# Clube da Mama
# Pós ASCO 2019

Loco/regional/adjuvante

Ruffo de Freitas Junior

# Conflito de interesses

## Ruffo de Freitas Júnior

| | | |
|---|---|---|
| **Como palestrante** | **Pfizer** | |
| | **Libbs** | |
| **Como pesquisador** | **Roche** | **TDM1** |
| | | **EMILIA, KAITLIN** |
| | | **Atezolizumabe** |
| | | **IMPASSION130** |
| | | **Ipatasertibe** |
| | **Astrazeneca** | **Fulvestranto** |
| | | **025, Efect, Newest, First** |
| | **Novartis** | **Letrozol** |
| | | **Femara Latan, Predict** |
| | **PUMA** | **Neratinibe** |
| | | **NALA** |
| | **MSD** | **Pembrolizumabe** |
| | **Libbs** | **LB1802 e LB1803** |
| **Socio proprietário** | **IMO** | **Intrabeam** |

# Clube da Mama
# Pós ASCO 2019
## Loco/regional/adjuvante

**Objetivos educacionais:**

- Neoadjuvancia o que vem aí?
- Duração de endocrinoterapia adjuvante
- Duração de trastuzumabe adjuvante
- De-escalonamento de radioterapia em pacientes idosas

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SweBCG SVENSKA BRÖSTCANCERGRUPPEN Swedish Breast Cancer Group

KAROLINSKA Universitetssjukhuset

# Docetaxel, trastuzumab sc, pertuzumab *versus* trastuzumab emtansine as neoadjuvant treatment of HER2 positive breast cancer

## Results from the Swedish PREDIX HER2 trial identifying a new potential de-escalation standard?

Jonas Bergh M.D., Ph.D., F.R.C.P. (London UK)

Anne Andersson, Judith Bjöhle, Ana Bosch, Lena Carlsson, Ann Charlotte Dreifaldt, Zakaria Einbeigi, Ellinor Elinder, Hanna Fredholm, Erika Isaksson-Friman, Theodoros Foukakis, Per Grybäck, Mats Hellström, Hemming Johansson, Tobias Lekberg, Henrik Lindman, Claudia Maes, Yvonne Brandberg, Thomas Hatschek

PREDIX

ClinicalTrials.gov Identifier: NCT02568839

# Treatment regimens

## Arm A (standard treatment)

Docetaxel 75/100 mg/m$^2$ iv + trastuzumab sc (Herceptin SC®, 600 mg) + pertuzumab (Perjeta®) 840 mg iv on day 1 starting dose, subsequently 420 mg iv, repeated every three weeks, six courses

## Arm B (experimental treatment)

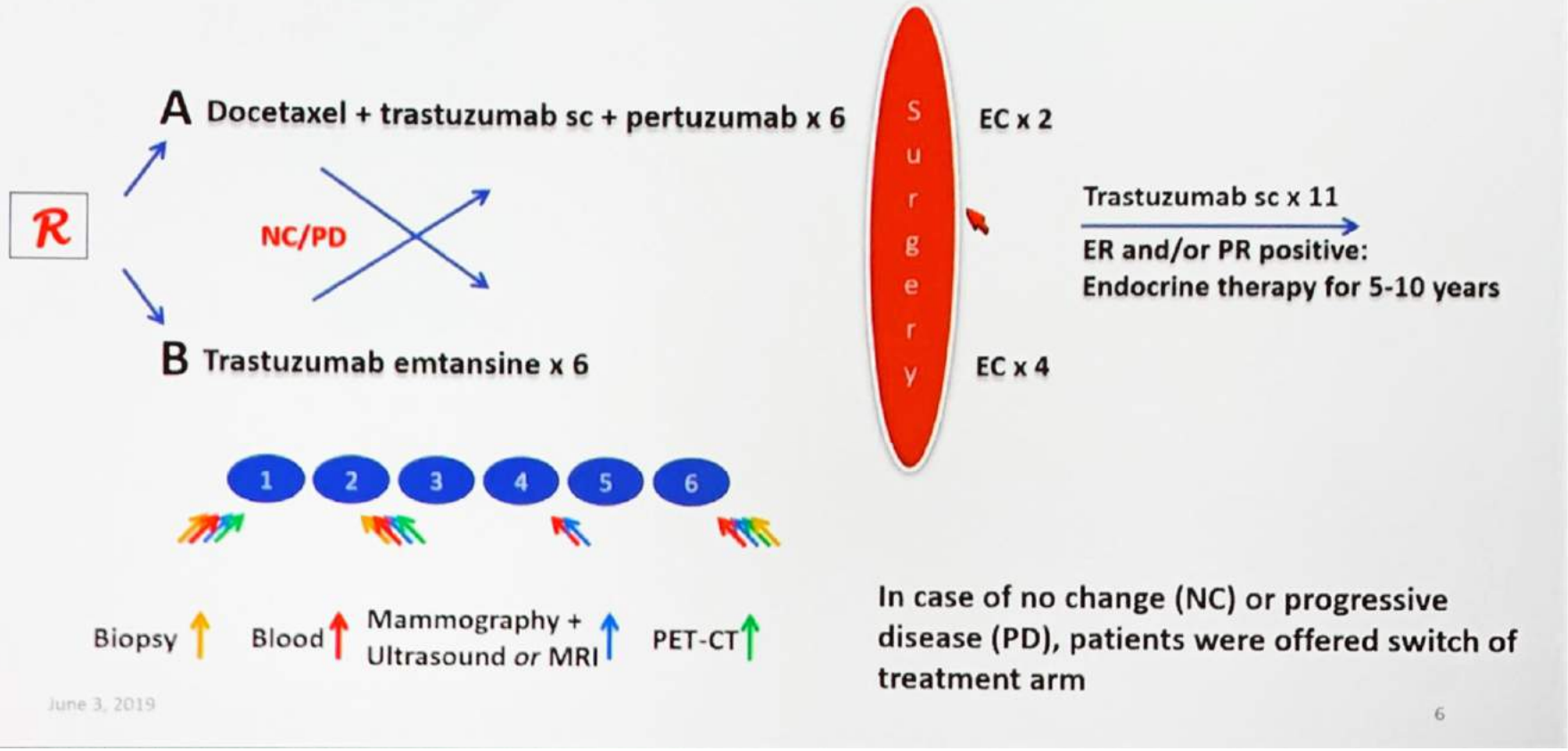
Trastuzumab emtansine (Kadcyla®) 3.6 mg/kg iv on day 1, repeated every three weeks, six courses

## Adjuvant therapy (both groups)

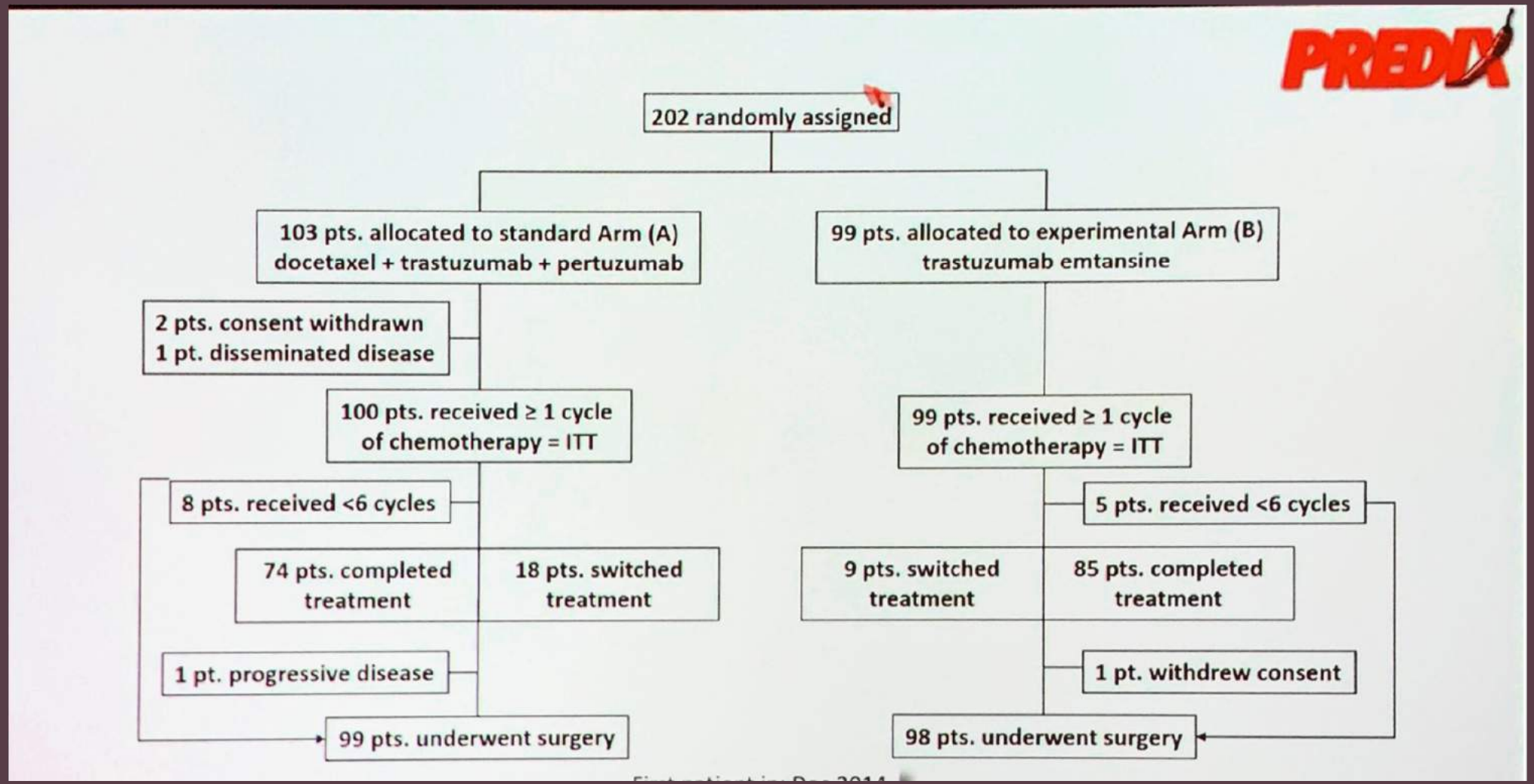
Epirubicin 90-100 mg/m$^2$ iv + Cyclophosphamide 600 mg/m$^2$ iv every three weeks (Arm A: two courses, Arm B: four courses)

Trastuzumab eleven courses

# PREDIX HER2 – a randomized phase II trial




In case of no change (NC) or progressive disease (PD), patients were offered switch of treatment arm


PREDIX
202 randomly assigned
103 pts. allocated to standard Arm (A) docetaxel + trastuzumab + pertuzumab
99 pts. allocated to experimental Arm (B) trastuzumab emtansine
2 pts. consent withdrawn
1 pt. disseminated disease
100 pts. received ≥ 1 cycle of chemotherapy = ITT
99 pts. received ≥ 1 cycle of chemotherapy = ITT
8 pts. received <6 cycles
5 pts. received <6 cycles
74 pts. completed treatment
18 pts. switched treatment
9 pts. switched treatment
85 pts. completed treatment
1 pt. progressive disease
1 pt. withdrew consent
99 pts. underwent surgery
98 pts. underwent surgery

# Objective response

| All patients | Docetaxel, trastuzumab, pertuzumab N = 99 (%) | Trastuzumab emtansine N = 98 (%) | |
|---|---|---|---|
| pCR | 46 (47) | 44 (45) | $Chi^2$ 2.049 |
| No pCR (SD or PR) | 53 (54) | 52 (53) | p = 0.359 |
| (PD by radiology) | 0 | 2 (2) | |
| **ER and PR negative** | **N = 33 (%)** | **N = 39 (%)** | |
| pCR | 22 (67) | 23 (59) | $Chi^2$ 0.451 |
| No pCR | 11 (33) | 16 (41) | p = 0.502 |
| **ER and/or PR positive** | **N = 66 (%)** | **N = 59 (%)** | |
| pCR | 24 (36) | 21 (36) | $Chi^2$ 0.008 |
| No pCR | 42 (64) | 38 (64) | p = 0.929 |

# Side effects
(CTC AE ver 4.0)

| | | Docetaxel, trastuzumab, pertuzumab N = 100 (%) | Trastuzumab emtansine N = 99 (%) |
|---|---|---|---|
| Febrile neutropenia | Grade 3-4 | 26 (26) | 3 (3) |
| Infection | Grade 1-2 | 15 (15) | 8 (8) |
| | Grade 3-4 | 11 (11) | 1 (1) |
| Mucositis | Grade 1-2 | 53 (53) | 34 (34) |
| | Grade 3-4 | 1 (1) | 0 |
| Diarrhea | Grade 1-2 | 59 (59) | 7 (7) |
| | Grade 3-4 | 14 (14) | 0 |
| Colitis | Grade 3-4 | 6 (6) | 0 |
| Sensory neuropathy | Grade 1-2 | 30 (30) | 17 (17) |
| | Grade 3-4 | 1 (1) | 0 |
| Edema | Grade 1-2 | 11 (11) | 1 (1) |
| Exanthema | Grade 1-2 | 44 (44) | 8 (8) |
| | Grade 3-4 | 3 (3) | 0 |

# Type of surgery

| Surgery type | Docetaxel, trastuzumab, pertuzumab N = 99 (%) | Trastuzumab emtansine N = 98 (%) | Total N = 197 (%) |
|---|---|---|---|
| Breast conserving surgery | **48** (48) | **47** (48) | **95** (48) |
| Modified radical mastectomy | **36** (36) | **40** (41) | **76** (39) |
| Modified radical mastectomy and primary reconstruction | **12** (12) | **7** (7) | **19** (10) |
| Other | **3** (3) | **4** (4) | **7** (4) |

## Conclusions

- Our data is based on a prospective randomized phase II trial
- No statistically significant difference in pCR rates between docetaxel, trastuzumab and pertuzumab *versus* trastuzumab emtansine
- Higher pCR rates for patients with Er and Pr negative cancers
- Similar efficacy, irrespective of tumor size
- Significantly less side effects in the trastuzumab emtansine group
- Better quality of life during treatment with trastuzumab emtansine (see Brandberg Y et al, **abstr. 583**)
- Lack of response at early evaluation motivates switch of treatment with the intention to improve outcome
- Exploratory analysis: Early steep decrease of $^{18}$F-FDG uptake indicates that PET/CT may be a useful tool to predict pCR

# Phase II Study Evaluating HER2 Heterogeneity as a Predictor of Response to Neoadjuvant T-DM1 and Pertuzumab (Dana-Farber Harvard Cancer Center 14-409)

Otto Metzger, Giuseppe Viale, Lorenzo Trippa, Tianyu Li, Denise Yardley, Ingrid Mayer, Vandana Abramson, Carlos Arteaga, Laura Spring, Adrienne Waks, Michalina Janiszewska, Eileen Wrabel, Michelle DeMeo, Shayna Stein, Franziska Michor, Aditya Bardia, Tari King, Kornelia Polyak, Eric Winer and Ian Krop

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

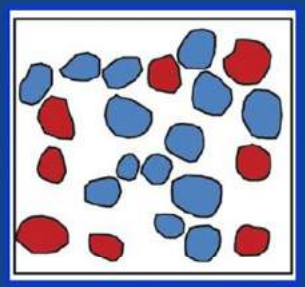
PRESENTED BY: Otto Metzger



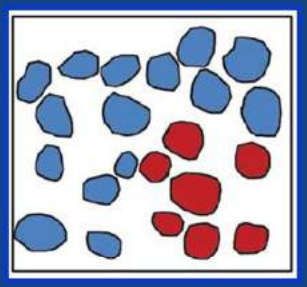
Presented By Otto Metzger Filho at 2019 ASCO Annual Meeting

# Background: HER2 Heterogeneity

- HER2 heterogeneity is defined by the presence of at least two distinct clones of cells with different levels of HER2 amplification within a tumor
- Estimates of prevalence of heterogeneity: 10-30% (depends on definition, population)



Scattered amplified cells (red)



Cluster of amplified cells (red)

Vance GH et al. Arch Pathol Lab Med 2009
Viale et al. Modern Pathology 2013
Lee, HJ. Am J Clin Pathol 2014
Lee, HJ. Am J Clin Pathol 2015





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# Study Hypothesis and Rationale

- HER2 heterogeneity is associated with inferior pathologic complete response (pCR) rate to neoadjuvant targeted anti-HER2 therapy


Investigating the impact of HER2 heterogeneity on response to therapy is an important step while we try to de-escalate chemotherapy and rely on HER2-targeted Rx

# Study Design

- Centrally-confirmed HER2+ BC
- Stage II and III (N = 164)

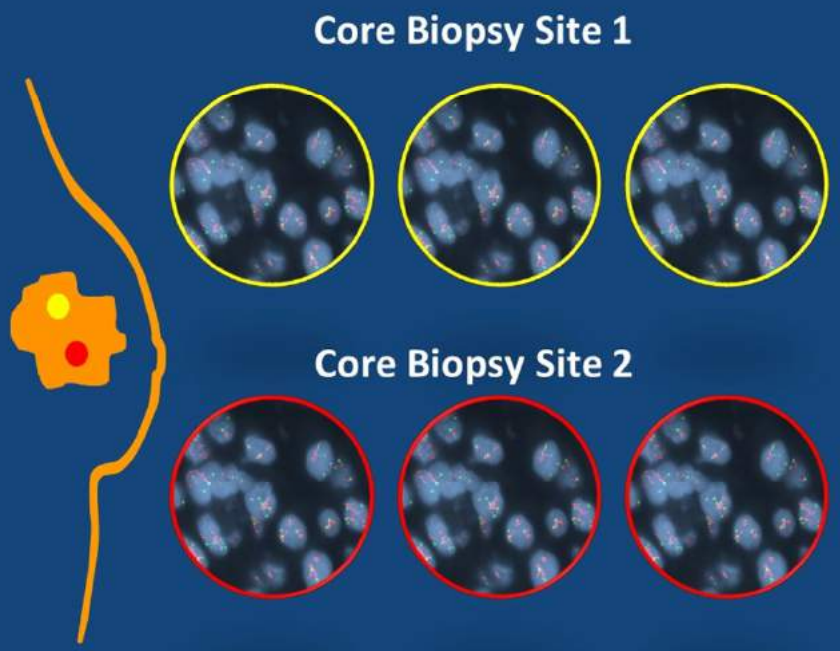
**Single Arm**

T-DM1 + Pertuzumab q3w x 6

SURGERY

● ● Image-guided research biopsies

# HER2 Heterogeneity: Method of Evaluation




HER2 Heterogeneity defined as either

1) HER2 positivity by FISH in > 5% and < 50% of tumor cells (i.e., CAP guideline)
2) An area of tumor that tested HER2 negative.

Assessment performed by central laboratory (European Institute of Oncology, Milan) and blinded to treatment outcome

Vance GH et al. Arch Pathol Lab Med 2009
Bartllett JM et al. J Clin Pathol 2011





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# Objectives

## Primary

To investigate the relationship between pCR (defined as Residual Cancer Burden = 0) and intratumor heterogeneity of HER2 amplification

## Secondary

Safety and tolerability
Objective response rate
Disease-free survival and overall survival

## Translational

Digital Spatial Profiling (DSP) of HER2 heterogeneity

# Statistical Considerations

- 160 patients to detect differences in pCR rate in the heterogeneous and non-heterogeneous groups assuming:
  - pCR rate of 40% in the overall population and 20% in the heterogenous population
  - 85% of enrolled patients will be evaluable for intratumor heterogeneity

- Effect-sizes (pCR heterogeneous versus non-heterogenous) according to prevalence of heterogeneity

| Heterogeneity Prevalence | 90% power |
|---|---|
| 10% | 9% vs. 43% |
| 20% | 17% vs. 46% |
| 30% | 22% vs. 48% |

- Analyses conducted using a stratified test to prevent confounding between hormone receptor status and pCR

# Baseline Characteristics

| Characteristic<br>N (%) | T-DM1 plus Pertuzumab<br>N = 163 |
|---|---|
| Median tumor size (IQR) | 2.8 cm (2.1-3.8 cm) |
| Hormone receptor status, n (%) | |
| ER+ and/or PR+ | 112 (68.7%) |
| ER- and PR- | 51 (31.3%) |
| Clinical stage | |
| I | 1 (0.6%) |
| II | 138 (84.7%) |
| III | 24 (14.7%) |
| HER2 IHC (central evaluation) | |
| 2+ | 40 (24.5%) |
| 3+ | 121 (74.2%) |
| Missing | 2 (1.2%) |





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# Safety Profile

## Common Adverse Events (AEs)

| Adverse Event (n= 163) | G1 N (%) | G2 N (%) | G3 N (%) |
|---|---|---|---|
| Fatigue | 109 (67) | 15 (9) | 1 (0.6) |
| Diarrhea | 86 (53) | 15 (9) | 4 (2) |
| Nausea | 86 (53) | 11 (7) | |
| Epistaxis | 50 (36) | | |
| AST | 56 (34) | 2 (1) | |
| ALT | 52 (32) | 8 (5) | |
| Platelet count | 13 (8) | 6 (4) | 2 (1) |
| Infusion-related reaction | 6 (3.7) | 30 (18) | |
| Rash | 37 (33) | | |

## Exposure to study treatment

| | N (%) |
|---|---|
| Cycles of T-DM1 + Pertuzumab( n) | |
| 3-5 | 9 (5) |
| 6 | 154 (95) |
| T-DM1 dose reduction, n (%) | 18 (11) |

AEs leading to tx discontinuation 2 (1.2%)
No Grade 4 or higher AEs





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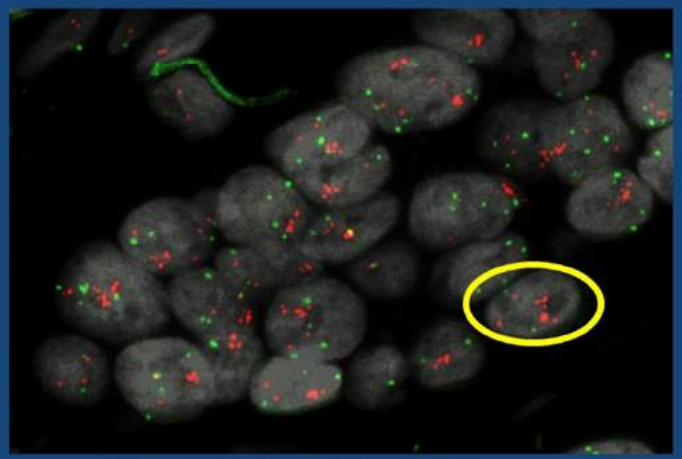
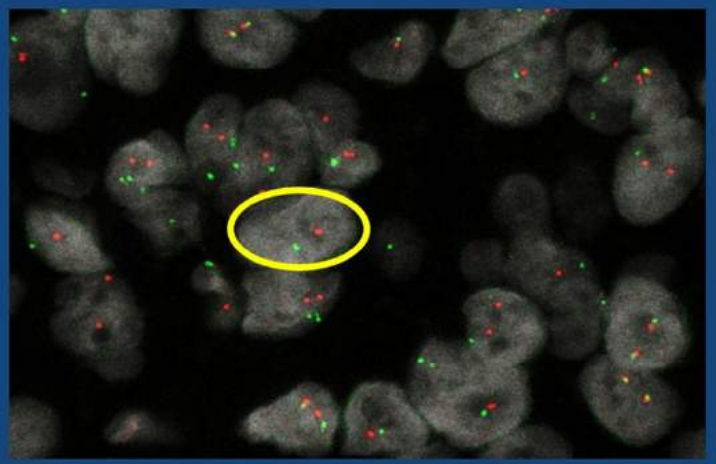
# Results: Prevalence of Heterogeneity

- 16/157(10%) of evaluable cases were classified as HER2 heterogenous
  - 13 (81%) hormone receptor positive and 3 (19%) hormone receptor negative

Example: Core biopsy site 1 amplified and site 2 non-amplified



FISH ratio = 3.85



FISH ratio = 1.1





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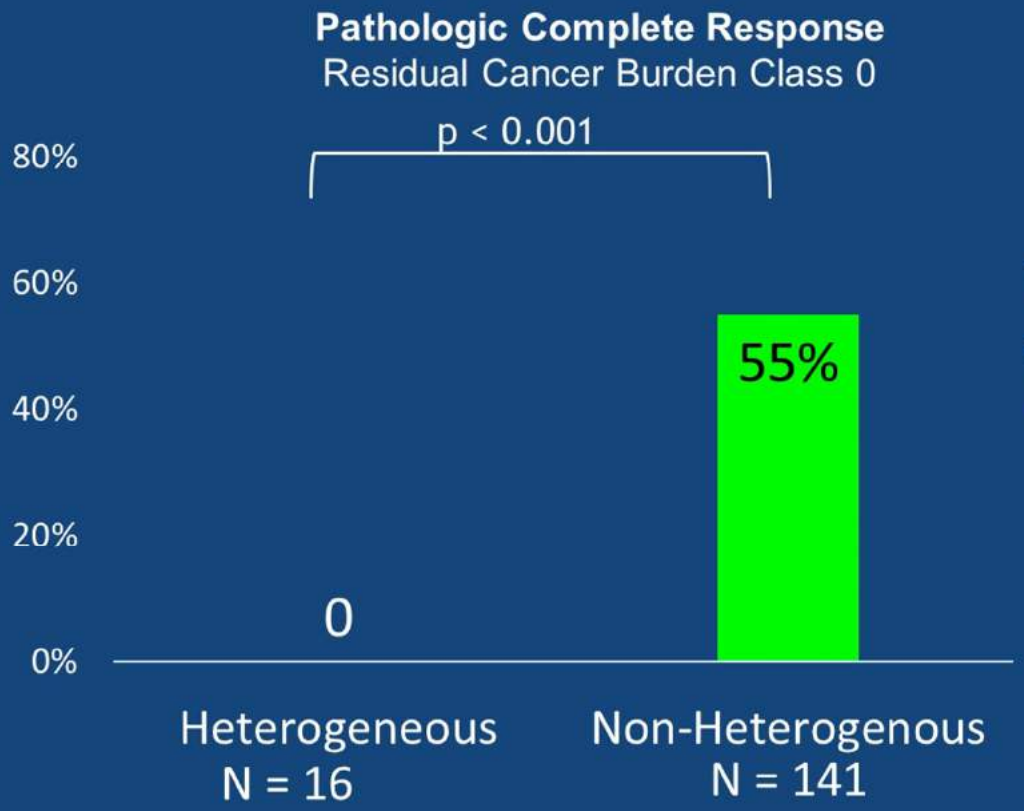
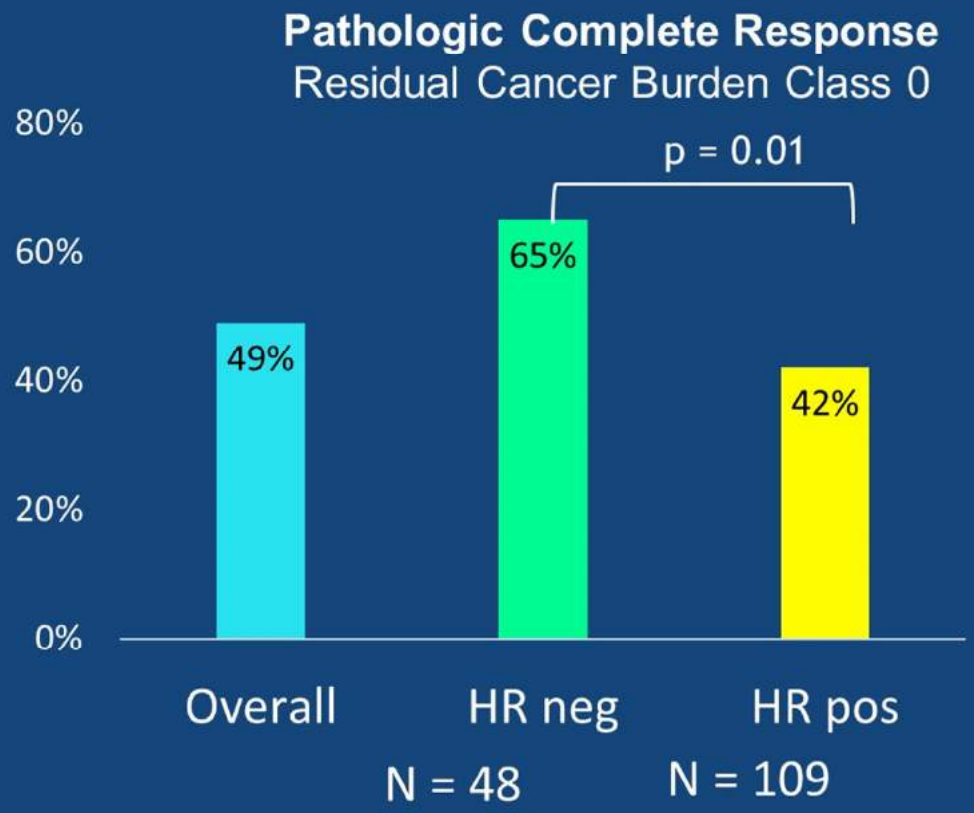
# Effect of Heterogeneity on pCR




The study met its primary endpoint by demonstrating a significant association between HER2 heterogeneity and pCR adjusted by ER status (p < 0.001)

# pCR by Hormone Receptor Status





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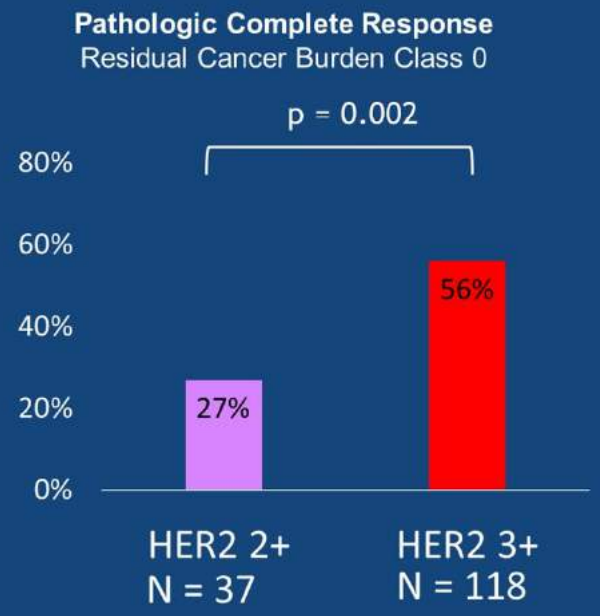
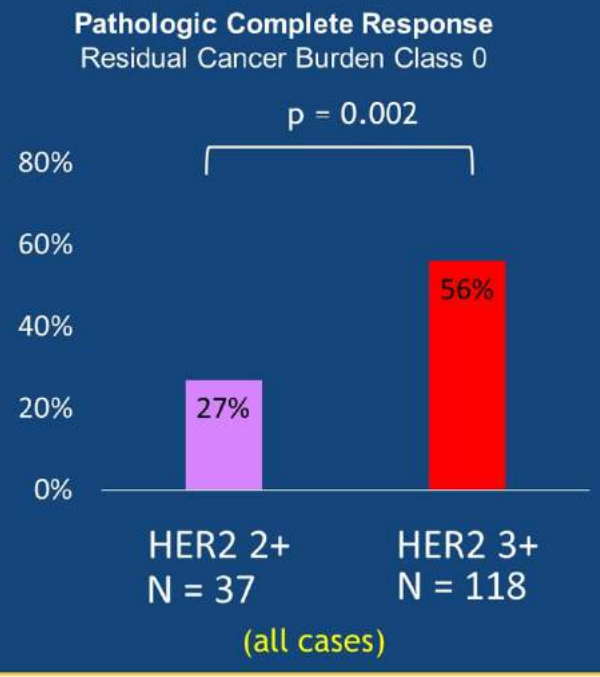
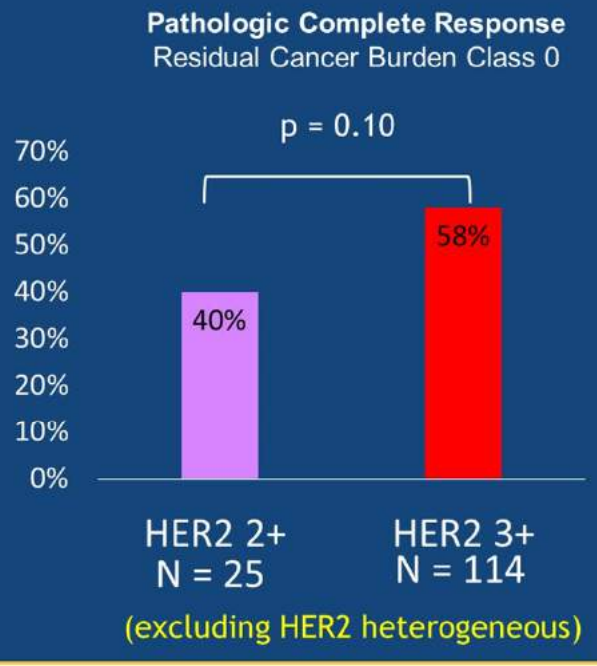
# Exploratory Analyses: pCR by HER2 IHC



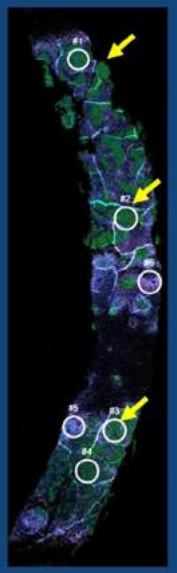

The association between HER2 heterogeneity and pCR remained significant when adjusted by ER status and HER2 IHC status (p = 0.002)

# Exploratory Analyses: pCR by HER2 IHC



# Translational Research: Digital Spatial Profiling



Measurement of HER2 protein level in multiple areas of each case

- FFPE slides stained with oligonucleotides antibodies (i.e. HER2)
- Pan-CK to select regions of interest (ROIs)
- Quantification via nCounter Assay (NanoString Technologies)

Patient Selection

- 30 cases
- Heterogeneous and non-heterogeneous cases (with or without pCR)
- Core biopsy site 1 and 2 profiled
- 3-4 Regions of Interest (ROI) per site





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# Conclusions

- Our study met its primary endpoint by demonstrating a significant association between HER2 heterogeneity and pCR
  - This effect was independent of ER status and HER2 protein expression by IHC
- The use of a clinical definition of HER2 heterogeneity defined by FISH should facilitate efforts to validate in other studies
- T-DM1 plus Pertuzumab is a well tolerated regimen with 95% of pts completing six cycles of tx
  - In the non-heterogeneous group pCR rate is 55%
- HER2 heterogeneous cancers may represent a distinct subset of HER2+ breast cancer
  - Lower rates of pCR
  - Lower levels of HER2 protein expression
  - Possibly require different treatment approaches

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# Câncer de mama, Tamoxifeno e desfechos clínicos

Varias mulheres com RE+ apresentam recidivas tardias.
Sendo este um desfecho importante de morte para pacientes com câncer de mama RE+

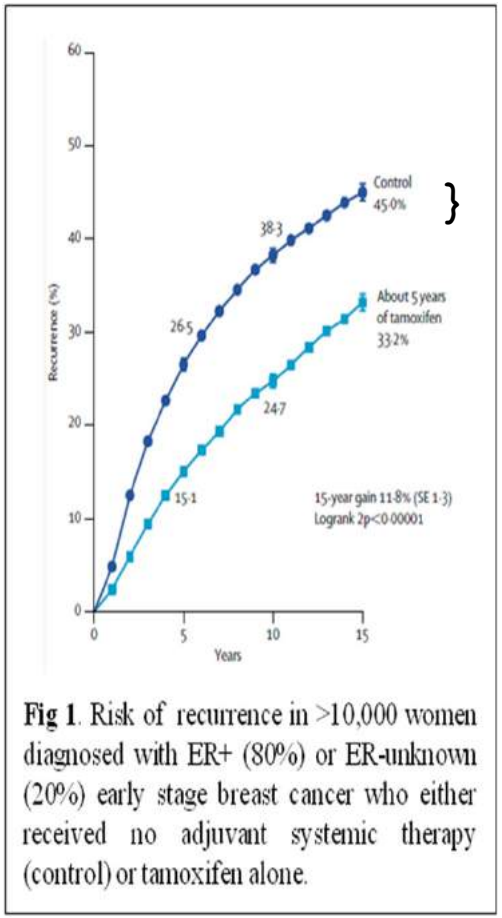
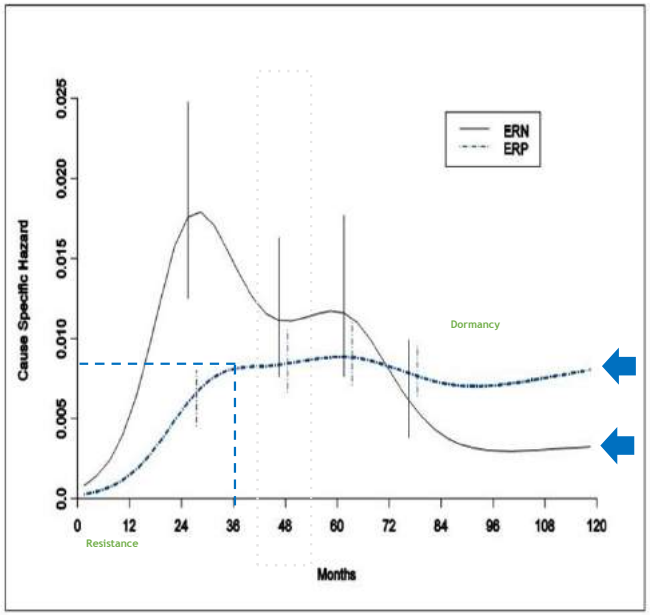



**Fig 1**. Risk of recurrence in >10,000 women diagnosed with ER+ (80%) or ER-unknown (20%) early stage breast cancer who either received no adjuvant systemic therapy (control) or tamoxifen alone.

Early Breast Cancer Trialists Group meta analyses

Recurrence-free benefit from TAM

Breast cancer mortality (ER+ vs ER-)



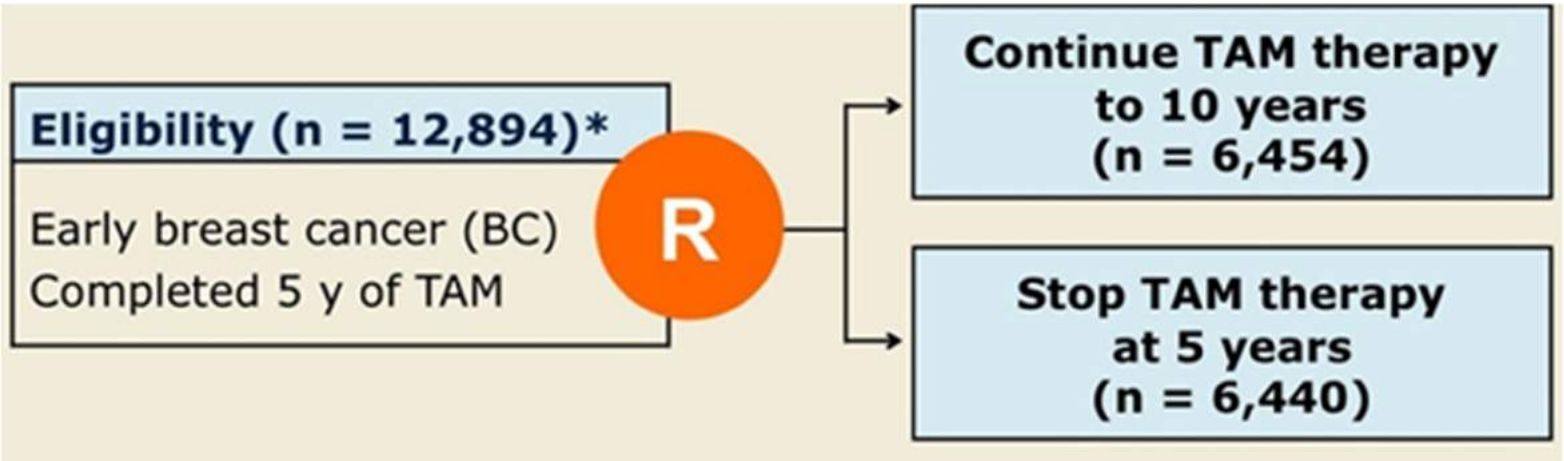

ER+

ER-

Adaptado de: Demicheli, *et al.*, *BMC Cancer*, 2010

# Estudo ATLAS

## DESENHO DO ESTUDO

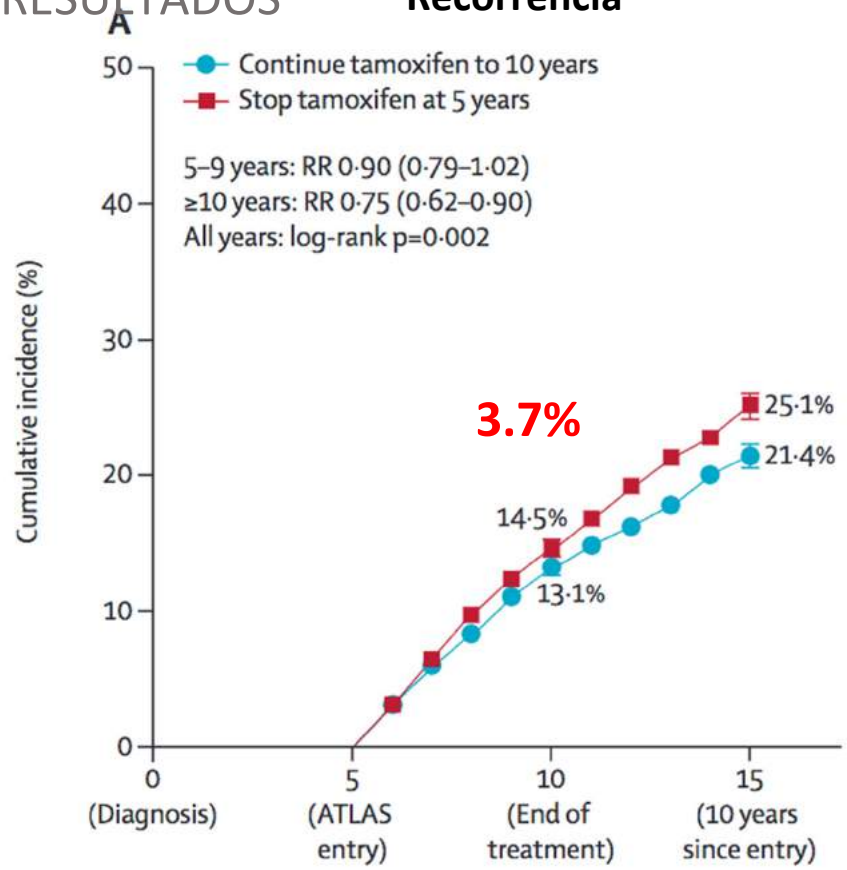



Lancet. 2013 Mar 9;381(9869):805-16

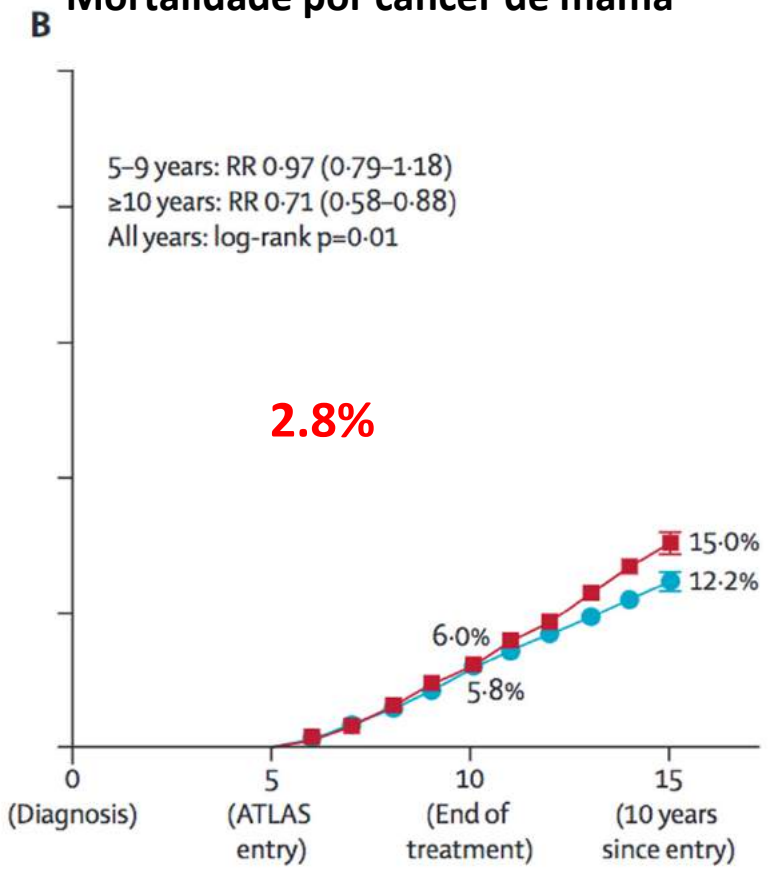
# Estudo ATLAS

RESULTADOS

**Recorrência**




**Mortalidade por câncer de mama**




Lancet. 2013 Mar 9;381(9869):805-16

# Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: A randomized, phase III study of the Gruppo Italiano Mammella (GIM)

Lucia Del Mastro[1,2], Mauro Mansutti[3], Giancarlo Bisagni[4], Riccardo Ponzone[5], Antonio Durando[6], Laura Amaducci[7], Alessandra Fabi[8], Antonio Fassoldati[9], Andrea Michelotti[10], Antonio Pazzola[11], Enrichetta Valle[12], Giovanni Sanna[13], Stefania Gori[14], Sabino De Placido[15], Ornella Garrone[16], Michela Donadio[6], Paolo Bruzzi[2], Claudia Bighin[2], Matteo Lambertini[1,2], Francesca Poggio[2] **on behalf of the Gruppo Italiano Mammella (GIM)**

1. DIMI, University of Genova; 2. Ospedale Policlinico San Martino, Genova; 3. ASIU Udine University Hospital; 4. Azienda USL/IRCCS Reggio Emilia; 5. Candiolo Cancer Institute, Torino; 6. Città della Salute e della Scienza ASO S. Anna, Torino; 7. Dipartimento oncologico Ospedale Faenza; 8. Regina Elena National Cancer Institute, Roma; 9. Ferrara University Hospital, Ferrara; 10. Ospedale S. Chiara, Pisa; 11. Ospedale Civile SS Annunziata; Sassari; 12. Ospedale Oncologico A. Businco, Cagliari; 13. Azienda Ospedaliera Universitaria; Sassari; 14. Ospedale Sacro Cuore Don Calabria, Negrar; 15. Università Federico II, Napoli; 16. S. Croce e Carlo Teaching Hospital, Cuneo

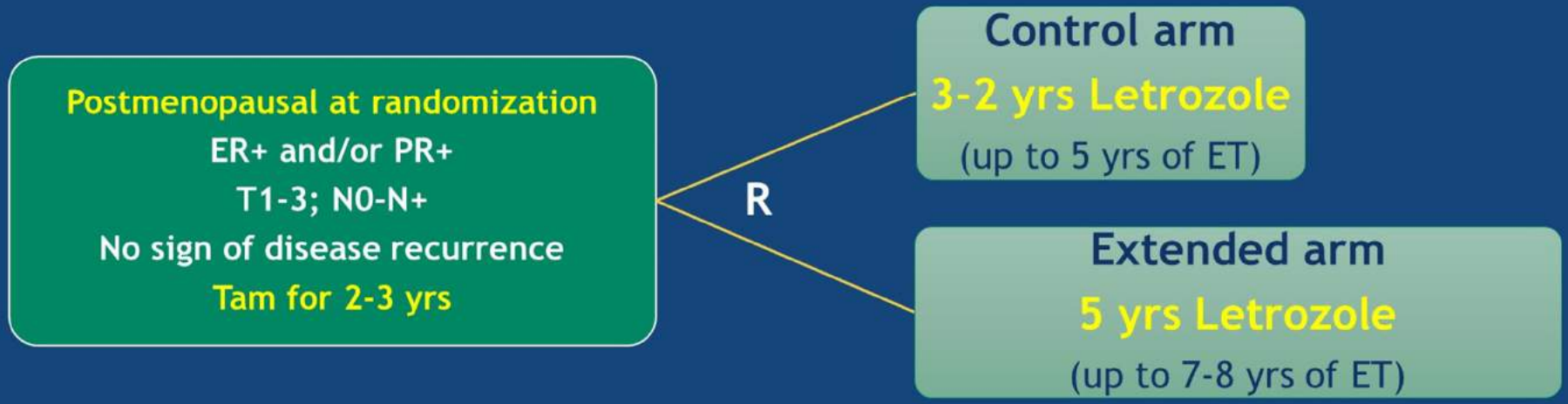
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Lucia Del Mastro, MD



Presented By Lucia Del Mastro at 2019 ASCO Annual Meeting

# GIM4 Study Design




**N=2056**
**Recruitment in 64 centres in Italy (GIM group), 2005-2010**
**Median follow-up: 10.4 years (IQR 8.8-11.4)**

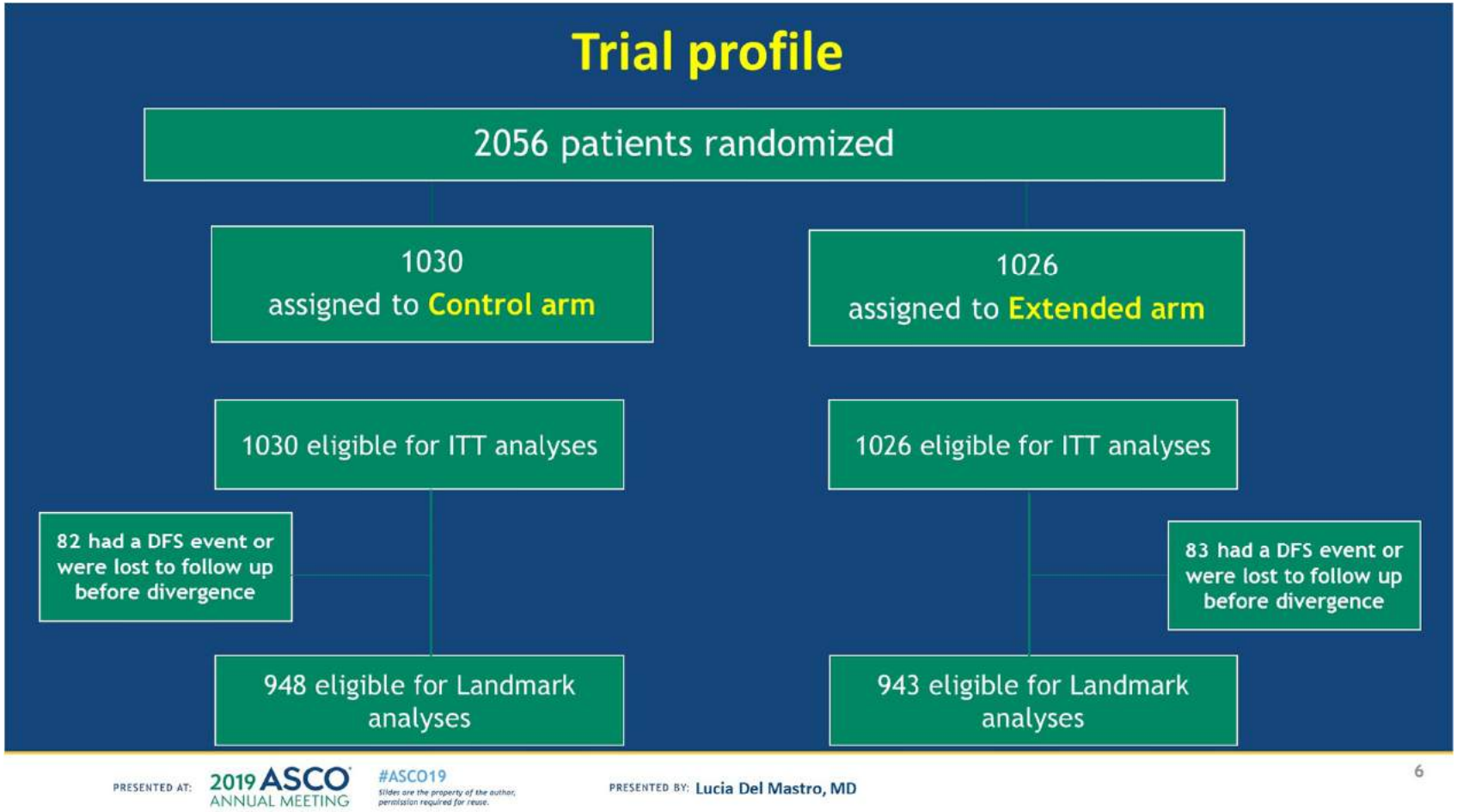
ClinicalTrials.gov: NCT01064635; EudraCT: 2005-001212-44

# GIM4 end-points and study populations

- **Primary study end-point**
  - Invasive Disease Free Survival (DFS)[1] (local recurrence, distant metastases, contralateral or ipsilateral breast tumour, excluding ductal carcinoma in situ, second primary malignancy, death from any cause, and loss to follow-up or end of study)
    - **Intention-To-Treat population**: DFS was computed from the date of randomization to the date of the event (or last follow-up) in the overall patient population
    - **Landmark analysis:** patients with a DFS event or lost to follow up before treatment divergence (2 to 3.3 years after randomization, depending on the duration of pre-random HT) were excluded. DFS was computed from the time of treatment divergence to the date of the event
- **Secondary end-points**
  - Overall survival
  - Adverse events

Beneficio absoluto em DFS (8anos) de 4%, HR: 0,77

1. Hudis, J Clin Oncol 2007; 25: 2127-32

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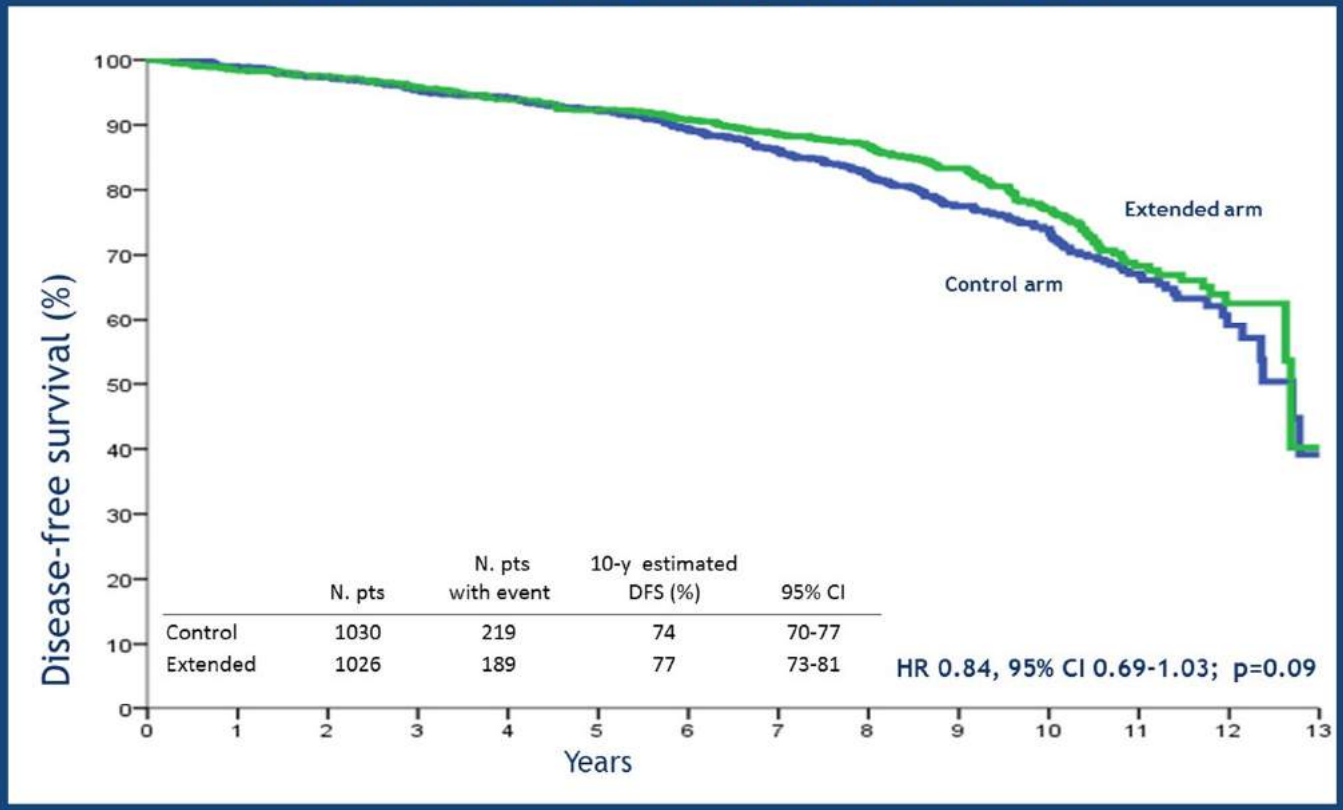
# Baseline characteristics

| | | Control arm 2-3 year letrozole (n=1030) | Extended arm 5-year letrozole (n=1026) |
|---|---|---|---|
| Age, median (range) | | 60 (34-86) | 61 (41-89) |
| Tumor size | pT1 | 704 (68%) | 703 (68%) |
| | pT2 | 261 (25%) | 252 (25%) |
| | pT3-4 | 34 (3%) | 43 (4%) |
| | Unknown | 31 (3%) | 28 (3%) |
| Nodal status | pN0 | 581 (56%) | 568 (55%) |
| | pN1-2-3 | 411 (40%) | 428 (42%) |
| | Unknown | 38 (4%) | 30 (3%) |
| Histological grade | G1 | 156 (15%) | 161 (16%) |
| | G2 | 564 (55%) | 589 (57%) |
| | G3 | 221 (21%) | 213 (21%) |
| | Unknown | 89 (9%) | 63 (6%) |
| HR status | ER+ and PR+ | 855 (83%) | 866 (84%) |
| | ER+ or PR+ | 153 (15%) | 146 (14%) |
| | Uknown | 22 (2%) | 14 (1%) |
| HER2 status | Positive | 63 (6%) | 60 (6%) |
| | Negative | 851 (83%) | 833 (81%) |
| | Unknown | 116 (11%) | 133 (13%) |
| Prior (neo)adjuvant CT | No | 455 (44%) | 450 (44%) |
| | Yes | 557 (54%) | 565 (55%) |
| | nknown | 18 (2%) | 11 (1%) |
| Prior duration of tamoxifen, years Median (IQR) | | 2.4 (1.9-3.3) | 2.5 (1.9-3.3) |

## Disease-Free Survival - ITT population. N=2056




| | N. pts | N. pts with event | 10-y estimated DFS (%) | 95% CI |
|---|---|---|---|---|
| Control | 1030 | 219 | 74 | 70-77 |
| Extended | 1026 | 189 | 77 | 73-81 |

HR 0.84, 95% CI 0.69-1.03; p=0.09

Number at risk

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 1030 | 999 | 967 | 919 | 873 | 805 | 731 | 611 | 485 | 332 | 236 | 135 | 35 | 5 |
| Extended | 1026 | 990 | 963 | 917 | 875 | 814 | 739 | 636 | 512 | 397 | 254 | 120 | 38 | 3 |

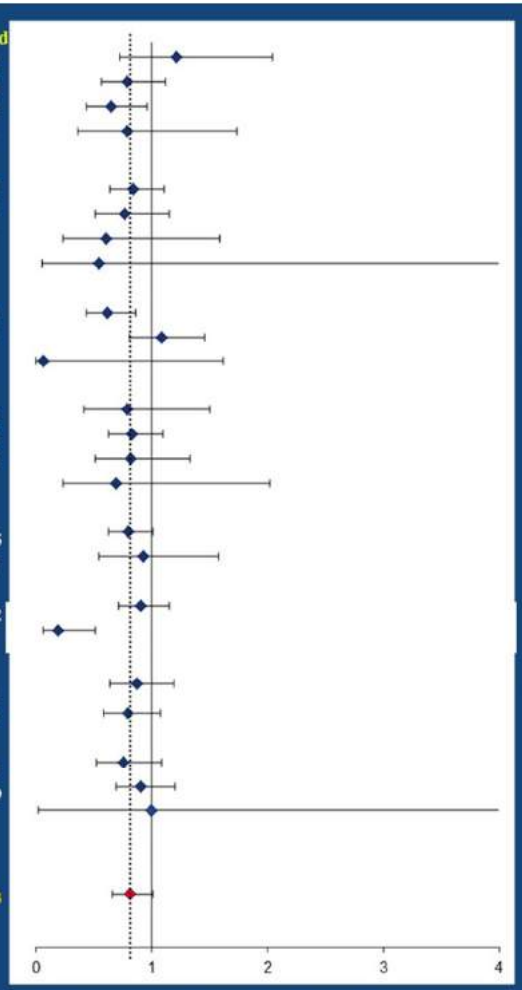
**Median follow up: 10.4 years**

# DFS first events by treatment

| | Control arm 2-3-year letrozole (n=1030) | | Extended arm 5-year letrozole (n=1026) | |
|---|---|---|---|---|
| First event | n. | % | n. | % |
| Distant recurrence | 77 | 7.5 | 69 | 6.7 |
| Local recurrence | 28 | 2.7 | 21 | 2.0 |
| Second primary cancer | 65 | 6.3 | 57 | 5.5 |
| Breast | 36 | 3.5 | 31 | 3.0 |
| Non -breast | 29 | 2.8 | 26 | 2.5 |
| Death without recurrence | 49 | 4.8 | 42 | 4.1 |
| Total first events | 219 | 21.2 | 189 | 18.4 |

# DFS
# Subgroup analysis

| | | events/patients control | events/patients extended | HR (95%CI) | P interaction |
|---|---|---|---|---|---|
| Age (years) | <55 | 26/258 | 36/252 | 1.22 (0.73-2.05) | 0.384 |
| | 55-64 | 75/365 | 61/354 | 0.80 (0.56-1.12) | |
| | 65-75 | 64/276 | 46/291 | 0.65 (0.44-0.96) | |
| | >=76 | 18/49 | 13/46 | 0.80 (0.36-1.74) | |
| Tumor size | pT1 | 108/659 | 97/656 | 0.85 (0.64-1.11) | 0.725 |
| | pT2 | 56/234 | 47/229 | 0.77 (0.52-1.15) | |
| | pT3-4 | 13/33 | 10/36 | 0.61 (0.23-1.59) | |
| | pTx | 6/22 | 2/22 | 0.55 (0.06-5.25) | |
| Nodal status | pN0 | 87/539 | 58/528 | 0.62 (0.44-0.87) | 0.034 |
| | pN+ | 87/381 | 96/389 | 1.08 (0.81-1.46) | |
| | pNx | 9/28 | 2/26 | 0.07 (0.00-1.62) | |
| Histological Grade | G1 | 21/145 | 20/154 | 0.79 (0.42-1.51) | 0.952 |
| | G2 | 104/524 | 97/545 | 0.84 (0.63-1.10) | |
| | G3 | 45/206 | 32/188 | 0.83 (0.51-1.34) | |
| | Gx | 13/73 | 7/56 | 0.70 (0.24-2.02) | |
| Hormone receptor * | ER+ and PR+ | 149/789 | 129/795 | 0.80 (0.64-1.02) | 0.662 |
| | ER + or PR+ | 29/146 | 26/137 | 0.93 (0.54-1.58) | |
| HER2 status * | negative | 143/788 | 133/772 | 0.91 (0.72-1.15) | 0.002 |
| | positive | 19/57 | 5/53 | 0.19 (0.071-0.512) | |
| Previous Tamoxifen | <=2.5 years | 96/508 | 70/461 | 0.87 (0.64-1,19) | 0.745 |
| | >2.5 years | 87/440 | 86/482 | 0.80 (0.59-1.08) | |
| Previous chemotherapy | NO | 69/420 | 53/419 | 0.76 (0.53-1.09) | 0.811 |
| | YES | 109/517 | 103/519 | 0.91 (0.69-1.20) | |
| | Unknown | 5/11 | 0/5 | 1.00 (0.03-39,5) | |
| All patients | | 183/948 | 156/943 | 0.81 (0.65-1.01) | |




*24 pts with missing HR and 221 pts with missing HER2 status excluded





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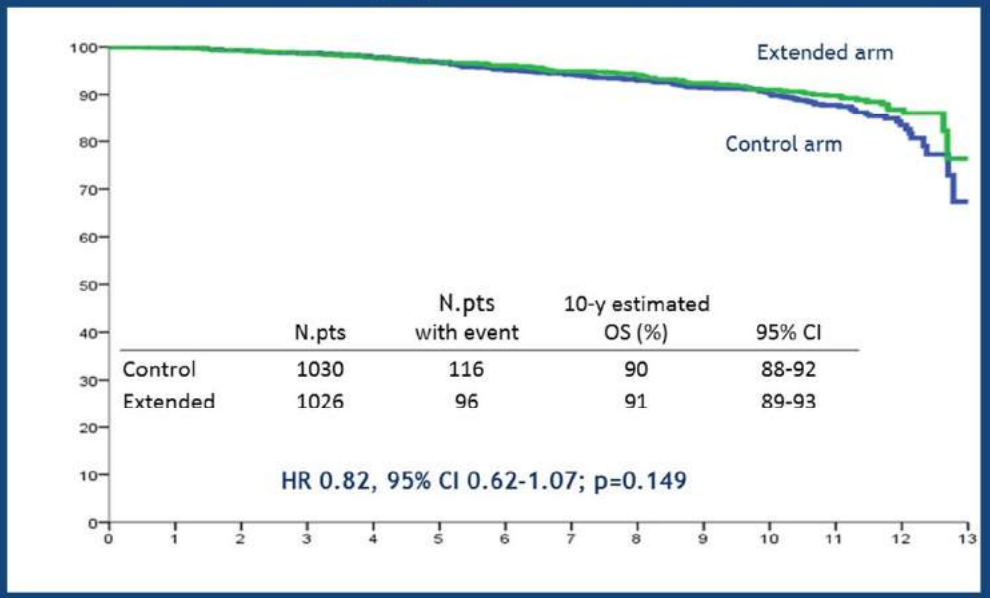
# Overall Survival

## ITT population N=2056

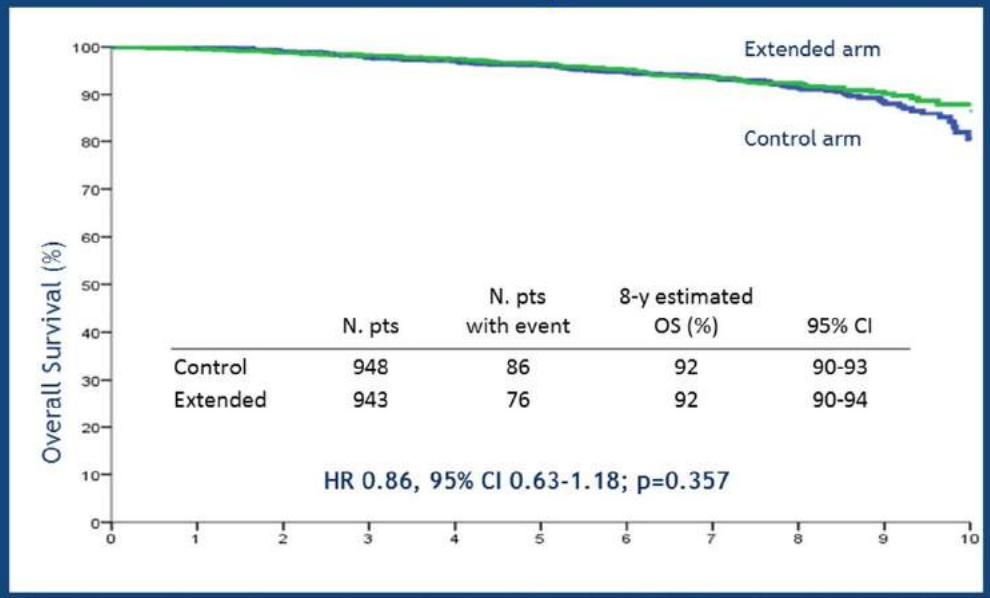



| | N.pts | N.pts with event | 10-y estimated OS (%) | 95% CI |
|---|---|---|---|---|
| Control | 1030 | 116 | 90 | 88-92 |
| Extended | 1026 | 96 | 91 | 89-93 |

HR 0.82, 95% CI 0.62-1.07; p=0.149

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 1030 | 1020 | 1004 | 988 | 966 | 927 | 886 | 853 | 788 | 665 | 523 | 335 | 107 | 7 |
| Extenden | 1026 | 1018 | 1004 | 986 | 966 | 942 | 913 | 861 | 807 | 693 | 545 | 339 | 111 | 6 |

## Landmark analysis N=1891




| | N. pts | N. pts with event | 8-y estimated OS (%) | 95% CI |
|---|---|---|---|---|
| Control | 948 | 86 | 92 | 90-93 |
| Extended | 943 | 76 | 92 | 90-94 |

HR 0.86, 95% CI 0.63-1.18; p=0.357

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 948 | 941 | 920 | 883 | 849 | 806 | 732 | 588 | 411 | 211 | 54 |
| Extended | 943 | 931 | 917 | 891 | 860 | 807 | 725 | 601 | 426 | 230 | 66 |

**Time 0 is time when treatment diverged in the two arms (i.e. 2-3 yrs after randomization)**

# Selected side effects

| | Control arm 2-3-year letrozole (n=983) | | Extended arm 5-year letrozole (n=977) | |
|---|---|---|---|---|
| | Grade 1-2 | Grade 3-4 | Grade 1-2 | Grade 3-4 |
| Arthralgia | 263 (27%) | 22 (2%) | 311 (32%) | 29 (3%) |
| Myalgia | 65 (7%) | 7 (1%) | 95 (10%) | 9 (1%) |
| Hot flashes | 119 (12%) | | 127 (13%) | |
| Alopecia | 31 (3%) | | 35 (4%) | |
| Osteoporosis | 47 (5%)[a] | | 81 (8%)[b] | |
| Bone fractures | 5 (<1%) | | 9 (1%) | |
| Hypercholesterolemia | 32 (3%) | | 22 (2%) | |
| Hypertension | 7 (1%) | | 19 (2%) | |
| Cardiovascular event | 1 (<1%) | | 6 (1%) | |

a. 103 pts (10%) and b. 79 pts (8%) had baseline osteoporosis





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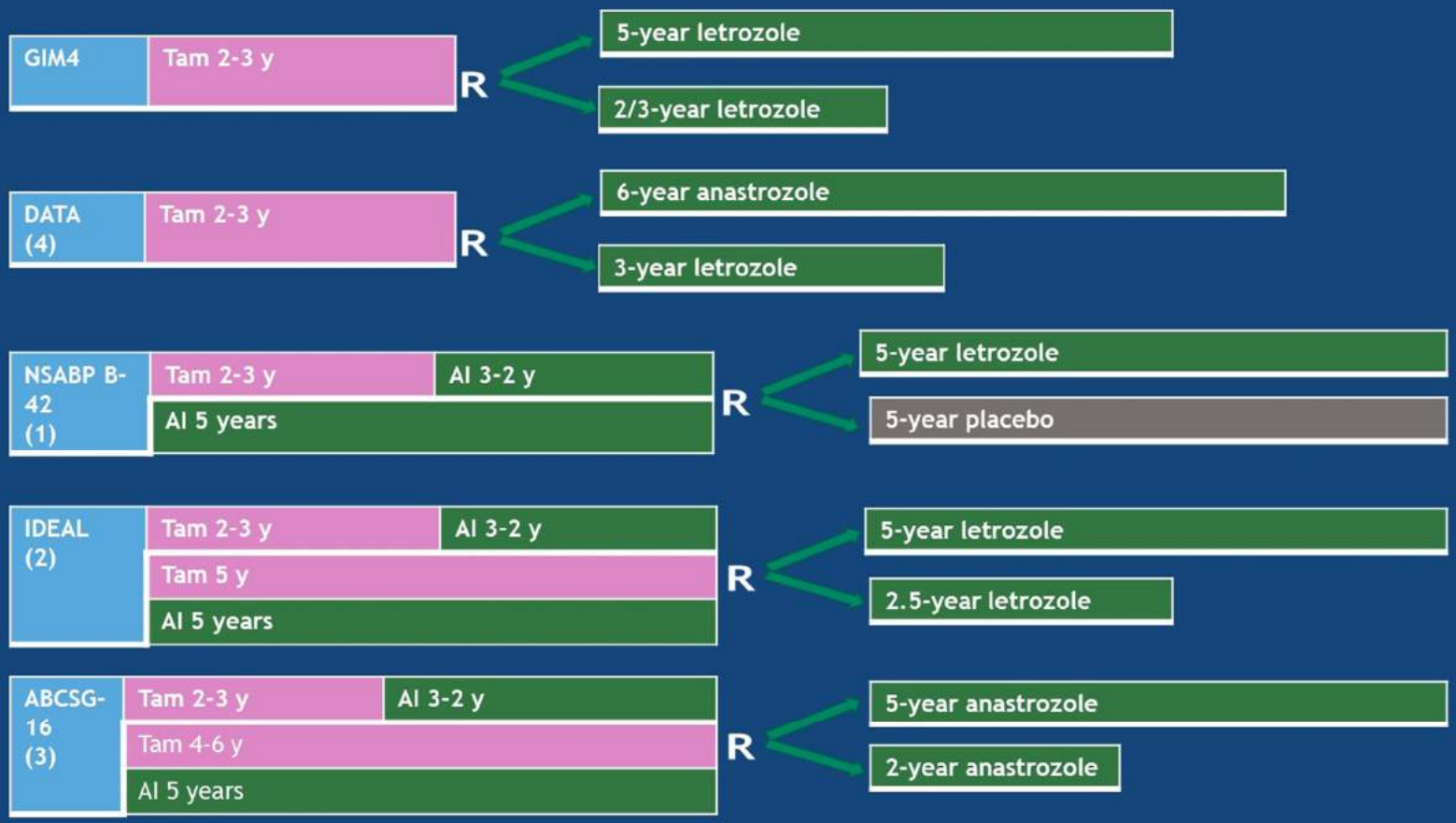
# Extended adjuvant AI studies




| ET duration, years | HR DFS |
|---|---|
| 5 vs 7/8 | 0.81 (0.65-1.00) |
| 5/6 vs 8/9 | 0.79 (0.62-1.02) |
| 5 vs 10 | 0.85 (0.62-1.02) |
| 7.5 vs 10 | 1.007 (0.87-1.16) |
| 7 vs 10 | 0.92 (0.74-1.16) |


1. Mamounas; Lancet Oncol. 2019; 20:88-99; 2. Blok; J Natl Cancer Inst 2018; 110:40-48; 3. Gnant; SABCS 2017;
2. 4. Tjan-Heijnen ; Lancet Oncol 2017; 18:1502-11



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# Conclusions

- After 2 to 3 years of tamoxifen, extended adjuvant treatment with additional 5 years of letrozole, is associated with a 19% reduction in iDFS events (HR 0.81; 0.65-1.00; p=0.051)
- These findings are consistent with the results of previous studies and suggest that tamoxifen for 2 to 3 years followed by AI for 5 to 6 years is a strategy of extended treatment which could be considered in breast cancer patients at residual risk of BC recurrence

O estudo foi negativo, mas talvez em pacientes de alto risco.
Quem são os pacientes de alto risco?

VOLUME 36 · NUMBER 19 · JULY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Integration of Clinical Variables for the Prediction of Late Distant Recurrence in Patients With Estrogen Receptor–Positive Breast Cancer Treated With 5 Years of Endocrine Therapy: CTS5

*Mitch Dowsett, Ivana Sestak, Meredith M. Regan, Andrew Dodson, Giuseppe Viale, Beat Thürlimann, Marco Colleoni, and Jack Cuzick*

https://www.cts5-calculator.com/

Dowsett et all. J Clin Oncol, 2018;36:1941-1948.

# CTS⑤ CALCULATOR

| | |
|---|---|
| Tumour size (mm) | 20 |
| Tumour Grade | Grade 1 |
| Patient age (years) | 55 |
| Number of nodes involved | 1 |

UPDATE RESULT ⇨


| CTS5 SCORE | 5–10 YEAR RISK | CTS5 RISK GROUP |
|---|---|---|
| 3.17 | 5.2% | Intermediate |

# #514: Clinical validity of CTS5 for estimating risk of late recurrence in unselected, non-trial patients with early ER+ breast cancer

The ROYAL MARSDEN NHS Foundation Trust

Juliet Richman[1], Alistair Ring[1], Mitch Dowsett[1], Ivana Sestak[2]

[1]Royal Marsden Hospital NHS Foundation Trust, [2]Centre for Cancer Prevention, Queen Mary University, London

Queen Mary University of London

## Introduction

The Clinical Treatment Score at 5 years (CTS5) is a prognostic tool to estimate distant recurrence risk after 5 years of endocrine therapy for postmenopausal women with estrogen receptor positive (ER+) breast cancer. It incorporates tumour size, grade, lymph node burden and patient age at diagnosis and was developed and validated in the ATAC and BIG 1-98 trials of endocrine therapy in postmenopausal women[1]. It is freely available at www.cts5-calculator.com.

## Objective

To determine whether the CTS5 can be extrapolated to unselected patients including pre-menopausal women for prediction of late distant recurrence. If validated CTS5 could be used as a decision aid for extended endocrine therapy beyond 5 years.

## Methods

The CTS5 was tested in a retrospective cohort of patients from the Royal Marsden. Patients were selected *only* on the basis of being diagnosed with early ER+ breast cancer from 2000-2007 and being alive and distant recurrence-free at 5 years. No other clinical variable was used for patient selection. The primary endpoint was distant recurrence in years 5-10. The primary cohort for analysis was post-menopausal women.

## Results

| | Post-menopausal (N=1662) | Pre-menopausal (N=766) |
|---|---|---|
| Age (years), median (IQR) | 62.5 (57-70) | 46 (41-49) |
| HER2 negative | 1383 (83.2%) | 612 (79.9%) |
| Tumour size (mm), median (IQR) | 18 (12-27) | 22 (14-30) |
| Grade 1 | 356 (21.4%) | 105 (13.7%) |
| Grade 2 | 919 (55.3%) | 405 (52.9%) |
| Grade 3 | 387 (23.3%) | 256 (33.4%) |
| Node negative | 1211 (72.9%) | 459 (59.9%) |
| Chemotherapy | 468 (28.2%) | 540 (70.5%) |
| <1 year endocrine therapy | 70 (4.2%) | 57( 7.4%) |
| 12-48 months endocrine therapy | 55 (3.3%) | 46 (6.0%) |
| 48-72 months endocrine therapy | 1318 (79.3%) | 481 (62.8%) |
| >72 months endocrine therapy | 219 (13.2%) | 182 (23.8%) |
| Distant recurrence after 5 years | 149 (9.0%) | 94 (12.3%) |
| Deaths after 5 years | 388 (23.4%) | 68 (8.9%) |
| Time to DR (years), median (IQR) | 8.3 (5.7-11.2) | 10.7 (7.8-13.0) |

**Table 1**: Baseline characteristics and endpoint events of post- and pre-menopausal cohorts

## CTS5 performs well in pre- and post-menopausal women

Continuous and categorical increase in CTS5 score is associated with increased risk of late DR for both pre- and postmenopausal women.

| | Post-menopausal (n=1662, DR=107) | | Pre-menopausal (n=766, DR=51) | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| CTS5 (continuous) | 1.95 (1.59-2.39) | <0.0001 | 1.72 (1.23-2.40) | 0.001 |
| CTS5 low | Reference | | Reference | |
| CTS5 intermediate | 2.28 (1.32-3.93) | 0.003 | 1.69 (0.84-3.51) | 0.16 |
| CTS5 high | 3.81 (2.27-6.41) | <0.0001 | 2.63 (1.29-5.34 | 0.008 |
| No chemotherapy | 2.26 (1.68-3.03) | <0.0001 | 1.58 (0.74-3.39) | 0.24 |
| Chemotherapy | 1.93 (1.32-2.82) | 0.001 | 2.13 (1.37-3.31) | <0.0001 |

**Table 2:** HR for late distant recurrence with continuous CTS5 and 3 risk categories.

## CTS5 categorises women into risk groups

CTS5 stratifies the post-menopausal cohort into 3 distinct risk groups with similar separation in post-menopausal women to the combined BIG1-98/ATAC training cohort. The separation was less distinct for pre-menopausal women.

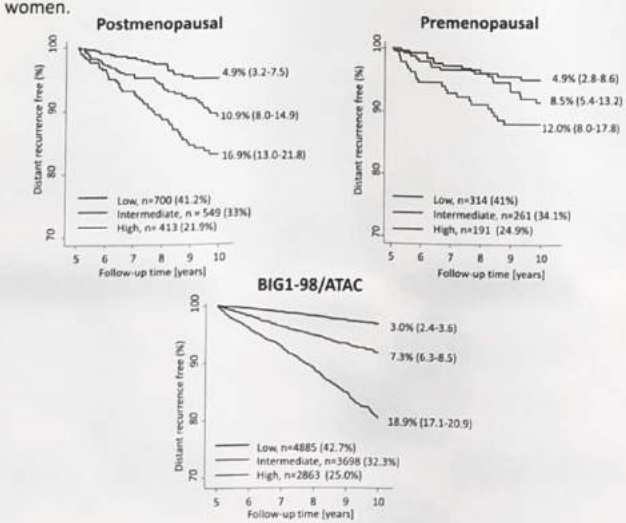


**Figure 1:** Kaplan-Meier curves showing recurrence events by risk category.

## CTS5 calibrates well in post-menopausal women

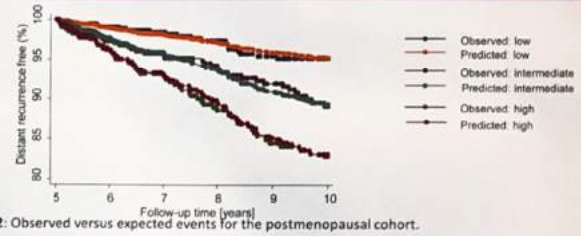


**Figure 2**: Observed versus expected events for the postmenopausal cohort.

## Conclusions

- CTS5 has prognostic value in an unselected cohort of women, including pre-menopausal women, and regardless of chemotherapy treatment.
- The scope of women in whom CTS5 can be applied extends beyond that of the development cohort.
- Calibration of CTS5 in pre-menopausal women was less accurate than in post-menopausal women.
- CTS5 requires further testing in pre-menopausal women and women with HER2+ breast cancer.
- The predictive ability of CTS5 for benefit from extended endocrine therapy is unknown therefore CTS5 should be used to identify a group in whom risk of recurrence is so low that extended therapy could not possibly be beneficial
- CTS5 could be used in conjunction with other prognostic models to further risk stratify women who fall into the intermediate risk categories (fig. 3)

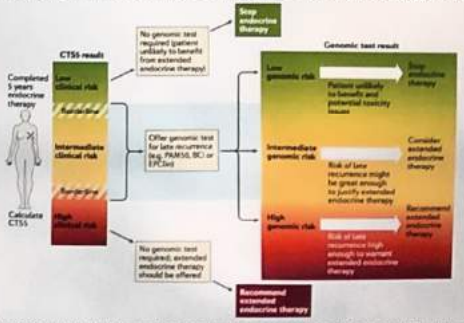


**Figure 3**: Proposed extended endocrine therapy decision algorithm, adapted from Richman and Dowsett, NCRO, 2018.

**References**

1. Dowsett, M. et al. Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor-positive breast cancer treated with 5 years of endocrine therapy: CTS5. *J. Clin. Oncol.* 36, 1941–1948 (2018).

**Acknowledgements**

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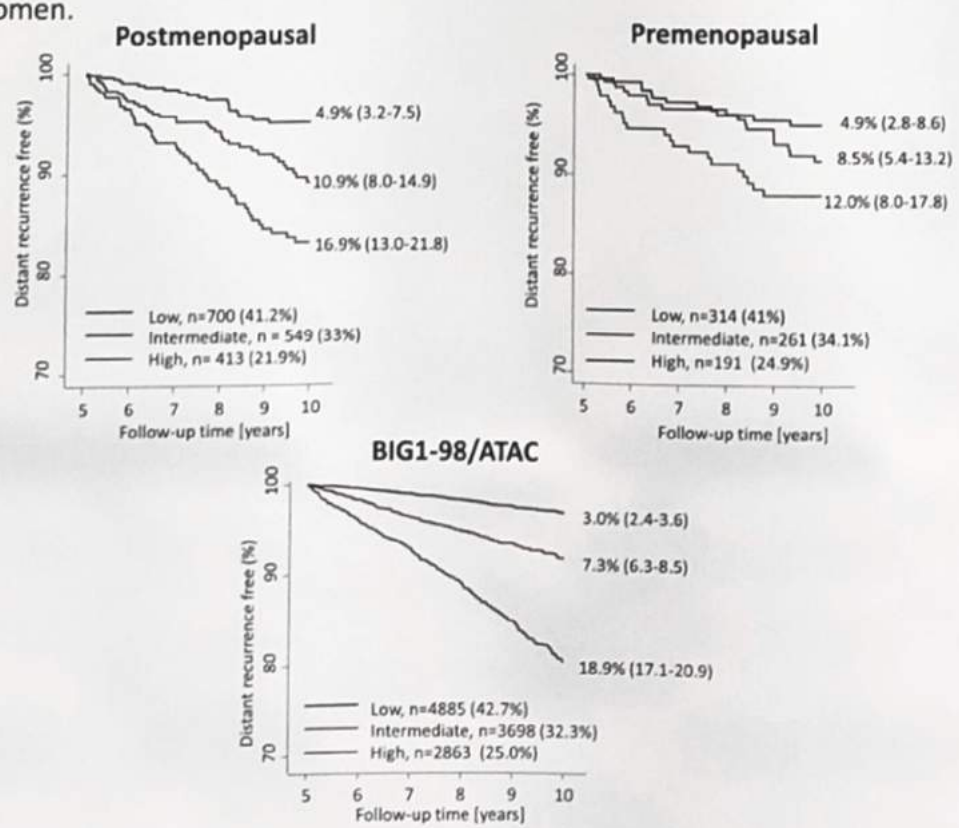


**Figure 1:** Kaplan-Meier curves showing recurrence events by risk category.

# Trans-aTTom: Breast Cancer Index predicts benefit of extended endocrine therapy in HR+ breast cancers treated in the Adjuvant Tamoxifen – To Offer More? (aTTom) trial

J. Bartlett, D. Sgroi, K. Treuner, Y. Zhang, T. Piper, R. Salunga, I. Ahmed, K. Basnet, E. Brachtel, S. Pirrie, C.A. Schnabel, and D. Rea on behalf of the Trans-aTTom Study Group

Abstract 505

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: John Bartlett, PhD <John.Bartlett@oicr.on.ca>



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# Breast Cancer Index (BCI)

- BCI is an 11-gene expression molecular signature comprised of two functional panels
  - Molecular Grade Index (MGI) - 5 genes measuring tumor proliferative status
  - *HOXB13* and *IL17BR* (H/I) – 2 gene ratio measuring estrogen signaling
- The BCI test provides both a prognostic BCI score for the risk of cumulative (0-10 years) and late (post-5 years) distant recurrence, and a prediction of the likelihood of EET benefit based on BCI (H/I)
- BCI (H/I) predicted endocrine response across several different endocrine treatment backgrounds with significant treatment to biomarker interaction[1-3]
- BCI (H/I) predicted benefit from extended endocrine therapy in a cohort from the MA.17 trial[1]
- The current study further examines the predictive performance of the BCI (H/I) in the EET setting in patients treated in the aTTom trial


1. Sgroi DC et al JNCI 2013; 105(14):1036-42
2. Zhang Y et al. CCR 2013; 19(15):4196-205
3. Sgroi DC et al. Cancer Res 2012; 72 (Supppl.): Abstract P2-10-5





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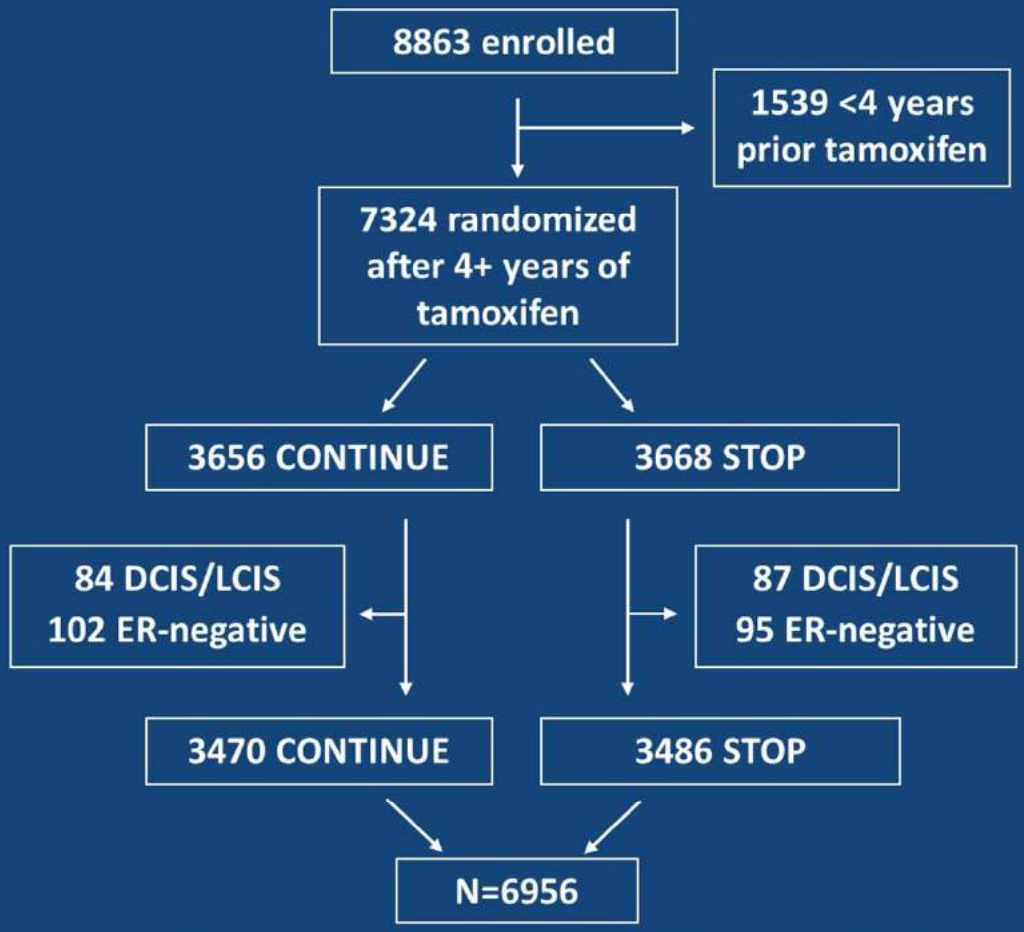
# aTTom Parent Study

- 6956 early stage patients who completed at least 4 years of tamoxifen randomized to either stop or continue tamoxifen for an additional 5 years
- Demonstrated benefit from 10 years tamoxifen in disease-free interval (DFI) at a median 8.9 years of follow-up
  - HR: 0.86, 95% CI 0.77-0.96, (p=0.006 )
- Extended tamoxifen treatment was associated with a significant increase in endometrial cancer (p<0.0001)
- Data available to 12.6 years median follow-up (2017)

Gray R et al. *J Clin Oncol* 2013; **31**: (suppl; abstr 5).




(78% ≥ 55 years old, 50% T1, 38% T2, 31% node-positive)



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# Study Objectives and Endpoints

- Objectives
  - Primary objective - to determine whether BCI (H/I) status (High vs Low) is predictive of the benefit of 10 years versus 5 years of tamoxifen
  - Secondary objective - to evaluate whether BCI (H/I), as a continuous index, demonstrates a statistically significant treatment to biomarker interaction with extended tamoxifen treatment

- Endpoints
  - Primary endpoint - Recurrence-Free Interval (RFI) including local, regional and distant recurrences
  - Secondary endpoint - Disease-Free Interval (DFI) including local, regional, distant recurrences and contralateral breast cancer



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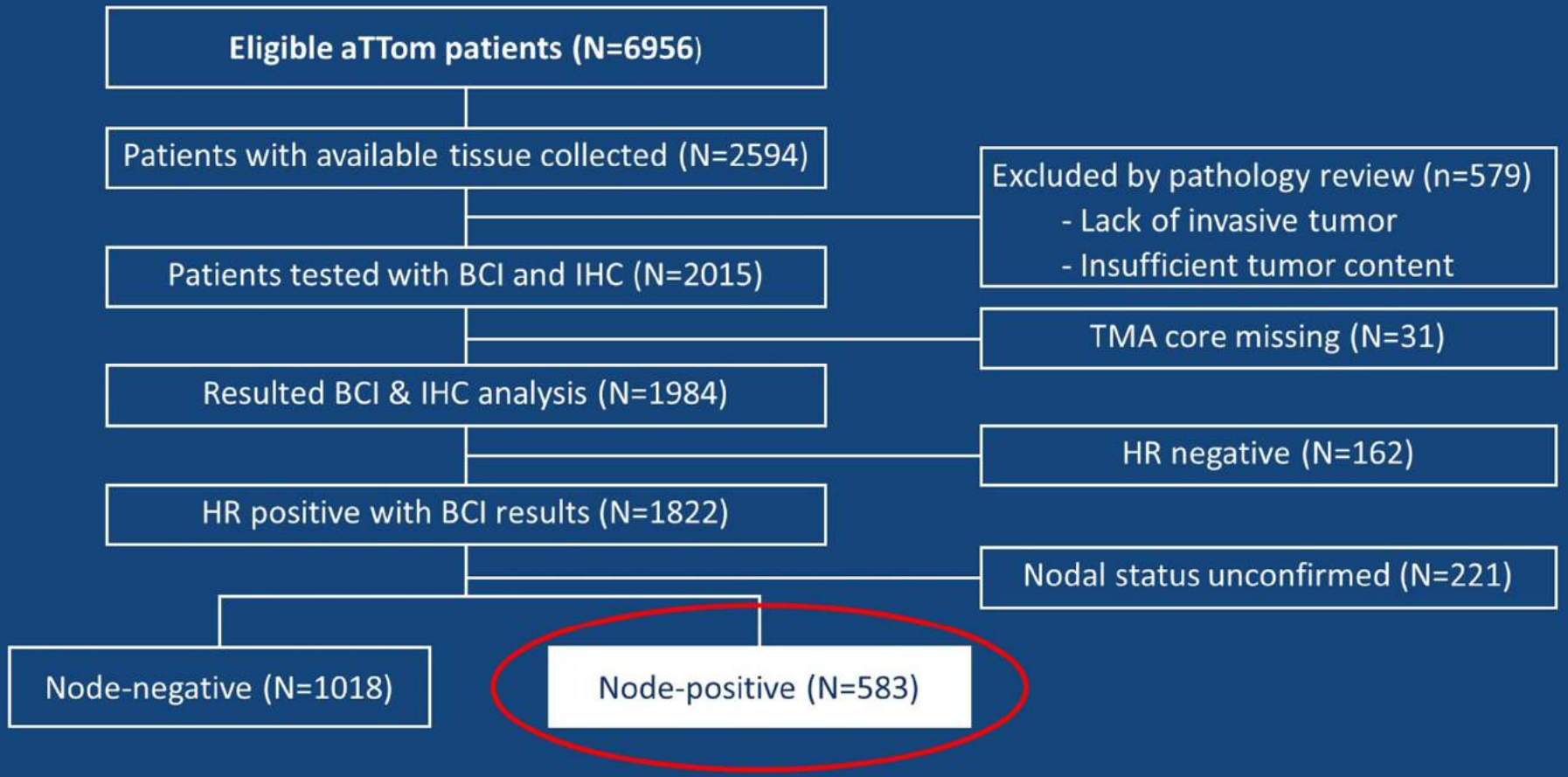
# Trans-aTTom Case Flow



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# Patient Characteristics

No statistically significant differences were observed between aTTom N+ and Trans-aTTom N+ cohorts

| | aTTom N+ (n=2136) | Trans-aTTom N+ (n=615) | P-value |
|---|---|---|---|
| Age | | | |
| <50 | 265 (12%) | 97 (16%) | 0.141 |
| 50-59 | 765 (36%) | 208 (34%) | |
| 60-60 | 612 (29%) | 163 (27%) | |
| ≥70 | 494 (23%) | 147 (24%) | |
| Menopause | | | 0.059 |
| Pre | 70 (3%) | 25 (4%) | |
| Post | 1798 (84%) | 527 (86%) | |
| Peri | 63 (3%) | 23 (4%) | |
| Unknown | 205 (10%) | 40 (7%) | |
| Tumor Size | | | 0.992 |
| T1 | 968 (45%) | 275 (45%) | |
| T2 | 903 (42%) | 262 (43%) | |
| T3 | 95 (4%) | 28 (5%) | |
| Unknown | 170 (8%) | 50 (8%) | |
| Histological Grade | | | 0.993 |
| Well differentiated - grade I | 313 (15%) | 92 (15%) | |
| Moderately differentiated - grade II | 953 (45%) | 272 (44%) | |
| Poorly differentiated - grade III | 467 (22%) | 133 (22%) | |
| Unknown | 403 (19%) | 118 (19%) | |
| Histology | | | 0.703 |
| Ductal | 1473 (69%) | 442 (72%) | |
| Lobular | 265 (12%) | 73 (12%) | |
| Tubular | 28 (1%) | 8 (1%) | |
| Other/Mixed | 70 (3%) | 17 (3%) | |
| Unknown | 300 (14%) | 75 (12%) | |



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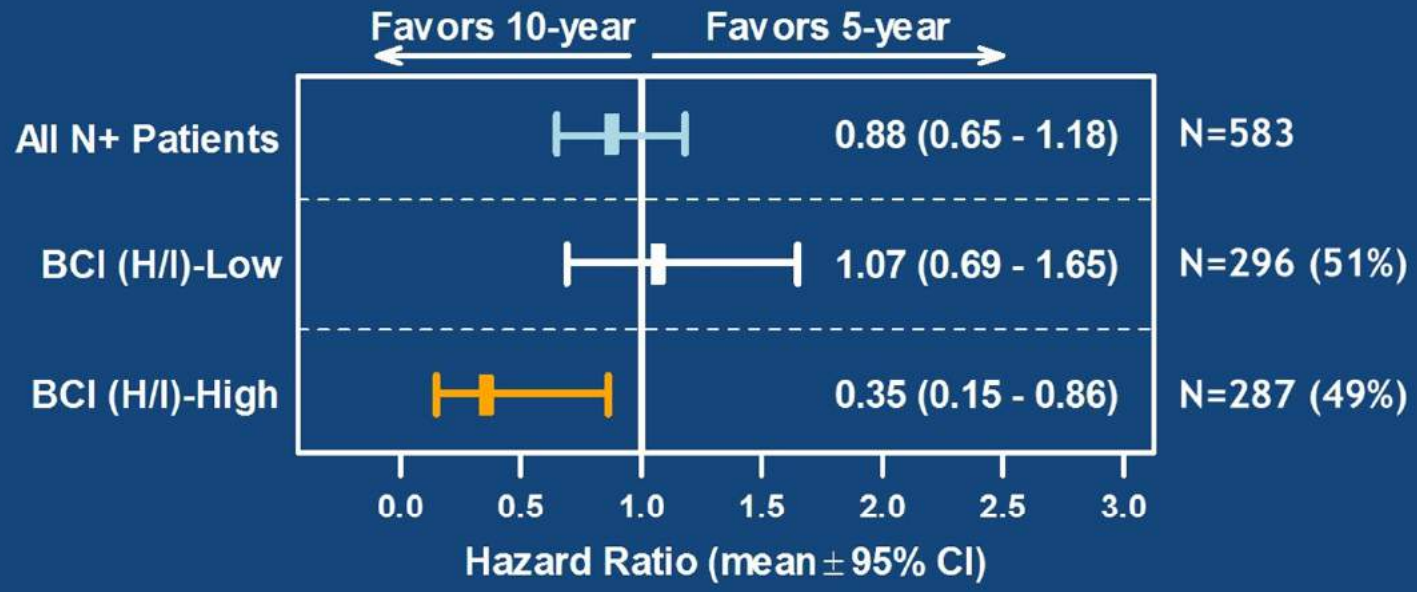
# Relative Benefit of Extended Tamoxifen by BCI (H/I) Status: Trans-aTTom N+ cases







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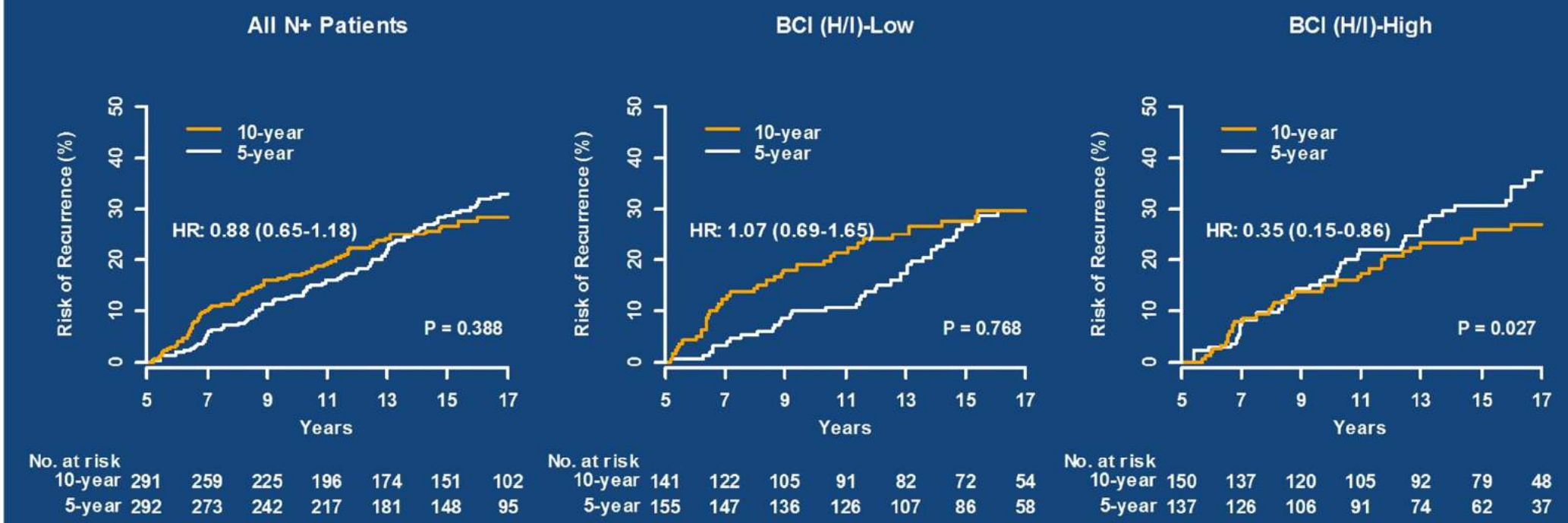
# Benefit of Extended Tamoxifen is Dependent on the Classification of BCI (H/I)



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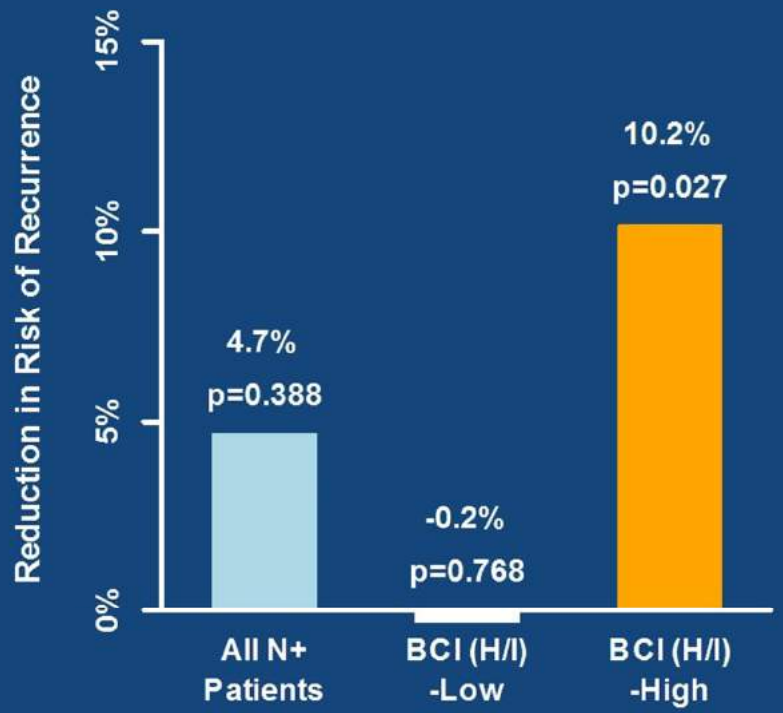
# Absolute Benefit of Extended Tamoxifen by BCI (H/I) Status



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# Summary of BCI (H/I) as Predictive Biomarker for EET

| Study Cohort | Relative Risk Reduction | Interaction P-Value |
|---|---|---|
| **Treatment: Extended AI vs Placebo** | | |
| MA.17 (n=249)[1] | H/I-High OR: 0.35 (0.16-0.75); p=0.007<br>H/I-Low OR: 0.68 (0.31-1.52), p=0.35 | 0.03 |
| **Treatment: Extended TAM vs Stop** | | |
| Trans-aTTom N+ (n=583) | H/I-High HR: 0.35 (0.15-0.86); p=0.027<br>H/I-Low HR: 1.07 (0.69-1.65), p=0.768 | 0.01 |

1. Sgroi DC et al JNCI 2013; 105(14):1036-42 2. Simon et al, JNCI 2009 101:1446-1452



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# Summary of BCI (H/I) as Predictive Biomarker *all trials*

| Study Cohort | Relative Risk Reduction | Interaction P-Value |
|---|---|---|
| **Treatment: Adjuvant TAM vs none** | | |
| **Stockholm (n=600)[1]** | H/I-High HR: 0.35 (0.19-0.65); p=0.0005<br>H/I-Low HR: 0.67 (0.36-1.24), p=0.204 | 0.003 |
| **Treatment: Extended AI vs Placebo** | | |
| **MA.17 (n=249)[2]** | H/I-High OR: 0.35 (0.16-0.75); p=0.007<br>H/I-Low OR: 0.68 (0.31-1.52), p=0.35 | 0.03 |
| **Treatment: Extended TAM vs Stop** | | |
| **Trans-aTTom N+ (n=583)** | H/I-High HR: 0.35 (0.15-0.86); p=0.027<br>H/I-Low HR: 1.07 (0.69-1.65), p=0.768 | 0.01 |

1. Zhang Y et al. CCR 2013; 19(15):4196-205 2. Sgroi DC et al JNCI 2013; 105(14):1036-42



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# Conclusions

- BCI (H/I) was predictive of endocrine response and identified a subset of HR+, N+ patients with significant benefit from 10 years vs 5 years of tamoxifen therapy
- 51% of N+ patients were identified as BCI (H/I)-Low and showed no statistically significant benefit from an additional 5 years of extended tamoxifen treatment
- These data provide further validation and establish level 1B evidence[1] for BCI as a predictive biomarker of benefit from extended endocrine treatment and outcome

1. Simon et al, JNCI 2009 101:1446-1452



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# Clube da Mama
# Pós ASCO 2019
## Loco/regional/adjuvante

**Objetivos educacionais:**

- Neoadjuvancia o que vem aí?
- Duração de endocrinoterapia adjuvante
- **Duração de trastuzumabe adjuvante**
- De-escalonamento de radioterapia em pacientes idosas

# Do all patients with HER2 positive breast cancer require one year of adjuvant trastuzumab? A systematic review and meta-analysis

Paul Stewart[1], Phillip Blanchette[1], Prakesh S. Shah[2,3], Xiang Y. Ye[3], R. Gabriel Boldt[4], Ricardo Fernandes[1], Ted Vandenberg[1], Jacques Raphael[1]

1 Department of Oncology, Division of Medical Oncology, The University of Western Ontario, London, Ontario 2 Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario 3 Department of Pediatrics, Mount Sinai Hospital, Toronto, Ontario 4 London Regional Cancer Program, London Health Sciences Centre, London, Ontario

## Background

- Adjuvant trastuzumab significantly improves survival in HER2-positive breast cancer
- Optimal duration of adjuvant trastuzumab remains uncertain
  - 1 year chosen by expert consensus
  - 2 years offers no benefit over 1 year (HERA trial)
- Role for shorter duration
  - FinHER trial led to several non-inferiority trials comparing shorter duration vs. 1 year
  - Approx. 50% less cardiac events
  - Decreased costs and resources

## Objectives

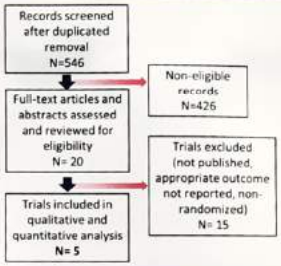
- **Objective:** To conduct a systematic review and meta-analysis of randomized trials in patients with HER2 positive breast cancer to assess different durations of adjuvant trastuzumab.
- **Hypothesis:** A shorter duration of adjuvant trastuzumab is non-inferior to one year of treatment.

## Methods

- **Outcomes:** DFS (primary) and OS (secondary)
- **Population:** Adjuvant HER2+ breast cancer patients
- **Search Method:**
  - PubMed, EMBASE and The Cochrane Library were searched for eligible randomized trials
  - 1 clinical librarian & 2 independent reviewers
- Pooled HR for DFS and OS
  - Weighted using generic inverse variance
  - Random-effects model to account for heterogeneity
- Calculated mean non-inferiority margin HR 1.29 for the pooled analysis
  - 3.9% non-inferiority margin for DFS
- Subgroup analyses

## Results

### Trial Selection and Characteristics




| Author | Year | Study | Duration of Trastuzumab | Number of patients | Primary Outcome | Concomitant Trastuzumab | Node Negative | ER Positive | Non-inferiority Margin |
|---|---|---|---|---|---|---|---|---|---|
| Mavroudis | 2015 | HORG | 6 months | 481 | DFS | 100% | 79% | 69% | 8% 3yr DFS HR 1.53 |
| Earl | 2018 | PERSEPHONE | 6 months | 4088 | DFS | 47% | 59% | 69% | 3% 4yr DFS HR 1.316 |
| Pivot | 2013 | PHARE | 6 months | 3380 | DFS | 56% | 45% | 60% | 2% 2yr DFS HR 1.15 |
| Conte | 2017 | Short-HER | 9 weeks | 1253 | DFS, OS | 100% | 47% | 67% | 5 yr DFS HR 1.29 |
| Joensuu | 2018 | SOLD | 9 weeks | 2176 | DFS | 100% | 40% | 66% | 4% 5 yr DFS HR 1.3 |

### Risk of Bias

| | Selection | Performance | Detection | Attrition | Reporting |
|---|---|---|---|---|---|
| HORG | L | L | L | L | L |
| PERSEPHONE | L | L | L | U | L |
| PHARE | L | L | U | L | L |
| Short-Her | U | U | U | L | L |
| SOLD | L | L | L | L | L |

L = low risk, H = high risk, U = unknown

### GRADE Recommendation

| Certainty assessment | | | | | | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|
| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | |
| DFS | | | | | | | | |
| 5 | randomised trials | not serious | serious [a] | not serious | not serious | none | ⨁⨁⨁◯ MODERATE | IMPORTANT |
| OS | | | | | | | | |
| 5 | randomised trials | not serious | not serious | not serious | serious [b] | none | ⨁⨁⨁◯ MODERATE | IMPORTANT |

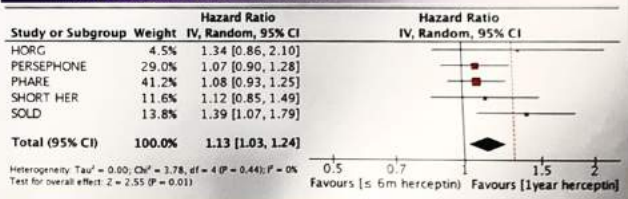
CI: Confidence interval

Explanations

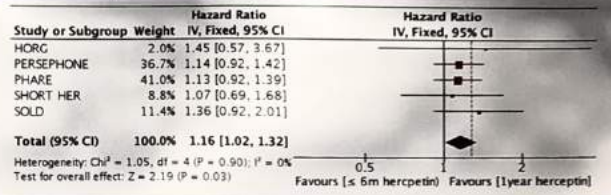
a. Only one trial was able to show non-inferiority

b. Wide confidence intervals in OS results

### Primary Outcome DFS – Forest Plot




### Secondary Outcome OS – Forest Plot




### Results Summary

- Primary Outcome DFS
  - HR 1.13 (1.03 – 1.24)
  - Shorter duration of trastuzumab non-inferior for DFS as 95% CI below HR margin of 1.29
- Secondary Outcome OS
  - HR 1.16 (1.02 – 1.32)
  - Shorter duration of trastuzumab not non-inferior for OS as 95% CI crosses HR margin

### Subgroups

| | | | | |
|---|---|---|---|---|
| ER Status | **ER positive** | **1.10** | **(0.95-1.28)** | ***Non-inferior*** |
| | ER negative | 1.22 | (1.06-1.41) | |
| Node status | Node negative | 1.12 | (0.93-1.35) | |
| | Node positive | 1.16 | (0.99-1.36) | |
| Duration | **6 months** | **1.09** | **(0.98-1.22)** | ***Non-inferior*** |
| | 9 weeks | 1.26 | (1.02-1.55) | |
| Timing | Concomitant | 1.25 | (1.07-1.45) | |
| | **Sequential** | **0.97** | **(0.75-1.27)** | ***Non-inferior*** |
| Age | age <50 | 1.12 | (0.93-1.35) | |
| | age ≤50 | 1.34 | (0.95-1.90) | |

## Conclusion

- Shorter duration of adjuvant trastuzumab in HER2 postive breast cancer patients, appears non-inferior to one year for DFS (approximate median follow-up of 4 years)
- Particularly in patients with ER positive disease and patients treated with 6 months of trastuzumab
- Further trials with appropriately chosen non-inferiority margins are needed to confirm optimal duration of trastuzumab in low-risk patients
- Potential cost and resource savings, especially in resource limited regions

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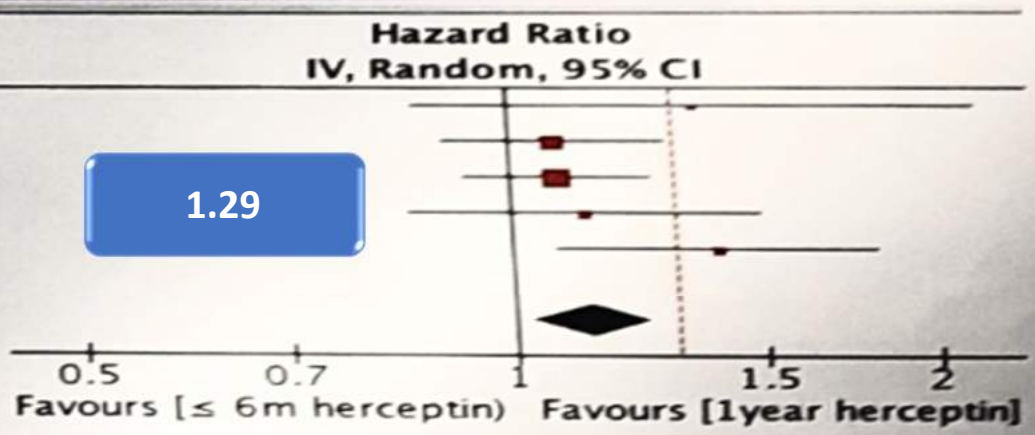
## Primary Outcome DFS – Forest Plot

| Study or Subgroup | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|
| HORG | 4.5% | 1.34 [0.86, 2.10] |
| PERSEPHONE | 29.0% | 1.07 [0.90, 1.28] |
| PHARE | 41.2% | 1.08 [0.93, 1.25] |
| SHORT HER | 11.6% | 1.12 [0.85, 1.49] |
| SOLD | 13.8% | 1.39 [1.07, 1.79] |
| **Total (95% CI)** | **100.0%** | **1.13 [1.03, 1.24]** |

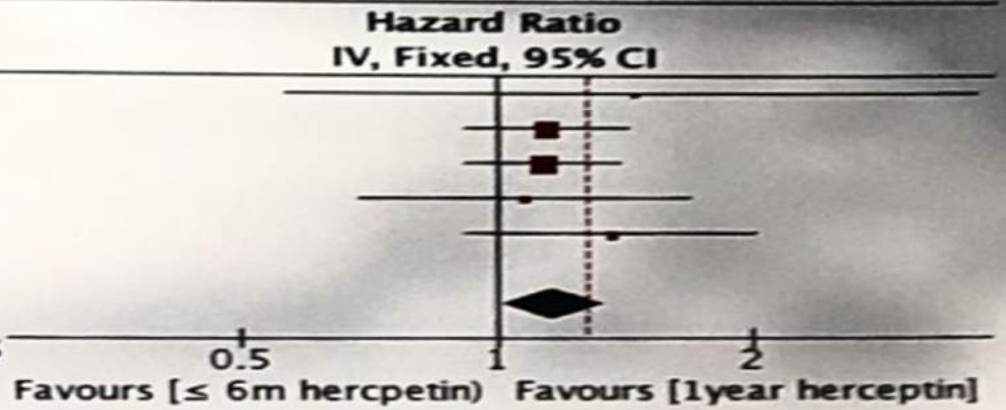
Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.55 (P = 0.01)




## Secondary Outcome OS – Forest Plot

| Study or Subgroup | Weight | Hazard Ratio IV, Fixed, 95% CI |
|---|---|---|
| HORG | 2.0% | 1.45 [0.57, 3.67] |
| PERSEPHONE | 36.7% | 1.14 [0.92, 1.42] |
| PHARE | 41.0% | 1.13 [0.92, 1.39] |
| SHORT HER | 8.8% | 1.07 [0.69, 1.68] |
| SOLD | 11.4% | 1.36 [0.92, 2.01] |
| **Total (95% CI)** | **100.0%** | **1.16 [1.02, 1.32]** |

Heterogeneity: Chi² = 1.05, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)



# De-escalating Adjuvant Trastuzumab in Human Epidermal Growth Factor Receptor 2 (HER2) Positive Early-Stage Breast Cancer: A Systemic Review and Meta-analysis

**Hadar Goldvaser[1,2], Yasmin Korzets[2,3], Daniel Shepshelovich[1], Rinat Yerushalmi[2], Michal Sarfaty[2], Domen Ribnikar[1], Paaladinesh Thavendiranathan[4] Eitan Amir[1]**

[1]Division of Medical Oncology, University of Toronto and Princess Margaret Cancer Centre, Canada, [2]Davidoff Cancer Center, Sackler Faculty of Medicine, Tel Aviv University, Israel [3] Radiation Oncology, University of Toronto and Princess Margaret Cancer Centre, Canada [4] Ted Rogers Program in Cardiotoxicity Prevention, Toronto General Hospital, Peter Munk Cardiac Center, Canada.

## Introduction

- One year of adjuvant trastuzumab in combination with chemotherapy is the standard of care in early-stage HER2 positive breast cancer.
- Existing data on shortening trastuzumab treatment show conflicting results.
- ***Objective:*** To conduct a meta-analysis of prospective trials comparing abbreviated trastuzumab treatment to 1 year treatment in early-stage HER2 positive breast cancer.

## Methods

- A search of PubMed and abstracts from key conferences between 2008-2018 to identified randomized trials that compared abbreviated trastuzumab therapy to one year of treatment in early-stage HER2 positive breast cancer was conducted.
- Hazard ratios (HRs) and 95% confidence intervals (CI) were extracted for disease free survival (DFS) and overall survival (OS).
- Odds ratios (ORs) and 95% CI were computed for pre-specified cardiotoxicity events including cardiac dysfunction and congestive heart failure (CHF).
- Subgroup analyses evaluated the effect of: nodal involvement, estrogen receptor (ER) expression and the duration of abbreviated trastuzumab (9-12 weeks versus 6 months).
- Absolute difference in outcomes and the number needed to treat (NNT) with shorter trastuzumab therapy in order to avoid one event were also computed.

## Results

- Analysis included 6 trials comprising 11603 patients.
- Shorter trastuzumab treatment was associated with worse DFS and OS (Fig. 1A-B )
- After an estimated median follow-up of 71 months, shorter treatment with trastuzumab was associated with an absolute increase in DFS events of **2.3%** (NNT 43).
- The effect on DFS was not influenced by nodal involvement (p for the subgroup difference 0.44, Fig. 1C), ER status (p=0.23, Fig. 1D), or the different duration of trastuzumab in the experimental arm (p=0.08, Fig. 1A).
- Shorter trastuzumab treatment was associated with lower odds of cardiac dysfunction (**OR=0.67, 95% CI 0.55-0.81, p<0.001**) and CHF (**OR=0.66, 95% CI 0.50-0.86, p=0.003**).
- The weighted absolute difference was **1.1%** with NNT of 89 for cardiac dysfunction and **1.0%** with a NNT of 101 for CHF.

Figure 1A: Hazard ratio for DFS

A

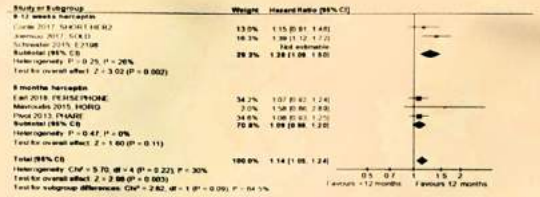


Figure 1B: Hazard ratio for OS

B

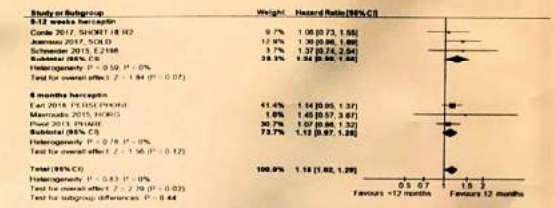


Figure 1C: Hazard ratio for DFS by nodal involvement

C

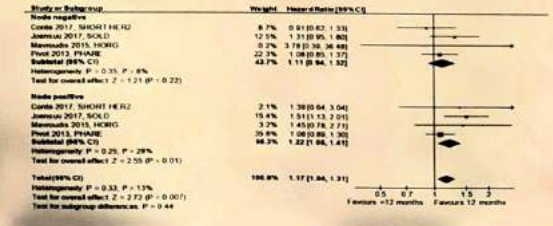
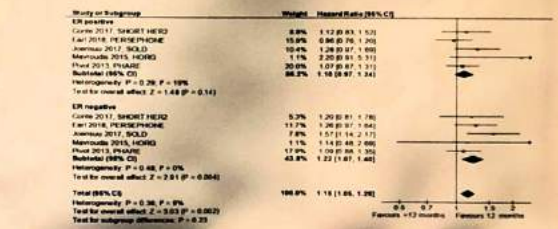


Figure 1C: Hazard ratio for DFS by ER status

D



## Summary

- Compared to one year, shorter duration of adjuvant trastuzumab is associated with significantly worse DFS and OS, despite favorable cardiotoxicity profile.
- One year of targeted HER2 treatment should remain the standard adjuvant treatment in early-stage HER2 positive disease with appropriate cardiac monitoring.

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# Clube da Mama
# Pós ASCO 2019
## Loco/regional/adjuvante

**Objetivos educacionais:**

- Neoadjuvancia o que vem aí?
- Duração de endocrinoterapia adjuvante
- Duração de trastuzumabe adjuvante
- **De-escalonamento de radioterapia em pacientes idosas**

# RT vs HT EXCLUSIVA EM IDOSAS EC I RE+

## Adjuvant endocrine monotherapy versus adjuvant breast radiation alone in healthy older women with stage I, estrogen receptor-positive breast cancer: An analysis of the National Cancer Database

Anthony H. Bui, Manjeet Chadha, Theresa H. Shao, Naamit K. Gerber, Sarah P. Cate, Susan K. Boolbol, Nicole J. Zubizarreta

*Icahn School of Medicine at Mount Sinai, New York, NY; New York University School of Medicine, New York, NY*

### INTRODUCTION

- The NCCN guidelines state that breast radiation therapy (RT) may be omitted in patients >70 years of age with estrogen receptor-positive (ER+), clinically node-negative, T1 breast cancer (BC) who receive adjuvant endocrine therapy (ET).
- Available data on older patients notes that local relapses are the most frequent site of failure, and distant relapse rates are low.
- The side effects of ET are not inconsequential and negatively affect QOL.

### OBJECTIVE

To examine overall survival (OS) in women ≥70 years of age treated by lumpectomy ET, RT, or ET+RT in the NCDB.

### METHODS

- The 2004-2013 NCDB was queried for women ≥70 years of age with ER+, HER-2 negative, stage I BC who underwent lumpectomy and had a minimum of one year of follow-up.
- Women who received no adjuvant therapy and women who received any chemotherapy were excluded.
- To limit the analysis to healthy women, we also excluded subjects with a Charlson/Deyo comorbidity index >0.
- We identified a total of **60,896** women, of whom **41,683** (**68.5%**) underwent **ET+RT**, **11,036** (**18.1%**) **ET**, and **8,177** (**13.4%**) **RT**.
- Median follow-up was 5.1 years (Interquartile Range [IQR] 3.1-7.3) in women who underwent ET+RT, 4.1 years (IQR 2.5-6.2) for ET, and 5.8 years (IQR 3.7-8.1) for RT.
- The median age of women who underwent ET+RT was 75 years (IQR 72-78), 79 years (IQR 75-83) for ET, and 77 years (IQR 73-81) for RT.
- Unadjusted comparison of OS between the three treatment groups was performed using Kaplan-Meier statistics and the log-rank test.
- Adjusted survival analyses were performed using Cox proportional hazards regression.

### RESULTS

**Table 1**. Median Survival Time and 5-Year Survival Probability, by Modality

| Adjuvant Modality | Median Survival Time, Years (95% CI) | 5-year Survival Probability (95% CI) |
|---|---|---|
| Endocrine+Radiation Therapy (ET+RT) | 11.76 (11.54-NE) | 90.9% (90.6-91.2%) |
| Endocrine Therapy (ET) | 9.69 (9.49-10.09) | 81.4% (80.5-82.3%) |
| Radiation Therapy (RT) | 11.08 (10.77-11.28) | 85.7% (84.8-86.5%) |

**Figure 1**. Kaplan-Meier Curves, by Modality

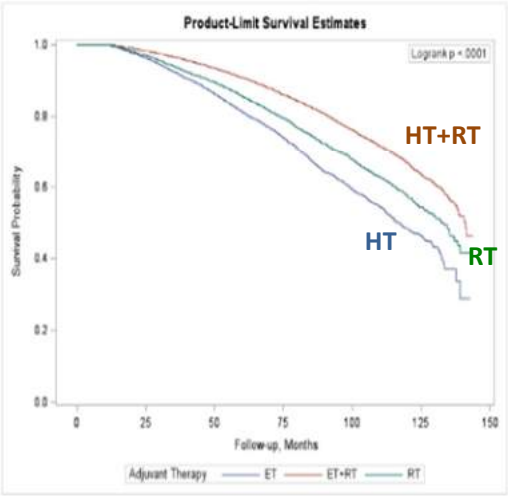


**Table 2**. Comparison of Adjuvant Therapies - Adjusted Hazard Ratios*

| Comparison | Hazard Ratio (95% CI) | p-value |
|---|---|---|
| ET vs. ET+RT | 1.429 (1.358-1.504) | <.0001 |
| RT vs. ET+RT | 1.276 (1.212-1.343) | <.0001 |
| RT vs. ET | 0.893 (0.840-0.949) | 0.0003 |

**Adjusted for year of diagnosis, tumor grade, margin status, progesterone receptor status, race, ethnicity, insurance, facility type, median zip code income, residence, and distance from hospital*

### CONCLUSION

- To our knowledge, this is the first large study comparing RT and ET monotherapy in healthy older women with stage I, ER+ BC.
- The OS with RT alone is not inferior to ET alone, and in this study population is noted to be better.
- However, both RT and ET alone appear to be inferior to ET+RT.
- While this analysis has various limitations not dissimilar from other NCDB database studies, our observations warrant further research with prospective studies.

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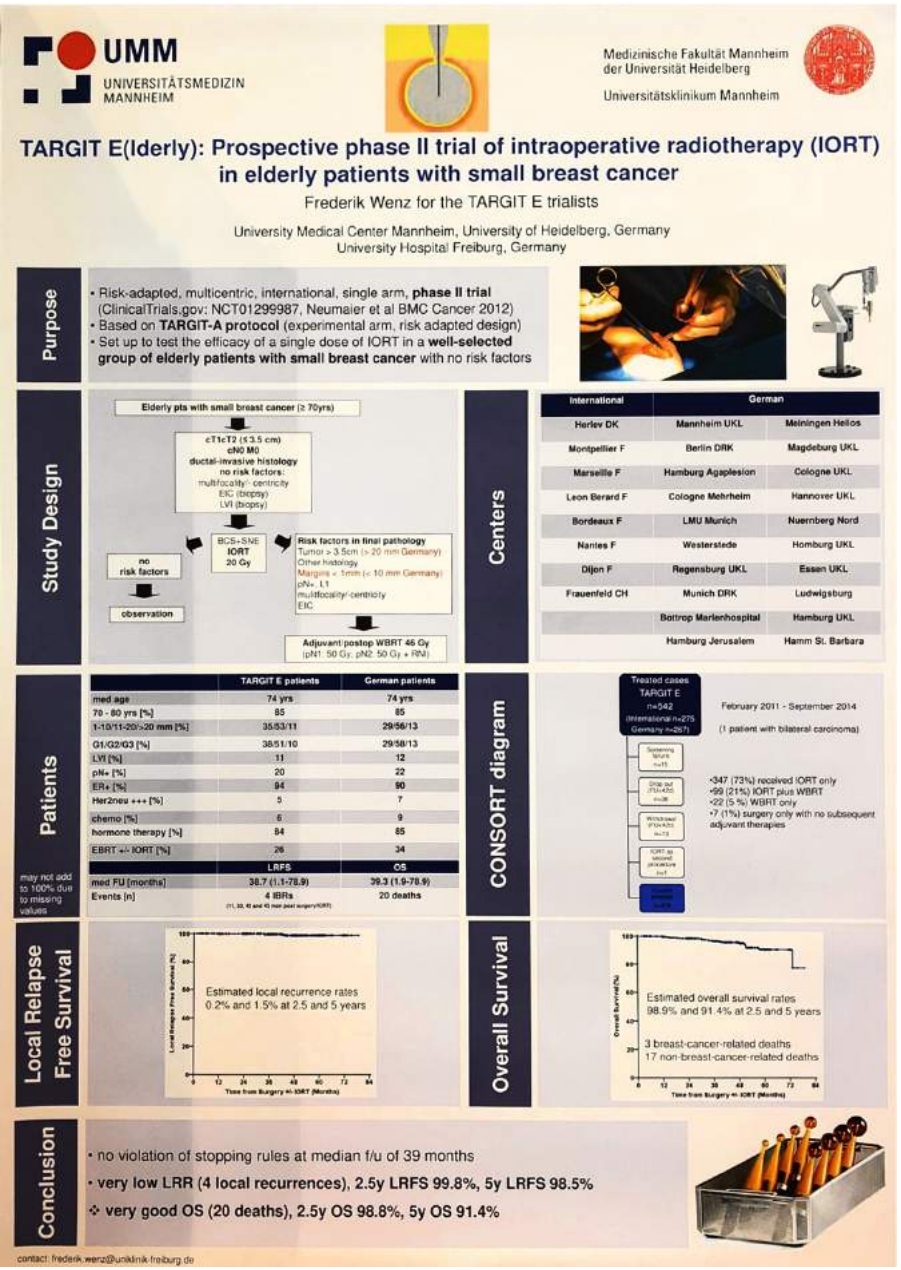



# Radioterapia intraoperatória com INTRABEAM, em pacientes ≥ 70 anos

**Critérios de inclusão**

≥ 70 anos

< 3,5 cm, N0

unifocal

IAV (-)

CDIS extenso (-)

**542 pacientes**

**73% IORT**

**21% IORT+WBRT**

**5% WBRT**

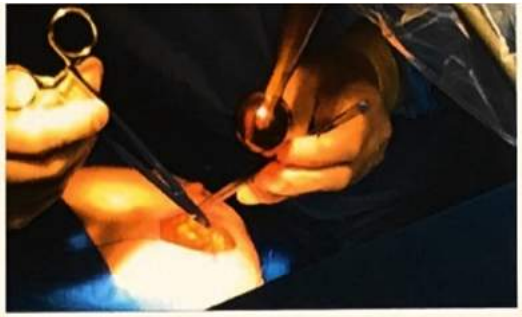
**1% só CIR**

**ASCO 2019**

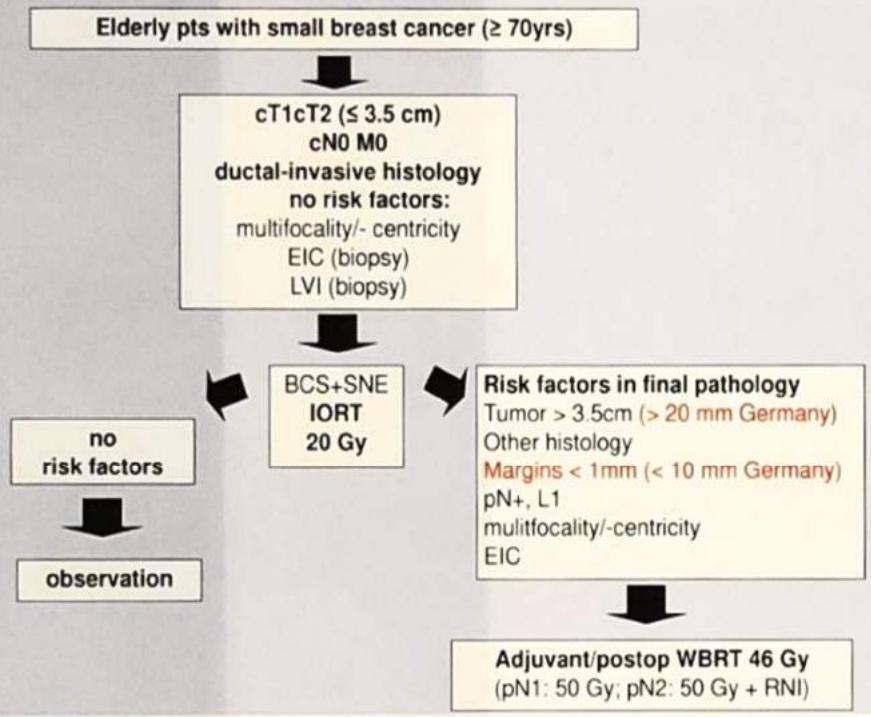
# TARGIT E(lderly): Prospective phase II trial of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer

## Purpose

- Risk-adapted, multicentric, international, single arm, **phase II trial** (ClinicalTrials.gov: NCT01299987, Neumaier et al BMC Cancer 2012)
- Based on **TARGIT-A protocol** (experimental arm, risk adapted design)
- Set up to test the efficacy of a single dose of IORT in a **well-selected group of elderly patients with small breast cancer** with no risk factors



## Study Design




## Centers

| International | German | |
|---|---|---|
| Herlev DK | Mannheim UKL | Meiningen Helios |
| Montpellier F | Berlin DRK | Magdeburg UKL |
| Marseille F | Hamburg Agaplesion | Cologne UKL |
| Leon Berard F | Cologne Mehrheim | Hannover UKL |
| Bordeaux F | LMU Munich | Nuernberg Nord |
| Nantes F | Westerstede | Homburg UKL |
| Dijon F | Regensburg UKL | Essen UKL |
| Frauenfeld CH | Munich DRK | Ludwigsburg |
| | Bottrop Marienhospital | Hamburg UKL |
| | Hamburg Jerusalem | Hamm St. Barbara |

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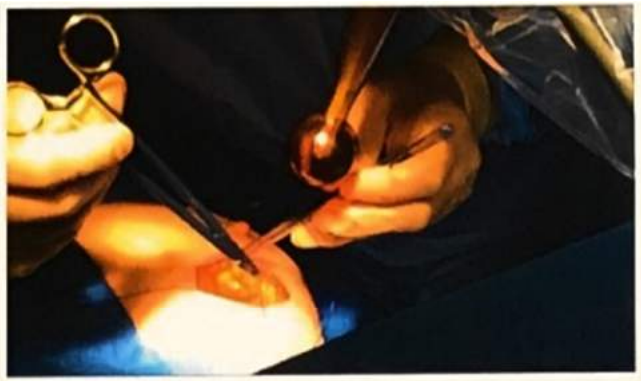
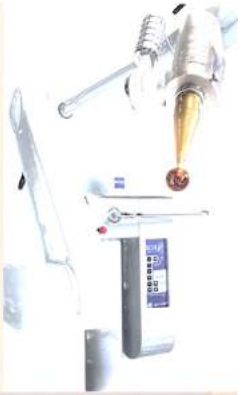
Universitätsklinikum Mannheim

# TARGIT E(lderly): Prospective phase II trial of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer

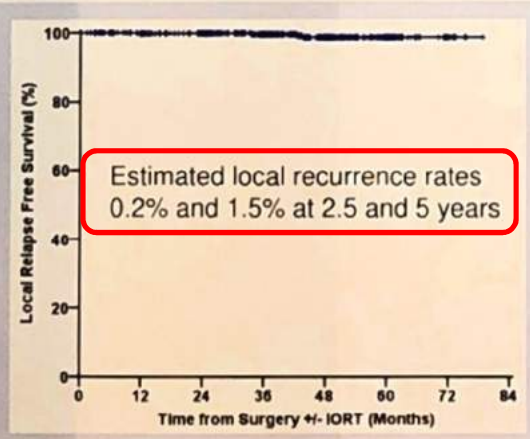
Frederik Wenz for the TARGIT E trialists

University Medical Center Mannheim, University of Heidelberg, Germany
University Hospital Freiburg, Germany



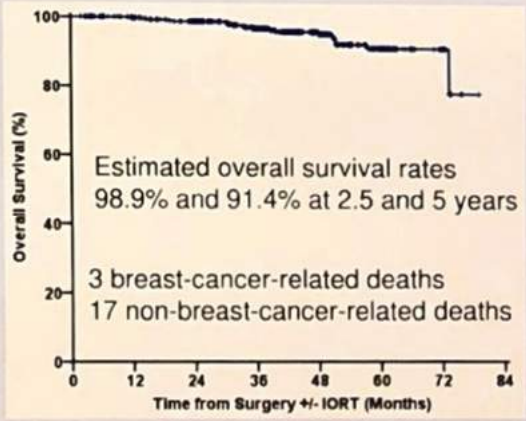


## Local Relapse Free Survival




Estimated local recurrence rates
0.2% and 1.5% at 2.5 and 5 years

## Overall Survival




Estimated overall survival rates
98.9% and 91.4% at 2.5 and 5 years

3 breast-cancer-related deaths
17 non-breast-cancer-related deaths

## Conclusion

- no violation of stopping rules at median f/u of 39 months
- **very low LRR (4 local recurrences), 2.5y LRFS 99.8%, 5y LRFS 98.5%**
- ❖ **very good OS (20 deaths), 2.5y OS 98.8%, 5y OS 91.4%**

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# Risk stratification in early stage luminal breast cancer patients treated with and without RT

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## BACKGROUND

- The goal was to develop and validate a biologic signature for 10-year ipsilateral invasive breast event (IBE) risk in luminal Stage 1 breast cancer (BC) patients treated surgically, with or without adjuvant radiotherapy (RT).

## MATERIALS & METHODS

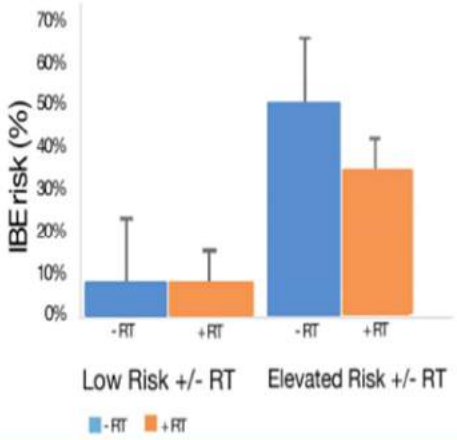
- This cohort was from Uppsala University and Västerås Hospitals diagnosed with Stage 1 BC and treated surgically between 1987 and 2004. Treatment was neither randomized nor strictly rules based, including adjuvant RT, hormone therapy (HT), and chemotherapy (CT).
- Biomarkers (HER2, PR, Ki67, COX2, p16/INK4A, FOXA1 and SIAH2) were assessed on tissue microarrays in PreludeDx's CLIA lab by board-certified pathologists. Risk groups were calculated using biomarkers and the clinical factors age and size. A multivariate Cox proportional hazards analysis was used to determine hazard ratio for biologic signature. The 10-year IBE risk was assessed using Kaplan-Meier survival analysis.

## RESULTS

- There were 423 luminal cases with biomarker data having 54 IBEs, during a median follow-up of 11.8 years. There were 372 patients treated with BCS and 51 with mastectomy, and 325 received RT, 169 received HT, and 47 received CT. In a multivariate analysis, the biologic signature (HR = 1.6, p = 0.019) and RT (HR = 0.51, p = 0.027) were associated with IBE risk adjusting for other treatments (HT and CT) and Luminal A status (p = 0.37). Luminal A* status was defined as PR neg (<1%), KI67 neg (< 15%) and HER2 neg (<3)
- For patients over 50 years of age with luminal A disease and treated without CT (n = 205), the biologic signature identified a subset of patients with an elevated risk; 15% (+/- 14%) 10-year IBE risk without RT (n = 38) compared to a 4% (+/-6%) IBE risk with RT (n = 72), while patients with a low biologic signature risk had a 10-year IBE risk of 4% (+/- 4%) without RT (n = 26) and 3% (+/-5%) IBE risk with RT (n = 69).

- The biologic risk signature identifies subgroups of patients with early-stage BC who will benefit from RT
- In Luminal A* breast cancer, the signature provides both prognostic and predictive value for RT benefit

## 10-YEAR IBE RISK




## DISCUSSION

- A biological risk signature based on 7 biomarkers and clinic-pathological factors identified a group of patients with invasive Luminal A breast cancer with a 10-year risk of 15% for local recurrence, and a substantial benefit from RT. A low risk group with a 4% risk of local recurrence at 10 years was also identified, with a minimal absolute benefit from RT.
- With further prospective validation, the biologic signature identified herein may provide a tool enabling improved management for women diagnosed with early luminal breast cancer.

## TABLE 1 – POPULATION CHARACTERISTICS

| ALL LUMINAL CASES (n=423) | - RT (%) | + RT (%) | (N) |
|---|---|---|---|
| **Age Group** | | | |
| <=50 years | 8 | 92 | 112 |
| >50 years | 29 | 71 | 311 |
| **Tumor Size Group** | | | |
| <= 10 mm | 29 | 71 | 205 |
| >=10 mm | 17 | 83 | 218 |
| **Nuclear Grade** | | | |
| Grade 1 & 2 | 24 | 76 | 389 |
| Grade 3 | 9 | 91 | 33 |
| **CT** | | | |
| No | 26 | 74 | 376 |
| Yes | 2 | 98 | 47 |
| **Luminal A** | | | |
| No | 20 | 80 | 137 |
| Yes | 25 | 75 | 286 |
| **HT** | | | |
| No | 28 | 72 | 254 |
| Yes | 17 | 83 | 169 |

## TABLE 2 – MULTIVARIATE ANALYSIS

LUMINAL A – NO CT, 10-YEAR IBE RISK +/- RT, (n=57)

| | IBE | | |
|---|---|---|---|
| | HR | [95 %, CI] | P-Value |
| **RT** | 0.51 | [0.28 - 0.93] | 0.03 |
| **Biosignature** | 1.58 | [1.08 - 2.32] | 0.02 |
| **Luminal A** | 0.77 | [0.43 - 1.37] | 0.37 |
| **CT** | 0.71 | [0.25 - 2.04] | 0.52 |
| **HT** | 0.75 | [0.46 - 1.24] | 0.26 |
| **Mastectomy** | 0.60 | [0.23 - 1.53] | 0.28 |

## TABLE 3 – 10-YEAR IPSILATERAL INVASIVE BREAST EVENT (IBE) RISK TREATED SURGICALLY AND EITHER WITH OR WITHOUT RADIATION THERAPY (RT)

| | BCS – RT | | | BCS + RT | | |
|---|---|---|---|---|---|---|
| | Risk [95%, CI] | Prevalence | (N) | Risk [95%, CI] | Prevalence | (N) |
| **Low Risk** | [0.88 – 1.0] | 4% (+/- 4%) | 26 | [0.93 – 1.0] | 3% (+/-5%) | 69 |
| **Elevated Risk** | [0.73 – 1.0] | 15% (+/- 14%) | 38 | [0.91 – 1.0] | 4% (+/-6%) | 72 |



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**Objetivos educacionais: Conclusões**

- Neoadjuvancia o que vem aí? TDM1, como alternativa, na impossibilidade clínica de QT + Duplo bloqueio com trastuzumabe e pertuzumabe.
- Duração de endocrinoterapia adjuvante: Verificar fatores de risco, Utilizar TCS5 (pos-menopausa) ou se possível BCI. Se axila +, com BCI alto, manter 10 anos.
- Duração de trastuzumabe adjuvante: Ainda 12 meses, porém, em casos de bom prognóstico, sem de-escalonamento de QT, 6 meses pode ser uma opção.
- De-escalonamento de radioterapia em pacientes idosas: Ainda não se tem uma ferramenta testada para omitir a radioterapia adjuvante. Nos casos de pacientes idosas, de bom prognóstico, a radioterapia intraoperatória com intrabeam é uma alternativa segura e com baixas taxas de eventos adversos.

Obrigado

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**Serviço de Ginecologia e Mama – HAJ/ACCG**

**Rede Brasileira de Pesquisa em Mastologia**