



Cancer du sein avancé RE+/HER2- Nouvelles orientations thérapeutiques

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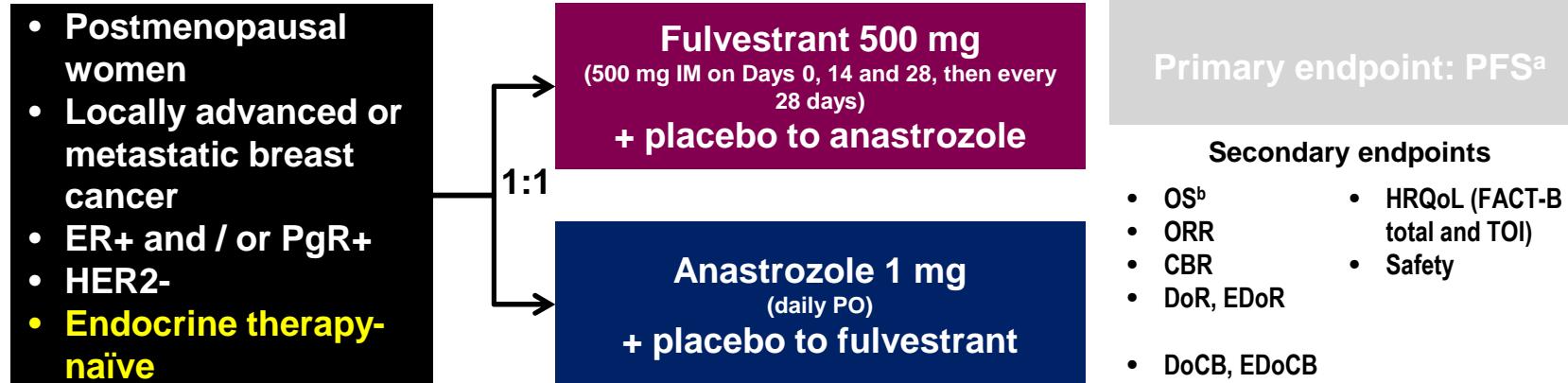
Liens d'intérêt

- Roche, Novartis, AstraZeneca, Pfizer, Nanostring

Rappels cliniques récents

1. Hormonothérapie seule
2. Combinaisons
3. Nouvelles molécules

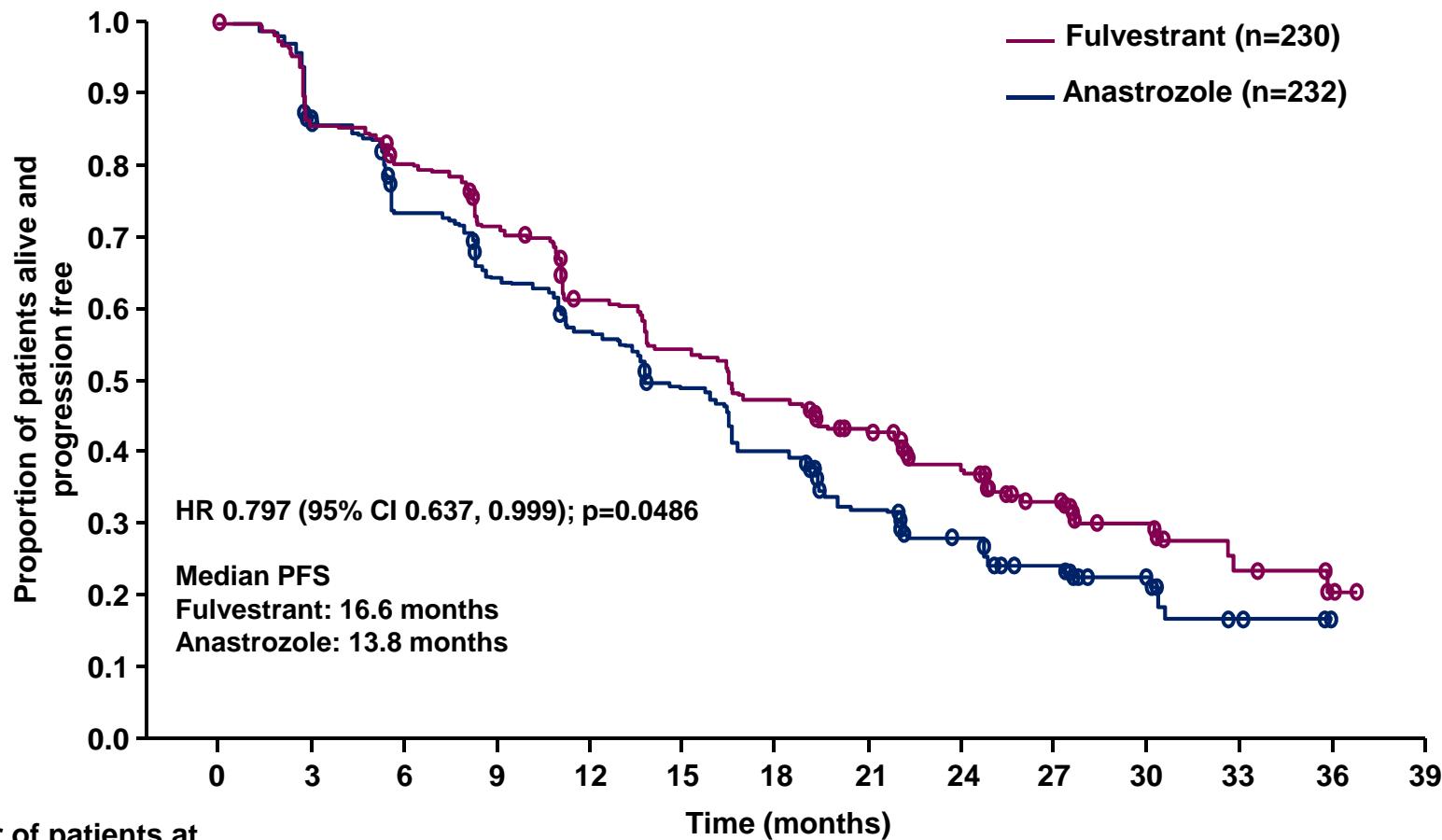
FALCON: PHASE III STUDY DESIGN



- Randomised, double-blind, parallel-group, international, multicentre study
- Follow-up for disease progression and survival
- Randomisation of 450 patients was planned to achieve 306 progression events; if the true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test)
- Stratification factors: prior chemotherapy for advanced disease (yes / no); measurable vs. non-measurable disease (at baseline); locally advanced vs. metastatic disease
- Subgroup analysis of PFS for pre-defined baseline covariates

^aAssessed via RECIST 1.1, surgery / radiotherapy for disease worsening, or death; ^bInterim analysis at the time of PFS analysis
EDoCB, expected duration of clinical benefit; EDoR, expected duration of response; FACT-B, Functional Assessment of Cancer Therapy - Breast;
TOI, Trial Outcome Index

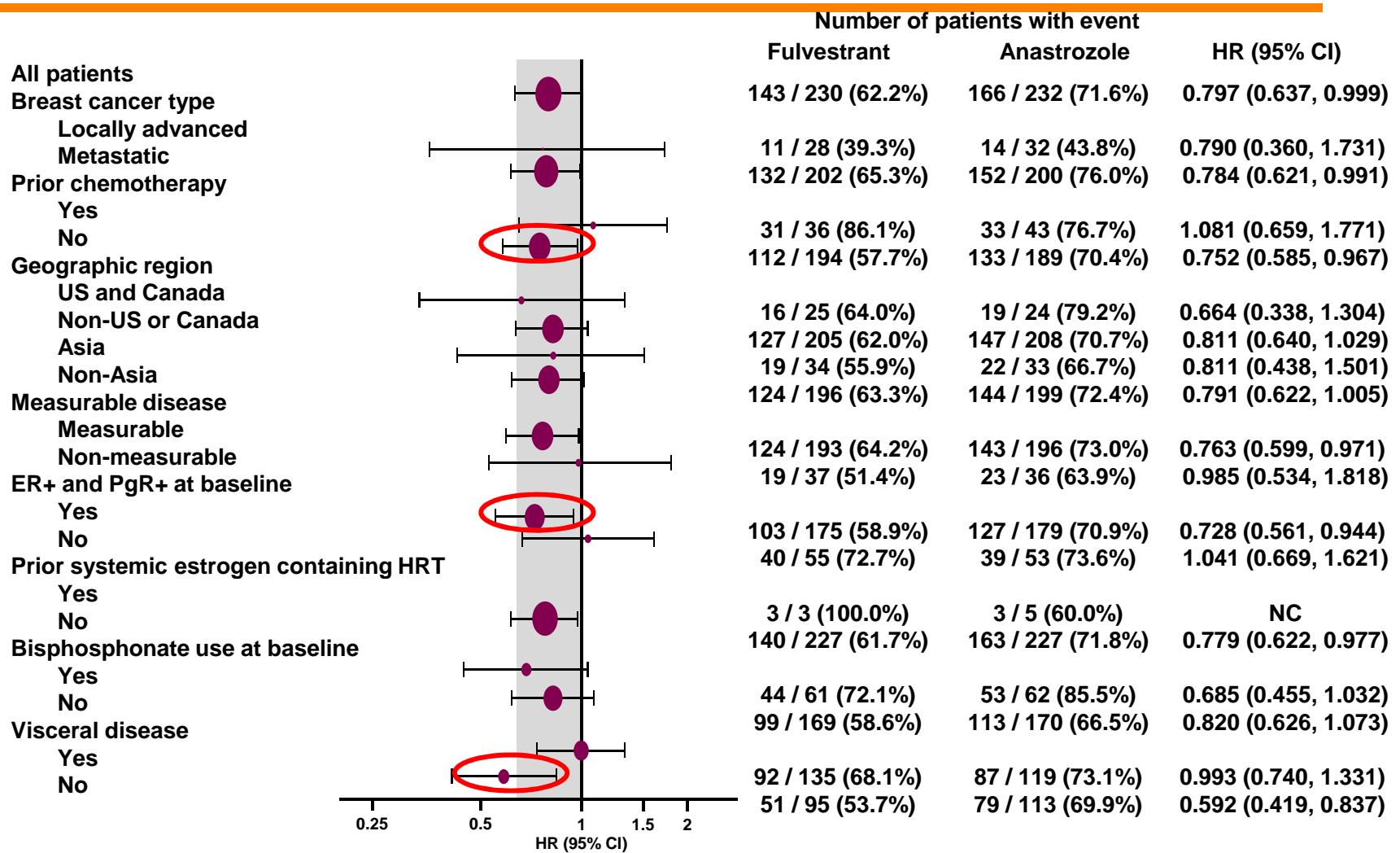
FALCON: PRIMARY ENDPOINT, PFS



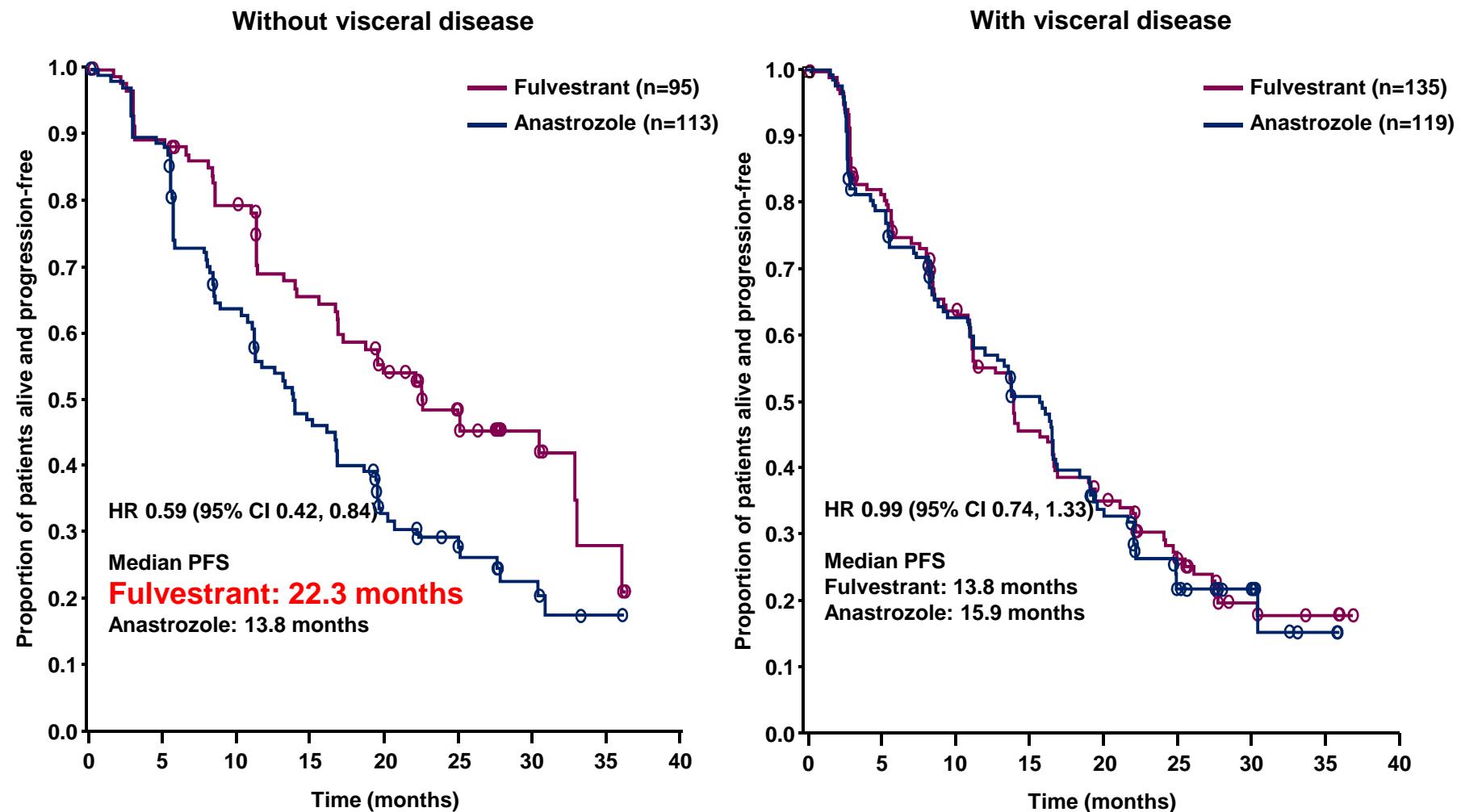
Number of patients at risk:

Fulvestrant	230	187	171	150	124	110	96	81	63	44	24	11	2	0
Anastrozole	232	194	162	139	120	102	84	60	45	31	22	10	0	0

FALCON: FOREST PLOT FOR PFS BY PATIENT SUBGROUP



FALCON: PFS IN PATIENTS WITH OR WITHOUT VISCERAL DISEASE



Ellis, ESMO 2016

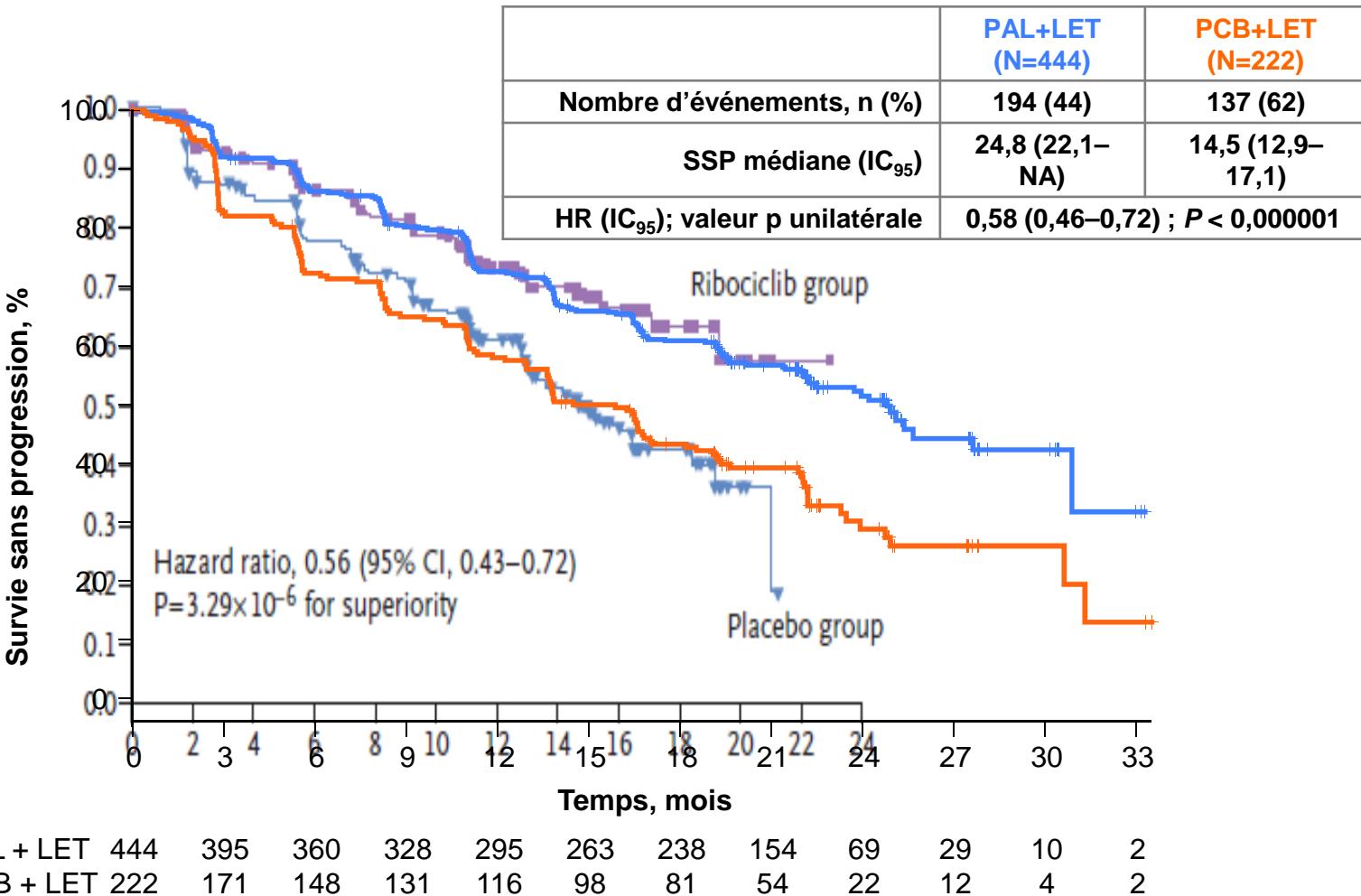
Post hoc interaction test $p < 0.01$
A circle represents a censored observation

CDKi (et mTORi) : populations

	Paloma 2	Monaleesa 2	Paloma 3	Bolero 2
N	444 vs 222	334 vs 334	347 vs 174	485 vs 239
Sites métas viscéraux	50%	59%	59%	59%
De novo	33%	34%	NA	NA
Intervalle libre > 12 mois	47%	65%	95%*	60%
Sensibilité « vraie »	80%	99%	Post hormono	Post IAs

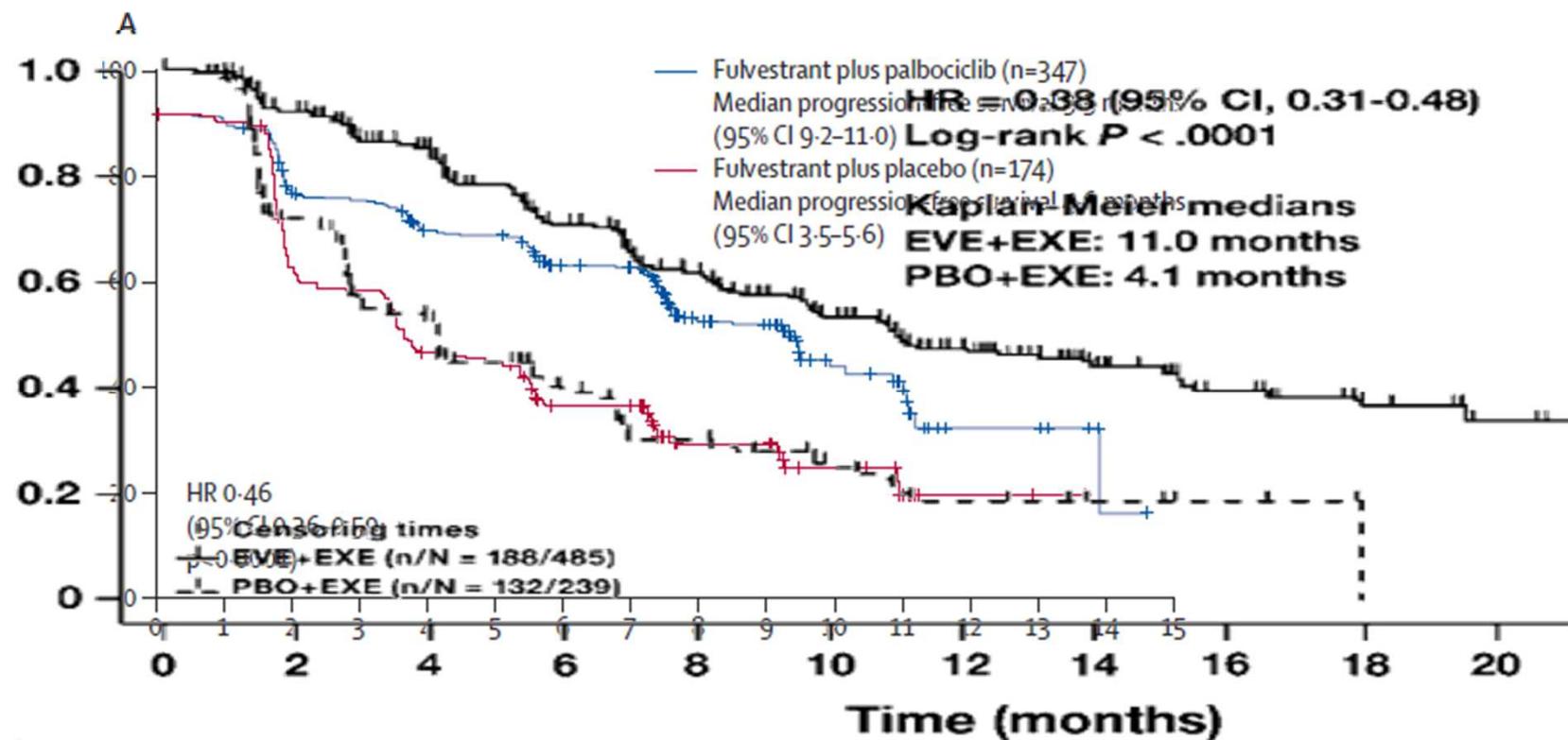
Finn, NEJM 2016
Hortobagyi, NEJM 2016
Turner, NEJM 2015
Baselga, NEJM 2012

SSP : P2 et M2



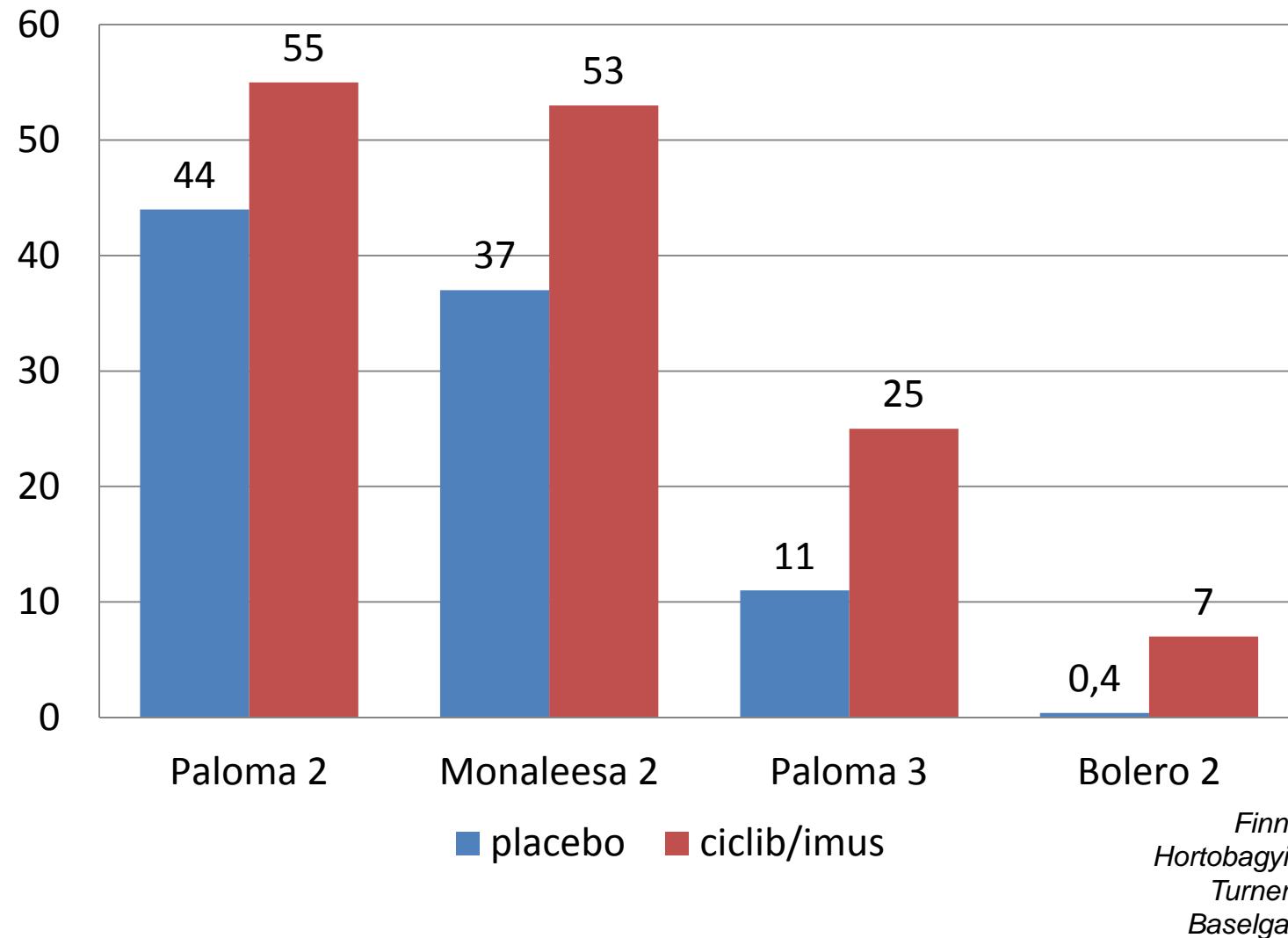
Finn, NEJM 2016
Hortobagyi, NEJM 2016

SSP : P3 et B2

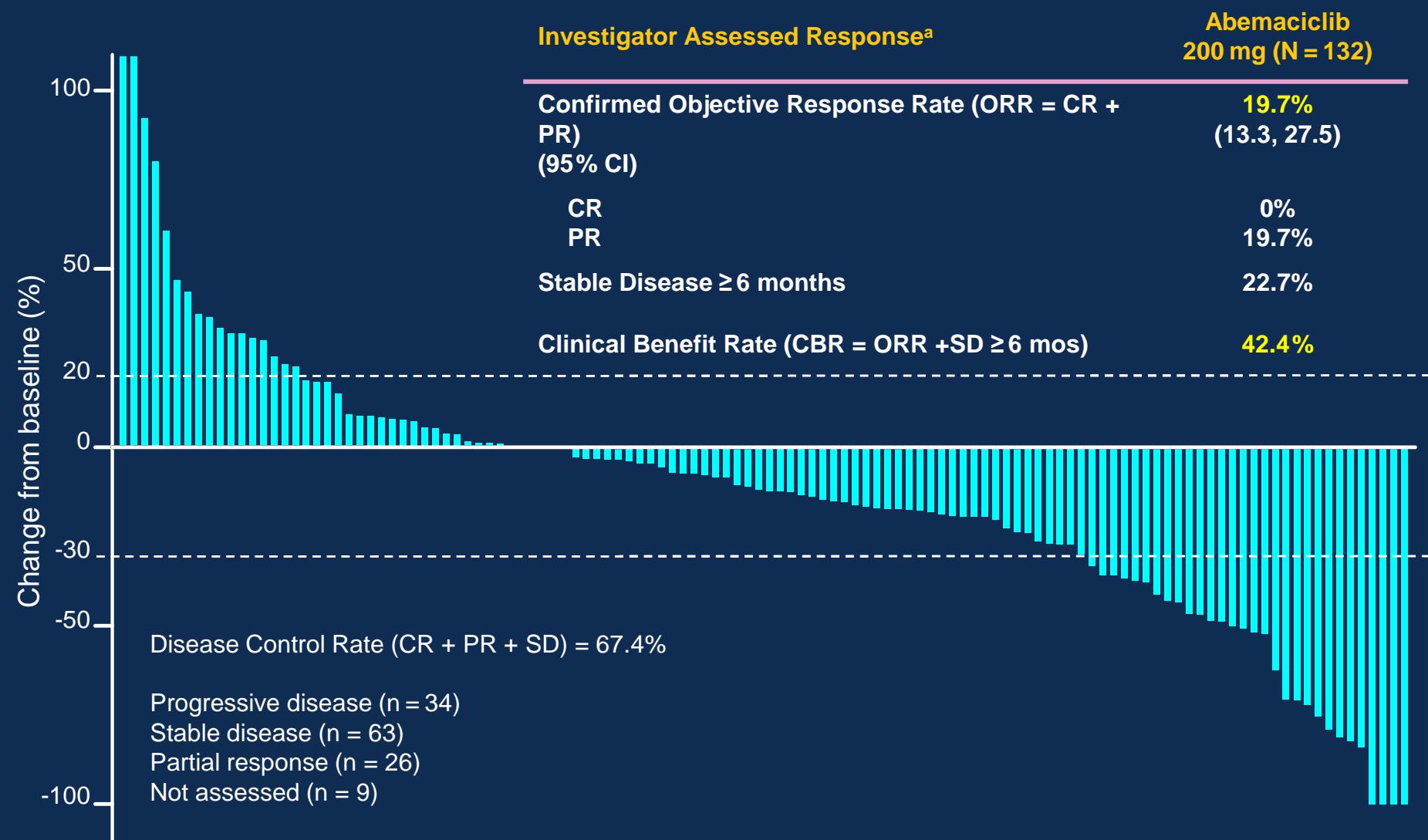


Turner, NEJM 2015
Baselga, NEJM 2012

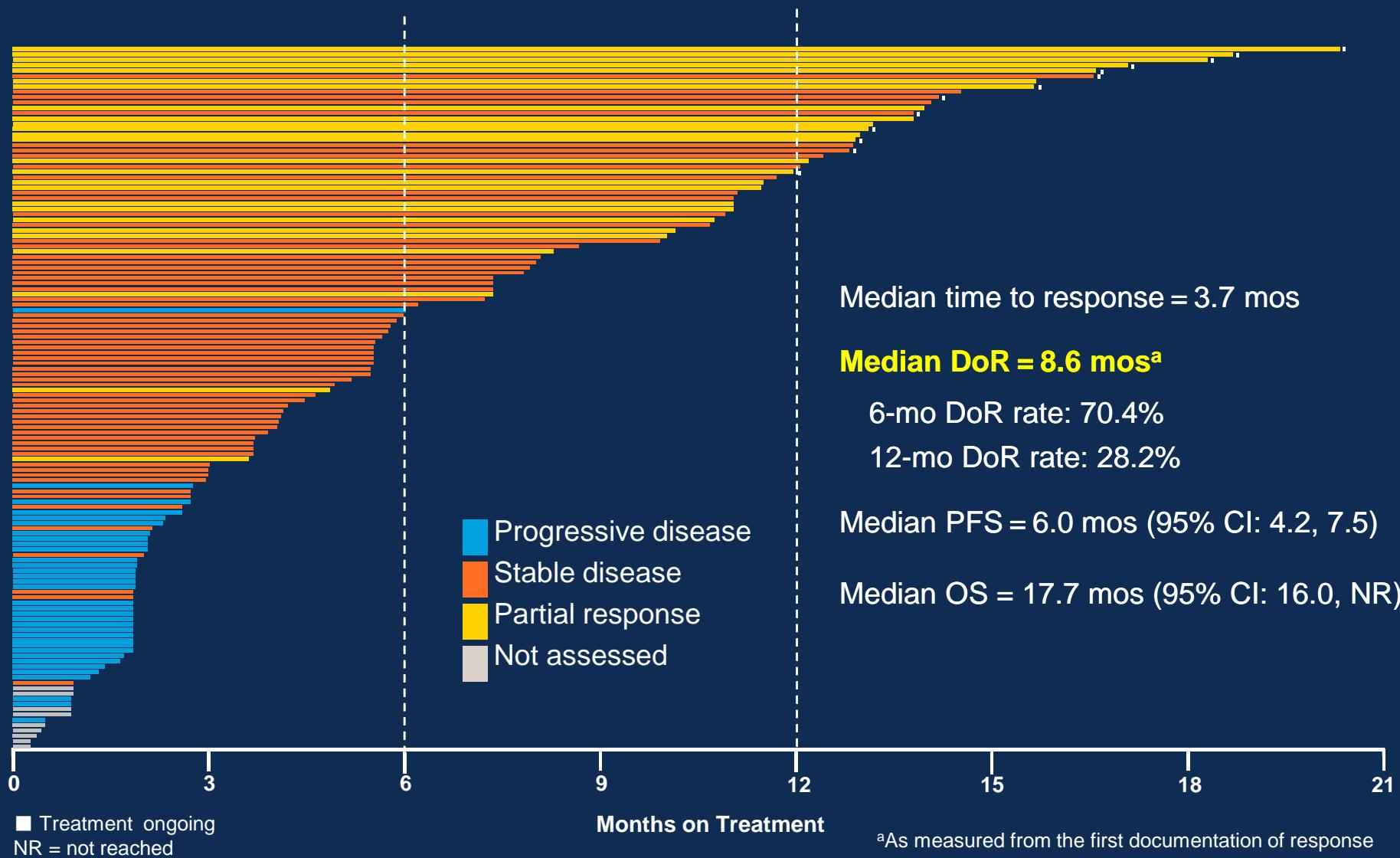
Réponse objective (maladie mesurable)



ABEMACICLIB (MONARCH 1) : Réponse



MONARCH 1: durée de traitement



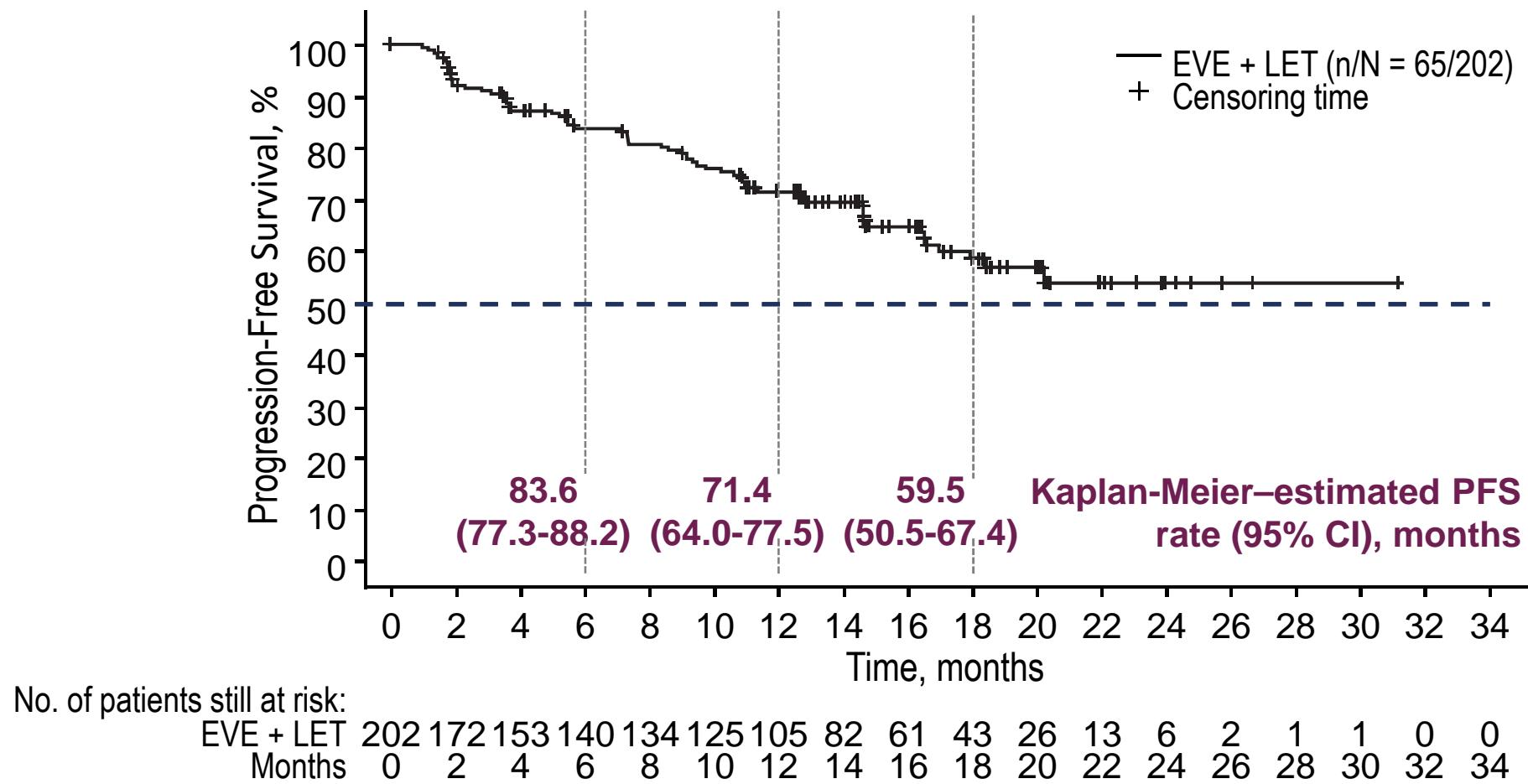
PRESENTED AT: ASCO ANNUAL MEETING '16

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Presented by: Maura N. Dickler, MD

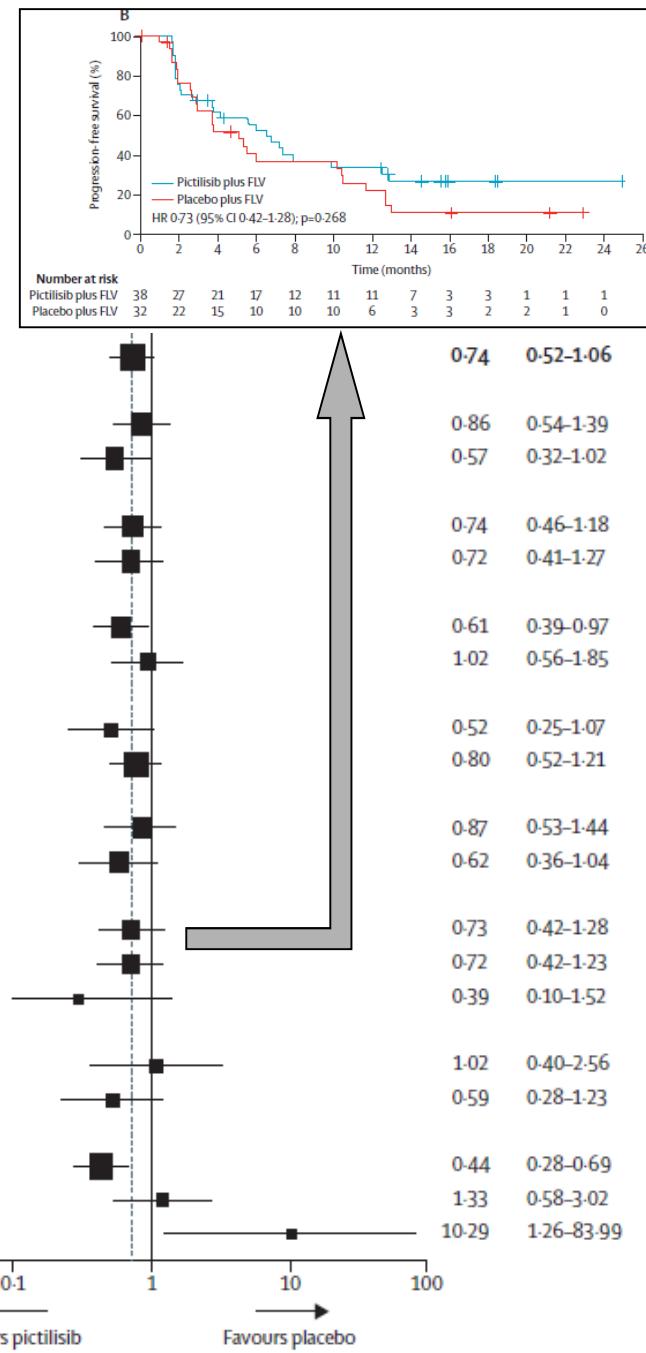
BOLERO-4 Primary End Point: PFS in the First Line

- Locally assessed median PFS in the first line was not yet reached with a median follow-up of 17.5 months



FERGI : pictilisib

All patients	168	79	61	5·1	3·6-7·3	89	59	6·6	3·9-9·8
Measurable disease									
Measurable	94	43	34	3·8	2·6-7·4	51	37	5·0	2·8-7·4
Non-measurable	74	36	27	5·1	2·9-10·5	38	22	9·8	5·6-16·0
Visceral disease									
Yes	93	42	34	3·5	1·9-5·5	51	37	5·0	2·7-6·5
No	75	37	27	6·0	3·7-12·6	38	22	12·5	6·6-16·0
Baseline ECOG score*									
0	106	45	36	3·7	2·9-5·5	61	40	6·7	3·7-12·5
1	61	33	25	7·4	2·6-10·4	28	19	5·0	2·3-11·1
Setting of last therapy									
Adjuvant or neoadjuvant	44	20	15	3·7	1·9-5·3	24	16	7·3	5·0-12·5
Metastatic	124	59	46	5·5	3·5-10·2	65	43	5·9	3·6-11·1
Endocrine therapy resistance									
Primary resistance	84	41	32	5·3	3·5-7·4	43	30	5·8	3·7-9·3
Secondary resistance	84	38	29	3·7	1·9-8·5	46	29	7·2	3·5-15·6
PIK3CA mutation status									
Positive	70	32	25	5·1	2·7-10·5	38	25	6·5	3·7-9·8
Wild-type	84	39	28	3·6	2·8-7·3	45	28	5·8	3·6-11·1
Unknown	14	8	8	7·4	1·7-12·8	6	6	11·5	1·7-18·3
PIK3CA mutation domain									
Helical	28	10	7	10·2	1·5-13·0	18	13	5·9	1·7-12·8
Kinase	42	22	18	3·7	1·9-10·4	20	12	6·5	3·7-NE
PR status†									
Positive	116	58	47	3·7	2·8-5·4	58	36	7·4	5·6-12·8
Negative	35	14	10	8·0	1·8-NE	21	14	5·0	1·7-12·5
Unknown	17	7	4	12·2	1·9-NE	10	9	2·9	1·6-8·2



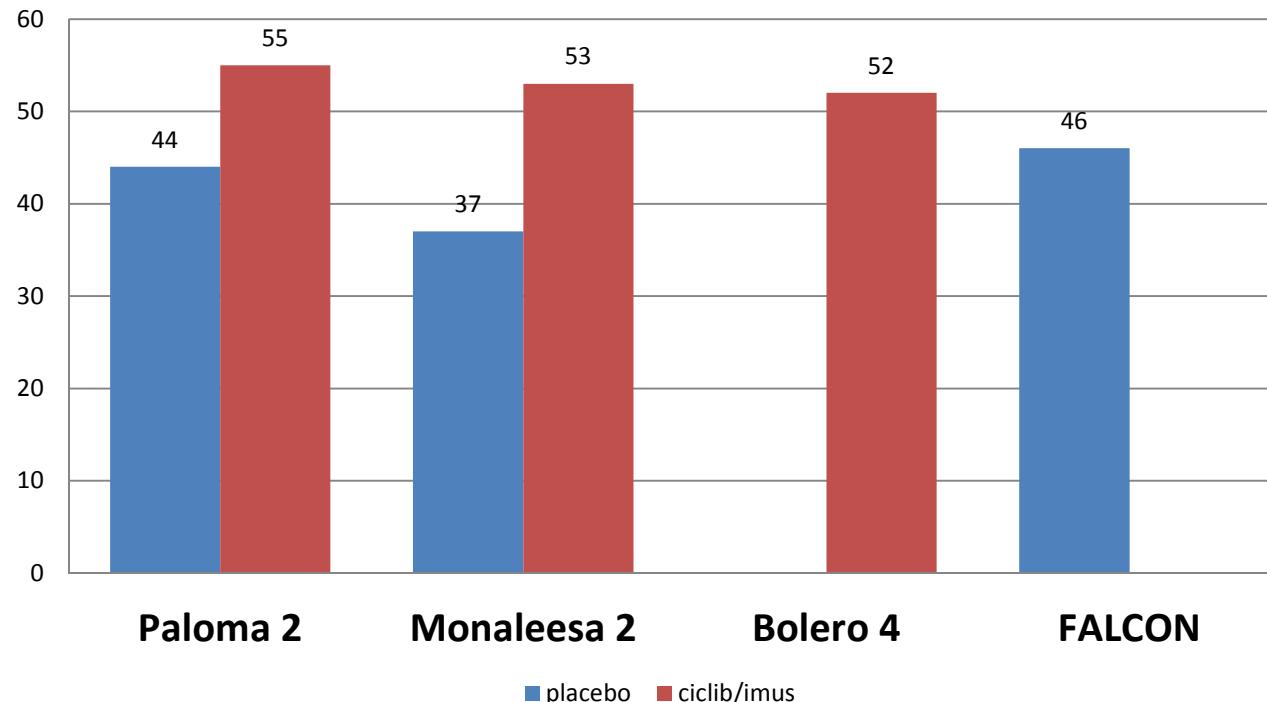
Cancer du sein avancé RE+ : prise en charge de précision ?

1. Hormonothérapie seule
2. Palbo & ribo
3. Everolimus

Cancer du sein avancé RH+ en première ligne

Nouveau paradigme

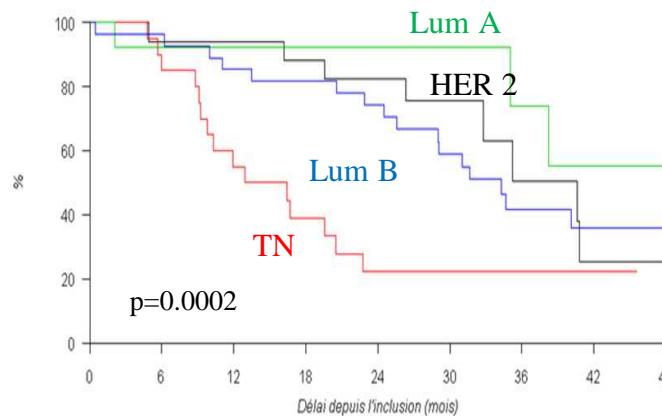
- PFS médiane : 22-24 mois
- Taux de réponse élevé
- Faible toxicité



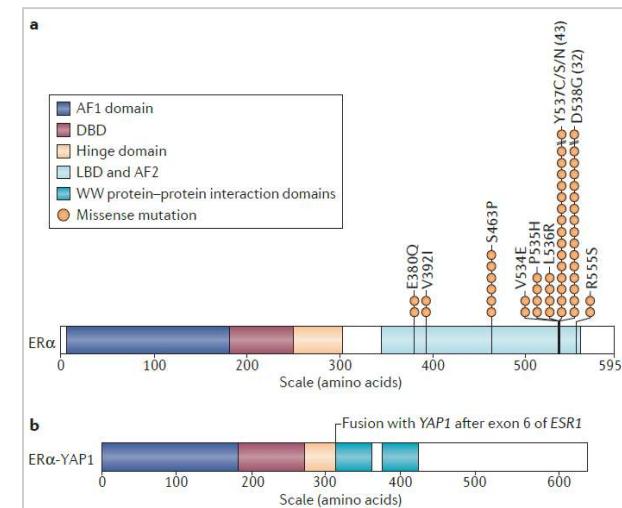
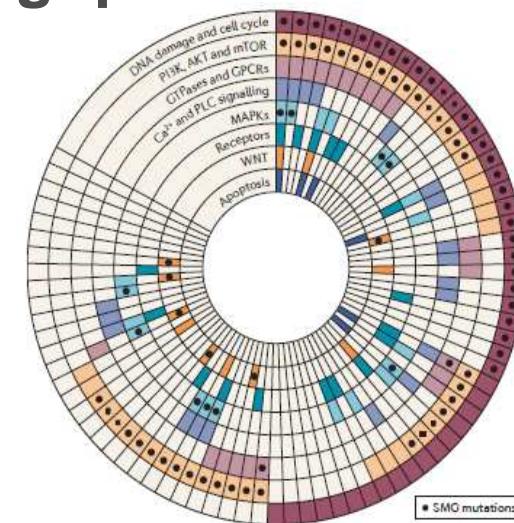
Quelle définition de l'hormonosensibilité ?

Clinique	
Définitions de l'ABC 3 (délais)	<ul style="list-style-type: none">- Primaire- Secondaire
Selon FALCON et SWOG 2206	<ul style="list-style-type: none">- HT « naïve »ET- Maladie extraviscérale

Hormonosensibilité : définition biologique ?



HBCx-22 TamR	HBCx-22 OvaR
Response to chemical stimulus	Nitrogen compound biosynthetic process
Response to wounding	Nucleotide metabolic process
Response to endogenous stimulus	Nucleoside phosphate metabolic process
Response to hormone stimulus	Antigen processing and presentation
Response to external stimulus	Purine nucleotide biosynthetic process
HBCx-34 TamR	HBCx-34 OvaR
Water-soluble vitamin biosynthetic process	Homophilic cell adhesion
Pyridine nucleotide biosynthetic process	Cell–cell adhesion
Regulation of phosphate metabolic process	Cell adhesion
Regulation of phosphorus metabolic process	Biological adhesion
Apoptotic mitochondrial changes	Response to vitamin

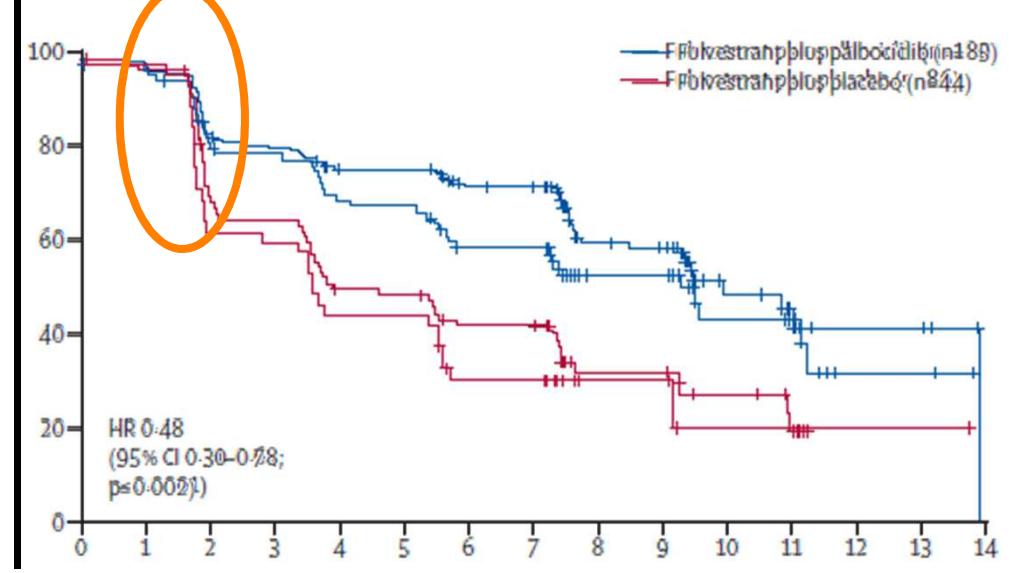
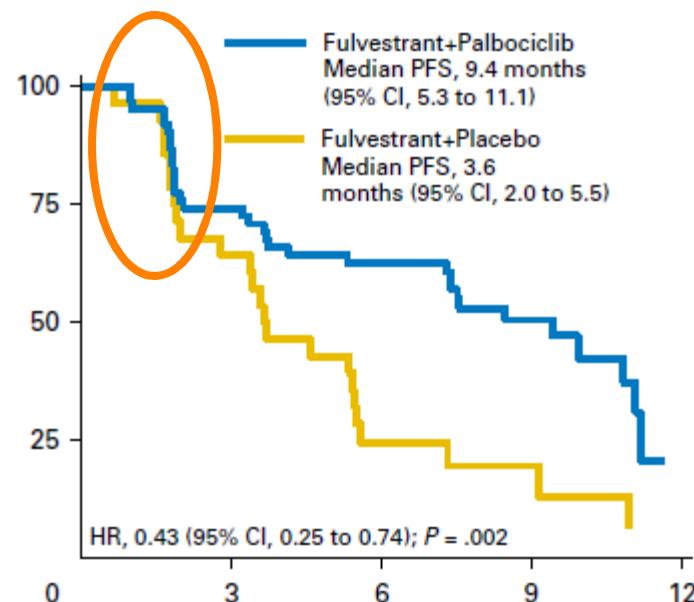


Comte et al, submitted
Cottu et al, CCR 2014
Ma et al, NRC 2015

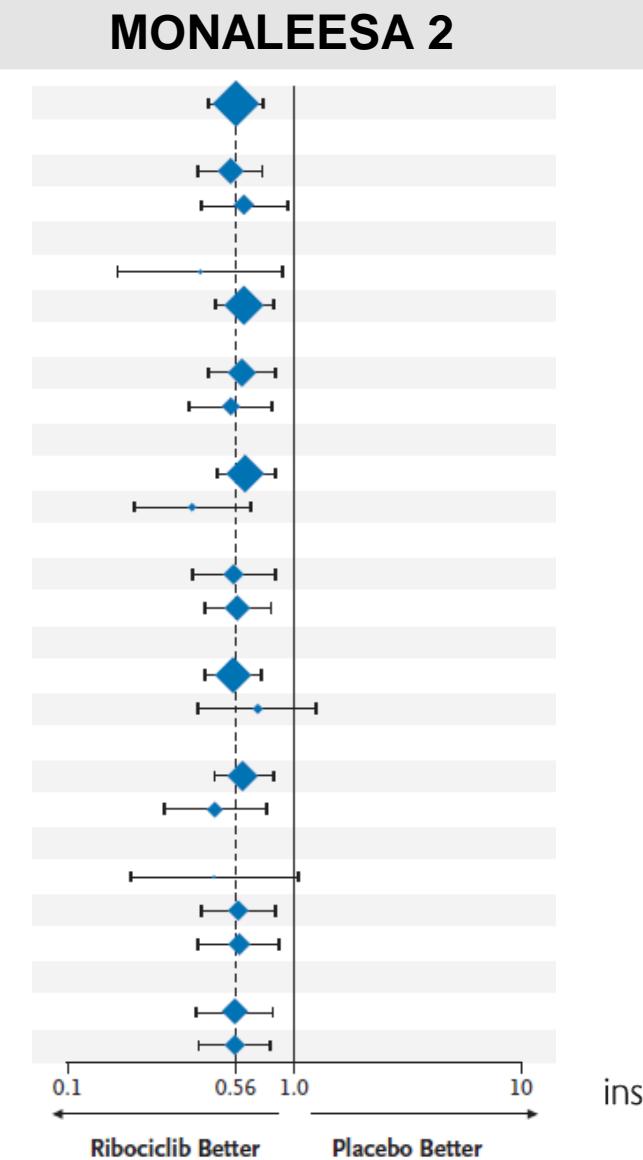
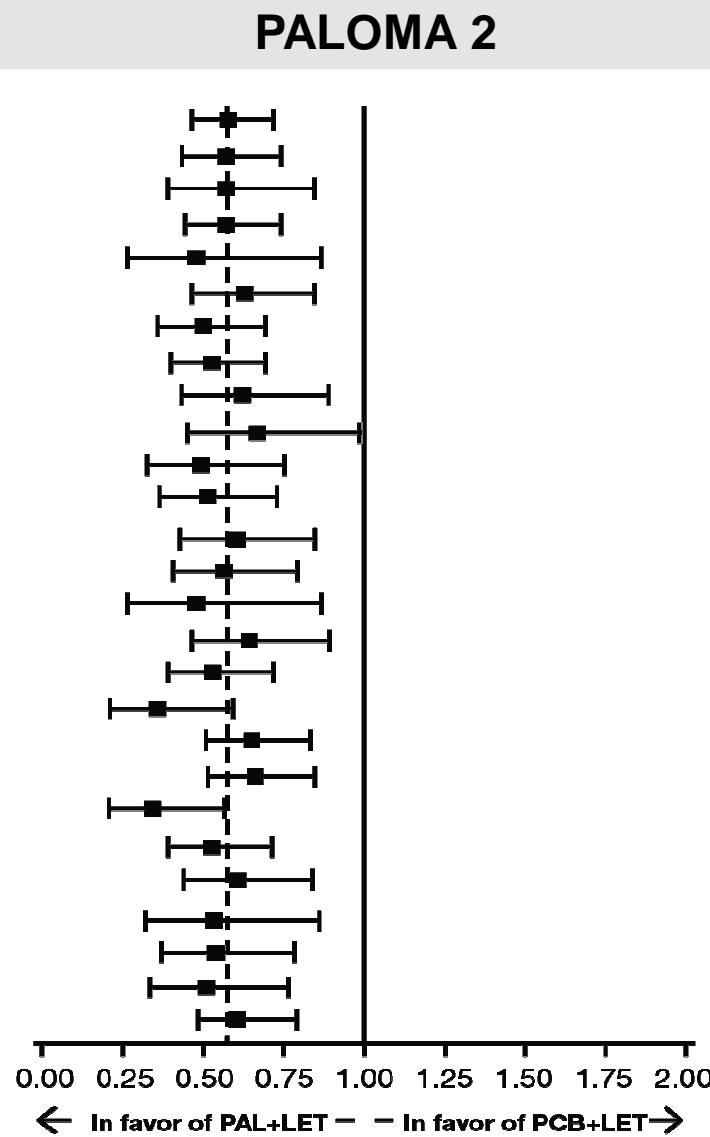
Hormonosensibilité : définition biologique ?

Dans des populations en progression après HT

ctDNA	PFS sous fulvestrant			
	ESR1 mut	ESR1 wt	PIK3CA Mut	PIK3CA Wt
SoFEA	5,7	5,4		
Paloma 3	3,6	5,4	5,8	4,6



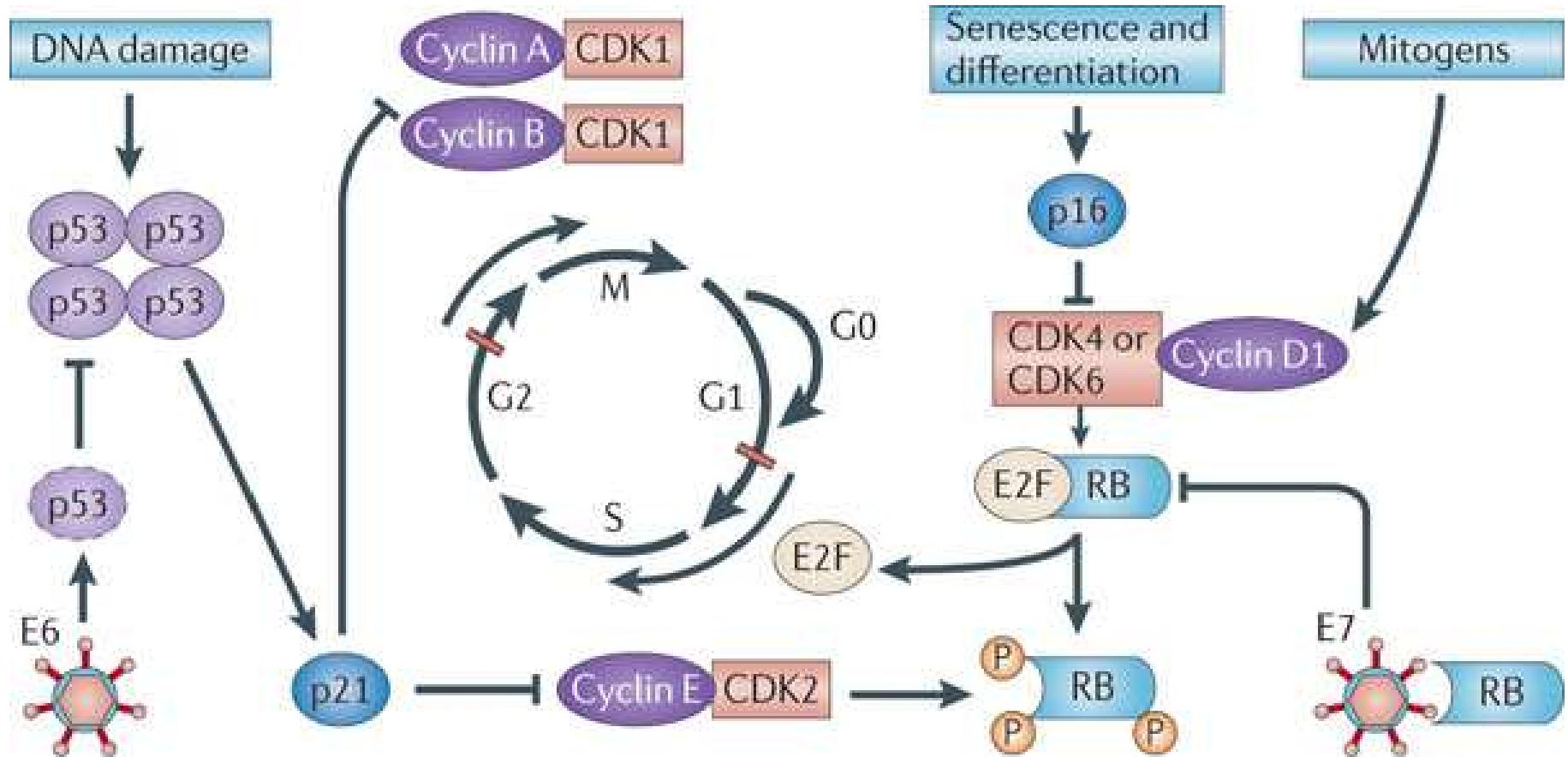
Qui bénéficie des ciclibs ?



Biomarqueurs Paloma 2 (Finn, ESMO 2016)

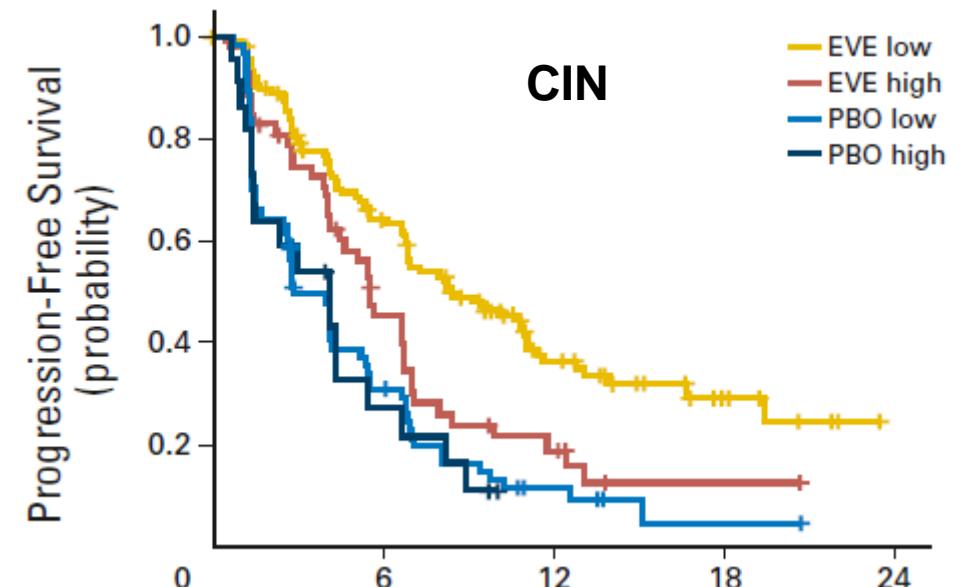
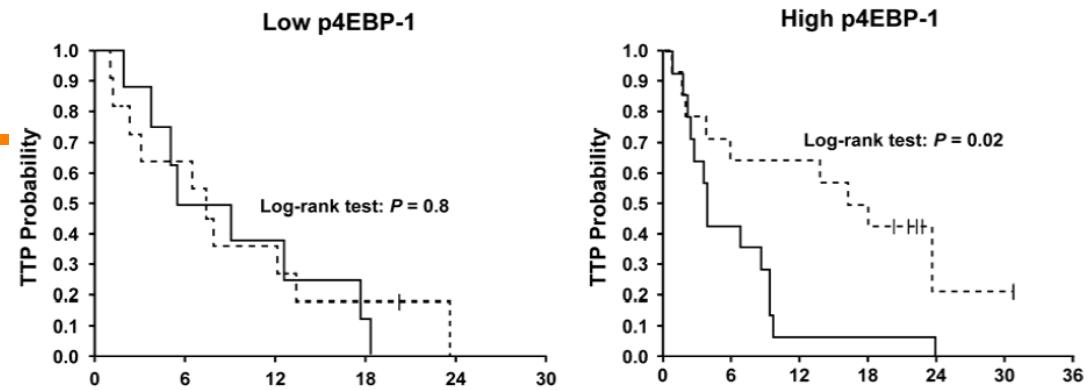
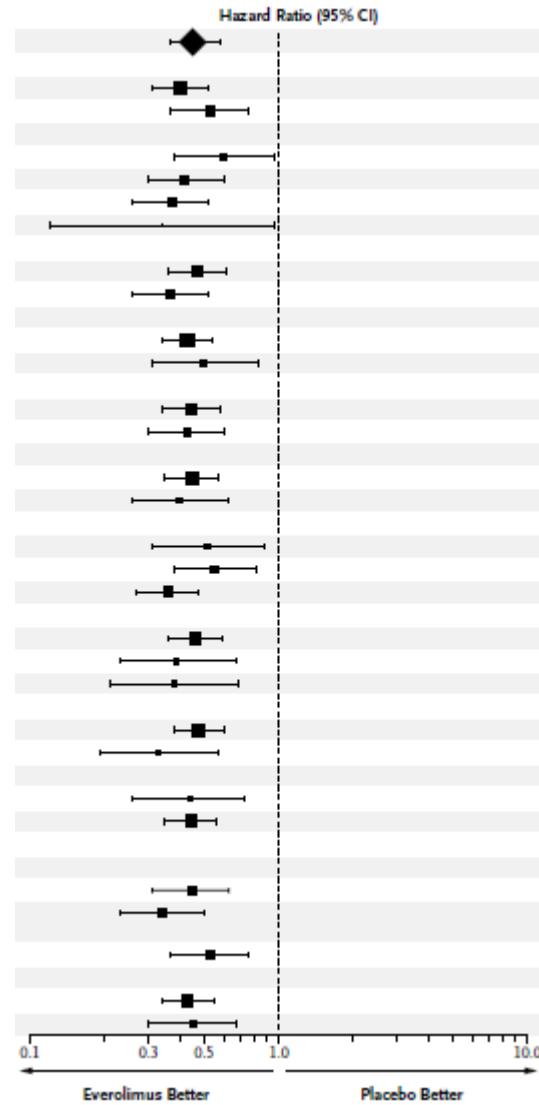
PFS		Letrozole	Letrozole Palbociclib
ER H score	Bas	11	22
	Interm	15	25
	Elevé	14	23
Rb H score	Bas	12	19
	Interm	13	25
	Elevé	11	19
CCDN1 H score	Bas	10	24
	Interm	15	24
	Elevé	12	21
p16	Pos	13	24
	Neg	13	14
Ki67	≤20%	16	27
	>20%	8	17

p16



Nature Reviews | Cancer

Everolimus



Baselga, NEJM 2012

Treilleux, Ann Oncol 2015

Hortobagyi, JCO 2015

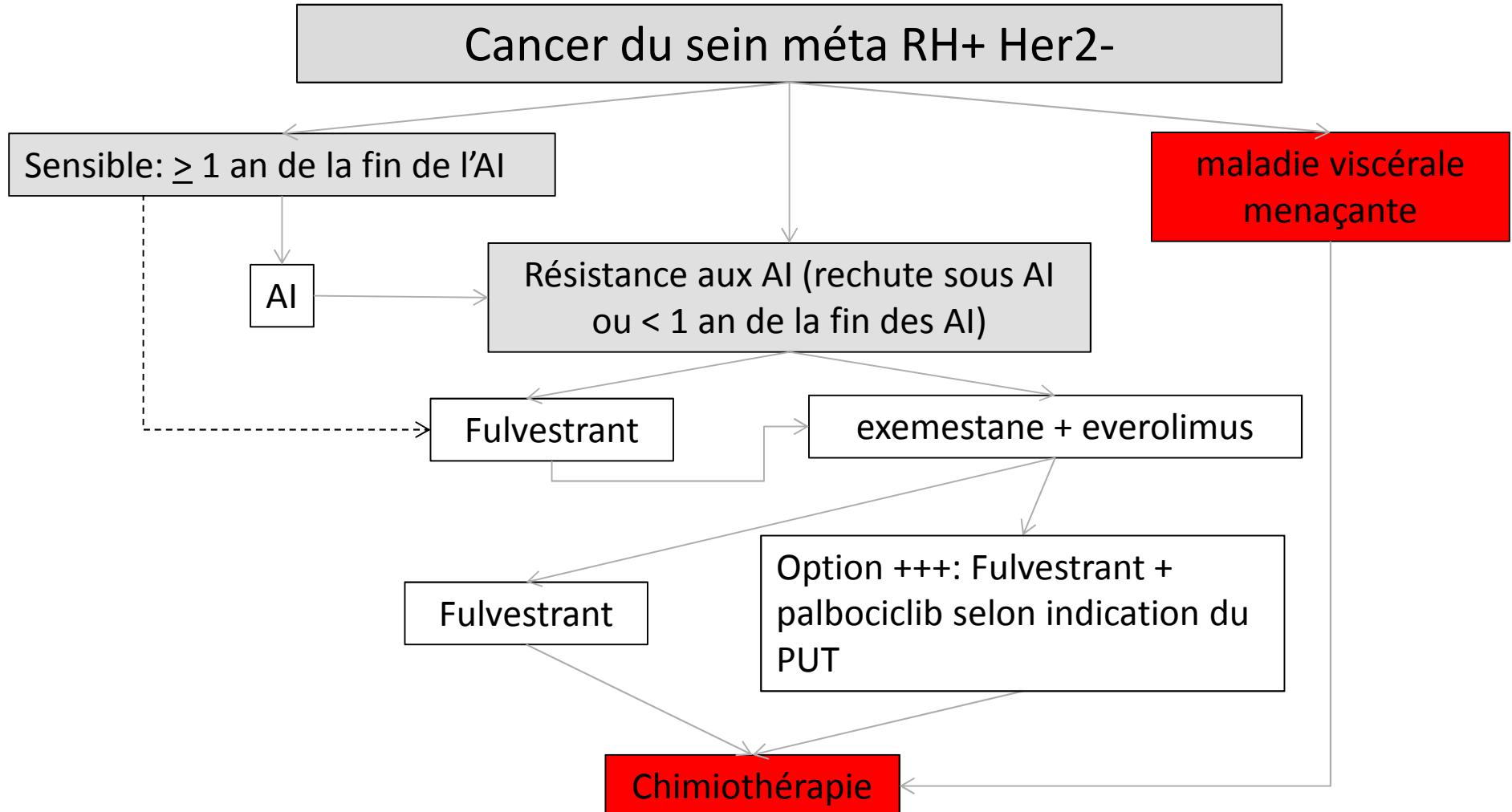
Conclusions

Quelle médecine de précision dans le cancer du sein RH+ avancé ?

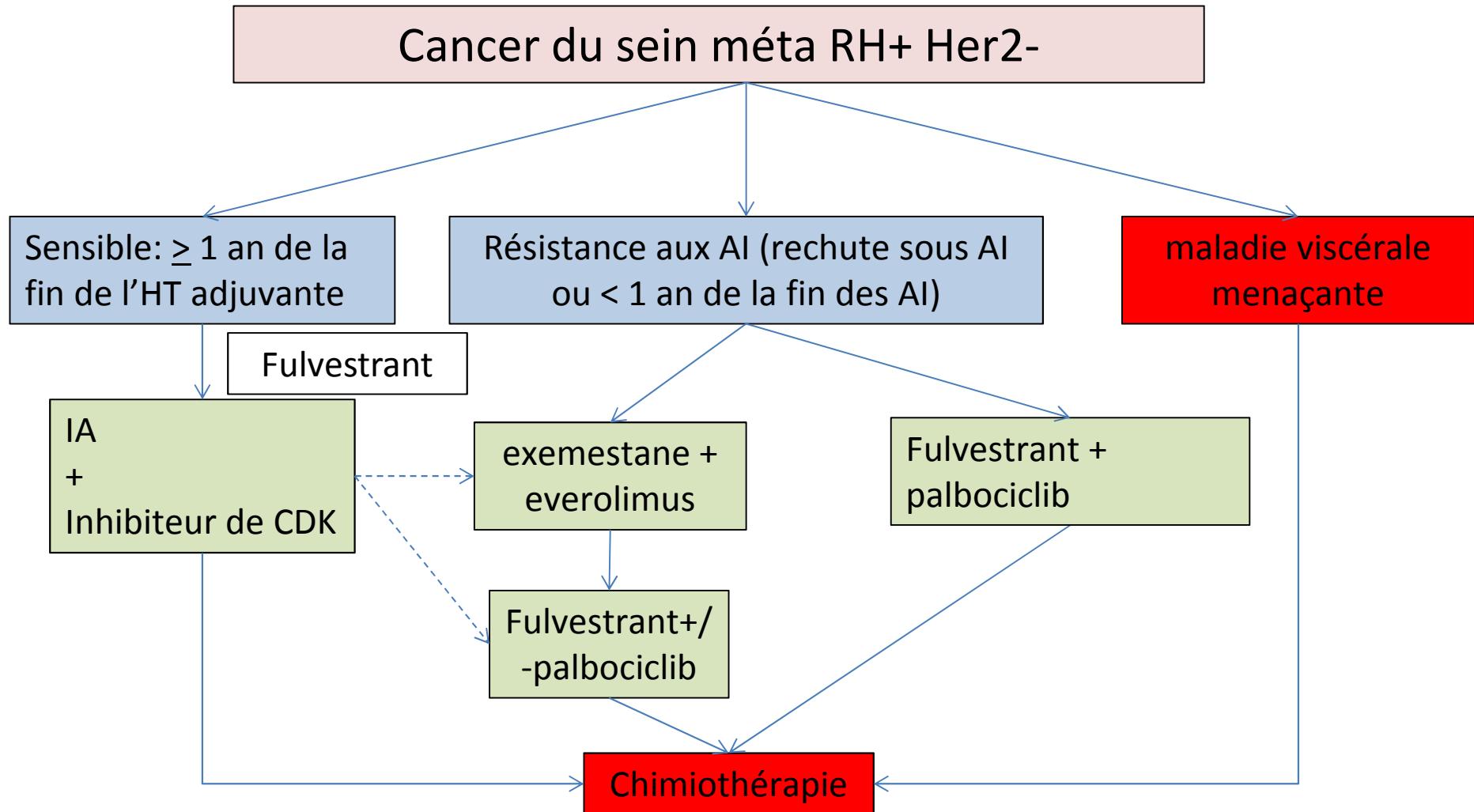
- **Aucune étude pivotale prospectivement basée sur des critères biologiques « de précision »**
 - ...en dehors du RE !
 - Plusieurs pistes ancillaires
 - FERGI négative !
- **Aucun sous-groupe clinique**
 - À l'exception des patientes non viscérales et non prétraitées (FALCON)
 - Efficacité majeure de certaines thérapies ciblées (CDKi, mTORi) dans toutes les situations



Dans le contexte du PUT palbociclib



Après l'AMM Palbociclib



En pointillé : options sans niveau de preuve, à valider en RCP

© Cottu, Delaloge et al

Et à la phase précoce ?

- **Néoadjuvant**

- Neopal
- Predix LumB
- POP

- **Adjuvant**

- Pallas
- Unirad/SWOG

