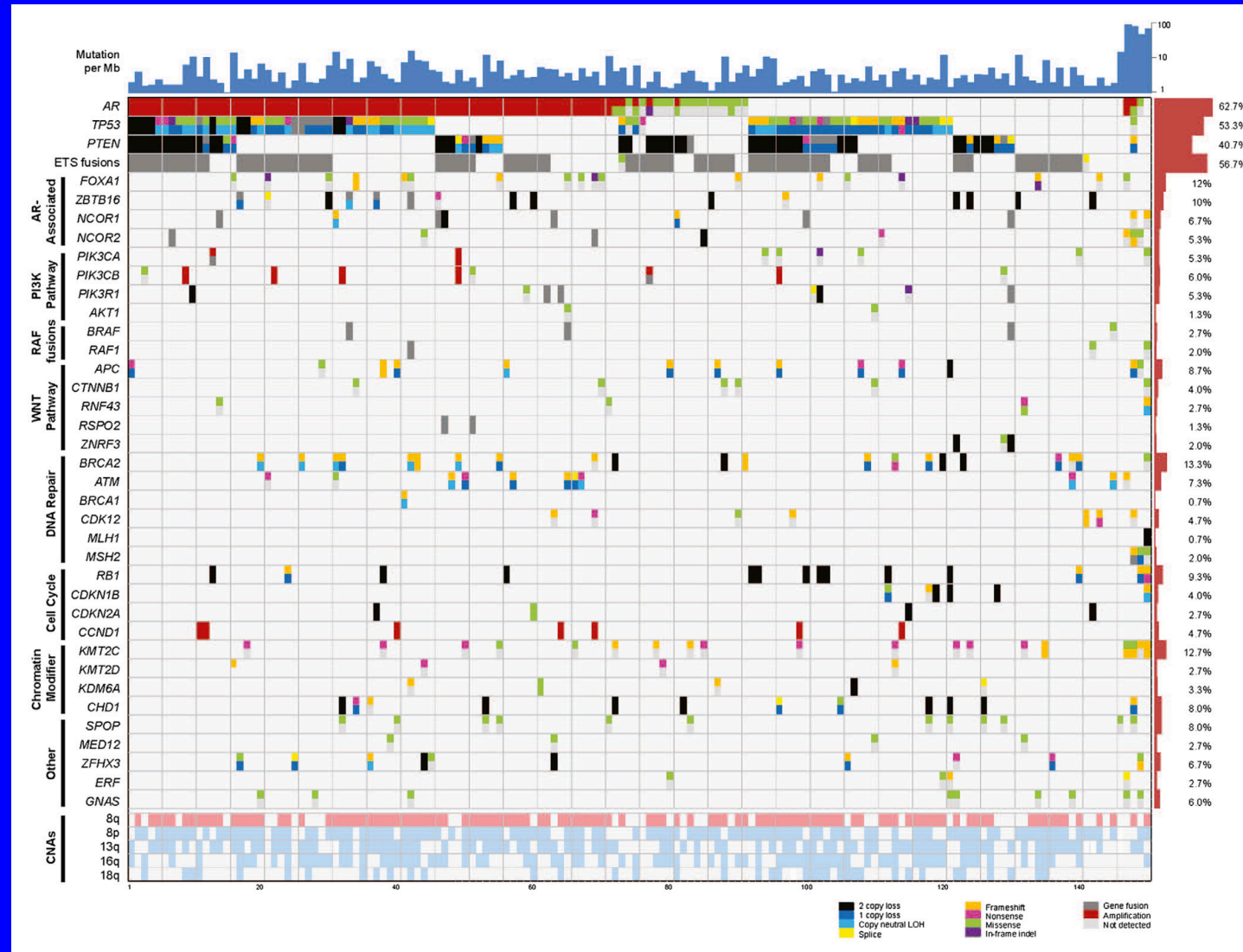
The land of “no indication”

- No indication to treat bone-metastases in men with hormone-sensitive disease responding to therapy
 - Zoledronic acid failed to provide benefit in two trials
- No indication to prevent onset of bone-metastatic disease in men with CRPC
 - Denosumab failed to provide benefit

Simple Categorization of Current Bone Targeted Therapies

| | Hormone-sensitive | CRPC |
|----------------|--------------------|---------------------------|
| Non-Metastatic | Treat osteoporosis | Treat osteoporosis |
| Metastatic | Treat osteoporosis | Improve survival and SREs |

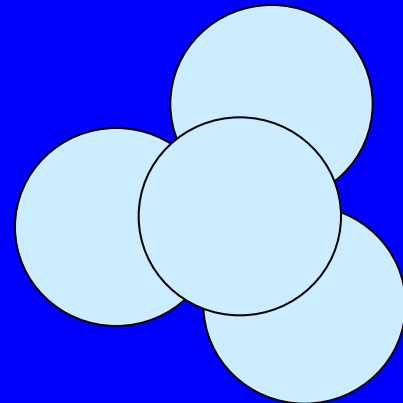
Challenge: Metastatic prostate cancer is a heterogeneous disease filled with undruggable targets



Key Challenge in Treating Advanced Prostate Cancer

- Androgen deprivation therapies (ADT) benefit men with advanced prostate cancer
 - But AR targeted drugs eventually fail
- How do we target advanced cancers driven by multiple undruggable targets?

Alpha radiation: No known resistance pathways to DNA double strand breaks

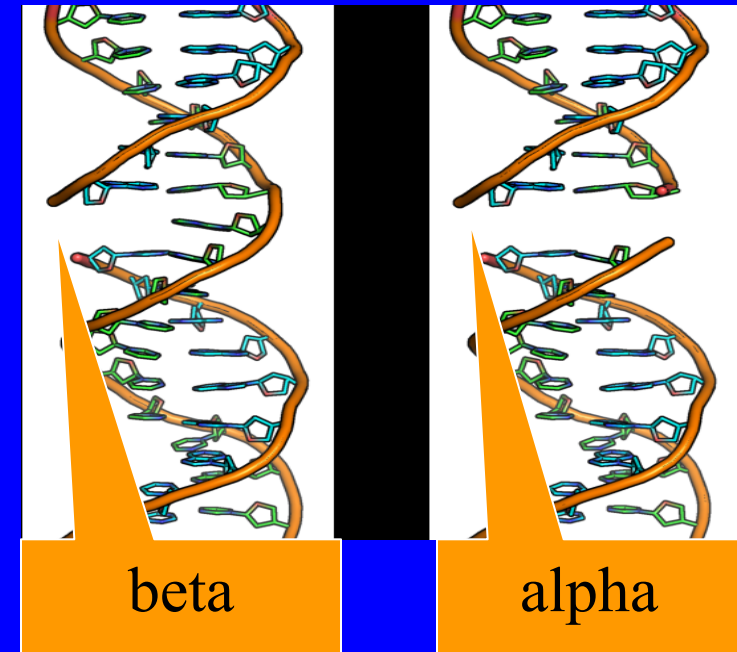


Alpha

Beta



| | α | β |
|-----------------------------------|----------|-----------|
| Relative particle mass | 7300 | 1 |
| Initial energy (MeV)/particle | 3–8 | 0.01–2.5 |
| Range in tissue (μm) | 40–100 | 50–5000 |
| * LET (KeV/ μm) | 60–230 | 0.015–0.4 |
| DNA hits to kill cells | 1–10 | 100–1000 |



*LET, linear energy transfer

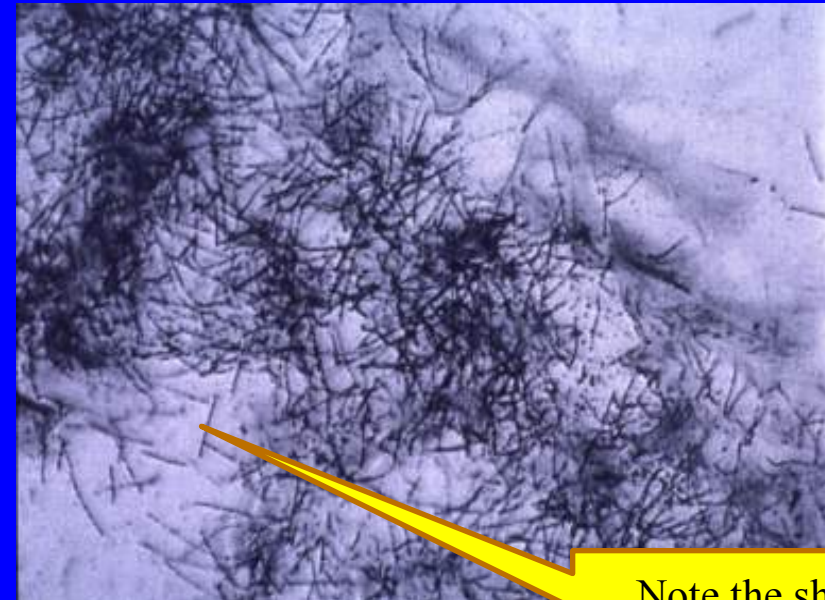
Henriksen G, et al. J Nucl Med. 2003;44(2):252-9

Deposition of radium-223 in an osteoblastic lesion compared to normal bone

Normal bone



Osteoblastic lesion



Note the short track length

Studies in Dog

Radium-223: Preferential Uptake in the Stroma of Osteoblastic Lesions Compared to Normal Bone and Bone Marrow

Bruland et al. *Clin Cancer Res.* 2006;12:6250s-6257s.

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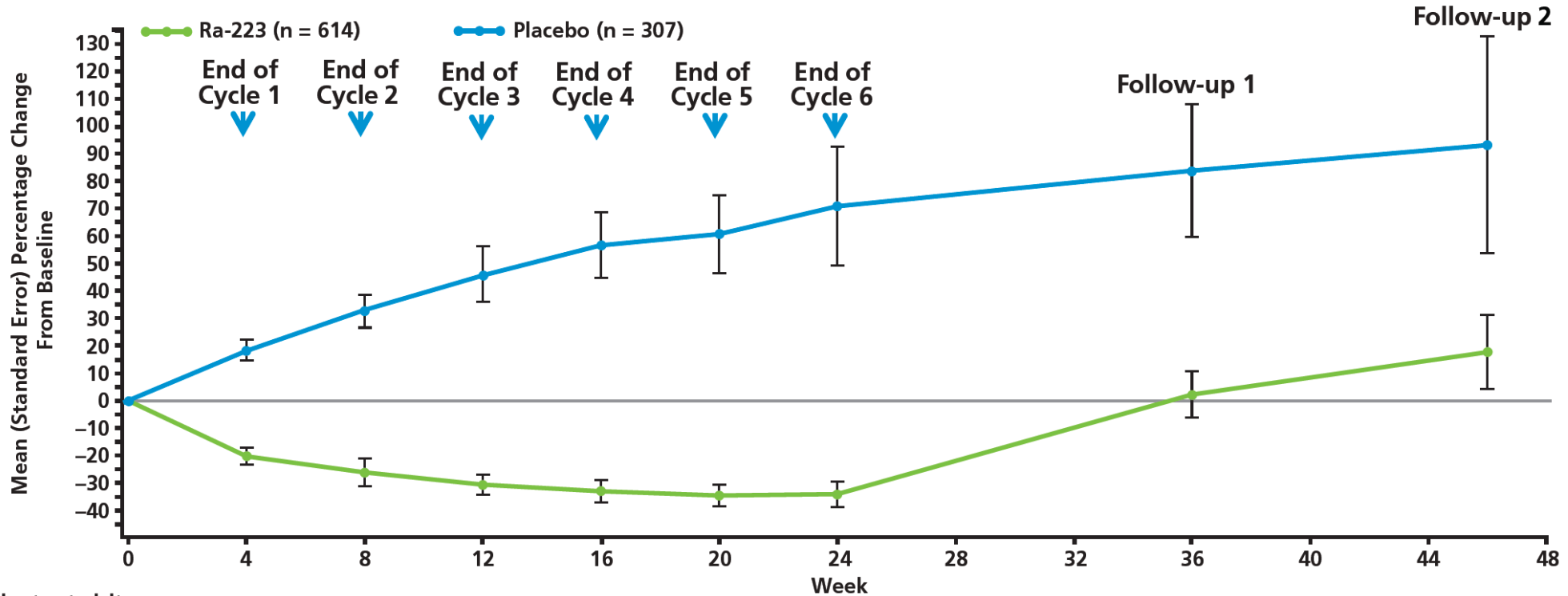
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Alpha Emitter Radium-223 and Survival
in Metastatic Prostate Cancer

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*

Kinetics of ALP Change in the ALSYMPCA Trial

Sartor et al. Ann Oncol Feb 16, 2017 (epub ahead of print)

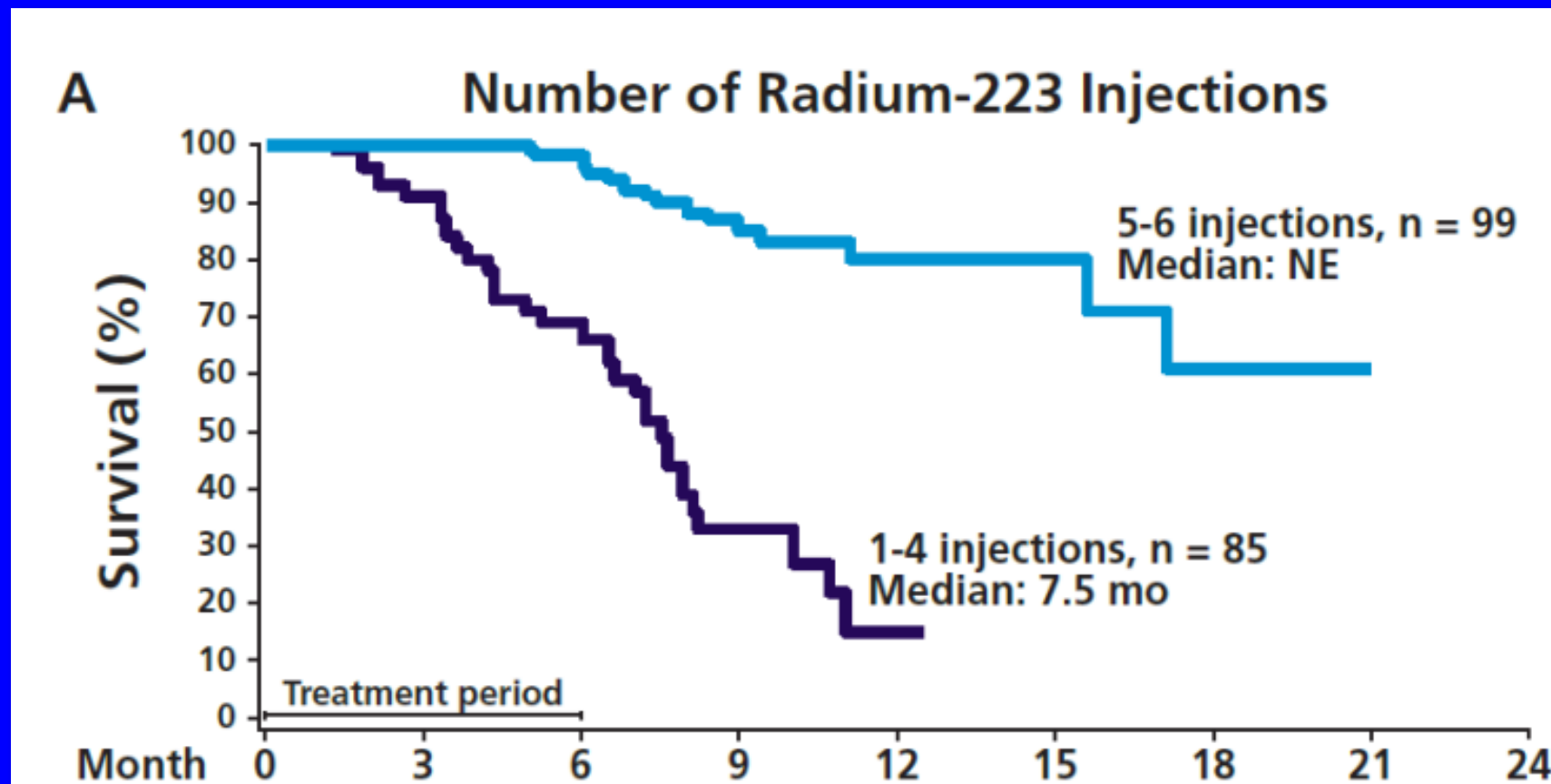


Patients at visit

| | | | | | | | | | | |
|---------|-----|---------|---------|---------|---------|---------|---------|--|---------|---------|
| Ra-223 | 614 | 582 | 561 | 517 | 465 | 413 | 353 | | 336 | 252 |
| Placebo | 307 | 286 | 260 | 231 | 193 | 159 | 130 | | 136 | 100 |
| P value | | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | | < 0.001 | < 0.001 |

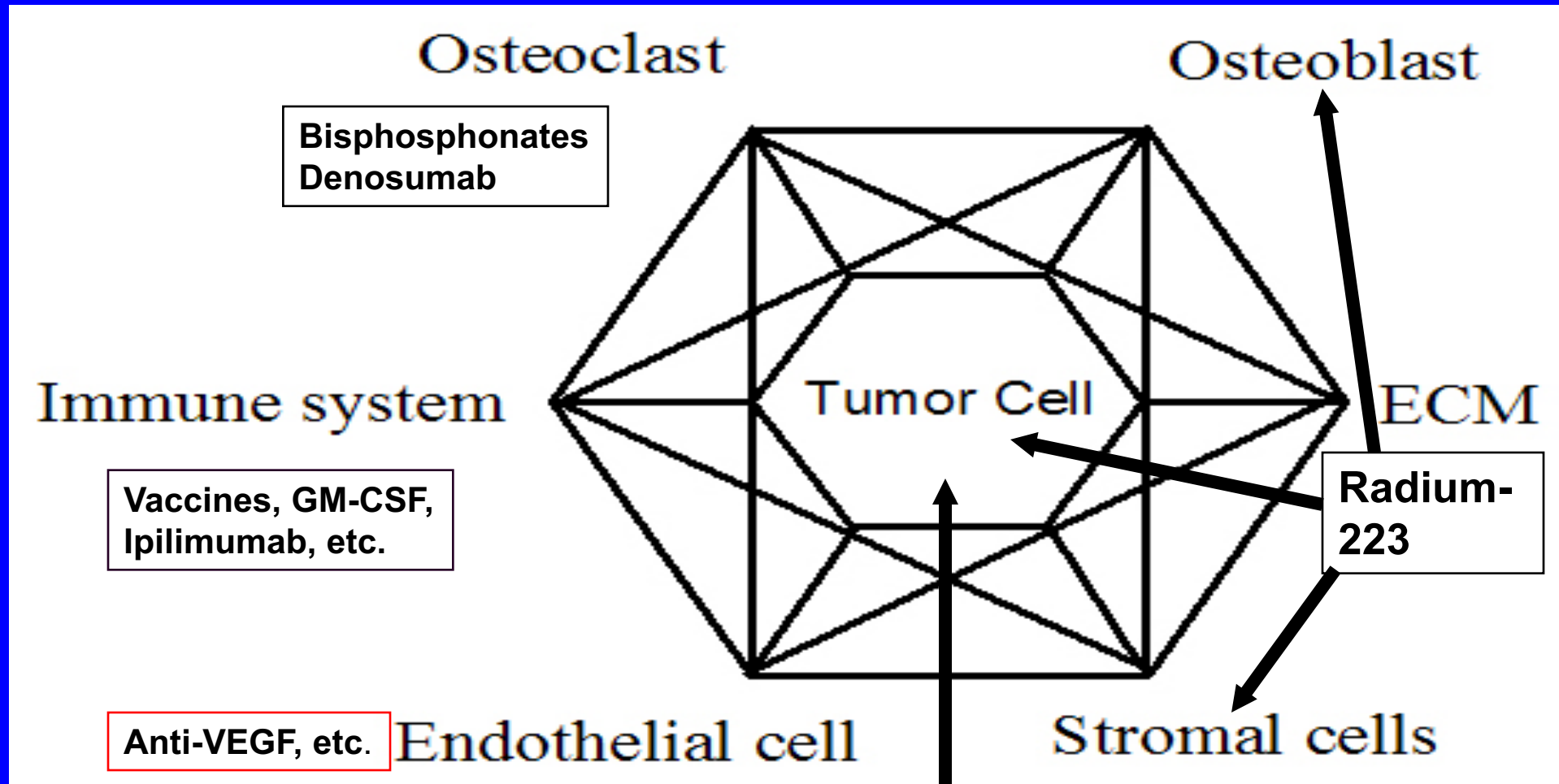
Radium-223: Survival after 1-4 injections versus 5-6 injections in EAP

Sartor et al. ASCO 2015, #5063



Multi-Targeted Therapy in Bone Metastases

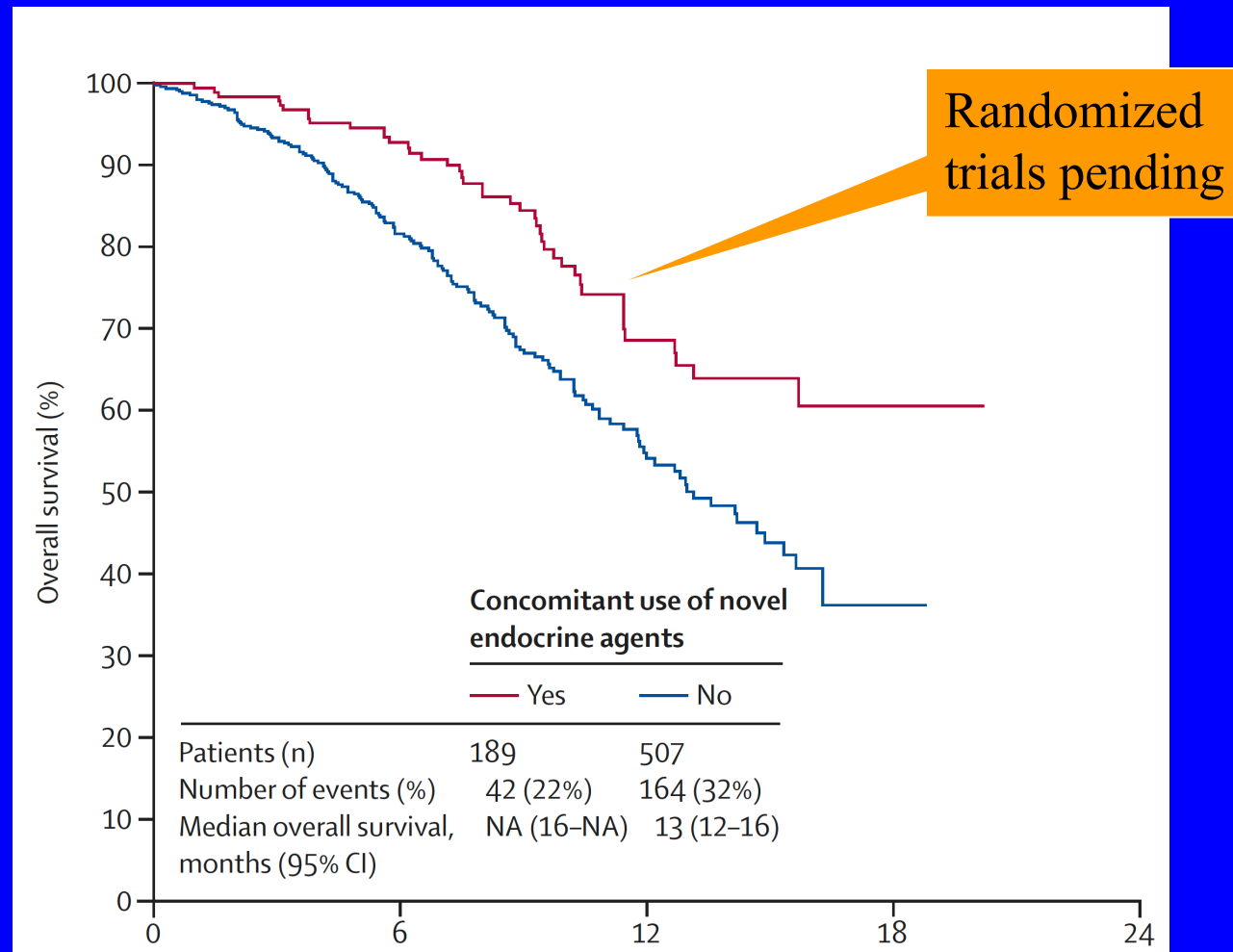
Modified from K. Pienta: U Michigan



AR targeted therapies, cytotoxics, etc.

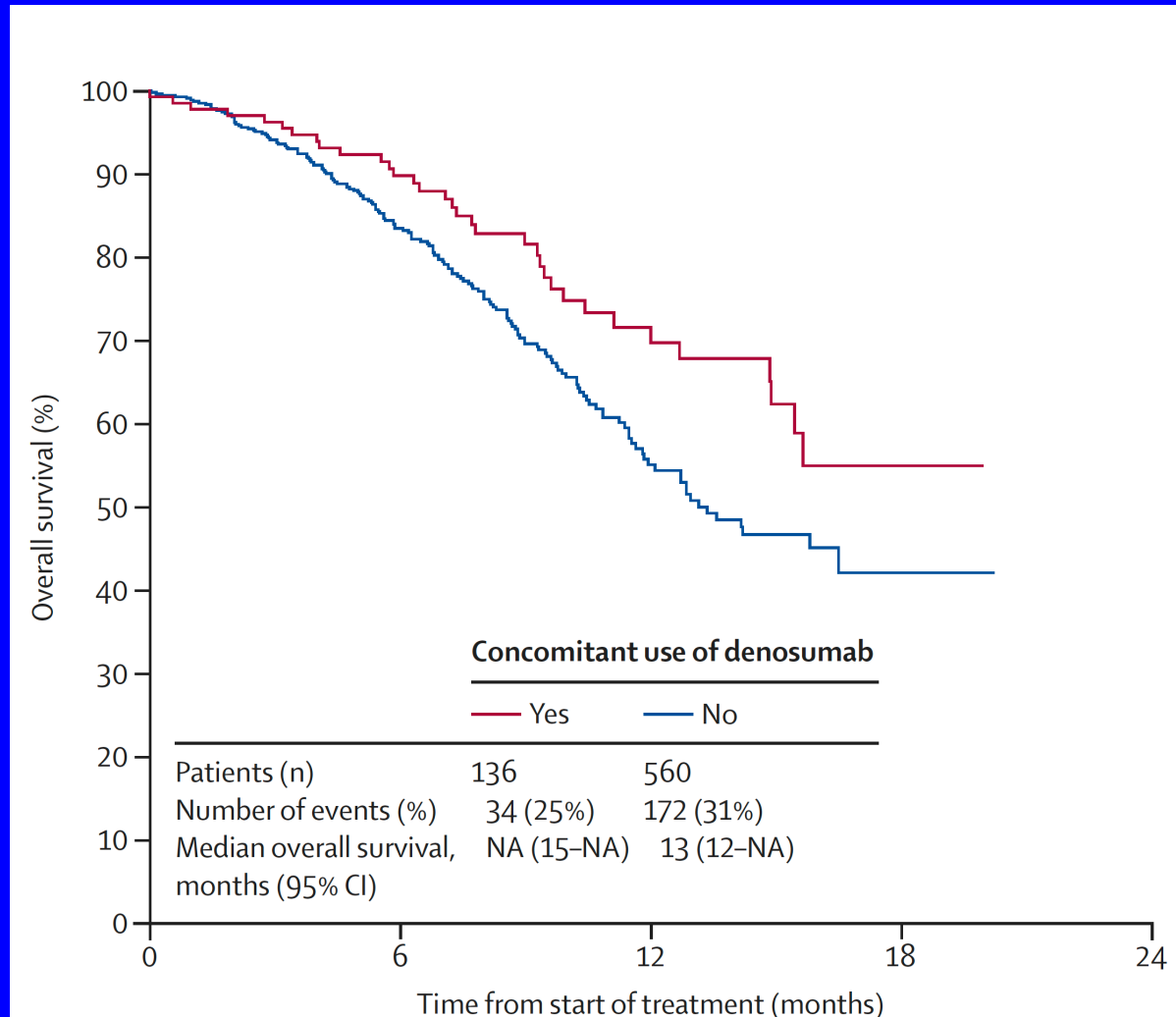
Concomitant abiraterone/enzalutamide and radium-223 in the international EAP: Non-randomized!!

Saad et al. Lancet Oncology online July 26, 2016

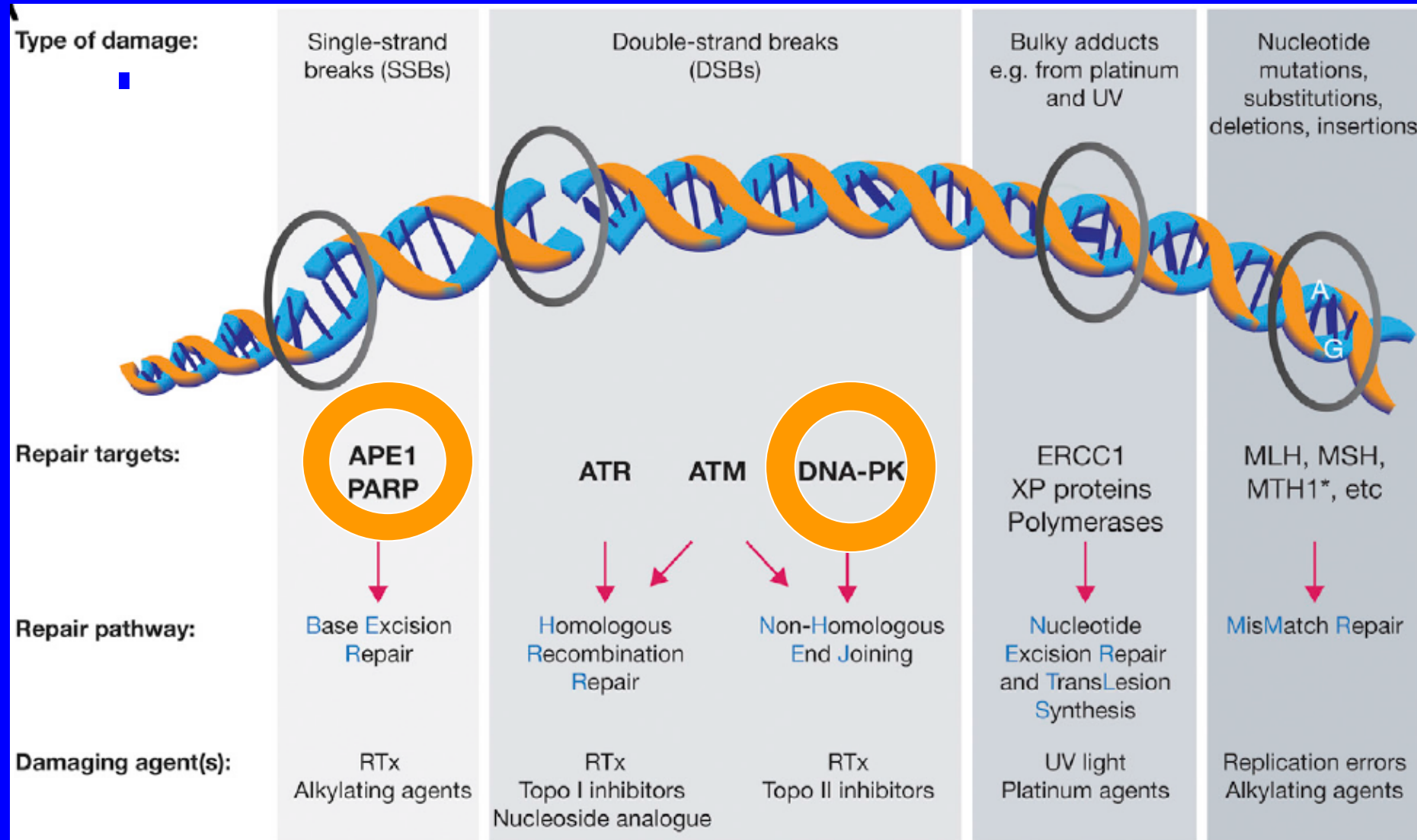


Concomitant denosumab and radium-223 in the international EAP: Non-randomized!

Saad et al. Lancet Oncology online July 26, 2016



Targeting DNA damage repair pathways in combination with XRT and Radionuclides



Radium-223 Only Goes to Bone!

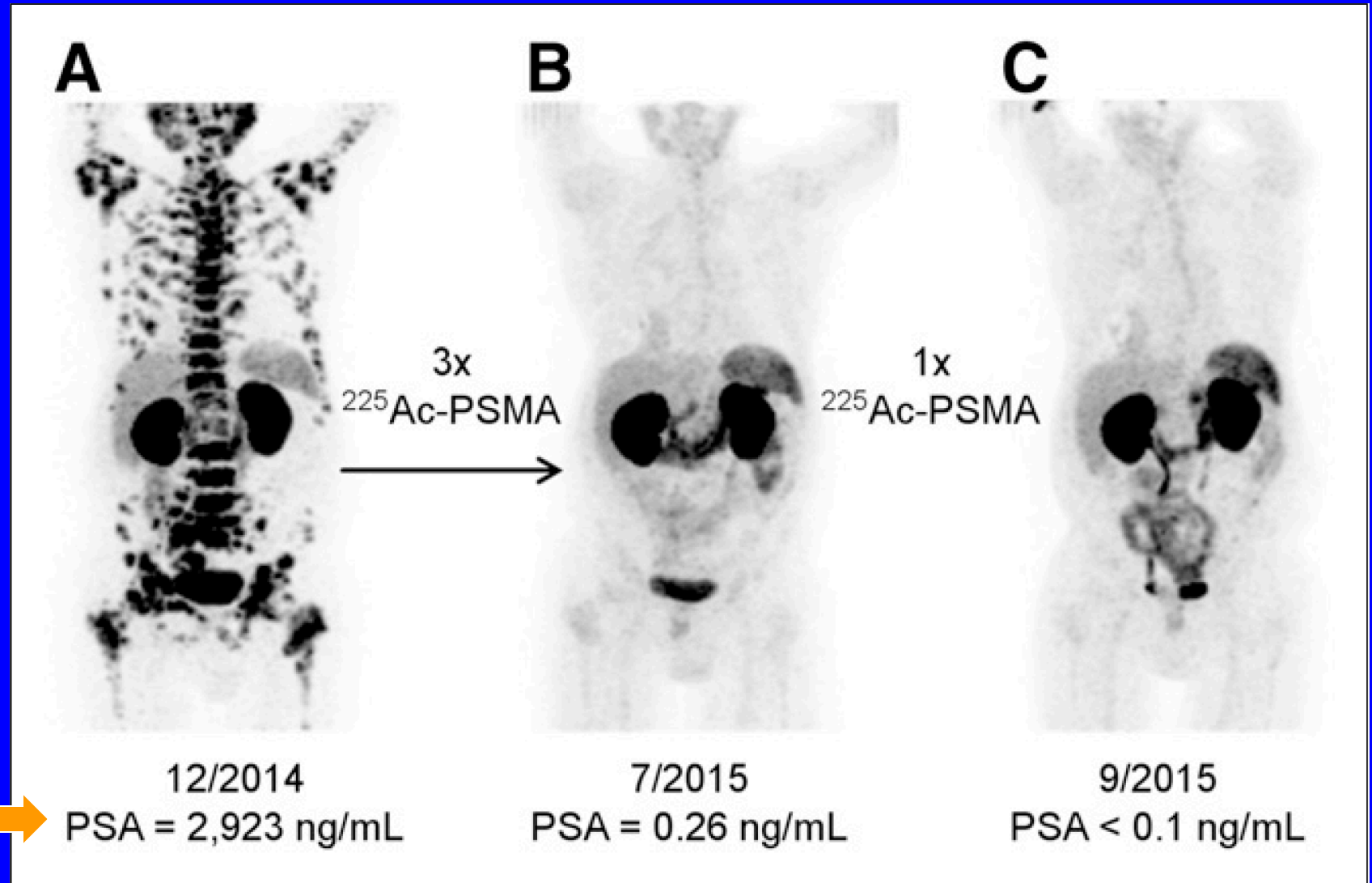
This agent does an excellent job in treating bone but other locations cannot be neglected

Radio-conjugates: PSMA targeted alpha emitters (Actinium-225) as 9th line treatment

Kratochwil et al. J Nuc Med 57: 1-4, 2016

Patient A

- Leuprorelin
- Zoledronate
- Docetaxel (50 cycles)
- Carmustine/epirubicin in hyperthermia
- Abiraterone
- Enzalutamide
- ²²³Ra (6 cycles)
- Abiraterone reexposition
- Estramustine



Genetically Heterogeneous Cancers Are a Challenge for “Molecularly Targeted” Therapy but Radiation Kills Them All!

