On-treatment biomarkers of EGFR inhibition in the treatment of colorectal cancer

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What is guiding our treatment in CRC?

- Burden and localisation of the disease
- Patient factors, unrelated to the disease
- Disease related factors – tumor symptoms
- Predefined treatment aim
- Strategy consideration of different „lines“ of tx.
- Anticipated toxicity
- Molecular predictive factors

ESMO Guideline 2012

What is guiding our treatment in CRC?

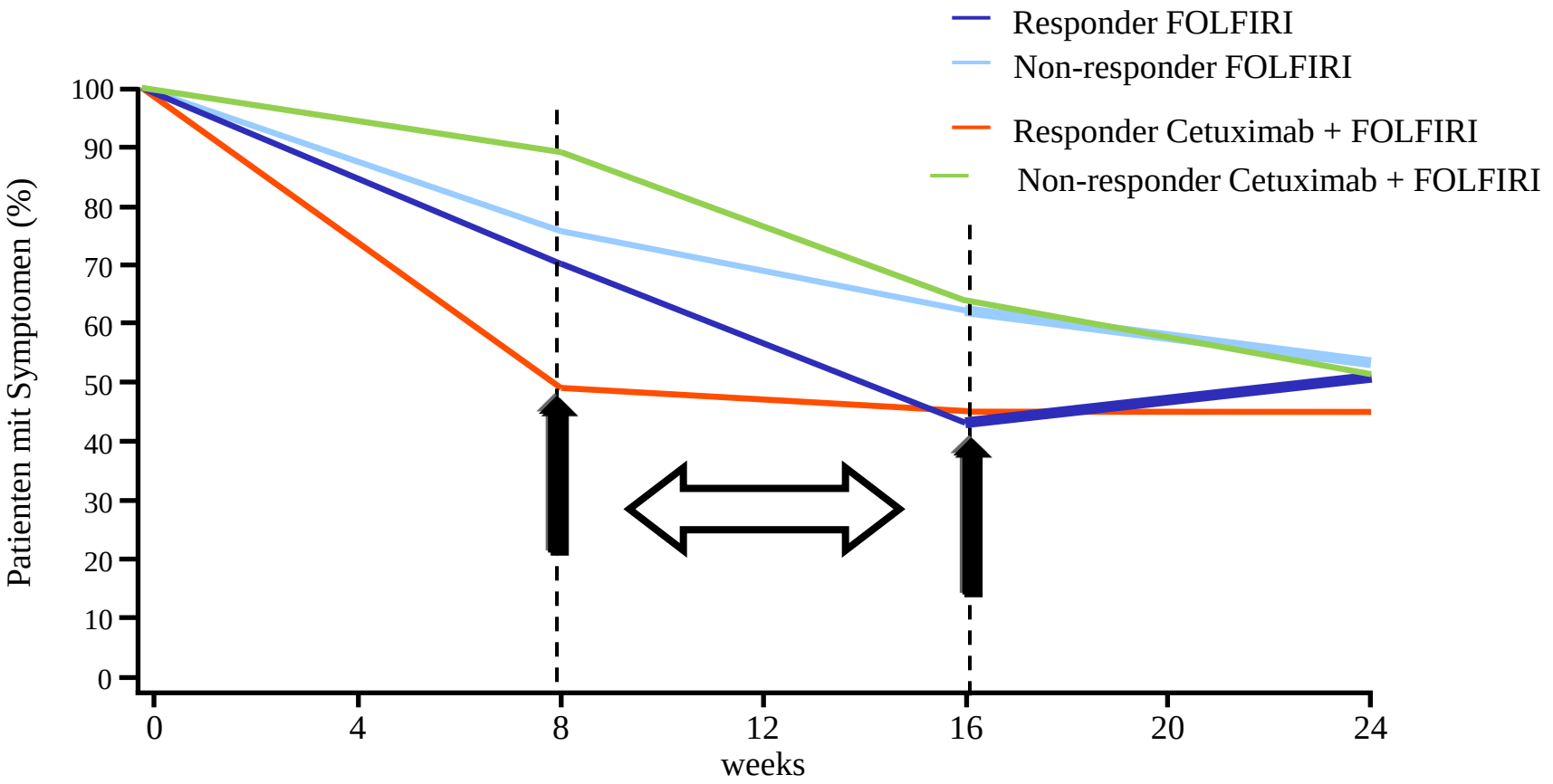
- Burden and localisation of the disease
- Patient factors, unrelated to the disease
- Disease related factors – tumor symptoms
- Predefined treatment aim
- Strategy consideration of different „lines“ of tx.
- Anticipated toxicity
- Molecular predictive factors
- *Any* information obtained during treatment?

ESMO Guideline 2012

Early response assessment

- Clinically: improvement of symptoms
- Metabolic imaging by PET scan
- Conventional imaging
- Biomarkers

Correlation with time to relief of symptoms in symptomatic patients



- Maximal relief of symptoms: after 8 weeks Cetuximab, after 16 weeks with FOLFIRI alone.

Griebsch et al. ASCO 2011; Abstract No. 3626

Early response assessment:

- Clinically: improvement of symptoms
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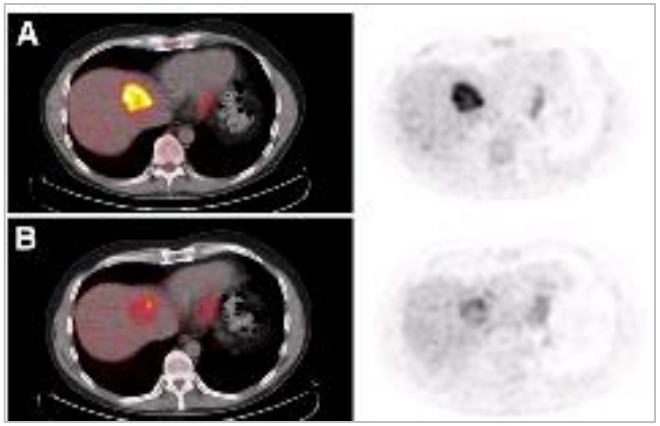
Monitoring with ^{18}F-FDG-PET

Metastatic CRC, after Ctx



Authors	Year	Reference	No. of patients	Therapy	Timing of PET evaluation	PET response criteria	Outcome measures	Results	P
Findlay et al.	1996	10	18	5-FU chemotherapy	1–2 wk, 4–5 wk	−ΔT:L > 15% (at 4–5 wk)	Morphologic response on CT scan at 12 wk (WHO criteria)	Sensitivity 100%; specificity 75%	
Bender et al.	1999	11	6	5-FU+FA chemotherapy	72 h	−ΔSUV	Morphologic response on CT scan at 6 wk (WHO criteria)	Responders −22%; nonresponders +13%	<0.01
Dimitrakopoulou-Strauss et al.	2003	12	28	FOLFOX chemotherapy	2 wk, 3 mo	SUV, FD	Morphologic response on CT scan at 12 wk (WHO criteria)	Correct classification rate: FD baseline PET 90% for PD; FD baseline PET 75% for SD	
Dimitrakopoulou-Strauss et al.	2004	13	25	FOLFOX chemotherapy	2 wk, 8 wk	SUV, k_1–k_4, FD, VB	OS	Correct classification rate: SUV 62% at 2 wk and 69% at 8 wk; k_1–k_4, FD, and VB 78% at 2 and 8 wk	
								OS–SUV correlation at 2 wk 0.426	0.035
								OS–SUV correlation at 8 wk 0.517	0.001
de Geus-Oei et al.	2007	14	50	Various chemotherapy schedules	2 mo, 6 mo	−ΔSUV, $-\Delta MR_{glu}$	OS	−ΔSUV at 2 mo	0.017
								$-\Delta MR_{glu}$ at 2 mo	0.049
							Progression-free survival	−ΔSUV at 2 mo	0.035
								$-\Delta MR_{glu}$ at 2 mo	0.026

ΔT:L = fractional change in tumor-to-liver ratio; FA = folinic acid; ΔSUV = fractional change in SUV; FD = fractal dimension; PD = progressive disease; SD = stable disease; k_1–k_4 = rate constants; VB = vascular fraction; OS = overall survival; ΔMR_{glu} = fractional change in MR_{glu}.

De Geus-Oei et al., J Nucl Med 2010

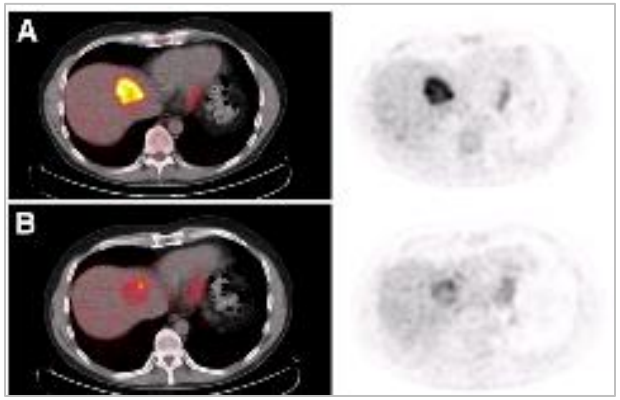
Serial FDG-PET/CT for early outcome prediction in patients with metastatic colorectal cancer undergoing chemotherapy.

- 41 pts. with mCRC
- PET/CT baseline & d14, after 1# of chemotherapy
- Response (SUV decrease >15%): 43%
- Correlation with RECIST RR: p< 0.002
- Metabolic responder vs. non-responder:
  - HR for OS: 0.28; p=0.008
  - HR for PFS: 0.57; p=0.14

Hendlisz et al., ASCO 2011; #3593

Monitoring with ^{18}F-FDG-PET

Metastatic CRC, after Ctx



- Few trials, heterogenous patients
- Heterogenous evaluation criteria:
  SUV, ROI
- Heterogenous time points for
  evaluation

But:	Interesting correlations!
Future:	Prospective evaluation with PFS and PRO
	Variations between schedules and drugs?
	New tracers and new response criteria for e.g. antiangiogenic drugs?

From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors

Richard L. Wahl[1,2], Heather Jacene[1], Yvette Kasamon[2], and Martin A. Lodge[1]

[1]*Division of Nuclear Medicine, Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; and*
[2]*Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland*

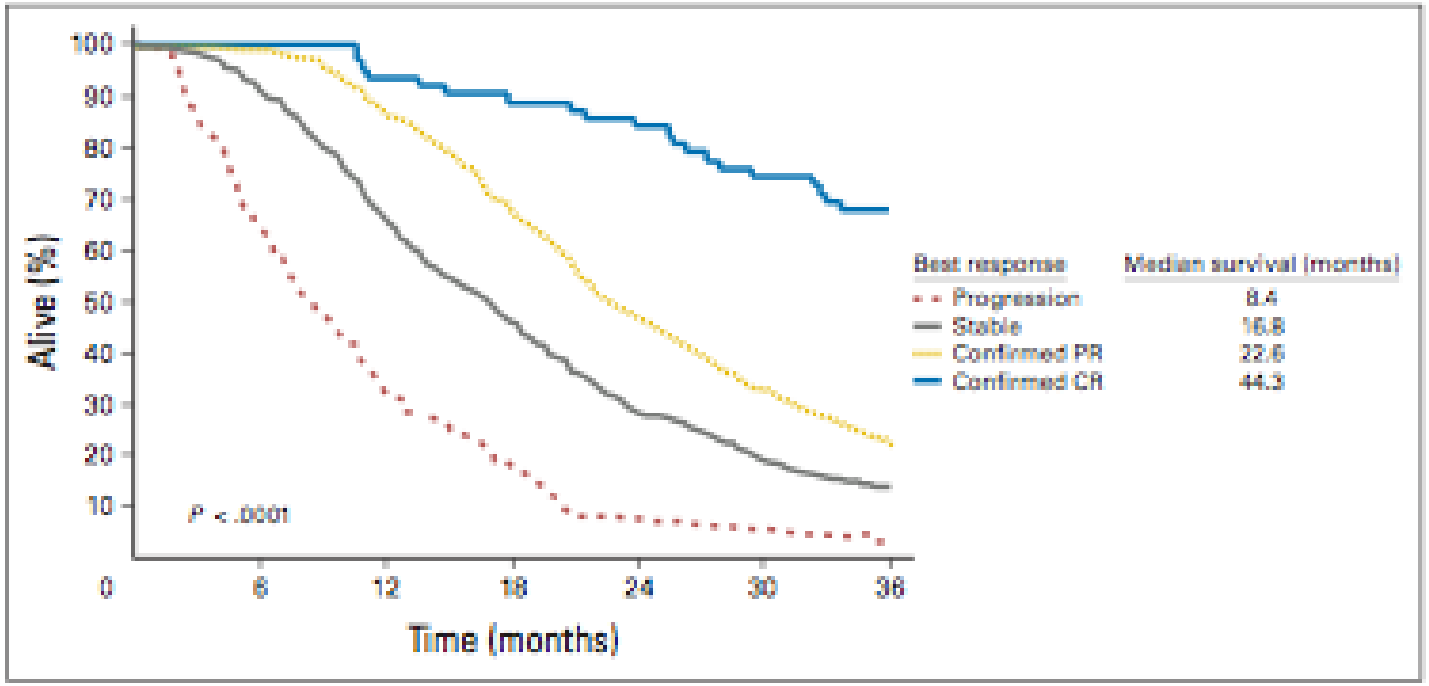
Science to Practice: Pilot Study of FPPRGD2 for Imaging $\alpha_v\beta_3$ Integrin—How Integral Are Integrins?

Wahl et al., J Nucl Med 2010; Choyke et al., Radiology 2012

Early response assessment:

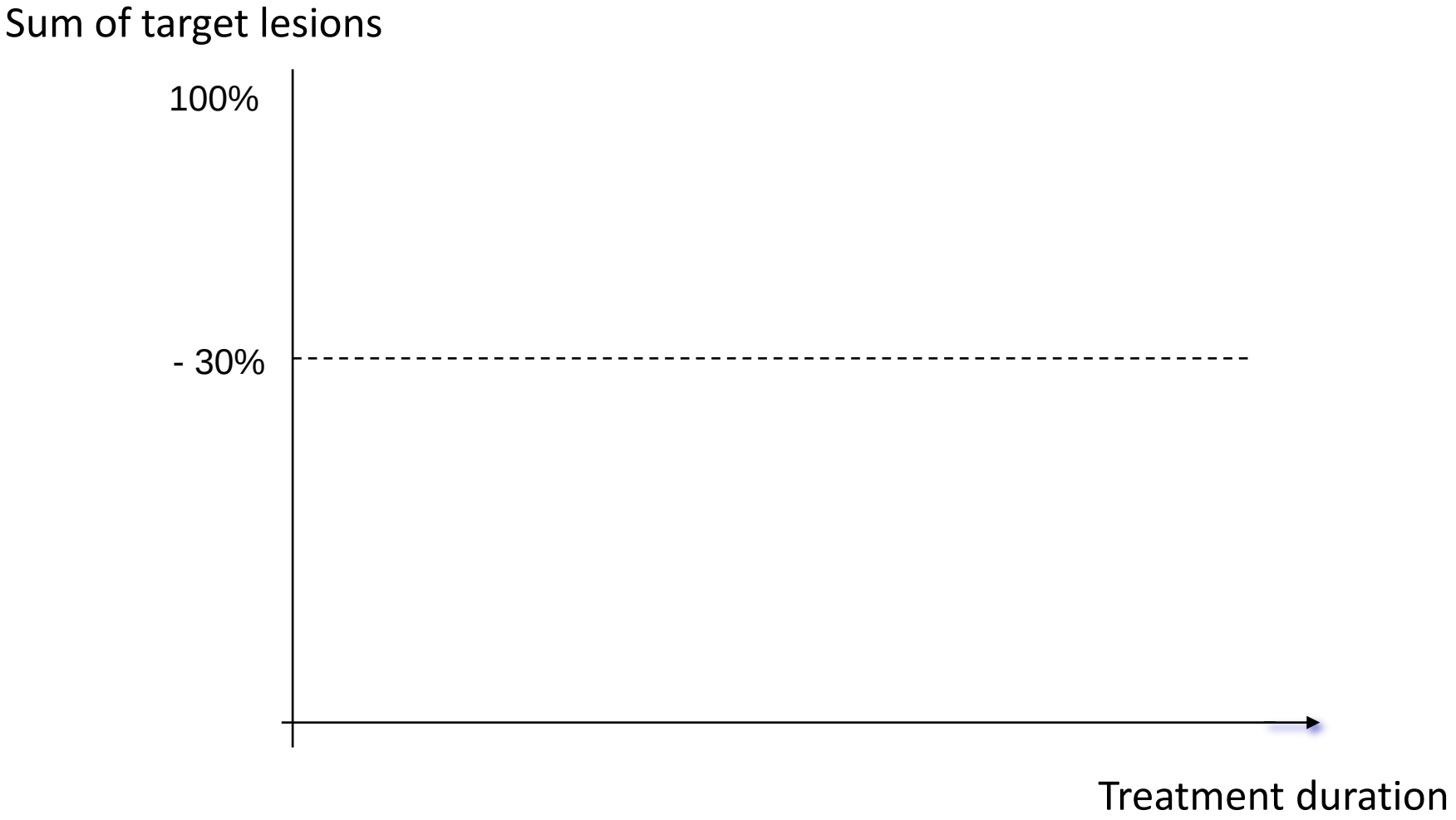
- Clinically: improvement of symptoms
- PET scan
- Conventional imaging
- Biomarkers

Response and time-to-event-parameters: Individual prognostic information given

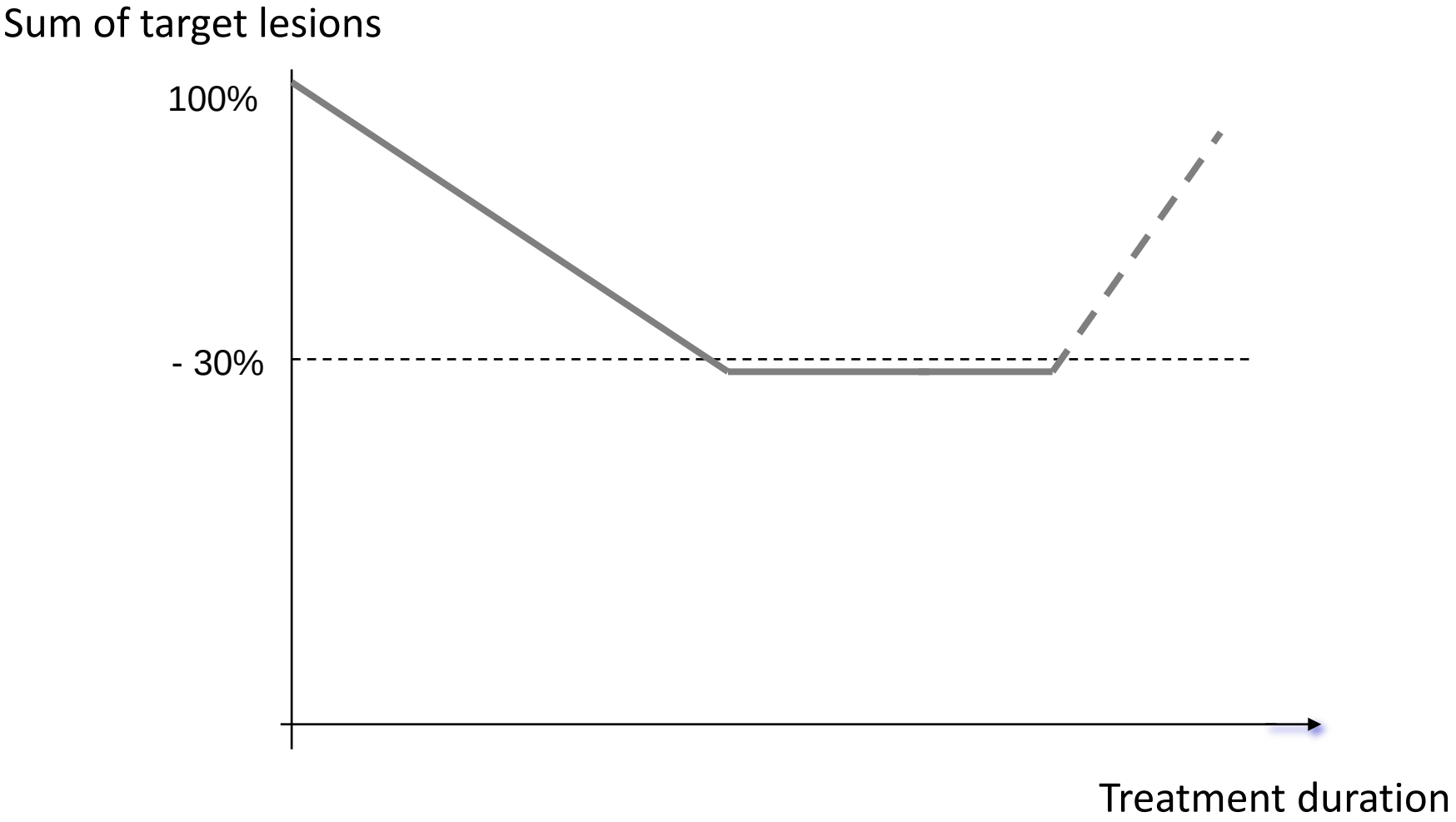


Dy et al., J Clin Oncol 2007

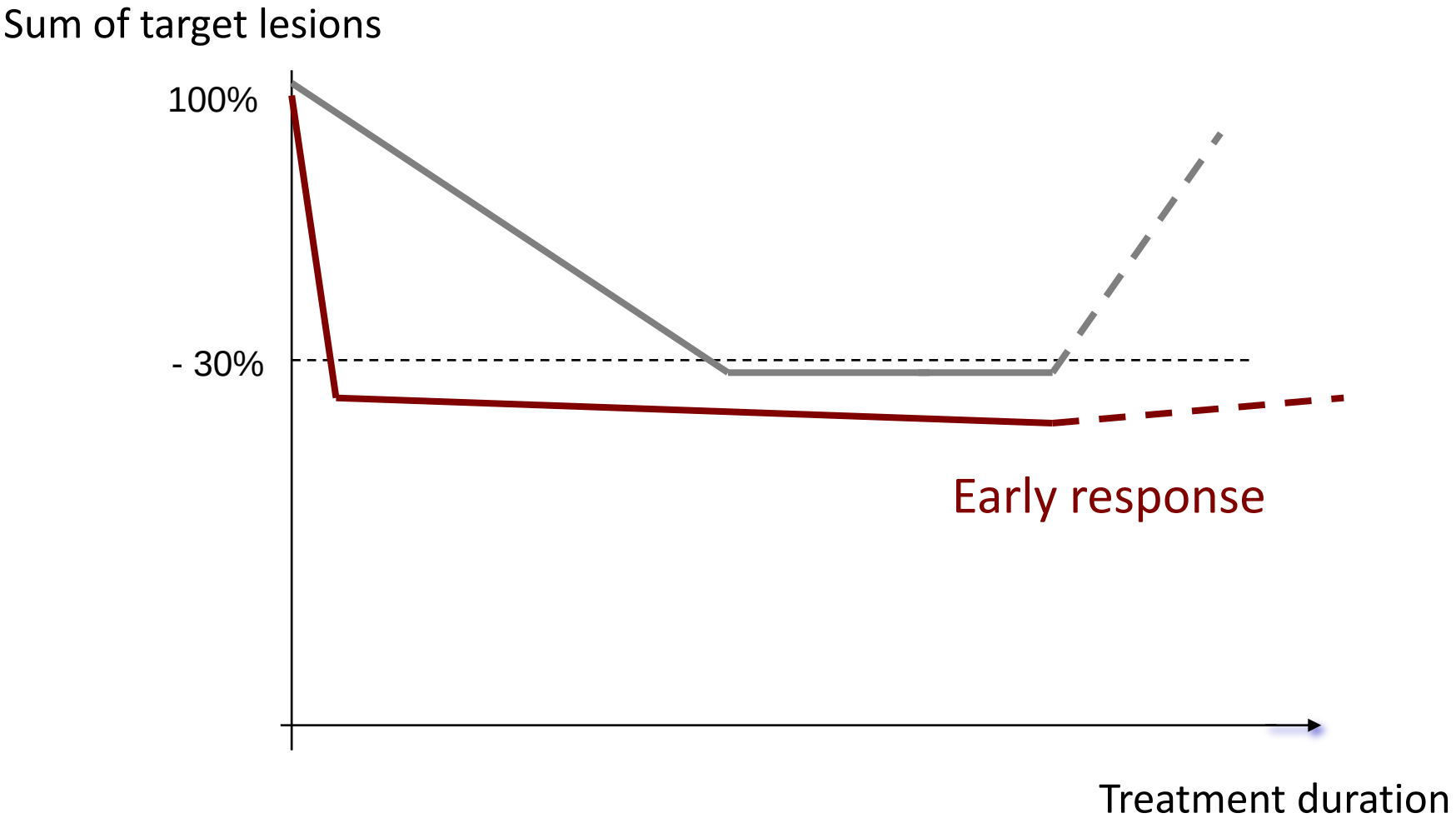
Radiographic response: Different meanings and implications



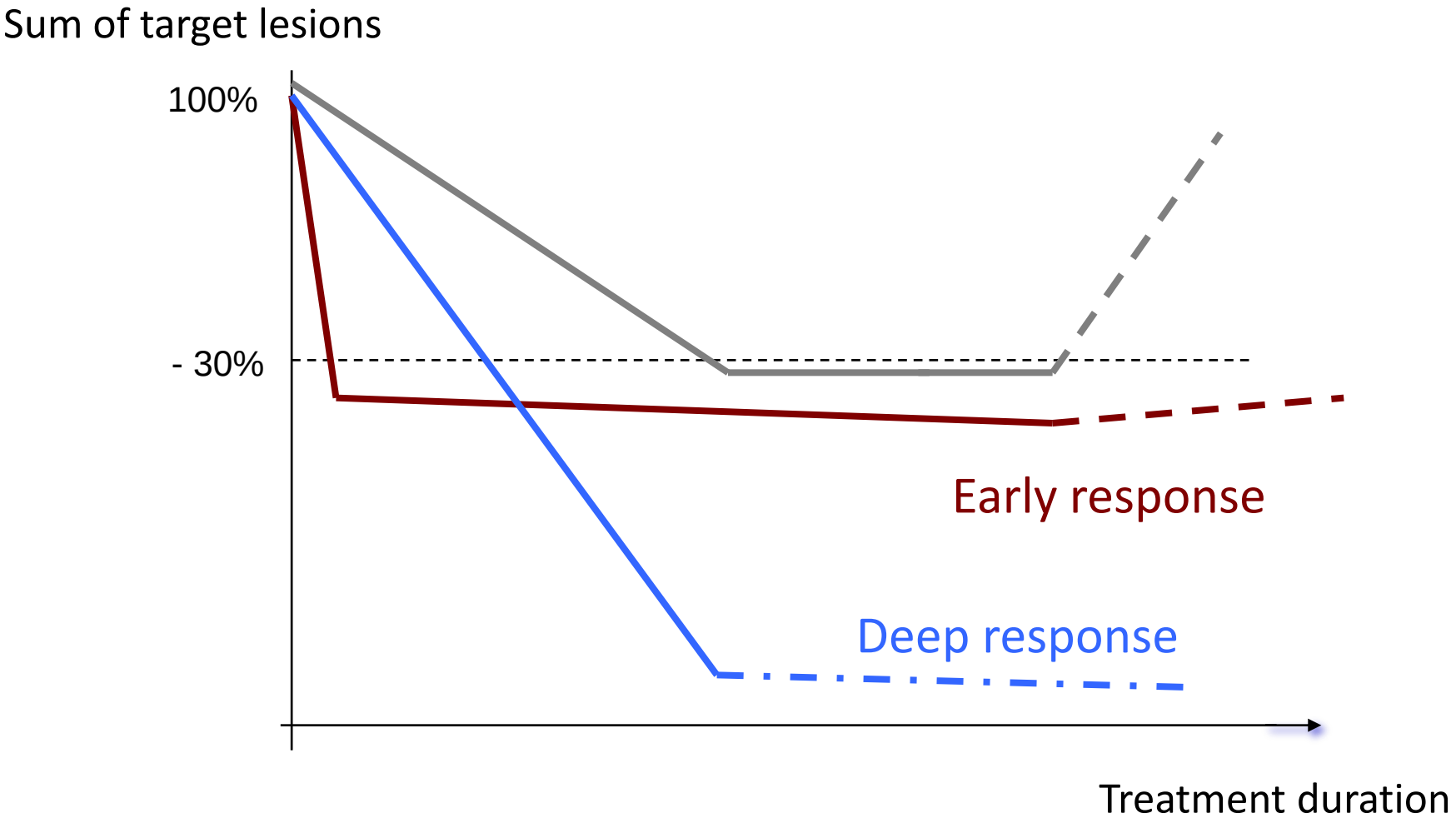
Radiographic response: Different meanings and implications



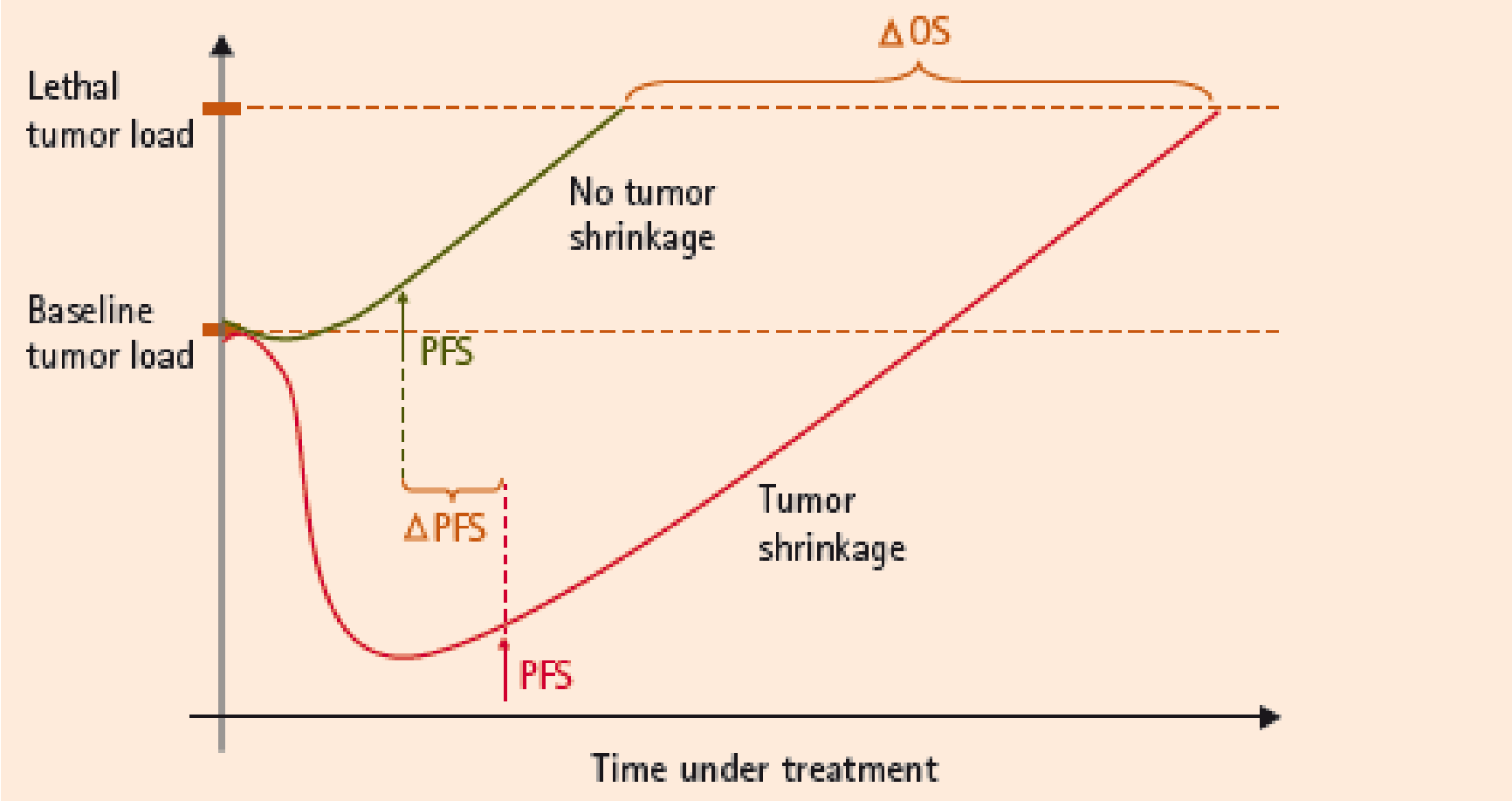
Radiographic response: Different meanings and implications



Radiographic response: Different meanings and implications

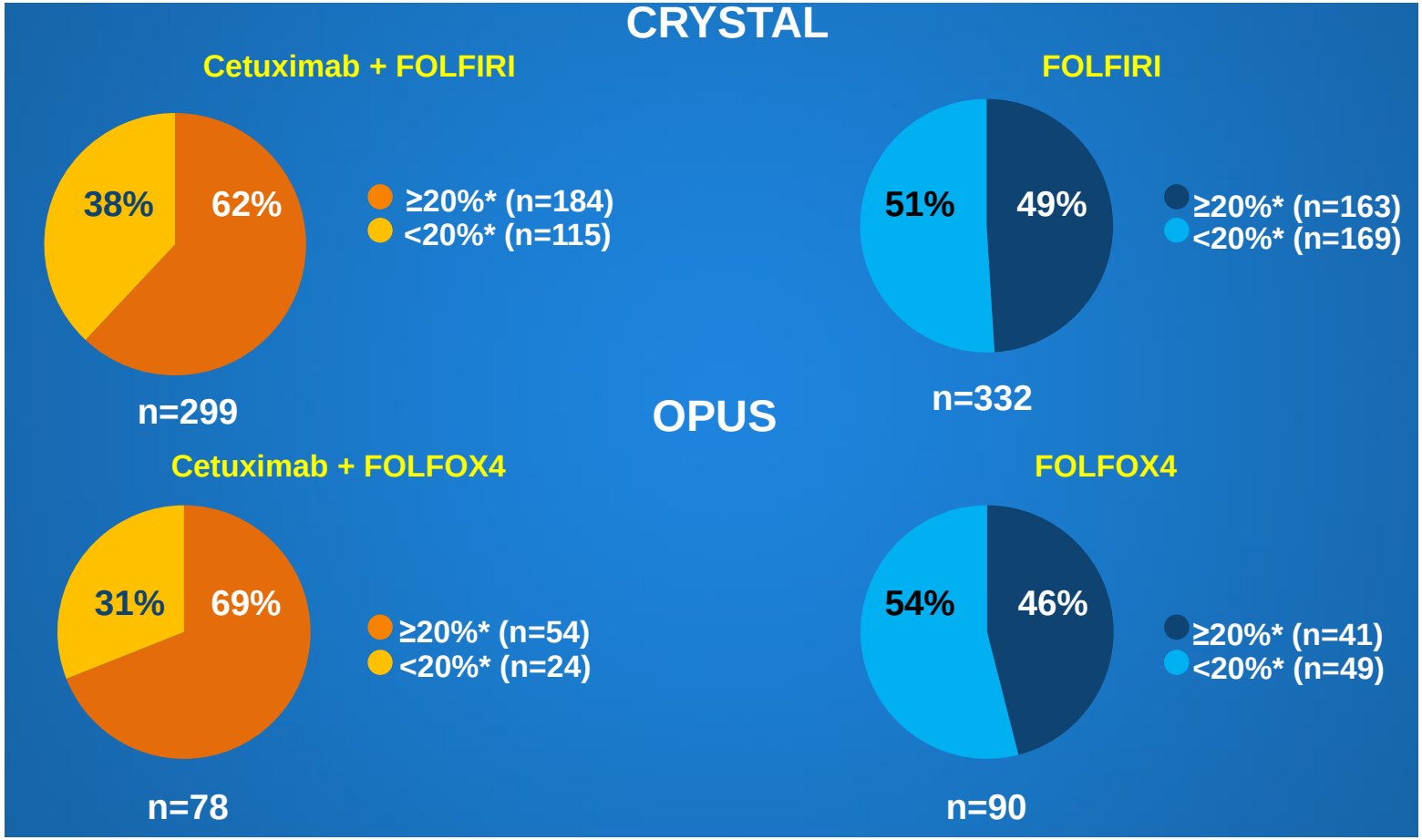


Conceptualizing the relevance of deepness of response for survival



Mansmann UR, et al. ASCO GI 2013 (Abstract no. 427)

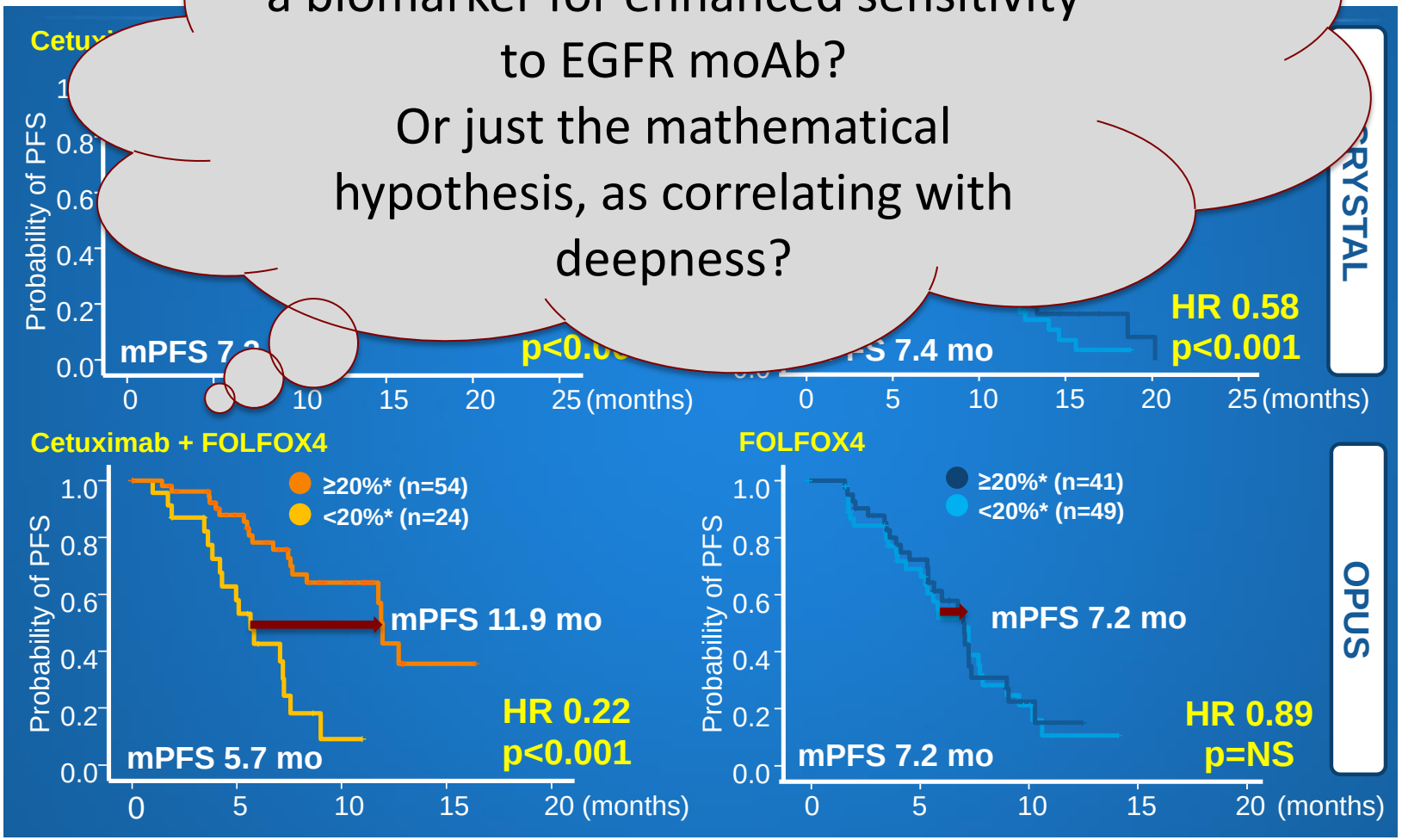
Early tumour shrinkage:
More often seen with more active treatment



Piessevaux et al., JSMO 2012

ETS under chemotherapy plus Cetuximab is ass

„Deeper“ response -
a biomarker for enhanced sensitivity
to EGFR moAb?
Or just the mathematical
hypothesis, as correlating with
deepness?



Piessevaux et al., JSMO 2012

Early response assessment

- Clinically: improvement of symptoms
- PET scan
- Conventional imaging
- Biomarkers

  Associated lab parameters

  Serial tumour biopsies

  Circulating cell compartment

  .....

„Biomarkers“: Surrogates for aggressiveness and/or activity

Decrease of CEA and CA 19-9 (cave: „flare phenomenon“)

Decrease of LDH

Normalization of impaired organ dysfuction
(AP, Bilirubin,...)

Serial biopsies: Interesting, but the relevant information may be missed

The NEW ENGLAND JOURNAL of MEDICINE

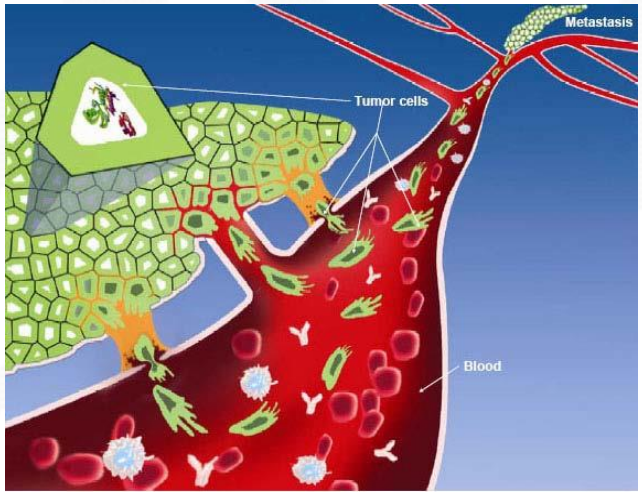
ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

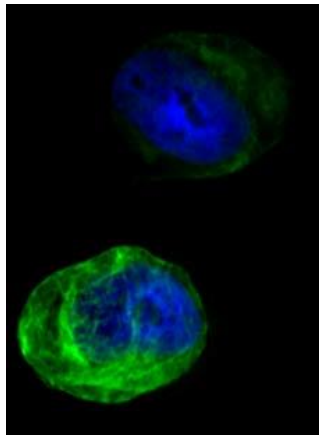
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

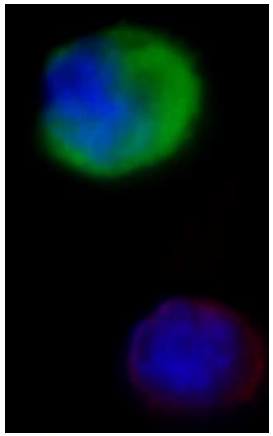
Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

CTC´s – the „liquid biopsy“

- **Cancer cells** shed from either the primary tumor or its metastases that circulate in the peripheral blood
- **Enumeration** of CTCs correlates with prognosis
- **Downstream** molecular characterization provides mechanistic information
- **Attractive alternative** to tumor biopsies for biomarker analysis:
  - Accessibility, less invasive
  - Multiple, real-time monitoring vs. archival biopsies
  - Early stage detection
- **Additional Rare Cells** for Analysis
  - Circulating Endothelial Cells (CECs)
  - Circulating Endothelial Progenitors (CEPs)
  - EMT cells
  - Stem Cells
  - CK-/CD45- Characterized Cells (various cancers)

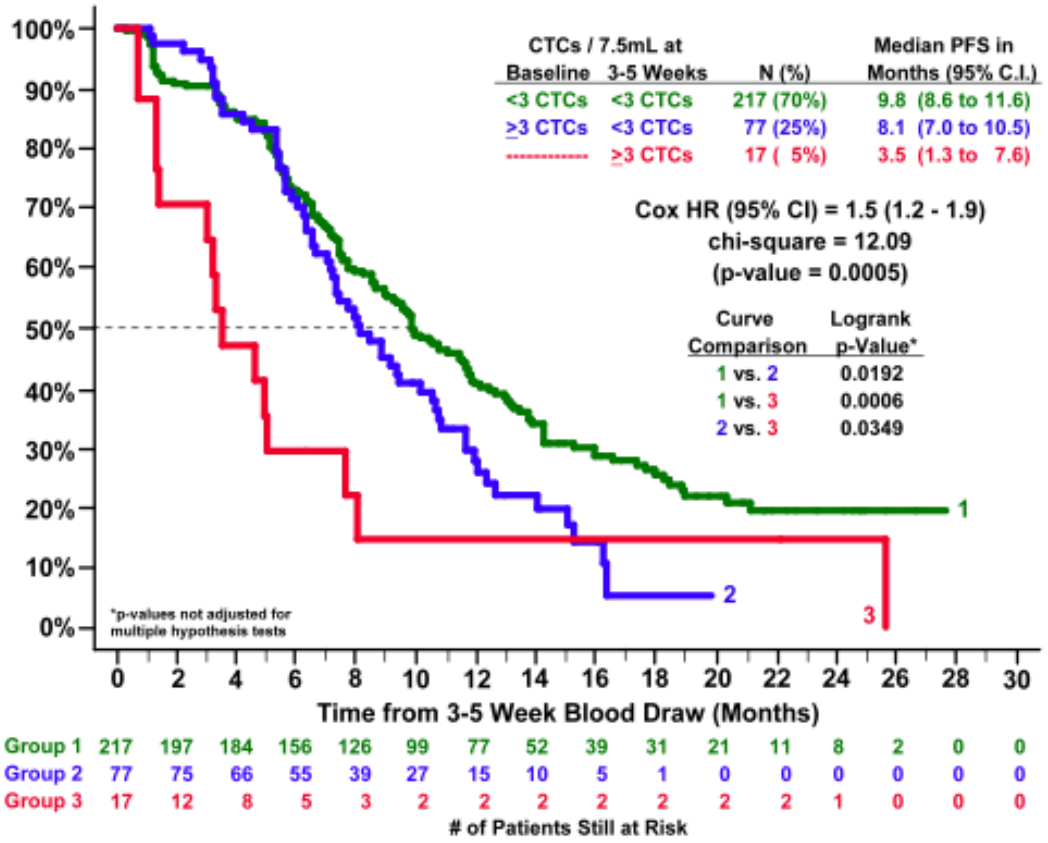






A

Changes in pattern of CTC after 3-5 wks



Koopman et al, ESMO 2008; Eur J Cancer 2009

Beyond counting tumor cells

Since the discovery of circulating tumor cells in 1869, researchers have been able to do little else beyond count them. This is about to change, as advanced technologies for harvesting and analyzing rare cells from blood are opening the window for characterization. Jim Kling reports.

NATURE BIOTECHNOLOGY VOLUME 30 NUMBER 7 JULY 2012

Heterogeneity of Epidermal Growth Factor Receptor Status and Mutations of *KRAS*/*PIK3CA* in Circulating Tumor Cells of Patients with Colorectal Cancer

CONCLUSIONS: Molecular characterization of single CTCs demonstrated considerable intra- and interpatient heterogeneity of EGFR expression and genetic alterations in *EGFR*, *KRAS*, and *PIK3CA*, possibly explaining the variable response rates to EGFR inhibition in patients with CRC.

Gasch et al., Clinical Chemistry 2013

KRAS and *BRAF* mutation status in circulating colorectal tumor cells and their correlation with primary and metastatic tumor tissue

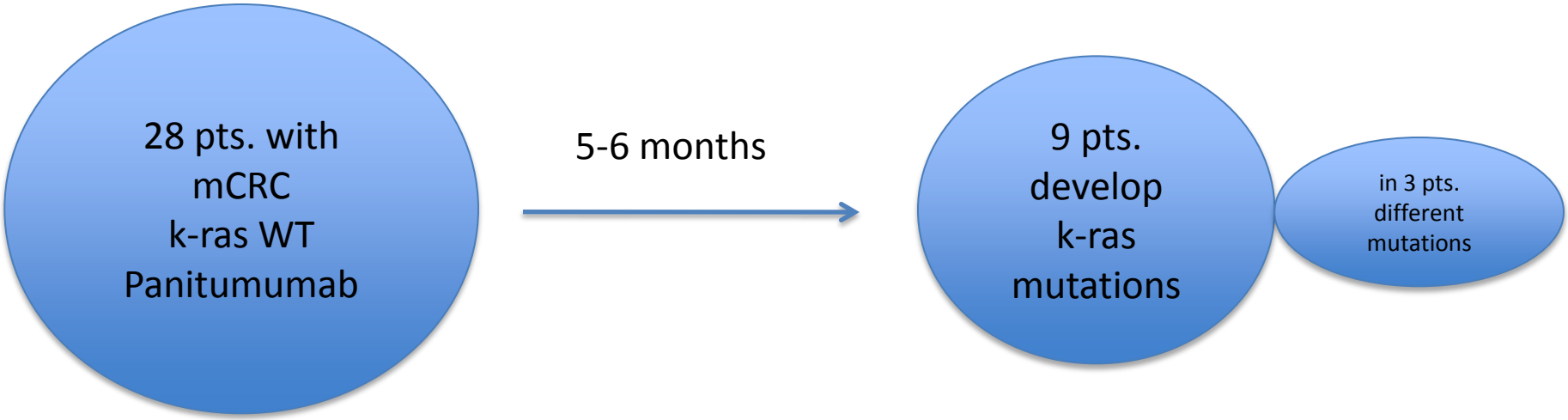
Bianca Mostert[1], Yuqiu Jiang[2], Anieta M. Sieuwerts[3], Haiying Wang[2], Joan Bolt-de Vries[3], Katharina Biermann[4], Jaco Kraan[1], Zarina Lalmahomed[5], Anne van Galen[3], Vanja de Weerd[3], Petra van der Spoel[1], Raquel Ramírez-Moreno[6], Cornelis Verhoef[5], Jan N.M. IJzermans[5], Yixin Wang[2], Jan-Willem Gratama[1], John A. Foekens[3], Stefan Sleijfer[1] and John W.M. Martens[3]

„ Inconclusive results....limited the interpretation of discrepancies between tissue and CTCs. Determination of KRAS and BRAF mutations in CTCs is challenging, but feasible.“

Mostert et al., Int J Cancer 2013 (epub ahead)

Molecular profiling: Assessing tumour evolution throughout treatment

Method: k-ras DNA in serum of treated patients

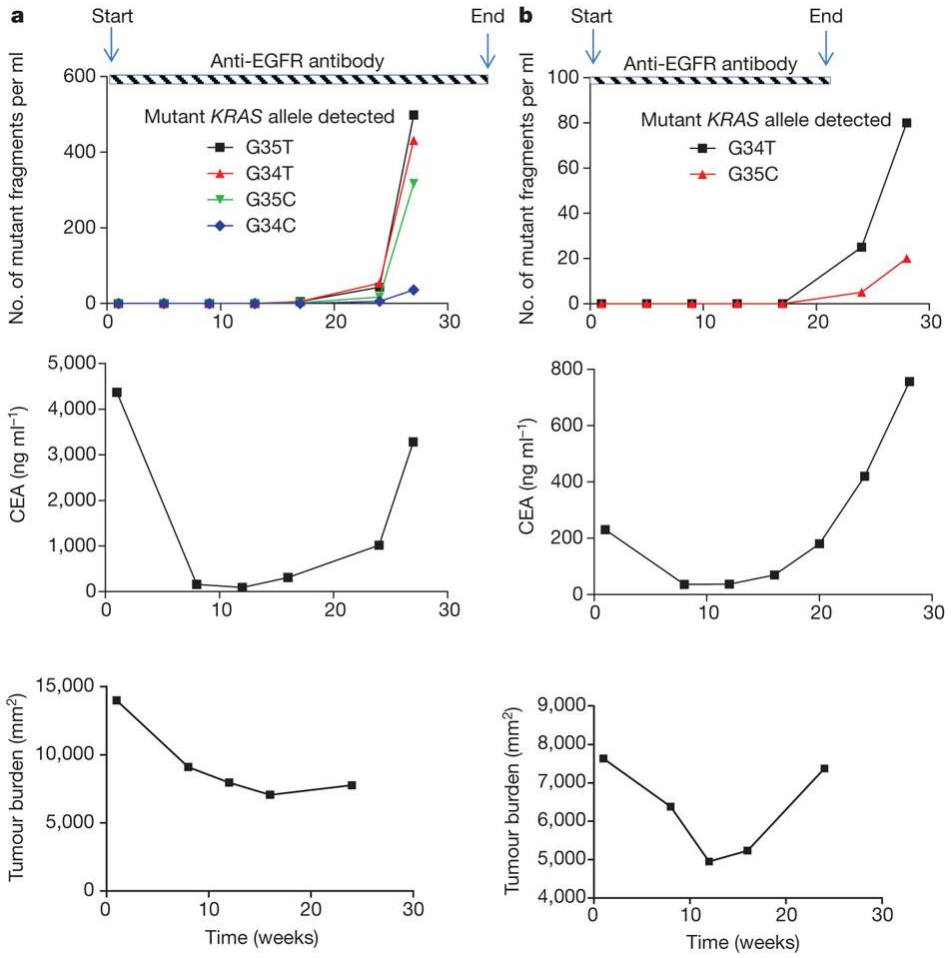


„Mathematical modelling“:
Mutations in subclones of primary existing – before start of *anti-EGFR treatment*
Detection of K-ras mutations -> result of selection by treatment?

Diaz et al., Nature 486(7404); 2012

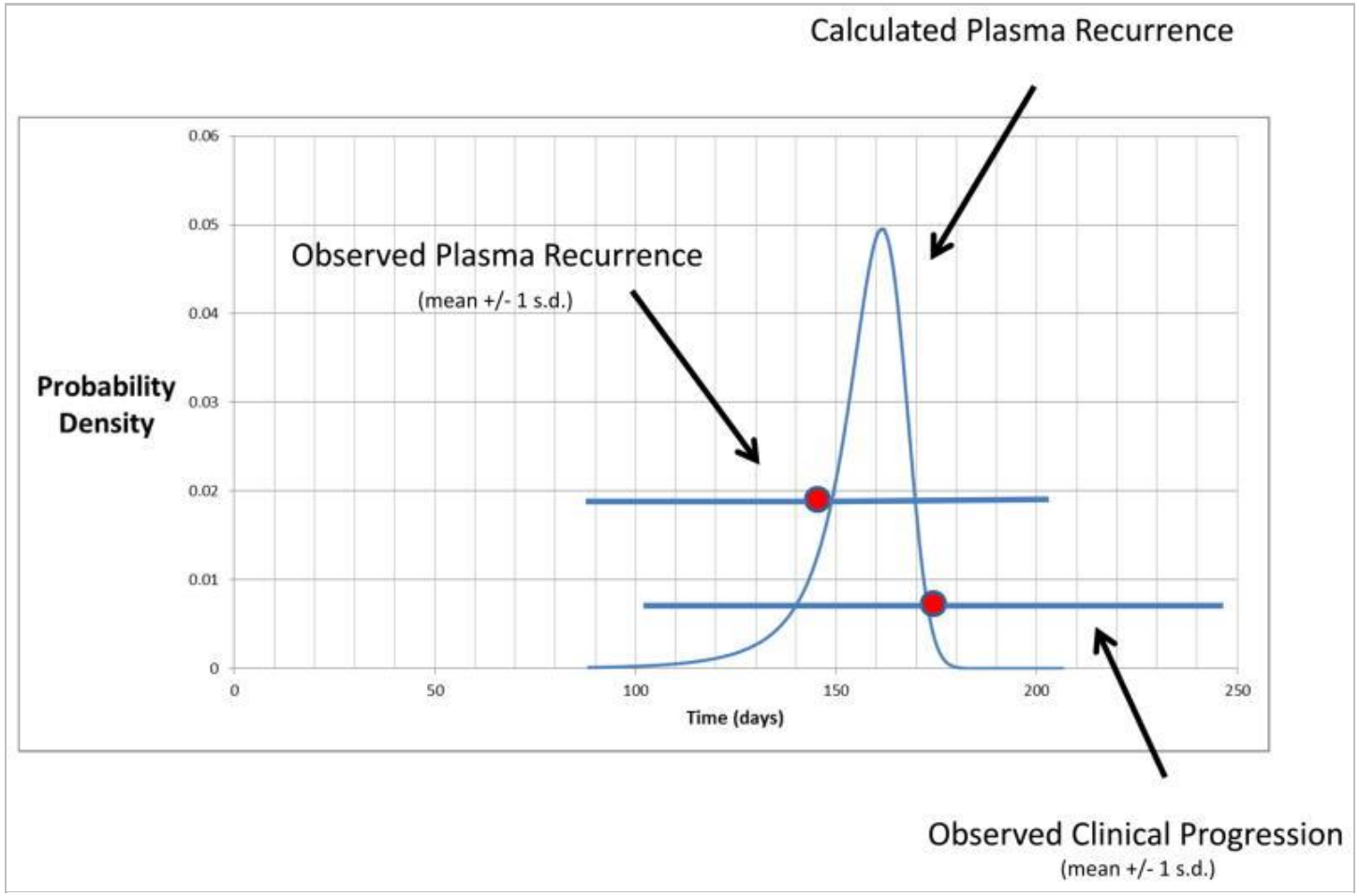
K-ras mutations as a selection marker throughout treatment with Panitumumab

- Interval from detection of mutated k-ras -> radiographic progress:
  21 weeks
- Doubling time of panitumumab resistant tumour cells:
  10 days
- 91.4% of metastases bear other mutations than k-ras



Diaz et al., Nature 486(7404); 2012

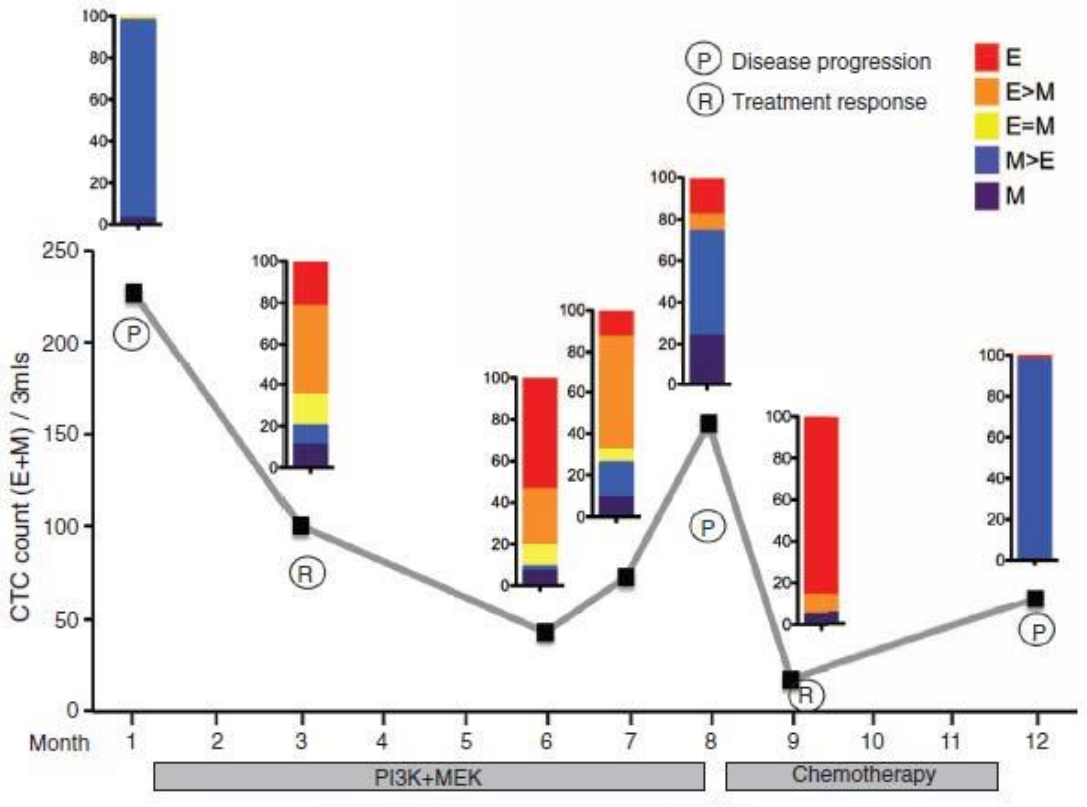
Predicted probability of times from tx. start until resistance mutations in circulating DNA



Diaz et al., Nature 486(7404); 2012

The next target: Dynamic changes in EMT during treatment for breast cancer

11 BC patients; continuous EMT characterization in CTC



Epithelial

Mesenchymal

Yu M et al., Science 339 (6119), 2013

Information obtained throughout treatment: Late, but not too late!

- **Functional imaging by PET:**
  High correlation and predictive values, but many open questions for standardization in patient-related and technical aspects
- **Early response prediction by CT (o MRI):**
  Easy access, but relatively late information. Standardization of response criteria needed.
- **Early response in biomarker profile:**
  May add drug-specific information – also for other drugs (anti VEGF → anti VEGF)

Information obtained throughout treatment: Potential clinical consequences

- Treatment may be de-escalated to avoid (cumulative) toxicity (e.g. oxaliplatin)
- Treatment may be escalated or modified if „early response resistance“ correlates with poor outcome
- Treatment strategy may be re-adjusted (e.g. resection if possible vs. continuation)
- Treatment may be „tailored“ in terms of specific drug use

Information obtained throughout treatment: Questions and demands

What is „more important“ – or combined algorithm?:

PET ←→ CT early response ←→ unspecific biomarker ←→ specific biomarker

Prospective validation needed!

And: The “elephant in the room”:
Investment in human and financial resources needed to bring such a strategy to clinical fruition...