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# **Bone-Targeted Therapies and Other Emerging Radiopharmaceuticals**

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**New Orleans, LA**

# Disclosures

|   |   |
|---|---|
| <b>Advisory Committee</b>                         | Bayer HealthCare Pharmaceuticals, EMD Serono Inc, Fusion Pharmaceuticals  |
| <b>Consulting Agreements</b>                      | Advanced Accelerator Applications, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Constellation Pharmaceuticals, Dendreon Pharmaceuticals Inc, EMD Serono Inc, Endocyte Inc, Hinovva Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Myovant Sciences, Pfizer Inc, Progenics Pharmaceuticals Inc, Sanofi Genzyme |
| <b>Contracted Research</b>                        | AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Constellation Pharmaceuticals, Dendreon Pharmaceuticals Inc, Endocyte Inc, Innocrin Pharmaceuticals Inc, Invitae, Johnson & Johnson Pharmaceuticals, Merck, Progenics Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi Genzyme, SOTIO LLC  |
| <b>Data and Safety Monitoring Board/Committee</b> | AstraZeneca Pharmaceuticals LP, Johnson & Johnson Pharmaceuticals, Myovant Sciences, Pfizer Inc   |
| <b>Ownership Interest</b>                         | Lilly   |

Based on available data and your own clinical experience, do you believe that radium-223 relieves pain?

Have you observed an improvement in bone pain in any patient receiving radium-223?

|   |                            | Pain relief | Observed bone-pain improvement |
|---|----------------------------|-------------|--------------------------------|
|    | EMMANUEL S ANTONARAKIS, MD | Yes         | Yes                            |
|    | A OLIVER SARTOR, MD        | Yes         | Yes                            |
|    | HOWARD ISCHER, MD          | Yes         | Yes                            |
|  | MATTHEW R SMITH, MD, PHD   | No          | No                             |
|  | CORA N STERNBERG, MD       | Yes         | Yes                            |

# How frequently does treatment with radium-223 lead to clinically relevant cytopenias?



EMMANUEL S  
ANTONARAKIS, MD

Somewhat frequently



A OLIVER SARTOR, MD

Occasionally



HOWARD ISCHER, MD

Depends on prior therapy and disease burden



MATTHEW R SMITH, MD, PHD

Occasionally



CORA N STERNBERG, MD

Somewhat frequently

**A patient who previously received sipuleucel-T now has progressive bone-only metastases and moderate pain in multiple locations, none of which requires immediate radiation therapy. The patient is being started on secondary hormonal therapy (eg, enzalutamide, abiraterone). Would you recommend adding radium-223?**



**EMMANUEL S  
ANTONARAKIS, MD**

No



**A OLIVER SARTOR, MD**

No



**HOWARD I SCHER, MD**

No



**MATTHEW R SMITH, MD, PHD**

No



**CORA N STERNBERG, MD**

No

# Radiation comes in many forms

- External beam
  - Fractionated, hypofractionated, SBRT
- Radiopharmaceuticals
  - Betas and Alphas
  - Bone targeted, tissue targeted (small molecules and antibodies)
- Brachytherapy
  - HDR and LDR
- Selective Internal Radiation Therapy (SIRT)
  - Y90 microspheres

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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, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the AL

No abiraterone  
and no  
enzalutamide



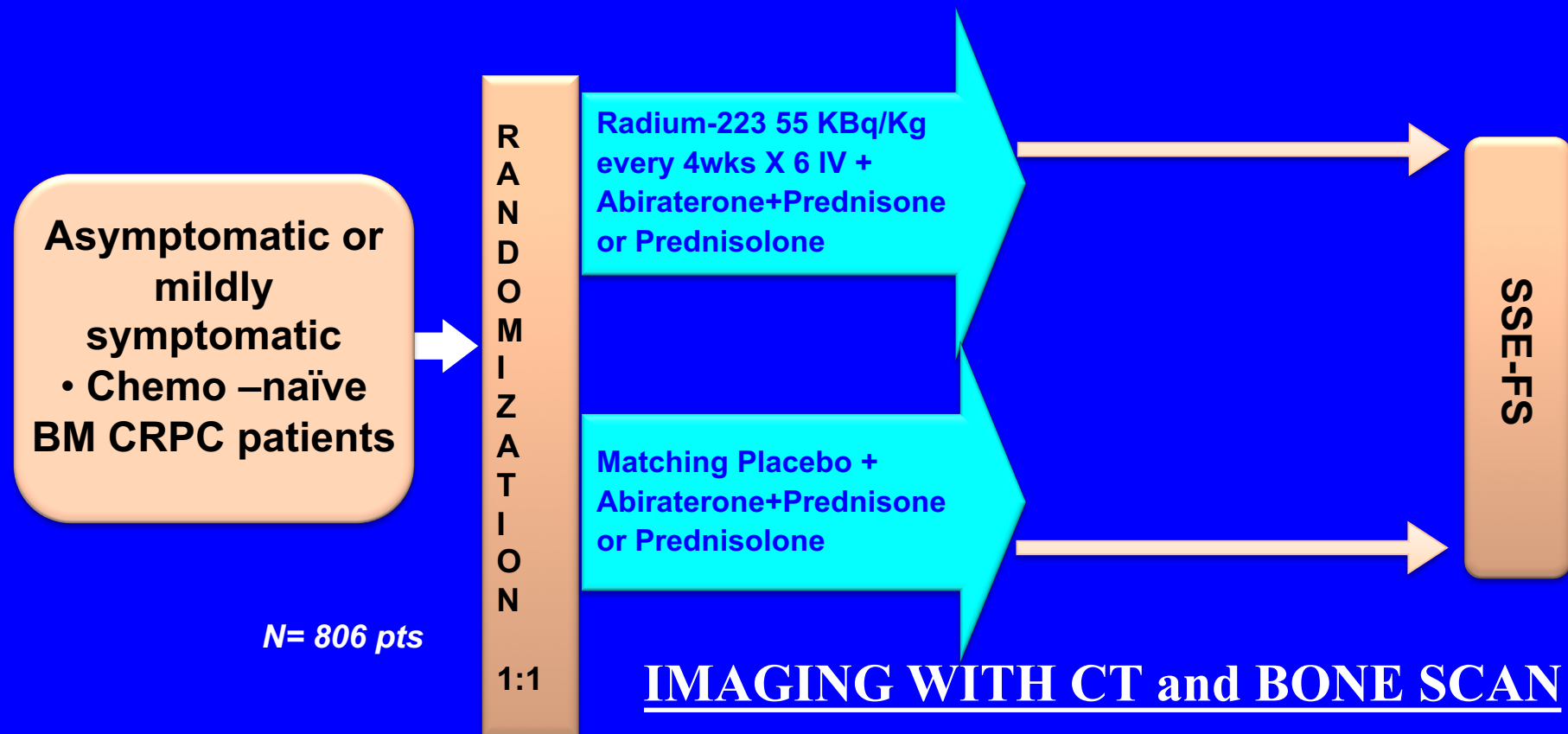
# **Can Radium add value to Abiraterone or Enzalutamide in Bone-Metastatic CRPC?**

## **Two large trials .....**

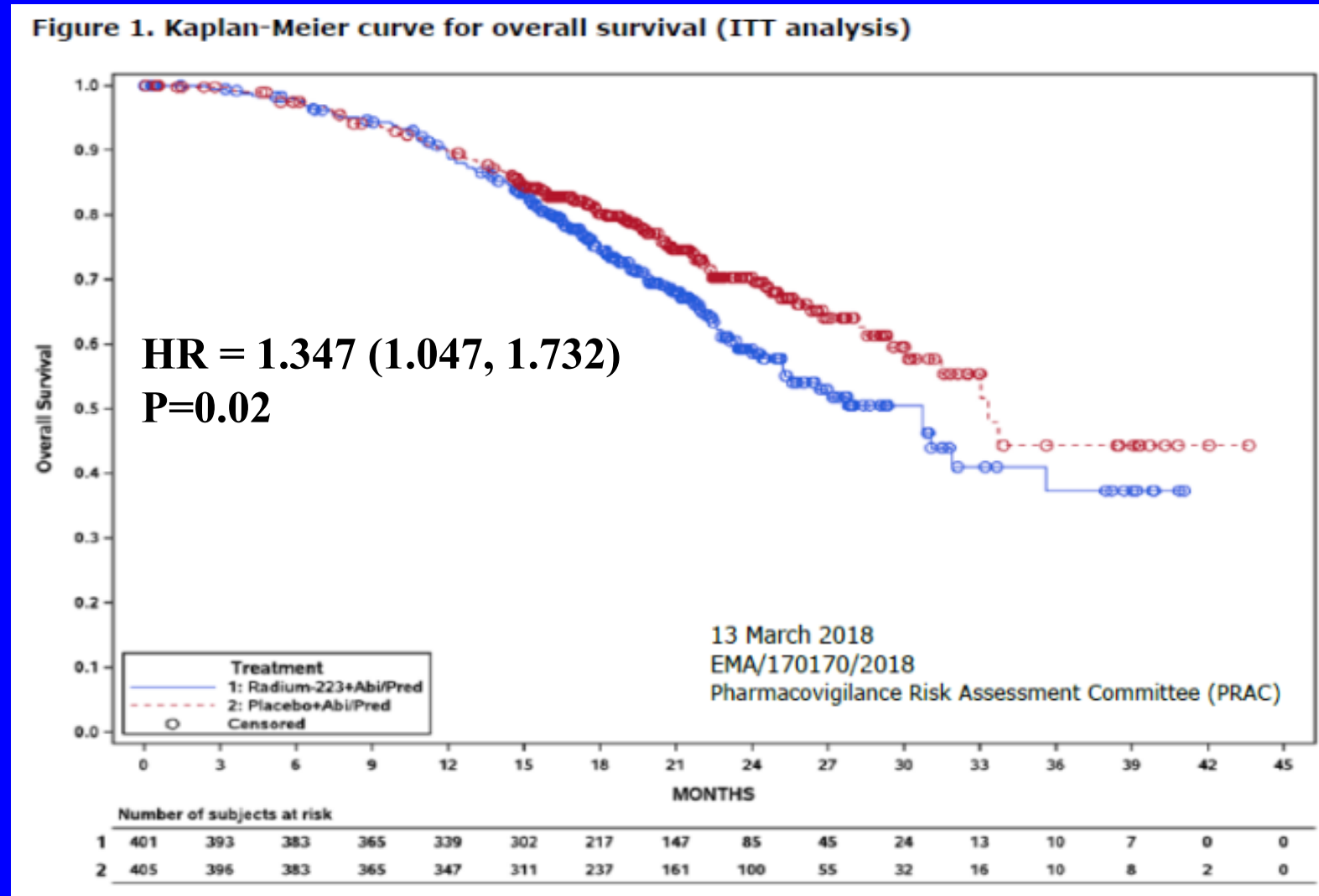
- Abiraterone +/- radium phase III (ERA 223)
  - Data monitoring committee (DMC) stopped the trial
  - Unblinded for safety
- Enzalutamide +/-radium phase III (PEACE III) trial underway
  - DMC has not stopped the trial

# ERA 223: Abiraterone+Prednisone or Prednisolone +/- Radium-223

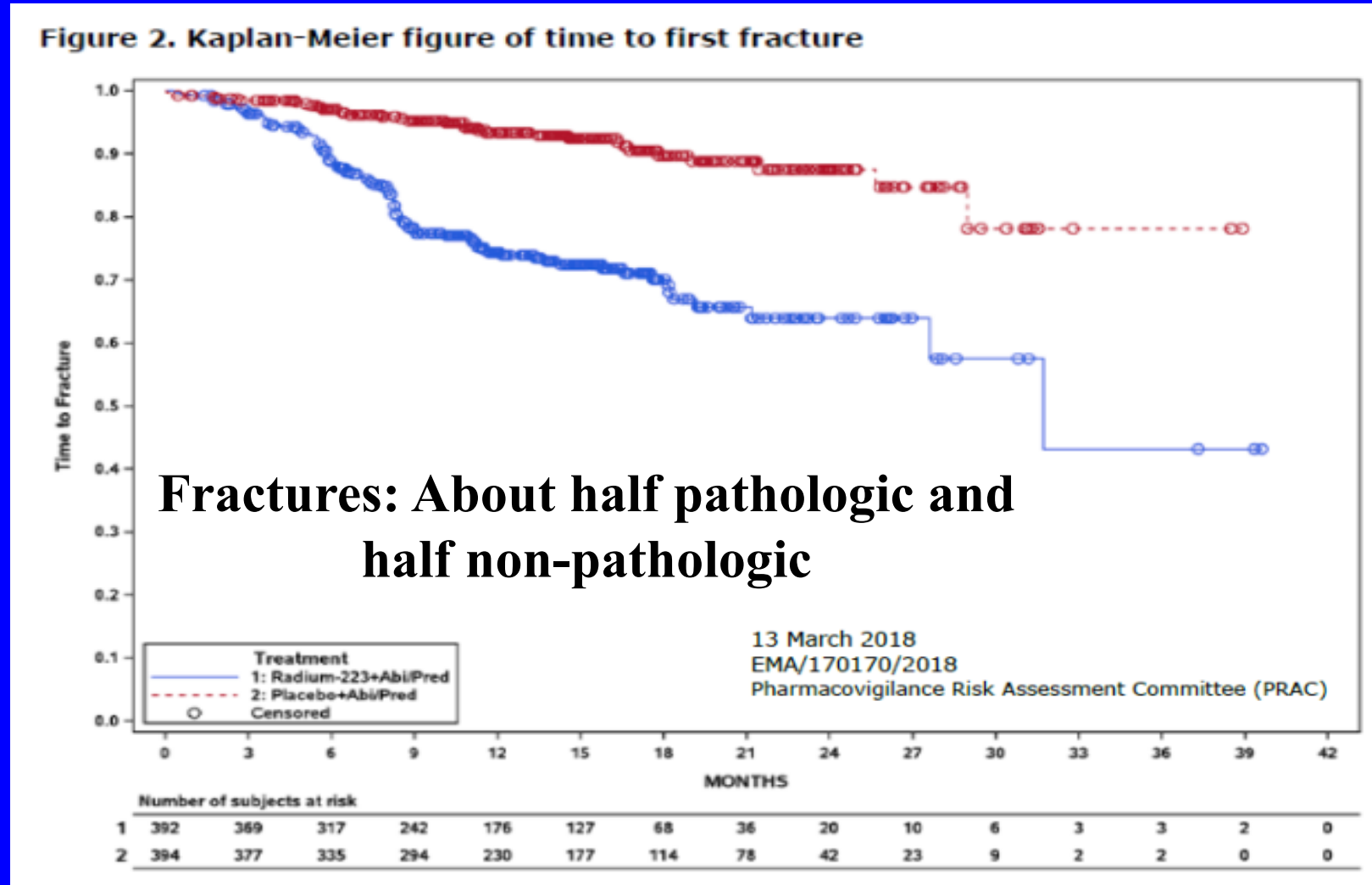
- // Patient not like ALSYMPCA (NCT00699751): asymptomatic, chemotherapy-naïve
- // Radium-223 starting at same time as abiraterone and prednisone
- // Conducted in North America, Europe, Asia, Australia, Brazil, and Israel at 168 sites.



# ERA 223 Stopped Early by IDMC for Adverse Findings: Fracture and Survival



# ERA 223 Stopped Early by IDMC for Adverse Findings: Fracture and Survival



**Table 2. Primary cause of death (safety analysis set)**

|   | <b>Radium-223<br/>+Abi/Pred<br/>N=392 (100%)</b> | <b>Placebo<br/>+Abi/Pred<br/>N=394 (100%)</b> |
|---|--|---|
| <b>Number (%) of deaths</b>   | <b>136 ( 34.7%)</b>                              | <b>111 ( 28.2%)</b>                           |
| <b>Primary cause of death</b>   |  |   |
| Progressive disease   | 93 ( 23.7%)                                      | 76 ( 19.3%)                                   |
| Adverse event associated with clinical disease progression <sup>b</sup>     | 13 ( 3.3%)                                       | 12 ( 3.0%)                                    |
| Adverse event not associated with clinical disease progression <sup>b</sup> | 12 ( 3.1%)                                       | 9 ( 2.3%)                                     |
| Unknown   | 10 ( 2.6%)                                       | 7 ( 1.8%)                                     |
| Other <sup>c</sup>  | 8 ( 2.0%)  | 7 ( 1.8%)                                     |

Progressive  
disease

**Table 3. Relationship between all fractures, SSE fractures and deaths (safety analysis set)**

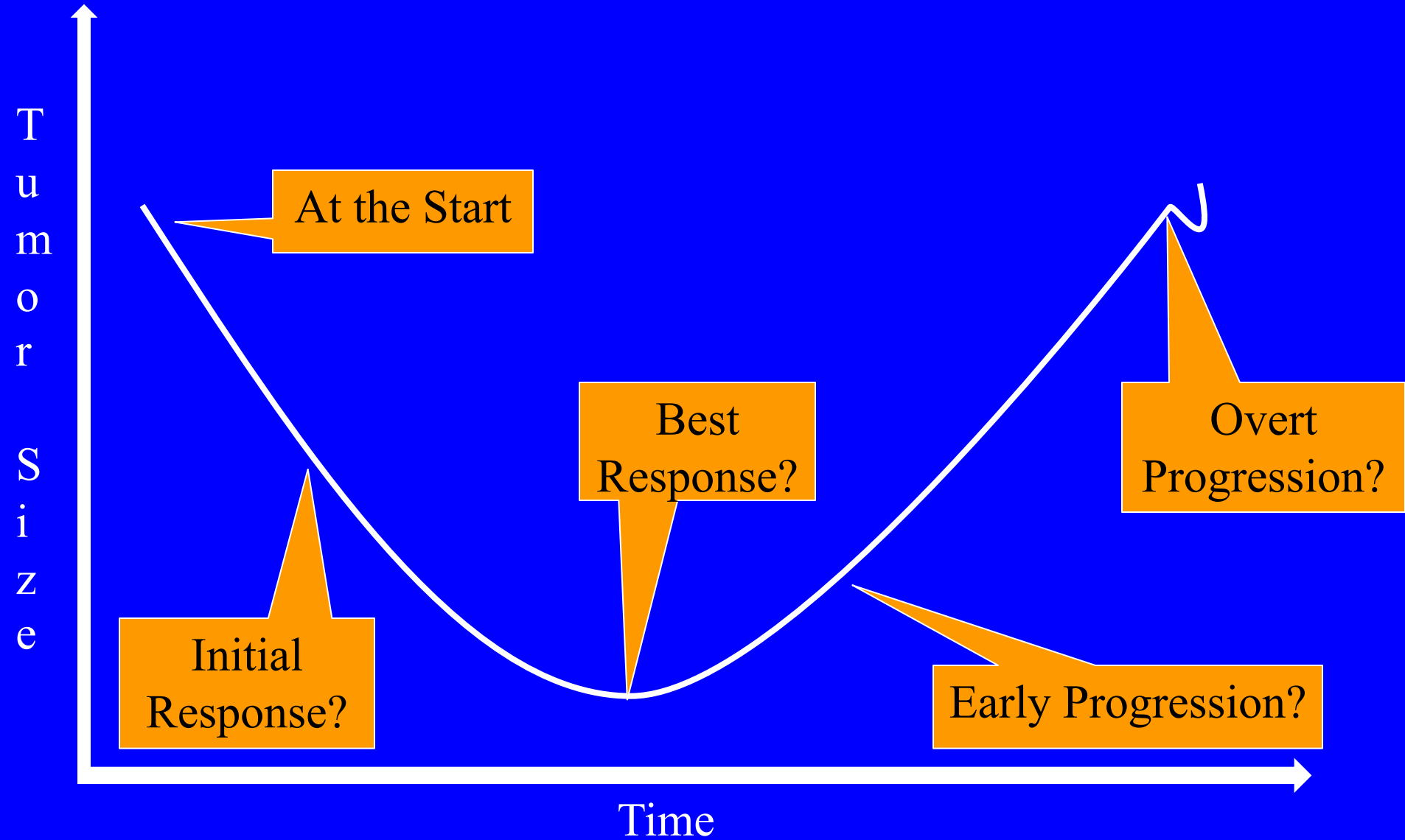
|                                    | <b>Ra223+Abi/Pred<br/>(n = 392)<br/>(=100%)</b> | <b>Placebo+Abi/Pred<br/>(n = 394)<br/>(=100%)</b> | <b>Relative Risk<br/>(RR)/ Risk<br/>difference (RD)<br/>(Ra223 vs. Plc)</b> |
|------------------------------------|---|---|---|
| <b>Number of deaths</b>            | <b>136<br/>(34.7%)</b>                          | <b>111<br/>(28.2%)</b>                            | <b>RD 6.5%<br/>RR 1.23</b>  |
| Death without any prior fractures  | 97<br>(24.7%)                                   | 99<br>(25.1%)                                     | RD -0,4%<br>RR 0.98   |
| Death with prior fractures         | 39<br>(9.9%)                                    | 12<br>(3.0%)                                      | RD 6.9%<br>RR 3.27  |
| Death with prior SSE fractures     | 20<br>(5.1%)                                    | 8<br>(2.0%)                                       | RD 3.1%<br>RR 2.51  |
| Death with prior non-SSE fractures | 23<br>(5.9%)                                    | 4<br>(1.0%)                                       | RD 4.9%<br>RR 5.78  |

RR = 0.98  
for death  
without  
fracture

# Bone Health Agents Markedly Reduce the Risk of Fractures in ERA 223 Radium-223 Arm

|                                      | Radium-223 +<br>Abi/Pred<br>n=155 | Radium-223 +<br>Abi/Pred<br>n=246 | Placebo +<br>Abi/Pred<br>n=169 | Placebo +<br>Abi/Pred<br>n=236 |
|--------------------------------------|-----------------------------------|-----------------------------------|--------------------------------|--------------------------------|
|                                      | With BHA                          | Without BHA                       | With BHA                       | Without BHA                    |
| <b>EBRT</b>                          | <b>25 (16.1%)</b>                 | <b>65 (26.4%)</b>                 | <b>32 (18.9%)</b>              | <b>52 (22.0%)</b>              |
| <b>Symptomatic<br/>bone fracture</b> | <b>2 (1.3%)</b>                   | <b>37 (15.0%)</b>                 | <b>4 (2.4%)</b>                | <b>11 (4.7%)</b>               |
| <b>Orthopedic<br/>surgery</b>        | <b>1 (0.6%)</b>                   | <b>9 (3.7%)</b>                   | <b>2 (1.2%)</b>                | <b>4 (1.7%)</b>                |
| <b>Spinal cord<br/>compression</b>   | <b>6 (3.9%)</b>                   | <b>5 (2.0%)</b>                   | <b>5 (3.0%)</b>                | <b>14 (5.9%)</b>               |

# What about timing of radiation relative to the start of abi/enza?

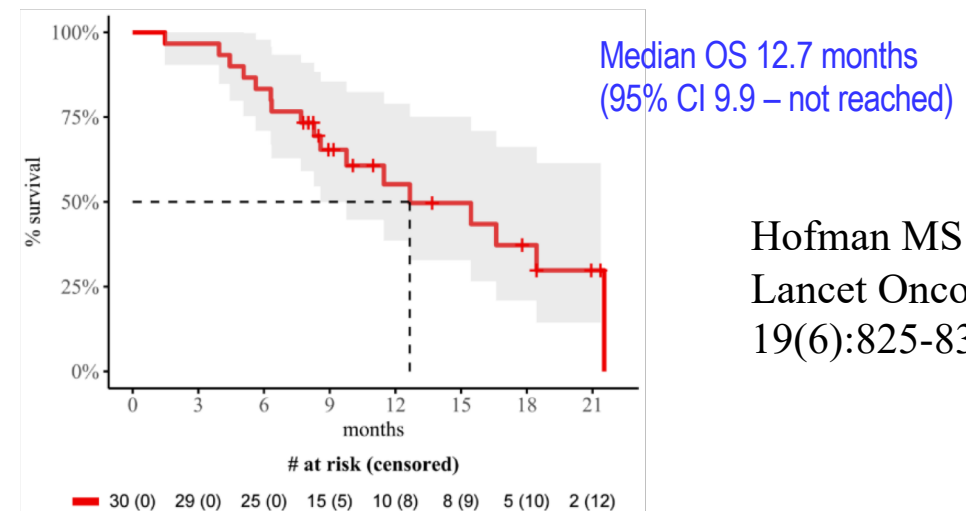
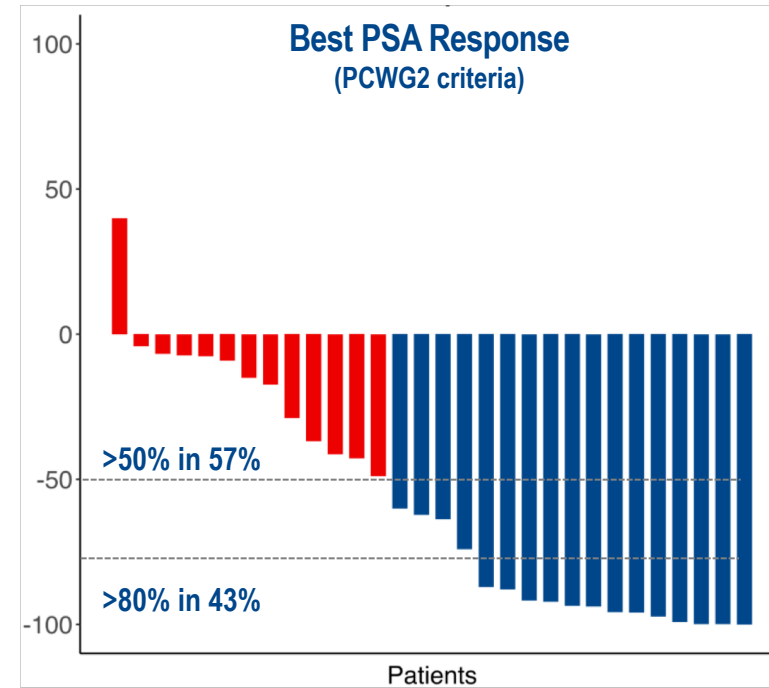
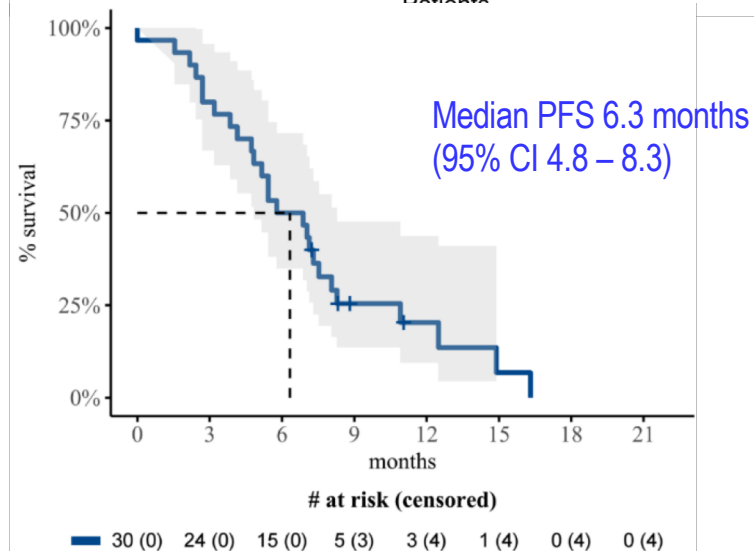
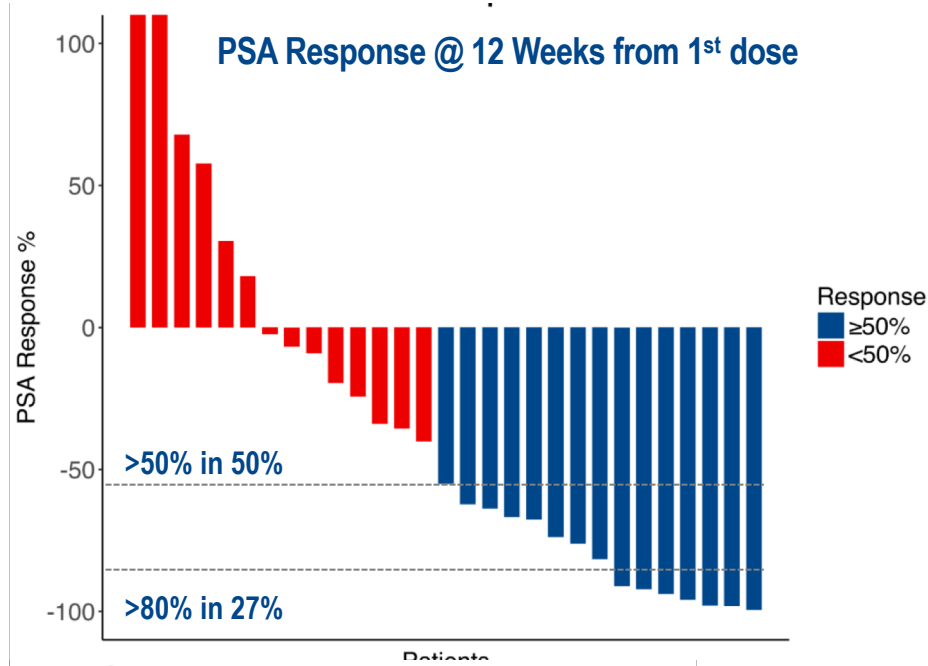


**Radium-223 Only Goes to Bone!**

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

**PSMA binding ligands do that.....**

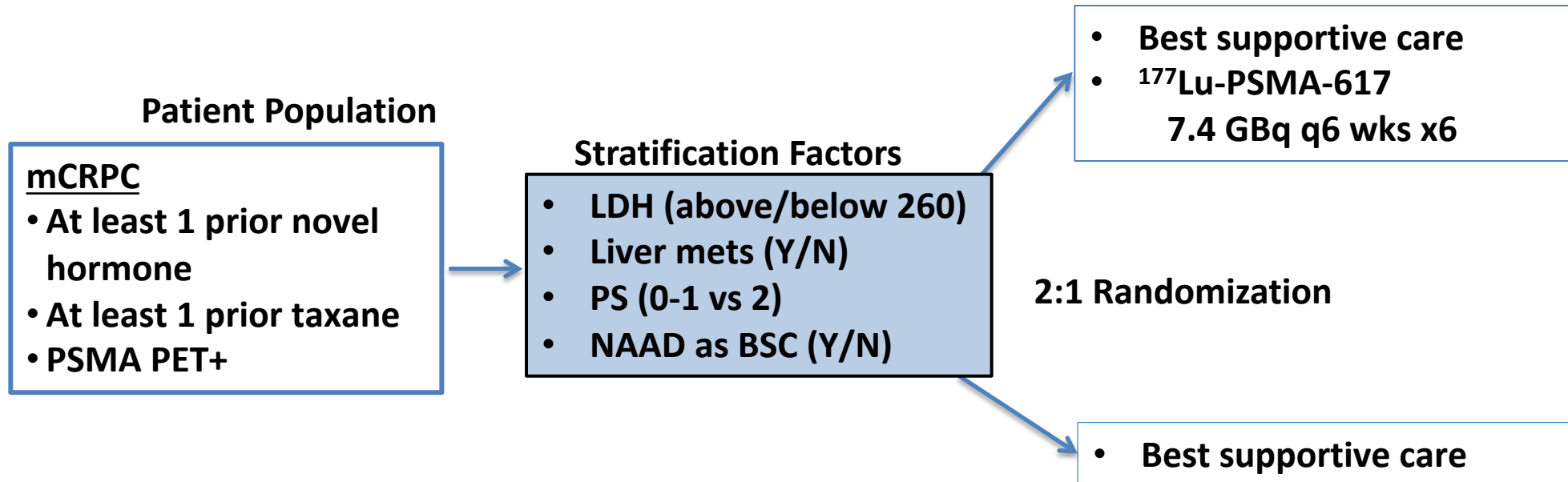




Hofman MS et al.  
Lancet Oncol 2018  
19(6):825-833.

# PSMA-Lu-177 ready for prime time?

## VISION

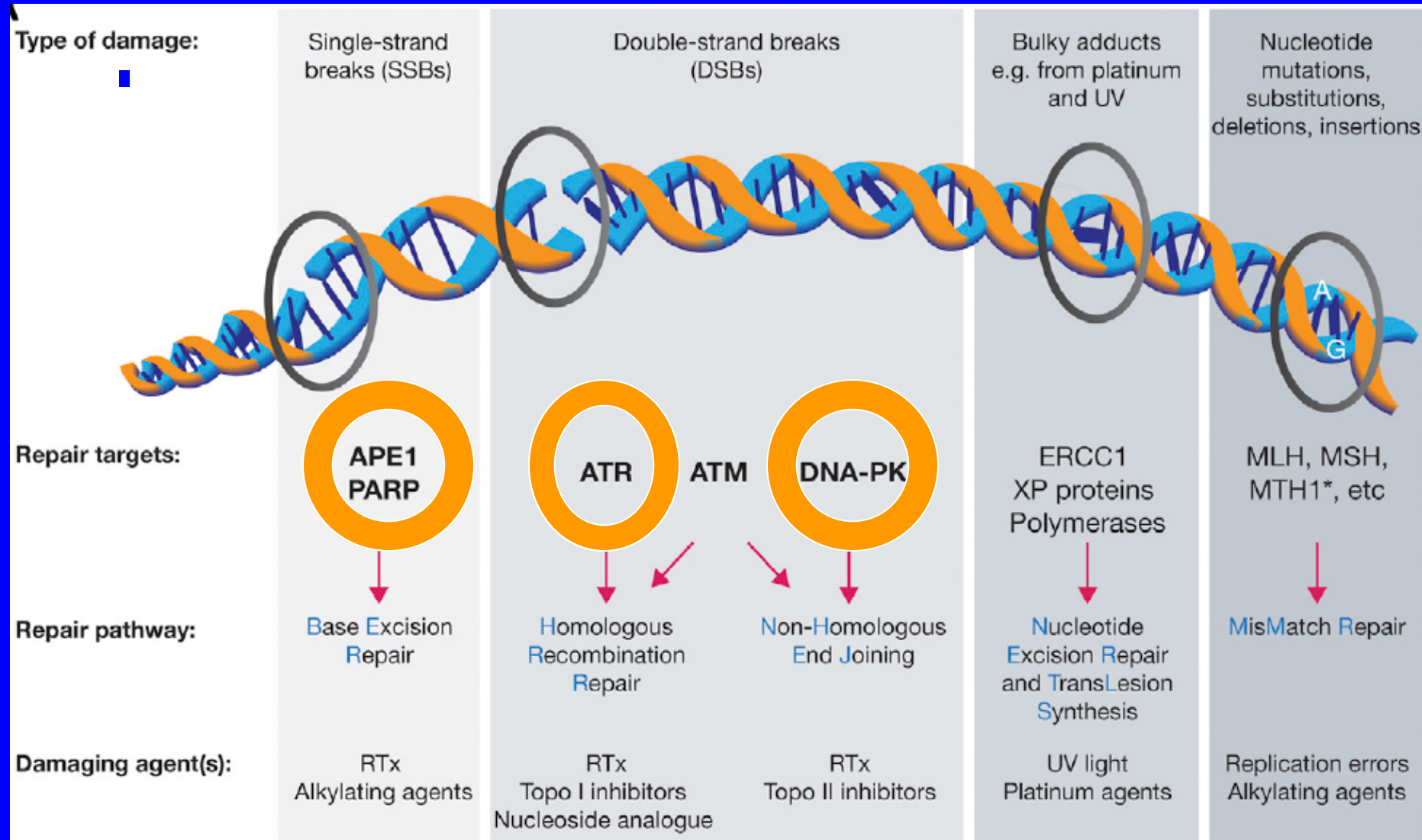


**N=750**

**Alternative 1<sup>o</sup> endpoint:**

**rPFS or OS**

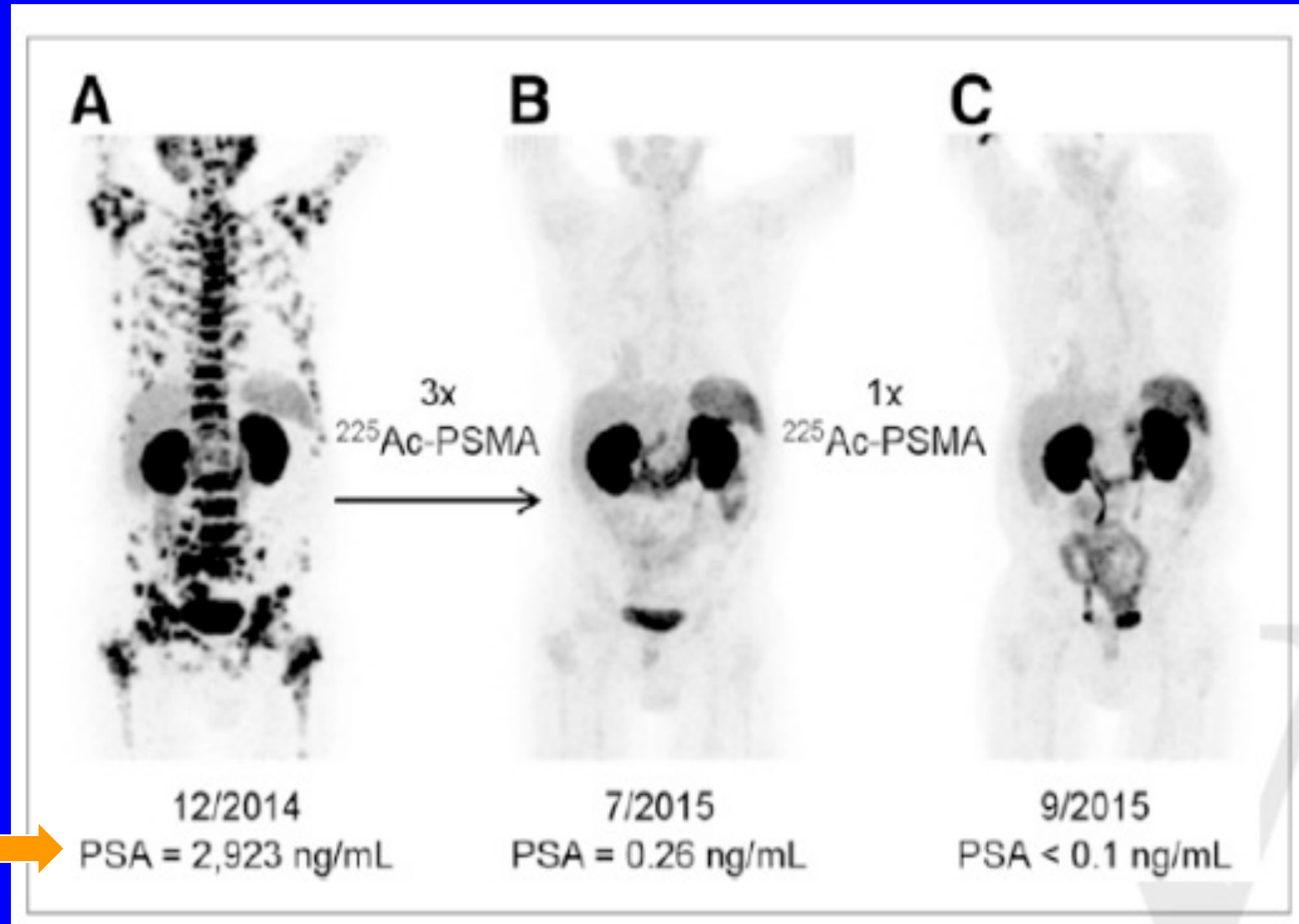
# Targeting DNA damage repair pathways with novel agents: Trials in Progress



# Radio-conjugates: PSMA targeted alpha emitters (Actinium-225) as 9<sup>th</sup> line treatment

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

| Patient A                             |
|---------------------------------------|
| Leuprolide                            |
| Zoledronate                           |
| Docetaxel (50 cycles)                 |
| Carmustine/epirubicin in hyperthermia |
| Abiraterone                           |
| Enzalutamide                          |
| <sup>223</sup> Ra (6 cycles)          |
| Abiraterone reexposition              |
| Estramustine                          |



Thank you!!!