

Radium-223 and Targeted Alpha Therapy Thinking About Tomorrow

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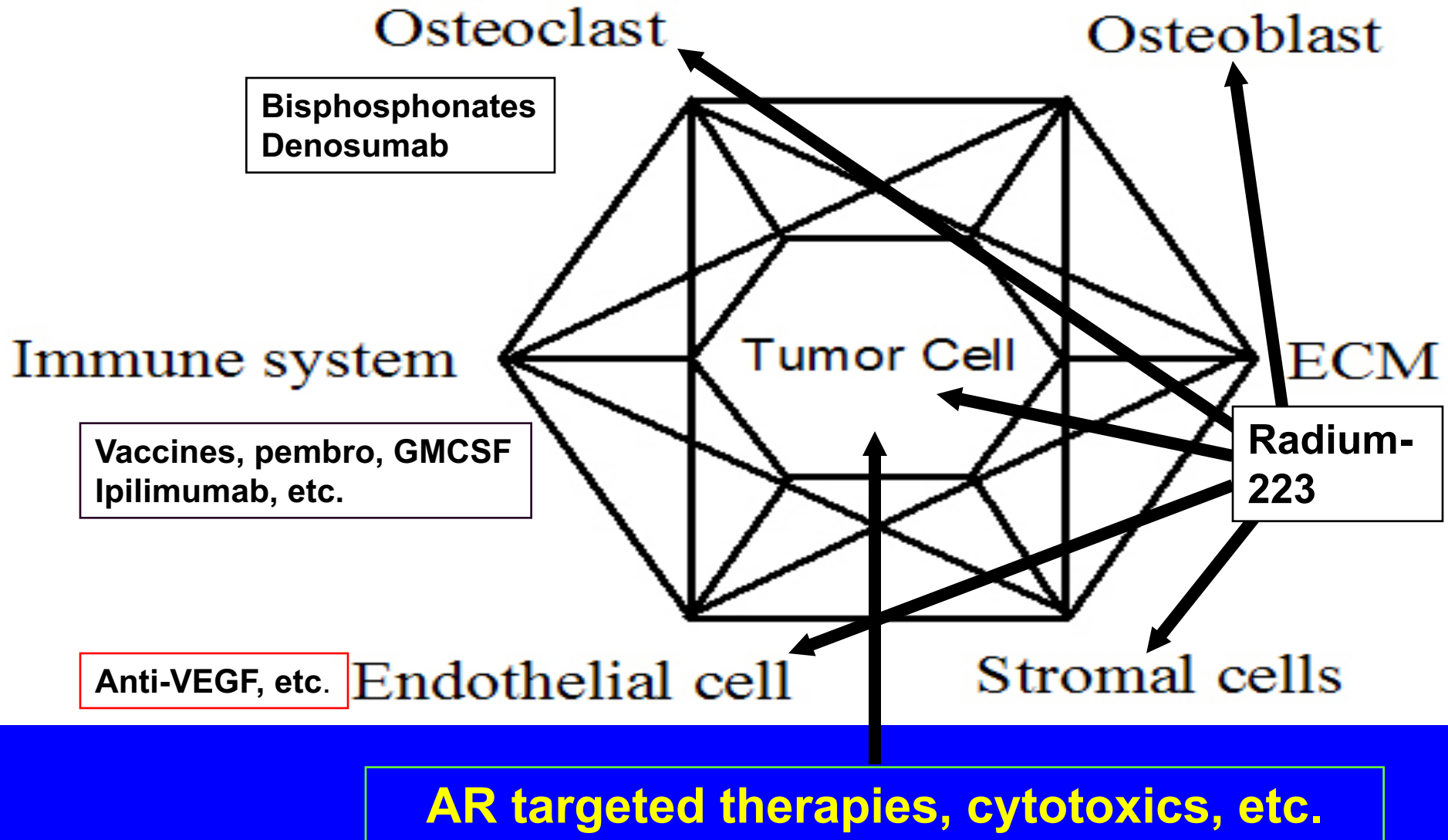
New Orleans, LA

Disclosures

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, OncoGenex Pharmaceuticals Inc, Sanofi Genzyme, Tokai Pharmaceuticals Inc
Contracted Research	Bayer HealthCare Pharmaceuticals, Endocyte Inc, Innocrin Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Sanofi Genzyme

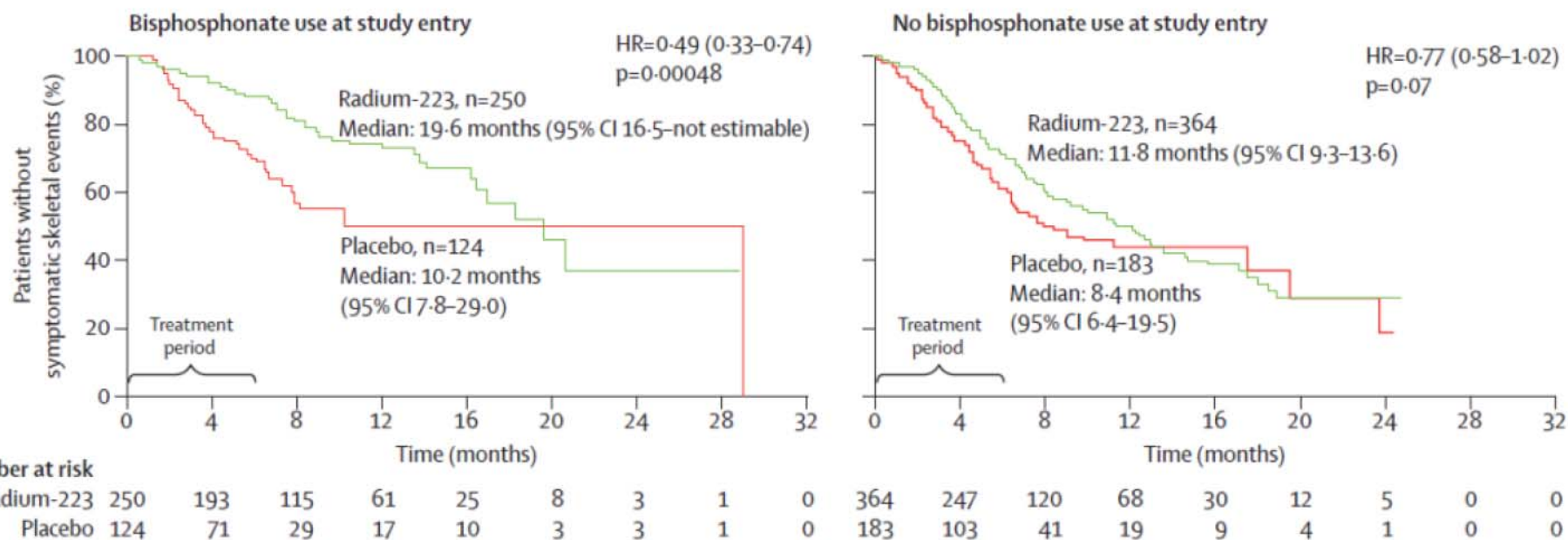
Combination Therapy in Bone Metastases

Modified from K. Pienta: U Michigan



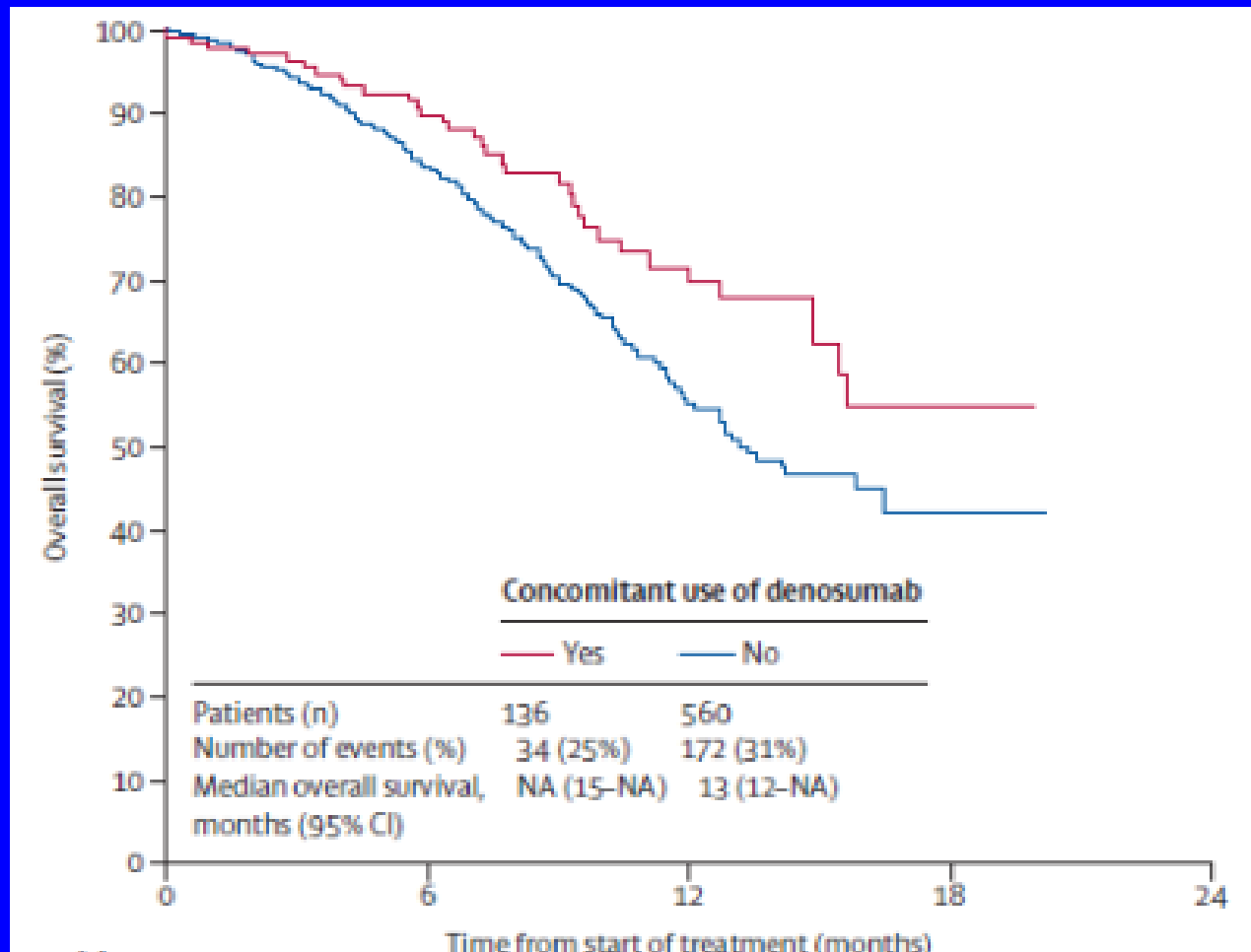
Radium-223 and bisphosphonates: No combined effect on survival but effect on SSE rate

Sartor et al. *Lancet Oncology* 2014;15:738



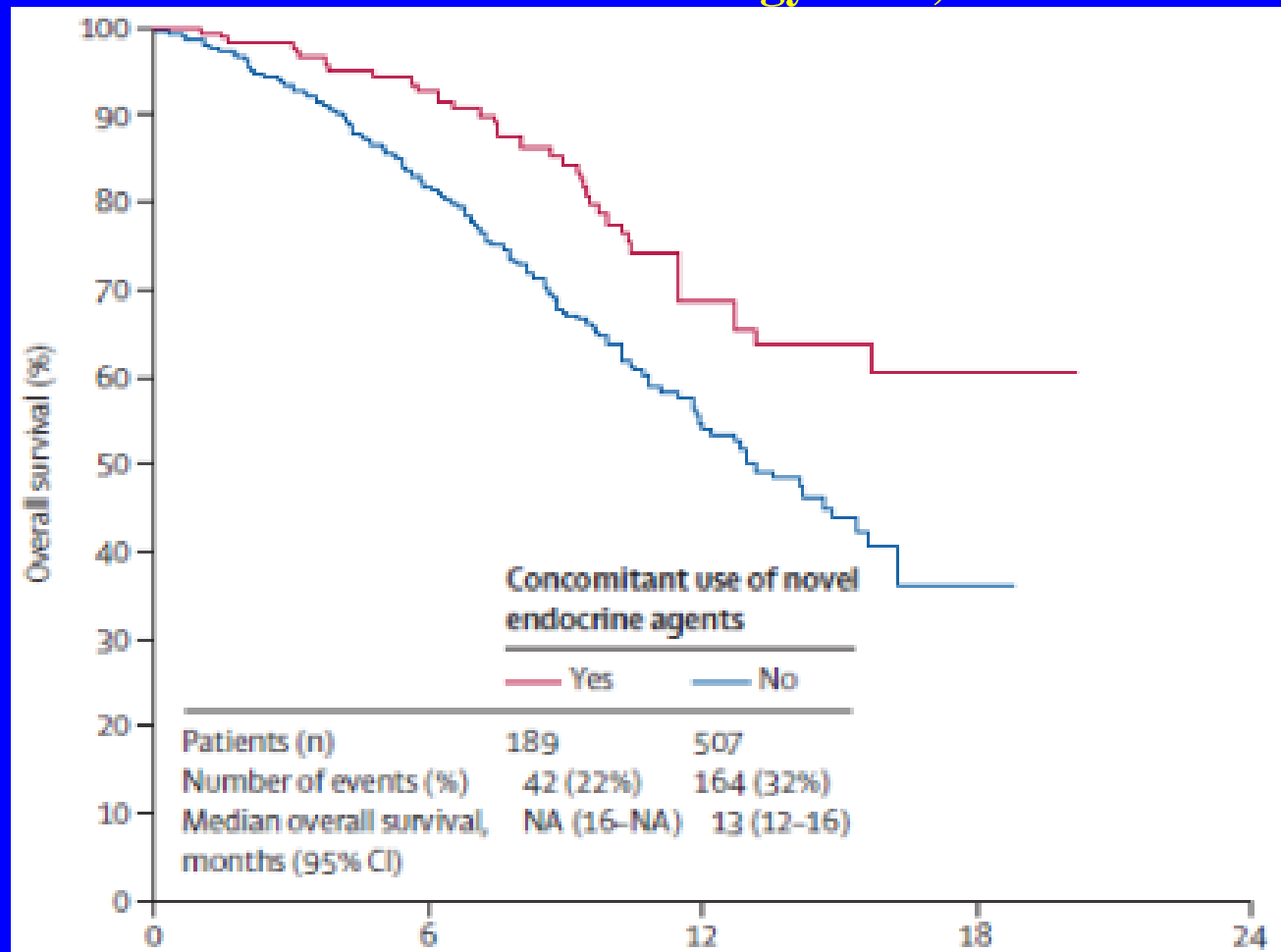
Concomitant denosumab and radium-223 in the International EAP: Non-randomized!!

Saad et al. Lancet Oncology 2016;17:1306



Concomitant abiraterone or enzalutamide and radium-223 in the International EAP: Non-randomized!!

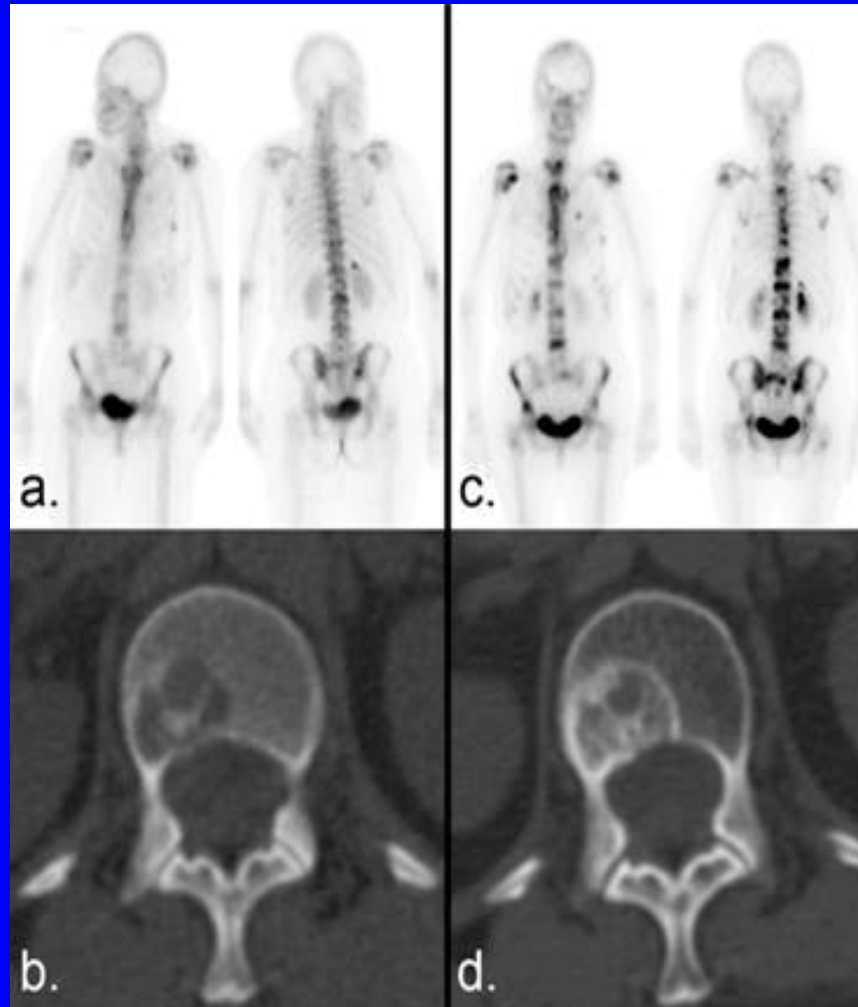
Saad et al. Lancet Oncology 2016;17:1306



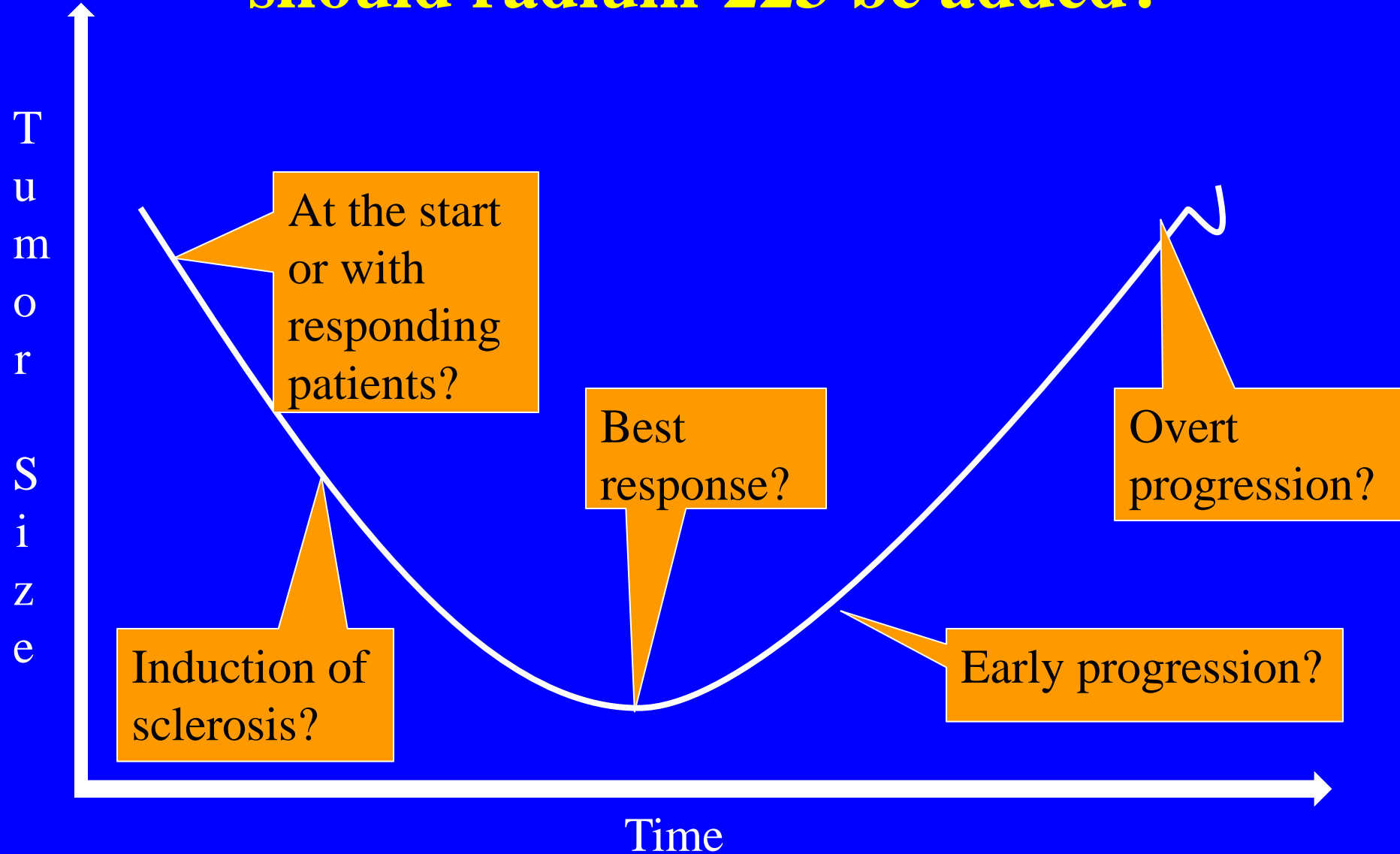
Can Radium Add Value to Abiraterone or Enzalutamide in Bone-Metastatic CRPC?

- Abiraterone +/- radium phase III ERA-223 trial completed accrual
 - Primary endpoint: Symptomatic skeletal event-free survival
- Enzalutamide +/- radium phase III PEACE-III trial under way
 - Primary endpoint: Radiologic PFS

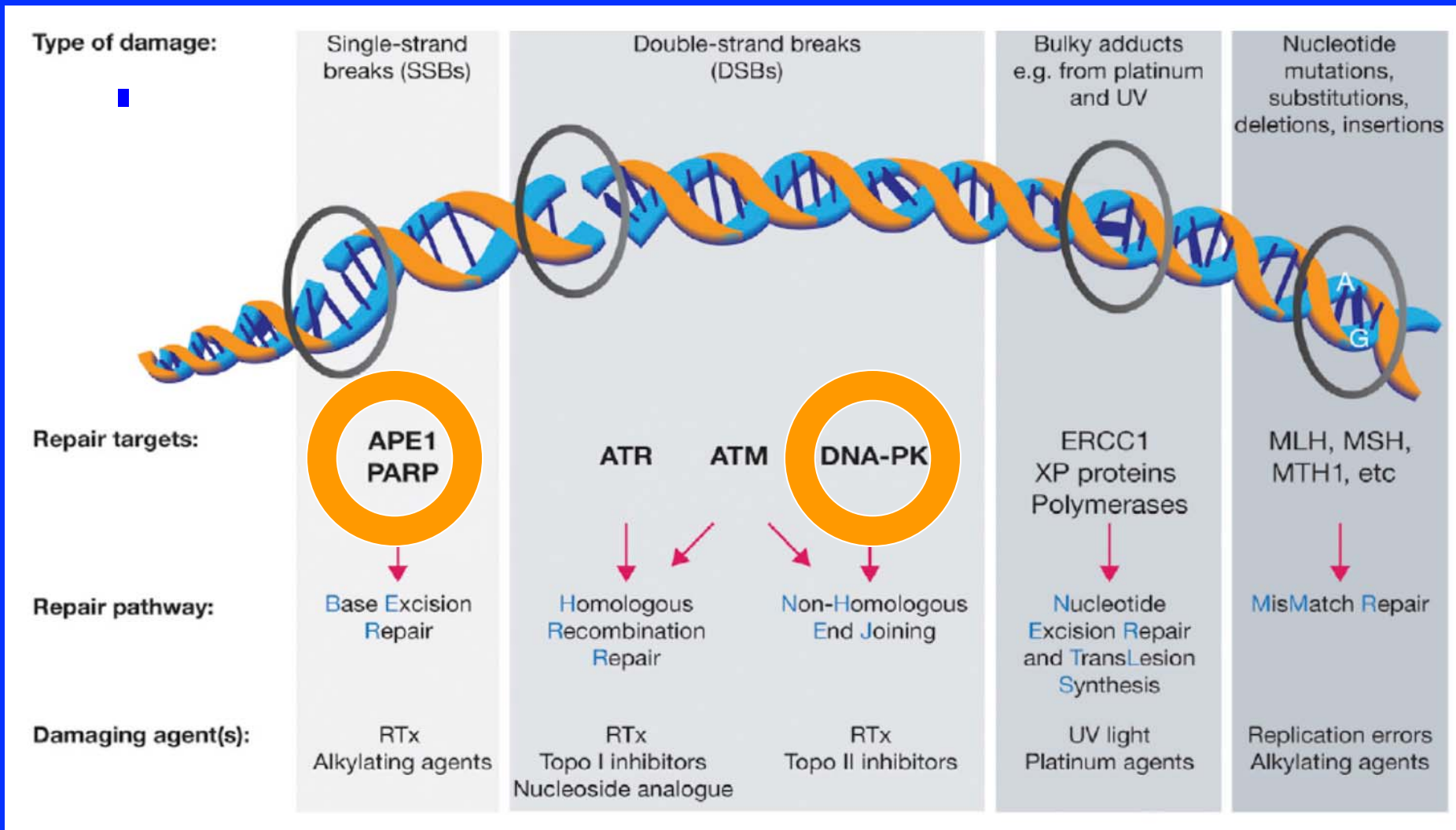
Can we take advantage of “flare” when giving a bone targeted therapy?



If “concomitant” abi/enza is used, when should radium-223 be added?



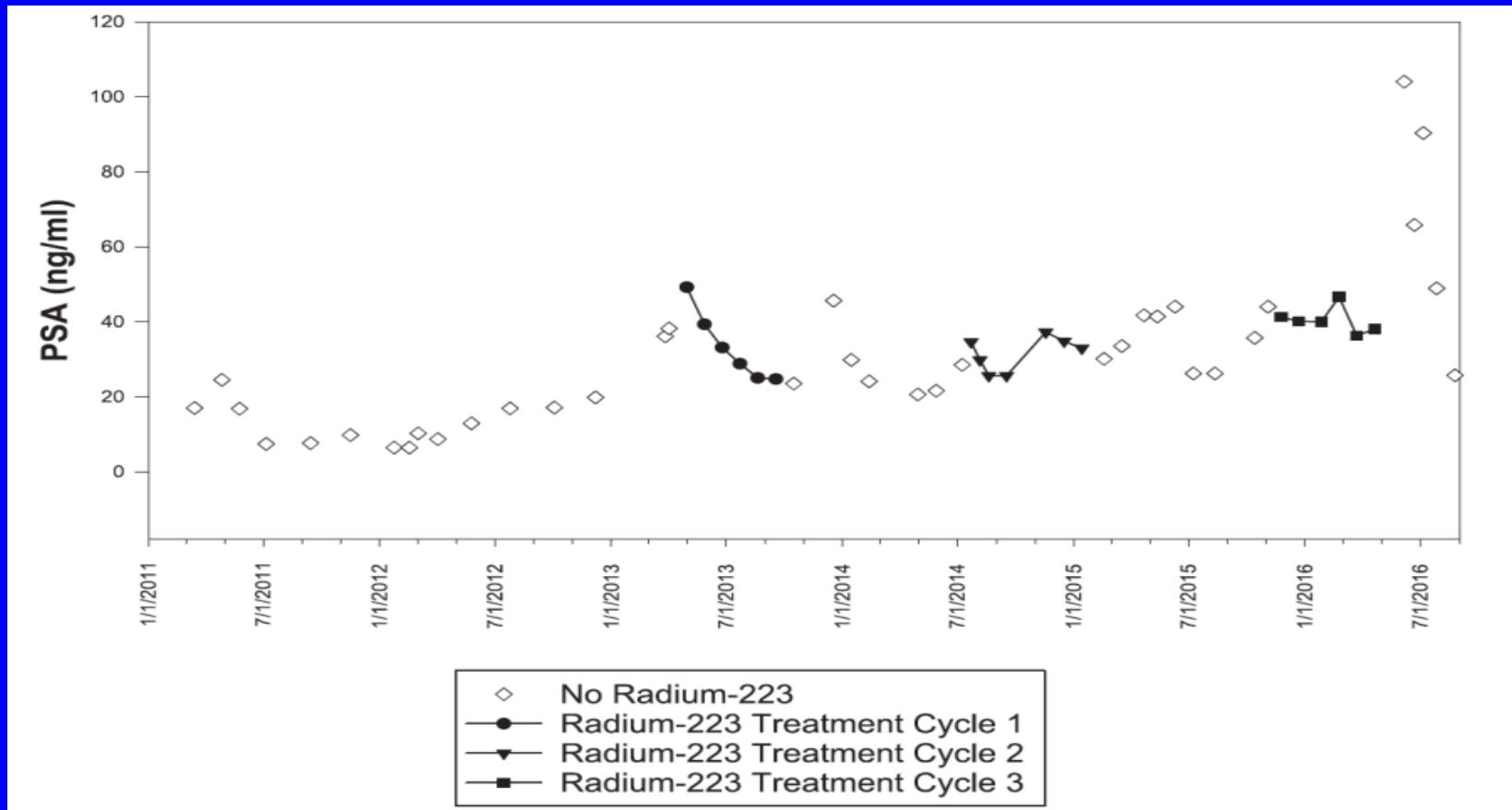
Targeting DNA damage repair pathways in combination with radionuclides



Exceptional Duration of Radium-223 in Prostate Cancer With a BRCA2 Mutation

Allie E. Steinberger, Patrick Cotogno, Elisa M. Ledet,
Brian Lewis, Oliver Sartor

Clin Genitourin Cancer 2017;15:e69

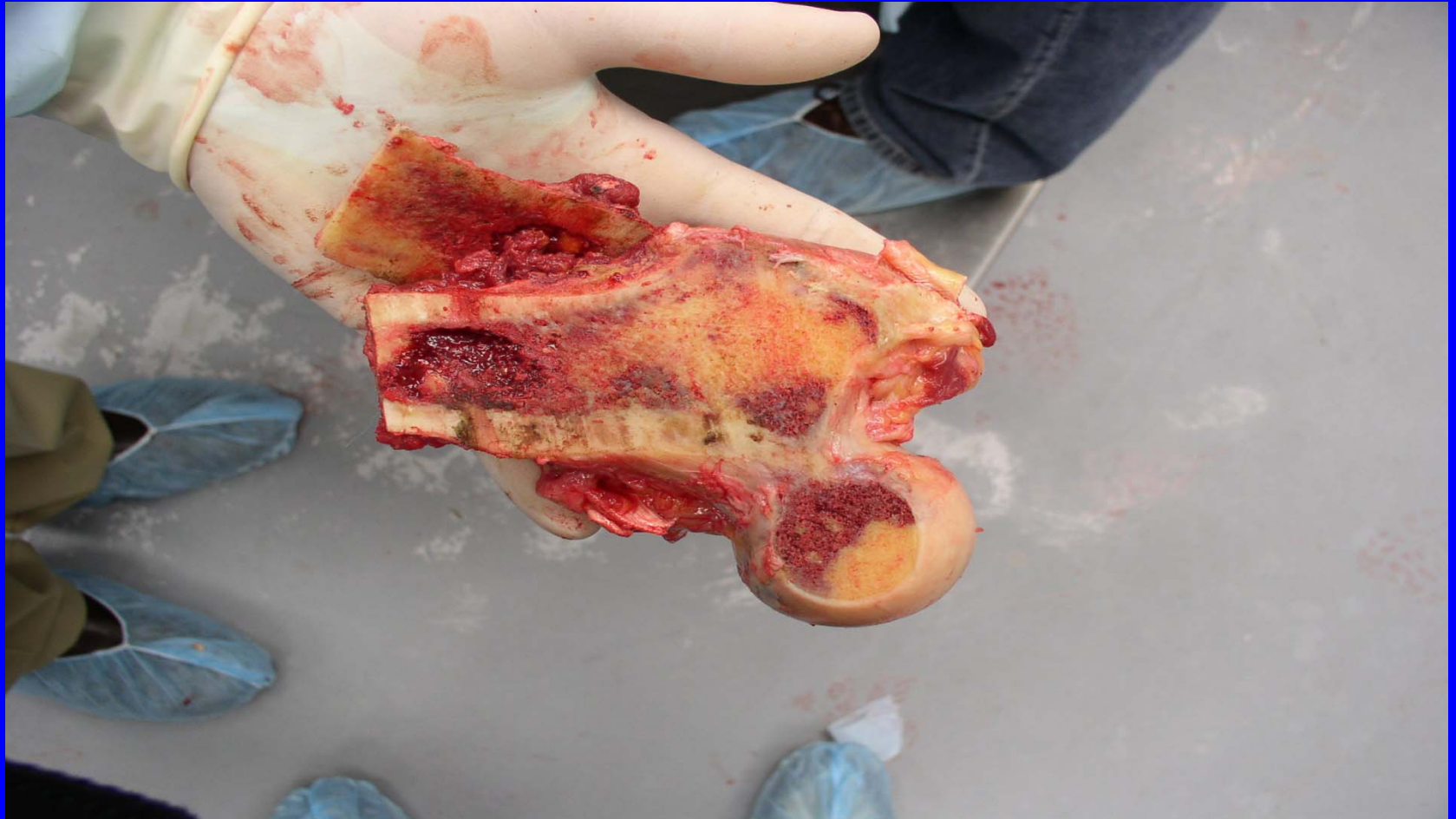


Radium-223 Only Goes to Bone!

**Radium-223 needs a partner to control
soft tissue disease and bone marrow
disease**

**We need to target tumors regardless
of location**

**Bone marrow metastasis...a true problem in
advanced prostate cancer
University of Michigan Autopsy Team**



⁶⁸Ga-PSMA-11 PET as a gate-keeper for the treatment of metastatic prostate cancer with radium-223: proof of concept

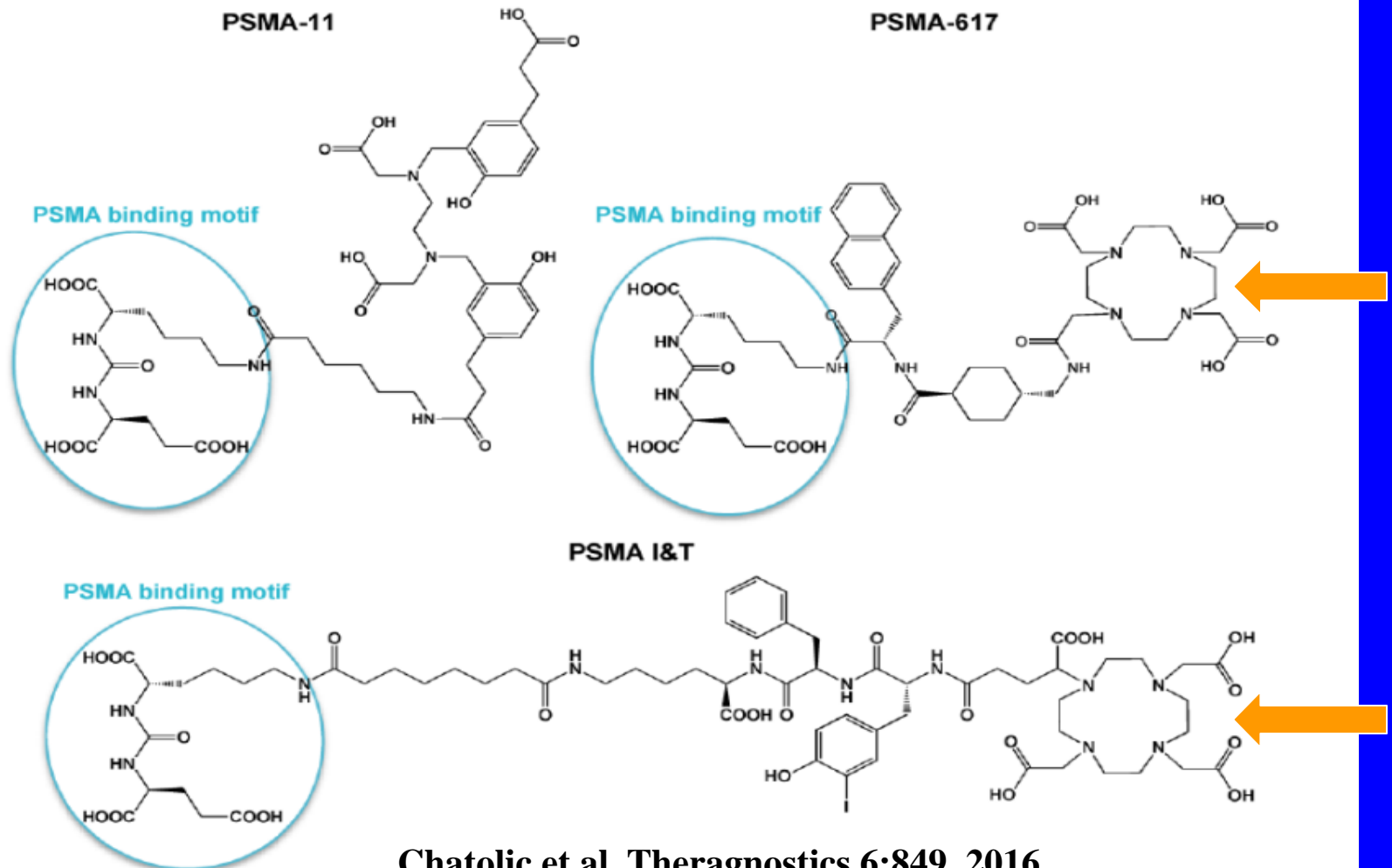
Hojjat Ahmadzadehfar, Kambiz Azgomi, Stefan Hauser, Xiao Wei, Anna Yordanova, Florian C Gaertner, Stefan Kürpig, Holger Strunk, Markus Essler

J Nucl Med 2016;[epub ahead of print]

Using PSMA-PET and bone scan criteria for selection, radionuclide therapy with radium-223 may be more effective and have more success in terms of those having PSA declines

“An increase in PSA during therapy cycles occurs due to disease progression”

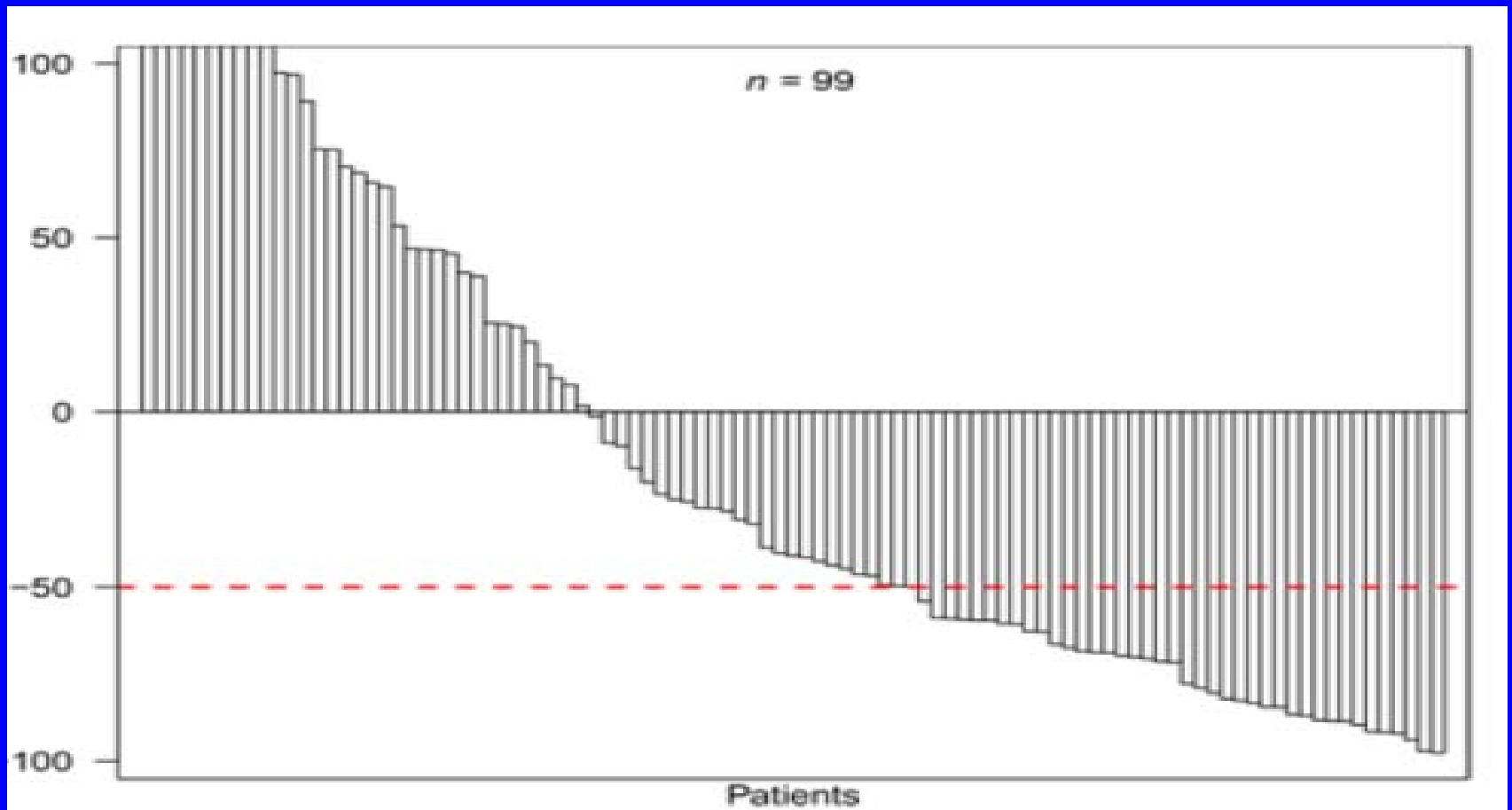
PSMA binding molecules can be linked to therapeutic agents, such as Lu-177, Sm-153, Y-90, Bi-213, Ac-225, or Th-229, by attaching a chelator



PSMA Lu-177

Waterfall Plots for PSA

Rahbar et al., J Nucl Med 2017;58(1):85-90



**Alphas seem better than betas... so we
need tumor targeted alpha emitters**

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

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

Patient A

Leuprorelin

Zoledronate

Docetaxel (50 cycles)

Carmustine/epirubicin in
hyperthermia

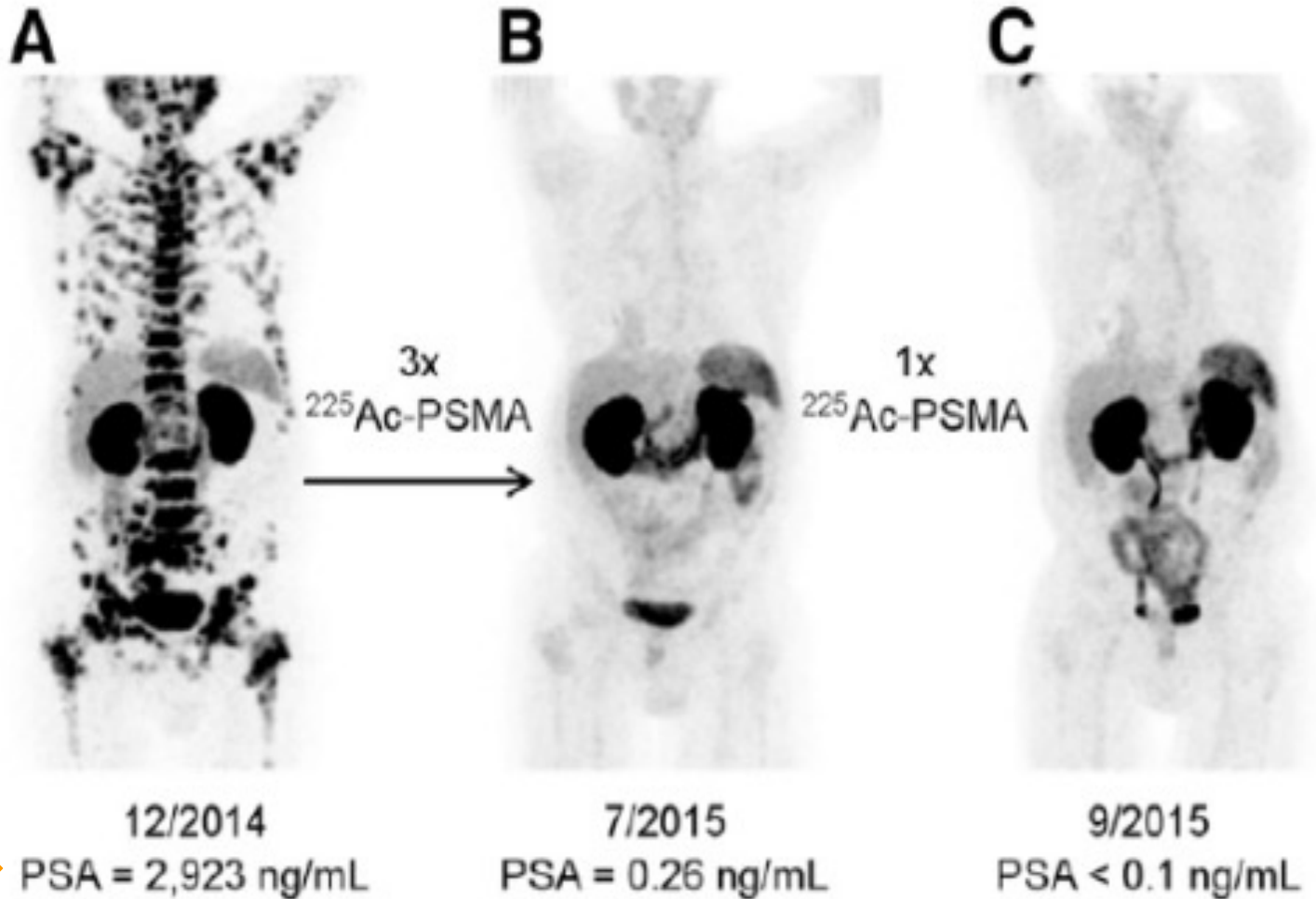
Abiraterone

Enzalutamide

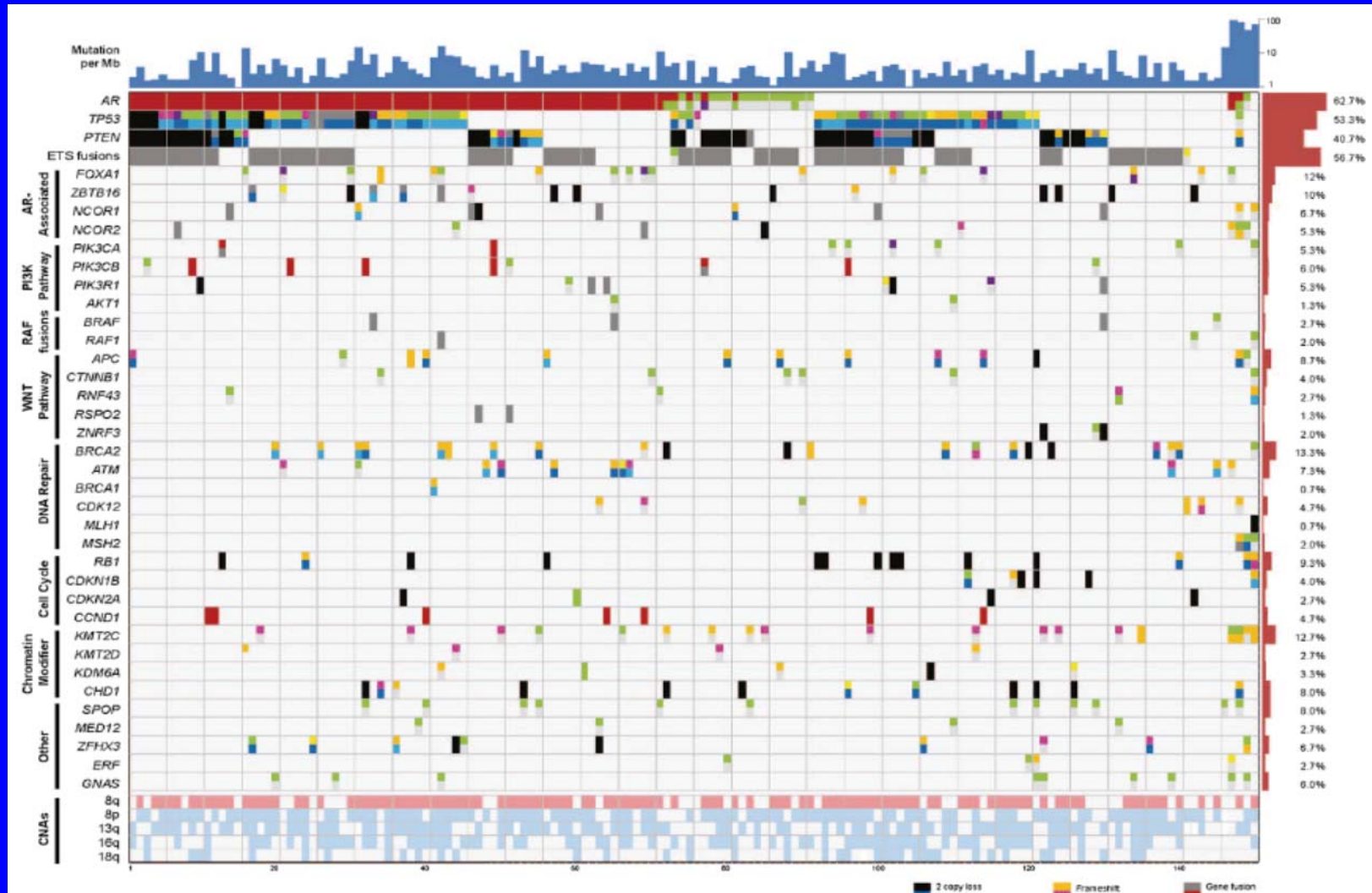
²²³Ra (6 cycles)

Abiraterone reexposition

Estramustine



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



Summary:

Radionuclides in Prostate Cancer

- Radionuclides in combination with other therapies are worth investigating... Attack the cancer from multiple angles and disrupt some tumor microenvironment too!
- All the bone targeted therapies will need a therapeutic partner — targeting the bone is not enough for the vast majority of patients
- Targeted alpha particles are here to stay. Now we need to get to the next level