Circulating Tumor Cells (CTCs): Clinical relevance

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SiRIC Institut Curie Site de Recherche Intégrée sur le Cancer

institutCurie

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (www.egappreviews.org/workingrp.htm)

- **Analytical performance**

  how accurately and reliably the test detects the analyte(s) of interest;

- **Clinical validity**

  how well the test relates to the clinical outcome of interest (such as survival or response to therapy);

- **Clinical utility**

  Whether the results of the test provide information that contributes to and improves current optimal management of the patient's disease

TMUGS – Clinical utility of tumor markers

Table 1 Tumor Marker Utility Grading System Levels of Evidence	
Level	**Definition**
I	Prospective, marker primary objective Well-powered or meta-analysis
II	Prospective, marker the secondary objective
III	Retrospective, outcomes, multivariate analysis (most currently published marker studies are level of evidence III)
IV	Retrospective, outcomes, univariate analysis
V	Retrospective, correlation with other marker, no outcomes

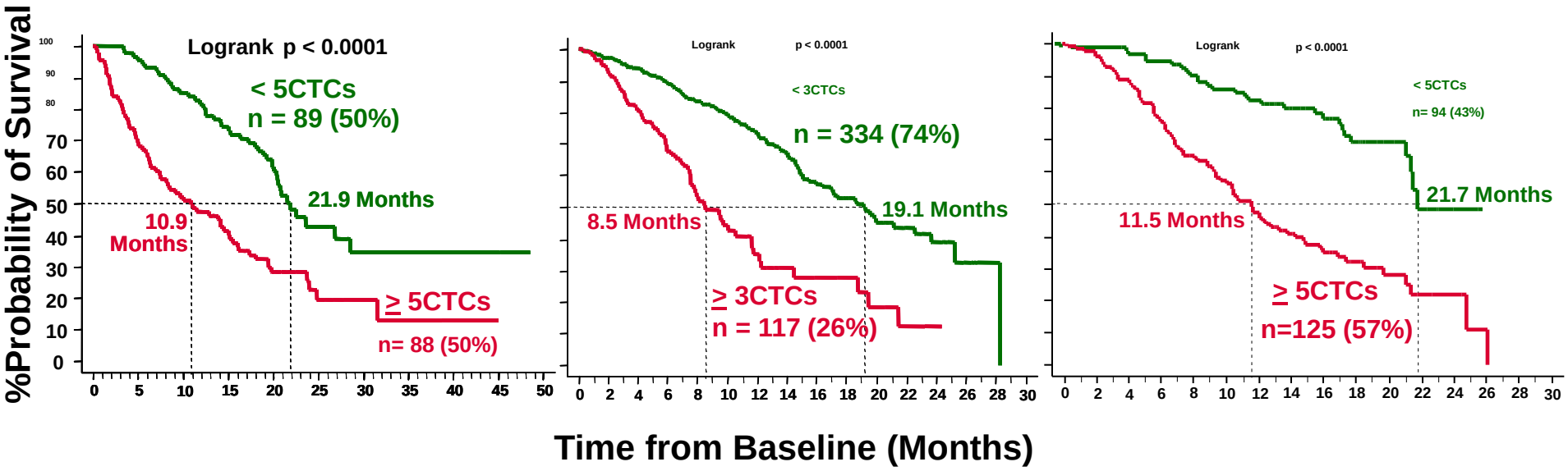
Adapted from Hayes DF, Bast RC, Desch CE, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst 1996;88:1464;

CTCs with Cellsearch Before Therapy: Predicting OS at metastatic stage

Breast
n=177

Colorectal
n=451

Prostate
n=219

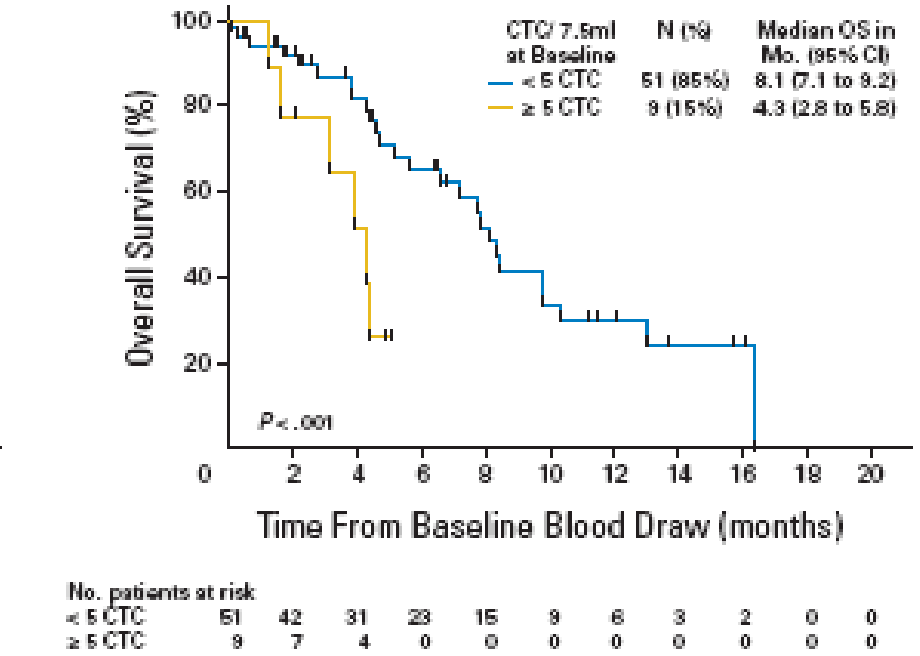


Cristofanilli et al
NEJM August 2004
JCO March 2005

Cohen et al
JCO July 2008

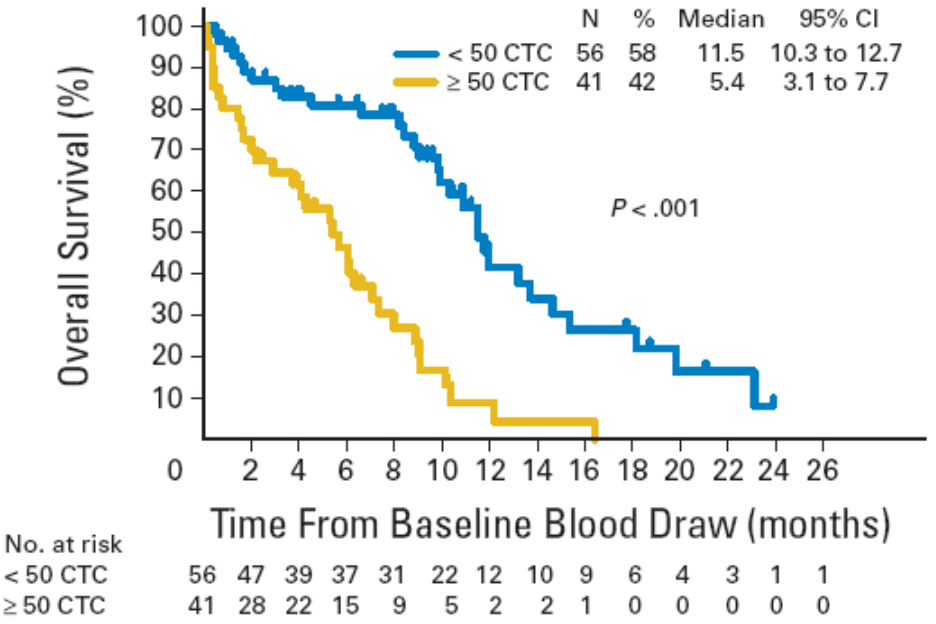
De Bono et al
CCR October 2008

Evaluation and Prognostic Significance of Circulating Tumor Cells in Patients With Non–Small-Cell Lung Cancer



MG Krebs *J Clin Oncol 29. © 2011*

Evaluation and Prognostic Significance of Circulating Tumor Cells in Patients With Small-Cell Lung Cancer



Jian-Mei Hou, J Clin Oncol 30. © 2012

M1 patients – Validity: Levels Of Evidence

Main studies In Metastatic Breast Cancer

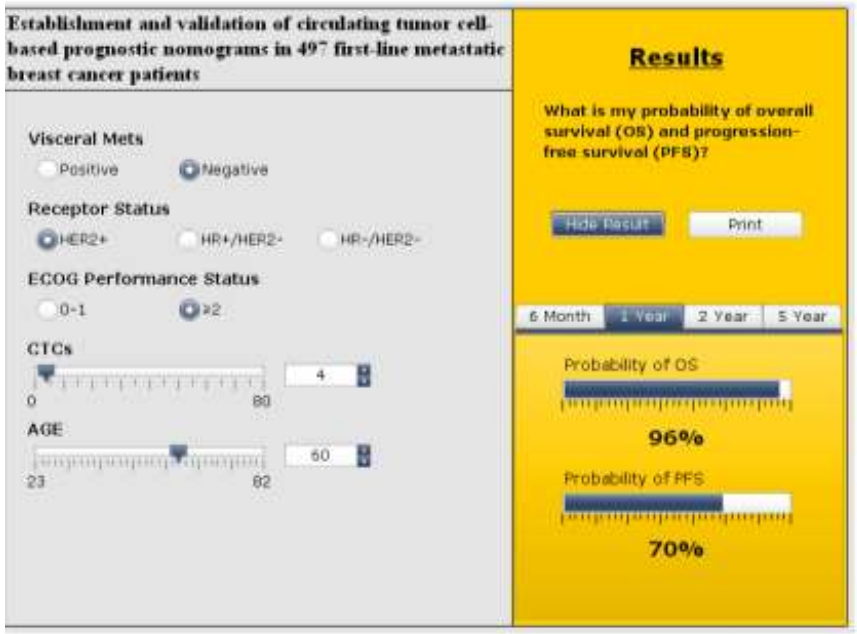
Ref	Year	N	Clinical outcome				LOE
			Baseline & PFS	Baseline & OS	Changes & PFS	Changes & OS	
Cristofanilli N Engl J Med J Clin Oncol	2004- 2005	177	yes	yes	yes	yes	III
Nolé Ann Oncol	2008	80	yes		yes		III
Liu J Clin Oncol	2009	74	yes		yes		III (II ?)
Nakamura Breast Cancer	2010	107		yes			III – II
Bidard Ann Oncol	2010	67	yes		no		III
Pierga Ann Oncol	2012	267	yes	yes	yes	yes	I
Müller Breast Cancer Res	2012	221	no	yes			II

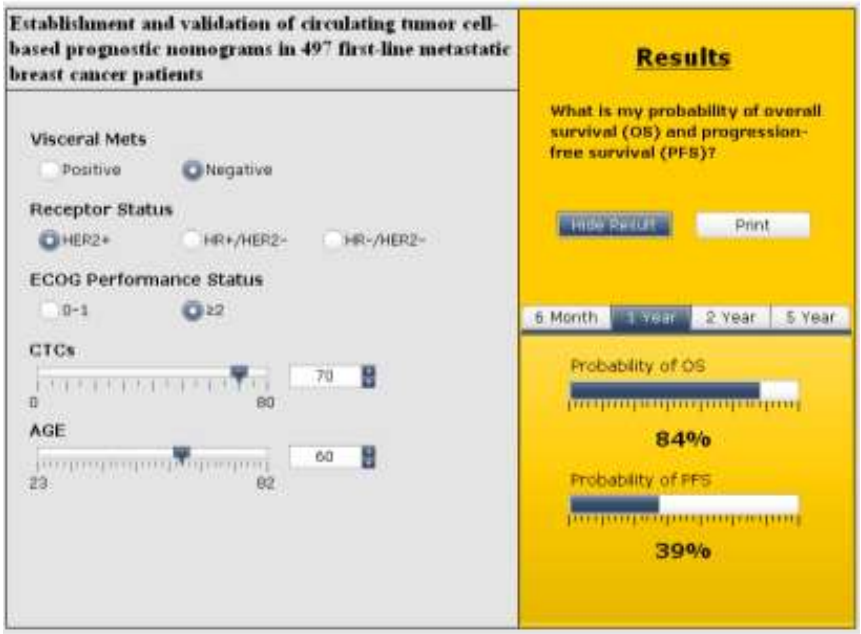
Prospective, multicentric, statistically powered with CTC validity as 1st objective

All pts received 1st line chemotherapy for MBC

Establishment and validation of circulating tumor cell-based prognostic nomograms in first-line metastatic breast cancer patients

- 1st line nomogram
  - > 500 1st line metastatic patients – in collaboration with MDACC
- Estimates of PFS and OS in an individual patient





Mostly validated for OS / Less significant for PFS

A Giordano[1], B Egleston[2], D Hajage[3], J Bland[2], G Hortobagyi[4], J Reuben[1], JY Pierga[5], M Cristofanilli[6], FC Bidard Clin Cancer Res 2013

http://cancernomograms.com/CTCOnline.html

International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)—MBC Task Force: Surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer

Nancy U. Lin [a,m], Christoph Thomssen [b,m], Fatima Cardoso [c,*], David Cameron [d], Tanja Cufer [e], Lesley Fallowfield [f], Prudence A. Francis [g], Stella Kyriakides [h], Olivia Pagani [i], Elzbieta Senkus [j], Alberto Costa [k,l], Eric P. Winer [a] on behalf of the ESO-MBC Task Force

The Breast 22 (2013) 203–210

Tumor markers

CA15-3, CEA, or CA-27.29, if elevated at time of treatment initiation, can be helpful for therapy monitoring.

However, they should not be used solely for decision making with respect to change of therapy.

In particular, an early rise in the tumor marker level within the first 4-6 weeks of starting new therapy may occur as a result of a tumor flare, and should not prompt a change in therapy unless there is other supportive evidence of progressive disease.

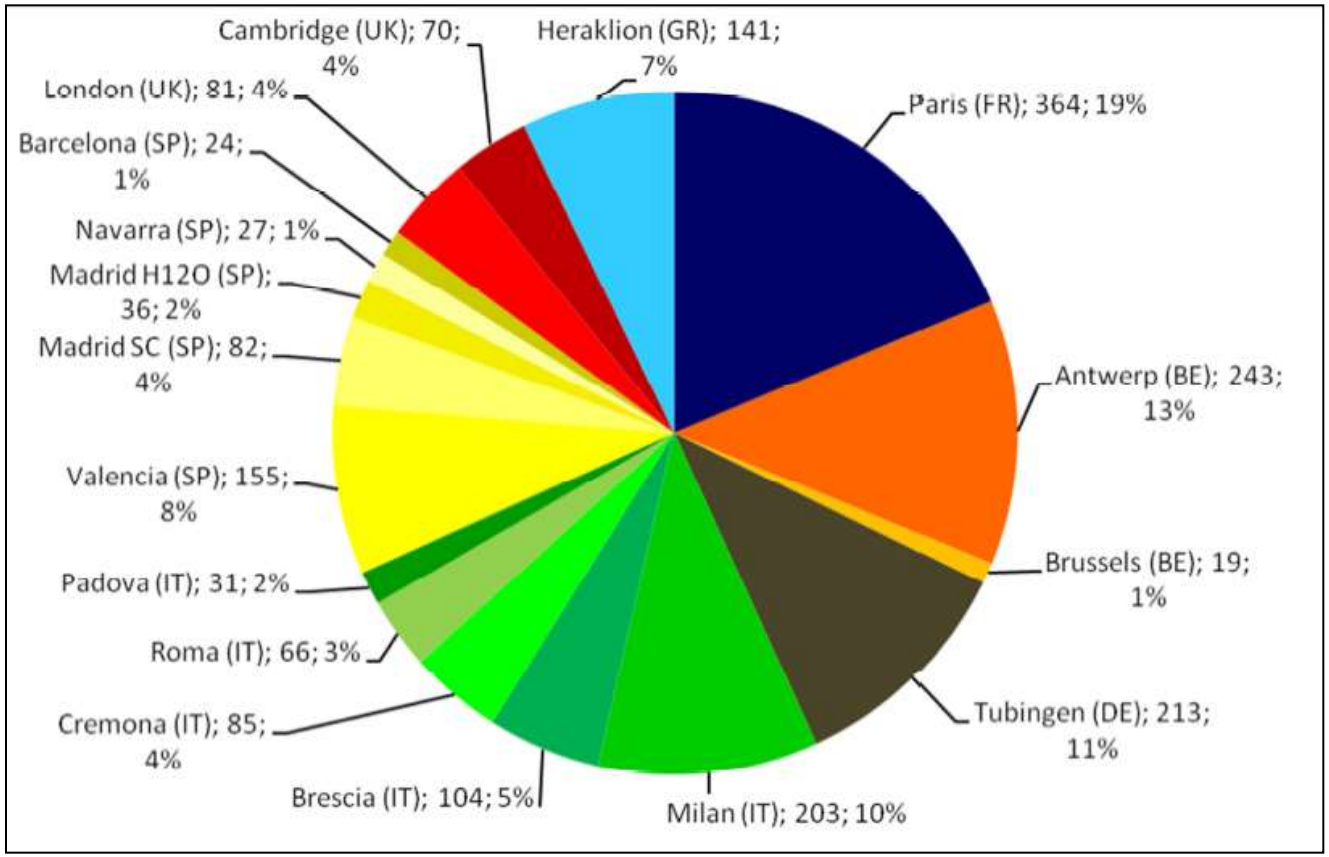
Circulating tumor cells (CTCs)

Detection and dynamics of CTCs after start of treatment for MBC have shown prognostic relevance and are associated with progression-free survival.

However, its proper role in the clinical management of patients with MBC has yet to be fully defined.

M1 patients – Validity: Ongoing European meta-analysis

1944 individual data from 20 studies, from 17 centers, from 7 European countries

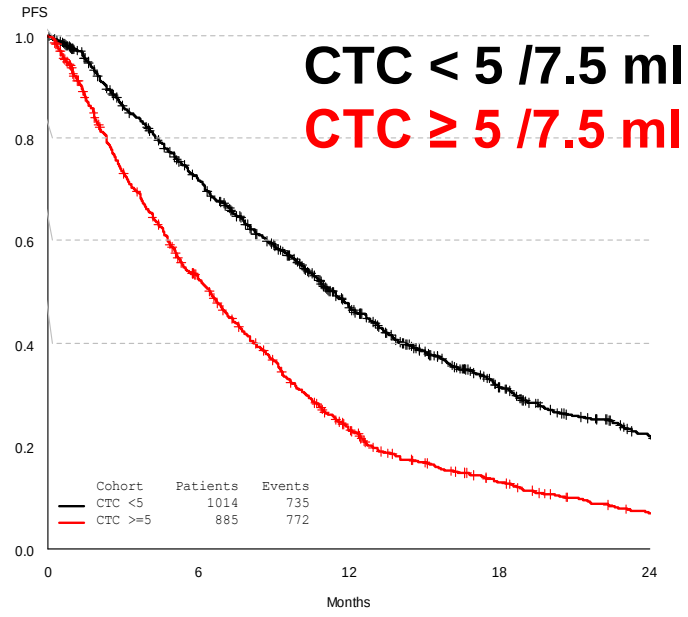


PFS & OS
Baseline
Changes
New thresholds
Comparison with markers
Nomograms
Value in patient with no evaluable disease

➔ next 2013' congresses (ESMO & SABCS) FC Bidard et al

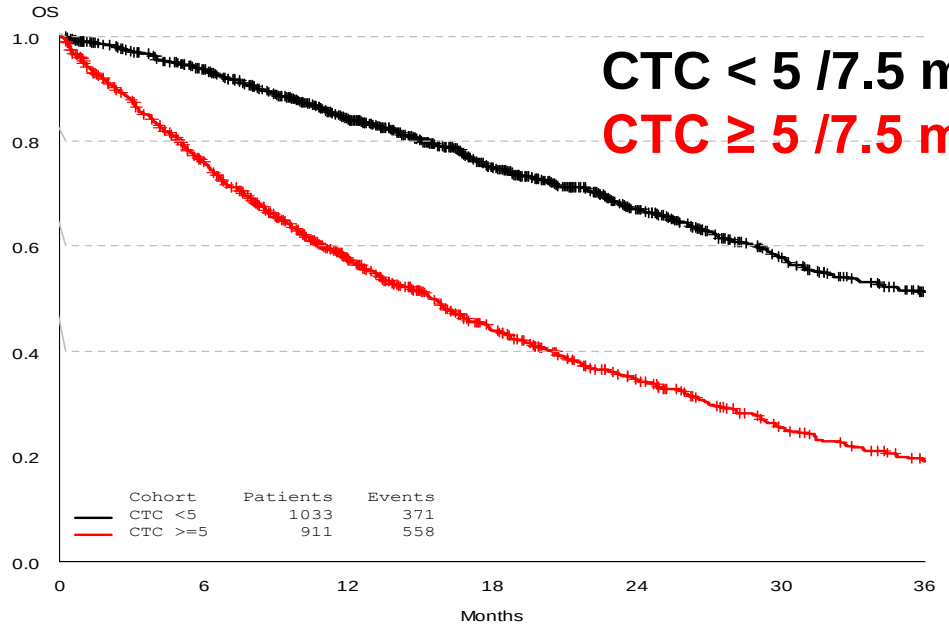
Results – *CTC at baseline*

Prognostic value – univariate analysis



Progression-Free Survival

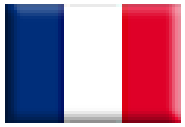
N= 1,899 patients
HR = 1.92
p<0.0001



Overall Survival

N= 1,944 patients
HR = 2.77
p<0.0001

Acknowledgments



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Pamplona
A Fernandez de Lascoiti

Nuovo-Soldati Fundation for cancer research

IDDI
H Johannes

Unconditional funding to IDDI
K Baeten

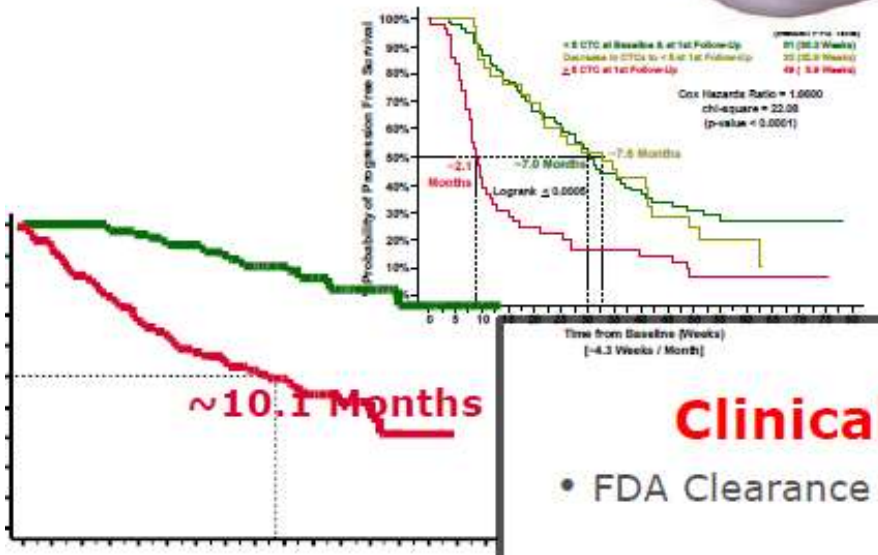
Clinically Maturing CTC Technology

Clinical Utility: Characterization

- DETECT 3

Clinical Validation: Characterization

- Endocrine Therapy Index



Clinical Utility: Enumeration

- SWOG S0500
- BioMarker Qualification
- CirCe01
- STIC

Clinical Validation: Enumeration

- FDA Clearance Breast, prostate, colorectal

R. Mc Cormack ACTC Athens 2012

STIC CTC METABREAST

Inclusion
N=994

- M+ HR+ HER2- patients before any treatment
- Patients who can be treated either by chemoT or hormone T.
- PS 0-2

Randomization

- Stratified on center, PS and metastasis-free interval

Standard arm N=497

BASELINE CTC COUNT BLINDED → clinician choice → Hormone therapy / Chemotherapy → Tumor evaluation untill progression → TUMOR SIZE

CTC-arm
N=497

BASELINE CTC COUNT DISCLOSED → CTC-driven decision

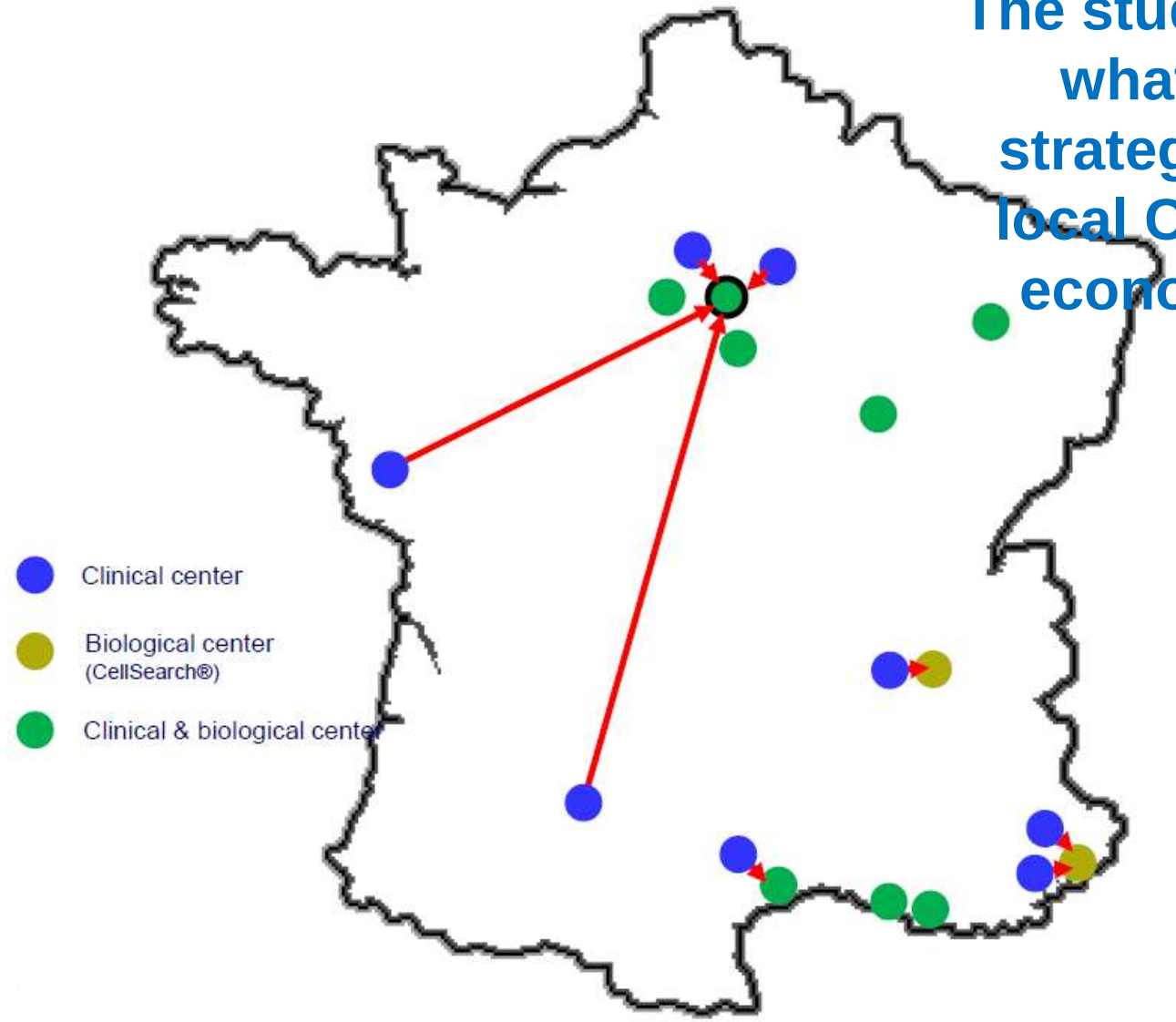
- < 5CTC/7.5ml → Hormone therapy
- ≥ 5CTC/7.5ml → Chemotherapy

Tumor evaluation untill progression → TUMOR SIZE

- **Primary medical endpoint: PFS (non-inferiority)**
- **Co-primary economical endpoint: cost/benefit ratio**
- **2nd endpoints: OS, toxicities, QoL, subgroup analyses**
- **The study will also adress what is the optimal strategy (centralized *vs* local CTC lab.) from the economical viewpoint**

Bidard FC, Fehm T, Ignatiadis M, Smerage JB et al, & Pierga Cancer Met Rev 2013

STIC CTC METABREAST



The study will also adress what is the optimal strategy (centralized *vs* local CTC lab.) from the economical viewpoint

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Institut Gustave Roussy
CHU de Montpellier
Centre Val d'Aurelle
Centre G.F. Leclerc
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CHU de Nice
Centre Antoine Laccassagne

Secondary objective of STIC Metabreast

Change in treatment given by physician according to CTC level in the first 77 patients in the investigational arm CTC (Arm B):

	Treatment planned by physician in absence of information on CTC = Hormonotherapy	*Level of CTC < 5 CTC*	*Level of CTC ≥ 5 CTC*
Number of patients	52	41	**11**

Hormonotherapy confirmed

Treatment with Chemotherapy (=21 % of patients)

	Treatment planned by physician in absence of information on CTC = Chemotherapy	*Level of CTC < 5 CTC*	*Level of CTC ≥ 5 CTC*
Number of patients	25	**15**	10

Treatment with Hormonotherapy (=60 % of patients)

Chemotherapy confirmed

In 33% of patients randomized in investigational arm CTC (*26/77 patients*), CTC level determination lead to change in first line treatment choice for ER positive HER2 negative metastatic breast cancer.

Change in treatment given by physician according to CTC level(*con't*)

Treatment planned by physician in absence of information on CTC = Hormonotherapy	Level of CTC	Number of patients
	0	24
	1	6
	2	2
	3	5
	4	4
	5	1
	16	2
	18	1
	27	1
	30	1
	32	1
	33	1
	42	1
	54	1
	65	1
	TOTAL	52

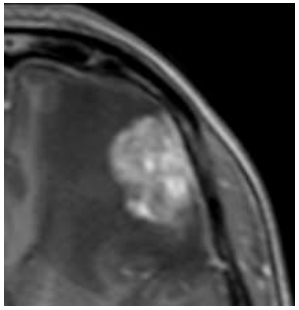
11 patients treated with Chemotherapy

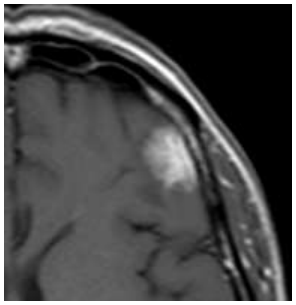
Treatment planned by physician in absence of information on CTC = Chemotherapy	Level of CTC	Number of patients
	0	8
	1	2
	2	5
	12	2
	13	1
	15	1
	22	1
	25	1
	34	1
	71	1
	170	1
	493	1
	TOTAL	25

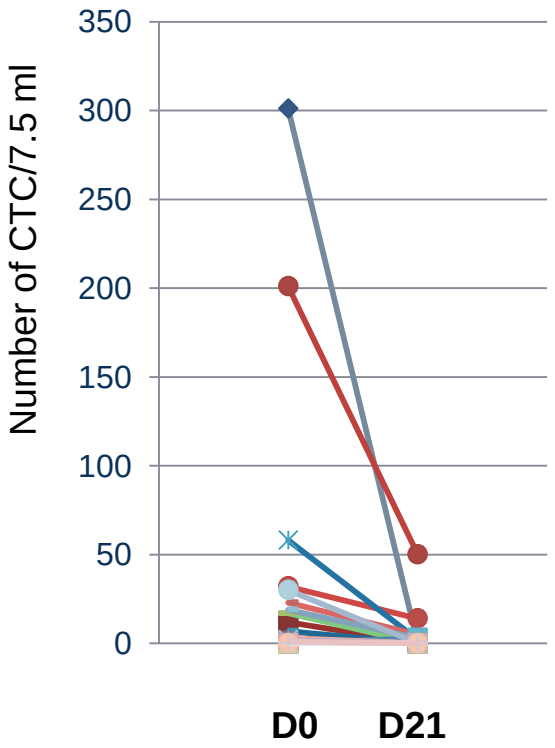
15 patients treated with Hormonotherapy

MONITORING INFORMATIONS

LANDSCAPE: a Unicancer phase II study with lapatinib and capecitabine in patients with brain metastases from HER2-positive metastatic breast cancer before whole brain radiotherapy







CTC/7.5ml at baseline and changes under treatment

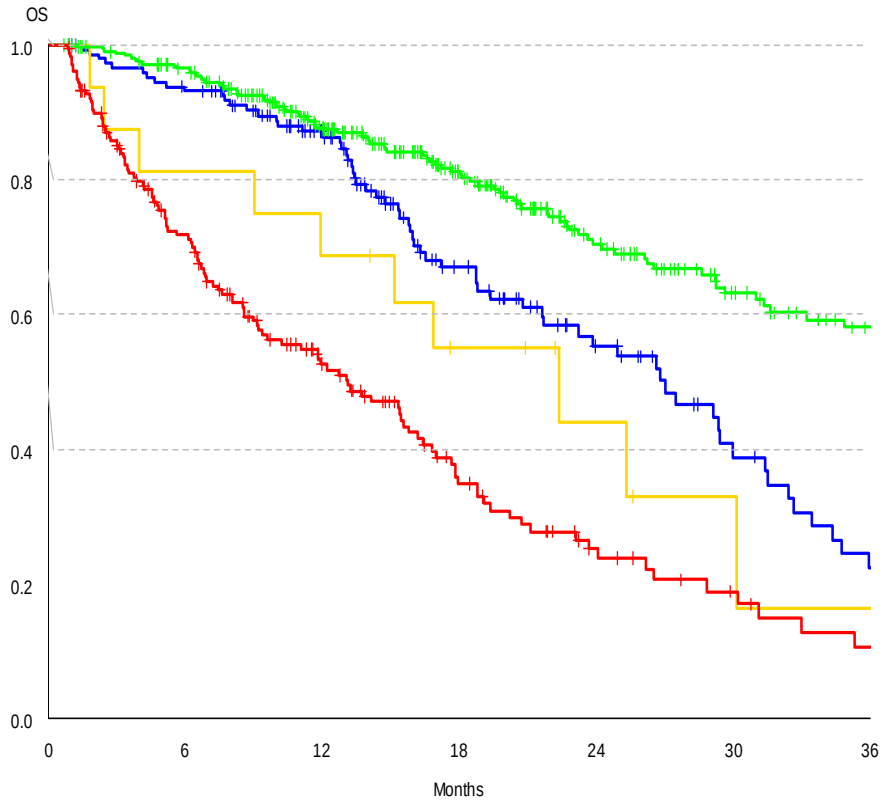
Correlation with CNS-OR, (n=40)

Date of sampling	CTC Status	CNS-OR (%)	*p*
Baseline (n=41)	0 at baseline	(81)	*NS*
	≥ 1 at baseline	(57.9)	
Day 21 (n=38)	0 at day 21	(80.6)	*0.03*
	≥ 1 at day 21	(33.3)	

Pierga 2013 Ann Oncol

Results – *Early CTC changes during treatment*

Baseline & week 3-5 *European Meta -Analysis*



Overall Survival

N= 672 patients; p<0.0001

	N Pts	N Events	Median OS months [95%CI]
Stable neg: <5 - <5	327	104	41 [37-53]
Decrease: ≥5 - <5	149	70	27 [22-31]
Increase: <5 - ≥5	17	10	22 [12-NE]
Stable pos: ≥5 - ≥5	179	116	13 [9-16]

Similar OS curves were obtained with later CTC changes (6-8 weeks) **Bidard FC et al**

M1 patients – Validity: Comparison vs serum

➔ **QUESTION**

Are elevated markers of prognostic impact for PFS in univariate analysis ?

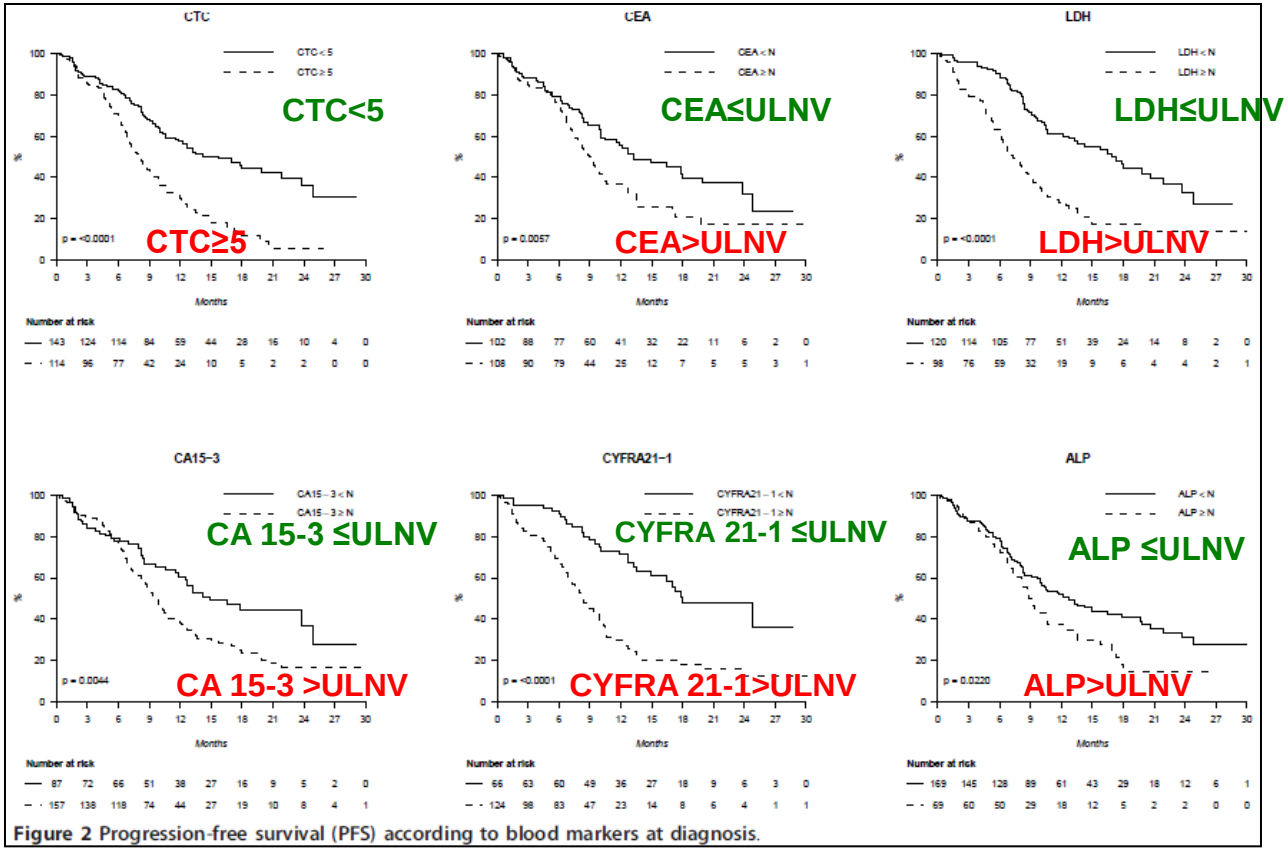
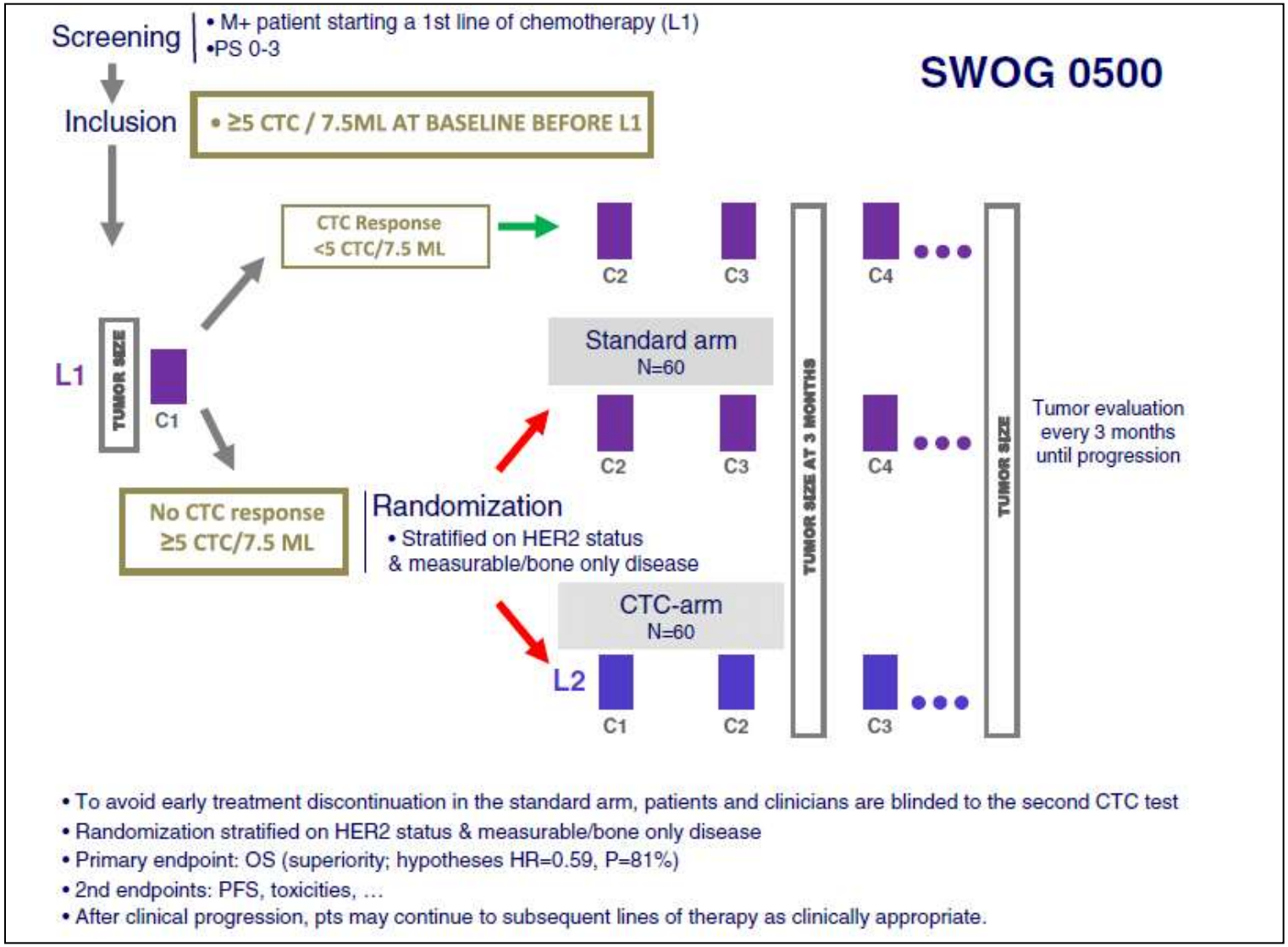


Figure 2 Progression-free survival (PFS) according to blood markers at diagnosis.

Not powered for comparison (c-index NS)

Bidard FC, Hajage D, Bachelot T, Delaloge S, Brain E, Campone M, Cottu P, Beuzeboc P, Rolland E, Mathiot C, Pierga JY
Breast Cancer Res 2012

M1 patients – Utility: SWOG 0500



Reviewed in Bidard FC, Fehm T, Ignatiadis M, Smerage JB, Alirx Panabieres C, Janni W, Messina C, Paoletti C, Muller V, Hayes DF, Piccart M, Pierga JY. Cancer Met Rev 2013

CirCe 01

Screening
N~600

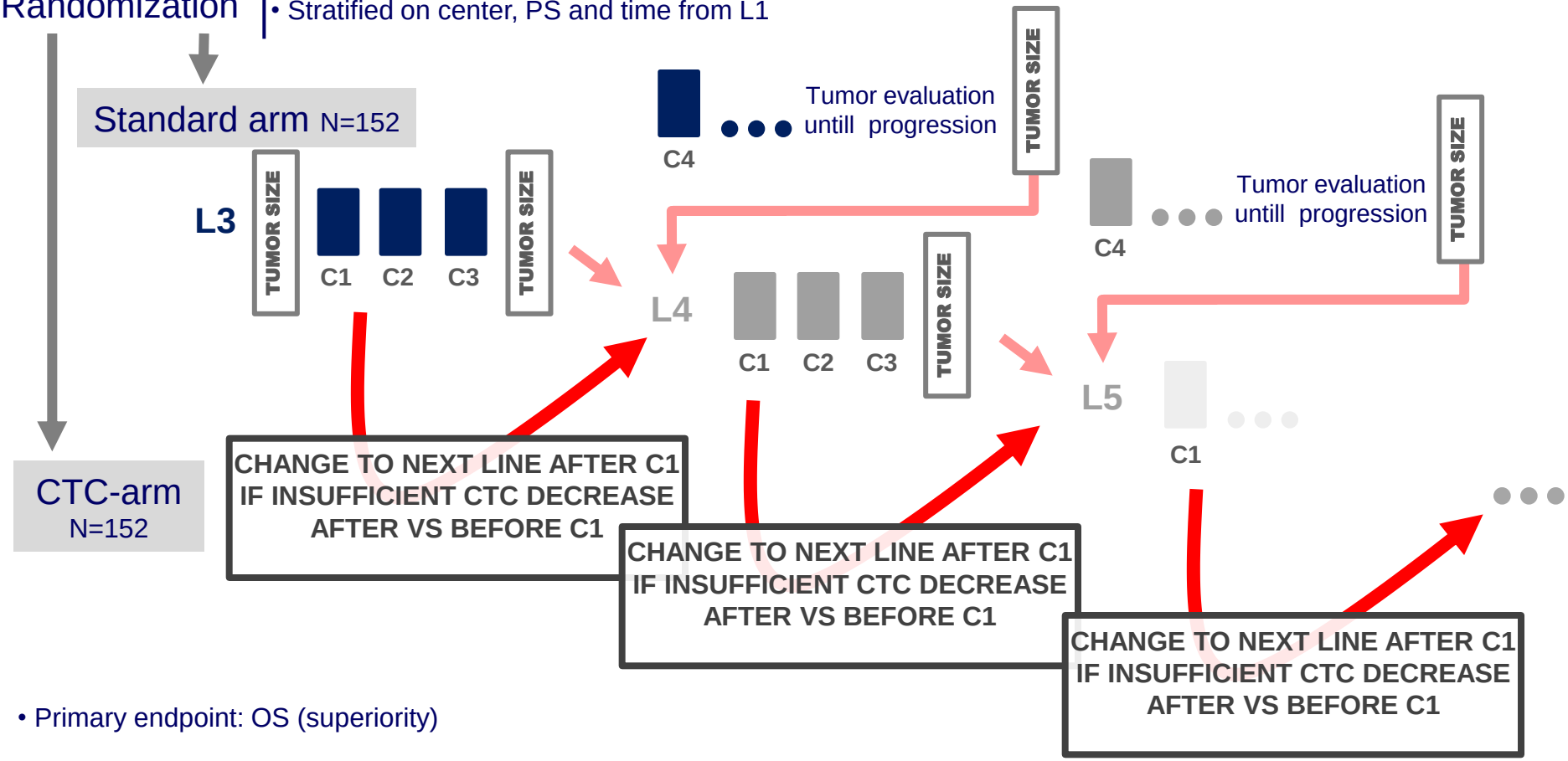
- M+ patient starting a 3rd line of chemotherapy (L3)
- PS 0-4

Inclusion

- ≥5 CTC / 7.5ML AT BASELINE BEFORE L3

Randomization

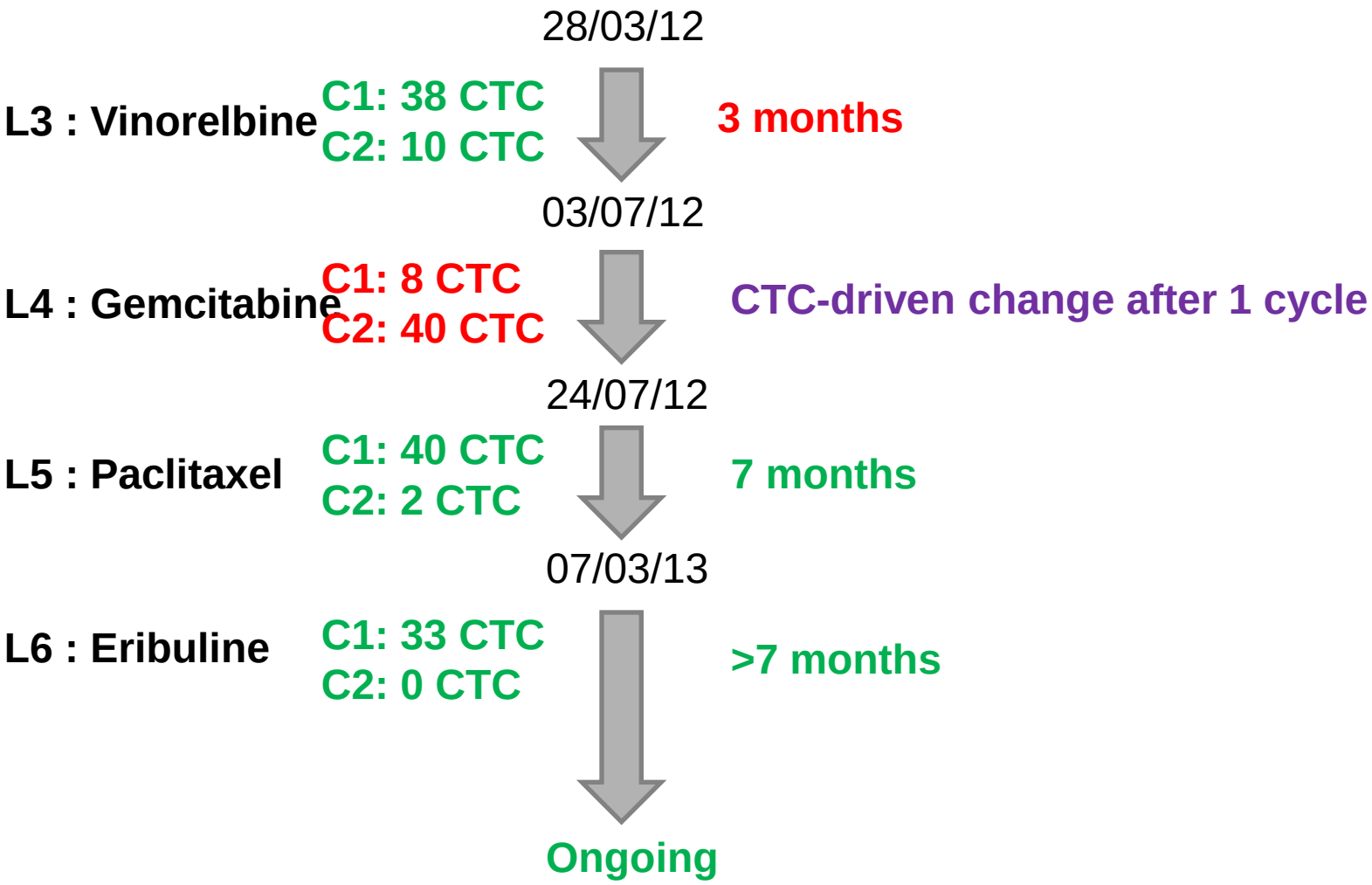
- Stratified on center, PS and time from L1



- Primary endpoint: OS (superiority)
- 2nd endpoints: PFS, medico-economic study, toxicities, QoL, anxiety…
- Threshold for « insufficient » CTC decrease has been obtained in a non-randomized preliminary part of the trial

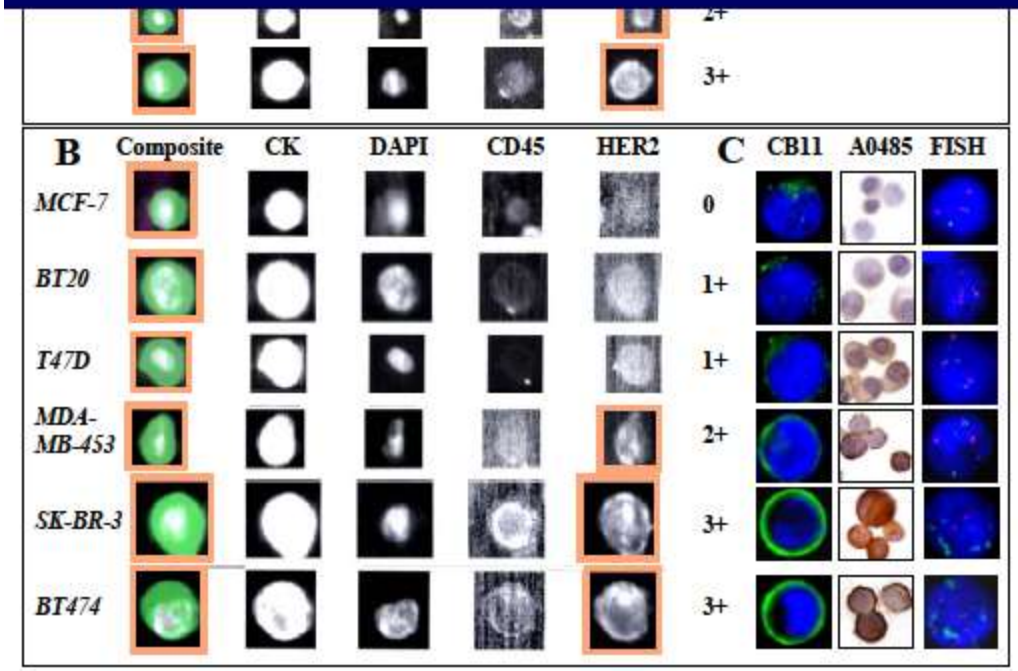
Bidard FC, Fehm T, Ignatiadis M, Smerage JB , (…) & Pierga JY Cancer Met Rev, 2013

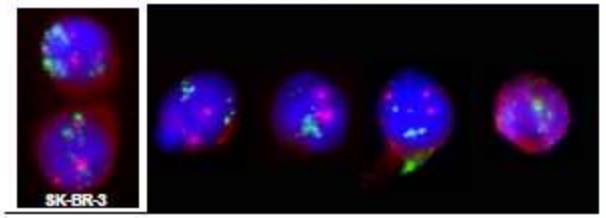
CirCe01 – CTC arm
Inclusion #1101063



Detection of therapeutic target molecules on CTC
Example: HER2 in breast cancer

Potential benefit from anti-HER2 therapy (e.g., trastuzumab) also in patients with „HER2-negative“ tumors (Paik *et al.*, NEJM 2008)





- **HER2-pos. CTC in pats w HER2-neg. primary tumors**
- **HER2-neg. & HER2-pos. CTC after trastuzumab**

Riethdorf/Pantel et al., Clinical Cancer Res 2010; Fehm/Pantel et al., Breast Cancer Res Treat 2010
Ignatiadis/Sotiriou et al, PlosONE, 2011

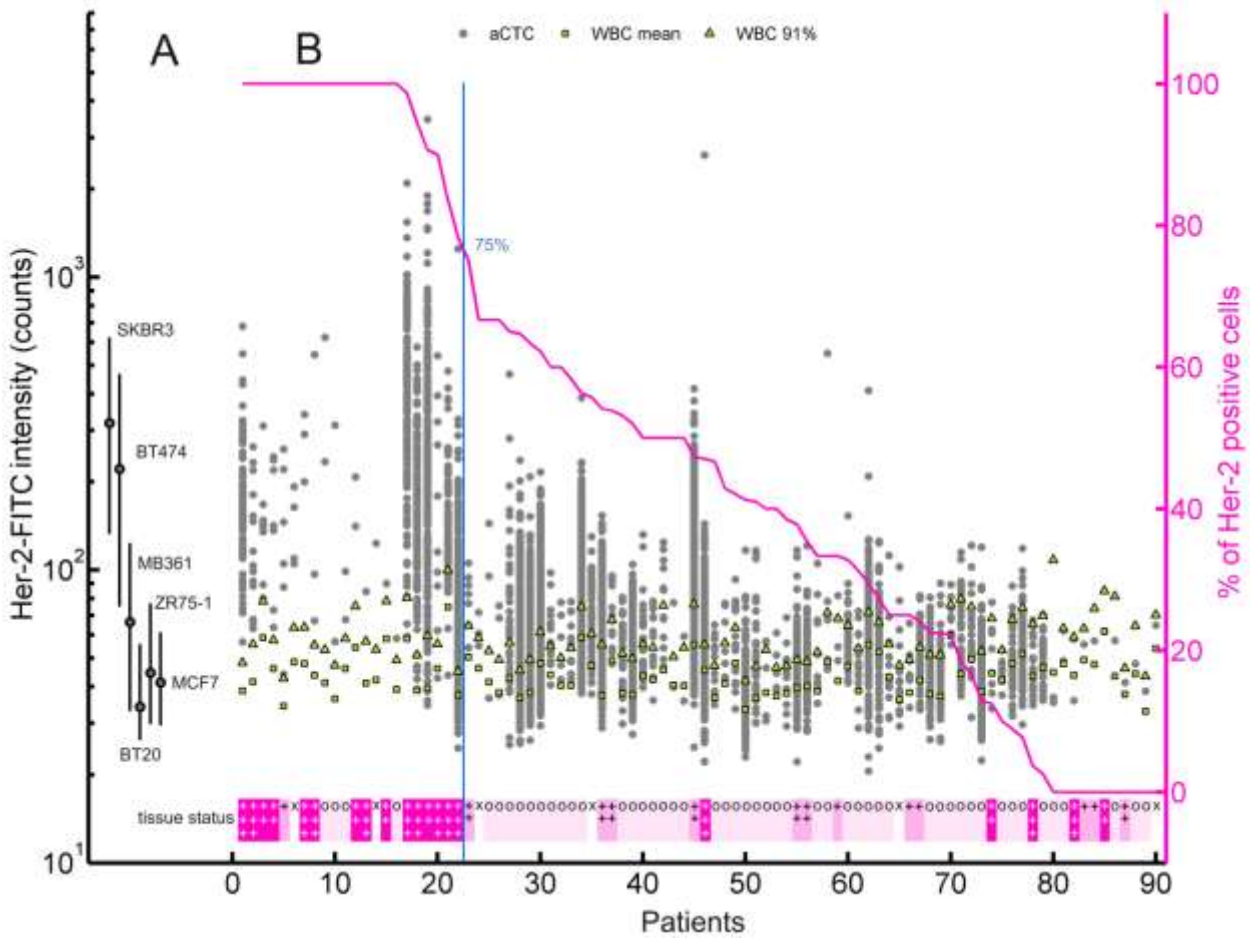
Quantitative image analysis for HER2 staining with Cellsearch

Heterogeneity of HER2 expression

In metastatic breast cancer patients N=117 Discordant results

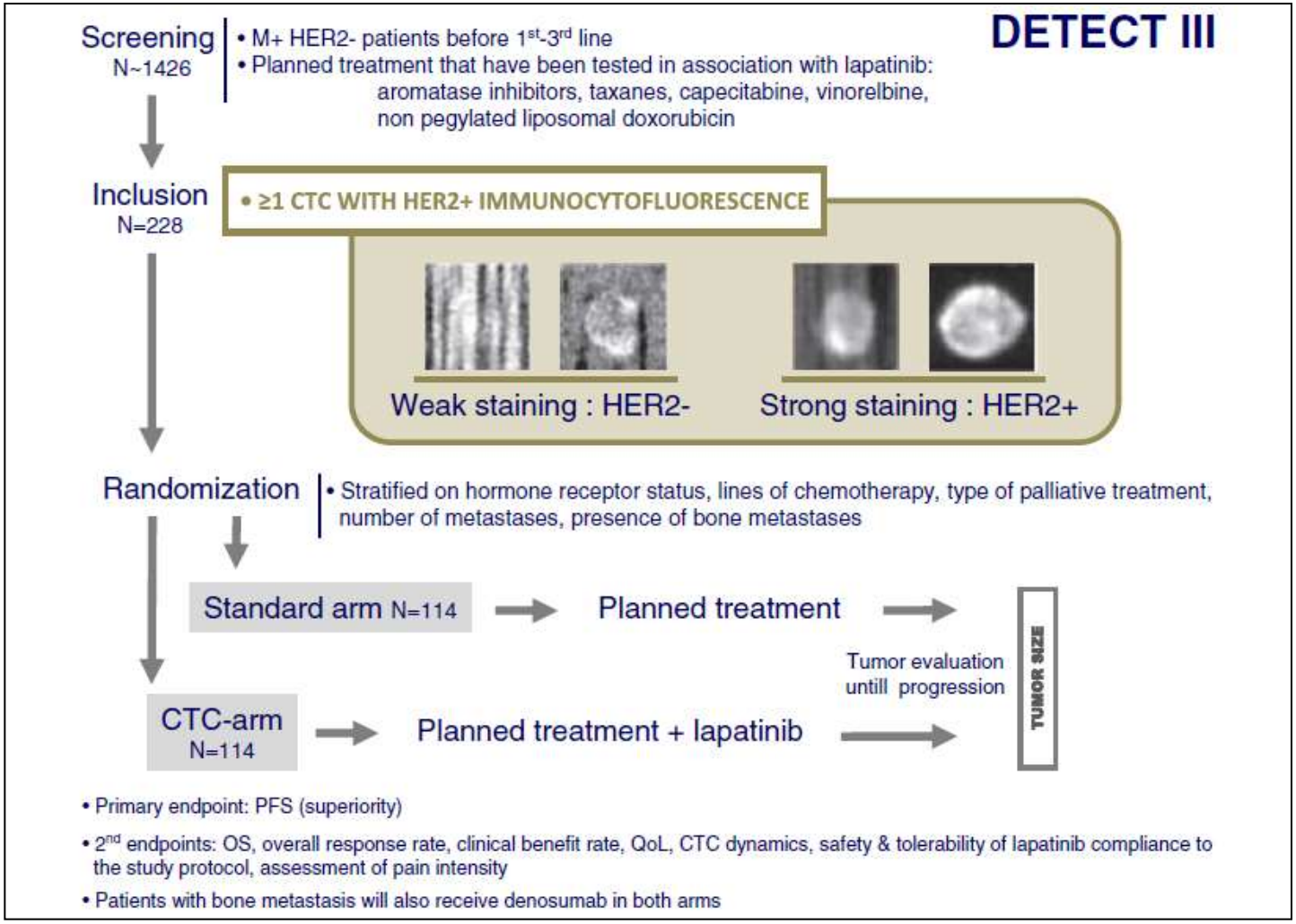
➔ **29% of patients with Her-2 positive primary tumor & ≥5 CTC count**

➔ **9% of patients with Her-2 negative primary tumor & ≥5 CTC count**



Ligthart S*, Bidard FC*, Decraene C, Bachelot T, Delaloge S, Brain E, Campone M, Viens P, Pierga JY, Terstappen LWMM Ann Oncol 2013

M1 patients – Utility: DETECT III



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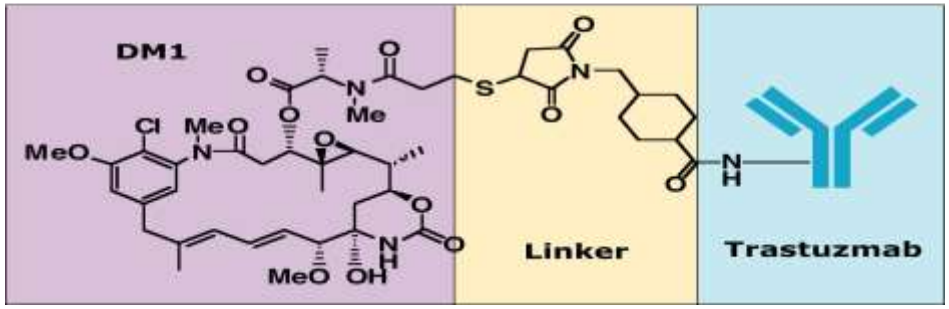


T-DM1 is a novel ADC

Target expression: HER2

Monoclonal antibody: Trastuzumab

Cytotoxic agent: DM1

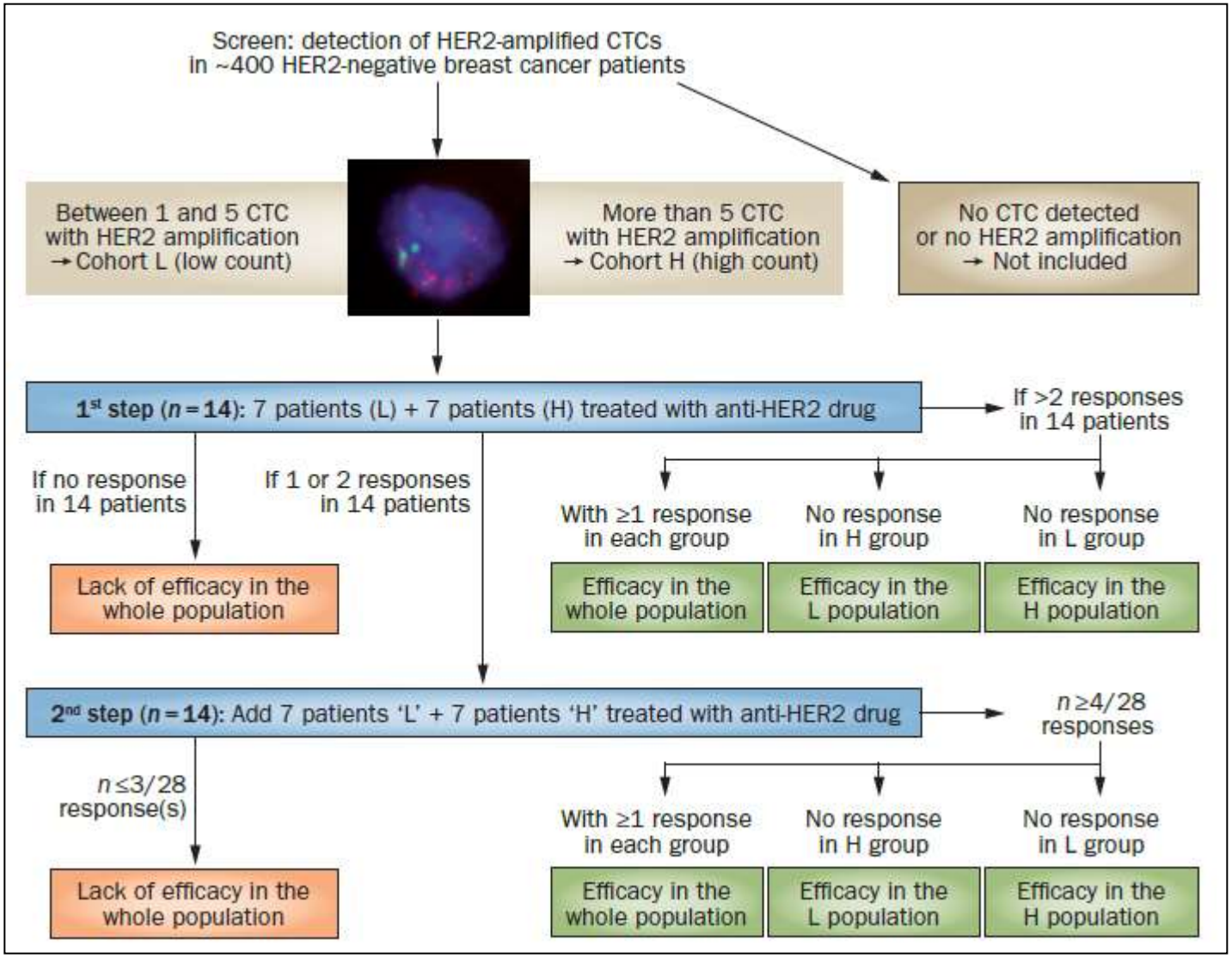
Highly potent cytotoxic agent

Linker: MCC

Systemically stable

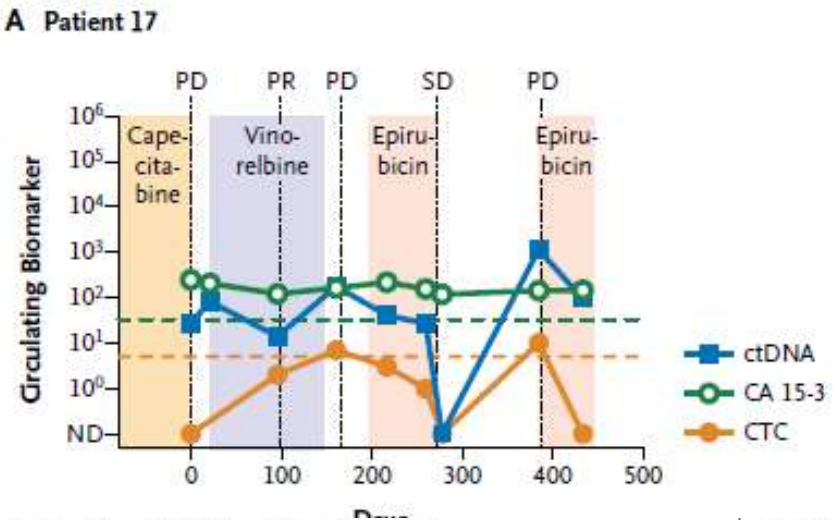
Average drug:
antibody ratio ≅3.5:1

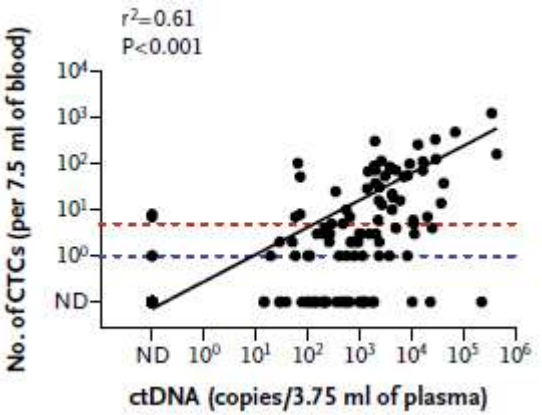
M1 patients – Utility: CirCe T-DM1

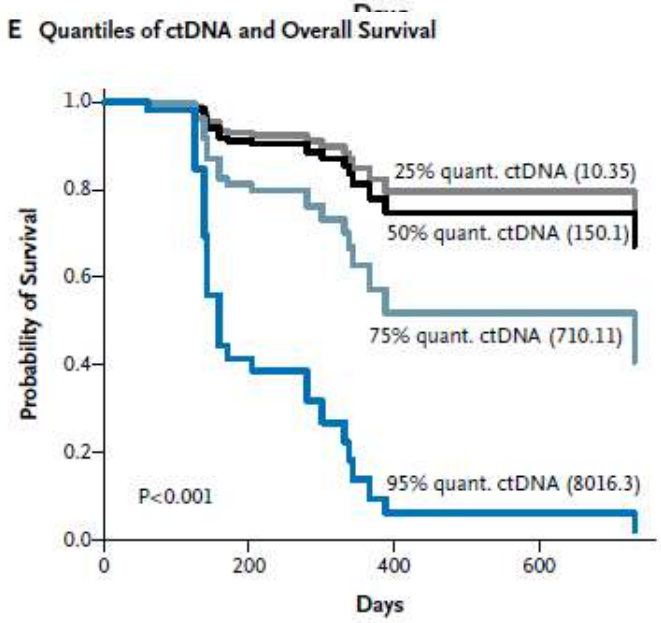


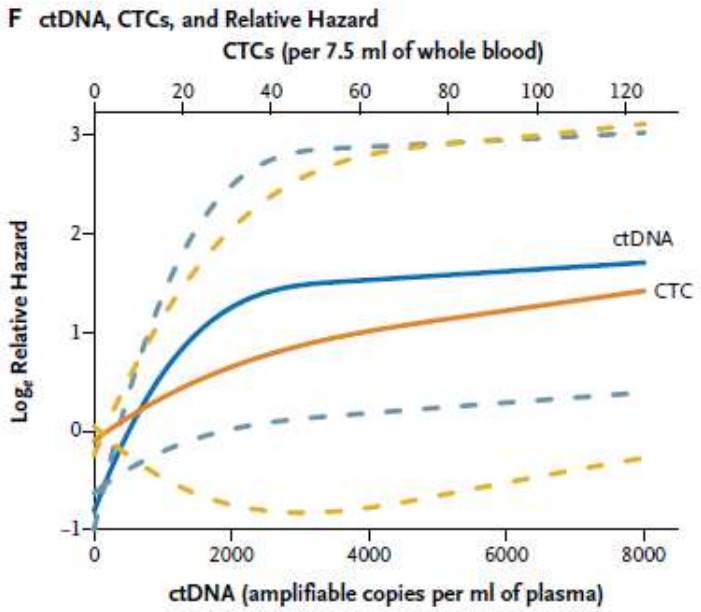
Bidard FC, Pierga JY, Soria JC, Thiery JP. Nat Rev Clin Oncol 2013

Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer



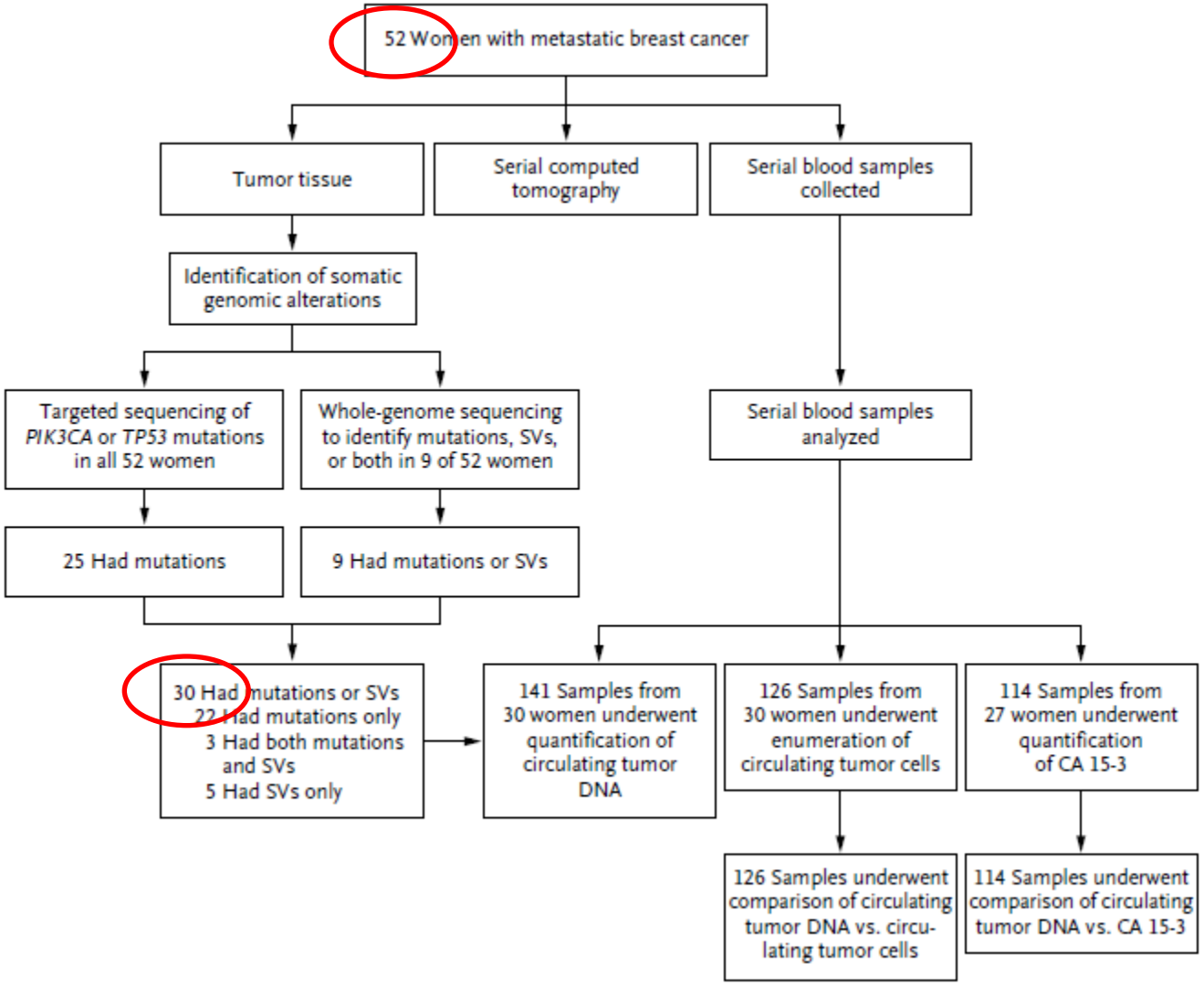






Dawson N Engl J Med 2013.

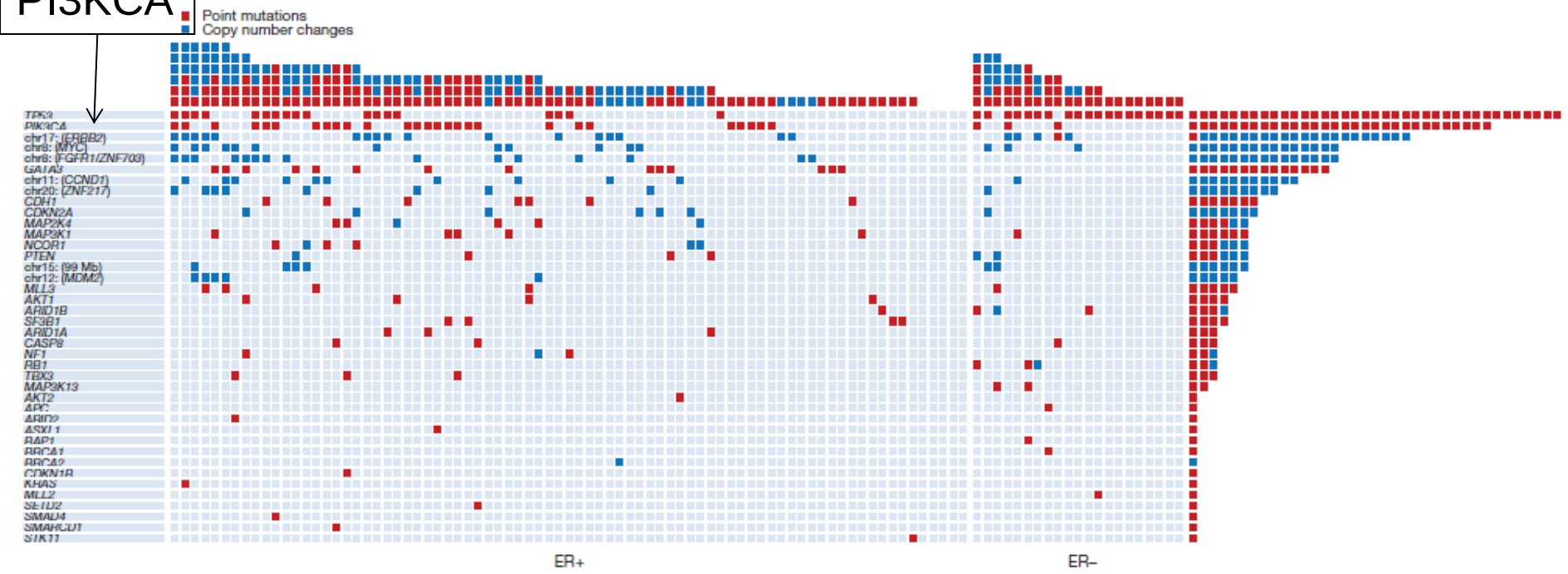
Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer



Dawson N Engl J Med 2013.

Genomic segmentation of breast cancer

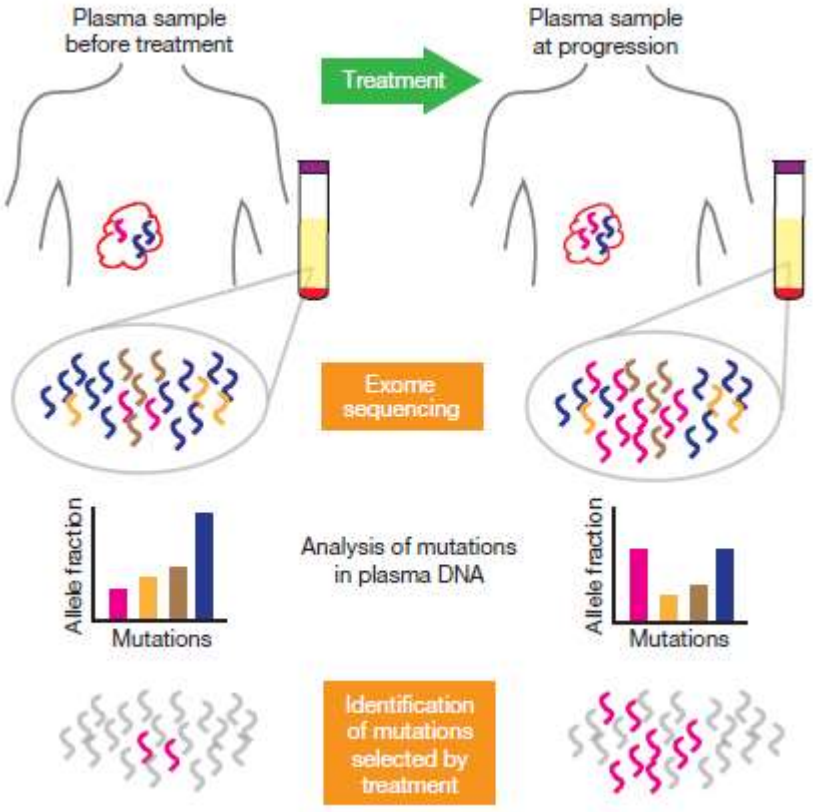
P53
PI3KCA

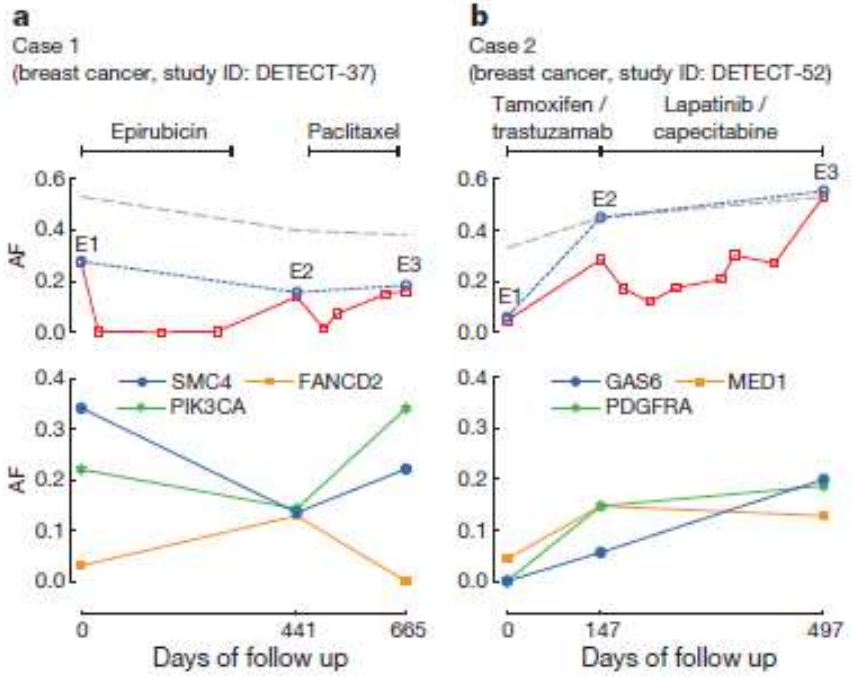


Breast cancer disease includes a large number of RARE genomic segments
Treatment should include specific agent for each segment

Stephens PJ *et al. Nature.* 2012 May 16;486(7403):400-4

Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA



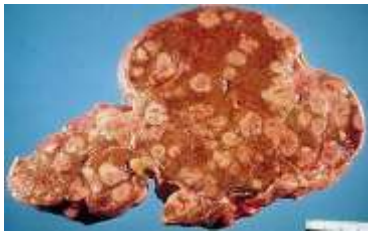


Murtaza Nature 2013

CTC or cfDNA could be a Liquid Biopsy

But is solid biopsy already a reference for treatment?

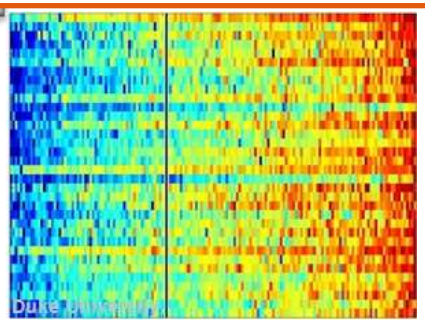
SAFIR01: Study Flow in Metastatic breast cancer



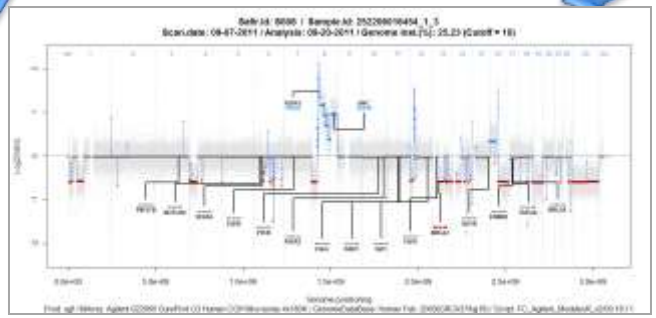
Tumor Biopsy

N=404

molecular profiling



Identification of the molecular alteration



Targeted therapy according to the molecular profile

F André ASCO 2013

Predictive parameters of failure to provide genomic analysis

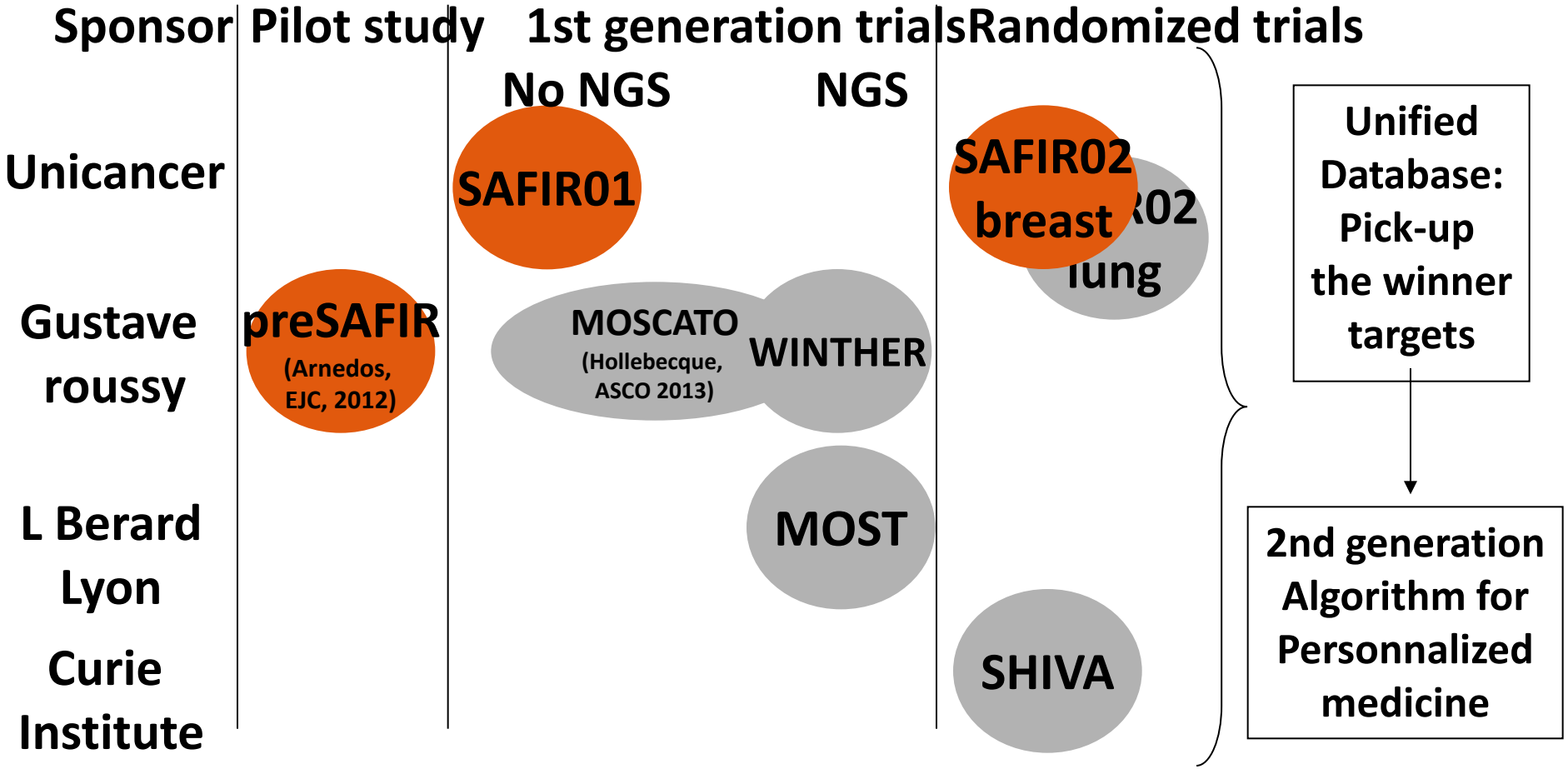
	p value	success	failure
Age	p = 0.7884		
Accrual	p = 0.0590		
Nb patient included in the center	p = 0.3053		
Organ	p < 0.0001		
Liver		131	43 (24%)
lymph node		57	17 (23%)
Skin		47	19 (29%)
Lung		10	16 (61%)
breast		17	9 (34%)
bone		3	11 (78%)
other		22	10 (31%)

No evidence for learning curve or center-effect

Liver and lymph nodes biopsies associated with a higher rate of success to provide genomic test

F André ASCO 2013

Ongoing personalized medicine program in France based on biopsy of metastasis



Overall : >2 000 planned patients (all tumor types), >800 already included

Breast Cancer: > 1 000 planned, >70 already treated

Goal: To generate optimal algorithm for individualized therapy

Conclusions

Enumeration of CTC in metastatic breast cancer

Prognostic marker

Monitoring tumor response

Level of evidence I Clinical Utility better than serum marker

Not only enumeration is needed

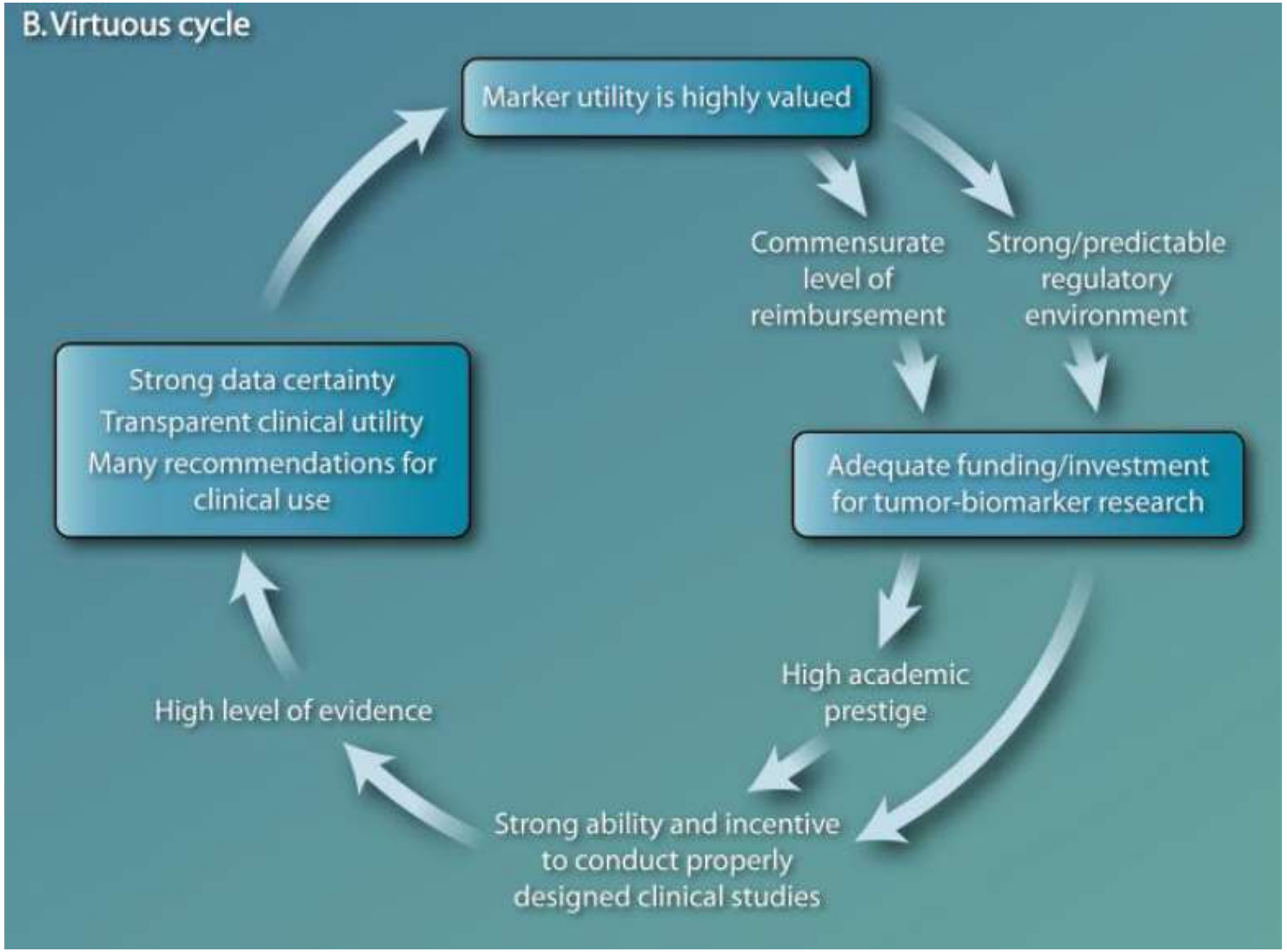
Liquid biopsy +++

Adjust strategy during treatment

CTC development paved the way for ctDNA:

Clinical Validity and Clinical Utility evaluation should follow the same process

TUMOR-BIOMARKER DIAGNOSTI CS
Breaking a Vicious Cycle



Daniel F. Hayes et al, ScienceTranslationalMedicine 2013, 5 ,196

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Statistics

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Grant supports

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