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# CÂNCER DE MAMA

LACOG - GBECAM 2023

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SAN ANTONIO  
BREAST CANCER  
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**cura.**

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GRUPO BRASILEIRO  
DE ESTUDOS EM CÂNCER  
DE MAMA

GERENCIAMENTO  
E PRODUÇÃO

  
**RV+**  
REPRESENTAÇÃO E GERENCIAMENTO DE MÍDIA

# Abordagem dos tumores HER2 positivos pequenos (<1 cm) e estratégias de descalonamento

**Dra Solange Moraes Sanches**

AC Camargo Cancer Center

[solange.sanches@accamargo.org.br](mailto:solange.sanches@accamargo.org.br)

@solangesanches

# Conflito de Interesses

De acordo com a Resolução do CFM no 1595/2000 e Resolução da Diretoria Colegiada da ANVISA no 96/2008, eu declaro que:

- *Apresentações científicas – Como palestrante: Pfizer, Astra Zeneca, MSD, Eli-Lilly, Novartis, Amgen, Daiichi Sankyo, Gilead*
- *Atividades de Consultoria – Como membro de Advisory Boards: Pfizer, Novartis, MSD, Amgen, Lilly, Pfizer, United Medical, Libbs, Daiichi Sankyo*
- *Declaro não ter ações em bolsa de valores das empresas supracitadas.*
- *Meus pré-requisitos para participar destas atividades são o intercâmbio científico, a autonomia do pensamento científico, independência de opinião e liberdade de expressão*

# Small HER2-positive breast cancer

T1mic

T1a

T1b

N0

- Limited evidence for treatment
- Practices vary between institutions
- Little is known regarding the added benefit of chemotherapy and HER2-directed treatments

# Distant invasive BC recurrence risk in HER-2 positive T1a and T1b node-negative localized breast cancer

- 16.975 patients ( 2000-2006)
  - 234 patients HER2 + BC - T1a/T1bN0M0
  - Median follow-up 5.8 years
    - 15 invasive recurrences
      - 47% locoregional
    - T1a/T1b patients not treated with trastuzumab or CT (171 pt)
      - 5y DRFS 98,2%
      - 99% for T1a
      - 97% for T1b
      - T1b - 1cm tumors : 24% da cohort and 75% of all recurrences
    - 5y Recurrence-free interval for 1cm T1b tumors = 84,5% (vs 97,4% for T1a)

# Trastuzumab in <1cm HER2 + BC

	n	Adjuvant trastuzumab	
Ali, 2022	91	39% (younger, 91% T1b)	RR: 3% vs 12% 5y-DFS: 94,8% vs 82,7%
Lee, 2020 (metanalysis)	1181	47%	Distant recurrence – ns Overall recurrence- OR 0.2
Hassing, 2022	605	76%	5y-IDFS= 97,4% vs 94,3% ns 5Y-OS= 97,4 vs 94,3% OS – T1b, ER-
Ramshorst, 2016	T1a=385 T1b=800 T1c=2327	92%	8y OS= 95 vs 84%

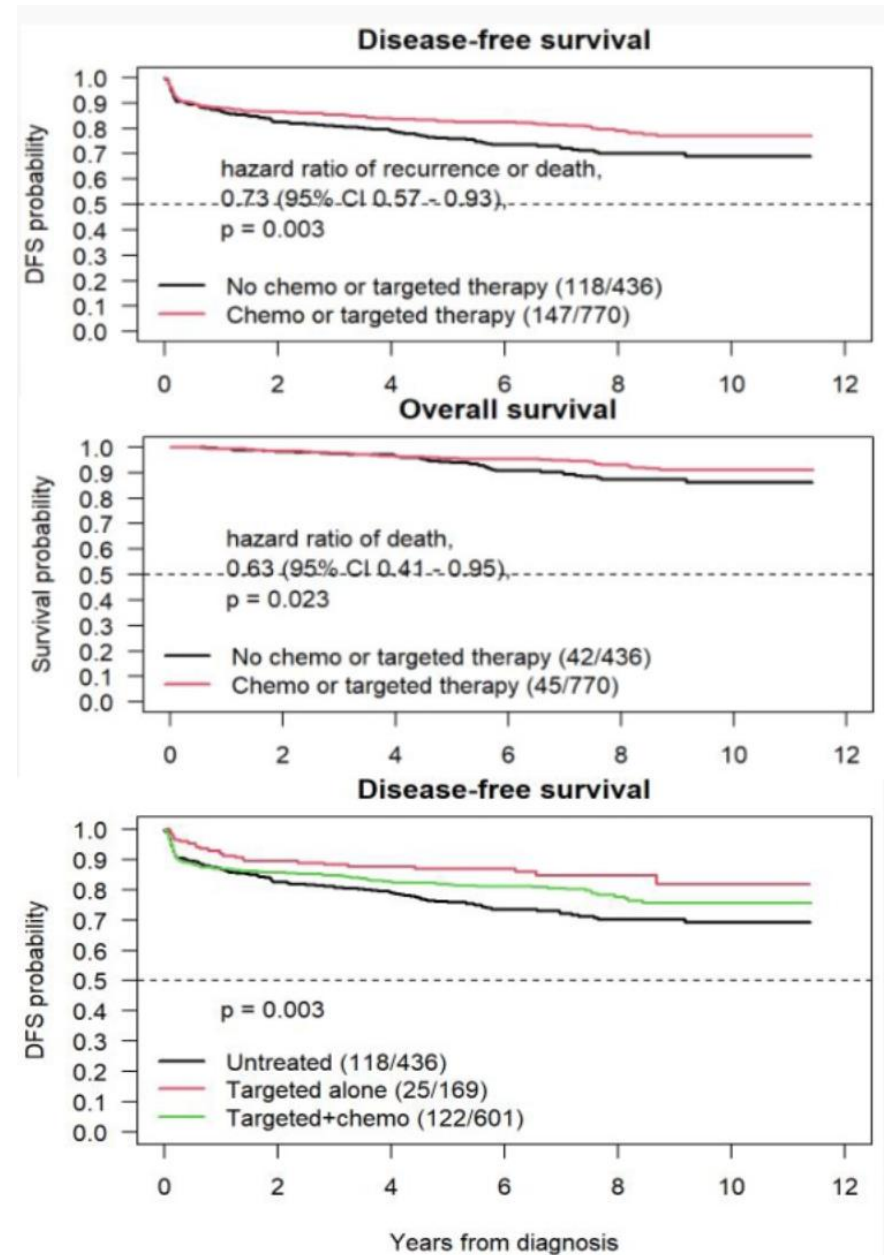
The survival benefit of anti-HER2 treatment in the management of small (T1mic, T1a, T1b, T1c), node-negative HER2+ breast cancer.

- Retrospective analysis (ASCO CancerLinq DataBase)
- 1206 patients – 2020-2021
  - 779 trastuzumab +/- CT

60% of treated pt - T1c

	Untreated (n=436)	Anti-HER2 monotherapy (n=169)	Anti-HER2 + chemotherapy (n=601)
Median age	62.9 [25.9-95.4]	59.1 [26.8-85.2]	58.8 [18.9-84.9]
Female sex	433 (99.3%)	169 (100%)	599 (99.7%)
Grade 1	73 (16.7%)	9 (5.3%)	47 (7.8%)
Grade 2	196 (45.0%)	73 (43.2%)	228 (37.9%)
Grade 3	154 (35.3%)	82 (48.5%)	306 (50.9%)
HR+ status	259 (59.4%)	83 (49.1%)	320 (53.2%)
T1mic	12 (2.8%)	2 (1.2%)	0 (0%)
T1a	98 (22.5%)	41 (24.3%)	67 (11.1%)
T1b	135 (31.0%)	33 (19.5%)	160 (26.6%)
T1c	178 (40.8%)	87 (51.5%)	365 (60.7%)
IDC	281 (64.4%)	103 (60.9%)	360 (59.9%)
ILC	129 (29.6%)	55 (32.5%)	214 (35.6%)
Mean # cycles anti-HER2	N/A	12.7 (4.6)	13.4 (4.9)

- Univariate analysis
  - iDFS (HR 0,73 p=0,01)
  - OS ( HR 0,62, p=0,029)
- Multivariate analysis (irrespective of tumor size)
  - iDFS (HR 0,75, p=0,030)
  - OS (HR 0,61 p=0,029)
- Three-arm analysis
  - iDFS ( p=0,003)
  - OS (p= 0,061)



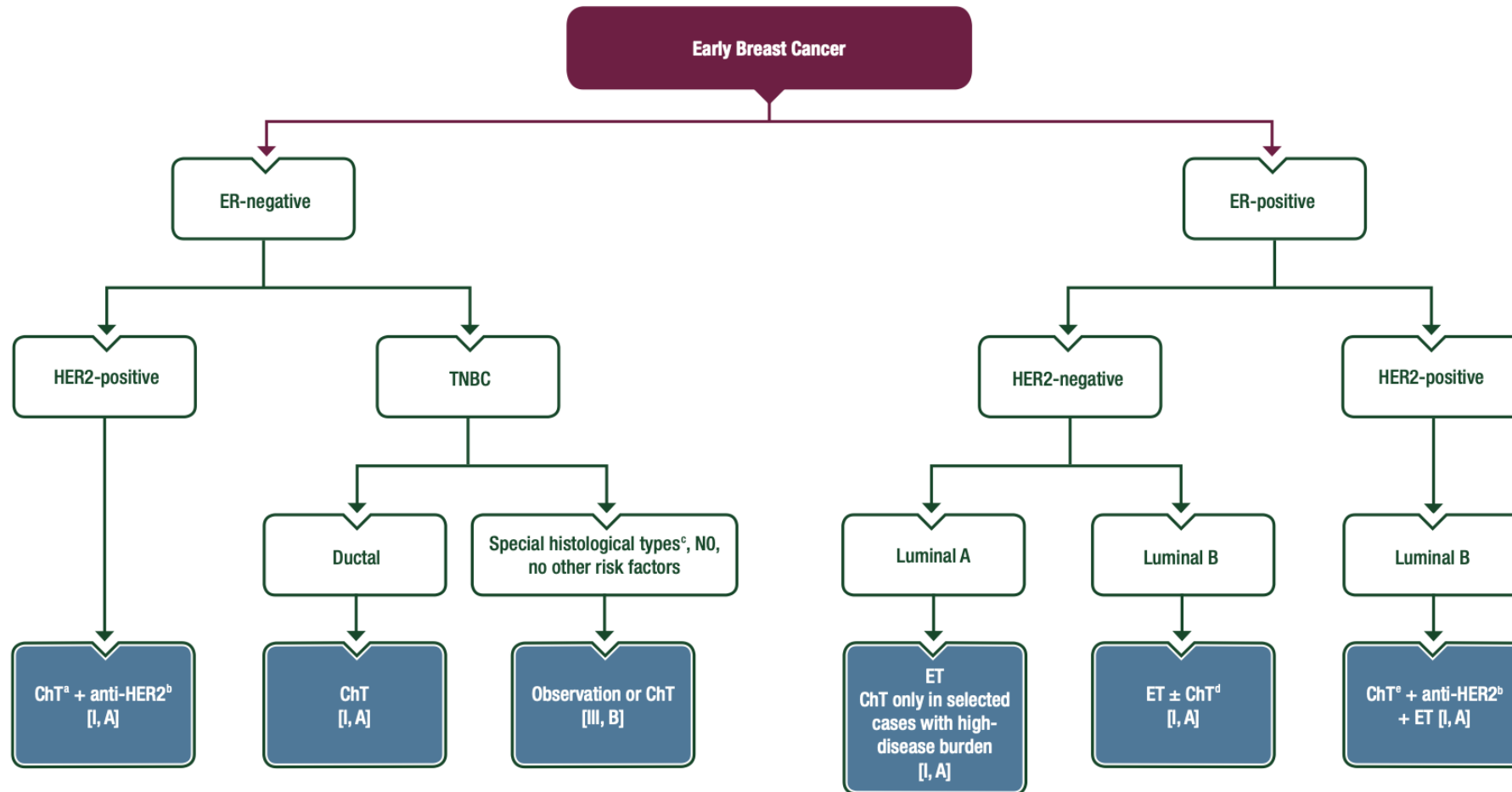
Similar iDFS with T +/-CT



# Consistently low distant recurrence rate in T1a/b N0 HER2+BC

Prognosis of pT1a-b pN0, HER2-positive breast cancer.

Reference	Sample size (No of patients)	pT1a-b pN0 (No of patients)	Median follow-up	Outcome of pT1a-b pN0 breast cancer
Joensuu et al. (2003)	852 <sup>a</sup>	313	9.5 years	<b>9-year DDFS (%)</b> 92% HER2-ve vs 67% HER2+ve (p = 0.003)
Amar et al. (2010)	421	421	2.8 years	<b>Mortality rate (%)</b> 6.4% HER2-ve vs 0% HER2+ve vs 7.1% TN
Livi et al. (2012)	704	704	4.9 years	<b>Recurrence incidence rate</b> 1.1% HER2-ve vs 7.1% HER2+ve vs 10.7% TN
Curigliano et al. (2009)	2130	2130	4.6 years	<b>RFS (%)</b> 90.3% HER2+ve vs 94% HER2-ve (p = 0.12)
Gonzalez-Angulo et al. (2009)	965	965	6.2 years	<b>DRFS (%)</b> 92% HER2+ve vs 96.9% HER2-ve (p = 0.045)
Chia et al. (2008)	2026 <sup>b</sup>	326	12.4 years	<b>5-year DFS rate (%)</b> pT1a HRs+ve: 97% HER2-ve vs 88% HER2+ve pT1a HRs-ve: 87% HER2-ve vs 93% HER2+ve pT1b HRs+ve: 99% HER2-ve vs 95% HER2+ve pT1b HRs-ve: 94% HER2-ve vs 85% HER2+ve
Vaz-Luis et al. (2014)	4113	4113	5.5 years	<b>5-year RFS rate (%)</b> 77.1% HER2+ve vs 93.7% HER2-ve (p < 0.001)
Fehrenbacher et al. (2014)	234	234	5.8 years	<b>5-year DRFS rate (%)</b> 86.4% HER2+ve vs 97.2% HER2-ve (p < 0.001)
				<b>10-years BCSS rate (%)</b> 93.3% HER2+ve vs 94% HER2-ve (p < 0.80)
				<b>10-years RFS rate for pT1b (%)</b> 68.4% HER2+ve vs 81.8% HER2-ve (p = 0.312)
				<b>5-year DRFS rate (%)</b> pT1a HR+ve: 98% HER2-ve vs 96% HER2+ve pT1a HR-ve: 93% HER2-ve vs 93% HER2+ve pT1b HR+ve: 96% HER2-ve vs 94% HER2+ve pT1b HR-ve: 90% HER2-ve vs 90% HER2+ve
				<b>5-year DRFI (%)</b> pT1a: 99% pT1b < 1 cm: 100% pT1b = 1 cm: 93.3% 98.1% HRs+ve vs 98.4% HRs-ve



**Figure 2.** (Neo)-adjuvant systemic treatment choice by marker expression and intrinsic phenotype.

<sup>a</sup>With possible exception of selected cases with very low risk T1abN0.

<sup>b</sup>Anti-HER2: trastuzumab ± pertuzumab.

<sup>c</sup>Adenoid cystic or apocrine, secretory carcinoma, low-grade metaplastic carcinoma.

<sup>d</sup>Depending on level of ER and PgR expression, proliferation, genomically assessed risk, tumour burden and/or patient preference.

<sup>e</sup>Except for very low-risk patients T1abN0 for whom ET/anti-HER2 therapy alone can be considered.

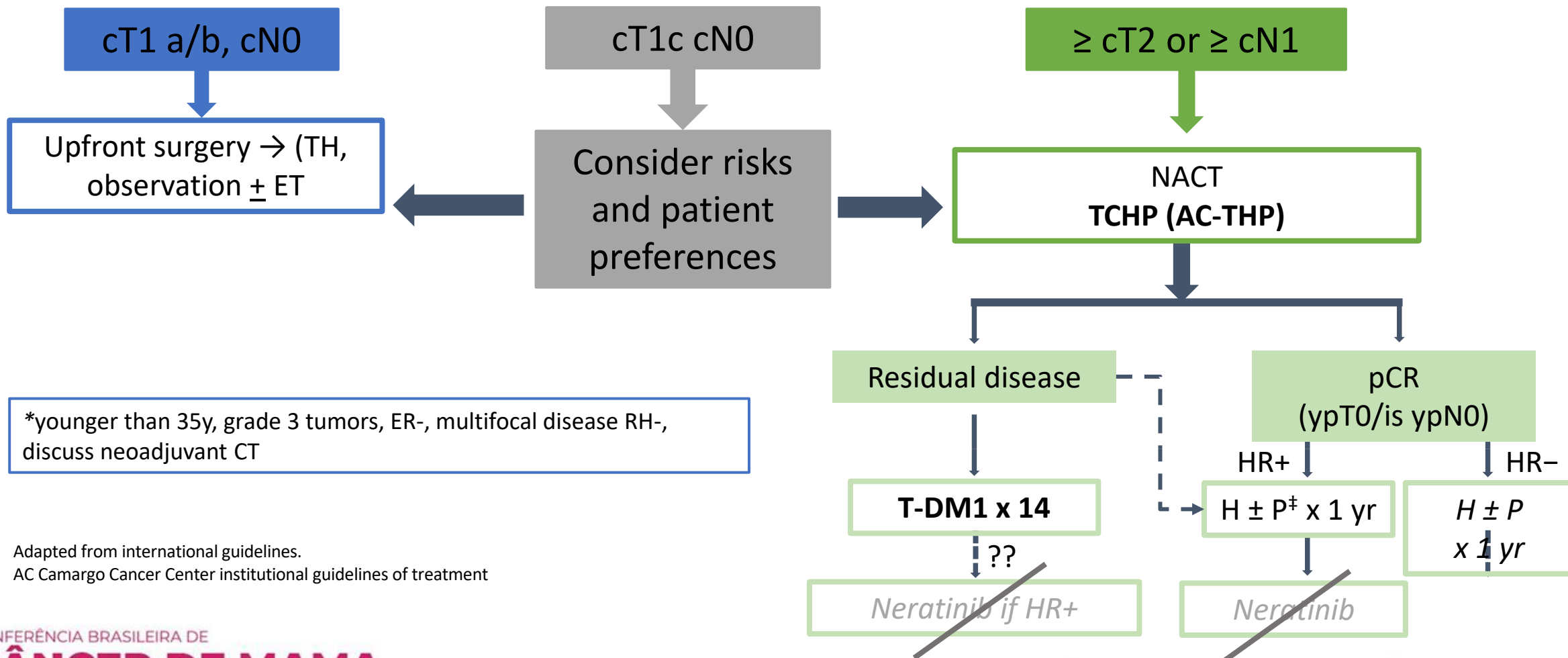
ChT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; N0, node-negative; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

# Retrospective data is the driver for treatment decisions

**High risk T1b and T1c = benefit of systemic treatment  
CT+ HER2 blockage vs toxicity**

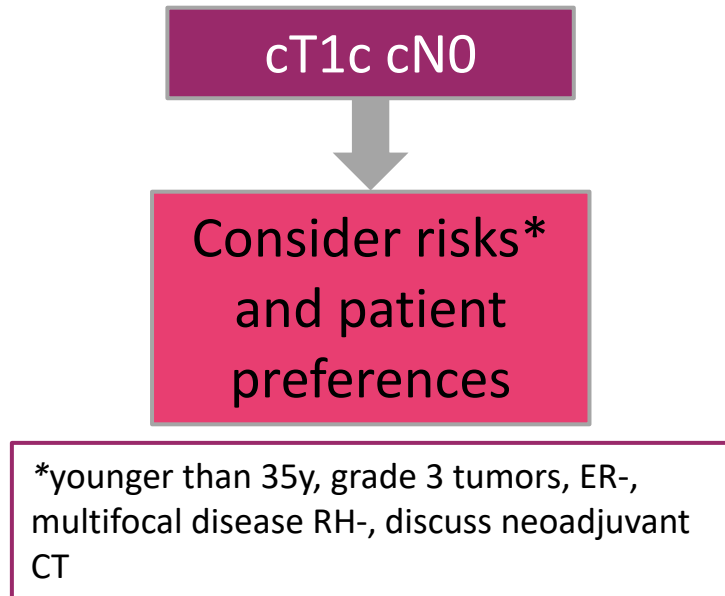
**T1mic and T1a = controversial, limited evidence of  
benefit, major risk of overtreatment**

# Management of HER2 + BC , clinical stages I-III



Adapted from international guidelines.  
AC Camargo Cancer Center institutional guidelines of treatment

# Neoadjuvant treatment for T1cN0 HER2+ BC



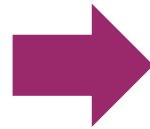
- There is uncertainty with regard to patients with T1c N0 disease, as these patients **were included in both the APT de-escalation trial and the KATHERINE trial.**
- Depending on the clinical circumstances, these patients could be considered for neoadjuvant chemotherapy.
  - there may be **additional benefit from T-DM1 if patients do not have a pCR** (3y IDFS of 81% in T group and lack of events in TDM1 group suggest suficiente risk to consider TDM1- 77 pt EC I, 6 recurrences, all in T arm);
  - however, there is a **risk of overtreatment based on the results of APT.**

# De-escalation strategies in HER2+ BC

Clinical Stage (stage I)/  
Age Approach (>70y)

Clinical Response Approach : pCR

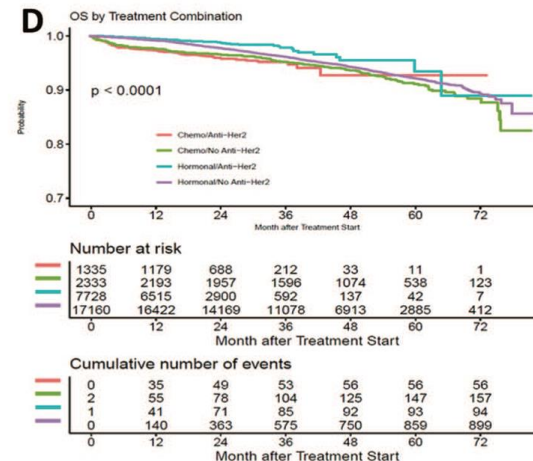
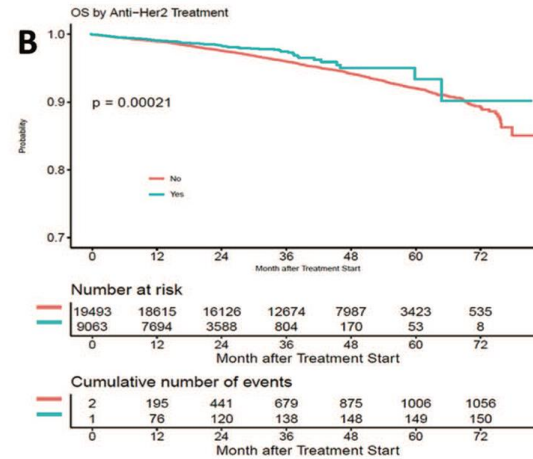
Molecular Approach: molecular  
determinants of response and resistance



- Duration of adjuvant trastuzumab
- De-escalating intensity of systemic therapy

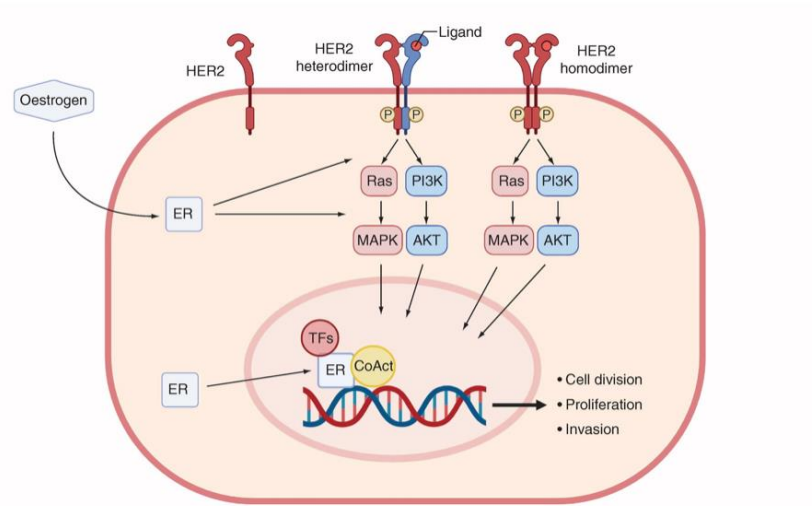
# Endocrine Therapy Plus Anti-HER2 Therapy as Adjuvant Systemic Therapy for Luminal HER2-Positive Breast Cancer: An Analysis of the National Cancer Database

- Retrospective analysis
- 37.777 stage I HER2+ BC
  - 86% ET
  - 14% CT
- 40% trastuzumab
- Do not specify tumor size



better OS with ET+T

# Crosstalk between ER and HER2 signalling



**Figure 2. Crosstalk between estrogen receptor and HER2 signaling.**

In the presence of estrogen, ER, which resides in both the cytoplasm and nucleus of a breast epithelial cell, can activate HER dimers and their downstream pathways (MAPK and AKT). In addition to the effects of these pathways, this signaling can lead to modulation of active nuclear ER, which interacts with other TFs and CoActs to regulate the expression of genes regulating processes essential to cell survival and cancer progression.

ER: Estrogen receptor; CoActs: Co-activators; TFs: Transcription factors.

HR+/HER2+ tumors often respond initially to hormone therapy and/or HER2-targeted therapy but develop resistance over time.

One reason may be the known crosstalk between the ER and HER2 signaling pathways and the involvement of other downstream pathways, such as PI3K and MAPK.

A study of HER2+ cell lines showed an increase in ER or its downstream signaling targets following treatment with lapatinib and trastuzumab, indicating ER signaling as a survival mechanism for HER2+ cells.

Upregulation of ER signaling is also evident in HER2+ tumors treated with trastuzumab, pertuzumab and lapatinib.

Kay et al, 2021



# Looking for Biomarkers of Response in Crosstalk between ER and HER2 signalling : **IL6ST**

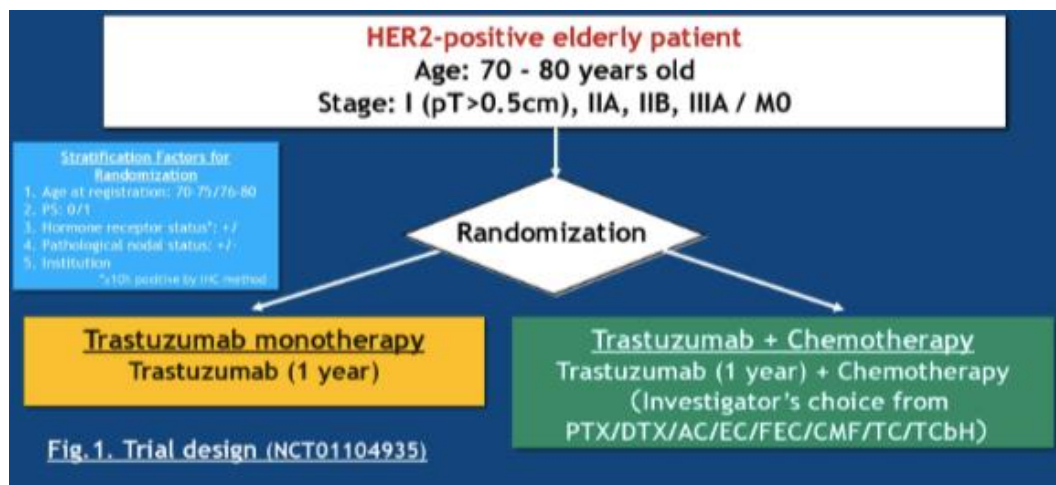
IL6ST, a surrogate for endocrine therapy response, may also be a **useful biomarker for ER+/HER2+ breast cancer.**

**Higher levels of IL6ST → active ER signaling and predictive of clinical response to neoadjuvant letrozole in ER+/HER2+ tumors .**

**Lower levels of IL6ST → lack of response to endocrine therapy and more active HER2 signaling.**

Turnbull et al, SABCS 2020

# Evaluation of Trastuzumab without Chemotherapy as a Postoperative Adjuvant Therapy in HER2-Positive Elderly Breast Cancer Patients: Randomized Controlled Trial (RESPECT)



275 patients  
(2009-2014)

Characteristic		H group (n=135) n (%)	H+CT group (n=131) n (%)	p value
Age	Mean (SD)	73.9 (2.8)	73.9 (3.0)	0.79
PS	0	126 (93.3)	121 (92.4)	0.76
	1	9 (6.7)	10 (7.6)	
Pathological Tumor Size	T1b	10 (7.4)	11 (8.4)	0.57
	T1c	55 (40.7)	54 (41.2)	
	T2	64 (47.4)	64 (48.9)	
Lymph node metastasis	Negative	106 (78.5)	97 (74.0)	0.39
	Positive	29 (21.5)	34 (26.0)	
Stage	I	58 (43.0)	58 (44.3)	0.80
	IIA	56 (41.5)	55 (42.0)	
	IIB	20 (14.8)	16 (12.2)	
	IIIA	1 (0.7)	2 (1.5)	
Surgery	Mastectomy	97 (71.9)	87 (66.4)	0.20
	Partial mastectomy	36 (26.7)	44 (33.6)	
	Others	2 (1.5)	0	
Hormone Receptor status	ER (-) and/or PgR (-)	62 (45.9)	65 (49.6)	0.55
	ER (+) and PgR (+)	73 (54.1)	66 (50.4)	
Major Comorbidity	Hypertension			0.83
	Absent	76 (56.3)	72 (55.0)	
Diabetes	Present	59 (43.7)	59 (45.0)	0.52
	Absent	119 (88.1)	112 (85.5)	
Osteoporosis	Present	16 (11.9)	19 (14.5)	0.13
	Absent	117 (86.7)	121 (92.4)	
Hypertlipidemia	Present	18 (13.3)	10 (7.6)	0.67
	Absent	101 (74.8)	95 (72.5)	
	Present	34 (25.2)	36 (27.5)	

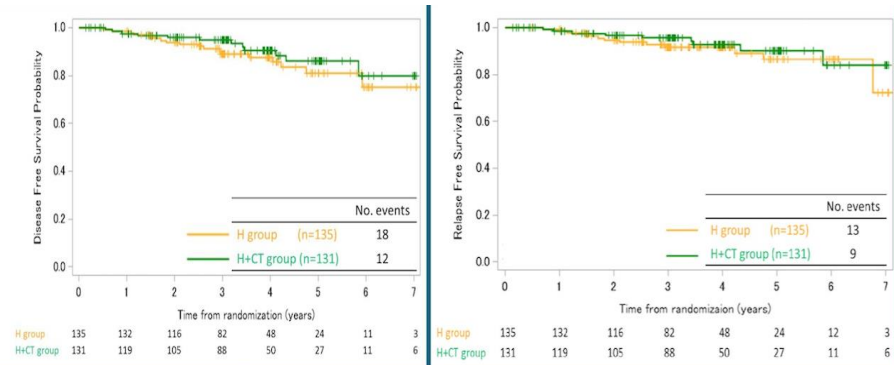
84,5% EC I-IIA

~ 50% RH+

# Trastuzumab monotherapy as an option for adjuvant therapy in elderly

**Note: early tumors, ~50% RH+ , PS 0/1, short follow-up**

**FUP= 3 years**  
**DFS = 89,2% vs 94,8%**



average time-to-event over a fixed follow-up period

**RMST (restricted mean survival time)**  
**3 years = 0,45m**  
**RFS= 91,7% vs 95,6%**

**Fig. 2A. DFS (n=266)**  
 DFS at 3 yrs was 94.8% in H+CT group vs 89.2% in H group (HR=1.42; 95% CI, 0.68 to 2.95, P=0.35). The difference in RMST between arms at 3 years was -0.45 months (95% CI, -1.71 to 0.80).

**Fig. 2B. RFS (n=266)**  
 RFS at 3 yrs was 95.6% (9 events with 4 deaths) in H+CT group vs 91.7% (13 events with 5 deaths) in H group. The difference in RMST between arms at 3 years was -0.41 months (95% CI, -1.51 to 0.68).

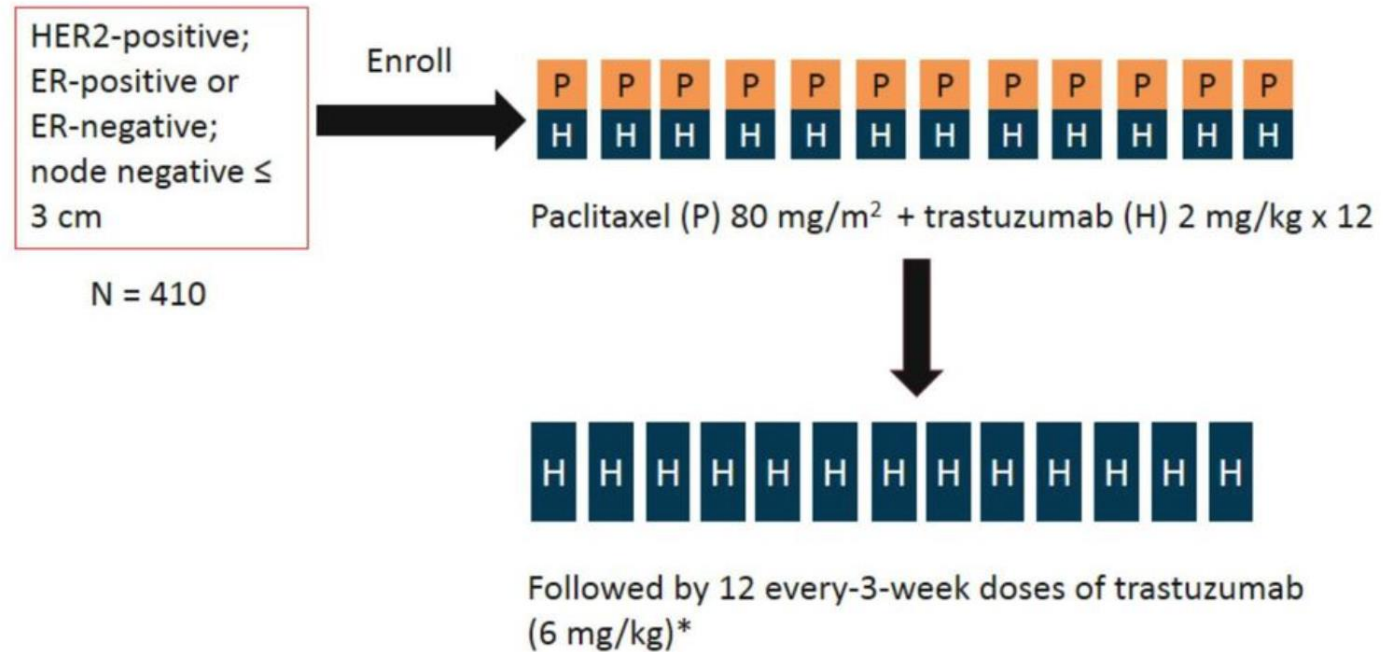


**Fig. 3. The total score of FACT-G**  
 Compared with the score at baseline, 5 point or more increase (decrease) are defined as A) clinically meaningful HRQOL improvement and B) deterioration.

**Less toxicity**  
**Better QoL**

- APT trial

- 2007-2010
- Phase II
- 410 patients



\*Patients received paclitaxel (80 mg/m<sup>2</sup>) with trastuzumab x 12 weekly, followed by trastuzumab (weekly or every 3 weeks) x 39 weeks

Tolaney SM, et al. ASCO 2017. Abstract 511.

# APT trial - 3y, 7y and 10y analysis

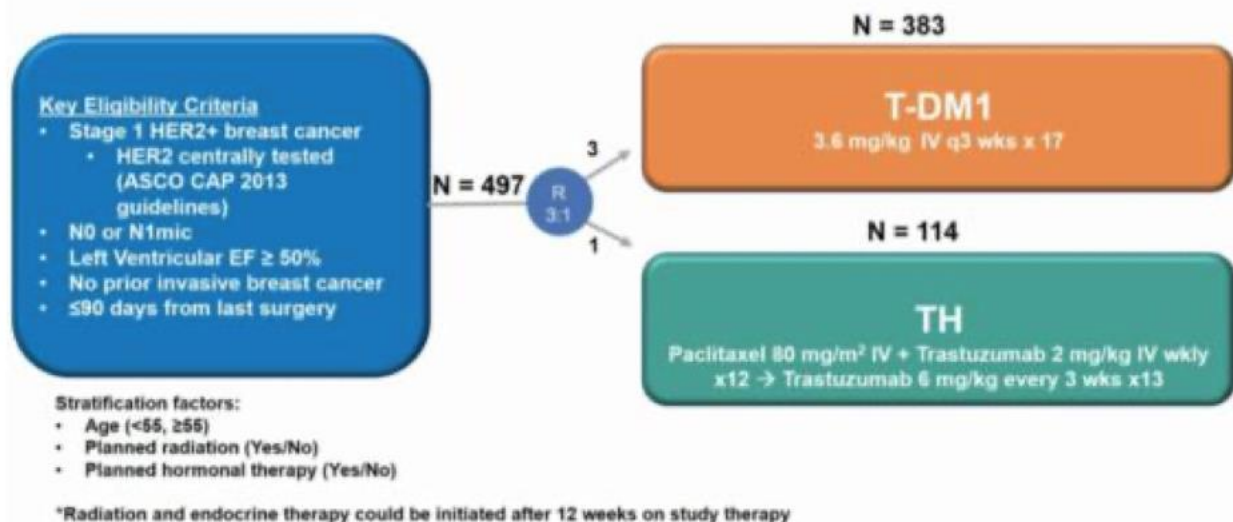
TNM stage	
T stage	
T1mi	10 (2.5%)
T1a	68 (16.7%)
T1b	123 (30.3%)
T1c	169 (41.6%)
T2	36 (8.9%)
N stage	
N0	400 (98.5%)
N1mi	6 (1.5%)
Hormone receptor status	
Positive	272 (67.0%)
Negative	134 (33.0%)
Premenopausal	
Yes	76 (18.7%)
No	330 (81.3%)

	Disease-free survival, %	95% confidence interval	P value
3-year <sup>[a]</sup>	98.7	97.6, 99.8	< .0001
7-year HR-positive <sup>[b]</sup>	94.6	91.8, 97.5	
7-year HR-negative <sup>[b]</sup>	90.7	84.6, 97.2	

10-year IDFS	91.3%	88.3, 94.4
10-year RFI	96.3%	94.3, 98.3
10-year OS	94.3%	91.8, 98.8
10-year BCSS	98.8%	97.6, 100

Tolaney et al, 2022

# ATEMPT trial - TDM 1 as an alternative for selected patients with stage I HER2+ BC



	T-DM1 (n = 383)	TH (n = 114)	All Patients (n = 497)
<b>Median Age (Range)</b>	56 (32-85)	55 (23-82)	56 (23-85)
<b>Tumor Size</b>			
<0.5 cm	42 (11%)	14 (12%)	56 (11%)
$\geq$ 0.5-1.0 cm	121 (32%)	38 (33%)	159 (32%)
$\geq$ 1.0-1.5 cm	118 (31%)	29 (25%)	147 (30%)
$\geq$ 1.5-2.0 cm	102 (27%)	33 (29%)	135 (27%)
<b>Histologic Grade</b>			
Well Differentiated	11 (3%)	4 (4%)	15 (3%)
Moderately Differentiated	148 (39%)	46 (40%)	194 (39%)
Poorly Differentiated	219 (57%)	62 (54%)	281 (57%)
Unknown	5 (1%)	2 (2%)	7 (2%)
<b>HR status</b>			
Positive	289 (75%)	84 (74%)	373 (75%)
Negative	94 (25%)	30 (26%)	124 (25%)
<b>HER2 Status (Central)</b>			
1+	5 (1%)	1 (1%)	6 (1%)
2+	92 (24%)	25 (22%)	117 (24%)
3+	277 (72%)	87 (76%)	364 (73%)
Not done*	9 (2%)	1 (1%)	10 (2%)

- 3y-DFS TDM1= 97,7%, with only 2 distant recurrences
  - CRTs were experienced by 46% of patients on T-DM1 and 47% of patients on TH ( $P = .83$ )
  - 17% discontinued therapy due to toxicity ( vs 6% in APT regimen arm)
  - Less neuropathy, less neutropenia, alopecia and fewer infusional reactions
  - More thrombocytopenia, transaminase and bilirubin increases

# Shortening duration of trastuzumab therapy

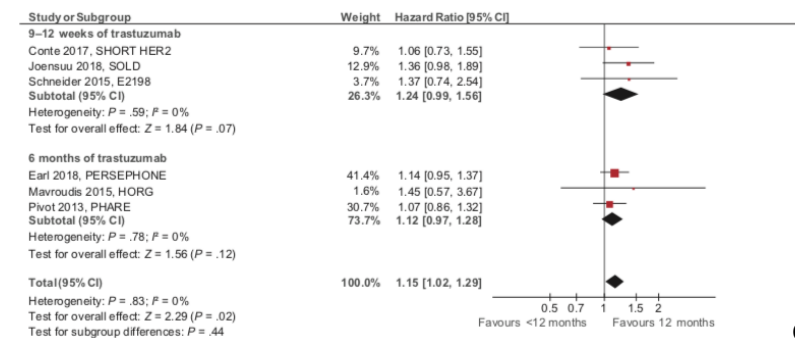
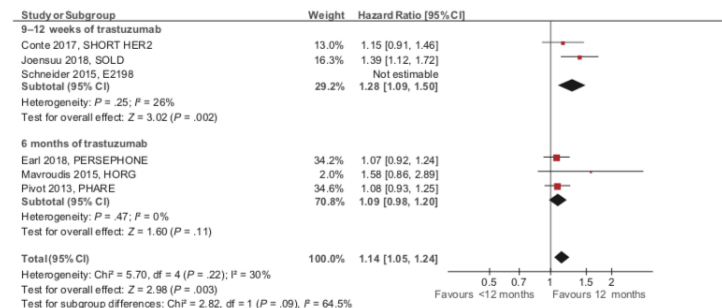
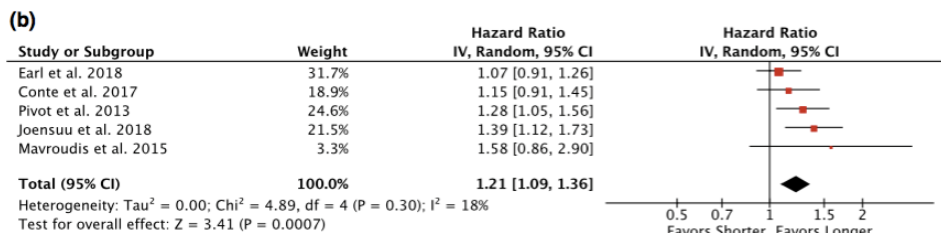
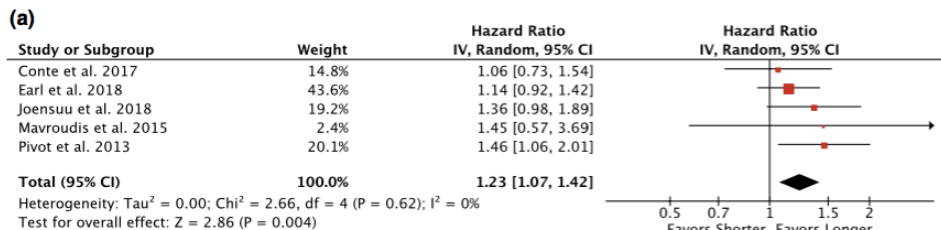
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# HERA trial: defined trastuzumab 1 year as “gold standard” therapy

## Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials

### META-ANALYSIS

## Deescalating Adjuvant Trastuzumab in HER2-Positive Early-Stage Breast Cancer: A Systemic Review and Meta-Analysis



PERSEPHONE, HORG, PHARE, SHORT HER, SOLD

Niraula et al, 2018

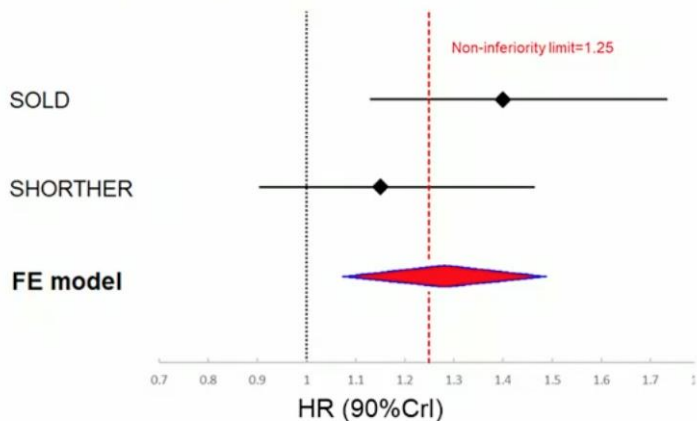
Goldvaser et al, 2019



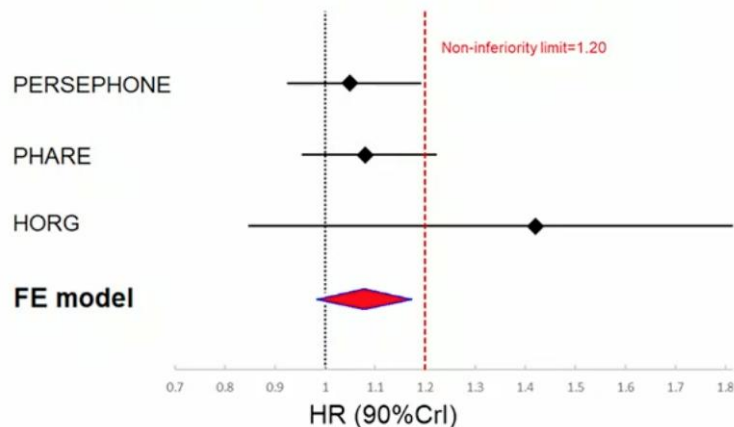
# LBA11 - Individual patient data meta-analysis of 5 non-inferiority RCTs of reduced duration single agent adjuvant trastuzumab in the treatment of HER2 positive early breast cancer

IPD, non inferior statistics

**12 Months vs. 9 Weeks**  
 5-year IDFS rates 91.40% and 89.22%  
 HR 1.27, non-inferiority p=0.56.



**12 vs. 6 Months:**  
 5-year IDFS rates 89.26% and 88.56%  
 HR 1.07, non-inferiority p=0.02.



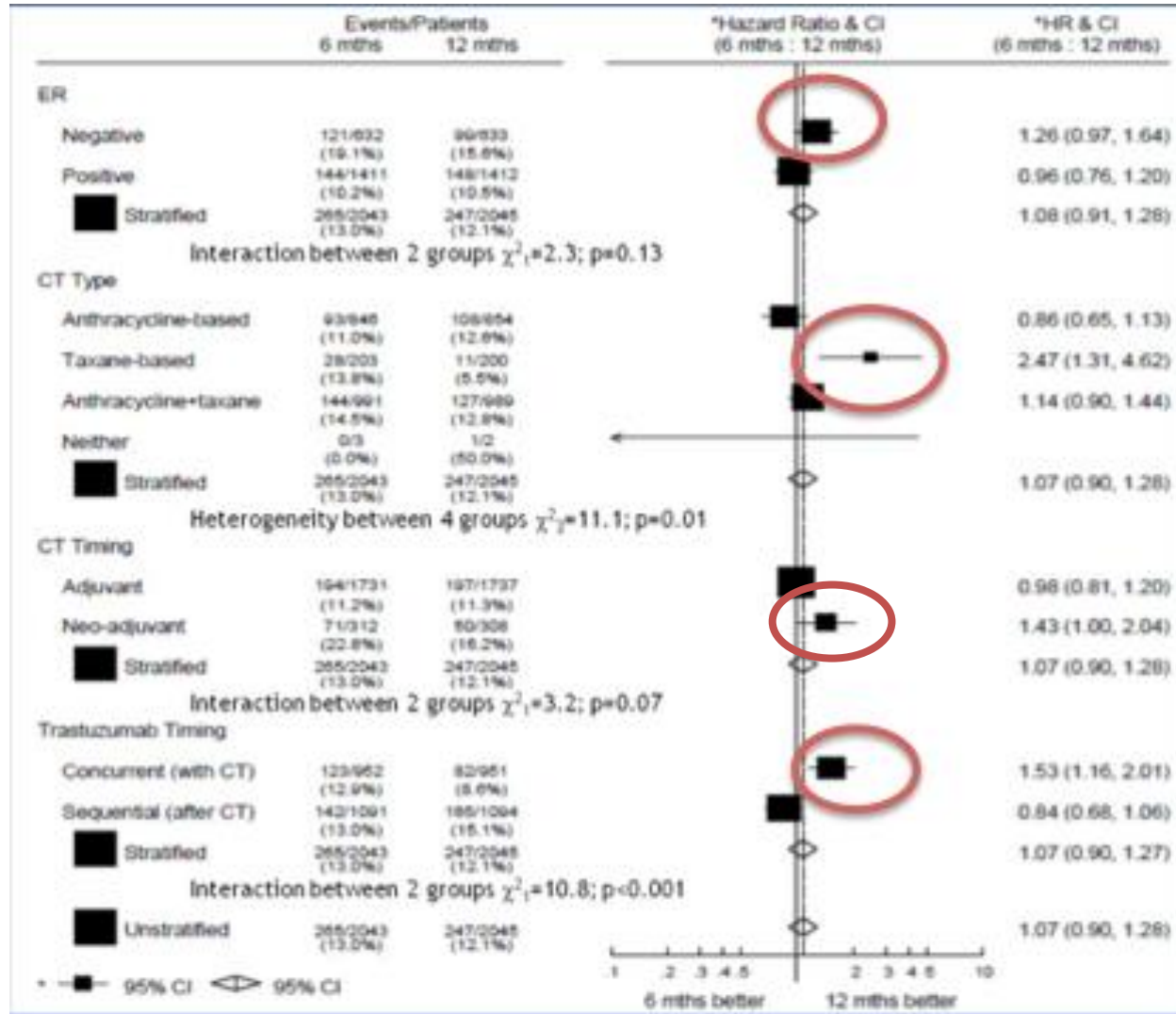
IDFS benefit 6-12m= 0,8%

## Similar Patient Characteristics

Nodal Status	N0
PHARE	55%
PERSEPHONE	59%
Tumor Size	<2 cm
PHARE	45%
PERSEPHONE	47%

Earl et al, ESMO 2021

# PERSEPHONE- Subgroups analysis – is 6 months equal to 12 months in all subgroups?



ER negative

Taxane-based CT  
( high and low risks)

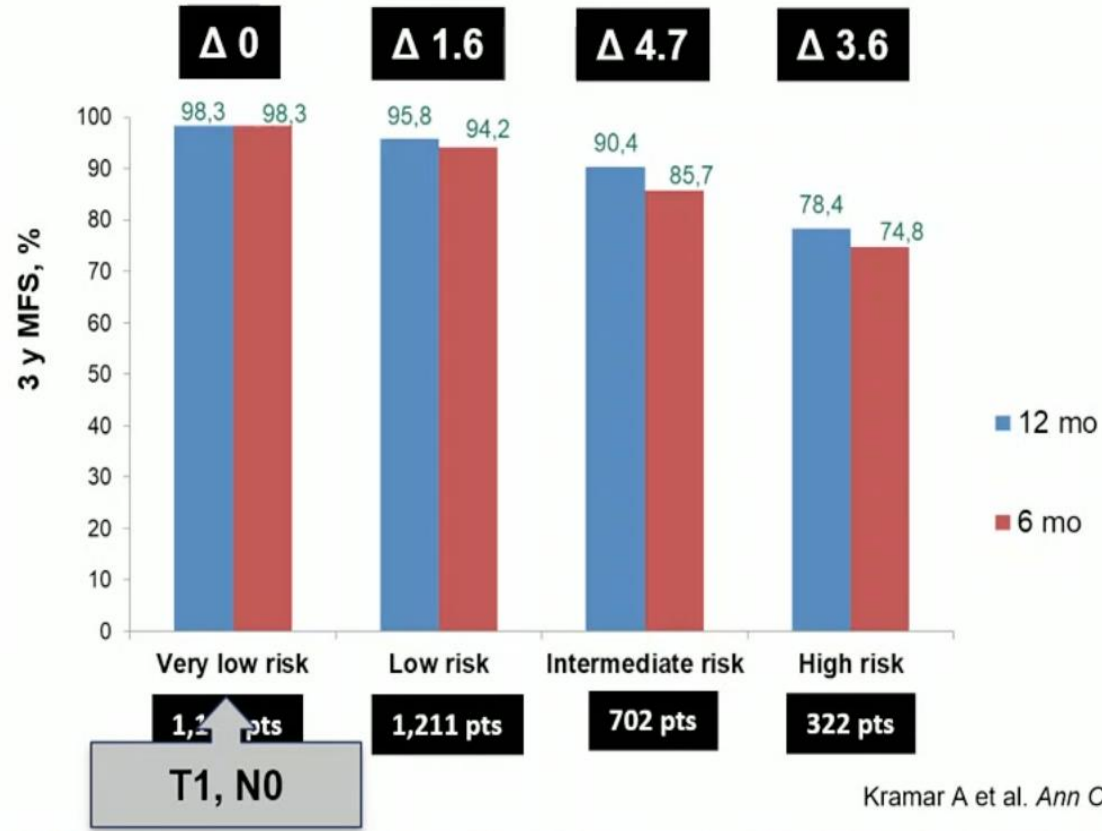
NACT  
(frequent)

Concurrent Trastuzumab  
(standard)

PHARE Study Benefit ratio  
by Risk Factors

Risk Factors:  
N 0; N 1-3; N > 4;  
T < 2 vs > 2cm

Very Low Risk = 0  
Low Risk = 1  
Intermediate Risk = 2  
High Risk = 3



Kramar A et al. *Ann Oncol.* 2014.

# De-escalating treatment intensity in neoadjuvant setting

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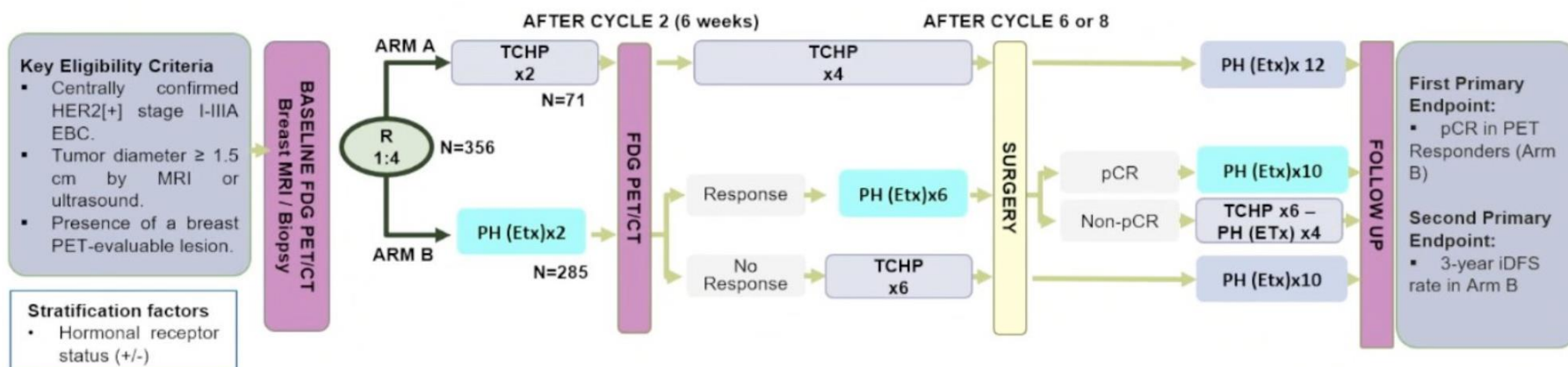
# Examples of de-escalation therapy in NACT - HER2+ BC

- **TRYPHAENA** (phase 2)
  - TCHP ( non- anthracycline CT) had similar results of FEC-THP
  - TCHP safer in terms of cardiotoxicity
- **TRAIN2** (phase 3)
  - Solidified non- anthracycline CT in NACT

# PHERGain Trial

## Adjustment of therapy based on early PET-CT response during NACT

Could be able to identify patients who will develop a pCR to dual HER2 blockade alone, potentially allowing them to avoid CT. Results on IDFS awaited.



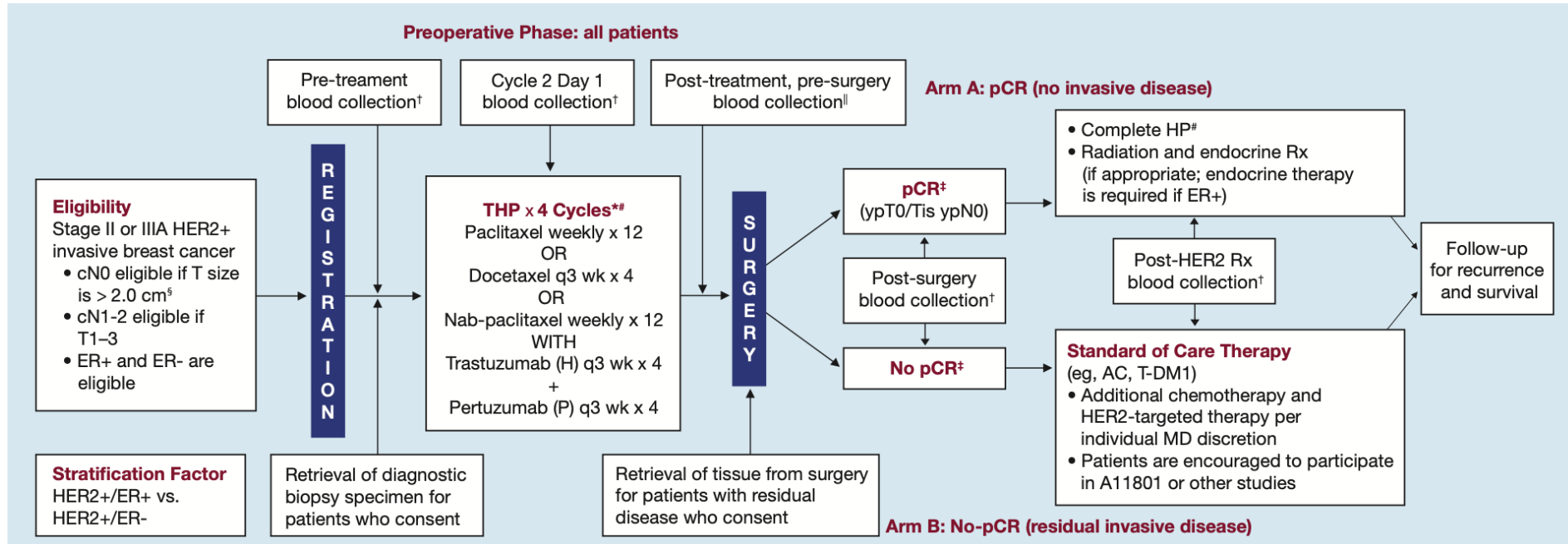
227 (80%) of 285 patients in group B were  $^{18}\text{F}$ -FDG-PET responders, of whom 86 (37.9%, 95% CI 31.6–44.5;  $p < 0.0001$  compared with the historical rate) of 227 had a pathological complete response.

Perez-Garcia et al, 2021

# De-escalating treatment upon clinical response after NACT

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# EA 1181/COMPASSHER2-pCR (COMprehensive use of Pathologic response ASSESSment to optimize therapy in HER2 positive breast cancer



Determine if 3-year recurrence-free survival (RFS) is greater than 92% among clinical stages II or IIIa (AJCC, 8th ed.) with HER2+/ER+, or HER2+/ER- breast cancer who achieve pCR (ypT0/is ypN0) after preoperative therapy with 12 weeks of THP



# DECRESCENDO Trial

**Patients (N=1065)**

HER2-positive HR-negative invasive non-metastatic BC

Tumor size:  $\geq 15\text{mm}$  and  $\leq 50\text{mm}$

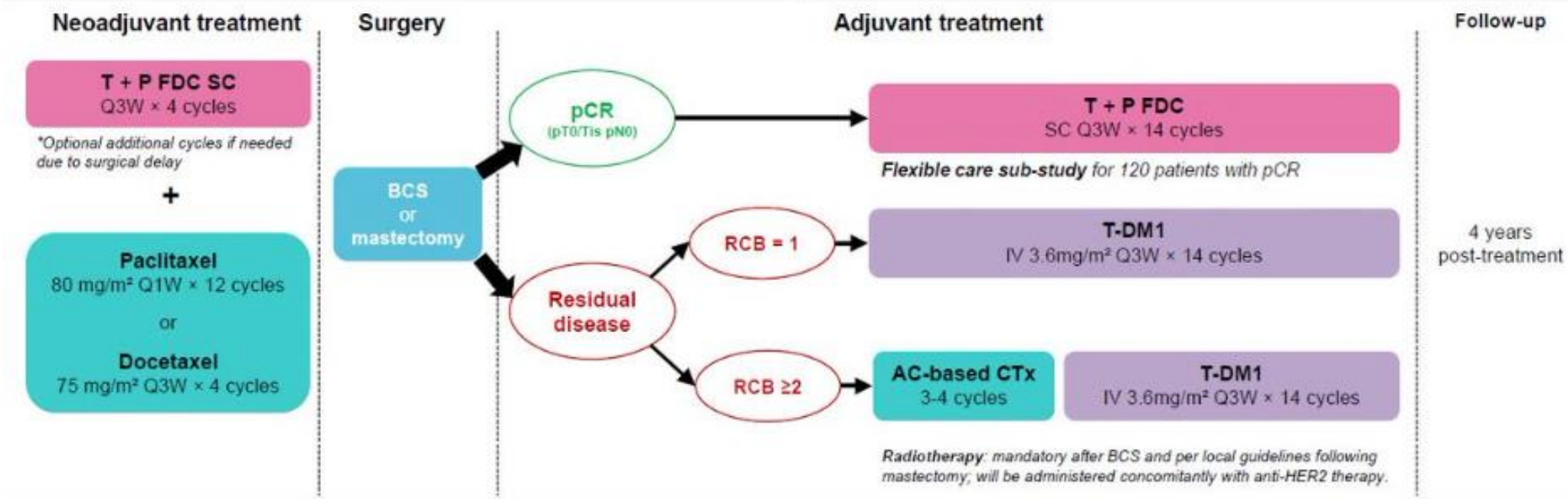
Nodal status: negative (N0)

**1° endpoint**

3-year RFS in 500 patients with pCR, HER2-enriched intrinsic subtype

**Key 2° endpoint (hierarchical testing)**

3-year RFS in all patients with pCR



## Are some HER2+ BC so dependent upon HER2 signalling that cure can be effected without chemotherapy?

- **Neosphere** – trastuzumab + pertuzumab arm – **pCR= 17%**
- **TBCRC 006** – lapatinib + trastuzumab – **pCR= 27% (21% in HR+/36% in HR-)**
- **PAMELA** – lapatinib+trastuzumab- **pCR= 31% (18% in HR+/ 33% in HR-)**
- **WSG-ADAPT** – trastuzumab+pertuzumab (\*plus ET in HR+)- **pCR= 36% (HR-),** 5y-OS 92% and **pCR= 24% (HR+)** - \* more recente data (ESMO2021) shows predictive impact of ESR1 and CD8 in IDFS

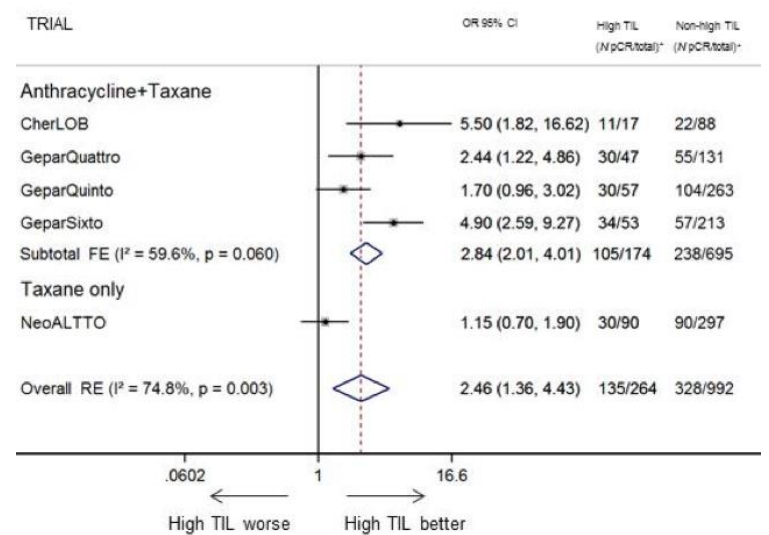
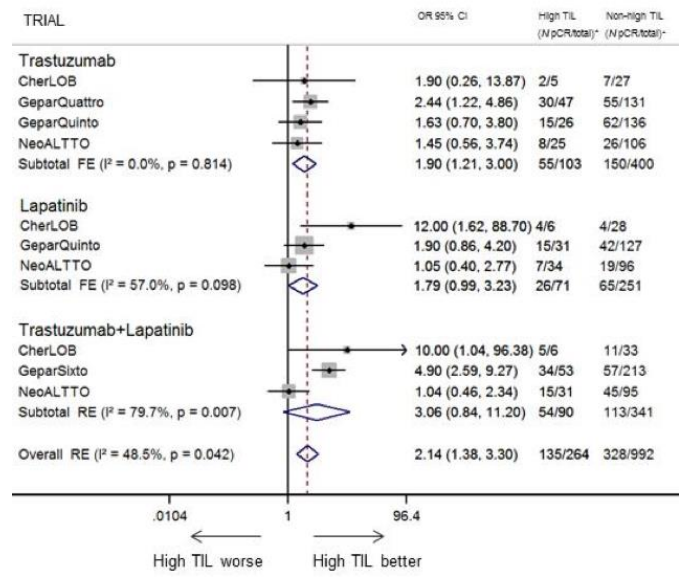
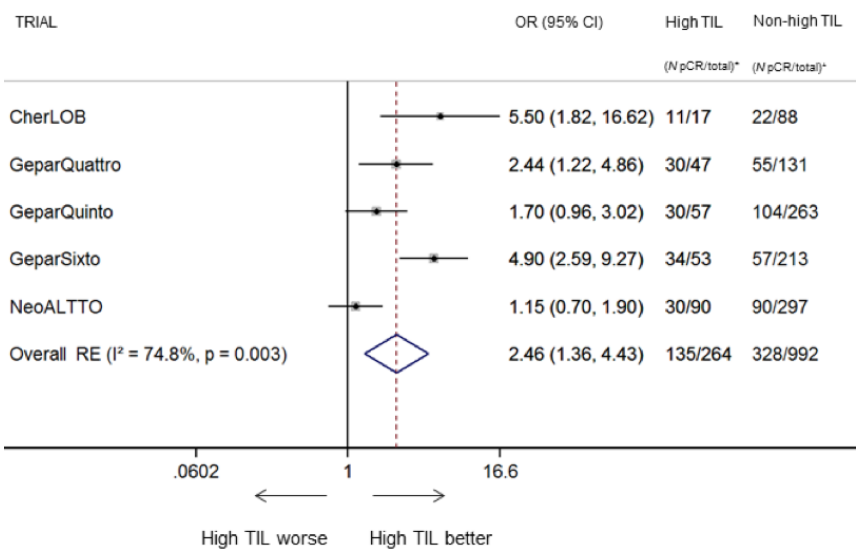
Does pCR obtained in these circumstances carry the same excellent prognosis as when obtained with more aggressive treatment?

# Tailoring treatment based on RNA profiling and TILs?

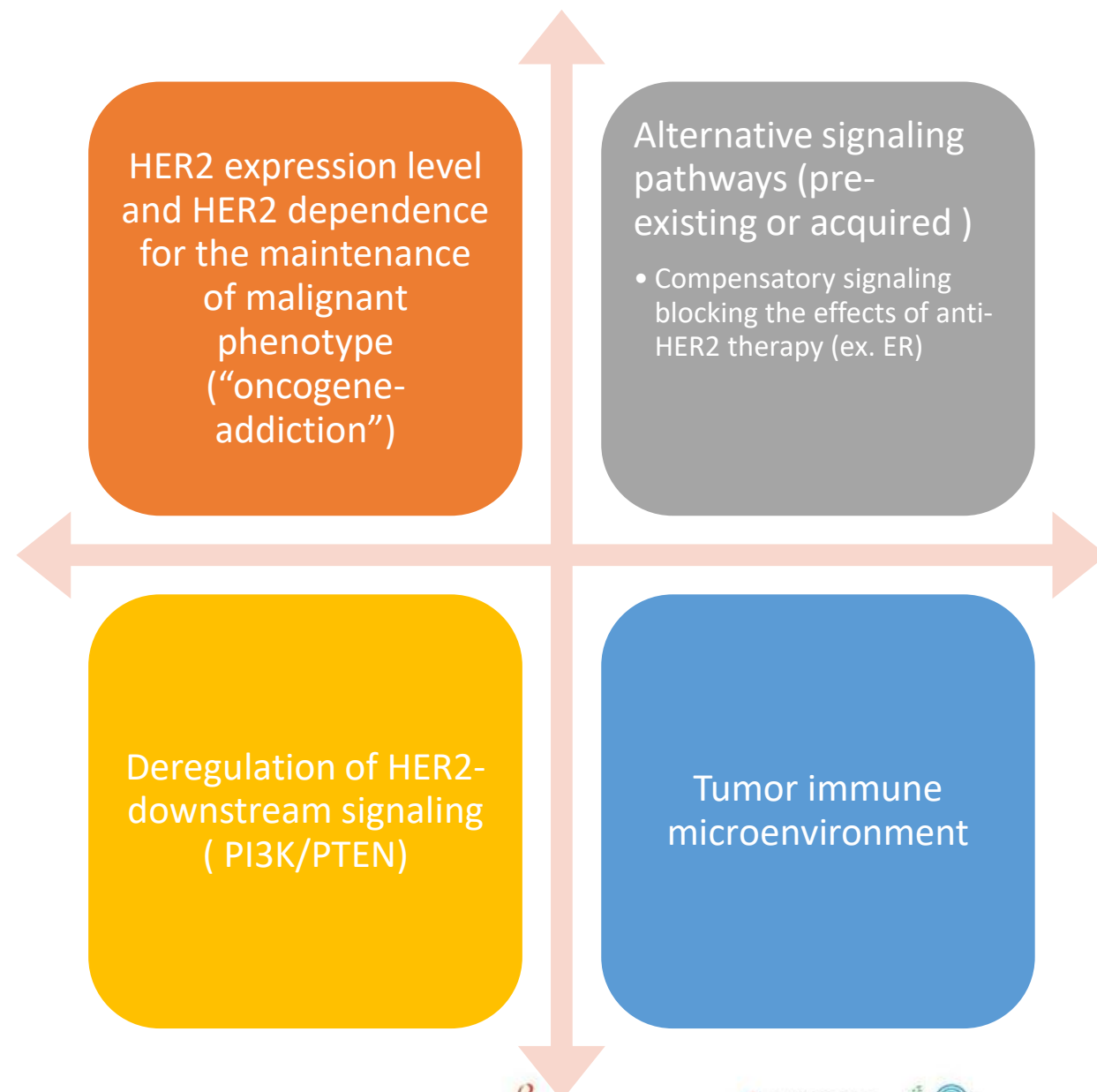
CALGB40601  
NOAH  
NSABP-B41 NeoALTO



pCR rates regardless of regimen were higher (>2X)  
in **HER2-enriched subtype**



**To de-escalate treatment, determinants of response and mechanisms of resistance should be considered**





Obrigada!

[solange.sanches@accamargo.org.br](mailto:solange.sanches@accamargo.org.br)  
[@solangesanches](https://www.instagram.com/solangesanches)