XVème Journées de Sénologie Interactive

Jeudi 20 et vendredi 21 septembre 2012

PARIS

Symposium GSK

Cancer du sein métastatique HER2+

Nouveaux challenges

Hormonothérapie –mécanisme de résistance

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Situation actuelle des thérapies ciblées

Biomarker	Molecular target	Cancer type	Drugs
Estrogen receptor (IHC)	ER	Breast cancer	tamoxifen, aromatase inhibitors
HER2 gene amplification (IHC, FISH)	HER2 receptor	Breast and upper GI cancers	trastuzumab, lapatinib, neratinib, pertuzumab, trastuzumab-DM1
BCR-ABL translocation	ABL kinase	CML	imatinib, dasatinib, nilotinib
EGFR kinase domain mutations (not T790M)	EGFR kinase	NSCLC	erlotinib, gefitinib
PML-RAR translocation	PML-RAR	APL	all-*trans* retinoic acid
BRCA1/2 mutation	PARP	Breast and ovarian cancer	olaparib, veliparib
B-RAF V600E mutation	B-RAF kinase	Melanoma	vemurafenib
Mutant *KIT*	KIT kinase	GIST	imatinib
Mutant *PDGFRβ*	PDGFR kinase	CMML	imatinib
EML4/ALK translocation	ALK kinase	NSCLC	crizotinib
EGFR-T790M	EGFR (drug resistant)	NSCLC	afatinib + cetuximab
TSC1 mutations	TORC1/2	Pancreas NET	everolimus
PIK3CA hot spot mutations	p110α	Breast, endometrial, colon cancer	PI3K inhibitors

Abbreviations: APL, acute promyelocytic leukemia; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; PDGFR, platelet-derived growth factor receptor.

: certitudes : promesses

(Artega et Baselga, Clin Cancer Res. 2012)

- Résistance hormonothérapie
  - Pharmacocinétique
  - Pharmacogénétique
  - Moléculaire

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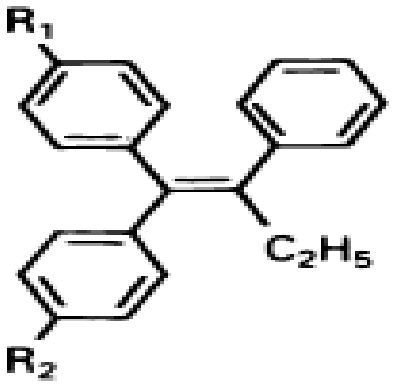
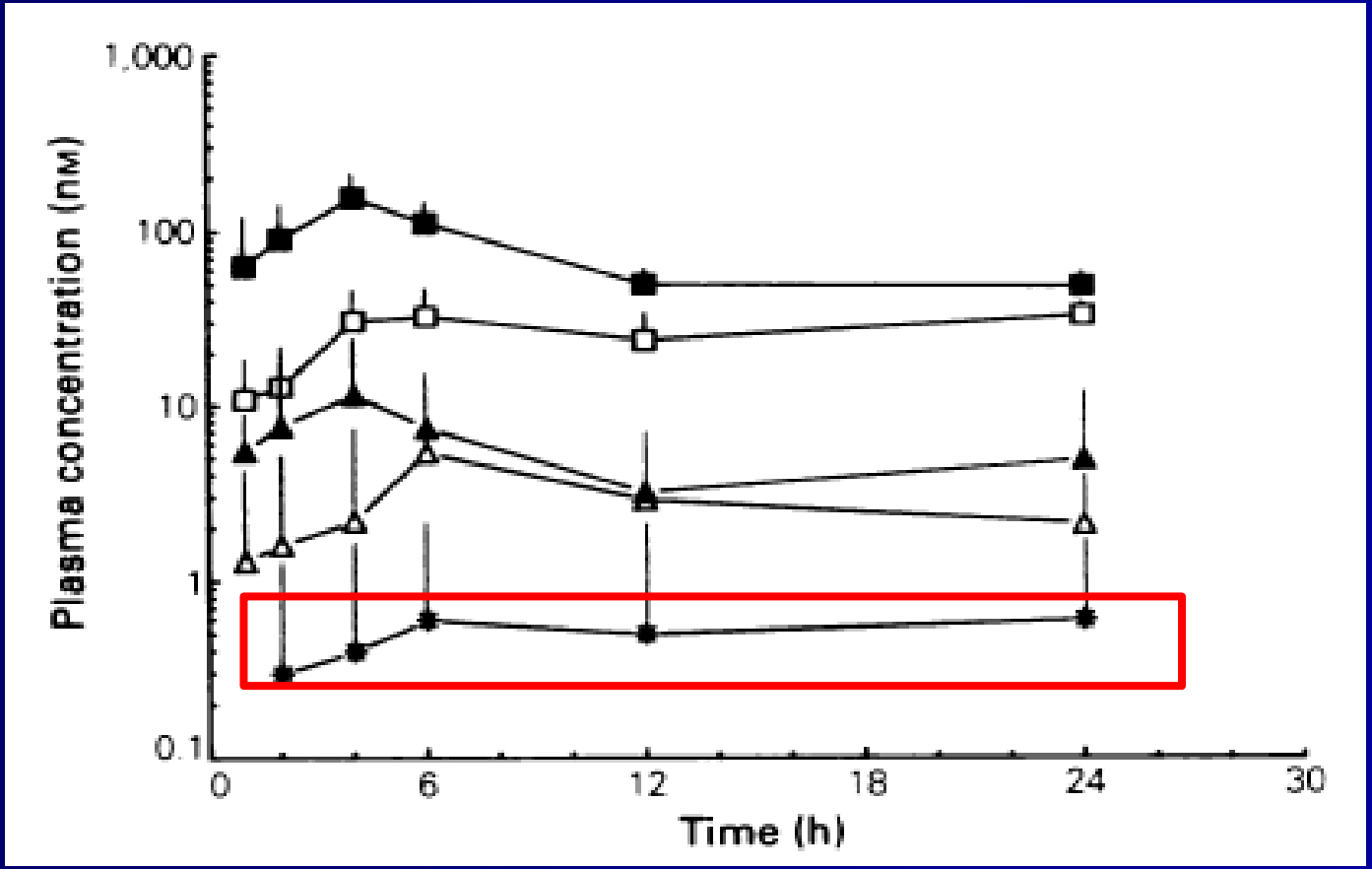
Le TMX et son métabolisme



	R_1	R_2
Tamoxifen (TMX)	$(CH_3)_2NCH_2CH_2O$	H
N-Desmethyl TMX (NDT)	$CH_3NHCH_2CH_2O$	H
Y	$OHCH_2CH_2O$	H
N-Desdimethyl TMX (Z)	$NH_2CH_2CH_2O$	H
4-Hydroxy TMX (4-OHT)	$(CH_3)_2NCH_2CH_2O$	OH

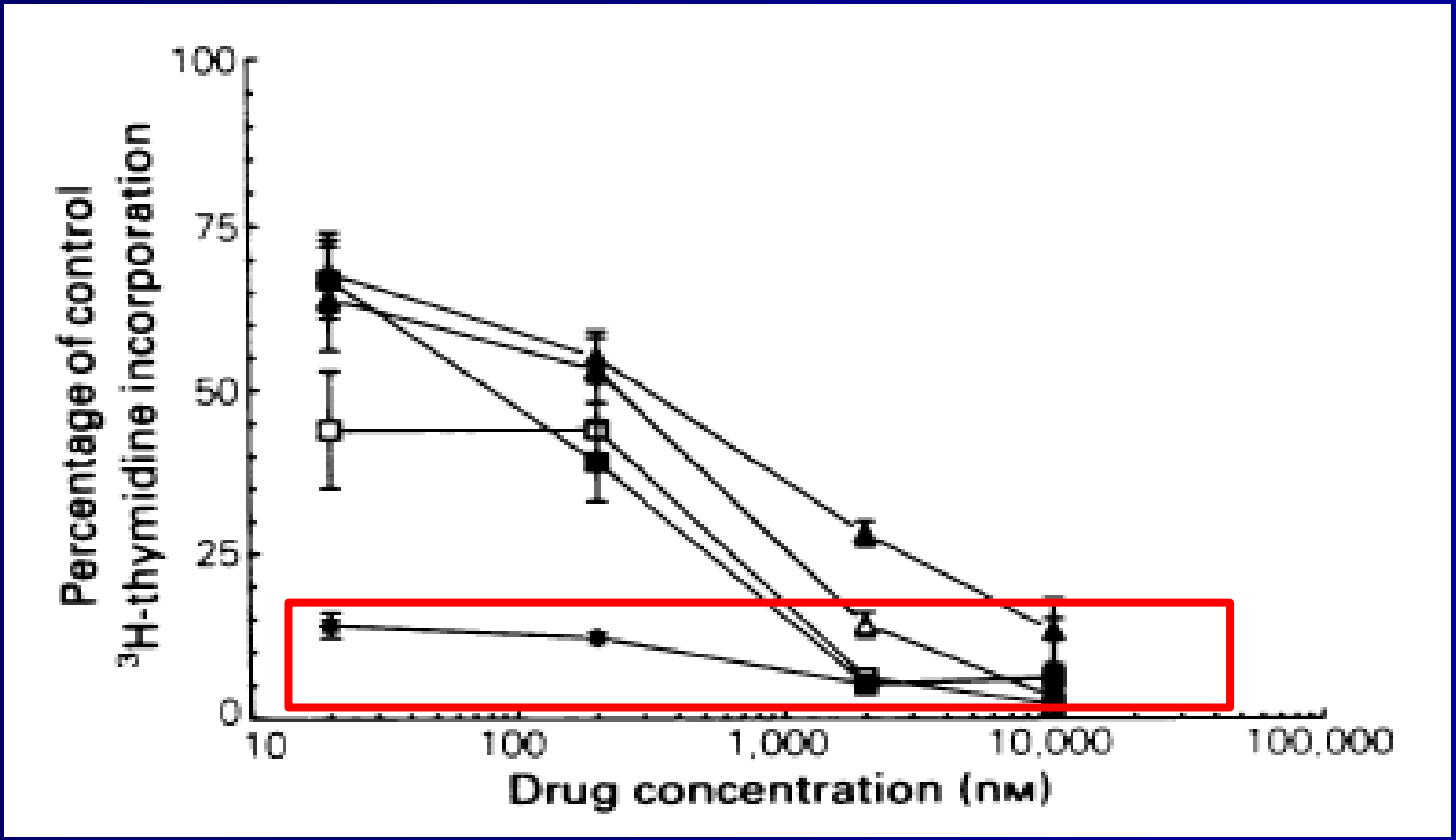
(Etienne et al, BJC 1989)

La pharmacocinétique du TMX



(Etienne et al, BJC 1989)

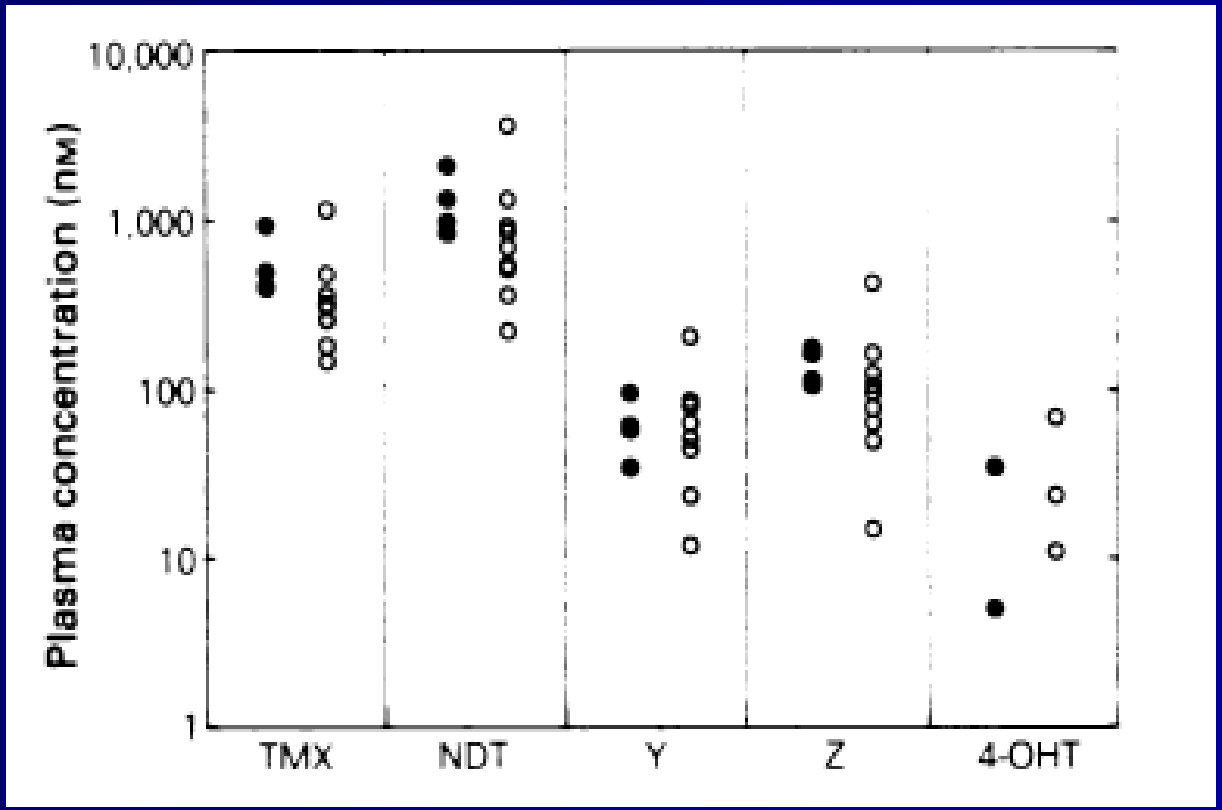
Activité pharmacologique du TMX et métabolites



(Etienne et al, BJC 1989)

TMX et métabolites : relations PK-PD

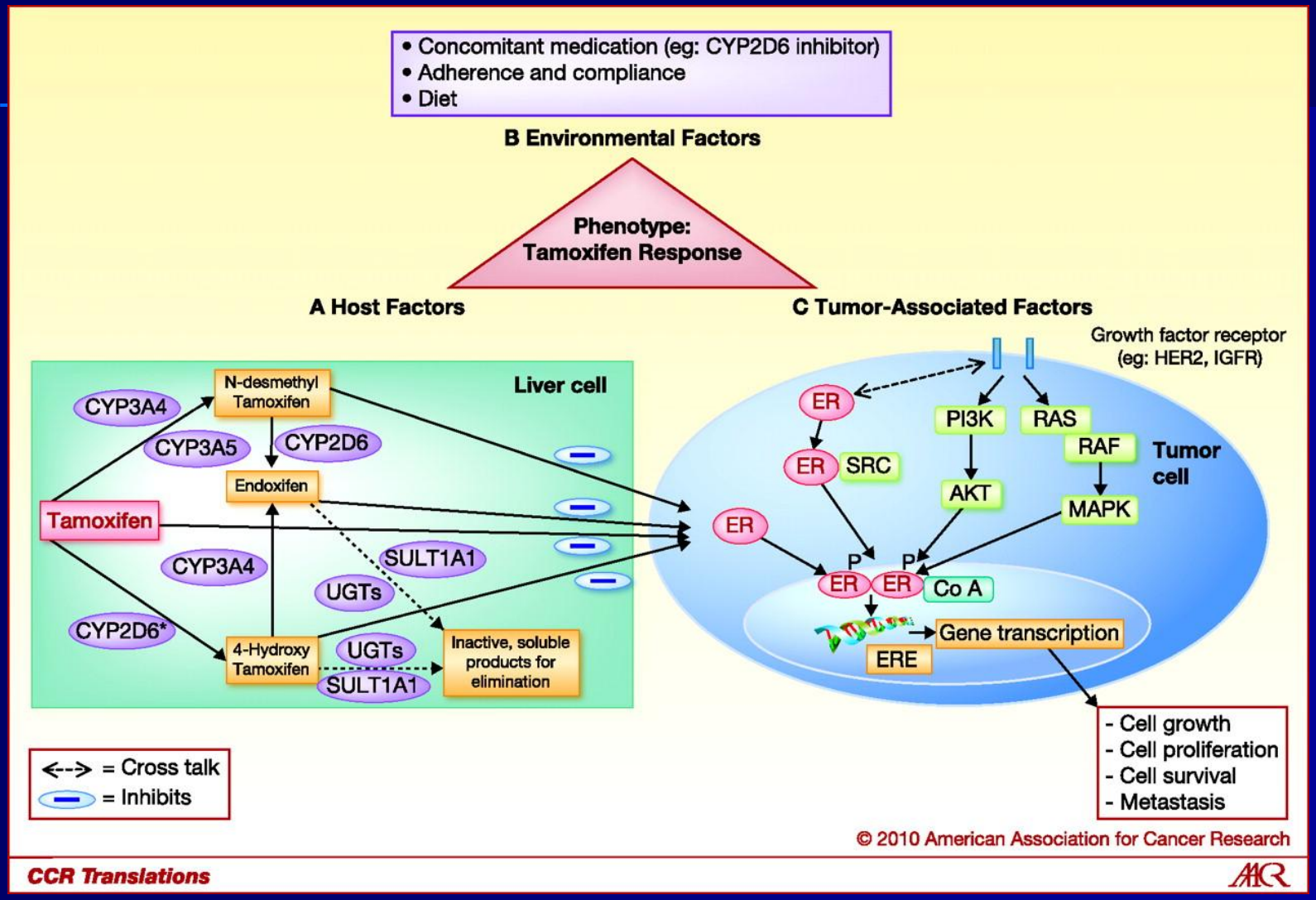
○ = PD
● = PR,stab



(Etienne et al, BJC 1989)

- Résistance hormonothérapie
  - Pharmacocinétique
  - Pharmacogénétique
  - Moléculaire

Traitement par tamoxifene : impact potentiel des variants du CYP2D6

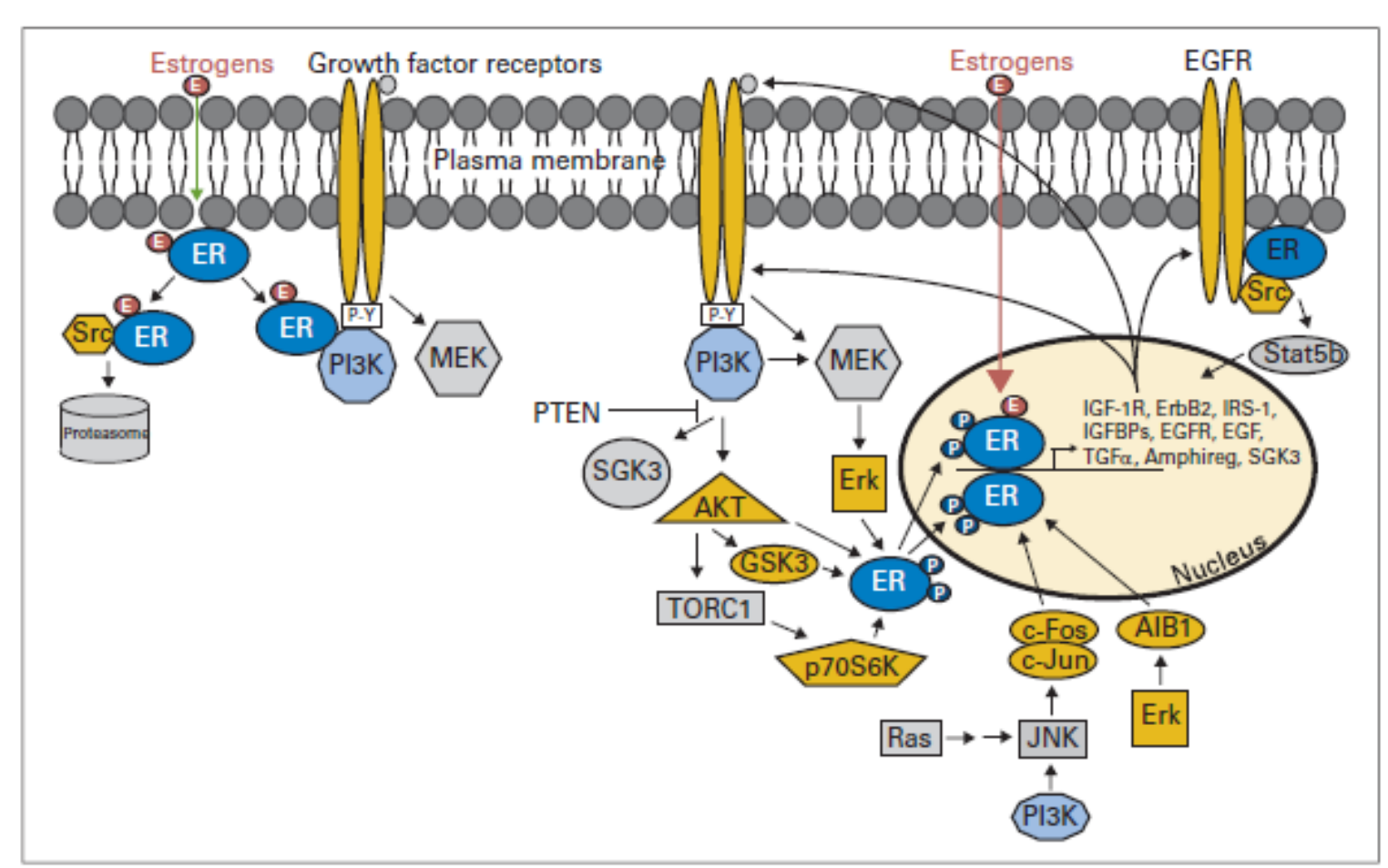


(Bardia A et Stearns V, Clin Cancer Res, 2010)

- Résistance hormonothérapie
  - Pharmacocinétique
  - Pharmacogénétique
  - Moléculaire

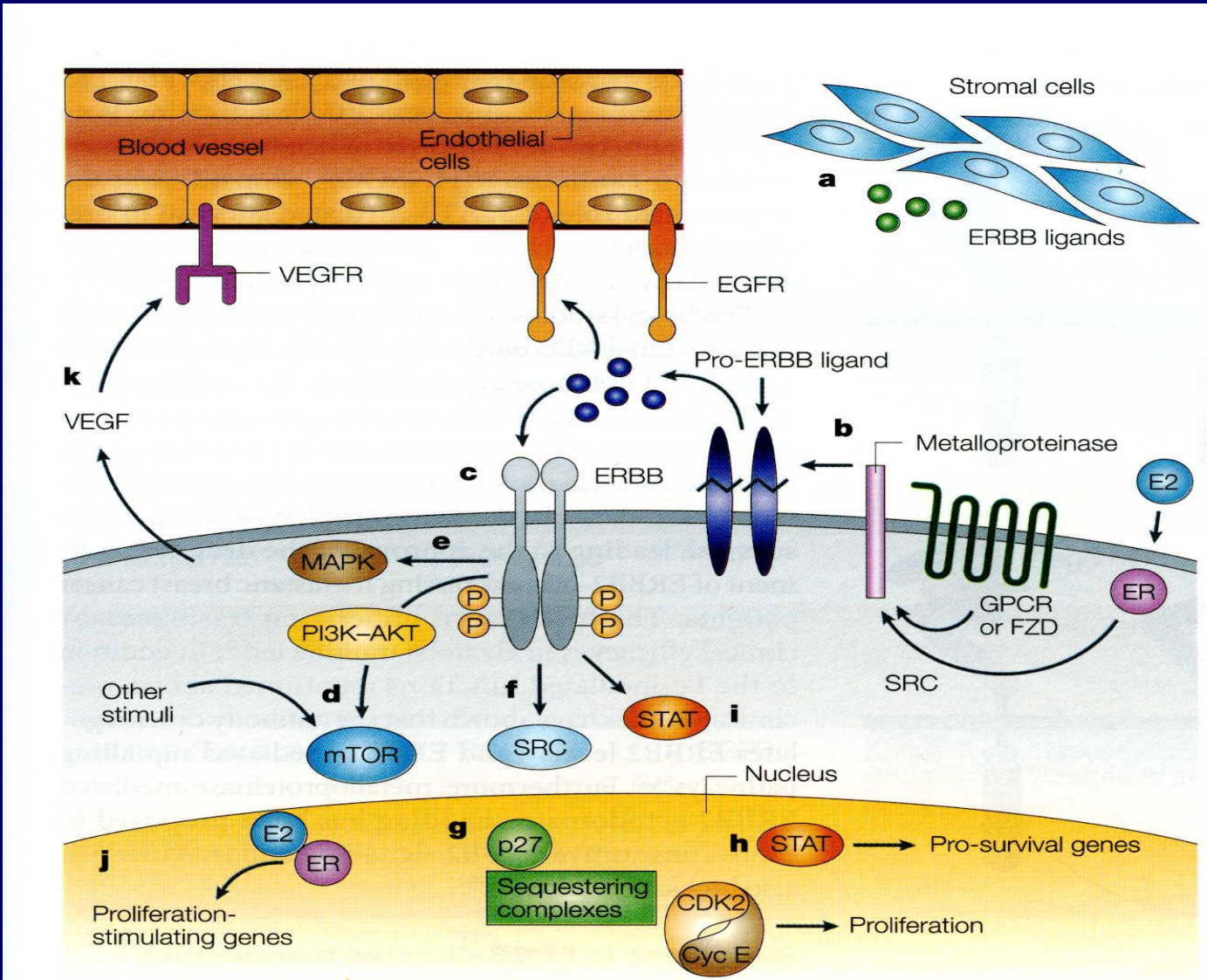
"Cross-Talk"

Interactions réciproques HER-ER



(Miller et al., J Clin Oncol 2011)

Impact du RE sur signalisation HER

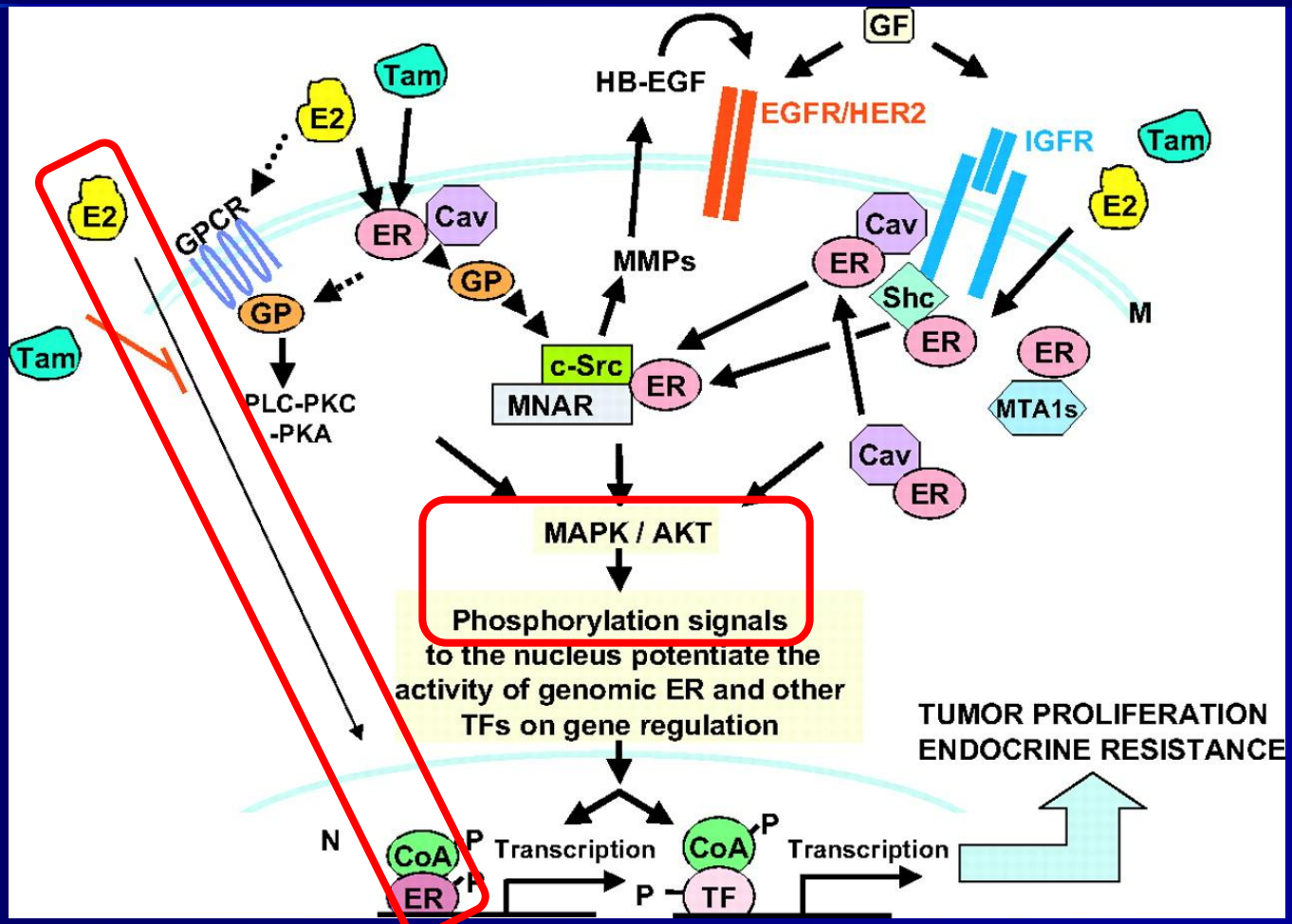


(Hynes et Lane, Nat Rev Cancer. 2005)

Cross Talk HER-ER induit la résistance aux AE

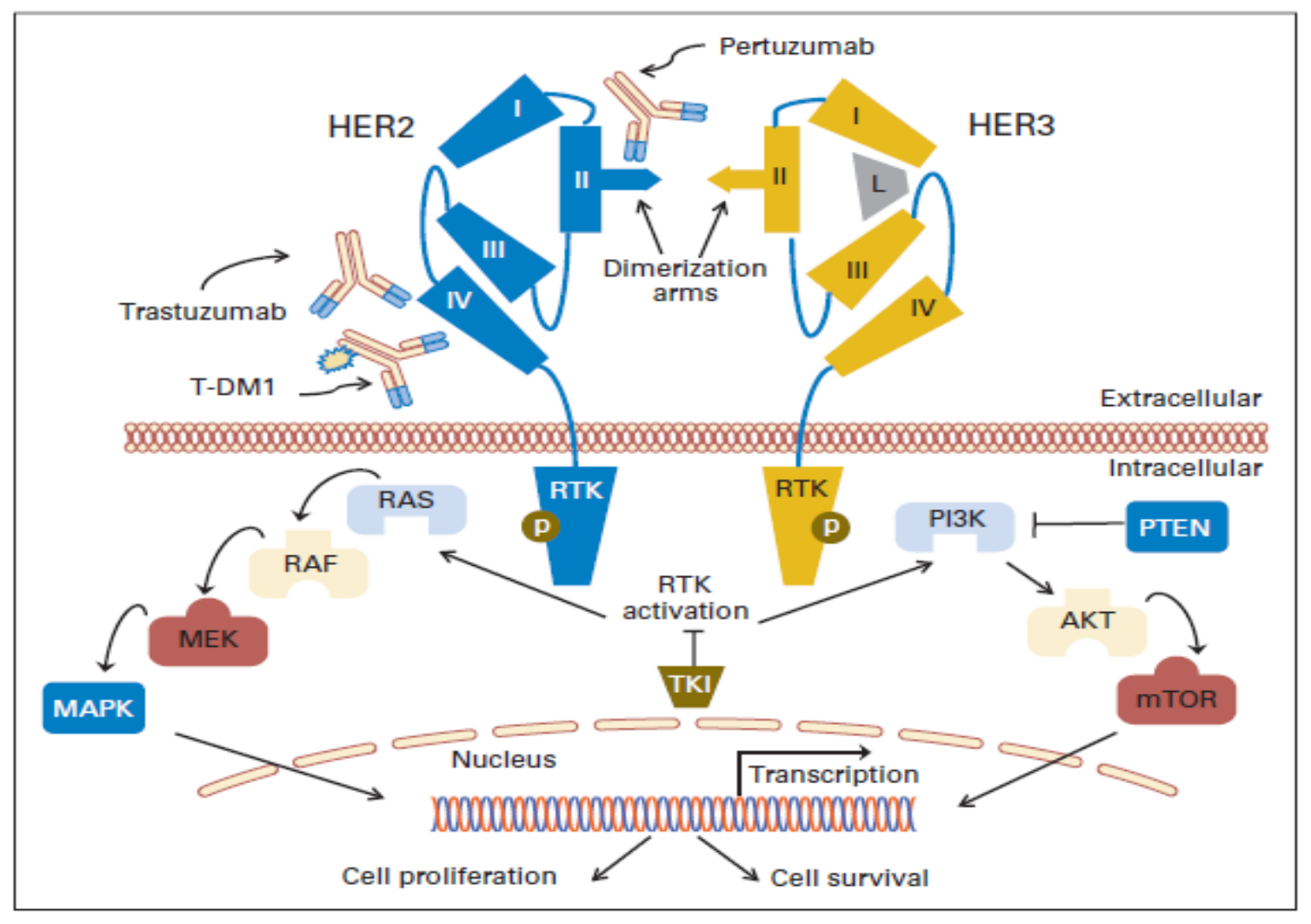
"Things should be made as simple as possible, but not simpler"

Einstein A (1950)



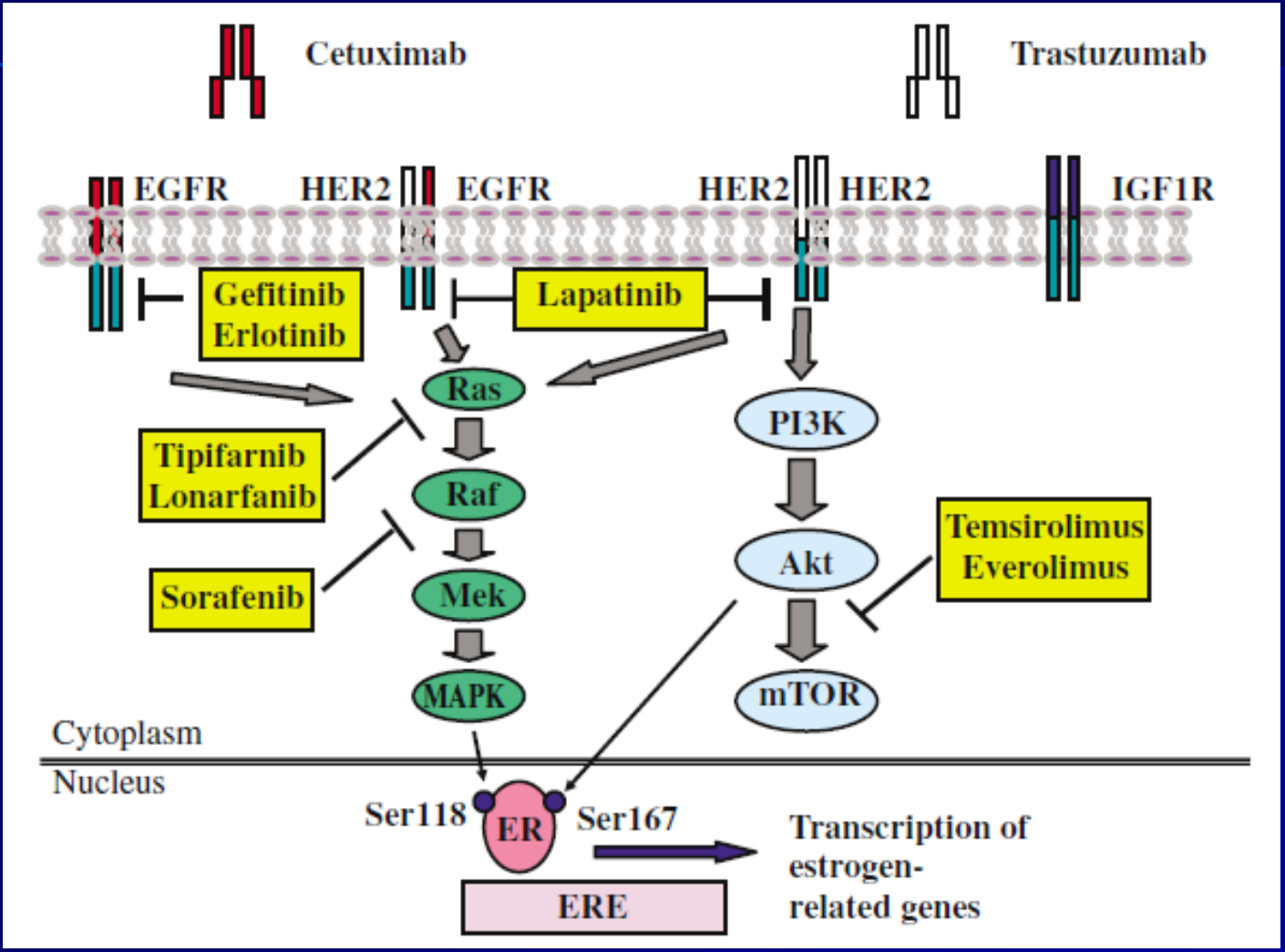
(Arpino et al., Endocrine Rev. 2008)

Stratégie de réplique au cross-talk HER-ER



(Olson M. J Clin Oncol 2012)

Traitement pharmacologique du cross –talk HER-RE



(Leary A. and Dowsett M., Br J Cancer, 2006)

Preuve du concept 1 : Verrou m-TOR

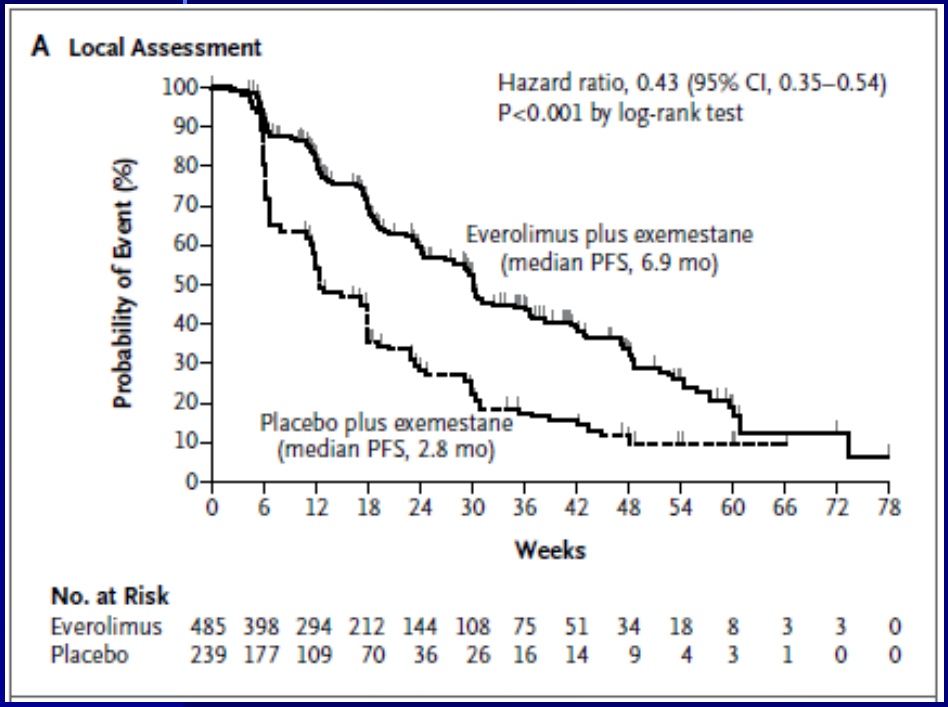
Inhibiteur de m-TOR + anti-aromatase
BOLERO - 2

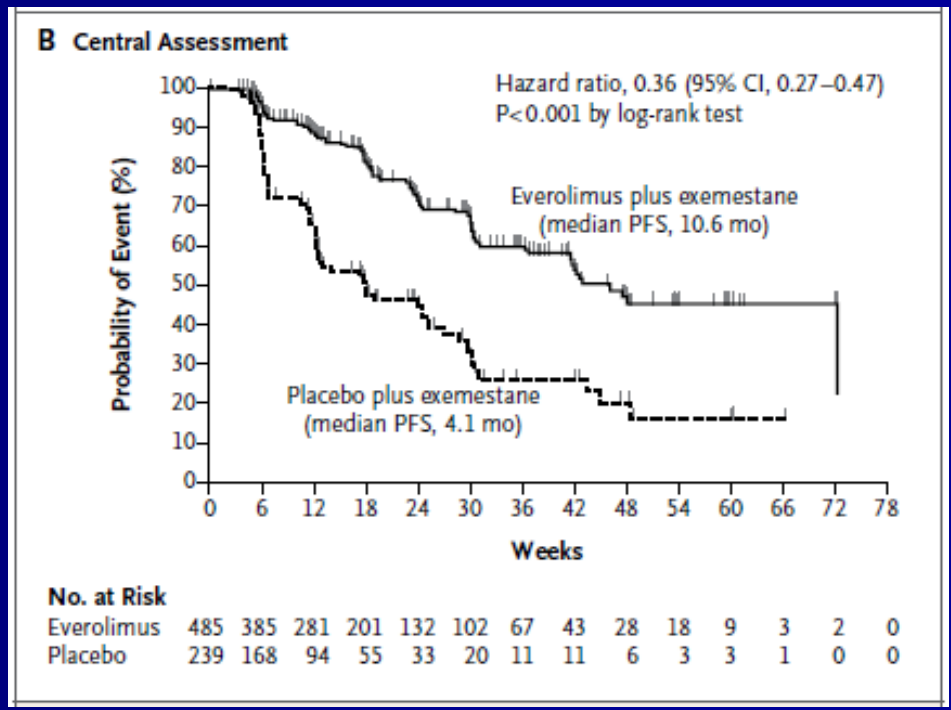
Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D.,and Gabriel N. Hortobagyi, M.D.

(NEJM, feb 9, 2012)

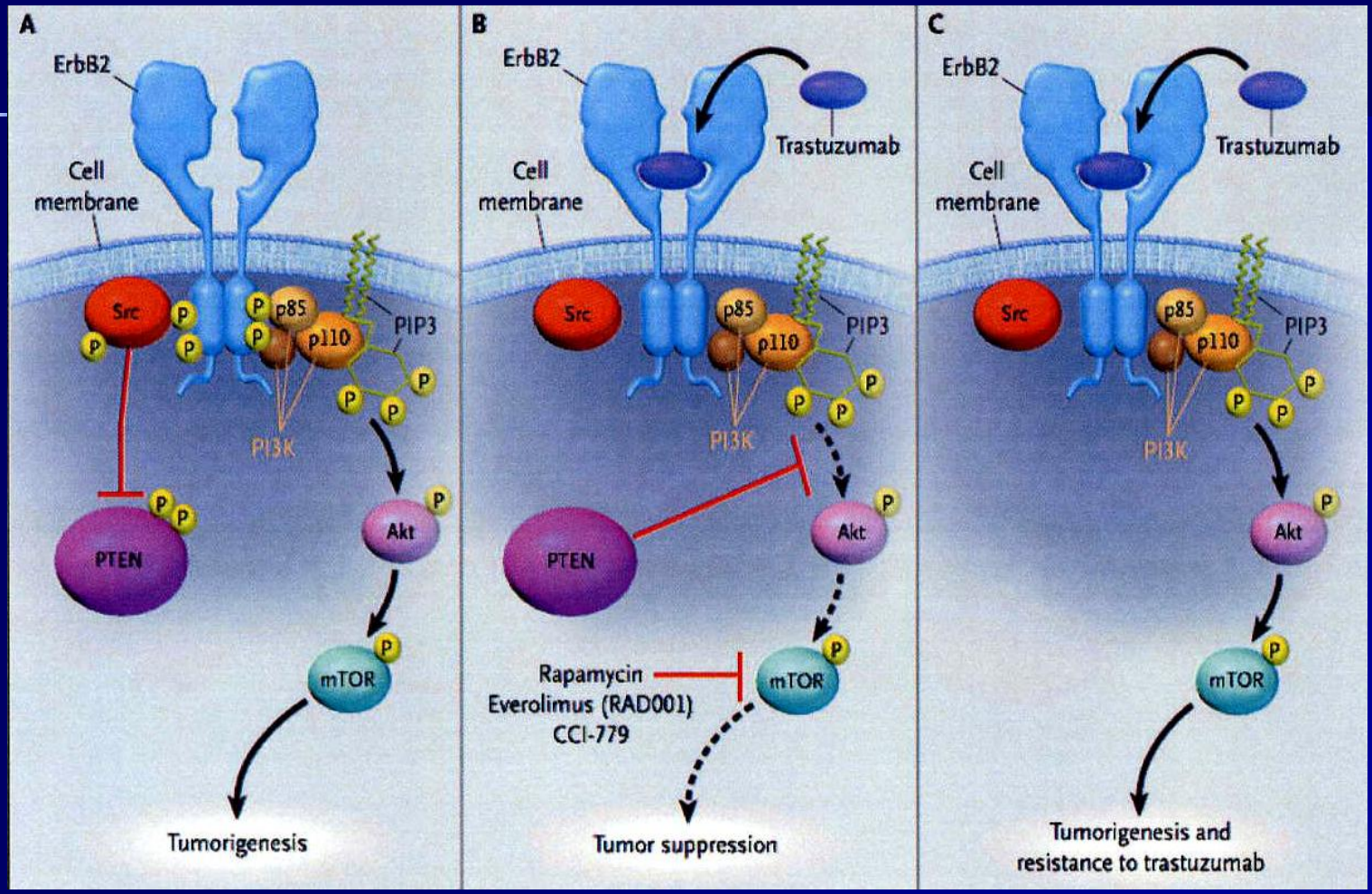
BOLERO -2 survie sans évènements





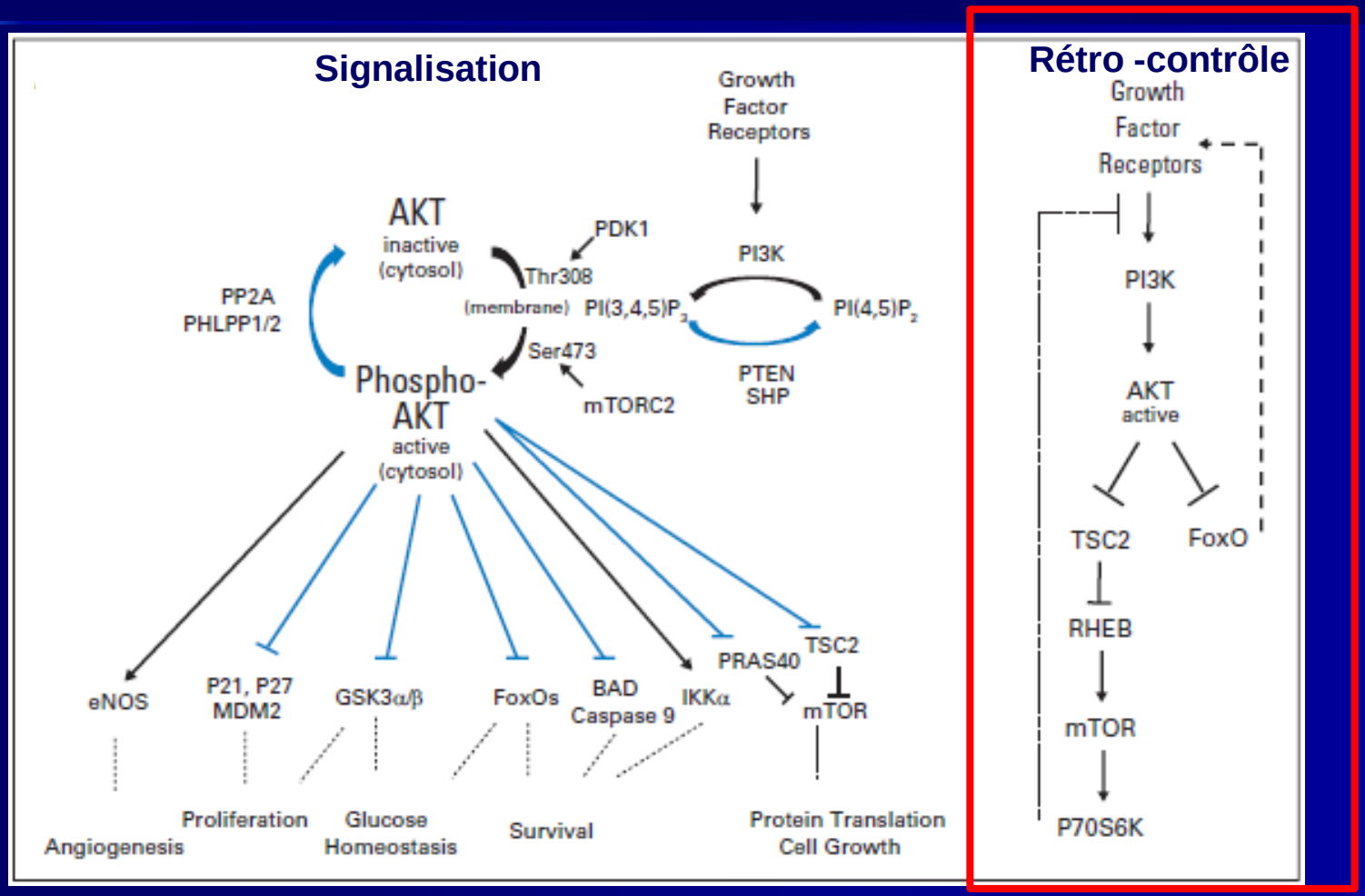
(Baselga J., NEJM, feb 9, 2012)

Trastuzumab agit principalement sur la vie PI3K CA



(Pandolfi, 2004)

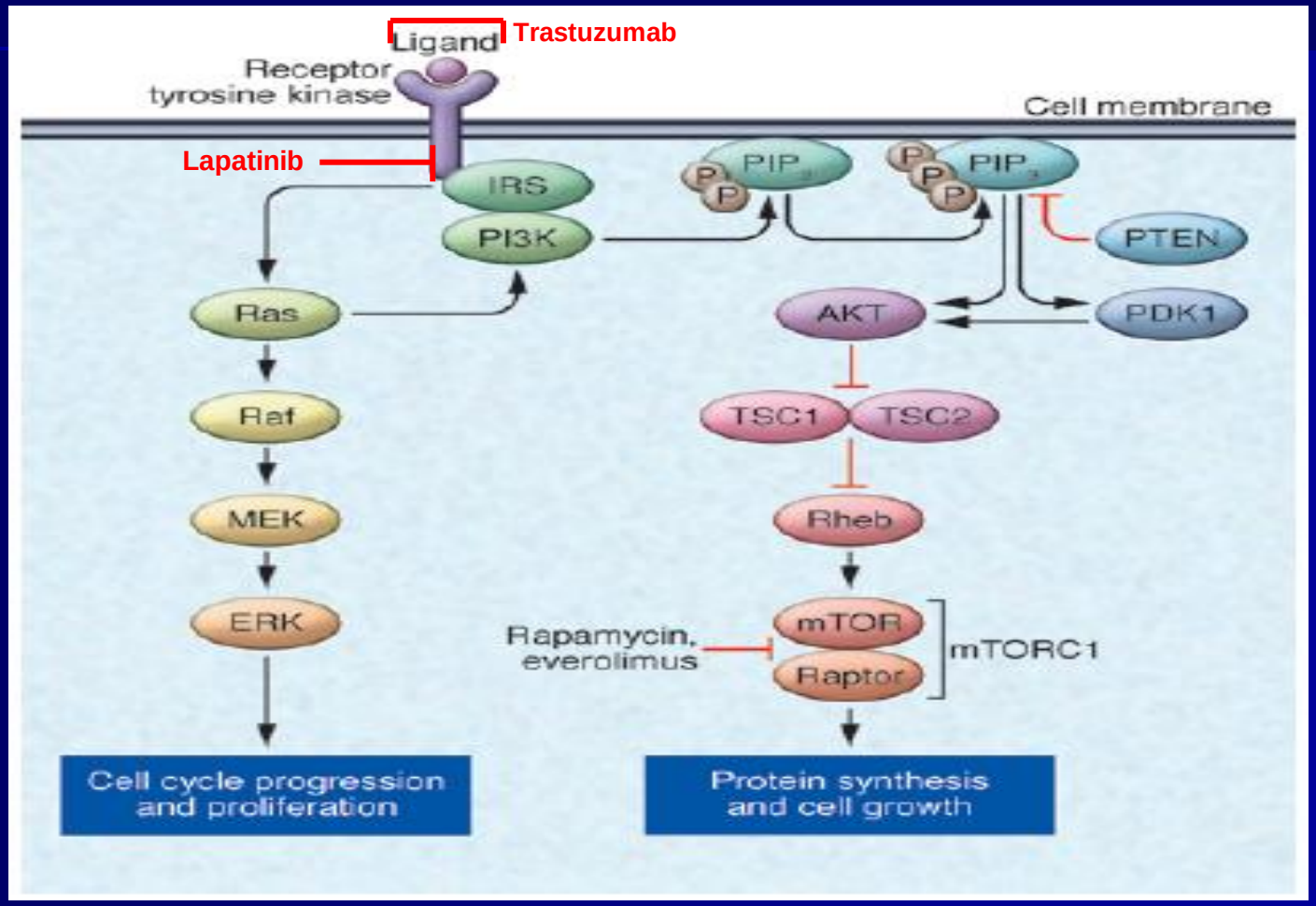
Voie PI3K rétro-contrôlée



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

Preuve du concept 2 :

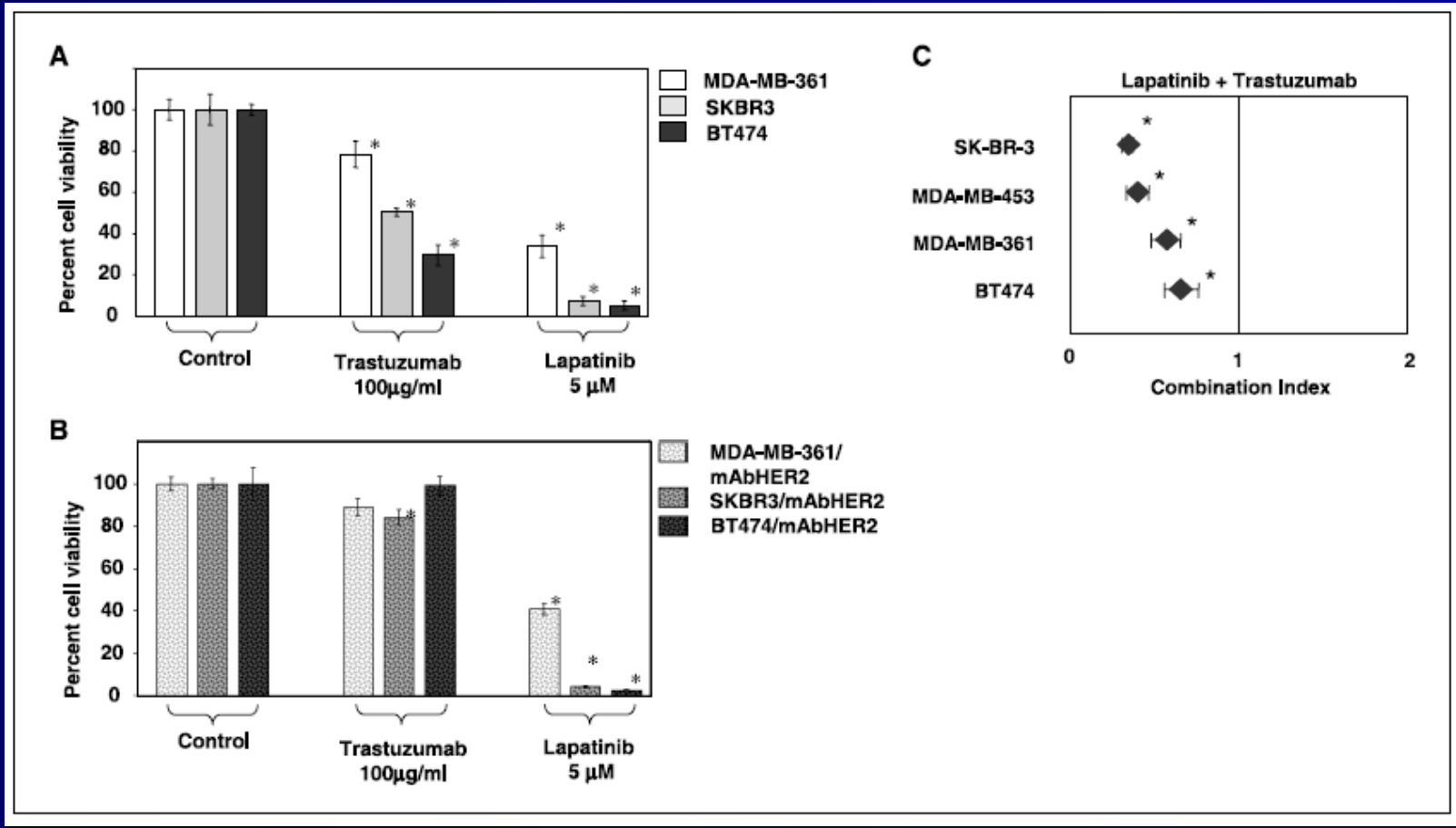
Verrou pharmacologique sur la voie PI3K et MAPK



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

Association trastuzumab-lapatinib

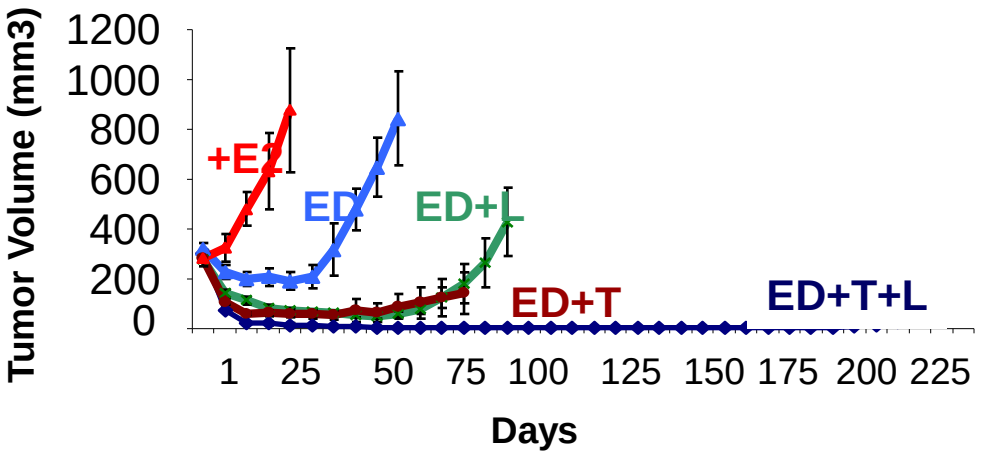
Effets supra-additifs



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

Efficacité anti-tumorale optimale de la double inhibition HER2 associée à un traitement par AE

Estrogen Deprivation (ED)



T – Trastuzumab
L – lapatinib
L+T – Trast + Lap

(M Rimawi et al. Clin Cancer Res 2011)

Double inhibition HER 2 plus hormonothérapie
Etude ALTERNATIVE : Study Design

Patient Population

- ER+ and/or PgR+ and HER2+
- Postmenopausal
- Stage IV
- Relapsed following neo-/ adjuvant trastuzumab and endocrine therapy
- No prior treatment for MBC

Stratification

- Aromatase Inhibitor chosen by Investigator
- Time since neo-/adjuvant trastuzumab (< 6months/ ≥ 6months)
- Sites of disease (bone only/ visceral or soft tissue)

1:1:1 RANDOMIZE

N=525

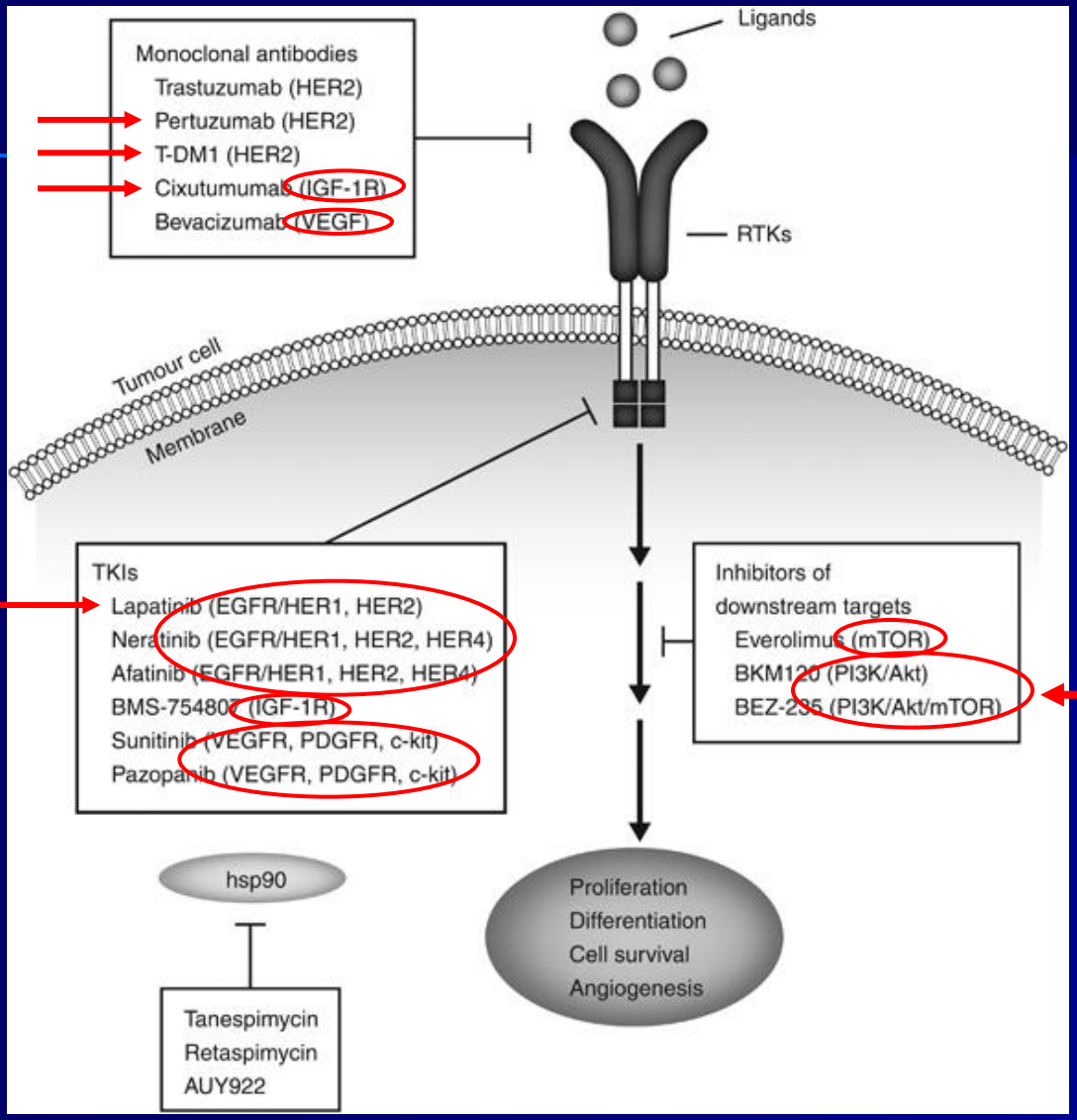
Treatment Group B
Trastuzumab (8 mg/IV load) → 6 mg/kg IV q3 weekly + AI*

Treatment Group C
Lapatinib 1500 mg po once daily + AI*

Treatment Group A
Lapatinib 1000 mg po once daily + Trastuzumab (8 mg/IV load) → 6 mg/kg IV q3 weekly + AI*

**AI=aromatase inhibitor chose by investigator-letrozole, anastrozole, or exemestane*

Nouvelles stratégies thérapeutiques post-HER2 dans le cancer du sein et traitement personnalisé



Impact des mutations PI3K ?

(Tsang et Finn, Br J Cancer. 2012)

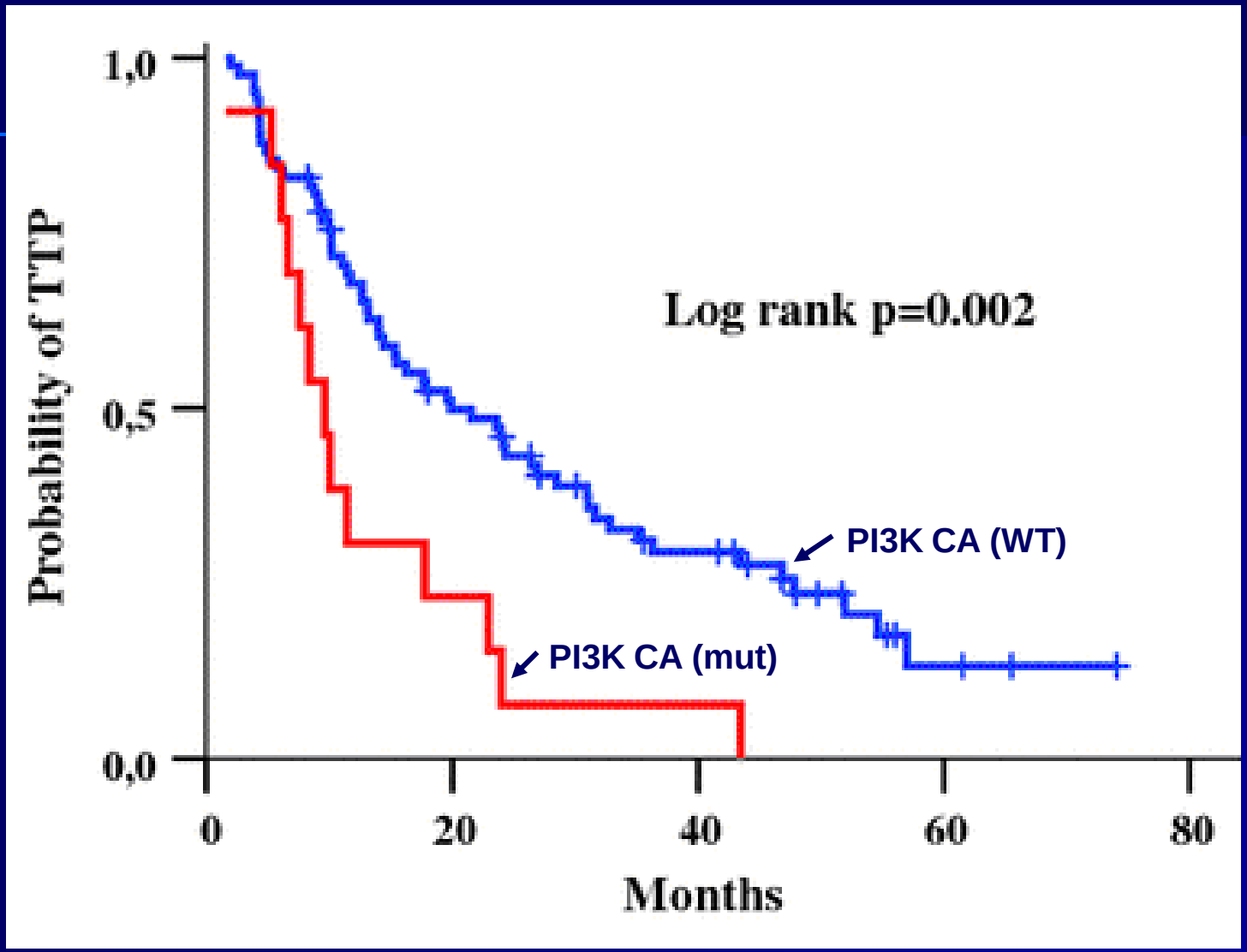
Echappement au verrou thérapeutique

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%)

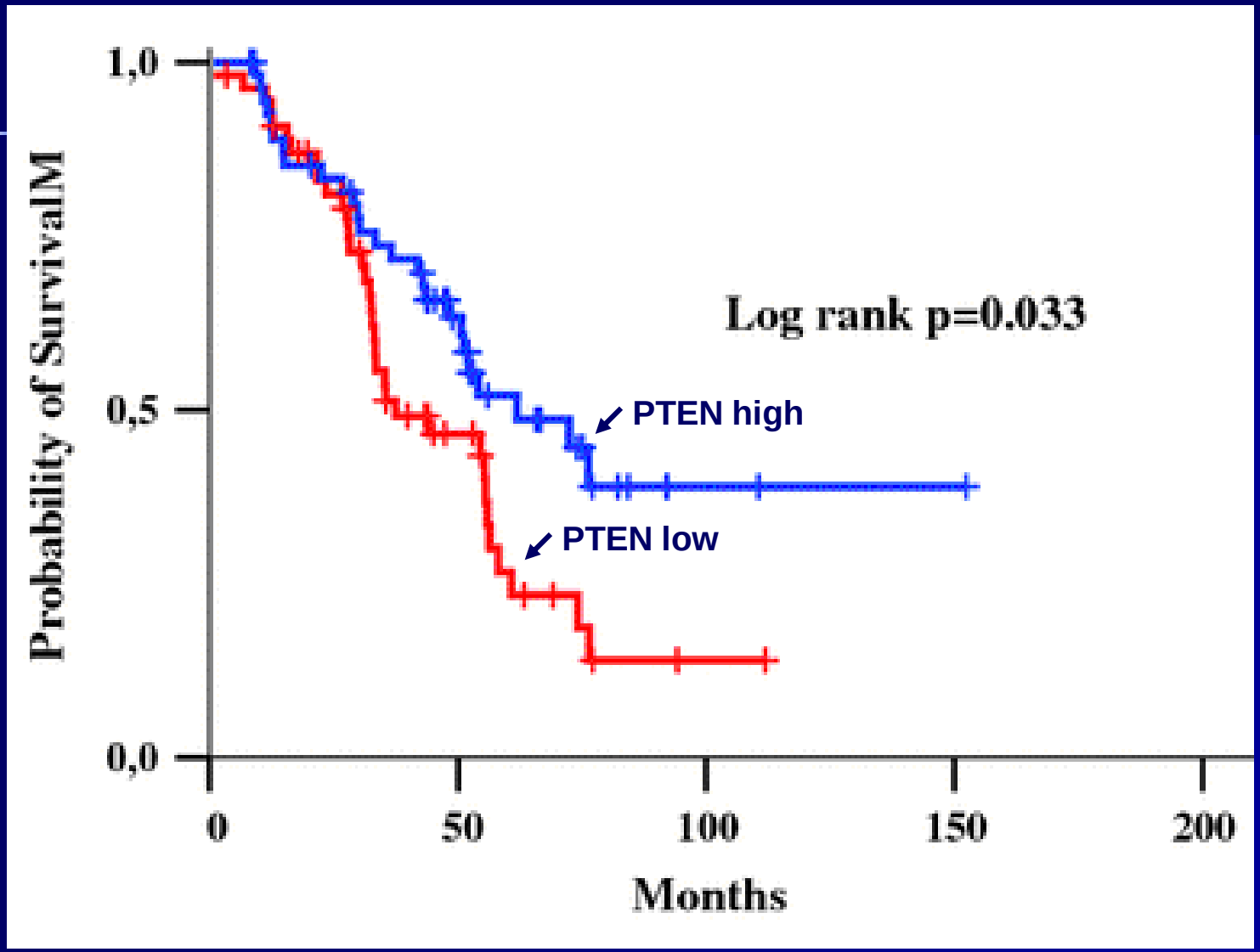
(Stemke-Hale et al., Cancer Res. 2008)

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



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

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



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

Mut PI3K CA favorables à l'activité des anti m-TOR

PI3K/AKT/mTOR Inhibitors in Patients With Breast and Gynecologic Malignancies Harboring *PIK3CA* Mutations

Filip Janku, Jennifer J. Wheler, Shannon N. Westin, Stacy L. Moulder, Aung Naing, Apostolia M. Tsimberidou, Siqing Fu, Gerald S. Falchook, David S. Hong, Ignacio Garrido-Laguna, Rajyalakshmi Luthra, J. Jack Lee, Karen H. Lu, and Razelle Kurzrock

See accompanying editorial on page 765

A B S T R A C T

Purpose
Mutations of the *PIK3CA* gene may predict response to phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) inhibitors. Concomitant mutations in the mitogen-activated protein kinase (MAPK) pathway may mediate resistance.

Patients and Methods
Tumors from patients with breast, cervical, endometrial, and ovarian cancer referred to the Clinical Center for Targeted Therapy (Phase I Program) were analyzed for *PIK3CA*, *KRAS*, *NRAS*, and *BRAF* mutations. Patients with *PIK3CA* mutations were treated, whenever feasible, with agents targeting the PI3K/AKT/mTOR pathway.

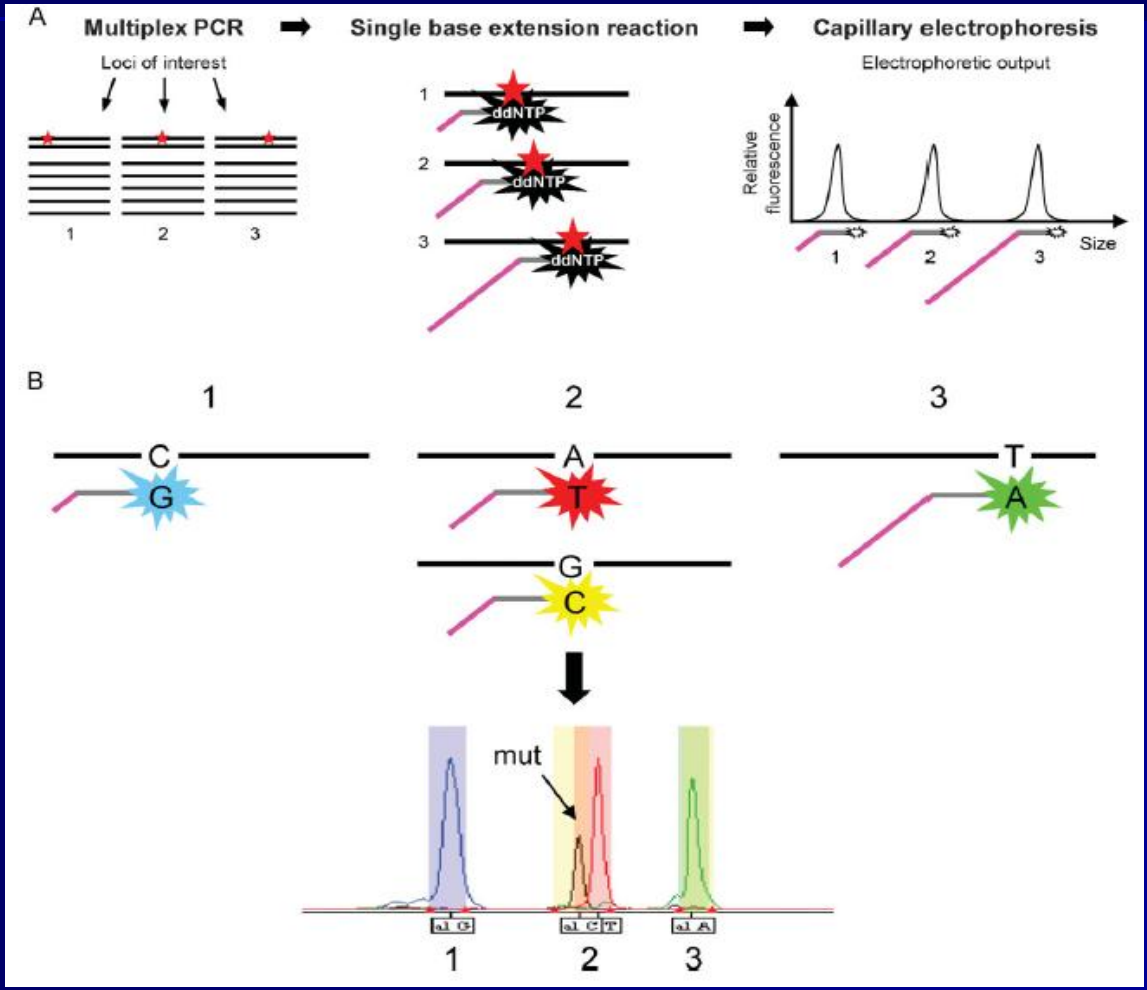
Results
Of 140 patients analyzed, 25 (18%) had *PIK3CA* mutations, including five of 14 patients with squamous cell cervical, seven of 29 patients with endometrial, six of 29 patients with breast, and seven of 60 patients with ovarian cancers. Of the 25 patients with *PIK3CA* mutations, 23 (median of two prior therapies) were treated on a protocol that included a PI3K/AKT/mTOR pathway inhibitor. Two (9%) of 23 patients had stable disease for more than 6 months, and seven patients (30%) had a partial response. In comparison, only seven (10%) of 70 patients with the same disease types but with wild-type *PIK3CA* treated on the same protocols responded ($P = .04$). Seven patients (30%) with *PIK3CA* mutations had coexisting MAPK pathway (*KRAS*, *NRAS*, *BRAF*) mutations (ovarian cancer, n = 5; endometrial cancer, n = 2), and two of these patients (ovarian cancer) achieved a response.

Conclusion
PIK3CA mutations were detected in 18% of tested patients. Patients with *PIK3CA* mutations treated with PI3K/AKT/mTOR inhibitors demonstrated a higher response rate than patients without mutations. A subset of patients with ovarian cancer with simultaneous *PIK3CA* and MAPK mutations responded to PI3K/AKT/mTOR inhibitors, suggesting that not all patients demonstrate resistance when the MAPK pathway is concomitantly activated.

J Clin Oncol 30:777-782. © 2012 by American Society of Clinical Oncology

Traitement personnalisé : recherche de mutations

Essai SNaP shot / PCR multiplex
Principe



(Dias – Santagata D., Mol Med, 2010)

Cancer du sein HER +
Nouveaux challenges

Hormonothérapie – mécanismes de résistance
Conclusion et perspectives

1 – Résistance multifocale potentiellement identifiable et modulable par la pharmacologie.

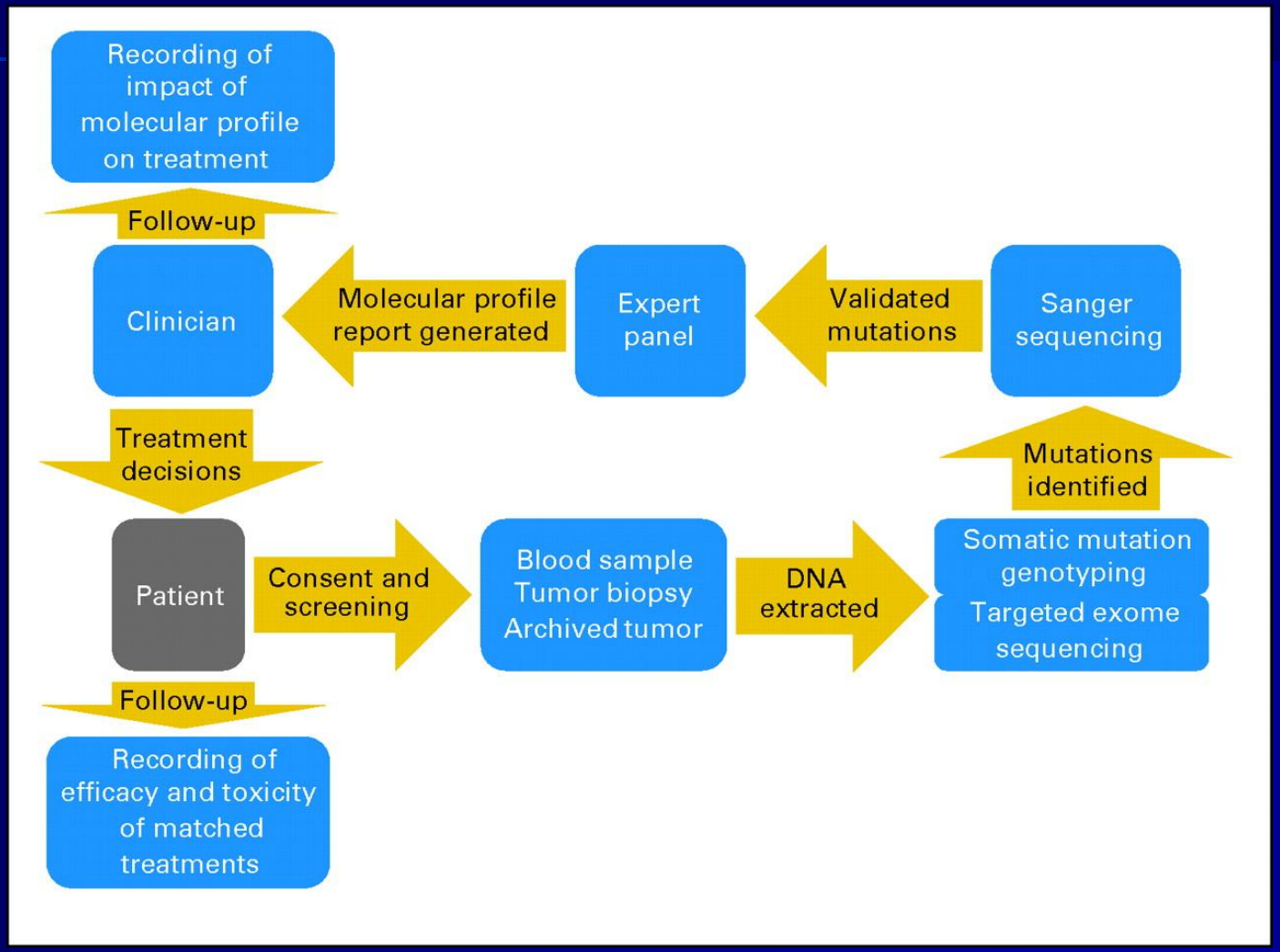
2 – L'interaction moléculaire (Cross-Talk) HER-ER est une cause de résistance à l'hormonothérapie.

3- Des verrous thérapeutiques sont possibles pour corriger cette résistance.

4 – Des sources de résistance primaire à ces verrous thérapeutiques sont identifiables (mut PI3KCA, PTEN). Elles peuvent avoir un impact différent selon les traitements ciblés utilisés.

5 – Un traitement personnalisé est nécessaire.

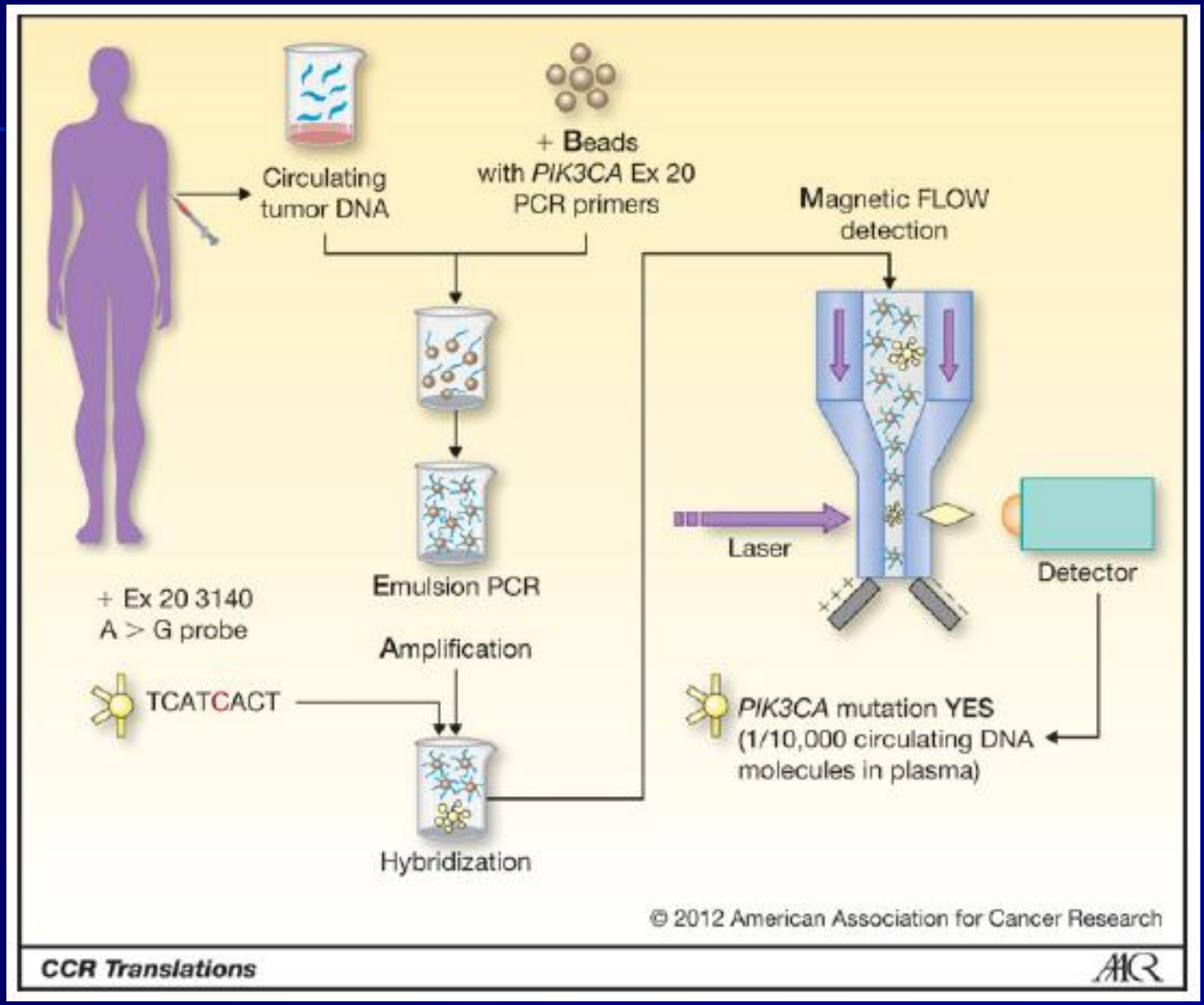
Prise en charge du patient basée sur la génomique
(Expérience actuelle du Princess Margaret Hospital – Ontario)



(Tran et al., J Clin Oncol. 2012)

Une évolution significative : BEAMing

La détection des mutations dans le sang circulant



(Richardson and Iglehart, Clin Cancer Res 2012)