A paradigm shift in early drug development: Individualizing to more patient benefit: Conclusions and perspectives

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VIENNA 2012 ESMO congress

The basis for individualized oncology:

Matching

1. The patient
2. The tumor
3. The target

} Context of vulnerability through whole disease progression

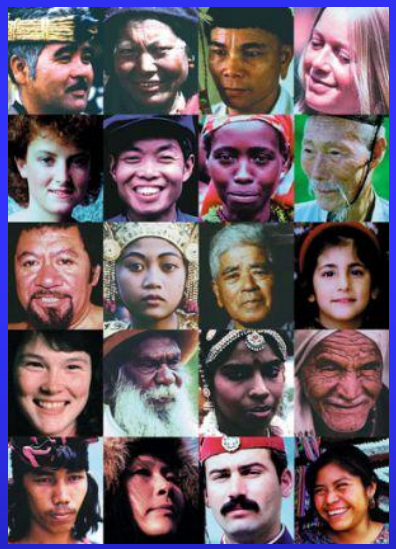
4. The test-platform } Reproducibility-validation
5. The drug-combination } Selective-multitargeted

The patient!

"Your pulse is very, very weak !"

Patient and tumor characteristics remain important in selecting targeted therapy: The example of NSCLC (1)

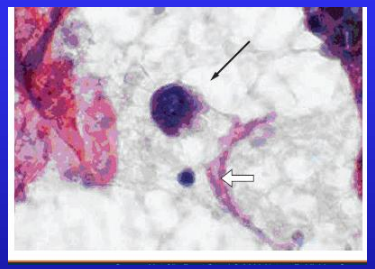
- Ethnicity, gender, smoking habit and small molecules EGFR inhibitors efficacy in NSCLC



- Location of metastatic sites in lung (central versus peripheral): Antiangiogenic agents and risk of hemorrhage

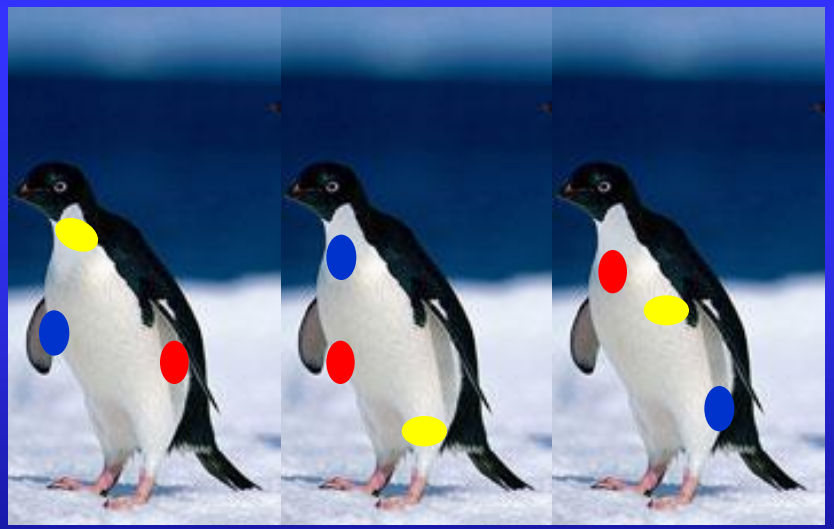
Patient and tumor characteristics remain important in selecting targeted therapy: The example of NSCLC (2)

- Histology (squamous versus non-squamous)
- Tumor molecular aberrations (drivers): EGFR, ALK, ROS1, …

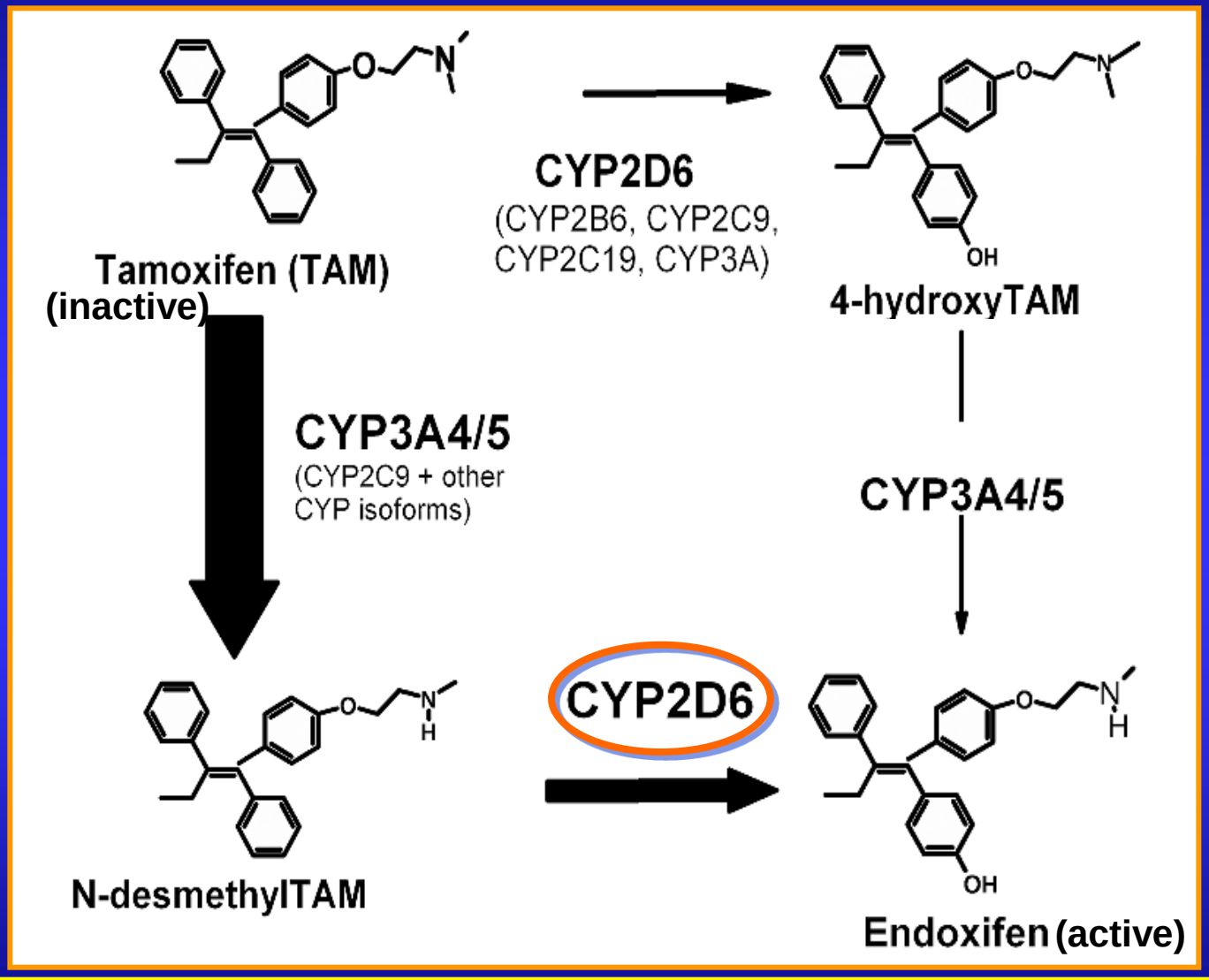


Pharmacogenetics is a key field but has difficulty to emerge in clinical practice

- e.g. Cyt 2D6 and tamoxifen metabolism in breast cancer



TAMOXIFEN METABOLIC PATHWAY



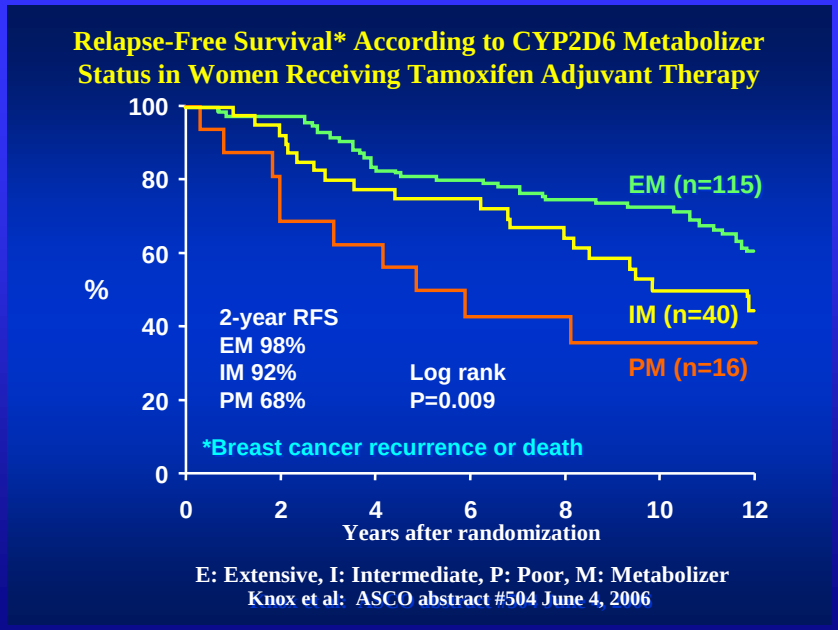
Jin Y et al: J Natl Cancer Inst 97:30, 2005

CYP2D6 AND THERAPEUTIC INDEX OF TAMOXIFEN

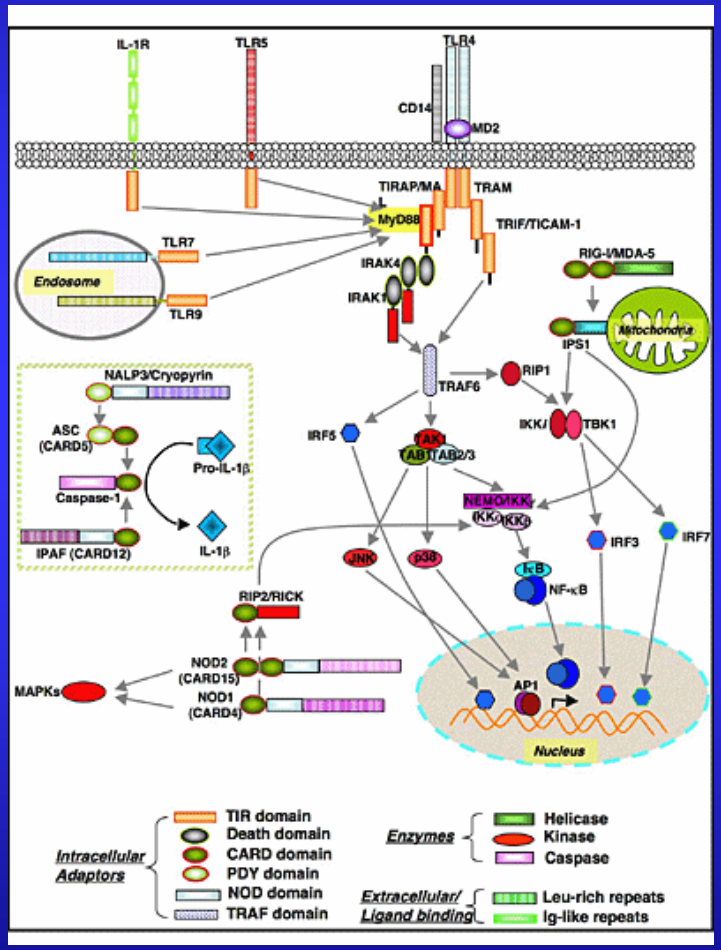
Marker(s) studied (Stroth et a. JCO2007)	Key findings	Implications for clinical practice
• Genotyping for CYP2D6 alleles *4, *5, *10 and *41 can identify pts who will have <u>little</u> benefit from adj. Tamoxifen • CYP2C19 *17 variant identifies pts likely to <u>benefit</u> from Tam.	Poor metabolizers (7% of population) show worse outcome	Avoidance of CYP 450 inhibitors such as haloperidol, amiodarone, cimetidin, fluoxetin, paroxetine, sertraline …!

<u>SABCS 2010</u>

No evidence to support CYP2D6 testing in clinical practice



The target!



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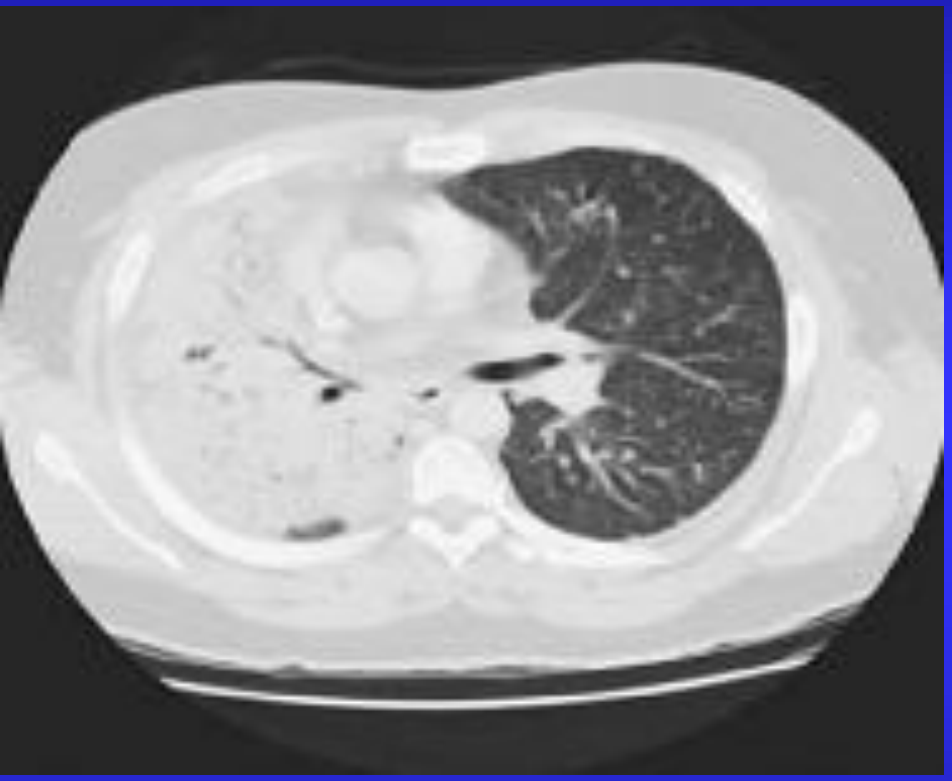
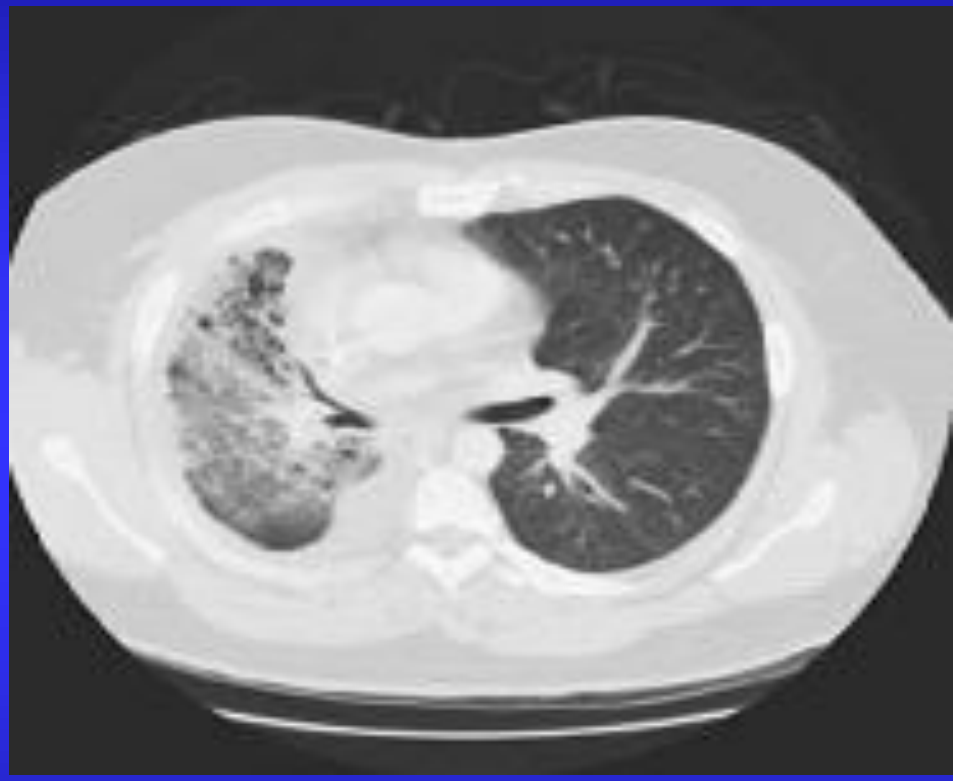
Successful targeted therapies in molecularly selected patients

Disease	Genetics	Target	Drugs
NSCLC (adenocarcinoma)	*EGFR* mutations	EGFR	EGFR TKIs (erlotinib, gefitinib, afatinib)
Breast cancer	*HER2* amplification	HER2	Trastuzumab, lapatinib, T-DM1, pertuzumab
GIST	*KIT* and *PDGFRA* mutations	KIT, PDGFRA	Imatinib, sunitinib
PRCC	*MET* mutations	MET	MET TKIs (ARQ197 and XL880)
Melanoma	*BRAF* mutation	BRAF V600E	BRAF and MEK inhibitors (vemurafenib, trametinib)
NSCLC	*EML4-ALK* rearrangement/ROS1	ALK/ROS1	ALK inhibitors (crizotinib)
Ewing's sarcoma	*EWS-FLI* translocation	IGF1R	Anti-IGF1R antibodies (figitumumab)
Medulloblastoma; BCC	*PTCH1* or *SMO* mutations	SHH pathway	SMO inhibitors (vismodegib)
Ovarian and breast cancer	*BRCA1/BRCA2* mutations	PARP	PARP inhibitors (olaparib)
NSCLC, RCC, melanoma	PD1/PD-L1	PD1/PD-L1	BMS-936558

J.Rodòn, et al. Nature reviews clinical oncology, June 2012; 9, 359-366

RESPONSE TO GEFITINIB IN A PATIENT WITH REFRACTORY EGFR-MUTATED NSCLC

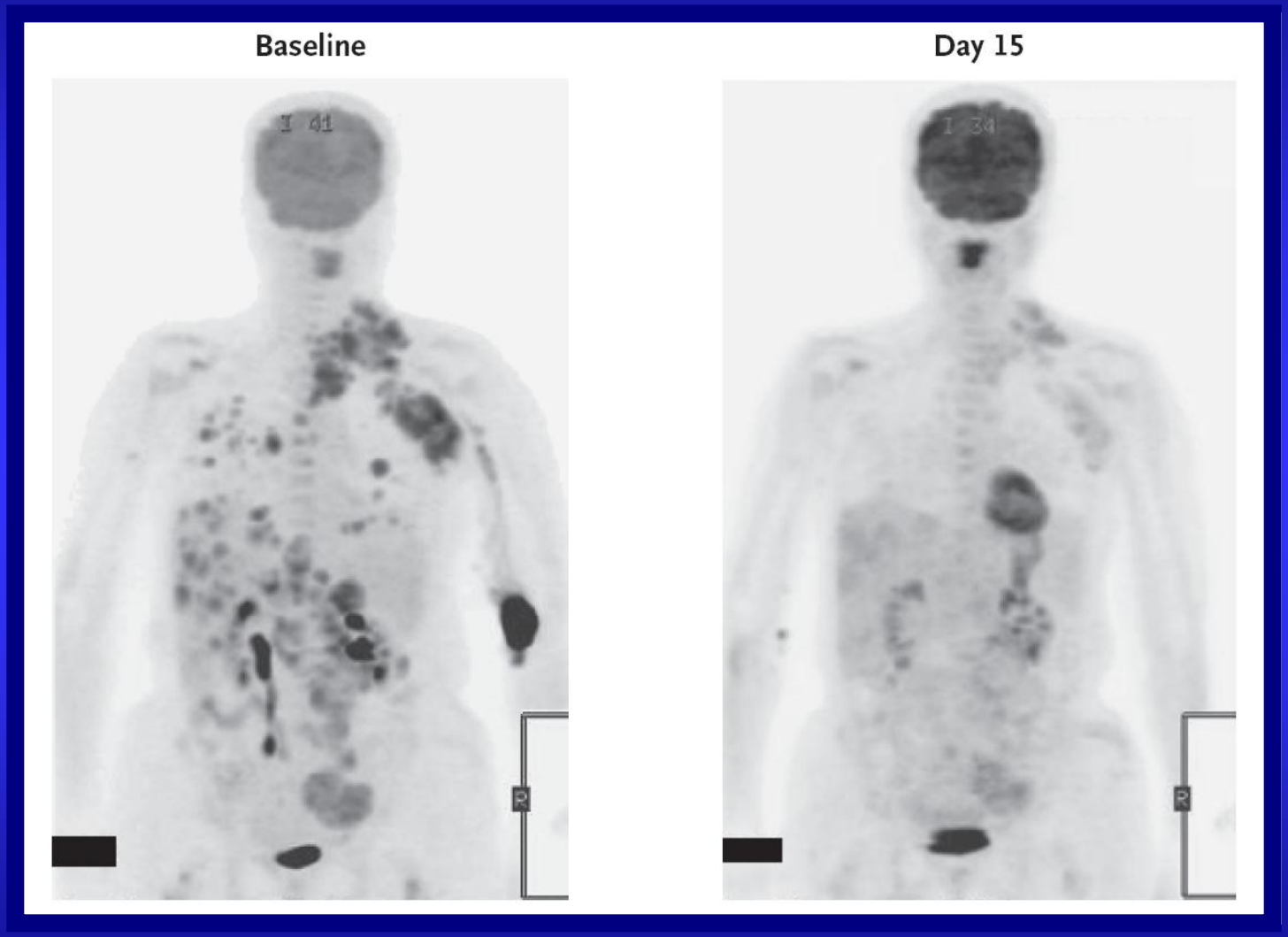




Unselected = cloudy

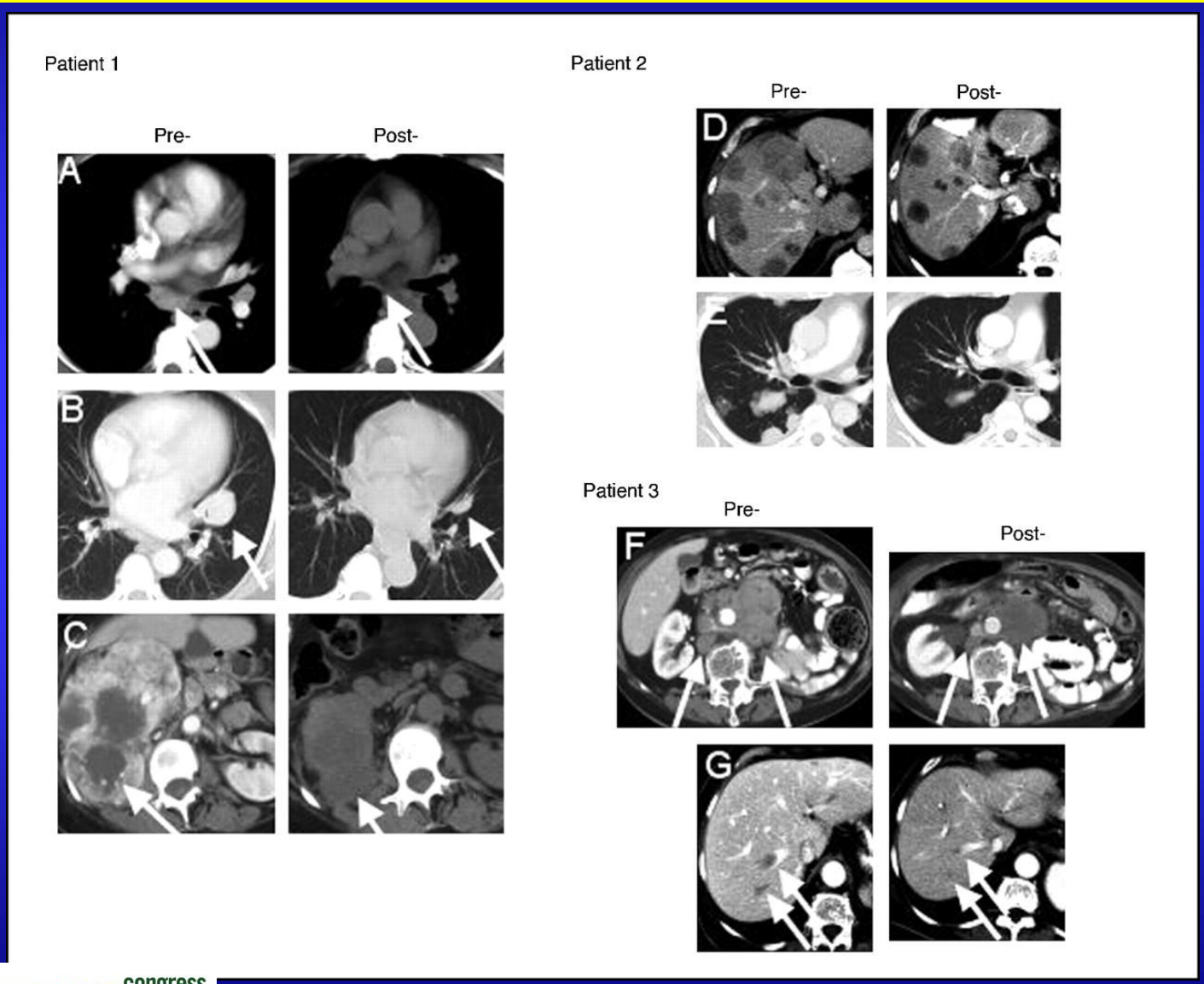
EGFR mutated + Gefitinib = cleared

TARGETING BRAF MUTATION IN ADVANCED MELANOMA – A PET RESPONSE TO VEMURAFENIB



Flaherty, KT. N Engl J Med 363;9 2010

Multitargeted kinases inhibitors : mainly antiangiogenic agents (e.g., in renal cancer)



Responses in patients with multiple metastatic sites from RCC

No molecular predictive markers of tumor response

Motzer et al, JCO 2006

THE DIFFICULT TASK OF TARGET / BIOMARKER EVALUATION

MEASURING THE TARGET / BIOMARKER

=

HUGE DIFFICULTIES IN

- **Ensuring reproducibility of measurement**
- **Selecting the right technology**
- **Validating the results**

The discovery of de novo or acquired resistance mechanisms to targeted agents remains a key field as well as the development of active agents or combinations to the resistant mutations

- K-Ras mutation and resistance to EGFR monoclonal antibodies
- C-Kit resistant mutations to imatinib in GIST
- EGFR resistant mutations to gefitinib and erlotinib in NSCLC

Rationale for combinations based on targeted agents

- To obtain maximum activity (synergy) without overlapping toxicity
- To overcome resistance by using non cross-resistant drugs

How to optimize clinical combinations of targeted agents (1)

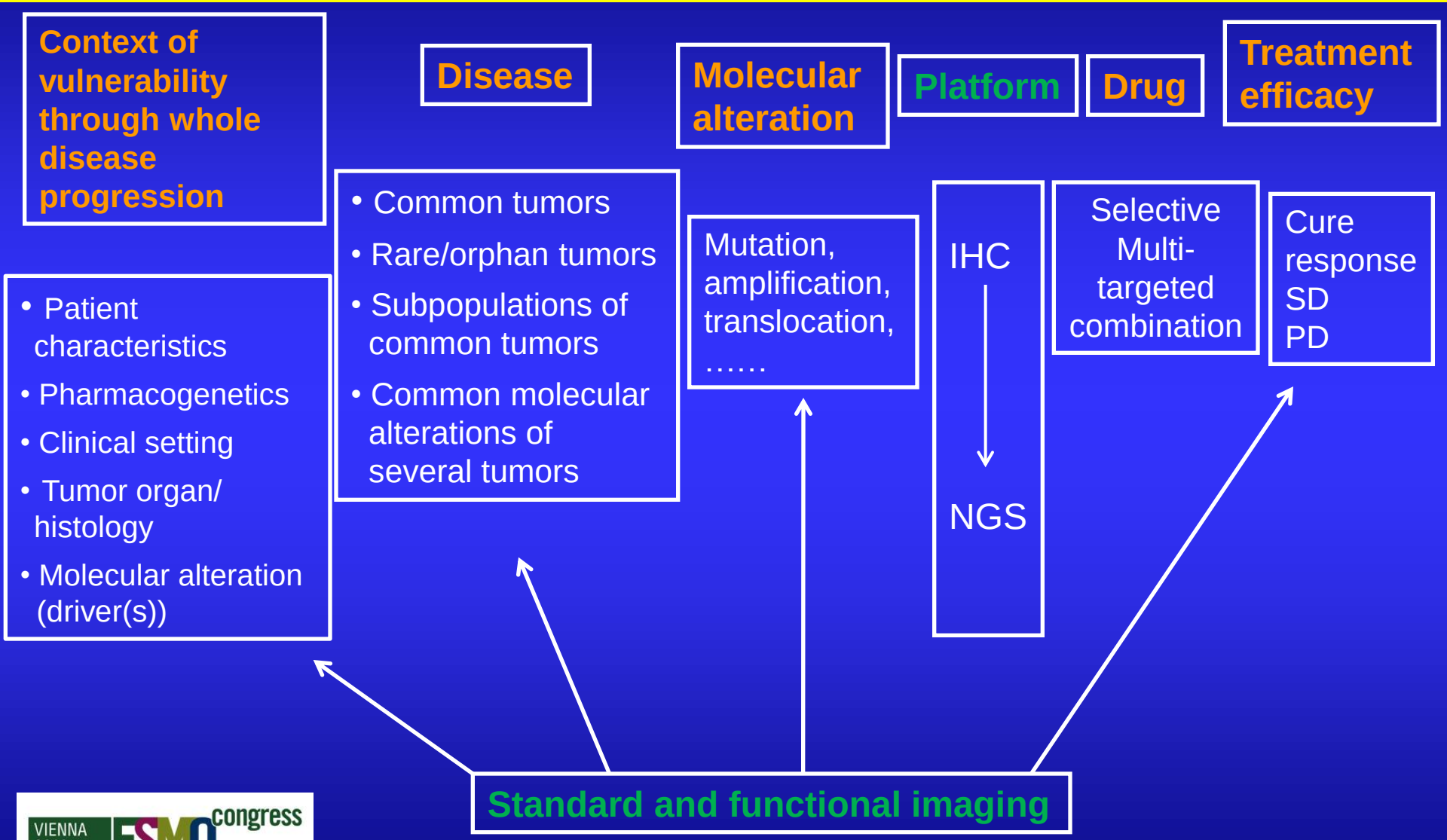
	Clinical strategy	Comments
1	Maximize target inhibition « dual-inhibition »	Promising stragety in BC and NSCLC
2	Maximize pathway inhibitor	Potential strategy in solid tumors
3	Inhibit parallel pathways	Ongoing clinical studies. Mitigated results. Toxicity issue.
4	Inhibit target and feed back loops	Ongoing studies. Results awaited

How to optimize clinical combinations based on targeted agents (2)

	Clinical	Comments
5	Combination of two different approaches (targeted + chemo, endocrine or RT)	Works [colon, NSCLC (beva, cetuximab); breast (trastuzumab, lapatinib, everolimus); H&N (RT + cetuximab)]
6	Combination of three different approaches	Fails [colon (chemo + EGFR inh. + bev.); H&N (RT + cetuximab + chemo)]

RT = radiotherapy

Matching patient / tumor / molecular aberration / test-platform / drug: The basis for individualized oncology



Basis of a molecular screening program in early drug development

Relative to the process	Relative to sample analysis	Relative to treatment
• IRB-approved protocol and consent form for sample analysis • Database for tracking samples, results and clinical data • Staff and funding • Process planning (matching tumour type, test, platform and trial)	• Samples (FFPE, fresh frozen, blood) • Platforms for DNA, RNA, and protein analysis • Staff laboratories • CLIA-like certification and GCLP process for laboratories	• Portfolio of early clinical trials with sufficient drugs and combinations • Sufficient population of patients with different tumors that may harbour targetable molecular aberrations • Phase I meetings to discuss matching patients, molecular alterations and drugs

CLIA, Clinical Laboratory Improvement Amendments; FFPE, Formalin-fixed paraffin-embedded; GCLP, Good clinical Laboratory Practice; IRB, Institutional Review Board

J.Rodòn, et al. Nature reviews clinical oncology, June 2012; 9, 359-366

Challenges in the implementation of a molecular screening program in early drug development (1)

Biology of cancer

- Molecular alteration do not present « full » tumor vulnerability (driver vs passenger)
- Tumor heterogeneity
- Clonal evolution during tumor progression (further molecular alterations)
- Biomarkers issues:
  - not appropriate for pts selection (due to complex intracellular pathways)
  - not applicable (eg. Multitargeted; antiangiogenic agents, …)

Challenges in the implementation of a molecular screening program in early drug development (2)

Platform

- Tumor availability
- Technical issues
- Validation and standardization issues
- Relevance of some findings is unknown

Challenges in the implementation of a molecular screening program in early drug development (3)

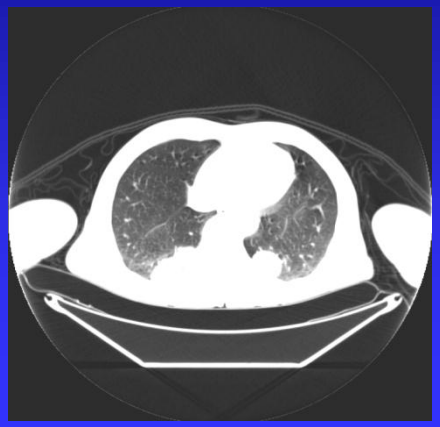
Clinical trial

- Lack of validated biomarkers early in the drug development process
- Patient attrition (no slot available at the time of PD, ↓ PS, eligibility criteria too strict, …)
- Cost, financial support and reimbursement issues
- Lack of a suitable targeted drug for a molecular alteration (clinician and patient frustration; Ethical issue)

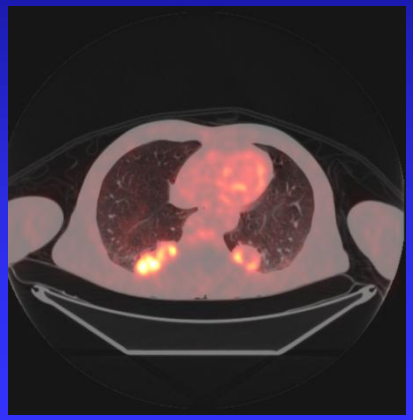
FUNCTIONAL IMAGING

FDG PET/CT in a head and neck patient treated with sorafenib

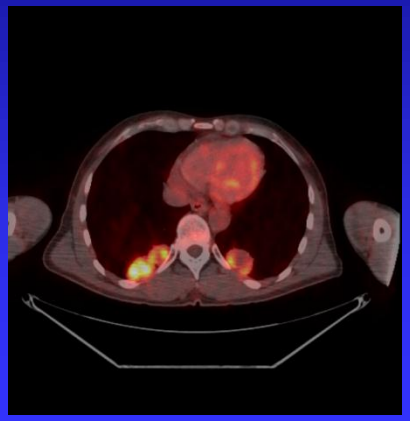
Baseline

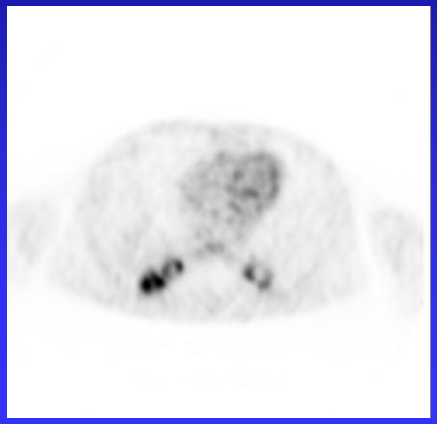


pulmonary CT Scan



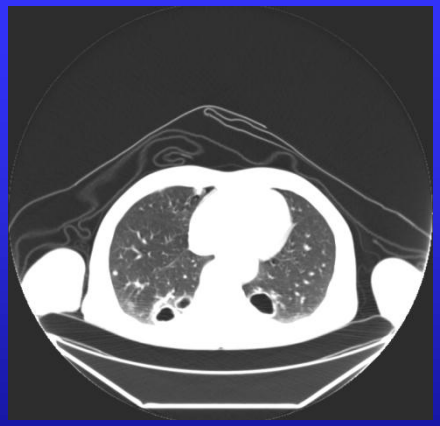
FDG PET/CT fusion images (pulmonary and mediastinal window)



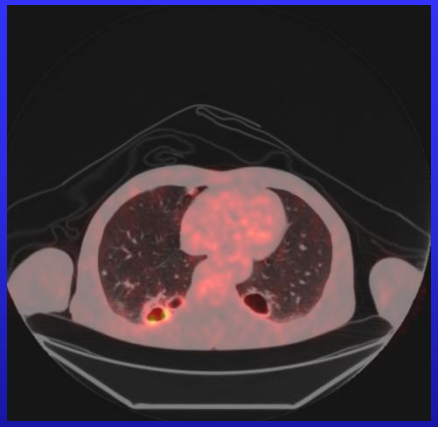


High FDG uptake in pulmonary lesions

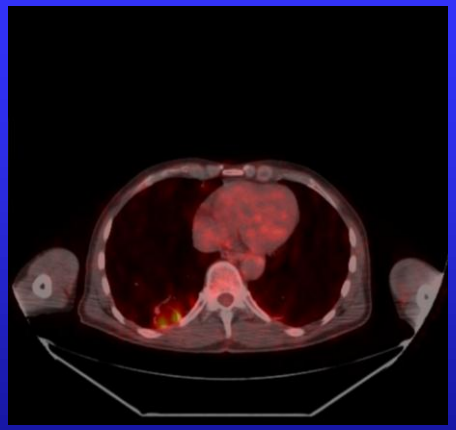
Better response assessment by FDG PET/CT (before D21)

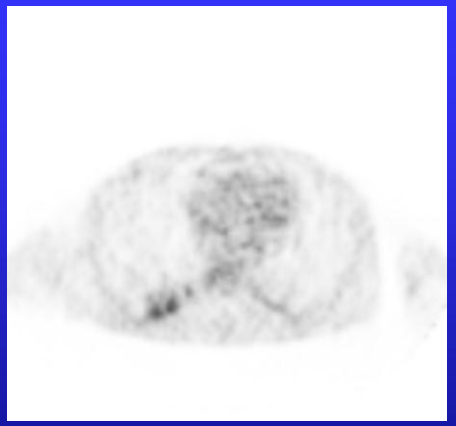


pulmonary CT showing Cavitated lesions



FDG PET/CT fusion images pulmonary and mediastinal window

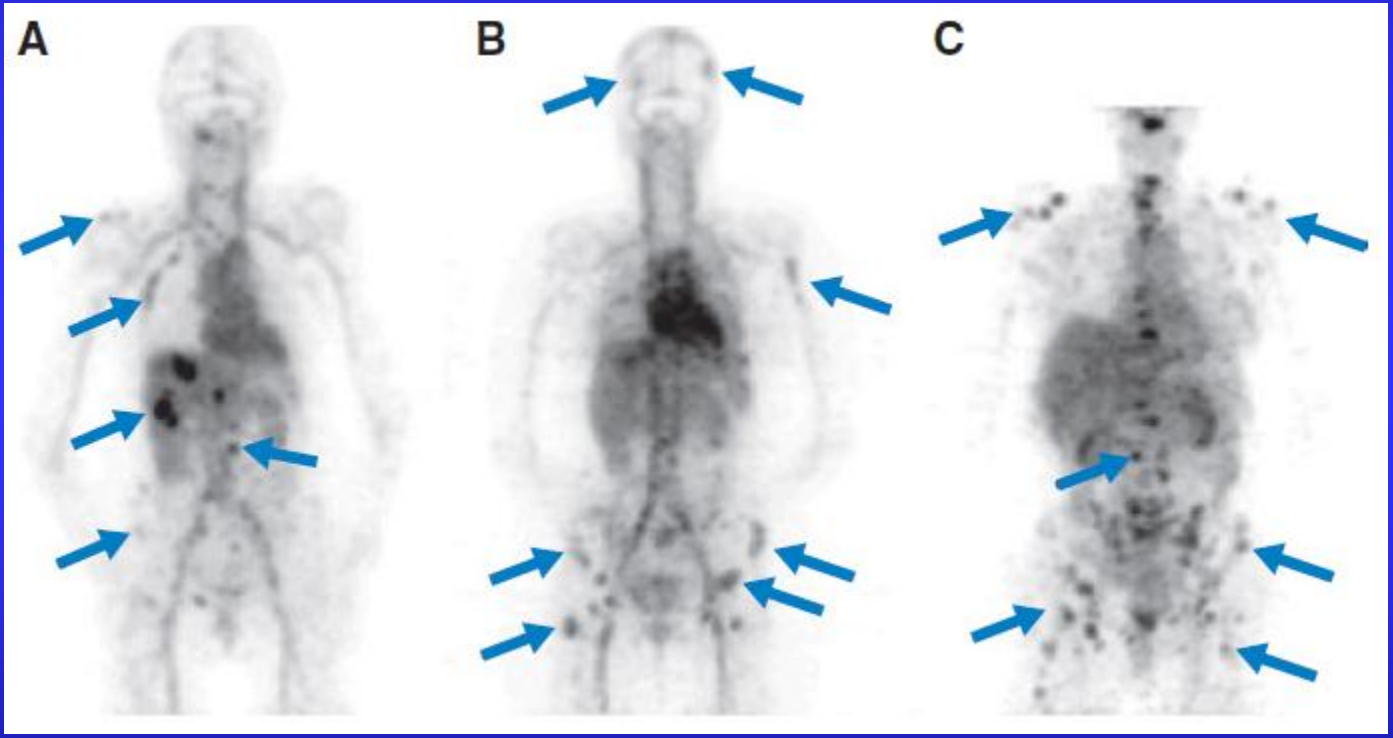




Net FDG Uptake decrease in same cavitated lesions

Courtesy of Y. Lalami

Zirconium-89-trastuzumab localizes to human epidermal growth factor receptor 2-expressing tumors (and heart) 5 days postinjection



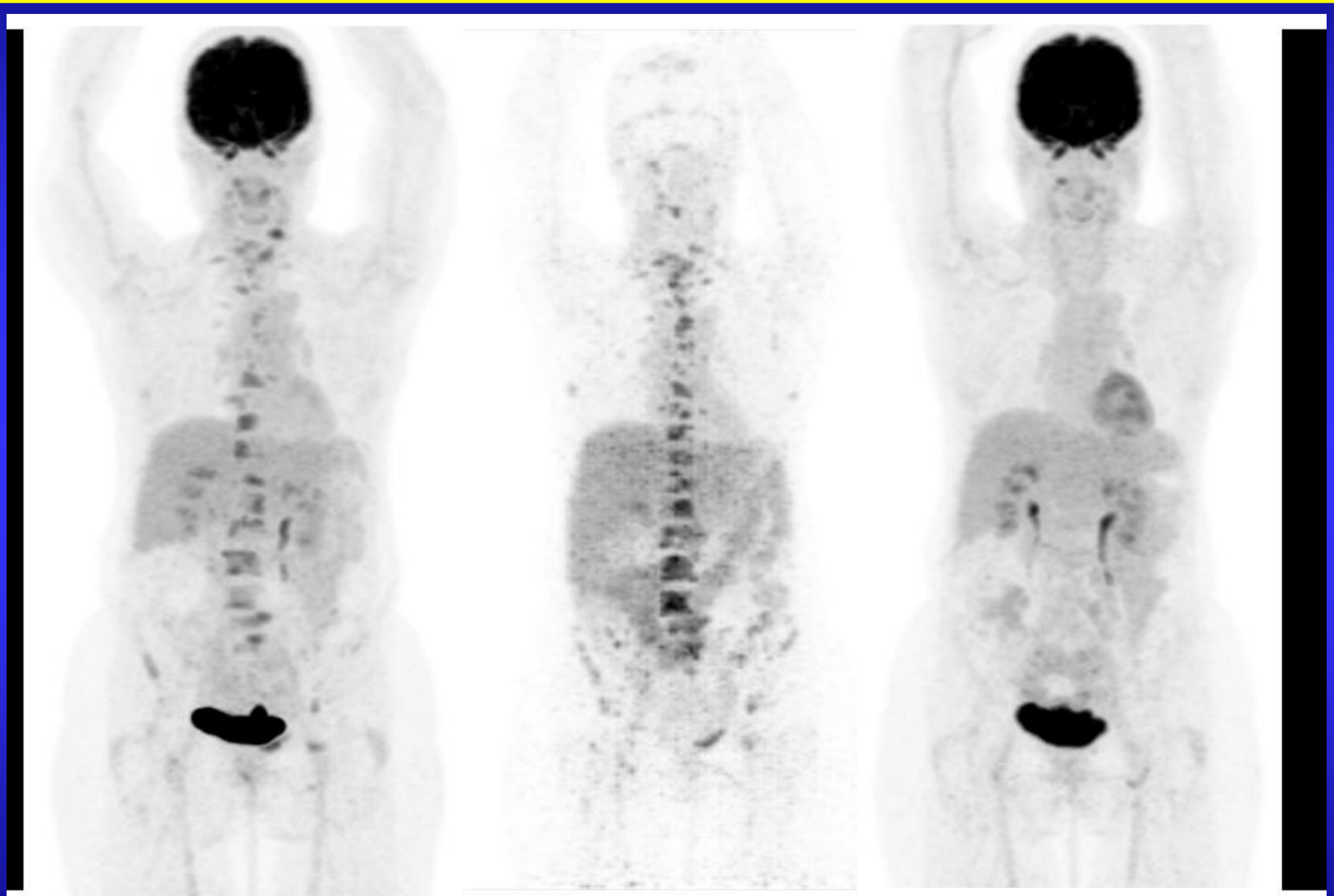
Bone & liver metastases

Bone metastases
Heart uptake

Massive bone metastases

S.M Knowles, JCO, 2012

FDG PET/CT and ^{89}Zr-Trastuzumab PET/CT in a patient (ER+/HER-2+) with bone metastases from breast cancer

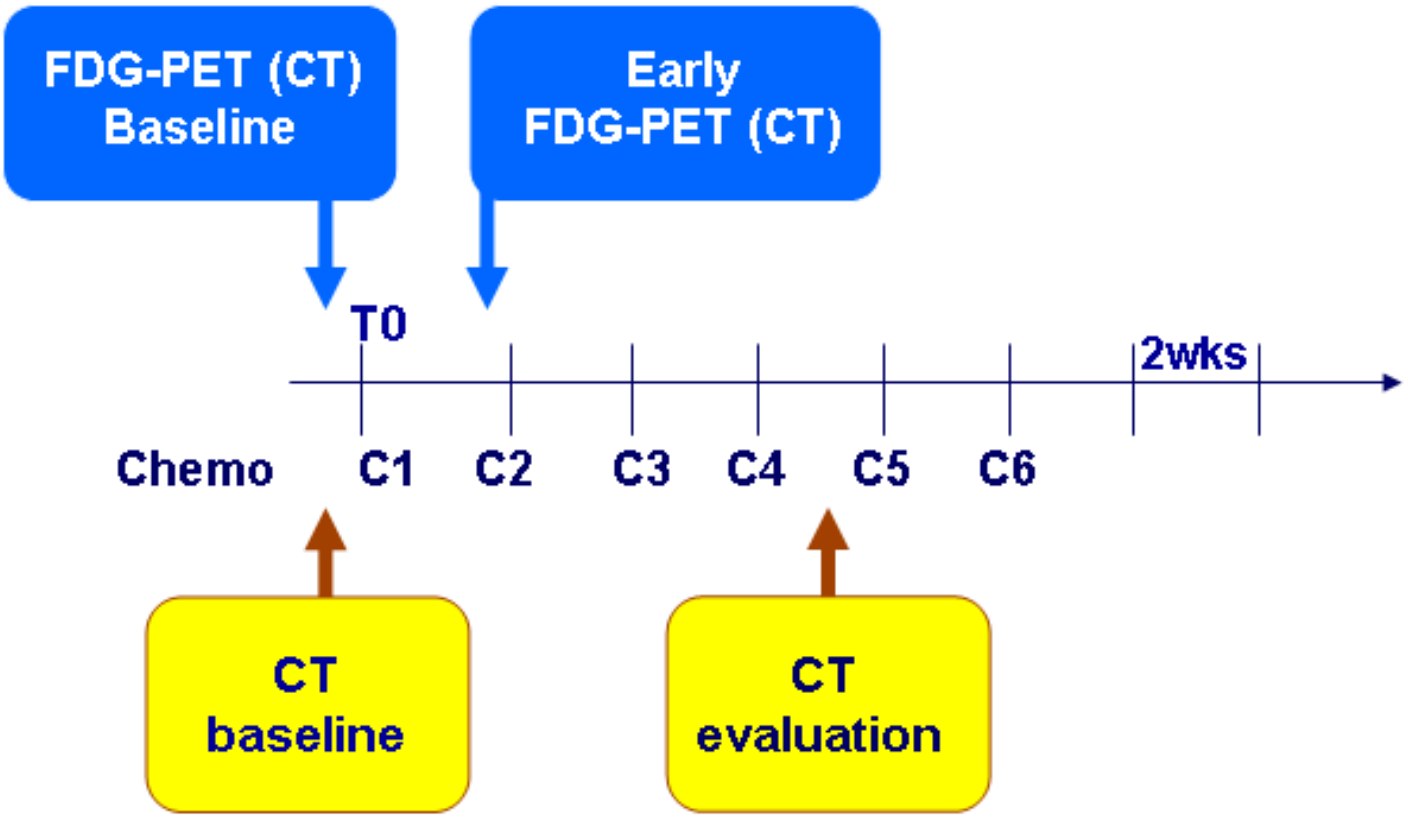


FDG PET/CT (baseline)

^{89}Zr-T PET/CT (baseline)

(Response after 2 months of exemestane+trastuzumab)

Early PET trial design in advanced colorectal cancer



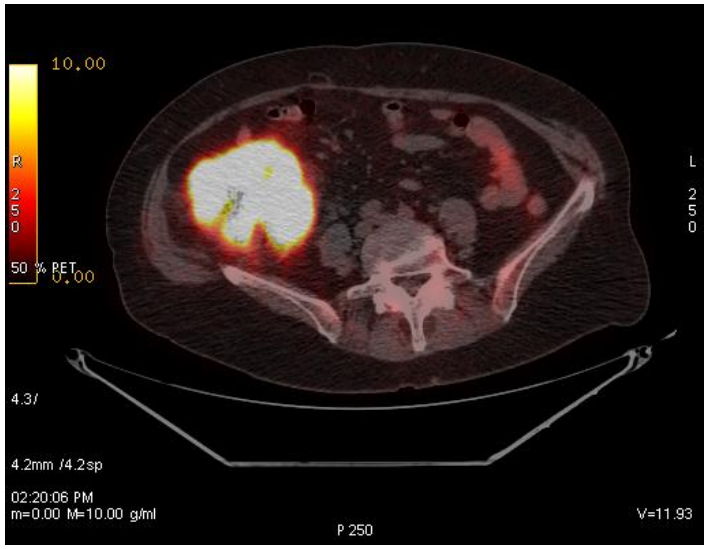
A. Hendlisz et al., Annals of Oncology 2011

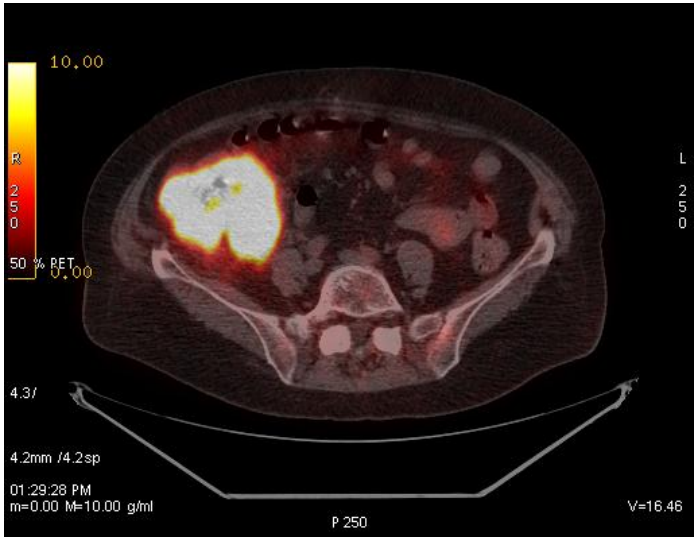
Primary Tumors Metabolic Response To One Cycle of FOLFOX

BASELINE PET

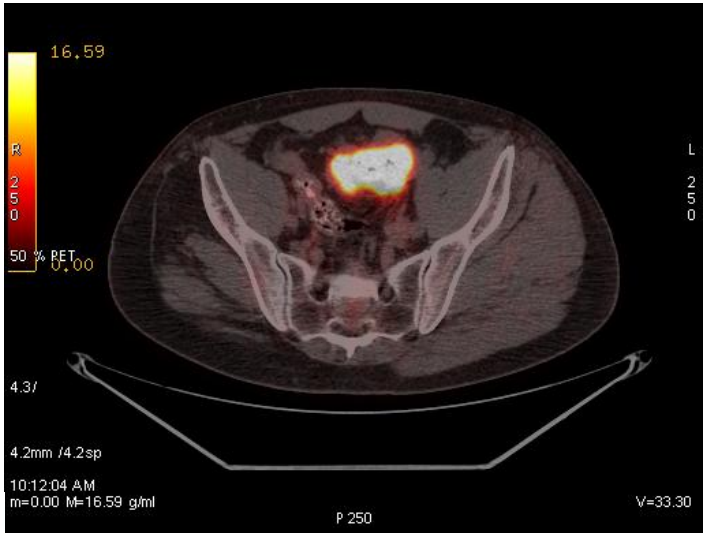
D14 PET

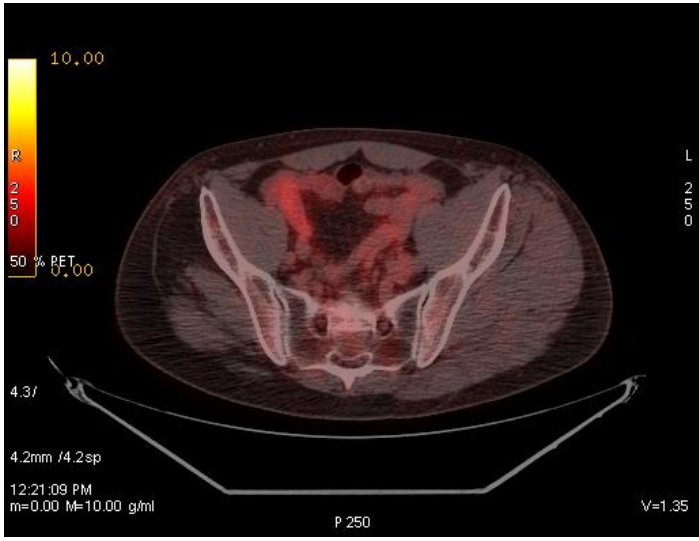
No-Response





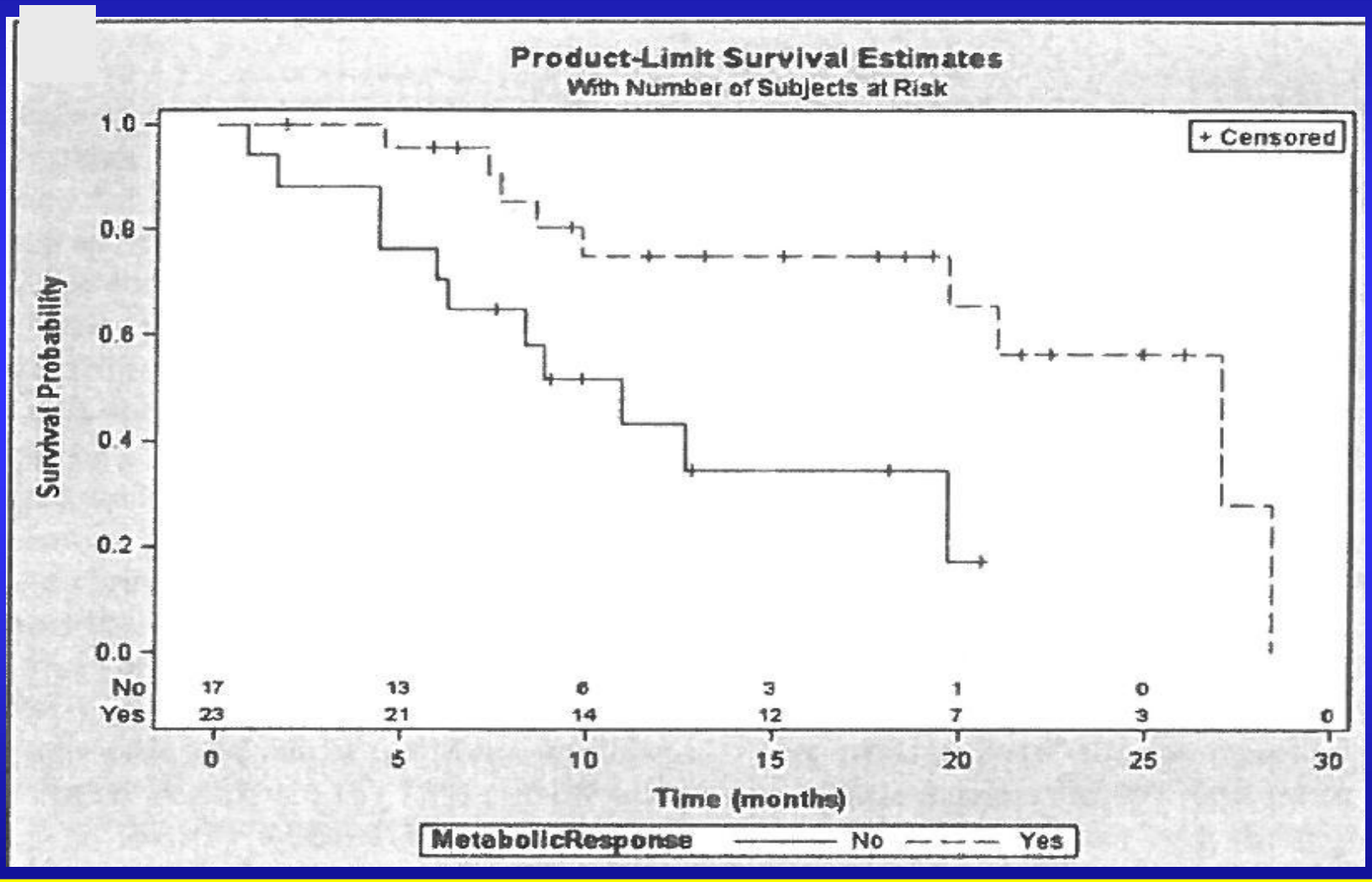
Response





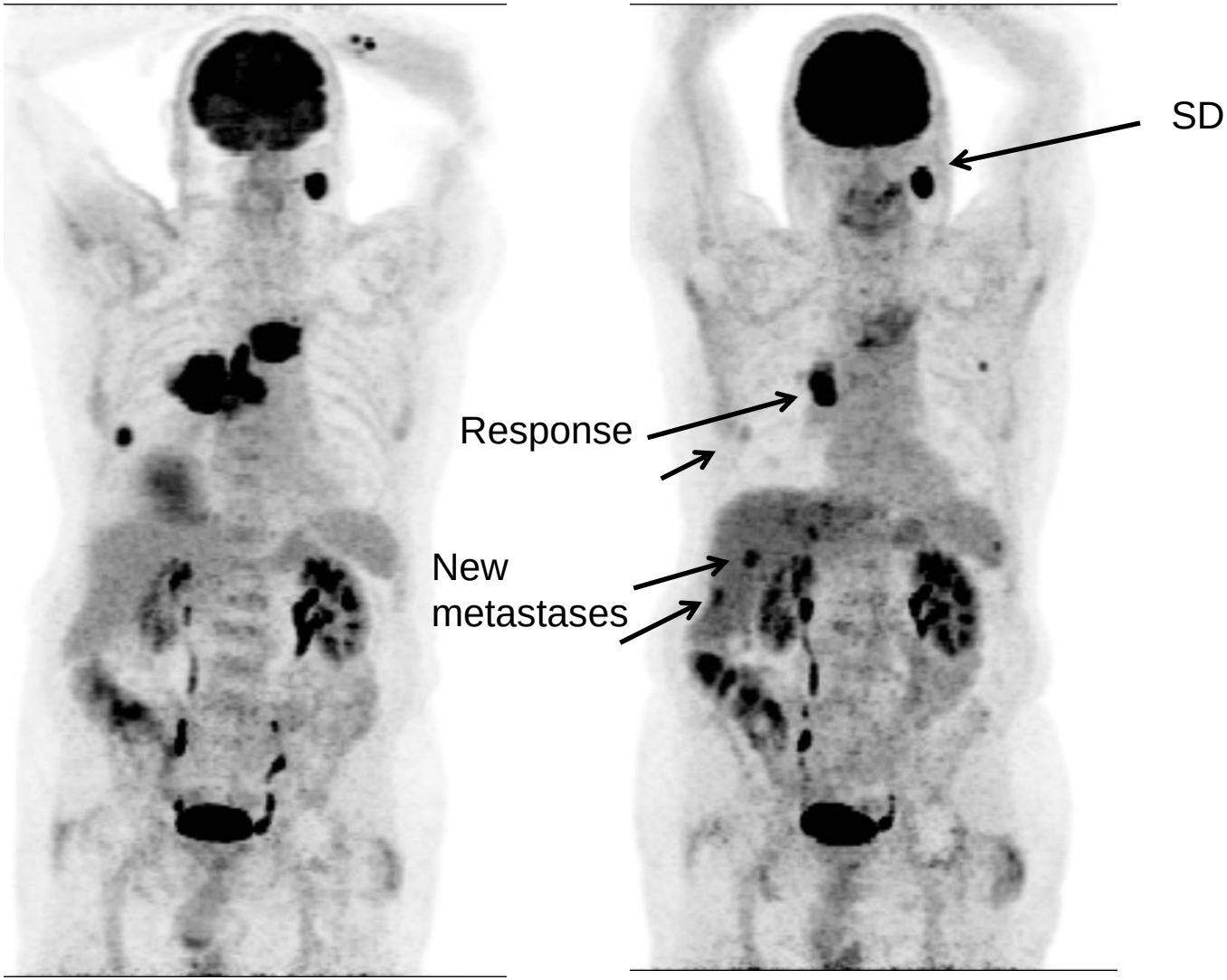
Courtesy of Hendlisz A.

Overall survival in advanced CRC study according to early metabolic response



A.Hendlisz, et al. Annals of Oncology, Jul. 2012; 23 (7),1687-1690

Tumour Heterogeneity: A Biological and Clinical Reality



Exam of 08/06/2012
(Baseline)

Exam of 22/08/2012
(Post treatment)

Conclusion

No single methodology to the development of new targeted agents is available. "Individualizing" and "innovative" drug development methodology are a key for success, taking into account the patient, the tumor, the target and technology advances (Platform, functional imaging, …)

Thank you