

Theranostics

Are we Ready ?

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Radioligand therapy works !

PRRT

Neuroendocrine tumors

N Engl J Med 2017

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ¹⁷⁷Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, E. Krenning, and for the NETTER-1 Trial Investigators*

The authors' full names, academic degrees, and affiliations are listed in the Appendix

PRLT

Prostate cancer

N Engl J Med 2021

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

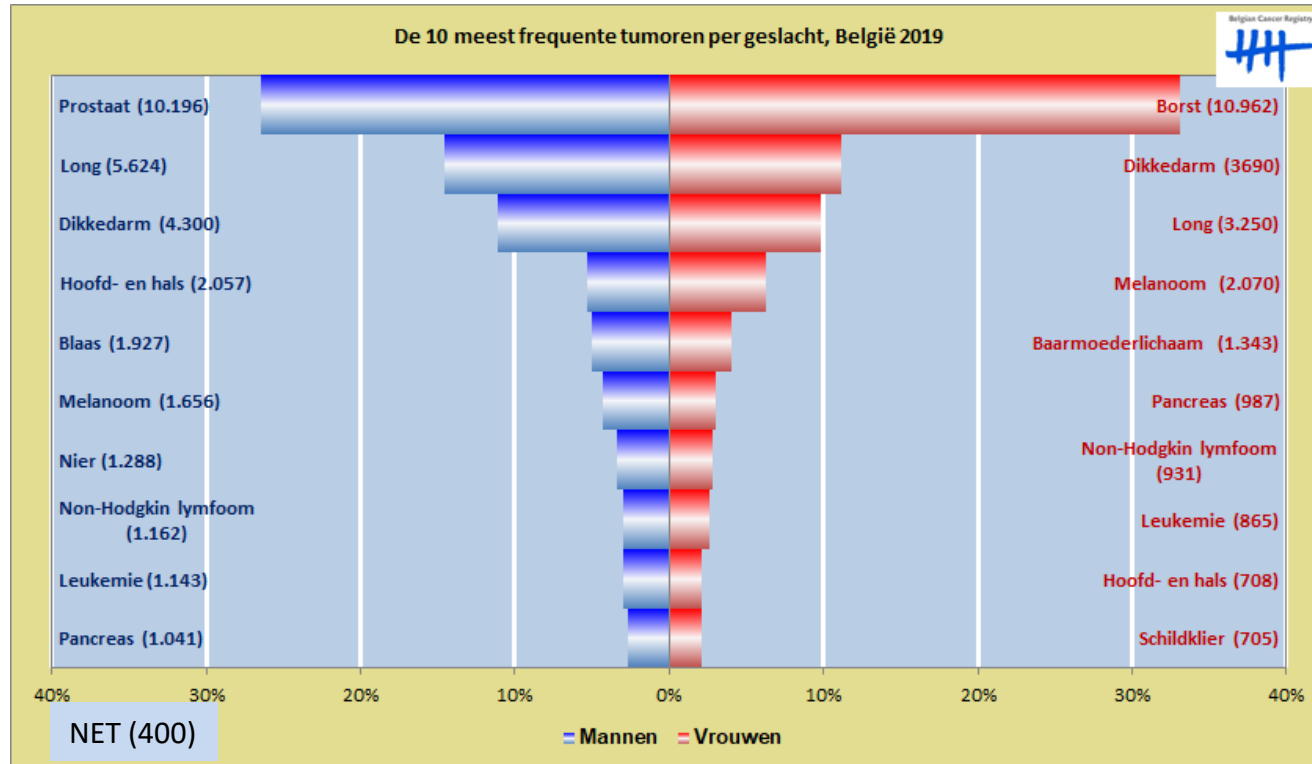
Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

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*

“one of the major accomplishments in the history of nuclear medicine”

Johannes Czernin

Tsunami alert



Cancer Registry Foundation:

Prostate Cancer : In 2017 : **1500 patients** died from prostate cancer

Challenges Radioligand Therapy (RLT)

- ♦ **Logistics**
- ♦ **Workload**
- ♦ **Financial aspects**
- ♦ **RLT supply chain**
- ♦ **Improving knowledge**

Additional Number of Patients & Treatments

◆ Prostate Cancer :

- ◆ Estimation : 50% of 1500 pts dying from M+ prostate ca
→ **750 patients / year**
 - ◆ (Mean nb of cycles administered VISION trial : n = 5)

◆ Neuroendocrine tumors

- ◆ Estimation :
→ **80 patients / year**
 - ◆ (Mean nb of cycles administered Netter-1 trial : n = 3,7)

Total : **4050 cycles / year**

Current status of Nuclear Medicine Therapy

Riziv/INAMI data obtained Nov 2021

	Geboekte gevallen				
AMB_HOS	2016	2017	2018	2019	2020
442013 - 442024	4.283	4.331	4.521	3.698	3.561

	Geboekte uitgaven				
AMB_HOS	2016	2017	2018	2019	2020
442013 - 442024	1.003.341,73	1.021.932,88	1.081.192,00	886.484,22	862.710,20

Voor 2019 betreft dit
Ambulant: 2911 gevallen
Gehospitaliseerd : 787 gevallen



+ Additional 4050 cycles / year

Dedicated Hospitalization Rooms

Data from FANC october 2021

- ♦ Actual nb of hospitals with non-ambulant therapy : $n = 34$
- ♦ Actual nb of registered metabolic rooms : $n = 66$
- ♦ Actual nb of hospitals equipped with retention tank(s): $n = 21$

Simulation (total need : $4050 + 787 = 4837$ treatments)

- ♦ Additional need for hospitalization rooms
 - ♦ Maximal capacity : Per room : max 3 treatments / week
→ 156 therapies / year → 21 extra rooms needed
 - ♦ Realistic mean capacity : Per room : 2 treatments / week
→ 104 therapies / year → 32 extra rooms needed

Max
capacity:
 $42 * 2 * 52 =$
4370
treatments

URGENT need for increasing hospitalization capacity

- > optimization of use of current rooms (hosp network)
- > construction of new rooms (> large cancer centers)
- > elegant way of waste collection (filter toilets)
- > (one day hospitalization ?)

Therapeutic Nuclear Medicine Workload

THE WORKFLOW

- Consultation : intake (45 minutes for intake)
- (Planning of) pre-RLT work up (need for care coordinators)
- Multidisciplinary Tumor Board (preparing + active participation)
- Hospitalization + treatment administration
- Post-therapy SPECT imaging : acquisition + reporting + dosimetry
- Management of radiation risks (room preparation and cleaning)
- Follow-up consultation (4-6 wks)
- Managing toxicity (BM-reserve) and disease related issues (e.g. pain)
- Communications / reporting with referring colleagues

➔ **Workload +++** for nuclear medicine department
(Physician / Physicist / Pharmacist / Techs / RPO)

➔ Need for additional staff

Nuclear Medicine Workforce

Number of Nuclear Medicine physicians in Belgium

België	NUCLEAIRE GENEESKUNDE	353	123	230
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Number of Nuclear Medicine physicians as planned till 2027 (FOD Public Health)

SPECIALITEIT	VL. Gem.	FR. Gem.	Totaal		VL. Gem.	FR. Gem.	Totaal		
Huisartsen	400	300	700	Medische onco.	7	7	14		
Psychiatrie (3)	36	27	63	Anesthesie-rea	50	35	85		
Acute en Urgentie	43	38	81	Plastische heelk.	5	3	8		
Geriatric	25	15	40	Neurochirurgie	4	3	7		
Reumatologie	11	9	20	Stomato	6	3	9		
Klinische biologie	12	8	20	Orthopedie	15	10	25		
Path. anatomie	9	6	15	Urologie	10	5	15		
Oftalmologie	22	14	36	Nucleaire	6	5	11		
ORL	12	8	20	Neurologie	24	15	39		
Dermato-venerologie	9	9	18	Gynaeco-verlosk.	19	15	34		
Inwendige geneesk.	45	35	80	Pediatrie	20	15	35		
Cardiologie	12	8	20	Radiotherapie	3	2	5		
Gastro-enterologie	15	8	23	Radiologie	15	10	25		
Pneumologie	10	6	16	Heelkunde	20	15	35		
Fysische geneesk. - revalidatie	11	7	18	FEDERAAL QUOTA KB 14/08/2021	876 977	905 107%	641 505	612 82,5%	1517 1482

Financial Issues

◆ Investments

- ◆ Additional staff needed
 - ◆ Nuc Med Physician / Medical Physics / Radiopharmacy
 - ◆ Technologists (coordination / drug administration)
- ◆ Infrastructure
 - ◆ Dedicated isolation rooms and waste management
 - ◆ Radiopharmacy (> magistral preparations)

◆ Reimbursement

- ◆ Radiopharmaceutical
- ◆ Honorarium

Availability and Reimbursement of RLT drugs

◆ **Pharmaceutic Industry**

- ◆ EMA approval + marketing authorization
- ◆ Reimbursement : ongoing negotiations at INAMI level

◆ **In house magistral preparation**

- ◆ No marketing authorization
- ◆ High logistic demands and investments
- ◆ Hospital specific reimbursement
 - ◆ available for PRRT and PRLT
 - ◆ Local use
 - + Hospital pharmacy outsourcing

FAGG

FANC

TRRI

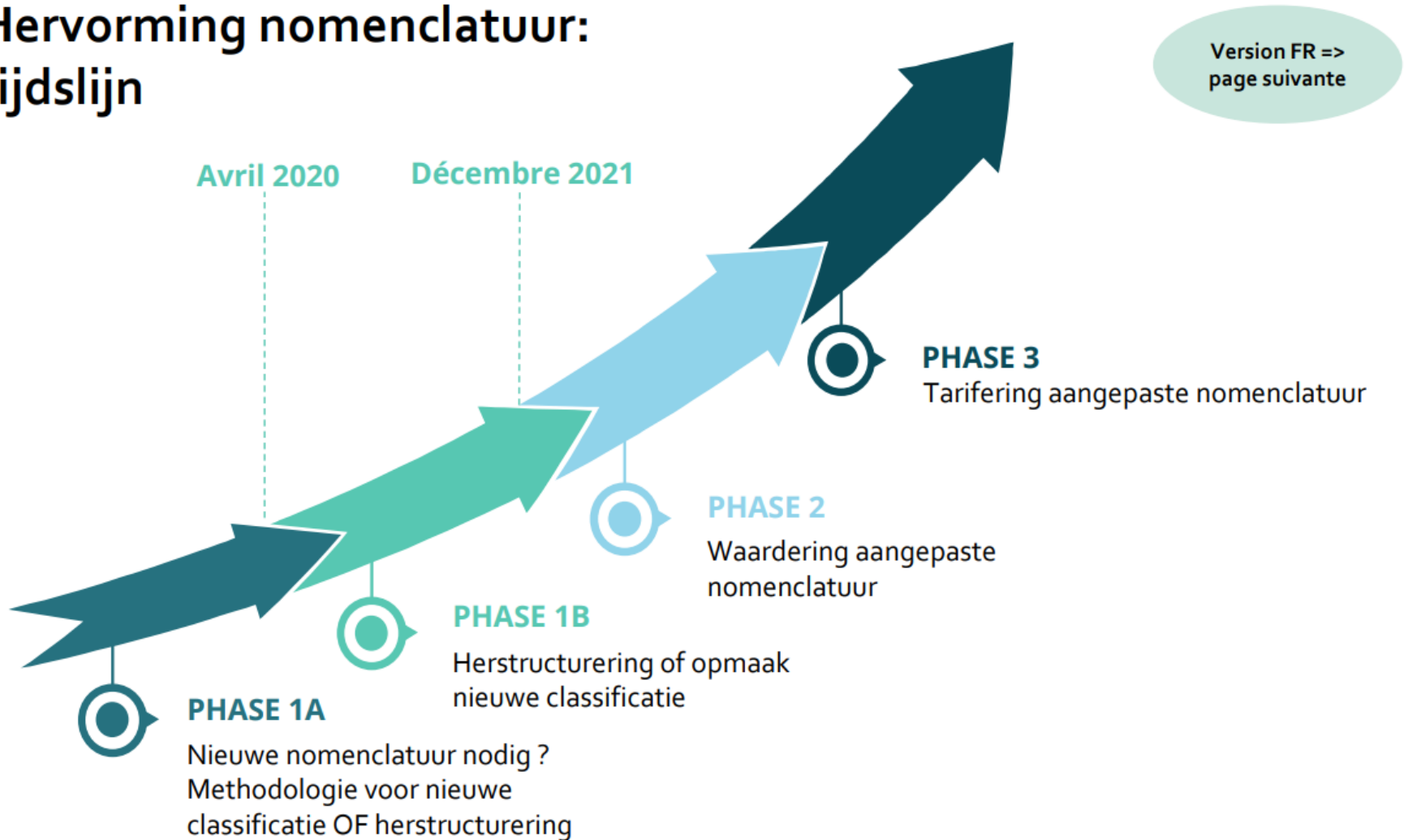
Honorarium for Nuclear Medicine Physician

- ◆ Consultation 25 Euro (X2)
- ◆ Hospitalization 0 Euro (BMF)
 - ◆ no honorarium supplements allowed
- ◆ CMO/MOC 0 Euro
- ◆ Drug administration 240 Euro
 - ◆ 442013 - 442023 (N330)
 - ◆ Valid for 3 months !!!

Deficit spending :
spending exceeds revenue

Revision of the Nomenclature

Hervorming nomenclatuur: tijdslijn



Revision of Nomenclature

Proposal of Nuc Med community

Le code suivant est à subdiviser :

442013 - 442024: Inspuiting(en) of absorptie(s) geldig voor drie maanden

Option 2 : subdivision en 8 catégories

	MEEST SIMPEL					MEEST COMPLEX			
	1	2	3	4	5	6	7	8	
Activiteitsprescriptie	Standaard	Standaard	Standaard	Standaard	Complexe IA berekening	Standaard	Standaard of complex	Standaard of complex	
Toedieningsroute	Oraal	Inj. vat, gewricht of tumor	Inj. vat, gewricht of tumor	Oraal	Inj. vat, gewricht of tumor	Inj. vat, gewricht of tumor	Inj. vat, gewricht of tumor	Inj. vat, gewricht of tumor	
Verblijf RINT kamer	Nee	Nee	Nee	Ja	Nee	Ja	Ja	Ja	
Collectie excreta	Nee	Nee	Ja	Ja	Nee	Ja	Ja	Ja	
Dosistempometing post-therapie	Nee	Nee	Ja	Ja	Nee	Ja	Ja	Ja	
Beeldvorming post-therapie	Nee	Nee	Ja	Ja	Ja	Ja - min 3 WB	Ja - min 3 punten - min 1 SPECT/CT	Ja - min 3 punten - min 1 SPECT/CT	
Staalname post-therapie	Nee	Nee	Nee	Nee	Nee	Optioneel	Nee	Ja	
Dosimetrie	Nee	Nee	Nee	Nee	a - min doelwit en non-doelwit	Ja - min WB dosis	Ja - min één doelwit en één non-doelwit	a - min beenmerg, één doelwit en één non-doelwit (= BM)	
Voorbeeld	Na131I - Benigne	Xofigo	Samarium-EDTMP	Na131I - SKCa	SIRT (90Y-166Ho)	MIBG veritas - 1e inj	Lutetium zonder bloedstaal	Lutetium met bloedstaal	
Prestaties volgens huidige nomenclatuur	442013	442013	442013	442013	442013	442013	442013	442013	
	IV infuus nummer?		442455	442514	442971	3 X 442455	1 tot 3X 442396	1 tot 3X 442396	
				442536	442536		1 tot 3X 442536	1 tot 3X 442536	
					2 x 444393	444393	0 tot 2x 442455	0 tot 2x 442455	
							444393	442212	
								444393	

NUC MED + MOBIUS



RIZIV / INAMI negotiation
(upcoming)

Supply Chain of Lutathera

AAA contacts the reactor to fix orders for target in the reactor (2-3 weeks prior to use)

Irradiation of target in the nuclear reactors takes place (Lu-177) (6 days)

Production and shipment of precursor isotope (Lu-177Cl3) in Baarle-Nassau site (1 day)

Lu-177 is received by AAA RLT site in Ivrea, Forli or Zaragoza (1 day shipment)

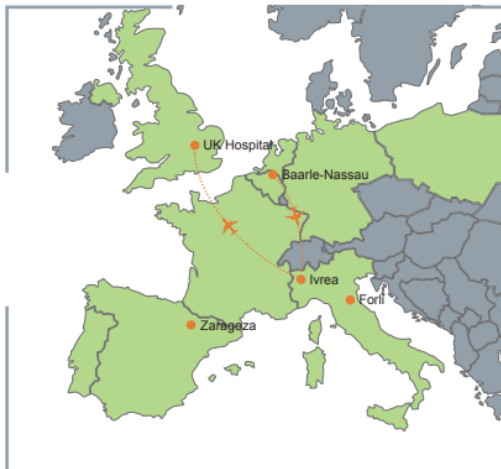
Time of injection (48-72 hours after end of production)

WEEK 1

WEEK 2

Each dose is manufactured specifically for a single patient and their injection time. The process is repeated every 8 weeks for 4 cycles, per patient.

▼ The distance Lutathera travels: from isotope manufacturing to patient



Lutathera production takes place (produce up to 72 hours before injection as starts the clock)

Lutathera is shipped from AAA site to hospital in Benelux (via air or road, up to 24 hours)

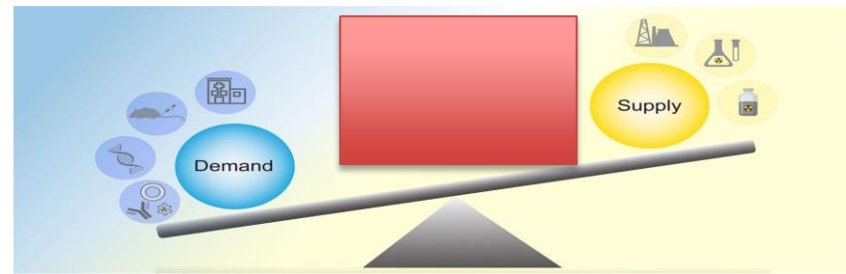
AAA Production Sites

¹⁷⁷Lu Production: 1 site in Baarle-Nassau (Netherlands)

Lutathera/RLT Production: 4 sites in Ivrea (Italy), Forli (Italy), Zaragoza (Spain) and Millburn (US).

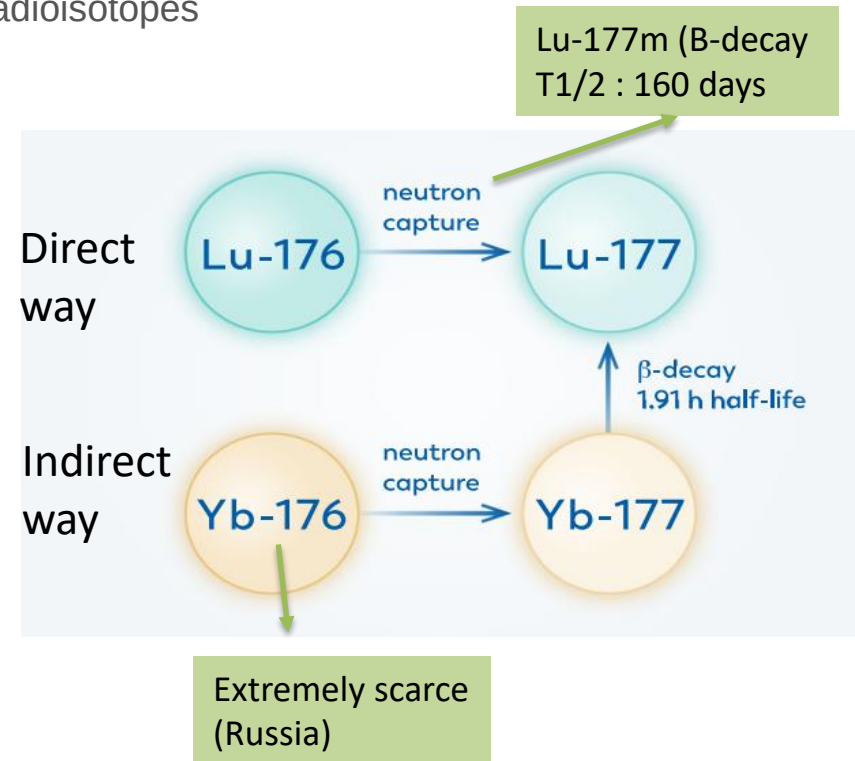
The 3 European sites are dual PET and RLT production facilities

Lu177- supply Chain



- ◆ Remember 2008-2010 :
 - 2 reactors (Canada / Petten) out of order → shortage medical isotopes
 - European Observatory on the supply of medical radioisotopes
- ◆ 2 methods for producing Lu177, both needing high neutron flux reactors
- ◆ 10 high neutron flux reactors world wide
 - BR2 (Belgium), → MYRRHA (partnership SCK + IBA)
 - FRM-II (Germany),
 - HFR (Petten; Netherlands), → PALLAS
 - IVV-2 M (Russia),
 - LVR-15 (Czech Republic),
 - Maria (Poland),
 - MURR (USA),
 - OPAL (Australia),
 - Safari (South Africa),
 - SM-3 (Russia).
 - → Jules Horowitz reactor (France)

> 40 yrs old

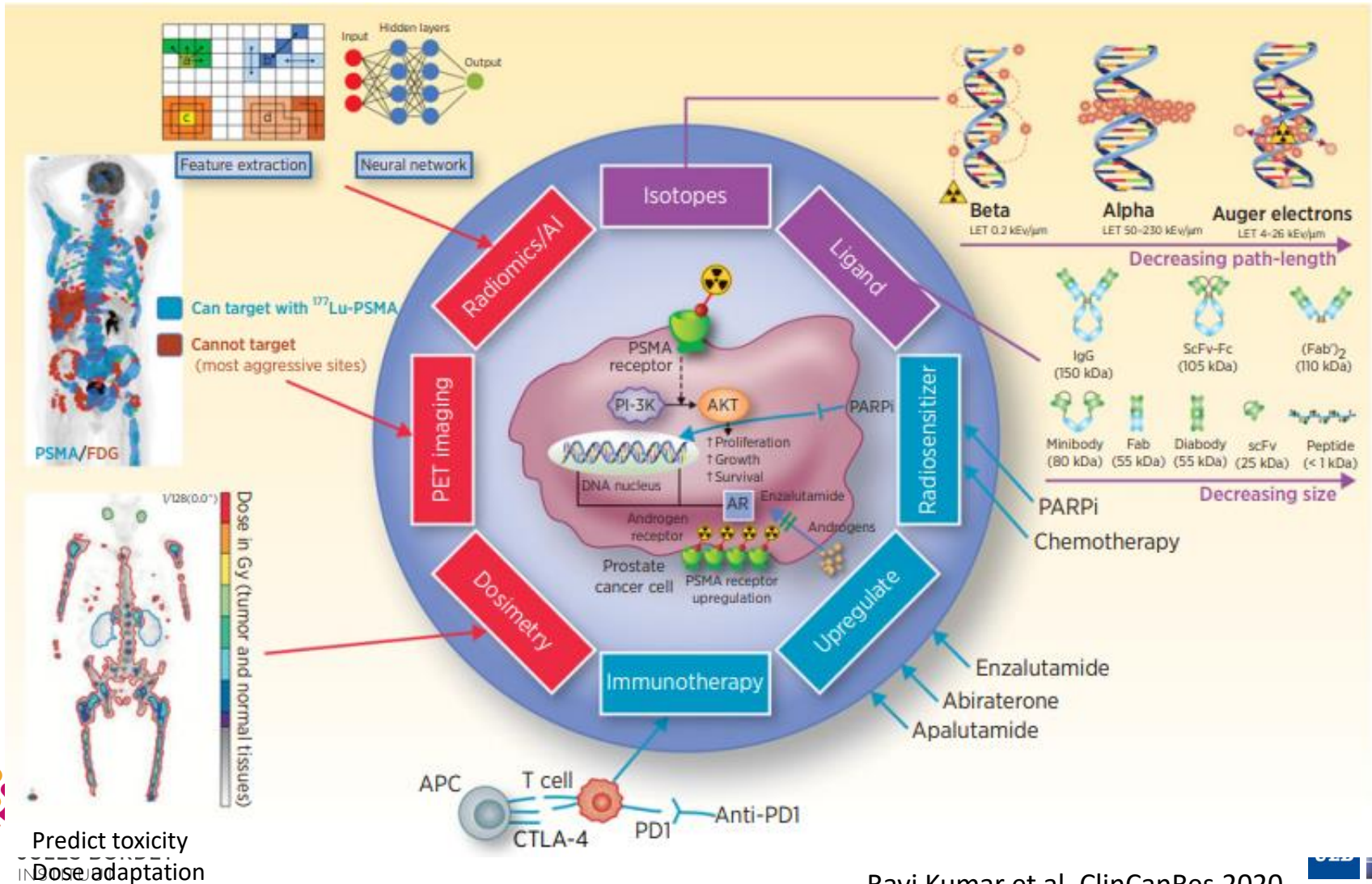


Radioligand Therapy is there to grow

- ◆ New indications of existing RLT
 - ◆ Earlier in the disease progress
 - ◆ Other tumors expressing the SSR or PSMA
- ◆ New targets for RLT
 - ◆ FAP / CCKR / neurotensin receptor
- ◆ New isotopes
 - ◆ Alpha emitters
- ◆ Optimization of current RLT
 - ◆ Combination with other drugs
 - ◆ Radiobiology

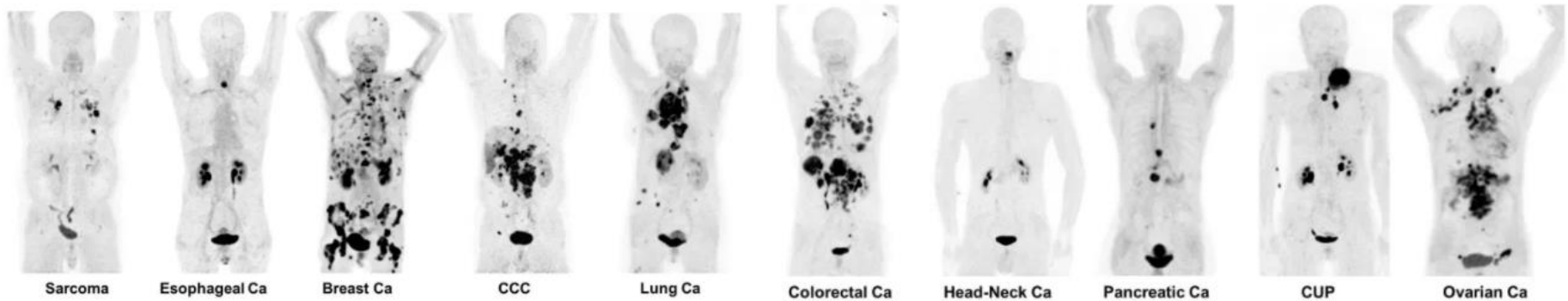
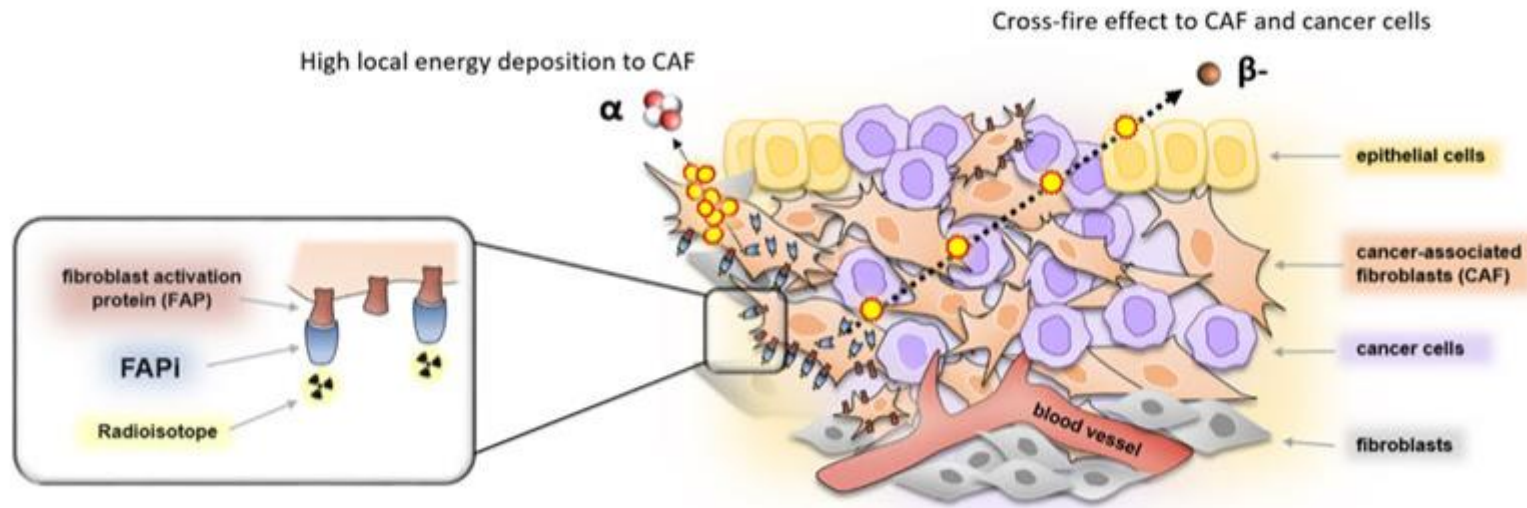
Research perspectives

Optimizing and personalizing PSMA radioligand therapy



NEW RADIOTRACER CAN IDENTIFY NEARLY 30 TYPES OF CANCER

68GA-FAPI PET/CT



Lack of Knowledge of RLT



European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:1588–1590

<https://doi.org/10.1007/s00259-019-04334-3>

LETTER TO THE EDITOR



Call to arms: need for radiobiology in molecular radionuclide therapy

Samantha Y. A. Terry¹  • Julie Nonnekens^{2,3} • An Aerts⁴ • Sarah Baatout⁴ • Marion de Jong² • Bart Cornelissen⁵ • Jean-Pierre Pouget^{6,7,8,9}

Received: 4 April 2019 / Accepted: 10 April 2019 / Published online: 8 May 2019

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Radiobiology of RLT: Call to arms

- ◆ No simple extrapolation of knowledge from EBRT
- ◆ Investigating the consequences of **physical parameters**
- ◆ Determine role of radiopharmaceutical and target distribution
- ◆ Determine the role of **tumour microenvironment** and systemic reactions
- ◆ Identify **predictive biomarkers** of therapy response
- ◆ Determine optimal **combination therapies**
- ◆ Determine effects of RLT on healthy tissues

European collaborative groups involved in RLT

- ♦ European Association of Nuclear Medicine
 - ♦ Committee: Oncology and Theranostics
 - ➔ Guidelines / promotion / education
- ♦ European Working Group on the Radiobiology of Molecular Radiotherapy (°2021)
 - ➔ Increase knowledge of RLT Radiobiology
- ♦ European Neuroendocrine Tumor Society (ENETS)
 - ➔ Accreditation of Centers of Excellence
- ♦ RLT is presently not covered by the existing cooperative cancer networks (e.g. OECI / EORTC / Oncodistinct)

Need and Opportunity for : Belgian/European RLT trial Network

- ♦ Analogy : Australasian Radiopharmaceutical Trials Network
- ♦ A network of nuclear medicine sites in Belgium/Europe with validated capabilities for molecular imaging and therapy using radiopharmaceuticals.
- ♦ Multidisciplinary consortium : bringing together medical specialists, radiopharmaceutical and radiation physics experts + experts in trial set up and conduct (legal / financial / regulatory ...)



To promote and facilitate innovative collaborative clinical trials

ProPSMA diagnostic phase 3 randomised study

Prostate Specific Membrane Antigen (PSMA) PET/CT

for imaging men with newly diagnosed prostate cancer



302 patients *randomised*
with untreated
prostate cancer



10 sites across
Australia



current method:
CT + Bone scan



studied method:
PSMA PET/CT

The data supports PSMA PET/CT imaging as a replacement to current standard-of-care CT and bone scan.

1

A small radioactive molecule is injected into a vein. It finds its way to cancer cells and binds with them.



2

The patient then goes into a PET (Positron Emission Tomography) scanner that images the whole body and shows cancerous cells.

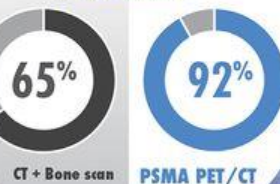


3

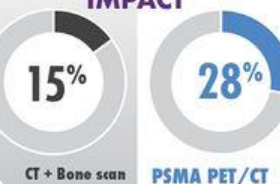
Patients were then followed for 6 months to determine accuracy.



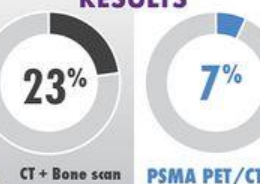
**SUPERIOR
ACCURACY**



**GREATER
TREATMENT
IMPACT**



**FEWER
UNCERTAIN
RESULTS**



**OTHER
FINDINGS:**



**LESS
EXPOSURE TO
RADIATION**



**HIGH
REPORTER
AGREEMENT**



**NO ADVERSE
EFFECTS SEEN**

Research
sponsored
by:

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

and
proudly
funded by:

MOVEMBER
FOUNDATION

**Prostate Cancer
Foundation
of Australia**

Conclusion

- ◆ Coming years will see a dramatic increase of therapeutic acts in Nuclear Medicine
- ◆ Challenges
 - ◆ Education / Ressources / Regulations / Financials
 - ◆ Increasing knowledge → R&D → RLT network
- ◆ Joining the forces within our Nuc Med community

- ◆ Call for your participation in the
Therapy Workgroup BELNUC



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Thank you



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