XVème Journées de Sénologie Interactive

Symposium GSK : Stratégies actuelles dans le cancer du sein métastatique

HER2 +

Président : Dr Marc ESPIE

- Données fondamentales et moléculaires du double blocage des récepteurs HER2.
  - Dr Gérard MILANO- Centre Lacassagne. Nice

- Quelles stratégies thérapeutiques dans le cancer du sein métastatique HER2 + ? Comment optimiser la prise en charge ?

Dr Sylvie GIACCHETTI – Hôpital Saint-Louis. Paris

gsk GlaxoSmithKline Oncology

XVIIes Journées de Sénologie Interactive
Journées du Centre des Maladies du Sein de l'Hôpital Saint-Louis

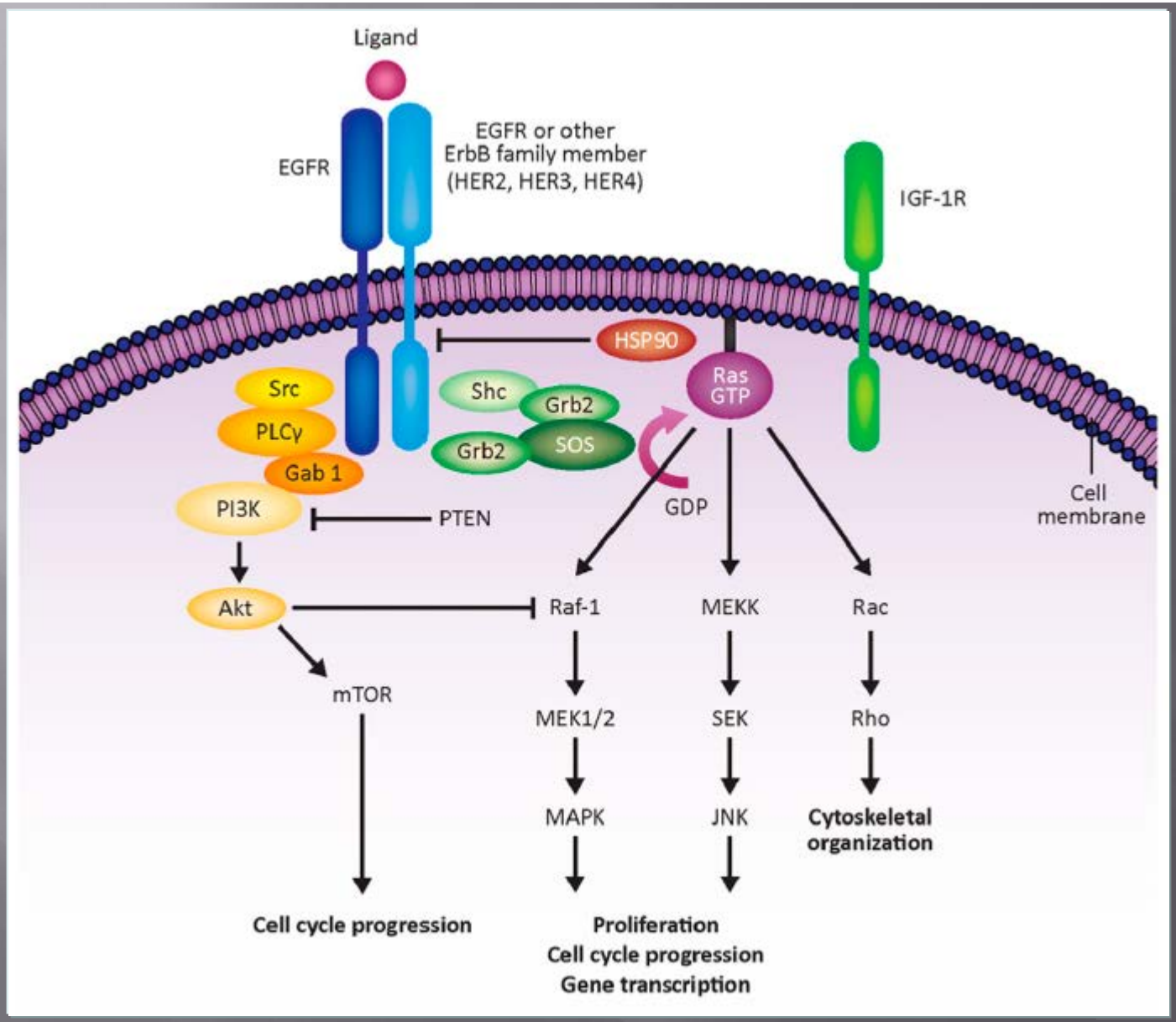
Paris, le 18 septembre 2014

Stratégies actuelles dans le cancer du sein métastatiques HER2+

Données fondamentales et moléculaires du double blocage des récepteurs HER2

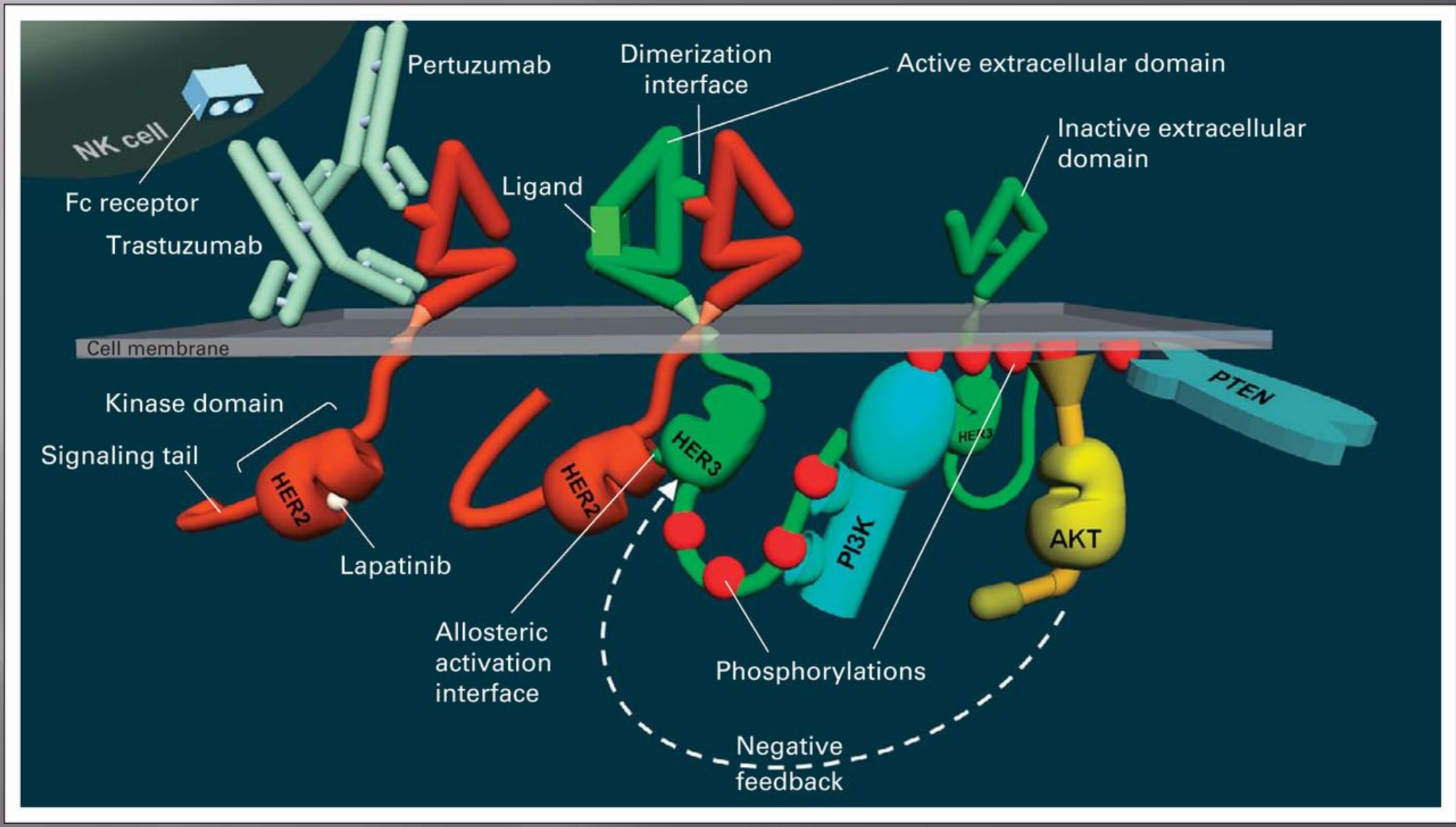
Gérard MILANO
Oncopharmacologie – UNS EA 3836
Centre Antoine Lacassagne, Nice
gerard.milano@nice.unicancer.fr

Ciblage thérapeutique de la famille HER
Efficacité établie !



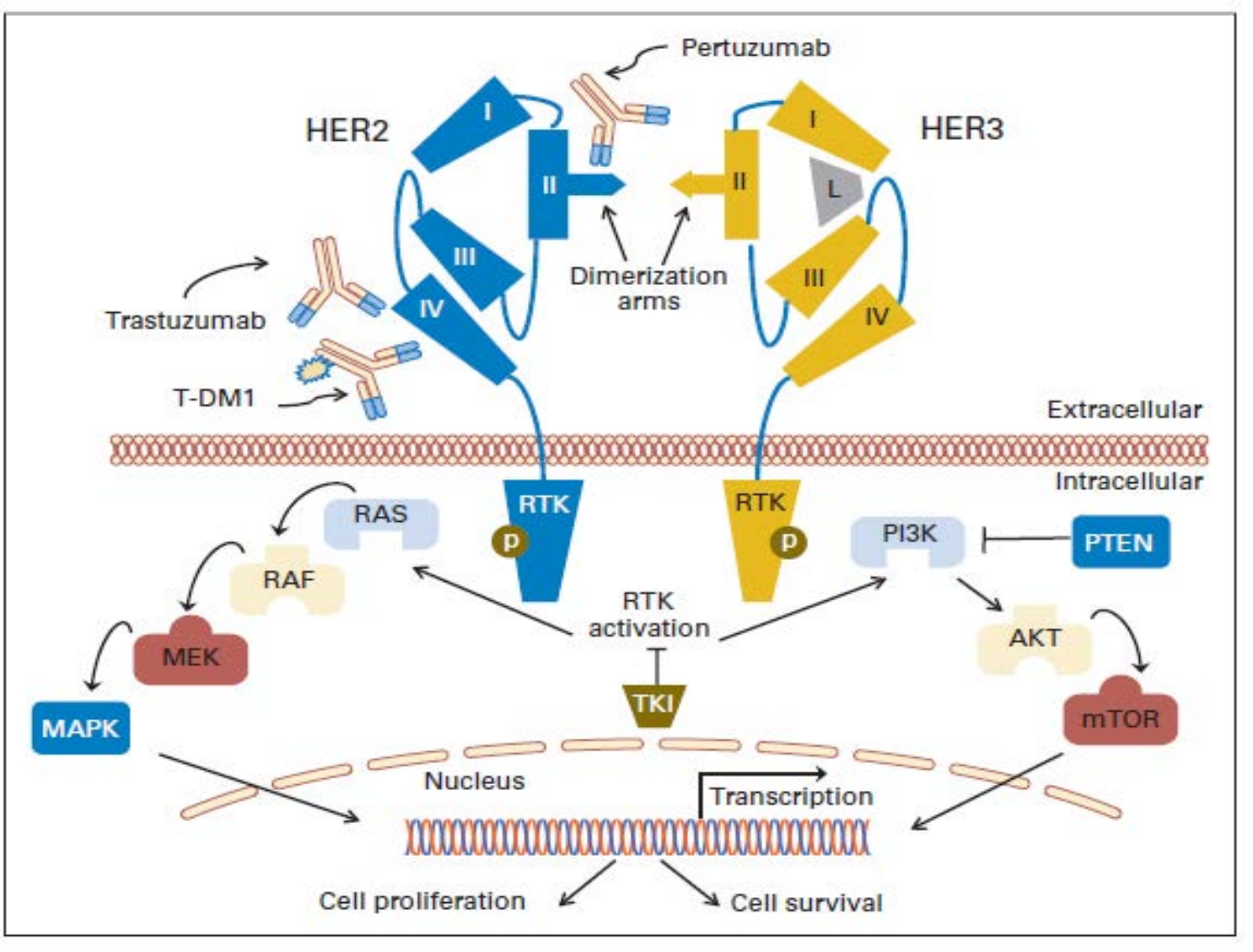
(Eroglu Z et al., The Oncologist 2014)

Ciblage HER2 : une approche plus sophistiquée



(Moasser MM et al., JCO 2014)

Ciblage HER2 et signalisation : Une prise en charge thérapeutique optimisée dans le cancer du sein



(Olson M., J Clin Oncol 2012)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other first-line agents for HER2-positive disease:

Trastuzumab alone or with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[3]

[1]There is no compelling evidence that combination regimens are superior to sequential single agents.

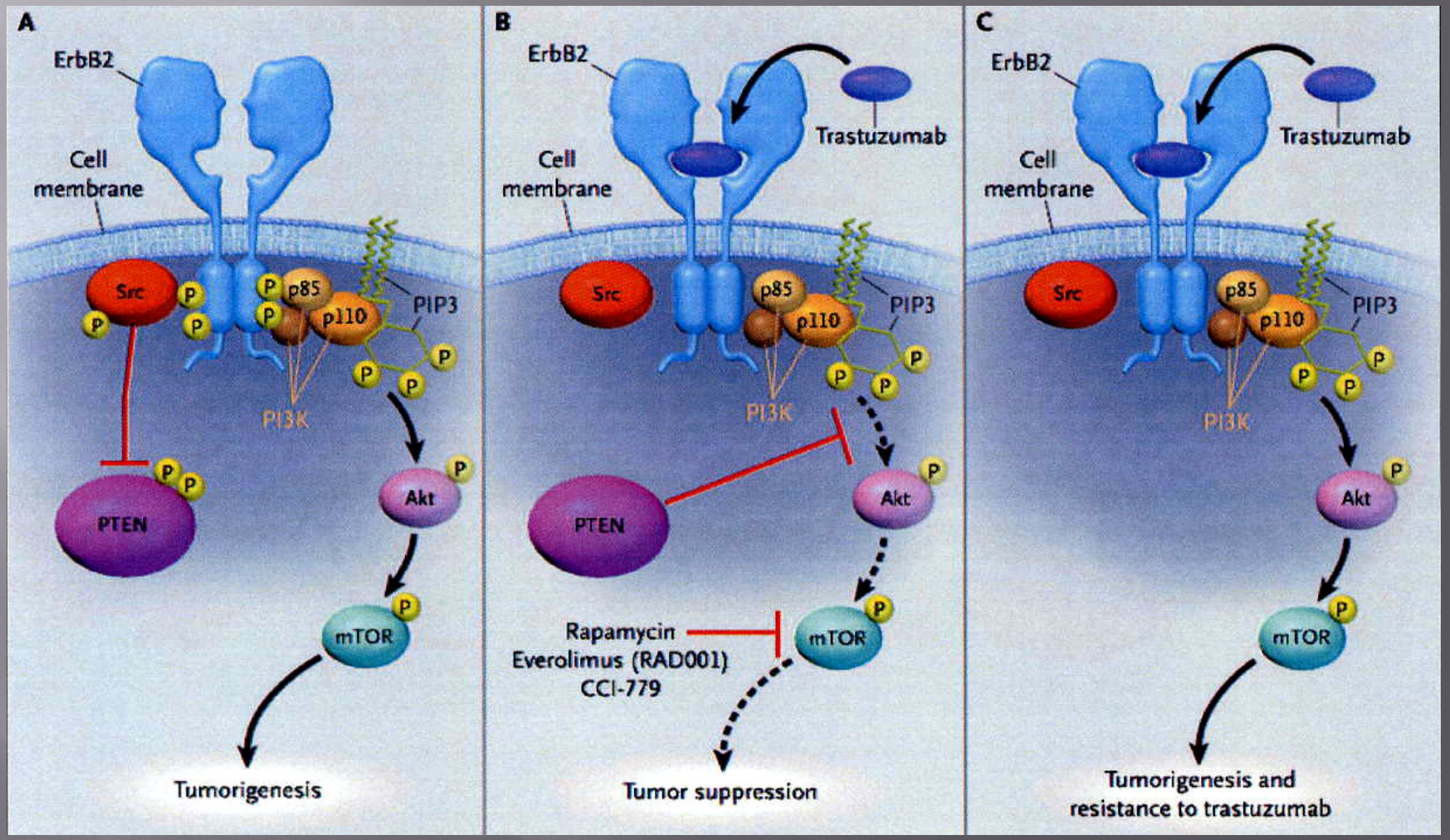
[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

[3]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

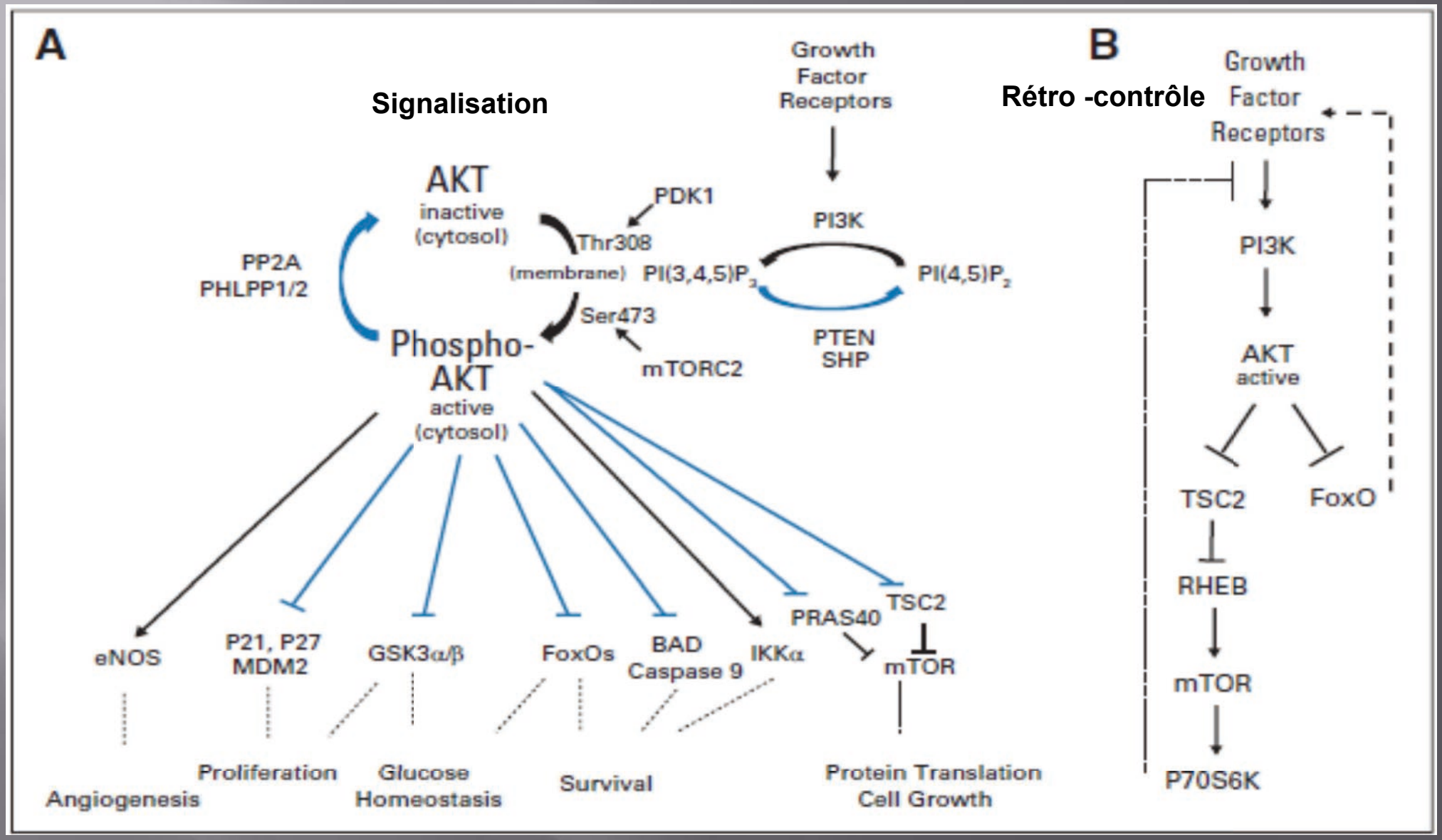
Trastuzumab agit principalement sur la voie PI3K CA

Indirectement prouvé/rôle de PTEN-résistance



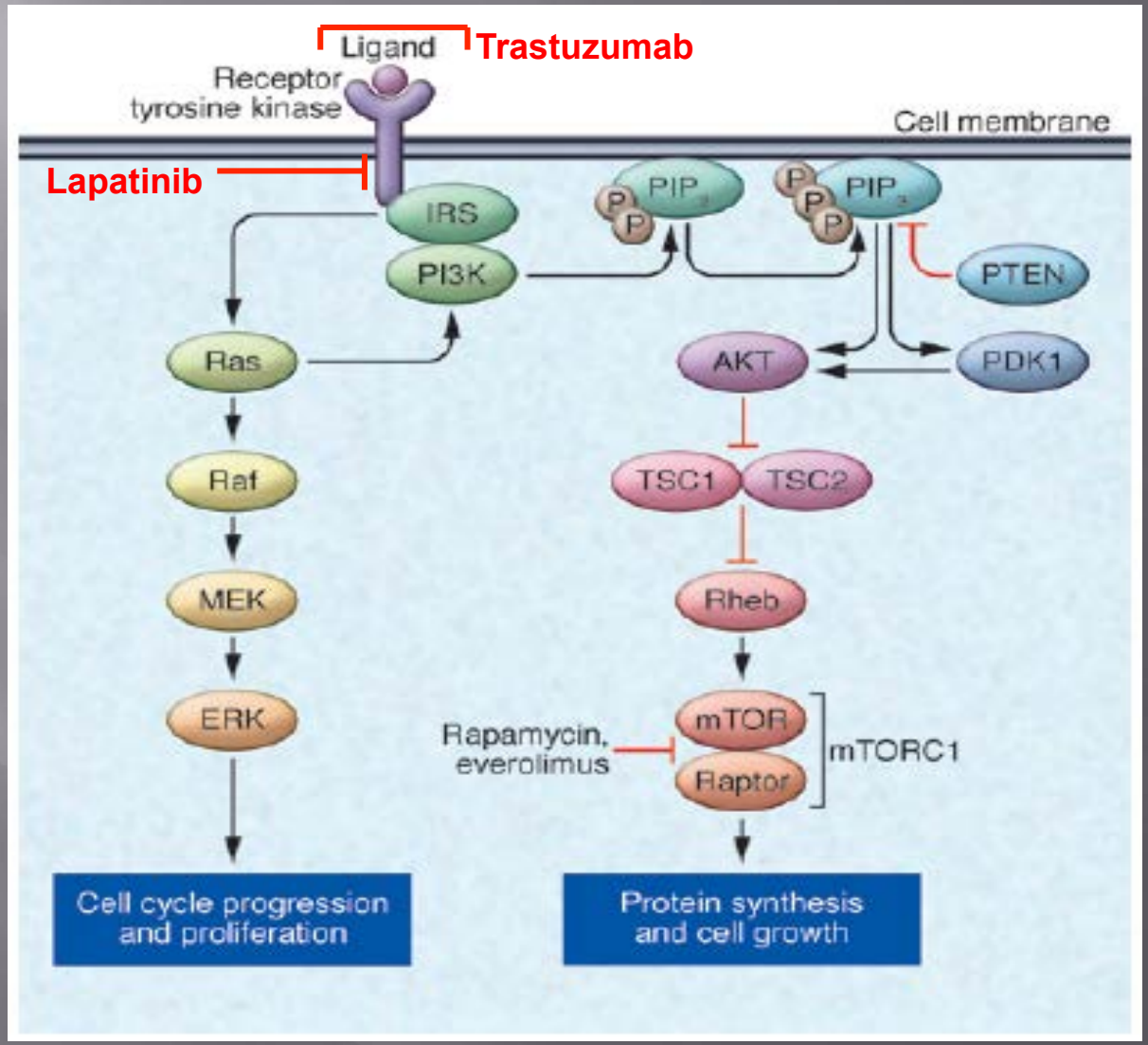
(Pandolfi, 2004)

Une vraie difficulté : Voie PI3K rétro-contrôlée



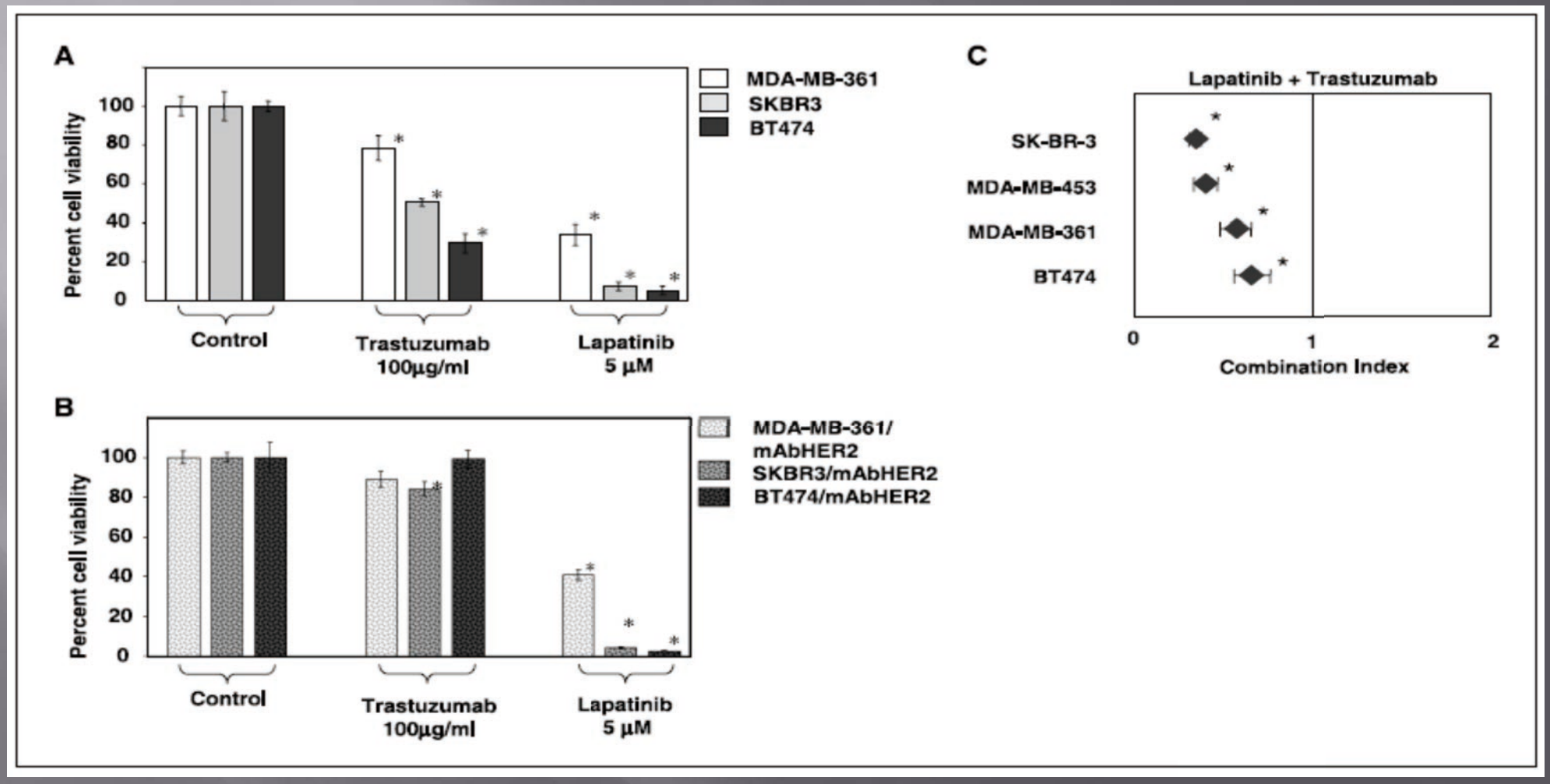
(Davies M.A., J Clin Oncol 2011)

Verrou pharmacologique optimal sur la voie HER2 (PI3K et MAPK) = trastuzumab-lapatinib



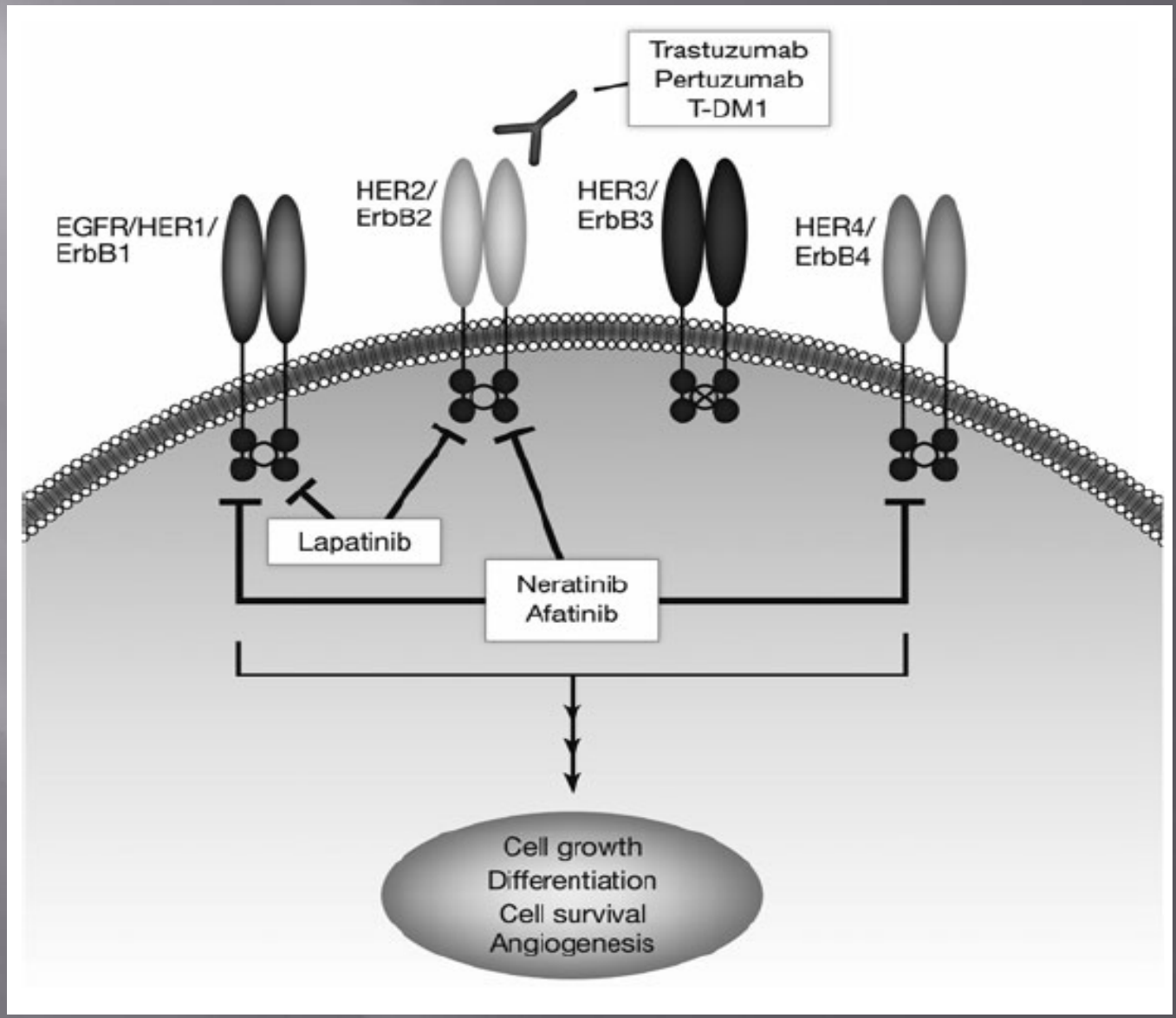
(Mohseni M.and Park B.H., JNCI 2010)

Données pré-cliniques
Association trastuzumab-lapatinib :
Effets supra-additifs



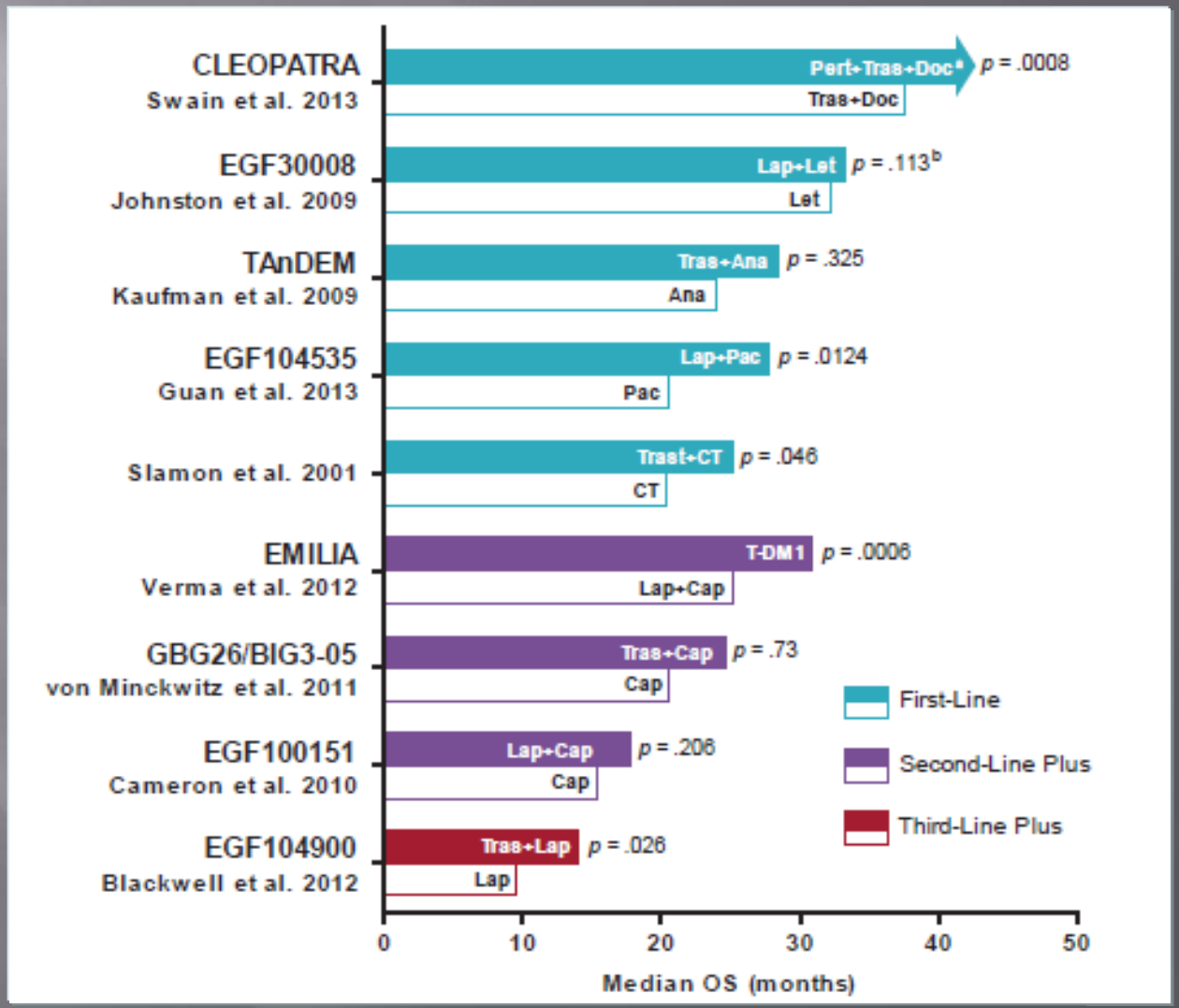
(Konecny G.E. et al, Cancer Res. 2006)

Cancer du sein : stratégie thérapeutique optimale anti HER



(Gradishar W.J., Ann Oncol 2013)

Avancées thérapeutiques majeures dans le ciblage du cancer du sein HER2+



(Verma S et al., The Oncologist 2013)

Therapeutics, Targets, and Chemical Biology

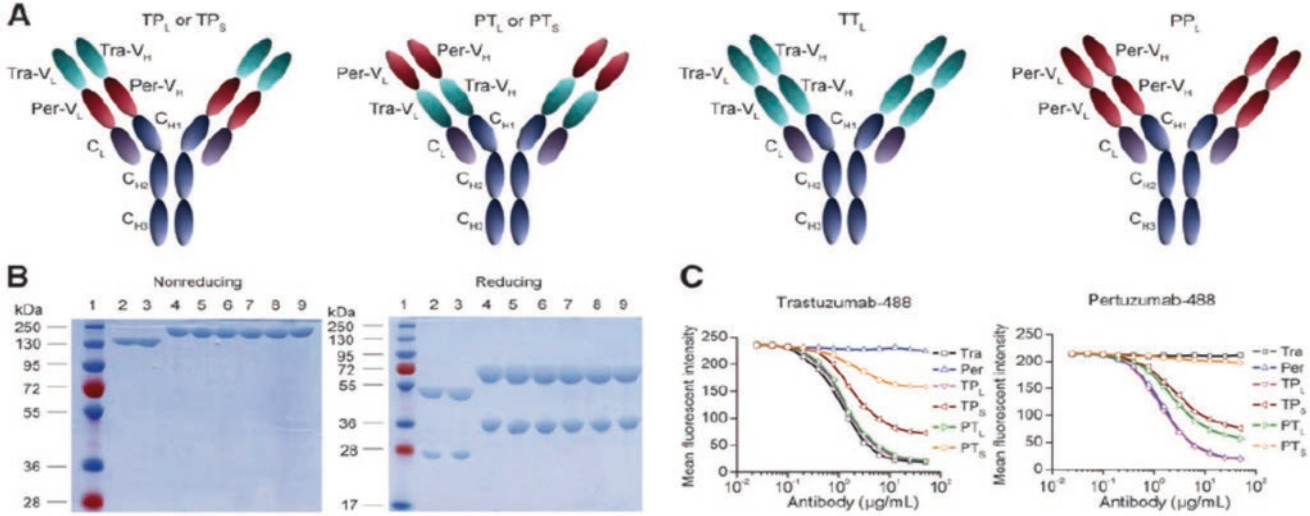
Cancer Research

Bispecific Antibody to ErbB2 Overcomes Trastuzumab Resistance through Comprehensive Blockade of ErbB2 Heterodimerization

Bohua Li[1,2,3,5], Yanchun Meng[1], Lei Zheng[1], Xunmin Zhang[1], Qing Tong[1], Wenlong Tan[4], Shi Hu[1], Hui Li[5], Yang Chen[5], Jinjing Song[1], Ge Zhang[1], Lei Zhao[1], Dapeng Zhang[1,2,3], Sheng Hou[1,2,3,5], Weizhu Qian[1,2,3], and Yajun Guo[1,2,3,4,5]

Abstract

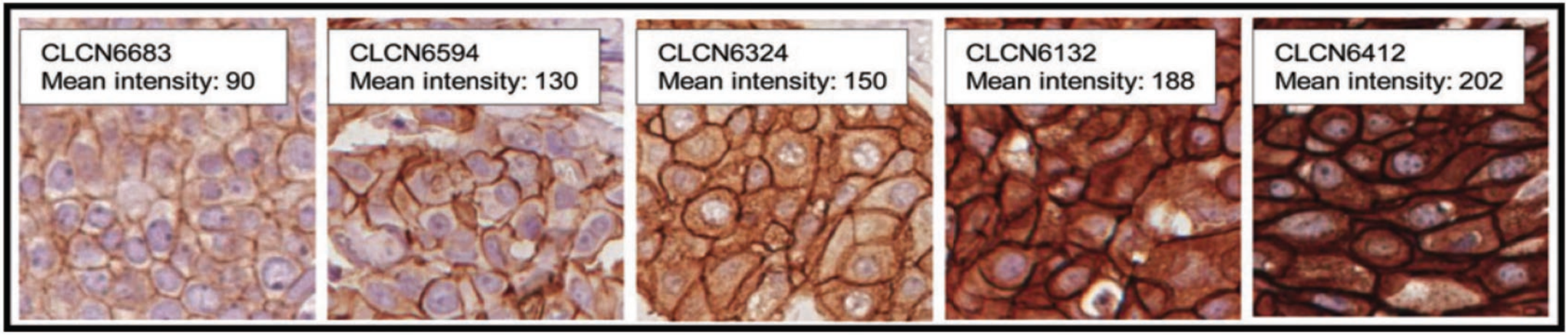
The anti-ErbB2 antibody trastuzumab has shown significant clinical benefits in metastatic breast cancer. However, resistance to trastuzumab is common. Heterodimerization between ErbB2 and other ErbBs may redundantly trigger cell proliferation signals and confer trastuzumab resistance. Here, we developed a bispecific anti-ErbB2 antibody using trastuzumab and pertuzumab, another ErbB2-specific humanized antibody that binds to a distinct epitope from trastuzumab. This bispecific antibody, denoted as TP_L, retained the full binding activities of both parental antibodies and exhibited pharmacokinetic properties similar to those of a conventional immunoglobulin G molecule. Unexpectedly, TP_L showed superior ErbB2 heterodimerization-blocking activity over the combination of both parental monoclonal antibodies, possibly through steric hindrance and/or inducing ErbB2 conformational change. Further data indicated that TP_L potently abrogated ErbB2 signaling in trastuzumab-resistant breast cancer cell lines. In addition, we showed that TP_L was far more effective than trastuzumab plus pertuzumab in inhibiting the growth of trastuzumab-resistant breast cancer cell lines, both *in vitro* and *in vivo*. Importantly, TP_L treatment eradicated established trastuzumab-resistant tumors in tumor-bearing nude mice. Our results suggest that trastuzumab-resistant breast tumors remain dependent on ErbB2 signaling and that comprehensive blockade of ErbB2 heterodimerization may be an effective therapeutic avenue. The unique potential of TP_L to overcome trastuzumab resistance warrants its consideration as a promising treatment in the clinic. *Cancer Res; 73(21); 6471–83. ©2013 AACR.*



Anticorps ciblant HER2 : encore plus de sophistication

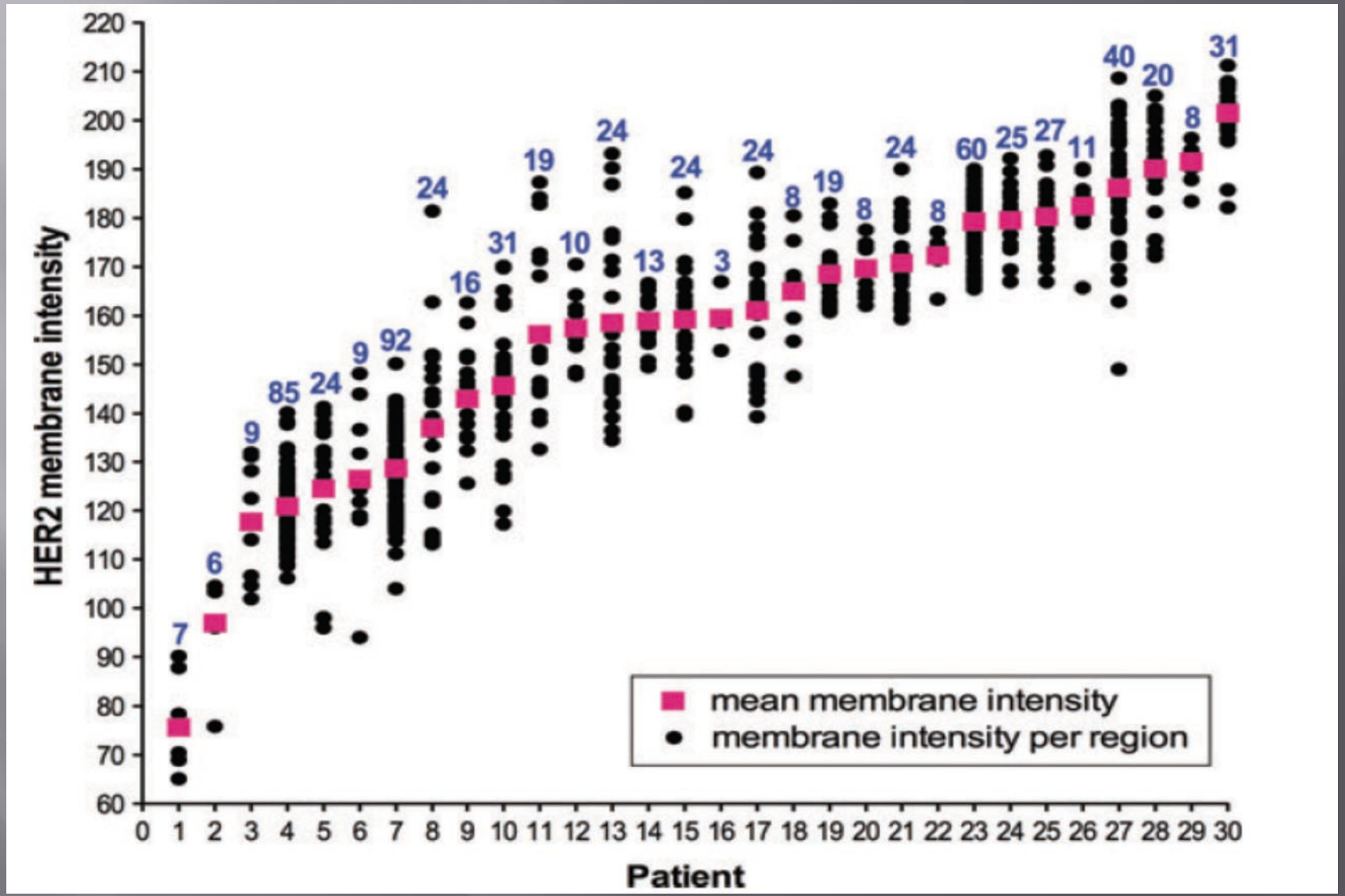
Difficulté centrale : variabilité intratumorale

Intensité du marquage HER2 (essai HERA)



(Zabaglo L. et al, Ann Oncol 2013)

Variabilité marquage HER2 intra-tumoral (HERA, n=30)



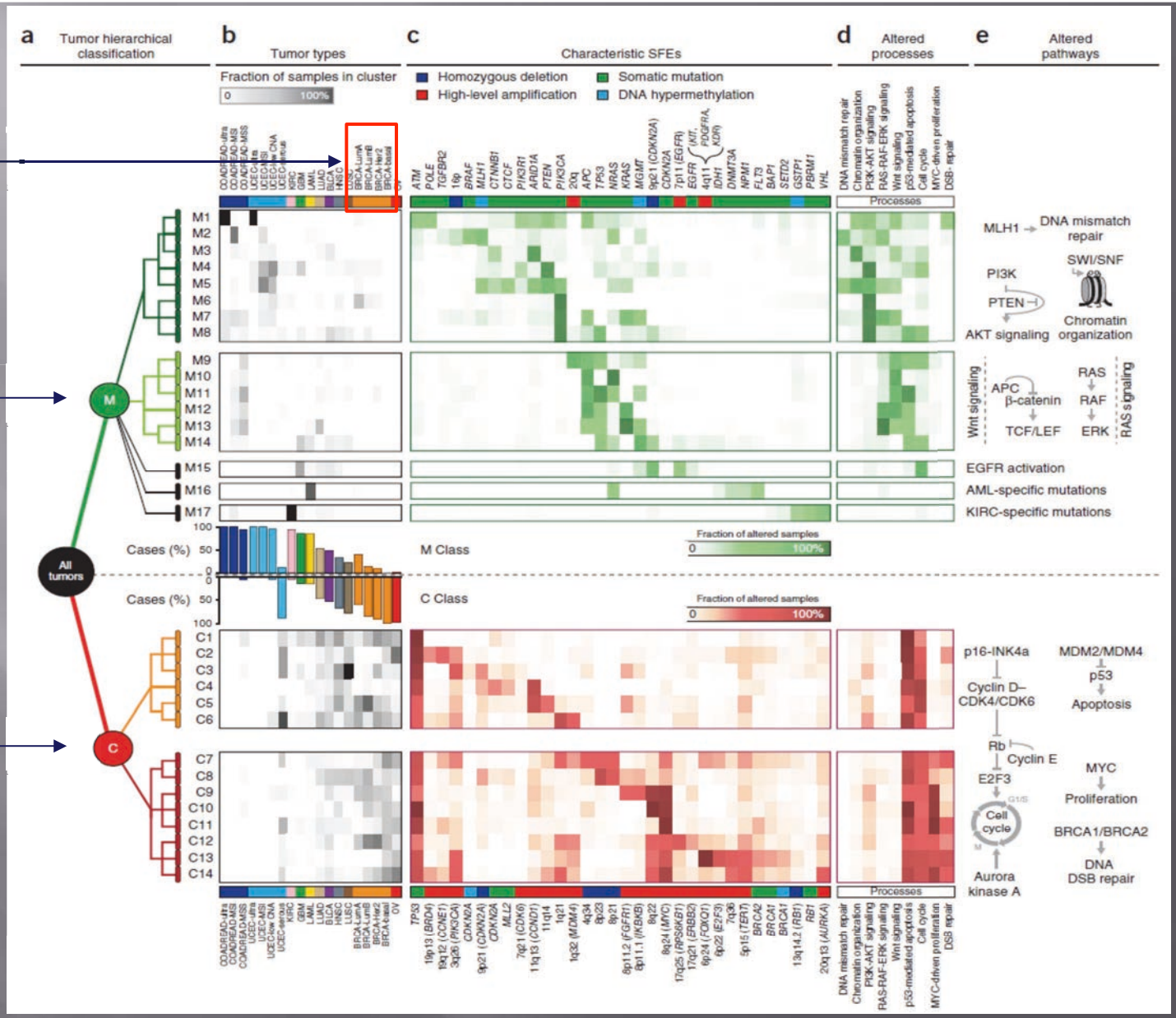
(Zabaglo L. et al, Ann Oncol 2013)

Classes de signatures oncogéniques : une variabilité génétique somatique

Cancers du sein

Mutations

Nombre de copies



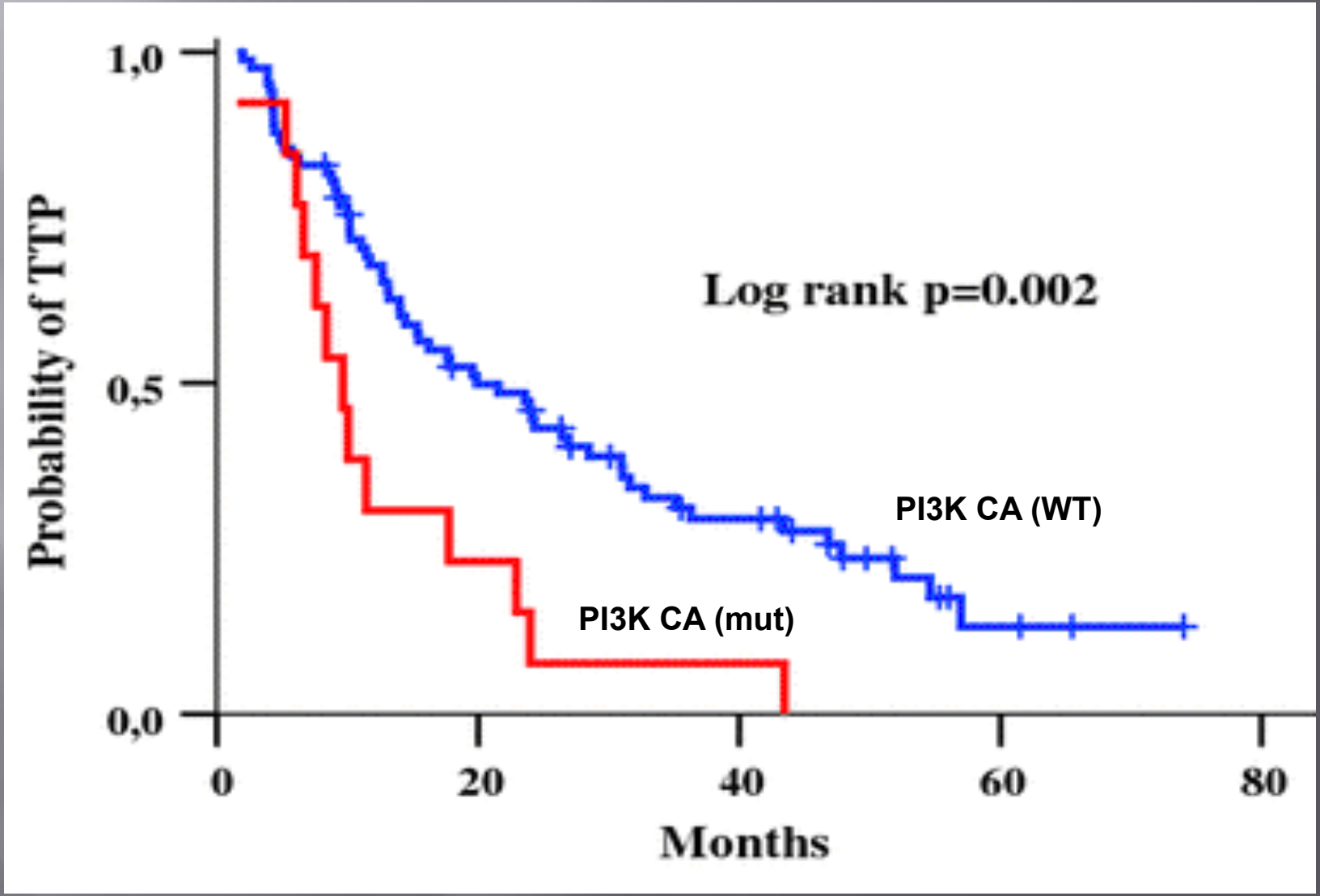
(Ciriello G. et al, Nature Gen. 2013)

Mutations PI3K CA, PTEN et cancer du sein (547 cancers et 41 lignées cellulaires)

Tumor subtype	Mutation				
	PIK3CA catalytic domain*	*PIK3CA* other†	*PIK3CA* total	*PTEN*‡	*AKT1* E17K
All human breast tumors	73/547 (13.3%)	44/547 (8.0%)	117/547 (21.4%)	2/88 (2.3%)	6/418 (1.4%)
Human breast HR+§	48/232 (20.7%)	32/232 (13.8%)	80/232 (34.5%)	2/58 (3.4%)	6/232 (2.6%)
ER+PR+	39/186 (21%)	22/186 (11.8%)	61/186 (32.8%)	1/48 (2.1%)	6/186 (3.2%)
ER+PR−	9/41 (22%)	10/41 (24.4%)	19/41 (46.3%)	1/8 (12.5%)	0/41 (0%)
ER−PR+	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/2 (0%)	0/5 (0%)
Human breast HER2+‖	13/75 (17.3%)	4/75 (5.3%)	17/75 (22.7%)	0/10 (0%)	0/75 (0%)
Human breast TN	12/240 (5.0%)	8/240 (3.3%)	20/240 (8.3%)	0/20 (0%)	0/111 (0%)
All breast cancer cell lines	7/41 (17.1%)	9/41 (22%)	16/41 (39%)	8/41 (20%)	0/41 (0%)
Breast cancer cell lines HR+	1/12 (8.3%)	3/12 (25%)	4/12 (33.3%)	5/12 (41.7%)	0/12 (0%)
Breast cancer cell lines HER2+	2/10 (20%)	4/10 (40%)	6/10 (60%)	0/10 (0%)	0/10 (0%)
Breast cancer cell lines TN¶	4/19 (21%)	2/19 (10.5%)	6/19 (31.6%)	3/19 (15.8%)	0/19 (0%)

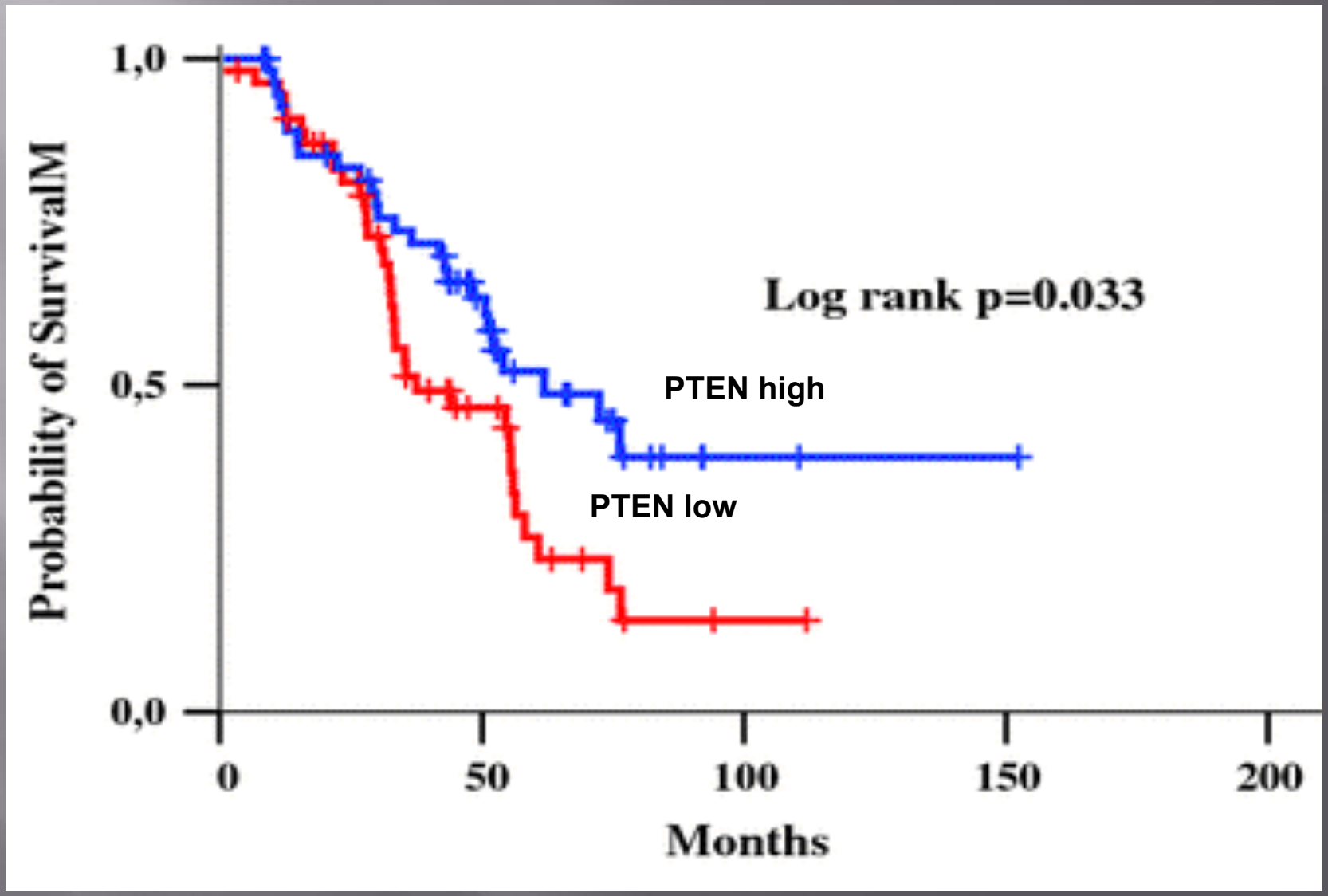
(Stemke-Hale et al., Cancer Res. 2008)

Impact défavorable mutation PI3K CA sur la survie (n = 175 cancers du sein / herceptin)



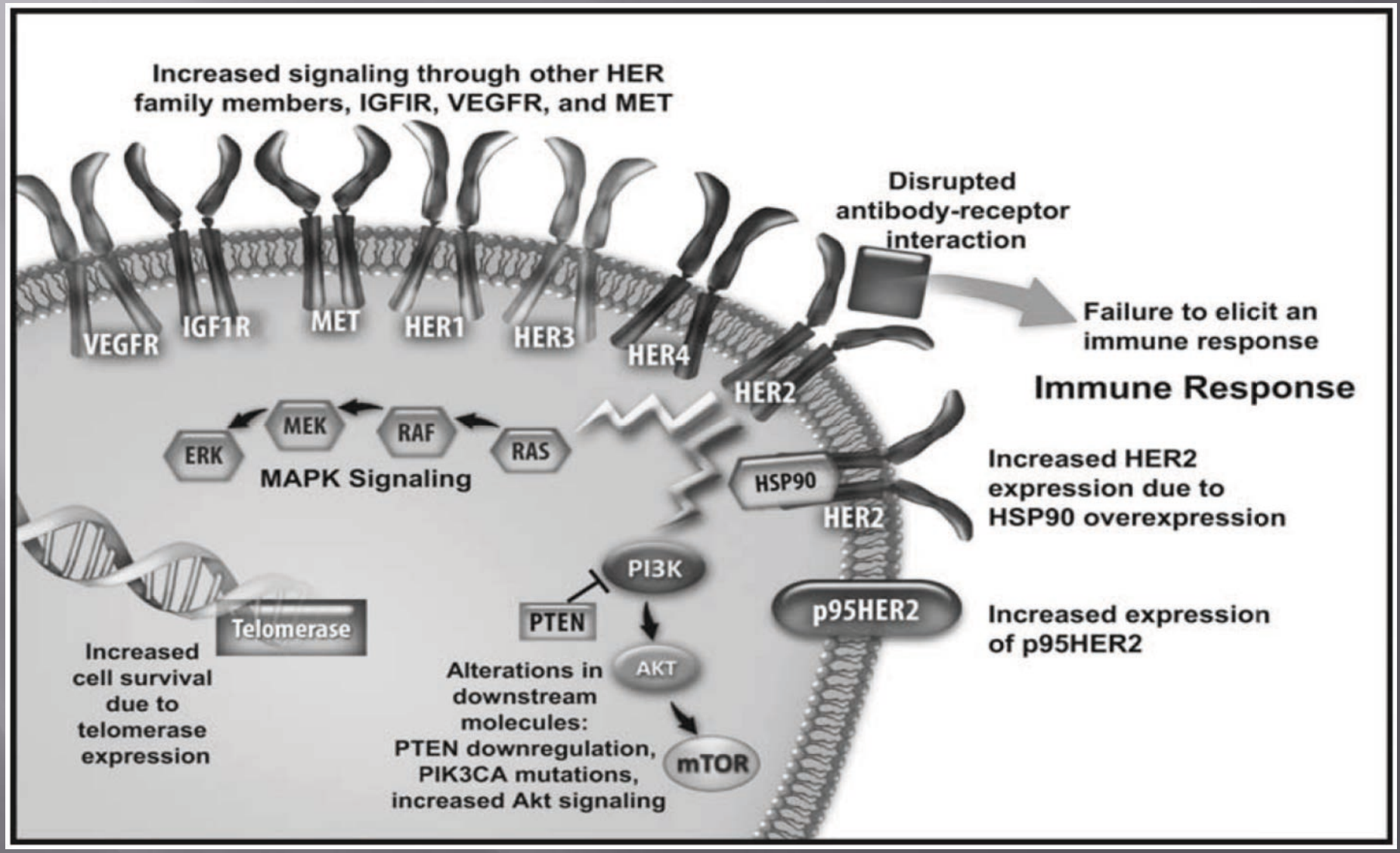
(Razis et al., Breast Cancer Res Treat. 2011)

Impact du statut PTEN sur la survie (n = 199 cancers du sein / herceptin)



(Razis et al., Breast Cancer Res Treat. 2011)

Résistance au ciblage de HER2 : un large panorama



(Mohd Sharial MSN et al., Ann Oncol 2012)

Cette nouvelle réalité biologique est génératrice d'hypothèses thérapeutiques

Clinical Cancer Research

Cancer Therapy: Preclinical

Targeting PI3K/mTOR Overcomes Resistance to HER2-Targeted Therapy Independent of Feedback Activation of AKT

Neil A. O'Brien[1], Karen McDonald[1], Luo Tong[1], Erika von Euw[1], Ondrej Kalous[1], Dylan Conklin[1], Sara A. Hurvitz[1], Emmanuelle di Tomaso[2], Christian Schnell[3], Ronald Linnartz[2], Richard S. Finn[1], Samit Hirawat[2], and Dennis J. Slamon[1]

Abstract

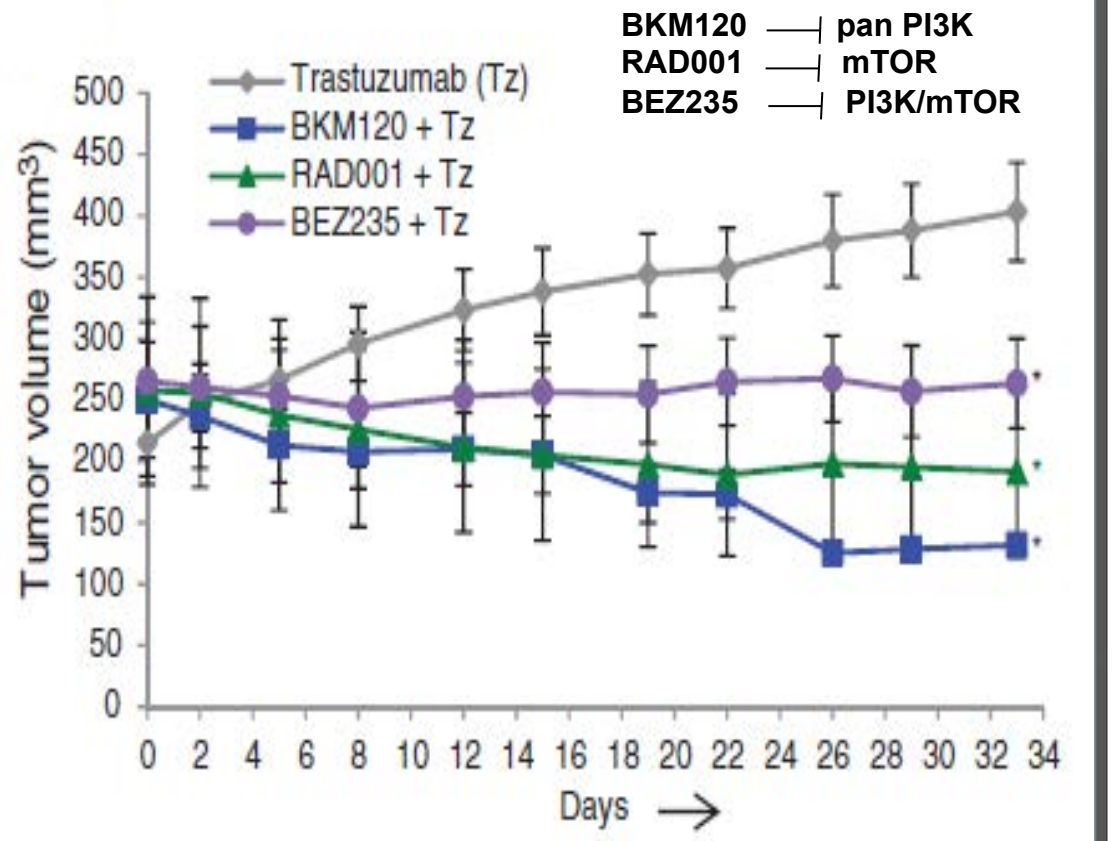
Purpose: Altered PI3K/mTOR signaling is implicated in the pathogenesis of a number of breast cancers, including those resistant to hormonal and HER2-targeted therapies.

Experimental Design: The activity of four classes of PI3K/mTOR inhibitory molecules, including a pan-PI3K inhibitor (NVP-BKM120), a p110α isoform–specific PI3K inhibitor (NVP-BYL719), an mTORC1-specific inhibitor (NVP-RAD001), and a dual PI3K/mTORC1/2 inhibitor (NVP-BEZ235), was evaluated both *in vitro* and *in vivo* against a panel of 48 human breast cell lines.

Results: Each agent showed significant antiproliferative activity *in vitro*, particularly in luminal estrogen receptor–positive and/or HER2$^+$ cell lines harboring PI3K mutations. In addition, monotherapy with each of the four inhibitors led to significant inhibition of *in vivo* growth in HER2$^+$ breast cancer models. The PI3K/mTOR pathway inhibitors were also effective in overcoming both *de novo* and acquired trastuzumab resistance *in vitro* and *in vivo*. Furthermore, combined targeting of HER2 and PI3K/mTOR leads to increased apoptosis *in vitro* and induction of tumor regression in trastuzumab-resistant xenograft models. Finally, as previously shown, targeting mTORC1 alone with RAD001 leads to consistent feedback activation of AKT both *in vitro* and *in vivo*, whereas the dual mTOR1–2/PI3K inhibitor BEZ235 eliminates this feedback loop. However, despite these important signaling differences, both molecules are equally effective in inhibiting tumor cell proliferation both *in vitro* and *in vivo*.

Conclusion: These preclinical data support the findings of the BOLERO 3 trial that shows that targeting of the PI3K/mTOR pathway in combination with trastuzumab is beneficial in trastuzumab-resistant breast cancer. *Clin Cancer Res; 20(13); 3507–20. ©2014 AACR.*

Sum 190 HER2+, résistance acquise Trastuzumab



(O'Brien NA et al., Clin Cancer Res 2014)

Comment cette nouvelle réalité biologique se confronte-t-elle à l'innovation thérapeutique ?

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

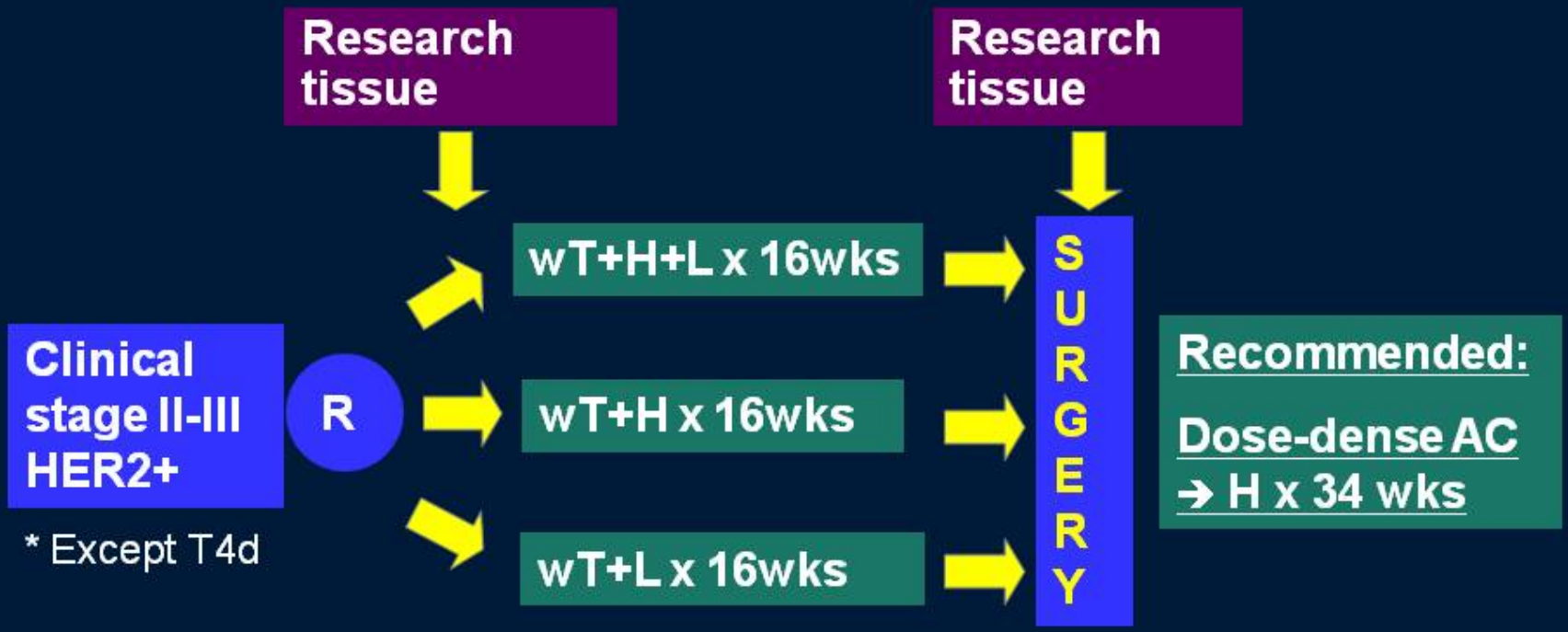
CALGB 40601: Phase III Trial of Lapatinib Added to Neoadjuvant Therapy of HER2+ Breast Cancer

Carey LA, Berry DA, Cirrincione C, Harris L, Ollila DW, Krop I, Henry NL, Weckstein D, Anders CK, Perou CM, Winer EP, Hudis CA

on behalf of the ALLIANCE

(Presented By Lisa A. Carey, MD at 2013 ASCO Annual Meeting)

C40601: Schema



*wT= weekly paclitaxel, H=trastuzumab, L=lapatinib

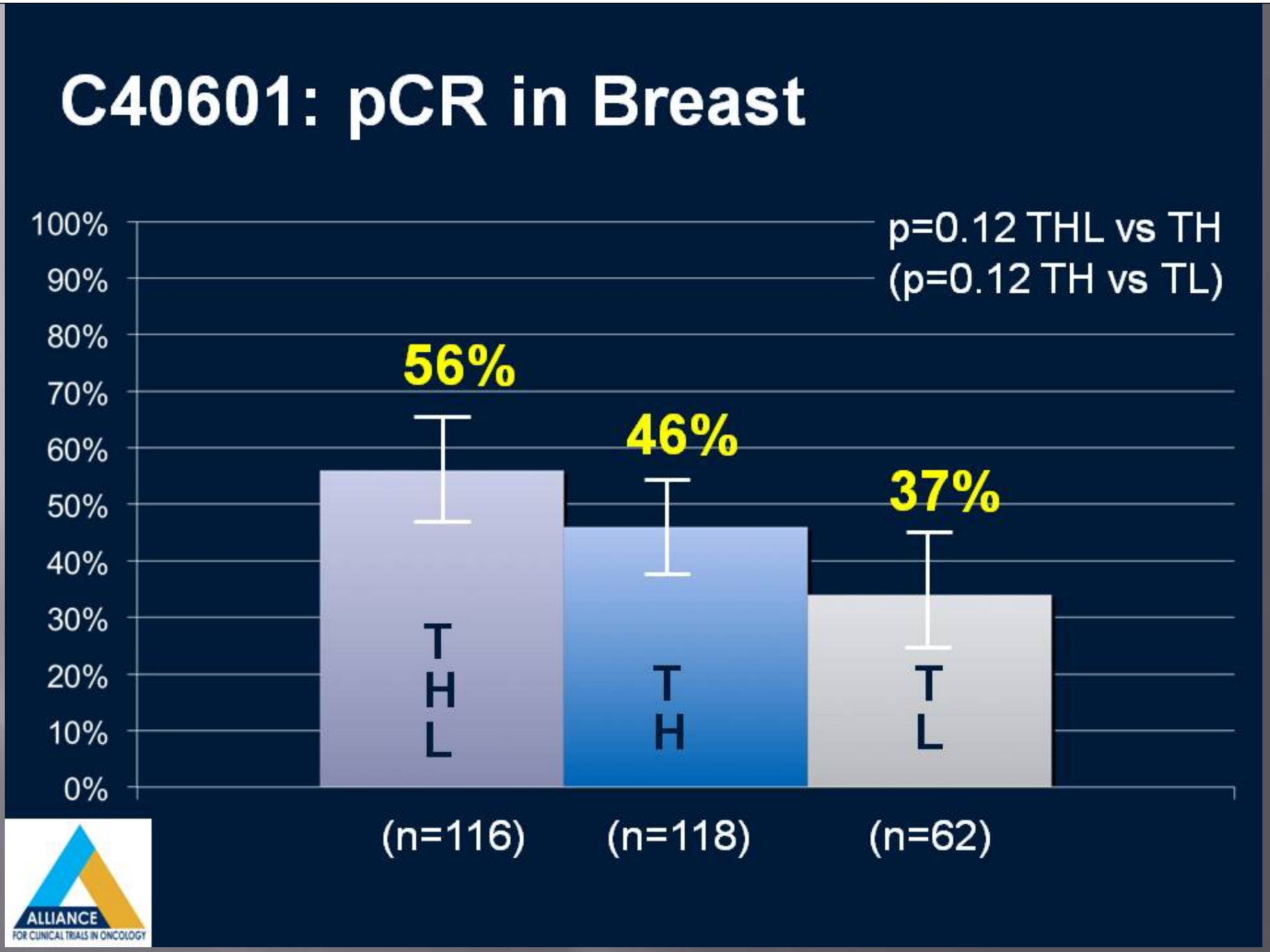
Primary endpoint: pCR breast (*ASCO 2013*)

Secondary endpoints:

- Clinical: pCR breast + axilla*, Toxicity*, RFS, OS
- Correlative science (*)

(Presented By Lisa A. Carey, MD at 2013 ASCO Annual Meeting)

C40601: pCR in Breast

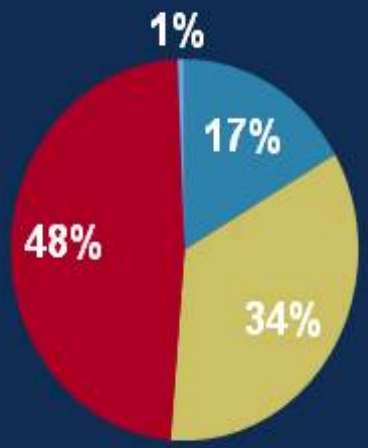


ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

(Presented By Lisa A. Carey, MD at 2013 ASCO Annual Meeting)

Pretreatment Subtype by Hormone Receptor Status

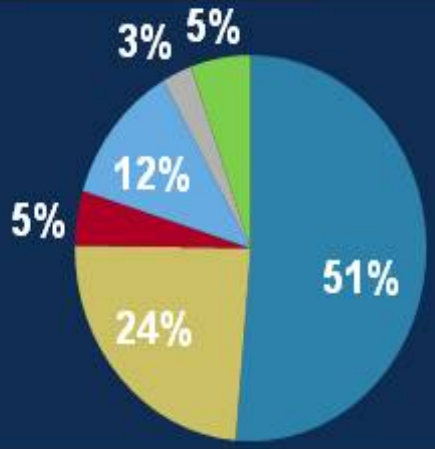
Hormone Receptor + (n=156)



- HER2-E (n=26)
- LumA (n=54)
- LumB (n=75)
- Basal-like (n=1)
- Claudin-low (n=0)
- Normal-like (n=0)

P<0.0001

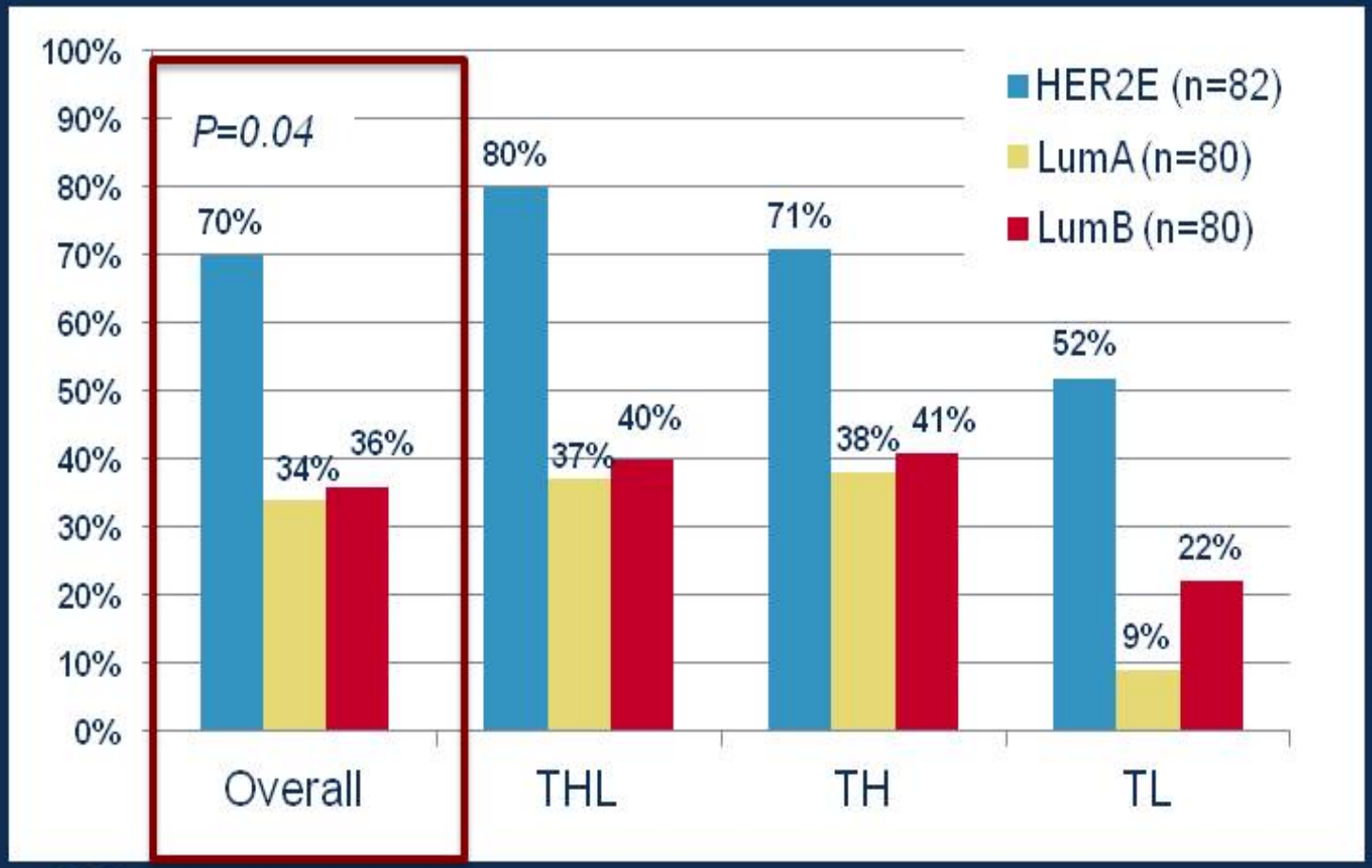
Hormone Receptor – (n=109)



- HER2-E (n=56)
- LumA (n=26)
- LumB (n=5)
- Basal-like (n=13)
- Claudin-low (n=3)
- Normal-like (n=6)

ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

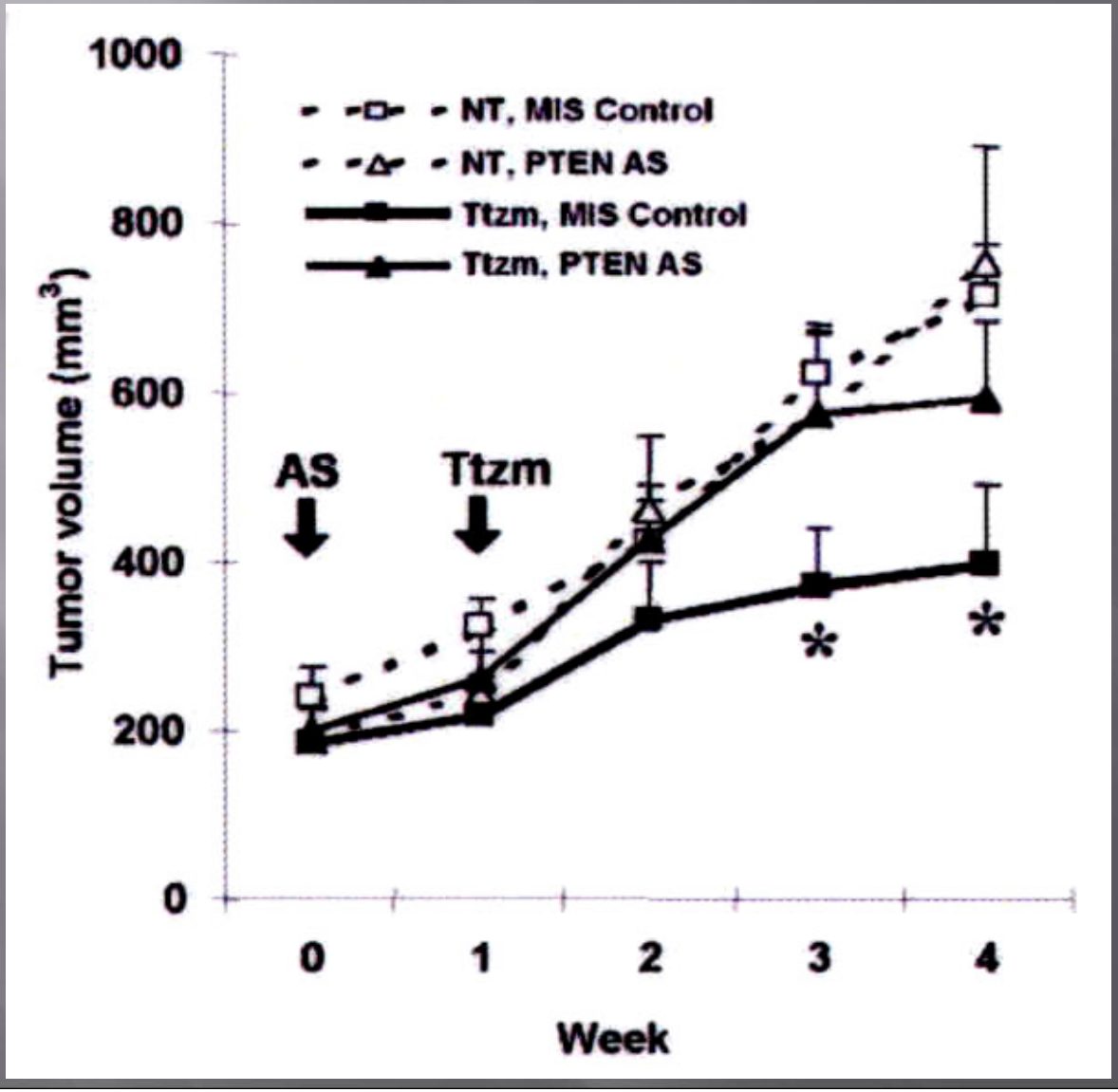
pCR by Intrinsic Subtype (All Arms, n=265)



Other subtypes:
3 Claudin-low (0 pCR)
14 basal-like (36% pCR)
Excluded "normal" (n=6)

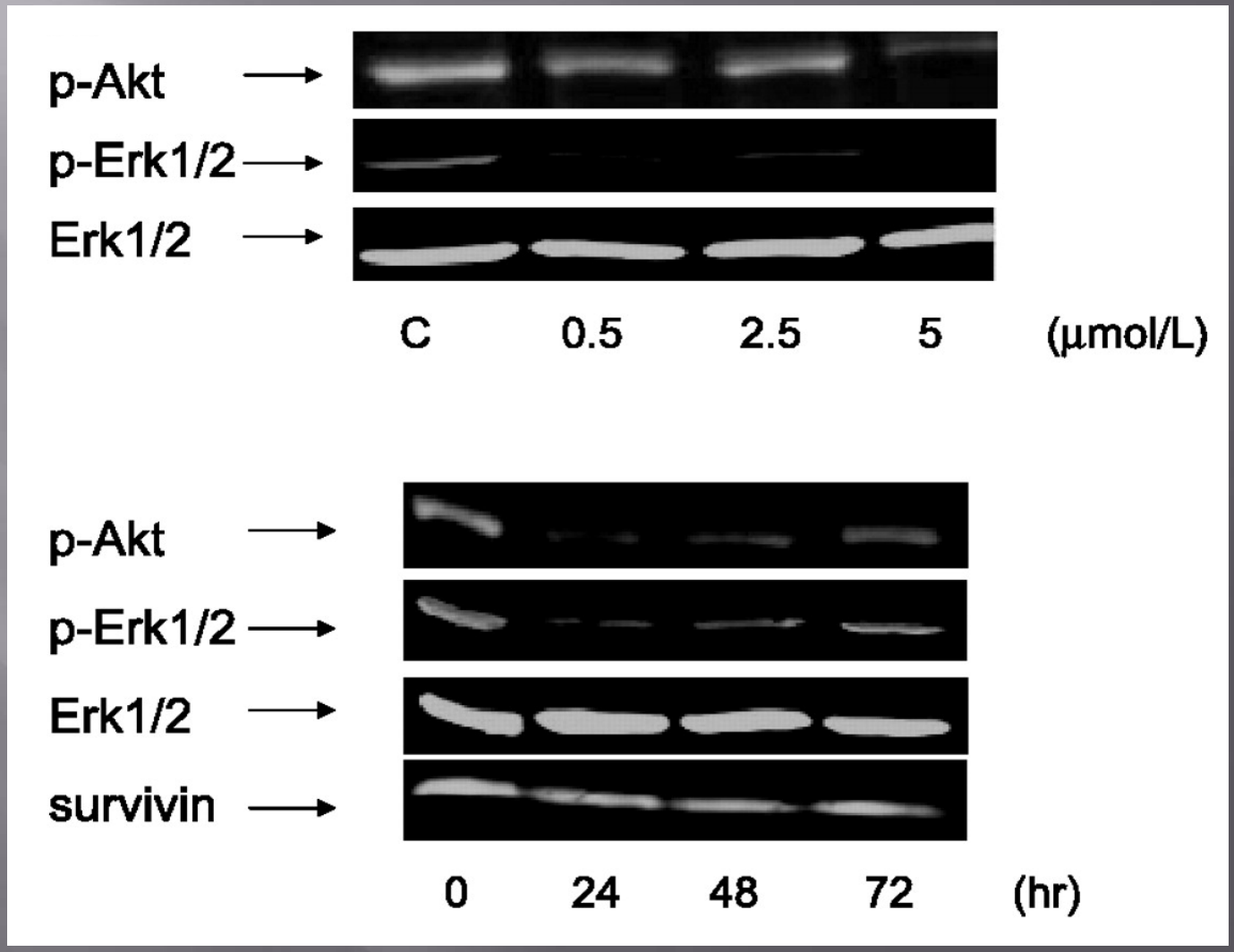
Résistance au trastuzumab et PTEN

Un modèle de xénogreffe BT474 déficient en PTEN et résistant au trastuzumab



(Nagata et al., 2004)

Le lapatinib inhibe pAKT dans un modèle PTEN-null MDA-MB-468



(Xia et al., 2007)

Réponse au lapatinib et statut tumoral PTEN : pas d'impact significatif

PTEN expression*	Clinical response (n = 15)	Progressive disease (n = 23)
0/1+	11 (73%)	18 (78%)
2/3+	4 (27%)	5 (22%)

NOTE: χ^2 (1, N = 38) = 0.122, P = 0.73.
*Immunohistochemistry.

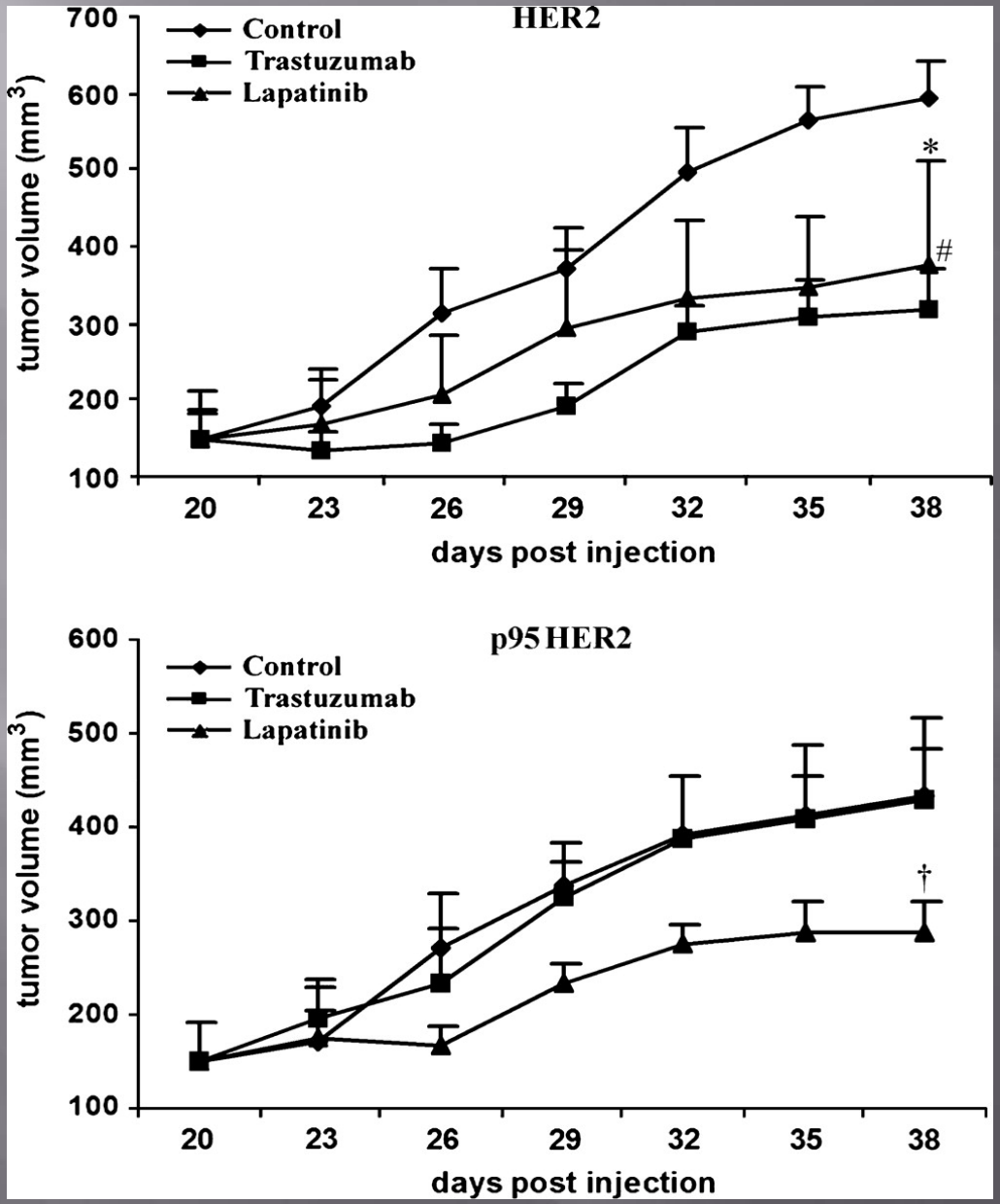
(Xia et al., 2007)

Ciblage HER2 et p95HER2

p95HER2 (*Molina et al., 2002*) :

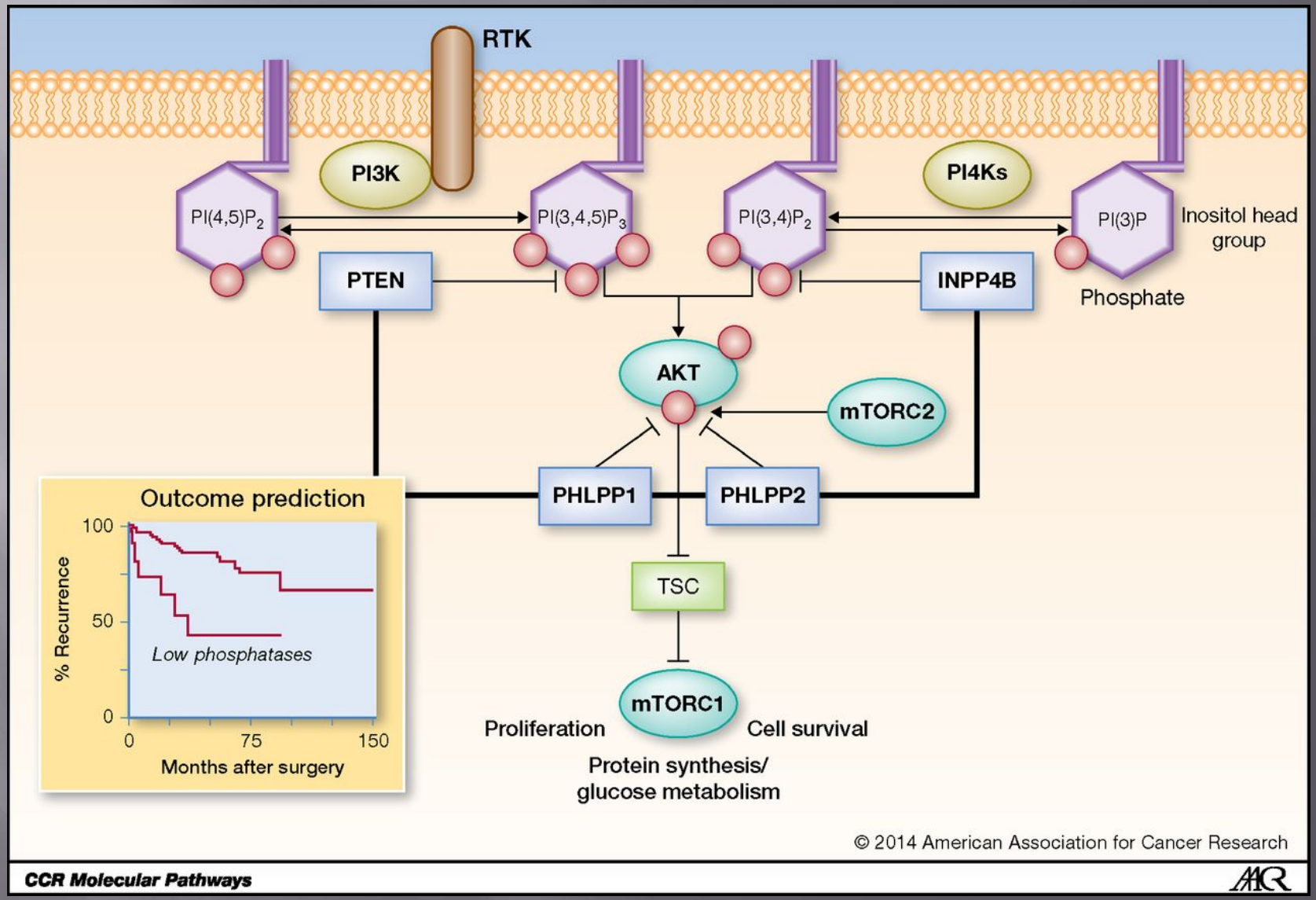
- **forme tronquée HER2/domaine extracellulaire**
- **coupure par metalloproteinase**
- **21 % dans $N^{\ominus}$ et 30-37% $N^{\oplus}$**
- **pas de lien avec l'âge, stade, type histologique, statut hormonal**

Effets différentiels des traitements anti-HER2



(Scaltriti et al., 2007)

Phosphatases : il n'y a pas que PTEN dans la voie PI3K !



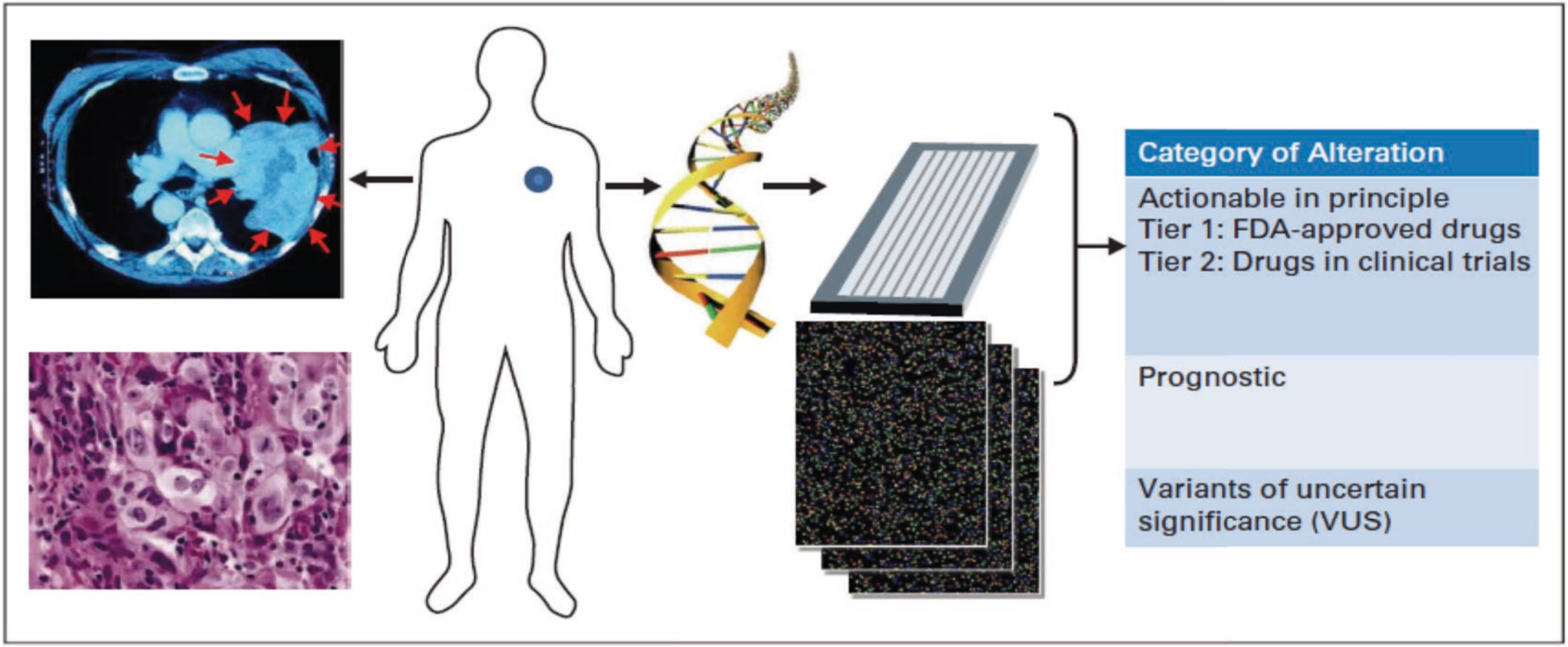
(Chen M et al., Clin Cancer Res 2014)

Impacts potentiels de la prise en compte des phosphatases ciblage voie PI3K

Kinase target(s)	Antagonistic phosphatase	Drug	Trial phase	Cancer	Trial ID
Protein kinase inhibitors					
AKT		GSK2110183	Phase II	Solid tumors, hematologic malignancies	NCT01531894
AKT		MK2206	Phase II	Relapsed or refractory acute myeloid leukemia	NCT01253447
mTORC1		Everolimus	Phase II	Melanoma	NCT01960829
mTORC1		Sirolimus	Phase II	Hepatocellular carcinoma	NCT01374750
mTORC1		Temsirolimus	Phase I/II	Advanced cancers	NCT00877773
mTORC1/2		INK128	Phase I	Advanced nonhematologic malignancies	NCT01899053
mTORC1/2	PHLPP1/2	OSI-027	Phase I	Solid tumor, lymphoma	NCT00698253
mTORC1/2		AZD8055	Phase I	Glioblastoma multiforme, other brain tumors	NCT01316809
Lipid kinase inhibitors					
PI3K		BAY80-6946	Phase II	Non-Hodgkin lymphoma	NCT01660451
PI3K		BKM120	Phase III	Metastatic breast cancer HR^+, $HER2^-$	NCT01633060
PI3K	PTEN	CAL101	Phase III	Chronic lymphocytic leukemia	NCT01659021
PI3K		GDC0941	Phase II	Non–small cell lung cancer	NCT01493843
PI3K		IPI145	Phase II	Indolent non-Hodgkin lymphoma	NCT01882803
PI3K		XL147	Phase I/II	Breast cancer, breast neoplasms	NCT01042925
Dual specificity inhibitors					
PI3K mTORC1/2		BEZ235	Phase II	Pancreatic neuroendocrine tumors (pNET)	NCT01628913
PI3K mTORC1/2	PTEN	BGT226	Phase I/II	Advanced breast cancer	NCT00600275
PI3K mTORC1/2		PF04691502	Phase II	Endometrial neoplasms	NCT01420081
PI3K mTORC1/2	PHLPP1/2	PF05212384	Phase II	Metastatic colorectal cancer	NCT01925274
PI3K mTORC1/2		XL765	Phase I	Glioblastoma, astrocytoma	NCT01240460

(Chen M et al., Clin Cancer Res 2014)

Traitement guidé par la génomique : on en parle beaucoup (trop ?)…



(Garraway LA et al, JCO 2013)

La génomique est un maillon supplémentaire dans la chaîne des marqueurs prédictifs/pronostiques

Clinical Cancer Research

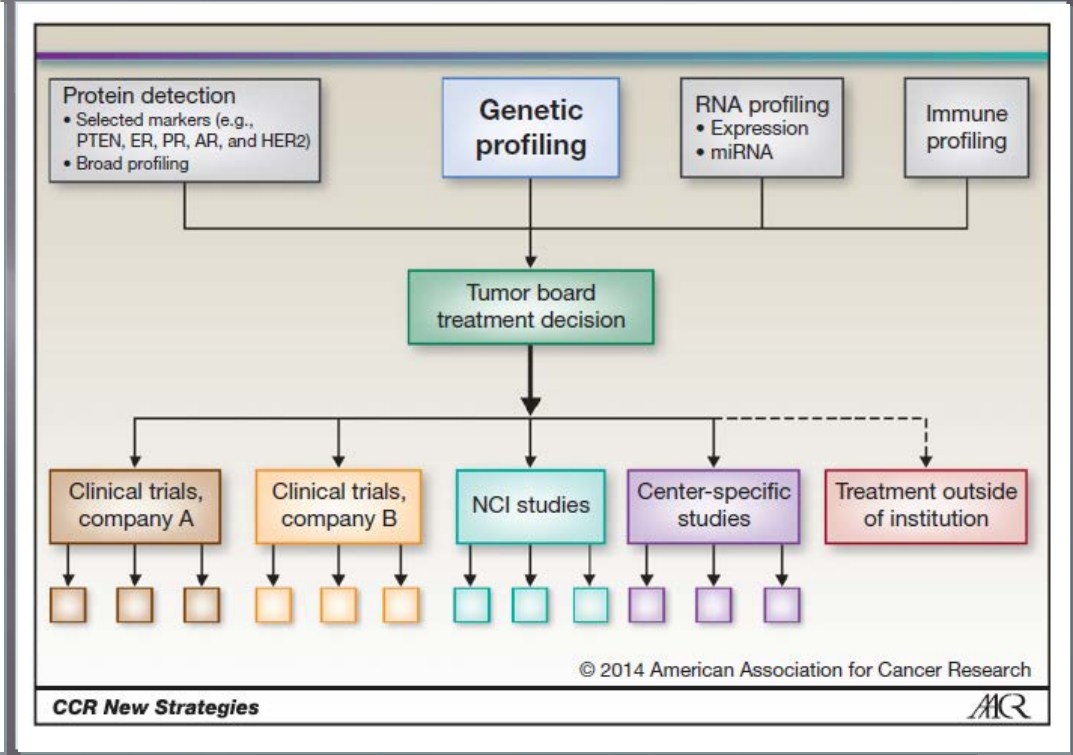
CCR New Strategies

New Strategies in Personalized Medicine for Solid Tumors: Molecular Markers and Clinical Trial Designs

Juliane M. Jürgensmeier, Joseph P. Eder, and Roy S. Herbst

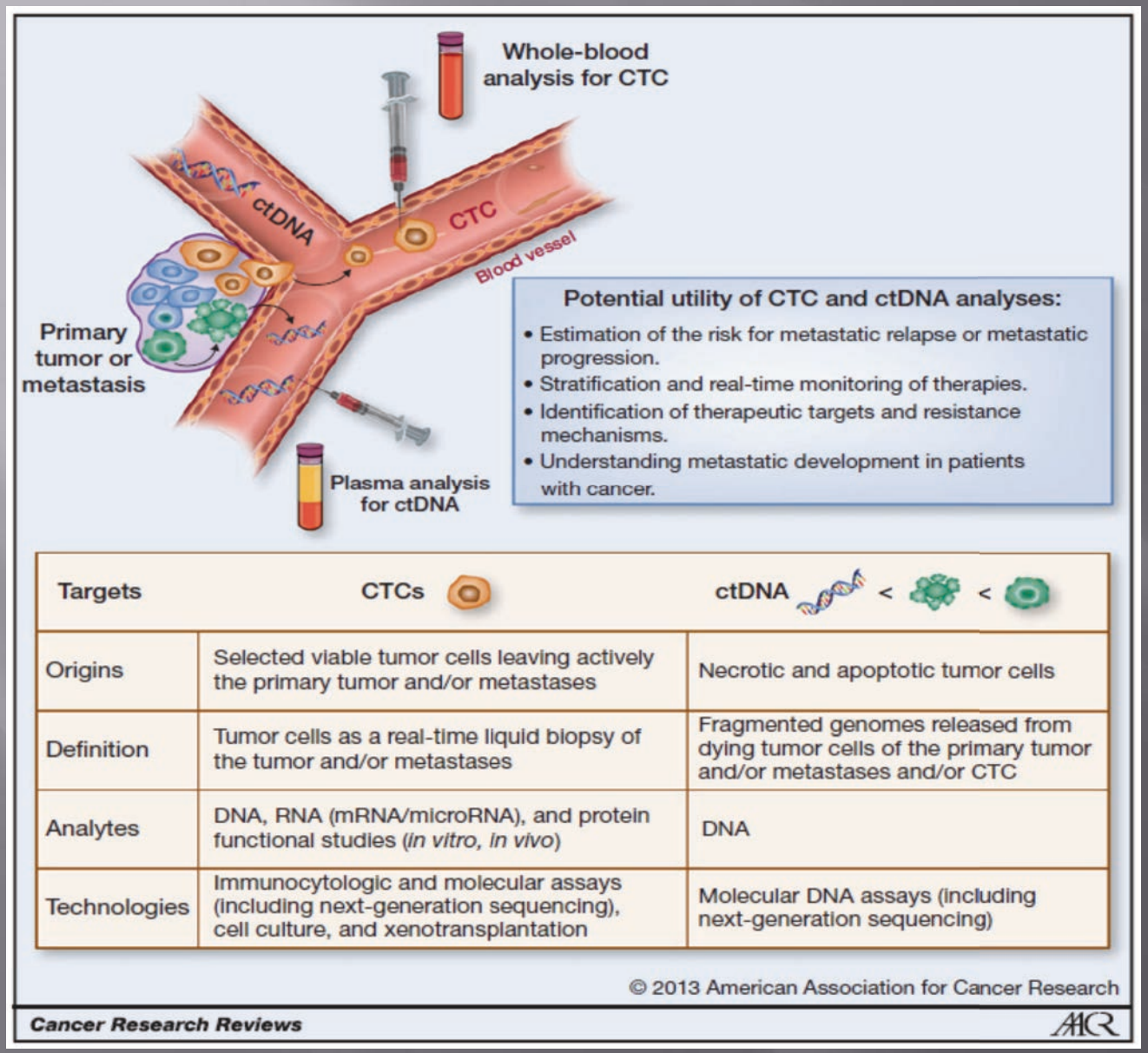
Abstract

The delineation of signaling pathways to understand tumor biology combined with the rapid development of technologies that allow broad molecular profiling and data analysis has led to a new era of personalized medicine in oncology. Many academic institutions now routinely profile patients and discuss their cases in meetings of personalized medicine tumor boards before making treatment recommendations. Clinical trials initiated by pharmaceutical companies often require specific markers for enrollment or at least explore multiple options for future markers. In addition to the still small number of targeted agents that are approved for the therapy of patients with histological and molecularly defined tumors, a broad range of novel targeted agents in development are undergoing clinical studies with companion profiling to determine the best-responding patient population. Although the present focus of profiling lies in genetic analyses, additional tests of RNA, protein, and immune parameters are being developed and incorporated in clinical research, and these methods are likely to contribute significantly to future patient selection and treatment approaches. As the advances in tumor biology and human genetics have identified promising tumor targets, the ongoing clinical evaluation of novel agents will now need to show if the promise can be translated into benefit for patients. *Clin Cancer Res; 20(17); 4425–35. ©2014 AACR.*



(Jürgensmeier JM et al., Clin Cancer Res 2014)

L'apport des biopsies liquides : une ouverture technologique à ne pas négliger

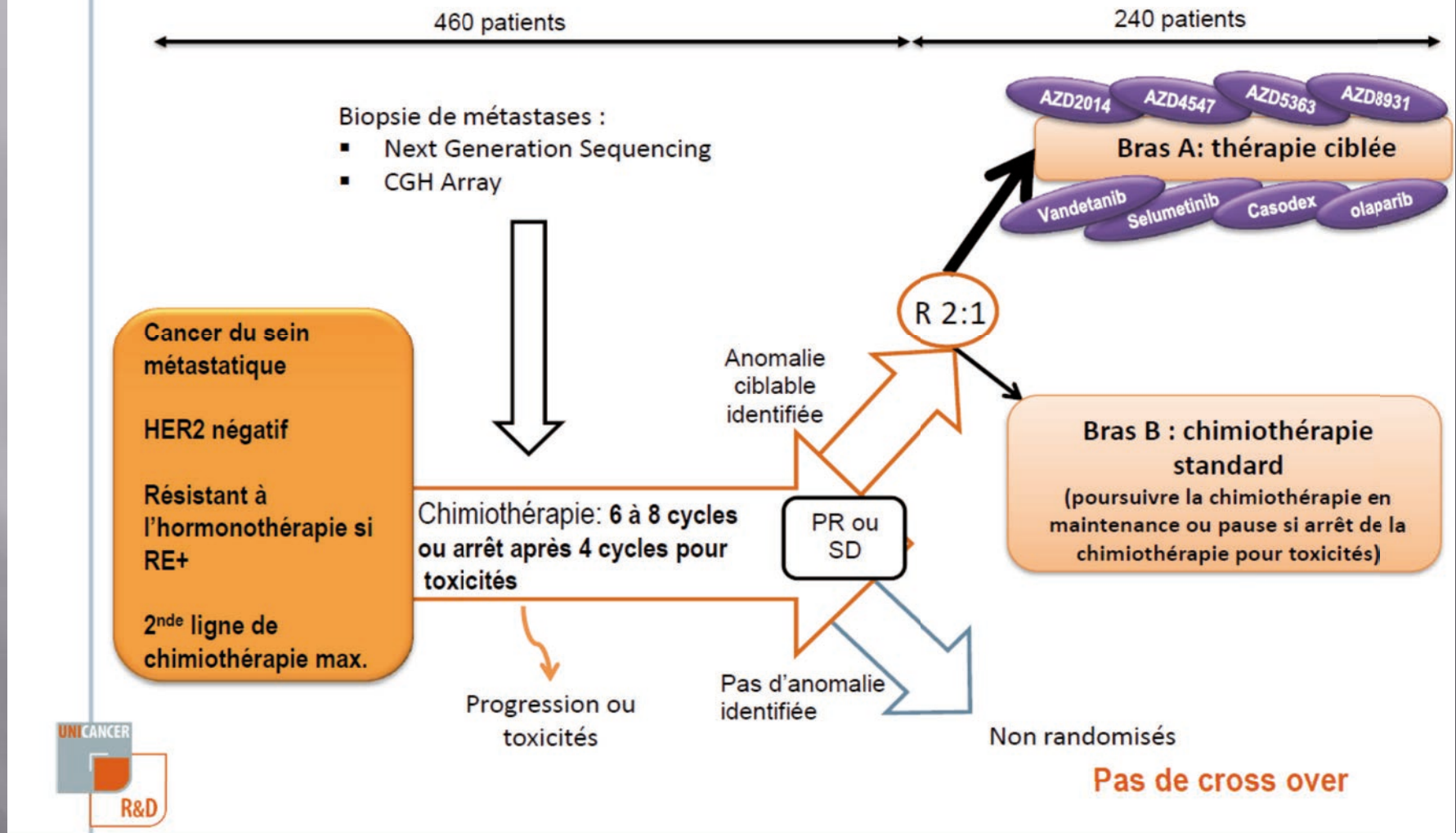


Targets	CTCs	ctDNA < <
Origins	Selected viable tumor cells leaving actively the primary tumor and/or metastases	Necrotic and apoptotic tumor cells
Definition	Tumor cells as a real-time liquid biopsy of the tumor and/or metastases	Fragmented genomes released from dying tumor cells of the primary tumor and/or metastases and/or CTC
Analytes	DNA, RNA (mRNA/microRNA), and protein functional studies (*in vitro, in vivo*)	DNA
Technologies	Immunocytologic and molecular assays (including next-generation sequencing), cell culture, and xenotransplantation	Molecular DNA assays (including next-generation sequencing)

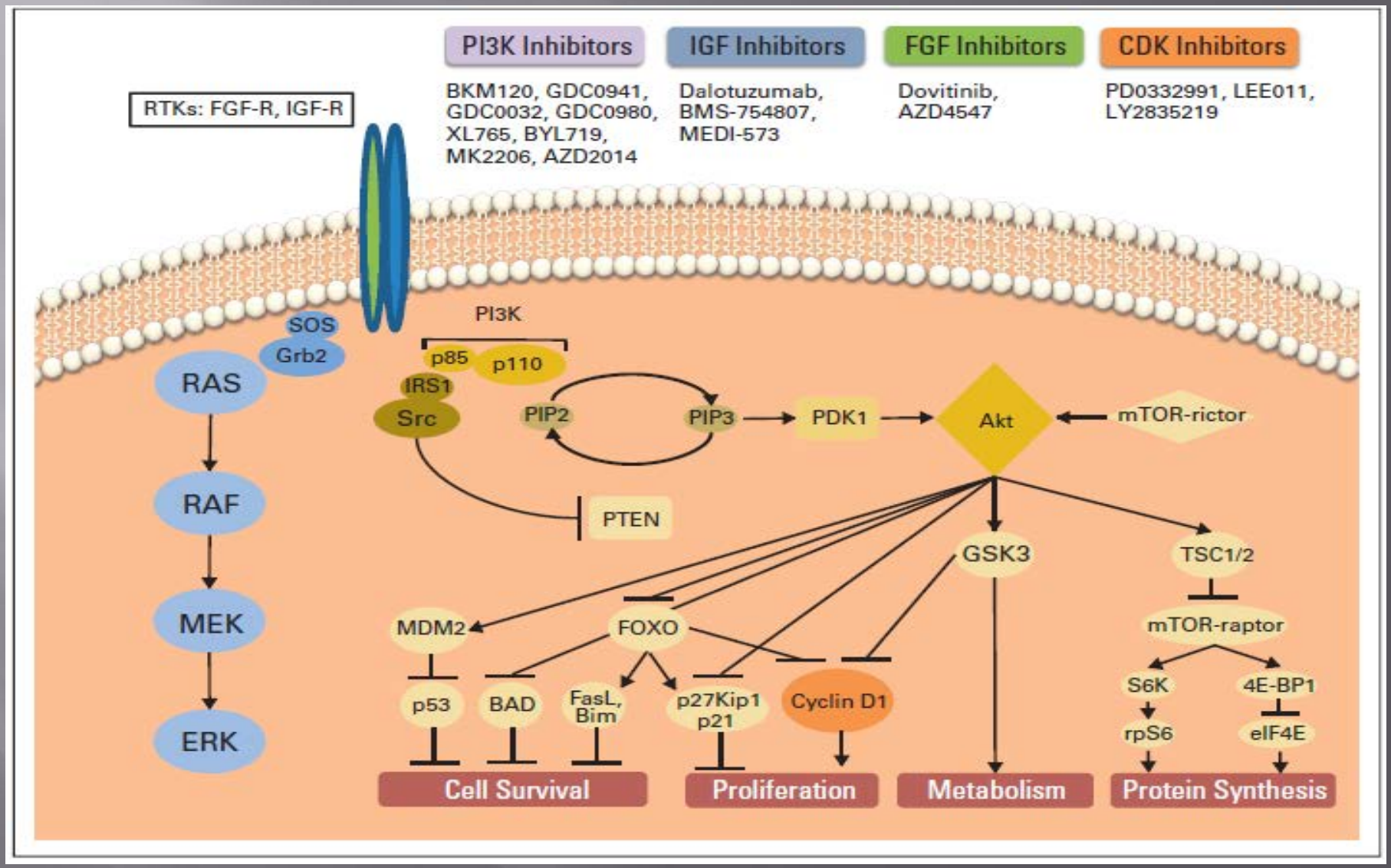
Cancer Research Reviews AACR

(Pantel K. and Panabières C.A., Cancer Res 2013)

DESIGN DE L'ETUDE : SAPHIR 2

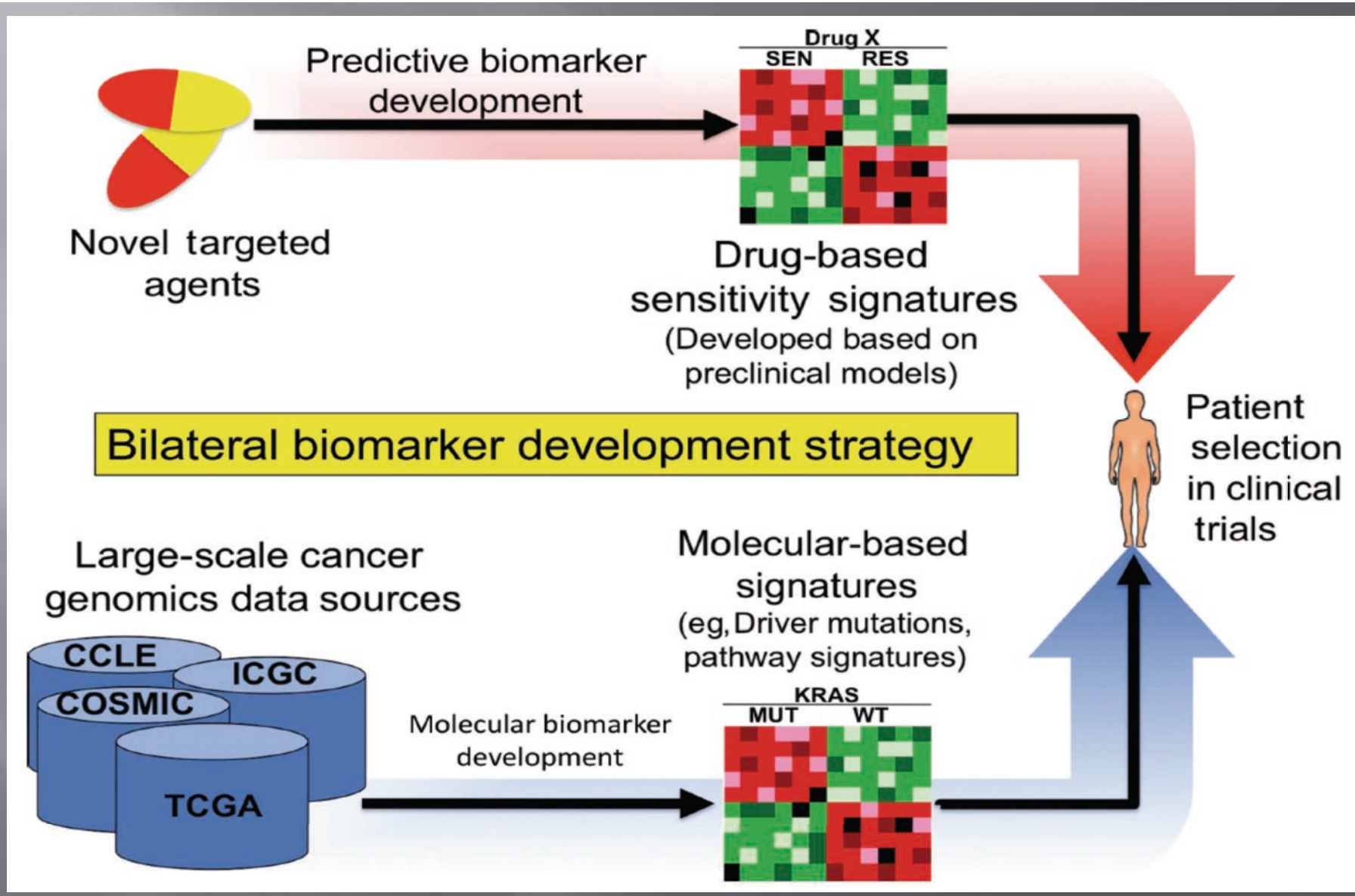


Stratégie optimale :
prise en compte des anomalies génétiques et thérapeutique adaptée



(Ades F et al; JCO 2014)

Stratégie optimale : la synthèse des approches (moléculaire + signatures d'expression)



(Lieu CH et al., JNCI 2013)

Conclusions

1- Une révolution conceptuelle, technologique et économique se met progressivement en place dans la prise en charge du cancer.

2- Le cancer du sein est au cœur de ce changement et le blocage des récepteurs HER2 en est un exemple significatif.

3- Il est impératif de tenir compte des caractéristiques tumorales moléculaires dans l'élaboration des ET quelque soit le type de prise en charge thérapeutique (néoadjuvant, métastatique, adjuvant) et plus largement au-delà des essais « preuve du concept ».

Hôpitaux Universitaires
SAINT-LOUIS
LARIBOISIÈRE
FERNAND-WIDAL

Evolution de la stratégie thérapeutique des cancers du sein métastatique HER2+++

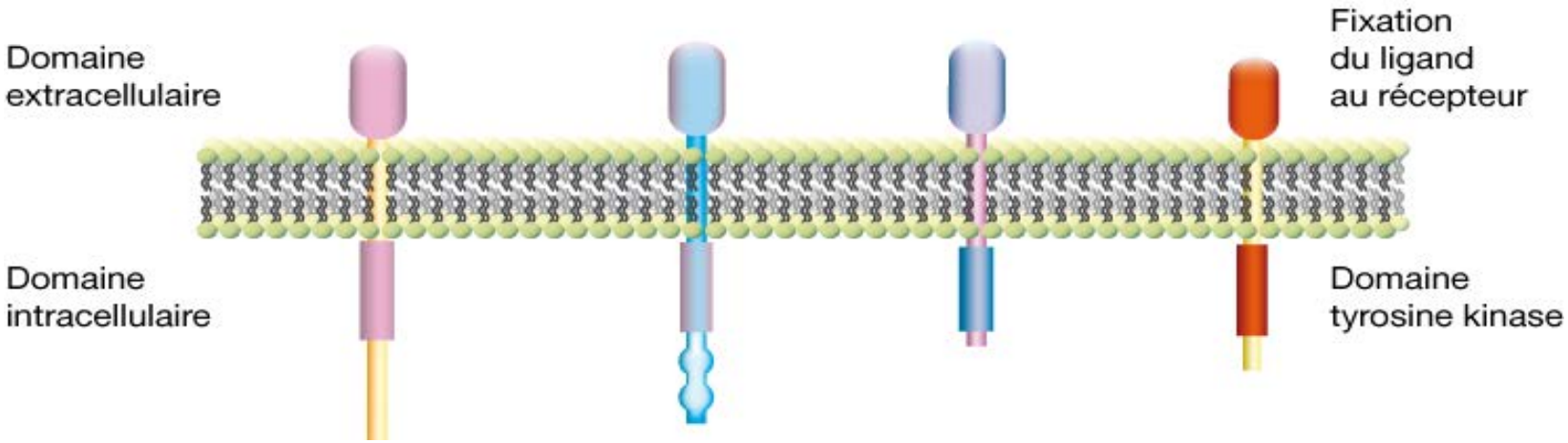
Sylvie Giacchetti

Centre des maladies du sein

hôpital Saint-Louis

Famille des récepteurs HER composé de 4 récepteurs transmembranaires à activité tyrosine kinase

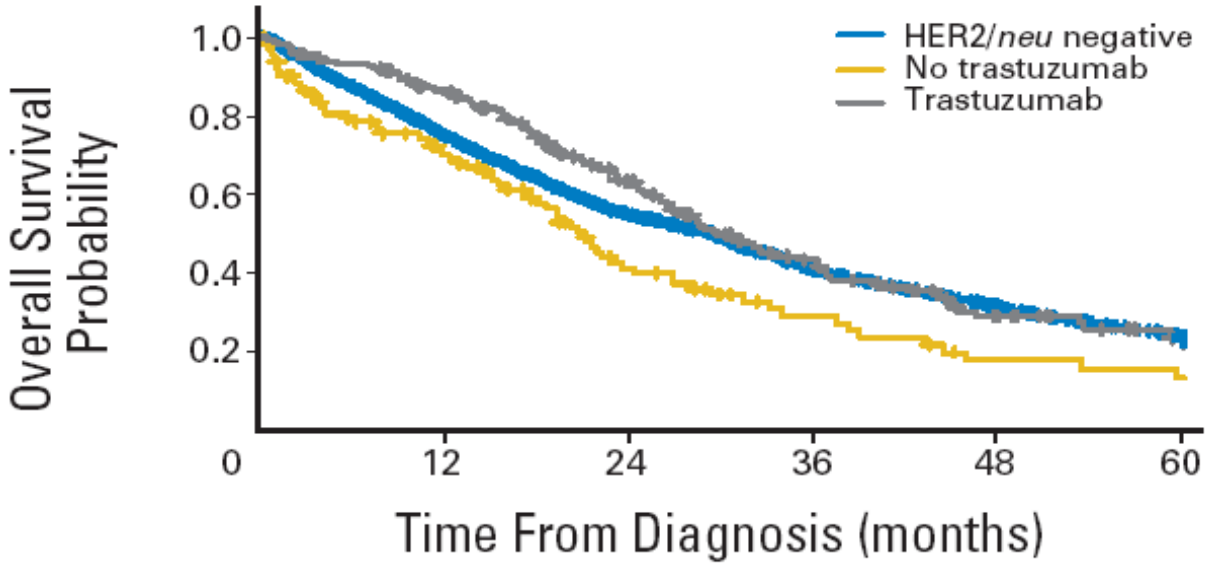
Récepteurs	ErbB-1 (EGFR) HER1	ErbB-2 HER2/*neu*	ErbB-3 HER3	ErbB-4 HER4
Ligands	EGF TGF-α Amphiréguline HB EGF Bétacelluline Épiréguline		Héréguline (Neuréguline)	Héréguline HB EGF Bétacelluline Épiréguline



- Les récepteurs sont activés après interaction avec des ligands, les facteurs de croissance ayant un degré variable de spécificité
- HER2 n'a pas de ligand spécifique mais joue le rôle d'un corécepteur pour l'ensemble des autres membres de la famille

Cancers du sein métastatique HER2+++

Survie prolongée

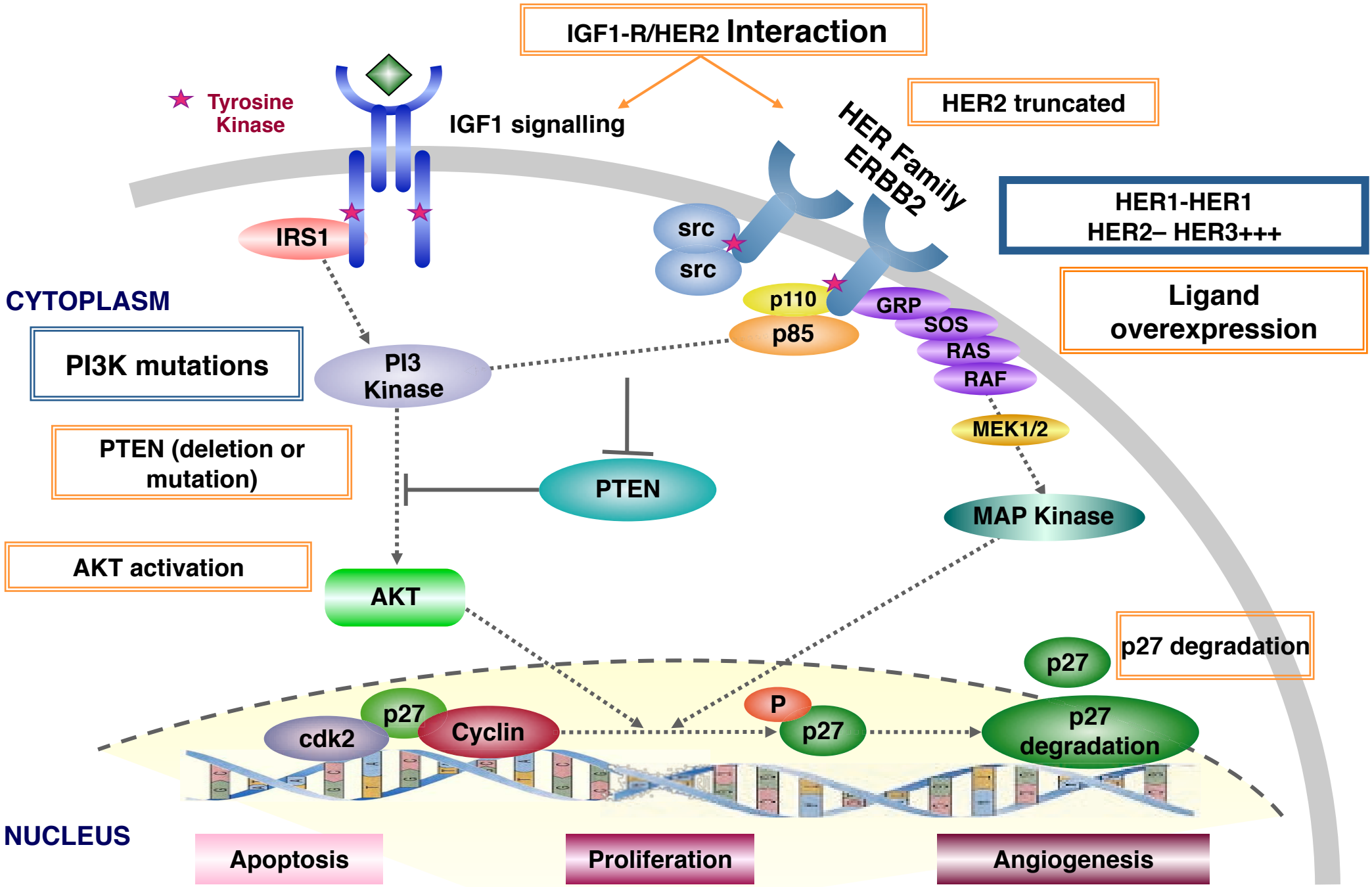


No. of patients at risk

HER2/*neu* negative	1,782	1,060	633	348	211	120
No trastuzumab	118	65	31	16	8	6
Trastuzumab	191	155	94	51	25	10

Pas ou peu de guérison….

Résistance au Trastuzumab



Dieras V, *et al*. *Bull Cancer* 2007; **94:**259–266; Diéras V & Bachelot T. *Target Oncol* 2013; ePub ahead of print.

Stratégies de traitement des cancers du sein métastatiques HER2+++

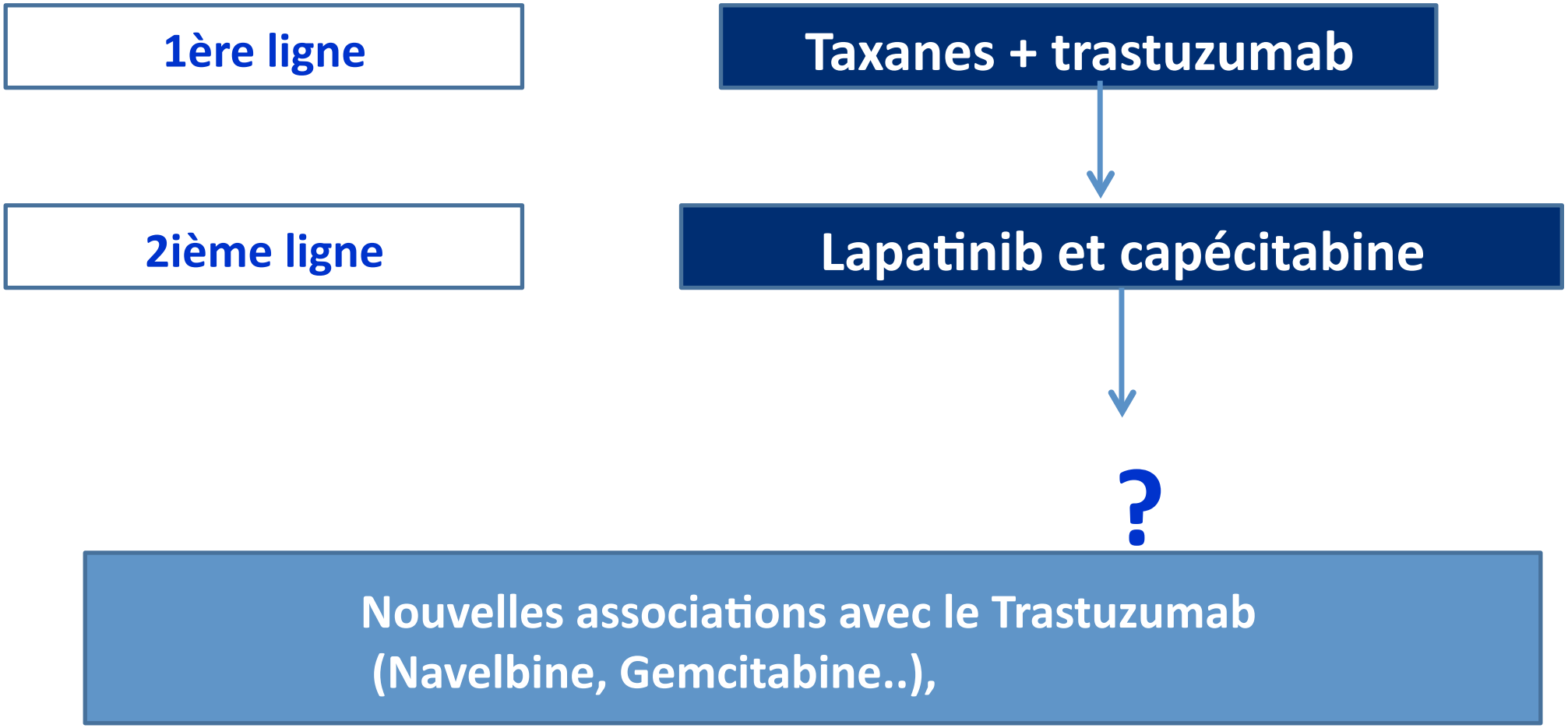
- 2000: AMM Trastuzumab
- 2008: AMM Lapatinib

Après une décennie de Trastuzumab et quelques années d'expérience avec le Lapatinib ….

De nouvelles (R)évolutions….

Cancer du sein métastatiques HER2 +++

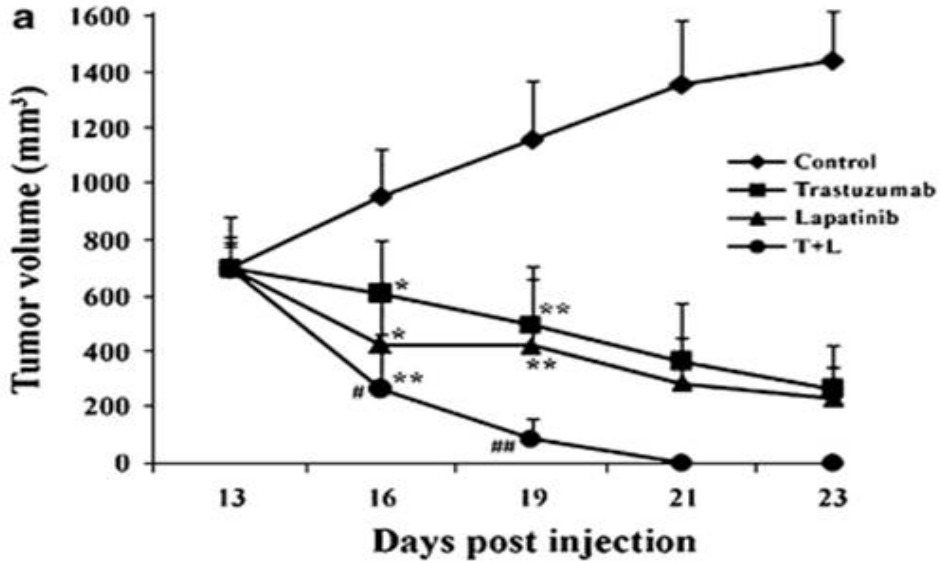
Séquence en pratique année 2007

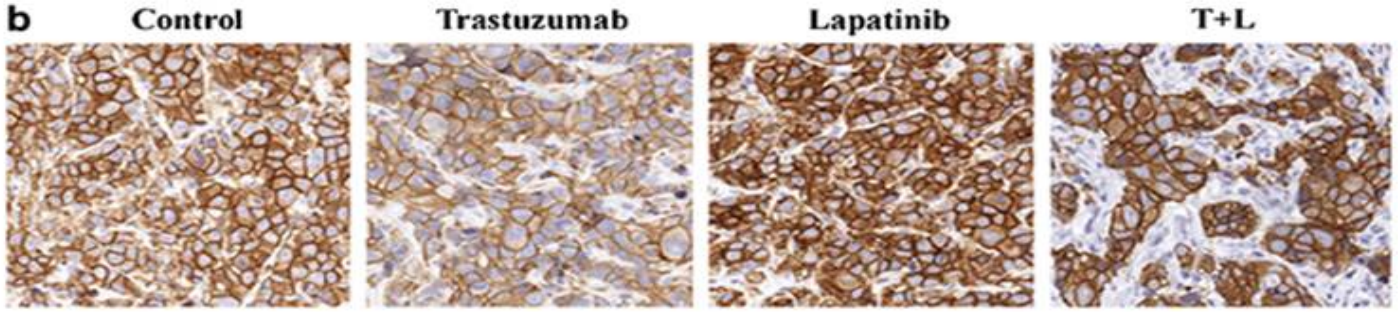


Besoin de nouvelles molécules et de nouvelles stratégie..

Le double blocage
Lapatinib+ Trastuzumab
après Trastuzumab

Preclinical Synergy Of Lapatinib + Trastuzumab In HER2+ Tumor Xenografts

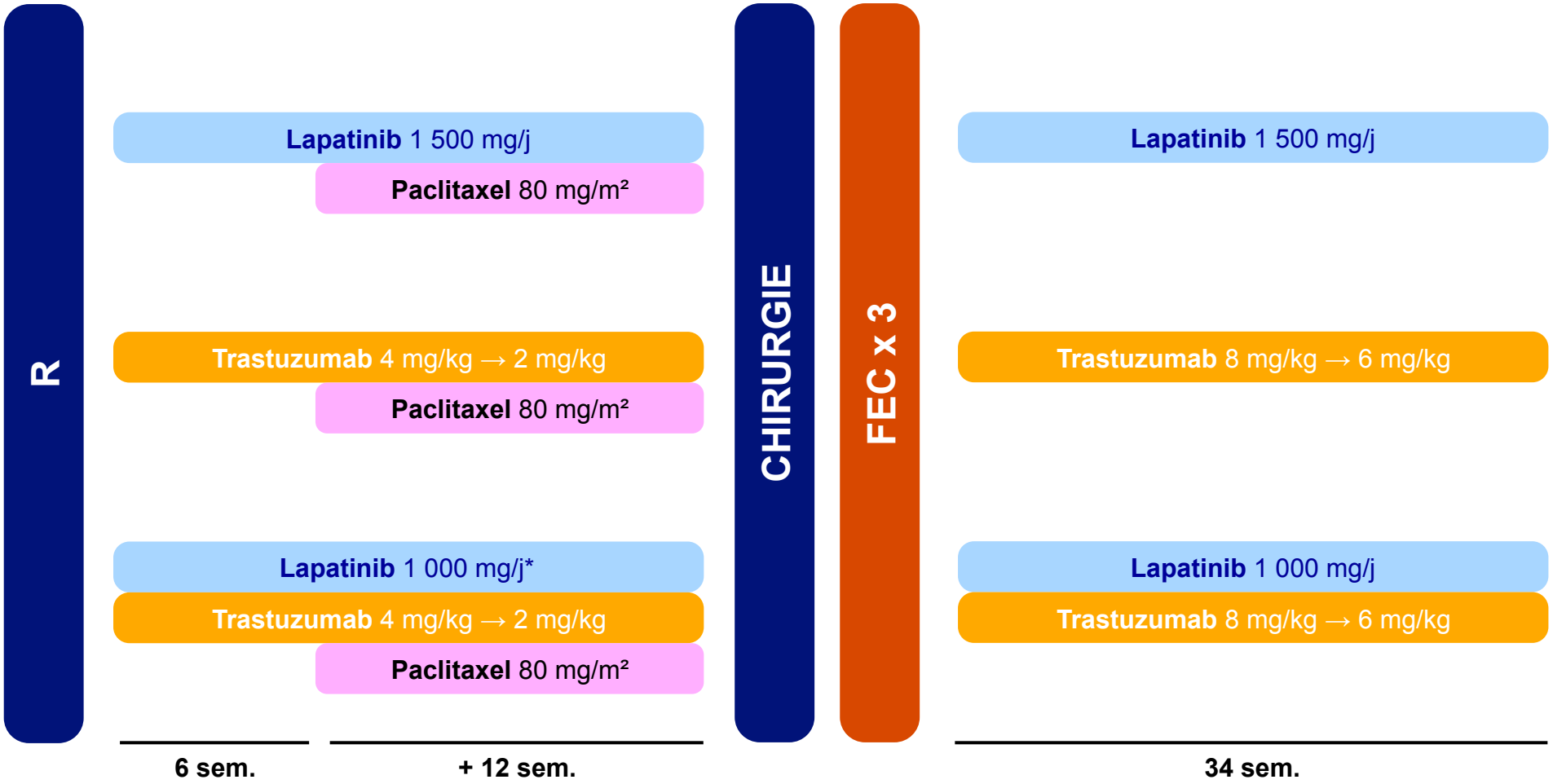




Greater antitumor activity with T+ L compared to either T or L alone

Étude Neo-ALTTO *(1)*

455 femmes HER2+ (ASCO®/CAP 2007) atteintes d'un cancer du sein, tumeur ≥ 2 cm



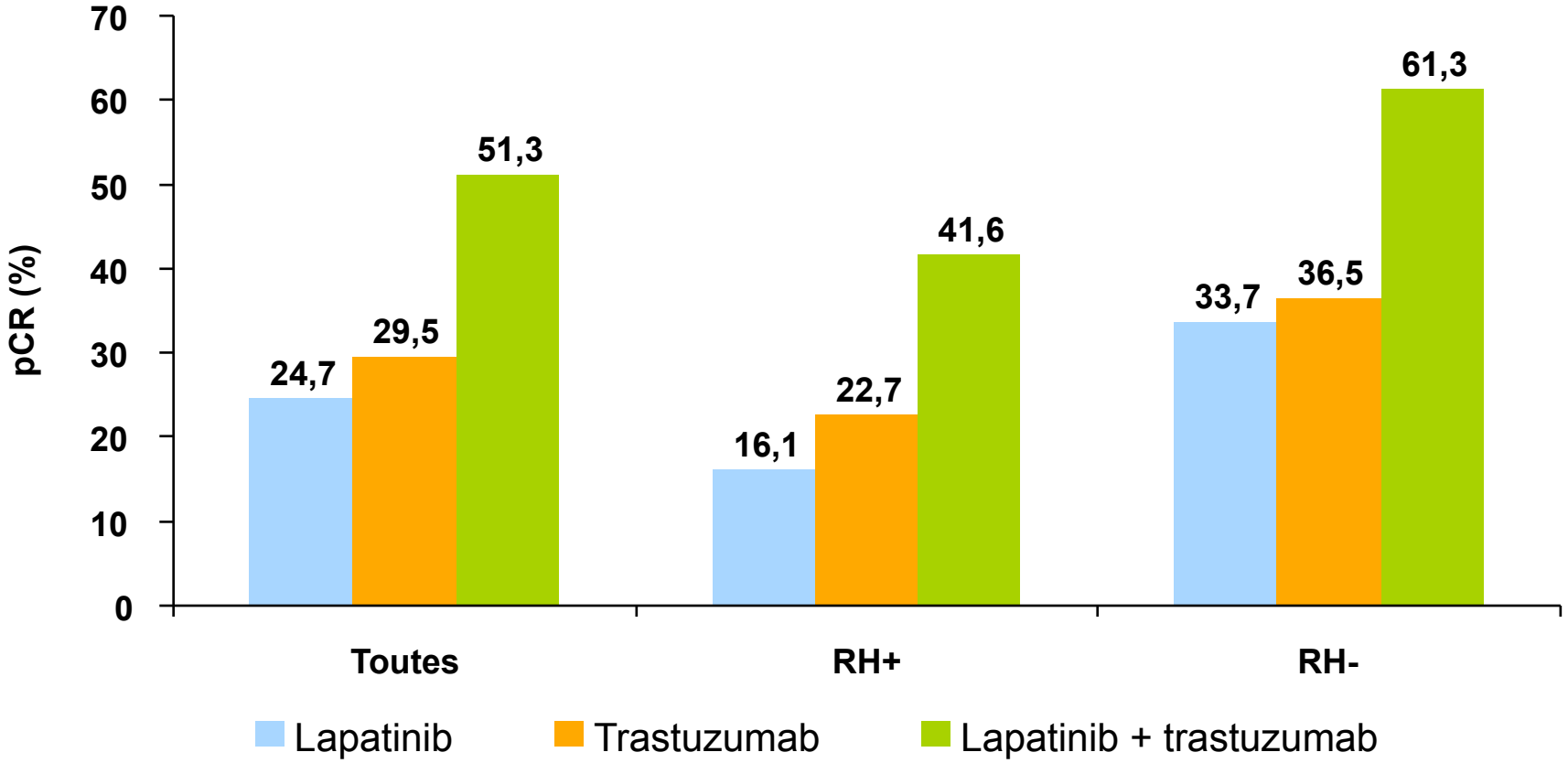
** Amendement du 2 octobre 2008 : réduction de la dose de lapatinib à 750 mg/j avec paclitaxel (n = 54 patientes sur 152)*

D'après Baselga J et al. SABCS® 2010 ; Lancet 2012.

SABCS® 2013 - D'après Piccart-Gebhart M et al., Abstr. S1-01 actualisé

Étude Neo-ALTTO *(2)*

Critère principal : pCR (n = 455)



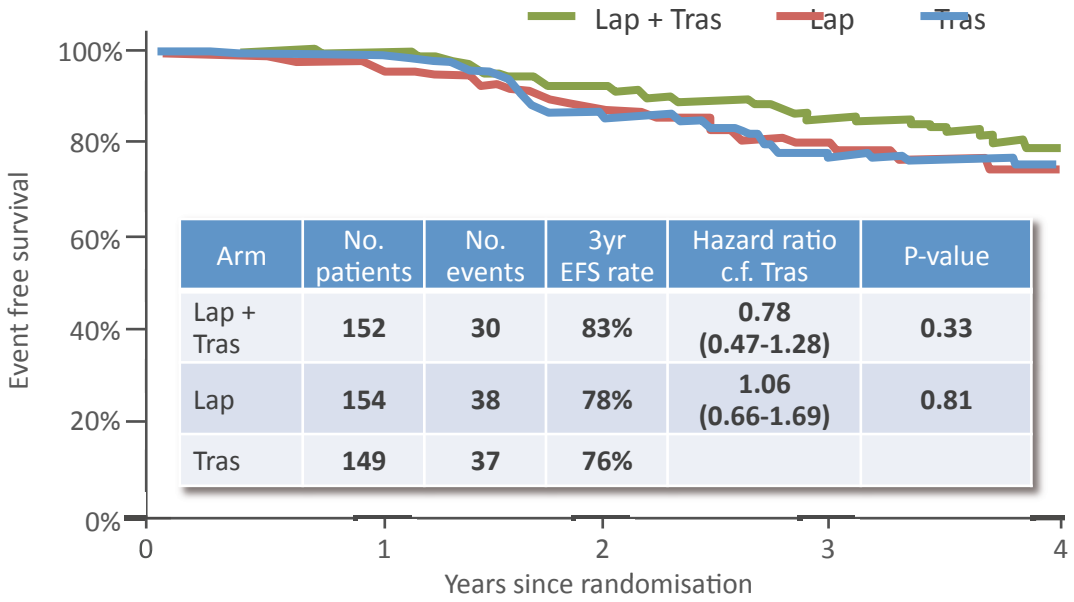
D'après Baselga J et al. SABCS 2010 ; Lancet 2012.

-Piccart-Gebhart M et al., SABCS 2013 Abstr. S1-01 actualisé; e Azambuja E et al Lancet Oncol. 2014

Etude Neo-ALTTO (BIG 1-06) : Survie sans événement (SSE)

- **SSE (suivi médian = 3,84 ans)**

All patients

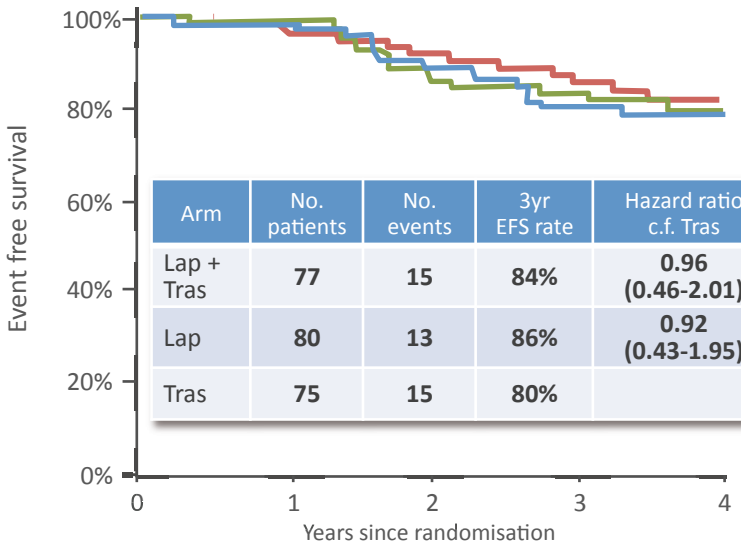


Arm	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	P-value
Lap + Tras	**152**	**30**	**83%**	**0.78 (0.47-1.28)**	**0.33**
Lap	**154**	**38**	**78%**	**1.06 (0.66-1.69)**	**0.81**
Tras	**149**	**37**	**76%**		

Test for interaction according to HR status

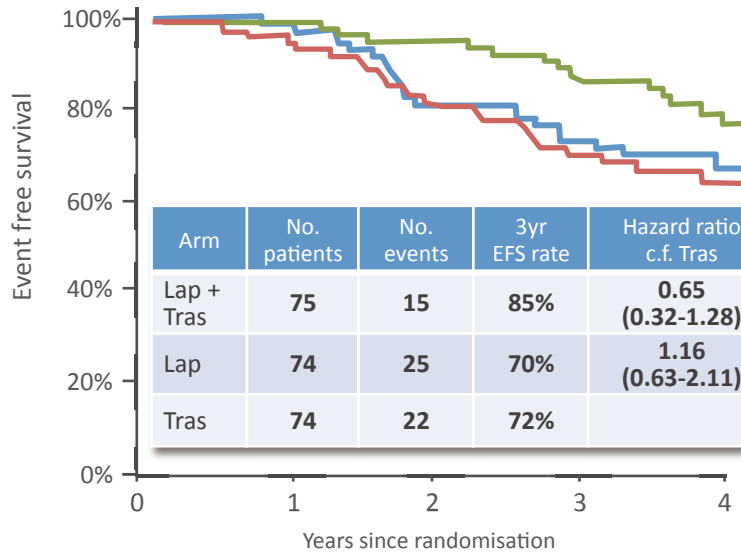
- **Lap + Tras *vs.* Tras *p=0.48***
- **Lap *vs.* Tras *p=0.56***

HR positive



Arm	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	P-value
Lap + Tras	**77**	**15**	**84%**	**0.96 (0.46-2.01)**	**0.92**
Lap	**80**	**13**	**86%**	**0.92 (0.43-1.95)**	**0.83**
Tras	**75**	**15**	**80%**		

HR negative



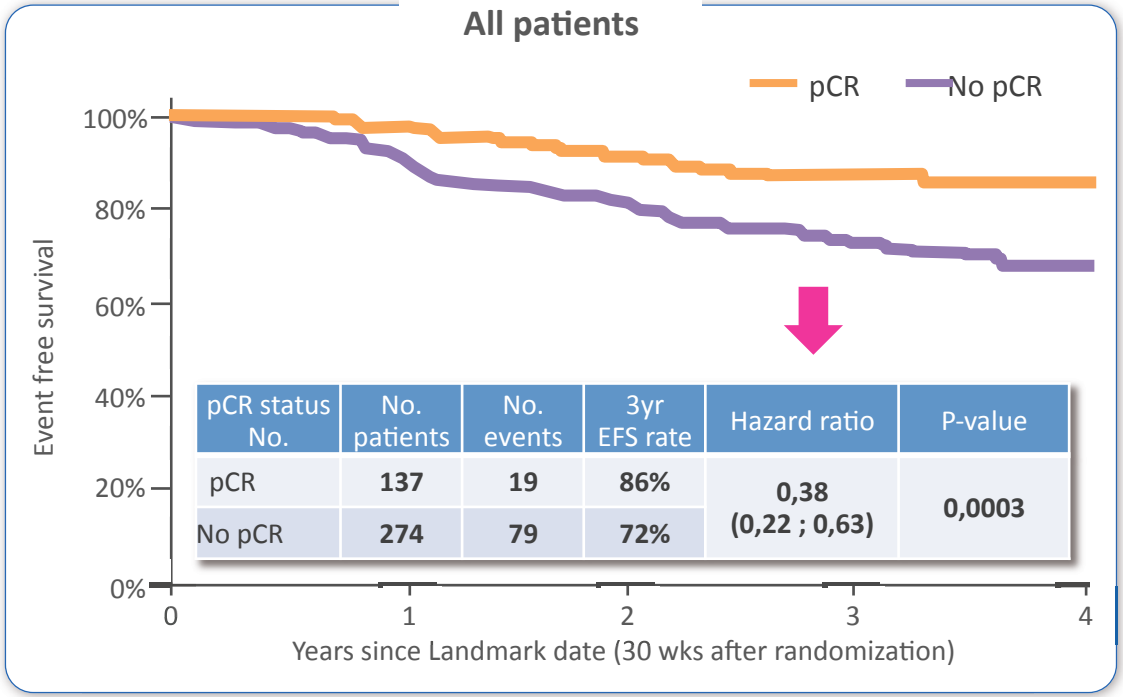
Arm	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	P-value
Lap + Tras	**75**	**15**	**85%**	**0.65 (0.32-1.28)**	**0.22**
Lap	**74**	**25**	**70%**	**1.16 (0.63-2.11)**	**0.64**
Tras	**74**	**22**	**72%**		

- **Pas de différences significatives entre les 3 bras**
- **Tendance pour un bénéfice de la combinaison en SSE dans les tumeurs RH-**
- **Données similaires en survie globale**

Piccart-Gebhart M et al., SABCS 2013, S1-01, de Azambuja E Lancet Oncol. 2014

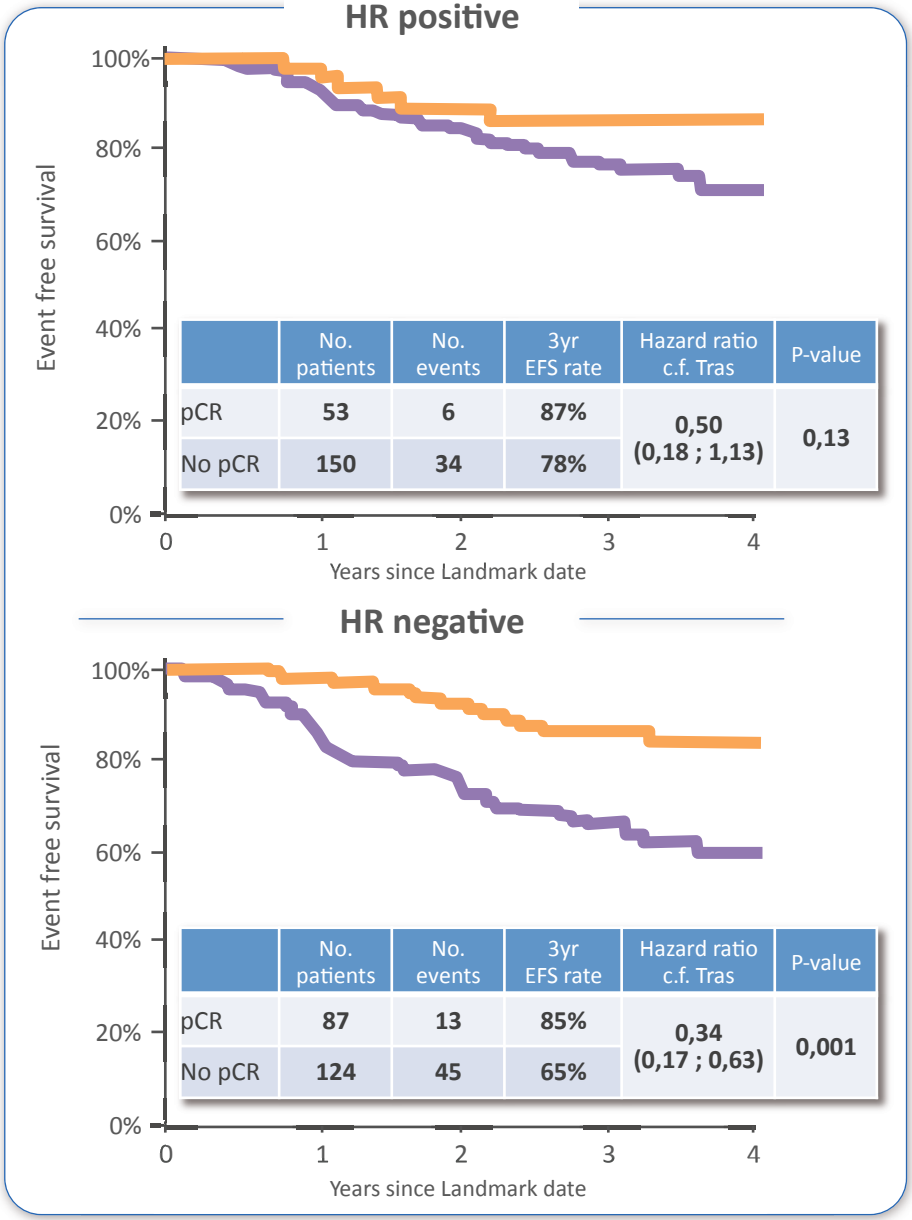
Etude Neo-ALTTO (BIG 1-06)- Impact pronostique de la pCR

- **SSE (Landmark analysis)**



pCR status No.	No. patients	No. events	3yr EFS rate	Hazard ratio	P-value
pCR	137	19	86%	0,38 (0,22 ; 0,63)	0,0003
No pCR	274	79	72%		

- **Impact pronostique de la pCR confirmé (plus net dans les RH-)**
- **Impact retrouvé dans chaque bras de traitement (L, T, L +T)**
- **Données similaires en survie globale**



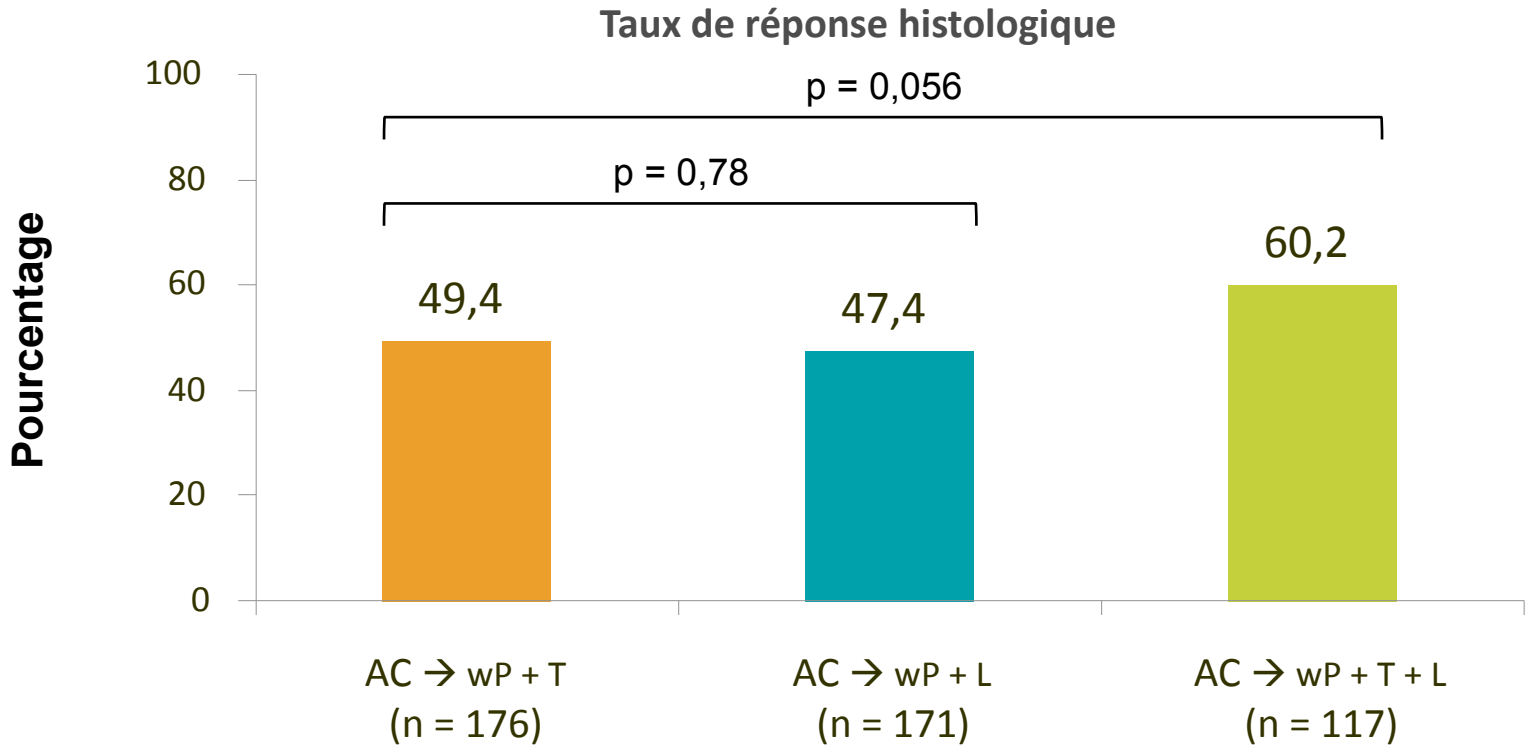
	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	P-value
pCR	53	6	87%	0,50 (0,18 ; 1,13)	0,13
No pCR	150	34	78%		

	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	P-value
pCR	87	13	85%	0,34 (0,17 ; 0,63)	0,001
No pCR	124	45	65%		

Piccart-Gebhart M et *al.*, SABCS 2013,; de Azambuja E Lancet Oncol. 2014

NSABP B-41 : évaluation du lapatinib en néo-adjuvant dans le cancer du sein HER2+ *(2)*

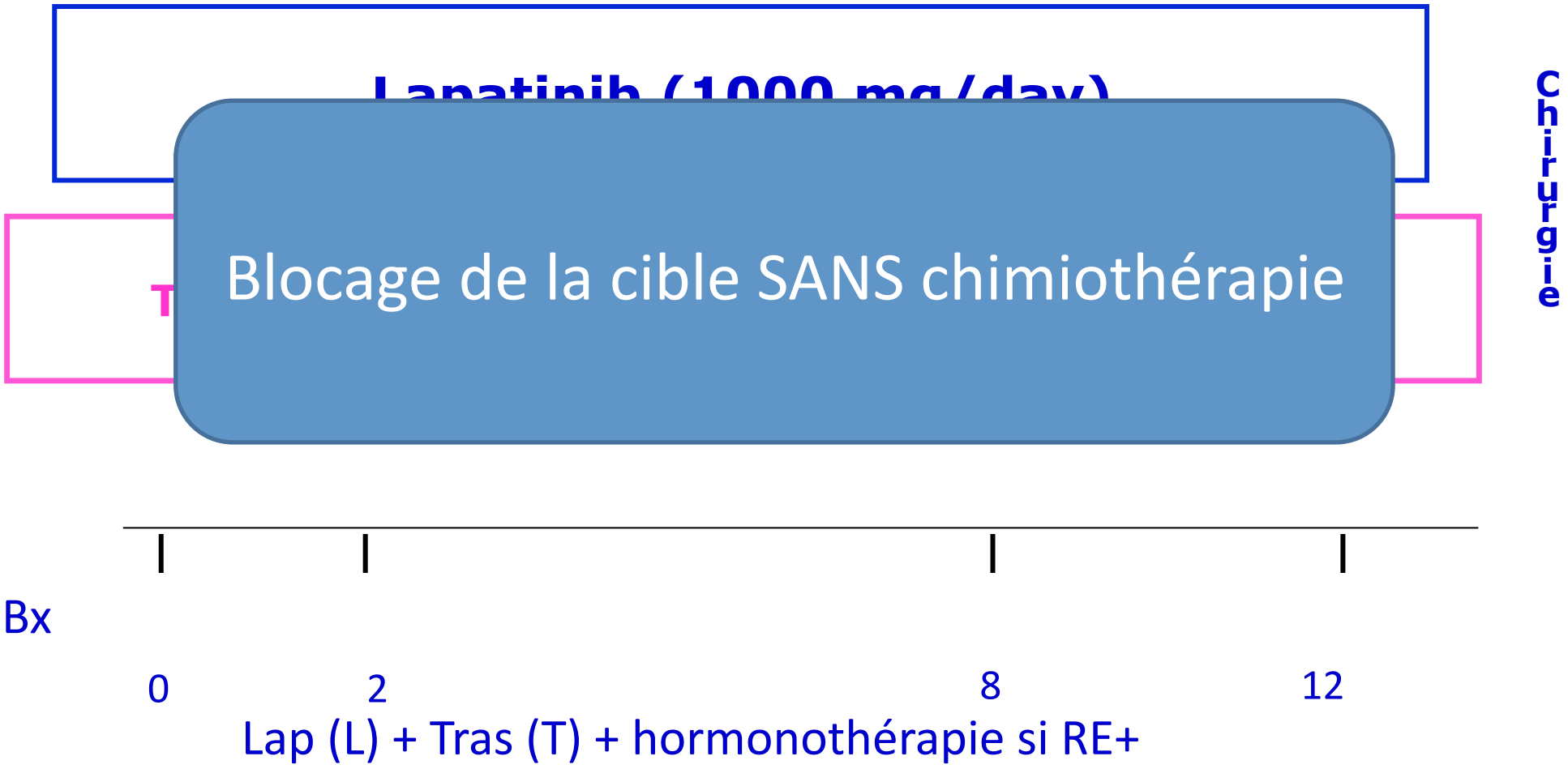
- Critère de jugement principal
  - Taux de réponse histologique dans la tumeur mammaire (différence non significative)
- Critère secondaire
  - pCR sein et ganglions : limite de la significativité



wP = paclitaxel hebdomadaire

Robidoux et al; Lancet Oncol. 2013 Nov;14(12)

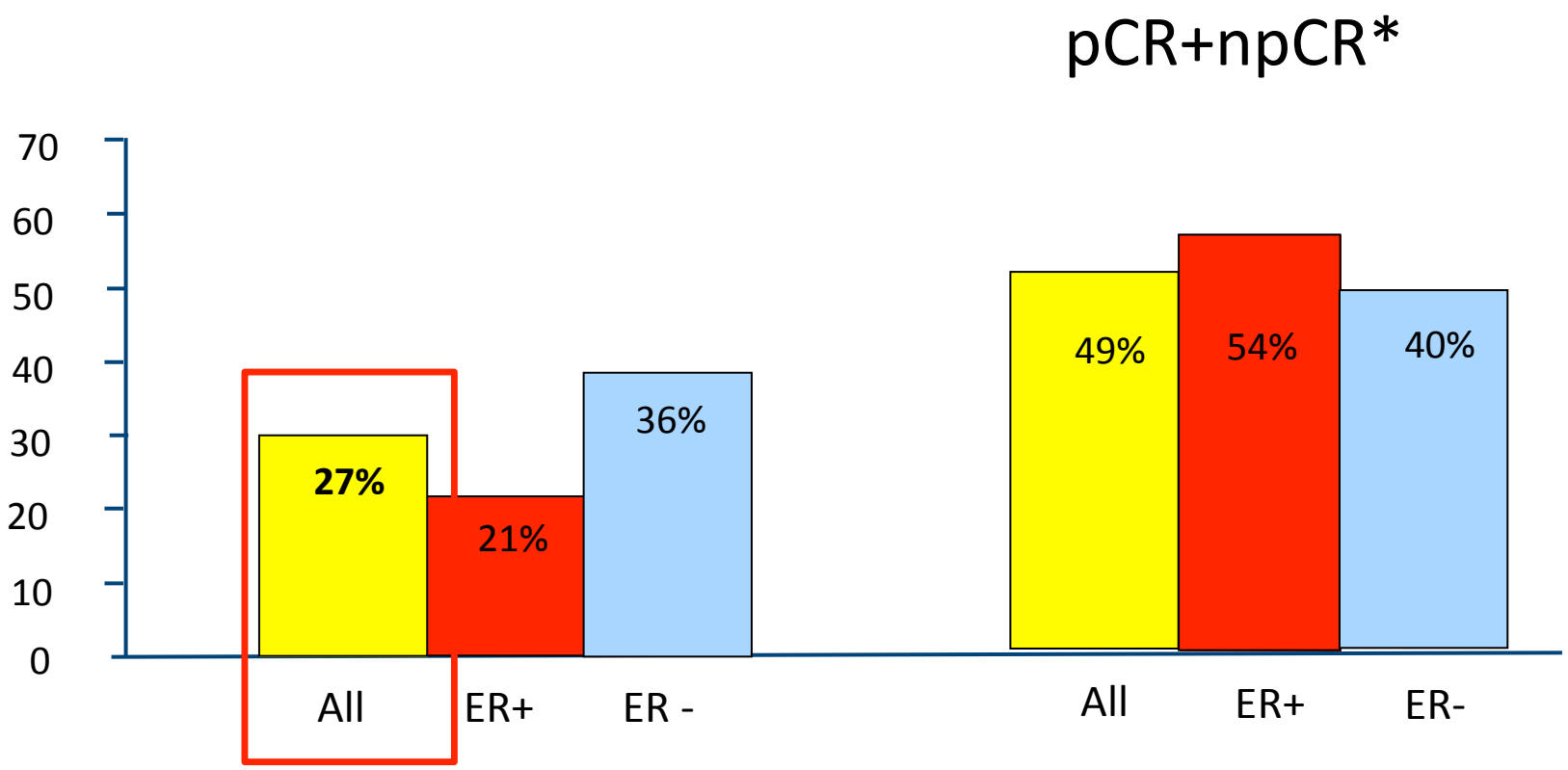
Neoadjuvant Lapatinib et Trastuzumab sans chimiothérapie



M .F. Rimawi, I A. Mayer; J Clin Oncol 31:1726-1731. 2013

Réponse histologique complète dans le sein

*npCR (near path complete response):Residual disease (<1 cm) in breast (ypT0-is plus ypT1a-b)



M .F. Rimawi, I A. Mayer; J Clin Oncol 31:1726-1731. 2013

Nouvelles données, cancers du sein métastatiques HER2 +++

Le double blocage

Lapatinib+ Trastuzumab

après Trastuzumab

Étude de Phase III évaluant le double blocage de HER2

Inclusion

- **HER2+(FISH+/ IHC3+) MBC**
- **Progression sous**
  - **Anthracycline**
  - **Taxane**
  - **Trastuzumab**
- **Progression sous traitement récent par trastuzumab**
- **Population lourdement prétraitée**

Stratification selon

- Méta viscérales
- Récepteurs Hormonaux

RANDOMISATION

Lapatinib 1500 mg/j per os
N=148

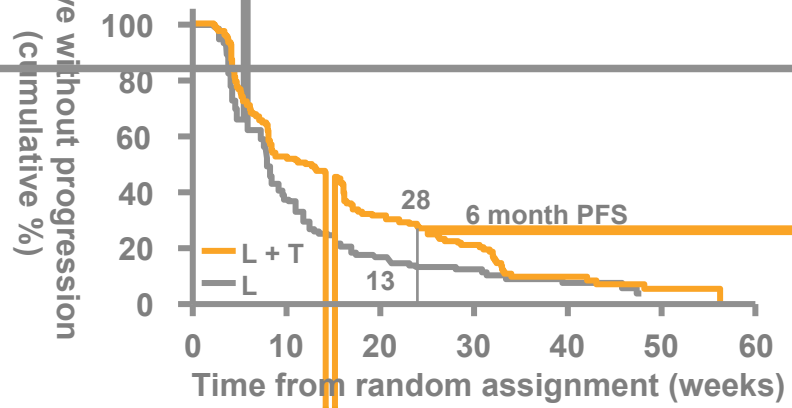
Cross over si progression après 4 sem traitement (n=77)

Lapatinib 1000 mg/j per os
Trastuzumab 4 → 2 mg/kg IV qw
N=148

O'Shaughnessy, et al. ASCO 2008; Blackwell, et al. J Clin Oncol JCO.2010

L'association Trastuzumab + lapatinib augmente la survie sans progression (EGF104900)

	Lapatinib n=145	Lapatinib + trastuzumab n=146
Progressed or died, n	128	127
Median, weeks	8.1	12.0
Hazard ratio (95% CI)	0.73 (0.57 to 0.93)	
P	.008	

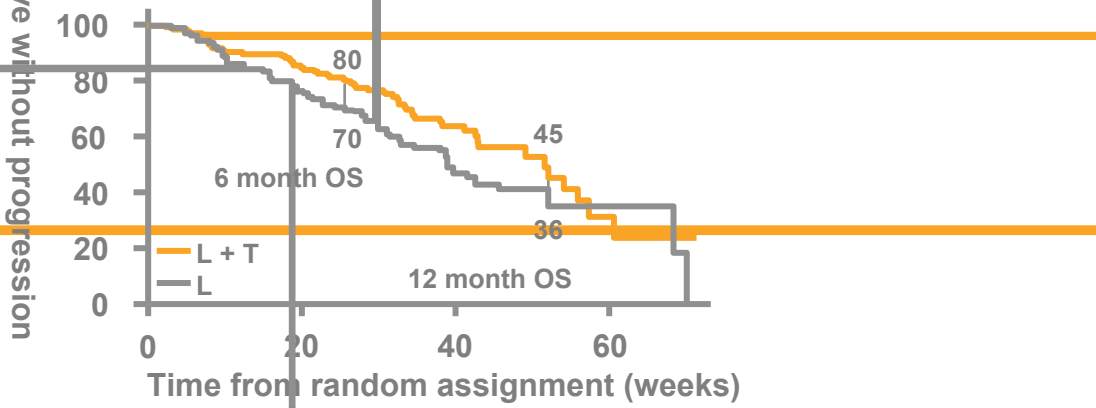


No. of patients at risk

L	148	53	21	13	5	0
L+T	148	73	42	27	8	2

Kaplan–Meier estimates of progression-free survival (PFS) in the intent-to-treat population.
L, lapatinib; L+T, lapatinib plus trastuzumab

	Lapatinib n=145	Lapatinib + trastuzumab n=146
Died, n	69	56
Median, weeks	39.0	51.6
Hazard ratio (95% CI)	0.75 (0.53 to 1.07)	
P	.106	



No. of patients at risk

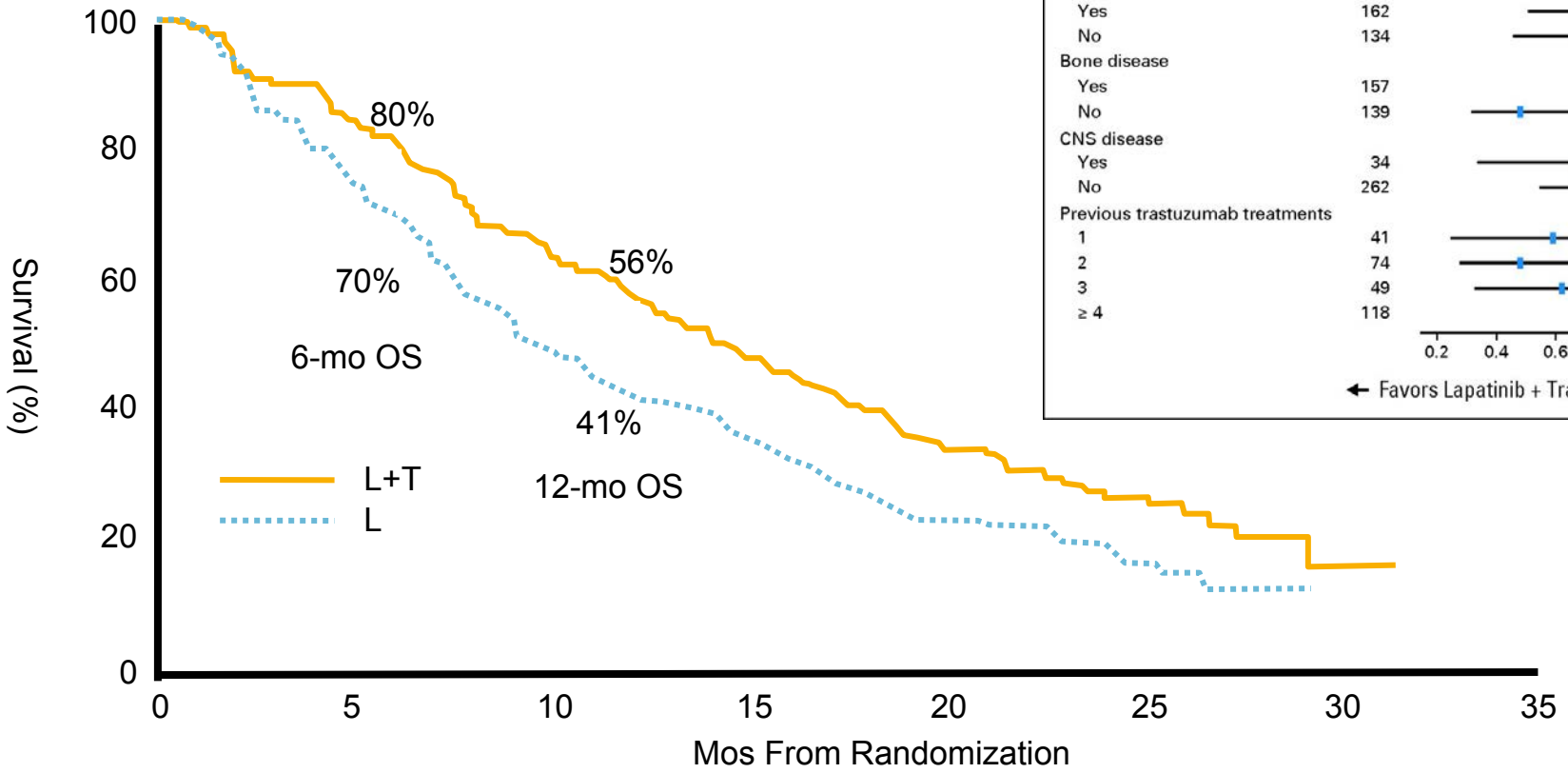
L	148	106	30	3
L+T	148	121	40	4

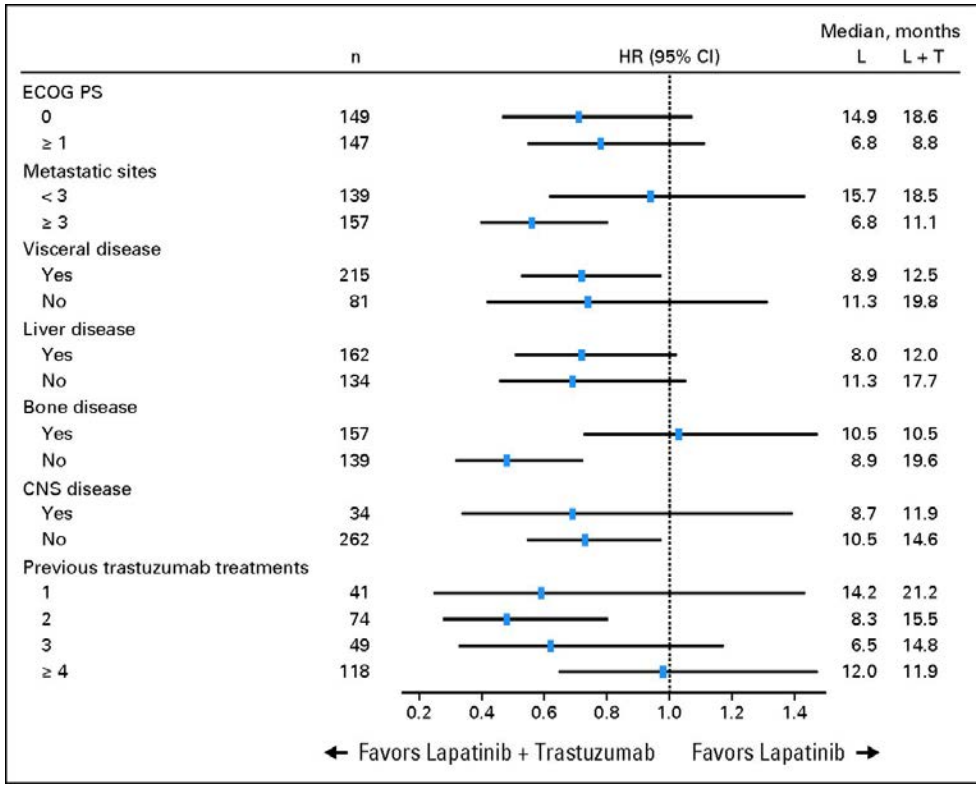
Kaplan–Meier estimates of overall survival (OS) in the intent-to-treat population.
L, lapatinib; L+T, lapatinib plus trastuzumab

Blackwell K, et al, J Clin Oncol 2010; 28:1124–1130.

Actualisation de la survie

	L (n = 145)	L+ T (n = 146)
Died, n (%)	113 (78)	105 (72)
Median, mos	9.5	14
HR (95% CI)	0.74 (0.57-0.97)	
Log-rank P value	.026	

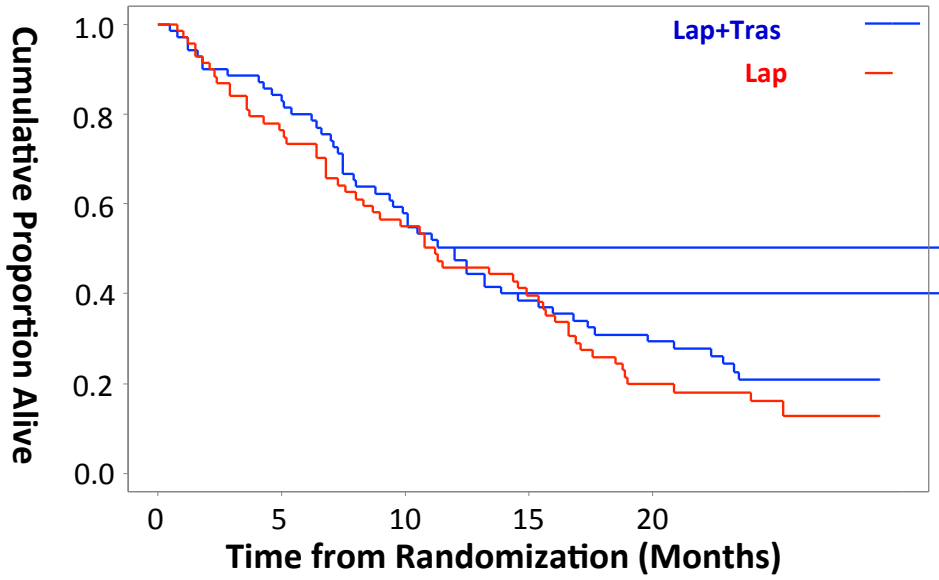




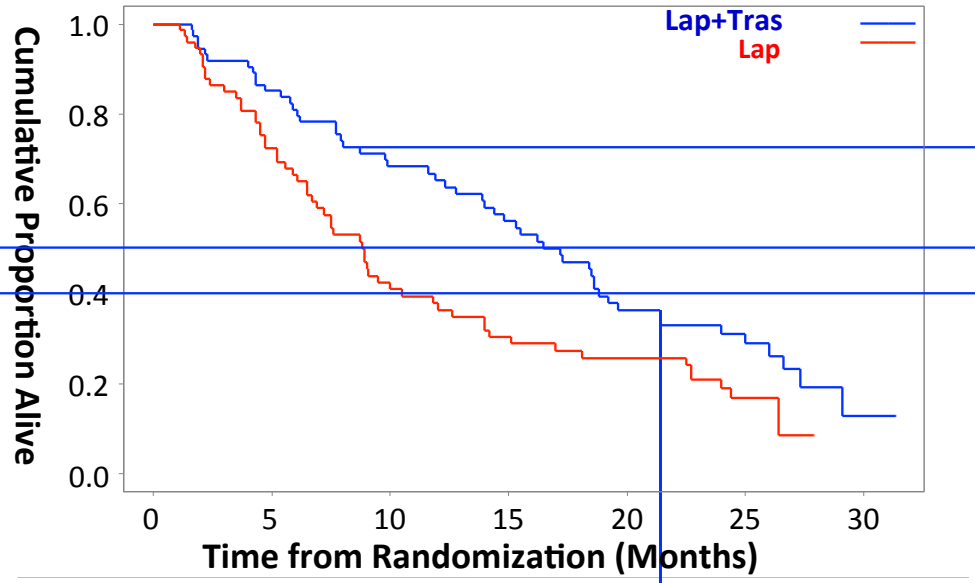
Blackwell K, *et al, J Clin Oncol* 2012; 30:2585–2592

Bénéfice significatif important d'OS chez les patientes HER2+/RH-

RH+



RH-



	Lap+Tras N=71	Lap N=70	OS HR (95% CI)
Median OS, mos	12.0	11.2	0.84 **(0.5-1.23)**

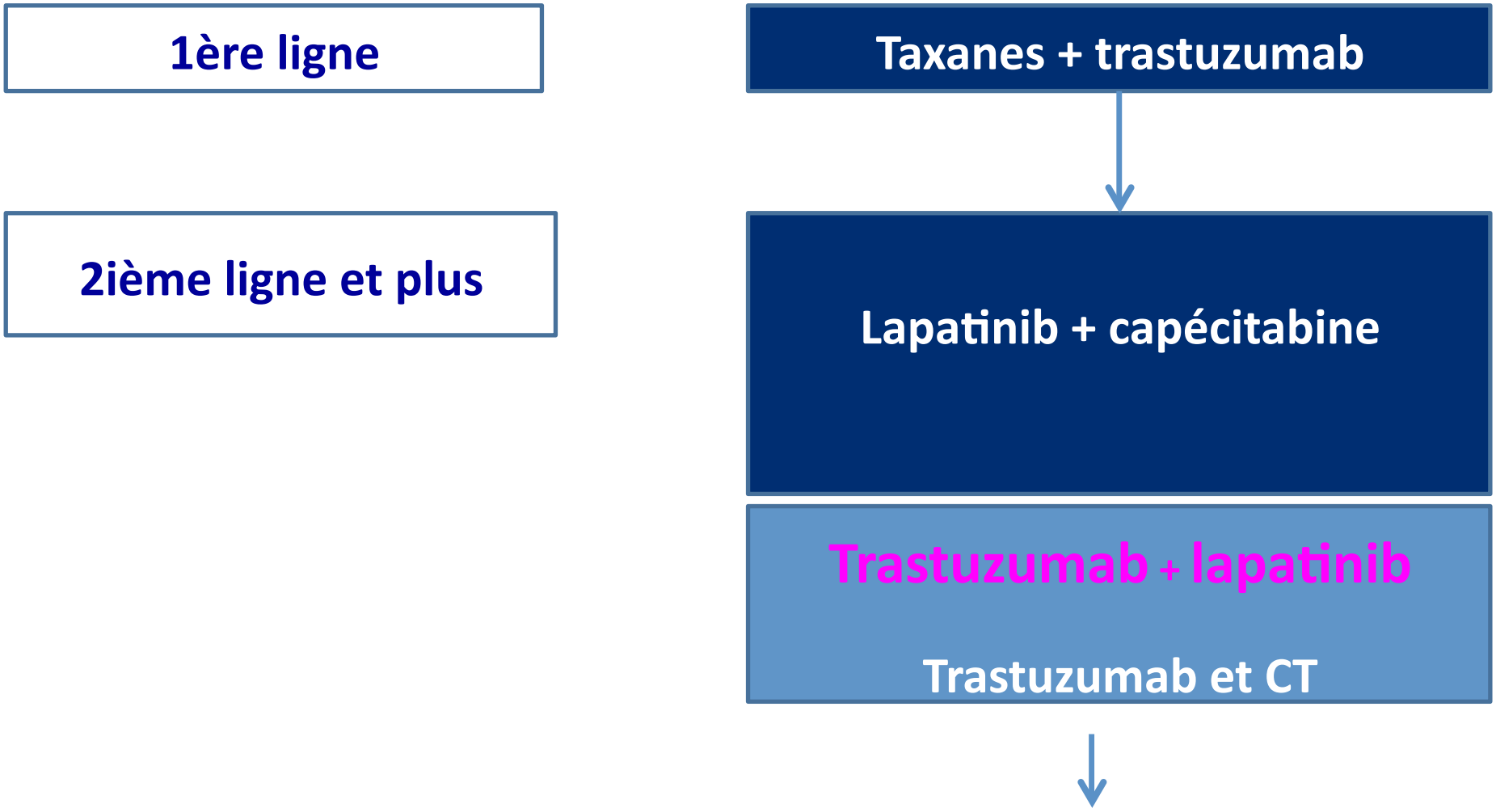
Δ=0,8 mois, NS

	Lap+Tras N=75	Lap N=75	OS HR (95% CI)
Median OS, mos	17.2	8.9	0.62 **(0.42-0.90)**

Δ=8,3 mois, significatif

Cancer du sein métastatiques HER2 +++

Séquence en pratique année 2009

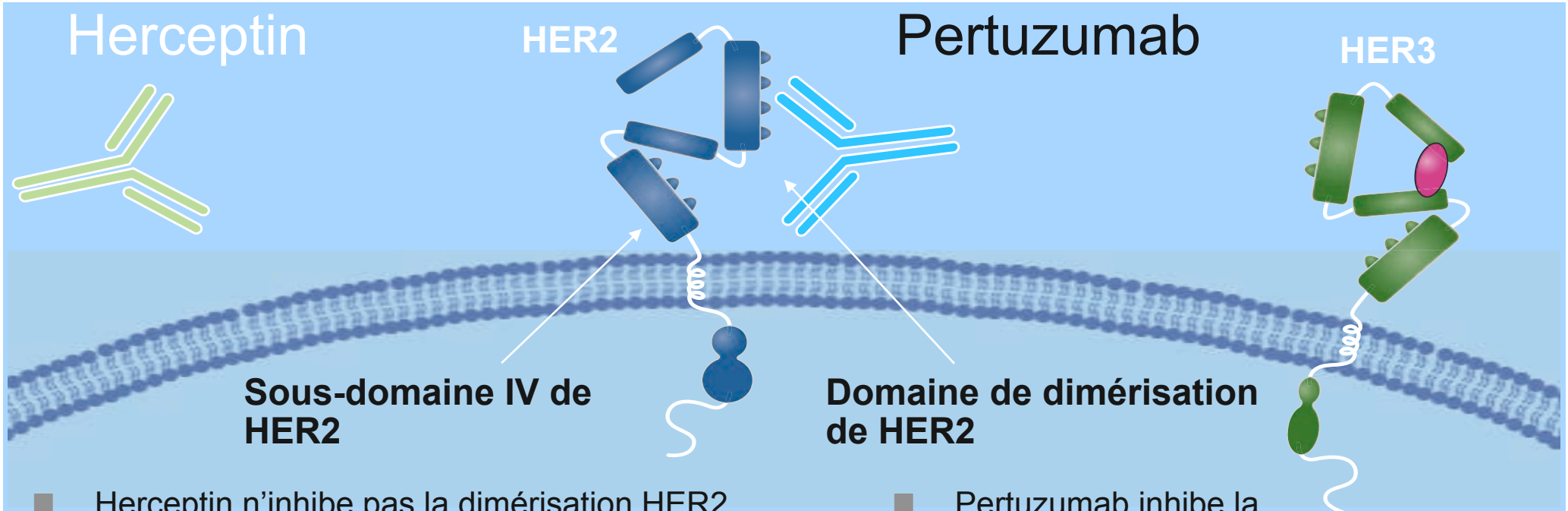


Nouvelles molécules et nouvelles stratégie..

Le double blocage
Lapatinib+ Trastuzumab
après Trastuzumab

Nouvel anticorps le Pertuzumab

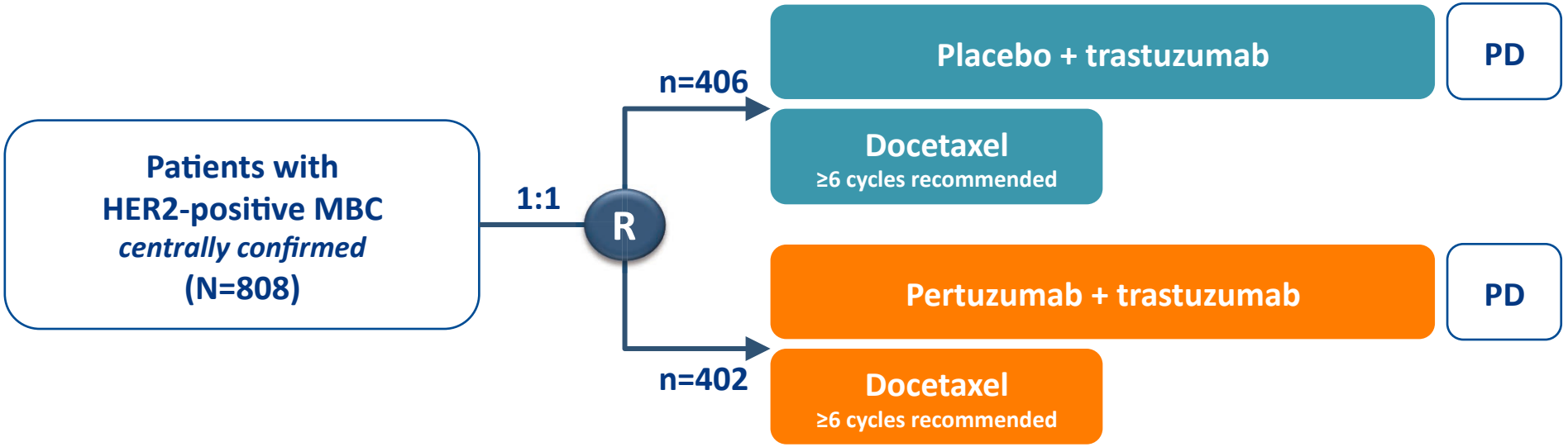
Herceptin et pertuzumab se lient à des domaines différents de HER2



- Herceptin n'inhibe pas la dimérisation HER2
- Herceptin empêche la multiplication du récepteur HER2 à la surface de la cellule.
- Herceptin bloque la voie de signalisation HER2.
- Herceptin présente les cellules à la destruction par le système immunitaire (ADCC).

- Pertuzumab inhibe la formation de dimères avec HER2.
- Pertuzumab présente les cellules à la destruction par le système immunitaire (ADCC).
- Pertuzumab n'empêche pas la multiplication du récepteur HER2 à la surface de la cellule.

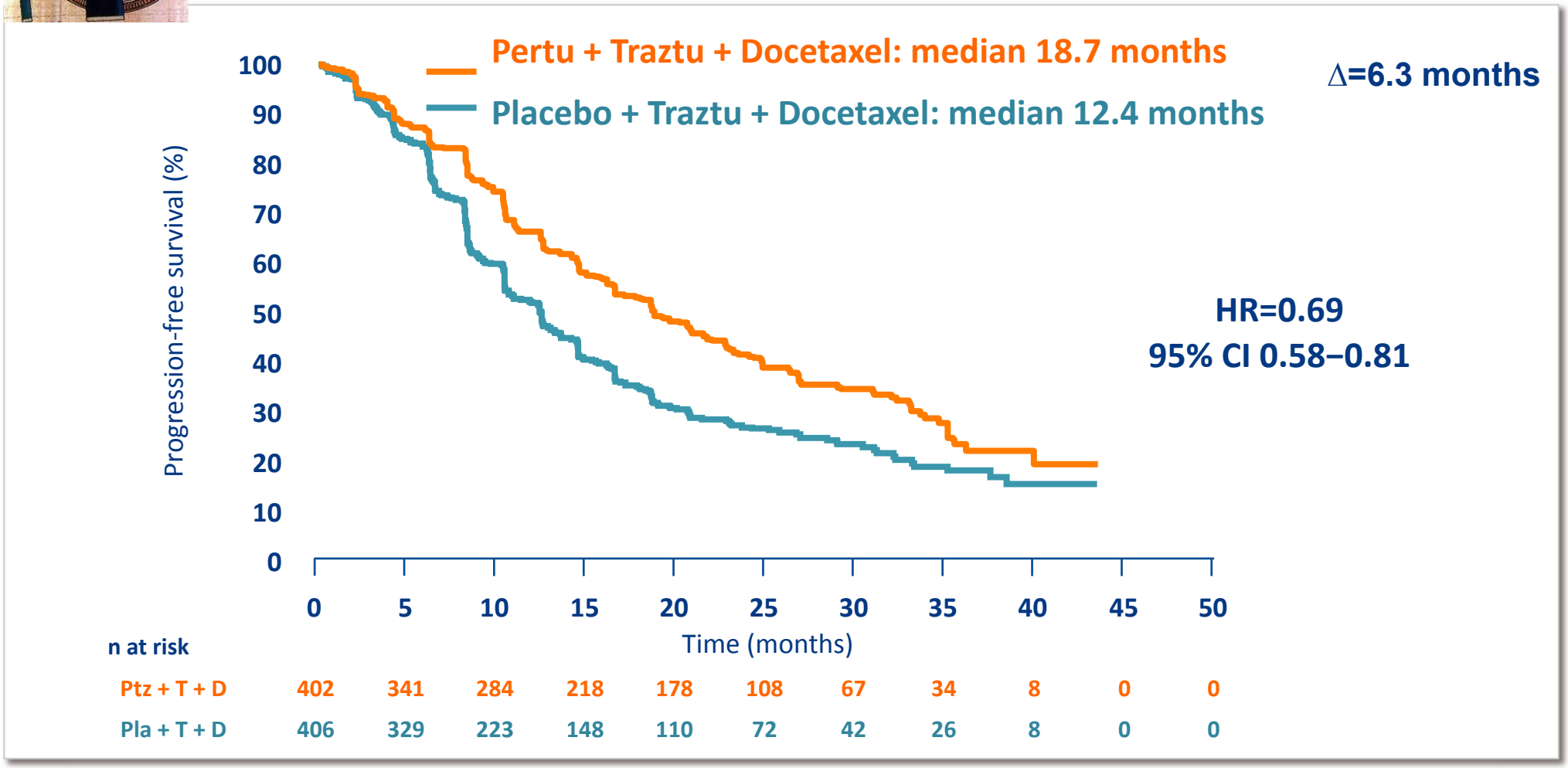
Essai CLEOPATRA



11% des patientes avaient reçu du Trastuzumab en adjuvant
Posologie Trastuzumab 75mg/m2 (vs 100 mg/m2 habituellement)

Baselga et al, New England J Med, 2012

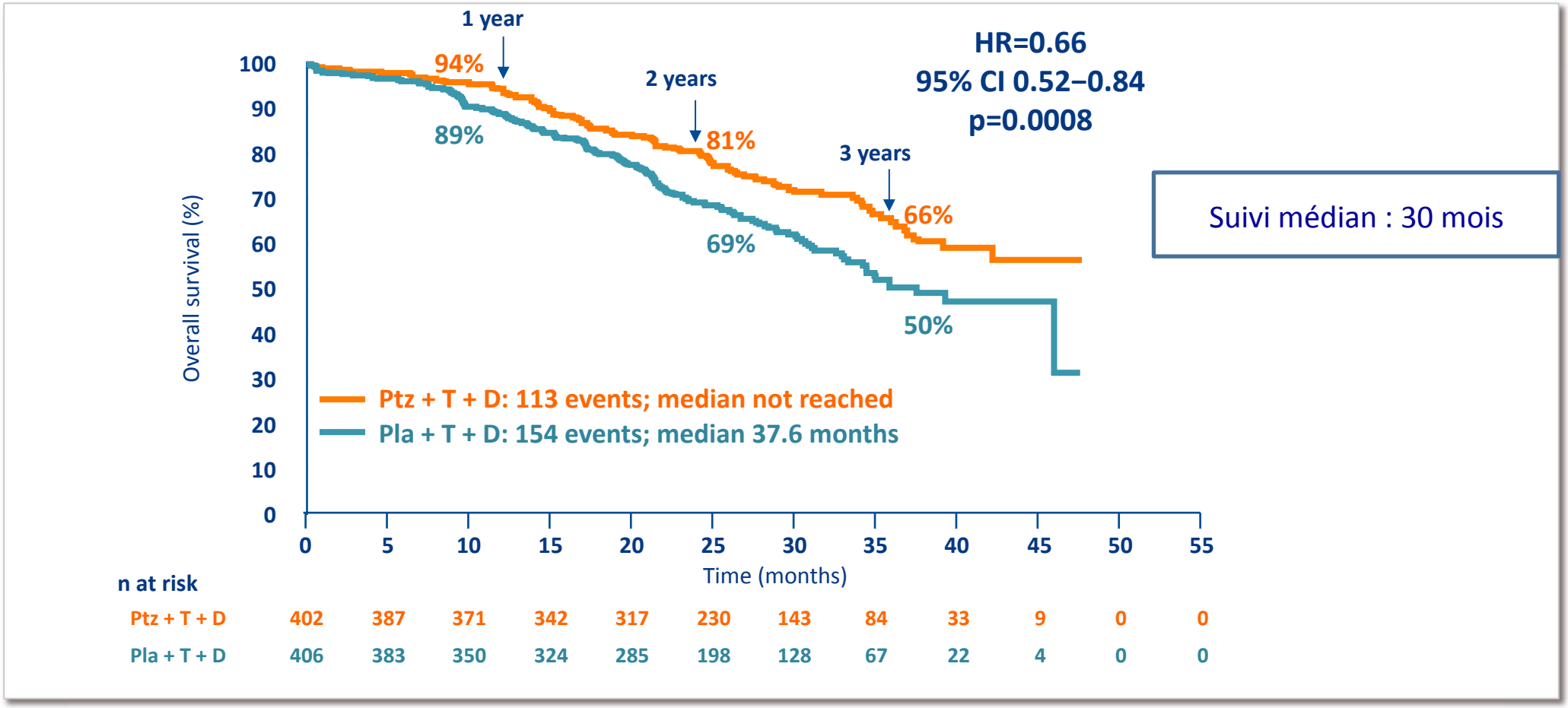
Essai CLEOPATRA : Survie sans progression



1Baselga J, *et al*. *N Engl J Med* 2012; **366**:109–119; 2.Swain SM, *et al*. *Lancet Oncol* 2013; **14**:461–471;

- 3. Swain SM, *et al*. *Oncologist* 2013; **18**:257–264; 4. Cortés J, *et al*. *Ann Oncol* 2013;

Essai CLEOPATRA Survie globale



Baselga J, *et al*. *N Engl J Med* 2012; **366**:109–119; Swain SM, *et al*. *Lancet Oncol* 2013; **14**:461–471;

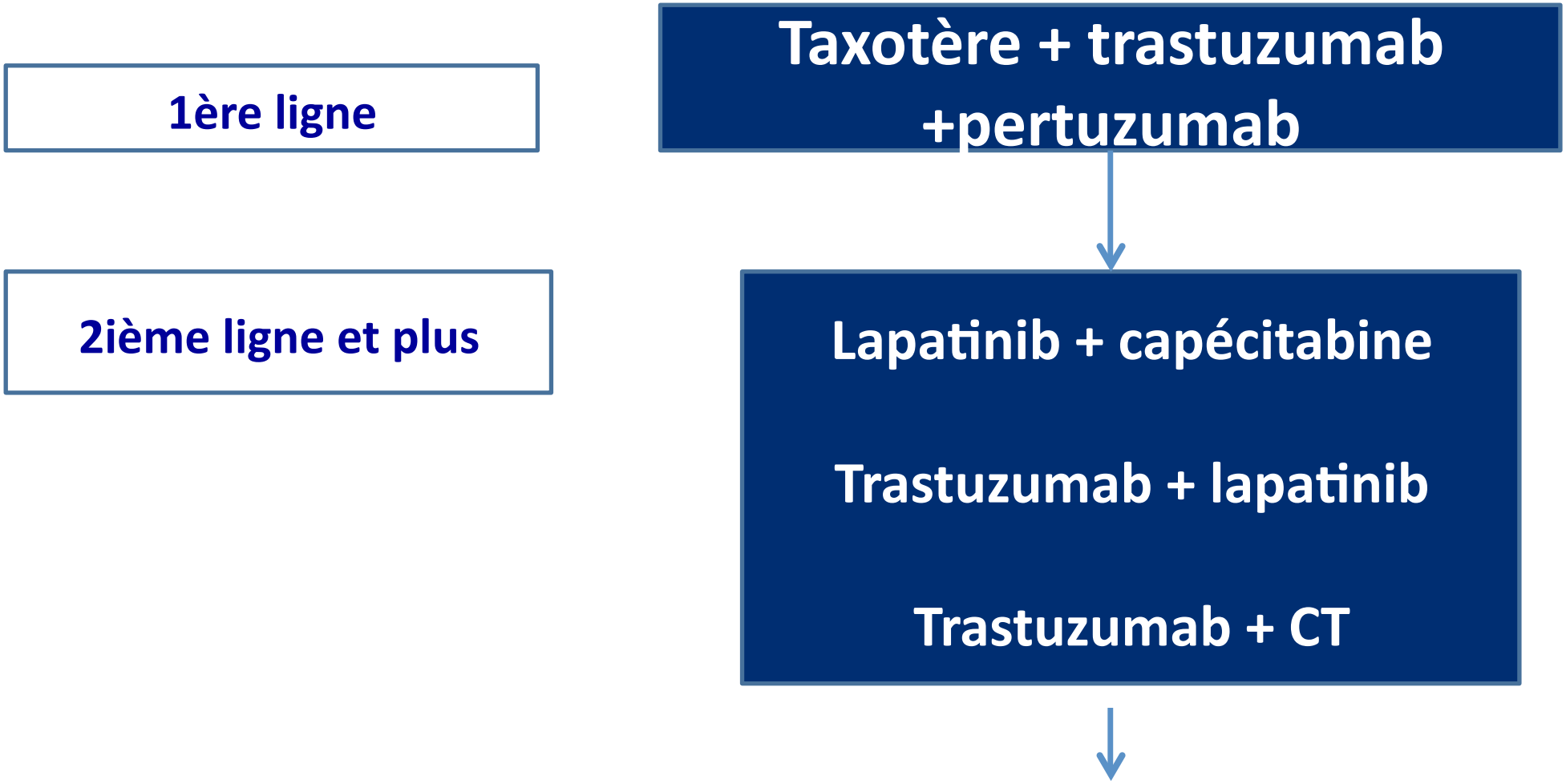
- 3. Swain SM, *et al*. *Oncologist* 2013; **18**:257–264; 4. Cortés J, *et al*. *Ann Oncol* 2013;

Enregistrement du pertuzumab depuis 07/2013 en 1 ère de ligne de chimiothérapie chez les patientes ayant un cancer du sein HER2+++

L'association Docetaxel + trastuzumab + Pertuzumab = 1ére ligne +++

Cancer du sein métastatiques HER2 +++

Séquence en pratique fin 2013début 2014



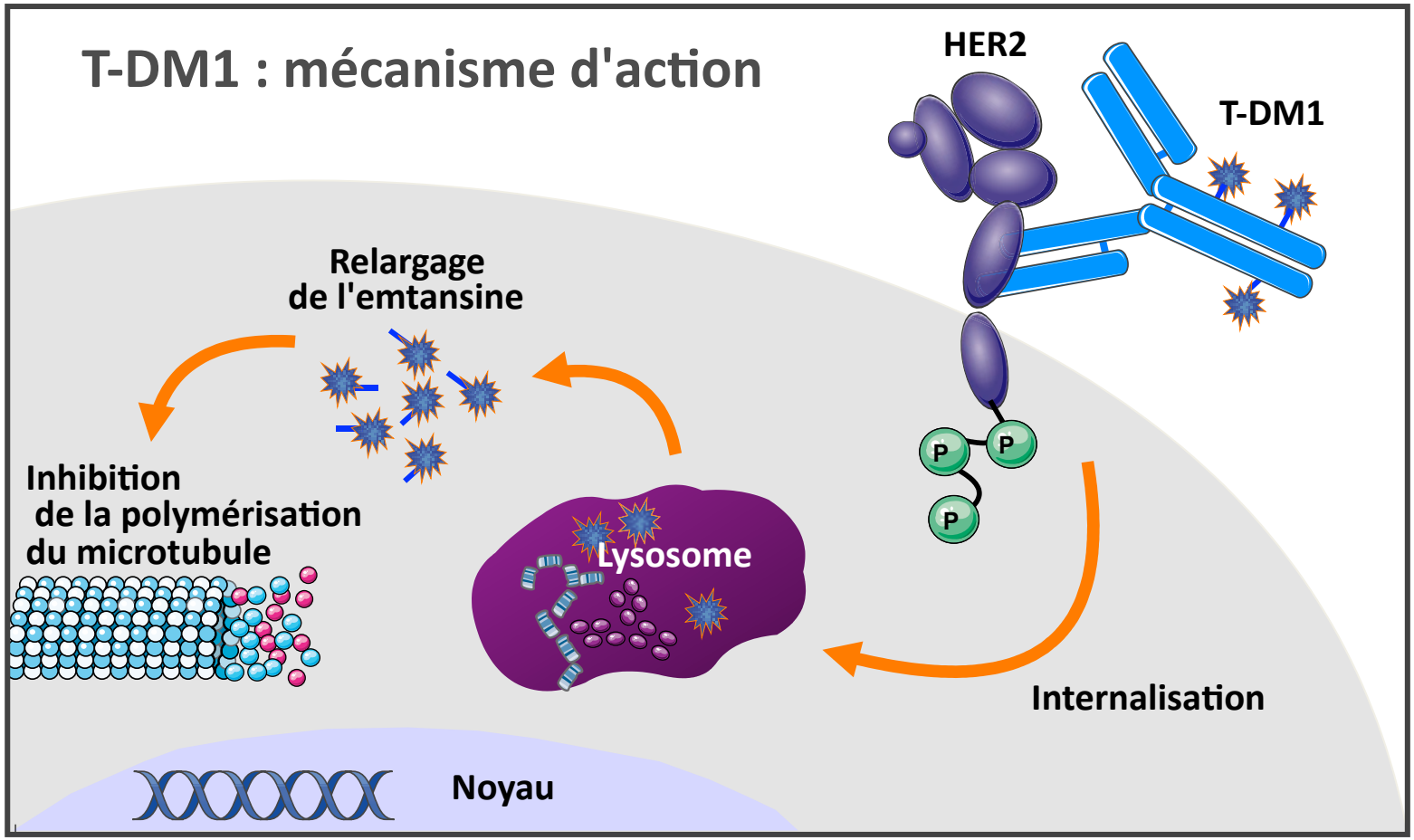
Nouvelles molécules et nouvelles stratégie..

Le double blocage
Lapatinib+ Trastuzumab
après Trastuzumab

Nouvel anticorps le
Pertuzumab

Une chimiothérapie couplée à
un anti corps…le TDM1

T-DM1 (trastuzumab-emtansine)



Adapté de LoRusso PM et al. Clin Cancer Res 2011.

Étude EMILIA : phase III comparant le T-DM1 (trastuzumab-emtansine) à capécitabine et lapatinib dans le cancer du sein métastatique HER2+ déjà traité par trastuzumab et taxanes

Cancer du sein localement avancé ou métastatique HER2+
(n = 980)

- Traitement antérieur par taxanes et trastuzumab
- Progression sous traitement (stade métastatique) ou dans les 6 mois (traitement adjuvant)

R 1:1

T-DM1
3,6 mg/kg x 3/sem. i.v.
(n = 495)

→ Progression

Capécitabine per os
1 000 mg/m^2 x 2/j,
J1-J14, x 3/sem.
+ **lapatinib per os**
1 250 mg/j en 1/j
(n = 496)

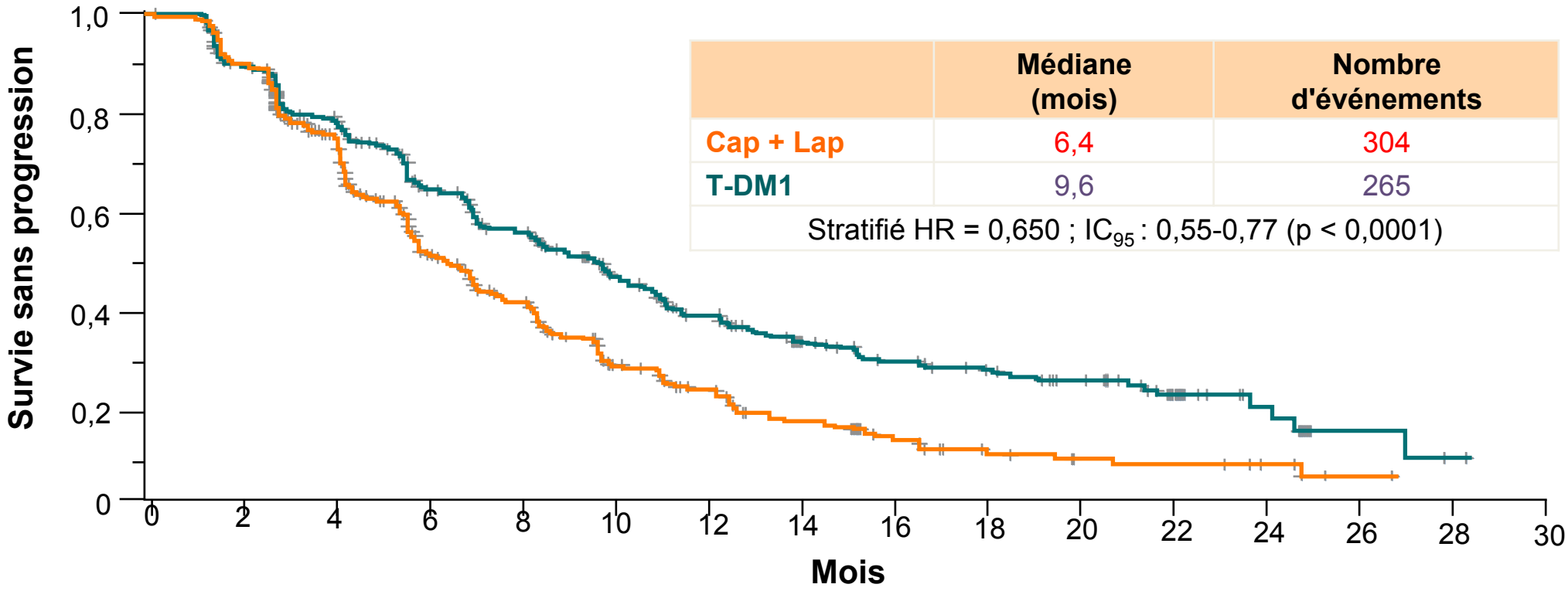
→ Progression

Critères principal: SSP (revue par un comité indépendant)
Critéres secondaires: SG
Tolérance

ASCO® 2012 - D'après Blackwell K et al., LBA1 actualisé
Welslau M et al, Cancer 2014

Étude EMILIA

Survie sans progression (revue indépendante)



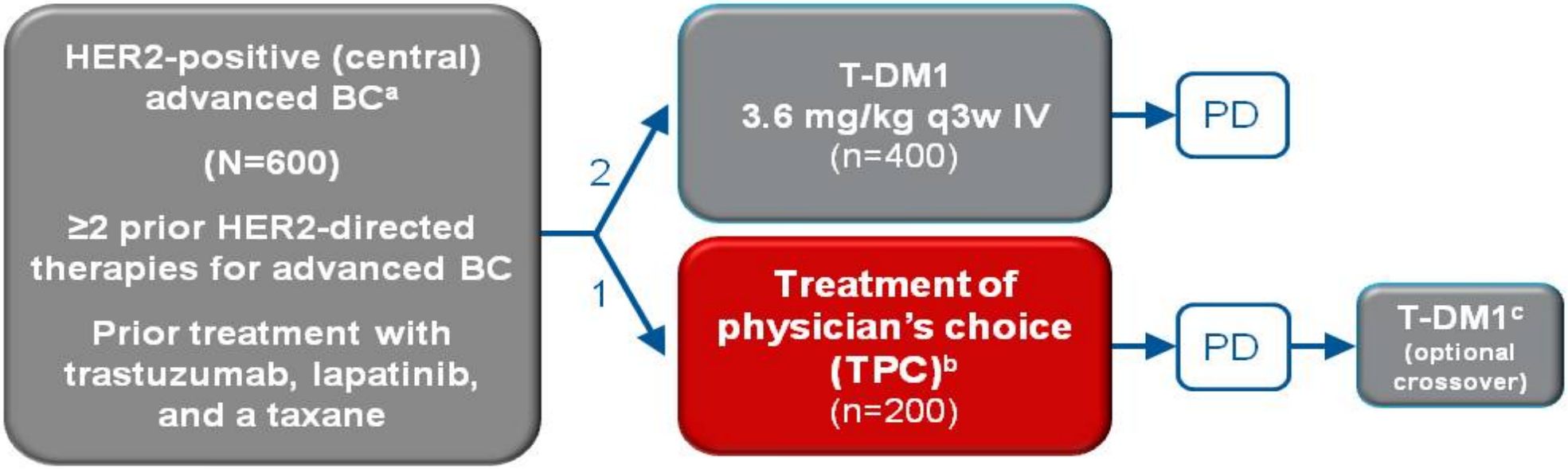
	Médiane (mois)	Nombre d'événements
Cap + Lap	6,4	304
T-DM1	9,6	265
Stratifié HR = 0,650 ; IC_{95} : 0,55-0,77 (p < 0,0001)		

Patients à risque par revue indépendante (n)

Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

ASCO® 2012 - D'après Blackwell K et al., LBA1 actualisé., Welslau M et al, Cancer 2014

TH3RESA Study Schema

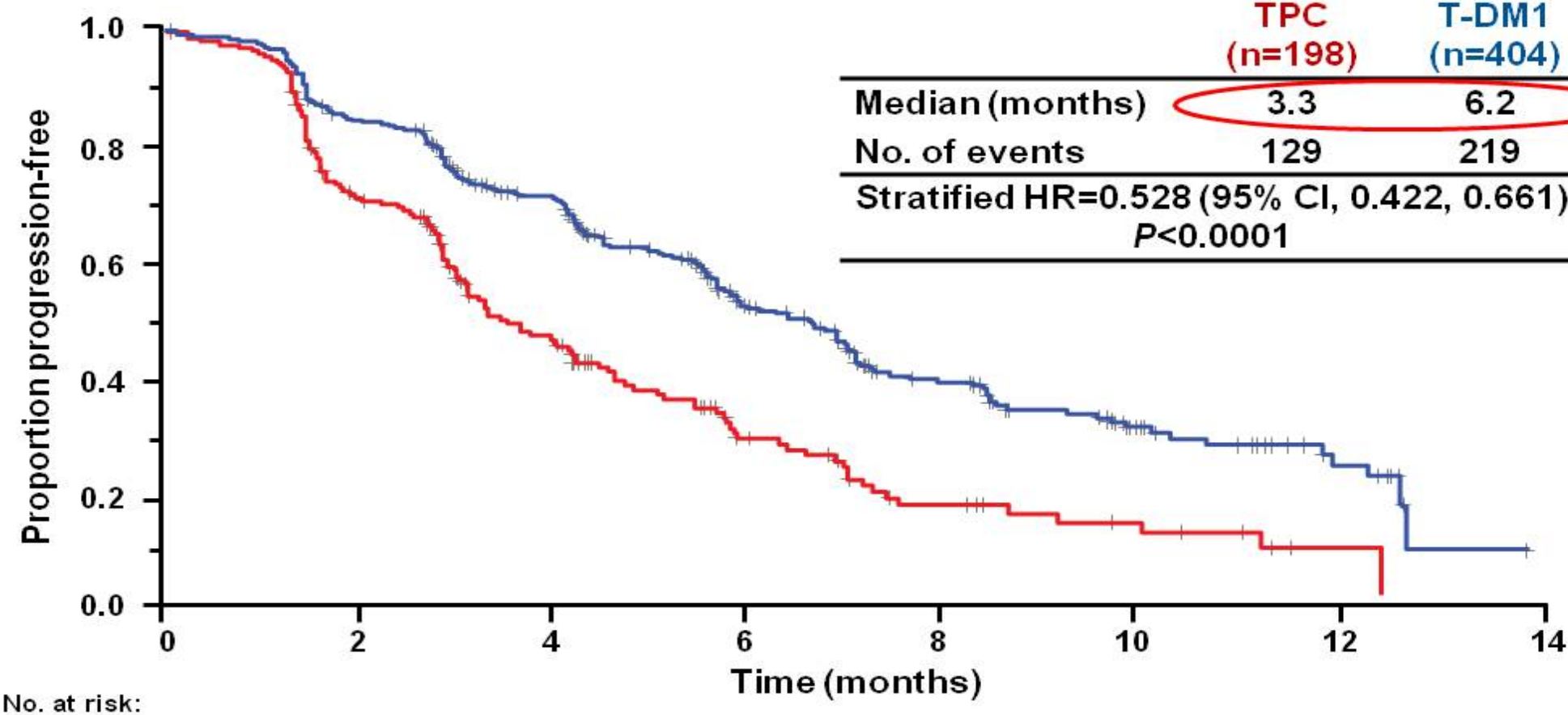


- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

[a] Advanced BC includes MBC and unresectable locally advanced/recurrent BC.
[b] TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
[c] First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.
[d] Excluding single-agent hormonal therapy.
BC, breast cancer; IV, intravenous; ORR, objective response rate; PD, progressive disease; q3w, every 3 weeks.

Krop I et al., Lancet May 2, 2014 [27]

PFS by Investigator Assessment



	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

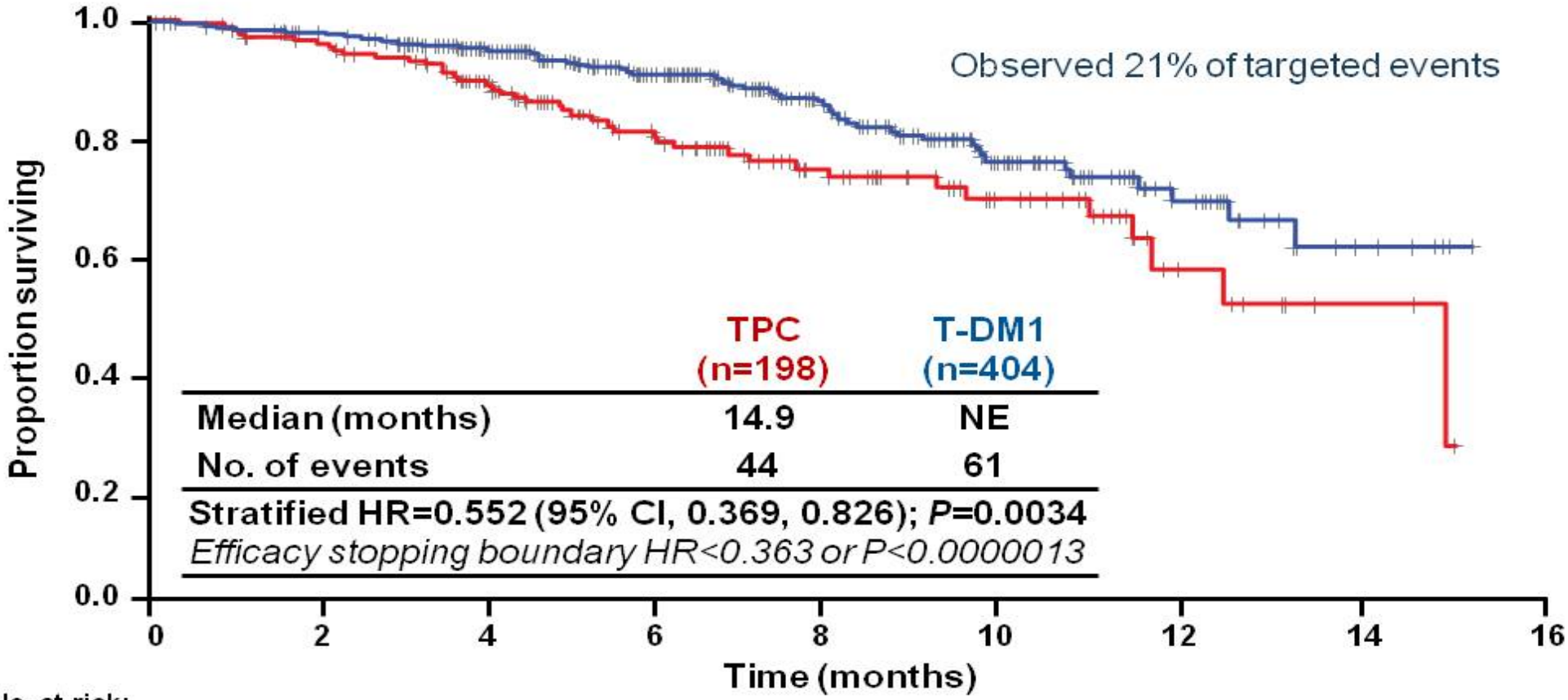
Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

No. at risk:								
TPC	198	120	62	28	13	6	1	0
T-DM1	404	334	241	114	66	27	12	0

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

Krop I et al., Lancet May 2, 2014

First Interim OS Analysis



	TPC (n=198)	T-DM1 (n=404)
Median (months)	14.9	NE
No. of events	44	61

Stratified HR=0.552 (95% CI, 0.369, 0.826); *P*=0.0034

Efficacy stopping boundary HR<0.363 or P<0.0000013

No. at risk:									
TPC	198	169	125	80	51	30	9	3	0
T-DM1	404	381	316	207	127	65	30	7	0

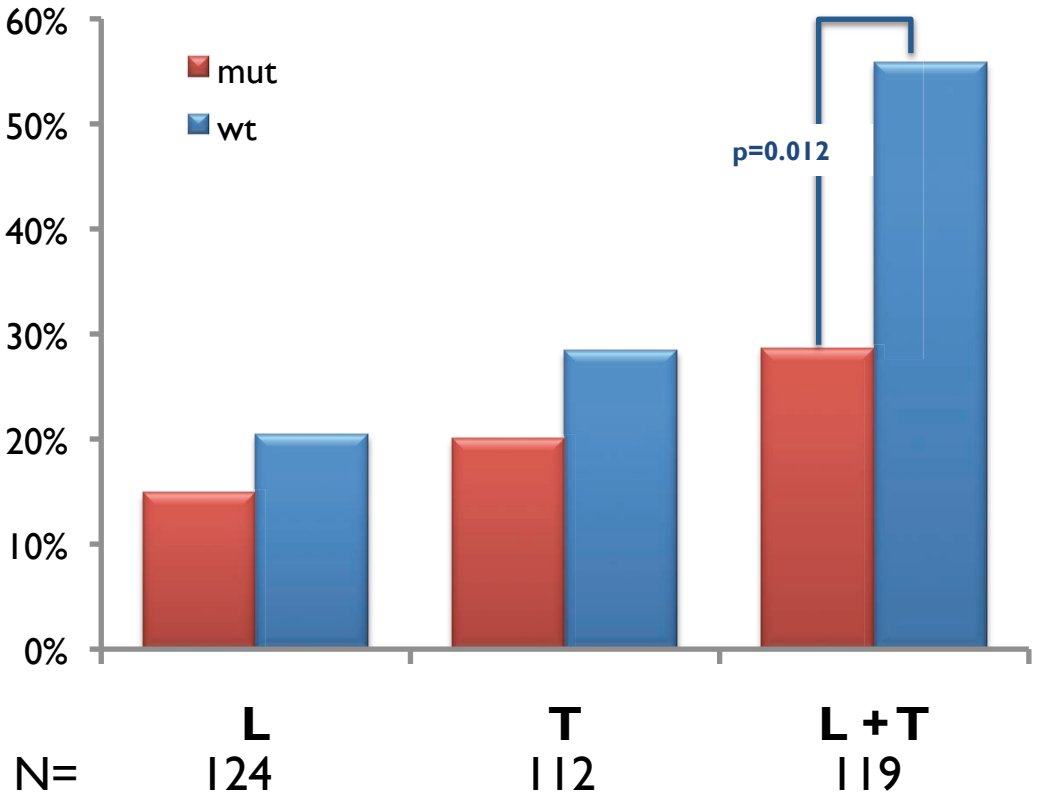
44 patients in the TPC arm received crossover T-DM1 treatment after documented progression.
Unstratified HR=0.57 (*P*=0.004).

Krop I et al., Lancet May 2, 2014

A l'heure de la recherche de traitements adaptés aux profils tumoraux, cette stratégie standardisée « the one fits all » a t-elle encore du sens?

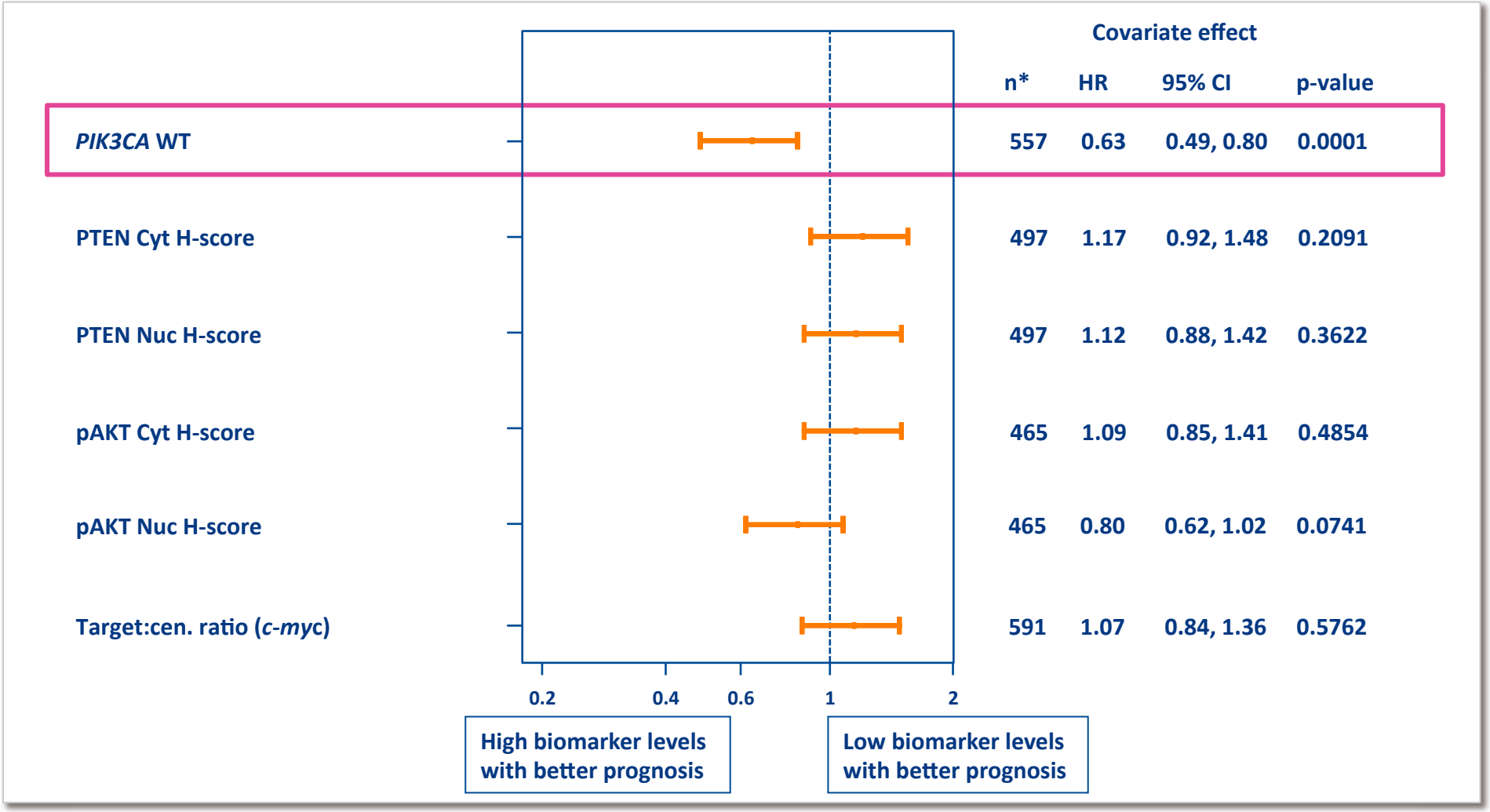
Association pCR et PIK3K selon traitement (NeoALTTO)

- pCR plus basse quand PI3K mutée
- Différence significative quand double blocage



Baselga;ESMO 2013

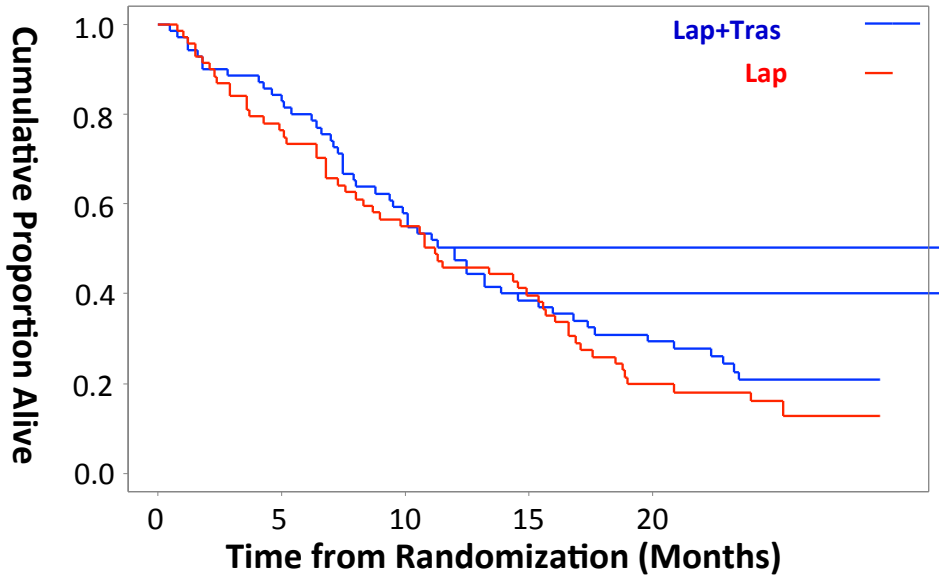
CLEOPATRA - Impact pronostique défavorable des mutations de *PIK3CA*



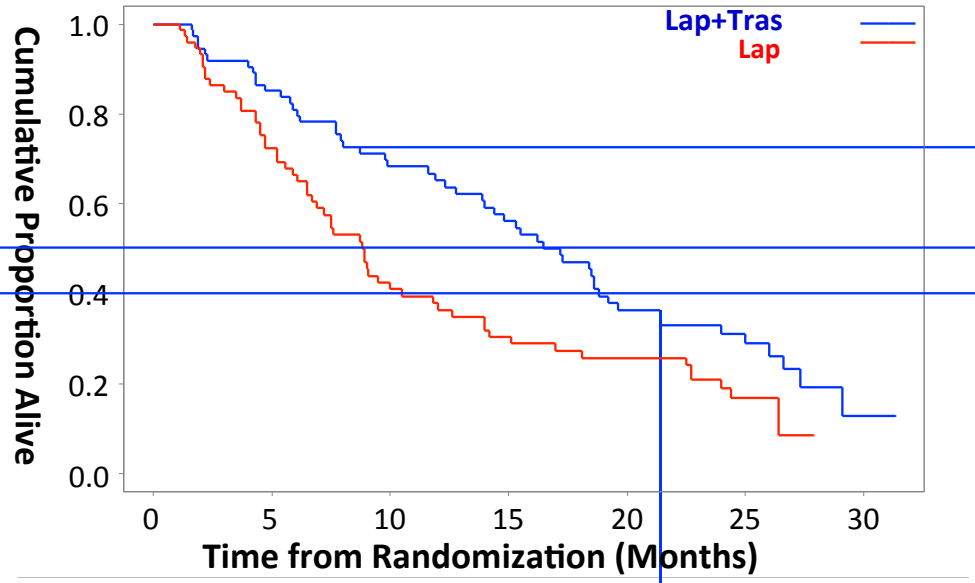
J. Baselga *et al.,* SABCS 2012, S5-1

Bénéfice significatif important d'OS chez les patientes HER2+/RH-

RH+



RH-



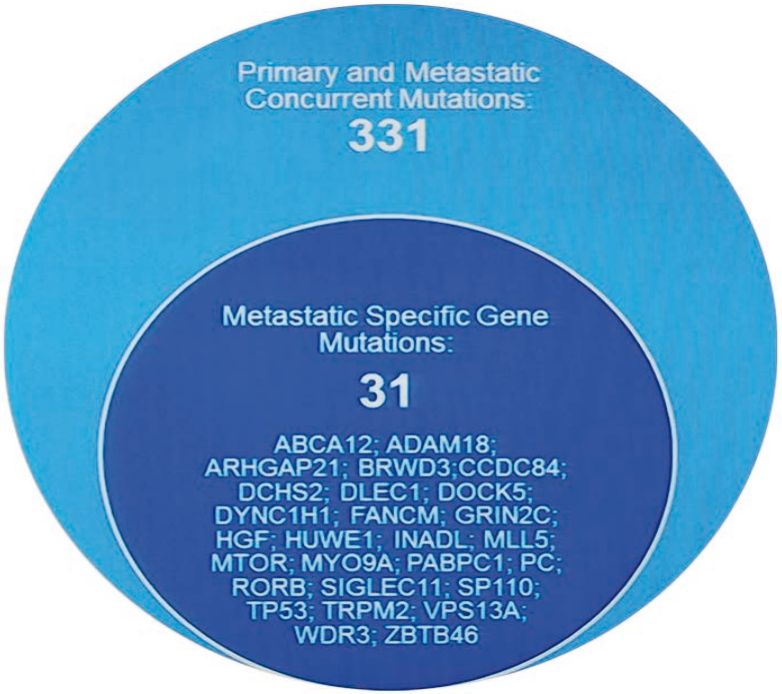
	Lap+Tras N=71	Lap N=70	OS HR (95% CI)
Median OS, mos	12.0	11.2	0.84 **(0.5-1.23)**

Δ=0,8 mois, NS

	Lap+Tras N=75	Lap N=75	OS HR (95% CI)
Median OS, mos	17.2	8.9	0.62 **(0.42-0.90)**

Δ=8,3 mois, significatif

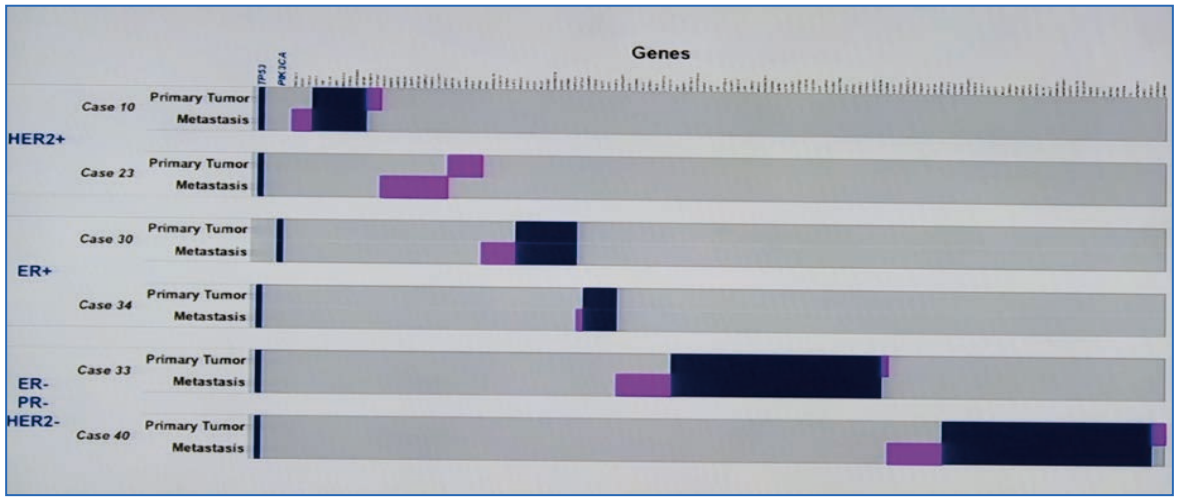
Variations génomique tumeurs primitive et métastases



K Blackwell

Comparaison tumeurs /mets après traitement

- 33 triplets
- Pression de sélection
- 8.6% nouvelles anomalies



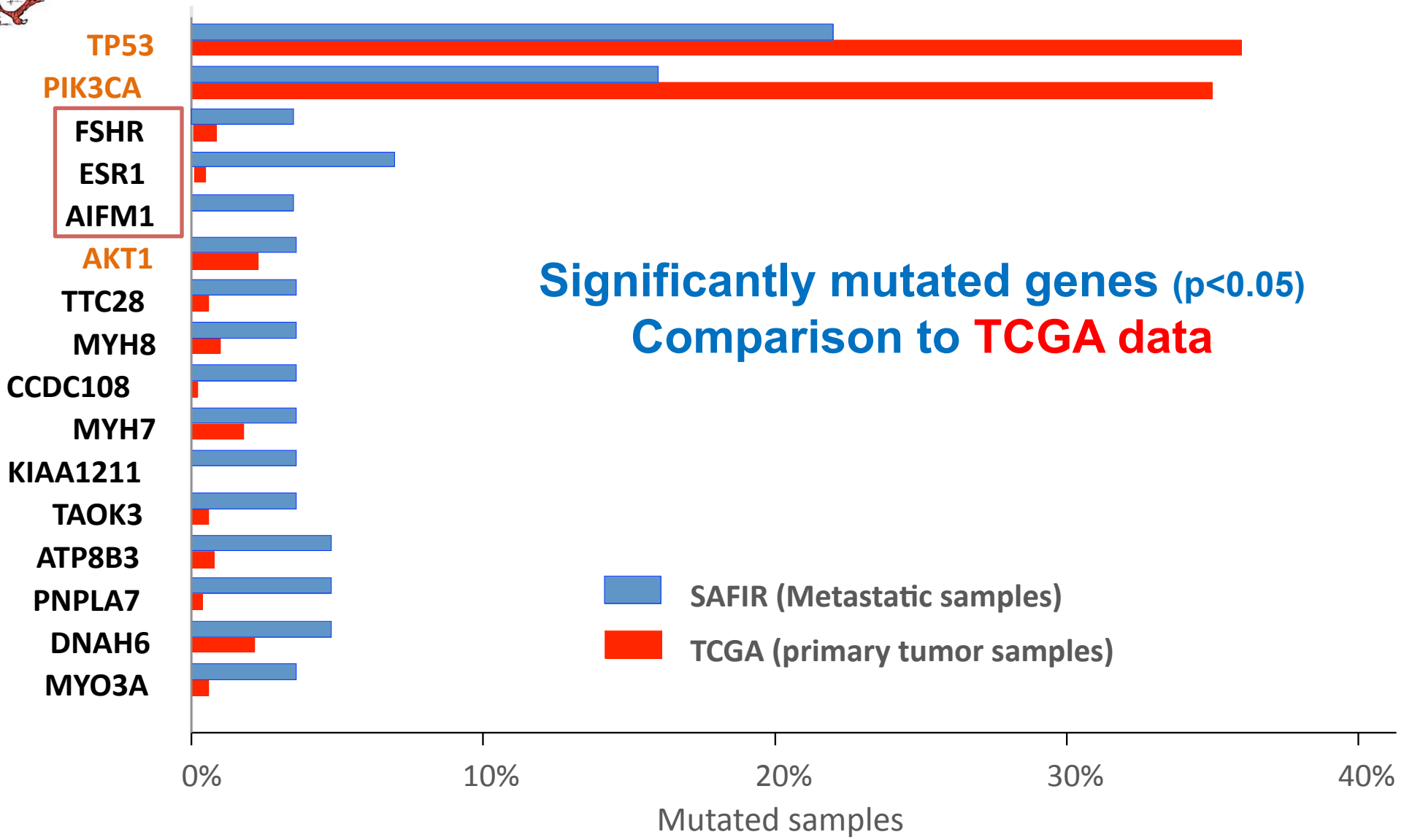
FC Bidard

6 cas (3 catégories RH+, HER2+ TNBC)
stades IV d'emblée
Mutations spécifiques des mets (EMT)
TCF7L2 pour ER+
SMAD4 pour HER2+
Suppresseur de tumeur: KRIT1 pour TNBC

Blackwell K *et al.*, SABCS 2013, S04-03

Bidard FC *et al.*, SABCS 2013, S06-06

Safir 001 biopsies métas seules



The Cancer Genome Atlas (TCGA), Nature. 2012; 490: 61–70

Conclusion

- La stratégie thérapeutique dans les cancers du sein métastatiques HER2+++ évolue très (trop) rapidement….
- Des questions..demeurent
  - Toutes les patientes ayant un cancer du sein métastatique doivent elles avoir un « double blocage »
    - Facteurs pronostic de gravité?
    - Facteurs prédictifs de réponse?
    - Les métastases RH negatifs?
  - Les patientes ayant de longue réponse doivent elles garder le trastuzumab?

Séquence en pratique 2014

Cancer du sein métastatiques HER2 +++

La liste s'allonge …et la survie aussi…….

rtuzumab

3ième lig

pécitabine

Trastuzumab et lapatinib

Trastuzumab et CT

TDM1 si non reçu en 2ème ligne

Je vous remercie

…