SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ADDARII
ONCOLOGIA MEDICA
S.ORSOLA-MALPIGHI BOLOGNA

mamazone
Frauen und Forschung gegen Brustkrebs EO
Donne e ricerca contro il tumore al seno ODV

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PROJEKT DIPLOMPATIENTIN

14ª Conferenza sul tumore al seno DIPLOMPATIENTIN®
„Paziente diplomata“ - un seminario per donne con e senza tumore al seno
Sabato, 16 ottobre 2021, ore 9.00 - 14.00
EURAC - Viale Druso 1, Bolzano

Studio PONS – KRONOS
Stato di avanzamento

Claudio Zamagni
Direttore Oncologia Medica Addarii
Policlinico S. Orsola-Malpighi
Bologna

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2014 Augsburg presentation

PONS-Nachsorgestudie – Wiedergutmachung einer alten italienischen Sünde

KRONOS PONS-Study Italy- Making up for an old Italian fault

KRONOS PONS-S Italy

Submission to Ethical Committee: June 19, 2014

Ethical Committee Approval : August 1, 2014

S.Orsola-Malpighi Director Authorization: August 13, 2014

Study activation: Oct 21, 2014

First pt enrolled October 23, 2014

C. Zamagni Augsburg Oct, 2014

The Fault

Impact of Follow-up Testing on Survival and Health-Related Quality of Life in Breast Cancer Patients

A Multicenter Randomized Controlled Trial

The GIVIO Investigators

(*JAMA*. 1994;271:1587-1592)

Intensive Diagnostic Follow-up After Treatment of Primary Breast Cancer

A Randomized Trial

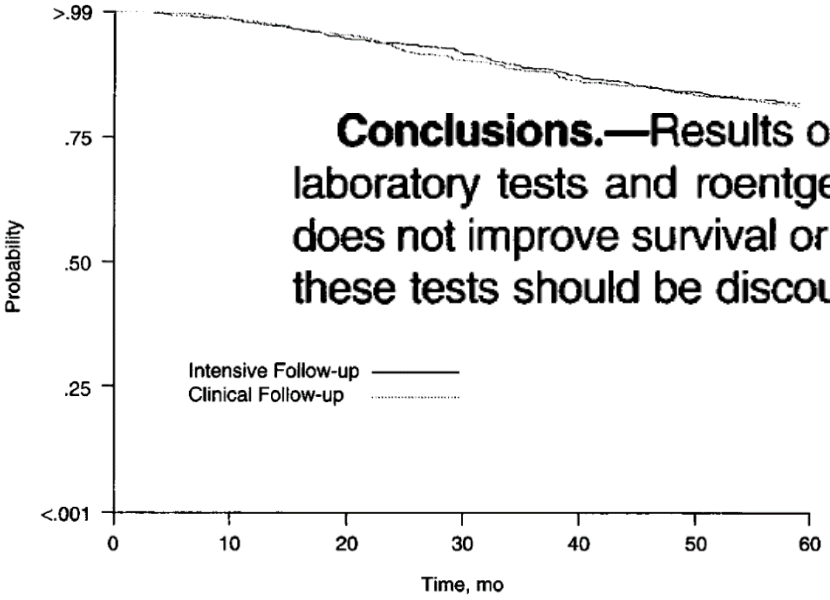
Marco Rosselli Del Turco, MD; Domenico Palli, MD; Angelo Cariddi, MD; Stefano Ciatto, MD; Paolo Pacini, MD; Vito Distante, MD; for the National Research Council Project on Breast Cancer Follow-up

(*JAMA*. 1994;271:1593-1597)

Old Follow-up Italian Randomized Trials

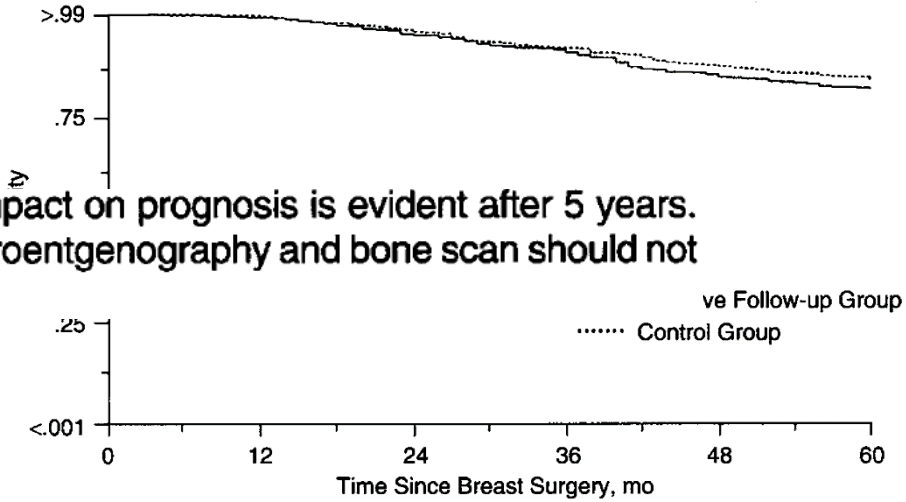
Control Arm (5 y) (both studies)	Physical Examination q3 mo.s y 1-2; q 6 mo.s y 3-5 Mammox q 12 mo.s
Experimental Arm (5 y) FONCaM **1985-1986**	As control arm + Chest x-Ray and Bone scan q 6 mo.s
Experimental Arm (5 y) GIVIO **1986-1988**	As control arm + Chest x-Ray q 6 mo.s Liver US and Bone scan q 12 mo.s Blood tests* q3 mo.s y 1-2 and q 6mo.s y 3-5 (*Alkaline Phosphatase and γ glutamyltranspeptidase)

Primary End-Point Overall Survival at 5 y in Both Trials



Conclusions.—Results of this trial support the view that a protocol of frequent laboratory tests and roentgenography after primary treatment for breast cancer does not improve survival or influence health-related quality of life. Routine use of these tests should be discouraged.

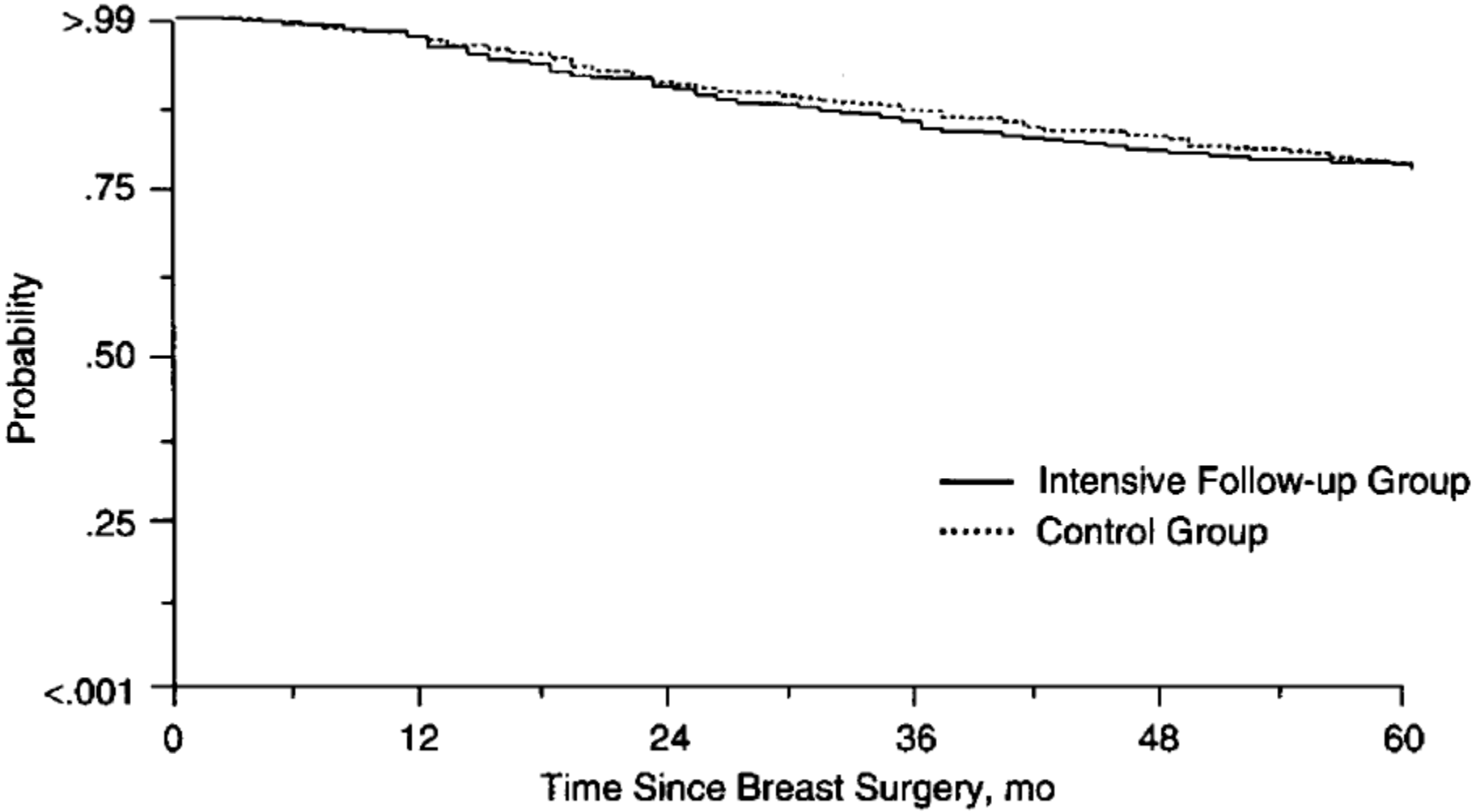
The GIVIO Investigators JAMA, 1994



l no impact on prognosis is evident after 5 years. Periodic intensive follow-up with chest roentgenography and bone scan should not be recommended as a routine policy.

Rosselli del Turco M et awl JAMA, 1994

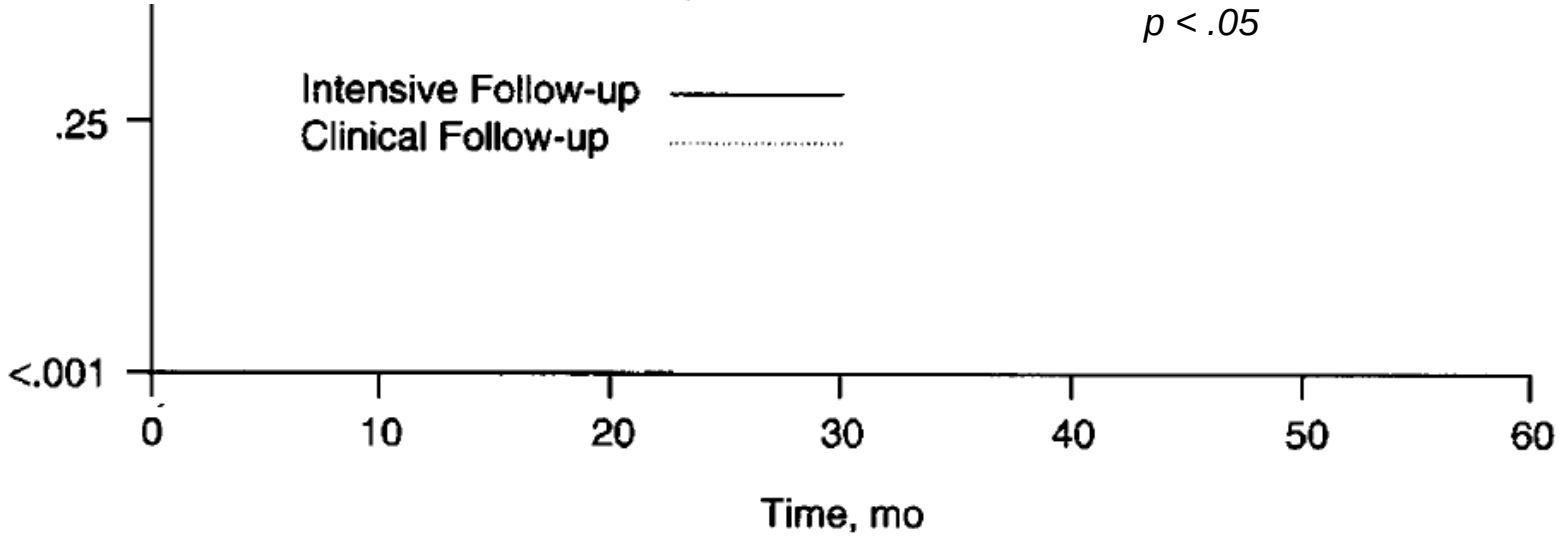
Time to Distant Metastasis by Follow-up Regimen



The GIVIO Investigators JAMA, 1994

Distant Relapse-free Survival by Randomization group

Conclusions.—Periodic chest roentgenography and bone scan allow earlier detection of distant metastases, but anticipated diagnosis appears to be the only effect of intensive follow-up, and no impact on prognosis is evident after 5 years. Periodic intensive follow-up with chest roentgenography and bone scan should not be recommended as a routine policy.



Rosselli del Turco et al. JAMA 1994

Follow-up strategies for women treated for early breast cancer (Review)

Rojas MPMP, Telaro E, Moschetti I, Coe L, Fossati R, Liberati A, Rosselli MDT

THE COCHRANE COLLABORATION®

Authors' conclusions

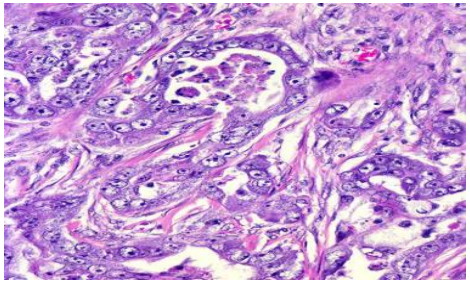
This updated review of RCTs conducted almost 20 years ago suggest that follow-up programs based on regular physical examinations and yearly mammography alone are as effective as more intensive approaches based on regular performance of laboratory and instrumental tests in terms of timeliness of recurrence detection, overall survival and quality of life.

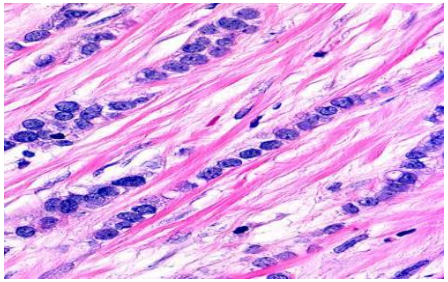
2012 The Cochrane Collaboration

Asymptomatic Breast Cancer Patients Follow-up Guidelines in 2017 (23 years after the publication of the Italian Follow-up Trials)

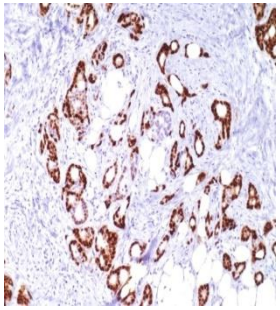
	Visit /PE	Mammography	Other imaging and serum tumor markers
ESMO	Every 3-6 mo.s (y 1-3) *6-12 mo.s (y 4-5 y)* *then annualy*	12 mo.s	no
ASCO	Every 3-6 mo.s (y 1-3) *6-12 mo.s (y 4-5 y)* *then annualy*	12 mo.s	no
NCCN	Every 4-6 mo.s (y 1-5) then annualy	12 mo.s	no
AIOM	Every 3-6 mo.s (y 1-5) then annualy	12 mo.s	no

Breast Cancer Classification in the 2 Old Italian Trials





invasive carcinoma

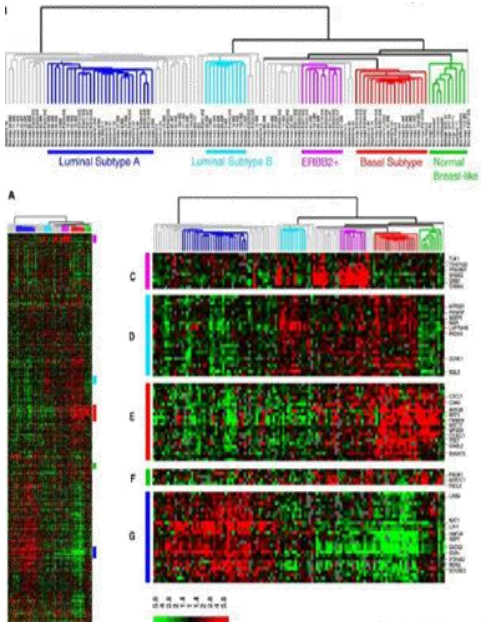


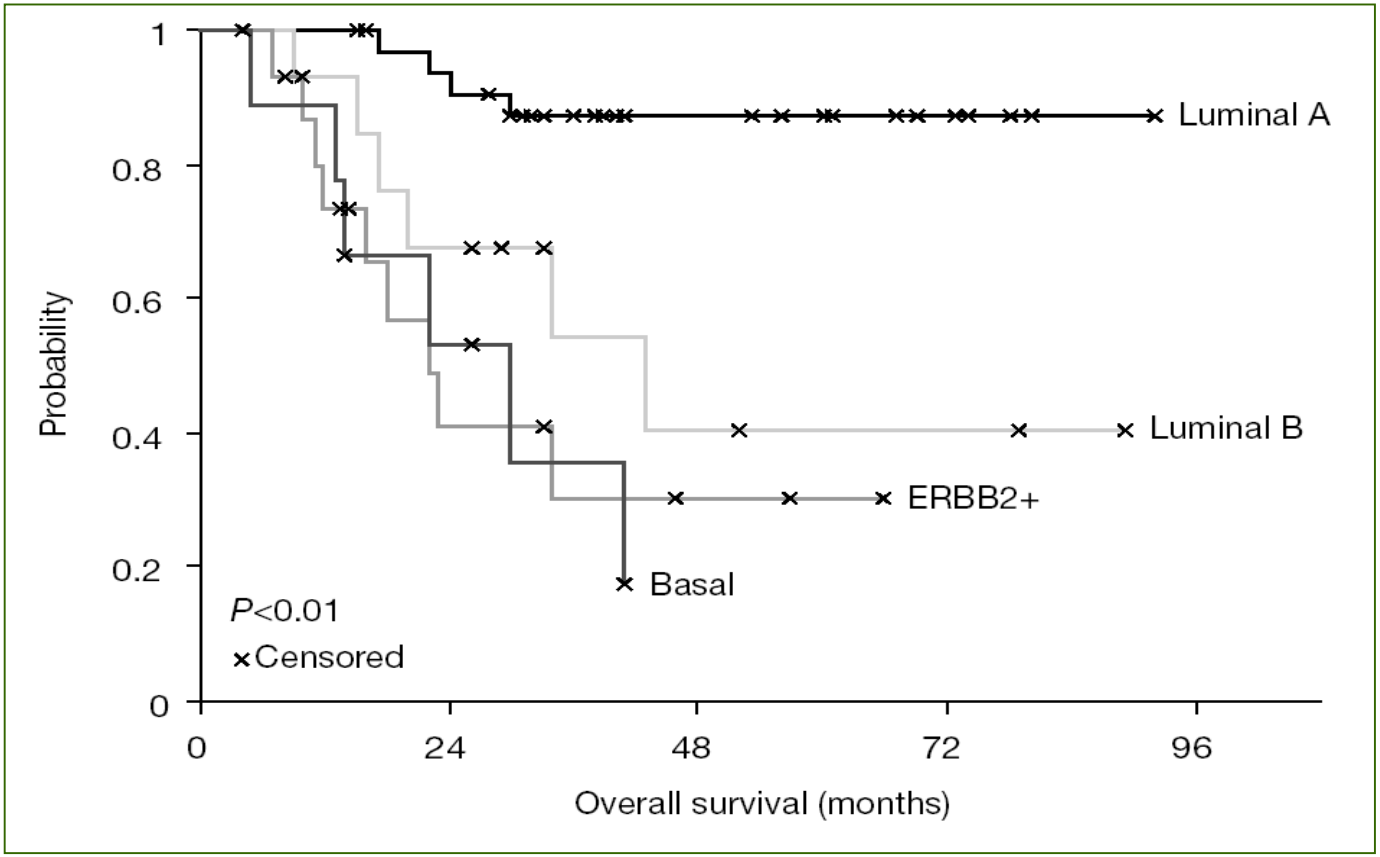
ER

In GIVIO Trial only
(and Unknown in 22%)

Breast Cancer Classification

"Breast Tumor Intrinsic" Subtype Classification



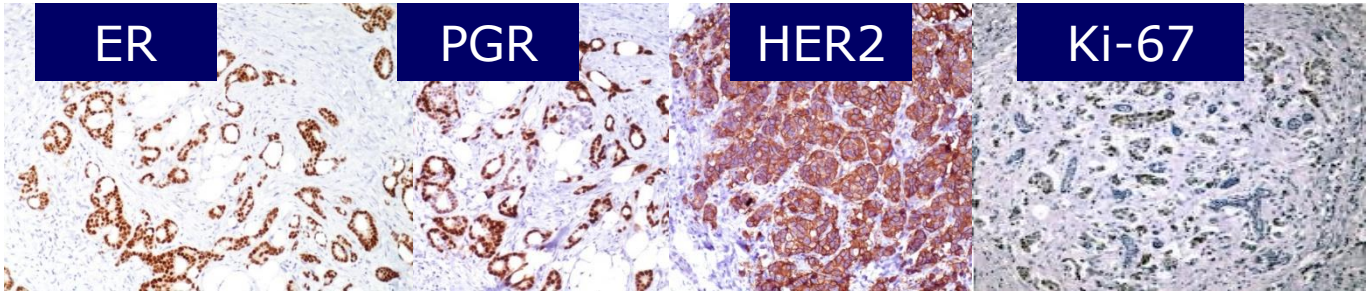


1. Luminal A
2. Luminal B
3. Normal breast-like
4. HER2
5. Basal-like

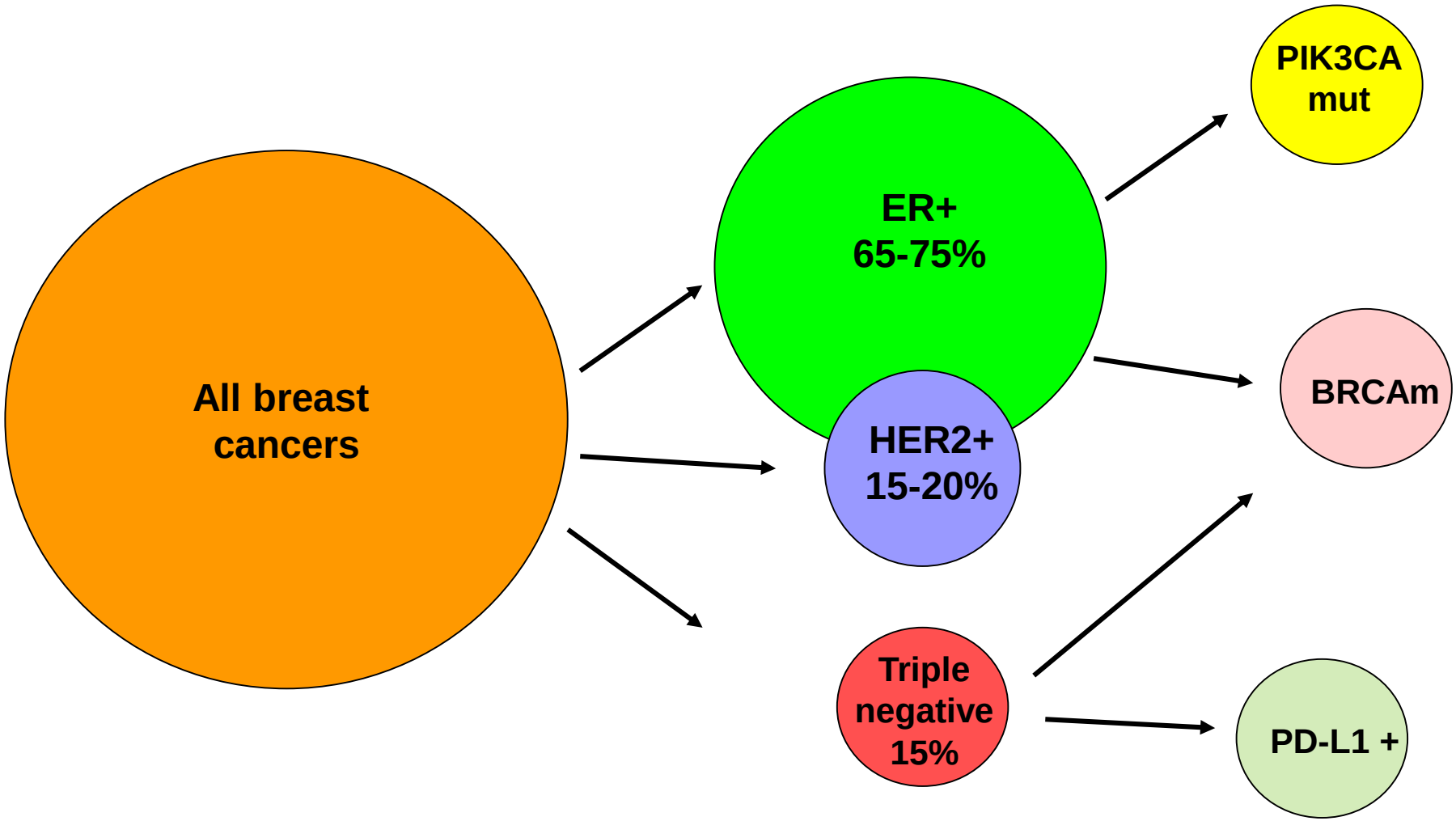
Sorlie T et al. Proc Natl Acad Sci USA 2001
Sorlie T,et al. Proc Natl Acad Sci USA 2003
Sotiriou C et al. Proc Natl Acad Sci USA 2003
Hu Z et al. BMC Genom 2006

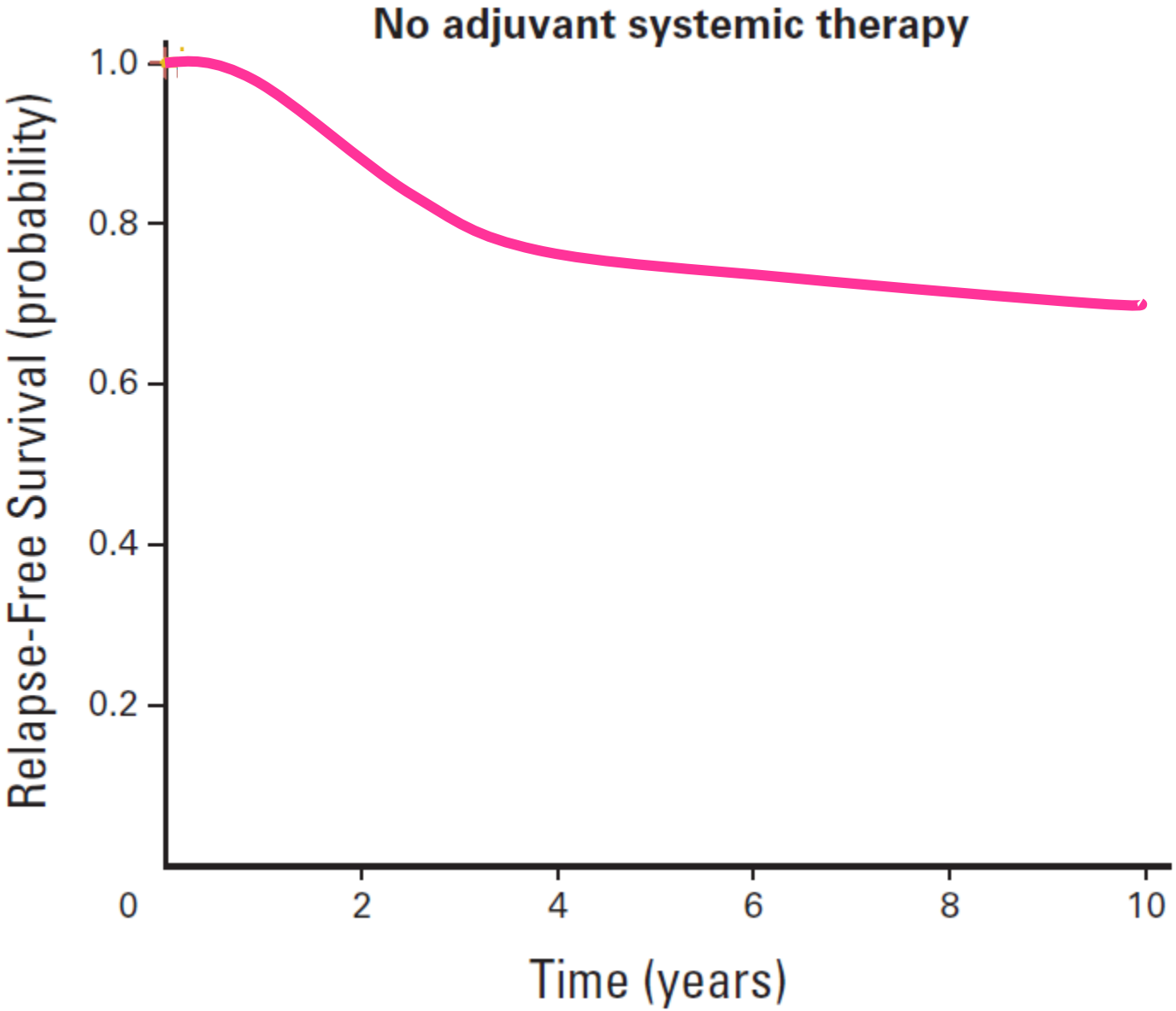
Breast Cancer Classification

Molecular subtype «like»	ER	PgR	HER2	Ki67
Luminal A	+	+	-	Low
Luminal B	+	+/-	-	High
Luminal/HER2	+	+/-	+	any
HER2 «enriched»	-	-	+	any
Triple Negative	-	-	-	any



Breast cancer subtypes ready for clinical decision-making



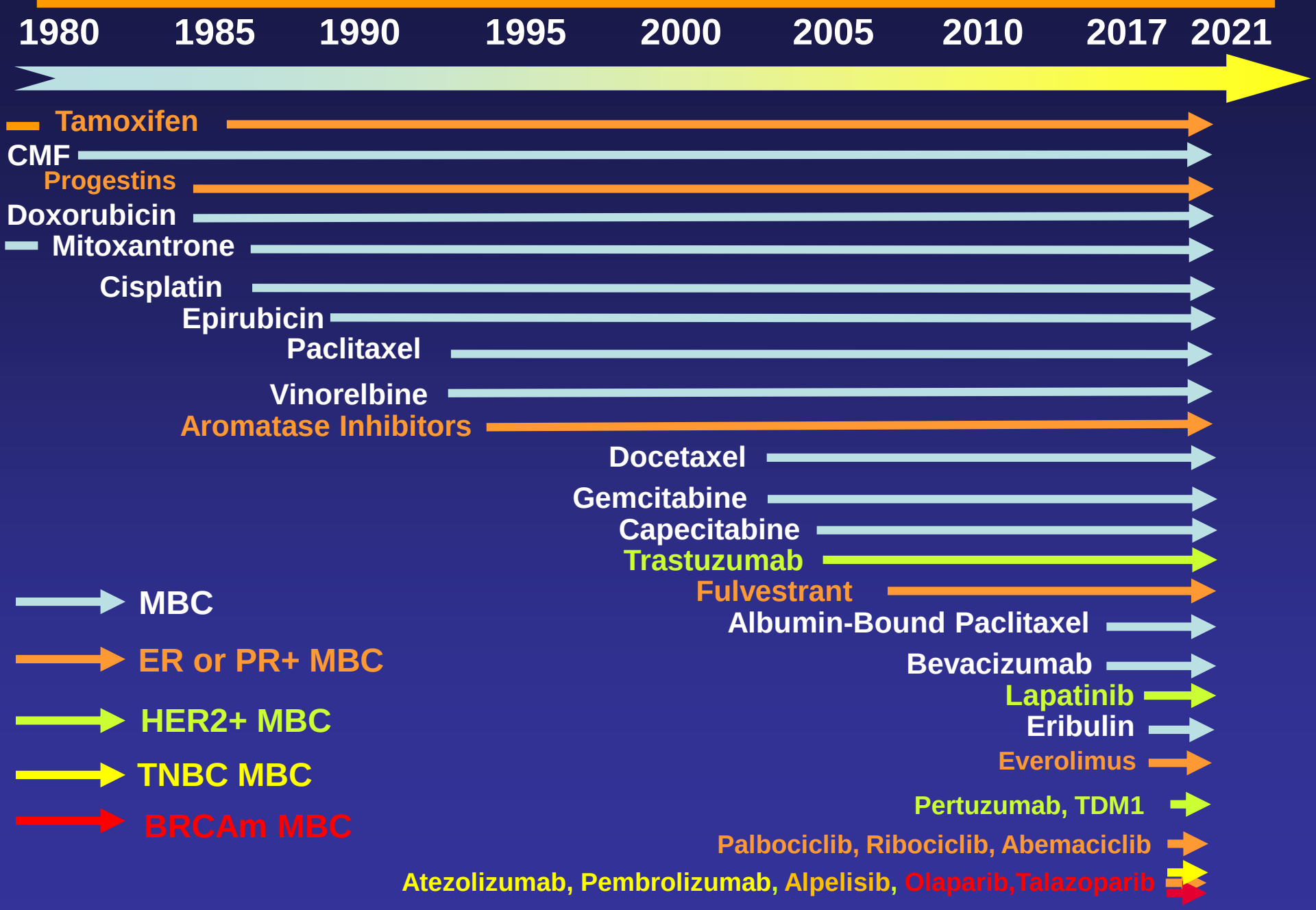

No adjuvant systemic therapy
Relapse-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
10
Time (years)

Progress in Systemic Treatment of MBC

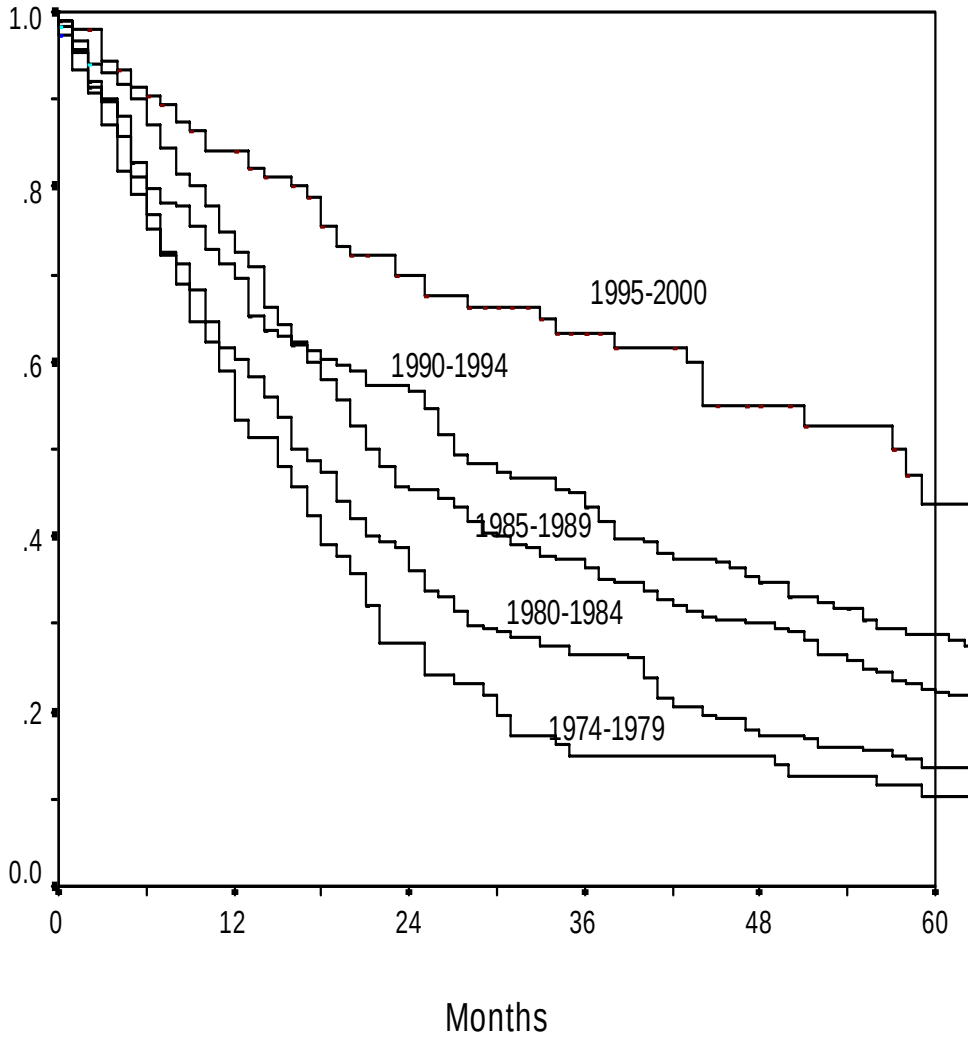
MBC

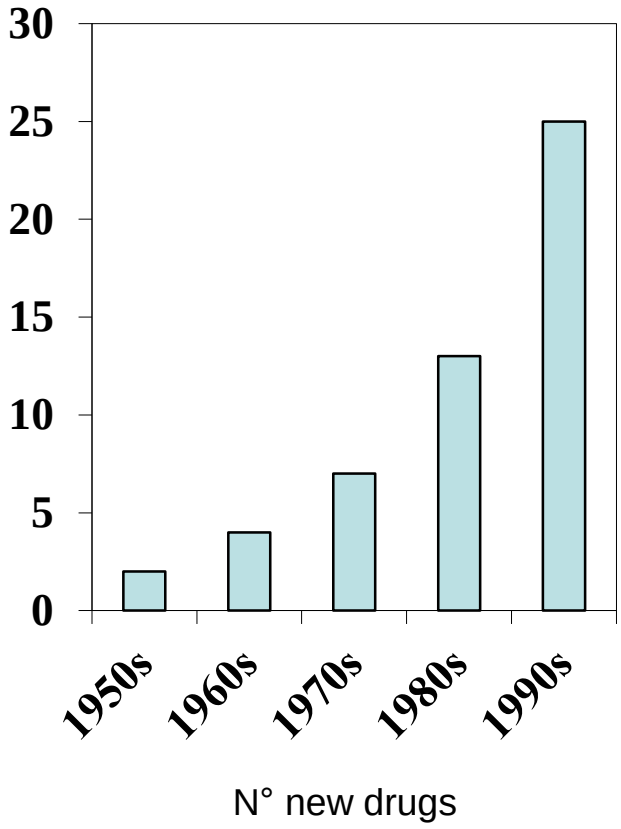
ER or PR+ MBC

Progress in Systemic Treatment of MBC



Survival of Patients with Metastatic Breast Cancer 1974 - 2000

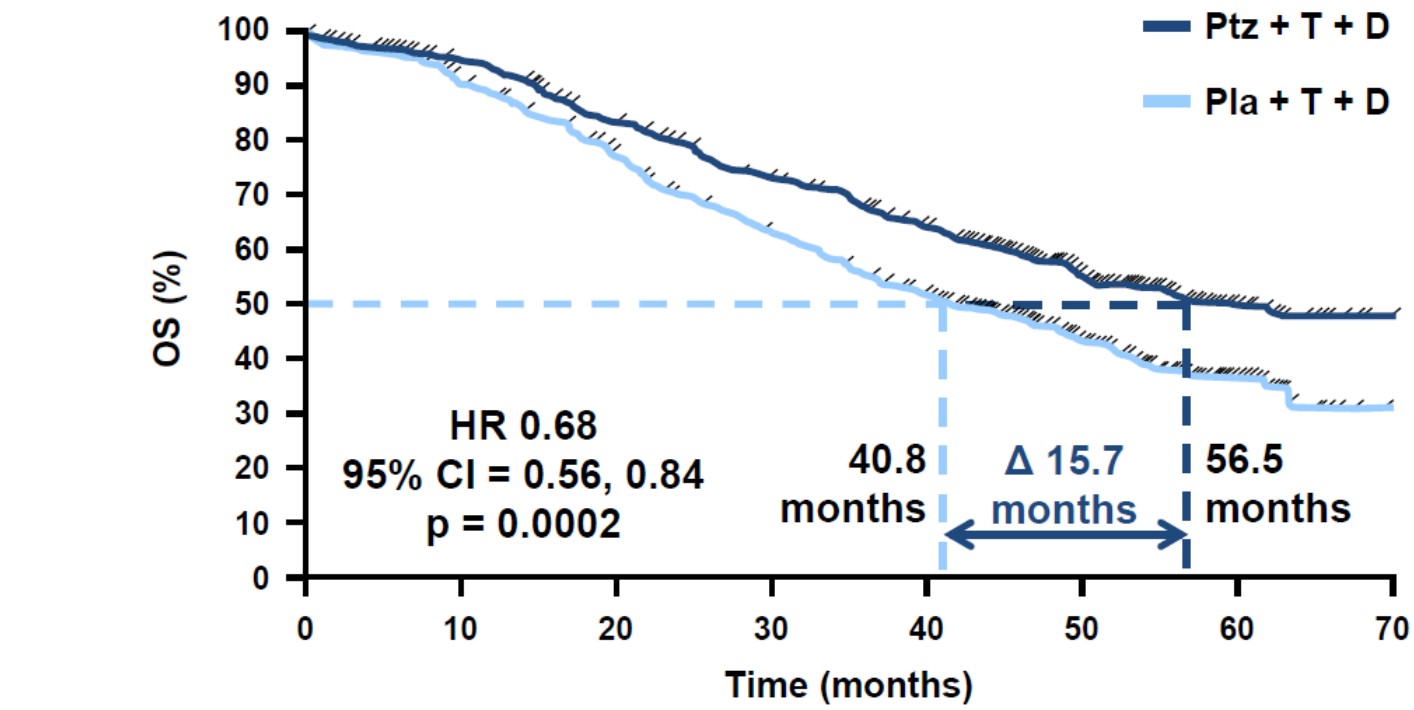




Giordano SH, et al, *Cancer* 100:44-52, 2004

Final OS Analysis

Median follow-up 50 months (range 0–70 months)

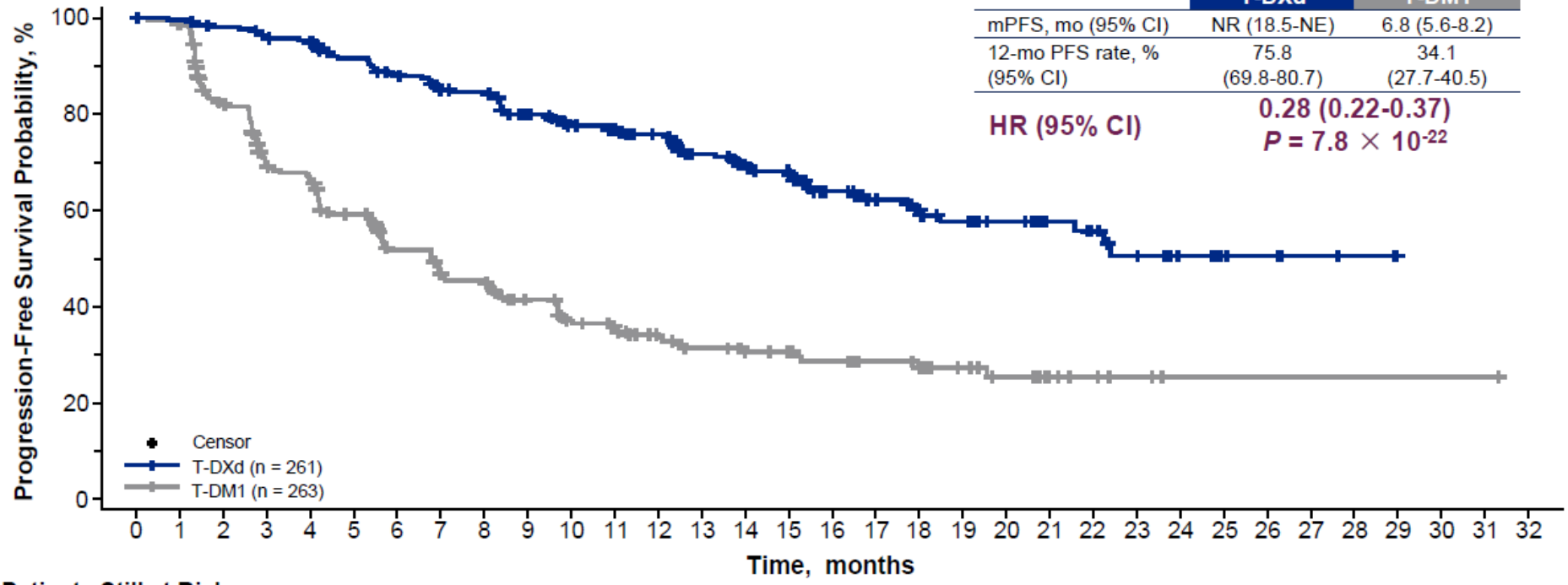


ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain S, ESMO 2014

DESTINY-Breast03

Primary Endpoint: PFS by BICR

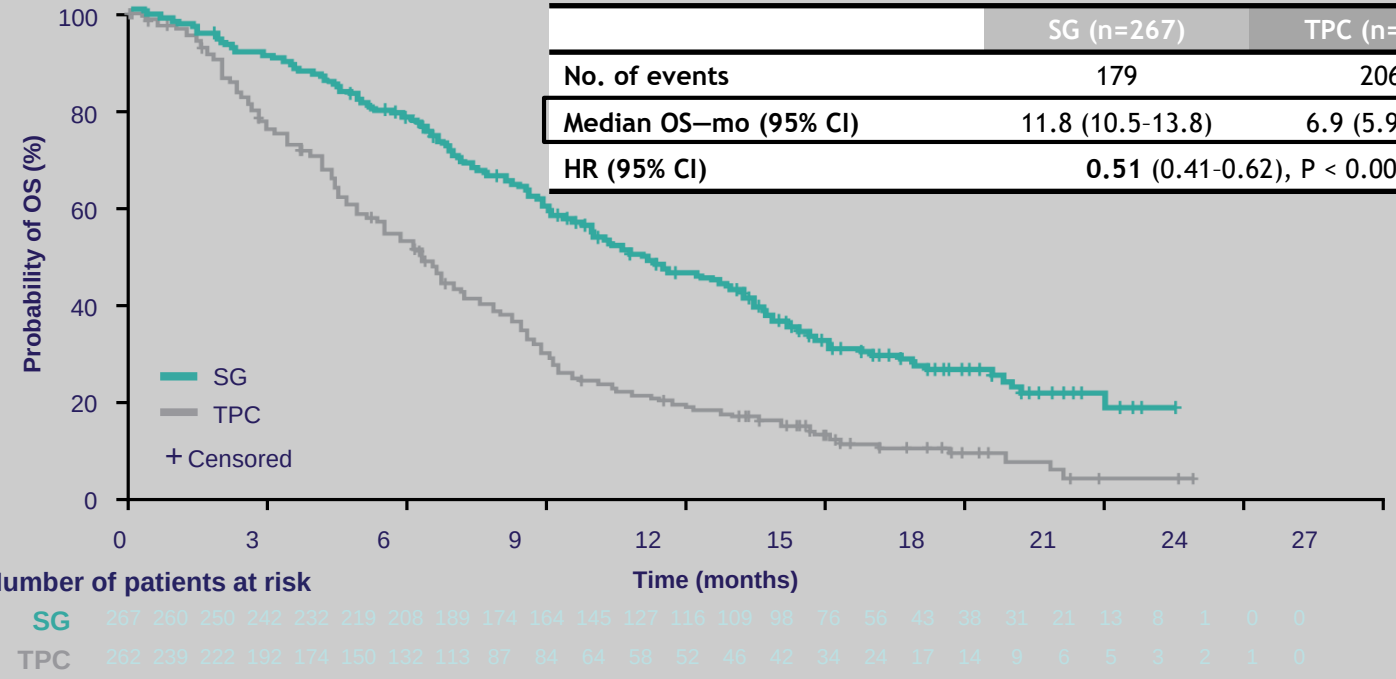


	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0	
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

ASCENT: Overall Survival (Full Population)[1]



	SG (n=267)	TPC (n=262)
No. of events	179	206
Median OS—mo (95% CI)	11.8 (10.5-13.8)	6.9 (5.9-7.7)
HR (95% CI)	**0.51** (0.41-0.62), P < 0.001	

SG demonstrated a significant OS benefit as compared with chemotherapy (TPC) in the full trial population of patients (with and without brain metastasis).[1]

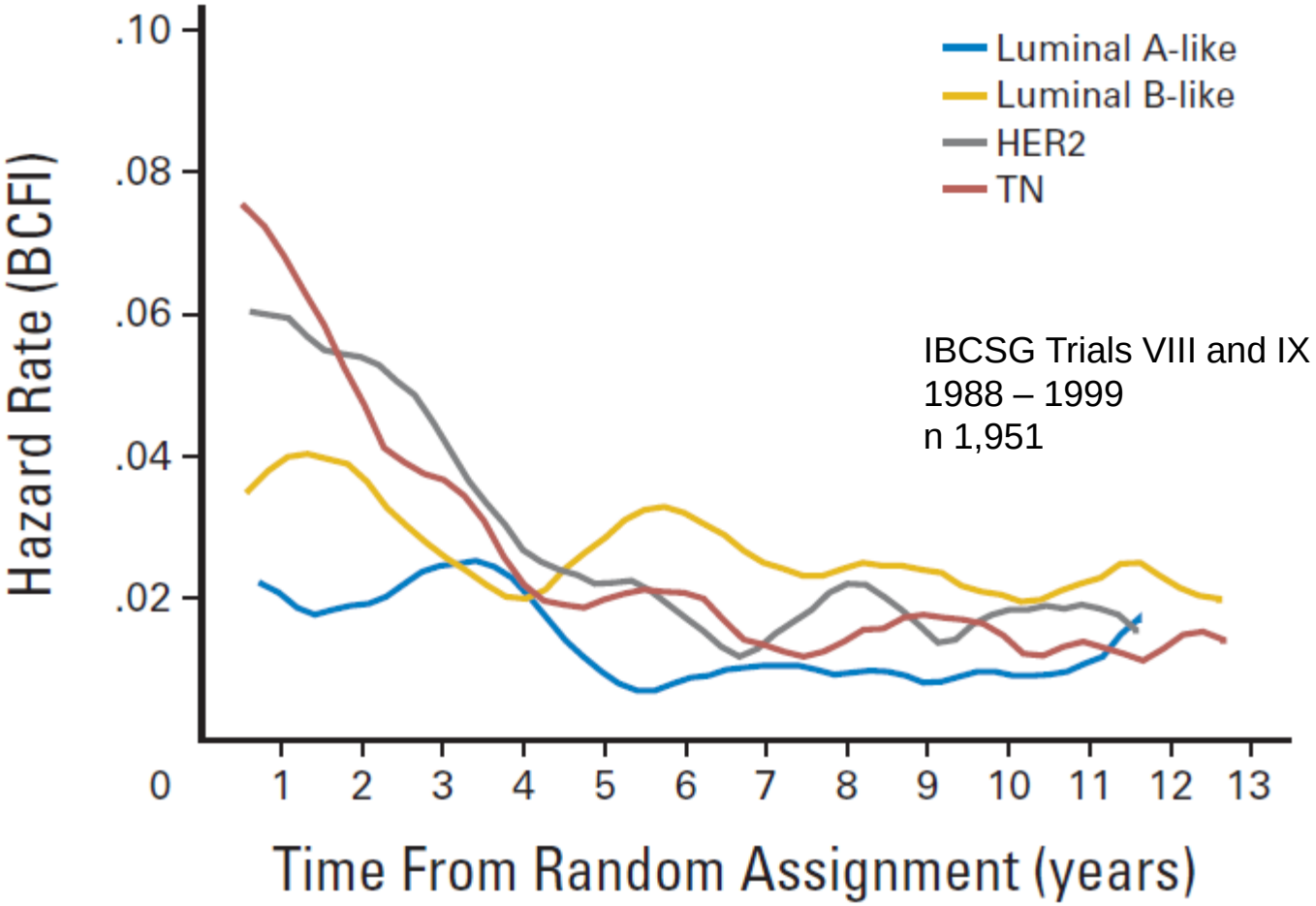
- Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541.

My Interpretation of the Old Italian Trials

- The follow-up performed with Chest x-ray, Bone scan (and liver US) performed every 6-12 mo.s did not improve overall survival in the therapeutic contest (local and systemic treatments) of the 80s / early 90s

- Chest x-ray and Bone scan repeated every 6 mo.s can anticipate the diagnosis of asymptomatic distant relapses

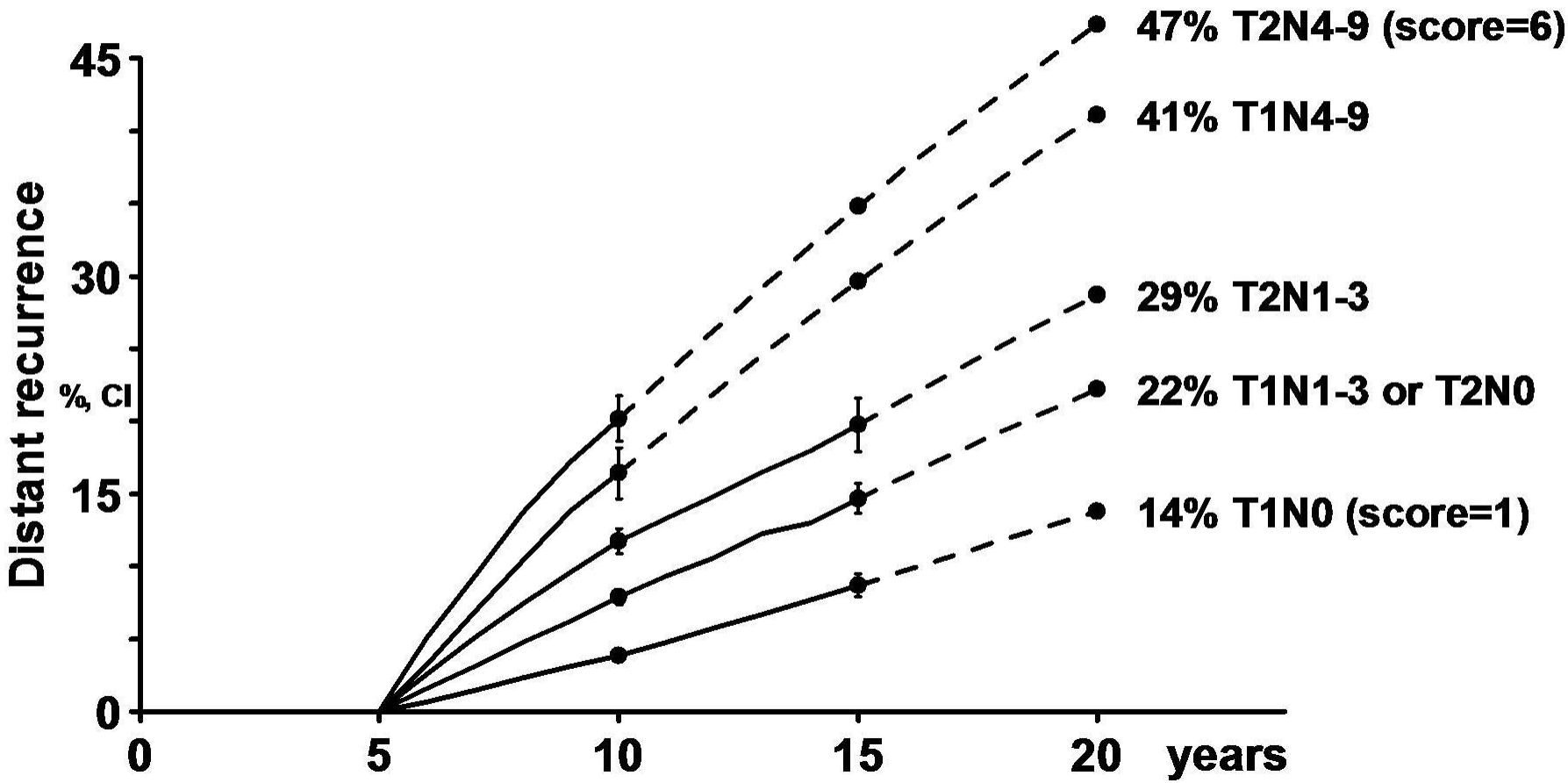
Hazard Rate of recurrence over time by BC subtype



Metzger-Filho O et al JCO 2013

Effect of additive "T+N score" (range 1-6)

Score: 1/ 2 for T1/ T2, plus 0/ 1/ 4 for N0/ N1-3/ N4-9



EBCTCG, 2016

Follow-up strategies for women treated for early breast cancer (Review)

Rojas MPMP, Telaro E, Moschetti I, Coe L, Fossati R, Liberati A, Rosselli MDT

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The current controversy stems from different views about the applicability of the results of these "old" trials to the current clinical practice. This would call for new RCTs testing different follow-up strategies using current treatments as baseline but it is unclear whether anyone wants to embark on this endeavour. The evidence from RCTs summarized here must, however, be interpreted with caution bearing in mind that studies were conducted almost two decades ago when some interventions currently used in the advanced setting, were not available.

2012 The Cochrane Collaboration

The real mistake is not to conduct new clinical trials on breast cancer follow-up

KRONOS STUDY

*P*atient-*O*riented KRO*N*O*S* *S*tudy - Italy
PONS-S Italy

Three-monthly dynamic evaluation of CEA and CA 15.3 *vs* usual practice in the follow-up of early breast cancer patients: a randomized study (KRONOS Study)

KRONOS PONS-S Italy

The study is conducted in two distinct parallel cohorts:

- *Cohort 1*: patients enrolled at the beginning of the follow-up after the conclusion of primary treatment (surgery +/- adjuvant chemotherapy +/- radiotherapy).

- *Cohort 2*: patients that have concluded without relapse the first 5 years of follow-up.

All patients will be followed-up (at least) until 10 years from surgery.

KRONOS Study- Version 1.0 – June 2014

ELIGIBILITY CRITERIA

- Histologically confirmed stage I-III breast cancer
- Adequate surgery of breast and axilla
- No evidence of distant metastases

Randomized 1:1

Stratification by
Nodal Status
ER status
HER2 status

ARM A (control):

Imaging studies and serum markers performed according to local practice

ARM B (experimental):
Serum CEA and CA 15.3 every 3 months

↓

Critical Δ
(CEA + 100% and/or CA 15.3 + 75%)

↓

Imaging (PET/CT scan)

No imaging allowed in asymptomatic patients in the absence of critical CEA and/or CA 15.3 increase

Treat also if asymptomatic!!!

Note: **The standard of care (i.e. physical examination every 6 months, yearly mammography and appropriate imaging studies in symptomatic patients) will be applied to both arms.**

www.clinicaltrials.gov

KRONOS PONS-S Italy

Primary objective:
to verify if the experimental arm can anticipate by at least 6 months the diagnosis of breast cancer metastases compared to the control arm (usual follow-up practice).

Secondary objectives:
- to evaluate the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV) of CEA and CA15.3 dynamic changes in the diagnosis of breast cancer metastases;
- to compare the number of imaging procedures performed in the 2 arms
- to compare the QoL in the 2 arms (GAD-7 and PO-Bado-BK modified)

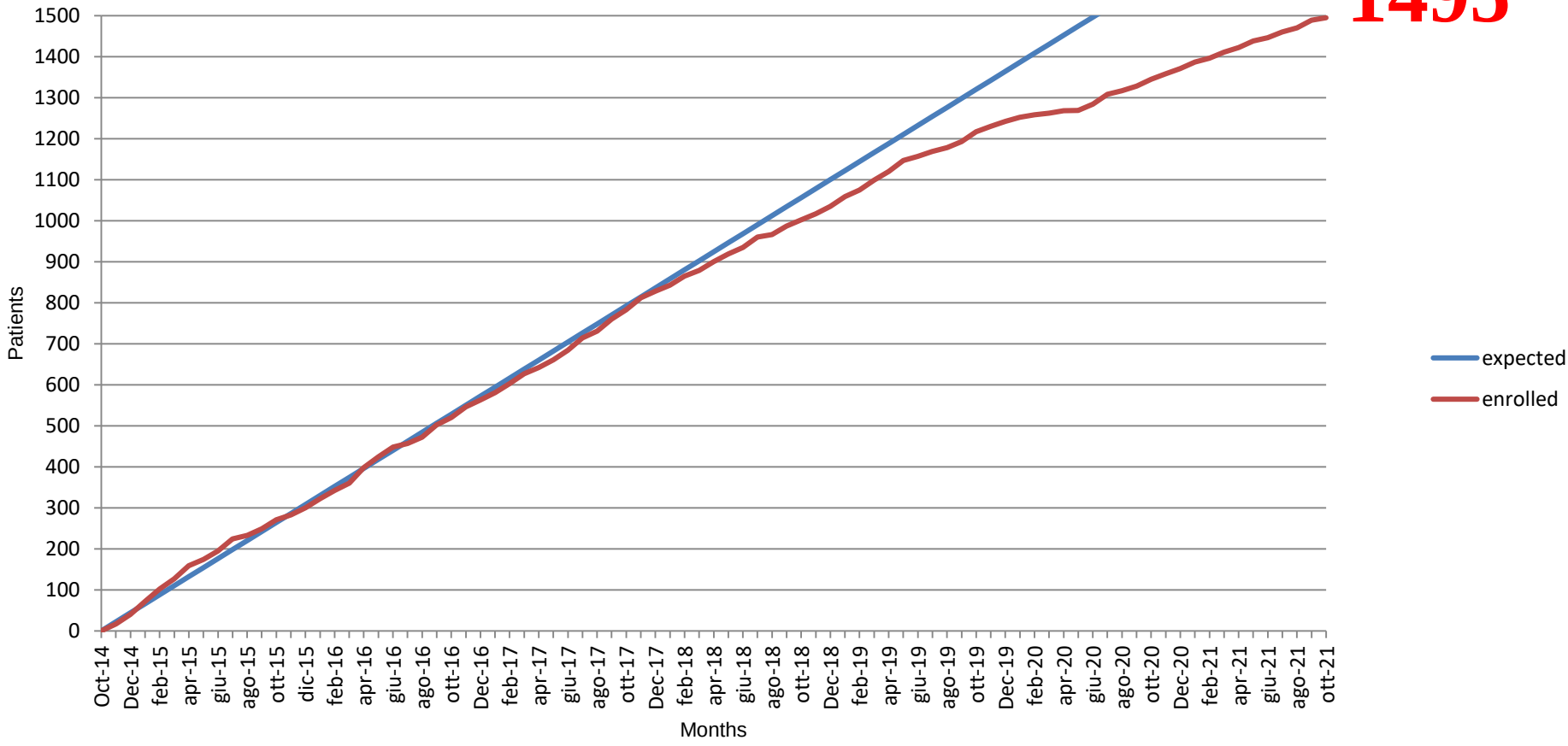
If the primary end-point of the trial will be met, the study will continue with the same design and the same eligibility criteria, to evaluate if the dynamic monitoring of CEA and CA 15.3 (experimental arm) can prolong of at least 3 months the overall survival compared to the control arm. In order to avoid the confounding effect of earlier diagnosis of metastases on the survival time, survival will be calculated from breast cancer diagnosis to death.
Before starting the second phase III of the trial, a new submission to the Ethical Committee will be done.

KRONOS PONS-S Italy

KRONOS PONS-S Italy

Enrollment State

1495



KRONOS PONS-S Italy

Enrollment Status at 15th October 2021

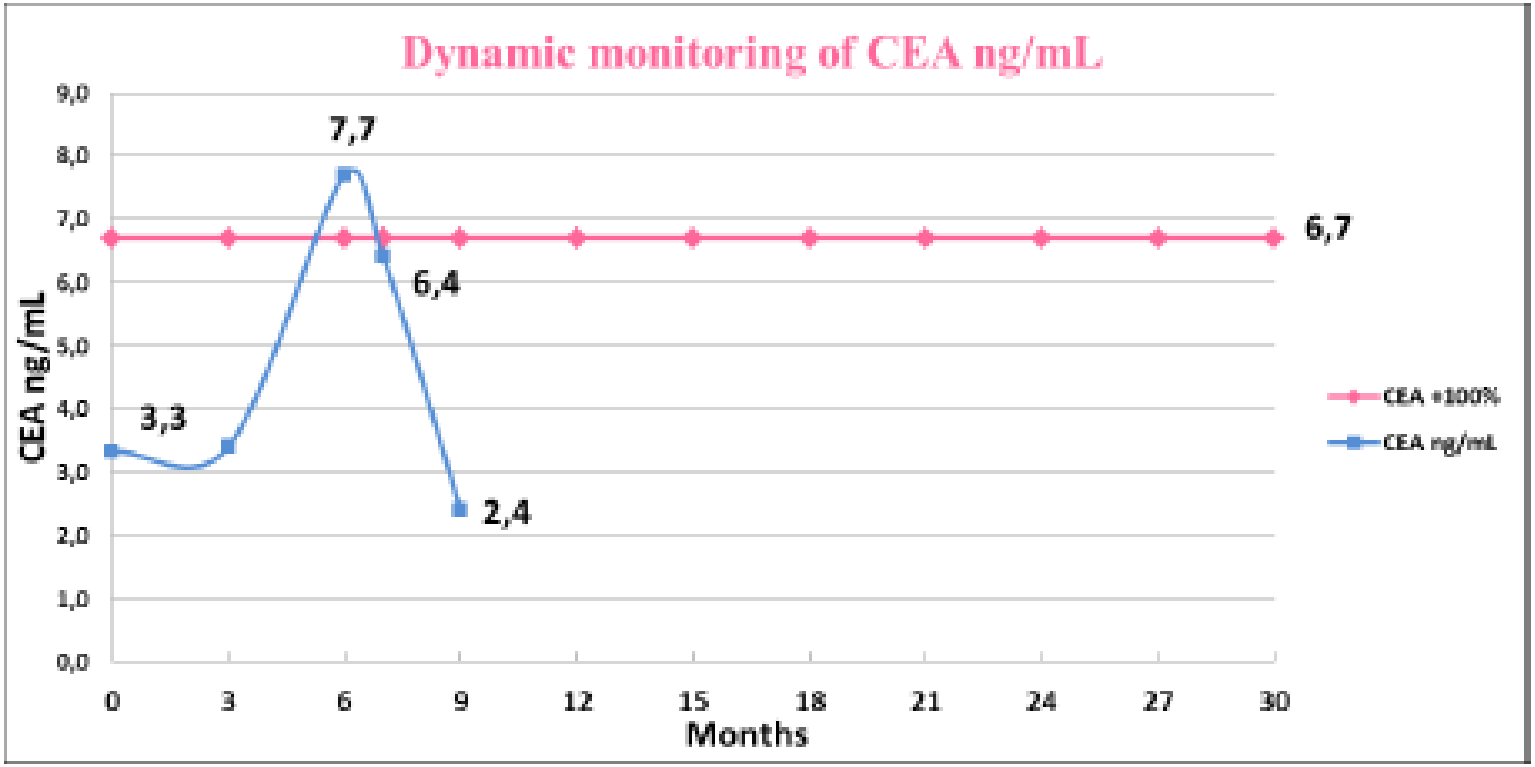
Total number of patients enrolled: 1495

Cohort 1: 1036 patients

Cohort 2: 459 patients

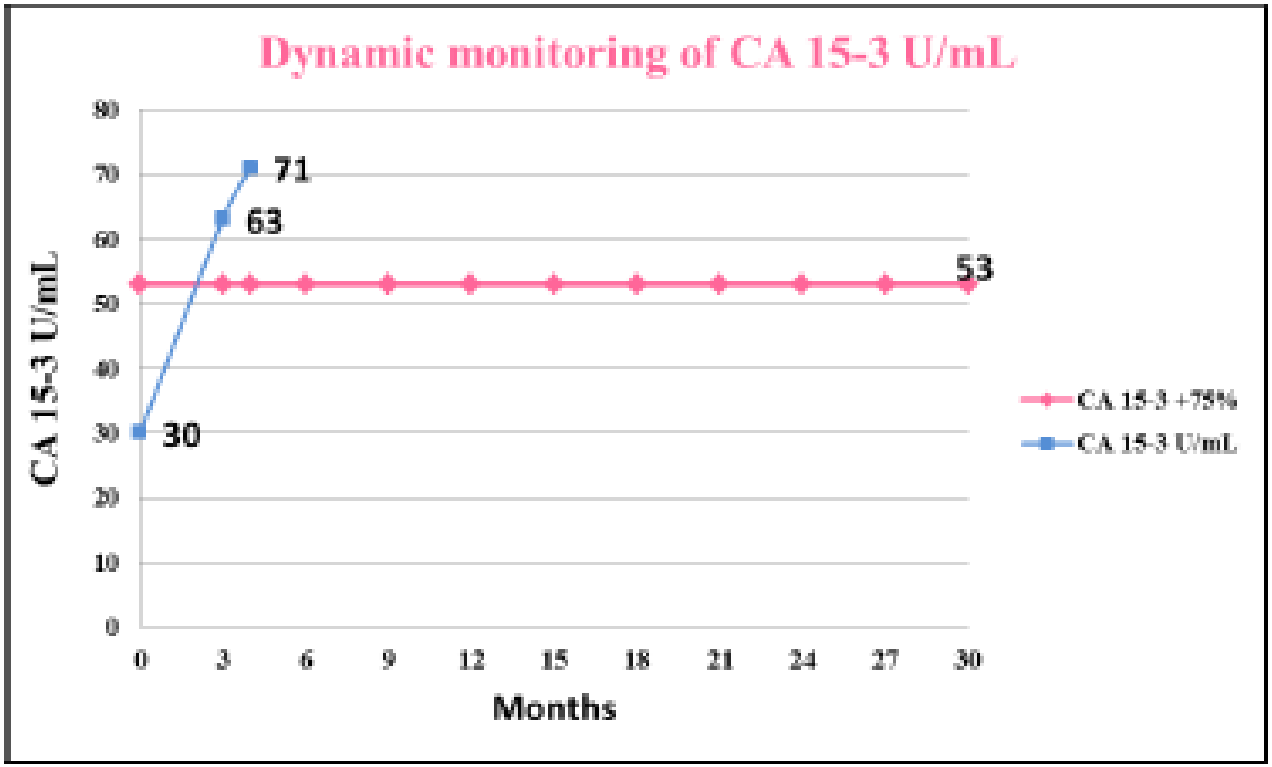
Example #1

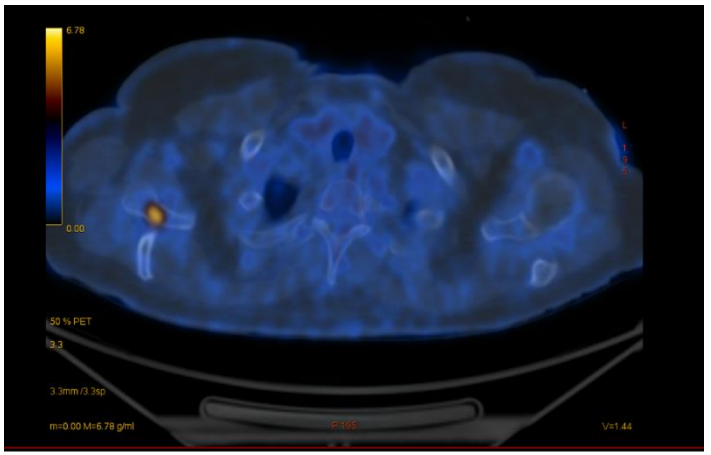
	Basal value	Critical value*	3 months	6 months	6 months repeated	9 months
CEA ng/mL	3,333	**6,7**	3,4	**7,7**	**6,4**	**2,4**
CA 15-3 U/mL	9	16	7	7	6	6

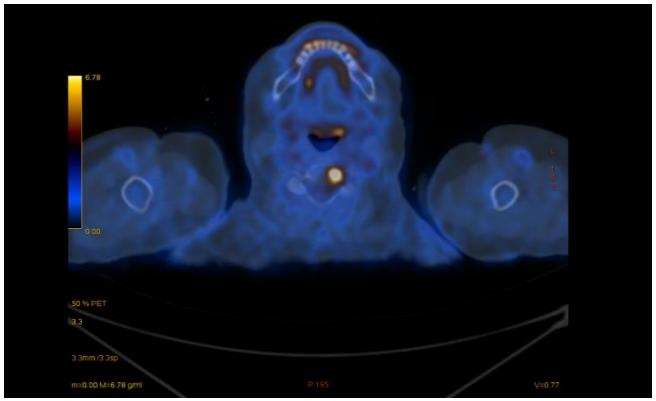


Example # 2

	Basal value	Critical value*	3 months	3 months repeated
CEA ng/mL	1.5	3	2.1	2
CA 15-3 U/mL	30	53	63	71







First-line therapy: Letrozole + Zoledronic Acid

Events update October 15, 2021: 107(7%)

Event	Control arm N 748	Exp. Arm N 747
Distant mets	26	34
Locoregional	2	9
New cancer (excluded breast)	16	14
Other causes	2	4
Total	46	61

many thanks for support

mamazone

Wer kämpft, kann verlieren,
Wer nicht kampft, hat schon verloren

Bertolt Brecht