foro debate oncología

Zaragoza 26-29 septiembre 2023

CÁNCER DE MAMA: DIÁLOGOS SOBRE ENFERMEDAD TEMPRANA

Cáncer de mama luminal: novedades en el tratamiento adyuvante

Dudas ante este nuevo escenario: ¿plataformas genómicas?. ¿HT extendida? ¿bloqueo estrogénico completo? ¿papel quimioterapia?

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Información

- Employment: OSAKIDETZA (Servicio Vasco de Salud)
- Consultant or Advisory Role: AstraZeneca, Pfizer, Roche, Palex, Seagen, Gilead, MSD
- Stock Ownership: no
- Research Funding: AstraZeneca, Pfizer, Novartis, Roche
- Speaking: AstraZeneca, Pfizer, Novartis, Roche, Eisai
- Grant support: No
- Other: Meetting inscription & travel expenses: AstraZeneca, Pfizer, Roche, Eisai, Lilly, Daichii-Sankyo

CM precoz RH+/HER2-

- Riesgo de recurrencia tardía

- RH (RE y RP) - Factor pronostico , predictivo
- HER2 - Low vs 0 - no dif pronóstica
- T y N - Factor pronóstico
- Grado - Factor pronóstico
- Firmas Genómicas - Factor pronostico, predictivo de beneficio a QT (High risk RScore), BCI (beneficio terapia endocrina extendida?)
- Ki 67 - Factor pronóstico. Factor predictivo de hormonosensibilidad- Descenso precoz - (problema de reproducibilidad)
- Respuesta patológica a tratamiento neoadyuvante -
  - QT - Baja tasa de pCR. Menos discriminante que en HER2 y TN
  - HT - PEPI score - Factor pronóstico - N o mide la respuesta sino el estatus tras HT independientemente de la respuesta

CONSENSO

Journal Pre-proof

Understanding breast cancer complexity to improve patient outcomes: The St. Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023

G. Curigliano, H.J. Burstein, M. Gnant, S. Loibl, D. Cameron, M.M. Regan, C. Denkert, P. Poortmans, W.P. Weber, B. Thürlimann

PII: S0923-7534(23)00835-9

DOI: https://doi.org/10.1016/j.annonc.2023.08.017

Reference: ANNONC 1265

To appear in: *Annals of Oncology*

Received Date: 18 July 2023

Accepted Date: 23 August 2023

New practice changing Studies in early Breast Cancer since St Gallen 2021 - HR+/Systemic Therapy - I

- The MONARCH-E trial showed that adjuvant abemaciclib reduced invasive disease-free survival in high risk, ER positive breast cancer.
- The NATALEE trial showed that adjuvant ribociclib reduced invasive disease-free survival in high risk, ER positive breast cancer.

St. Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023 - Ann Onc 2023 - DOI:https://doi.org/10.1016/j.annonc.2023.08.017

New practice changing Studies in early Breast Cancer since St Gallen 2021 - HR+/Systemic Therapy - II

- After 13 years of follow up of the SOFT and TEXT trials, the addition of OFS to adjuvant endocrine therapy confirmed a clinically significant OS benefit in high-risk pre-menopausal patients.

- The RxPonder study shows that there is no benefit to chemotherapy in postmenopausal patients with lower genomic risk N1 tumors, but that chemotherapy can reduce the risk of recurrence in premenopausal patients, possibly due to chemo-induced amenorrhea.
- After 11 years of follow-up, ET was confirmed as non-inferior to chemo-ET in patients with HR-positive, HER2-negative, node-negative early BC and a RS 11-25.

- In postmenopausal patients with stage 1 or 2, HR positive breast cancer who had received 5 years of adjuvant endocrine therapy, extending hormone therapy by 5 years provided no benefit over a 2-year extension but was associated with a greater risk of bone fracture.

St. Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023 - Ann Onc 2023 - DOI:https://doi.org/10.1016/j.annonc.2023.08.017

New practice changing Studies in early Breast Cancer since St Gallen 2021 - HR+/Systemic Therapy - III

- The OlympiA trial demonstrates that adjuvant therapy with olaparib increases overall survival in patients with breast cancer harboring germline BRCA1/2mutation.

- After 8 years, adjuvant denosumab during adjuvant therapy with AI confirmed to markedly reduce treatment-induced clinical fractures

- Among select patients with previous HR-positive early BC, temporary interruption of ET to attempt pregnancy did not confer a greater short-term risk of BC events, including distant recurrence, than that in the external control cohort.

St. Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023 - Ann Onc 2023 - DOI:https://doi.org/10.1016/j.annonc.2023.08.017

***Risk stratification HR(+)/HER2(-):**

Favorable biology:

- ✓ lower risk genomic signature
  - recurrence score < 25 (postm N0/N1-3) or (prem 16 to 25 N0),
  - or 70-gene signature 'low');
- ✓ strongly ER positive with low to intermediate grade,
- ✓ and/or lower baseline Ki67,
- ✓ or decrease in Ki67 with preoperative exposure to endocrine therapy.

Less favorable biology:

- ✓ higher risk genomic signature (e.g. recurrence score > 25 or 70-gene signature 'high');
- ✓ lower ER expression, intermediate to high grade,
- ✓ and/or higher baseline Ki67,
- ✓ or lack of decline in Ki67 with preoperative exposure to endocrine therapy.

CONSENSO

Table 3 Systemic Therapy for ER+ HER2- breast cancer

Anatomic Stage	TN	Type and duration of endocrine therapy*	Ovarian Suppression	Chemotherapy°/Abemaciclib		Olaparib
				Premenopausal	Postmenopausal	Premenopausal and postmenopausal
Stage 1	T1ab N0	AI or Tam, 5 years§	No OFS	No	No	No
	T1c N0	AI or Tam, 5 years	Consider OFS and AI/tam for higher risk, particularly those warranting chemotherapy, age < 40, high grade, or intermediate genomic scores (e.g. recurrence score 16 to 25)	Consider no chemotherapy for favorable biology tumors especially if not pursuing OFS*** Yes for less favorable biology tumors	No for favorable biology tumors*** Yes for less favorable biology tumors	No

*Historically, the St Gallen Panel has favored AI-based therapy in higher risk tumors defined by T and N stage, grade, and Ki67 score
§ minimal risk may be managed without adjuvant treatment

CONSENSO

Table 3 Systemic Therapy for ER+ HER2- breast cancer

Anatomic Stage	TN	Type and duration of endocrine therapy*	Ovarian Suppression	Chemotherapy°/Abemaciclib		Olaparib
				Premenopausal	Postmenopausal	Premenopausal and postmenopausal
Stage 2	N0 (node negative)	Consider extended therapy**, especially after initial 5 years of tamoxifen	OFS and AI/tam for higher risk, particularly those warranting chemotherapy, age < 40, high grade, or intermediate genomic scores (e.g. recurrence score 16 to 25)	Consider CT for favorable biology tumors especially if not pursuing OFS *** Yes for less favorable biology tumors	No for favorable biology tumors*** Yes for less favorable biology tumors	No
	N1 (1-3+ LN)	Extended therapy**	OFS and AI/Tam	Consider for favorable biology tumors*** Yes for less favorable biology tumors Abemaciclib for 2 years	No for favorable biology tumors*** Yes for less favorable biology tumors Abemaciclib for 2 years for high risk stage II	No[&]

**Extended therapy implies 10 years of treatment though some studies indicate that 10 years may not offer benefit beyond that seen with 7.5 - 8 years of endocrine therapy

CONSENSO

Table 3 Systemic Therapy for ER+ HER2- breast cancer

Anatomic Stage	TN	Type and duration of endocrine therapy*	Ovarian Suppression	Chemotherapy°/Abemaciclib		Olaparib
				Premenopausal	Postmenopausal	Premenopausal and postmenopausal
Stage 3		Extended therapy**	OFS and AI/Tam	Yes Abemaciclib for 2 years	Yes Abemaciclib for 2 years	Yes for pN ≥4 the adjuvant setting Yes for non pCR AND a clinical and pathological stage (CPS&EG) score ≥3.

**Extended therapy implies 10 years of treatment though some studies indicate that 10 years may not offer benefit beyond that seen with 7.5 - 8 years of endocrine therapy

When Chemo is considered indicated -

°The Panel recommended

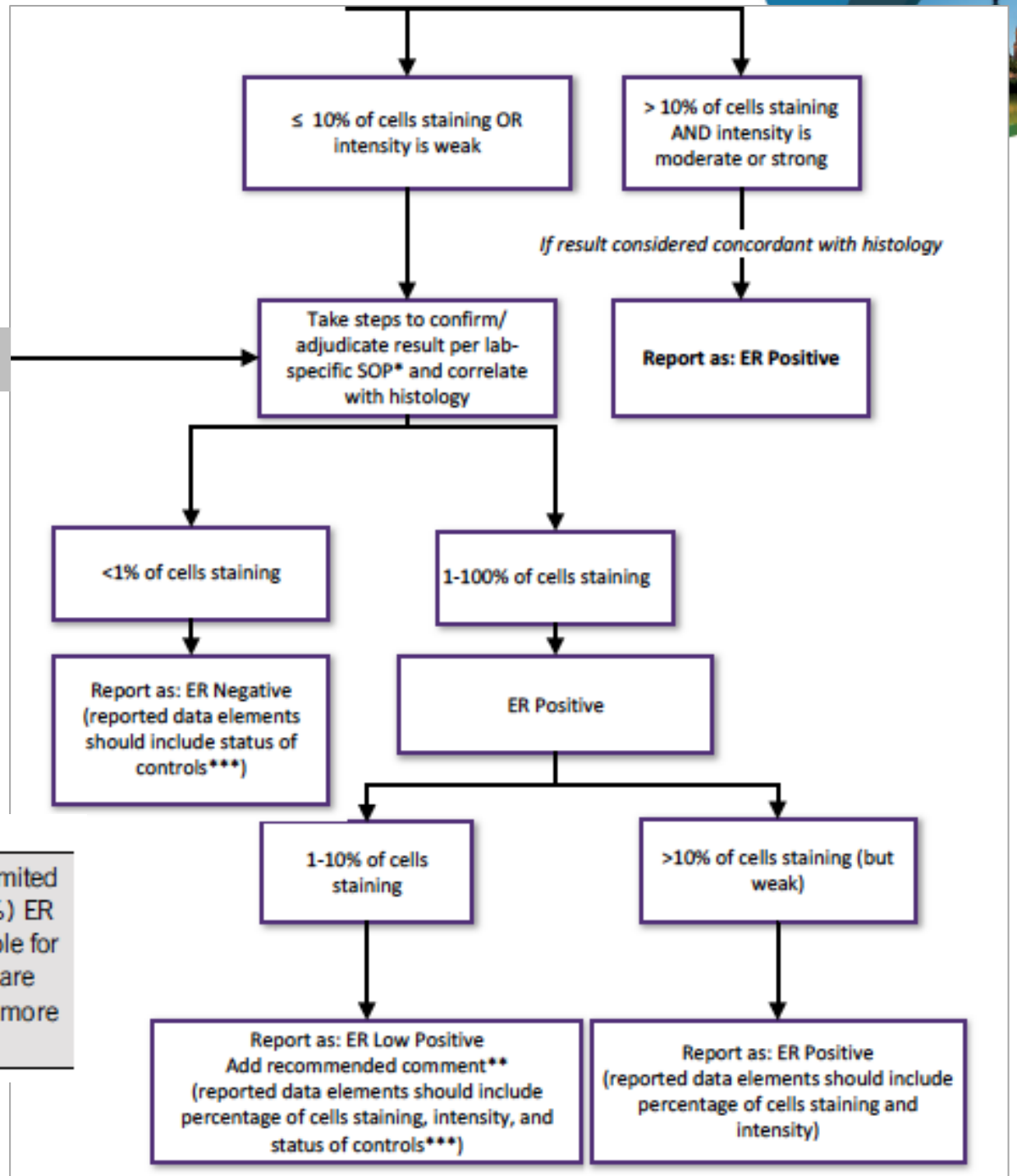
- ✓ anthracycline- and taxane-based adjuvant chemotherapy regimens for stage 3, ER positive tumors;

- ✓ for stage 1 or 2 presenations, the Panel was divided between
  - taxane-based regimens (e.g. TC, 44%),
  - anthracycline-only regimens (e.g. AC, 14%),
  - anthracycline- and taxane-based regimens (42%).

Definición de RH+

RE (+) - 1-10% ¿Como considerarlo?

ASCO-CAP guidelines



Result
1%-10% cells staining

Additional Recommended Comment

The cancer in this sample has a low level (1%-10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with low level (1%-10%) ER expression, but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER-negative cancers.

Allison K JCO 2020

plataformas genómicas

Genomics platforms are multigene profiles, based on DNA or RNA expression, aimed at prognosticating the outcome and/or predicting the response to systemic therapies

→ Treatment decisión making

Research

oncotype DX®	HR+, 21 gene Continuous Recurrence Score, Prognostic Risk Groups, Benefit of therapy **Prospective trials in HR+/HER2- TailorX (N0), RxPONDER (N+ 1-3)**
mammaprint	70 gene - Low/High risk, prognostic groups **Prospective trial – MINDACT (N0,N+1-3)**
Prosigna	PAM50 Intrinsic Subtypes; Risk of Recurrence – ROR in HR+ (+ T & N) Prospective trial – OPTIMA (ongoing)
EndoPredict'	11 Gene, HR+/HER2- ; Low/high risk; EP, EP clin (+T&N)
breast cancer index	BCI prognostic score: 2 functional biomarker panels: HOXB13/IL17BR (H/I) ratio + the molecular grade index (MGI); Low/High risk. H/I: Benefit of extended endocrine therapy?

¿Son concordantes en la categorización de riesgo pronóstico?

NO

Table 3. Risk categorization by each test

Risk group	Oncotype DX* No. (%)	MammaPrint† No. (%)	Prosigna No. (%)	IHC4 No. (%)	IHC4-AQUA‡ No. (%)
No. of patients (%)	301 (99.7)	298 (98.9)	299 (99.0)	257 (85.1)	271 (89.7)
Low risk	163 (54.2)	183 (61.4)	108 (36.1)	62 (24.1)	87 (32.1)
Intermediate risk	84 (27.9)	–	88 (29.4)	123 (47.9)	80 (29.5)
Mid risk	–	–	–	–	55 (20.3)
High risk	54 (17.9)	115 (38.6)	103 (34.5)	72 (28.0)	49 (18.1)

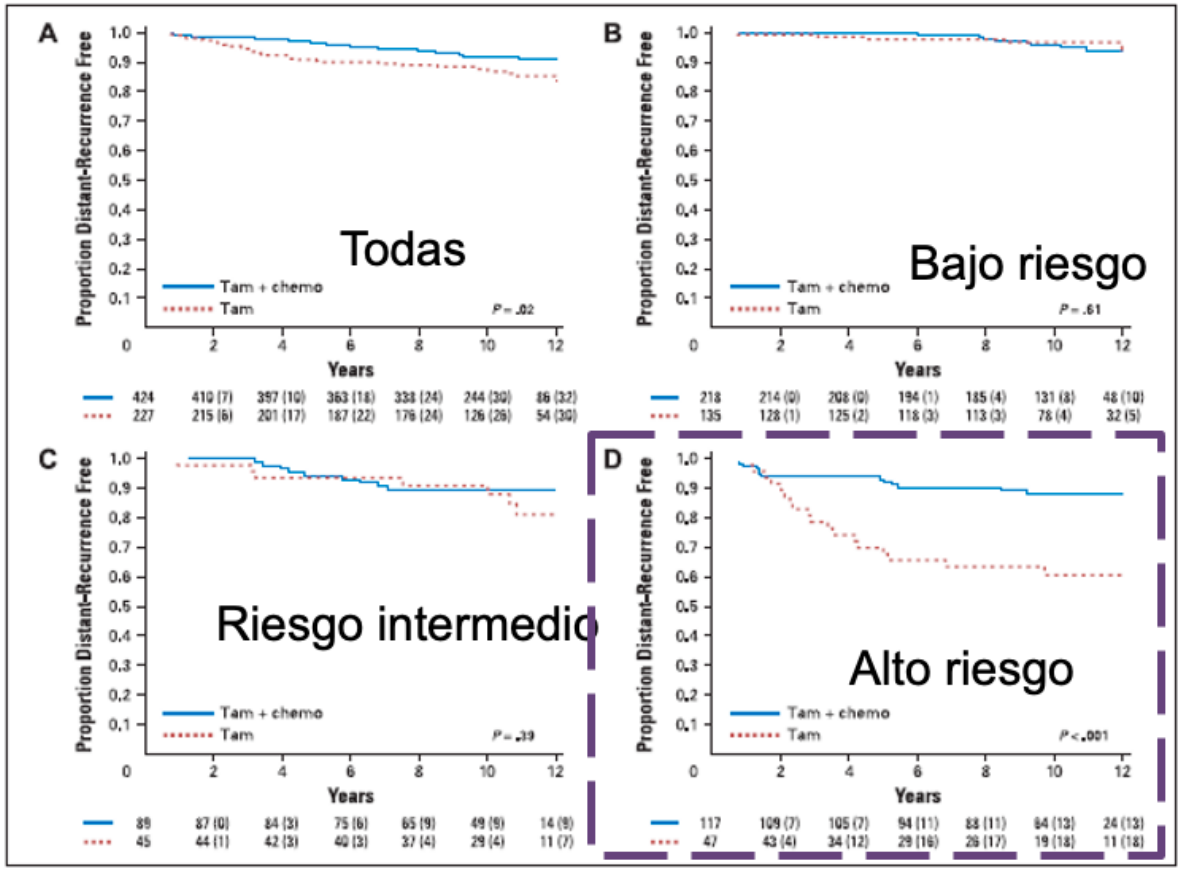
Bartlett J et al. JNCI 2016

¿Predicción de beneficio terapéutico?

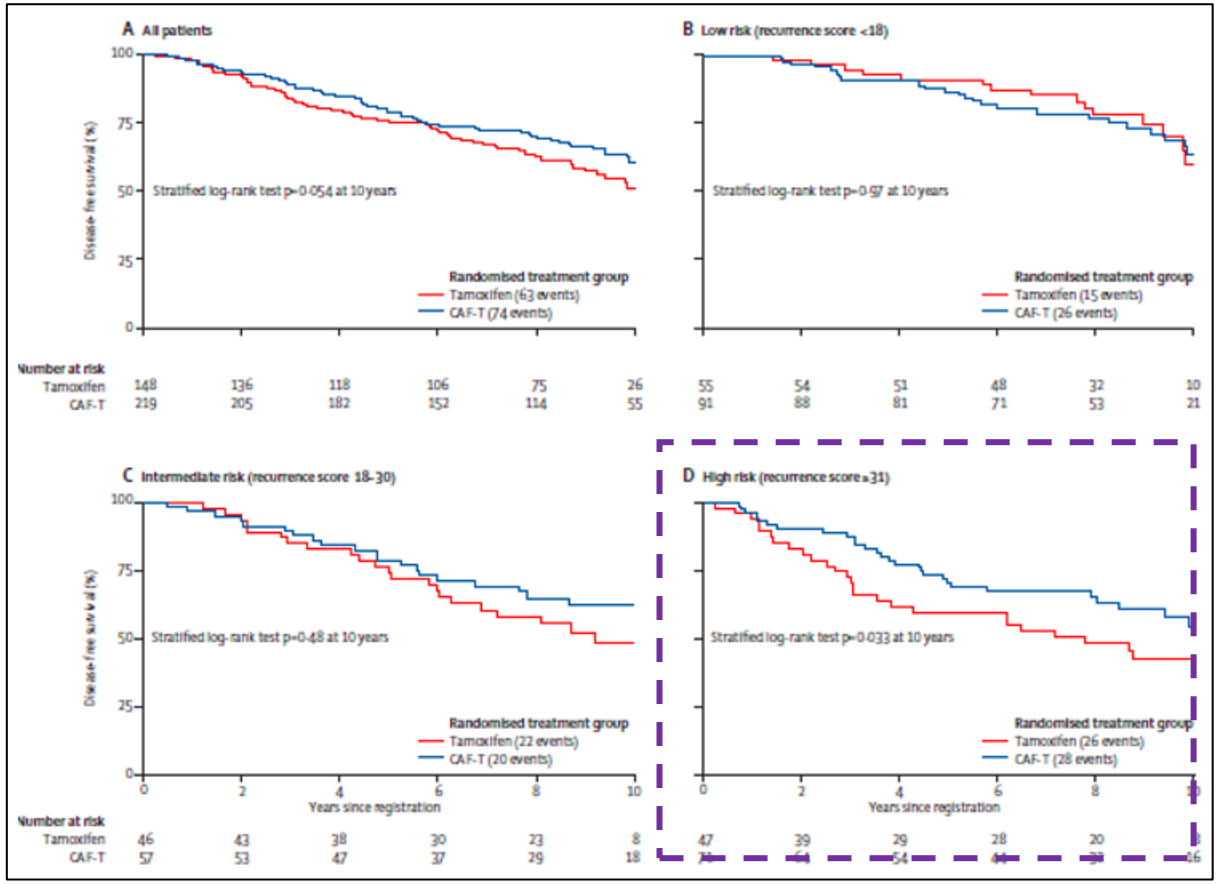
QT - BENEFICIO
Alto Riesgo

ONCOTYPE-DX - RS

NSABP B20 (TvsT+QT-CMFMF)(N0)



SWOG 8814(TvsT+QT-FAC)(N+)

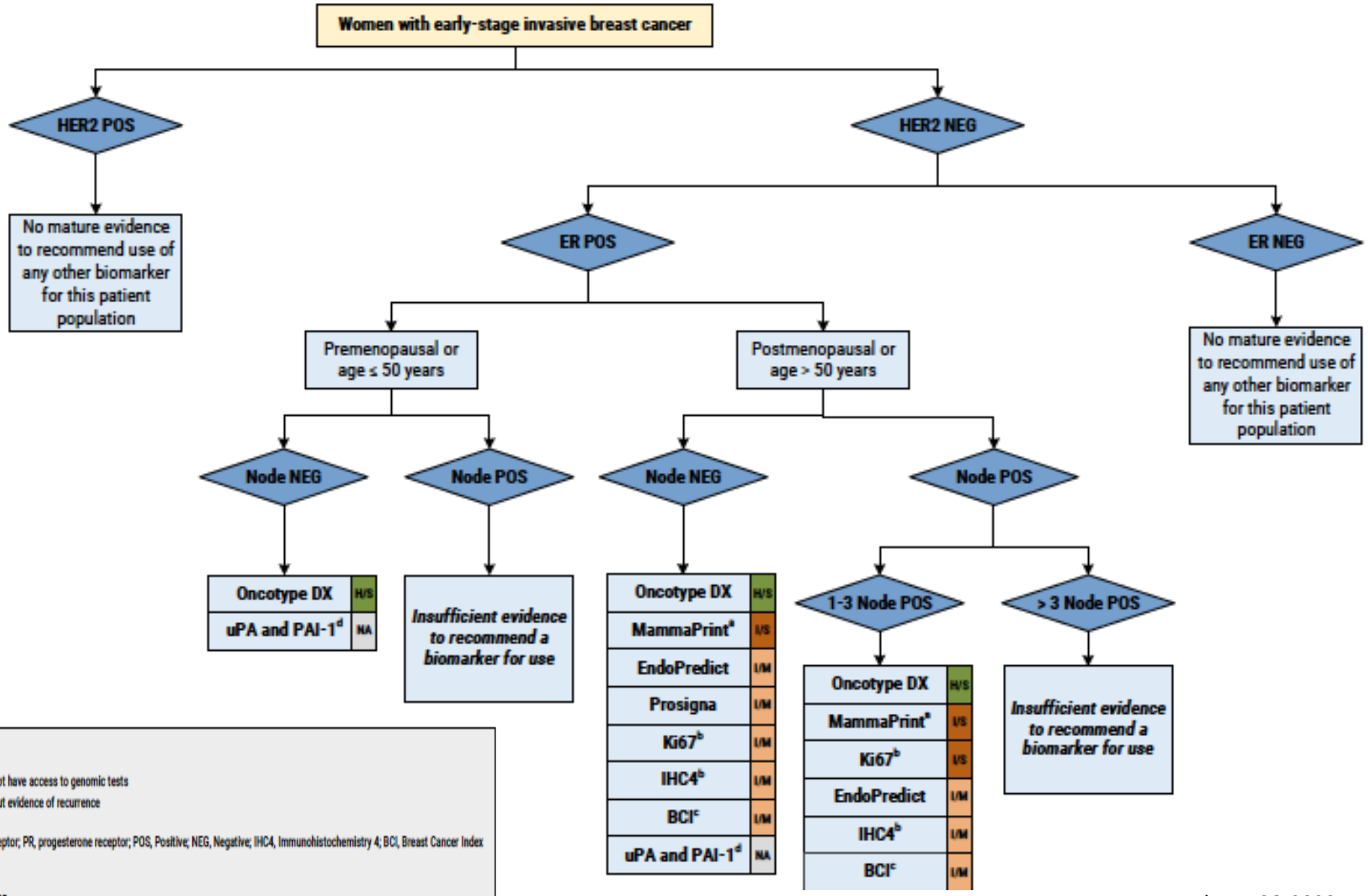


Paik S. JCO 2006
Albain K Lancet Onc 2009

ALTO RIESGO GENOMICO -
NO INCLUIDO EN LOS ENSAYOS PROSPECTIVOS TAYLOR, RXPONDER

ASCO Guidelines

Algorithm on Biomarkers to Guide Decisions on Adjuvant Endocrine and Chemotherapy



Notes:

[a] Only in patients with high clinical risk per MINDACT categorization

[b] Only if locally validated and together with other parameters in patients who do not have access to genomic tests

[c] May also be offered to patients who received 5 years of endocrine therapy without evidence of recurrence

[d] This biomarker is no longer in use

Abbreviations: HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; POS, Positive; NEG, Negative; IHC4, Immunohistochemistry 4; BCI, Breast Cancer Index

H/S *High quality of evidence/Strong strength of recommendation*

I/S *Intermediate quality of evidence/Strong strength of recommendation*

I/M *Intermediate quality of evidence/Moderate strength of recommendation*

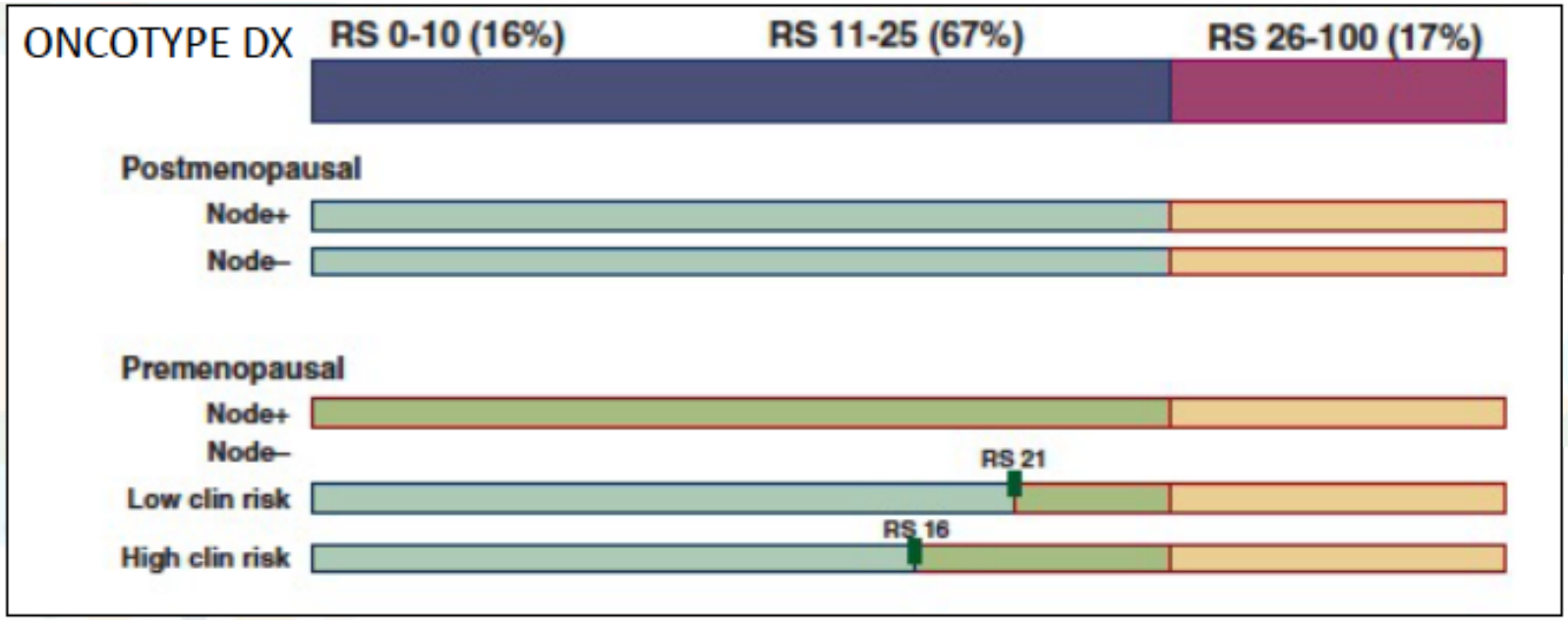
Andre F JCO 2022

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

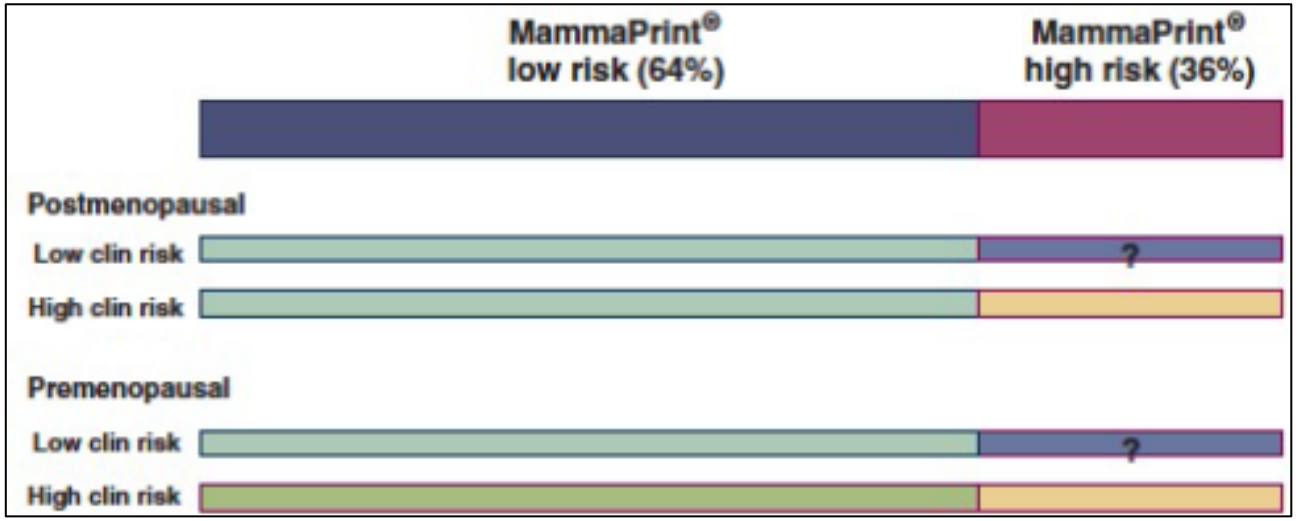
Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk and Treatment Implications
21-gene (Oncotype Dx) (for pN0)	Yes	Yes	Preferred	1	BINV-N (2)
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)[c]	Yes	Yes	Postmenopausal: Preferred	1	BINV-N (2)
			Premenopausal: Other	2A	
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1	BINV-N (3)
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3)
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3)
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A	BINV-N (4)

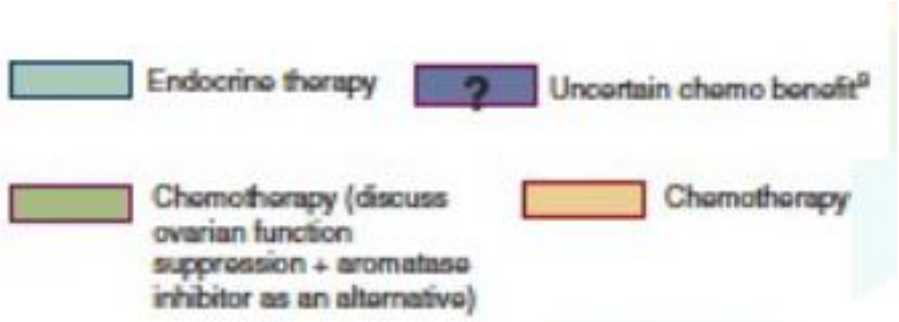
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Plataformas genómicas y decisión de QT adyuvante



Age (≤50, >50) and menopause (pre, post)
- TAILOR & MINDACT – used 50 y as cut point and as a "surrogate" for menopause





Piccart M. 17th St.Gallen International Breast Cancer Conference. 2021
Piccart M et al. Ann Oncol. 2021 Sep;32(9):1077-1082

¿Podría explicarse el beneficio de la QT en mujeres premenopáusicas como un efecto endocrino indirecto secundario a la supresión de la función ovárica producida producida por la QT?

¿Sobre todo en los grupos de riesgo intermedio?

May be....

- Indirect evidence for trials
- Low use of OS in these 3 trials
- Data from SOFT and TEXT trial

But no direct comparison in phase III trials

Piccart M et al. Ann Onc 2021
Alvarez I - SEOM 2021

Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline

Check for updates

Larissa A. Korde, MD[1]; Mark R. Somerfield, PhD[2]; Lisa A. Carey, MD[3]; Jennie R. Crews, MD[4]; Neelima Denduluri, MD[5]; E. Shelley Hwang, MD[6]; Seema A. Khan, MD[7]; Sibylle Loibl, MD, PhD[8]; Elizabeth A. Morris, MD[9]; Alejandra Perez, MD[10]; Meredith M. Regan, ScD[11]; Patricia A. Spears, BS[3]; Preeti K. Sudheendra, MD[12]; W. Fraser Symmans, MD[13]; Rachel L. Yung, MD[4]; Brittany E. Harvey, BS[2]; and Dawn L. Hershman, MD[14]

Clinical Question 1

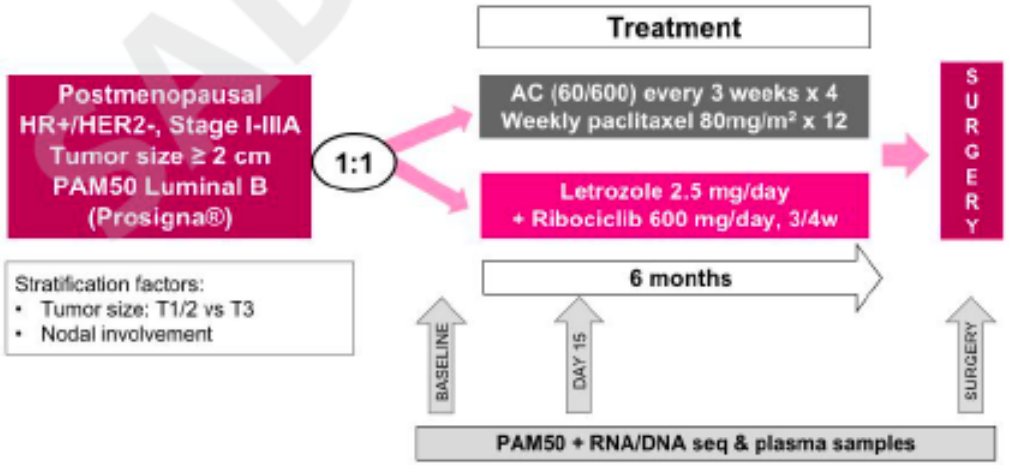
Which patients with breast cancer are appropriate candidates for neoadjuvant systemic therapy?

J Clin Oncol 00. © 2021 by American Society of Clinical Oncology

https://doi. org/10.1200/JCO.20. 03399

Recommendation 1.2. Tumor histology, grade, stage and estrogen, progesterone, and HER2 expression should routinely be used to guide clinical decisions as to whether or not to pursue neoadjuvant chemotherapy. There is insufficient evidence to support the use of other immunochemical markers, morphological markers (eg, tumor-infiltrating lymphocytes [TILs]), or genomic profiles to guide a clinical decision as to whether or not to pursue neoadjuvant chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

HR+/HER2-, NECT vs NET+CDKi(Ribociclib(CORALEEN)



106 p

PE: MOLECULAR DOWNSTAGE *- proportion of patients with low-ROR disease after neoadjuvant treatment according to the standard PAM50.*

80% T2, 60% N0,
KI 67> 14% 94%,
Median proportion of cells with Ki67 in a simple 22-40%
ROR class . High 85% Int 15%

PAM50 (Prosigna) assay, ROR

Low-ROR was at least 40 points if N0 and at least 15 points if 1-3 N+

Intermediate-ROR 41–60 points if N0 and 16–40 points if 1-3 N+.

High-ROR disease 61–100 points if N0 and 41–100 points if 1-3 N+

At surgery, low-ROR

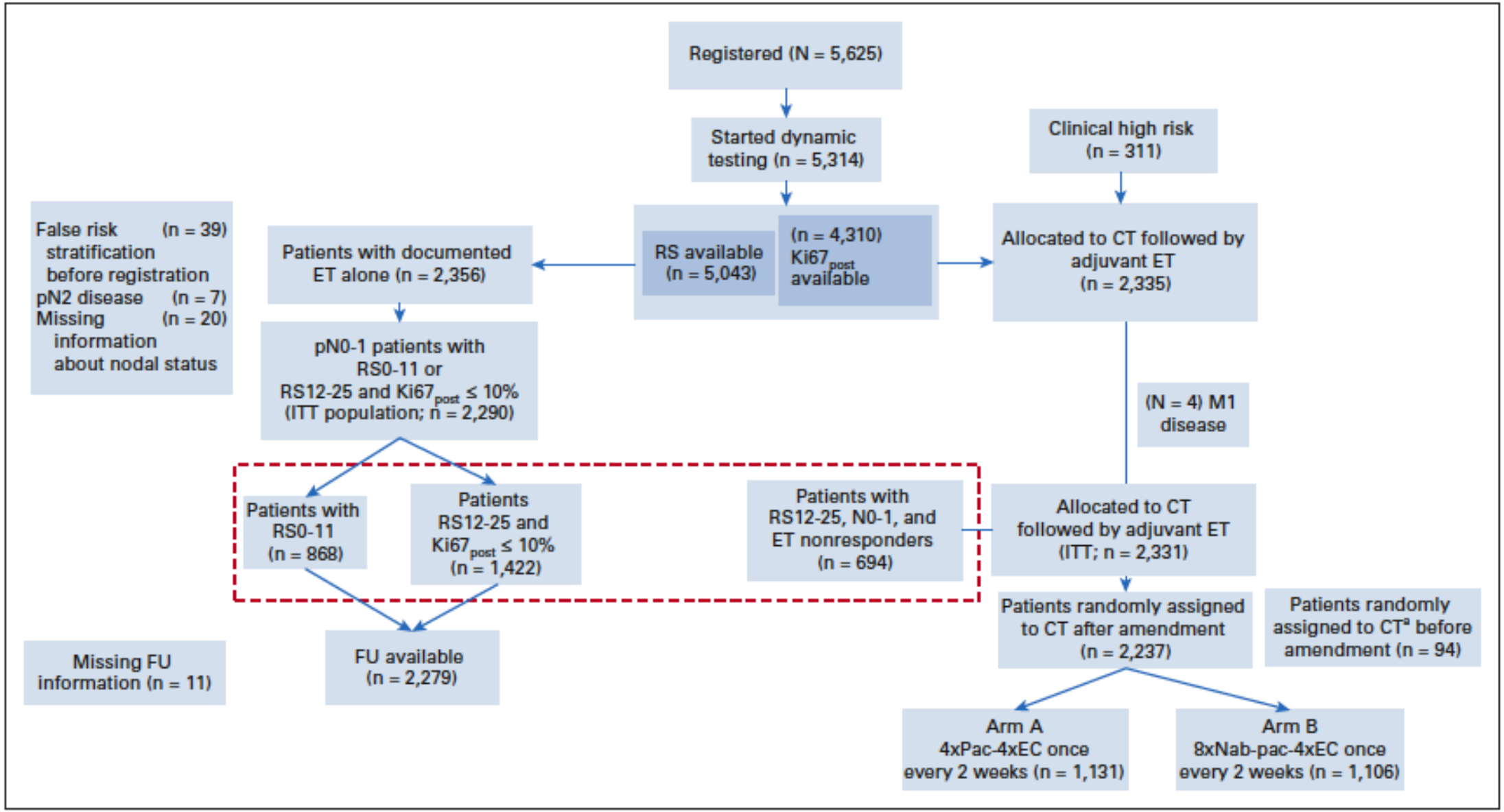
23/49 (46·9%; 95% CI 32·5–61·7) ribociclib plus letrozole group
24/52 (46·1%; 32·9–61·5) chemotherapy group.

	Ribociclib and letrozole group (n=49)		Chemotherapy group (n=52)	
	n (%)	95% CI	n (%)	95% CI
RCB (central)				
0–1	3 (6·1%)	1·3–16·8	6 (11·8%)	4·5–27·8
2–3	46 (93·9%)	83·2–98·7	45 (88·2%)s	76·2–95·5
pCR_{BL}	0 (0%)	0·0–7·25	3 (5·8%)	1·4–16·6

Prat A et al Lancet Oncol 2020

Alvarez I - GEICAM 2021

WSG-ADAPT-HR1/HER2–



Nitz U et al JCO 2022

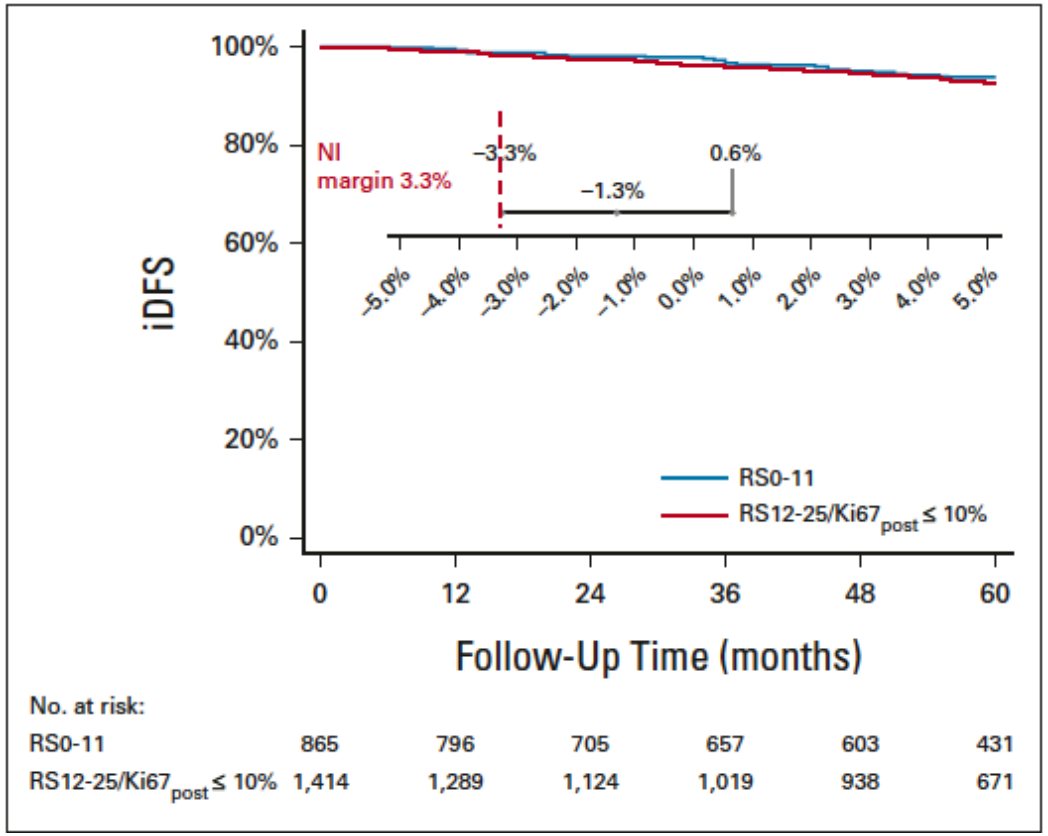
WSG-ADAPT-HR1/HER2– Endocrine trial

n = 5,625 registered
Endocrine trial (2,290 p (n = 1,422 experimental v n = 868 control)

all patients received exclusively ET:
(pN) 0-1 (ie, 0-3 involved lymph nodes) entered
control arm if RS ≤ 11
experimental arm if RS12-25 with ET response (Ki67post ≤ 10%).

Primary end point of the endocrine trial was noninferiority
of 5y-iDFS in experimental v control arm

5y-iDFS dif= –3.3%, establishing prespecified noninferiority (P 5 .05).
92.6% (95% CI, 90.8 to 94.0) exp vs **93.9%** (95% CI, 91.8 to 95.4)control
5-year distant DFS - 95.6% versus 96.3%,
5-year OS 97.3% versus 98.0%,
ET response was more likely with aromatase inhibitors (mostly postmenopausal) than with tamoxifen (mostly premenopausal):
78.1% versus 41.1% (P , .001).
ET response was 78.8% in RS0-11, 62.2% in RS12-25, and 32.7% in RS > 25 (n 5 4,203, P , .001).



¿bloqueo estrogénico completo?

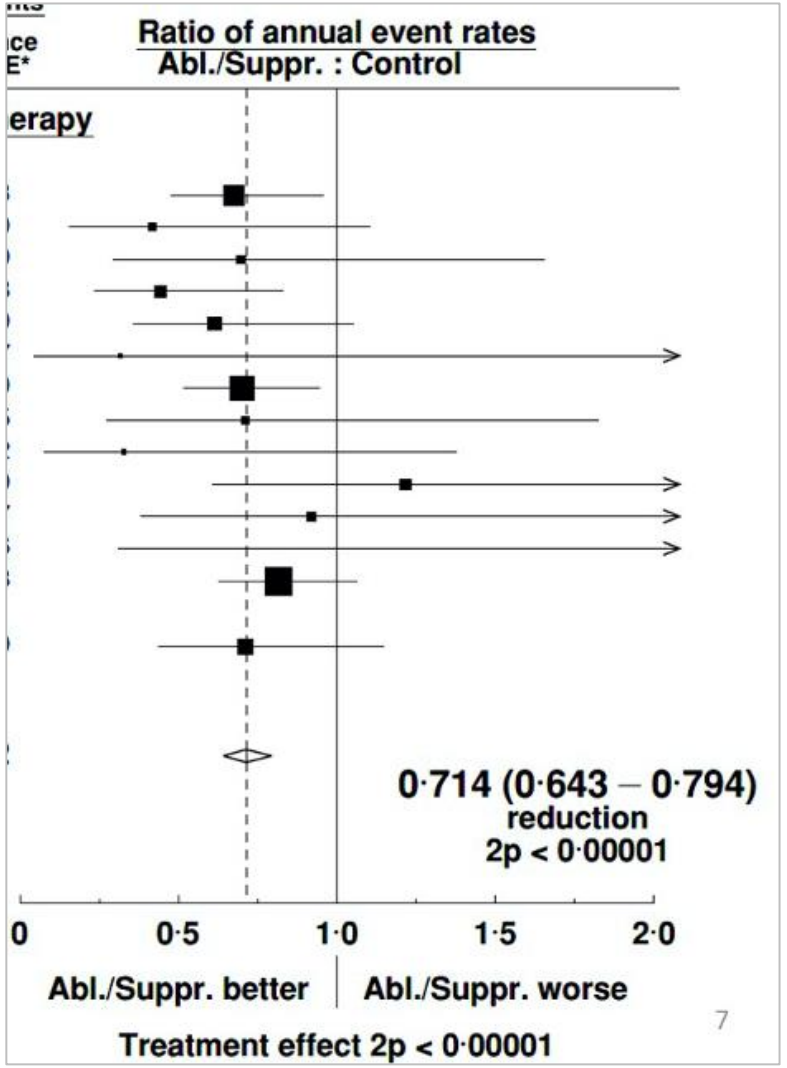
¿Mejor que TMX en mujeres premenopáusicas?

Ablación ovárica -

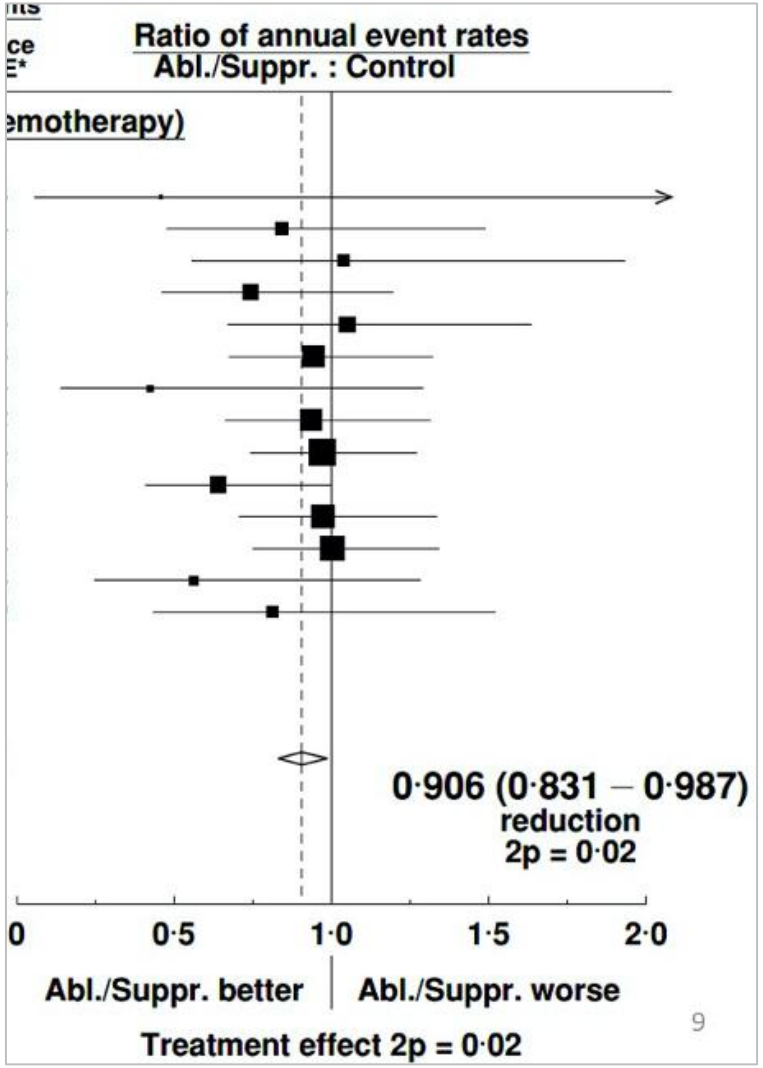
Effects of ovarian ablation or suppression on breast cancer recurrence and survival: patient-level meta-analysis of 14,999 pre-menopausal women in 25 randomized trials

Early Breast Cancer Trialists Collaborative Group (EBCTCG)

(A) No chemotherapy or premenopausal after chemotherapy

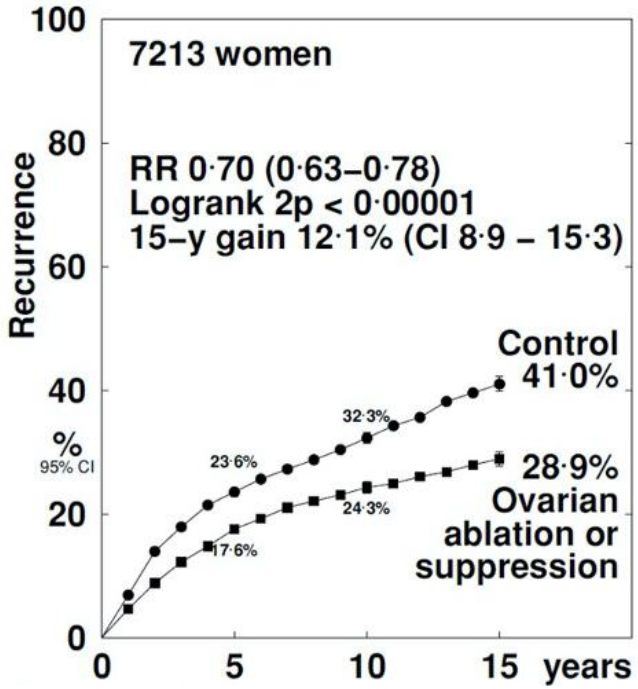


(B) Premenopausal before chemotherapy, uncertain after

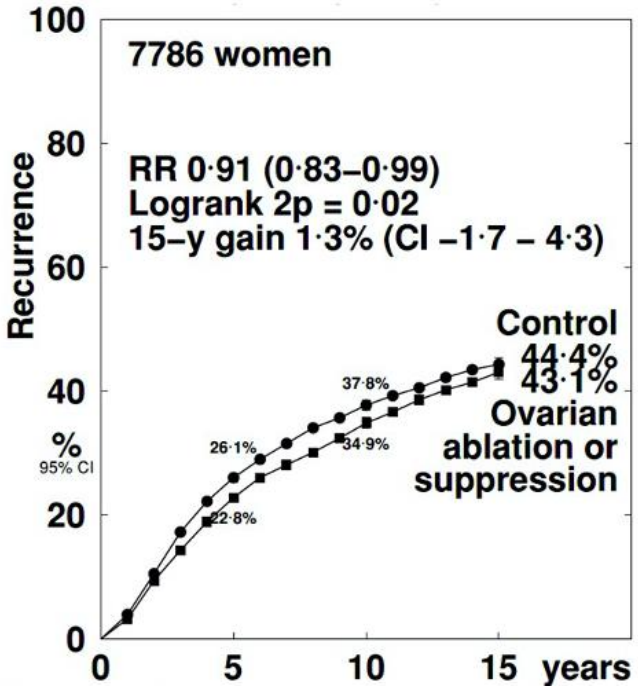


ASCO 2023

(A) No chemotherapy or premenopausal after chemotherapy

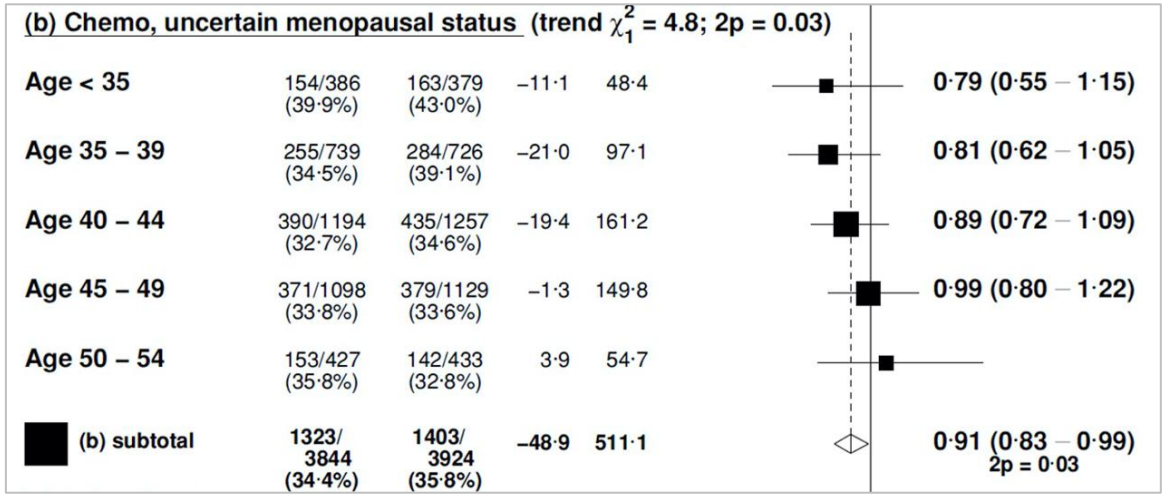


(B) Premenopausal before chemotherapy, uncertain after



AGE -

- No chemo or prem after chemo - all groups Benefit
- But - uncertain after chemo…

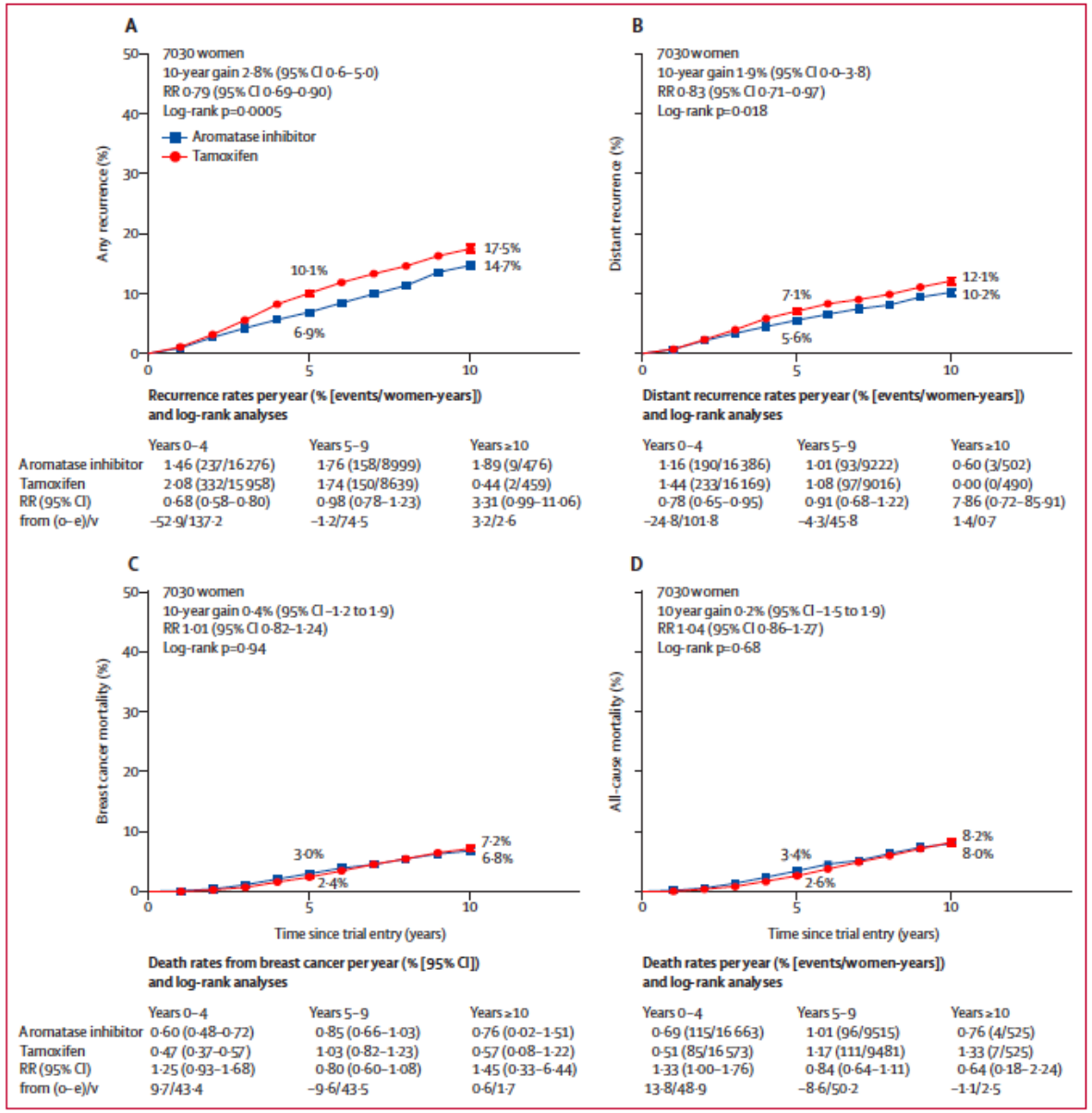


AEBCTCG ASCO 2023

Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

	Allocated aromatase inhibitor	Allocated tamoxifen	
By trial (χ^2_3=8·8; p=0·032)			
ABCSG XII[5,6]	114/855 (13·3%)	103/839 (12·3%)	1·07 (0·75–1·54)
TEXT[7,8]	137/1324 (10·3%)	195/1311 (14·9%)	0·64 (0·48–0·85)
SOFT[7,8]	115/999 (11·5%)	139/999 (13·9%)	0·83 (0·60–1·16)
HOBOE[9]	38/350 (10·9%)	47/353 (13·3%)	0·72 (0·41–1·27)



Interpretation:

Using an aromatase inhibitor rather than tamoxifen in premenopausal women receiving ovarian suppression reduces the risk of breast cancer recurrence.

Longer follow-up is needed to assess any impact on breast cancer mortality.

Lancet Oncol 2022; 23: 382–92

SOFT & TEXT trials

TEXT

Population: Premenopausal women with endocrine-responsive early breast cancer who should receive OFS from the start of adjuvant therapy.

Enrollment November 2003 through April 2011
Final accrual: 2672 (revised target: 2639)

Stratify:

- Chemo planned
- Nodal Status

RANDOMIZE

- Tamoxifen + OFS (Triptorelin)
- Exemestane + OFS (Triptorelin)

SOFT

Population: Premenopausal women with endocrine-responsive early breast cancer who remain premenopausal after chemotherapy or after surgery alone.

Enrollment December 2003 through January 2011
Final accrual: 3066 (target: 3000)

Stratify:

- Prior chemo
- Intended OFS
- Nodal Status

RANDOMIZE

- Tamoxifen
- Tamoxifen + OFS
- Exemestane + OFS

Pagani O NEJM 2014

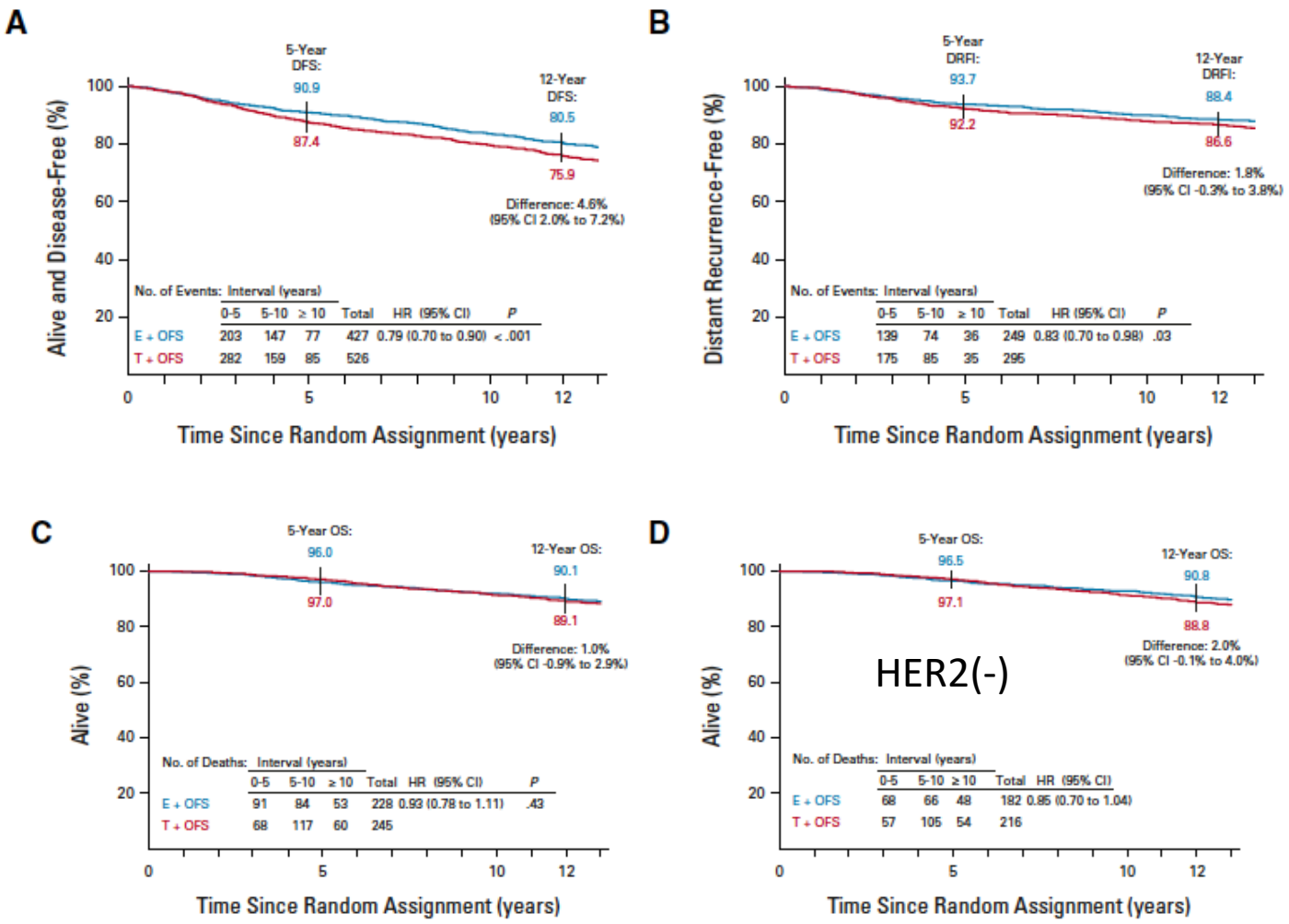
Combined TEXT and SOFT Trials -12-year results

DFS (4.6% - HR 0.79; 95% CI, 0.70-0.90; P < .001)
DRFI (1.8% - HR, 0.83; 95% CI, 0.70 to 0.98; P = .03),

Not OS (90.1% v 89.1%, HR, 0.93; 95% CI, 0.78-1.11),

HER 2-negative tumors (86.0% of the ITT population),

- OS with exemestane + OFS (absolut benefit)
- 2.0% (HR, 0.85; 95% CI, 0.70 to 1.04)
- 3.3% in those who received chemotherapy (45.9% of the ITT population).
- Clinically significant in **high-risk patients,**
  - < 35 years (4.0%)
  - > 2 cm (4.5%)
  - grade 3 tumors (5.5%).



Pagani O. JCO 2022

12-Year Results From SOFT

DFS

TMX + OFS vs TMX (HR, 0.82; 95% CI, 0.69 to 0.98)

71.9% (TMX) - 76.1% TMX+ OFS - 79.0% EXE+ OFS.

OS

TMX + OFS vs TMX (HR, 0.78; 95% CI, 0.60 to 1.01)

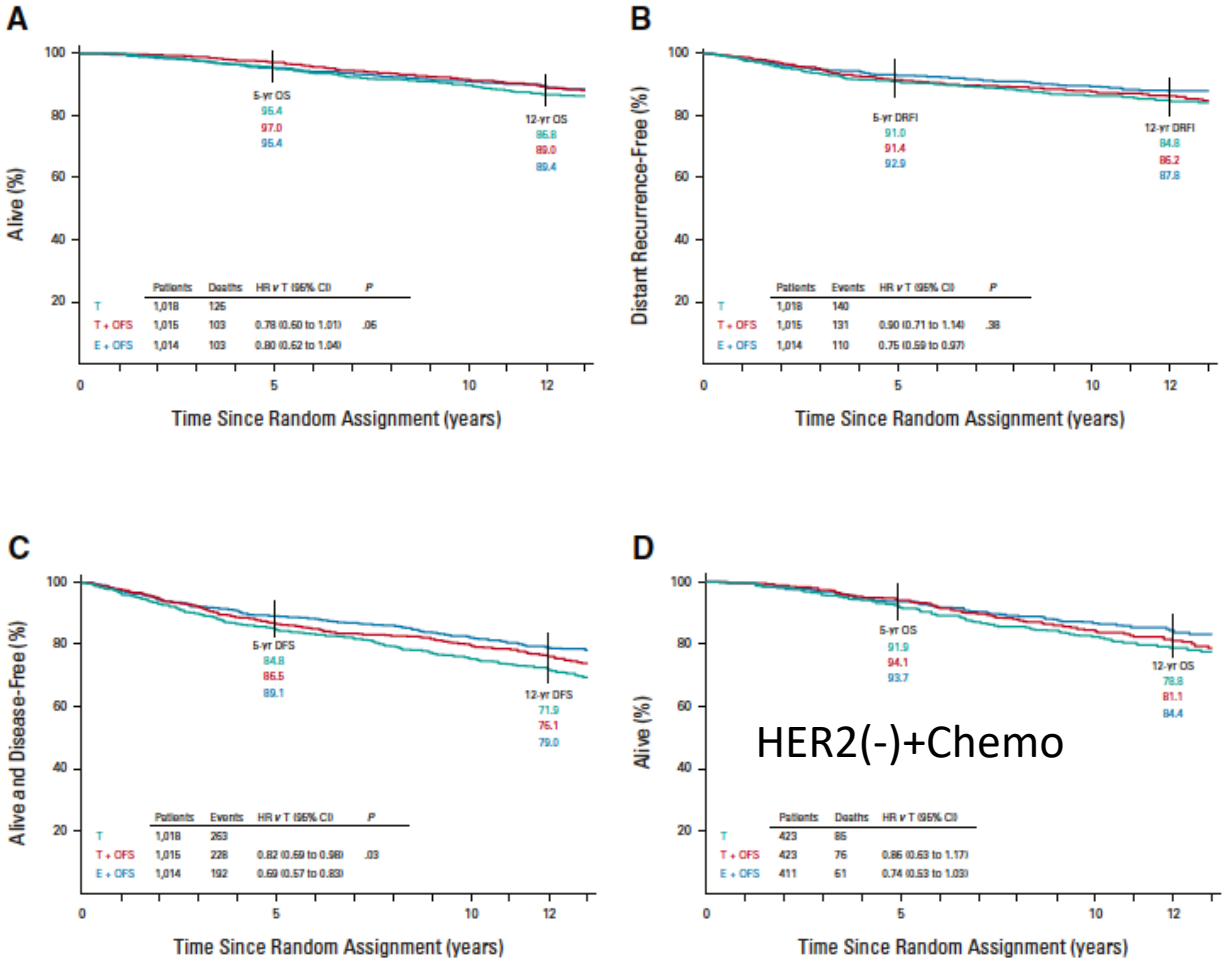
86.8% (TMX) - 89.0% TMX+ OFS - 89.4% EXE+ OFS.

HER2 (-) + Chemo

78.8% TMX,

81.1% TMX+ OFS

84.4% EXE+ OFS



Francis P JCO 2022

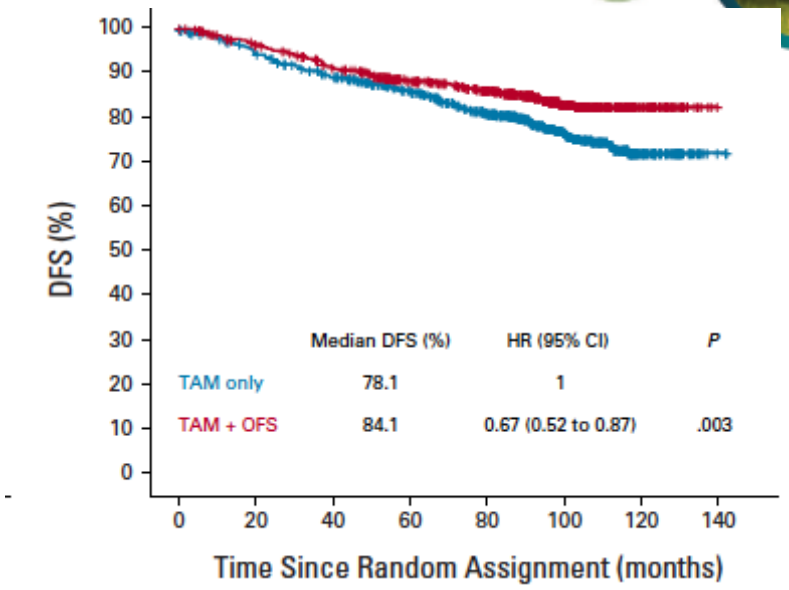
8-Year Follow-Up ASTRRA Trial

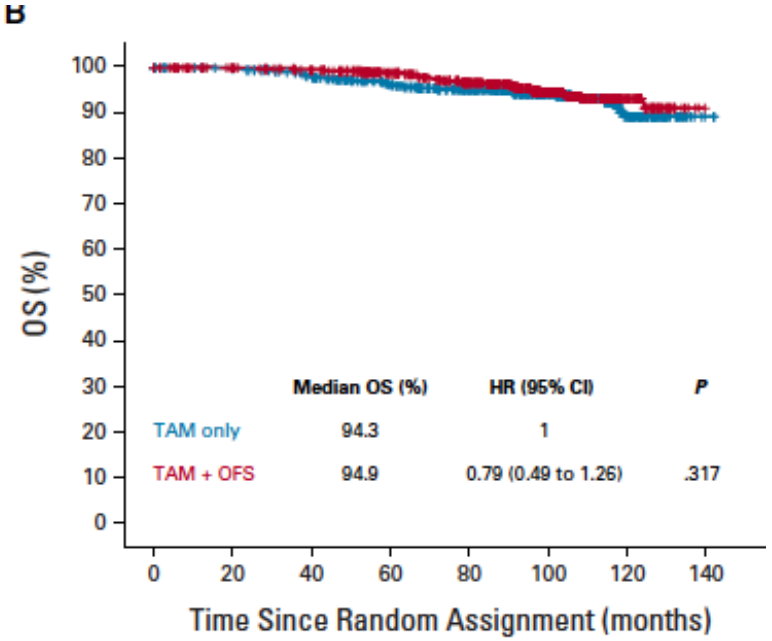
1,483 premenopausal
< 45 years
Neo/adjuvante chemotherapy
Who Remain Premenopausal or Regain Vaginal Bleeding After Chemotherapy

1:1 ratio 5y TMX vs 5y TMX + OFS 2y

DFS
85.4% TMX + OFS - 80.2% TMX
(HR 0.67; 95% CI, 0.51 to 0.87).

OS (no significant)
96.5% TMX + OFS - 95.3% TMX
(HR, 0.78; 95% CI, 0.49 to 1.25).





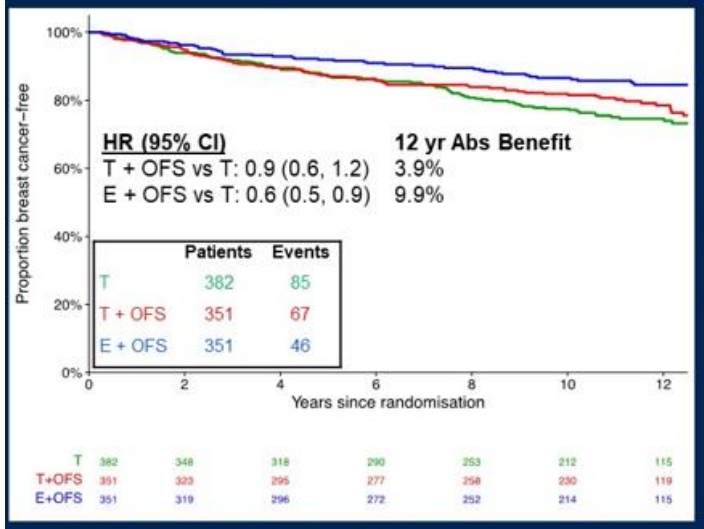
Baek SY JCO 2023

PAM50 – ROR – SOFT-trial

PAM50 ROR Predictive results– overall cohort

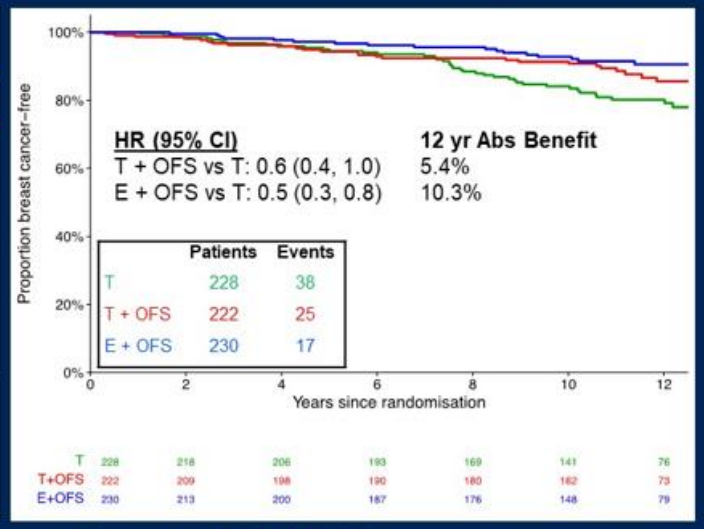
[Endpoint = BCFI]

Unselected (N=1084)



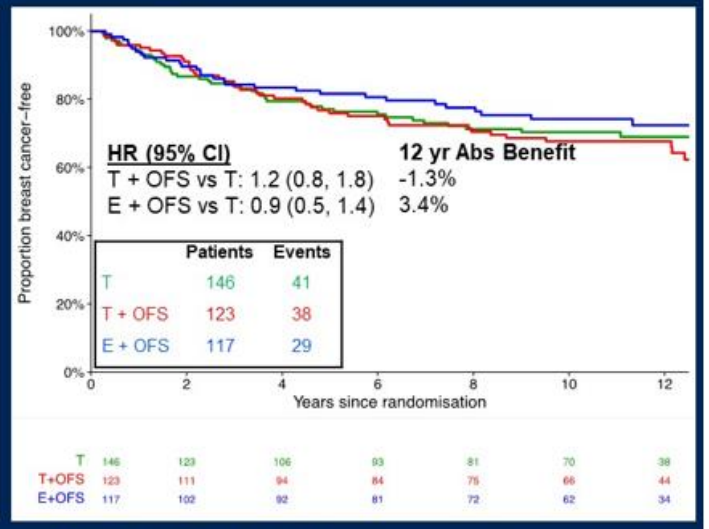
Chemo n=543 (50.1%)

ROR low/int (N=680, 64%)



Chemo n=212 (31.1%)

ROR high (N=386, 36%)



Chemo n=315 (81.6%)

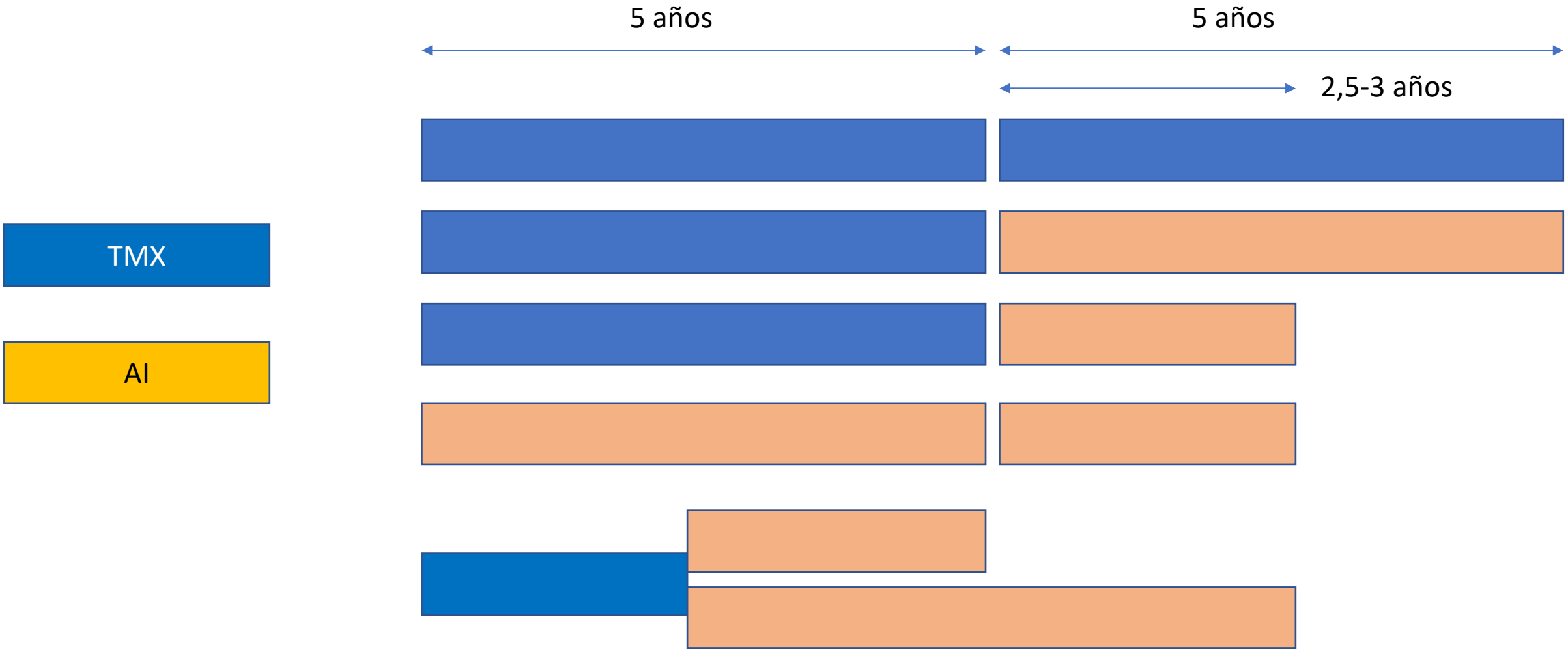
p_{int} (E + OFS) = 0.1; (T + OFS) = 0.2

- Very young women had significant enrichment of aggressive disease biology
  - *<40yrs vs ≥40yrs had significantly more Luminal B subtype (39% vs 21%)*
  - *<40yrs vs ≥40yrs with Luminal A subtype had higher rates of distant recurrence at 10yrs (10-yr DRFI 83.4% vs 92.1%)*
  - *More frequent high ROR scores in node negative (36% vs 14%) and node positive (80% vs 66%) subgroups*
- PAM50 ROR score was not predictive of OFS benefit in premenopausal women

Brown LC – ASCO 2023

HT extendida

Diseño de los estudios de HT extendida



ESTUDIO 1er tratamiento	INTERVENCIÓN	BENEFICIO ABSOLUTO	HR – SLE (RAMA EXPERIMENTAL)
NSABP 14 **N0, 5a TMX**	TMX 5a Placebo	SLE 7a 4% (placebo) SG 7a 3%	1,4 (0,9-2,2)
ATLAS **5a TMX**	TMX 5a No tto	SLE 10a3,7% SG (específica) 10a 2,8%	0,84 (0,76-0,94)
aTToM **5a TMX**	TMX 5a No tto	SLE 2,6% SG 1,6%	0,75 (0,66-0,86) en el año 10 o posterior
NSABP B33 **Postm, 5a TMX**	EXEMESTANO 5a Placebo	SLE 4a 2%	0,68 (NA)
MA17 **Postm, 5a TMX**	LETROZOL 5a Placebo	SLE 4a 4,6% SG 4a0,4%	0,58 (0,45-0,76)
ABCSG 6a **Postm, 5a TMX+/-IA**	ANASTROZOL 3a No tto	SLE 6a 4,6% SG 6a 1,4%	0,62 (0,40-0,96)
NSABP-B42 **Postm, 5a, cualquier t endocrino**	LETROZOL 5a Placebo	SLE 10a 3,3% SG 10a 0,5% (placebo)	0.86, P = .047
MA17R **Postm, 5a IA+/- TMX previo**	LETROZOL 5a Placebo	SLE 5a 4% SG 5a 1%	0,66 (0,48-0,91)
DATA **Postm 2-3a TMX**	ANASTROZOL 6a ANASTROZOL 3a	SLE 5a 3,7% SG 5a 1%	0,79 (0,62-1,02)
IDEAL **Postm, 5a cualquier t endocrino**	ANASTROZOL 5a ANASTROZOL 2,5	SLE 5a 1,4% SG 5a 0,8%	0,92 (0,74-1,16)
ABCSG 16 **Postm, 5a cualquier t endocrino**	ANASTROZOL 5a ANASTROZOL 2a	SLE 10a 0,8% (2y) SG 10a 0,4% (2y)	1,007 (0,87-1,16)
N-SAS BC 05 (AERAS) **Postm, 5a IA/TMX-IA**	ANASTROZOL 5a No tto	SLE 5a 5% SG 5a no diferencia	0,61 (0.46 to 0.82) 1.13 (0.61 to 2.10)
GYM-4 **Postm, TMX 2-3 a**	LETROZOL 2-3a LETROZOL 5 a	SLE 12a 4,7% SG 12a 4% (84 vs 88%)	0,78 (0·65–0·93) 0·77 (0·60–0·98); p=0·036

Terapia extendida - meta-análisis - 15 EC randomizados

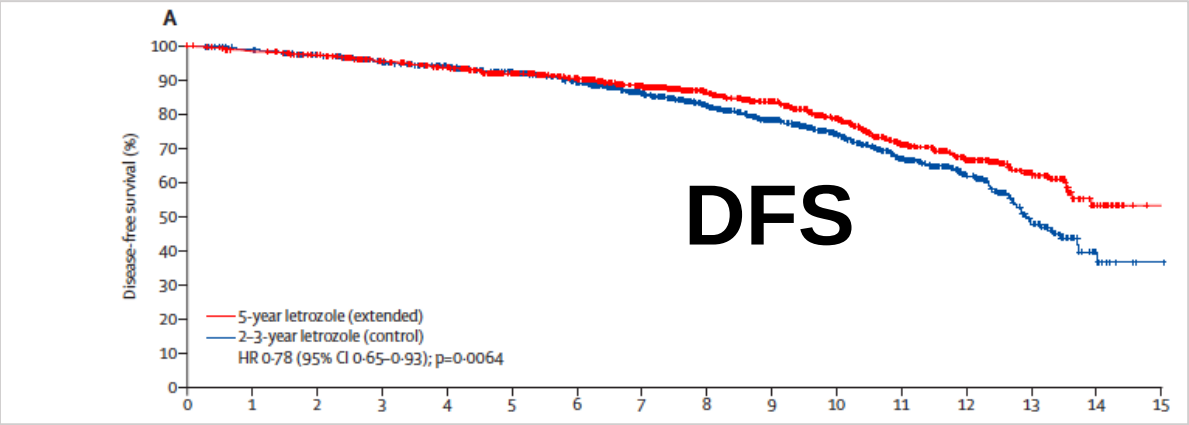
	Outcome and subgroups	Number of studies	Number of patients	Meta-analysis				Heterogeneity	
				HR	95% CI	P value	95% PI	I^2, Tau^2	P value
DFS	Subgrouped by the duration of adjuvant endocrine therapy (Subgroup 2)								
	Adjuvant endocrine therapy for 10 years vs 5 years	5	11160	0.790	0.632-0.988	0.039	0.371-1.685	73.0%, 0.0436	0.005
	Adjuvant endocrine therapy for 10 years vs 7-8 years	3	6024	0.896	0.745-1.078	0.243	0.137-5.858	48.8%, 0.0130	0.142
	Adjuvant endocrine therapy for 7-8 years vs 5 years	2	3716	0.783	0.677-0.906	0.001	–	0%, 0	0.935
	Subgrouped by lymph node positive/negative (Subgroup 4)								
	Positive	1	992	0.670	0.469-0.958	0.028	–	–	–
	Negative	1	1152	1.380	0.988-1.927	0.059	–	–	–
	Mixed (positive or negative)	7	17434	0.804	0.707-0.914	<0.001	0.561-1.152	54.4%, 0.0153	0.041
OS	Subgrouped by the duration of adjuvant endocrine therapy duration (Subgroup 2)								
	Adjuvant endocrine therapy for 10 years vs 5 years	6	16601	0.861	0.785-0.944	0.001	0.675-1.148	26.4%, 0.0055	0.236
	Adjuvant endocrine therapy for 10 years vs 7-8 years	3	6024	1.011	0.864-1.183	0.893	0.365-2.796	0%, 0	0.851
	Adjuvant endocrine therapy for 7-8 years vs 5 years	2	3716	0.814	0.668-	0.044	–	0%, 0	0.437

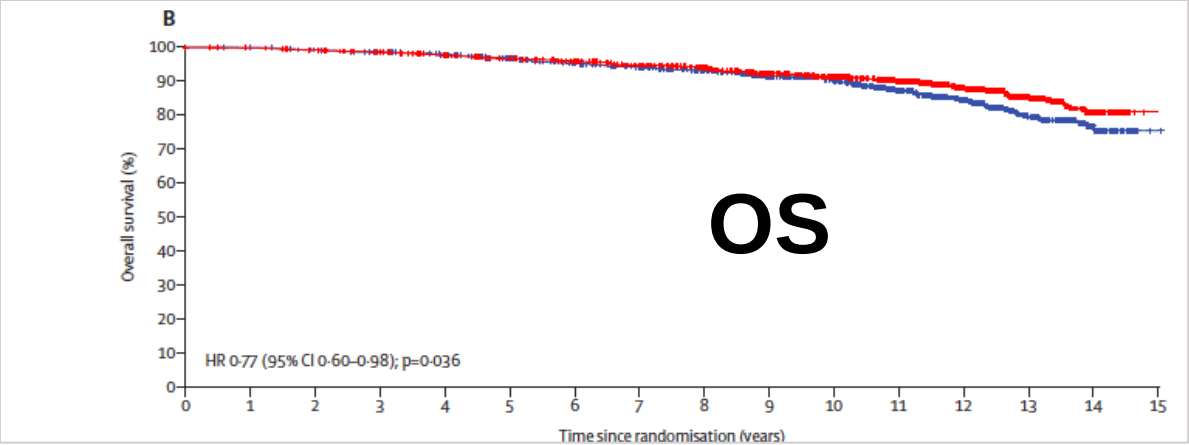
Xie M Front Onc 2023
Alvarez i - SEOM 2023

Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial

Lucia Del Mastro, Mauro Mansutti, Giancarlo Bisagni, Riccardo Ponzone, Antonio Durando, Laura Amaducci, Enrico Campadelli, Francesco Cognetti, Antonio Frassoldati, Andrea Michelotti, Silvia Mura, Ylenia Urracci, Giovanni Sanna, Stefania Gori, Sabino De Placido, Ornella Garrone, Alessandra Fabi, Carla Barone, Stefano Tamberi, Claudia Bighin, Fabio Puglisi, Gabriella Moretti, Grazia Arpino, Alberto Ballestrero, Francesca Poggio, Matteo Lambertini, Filippo Montemurro, Paolo Bruzzi, on behalf of the Gruppo Italiano Mammella investigators*

GYM-4 12 Y FU





<u>DFS</u>

Events: (25·4%) control and 212 (20·7%) of 1026 in the extended group.

12-year DFS 62% (95% CI 57–66) control group and 67% (62–71) extended group (HR 0·78, 95% CI 0·65–0·93; p=0·0064).

<u>OS</u>

263 (12·8%) deaths

147 control group and 116 in the extended group.

12-year OS: 84% (95% CI 82–87) control group and 88% (86–90) extended group (HR 0·77, 95% CI 0·60–0·98; p=0·036;

DISCONTINUATION (in the absence of disease progression)

189 (19·5%) control group

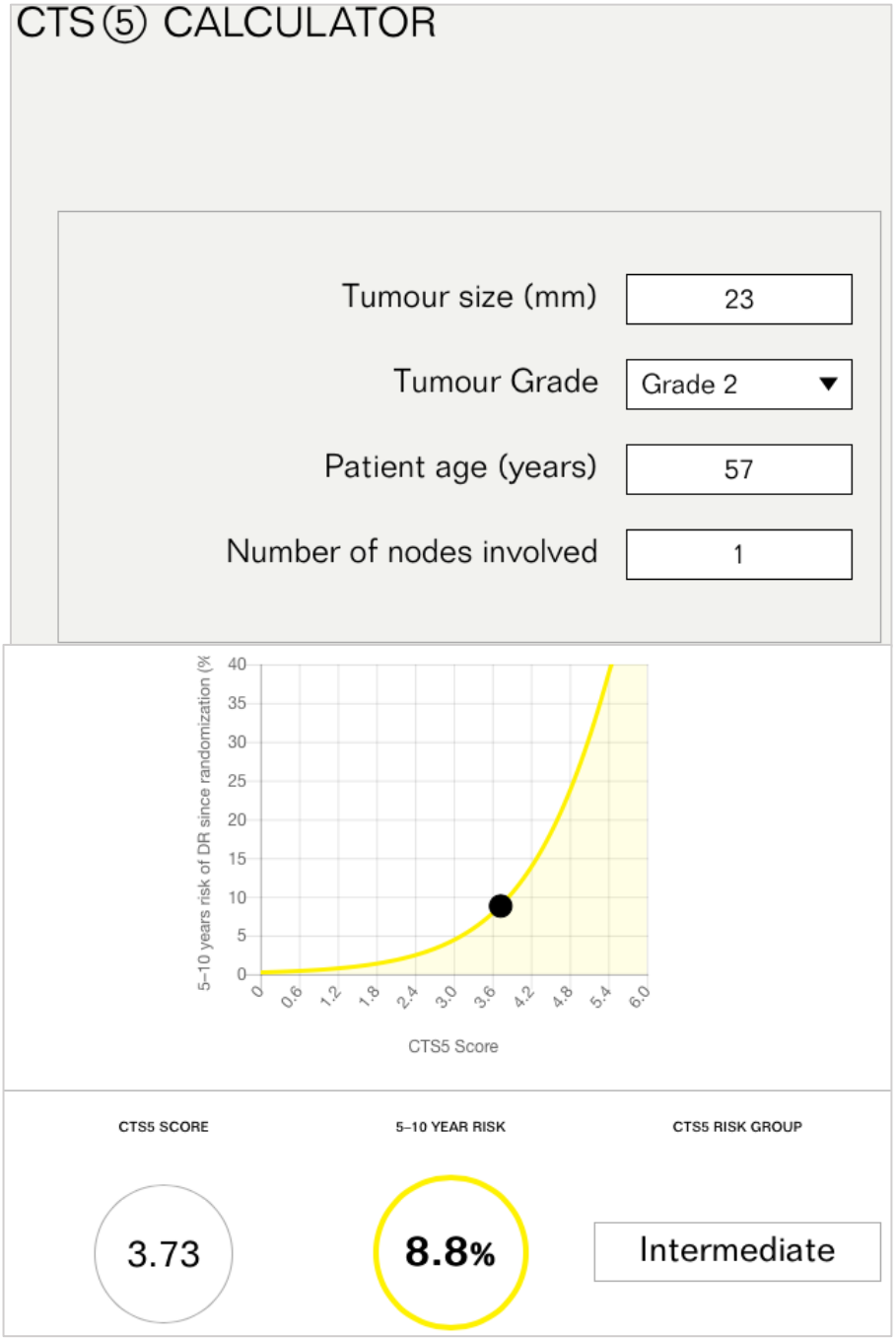
344 (37·1%) extended group

Del Mastro L -Lancet Onc 2022

Alvarez I - SEOM 2023

Factores para la toma de decisión

- Factores clásicos, el T, el N y el Grado, (N el más importante)
- T, el N y el grado se han integrado en una calculadora pronóstica (CTS5 www.cts5-calculator.com) == > riesgo de recaídas entre los 5-10 años (postm)
- Plataformas genómicas (Oncotype DX, Mammaprint, Prosigna-ROR, Endopredict, BCI)
  - factor pronóstico para la recurrencia tardía - Prosigna-ROR, Endopredict y el Breast Cancer Index (BCI)
  - Factor predictivo beneficio terapia extendida - BCI,
    - 2 paneles de biomarcadores: MGI “5 gene molecular grade Index + la ratio de HoxB13 e interleukina-17B (H/I
    - 2 grupos de riesgo, bajo (score 0-5) o alto (score 5.1-10)



Breast Cancer Index (BCI)

Población	N	Plataforma	Valor predictivo de beneficio de ET extendida	P
IDEAL trial **RH+, N-/+, postm** **5 años de HT (cualquiera) seguido de IA 2,5 vs 5 años**	908	BCI (BCI (H/I) alto o bajo	5+5 vs 5+2,5 - (RFI) **BCI (H/I) Alto** (429 p) HR 0.42 (95% IC 0.21-0.84) Beneficio absoluto de reducción del riesgo de recurrencia 9,8% **BCI (H/I) Bajo** (479 p) HR 0.95 (95% IC 0.58-1.56)	.011 0.835
Trans-aTTom **RH+, N+, pre y post** **5 años de TMX seguido de 5 años de TMX vs no mas tratamiento**	789	BCI (BCI (H/I) alto o bajo	5+5 vs 5 **BCI(H/I) Alto** 404 HR 0.33 (95% IC 0.14-0.75) Beneficio absoluto de reducción del riesgo de recurrencia 9,7% **BCI (H/I) Bajo** (385p) HR 1.08 (95% IC 0.76-1.74)	0.014
NSABP-B42 **RH+, N+, postm** **5 años (TMX->IA o IA) → 5 años de Letrozol vs Placebo**	20179	BCI (BCI (H/I) alto o bajo	Test para la interacción tratamiento- BCI alto/bajo	0.55

Revisión Alvarez I. Hot topics, 2021

Mammaprint - NSABP-B42

Endpoint	MP	10-yr risk Letrozole (%)	10-yr risk Placebo (%)	Absolute benefit (%)	HR (95%CI)	p	P interaction
DFS events	Low	20.3	28.1	7.8	0.67 (0.52,0.85)	<0.001	0.015
	High	28.8	27.2	-1.6	1.10 (0.82,1.47)	0.55	
BCFI	Low	8.4	15.4	7.0	0.51 (0.35,0.74)	<0.001	0.006
	High	14.6	11.6	-3.0	1.15 (0.74,1.79)	0.53	

- Absolute benefit of L *vs.* P was limited to MP-L for both DFS and BCFI
- Tests for treatment-by-MP risk group interaction were statistically significant

BCFI: time from randomization to first invasive breast tumor recurrence

Rastogi P: ASCO 2021
Alvarez I - SEOM 2023

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

Extended Endocrine Therapy for ER-Positive HER2-Negative Breast Cancer

Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4.

Recommendation 1.23. If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Onco*type* DX, EndoPredict, Prosigna, Ki67, or IHC4 scores to guide decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Breast Cancer Index.

Recommendation 1.24. If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.25. If a patient has node-positive breast cancer with ≥ 4 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical treatment score post-5 years.

Recommendation 1.26. If a patient is postmenopausal and had invasive breast cancer and is recurrence-free after 5 years of adjuvant endocrine therapy, the clinical treatment score post-5 years (CTS5) web tool may be used to calculate the estimated risk of late recurrence (recurrence between years 5-10), which could assist in decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

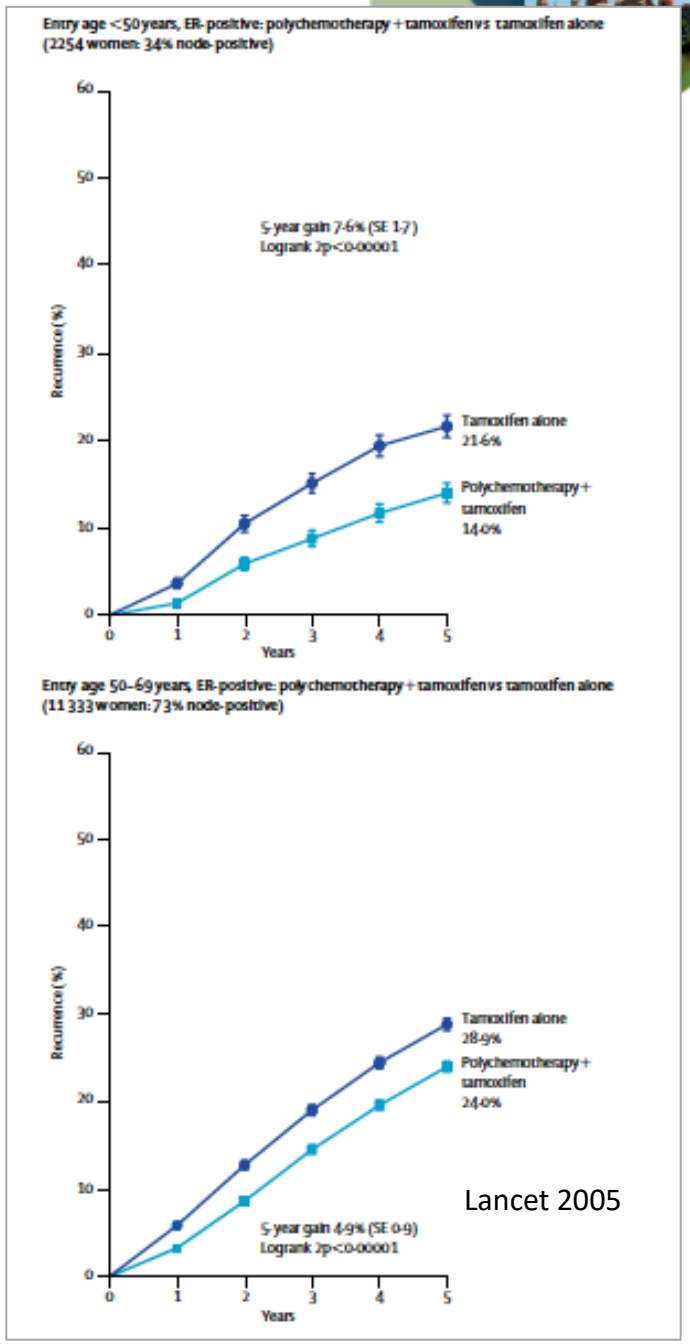
Andre et al, JCO 2022

¿papel quimioterapia?

QT neo/adyuvante en CM RH+/HER2-

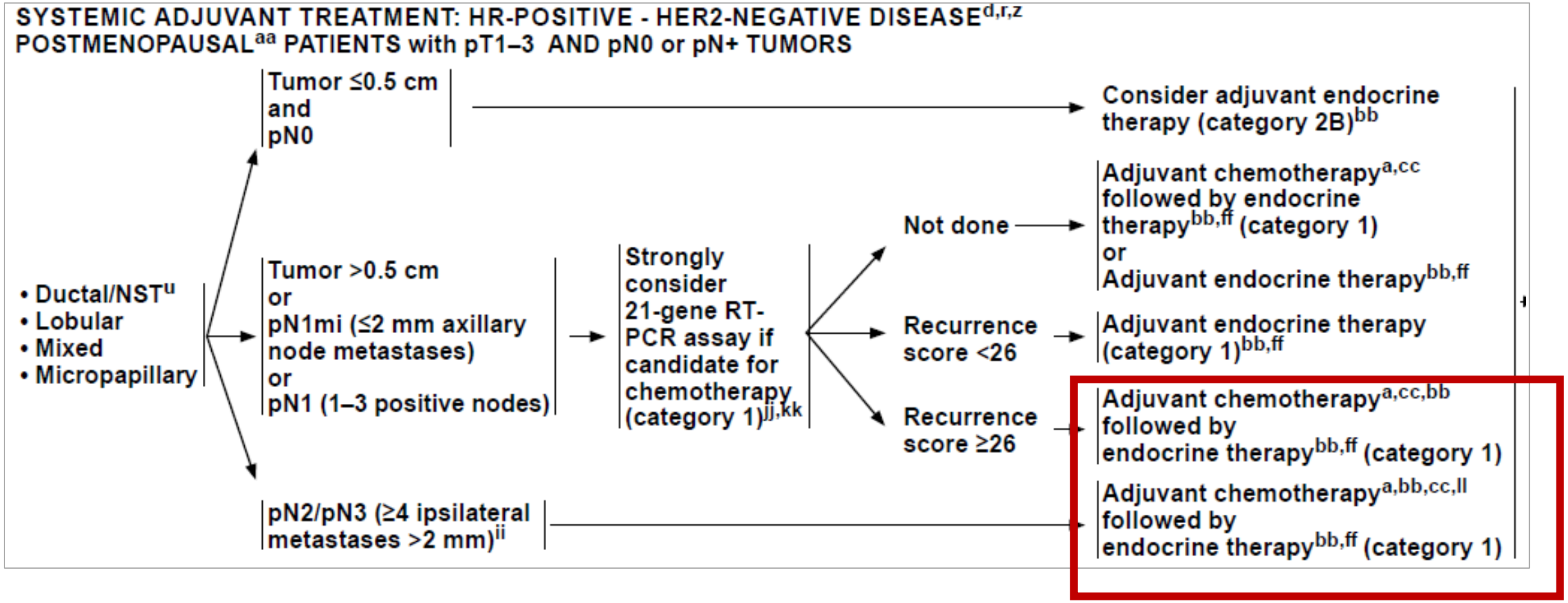
- EBCTCG meta-análisis QT (https://www.ctsu.ox.ac.uk/research/the-early-breast-cancer-trialists-collaborative-group-ebctcg/ebctcg-publications)
  - Beneficio independiente de la expresión de RE, N
  - Mayor absoluto en N+, RE neg, < 50 años
  - Tipos QT
    - Antras > CMF,
    - Antras + Taxanos > antras solas,
    - Taxanos sin antras vs taxanos + antras (¿?)

- Mayoría estudios era preHER2 y mezclando RH+ y RH(-)
- QT neo
  - baja tasa de pCR
  - Valor de la respuesta patológica < HER2+ y TN
- Plataformas genómicas - toma de decisión
- ASCO guidelines - últimas en 2016

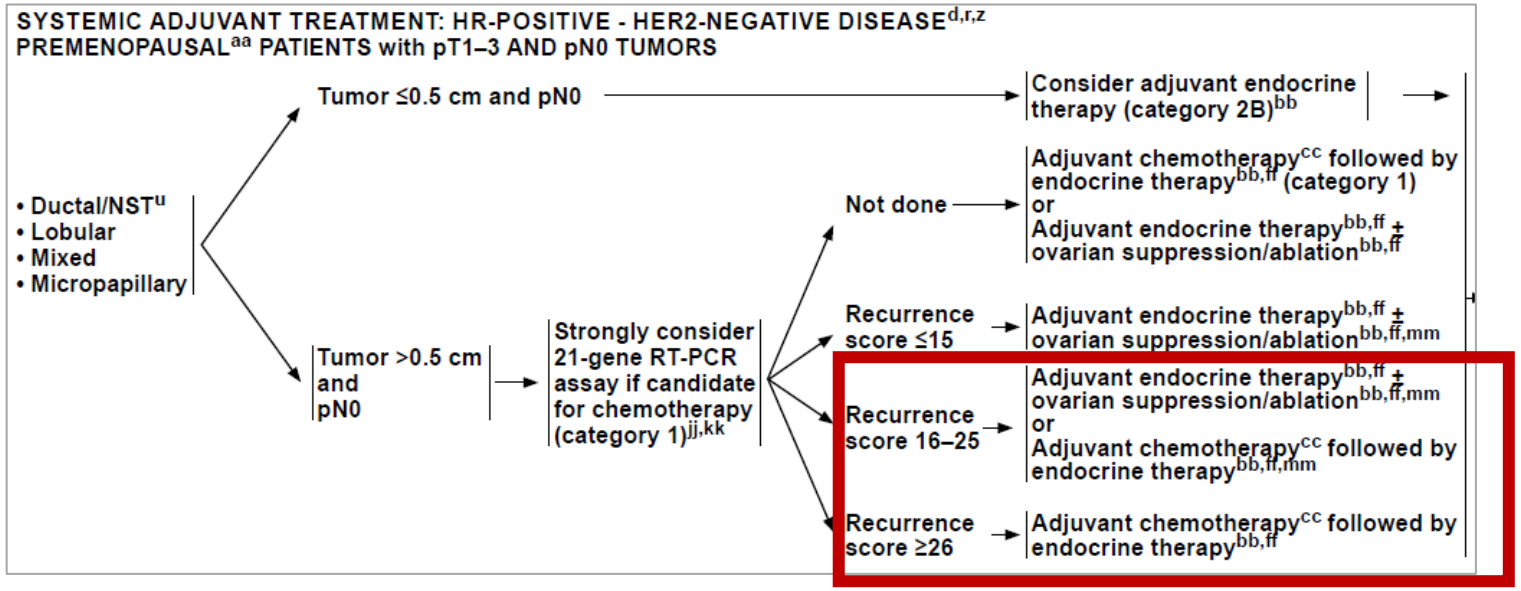


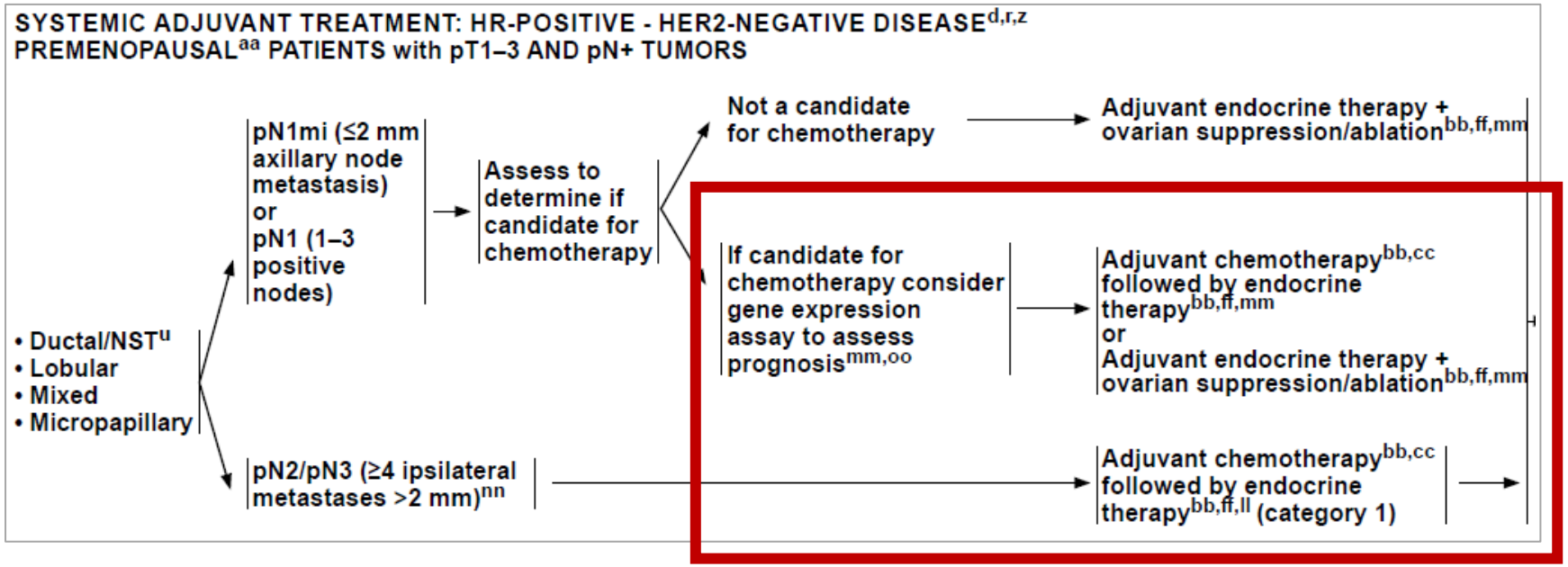
Lancet 2005

NCCN Guidelines Version 4.2023



NCCN Guidelines Version 4.2023



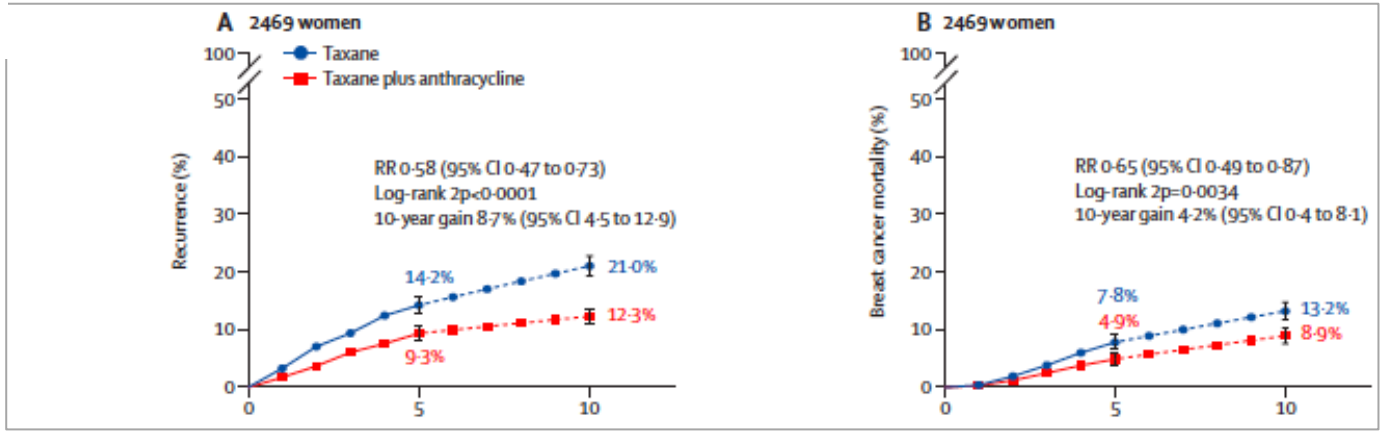


¿Antraciclinas?

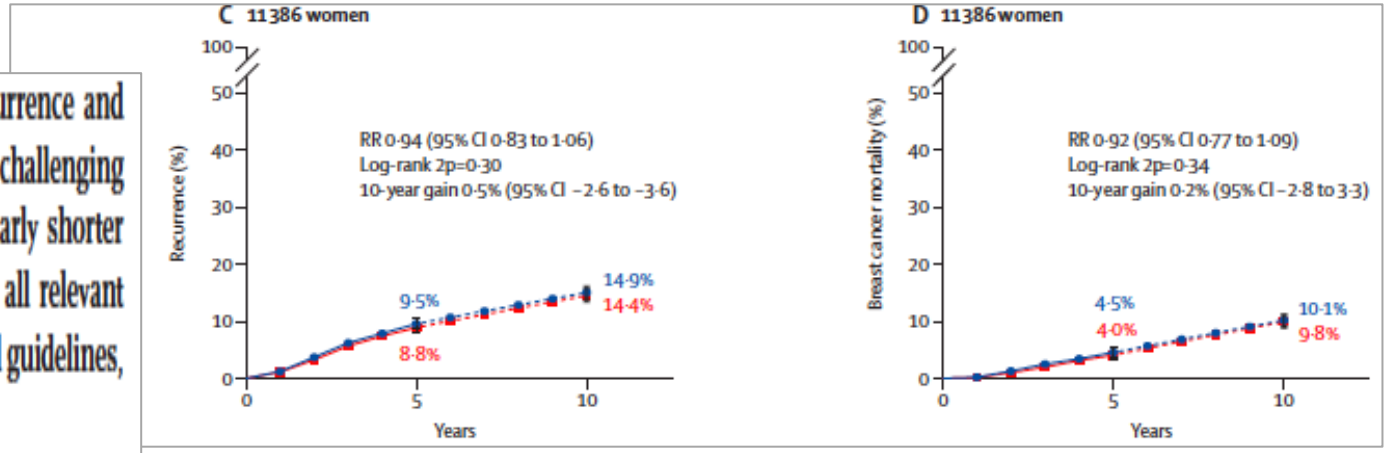
Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Concurrent anthracycline plus docetaxel plus cyclophosphamide Vs Tax-Cyclo



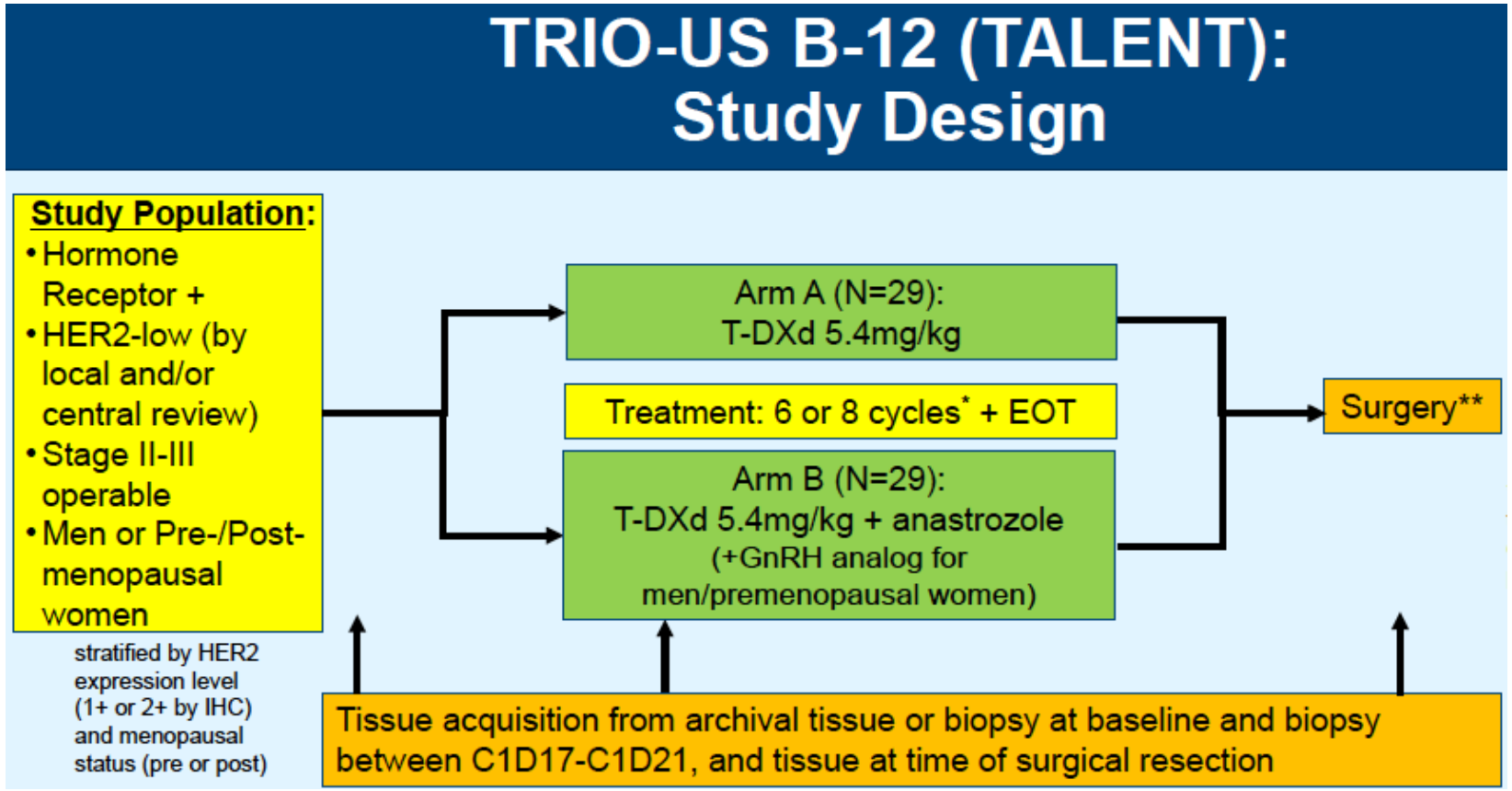
Sequential anthracycline plus docetaxel plus cyclophosphamide Vs Tax- Cyclo



Interpretation Anthracycline plus taxane regimens are most efficacious at reducing breast cancer recurrence and death. Regimens with higher cumulative doses of anthracycline plus taxane provide the greatest benefits, challenging the current trend in clinical practice and guidelines towards non-anthracycline chemotherapy, particularly shorter regimens, such as four cycles of docetaxel–cyclophosphamide. By bringing together data from almost all relevant trials, this meta-analysis provides a reliable evidence base to inform individual treatment decisions, clinical guidelines, and the design of future clinical trials.

Lancet 2023; 401: 1277–92

¿Algún dato con ADC?



- ORR: 68% (T-DXd alone, Arm A); 58% (T-DXd with anastrozole, Arm B)
- RCB 0/1 rate: 15% (both arms); surgical outcomes pending (24% in arm A; 31% in Arm B)

Hurvitz S - SABCS 2022

Quimioterapia y CDKis

¿sustituirán los CDKis a la QT en algún subgrupo?

¿Beneficio diferencial?

¿Siempre juntos ? - ¿Efecto aditivo?

EC en marcha

¿plataformas genómicas?.

- si, pero necesitamos algo mejor que las actuales para hacer medicina de precisión

¿HT extendida?

- Efecto moderado
- Pacientes de riesgo (T y N y G, ¿BCI?)
- TMX 10 años, IA (7-8 años (10 años no datos concluyentes)
- ¿Premenopausicas de alto riesgo tratadas con SO + IA?
- Impacto de CDKis, papel de nuevos SERD/SERM

¿bloqueo estrogénico completo?

- Efecto moderado
- Alto riesgo
- ¿Todas las mujeres muy jóvenes (< 35) independientemente del estadío?

¿papel quimioterapia? - todavía sí


Thank you
Merci
Gracias
Mila esker
Thank you
Merci
Gracias
Mila esker
Merci
Mila esker
Gracias
Merci
Thank you
Mila esker
Gracias
Merci
Gracias
Thank you