SOCIÉTÉ FRANÇAISE DE SÉNOLOGIE ET DE PATHOLOGIE MAMMAIRE

Institut de Cancérologie de l'Ouest

Peut-on ne pas proposer de traitement adjuvant pour un cancer HER2+ ?

SFSPM_12.06.15

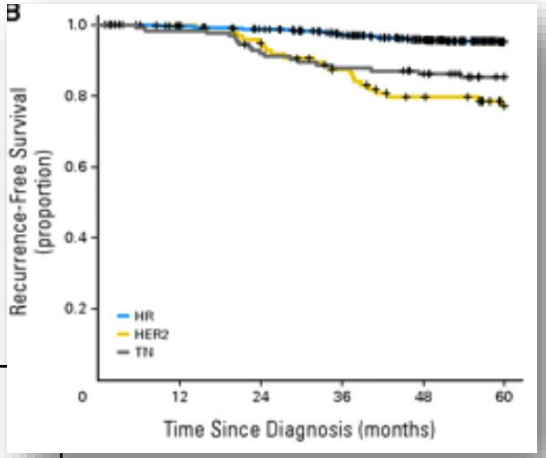
Anne PATSOURIS

ICO Paul Papin, Angers

Plan

- **Séries historiques** : histoire naturelle des tumeurs HER2 …
- Le Trastuzumab : «***not evolutionary but revolutionary ! »***
- Redéfinition du **statut HER2**
- Traitement des ≥ pT1c et ou N+ HER2+ , et les tumeurs infracentimétriques … ?
- **Avec ou sans anthracyclines** ?
- Autres facteurs pronostics et/ou prédictifs ?

Séries historiques pT1abN0



		HER2 +	T1a	T1b
Gonzalez-Angulo, 2009 (N = 965)	RFS 5 y	(N = 98) **77.1%**		
	DRFS 5 y	**86.4%**		
Curigliano, 2009 (N = 2130)	DFS 5 y	(N = 150) **92%**	RH+ : 88% RH - : 93%	95% 85%
Park, 2010 (N = 427)	RFS		HR = 8.8 IC95% [2.1 to 37.2] HR = 5 IC95% [1.8 to 30.2]	

Gonzalez-Angulo et al, JCO, 2009

1988 : Trastuzumab [Herceptin®] approuvé par la FDA
+ [HercepTest ®] et HIS

Editorial de G Hortobagyi, 20 octobre 2005, NEJM

« Clearly, the results reported in this issue of the journal are not evolutionary but revolutionary »

(accompagnant les études HERA et NSABP B31 et NCCTG N9831)

Essais Trastuzumab adjuvant

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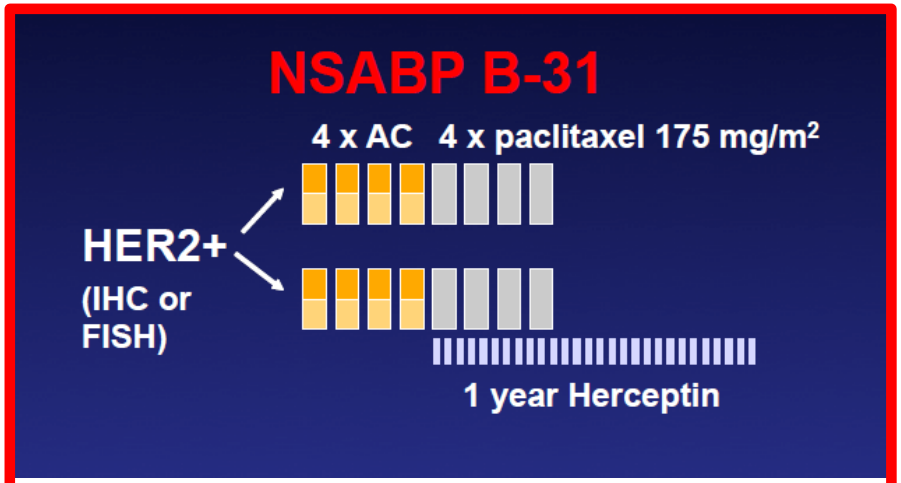

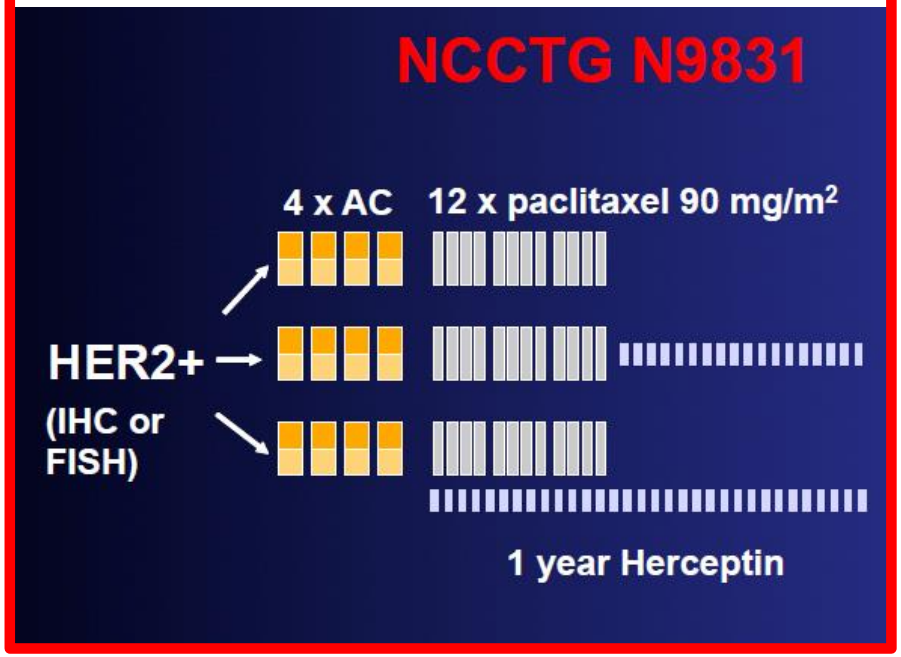

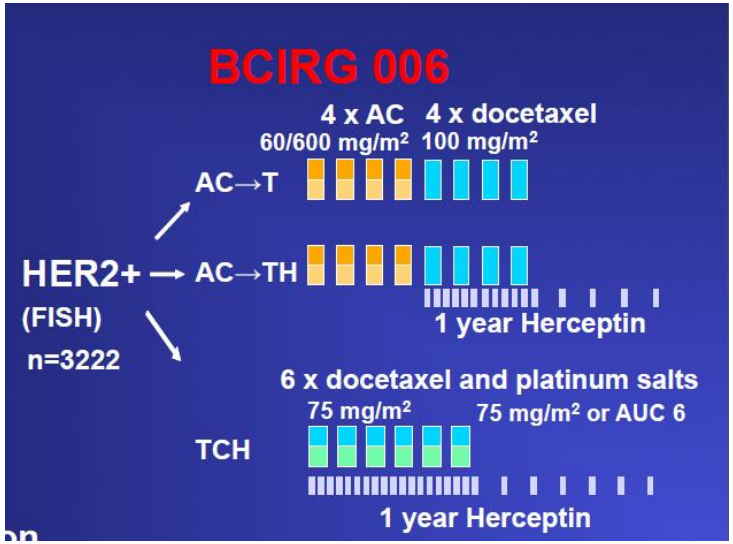

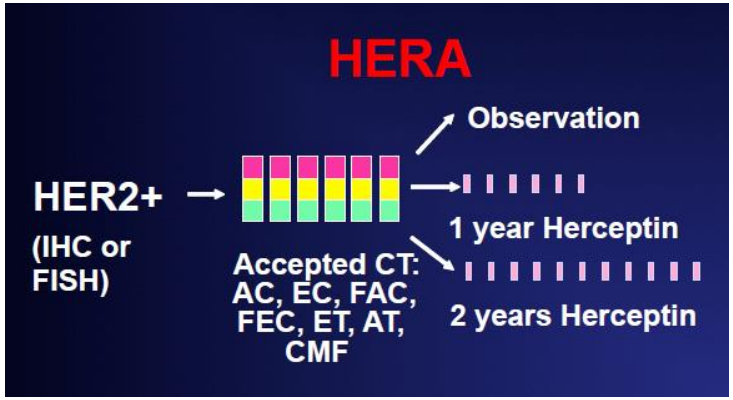

Essais Trastuzumab adjuvant

		DFS	OS
NSABP B31 + NCCTG N 9831	N = 4046	**10y : HR = 0.60** IC 95%[0.53 to 0.68]	**10y : HR = 0.63** IC 95%[0.54 to 0.73] **10y OS of 62.2 %vs 73.7%**
NCCTG N 9831		5 y DFS = 71.8% vs 80.1% vs 84.4%	
BCIRG 006	N = 3222	**5 y :** 75% AC-T = **84% AC-TH (HR = 0.64)** = **81% pour TCH (HR = 0.75)**	**5 y :** 87%, 92% (HR = 0.63), 91% (HR = 0.77)
HERA	N = 5102		**84.4 vs 87.6%**

Méta-analyse Cochrane 2012:
DFS : **HR = 0.60** [0.50-0.71], p < 0.00001
OS : **HR = 0.66** [0.57-0.77], p < 0.00001

Romond *et al*, NEJM, 2005
Perez *et al*, JCO, 2014
Slamon *et al*, NEJM, 2011
Joensuu *et al*, JCO, 2009
Moja *et al*, Cochrane database, 2012

Au prix d'une toxicité cardiaque

		ICardiaque	Altération FEVG > 10%
NSABP B31 + NCCTG N 9831	N = 4046	**4.1 vs 0.8 %**	
BCIRG 006	N = 3222	**2%** (AC-TH) vs **0.7%** (AC-T) Vs **0.4%** (TCH)	**18.6%** (AC-TH) vs **11.2%** (AC-T) Vs **9.4%** (TCH)
HERA	N = 5102		**7.2%** vs **4.1%**
Meta analyse		**HR = 1.83** [1.36-2.47], p = 0.0008	

Trastuzumab 12 vs 6 mois ?

Essai PHARE : Phase III de non infériorité

N = 1691, médiane suivi 42.5 mois

DFS **93.6 %** IC95 [92.6;94.9] vs **91.1 %** IC [89.7;92.4]

Essai HORG de non infériorité

4 FEC dose dense puis 4 docetaxel J1-J15

N = 481, 3 y DFS 95.7% vs 93.3 %

Pivot *et al*, Lancet Oncol 2013
Mavoudris *et al*, Ann Oncol 2015

Statut HER2

Eviter les faux négatifs !

Nouvelles recommandations de l'ASCO/CAP 2013

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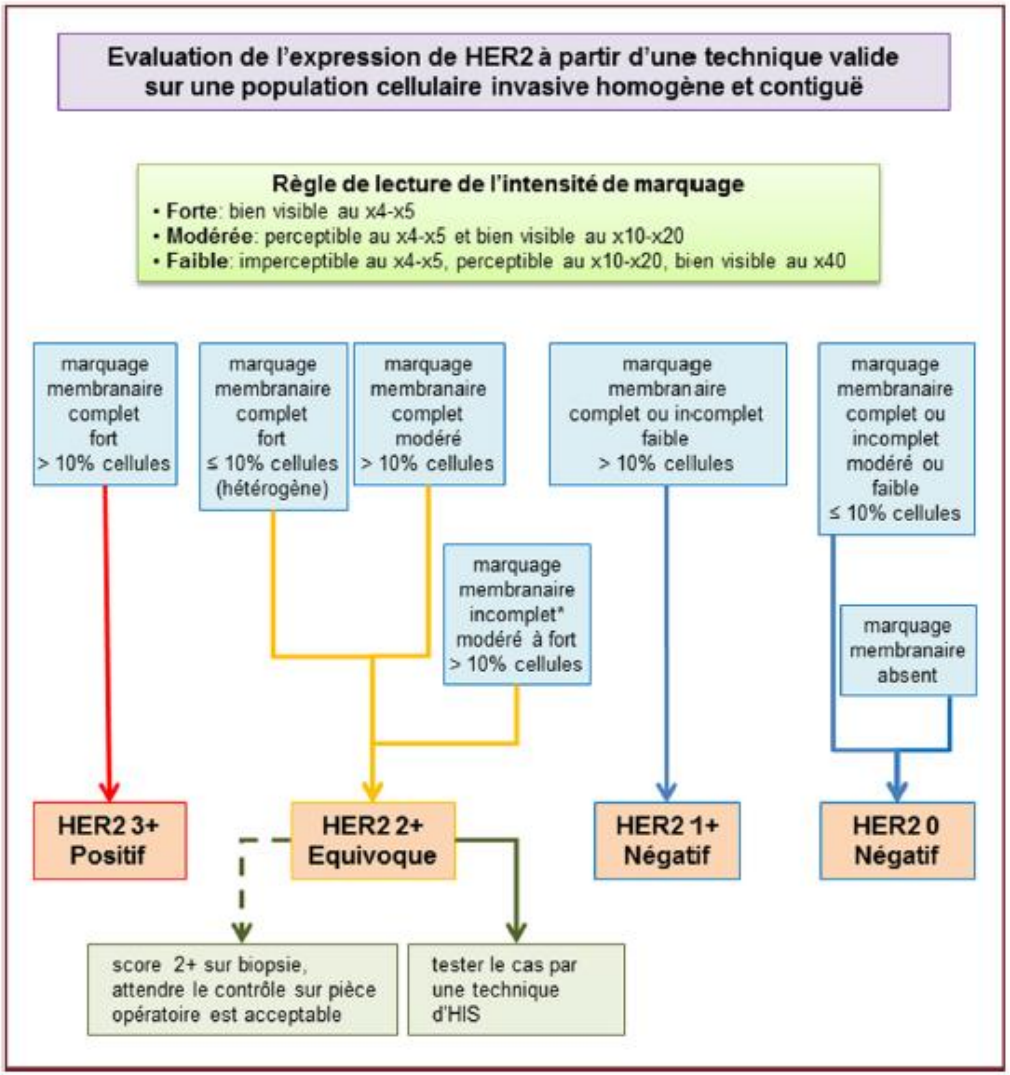
IHC	2007	2013
0	-Absence de Marquage -Marquage -Faible -Incomplet -<10 % des cellules	-Absence de marquage -Marquage -Faible -Incomplet -<10 % des cellules
1+	-Marquage -Faible -Incomplet ->10 % des cellules	-Marquage -Faible -Incomplet ->10 % des cellules
2+	-Marquage évident circonférentiel -faible ou modéré -complet ->10 % des cellules	-Marquage évident circonférentiel -modéré -**Incomplet** ->10 % des cellules -Marquage évident circonférentiel -Fort -Complet -<10 % des cellules
3+	-Marquage évident circonférentiel -Fort -Complet **->30% des cellules**	-Marquage évident circonférentiel -Fort -Complet **->10% des cellules**

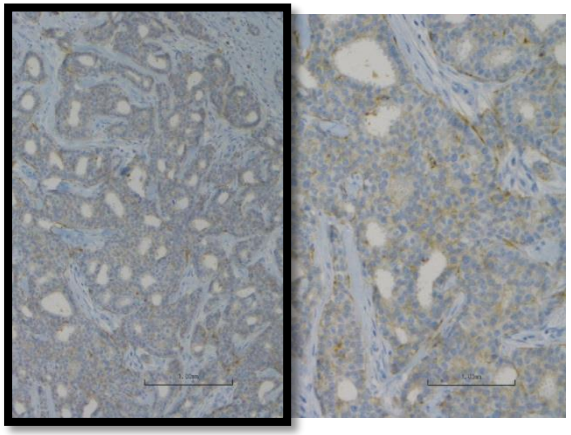
Toutes situations ?

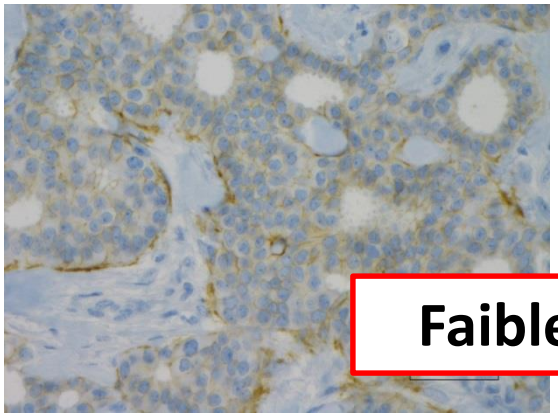
MC>10% - Intensité Forte	3+
MC>10% - Intensité Modérée	2+
MC>10% - Intensité Faible	?
MC <= 10% - Intensité Forte	2+
MC <= 10% - Intensité Modéré	?
MC <= 10% - Intensité Faible	?
MI > 10% - Intensité Forte	?
MI > 10% - Intensité Modérée	2+
MI > 10% - Intensité Faible	1+
MI <= 10% - Intensité Forte	?
MI <= 10% - Intensité Modérée	?
MI <= 10% - Intensité Faible	0
MC = 0 et MI = 0	0



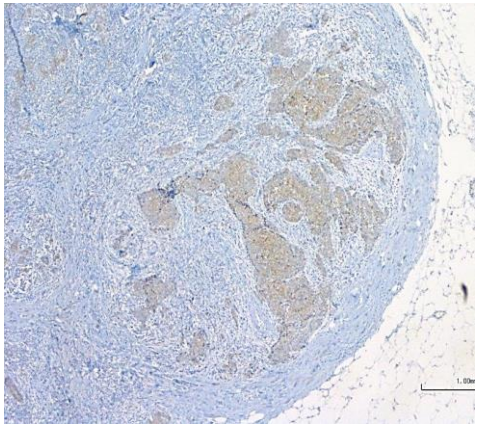
GEFPICS 2014

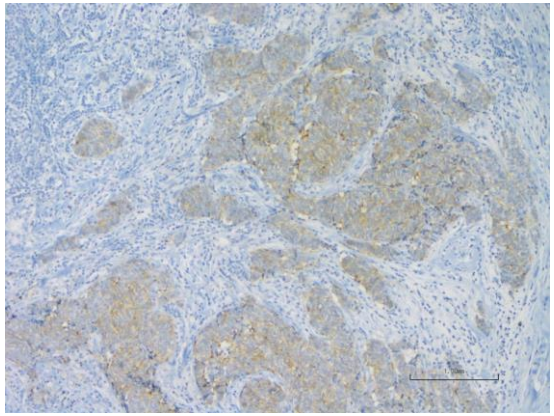
X 4 X 10 X 20 X 40

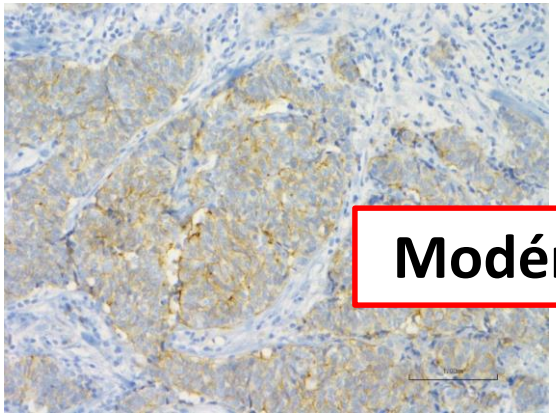




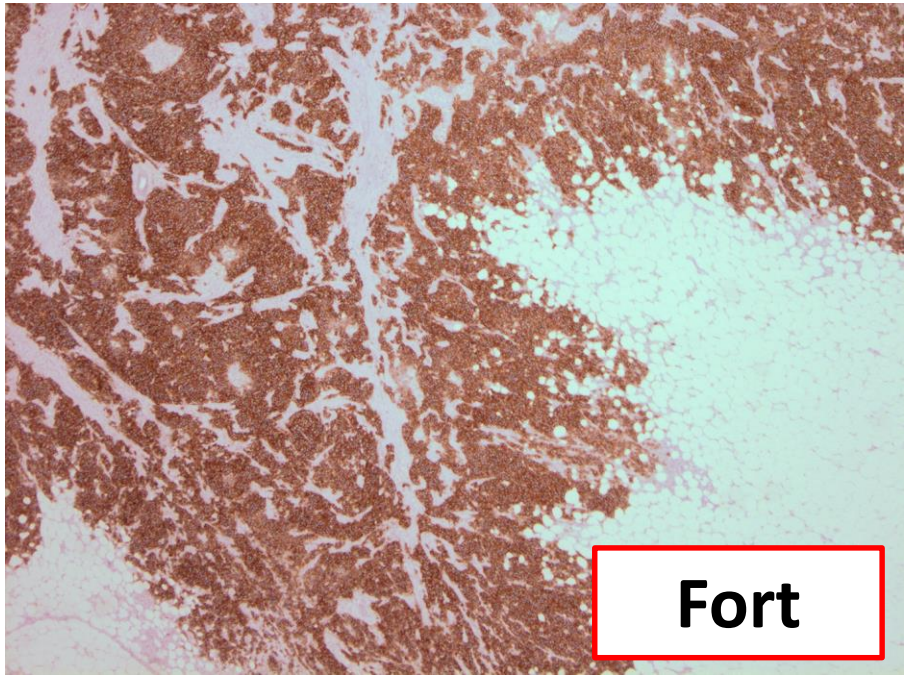
Faible

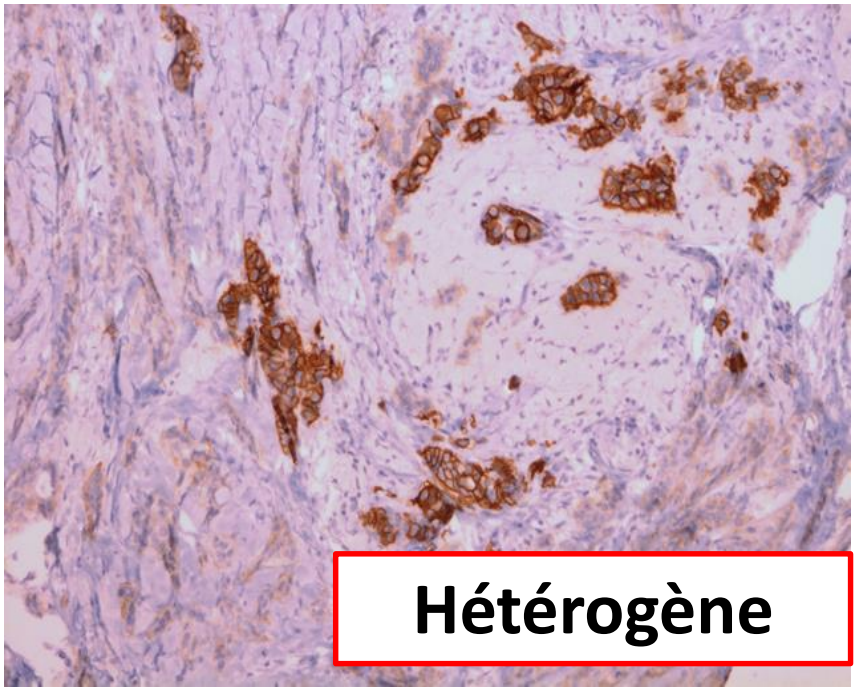






Modéré



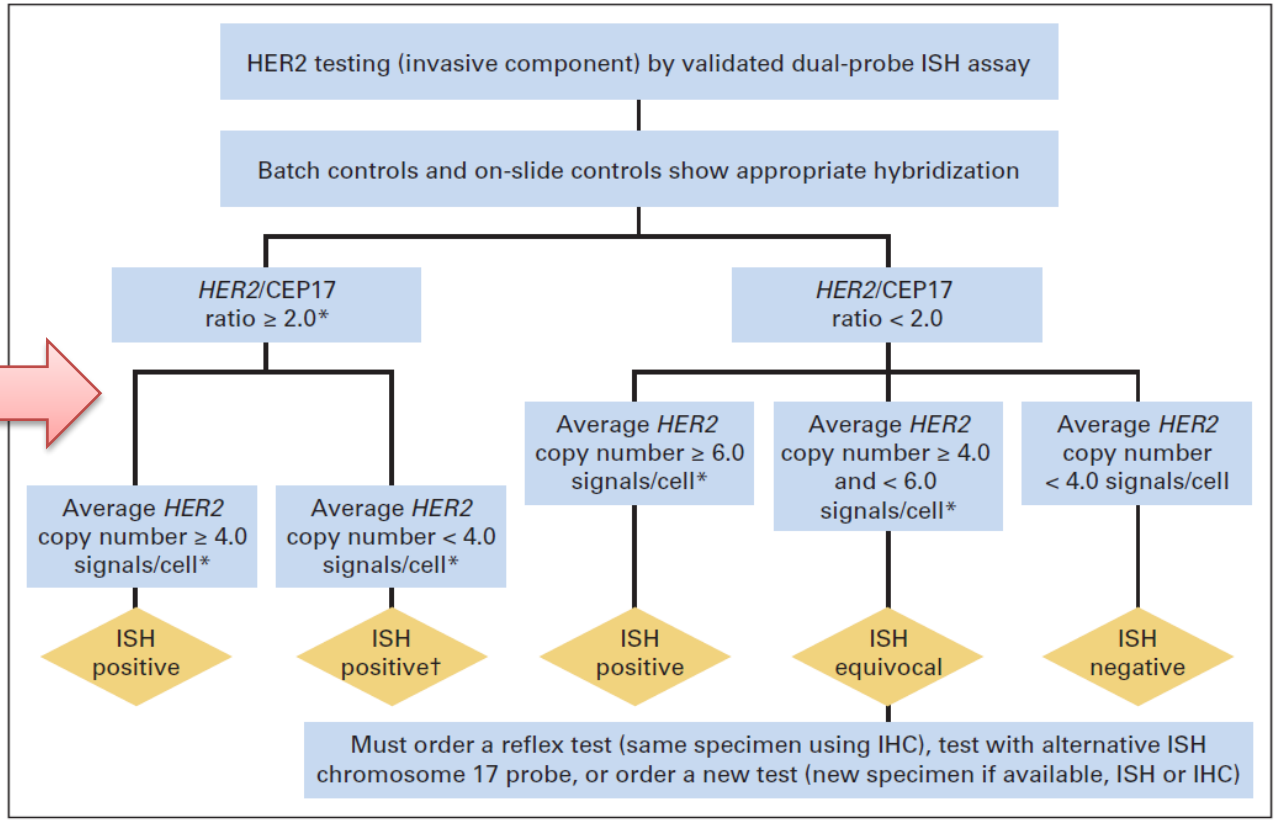


X 2

ASCO/ CAP 2007

ASCO/ CAP 2013

- **Ratio HER2 / CEP17 > 2.2**
- **Nombre de copies de HER2 > 6**

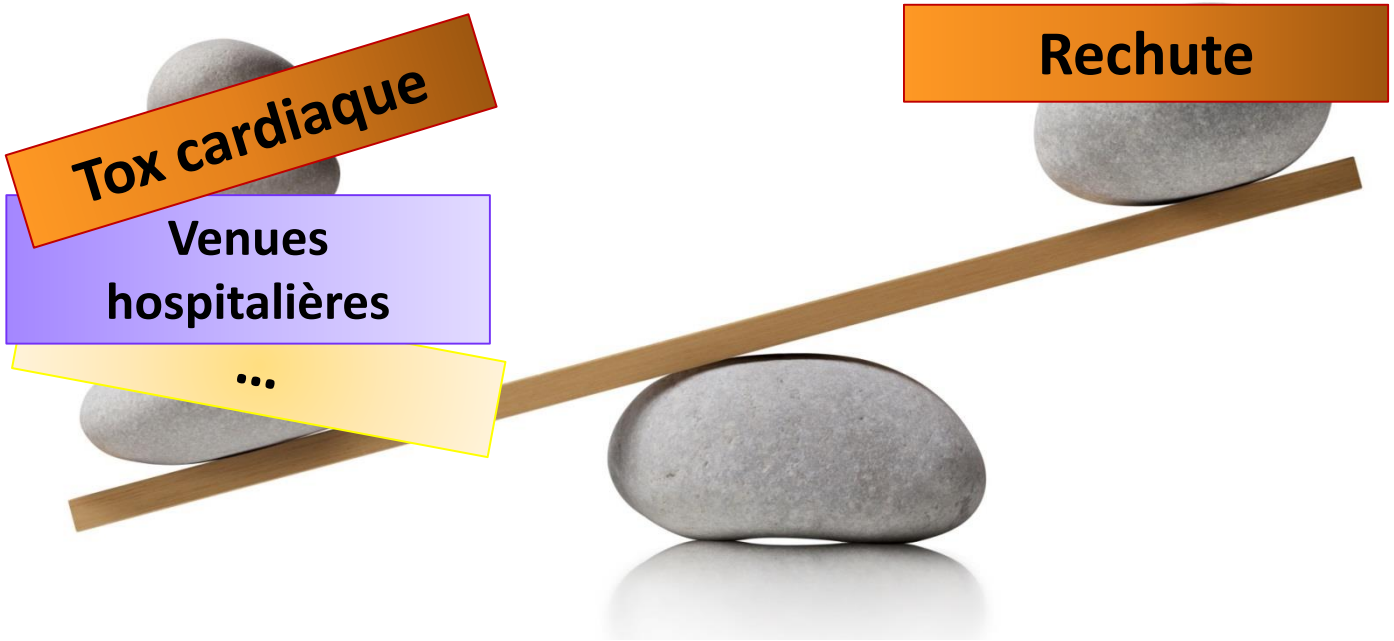


Augmentation du nombre d'HIS …. Et du coût ! (+52%)

Que fait-on des équivoques IHC et HIS ?

Garbar *et al*, ISRN Oncology 2014

Tumeurs pT1abN0 ?



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Séries historiques pT1abN0

		HER2 +	T1a	T1b
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Vaz-Luis, 2014 (N = 4113)	DRFS 5 y OS 5 y	(N = 257)	**RH+** (n = 102) 96 % 95 %	(n=89) 94 % 96 %
	DRFS 5 y OS 5 y		**RH-** (n = 49) 93 % 93 %	(n=17) 94 % 100 %

Trastuzumab sous-cutané

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Etude HannaH : Phase III randomisée de non infériorité

N = 596, Neoadj et adjuvant

Trastuzumab sous-cutanée, dose fixe 600 mg

EFS 95% dans les 2 groupes à 1 an

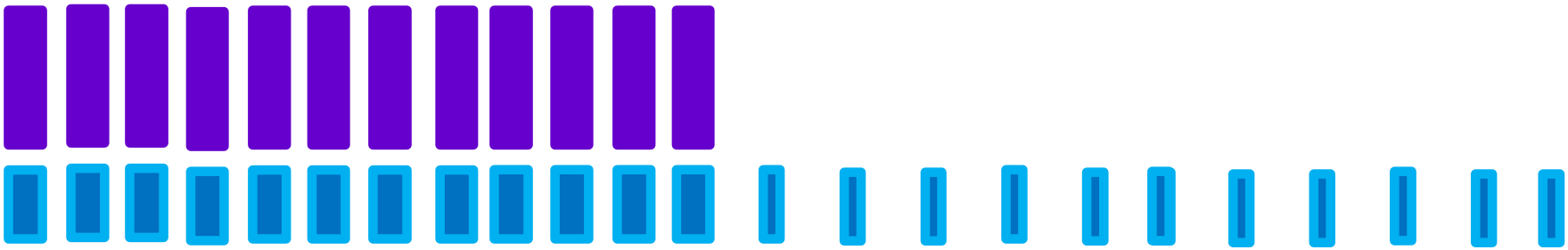
Réduction des venues hospitalières,
Du temps de perfusion ….

Schémas sans anthracyclines ?

Phase II monobras, N = 406 ptes

T< 3 cm, N0 (mi included)

Paclitaxel et trastuzumab hebdomadaire



Médiane suivi : 4 ans

3 y RFS : **98.7%** IC95%[97.6 to 99.8]

Tx Icardiaque : 0.5%, réversible

Tolaney, NEJM, 2015

Schémas sans anthracyclines ?

		Phase		DFS	OS
BCIRG 006	ADJ	III	N = 3222	**5 y :** 75% AC-T = **84% AC-TH (HR = 0.64)** = **81% pour TCH (HR = 0.75)**	**5 y :** 87%, 92% (HR = 0.63), 91% (HR = 0.77)
Coudert, 2006	NEOADJ	II	N = 33	Weekly doce + H	
Coudert, 2007	NEOADJ	II	N = 70	Doce 75mg/m² + Carbo AUC6 + H	
GEPARSixto	NEOADJ			Intérêt ajout Carboplatine ?	

TOP2A : amplification, délétion, facteur prédictif de réponse aux anthracyclines ?

Slamon, NEJM, 2011
Coudert, Ann Oncol 2006
Coudert, JCO 2007
Von minckwitz, ASCO 2013, abst 1004
Di Leo, Lancet Oncol 2011

Grade Immunologique ?

Corrélation entre présence de Tils et réponse au Trastuzumab

Association paramètres immunologiques (contexture immunitaire) et pCR
Indépendamment du type de chimiothérapie

Méthodologie à standardiser : Tils Working group 2014

Salgado *et a*l, Ann of Oncol 2014

NEOADJUVANT/ADJUVANT CHEMOTHERAPY [1,2,3,4]

Regimens for HER2-negative disease (all category 1)[5]

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- FEC/CEF followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)
- FAC followed by T (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab[9]
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- Paclitaxel + trastuzumab[10]
- Pertuzumab + trastuzumab + docetaxel followed by FEC[9]
- Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]

[1] Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.

[2] Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

[3] CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.

[4] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.

[5] The regimens listed for HER2-negative disease are all category 1 when used in the adjuvant setting.

[6] In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).

[7] Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.

[8] A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer. Patients who have not received a neoadjuvant pertuzumab-containing regimen can receive adjuvant pertuzumab.

[9] 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.

[10] Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

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.

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special article

Annals of Oncology 00: 1–14, 2015
doi:10.1093/annonc/mdv221

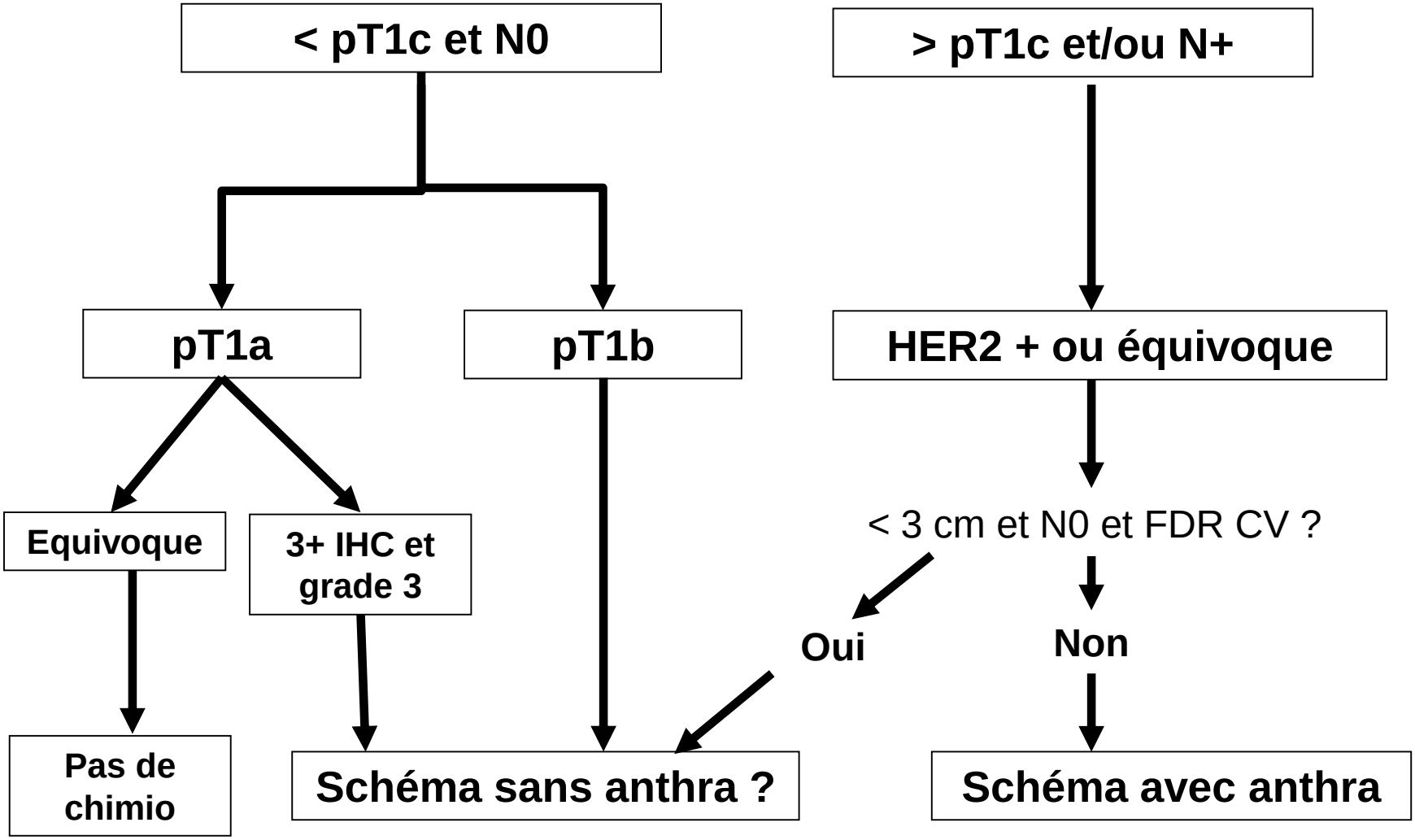
Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

A. S. Coates[1], E. P. Winer[2], A. Goldhirsch[3*], R. D. Gelber[4], M. Gnant[5], M. Piccart-Gebhart[6], B. Thürlimann[7], H.-J. Senn[8] & Panel Members[†]

Adjuvant anti-HER2 therapy

A phase II study of adjuvant paclitaxel and trastuzumab, without anthracycline, showed excellent outcome in node-negative, HER2-positive, pT1b and pT1c tumors. Despite the absence of a control group in this study, the regimen is now widely accepted as a standard of care for patients with small, node-negative, HER2-positive tumors [111].

Proposition arbre décisionnel



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Merci de votre attention !