



**IRCCS AOM**  
AZIENDA OSPEDALIERA METROPOLITANA

# Radioligand therapy: which one and when?

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**13<sup>th</sup> Belgian Multidisciplinary  
Meeting on Urological Cancers**

# Conflicts of interest

I have the following potential conflicts of interest to report

| Type of affiliation / financial interest               | Name of commercial company                     |
|--------------------------------------------------------|------------------------------------------------|
| Receipt of grants/research supports:                   |                                                |
| Receipt of honoraria or consultation fees:             | Novartis, Bayer, Telix Pharmaceuticals, ACCMED |
| Participation in a company sponsored speaker's bureau: | Novartis, Recordati, Johnson & Johnson         |
| Stock shareholder:                                     |                                                |
| Spouse/partner:                                        |                                                |
| Other support (please specify):                        |                                                |



# From Imaging to Therapy: Theranostics in Prostate Cancer

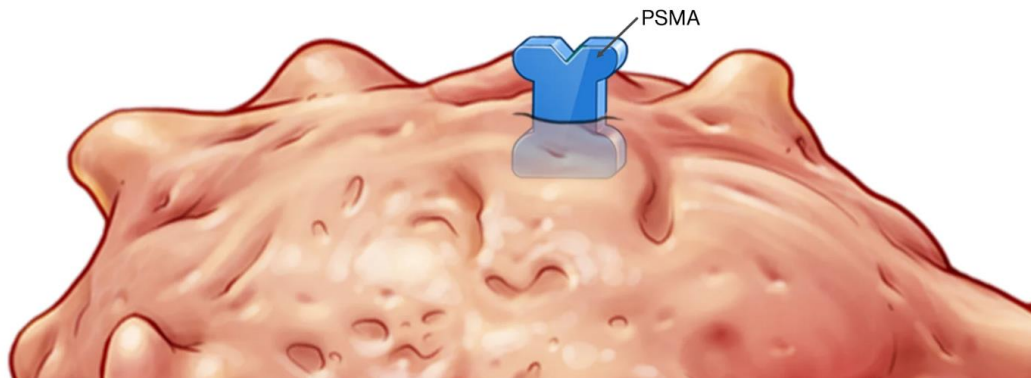
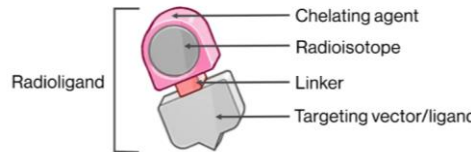
Positron Emission  
Tomography (PET)

Radioligand Therapy (RLT)

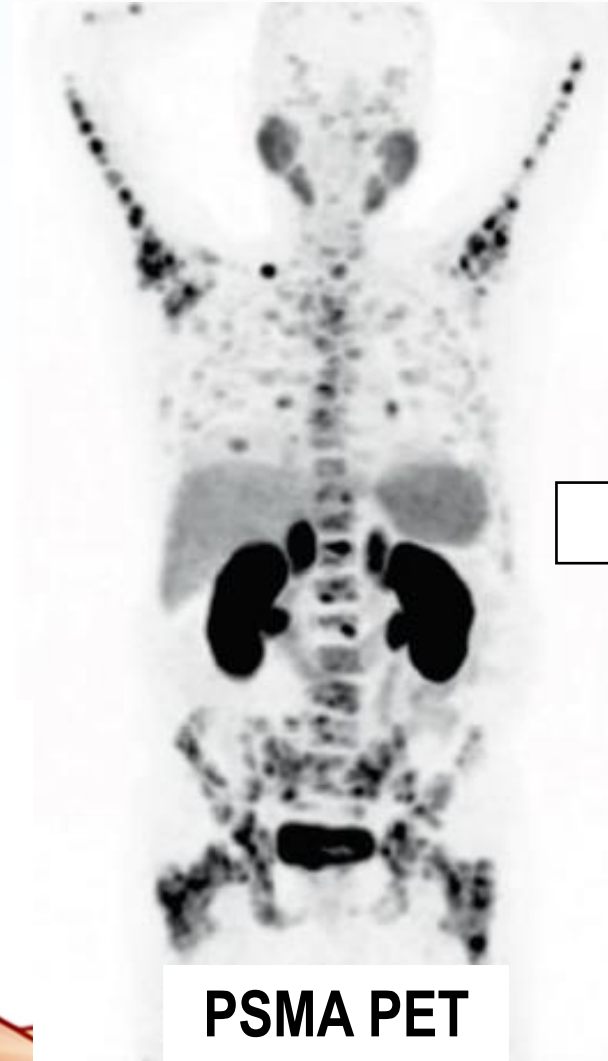
$^{68}\text{Ga}$

$^{18}\text{F}$

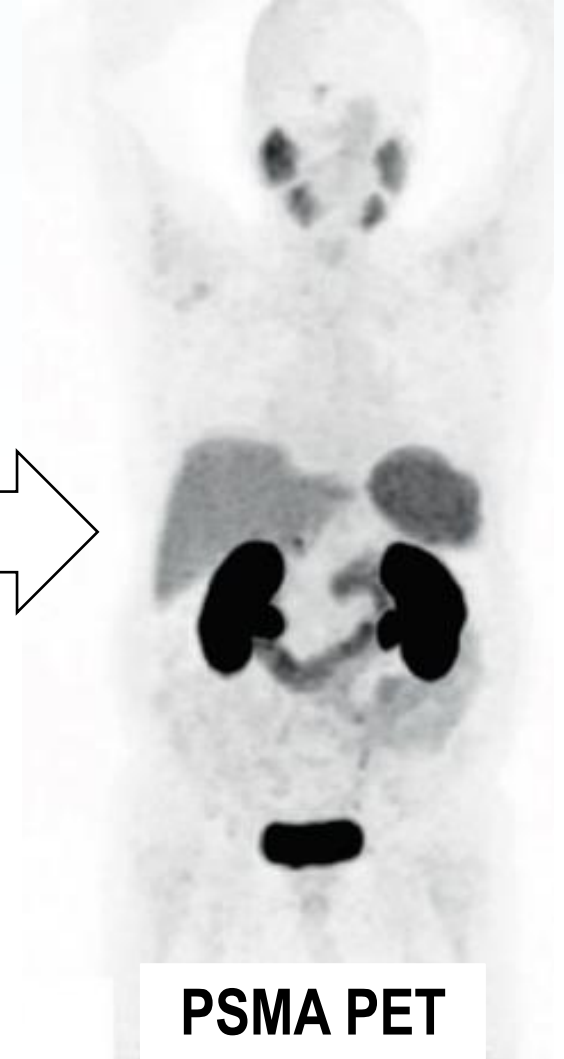
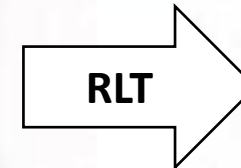
$^{177}\text{Lu}$



PSMA



PSMA PET



PSMA PET

# Currently Available Clinical Trials on PSMA-RLT in **mCRPC**

| Trial               | Phase | Setting          | Trial Design                           |         |             |         | Median follow-up | rPFS<br>(Exp/Ctr)<br>(HR, 95%CI; p-value)                          | PSA 50 RR<br>(Exp/Ctr) | mOS<br>(Exp/Ctr)<br>(HR, 95%CI; p-value)                       | ORR<br>(Exp/Ctr)             |
|---------------------|-------|------------------|----------------------------------------|---------|-------------|---------|------------------|--------------------------------------------------------------------|------------------------|----------------------------------------------------------------|------------------------------|
|                     |       |                  | Exp                                    |         | Ctr         |         |                  |                                                                    |                        |                                                                |                              |
|                     |       |                  | Drug                                   | Pts (n) | Drug        | Pts (n) |                  |                                                                    |                        |                                                                |                              |
| <i>VISION [1]</i>   | 3     | Pretreated mCRPC | [ <sup>177</sup> Lu]Lu-PSMA-617 + SOC  | 551     | SOC         | 280     | 20.9 mo          | 8.7 vs 3.4 mo<br>(HR 0.40; 95% CI 0.29-0.57; p<0.001) <sup>#</sup> | 46% vs 7.1%            | 15.3 vs 11.3 mo<br>(HR 0.62, 0.52–0.74; p<0.001)               | 29.8% vs 1.7%                |
| <i>Thera-P [2]</i>  | 2     | Pretreated mCRPC | [ <sup>177</sup> Lu]Lu-PSMA-617        | 99      | Caba        | 101     | 35.7 mo          | 5.1 vs 5.1 mo<br>(HR 0.63, 95%CI 0.46-0.86; p=0.0028)              | 66% vs 37%             | 16.4 vs 19.4 mo<br>(HR 0.97, 0.70-1.35; p=0.99)                | 49% vs 24%                   |
| <i>ENZA-P [3]</i>   | 2     | Untreated mCRPC  | [ <sup>177</sup> Lu]Lu-PSMA-617 + Enza | 83      | Enza        | 79      | 20.0 mo          | 16 vs 12 mo<br>HR 0.67 (95% CI 0.44–1.01)                          | 93% vs 68%             | NR                                                             | NR                           |
| <i>PSMAfore [4]</i> | 3     | Pretreated mCRPC | [ <sup>177</sup> Lu]Lu-PSMA-617        | 234     | Enza or Abi | 234     | 15.9 mo          | 12.02 vs 5.59 mo<br>(HR 0.43, 95%CI 0.33-0.54; P<0.0001)           | 57.6% vs 20.4%         | 19.25 vs 19.71 mo<br>(HR 1.16, CI: 0.83-1.64)                  | 50.7% vs 14.9% <sup>##</sup> |
| <i>SPLASH [5]</i>   | 3     | Pretreated mCRPC | [ <sup>177</sup> Lu]Lu-PSMA-I&T        | 276     | Enza or Abi | 136     | 12 mo            | 9.5 vs 6 mo (HR: 0.71, 95% CI: 0.55–0.92, p=0.0088)                | 35.7% vs 14.6%         | 20.8 mo vs NE (HR: 1.11, CI: 0.73–1.69; p=0.62) <sup>###</sup> | 38.1% vs 12%                 |

<sup>#</sup> Data on 581 patients (385 in the experimental arm vs. 196 in the control arm) after the implementation of enhanced trial-site education measures

<sup>##</sup> Radiographic response rate of measurable disease

<sup>###</sup> potential violation of the "common treatment effect" assumption in the Rank Preserving Structural Failure Time Model (RPSFTM) method.

[1] Sartor N Eng J Med 2021; [2] Hofman Lancet 2021; [3] Emmett Lancet Oncol 2024; [4] Morris Lancet 2024; [5] Sartor Ann Oncol 2024

# Current Criterion for Evaluating RLT Eligibility According to PSMA PET



European Journal of Nuclear Medicine and Molecular Imaging (2023) 50:2830–2845  
<https://doi.org/10.1007/s00259-023-06255-8>

## GUIDELINES



### Joint EANM/SNMMI procedure guideline for the use of $^{177}\text{Lu}$ -labeled PSMA-targeted radioligand-therapy ( $^{177}\text{Lu}$ -PSMA-RLT)

#### PSMA-positive disease sites

tumor uptake  $\geq 0.5$ -fold of parotid

or

tumor uptake  $> 1.0$ -fold liver-uptake (when using  $[^{68}\text{Ga}]\text{Ga}$ -PSMA-11)

#### No PSMA-negative disease sites

$\varnothing > 1$  cm solid organs

or

$\varnothing > 1$  cm soft tissue component of bone mets

or

$\varnothing > 2.5$  cm lymph nodes

# Current Positioning of PSMA RLT in the Therapeutic Landscape

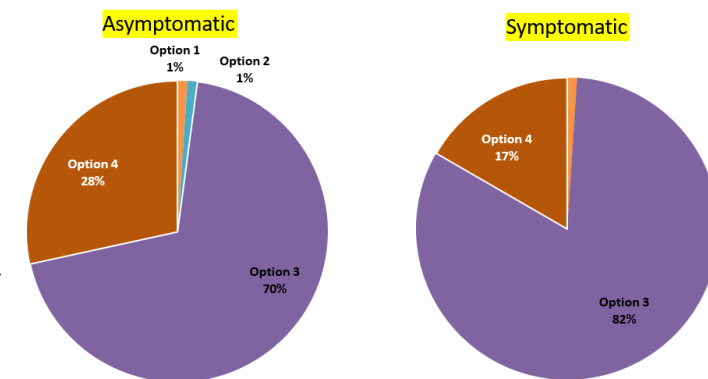


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| Recommendations                                                                                                                                                                                                  | Strength rating |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Offer <sup>177</sup> Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan. | Strong          |

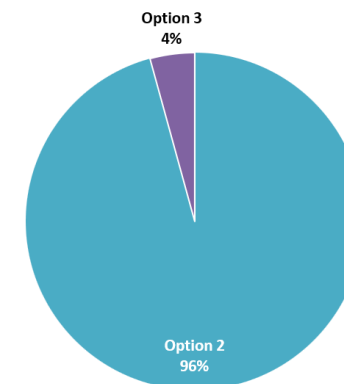
For the majority of **chemotherapy fit** patients with PSMA imaging-positive **mCRPC** who meet relevant PET criteria for <sup>177</sup>Lu-PSMA therapy, who have received **one line of ARPI and no chemotherapy**, what is your preferred treatment option assuming treatments are readily available and there is no actionable molecular alteration?

1. Alternate ARPI
2. ARPI + PARPi
3. Docetaxel
4. <sup>177</sup>Lu-PSMA
5. Radium-223
6. Abstain/unqualified to answer

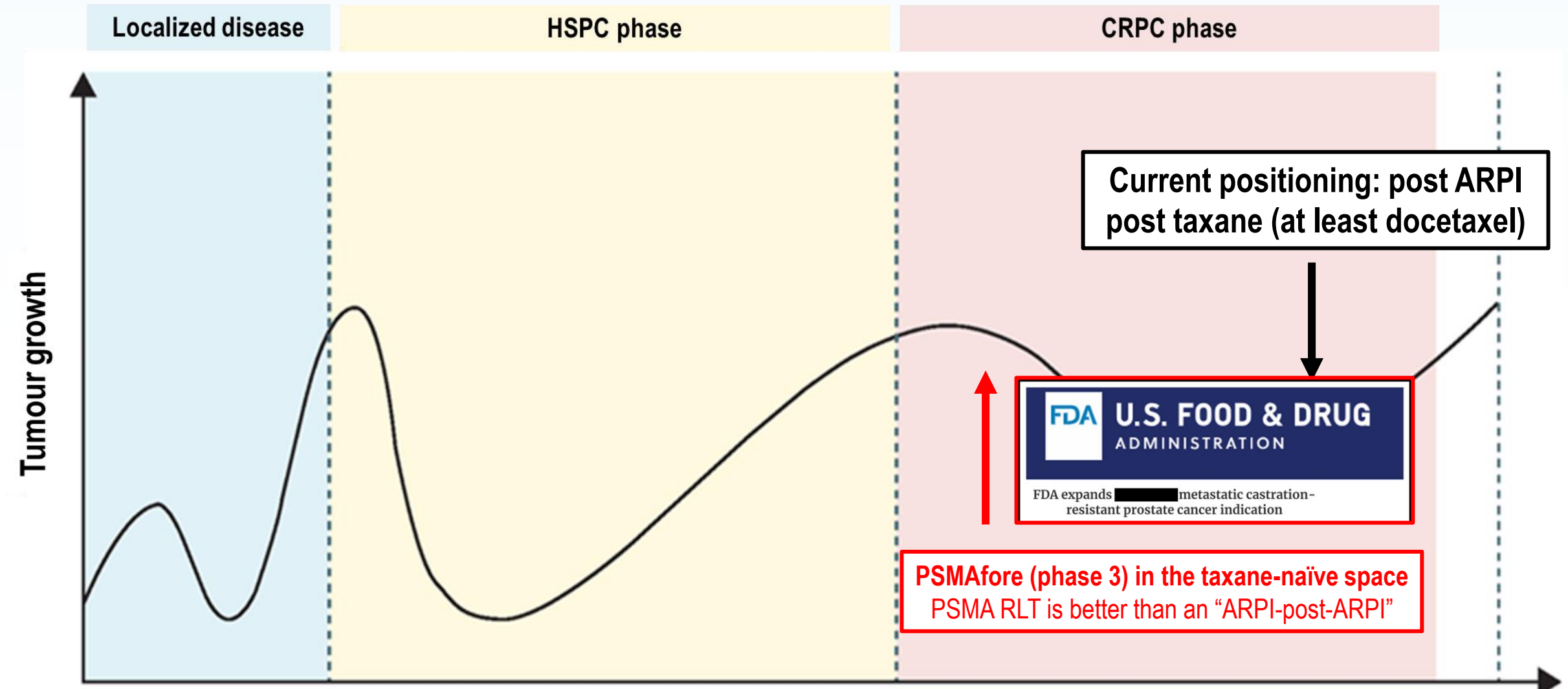


For the majority of **chemotherapy fit** patients with PSMA imaging-positive **mCRPC** who meet relevant PET criteria for <sup>177</sup>Lu-PSMA therapy, who have received **one line of ARPI and one line of taxane-based chemotherapy**, what is your preferred treatment option assuming treatments are readily available and there is no actionable molecular alteration?

1. Alternate ARPI
2. <sup>177</sup>Lu-PSMA
3. Cabazitaxel
4. Radium-223
5. Abstain/unqualified to answer



# When should $^{177}\text{Lu}$ -PSMA be positioned in the treatment landscape?



# Current Positioning of PSMA RLT in the Therapeutic Landscape



National  
Comprehensive  
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## NCCN Guidelines Version 5.2026 Prostate Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

### SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA<sup>g,aa,jjj,kkk</sup>

| Pre-ARPI <sup>aa,III</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Post-ARPI <sup>III</sup> /Pre-Docetaxel <sup>aa</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Post-ARPI <sup>III</sup> /Post-Docetaxel <sup>aa</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Preferred:</b></p> <ul style="list-style-type: none"> <li>• Abiraterone (category 1)</li> <li>• Enzalutamide (category 1)</li> </ul> <p><b>Other Recommended:</b></p> <ul style="list-style-type: none"> <li>• Docetaxel<sup>hhh</sup> (category 1)</li> </ul> <p><b>Useful in Certain Circumstances:</b></p> <ul style="list-style-type: none"> <li>• <u>Molecular Biomarker-Directed Therapy</u> <ul style="list-style-type: none"> <li>▶ <i>BRCA</i> mutation <ul style="list-style-type: none"> <li>◊ Niraparib/abiraterone<sup>mmm</sup> (category 1)</li> <li>◊ Olaparib/abiraterone<sup>mmm</sup> (category 1)</li> <li>◊ Talazoparib/enzalutamide<sup>mmm</sup> (category 1)</li> </ul> </li> <li>▶ <i>HRRm</i> (other than <i>BRCA1/2</i>) <ul style="list-style-type: none"> <li>◊ Talazoparib/enzalutamide<sup>mmm</sup> (category 1)</li> </ul> </li> </ul> </li> <li>• <u>Disease State-Specific Therapy</u> <ul style="list-style-type: none"> <li>▶ Bone metastases <ul style="list-style-type: none"> <li>◊ Radium-223<sup>ooo</sup>/enzalutamide</li> </ul> </li> </ul> </li> </ul> | <p><b>Preferred:</b></p> <ul style="list-style-type: none"> <li>• Docetaxel<sup>hhh</sup> (category 1)</li> </ul> <p><b>Useful in Certain Circumstances:</b></p> <ul style="list-style-type: none"> <li>• <u>Molecular Biomarker-Directed Therapy</u> <ul style="list-style-type: none"> <li>▶ <i>BRCA</i> mutation <ul style="list-style-type: none"> <li>◊ Olaparib<sup>mmm</sup> (category 1, preferred)</li> <li>◊ Rucaparib<sup>mmm</sup> (category 1, preferred)</li> <li>◊ Niraparib/abiraterone<sup>mmm</sup> (category 2B)</li> <li>◊ Talazoparib/enzalutamide<sup>mmm</sup> (category 2B)</li> </ul> </li> <li>▶ <i>HRRm</i> (other than <i>BRCA1/2</i>) <ul style="list-style-type: none"> <li>◊ Olaparib<sup>mmm</sup></li> <li>◊ Talazoparib/enzalutamide<sup>mmm</sup> (category 2B)</li> </ul> </li> </ul> </li> <li>• <u>Disease State-Specific Therapy</u> <ul style="list-style-type: none"> <li>▶ PSMA-positive metastases <ul style="list-style-type: none"> <li>◊ Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)<sup>qqq</sup></li> </ul> </li> <li>▶ Aggressive variant<sup>iii</sup> <ul style="list-style-type: none"> <li>◊ Cabazitaxel/Carboplatin<sup>hhh</sup></li> </ul> </li> </ul> </li> </ul> | <p><b>Preferred:</b></p> <ul style="list-style-type: none"> <li>• Cabazitaxel<sup>hhh</sup> (category 1)</li> <li>• Docetaxel rechallenge<sup>hhh</sup></li> </ul> <p><b>Useful in Certain Circumstances:</b></p> <ul style="list-style-type: none"> <li>• <u>Molecular Biomarker-Directed Therapy</u> <ul style="list-style-type: none"> <li>▶ <i>BRCA</i> mutation <ul style="list-style-type: none"> <li>◊ Olaparib<sup>mmm</sup> (category 1)</li> <li>◊ Rucaparib<sup>mmm</sup></li> </ul> </li> <li>▶ <i>HRRm</i> (other than <i>BRCA1/2</i>) <ul style="list-style-type: none"> <li>◊ Olaparib<sup>mmm</sup></li> </ul> </li> <li>▶ Other FDA-approved agents for tissue agnostic indications<sup>hhh</sup></li> </ul> </li> <li>• <u>Disease State-Specific Therapy</u> <ul style="list-style-type: none"> <li>▶ PSMA-positive metastases <ul style="list-style-type: none"> <li>◊ Lu-177-PSMA-617<sup>qqq</sup> (category 1)</li> </ul> </li> <li>▶ Aggressive variant<sup>iii</sup> <ul style="list-style-type: none"> <li>◊ Cabazitaxel/carboplatin<sup>hhh</sup></li> </ul> </li> <li>▶ Palliation for symptomatic patients unable to tolerate other therapies <ul style="list-style-type: none"> <li>◊ Mitoxantrone<sup>hhh</sup></li> </ul> </li> </ul> </li> </ul> |

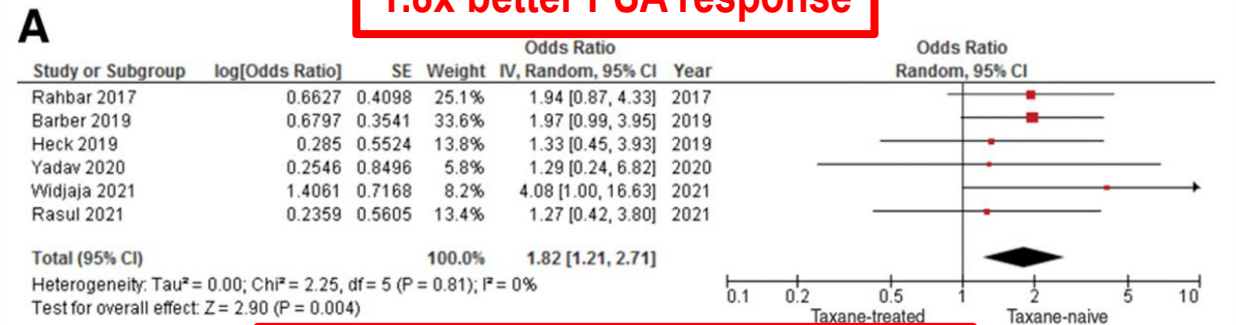
# What about PSMA RLT in the taxane-naïve space?

Systematic review and meta-analysis (13 articles, n= 2.068 pts)

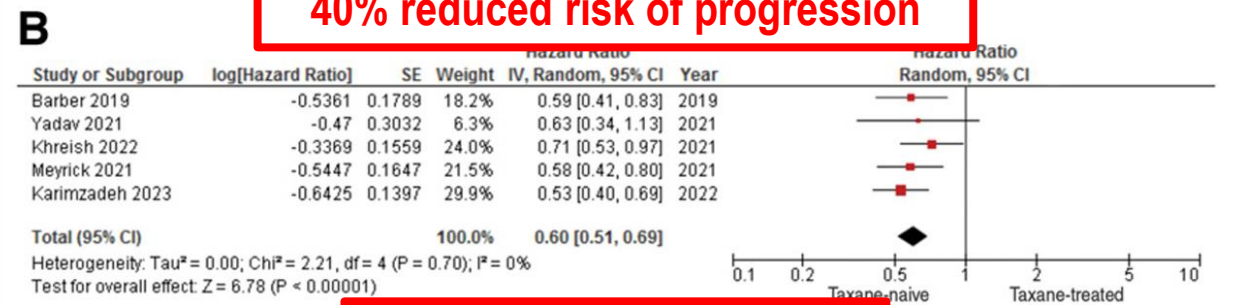
| Study                     | Sample size (n) | Prior status     |                    | Univariate OR for PSA response | Univariate HR for PFS          | Univariate HR for OS           |
|---------------------------|-----------------|------------------|--------------------|--------------------------------|--------------------------------|--------------------------------|
|                           |                 | Taxane-naïve (n) | Taxane-treated (n) |                                |                                |                                |
| Bräuer (14)               | 59              | 12 (20.3%)       | 47 (79.7%)         | NS                             | NS                             | 0.62 (0.22–1.79)               |
| Rahbar (15)               | 145             | 66 (45.5%)       | 79 (54.5%)         | 1.94 (0.87–4.33)*              | NS                             | NS                             |
| Barber (16)               | 167             | 84 (50.3%)       | 83 (49.7%)         | 1.97 (0.99–3.95) <sup>†</sup>  | 0.59 (0.41–0.83)               | 0.39 (0.25–0.62)               |
| Heck (17)                 | 100             | 16 (16.0%)       | 84 (84.0%)         | 1.33 (0.45–3.93)               | Excluded <sup>‡</sup>          | Excluded <sup>‡</sup>          |
| Ahmadzadehfard (18)       | 416             | 102 (24.5%)      | 314 (75.5%)        | NS                             | NS                             | 0.67 (0.51–0.87)               |
| Yadav (19)                | 90              | 6 (6.7%)         | 84 (93.3%)         | 1.29 (0.24–6.82)               | NS                             | NS                             |
| Khreish (20)              | 254             | 66 (26.0%)       | 188 (74.0%)        | NS                             | 0.71 (0.53–0.97)               | 0.63 (0.39–1.01)               |
| Meyrick <sup>§</sup> (21) | 191             | 72 (37.7%)       | 118 (61.8%)        | NS                             | 0.58 (0.42–0.80)               | 0.29 (0.18–0.47)               |
| Rasul (22)                | 61              | 19 (31.1%)       | 42 (68.9%)         | 1.27 (0.42–3.80)               | NS                             | NS                             |
| Widjaja (23)              | 71              | 12 (16.9%)       | 59 (83.1%)         | 4.08 (1.00–16.63)              | NS                             | NS                             |
| Yadav (24)                | 121             | 20 (16.5%)       | 101 (83.5%)        | NS                             | 0.63 (0.34–1.13)               | 0.50 (0.27–0.91)               |
| Hartrampf (25)            | 92              | 28 (30.4%)       | 64 (69.6%)         | NS                             | NS                             | 0.67 (0.40–1.13)               |
| Karimzadeh (26)           | 301             | 87 (28.9%)       | 214 (71.1%)        | NS                             | 0.53 (0.40–0.69) <sup>  </sup> | 0.67 (0.45–0.98) <sup>  </sup> |

| Variable                   | Pooled OR for PSA response |                | Pooled HR for PFS |                | Pooled HR for OS |                |
|----------------------------|----------------------------|----------------|-------------------|----------------|------------------|----------------|
|                            | 95% CI                     | I <sup>2</sup> | 95% CI            | I <sup>2</sup> | 95% CI           | I <sup>2</sup> |
| Study design               |                            |                |                   |                |                  |                |
| Retrospective              | 1.85 (1.22–2.81)           | 0%             | 0.56 (0.47–0.67)  | 0%             | 0.53 (0.41–0.68) | 53%            |
| Prospective                | 1.29 (0.24–6.82)           | NA             | 0.71 (0.53–0.97)  | NA             | 0.63 (0.39–1.01) | NA             |
| Sample size                |                            |                |                   |                |                  |                |
| <100 patients              | 1.87 (1.07–3.25)           | 0%             | NA                | NA             | 0.66 (0.42–1.05) | 0%             |
| ≥100 patients              | 1.76 (0.98–3.16)           | 0%             | NA                | NA             | 0.52 (0.39–0.68) | 60%            |
| RLT agent                  |                            |                |                   |                |                  |                |
| <sup>177</sup> Lu-PSMA-617 | 1.87 (1.07–3.25)           | 0%             | 0.69 (0.53–0.91)  | 0%             | 0.64 (0.51–0.78) | 0%             |
| <sup>177</sup> Lu-PSMA-I&T | 1.33 (0.45–3.93)           | NA             | 0.53 (0.40–0.69)  | NA             | 0.67 (0.49–0.91) | 0%             |

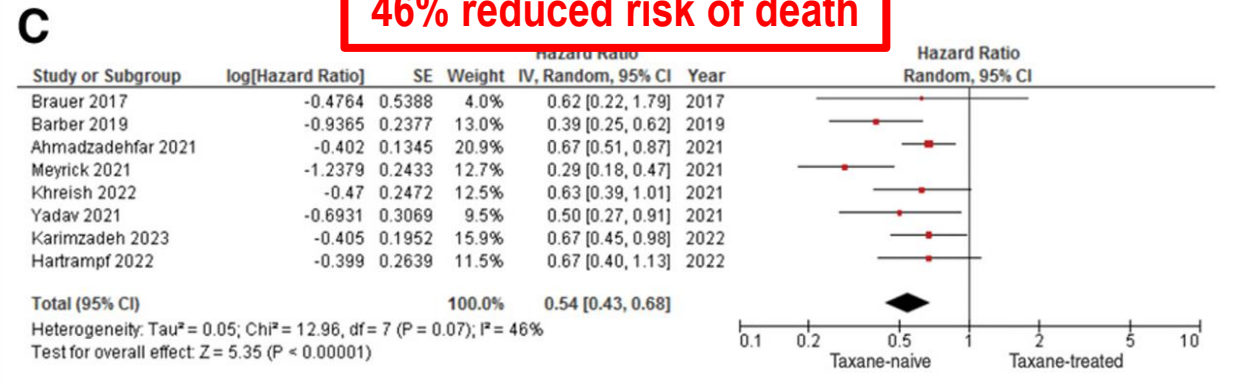
**1.8x better PSA response**



**40% reduced risk of progression**



**46% reduced risk of death**



# PSMA-RLT: Earlier Use Reduces Toxicity

## VISION

| Event                                                                    | <sup>177</sup> Lu-PSMA-617 plus Standard Care (N=529) |            | Standard Care Alone (N=205) |           |
|--------------------------------------------------------------------------|-------------------------------------------------------|------------|-----------------------------|-----------|
|                                                                          | All Grades                                            | Grade ≥3   | All Grades                  | Grade ≥3  |
|                                                                          | number of patients (percent)                          |            |                             |           |
| Any adverse event                                                        | 519 (98.1)                                            | 279 (52.7) | 170 (82.9)                  | 78 (38.0) |
| Adverse event that occurred in >12% of patients                          |                                                       |            |                             |           |
| Fatigue                                                                  | 228 (43.1)                                            | 31 (5.9)   | 47 (22.9)                   | 3 (1.5)   |
| Dry mouth                                                                | 205 (38.8)                                            | 0          | 1 (0.5)                     | 0         |
| Nausea                                                                   | 187 (35.3)                                            | 7 (1.3)    | 34 (16.6)                   | 1 (0.5)   |
| Anemia                                                                   | 168 (31.8)                                            | 68 (12.9)  | 27 (13.2)                   | 10 (4.9)  |
| Back pain                                                                | 124 (23.4)                                            | 17 (3.2)   | 30 (14.6)                   | 7 (3.4)   |
| Arthralgia                                                               | 118 (22.3)                                            | 6 (1.1)    | 26 (12.7)                   | 1 (0.5)   |
| Decreased appetite                                                       | 112 (21.2)                                            | 10 (1.9)   | 30 (14.6)                   | 1 (0.5)   |
| Constipation                                                             | 107 (20.2)                                            | 6 (1.1)    | 23 (11.2)                   | 1 (0.5)   |
| Diarrhea                                                                 | 100 (18.9)                                            | 4 (0.8)    | 6 (2.9)                     | 1 (0.5)   |
| Vomiting                                                                 | 100 (18.9)                                            | 5 (0.9)    | 13 (6.3)                    | 1 (0.5)   |
| Thrombocytopenia                                                         | 91 (17.2)                                             | 42 (7.9)   | 9 (4.4)                     | 2 (1.0)   |
| Lymphopenia                                                              | 75 (14.2)                                             | 41 (7.8)   | 8 (3.9)                     | 1 (0.5)   |
| Leukopenia                                                               | 66 (12.5)                                             | 13 (2.5)   | 4 (2.0)                     | 1 (0.5)   |
| Adverse event that led to reduction in <sup>177</sup> Lu-PSMA-617 dose   | 30 (5.7)                                              | 10 (1.9)   | NA                          | NA        |
| Adverse event that led to interruption of <sup>177</sup> Lu-PSMA-617†    | 85 (16.1)                                             | 42 (7.9)   | NA                          | NA        |
| Adverse event that led to discontinuation of <sup>177</sup> Lu-PSMA-617† | 63 (11.9)                                             | 37 (7.0)   | NA                          | NA        |
| Adverse event that led to death‡                                         | 19 (3.6)                                              | 19 (3.6)   | 6 (2.9)                     | 6 (2.9)   |

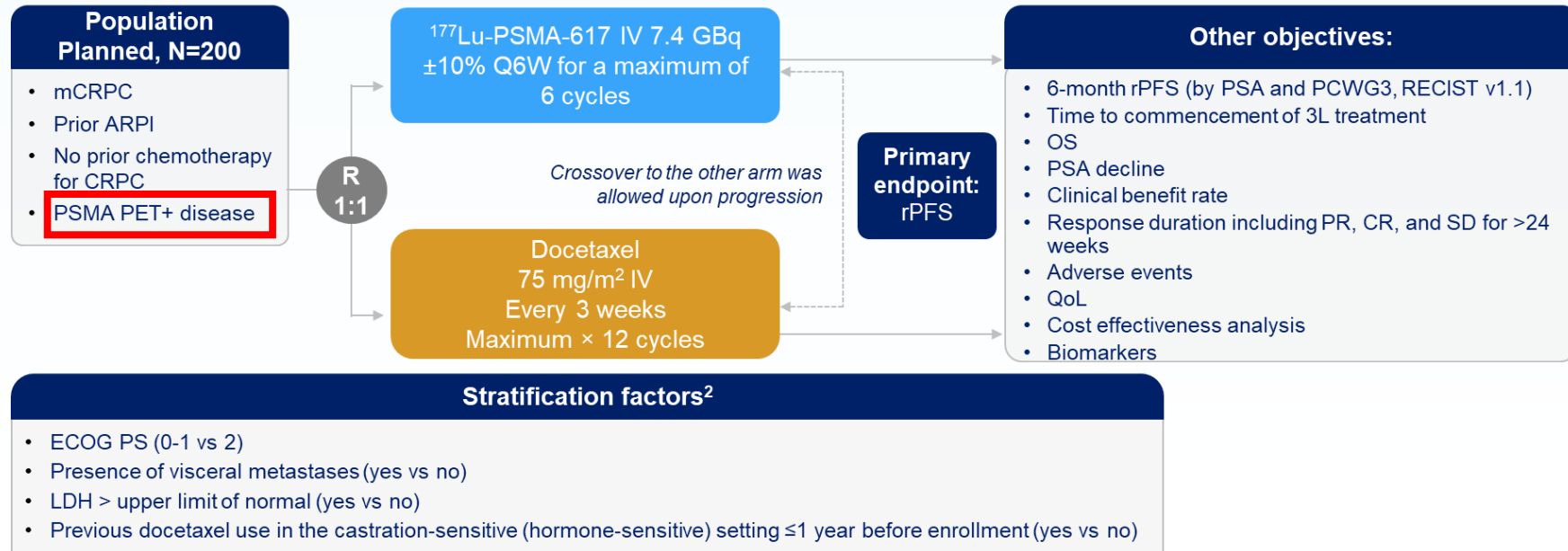
## PSMAfore

|                                         | <sup>177</sup> Lu-PSMA-617 group (n=227) |           | ARPI change group (n=232) |            |
|-----------------------------------------|------------------------------------------|-----------|---------------------------|------------|
|                                         | Any grade                                | Grade ≥3  | Any grade                 | Grade ≥3   |
| Any                                     | 224 (99%)                                | 81 (36%)* | 226 (97%)                 | 112 (48%)* |
| Occurring in >10% of patients           |                                          |           |                           |            |
| Dry mouth                               | 131 (58%)†                               | 2 (1%)    | 6 (3%)†                   | 0          |
| Asthenia                                | 74 (33%)                                 | 2 (1%)    | 67 (29%)                  | 8 (3%)     |
| Nausea                                  | 72 (32%)                                 | 0         | 27 (12%)                  | 1 (<1%)    |
| Anaemia                                 | 61 (27%)                                 | 14 (6%)   | 44 (19%)                  | 16 (7%)    |
| Fatigue                                 | 53 (23%)                                 | 1 (<1%)   | 59 (25%)                  | 4 (2%)     |
| Constipation                            | 50 (22%)                                 | 1 (<1%)   | 33 (14%)                  | 0          |
| Decreased appetite                      | 49 (22%)                                 | 0         | 43 (19%)                  | 1 (<1%)    |
| Arthralgia                              | 45 (20%)                                 | 0         | 54 (23%)                  | 1 (<1%)    |
| Diarrhoea                               | 38 (17%)                                 | 0         | 21 (9%)                   | 1 (<1%)    |
| COVID-19                                | 36 (16%)                                 | 1 (<1%)   | 27 (12%)                  | 1 (<1%)    |
| Back pain                               | 31 (14%)                                 | 3 (1%)    | 46 (20%)                  | 6 (3%)     |
| Vomiting                                | 26 (11%)                                 | 0         | 11 (5%)                   | 0          |
| Oedema peripheral                       | 19 (8%)                                  | 0         | 28 (12%)                  | 0          |
| Pain in extremity                       | 17 (7%)                                  | 1 (<1%)   | 25 (11%)                  | 1 (<1%)    |
| Weight loss                             | 15 (7%)                                  | 1 (<1%)   | 32 (14%)                  | 3 (1%)     |
| Leading to adjustment of dose           | 8 (4%)                                   | 3 (1%)    | 36 (16%)                  | 7 (3%)     |
| Leading to interruption of treatment    | 28 (12%)                                 | 13 (6%)   | 45 (19%)                  | 20 (9%)    |
| Leading to discontinuation of treatment | 13 (6%)                                  | 8 (4%)    | 12 (5%)                   | 9 (4%)     |
| Leading to death                        | 4 (2%)                                   | 4 (2%)    | 5 (2%)                    | 5 (2%)     |
| Cardiac arrest                          | 1 (<1%)‡                                 | 1 (<1%)‡  | 1 (<1%)‡                  | 1 (<1%)‡   |
| Cerebrovascular accident                | 0                                        | 0         | 1 (<1%)§                  | 1 (<1%)§   |
| Coma                                    | 0                                        | 0         | 1 (<1%)‡                  | 1 (<1%)‡   |
| COVID-19 pneumonia                      | 1 (<1%)‡                                 | 1 (<1%)‡  | 0                         | 0          |
| Dyspnoea                                | 0                                        | 0         | 1 (<1%)‡                  | 1 (<1%)‡   |
| Intestinal ischaemia                    | 1 (<1%)‡                                 | 1 (<1%)‡  | 0                         | 0          |
| Multiple organ dysfunction syndrome     | 0                                        | 0         | 1 (<1%)‡                  | 1 (<1%)‡   |
| Sepsis                                  | 1 (<1%)‡                                 | 1 (<1%)‡  | 0                         | 0          |

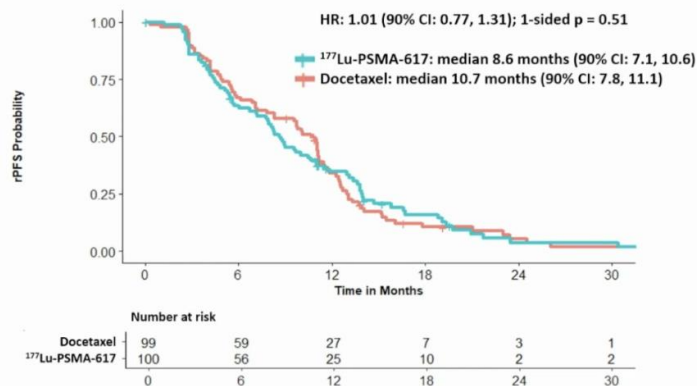
# What about PSMA RLT in the taxane-naïve space?

## Open issues

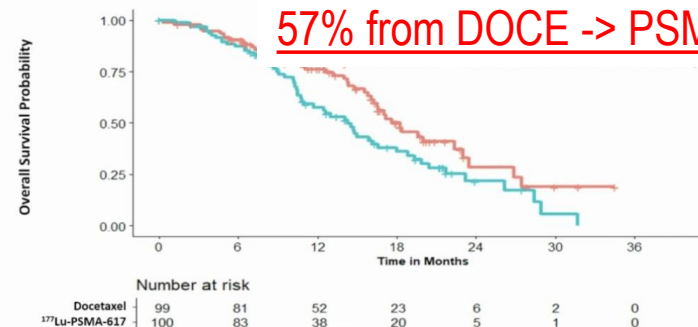
PSMA PET+: any lesion with PSMA expression score  $\geq 2$ , excluding PSMA negative lesions if  $>50\%$  or  $>5\text{cm}$



## Primary Endpoint: rPFS (ITT)



## Overall Survival

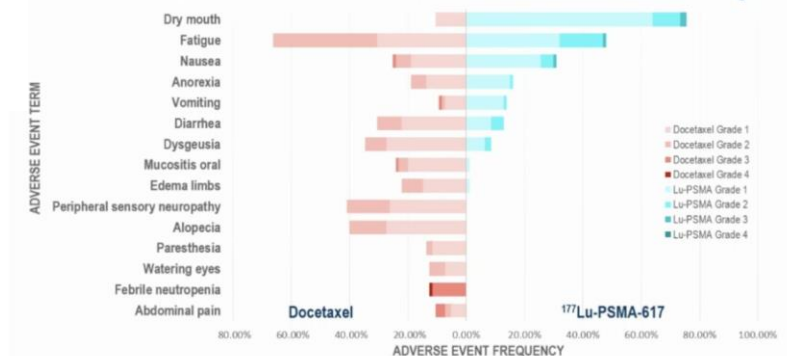


54% cross-over

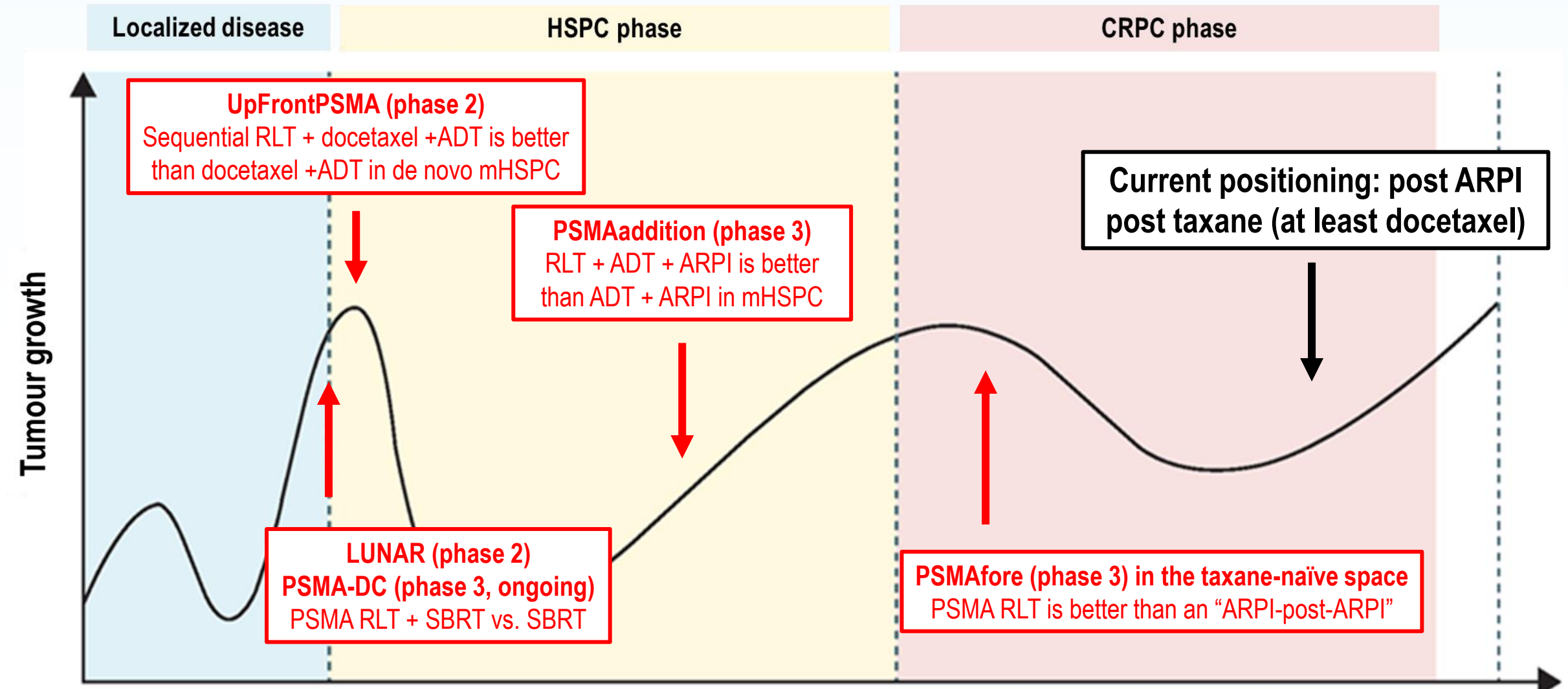
38% from PSMA RLT  $\rightarrow$  DOCE

57% from DOCE  $\rightarrow$  PSMA RLT

## Treatment Related Adverse Events $>10\%$ Frequency



# When should $^{177}\text{Lu}$ -PSMA be positioned in the treatment landscape?



Azad et al. Lancet Oncol 2024 Tagawa et al. @ ESMO 2025; Kishan et al. @ ASTRO 2025 and Calais et al. @ ESMO 2025; NCT05939414  
Morris et al. Lancet 2024; James et al. Lancet 2024; Turco et al. J Nucl Med 2025

# PSMA-targeted radioligands: one like the other?

## Medical Services Advisory Committee (MSAC) Public Summary Document

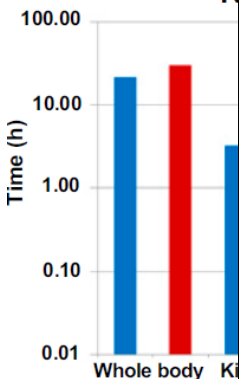
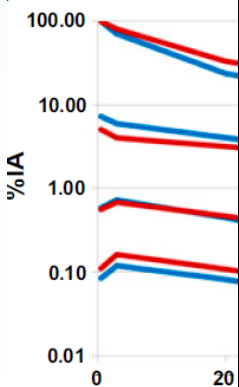
### *Application No. 1686.1 – $^{177}\text{Lu}$ PSMA i&t for metastatic castrate resistant prostate cancer*

**Applicant:**

A group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine Specialists (AANMS)

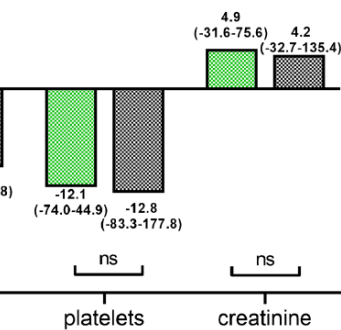
**Date of MSAC consideration:** 4-5 April 2024

MSAC considered that there was no new substantive clinical trial data that changed MSAC's previous conclusion of mutual noninferiority for patient outcomes between the two products –  $^{177}\text{Lu}$  PSMA i&t and  $^{177}\text{Lu}$  PSMA-617 have similar safety, efficacy, biodistribution and are radioequivalent, despite both products using different dosing schedules. MSAC also acknowledged that direct evidence comparing  $^{177}\text{Lu}$  PSMA i&t and  $^{177}\text{Lu}$  PSMA-617 was not available and would be unlikely to eventuate. Therefore, based on the totality of the available evidence and additional perspectives comparing  $^{177}\text{Lu}$  PSMAi&t and  $^{177}\text{Lu}$  PSMA-617 products, MSAC reaffirmed previous conclusions that the two products are mutually noninferior for patient outcomes, and thus considered the evidence for  $^{177}\text{Lu}$  PSMA-617 to be relevant for  $^{177}\text{Lu}$  PSMA i&t, and therefore accepted the results of the clinical evaluation and the clinical



■  $^{177}\text{Lu}$ -PSMA i&t

| $^{177}\text{Lu}$ PSMA-617 | P-value |
|----------------------------|---------|
| 70 (43–86)                 | 0.89    |
| 63 (4–241)                 | 0.37    |
| 3 (2–8)                    | 0.77    |
| 19.0 (7.9–45.8)            | 0.21    |
| 6.2 (3.9–9.6)              | 0.11    |
| 9 (6–10)                   | 1.0     |



$^{177}\text{Lu}$ -PSMA i&t  
 $^{177}\text{Lu}$ -PSMA-617

# PSMA-targeted radioligands: one like the other?

$^{177}\text{Lu}$ -PSMA vs. ARPI switch



Original Article – Editor's choice

Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC)



**Q143: In the majority of patients with response (PSA and/or clinical and/or radiological) to  $^{177}\text{Lu}$ -PSMA therapy after 4 cycles, do you recommend completion of the 6 cycles if PSMA-based imaging shows significant remaining uptake (as defined by the treating physician)?**

- Yes, in the majority of patients: 76% (71 votes)
- Yes, but only in selected patients: 18% (17 votes)
- No: 6% (5 votes)
- Abstain/unqualified to answer (13 votes)

median rPFS (95%CI): **12.02** vs 5.59 mo

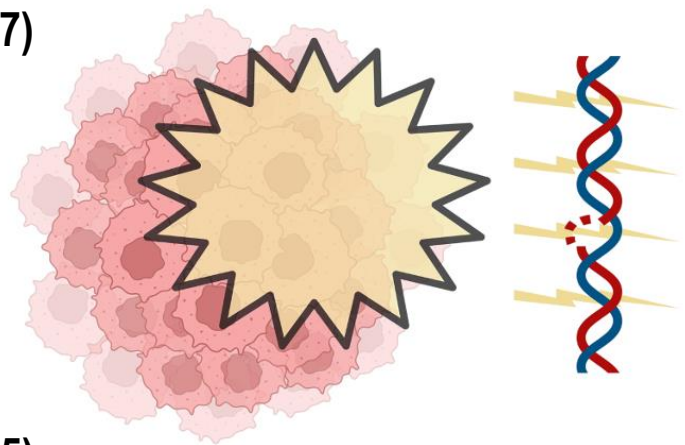
\* **1<sup>st</sup> interim** median rPFS (95%CI): **9.5** vs. 6 mo

Morris et al. Lancet 2024

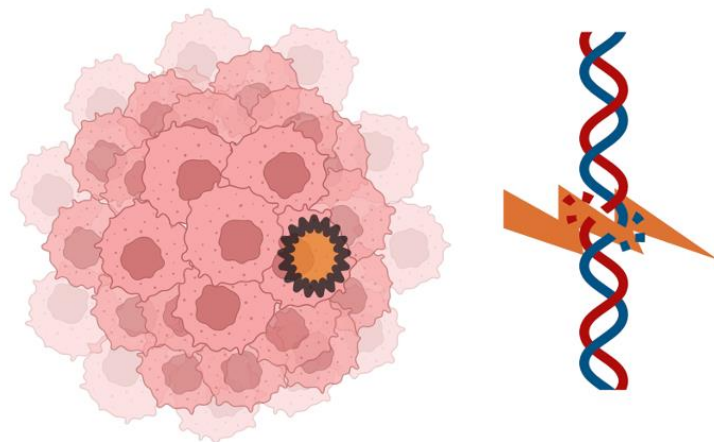
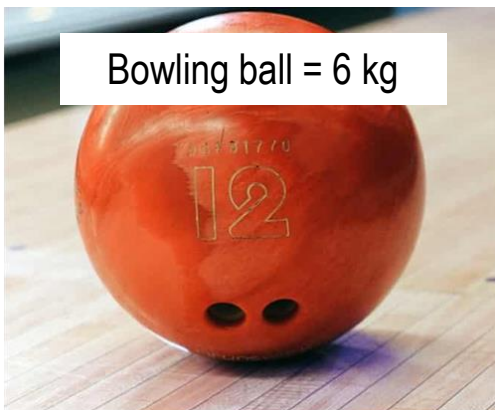
Sartor et al. @ ESMO 2024

# Future directions for PSMA-RLT: $\alpha$ -emitting ligands

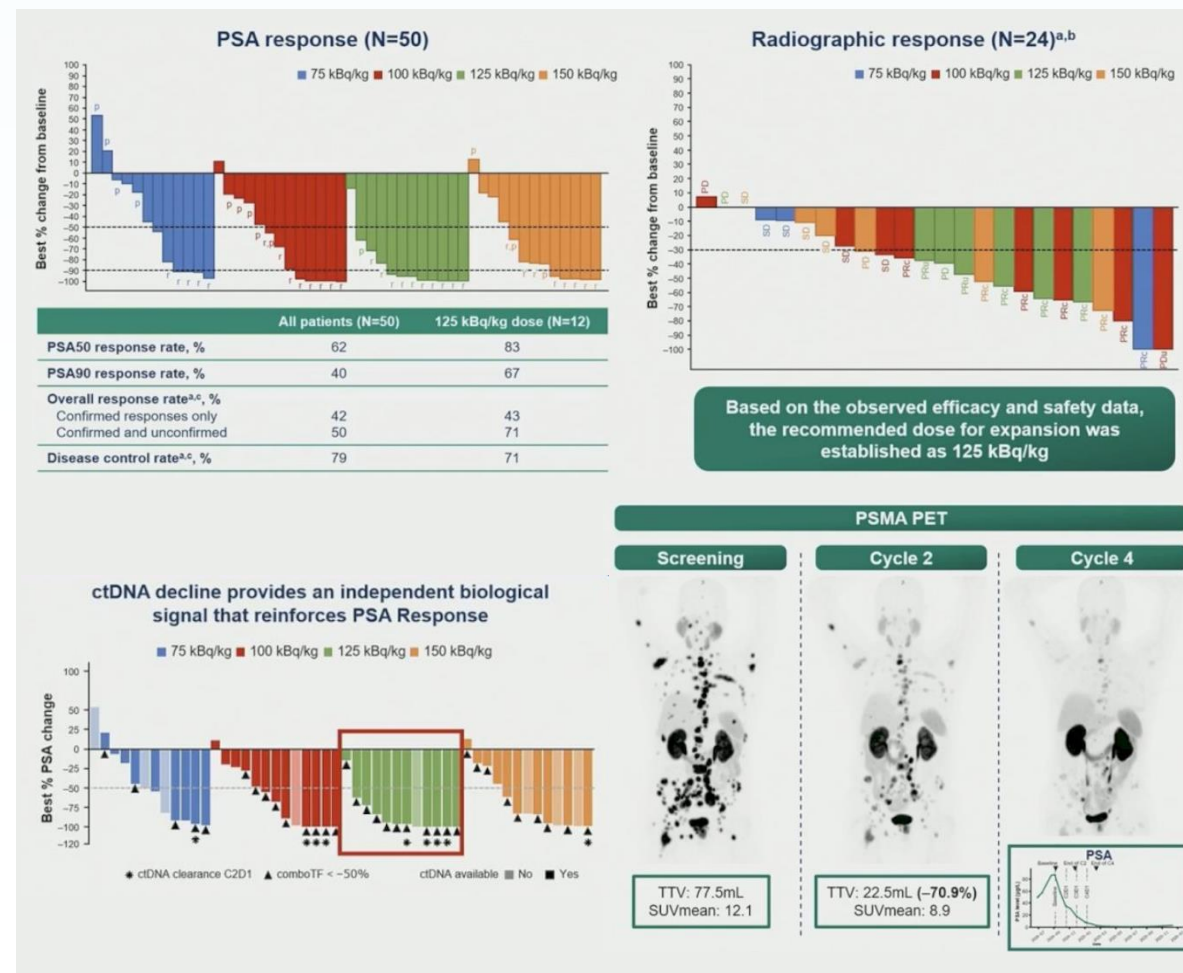
## $\beta$ - radiation (i.e., Lutetium-177)



## $\alpha$ radiation (i.e., Actinium-225)



Phase 1 PAnTHA (NCT06217822) study, assessing the safety and efficacy of  $^{225}\text{Ac}$ -PSMA-Trillium q6w x4 in a VISION-like setting.





Single-centre  
Single-arm  
Phase I/II study  
NCT05521412

# Terbium-161-PSMA-I&T radioligand treatment in patients with metastatic castration-resistant prostate cancer (mCRPC)

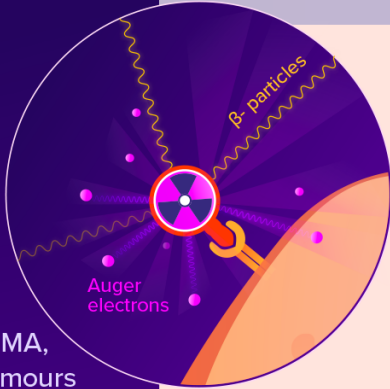
## Why this trial?

### Terbium-161- PSMA-I&T

attaches to PSMA receptors on the cancer cells and emits  $\beta$ -particles like Lutetium-177-PSMA, killing large sized tumours with abundant crossfire.

Additionally, Terbium-161 emits Auger electrons, delivering higher concentrations of radiation over ultrashort pathlengths.

Preclinical studies support this may better kill micrometastases.



## Phase I - 3+3 trial design

### Dose escalation

  
**12** patients

**Radioactivity  
level 1**  
 **n = 3**  
 1<sup>st</sup> cycle:  
**4.4 GBq**

**Radioactivity  
level 2**  
 **n = 3**  
 1<sup>st</sup> cycle:  
**5.5 GBq**

**Radioactivity  
level 3**  
 **n = 6**  
 1<sup>st</sup> cycle:  
**7.4 GBq**

**7.4 GBq**

## Phase II

### Dose expansion



**18** additional  
patients

### Eligibility criteria

 **Progressive mCRPC**  
after  $\geq 1$  taxane (unless medically unsuitable) + ARPI

 **PSMA positive  
+ no FDG discordance**

 Adequate bone marrow,  
hepatic and renal function;  
ECOG PS  $\leq 2$

**Up to  
6 cycles  
every 6 weeks**  
 $\downarrow 0.4$  GBq per cycle

## Results

Median follow-up:  
11.9 months

 **No dose-limiting  
toxicities**

 **Few high-grade  
treatment-related  
adverse events**

- Grade 3: pain (3%)  
and lymphopenia (3%)
- Grade 4 or deaths: none

## Conclusions

 **Encouraging  
efficacy**

 **Favourable  
safety  
profile**

 **Additional  
radioactivity level  
(9.5 GBq) recruiting**

|                                                                                                                  |                                           |
|------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
|  <b>PSA50-RR</b>              | <b>70%</b><br>[95% CI 51 – 85]            |
|  <b>PSA90-RR</b>              | <b>40%</b><br>[95% CI 23 – 59]            |
|  <b>Median<br/>PSA-PFS</b>    | <b>9.0 months</b><br>[95% CI 5.7 – 15.1]  |
|  <b>Radiographic<br/>PFS</b> | <b>11.1 months</b><br>[95% CI 6.6 – 11.7] |



@DrMHofman



# There's Life Beyond PSMA!

## Novel (and old) targets for treating PCa with radiopharmaceuticals

Clinicaltrials.gov search:

**GRPR-peptide binders**

**DLL3**

**H5A10-mab**

**Human Kallikrein 2  
(JNJ-69086420)**

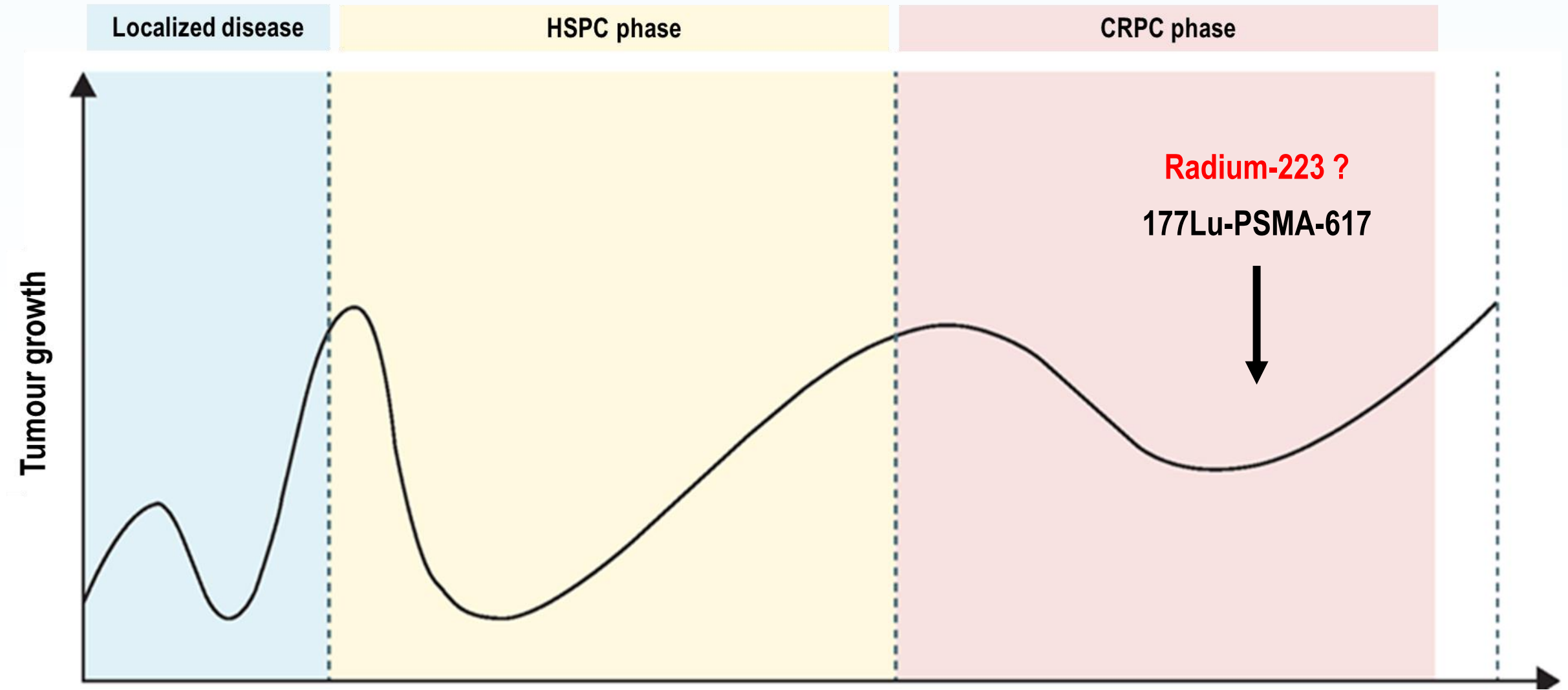
**FAP**

**LRRC15-binders**

**SSTR2**

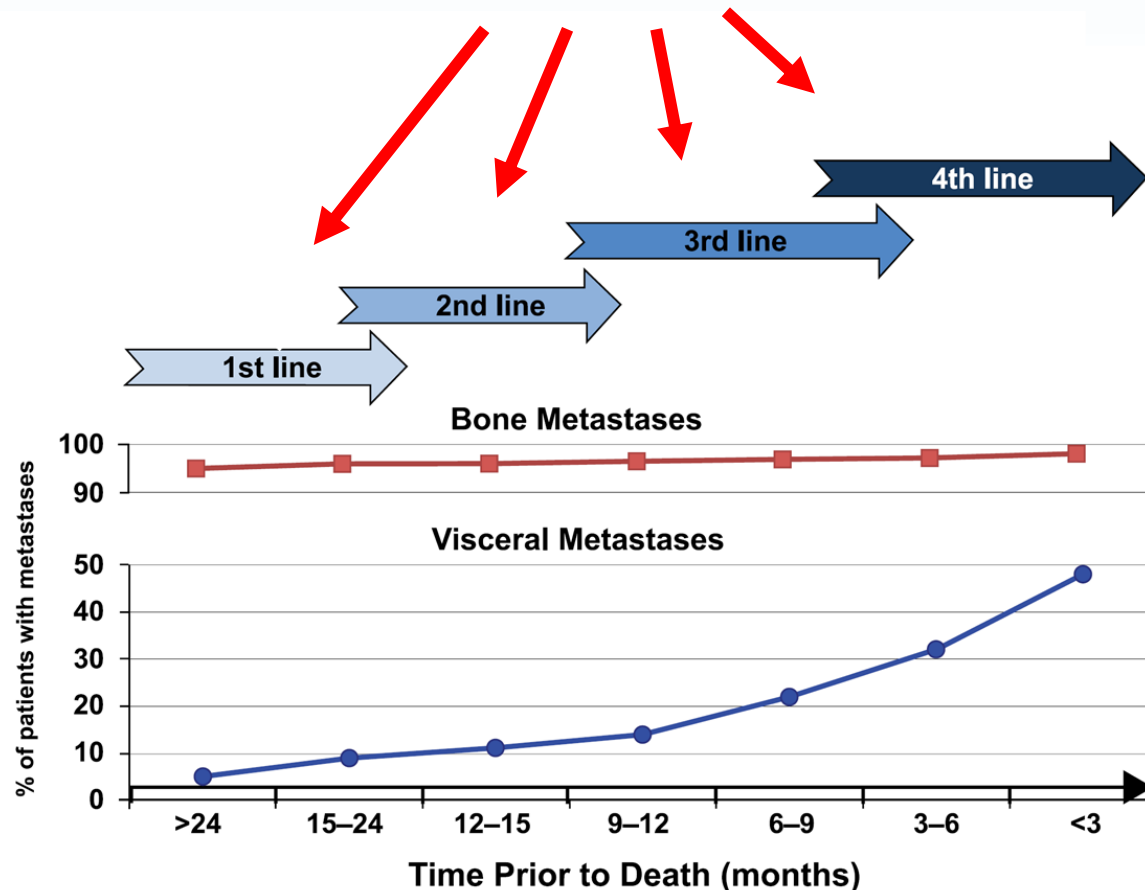
...and many more!

# What about Radium-223 in the PSMA RLT era?



# The Radium-223 Parabola: From Decline to Comeback

## Radium-223



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

19 September 2013  
EMA/CHMP/411215/2013  
Committee for Medicinal Products for Human Use (CHMP)

mCRPC

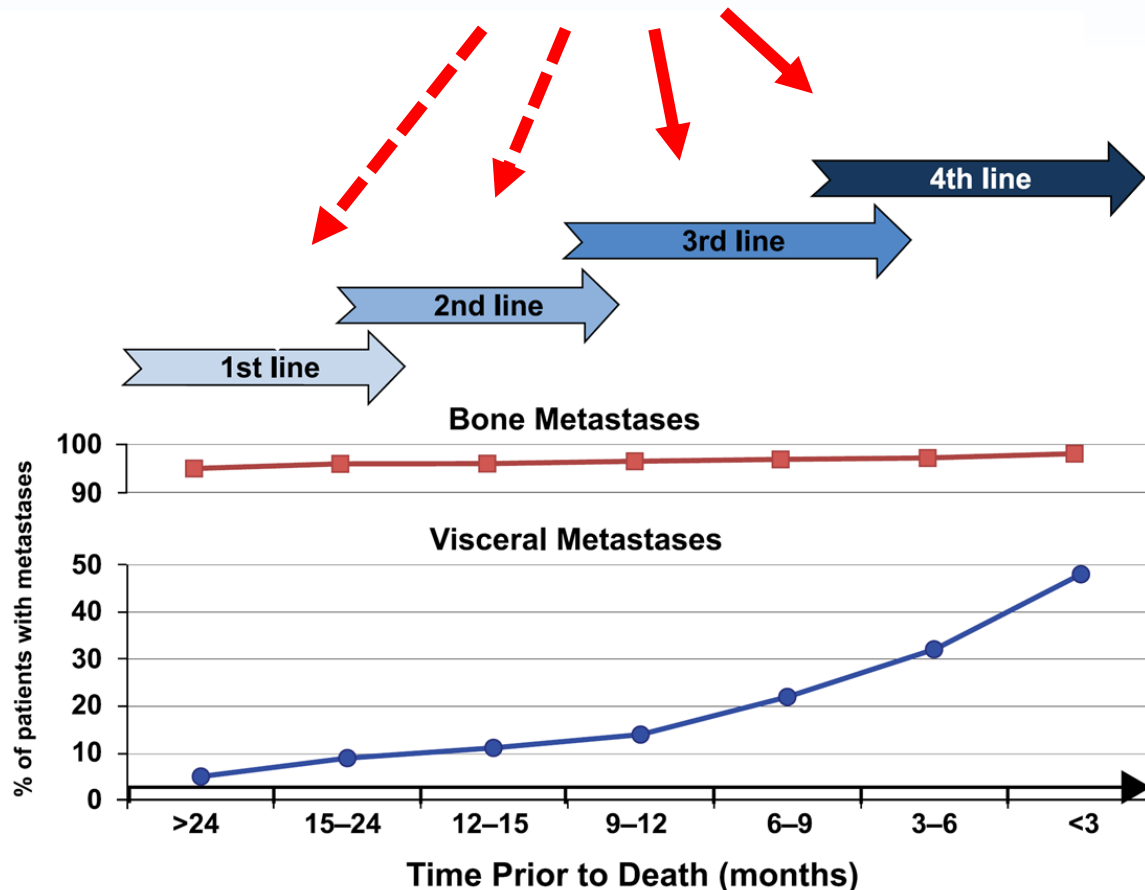
Symptomatic bone lesions

Pathologic lymph nodes  $\leq 3$  cm

No visceral metastases

# The Radium-223 Parabola: From Decline to Comeback

## Radium-223



27 July 2018  
EMA/500948/2018



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA restricts use of prostate cancer medicine

Medicine to be used only after two previous treatments or when other treatments cannot be taken

mCRPC

Symptomatic **bone lesions  $\geq 6$**

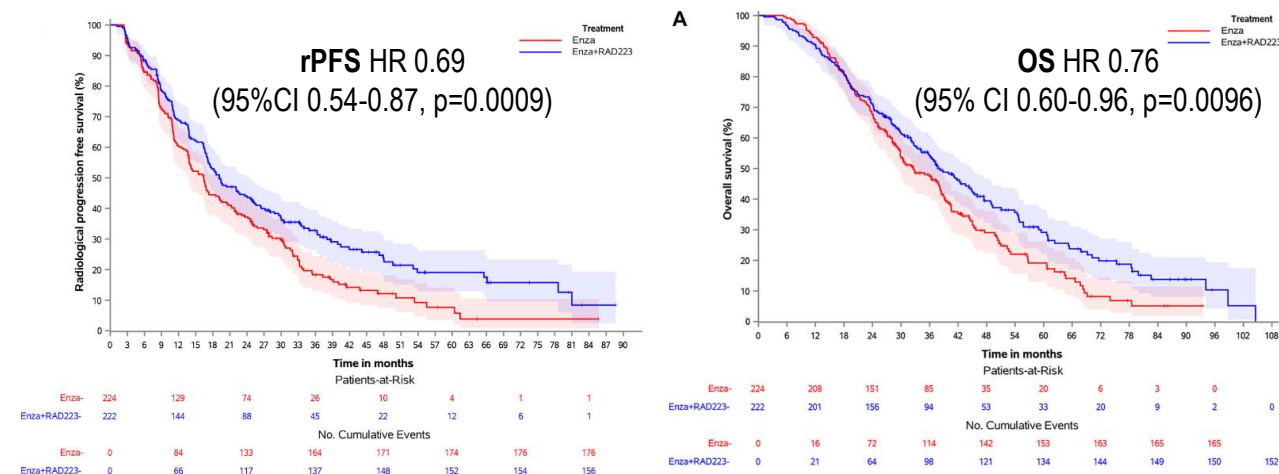
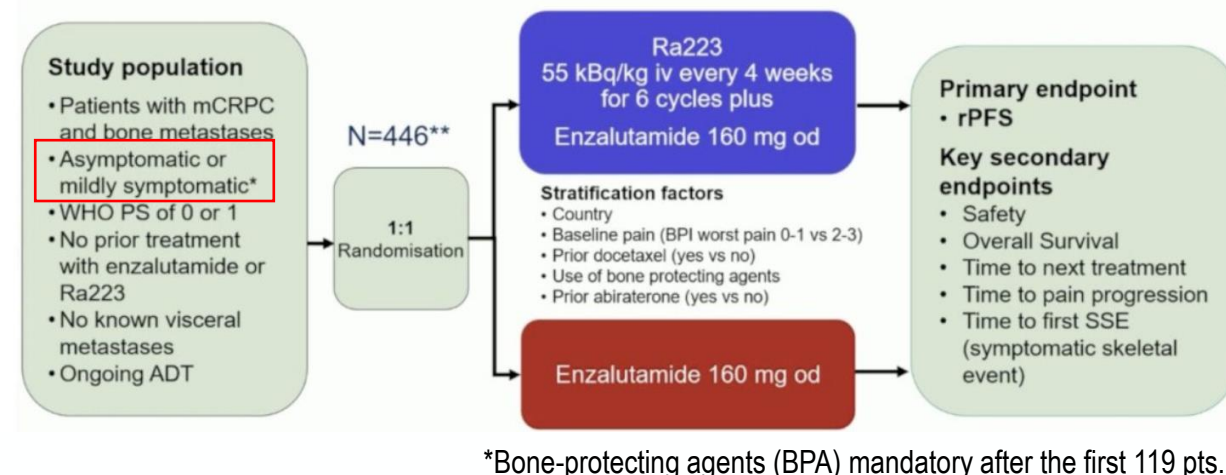
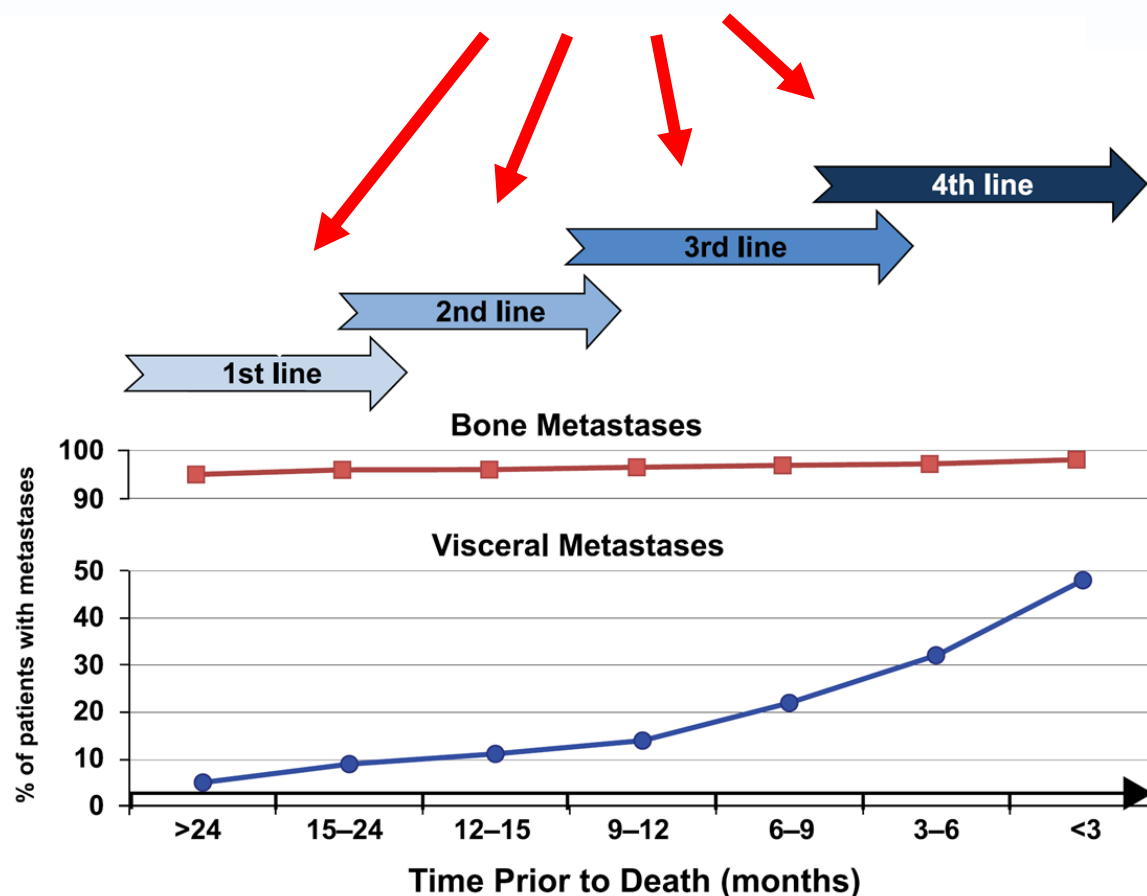
Pathologic lymph nodes  $\leq 3$  cm

No visceral metastases

**Progression after at least 2 lines of systemic therapy  
or ineligible for any available systemic treatment**

# The Radium-223 Parabola: From Decline to Comeback

## Radium-223 (+ enzalutamide)

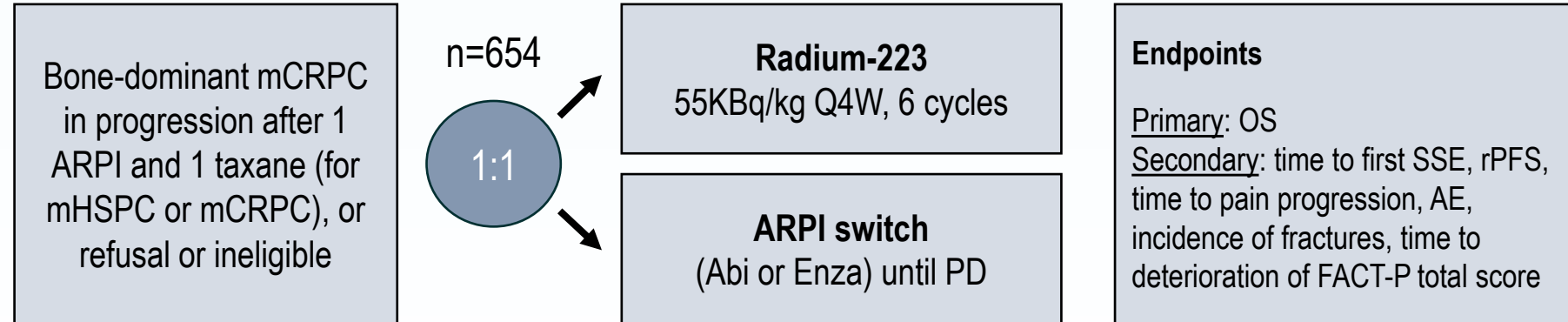


# The Radium-223 Parabola: From Decline to Comeback

## RADIANT (phase 4) NCT04597125

Study Completion (Estimated) ⓘ

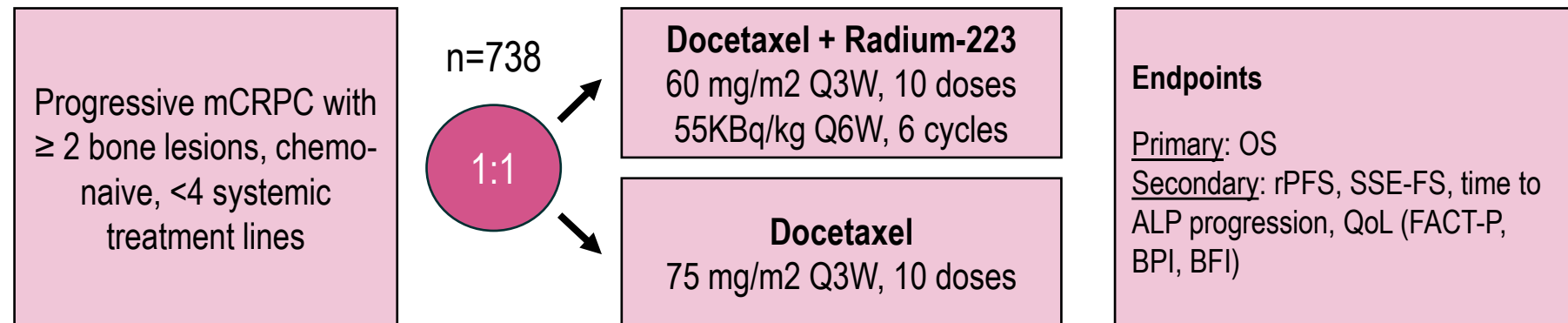
2026-10-12



## DORA (phase 3) NCT03574571

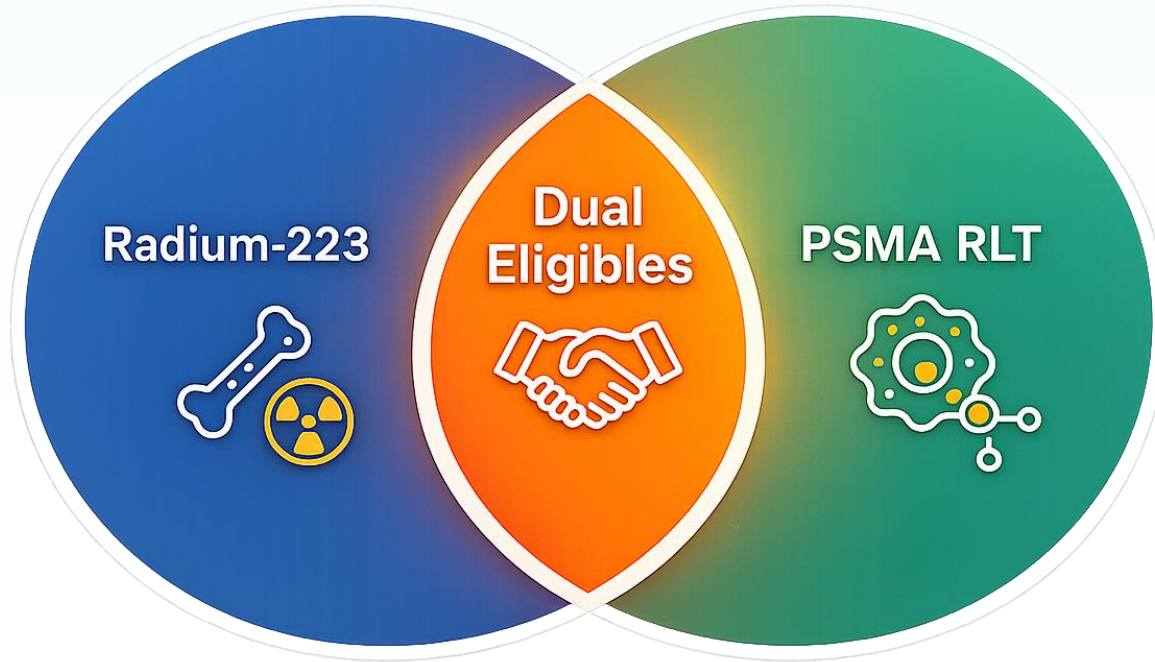
Study Completion (Estimated) ⓘ

2027-04-01



Stratified by:  
Docetaxel in mHSPC,  
visceral disease

# Radium-223 in the PSMA RLT era: challenges and open issues



## Looking Ahead:

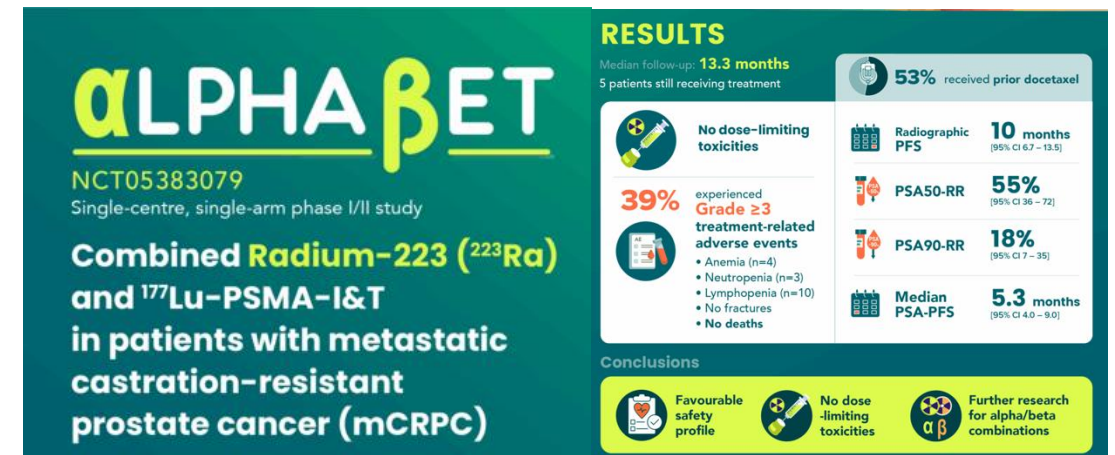
- ➡ Like eligibility, “dual eligibility” is dynamic and evolving
- 🧭 With ENZA-P and PEACE-3 data, when and in whom should radiopharmaceuticals be combined with ARPIs?

## Who are “Dual-Eligible” Patients Today?

- 👤 mCRPC after  $\geq 2$  lines (ARPI  $\pm$  docetaxel)
- 💉 Symptomatic disease
- 🦴 Bone-only metastases ( $\geq 6$ )  $\pm$  LN  $\leq 3$  cm
- 🦋 No visceral metastases
- 🔍 No PSMA-negative lesions (VISION)

## How to manage “Dual-Eligible” Patients?

- 🕒 Radium-223 first to preserve  $^{177}\text{Lu}$ -PSMA eligibility?
- ⚖️ Symptom-driven choice (ALSYMPCA vs VISION)?



## Take-home messages

PSMA radioligand therapy is now a **cornerstone in mCRPC**, with a clear survival benefit after ARPI and taxanes.

**PSMA RLT positioning is rapidly evolving**, moving earlier toward the HSPC setting.

**Radium-223 may still play a role**, particularly in selected patients with symptomatic, bone-only disease and no visceral metastases, and within the emerging concept of “dual-eligible” patients.

Radioligand therapy is no longer one drug, one isotope, one target: **multiple ligands, multiple radioisotopes**, and **novel targets** will define the next era of prostate cancer care.



**Thank you for your attention**

**Special thanks to:**

**GU Disease Management Team  
IRCCS Azienda Ospedaliera  
Metropolitana, Genova, Italy**

**IRCCS AOM**  
AZIENDA OSPEDALIERA METROPOLITANA

