CLINICAL TRIALS WITH BIOLOGICAL ENDPOINT IN ESOGASTRIC CANCER

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Present biological endpoints

Table 3. Possible endpoints (advantages and disadvantages)

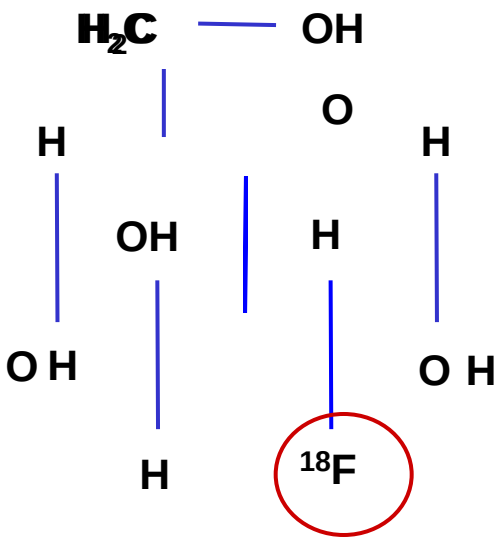
Proposed endpoint	Advantage	Disadvantage
Response rate	Standardized	Not feasible for some disease (CRPC, ovarian cancer with peritoneal masses and so on)
Progression arrest rate	Easily measurable	Imprecision measures
Progression-free rate at fixed time point	Central review easily feasible	Idem with interference with physician/patient point of view ('symptomatic progression')
TTP	Early outcome	With time assessment biases
	Cheap method	
GMI	Attractive assessment in couples (patient/tumour) that are their own control	Not standardized
		Need to know the correlation between TTP1 and TTP2
FDG-PET	Measurement of other effect of the drug on the tumour	Absence of standardization
DCE-CT scan and DCE-MRI	Measurement of other effect of the drug on the tumour	Absence of standardization
DCE-US	Measurement of other effect of the drug on the tumour	Ongoing standardization
		Central review feasible with difficulties

Cousin, S.: Curr Opin Oncol: 24:338-44, 2012

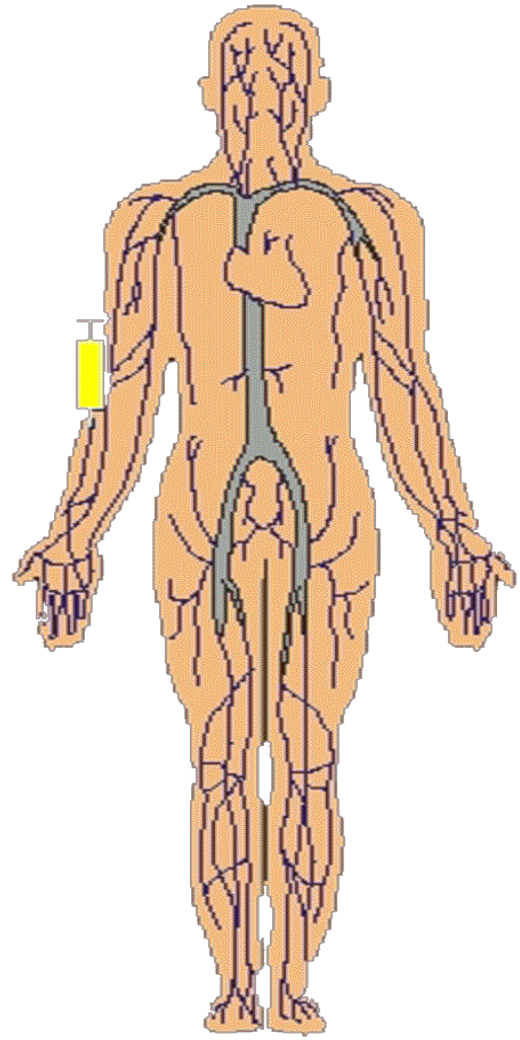
Why do we need biological endpoints in esogastric cancers?

- Major curative treatment programs involve neoadjuvant (radio-)chemotherapy or perioperative chemotherapy
- There is no good way to assess the response to such TTT before surgery
  - Primary gastric tumors often difficult to assess
  - Esophageal cancer can be misleading
- To avoid unecessary neoadjuvant TTT in non-responding tumors
  - Upper GI tumors $\not\simeq$ breast cancer

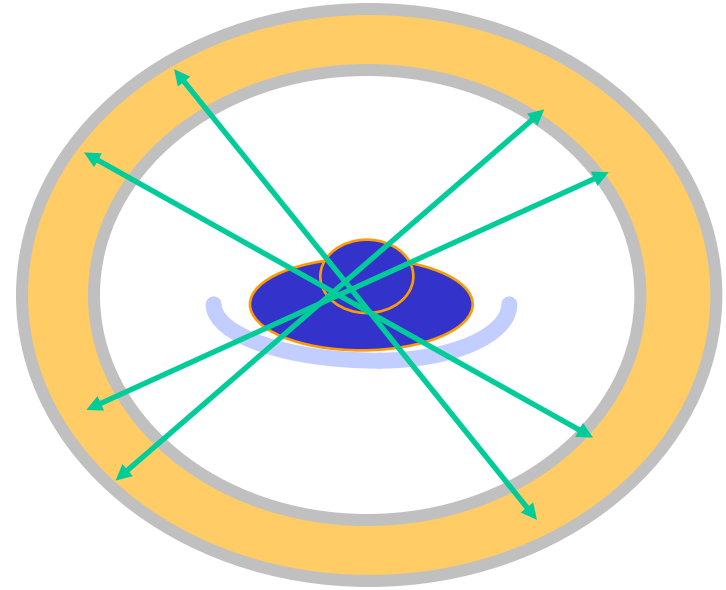
[18F]-Fluorodeoxyglucose (FDG) - PET



F18 substituted glucose molecule

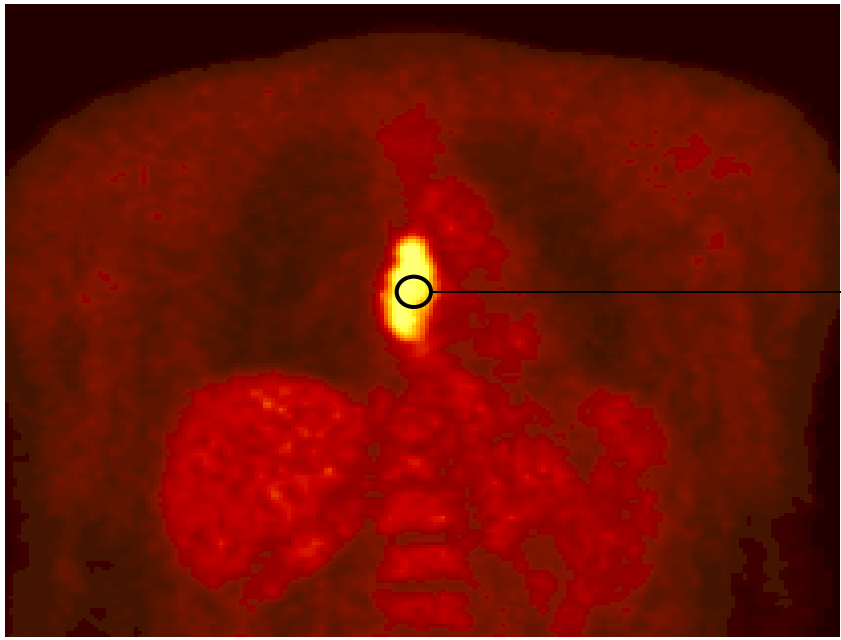


Courtesy F. Lordick

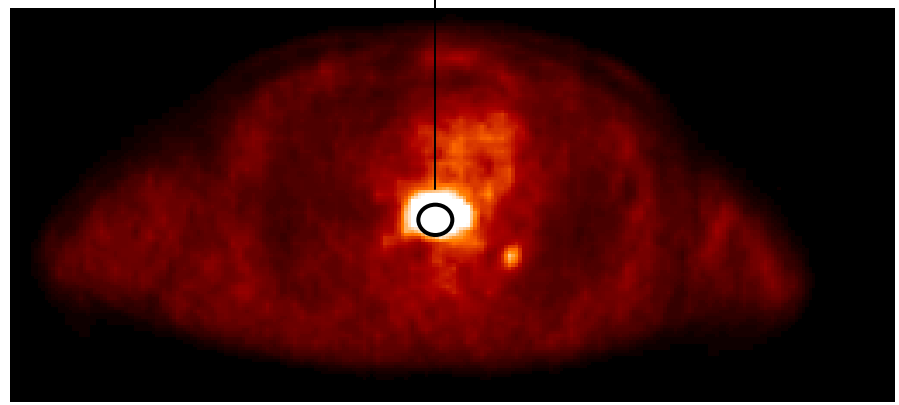


PET Scanner

Standard Uptake Value (SUV)



Region of interest (ROI)
1,5 cm around the maximal SUV

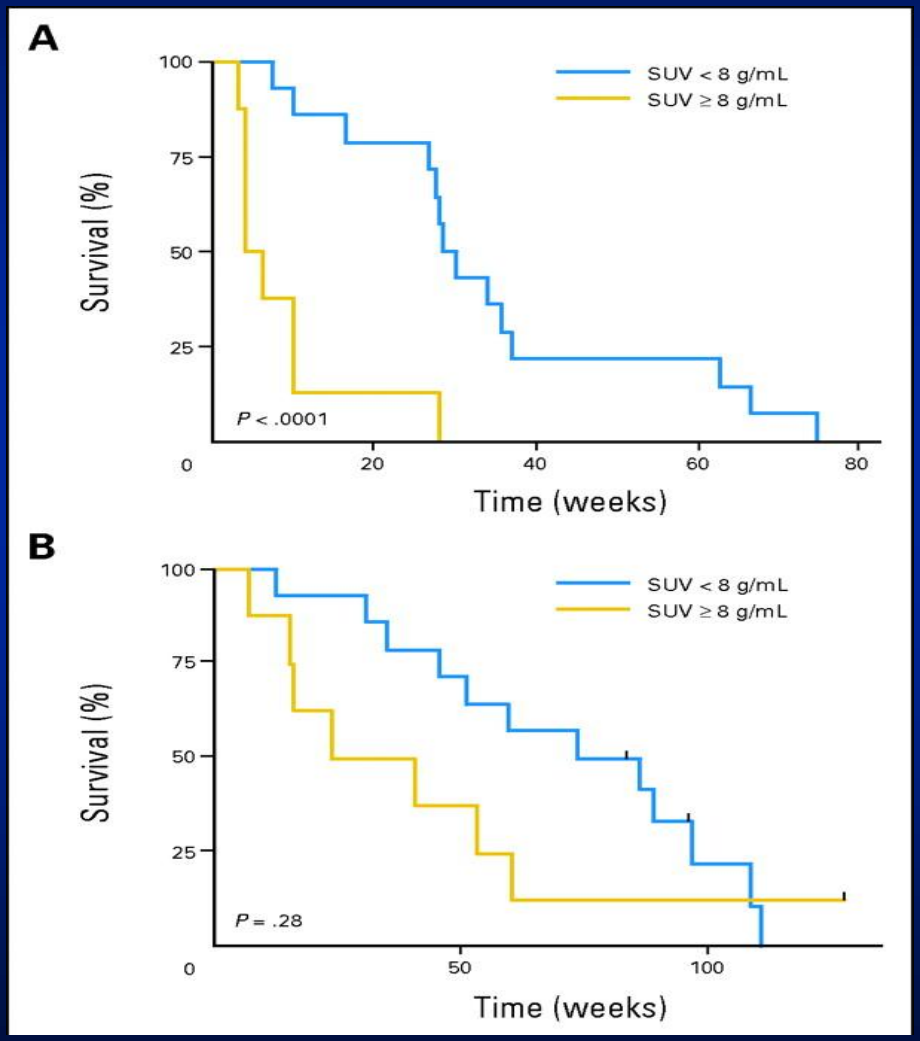


Standard uptake value (SUV)

$$SUV_{BW} = \frac{Q_{tumor}\ [MBq/l] \times W\ [kg]}{Q_{injected}\ [MBq/l]}$$

Courtesy F. Lordick

Second line sunetinib in GIST
PET-CT predictive value



(A)Progression-free survival

(B) overall survival

according to 18F-fluorodeoxyglucose positron emission tomography activity at 4 weeks

(standardized uptake value: < 8 g/mL, blue; ≥ 8 g/mL, yellow)

Prior J O et al. JCO 2009;27:439-445

Biol. endpoints ESMO 2012

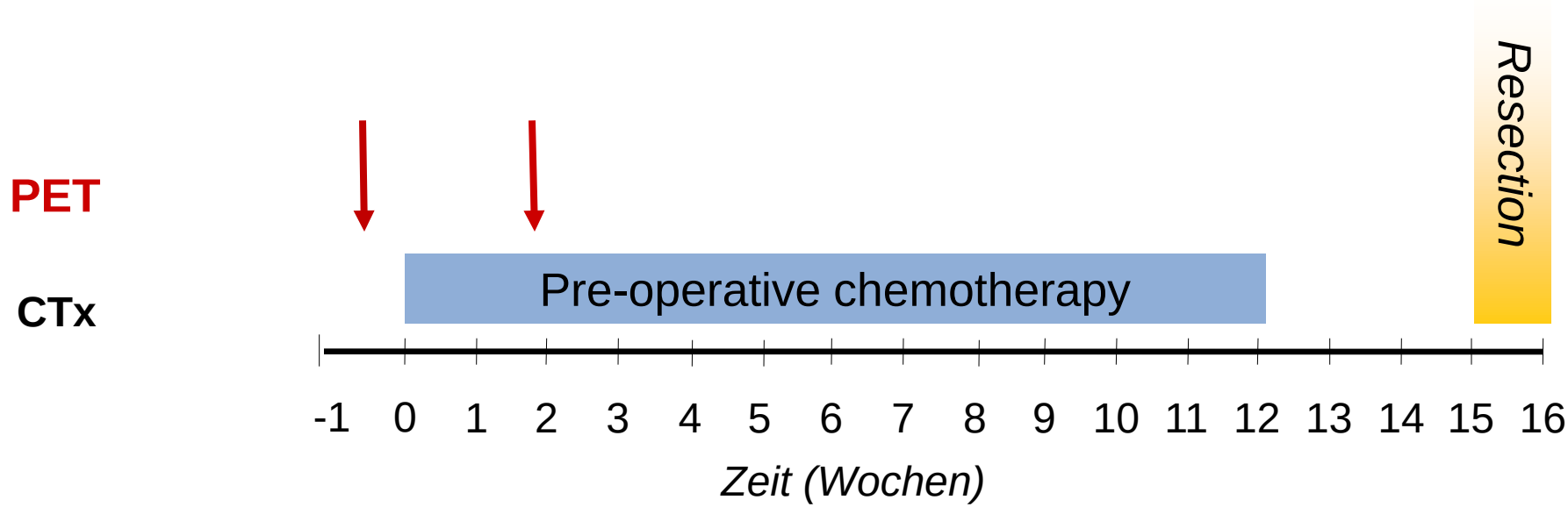
Quantitative Changes of the SUV during Treatment in esogastric cancer

Early metabolic response

Can PET help to
tailor treatment according to response?

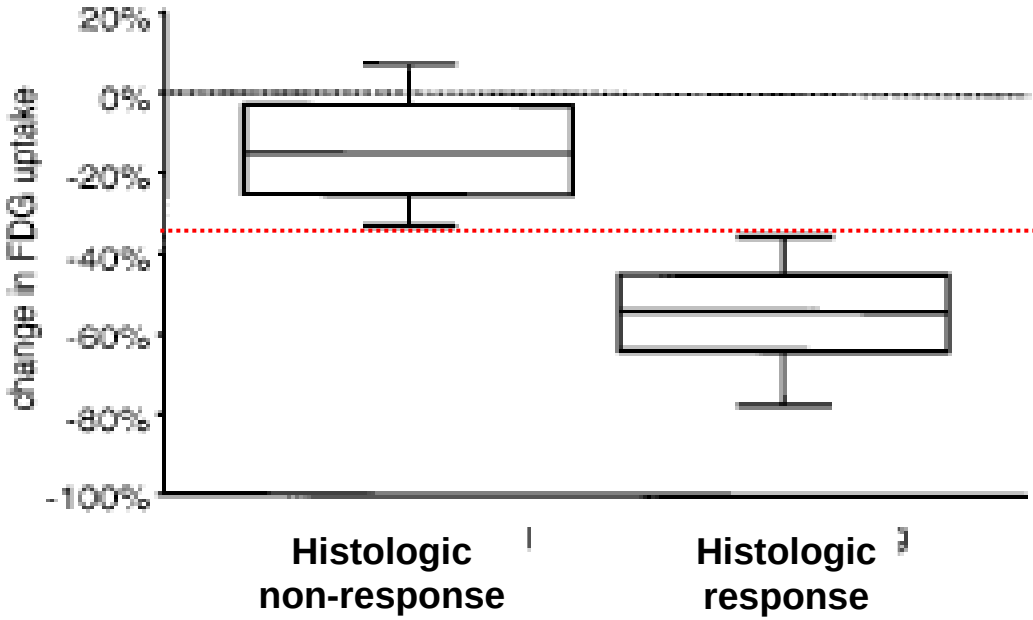
Courtesy F. Lordick

Early Metabolic Response During Chemotherapy



Courtesy F. Lordick

Early Metabolic Response

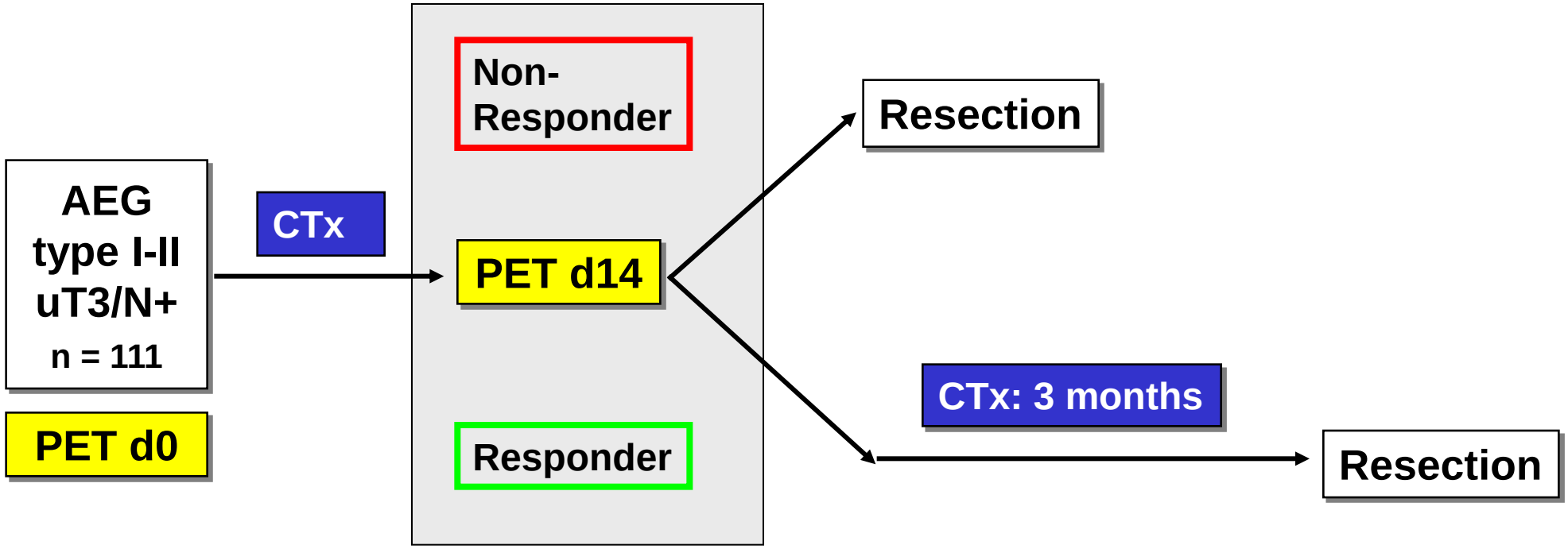


Cut-off value:
-35% decrease of SUV

Accuracy:
- sensitivity 93%
- specificity 95%

Weber et al. *J Clin Oncol*, 2001; 19:3058-3065

The MUNICON-I Algorithm



Response definition: **Decrease of the SUV_{mean} PET_{d14} / $PET_{baseline}$ $\geq$ 35%**

Weber et al. *J Clin Oncol* 2001;19:3058-65 Ott et al. *J Clin Oncol* 2006;24:4692-8

Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

MUNICON-I – Histopathologic Response

	PET-Responder (n = 50)	PET-Non-Responder (n = 54)
Complete remission (1a) 0% residual tumor	16.0% (n=8)	0% (n=0)
Subtotal remission (1b) < 10% residual tumor	42.0% (n=21)	0% (n=0)
Moderate remission (2) 10-50% residual tumor	20.0% (n=10)	3.7% (n=2)
No remission (3) > 50% residual tumor	22.0% (n=11)	96.3% (n=52)
Major remission (1a + 1b) **0 - 10% residual tumor**	**58.0%** **(n=29)**	**0%** **(n=0)**

Remissions scored according to Becker et al. *Cancer* 2003; 98: 1521-30

χ^2-test: p<0.001

Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

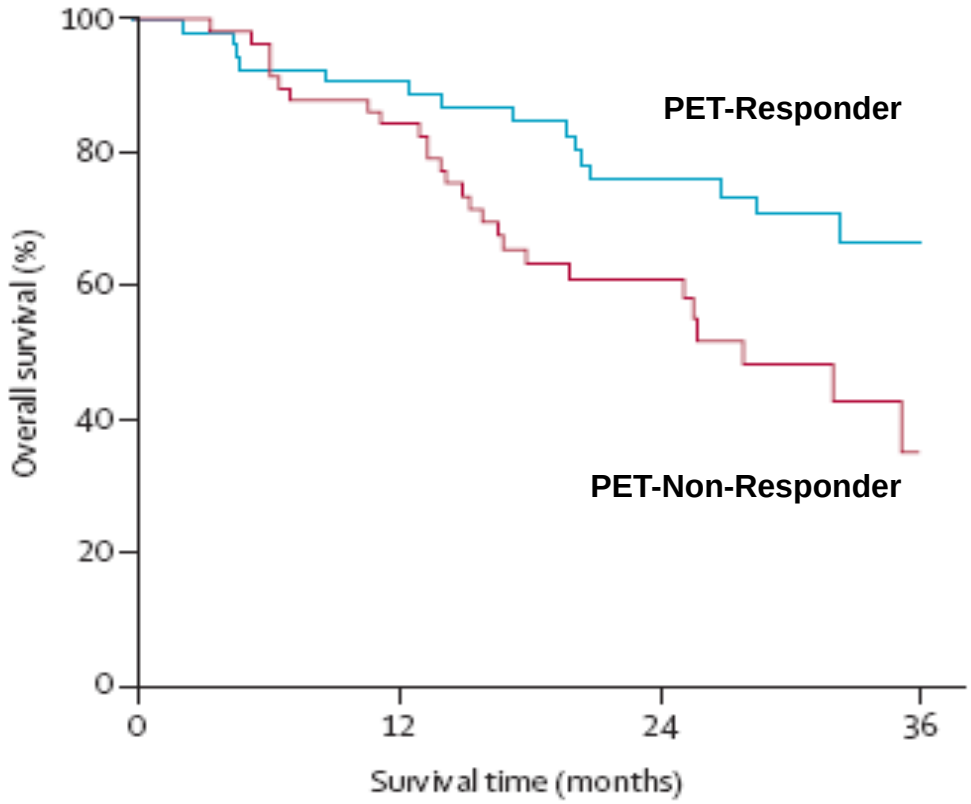
MUNICON-I – R0 Resections

	PET-Responder (n = 50)	PET-Non-Responder (n = 54)
R0	**96%** (n=48)	**74%** (n=40)
R1	4% (n=2)	26% (n=14)

χ^2-test: p=0.002

Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

MUNICON-I - Survival



Number at risk				
PET responders*	54	46	30	13
PET non-responders†	56	45	21	4

Median survival [95% CI] in months:

Metabolic Responder: Not reached

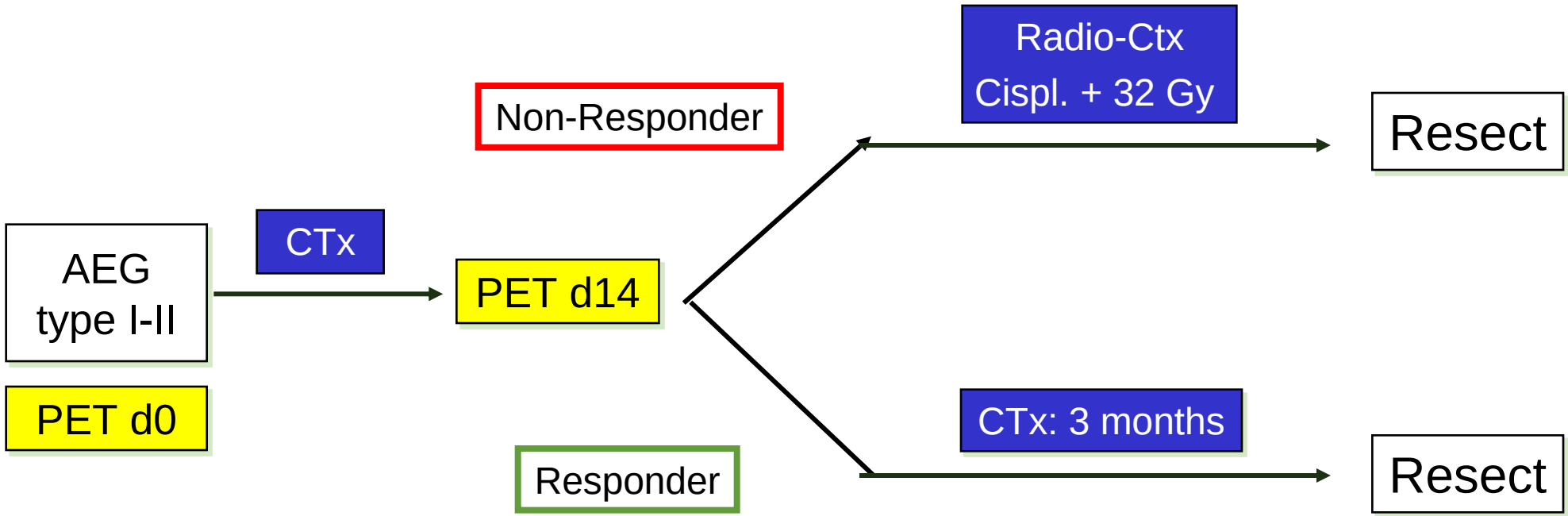
Metabolic Non-Responder: 25.8 [19.4; 32.3]

Hazard ratio 2.13 [1.14-3.99]
Log-rank p-value: p=0.015

Median follow-up: 28.0 months

Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

MUNICON II – Study Design



Response definition: Decrease of the SUV_{mean} PET_{d14} / $PET_{baseline}$ $\geq$ 35%

Weber et al. *J Clin Oncol* 2001;19:3058-65 Lordick et al. *Lancet Oncol* 2007;8:797-85

AEG: adenocarcinoma of the esophago-gastric junction; C: cisplatinum; d: day
CTX: chemotherapy PET: positron emission tomography; SUV: standard uptake value

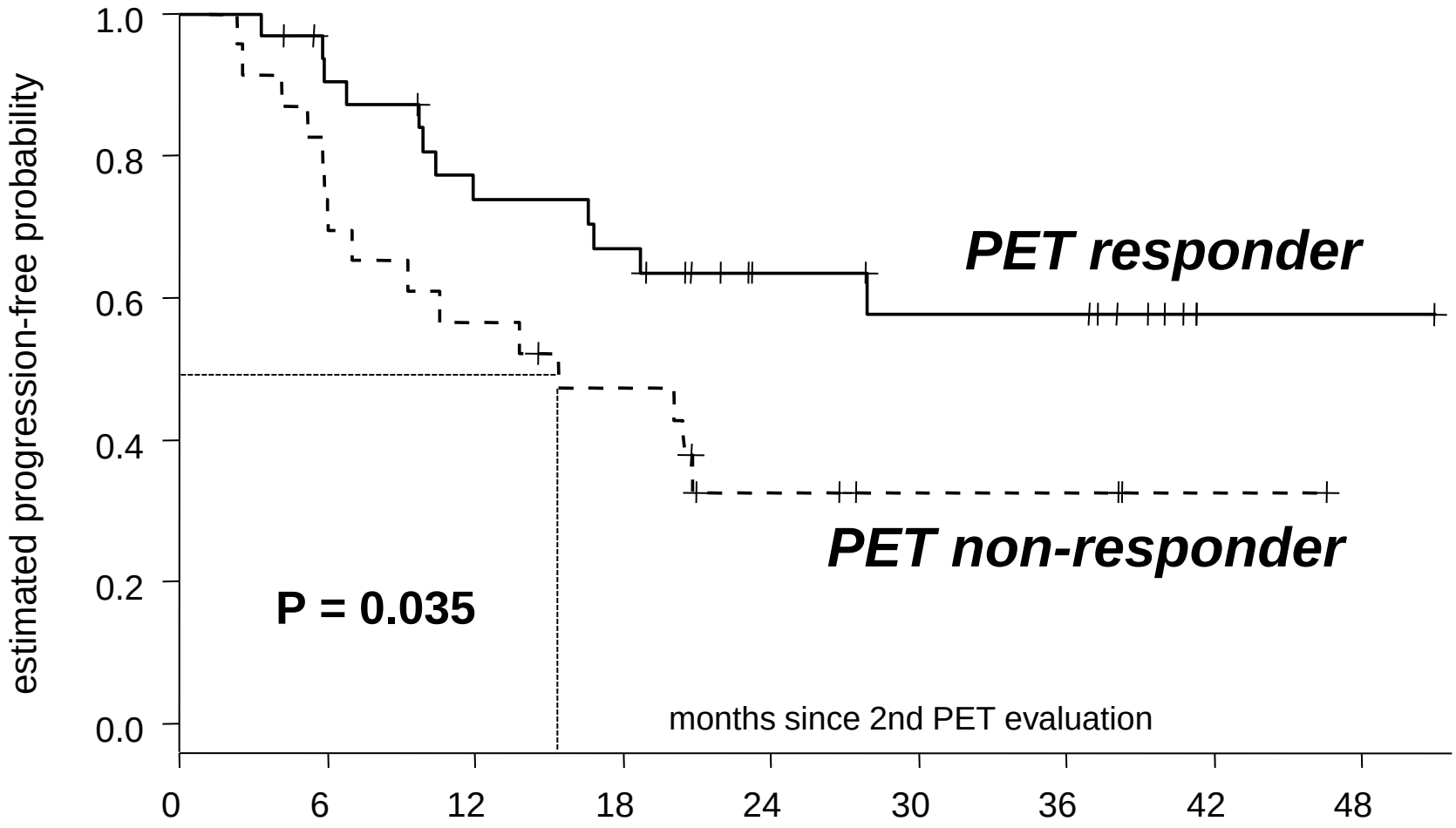
Lordick et al. *ASCO GI* 2011 abstr. 3

MUNICON-II – R0 Resections

	PET-Responder (n = 32)	PET-Non-Responder (n = 22)
R0	**82%** (n=27)	**70%** (n=16)
R1	6% (n=2)	13% (n=3)

Lordick et al. *ASCO GI* 2011 abstr. 3

MUNICON II – Progression Free Survival



Lordick et al. *ASCO GI* 2011 abstr. 3

MUNICON II – Conclusion

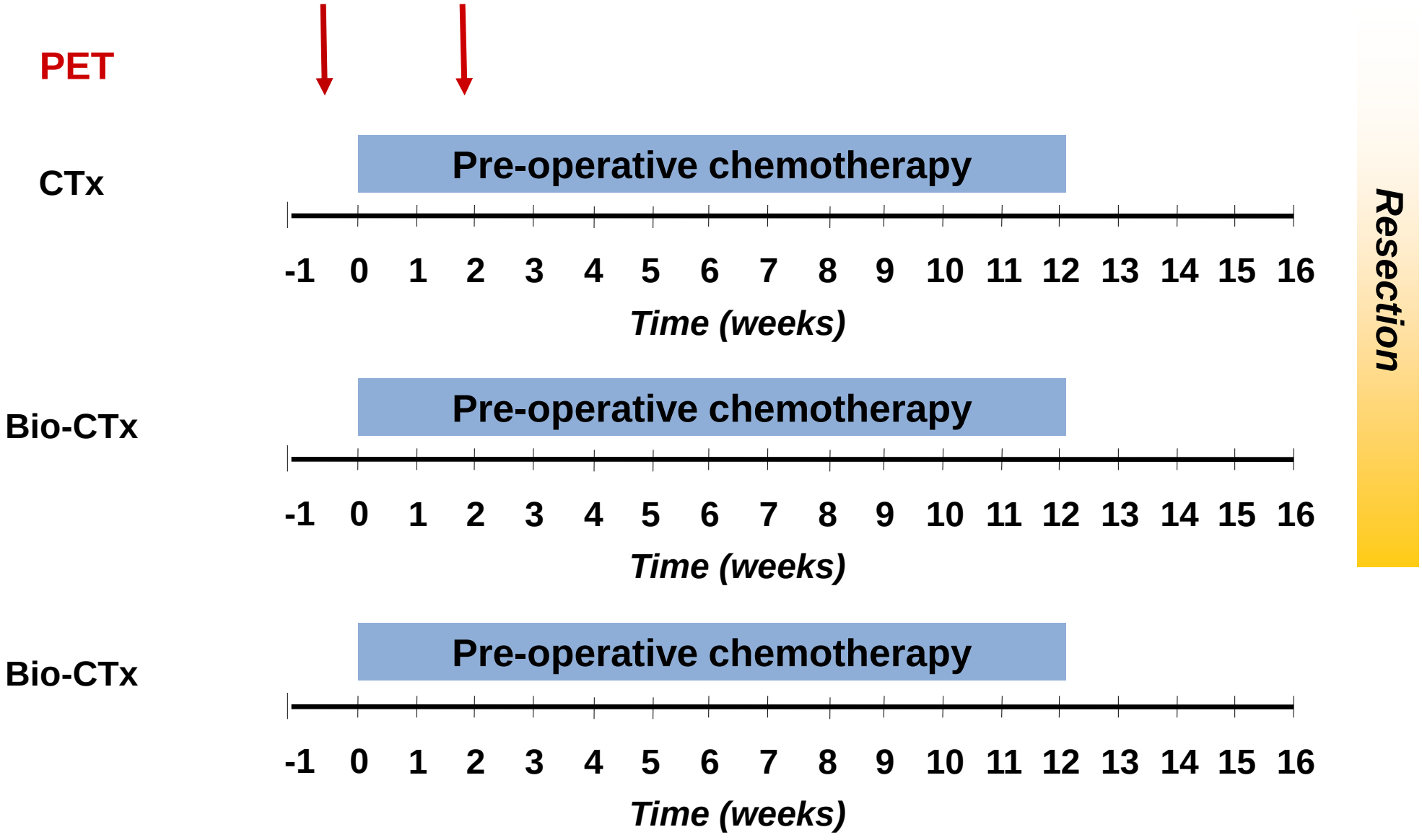
- Previous data (MUNICON-1) could be confirmed:
  Early PET response during chemo-Tx is prognostic

- Outcome is poor in metabolic non-responders
  despite the addition of radiation therapy

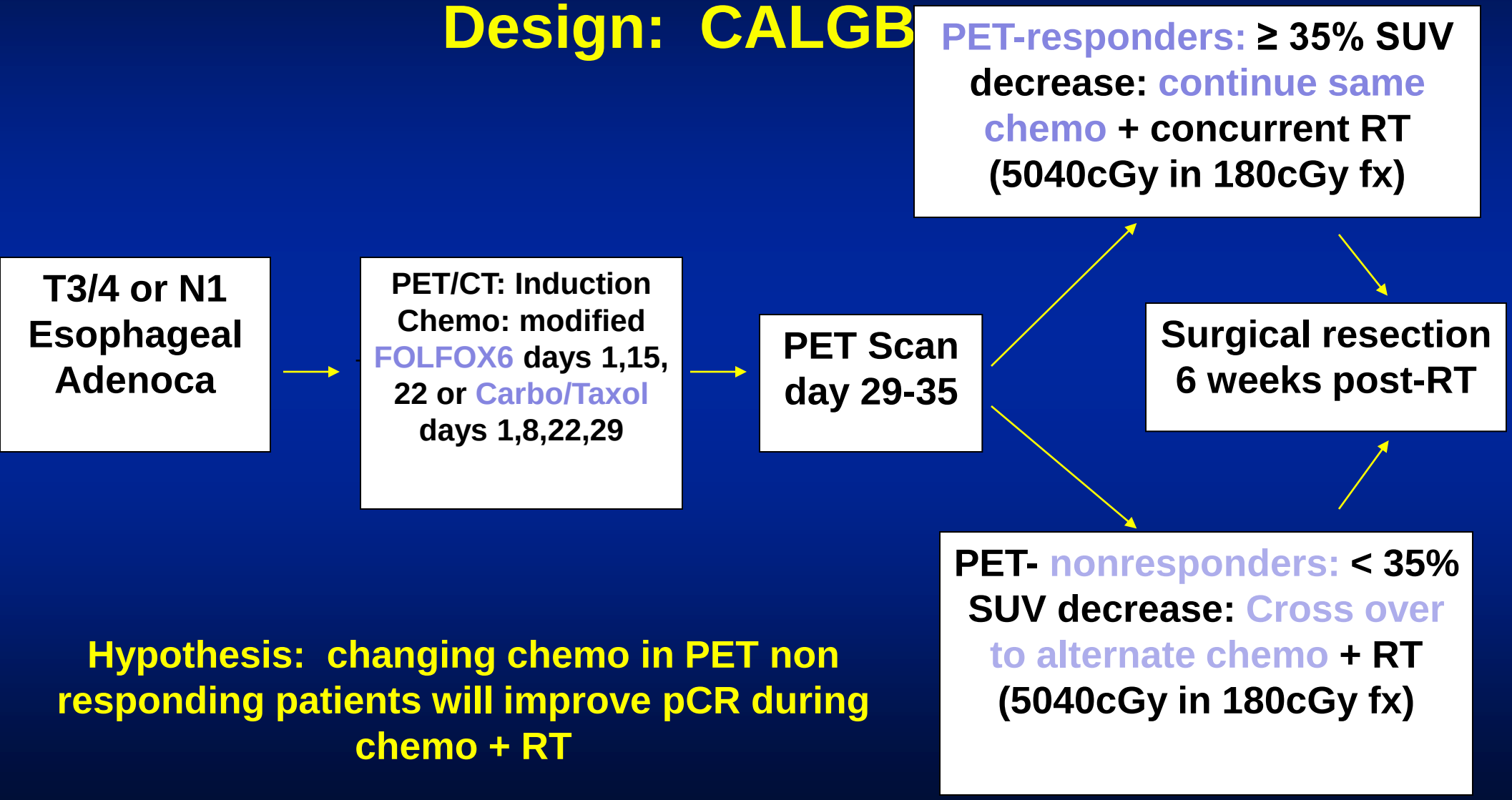
- Early metabolic response assessment by FDG-PET allows to identify tumors with a dismal biology & poor prognosis

Lordick et al. *ASCO GI* 2011 abstr. 3

EORTC Approach
Multicenter Validation



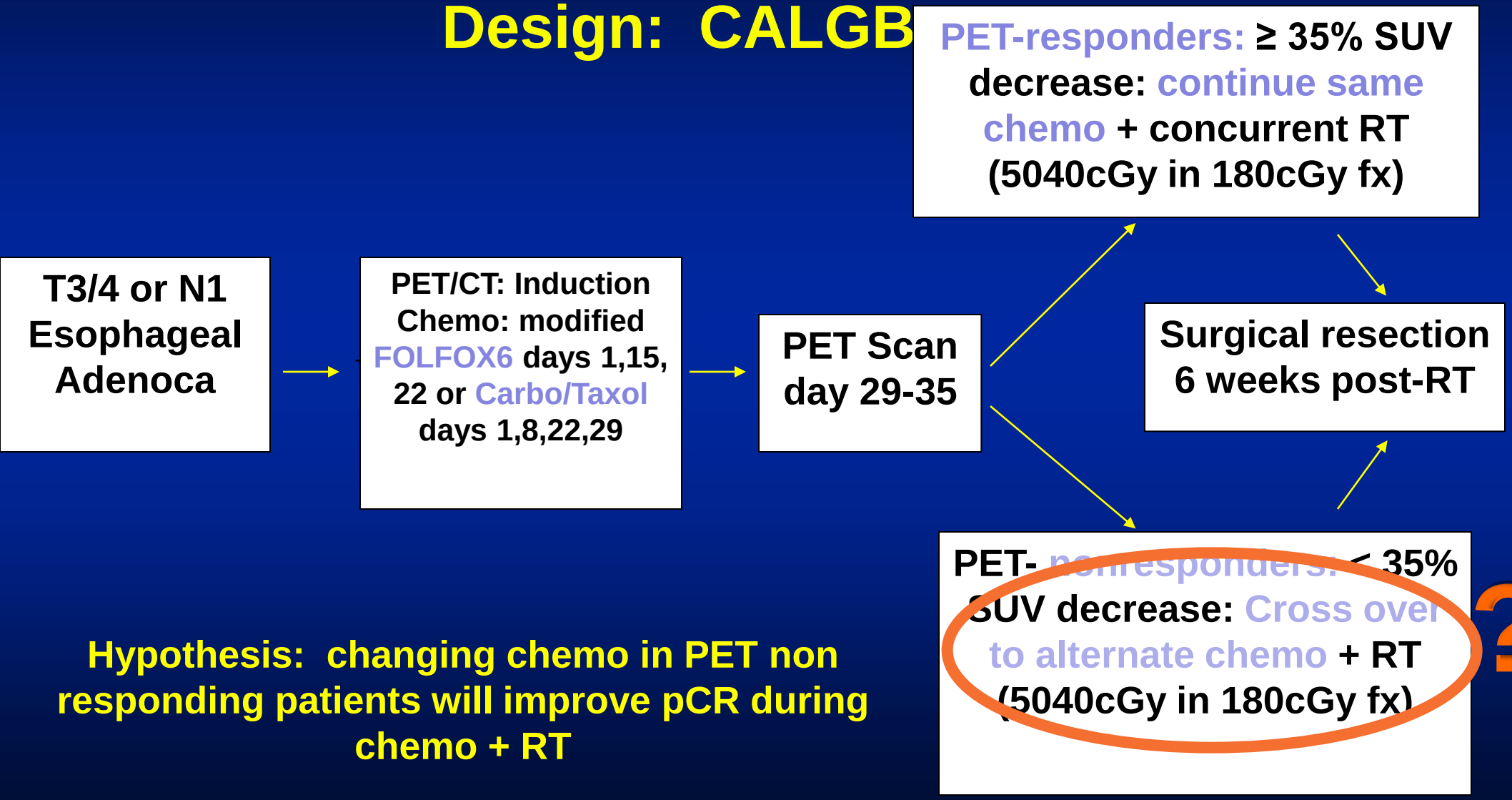
PET Scan Directed Therapy Trial Design: CALGB



Hypothesis: changing chemo in PET non responding patients will improve pCR during chemo + RT

Biol. endpoints ESMO 2012

PET Scan Directed Therapy Trial Design: CALGB



Hypothesis: changing chemo in PET non responding patients will improve pCR during chemo + RT

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Major problems with PET-CT in this setting in esogastric tumors

- Insufficient reliability of the results for adequate use in the clinic
- Financial support of PET-CT trials
- In esogastric tumor, lack of evidence for efficient alternative therapy
  - Would a non responding tumor respond to something else??
- A surrogate tool to look at tumor biology…….

We need molecular tools to select patients most likely to respond to TTT

nature medicine

A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer

Pierre Farmer[1,2,18], Hervé Bonnefoi[3–6], Pascale Anderle[1,7], David Cameron[8,18], Pratyakasha Wirapati[2], Véronique Becette[9,18], Sylvie André[1], Martine Piccart[10], Mario Campone[11], Etienne Brain[9], Gaëtan MacGrogan[3], Thierry Petit[12], Jacek Jassem[13], Frédéric Bibeau[14], Emmanuel Blot[15], Jan Bogaerts[6], Michel Aguet[1], Jonas Bergh[16], Richard Iggo[1,3,17] & Mauro Delorenzi[1,2]

Farmer, P.: Nat. Med. 15:68-74, 2009

Biol. endpoints ESMO 2012

Metagene « technology »

Table 2. Predictive factors for pCR

◂ Previous table ▴ Figures and tables index

EORTC	Univariate[b]		Multivariate[b]	
Variable[a]	**Coefficient**	***P* value**	**Coefficient**	***P* value**
Clinical node (N0 versus N1 and N2)	-0.099	0.862	0.014	0.982
Clinical size (T1 and T2 versus T3)	-0.076	0.895	-0.222	0.736
Grade (grade 1 and 2 versus 3)	1.030	0.080	0.923	0.141
ERBB2 (low versus high)				0.882
Stromal metagene score (low versus high)	1.658	0.022	1.673	0.036

MDA	Univariate[b]		Multivariate[b]	
Variable[a]	Coefficient	*P* value	Coefficient	*P* value
Clinical node (N0 versus N1 and N2)	0.789	0.231	1.844	0.044
Clinical size (T1 and T2 versus T3)	-0.357	0.54	-1.698	0.040
Grade (grade 1 and 2 versus 3)	1.191	0.181	1.009	0.333
ERBB2 (negative versus positive)	0.577	0.336	0.489	0.477
Stromal metagene score (low versus high)	1.217	0.043	1.605	0.039

Farmer, P.: Nat. Med. 15:68-74, 2009

We need to develop biological endpoints

- We need to improve our understanding of tumor biology
  - Selection of patient population most likely to respond
  - Early biological markers of response
    - Reliable apoptosis markers
    - Other histological/molecular markers
    - Serum markers
- We need to have easier access to tumor material
  - Increasing public awareness of the role of tumor biology (patient advocacy groups)
  - Lobbying (authorities and ECs)

CONCLUSIONS

- We need good biological markers of response to tailor treatment in esogastric cancer
- PET-CT Scan is a surrogate biological marker of response with serious limitations
- We need to have a wider access to biopsy material in order to develop new biological tools of patient selection and early response assessment to therapy