

# The contribution of molecular imaging to investigate tumor heterogeneity and early evaluation of response to anti-HER2 agents in Breast Cancer

4th International conference « TRANSLATIONAL  
RESEARCH IN ONCOLOGY »  
Geraldine Gebhart

**ULB**



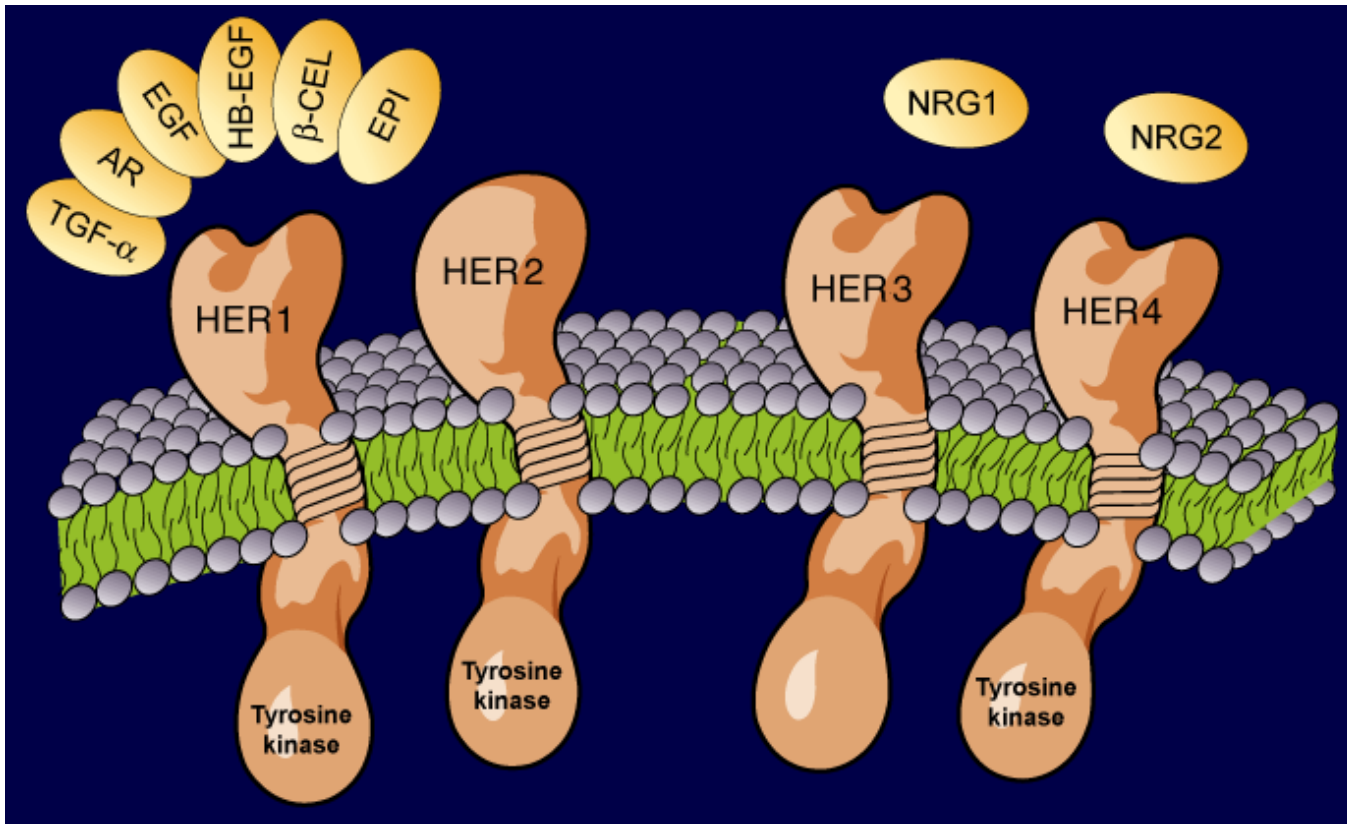
INSTITUT  
**JULES BORDET**  
INSTITUUT 1

# Outline

- Part 1: HER2 receptor, Anti-HER2 therapies and molecular imaging in breast cancer
- Part 2: Response prediction to neoadjuvant anti-HER2 therapies using FDG PET/CT: the Neo-ALTTO trial
- Part 3: Heterogeneity of HER2 imaging across metastatic lesions and prediction of response to T-DM1 using FDG and/or  $^{89}\text{Zr}$ -trastuzumab PET/CT: the ZEPHIR trial
- Conclusions and perspectives

# Epidermal growth factor receptor family

Extracellular domain

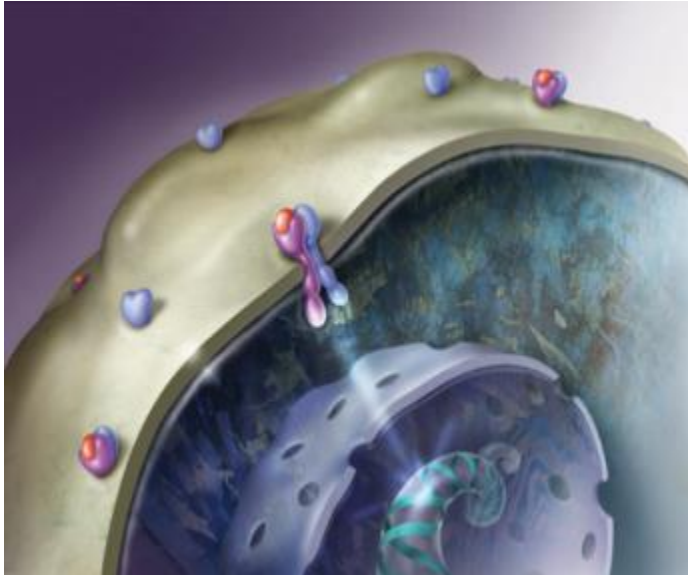


Intracellular domain

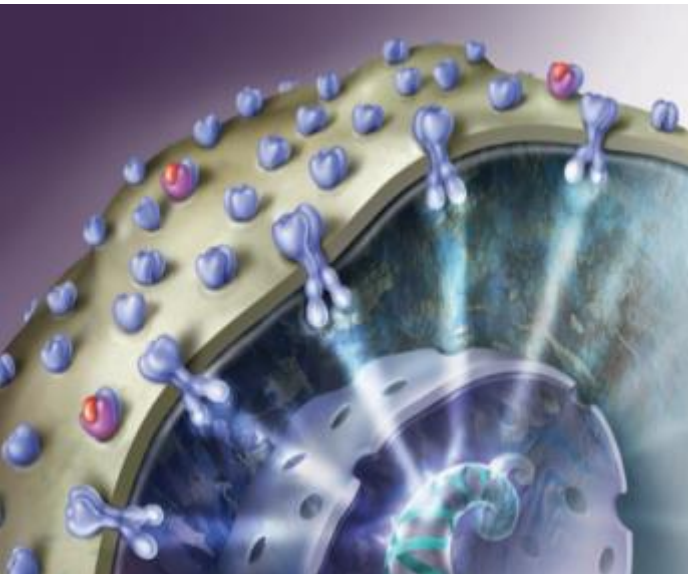
Adapted from Tzahar and Yarden. *Biochim Biophys Acta*. 1998;1377:M25.

# HER2 + Breast Cancer

Normal HER2 gene



Amplified HER2 gene  
(15-20 % of breast cancer)



1984 – HER2 gene discovery (*Weinberg and associates*)

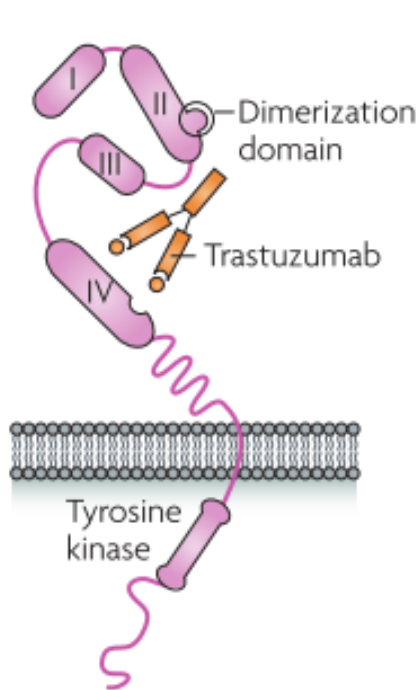
1987 – Aggressive Biology (*Slamon*)

1992 – Humanized anti HER2 mAb (*Carter*)

Start of clinical development in breast cancer

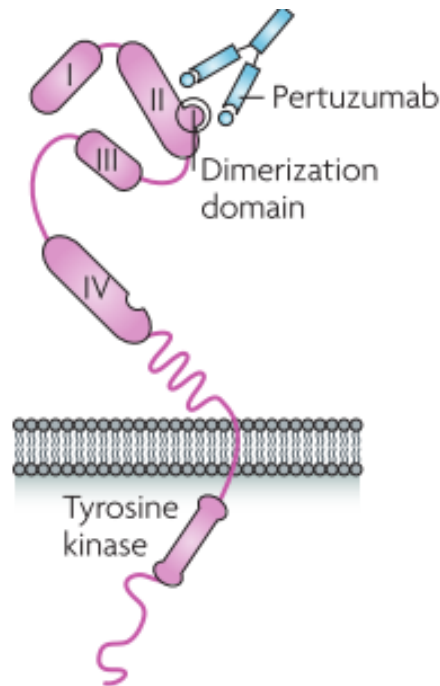
# Anti-HER2 therapies used in the clinic

Inhibition through direct antibody binding



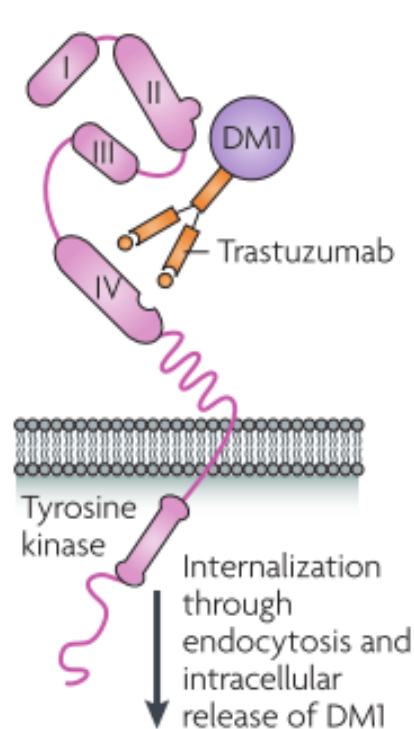
**TRASTUZUMAB**

Inhibition through dimerization inhibition



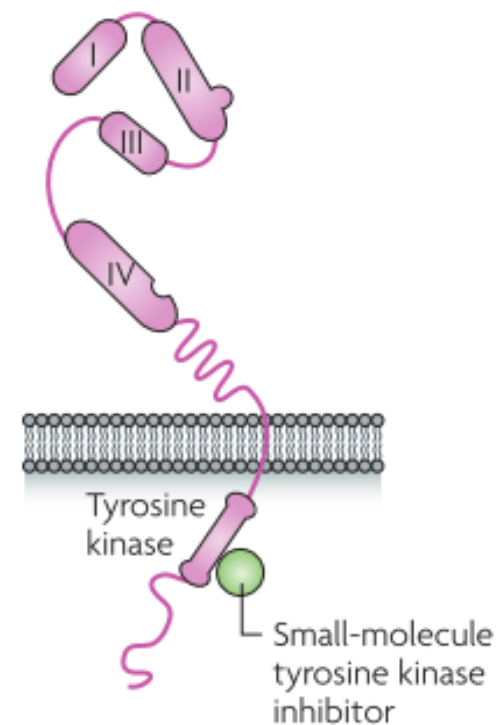
**PERTUZUMAB**

Targeting for intracellular drug delivery



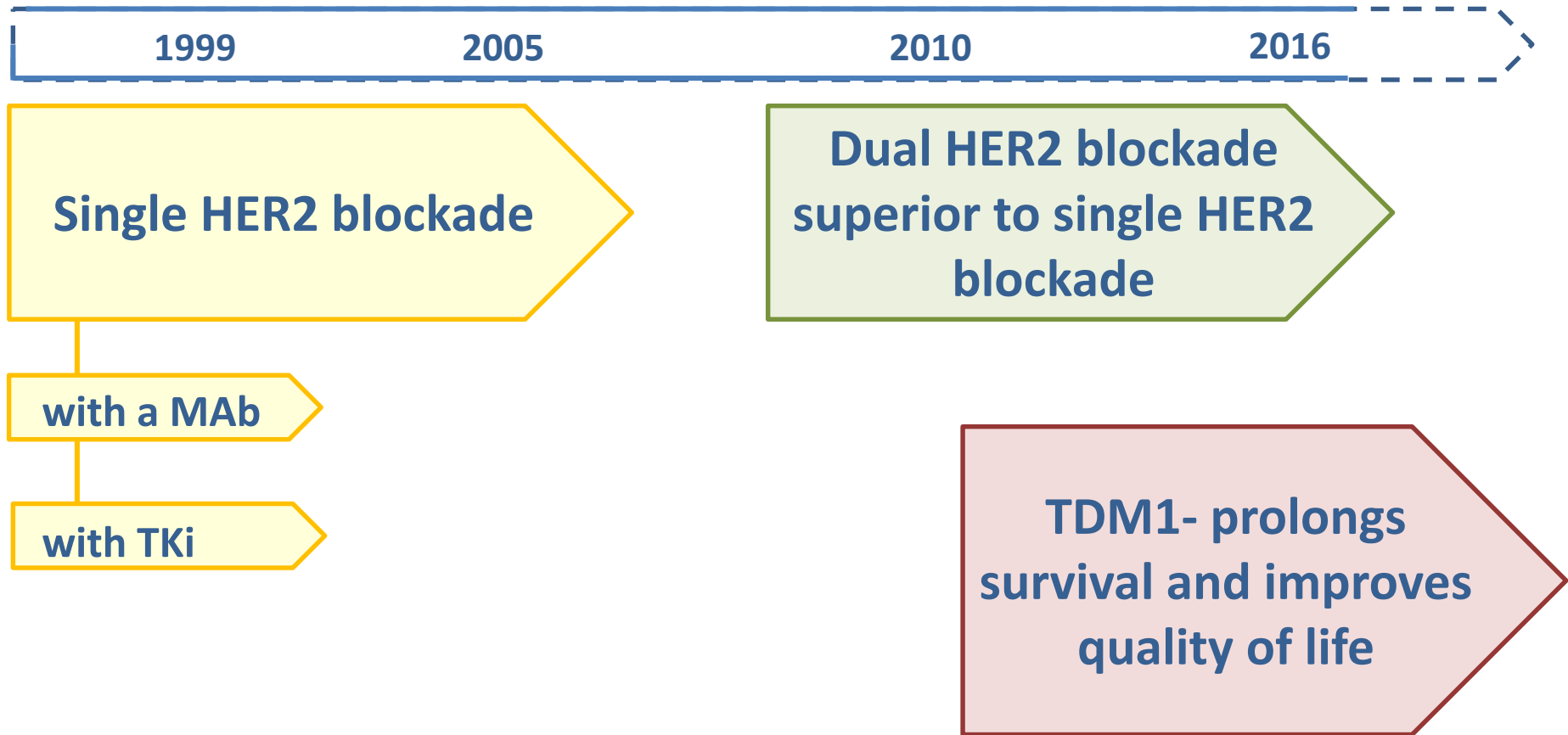
**T-DM1**

Inhibition of tyrosine kinase activity



**LAPATINIB**

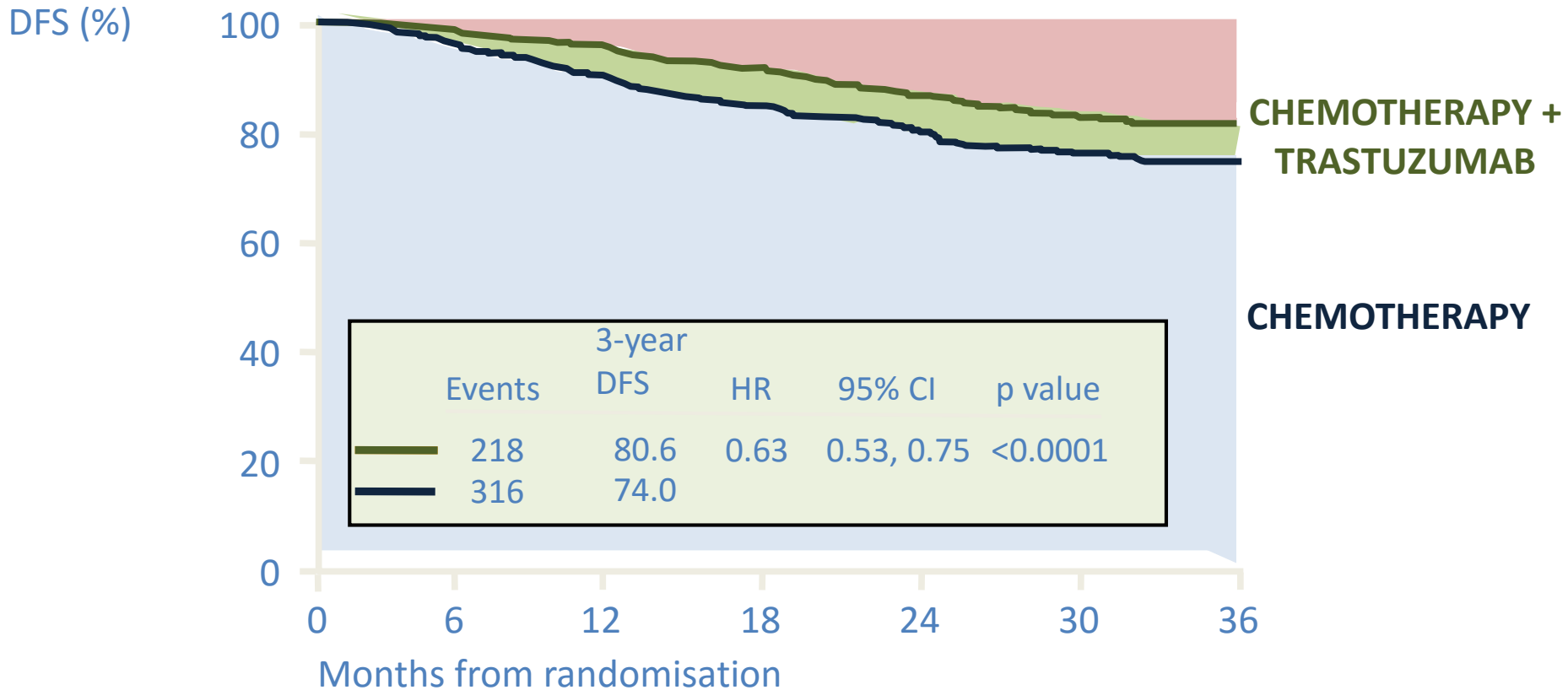
# The medical treatment of HER2 positive Breast Cancer



*Mab: monoclonal antibody*  
*Tki: Tyrosine kinase inhibitor*

# The context of trastuzumab resistance: early disease

*HERA Trial*



No.		1703	1591	1434	1127	742	383	140
at risk		1698	1533	1301	930	606	322	114



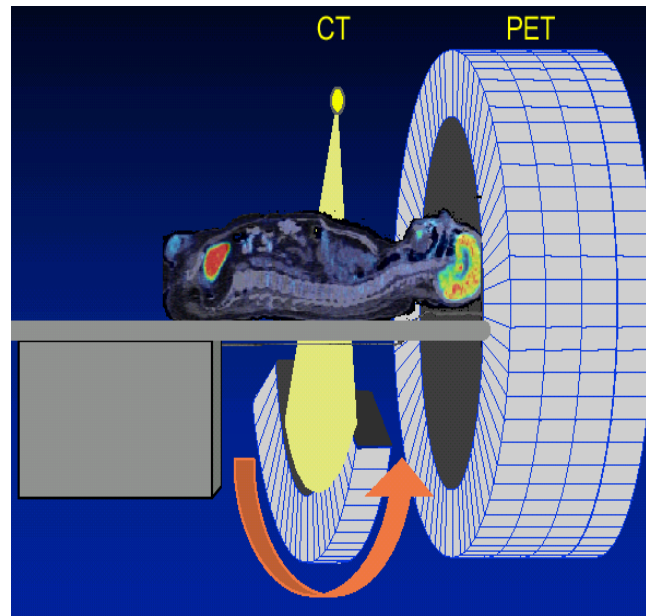
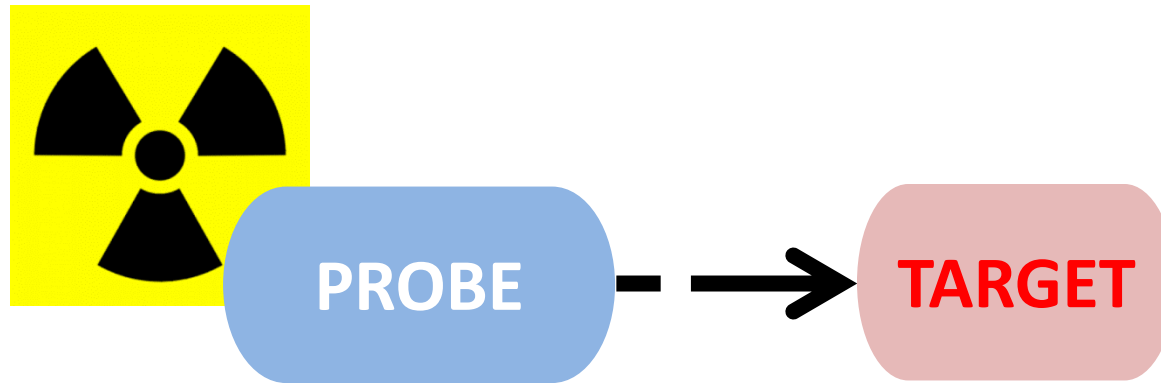
# Predictive factors in HER2 positive breast cancer



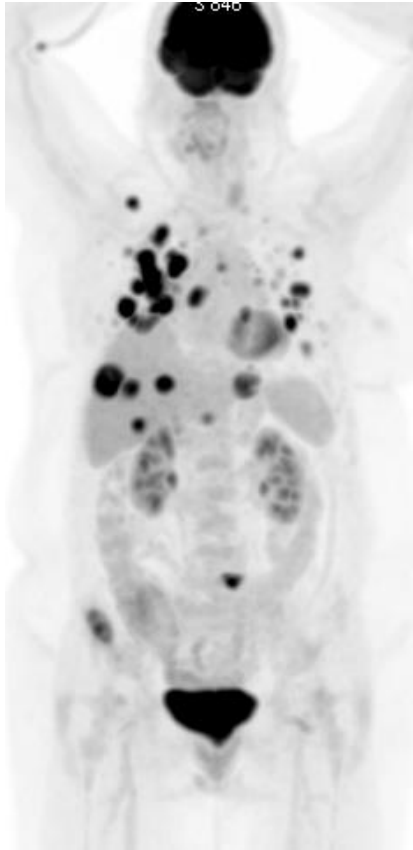
**HER2**



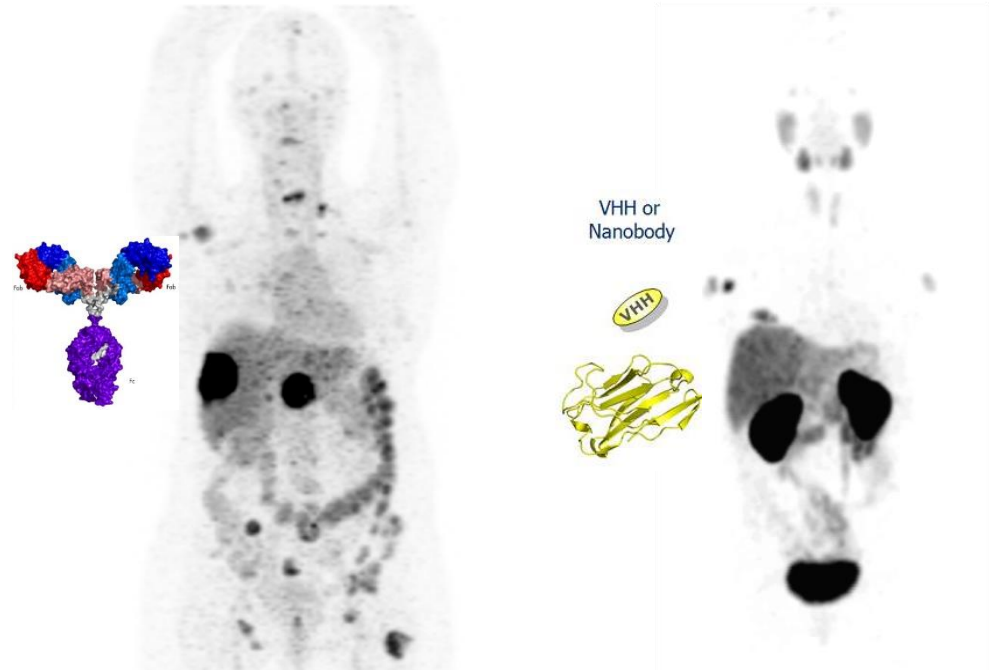
# PET: Positron-Emitting Tomography



# Molecular imaging in HER2 positive BC

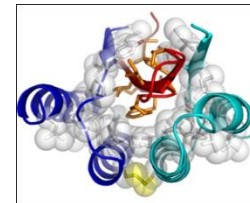


**FDG PET/CT**



*Monoclonal antibodies*

*Nanobodies*



*Affibodies*

**HER2 PET/CT or SPECT/CT**

\*Dijkers et al. Clin Pharmacol Ther 2010

\*Keyaerts et al. JNM 2016

# Molecular imaging in HER2 positive BC clinical trials

## The literature

- 6 trials\* (1 multicentric)
- Neoadjuvant chemotherapy + trastuzumab
- FDG PET/CT repeated after one or 2 cycles
- FDG PET correlated with pCR in 5/6 trials
- Variable SUVmax criteria (absolute value versus  $\Delta$  SUVmax)

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## Our Experience

Molecular imaging could contribute to better treatment individualization

**Neo-ALTTO**

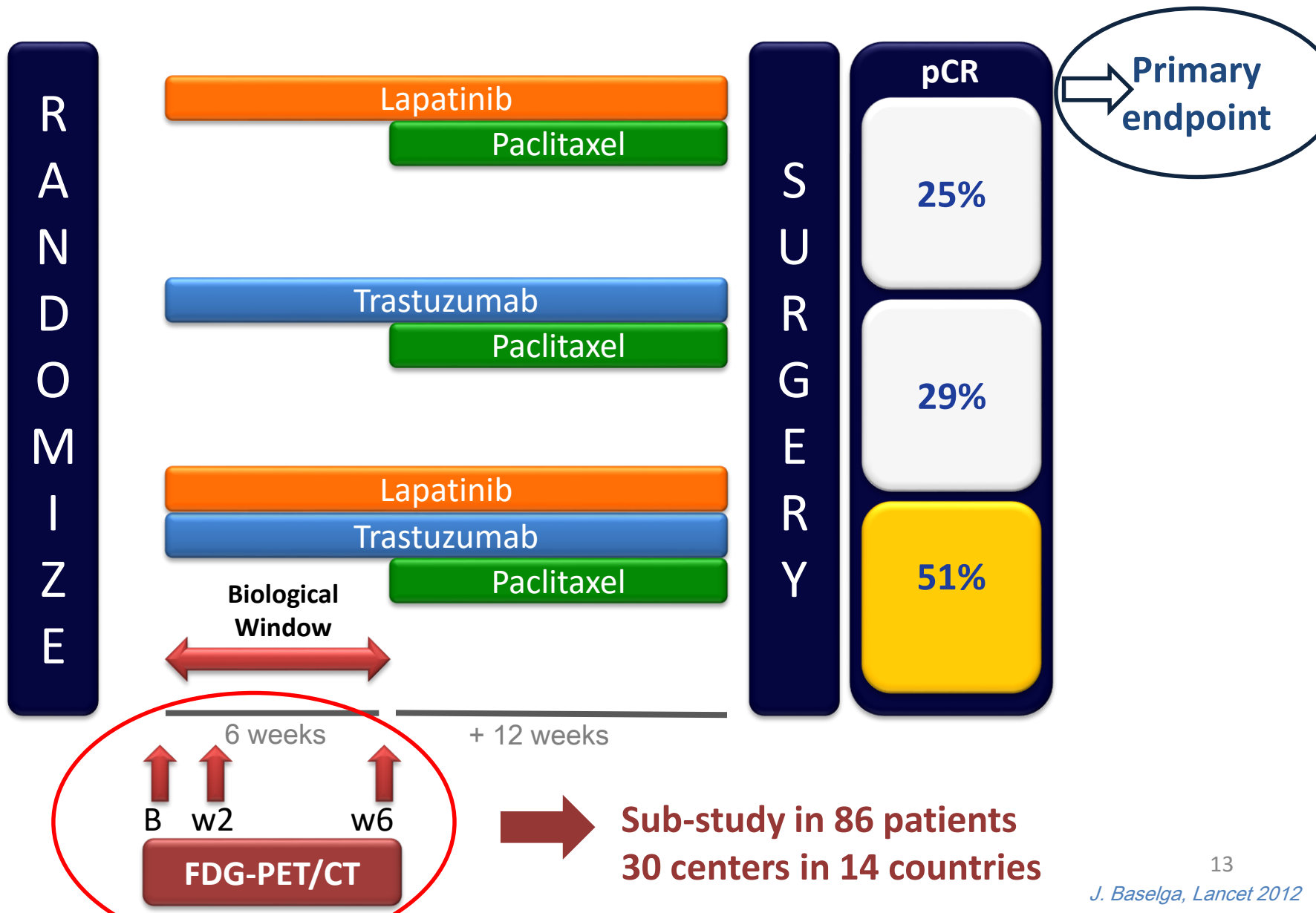
**ZEPHIR**

# Part 2



## **FDG-PET/CT for Early Prediction of pathological complete Response to Neoadjuvant Lapatinib, Trastuzumab, and their Combination in HER2 Positive Breast Cancer Patients: The Neo-ALTTO PET Study Results**

# Neo-ALTTO Study (N = 455 women 86 sites in 23 countries in Europe, Asia, North and South America, and South Africa)



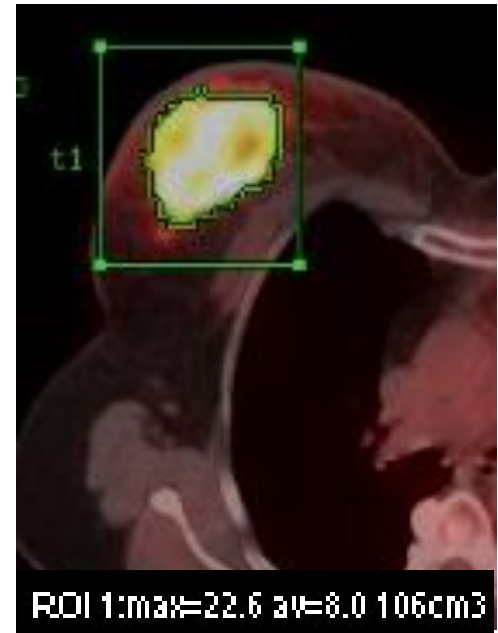
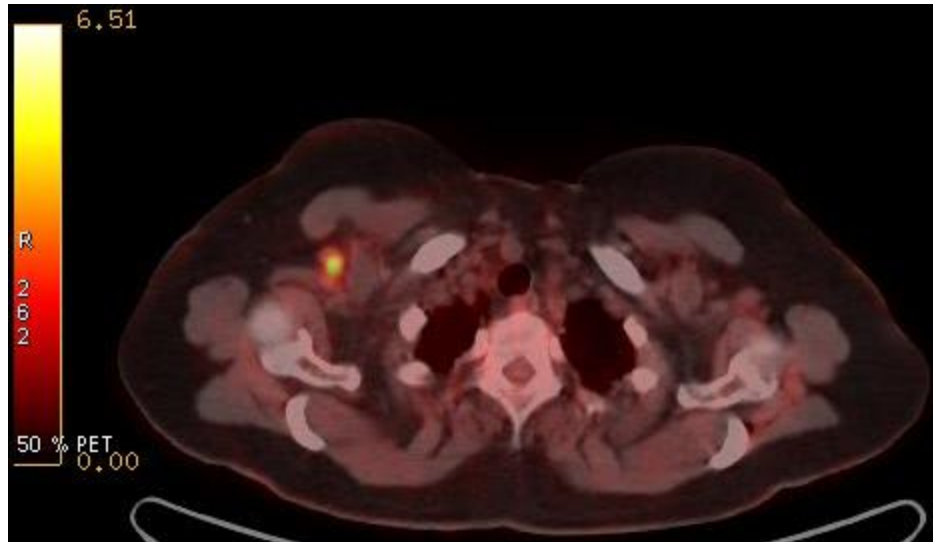
# Objectives of the Neo-ALTTO PET sub-study

1. To evaluate early metabolic changes in primary tumor during anti-HER2 therapies (at week 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



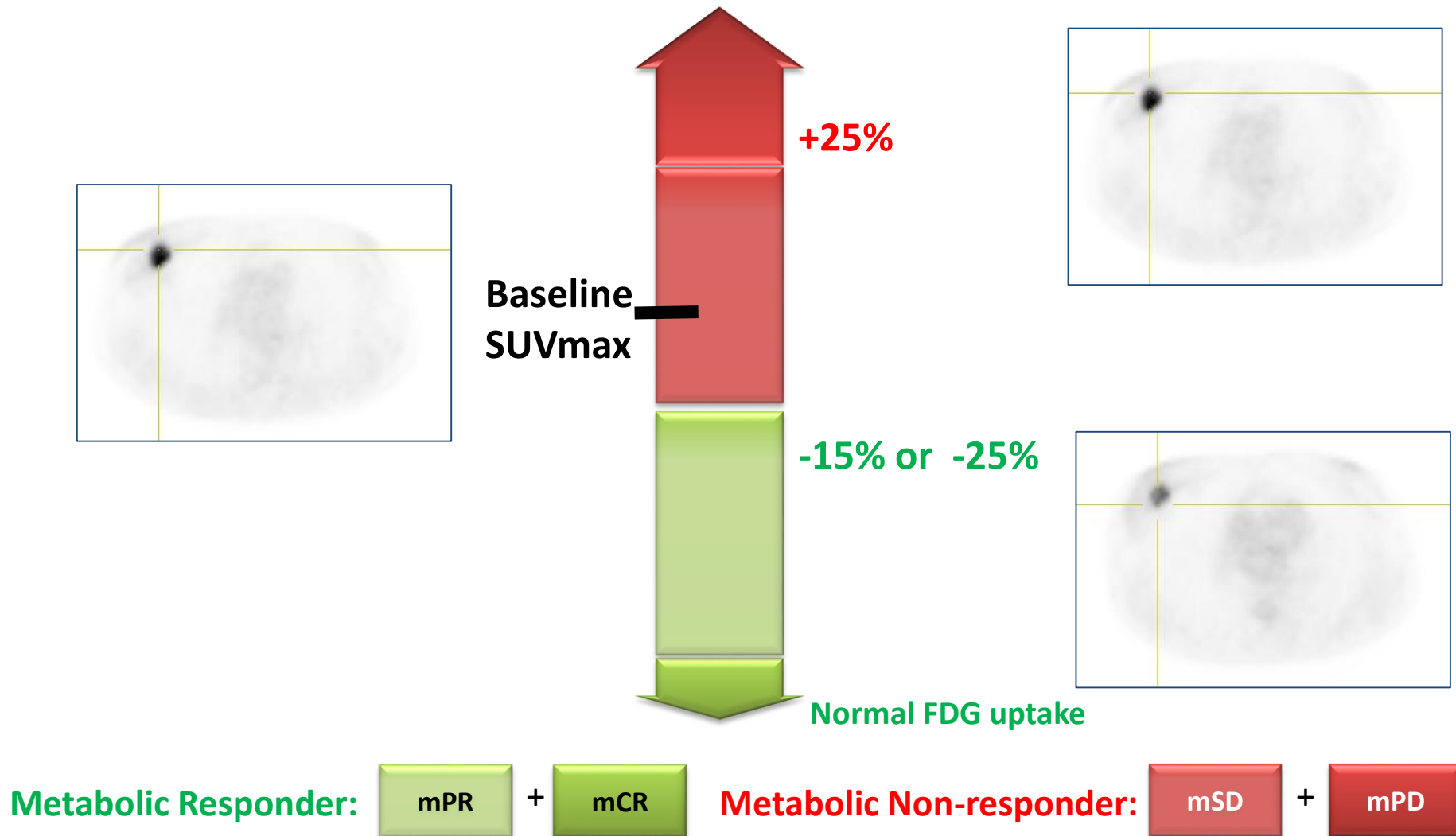
# Methods

- Standardized PET/CT acquisition protocol
- PET/CT analysis based on SUV max of the primary tumor (EORTC criteria)



- Central imaging analysis performed by 2 independent nuclear medicine experts blinded to the assigned therapies (Bellvitge-Barcelona & Bordet-Brussels)

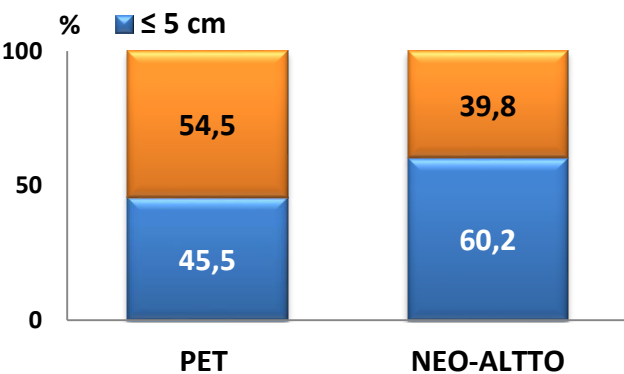
# EORTC criteria



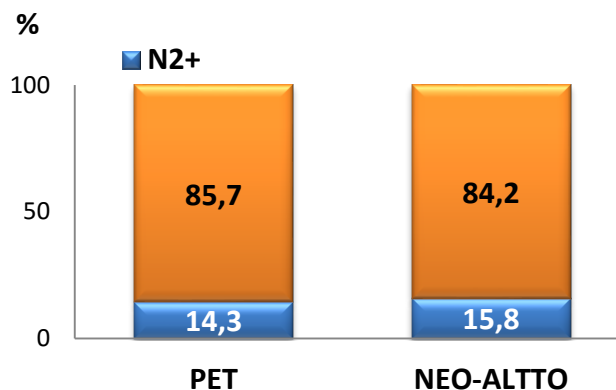
# Neo-ALTTO STUDY : RESULTS

# Comparison Neo-ALTTO and PET sub-study cohort

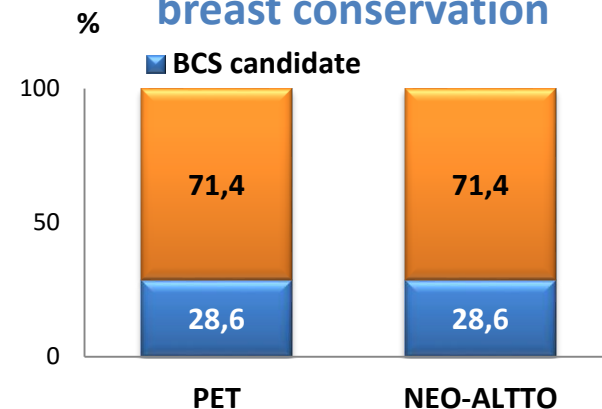
## Tumor Size



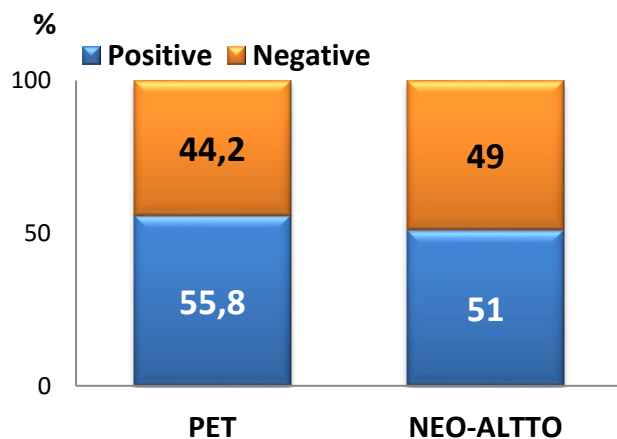
## Clinical Node Status



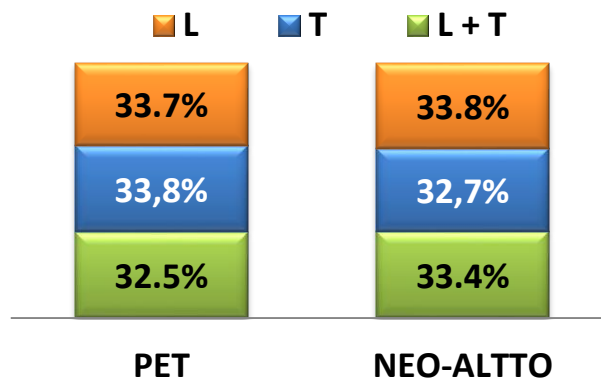
## Candidates for breast conservation



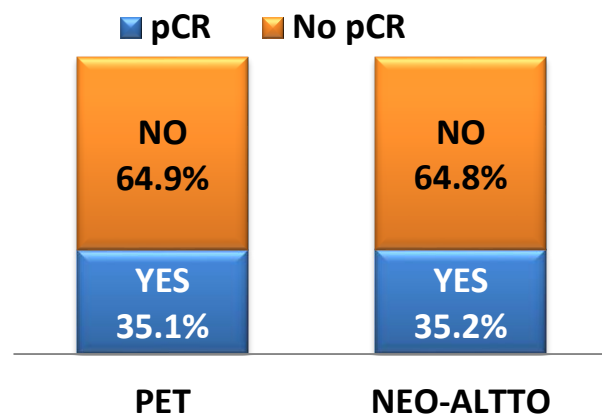
## Hormone Receptor Status



## Treatment Allocation

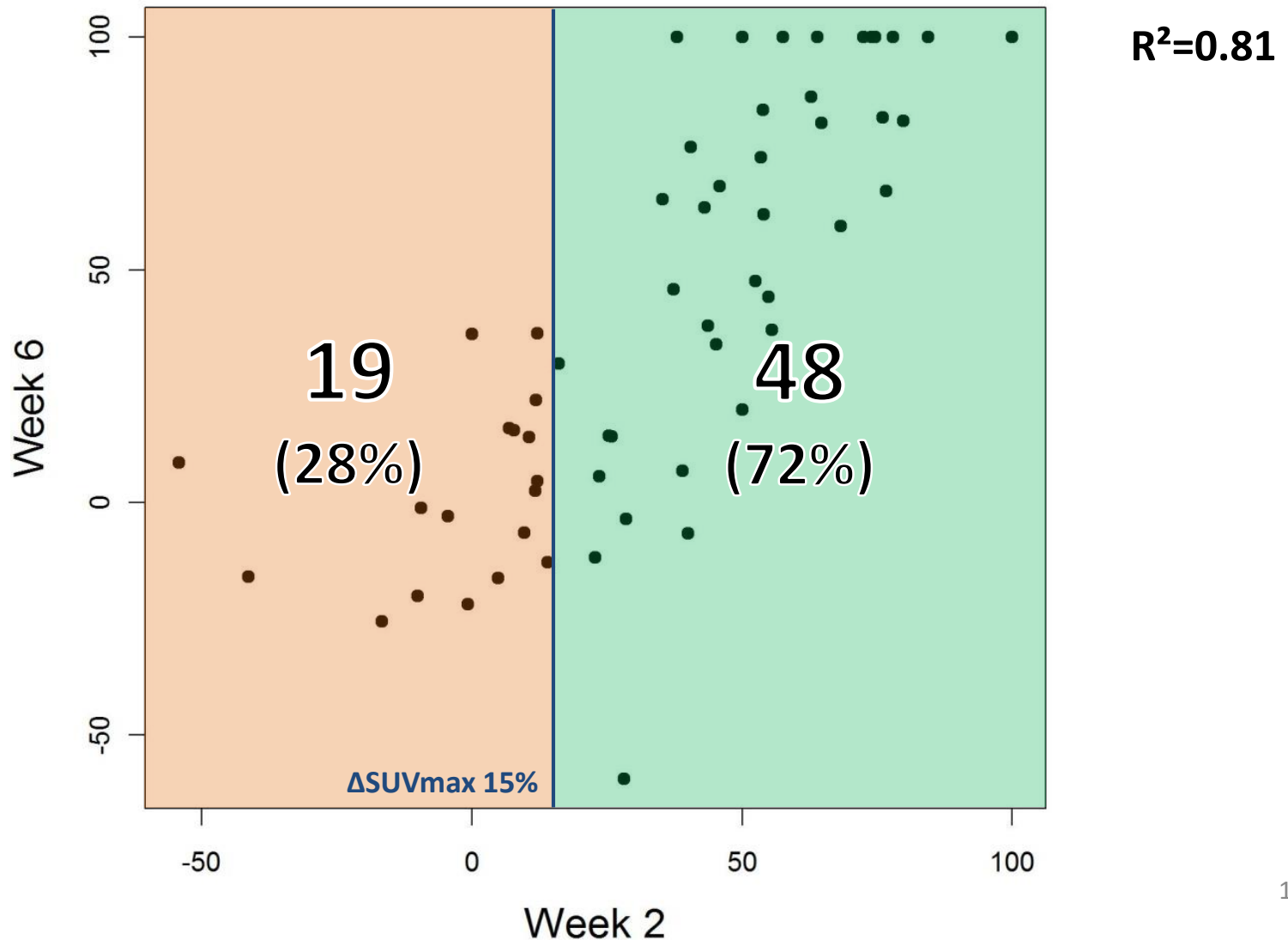


## pCR at Surgery



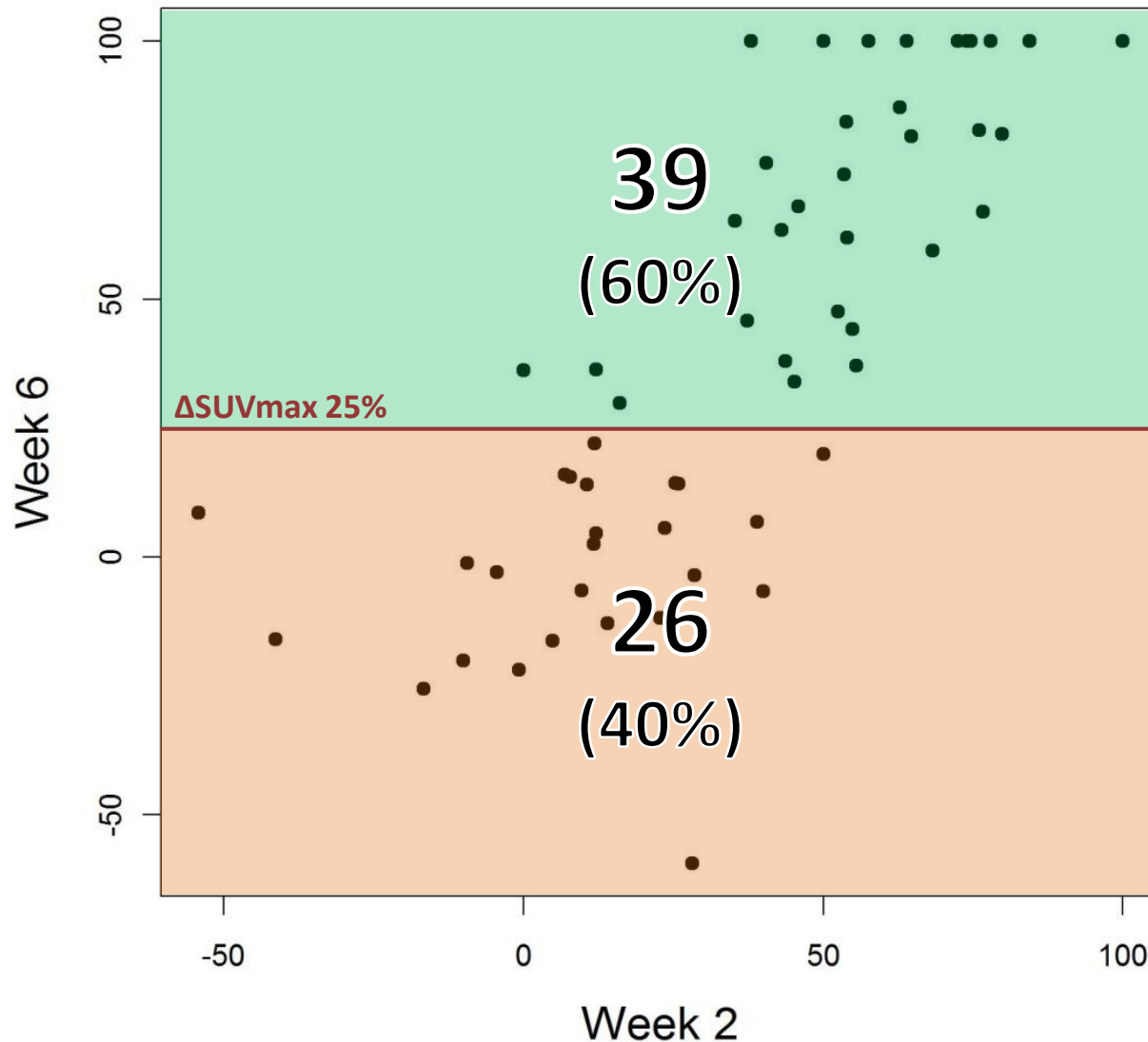
# Description of the metabolic changes observed during the biological window

## Reduction in SUVmax



# Description of the metabolic changes observed during the biological window

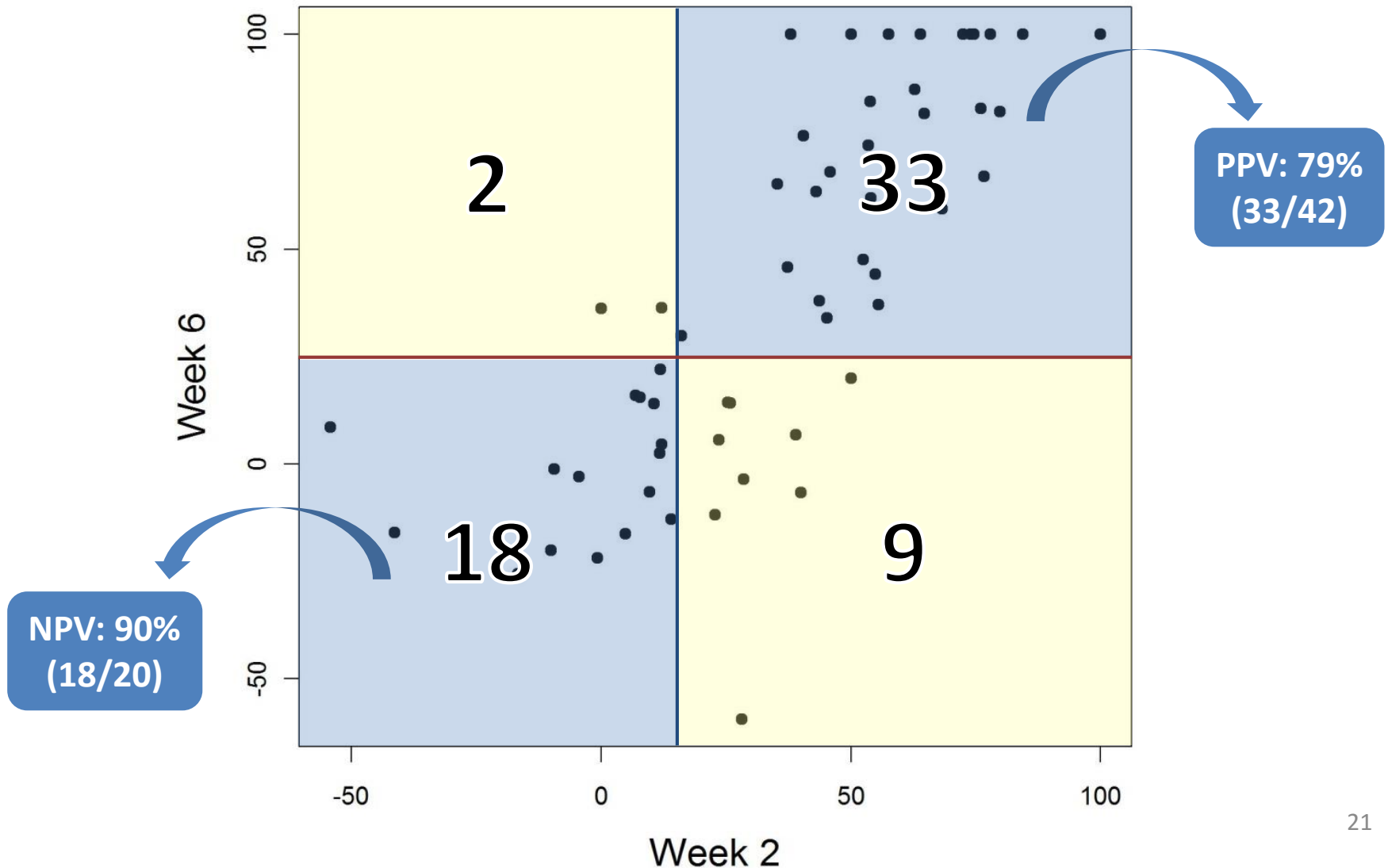
## Reduction in SUVmax





# Description of the metabolic changes observed during the biological window

## Reduction in SUVmax



# Metabolic responder...

**BASELINE**



**WEEK 2**

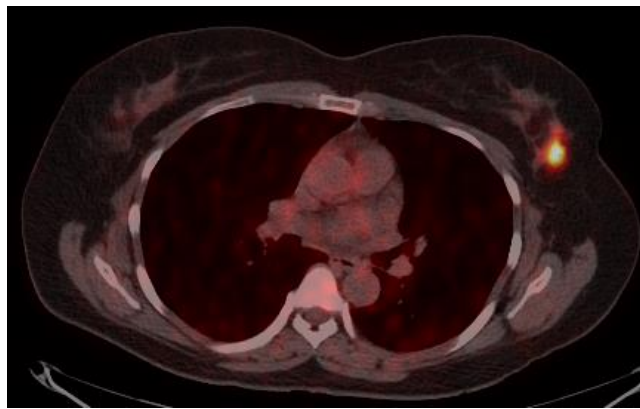


**WEEK 6**

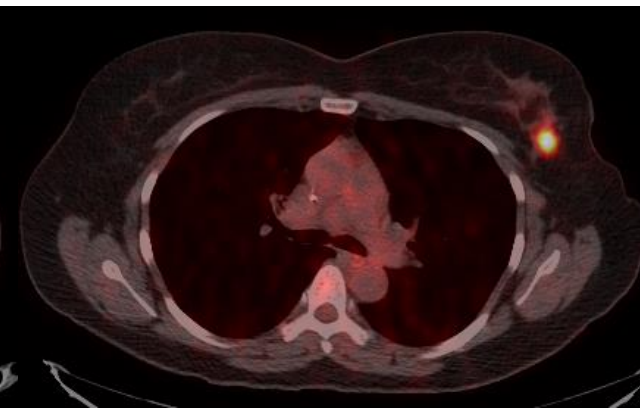


# ... and metabolic non-responder

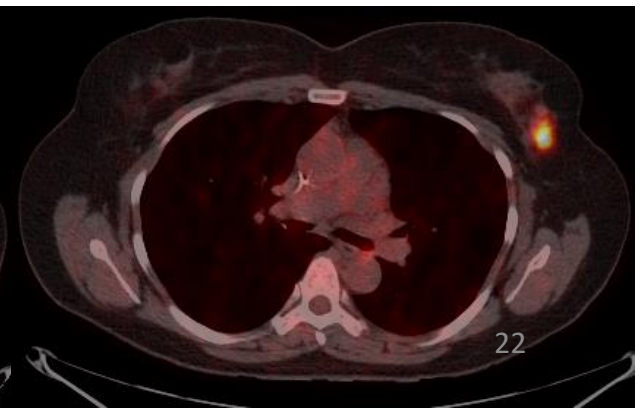
**BASELINE**



**WEEK 2**

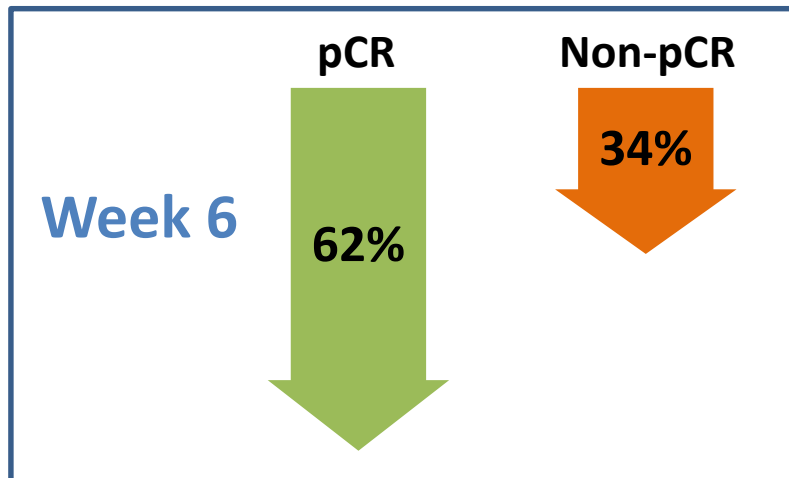
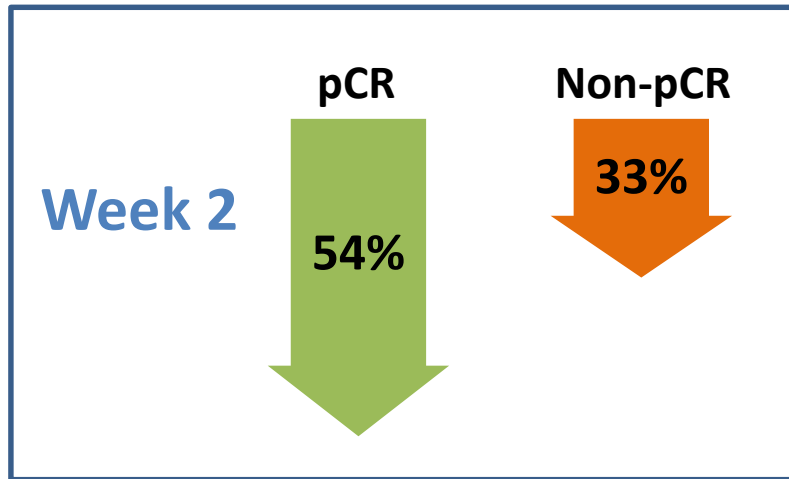


**WEEK 6**

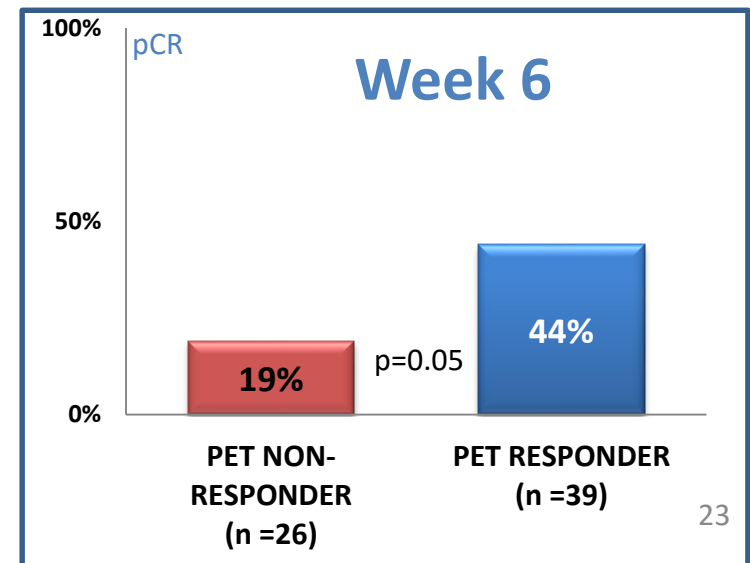
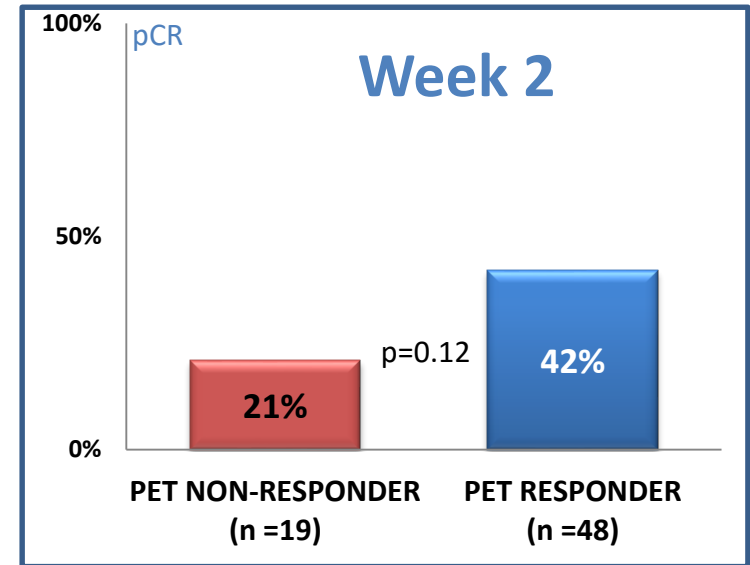


# Correlation between metabolic response & pCR

Mean SUVmax reduction as a function of pCR status



pCR rate as a function of metabolic response

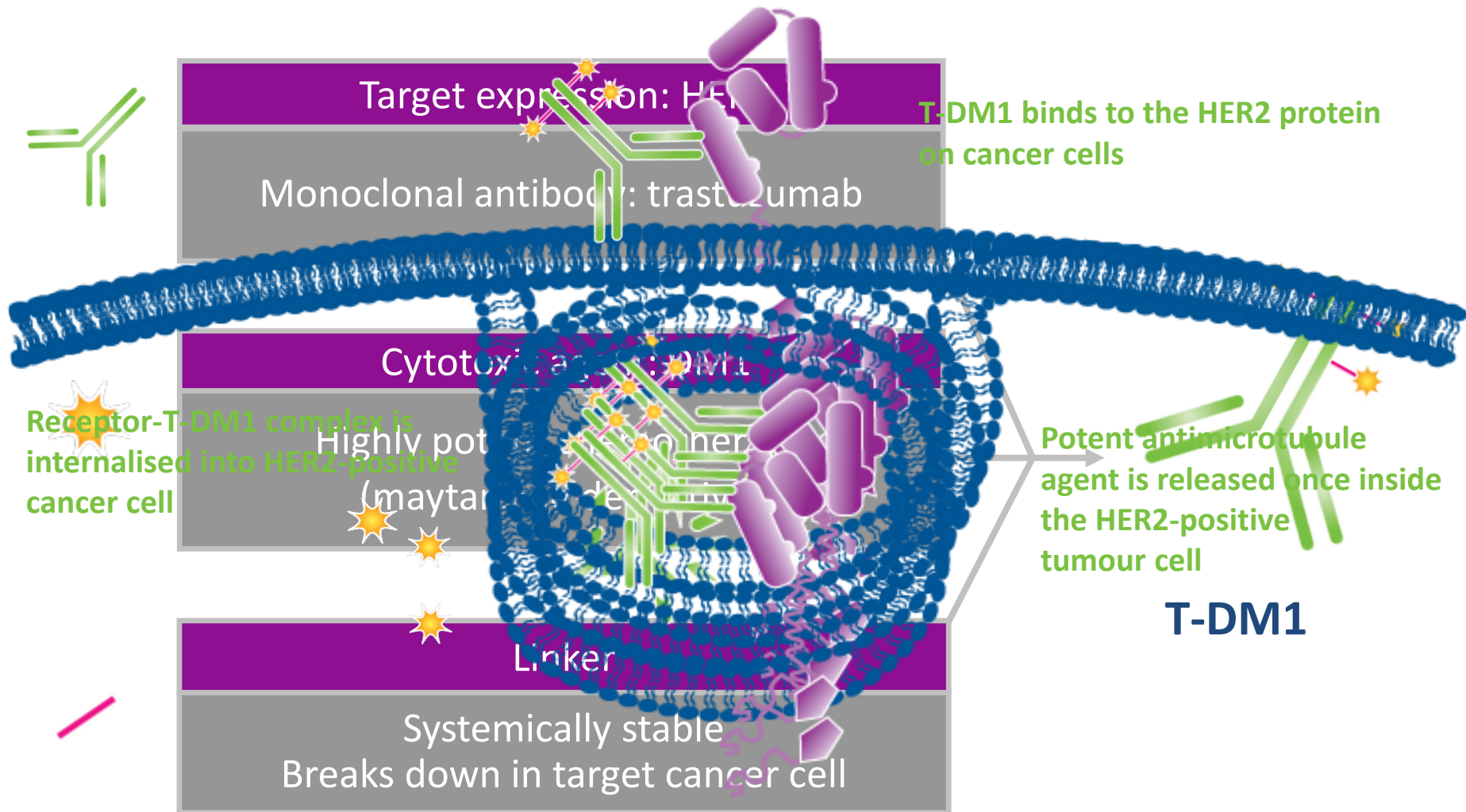


# PART 3

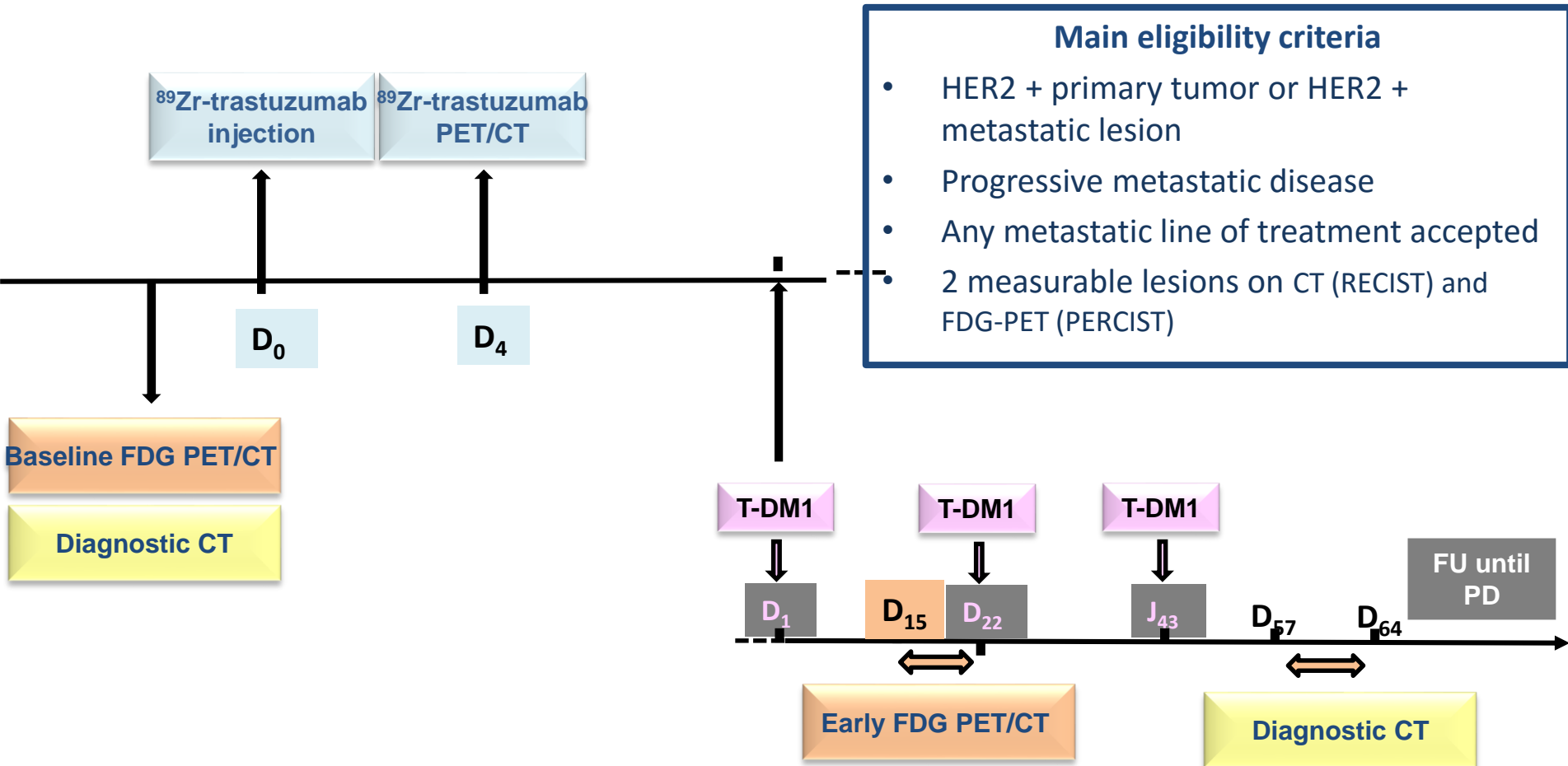
**MOLECULAR IMAGING AS A TOOL TO INVESTIGATE  
HETEROGENEITY  
OF ADVANCED HER2-POSITIVE BREAST CANCER  
AND TO  
PREDICT PATIENT OUTCOME UNDER  
TRASTUZUMAB EMTANSINE  
(T-DM1)**

**THE ZEPHIR TRIAL**

# T-DM1: 1st-in-class HER2 antibody-drug conjugate (ADC)



# Zephir trial design

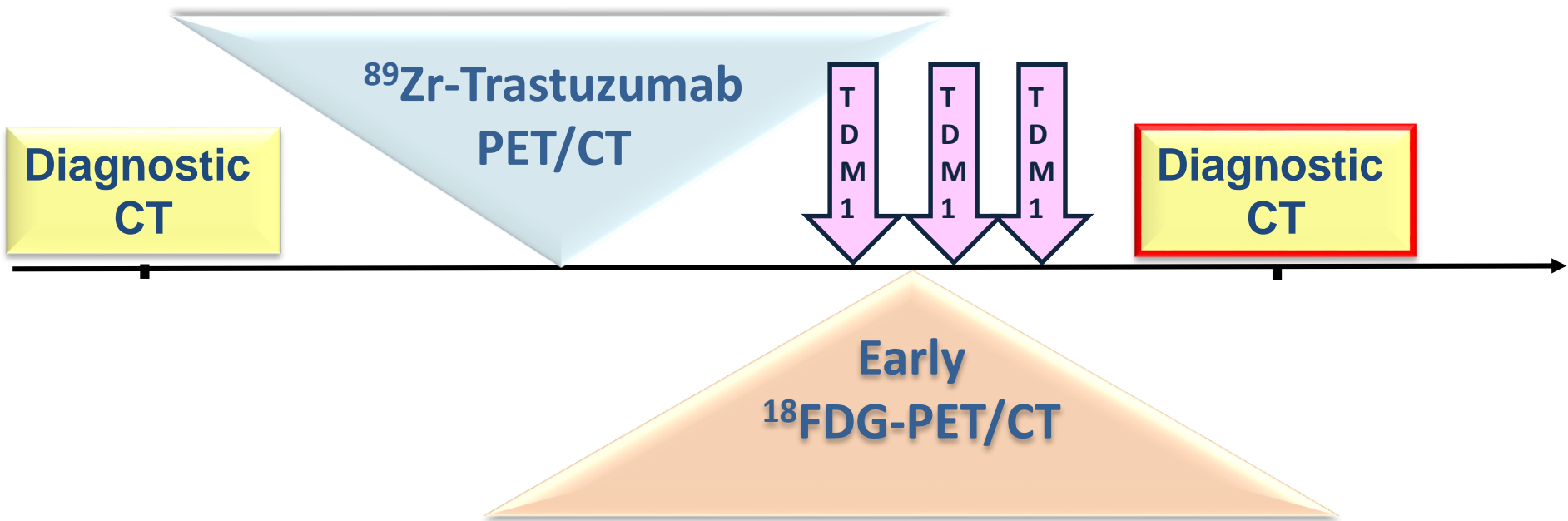




# ZEPHIR trial



# Prediction of morphological response

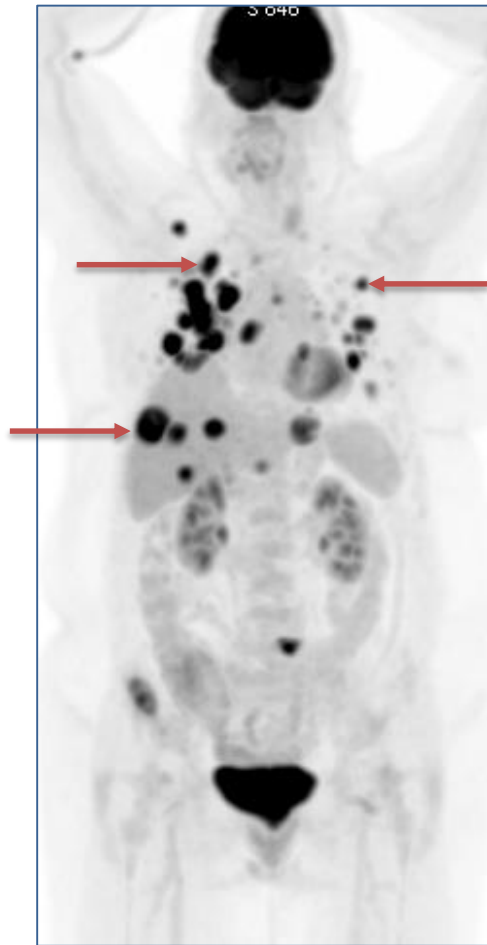


# Methodology

**HER2 PET/CT**

**FDG PET/CT**

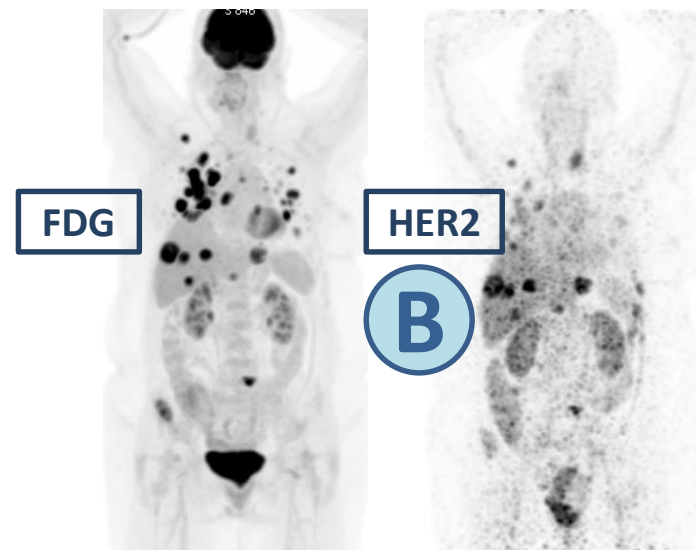
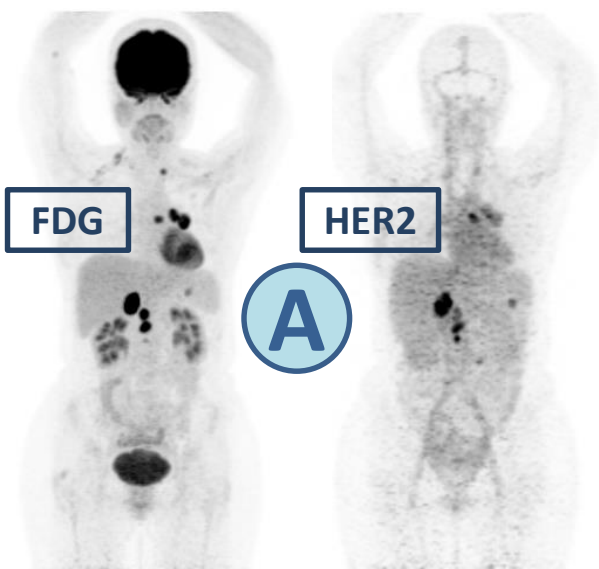
# ZEPHIR: two different ways to image the disease



FDG

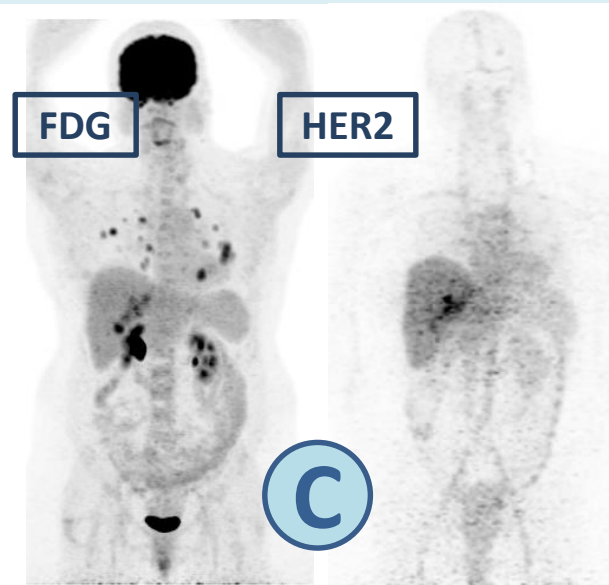


HER2

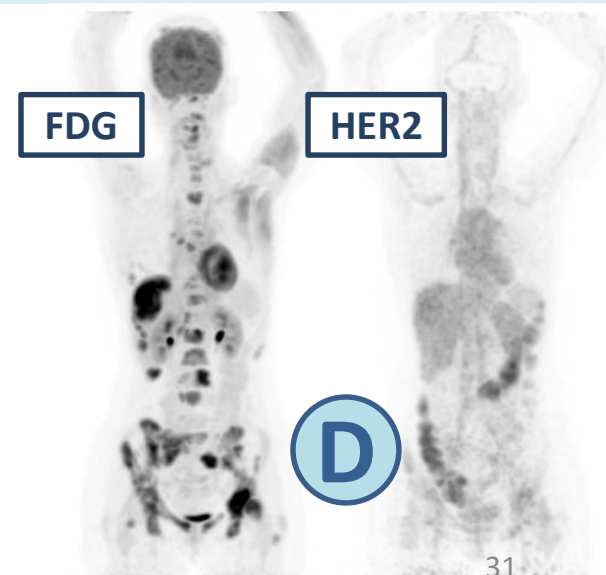


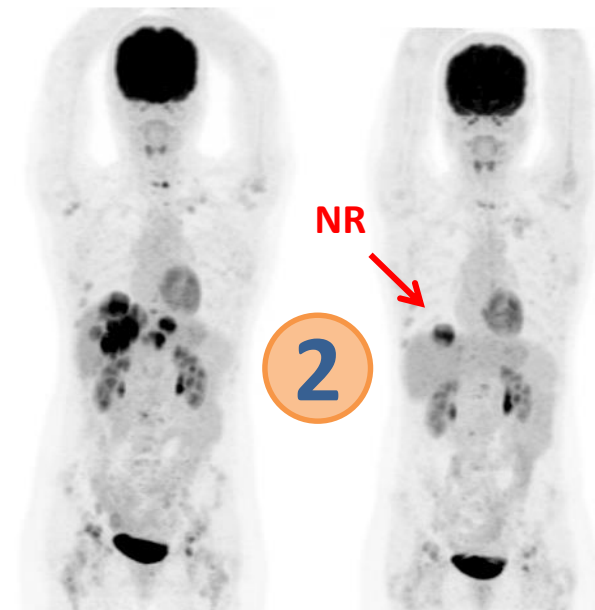
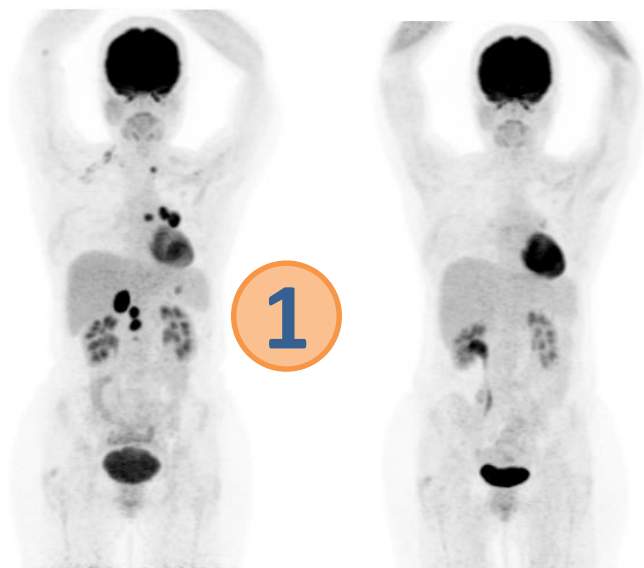
+

## HER2 PET Classification



-

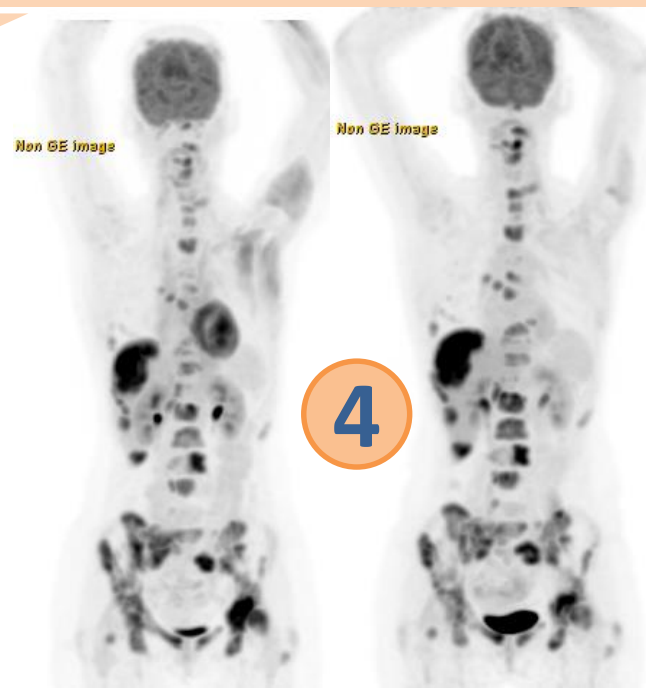




Response

## FDG PET response classification

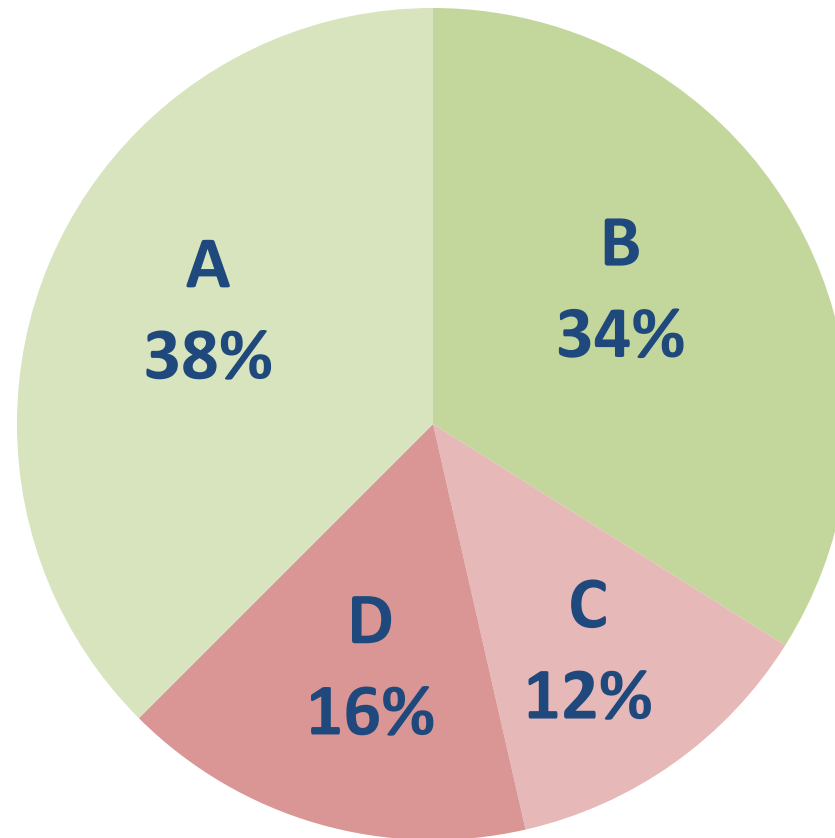
Non Response





# **ZEPHIR STUDY : RESULTS**

# Patterns of HER2 expression revealed by HER2 PET/CT imaging



All or most of the tumor load is seen on  $^{89}\text{Zr}$ -Trastuzumab PET/CT



Minority of tumor load or no lesions are seen on  $^{89}\text{Zr}$ -Trastuzumab PET/CT

# Correlation between molecular imaging and morphological Response

		RECIST 1.1		
		R	NR	Total
HER2 PET	+	28	11	39
	-	2	14	16

PPV: 72%

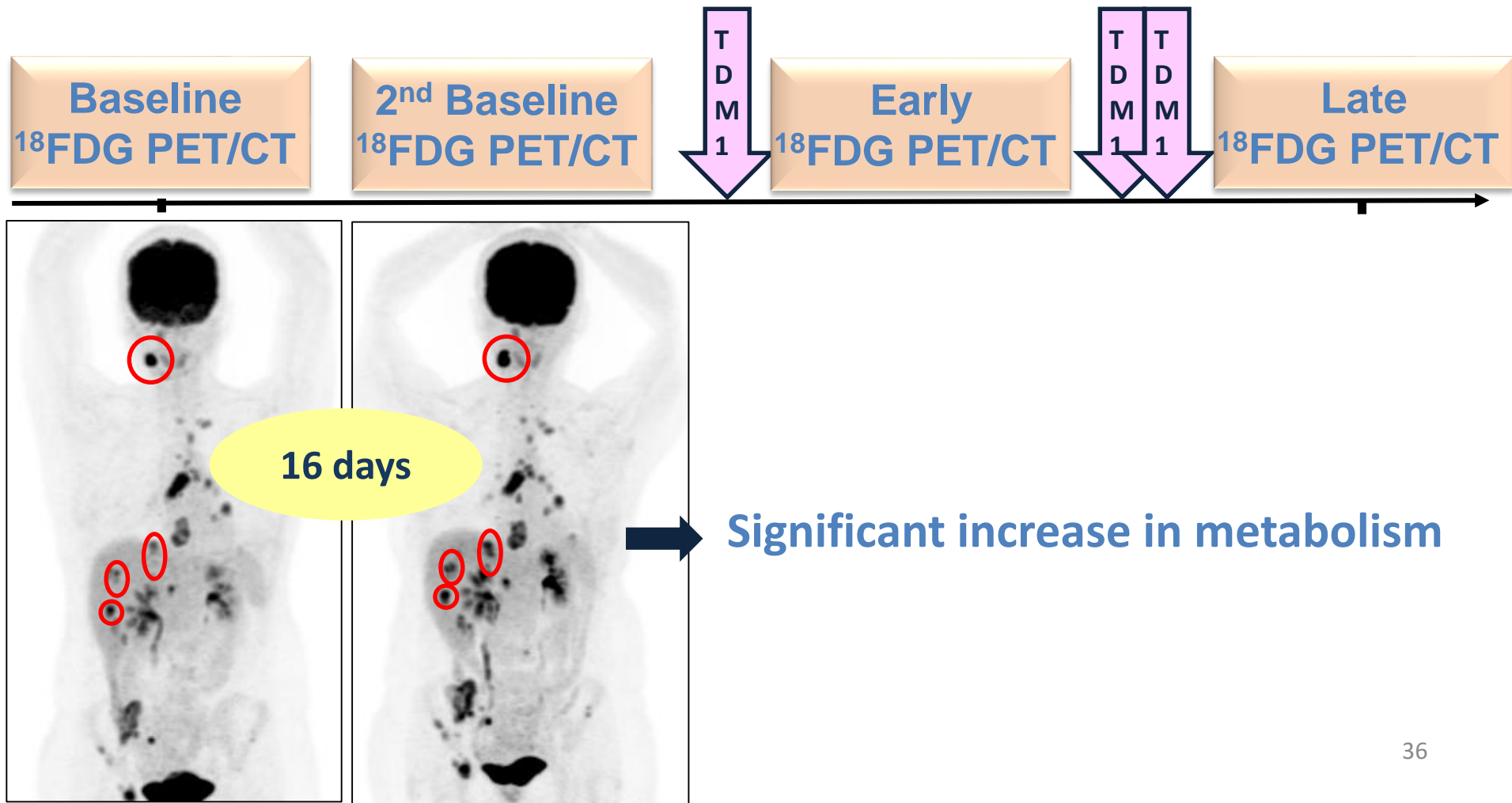
NPV: 88%

		RECIST 1.1		
		R	NR	Total
Early FDG	R	26	1	27
	NR	5	24	29

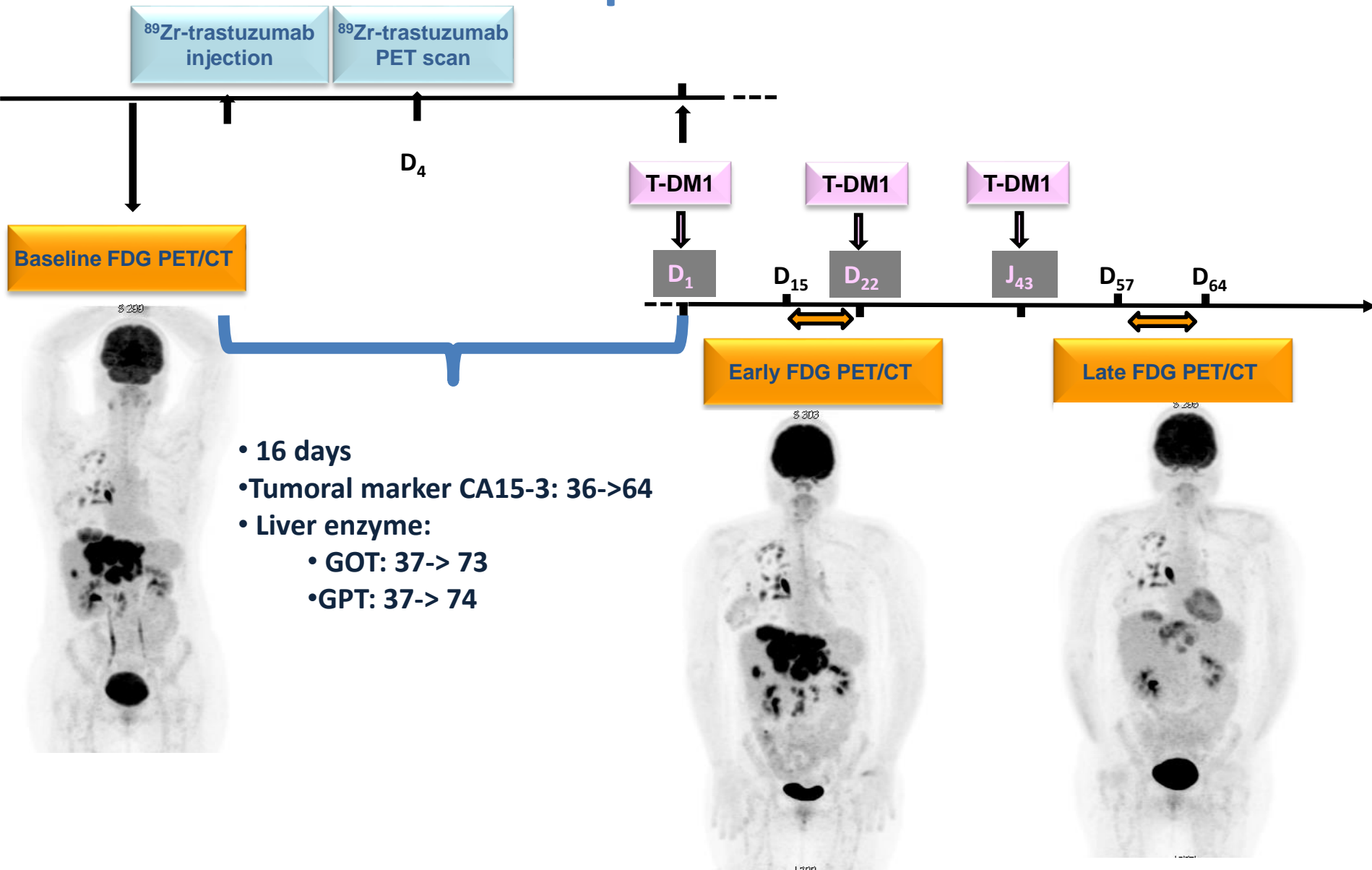
PPV: 96%

NPV: 83%

# Suboptimal NPV of early FDG PET/CT: potential explanation



# Suboptimal NPV of early FDG PET/CT: potential explanation



# Combined imaging modalities predicting morphological response

		RECIST 1.1		
		R	NR	Total
HER2 PET +	eR	24	0	24
	eNR	4	11	15
HER2 PET -	eR	2	1	3
	eNR	0	13	13

PPV:  
100%

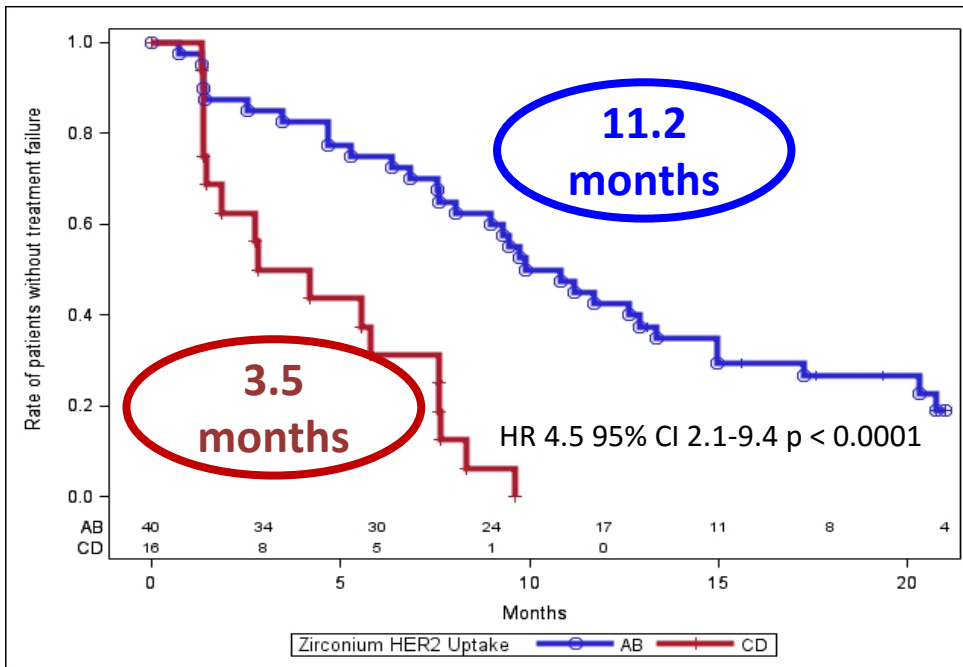


NPV:  
100%

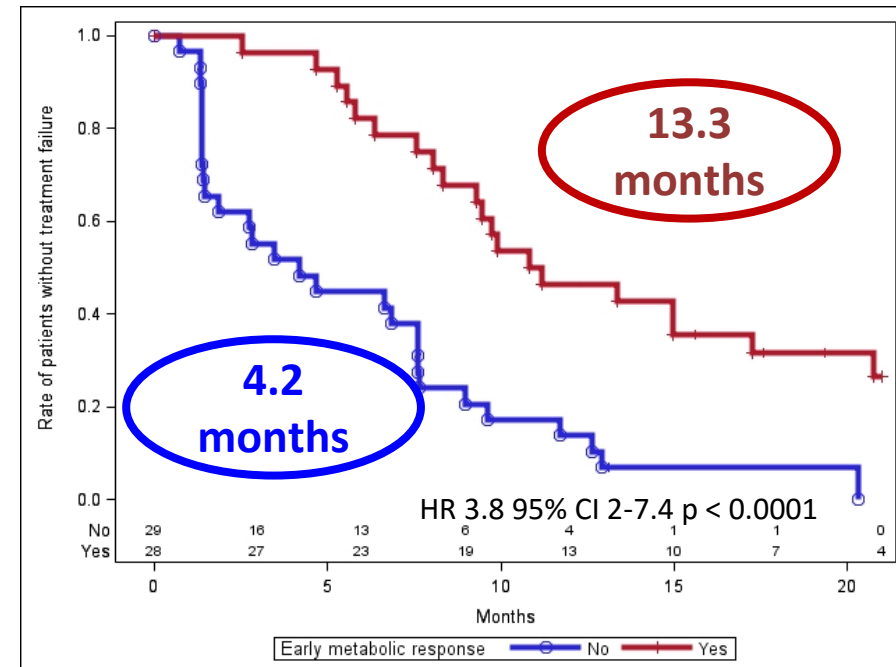
# Time to treatment failure

TTF: Time from start of T-DM1 until its discontinuation

## <sup>89</sup>Zr-trastuzumab PET/CT



## Early FDG PET/CT



# Summary

## Neo-ALTTO

1. Metabolic changes at week 2 correlate with week 6.
2. pCR is associated with greater SUVmax reductions.
3. pCR rates are twice as high in patients who are FDG-PET/CT responders compared to non-responders.

## ZEPHIR

1. Metastatic HER2 positive BC is highly heterogeneous in terms of HER2 imaging.
2. HER2 imaging and early FDG response assessment: promising in identifying patients unlikely to respond.
3. HER2 imaging and early FDG responses discriminate patients with significantly different TTF.



# Conclusion

Potential value of molecular imaging in the context of both early and advanced BC

## Perspectives

- Design future trials using imaging as a tool for treatment adaptation with proof of clinical utility
- Evaluate early the clinical potential of new antiHER2 drugs
- Analyze the primary endpoint of ZEPHIR trial (lesion-based analysis)
- Perform translational research on ZEPHIR biopsies

**Thank you for your attention**