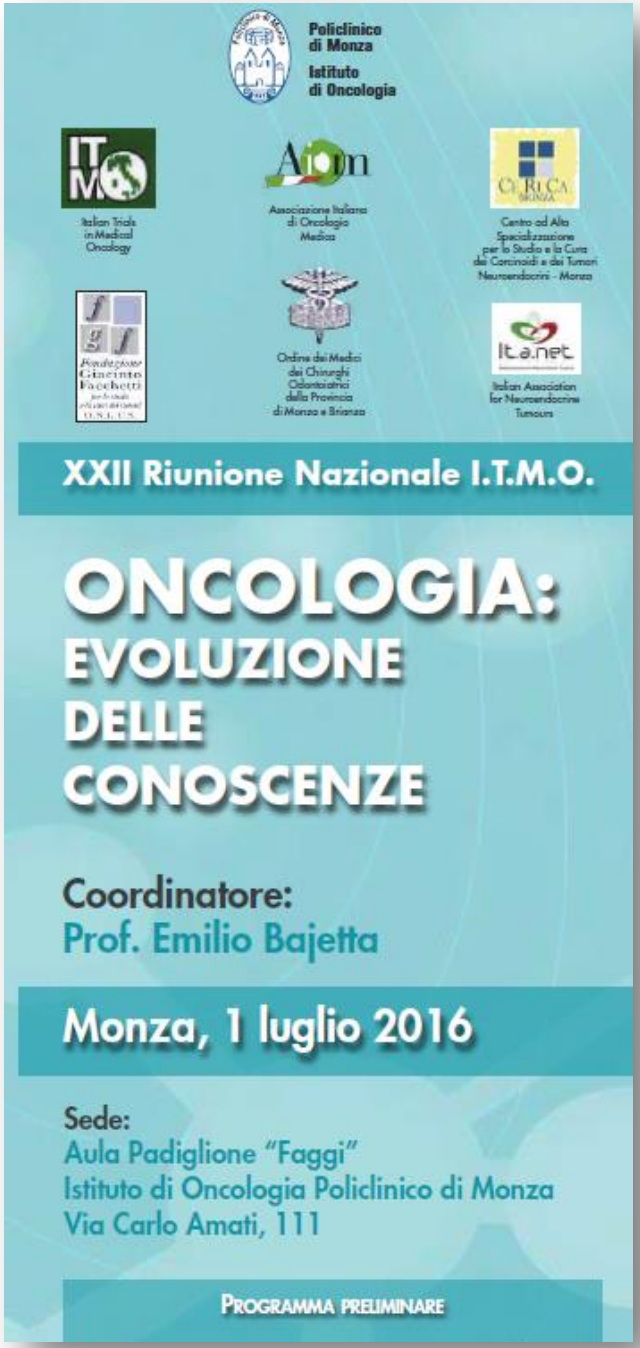


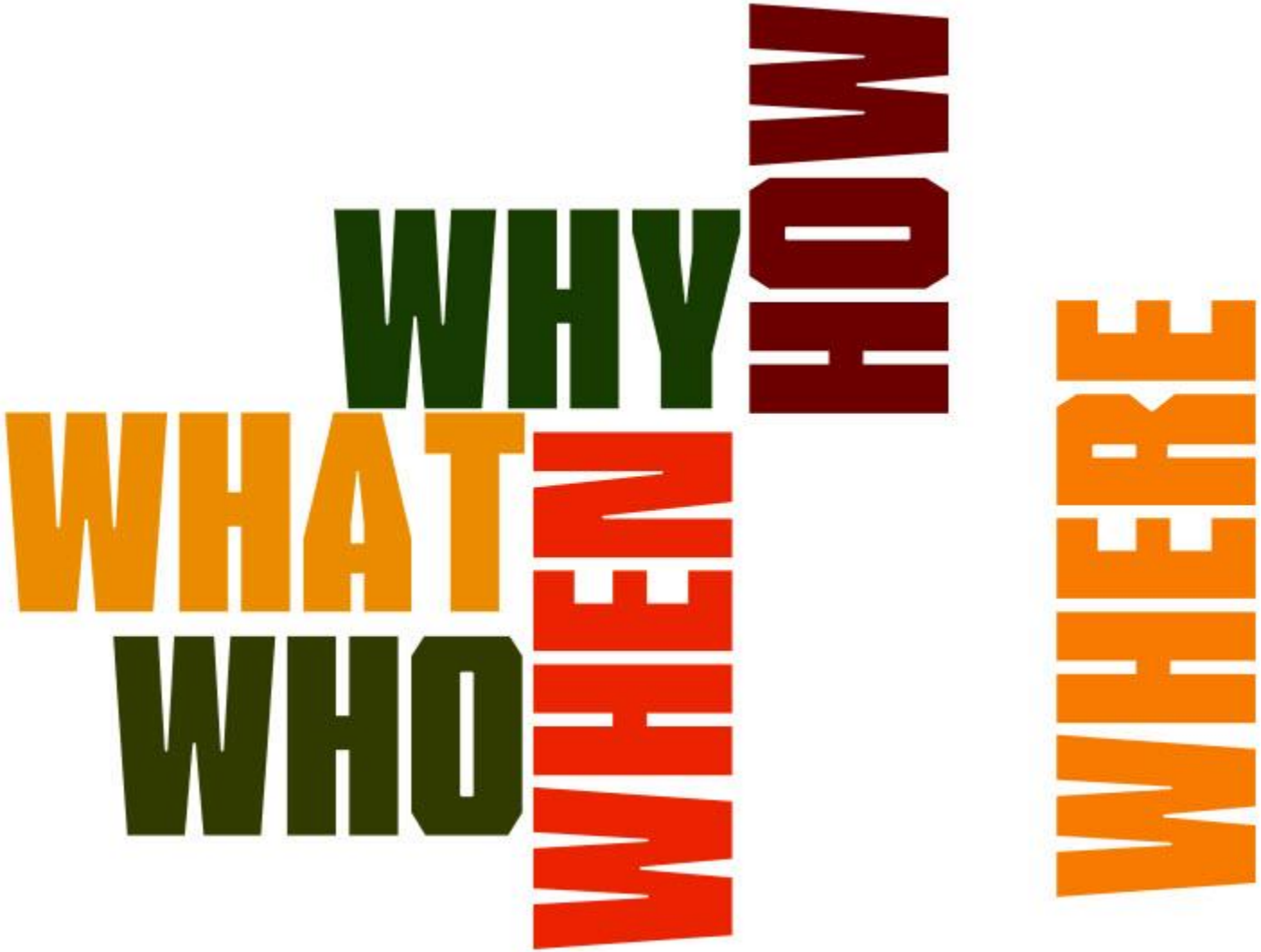
FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Sistema Sanitario Regione Lombardia

Ca. della Mammella: Terapia Medica Fase adiuvante

Serena Di Cosimo
Istituto Nazionale dei Tumori
Milano

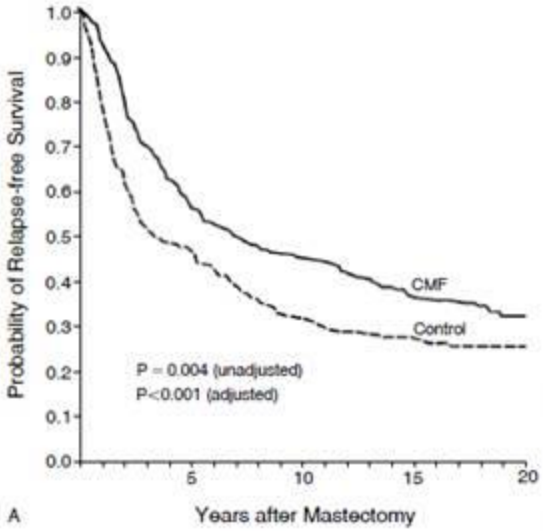
Breast cancer adjuvant therapy



The New England
Journal of Medicine

Volume 294 FEBRUARY 19, 1976 Number 8

COMBINATION CHEMOTHERAPY AS AN ADJUVANT TREATMENT IN OPERABLE BREAST CANCER



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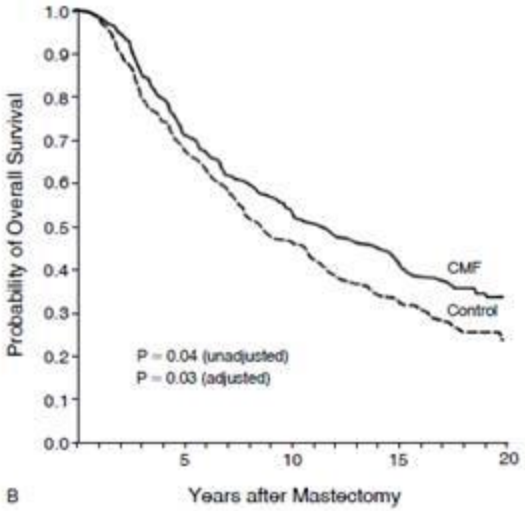
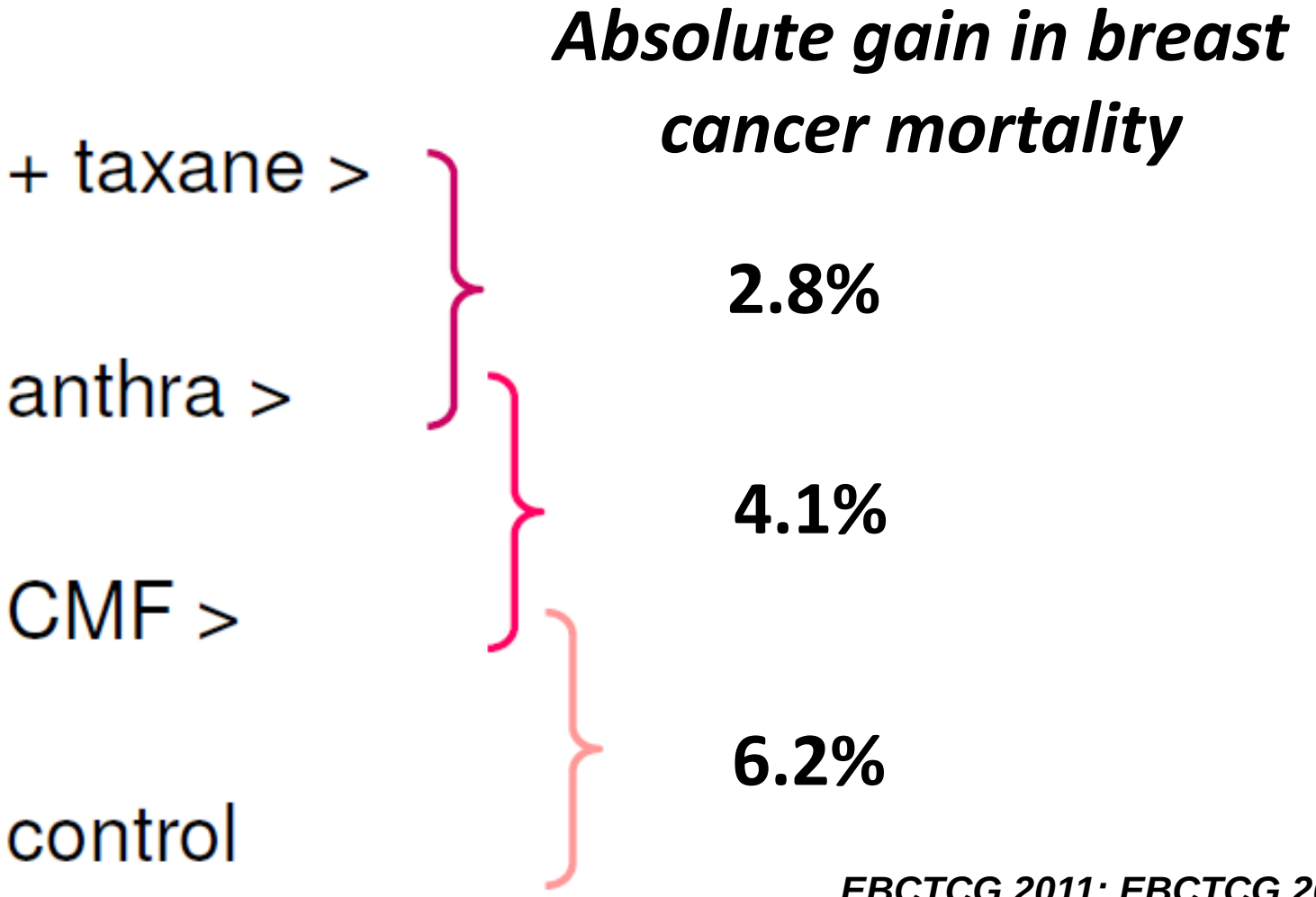


B

Lesson from 30 years of research



EBCTCG 2011; EBCTCG 2012

Pro ors

Is It Time to Redefine Prognostic and Predictive in Oncology?

To the Editor: Ballman[1] recently restated the often-quoted definition of prognostic and predictive oncology biomarkers by writing, "A prognostic biomarker informs about a likely cancer outcome…independent of treatment received," and continues, "A biomarker is predictive if the treatment effect…is different for biomarker-positive patients as compared with biomarker-negative patients."[1(p3968)] Although these terms served a past purpose, they do not work well in today's sophisticated diagnostic and treatment settings.

An examination of titles of articles published in *Journal of Clinical Oncology* in the last two years revealed that the word prognostic appeared 33 times and predictive appeared 10 times (Reference Manager search). This reveals the confusion engendered by these terms; examples of titles include "Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies,"[2] "Prognostic Value of Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancers From Two Phase III Randomized Adjuvant Breast Cancer Trials: ECOG 2197 and ECOG 1199,"[3] and "Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07)."[4] In the first two studies, prognostic could have been replaced with predictive, using the definitions noted previously. The last study used the term predictive in the title but prognostic throughout the text.

It is unlikely that the authors, reviewers, or editors were unaware of the standard definitions of prognostic versus predictive but, rather, were demonstrating a reasonable shift in their use of language. When the terms were first applied, the methodologies for interrogating the nature of a malignant tissue, extent of the disease, and means to deal with the disease were limited to local methods, such as surgery and radiation. However, over the past decades, there have been dramatic improvements in our understanding of malignant disease and its treatment. Although the concepts of prognostic and predictive markers are still relevant, it would be useful to redefine them to include the following three caveats: (1) apply to these patients; (2) receiving this therapy; and (3) at this time. Using these criteria, and in keeping with the usage in the previously cited articles, a prognostic biomarker is a characteristic/measurement that provides information about differences in outcome of a group of patients when treated in a defined manner. A prognostic biomarker is one that is associated with the outcome but may or may not be informative as to the reason for the differential response. A predictive biomarker, in this molecular age of personalized medicine, is one the presence of which is required for the treatment to work. In contrast to the prognostic biomarker, the predictive biomarker almost completely explains response to treatment. The differences are illustrated in the following discussion.

In the myelodysplastic syndromes, patients with del(5q) receiving supportive care alone have a better outcome compared with patients with multiple chromosome abnormalities. Here, the presence of del(5q) is prognostic. Patients with del(5q) also have a greater chance of benefitting from oral lenalidomide.[5] Using the older terminology, del(5q) would be a predictive factor, but using the new terminology, it is a prognostic factor because only an association exists between the chromosome change and response to drug. Similarly, in the third article claiming positron emission tomography scanning to be predictive, the title would be reworded to, "Final Results of a Prospective Evaluation of the Prognostic Value…" because the change in the positron emission tomography scan is associated with the outcome but does not explain it.

To reduce the ambiguity between what is a prognostic or predictive biomarker, the term predictive should be reserved for instances in which the biomarker is the target of the therapy and needs to be present for the treatment response to occur. For example, in chronic myeloid leukemia, the presence of the Bcr-abl transcript/protein predicts a high rate of response to imatinib-mediated tyrosine kinase inhibition.[6] Similarly, in solid tumors, the presence of mutations in *EGFR* and *BRAF* predict the response to drugs, such as gefitinib in lung cancer and vemurafinib in melanoma, respectively.[7,8]

In conclusion, a biomarker should be considered prognostic when its presence or absence is associated with a better or worse outcome in a defined group of patients treated in an identical manner; of note, the prognostic relevance of a marker can change if there is a change in the patient population or treatment. The term predictive biomarker should be reserved for instances in which the marker is the target of the therapeutic agent and must be present for the drug to work.

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Princess Margaret Cancer Centre, Toronto, Canada

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at www.jco.org.

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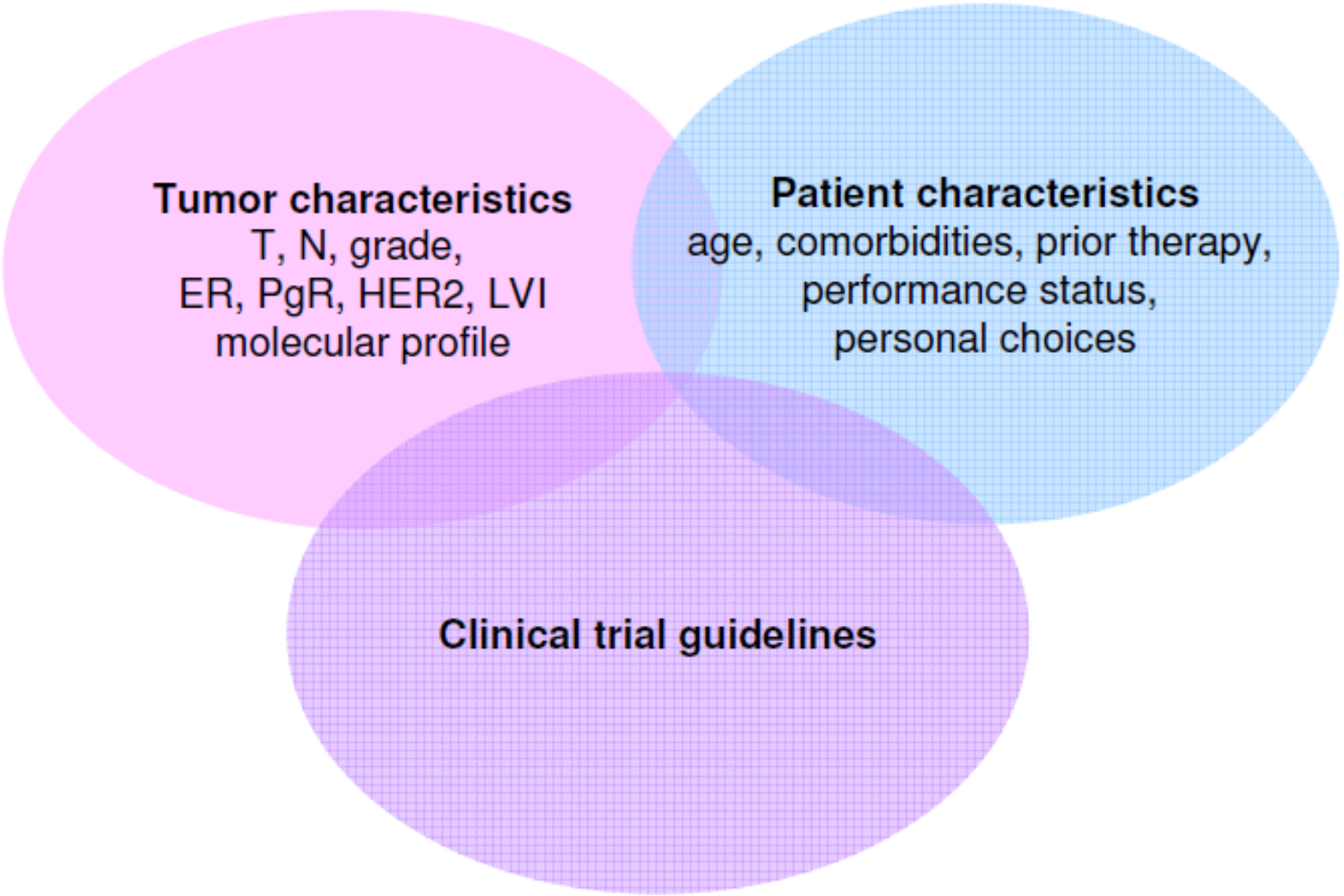
Ada

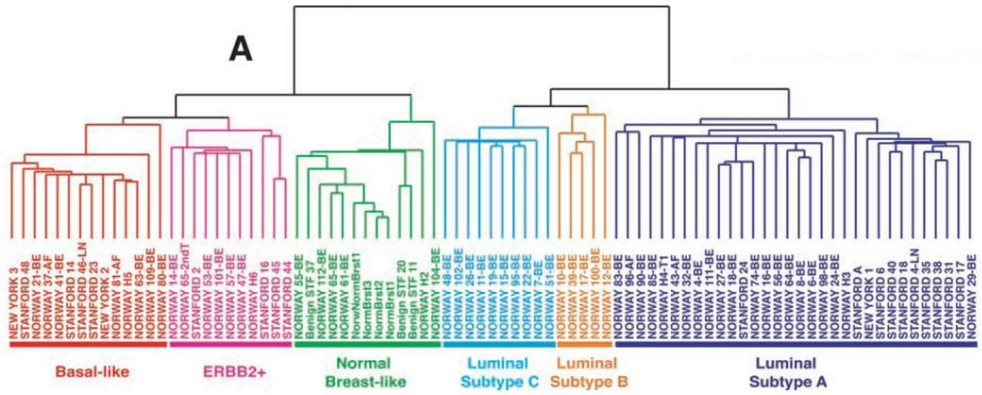
Prognostic fac dent of
therapy, and c rrence.

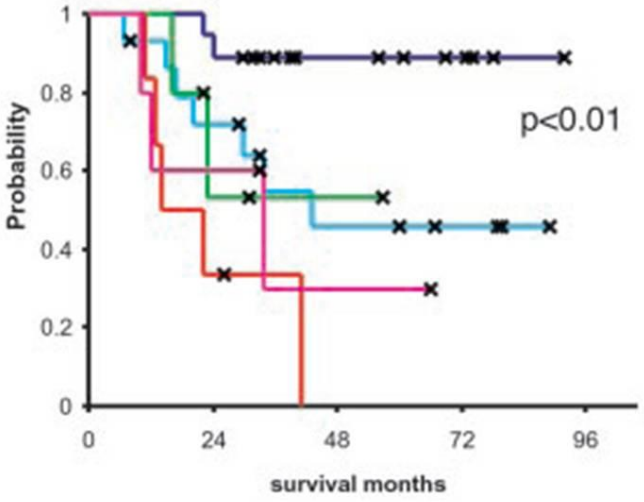
Predictive fac to a given
therapeutic m apy.

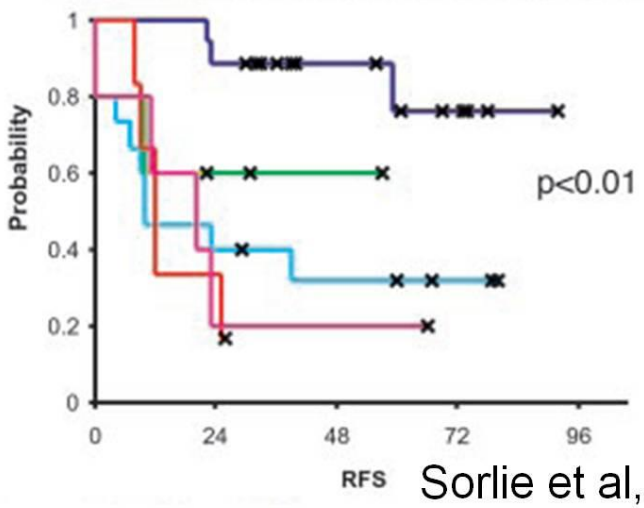
Decision making



PROGNOSTIC SIGNIFICANCE OF 5 INTRINSIC SUBTYPES OF BREAST CANCER







X Censored
Lum A,
NorB-like,
Lum B+C,
ERBB2+
Basal.

Sorlie et al, PNAS 2001

Common commercially available prognostic gene signatures

	MammaPrint	Oncotype DX	Breast Cancer Index	Mapquant DX	PAM 50 ROR	EndoPredict
Provider	Agendia	Genomic Health	Biotheranostics	Ipsogen	NanoString	Sividon
Type of Assay	70-gene assay	21-gene recurrence score	2-gene ratio (H/I) and molecular grade index	Genomic grade	50-gene assay	12-gene assay
Type of Sample	Fresh or frozen or FFPE	FFPE	FFPE	Fresh or frozen or FFPE	FFPE	FFPE
Technique	DNA microarray or qRT-PCR	qRT-PCR	qRT-PCR	DNA microarray or qRT-PCR	qRT-PCR	qRT-PCR
Clinical Application	Prognosis of N0, $<$ 5 cm, stage I/II, age $<$ 61	Prediction of recurrence risk in ER+ and N0 treated with TAM	Prognostic in ER+, prediction of response to TAM	Molecular grading for ER+, histologic grade II disease	Originally for intrinsic subtyping, recurrence prediction	Recurrence prediction for ER+ HER2–
Results Presentation	Dichotomous, good or poor prognosis	Continuous variable	Continuous variable	Dichotomous, GGI I or GGI III	Continuous variable	Dichotomous, low or high risk
Level of Evidence	II	I	III	III	I	I
FDA Approval	YES	NO	NO	NO	YES	NO

Abbreviations: ER+, estrogen receptor–positive; FDA, U.S. Food and Drug Administration; FFPE, formalin-fixed, paraffin-embedded; GGI, Genomic Grade Index; qRT-PCR, quantitative reverse transcription polymerase chain reaction; TAM, tamoxifen.

Oncotype Dx or RS assay for patients with ER+, LN- disease:

- 16 cancer and 5 reference genes from 3 studies:

PROLIFERATION	ESTROGEN	INVASION	HER-2	OTHER	REFERENCE
- Ki-67	- ER	- Stremolysin 3	- GRB-7	- GSTM1	- Beta-actin
- STK-15	- PR	- Cathepsin L2	- HER-2	- BAG-1	- GAPDH
- Survivin	- BCL-2			-CD-68	- RPLPO
- Cyclin B1	- SCUBE-2				- GUS
- MYBL2					- TFRC

A

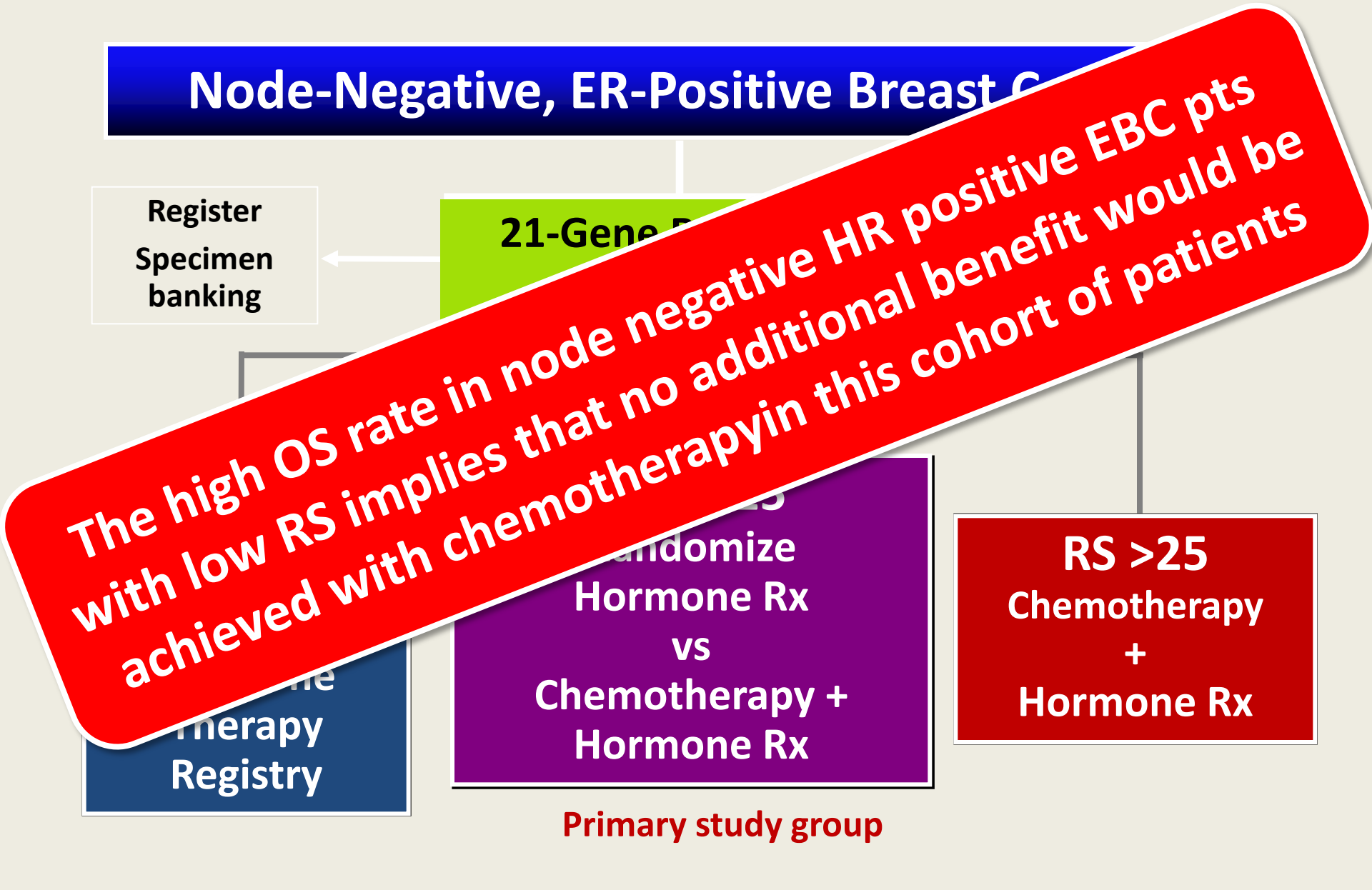
Recurrence Score =

+ 0.47 x HER-2 Group Score
- 0.35 x ER-2 Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD-68
-0.08 x GSTM1
- 0.07 x BAG-1

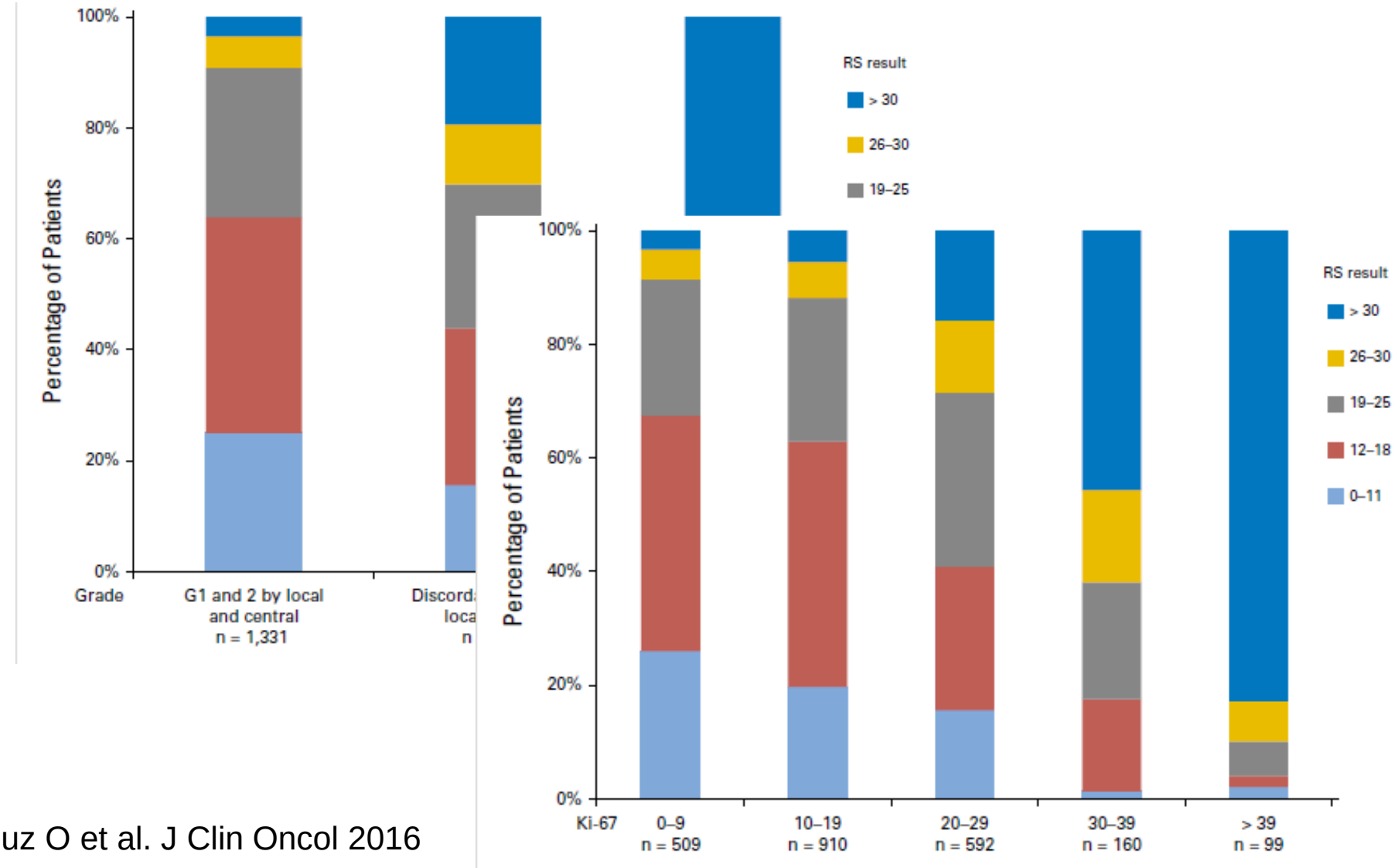
B

Category	RS 0-100
Low risk	RS <18
Intermediate risk	RS ≥18 to ≤31
High risk	RS ≥ 31

NCI Cooperative Groups TAILORx



Recurrence Score distribution by grade and by Ki-67



Gluz O et al. J Clin Oncol 2016

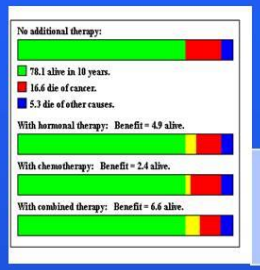
Utility of OncotypeDx (in the presence of a dedicated path)

It has been argued that RS can be supplanted by improvements in pathologic grading and quantitative hormone receptor scoring.

However, the PlanB study suggests that this may not be true. Even with central laboratory grading, **6 percent of high-grade tumors had a low RS** and **5 percent of low Ki67 tumors had a high RS**.

Further, the reproducibility of grade as well as measures of proliferation such as immunohistochemistry analysis of Ki67, is poor between central and local laboratories.

MINDACT TRIAL DESIGN

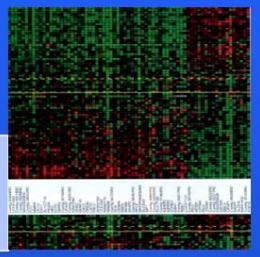


Registration & Screening
Surgery

N= 6600

Clinical-Pathological (C) risk
(Adjuvant! Online)

Genomic (G) risk
(70-gene signature)



C-high/ G-high

Discordant cases
C-high/G-low or C-low/G-high

C-low/G-low

1st randomization to treatment
use Clinical vs. Genomic risk

Chemotherapy

2nd randomization
Anthracycline –based vs. Capecitabine-Docetaxel

No Chemotherapy

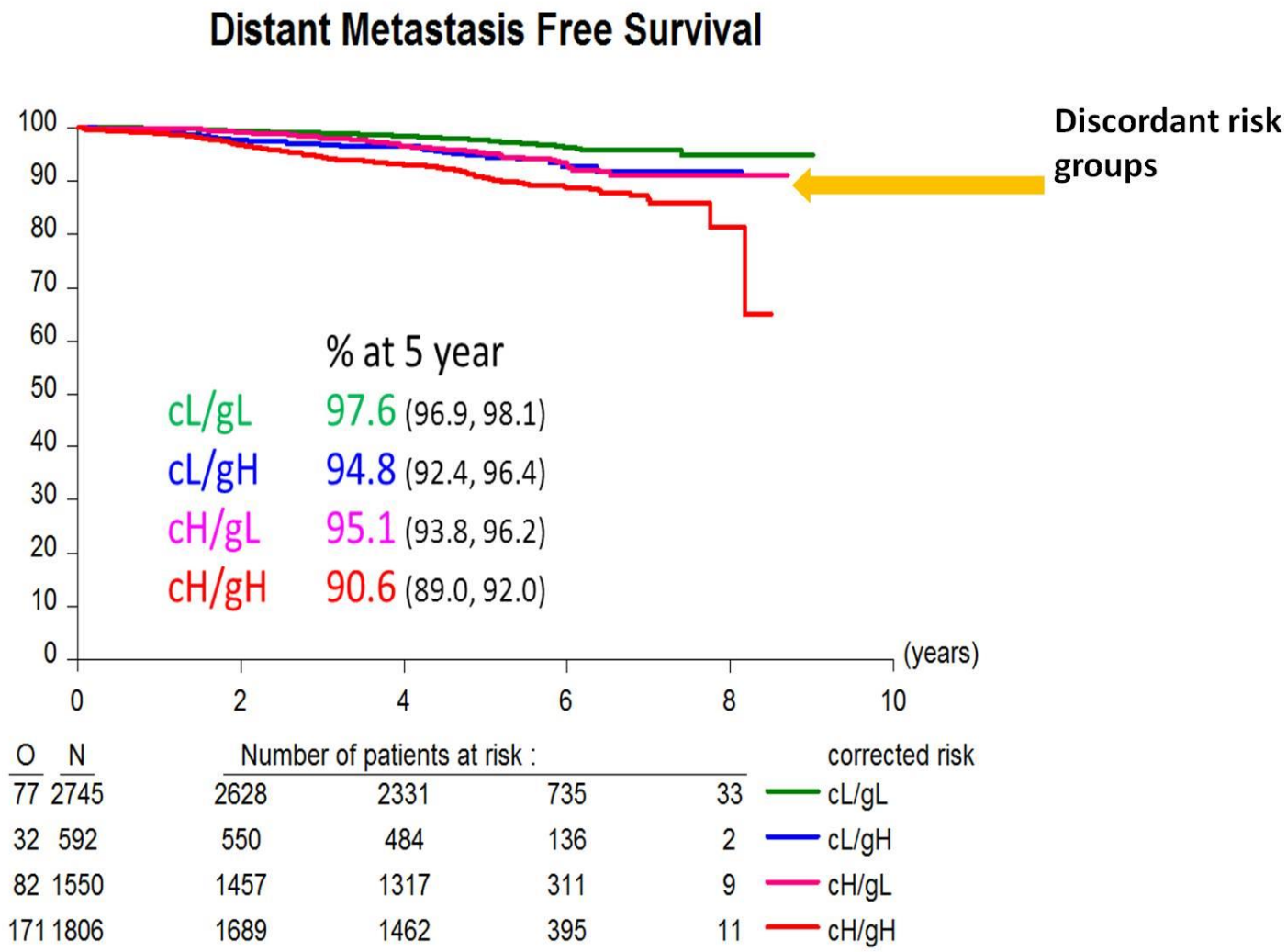
HR+

Endocrine therapy

HR+

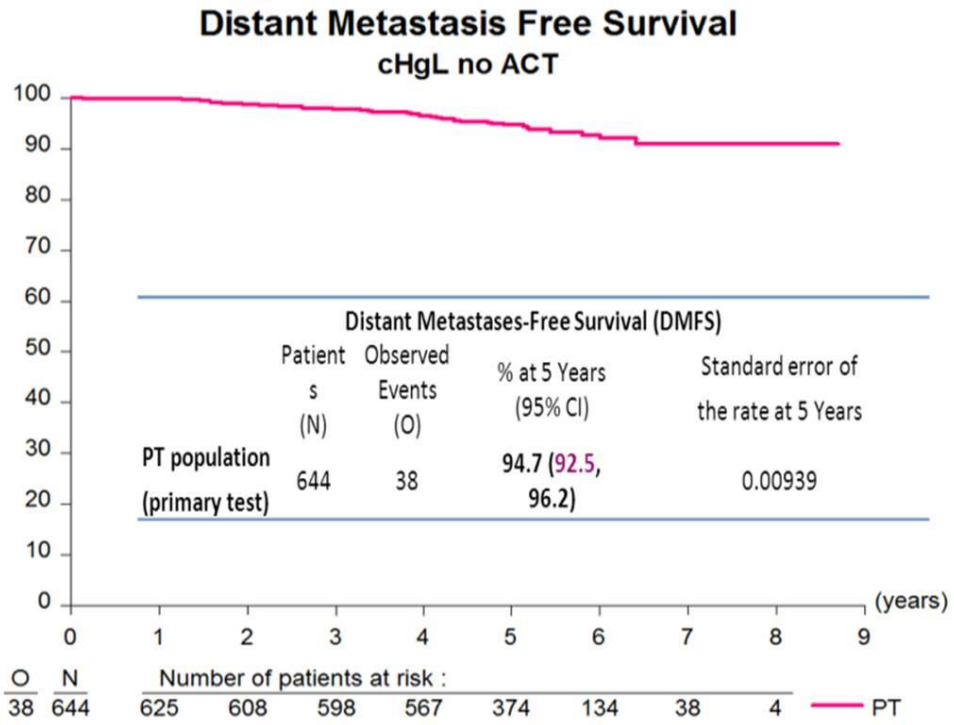
3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

MINDACT population at 5y median follow-up
DMFS IN ALL 4 RISK GROUPS



MINDACT population at 5y median follow-up
DISCORDANT RISK GROUPS: PRIMARY TEST

The primary statistical test
(DMFS at 5Y)

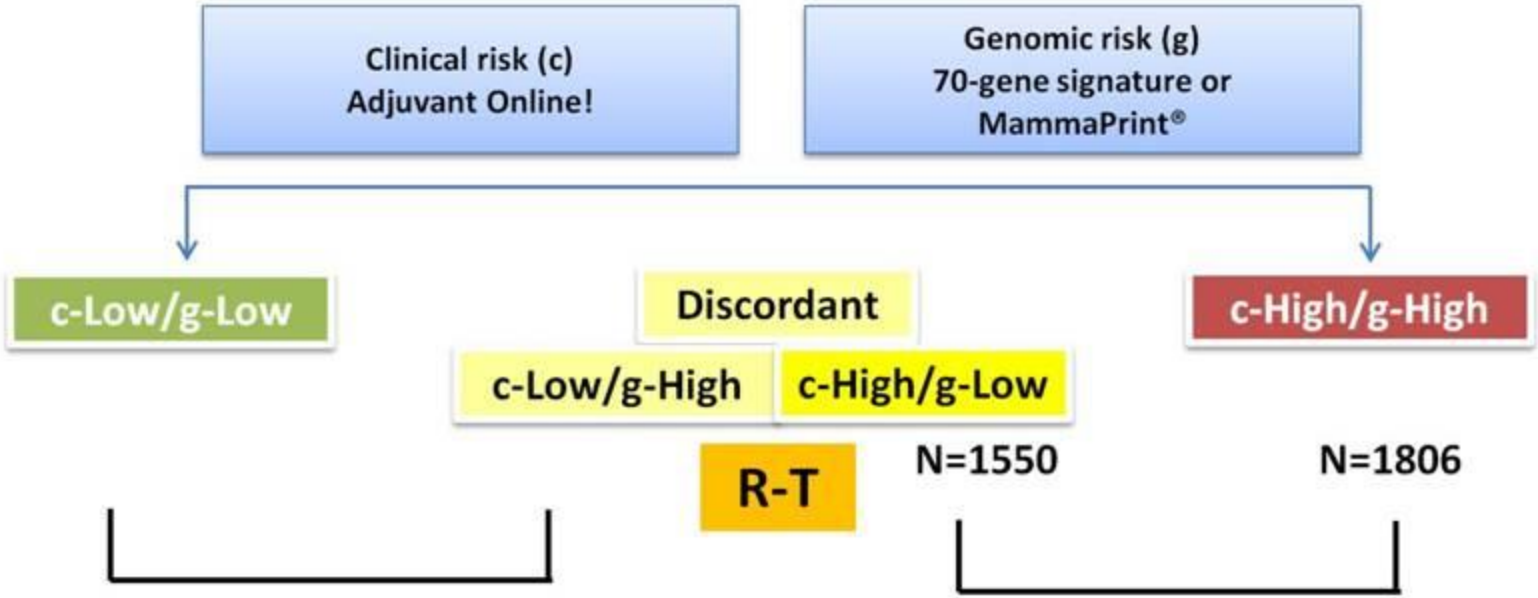


Null Hypothesis: set at 92%

Observed 5Y DMFS = 94.7%

95% CI ≈ 92.5 – 96.2% excludes 92% !!!

Proposed future clinical use of MammaPrint®



Presented By Fatima Cardoso at 2016 ASCO Annual Meeting

- Mindact results provide level 1A evidence of the clinical utility of MammaPrint® for assessing the lack of a clinically relevant chemotherapy benefit in the clinically high risk (c-High) population.
- c-High/g-Low patients, including 48% Node positive, had a 5-year DMFS rate in excess of 94%, whether randomized to adjuvant CT or no CT.
- In the entire MINDACT population, the trial confirmed the hypothesis that the « genomic » strategy leads to a 14% reduction in CT prescription versus the « clinical » strategy.
- Among the c-High risk patients, the clinical use of MammaPrint® is associated with a 46% reduction in chemotherapy prescription.

Considerations for the future

Disseminated tumor cells (DTC) on BMA assessment	Prognostic in EBC Marker of recurrence
Circulating tumor cells (CTC)	Poor survival after NACT or primary breast cancer surgery
cf-DNA (cell free-DNA) Plasma miRNA	Markers of relapse in EBC

Grazie

EBCTCG 2011

Compared with no treatment, the use of anthracycline-containing regimen was associated with the following outcomes at 10 years:

Risk of recurrence	Significant improvement	RR 0.73	Absolute gain of 8%
Breast cancer mortality	Significant reduction	RR 0.79	Absolute gain of 6.5%
Overall mortality	Significant reduction	RR 0.84	Absolute gain of 5%

Compared with no treatment, the use of CMF was associated with these outcomes at 10 years:

Risk of recurrence	Significant improvement	RR 0.7	Absolute gain of 10.2%
Breast cancer mortality	Significant reduction	RR 0.76	Absolute gain of 6.2%
Overall mortality	Significant reduction	RR 0.84	Absolute gain of 4.7%

Anthracycline-based therapy vs. CMF

The use of "standard" doses of anthracyclines was associated with the following outcomes at 10 years compared with CMF (n=5122 women)

No improvement in the risk of recurrence (RR 0.99)
No improvement in breast cancer mortality (RR 0.98)
No improvement in overall mortality (RR 0.97)

The use of higher cumulative doses of anthracyclines (> 4 cycles, to cumulative dose of >240 mg/m^2) compared with CMF was associated with the following outcomes at 10 years (n=9572)

Reduction in risk of recurrence	RR 0.89	Absolute gain of 2.6%
Reduction in breast cancer mortality	RR 0.80	Absolute gain of 4.1%
Reduction of overall mortality	RR 0.84	Absolute gain of 3.9%

EBCTCG 2012 meta-analysis

Trials where the same control regimen was used in both arms (n=11,167 women) (8 year outcome):

Reduction in risk of recurrence	RR 0.84	Absolute gain of 4.6% in RFS
Reduction in breast cancer mortality	RR 0.86	2.8% improvement in breast cancer-specific OS
Reduction in overall mortality	RR 0.86	3.2% improvement in OS

Trials where the number of cycles in the control anthracycline regimen was doubled to mirror the addition of cycles of taxanes to anthracyclines (n=33,084) (5 year outcome):

Reduction in risk of recurrence	RR 0.86	Absolute gain of 2.9%
Reduction in breast cancer mortality	RR 0.88	Absolute improvement of 1.4%
Reduction in overall mortality	RR 0.9	Absolute improvement of 1.2%

Adjuvant treatment and survival improvement over the past 40 years