Terapia Adjuvante para Câncer de Mama HER2 positivo: menos é mais?

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Conflitos de Interesse

- Nenhum conflito para essa apresentação

O que abordaremos?

Descalonamento de terapias no câncer de mama inicial HER2+:

- Menos tempo de tratamento com trastuzumabe?
- Menos quimioterapia?

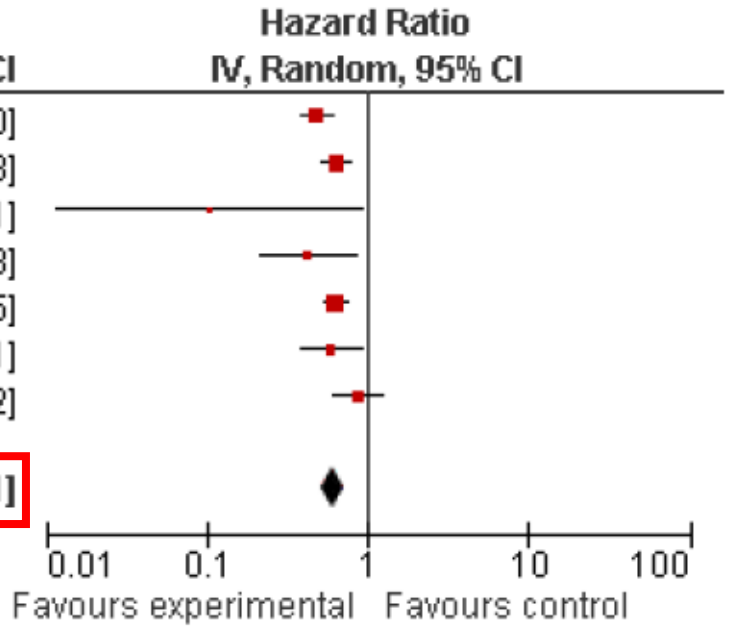
Trastuzumab containing regimens for early breast cancer (Review)

Figure 7. Disease-free survival: all studies.

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
B31 (1)	-0.73	0.11	1672	1679	21.8%	0.48 [0.39, 0.60]
BCIRG006	-0.45	0.1	1074	1073	23.2%	0.64 [0.52, 0.78]
Buzdar	-2.27	1.11	23	19	0.6%	0.10 [0.01, 0.91]
FinHer	-0.87	0.35	115	116	5.2%	0.42 [0.21, 0.83]
HERA	-0.46	0.09	1703	1698	24.7%	0.63 [0.53, 0.75]
NOAH	-0.53	0.22	117	118	10.7%	0.59 [0.38, 0.91]
PACS-04	-0.15	0.18	260	268	13.8%	0.86 [0.60, 1.22]
Total (95% CI)			**4964**	**4971**	**100.0%**	**0.60 [0.50, 0.71]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 12.25$, df = 6 (P = 0.06); $I^2 = 51\%$

Test for overall effect: Z = 5.89 (P < 0.00001)



(1) B31+N9831

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Cochrane Database of Systematic Reviews 2012, Issue 4

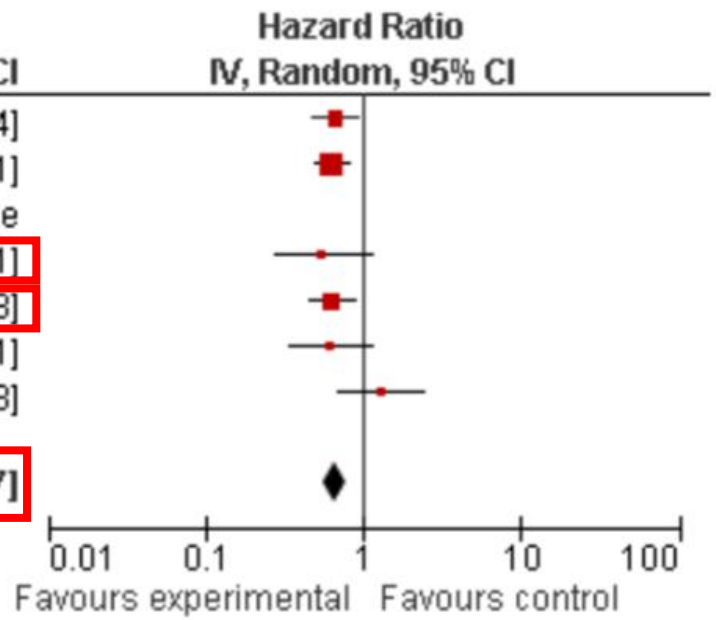
Trastuzumab containing regimens for early breast cancer (Review)

Figure 4. Overall survival: all studies.

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
B31 (1)	-0.4	0.17	1672	1679	22.0%	0.67 [0.48, 0.94]
BCIRG006	-0.46	0.13	1074	1073	37.7%	0.63 [0.49, 0.81]
Buzdar	0	0	23	19		Not estimable
FinHer	-0.6	0.36	115	116	4.9%	0.55 [0.27, 1.11]
HERA	-0.46	0.17	1703	1698	22.0%	0.63 [0.45, 0.88]
NOAH	-0.48	0.3	117	118	7.1%	0.62 [0.34, 1.11]
PACS-04	0.24	0.32	260	268	6.2%	1.27 [0.68, 2.38]
Total (95% CI)			**4964**	**4971**	**100.0%**	**0.66 [0.57, 0.77]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.70$, df = 5 (P = 0.45); $I^2 = 0\%$

Test for overall effect: Z = 5.16 (P < 0.00001)



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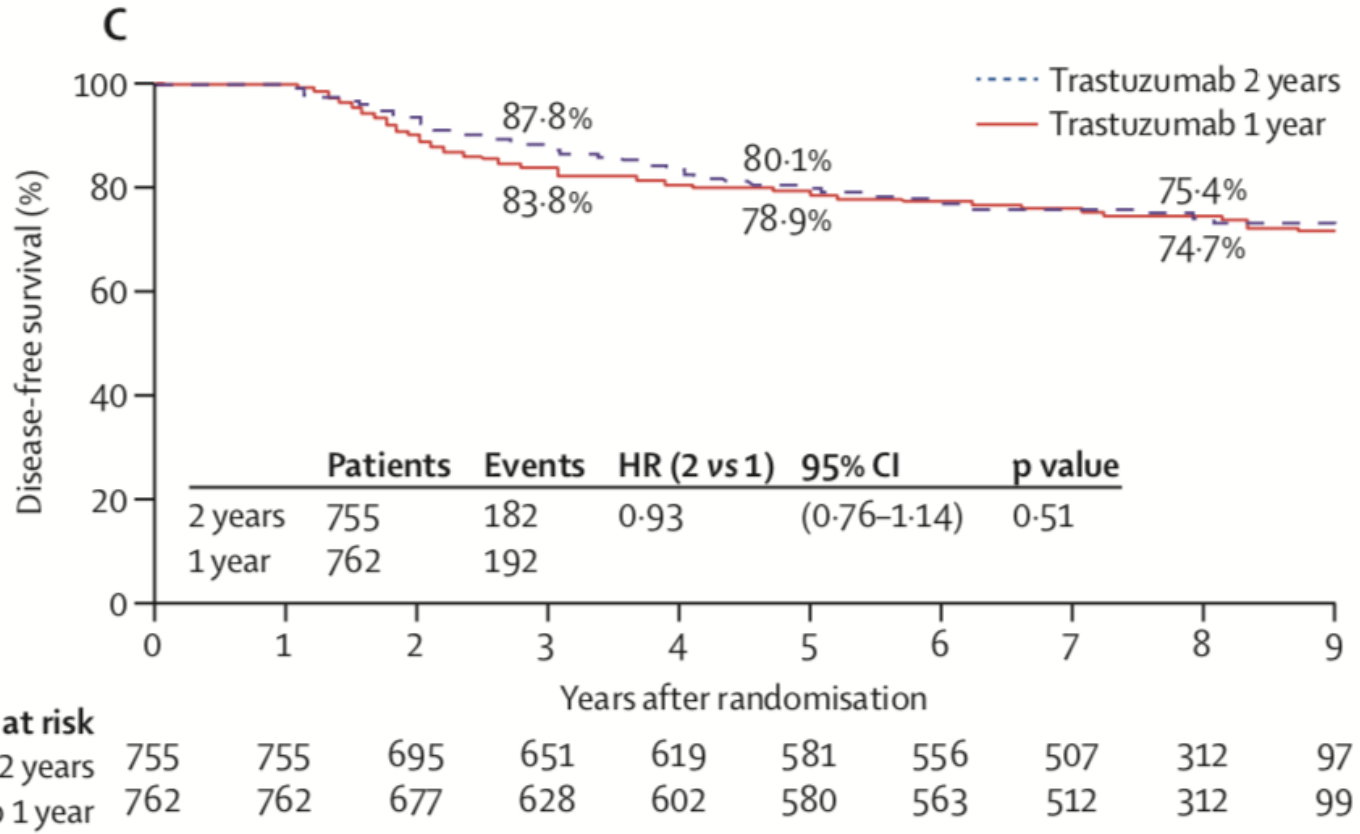
HERA trial

2 years versus 1 year of ajuvant trastuzumab for HER2 positive breast cancer (HERA): an open-label, randomised controlled trial



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Goldhirsch et al. Lancet 2013; 382: 1021–28

Qual é a duração ideal de trastuzumabe no cenário adjuvante?

Hypotesis:

A shorter duration of trastuzumab administered concomitantly with chemotherapy might produce comparable efficacy with significantly lower toxicities and costs.

PHARE trial

6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial

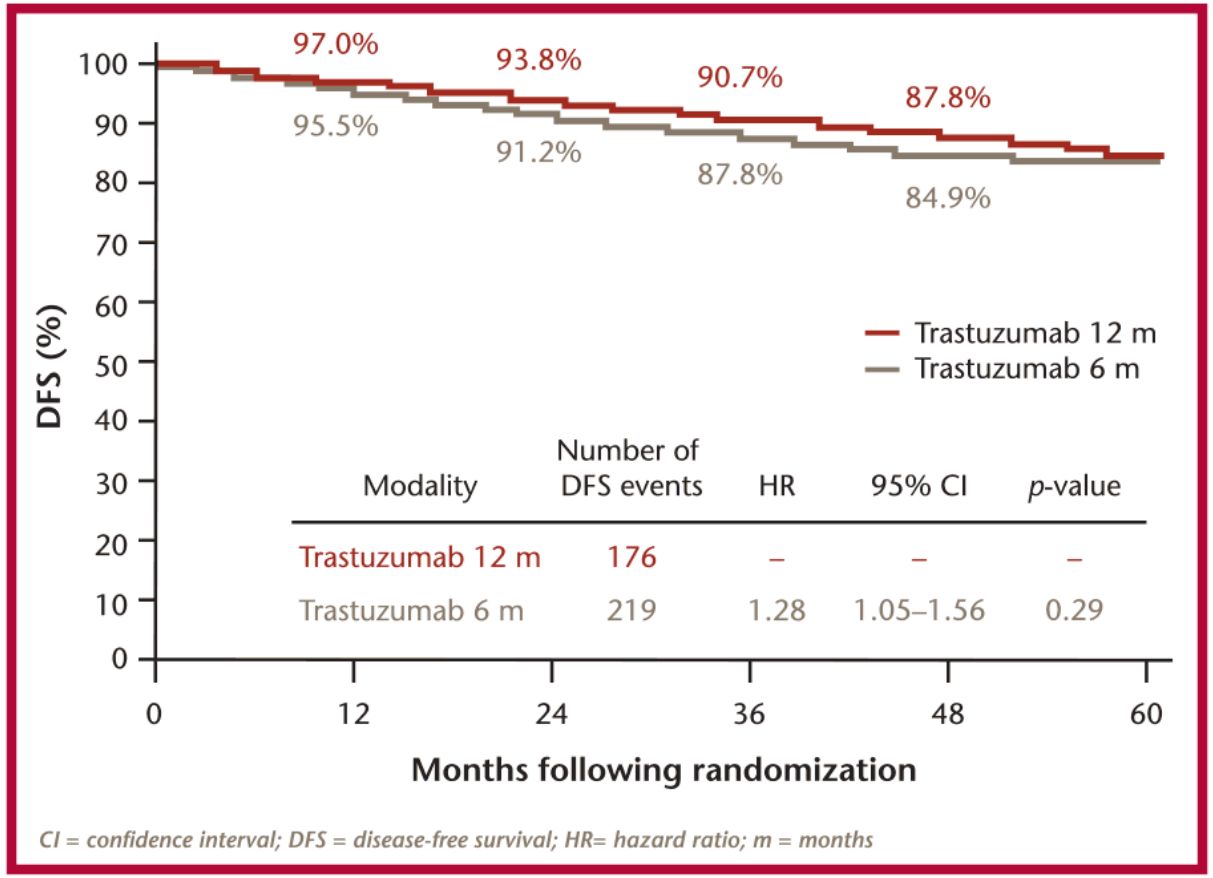
Eligibility

- HER2-positive, operable breast cancer
- Node-positive or node-negative
- Tumor size ≥10 mm
- ≥4 cycles of (neo)adjuvant chemotherapy
- Received 6 months of trastuzumab

R

Trastuzumab
Up to 12 months
(n = 1,690)

Stop trastuzumab
(n = 1,690)



CI = confidence interval; DFS = disease-free survival; HR= hazard ratio; m = months

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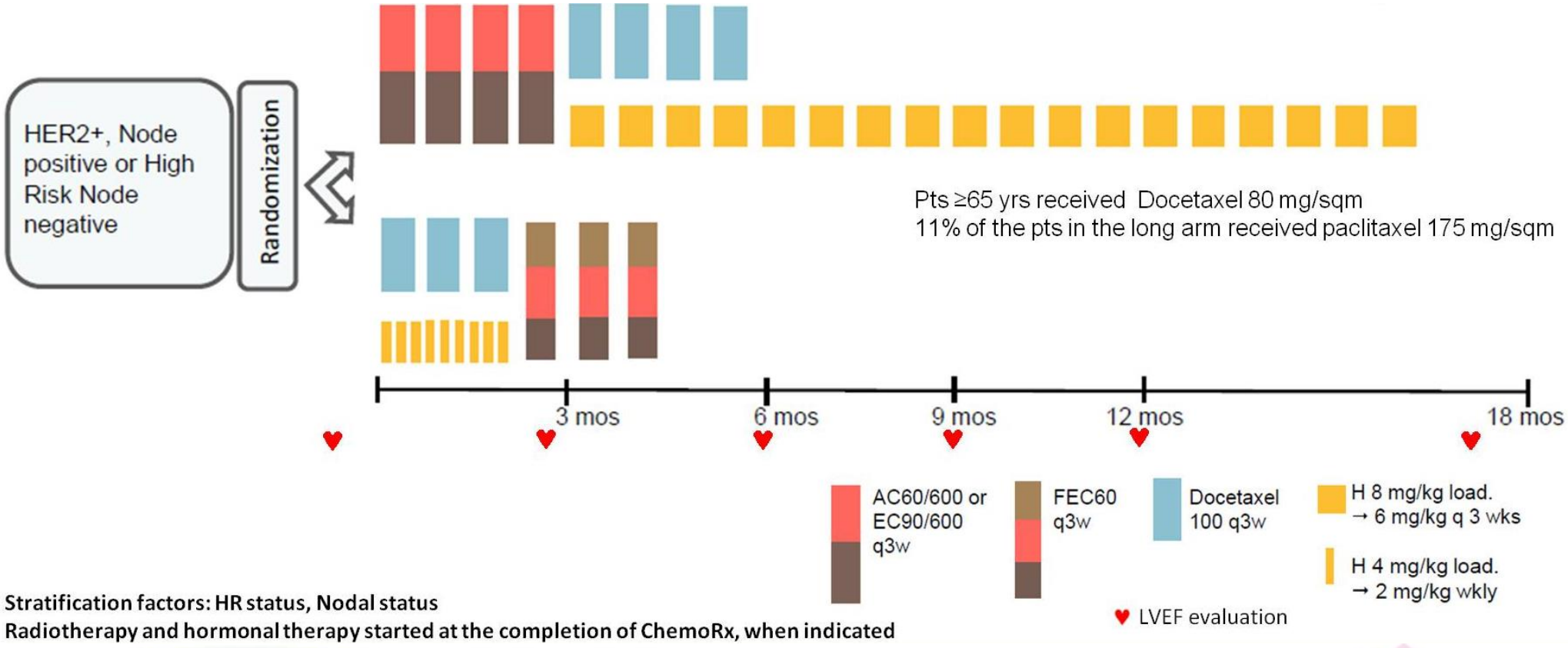
Lancet Oncol 2013; 14: 741–48

Short-HER

9 weeks versus 1 year adjuvant trastuzumab in combination with chemotherapy: results of the phase III multicentric Italian Short-HER Study



Stratification factors: HR status, Nodal status
Radiotherapy and hormonal therapy started at the completion of ChemoRx, when indicated

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Conte at al. ASCO 2017

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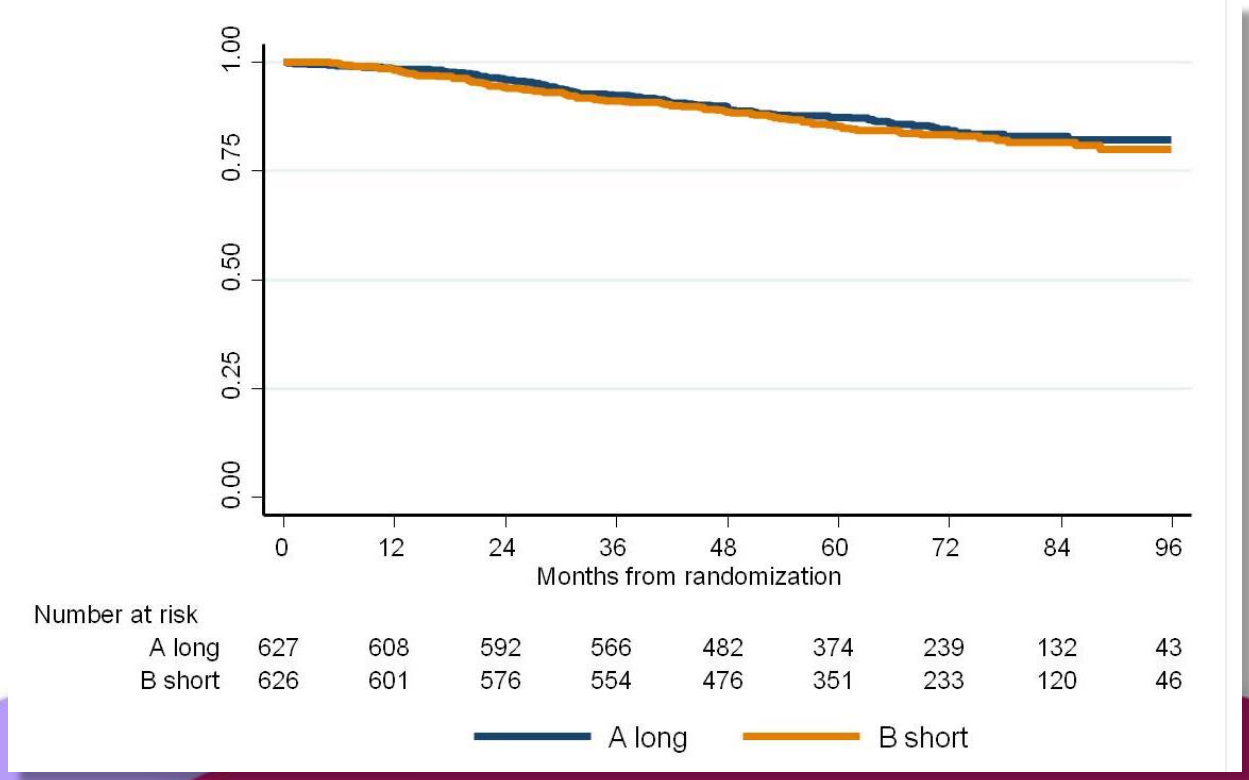
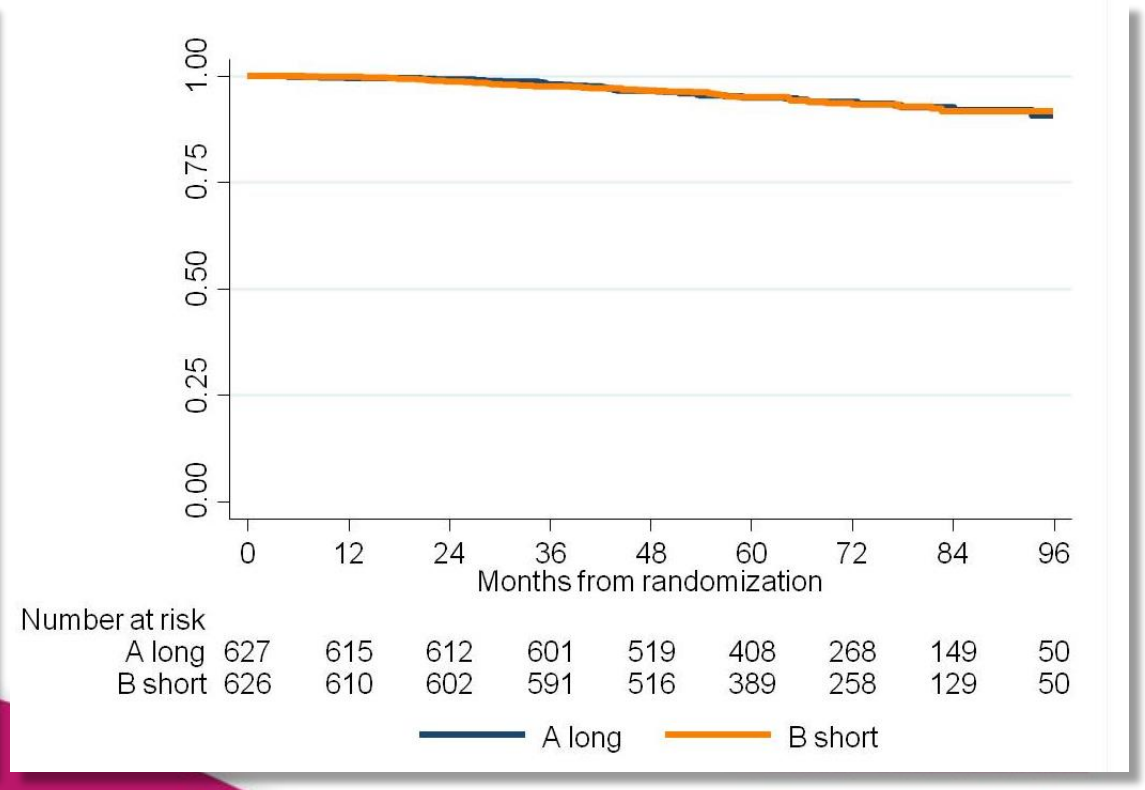
Disease-Free Survival



Overall Survival



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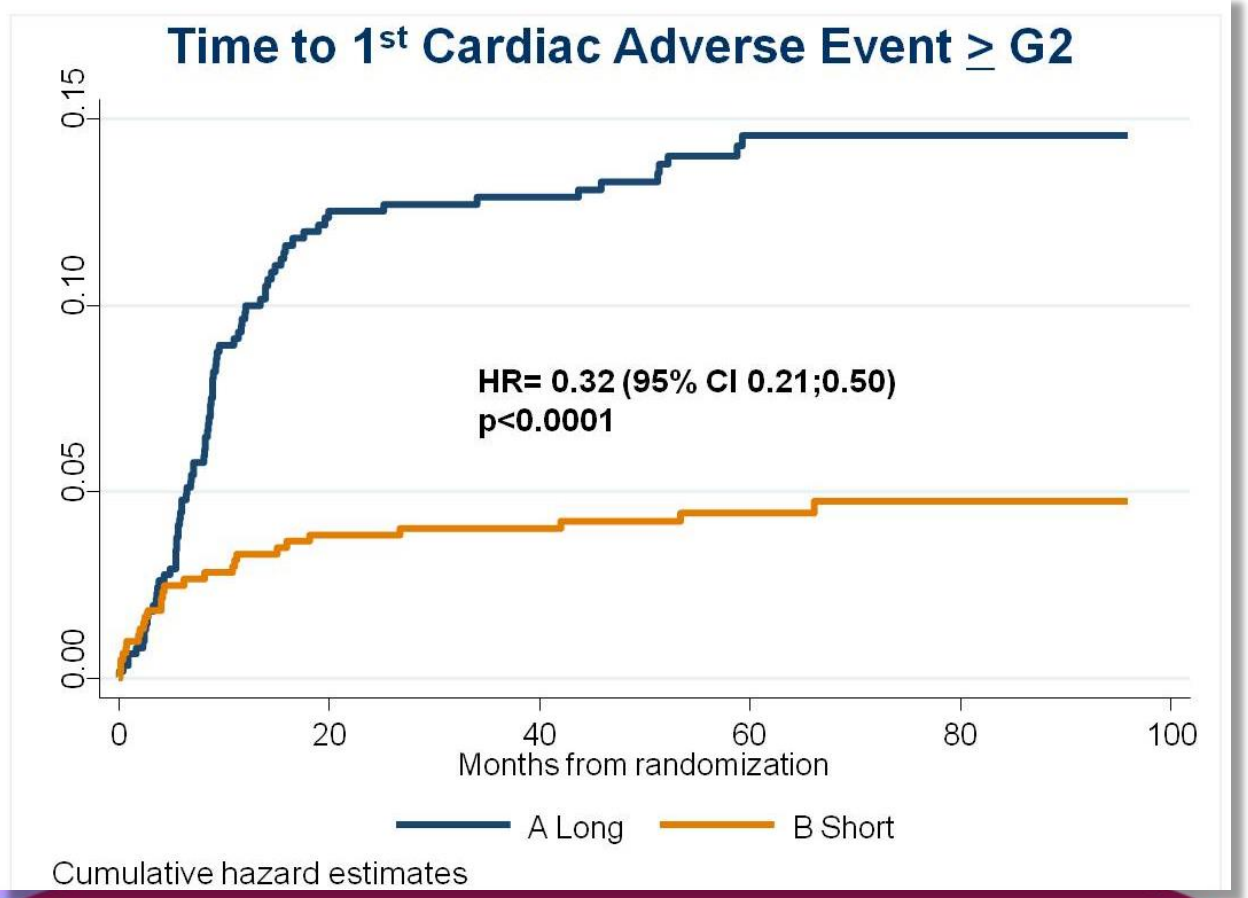

Number of cardiac events

Grade	Long N(%)	Short N(%)
2	70 (11.2)	22 (3.5)
3	17 (2.7)	7 (1.1)
4	3 (0.5)	3 (0.5)
Total	**90 (14.4)**	**32 (5.1)**

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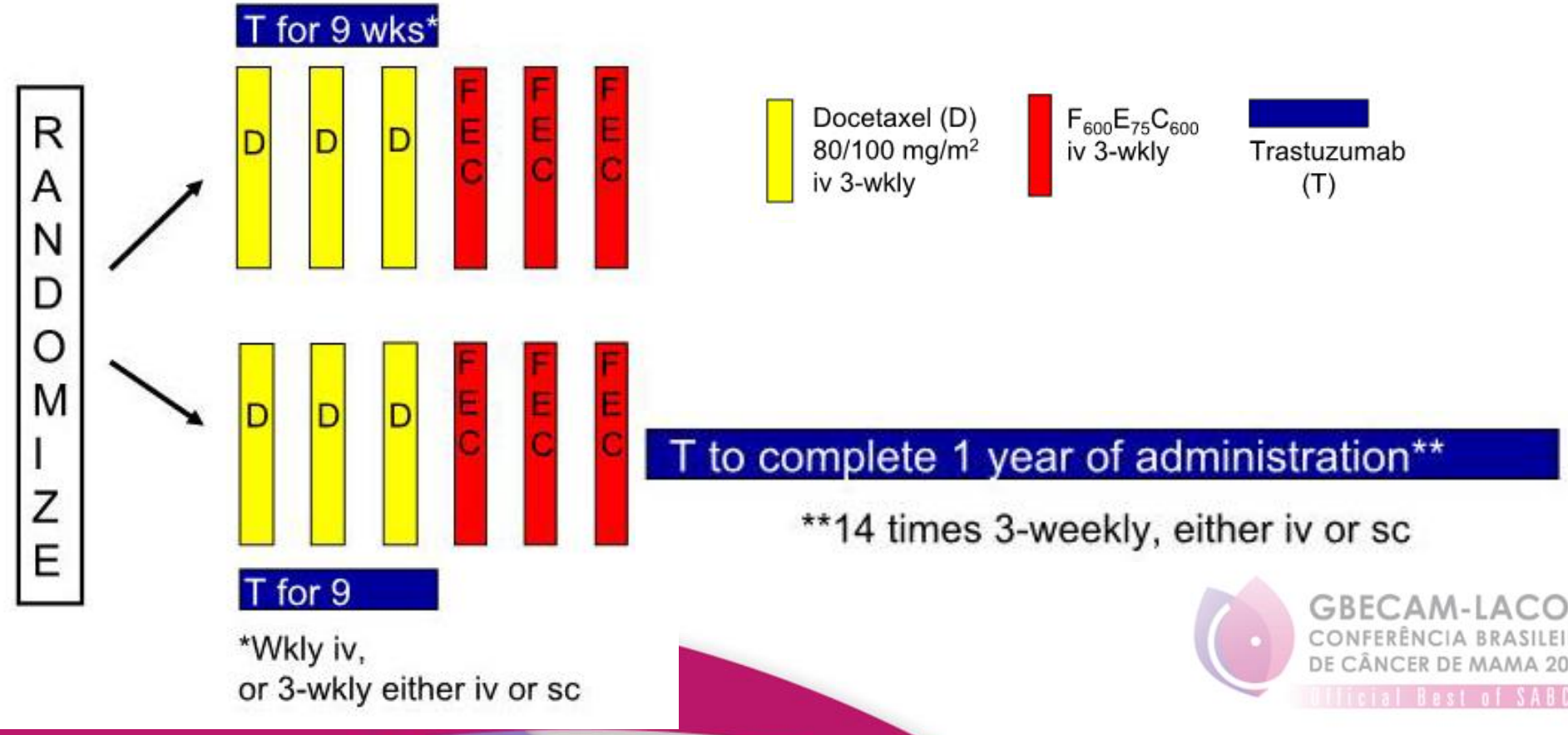
Conte at al. ASCO 2017

SOLD

A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer

- PS 0-1
- Câncer de mama HER2 positivo
- LN+ ou LN neg com tamanho >5mm
- LVEF 50%



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Joensuu et al. SABCS 2017

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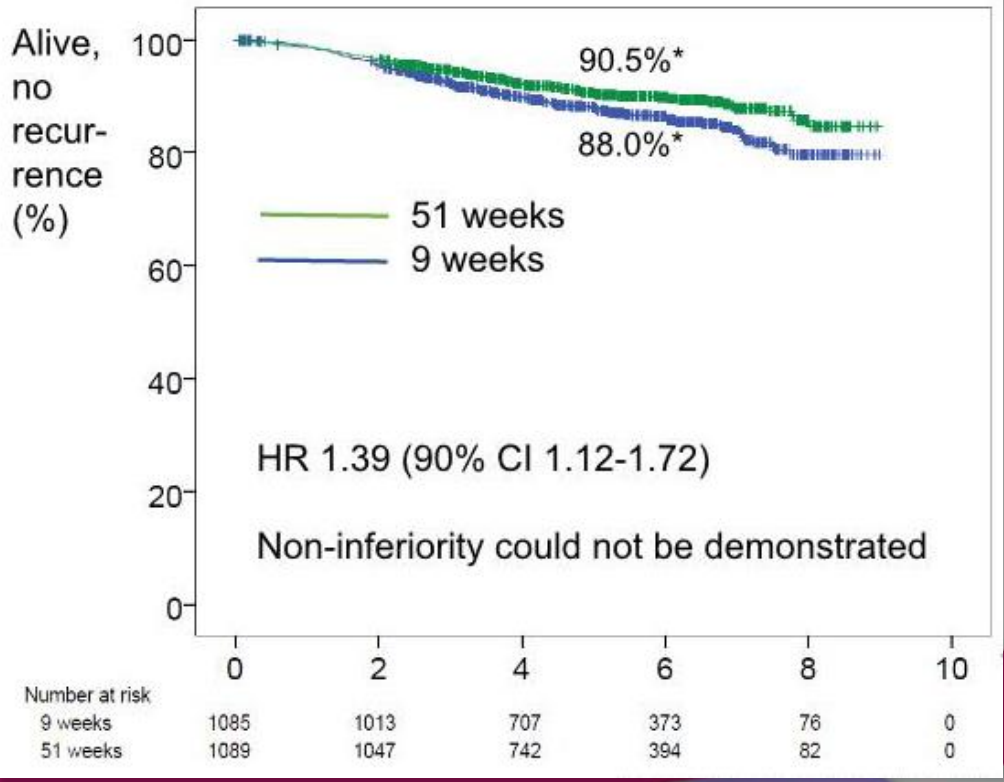
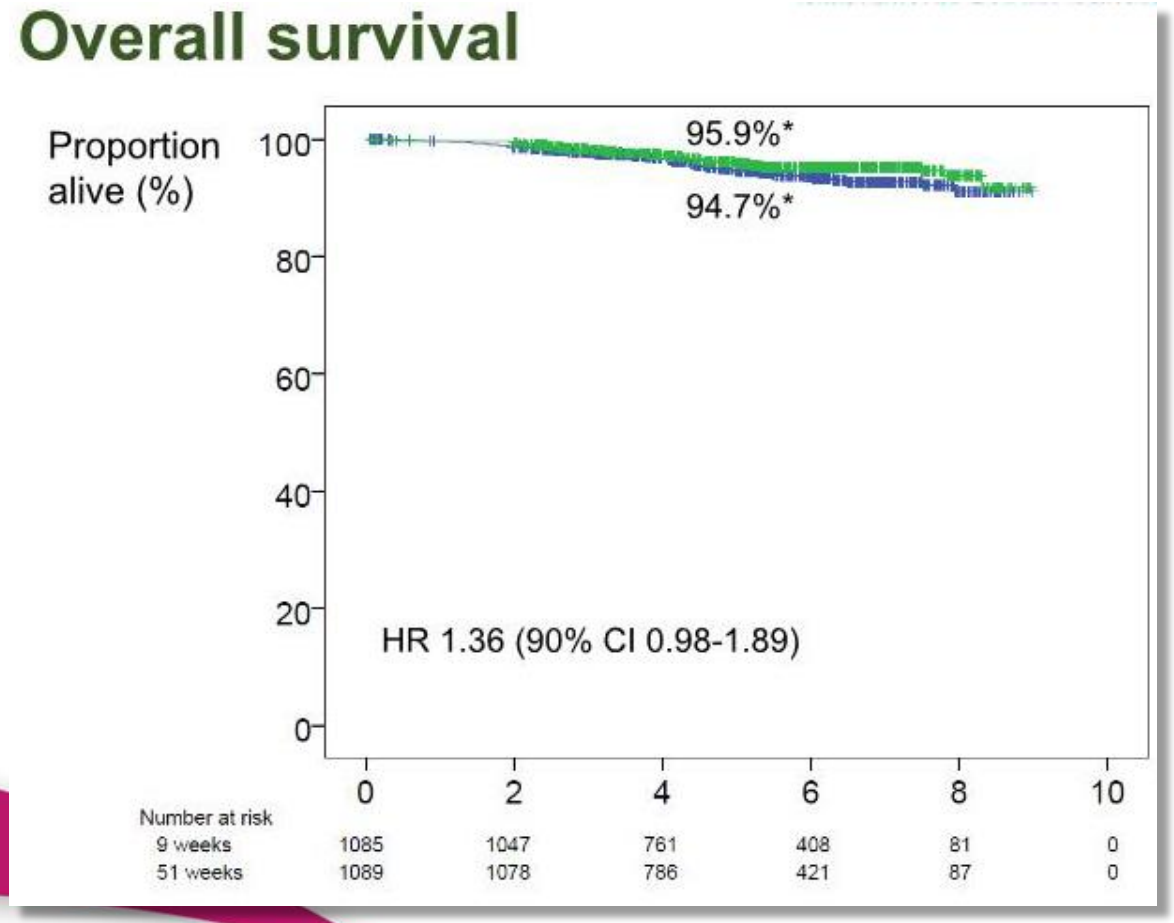
Disease-free survival



Overall survival



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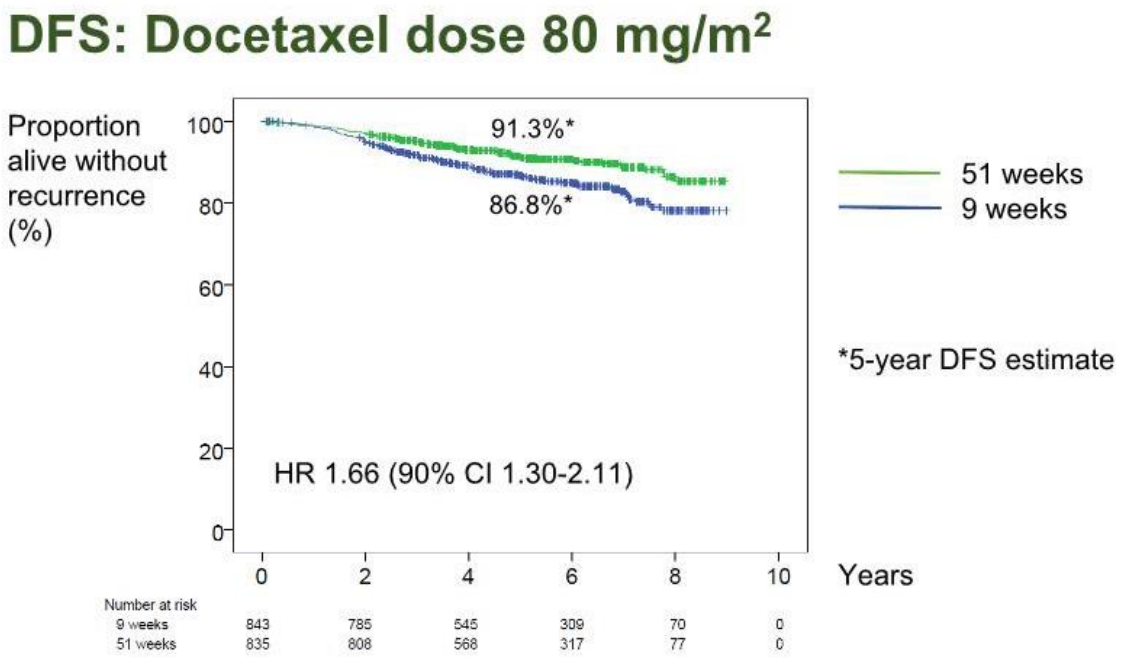

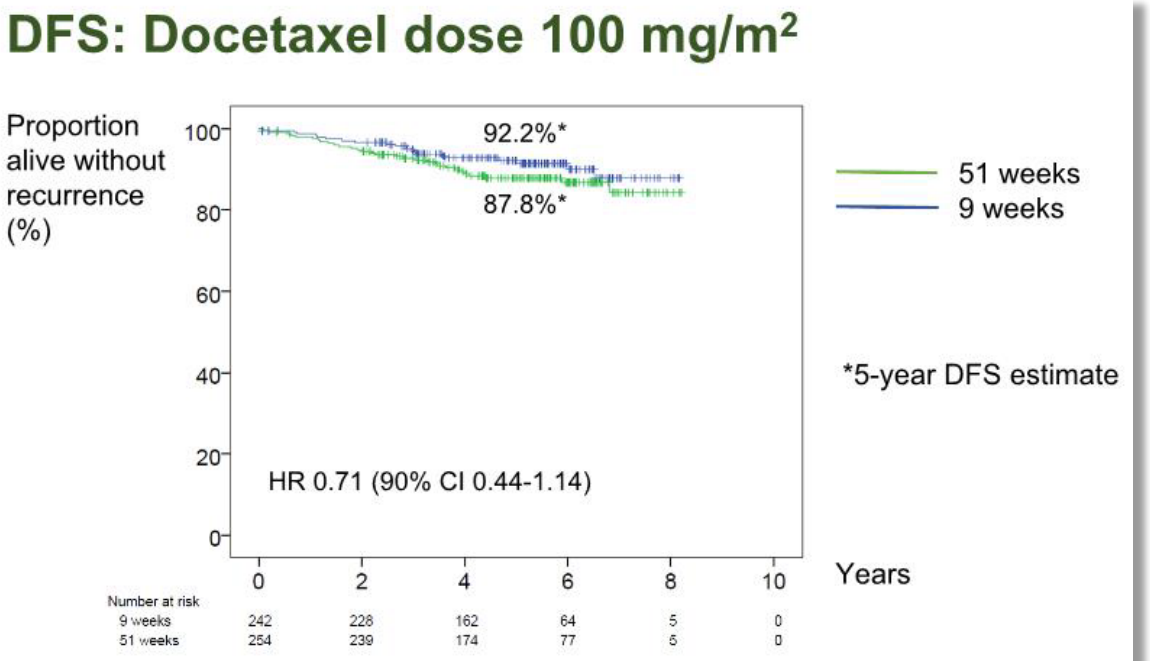

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SOLD

Cardiac safety

- Less cardiac toxicity was observed in the 9-week group

Event	9-week group n (%)	1-year group n (%)
Any protocol-defined cardiac adverse event*	22 (2.0)	42 (3.9)*
Congestive heart failure	21 (1.9)	36 (3.3)**

*P = 0.012

**P = 0.046

*Any Gr. 3 or 4 cardiac event; symptomatic cardiac failure; cardiac failure requiring medical management; LVEF decrease >10 percentage points and to a value <50%; LVEF decrease to <45% from any baseline value

Joensuu et al. SABCS 2017

Comparação entre os estudos

	PHARE	SHORT-HER	SOLD
Desenho	Fase III randomizado, não inferioridade	Fase III randomizado, não inferioridade	Fase III randomizado, não inferioridade
N	3.380	1.253	2.176
Duração	6 meses vs 1 ano	9 semanas vs 1 ano	9 semanas vs 1 ano
Quimioterapia	74% A+T	100% A+T	100% A+T
N	N0: 55% 1-3 LN+: 30% >3 LN+: 15%	N0: 54% 1-3 LN+: 30% >3 LN+: 16%	N0: 60% 1-3 LN+: 30% >3 LN+: 11%
RH+	60%	68%	66%
Endpoint Primário	SLD 2 anos 91.2% vs 93.8%	SLD 5 anos 85.4% vs 87.5%	SLD 5 anos 88.0% vs 90.5%

Conclusão I (duração)

Estudos *Phare, Short-HER e SOLD* não conseguiram demonstrar não inferioridade dos regimes de curta duração versus tratamento padrão com 1 ano de trastuzumabe.

Menos quimioterapia?

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2017
Invasive Breast Cancer

HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE[c]

- Tumor ≤0.5 cm including microinvasive
  - pN0 → Consider adjuvant endocrine therapy[z,aa] ± adjuvant chemotherapy[bb,cc] with trastuzumab[dd,ee] (category 2B)
  - pN1mi → Adjuvant endocrine therapy[z,aa] or Adjuvant chemotherapy[aa,bb] with trastuzumab[dd] and endocrine therapy[z,aa]
- Tumor 0.6–1.0 cm → Adjuvant endocrine therapy[z,aa] or Adjuvant chemotherapy[aa,bb] with trastuzumab[dd] and endocrine therapy[z,aa]

HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE[c]

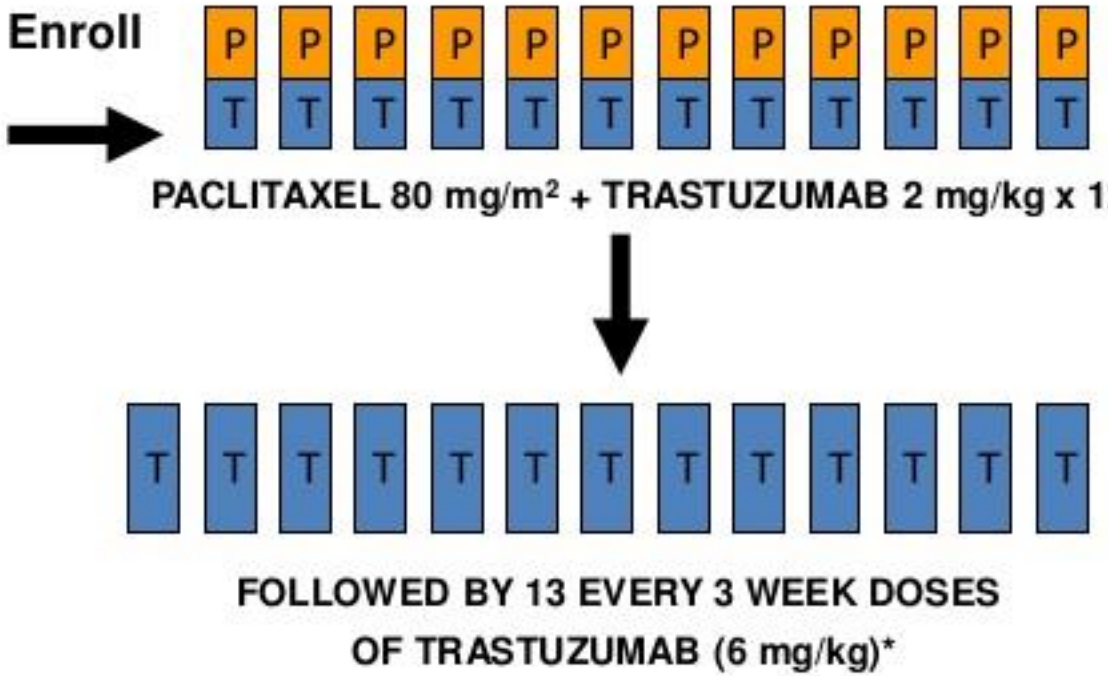
- Tumor ≤0.5 cm including microinvasive
  - pN0 → Consider adjuvant chemotherapy[cc,ii] with trastuzumab[z,dd,ee] (category 2B)
  - pN1mi → Consider adjuvant chemotherapy[cc,ii] with trastuzumab[z,dd]
- Tumor 0.6–1.0 cm → Consider adjuvant chemotherapy[cc,ii] with trastuzumab[z,dd]

APT trial

Study Design (APT Trial)

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400



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SABCS 2013
Tolaney et al. N Engl J Med 2015;372:134-41

APT trial

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients (N = 406)
	no. (%)
Age group	
<50 yr	132 (32.5)
50–59 yr	137 (33.7)
60–69 yr	96 (23.6)
≥70 yr	41 (10.1)
Sex	
Female	405 (99.8)
Male	1 (0.2)
Race†	
White	351 (86.5)
Black	28 (6.9)
Asian	11 (2.7)
Other	16 (3.9)
Primary tumor	
Size	
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0 cm	36 (8.9)
Nodal status	
N0	400 (98.5)
N1mic	6 (1.5)
Histologic grade	
I: well-differentiated	44 (10.8)
II: moderately differentiated	131 (32.3)
III: poorly differentiated	228 (56.2)
Unknown	3 (0.7)
HER2-positive status	406 (100)
Estrogen-receptor status	
Positive	260 (64.0)
Negative	141 (34.7)
Borderline	5 (1.2)
Progesterone-receptor status	
Positive	201 (49.9)
Negative	196 (48.3)
Borderline	8 (2.0)
Unknown	1 (0.2)
Hormone-receptor status	
Positive	272 (67.0)
Negative	134 (33.0)

Tolaney et al. N Engl J Med 2015;372:134-41

APT trial

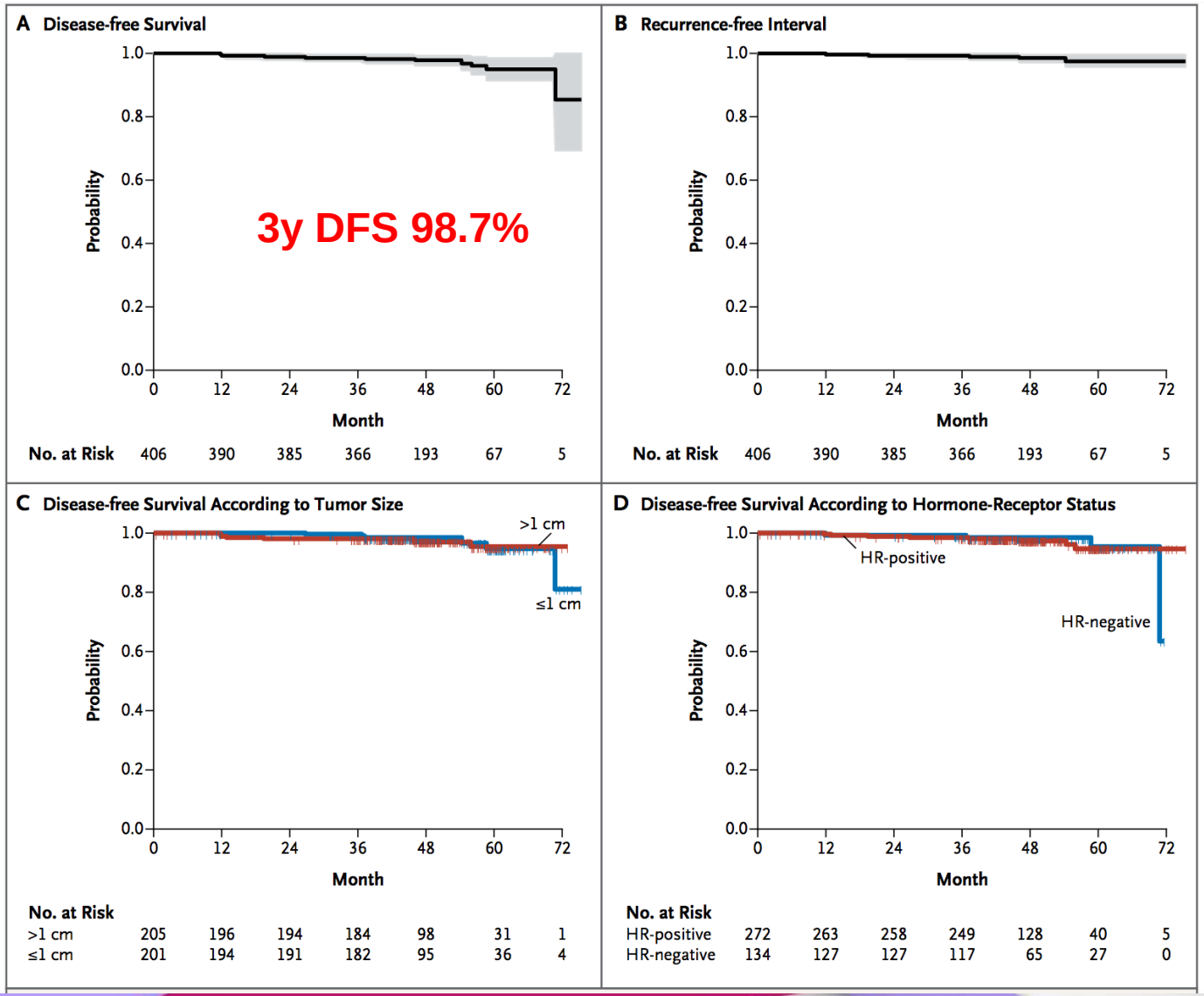

Table 3. Most Common Adverse Events Occurring during Protocol Therapy.

Event	Maximum Grade			Total
	Grade 2	Grade 3	Grade 4	
	number of patients (percent)			
Fatigue	81 (20.0)	9 (2.2)	0	90 (22.2)
Diarrhea	47 (11.6)	6 (1.5)	0	53 (13.1)
Neuropathy	39 (9.6)	14 (3.4)	0	53 (13.1)
Neutropenia	26 (6.4)	15 (3.7)	2 (0.5)	43 (10.6)
Hyperglycemia	35 (8.6)	7 (1.7)	0	42 (10.3)
Leukopenia	28 (6.9)	10 (2.5)	0	38 (9.4)
Allergic reaction	28 (6.9)	6 (1.5)	1 (0.2)	35 (8.6)
Elevated alanine amino-transferase level	23 (5.7)	7 (1.7)	0	30 (7.4)
Anemia	28 (6.9)	1 (0.2)	0	29 (7.1)

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Tolaney et al. N Engl J Med 2015;372:134-41

APT trial

Seven-year follow up – ASCO 2017

Disease Free Survival

	Point Est.	95% Conf. Interval	No. of Events
3-yr DFS	98.5%	97.2-99.7%	6
5-yr DFS	96.3%	94.4-98.2%	14
7-yr DFS	93.3%	90.4-96.2%	23

Overall Survival

	Point Est.	95% Conf. Interval	No. of Events
3-yr OS	99.7%	99.2-99.9%	1
5-yr OS	98.7%	97.5-99.8%	5
7-yr OS	95.0%	92.4-97.7%	14

DFS events

DFS Event	N (%)	Time to event [months; mean (range)]
Any recurrence or death	23 (5.7)	
Local/Regional Recurrence*	5 (1.2)	
Ipsilateral axilla (HER2+)	3	29 (12-54)
Ipsilateral breast (HER2+)	2	51 (37-65)
New Contralateral Primary Breast Cancer	6 (1.5)	
HER2+	1	56
HER2-	3	36 (12-59)
Unknown	2	87 (84-90)
Distant Recurrence	4 (1.0)	49 (27-63)
Death		
Non-breast cancer related	8 (2.0)	58 (13-71)

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Conclusão II

Terapia adjuvante para câncer de Mama HER2 positivo: menos é mais?

1) Menos tempo de tratamento com trastuzumabe?

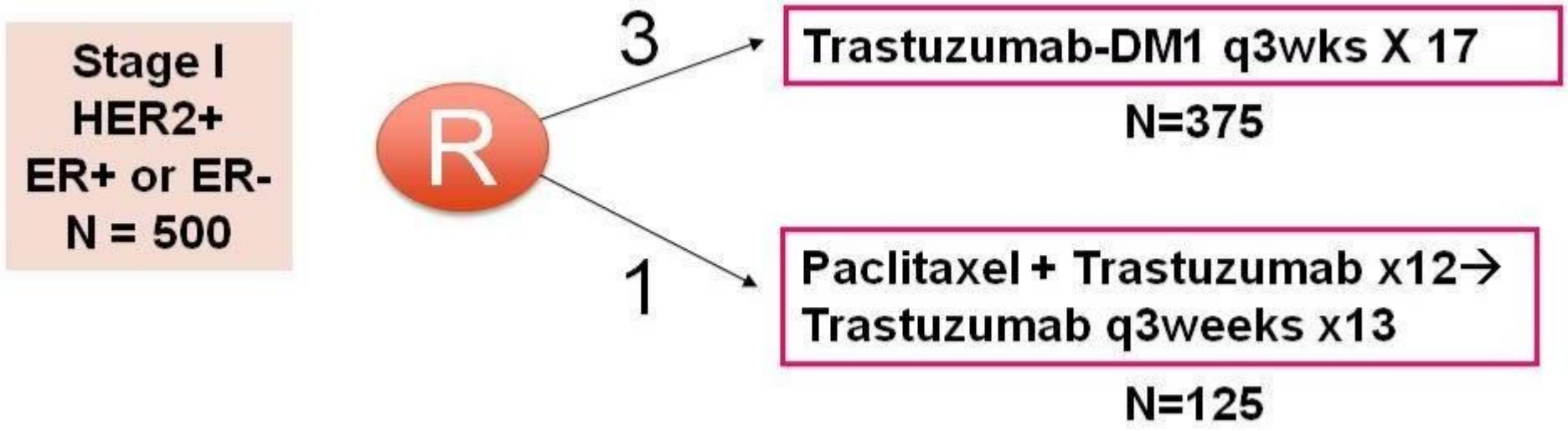
NÃO (Phare, Short-HER e SOLD negativos)

2) Menos quimioterapia?

SIM, para T≤2cm e axila negativa (APT trial)

ATEMPT trial

Haverá papel para T-DM1 na doença inicial?



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https://www.clinicaltrials.gov

Obrigado!!!

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