Update sulla terapia ormonale nel carcinoma della mammella

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SS Sviluppo Terapie Innovative

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Ormonoterapia del carcinoma mammario

- Terapia adiuvante
- Terapia della malattia metastatica
- Prospettive future

Sede	Maschi	Femmine
Vie aerodigestive superiori	38	176
Esofago	166	621
Stomaco	29	60
Colon-retto	10	17
Colon	14	23
Retto	33	62
Fegato	34	92
Colecisti e vie biliari	139	151
Pancreas	52	64
Polmone	9	36
Osso	876	1.363
Cute (melanomi)	69	82
Cute (non melanomi)	8	14
Mesotelioma	268	843
S. di Kaposi	591	1.884
Tessuti molli	279	436
Mammella	521	8
Utero cervice		163
Utero corpo		47
Ovaio		75
Prostata	7	
Testicolo	222	
Rene, vie urinarie*	36	86
-Parenchima renale	44	100
-Pelvi renale e vie urinarie	191	594
Vescica**	14	74
Sistema nervoso centrale	100	139
Tiroide	139	52
Linfoma di Hodgkin	298	391
Linfomi non-Hodgkin	43	60
Mieloma	106	143
Leucemie	64	106
Tutti i tumori, esclusi carcinomi della cute	2	3

TABELLA 1 Numero di soggetti che è necessario seguire nel corso della vita (da 0 a 84 anni) per trovarne uno che sviluppi un tumore, per sesso e tipo tumorale. Pool Airtum 2006-2008.

Sede	Maschi	Femmine
Vie aerodigestive superiori	7.400	2.100
Esofago	1.500	600
Stomaco	8.100	5.500
Colon-retto	29.300	22.300
Colon	20.400	16.300
Retto	8.900	6.000
Fegato	8.500	4.200
Colecisti e vie biliari	2.000	2.500
Pancreas	5.500	5.900
Polmone	28.600	9.900
Osso	400	300
Cute (melanomi)	5.200	4.500
Cute (non melanomi)	38.800	27.900
Mesotelioma	1.000	400
Sarcoma di Kaposi	500	200
Tessuti molli	1.100	800
Mammella	300	46.300
Utero cervice		2.200
Utero corpo		7.900
Ovaio		4.900
Prostata	36.300	
Testicolo	2.100	
Rene, vie urinarie*	7.800	4.000
-Parenchima renale	6.500	3.400
-Pelvi renale e vie urinarie	1.300	600
Vescica**	19.500	5.100
Sistema nervoso centrale	3.100	2.600
Tiroide	3.200	10.900
Linfoma di Hodgkin	1.200	1.000
Linfomi non-Hodgkin	6.800	5.900
Mieloma	2.700	2.600
Leucemie	4.400	3.300
Tutti i tumori, esclusi carcinomi della cute	202.500	162.000

TABELLA 2. Numero di nuovi casi tumorali, totale e per alcune delle principali sedi, stimati per il 2012 (Popolazione italiana residente da previsioni ISTAT – www.demo.istat.it).

Hereditary breast cancer

- Estimate the likelihood that BRCA1-2 mutation is present
- BRCA1 (cr.17)/BRCA2 (cr.13)
  - High penetrance: 45-84% lifetime risk of BC. Increased risk of contralateral BC (up to 60%). 11-62% lifetime risk of ovarian cancer
- BRCA1
  - More likely triple negative
  - BRCA1 mutation: 11-28% of patients with triple negative BC
  - Triple negative BC at age <= 40 y: BRCA1 mutation in 11-47%
- Management of patients with BRCA1/2 mutations
  - Consider bilteral risk reduction mastectomy
  - Consider bilateral risk reduction salpingo-oophorectomy after completion of childbearing

Tamoxifen and Risk of Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers

J Clin Oncol 31:3091-3099. © 2013

Table 1. Participant Characteristics

Characteristic	*BRCA1* Mutation Carriers (n = 1,583) No.	%	*BRCA2* Mutation Carriers (n = 881) No.	%
Data available				
Retrospective only	926	58	455	52
Prospective	657	42	426	48
Took tamoxifen for first BC				
No	1,200	76	427	48
Yes	383	24	454	52
Yes, ER-negative first BC	76	15	25	25
Yes, ER-positive first BC	94	60	234	71
Chemotherapy administered for first BC				
No	233	15	148	17
Yes	717	45	366	42
Unknown	633	40	367	42
Bilateral oophorectomy				
No	1,002	63	592	67
Yes	581	37	289	33

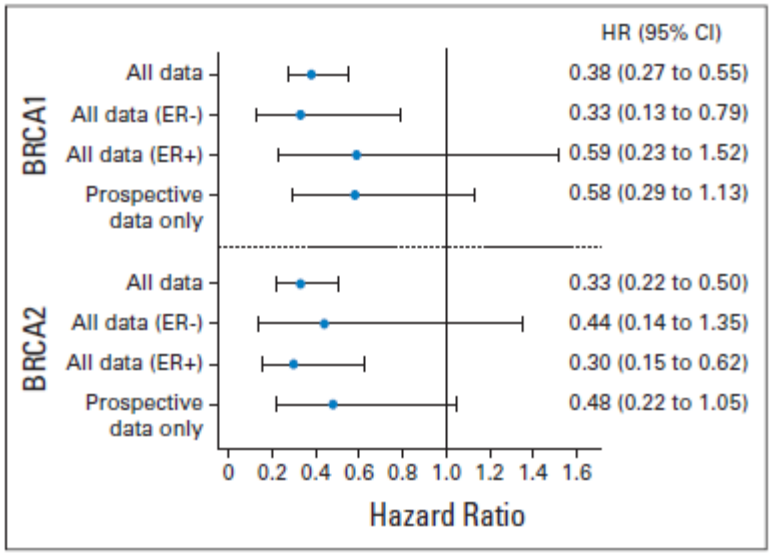


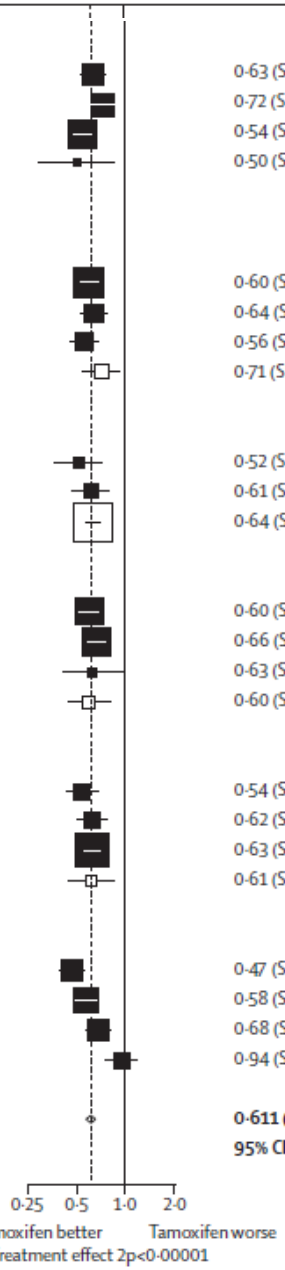
Fig 1. Hazard ratio (HR) estimates (represented by circles) and corresponding 95% CIs (represented by horizontal lines) for risk of contralateral breast cancer associated with tamoxifen use by women with *BRCA1* mutations (BRCA1) and *BRCA2* mutations (BRCA2). Separate estimates are provided based on combined retrospective and prospective data, overall, and by estrogen receptor (ER) status and on prospective data only.

Ormonoterapia del carcinoma mammario

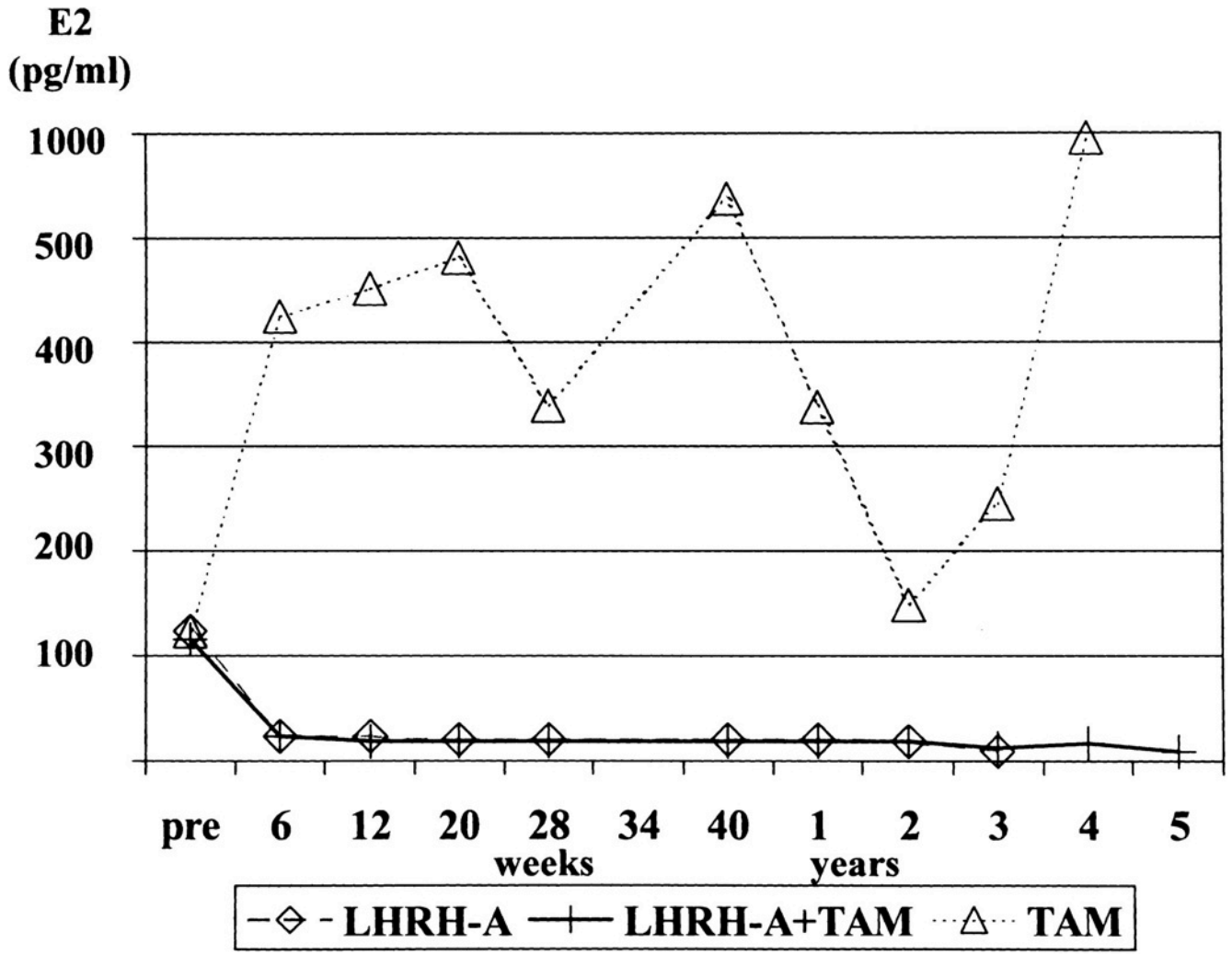
- **Terapia adiuvante**
  - Trattamento in premenopausa
    - Ruolo degli LH-RH analoghi
  - Durata del trattamento
- Terapia della malattia metastatica
- Prospettive future

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
(d) Entry age (years) (trend χ^2_1=5·5; 2p=0·02)					
<45	406/11 846 (3·4)	572/10 690 (5·4)	−105·1	226·9	0·63 (SE 0·05)
45–54	494/16 768 (2·9)	615/15 678 (3·9)	−83·8	256·8	0·72 (SE 0·05)
55–69	712/26 610 (2·7)	963/21 215 (4·5)	−228·8	374·9	0·54 (SE 0·04)
≥70	41/1512 (2·7)	68/1293 (5·3)	−15·8	22·8	0·50 (SE 0·15)
Age unknown	0/11 (0·0)	0/0			
(e) Nodal status (trend χ^2_1=0·2; 2p=0·7)					
N0/N–	753/37 672 (2·0)	1105/33 174 (3·3)	−227·6	443·3	0·60 (SE 0·04)
N1–3	348/10 126 (3·4)	445/8464 (5·3)	−79·8	180·1	0·64 (SE 0·06)
N4+	355/5097 (7·0)	432/3776 (11·4)	−93·2	161·3	0·56 (SE 0·06)
Other/unknown	197/3852 (5·1)	236/3462 (6·8)	−33·0	96·7	0·71 (SE 0·09)
(f) Tumour differentiation (χ^2_1=1·1; 2p=0·3)					
Poorly differentiated	101/2022 (5·0)	170/1730 (9·8)	−38·5	58·1	0·52 (SE 0·10)
Moderately/well	201/4285 (4·7)	251/3513 (7·1)	−48·8	99·3	0·61 (SE 0·08)
Grade unknown	1351/50 461 (2·7)	1797/43 645 (4·1)	−333·2	734·9	0·64 (SE 0·03)
(g) Tumour diameter (mm) (trend χ^2_1=1·2; 2p=0·3)					
1–20 (T1)	647/29 188 (2·2)	905/25 511 (3·5)	−188·2	365·8	0·60 (SE 0·04)
21–50 (T2)	771/20 603 (3·7)	1000/17 847 (5·6)	−169·0	403·5	0·66 (SE 0·04)
>50 (T3/T4)	78/1462 (5·3)	110/1337 (8·2)	−17·2	36·9	0·63 (SE 0·03)
Other/unknown	157/5495 (2·9)	203/4173 (4·9)	−40·5	78·8	0·60 (SE 0·09)
(h) Site of first recurrence (χ^2_3=2·1; p=0·4)					
Isolated local	205/34 320 (0·6)	317/29 618 (1·1)	−74·6	121·7	0·54 (SE 0·07)
Contralateral	237/54 952 (0·4)	327/47 539 (0·7)	−65·1	136·8	0·62 (SE 0·07)
Distant/multiple	1098/54 960 (2·0)	1417/47 560 (3·0)	−262·4	558·8	0·63 (SE 0·03)
Unknown	113/56 714 (0·2)	157/48 827 (0·3)	−31·4	64·1	0·61 (SE 0·10)
(i) Time since randomisation (years) (trend χ^2_1=43·7; 2p<0·00001)					
0–1	343/10 229 (3·4)	676/9825 (6·9)	−175·3	230·2	0·47 (SE 0·05)
2–4	548/13 434 (4·1)	790/11 894 (6·6)	−168·0	304·9	0·58 (SE 0·04)
5–9	454/17 258 (2·6)	499/14 372 (3·5)	−82·5	217·6	0·68 (SE 0·06)
≥10	308/15 631 (2·0)	253/12 610 (2·0)	−7·7	128·8	0·94 (SE 0·09)
Total	**1653/56 747 (2·9% per year)**	**2218/48 876 (4·5% per year)**	**−433·5**	**881·4**	**0·611 (SE 0·027; 95% CI 0·57–0·65)**

99% or <I> 95% CIs



Mean plasma estradiol levels before and during therapy with the three treatment regimens



Klijn, J. G. M. et al. J Natl Cancer Inst 2000;92:903-911

JNCI Journal of the National Cancer Institute

ASCO Guidelines

Clinical Tools and Resources

American Society of Clinical Oncology Endorsement of the Cancer Care Ontario (CCO) Practice Guideline on Adjuvant Ovarian Ablation (OA) in the Treatment of Premenopausal Women with Early Stage Invasive Breast Cancer

Guideline Clinical Questions

Question 1: How does adjuvant ovarian ablation (OA) as systemic therapy improve clinically meaningful outcomes (disease-free survival, overall survival, quality of life and toxicity) when compared with and/or added to other systemic therapies, specifically chemotherapy and tamoxifen?

Question 2: What is the best way to ablate or suppress ovarian function: surgical oophorectomy, ovarian irradiation or medical suppression

CCO Guideline Development

Databases searched:

- MEDLINE searched from 1966 – September 2009
- Cochrane Library search through September 2009

Online conference proceedings, all searched through September 2009:

- ASCO Annual Meeting
- San Antonio Breast Cancer Symposium
- Canadian Medical Association Infobase
- National Guideline Clearing House

ASCO Guidelines
Clinical Tools and Resources

Recommendations

- Clinical Question 1: What is the clinical efficacy of OA versus other systemic therapy +/- OA?
  - OA should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy.
  - OA alone is not recommended as an alternative to any other form of systemic therapy except in the specific case of patients who are candidates for other forms of systemic therapy but who for some reason will not receive any other systemic therapy (e.g., patients who cannot tolerate other forms of systemic therapy or patients who choose no other form of systemic therapy).

OT adiuvante in premenopausa

LHRH analogo

	Indicazioni	Durata LHRH analogo
NCCN[1]	Tamoxifene ± ablazione o soppressione ovarica	Non specificata
SAN GALLEN[2]	Tamoxifene ± soppressione ovarica	Non specificata
ESMO[3]	Tamoxifene ± ablazione ovarica (LHRHa o ovariectomia)	Almeno 2 anni (durata ottimale sconosciuta)
AIOM[4]	Tamoxifene ± ablazione o soppressione ovarica	2-5 anni

1 NCCN National Comprehensive Cancer Network®

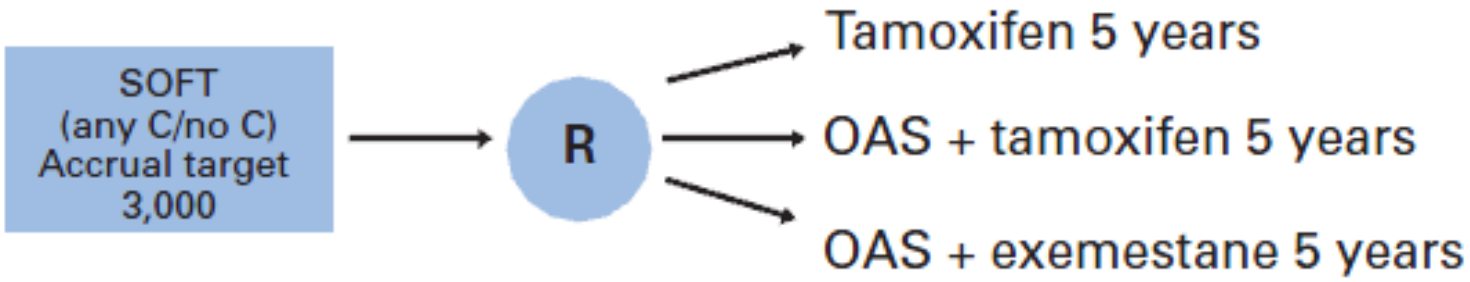
V. 3. 2013

2 BCC 2013

3 2012 ESMO GUIDELINES

4 Aiom

Ongoing adjuvant trials in premenopausal women



-ER+ /PgR+
-Localized disease to breast and nodes, fully resected
-Estradiol in premenopausal range

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Table 1
Long-term recurrence rates of estrogen receptor positive breast cancer treated with 5 years of adjuvant tamoxifen according to PR expression and nodal status [2].

	ER-positive without knowledge of PR	ER-positive and PR-positive	ER-positive and PR-poor	ER-poor and PR-positive	ER-positive and node negative no chemotherapy	ER-positive and node positive no chemotherapy
Recurrence						
5 years	16.4%	15.4%	19.2%	20.8%	11.8%	25.3%
10 years	25.9%	24.8%	28.6%	30.9%	19.1%	41.5%
15 years	33.0%	–	–	–	–	–

ER, estrogen receptor; PR, progesterone receptor. Positive ≥10 fmol/mg.

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2005; 365: 1687–1717

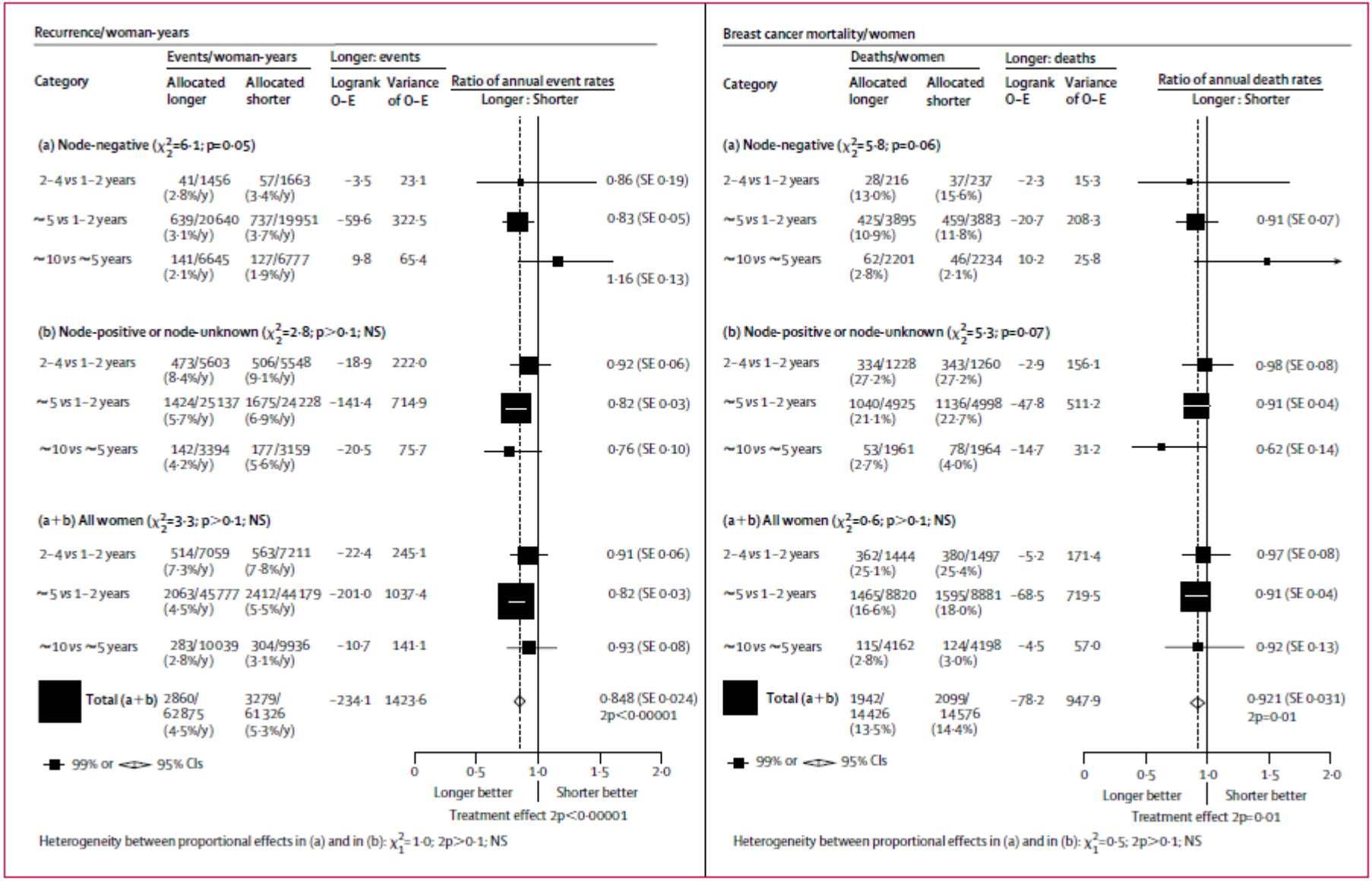

Figure 11: Longer versus shorter tamoxifen duration in ER-positive (or ER-unknown) disease, by treatment type and nodal status: event rate ratios

Extended adjuvant endocrine therapy in hormone dependent breast cancer: The paradigm of the NCIC-CTG MA.17/BIG 1–97 trial

Michaela J. Higgins [a], Pedro E.R. Liedke [a,b], Paul E. Goss [a,*]

Outcomes for patients treated with extended letrozole.

	Disease free survival HR (95% CI)	Distant disease free survival HR (95% CI)	Overall survival HR (95% CI)
ITT analysis			
Follow-up 30 months [25]	0.58 (0.45–0.76)	0.60 (0.43–0.84)	0.76 (0.48–1.12)
Follow-up 64 months [29]	0.68 (0.55–0.83)	0.81 (0.63–1.03)	0.98 (0.78–1.22)
Analysis by IPCW [30]			
Follow-up 64 months	0.52 (0.45–0.61)	0.51 (0.42–0.61)	0.61 (0.52–0.71)
Analysis by nodal status [25]			
Negative	0.45 (0.27–0.73)	NA	1.52 (0.76–3.06)
Positive	0.61 (0.45–0.84)		0.61 (0.38–0.98)
Analysis of crossover patients [45]			
Late extended therapy versus no extended therapy	0.37 (0.23–0.61)	0.39 (0.20–0.74)	0.30 (0.17–0.53)
Analysis by age groups[a] [32]			
<60 years	1.00	1.00	1.00
≥60 and <70 years	1.15 (0.85–1.57)	1.34 (0.90–2.00)	1.45 (0.81–2.62)
>70 years	1.08 (0.75–1.55)	1.37 (0.86–2.16)	4.04 (2.35–6.95)
Analysis by menopausal status at diagnosis [34]			
Premenopausal	0.25 (0.12–0.51)	0.42 ($P=0.03$)	0.36 ($P=0.19$)
Postmenopausal	0.69 (0.52–0.91)	0.65 ($P=0.02$)	0.85 ($P=0.4$)
Analysis by ER and PR status [35]			
ER+/PR+	0.49 (0.36–0.67)	0.53 (0.35–0.80)	0.58 (0.37–0.90)
ER+/PR−	1.21 (0.63–2.34)	1.25 (0.56–2.80)	1.52 (0.54–4.30)
ER−/PR+	0.56 (0.15–2.12)	0.55 (0.12–2.47)	2.16 (0.22–20.77)

ITT, intention to treat; IPCW, inverse probability of censoring weighted; HR, hazard ratio; 95% CI, 95% confidence interval; ER, estrogen receptor; PR, progesterone receptor; NA, not available.

[a] HR are expressed as comparisons of higher age groups to the <60 years age group.

Annals of Oncology 24: 355–361, 2013
doi:10.1093/annonc/mds330
Published online 1 October 2012

Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole

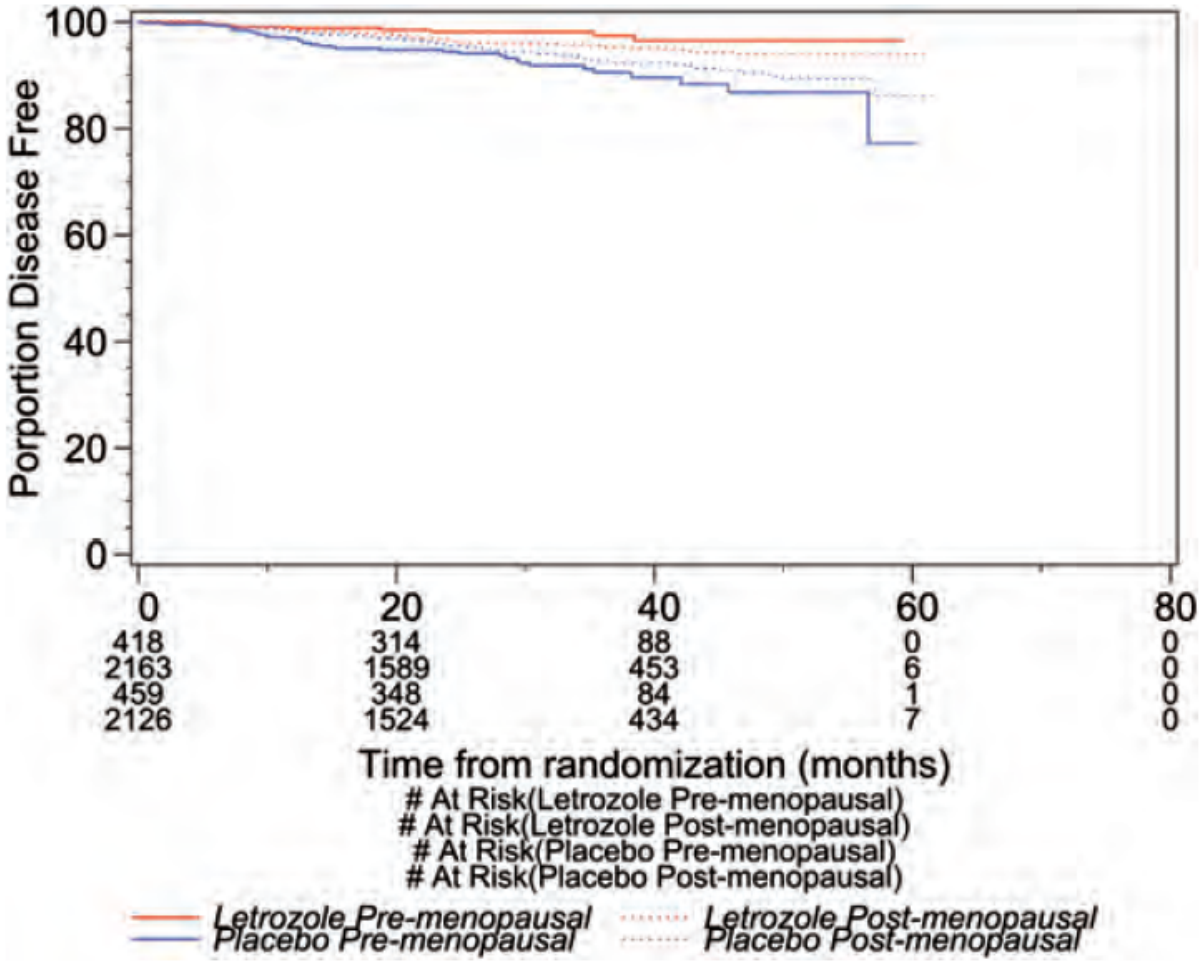

Figure 1. Kaplan–Meier curves for DFS by treatment and menopausal status

Annals of Oncology 24: 355–361, 2013
doi:10.1093/annonc/mds330
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Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole

Conclusions: Extended LET after 5 years of tamoxifen was effective in pre- and postmenopausal women at diagnosis, and significantly better in those premenopausal. Women premenopausal at diagnosis should be considered for extended adjuvant therapy with LET if menopausal after completing tamoxifen.

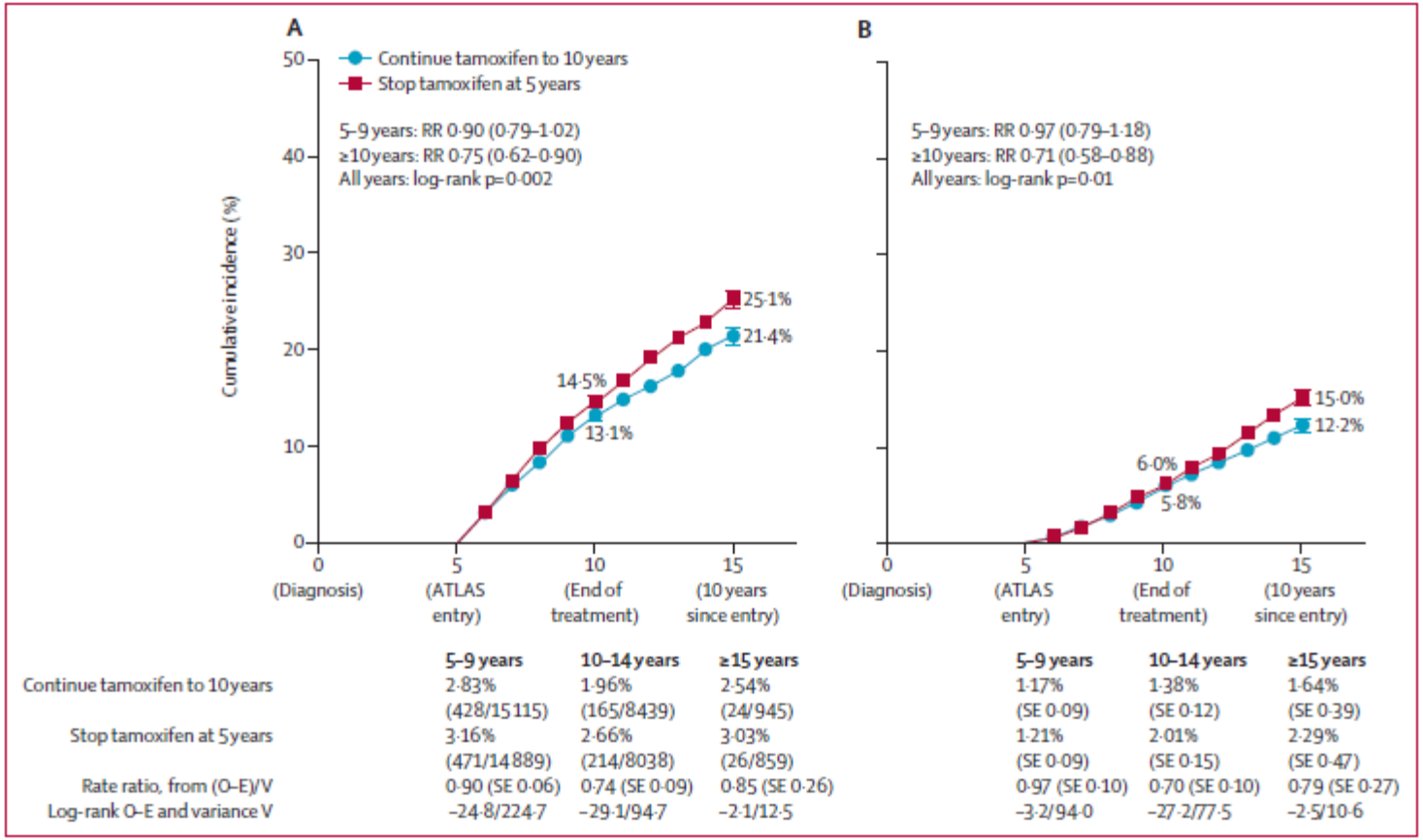
ATLAS: 5 vs 10 Yrs of Tamoxifen in ER-Positive Disease

- 12,894 patients with early breast cancer (enrolled from 1996-2005), who completed 5 yrs of tamoxifen
  - Randomized 1:1 to continue tamoxifen to 10 yrs or stop at 5 yrs (open control)
  - Annual follow-up to record recurrence, second cancer, hospital admission, or death
  - Report cancer outcomes among the 6846 patients with ER+ disease, adverse events among all patients (with positive, negative, or unknown ER status)
  - Long-term follow-up continues

Davies C, et al. SABCS 2012. Abstract S1-2. Davies C, et al. Lancet. 2012;[Epub ahead of print].

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

Lancet 2013; 381: 805–16



	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15 115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14 889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	−24·8/224·7	−29·1/94·7	−2·1/12·5	−3·2/94·0	−27·2/77·5	−2·5/10·6

Figure 3: Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease

Interpretation For women with ER-positive disease, continuing tamoxifen to 10 years rather than stopping at 5 years produces a further reduction in recurrence and mortality, particularly after year 10. These results, taken together with results from previous trials of 5 years of tamoxifen treatment versus none, suggest that 10 years of tamoxifen treatment can approximately halve breast cancer mortality during the second decade after diagnosis.

aTTom: 10 vs. 5 years Tamoxifen N=6953

- Recurrence RR = 0.85 (95% CI 0.76-0.95; p=0.003)
  - Absolute reduction 4%

- Breast Cancer Mortality RR = 0.88 (95%CI 0.77-1.01; p=0.06)
  - Absolute reduction 2%

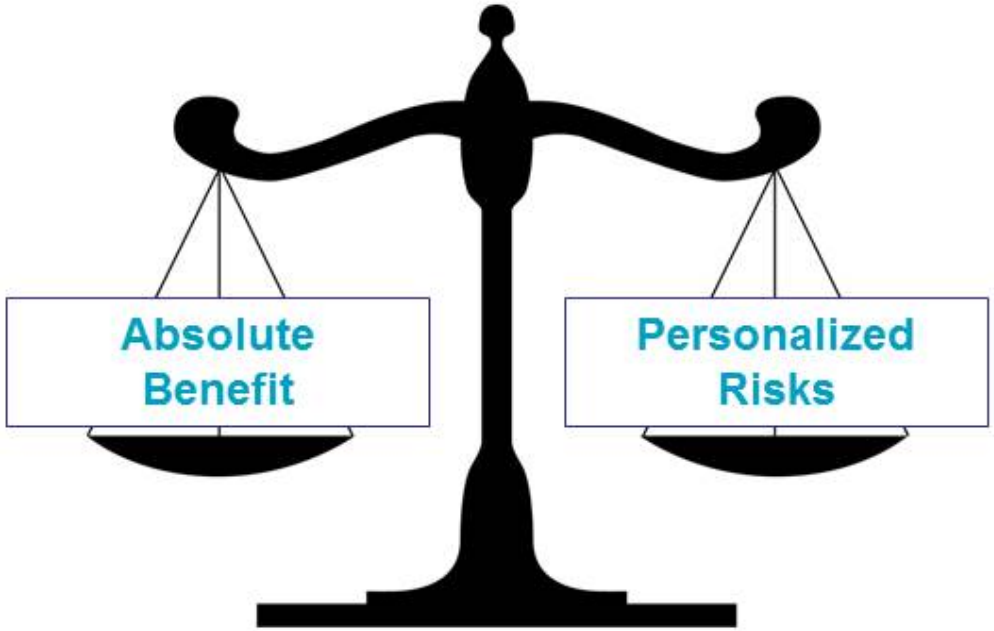
Gray *et al.*, Abstract 5, ASCO 2013

aTTom 10 vs. 5 Years Tamoxifen

- No benefit seen until year 10
- Death without recurrence = no difference
- Overall mortality = no difference, yet

Gray *et al*., Abstract 5, ASCO 2013

How Can We Use These Data to Make Decisions with Our Early Breast Cancer Survivors?



Presented By Ann H. Partridge, MD, MPH at 2013 ASCO Annual Meeting

Assessing the Risks for the Individual Patient

- Serious Adverse Events
  - Endometrial cancer- 3.1% (mortality 0.4%) vs. 1.6%
  - Cardiovascular events- ↑ PE, ↓ Ischemic heart disease

    (Davies *et al*. Lancet 2012)
- Symptoms/Quality of Life
  - Vasomotor symptoms, alterations in mood, sexual functioning, musculoskeletal problems
- Patient Preferences and Values
  - Minor side effects can become deeply troubling over time

Presented By Ann H. Partridge, MD, MPH at 2013 ASCO Annual Meeting

Extended Endocrine Therapy Options Largely Driven by Menopausal Status and Prior Treatment

Options for Postmenopausal Women

- Continue tamoxifen if contraindication, intolerance, or lack of availability of AI
- ~~Begin tamoxifen if completing 5 years of an AI~~
- These data do not provide support for continuing AI beyond 5 years
- STOP ~~or take a break~~

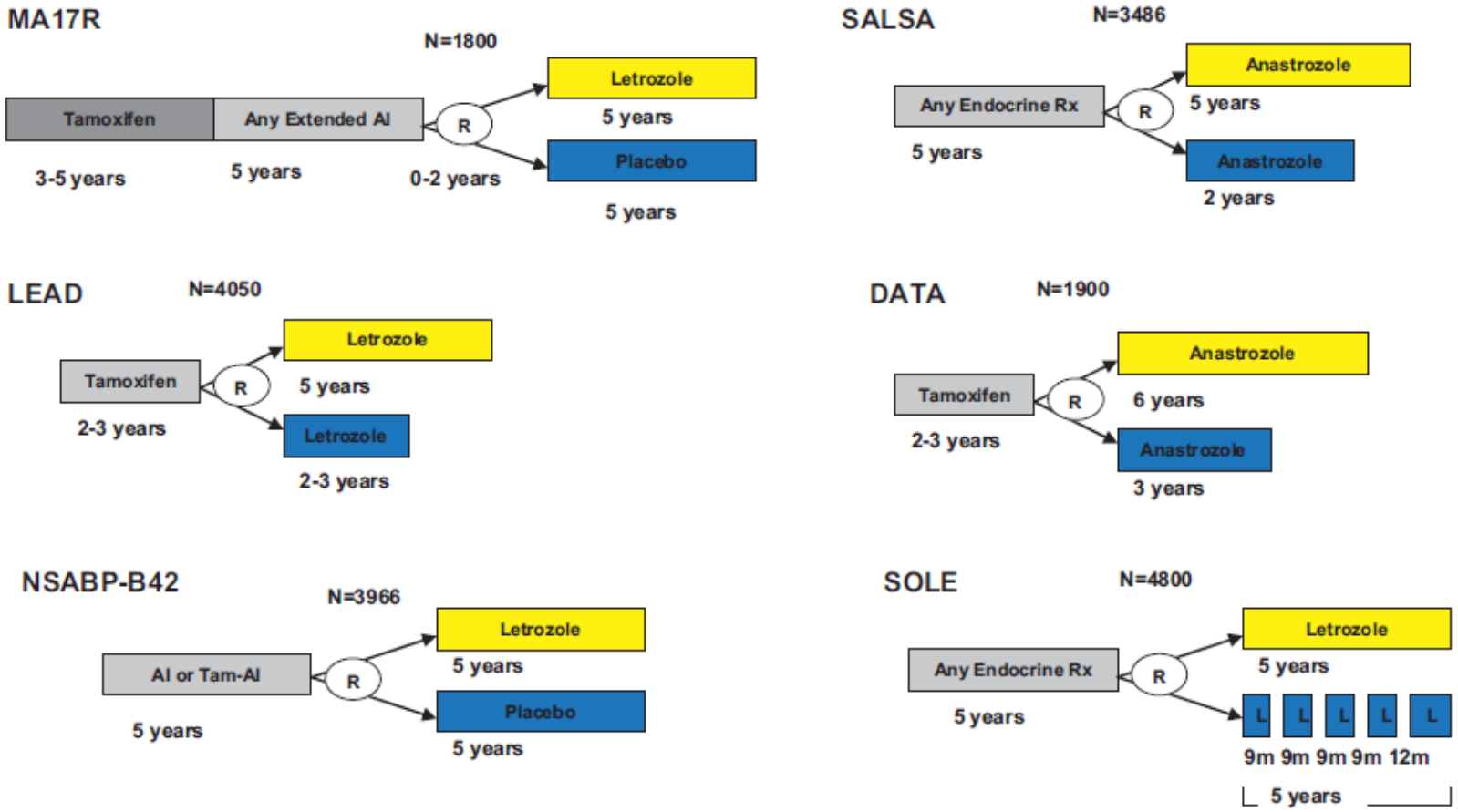
Options for Women with Amenorrhea

- Switch to AI after tamoxifen
- If continued ovarian function, continue tamoxifen
- STOP ~~or take a break~~

Options for Premenopausal Women

- Continue tamoxifen
- STOP ~~or take a break~~

Presented By Ann H. Partridge, MD, MPH at 2013 ASCO Annual Meeting



LEAD: Letrozole Adjuvant Therapy Duration trial; SALSA: Secondary Adjuvant Long-term Study with Arimidex trial; DATA: Different Durations of Anastrozole after Tamoxifen trial; SOLE: Study of Letrozole Extension trial AI: aromatase inhibitor; Tam: tamoxifen; L: letrozole; R: randomized; Rx: therapy; m: month

Fig. 1. Schemata of ongoing clinical trials of extended aromatase inhibitor therapy.

Ormonoterapia del carcinoma mammario

- Terapia adiuvante
- **Terapia della malattia metastatica**

K mammario metastatico

- Nuovi casi di K mammario metastatico/anno
  - 12.000
- N. donne che attualmente in Italia hanno K mammella metastatico
  - Circa 30.000.
  - 75% RO positivi

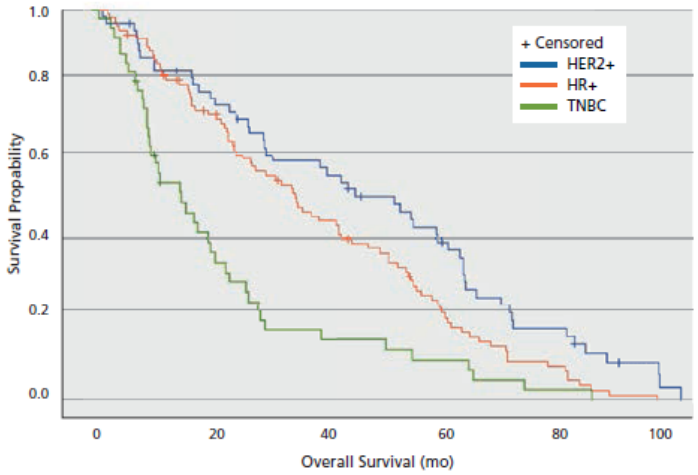
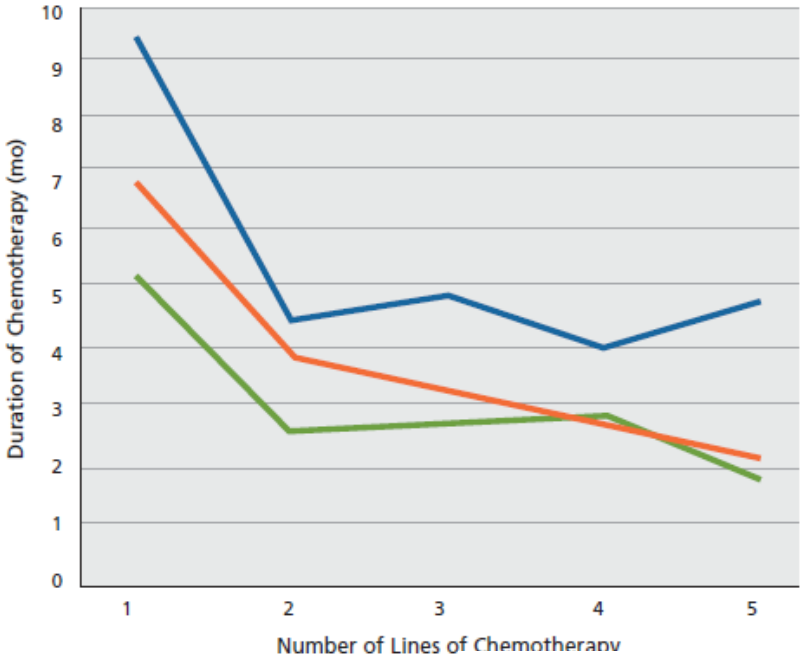


Figure 4 Kaplan-Meier curves for overall survival by subtype from the date of metastatic breast cancer diagnosis.
Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.



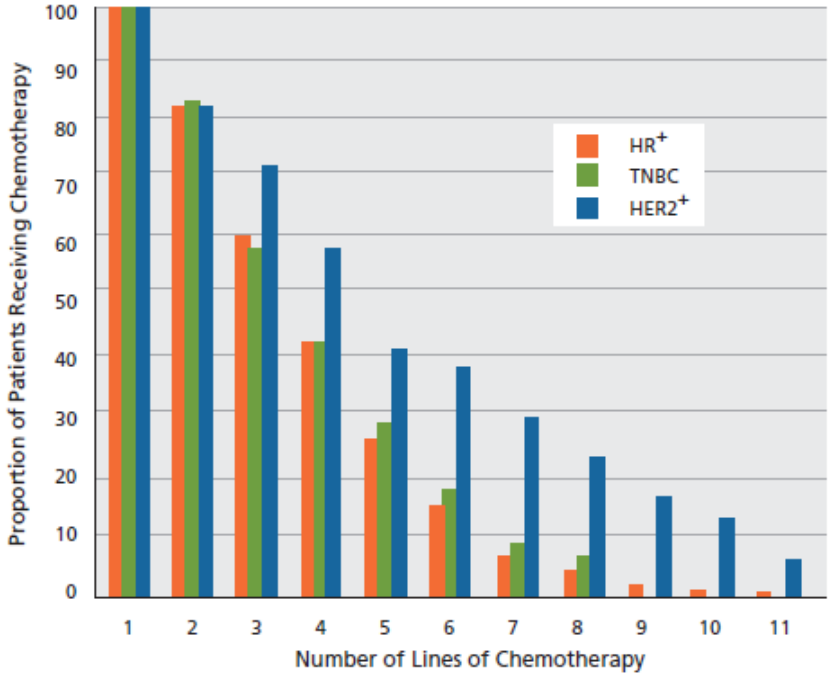
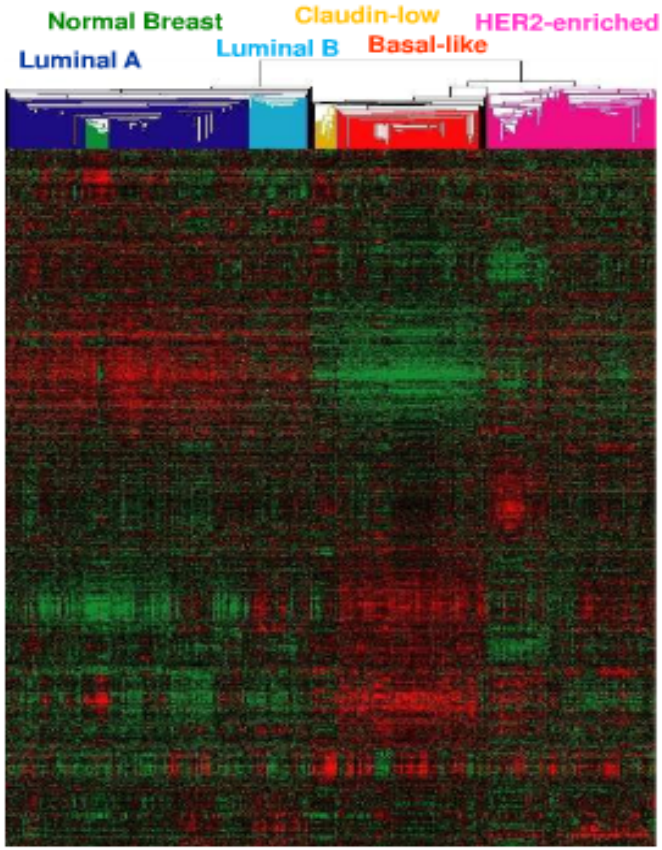


Figure 2 Number of lines of chemotherapy by line and subtype.
Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.



Intrinsic Subtypes

Perou et al., Nature, 2000
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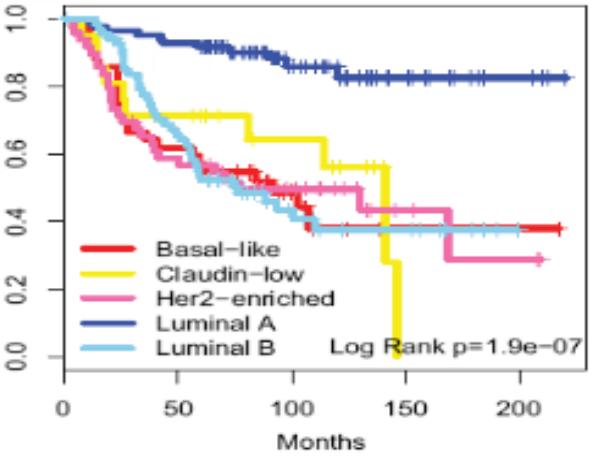
Prat et al., Submitted



VOLUME 28 · NUMBER 20 · JULY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

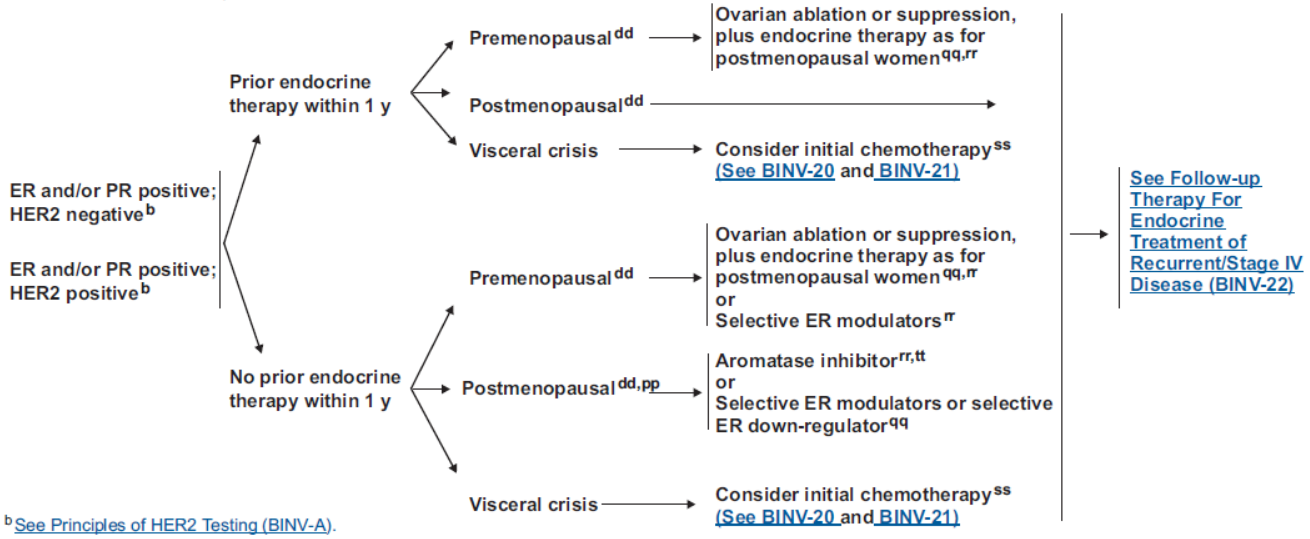
ORIGINAL REPORT

Metastatic Behavior of Breast Cancer Subtypes

Hagen Kennecke, Rinat Yerushalmi, Ryan Woods, Maggie Chon U. Cheang, David Voduc, Caroline H. Speers, Torsten O. Nielsen, and Karen Gelmon

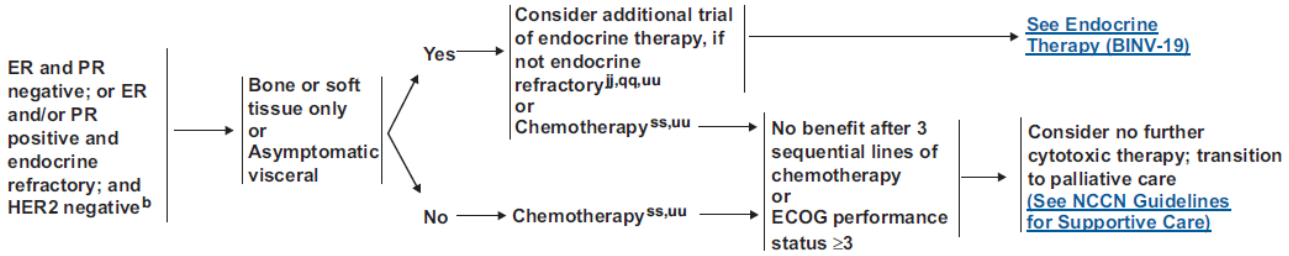
	Distant metastases development	Distant mts within the first 5 years	
	No.	No.	%
Luminal A	458	164	36
Luminal B	378	220	58
Total	836	384 (46%)	

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE

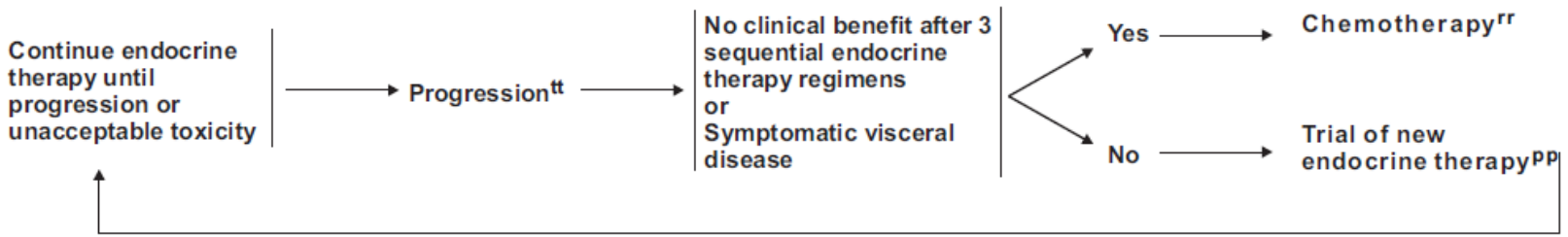


[b] See Principles of HER2 Testing (BINV-A).

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; HER2 NEGATIVE



FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENT OR STAGE IV DISEASE



Performance of Endocrine therapy in different patient subgroups

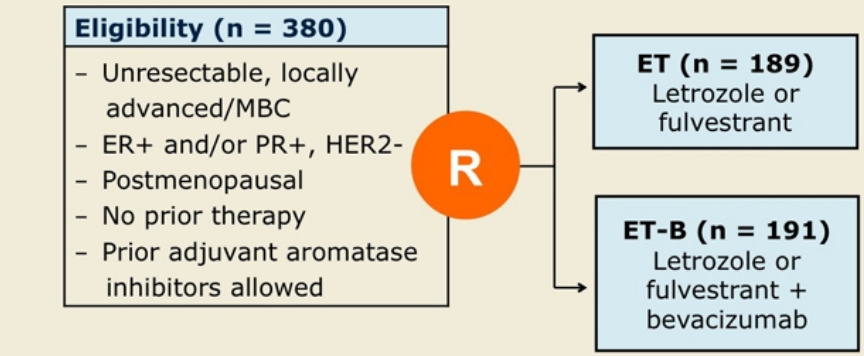
- Tam-naive or sensitive
- Tam resistant
- NS Aromatase inhibitor-resistant

The TAM Sensitivity Status (naive or pretreated without PD <12 m)

HT	Adjuvant TAM	PFS/TTP (mos)	
TAM	11%	**8.2**	**Bonneterre, JCO 2000**
ANA	12%	**8.3**	
TAM	22%	**5.8**	**Paridaens , JCO 2008**
EXE	21%	**9.9**	
ANA	22%	**12.5**	**Robertson, JCO 2009**
FUL 500	27%	**>12.5**	
ANA	40%	**13.5**	**Metha, NEJM 2012**
FUL250 + ANA	40%	**15.0**	
LET	44%	**14.4**	**Loibl, ECCO-ESMO2013**
LET	40%*	**9.0**	**Wolff, JCO 2013**
LET+ Temsirolimus	43%*	**8.9**	

*Without PD < 6 months

LEA Phase III Study Design



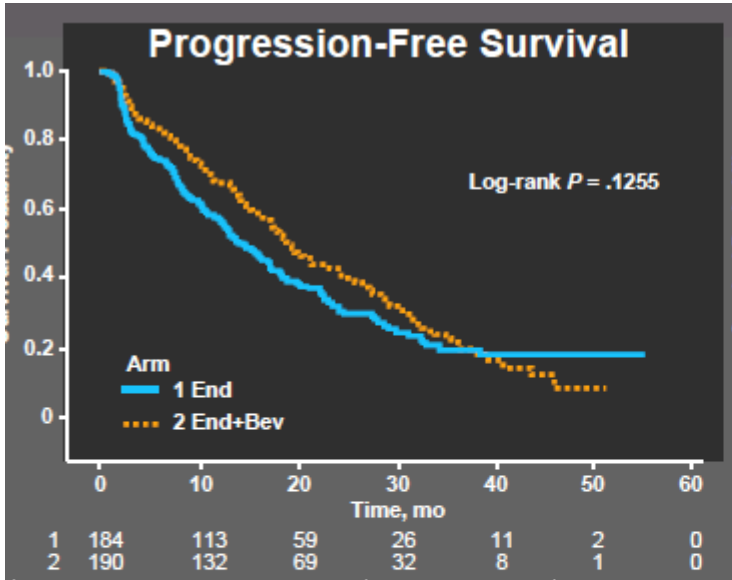
A median progression-free survival (PFS) improvement from 9 months in the ET arm to 13 months in the ET-B arm was assumed (HR = 0.69), requiring a total of 232 PFS events and 354 patients (80% power, 2-sided alpha level of 5%).

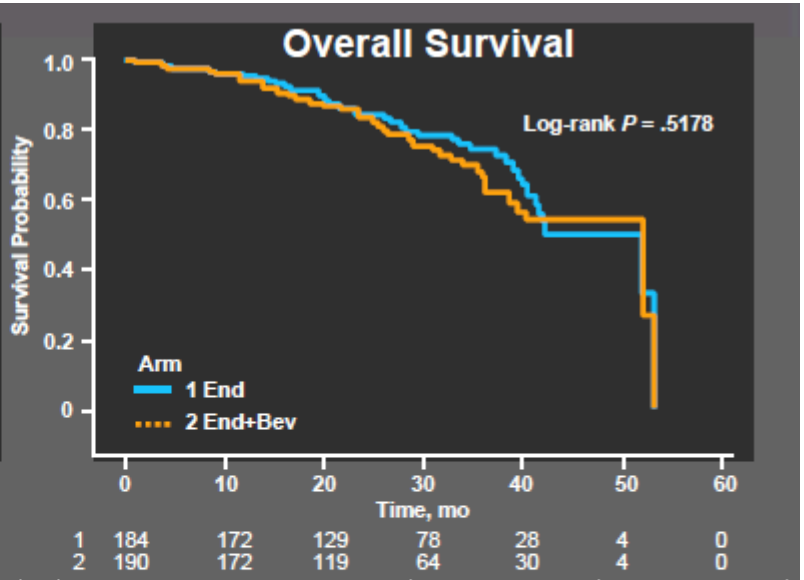
Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

	ET n= 189	ET-B n= 191
Endocrine treatment received		
Letrozole	89%	91.6%
Fulvestrant	11%	8.4%

	ET n= 189	ET-B n= 191
Previous adjuvant endocrine therapy		
Antiestrogens	31.2%	33.5%
Aromatase inhibitor	7.4%	4.2%
Both	12.7%	14.7%
None	48.7%	47.6%

Phase 3 LEA: First-line Bevacizumab Plus Endocrine Therapy Did Not Provide Clinical Benefit in ABC[1]





Events	ET n = 184	ET-B n = 190
PFS, median mo	14.4	19.3
P value, log-rank	0.126	
HR (95% CI)	0.83 (0.65-1.06)	
PFS events (total)	135	128
Censored	49	62

Events	ET n = 184	ET-B n = 190
OS, median mo	51.8	52.1
P value, log-rank	0.518	
HR (95% CI)	0.87 (0.58-1.32)	
PFS events (total)	46	47
Censored	138	143

1. Loibl S, et al. ECCO-ESMO 2013; Abst E17-2128.

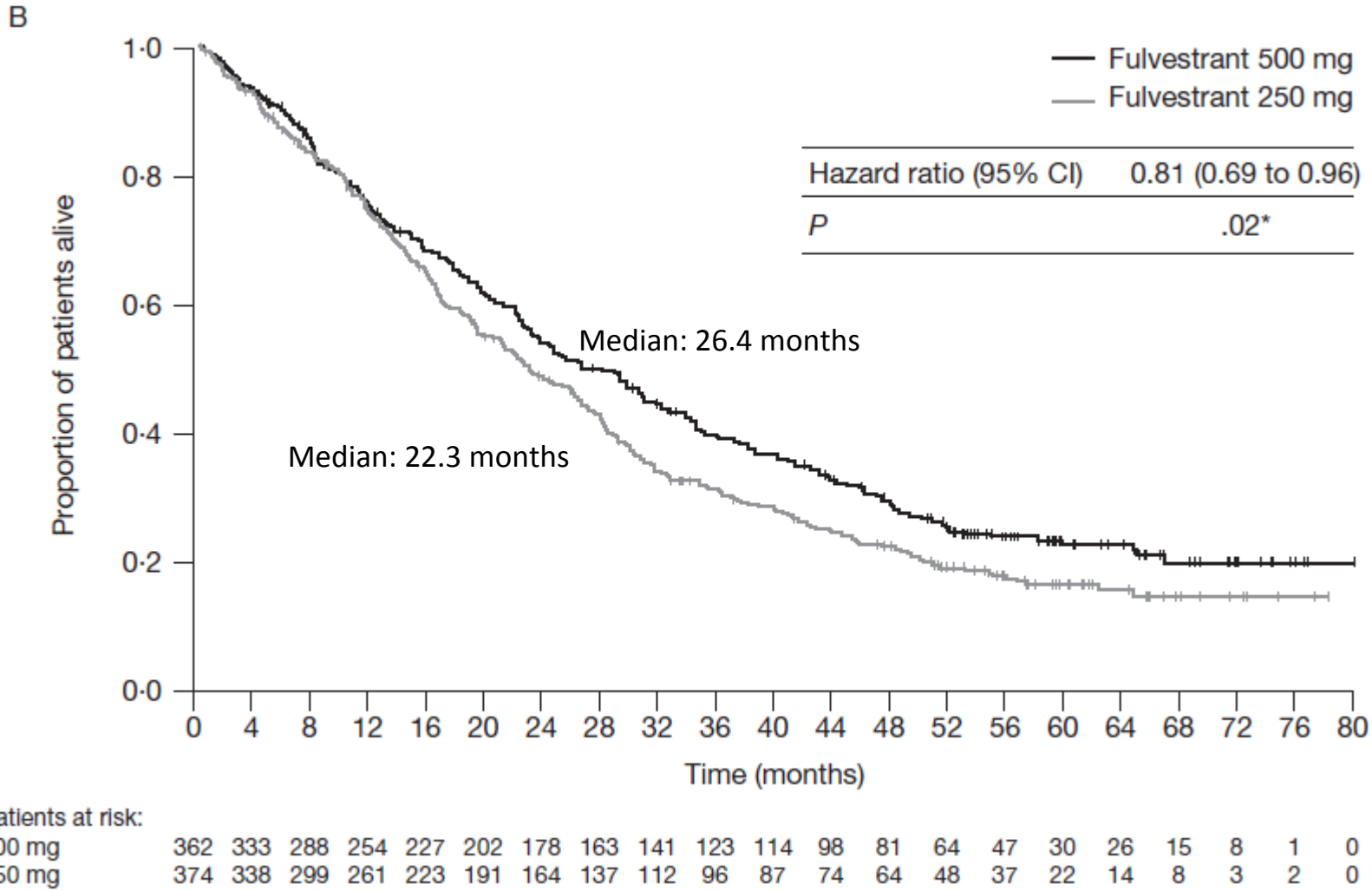
Images are not actual patients.

The TAM Resistance Status (PD during tam for adj or mts disease)

HT	PFS/TTP (mos)	
ANA	5.1	Howell, JCO 2002
FUL250	5.5	
ANA	3.4	Osborne, JCO 2002
FULV250	5.4	
EXE	5.1	Kaufmann, JCO 2000
MA	4.1	
FULV500*	6.5	Di Leo, JCO 2010

*43% of pts AI-resistant; 57% of pts anti-estrogen resistant

Final Overall Survival: Fulvestrant 500 mg vs 250 mg in the Randomized CONFIRM Trial



J Natl Cancer Inst;2014;106:1–7

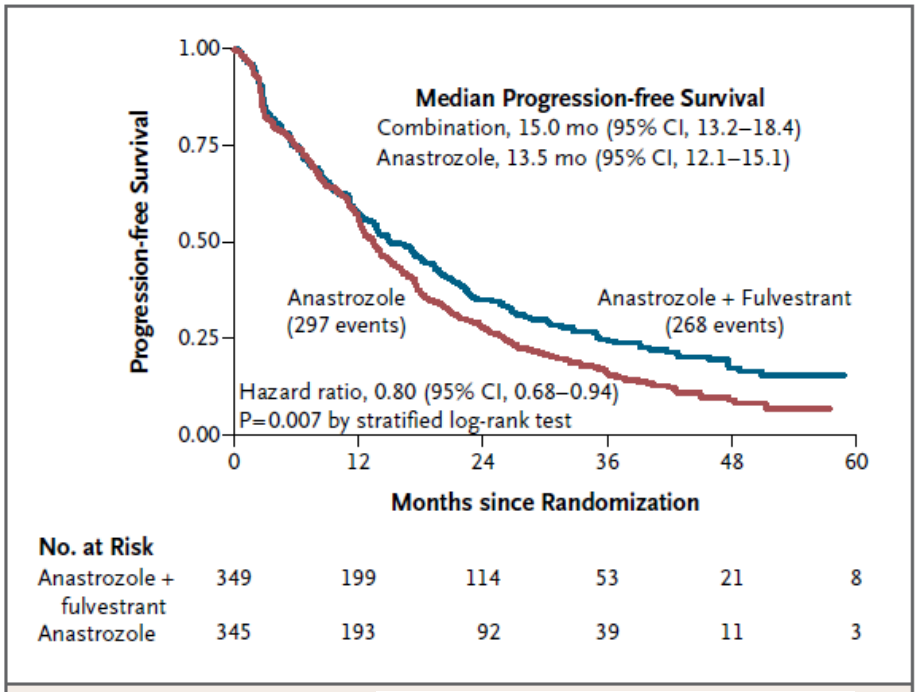
The NSAI Resistance Status

HT	PFS/TTP (mos)	
EXE	3.4	Johnston, Lancet Oncol 2013
FUL250 + ANA	4.4	
FUL250	4.8	
FUL250	3.0	Ingle, JCO 2006
FUL250	3.7	Chia, JCO 2008
EXE	3.7	
FUL500*	6.5	Di Leo, JCO 2010

*43% of pts AI-resistant; 57% of pts anti-estrogen resistant

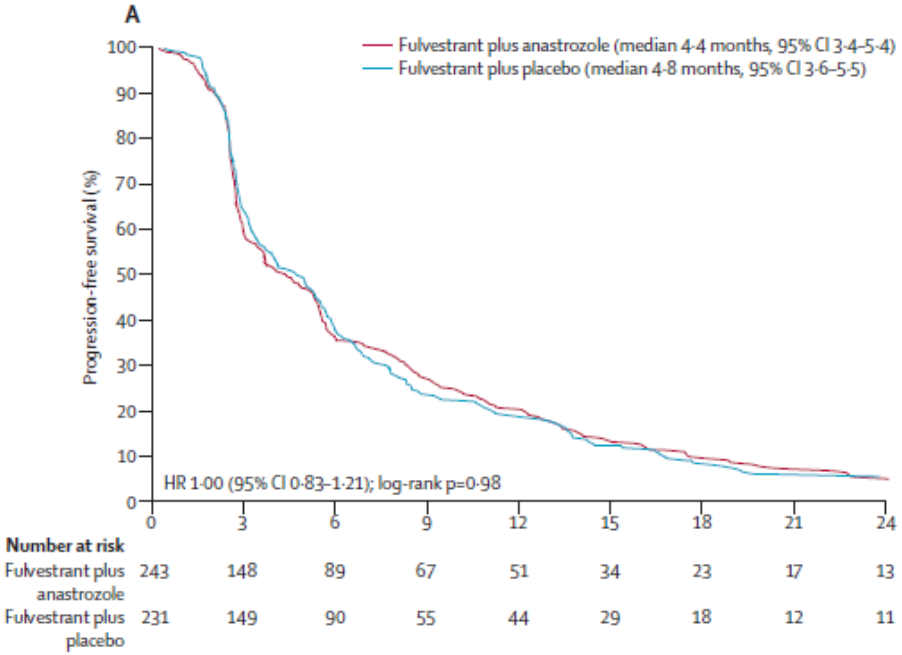
Performance of Endocrine therapy in different patient subgroups

Tam-naive/sensitive



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

NSAI-resistant



Lancet Oncol 2013; 14: 989–98

BOLERO-2. PFS

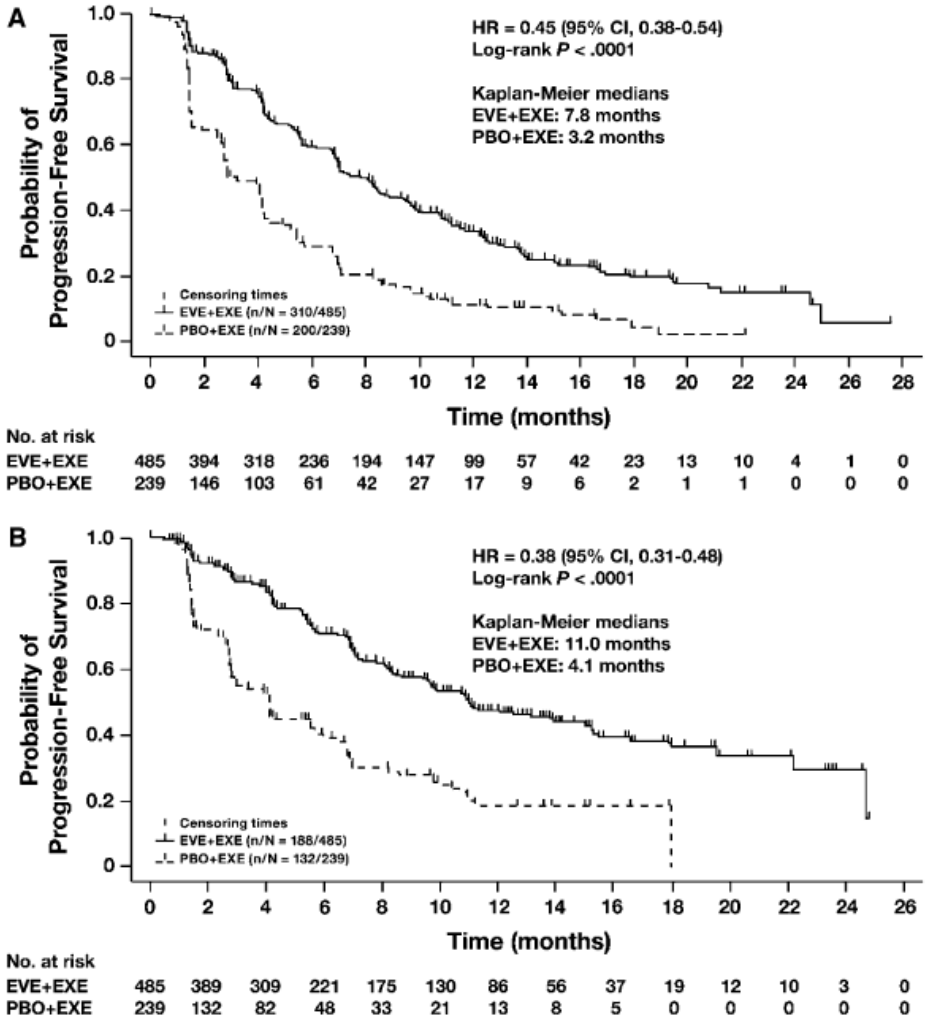


Fig. 1 Kaplan–Meier estimates of progression-free survival of patients treated with everolimus plus exemestane versus exemestane alone based on assessment by a local investigator or **b** central review. *CI* confidence interval, *HR* hazard ratio, *EVE* everolimus, *EXE* exemestane, *PBO* placebo

D Yardley, Adv Ther 2013

Visceral Mts.

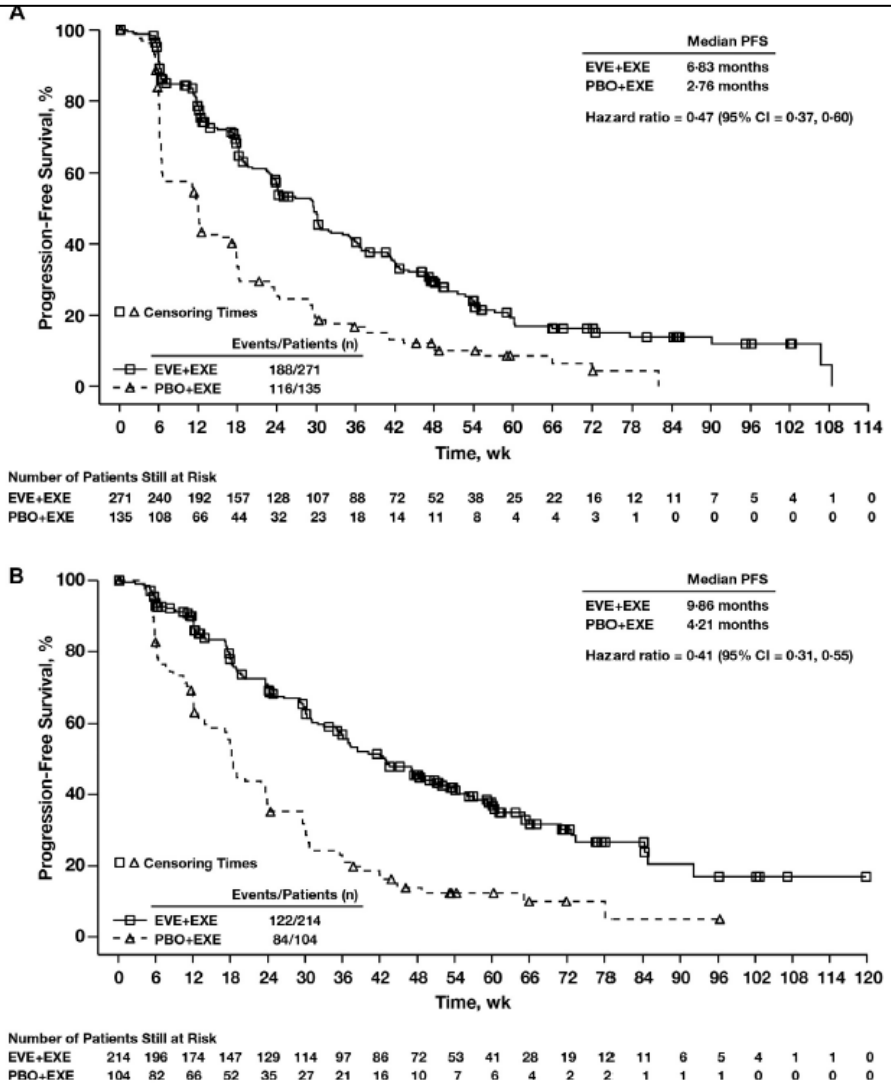
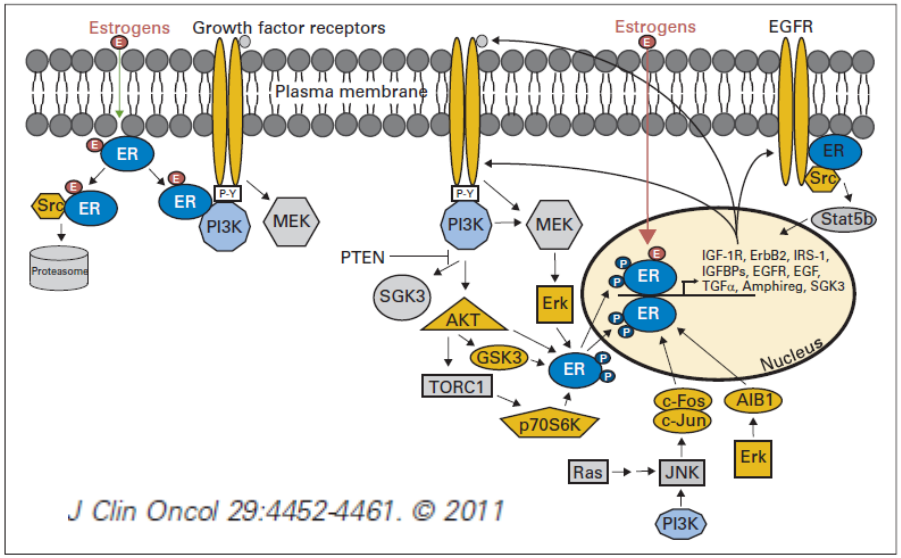


Fig. 2. Kaplan–Meier curve for PFS in patients (A) with and (B) without visceral involvement. *Abbreviations:* CI, confidence interval; EVE, everolimus (10 mg/day); EXE, exemestane (25 mg/day); PBO, placebo; PFS, progression free survival.

M Campone, Eur J Cancer 2013



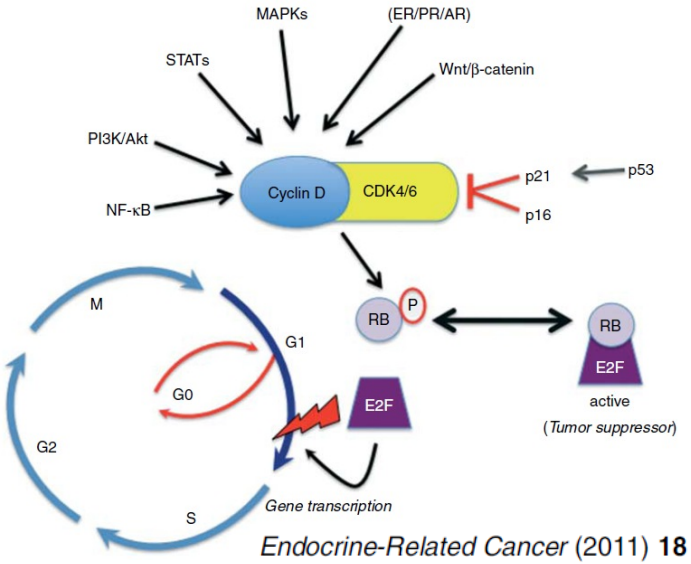
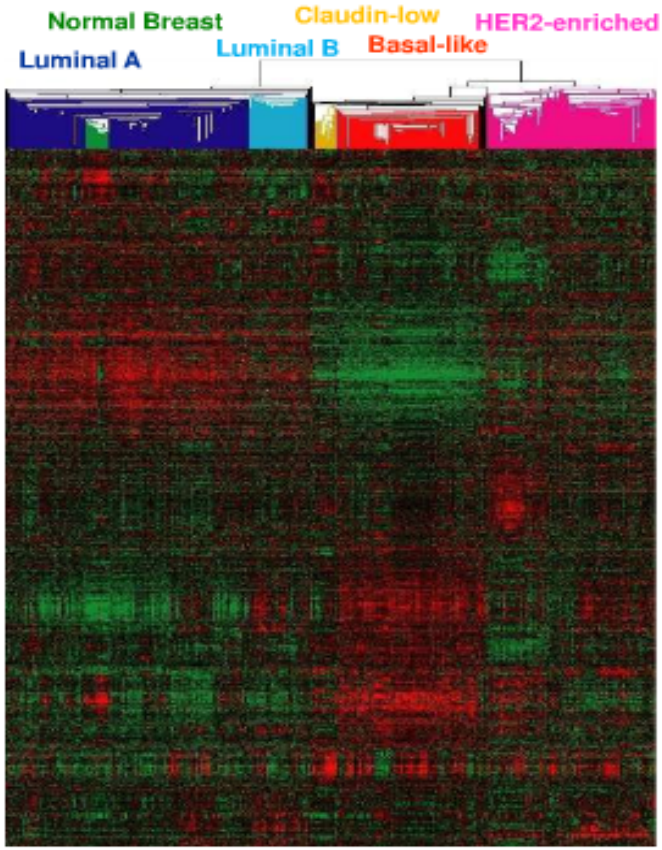


TABLE 3. Targeting Additional Pathways in Addition to Hormone Therapy in HR+ MBC

	Kaufman 2009[26]		Johnston 2009[27]		Cristofanilli 2010[29]		Osborne 2011[30]		Baselga 2012[31]		Finn 2012[34]	
	Ana	Ana + Tras	Let + Placebo	Let + Lapatinib	Ana + Placebo	Ana + Gefitinib	Tam + Placebo	Tam + Gefitinib	Exe + Placebo	Exe + Everolimus	Let	Let + PD0332991
n	104	103	108	111	50	43	101 Stratum 1	105 Stratum 1	239	485	81	84
CBR	27.9%	42.7%	29%	48%	34%	49%	45.5%	50.5%	NR	NR	44%	68%
PFS (months)	3.8	5.6*	3.0	8.2*	8.4	14.7*	8.8	10.9*	2.8	6.9*	7.5	26.2*
OS (months)	23.9	28.5	NR		NR		NR		NR		NR	
Significance*	hazard ratio = 0.63 95% CI: 0.47-0.84		hazard ratio = 0.71 95% CI: 0.53-0.96		hazard ratio = 0.55 95% CI: 0.32-0.94		hazard ratio = 0.84 95% CI: 0.59-1.18		hazard ratio = 0.43 95% CI: 0.35-0.54		hazard ratio = 0.32 95% CI: 0.19-0.56	
Target	HER2		HER2		EGFR		EGFR		mTOR		CDK 4/6	

Ormonoterapia del carcinoma mammario

- Terapia adiuvante
- Terapia della malattia metastatica
- **Prospettive future**



Intrinsic Subtypes

Perou et al., Nature, 2000
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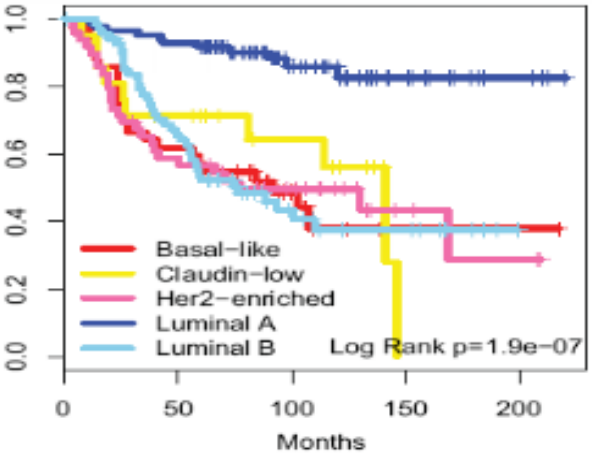
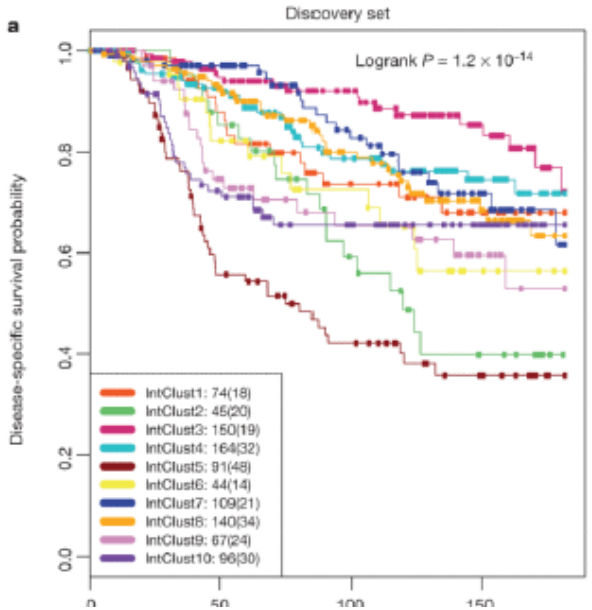
Hu et al., BMC Genomics, 2006
Perreard et al., BCR 2006
Herschkowitz et al., GB, 2007
Mullins et al., Clin Chem, 2007
Parker et al., JCO, Feb 2009
Prat et al., Submitted

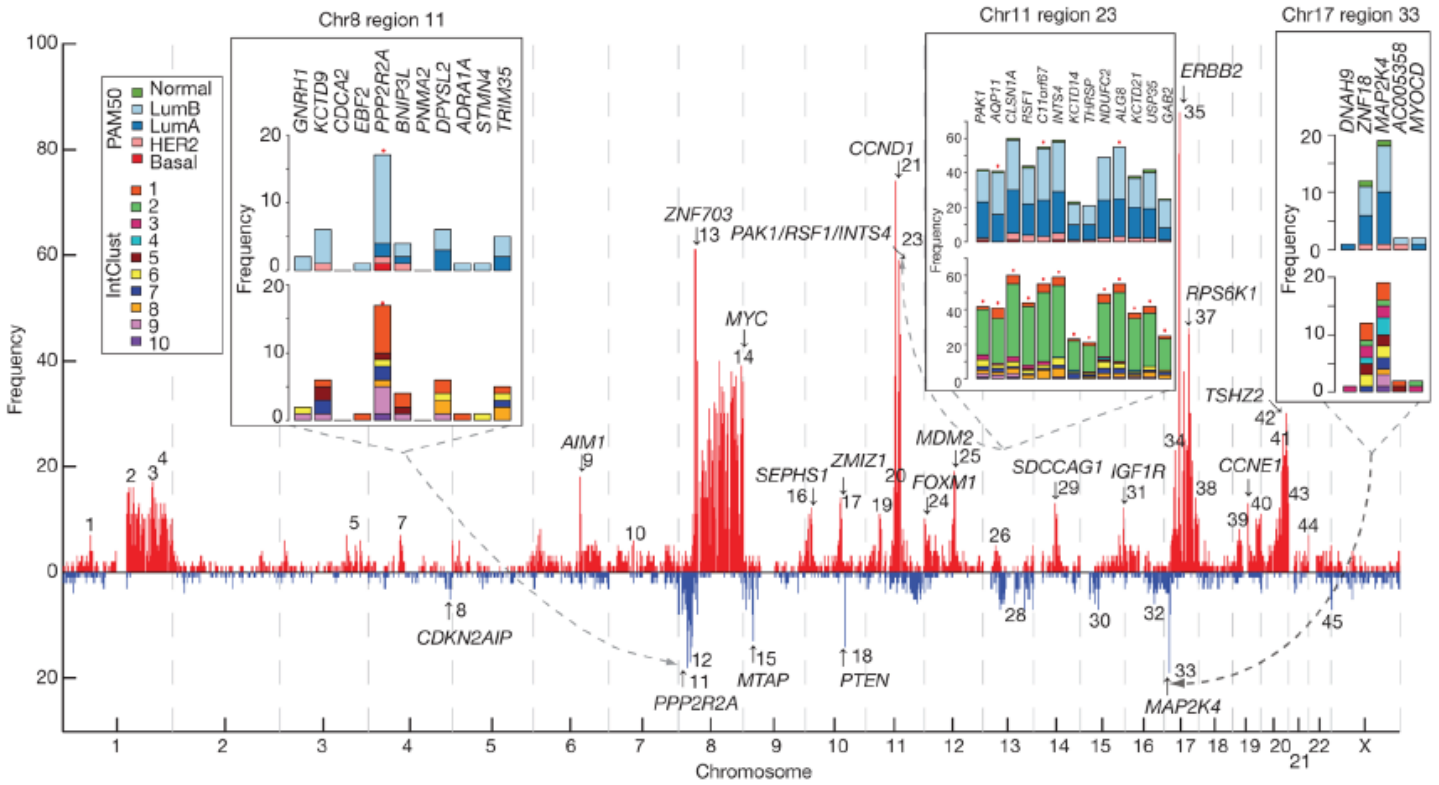


Changing landscape of breast cancer

«The hope is that as the capacity increases to molecularly interrogate breast tumor on a real-time basis we can understand the mutational evolution that occurs with disease progression, identify potentially «actionable» genomic aberrations, and ultimately use the information to better select therapeutic agents» *Wilson 2013 ASCO Educ. book*



Nature. ; 486(7403): 346–352. doi:10.1038/nature10983.



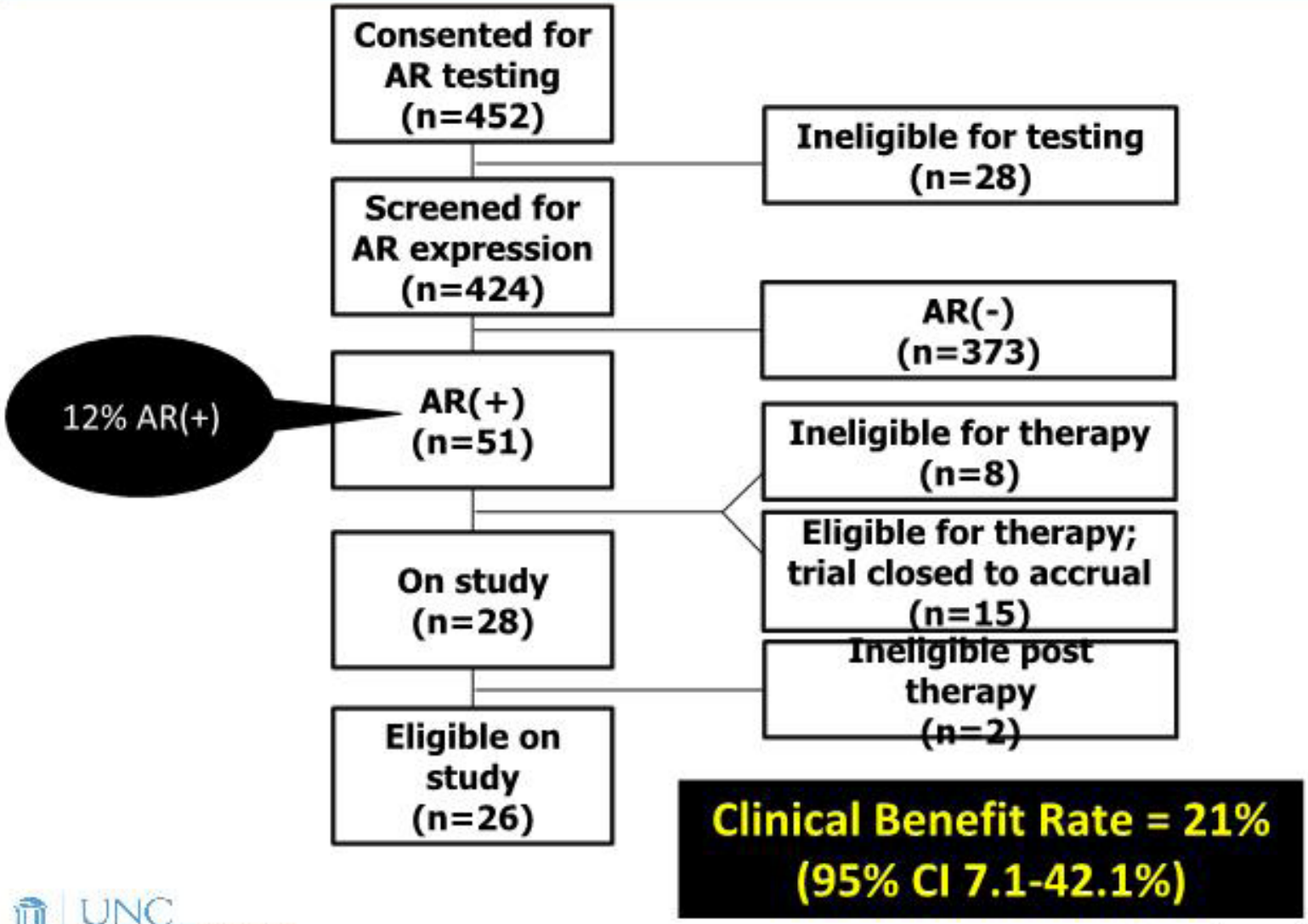
Lehmann : *J Clin Invest.* 2011:121(7):2750–2767. doi:10.1172/JCI45014.

Subtypes Characteristics

Subtype	Gene Ontology	IHC analysis	Hysto type	Possible sensitivity
Basal-like 1	Cell cycle and cell division DNA damage response	High Ki67	--	Cisplatin PARP-Inhibitors
Basal-like 2	Growth gactor signaling (EGFR, MET)	--	Medullary	Anti-EGFR
Immuno-modulatory	Immune cell processes	--	--	
Mesenchymal-like	Cell motility and cell differentation (TGF-β, Src); GF patways	--	Metaplastic	PI3K-mTOR Inh (BEZ235) Src-Inhibitors (Dasatinib)
Mesenchymal Stem-like	Angiogenesis Low levels prolif genes Claudin-low	--		Anti-angio
Luminal AR	Hormonally regulated pathways	AR +	Molecular Apocrine	AR antagonist

Lehmann et al, J Clin Inv 2011

TBCRC 011: Bicalutamide in AR+ TNBC



UNC

Gucalp et al, ASCO 2012