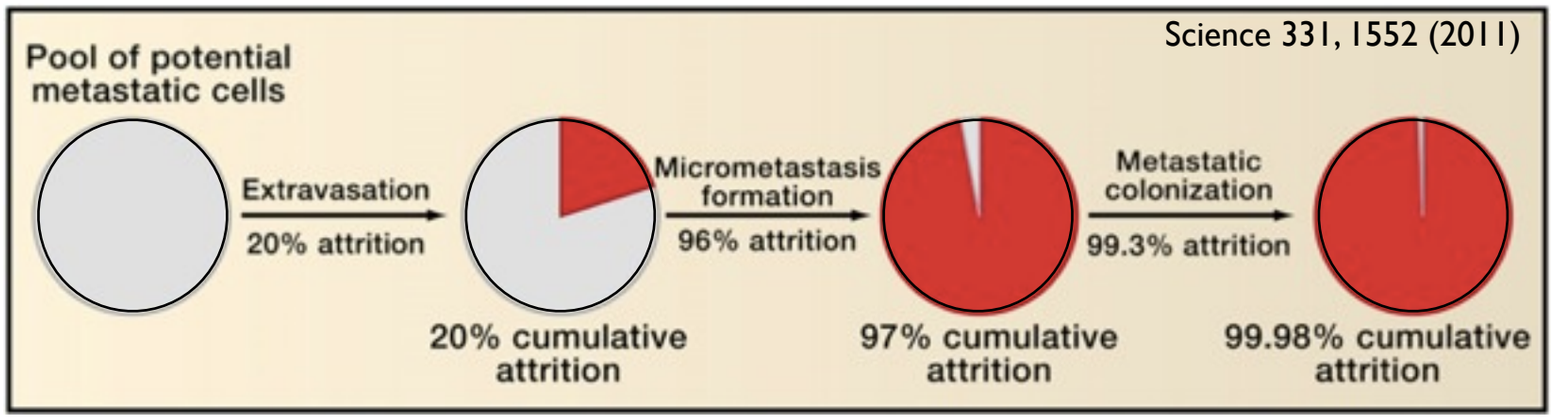
METÁSTASIS CEREBRALES

Inmunoterapia y pequeñas moléculas: Aplicaciones y limitaciones

1. Cascada metastásica



2. Predicción y prevención
3. Tratamiento

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REDLANO
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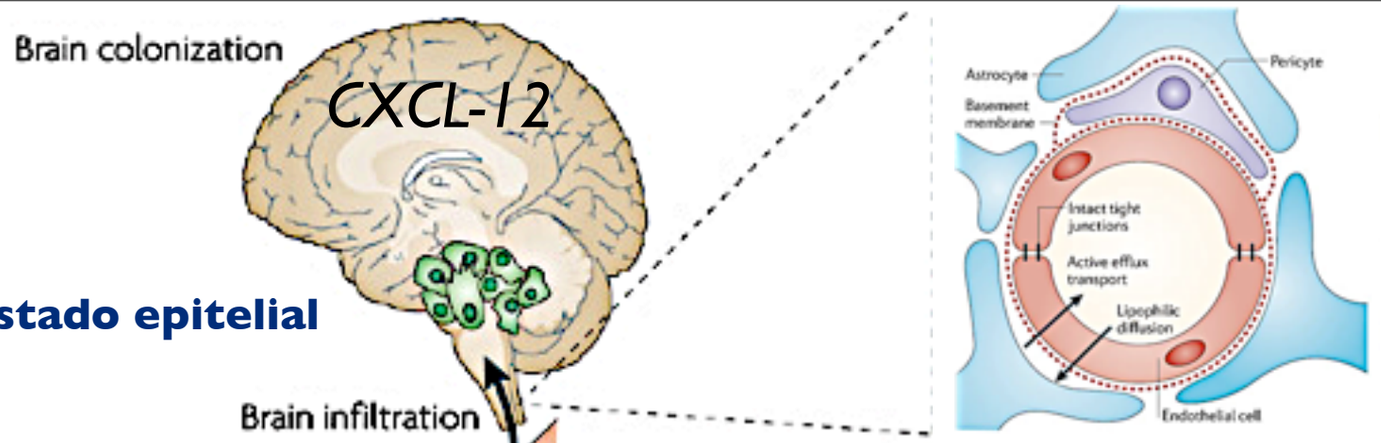
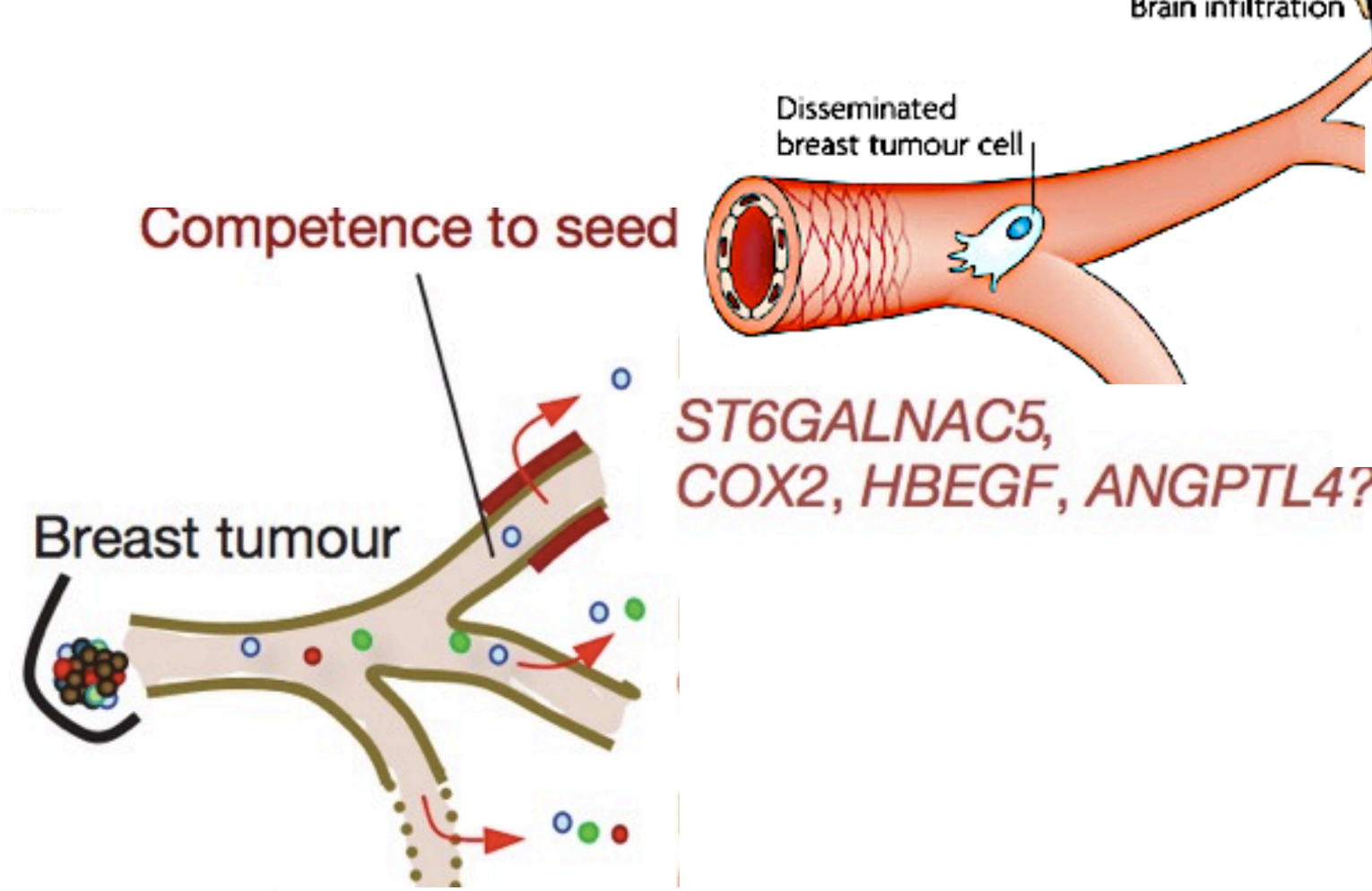
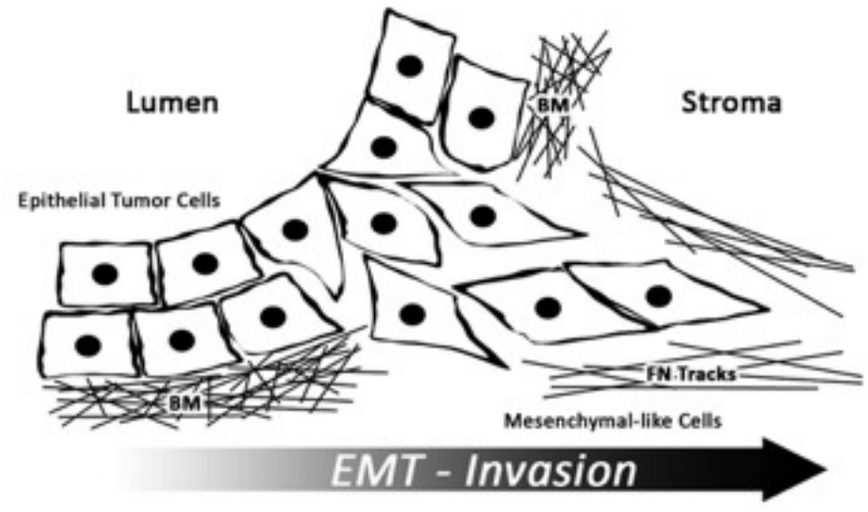
IDC Las Américas
INSTITUTO DE CANCEROLOGÍA



La mayoría vuelven al estado epitelial

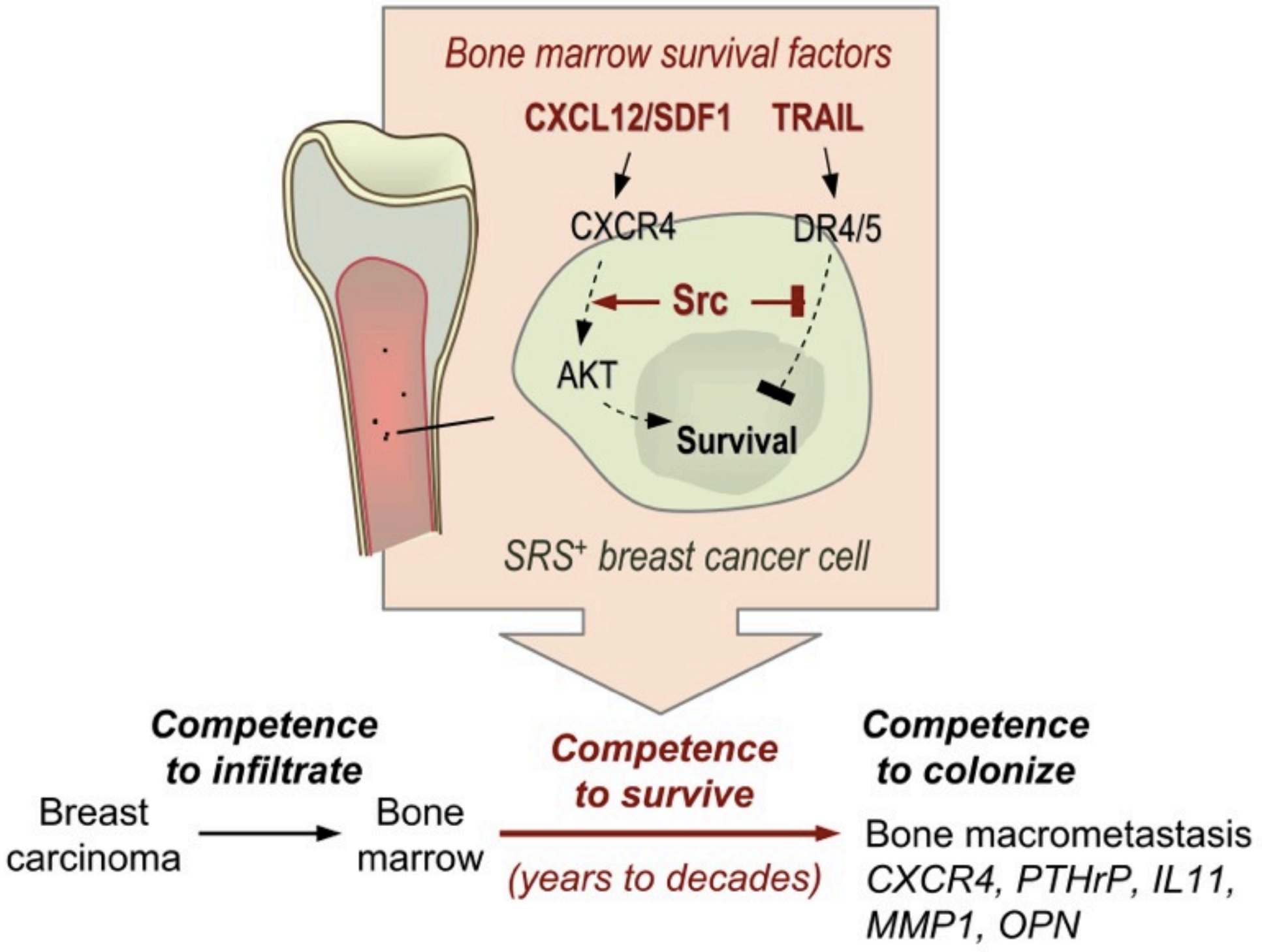




Transición epitelio mesenquimal

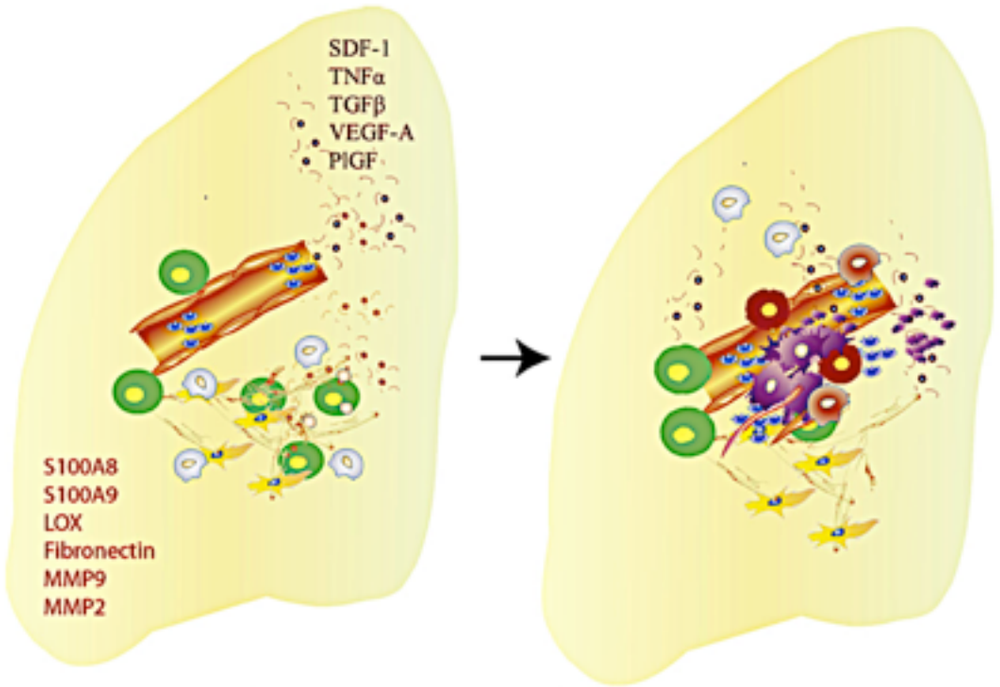
Nature, vol 549, 18 June 2009

En algunos casos las células se quedan quiescentes aún muchos años



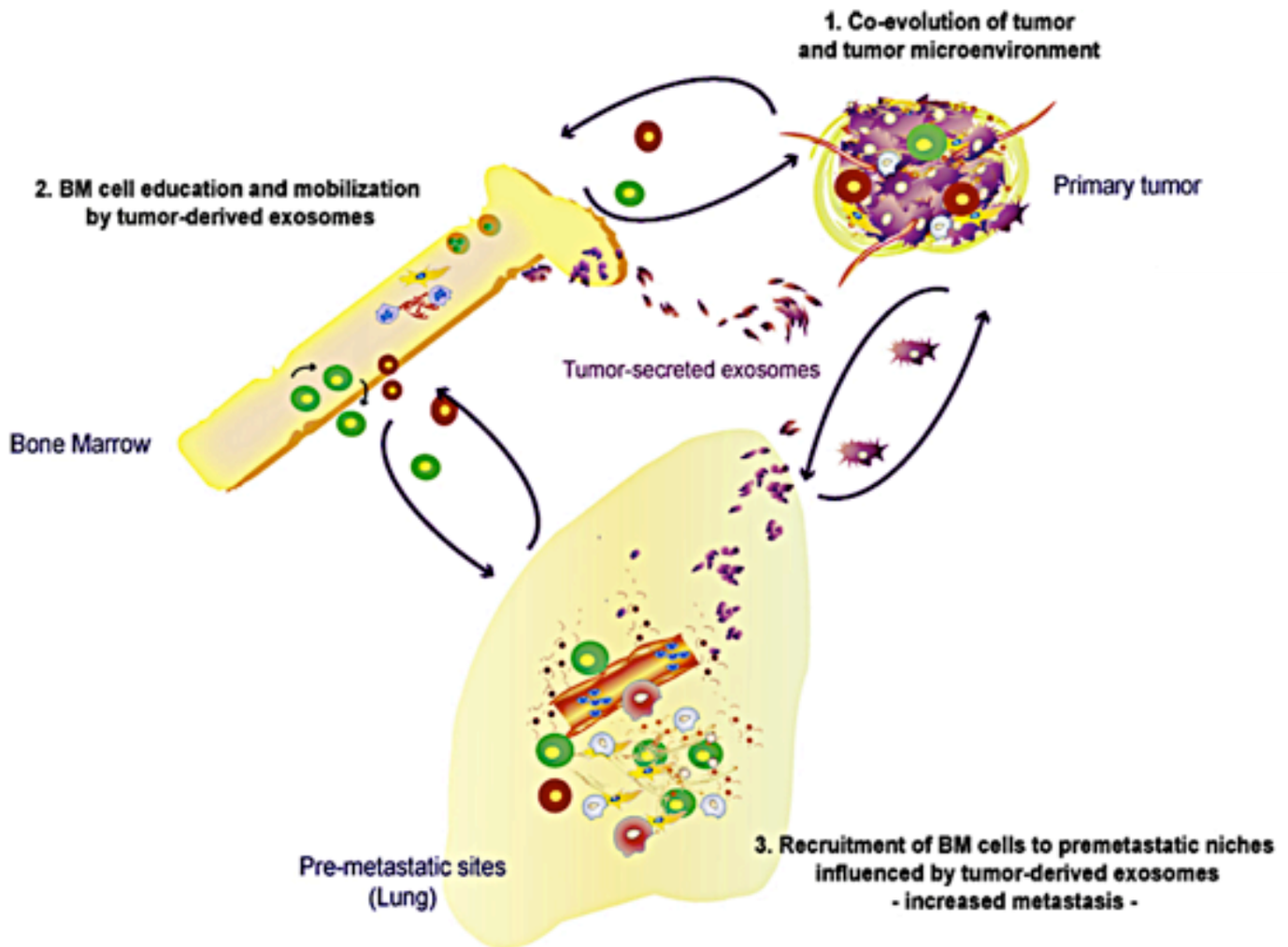
Cancer Cell 16, 67-78, July 2009

Nicho pre-metastásico y retroalimentación



a. Pre-metastatic niche

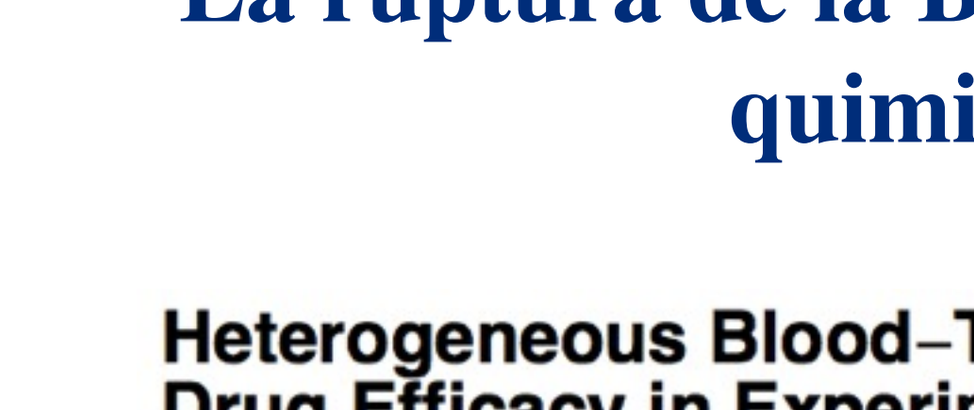
b. Micro- and macrometastatic foci

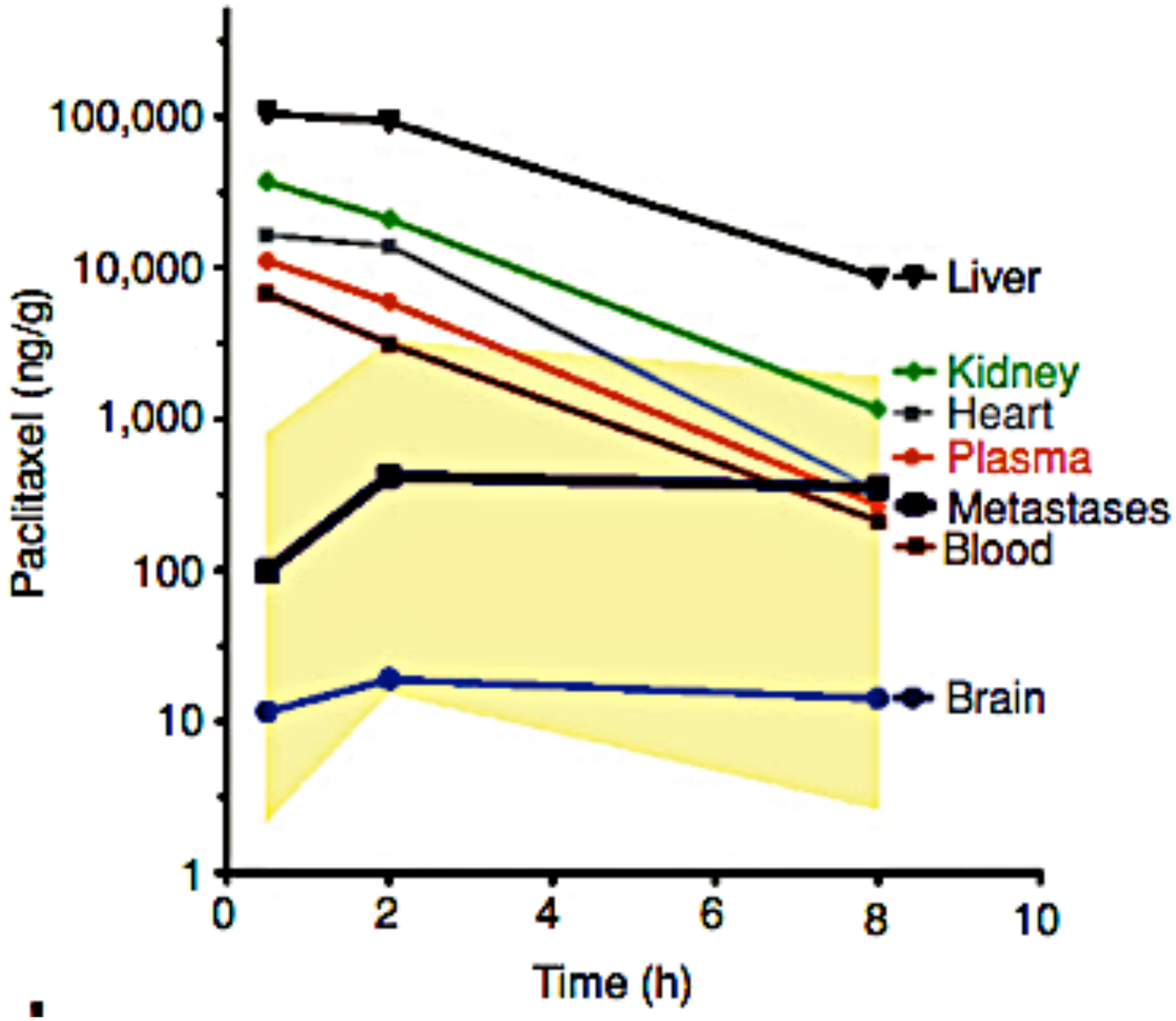


Seminars in Cancer Biology 21 (2011) 139-146

La ruptura de la BHE no asegura la llegada de la quimioterapia estándar

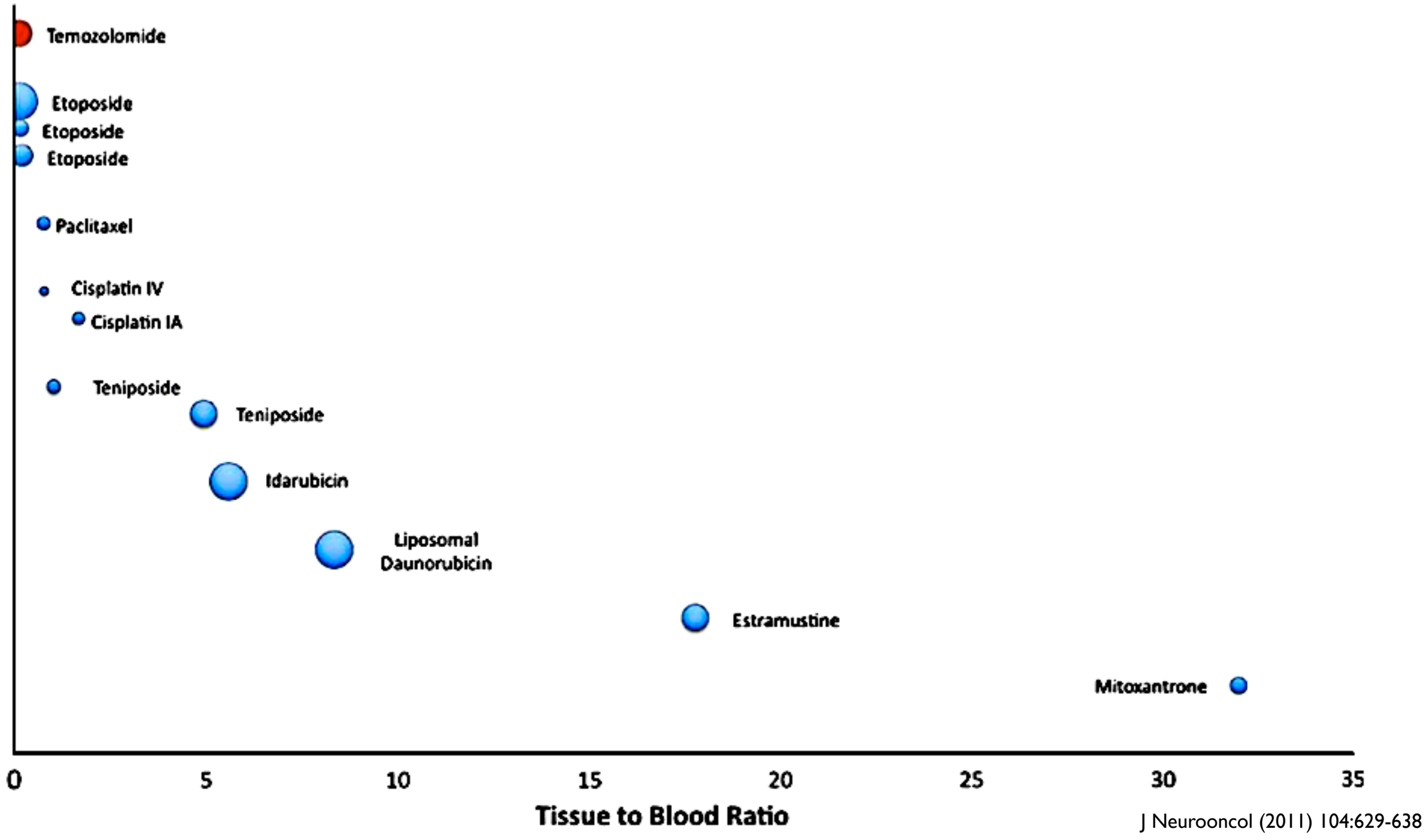
Heterogeneous Blood–Tumor Barrier Permeability Determines Drug Efficacy in Experimental Brain Metastases of Breast Cancer





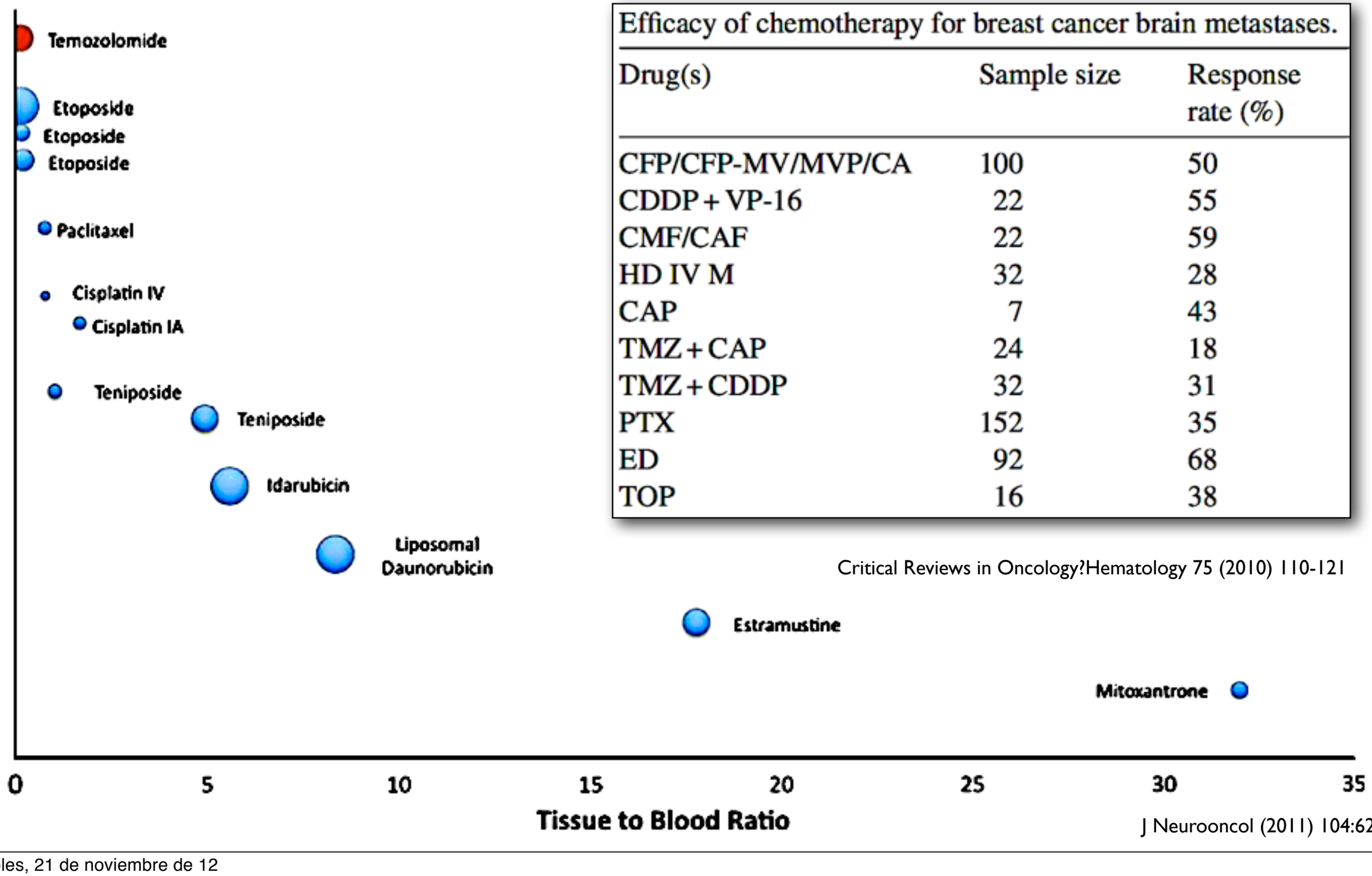
Clin Cancer Res; 16(23) December 1, 2010

Metástasis, aplicación IV
Relación “ruptura” BHE/sangre



J Neurooncol (2011) 104:629-638

Metástasis, aplicación IV
Relación "ruptura" BHE/sangre

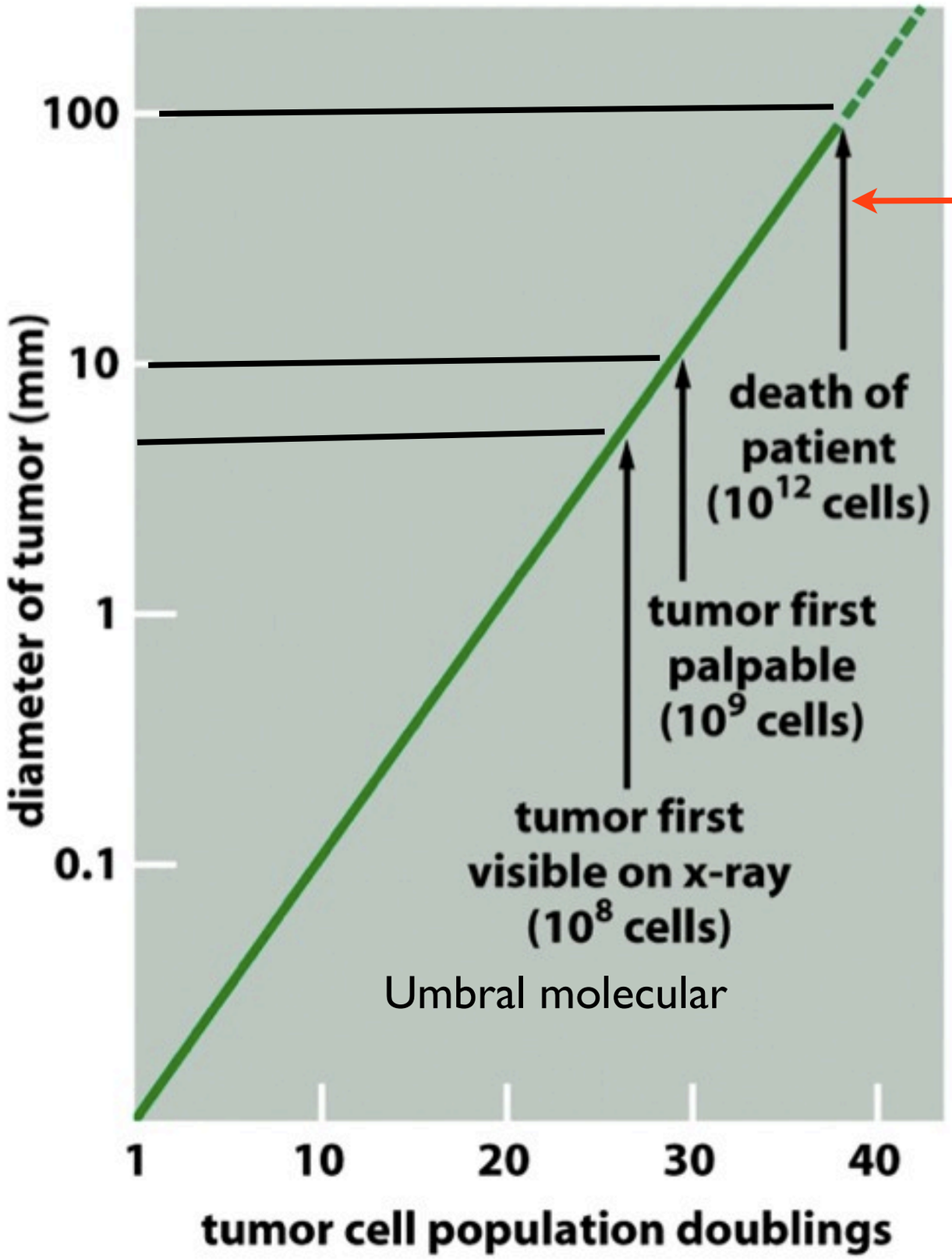


Efficacy of chemotherapy for breast cancer brain metastases.		
Drug(s)	Sample size	Response rate (%)
CFP/CFP-MV/MVP/CA	100	50
CDDP + VP-16	22	55
CMF/CAF	22	59
HD IV M	32	28
CAP	7	43
TMZ + CAP	24	18
TMZ + CDDP	32	31
PTX	152	35
ED	92	68
TOP	16	38

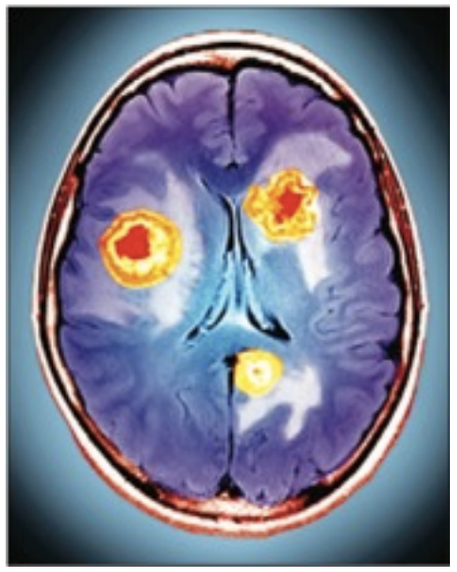
Critical Reviews in Oncology?Hematology 75 (2010) 110-121

J Neurooncol (2011) 104:629-638

2. Predicción



6 meses



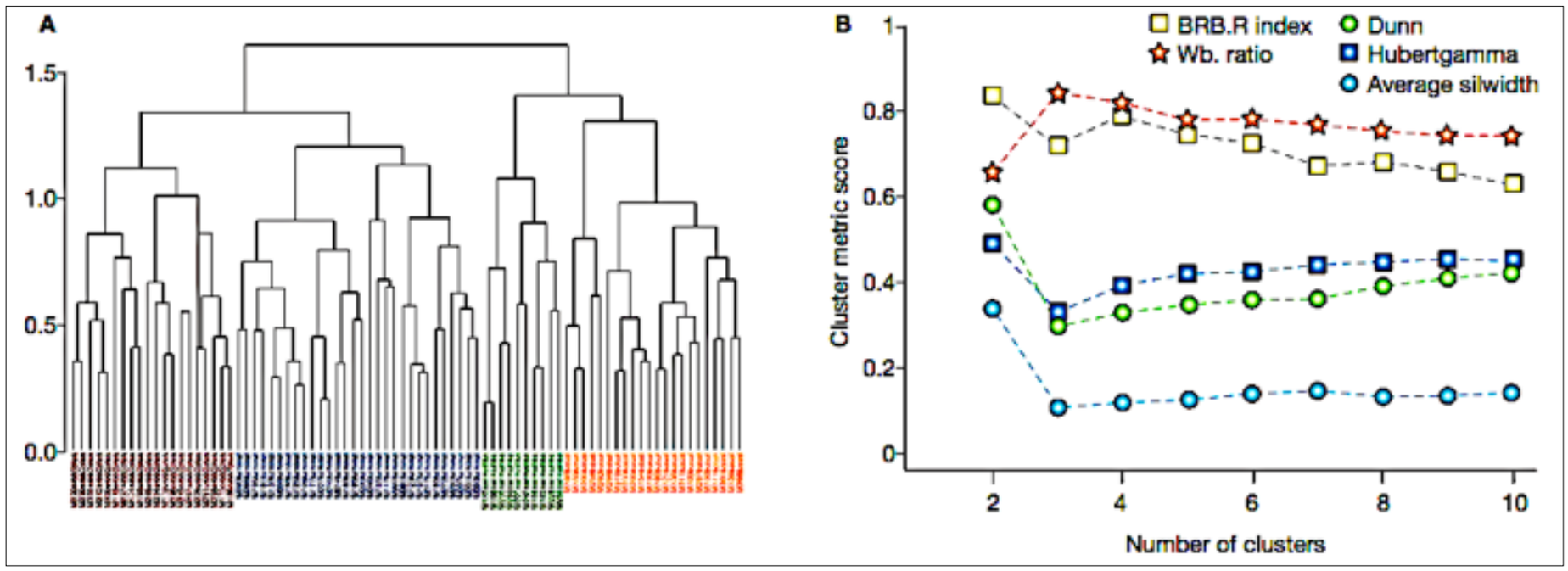
Tratar de evitar el desarrollo de metástasis cerebrales

Molecular Biology of the Cell (Garland Science 2008)

Perfil de expresión génica

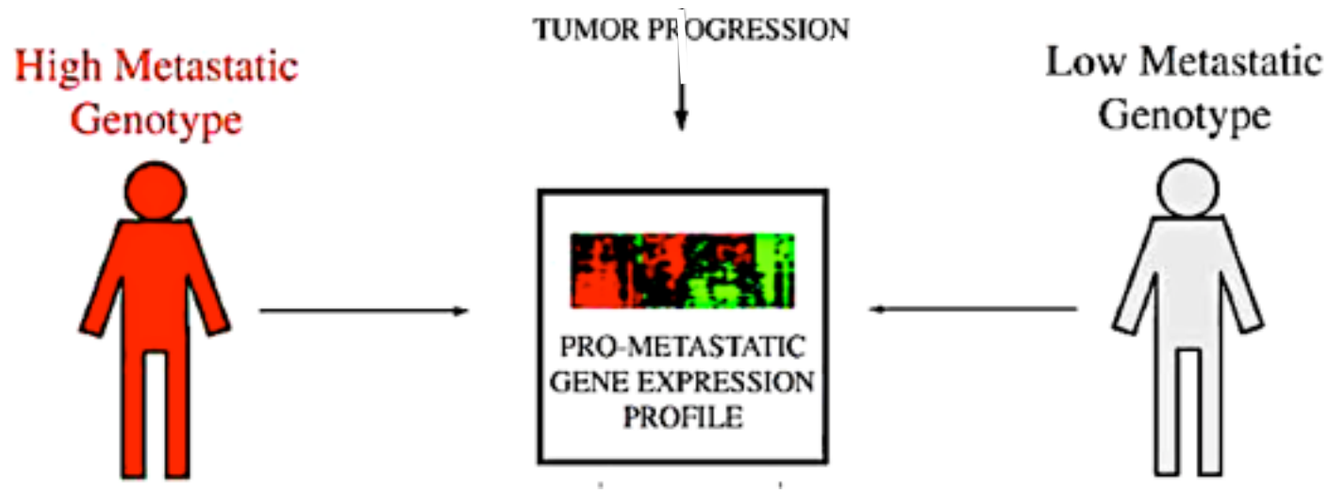
Microarrays de ADN

R-PCR



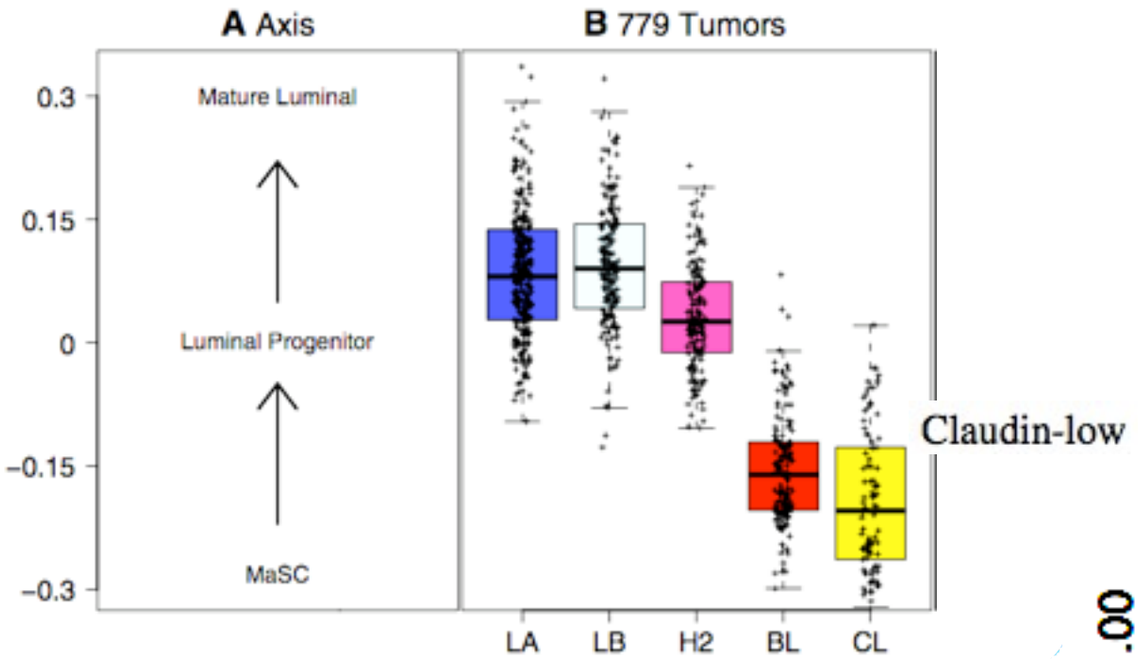
70 genes MammaPrint
21 genes Oncotype DX
50 genes PAM50

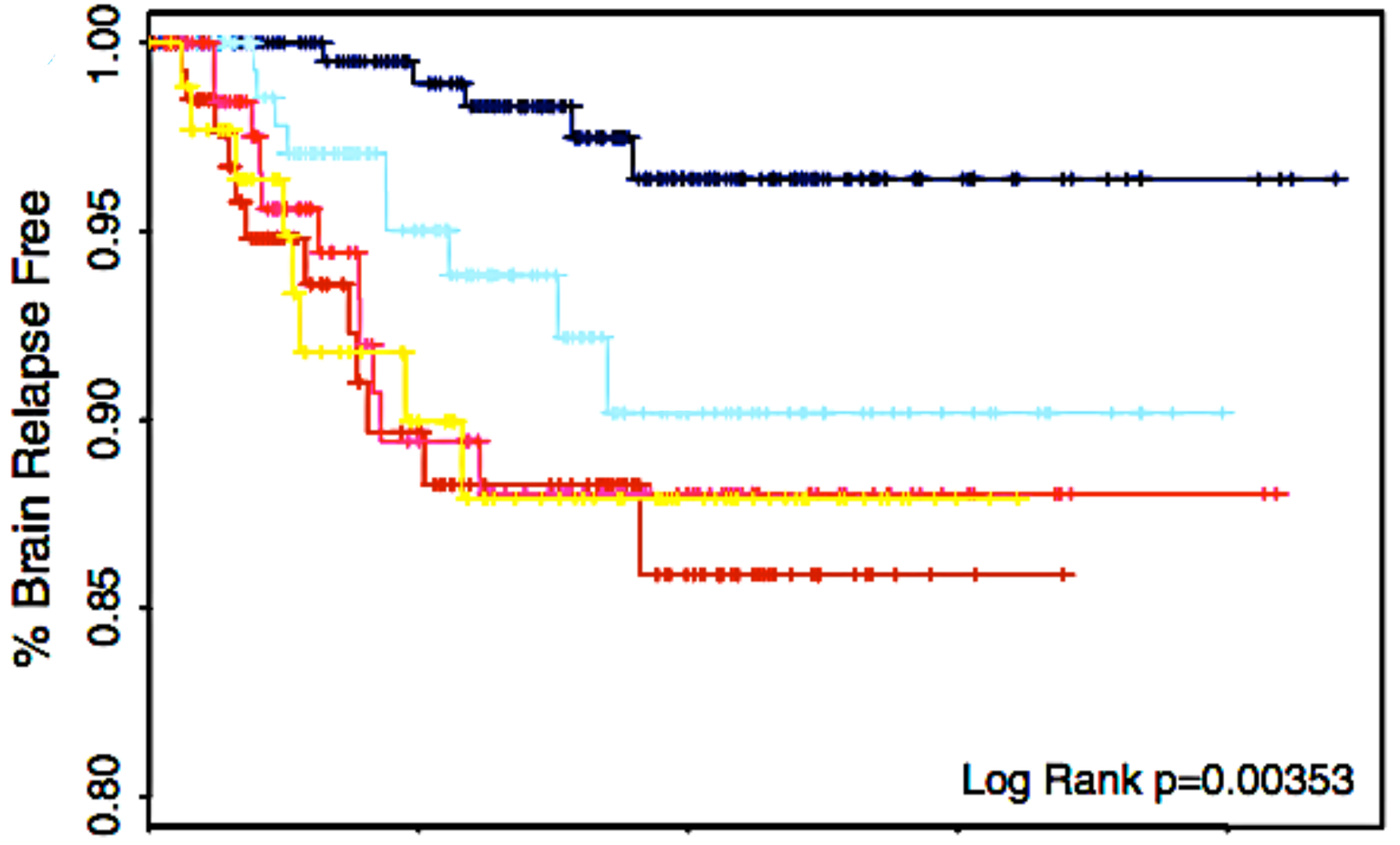
Aun no validados en ensayos clínicos prospectivos



Genomic analysis identifies unique signatures predictive of brain, lung, and liver relapse

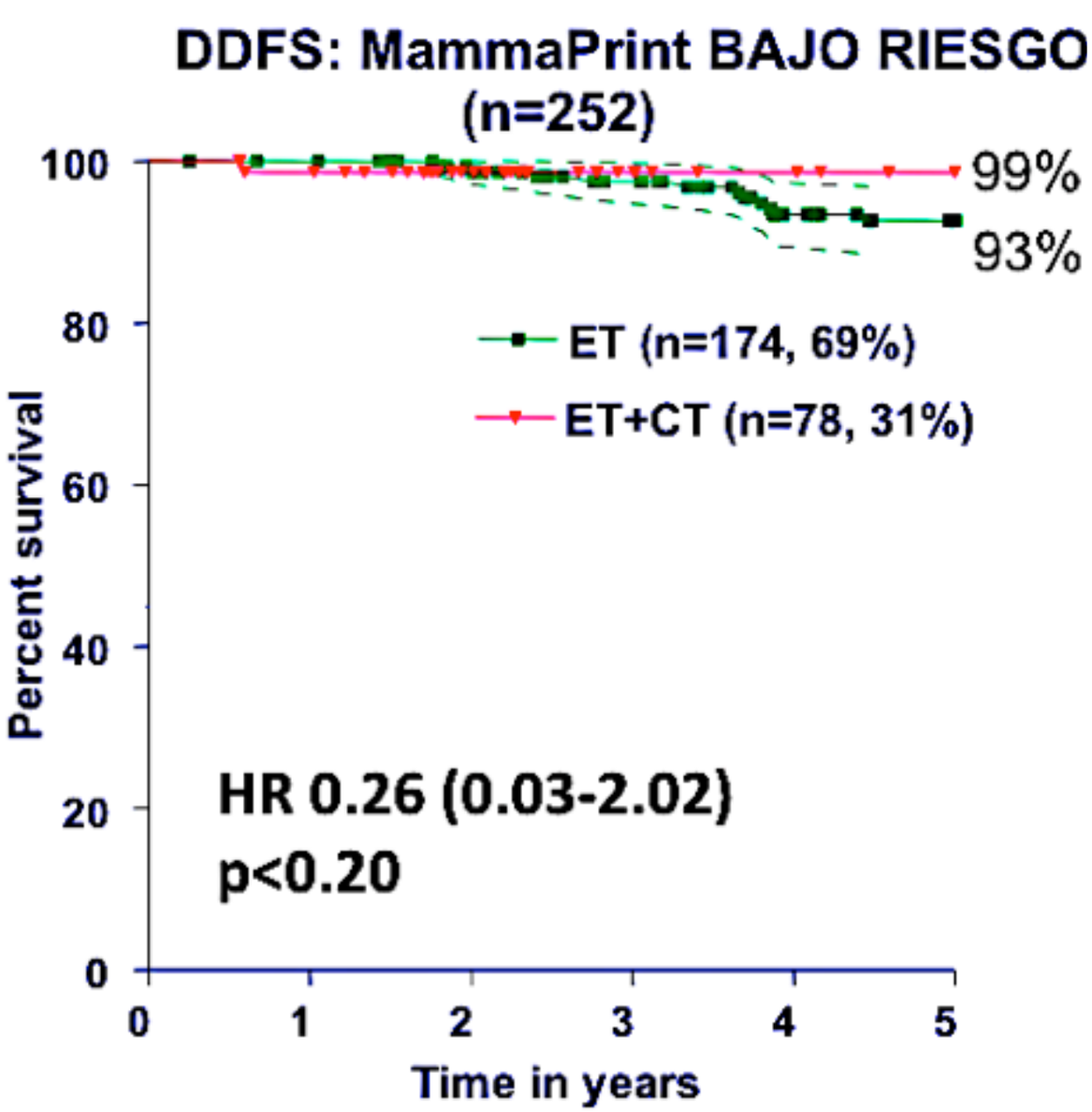
PAM50

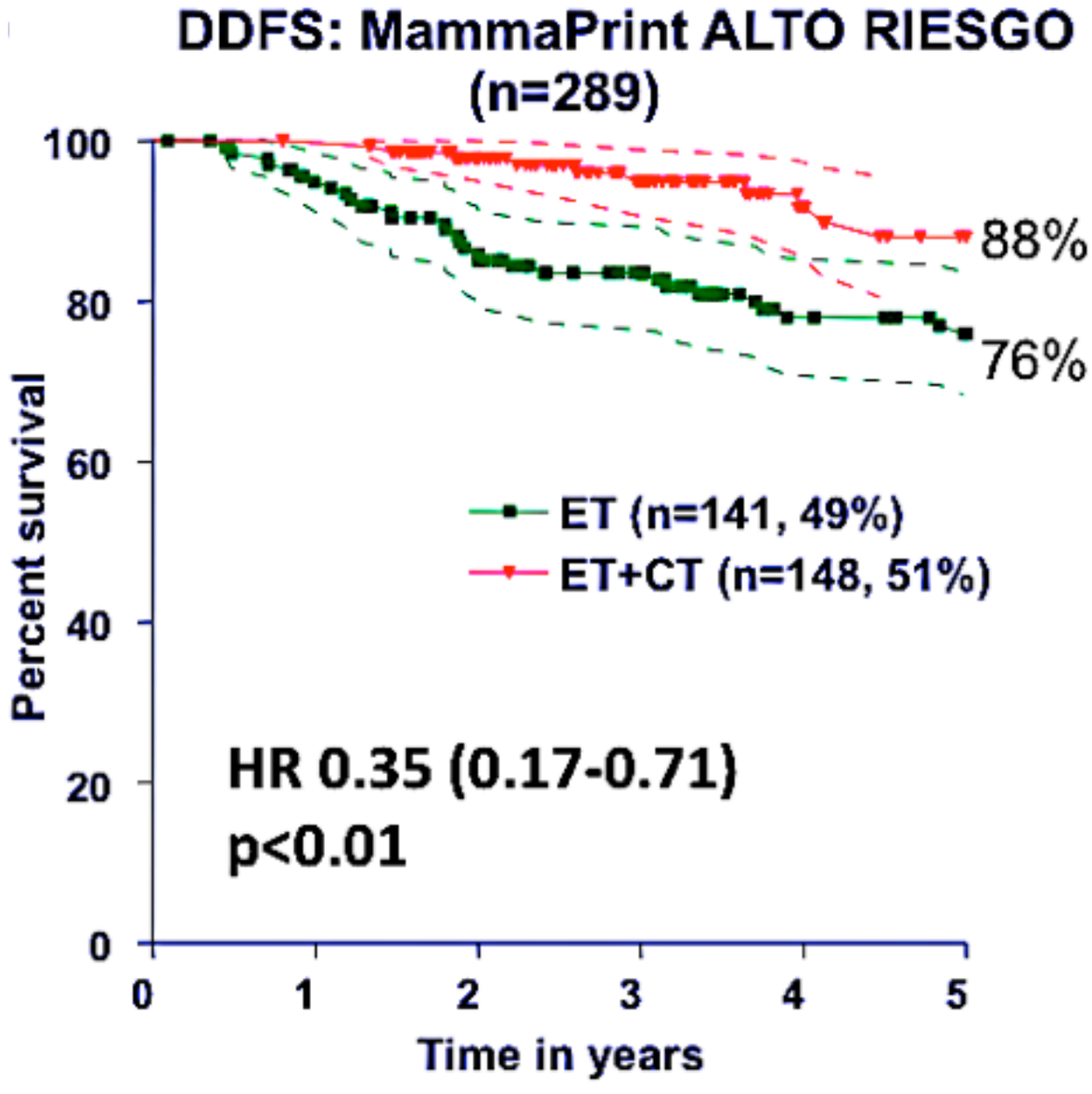




Breast Cancer Res Treat (2012) 132:523-5335

Sobrevida libre de metástasis a distancia en pacientes tratadas con quimioterapia en base a su riesgo con mammaprint



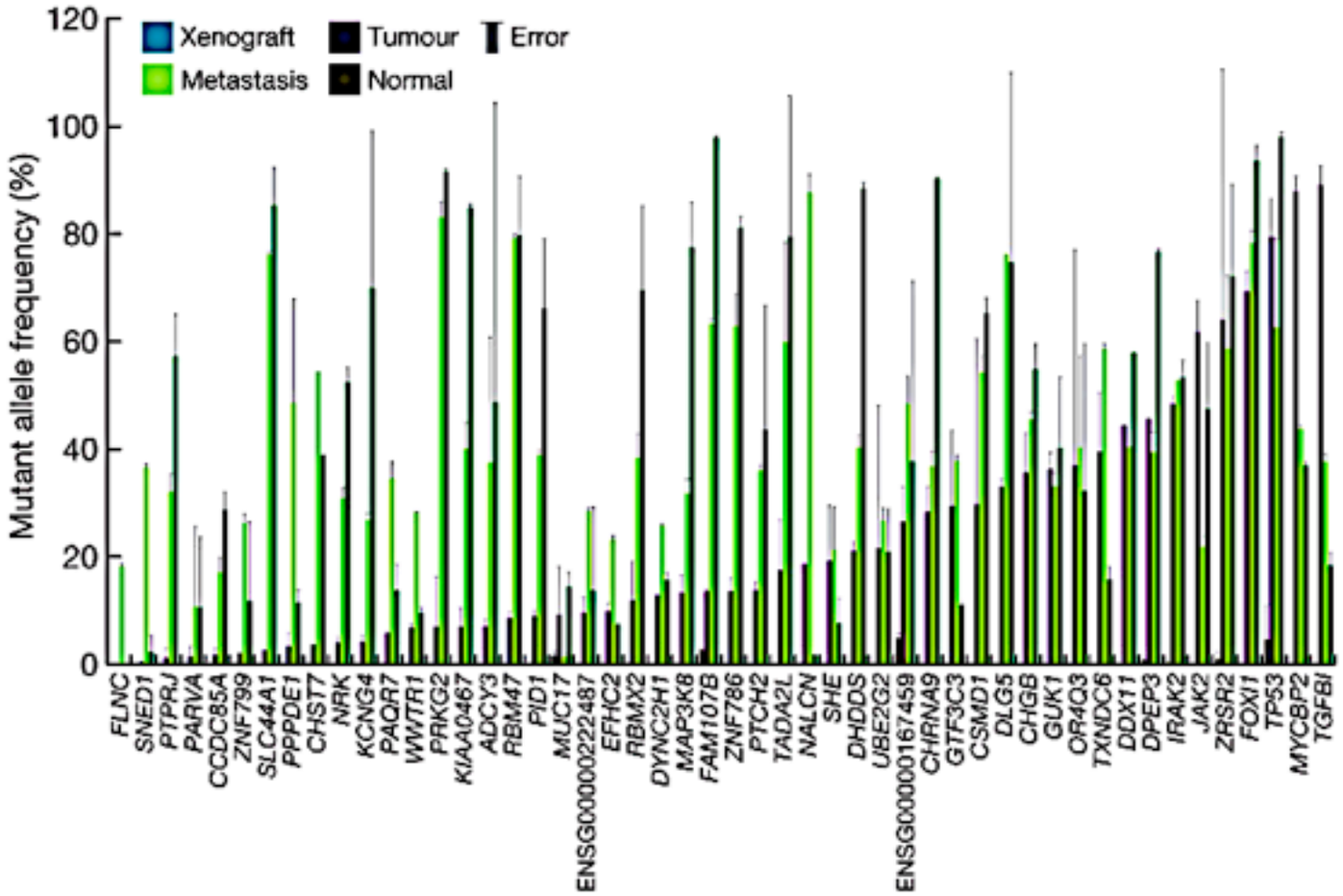


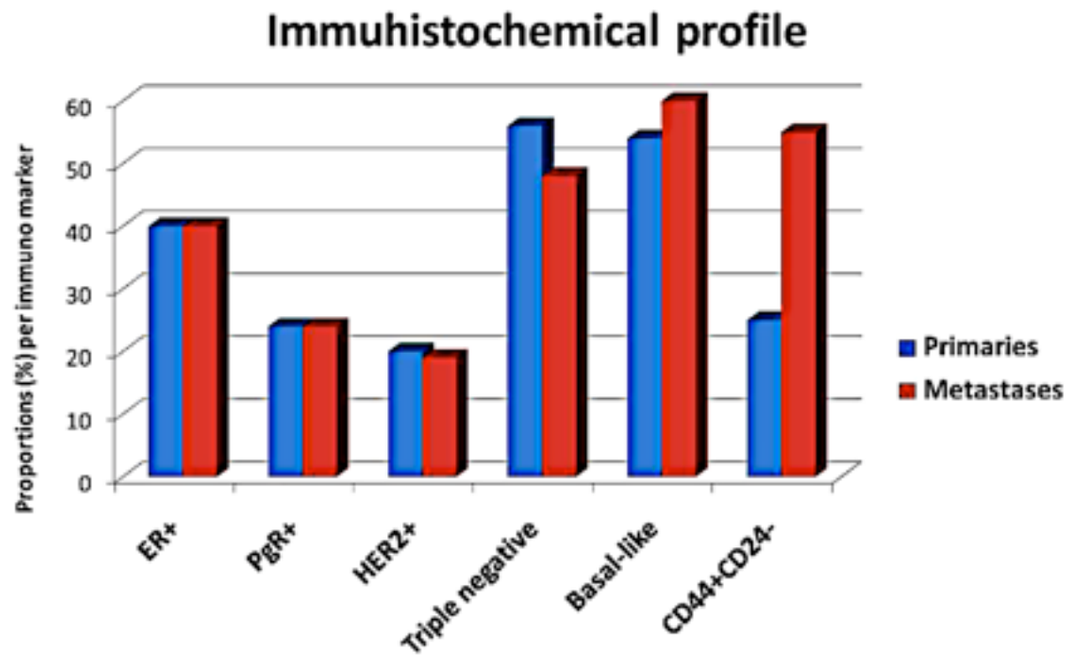
12% absolute benefit
50% relative benefit

Breast Cancer Res Treat (2010) 120:655-661

Distintos genes dentro primario y entre las Mtt

Genome remodelling in a basal-like breast cancer metastasis and xenograft





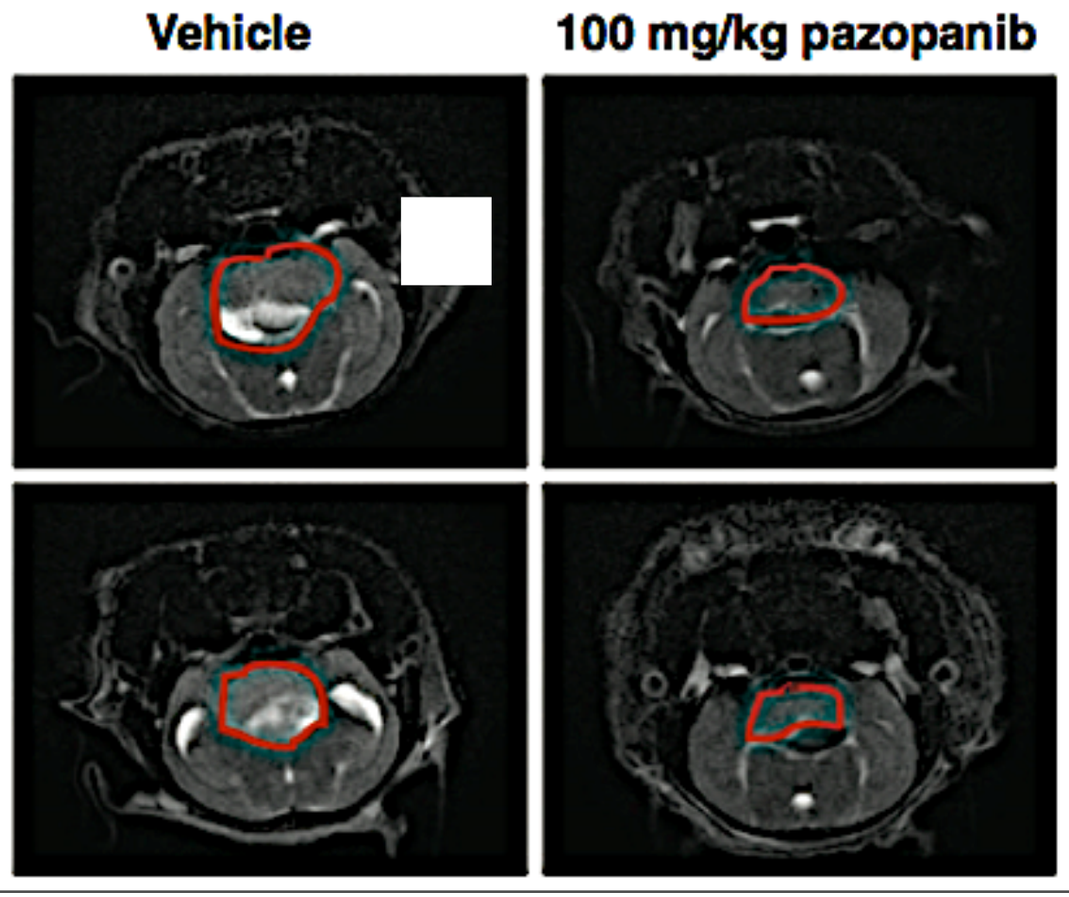
Nature 464, 999-1005 (15 April 2010)

2. Prevención

Pazopanib Reveals a Role for Tumor Cell B-Raf in the Prevention of HER2 $^{+}$ Breast Cancer Brain Metastasis

Pazopanib prevention of brain metastatic colonization[a]

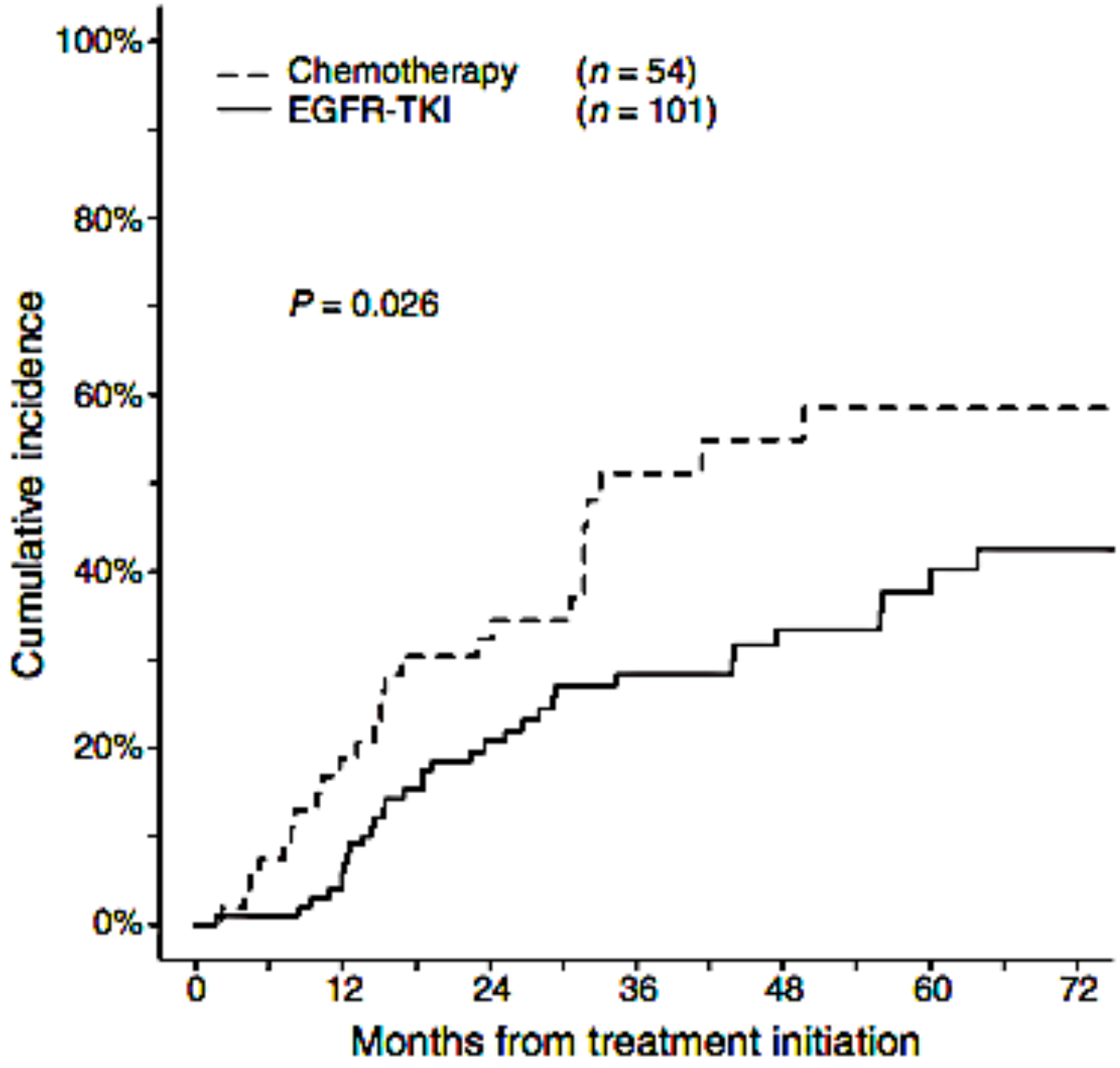
Pazopanib dose, mg/kg	No. of mice	Mean large metastases (95% CI)	*P*	Mean micrometastases (95% CI)	*P*
0	10	3.92 (3.05–4.79)		101.9 (84.2–119.6)	
30	11	1.93 (1.59–2.26)	0.0002	76.4 (59.5–93.2)	NS
100	11	1.05 (0.72–1.39)	<0.0001	61.7 (44.8–78.6)	0.004



Clin Cancer Res;17(1) January 1, 2011

The Impact of Initial Gefitinib or Erlotinib versus Chemotherapy on Central Nervous System Progression in Advanced Non –Small Cell Lung Cancer with *EGFR* Mutations

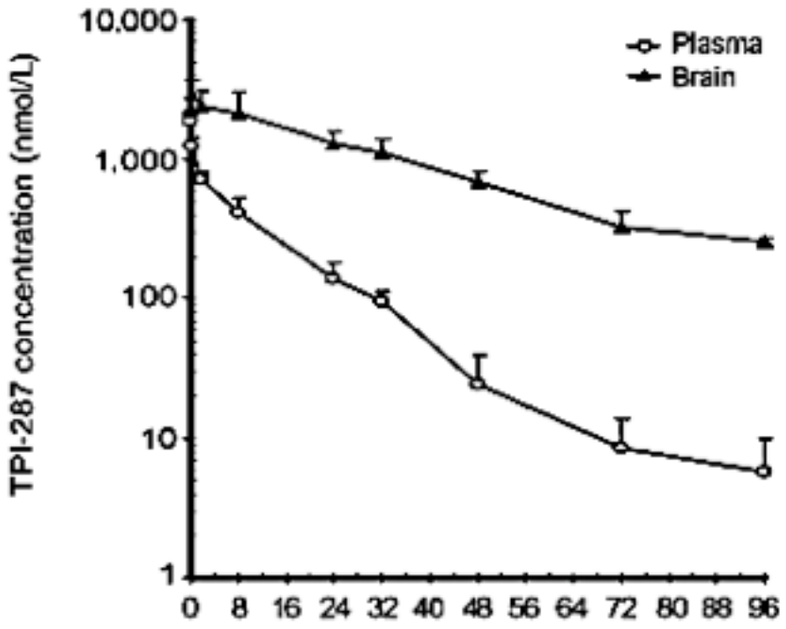
Incidencia acumulativa de progresión SNC

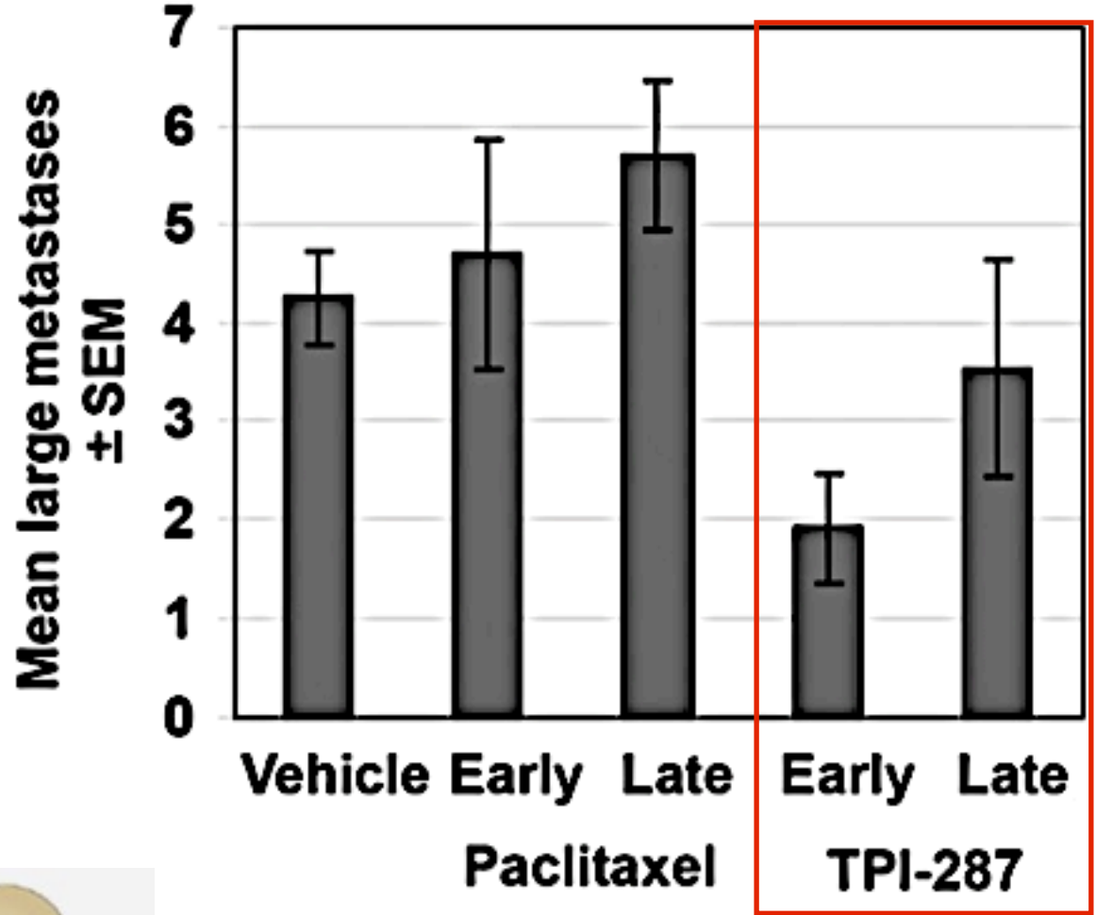


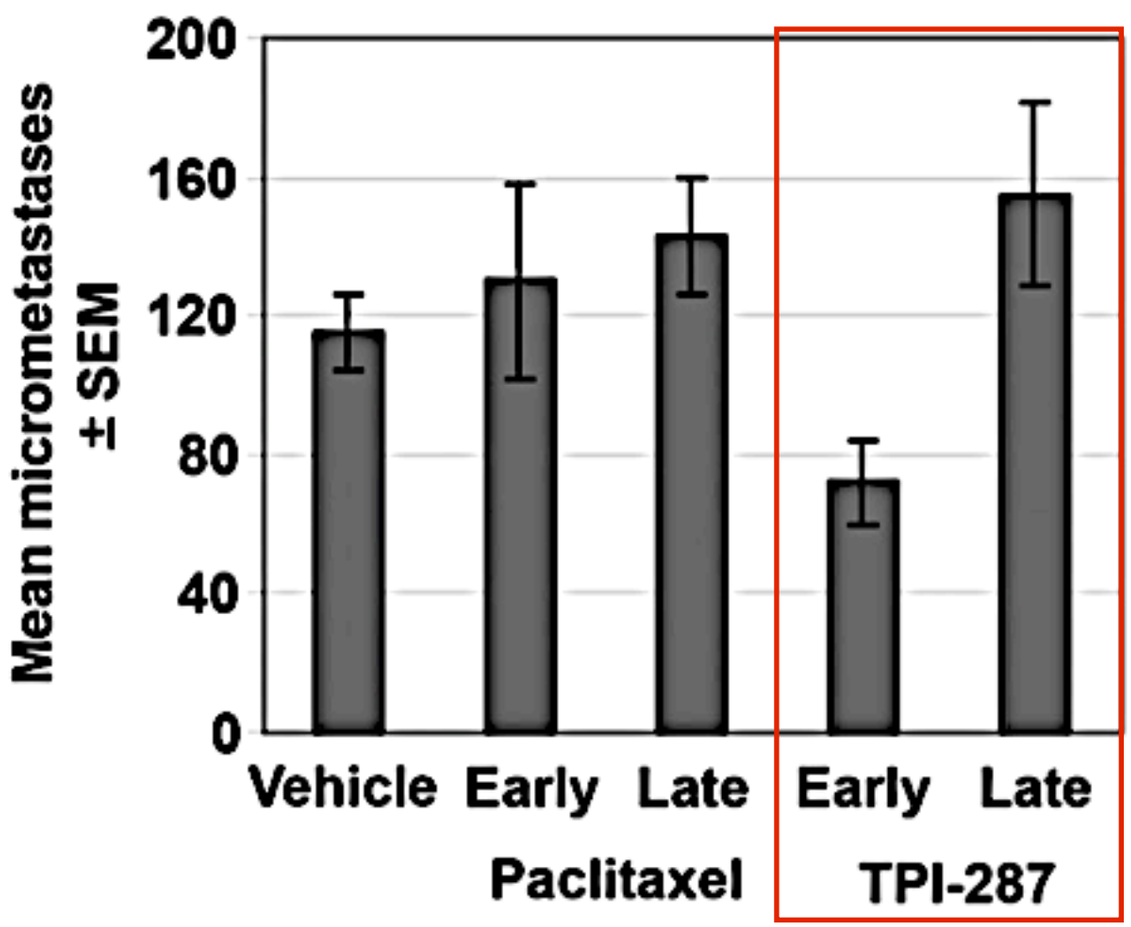
Pacientes sin previo compromiso del SNC

Clin Cancer Res 2012;18:4406-4414

TPI-287, a New Taxane Family Member, Reduces the Brain Metastatic Colonization of Breast Cancer Cells







Mol Cancer Ther 2012;11:1959-1967

3. Tratamiento

6% hacen metástasis cerebrales
10:1 primarios

Estimated incidence of brain metastasis by selected primary site United States cancer incidence, 2007

	Selected incidence proportion (IP)	Site incidence	Brain metastasis incidence
Single Primary Site	IP%	N	N
Lung and Bronchus[7]	19.9	209 969	41 784
Renal[8]	7.0	49 575	3470
Melanoma[7]	6.9	59 700	4119
Breast (both genders)[7]	5.1	208 973	10 658

(IP: 1973 a 2001)

Neuro-Oncology 14(9):1171-1177, 2012

Desgraciadamente:
Metástasis y quimio-resistencia van de la mano

EMT-ATFs confer resistance to chemotherapy and radiotherapy

	Evidence	Resistance
ZEB1	Breast carcinoma cell lines	Doxorubicin
	Head and neck squamous carcinoma cell lines	Ertotinib
	Non-small lung carcinoma cell lines	Gefitinib
	Pancreatic carcinoma cell lines	Gemcitabine, 5-Fluorouracil, Cisplatin
ZEB2	Bladder and squamous carcinoma cell lines	Cisplatin, UV radiation
	Primary transitional cell carcinomas of the bladder	Radiotherapy
Snail1	Breast cancer cell line	5-Fluorouracil
	Lung carcinoma cell lines	Cisplatin
	Ovarian adenocarcinoma cell lines and primary tumors	Cisplatin
Snail2	Malignant mesothelioma	Doxorubicin, Paclitaxel, Vincristine
	Non-small cell lung carcinoma cell lines and Primary lung adenocarcinoma	Gefitinib
	Ovarian adenocarcinoma cell lines and primary tumors	Cisplatin
Twist1	Breast cancer cell lines	Doxorubicin
	Breast cancer cell lines	Paclitaxel
	Nasopharyngeal carcinoma cell lines	Paclitaxel
	Prostate carcinoma cell lines	Daunirubicin, cisplatin
	Prostate carcinoma cell lines	Paclitaxel, Cisplatin
	Various carcinoma cell lines (bladder, nasopharyngeal, ovarian, prostate)	Paclitaxel, Vincristine
Twist2	Prostate adenocarcinoma cell lines	Daunirubicin, Cisplatin

Cell. Mol. Life Sci (2012) 69:3429-3456

Effect of chemotherapy on survival after whole brain radiation therapy for brain metastases: a single-center retrospective analysis

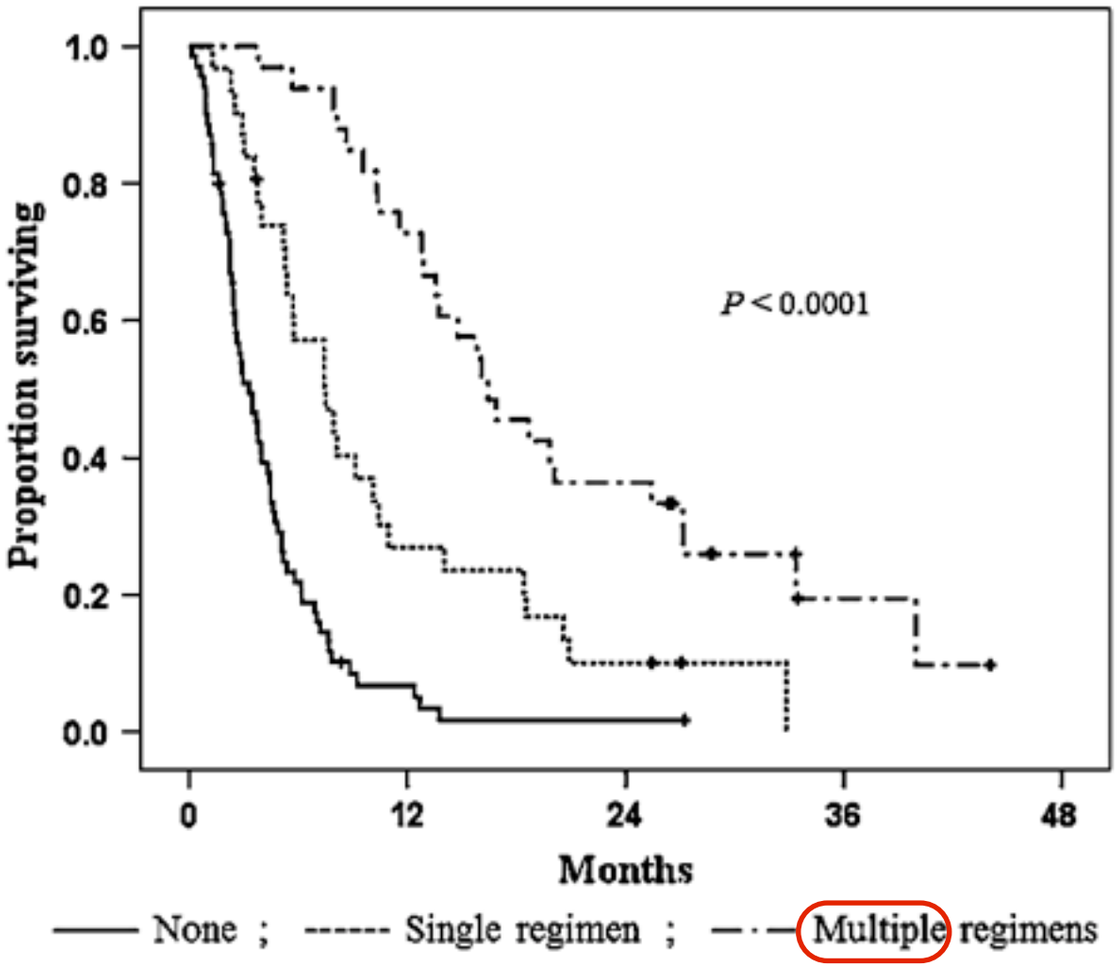


Fig. 2 Kaplan–Meier overall survival curve by the use of chemotherapeutic regimen after WBRT

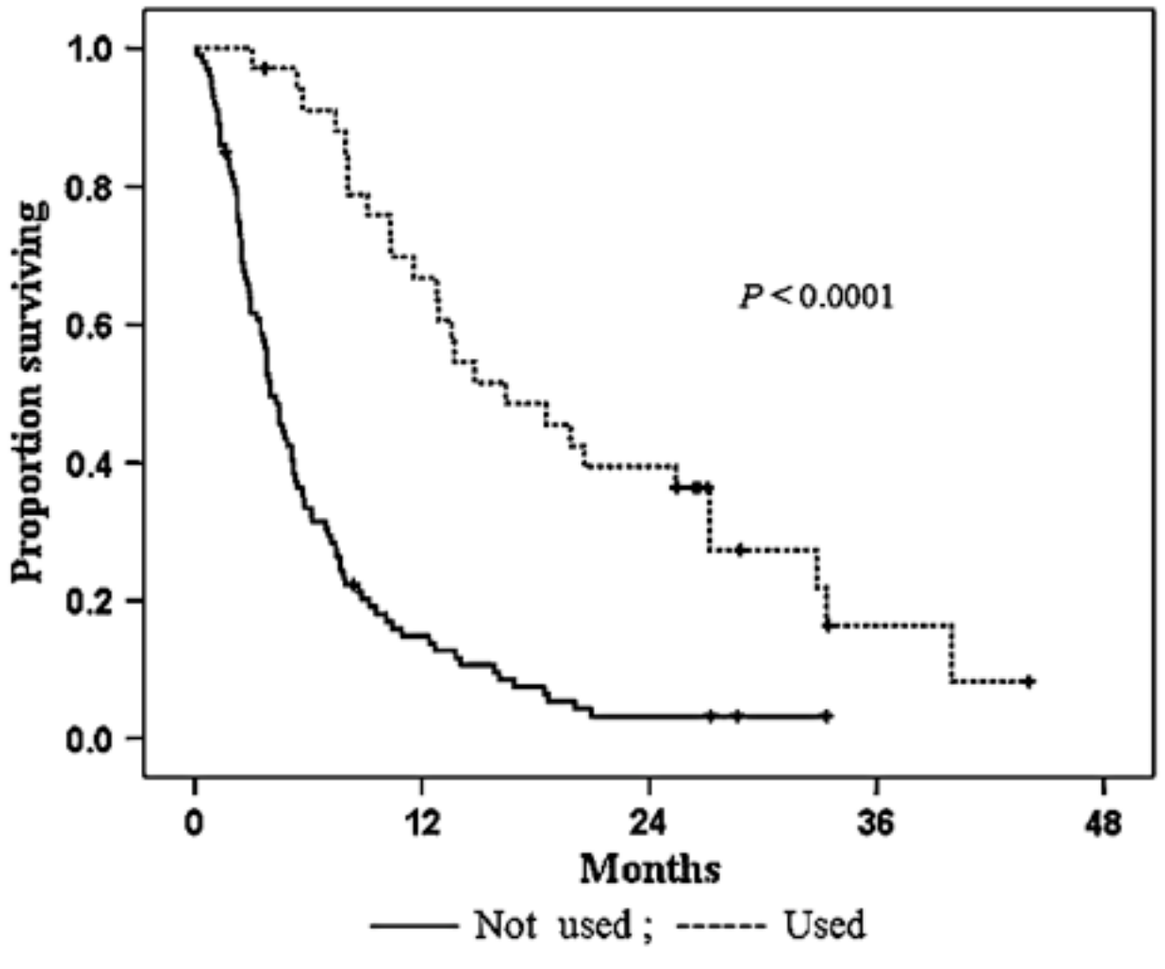


Fig. 3 Kaplan–Meier overall survival curve by the use of molecular-targeted therapy after WBRT

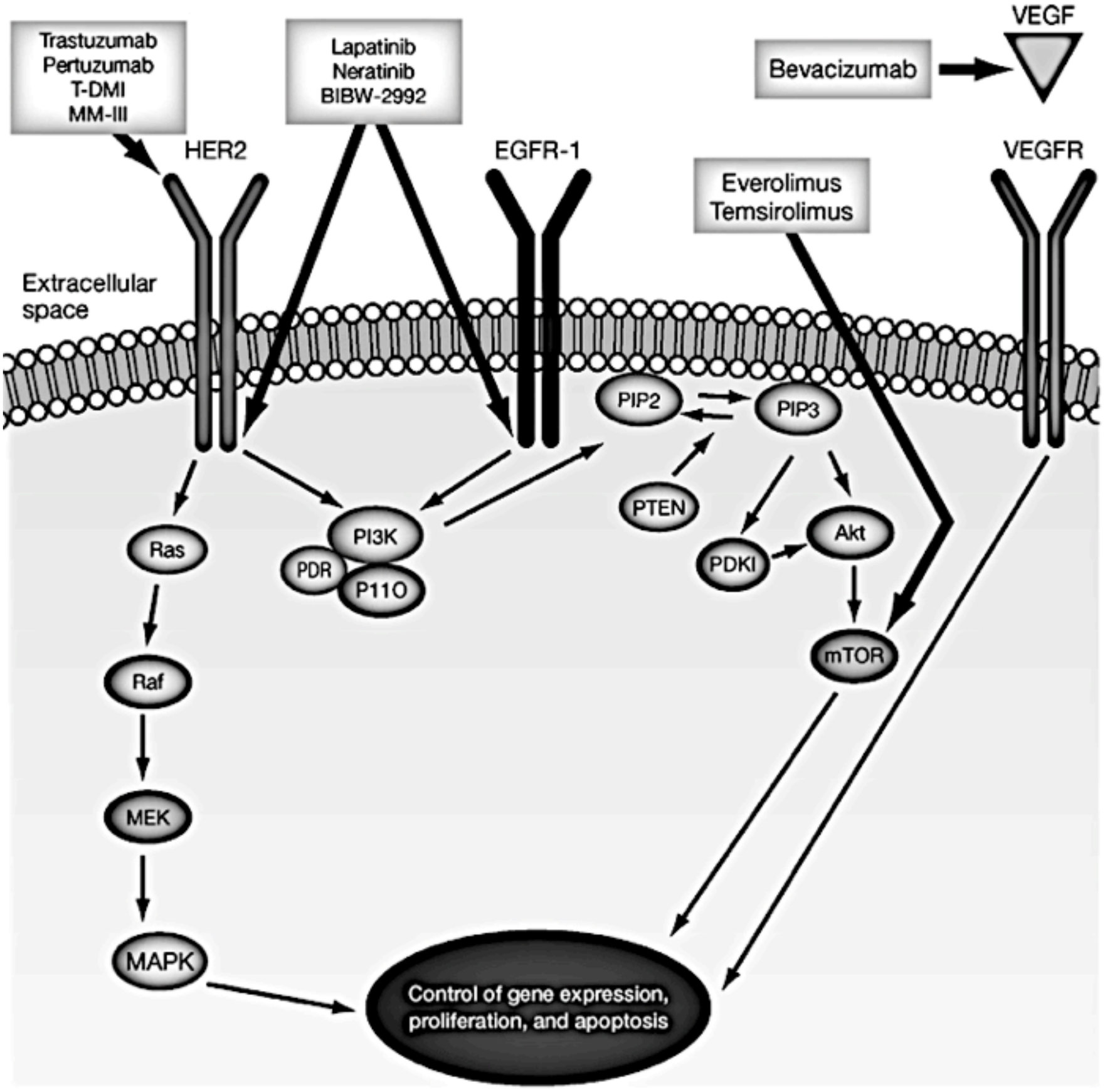
Atraviesan BHE o nicho perivascular
Menos toxicidad hematológica

J Cancer Res Clin Oncol (2012) 138:1239-1247

Breast Cancer Subtypes and Response to Systemic Treatment After Whole-Brain Radiotherapy in Patients With Brain Metastases

Biological Subtype	No Systemic Treatment	Chth/Ht	Chth/Ht With Targeted Therapy	*P*
Luminal A (HER2-negative ER/PgR-positive):				
Median survival, mo	3	12	–	
95% CI	0.01-7.68	8.40-16.44	–	.003
1-y survival rate	10%	51%	–	
Luminal B (HER2-positive ER/PgR-positive):				
Median survival, mo	2	9	15	
95% CI	2.04-2.76]	6.60-11.52	10.08-19.80	
1-y survival rate	0	33%	58%	<.0001
HER2 (HER2-positive ER/PgR-negative):				
Median survival, mo	4	6	13	
95% CI	(3.36-4.32	4.56-7.92	9.96-16.44]	
1-y survival rate	5%	33%	55%	<.0001
Triple-negative:				
Median survival, mo	3	4	–	
95% CI	1.44-4.08	1.32-7.32	–	
1-y survival rate	14%	23%	–	.16

Cancer September 15, 2010

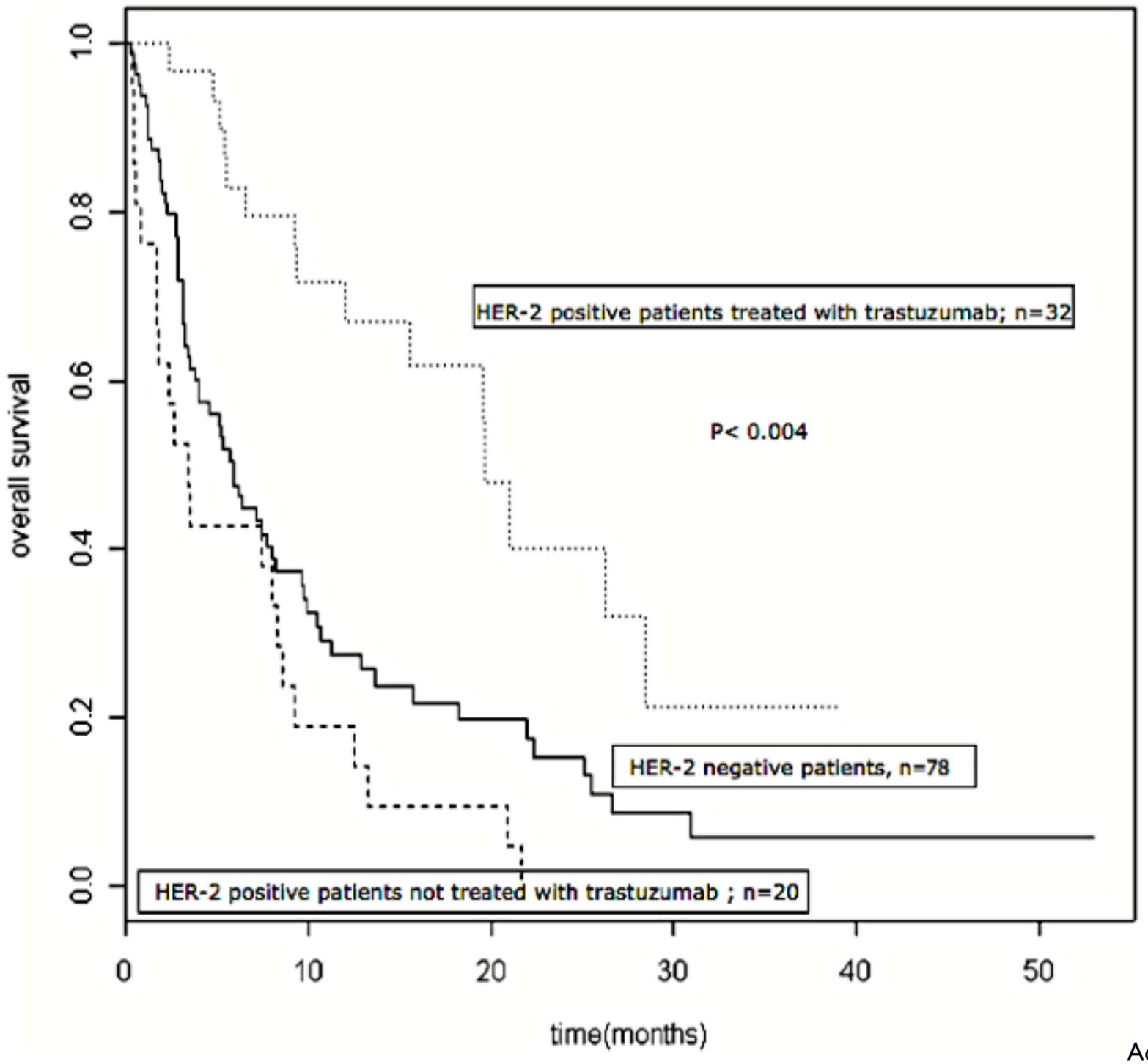


Cellular targets of biological agents in development for breast cancer.

Cancer Treatment Reviews 38(2012)494-504

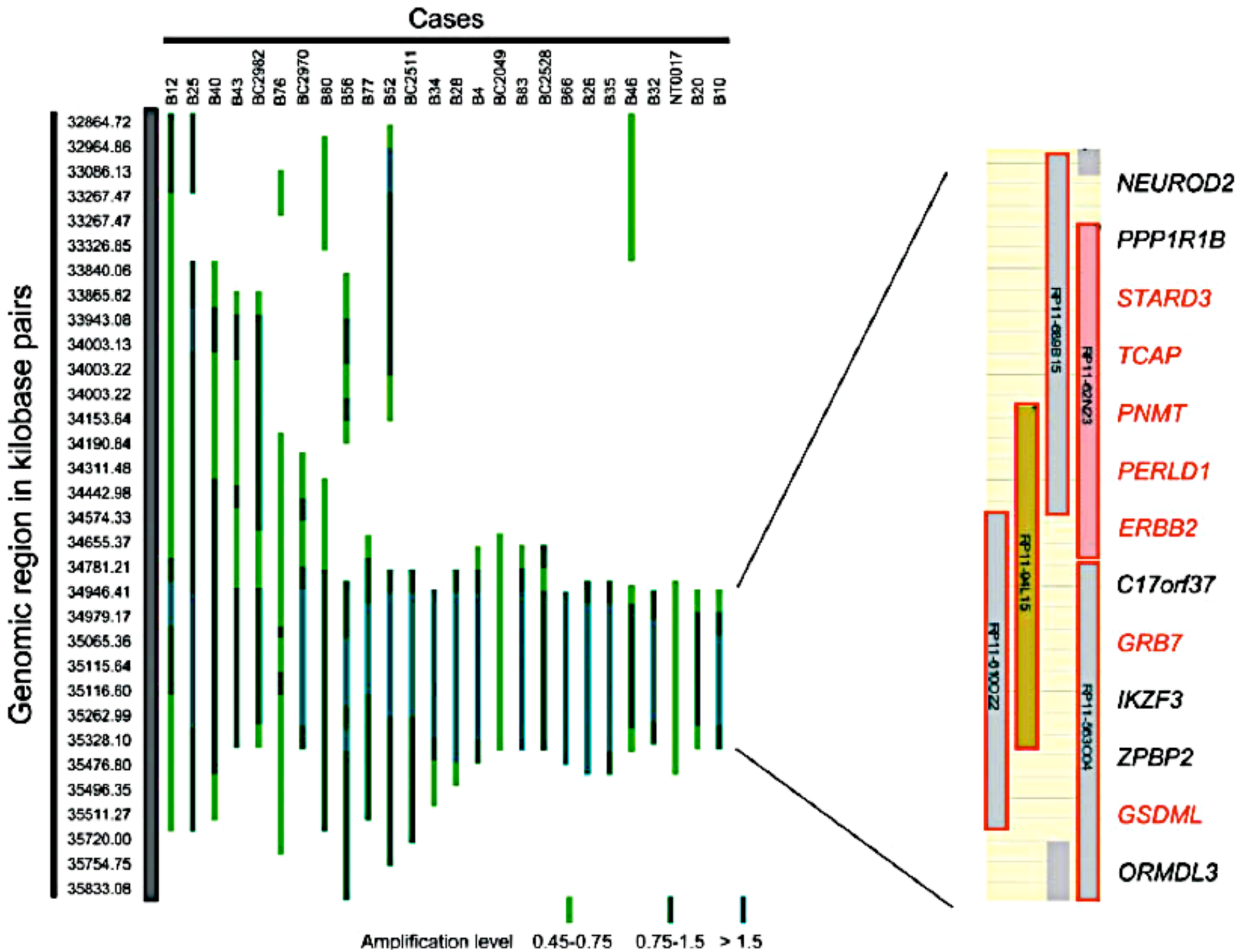
Her2+ sin trastuzumab es pésimo pronóstico

Brain metastases from breast cancer: prognostic significance of HER-2 overexpression, effect of trastuzumab and cause of death

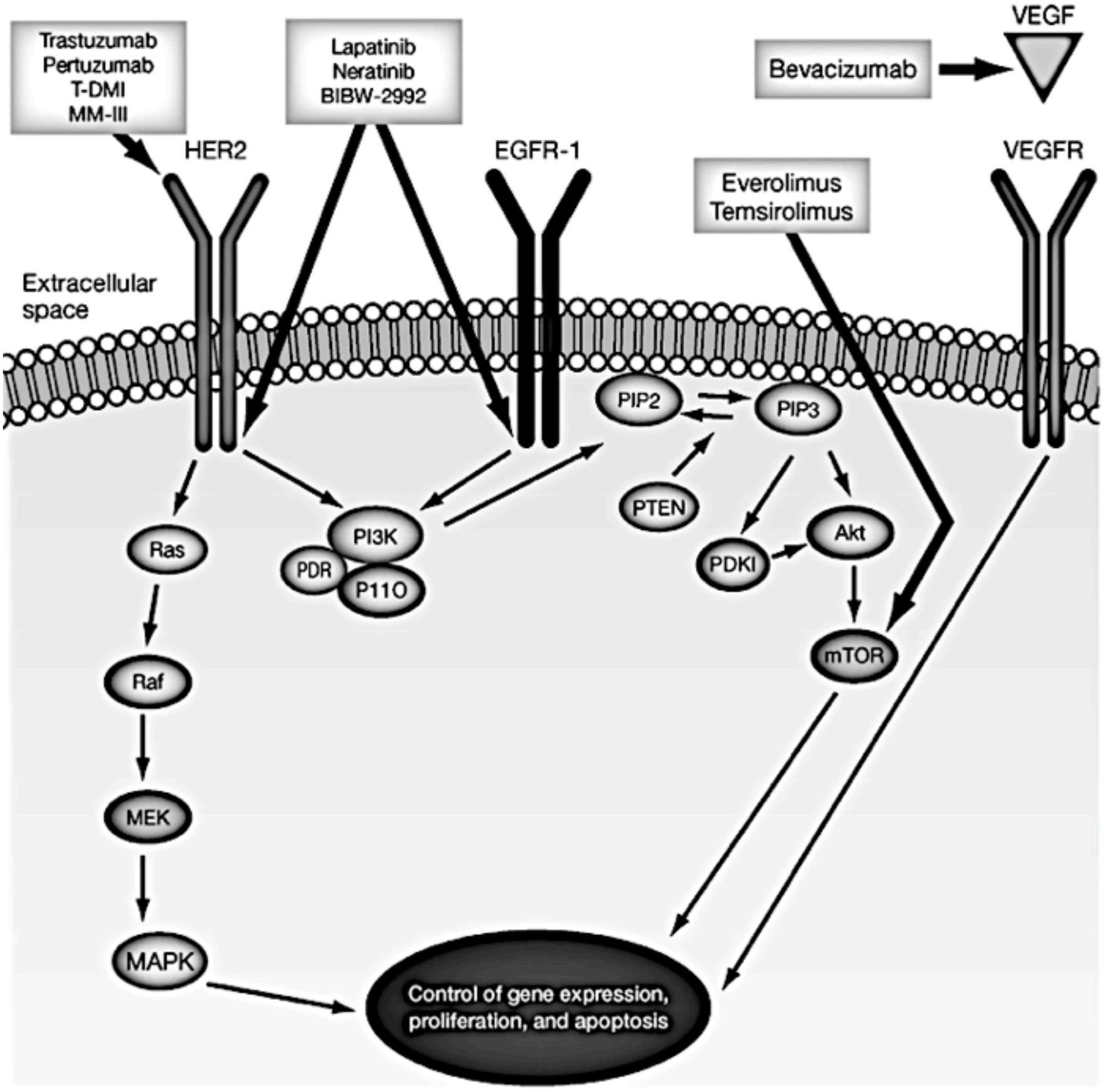


Acta Neuropathol (2012) 123:205-222

The 17q12 amplicon: SRA in 26 *HER2*–amplified breast carcinomas



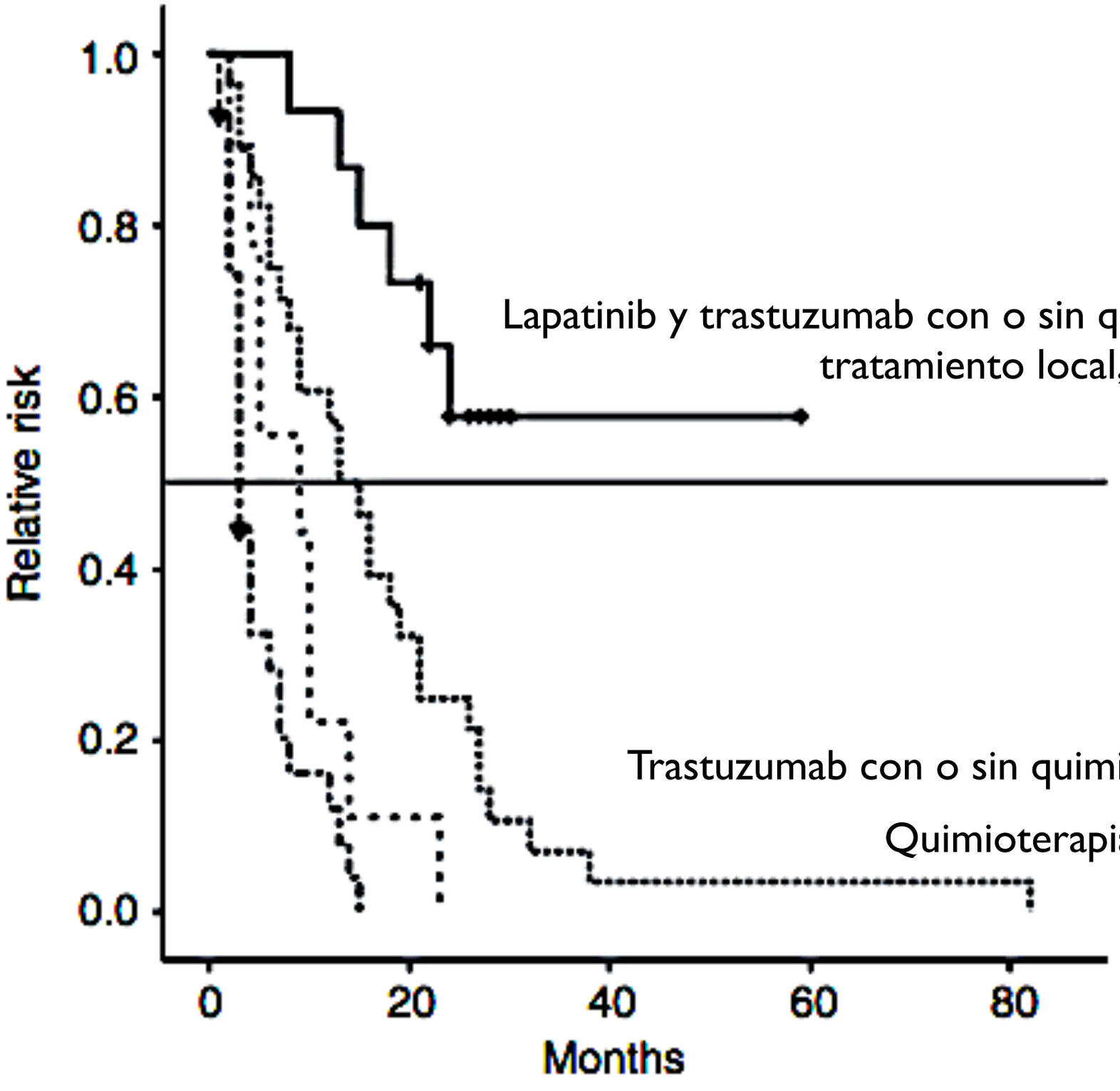
J Pathol 2008;216:399-407



Cellular targets of biological agents in development for breast cancer.

Cancer Treatment Reviews 38(2012)494-504

Impact of anti-HER2 therapy on overall survival in HER2-overexpressing breast cancer patients with brain metastases



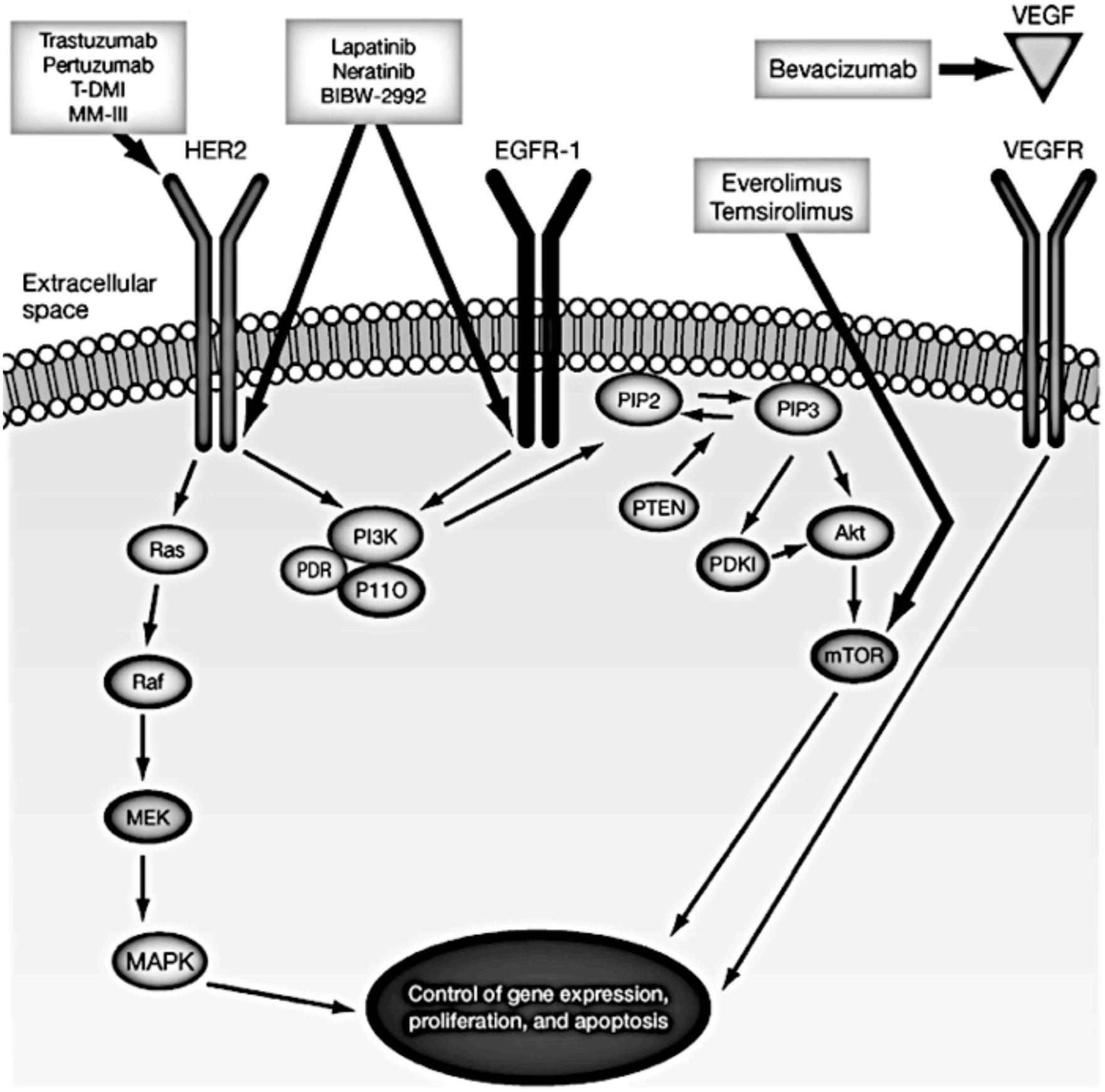
Lapatinib y trastuzumab con o sin quimioterapia después de tratamiento local, n=15

Trastuzumab con o sin quimioterapia, n=28

Quimioterapia sin anti HER2, n=9

Ninguna terapia sistémica, n=28

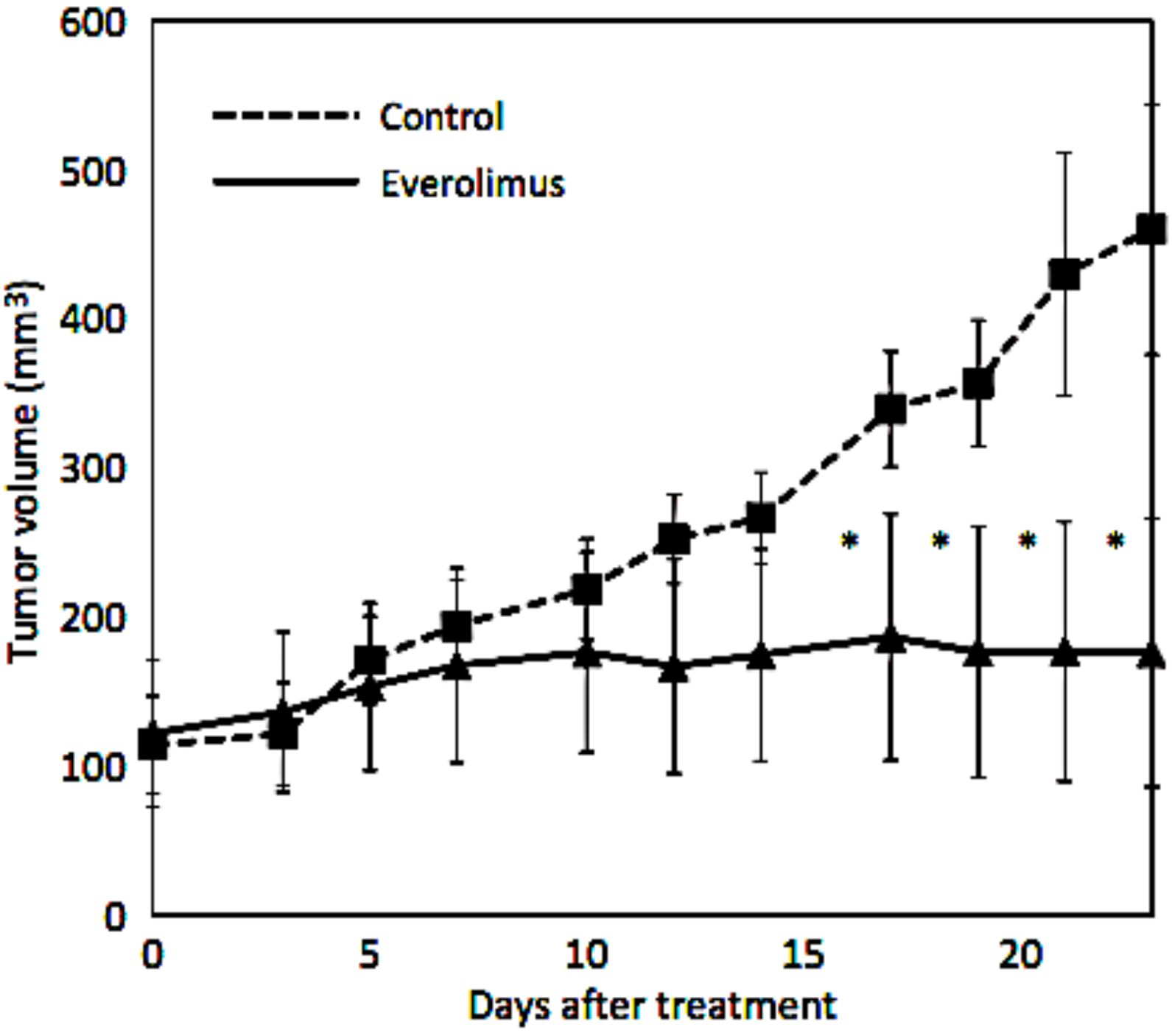
British Journal of Cancer (2012) 106:25-31



Cellular targets of biological agents in development for breast cancer.

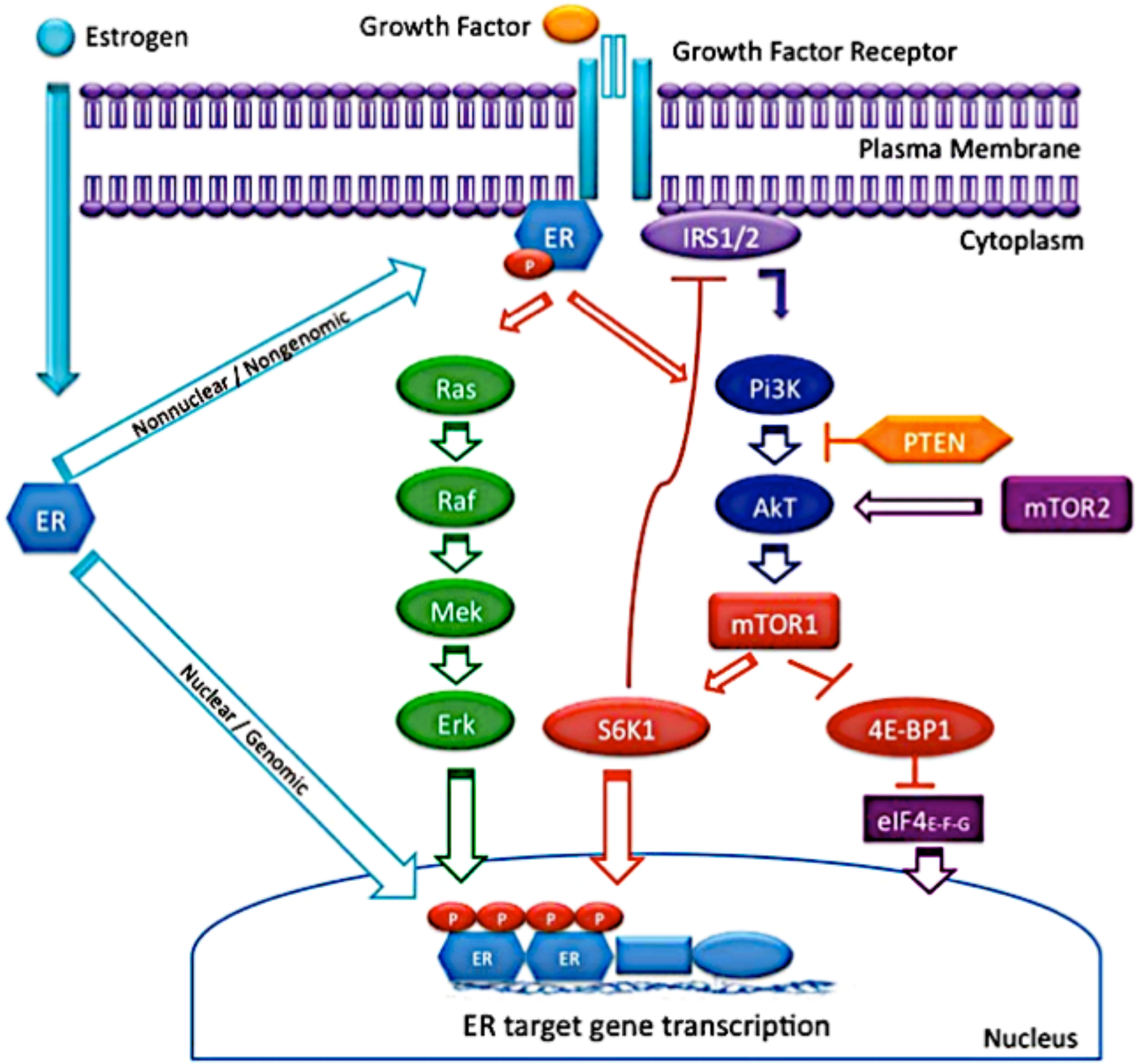
Cancer Treatment Reviews 38(2012)494-504

Efficacy of everolimus, a novel mTOR inhibitor, against basal-like triple-negative breast cancer cells



Cancer Sci, September 2012, Vol 103, N9

mTOR inhibitors in the management of hormone receptor-positive breast cancer



Annals of Oncology 23:2526-2535, 2012

Fase II y III randomizados de everolimus en mama metastásico

ESTUDIO	COHORTE 1	COHORTE 2
BOLERO-1	Everolimus + Plaquitaxel + Trastuzumab (n=717)	Placebo + Paclitaxel + trastuzumab (n=717)
BOLERO-2	Everolimus + exemestane (n=485)	Placebo + exemestane (n=239)
BOLERO-3	Everolimus + trastuzumab + vinorelbine + (n=572)	Placebo + vinorelbine + trastuzumab (n=572)

The Oncologist 2012;17:1014-1026

New Insights and Emerging Therapies for Breast Cancer Brain Metastases

ClinicalTrials.gov

NCT01305941

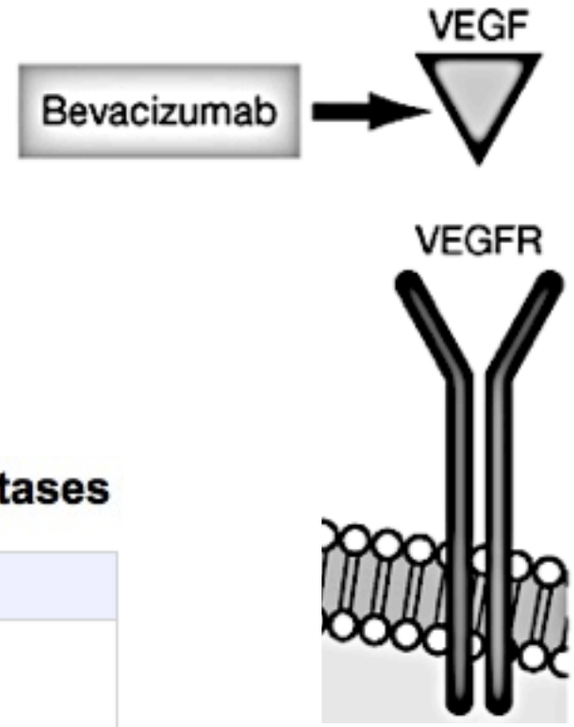
Everolimus, Trastuzumab And Vinorelbine In HER2-Positive Breast Cancer Brain Metastases

Condition	Intervention	Phase
HER-2 Positive Breast Cancer	Drug: Everolimus Drug: Vinorelbine Drug: Trastuzumab	Phase 2

ONCOLOGY, Vol 26, N7, July 12, 2012

New Insights and Emerging Therapies for Breast Cancer Brain Metastases

ClinicalTrials.gov



NCT01004172

Carboplatin and Bevacizumab for Progressive Breast Cancer Brain Metastases

Condition	Intervention	Phase
Metastatic Breast Cancer Breast Cancer Progressive Breast Cancer	Drug: carboplatin Drug: bevacizumab Drug: herceptin	Phase 2

NCT01281696

Bevacizumab With Etoposide and Cisplatin in Breast Cancer Patients With Brain and/or Leptomeningeal Metastasis

Condition	Intervention	Phase
Breast Neoplasms Leptomeningeal Metastasis Brain Metastases	Drug: Bevacizumab, etoposide, cisplatin Drug: Intrathecal methotrexate	Phase 2

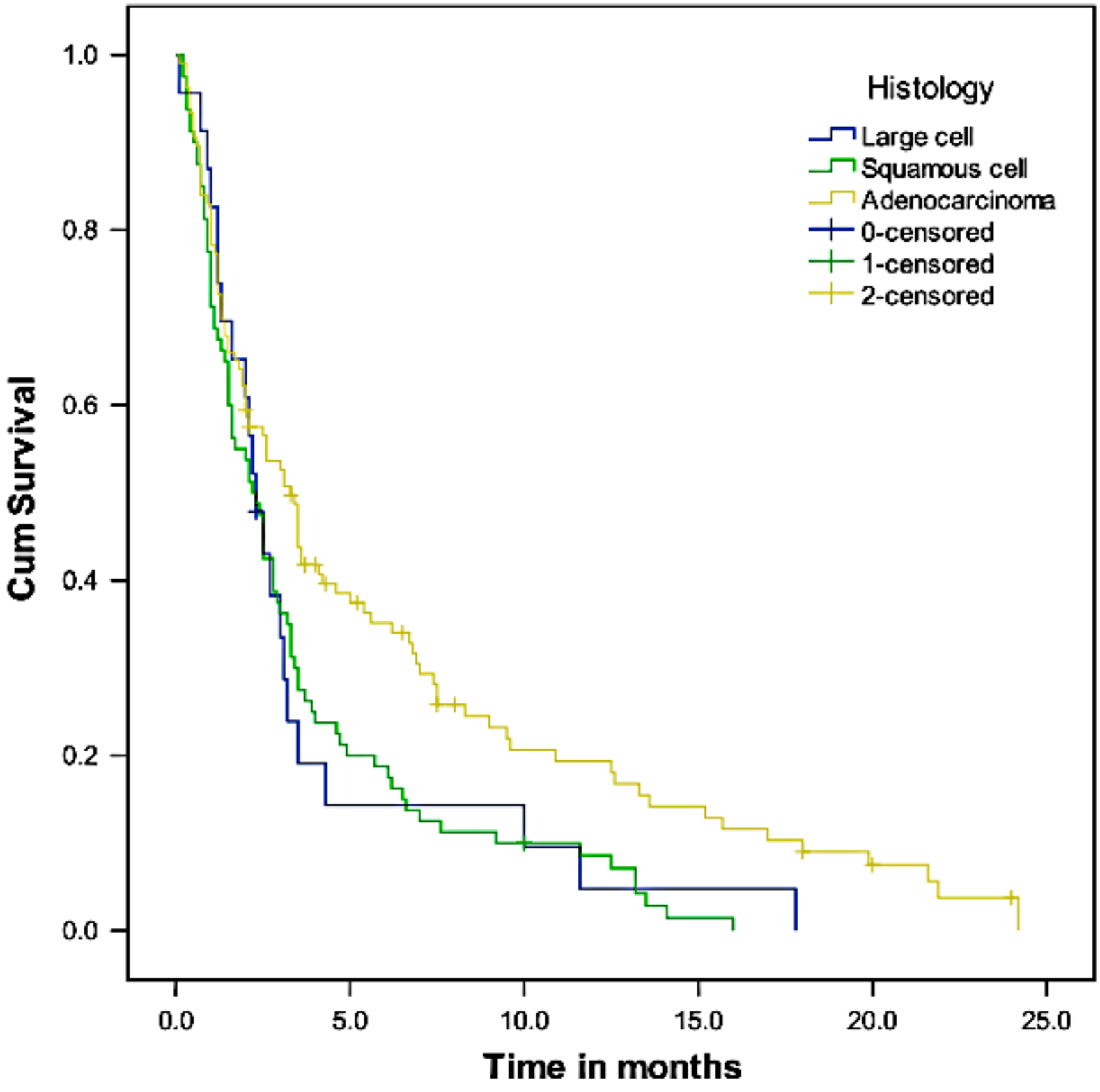
NCT01332929

Safety Evaluation of a Combination of Brain Radiation Therapy and Bevacizumab (Avastin®) for Treatment of Brain Metastasis

Condition	Intervention	Phase
Metastatic Malignant Neoplasm to Brain	Drug: Bevacizumab	Phase 1

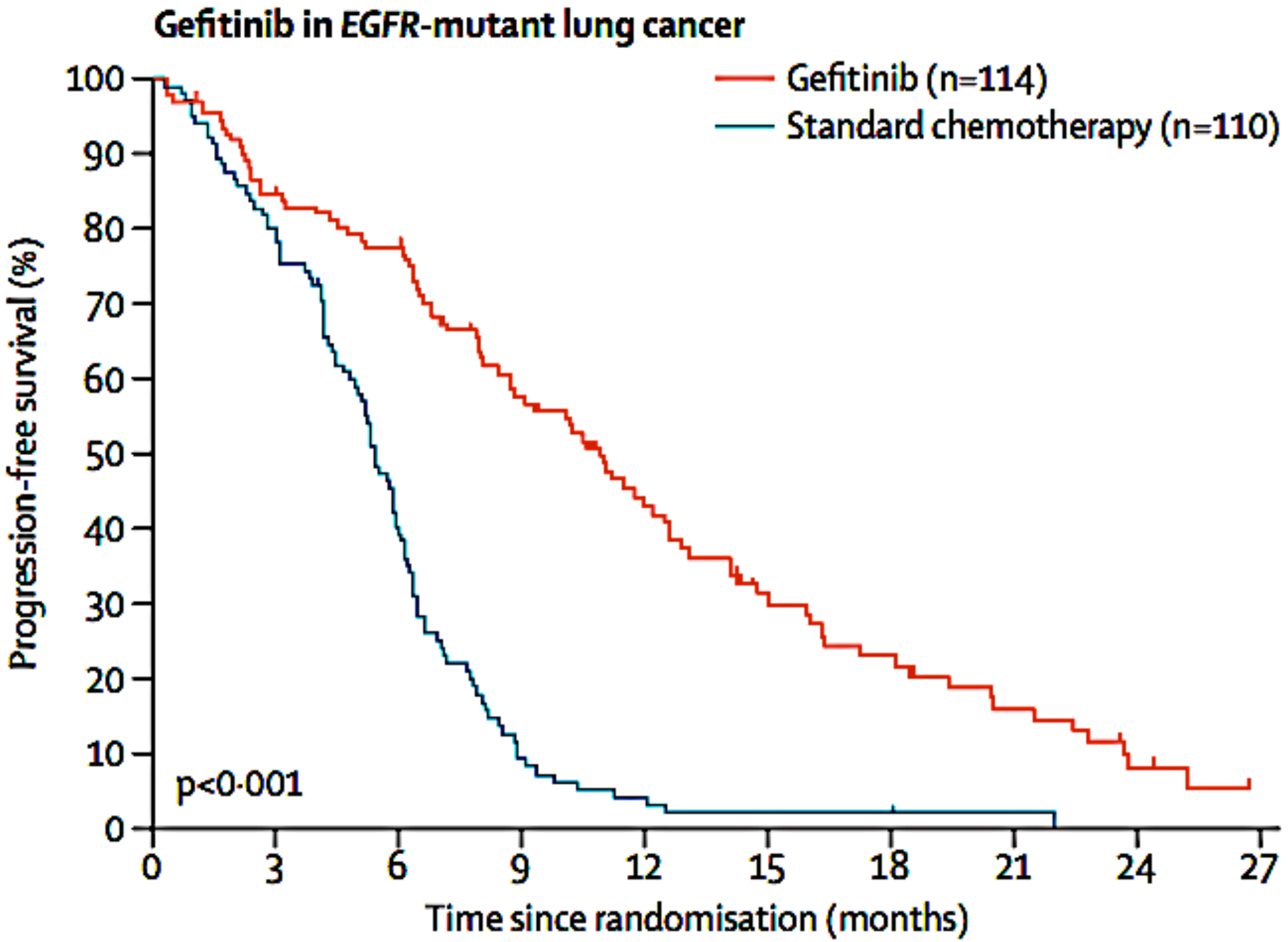
ONCOLOGY, Vol 26, N7, July 12, 2012

Non-small cell lung cancer histological subtype has prognostic impact in patients with brain metastases



Med Oncol (2012) 292664-2668

Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation



Lung Cancer 77 (2012) 556-560

Lancet Oncol 2012;13:e178-85

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in the Treatment of Epidermal Growth Factor Receptor –Mutant Non–Small Cell Lung Cancer Metastatic to the Brain

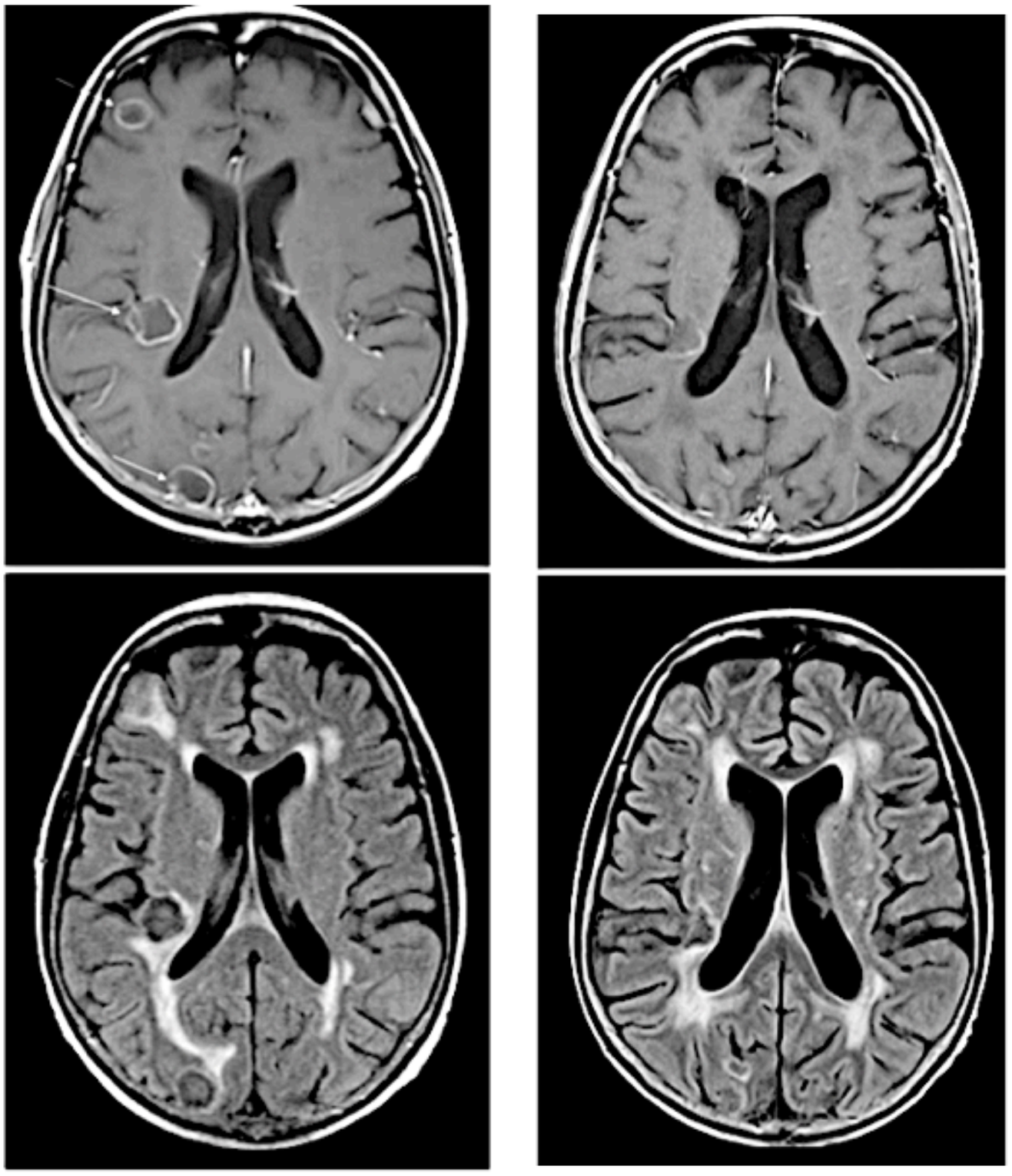
Treatment	Selection	Phase	*N*	RR (%)	Survival
Gefitinib	European	II	41	27	PFS 3 mo
Gefitinib	East Asian, adenocarcinoma	II	40	32	PFS 9 mo
Gefitinib	East Asian	II	57	43	
Erlotinib	*EGFR* mutation	II	69	82	OS 12.9 mo
Gefitinib or erlotinib	*EGFR* mutation, East Asian, adenocarcinoma	II	23	70	PFS 6.6 mo, OS 19.8 mo
Gefitinib	*EGFR* mutation, East Asian	II	110	89	
Erlotinib	East Asian, *EGFR* mutation, and/or adenocarcinoma	II	48	56	PFS 23.2 mo
Gefitinib or erlotinib	East Asian, never-smoker, adenocarcinoma	II	23	74	PFS 7.1 mo, OS 18.8 mo

Clin Cancer Res 2012;18:938-944

Prolonged activity of bevacizumab in adenocarcinoma of the lung with multiple brain metastases

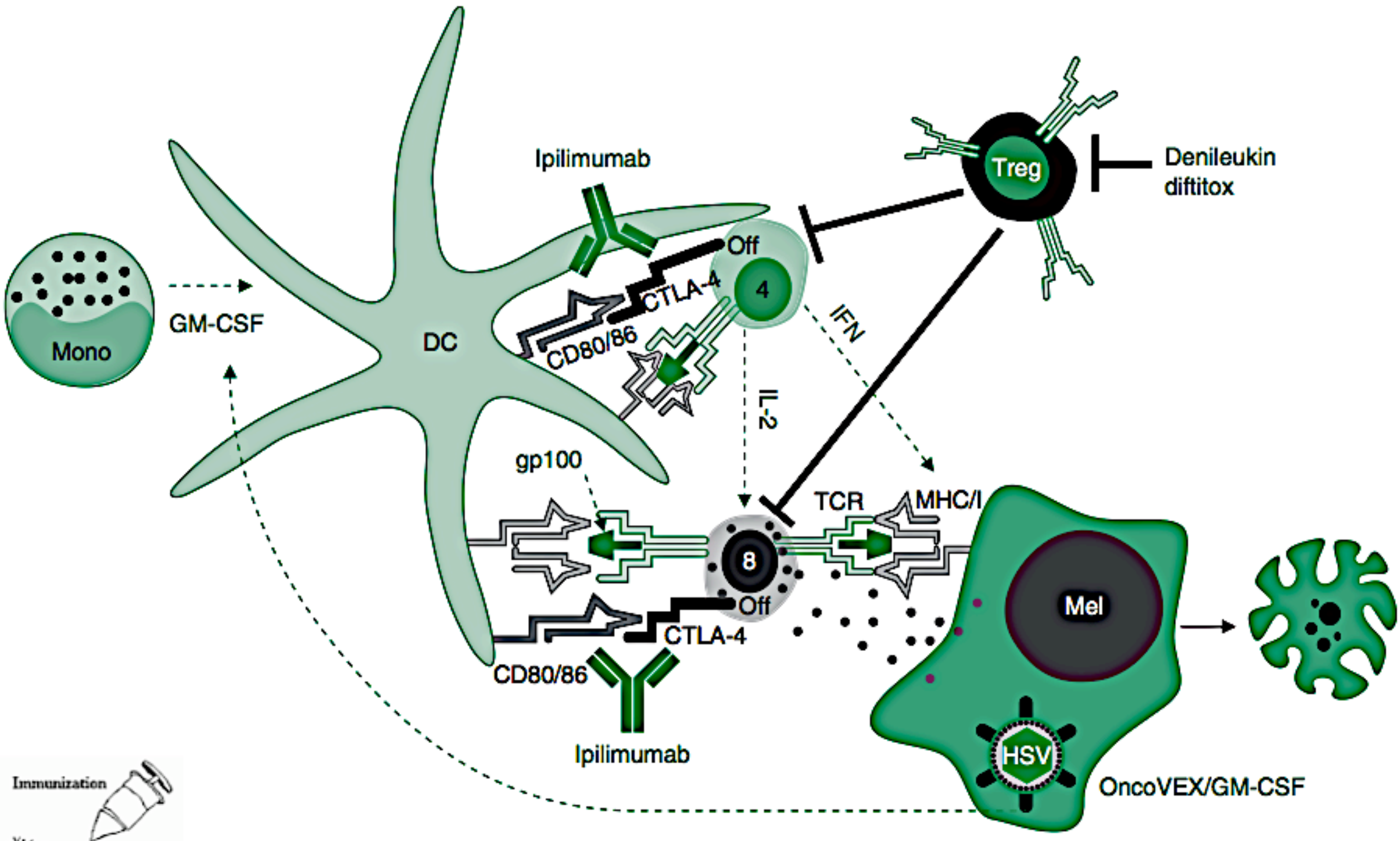
Pre

Post



Med Oncol (2012) 29:2619-2622

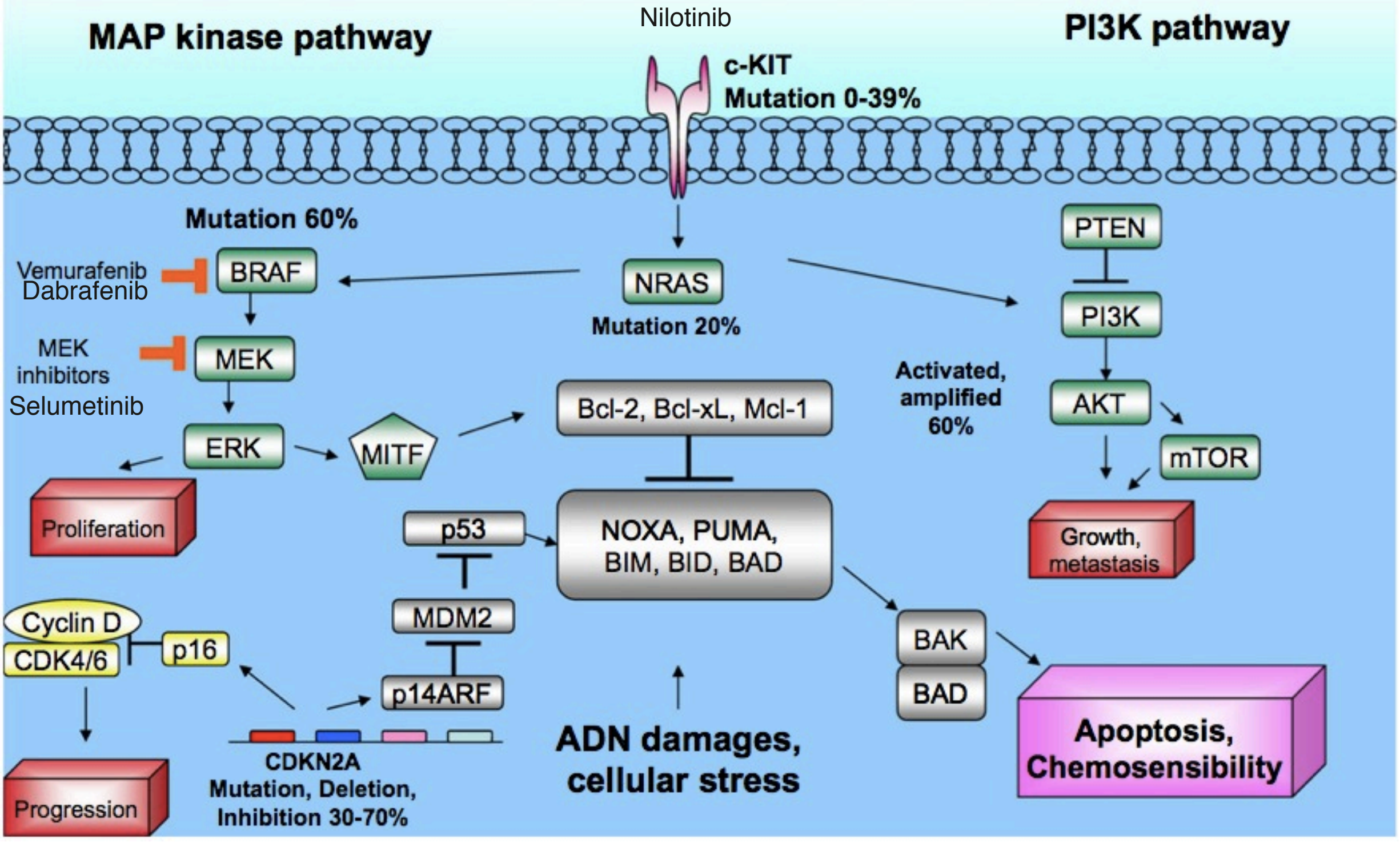
Ipilimumab in patients with melanoma and brain metastases:



Drugs 2011;71(10) 1233-1250

The Lancet/oncology, Vol 13, May 2012

Rápida resistencia

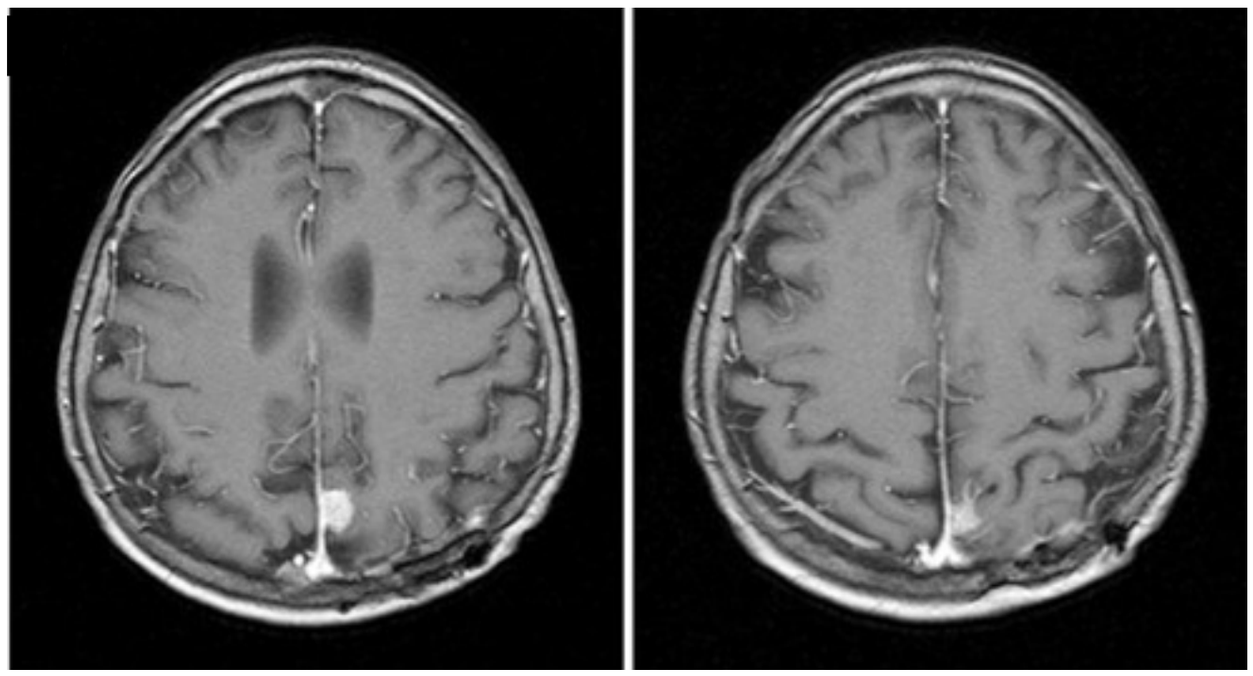


Dermatologic Therapy, Vol 25, 2012, 452-457

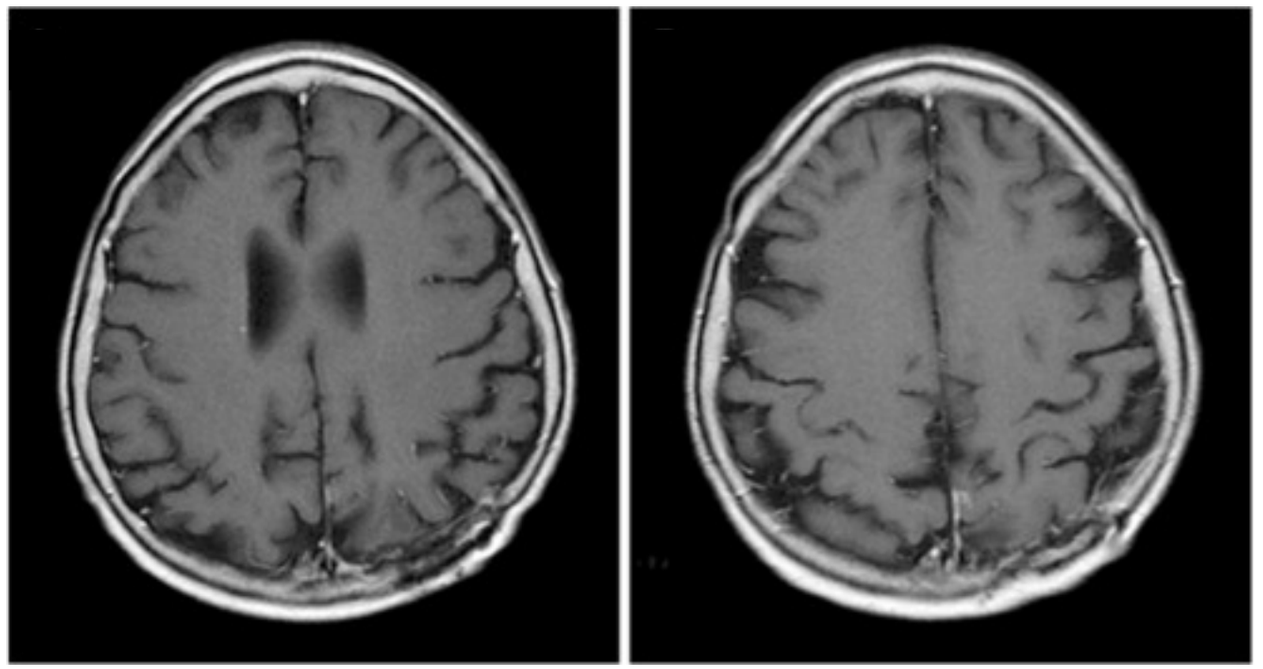
Long-lasting successful cerebral response with sorafenib in advanced renal cell carcinoma

J Neurooncol (2009)91:47-50

Dx



Luego de 4 meses tratamiento



Incidence of brain metastases in renal cell carcinoma treated with sorafenib

Annals of Oncology 21: 1027-1031, 2010

Inmunoterapia y pequeñas moléculas: Aplicaciones y limitaciones

CONCLUSIONES

- La barrera hematoencefálica sigue siendo un obstáculo para la quimioterapia estándar
- Los Ac-m actúan en el nicho perivascular y los TKI atraviesan la BHE
- Se imponen luego de la Cx/Rcx
- A medida que se profundiza en biología molecular mas alternativas
- Perfil toxicidad diferente
- Costosas