PSMA THERAPIE: LITERATUUR, ERVARING EN TOEKOMST

Sui wai Ling, MD, PhD kandidaat

Afdeling Radiologie & Nucleaire Geneeskunde

Erasmus MC

INHOUD

- Introductie
- PSMA: werking en toepassing
- ^{177}Lu-PSMA: Literatuur
- ^{177}Lu-PSMA: Eigen ervaring
- ^{225}Ac-PSMA: Literatuur
- ^{225}Ac-PSMA: Eigen ervaring
- Toekomst PSMA therapie
- Conclusie
- Dankwoord

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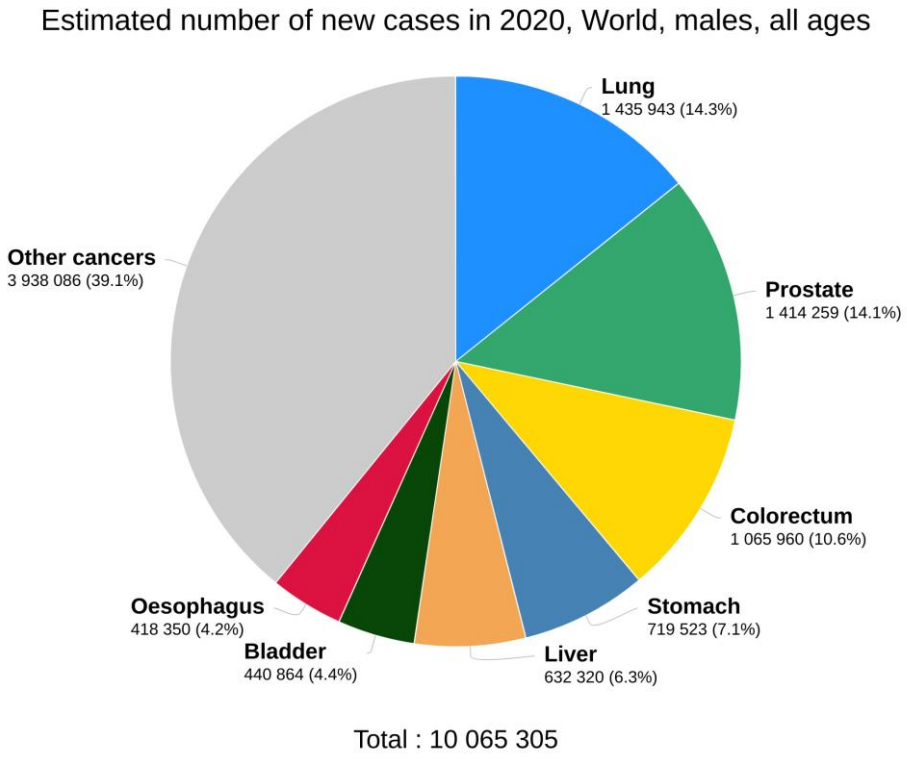
INTRODUCTIE

Prostaatkanker wereldwijd

- Meest voorkomende type kanker in mannen
- Incidentie van 1.414.259 patiënten per jaar (2020)
- Mortaliteit van 375.304 patiënten per jaar (2020)



https://gco.iarc.fr/

PSMA: WERKING EN TOEPASSING

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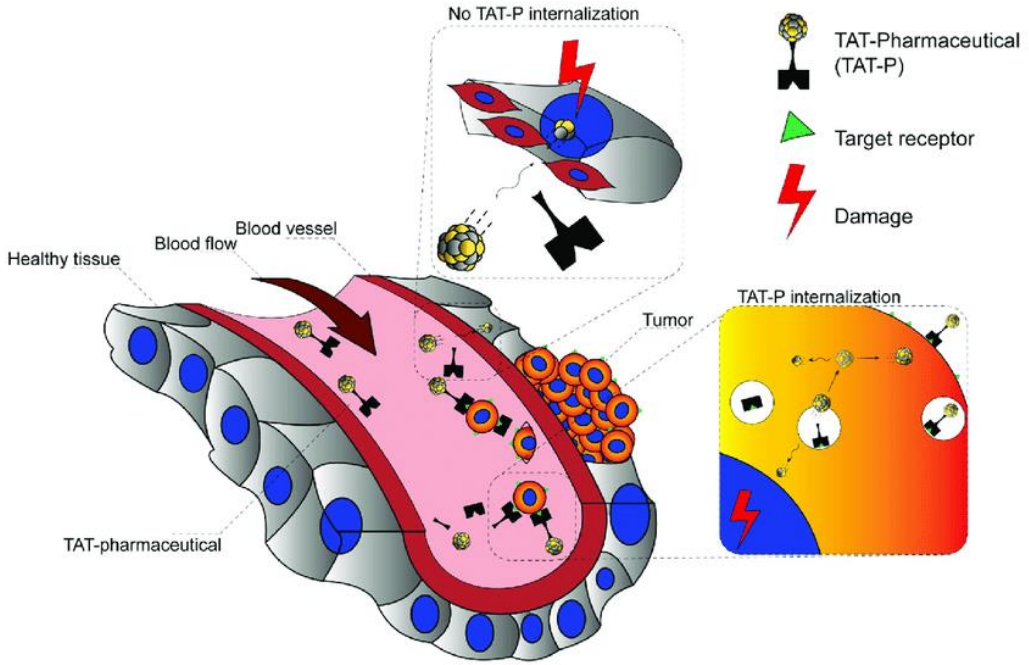
PROSTAAT SPECIFIEK MEMBRAAN ANTIGEN

- Transmembraan glycoproteine (Glutamaat Carboxypeptidase type II)
- Ook expression: speekselklieren en nieren

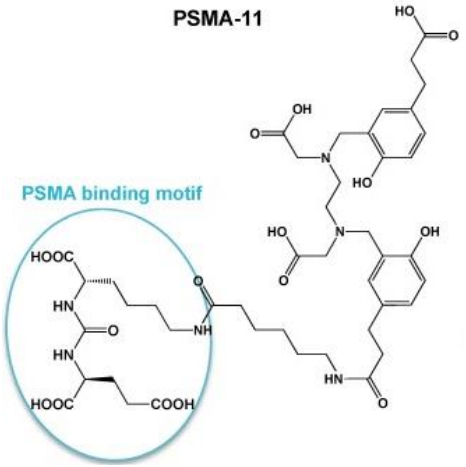


Ruigrok EAM, et al. Pharmaceutics. 2019 Oct 29;11(11):560.

TOEPASSING PSMA

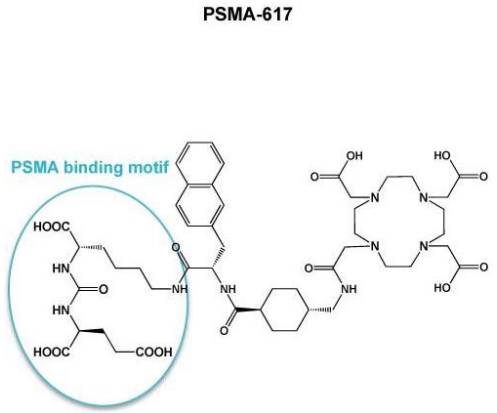
Imaging

- PSMA-11

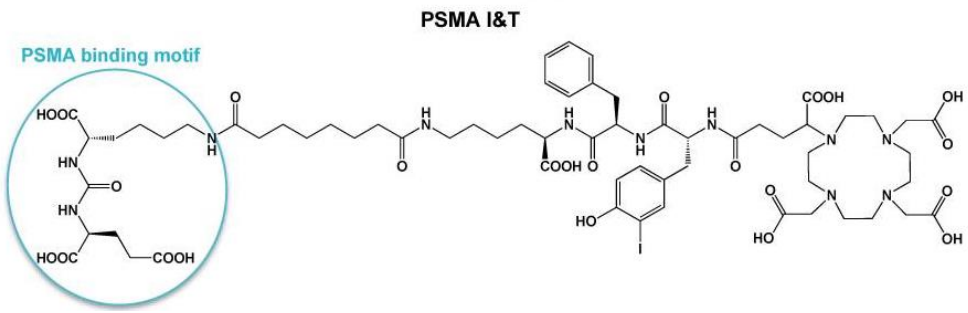


Therapy

- PSMA-617



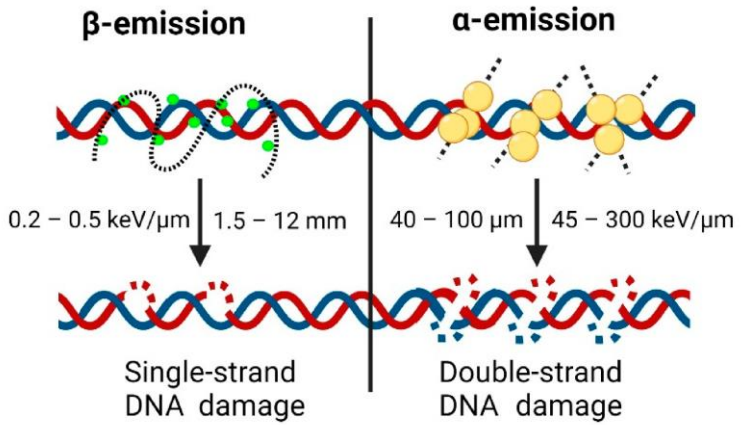
- PSMA I&T



Chatalic KL, et al Theranostics. 2016 Apr 12;6(6):849-61 (all images)

BETA VS ALFA STRALING

- Lutetium-177
  - Beta-straler
  - Beta partikels
  - 490 KeV
  - Range 0.7 – 2.1 millimeters
  - $T_{1/2}$ van 6.7 dagen
- Actinium-225
  - Alfa-straler
  - 4 alfa partikels
  - 5.8 – 8.4 MeV
  - Range 47 – 85 micrometers
  - $T_{1/2}$ van 9.9 dagen



El Fakiri, M., et al. (2021). *Cancers*, *13*(16), 3967.

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^{177}LU-PSMA: LITERATUUR

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^{177}LU-PSMA

Literatuur

Table 1. Summary of 177Lu-PSMA studies.

Author	N	Number of Cycles	Injected Activity (GBq)	PSA Response (%)	Radiological Response (%)	PFS and/or rPFS(mo)	OS and/or rOS (mo)
Heck et al. (2016) [6]	19	40 (total in study)	7.3 per cycle	≥30% in 10/19 (53) ≥50% in 6/19 (32) ≥90% in 2/19 (11)	NR	4.1 (PFS)	12.9 (OS)
Kesavan et al. (2018) [8]	20	Median 4 per patient	5.5 per cycle	≥50% in 8/20 (40)	NR	NR	NR
Heck et al. (2019) [9]	100	319 (total in study)	7.4 per cycle	≥30% in 47/100 (47) ≥50% in 38/100 (38) ≥90% in 11/100 (11)	NR	NR	NR
Barber et al. (2019) [10]	131	Median 3 per patient	6.3 per cycle	Any in 25/62 T-pretreated (40) Any in 40/70 T-naïve (57)	NR	6 in T-pretreated (rPFS) 8.8 in T-naïve (rPFS)	10.7 in T-pretreated (OS) 27.1 in T-naïve (OS)
Von Eyben et al. (2019) [11]	45	Median 3 per patient	Cumulative median 14.5	>50% in 36/45 (80) >90% in 25/45 (56)	NR	16 (PFS) 18 (rPFS)	NR
Suman et al. (2019) [12]	40	Median 3 per patient	4.4–5.5 per cycle	CR (>50%) in 17/40 (43) PR (30–50%) in 2/40 (5) SD (<30%) in 2/40 (5) PD (any increase) in 19/40 (48)	CR in 2/40 (5) PR in 5/40 (13) SD in 9/40 (23) PD in 21/40 (53)	NR	NR
Gallyamov (2020) [13]	110	327 (total in study)	6.34 per cycle (mean)	>50% in 60/110 (55) <50% or failure in 38/110 (35)	NR	NR	NR
Bulbul et al. (2020) [14]	45	164 (total in study)	7.4 per cycle	≥50% in 15/45 (33) ≥25% in 20/45 (44)	NR	7.4	17.1 (OS)
Hofman (2021) [15]	89	Median 5 per patient	6–8.5 per cycle	>50% in 66%	NR	5.1	NR
Sartor (2021) [16]	831	Maximum 6 per patient	7.4 per cycle	≥50% in 177/385 (46) ≥80% in 127/385 (33)	CR in 17/184 (9) PR in 77/184 (42)	8.7 (rPFS)	15.3 (OS)
Rosar (2022) [42]	66	2 per patient	7.1 per cycle (mean)	PR in 34/66 (51.5) SD in 20/66 (30.3) PD in 12/66 (18.2)	PR in 40/66 (60.6) SD in 19/66 (28.7) PD in 7/66 (10.6)	NR	18 (OS)

GBq = gigabecquerel. PSA = prostate-specific antigen. N = number of patients. PFS = progression-free survival (both clinical and radiological). rPFS = radiographic PFS. OS = overall survival. Mo = months. NR = not reported. CR = complete remission. PR = partial remission. SD = stable disease. PD = progression disease. T-pretreated = taxane chemotherapy-pretreated. T-naïve = Taxane-naïve.

Ling, S. W., et al (2022). *Pharmaceutics*, *14*(10), 2166.

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^{177}LU-PSMA

Literatuur

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*

ABSTRACT

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

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†*

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^{177}LU-PSMA

Literatuur

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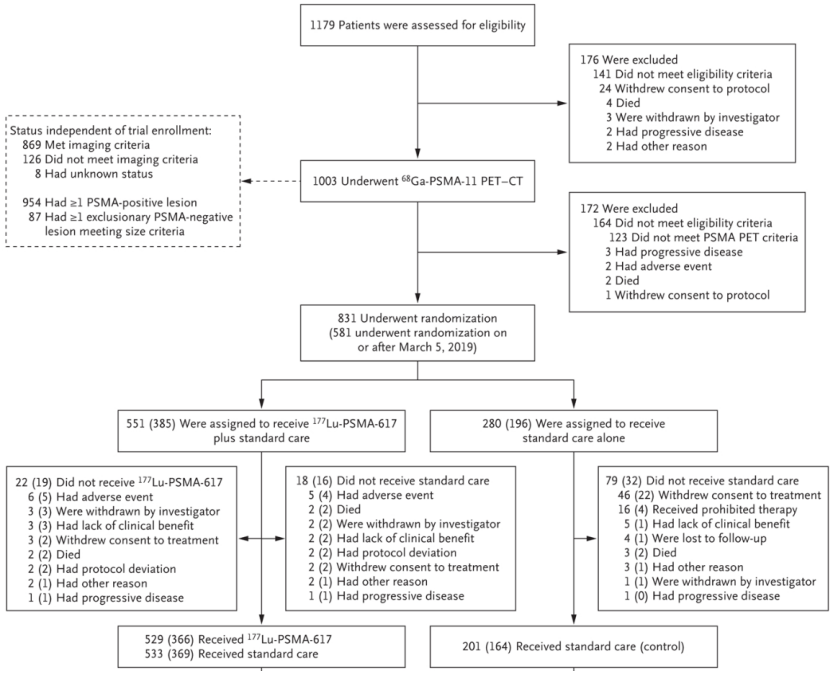
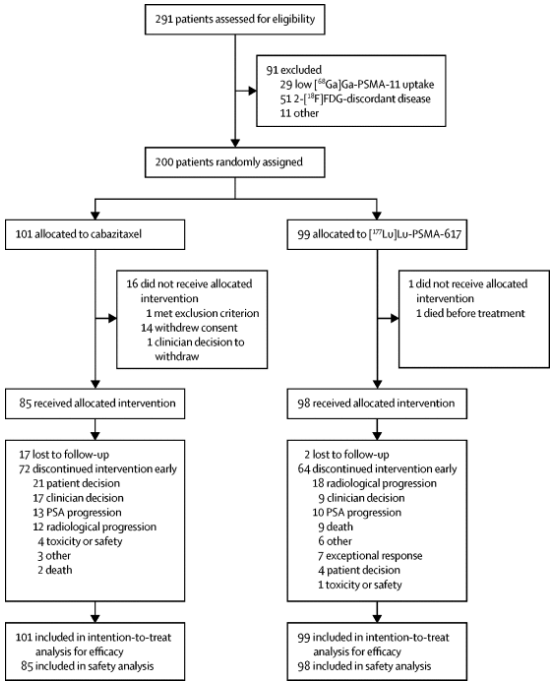


TheraP



Sartor, O., et al (2021). *The New England journal of medicine*, *385*(12), 1091–1103 (left image). Hofman, M. S., et al (2021 *Lancet (London, England)*, *397*(10276), 797–804 (right image)

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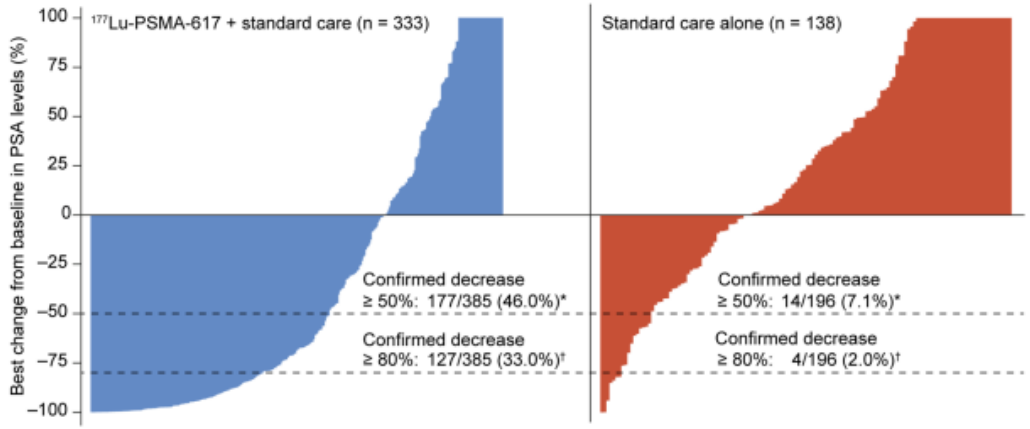
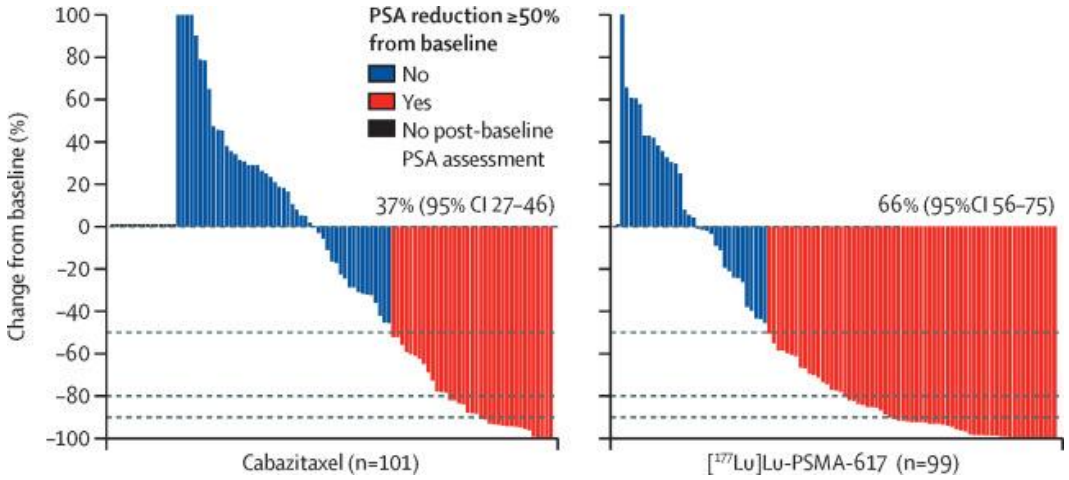


TheraP



Sartor, O., et al (2021). *The New England journal of medicine*, *385*(12), 1091–1103 (left image). Hofman, M. S., et al (2021 *Lancet (London, England)*, *397*(10276), 797–804 (right image)

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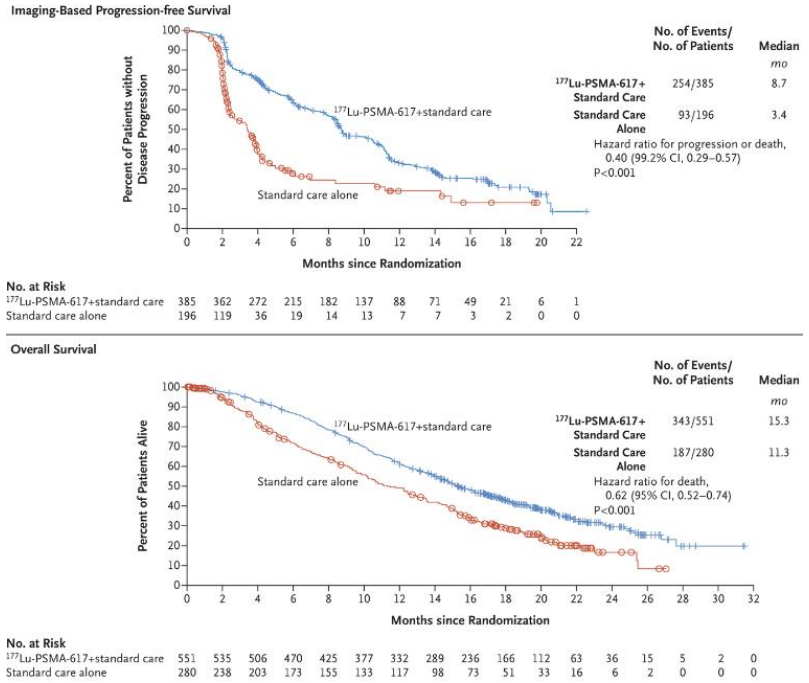
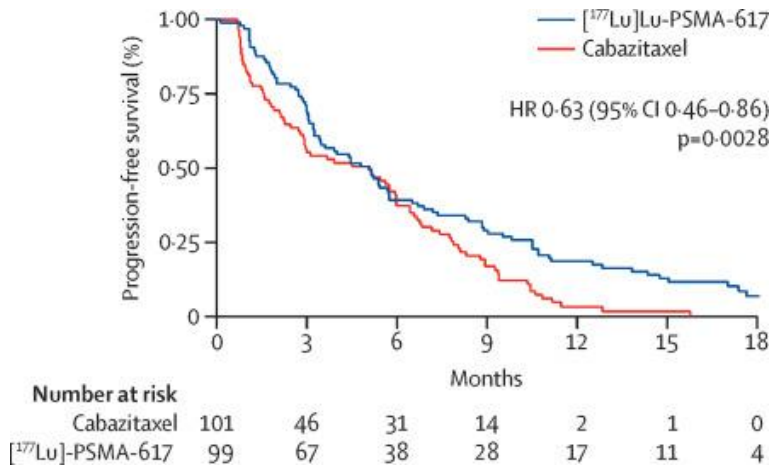


TheraP



Sartor, O., et al (2021). *The New England journal of medicine*, *385*(12), 1091–1103 (left image). Hofman, M. S., et al (2021 *Lancet (London, England)*, *397*(10276), 797–804 (right image)

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^{177}LU-PSMA

Literatuur

VISION

Adverse Events.*

Event	^{177}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 ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ^{177}Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ^{177}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)

TheraP

	[^{177}Lu]Lu-PSMA-617 (n=98)		Cabazitaxel (n=85)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Fatigue	69 (70%)	5 (5%)	61 (72%)	3 (4%)
Pain*	60 (61%)	11 (11%)	52 (61%)	4 (5%)
Dry mouth	59 (60%)	0	18 (21%)	0
Diarrhoea	18 (18%)	1 (1%)	44 (52%)	4 (5%)
Nausea	39 (40%)	1 (1%)	29 (34%)	0
Thrombocytopenia	18 (18%)	11 (11%)	4 (5%)	0
Dry eyes	29 (30%)	0	3 (4%)	0
Anaemia	19 (19%)	8 (8%)	11 (13%)	7 (8%)
Neuropathy†	10 (10%)	0	22 (26%)	1 (1%)
Dysgeusia	12 (12%)	0	23 (27%)	0
Haematuria	3 (3%)	1 (1%)	12 (14%)	5 (6%)
Neutropenia‡	7 (7%)	4 (4%)	4 (5%)	11 (13%)
Insomnia	9 (9%)	0	12 (14%)	1 (1%)
Vomiting	12 (12%)	1 (1%)	10 (12%)	2 (2%)
Dizziness	4 (4%)	0	11 (13%)	0
Leukopenia	10 (10%)	1 (1%)	5 (6%)	1 (1%)
Any adverse event	53 (54%)	32 (33%)	34 (40%)	45 (53%)

Data are n (%). Events that occurred in at least 10% of participants are shown. ^{177}Lu=Lutetium-177. PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Febrile neutropenia.

Table 2: **Adverse events**

Sartor, O., et al (2021). *The New England journal of medicine*, *385*(12), 1091–1103 (left image). Hofman, M. S., et al (2021 *Lancet (London, England)*, *397*(10276), 797–804 (right image)

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GOEDKEURING

- FDA goedkeuring sinds 23 maart 2022 voor ^{177}Lu-PSMA-617 in USA

- cieBOM goedkeuring sinds juni 2023 voor ^{177}Lu-PSMA-617
  - In afwachting voor de vergoeding zijn we gestart met ^{177}Lu-PSMA I&T

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^{177}LU-PSMA: EIGEN ERVARING

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^{177}LU-PSMA

Ervaring in het Erasmus MC

- Sinds februari 2022 gestart met ^{177}Lu-PSMA I&T
- Setting: gemetastaseerd castratie-resistent prostaatcarcinoom

- Huidige stand van zaken:
  - 48 patiënten
  - 106 cycli ^{177}Lu-PSMA I&T (max 4 cycli per patiënt)

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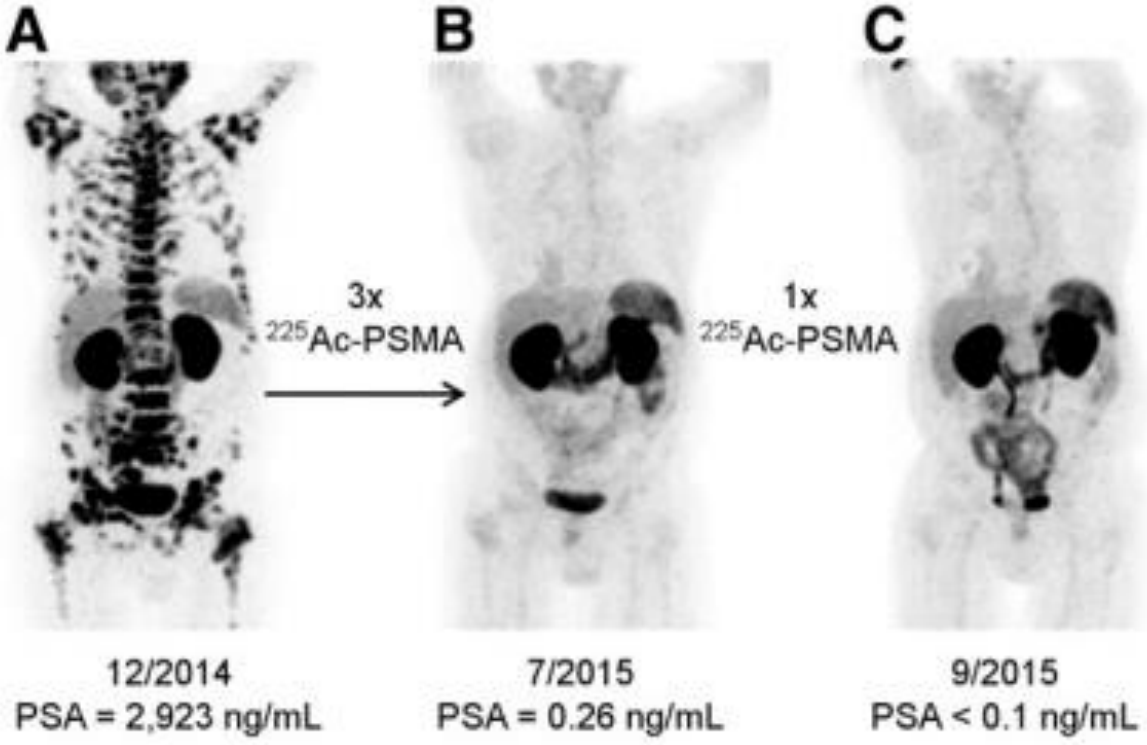
^{225}AC-PSMA: LITERATUUR

Erasmus MC

^{225}AC-PSMA

Literatuur

- Goede resultaten in kleine groepen patiënten
- Nieuwe optie:
  - Betere prognose
  - Verbeteren van kwaliteit van leven
- Geen fase 1 dosisescalatie studie



Kratochwil C et al. J Nucl Med. 2016 Dec;57(12):1941-1944.

Erasmus MC

^{225}AC-PSMA

Literatuur

Table 3. Summary of ^{225}Ac-PSMA studies.

Author	N	Number of Cycles	Injected Activity (MBq)	PSA Response	Radiological Response	Median PFS (mo)	Median OS (mo)
Kratochwil (2017) [18]	14	NR	50, 100, 150 or 200 kBq/kg	NR	NR	6	>12
Kratochwil (2018) [19]	40	3–5 per patient	100 kBq/kg per cycle	Any in 33/38 (87) >50% in 24/38 (63)	NR	NR	NR
Sathekge et al. (2019) [20]	17	59 (total in study)	7.4 per cycle	≥90% in 14/17 (82)	>50% in 15/17 (88)	NR	NR
Sathekge et al. (2020) [21]	73	210 (total in study)	8 (first cycle) 7, 6 or 4 (subsequent cycles)	Any in 60/73 (82) ≥50% in 51/73 (70)	NR	15.2	18
Zacherl et al. (2020) [22]	14	34 (total in study)	7.8 per cycle (mean)	Any in 11/14 (79) >50% in 7/14 (50)	NR	NR	NR
Yadav et al. (2020) [23]	28	85 (total in study)	100 kBq/kg per cycle	Any in 22/28 (79) >50% in 11/28 (39)	CR in 2/22 (9) PR in 10/22 (45) SD in 2/22 (9)	12	17
Feuerecker et al. (2021) [24]	26	61 (total in study)	9 per cycle (mean)	Any in 23/26 (88) ≥50% in 17/26 (65)	NR	4.1	7.7
Van der Doelen (2020) [25]	13	3 per patient (median)	8 (first cycle) 6 (subsequent cycles)	≥50% in 9/13 (69) ≥90% in 6/13 (46)	NR	NR	8.5
Satapathy et al. (2020) [26]	11	25 (total in study)	100 kBq/kg per cycle	≥50% in 5/11 (45)	NR	NR	NR
Sanli et al. (2021) [27]	12	25 (total in study)	7.4 per cycle (median)	After first cycle: Any in 9/12 (75) >50% in 6/12 (50) >85% in 5/12 (42)	CR in 4/10 (40) PR in 5/10 (50)	4	10

MBq = megabecquerel. kBq = kilobecquerel. PSA = prostate-specific antigen. N = number of patients. PFS= median progression-free survival. rPFS = radiographic PFS. OS = median overall survival. mo = months. NR = not reported. CR = complete remission. PR = partial remission. SD = stable disease.

Ling, S. W., et al (2022). *Pharmaceutics*, *14*(10), 2166.

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0.5 MM DURA - FLEX
8
Erasmus MC

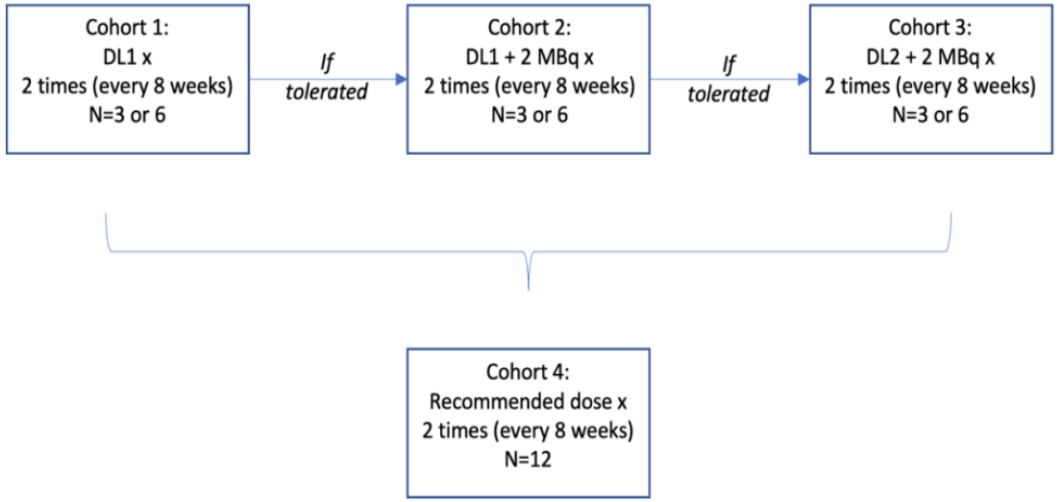
^{225}AC-PSMA

Ervaring in het Erasmus MC

- Sinds april 2022 gestart met ^{225}Ac-PSMA I&T (Fase 1 studie)
  - 3+3 design met maximaal 4 cohorten
  - 1 DLT = expanderen cohort
  - 2 DLTs = stop dosisescalatie
  - Maximaal 30 patiënten

- Setting: gemetastaseerd castratie-resistent prostaatcarcinoom

- Huidige stand van zaken:
  - 9 patiënten (dosisescalatie cohorten)
  - 17 cycli ^{225}Ac-PSMA I&T (max 2 cycli per patiënt)



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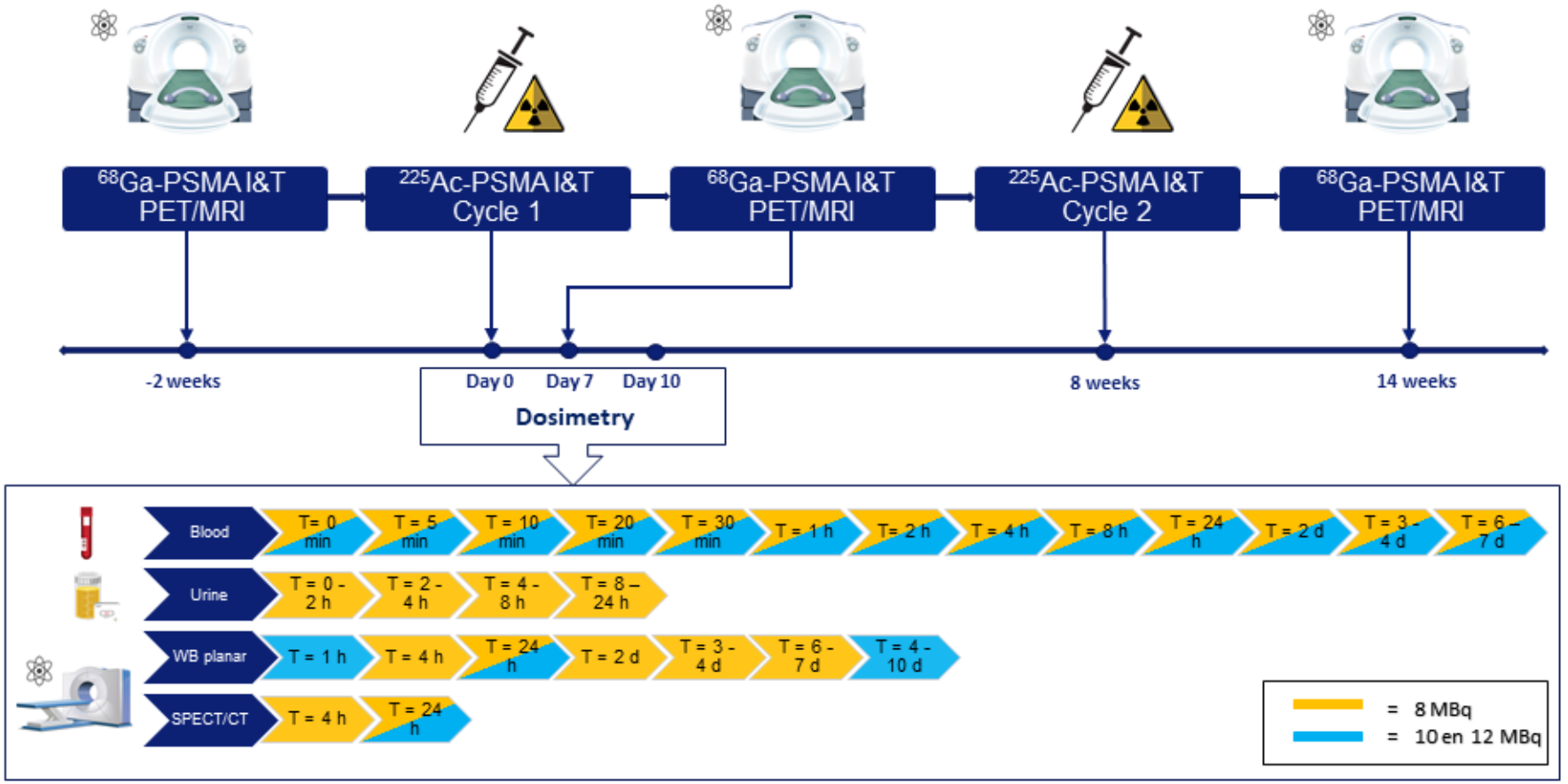
^{225}AC-PSMA

Studie design



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TOEKOMST PSMA THERAPIE

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PSMA THERAPIE

Toekomst

- Vraag naar lutetium-177 stijgt
  - ^{177}Lu-DOTATATE voor NETs
  - ^{177}Lu-PSMA voor prostaatcarcinoom (sinds goedkeuring FDA)

- Productie van lutetium-177
  - Twee manieren
  - Allebei via neutronen irradiatie

- Toekomst
  - Productie verhogen door meer high flux neutronen reactors
  - Alternatief voor lutetium-177 > terbium-161

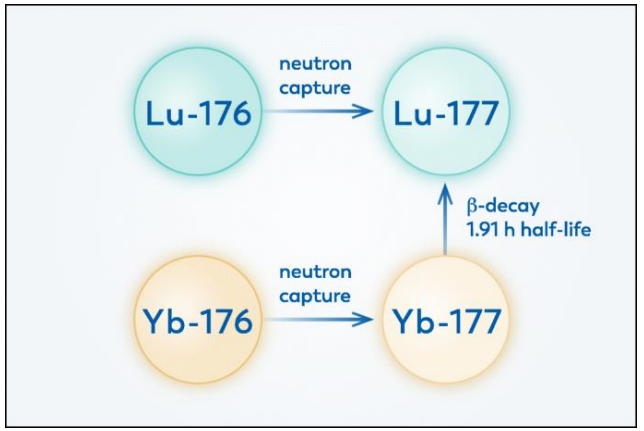

Table 1 Decay properties of ^{161}Tb and ^{177}Lu [3]

Radionuclide	^{161}Tb	^{177}Lu
Half-life	6.9 d	6.7 d
$E\beta^-_{av}$ (intensity)	154 keV (1.00)	134 keV (1.00)
Eγ (intensity)	25.7 keV (0.23)	112.9 keV (0.062)
	45 (0.18)*	208.4 keV (0.104)
	48.9 keV (0.17)	
	74.6 keV (0.10)	
E of Auger and conversion electrons (intensity)	0–0.1 keV (0.72)	0–0.1 keV (0.27)
	0.1–1 keV (7.38)	0.1–1 keV (0.55)
	1–10 keV (3.03)	1–10 keV (0.30)
	10–20 keV (0.42)	
	20–30 keV (0.18)	
	30–40 keV (0.39)	
	30–40 keV (0.72)	
	40–50 keV (0.23)	40–50 keV (0.05)
	0–50 keV (12.4)	0–50 keV (1.11)

*x-ray

Vogel, W. V., et al (2021). *European journal of nuclear medicine and molecular imaging*, *48*(8), 2329–2335 (upper image). Haller, S., et al. (2016). *EJNMMI research*, *6*(1), 13 (lower image).

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PSMA THERAPIE

Toekomst

- Actinium-225 schaars
  - Productie wereldwijd door 3 centra:
    - Institute for Transuranium Elements (Karlsruhe, Duitsland)
    - Oak Ridge National Laboratory (Oak Ridge, USA)
    - Institute of Physics and Power Engeneering (Obninsk, Rusland)

- Productie van actinium-225
  - Thorium-229 “koe” > elke 2 maanden

- Toekomst
  - Alternatieve productie routes[a]
    - Thorium-232 proton irradiatie > co-productie actinium-227 (half-life 21.7 jaar)
    - Radium-226 proton irradiatie > co-productie radon-222 gasvorming (half-life 3.82 dag)
  - Alternatieve radionuclides[a]
    - “Hopeful eight” > astatine-211, bismuth-213, terbium-149, thorium-227, lead-212

[a]Eychenne R, et al. Pharmaceutics. 2021 Jun 18;13(6):906

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CONCLUSIE

- PSMA therapie is veelbelovend

- ^{177}Lu-PSMA wereldwijd klinische toepassing
  - Patiënten kunnen verwezen worden naar het Erasmus MC

- ^{225}Ac-PSMA in studieverband
  - in 2024 gaat de studie weer open in het Erasmus MC

- Vraag groter dan aanbod
  - Nieuwe productiemethoden en alternatieve radionucliden voor ^{177}Lu-PSMA en ^{225}Ac-PSMA in ontwikkeling

Erasmus MC

DANKWOORD

ALLE PATIËNTEN DIE DEELGENOMEN HEBBEN!

Erasmus MC
Universitair Medisch Centrum Rotterdam

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