



17.05

TALK SHOW: L'evoluzione della
ricerca sul carcinoma mammario
"is more always better?"

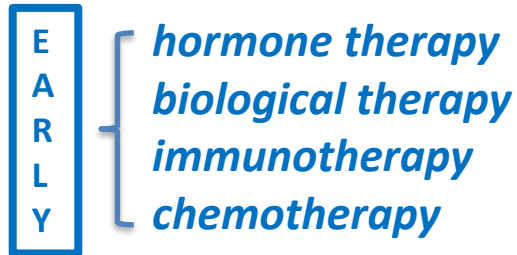
Intervista: G. BIANCHINI

Interviene: A. SANTORO

IS MORE ALWAYS BETTER?

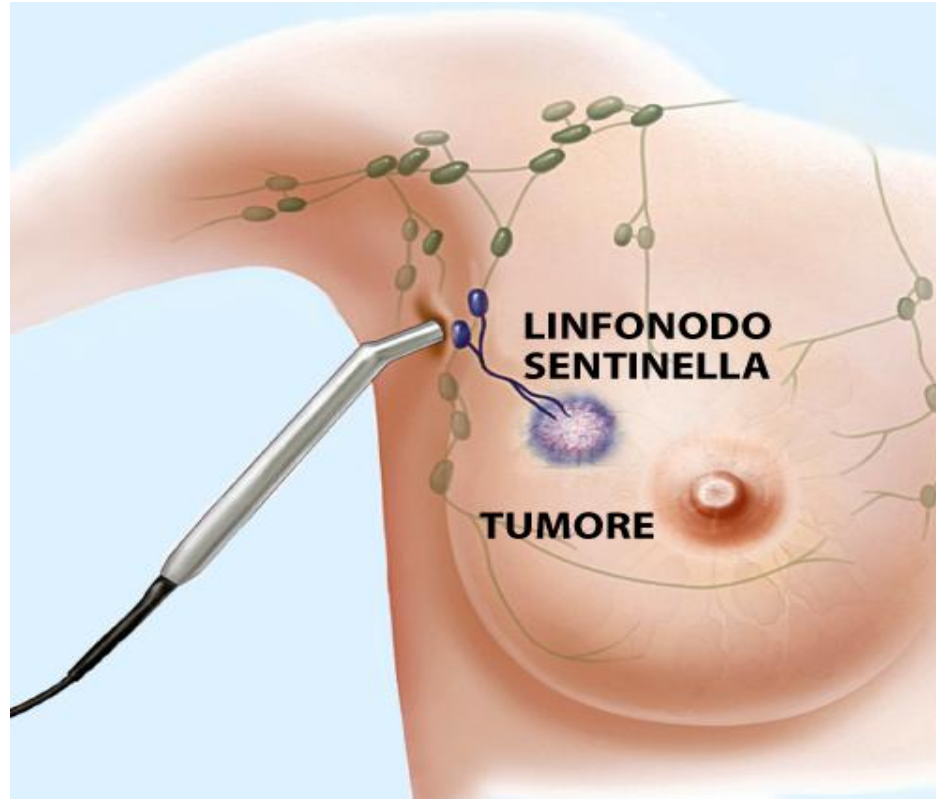
AGENDA

- **CHIRURGIA**
- **RADIOTERAPIA**
- **FOLLOW-UP MAMMOGRAFICO**
- **DE-ESCALATION**



- **TAKE HOME A MESSAGE**

CHIRURGIA



CHIRURGIA SINODAR-ONE: SENTINEL VS AXILLARY NODE DISSECTION

Eligibility

Age ≥ 40 and ≤ 75 years

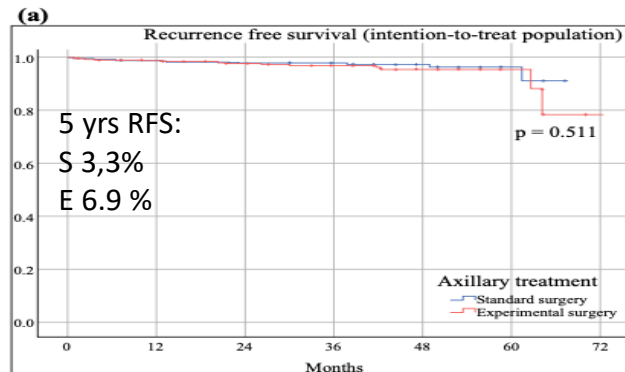
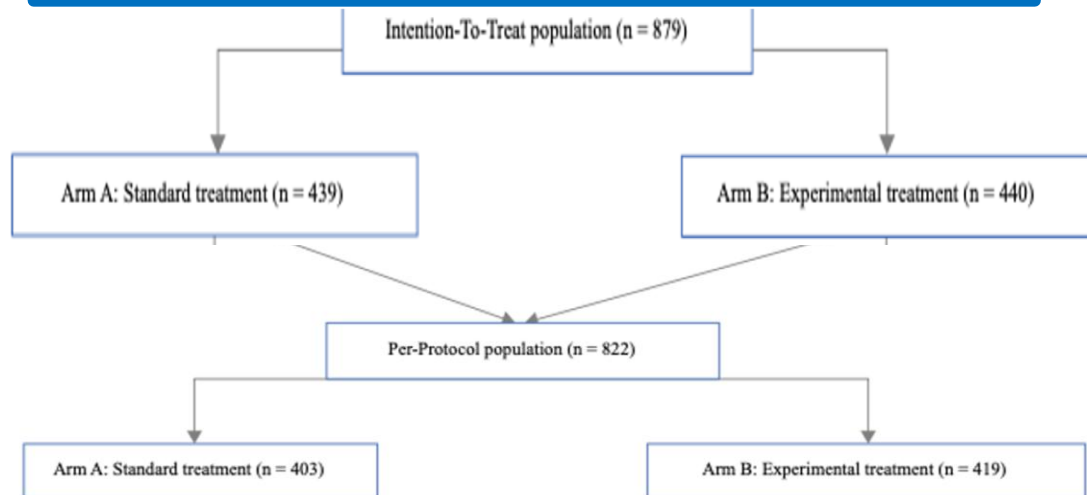
Invasive BC (cytology/core biopsy assessment)

Unilateral lesion

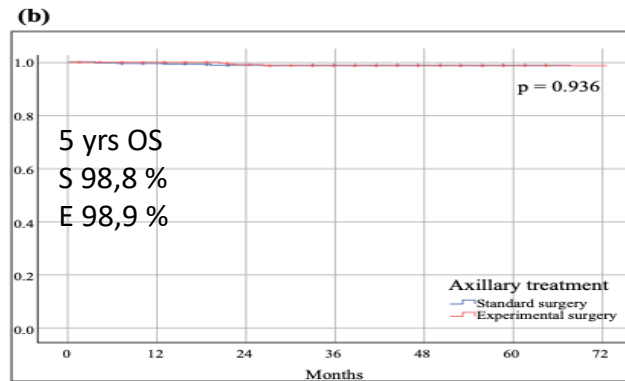
Tumor size ≤ 5 cm (cT1–2) (ultrasound/mammography assessment)

Clinically negative axillary nodes (N0) (ultrasound assessment)

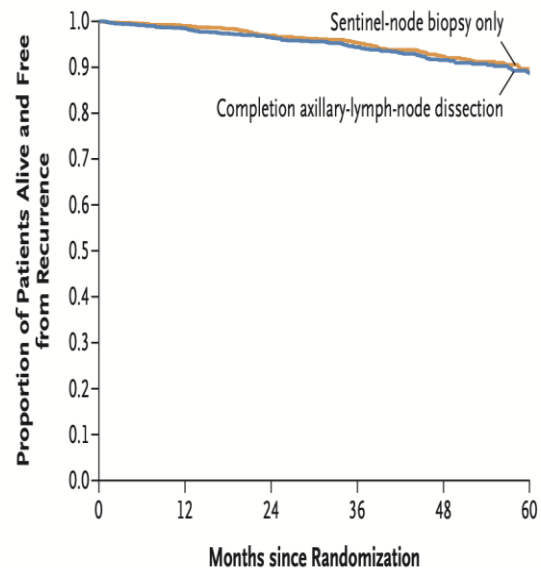
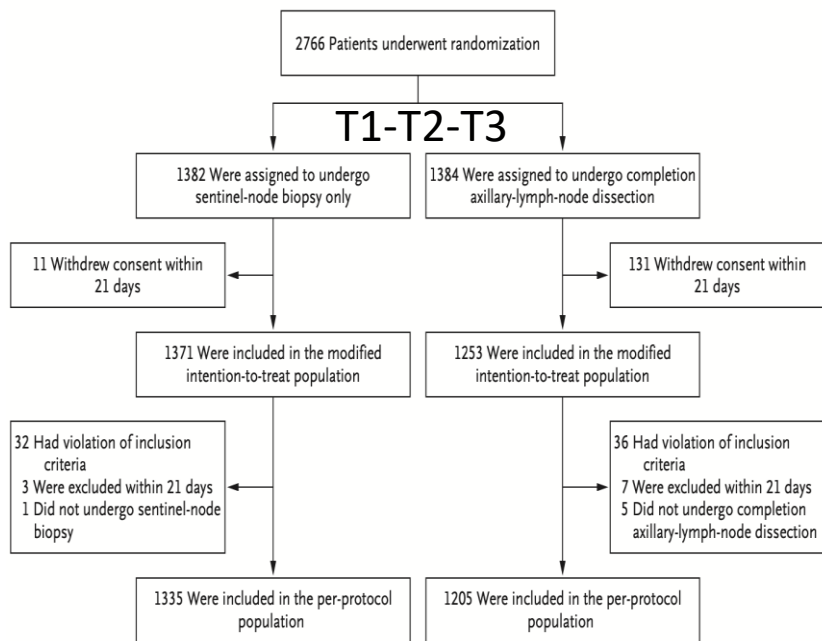
No more than two SLNs proven metastatic (histological assessment)



| Patients at risk | 0 | 1 year | 2 years | 3 years | 4 years | 5 years |
|----------------------|-----|--------|---------|---------|---------|---------|
| Standard surgery | 439 | 374 | 286 | 189 | 105 | 26 |
| Experimental surgery | 440 | 400 | 300 | 194 | 98 | 26 |



CHIRURGIA OMITTING AXILLARY DISSECTION IN SENTINEL-NODE METASTASES

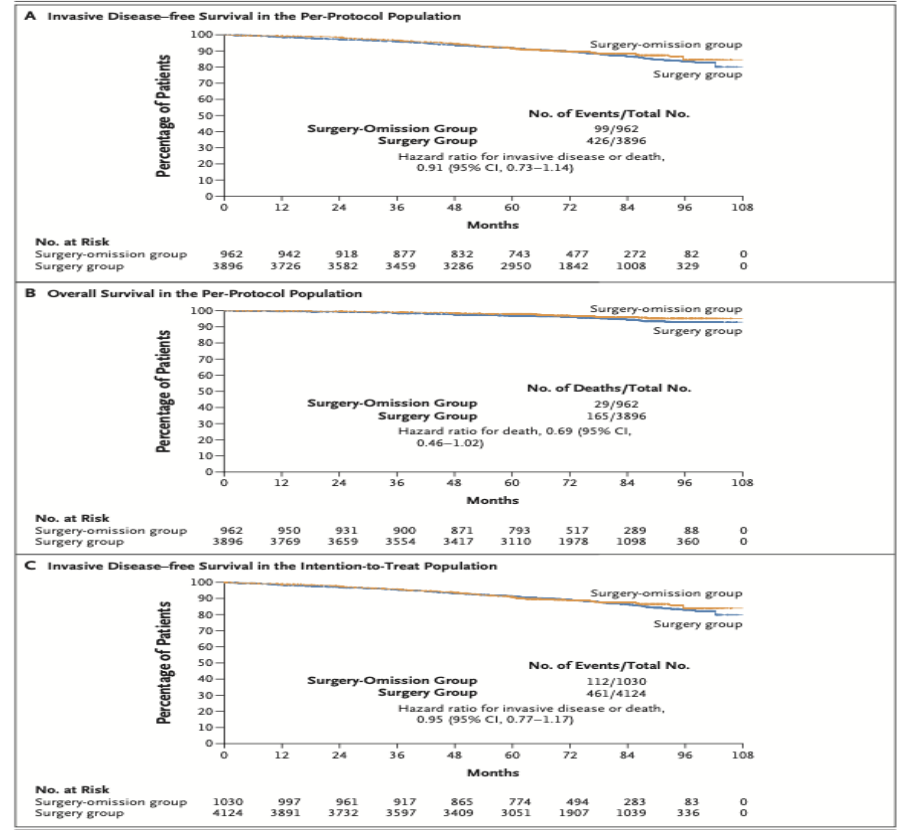
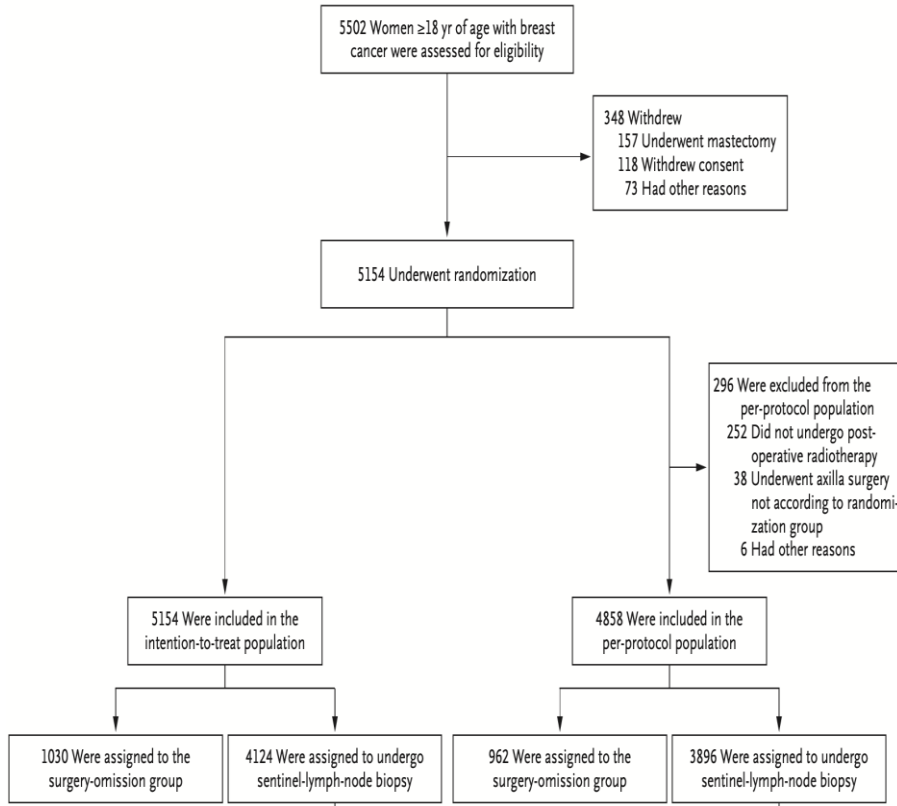


| | No. of Events | Recurrence-free Survival (95% CI) percent |
|---------------------------|---------------|---|
| Sentinel-Node Biopsy Only | 89 | 89.7 (87.5–91.9) |
| Dissection | 91 | 88.7 (86.3–91.1) |

Hazard ratio for recurrence or death, 0.89 (95% CI, 0.66–1.19)
P<0.001 for noninferiority

| | No. at Risk | | | | | |
|---------------------------|-------------|------|------|-----|-----|-----|
| Sentinel-node biopsy only | 1335 | 1276 | 1069 | 832 | 577 | 307 |
| Dissection | 1205 | 1159 | 1009 | 772 | 544 | 274 |

CHIRURGIA INSEMA Trial: AXILLARY SURGERY IN BREAST CANCER cT1-2 cN0 (Pts 5502)





Axillary Dissection — The Bell Tolls for Thee

..... axillary lymphnode dissection has fallen out of favor in many circumstances.
(de Boniface paper)



Sentinel-Lymph-Node Biopsy in Early-Stage Breast Cancer — Is It Obsolete?

Patients with G 1 or 2, cT1 tumors are ideal candidates for this approach. If surgical pathological examination reveals a larger T2 tumor, a high-grade tumor, or vascular invasion — factors that increase the likelihood of nodal metastases— patients can then undergo sentinel-lymph-node biopsy. This approach will avoid axillary surgery for the majority while minimizing undertreatment. (Reimer Paper)

PROPOSAL

cT1, pT1, cN0 (low risk) No sentinel lymphnode

cT2, cNo (high risk) Sentinel lymphnode, no axillary dissection

cT3-T4 cN +/- Biopsy, before neoadjuvant therapy

*cT1-T4, cN +/- After neoadjuvant therapy: sentinel +/- dissection
(according to nodal status?)*

Radiation therapy

External radiation *versus* Internal radiation

comes from a machine
outside the body



comes from implants
placed inside the body



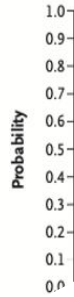
Cancer

Characteristics of the Patients*

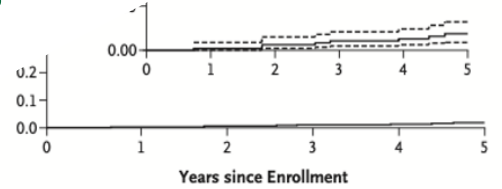
| Characteristic | All Patients (N = 500) |
|---------------------------|------------------------|
| Age | |
| Median (IQR) — yr | 67.1 (62.9–71.6) |
| Distribution — no. (%) | |
| 55 to <60 yr | 61 (12) |
| 60 to <65 yr | 138 (28) |
| 65 to <70 yr | 136 (27) |
| 70 to <75 yr | 107 (21) |
| 75 to <80 yr | 42 (8) |
| ≥80 yr | 16 (3) |
| Tumor size | |
| Median (IQR) — cm | 1.0 (0.7–1.4) |
| Distribution — no. (%) | |
| ≤0.5 cm | 39 (8) |
| 0.5–1.0 cm | 166 (33) |
| 1.1–2.0 cm | 235 (47) |
| Tumor grade — no. (%) | |
| 1 | 10 (2) |
| 2 | 107 (21) |
| Histologic type | |
| Ductal carcinoma in situ | 16 (3) |
| Invasive ductal carcinoma | 12 (2) |

* Incidence of local recurrence, any recurrence, or contralateral breast cancer was 5% or less

A Local Recurrence



B Contralateral Breast Cancer



No. at Risk 500 477 463 449 398 246

C Any Recurrence (local, regional, or distant)

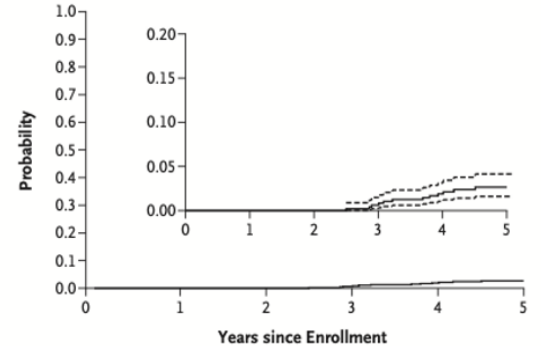


Figure 1. Incidence of Local Recurrence, Contralateral Breast Cancer, and Any Recurrence. The probabilities of local recurrence in the ipsilateral breast (Panel A), contralateral breast cancer (Panel B), and any recurrence (Panel C) among the 500 patients with luminal A breast cancer who were enrolled in the study. The red horizontal line at 5% (Panel A) represents the prespecified boundary for an acceptable incidence of local recurrence at 5 years. Dashed lines indicate the 90% confidence interval, and the insets show the same data on an expanded y axis.

Among women who were at least 55 years of age and had T1N0, grade 1 or 2, luminal A breast cancer that were treated with breast-conserving surgery and endocrine therapy alone, the incidence of local recurrence at 5 years was low with the omission of radiotherapy.

RADIOTHERAPIA PROSPECT TRIAL: POSTOPERATIVE RT OMISSION IN EARLY BC AFTER BREAST MRI

METHODS. PROSPECT is a prospective two-arm, non-randomised trial of RT omission in patients selected using preoperative MRI and postoperative tumour pathology: age 50 years or older, unifocal cT1N0, non-TN, pT1N0 or N1mi, breast-conserving surgery (BCS) and, if pT1N0 or N1mi.

All received systemic therapy.

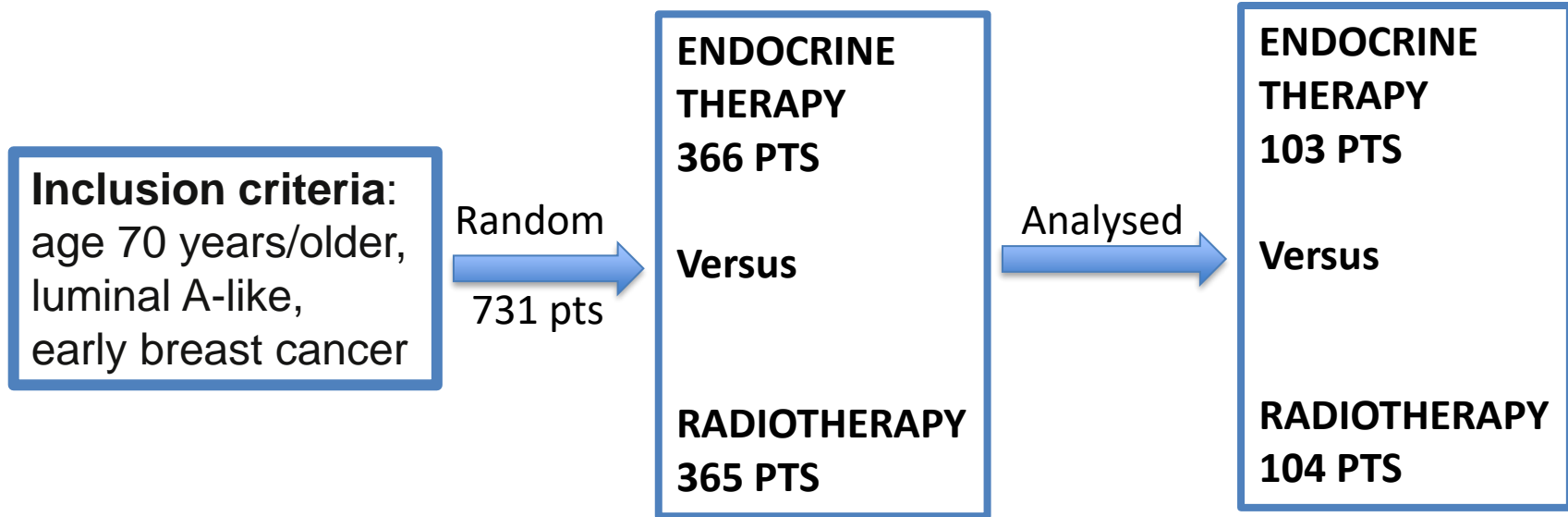
THE PRIMARY OUTCOME WAS IPSILATERAL INVASIVE RECURRENCE RATE(IIRR) AT 5 YEARS. QALYS AND COST-EFFECTIVENESS OF THE PROSPECT PATHWAY WERE ANALYSED.

FINDINGS. 443 patients with BC underwent MRI. Median age was 63.0 years. Of the eligible 201 were eligible for BCS without radiotherapy:

IIRR at 5 years was 1.0% (upper 95% CI 5.4%) with an increased QALYs by 0.019 (95% CI 0.008–0.029) and saved AU\$1980 (95% CI 1396–2528) or £953 (672–1216) per patient

INTERPRETATION. PROSPECT SUGGESTS THAT WOMEN WITH UNIFOCAL BC ON MRI AND FAVOURABLE PATHOLOGY CAN SAFELY OMIT RADIOTHERAPY

RADIOTHERAPIA EUROPA TRIAL: HT vs RT after breast-conserving surgery



NO DIFFERENCE IN RELAPSE RATE

BETTER HRQOL FOR RADIOTHERAPY

RADIOTHERAPIA Omitting Regional Nodal RT after Response to Neoadjuvant CT

RANDOMIZED PHASE 3 STUDY

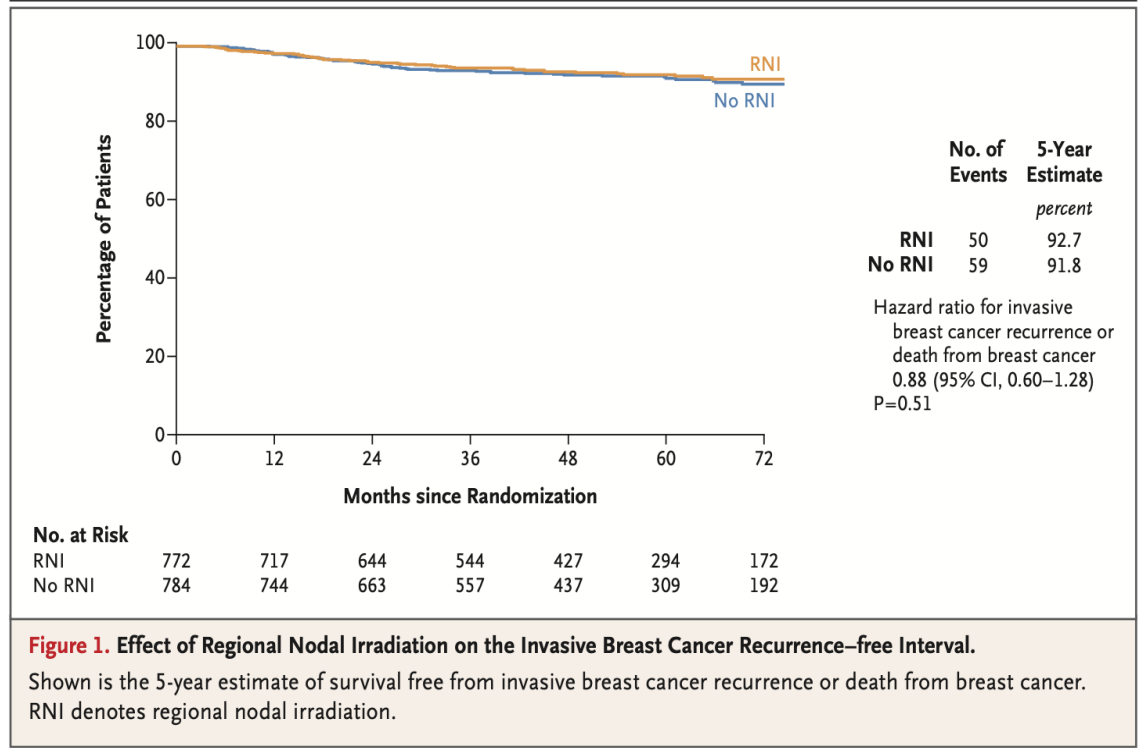
Patients 1556

T1-T3 N1 Mo → ypN0

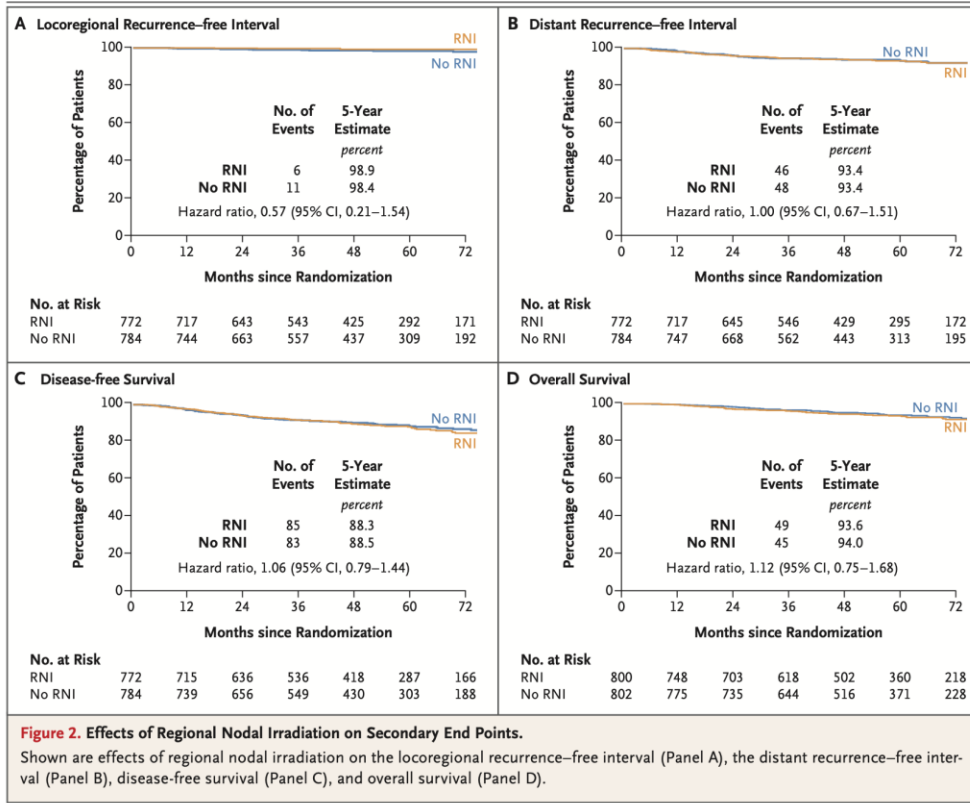
Random:

RNI 772

No RNI 784



RADIOTERAPIA Omitting Regional Nodal RT after Response to Neoadjuvant CT



CONCLUSIONS

The addition of adjuvant regional nodal RT did not decrease the risk of invasive breast cancer recurrence or death in patients who had negative axillary nodes after neoadjuvant chemotherapy.



FOLLOW UP MAMMO-50: Annual vs less frequent mammography in BC over 50 ys in the UK: a randomised, phase 3, non-inferiority trial

TUMOR CHARACTERISTICS

Patients 5235

RANDOM:

Mrx every year (2618)

VS

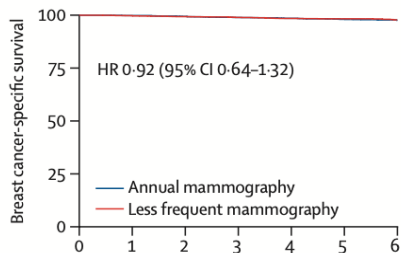
Mrx yearly x 2yrs

and after

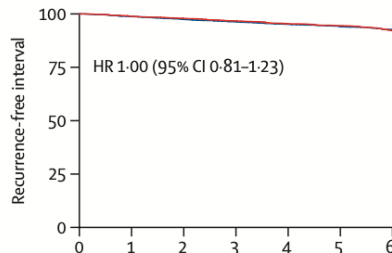
every 2-3 years (2617)

| | Annual mammography group (n=2618) | Less frequent mammography group (n=2617) | Total (n=5235) |
|--|-----------------------------------|--|----------------|
| (Continued from previous page) | | | |
| Distance from closest radial margin, mm | | | |
| <1 | 242 (10.6%) | 245 (10.7%) | 487 (10.6%) |
| ≥1 to <2 | 239 (10.5%) | 187 (8.2%) | 426 (9.3%) |
| ≥2 to <5 | 523 (22.9%) | 510 (22.3%) | 1033 (22.6%) |
| ≥5 | 987 (43.2%) | 1029 (45.0%) | 2016 (44.1%) |
| Not known | 296 (12.9%) | 318 (13.9%) | 614 (13.4%) |
| ER status | | | |
| Positive | 2047 (89.5%) | 2039 (89.1%) | 4086 (89.3%) |
| Negative | 233 (10.2%) | 241 (10.5%) | 474 (10.4%) |
| Not evaluated | 7 (0.3%) | 9 (0.4%) | 16 (0.3%) |
| Progesterone receptor status | | | |
| Positive | 1091 (47.7%) | 1033 (45.1%) | 2124 (46.4%) |
| Negative | 408 (17.8%) | 439 (19.2%) | 847 (18.5%) |
| Not evaluated | 788 (34.5%) | 817 (35.7%) | 1605 (35.1%) |
| HER2 status | | | |
| Positive | 255 (11.1%) | 269 (11.8%) | 524 (11.5%) |
| Negative | 2002 (87.5%) | 1988 (86.9%) | 3990 (87.2%) |
| Not evaluated | 30 (1.3%) | 32 (1.4%) | 62 (1.4%) |
| Receptor status grouping | | | |
| HER2 positive; any ER and progesterone receptor status | 255 (11.1%) | 269 (11.8%) | 524 (11.5%) |
| HER2 negative; ER positive or progesterone receptor positive | 1846 (80.7%) | 1824 (79.7%) | 3670 (80.2%) |
| Triple negative | 134 (5.9%) | 144 (6.3%) | 278 (6.1%) |
| HER2 negative; ER and progesterone receptor negative, or both ER and progesterone receptor not known or not evaluated | 22 (1.0%) | 20 (0.9%) | 42 (0.9%) |
| Not known or not evaluated | 30 (1.3%) | 32 (1.4%) | 62 (1.4%) |
| Data are n (%) unless indicated otherwise. Percentages might not add to 100% due to rounding. DCIS=ductal carcinoma in situ. ER=oestrogen receptor. NPI=Nottingham Prognostic Index. | | | |

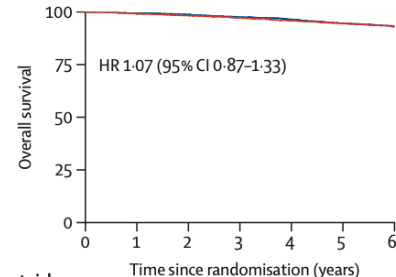
FOLLOW UP MAMMO-50: Annual vs less frequent mammography in BC over 50 yrs in the UK: a randomised, phase 3, non-inferiority trial



| | Number at risk (number censored) | | | | | | |
|---------------------------|-------------------------------------|--------------|---------------|---------------|---------------|---------------|---------------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Annual mammography | 2618 (0) | 2591 (23) | 2554 (50) | 2500 (91) | 2426 (155) | 1906 (664) | 538 (2026) |
| Less frequent mammography | 2617 (0) | 2514 (97) | 2456 (145) | 2398 (193) | 2307 (237) | 1837 (739) | 471 (2100) |



| | Number at risk (number censored) | | | | | | |
|---------------------------|-------------------------------------|--------------|---------------|---------------|---------------|---------------|---------------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Annual mammography | 2618 (0) | 2563 (23) | 2502 (47) | 2439 (84) | 2346 (146) | 1835 (634) | 515 (1932) |
| Less frequent mammography | 2617 (0) | 2494 (96) | 2425 (138) | 2353 (182) | 2244 (259) | 1779 (703) | 442 (2011) |



| | Number at risk (number censored) | | | | | | |
|---------------------------|-------------------------------------|--------------|---------------|---------------|---------------|---------------|---------------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Annual mammography | 2618 (0) | 2591 (18) | 2554 (36) | 2501 (59) | 2426 (105) | 1906 (580) | 538 (1926) |
| Less frequent mammography | 2617 (0) | 2514 (84) | 2456 (120) | 2398 (149) | 2307 (227) | 1837 (646) | 471 (1993) |

IMPLICATIONS OF ALL THE AVAILABLE EVIDENCE

Data from this study indicate that offering less frequent mammographic surveillance to this group of women from 3 years post diagnosis is safe and has no detrimental impact on survival, detection of recurrences, or detection of new primary cancers, and has the potential for considerable cost savings.

Evidence from Mammo-50 could be used to amend guidelines on mammographic surveillance in this patient group.

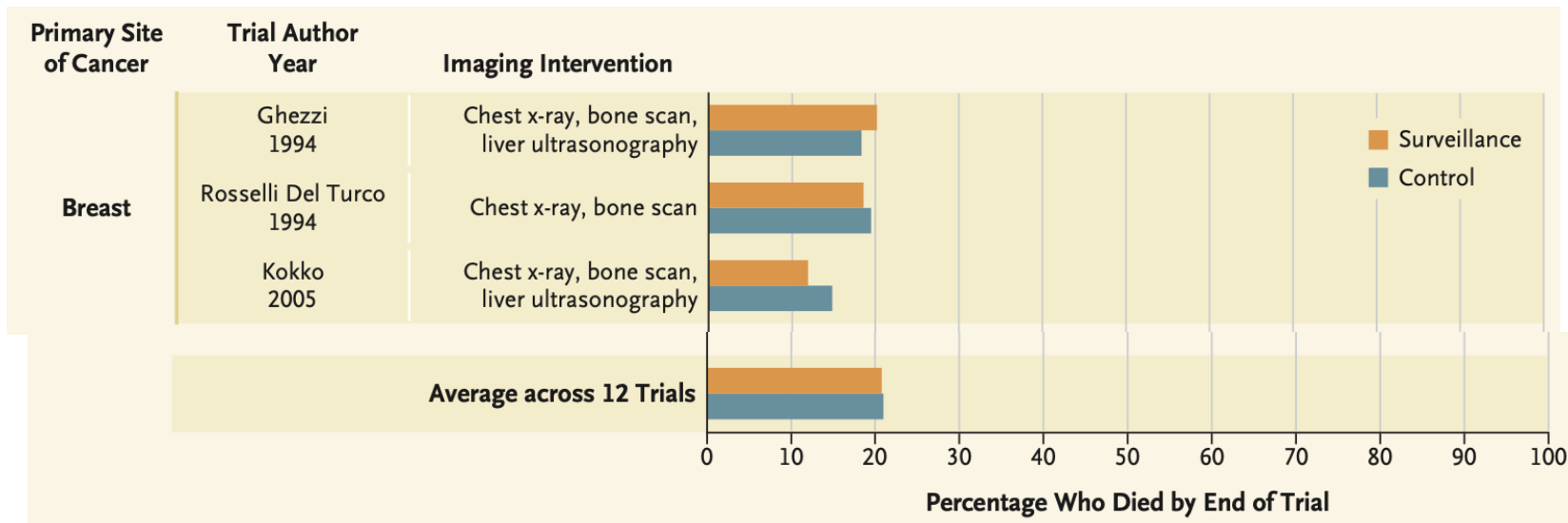
FOLLOW UP

RETHINKING SURVEILLANCE AFTER BREAST CANCER



ROUTINE SURVEILLANCE FOR CANCER METASTASES — DOES IT HELP OR HARM PATIENTS?

Risk of Death in the Surveillance and Control Groups among Persons with Cancer.



**THE PRIMARY EFFECT OF SURVEILLANCE IS TO GIVE PATIENTS BAD NEWS SOONER.
ON THE BASIS OF EXISTING DATA, LESS SURVEILLANCE WOULD BE BETTER FOR PATIENTS.**

HORMONE THERAPY

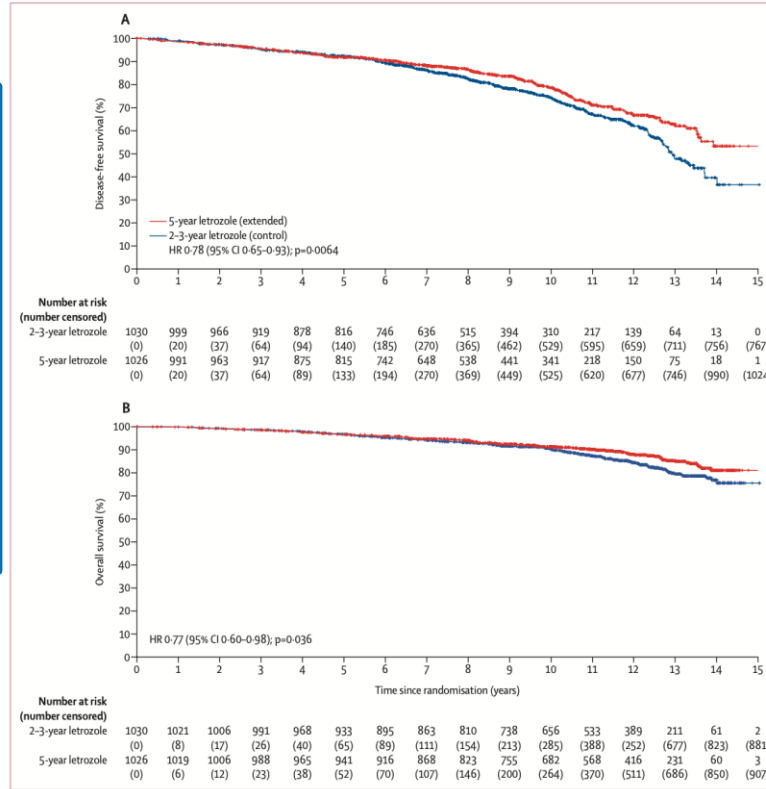


HORMONE THERAPY

Extended adjuvant letrozole in postmenopausal pts with early-stage BC: a multicentre, randomised, phase 3 trial

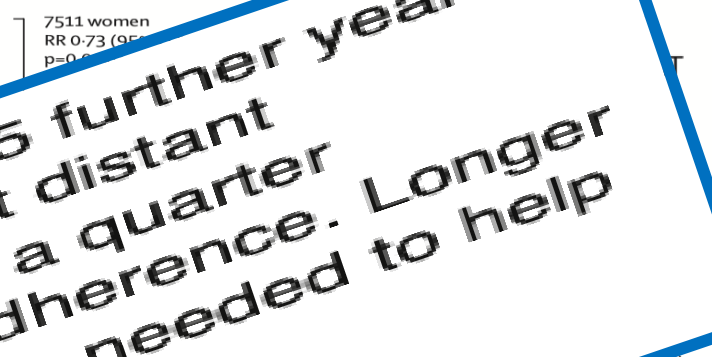
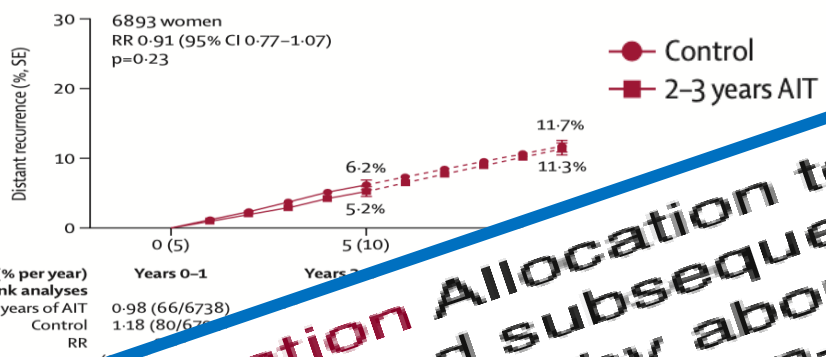
Pts:
2056 after 2-3 yrs
on Tamoxifene

Random:
Letrozolo for 2-3 yrs
Vs
Letrozole for 5 yrs



INTERPRETATION
5 years of letrozole resulted in a significant improvement in disease-free survival. Sequential endocrine therapy with tamoxifen for 2–3 years followed by letrozole for 5 years should be considered as one of the optimal standard

HORMONE THERAPY Extended HT for early BC pts (meta-analysis of 12 R trials) of HT in 22 031 postmenopausal women after at least 5 yrs of HT



Interpretation Allocation to 5 further years of AIT reduced subsequent distant recurrence rates by about a quarter despite substantial non-adherence. Longer follow-up would have been needed to help assess directly any effects on mortality.

Event rate (% per year) and logrank analyses
 2-3 years of AIT RR 0.98 (66/6738)
 Control RR 1.18 (80/6738)

| | Years since diagnosis | | | | Years since allocated treatments differed (and approximate years since diagnosis) | | | |
|----------------|-------------------------|-------------------------|-------------------------|-------------------------|---|-------------------------|-------------------------|-------------------------|
| | Years 0-1 | Years 2-4 | Years 5-9 | Years ≥10 | Years 0-1 | Years 2-4 | Years 5-9 | Years ≥10 |
| 5 years of AIT | 0.25 (18/7322) | 0.58 (59/10115) | 0.45 (44/9792) | 0.34 (3/884) | 0.25 (18/7322) | 0.58 (59/10115) | 0.45 (44/9792) | 0.34 (3/884) |
| Control | 0.11 (8/7392) | 0.59 (60/10215) | 0.59 (59/9921) | 1.23 (11/892) | 0.11 (8/7392) | 0.59 (60/10215) | 0.59 (59/9921) | 1.23 (11/892) |
| RR | 2.21 (95% CI 1.02-4.82) | 0.99 (95% CI 0.69-1.42) | 0.73 (95% CI 0.49-1.09) | 0.33 (95% CI 0.11-0.97) | 2.21 (95% CI 1.02-4.82) | 0.99 (95% CI 0.69-1.42) | 0.73 (95% CI 0.49-1.09) | 0.33 (95% CI 0.11-0.97) |
| (O-E)/V | 5.0/6.3 | -0.4/28.8 | -7.7/24.5 | -3.7/3.4 | 5.0/6.3 | -0.4/28.8 | -7.7/24.5 | -3.7/3.4 |



IBC SG

TEXT and SOFT Designs

**HORMONE
THERAPY**

Enrolled: Nov 2003 – Apr 2011
Premenopausal ER and/or PR \geq 10%

- Premenopausal HR+
- Planned OFS
- No planned chemo (40%)
OR planned chemo (60%)

TEXT

R
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TAMOXIFEN AND EXEMESTANE TRIAL (N=2672)

Tamoxifen+OFS x 5y
Exemestane+OFS x 5y

- Premenopausal HR+
- No chemo (47%)
OR
- Remain premenopausal \leq 8 mos after chemo (53%)

SOFT

R
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E

Tamoxifen x 5y
Tamoxifen+OFS x 5y
Exemestane+OFS x 5y

Joint Analysis
(N=4690)

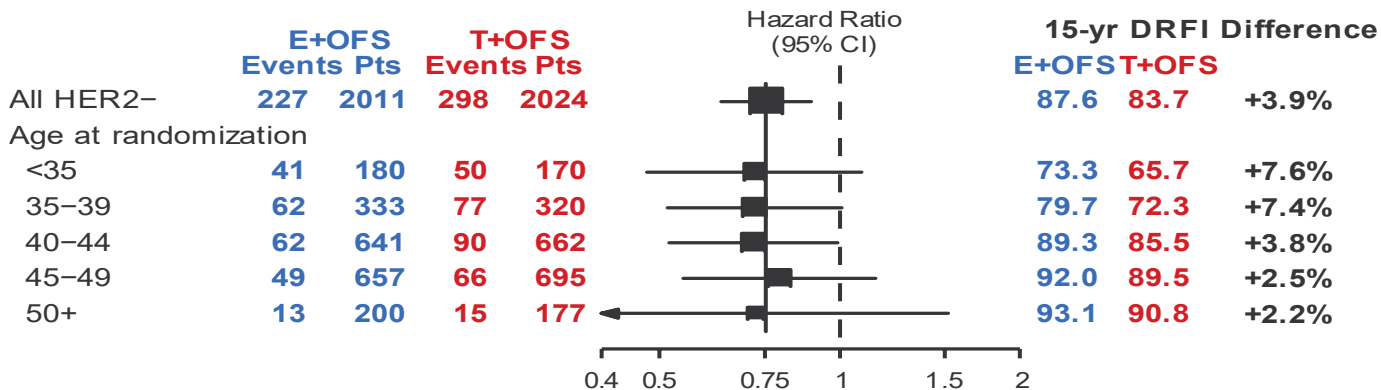
Tamoxifen+OFS x 5y
Exemestane+OFS x 5y

Median follow-up 16 years (max 21 years)

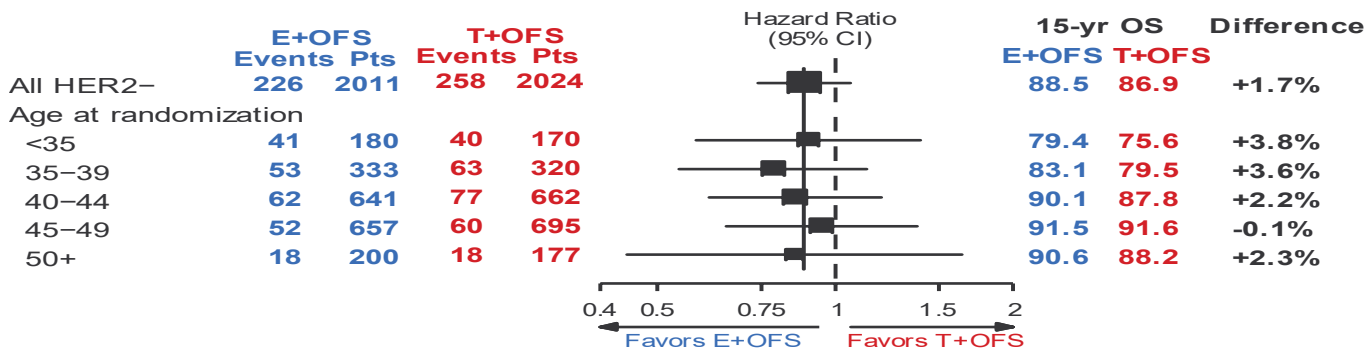
SOFT & TEXT Joint Analysis HER negative

E+OFS vs T+OFS Treatment Effect by Age

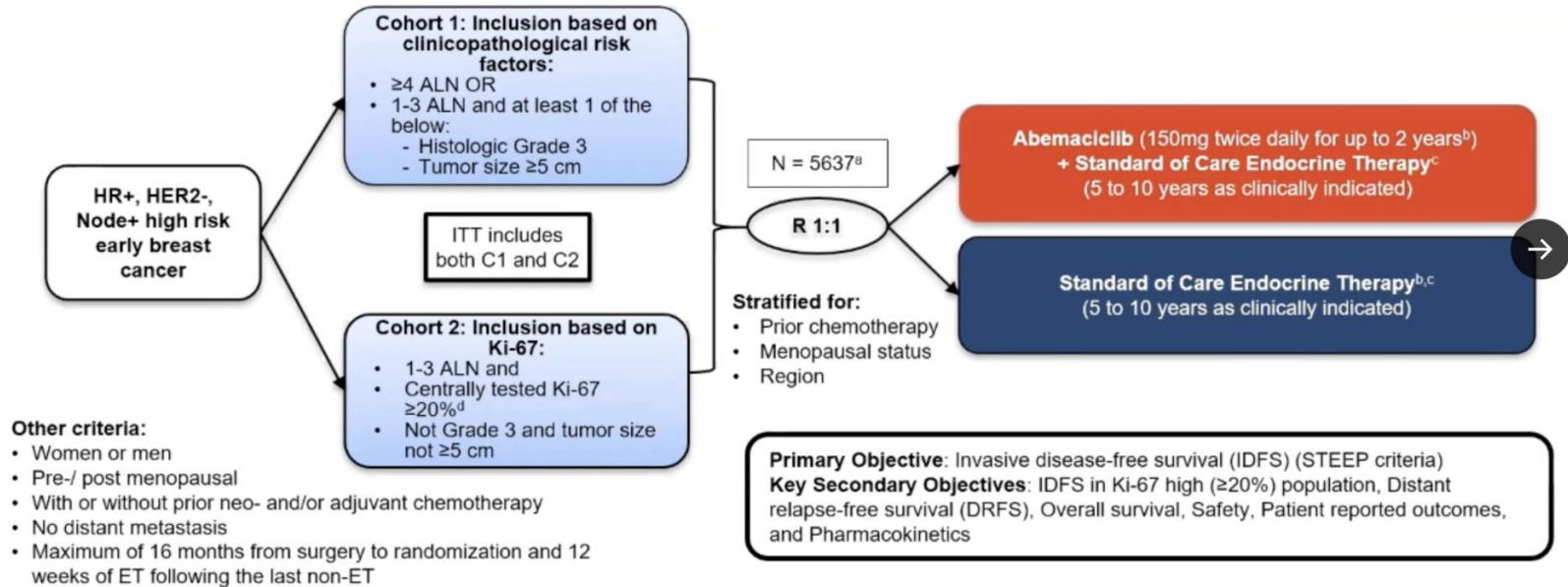
DRFI



Overall Survival

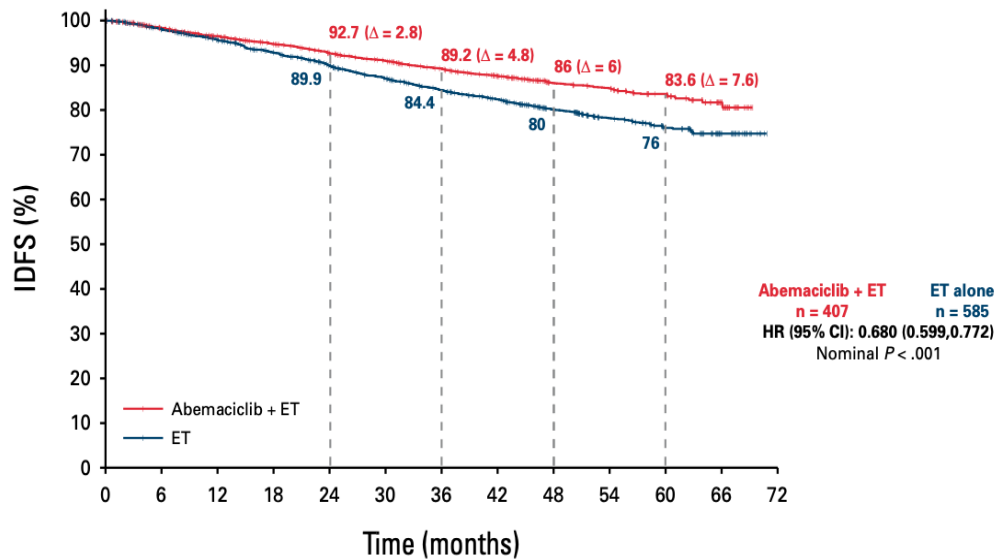
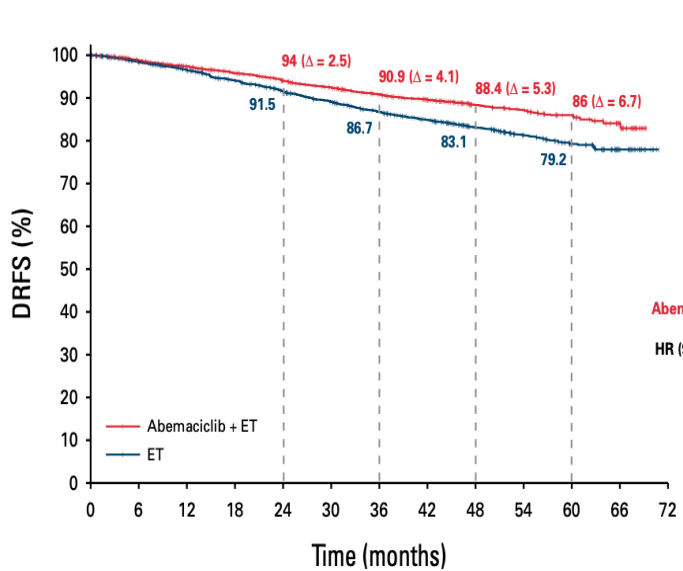


HORMONE THERAPY Study design – MONARCHE (Abemaciclib)



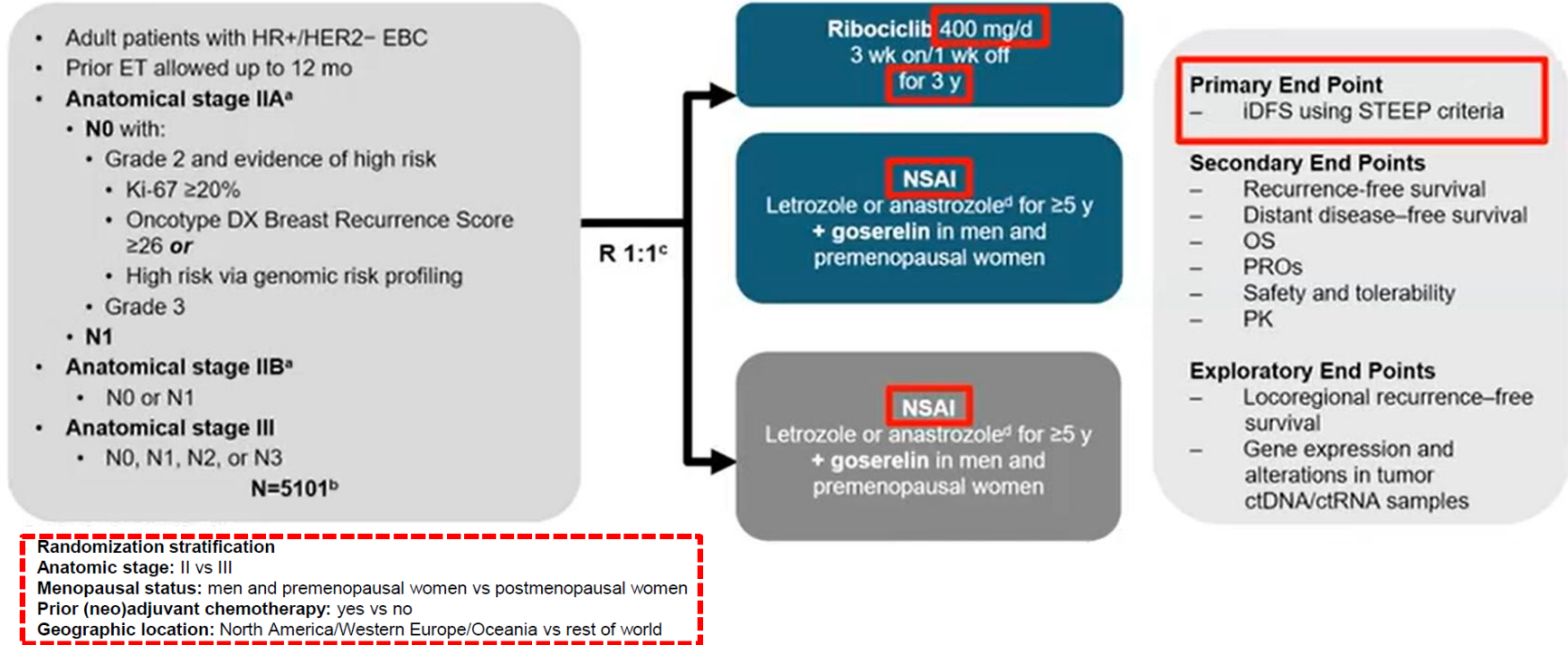
^aRecruitment from July 2017 to August 2019; ^bTreatment period = first 2 years on study treatment after randomization; ^cEndocrine therapy of physician's choice [e.g. aromatase inhibitors, tamoxifen, LHRH agonist]; ^dKi-67 expression assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent
Abbreviations: ALN, positive axillary lymph nodes; R, randomized

HORMONE THERAPY Study design – MONARCHE (Abemaciclib)

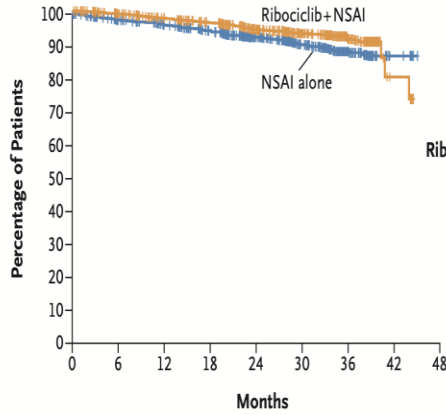


CONCLUSIONS

At the pivotal 5-year mark for adjuvant EBC trials, adjuvant abemaciclib plus ET continued to reduce the risk of developing invasive and distant disease



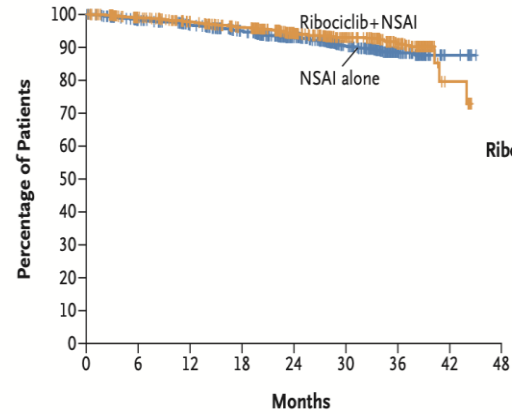
Recurrence-free Survival



| | No. of Patients with Event/ Total No. (%) | 3-Yr Recurrence-free Survival percent |
|-----------------|---|--|
| Ribociclib+NSAI | 159/2549 (6.2) | 91.7 |
| NSAI alone | 207/2552 (8.1) | 88.6 |

Hazard ratio for recurrence or death, 0.72 (95% CI, 0.58–0.88)

Distant Disease-free Survival



| | No. of Patients with Event/ Total No. (%) | 3-Yr Distant Disease-free Survival percent |
|-----------------|---|---|
| Ribociclib+NSAI | 167/2549 (6.6) | 90.8 |
| NSAI alone | 212/2552 (8.3) | 88.6 |

Hazard ratio for distant disease or death, 0.74 (95% CI, 0.60–0.91)

No. at Risk

| | 2549 | 2358 | 2283 | 2210 | 1733 | 1124 | 314 | 12 | 0 |
|-----------------|------|------|------|------|------|------|-----|----|---|
| Ribociclib+NSAI | 2549 | 2358 | 2283 | 2210 | 1733 | 1124 | 314 | 12 | 0 |
| NSAI alone | 2552 | 2247 | 2174 | 2086 | 1646 | 1080 | 290 | 13 | 0 |

No. at Risk

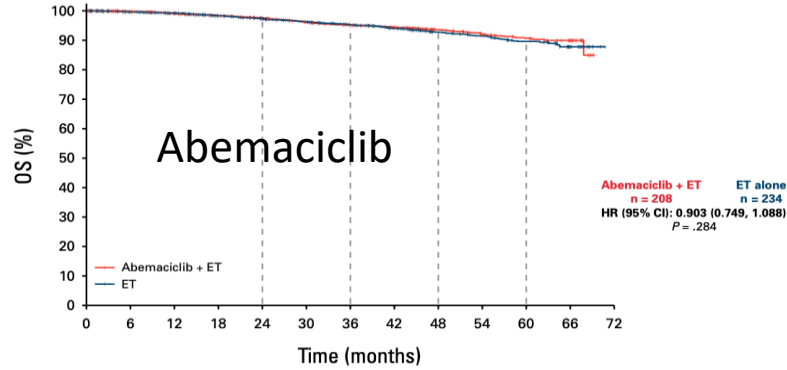
| | 2549 | 2352 | 2280 | 2199 | 1729 | 1119 | 311 | 12 | 0 |
|-----------------|------|------|------|------|------|------|-----|----|---|
| Ribociclib+NSAI | 2549 | 2352 | 2280 | 2199 | 1729 | 1119 | 311 | 12 | 0 |
| NSAI alone | 2552 | 2244 | 2168 | 2080 | 1643 | 1076 | 288 | 13 | 0 |

CONCLUSIONS

Ribociclib plus an NSAI significantly improved invasive disease-free survival among patients with HR-positive, HER2-negative stage II or III early breast cancer.

| ADVERSE EVENTS | MonarchE | NATALEE |
|----------------------------------|---------------------|---------------------|
| Any grade neutropenia (>G3) | 45.8% (19.6%) | 62.8% (44.4%) |
| Liver related AE (>G3) | 9.5% (2.1%) | 26.7% (8.6%) |
| Diarrhea (> G3) | 83.5% (7.8%) | 14.6% (0.6%) |
| QT prolongation (> G3) | 0.0% | 5.4% (1.0%) |
| ILD pneumonitis (> G3) | 2.7% (0.3%) | 1.6% (0.0%) |

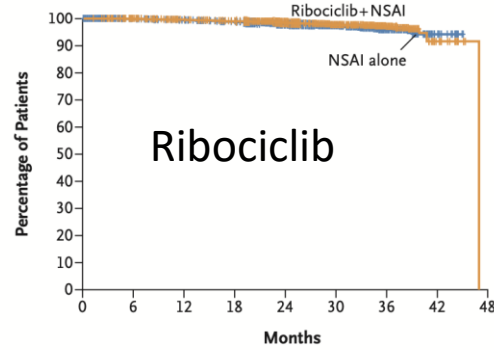
HORMONE THERAPY



Number at risk:

| Time (months) | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 | 72 |
|------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-----|----|----|
| Abemaciclib + ET | 2,808 | 2,666 | 2,614 | 2,566 | 2,518 | 2,455 | 2,407 | 2,373 | 2,260 | 1,271 | 528 | 80 | 0 |
| ET | 2,829 | 2,705 | 2,664 | 2,599 | 2,545 | 2,496 | 2,440 | 2,382 | 2,243 | 1,279 | 538 | 77 | 0 |

Overall Survival



No. at Risk

| | | | | | | | | | |
|-----------------|------|------|------|------|------|------|-----|----|---|
| Ribociclib+NSAI | 2549 | 2405 | 2337 | 2303 | 1905 | 1338 | 451 | 21 | 0 |
| NSAI alone | 2552 | 2303 | 2256 | 2209 | 1823 | 1273 | 385 | 22 | 0 |

No. of Patients with Event/ Total No. (%)

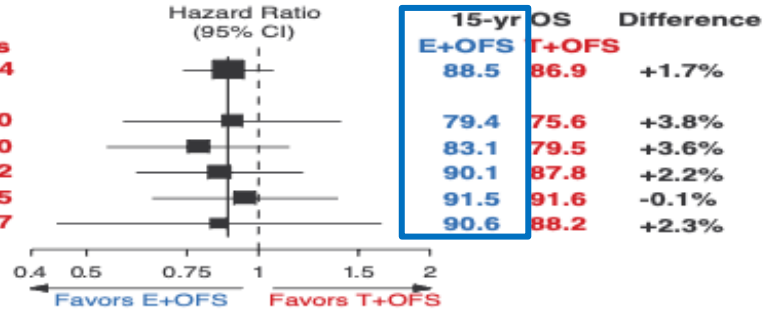
Ribociclib+NSAI 61/2549 (2.4)
 NSAID alone 73/2552 (2.9)

Hazard ratio for death, 0.76 (95% CI, 0.54–1.07)

TEXT + SOFT

Overall Survival

| All HER2- | E+OFS | | T+OFS | |
|----------------------|--------|------|--------|------|
| | Events | Pts | Events | Pts |
| Age at randomization | 226 | 2011 | 258 | 2024 |
| <35 | 41 | 180 | 40 | 170 |
| 35-39 | 53 | 333 | 63 | 320 |
| 40-44 | 62 | 641 | 77 | 662 |
| 45-49 | 52 | 657 | 60 | 695 |
| 50+ | 18 | 200 | 18 | 177 |



To the Editor: The **NATALEE trial showed that** among patients HR-positive, HER2-negative BC, **invasive DFS at 3 years (primary end point) was higher by 3.3 %** among those who received adjuvant ribociclib plus endocrine therapy than among those who received endocrine therapy alone. **The cost of 3 years of ribociclib treatment in the United States is approximately \$500,000.** Improvements in invasive DFS generally predict smaller (or no) improvements in OS. The optimistic assumption that 3.3 % improvement in RFS – point improvement in OS, **translates into a requirement 30 pts be treated (and have toxic effects) to save 1 life, at a cost of approximately USD 15 million-** far beyond reasonable limits of cost-effectiveness. And why 3 years of treatment? The median time that patients with advanced disease receive ribociclib before disease progression is 20 months. **The trial has several other problems, such as those of MONARCHE trial** evaluating adjuvant abemaciclib, that cast doubt on the validity of the conclusions. **The world, included the United States, cannot afford 3 years of adjuvant ribociclib.**





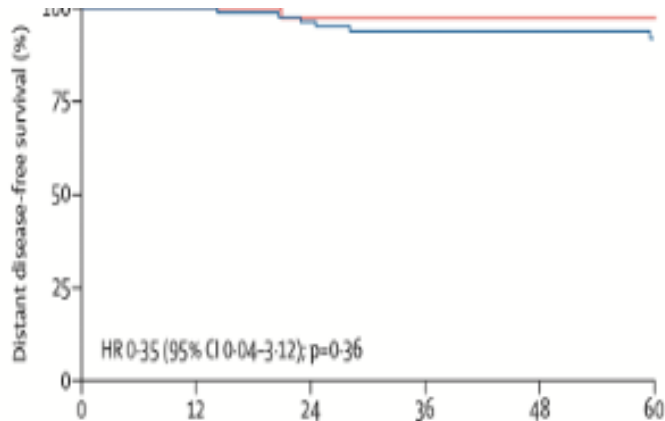
**SAFETY
FIRST**

**DE-ESCALATION
OF THERAPY**

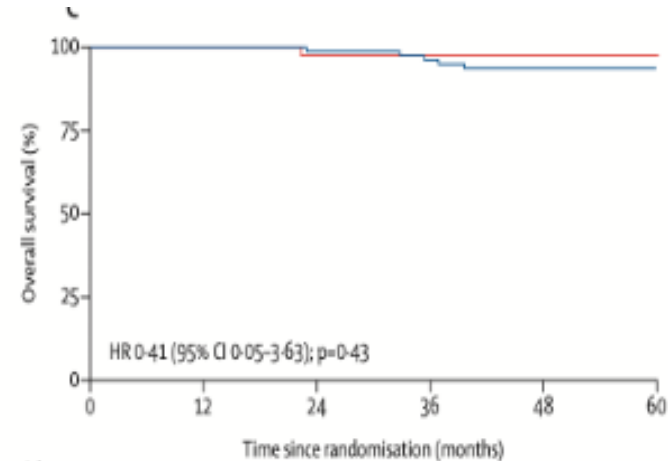
DEESCALATION De-escalated neoadjuvant pertuzumab + trastuzumab therapy +/- weekly paclitaxel in HER2-positive, HR negative early BC (WSG-ADAPT-HER2+/HR-): survival outcomes from a multicentre, open-label, randomised, phase 2 trial (Pts 134)

In EARLY BC

HER2 3+



| | 0 | 12 | 24 | 36 | 48 | 60 |
|---|--------|--------|---------|---------|---------|---------|
| Number at risk (number censored) | | | | | | |
| Trastuzumab plus pertuzumab | 92 (0) | 88 (4) | 79 (10) | 74 (13) | 68 (19) | 41 (86) |
| Trastuzumab plus pertuzumab plus paclitaxel | 42 (0) | 41 (1) | 40 (1) | 37 (4) | 35 (6) | 21 (41) |



| | 0 | 12 | 24 | 36 | 48 | 60 |
|---|--------|--------|---------|---------|---------|---------|
| Number at risk (number censored) | | | | | | |
| Trastuzumab plus pertuzumab | 92 (0) | 88 (4) | 81 (10) | 76 (13) | 68 (19) | 41 (87) |
| Trastuzumab plus pertuzumab plus paclitaxel | 42 (0) | 41 (1) | 40 (1) | 37 (4) | 35 (6) | 21 (41) |

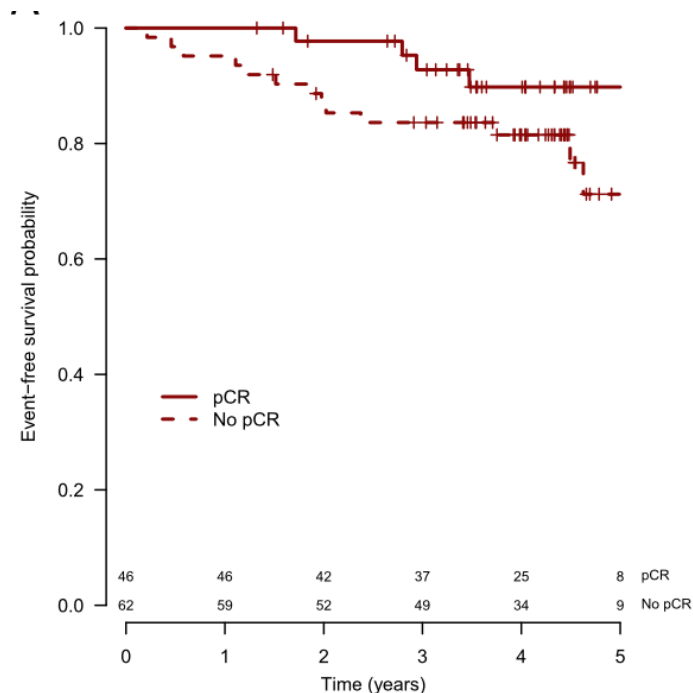
Further chemotherapy could be omitted in patients with a pCR

DE-ESCALATION
In EARLY BC
(HER2 3+)

The TRAIN-study: Trastuzumab plus weekly paclitaxel and carboplatin as neoadjuvant treatment for HER2-positive BC (Pys 111, Stage II and III)

Pathologic complete response rate in breast and axilla with 95% confidence intervals, overall and according to different baseline characteristics (n = 108).

| | % | (95% CI) | p |
|--------------------------------|----|----------|------|
| Overall | 43 | (33–52) | — |
| Age (years) | | | 0.57 |
| <50 | 40 | (26–54) | |
| ≥50 | 45 | (32–59) | |
| Clinical tumour stage | | | 0.84 |
| T1-2 | 44 | (31–57) | |
| T3-4 | 41 | (26–57) | |
| Clinical nodal stage | | | 1.00 |
| Negative | 41 | (21–64) | |
| Positive | 43 | (32–54) | |
| Clinical disease stage | | | 1.00 |
| II | 43 | (30–56) | |
| III | 43 | (28–58) | |
| Histology | | | 0.83 |
| Ductal | 42 | (32–52) | |
| Lobular | 60 | (15–95) | |
| Other | 50 | (1–99) | |
| Hormone receptor status | | | 0.08 |
| ER– and PR– | 53 | (38–68) | |
| ER+ and/or PR+ | 34 | (23–48) | |

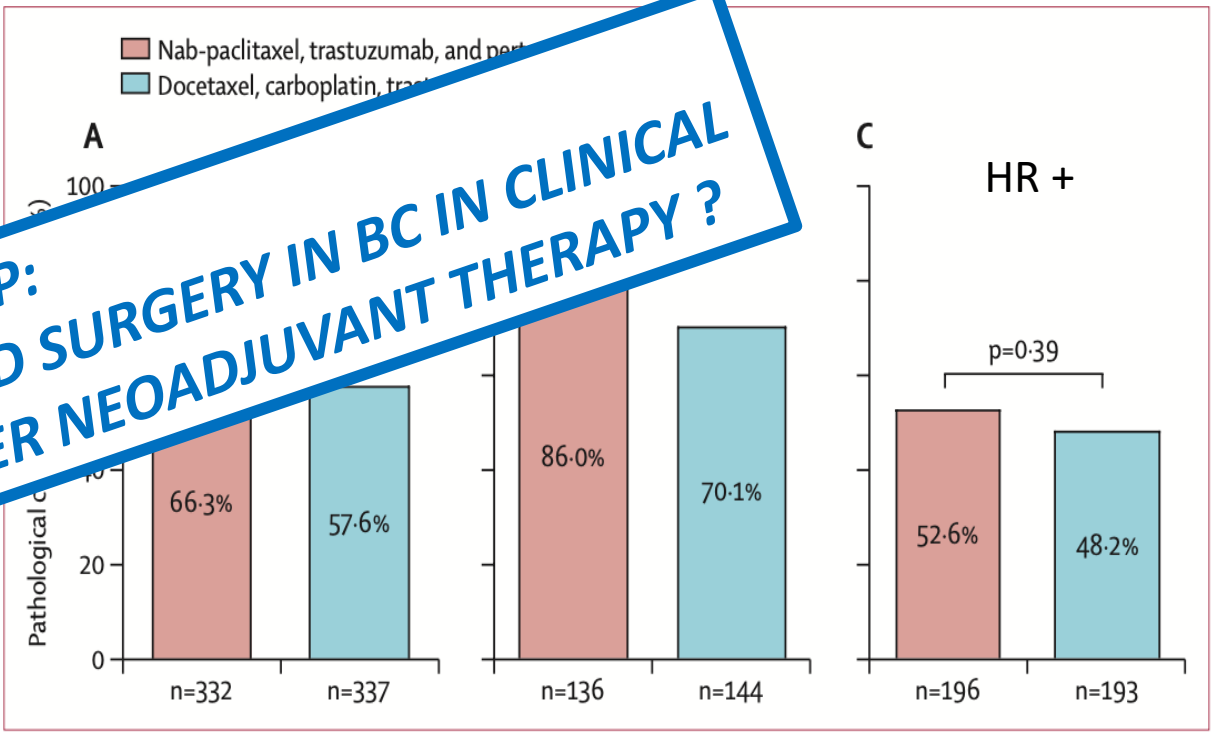


**DE-ESCALATION
In EARLY BC
(HER2 3+)**

**HELEN-006: A MULTICENTRE, RANDOMISED, PHASE 3 TRIAL
De-escalated neoadjuvant nab-paclitaxel/trastuzumab/pertuzumab vs
docetaxel/carboplatin/trastuzumab/pertuzumab in HER2 + early BC**

| | Nab-paclitaxel, trastuzumab, and pertuzumab group (n=332) | Docetaxel, carboplatin, trastuzumab, and pertuzumab group (n=337) |
|--------------------------|---|---|
| Median age, years | 50 (41-55) | 50 (44-56) |
| Age, years | | |
| ≤50 | 175 (53%) | 171 (51%) |
| >50 | 157 (47%) | 166 (49%) |
| Women | 332 (100%) | 337 (100%) |
| Asian | 332 (100%) | 337 (100%) |
| Menopausal status | | |
| Premenopausal | 180 (54%) | 184 (55%) |
| Postmenopausal | 152 (46%) | 153 (45%) |
| T stage | | |
| T1 to T2 | 277 (83%) | |
| T3 to T4 | 55 (17%) | |
| Nodal status | | |
| Positive | 241 (73%) | |
| Negative | 91 (27%) | |
| Disease stage | | |
| Stage II | 214 (64%) | |
| Stage III | 118 (36%) | |
| Histological tumour type | | |
| Ductal | 315 (95%) | |
| Lobular | 3 (1%) | |
| Other | 14 (4%) | |
| Tumour grading | | |
| G1 | 1 (<1%) | |
| G2 | 141 (42%) | 142 (42%) |
| G3 | 190 (57%) | 194 (58%) |
| Hormone receptor status* | | |
| Positive | 196 (59%) | 193 (57%) |
| Negative | 136 (41%) | 144 (43%) |
| Ki-67 index | | |
| ≤30% | 73 (22%) | 75 (22%) |
| >30% | 259 (78%) | 262 (78%) |

**NEXT STEP:
TO AVOID SURGERY IN BC IN CLINICAL
CR AFTER NEOADJUVANT THERAPY ?**



DE-ESCALATION
In EARLY BC
(HER2 3+)

HELEN-006: A MULTICENTRE, RANDOMISED, PHASE 3 TRIAL
 De-escalated neoadjuvant nab-paclitaxel/trastuzumab/pertuzumab vs docetaxel/carboplatin/trastuzumab/pertuzumab in HER2 + early BC

| | Nab-paclitaxel, trastuzumab, and pertuzumab group (n=332) | | | Docetaxel, carboplatin, trastuzumab, and pertuzumab group (n=337) | | |
|--------------------------------------|---|---------|---------|---|---------|---------|
| | Grade 1-2 | Grade 3 | Grade 4 | Grade 1-2 | Grade 3 | Grade 4 |
| Haematological adverse events | | | | | | |
| Anaemia | 298 (90%) | 2 (1%) | 0 | 289 (86%) | 13 (4%) | 0 |
| Leukopenia | 114 (34%) | 1 (<1%) | 0 | 120 (36%) | 17 (5%) | 0 |
| Neutropenia | 226 (68%) | 0 (0%) | 0 | 206 (61%) | 20 (6%) | 0 |

Interpretation These findings might suggest a potential advantage of nab-paclitaxel combined with trastuzumab and pertuzumab compared with the standard regimen in neoadjuvant therapy for patients with HER2-positive early breast cancer, suggesting that this new combination might establish a new standard for neoadjuvant treatment in this patient population.

| | | | | | | |
|--------------------------------------|-----------|---------|---------|-----------|---|---|
| Increased aspartate aminotransferase | 164 (49%) | 13 (4%) | 0 | 128 (38%) | 0 | 0 |
| Increased alkaline phosphatase | 175 (53%) | 0 | 0 | 125 (37%) | 0 | 0 |
| Increased creatinine | 10 (3%) | 0 | 0 | 38 (11%) | 0 | 0 |
| Hypokalaemia | 21 (6%) | 1 (<1%) | 0 | 80 (24%) | 0 | 0 |
| Hyponatraemia | 31 (9%) | 1 (<1%) | 0 | 32 (9%) | 0 | 0 |
| Hypocalcaemia | 20 (6%) | 1 (<1%) | 1 (<1%) | 19 (6%) | 0 | 0 |

Data are all grade 1 or grade 2 adverse events that occurred in ≥10% of patients in either treatment group and all grade 3 and grade 4 adverse events. No deaths occurred in either group. Patients might have had more than one adverse event. NA=not applicable.

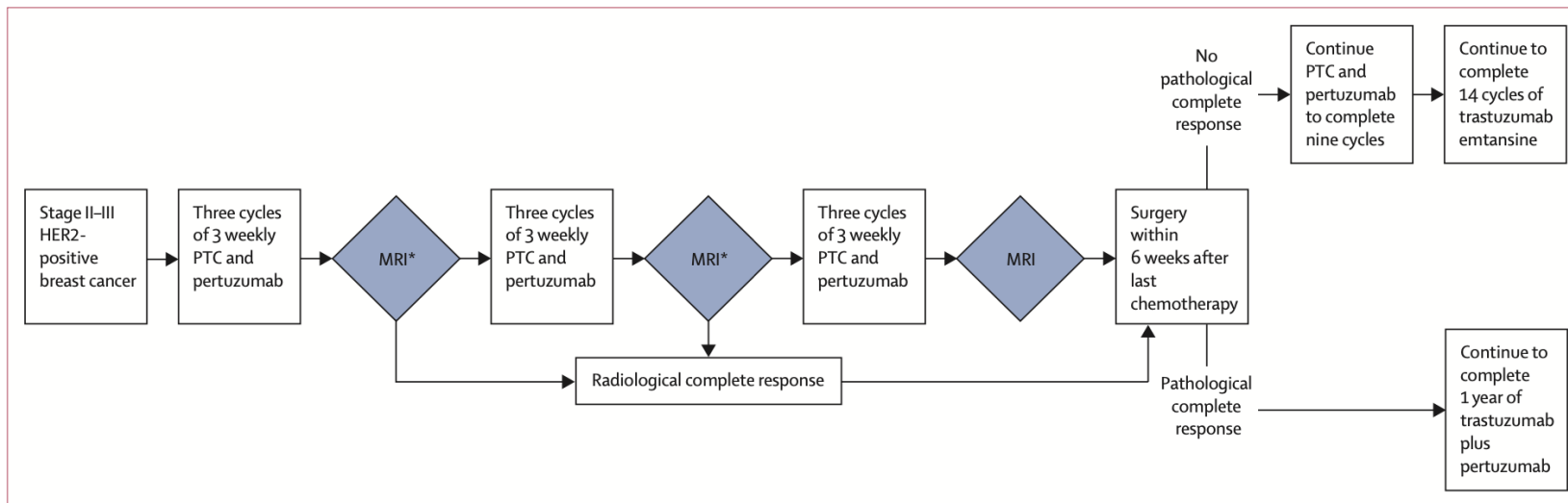
DE-ESCALATION

In EARLY BC

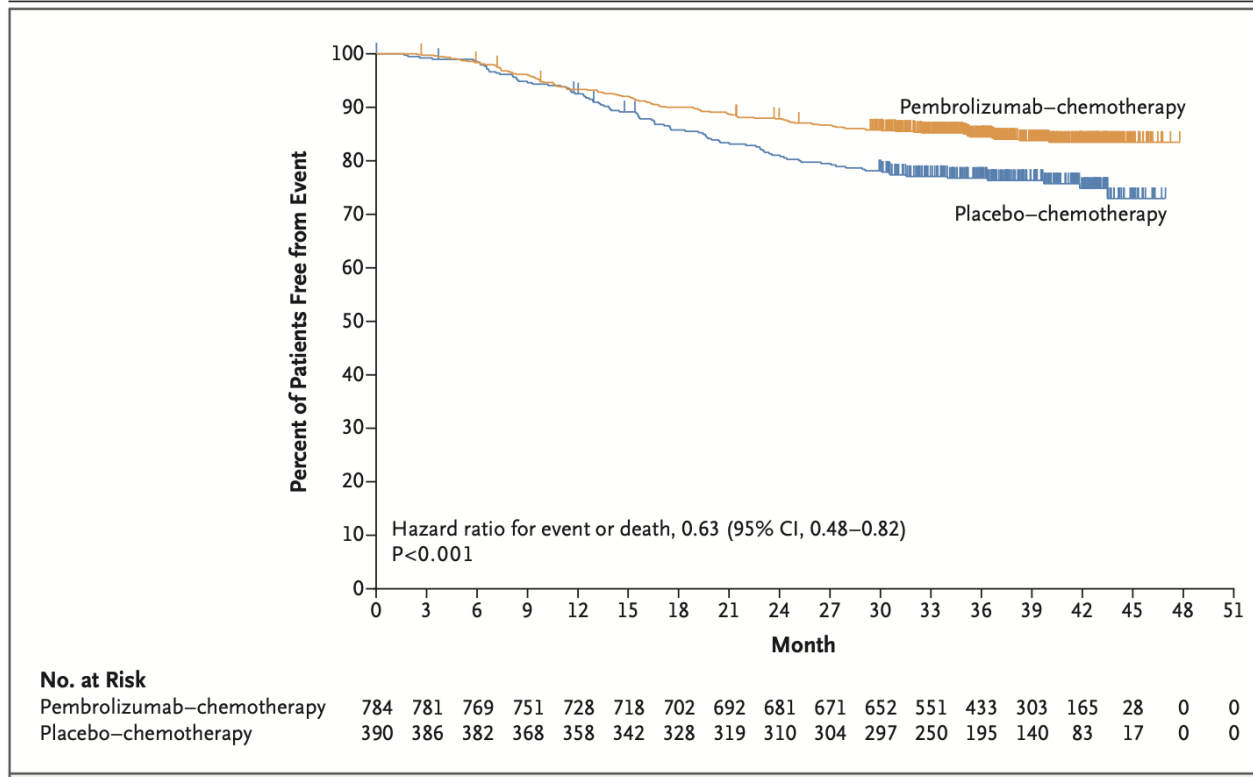
HER2» 3+

TRAIN-3: a multicentre, single-arm, phase 2 study MRI-guided optimisation of neoadjuvant CT duration in stage II–III HER2-positive breast cancer. (235 pts)

HER2=human epidermal growth factor 2. PTC=paclitaxel, trastuzumab, and carboplatin. *If a radiological complete remission on breast MRI was observed in patients with clinical lymph node-positive disease, a targeted biopsy of the at-baseline marked lymph node was warranted—ie, an ultrasound guided targeted biopsy (fine needle aspiration or core biopsy). In hormone receptor-positive disease, a non-PCR could also be detected using vacuum-assisted core biopsies.



TN EARLY BC KEYNOTE 522: Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer



TN EARLY BC Tailoring CT-IO de-escalation in early-stage TN BC

The KEYNOTE-522 trial¹ has shown substantial and clinically meaningful improvements in pCR, EFS and OS when neoadjuvant chemotherapy was combined with preoperative and postoperative pembrolizumab for patients with stage II–III TN BC.

Consequently, the KEYNOTE regimen—a 24-week and four-drug polychemotherapy (carboplatin and paclitaxel followed by doxorubicin [or epirubicin] and cyclophosphamide) has become the standard of care. However, this approach is associated with substantial adverse events, some of which are severe and irreversible

Showing the feasibility of an even more substantial de-escalation of neoadjuvant CT-IO, as explored in the Neo-N study, will likely require stringent patient selection criteria, which could include limiting tumour burden to stage I–II or node-negative disease (or both) and incorporating biomarkers of baseline immune activation,⁷ DNA damage repair,⁸ and genomic signatures.⁹ Additionally, adaptive trial designs incorporating serial imaging techniques and ctDNA based monitoring to dynamically guide

RESPONSE RELATED TO HR STATUS



TAKE HOME A MESSAGE

1. Common sense of oncology: outcomes that matter. Booth CM et al, Lancet Oncol 2023

For both patients and clinicians, cancer treatment decisions are increasingly complicated. **While some cancer treatments provide large benefits, many new approved treatments do not help patients live longer or better.** All cancer treatments have side-effects, can cause substantial financial burden, and can result in lost time for patients spent in hospital rather than with friends and family. Thus, it is important to not only study and promote treatments that improve survival or quality of life (or both), but also to identify treatments that do not. **Cancer systems now face a troubling paradox. In some circumstances there is substantial overuse of treatments with very small benefits, and at the same time many patients worldwide do not have access to the treatments that can make a very meaningful difference in their lives**

TAKE HOME A MESSAGE

1. Common sense of oncology: outcomes that matter. (Booth CM et al, Lanct Onco 2023)
2. Immunotherapy: balancing the risks and benefits

Immunotherapy undeniably plays an important part in cancer treatment—contributing to a future that transforms cancer from an acute diagnosis to a chronic manageable disease. But no anticancer treatment comes without risk. Additional research on the nature of immunotherapy-related adverse events, their association and mechanistic overlap with overall patient response, and the mitigation of severe life-threatening events is warranted.

TAKE HOME A MESSAGE

1. Common sense of oncology: outcomes that matter. (Booth CM et al, Lancet Onco 2023)
2. Immunotherapy: balancing the risks and benefits
3. When less is more—reducing complexity in cancer trials.(Patel TH, Lancet Oncol 2025)

FDA Oncology is committed to modernising evidence generation in a way that can encourage participation in clinical trials. We call upon the oncology drug development community to work to find opportunities to bring simplicity back to clinical trials—because when there is a focused question, less could be more.

TAKE HOME A MESSAGE

- 1. Common sense of oncology: outcomes that matter. (Booth CM et al, Lanct Onco 2023)**
- 2. Immunotherapy: balancing the risks and benefits**
- 3. When less is more—reducing complexity in cancer trials.(Patel TH, Lancet Oncol 2025)**
- 4. The need for pragmatic, affordable, and practice-changing real-life clinical trials in oncology (leary A et al , Lancet 2024)**
- 5. Putting patient safety first: a global imperative (Lancet Oncol, 2024)**
- 6. Evidence for a reduction in number of cycles of immune checkpoint inhibitors (Lancet Oncol)**
- 7. Shifting perspectives: a reflection on cancer-specific QoL metrics in cancer care economics**

THANK YOU

