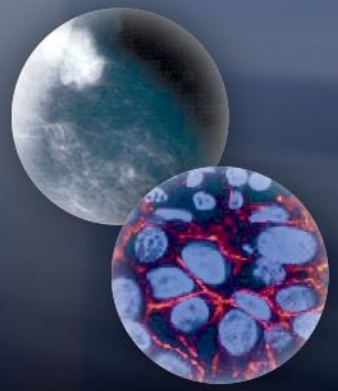
Câncer de Mama HER2 positivo

Laura Testa
Instituto do Câncer do Estado de São Paulo

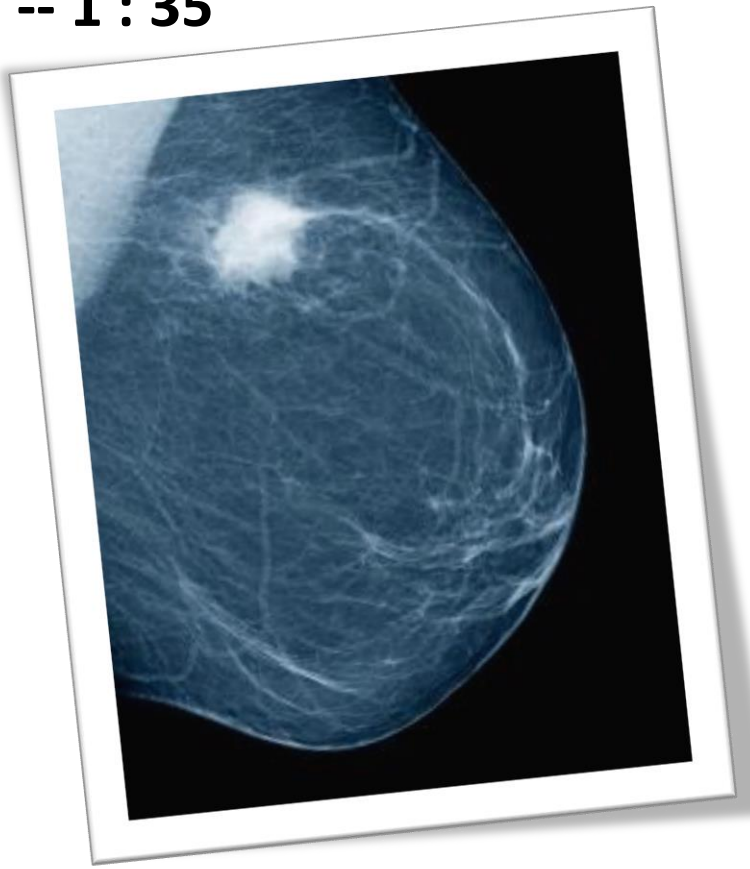


Câncer de Mama HER2 positivo

- Introdução
  - ✓ Câncer de Mama
  - ✓ HER2
- Tratamento adjuvante
- Neoadjuvancia
- 1ª linha metastática

Câncer de Mama

- **Risco de Câncer de Mama invasivo durante a vida -- 1 : 8**
- **Risco de Óbito por Câncer de Mama -- 1 : 35**
- **Mortalidade diminuindo**
  - ✓ Melhores tratamentos
  - ✓ Menos uso de TRH
  - ✓ Diagnóstico precoce



American Cancer Society

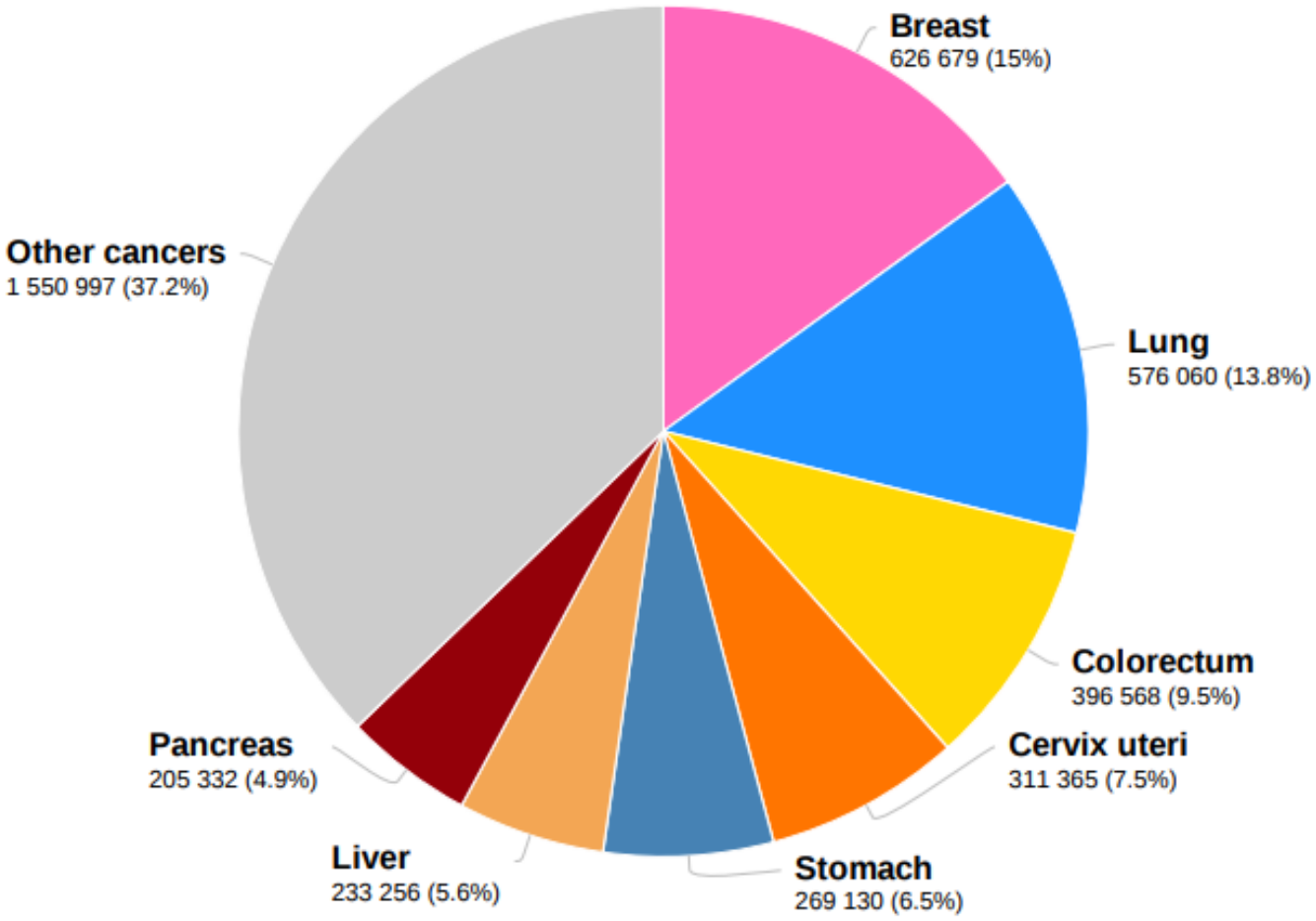
Câncer de Mama

TENDÊNCIAS DAS ÍNDICES DE SOBREVIDA EM 5 ANOS (%) POR ANO DE DIAGNÓSTICO, ESTADOS UNIDOS, 1975-2008			
	1975-1977	1987-1989	2002-2008
Câncer de mama	75	84	90

Embora a mortalidade venha caindo é o que mais mata as mulheres.

Câncer de Mama

Estimated number of deaths in 2018, worldwide, all cancers, females, all ages

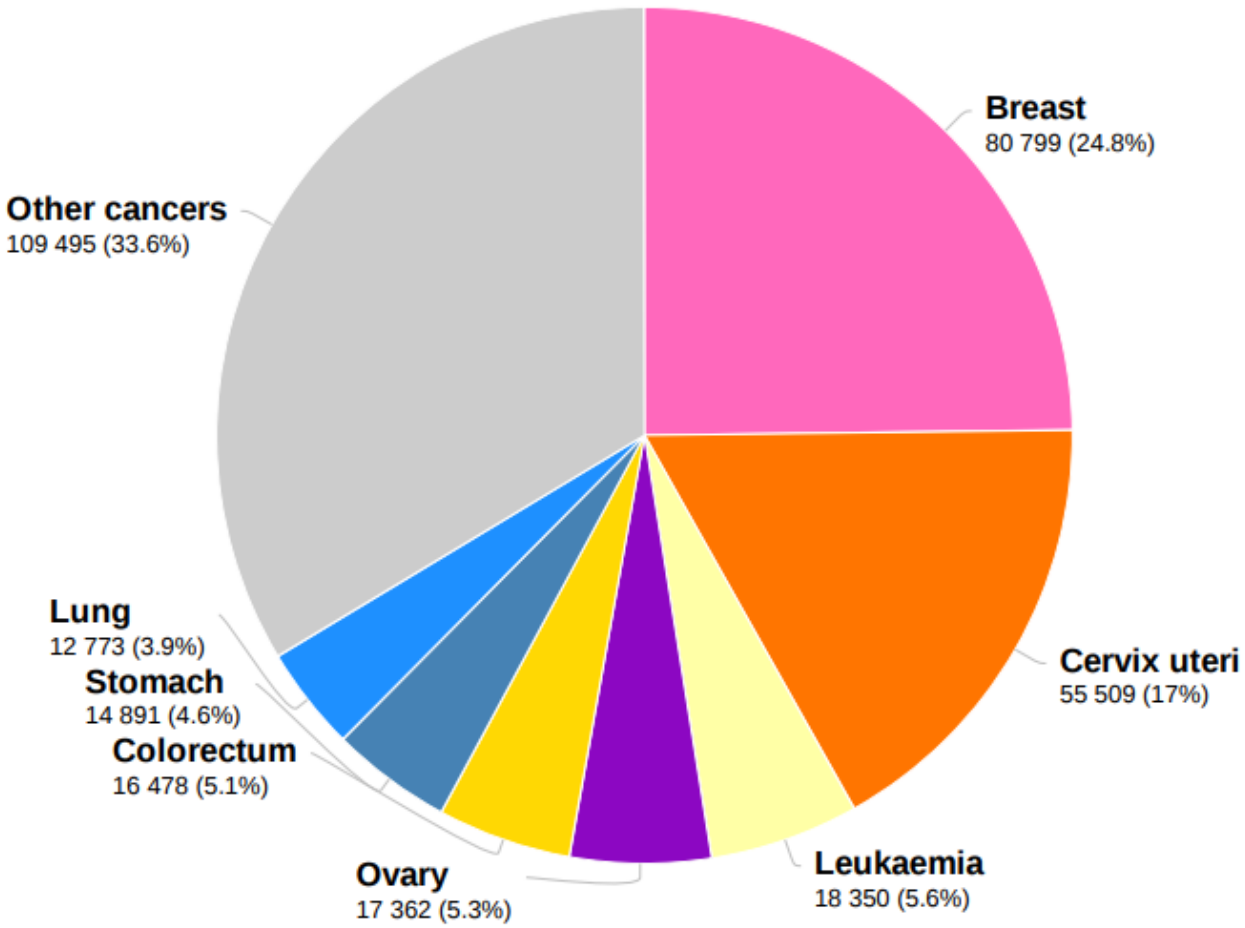


Total : 4 169 387

GLOBOCAN

Câncer de Mama

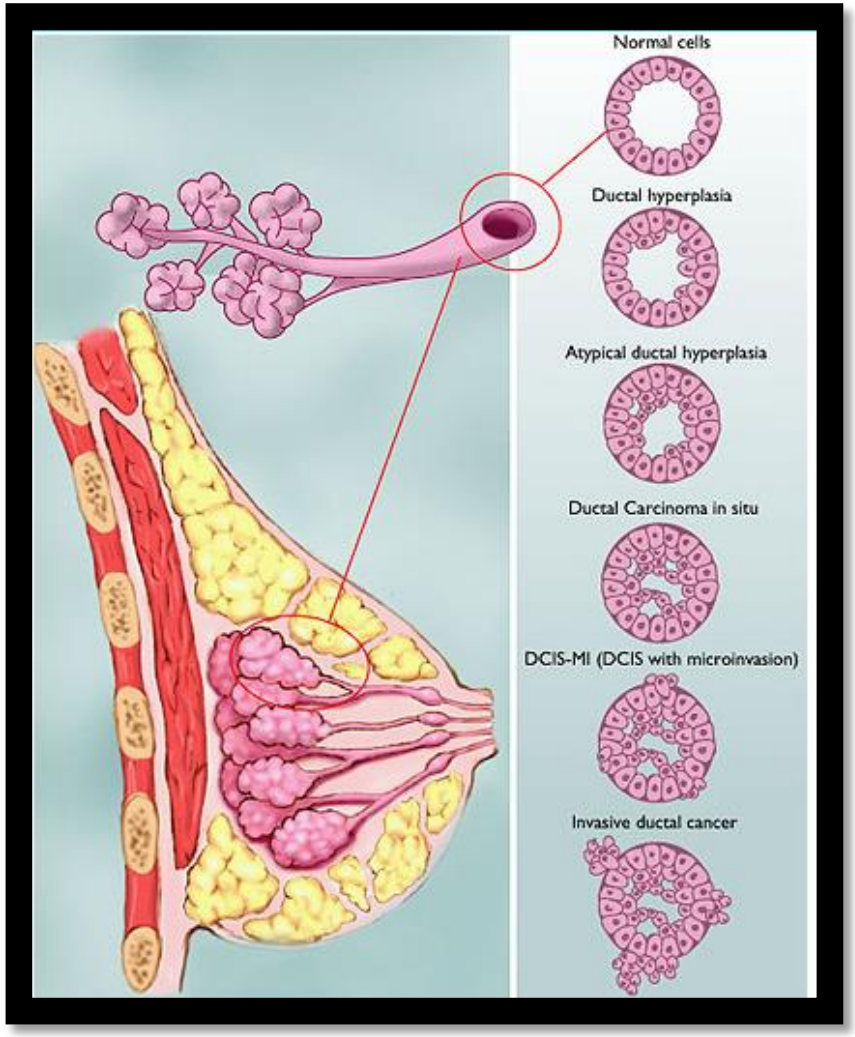
Estimated number of deaths in 2018, worldwide, all cancers, females, ages 25-44

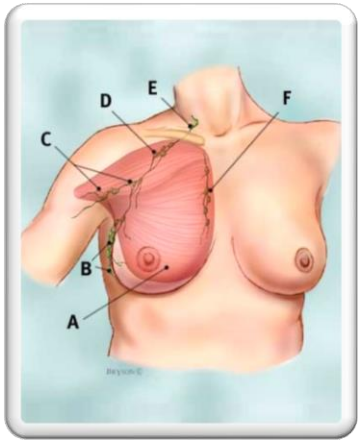


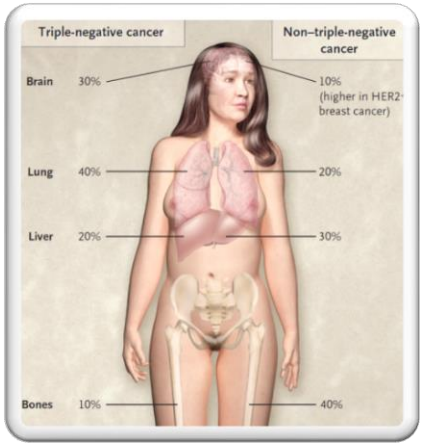
Total : 325 657

GLOBOCAN

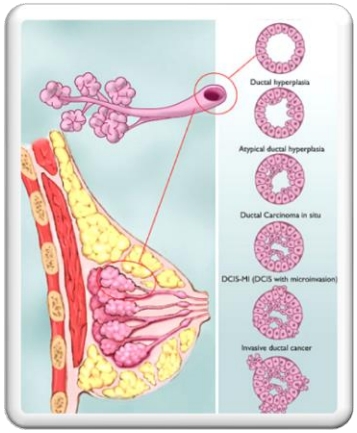
Carcinogênese e disseminação

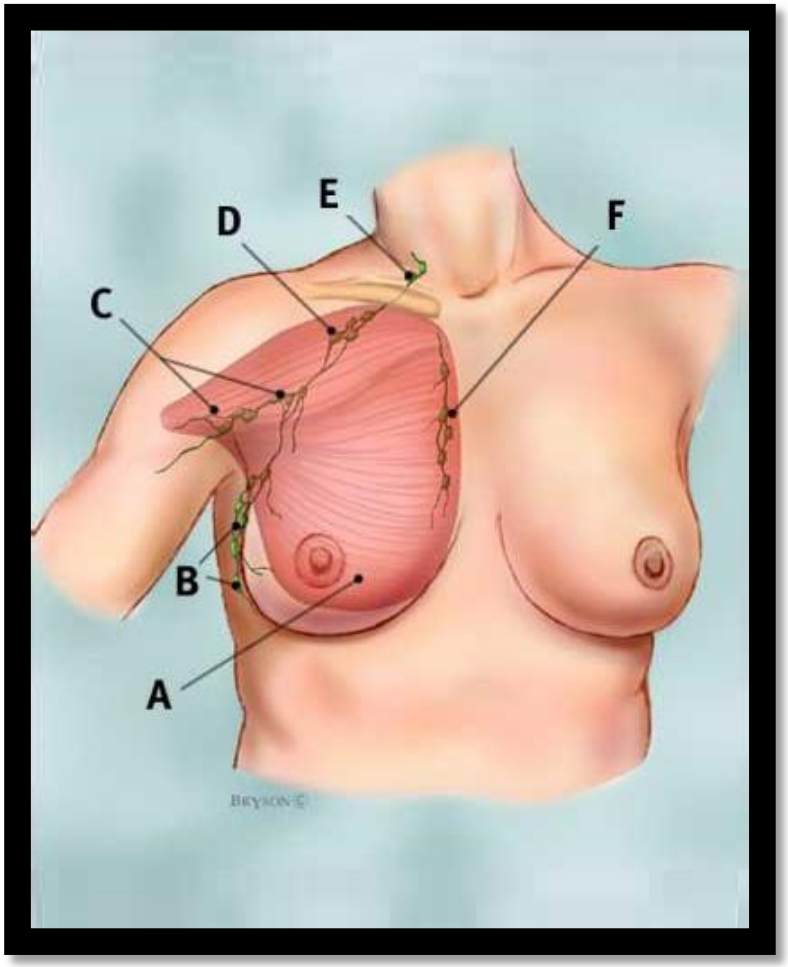


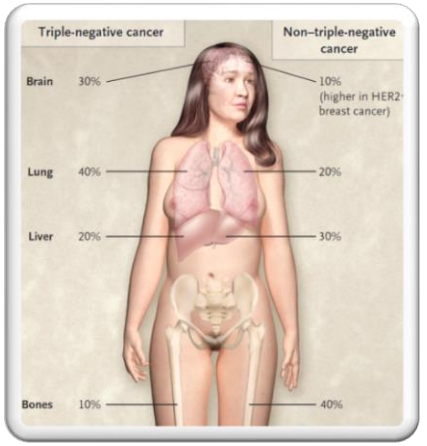




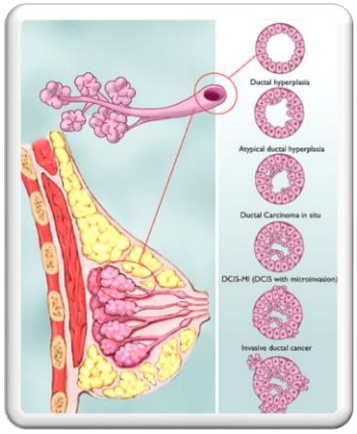
Carcinogênese e disseminação

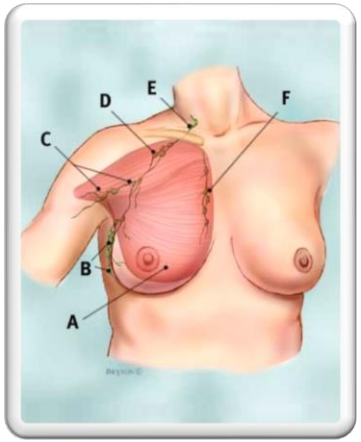


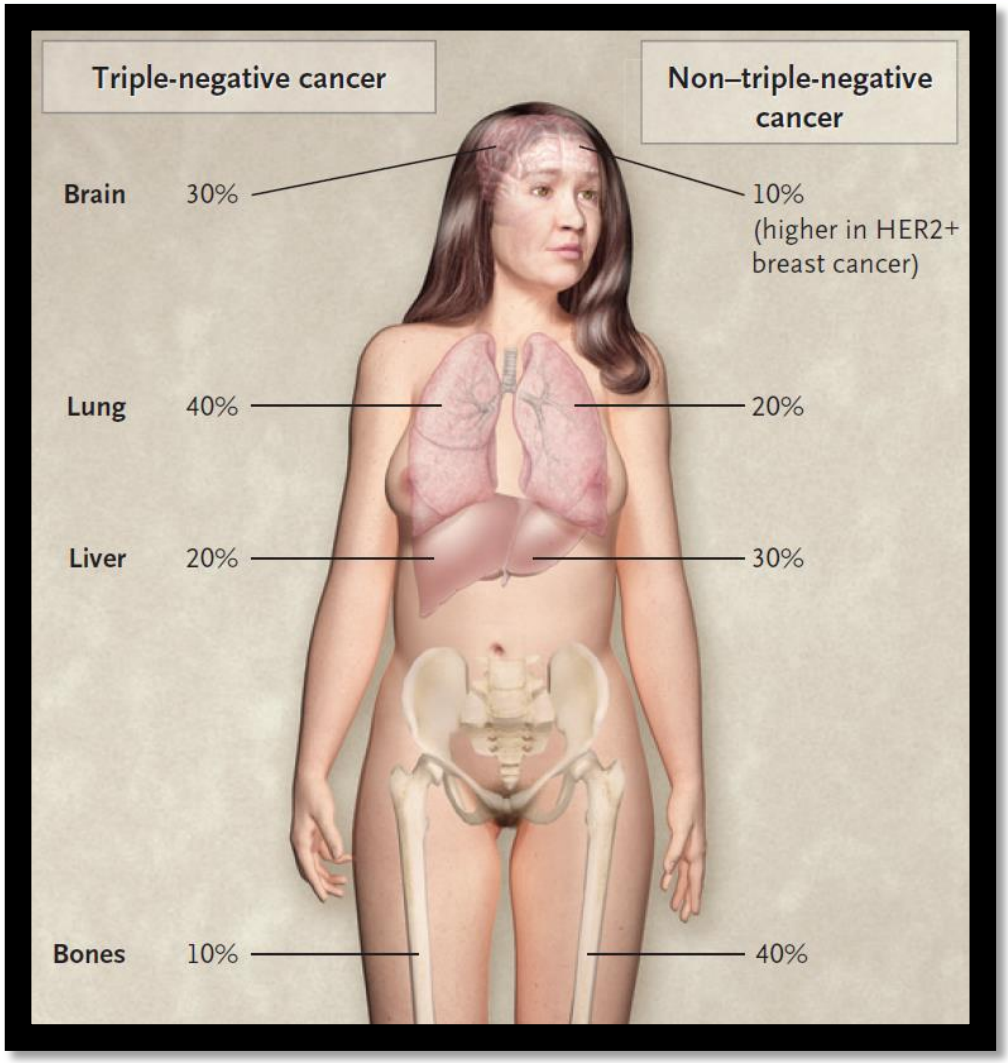




Carcinogênese e disseminação





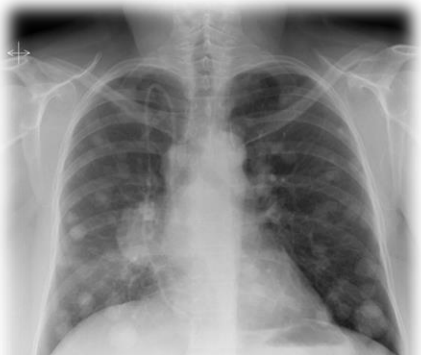


Câncer de mama

Doença localizada

(não-metastática e operável)

- Potencialmente curável
- Tratamento visa a cura ou retardo da recidiva
- Tratamento agressivo
- Tratamento CURATIVO



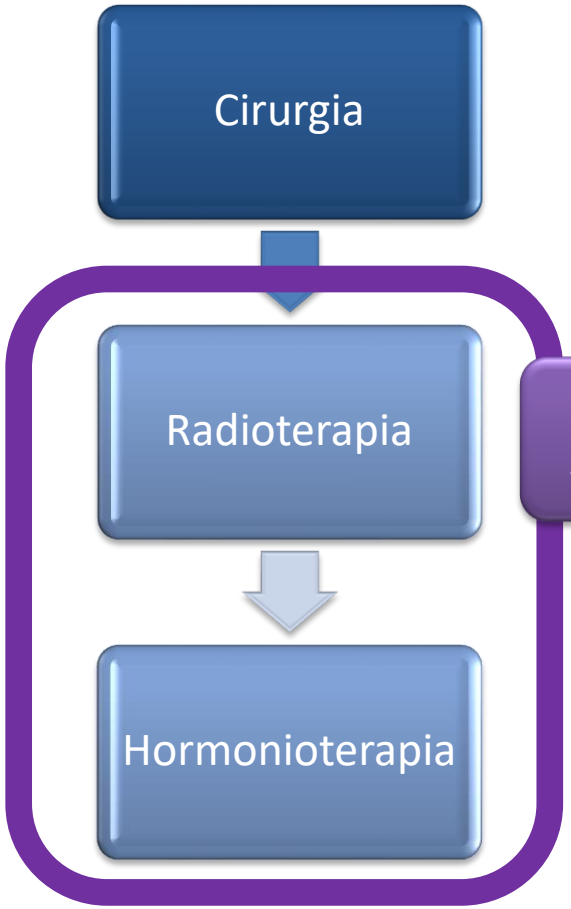
Doença avançada

(metastática ou inoperável)

- Incurável
- Prolongar sobrevida mas também melhorar a qualidade de vida
- Tratamento PALIATIVO
- Doença ‘crônica’ exigindo tratamento quase contínuo
- Sequencia de linhas de tratamento:
- 1ª linha -> 2ª linha -> 3ª linha....

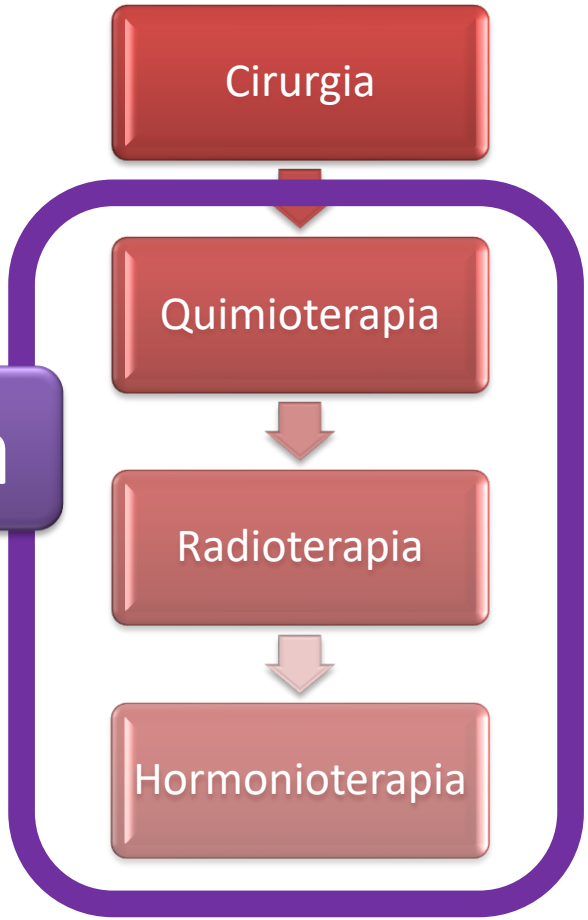
Câncer de mama não metastático

Risco baixo



Adjuvância

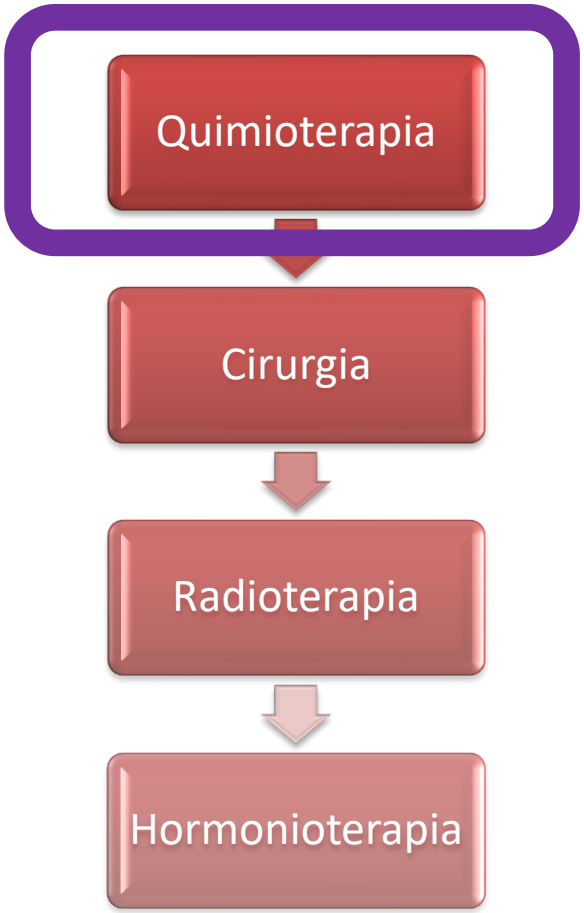
Risco médio/alto



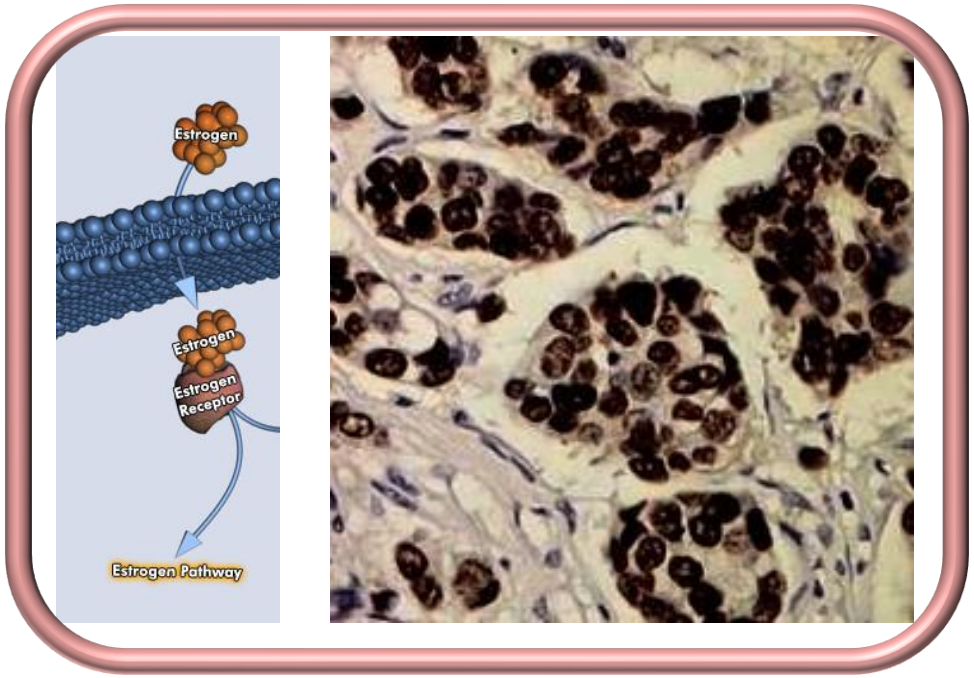
Câncer de mama não metastático

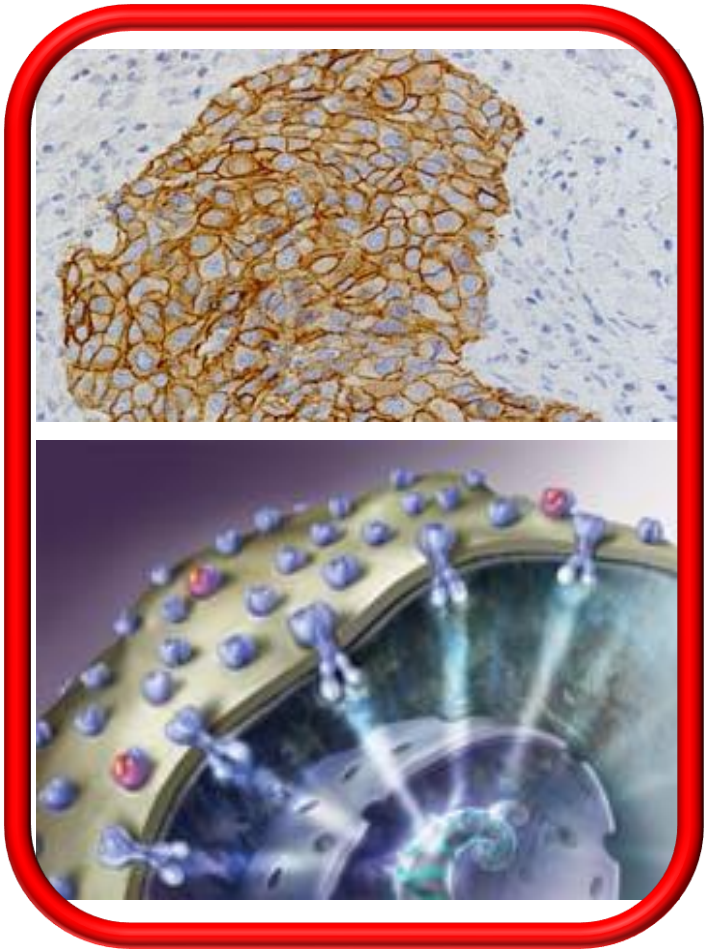
Neoadjuvância

Risco alto



Subtipos moleculares e fenotípicos

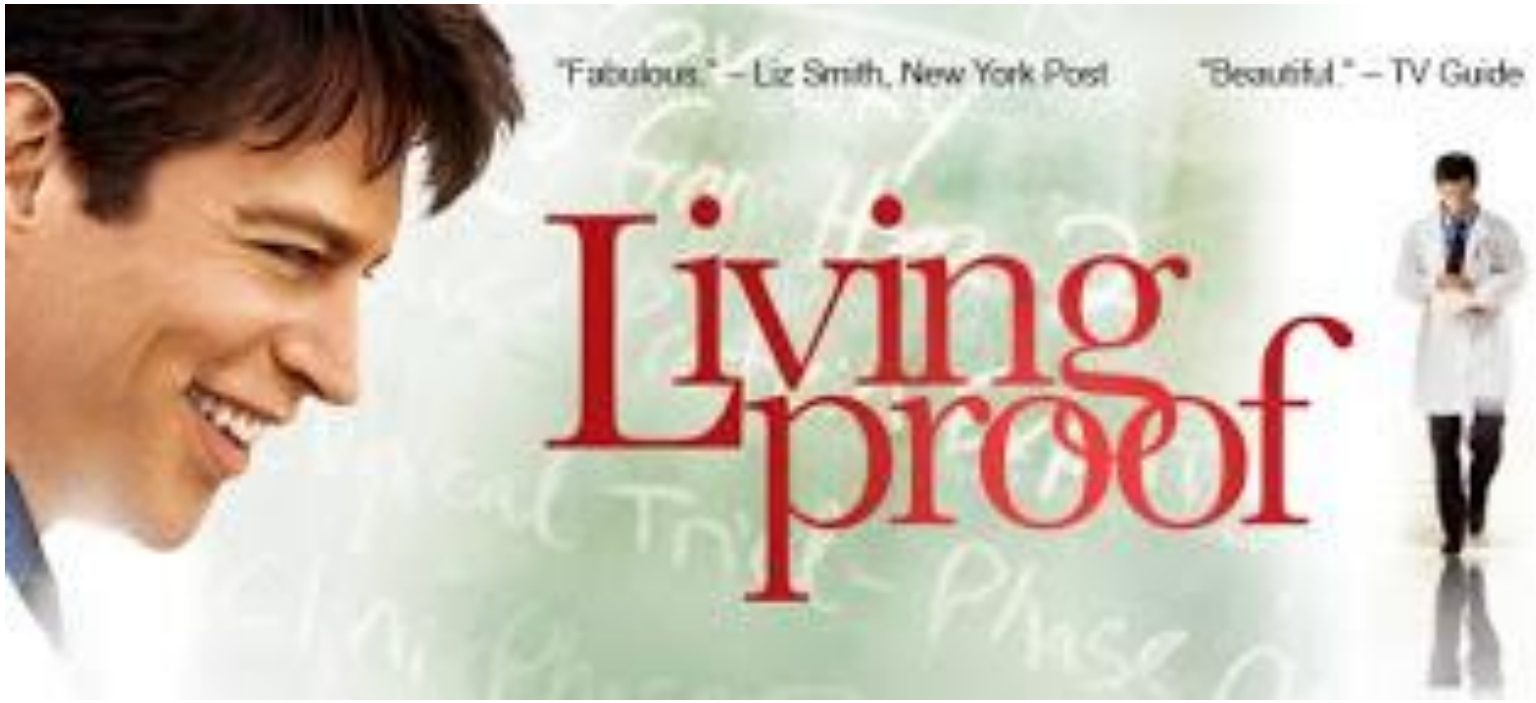




Receptores Hormonais

HER 2

Uma história de +30 anos



Uma Chance para Viver - 2008

Uma história de +30 anos

Article

Nature **312**, 513-516 (6 December 1984) | doi:10.1038/312513a0; Accepted 19 September 1984

The *neu* oncogene: an *erb-B*-related gene encoding a 185,000-M_r tumour antigen

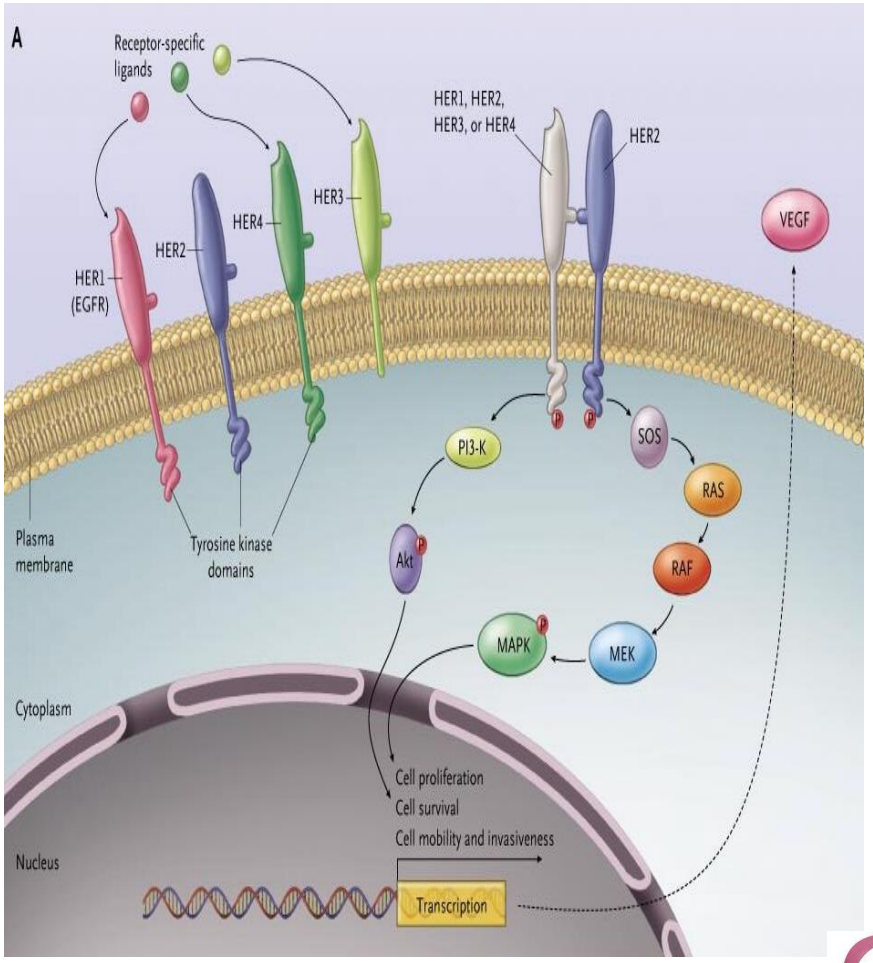
Alan L. Schechter*, David F. Stern*, Lalitha Vaidyanathan*, Stuart J. Decker†, Jeffrey A. Drebin‡, Mark I. Greene‡ & Robert A. Weinberg*

1. *Whitehead Institute for Biomedical Research, Center for Cancer Research, and Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA
2. †The Rockefeller University, New York, New York, USA
3. ‡Department of Pathology, Harvard Medical School, 25 Shattuck St, Boston, Massachusetts 02115, USA

Nature 312, 513-516 (6 dec 1984)

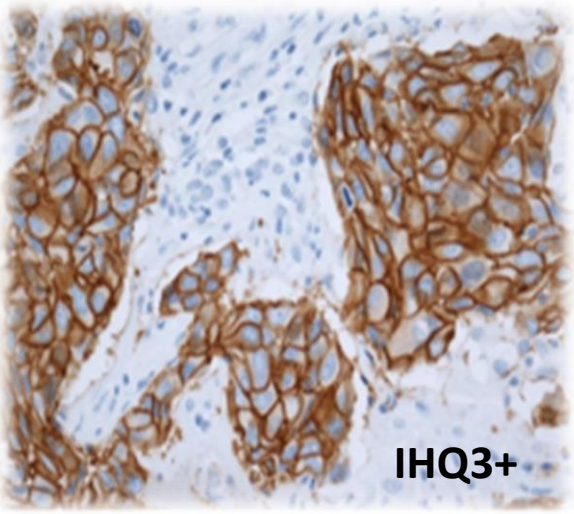
Una historia de +30 anos

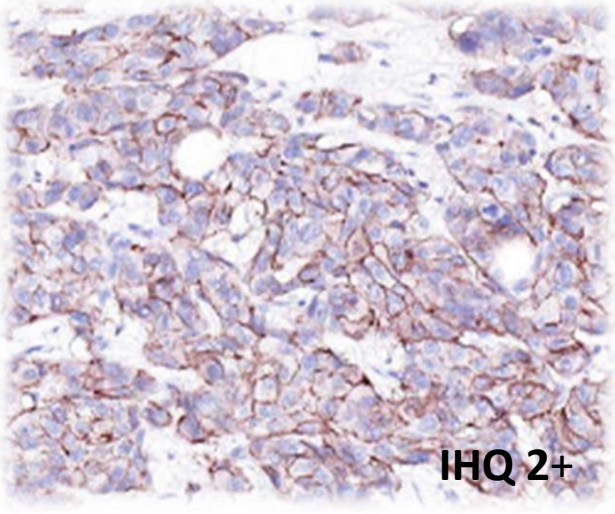
- Em 1987 a hiperexpressão de HER2 foi identificada como fator preditivo de resultados piores em cancer de mama, conferindo um fenotipo mais agressivo e com pior prognostico.
- Cerca de 20% das neoplasias de mama tem hiperexpressão ou amplificação do gene HER 2.
- A proteína HER 2 se mostrou um alvo importante para o desenvolvimento de terapias especificas.

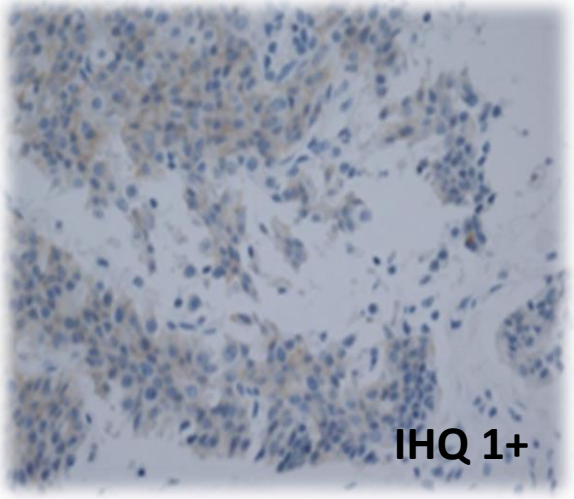


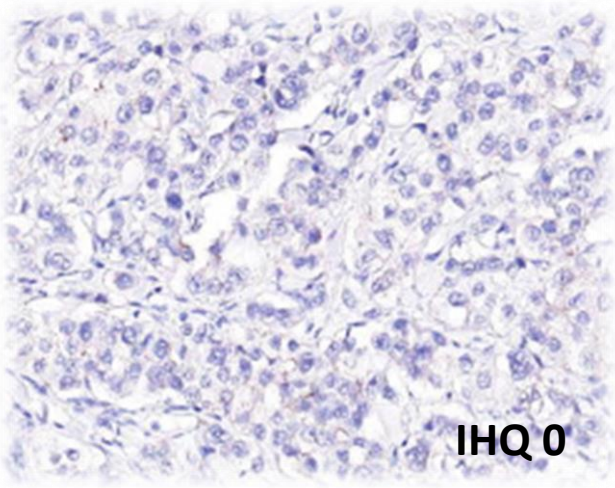
Science. 1987 Jan 9;235(4785):177-82.

HER2 - IHQ

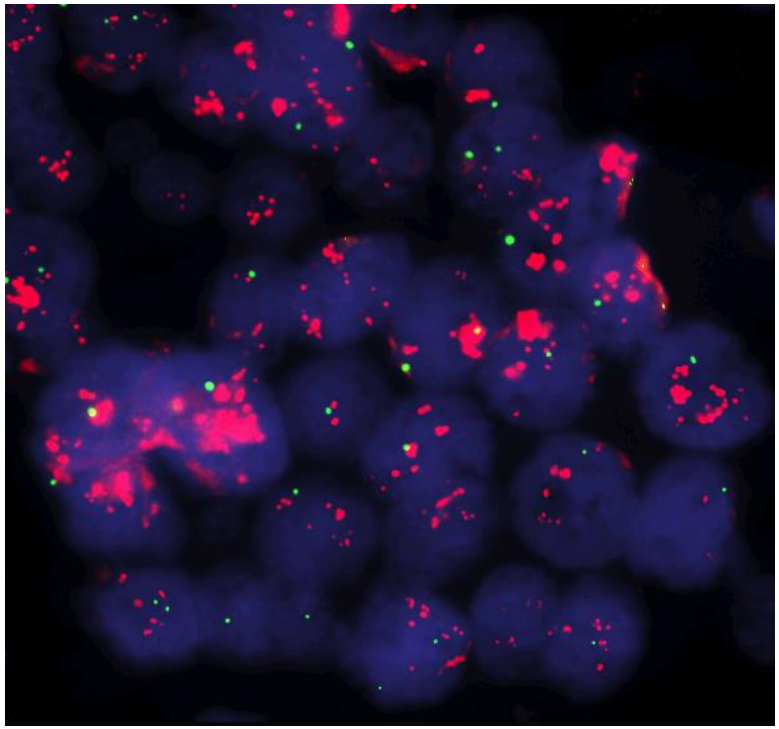


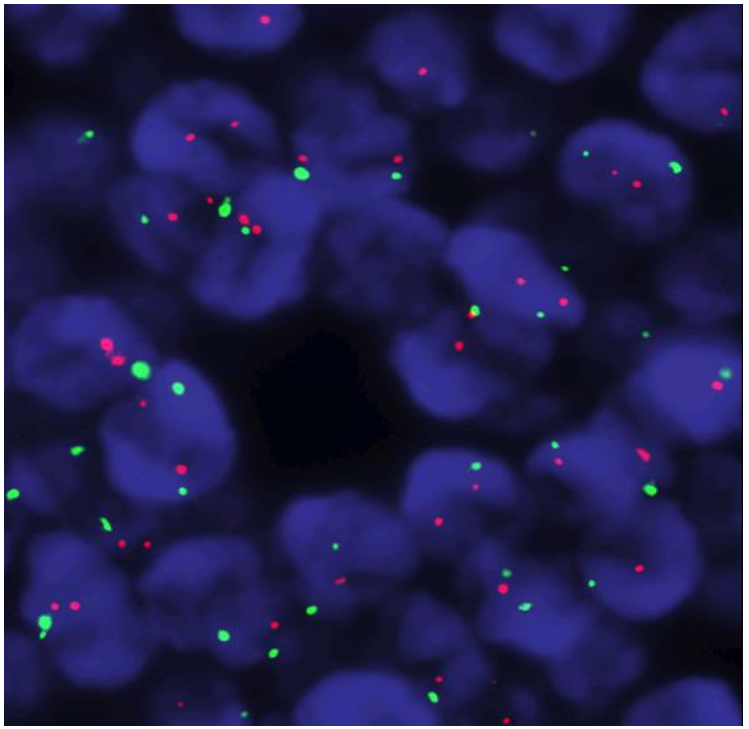






HER2 - FISH



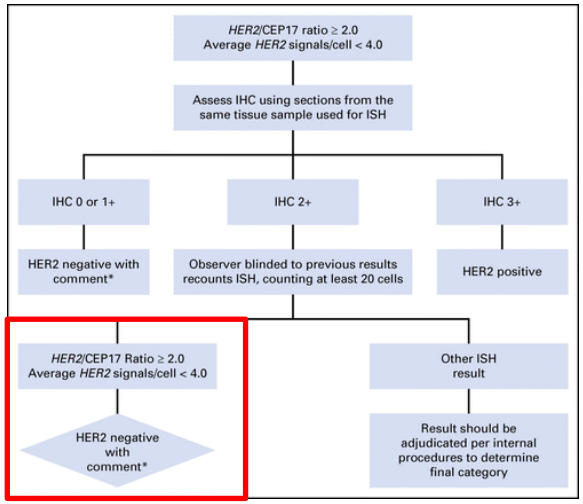


HER2 - FISH

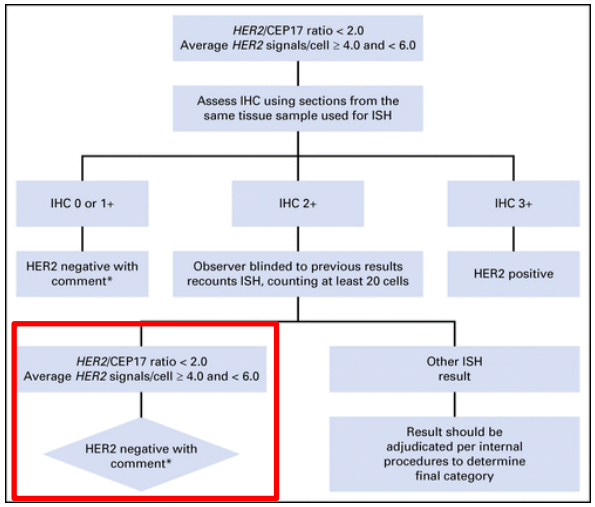
VOLUME 36 · NUMBER 20 · JULY 10, 2018
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/ College of American Pathologists Clinical Practice Guideline Focused Update

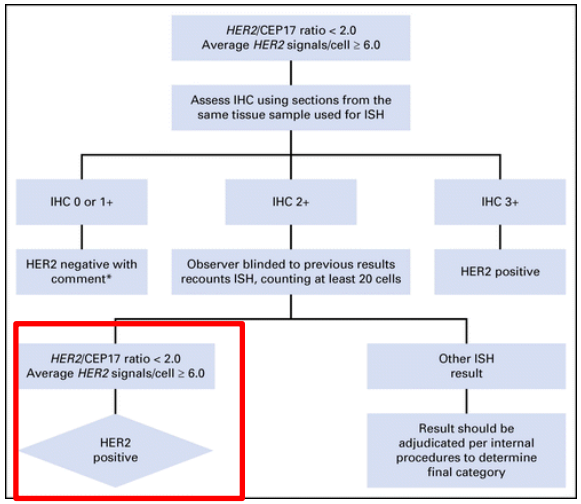
Antonio C. Wolff, M. Elizabeth Hale Hammond, Kimberly H. Allison, Brittany E. Harvey, Pamela B. Mangu, John M.S. Bartlett, Michael Bilous, Ian O. Ellis, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, Lisa M. McShane, and Mitchell Dowsett



Relação HER2/CEP17 ≥ 2.0
No cópias < 4.0 →
FISH Negativo -> Repetir



Relação HER2/CEP17 < 2.0
No cópias ≥ 4.0 e < 6.0 →
FISH Negativo -> repetir



Relação HER2/CEP17 ≤ 2.0
No cópias ≥ 6.0 →
FISH Positivo

Câncer de mama

Doença localizada

(não-metastática e operável)

- Potencialmente curável
- Tratamento visa a cura ou retardo da recidiva
- Tratamento agressivo
- Tratamento CURATIVO

PERGUNTAS FUNDAMENTAIS

1. **TRASTUZUMABE REALMENTE APRESENTA BENEFÍCIO ?**
   - **Ganho real em SLD ?**
   - **Ganho real em SG ?**

2. **QUAL A MELHOR FORMA DE ADMINISTRACAO DO TRASTUZUMABE?**
   - **Sequencial vs Concomitante ?**
   - **Qual o regime de QT mais apropriado *(AC-TH, TCH, TH)* ?**

3. **DURAÇÃO DO TRATAMENTO COM TRASTUZUMABE ?**
   - **1 ano ? 6 meses ? 9 meses ?**

4. **INCORPORACAO DE NOVAS DROGAS ?**
   - **Pertuzumabe ?**
   - **Neratinibe ?**

1. TRASTUZUMABE REALMENTE APRESENTA BENEFÍCIO ?

NSABP-B31

AC-TH vs AC-T

HR 0.54

HERA trial

Herceptin apos termino QT adj

1ano vs 2anos vs observacao

HR 0.54

BCIRG 006

AC-T versus AC-TH versus TCH

HR 0.60

NCCTG trial N9831

AC-T versus AC-TH versus AC→T→H

HR 0.48

FINHer

FEC→D/Vino→H versus FEC→D/Vino

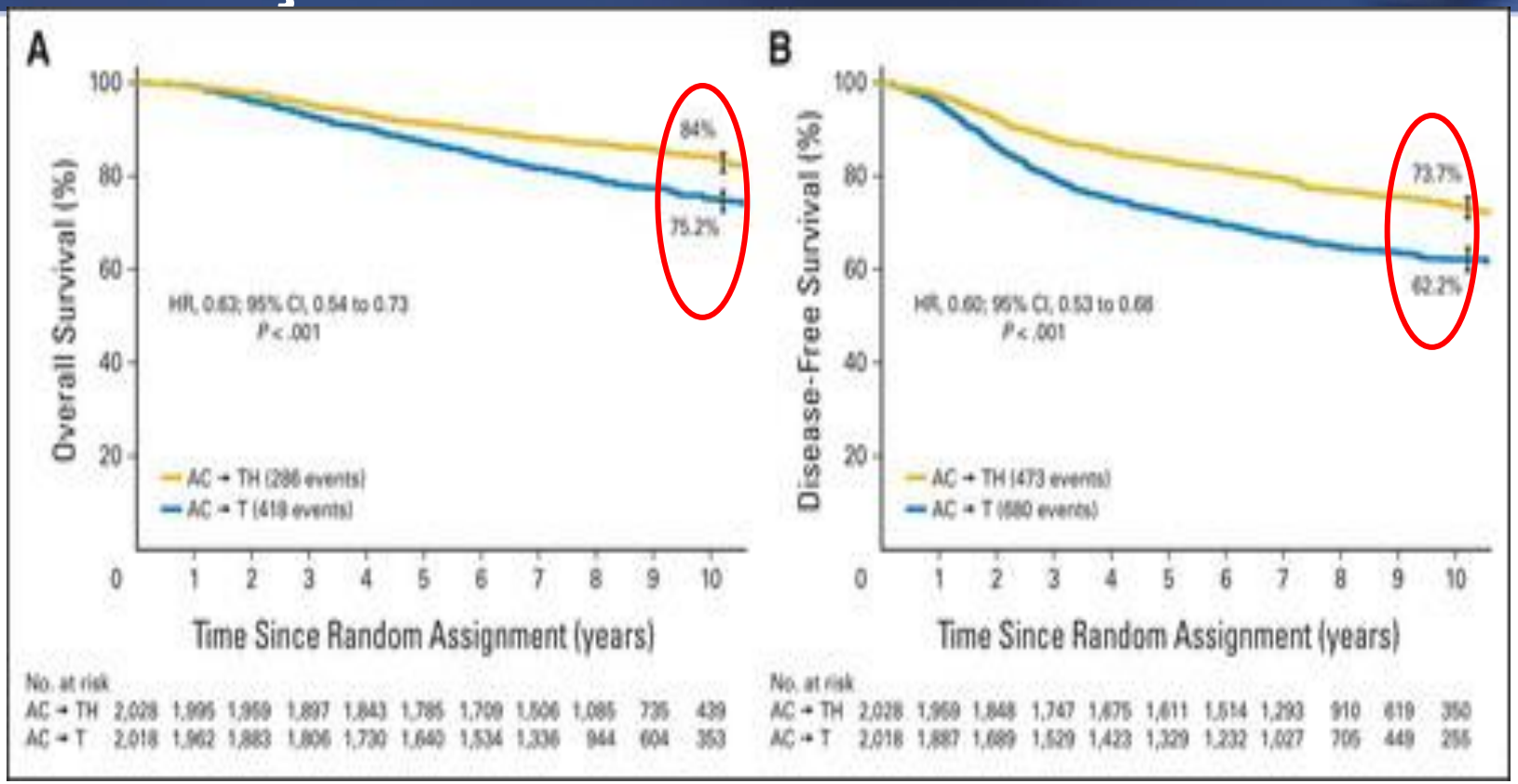
HR 0.42

PACS 04

FEC ou ED vs FEC ou D + Herceptin

HR 0.86

Atualização NSABP-B31 + N9831: 10 anos



BENEFÍCIO ABSOLUTO em OS: 9% HR 0.63 95% CI 0.54-0.73

BENEFÍCIO ABSOLUTO em DFS: 11% HR 0.60 95% CI 0.53-0.68

Perez E A et al. JCO 2014;32:3744-3752

Atualização NSABP-B31 + N9831: 10 anos

Table 4. Doxorubicin and Cyclophosphamide, Then Paclitaxel and Trastuzumab Compared With Doxorubicin and Cyclophosphamide, Then Paclitaxel: Hazard of Death and Hazard of Disease Event Within Subgroups

Factor	No. of Patients	OS		DFS	
		HR	95% CI	HR	95% CI
Age, years					
< 40	654	0.67	0.46 to 0.99	0.50	0.37 to 0.67
40-49	1,373	0.65	0.49 to 0.86	0.64	0.51 to 0.78
50-59	1,336	0.68	0.52 to 0.90	0.64	0.52 to 0.79
≥ 60	683	0.51	0.37 to 0.69	0.63	0.49 to 0.82
Hormone receptor status					
ER-negative and PgR-negative	1,828	0.65	0.53 to 0.80	0.62	0.52 to 0.73
ER-positive or PgR-positive	2,215	0.61	0.49 to 0.76	0.61	0.51 to 0.72
Tumor size, cm					
0.1-2	1,598	0.51	0.38 to 0.69	0.55	0.44 to 0.68
2.1-5.0	2,096	0.68	0.56 to 0.82	0.65	0.56 to 0.76
≥ 5.1	345	0.58	0.39 to 0.88	0.47	0.33 to 0.67

Abbreviations: DFS, disease-free survival; ER, estrogen receptor; HR, hazard ratio; OS, overall survival; PgR, progesterone receptor.

Joint Analysis

10 yr DFS by Regimen

Factor	AC ➡ P+H (%) n=2028	AC ➡ P (%) n=2018	Difference (%)
Age: < 40 yrs	77.6	61.9	15.7
40-49 yrs	78.3	69.5	8.8
50-59 yrs	77.3	68.2	9.1
60+ yrs	66.4	60.1	6.3
No. Positive nodes			
0	---	---	---
1-3	80.9	73.0	7.9
4-9	73.6	60.9	12.7
≥ 10	64.7	41.1	23.6
Hormone receptors			
ER- and PR-	73.9	62.9	11.0
ER+ and/or PR+	79.0	69.1	9.9
Tumor size (cm)			
0-2	83.5	73.0	10.5
2.1-5.0	72.8	63.3	9.5
> 5.0	70.8	49.3	21.5

Perez E A et al. JCO 2014;32:3744-3752
Romond et al. SABCS 2012

1. TRASTUZUMABE REALMENTE APRESENTA BENEFÍCIO ?

- Ganho real em DFS ? **SIM**
- Ganho real em OS ? **SIM**

2. QUAL A MELHOR FORMA DE ADMINISTRAÇÃO DO TRASTUZUMABE?

- **Sequencial vs Concomitante ?**

N9831: Comparação direta

AC→ TH vs AC→ T → H

84,5% vs 80.1%

HR 0.77 IC 95% 0.53-1.11

Mesmo perfil de efeitos colaterais e disfunção ventricular

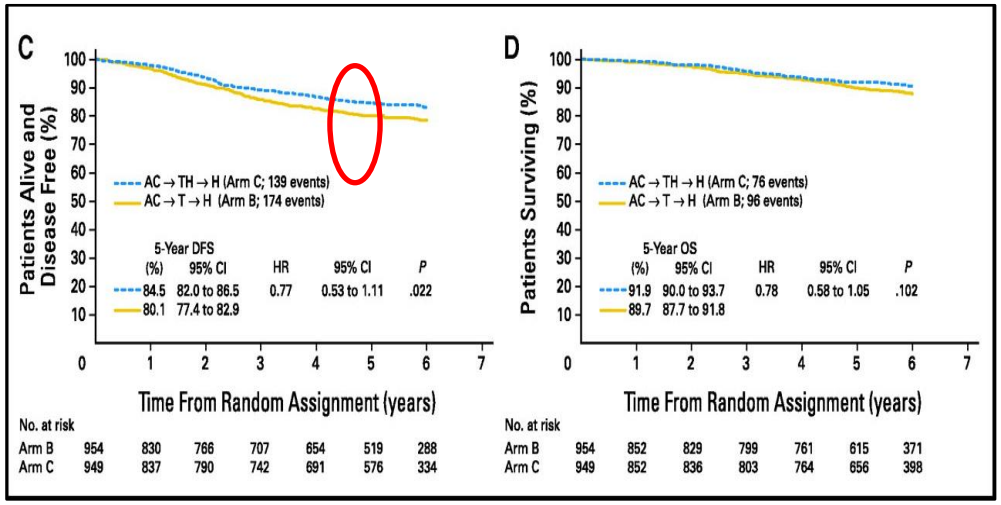


Table A1. Common Adverse Events Reported*

Adverse Event	Arm A v Arm B Comparison (%)† Arm A (n = 1,087)	Arm B (n = 1,097)	Arm B v Arm C Comparison (%)† Arm B (n = 954)	Arm C (n = 949)
Grade ≥ 4 hematologic toxicities				
Leukopenia	8.6	7.2	7.2	8.2
Neutropenia	26.5	27.5	26.7	30.6
Prespecified grade ≥ 2 nonhematologic toxicities				
Arthralgia	7.7	10.0	11.6	8.5
Left ventricular ejection fraction	2.1	7.9	9.7	10.7
Myalgia	7.1	10.7	11.7	5.4
Nail changes	4.0	5.4	7.7	4.7
Neuromotor difficulties	3.0	5.1	6.1	2.3
Neurosensory difficulties	13.4	14.67	19.7	8.7
Other grade ≥ 3 nonhematologic toxicities				
Nausea	5.4	4.9	4.7	5.5
Febrile neutropenia	4.1	4.3	3.7	6.6

*Reporting requirements included grade ≥ 4 hematologic toxicities, grade ≥ 2 neuropathies, nail changes, myalgias, arthralgias, and other grade ≥ 3 nonhematologic toxicities.

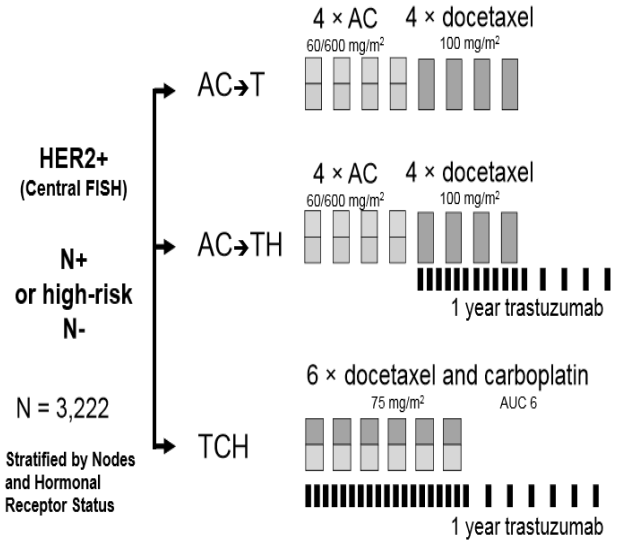
Concomitante	Beneficio DFS	Hazard Ratio
NSABP-B31	SIM	HR 0.60 95% CI 0.53-0.68, P < .001
BCIRG-006	SIM	HR 0.64; 95% CI, 0.53-0.78; P < .001 (AC-TH) HR 0.75; 95% CI, 0.63-0.90; P = .040 (TCH)
Sequencial		
HERA	SIM	HR, 0.76; 95% CI, 0.6-0.87; P < .001
N9831 (ARM B)	SIM	HR, 0.69; 95% CI, 0.57-0.85; P < .001
FNCLCC-PACS-04	NS	HR, 0.86; 95% CI, 0.61-1.22; P = .41

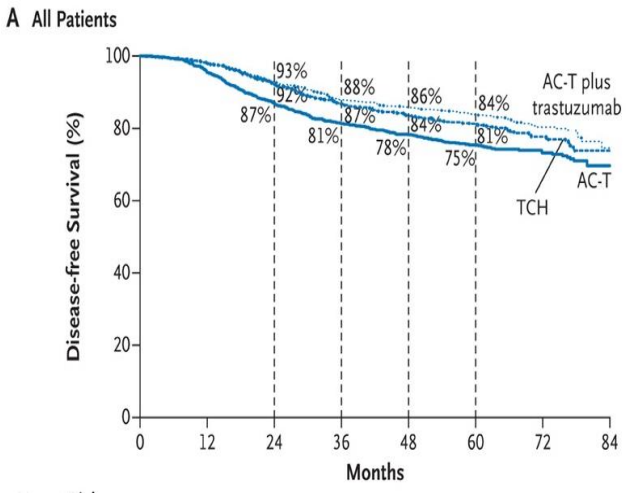
2. QUAL A MELHOR FORMA DE ADMINISTRAÇÃO DO TRASTUZUMABE?

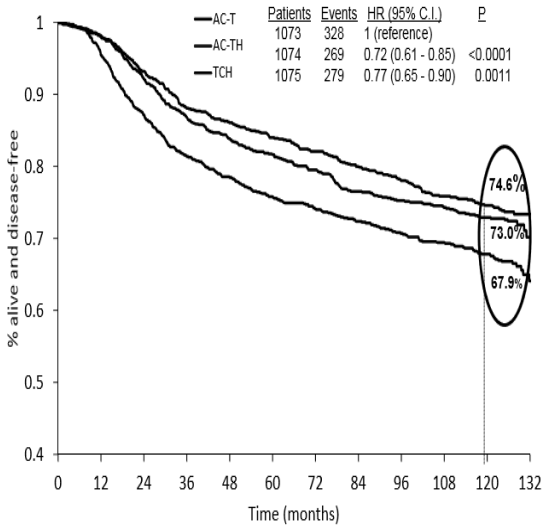
- Qual o regime de QT mais apropriado ***(AC-TH, TCH, TH)*** ?

  AC-TH versus TCH

BCIRG 006







Slamon et al. NEJM 2011
Slamon et al, SABCS 2015

Follow up 65 meses

Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
		number of events	
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1†

Follow up 10 anos

10 Years

	AC-TH	TCH
Disease-free survival events	269	279
Grade 3/4 congestive heart failure	21 (2%)	4 (0.4%)
Total disease-free survival events	290	283
Treatment-related leukemia	7	0
Sustained LVEF loss > 10%	200	97

AC-TH = doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab; TCH = docetaxel, carboplatin, and trastuzumab; LVEF = left ventricular ejection fraction.

- Estudo não tem poder para comparar os regimes
- AC-TH apresenta numericamente menos recorrências
- Toxicidade hematológicas similares
- Um total de 21 casos de ICC grau ¾ com AC-TH comparado com apenas 4 casos no braço TCH (P = .0005)
- Um total de 200 pacientes com queda ≥ 10% na fração de ejeção ventricular com AC-TH, versus 97 no braço TCH (P < .0001)
- 7 casos de leucemia no braço AC-TH versus 0 no braço TCH

Mas será que todos os casos precisam de antraciclinas e/ou regime intenso?

- APT trial: TH x 12

✓ 406 pacientes

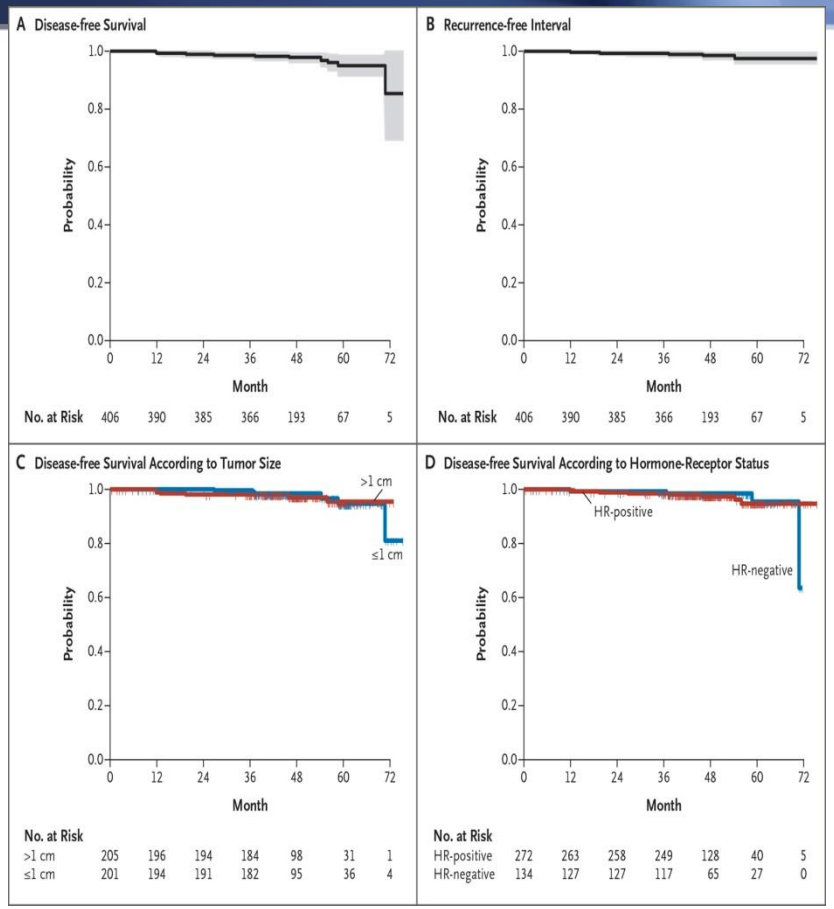
✓ tumores ≤ 3cm

✓ N0

✓ Braço unico

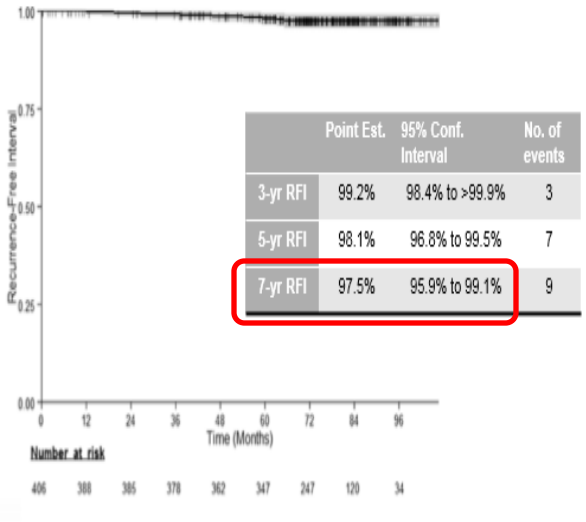
✓ Median Follow up: 4 anos

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)



Distant recurrence*		
Skeletal tissue, HER2-positive	1 (0.2)	27
Soft tissue, HER2-negative	1 (0.2)	46
Death		
Breast-cancer–related	0	
Not breast-cancer–related	2 (0.5)	13, 71

Atualização 7 anos APT trial



	Point Est.	95% Conf. Interval	No. of events
3-yr RFI	99.2%	98.4% to >99.9%	3
5-yr RFI	98.1%	96.8% to 99.5%	7
7-yr RFI	97.5%	95.9% to 99.1%	9

Disease-Free Survival Events with Median Follow-up of 7 Years

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)

Recurrence-free interval 7 anos: 97.5%

Nenhuma morte cancer específica

Apenas 4 (1.0%) recorrências a distância

Tolaney et al, ASCO 2017

2. QUAL A MELHOR FORMA DE ADMINISTRAÇÃO DO TRASTUZUMABE?

- Sequencial vs Concomitante ?

Uso de trastuzumabe concomitante a QT parece ser superior ao uso sequencial

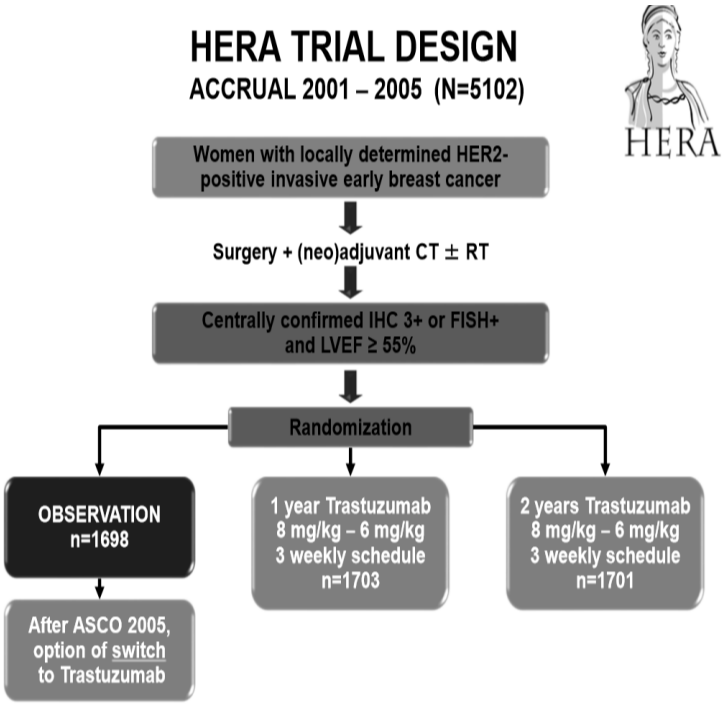
- Qual o regime de QT mais apropriado ***(AC-TH, TCH, TH)*** ?

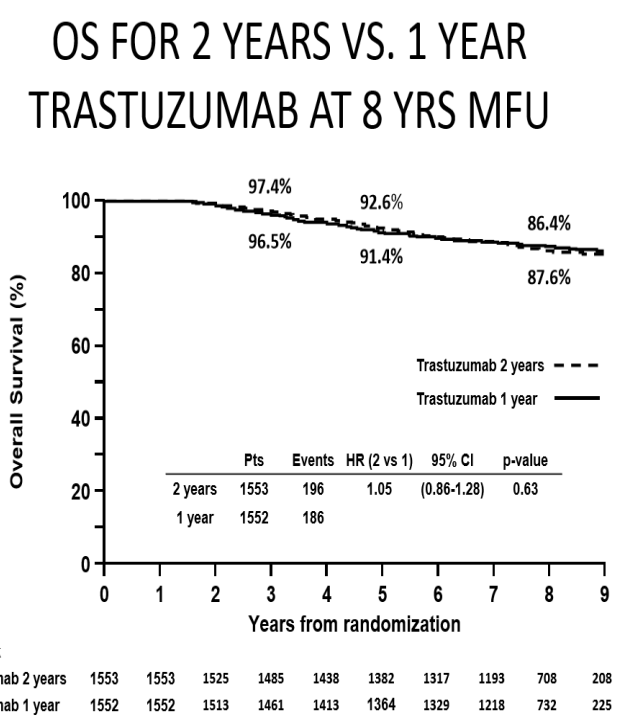
TH em tumors de baixo risco (≤ 2cm, N-) aparece como uma ótima opção, com um índice de recidiva a distância muito baixo!

AC-TH ou TCH (principalmente em pacientes com risco cardiovascular)

3. DURAÇÃO DO TRATAMENTO COM TRASTUZUMABE ?

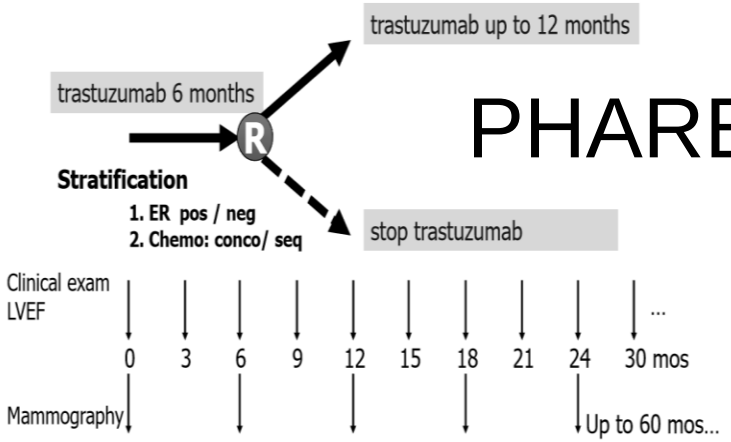
HERA trial





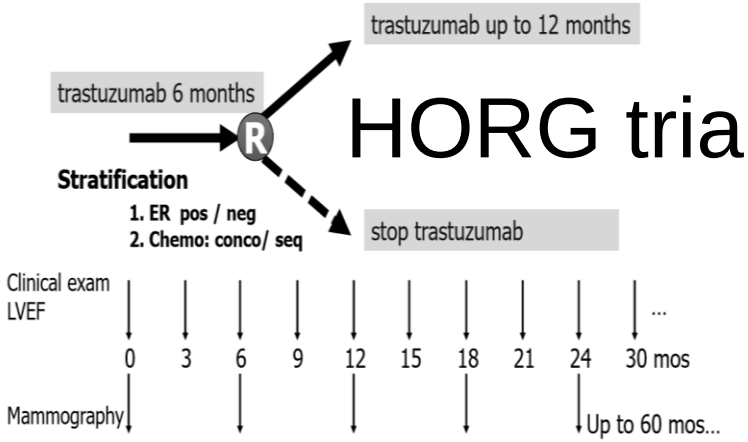
1 ano = 2 anos

E uma terapia mais curta?



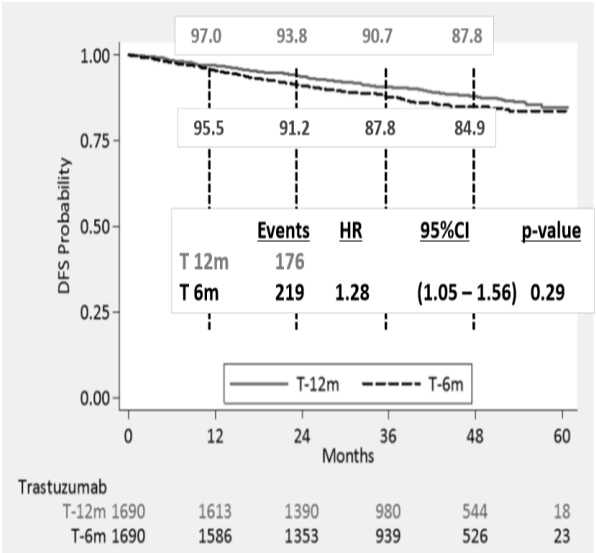
PHARE trial

R: Randomization after informed consent



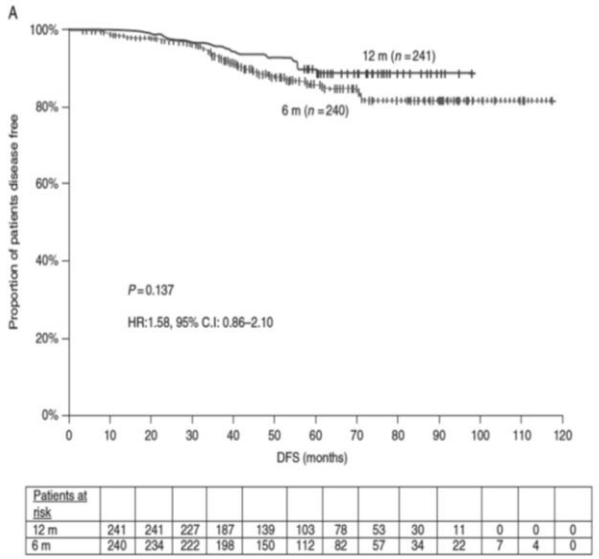
HORG trial

R: Randomization after informed consent



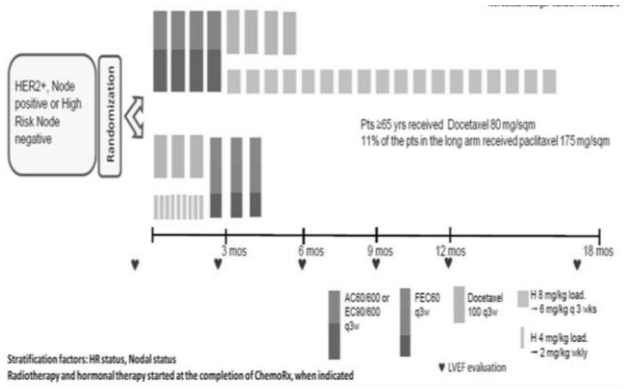
← HR 1.28 (1.05-1.56)
HR para NI 1.15

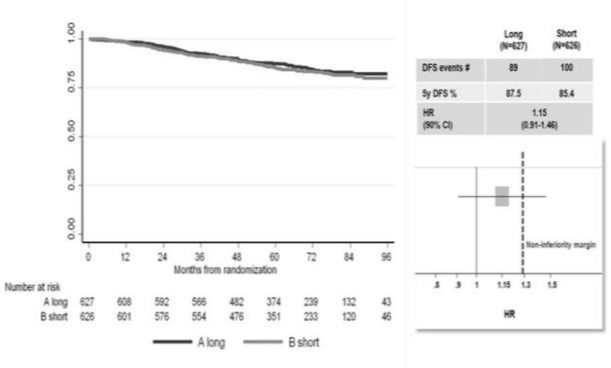
HR 1.57 (0.86-2.10) →
HR para NI 1.53



E uma terapia mais curta?

Short-HER trial



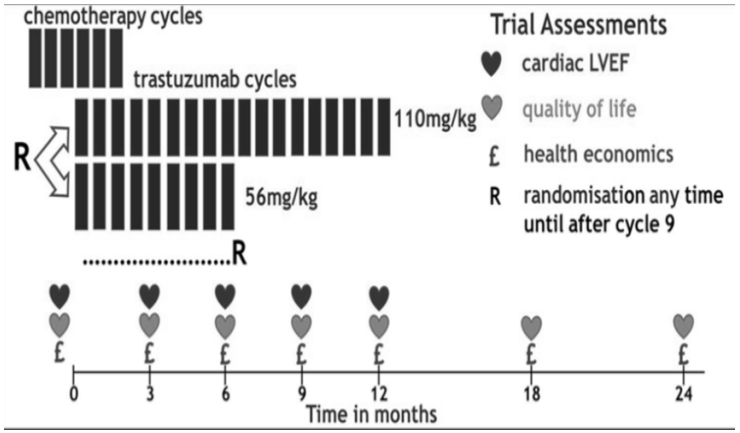


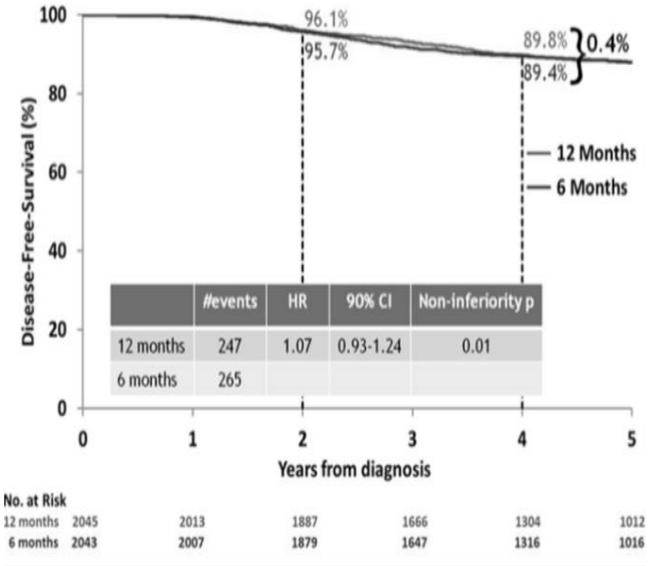
HR pata NI 1.3

HR 1.07→

NI ≤ 3%

PERSEPHONE trial





TRIAL	Design	Result
PHARE	6m versus 12m Não inferioridade HR para NI 1.15	Negativo para não-inferioridade HR 1.28 (1.05-1.56)
HORG	6m versus 12m Não inferioridade HR para NI 1.53	Negativo para não-inferioridade HR 1.57 (0.86-2.10)
SHORT-Her	9 sem versus 12m Não inferioridade HR para NI 1.3	Negativo para não inferioridade HR 1.15 (0.91-1.46)
PERSEPHONE	6m versus 12m Não inferioridade NI: “ ≤3%”	POSITIVO HR 1.07 (0.93-1.24)

3. DURAÇÃO DO TRATAMENTO COM TRASTUZUMABE ?

- PERSEPHONE utilizou um cut-off para não-inferioridade diferente dos outros estudos
- No PERSEPHONE, pacientes que receberam QT concomitante (padrão atual) apresentaram melhor DFS com trastuzumabe por 1 ano
- Apenas 1 de 4 estudos clinicos mostrou nao inferioridade

✓ 1 ano de trastuzumabe ainda deve ser o padrão

✓ 6 meses pode ser considerado (alto risco CV)

4. INCORPORAÇÃO DE NOVAS DROGAS ?
- Pertuzumabe? APHINITY TRIAL

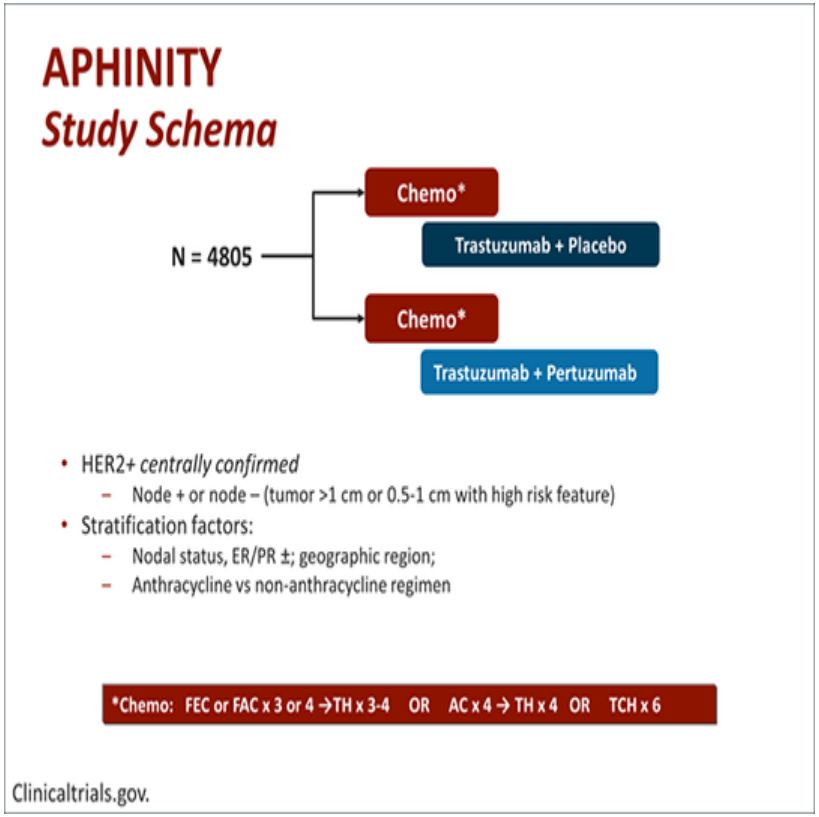


Table 1. Demographic and Baseline Disease Characteristics of the Patients.

Characteristic	Pertuzumab Group (N=2400)	Placebo Group (N=2404)
Nodal status — no. of patients (%)		
0 positive nodes and tumor ≤1 cm*	90 (3.8)	84 (3.5)
0 positive nodes and tumor >1 cm*	807 (33.6)	818 (34.0)
1–3 positive nodes	907 (37.8)	900 (37.4)
≥4 positive nodes	596 (24.8)	602 (25.0)
Adjuvant chemotherapy regimen — no. of patients (%)†		
Anthracycline-containing regimen	1865 (77.7)	1877 (78.1)
Non–anthracycline-containing regimen	535 (22.3)	527 (21.9)
Hormone-receptor status — no. of patients (%)‡		
Negative	864 (36.0)	858 (35.7)
Positive	1536 (64.0)	1546 (64.3)
Protocol version — no. of patients (%)*		
Protocol A	1828 (76.2)	1827 (76.0)
Protocol B	572 (23.8)	577 (24.0)
Age — no. of patients (%)		
<40 yr	326 (13.6)	327 (13.6)
40–64 yr	1759 (73.3)	1784 (74.2)
≥65 yr	315 (13.1)	293 (12.2)
Pathological tumor size — no. of tumors/total no. (%)§		
0 to <2 cm	978/2400 (40.8)	948/2405 (39.4)
2 to <5 cm	1275/2400 (53.1)	1283/2405 (53.3)
≥5 cm	147/2400 (6.1)	174/2405 (7.2)

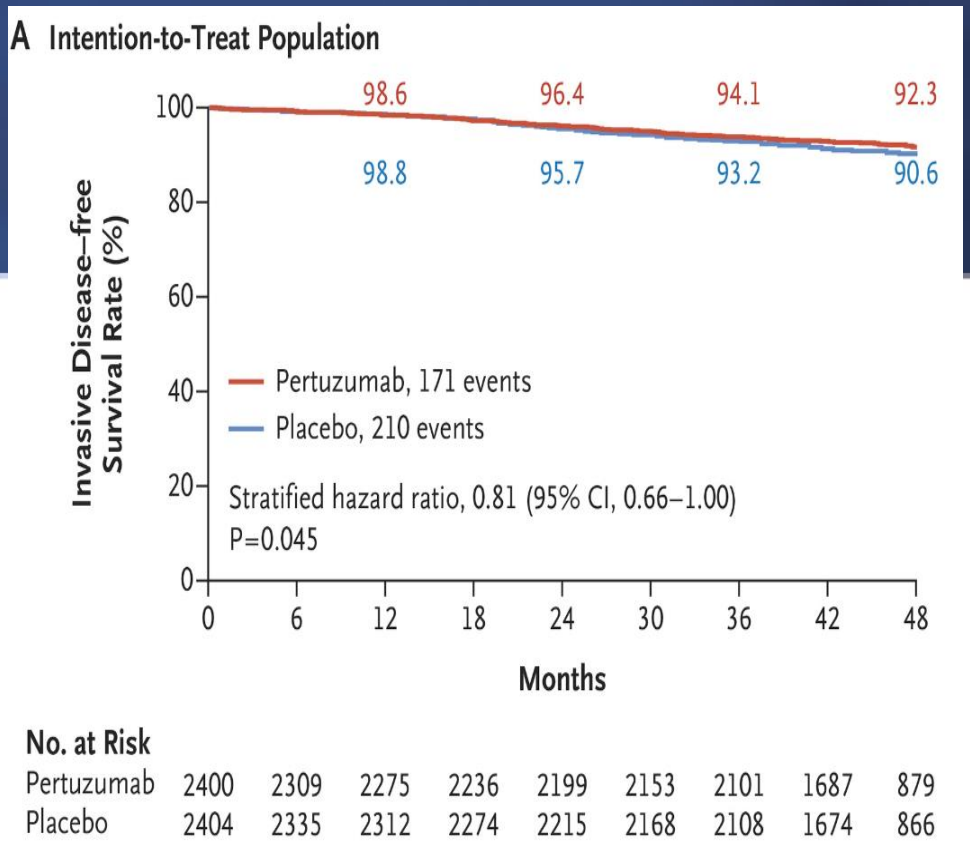
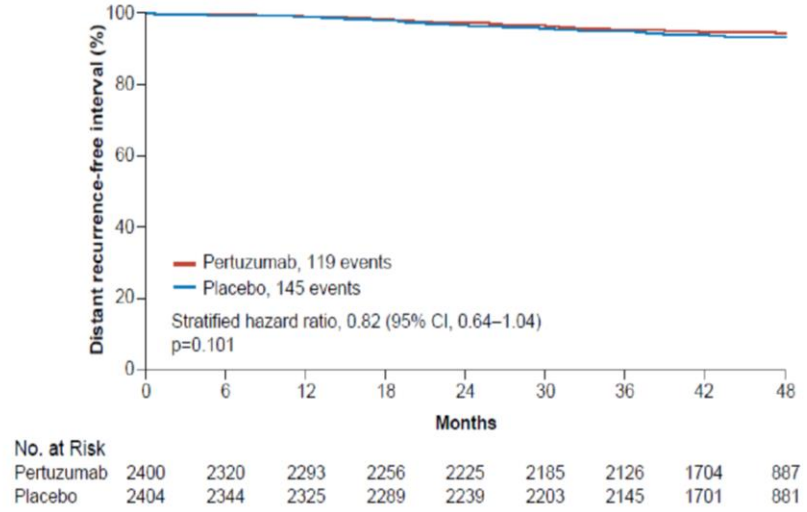


Table 2. Site of First Invasive-Disease Event.*

Event	Pertuzumab Group (N=2400)	Placebo Group (N=2404)
	no. of patients (%)	
Any invasive-disease event	171 (7.1)	210 (8.7)
Category of first invasive-disease event		
Distant recurrence	112 (4.7)	139 (5.8)
CNS metastases	45 (1.9)	44 (1.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without previous event	28 (1.2)	26 (1.1)

Figure S4. Kaplan–Meier Plots of Distant Recurrence-Free Interval.

CI denotes confidence interval.

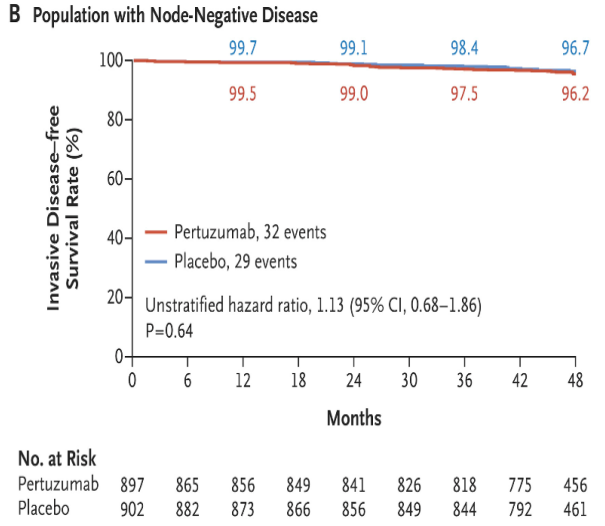


4 yr IDFS HR= 0.81 (p = 0.045)

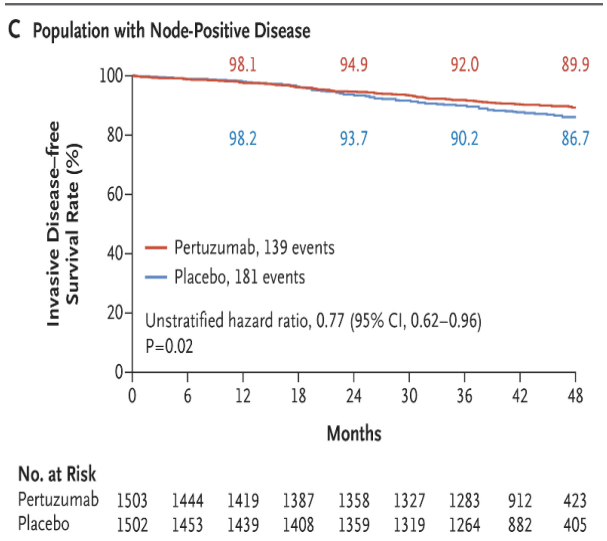
Benefício Absoluto= 1.7%

APHINITY TRIAL: Análises de Subgrupos

Status Linfonodal

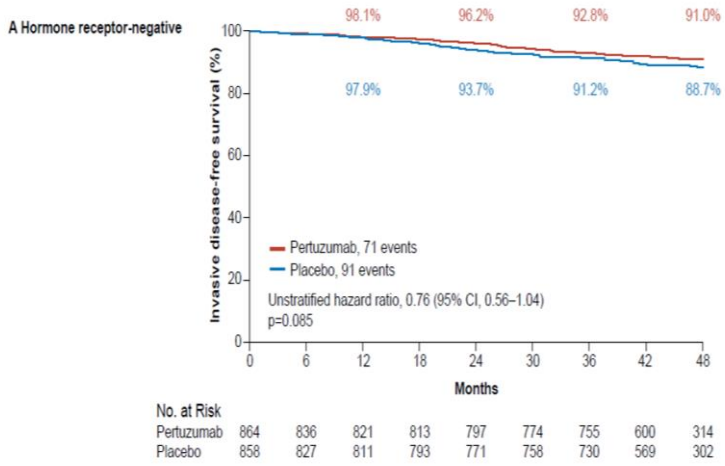


N –
HR=1.13
P=0.644
Δ=0.5%

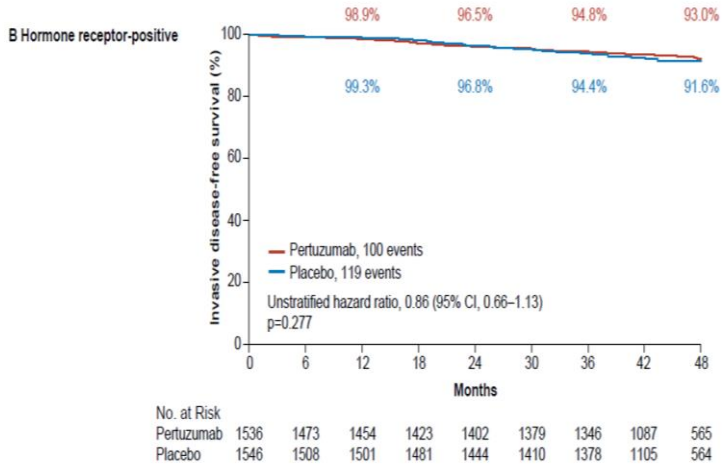


N +
HR=0.77
P=0.019
Δ=3.2%

Status Hormonal

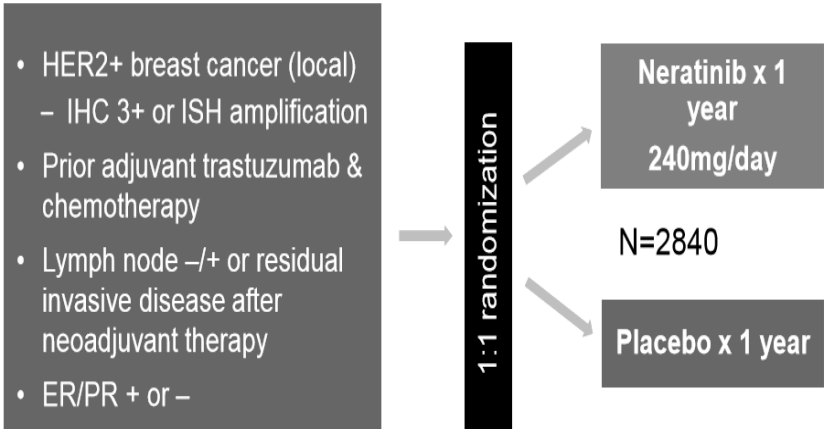


RE negativo
HR=0.76
P=0.085
Δ=2.3%



RE Positivo
HR=0.86
P=0.277
Δ=1.4%

4. INCORPORAÇÃO DE NOVAS DROGAS ?
- Neratinibe? ExteNET TRIAL



n (%)	Neratinib (n=1420)	Placebo (n=1420)
Nodal status		
• Negative	335 (23.6)	336 (23.7)
• 1–3 positive nodes	664 (46.8)	664 (46.8)
• ≥4 positive nodes	421 (29.6)	420 (29.6)
Hormone receptor status		
• Positive	816 (57.5)	815 (57.4)
• Negative	604 (42.5)	605 (42.6)
(Neo)Adjuvant chemotherapy		
• Yes	1420 (100)	1420 (100)
Trastuzumab	1420 (100)	1420 (100)
Anthracycline only	136 (9.6)	135 (9.5)
Anthracycline + taxane	962(67.8)	965 (68.0)
Taxane only	318 (22.4)	316 (22.3)
Non-anthracycline / taxane	4 (0.3)	4 (0.3)
Concomitant endocrine therapy in hormone-positive patients		
• Anti-estrogen only	375 (26.4)	347 (24.4)
• Aromatase inhibitor only	362 (25.5)	379 (26.7)
• Anti-estrogen + aromatase inhibitor	20 (1.4)	34 (2.4)
• Non-anti-estrogen or aromatase inhibitor	3 (0.2)	4 (0.3)

4. INCORPORAÇÃO DE NOVAS DROGAS ?

- Pertuzumabe ?

Maior benefício em LN +, porém considerar o risco absoluto. T3N0 podem ter benefício. Ainda não esta claro o benefício em subgrupos RE – e RE +, porém RE – parece apresentar maior ganho

- Neratinibe ?

Benefício em pacientes alto risco, N+

Considerar prós e contras da toxicidade

Ausência de evidência em pacientes expostas ao Pertuzumabe

Câncer de mama

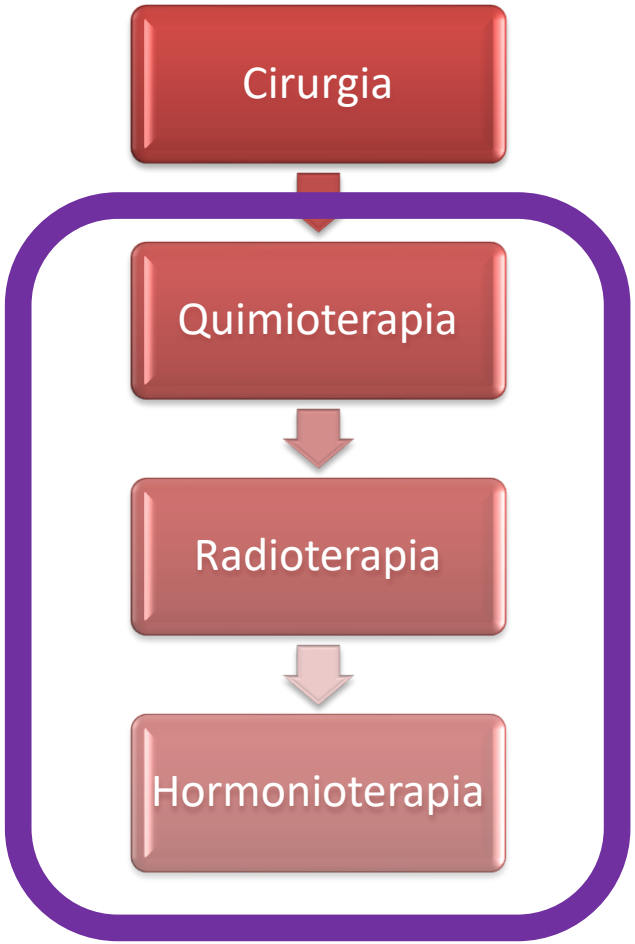
Adjuvância

Doença localizada

(não-metastática e operável)

- Potencialmente curável
- Tratamento visa a cura ou retardo da recidiva
- Tratamento agressivo
- Tratamento CURATIVO

Risco médio/alto

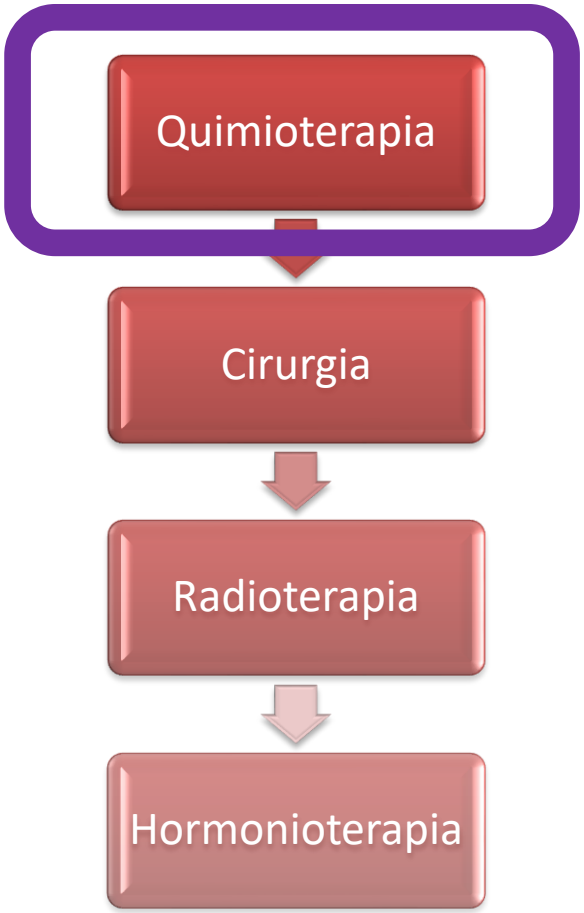


Câncer de mama

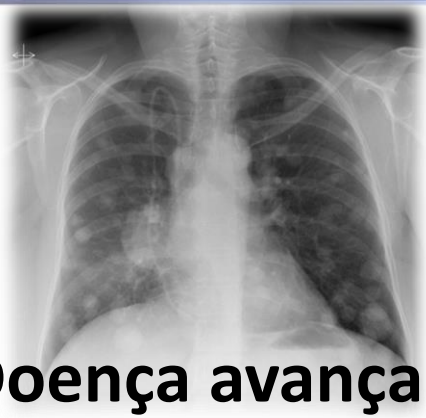
Neoadjuvância

Redução da extensão da cirurgia
NA MAMA
E NA AXILA

Risco alto



Câncer de mama

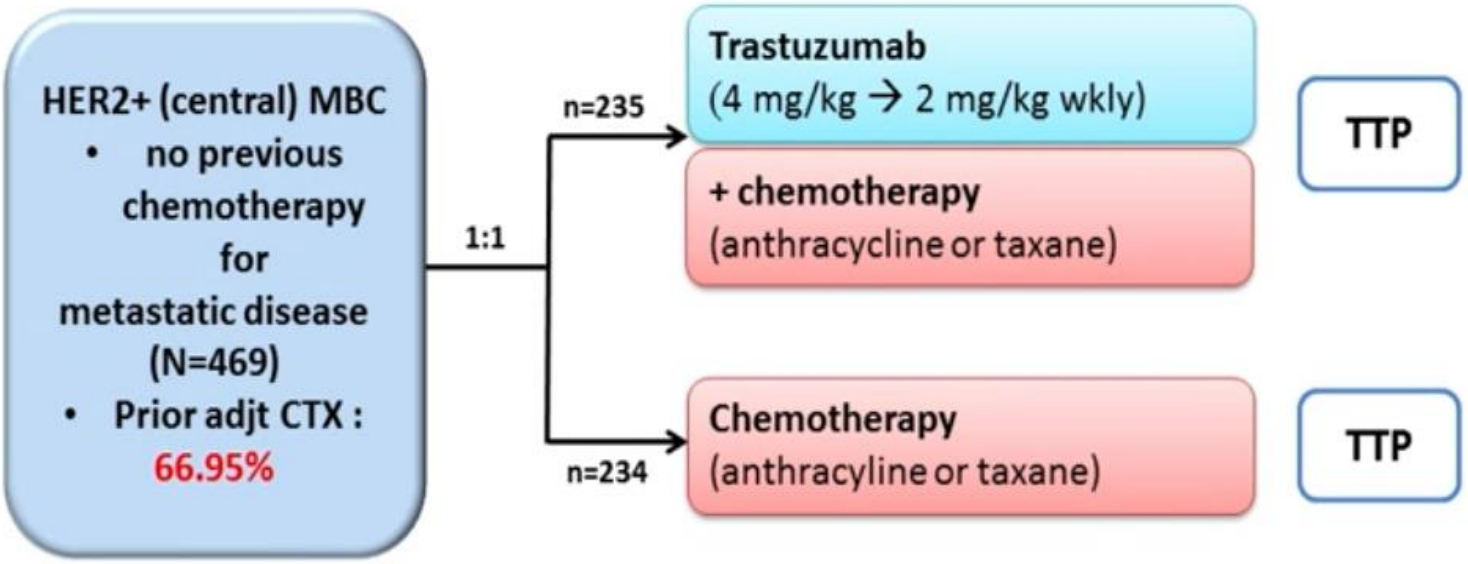


Doença avançada

(metastática ou inoperável)

- Incurável
- Prolongar sobrevida mas também melhorar a qualidade de vida
- Tratamento PALIATIVO
- Doença ‘crônica’ exigindo tratamento quase contínuo
- Sequencia de linhas de tratamento:
- 1ª linha -> 2ª linha -> 3ª linha....

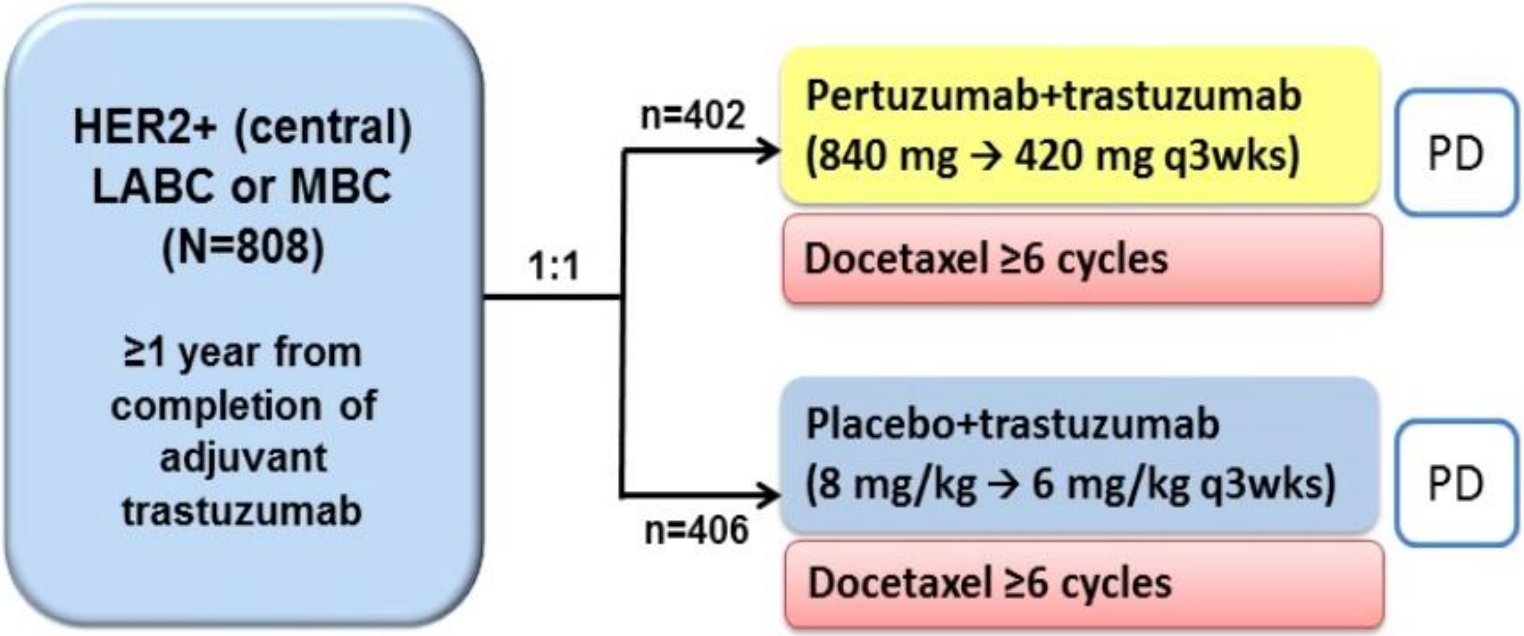
Primeira Linha



	QT + Trast	QT	p value
RR	50%	32%	<0,001
TTP	7,4 meses	4,6 meses	<0,001
OS	25,1 meses	20,4 meses	0,046

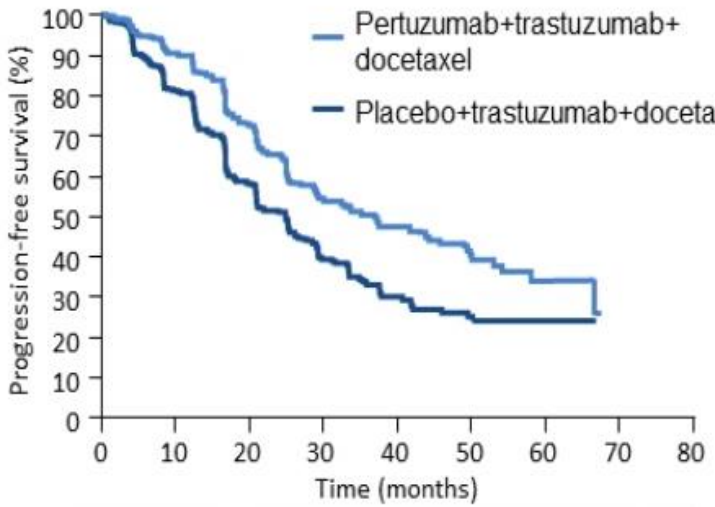
N Engl J Med. 2001 Mar 15;344(11):783

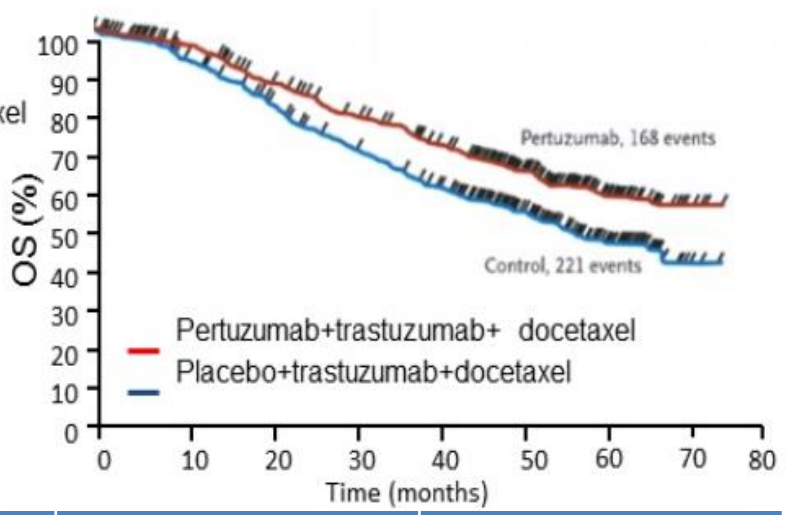
Primeira Linha (CLEOPATRA)



N Engl J Med. 2012 Jan 12;366(2):109-1

Primeira Linha (CLEOPATRA)



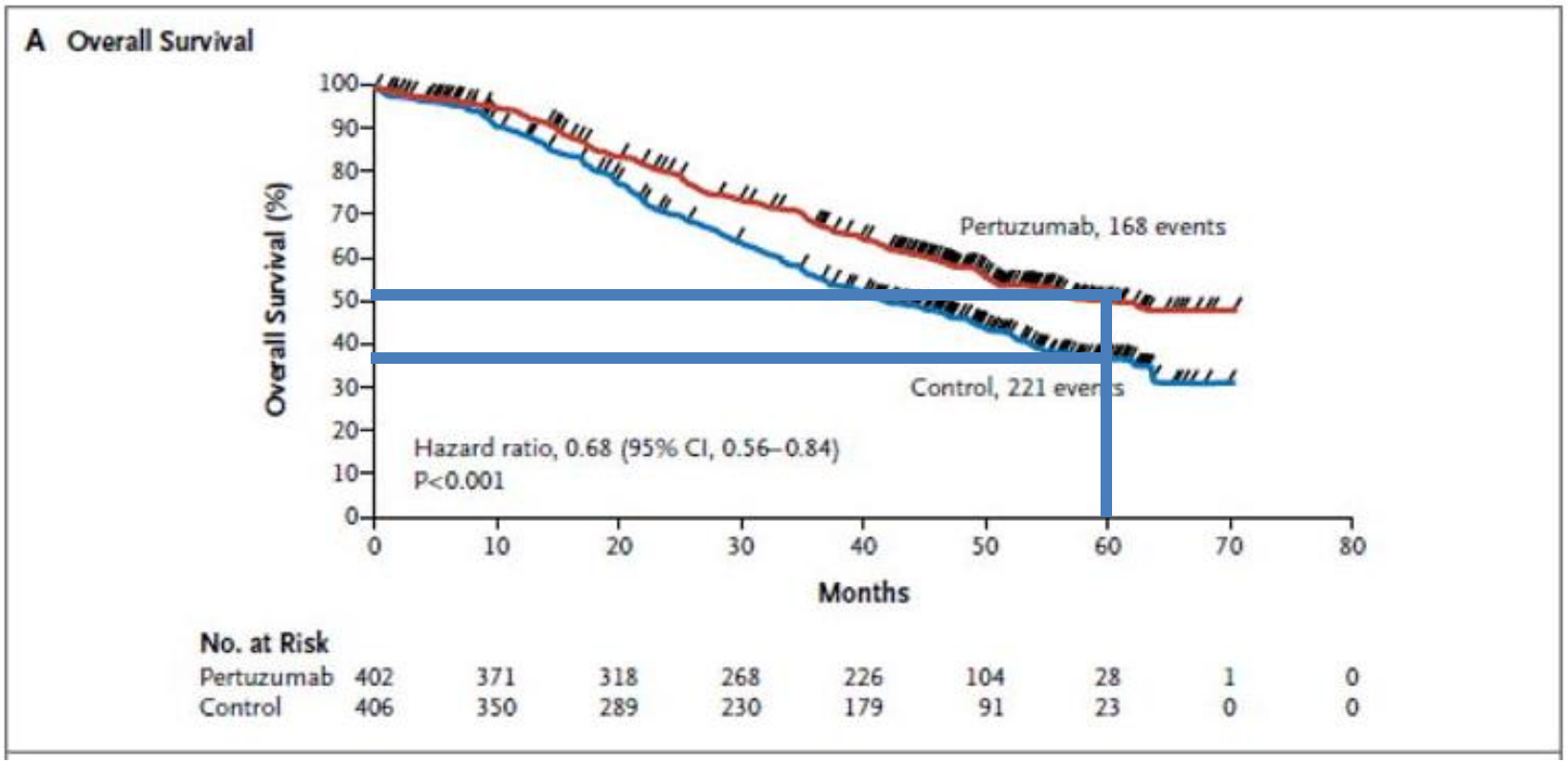


	Docetaxel + TP	Docetaxel+ T	p value
RR	80,2%	69,3%	<0,001
PFS	18,7 meses	12,4 meses	<0,001
OS	56,5 meses	40,8 meses	<0,001

- **Toxicidades G3-4 no braço Docetaxel + TP**
  - Neutropenia 48%, neutropenia febril 14%, diarreia 8%

N Engl J Med. 2012 Jan 12;366(2):109-1
N Engl J Med. 2015 Feb 19;372(8):724-3

Primeira Linha (CLEOPATRA)



N Engl J Med. 2015 Feb 19;372(8):724-3

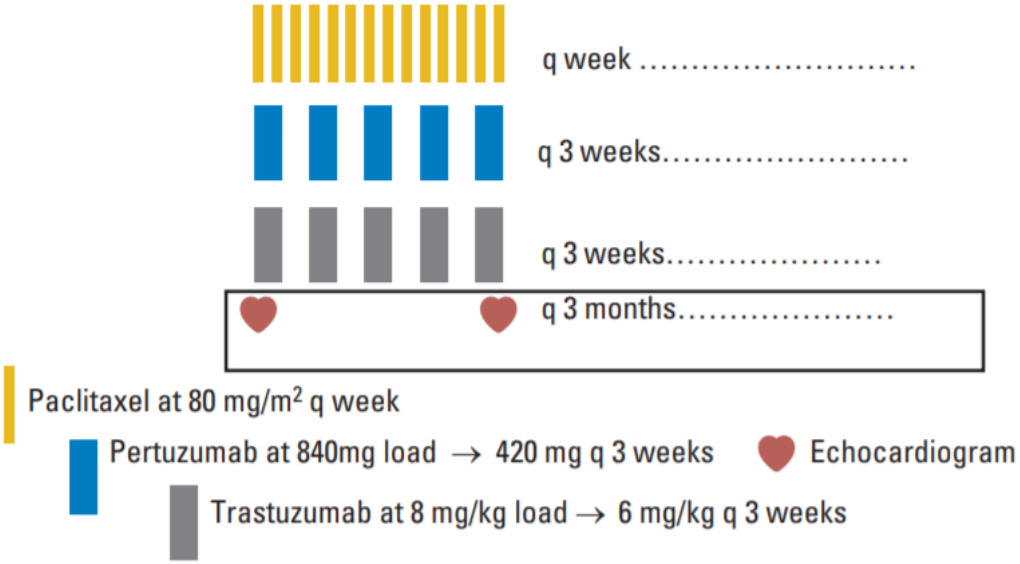
Primeira Linha (CLEOPATRA)

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Placebo plus Trastuzumab plus Docetaxel (N=397)	Pertuzumab plus Trastuzumab plus Docetaxel (N=407)
	number (percent)	
Grade 3 or higher events‡		
Neutropenia	182 (45.8)	199 (48.9)
Febrile neutropenia	30 (7.6)	56 (13.8)
Leukopenia	58 (14.6)	50 (12.3)
Diarrhea	20 (5.0)	32 (7.9)
Peripheral neuropathy	7 (1.8)	11 (2.7)
Anemia	14 (3.5)	10 (2.5)
Asthenia	6 (1.5)	10 (2.5)
Fatigue	13 (3.3)	9 (2.2)
Granulocytopenia	9 (2.3)	6 (1.5)
Left ventricular systolic dysfunction	11 (2.8)	5 (1.2)
Dyspnea	8 (2.0)	4 (1.0)

N Engl J Med. 2012 Jan 12;366(2):109-1

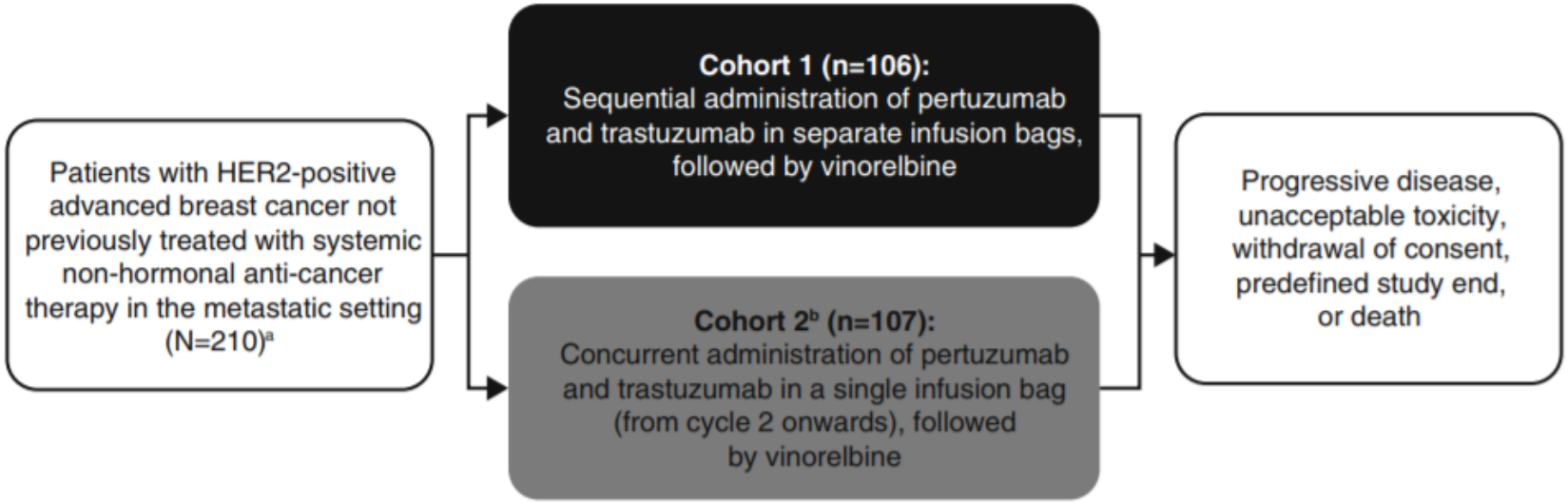
Paclitaxel + Trastuzumabe + Pertuzumabe



	VNM + Trast + Per
RR	59%
PFS	19.5 m
OS	43.4m

J Clin Oncol. 2015 Feb 10;33(5):442-7

Vinorelbina + Pertuzumabe + Trastuzumab (VELVET)



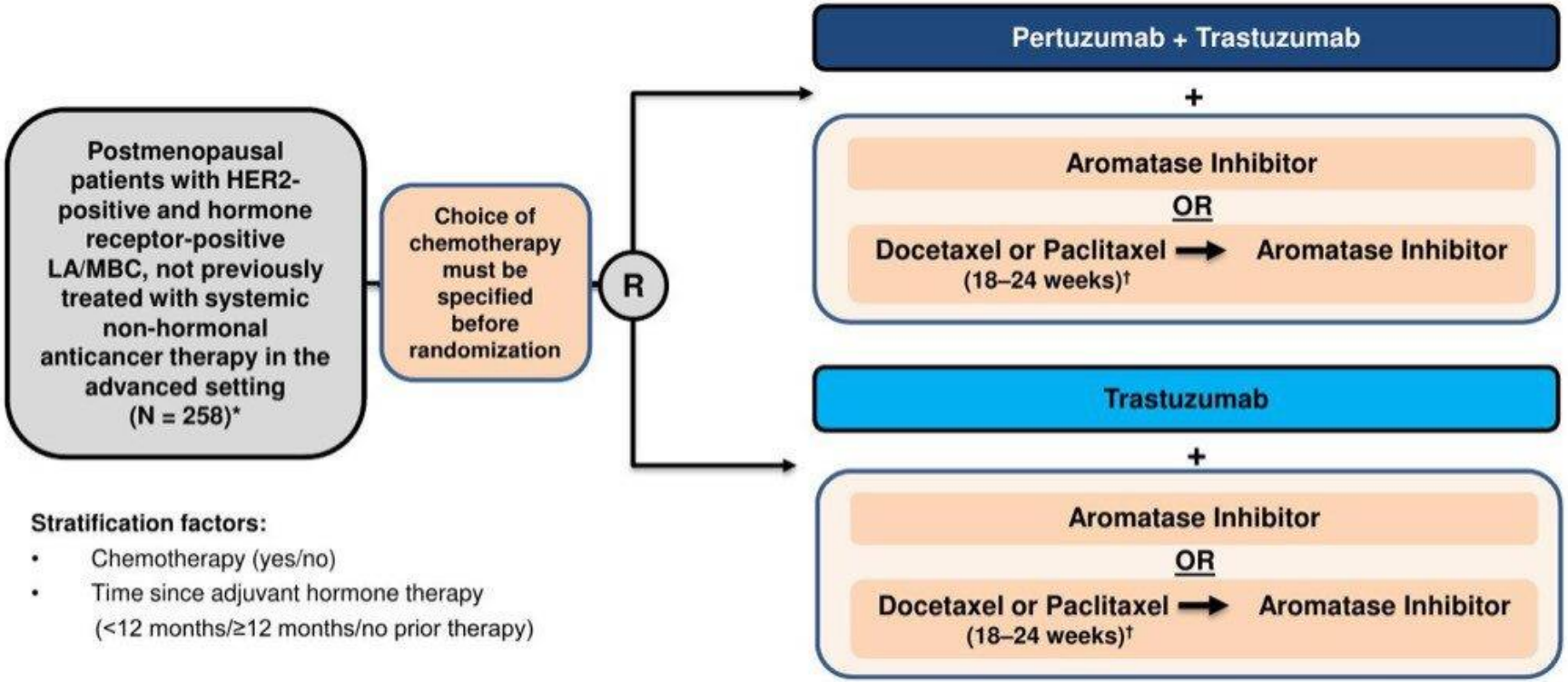
	VNM + Trast + Per
RR	74.2%
PFS	14.3 m
OS	NA

Breast Cancer Research (2016) 18:126

PERTAIN

San Antonio Breast Cancer Symposium, December 6–10, 2016

PERTAIN Study Design (Phase II Trial)



Stratification factors:

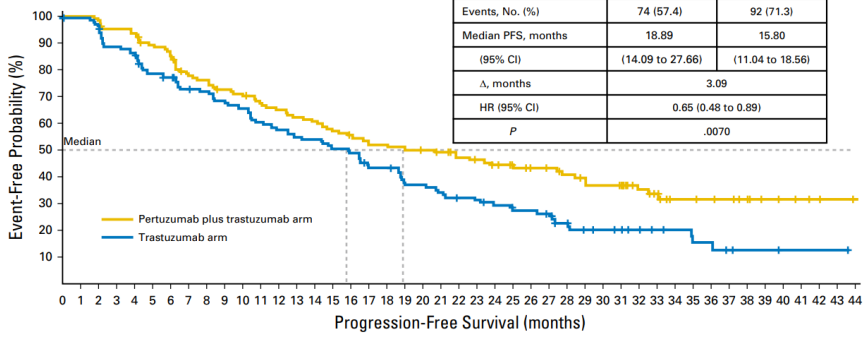
- Chemotherapy (yes/no)
- Time since adjuvant hormone therapy (<12 months/≥12 months/no prior therapy)

* 165 events to detect significant improvement in PFS from 7 months to 10.8 months (i.e. HR 0.645) with 80% power and a 2-sided log-rank test at an alpha level of 0.05.
† Choice of chemotherapy must be specified before randomization; administered per product labelling. LA, locally advanced; R, randomization.

J Clin Oncol 36:2826-2835.

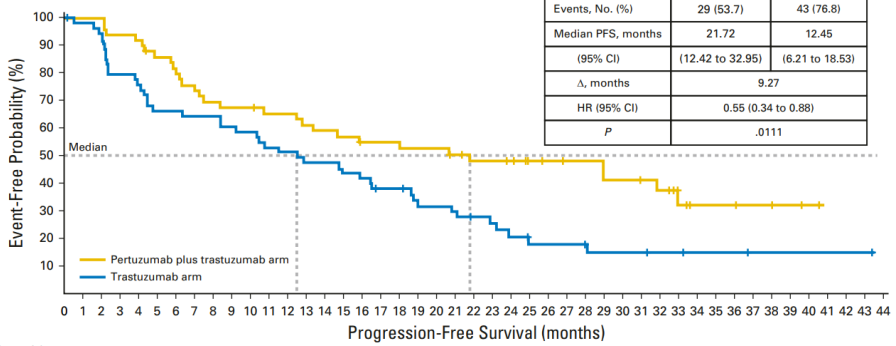
PERTAIN

A



	Pertuzumab Plus Trastuzumab Arm (n = 129)	Trastuzumab Arm (n = 129)
Events, No. (%)	74 (57.4)	92 (71.3)
Median PFS, months	18.89	15.80
(95% CI)	(14.09 to 27.66)	(11.04 to 18.56)
Δ, months	3.09	
HR (95% CI)	0.65 (0.48 to 0.89)	
P	.0070	

C



	Pertuzumab Plus Trastuzumab Arm (n = 54)	Trastuzumab Arm (n = 56)
Events, No. (%)	29 (53.7)	43 (76.8)
Median PFS, months	21.72	12.45
(95% CI)	(12.42 to 32.95)	(6.21 to 18.53)
Δ, months	9.27	
HR (95% CI)	0.55 (0.34 to 0.88)	
P	.0111	

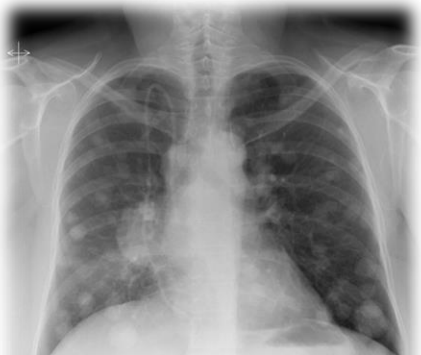
J Clin Oncol 36:2826-2835.

Câncer de mama

Doença localizada

(não-metastática e operável)

- Potencialmente curável
- Tratamento visa a cura ou retardo da recidiva
- Tratamento agressivo
- Tratamento CURATIVO



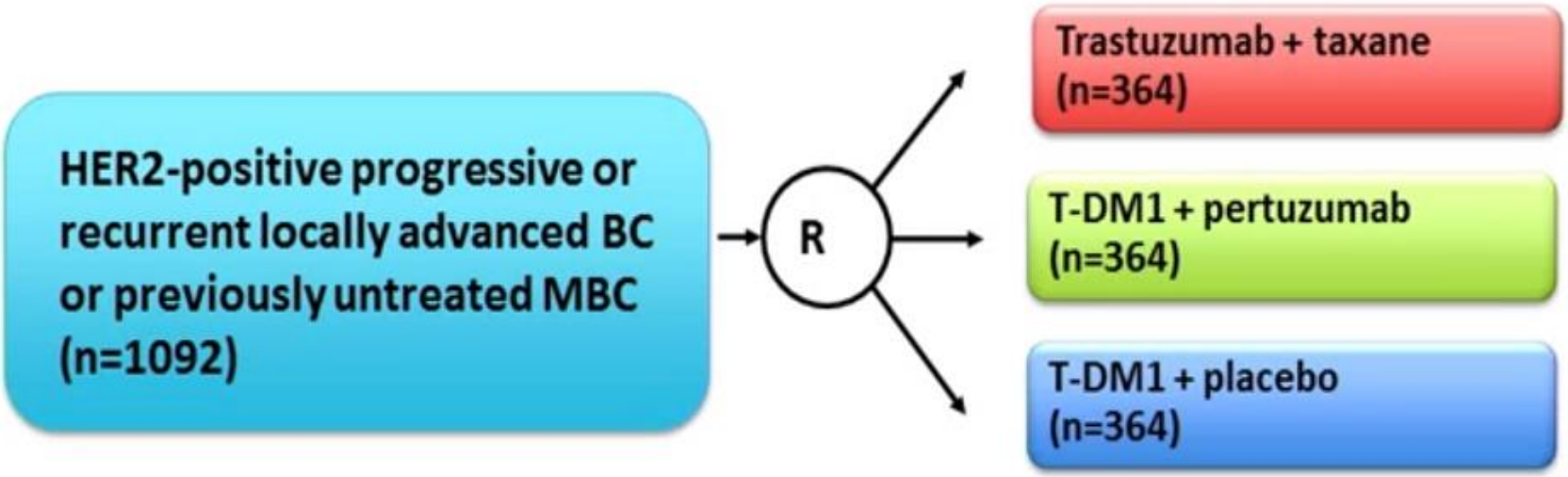
Doença avançada

(metastática ou inoperável)

- Incurável
- Prolongar sobrevida mas também melhorar a qualidade de vida
- Tratamento PALIATIVO
- Doença ‘crônica’ exigindo tratamento quase contínuo
- Sequencia de linhas de tratamento:
- 1ª linha -> 2ª linha -> 3ª linha....


Obrigada!
lauratesta@gmail.com

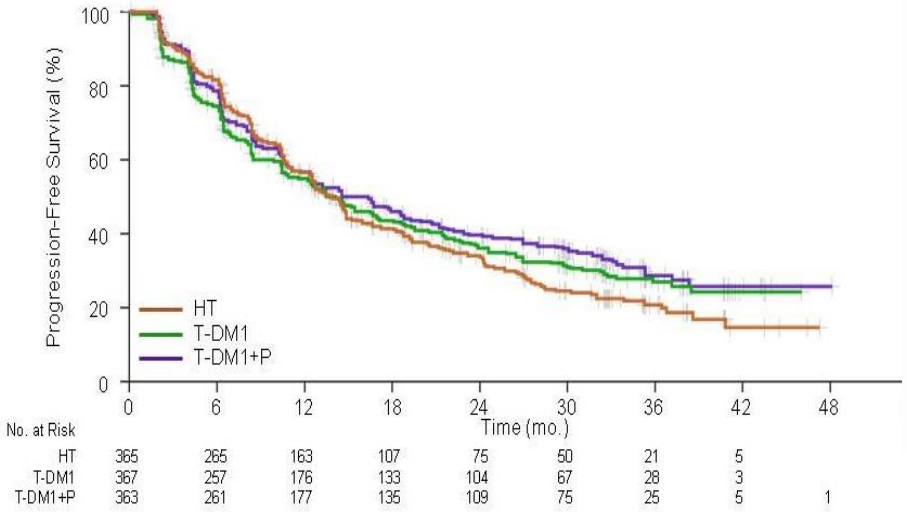
TDM1 e TDM1 + Pertuzumabe (MARIANNE)

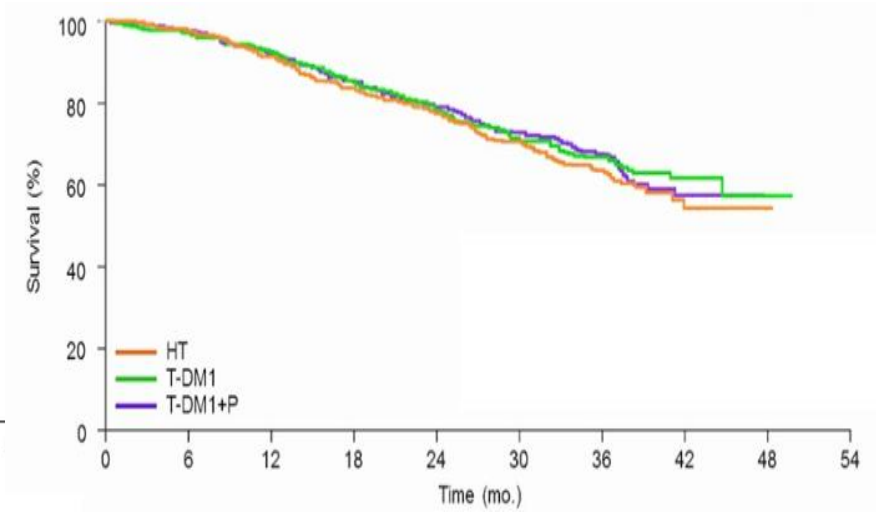


- **Pontos Importantes**
  - Resultados do Cleopatra nao disponiveis no desenho do estudo.
  - Aproximadamente 30% das pacientes receberam trastuzumabe previamente em cenário (neo)adjuvante.

J Clin Oncol. 2015 May 10;33(14):1574-83

TDM1 y TDM1 Combinado a Pertuzumabe (MARIANNE)





	Tras + Tax	TDM1 + Pl	TDM1 + Per	p value
RR	67,9%	59,7%	64,2%	NS
PFS	13,7 m	14,1 m	15,2m	p 0,31 P 0,14
OS	NA	NA	NA	NS

J Clin Oncol. 2015 May 10;33(14):1574-