DEFINING ELIGIBILITY FOR THERANOSTICS: EVOLVING CRITERIA

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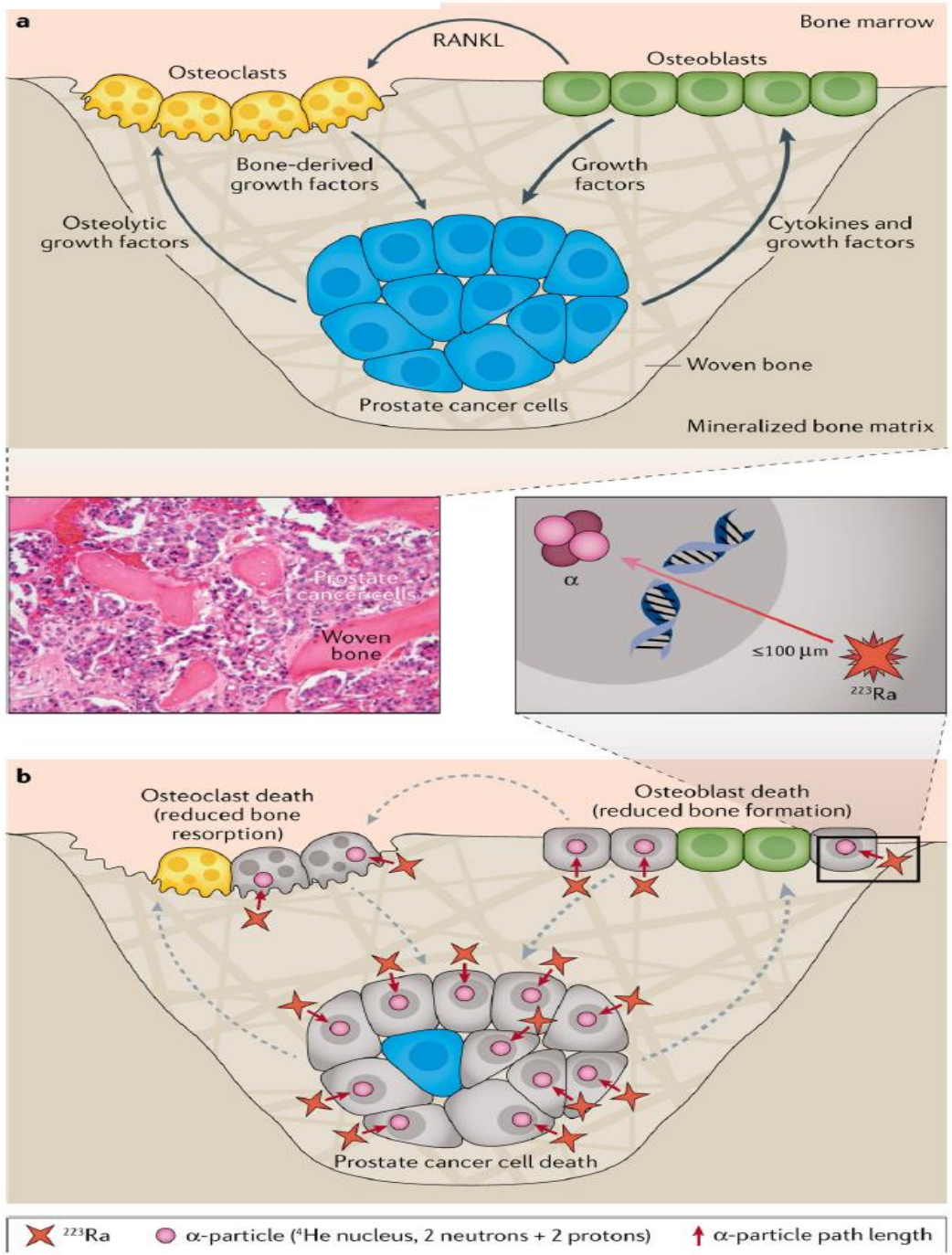
RADIUM 223 DICHLORIDE

Table 1 Decay of Ra-223

Nuclide	α Energy	β Energy	T½
Ra-223	5.64 MeV	—	11.4 d
Rn-219	6.75 MeV	—	3.96 s
Po-215	7.39 MeV	—	1.78 ms
Pb-211	—	0.47 MeV	36.1 min
Bi-211	6.55 MeV	—	2.17 min
Tl-207	—	0.47 MeV	4.77 min

Data are from US Patent EP1140211A2.[23]

Nat Rev Urol. 2019 December ; 16(12): 745–756.



Radium-223 mechanism of action: implications for use in treatment combinations

Michael J. Morris[1,*], Eva Corey[2], Theresa A. Guise[3], James L. Gulley[4], William Kevin Kelly[5], David I. Quinn[6,7], Arne Scholz[8], George Sgouros[9]

The NEW ENGLAND JOURNAL of MEDICINE

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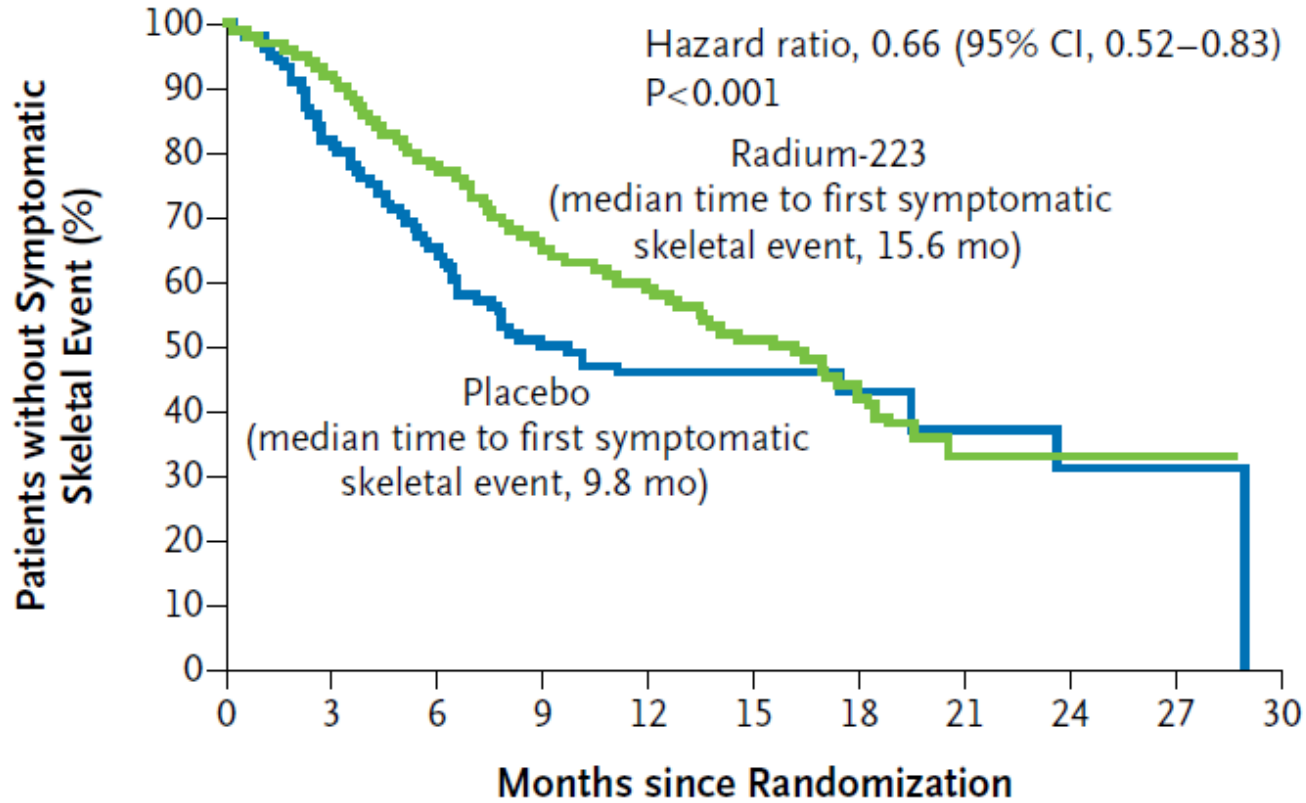
Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

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*

Table 1. Baseline Characteristics of the Patients.*

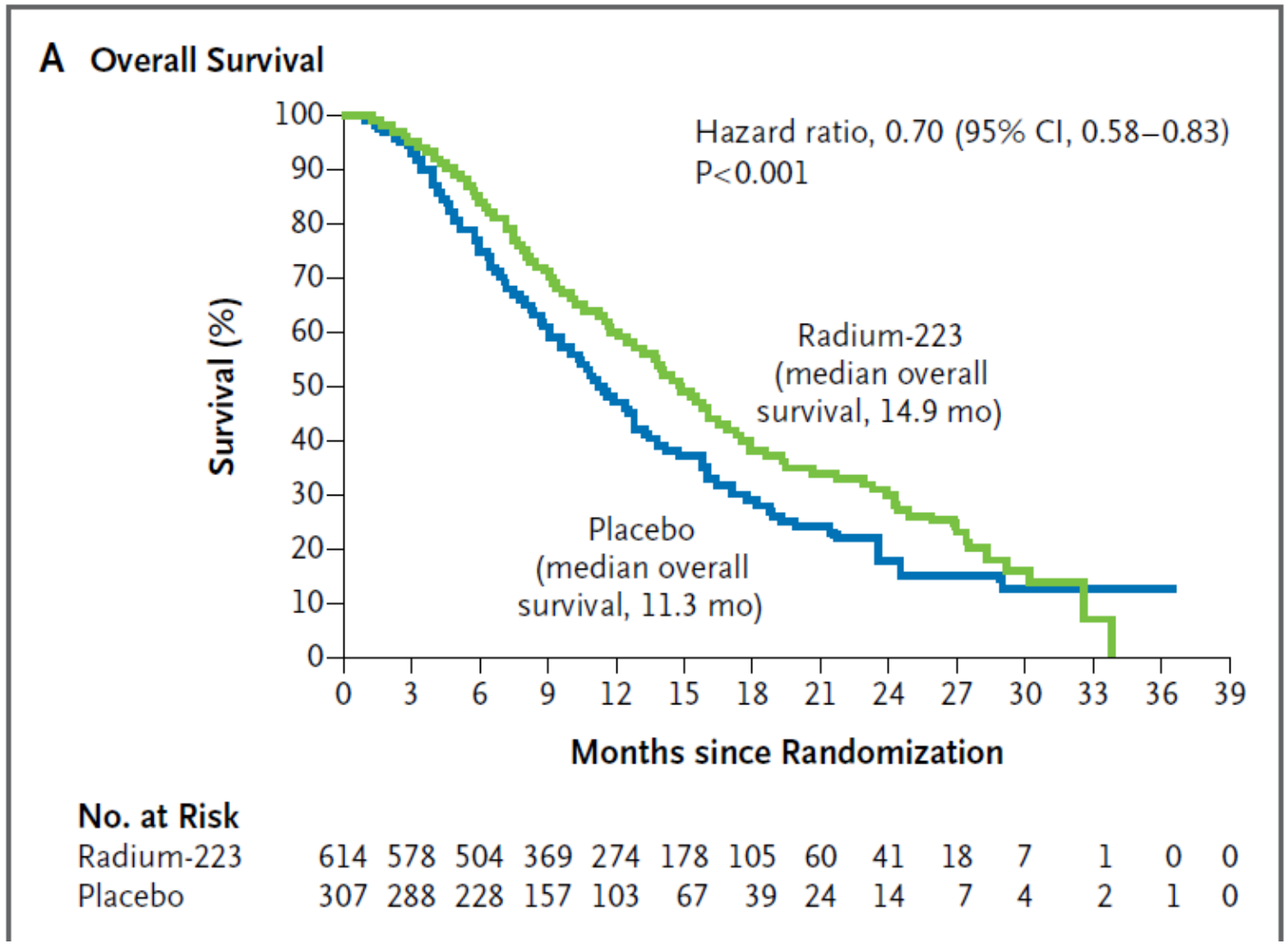
Characteristic	Radium-223 (N=614)	Placebo (N=307)
Age		
Median (range) — yr	71 (49–90)	71 (44–94)
>75 yr — no. (%)	171 (28)	90 (29)
White race — no. (%)†	575 (94)	290 (94)
Total alkaline phosphatase — no. (%)		
<220 U/liter	348 (57)	169 (55)
≥220 U/liter	266 (43)	138 (45)
Current use of bisphosphonates — no. (%)		
Yes	250 (41)	124 (40)
No	364 (59)	183 (60)
Any previous use of docetaxel — no. (%)		
Yes	352 (57)	174 (57)
No	262 (43)	133 (43)
ECOG performance-status score — no. (%)‡		
0	165 (27)	78 (25)
1	371 (60)	187 (61)
≥2	77 (13)	41 (13)
WHO ladder for cancer pain — no. (%)§		
1	257 (42)	137 (45)
2	151 (25)	78 (25)
3	194 (32)	90 (29)
Extent of disease — no. (%)		
<6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
>20 metastases	195 (32)	91 (30)
Superscan¶	54 (9)	30 (10)

B **Time to First Symptomatic Skeletal Event**



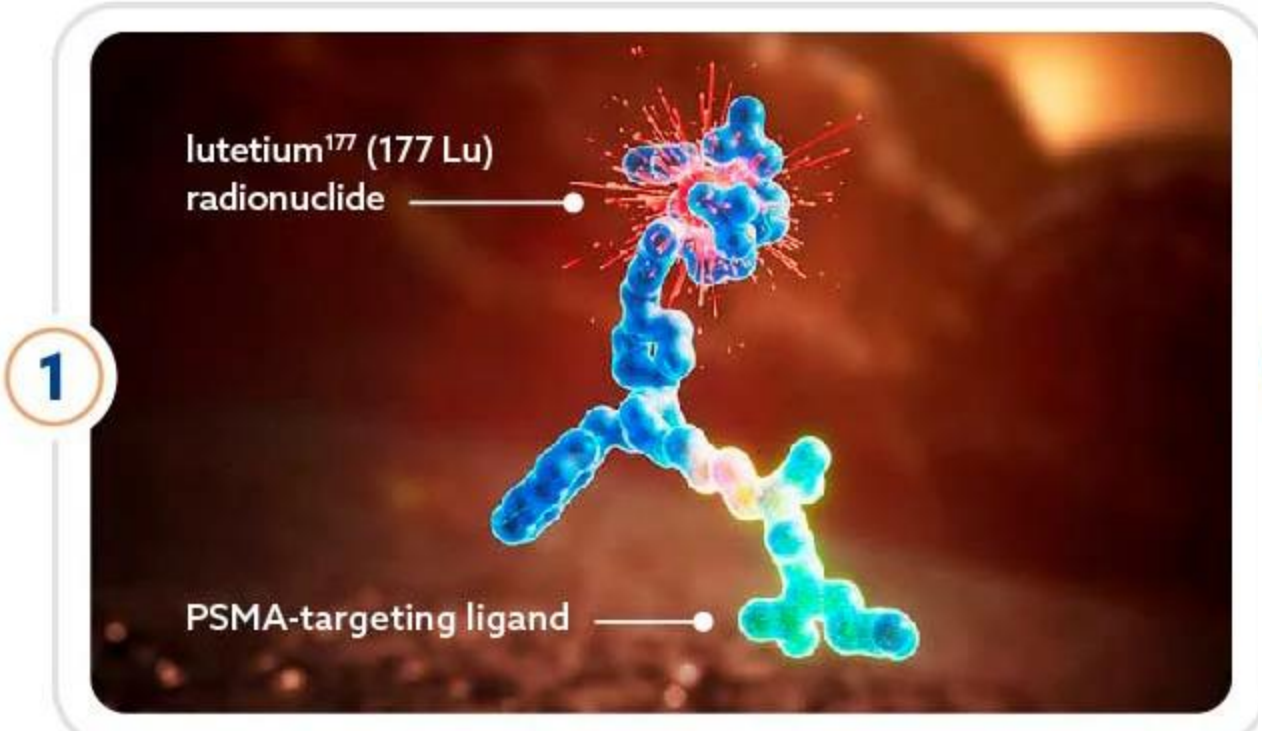
No. at Risk

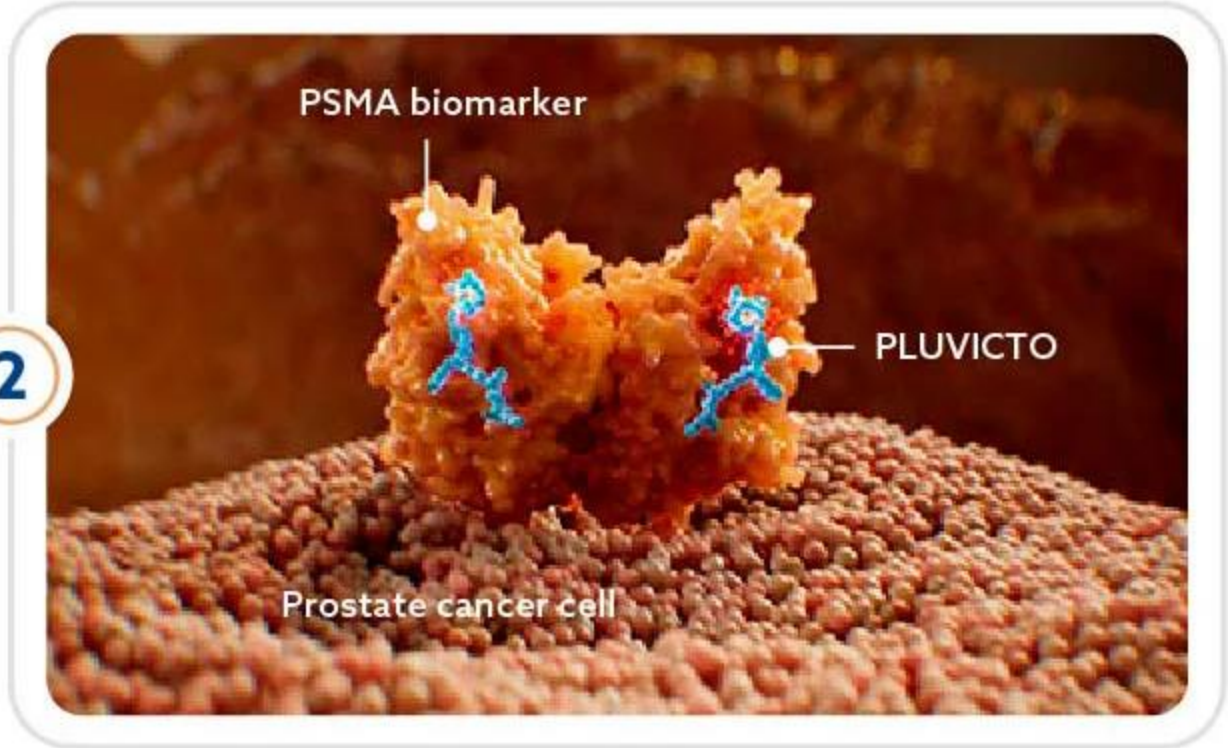
Radium-223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

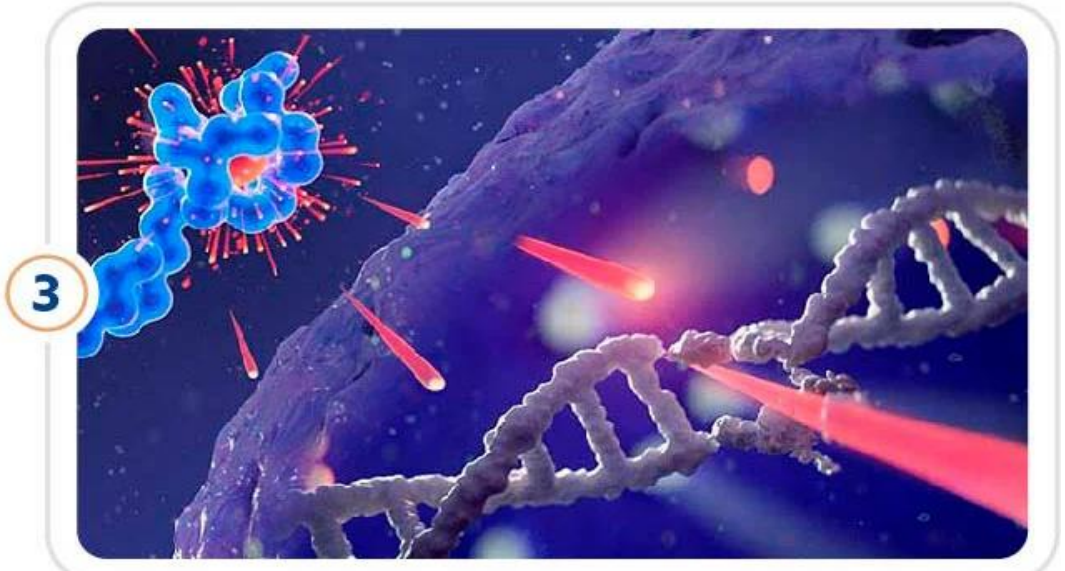

A Overall Survival
Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Hazard ratio, 0.70 (95% CI, 0.58–0.83)
P<0.001
Radium-223
(median overall
survival, 14.9 mo)
Placebo
(median overall
survival, 11.3 mo)
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Months since Randomization
No. at Risk
Radium-223 614 578 504 369 274 178 105 60 41 18 7 1 0 0
Placebo 307 288 228 157 103 67 39 24 14 7 4 2 1 0

LUTETIUM – 177 PSMA

Mechanism of Action







INDICATIONS

- TRIALS TESTING Lut – 177 PSMA therapy were done on castration resistant prostate cancer
- Usually done in 2nd or 3rd line clinical situations
- Results from trials provide the guidelines for current use
- Patients must have at least 1 site that shows uptake on PSMA Pet scan.
- Patients with metastatic sites which do not show uptake on PSMA Pet are not eligible for Lut-177 therapy

Radioligand Therapy With ^{177}Lu-PSMA for Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis

Yadav et al. AJR:213, August 2019

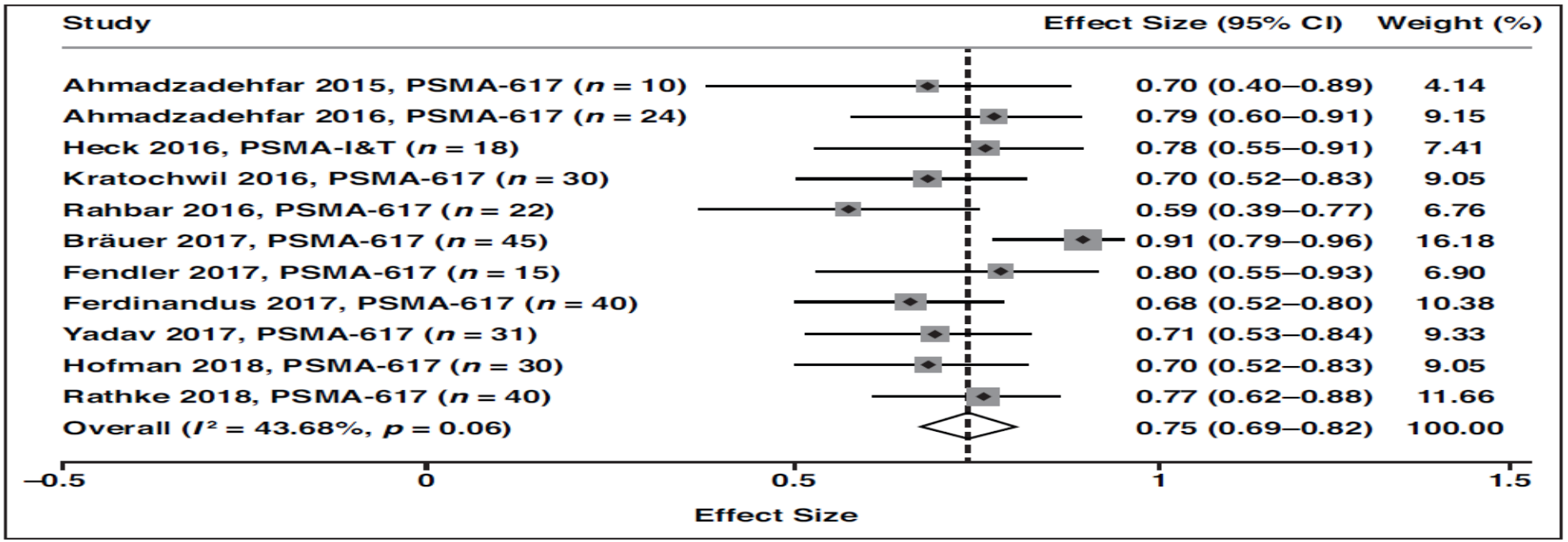


Fig. 4—Forest plot shows results of subgroup analysis for any prostate-specific antigen decline in 11 articles with patient population less than 50. PSMA = prostate-specific membrane antigen, I&T = imaging and therapy.

[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

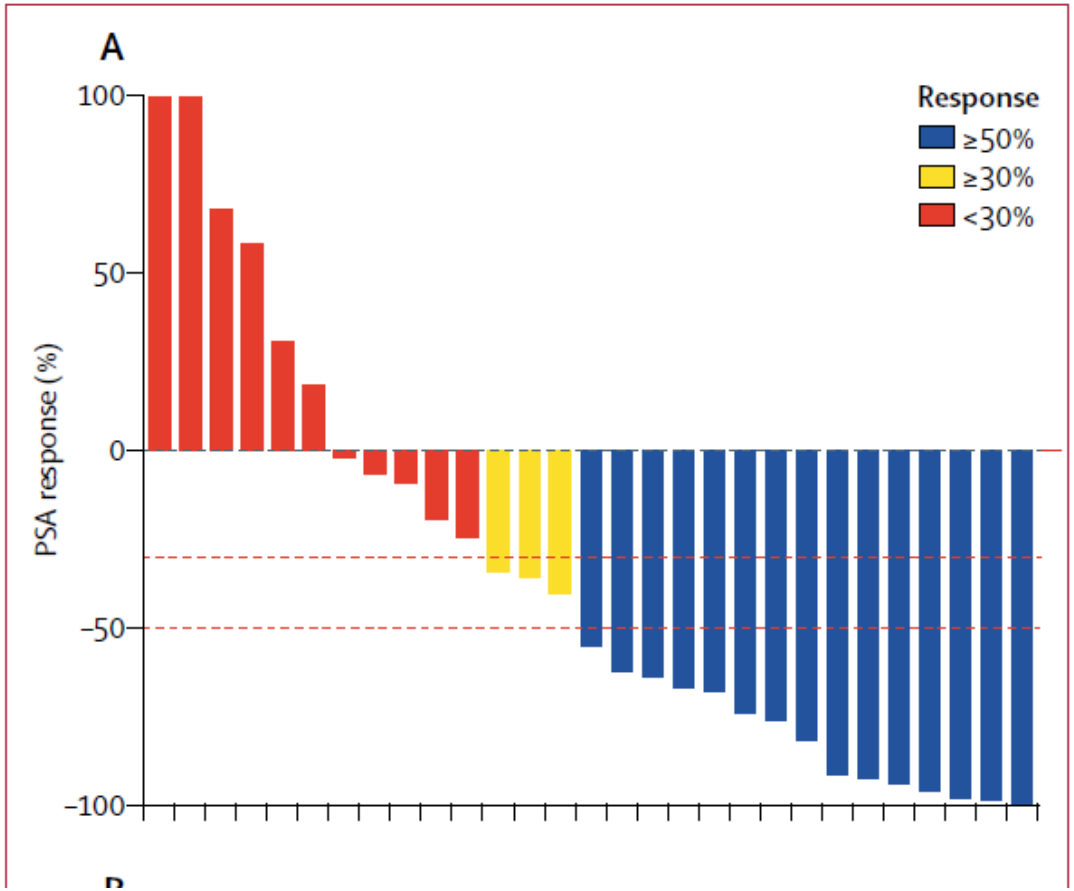
Michael S Hofman, John Violet*, Rodney J Hicks, Justin Ferdinandus, Sue Ping Thang, Tim Akhurst, Amir Iravani, Grace Kong, Aravind Ravi Kumar, Declan G Murphy, Peter Eu, Price Jackson, Mark Scalzo, Scott G Williams, Shahneen Sandhu*

www.thelancet.com/oncology Vol 19 June 2018

Number of previous chemotherapy regimens	
1	12 (40%)
2	12 (40%)
≥3	2 (7%)
Previous treatments	
Abiraterone or enzalutamide or both	25 (83%)
Docetaxel	24 (80%)
Cabazitaxel	14 (47%)
Palliative-intent radiotherapy	14 (47%)
Bisphosphonate or denosumab	22 (73%)

Outcomes

The primary endpoint of the trial was PSA response rate according to Prostate Cancer Clinical Trials Working Group 2 (PCWG)[21] criteria defined as a 50% or more PSA decline from baseline with confirmation 3–4 weeks apart



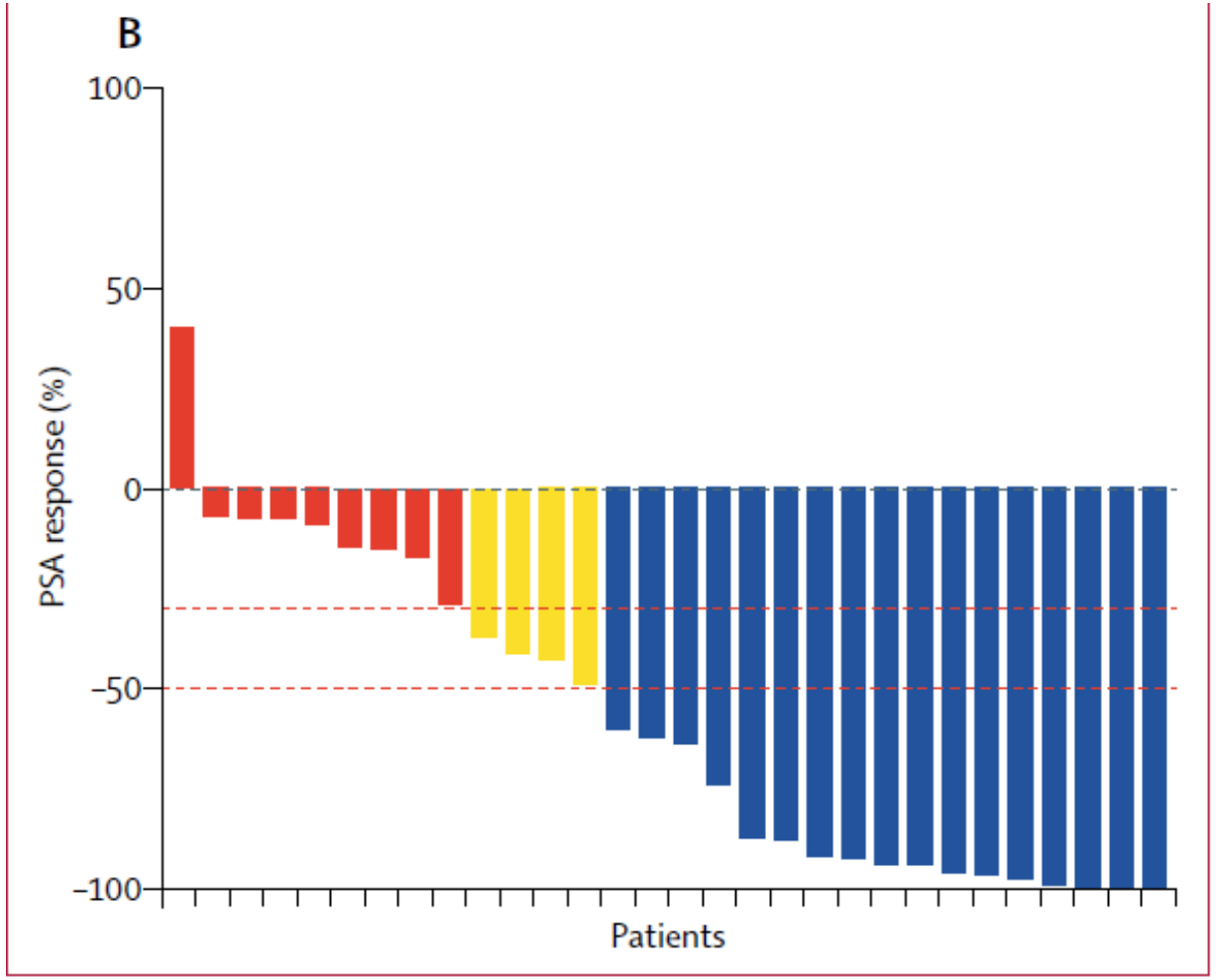


Figure 3: (A) PSA response after 12 weeks* and (B) best PSA response from baseline

Two dashed lines represent PSA response greater than 30 and 50%. PSA=prostate-specific antigen. *One patient deceased by 12 weeks (non-prostate related).

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2021;385:1091-103.

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

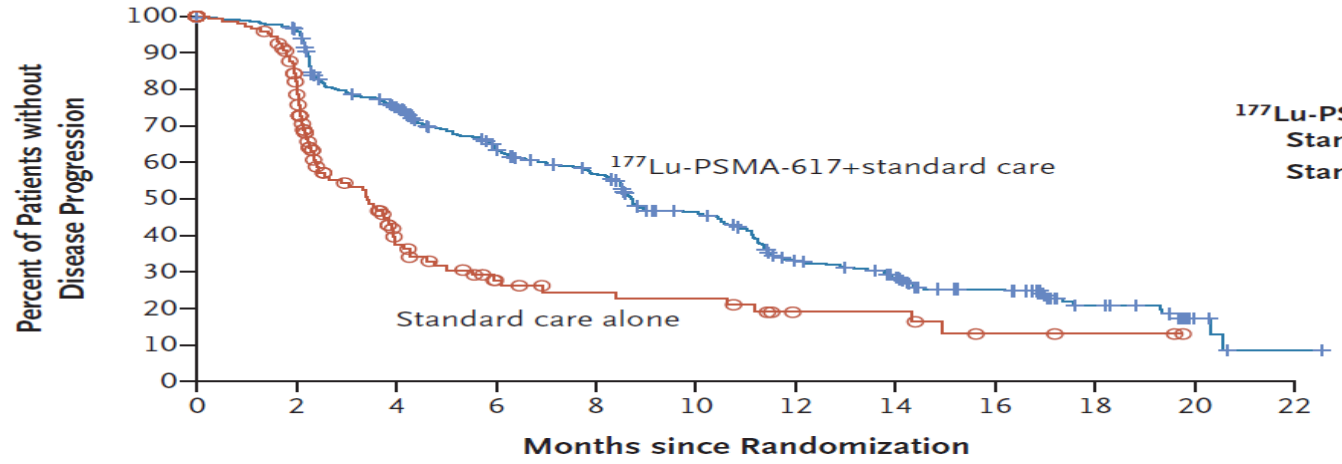
METHODS

We conducted an international, open-label, phase 3 trial evaluating ^{177}Lu-PSMA-617 in patients who had metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane regimens and who had PSMA-positive gallium-68 (^{68}Ga)–labeled PSMA-11 positron-emission tomographic–computed tomographic scans. Patients were randomly assigned in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for four

Site of disease — no. (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
Median PSA level (range) — ng/ml	93.2 (0–6988)	90.7 (0–6600)	77.5 (0–6988)	74.6 (0–8995)

Previous androgen-receptor–pathway inhibitor — no. (%)‖				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy — no. (%)**				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

A **Imaging-Based Progression-free Survival**



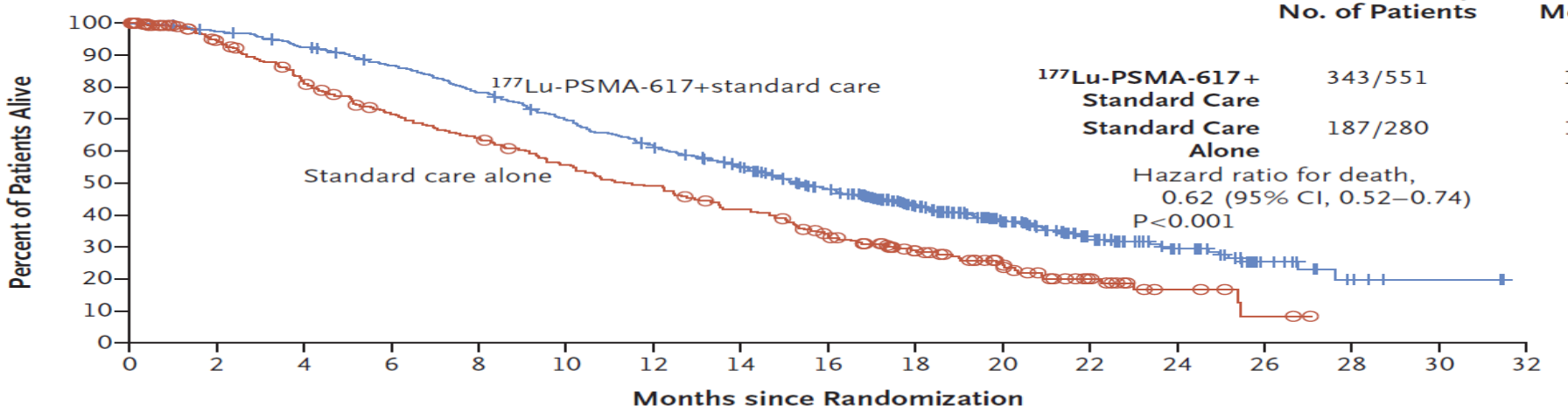
	No. of Events/ No. of Patients	Median (mo)
^{177}Lu-PSMA-617+ Standard Care	254/385	8.7
Standard Care Alone	93/196	3.4

Hazard ratio for progression or death, 0.40 (99.2% CI, 0.29–0.57)
P<0.001

No. at Risk

^{177}Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

B **Overall Survival**



	No. of Events/ No. of Patients	Median (mo)
^{177}Lu-PSMA-617+ Standard Care	343/551	15.3
Standard Care Alone	187/280	11.3

Hazard ratio for death, 0.62 (95% CI, 0.52–0.74)
P<0.001

No. at Risk

^{177}Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

Lancet 2021; 397: 797–804

Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherford, Andrew Weickhardt , Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Guminski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†*

Methods We did this multicentre, unblinded, randomised phase 2 trial at 11 centres in Australia. We recruited men with metastatic castration-resistant prostate cancer for whom cabazitaxel was considered the next appropriate standard treatment. Participants were required to have adequate renal, haematological, and liver function, and an Eastern Cooperative Oncology Group performance status of 0–2. Previous treatment with androgen receptor-directed therapy was allowed. Men underwent gallium-68 [^{68}Ga]Ga-PSMA-11 and 2-flourine-18[^{18}F]fluoro-2-deoxy-D-glucose (FDG) PET-CT scans. PET eligibility criteria for the trial were PSMA-positive disease, and no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings. Men were randomly assigned (1:1) to [^{177}Lu]Lu-PSMA-617 (6·0–8·5 GBq intravenously every 6 weeks for up to six cycles) or cabazitaxel (20 mg/m^2 intravenously

Patients were selected on the basis of molecular imaging phenotype using the combination of PSMA and 2-[^{18}F]FDG PET-CT, to maximise the probability of observing benefit. These stringent imaging criteria resulted in 28% of men who were screened for TheraP not meeting the eligibility criteria, mainly due to [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET-CT discordance.

Disease stage		
Lymph node only	7 (7%)	9 (9%)
Bone metastases	90 (91%)	90 (89%)
Visceral metastases	7 (7%)	13 (13%)
Previous treatment		
Abiraterone only	21 (21%)	24 (24%)
Enzalutamide only	49 (50%)	58 (57%)
Both	21 (21%)	9 (9%)

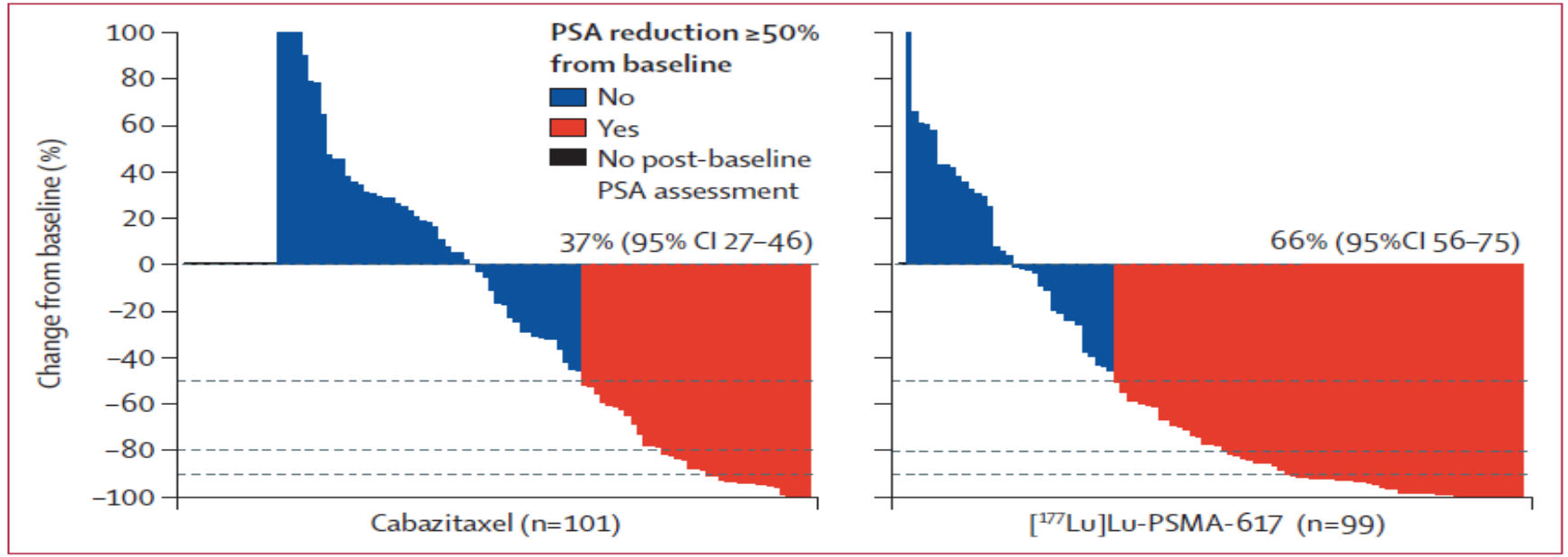


Figure 2: **PSA response**
PSA=prostate-specific antigen. ^{177}Lu=lutetium-177.

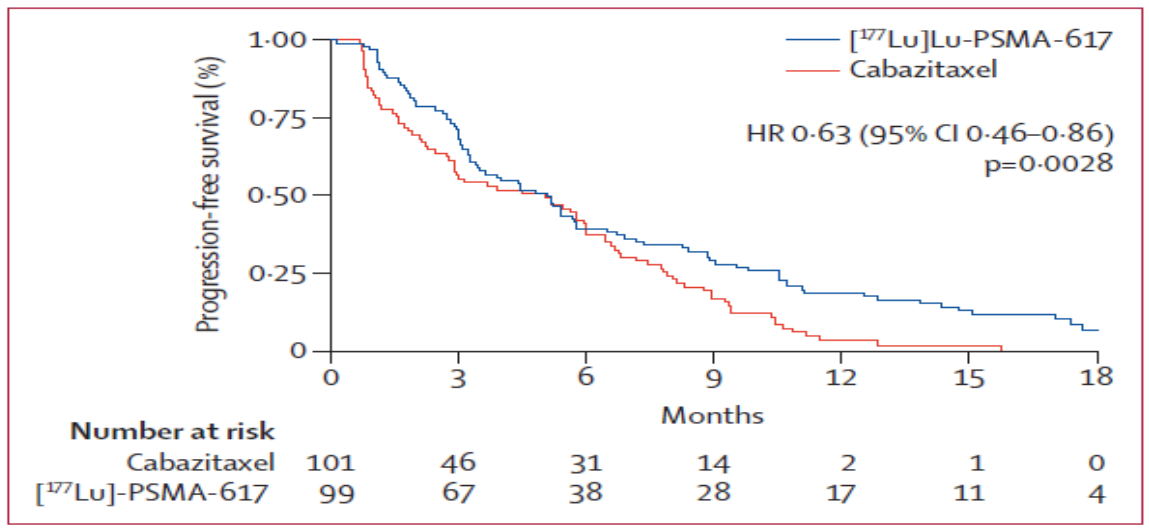


Figure 3: **Radiographic or PSA progression-free survival**
HR=hazard ratio. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. ^{177}Lu=lutetium-177.

^{177}Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial

Michael J Morris, Daniel Castellano, Ken Herrmann, Johann S de Bono, Neal D Shore, Kim N Chi, Michael Crosby, Josep M Piulc Xiao X Wei, Hakim Mahammedi, Guilhem Roubaud, Hana Študentová, James Nagarajah, Begoña Mellado, Álvaro Montesa-Pi Euloge Kpamegan, Samson Ghebremariam, Teri N Kreisl, Celine Wilke, Katja Lehnhoff, Oliver Sartor*, Karim Fizazi*, for the PSM Investigators†*

Lancet 2024; 404: 1227–39

Methods In this phase 3, randomised, controlled trial conducted at 74 sites across Europe and North America, taxane-naive patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer who had progressed once on a previous ARPI were randomly allocated (1:1) to open-label, intravenous ^{177}Lu-PSMA-617 at a dosage of 7·4 GBq (200 mCi) ± 10% once every 6 weeks for six cycles, or a change of ARPI (to abiraterone or enzalutamide, administered orally on a continuous basis per product labelling). Crossover from ARPI change to

The criteria for PSMA-positive, metastatic, castration-resistant prostate cancer on centrally read baseline [^{68}Ga]Ga-PSMA-11 (^{68}Ga-PSMA-11) PET-CT scans required patients to have at least one PSMA-positive metastatic lesion (^{68}Ga-PSMA-11 uptake greater than in liver parenchyma), and no PSMA-negative lesions exceeding specified minimum dimensions. All lymph nodes measuring 25 mm or greater in the short axis, bone metastases with a soft tissue component 10 mm or greater in the longest diameter, solid organ metastases 10 mm or greater in the longest diameter, and all intraprostatic lesions had to be PSMA-positive on ^{68}Ga-PSMA-11 PET-CT.

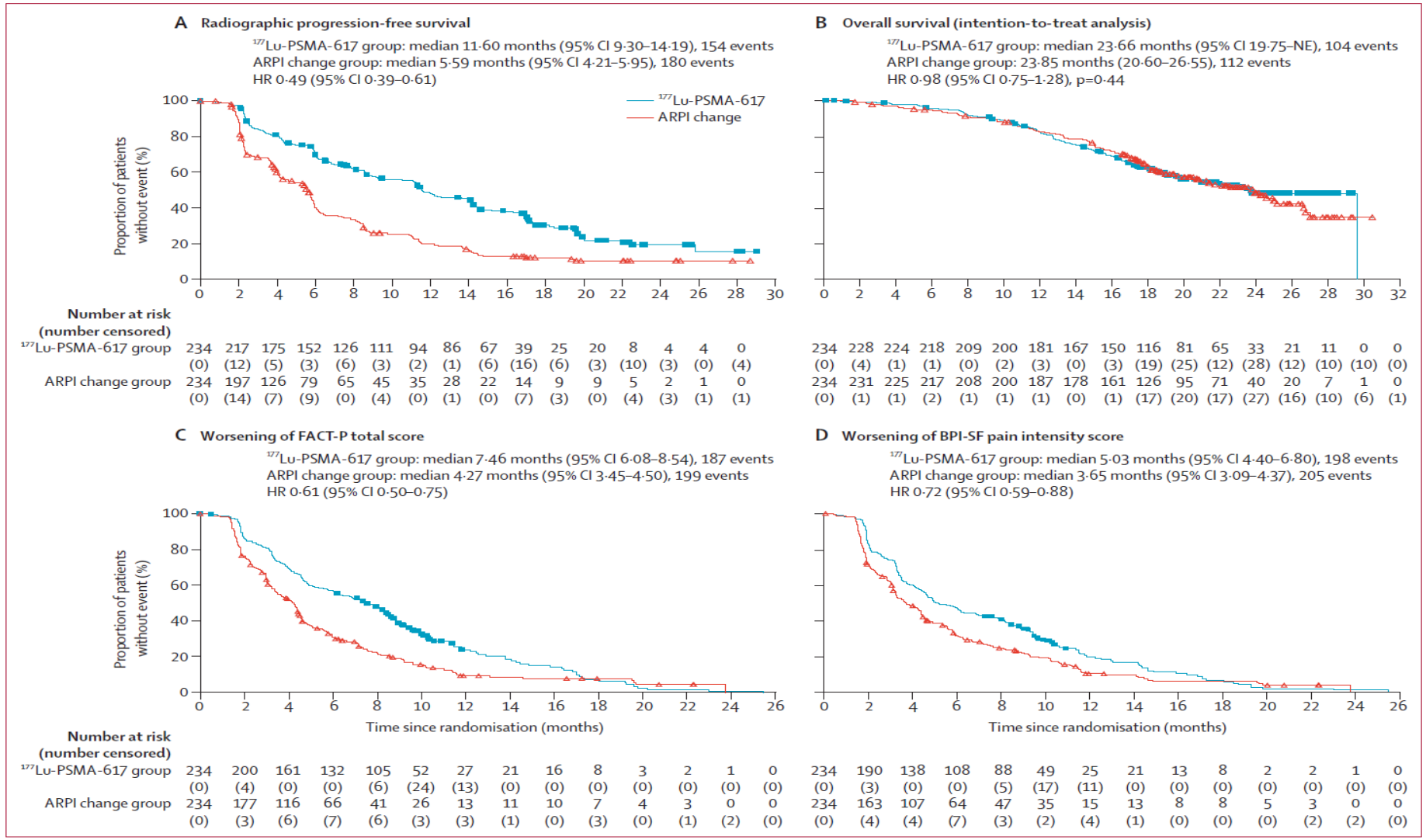


Figure 2: **Time-to-event endpoints at the time of third data cutoff**

(A) Updated radiographic progression-free survival (see appendix 1 p 10 for primary analysis); events were radiographic disease progression (determined by blinded independent central review per the Prostate Cancer Clinical Trials Working Group 3-modified[38] Response Evaluation Criteria in Solid Tumours v1.1) or death. (B) Overall survival (intention-to-treat analysis; three patients died before receiving ^{177}Lu-PSMA-617). (C) Time to worsening of FACT-P total score; events were a decrease of ≥10 points,[40,41] clinical disease progression, or death. (D) Time to worsening on BPI-SF pain intensity scale; events were an increase of ≥2 points,[42,43] clinical disease progression, or death. See appendix 1 (p 9) for the schedule of investigations. ARPI=androgen receptor pathway inhibitor. BPI-SF=Brief Pain Inventory—Short Form. FACT-P=Functional Assessment of Cancer Therapy—Prostate. HR=hazard ratio. NE=not estimable. PSMA=prostate-specific membrane antigen.

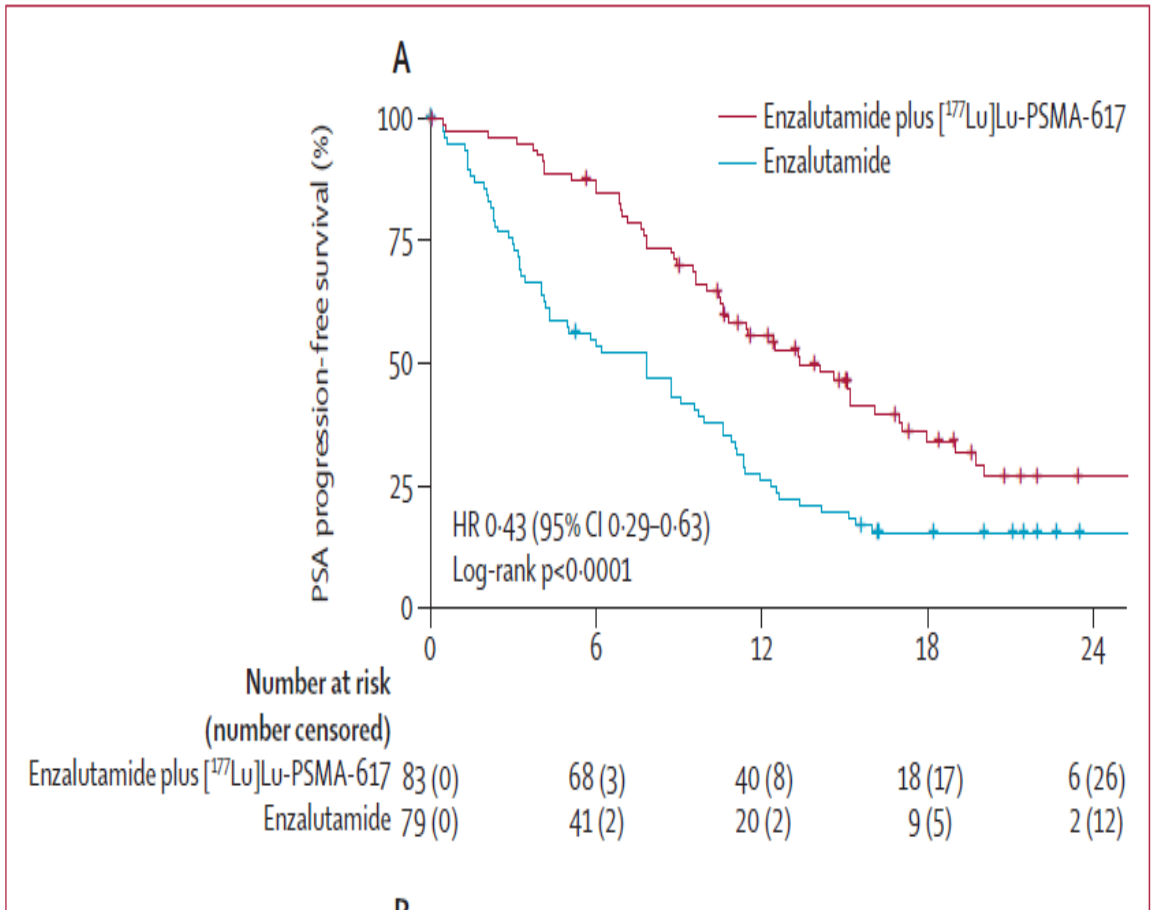
[^{177}Lu]Lu-PSMA-617 plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): an open-label, multicentre, randomised, phase 2 trial

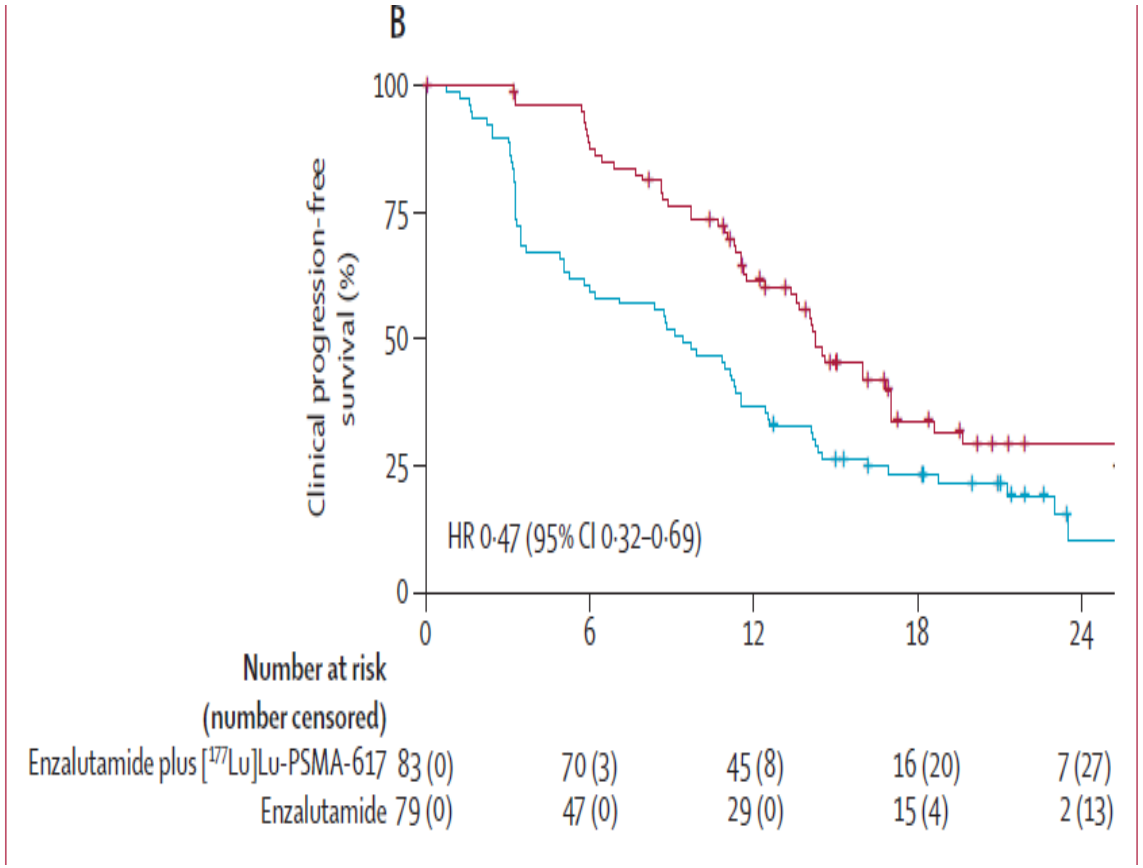
Louise Emmett, Shalini Subramaniam, Megan Crumbaker, Andrew Nguyen, Anthony M Joshua, Andrew Weickhardt, Sze-Ting Lee, Siobhan Ng, Roslyn J Francis, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Craig Gedye, Natalie K Rutherford, Shahneen Sandhu, Aravind Ravi Kumar, David Pook, Shakher Ramdave, David P Nadebaum, Mark Voskoboynik, Andrew D Redfern, William Macdonald, Laurence Krieger, Geoff Schembri, Wei Chua, Peter Lin, Lisa Horvath, Patricia Bastick, Patrick Butler, Alison Yan Zhang, Sonia Yip, Hayley Thomas, Ailsa Langford, Michael S Hofman, Margaret McJannett, Andrew James Martin, Martin R Stockler, Ian D Davis*, for the ENZA-p Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†*

Lancet Oncol 2024; 25: 563–71

Methods ENZA-p was an open-label, randomised, controlled phase 2 trial done at 15 hospitals in Australia. Participants were men aged 18 years or older with metastatic castration-resistant prostate cancer not previously treated with docetaxel or androgen receptor pathway inhibitors for metastatic castration-resistant prostate cancer, gallium-68 [^{68}Ga]Ga-PSMA-PET-CT (PSMA-PET-CT) positive disease, Eastern Cooperative Oncology Group performance status of 0–2, and at least two risk factors for early progression on enzalutamide. Participants were randomly assigned (1:1) by a centralised, web-based system using minimisation with a random component to stratify for study site, disease burden, use of early docetaxel, and previous treatment with abiraterone acetate. Patients were either given oral enzalutamide 160 mg daily alone or with adaptive-dosed (two or four doses) intravenous 7·5 GBq [^{177}Lu]Lu-PSMA-617 every 6–8 weeks dependent on an interim PSMA-PET-CT (week 12). The primary endpoint was prostate-specific

All potential participants underwent screening with gallium-68 [^{68}Ga]Ga-PSMA-11 PET-CT (PSMA-PET-CT). PET eligibility criteria for the trial were PSMA-positive disease with a maximum standardised uptake value (SUVmax) of at least 15 at a minimum of one site of disease, and SUVmax of at least 10 at all larger sites of disease (not affected by partial volume effect).


A
PSA progression-free survival (%)
100
75
50
25
0
Enzalutamide plus [177Lu]Lu-PSMA-617
Enzalutamide
HR 0·43 (95% CI 0·29–0·63)
Log-rank p<0·0001
0
6
12
18
24
Number at risk
(number censored)
Enzalutamide plus [177Lu]Lu-PSMA-617 83 (0) 68 (3) 40 (8) 18 (17) 6 (26)
Enzalutamide 79 (0) 41 (2) 20 (2) 9 (5) 2 (12)


B
Clinical progression-free survival (%)
100
75
50
25
0
HR 0·47 (95% CI 0·32–0·69)
0
6
12
18
24
Number at risk
(number censored)
Enzalutamide plus [177Lu]Lu-PSMA-617 83 (0) 70 (3) 45 (8) 16 (20) 7 (27)
Enzalutamide 79 (0) 47 (0) 29 (0) 15 (4) 2 (13)

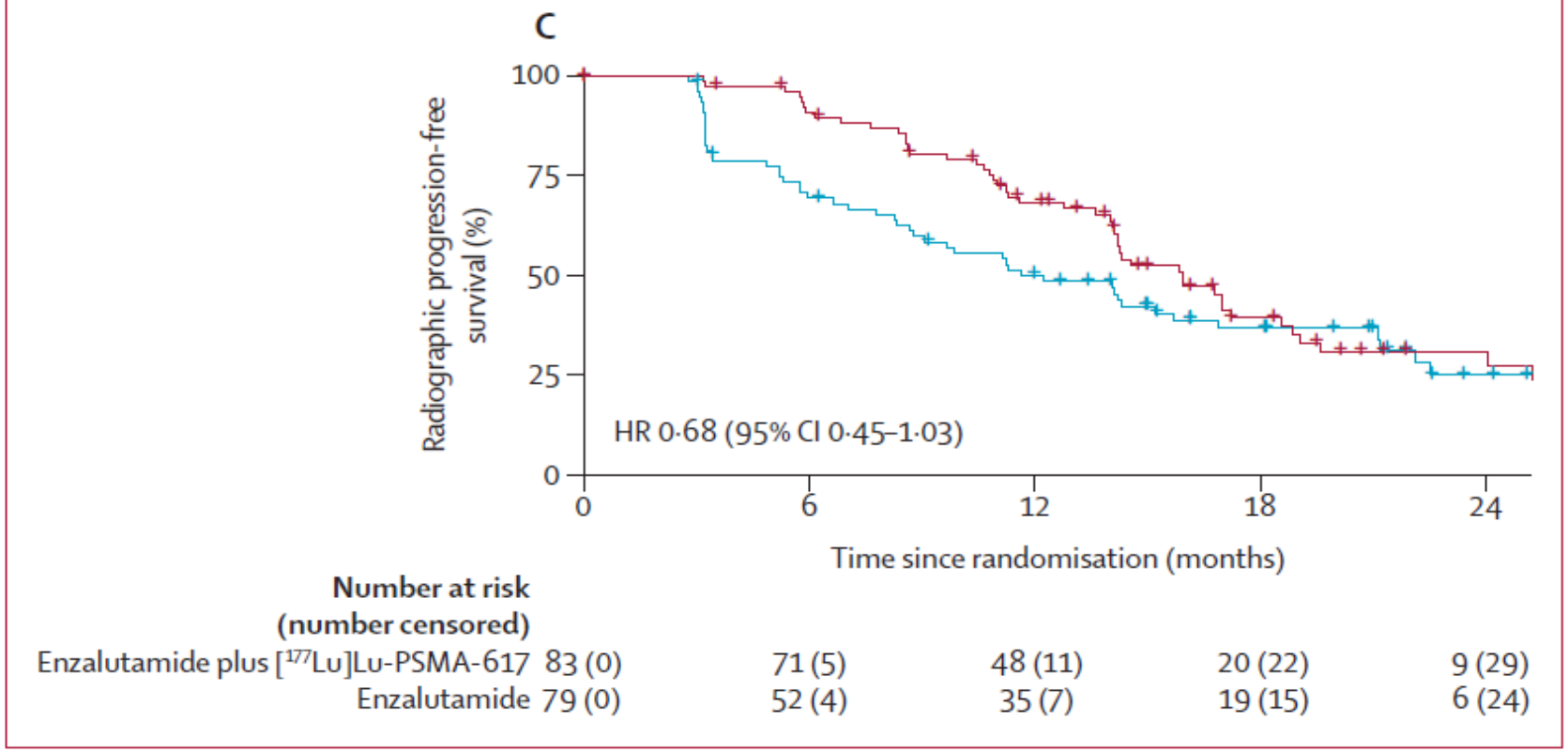


Figure 2: **PSA progression-free survival, clinical progression-free survival, and radiographic progression-free survival**

Kaplan–Meier curves for PSA progression-free survival (A), clinical progression-free survival as determined by results on imaging, symptoms, or changes in therapy (B), and radiographic progression-free survival as determined by results on imaging (C). Control of the study-wide type I error rate was confined to the primary endpoint (PSA progression-free survival); therefore, analyses of secondary endpoints are reported with 95% CIs, and without p values. ^{177}Lu=lutetium-177. HR=hazard ratio. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen.

Sequential [^{177}Lu]Lu-PSMA-617 and docetaxel versus docetaxel in patients with metastatic hormone-sensitive prostate cancer (UpFrontPSMA): a multicentre, open-label, randomised, phase 2 study

Lancet Oncol 2024; 25: 1267–76

*Arun A Azad, Mathias Bressel, Hsiang Tan, Mark Voskoboynik, Aneta Suder, Andrew J Weickhardt, Alexander Guminski, Roslyn J Francis, Javad Saghebi, Nattakorn Dhiantravan, Anthony M Joshua, Louise Emmett, Lisa Horvath, Declan G Murphy, Edward Hsiao, Bavanthi Balakrishnar, Peter Lin, Andrew Redfern, William Macdonald, Siobhan Ng, Sze-Ting Lee, David A Pattison, David Nadebaum, Ian D Kirkwood, Michael S Hofman, on behalf of the UpFrontPSMA Study Team**

Background **Lutetium-177 [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617 improves survival and quality of life in patients with metastatic castration-resistant prostate cancer, but whether it confers a benefit in hormone-sensitive disease is unknown. We aimed to evaluate [^{177}Lu]Lu-PSMA-617 before docetaxel treatment in patients with de-novo high-volume metastatic hormone-sensitive prostate cancer.**

or both; PSMA-avid disease with a maximum standardised uptake value or more than 15 and high-volume metastases (defined as visceral disease, four or more bone metastases with at least one outside the axial skeleton on PSMA PET, or both); and absence of extensive discordant fluorodeoxyglucose (FDG)-positive, PSMA-negative disease, defined as presence of FDG-positive disease with minimal PSMA expression in multiple sites (more than five) or in more than 50% of the total tumour volume. Written, informed consent was

Randomisation and masking

Patients were randomly assigned (1:1) to the experimental treatment ([^{177}Lu]Lu-PSMA-617 7·5 GBq followed 6 weeks later by docetaxel) or standard-of-care treatment (docetaxel alone) using computer-based block randomi-

Methods UpFrontPSMA was an investigator-initiated, multicentre, open-label, randomised, phase 2 trial done at 11 Australian hospitals. Eligible patients had prostate adenocarcinoma without clinically significant neuroendocrine differentiation or small-cell histology, were aged 18 years or older, had less than 4 weeks on androgen deprivation therapy, had an Eastern Cooperative Oncology Group performance status of 0–2, and had high-volume PSMA-avid disease on [^{68}Ga]Ga-PSMA-11 PET-CT with no major discordance on 2-[^{18}F] fluorodeoxyglucose-PET-CT. Patients were randomly assigned (1:1) to the experimental treatment ([^{177}Lu]Lu-PSMA-617 followed 6 weeks later by docetaxel) or standard-of-care treatment (docetaxel alone) using computer-based block randomisation with random block sizes, stratified by disease volume by conventional imaging and duration of androgen deprivation therapy at the time of registration. Neither patients nor investigators were masked to treatment assignment. Patients in the experimental group received two cycles of [^{177}Lu]Lu-PSMA-617 7·5 GBq every 6 weeks intravenously, followed 6 weeks later by six cycles of docetaxel 75 mg/m^2 every 3 weeks intravenously, whereas patients in the standard-of-care treatment group received six cycles of docetaxel 75 mg/m^2 every 3 weeks intravenously. All patients received continuous androgen deprivation therapy. The primary endpoint was undetectable prostate-specific antigen (≤0·2 ng/mL) at 48 weeks, assessed using a modified intention-to-treat analysis. The trial is registered with ClinicalTrials.gov, NCT04343885.

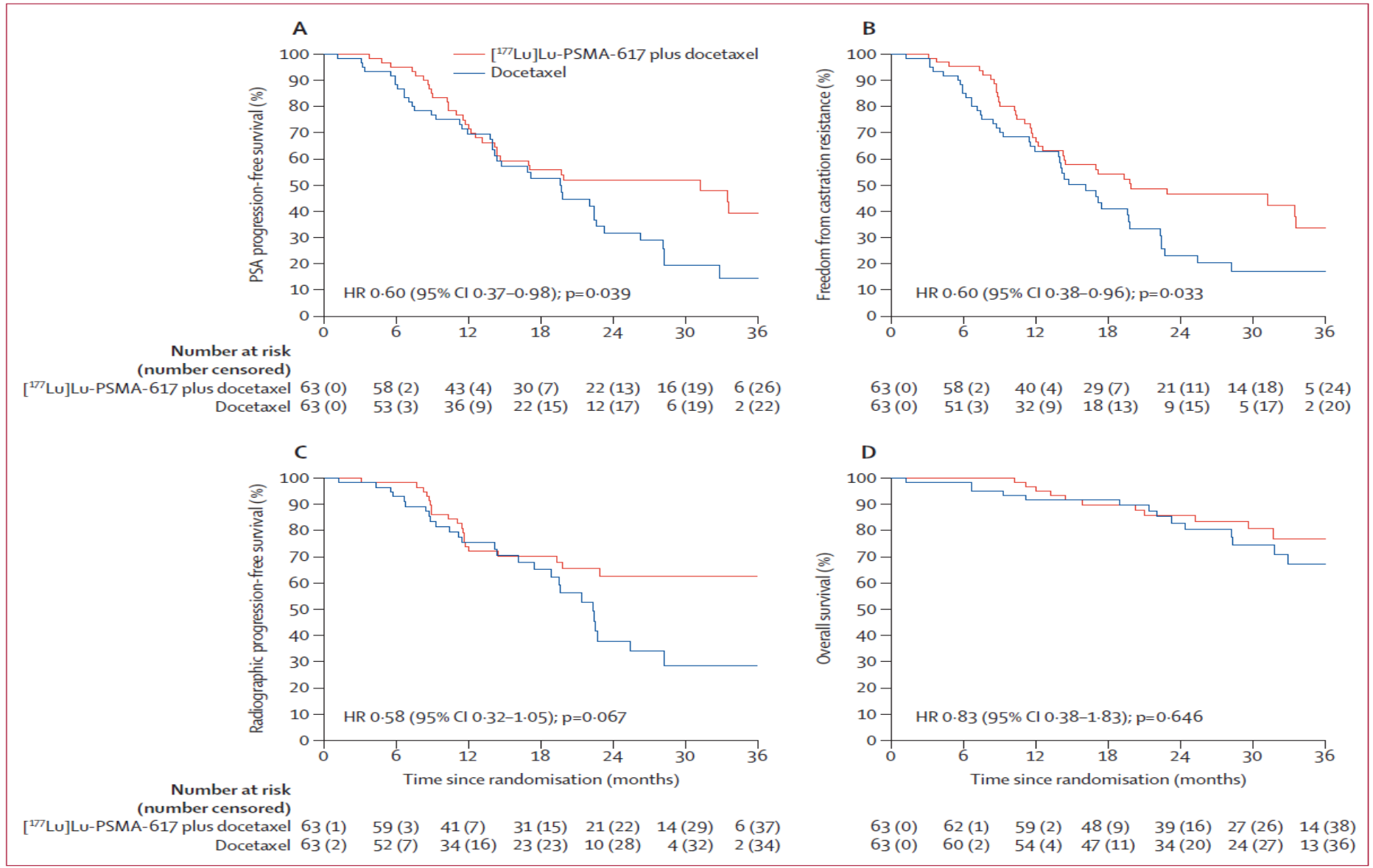


Figure 2: **PSA progression-free survival (A), freedom from castration resistance (B), radiographic progression-free survival (C), and overall survival (D)**
[177Lu]Lu-PSMA-617= lutetium-177 Lu-prostate-specific membrane antigen-617. HR=hazard ratio. PSA=prostate-specific antigen.

In conclusion, to our knowledge, UpFrontPSMA is the first randomised study in patients with high-volume metastatic hormone-sensitive prostate cancer to show benefit from the addition of [^{177}Lu]Lu-PSMA-617 to standard-of-care treatment. These data suggest that [^{177}Lu]Lu-PSMA-617 could potentially have a role in the therapeutic management of metastatic hormone-sensitive prostate cancer.

Annals of Oncology

Enzalutamide plus radium-223 in metastatic castration-resistant prostate cancer: results of the EORTC 1333/PEACE-3 trial

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Background: The EORTC 1333 'PEACE-3' study investigated the combination of enzalutamide and 6 monthly injections of radium-223 (Ra223) in patients with metastatic castration-resistant prostate cancer (mCRPC) and bone metastases.
Materials and methods: From November 2015 to March 2023, 446 patients, including 11 who received abiraterone, were randomized to enzalutamide (without placebo) or enzalutamide combined with six cycles of Ra223. As of March 2018, the co-administration of zoledronic acid or denosumab was mandatory. The primary endpoint was radiological progression-free survival (rPFS) by investigator assessment. Key secondary endpoints included overall survival (OS), time to subsequent systemic treatment, pain progression, and symptomatic skeletal event.

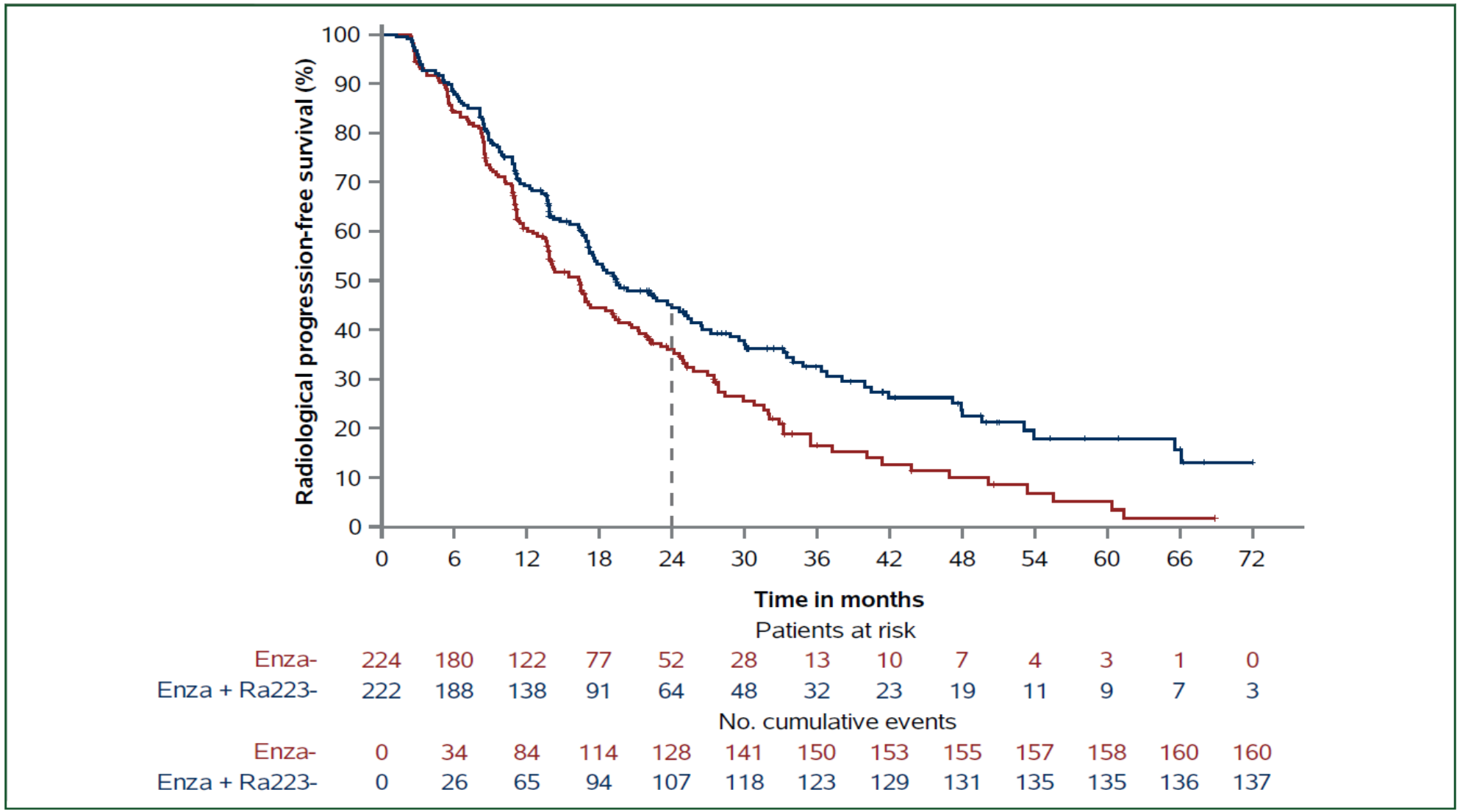

Figure 1. Radiological progression-free survival was assessed by the local investigator in the ITT population. The hazard ratio (HR) and 95% confidence interval (95% CI) for all patients are based on a Cox model stratified by baseline pain score, prior docetaxel, and bone-protecting agent use at randomization.
Enza, enzalutamide; ITT, intent-to-treat; Ra223, radium-223.

CONCLUSIONS

- There are no strict guidelines for the use of radium 223 and Lu-177 PSMA in metastatic prostate cancer.
- The use of radium 223 has declined in favor of Lu-177. The new PEACE-3 trial demonstrates the continued applicability of radium 223, especially in bone predominate disease.
- Lu-177 is still primarily used for castrate resistant disease after failure of first line triplet or doublet therapy.
- Lu-177 is being moved earlier in time for metastatic disease treatment. Maturation of clinical trials will determine its use in castrate sensitive disease