Les phénotypes (et génotypes) du cancer du sein: Vision du clinicien Implications pour la médecine nucléaire

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Beating cancer together

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Conflits d’intérêts

Participation à des “boards”: Roche, Pfizer, Novartis, Janssen, Sanofi, Pierre Fabre Oncology, Debiopharm

Honoraires entièrement reversés à mon institution: CGFL

Introduction (1)

- Le cancer du sein est la première cause de décès par cancer chez la femme dans le monde et en France

- En France, 2015 54 062 nouveaux cas et 11 913 décès
  - ✓ Survie nette: 86 % à 5 ans, 76% à 10 ans.

- Bien que des avancées significatives aient été obtenues dans la prise en charge des cancers du sein, la maladie métastatique est toujours considérée comme incurable

Introduction (2) Avant 2000

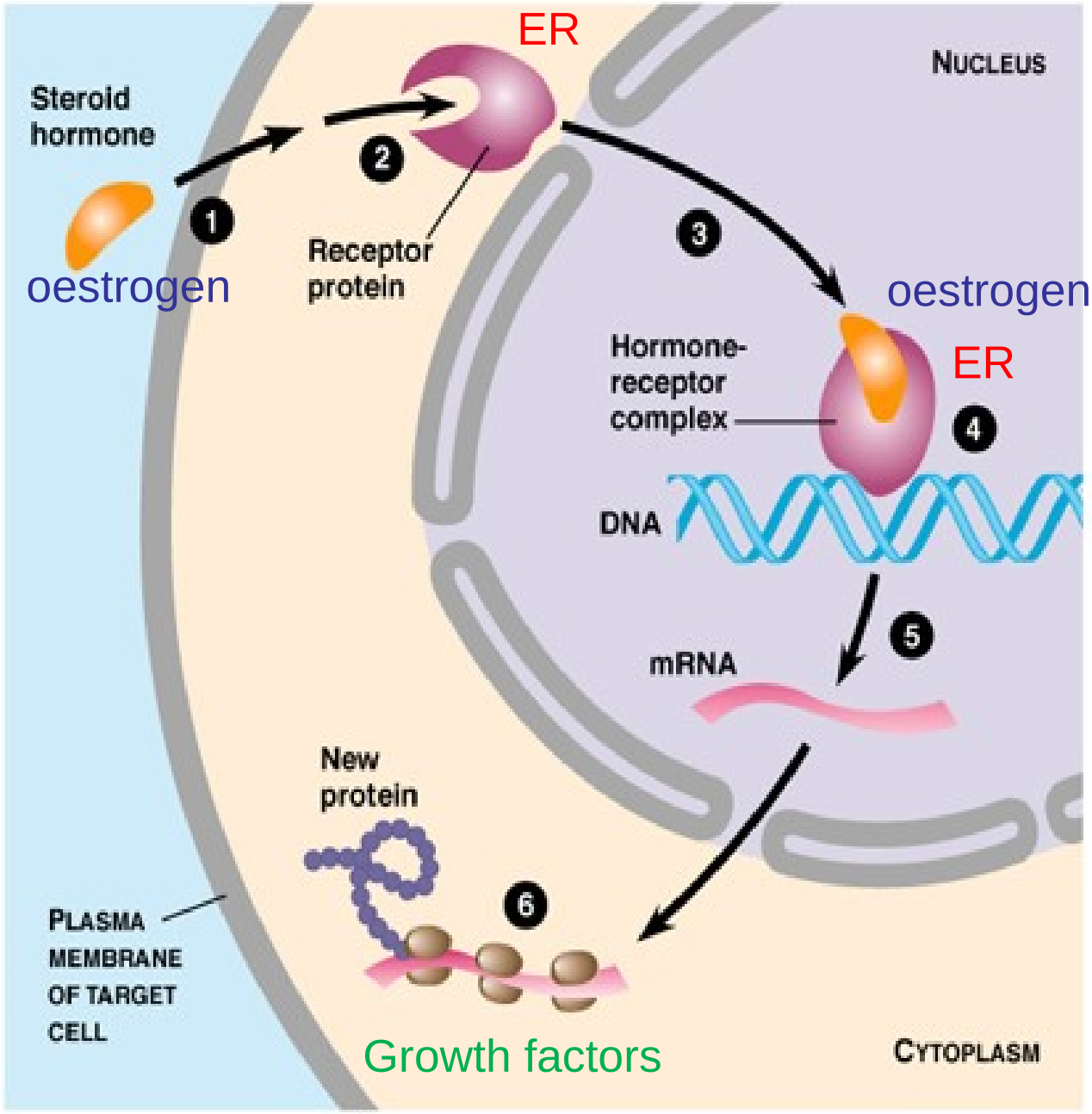
- Le cancer du sein (CS): une maladie unique
- Traitement primaire du cancer du sein : la chirurgie suivie par un traitement adjuvant (une chimiothérapie et/ou une thérapie hormonale) en fonction de facteurs pronostiques dans le but d'éviter les rechutes

- Années 70, Récepteurs hormonaux (RO, RP); 2/3 CS

- A la fin des années 90,

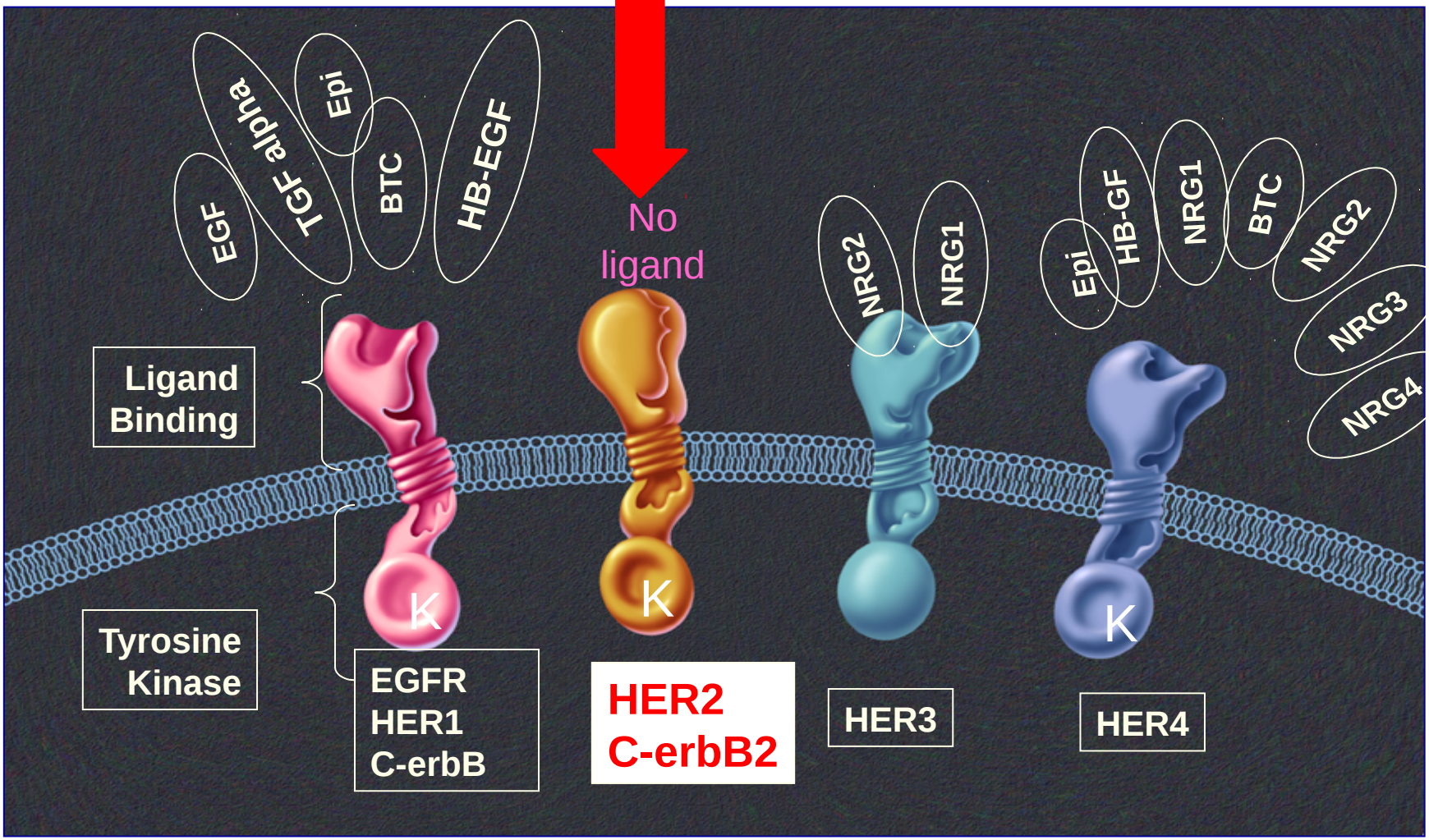
  amplification / Hyperexpression HER2; 15-20% CS

Années 70

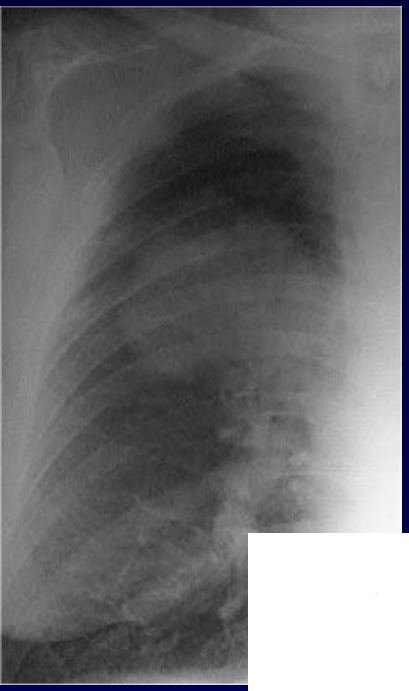


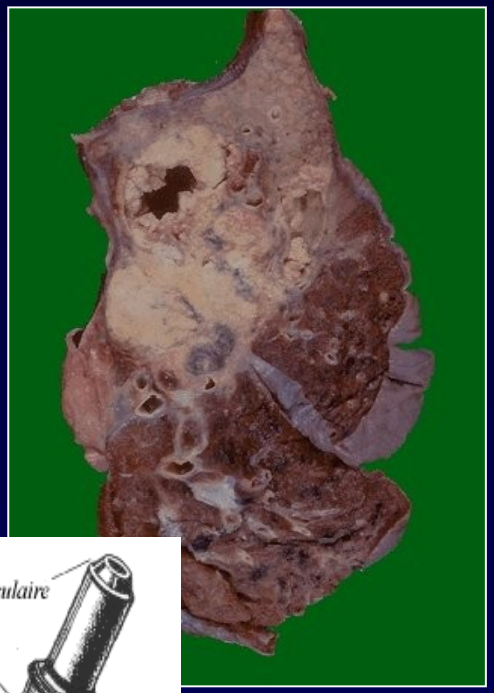
Famille HER2

Fin des années 90



Définition du cancer? La vision ancienne



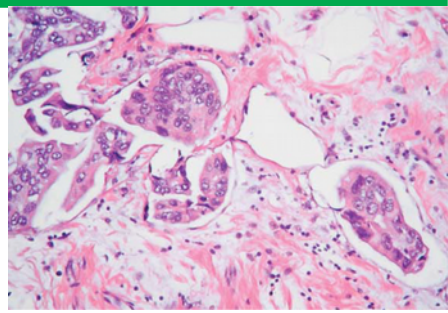


Une tumeur

un organe

Un échantillon tumoral

Introduction (3)



- Cancers infiltrants Adénocarcinomes
  - Galactophoriques 85%
    - ✓ Classiques +++
    - ✓ Tubulaires
    - ✓ Cribriformes
    - ✓ Mucineux
    - ✓ Médullaires
    - ✓ Papillaires – Micropapillaires
    - ✓ Neuroendocrines
    - ✓ Métaplasiques
    - ✓ Sécrétoires – Oncocytiques – Cytiques adénoïdes – Actiniques
  - Lobulaires 15%
    - ✓ Classiques +++
    - ✓ Pleïomorphiques
    - ✓ Histiocytoïdes
    - ✓ Tubulolobulaires

Introduction (4) Avant 2000

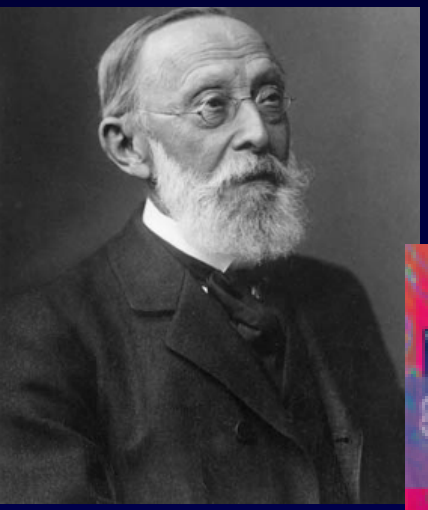
Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma

Hogan MP et al, *J Nucl Med. 2015 Nov;56(11):1674-80*

CONCLUSION:

(18)F-FDG PET/CT was more likely to reveal unsuspected distant metastases in stage III IDC patients than in stage III ILC patients. In addition, some ILC patients were upstaged by non-(18)F-FDG-avid lesions visible only on the CT images. Overall, the impact of PET/CT on systemic staging may be lower for ILC patients than for IDC patients.

Définition actuelle du cancer: une maladie génomique



Une tumeur

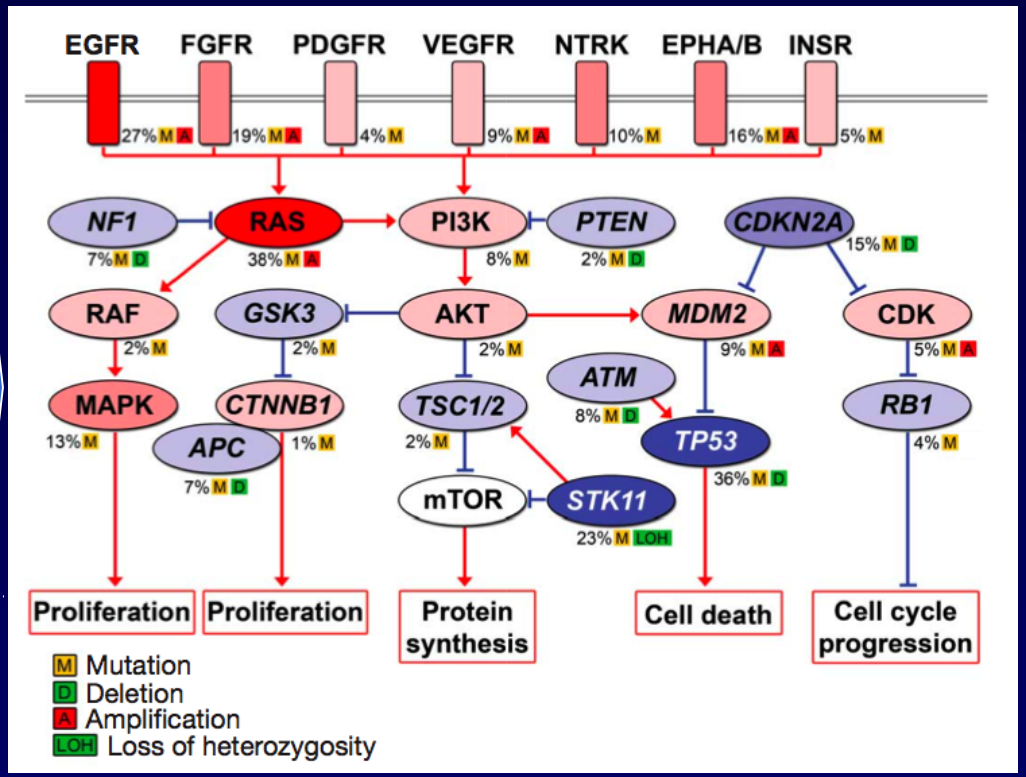
Un organe

Un échantillon tumoral

=

Une définition du XIX^éme siècle

Mutations génomiques significatives



Ding et al. Nature 455, 1069, 2008

Introduction (5) 2000 et après…

- L'ère de la génomique – NGS
- Une meilleure connaissance des voies moléculaires et la transduction de signal avec le développement de thérapie ciblée (ex inhibition HER2)
- L'utilisation de l'imagerie fonctionnelle (PET scan, DCE MRI..)

❖**Un concept de recherche translationnelle permettant une médecine personnalisée / de précision**

Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

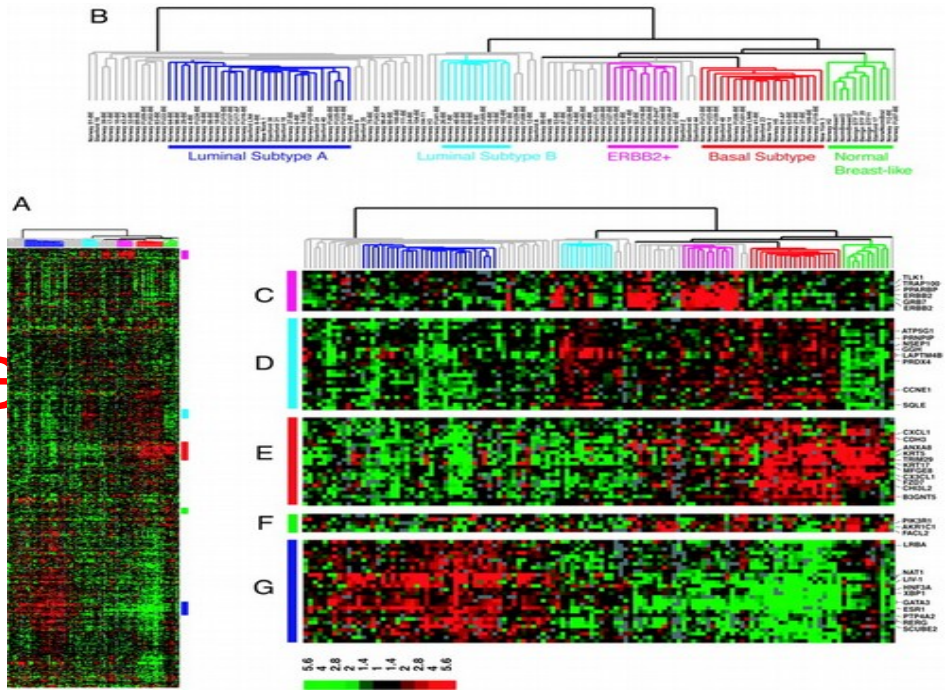
Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[b], Trevor Hastie[e], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[j], Thor Thorsen[k], Hanne Quist[l], John C. Matese[c], Patrick O. Brown[m], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[b,n]

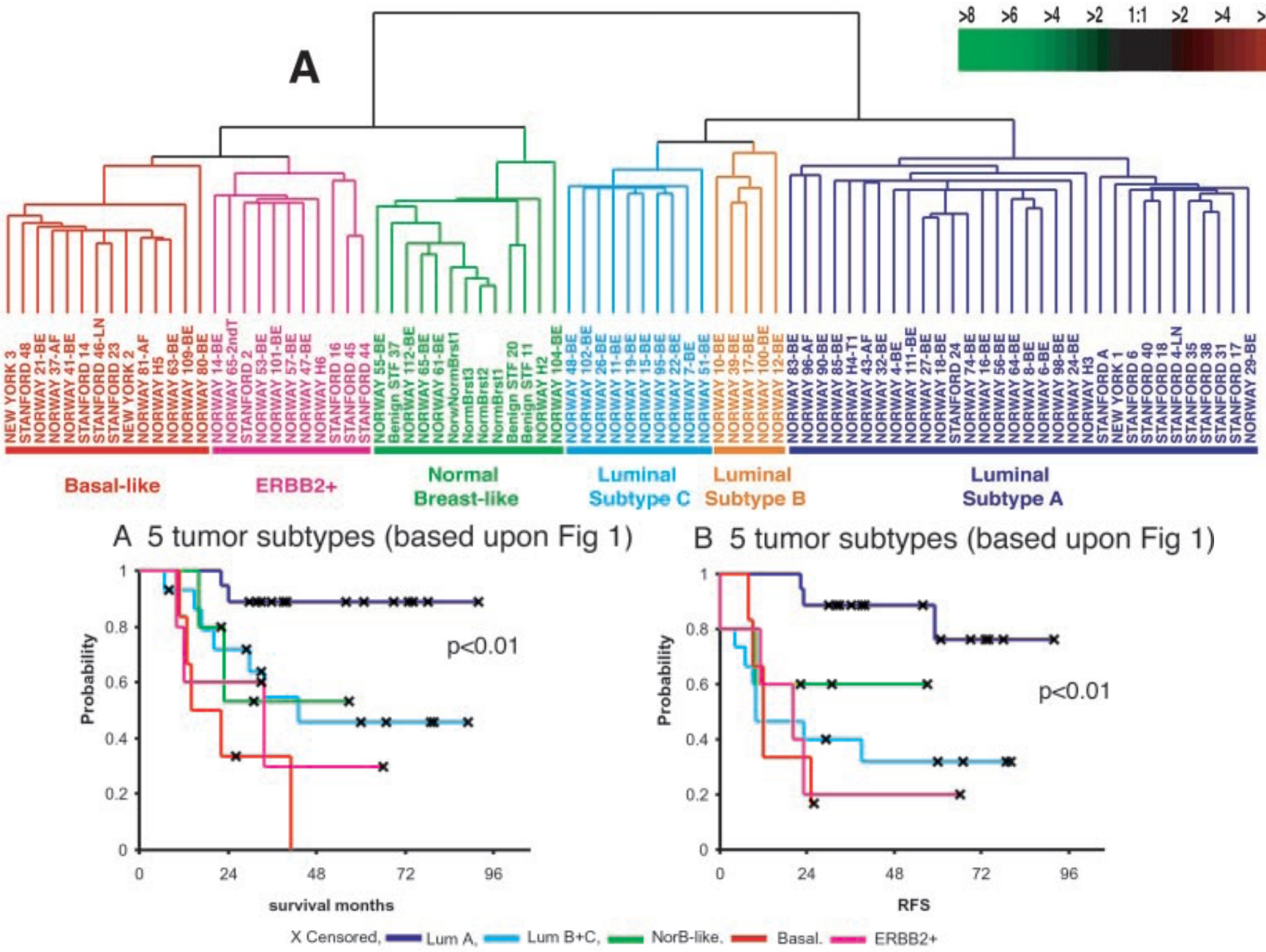
Departments of [b]Genetics and [l]Surgery, The Norwegian Radium Hospital, Montebello, N-0310 Oslo, Norway; [d]Department of Genetics and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599; Departments of [e]Health Research and Policy and Statistics, [c]Genetics, [i]Pathology, [j]Surgery, and [m]Biochemistry and Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA 94305; Departments of [g]Medicine (Section of Oncology), [f]Surgery, and [k]Biochemical Endocrinology, Haukeland University Hospital, N-5021 Bergen, Norway; and [h]Life Sciences Division, Lawrence Orlando Berkeley National Laboratories, and Department of Molecular and Cellular Biology, University of California, Berkeley, CA 94720

Contributed by David Botstein, July 17, 2001

PNAS September 11, 2001 vol. 98, no. 19, 10869–10874

L'ère de la génomique

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STANFORD 48
NORWAY 21-BE
NORWAY 37-AF
NORWAY 41-BE
STANFORD 14
STANFORD 46-LN
STANFORD 23
NEW YORK 2
NORWAY 81-AF
NORWAY H5
NORWAY 63-BE
NORWAY 109-BE
NORWAY 80-BE
NORWAY 14-BE
NORWAY 65-2ndT
STANFORD 2
NORWAY 53-BE
NORWAY 101-BE
NORWAY 57-BE
NORWAY 47-BE
NORWAY H6
STANFORD 16
STANFORD 45
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NORWAY 55-BE
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NORWAY 112-BE
NORWAY 65-BE
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NormBrst2
NormBrst1
Benign STF 20
Benign STF 11
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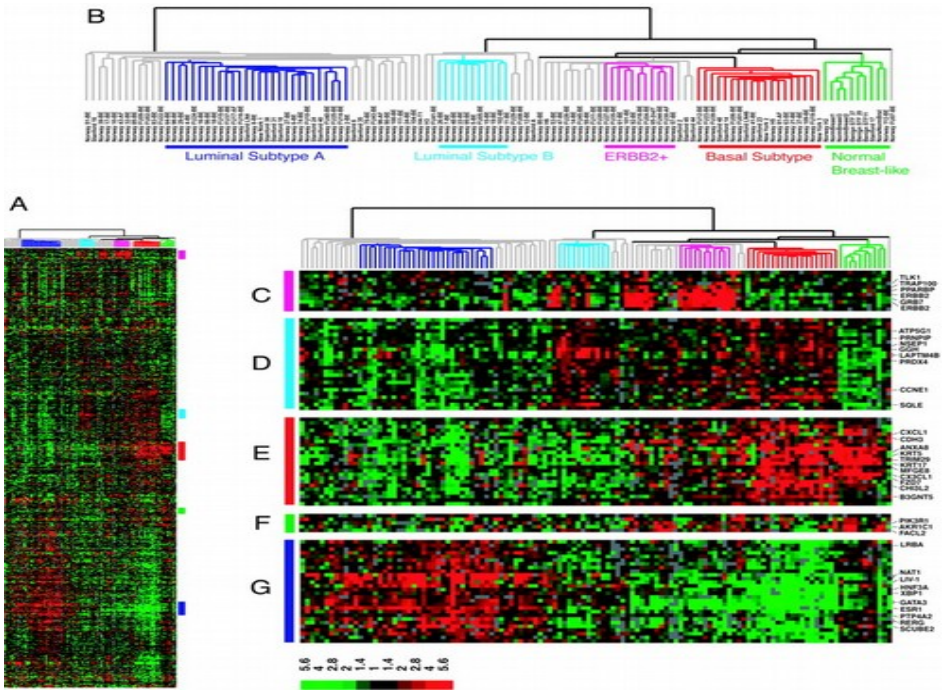
STANFORD 24
NORWAY 74-BE
NORWAY 16-BE
NORWAY 56-BE
NORWAY 64-BE
NORWAY 8-BE
NORWAY 6-BE
NORWAY 98-BE
NORWAY 24-BE
NORWAY H3
STANFORD A
NEW YORK 1
STANFORD 6
STANFORD 40
STANFORD 18
STANFORD 4-LN
STANFORD 35
STANFORD 38
STANFORD 31
STANFORD 17
NORWAY 29-BE
Basal-like
ERBB2+
Normal Breast-like
Luminal Subtype C
Luminal Subtype B
Luminal Subtype A
A 5 tumor subtypes (based upon Fig 1)
Probability
p<0.01
survival months
B 5 tumor subtypes (based upon Fig 1)
Probability
p<0.01
RFS
X Censored, Lum A, Lum B+C, NorB-like, Basal, ERBB2+

Cancer du sein: « Intrinsic Subtypes »
2000 – 2016 caractéristiques moléculaires

1. Luminal A
2. Luminal B
3. HER2-enriched
4. Basal - Like



Cancer du sein: « Intrinsic Subtypes »
2000 – 2016 caractéristiques moléculaires

1. Luminal A

2. Luminal B

- **Expression du récepteur oestrogénique**
- Différences entre luminal B Vs luminal A:
  - ✓ Expression plus élevée de gènes ou protéines en rapport avec la prolifération et/ou le cycle cellulaire **Ki67**, AURKA
  - ✓ Expression plus faible de gènes ou protéines en rapport avec le caractère luminal Récept. Progestérone, FOXA1
- Au niveau ADN, différences entre luminal B & Vs luminal A:
  - ✓ Nombre de mutations TP53 plus élevées
  - ✓ Nombre de mutations PIK3CA et MAP3K1 plus faibles

- Quelques tumeurs luminales HER2 amplification/ hyperexpression

Cancer du sein: « Intrinsic Subtypes »
2000 – 2016 caractéristiques moléculaires

3. HER2-enriched

- Hyperxpression HER2

- Au niveau ADN, augmentation globale des mutations, TP53, PI3KCA, APOBEC3B

- Expression intermédiaire gènes liés aux caractères luminal, ESR1, PgrR

- Faible expression gènes liés aux caractères basal, keratin 5, FOXC1

- Récepteur oestrogénique -

Cancer du sein: « Intrinsic Subtypes »
2000 – 2016 caractéristiques moléculaires

4. Basal-like

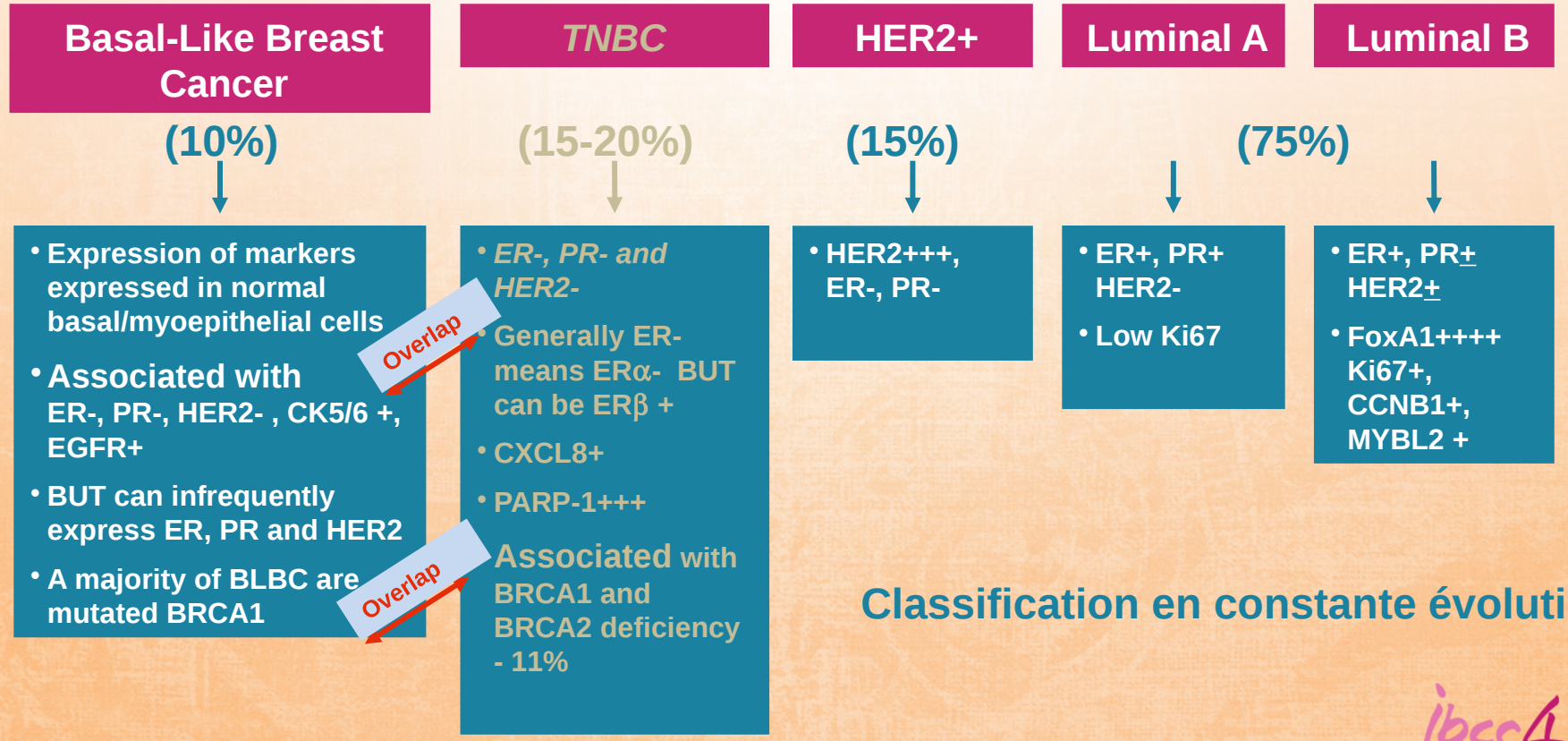
- Au niveau de l'ARN et des protéines; expression élevée liée à la prolifération **Ki67** et aux kératines exprimées par la couche basale Kératines 5,14, 17

- Expression très faible des gènes liés aux caractères luminal, ESR1, PgrR
- Au niveau ADN, augmentation globale des mutations, TP53, PI3KCA

- Association aux mutations constitutionnelles BRCA1/2

Classification des cancers du sein

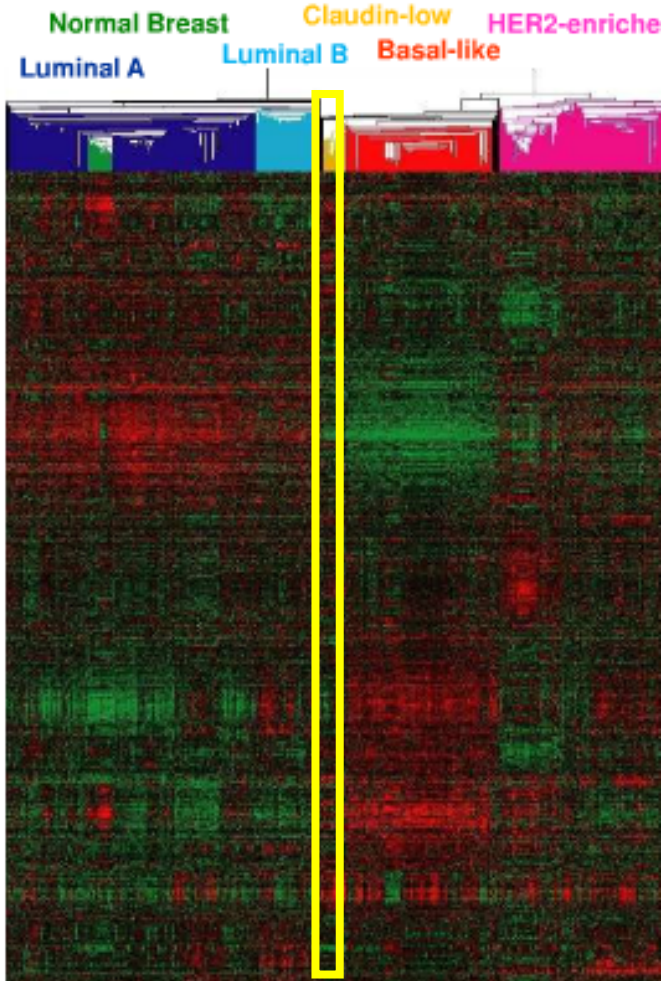
Maladie hétérogène en tenant compte des altérations moléculaires, du phénotype cellulaire et de l'évolution clinique



Classification en constante évolution

ibcc4
International breast cancer conference 4

Claudin-low intrinsic subtype



- 5-10% of breast cancer
- RE-, RP-, Her2-
- high enrichment for epithelial-to-mesenchymal transition markers
- immune response genes and cancer stem cell-like features
- response rate to standard preoperative chemotherapy that is intermediate between that of basal-like and luminal tumors

Perou CM SABCS 2009 AACR reward

➢ Transcriptome analysis of triple negative breast cancers*

6 distinct biological subgroups

2 basal-like 1&2 (cell cycle & DNA damage response genes)

2 mesenchymal-like (M & MSL) enriched in cell differentiation, epithelial-cell transition and growth factor pathways

Immunomodulatory (IM) defined by immune cell surface antigens, receptors and signal transduction genes

Luminal subgroup (LAR) driven by androgen receptor signaling

* Lehman BD et al SABCS 2010, Abstract PD01-07

Cancer du sein: classification

Classification: « intrinsic » sous-types – St Gallen 2011 consensus

1. Luminal A: RO et/ou RP positif, HER2-, Ki-67 bas
2. Luminal B (HER2-): RO et/ou RP positif, HER2-, Ki-67 élevé
3. Luminal B (HER2+): RO et/ou RP positif, HER2+, Ki-67 bas/élevé
4. HER2+ (non luminal): RO et RP négatif, HER2+
5. Triple négatif: RO et RP négatif, HER2-

Implications cliniques (1-2)
RH+ / HER2- Luminal

Pronostic

- ✓ plus mauvais pronostic, luminal B (taille tumorale, envahissement gg axillaire)
- ✓ Rechutes tardives – métastases osseuses

Thérapie

- ✓ Bénéfice de l'hormonothérapie luminal A&B
- ✓ Bénéfice de la chimiothérapie surtout pour luminal B
- ✓ Intérêt des signatures génomiques (Oncotype DX, PAM50…)

Implications cliniques (3-4)
HER2+

Pronostic

- ✓ plus mauvais pronostic, HER2+ / RH-, rechutes à 5 ans, métastases viscérales et cérébrales)
- ✓ Peu de rechutes après 5 ans

Thérapie

- ✓ Bénéfice des traitements anti-HER2 plus chimiothérapie
- ✓ Bénéfice d’un double blocage anti-HER2 pour HER2+ / RH-

Implications cliniques (3)
Triple négatif (RO-, RP-, HER2-)

Maladie hétérogène

Pronostic

- ✓ Mauvais pronostic, femme jeune, mutations BRCA1/2
- ✓ Peu de rechutes après 4-5 ans

Thérapie

- ✓ Bénéfice de la chimiothérapie
  - ❖ Non basal-like, docetaxel
  - ❖ BRCA1/2 mutation, carboplatin
- ✓ Bénéfice d'un anti-angiogénique, basal-like
- ✓ Bénéfice d'un anti-androgène, luminal subgroup (LAR) driven by androgen receptor signaling?
- ✓ Bénéfice d'une immunothérapie anti PD-1, PDL-1, Immunomodulatory?

➢ Transcriptome analysis of triple negative breast cancers*

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Implications cliniques (3)
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Maladie hétérogène

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Les phénotypes (et génotypes) du cancer du sein: Vision du clinicien

Implications pour la médecine nucléaire

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Impact of the different breast cancer subtypes on PET imaging (1)

- **Aim**

  - To evaluate the impact of the different breast cancer subtypes on the tumor 18F-FDG uptake (SUV) at baseline

    Luminal A/B ER and/or PgR +
    Triple negative ER and PgR -; HER2-
    HER2+

  - Changes after the first course of neoadjuvant chemotherapy

Humbert O. et al Annals of Oncology 23: 2572–2577, 2012

Impact of the different breast cancer subtypes on PET imaging (2)

- **Methods**

  - 115 patients treated by neoadjuvant chemotherapy (6 cycles) followed by surgery
    - 37 pts HER2+; TH 6 cycles
    - 78 pts HER2 -, FEC 100, 6 cycles or 3 FEC 100 followed by 3 Taxotere

  - Tumor uptake of FDG evaluated before and after the first course (day 20) of neoadjuvant chemotherapy

Humbert O. et al Annals of Oncology 23: 2572–2577, 2012

Impact of the different breast cancer subtypes on PET imaging (3)

- **Results**

✓ Tumoral subtypes
- Overall 115
- Luminal 53 (46%)
- HER2 positive 37 (32%)
- Triple negative 25 (22%)

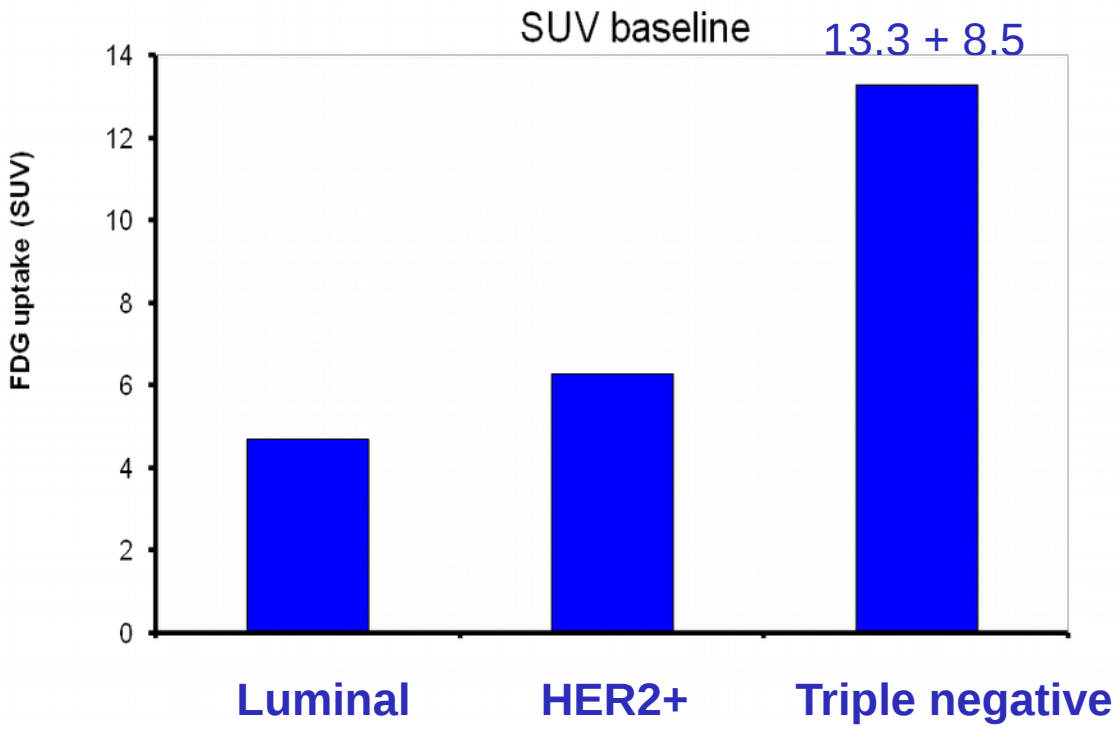
✓ pCR
- Luminal (2%)
- HER2 positive (38%)
- Triple negative (36%)

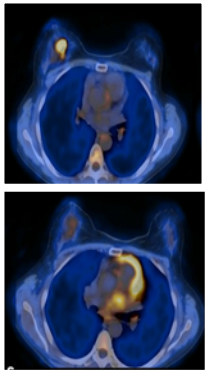
Humbert O. et al Annals of Oncology 23: 2572–2577, 2012

Impact of the different breast cancer subtypes on PET imaging (4)

- **Results**

Triple negative tumors presented the highest baseline SUV (13.3 ± 8.5; p<0.0001)



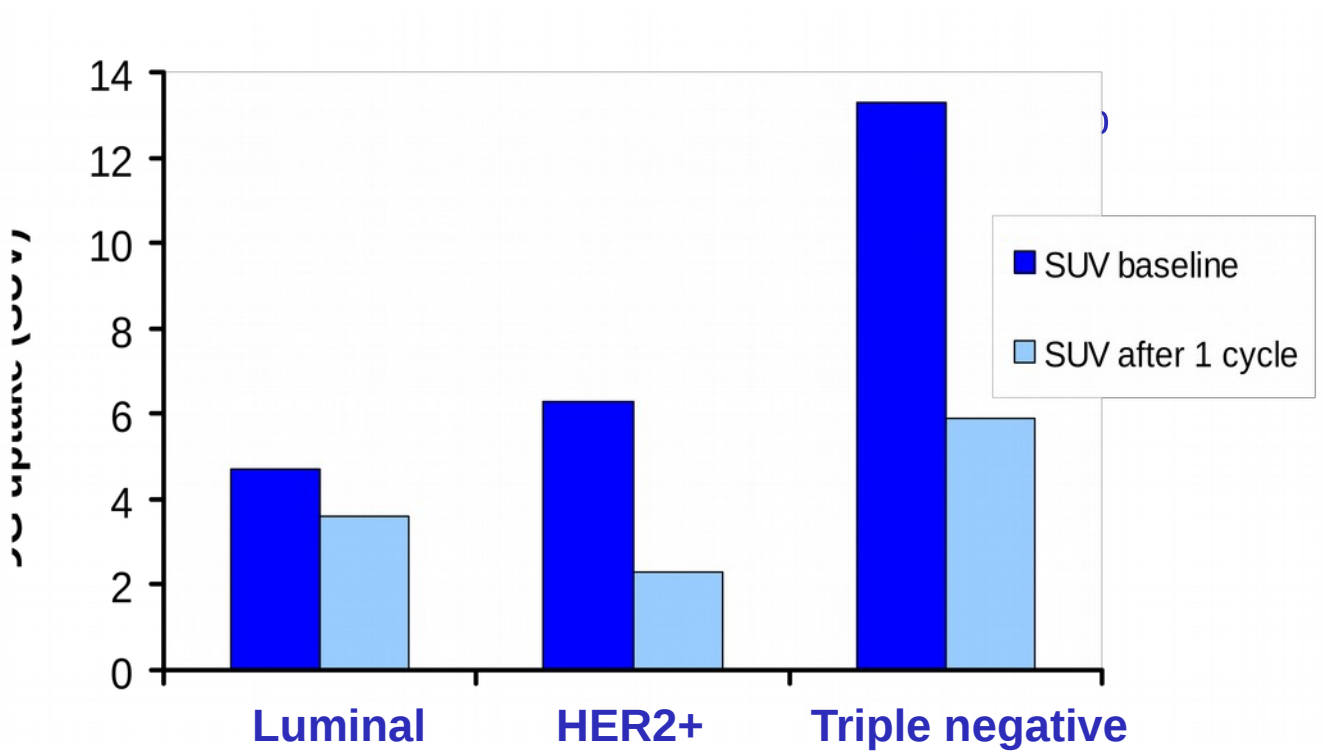


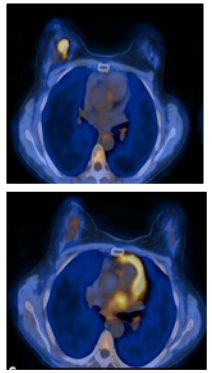
Humbert O. et al Annals of Oncology 23: 2572–2577, 2012

Impact of the different breast cancer subtypes on PET imaging (5)

- **Results**

Decrease of SUV after the first course of NAC (ΔSUV) significantly higher in triple negative and HER2 positive subtypes (p<0.0001)





Humbert O. et al Annals of Oncology 23: 2572–2577, 2012

Impact of the different breast cancer subtypes on PET imaging (6)

- **Results**

ΔSUV, predictive factor of pCR only in HER2 positive tumors

Metabolic characteristics according to pathological response in HER2 positive and triple negative subtypes.

		N	SUV1	SUV2	ΔSUV (%)
HER2 positive	pCR	14	6.2 ± 3.5	1.5 ± 0.1	-71 ± 24
	non pCR	23	6.5 ± 5.2	2.9 ± 2.4	-47 ± 29
	p value*		0.67	0.01	0.01
Triple negative	pCR	9	10.7 ± 5.1	5.1 ± 2.6	-45 ± 30
	non pCR	16	11.7 ± 9.9	6.4 ± 5.3	-45 ± 22
	p value*		0.82	0.95	0.50

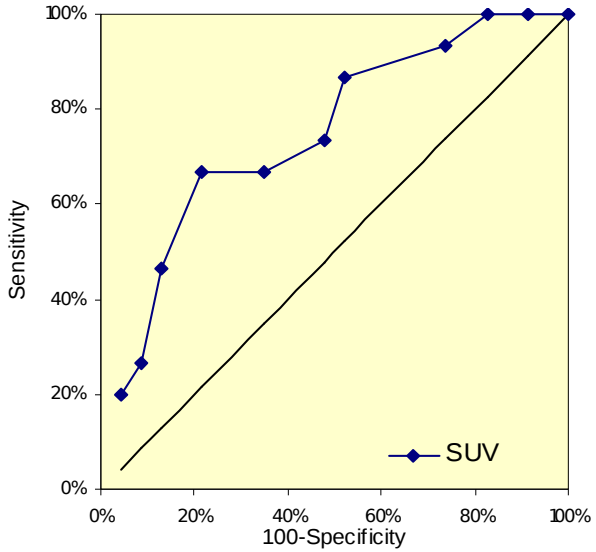
Data are mean ± SD. Luminal tumors are not shown due to the very low rate of pCR.
*Mann-Whitney test

Humbert O. et al Annals of Oncology 23: 2572–2577, 2012

Impact of the different breast cancer subtypes on PET imaging (7)

- **Results**

ΔSUV, predictive factor of pCR only in HER2 positive tumors



ROC Analysis

ΔSUV between PET1 and PET2 **Cut-off = -75%**

Se = 67%

Sp = 82%

NPV = 78%

Accuracy = 76%

Impact of the different breast cancer subtypes on PET imaging (8)

- **Conclusions**

The baseline 18F-FDG tumoral uptake but also its early metabolic response to neoadjuvant treatment is different according to the subtypes of breast cancer

Humbert O. et al Annals of Oncology 23: 2572–2577, 2012

Prognostic relevance at 5 years of the early monitoring of neoadjuvant chemotherapy using FDG-PET in luminal HER2-negative breast cancer

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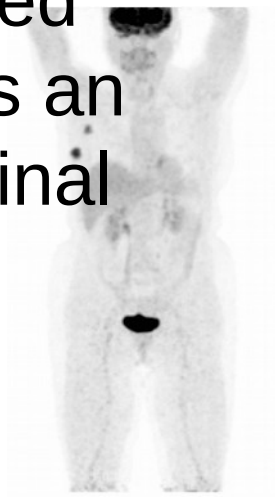
Introduction

- pCR is rarely obtained in the **luminal HER2 negative subtype***; this surrogate endpoint is questionable in this subtype.

- Early metabolic changes during NAC may predict pCR*

- Aim: Can the early metabolic response, evaluated with PET after the first cycle of NAC, be used as an early surrogate endpoint for outcome in the luminal HER2 negative breast cancer subtype?



Materials and Methods

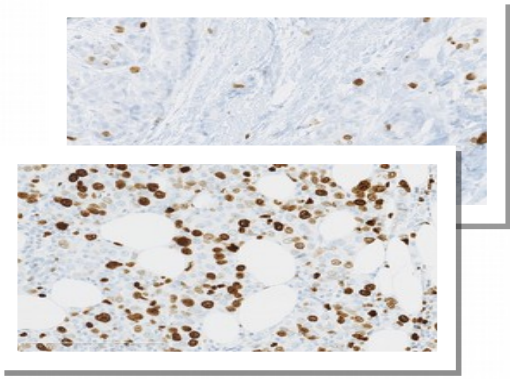
- 61 women with Stage II and IIIA luminal HER2 negative breast cancer (positive hormone receptor status / HER2 negative)
- A prospective study from April 2004 to August 2009

Ki-67 tumor expression*:

Luminal A (Ki-67< 14%)

Luminal B (Ki-67≥ 14%)

*Cheang *et al*, J Natl Cancer Inst 2009



Materials and Methods

Treatments

1. 6 courses of NAC: antracyclines ± taxane-based regimen
2. Surgery after 6 courses: 49% conservative / 51% mastectomy
3. Radiotherapy
4. ± adjuvant chemotherapy (26%)
5. Hormone therapy (100%)

Results

Population

median age = 50 years

Tumor stage :

90% T2 - 10% T3

39% N0 - 61% N1

Pathology:

80% Ductal - 20% Lobular

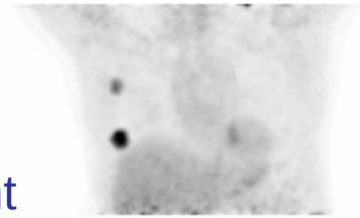
11.5% SBR1 - 75.5% SBR2 - 11.5% SBR3

Ki-67 expression analysis:

14% luminal A - 86% luminal B

pCR rate = 1.6% (1/61)

Results



1st PET Exam

Baseline metabolism assessment
Mean SUV = 4.1 ± 3.4

31%

69%

Low metabolic tumors
Mean SUV = 1.6 ± 0.5

Hypermetabolic tumors
Mean SUV = 5.2 ± 3.6

Hepatic uptake

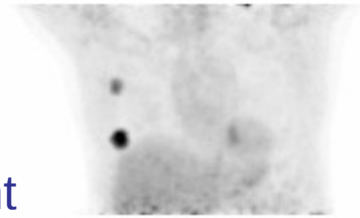
low proliferation

high proliferation

				P	overall
Lobular carcinoma		42.1 %	9.5 %	**0.006**	20%
Luminal	**A**	33.3 %	5.9 %	**0.02**	14%
	B	66.7 %	94.1 %		86%
SBR	**1**	26.3 %	4.9%	**0.04**	11.7%
	2+3	73.7 %	95.1%		88.3%
Mitosis	**1**	94.4 %	61.0 %	**0.009**	71.2%
	2+3	5.6 %	39.0 %		28.8%

Results

1st PET Exam



Baseline metabolism assessment
Mean SUV = 4.1 ± 3.4

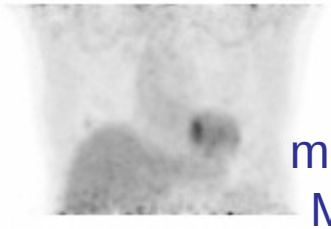
31%

69%

Low metabolic tumors
Mean SUV = 1.6 ± 0.5

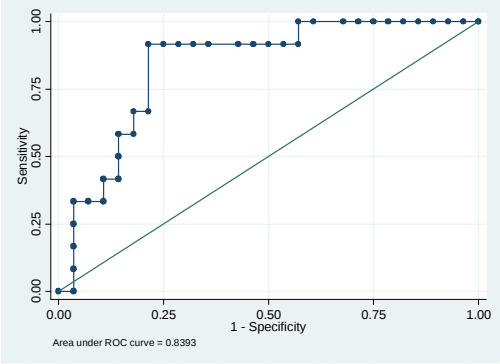
Hypermetabolic tumors
Mean SUV = 5.2 ± 3.6

No 2nd PET



2nd PET exam

metabolic response assessment
Mean ΔSUV = 16.8% ± 36.6%



Good metabolic response to NAC

Poor metabolic response to NAC

ΔSUV = 16%

Outcome analysis: relapse free survival

LUMINAL BREAST CANCER

1st PET

31%

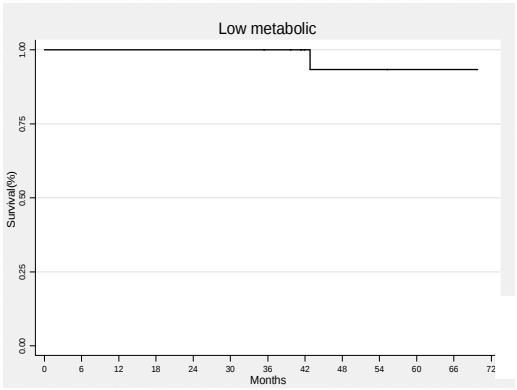
69%

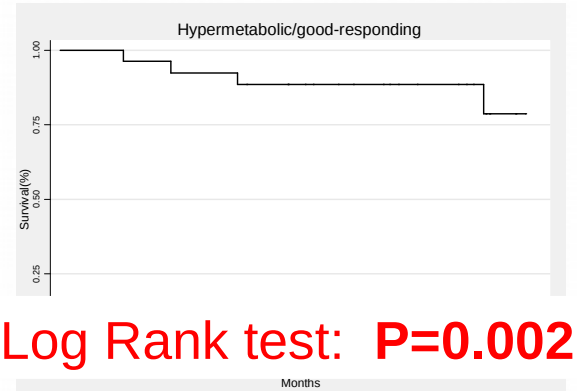
2nd PET

44%

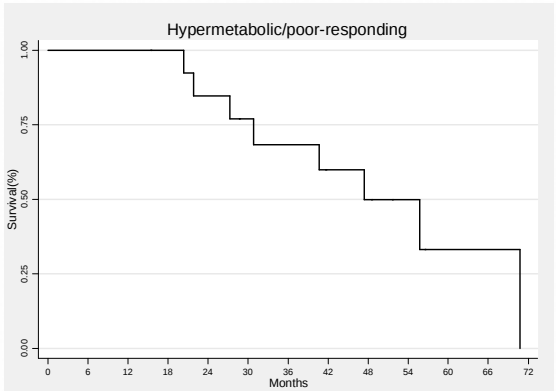
25%

Baseline low-metabolism	Baseline hypermetabolism +***good*** metabolic response	Baseline hypermetabolism + ***poor*** metabolic response
RFS 5 years = 93.3%	RFS 5 years = 88.5%	RFS 5 years = 33.2%





Log Rank test: **P=0.002**



Outcome analysis: overall survival

LUMINAL BREAST CANCER

1st PET

69%

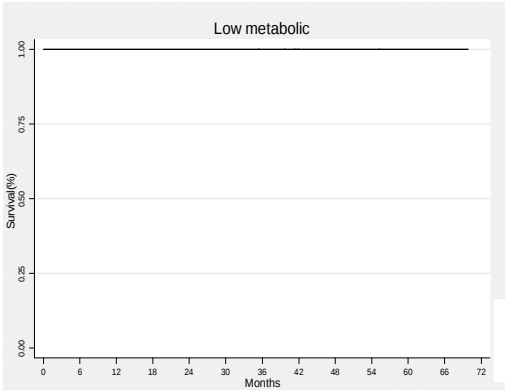
31%

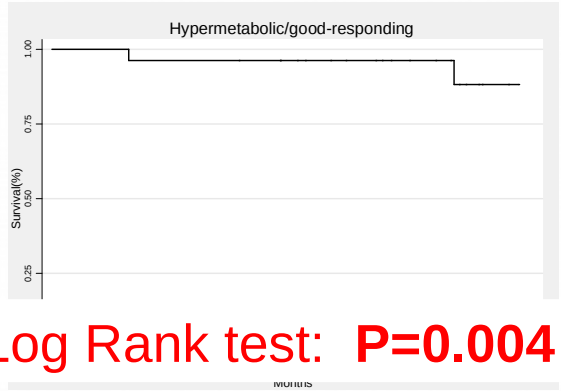
2nd PET

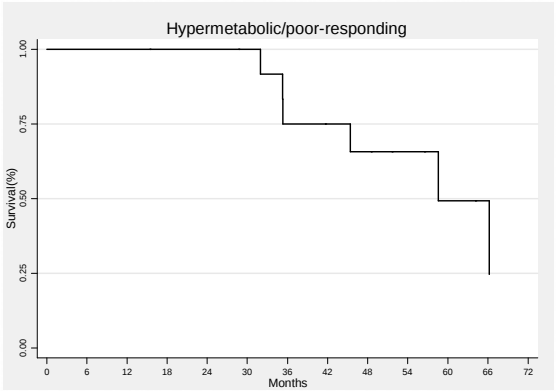
44%

25%

Baseline low-metabolism	Baseline hypermetabolism +***good*** metabolic response	Baseline hypermetabolism + ***poor*** metabolic response
OS 5 years = 100%	OS 5 years = 96.1%	OS 5 years = 49.2%







Log Rank test: **P=0.004**

Overall survival analysis (univariate Cox)

		HR	*95% CI*	*p*
Tumor size	≤ 5cm (T1-T2) **> 5cm (T3-T4)**	1 **6.52**	 **[1.60-26.6]**	**0.009**
Lymph node status	Negative Positive	1 1.45	 [0.36-5.79]	0.60
Histological type	Ductal Lobular	1 0.9	 [0.18-4.43]	0.89
Tumor grading	SBR I et II SBR III	1 0.84	 [0.10-6.88]	0.87
Progesterone receptor	Positive **Negative**	1 **4.07**	 **[1.07-15.4]**	**0.04**
Luminal subtype	A (Ki67<13.25%) B (Ki67≥13.25%)	1 ND	-	-
Baseline metabolism	Low metabolism High metabolism	1 6.9	 [0.83-57.6]	0.07
Baseline metabolism + response (ΔSUV)	Low metabolic ΔSUV ≥16% **ΔSUV <16%**	0.32 1 **10.5**	[0.03-3.64] **[1.84-60.4]**	**0.004**

Conclusion

NAC is questionable in luminal HER2 negative breast cancer: difficulty to predict which tumors are likely to respond to NAC.

^{18}FDG PET

↓

3 groups of luminal HER2 negative tumors with different proliferation indexes, chemo-sensitivities and outcomes.

Conclusion

1) **Low metabolic tumors** = low proliferation characteristics
= excellent prognosis at 5 years

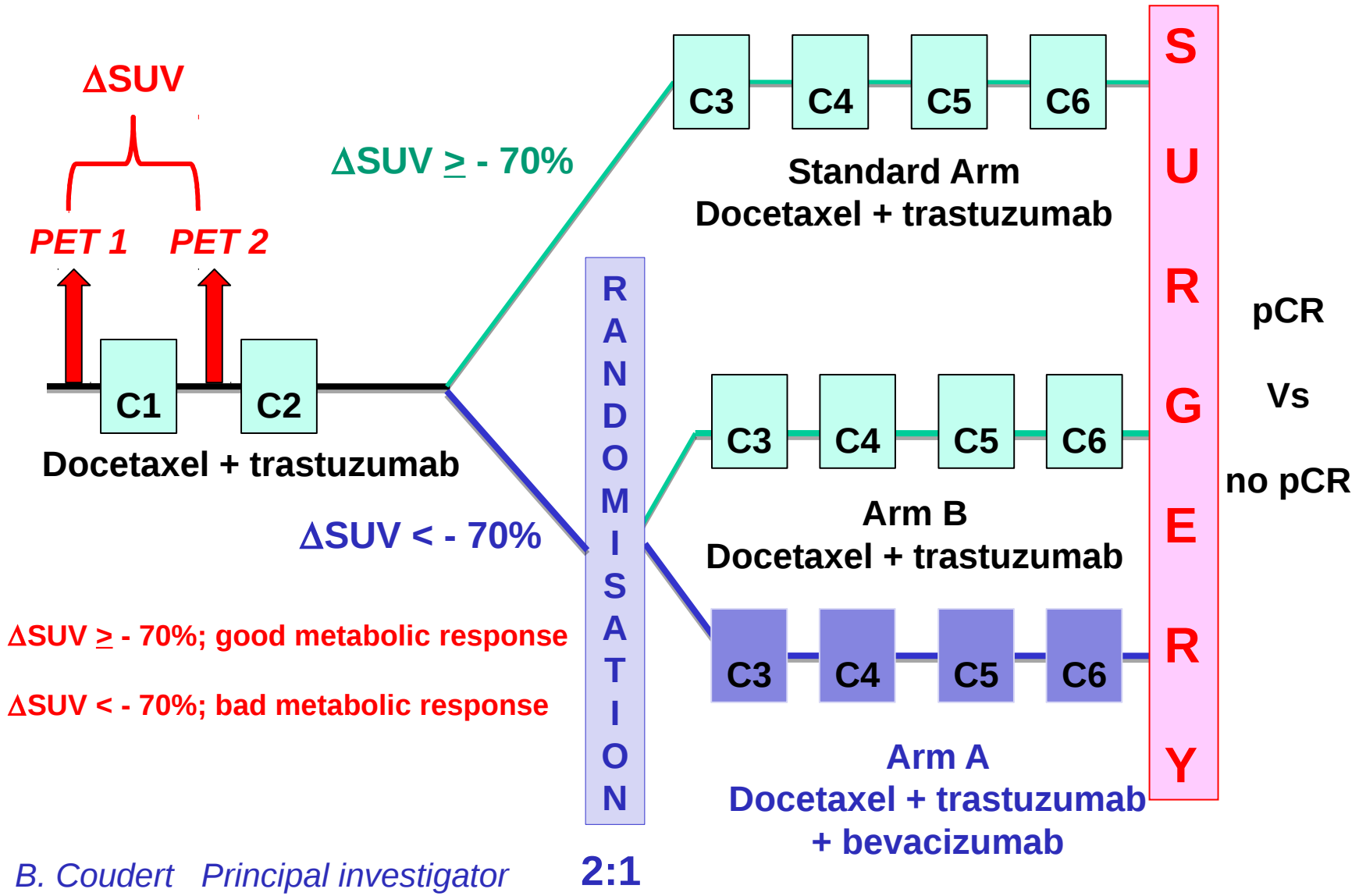
2) **Hypermetabolic tumors with a good metabolic response**
= good prognosis

3) **Hypermetabolic tumors with a poor metabolic response**
= poor prognosis
= alternative treatment?

FDG PET could help to tailor the NAC regimen to the metabolic response early

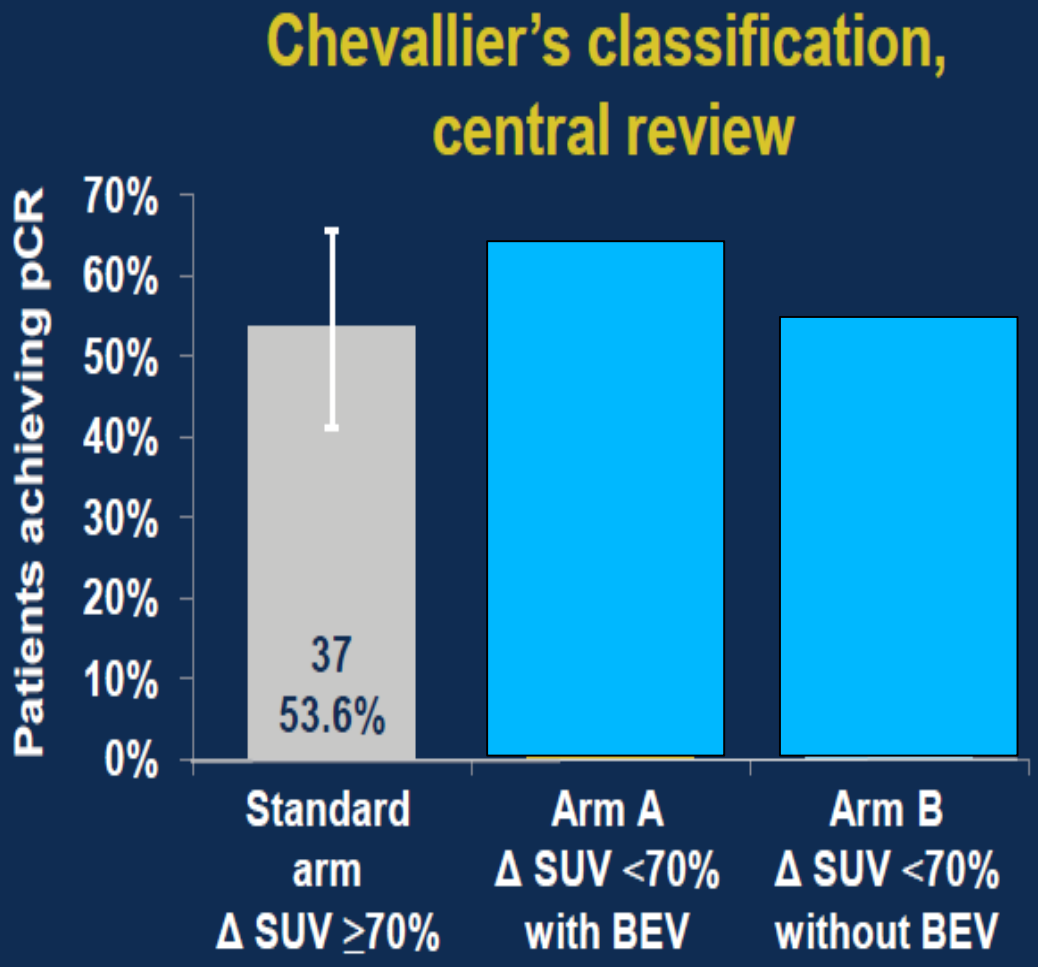
AVATAXHER

- **Methods**; Neoadjuvant setting HER2+



B. Coudert Principal investigator

AVATAXHER: Primary objective (ITT)



CI, confidence interval; pCR, pathological complete response

Conclusions

- Des cancers du sein avec différents sous-types moléculaires
- Des réelles implications pour la médecine nucléaire
- ^{18}F-FDG PET/CT
- ^{18}Fluoroestradiol (FES) PET, ^{89}Zr-trastuzumab….

Les cliniques du sein dans l'avenir