

Progetto CANOA: quali novità per il 2024?

AIGOM

ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Progetto **CANOA**

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2024?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Coordinatori scientifici:

Stefania Gori

Giovanni L. Pappagallo

Verona, 22-23 Marzo 2024
Hotel Leon d'Oro

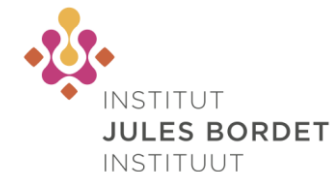
Dopo 5 anni di terapia ormonale: cosa fare?

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IRCCS Ospedale Policlinico San Martino - Università degli studi di Genova

Institut Jules Bordet, Bruxelles, Belgium



DISCLOSURE

Luca Arecco:

- Nessun conflitto d'interesse

OUTLINE

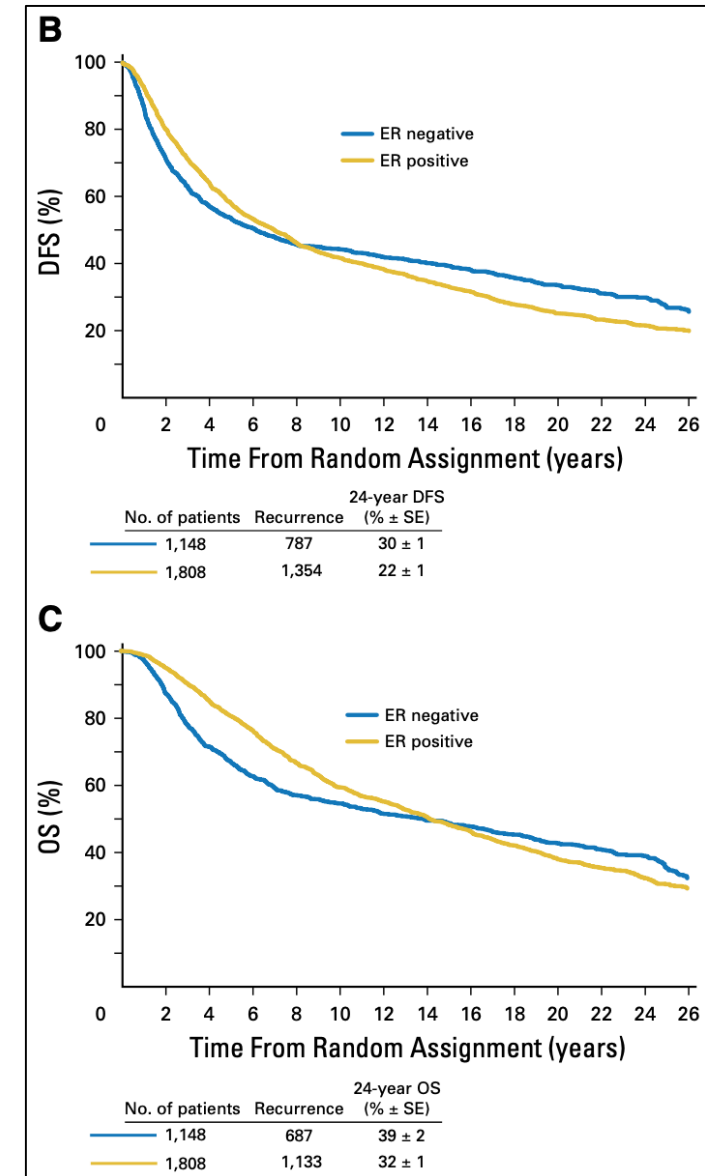
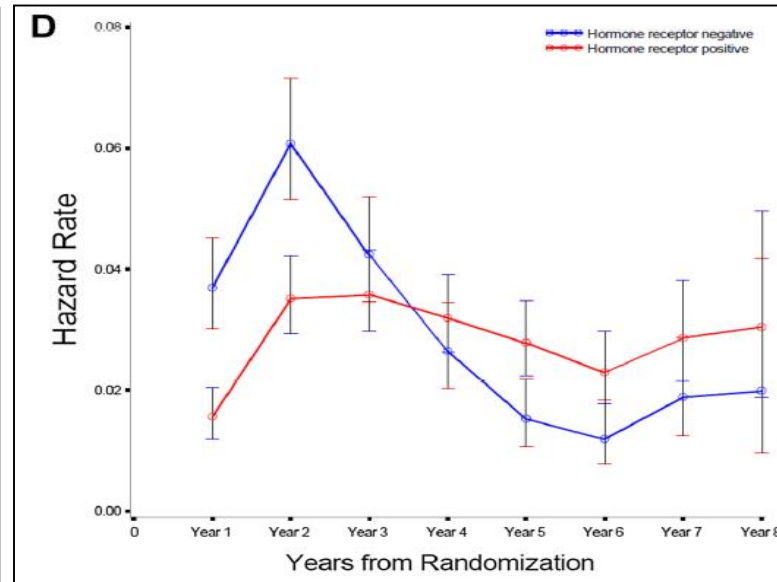
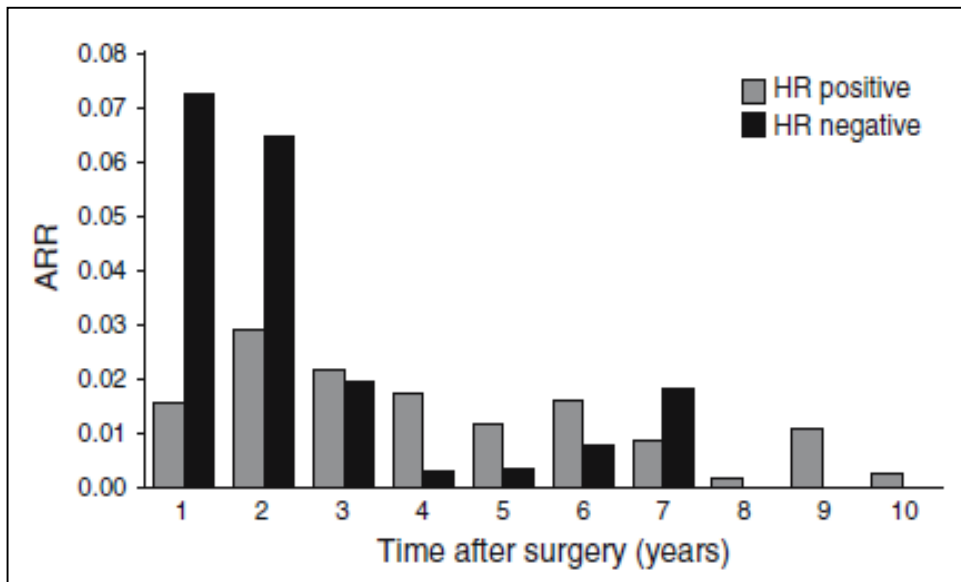
- **INTRODUZIONE**
- **PAZIENTI IN PRE-MENOPAUSA**
- **PAZIENTI IN POST-MENOPAUSA**
- **PREDIRE IL RISCHIO DI RECIDIVA**
- **CONCLUSIONI**

OUTLINE

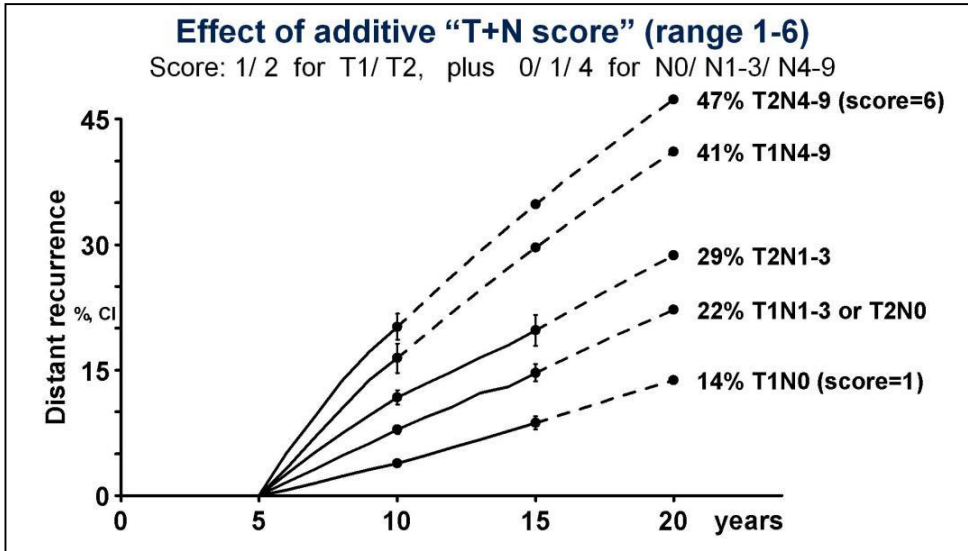
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- CONCLUSIONI

INTRODUZIONE

- **Malattia recettori ormonali positivi:** tasso di di recidive raggiunge un picco entro 2 anni dall'intervento e successivamente cala gradualmente.
- **Malattia recettori ormonali negativi:** tasso di recidive raggiunge un picco 2/3 anni dall'intervento e poi rimane costante durante il follow-up.

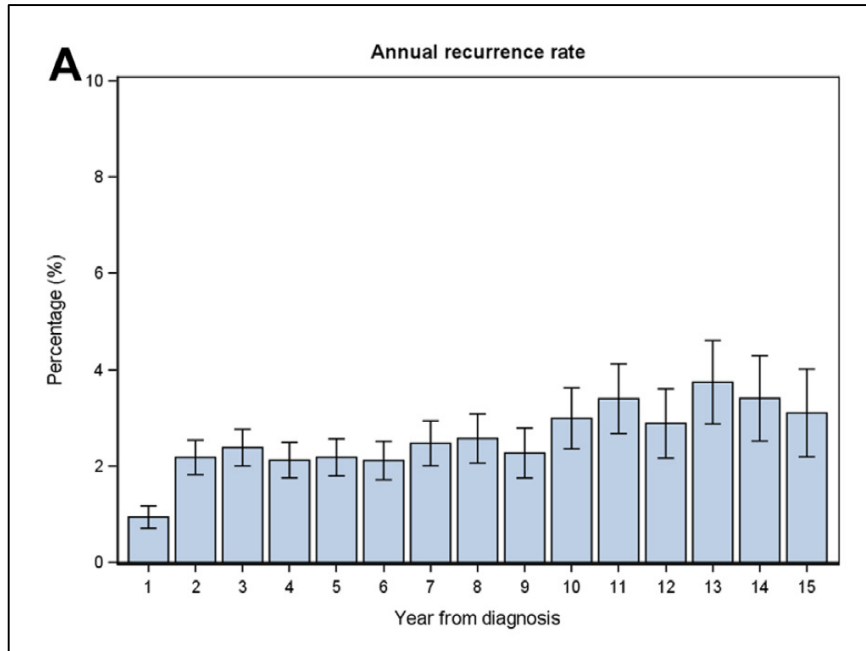
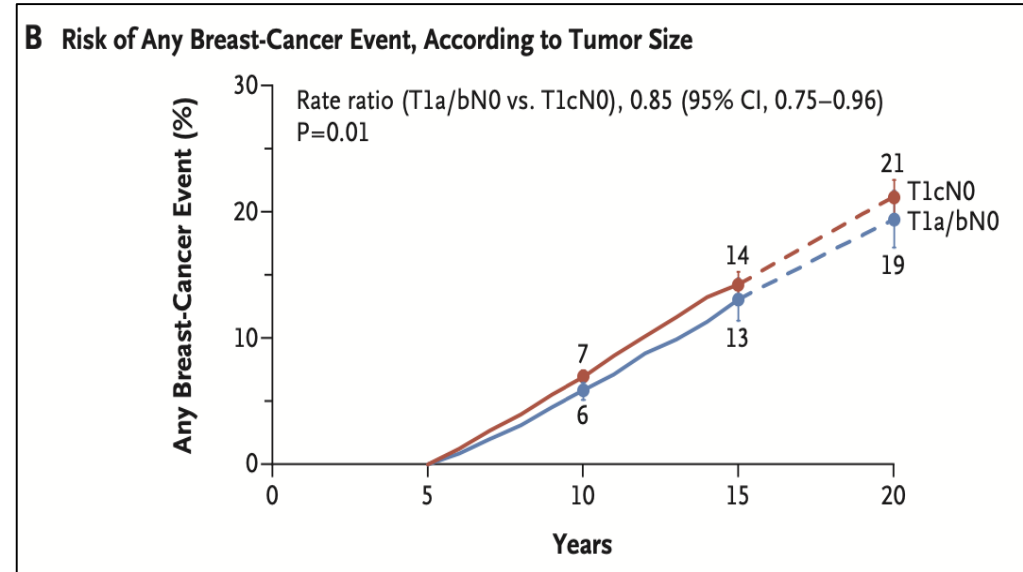


RISCHIO DI RECIDIVA DOPO 5 ANNI DALLA DIAGNOSI



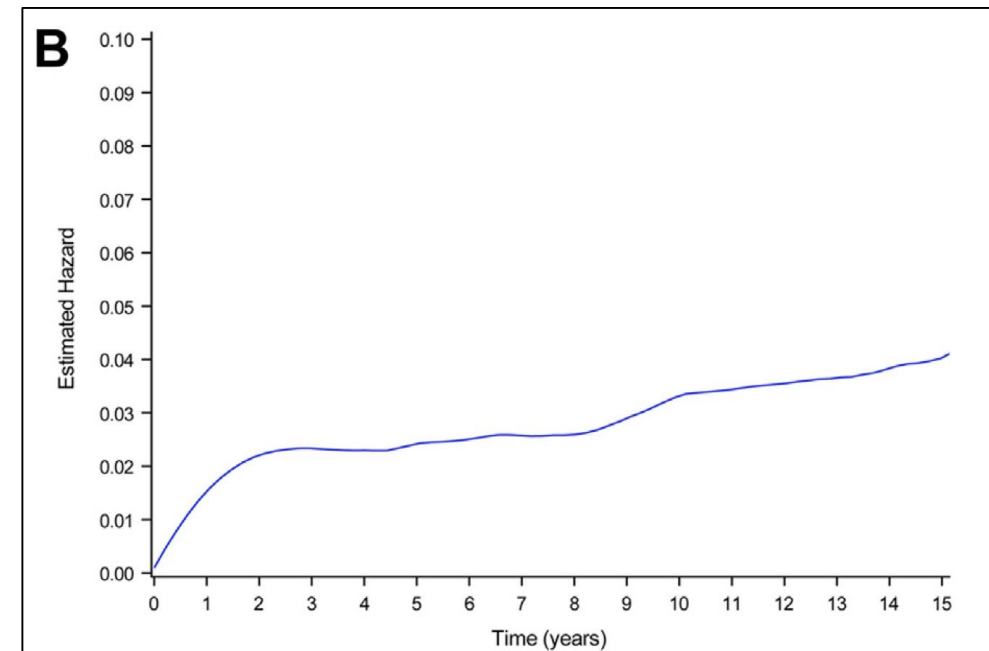
88 trials
62,923 pazienti

Tasso di recidive/anno fortemente legato allo stato linfonodale (P<0.001)



MIG/GIM
6,612 pazienti

Tasso di recidive annuali in 15 anni: ≈3%/anno



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- INTRODUZIONE
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- PAZIENTI IN POST-MENOPAUSA
- TEST GENOMICI?
- CONCLUSIONI

PAZIENTI IN PRE-MENOPAUSA

Pazienti giovani con malattia luminal-like sono quelle a maggior rischio di recidive tardive

Loco-regional recurrence

				<u>Years 0-5 (on endocrine, 74,194 women)</u>		<u>Years 5-20 (off endocrine, 62,923 women)</u>					
				Events Women		RR (95% CI)		Events Women		RR (95% CI)	
Analyses given TN status:											
Age at diagnosis (years)											
<35	76	1585		3.16 (2.50-3.99)		30	1009	1.87 (1.30-2.70)			
35-44	276	10344	■	1.57 (1.37-1.79)		217	7859	1.57 (1.35-1.82)			
45-54	390	22568	■	0.92 (0.83-1.01)		337	19326	0.90 (0.81-1.01)			
55-64	471	25439	■	0.88 (0.80-0.97)		408	22337	0.90 (0.81-1.00)			
65-74	220	14258	■	0.69 (0.59-0.80)		219	12392	0.90 (0.77-1.04)			

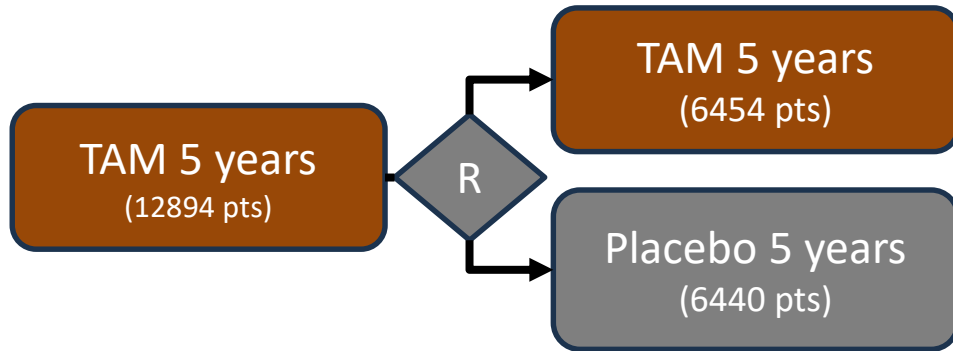
Distant recurrence

Analyses given TN status:											
Age at diagnosis (years)											
<35	338	1585		2.18 (1.96-2.43)		114	1009	1.51 (1.26-1.83)			
35-44	1288	10344	■	1.22 (1.15-1.29)		623	7859	1.00 (0.92-1.09)			
45-54	2017	22568	■	0.88 (0.84-0.92)		1267	19326	0.86 (0.81-0.91)			
55-64	2430	25439	■	0.97 (0.93-1.02)		1736	22337	1.04 (0.99-1.09)			
65-74	1267	14258	■	0.95 (0.89-1.01)		957	12392	1.12 (1.04-1.20)			

Cosa fare al termine dei 5 anni di terapia ormonale adiuvante?

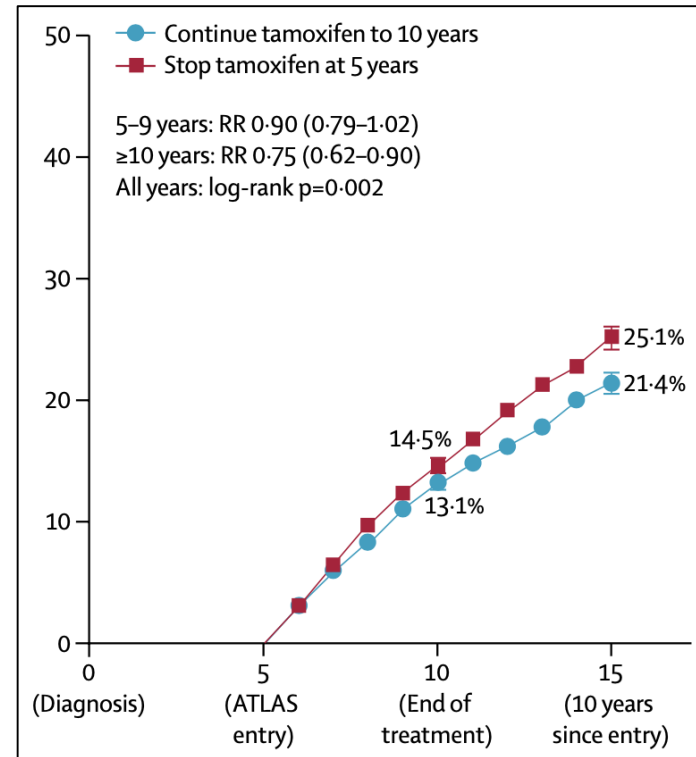
TAM → TAM PER 5 ANNI (5 anni vs. 10 anni totali)

ATLAS

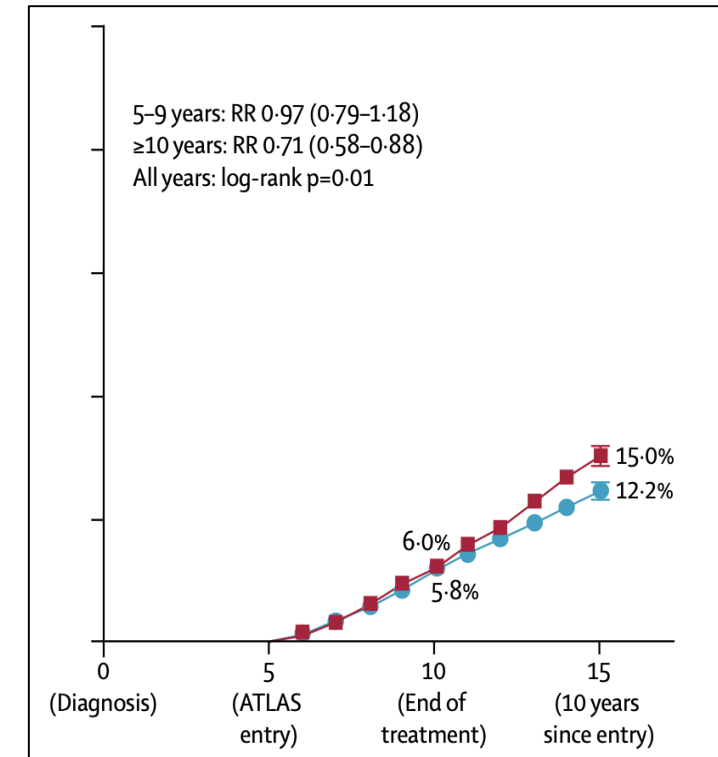


Nodal status				
Node-negative	3360 (52%)	3354 (52%)	1832 (53%)	1845 (54%)
N1-3	1667 (26%)	1621 (25%)	938 (27%)	893 (26%)
N4 or more	968 (15%)	965 (15%)	536 (16%)	534 (16%)
Unknown	459 (7%)	500 (8%)	122 (4%)	146 (4%)
Tumour diameter				
1-20 mm	2462 (38%)	2463 (38%)	1660 (48%)	1620 (47%)
21-50 mm	2749 (43%)	2727 (42%)	1309 (38%)	1328 (39%)
>50 mm	620 (10%)	628 (10%)	251 (7%)	252 (7%)
Unknown	623 (10%)	622 (10%)	208 (6%)	218 (6%)

Recurrence



Breast cancer mortality



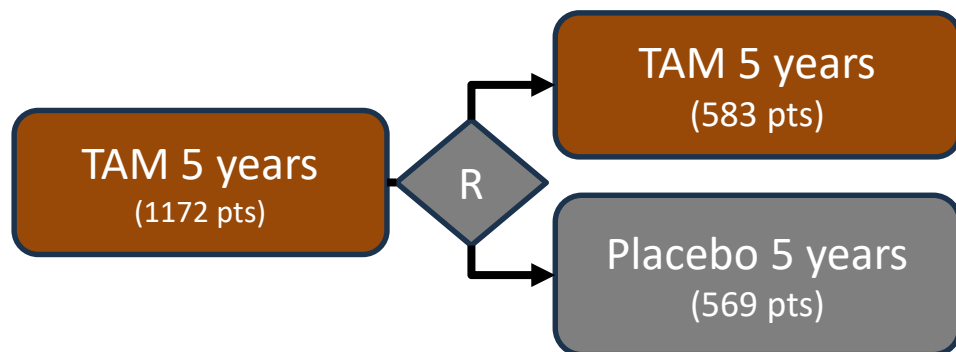
PREMENOPAUSA=8%

Menopausal status at ATLAS entry (p=0.79)

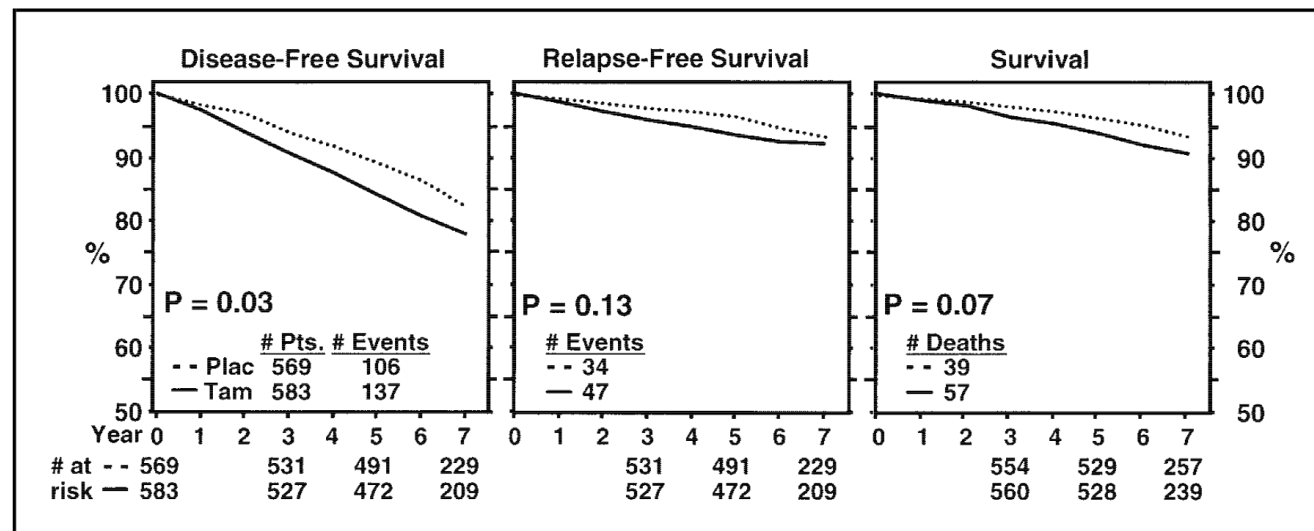
Premenopausal	64/326 (20%)	73/304 (24%)	-7.2	34.2	0.81 (0.15)
Postmenopausal or unknown	553/3102 (18%)	638/3114 (20%)	-48.8	297.6	0.85 (0.05)

TAM → TAM PER 5 ANNI (5 anni vs. 10 anni totali)

NSABP B-14

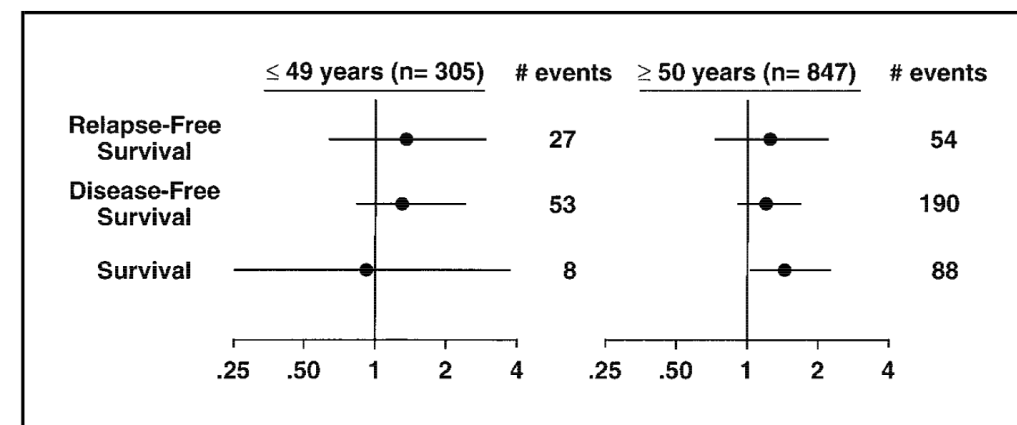


Characteristic*	Placebo, % (n = 569)	Tamoxifen, % (n = 583)
Age, y		
≤49	26	26
50–59	30	30
≥60	44	44
Mean ± standard deviation	56 ± 9	56 ± 10
Menopausal status		
Premenopausal/perimenopausal	25	27
Postmenopausal	74	73
Unknown	1	<1
Type of surgery		
Total mastectomy	56	56
Lumpectomy + XRT†	44	44
Clinical tumor size, cm		
≤2.0	65	68
2.1–4.0	33	28
≥4.1	2	4
Mean ± standard deviation	2.1 ± 1.1	2.0 ± 1.2



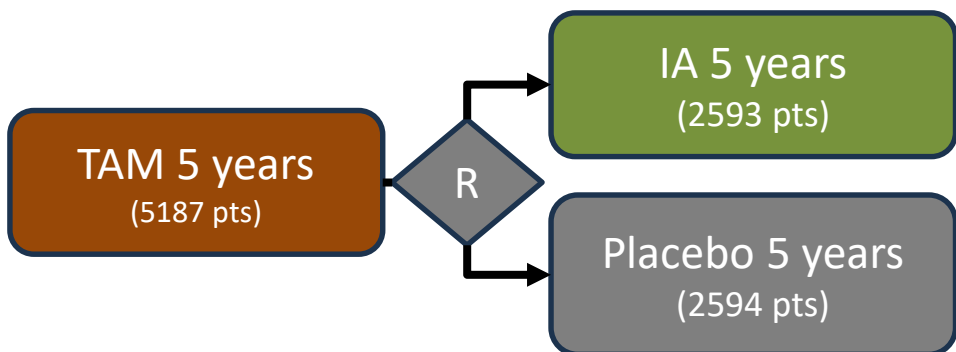
**NODE-NEGATIVE:
100%**

**PREMENOPAUSA
≈ 25%**



TAM → IA PER 5 ANNI (5 anni vs. 10 anni totali)

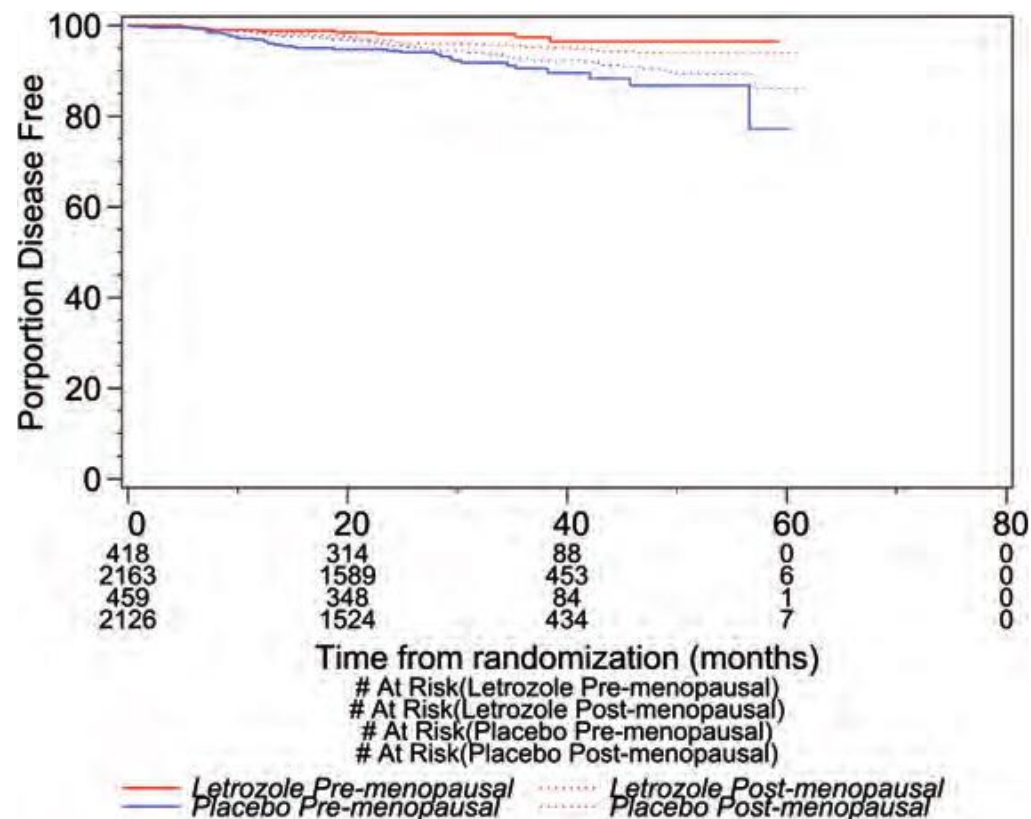
National Cancer Institute of Canada (NCIC CTG) - MA17



Characteristics	Premenopausal (N = 877) No. (%)	Postmenopausal (N = 4289) No. (%)	P (uni -variate)	P (multi -variate)
Treatment			0.14	0.04
Letrozole	418 (48)	2163 (50)		
Placebo	459 (52)	2126 (50)		
Age at randomization (years)				
<60	877 (100)	1271 (30)	<0.001	0.99
60–70	0 (0)	1694 (40)		
≥70	0 (0)	1323 (31)		
Missing	0 (0)	1 (0)		
Race				
White	779 (89)	3925 (92)	0.005	0.002
Black	33 (4)	146 (3)		
Other	54 (6)	150 (4)		
Unknown	5 (1)	39 (1)		
Missing	6 (1)	29 (1)		
Axillary lymph node status				
Negative	369 (42)	2198 (51)	<0.001	0.11
Positive	495 (56)	1863 (43)		
Unknown	12 (1)	214 (5)		

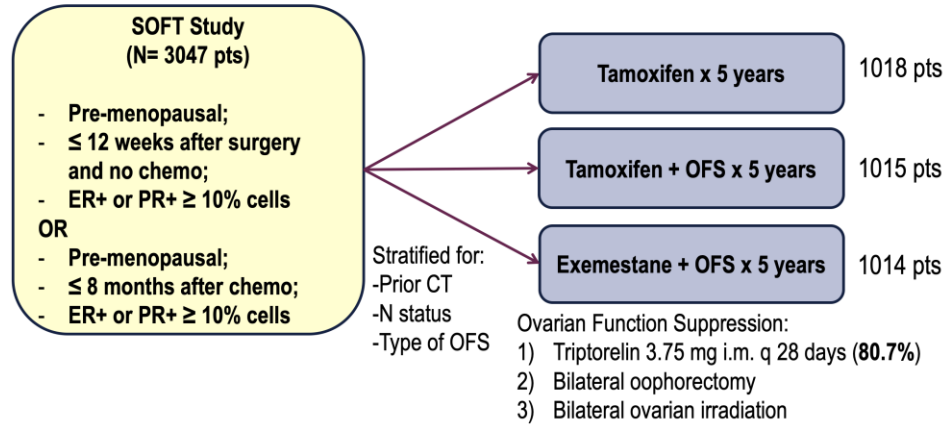
PREMENOPAUSA = 877 pazienti

DFS HR 0.26 (0.13–0.55); P=.0003



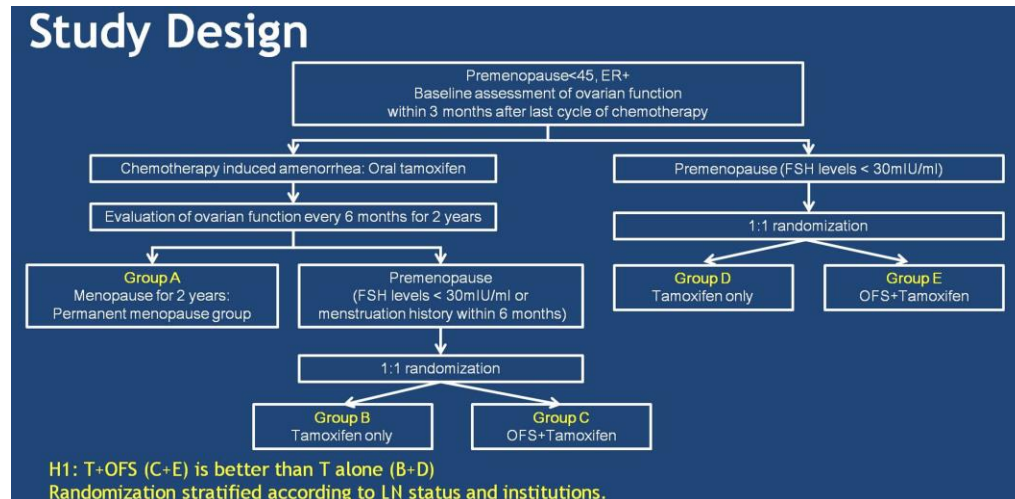
RUOLO DELLA SOPPRESSIONE OVARICA DOPO 5 ANNI DI OT

SOFT Trial = 5 anni soppressione ovarica



Non ci sono evidenze a sostegno della soppressione ovarica oltre i 5 anni

ASTRRA Trial = 2 anni soppressione ovarica



Original Study

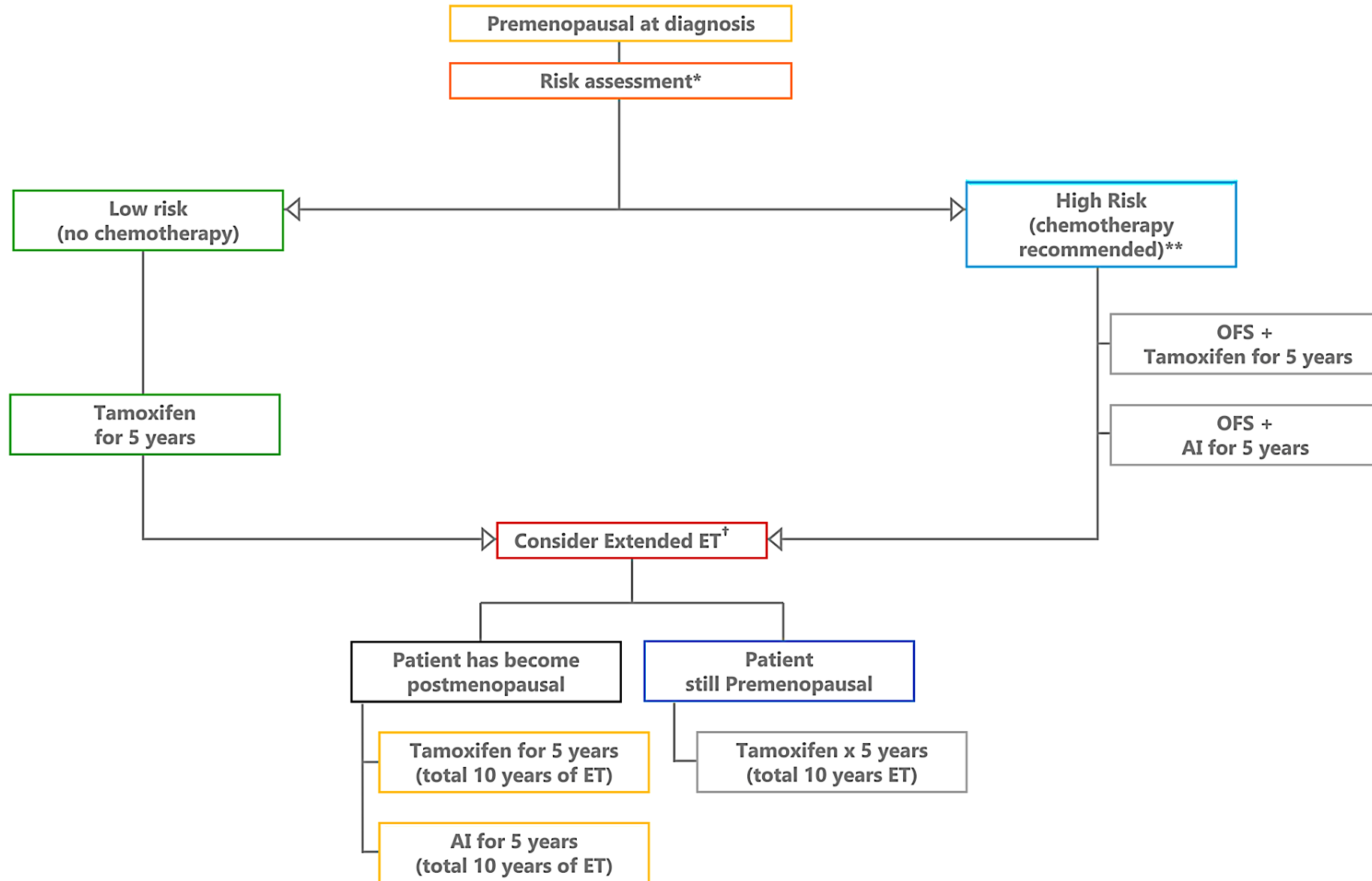


Extended Therapy With Letrozole and Ovarian Suppression in Premenopausal Patients With Breast Cancer After Tamoxifen

Kathryn J. Ruddy,¹ Stephen D. DeSantis,² William Barry,³ Hao Guo,³ Caroline C. Block,⁴ Virginia Borges,⁵ Eric P. Winer,² Ann H. Partridge²

Studio di fase II - chiusura anticipata dopo aver incluso solo 16/50 pazienti per 3.5 anni

EXTENDED ET IN PAZIENTI IN PRE-MENOPAUSA

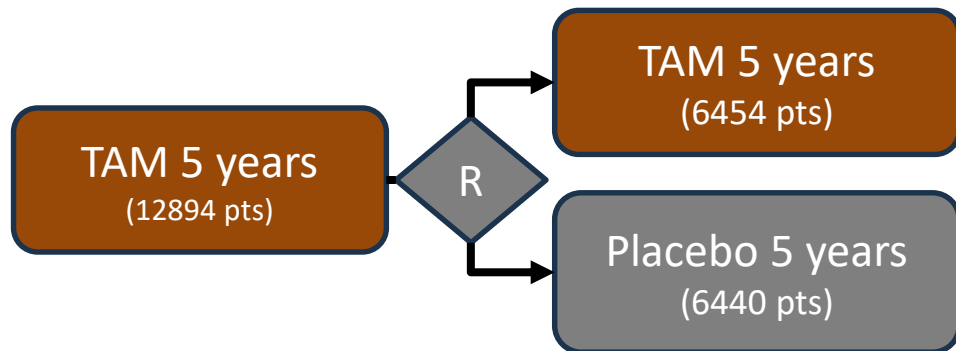


OUTLINE

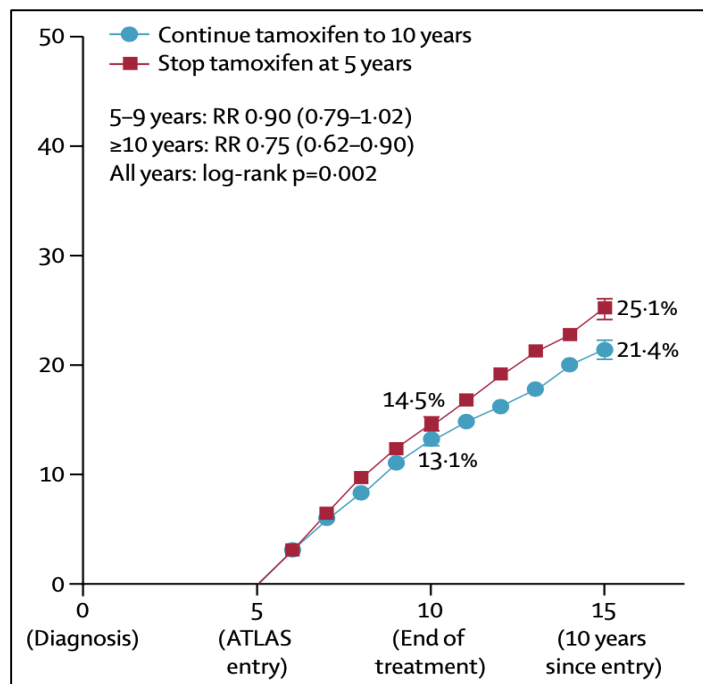
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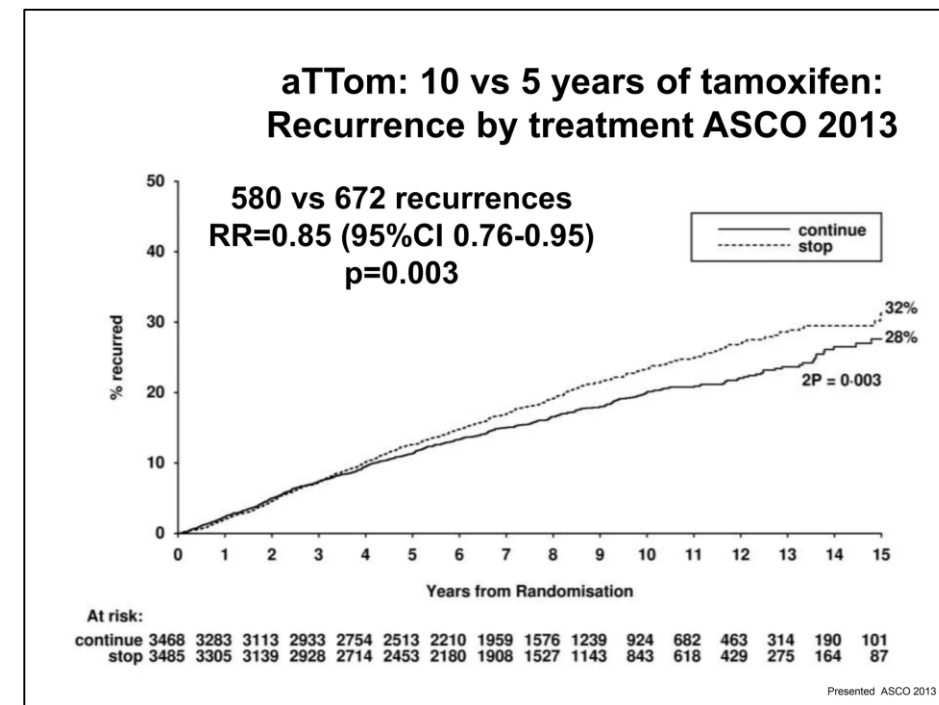
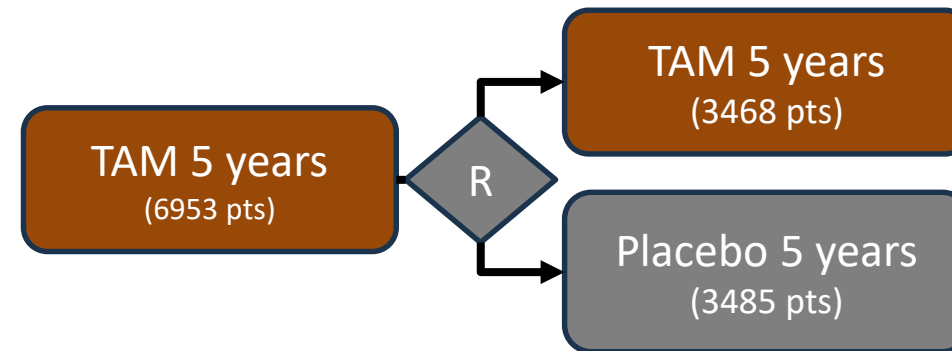
STUDIO ATLAS



Breast cancer recurrence

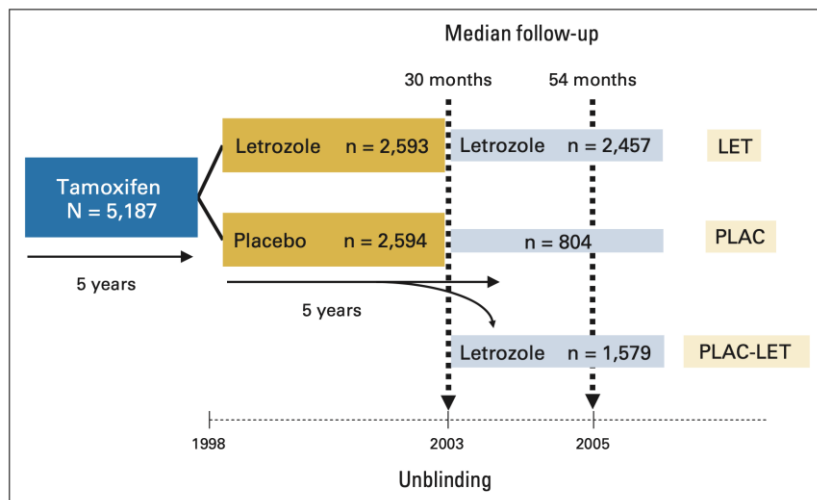
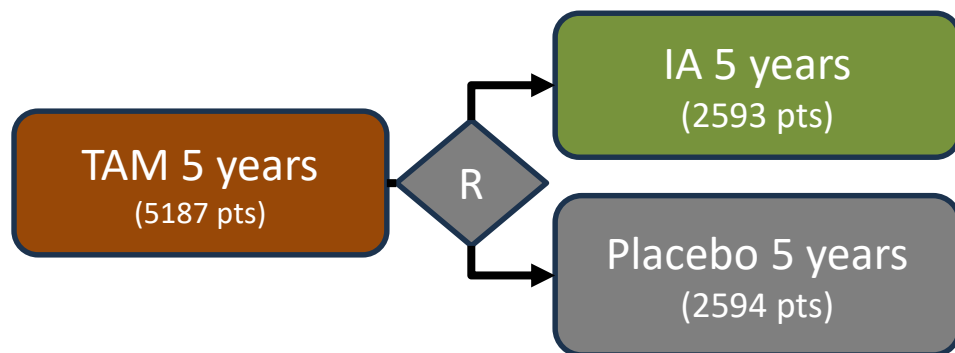


STUDIO aTTom

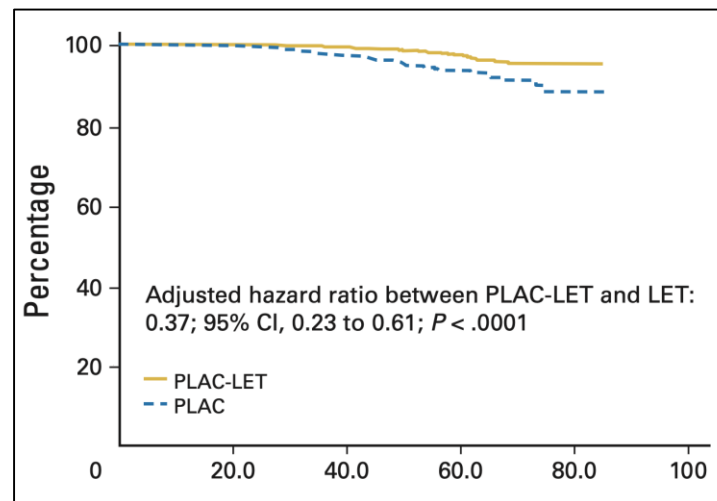


TAM → IA PER 5 ANNI (5 anni vs. 10 anni totali)

National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) - MA17



Node-positive ≈ 40%

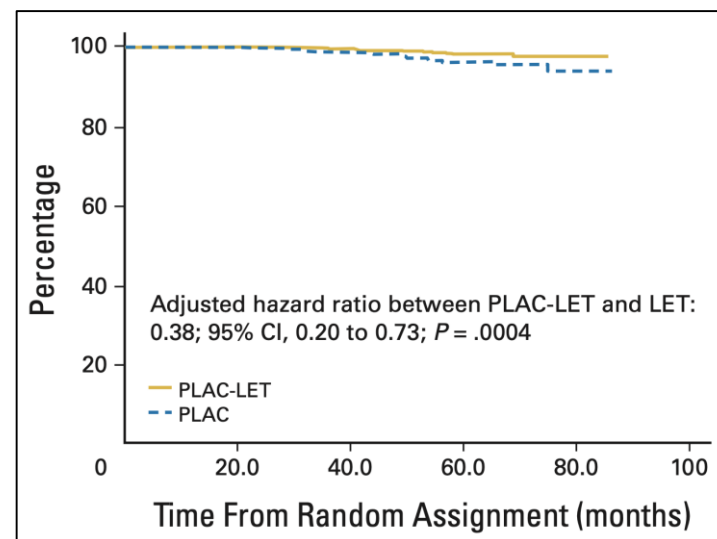


5.3 years

DFS

2.0% vs. 4.9%

$P < .0001$



DDFS

1.0% vs. 2.4%

$P = .0004$

OS

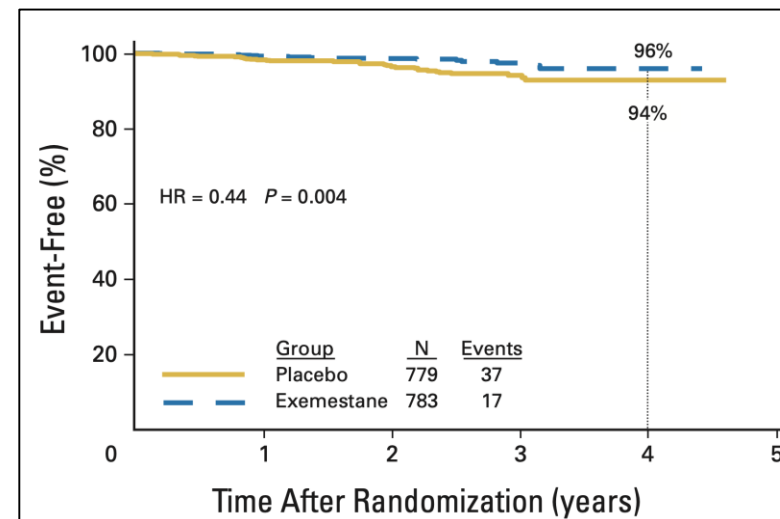
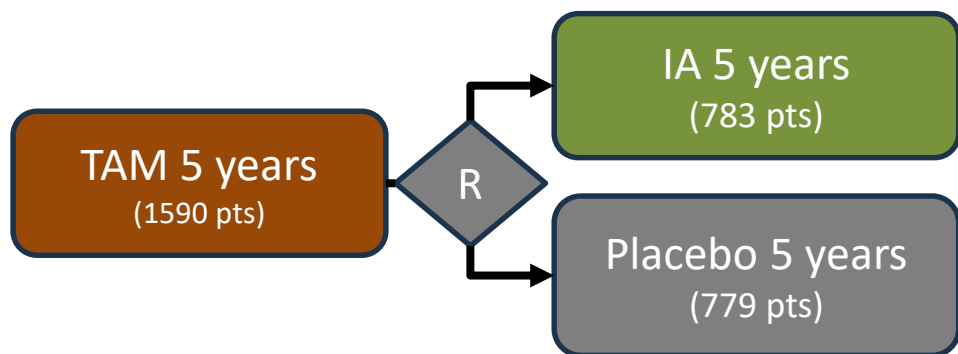
0.61 (0.52 to 0.71)

$P = .001$

TAM → IA PER 5 ANNI (5 anni vs. 10 anni totali)

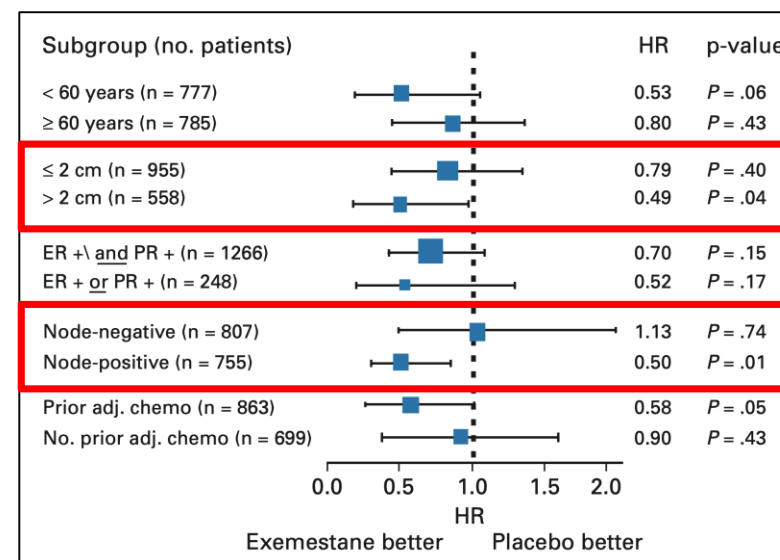
NSAPB B-33

Relapse-free survival



94% v 96%
HR 0.44, P=.004

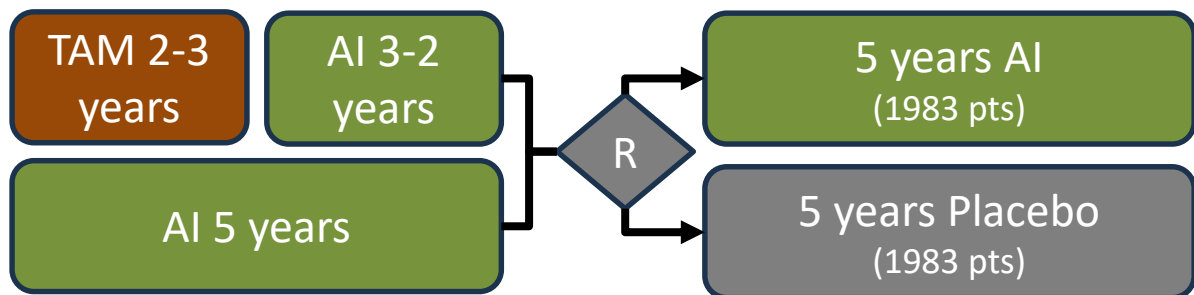
Characteristic	%		
	Exemestane (n = 799)	Placebo (n = 799)	All Patients (N = 1,598)
Age, years			
< 60	49	51	50
≥ 60	51	49	50
Tumor size, cm			
0-2	61	61	61
> 2	38	38	38
Unknown	1	1	1
No. of positive nodes			
0	52	52	52
1-3	33	33	33
4+	15	15	15



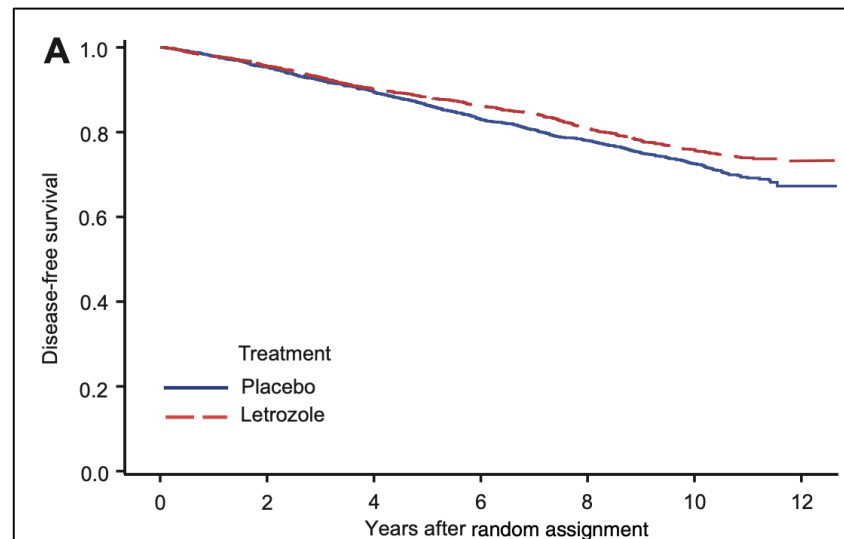
DFS EVENTS

TAM e/o IA → IA (5 anni vs. 10 anni totali)

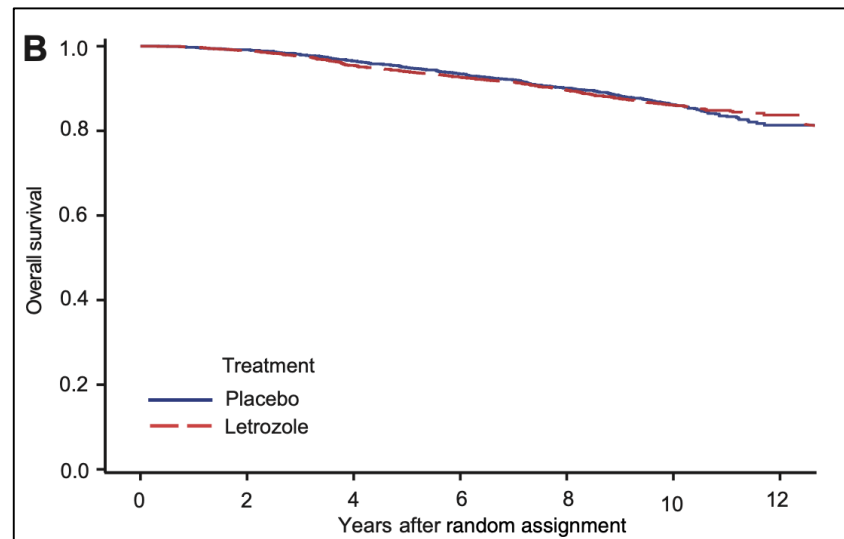
NSABP-B42



	Placebo group (n=1983)	Letrozole group (n=1983)
Age at randomisation, years		
<60	675 (34.0%)	685 (34.5%)
≥60	1308 (66.0%)	1298 (65.5%)
Race		
White	1840 (92.8%)	1848 (93.2%)
Black	81 (4.1%)	70 (3.5%)
Asian	39 (2.0%)	39 (2.0%)
Other or unknown	23 (1.2%)	26 (1.3%)
Pathological node status		
Negative	1134 (57.2%)	1145 (57.7%)
Positive	849 (42.8%)	838 (42.3%)



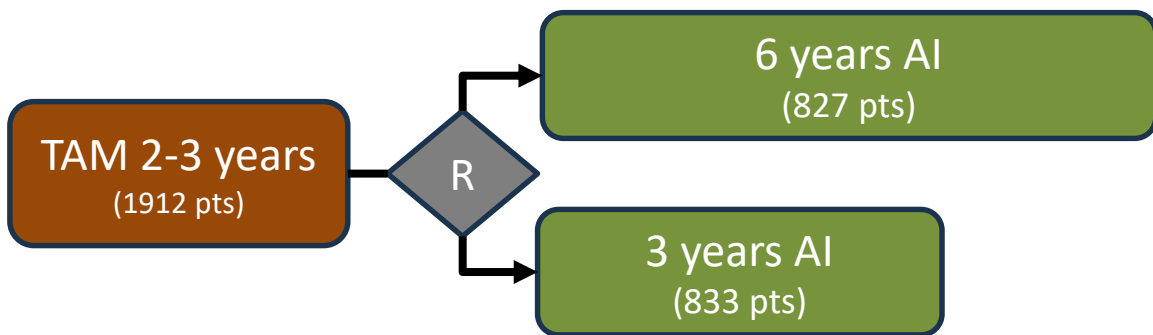
DFS
+3.3%
HR 0.85
P=0.01



OS
-0.1%
HR 0.97
P=0.74

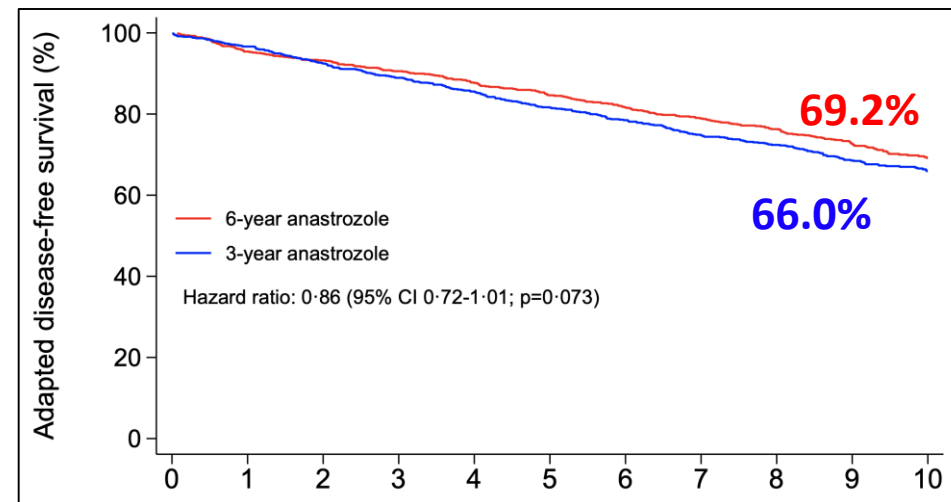
TAM→IA (5/6 anni vs. 8/9 anni totali)

DATA

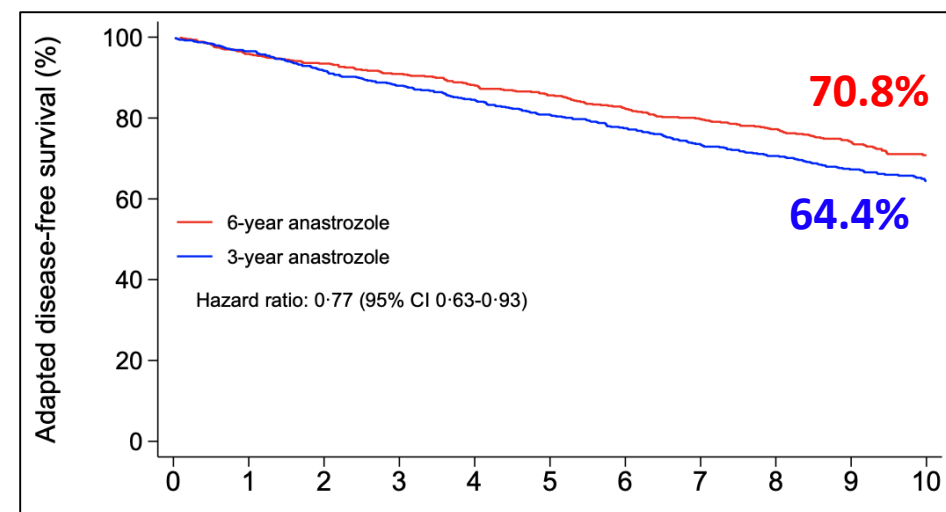


Characteristic ^a	6-year anastrozole (N = 827)	3-year anastrozole (N = 833)
Median age – years (IQR)	57 (51–64)	57 (51–64)
Age at randomisation – no. (%)		
<60 years	483 (58)	488 (59)
≥60 years	344 (42)	345 (41)
Pathological tumour status – no. (%)		
T1	376 (45)	383 (46)
T2	392 (47)	382 (46)
T3/4	58 (7)	67 (8)
Unknown	1 (<1)	1 (<1)
Pathological nodal status – no. (%)		
Negative	266 (32)	282 (34)
Positive	561 (68)	551 (66)
Tumour grade – no. (%)		
G1	139 (17)	158 (19)
G2	430 (52)	415 (50)
G3	229 (28)	238 (29)
Unknown	29 (4)	22 (3)

Disease-free survival

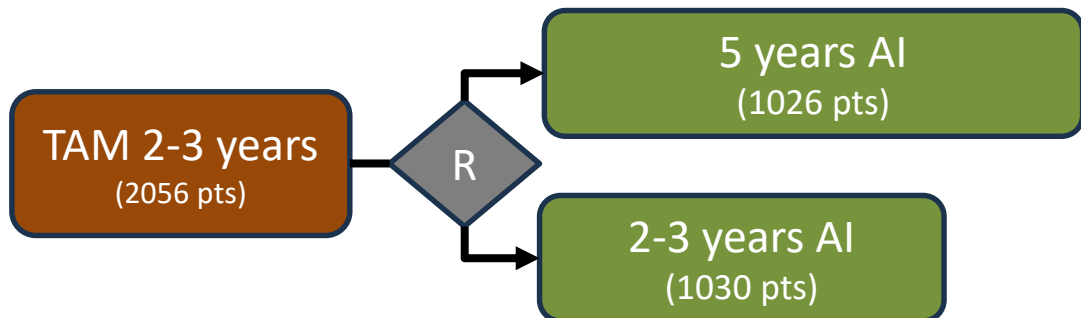


In popolazione ER+ e PgR+



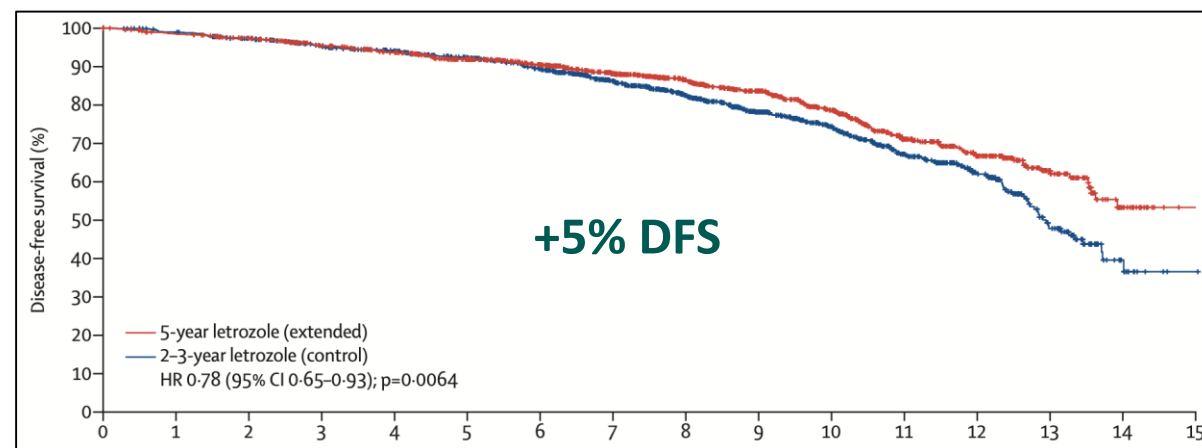
TAM → IA (5 anni vs. 7/8 anni totali)

GIM 4

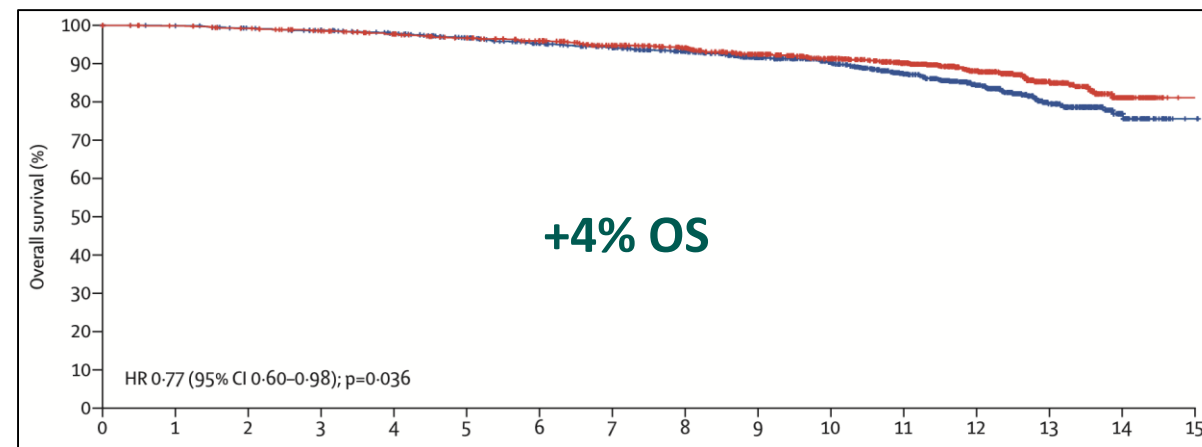


	2-3-year letrozole group (n=1030)	5-year letrozole group (n=1026)
Age, years	60 (54-67)	61 (54-68)
Tumour size		
pT1	704 (68.3%)	703 (68.5%)
pT2	261 (25.3%)	252 (24.6%)
pT3-4	34 (3.3%)	43 (4.2%)
Unknown	31 (3.0%)	28 (2.7%)
Type of breast surgery		
Breast-conserving surgery	777 (75.4%)	772 (75.2%)
Mastectomy	232 (22.5%)	246 (24.0%)
Unknown	15 (1.5%)	8 (0.8%)
Nodal status		
pN0	581 (56.4%)	568 (55.4%)
pN1-2-3	411 (39.9%)	428 (41.7%)
Unknown	38 (3.7%)	30 (2.9%)
Tumour grade		
G1	156 (15.1%)	161 (15.7%)
G2	564 (54.8%)	589 (57.4%)
G3	221 (21.5%)	213 (20.8%)

Disease-free survival

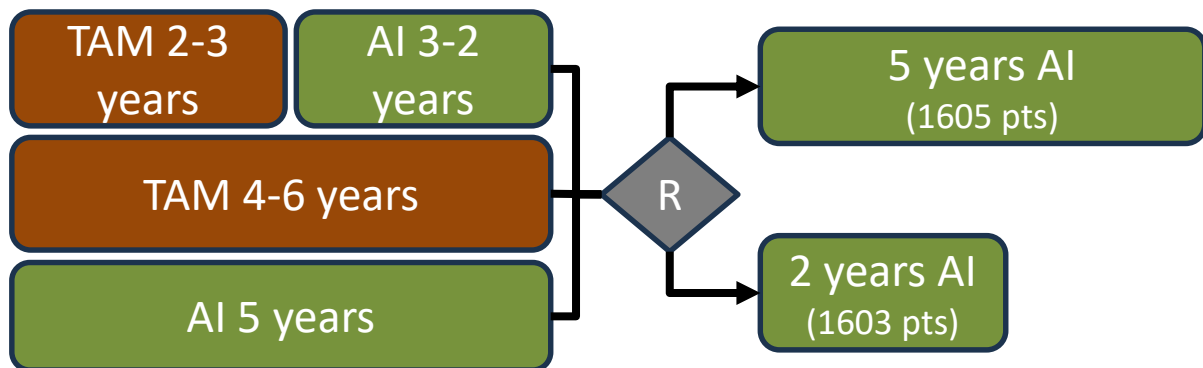


Overall survival

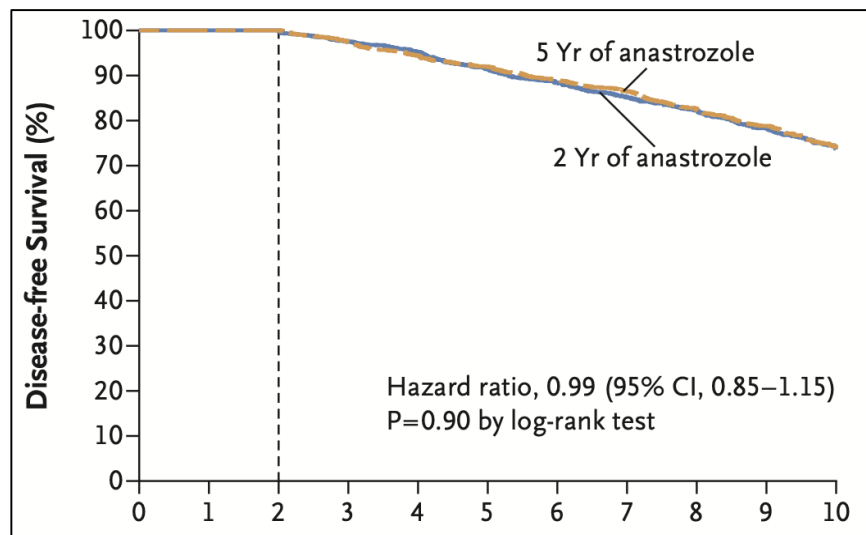


TAM e/o IA → IA (7/8 anni vs. 10 anni totali)

ABCSG-16

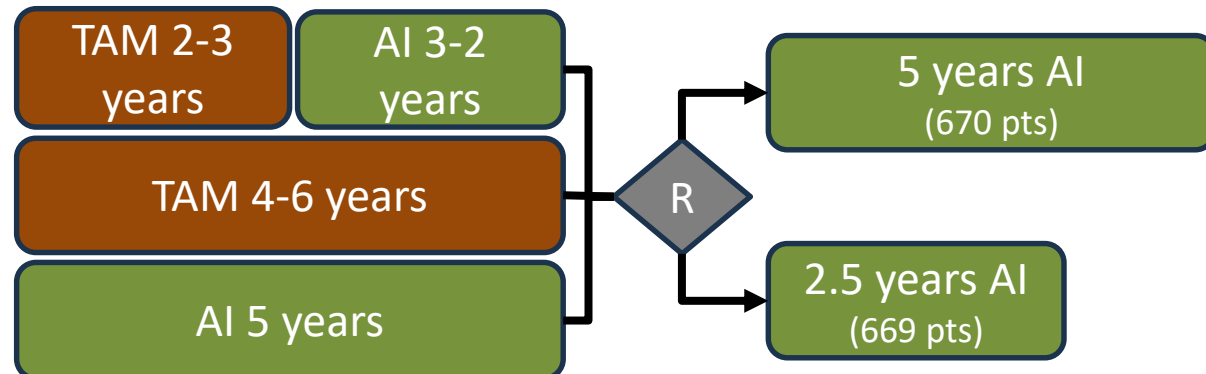


Disease-free survival

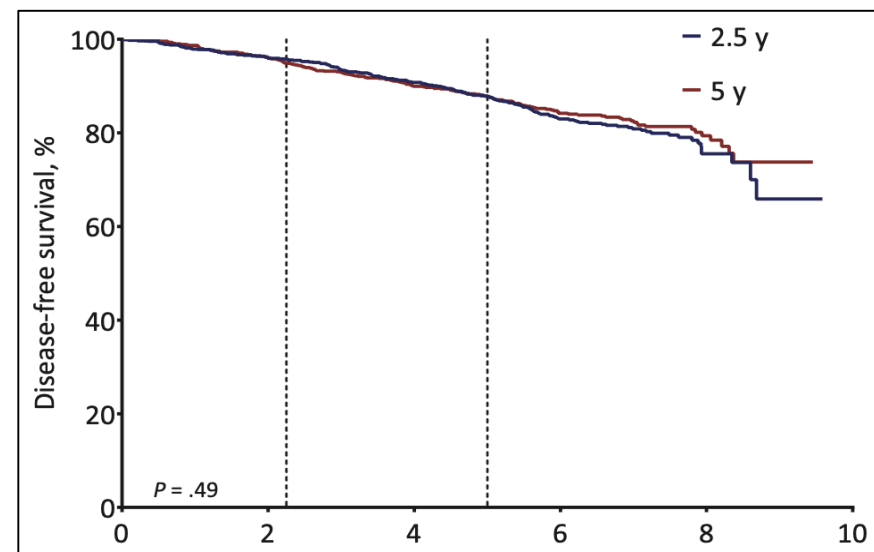


**Node positive:
≈ 30%**

IDEAL



Disease-free survival



**Node positive:
> 50%**

QUALE DURATA DI EXTENDED THERAPY?

Total ET Duration	Trial	Population	Adjuvant ET Prior to Random Assignment	Treatment	No. of Patients	Follow-up, months	iDFS (95% CI)	OS (95% CI)	Adherence
10 years or more vs. 5 years	ATTOM ¹⁰	Pre- and postmenopausal, stage I-III, known ER+ 39%	5 years of TAM	5 years of TAM vs. observation	6,953	108	≥ 10-year RR, 0.75; 0.66-0.86	≥ 10-year RR 0.86; 0.75-0.97	NA
	ATLAS ¹¹	Pre- and postmenopausal, stage I-III	5 years of TAM	5 years of TAM vs. observation	6,846	≈ 120	≥ 10-year RR, 0.75; 0.62-0.90	BCSS ≥ 10-year RR, 0.71; 0.58-0.88	≈ 80%
	MA-17 ¹²	Postmenopausal, stage I-III	5 years of TAM	5 years of LET vs. placebo	5,187	30	0.58; 0.45-0.76	0.82; 0.57-1.19; N+, 0.61; 0.38-0.98	≈ 80%
	NSAPB B-33 ¹³	Postmenopausal, stage I-III	5 years of TAM	5 years of EXE vs. observation	1,598	30	0.68; p = .07; N+, 0.50; 0.30-0.86	No difference	NA
	NSAPB B-42 ¹⁴	Postmenopausal, stage I-III	5 years of ET (AIs or TAM + AIs)	5 years of LET vs. placebo	3,923	82.8	0.85; 0.73-0.999; p = .048	1.15; 0.92-1.44	62.5%
	AERAS ¹⁵	Postmenopausal, stage I-III	5 years of ET (ANA or TAM + ANA)	5 years of ANA vs. observation	1,697	58.8	0.548; p = .0004	1.389; p = .665	78%
	MA-17R ⁷	Postmenopausal women, stage I-III	4.5-6 years of AIs and prior TAM, any duration	5 years of LET vs. placebo	1,918	75.6	0.66; 0.48-0.91	0.97; 0.73-1.28	62.5%
7-8 years vs. 5 years	DATA ¹⁷	Postmenopausal, stage I-III	2-3 years of TAM	6 years of ANA vs. 3 years of ANA	1,860	49.2	0.79; 0.62-1.02*	0.91; 0.65-1.29*	67.2%, 6 years; 78.6%, 3 years
	GIM-4 ¹⁸	Postmenopausal, stage I-III	2-3 years of TAM	2-3 years of LET vs. 5 years of LET	2,056	140.4	0.78; 0.65-0.93	0.77; 0.60-0.98	63%, 5 years; 80%, 2-3 years
7.5 years vs. 10 years	IDEAL ¹⁶	Postmenopausal, stage I-III	5 years of any ET	2.5 years of LET vs. 5 years of LET	1,824	79.2	0.92; 0.74-1.16	1.04; 0.78-1.38	59.9%, 5 years; 78%, 2.5 years
	ABCSG 16 ¹⁹	Postmenopausal, stage I-III	4-6 years of ET (AIs, TAM, or TAM + AIs)	2 years of ANA vs. 5 years of ANA	3,484	118.0	0.99; 0.85-1.15**	1.02; 0.83-1.25**	80%, 2 years; 67%, 5 years

DURATA:
10 anni > 5 anni
7/8 anni > 5 anni
10 anni ≈ 7/8 anni

7-8 anni di durata ottimale nelle pazienti a rischio Intemedio/alto

OUTLINE

- INTRODUZIONE
- PAZIENTI IN PRE-MENOPAUSA
- PAZIENTI IN POST-MENOPAUSA
- **PREDIRE IL RISCHIO DI RECIDIVA**
- CONCLUSIONI

PREDIRE RISCHIO DI RECIDIVA DOPO 5 ANNI

CTS-5

Prevedere il rischio di recidiva a 10 anni nelle pazienti senza recidiva nei primi 5 anni

Donne in post-menopausa
Rischio basso (<5%) - intermedio - alto (>10%)

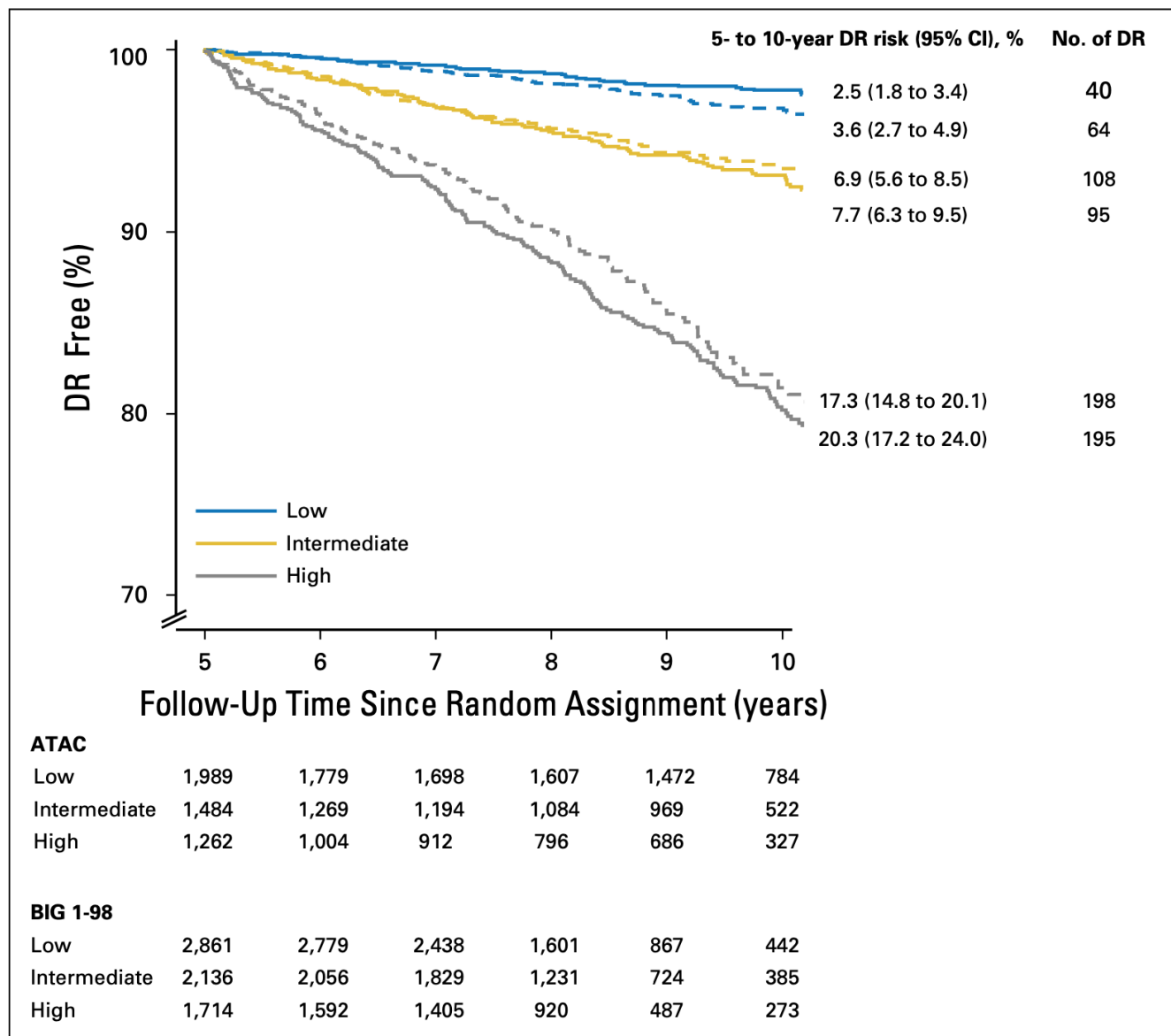
Tumour size (mm)

Tumour Grade

Patient age (years)

Number of nodes involved

CALCULATE RESULT ⇨



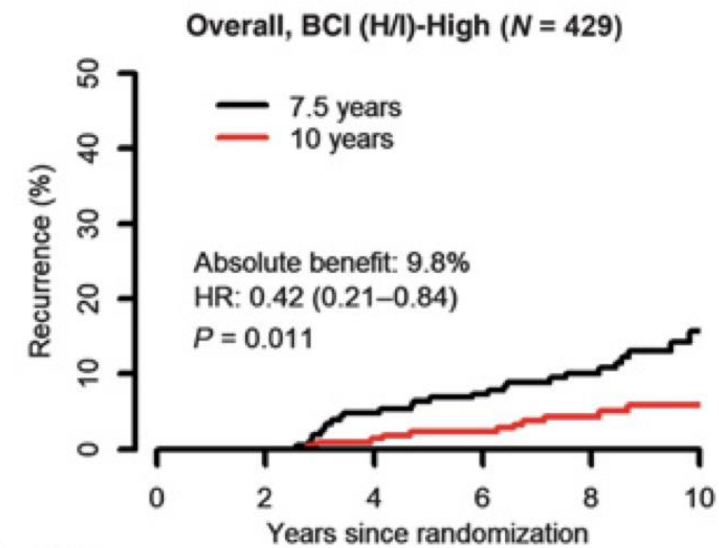
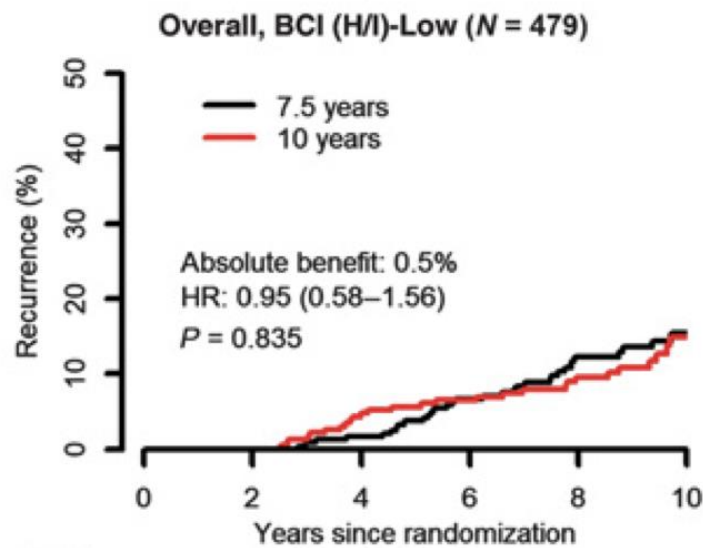
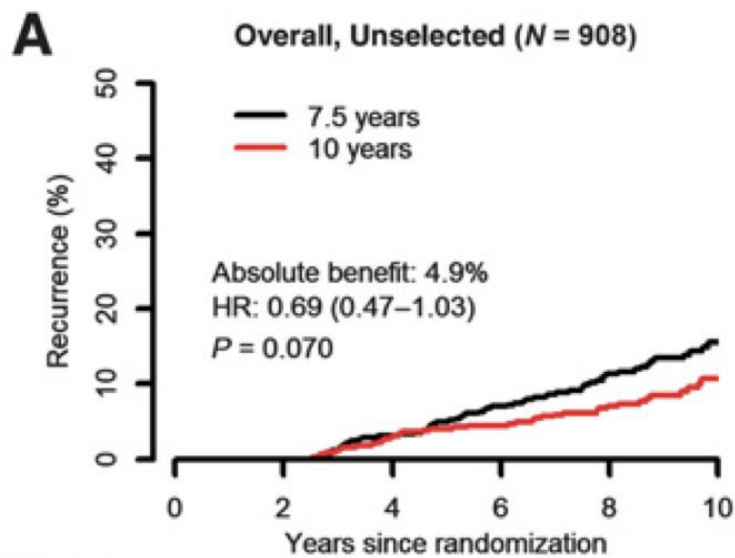
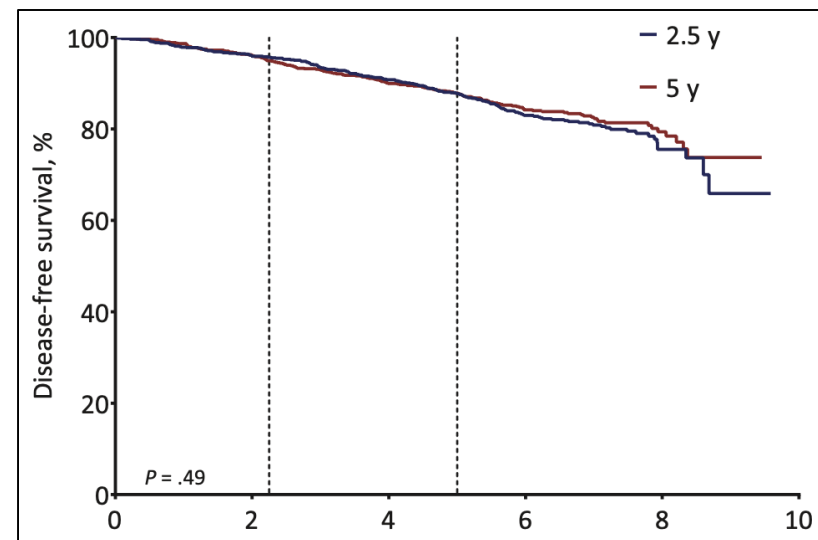
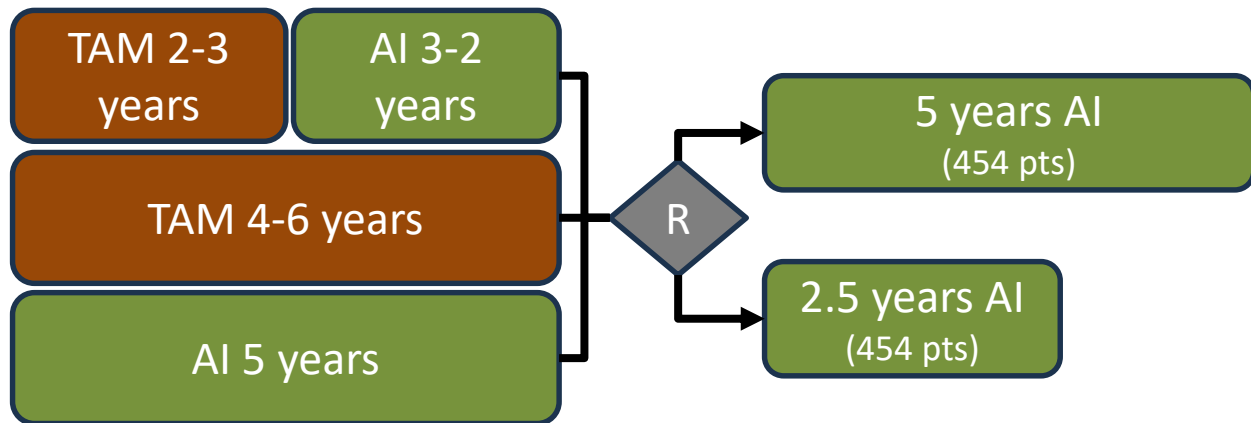
TEST GENOMICI

RUOLO DEI TEST GENOMICI NELLA PREDIZIONE DELLE RECIDIVE TARDIVE

	Oncotype DX	Prosigna (PAM50)	EndoPredict	MammaPrint	Breast Cancer Index (BCI)
Type of assay	<u>21-gene</u> recurrence score Centralized	<u>50-gene</u> assay Decentralized	<u>12-gene</u> assay Decentralized	<u>70-gene</u> assay Centralized	<u>2-gene</u> ratio (H/I) & <u>molecular grade index</u> Decentralized
Tissue sample	FFPE	FFPE	FFPE	Fresh frozen or FFPE	FFPE
Technique	qRT-PCR	qRT-PCR	qRT-PCR	DNA microarray & qRT-PCR	qRT-PCR
Results presentation	Low, intermediate & high-risk groups	Continuous variable	Dichotomous: Low & high-risk groups	Dichotomous: Good & poor prognosis	Continuous variable
Clinical validation for late recurrence	TransATAC trial (n=785 pts)	TransATAC (n=785 pts) ABC SG-8 (n=1,246 pts)	ABC SG-6 and ABC SG-8 trials (n=1,702 pts)	ABC SG-8 (n=658 pts)	TransATTOM (n=583) MA-17 (n=249 pts) IDEAL (n=454 pts) NSABP-B42 (n=2,179 pts)
Clinical application of the assay	Early relapses Predictive and Prognostic for pN0 and pN1 (1-3 positive nodes)	Early & late relapses Prognostic for pN0 and pN1 (1-3 positive nodes)	Early & late relapses Prognostic for pN0 and pN1 (1-3 positive nodes)	Early relapses Prognostic for pN0 and pN1 (1-3 positive nodes)	Early & late relapses Predictive and prognostic of benefit of extended adjuvant ET

BREAST CANCER INDEX

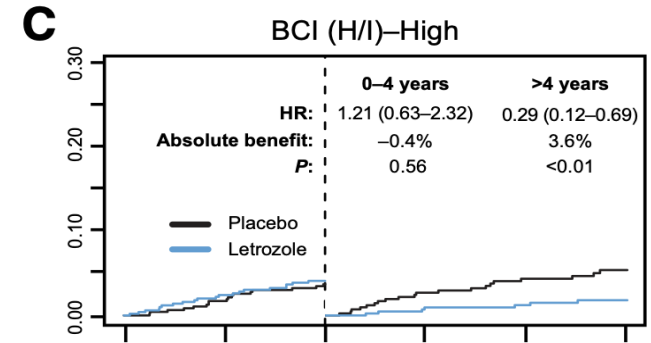
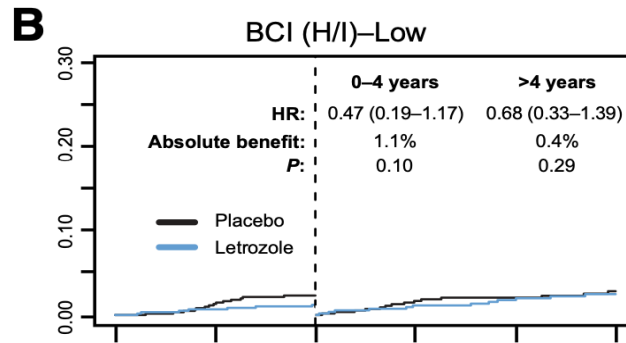
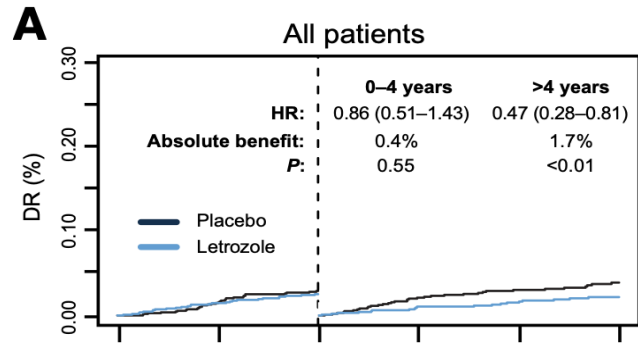
IDEAL



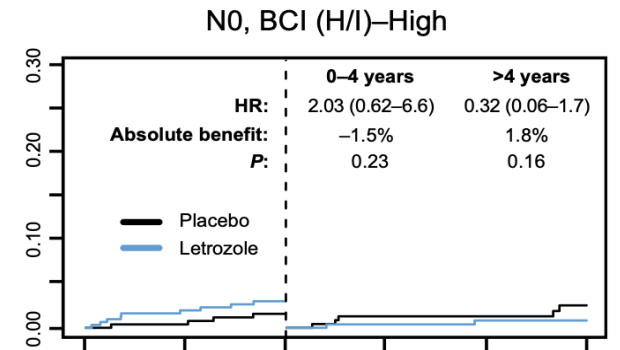
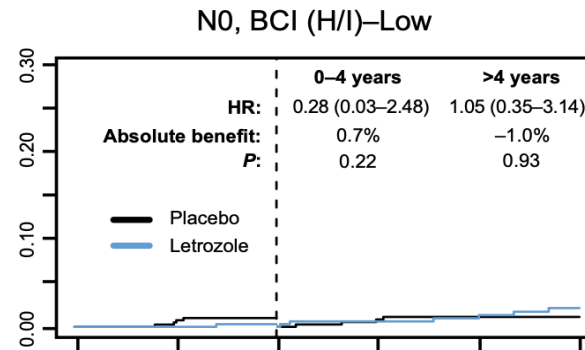
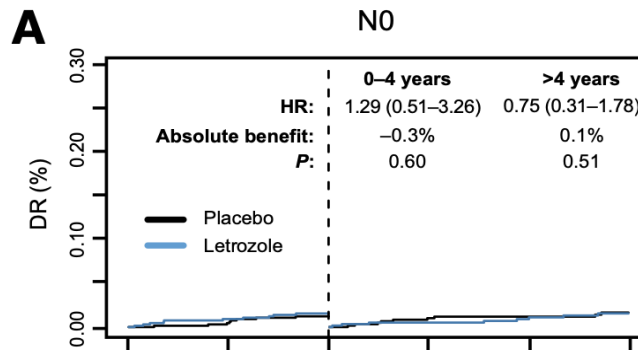
BREAST CANCER INDEX

NSABP-B42

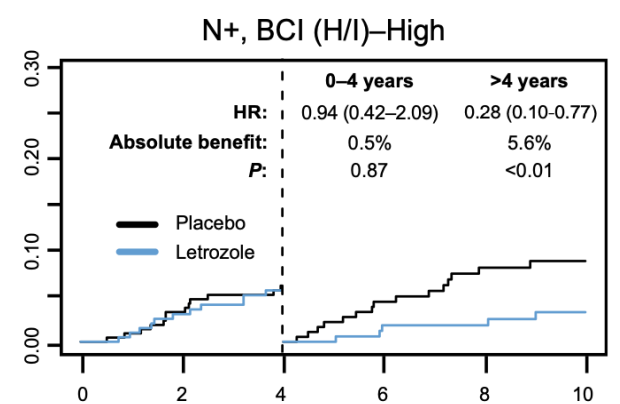
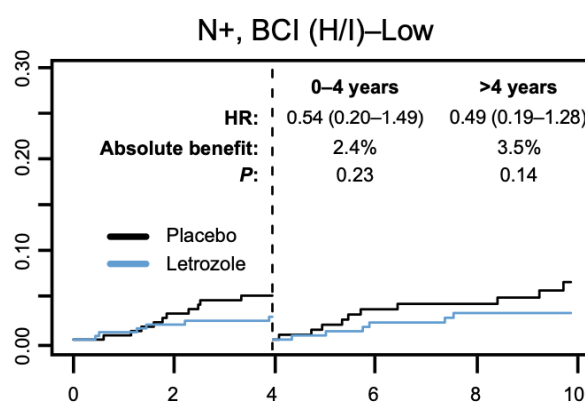
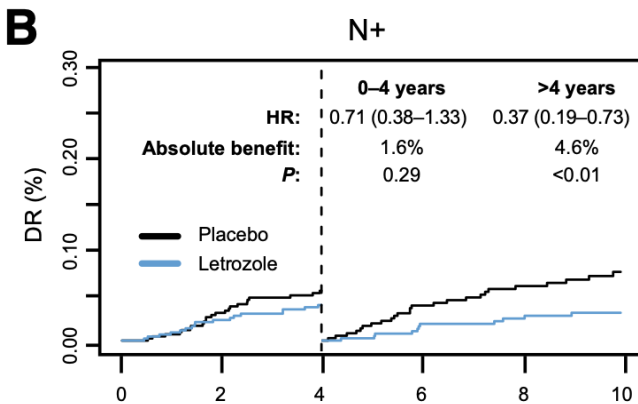
2,178
PAZIENTI



OVERALL

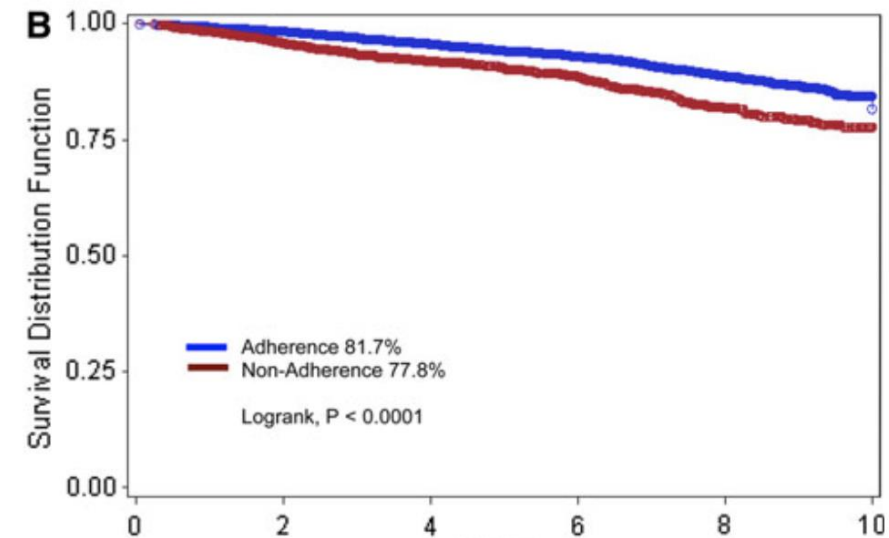
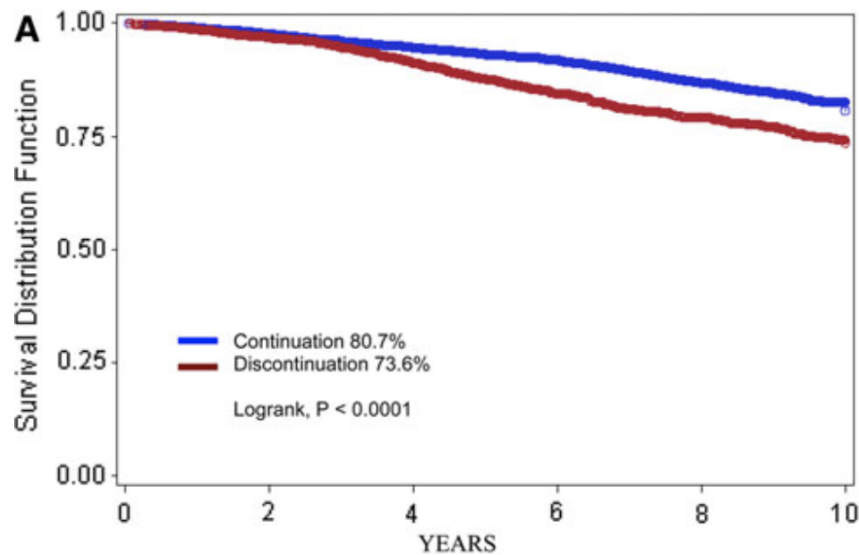
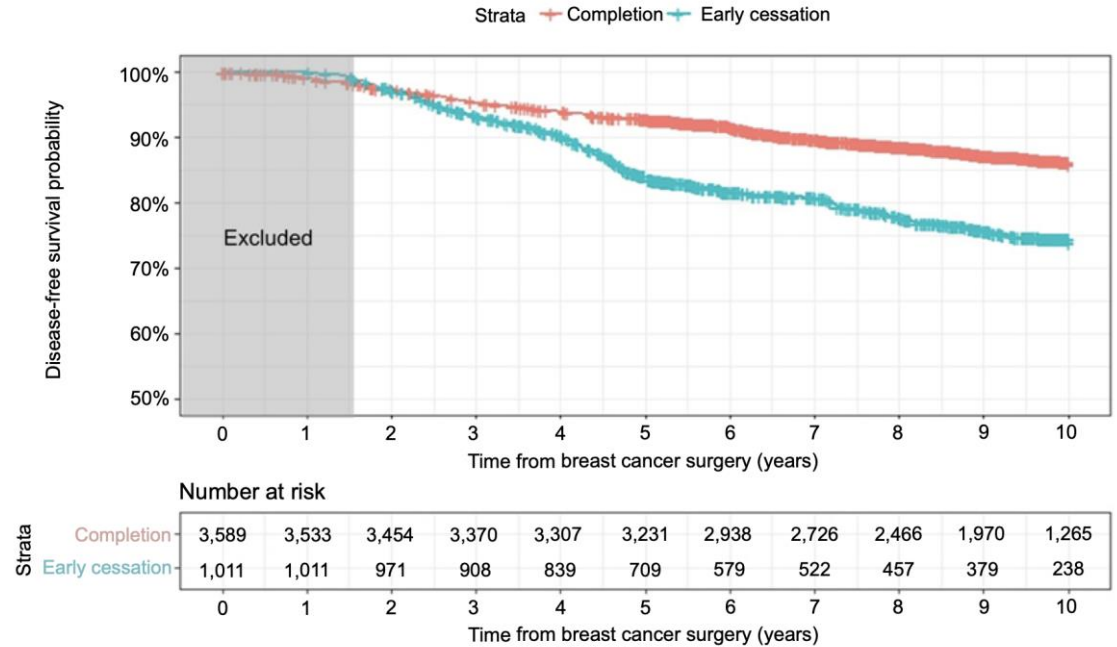
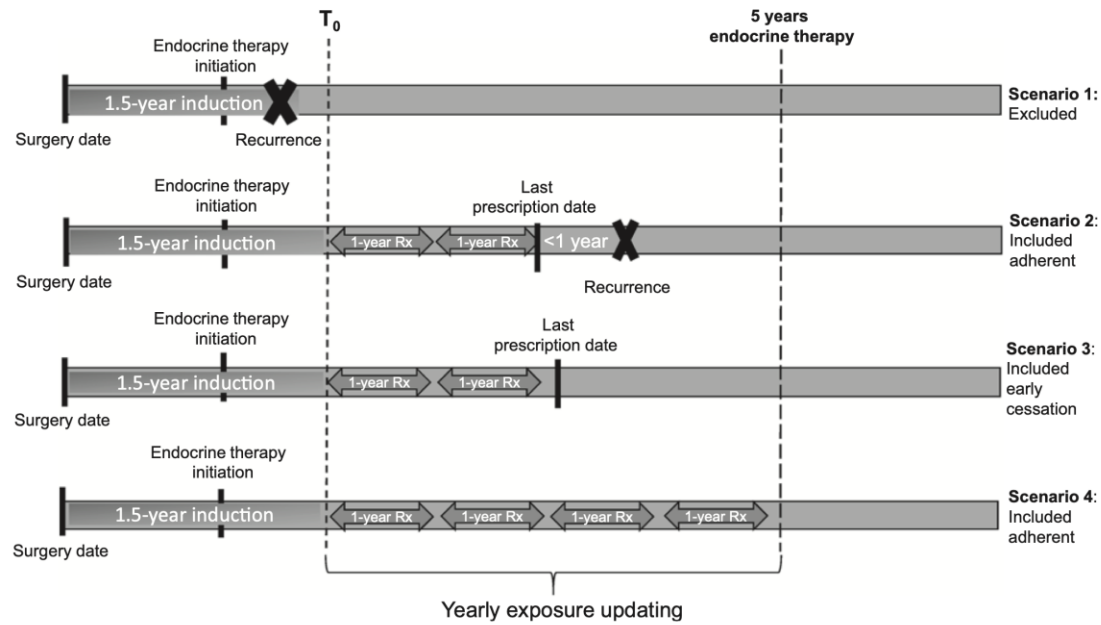


NODE
NEGATIVE



NODE
POSITIVE

ADERENZA ALLA TERAPIA ENDOCRINA ADIUVANTE E OUTCOMES



OUTLINE

- INTRODUZIONE
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- PAZIENTI IN POST-MENOPAUSA
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- **CONCLUSIONI**

CONCLUSIONI

La durata della terapia endocrina si basa soprattutto su **rapporto rischi/benefici** per ogni paziente.

Premenopausa:

- Pazienti a basso rischio: Tam 5 anni.
- Pazienti a rischio intermedio/alto: OFS + Tam o IA per primi 5 anni e successivamente Tam/IA.
- Non ci sono dati sulla prosecuzione di OFS oltre il 5° anno.

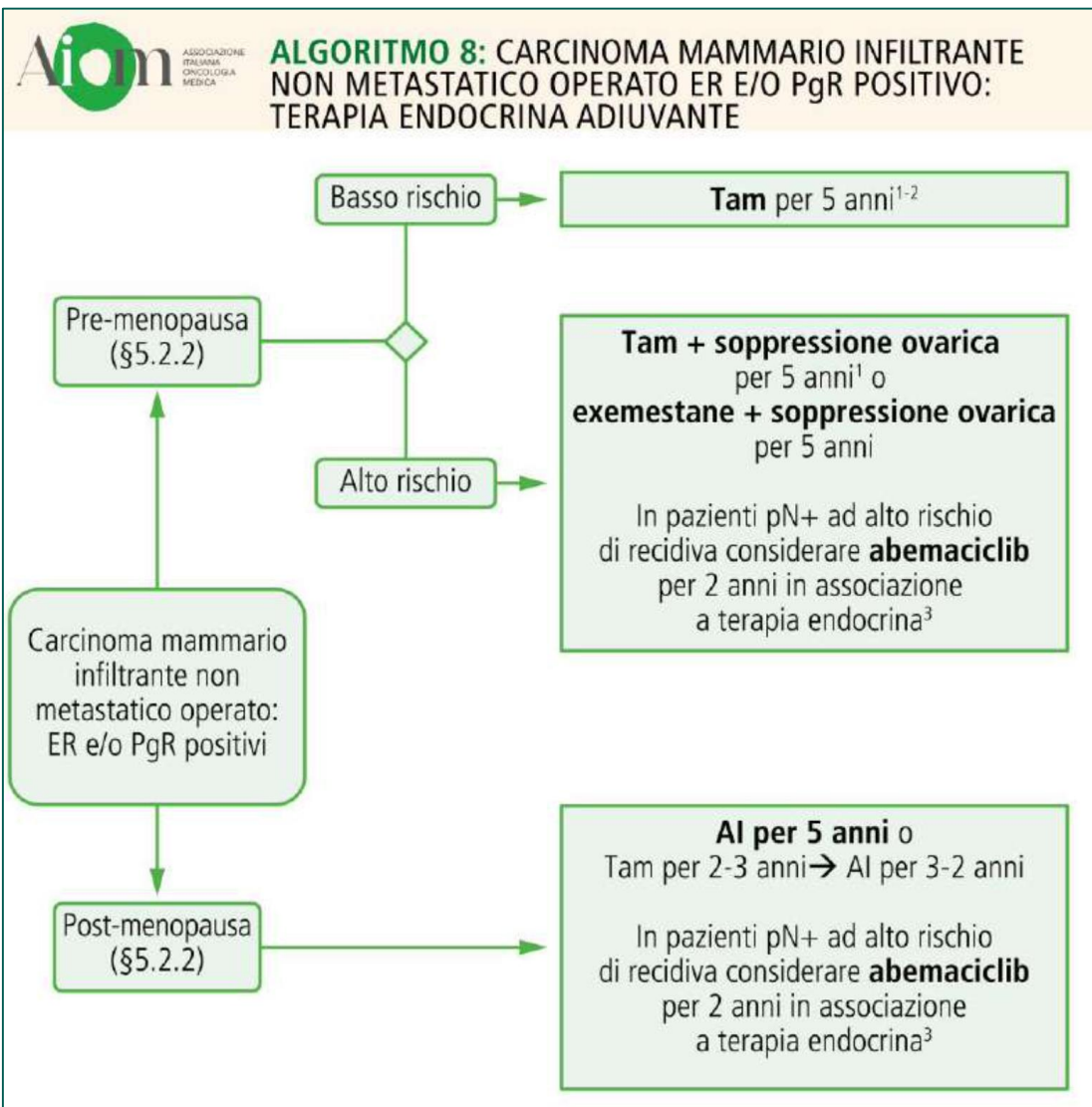
Postmenopausa:

- Pazienti a basso rischio: Tam e/o AI per primi 5 anni.
- Pazienti a rischio intermedio/alto: 7/8 anni standard per la maggior parte delle pazienti.
- Pazienti a rischio molto alto: considerare 10 anni totali, se terapia tollerata, rapporto rischi/benefici.

Ruolo emergente dei **test genomici per la previsione del rischio di recidive tardive.**

La migliore terapia endocrina adiuvante è **quella che la paziente riesce a tollerare meglio.**

CONCLUSIONI



Stage	ET type	ET years	OFS in premenopausal women	Bisphosphonates (postmenopausal or OFS)
T1ab N0	TAM (or AI)	5	No	No
T1c N0	TAM or AI	5	Consider for high-risk or if AI	No
T2-3 N0	TAM or AI	7-10	Consider (Yes if AI)	Yes
T1-2 N1	TAM or AI	7-10	Yes	Yes
Stage 3	AI	7-10	Yes	Yes

Progetto CANOA: quali novità per il 2024?

AIGOM

ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Progetto **CANOA**

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2024?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Coordinatori scientifici:

Stefania Gori

Giovanni L. Pappagallo

Verona, 22-23 Marzo 2024
Hotel Leon d'Oro

Grazie per l'attenzione!

Dr. Luca Arecco

U.O.C. Clinica di Oncologia Medica

IRCCS Ospedale Policlinico San Martino - Università degli studi di Genova

Institute Jules Bordet, Bruxelles, Belgium

