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ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ADDARII
ONCOLOGIA MEDICA
S.ORSOLA-MALPIGHI BOLOGNA

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

mamazones
PROJEKT DIPLOMPATIENTIN

18ª Conferenza sul tumore al seno DIPLOMPATIENTIN®
„Paziente diplomata“ - un seminario per donne con e senza tumore al seno
Sabato, 25 ottobre 2025, ore 9.00 - 14.00
EURAC - Viale Druso 1, Bolzano

Risultati dello studio PONS-KRONOS

Claudio Zamagni
Direttore Oncologia Medica senologica e ginecologica & Breast Unit
IRCCS Azienda Ospedaliero-universitaria di Bologna
Ospedale di Sant’Orsola, Bologna

Asymptomatic Breast Cancer Patients Follow-up Guidelines in 2025 (31 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 3-6 mo.s (y 1-5) then annualy	12 mo.s	no
AIOM	Every 3-6 mo.s (y 1-3) *6-12 mo.s (y 4-5 y)* *then annualy*	12 mo.s	no

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

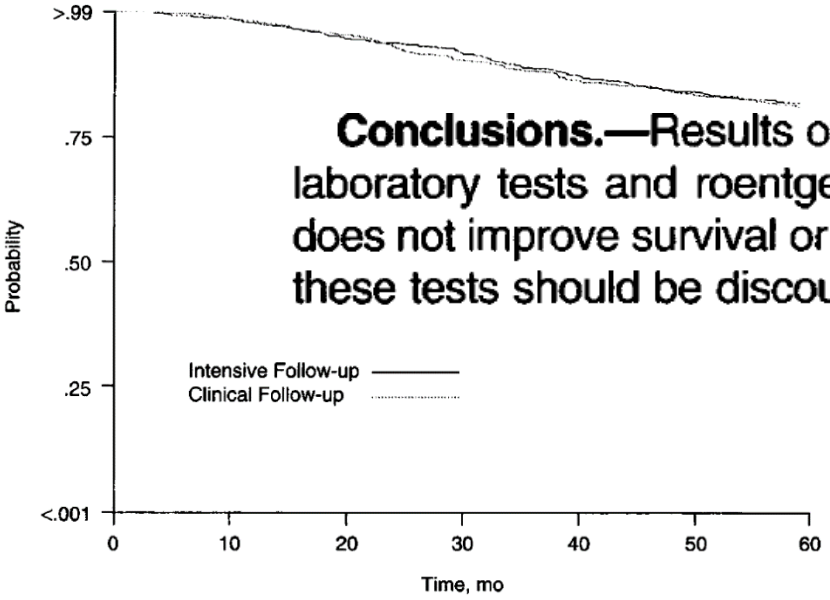
As control arm +
Chest x-Ray and Bone scan q 6 mo.s

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

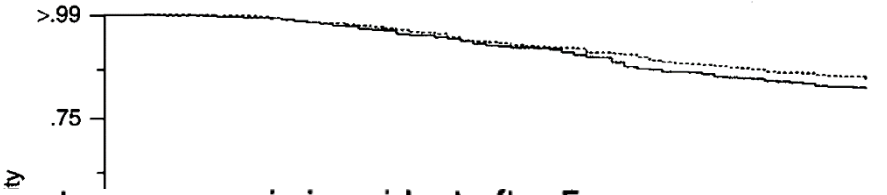
(*Alkaline Phosphatase and γ glutamyltranspeptidase)

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

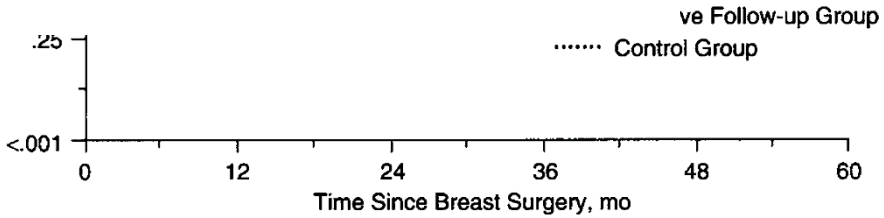


Conclusions.—Results of this trial support the view that a protocol of frequent laboratory tests and roentgenography after primary treatment for breast cancer does not improve survival or influence health-related quality of life. Routine use of these tests should be discouraged.

The GIVIO Investigators JAMA, 1994

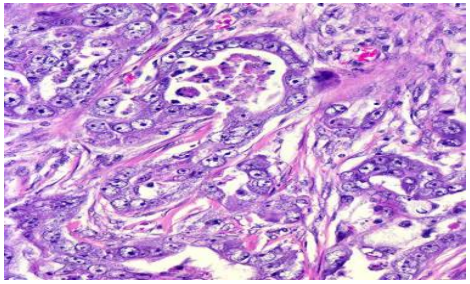


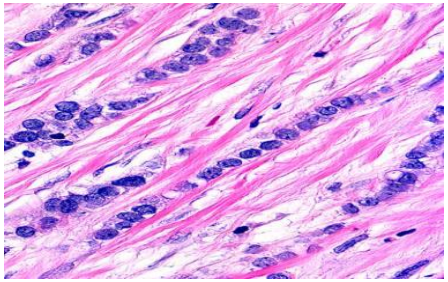
l no impact on prognosis is evident after 5 years. Periodic intensive follow-up with chest roentgenography and bone scan should not be recommended as a routine policy.



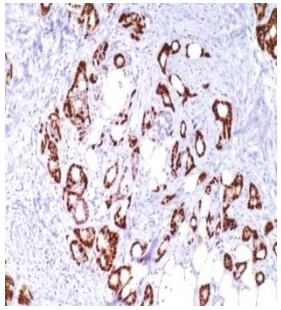
Rosselli del Turco M et al JAMA, 1994

Breast Cancer Classification in the 2 Old Italian Trials





invasive carcinoma

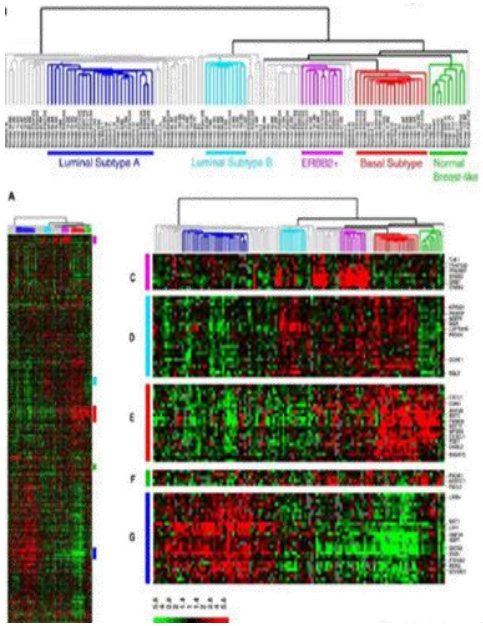


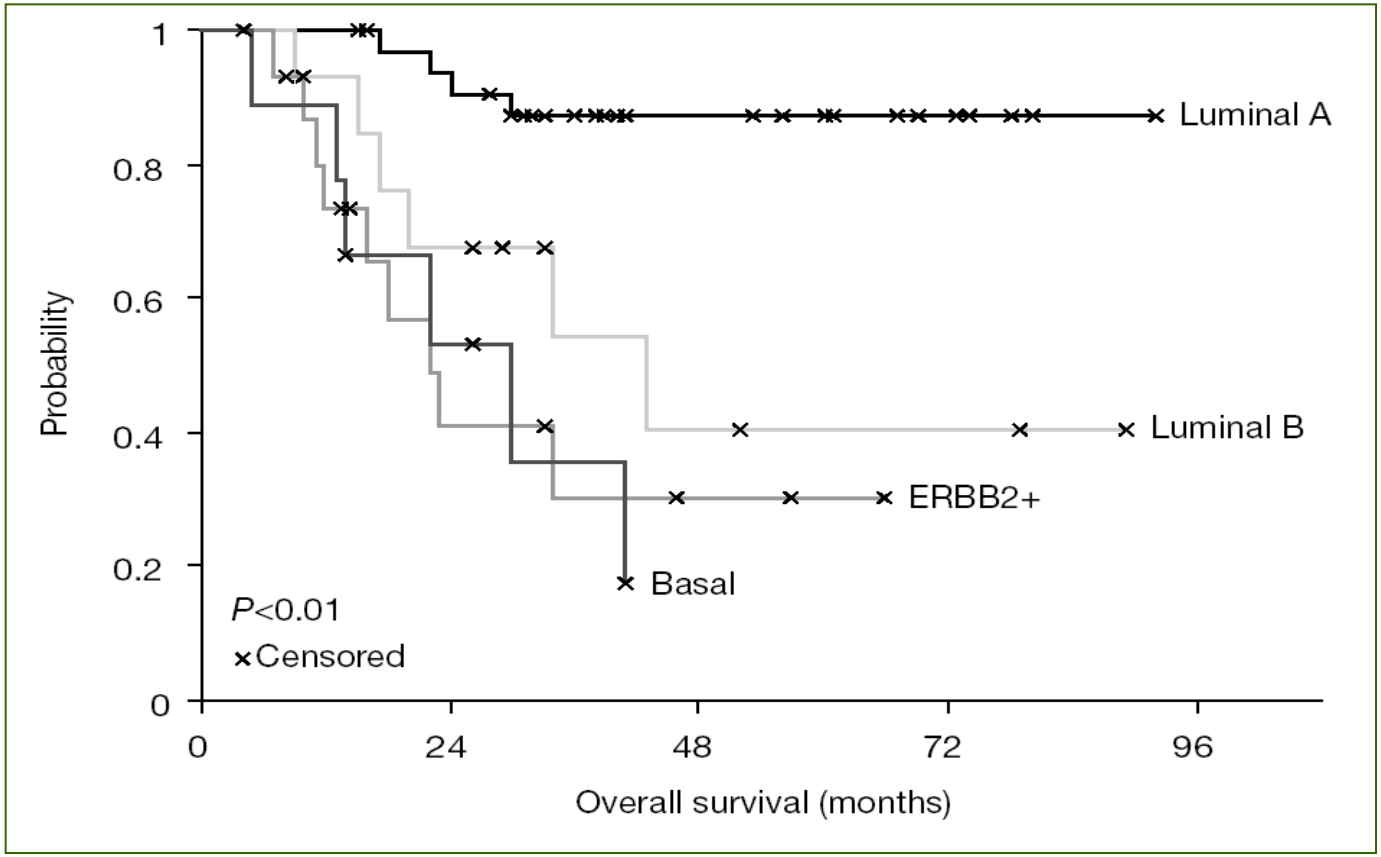
ER

In GIVIO Trial only
(and Unknown in 22%)

Breast Cancer Classification

"Breast Tumor Intrinsic" Subtype Classification



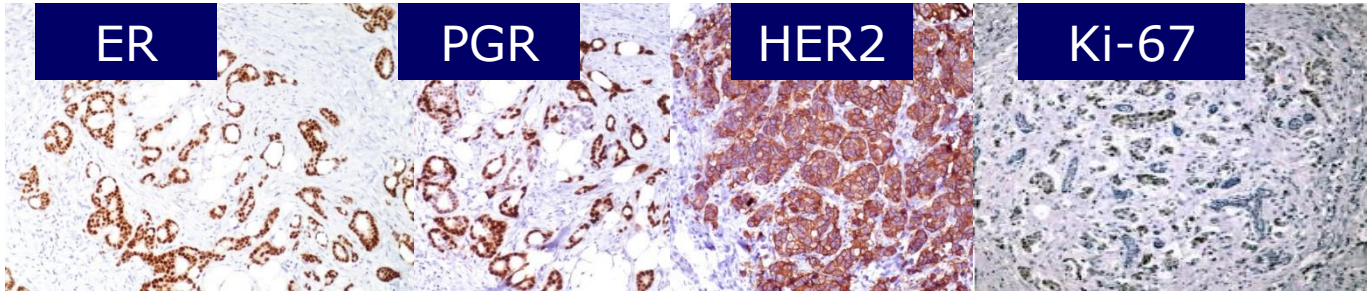


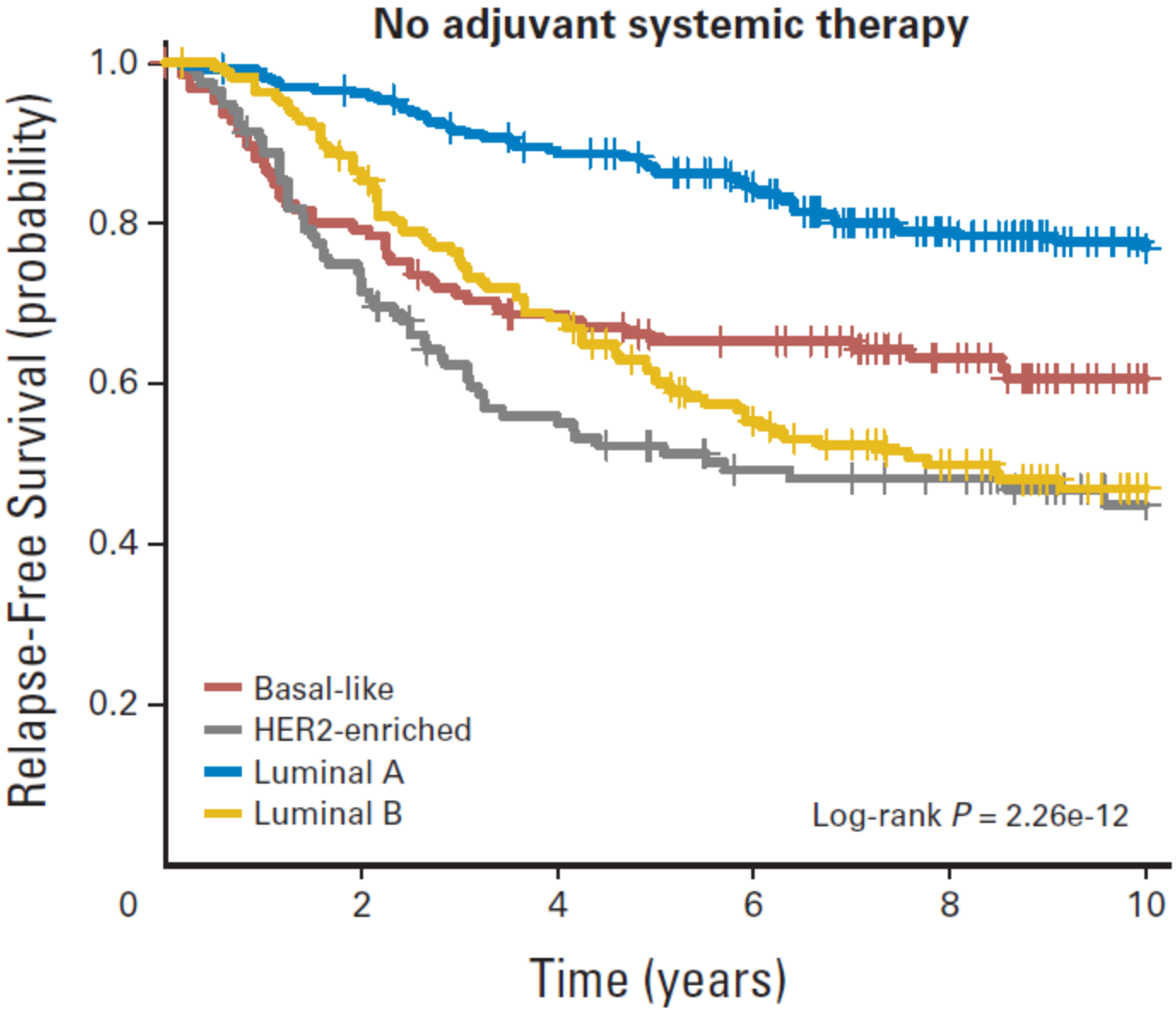
1. Luminal A
2. Luminal B
3. Normal breast-like
4. HER2
5. Basal-like

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	PR	HER2	Ki67
Luminal A	+	+	-	Low
Luminal B	+	+/-	-	High
Luminal/HER2	+	+/-	+	any
HER2 «enriched»	-	-	+	any
Triple Negative	-	-	-	any



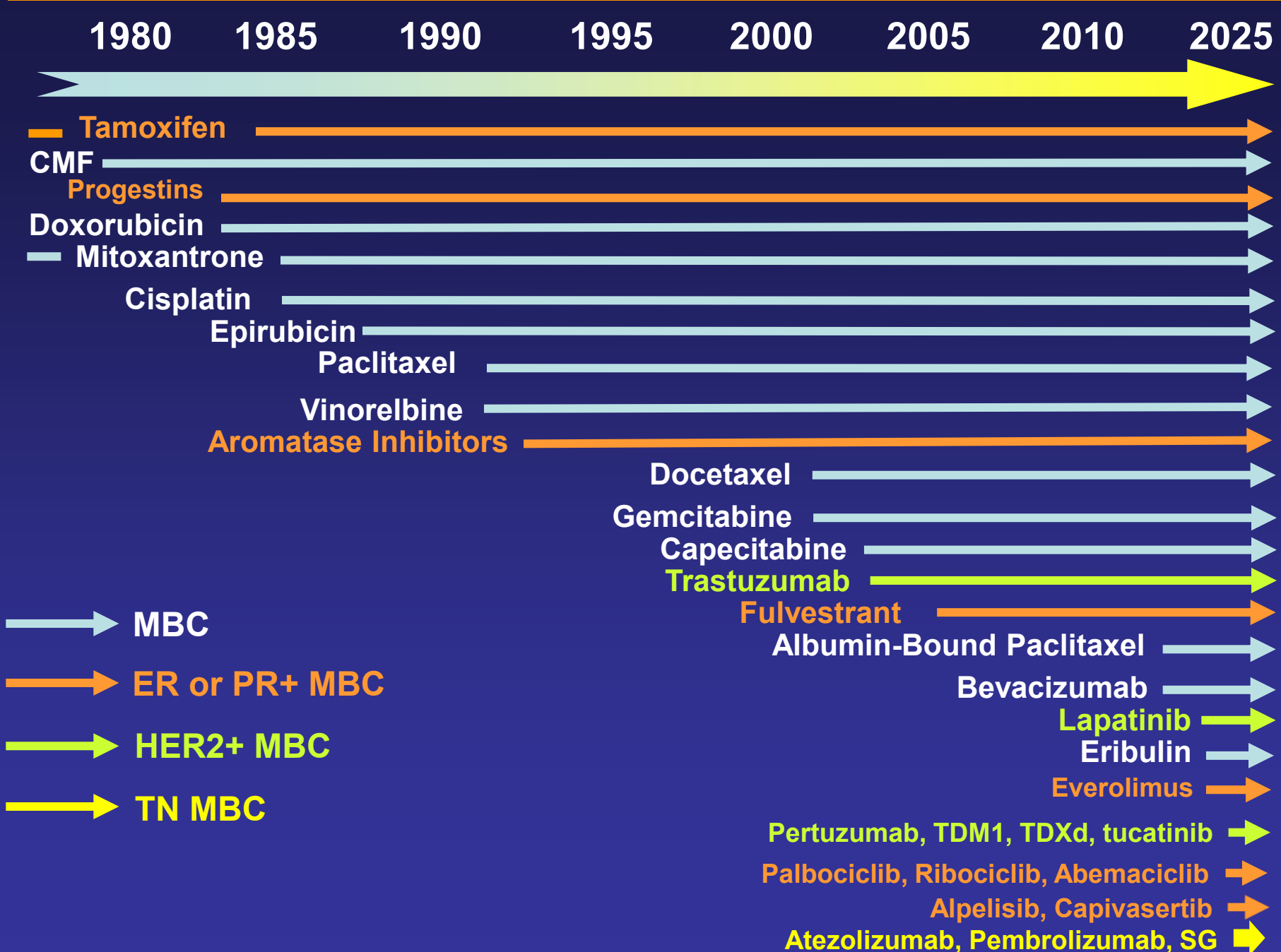

No adjuvant systemic therapy
Relapse-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
10
Time (years)
Basal-like
HER2-enriched
Luminal A
Luminal B
Log-rank P = 2.26e-12

Progress in Systemic Treatment of MBC

MBC

ER or PR+ MBC

Progress in Systemic Treatment of MBC



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1194–1220, 2019
doi:10.1093/annonc/mdz173
Published online 4 June 2019

SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1], S. Kyriakides[2], S. Ohno[3], F. Penault-Llorca[4,5], P. Poortmans[6,7], I. T. Rubio[8], S. Zackrisson[9] & E. Senkus[10], on behalf of the ESMO Guidelines Committee*

Very importantly, most available data for follow-up recommendations come from an era of less sophisticated diagnostic procedures and less efficacious treatment of advanced disease, and new trials are urgently needed to reassess this question. In

October 2014

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 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 CT-, Bone-, PET-scan are allowed in asymptomatic patients in the absence of critical CEA and/or CA 15.3 increase

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.**

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

↓

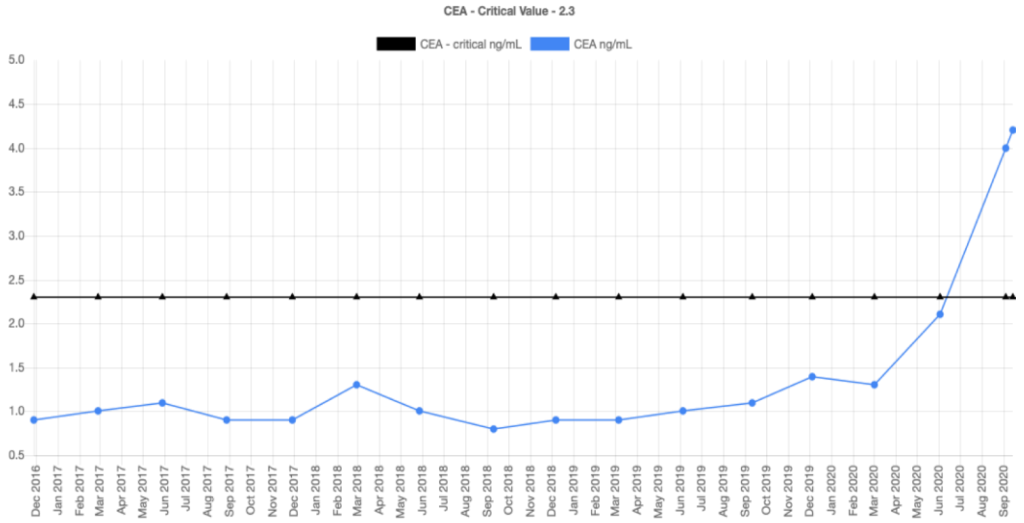
Imaging (PET/CT scan)

No CT-, Bone-, PET-scan 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


CEA - Critical Value - 2.3
CEA - critical ng/mL
CEA ng/mL
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Dec 2016
Jan 2017
Feb 2017
Mar 2017
Apr 2017
May 2017
Jun 2017
Jul 2017
Aug 2017
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Oct 2017
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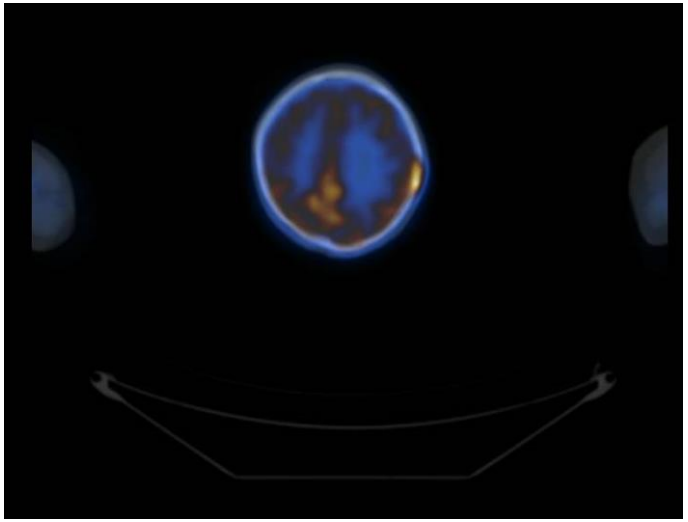
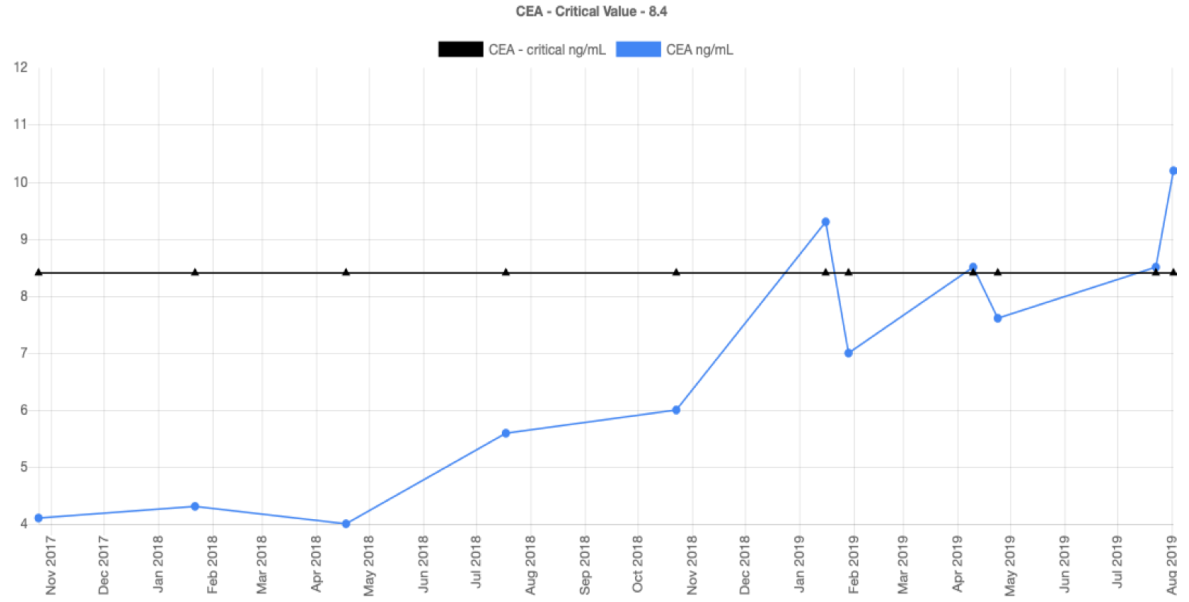
Sep 2020




CEA - Critical Value - 8.4
CEA - critical ng/mL
CEA ng/mL
12
11
10
9
8
7
6
5
4
Nov 2017
Dec 2017
Jan 2018
Feb 2018
Mar 2018
Apr 2018
May 2018
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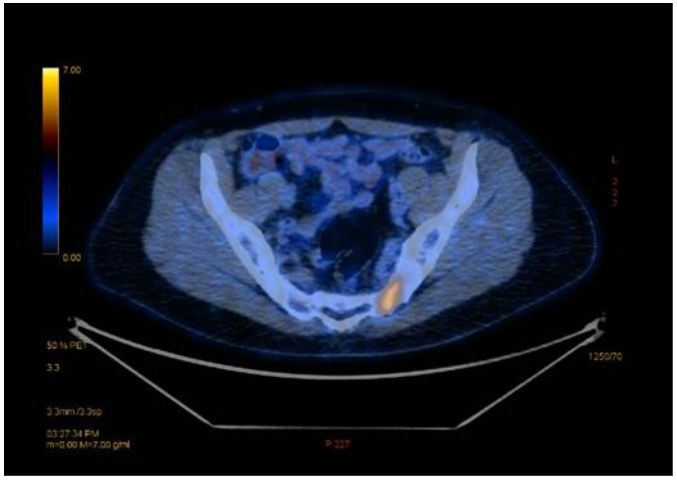
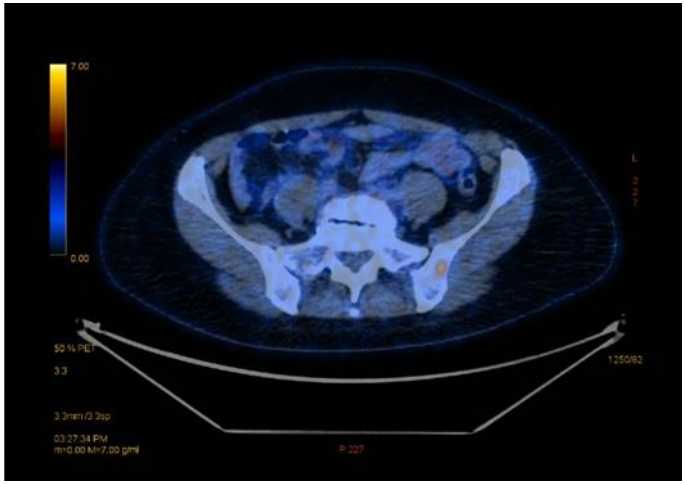




KRONOS PONS-S Italy

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 PONS-S Italy

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

The goal is to achieve 90% power to detect a reduction of *three months* in restricted mean survival time in the experimental arm compared to the control arm, based on a two-sided test at the 5% significance level.
For such a calculation, we made the assumption of a 20% baseline 5-year incidence of relapse, later updated to a more realistic 15%. *The target reduction of three months in restricted mean survival implies a median time of diagnostic anticipation, conditional on having breast cancer recurrence, of 10 months.*
Such an anticipation is both clinically meaningful and compatible with past experience

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.

Accrual time from Oct 2014 to Nov 2021
Total Accrual 1507

Median follow-up 7 years

Bologna
Mirano (VE)
Merano (BZ)
Bressanone (BZ)
Reggio Emilia
Piacenza
Ferrara
Bolzano
Guastalla (RE)

Accrual time from Oct 2014 to Nov 2021
Total Accrual 1507

Median follow-up 7 years

Node status and Stage

	COHORT 1		COHORT 2	
	1047 pts		460 pts	
N -	708	**67.6%**	308	**67.0%**
N+	339	**32.4%**	152	**33.0%**
Stage				
I	533	**50.9%**	251	**54.6%**
II	380	**36.3%**	146	**31.7%**
III	134	**12.8%**	63	**13.7%**

Accrual by Breast Cancer Subtype

Breast cancer subtype	Cohort 1 (n 515)	Cohort 1 (n 532)	Total Cohort 1 (n 1047)	COHORT 2 (n 227)	COHORT 2 (n 233)	Total Cohort 2 (n 460)
	Control arm	Experimental arm		Control arm	Experimental arm	
Luminal-like HER-2 negative	62.2%	60.2%	**61.2%**	75.2%	71.3%	**73.2%**
HER-2 positive	27.5%	29.8%	**28.7%**	18.6%	20.0%	**19.3%**
TRIPLE NEGATIVE	10.4%	10.0%	**10.2%**	6.2%	8.7%	**7.5%**

Print this Page for Your Records Close Window

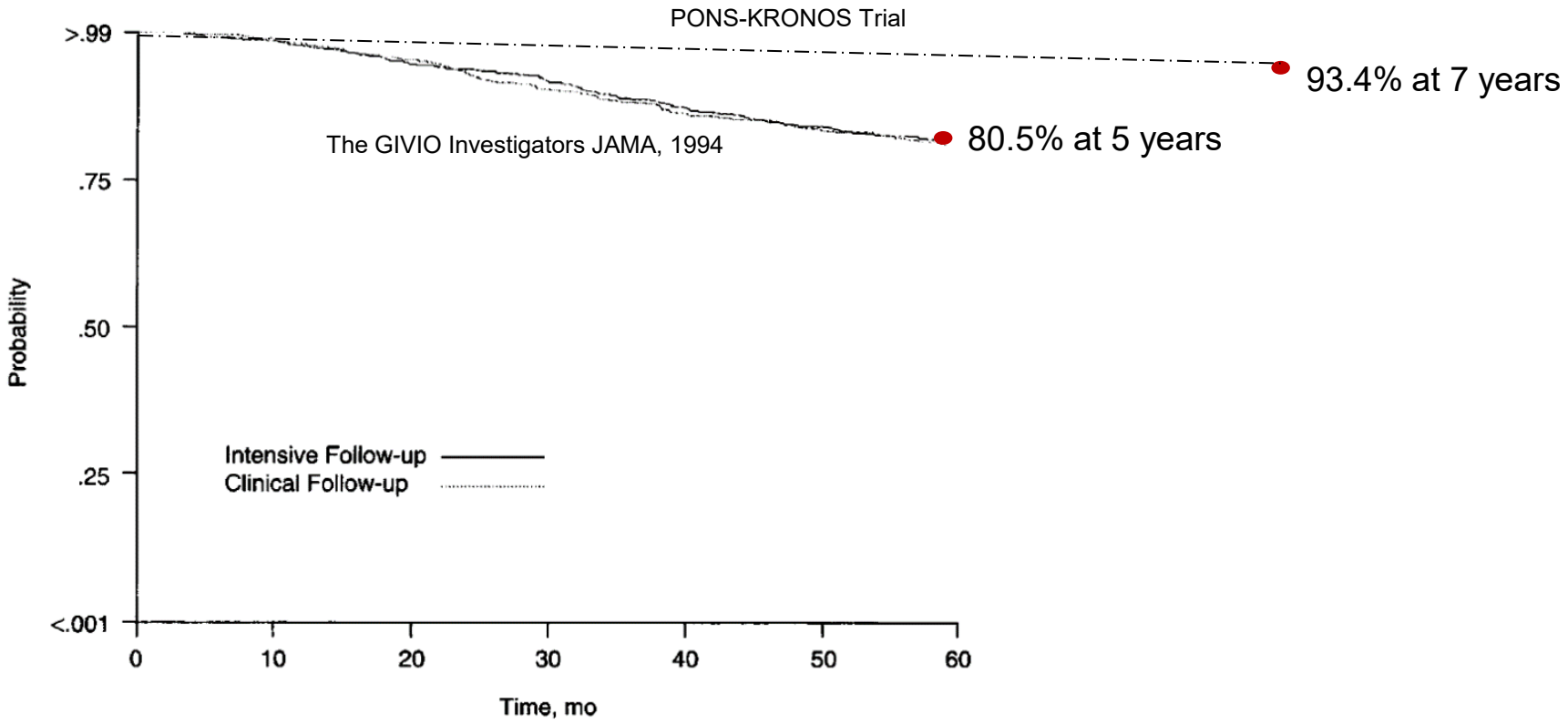
Control/Tracking Number: 2025-LB-3657-SABCS
Activity: Late Breaking Abstract
Current Date/Time: 10/1/2025 2:35:30 AM

Carcinoembryonic antigen (CEA), Cancer Antigen 15.3 (CA 15.3), and 18-FDG-PET in Early Breast Cancer Follow-up: Findings from the KRONOS Trial

Author Block: C. Zamagni[1], R. Wirtz[2], V. Torri[3], D. Sartori[4], M. Carapelle[1], L. Vivona[1], P. Stieber[5], J. Hubner[6], M. Bergamo[7], L. Tondulli[8], C. Pizzirani[1], S. Coccato[4], N. Cacciari[1], A. Baldoni[4], A. Bernardi[1], T. Dalsass[6], S. Quercia[1], S. Prader[7], E. Haspinger[8], D. Rubino[1], A. Mandrioli[1], M. Cubelli[1], F. Abbati[1], M. Massucci[1], R. Pagani[1], S. Fanti[9], M. Gion[10],

[1]IRCCS Azienda Ospedaliero-universitaria di Bologna, Bologna, ITALY, [2]Stratifyer Molecular Pathology and PONS-S Stiftung, Cologne and Munich, GERMANY, [3]Istituto di Ricerche Farmacologiche Mario Negri, IRCCS, Milan, ITALY, [4]UOC Oncologia AULSS3 Serenissima, Mirano, ITALY, [5]PONS-S Stiftung, Munich, GERMANY, [6]Dept. Gynecology and Obstetrics Ospedale di Merano, Merano-Meran, ITALY, [7]Dept. Gynecology and Obstetrics Hospital of Bressanone (SABES-ASDAA), Bressanone-Brixen, ITALY, [8]Oncologia Medica Ospedale di Bolzano, Bolzano-Bozen, ITALY, [9]IRCCS Azienda Ospedaliero-universitaria di Bologna and Bologna University, Bologna, ITALY, [10]AULSS 3 Veneto, Venezia, ITALY.

Improvement of Early Breast Cancer Survival Overall Survival over 4 Decades



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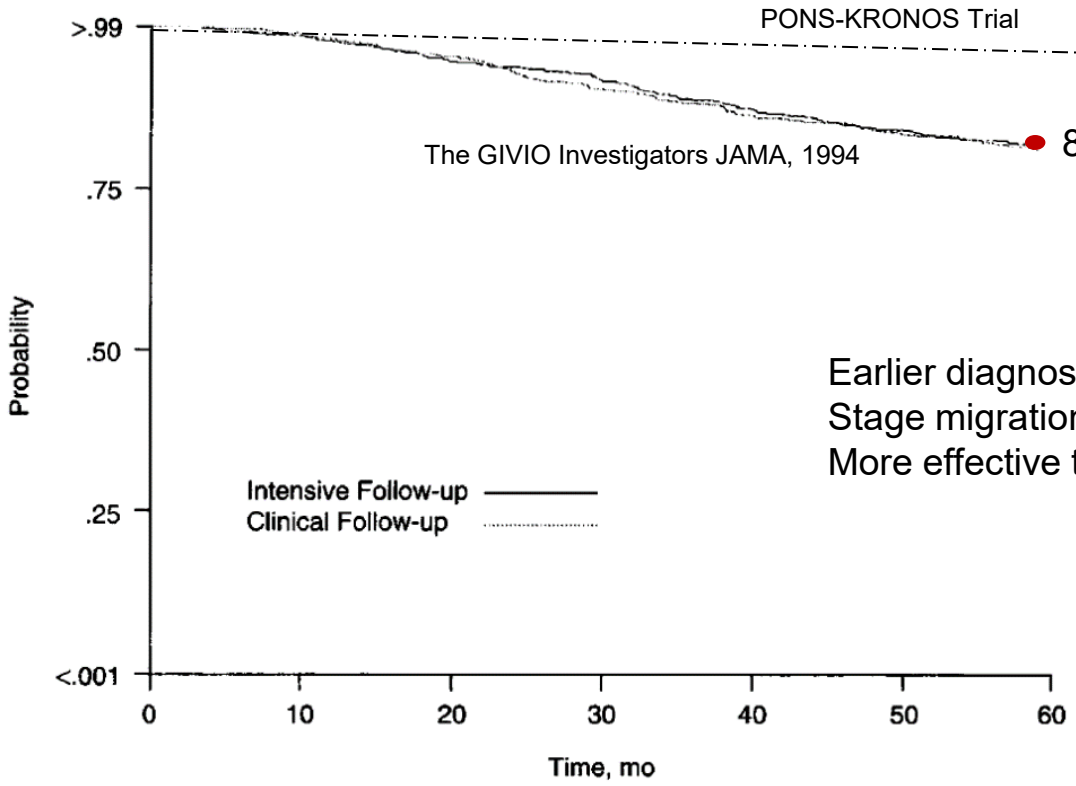
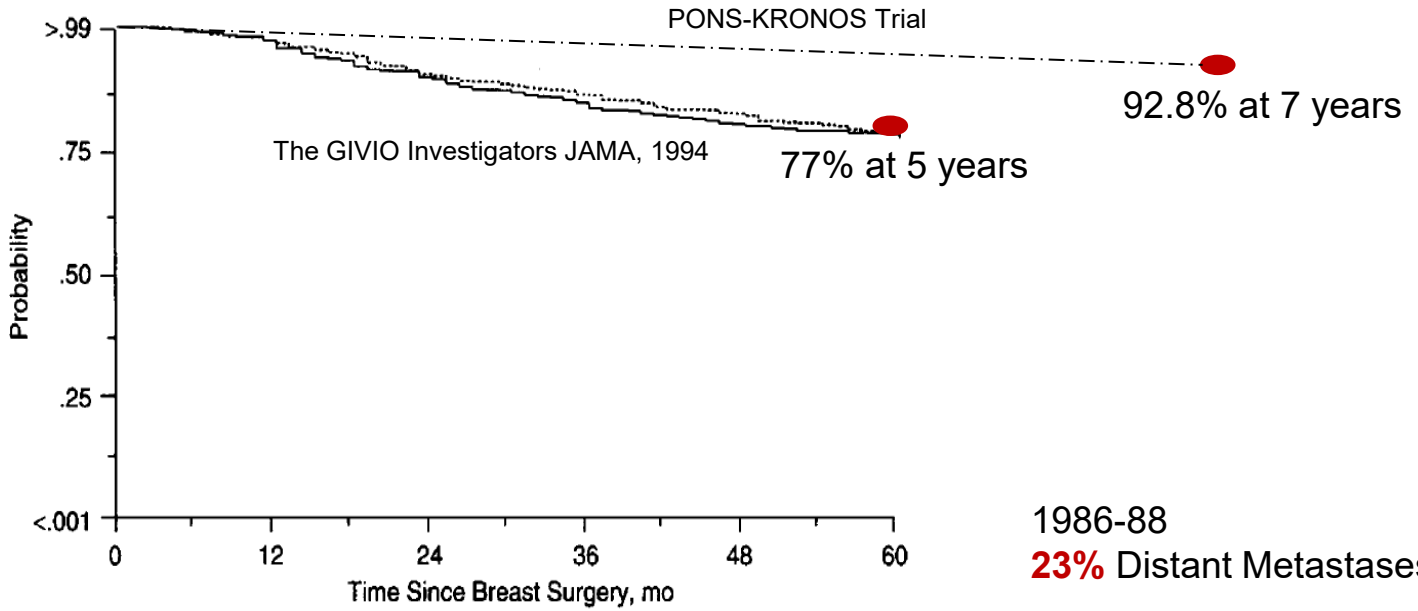


Earlier diagnosis
Stage migration (I-III > IV)
More effective therapies in (neo)-adjuvant/advanced setting

Improvement of Early Breast Cancer Distant Disease-free Survival Over 4 Decades



1986-88
23% Distant Metastases at **5** years

2014-21
7.2% Distant Metastases at **7** years

2025 Take-home message

First report of the PONS-S Kronos trial at SABCS 2025 (Late-breaking abstract submitted)

No signals of detrimental effect of «intensive» follow-up (no excess of false alarms, no excess of PET scan performed)

The compliance of patients in the experimental arm is good

The sensitivity to follow-up research in breast cancer has grown (ESMO statement, new German and Japanese trials, new biomarkers, i.e ctDNA): we are no longer alone

The very good new: A remarkable improvement in breast cancer distant disease-free and overall survival has been observed also in the Kronos trial (be aware: this was not a selected population, i.e. these results are obtained in daily clinical practice)

Many thanks for support

mamazones

In loving memory

Wer kämpft, kann verlieren,
wer nicht kämpft, hat schon verloren.

Bertolt Brecht