The role of molecular imaging in early drug development

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Disclosure slide

- I have no conflicts of interest to declare

Molecular Imaging

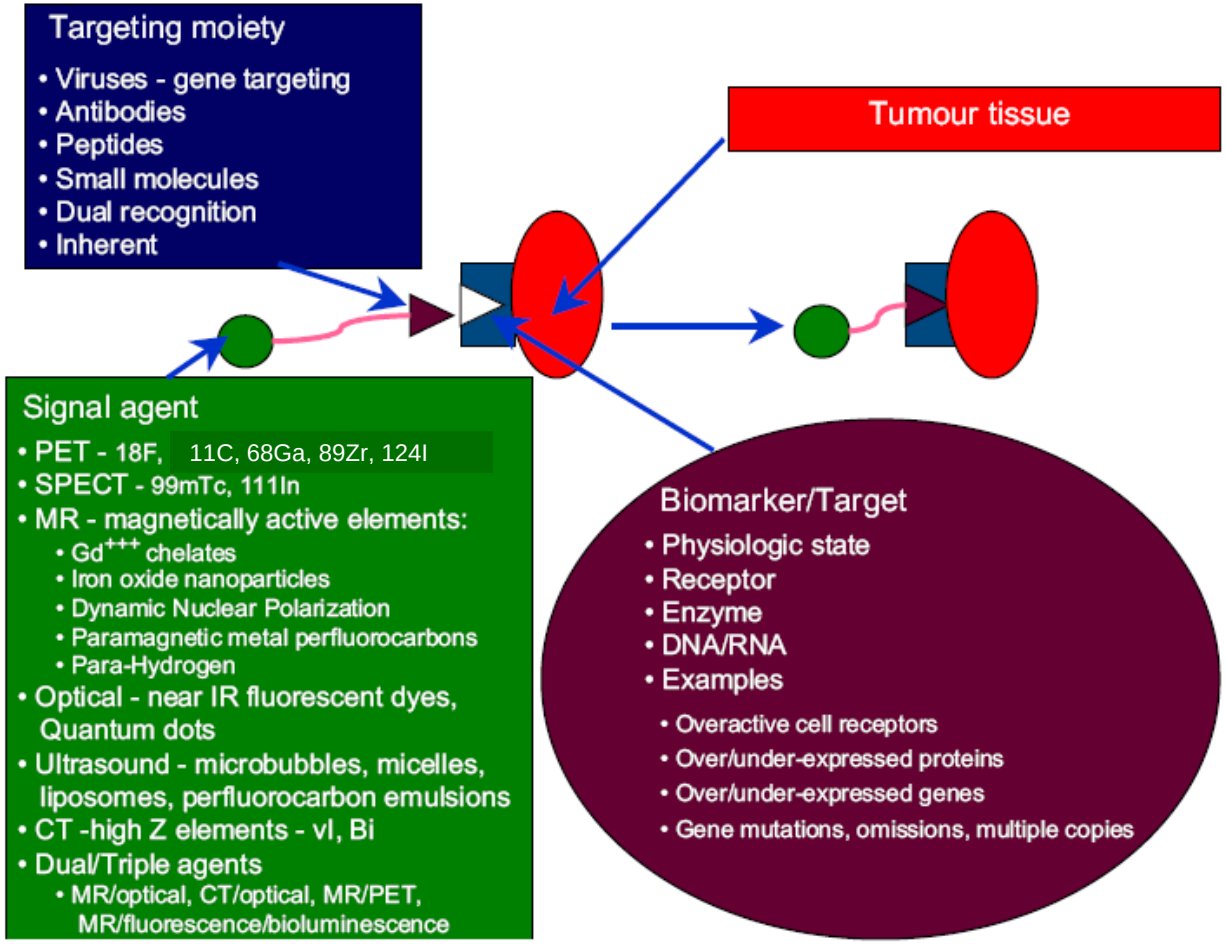


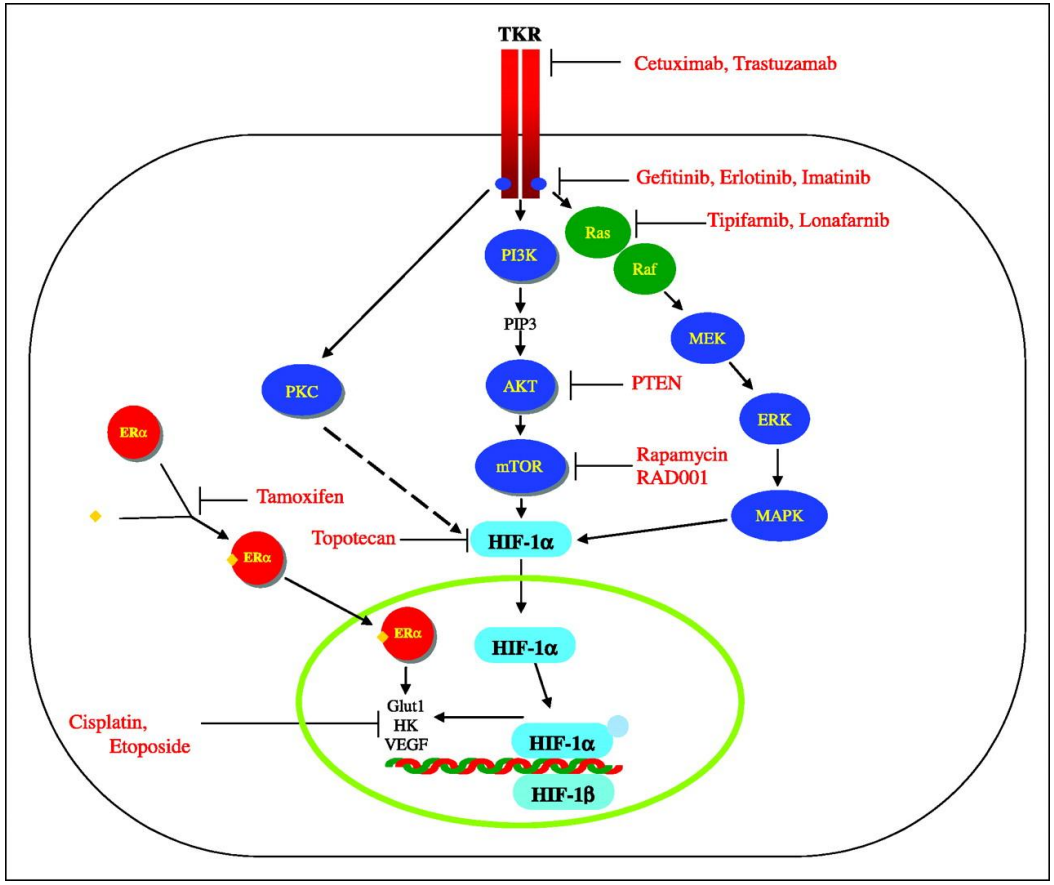
Figure 6 – Biomarker imaging.

Increased use of imaging biomarkers to evaluate:

- metabolism,
- cell proliferation
- cell migration
- receptor expression
- gene expression
- signal transduction
- hypoxia
- apoptosis
- angiogenesis
- Vascular function

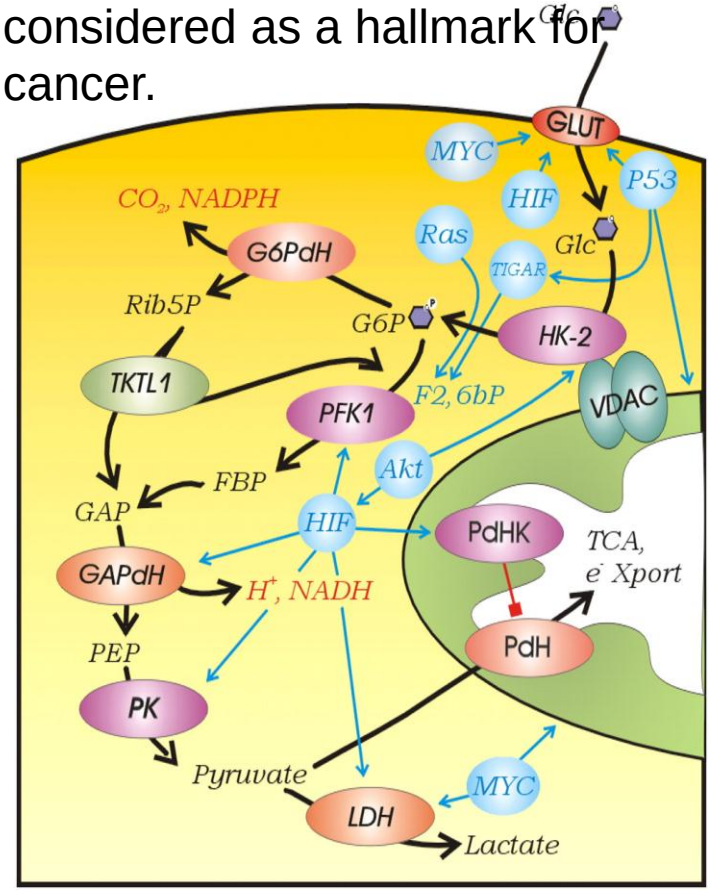
L Fass, Molecular Oncology, 2008

Molecular cancer biology revealed an ever-increasing number of disease regulating intracellular and extracellular tumour targets, which lead to the development of a broad range of targeted therapeutic agents.



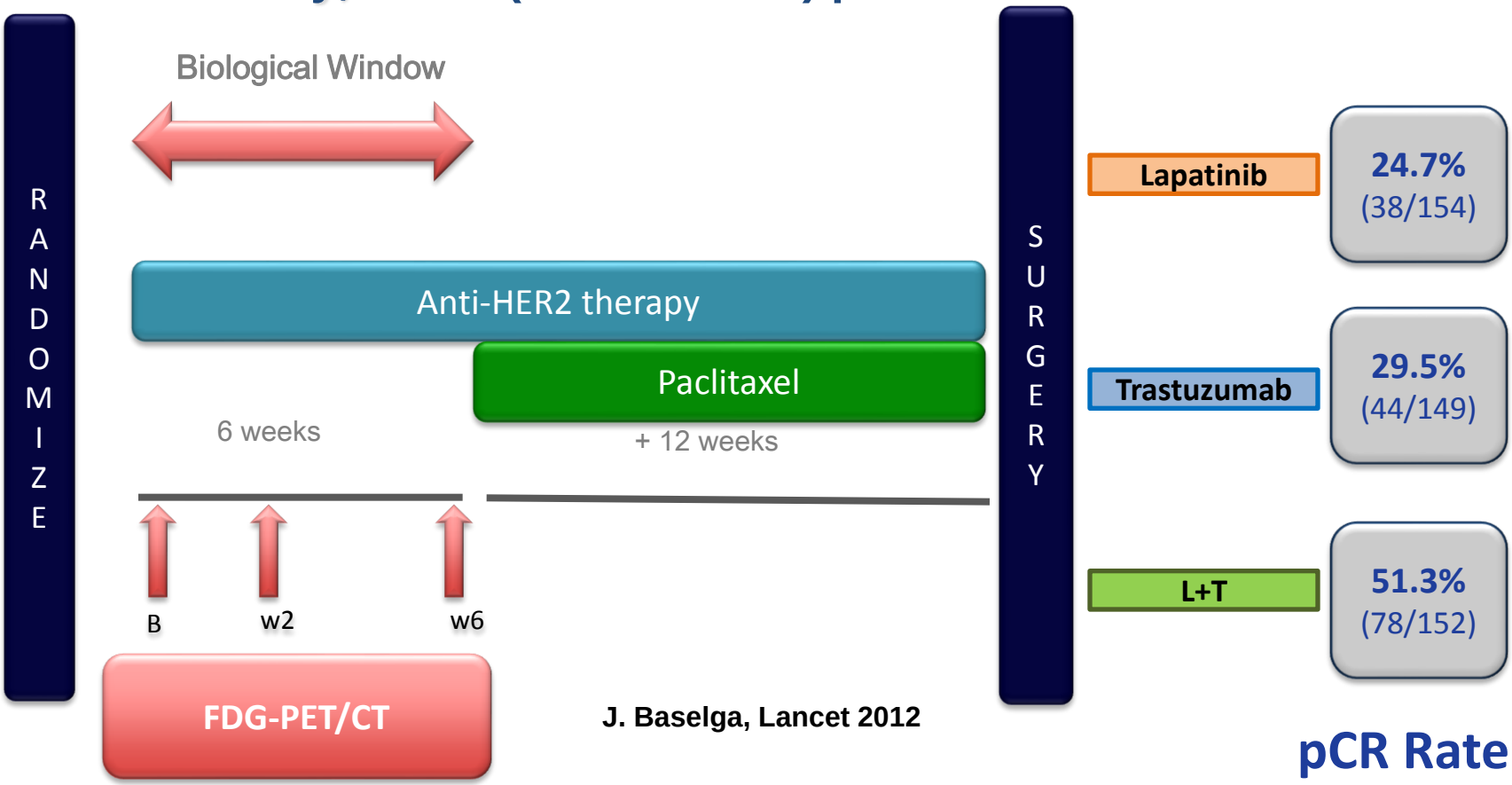
Kelloff G J et al. Clin Cancer Res 2005;11:2785-2808

Few targets have been identified that cover all types of cancer from a given site of origin. However, the common phenotype of elevated glucose consumption is considered as a hallmark for cancer.



Gillies R J et al.J Nucl Med 2008; 49:24S–42S

Trial design Neo-ALTTO study; N = 455 patients in 23 countries
PET substudy; N= 86 (77 evaluable) patients in 14 countries



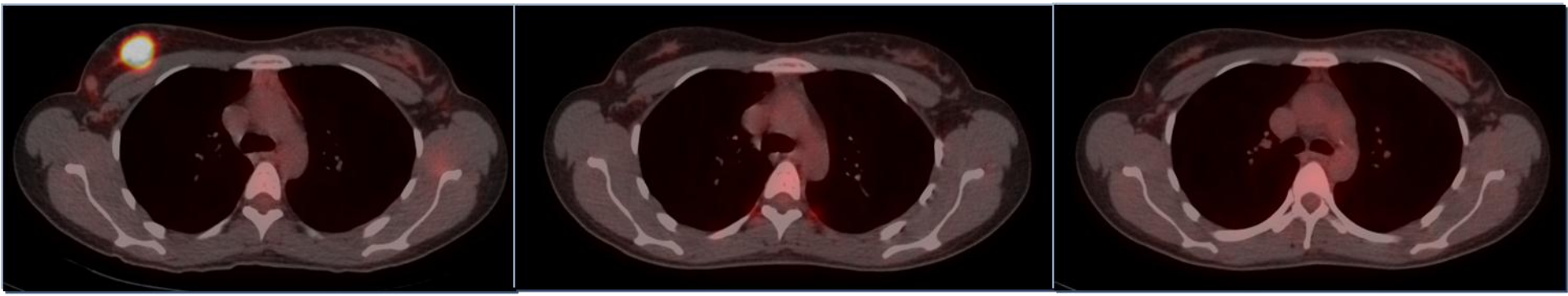
J. Baselga, Lancet 2012

pCR Rate

1. To evaluate early metabolic changes in primary tumor after anti-HER2 therapies in patients with invasive operable breast cancer (biological therapy window: weeks 2 and 6)
2. To test whether FDG-PET metabolic response with anti-HER2 therapies alone predicts Pathological Complete Response (pCR) at the time of surgery

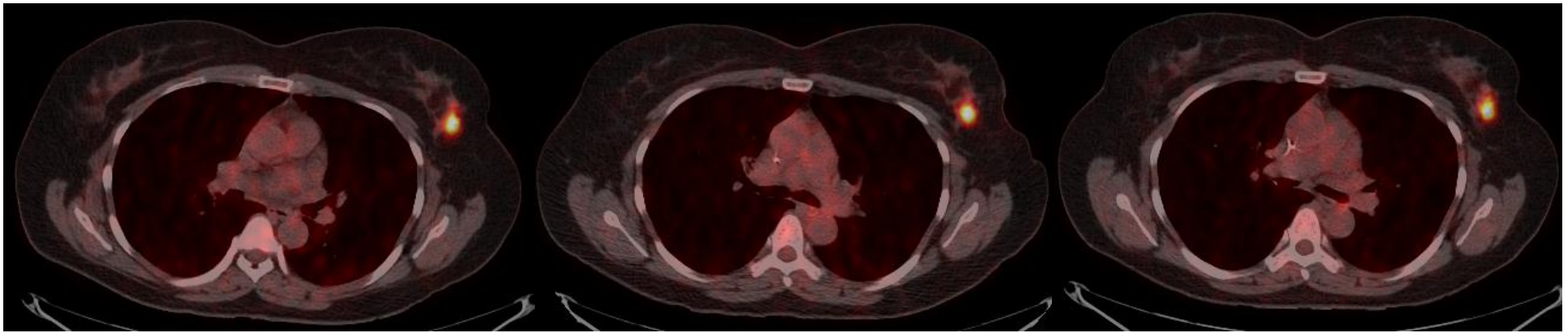
Metabolic responder

BASELINE | WEEK 2 | WEEK 6



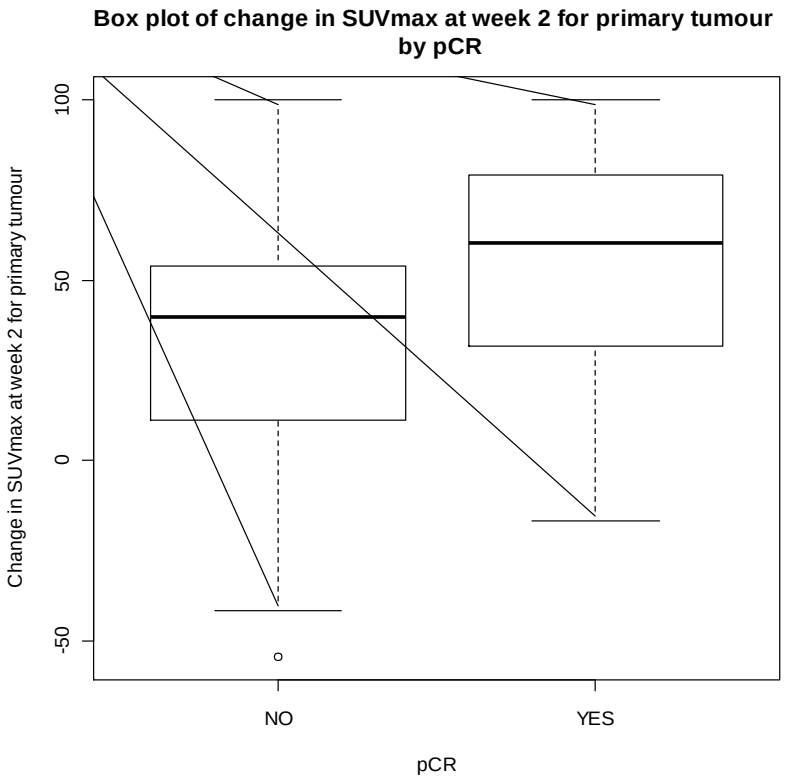
Metabolic non-responder

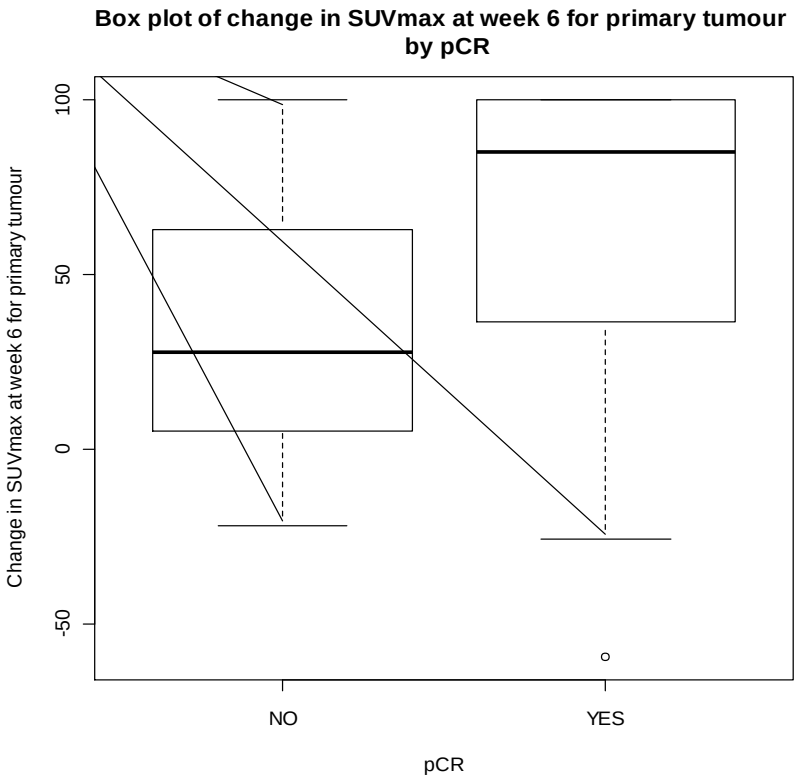
BASELINE | WEEK 2 | WEEK 6



Results Neo-ALTTO PET substudy

Boxplots of the changes in SUVmax



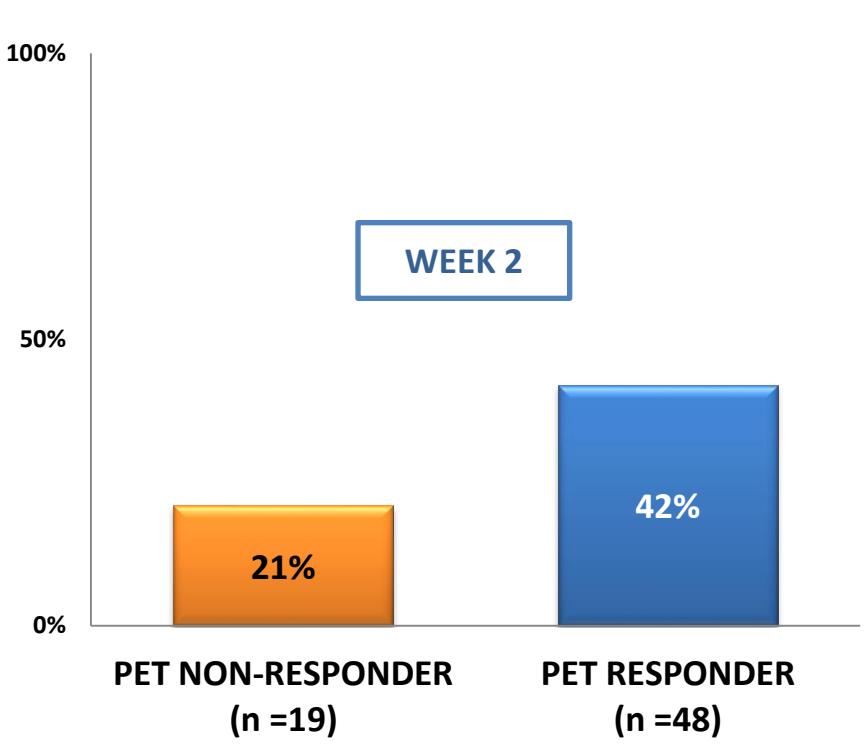


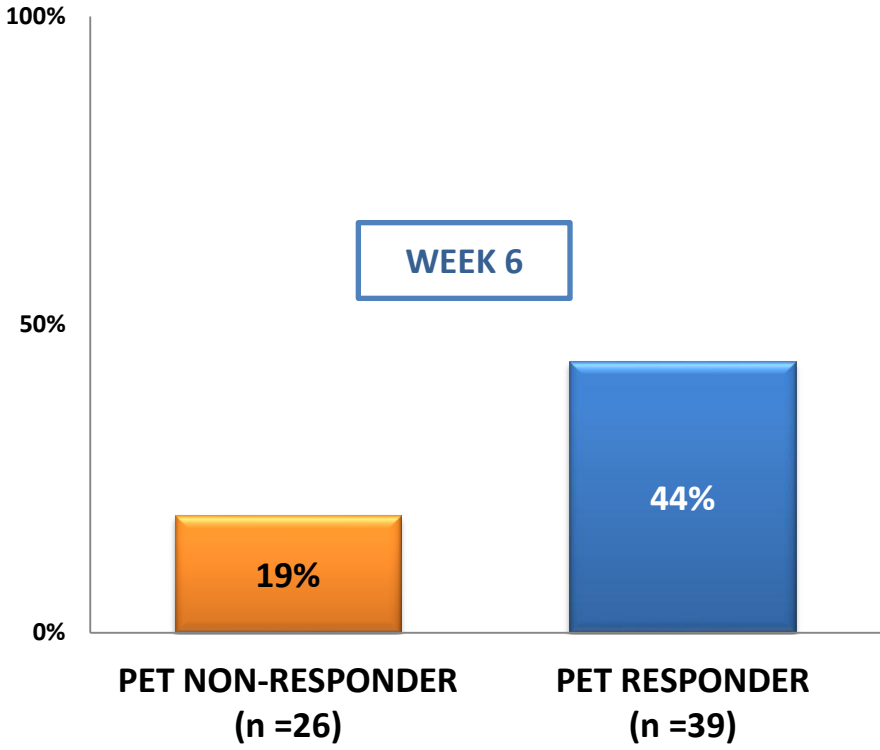
- pCR is associated with greater SUVmax reductions at week 2 and week 6 (p = 0.02 for both).

G. Gebhart et al., SNM 2012

Results Neo-ALTTO PET substudy

Correlation between metabolic response and pCR (EORTC criteria)





- pCR rates are twice as high in patients who are FDG-PET/CT responders compared to non-responders according to EORTC criteria (41% versus 21% at week 2 (p= 0.12) and 43% versus 19% at week 6 (p= 0.05)).

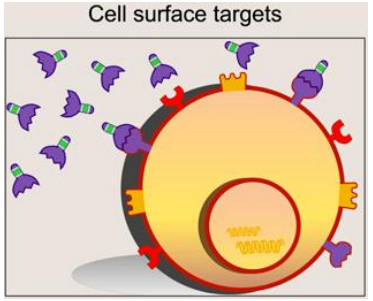
Receptor Imaging

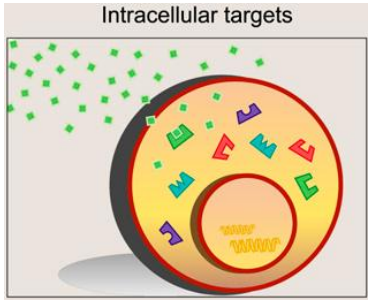
The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Cancer Therapies That Target Oncogenic Proteins.*

Anticancer Drug	Target	Disease
Monoclonal antibodies		
Trastuzumab (Herceptin, Genentech)	ERBB2	Breast cancer
Cetuximab (Erbitux, ImClone)	EGFR	Colorectal cancer
Bevacizumab (Avastin, Genentech)	VEGF	Colorectal cancer, non–small-cell lung cancer
Small molecules		
Imatinib (Gleevec, Novartis)	ABL, PDGFR, KIT	Chronic myelogenous leukemia, gastrointestinal stromal tumors, chordoma
Gefitinib (Iressa, AstraZeneca)	EGFR	Non–small-cell lung cancer
Erlotinib (Tarceva, Genentech)	EGFR	Non–small-cell lung cancer
Sorafenib (Nexavar, Bayer/Onyx)	VEGFR, PDGFR, FLT3	Renal-cell carcinoma
Sunitinib (Sutent, Pfizer)	VEGFR, PDGFR, FLT3	Gastrointestinal stromal tumors, renal-cell carcinoma

* EGFR denotes epidermal growth factor receptor, FLT3 FMS-like tyrosine kinase 3, PDGFR platelet-derived growth factor receptor, and VEGF vascular endothelial growth factor.



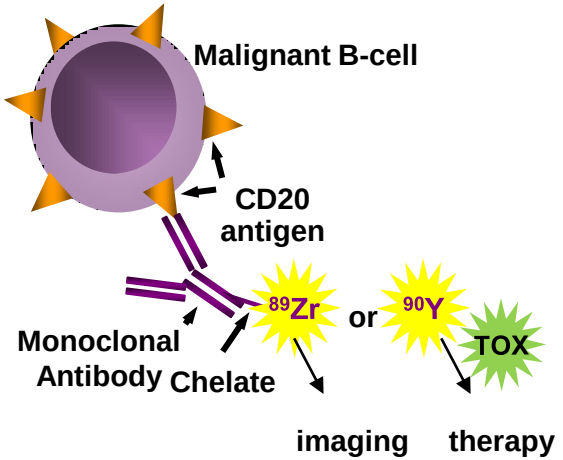


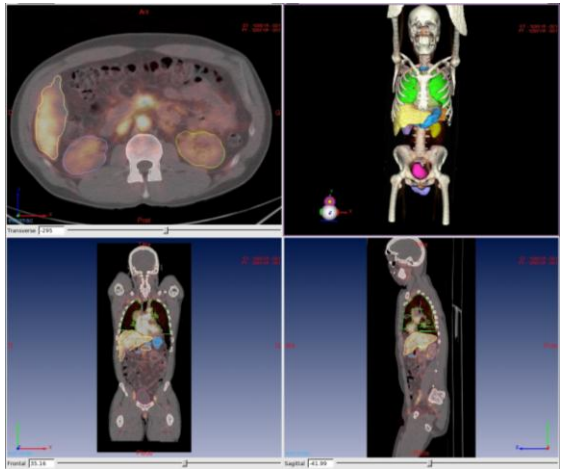
Croce CM, N Engl J Med 2008; 358:502-511

WU A M, J Nucl Med 2009; 50:2–5

Immuno-PET/CT

Immunohistochemical staining in vivo

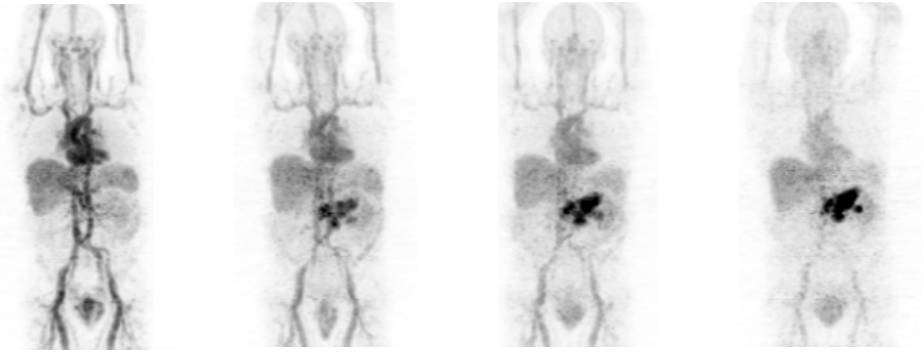




- ^{89}Zr-immuno-PET/CT combines the high sensitivity of PET/CT with the specificity of the chimeric monoclonal antibody (mAb) for the antigen expressed on the surface of cancer cells.
- Zirconium-89 (^{89}Zr) is a positron emitter with a half-life of 78.4 hours, which is compatible with the time needed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

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

Intra-abdominal relapse of a follicular lymphoma.



1 hour p.i. | 1 day p.i. | 3 days p.i. | 6 days p.i.

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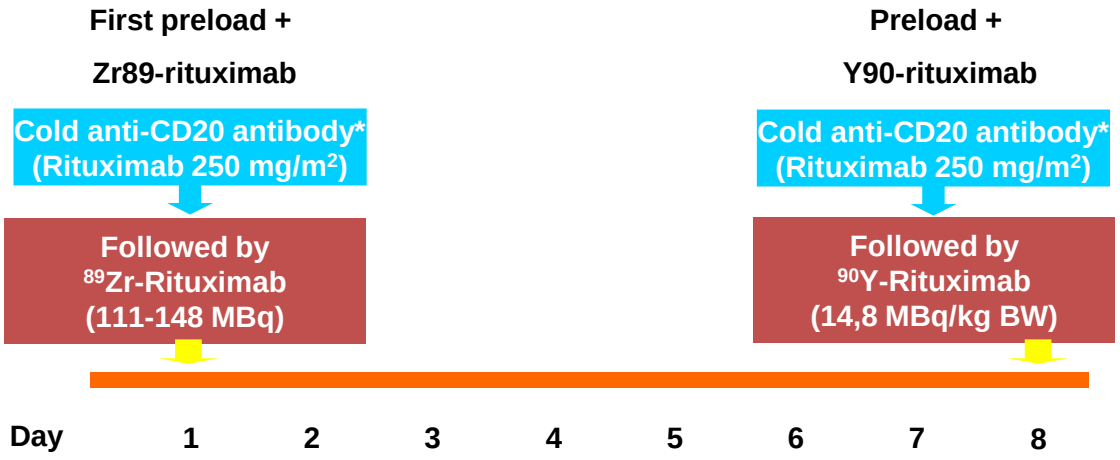
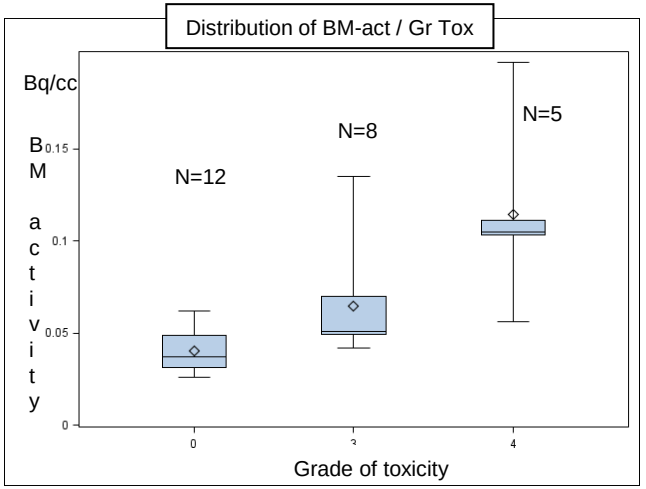
Immuno-PET/CT

Prediction of toxicity (Zr89-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





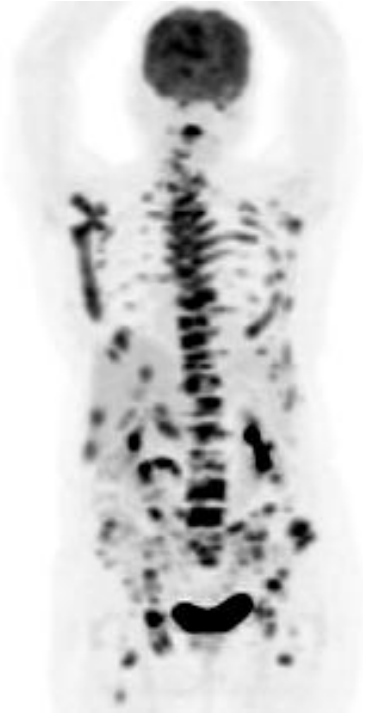
Significant differences were observed in BM activity concentration between between patients with < grade 3, grade 3 and grade 4 toxicities (p=0.0009 Kruskal-Wallis test).

K. Muylle, J. Bordet Institute, Brussels

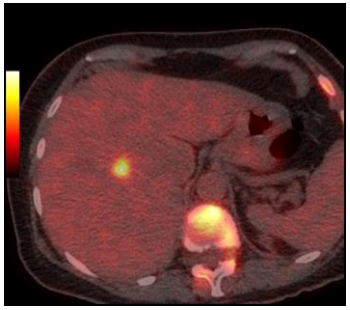
Immuno-PET/CT

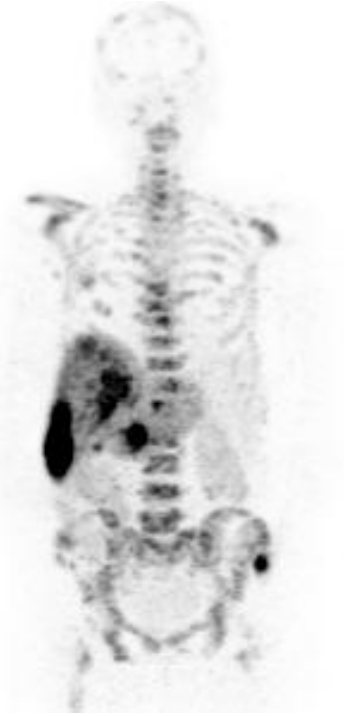
Tumour heterogeneity (Zr89-trastuzumab)

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

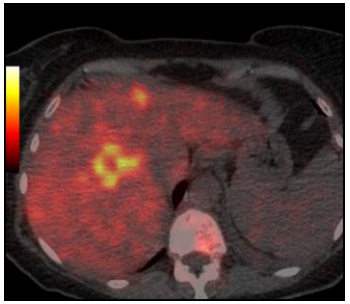


FDG
1 h p.i.





Zr89-trastuzumab
4 days p.i.



Immuno-PET/CT

Prediction of response (Zr89-rituximab)

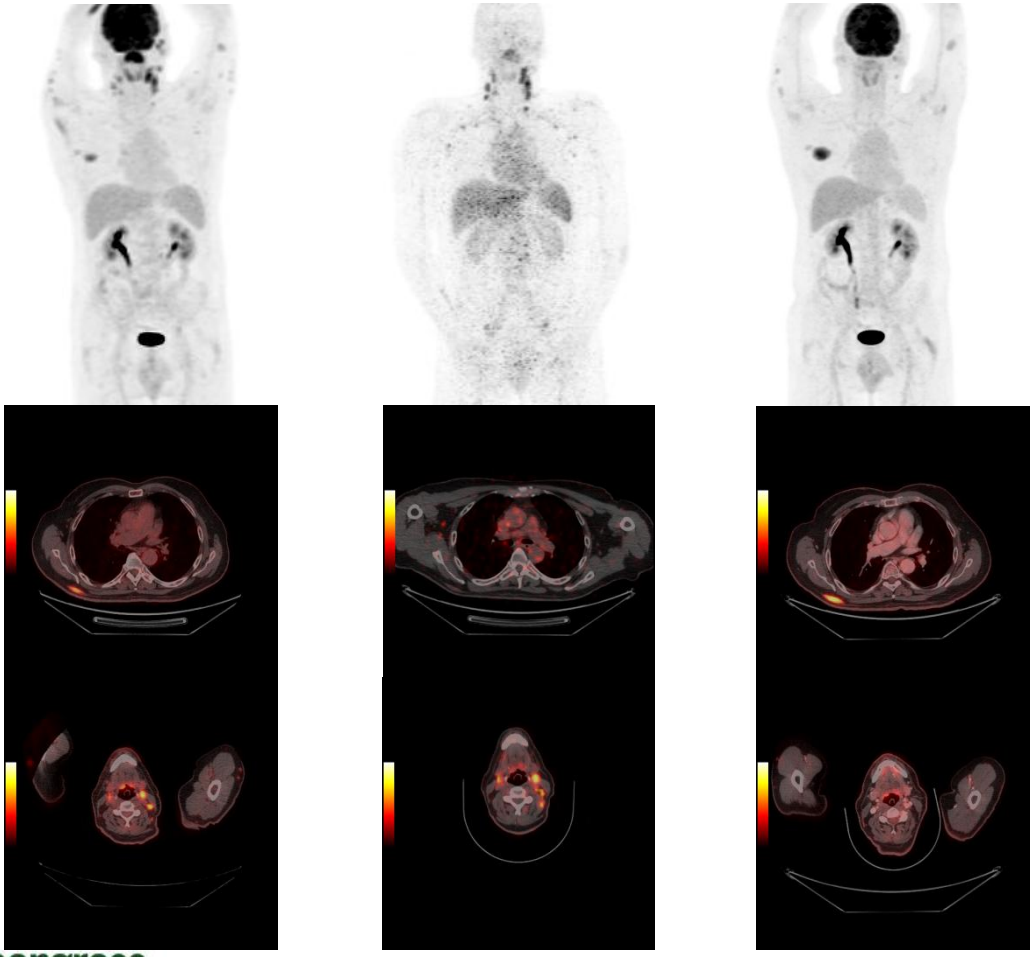
NHL

Biopsy proven CD20+

subcutaneous lesions

&

lymph node involvement



FDG-PET/CT Pre-treatment

Immuno-PET/CT Pre-treatment

FDG-PET/CT Post-treatment

Difference in accessibility: preferential sites of receptor-binding

Less accessible receptors: No mAb-uptake No response

&

High accessible receptors: high mAb-uptake complete response

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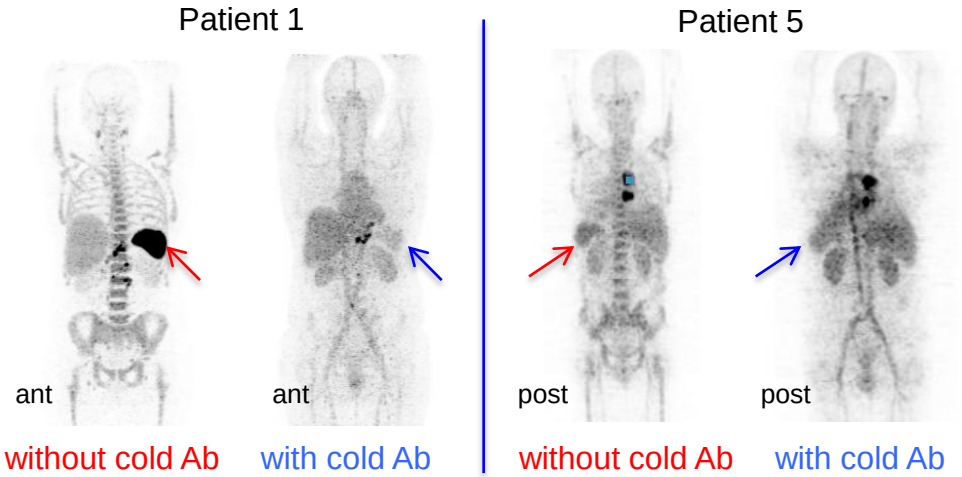
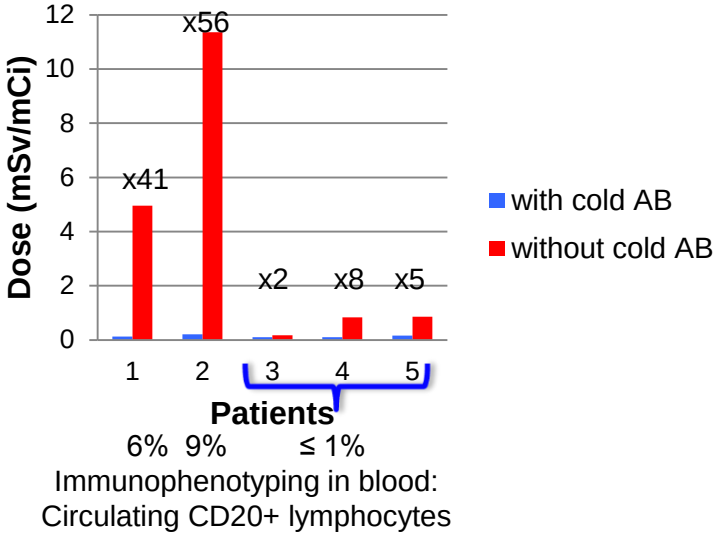
Evaluate and adapt therapeutic regimens in function of patient characteristics (Zr89-rituximab)

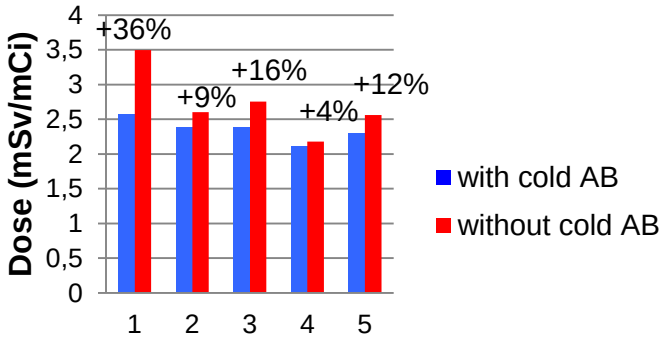
Zr89-rituximab Immuno-PET/CT 6d p.i.



Spleen dosimetry



Bone marrow dosimetry



- Influence of a preload of rituximab on the distribution of the radioconjugate, especially the uptake in the spleen, highly depends on the amount of circulating CD20+ lymphocytes.
- Preload: minor influence on the radiation dose to the spleen in patients with B-cell depletion.
- Without preload: moderate increase of the bone marrow dose by 4-36%

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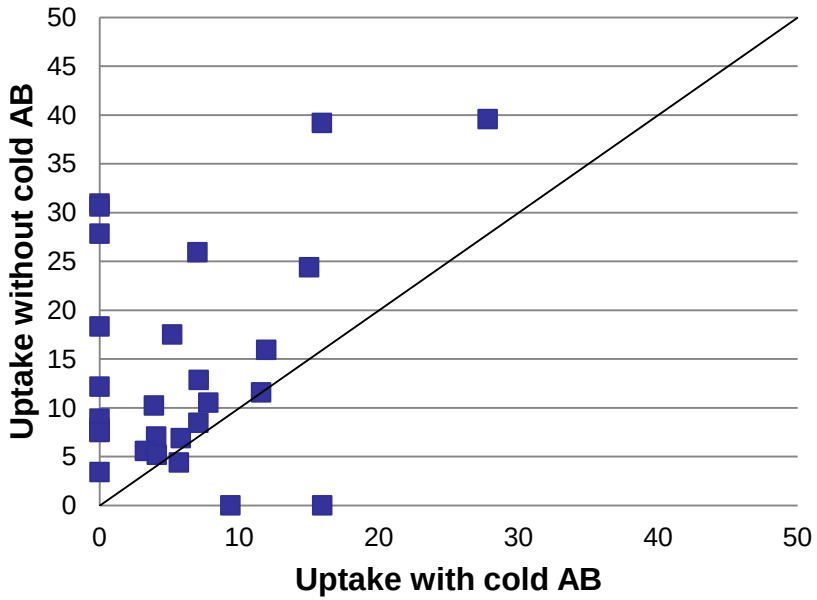
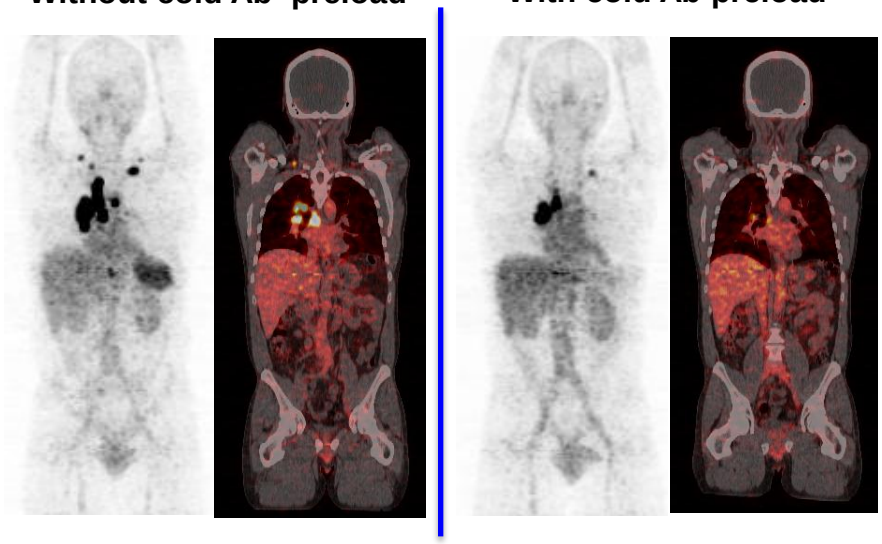
Evaluate and adapt therapeutic regimens in function of patient characteristics (Zr89-rituximab)

Lesion uptake with AB vs without AB



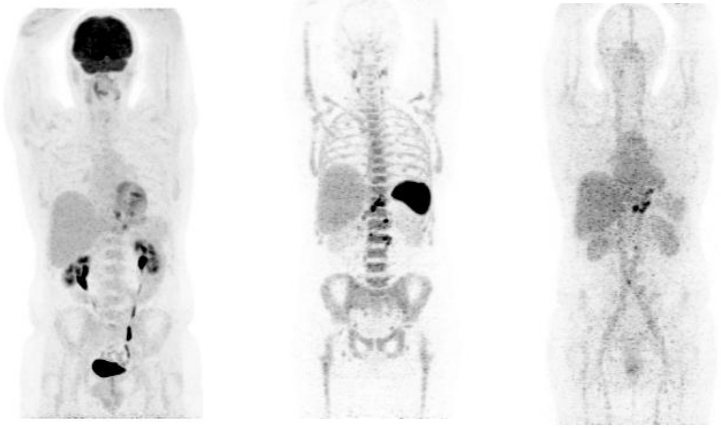
Zr89-rituximab Immuno-PET/CT 6d p.i.

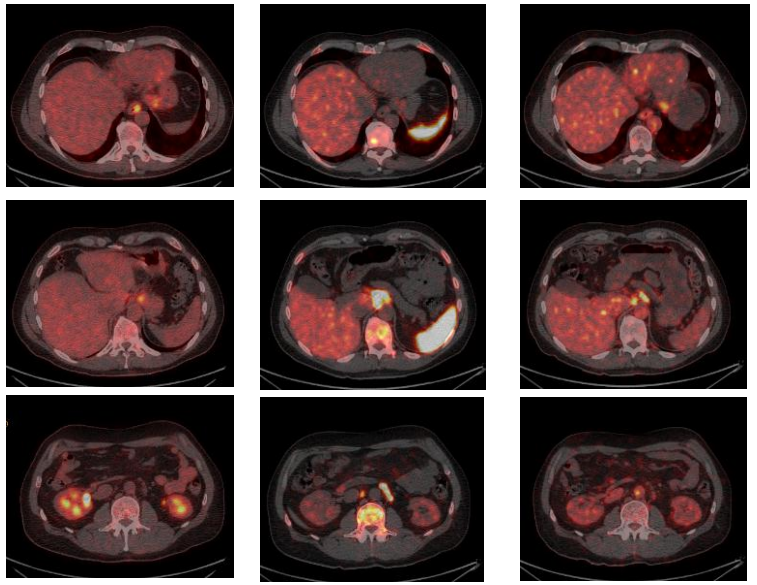
Without cold Ab preload **With cold Ab preload**



- Lesion uptake / tumor targetting is consistently higher without a preload, at least in patients with B-cell depletion…
- 3 lesions show less or no uptake without preload, all 3 in patients without B-cell depletion.

Evaluate and adapt therapeutic regimens in function of patient characteristics (Zr89-rituximab)





In this patient without B-cell depletion:

- Preload impairs uptake in involved lymph nodes < (partial) saturation with cold mAbs.
- Preload enhances uptake in the 2 visceral lesions < reducing the uptake in the spleen

> higher residence time of the radioconjugate in blood > binding in less accessible regions.

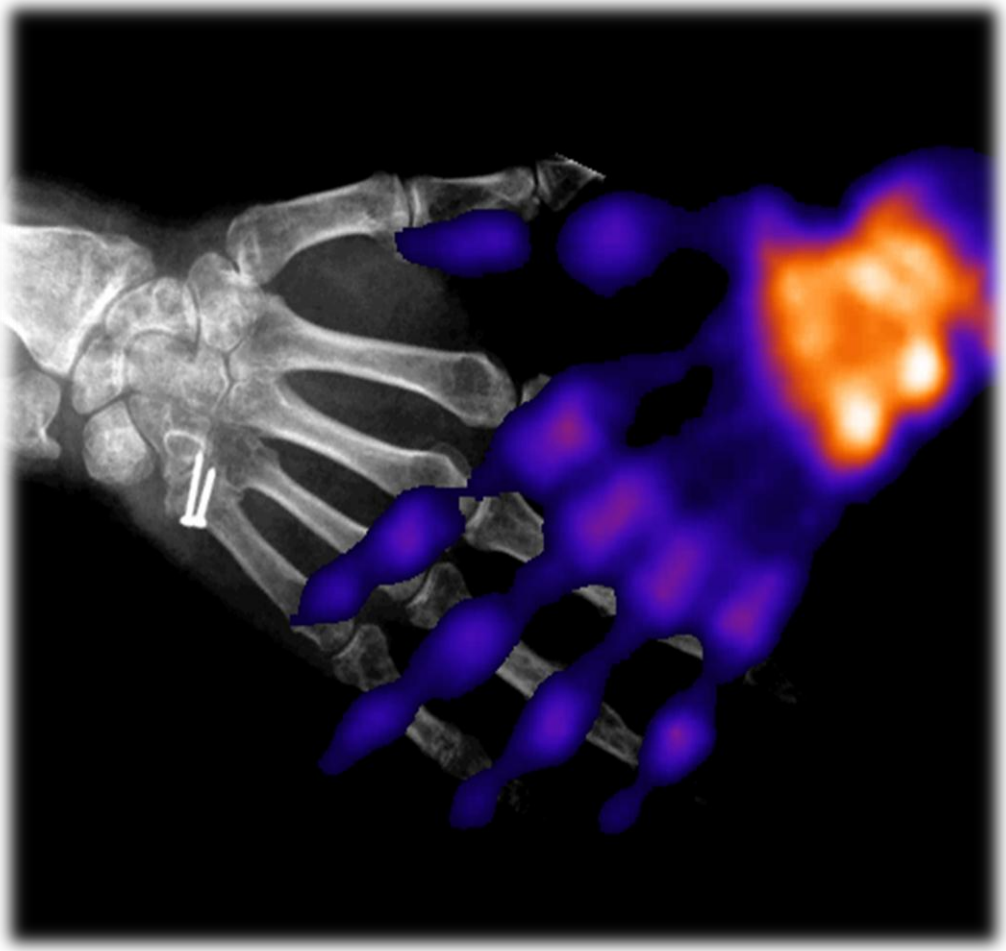
Role of molecular imaging in early drug development

Implementation of molecular imaging in clinical trials has high potential in terms of:

- non-invasiveness
- the potential for serial studies for evaluation of the in vivo effects of a drug on the target
- ability to quantify cellular targets for the entire disease burden
- Identification of heterogeneous receptor expression

  > avoid sampling errors
- prediction of treatment outcome

  > avoid unnecessary toxicity
- enriching patient selection by assessing drug targeting and/or early-on response prediction > reduction of costs
- evaluation and adaptation of therapeutic regimens > reduction of costs
- development of patient tailored image guided therapy



THANKS