CTC and DTC in breast cancer - what is and will be the clinical utility?

Wolfgang Janni

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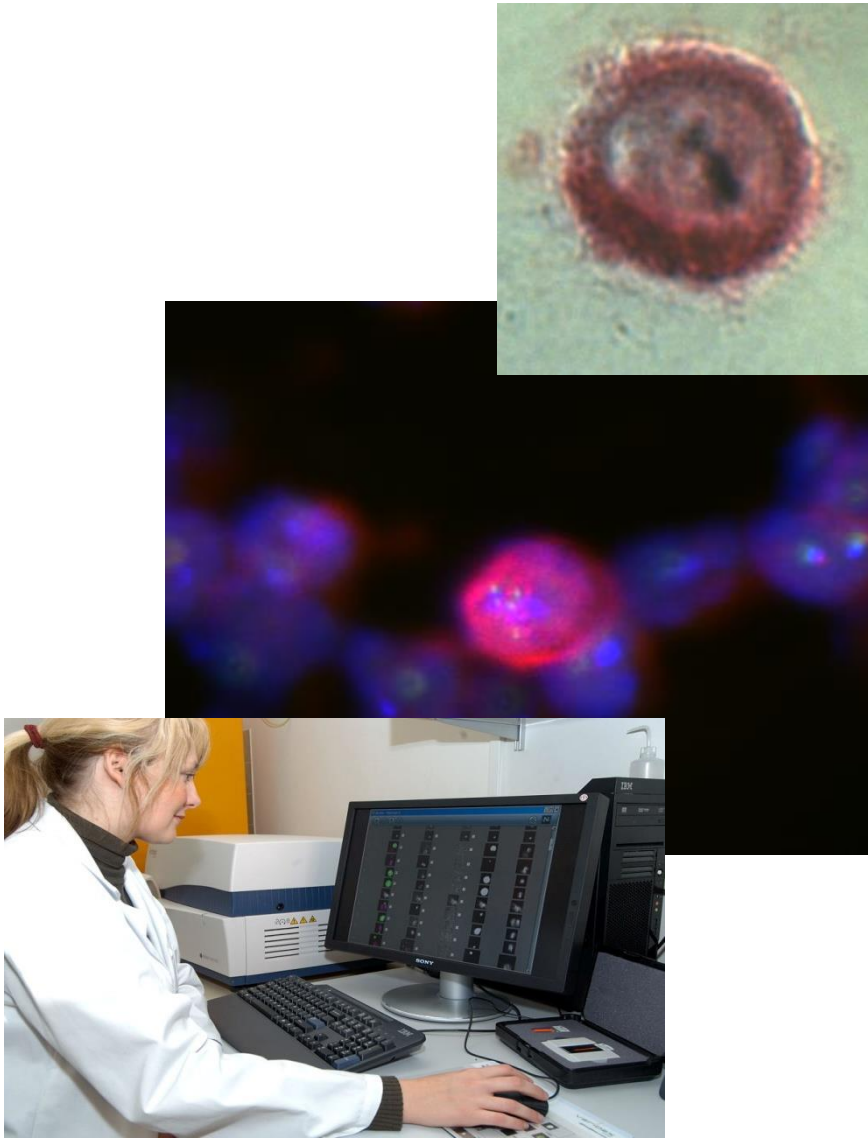
University of Ulm

Germany

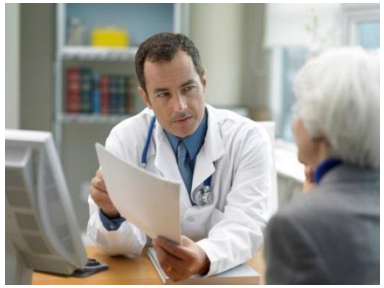


Disclosures

Research Grants and/or honoraria from:
Sanofi-Aventis, Novartis, Roche, Pfizer, AstraZeneca, Chugai, GSK, Eisai, Cellgene, Johnson&Johnson

What Do Clinicians Want from Tests?

(or: how to make a clinician happy)



- It should be easy – we have little time
- It should be easy to understand – we are only clinicians
- It should add information, helpful for patients – we like to look smart in front of the patients
- It should add to decision making – this is one of our prime duties
- It should help guide treatment – this is what clinicians are for

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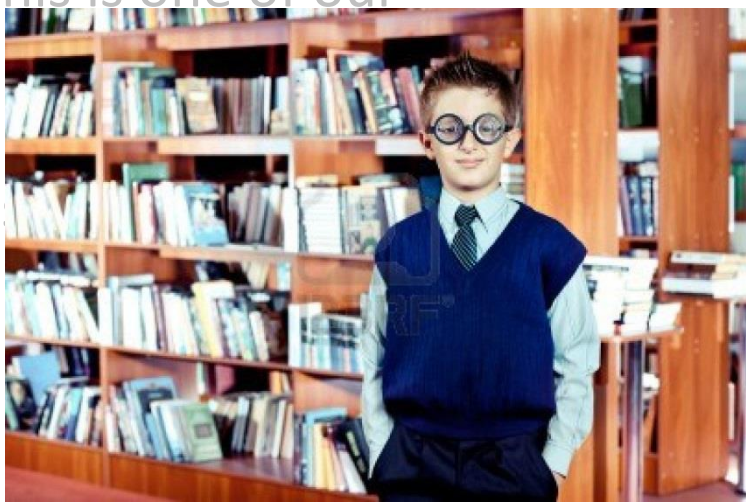

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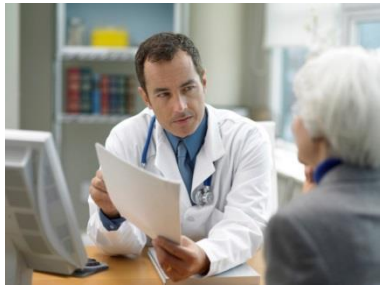

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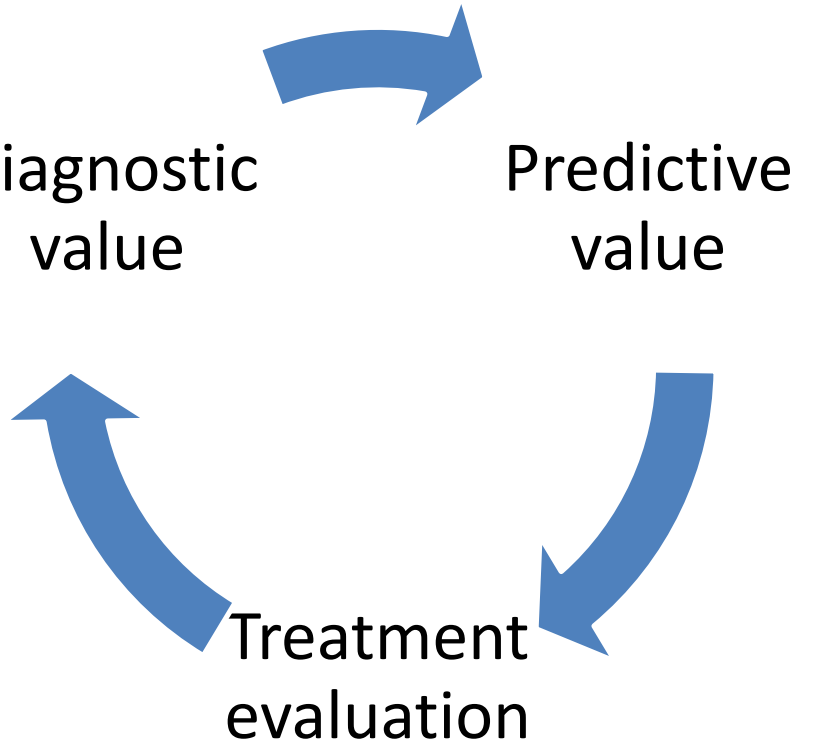
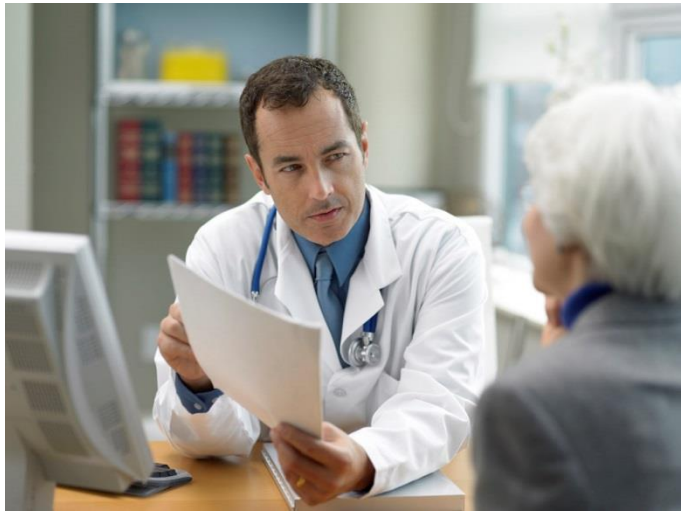
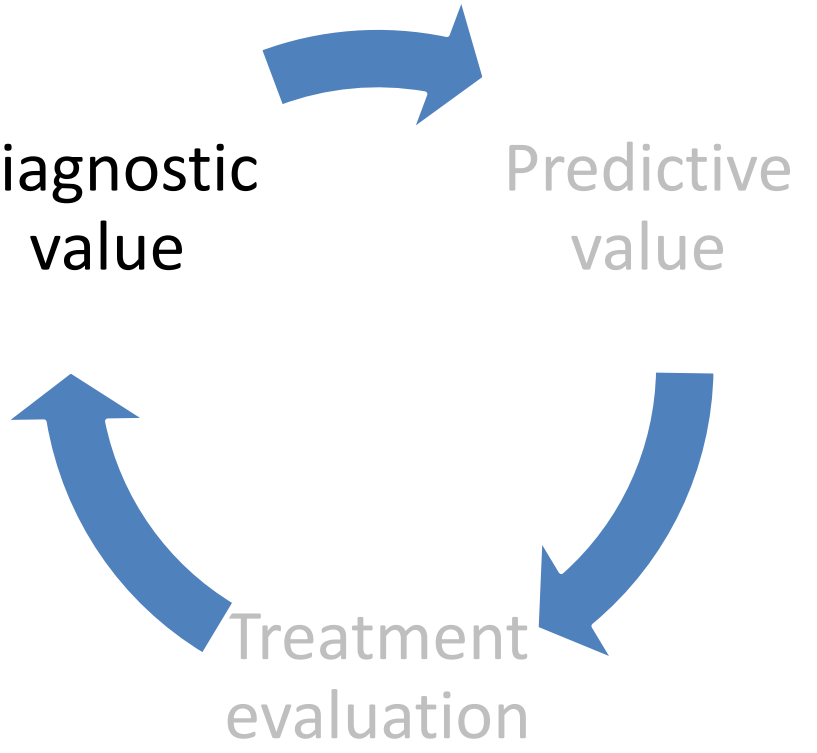
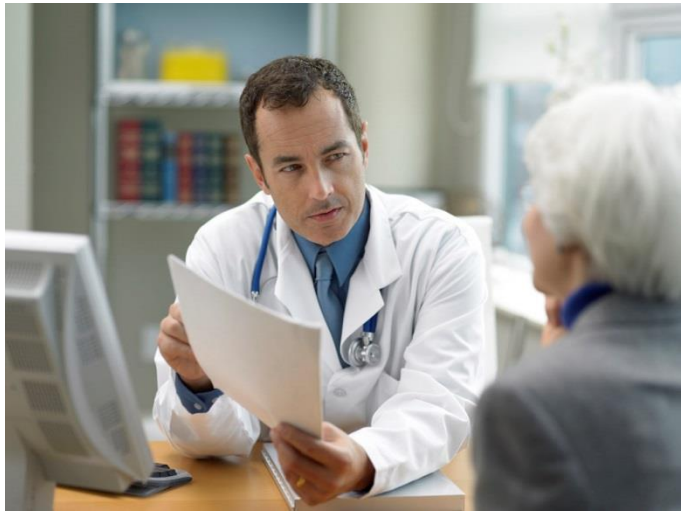
Clinical Utility of Biomarkers in Cancer?



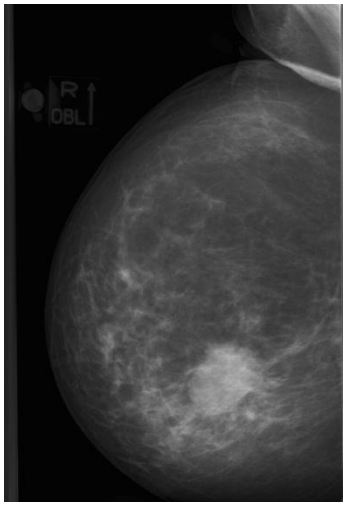


Clinical Utility of Biomarkers in Cancer?





Diagnostic Utility of DTC/CTC



Primary Diagnosis

Follow-up

Recurrence

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Pooled Analysis of Bone Marrow Micrometastasis in Breast Cancer

Stephan Braun, M.D., Florian D. Vogl, M.D., Bjørn Naume, M.D., Wolfgang Janni, M.D., Michael P. Osborne, M.D., R. Charles Coombes, M.D., Günter Schlimok, M.D., Ingo J. Diel, M.D., Bernd Gerber, M.D., Gerhard Gebauer, M.D., Jean-Yves Pierga, M.D., Christian Marth, M.D., Daniel Oruzio, M.D., Gro Wiedswang, M.D., Erich-Franz Solomayer, M.D., Günther Kundt, M.D., Barbara Strobl, M.D., Tanja Fehm, M.D., George Y.C. Wong, Ph.D., Judith Bliss, M.Sc., Anne Vincent-Salomon, M.D., and Klaus Pantel, M.D.*

ABSTRACT

BACKGROUND

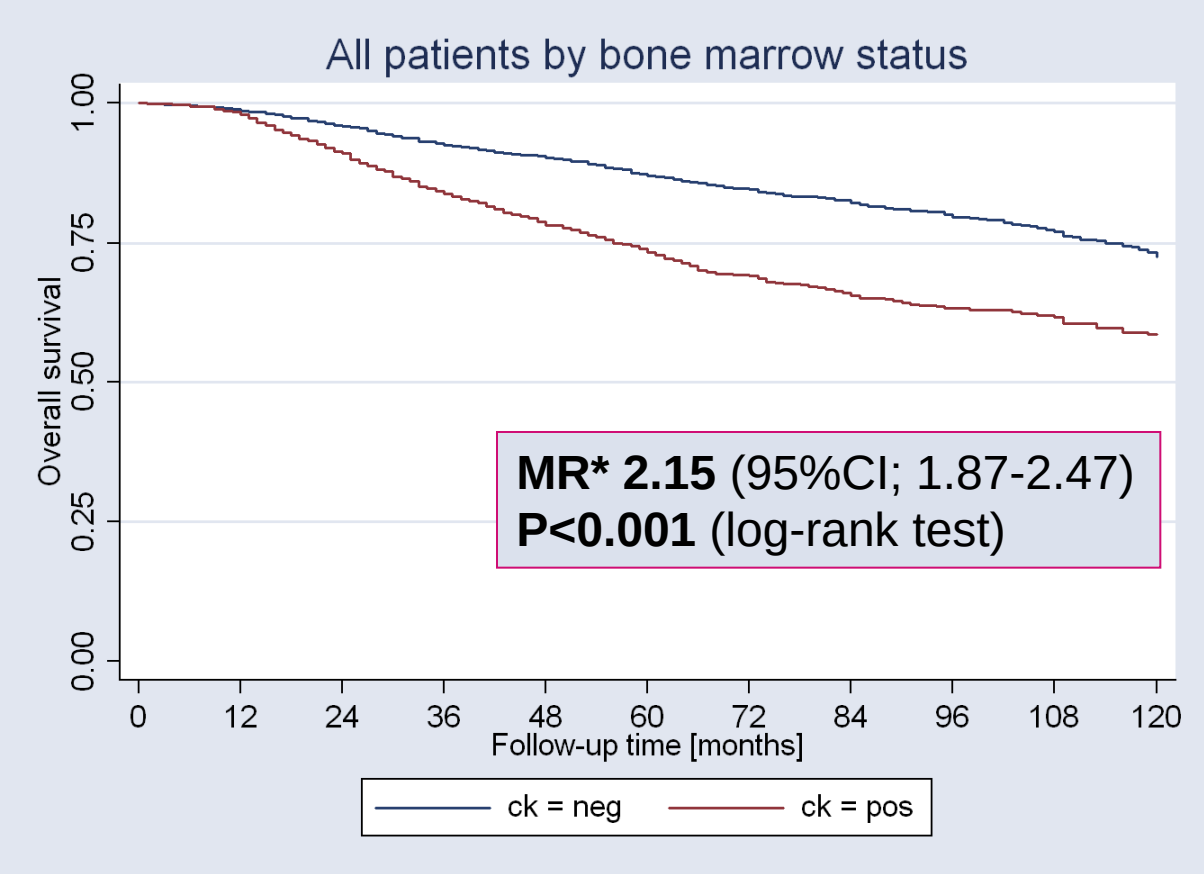
We assessed the prognostic significance of the presence of micrometastasis in the bone marrow at the time of diagnosis of breast cancer by means of a pooled analysis.

From the Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria (S.B., C.M.); Department of Obstetrics and Gynecology, General Hospital, Merano, Italy (F.D.V.); Department of Oncology, Norwegian Radium Hospital, Oslo (B.N.); Department of Obstetrics and Gynecology, Ludwig-Maximilians University, Munich, Germany (W.J., B.S.); Department of Surgery, New York Presbyterian Hospi-

Pooled Analysis of Bone Marrow Aspirations at Primary Diagnosis in 9 Centers (n=4.703)

ulm university universität uulm

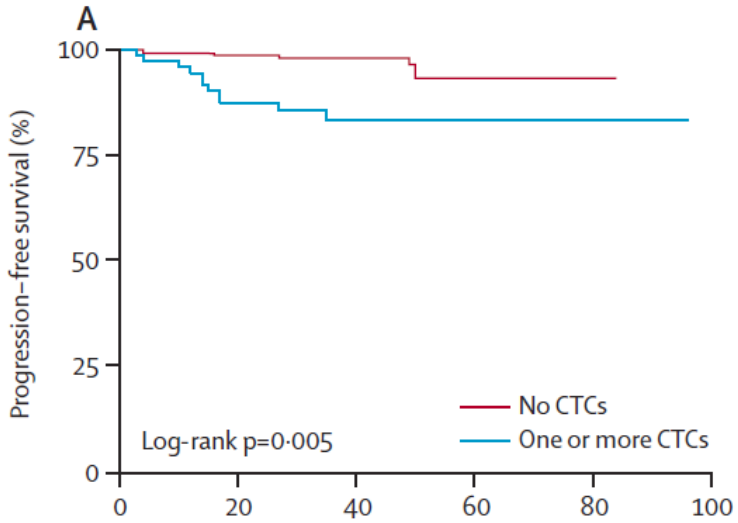
Overall Survival by Bone Marrow Status



Median follow-up 62 months

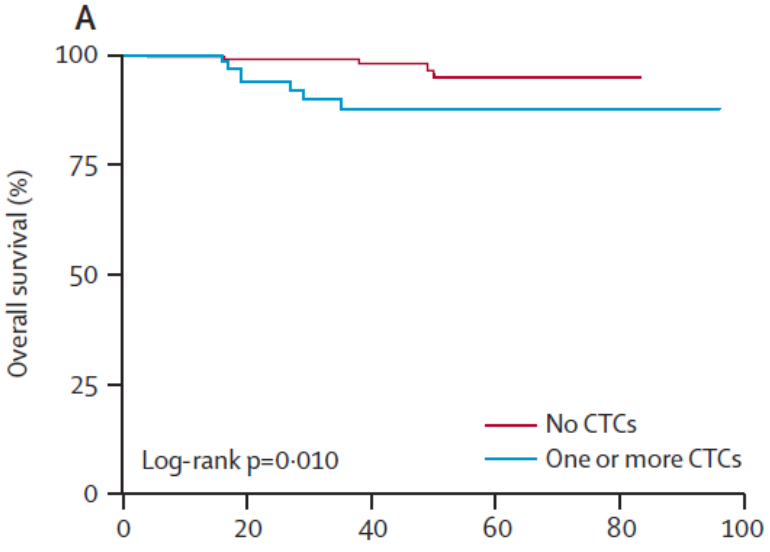
Circulating tumour cells in non-metastatic breast cancer: a prospective study

Anthony Lucci, Carolyn S Hall, Ashutosh K Lodhi, Anirban Bhattacharyya, Amber E Anderson, Lianchun Xiao, Isabelle Bedrosian, Henry M Kuerer, Savitri Krishnamurthy



Number at risk

No CTCs	229	183	88	36	12	0
One or more CTCs	73	57	32	23	5	0



Number at risk

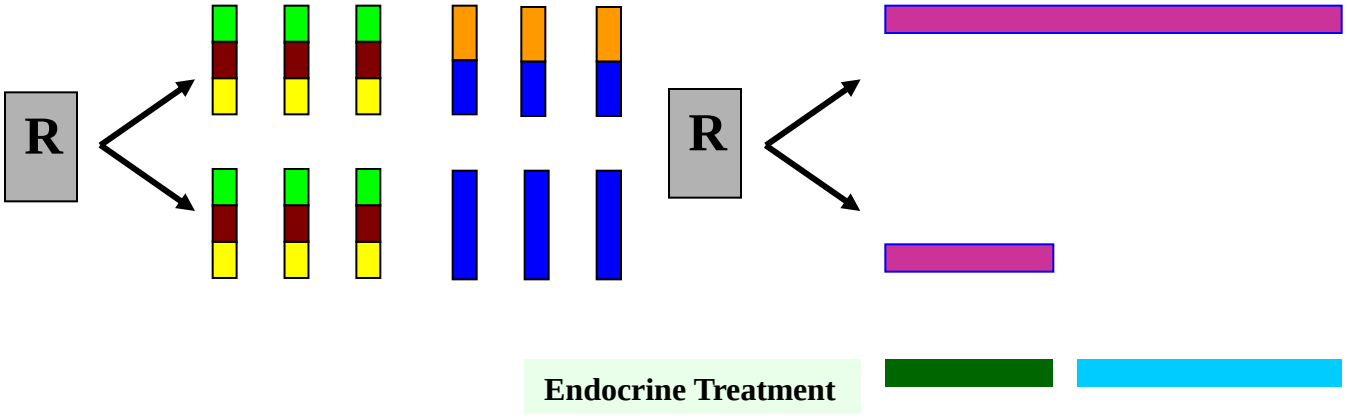
No CTCs	229	183	88	36	12	0
One or more CTCs	73	59	33	23	5	0

Lucci et al., Lancet Onc 2012

SUCCESS Study

Simultaneous Study of Docetaxel-Gemcitabine Combination adjuvant treatment, as well as Extended Bisphosphonate and Surveillance-Trial

- Prospektive randomised controlled phase III study
- 2x2 faktorial design
- High risk N0 and N+ primary breast cancer pts
- n = 3.658



5- FU 500 mg/m², Epirubicin 100 mg/m², Cyclophosphamide 500 mg/m² q3w

Docetaxel 100 mg/m² q3w

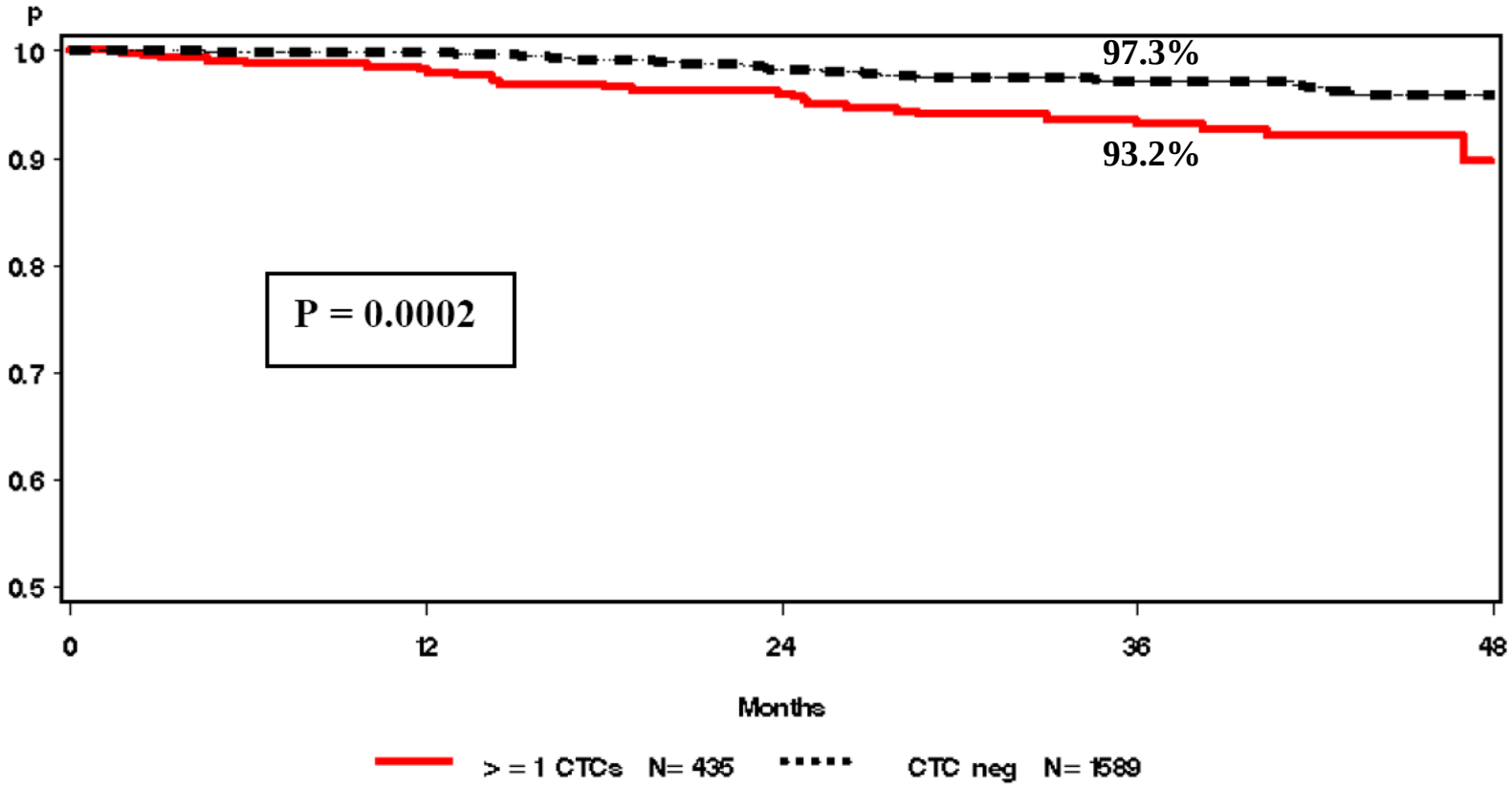
Docetaxel 75 mg/m², Gemcitabine 1000mg/m² D1,8 q3w

Zoledronate 4mg x 2a vs 5a (q3mx24m, vs. q3mx24m followed by q6mx36m)

Tamoxifen 20 mg qid p.o.x 2 a
(plus Goserelin 3.6 mg depot x 2 a in premenopausal women)

Anastrozole 1 mg qid p.o.x 3 a in postmenop. pts (Tam in premenop. pts)

Overall Survival



	CTC+	CTC-
Recurrences	23 / 436	33 / 1589

Multivariate Analysis for OAS

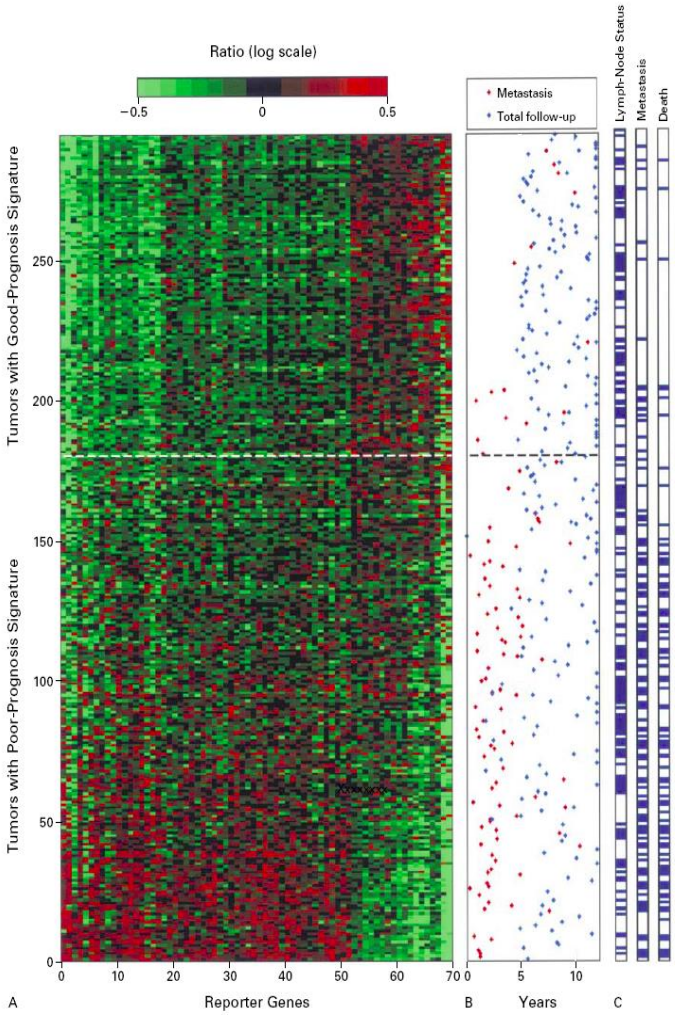
Variable	HR	95% CI	p-value
CTCs in blood			
pos/neg	**1.907**	**1.142 – 3.183**	**0.0136**
Hormone receptor status			
pos/neg	3.326	1.948 – 5.678	<.0001
Lymph Node Involvement			
pos/neg	1.835	1.448 – 2.327	<.0001
Grading			
G1 vs. G2-3	3.287	1.782 – 6.064	0.0001
Tumor size			
T1 vs. T2-4	1.879	1.363 – 2.590	0.0001

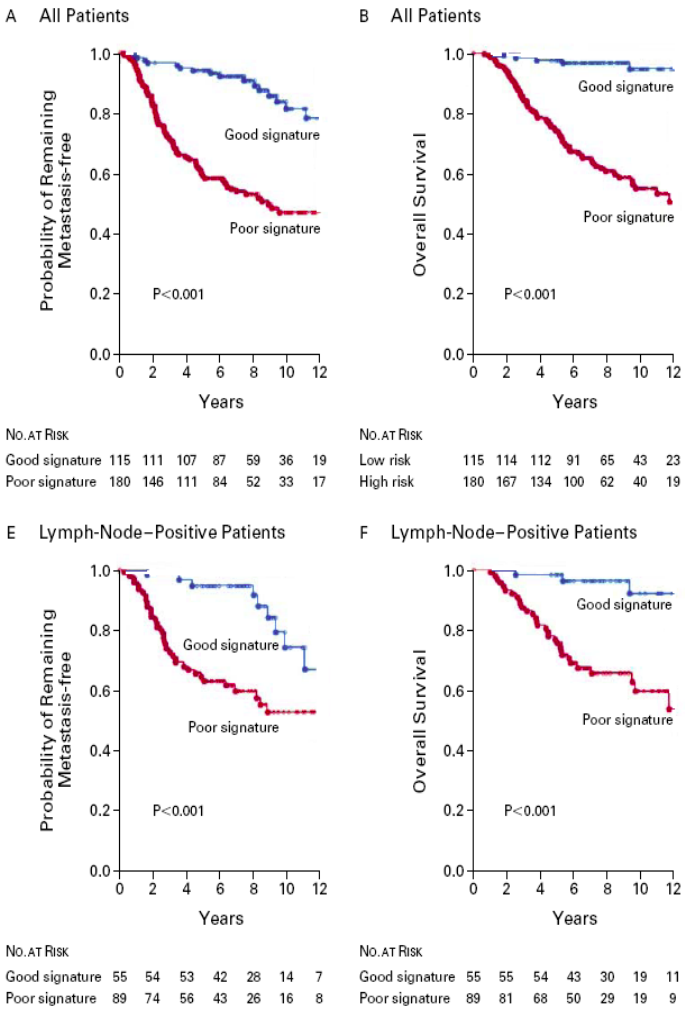
A Pooled Analysis of the Prognostic Relevance of Circulating Tumor Cells in Early Breast Cancer

Wolfgang J. Janni (1), Brigitte Rack (2), Leon M.W.W. Terstappen (3), Jean-Yves Pierga (4), Tanja Fehm (5), Carolyn Hall (8), Marco Groot(7), François-Clement Bidard (4), Franziska Meier-Stiegen (9), Thomas W.P. Friedl (1), Peter A. Fasching (6), Anthony Lucci (8)

Pathological Work-up Breast Ca

Parameter / AGO recommandation according to GPC	Invasive carcinoma	Ductal in situ	LIN
Total metric extent (plus pT stage)	++	++	-
Width of tumour-free margin (3 dimensions)	++	++	-
Histologic type	++	+/-	++
Grading	++	++	+/- LIN1-3
Hormone receptors	++	++	-
HER-2	++	-	-
Proliferation	+	-	-
Intraductal component (Quantification)	++	n.a.	-
Angioinvasion (only when obvious, limited reproducibility)	++	n.a.	n.a.


Ratio (log scale)
−0.5
0
0.5
Metastasis
Total follow-up
Lymph-Node Status
Metastasis
Death
Tumors with Good-Prognosis Signature
Tumors with Poor-Prognosis Signature
Reporter Genes
Years
A
B
C


A All Patients
B All Patients
Probability of Remaining Metastasis-free
Overall Survival
Good signature
Poor signature
P<0.001
Years
No. at Risk
Good signature 115 111 107 87 59 36 19
Poor signature 180 146 111 84 52 33 17
Low risk 115 114 112 91 65 43 23
High risk 180 167 134 100 62 40 19
E Lymph-Node–Positive Patients
F Lymph-Node–Positive Patients
Good signature 55 54 53 42 28 14 7
Poor signature 89 74 56 43 26 16 8
Good signature 55 55 54 43 30 19 11
Poor signature 89 81 68 50 29 19 9

Detection of DTC/CTC in **Primary** Breast Cancer – diagnostic utility

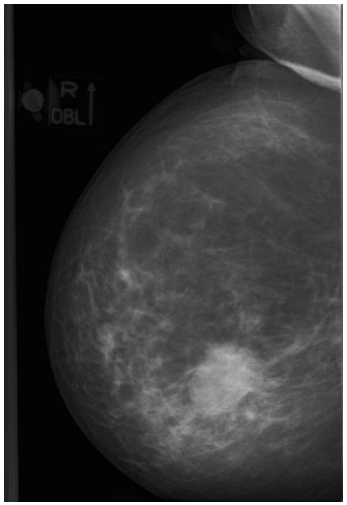
Pro

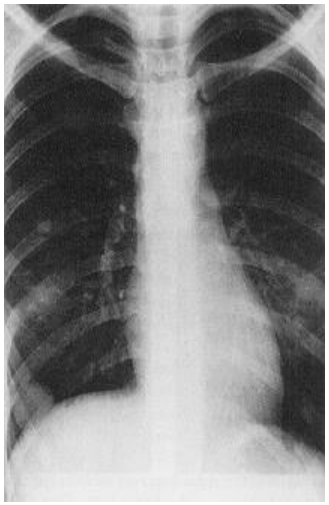
- To identify patients with increased risk for distant recurrence after/during treatment

Caveats

- Primary tumor yields ample information for primary treatment decision
- Diagnostic information on primary tumor increased by molecular methods

Diagnostic Utility of DTC/CTC





Primary Diagnosis

Follow-up

Recurrence

Detection Circulating Tumor Cells in Peripheral Blood in MBC

- Number of CTC independent predictor of PFS and OS
- Strongest Predictor in multivariate analysis

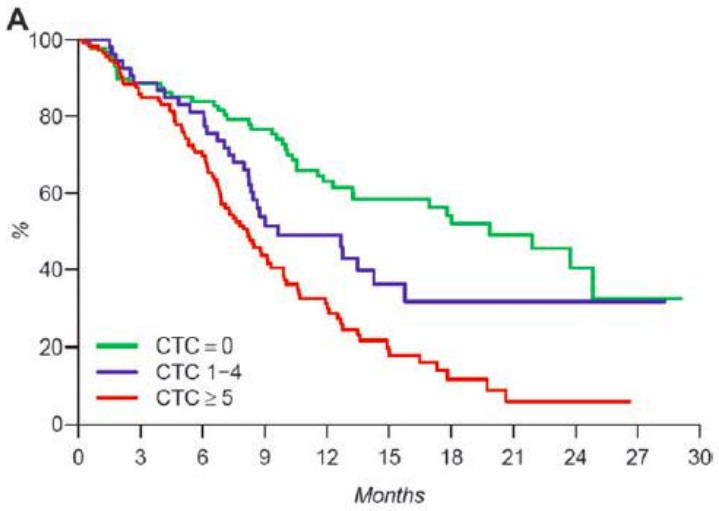
Table 3. Prediction of Progression-free Survival and Overall Survival.*

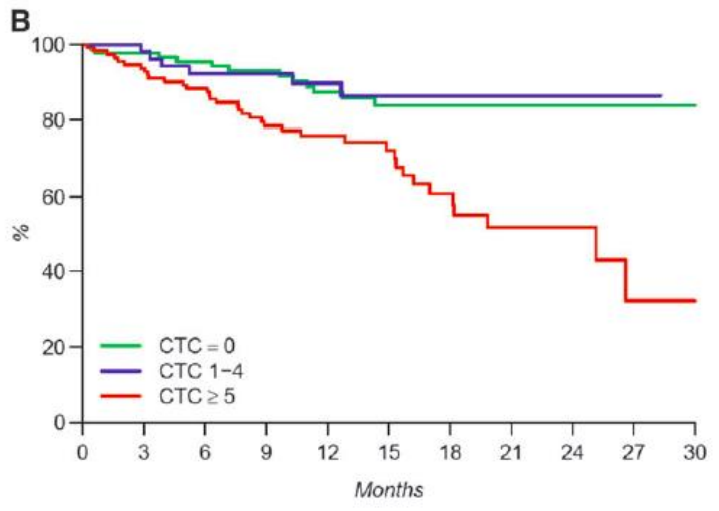
Variable	Progression-free Survival		Overall Survival	
	Hazard Ratio	P Value	Hazard Ratio	P Value
Analysis with baseline CTC count				
≥5 CTC vs. <5 CTC	1.76	0.001	4.26	<0.001
Second or subsequent line of therapy vs. first	1.73	0.002	2.58	0.001
Chemotherapy vs. hormone therapy, immunotherapy, or both	1.61	0.02	2.54	0.02
ECOG score 2 vs. 1 vs. 0	NS	NS	1.48	0.02
Time to metastasis	NS	NS	0.92	0.03
Analysis with CTC count at first follow-up visit				
≥5 CTC vs. <5 CTC	2.52	<0.001	6.49	<0.001
Positive ER/PR status vs. negative	NS	NS	0.35	<0.001
Second or subsequent line of therapy vs. first	1.58	0.01	2.29	0.006
ECOG score 2 vs. 1 vs. 0	NS	NS	1.53	0.03

Cristofanilli M., et al. *NEJM* 2004 351(8):781-91

High independent prognostic and predictive value of circulating tumor cells compared with serum tumor markers in a large prospective trial in first-line chemotherapy for metastatic breast cancer patients

J.-Y. Pierga[1,2*], D. Hajage[3], T. Bachelot[4], S. Delaloge[5], E. Brain[6], M. Campone[7], V. Diéras[1], E. Rolland[3], L. Mignot[1], C. Mathiot[8] & F.-C. Bidard[1,2]





PFS

OS

Pierga J.-Y.., et al. AnnOnc 2012

Detection of DTC/CTC in **Metastatic** Breast Cancer – diagnostic utility

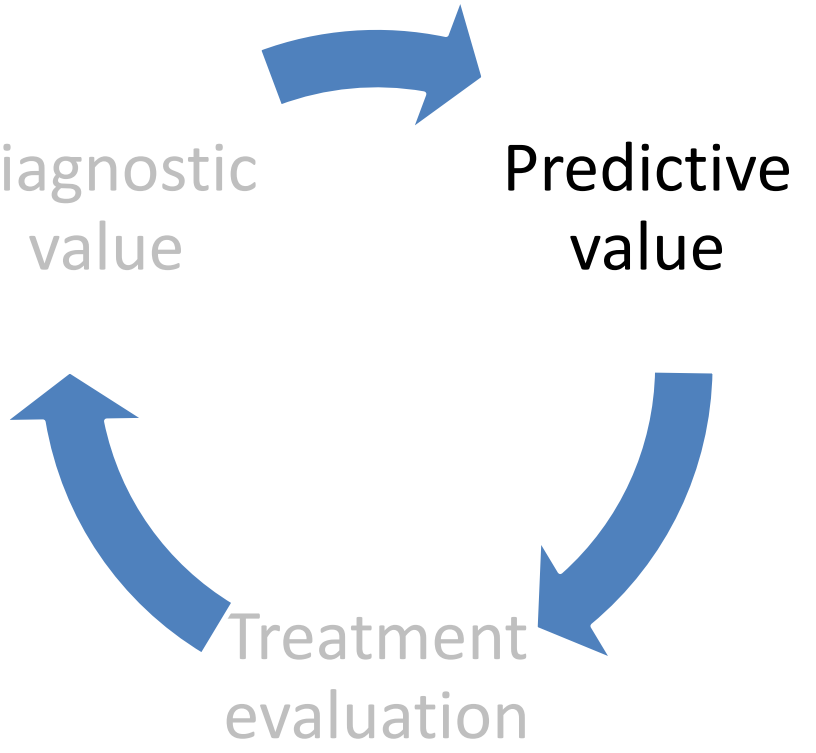
Pro

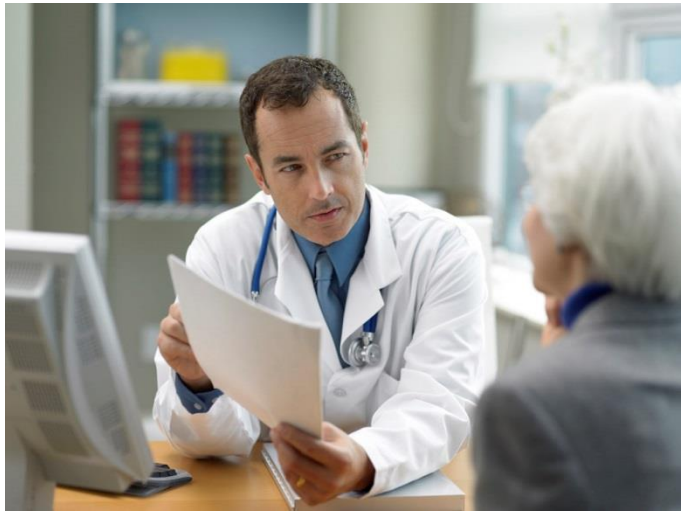
- Potential additional diagnostic information
- To early dertermine treatment response
- To early guide further treatment decision based upon CTC response

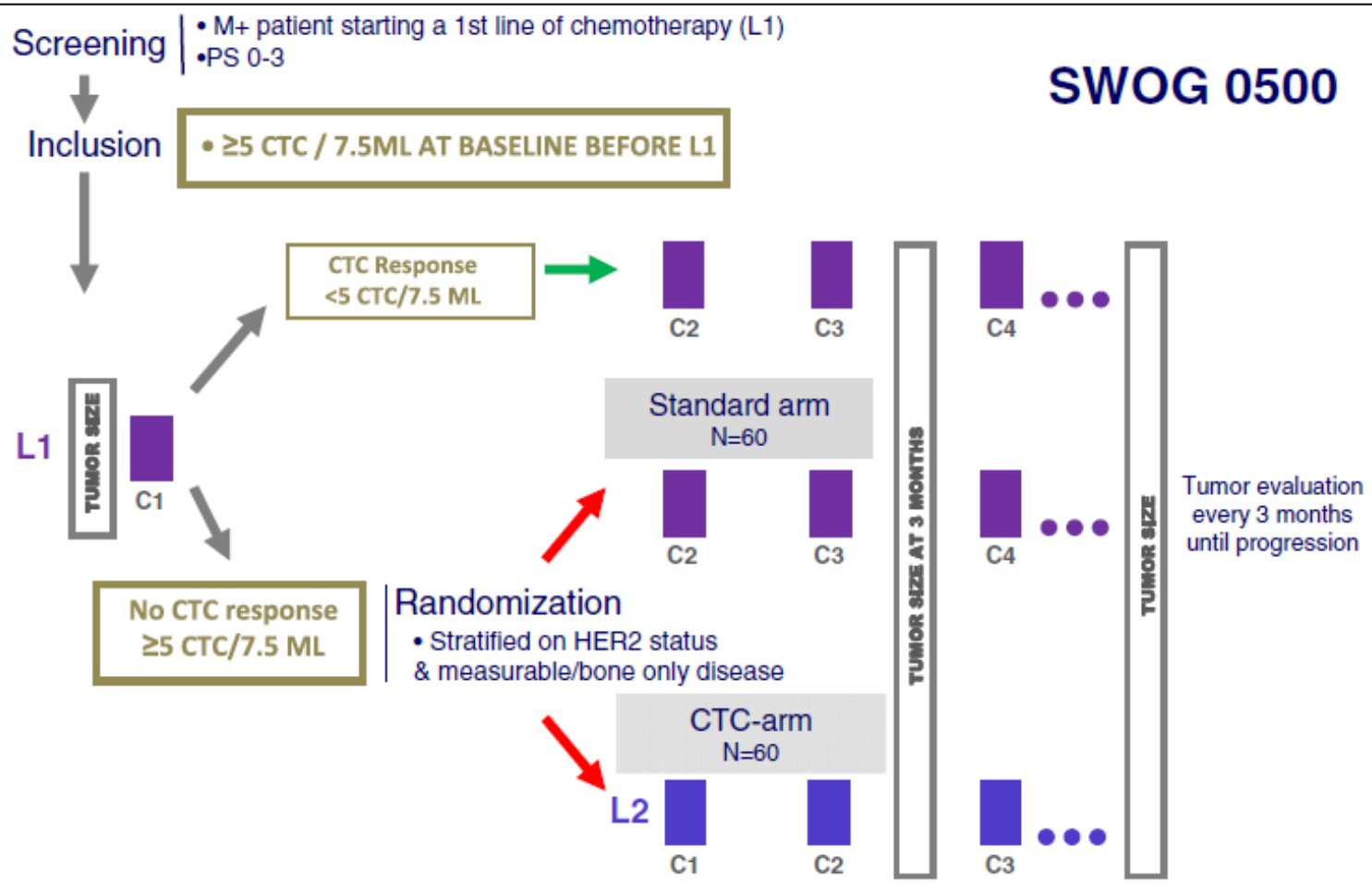
Caveats

- Treatment response can be determined by imaging
- Survival benefit not established yet

Clinical Utility of Biomarkers in Cancer?







- To avoid early treatment discontinuation in the standard arm, patients and clinicians are blinded to the second CTC test
- Randomization stratified on HER2 status & measurable/bone only disease
- Primary endpoint: OS (superiority; hypotheses HR=0.59, P=81%)
- 2nd endpoints: PFS, toxicities, …
- After clinical progression, pts may continue to subsequent lines of therapy as clinically appropriate.

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

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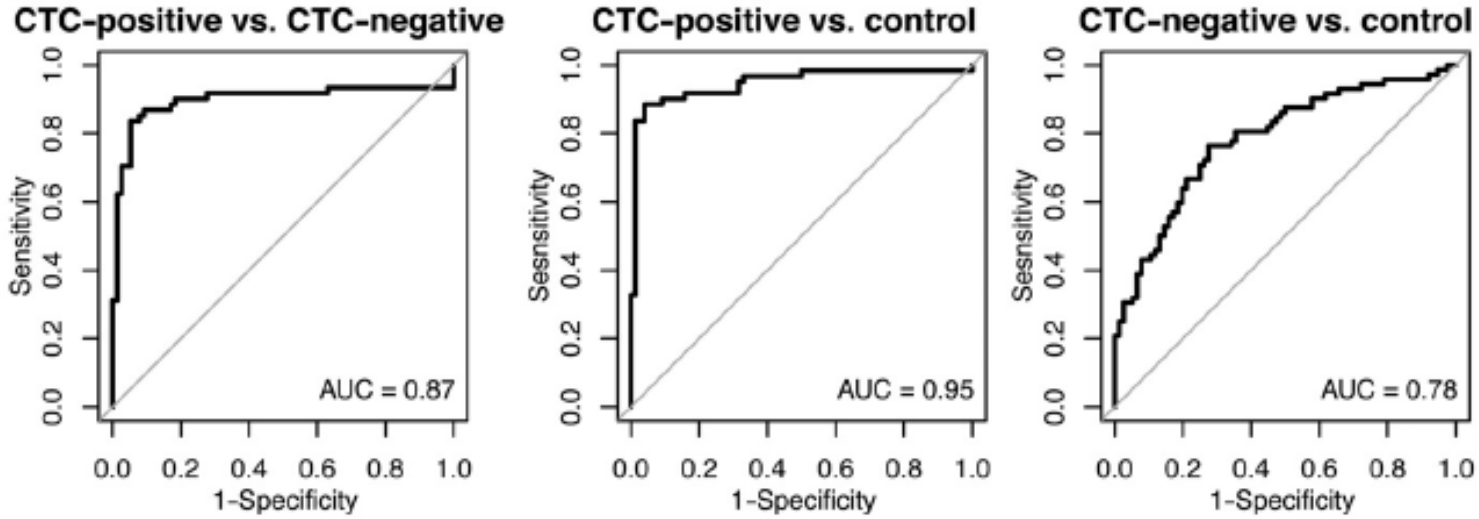
Clinical Cancer Research

Circulating miRNAs as Surrogate Markers for Circulating Tumor Cells and Prognostic Markers in Metastatic Breast Cancer

Dharanija Madhavan, Manuela Zucknick, Markus Wallwiener, et al.

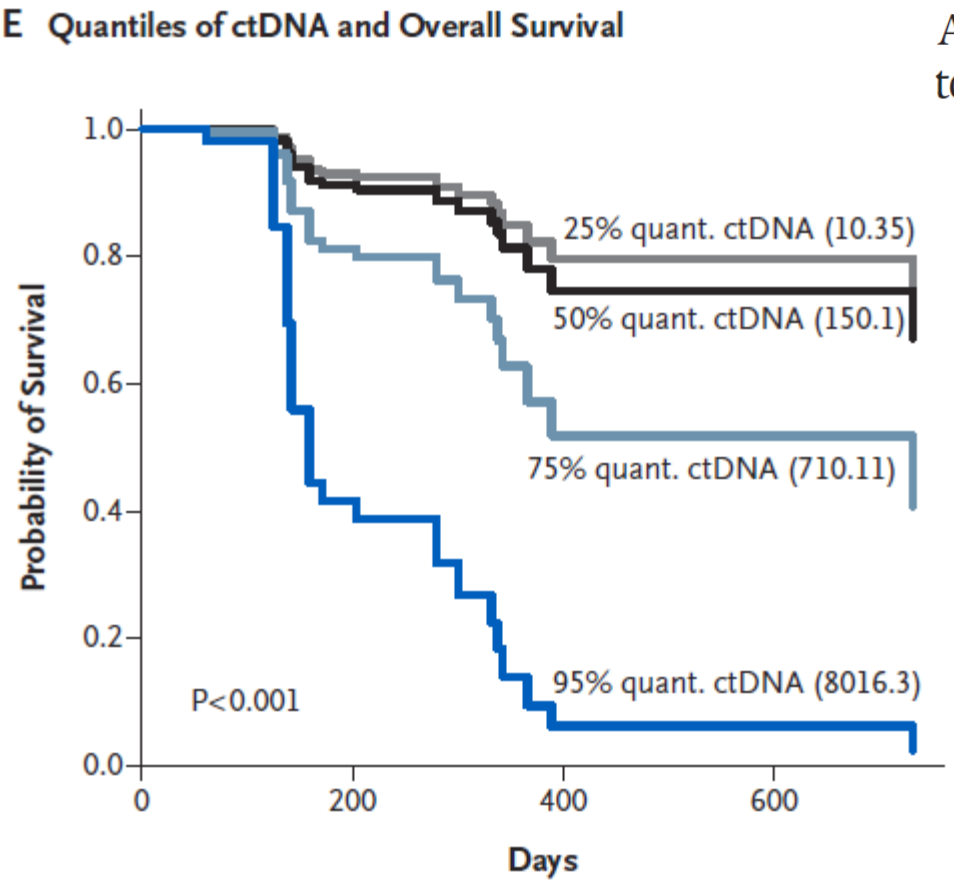


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

Sarah-Jane Dawson, F.R.A.C.P., Ph.D., Dana W.Y. Tsui, Ph.D.,



Dawson et al., N Engl J Med. 2013;368(13)

Breast Cancer Res Treat (2010) 124:403–412
DOI 10.1007/s10549-010-1163-x

CLINICAL TRIAL

HER2 status of circulating tumor cells in patients with metastatic breast cancer: a prospective, multicenter trial

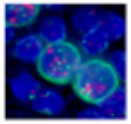
Tanja Fehm · Volkmar Müller · Bahriye Aktas · Wolfgang Janni · Andreas Schneeweiss · Elmar Stickeler · Claus Lattrich · Christian R. Löhberg · Erich Solomayer · Brigitte Rack · Sabine Riethdorf · Christoph Klein · Christian Schindlbeck · Kerstin Brocker · Sabine Kasimir-Bauer · Diethelm Wallwiener · Klaus Pantel

Received: 4 July 2010 / Accepted: 2 September 2010 / Published online: 22 September 2010

ICC HER2 Status on CTC

CellSearch: n=245
Positivity rate: 122 (50%)
HER2 pos. fraction: 50 (41%)

n=122	**Primary Tumor**		
CTC	HER2 neg	HER2 pos	HER2 unknown
HER2 neg	51 (67)	13 (42)	8 (53)
HER2 pos	**25 (33)**	18 (58)	7 (47)
All	78 (100)	31 (100)	15 (100)



DETECT

Screening-Phase
N ≈ 2000
metastatic breast cancer,
HER2-negative
Primary tumor*

CTC-determination
Determination of the HER2 status on CTCs

DETECT III

CTC+ [HER2+]

R

Standard treatment
N = 114
+ Denosumab**

Standard treatment
+ Lapatinib
N = 114
+ Denosumab**

DETECT IV

CTC+ [HER2-]

Primary tumor:
Hormone-receptor positive

Everolimus
+
Endocrine therapy
(exemestane, tamoxifen, letrozole, anastrozole)
N = 400

DETECT V

Primary tumor:
Hormone-receptor negative

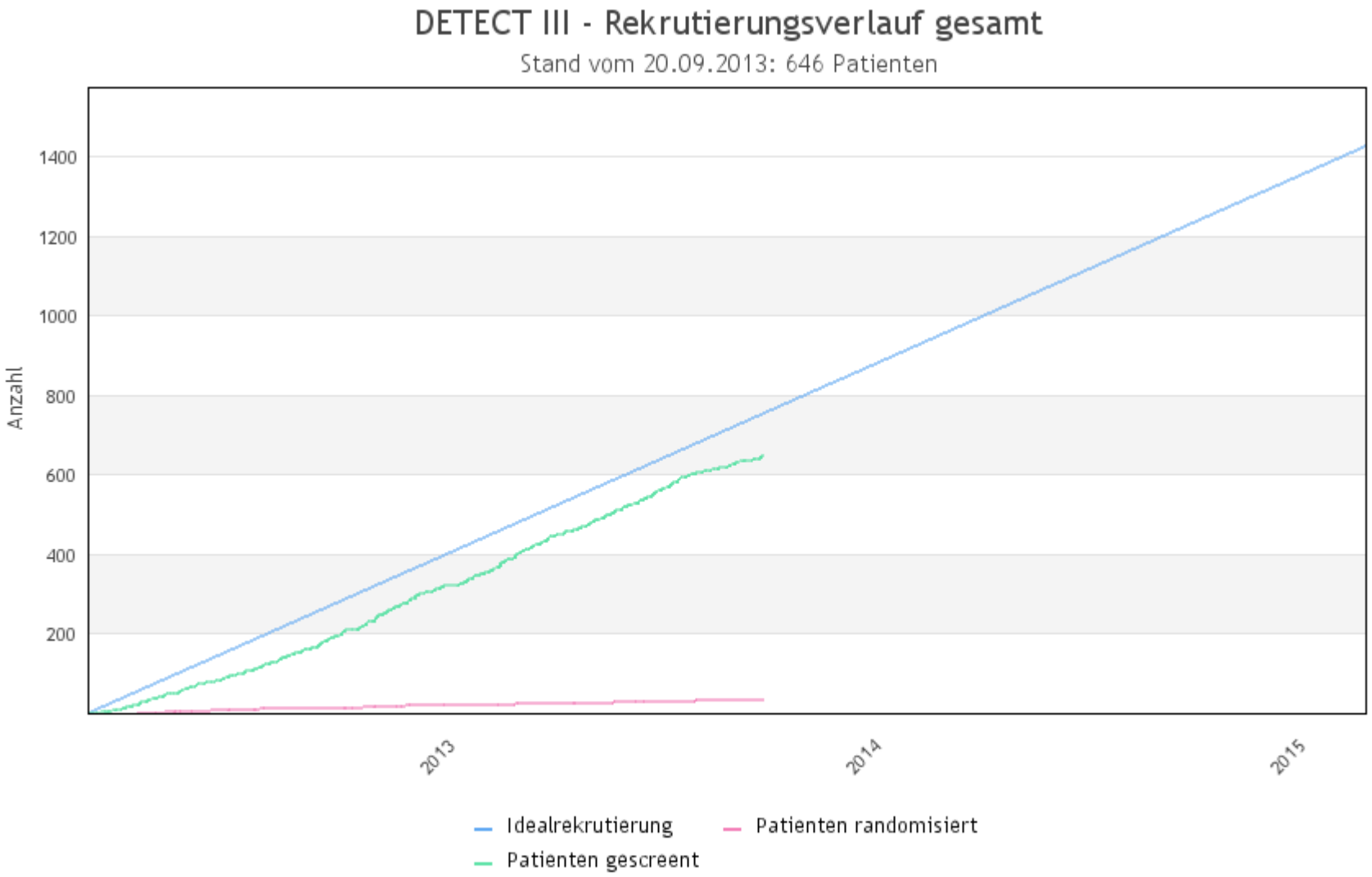
Eribulin

CTC-negative

Not eligible in
D III, D IV or D V

* including HER2-negative metastatic disease in case a biopsy was performed; ** in patients with bone metastases

Courtesy of F. Schochter


DETECT III - Rekrutierungsverlauf gesamt
Stand vom 20.09.2013: 646 Patienten
Anzahl
1400
1200
1000
800
600
400
200
2013
2014
2015
Idealrekrutierung
Patienten randomisiert
Patienten gescreent

Treatment of Metastatic Breast Cancer
Predictive Factors

Guidelines Breast
Version 2013.1

Therapy	Factor	Oxford / AGO LoE / GR		
Endocrine therapy	ER / PR (primary tumor, metastasis)	1a	A	++
	previous response	2b	B	++
Chemotherapy	previous response	1b	A	++
Anti-HER2-drugs	HER2 (primary tumor, better metastasis)	1a	A	++
Bone modifying drugs	bone metastasis	1a	A	++
Any therapy	CTC monitoring	1b	A	+*

(other potentially biological factors see chapter „predictive factors“)

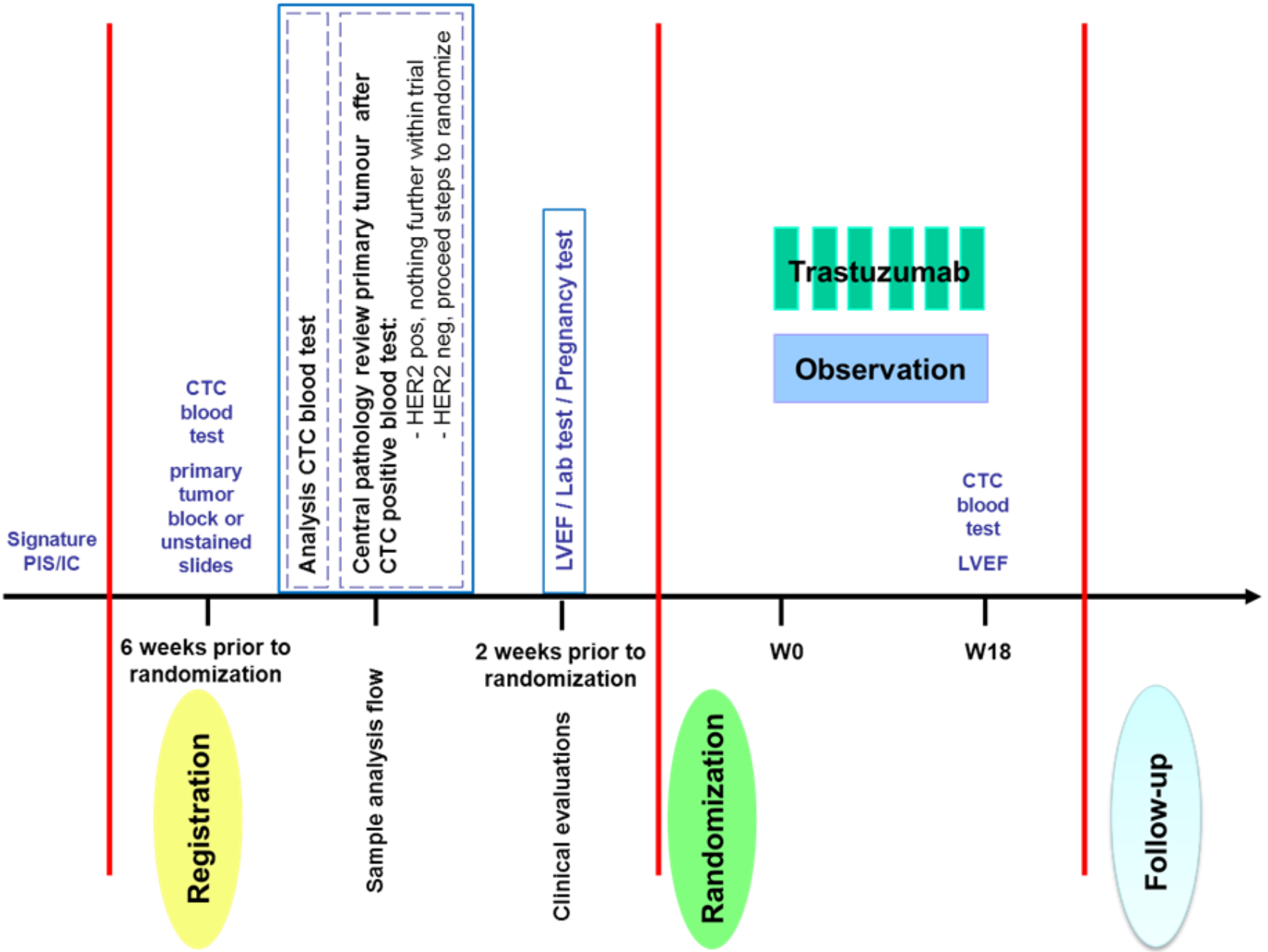
*within clinical trials

www.ago-online.de

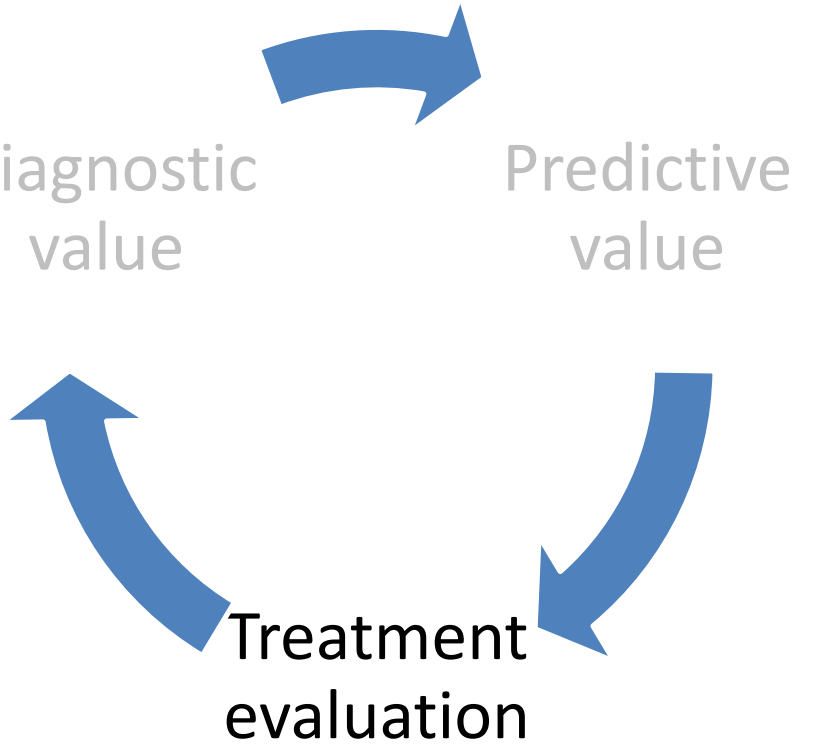
Further Information

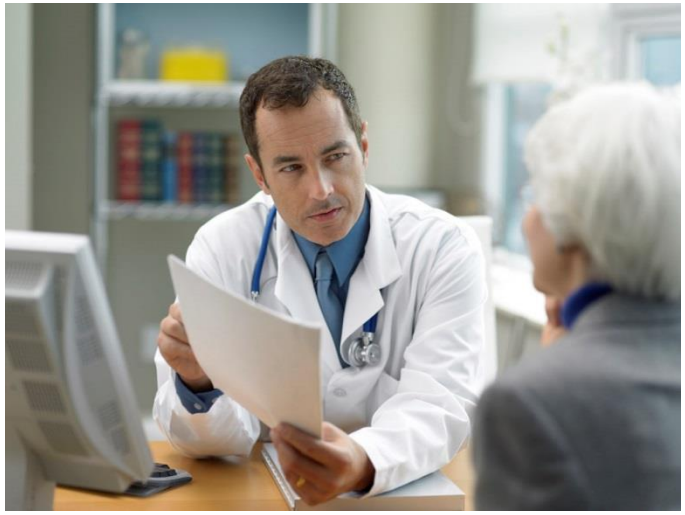
References

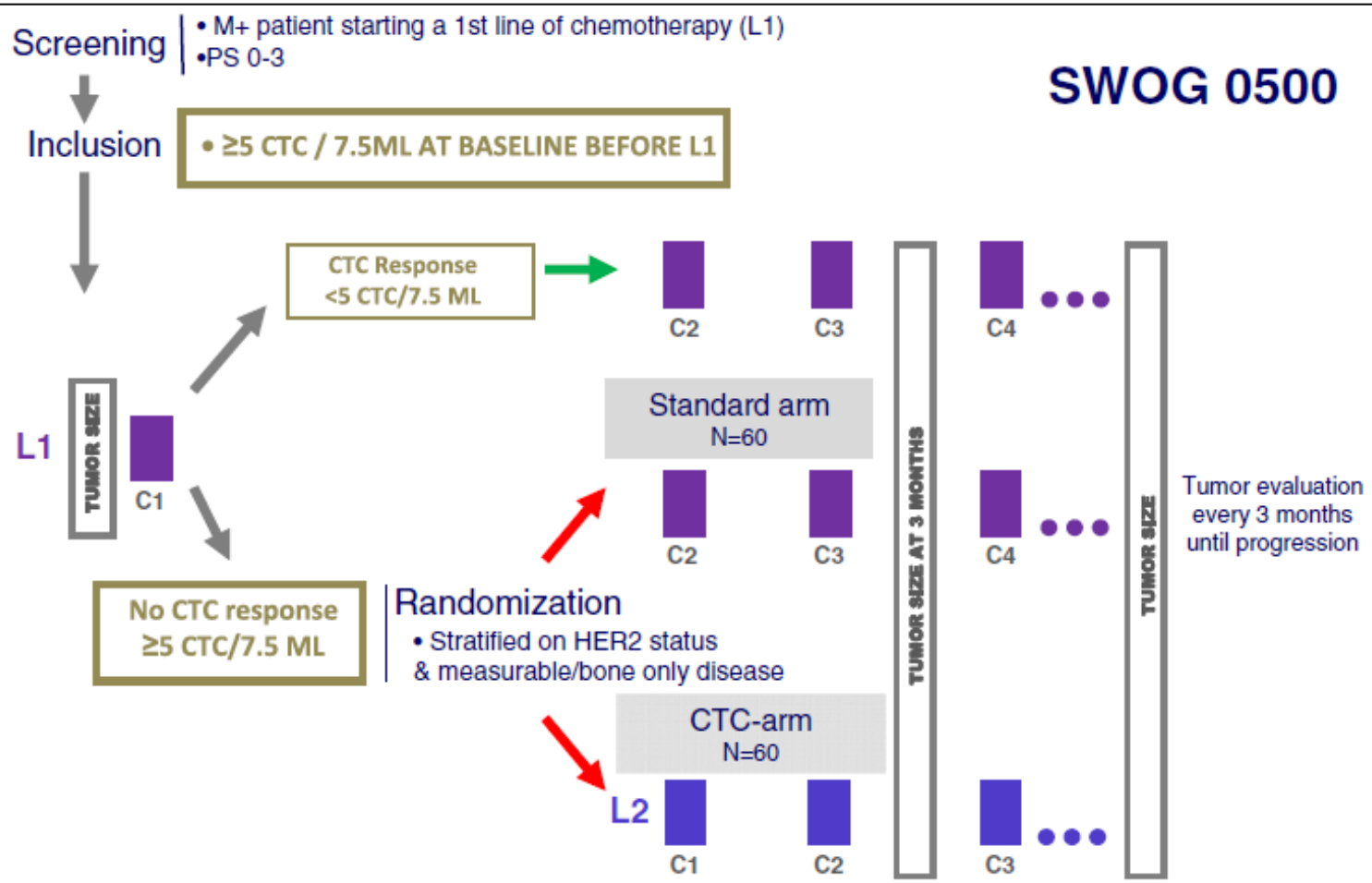
TREAT CTC TRIAL DESIGN



Clinical Utility of Biomarkers in Cancer?

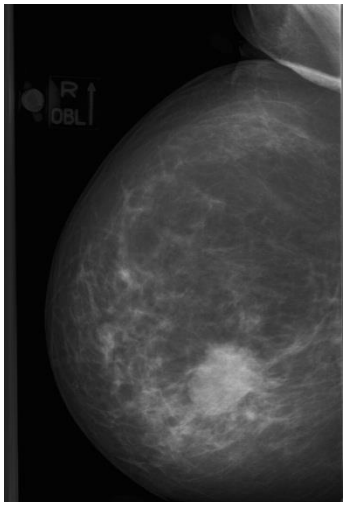






- To avoid early treatment discontinuation in the standard arm, patients and clinicians are blinded to the second CTC test
- Randomization stratified on HER2 status & measurable/bone only disease
- Primary endpoint: OS (superiority; hypotheses HR=0.59, P=81%)
- 2nd endpoints: PFS, toxicities, …
- After clinical progression, pts may continue to subsequent lines of therapy as clinically appropriate.

Visualizing the Disease



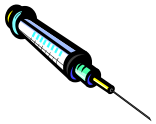
Clinical Cancer Research

AACR

Persistence of Disseminated Tumor Cells in the Bone Marrow of Breast Cancer Patients Predicts Increased Risk for Relapse—A European Pooled Analysis

Wolfgang Janni, Florian D. Vogl, Gro Wiedswang, et al.

Clin Cancer Res 2011;17:2967-2976. Published OnlineFirst March 17, 2011.

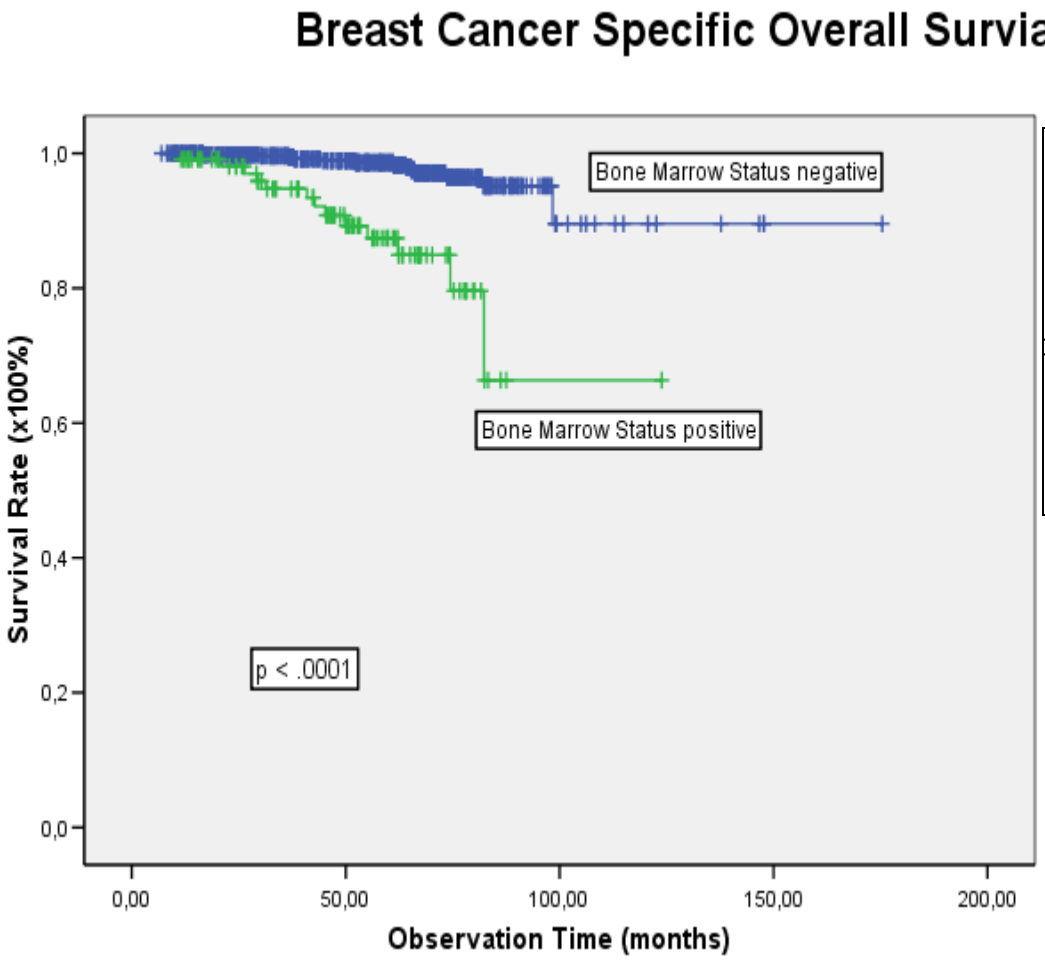


Primary Diagnosis

Follow-up

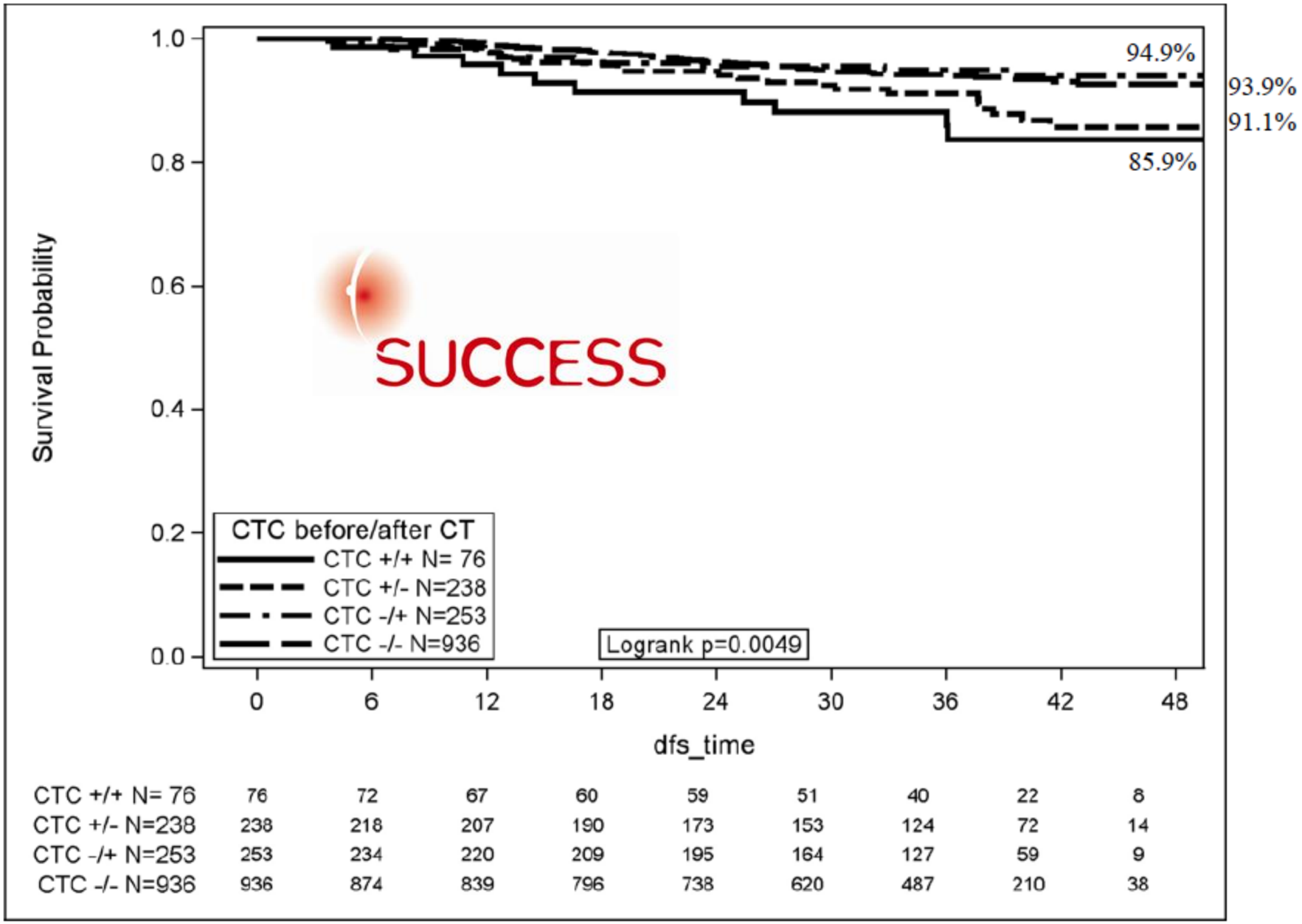
Recurrence

Overall Survival (OS)



Mean DFS **165.6** mos (156.8 – 174.5 95%CI)
Mean DFS **103.3** mos (91.0 – 115.7 95% CI)

Janni, Clin Can Res 2011



Rack et al., unpublished data

Monitoring of DTC/CTC in Breast Cancer – clinical utility

Pro

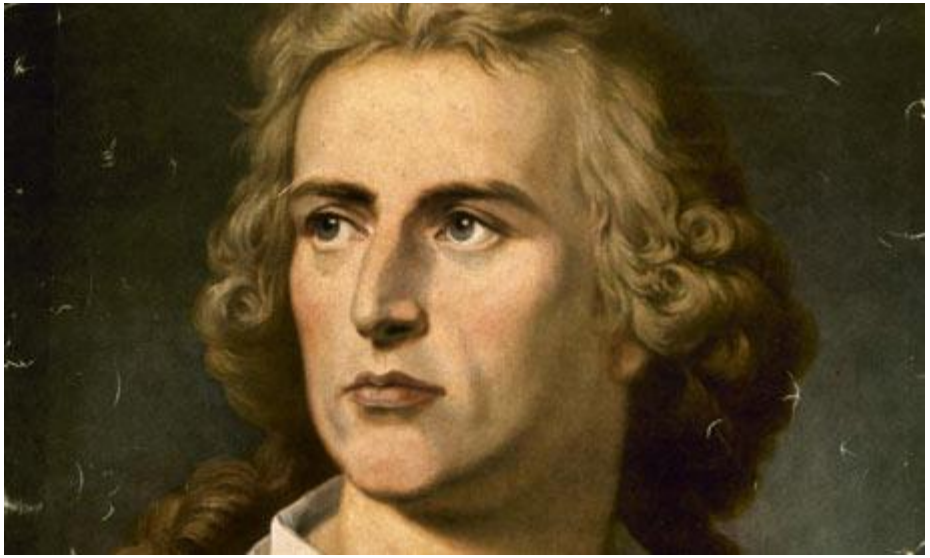
- Persisting DTC in early breast cancer of prognostic relevance
- CTC as early response marker in ABC well established
- Preliminary data suggest the same in EBC

Caveats

- Clinical benefit of CTC monitoring in ABC to be proven (SWOG…)
- Sensitivity of CTC monitoring in EBC currently not sufficient

My Conclusion as a Clinician

- Prognostic relevance of DTC and CTC in EBC and ABC without doubt – level of evidence I
- However, prognostic information in the treatment reality of BC in 2013 only of limited relevance
- Predictive relevance might decide on the future clinical utility of CTC testing in BC
- Characterization of CTC would add significantly to predictive relevance
- Therapeutic monitoring in EBC much wanted – but currently beyond methodological limits



Utility is the great idol of the age,
to which all powers must do service and
all talents swear allegiance.

Friedrich Schiller