Sociedad Española
de Senología y Patología Mamaria

HER2 en cáncer de mama: un paradigma en evolución

La vía de HER2, su interacción con los receptores de estrógeno y el papel de HER3.

Vicente Peg

H.U. Vall d'Hebron

Anatomía Patológica

Papel del HER2 en el cáncer de mama

Ann. Rev. Biochem. 1979. 48:193–216

EPIDERMAL GROWTH FACTOR

❖12007

Graham Carpenter

Department of Biochemistry and Division of Dermatology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

Stanley Cohen

Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

1984-86

- HER2 clonado

Yamamoto T et al. Nature. 1986

1987

- Amplificación HER2 y pronóstico

Slamon DJ et al. Science. 1987

1989

- Ac monoclonal (trastuzumab – Herceptin ® -)
- Fase I en 1992 fase II 1993, fase III 1995-97

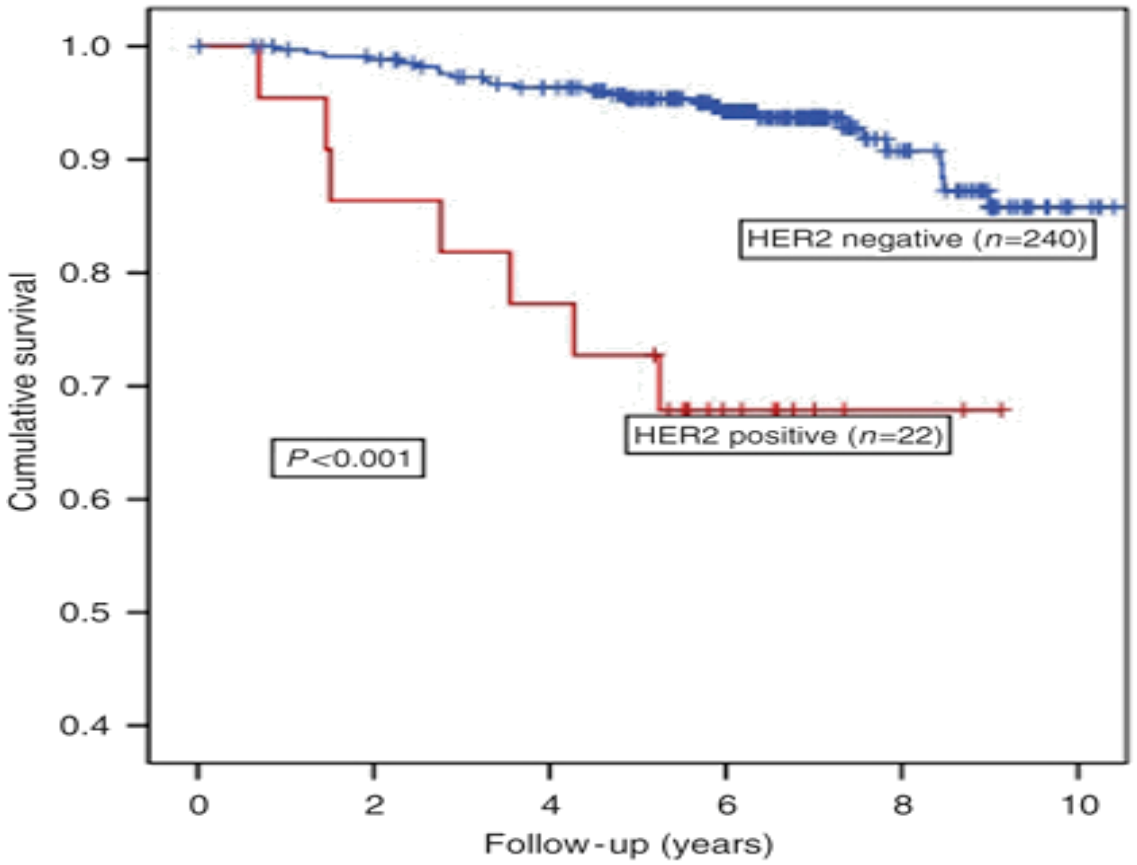
1998

- Aprobación FDA 1ª línea (+ paclitaxel) para mBC HER2 +

2006

- Aprobación FDA

Papel del HER2 en el cáncer de mama



Tovey SM et al, British Journal of Cancer, 2009

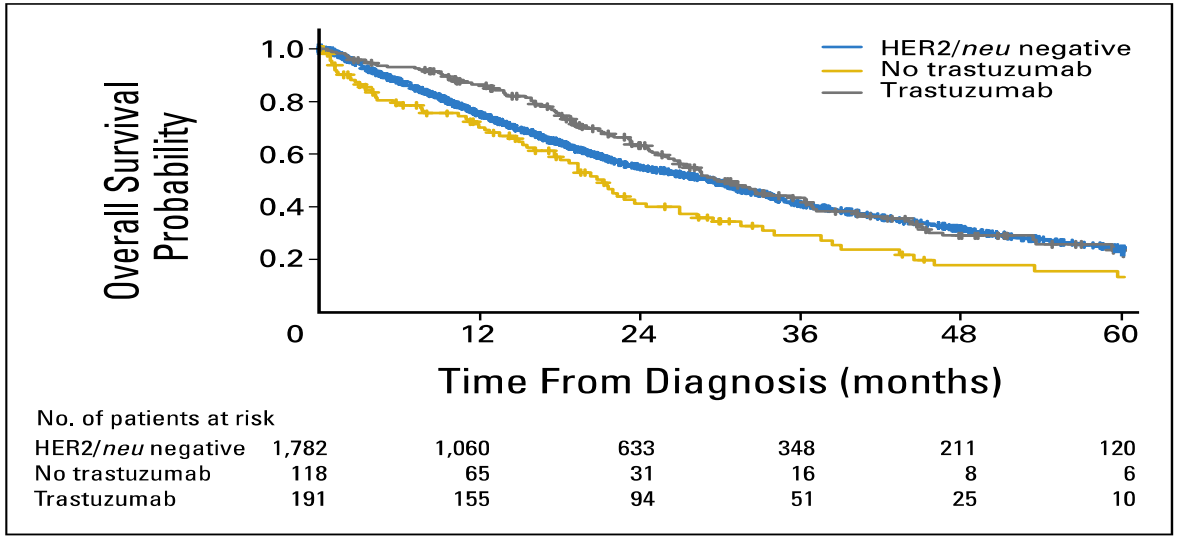


Fig 1. Overall survival by trastuzumab treatment group.

Dawood et al., J Clin Oncol, 2010

Guías de valoración de HER2

VOLUME 25 · NUMBER 1 · JANUARY 1 2007

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, Karen L. Hagerty, D. Craig Allred, Richard J. Cote, Mitchell Dowsett, Patrick L. Fitzgibbons, Wedad M. Hanna, Amy Langer, Lisa M. McShane, Soonmyung Paik, Mark D. Pegram, Edith A. Perez, Michael F. Press, Anthony Rhodes, Catharine Sturgeon, Sheila E. Taube, Raymond Tubbs, Gail H. Vance, Marc van de Vijver, Thomas M. Wheeler, and Daniel F. Hayes

A B S T R A C T

Purpose
To develop a guideline to improve the accuracy of human epidermal growth factor receptor 2 (HER2) testing in invasive breast cancer and its utility as a predictive marker.

Methods
The American Society of Clinical Oncology and the College of American Pathologists convened an expert panel, which conducted a systematic review of the literature and developed recommendations for optimal HER2 testing performance. The guideline was reviewed by selected experts and approved by the board of directors for both organizations.

Results
Approximately 20% of current HER2 testing may be inaccurate. When carefully validated testing is performed, available data do not clearly demonstrate the superiority of either immunohistochemistry (IHC) or in situ hybridization (ISH) as a predictor of benefit from anti-HER2 therapy.

Recommendations
The panel recommends that HER2 status should be determined for all invasive breast cancer. A testing algorithm that relies on accurate, reproducible assay performance, including newly available types of brightfield ISH, is proposed. Elements to reliably reduce assay variation (for example, specimen handling, assay exclusion, and reporting criteria) are specified. An algorithm defining positive, equivocal, and negative values for both HER2 protein expression and gene amplification is recommended: a positive HER2 result is IHC staining of 3+ (uniform, intense membrane staining of > 30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than six *HER2* gene copies per nucleus or a FISH ratio (*HER2* gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 *HER2* gene copies per nucleus, or FISH ratio of less than 1.8. Equivocal results require additional action for final determination. It is recommended that to perform HER2 testing, laboratories show 95% concordance with another validated test for positive and negative assay values. The panel strongly recommends validation of laboratory assay or modifications, use of standardized operating procedures, and compliance with new testing criteria to be monitored with the use of stringent laboratory accreditation standards, proficiency testing, and competency assessment. The panel recommends that HER2 testing be done in a CAP-accredited laboratory or in a laboratory that meets the accreditation and proficiency testing requirements set out by this document.

J Clin Oncol 25:118-145. This guideline was developed through a collaboration between American Society of Clinical Oncology and College of American Pathologists and has been published jointly by invitation and consent in both the Journal of Clinical Oncology *and the* Archives of Pathology & Laboratory Medicine.

From the American Society of Clinical Oncology, Alexandria, VA; and the College of American Pathologists, Northfield, IL.

Submitted September 20, 2006; accepted September 27, 2006; published online ahead of print at www.jco.org on December 11, 2006.

Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, and Daniel F. Hayes are American Society of Clinical Oncology/College of American Pathologists Expert Panel co-chairs.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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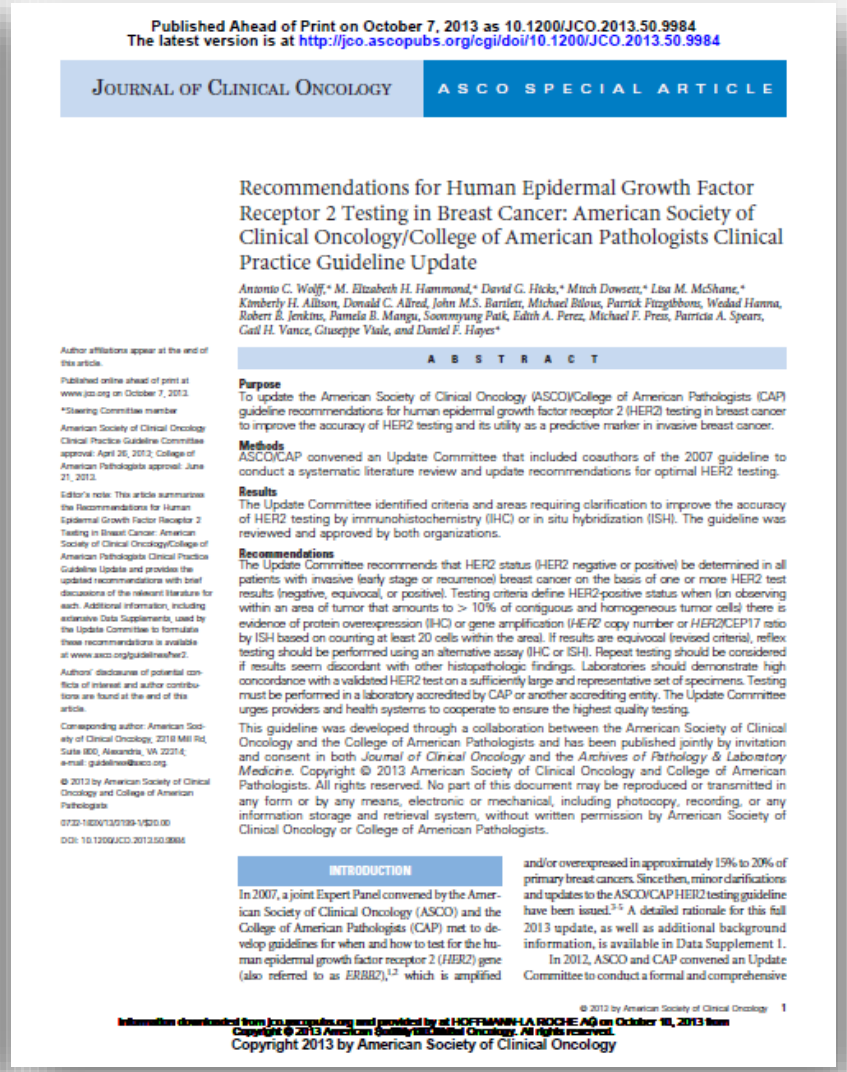
This guideline was developed through a collaboration between American Society of Clinical Oncology and College of American Pathologists and has been published jointly by invitation and consent in both the *Journal of Clinical Oncology* and the *Archives of Pathology & Laboratory Medicine*.

0732-183X/07/2501-118/$20.00

DOI: 10.1200/JCO.2006.09.2775

Wolff AC et al. J Clin Oncol. 2007



Published Ahead of Print on October 7, 2013 as 10.1200/JCO.2013.50.9984
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.50.9984

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

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

Antonio C. Wolff, M. Elizabeth H. Hammond,* David G. Hicks,* Mitch Dowsett,* Lisa M. McShane,* Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes**

A B S T R A C T

Purpose
To update the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer to improve the accuracy of HER2 testing and its utility as a predictive marker in invasive breast cancer.

Methods
ASCO/CAP convened an Update Committee that included coauthors of the 2007 guideline to conduct a systematic literature review and update recommendations for optimal HER2 testing.

Results
The Update Committee identified criteria and areas requiring clarification to improve the accuracy of HER2 testing by immunohistochemistry (IHC) or in situ hybridization (ISH). The guideline was reviewed and approved by both organizations.

Recommendations
The Update Committee recommends that HER2 status (HER2 negative or positive) be determined in all patients with invasive (early stage or recurrence) breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). Testing criteria define HER2-positive status when (on observing within an area of tumor that amounts to > 10% of contiguous and homogeneous tumor cells) there is evidence of protein overexpression (IHC) or gene amplification (*HER2* copy number or *HER2*/CEP17 ratio by ISH based on counting at least 20 cells within the areal. If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH). Repeat testing should be considered if results seem discordant with other histopathologic findings. Laboratories should demonstrate high concordance with a validated HER2 test on a sufficiently large and representative set of specimens. Testing must be performed in a laboratory accredited by CAP or another accrediting entity. The Update Committee urges providers and health systems to cooperate to ensure the highest quality testing.

INTRODUCTION

In 2007, a joint Expert Panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) met to develop guidelines for when and how to test for the human epidermal growth factor receptor 2 (*HER2*) gene (also referred to as *ERBB2*),[1,2] which is amplified and/or overexpressed in approximately 15% to 20% of primary breast cancers. Since then, minor clarifications and updates to the ASCO/CAP HER2 testing guideline have been issued.[3-5] A detailed rationale for this full 2013 update, as well as additional background information, is available in Data Supplement 1.

In 2012, ASCO and CAP convened an Update Committee to conduct a formal and comprehensive

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on October 7, 2013.

*Steering Committee member

American Society of Clinical Oncology Clinical Practice Guideline Committee approval: April 26, 2013; College of American Pathologists approval: June 21, 2013.

Editor's note: This article summarizes the Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update and provides the updated recommendations with brief discussions of the relevant literature for each. Additional information, including extensive Data Supplements, used by the Update Committee to formulate these recommendations is available at www.asco.org/guidelines/her2.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

0732-183X/13/3199-1/$20.00

DOI: 10.1200/JCO.2013.50.9984

Wolff AC et al. J Clin Oncol. 2013

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

A B S T R A C T

Purpose
To update key recommendations of the American Society of Clinical Oncology/College of American Pathologists human epidermal growth factor receptor 2 (HER2) testing in breast cancer guideline.

Methods
Based on the signals approach, an Expert Panel reviewed published literature and research survey results on the observed frequency of less common in situ hybridization (ISH) patterns to update the recommendations.

Recommendations
Two recommendations addressed via correspondence in 2015 are included. First, immunohistochemistry (IHC) 2+ is defined as invasive breast cancer with weak to moderate complete membrane staining observed in > 10% of tumor cells. Second, if the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may (not "must") be ordered on the excision specimen based on specific clinical criteria. The HER2 testing algorithm for breast cancer is updated to address the recommended work-up for less common clinical scenarios (approximately 5% of cases) observed when using a dual-probe ISH assay. These scenarios are described as ISH group 2 (*HER2*/chromosome enumeration probe 17 [CEP17] ratio ≥ 2.0; average *HER2* copy number < 4.0 signals per cell), ISH group 3 (*HER2*/CEP17 ratio < 2.0; average *HER2* copy number ≥ 6.0 signals per cell), and ISH group 4 (*HER2*/CEP17 ratio < 2.0; average *HER2* copy number ≥ 4.0 and < 6.0 signals per cell). The diagnostic approach includes more rigorous interpretation criteria for ISH and requires concomitant IHC review for dual-probe ISH groups 2 to 4 to arrive at the most accurate HER2 status designation (positive or negative) based on combined interpretation of the ISH and IHC assays. The Expert Panel recommends that laboratories using single-probe ISH assays include concomitant IHC review as part of the interpretation of all single-probe ISH assay results.

Find additional information at www.asco.org/breast-cancer-guidelines.

J Clin Oncol 36:2105-2122. © 2018 by American Society of Clinical Oncology and College of American Pathologists

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on May 30, 2018.

A.C.W. and M.E.H.H. were Expert Panel Co-Chairs. K.H.A., L.M.M., and M.D. were Expert Panel Steering Committee members.

Clinical Practice Guideline Committee approved: October 2, 2017.

Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/18/3620w-2105w/$20.00

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2018.77.8738

Data Supplement
DOI: https://doi.org/10.1200/JCO.2018.77.8738

DOI: https://doi.org/10.1200/JCO.2018.77.8738

INTRODUCTION

First released in 2007 and updated in 2013, the recommendations by the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) human epidermal growth factor receptor 2 (HER2) testing Expert Panel are aimed at improving the analytic validity of HER2 testing and the clinical utility of HER2 as a predictive biomarker for potential responsiveness to therapies targeting the HER2 protein.[1-4] Activating mutations of the tyrosine kinase and extracellular domains of HER2 in the absence of amplification or overexpression offer an alternative and much less common mechanism for HER2-targeted therapy that is being explored in clinical trials of small molecule kinase inhibitors.[5] Data from

Wolff AC et al. J Clin Oncol. 2018

Función biológica de HER2

- EGF descubierto en 1959
- Objetivo:
  - Describir la interacción con los receptores de membrana, internalización y degradación
  - Analizar las proteínas fosforiladas por los EGF in vitro
  - Determinar la secuencia de los eventos bioquímicos que conducen a la proliferación celular
  - Definir el papel fisiológico del los EGF endógenos

CONCLUDING REMARKS

Among the many alternative hypotheses that may be considered in attempting to understand the mechanisms by which EGF exerts its effect are:

1. All of the biological effects of EGF are exerted at the plasma membrane and the internalization process merely serves to remove the stimulus.
2. Membrane binding is necessary for some of the observed effects (such as transport) whereas others (such as DNA synthesis) require internalization of the cell-bound hormone.
3. Phosphorylation of membrane components induced by EGF is related to altered transport of ions and nutrients or internalization of the cell-bound growth factor.
4. A degradation product of EGF is biologically active within the cell.
5. Internalization of the receptor, with or without degradation, is related to the mitogenic signal.
6. Activation and internalization of the membrane phosphorylating systems (receptor related?) is required for mitogenicity. This could serve to phosphorylate specific membrane-associated cytoplasm proteins which in turn could act as metabolic signals.

Carpenter G, Cohen S, Ann Rev Biochem, 1979

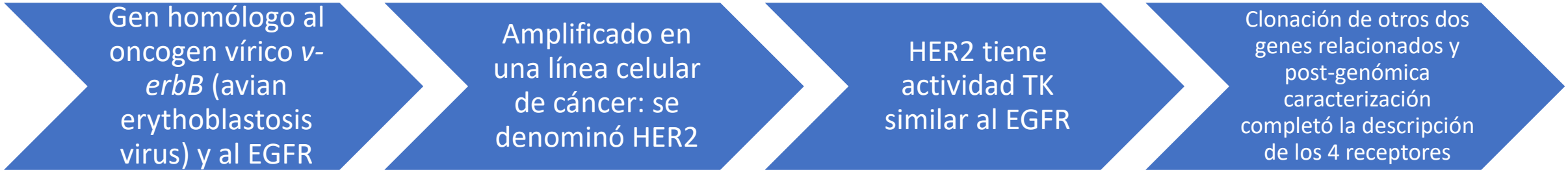
Amplificación de HER2

s degree of HER-2/*neu*
with 12 µg of Eco RI–
umor 31 (Fig. 1), which
2/*neu* gene. Lane g is
with >20 copies of the
:100, 1:20, 1:10, 1:5,
g. Lane k is DNA from
ing two to five copies of
ns (1:10, 1:5, and 1:2,
is DNA from tumor 34
pies of the HER-2/*neu*
:5, and 1:2, respective-
red and hybridized with
mple of arginase probe
nts of tumor DNA were
ntaining lanes 30 to 40
ing in a buffer made up
65°C for 20 minutes,
ch in 0.1× SSC at room
AR-5 film (Kodak) to
dized as in Fig. 1 with a

pN +

amplification. It is well known that the number of positive nodes is the best prognostic factor for disease recurrence and survival in

Descripción de la familia de receptores HER



Schechter et al. 1985; Schechter et al. 1984

King et al. 1985

Akiyama et al. 1986

Kraus et al. 1989; Plowman et al. 1993; Manning et al. 2002

- EGFR (HER1, erbB1)
- HER2 (erbB2, HER2/neu)
- HER3 (erbB3)
- HER4 (erbB4).

Adaptado de Moasser MM, Oncogene, 2007

Función biológica de HER2

- HER/*erbB*: familia de 4 receptores de membrana (HER1/4)
- Papel en la proliferación y diferenciación celular
- Distintos EGF actúan como ligandos (salvo para HER2)
- Los receptores HER existen como monómeros o dímeros (homo-hetero). La unión con el ligando induce la dimerización, especialmente con HER2 (señales más potentes)
- En células normales, escasas moléculas de HER2 (señales controlables)

lipophilic segment, and an intracellular domain with tyrosine kinase catalytic activity (Figure 1) [9]. A terminal carboxyl autophosphorylation segment is most likely to be responsible for translation of the activation signals initiated by extracellular ligand binding into physiologic action.

Ligands of HER receptors

An understanding of the action of ligands of HER receptors is crucial to understanding the role of the receptors themselves. The HER receptors exist as monomers. However, on ligand binding they form receptor

Rubin I, Yarden Y, Ann Oncol, 2001

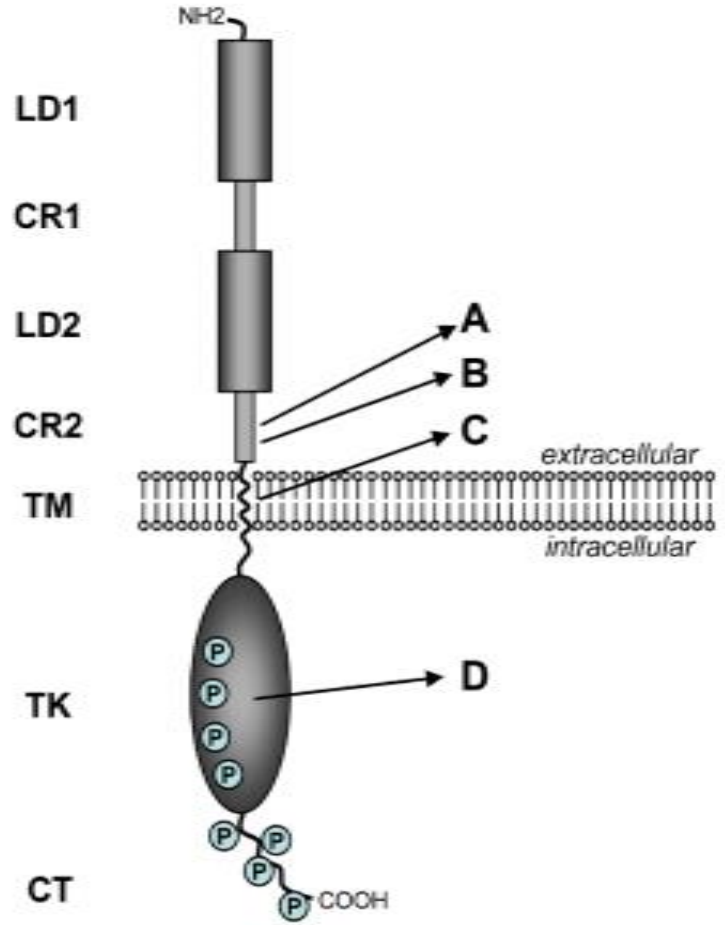
Señalización mediada por las proteínas HER

Unión con ligando (al menos 12 distintos) **inactivo**

Dimerización – cambio conformación dominio EC **activación**

Fosforilación dominio intracelular

HER2 siempre forma activa

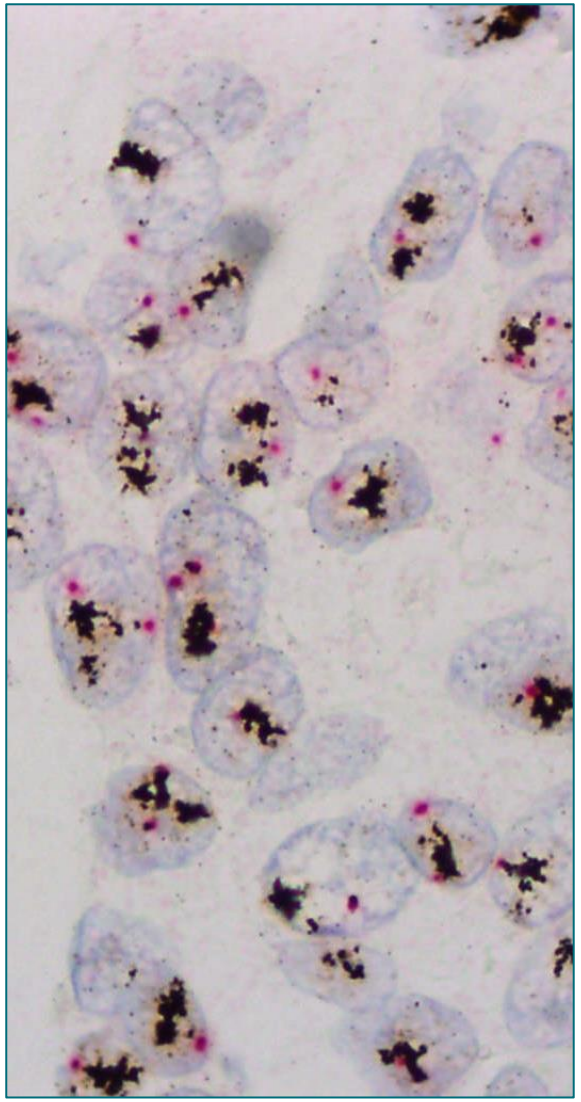


Moasser MM, Oncogene, 2007

Expresado en múltiples tejidos no hematopoyéticos – implicado en desarrollo cerebro, piel, pulmón y tracto GI

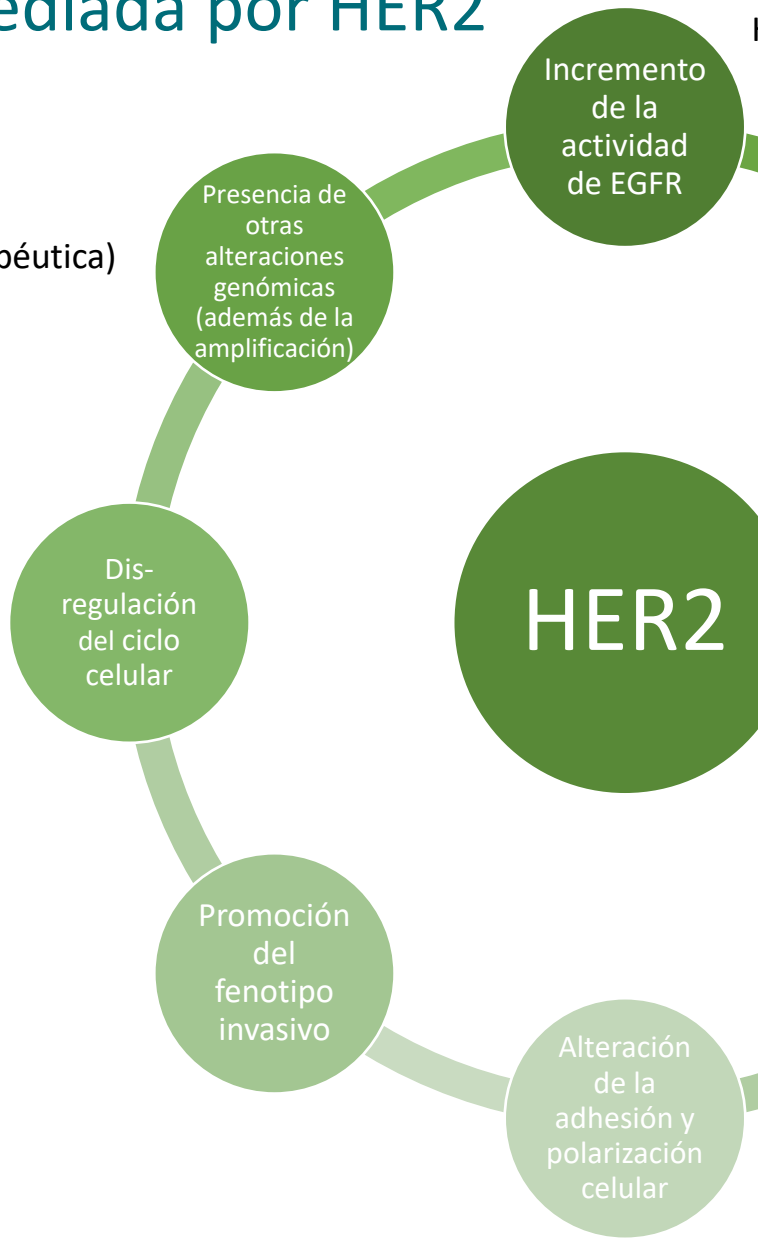
Sobreexpresión de HER2

- Por amplificación o alteración de la regulación transcripcional (20-50 copias o incremento de 40-100 de la expresión proteica en cáncer de mama)
- Evento temprano en el desarrollo del cáncer de mama
- Presente hasta el 50% de CDIS
- Entidad propia con características propias (ej. propensión a M1 SNC, sensibilidad a determinados citotóxicos y resistencia a terapias hormonales)



Slamon DJ. Science 1989
Lohrisch C, Piccart M, Semin Oncol 2001
Park K, Histopathology 2006
Gabos Z, J Clin Oncol 2006

Tumorogénesis mediada por HER2



Heterodímero EGFR-HER2 evade degradación endocítica de EGFR

Mediada por HER2-HER3

Mayor actividad independiente del ligando y potencia similar al gen *neu* mutado

Como TOPO2A (posible diana terapéutica)

Mediada por ciclina D1 y p27

Moasser MM, Oncogene, 2007

PAPEL DEL RECEPTOR HER3

Papel del receptor HER3

- Receptor “inactivo” (o débilmente) por carecer de actividad TK
- Activación de la vía PI3K/Akt (supervivencia, evasión apoptosis)
- Sobreexpresado en 40-70% cáncer de mama
- Asociación con metástasis a distancia, tamaño y riesgo de recidiva aunque con resultados contradictorios (heterogeneidad? Forma de detección? Distinto papel según subtipo molecular?)

Lyu H, Acta Pharmaceutica Sinica B, 2018

Table 2. Evaluation of human epidermal growth factor receptor 3 (HER3) by immunohistochemistry (IHC) in the selected studies

Tumor type (Reference)	HER3 overexpression, %	Antibody used for the evaluation of HER3 by IHC	Cutoff for overexpression
Pancreatic (18)	41.3%	Nanotools, Teningen, Germany	Cytoplasmic and membrane-staining intensity Positive: moderate staining is observed in >10% tumor cells (score 2+) and strong staining is observed in >10% tumor cells (score 3)
Breast (19)	43.0%	Clone 2F12, Labvision, Cheshire, UK	Cytoplasmic. Proximity ligation assay. Positive: Optimal cutoffs for HER2:HER3 dimers were assessed by performing a minimum *P* value estimation using approximate 5% cutoffs (5% of cases per interval) across the entire dataset using relapse-free survival as an endpoint.
Breast (20)	17.5%	IgG1, Neomarkers, UK	4-point scale, where 0 = no staining, 1 = light staining, 2 = moderate staining, and 3 = strongstaining Positive: 3 strong staining
Colorectal (21)	17.0%*	MAb-MS-725-P, Neomarkers, Fremont, CA	Cytoplasmic and membrane Positive: Membranous staining: >1% of tumor cells stained. Cytoplasmic staining: 2+: moderate immunostaining in >10% of tumor cells and 3+: strong immunostaining in >10% of tumor cells.

Ocaña A, JNCI, 2013

Table 3. Odds ratios of human epidermal growth factor receptor 3 (HER3) overexpression (experimental) vs normal HER3 expression (control) for death at 3 and 5 years based on cancer by site and staining method*

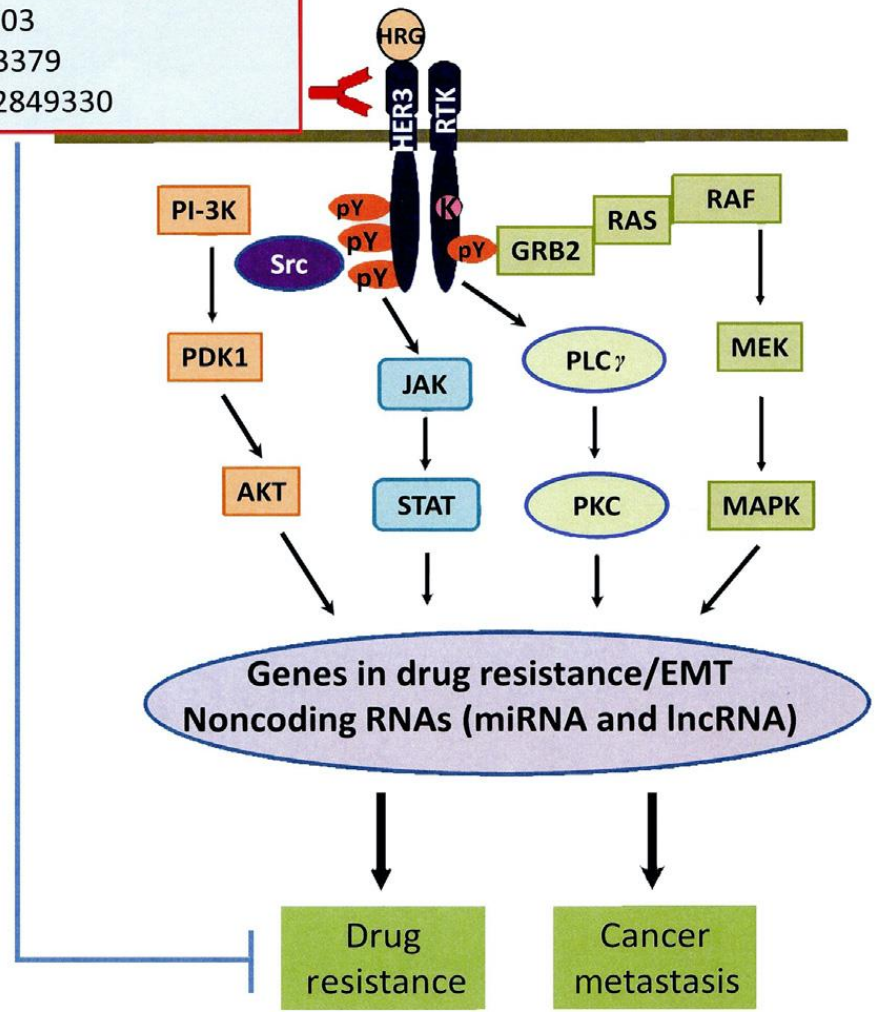
Studies	Number of studies	Pooled OR (95% CI); *P*	Subgroup difference *P*
Colorectal cancer (21, 22, 24)	3	3-year OS: 0.82 (0.44 to 1.51); .52	<.001
		5-year OS: 1.07 (0.63 to 1.80); .80	.002
Gastric cancer (23, 25)	2	3-year OS: 3.71 (2.19 to 6.29); <.001	.03
		5-year OS: 2.99 (1.81 to 4.95); <.001	.21
Breast cancer (19, 20)	2	3-year OS: 2.48 (1.50 to 4.11); <.001	.66
		5-year OS: 2.89 (1.84 to 4.53); <.001	.17
HER2-overexpressing tumors (19, 20, 23, 25, 27)	5	3-year OS: 3.12 (2.24 to 4.37); <.001	.004
		5-year OS: 2.84 (2.09 to 3.88); <.001	.02
ER-positive tumors (19, 20, 27)	3	3-year OS: 2.77 (1.82 to 4.22); <.001	.24
		5-year OS: 2.75 (1.86 to 4.08); <.001	.17
Cytoplasmic and membrane staining (18, 19, 21–23, 25–27)	8	3-year OS: 2.15 (1.61 to 2.85); <.001	.59
		5-year OS: 2.21 (1.68 to 2.90); <.001	.79
Membrane staining (20, 24, 28)	3	3-year OS: 2.45 (1.62 to 3.71); <.001	.61
		5-year OS: 2.18 (1.45 to 3.27); <.001	.95

CI = confidence interval; ER = estrogen receptor; OR = odds ratio; OS = overall survival.

Ocaña A, JNCI, 2013

Patritumab/U3-1287
Seribantumab/MM-121
Elgemtumab/LJM716
Lumretuzumab/RG7116
AV-203
KTN3379
GSK2849330

Human or humanized mono-specific Abs targeting HER3 in clinical trials

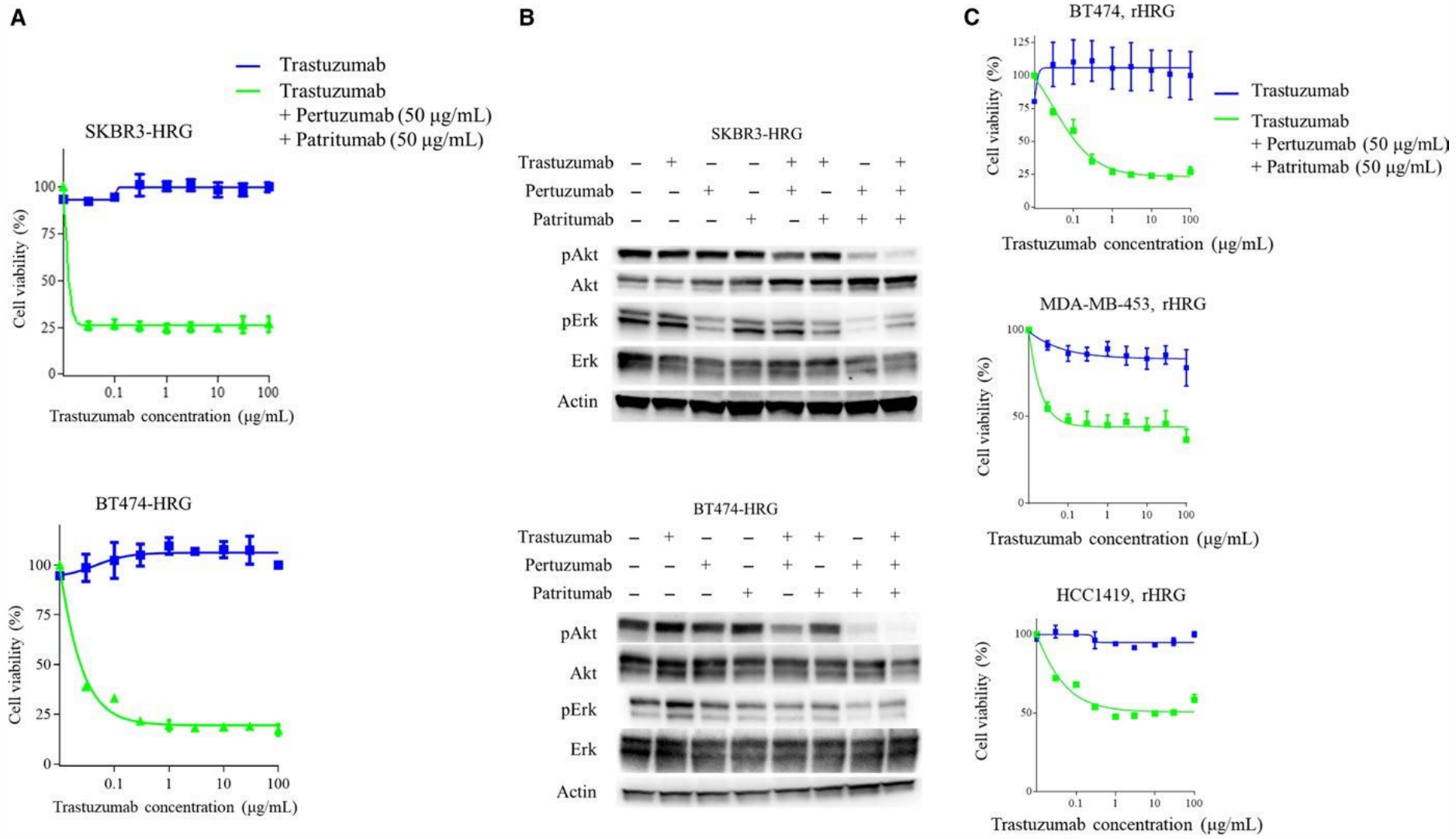


Metástasis a distancia

Resistencia a tto

Lyu H, Acta Pharmaceutica Sinica B, 2018

HER3 como posible diana terapéutica



Watanabe S, Cancer Med, 2019

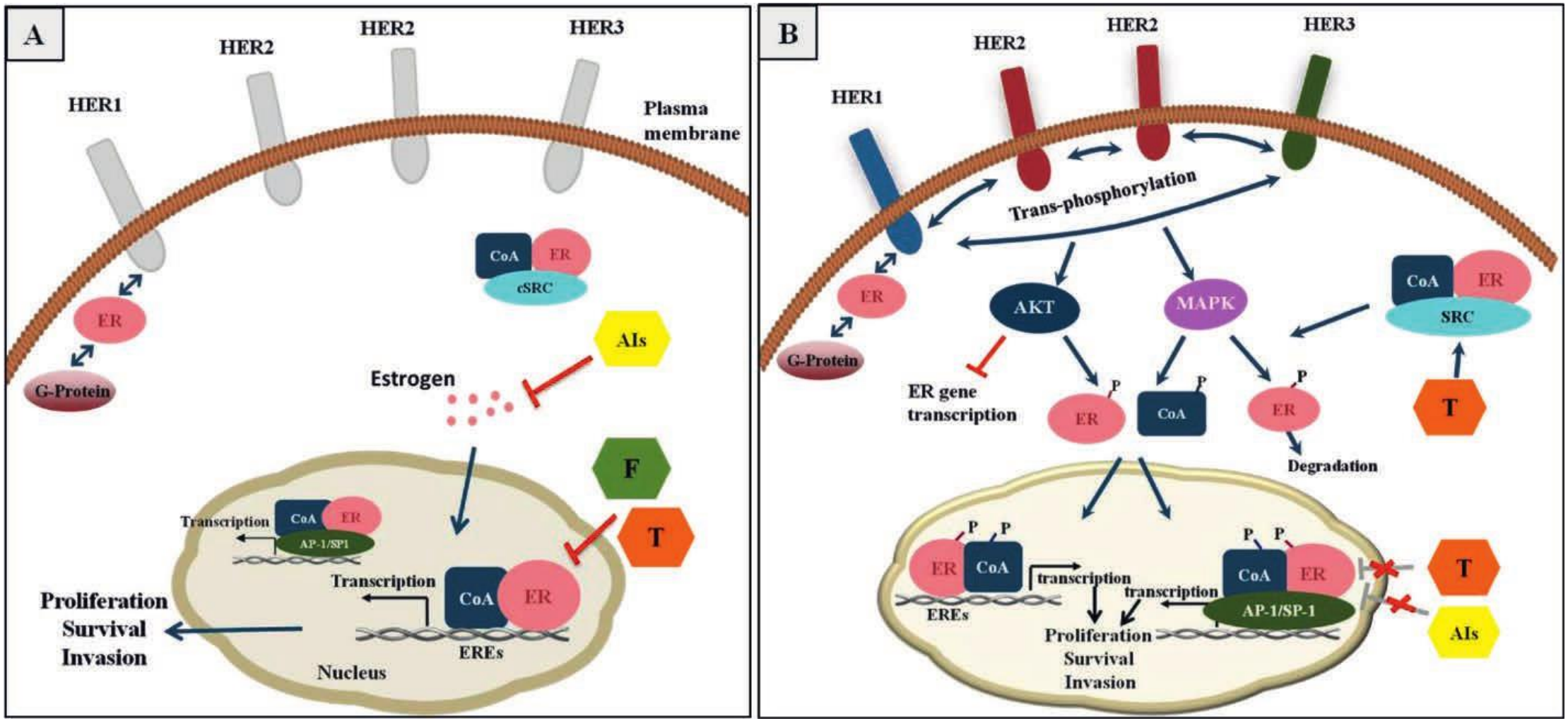
Table 4. Ongoing studies evaluating anti–human epidermal growth factor receptor 3 (HER3) therapeutic strategies*

Study/sponsor	Phase/setting	Experimental arm(s)
NCT01482377	Phase I, 3-part dose escalating study	RO5479599RO5479599 + cetuximab
Hoffmann–La Roche	Malignant/locally advanced HER3-positive solid tumors	RO5479599 + erlotinib
NCT01451632	Phase I	MM-121 (SAR256212) + cetuximab + irinotecan
Merrimack Pharmaceuticals	Advanced cancers	
NCT01447225	Phase I	MM-121(SAR256212) + gemcitabine
Merrimack Pharmaceuticals	Advanced-stage solid tumors	MM-121 (SAR256212) + carboplatin MM-121 (SAR256212) +pemetrexed MM-121 (SAR256212) + cabazitaxel
NCT01209195	Phase I	MM-121+ paclitaxel
Merrimack Pharmaceuticals	Advanced gynecological cancers or HER2-negative breast cancers	
NCT00734305	Phase I	MM-121
Merrimack Pharmaceuticals	Advanced solid tumors resisting ordinary treatment	
NCT01436565	Phase I	MM-121(SAR256212) + SAR245408
Sanofi-AventisMerrimack Pharmaceuticals	Locally advanced or metastatic solid tumors (PI3K mutation present)	
NCT01151046	Phase II	Arm A: MM-121 (SAR256212) + exemestane
Merrimack Pharmaceuticals	Locally advanced or metastatic estrogen receptor–positive and/or progesterone receptor–positive HER2-negative breast cancer	Arm B: placebo+ exemestane
NCT01421472	Phase II	Arm A: MM-121 (SAR256212) + paclitaxel→doxorubicin, cyclophosphamide→surgery
Merrimack Pharmaceuticals	Early HER-2 negative breast cancer	Arm B: paclitaxel→doxorubicin, cyclophosphamide→surgery
NCT00994123	Phase I–II	Arm A: MM-121 (SAR256212) + erlotinib Arm B: erlotinib
Merrimack Pharmaceuticals	Advanced non-small-cell lung cancer	
NCT01447706	Phase II	Arm A: MM-121 (SAR256212) + paclitaxel
Merrimack Pharmaceuticals	Platinum-resistant or refractory recurrent/advanced ovarian cancers	Arm B: paclitaxel
NCT01097460	Phase I	MM-111 + trastuzumab
Merrimack Pharmaceuticals	Advanced HER2-amplified, heregulin-positive breast cancer	
NCT01603979	Phase I	AV-203
AVEO Pharmaceuticals	Metastatic or advanced solid tumors	
NCT01479023	Phase I	U3-1287
Washington University School of Medicine	Advanced solid tumors	

Ocaña A, JNCI, 2013

INTERACCIÓN CON LA VÍA DE LOS RECEPTORES DE ESTRÓGENO

Interacción vías r. estrógeno y HER2



Giuliano M, Breast Care, 2013

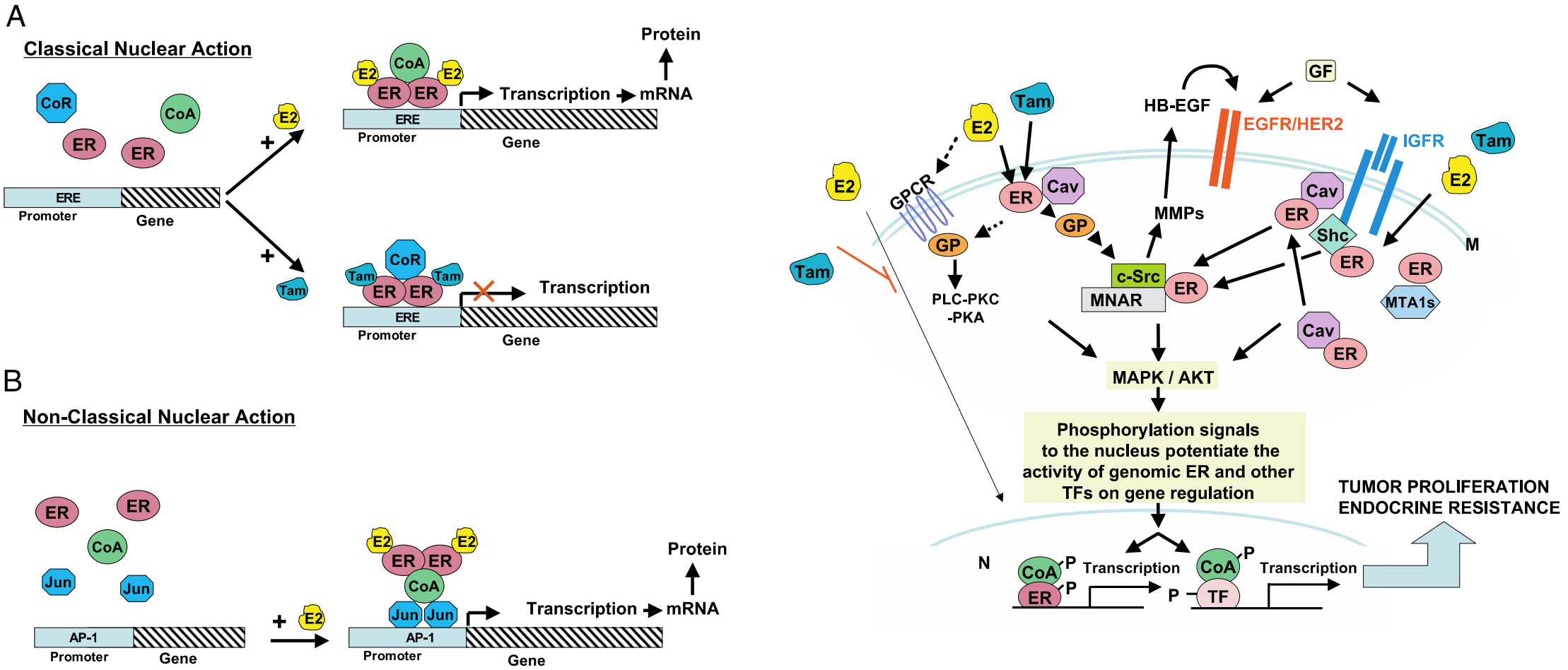
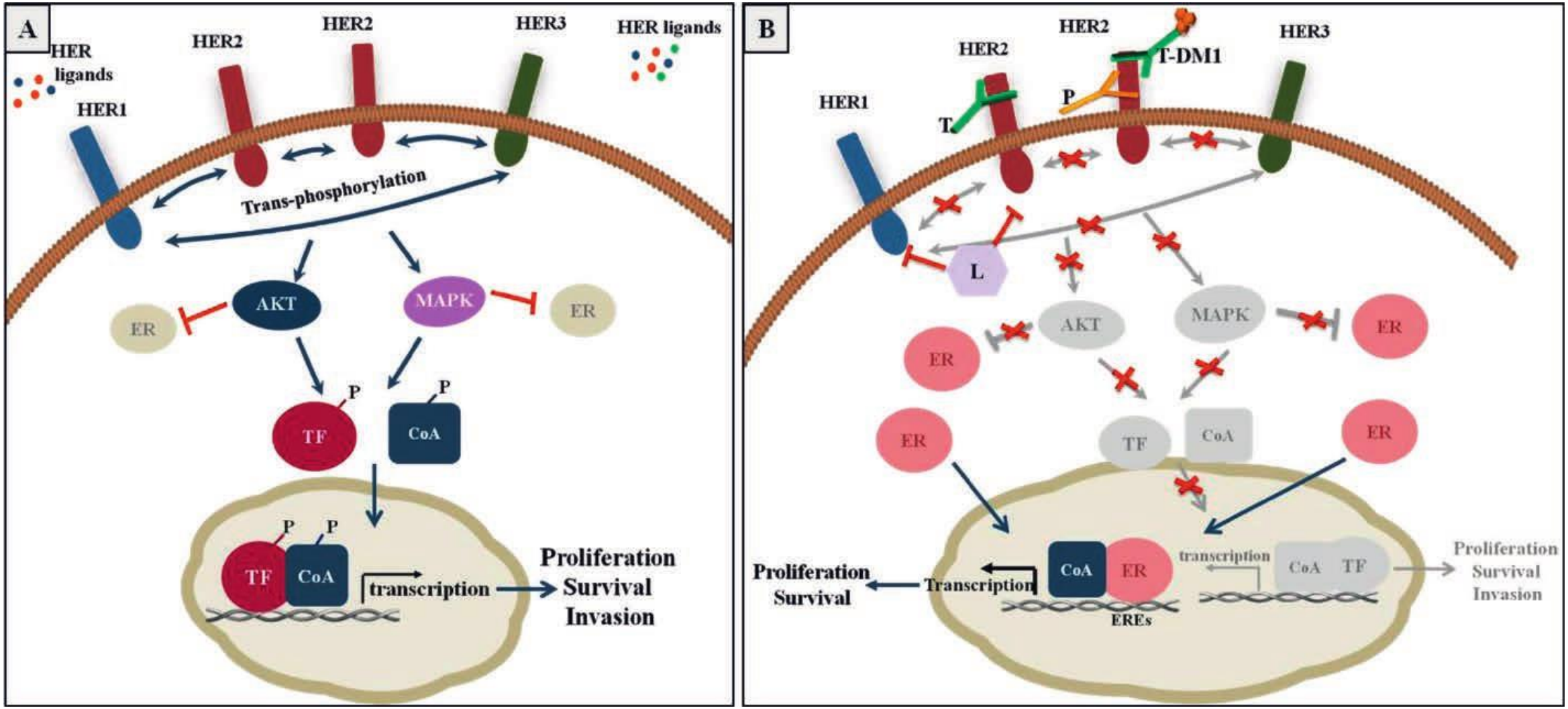


TABLE 1. Response to estrogen deprivation/SERMs in the neoadjuvant setting

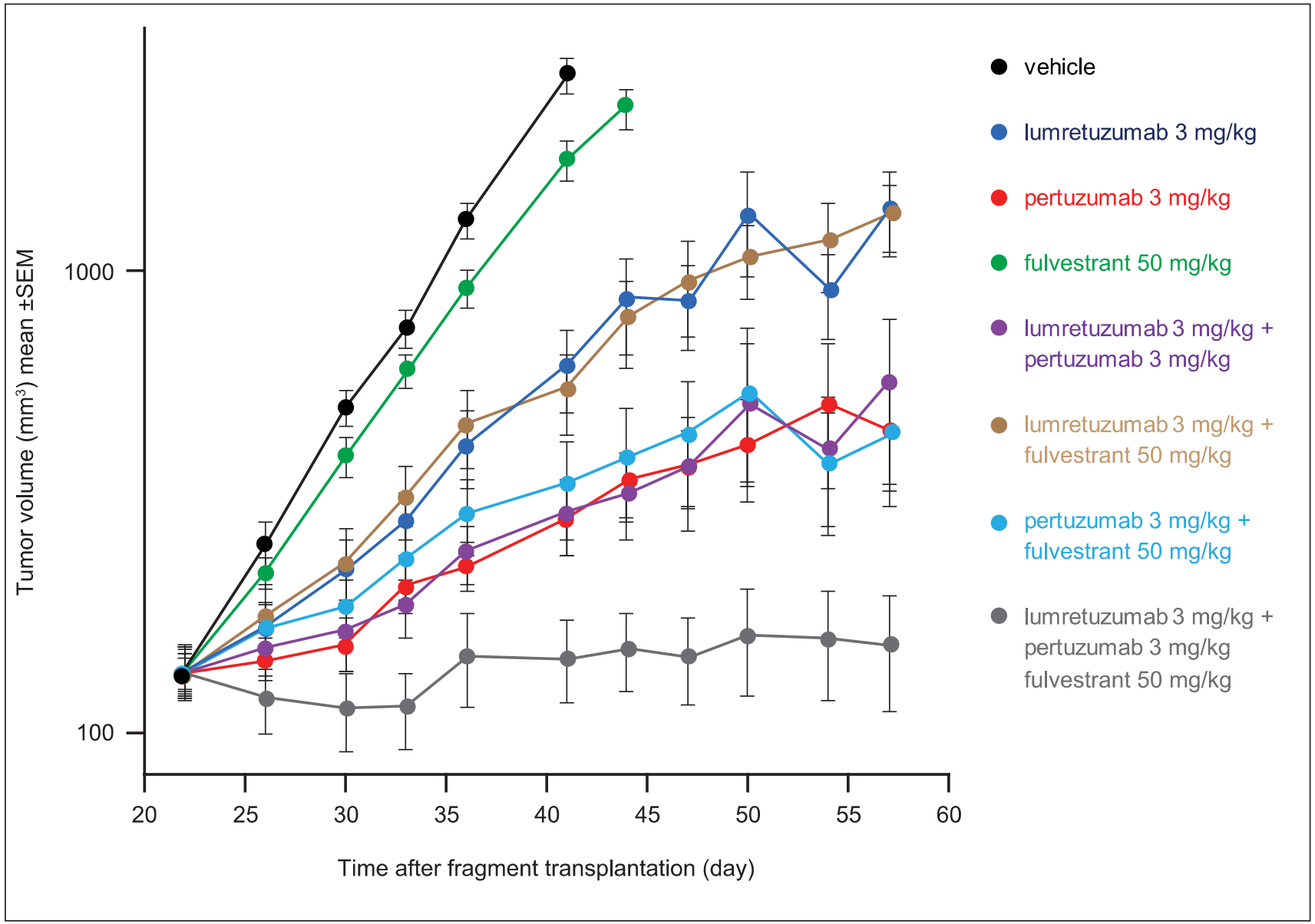
	Study 1 Ellis (117)		Study 2 Zhu (118)		Study 3 Smith (11)	
	Letrozole	Tamoxifen	Letrozole	Tamoxifen	Letrozole	Tamoxifen
EGFR/HER2 negative	54%	42%	35%	–	41%	43%
EGFR/HER2 positive	88%	21%	75%	–	58%	22%

Arpino G. Endocrine Reviews, 2008

Interacción vías r. estrógeno y HER2



Giuliano M, Breast Care, 2013



Collins D, PLOS ONE, 2017

CONCLUSIONES

Conclusiones

- HER2 juega un papel fundamental en el cáncer de mama, como factor pronóstico y predictivo de respuesta a tratamiento dirigido
- Afinidad por formar hetero-dímeros con HER3 (¿posible diana?)
- Reacción cruzada con la vía de los receptores de estrógeno, posible causa de resistencias al tratamiento