SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Sensitivity and Resistance to Hormonal therapy: *which criteria for clinical use?*

Antonio Frassoldati
Oncologia Clinica
AOU di Ferrara

Sensitivity and Resistance

- Two faces of the same coin?


?


  - Sensitivity: predict it and use for treatment choice; assess it
  - Resistance: assess it; use it for tuning treatment

- Not so simple to be defined

Which point of view?

Biological view

Clinical view

How can we integrate them?

Choice of therapy, assessment of efficacy, evaluation at progression, subsequent therapies

Data supporting the relevance of biology

- ER expression level is predictive of the clinical effect of hormonal drugs.

- The inhibition of the ER-related pathway (both by blocking the receptor and by downregulating the level of ligand) demonstrated to abrogate or to reduce the tumor cell growth

Relationship of ER to response to endocrine therapy in advanced breast cancer

TABLE 1. Early Clinical Correlations

Investigator	Year	Patients	Objective remissions: Positive	Objective remissions: Borderline and negative
Jensen *et al.*	1970[14]	26	4/6	1/20
	1971[16]	42	10/13	1/29
	1973[15]	54	13/17	2/37
Maass *et al.*	1972[23]	21	6/7	0/14
	1973[24]	59	13/24	2/35
Englesman *et al.*	1973[5]	37	14/17	2/20
Leung *et al.*	1973[21]	20	10/10	2/10
Savlov *et al.*	1974[29]	11	3/5	0/6
TOTAL (through 1974)		181	53/73	8/108

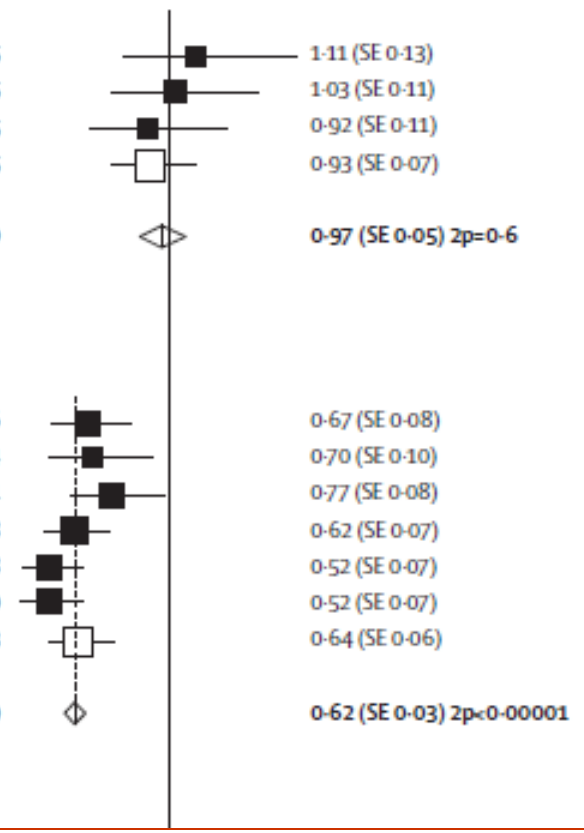
Response Rates ER+73% ER- 7%

Jensen E. Cancer 1980;46:2759

Supplement: Steroid Receptors in Breast Cancer An NIH Consensus Development Conference Bethesda, Maryland

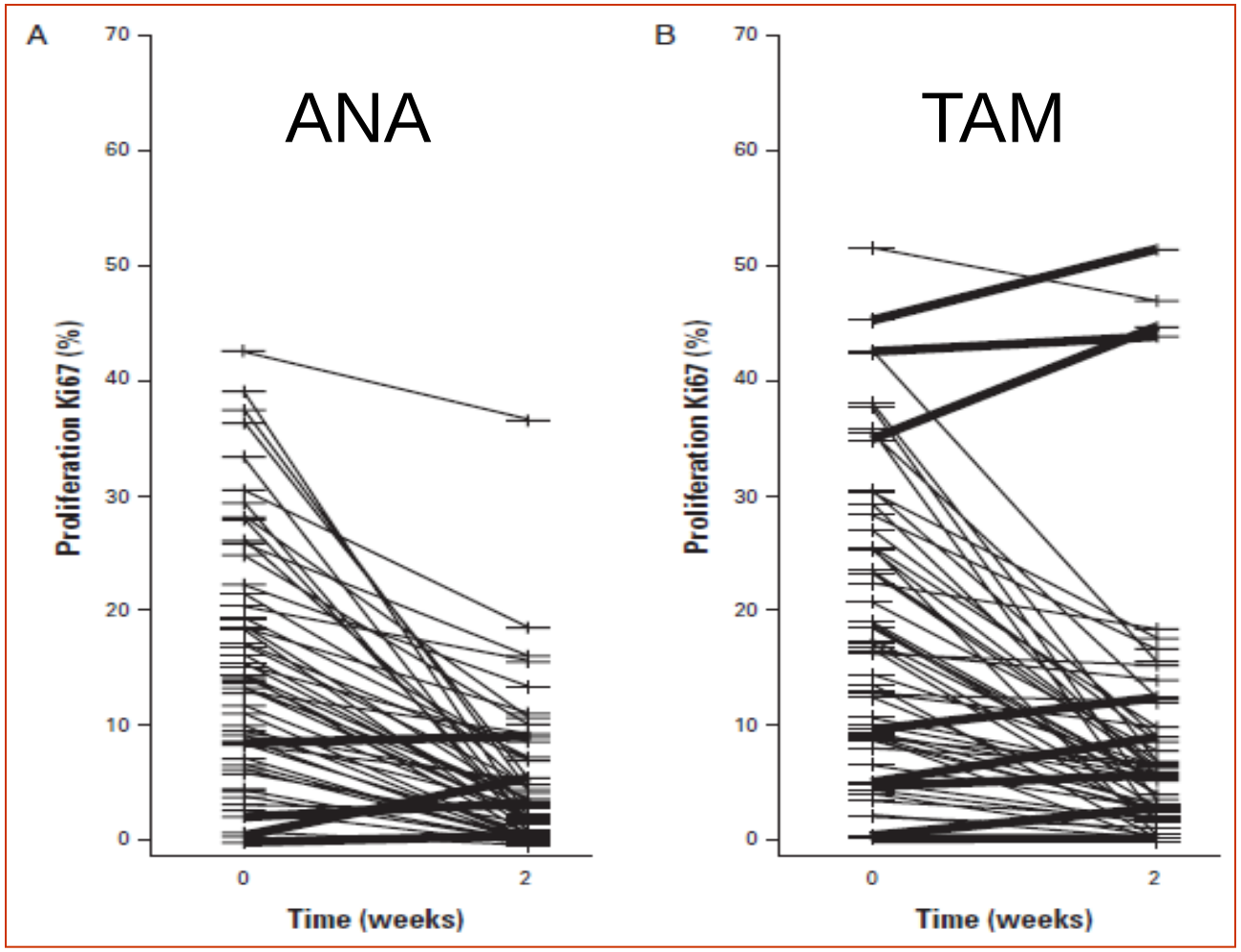
Estrogen receptor level and effect of tamoxifen

Category	Events/woman-years (rate [% per year])		Tamoxifen events		Ratio of annual event rates
	Allocated tamoxifen	Allocated control	Log-rank O-E	Variance of O-E	Tamoxifen : control
(a) ER-poor					
ER=0	162/5060 (3·2)	163/5941 (2·7)	7·4	69·5	1·11 (SE 0·13)
ER 1–3	202/6645 (3·0)	192/6357 (3·0)	2·2	85·5	1·03 (SE 0·11)
ER 4–9	185/5490 (3·4)	188/5588 (3·4)	−6·6	77·5	0·92 (SE 0·11)
Other ER-poor	449/9528 (4·7)	451/8995 (5·0)	−14·9	195·5	0·93 (SE 0·07)
(a) Subtotal	**998/26723 (3·7% per year)**	**994/26881 (3·7% per year)**	**−12·0**	**428·0**	**0·97 (SE 0·05) 2p=0·6**
Test for trend χ^2_1=1·4; 2p=0·2					
(b) ER-positive by ER measurement					
ER 10–19	232/8173 (2·8)	316/7252 (4·4)	−47·4	120·6	0·67 (SE 0·08)
ER 20–29	158/5104 (3·1)	197/4630 (4·3)	−27·3	76·4	0·70 (SE 0·10)
ER 30–49	235/8107 (2·9)	260/6952 (3·7)	−29·0	112·1	0·77 (SE 0·08)
ER 50–99	293/10650 (2·8)	361/8973 (4·0)	−69·6	144·8	0·62 (SE 0·07)
ER 100–199	211/8429 (2·5)	344/7376 (4·7)	−80·4	122·8	0·52 (SE 0·07)
ER≥200	216/8279 (2·6)	325/6672 (4·9)	−78·2	119·0	0·52 (SE 0·07)
Other ER+	308/7868 (3·9)	415/6898 (6·0)	−72·9	161·3	0·64 (SE 0·06)
(b) Subtotal	**1653/56610 (2·9% per year)**	**2218/48753 (4·5% per year)**	**−404·8**	**856·9**	**0·62 (SE 0·03) 2p<0·00001**
Test for trend χ^2_1=9·5; 2p=0·002					



EBCTCG, Lancet 2011

Effect of estrogen deprivation on breast cancer proliferation in the IMPACT trial



After 2 weeks of therapy

Dawsett, JCO 2005

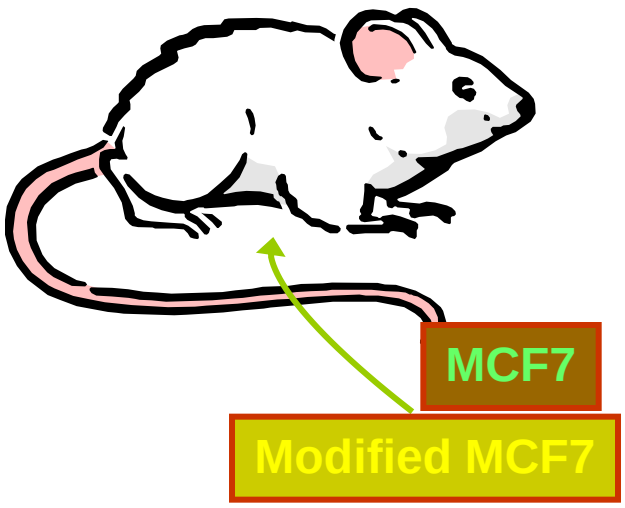
ER and sensitivity

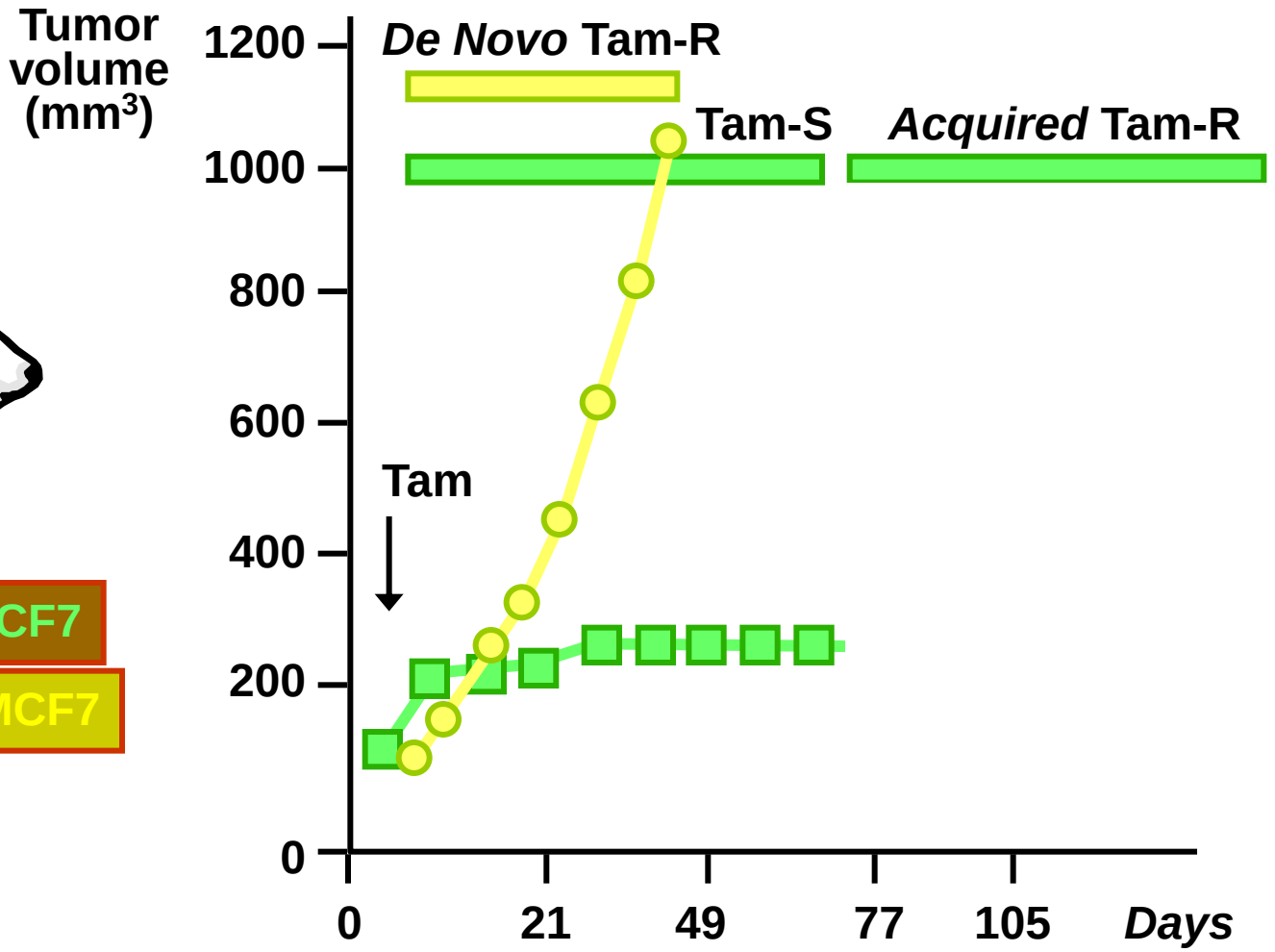
- It is increasingly apparent that ERa-expression is not synonymous with HT sensitivity

- ERa-positive tumours:
  - do not invariably respond to endocrine therapy,
  - exhibit considerable response heterogeneity to any given endocrine agent,
  - may be refractory to one class of endocrine therapy and sensitive to others
  - frequently progress from responsive to resistant phenotypes, despite retaining ERa expression.

- Such apparent inconsistencies suggest that:
  - **ERa expressing tumours are not a homogenous group**
  - **the classical model of E-dependent ERa function does not adequately represent the full repertoire of E and ERa activity**.

Sensitivity and resistance



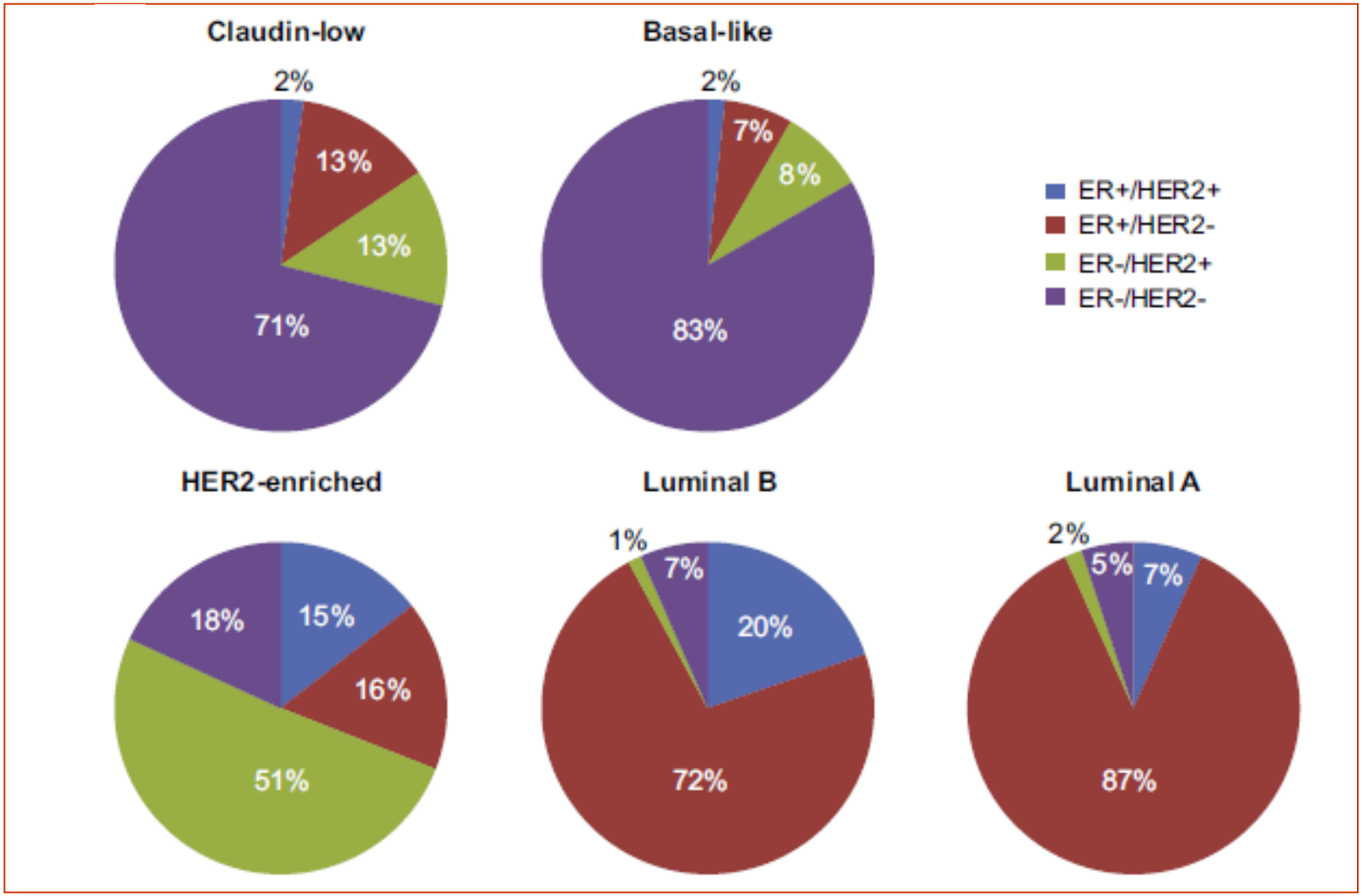


Osborne, JNCI 1994

Hormone resistance

- Primary (intrinsic or de-novo)
  - IIC vs intrinsic subtypes
  - Alternative pathways already active
  - The milieu of ER coactivator and repressor
- Secondary (acquired)
  - Estrogen receptor mutations or epigenetic suppression
  - Activation of alternative pathways
  - Occurence of mutation in downstream effectors
  - Clonal selection or adaptive changes

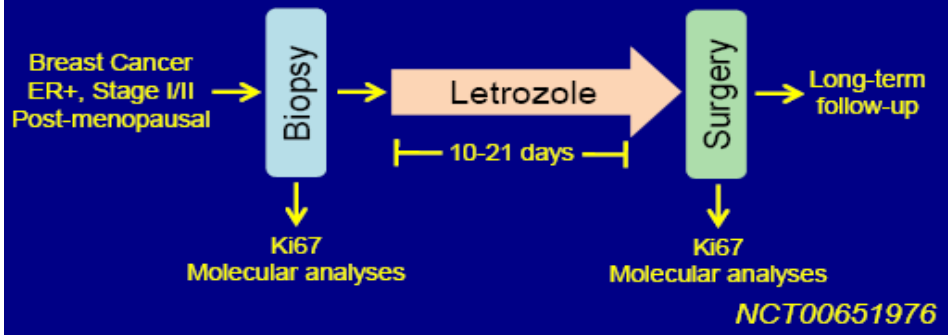
IIC vs intrinsic subtype

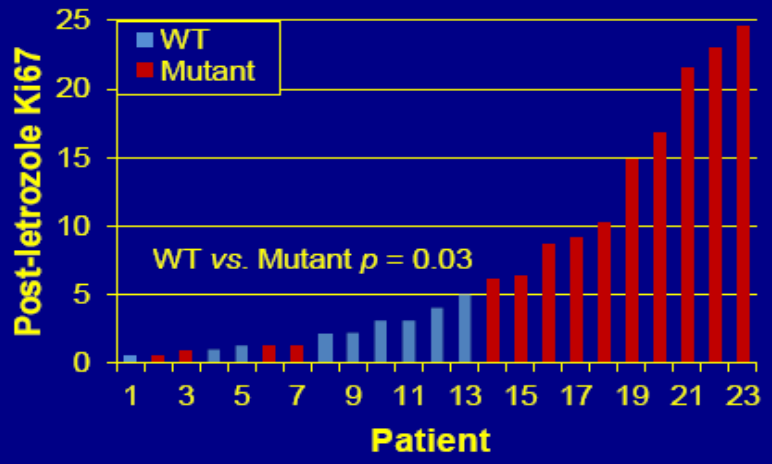


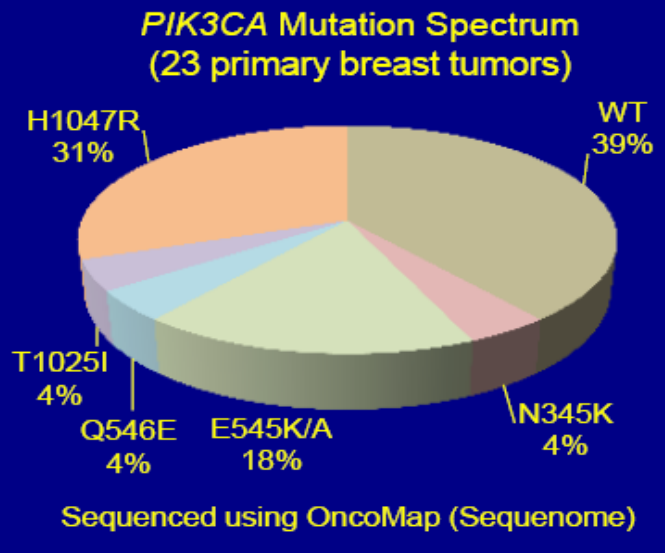
Prat, Mol Oncol 2011

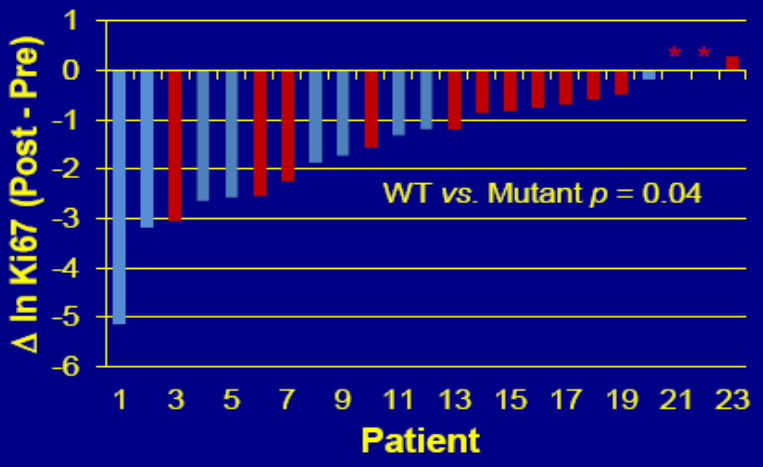
Alternative pathways already active

PIK3CA mutations correlate with a lower anti-proliferative response to pre-surgical letrozole





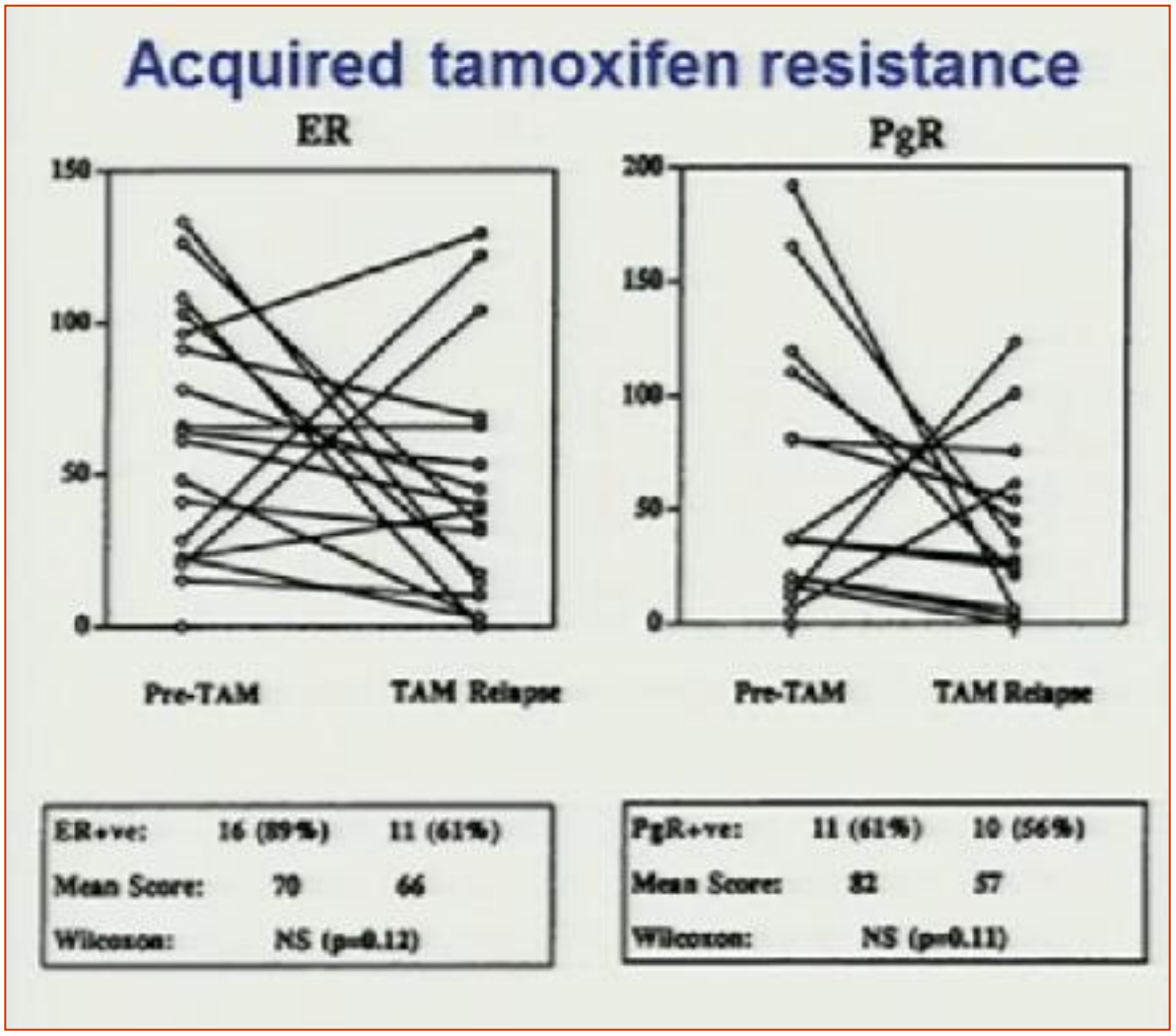




Regulation of ER-dependent signalling

- Ligands
- Levels of receptors
- Receptor co-regulatory proteins (co-activators and co-repressors)
- Binding of other transcriptional factors and other nuclear receptors
- Phosporylation and other post-trascriptional modifications

ER expression is frequently retained at time of resistance



Retained ERa is not only functional, but continues to represent a legitimate therapeutic target.

Johnston, Cancer Res 1995

Ligand-binding domain mutations are frequent in aromatase inhibitor-resistant breast cancer

Metastatic samples (**22%**):

- 6 of 11 (55%) by Robinson et al, 2013
- 9 of 36 (25%) by Toy et al, 2013
- 5 of 44 (11%) in BOLERO Trial, 2013

Primary Samples (**<1%**):

- 6 of 183 (3%) in BOLERO Trial
- 0 of 46 (0%) by Ellis et al., 2012
- 0 of >500 (0%) in TCGA

Shao, SABCS 2013

Possible therapeutic fallout of ESR1 gene alteration identication

- Ligand-binding domain mutation may be treatable with higher doses of fulvestrant or alternative anti-estrogens with higher potencies, but not with estrogen deprivation (AIs)
- Gene-traslocation cannot be treated with classical endocrine therapies and require alternative therapies
- Gene-amplification could be treatable with both estradiol and anti-estrogens, but not estrogen deprivation (AIs)

Shao, SABCS 2013

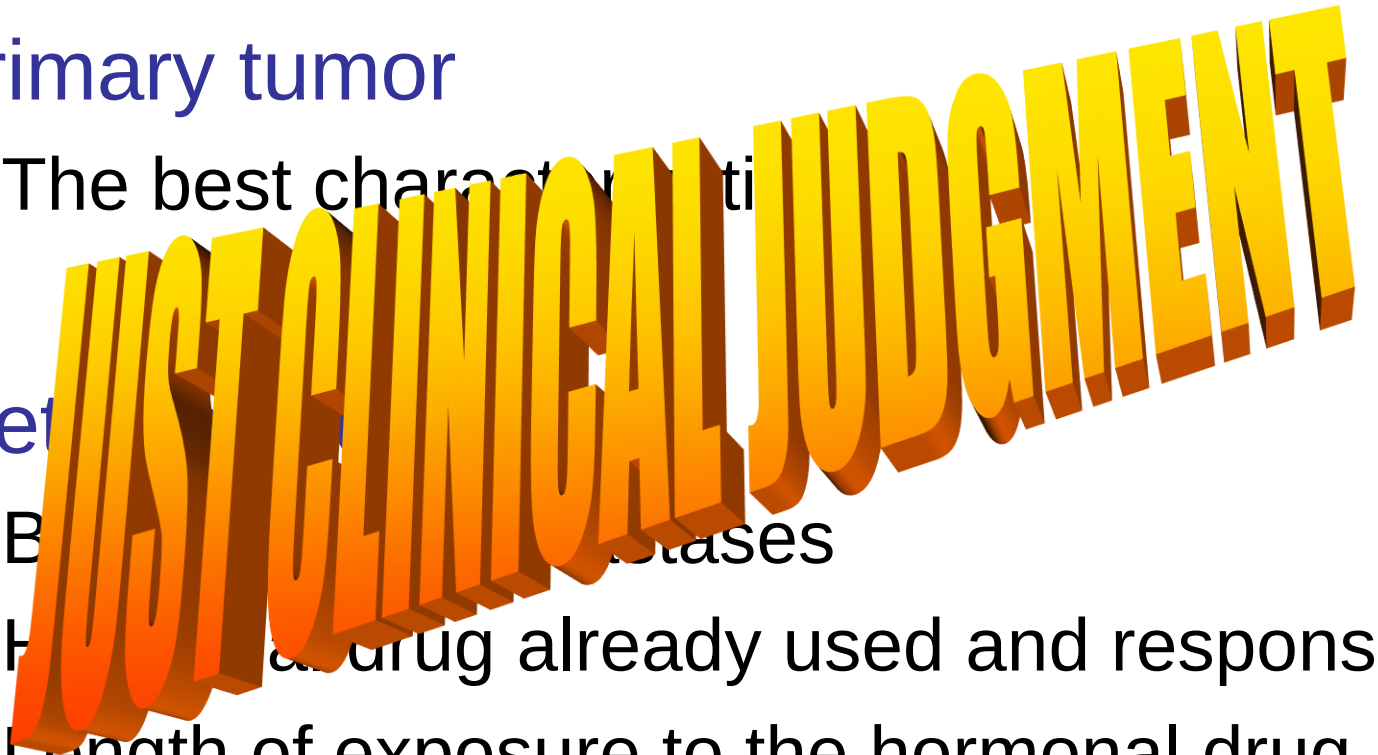
Hormonal drugs can switch on several alternative signalling pathways

- ER and HER-family pathways

- ER and novel pathways
  - PI3K/AKT/mTOR
  - Histone Deacetylase and transcription
  - Angiogenesis
  - Src-kinase
  - FGFR
  - Insulin-like growth factor 1
  - Cycline-dependent kinase and cell cycle

How translating these knowledges to the clinical practice?

1. Primary tumor
   - The best charact[illegible]ti[illegible]
2. Met[illegible]
   - B[illegible]stases
   - H[illegible]a drug already used and response
   - Length of exposure to the hormonal drug
   - DFI and TTP



Characterize the tumor biology

Intrinsic subtype	Clinico-pathologic surrogate definition	Notes
Luminal A	**'Luminal A-like'** *all of:* ER and PgR positive HER2 negative Ki-67 'low'[a] Recurrence risk 'low' based on multi-gene-expression assay (if available)[b]	The cut-point between 'high' and 'low' values for Ki-67 varies between laboratories.[a] A level of <14% best correlated with the gene-expression definition of Luminal A based on the results in a single reference laboratory [23]. Similarly, the added value of PgR in distinguishing between 'Luminal A-like' and 'Luminal B-like' subtypes derives from the work of Prat et al. which used a PgR cut-point of ≥20% to best correspond to Luminal A subtype [24]. Quality assurance programmes are essential for laboratories reporting these results.
Luminal B	**'Luminal B-like (HER2 negative)'** ER positive HER2 negative and *at least one of:* Ki-67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)[b] **'Luminal B-like (HER2 positive)'** ER positive HER2 over-expressed or amplified Any Ki-67 Any PgR	'Luminal B-like' disease comprises those luminal cases which lack the characteristics noted above for 'Luminal A-like' disease. Thus, either a high Ki-67[a] value or a low PgR value (see above) may be used to distinguish between 'Luminal A-like' and 'Luminal B-like (HER2 negative)'.
Erb-B2 overexpression	**'HER2 positive (non-luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	There is an 80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype. Some cases with low-positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. 'Triple negative' also includes some special histological types such as adenoid cystic carcinoma.

[a]A majority of the Panel voted that a threshold of ≥20% was indicative of 'high' Ki-67 status. Others, concerned about the high degree of inter-laboratory variation in Ki-67 measurement [26] and the possibility for undertreatment of patients with luminal disease who might benefit from chemotherapy, would use a lower (local laboratory specific) cut-point to define Ki-67 'high' or use multi-gene-expression assay results, if available.

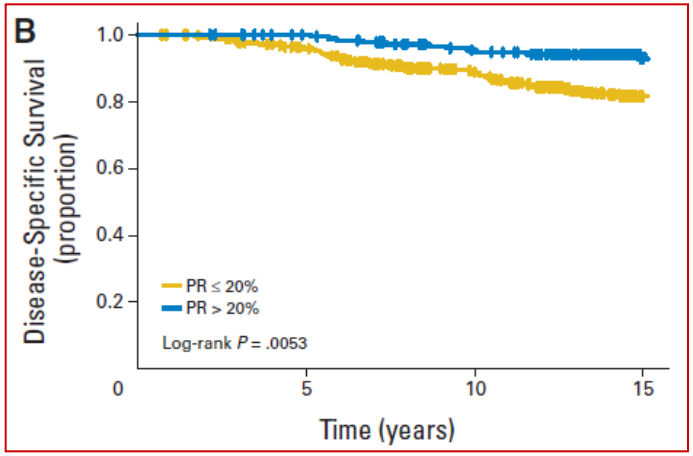
[b]This factor was added during Panel deliberations after circulation of the first draft of the manuscript, to reflect a strong minority view. Although neither the 21-gene RS nor the 70-gene signature was designed to define intrinsic subtypes, a concordance study noted that over 90% of cases with a low RS and almost 80% of those with a 70-gene low-risk signature were classified as Luminal A [95].

StGallen 2013

How to define Luminal A tumors without gene predictors

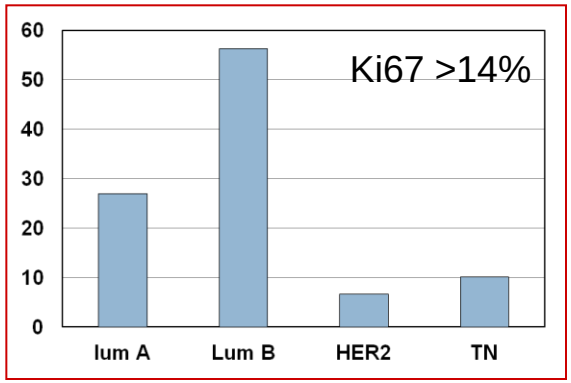
- Progesterone receptors > 20%

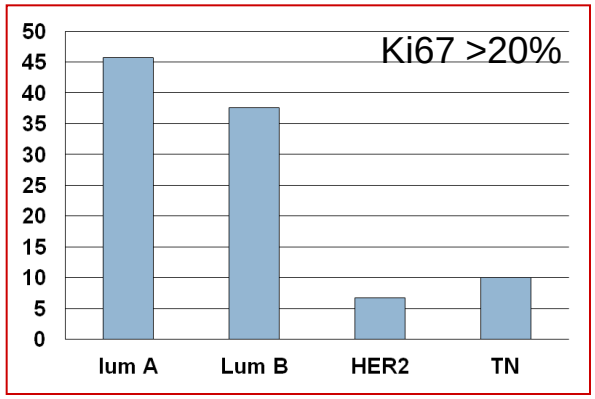
Prat JCO 2013



- KI67 > 20%

5704 pts reclassified at IEO





Change in ER between primary BC and corresponding metastases

Author/Publication	Patients, *N*	Discordant patients	
		n	%
Klarsson et al., 2010 ASCO abstract	486	170	35
Locatelli et al., 2010 ASCO abstract	255	37	14.5
Simmons et al., 2009 Ann Oncol	29	12	40
Liedtke et al., 2009 Ann Oncol	228	42	18.4
Broom et al., 2009 Anticancer Res	62	11	17.7
Simmons et al., 2009 Ann Oncol	25	10	40
Amir et al., 2008 Clin Oncol	9	5	55.6
Guarneri et al., 2008 Oncologist	75	17	22.7
Wu et al., 2008 Clin Cancer Res	10	2	20
Lower et al., 2005 Breast Cancer Res Treat	200	60	30
Wang et al., 2004 Ai Zheng	65	23	35.4
Nedergaard et al., 1995 APMIS	101	21	20.8
Kamby et al., 1989 Br J Cancer	62	23	37.1

Mean discordance 29,7%

Kasraw, Curr Oncol Rep 2011

Change in receptors between primary BC and corresponding metastases *(liver)*

	Neg to Pos	Pos to Neg
ER	26%	11%
PG	19.8%	64.6%
HER2	5.9%	31.5%

Discordance on Bone Mets: ER: 20%, HER2: 7%

Curigliano, Ann Oncol 2011

Efficacy of hormones as first line therapy in ER+ postmenopausal MBC

	Bonneterre 2000 (TARGET)[2]		Nabholtz 2000[1]		Bonneterre 2001 (Combined)[3]		Mouridsen 2007 (PO25)[4]		Paridaens 2008[5]		Robertson 2009 (FIRST)[6]		Mehta 2012 (SWOG S0226)[8]		Bergh 2012 (FACT)[9]	
	Tam	Ana	Tam	Ana	Tam	Ana	Let	Tam	Exe	Tam	Ful	Ana	Ful + Ana	Ana	Ful + Ana	Ana
N =	340	328	171	182	511	510	453	454	182	189	102	103	349	345	258	256
CBR%	56	56	59	46	57	52	49	38	Not done	Not done	72.5	67	73	70	55	55.1
Median TTP	8.2	8.3	11.3	5.6	8.5	7	9.4	6	9.9 (PFS)	5.8 (PFS)	23.4	13.1	15 (PFS)	13.5 (PFS)	10.8	10.2
Cross-over							51% crossover (double-blind cross over permitted)						41% cross over to combination arm at progression. Cross-over from either arm to Ful 500 mg allowed at progression.			
	hazard ratio = 0.99 95% CI: 0.86-NR; p = 0.941		hazard ratio = 1.44 95% CI, 1.16-NR; p = 0.005		hazard ratio = 1.13 95% CI, 1.00-NR p = 0.103		hazard ratio = 0.72 p < .0001		Log-rank p = .121 (p = 0.028 using Wilcoxon test)		hazard ratio = 0.66 95% CI 0.47-0.92 *P* = .01		p = 0.007		hazard ratio = 0.99, 95% CI 0.81 to 1.20, p = 0.91	
HR+ %	45		89		60		66		93		100		100		100	

Mean TTP: 9.6 months

Wilson & Chia, ASCO 2013

Results of hormones as second line therapy in ER+ postmenopausal MBC

	Buzdar 1998[15]		Dombernowsky 1998[36]		Kaufmann 2000[37]		Rose 2003[17]		Chia 2008[20]		Johnston 2012[21]			Di Leo 2010[22]	
	Ana	Meg	Let 2.5 mg	Meg	Exe	Meg	Let	Ana	Ful	Exe	Ful	Ful + Ana	Exe	Ful 500	Ful 250
n	263	253	174	189	366	403	356	357	351	342	231	243	249	362	374
CBR			35	32	37.4	34.6	27	23	32.2	31.5	Not available	45.6	39.6		
TTP months	4.8	4.6	5.6	5.5	4.7	3.9	5.7	5.7	3.7	3.7	4.8	4.4	3.4	6.5	5.5
Significance	hazard ratio = 0.94; p = .49) (0.76, 97.5% CI, 1.16)		p = 0.07		p = 0.0370				p = 0.653		p = 0.98; p = 0.56			hazard ratio= 0.80; 95% CI, 0.68 to 0.94 p = 0.006	
Known HR +	26%		42%		68%		49%		98%		100%			100%	100%

Mean TTP: 4.8 months

Wilson & Chia, ASCO 2013

SELECTION CRITERIA IN SECOND LINE TRIALS

	EFECT	CONFIRM	SOFEA	BOLERO2
Eligibility criteria	Relapse during treatment with (or within 6 months of discontinuation of) an adjuvant NSAI, or progression during treatment with a NSAI for metastatic disease.	Relapse during adjuvant HT or within 1 year from its completion. PD after a previous treatment with either an TAM or an AI as a first-line therapy in case of relapse after >1 year from adjuvant HT or for de novo ABC	Relapse after NSAI as adjuvant for at least 12 months, or as first-line in ABC for at least 6 months	Recurrence during or within 12 mos after the end of adjuvant HT or progression during or within 1 mos after the end of treatment for ABC. *Letro or Ana not to be the last therapy.*

Should these criteria be translated in clinical practice for selecting patients resistant to hormonal drugs?

Have these criteria a biological rationale?

Criteria of sensitivity and resistance used in clinical trial

	EFECT	CONFIRM	BOLERO2
Criteria of sensitivity	• CR, PR or SD for at least 6 mos during treatment for ABC.	• At least 2-year DFS while on the adjuvant HT • CR, PR or SD for 6 mos for ABC	• At least 2 yrs of HT before recurrence in the adjuvant setting • A response or stabilization for at least 6 mos of HT for ABC
Criteria of resistance	• All other pts, including all those treated with adjuvant AI	• Recurrence within the first 2 yrs on adjuvant HT • SD for <6 mos • PD as the best response to first line for ABC	• Recurrence during or within 12 mos after the end of adjuvant HT • Progression during or within 1 mos after the end of treatment for ABC.

Patients treated in phase III RCT have heterogeneous sensitivity

	020 F vs A	FIRST* HDF vs A	S0226 FA vs A	FACT FA vs A	SOFEA FA vs F vs E	CONFIRM HDF vs F	BOLERO2 EE vs E	TAMRAD* TE vs T
n.Pts	451	206	707	514	716	736	724	111
HT Naive (%)	2	74	60	32	0	0	0	0
HT Adj (%)	53	25	40	61	80	63	19	41
>12m 0-12 During	nr	nr	nr	31 6 24	nr	46 5 12	81 19**	nr
HT for ABC (%)	56	0	0	0	80	34	82	67

* Randomized Phase II trial ** during or within 12 m

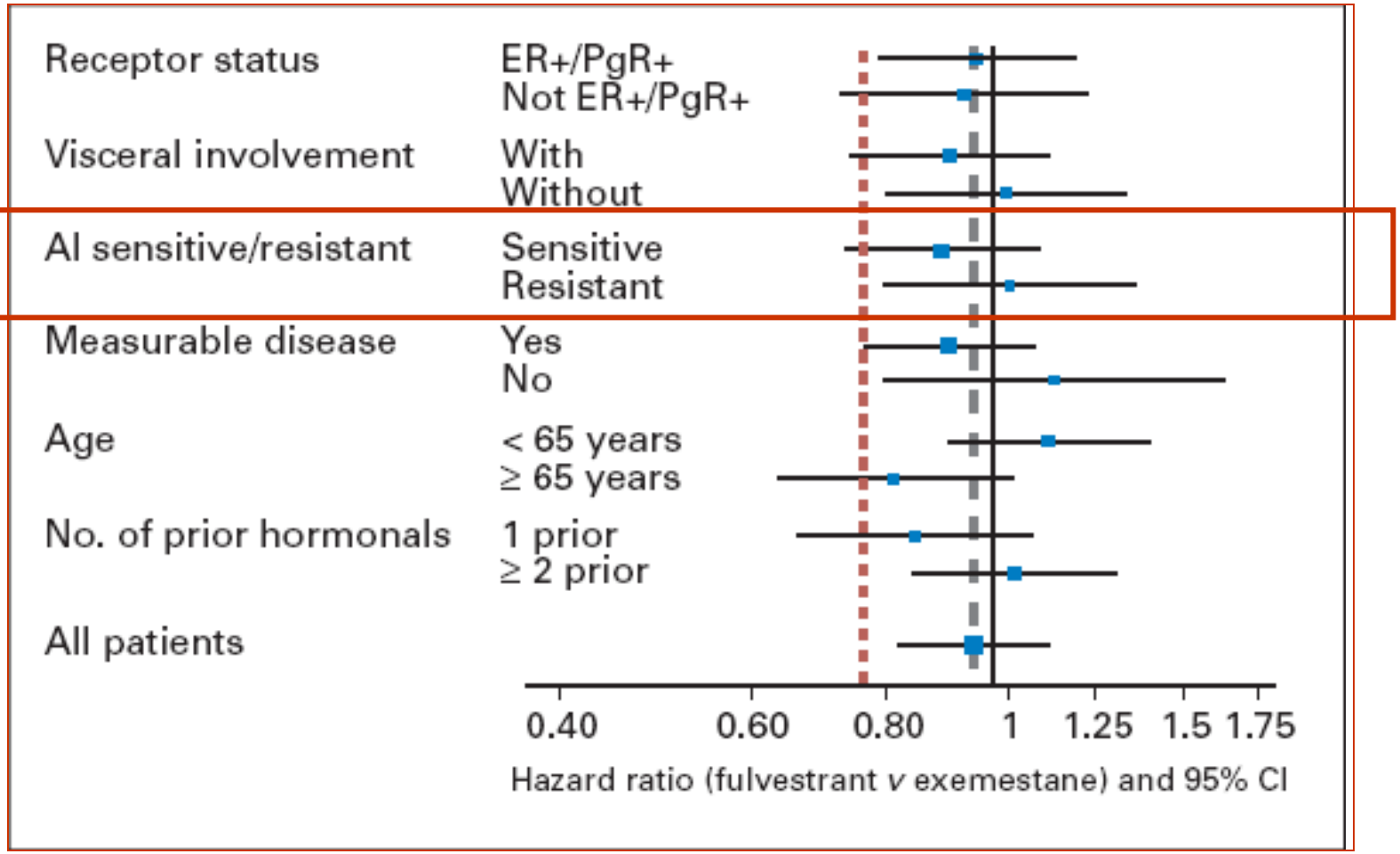
Do the criteria of sensitivity/resistance used in RCT pick up patients with different probability of treatment effect ?

Assessment of sensitivity/resistance

- RCT used PFS to measure the efficacy of treatment
- Subgroup analyses give some information about the behavior of tumors stratified by sensitivity status
- Response rate data are always reported in aggregated form.
- Many patients with bone disease only (difficult to be evaluated)

- Several limitations in understanding the value of the sensitivity status on the effect of a new hormonal treatment

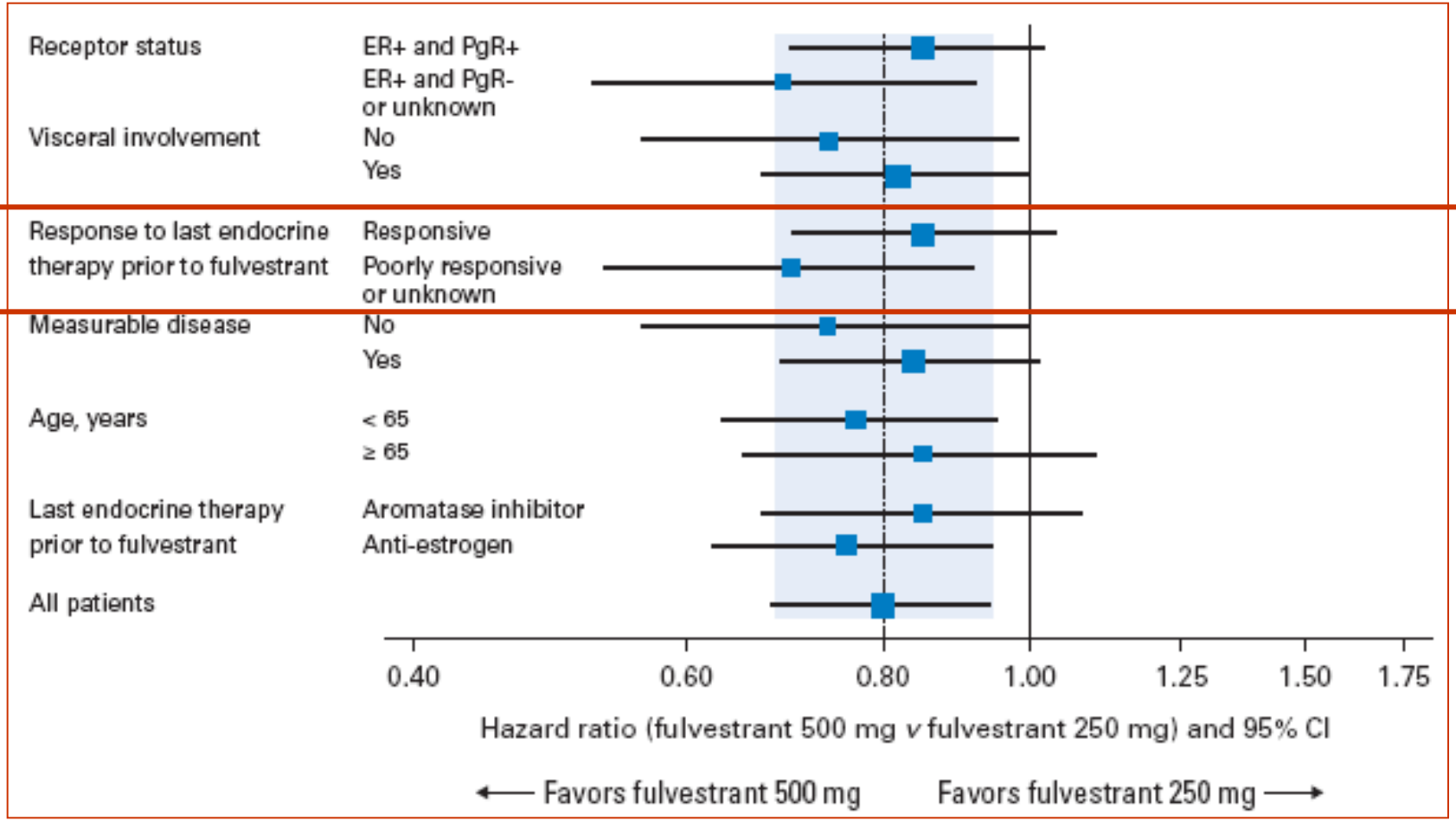
Effect by sensitivity/resistance



EFECT trial

Chia, JCO 2008

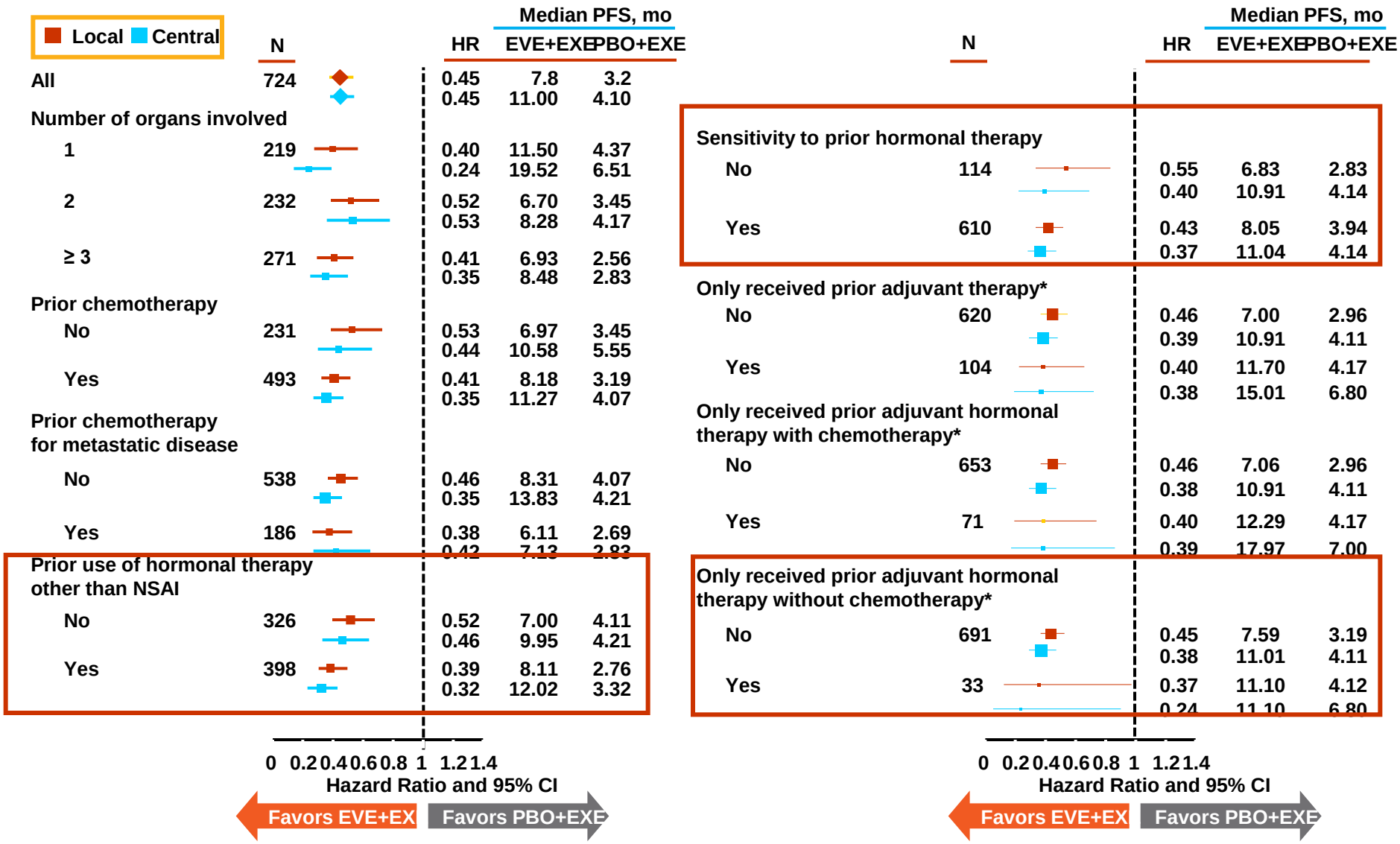
Effect by sensitivity/resistance



CONFIRM trial

Di Leo, JCO 2010

Effect by sensitivity/resistance



BOLERO-2 trial

SWOG 0226

ANA vs ANA/FUL in first line

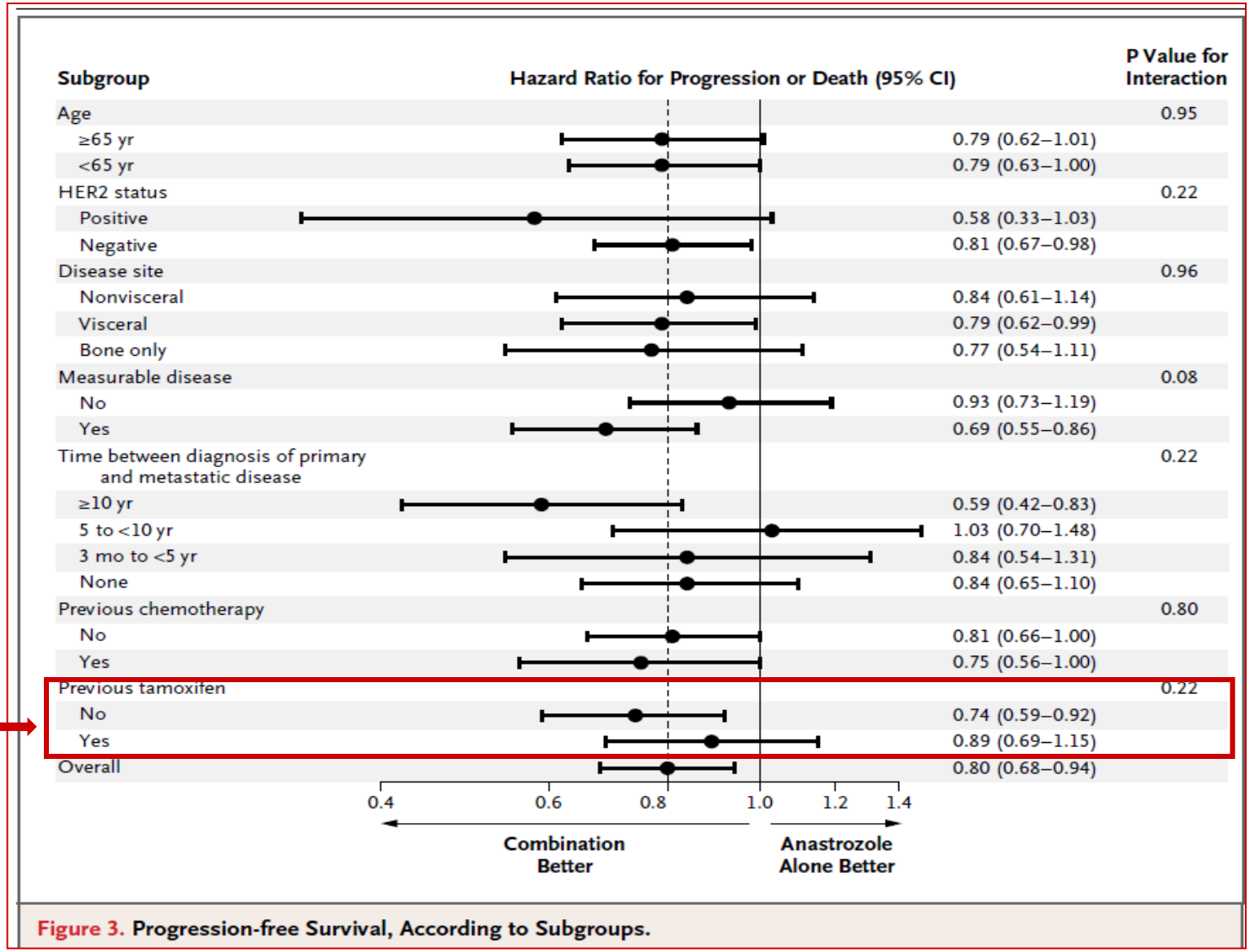


Figure 3. Progression-free Survival, According to Subgroups.

Prior Tamoxifen: 280/707 (40,3%)

Mehta N Engl J Med 2012;367:435-44.

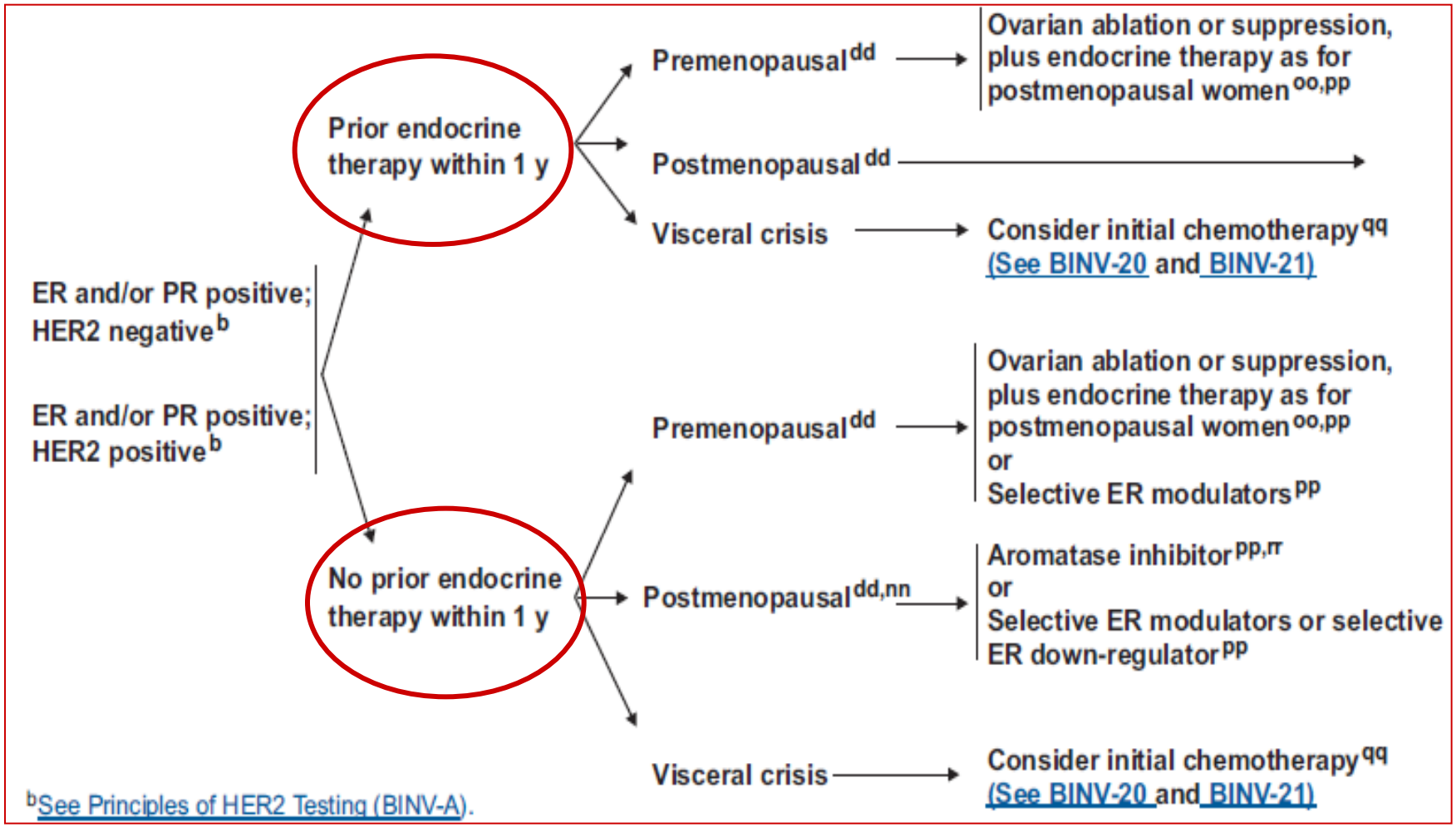
Conclusions from literature

- Sensitivity
  - At least 2-year DFS while on the adjuvant HT
  - CR, PR or SD for at least 6 mos for ABC
- Resistance
  - More confused criteria
    - Loose of hormone receptors
    - Recurrence during or within 1-2 years after the end of adjuvant HT
    - Progression during (or < 6 mos) or within 1 mos after the end of treatment for ABC.
    - PD as best response to treatment
    - All non sensitive pts
- These criteria did not select patients with really different results

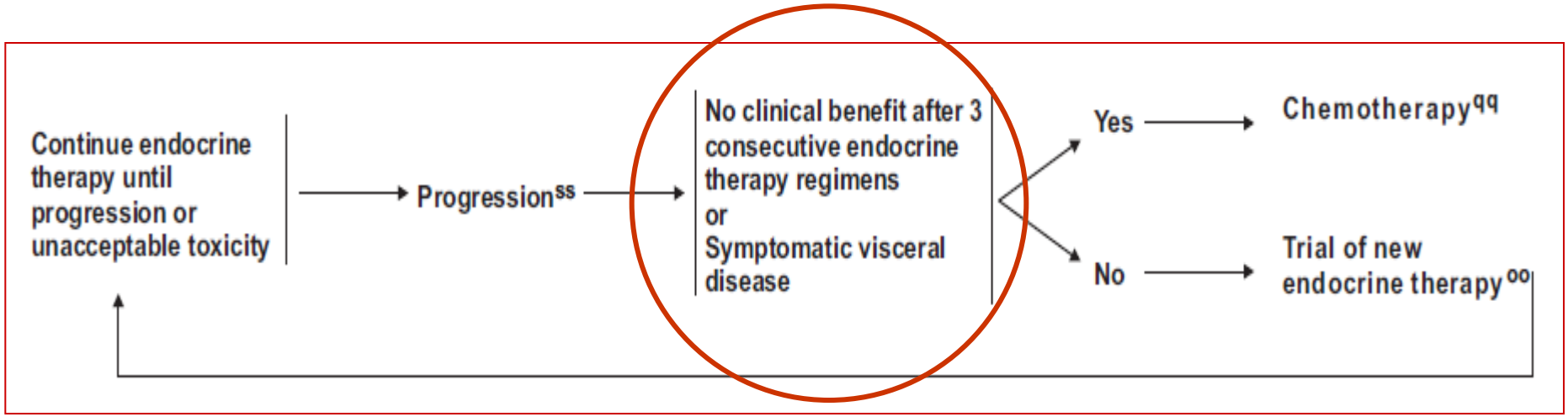
Translation to the clinics

Guideline recommendations

NCCN 2013 Guidelines



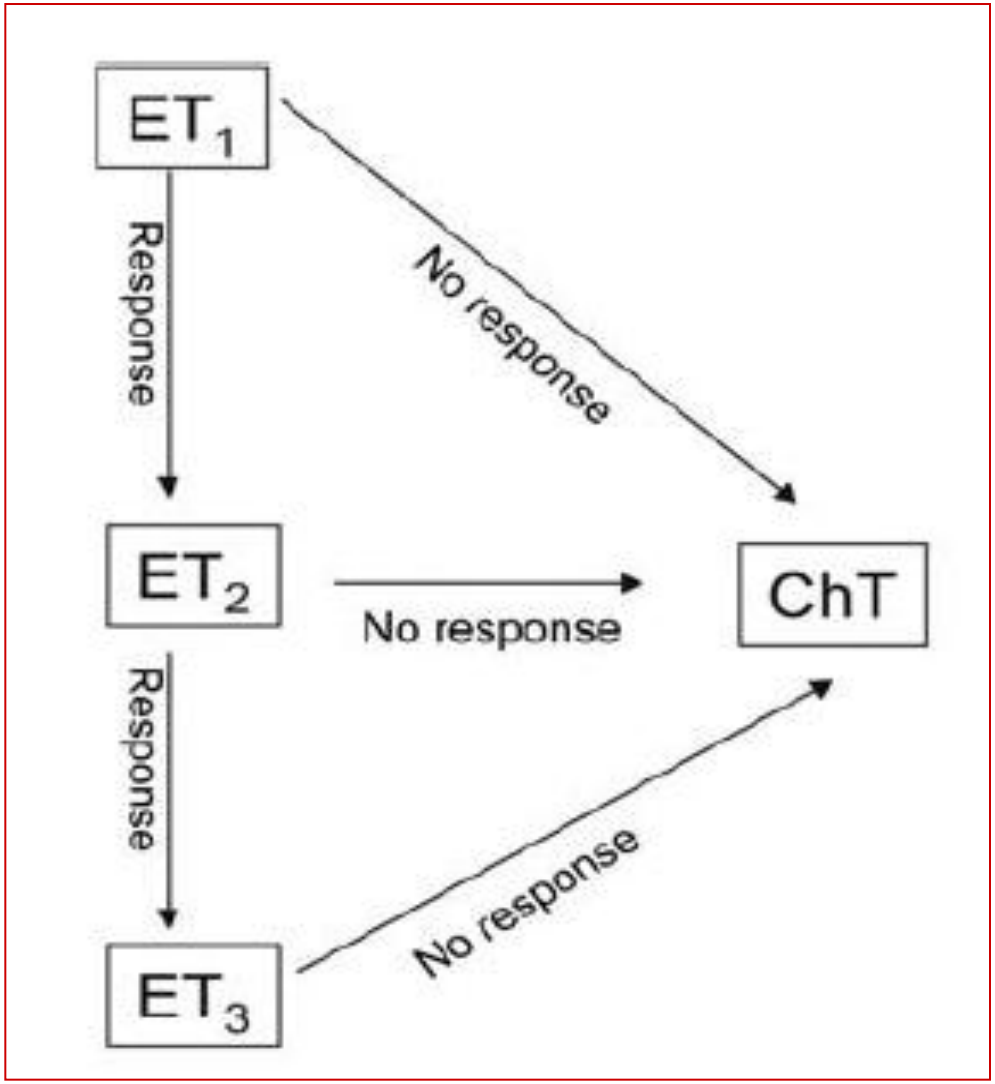
NCCN 2013 guidelines



ESMO 2013 Guidelines

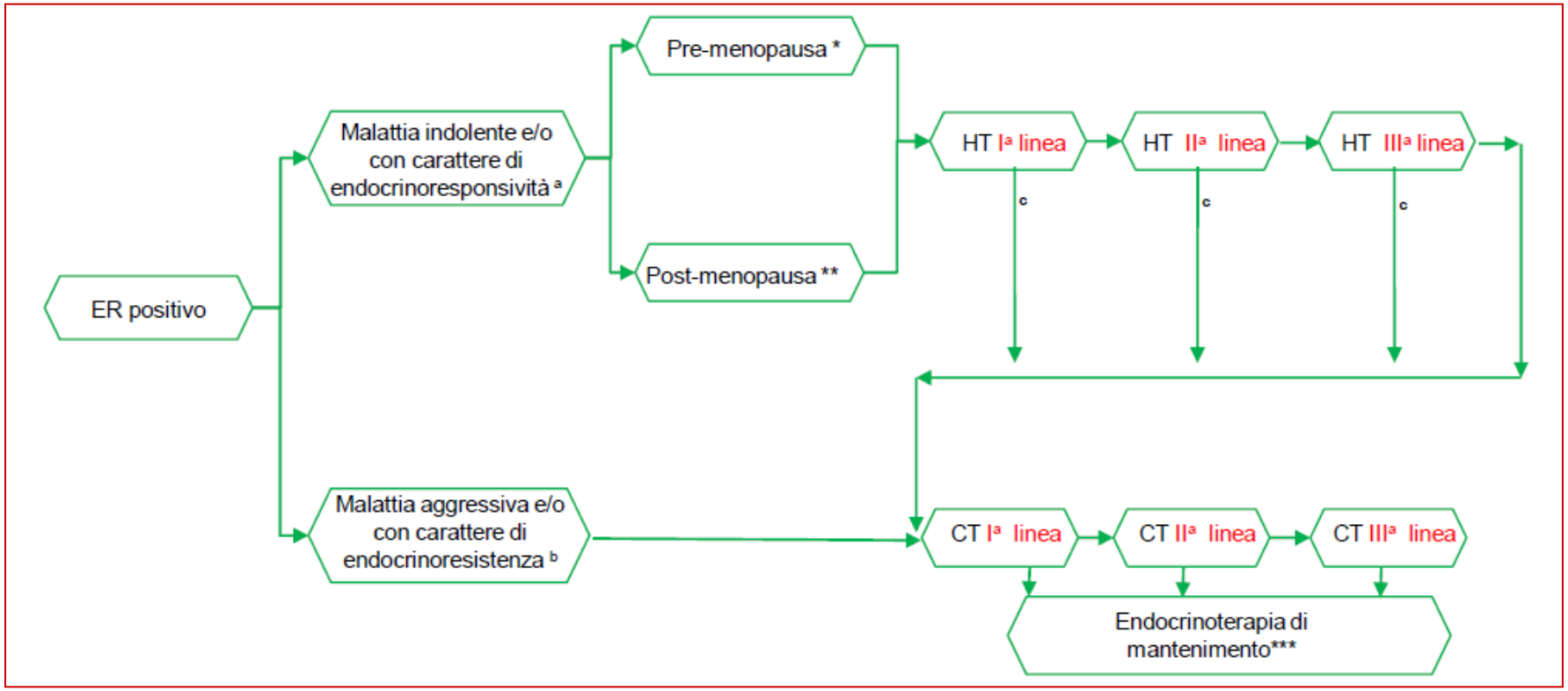
ET1: If not used in the adjuvant setting or if discontinued for >12 months, AIs are the preferred option

ET2,3: factors that need to be taken into account in this treatment decision include response to previous endocrine therapies and its duration



Cardoso, Ann Oncol 2013

AIOM 2013 guidelines



Legenda: HT=Endocrinoterapia; PD=Progressione di malattia; CT= Chemioterapia; ER= Recettore Estrogenico; TNBC= carcinoma mammario a fenotipo triplo negativo

Nota a - Ad esempio: lungo intervallo libero tra chirurgia del tumore primitivo e metastasi, basso carico tumorale, bassa proliferazione (se disponibile valutazione Ki-67 sulla sede metastatica), elevata espressione di recettori ormonali.

Nota b - Ad esempio: breve intervallo libero da malattia dopo chirurgia, malattia a pattern viscerale esteso, grave sintomatologia, alta proliferazione (se disponibile valutazione Ki-67 sulla sede metastatica), scarsa espressione recettoriale ormonale.

Nota c- In caso di progressione durante una linea ormonale, il passaggio ad endocrinoterapia di linea successiva o a chemioterapia va valutato caso per caso

Conclusions

- No homogeneous definition
- Arbitrarily time-dependent definition
- No easily evaluable biological criteria
- No firm clinical criteria can be drawn from clinical trials

- Need for a more strict definition of sensitivity and resistance, and of surrogate biomarkers useful to understand the biological changes occuring in the tumor