Biosimilares no câncer de mama HER2-positivo: Atualizações

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DECLARAÇÃO

SOBRE CONFLITOS DE INTERESSE

De Acordo Com a Resolução RDC 96/2008 da Agência de Vigilância Sanitária declaro que:

Desempenhei o papel de **SPEAKER** para as seguintes empresas:Roche, Fleury, MSD, Novartis

ADVISORY BOARD: Roche, Eisai

Trabalho como **ONCOLOGISTA** no: Hospital Sírio Libanês

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HER2+ Disease

- Amplification or overexpression of HER2 implicated in the pathophysiology of approximately 15-20% of Breast tumors

Estimated New Female Breast Cancer US (2013)

	Invasive Cases	Deaths
All ages	232,340	39,620

Limited access to treatment is a worldwide issue for patients with breast cancer

Full one-year course of Herceptin treatment costs about **$70,000**

Significant financial impact for Reference drug :
Heath insurance, government, patient co-pays

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Carol de Santis et al, 2013. doi: 10.3322/caac.21203
Slamon DJ *Science* 235, 177–182 (1987)

Trastuzumab Timeline

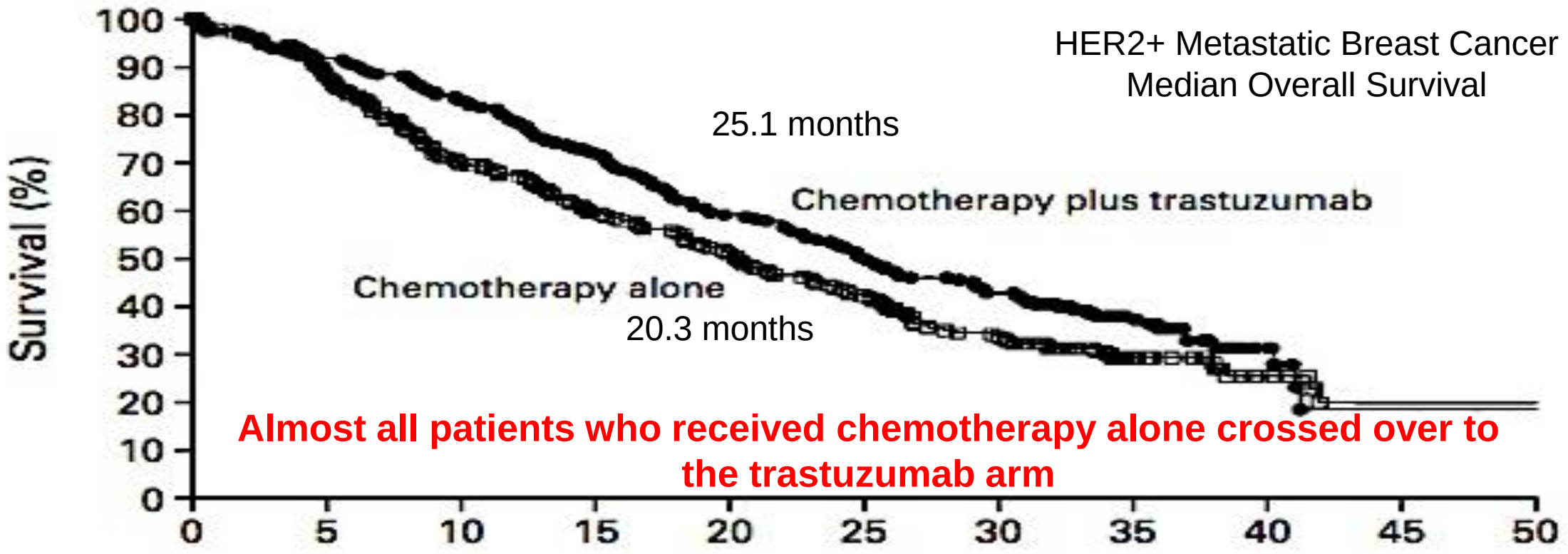
1998

Approved for Metastatic HER-2+ BC

2006

Approved for Adjuvant Treatment of HER-2+ BC

Slamon Pivotal Trial



Almost all patients who received chemotherapy alone crossed over to the trastuzumab arm

Slamon et al. N Engl J Med, Vol. 344, No. 11 · March 15, 2001

Trastuzumab – HER2+ Locoregional Disease

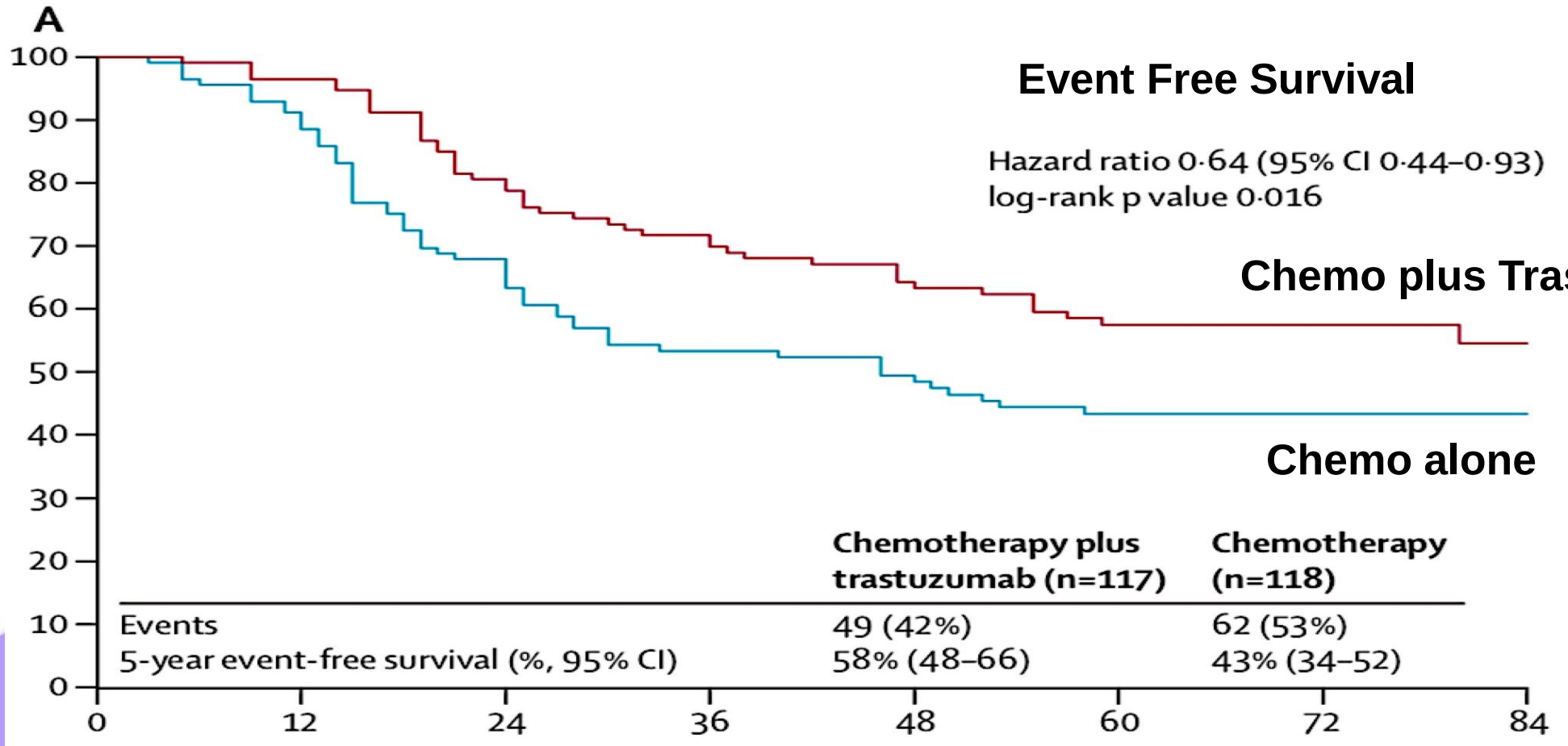
Adding Trastuzumab to Adjuvant Chemotherapy in Localized HER2+ BC

37% relative improvement in OS : 10-year OS rate from 75.2% to 84

40% relative improvement in DFS: 10-year DFS rate from 62% to 73.7%

Adding Trastuzumab to NEOadjuvant Chemotherapy in Localized HER2+ BC

Double pCR rates ; Improvement in survival endpoints



E Perez et al, JCO 2014. 10.1200/JCO.2014.55.5730

Lucca Gianni et al, Lancet 2014 x.doi.org/10.1016/ S1470-2045(14)70080-4

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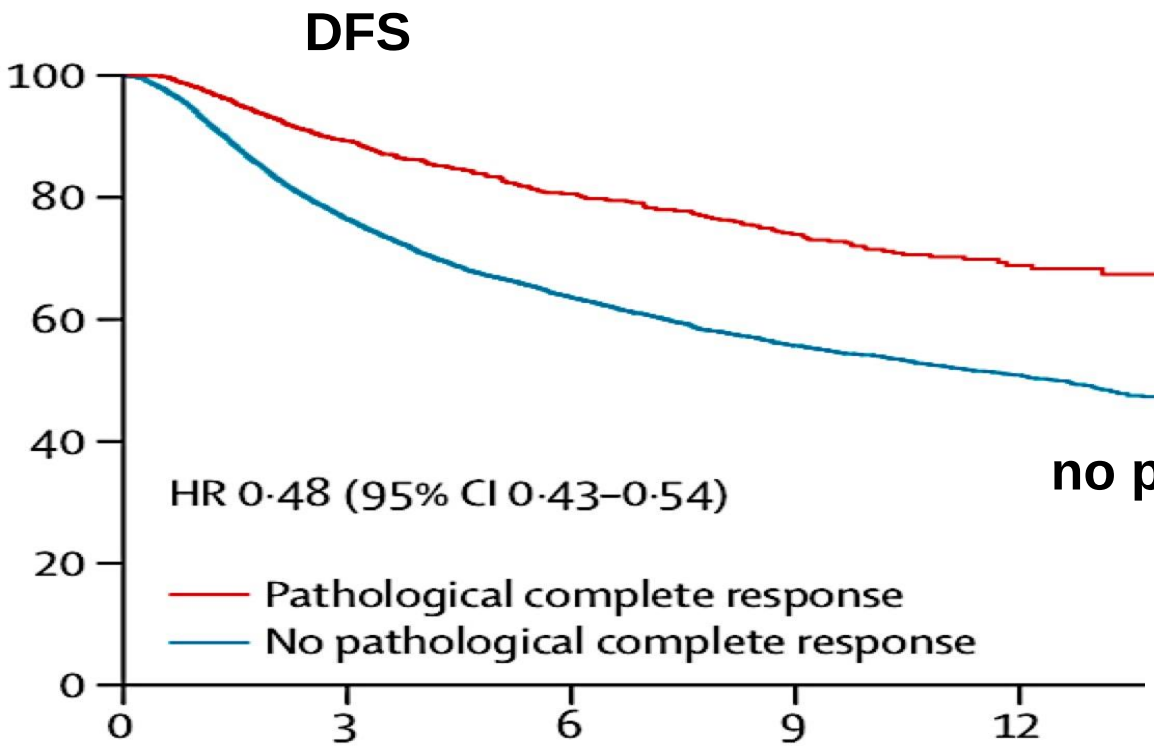
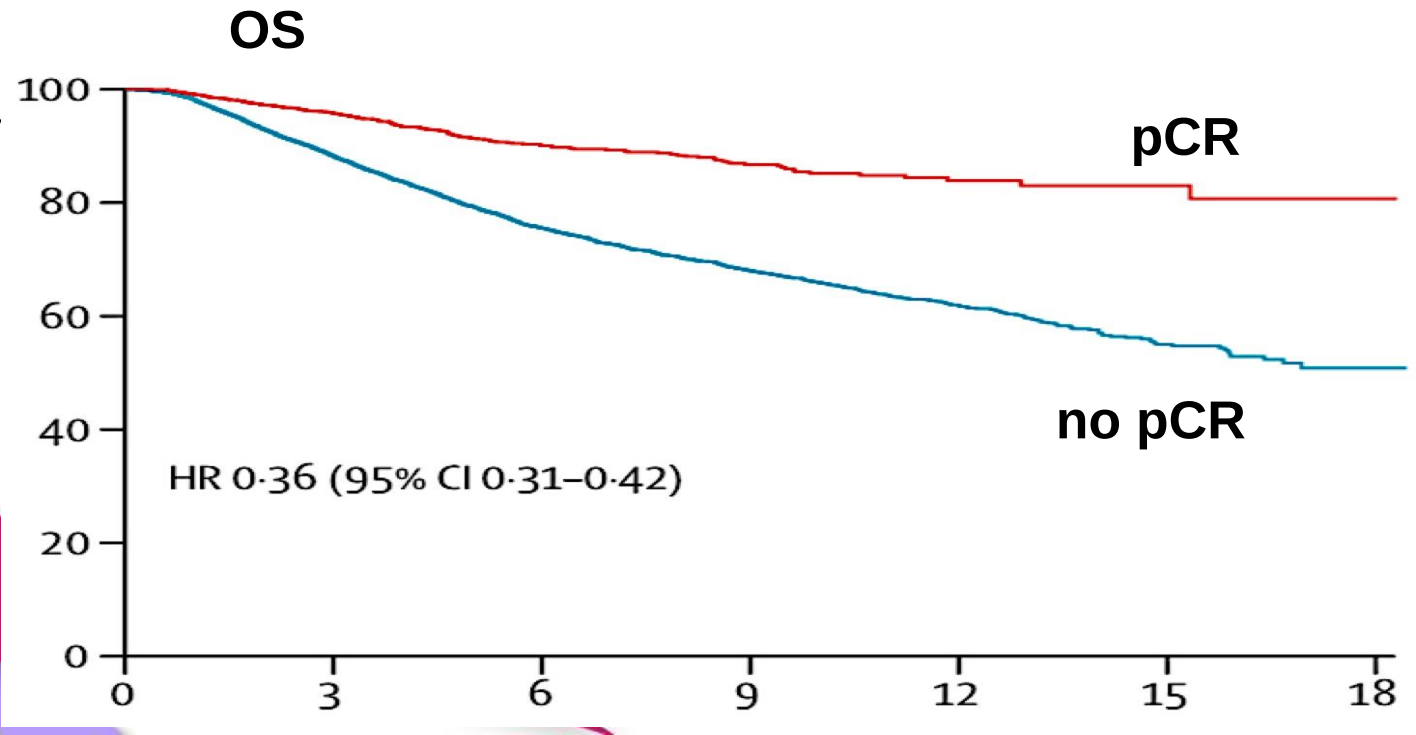
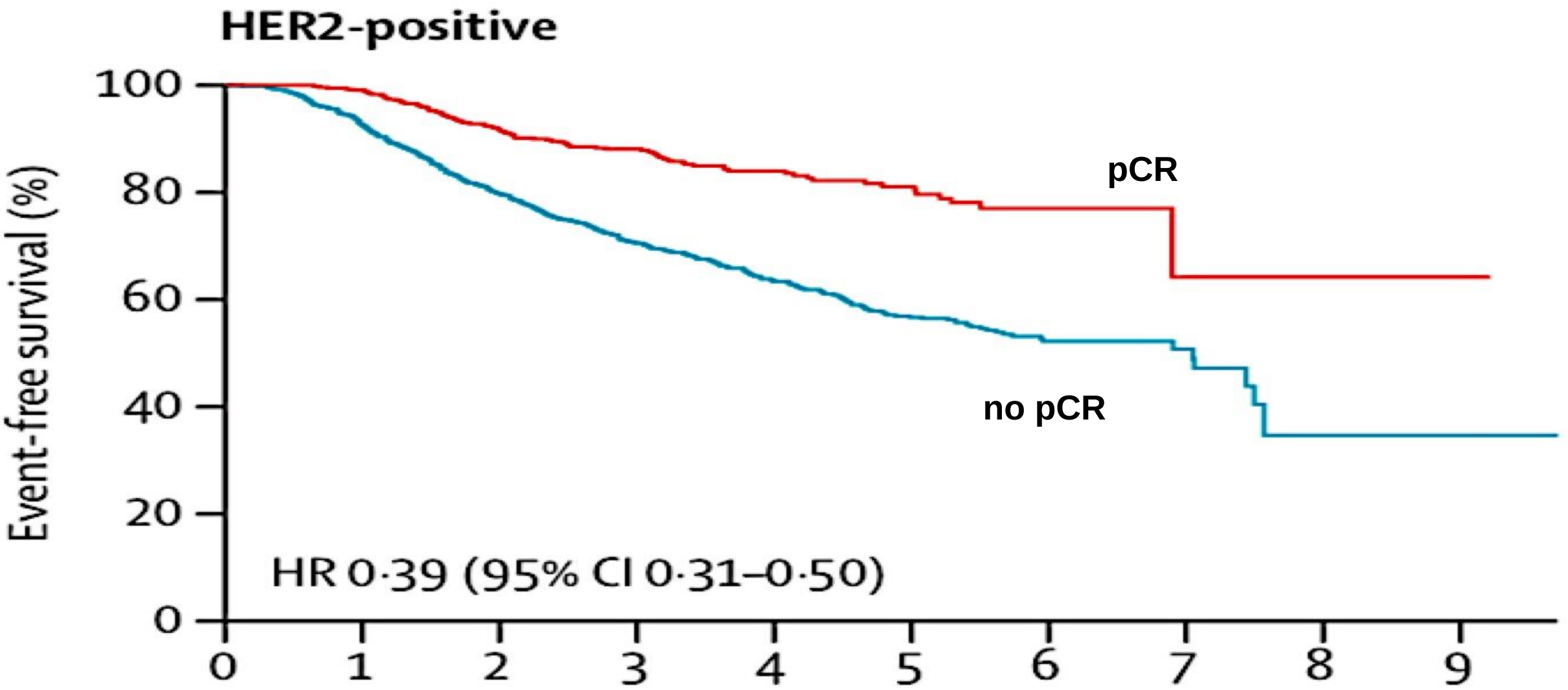
pCR and Prognosis: Highly correlated, especially among HER2 and TNBC subtypes





Cortazar et al, Lancet Oncol 2014 doi.org/10.1016/S0140-6736(13)62422-8

pCR and Prognosis: HER2+ Breast Cancer



Cortazar et al, Lancet Oncol 2014 doi.org/10.1016/S0140-6736(13)62422-8

Metastatic HER2 positive Breast Cancer:
Paradigms with Herceptin plus chemotherapy
First Line Setting

Chemotherapy + Trastuzumab in HER2+ Breast Cancer

Trastuzumab + Docetaxel or Navelbine	RR 59.3%
Trastuzumab + weekly Paclitaxel	RR 72%
Trastuzumab + Paclitaxel + Carboplatin	RR 72%
Trastuzumab + Chemotherapy	RR 50%
Trastuzumab + Taxane	RR 67.9%

Median PFS

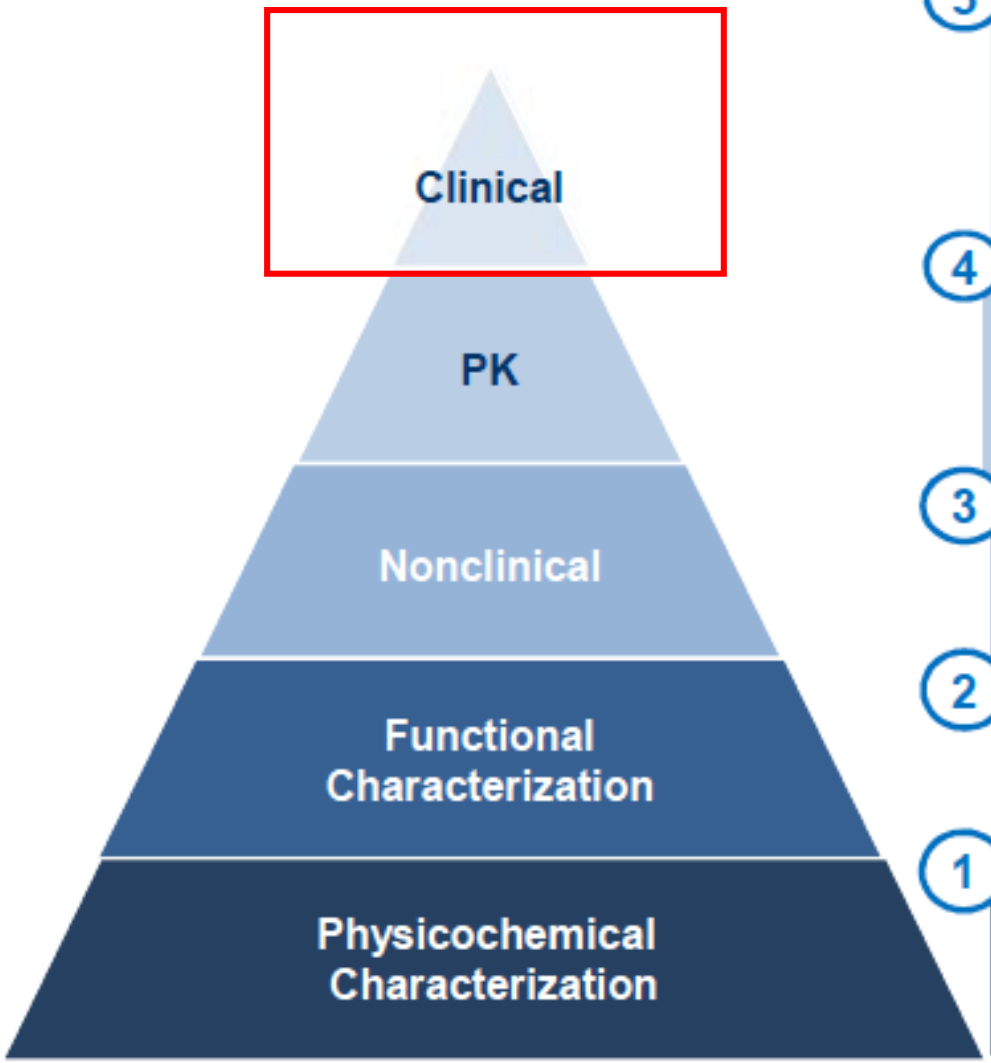
10-12 months

Median OS

25-35 months

Anderson et al, JCO 2011. DOI: 10.1200/JCO.2010.30.8213
V Valero et al, JCO 2011. 10.1200/JCO.2010.28.6450
Slamon et al, NEJM 2001. DOI: 10.1056/NEJM2001031534411
E Perez et al, JCO, 2016. DOI: 10.1200/JCO.2016.67.4887
Kaufman et al, JCO 2009. DOI: 10.1200/JCO.2008.20.68

Programa Trastuzumabe biossimilar:
conceito de totalidade de evidência



5 **HERITAGE**
Confirmatory efficacy and safety study in patients with HER2+ Metastatic Breast Cancer (500 patients)
A sensitive population.
1 supportive MBC study (135 patients)

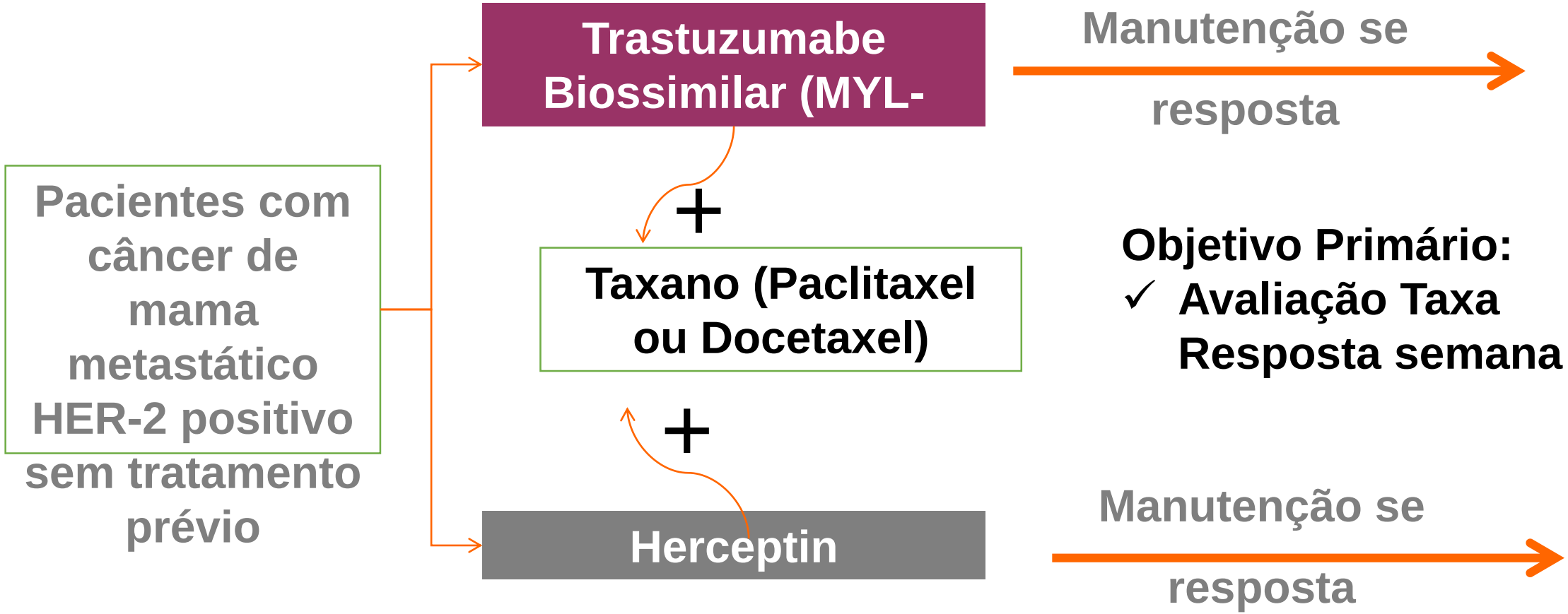
4 **PK Similarity**
1 PK 3 way bridging study (132 NHV)
1 supportive PK study (22 NHV)

3 **Nonclinical Safety**
2 Cell-based studies, 2 safety pharmacology studies in Cynomolgus Monkey

2 **Function**
Focus on aspects of **molecule and function** relevant to MOA, efficacy, safety, PK, and immunogenicity

1 **Structure**
Extensive characterization of Herceptin and MYL-1401O applying highly sensitive analytics across a wide range of product characteristics

Estudo Heritage



Objetivo Primário:

- ✓ **Avaliação Taxa Resposta semana 24**

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Hugo HS et al. JAMA Oncol 2017

Participating Countries

Bulgaria, Chile, Czech Rep., Georgia, Hungary, India, Latvia, Philippines, Poland, Republic of South Africa, Romania, Russia, Serbia, Slovakia, Taiwan, Thailand, Ukraine

Region, n (%)	
Africa	11 (2.4)
Asia Pacific	142 (31.0)
Latin America	5 (1.1)
Eastern Europe	300 (65.5)

First patient in December 2012, last patient in July 2015.

Effect of a Proposed Trastuzumab Biosimilar Compared With Trastuzumab on Overall Response Rate in Patients With ERBB2 (HER2)-Positive Metastatic Breast Cancer

A Randomized Clinical Trial

ESTUDO DE EQUIVALÊNCIA

EMA
Desfecho primário: DIF. TAXA RESPOSTA
IC 95% todo entre -15 a +15%

FDA
Desfecho primário: RAZÃO TAXA RESPOSTA
IC90% todo entre 0,81 a 1,24

TABLE 2. Primary Outcome: Ratio and Difference of Overall Response Rate at Week 24 in the Intention-to-Treat Population

	PROPOSED BIOSIMILAR + TAXANE (n = 230)	TRASTUZUMAB + TAXANE (n = 228)		
RESPONSE[a]			**DIFFERENCE,%**	**RATE RATIO**
Overall response, No. (%)	**160 (69.6)**	**146 (64.0)**	5.53	1.09
90% CI, %	64.57 to 74.56	58.81 to 69.26	-1.70 to 12.69	**0.974 to 1.21**
95% CI, %	63.62 to 75.51	57.81 to 70.26	**3.08 to 14.0**	0.954 to 1.23
			-3.08 to 14.0	**0.97 to 1.21**

Hope S. Rugo, et al. JAMA, December 1,2016

HERITAGE

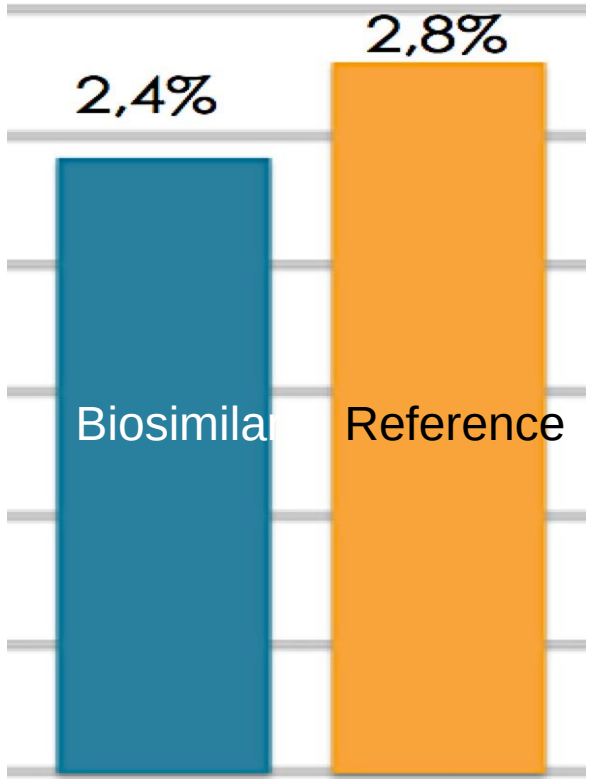
Time to Tumor Progression and Overall Survival at Week 48

	Proposed Biosimilar + Taxane	Trastuzumab + Taxane
TTC at week 48	41.3%	43%
Median TTP	11.1 m	11.1 m
OS at week 48	89.1%	85.1%

Imunogenicity

Pre Treatment Antidrug Antibody Positivity

5.9% in the proposed Biosimilar
8.9% in the Trastuzumab



Hugo HS et al. JAMA, 2017 10.1001/jama.2016.18305

Adverse Event	Proposed Biosimilar + Taxane	Trastuzumab + Taxane
Peripheral Neuropathy	24,8%	23,1%
Diarrhea	20,7%	20,6%
Neutropenia	53,3%	57,5%

Cardiac Function (LVEF Values) Change from Baseline

	Biosimilar	Reference
Week 24		
Mean (95% CI)	−0.6 (−1.5 to 0.2)	−0.9 (−1.8 to −0.1)

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Hugo HS et al. JAMA, 2017 10.1001/jama.2016.18305

HERITAGE Data in Clinical Perspective

	MYL-1401O	Ref Trastuzumab	Historical Data
ORR at 24 weeks	70%	64%	50-70%
TTP 48 weeks	11.1 months	11.1 months	11.3-12.4 months
OS at 48 weeks	89.1%	85.1%	75-89%
Safety and Toxicity	Comparable		Consistent
Immunogenicity	3.9%	4.4%	3.4-7.1%

FDA U.S. FOOD & DRUG ADMINISTRATION

Dec, 2017

U.S. FDA approved Ogivri (trastuzumab-dkst) as a biosimilar to Herceptin for the treatment of patients with breast or metastatic stomach cancer whose tumors overexpress the HER2 gene

ANVISA
AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA

Aprovou Zedora (MYL-1401O) para tratamento de Câncer de Mama HER2+

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CT-P6 Phase 3 Neoadjuvant equivalence trial
Stage I–IIIa operable HER2+ Breast Cancer

Randomized
N 549

CT-P6	Reference Trastuzumab
8 cycles q 3w	8 cycles q 3w

*Concomitantly with 4 cycles of Docetaxel followed by 4 cycles of FEC

	CT-P6 (n=248)	Reference trastuzumab (n=256)
pCR	116 (46·8%; 40·4 to 53·2)	129 (50·4%; 44·1 to 56·7)
Breast pCR	128 (51·6%; 45·2 to 58·0)	141 (55·1%; 48·8 to 61·3)
pCR without DCIS	99 (39·9%; 33·8 to 46·3)	106 (41·4%; 35·3 to 47·7)

Estimated treatment outcome diference (–0·04 [95% CI –0·12 to 0·05]) was within the equivalence margin

*Long-term safety and eficacy for 3 years after the last patient was enrolled

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Stebbing et al, Lancet 2017. doi.org/10.1016/ S1470-2045 (17) 30434-5

CT-P6 Phase 3 Neoadjuvant Equivalence trial
Stage I–IIIa operable HER2+Breast Cancer

	CT-P6 (n=271)	Reference trastuzumab (n=278)
TEAEs		
Total number of TEAEs	2424	2660
TEAEs	255 (94%)	264 (95%)
Treatment-related	112 (41%)	129 (46%)
Grade 1–2	95 (35%)	106 (38%)
Grade 3	11 (4%)	9 (3%)
Grade 4	6 (2%)	13 (5%)
Grade 5	0	1 (<1%)

	CT-P6	Ref Trastuzumab
Cardiac Disorders	23 (8%)	28 (10%)
Infusion Recations	23 (8%)	25 (9%)

Stebbing et al, Lancet 2017. doi.org/10.1016/ S1470-2045 (17) 30434-5

SB3
8 cycles q 3w

Randomized
N 800

Reference Trastuzumab
8 cycles q 3w

*Concomitantly with 4 cycles of Docetaxel followed by 4 cycles of FEC

Breast Pathologic Complete Response and pCR

	SB3	Trastuzumab
Breast pCR	51.7%	42%
pCR	45.8%	35.8%
Overall RR	96.6%	95.2%

*Safety and immunogenicity were comparable

Pivot et al, JCO 2018. https://doi.org/10.1200/JCO. 2017.74.0126

Conclusions

- **Biosimilars are not generics**

Biosimilars are biological entities that require a very complex mechanism of manufacturing and framework for us to assess whether equivalence can be ensured with the reference medication

- In breast cancer, the 2 most sensitive endpoints to assure efficacy comparison are response rate and pCR

- Trastuzumab biosimilar was approved based on full accomplishment of the totality of evidence. The Heritage study demonstrated similar efficacy and safety compared to Herceptin

Price

Until Dec 2017

Filgrastim-sndz [Zarxio]
10% discount

27 marketed biosimilars
40% discount

Newly diagnosed patients with HER2+ disease will have the option to start with a lower cost biosimilar, potentially enabling access to a broader patient population to anti HER2 therapy

obrigada

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