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XIX CONGRESSO SUL-BRASILEIRO
DE GINECOLOGIA E OBSTETRÍCIA
IV JORNADA SUL-BRASILEIRA
DE MASTOLOGIA



Câncer de mama HER2-positivo

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Câncer de mama HER2-positivo

- Histórico
- Epidemiologia
- Biologia molecular
- Agentes anti-HER2
- Manejo atual
 - Doença metastática
 - Doença localmente avançada
 - Doença inicial
- Desafios
- Take-home messages

HER2 Story: 30 years in the making

nature

International weekly journal of science

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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

A series of rat neuro/glioblastomas all contain the same transforming gene (*neu*) which induces synthesis of a tumour antigen of relative molecular mass (M_r) 185,000 (p185). The *neu* oncogene bears homology to *erb-B* and the tumour antigen, p185, is serologically related to the epidermal growth factor (EGF) receptor. The two proteins, EGF receptor and p185 appear to be distinct, as they coexist in nontransformed Rat-1 cells.

▲ Top

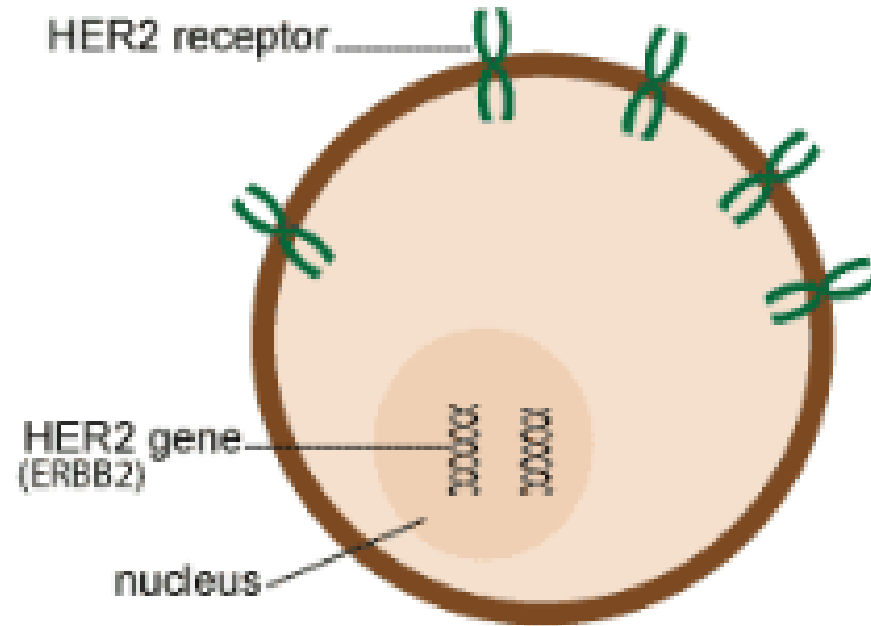
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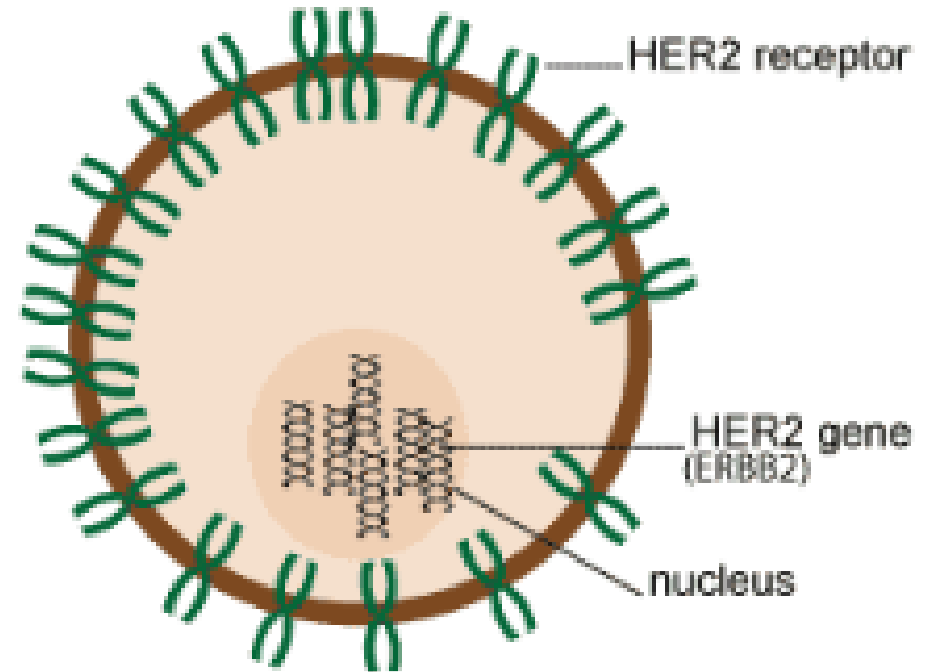
SEARCH PUBMED FOR

- ▶ Alan L. Schechter
- ▶ David F. Stern
- ▶ Lalitha Vaidyanathan
- ▶ Stuart J. Decker
- ▶ Jeffrey A. Drebin
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NORMAL CELL



HER2+ CELL

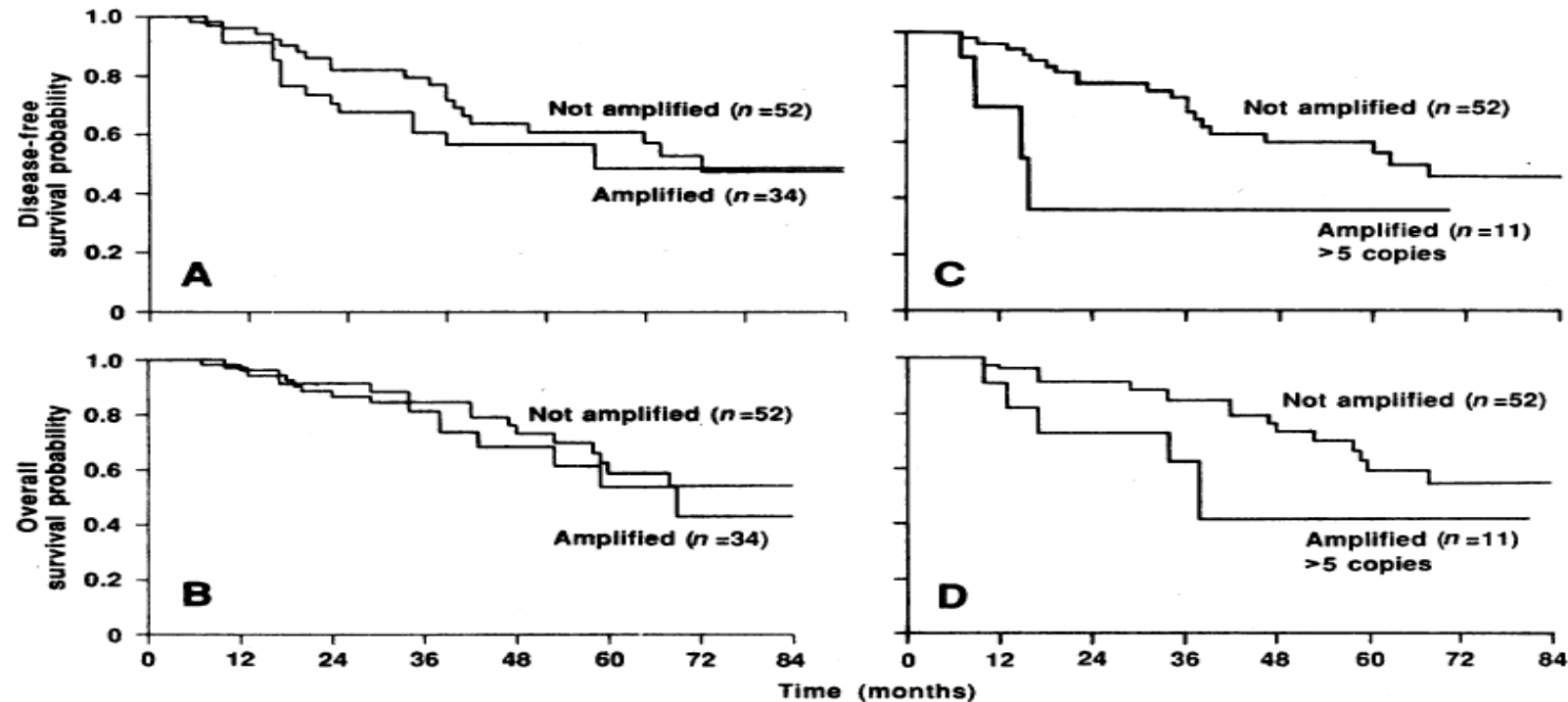


Amplification - multiple HER2 genes
Overexpression - many HER2 receptors

HER2 Story: Poor Prognostic Marker

Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

DENNIS J. SLAMON,* GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN,
AXEL ULLRICH, WILLIAM L. MCGUIRE

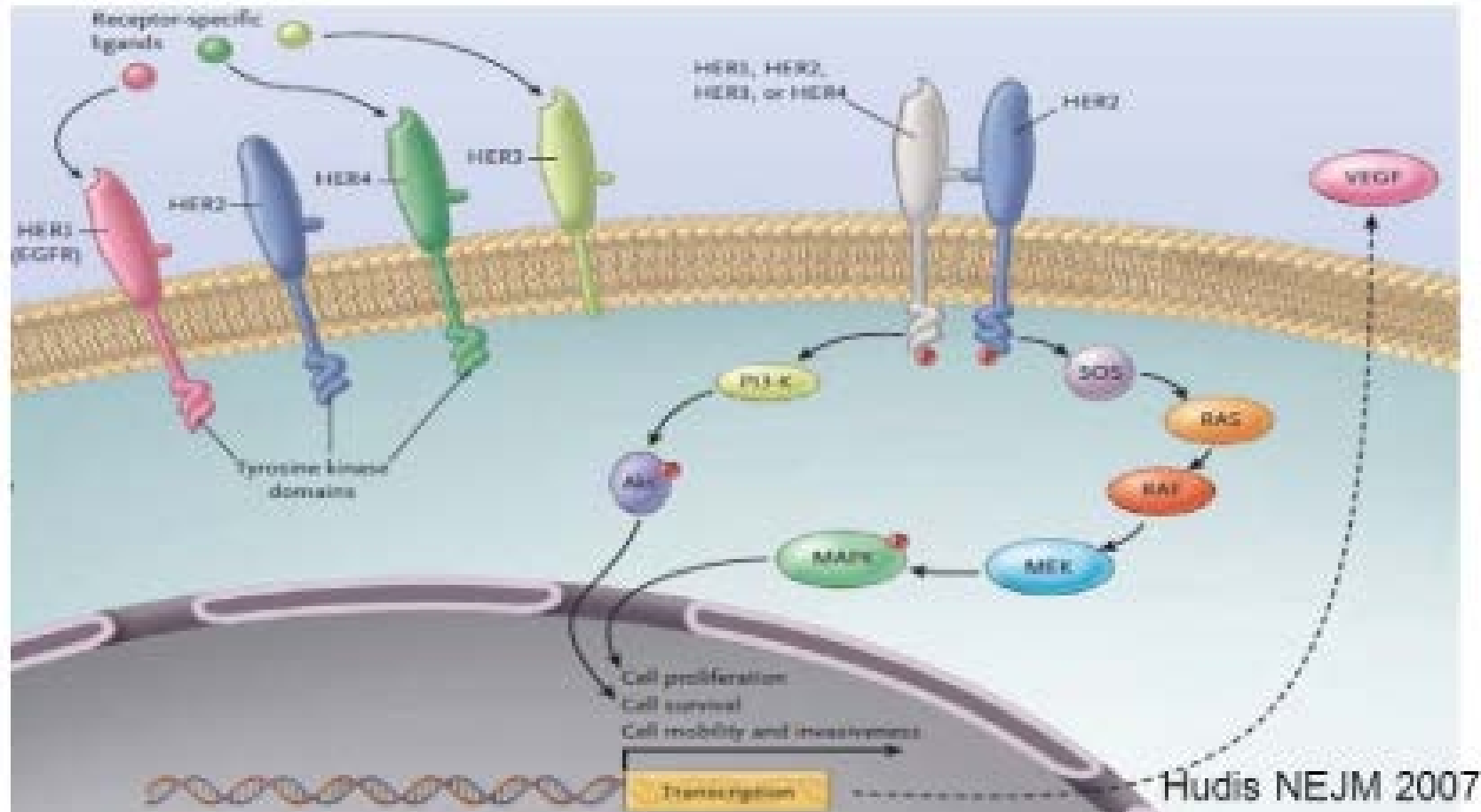


Câncer de mama HER2-positivo

- Aproximadamente 20-25% dos cânceres de mama
- No Brasil cerca de 12mil novos casos ao ano de câncer de mama HER2+
- Cerca de 2mil mulheres ao ano com diagnóstico de câncer de mama HER2+ metastático
- ASCO/CAP Guidelines:
 - IHQ 3+
 - FISH HER2/CEP17 >2.0
- Atenção: Novo guideline ASCO/CAP publicado hoje!!!

HER2-“Positive” Breast Cancer

- 20-25% of invasive breast cancers
- Overexpression can activate signaling
- Promotes cell proliferation and survival



The New England Journal of Medicine

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VOLUME 344

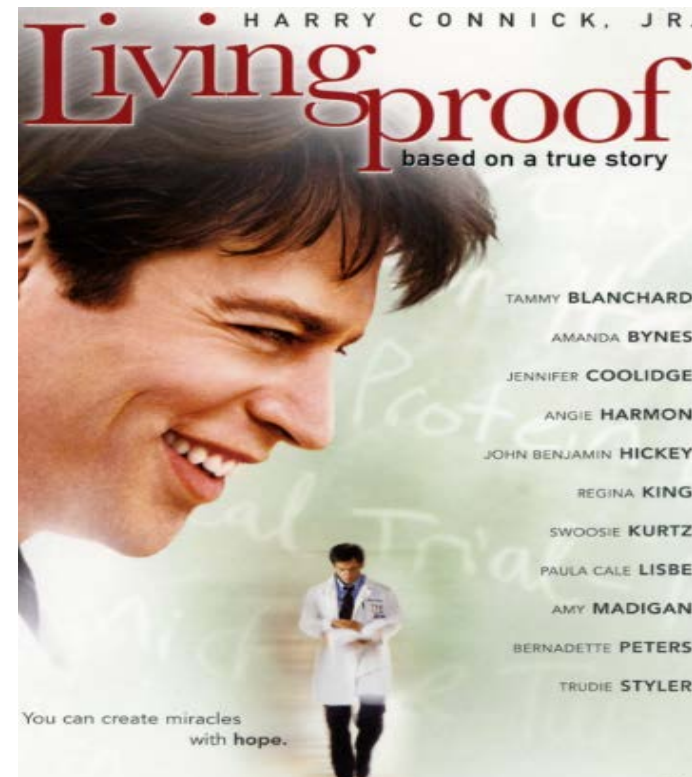
MARCH 15, 2001

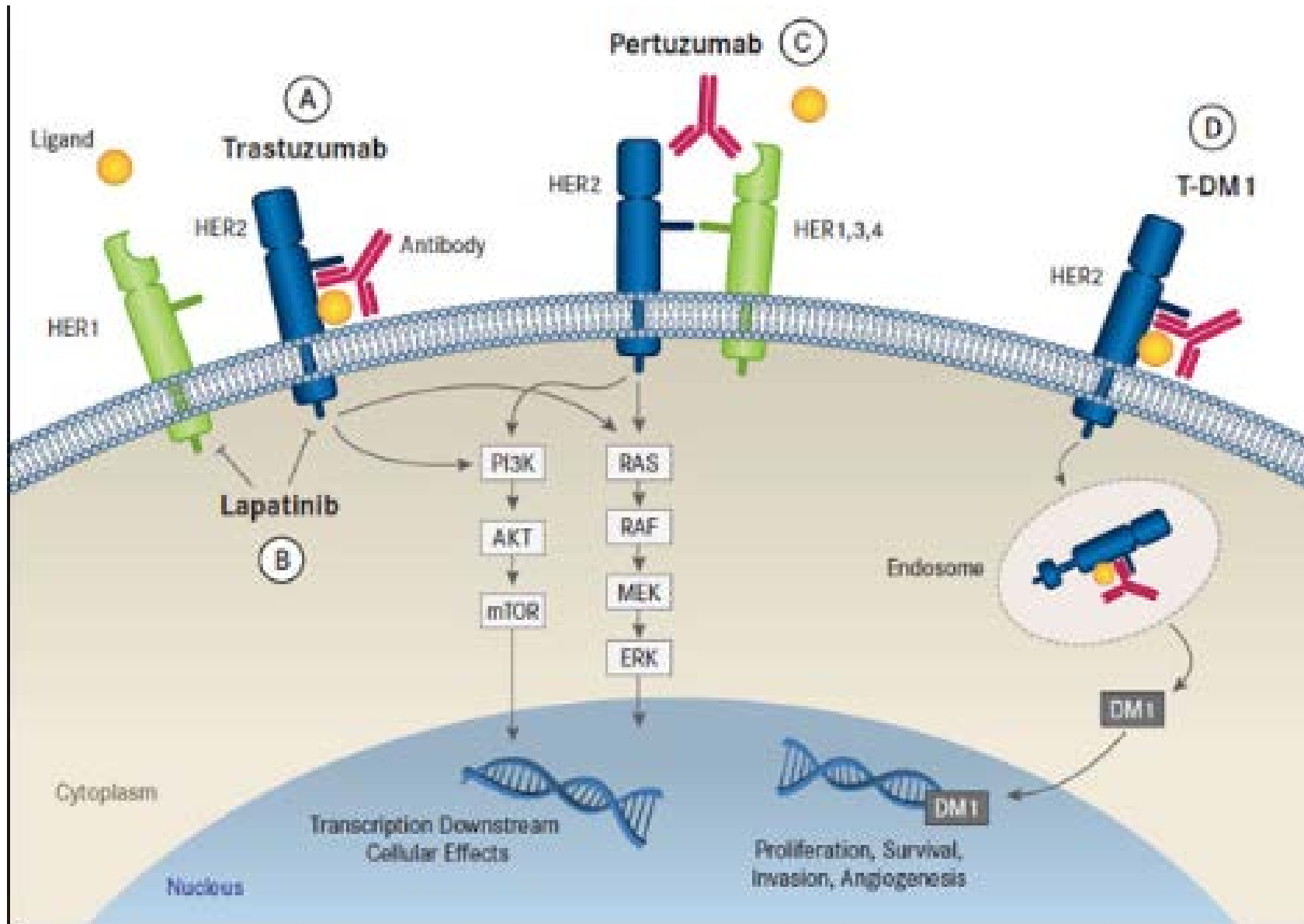
NUMBER 11



USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D.,
VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D.,
JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*





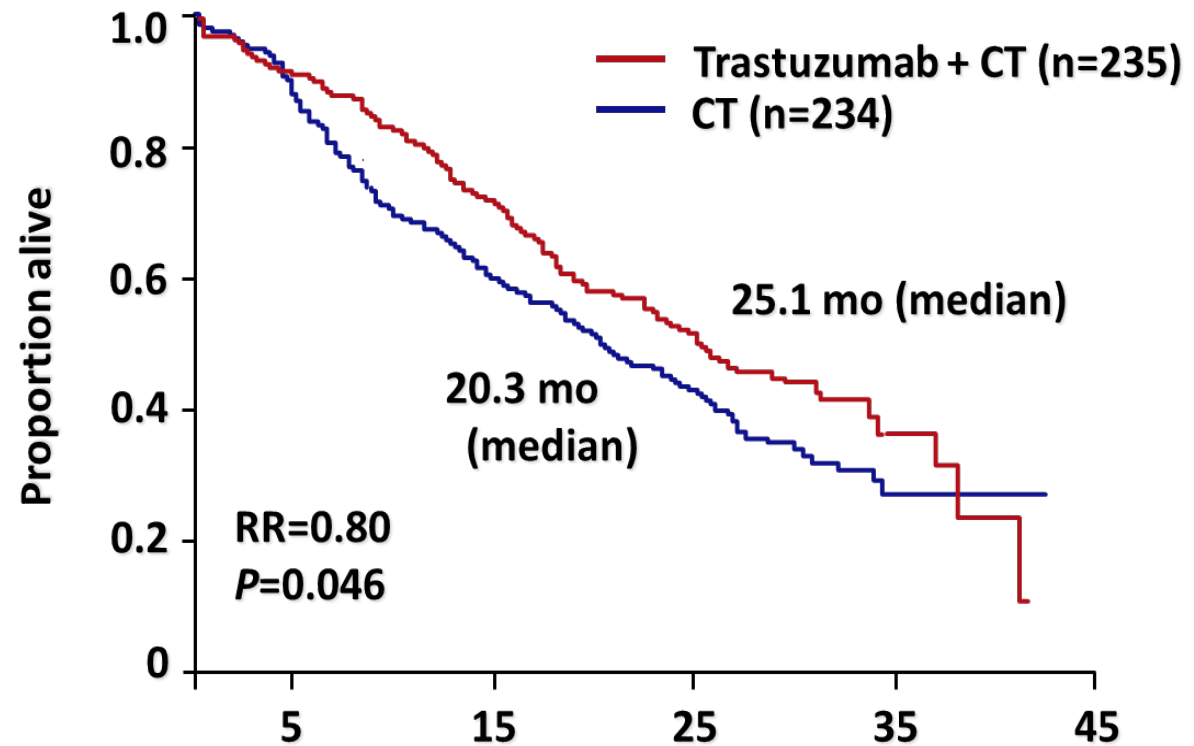
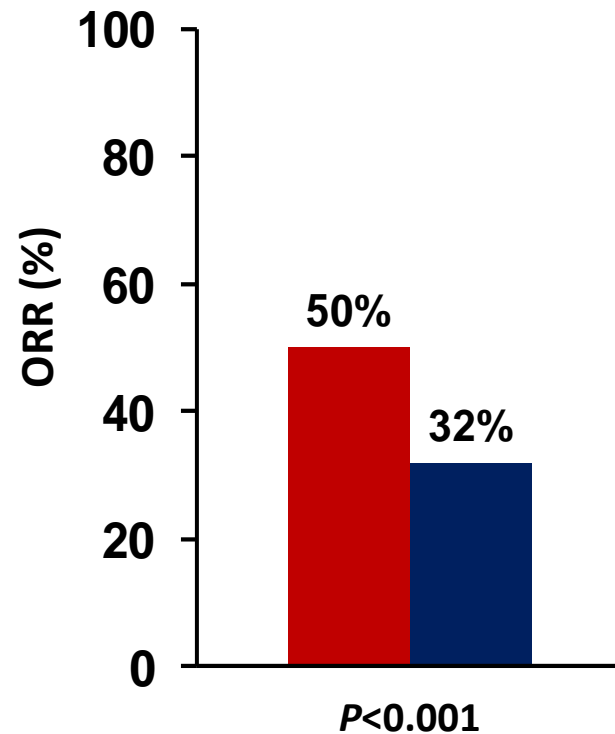
Câncer de mama HER2-positivo

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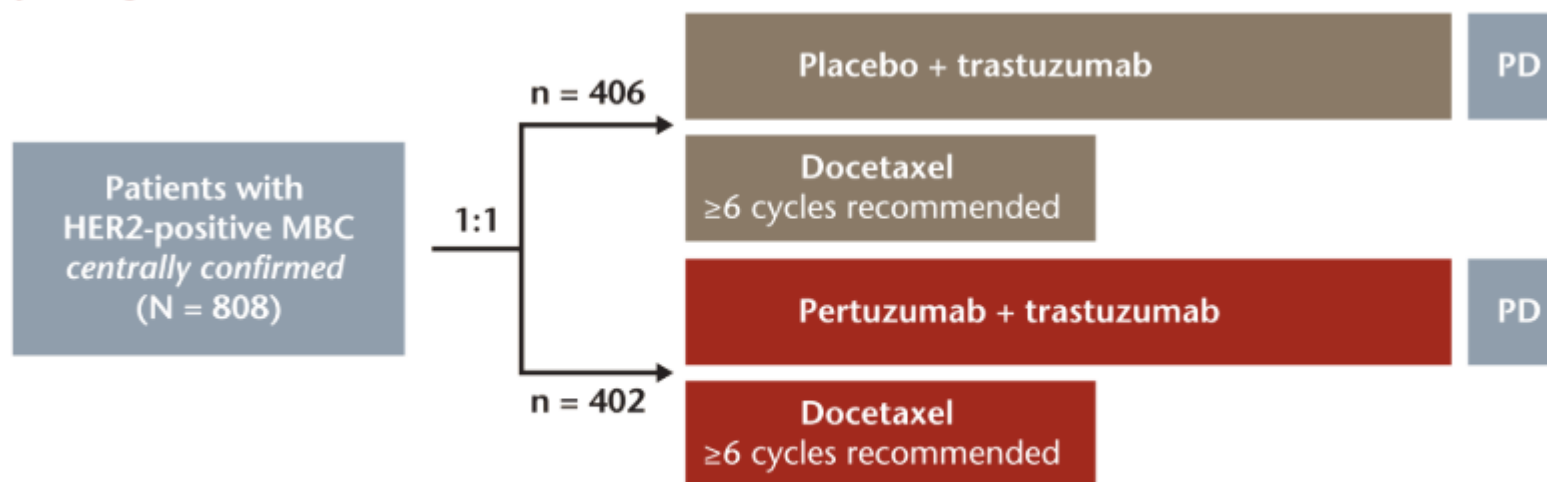
JANUARY 12, 2012

VOL. 366 NO. 2

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D.,
Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D.,
Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M.,
and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

Study design

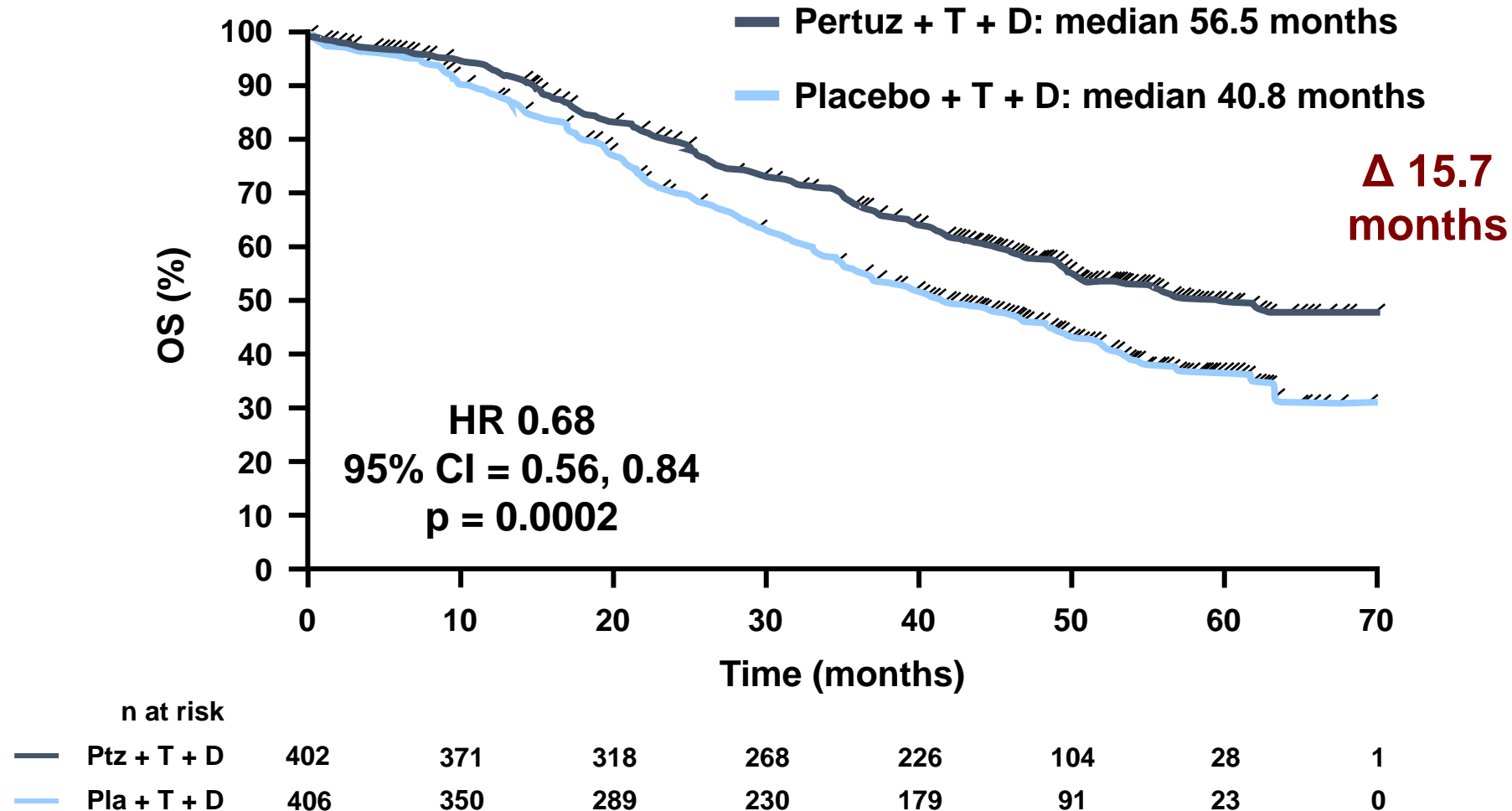


Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)

HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; N/n = number of patients; PD = progressive disease

Cleopatra: Final OS Analysis

Median follow-up 50 months (range 0–70 months)



ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain S, et al. ESMO 2014

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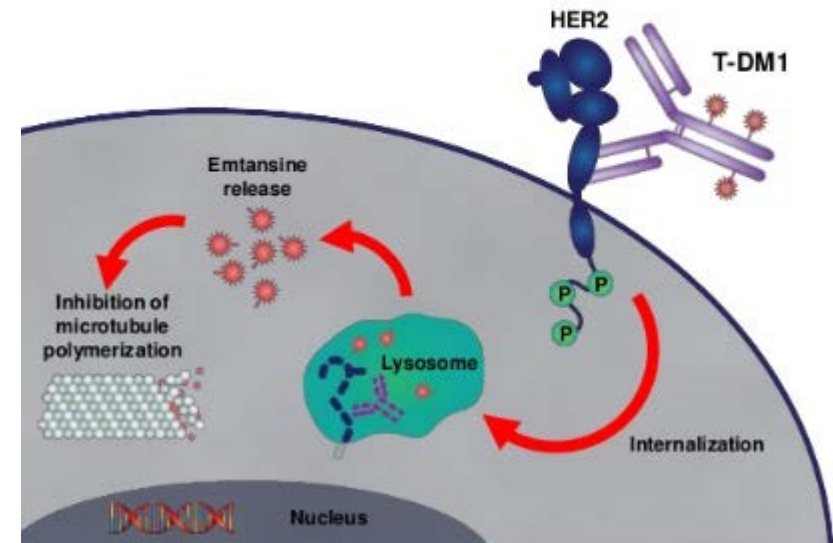
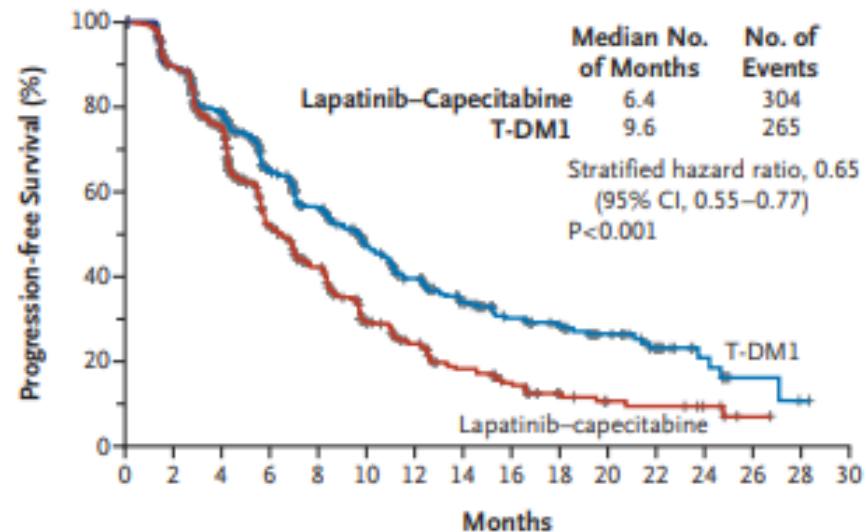
NOVEMBER 8, 2012

VOL. 367 NO. 19

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

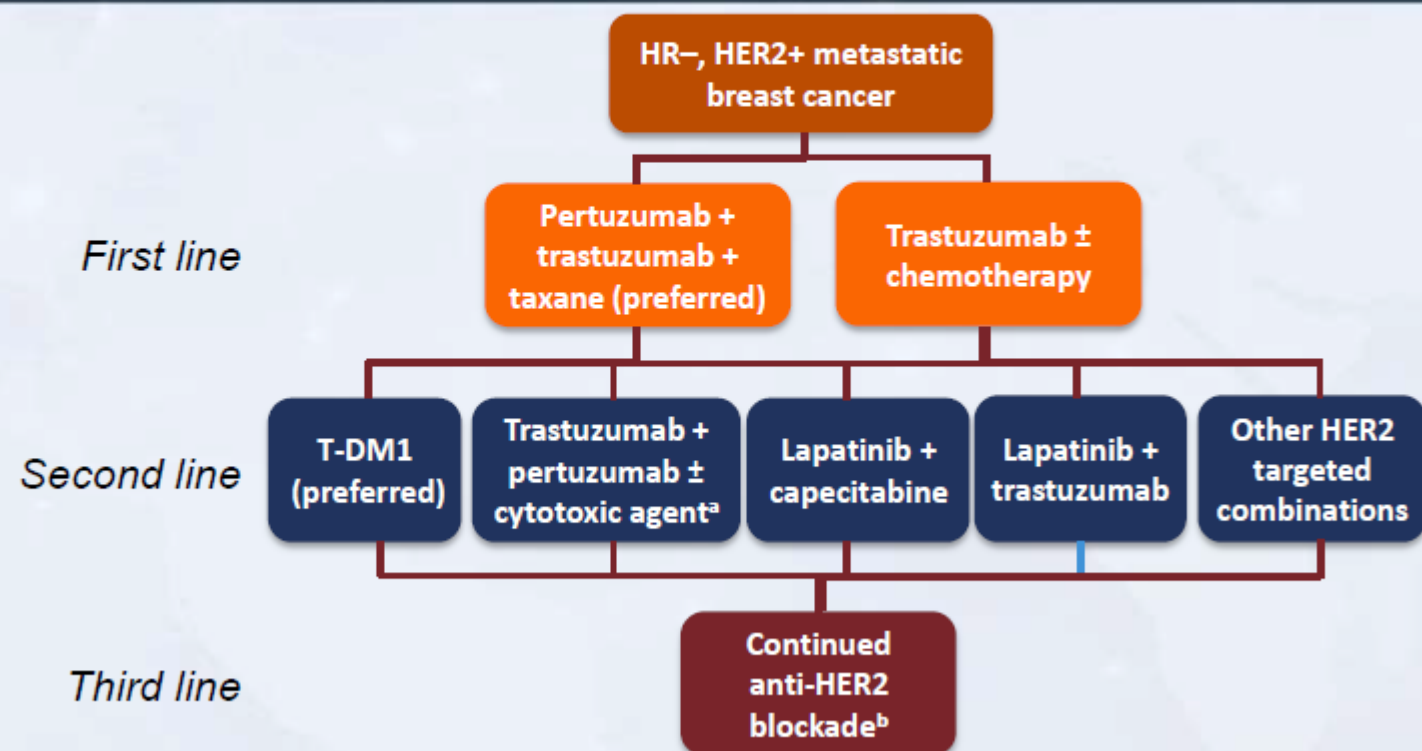
Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D.,
José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D.,
Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D.,
and Kim Blackwell, M.D., for the EMILIA Study Group

T-DM1: Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

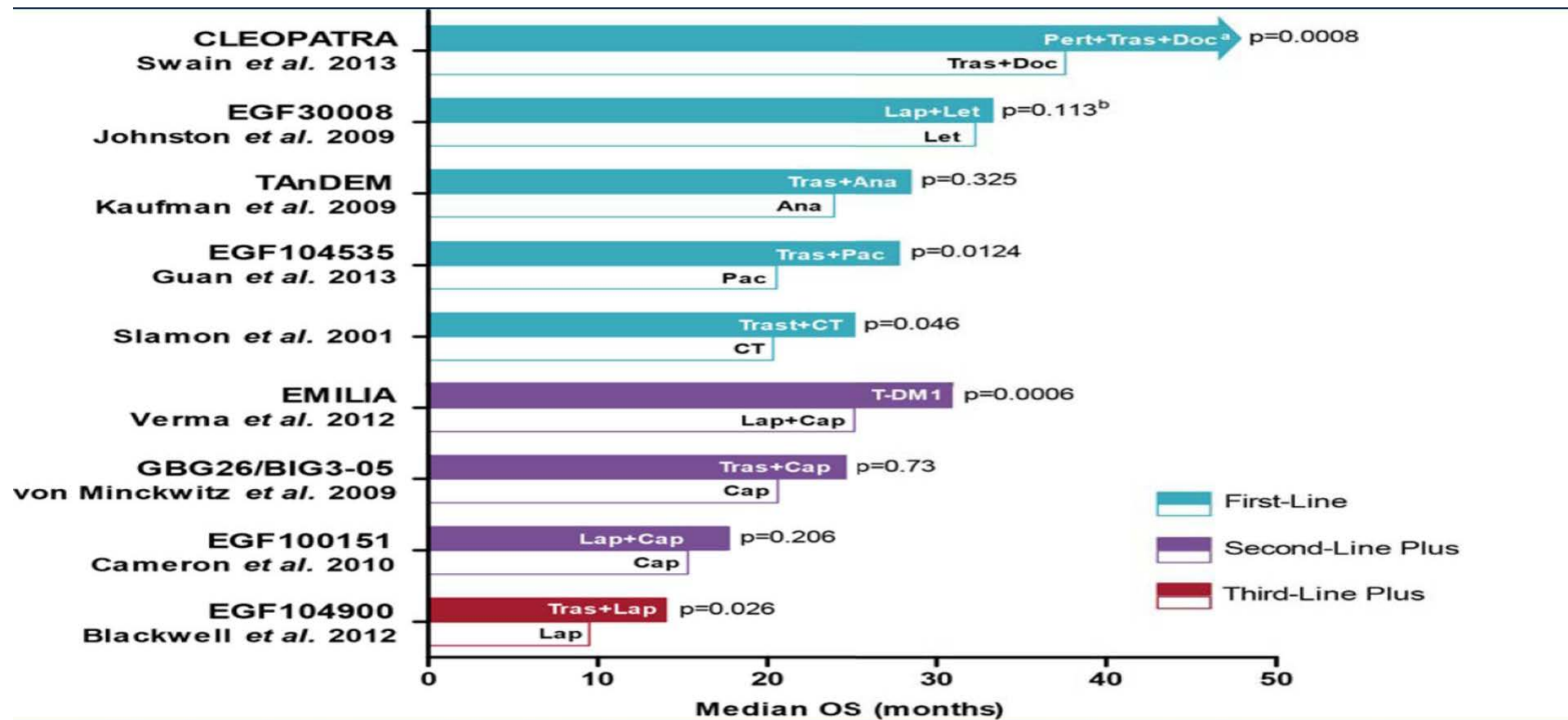
ASCO, NCCN, and ABC2 Treatment Guidelines in HER2+ Advanced Breast Cancer



^a If pertuzumab not previously received.

^b No benefit after 3 rounds of sequential cytotoxic therapy or Eastern Cooperative Oncology Group (ECOG) performance status ≥ 3 , consider no further cytotoxic therapy and palliative care.
1. Giordano SH, et al. *J Clin Oncol*. 2014;32(19):2078-2100; 2. NCCN Guidelines: Breast Cancer. Version 3.2015; 3. Cardoso F, et al. *Ann Oncol*. 2014;25(10):1871-1888.

Avanços no tratamento do câncer de mama HER2+ avançado



Abbreviations: Ana, anastrozole; Cape, capecitabine; CT, chemotherapy; Doc, docetaxel; Lap, lapatinib; Let, letrozole; OS, overall survival; Pac, paclitaxel; pertuzumab; T-DM1, trastuzumab emtansine; Tras, trastuzumab.

Por que precisamos de dados de vida real

Paciente idosa com câncer de mama em um ensaio clínico randomizado



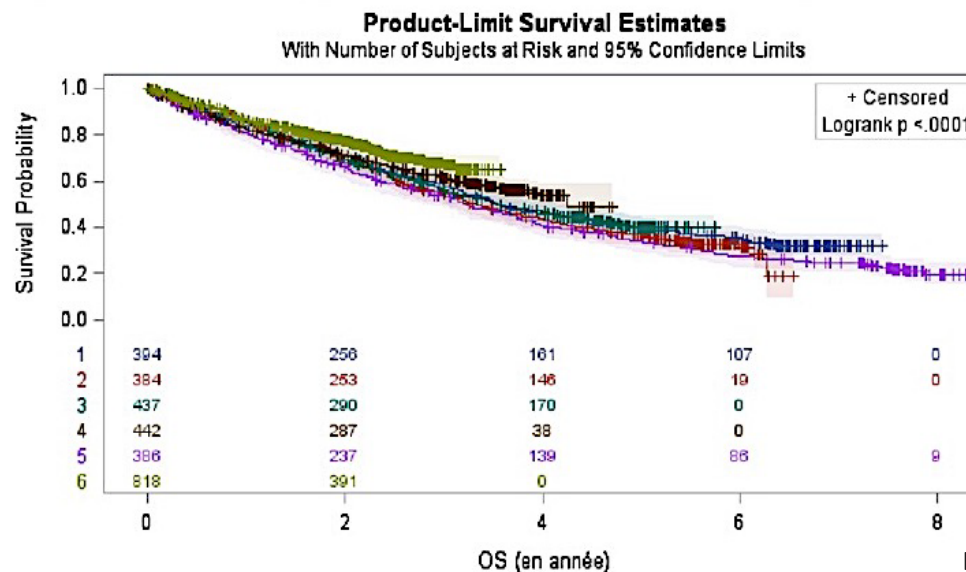
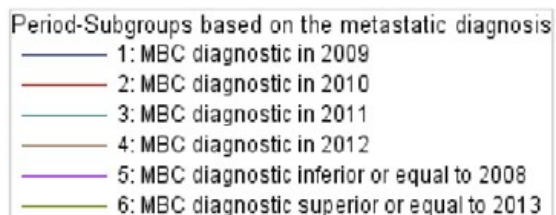
Paciente idosa com câncer de mama no nosso consultório



Real World Data on OS in MBC

	Year of Diagnosis					
OS (m)	2008	2009	2010	2011	2012	2013
HR+ HER2- (N=9.908)	43.7 (40.2-46.6)	42.0 (38.9-44.6)	40.9 (38.0-43.4)	42.0 (39.2-45.0)	44.5 (41.8-47.3)	40.3 (37.8-ND)
HER2+ (N=2.861)	38.6 (33.6-44.6)	42.3 (38.3-50.8)	40.1 (35.2-45.6)	42.3 (36.5-49.8)	51.1 (46.5-NR)	Not Reached
HR- HER2- (N=2.317)	15.1 (12.7-16.4)	15.1 (13.0-17.4)	14.7 (13.2-17.0)	14.0 (11.4-15.9)	13.9 (11.4-15.9)	14.1 (12.5-15.5)

OS per year of diagnosis in HER2 positive patients

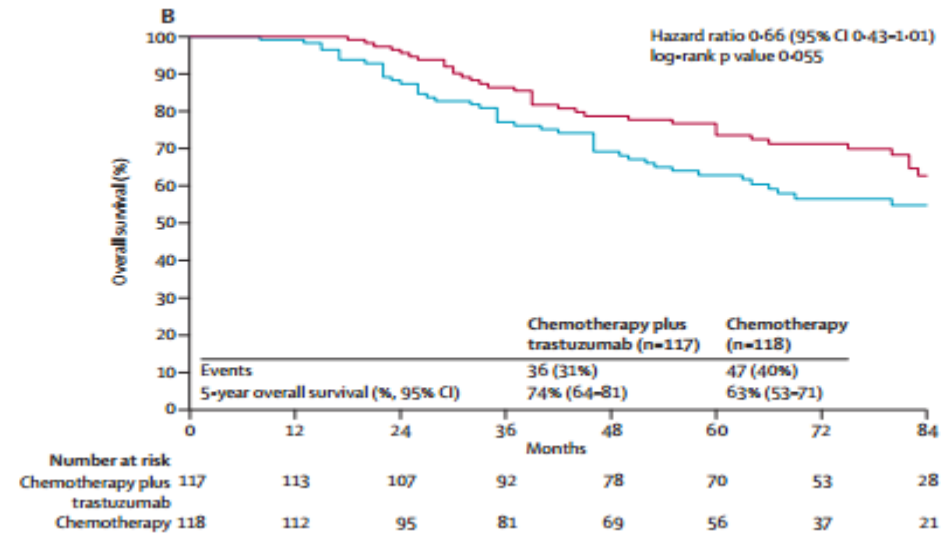
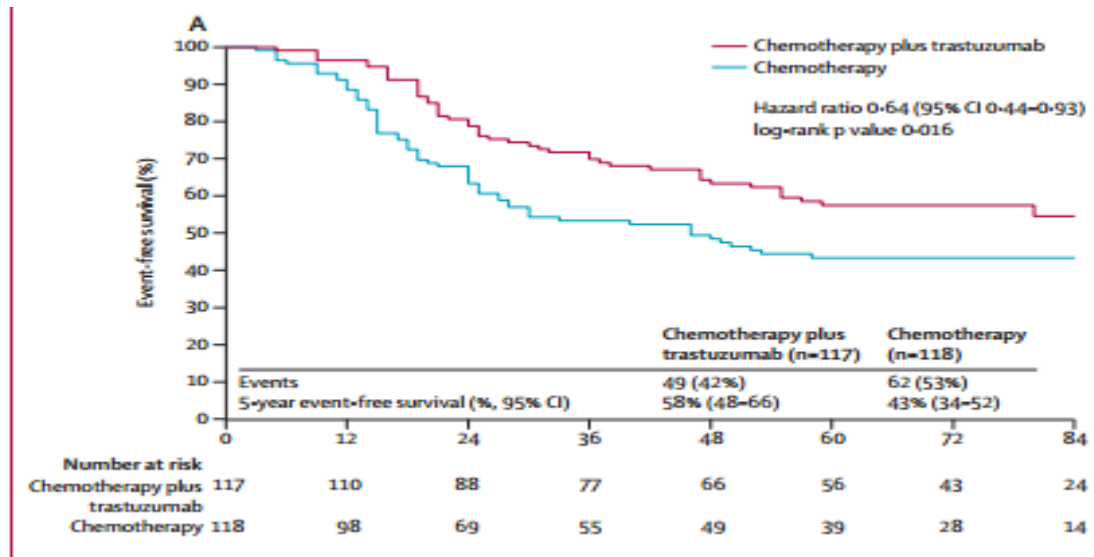


Câncer de mama HER2-positivo

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- Perspectivas futuras
- Take-home messages

Neoadjuvant Treatment of Breast Cancer: Lessons from HER2 positive disease

NOAH trial



	Hazard ratio (95% CI)	p value	P-interaction
Multivariate analyses			
Trastuzumab (n=117) vs no trastuzumab (n=118)	0.77 (0.53-1.13)	0.1870	0.037
pCR (n=68) vs no pCR (n=167)	0.32 (0.19-0.54)	<0.0001	--
Subgroup analyses			
pCR			
Trastuzumab (n=45) vs no trastuzumab (n=23)	0.29 (0.11-0.78)	0.0135	--
No pCR			
Trastuzumab (n=72) vs no trastuzumab (n=95)	0.92 (0.61-1.39)	0.6987	--
Trastuzumab			
pCR (n=45) vs no pCR (n=72)	0.17 (0.08-0.38)	<0.0001	--
No trastuzumab			
pCR (n=23) vs no pCR (n=95)	0.57 (0.29-1.13)	0.1089	--

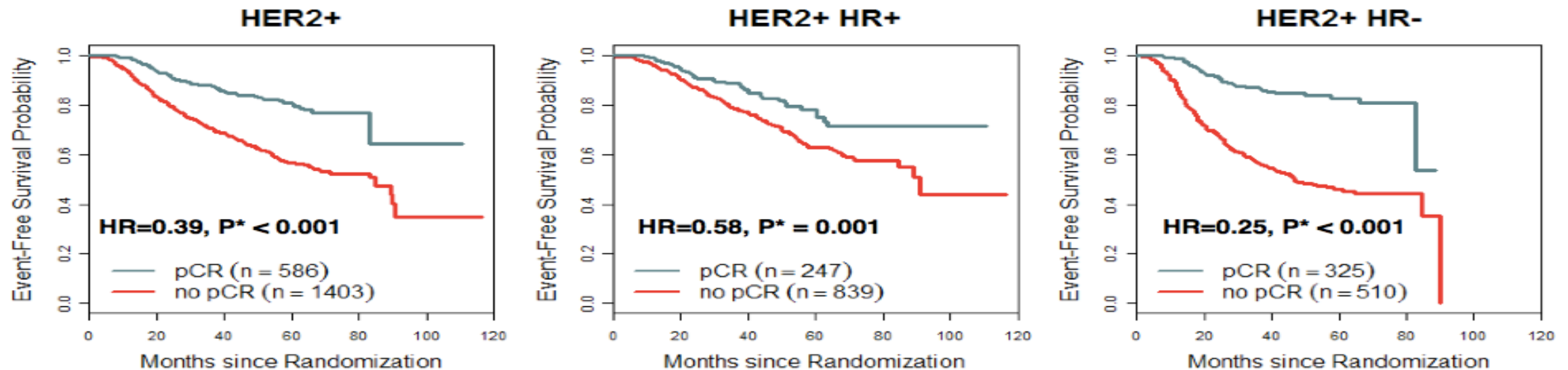
pCR=pathological complete response.

Table 4: Multivariate and subgroup analyses of pCR and event-free survival

Neoadjuvant Treatment of Breast Cancer: Lessons from HER2 positive disease

FDA CTNeoBC Meta-analysis

pCR is associated with improved EFS for Her2 positive



pCR=ypT0/is ypN0

* Nominal p-value

Cortazar P, Zhang L, et al. Meta-analysis Results from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC).

Cancer Res December 15, 2012; 72 (24 Supplement): S1-11.

Avanços na neoadjuvância em câncer de mama HER2-positivo

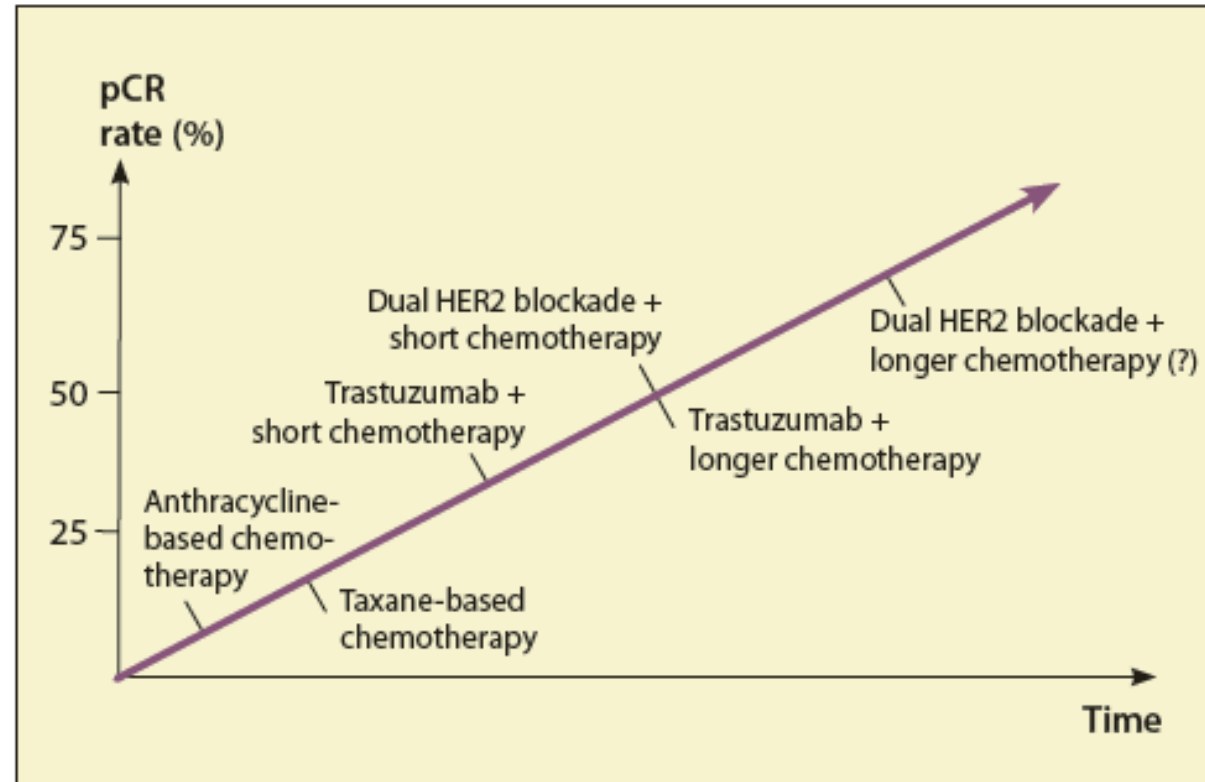
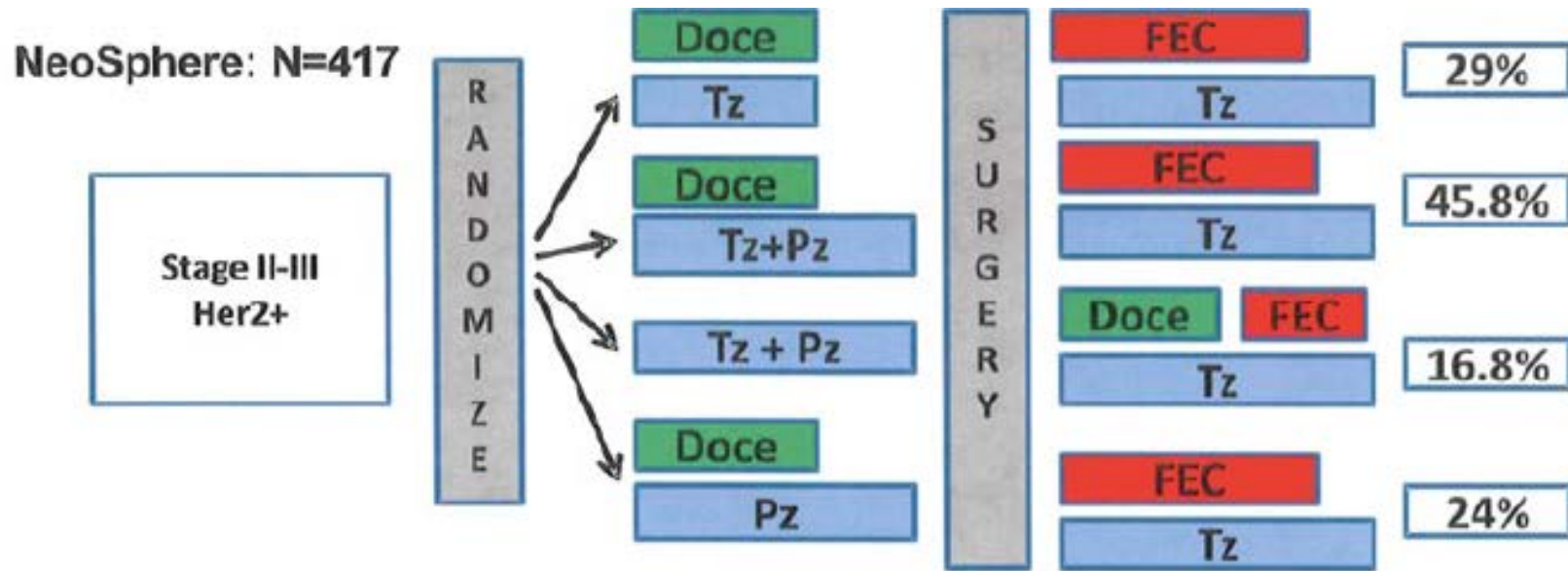
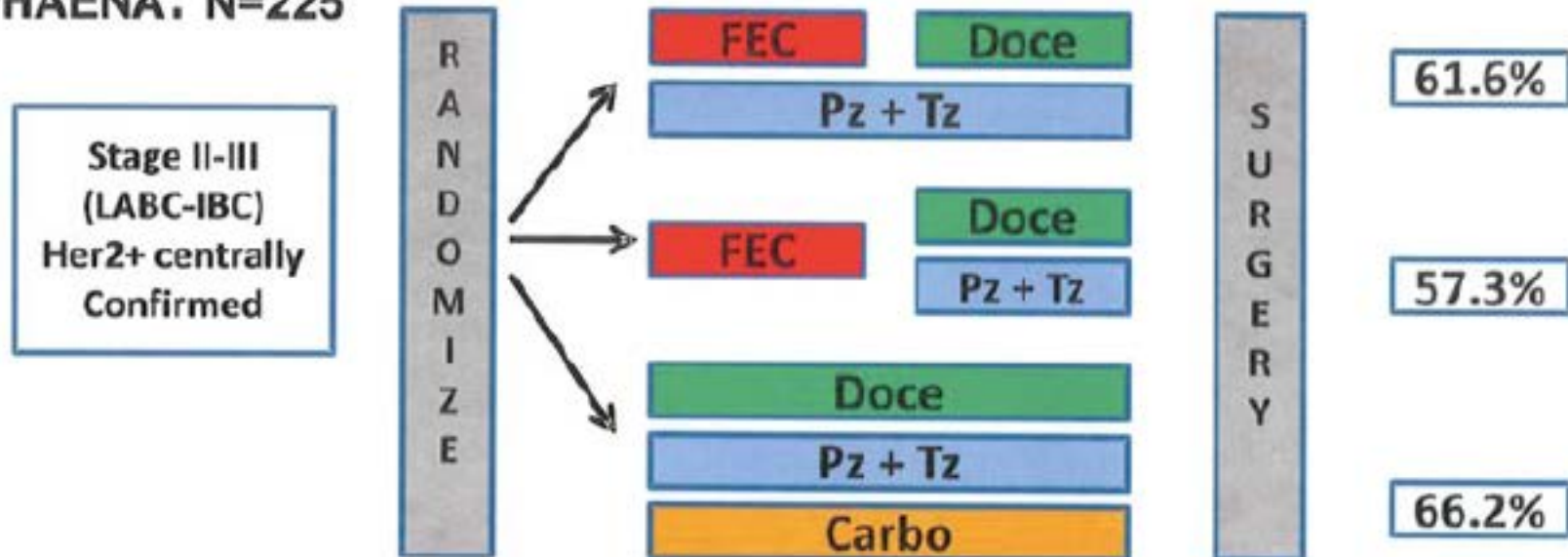


Figure 1: Incremental Improvement in Pathologic Complete Remission (pCR) Rates by Optimizing Systemic Neoadjuvant Treatment of HER2-Positive Breast Cancer.

NEOADJUVANT TRIALS ASSESSING PERTUZUMAB



TRYPHAENA: N=225



Adapted from Alvarez et. al Breast Cancer 2013

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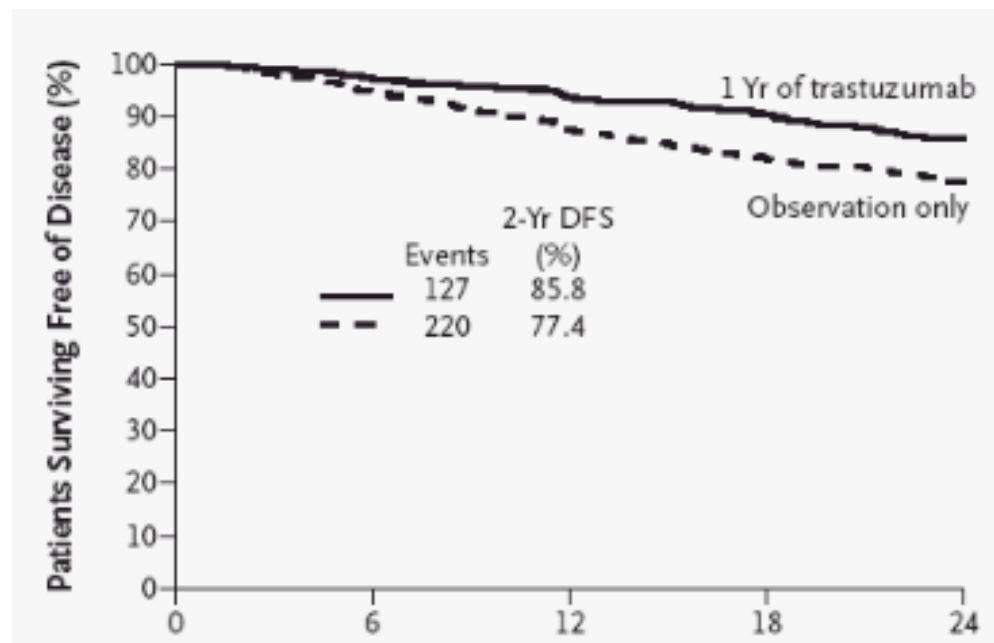
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OCTOBER 6, 2011

VOL. 365 NO. 14

Adjuvant Trastuzumab in HER2-Positive Breast Cancer

Dennis Slamon, M.D., Ph.D., Wolfgang Eiermann, M.D., Nicholas Robert, M.D., Tadeusz Pienkowski, M.D., Miguel Martin, M.D., Michael Press, M.D., Ph.D., John Mackey, M.D., John Glaspy, M.D., Arlene Chan, M.D., Marek Pawlicki, M.D., Tamas Pinter, M.D., Vicente Valero, M.D., Mei-Ching Liu, M.D., Guido Sauter, M.D., Gunter von Minckwitz, M.D., Frances Visco, J.D., Valerie Bee, M.Sc., Marc Buyse, Sc.D., Belguendouz Bendahmane, M.D., Isabelle Tabah-Fisch, M.D., Mary-Ann Lindsay, Pharm.D., Alessandro Riva, M.D., and John Crown, M.D., for the Breast Cancer International Research Group*



Escalonamento no tratamento adjuvante em câncer de mama HER2-positivo

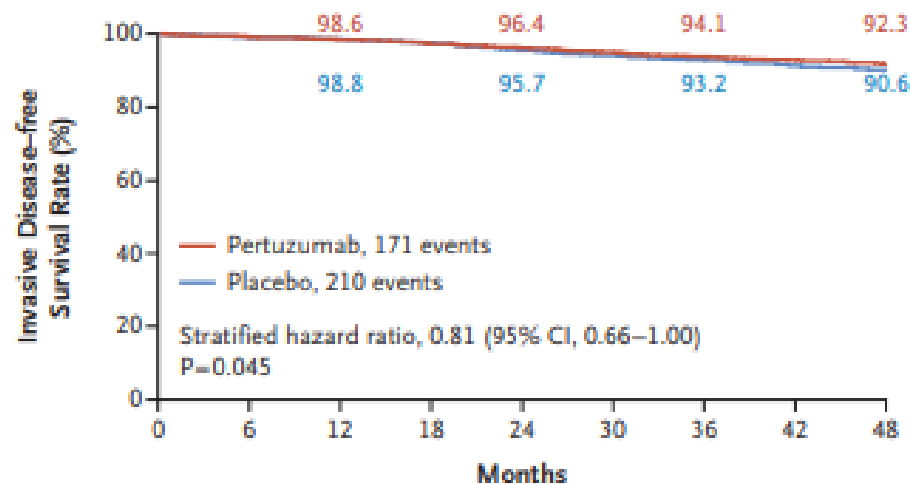
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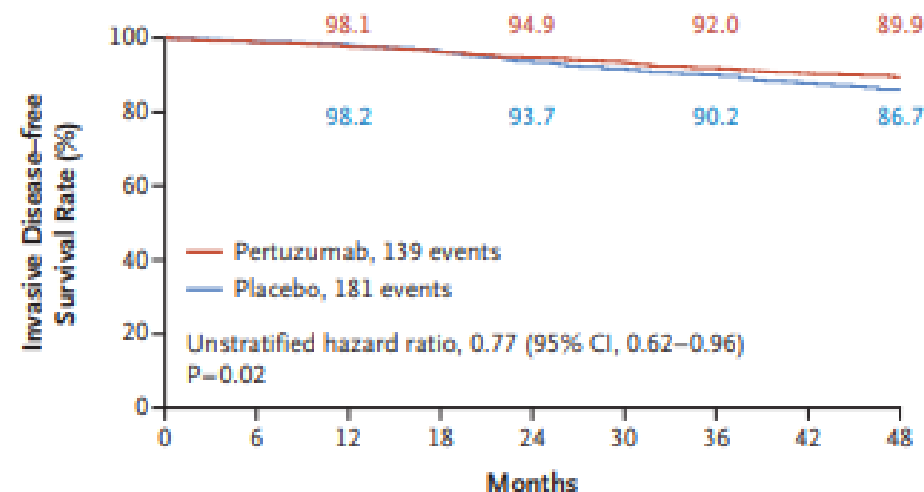
Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

Gunter von Minckwitz, M.D., Marion Procter, Ph.D., Evandro de Azambuja, M.D.,
Dimitrios Zardavas, M.D., Mark Benyunes, M.D., Giuseppe Viale, M.D., Thomas Suter, M.D.,
Amal Arahmani, Ph.D., Nathalie Rouchet, M.Sc., Emma Clark, M.Sc., Adam Knott, Ph.D.,
Istvan Lang, M.D., Christelle Levy, M.D., Denise A. Yardley, M.D., Jose Bines, M.D.,
Richard D. Gelber, Ph.D., Martine Piccart, M.D., and Jose Baselga, M.D.,
for the APHINITY Steering Committee and Investigators*

A Intention-to-Treat Population



C Population with Node-Positive Disease



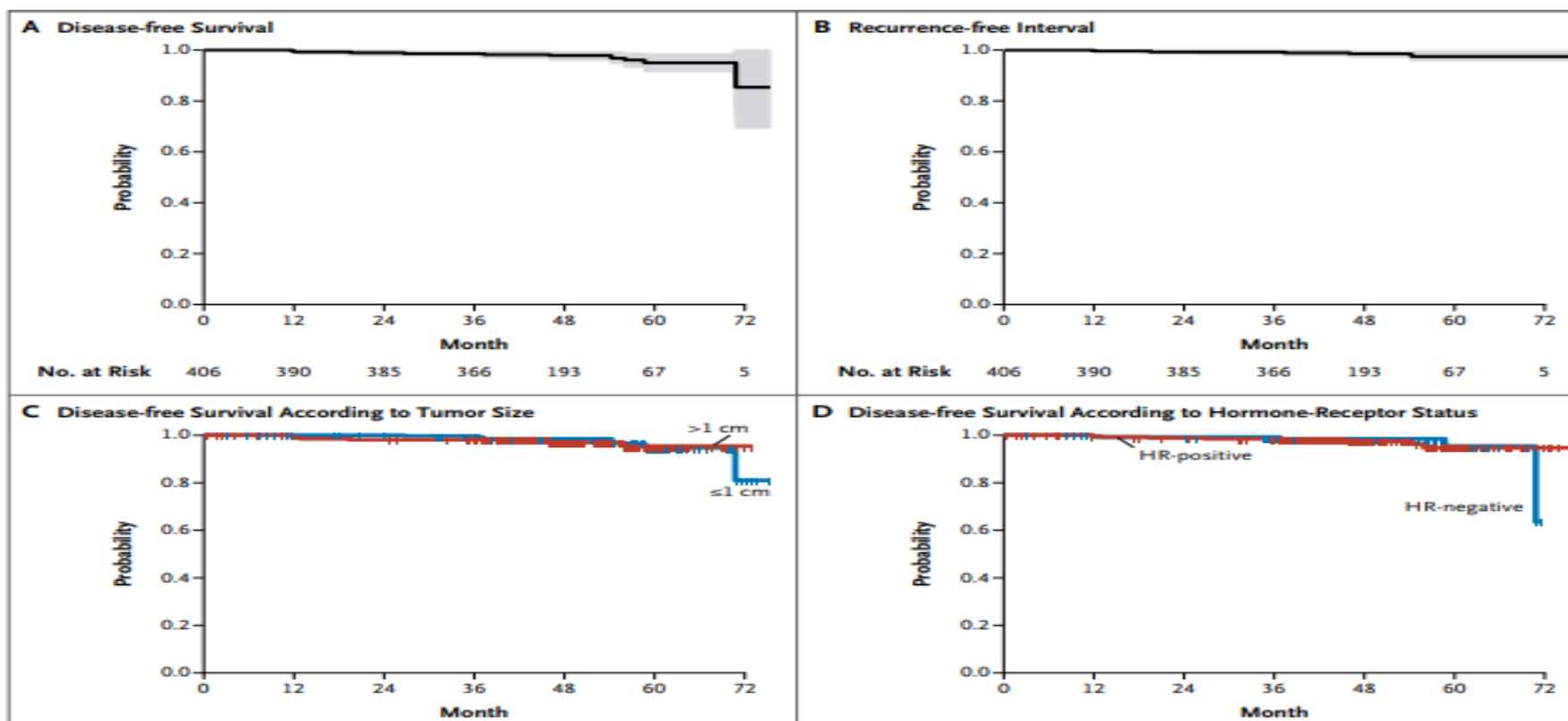
De-escalamento no tratamento adjuvante em câncer de mama HER2-positivo

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ORIGINAL ARTICLE

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

Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D., Denise A. Yardley, M.D., Beverly Moy, M.D., M.P.H., P. Kelly Marcom, M.D., Kathy S. Albain, M.D., Hope S. Rugo, M.D., Matthew Ellis, M.B., B.Chir., Ph.D., Iuliana Shapira, M.D., Antonio C. Wolff, M.D., Lisa A. Carey, M.D., Beth A. Overmoyer, M.D., Ann H. Partridge, M.D., M.P.H., Hao Guo, M.S., Clifford A. Hudis, M.D., Ian E. Krop, M.D., Ph.D., Harold J. Burstein, M.D., Ph.D., and Eric P. Winer, M.D.

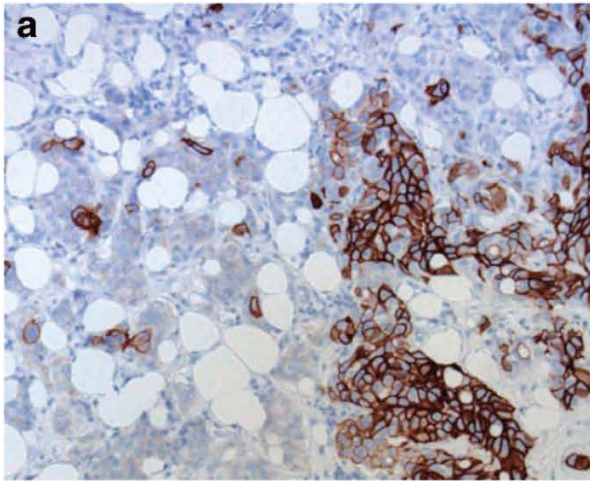


Desafios no câncer de mama HER2-positivo

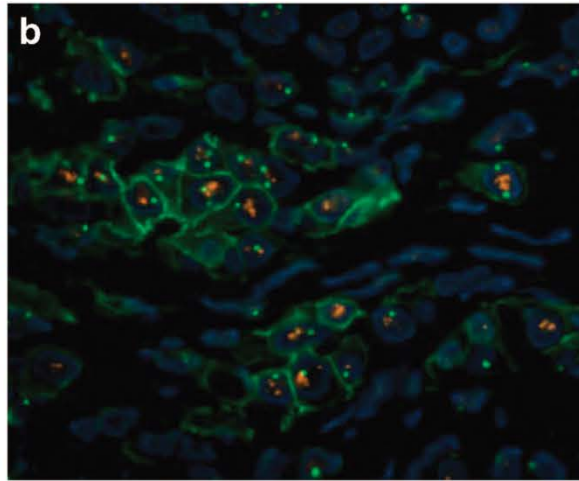
- Heterogeneidade intra-tumoral
- Heterogeneidade inter-tumoral
- De-escalamento
- Mecanismos de resistência
- Disparidade
- Toxicidade financeira

Example of HER2 heterogeneity analyzed by different methods

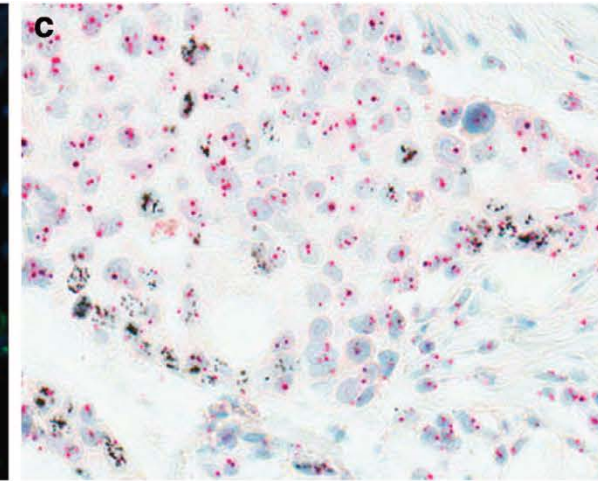
Figure 1: Heterogeneous tumor analyzed by different methods



IHC staining showing clusters of HER2+ cells (brown staining)



Double FISH/IHC showing HER2 protein expression (green) and HER2 gene amplification (red)

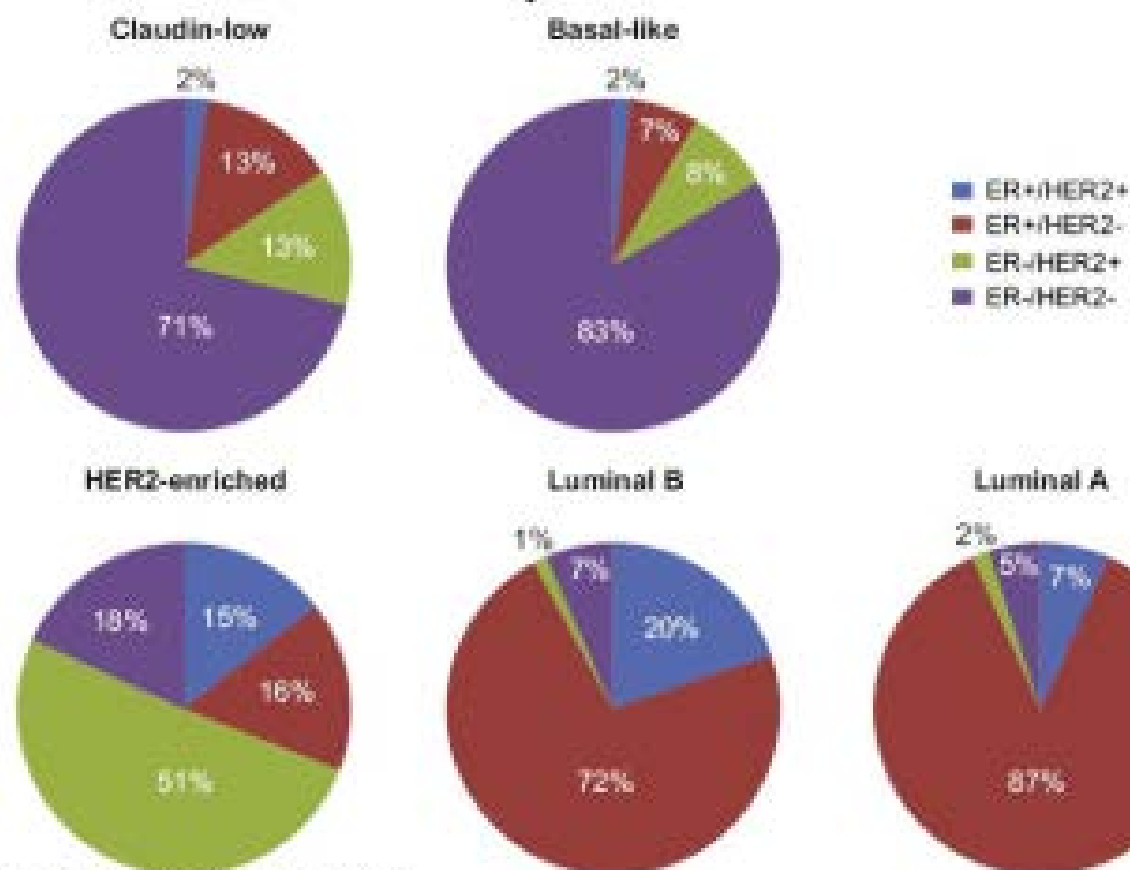


Dual-color in situ hybridization (HER2 black, chromosome 17 red)

Desafios no câncer de mama HER2-positivo

- Heterogeneidade intra-tumoral
- Heterogeneidade inter-tumoral
- De-escalamento
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- Toxicidade financeira

Breast cancer intrinsic subtypes vary in subsets defined by ER and HER2



HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial

Antonio Llombart-Cussac, Javier Cortés, Laia Paré, Patricia Galván, Begoña Bermejo, Noelia Martínez, Maria Vidal, Sònia Pernas, Rafael López, Montserrat Muñoz, Paolo Nuciforo, Serafín Morales, Mafalda Oliveira, Lorena de la Peña, Alexandra Peláez, Aleix Prat

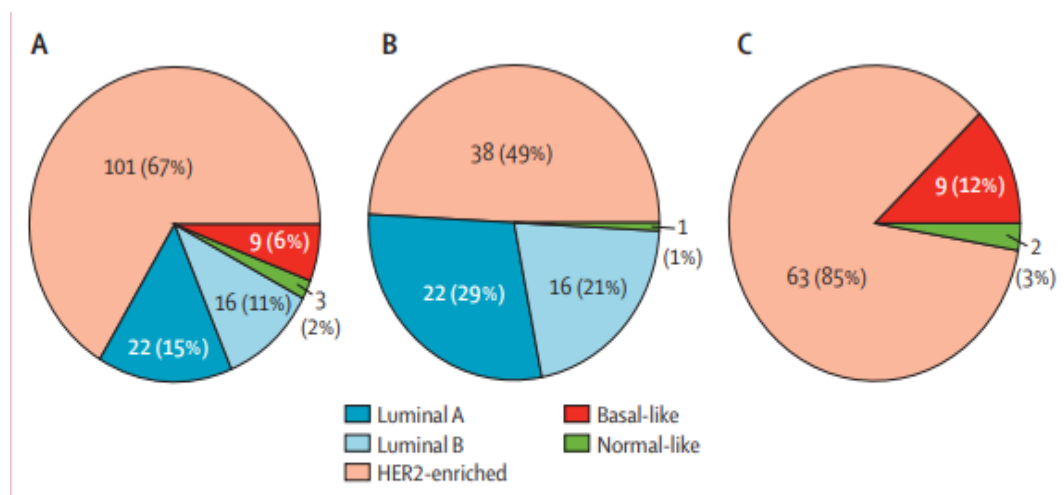


Figure 2: Distribution of intrinsic molecular subtypes at baseline

(A) All patients (n=151). (B) Patients with hormone receptor-positive disease (n=77). (C) Patients with hormone receptor-negative disease (n=74).

	Number of patients with molecular subtype at baseline	Number of patients achieving pathological complete response	Pathological complete response (95% CI)
Total	151	46	30% (23–39)
Luminal A	22	0	0%
Luminal B	16	2	13% (4–36)
HER2-enriched	101	41	41% (31–51)
Basal-like	9	1	11% (2–44)
Normal-like	3	2	67% (21–94)

Table 2: Pathological complete response at the time of surgery, by intrinsic molecular subtype assessed at baseline

Desafios no câncer de mama HER2-positivo

- Heterogeneidade intra-tumoral
- Heterogeneidade inter-tumoral
- De-escalamento
- Mecanismos de resistência
- Disparidades de acesso
- Toxicidade financeira

Tumores “triplo-positivos” necessitam de quimioterapia?

Editorial

Sparing chemotherapy with dual HER2 blockade in combination with endocrine therapy for advanced HER2 positive breast cancer

Gustavo Werutsky^{1,2}, Tomás Reinert^{1,3,4}, André Poisl Fay^{1,2}

Podemos diminuir a duração da adjuvância sem comprometer desfechos?

Persephone Trial: Cutting Trastuzumab Duration by Half Safer, Efficacious in HER2-Positive Breast Cancer

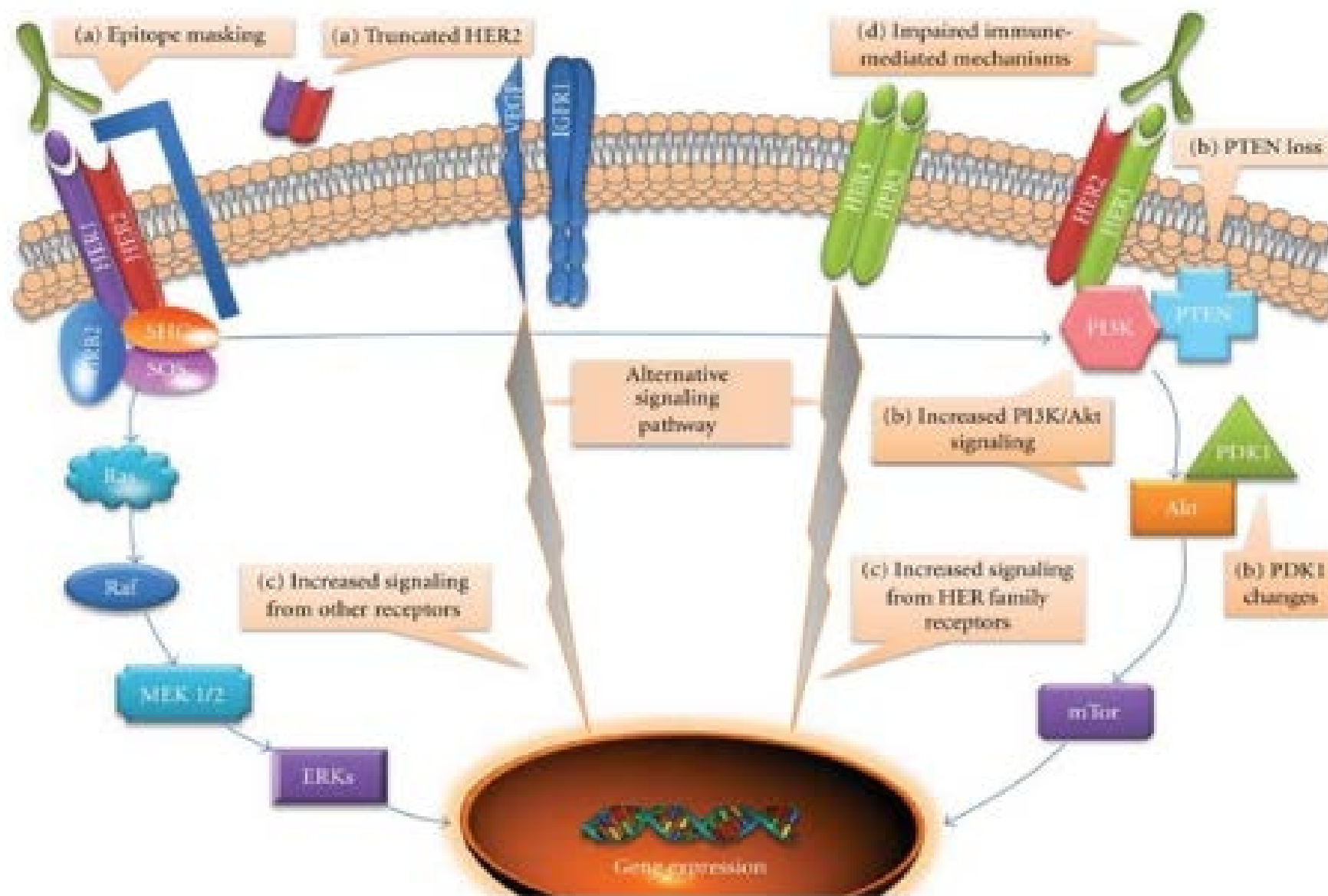
Surabhi Dangi-Garimella, PhD

During a press cast hosted by the American Society of Clinical Oncology ahead of the annual meeting, women with HER2-positive early-stage breast cancer who were treated with trastuzumab (Herceptin) for 6 months had a similar rate of disease-free survival as women who received the drug for 12 months, which is the current standard of care.

Desafios no câncer de mama HER2-positivo

- Heterogeneidade intra-tumoral
- Heterogeneidade inter-tumoral
- De-escalamento
- Mecanismos de resistência
- Disparidades de acesso
- Toxicidade financeira

Mecanismos de resistência ao trastuzumabe



Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

*Miguel Martin, Frankie A Holmes, Bent Ejlersen, Suzette Delaloge, Beverly Moy, Hiroji Iwata, Gunter von Minckwitz, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Zorica Tomašević, Neelima Denduluri, Robert Šeparović, Erhan Gokmen, Anna Bashford, Manuel Ruiz Borrego, Sung-Bae Kim, Erik Hugger Jakobsen, Audrone Ciceniene, Kenichi Inoue, Friedrich Overkamp, Joan B Heijns, Anne C Armstrong, John S Link, Anil Abraham Joy, Richard Bryce, Alvin Wong, Susan Moran, Bin Yao, Feng Xu, Alan Auerbach, Marc Buyse, Arlene Chan, for the ExteNET Study Group**

Is extended therapy with neratinib ready to be a new standard of care?

YES!

- Positive DFS data
- Similar results to the adjuvant trastuzumab trials at 2 years f/u



WAIT!

- No OS data
- Pertuzumab is an option in the neoadjuvant setting for high risk patients, so would the neratinib benefit still persist in this group?
- For lower risk patients, does the toxicity justify the small potential for benefit?

Desafios no câncer de mama HER2-positivo

- Heterogeneidade intra-tumoral
- Heterogeneidade inter-tumoral
- De-escalamento
- Mecanismos de resistência
- Disparidades de acesso
- Toxicidade financeira

original report

Estimation of Premature Deaths From Lack of Access to Anti-HER2 Therapy for Advanced Breast Cancer in the Brazilian Public Health System

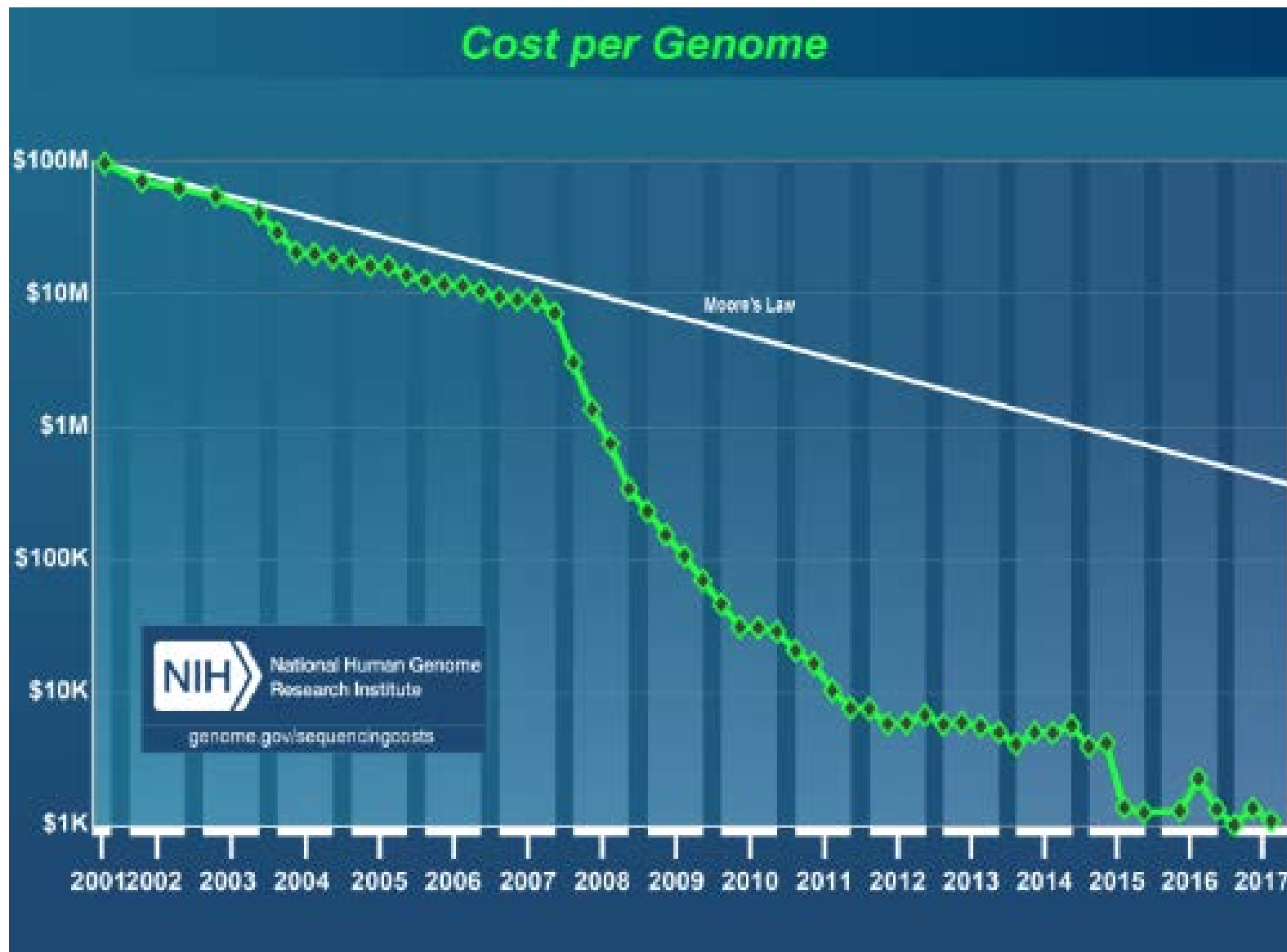
Márcio Debiasi
Tomás Reinert
Rafael Kaliks
Gilberto Amorim
Maira Caleffi
Carlos Sampaio
Gustavo dos Santos
Fernandes
Carlos H. Barrios

- 2008 mulheres com câncer de mama HER2 positivo diagnosticadas em 2016
- Apenas 808 estarão vivas em 2018 caso tratadas apenas com quimioterapia
- 1408 estariam vivas caso tratadas com quimioterapia + trastuzumabe
- 1576 estariam vivas caso tratadas com quimioterapia + trastuzumabe + pertuzumabe

Desafios no câncer de mama HER2-positivo

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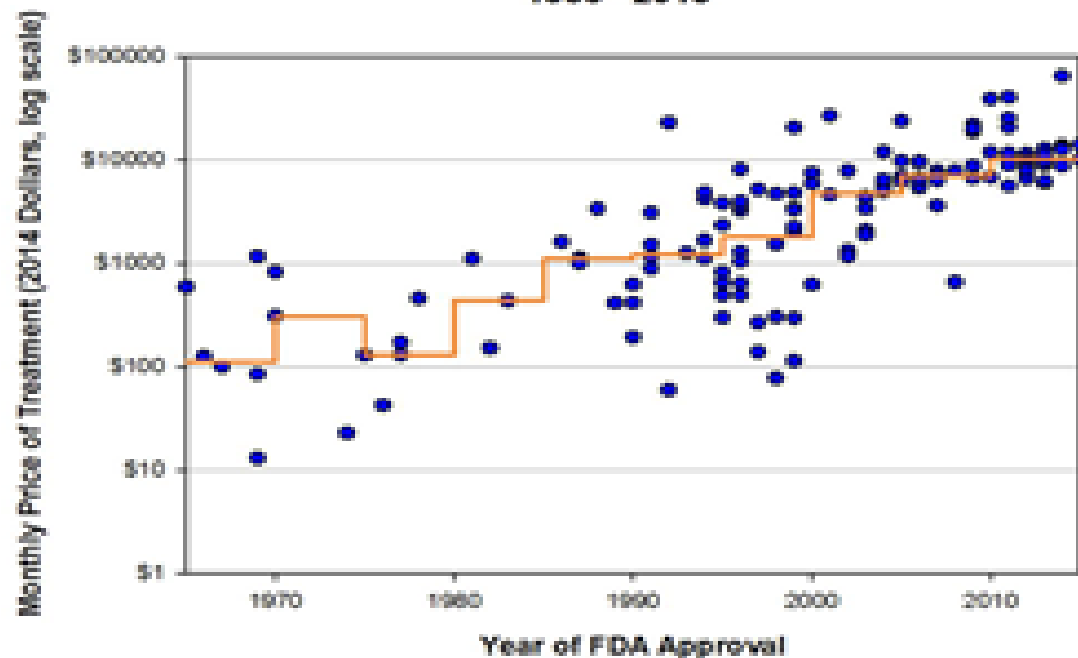
Lei de Moore – Diminuição progressiva do custo de novas tecnologias



Inexorable Rise of Monthly Costs

P. Bach, MSKCC.org

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965 - 2015



JAMA | **Original Investigation**

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

**ANVISA aprova MYL-14010:
biossimilar de trastuzumabe
para câncer de mama HER2+**

A aprovação pode ser uma alternativa para o aumento do acesso a drogas de alto custo.



Take-home messages

- Tumores HER2-positivos formam um subgrupo distinto de câncer de mama
- Terapias anti-HER2 → revolução e modelo de desenvolvimento de novas estratégias terapêuticas
- Avanços em todos cenários
 - Neoadjuvante → altas taxas de pCR
 - Adjuvante → altas taxas de cura
 - Metastático → tumores HER2-positivo já podem ser considerados como tendo melhor prognóstico do que outros subtipos

Take-home messages

- Heterogeneidade intra- e inter- tumoral
- Necessidade de personalização do tratamento
 - Escalonamento
 - De-escalonamento
- Desigualdades sócio-econômicas
- Toxicidade financeira → precisamos buscar alternativas

**31 MAIO
A 2 JUN
2018**

XIX CONGRESSO SUL-BRASILEIRO
DE GINECOLOGIA E OBSTETRÍCIA
IV JORNADA SUL-BRASILEIRA
DE MASTOLOGIA



Obrigado pela atenção!

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