

European Commission H2020 INFRAIA call- MEDICIS-ProMed EANM perspective

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Innsbruck, Austria**

Erice, April 30th 2019



— THE —
EANM

an introduction

The logo for the European Association of Nuclear Medicine (EANM) is displayed on a blue background. It features the acronym "EANM" in white, with a registered trademark symbol, enclosed in a stylized oval. Below the acronym, the full name "European Association of Nuclear Medicine" is written in a smaller font. To the right of the logo, on an orange background, is the tagline "BIOMEDICAL IMAGING AND THERAPY FOR PERSONALIZED HEALTHCARE" in white, uppercase letters.

About the European Association of Nuclear Medicine (EANM)

- Medical **non-profit association** incorporated in Austria
- Aim: improving public health and promoting science and education in the field of nuclear medicine
- Core business: **Science, education, standardisation and quality control**
- Governance structure:
 - EANM Board (7 members)
 - 15 EANM Committees (approx. 150 volunteer experts)
 - Additional work groups and task forces on demand
 - EANM Executive Office in Vienna

ESMIT

European School of Multimodality
Imaging and Therapy

**RESEARCH
4LIFE[®]**

an EANM initiative

About the EANM Community

- Approx. **3,000 members**, including
 - Nuclear medicine physicians
 - Physicists
 - Technologists
 - Scientists etc.
- Annual Congress: > 6,000 participants – **largest NM conference world wide**
- More than 9,000 member state members
- Serving a community of more than 16,000 specialists

EANM Committees

Bone & Joint	Chair: F. Paycha (France)
Cardiovascular	Chair: H. Verberne (Netherlands)
Dosimetry	Chair: M. Konijnenberg (Netherlands)
Drug Development	Chair: J. Vercouillie (France)
Ethics	Chair: W.H. Knapp (Germany)
Inflammation & Infection	Chair: A. Glaudemans (Netherlands)
Neuroimaging	Chair: I. Law (Denmark)
Oncology & Theranostics	Chair: K. Herrmann (Germany)
Paediatrics	Chair: Z. Bar-Server (Israel)
Physics	Chair: C. Hindorf (Sweden)
Radiation Protection	Chair: S. Holm (Denmark)
Radiopharmacy	Chair: M. Patt (Germany)
Technologist	Chair: A. Santos (Portugal)
Thyroid	Chair: M. Luster (Germany)
Translational Molecular Imaging & Therapy	Chair: F. Van Leeuwen (Netherlands)

EANM Activities

- **Education, Training and Research**

- Annual Congress (EANM'19 in Barcelona/Spain, October 12-16, 2019)
The World Leading Meeting in the field with more than 6,200 participants
- European School of Multimodality Imaging & Therapy (ESMIT)
3-level high quality training, focusing on multimodality
- EANM Research Ltd („EARL“) e.g. FDG-PET/CT Accreditation programme
earl.eanm.org

- **Publications:**

- Guidelines & Position Papers
- EANM Paediatric Dosage Card, Dosage Calculator & PedDose App
- EANM Technologist's Guide Book
- EANM Press Releases

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EANM'19

WORLD LEADING MEETING



Barcelona, Spain

Annual Congress of the
European Association of Nuclear Medicine

October 12 – 16, 2019
Barcelona, Spain

eanm19.eanm.org

The 3-level system



eLearning (basic)
no limits, full
education
eLearning.eanm.org



School Meetings (intermediate)
compressed learning,
unique experience



High End Courses (advanced)
summit of CME

High End Courses 2019

Vienna/AT



Level
3

- » **Brain Tumours** (March 7-8)
- » **Bone SPECT/CT in Complications of Skeletal Metalwork** (April 4-5)
- » **Quantification in SPECT and PET (Oncology)** (June 6-7)

EARL Activities: FDG PET/CT Accreditation

EARL initiated this accreditation programme in order to support imaging sites, which perform FDG-PET/CT oncology examinations, in meeting the requirements indicated in the EANM imaging guideline.

- aims at providing a minimum standard for the acquisition and interpretation of PET and PET/CT scans with [18F]-fluorodeoxyglucose (FDG).
- goal is to enhance the quality standard of PET/CT investigations for both daily use and for multicentre studies
- PET/CT accreditation ensures similar performance of PET/CT systems within a multicentre setting by harmonising acquisition and processing of PET/CT scans.
- Accredited PET/CT centres of excellence can compare, exchange and combine FDG-PET/CT findings, including SUV values, since data are collected and processed in a standardised manner.



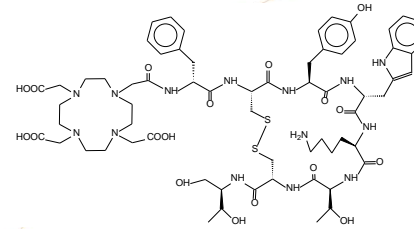
EANM Activities

- **Networking & Public Affairs:**
 - representing the community's interests towards the EU, national and international societies, non-governmental institutions, legislative bodies etc.
 - covering topics such as: radiopharmaceutical legislation, radiation protection, harmonization of education and competencies
 - providing a platform for exchange for the EANM's member societies
 - fostering relationships with the „sister“ societies as well as partner associations in related disciplines through joint publications and other projects

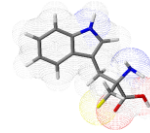
- **Collaboration with Springer on the EJNMMI Journal Family:**
 - EJNMMI (European Journal of Nuclear Medicine & Molecular Imaging)
 - EJNMMI Physics
 - EJMMI Radiopharmacy and Chemistry
 - EJNMMI Research
 - European Journal of Hybrid Imaging – The EJNMMI Multimodality Journal (since 2017)

(Novel) Applications in Therapy / Theranostics

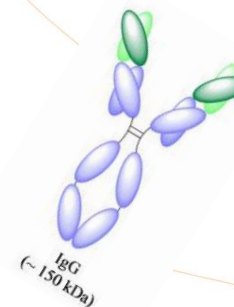
Peptides (STSR)



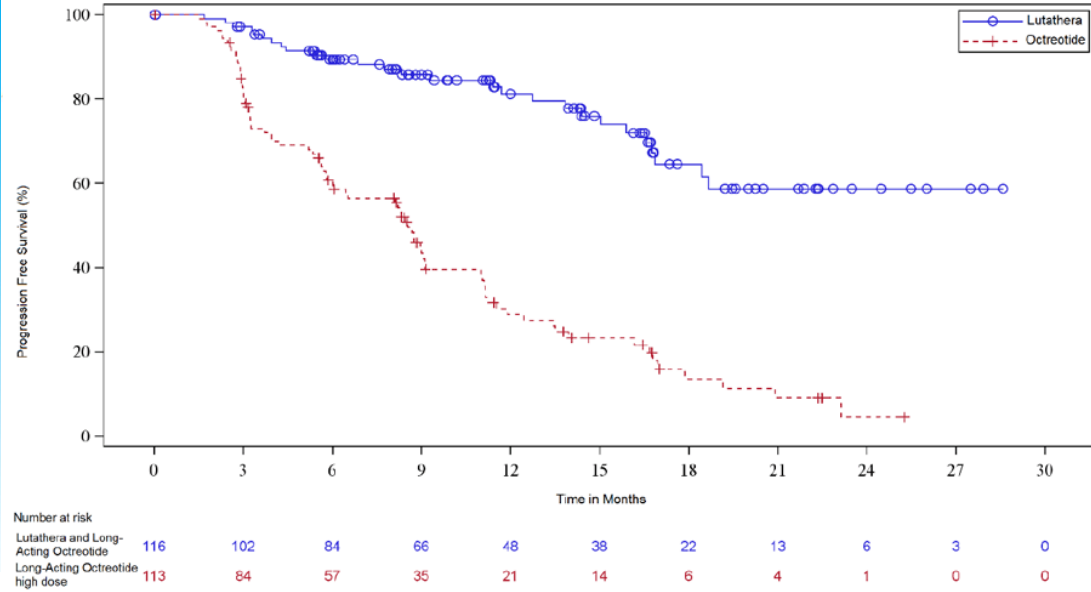
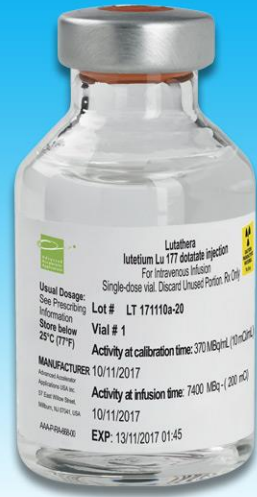
Small molecules



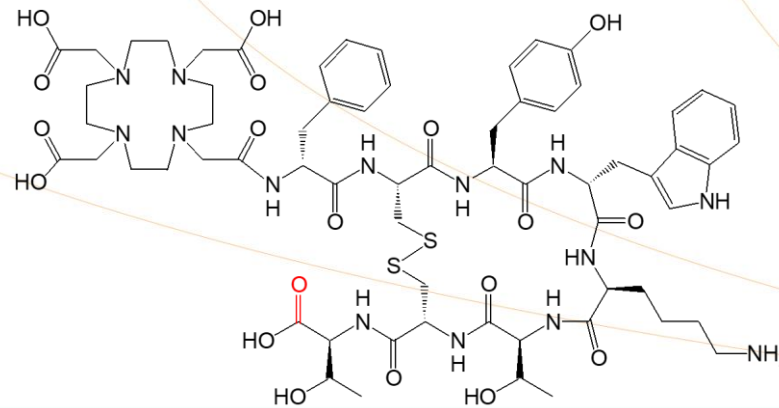
Proteins



Somatostatin Analogues – Marketing Authorization



¹⁷⁷Lu-DOTATATE (Oxodotretotide)



Thr[®]

DOTATATE



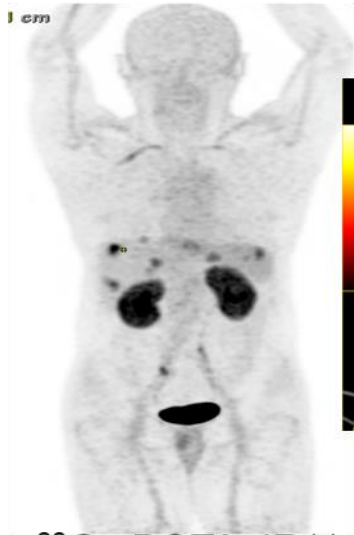
BIOMEDICAL
IMAGING AND
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somatostatin antagonists ^{68}Ga -OPS201 and ^{177}Lu -OPS201

Diagnostic phase



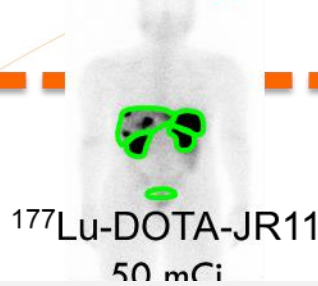
G2 Gastric NET, previous surgery, TAE and SSA



^{68}Ga -DOTA-JR11
60 min p.i. (MIP)

Therapeutic phase

Dosimetry



Cycle 1



^{177}Lu -DOTA-JR11
Activity / cycle dosimetry

Cycle 2



Follow-up



- 20 heavily pretreated pts: 8 completed 2 cycles, 12 had 1 cycle
- After only 1 cycle, evaluable pts had (RECIST 1.1):
 - PR in 7/19 (37%), SD in 9/19 (47%), PD in 3/19 (16%)
- Prolonged but reversible G3/4 toxicity in 4/8 (50%) treated with 2 cycles
- Favorable response justifies continuation

Complete response!

^{68}Ga -DOTA-JR11
fused transaxial image

Contrast CT, arterial phase

Contrast CT, arterial phase

Peptides for Molecular Imaging in Oncology

Peptide

Target

Application

Somatostatin

sst1-sst5, sst2

Neuroendocrine Tumors

Gastrin, CCK

CCK2

Medullary Thyroid Carcinoma
Small Cell Lung Cancer, GEP-NET *

Neurotensin

NTS1, *nts2, nts3*

Ewing Sarcoma
Exocrine Pancreatic Tumors

Substance P

NK-1, Neurokinin-1

Astrocytomas, Glioblastomas

Bombesin (BB1-3)

NMB, Neuromedin-B,
GRP, Gastrin rel. Peptide R
BB3

Ileal Carcinoids
Prostate Cancer, Breast Cancer
Bronchial Carcinoids, Glucagonomas

MCR (MC1R)

melanocortin receptor

Melanoma

Neuropeptide Y

Y1-Y6

Breast Cancer, Brain

GLP-1

glucagon like peptide R

Insulinoma

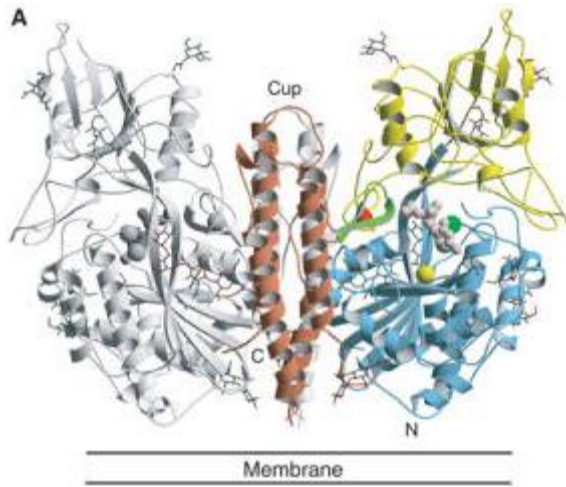
RGD

$\alpha_v\beta_3$ Integrin

Angiogenesis

G-protein coupled receptors

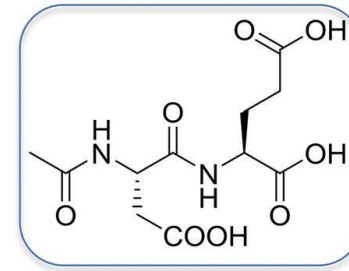
PSMA-Targeting



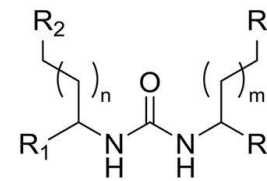
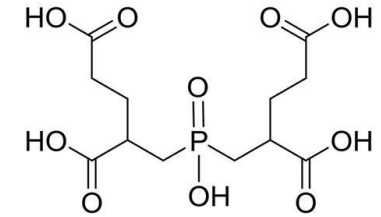
Mesters JR et al. EMBO J 2006; 25: 1375-1384.

N-acetyl-L-aspartyl-L-glutamate (NAAG)
Folate-Polyglutamate

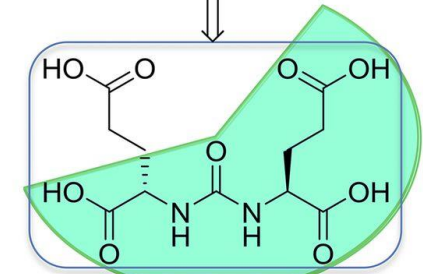
N-acetyl-L-aspartate + L-glutamate
Poly-glutamate + Folate



NAAG



$R^1/R^2 = \text{COOH, SH, SBu}^t; m, n = 0, 1$



Glu-C(O)-Glu

DUPA, $K_i = 8 \text{ nM}$

Glu-ureido-based PSMA inhibitor

exemplifying rational design of urea-based glutamate carboxypeptidase II inhibitors. Klaus Kopka et al. J Nucl Med 2017;58:17S-26S

RADIOPHARMACEUTICAL OF THE YEAR

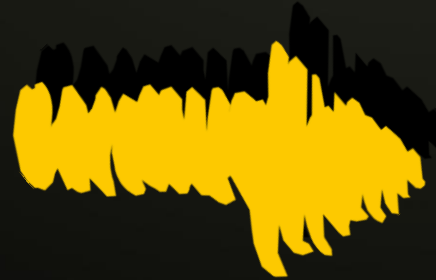
²²⁵Actinium-PSMA-617

CRPC

DIFFUSE BONE
DISEASE

ALREADY TREATED
WITH EVERYTHING

PSA > 400



CRPC

AFTER 1 CYCLE

PSA = 3



Development of quinoline based theranostic ligands for the targeting of fibroblast activation protein (FAP)

- Targeting non-malignant tumour stroma (up to 90% of tumour volume)
- Cancer associated fibroblasts express fibroblast activating protein (glycoprotein, peptidase) in epithelial tumours

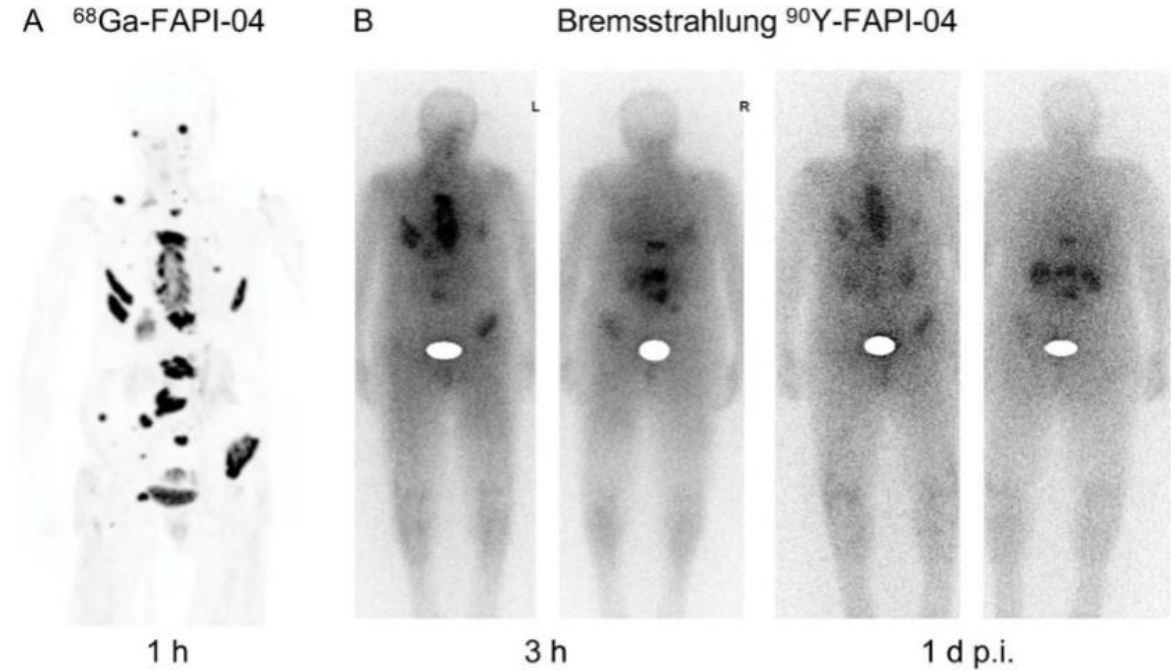
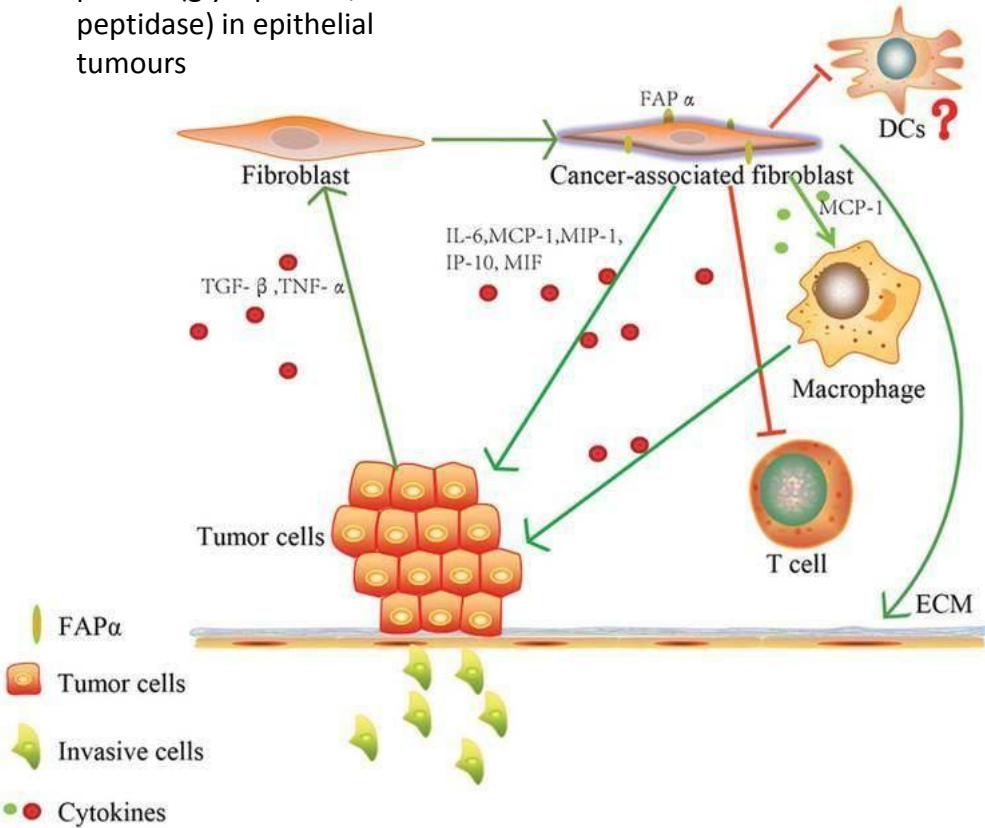


FIGURE 7. A. Maximum intensity projection (MIP) 1 h after intravenous administration of 270 MBq ⁶⁸Ga-FAPI-04 to one patient with metastasized breast cancer. B. Imaging of Bremsstrahlung 3 h and 1 day after therapeutic treatment with ⁹⁰Y-FAPI-04 of the same patient.

Bi-213 anti-EGFR-MAb therapy of recurrent bladder cancer

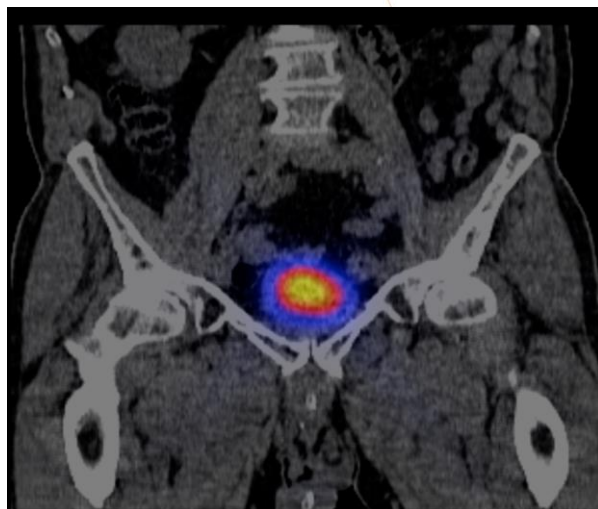
High grade bladder cancer (pT1 GIII, CIS)

- = flat, high-grade (GIII), noninvasive urothelial carcinoma
- high risk for extravesical „recurrence“ (20%) → therapy by cystectomy
- associated with >50% rate of progression (no watchful waiting)

→ Targeting w intravesical Bi-213-anti-EGFR immunoconjugates

Local instillation of 350 to 820 MBq (40 ml) Bi-213-anti-EGFR(Cetuximab)

- 12 patients treated: CIS refractory to BCG instillation, histol. proven tu



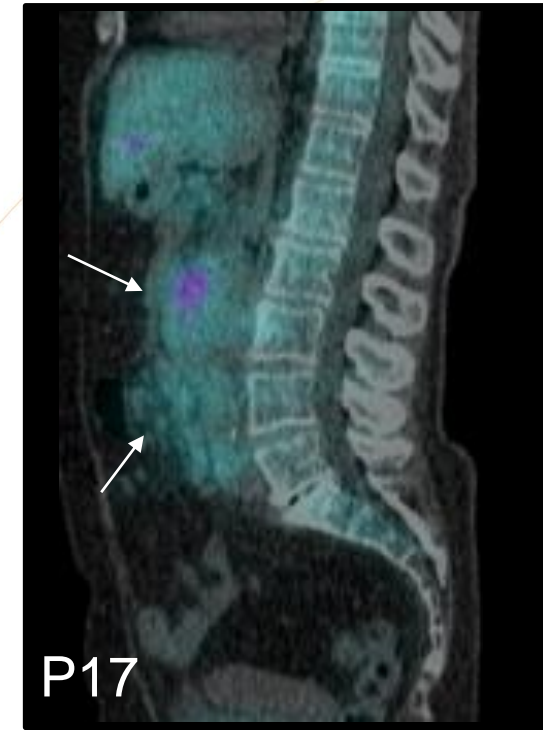
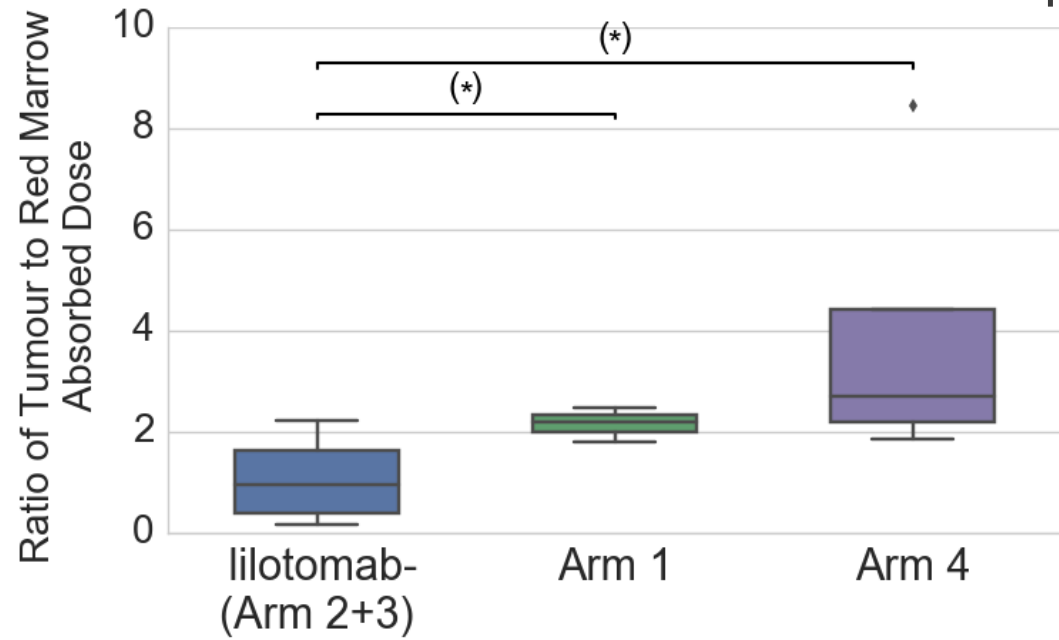
Results

- Excellent local tolerance w/o any side effects
- 4 / 12 CR (long lasting, up to > 44 months)
→ avoiding cystectomy
- 4 / 12 SD → postponing surgery/cystectomy



Promising new therapy option

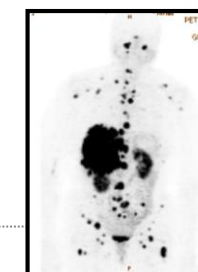
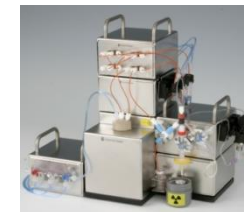
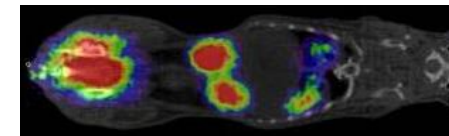
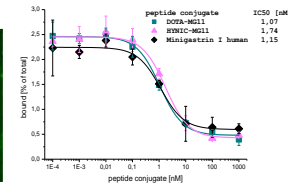
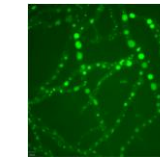
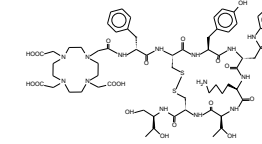
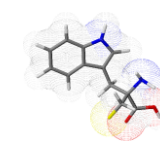
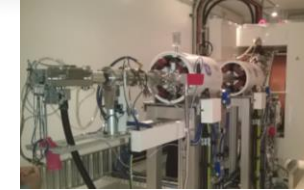
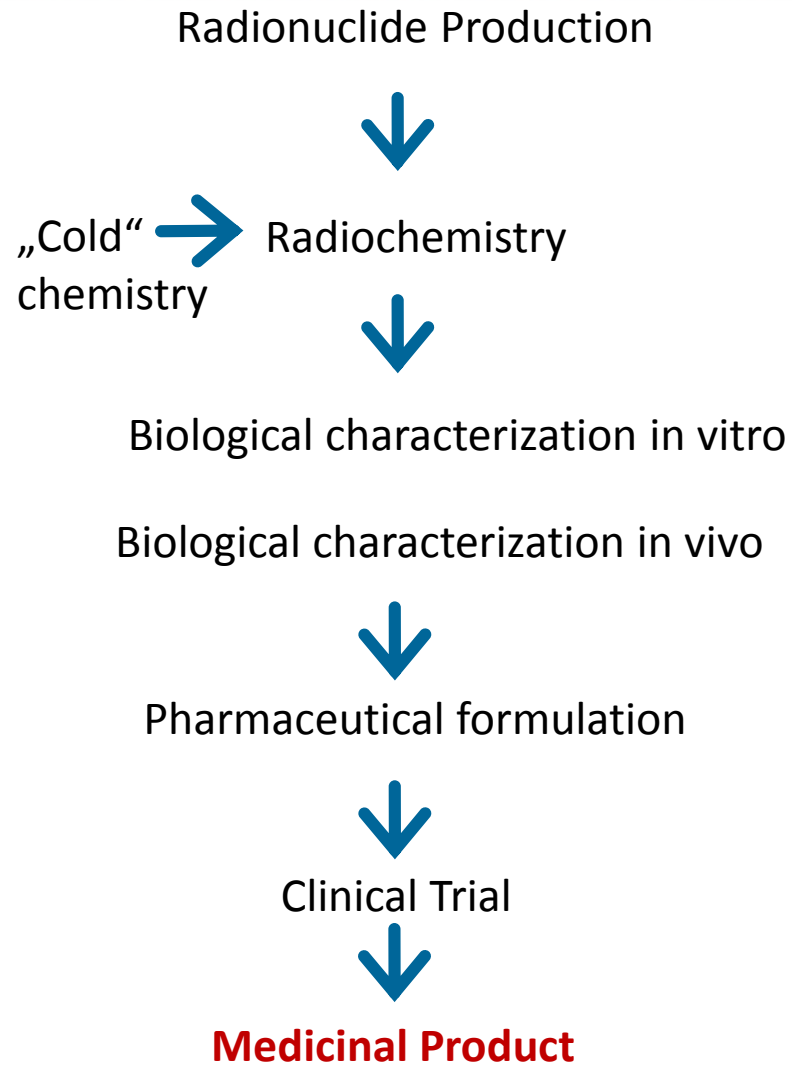
^{177}Lu -lilotomab satetraxetan



Arm 1	rituximab [†]	lilotomab 40 mg	^{177}Lu -lilotomab satetraxetan
Arm 4	rituximab [†]	lilotomab 100 mg/m ²	^{177}Lu -lilotomab satetraxetan
lilotomab- (Arm 2+3)	rituximab [†]		^{177}Lu -lilotomab satetraxetan

[†] Different regimens of rituximab

Path of a „new“ Radioisotope to the patient



What are (therapeutic) Radiopharmaceuticals?

Medical Devices vs. Medicinal Products

- **Sealed sources** (SIRTEX[®], TheraSphere[®]): **Medical Device**
- Other therapeutic radiopharmaceuticals: **Medicinal Products**
 - new (therapeutic) radiopharmaceuticals are usually **Investigational Medicinal Products (IMPs)**

EANM support for

- Development within **controlled, prospective Clinical Trials according to current regulations**

Are all clinical translations of radiopharmaceuticals in Europe „Clinical Trials“?

National regulations allow(ed) the use of (new) radiopharmaceuticals **outside the strict EU definition** of a clinical trial

- „Compassionate Use“
- „Experimental Radiopharmaceuticals“
- „Compounding“ Practice
- Other specific National Procedures

May require authorisation by an **ethical board, local or national authority**
Authorisation of a „trial“, Authorisation of the „drug“

→ $^{68}\text{Ga}/^{177}\text{Lu}$ -DOTA-Somatostatin analogues

→ ^{68}Ga -PSMA-11, CXCR4, Bombesins...

Not supported by EANM

A radiopharmaceutical (and Medicinal Product) is?

Directive 2001/83/EC, Article 1

6. *Radiopharmaceutical:*

Any **medicinal product** which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7. *Radionuclide generator:*

Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8. *Kit*

Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

9. *Radionuclide precursor:*

Any other radionuclide produced for the radiolabelling of another substance prior to administration

Legal Implications: Directive applies to these products including requirement for authorisation of the institution, licensing (marketing authorization), responsibilities, distribution, labelling



**COMMITTEE FOR HUMAN MEDICINAL PRODUCTS
(CHMP)**

GUIDELINE ON RADIOPHARMACEUTICALS

DRAFT AGREED BY QWP	September 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	September 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	March 2008
AGREED BY QWP	October 2008
ADOPTION BY CHMP	November 2008
DATE FOR COMING INTO EFFECT	May 2009

This guideline replaces the Guideline on Radiopharmaceuticals / eudralex 3AQ20a

KEYWORDS	<i>Radiopharmaceuticals; Pharmaceutical and chemical documentation; Development; Manufacture; Quality control; Stability.</i>
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- Radiopharmaceuticals, radionuclide generators, kits and **radionuclide precursors** are **Medicinal (Drug) Products**
- In radionuclide generators both mother and daughter radionuclide are considered as **Drug Substance (Active Substance, Active pharmaceutical ingredient API)**

A new radionuclide legally has to be considered either as Medicinal Product or API

GMP AND RPs: ANNEX 3 - RADIOPHARMACEUTICALS

Type of manufacture	Non-GMP*	GMP Part I & II (increasing) including relevant annexes			
RPs, PET RPs, radioactive precursors	Reactor/cyclotron production	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
Radionuclide generators	Reactor/cyclotron production	Processing			

**target and transfer systems from cyclotron to synthesis rig may be considered as the first step of active substance manufacture*

GMP – Good Manufacturing Practices

Directive 2003/94/EG → **GMP** Annex 13 (IMP`s)

GMP is mandatory for IMP Production

A new radiopharmaceutical is an IMP

Valid for:

Radiopharmaceutical in clinical Trial

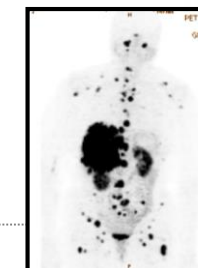
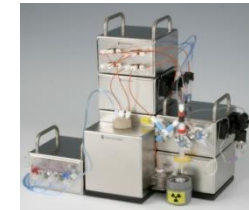
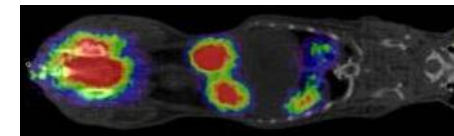
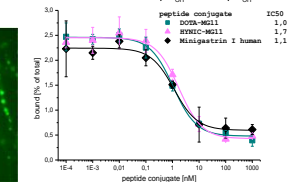
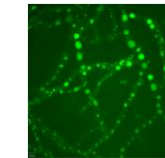
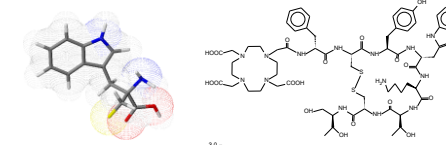
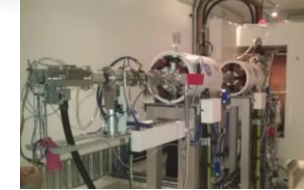
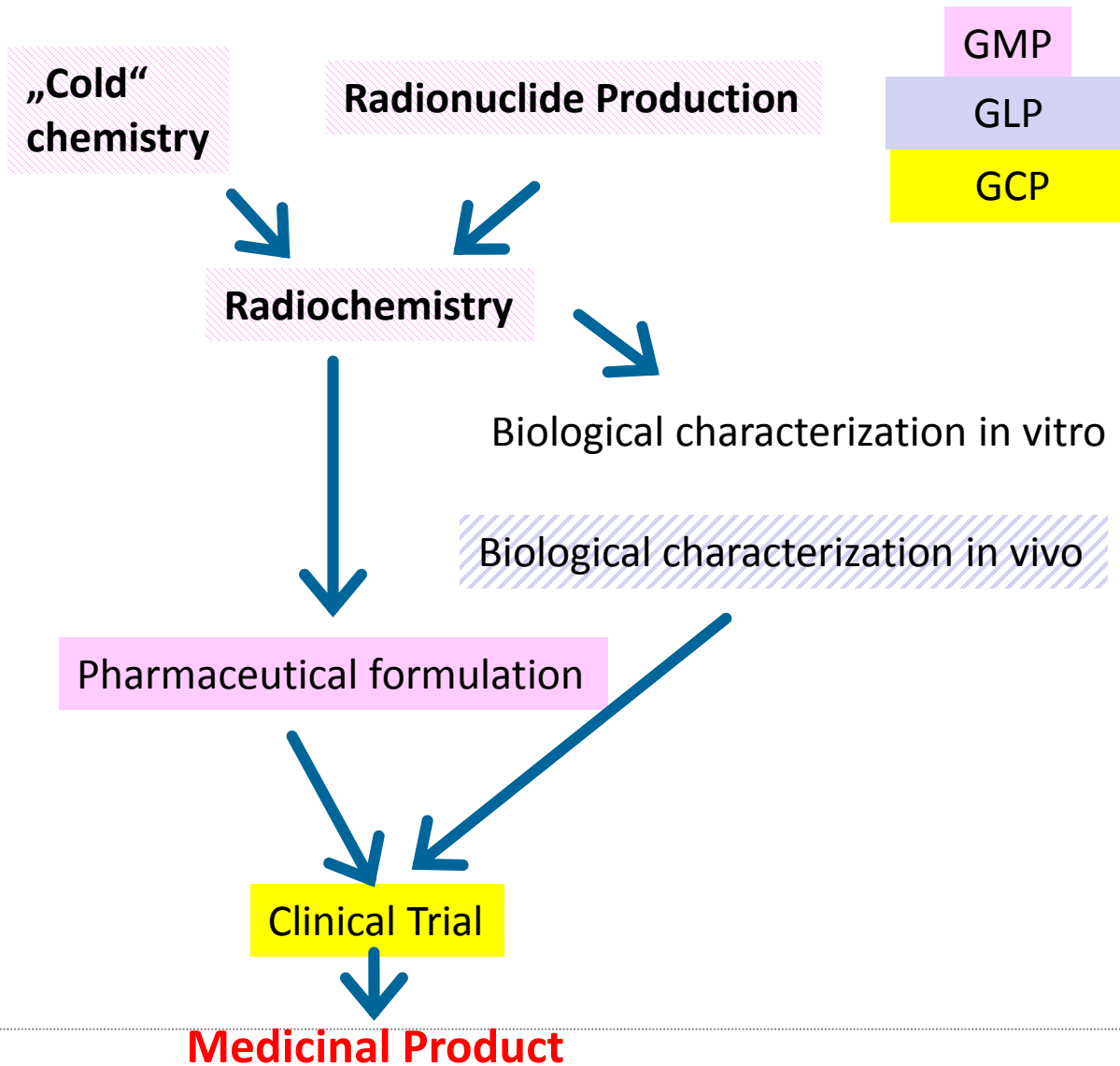
Active Pharm.Ingredient (API, “**drug substance**”)

“API starting materials” (**chemical precursors**)?

Radionuclide Precursors ?

Path of a „new“ Radioisotope to the patient

Be ware of G`s



EANM & „novel“ Radionuclides

- EANM understands itself as representing the whole NM community, and has not defined a particular research area of interest
- EANM cannot serve as official partner in research projects, but is glad to provide support (suggesting experts, providing dissemination channels, networking, regulatory activities,...)
- **Therapeutic radiopharmaceuticals** are seen as a **very important** segment for NM in the years to come
- EANM is supporting the translation of novel (theranostic) radiopharmaceuticals within **controlled prospective clinical trials**
- The **regulatory** environment is seen as a **major hurdle** and in particular initiatives for easy and reliable provision of (novel) radionuclides are in the focus of the EANM



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EANM

Thank you for your attention

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