



Radiolabeled antibodies as a theranostic tool in oncology

BELNUC '23 Dolce symposium

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Kristoff Muylle

University Hospital Brussels (UZ Brussel)

AZ Delta, Roeselare

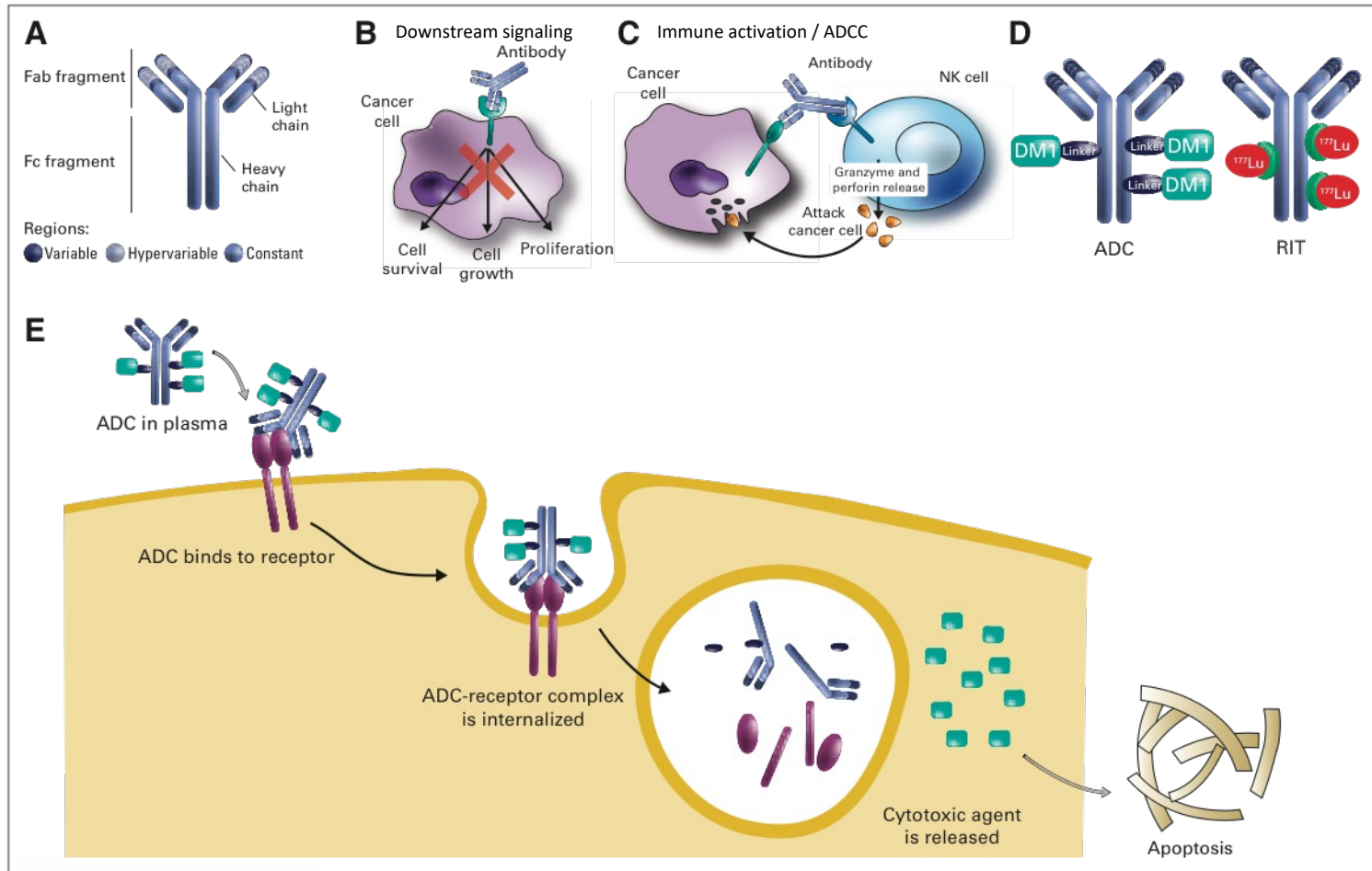


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Vrije Universiteit Brussel

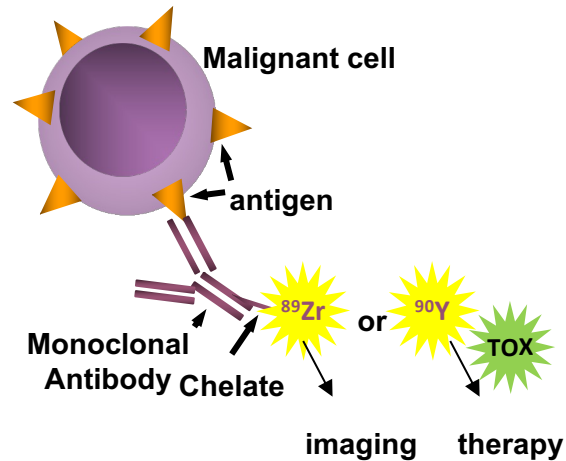
Design and mode of action of monoclonal antibodies



More than 50 monoclonal antibodies (mAbs), including several antibody–drug conjugates, are in advanced clinical development as molecularly targeted anticancer therapeutics.

Immuno-PET

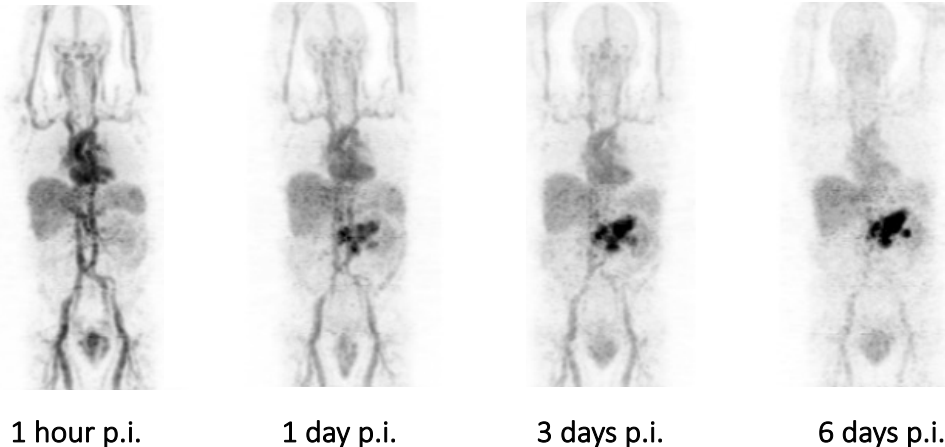
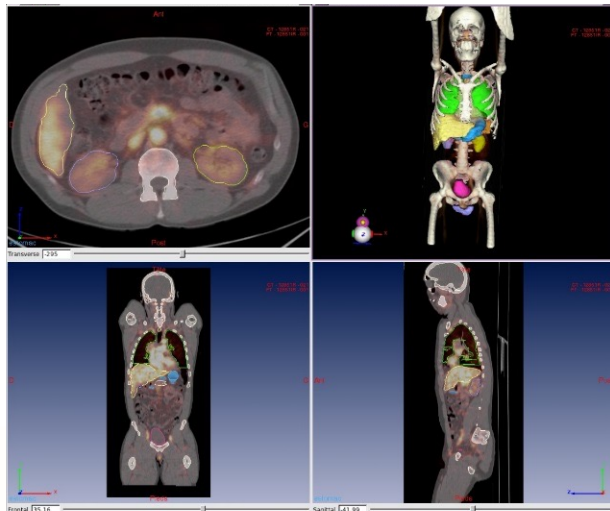
PET using monoclonal antibodies



- ^{89}Zr -immuno-PET/CT combines the high sensitivity of PET/CT with the specificity of a mAb for the antigen/receptor expressed on the surface of cancer cells.
- Zirconium-89 (^{89}Zr) is a positron emitter with a half-life of 78.4 hours, which is compatible with the time needed for intact mAb to achieve optimal tumour-to-background ratios.

^{89}Zr -rituximab Immuno-PET/CT

Intra-abdominal relapse of a follicular lymphoma.



Immuno-Positron Emission Tomography with Zirconium-89-Labeled Monoclonal Antibodies in Oncology: Initial Clinical Trials

Author	Year	Target	mAb	Tumor type	N
Börjesson	2006	CD44v6	cmAb U36	Head and neck cancer	20
	2009				
Dijkers	2010	HER2	trastuzumab	Breast cancer	14
Rizvi	2012	CD20	ibritumomab-tiuxetan	B-cell lymphoma	7
Gaykema	2013	VEGF-A	bevacizumab	Breast cancer	23
van Zanten	2013	VEGF-A	bevacizumab	Glioma	3
van Asselt	2014	VEGF-A	bevacizumab	Neuroendocrine tumors	14
Bahce	2014	VEGF-A	bevacizumab	Non-small cell lung cancer	7
Pandit-Taskar	2014	PSMA	Hu-J591	Prostate cancer	50
	2015				
Den Hollander	2015	TGF- β	fresolimumab	Glioma	12
Gaykema	2015	HER2	trastuzumab	Breast cancer	10
		VEGF-A	bevacizumab		6
Gebhart	2015	HER2	trastuzumab	Breast cancer	56
Lamberts	2015	MSLN	MMOT0530A	Pancreatic cancer	11
				Ovarian cancer	4
Menke-van der Houven van Oordt	2015	EGFR	cetuximab	Colorectal cancer	10
Muyllé	2015	CD20	rituximab	B-cell lymphoma	5
Oosting	2015	VEGF-A	bevacizumab	Renal cell carcinoma	22

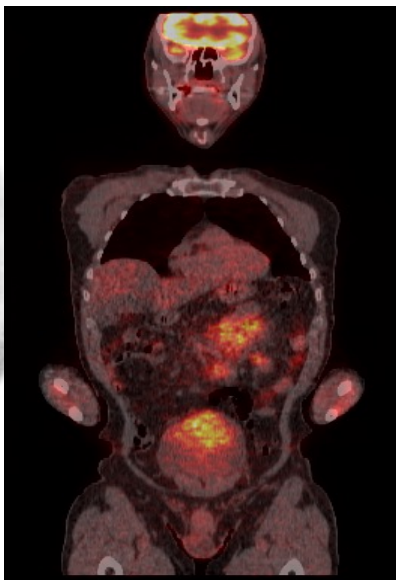
Immuno-PET/CT

Simulation of radioimmunotherapy

FDG-PET/CT before
treatment with ^{90}Y -
rituximab



MIP

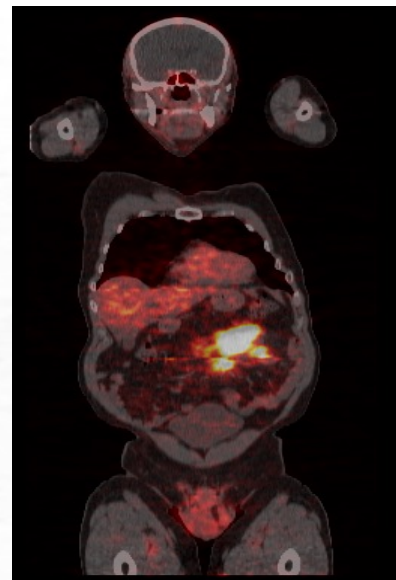


Coronal slice

Immuno-PET/CT
6 days p.i. of $\text{Zr}89$ -
rituximab



MIP

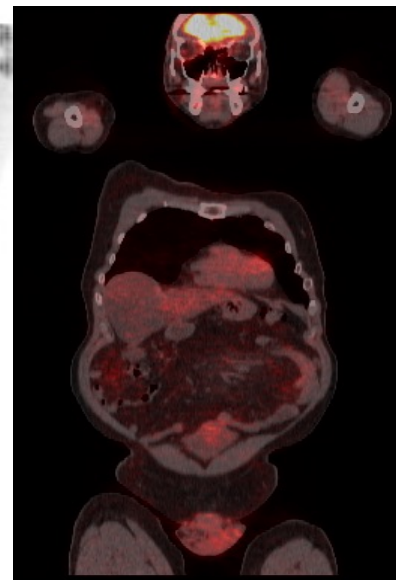


Coronal slice

FDG-PET/CT 6 months after treatment
with ^{90}Y -rituximab (0,4 mCi/kg) showing a
complete remission



MIP

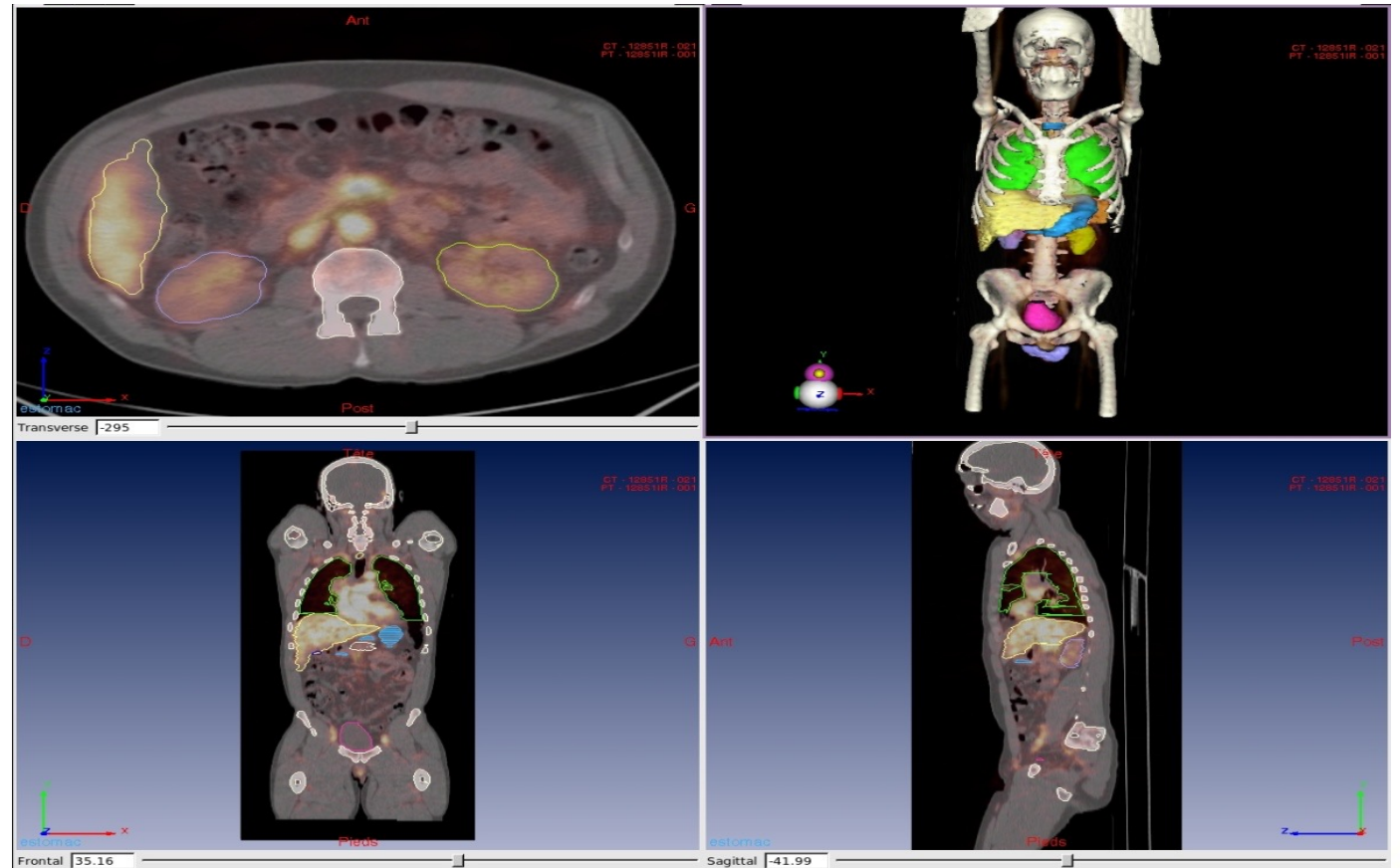


Coronal slice

Immuno-PET/CT

3D-dosimetry

- 3D delineation of organs and lesions for dosimetry as a prelude to radioimmunotherapy opens the door for:
 - dose-response correlation
 - prediction of treatment outcome
 - better selection of patients for receptor-targeted therapy
 - patient tailored image-guided therapy.

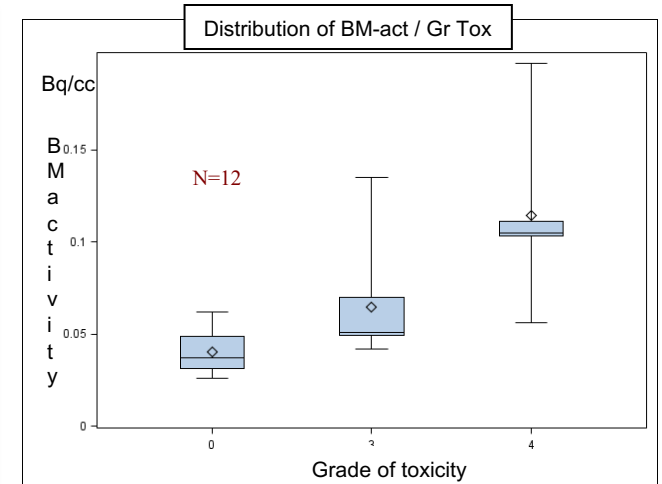
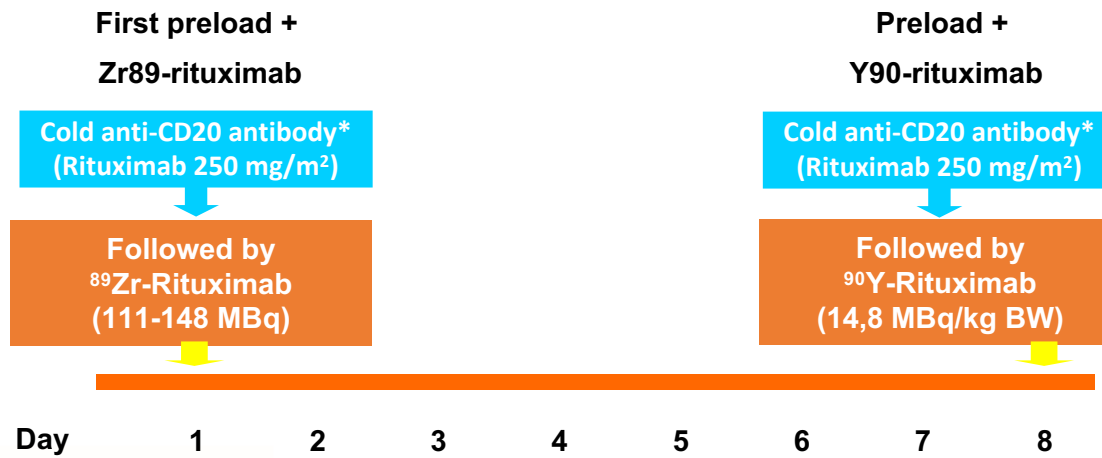


Immuno-PET/CT

Prediction of toxicity (^{89}Zr -rituximab)

- Toxicity observed with radioimmunotherapy is primarily hematological and difficult to predict.
- The aim of this study was to evaluate whether bone marrow (BM) activity on immuno-PET/CT with ^{89}Zr -rituximab was correlated to hematological toxicity in 25 lymphoma patients treated with ^{90}Y -rituximab.

Therapeutic Regimen



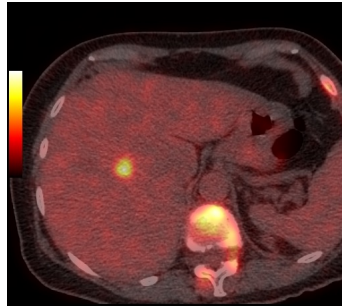
Significant differences were observed in BM activity concentration between patients with < grade 3, grade 3 and grade 4 toxicities ($p=0.0009$ Kruskal-Wallis test).

Immuno-PET/CT

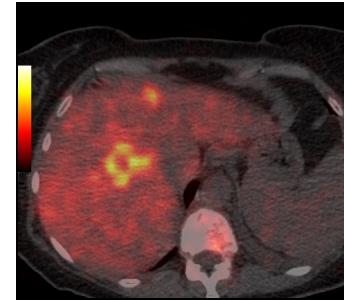
Tumour heterogeneity (Zr89-trastuzumab)



FDG
1 h p.i.



Zr89-trastuzumab
4 days p.i.



G. Gebhart, J. Bordet Institute, Brussels

- ability to quantify cellular targets for the entire disease burden
- Identify heterogeneous receptor expression > avoid the sampling error

Immuno-PET/CT

Response prediction (Zr89-rituximab)

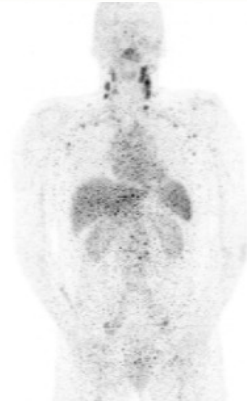
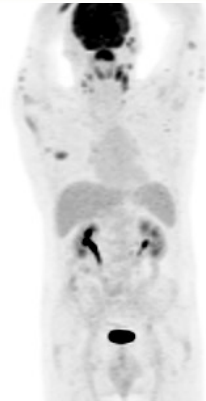
NHL

Biopsy proven
CD20+

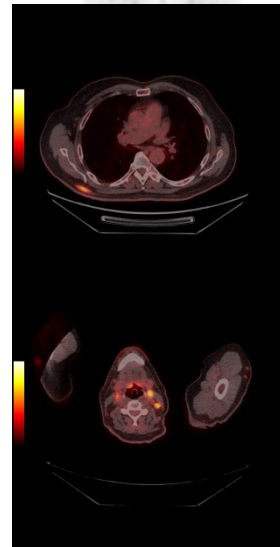
subcutaneous
lesions

&

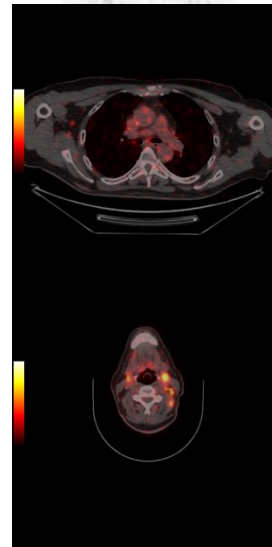
lymph node
involvement



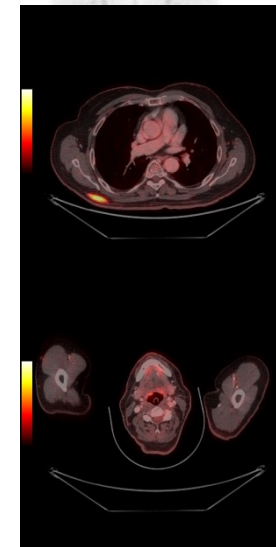
Difference in
accessibility:
preferential sites of
receptor-binding



FDG-PET/CT
Pre-treatment



Immuno-PET/CT
Pre-treatment



FDG-PET/CT
Post-treatment

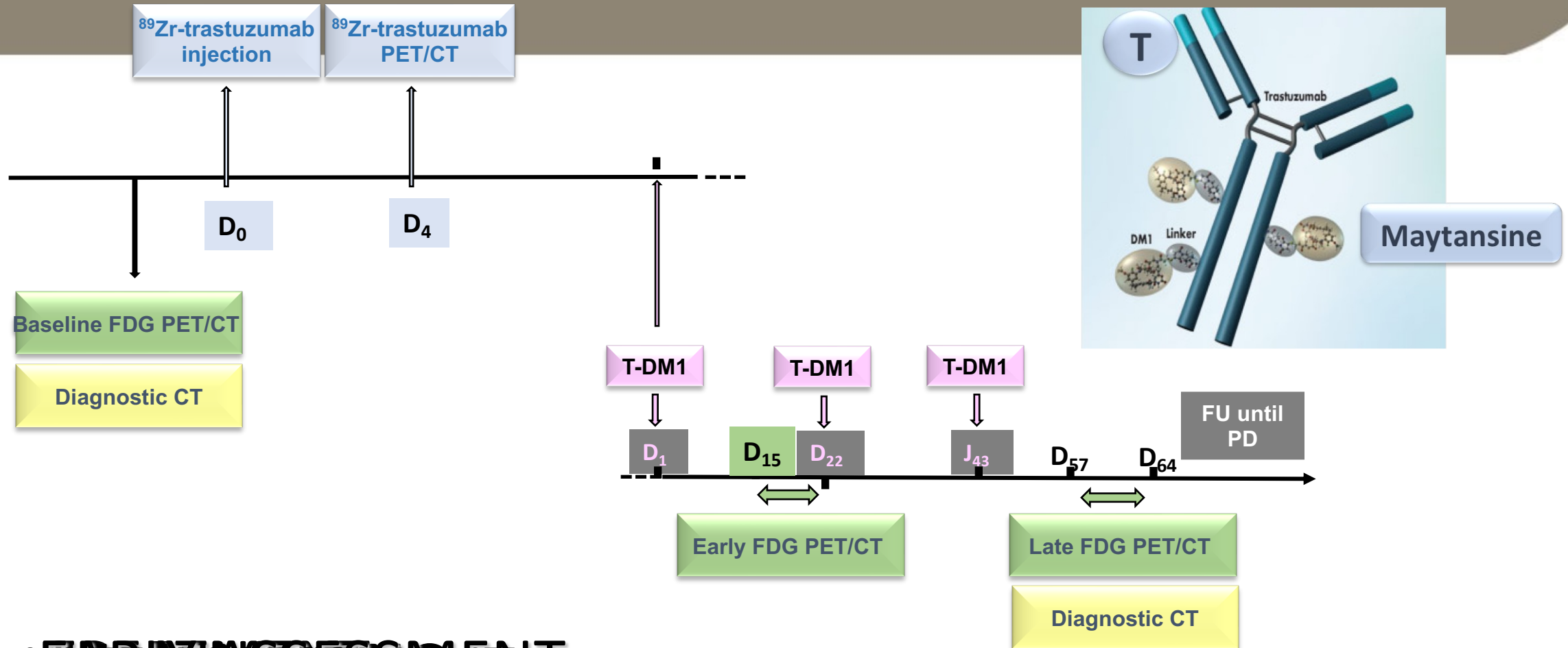
Less accessible
receptors:
No mAb-uptake
No response
&
High accessible
receptors:
high mAb-uptake
complete response

ZEPHIR TRIAL: TRASTUZUMAB-DM1 IN HER2+Metastatic Breast Cancer



➤ Inclusion of molecular imaging / immuno-PET + early response assessment with FDG-PET in the study protocol

ZEPHIR TRIAL: TRASTUZUMAB-DM1 IN HER2+Metastatic Breast Cancer

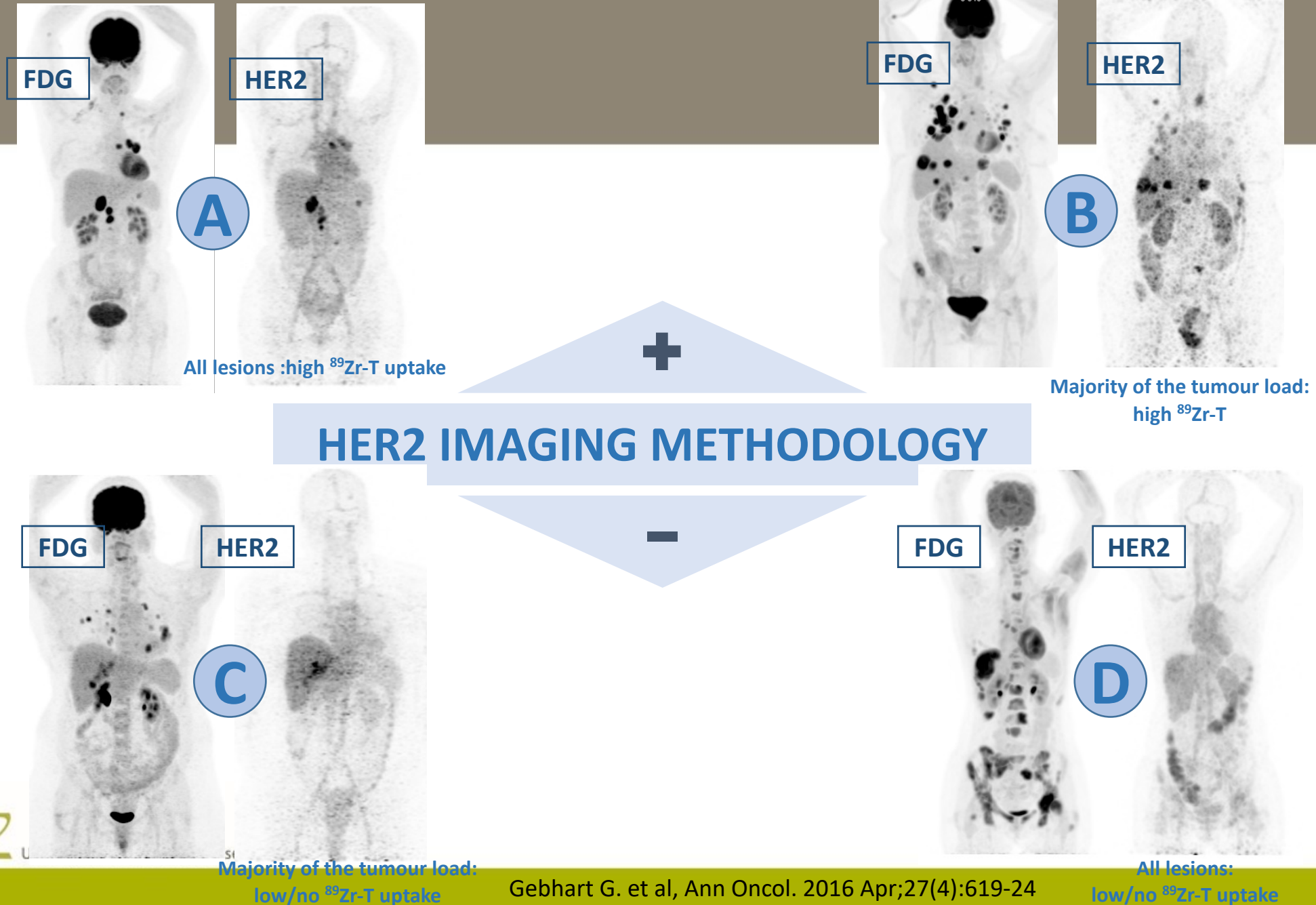


LATE ASSESSMENT



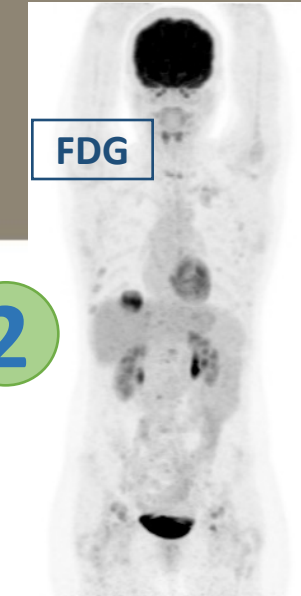
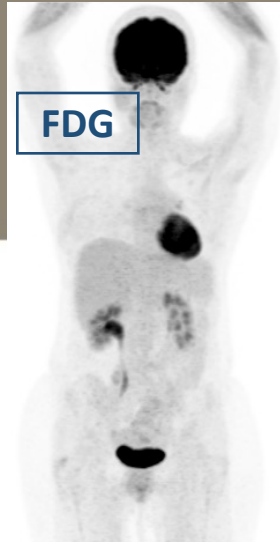
Universitair Ziekenhuis Brussel

Patterns of ^{89}Zr -trastuzumab PET/CT confronted with FDG-PET/CT



Patient-based metabolic response

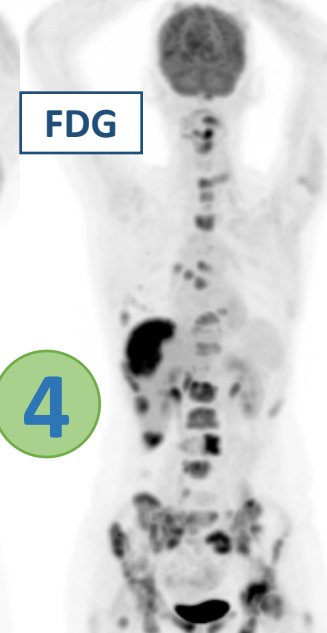
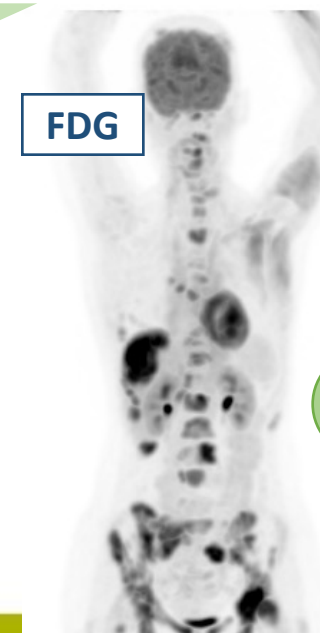
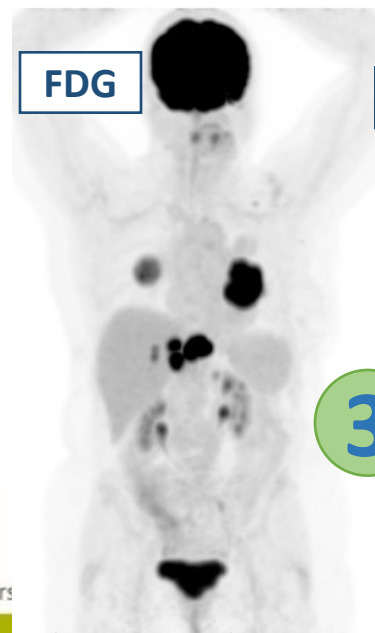
Hendlisz et al., Annals of oncology, 2012



Response

FDG IMAGING METHODOLOGY

Non Response

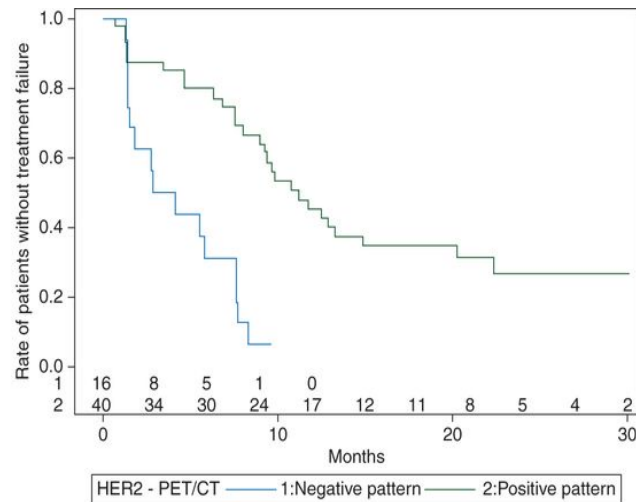


COMBINED IMAGING MODALITIES PREDICTING RECIST RESPONSES

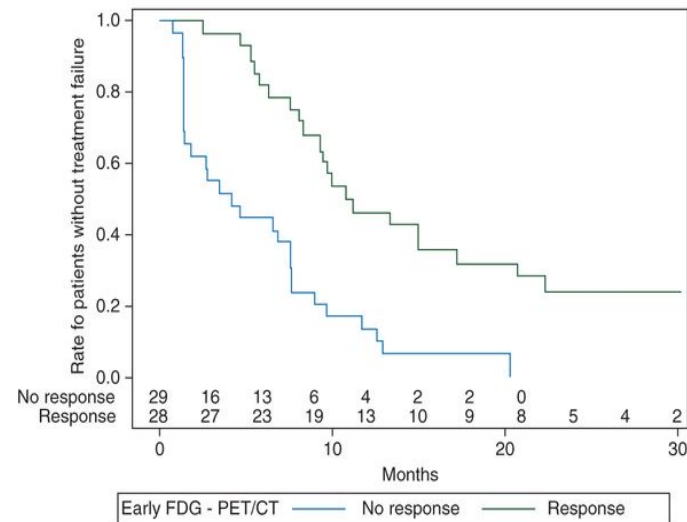
		RECIST 1.1			
		R	NR	Total	
HER2 PET +	eR	23	0	23	PPV: 100%
	eNR	4	9	13	
HER2 PET -	eR	1	1	2	NPV: 100%
	eNR	0	14	14	

- avoid unnecessary toxicity and costs by better / upfront selection of patients

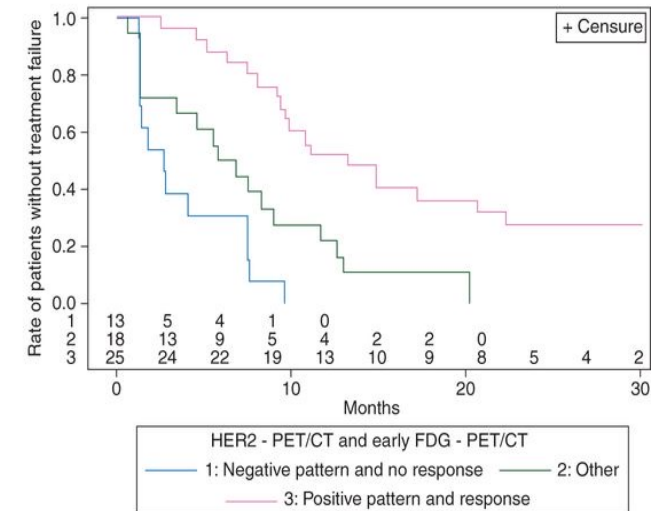
Time-to-treatment failure according to HER2-PET/CT and/or early FDG-PET/CT



HER2: TTF 11.2 vs. 3.5 months

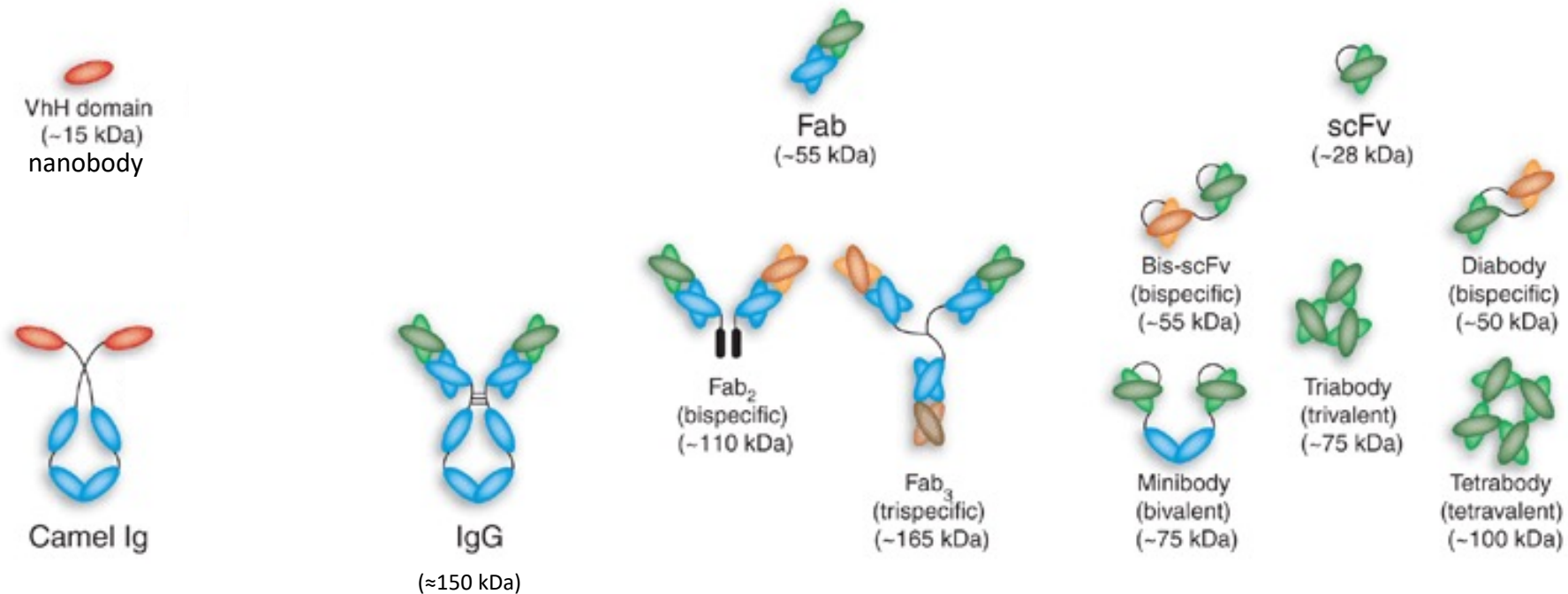


FDG: TTF 13.3 vs. 4.2 months



HER2 + FDG: TTF 15 vs. 2.8 months
(6.2 months for discordant HER2/FDG)

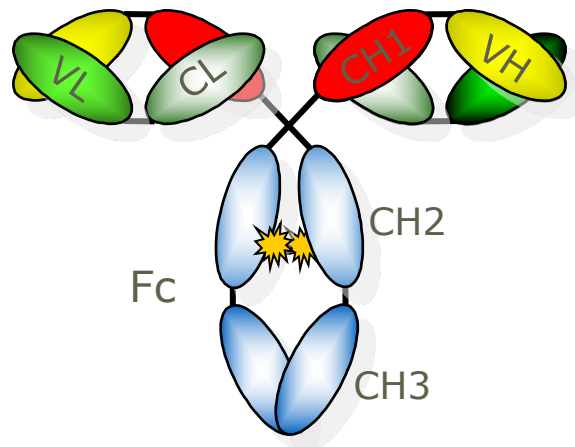
antibody fragments and nanobodies



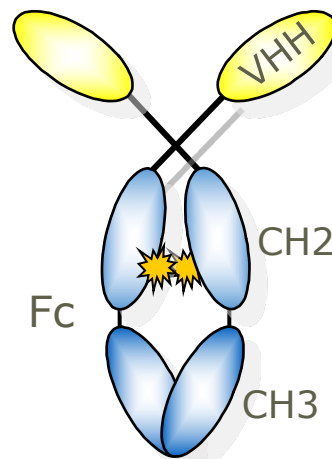
Kathie Rits

The potential of nanobodies in Molecular Imaging and Theranostics

Antigen-binding fragments derived from heavy chain only antibodies that naturally occur in camelidae



all mammals



camelidae

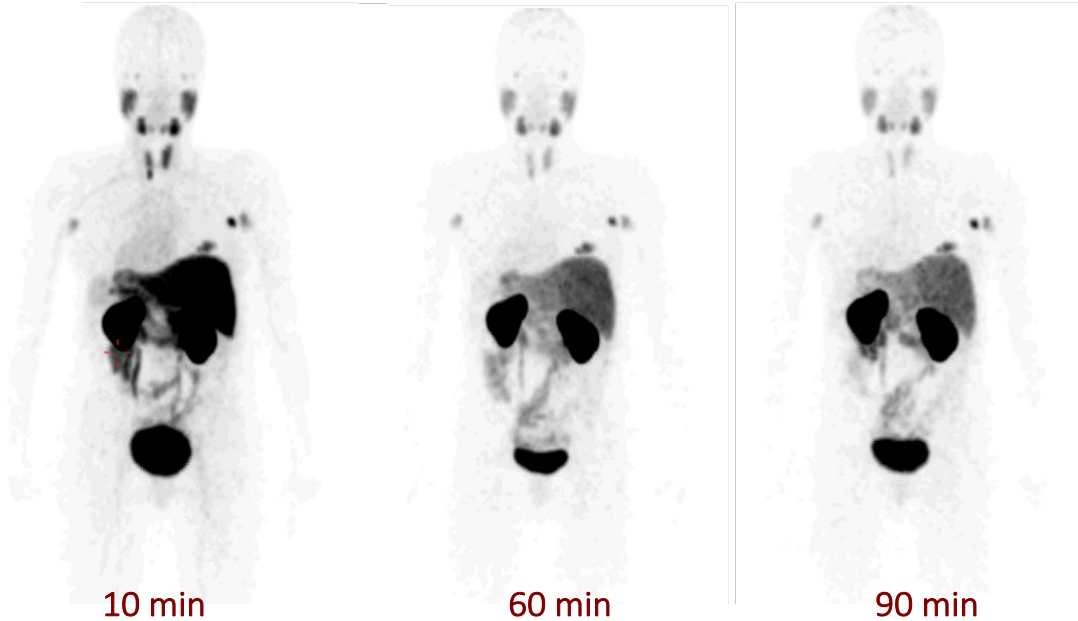
- high affinity (nM)
- good stability
- very specific
- easy labeling:
 ^{99m}Tc , ^{68}Ga , ^{18}F , ^{177}Lu , ^{131}I
- fast renal clearance
- rapid & high contrast
- low radiation burden

Immuno-PET

Nanobodies versus monoclonal antibodies

⁶⁸Ga-NOTA-anti-HER2 Nanobody

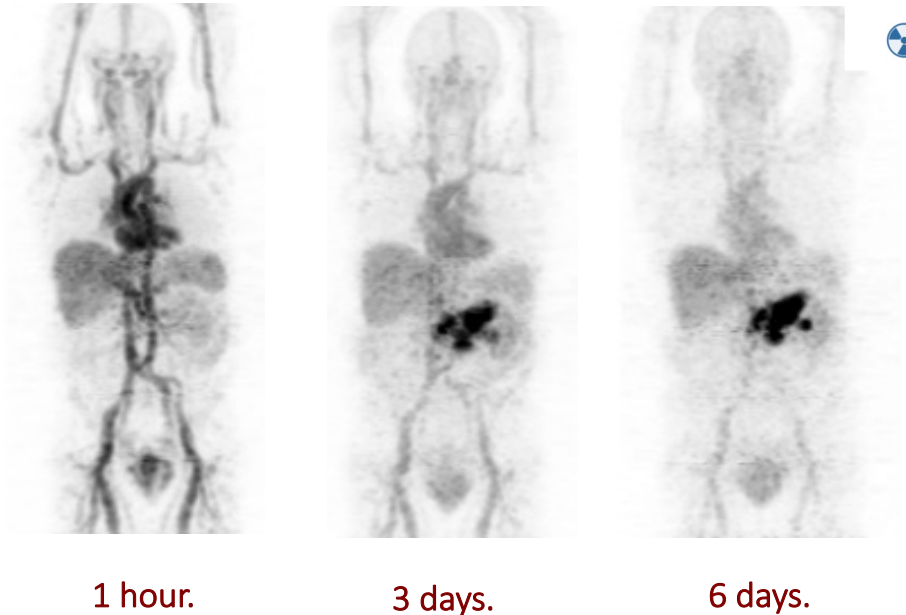
HER2+ breast cancer + axillary node.



- Fast biokinetics (size: 15 kDa)
- fast blood clearance & tumour targeting
- Renal clearance ++
- Mean effective dose: 0.042 ± 0.005 mSv/MBq
- Dose for 105 MBq: 4.5 mSv
- Better suited for diagnosis / receptor assessment

⁸⁹Zr-rituximab

Intra-abdominal relapse of a follicular lymphoma.



- Slow biokinetics (size: 15 kDa)
- slow blood clearance & tumour targeting
- No renal clearance
- Mean effective dose: 0.41 ± 0.02 mSv/MBq
- Dose for 105 MBq: 43 mSv
- Better suited for treatment simulation / dosimetry

Increasing evidence of the sdAb platform in immuno-oncology

SdAbs as targeting moieties for nuclear theranostics

- Extensive number of preclinical PoCs using the sdAb platform
- SdAbs radiolabeled with a variety of diagnostic and therapeutic isotopes
- Clinical evidence:
 - **HER2**: NCT02683083; NCT03924466; NCT04591652; NCT03331601; NCT04467515
 - **CD206**: NCT04758650; NCT04168528
 - **VCAM1**: NCT04483167 (cardiology)

Target	SPECT imaging	PET imaging	Optical imaging	Cancer directed therapy	DC vaccination	Cytolytic cell therapy	Immune restoration	CAR-T cell therapy	References
HER2	✓	✓	✓	✓				✓	(73, 93-95, 132, 136, 142, 143, 145, 147, 148)
EGFR	✓		✓	✓				✓	(138, 139, 141, 187, 211)
CD20	✓	✓		✓				✓	(96, NCT03881761)
MMR	✓	✓					✓		(113-116, 208)
M protein	✓			✓					(144)
MHC-II			✓	✓	✓				(161, 213)
DC specific antigens	✓		✓		✓	✓			(47, 49, 50, 55, 57, 119, 161, 169, 215)
CTLA-4		✓				✓	✓		(107, 197)
PD-L1	✓	✓		✓		✓	✓	✓	(108-112, 174, 198, 199, 216)
CD38			✓	✓				✓	(53, 130)

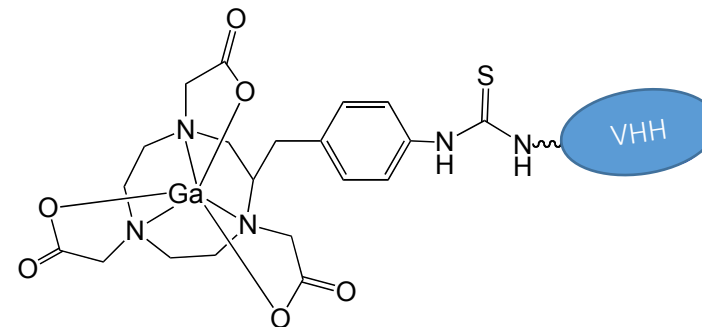
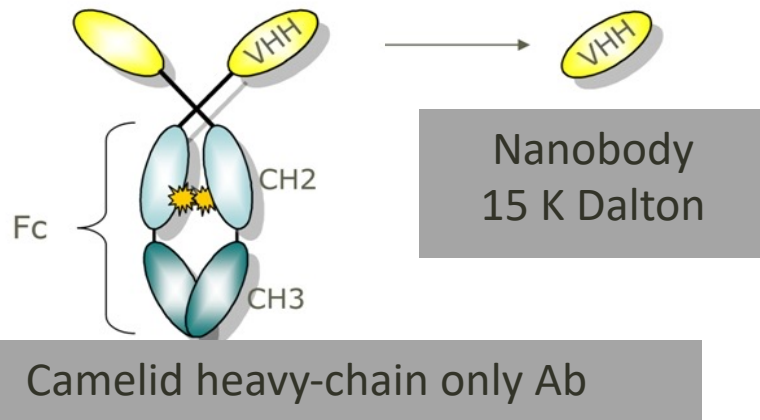
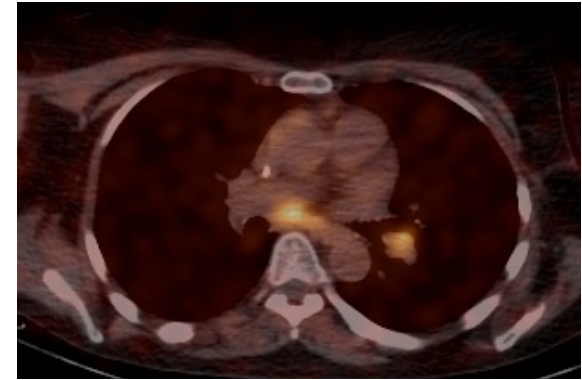
(Pre-)clinical reports on use of sdAbs in immuno-oncology

Lecocq Q et al., 2019, *TNO*

anti-HER2 Nanobody

Nanobodies

- the antigen-binding fragments derived from heavy chain only antibodies that naturally occur in camilidae.
- smallest intact antigen-binding fragments derived from a functional antibody (15 kDa; below kidney treshold of 50-60 kDa)

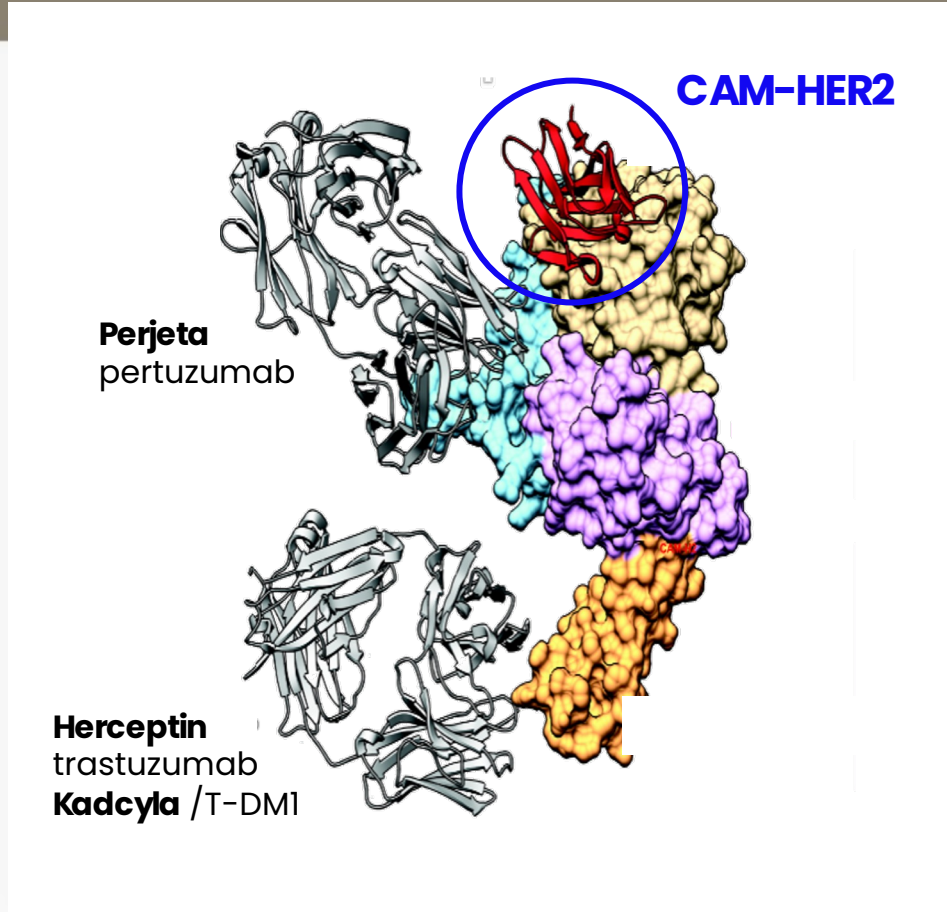


^{68}Ga -NOTA-anti-HER2 Nanobody

- Easy and fast labeling with a NOTA-chelator
- high affinity, high stability, high solubility



CAM-HER2 clinical candidate



D'Huyvetter M et al., 2017, *Clin Cancer Res*

Resistance to HER2 therapy is an issue for approved drugs, CAM-HER2 targets a different epitope and brings a new mechanism of action

Combination therapy with standard-of-care feasible

Intra-tumoral HER2 heterogeneity is associated with poor survival, radiolabeled CAM-HER2 has crossfire effect that can target heterogeneous HER2-positive tumors

Tissue penetration is an issue for approved mAbs, CAM-HER2 penetrates cancer tissues within minutes, including brain lesions

Preclinical validation of theranostic CAM-HER2

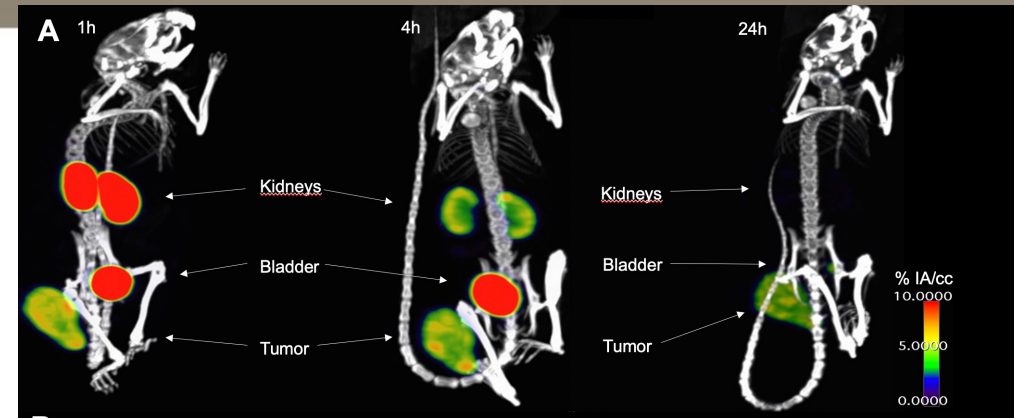
Preclinically validated as effective
theranostic radiopharmaceutical

Imaging potential described using a
variety of SPECT and PET isotopes

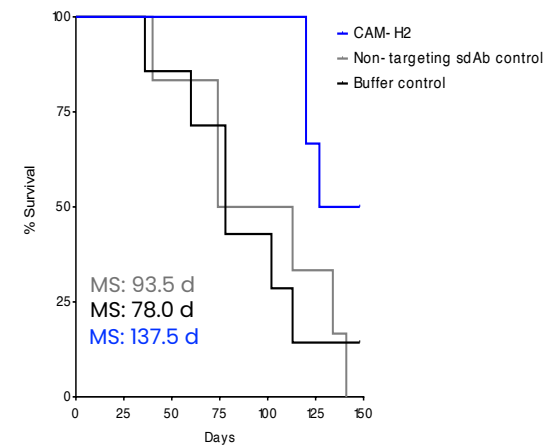
CAM-HER2 improves survival in
preclinical **breast, ovarian** and **brain
metastasis** xenograft models in
combination with beta- and alpha
particle emitters

Additive effects in **combination with
Trastuzumab or Kadcyla** (data not
shown)

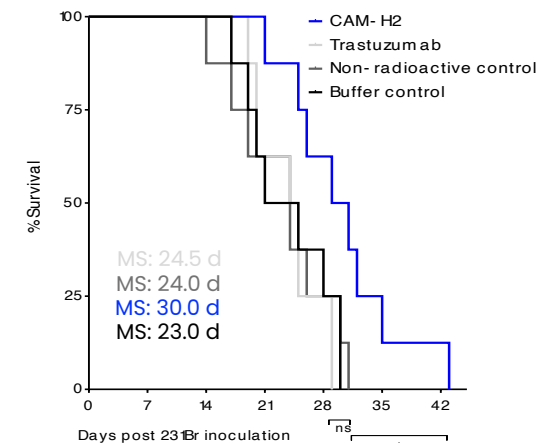
Theranostic CAM-HER2-I-131



BT474/M1 xenografts



Intracranial 231Br tumors



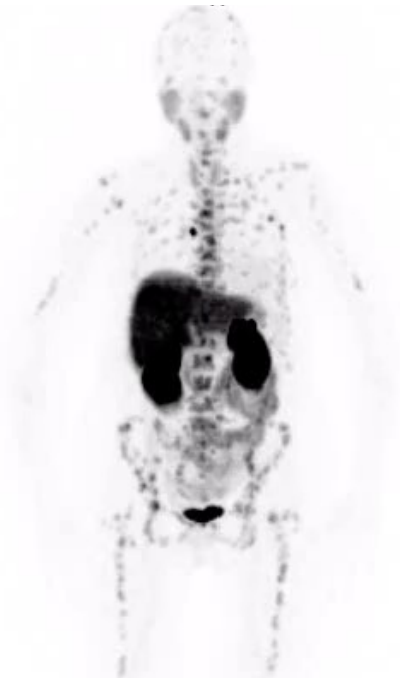
PET imaging biomarker supports development

CAM-HER2-Ga-68 demonstrates targeting in HER2-positive breast cancer

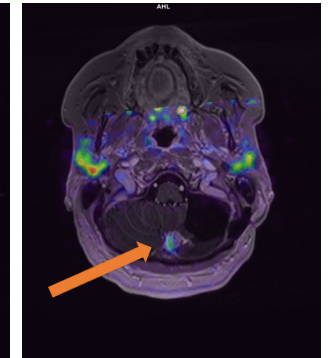
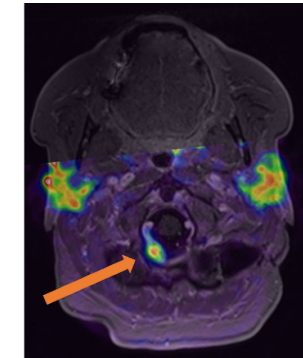
Primary



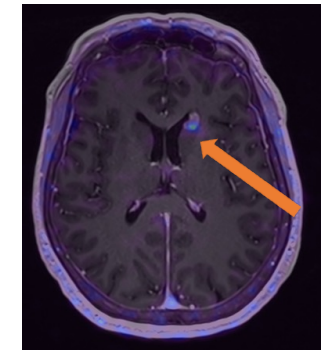
Metastatic



Brain



Leptomeningeal
disease in
patient with
HER2-positive
breast cancer

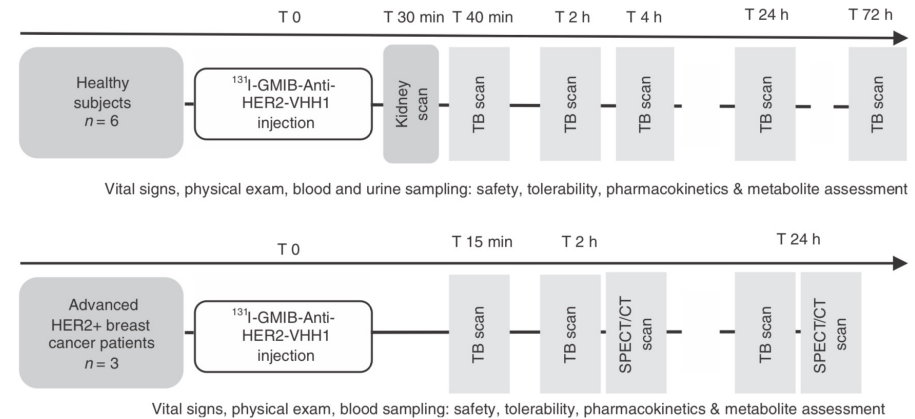


Keyaerts et al. VUB Brussels

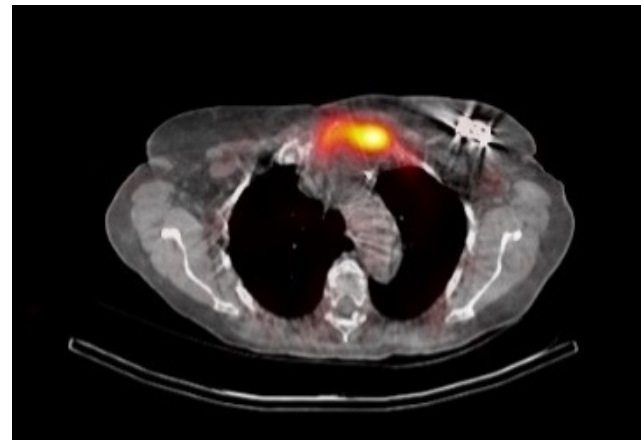
Phase I biomarker study CAM-HER2-I-131

6 healthy subjects, 3 patients
biomarker dose

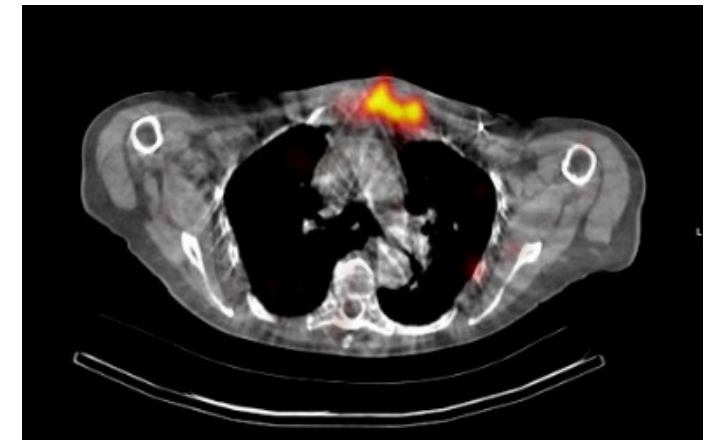
- No drug-related adverse events
- Rapid blood clearance: 2.5h half-life in elimination phase
- Biological half-life: 7.7h
- Metabolites identified in urine samples (indicating renal metabolization)
- Kidney is dose-limiting organ, no accumulation in other organs
- Confirmed tumor targeting



2h



24h



D'Huyvetter M et al., 2021, *JNM*

Immuno-PET: a key for patient-tailored image guided therapy

- Molecular / receptor imaging with immuno-PET
 - In vivo evaluation / simulation of the distribution of therapeutic agents & the ability to quantify cellular targets for the entire disease burden
 - Proof of concept in early phase clinical trials
 - Enriching patient selection in clinical trials by assessing drug targeting
 - Reduction of costs for drug development
 - Identify heterogeneous receptor expression
 - avoid the sampling error
 - better selection of patients
 - prediction of treatment outcome (response & toxicity), particularly in targeted therapy with ADC or RIT
 - avoid unnecessary toxicity and costs by better / upfront selection of patients



Thanks

