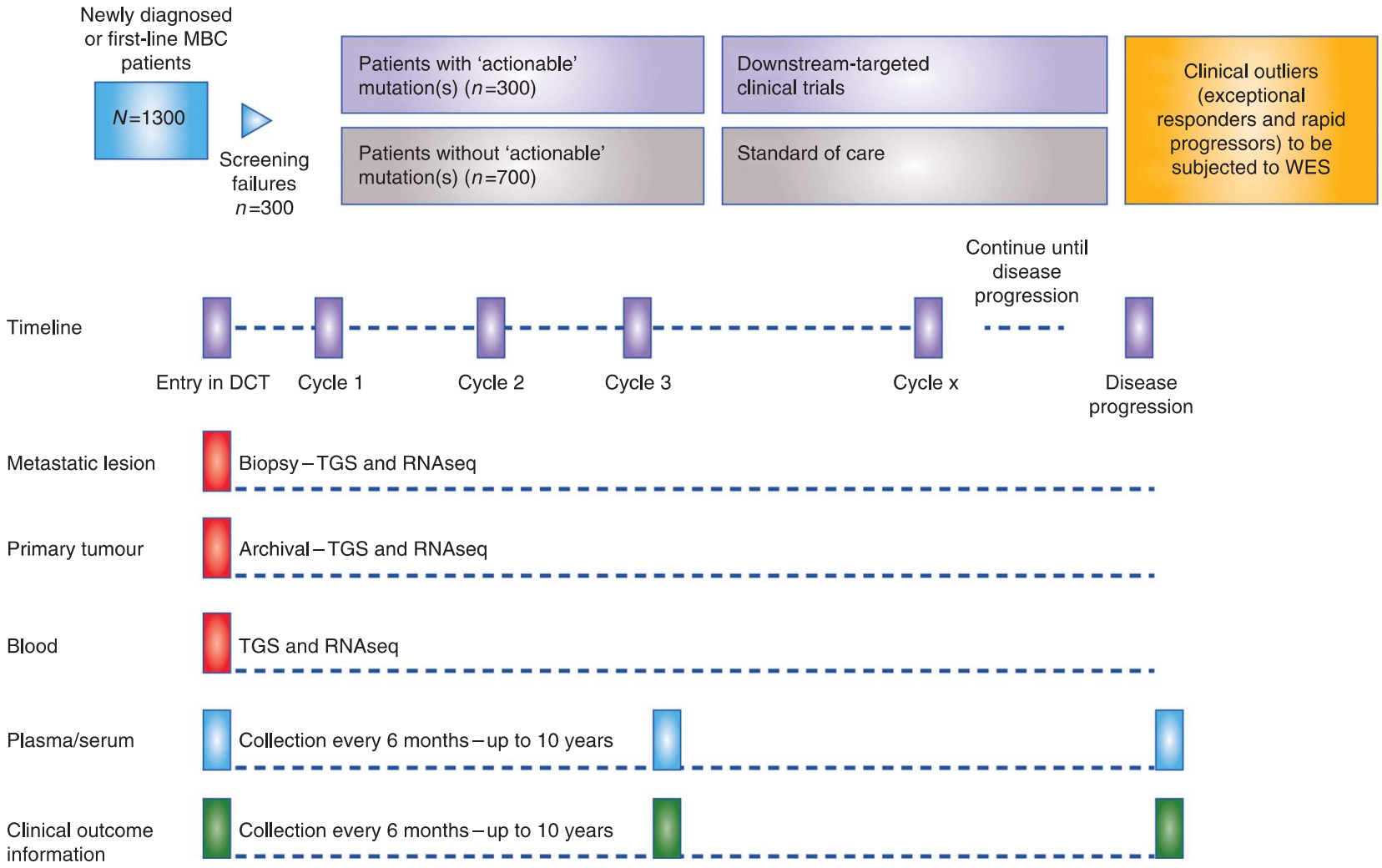
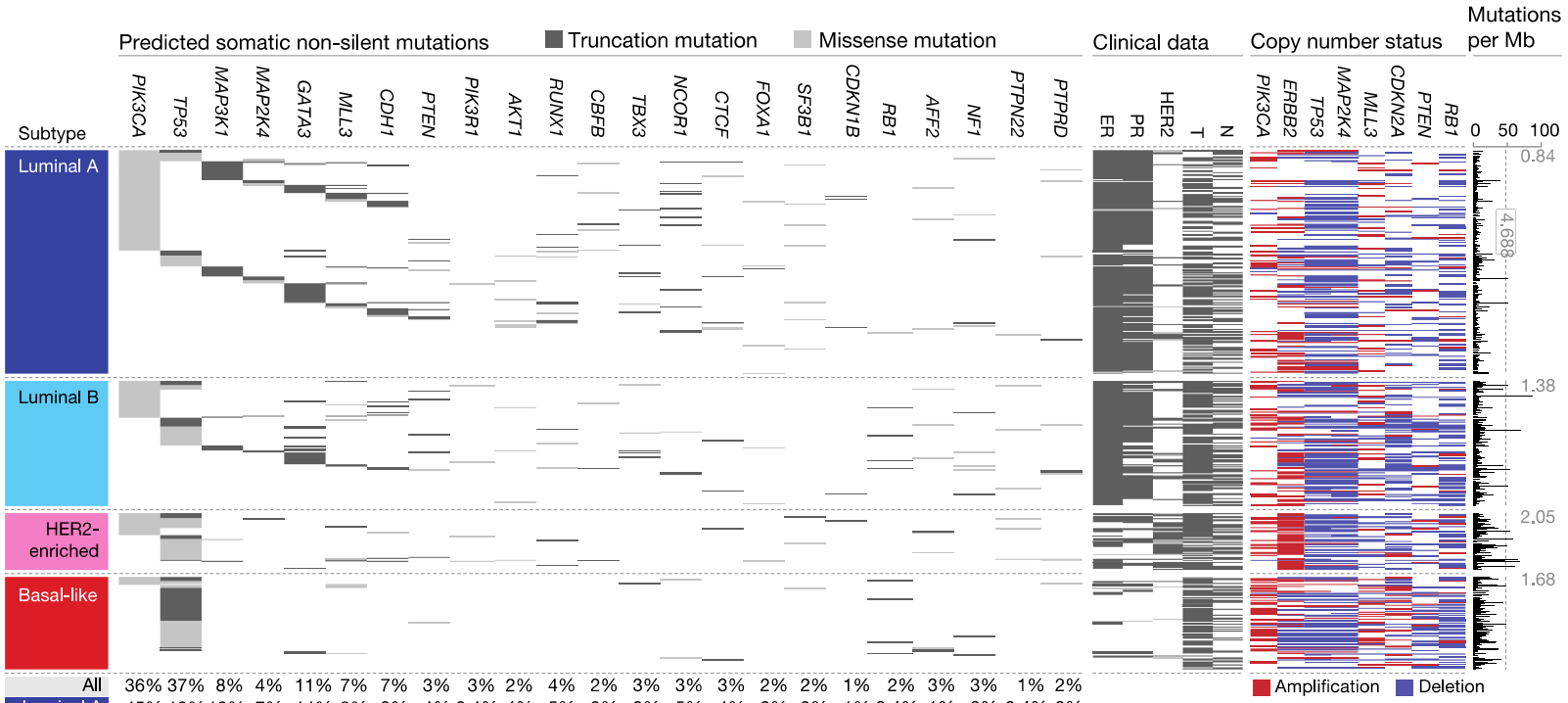
Should I order sequencing for my ER+ metastatic breast cancer patients?

Soonmyung Paik, MD
Division of Pathology, NSABP Foundation/NRG Oncology
Breast Center and Institute for Personalized Cancer Therapy, Yonsei Cancer Center
Yonsei Genome Center, Severance Biomedical Science Institute



Zardavas et al, British J Cancer 2014



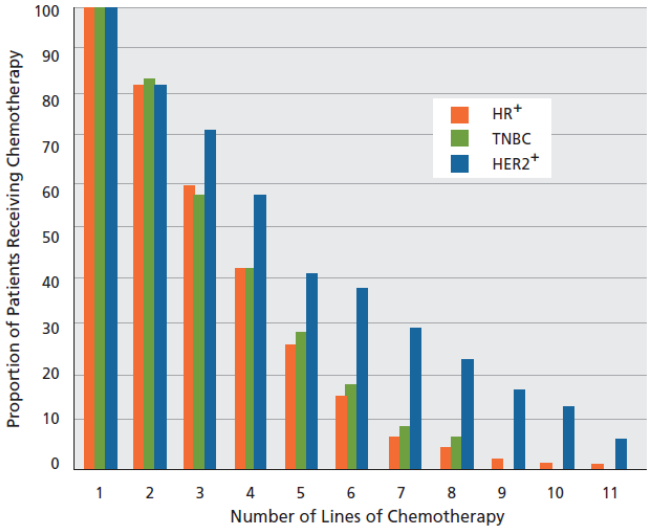
TCGA, Nature 2012

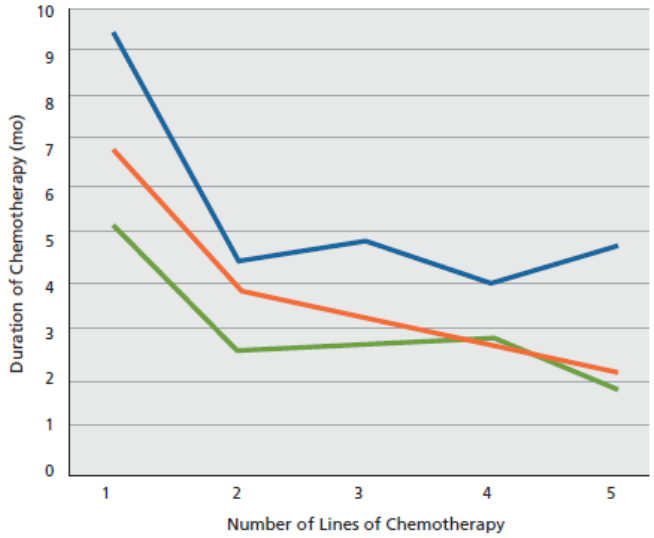
Intrinsic subtype change during progression

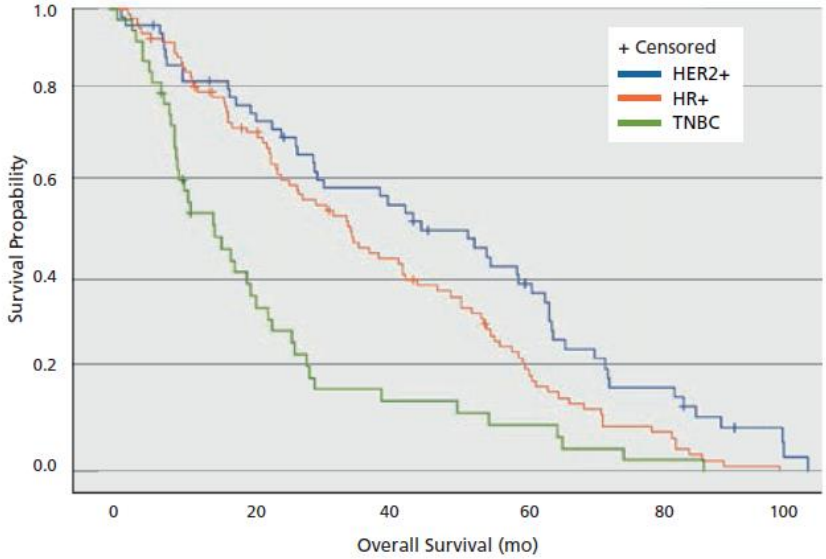
Should Rx based on subtyping of the metastatic site?

Duration of chemotherapy in metastatic pts according to subtype and line of therapy at Dana Farber Cancer Institute (N=199, between 2004 and 2007)

Seah D et al, J Natl Comprehensive Cancer Network 2014

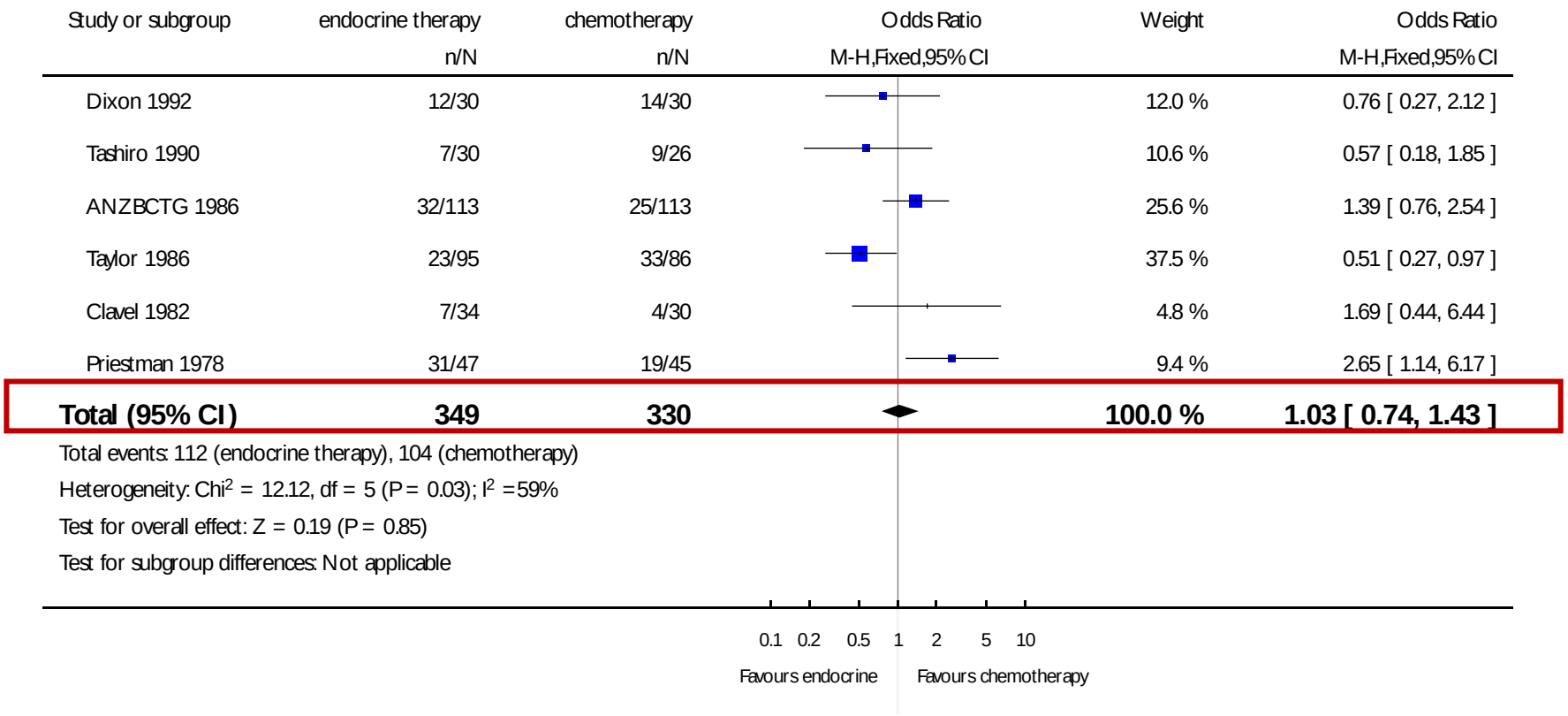






Can chemotherapy be safely delayed to later lines of Rx?

Meta-analysis of chemotherapy vs endocrine therapy for metastatic ER+ BC for mortality (Wilcken et al, Cochrane database)



Hart CD et al, Nat Rev Clin Oncol, 2015

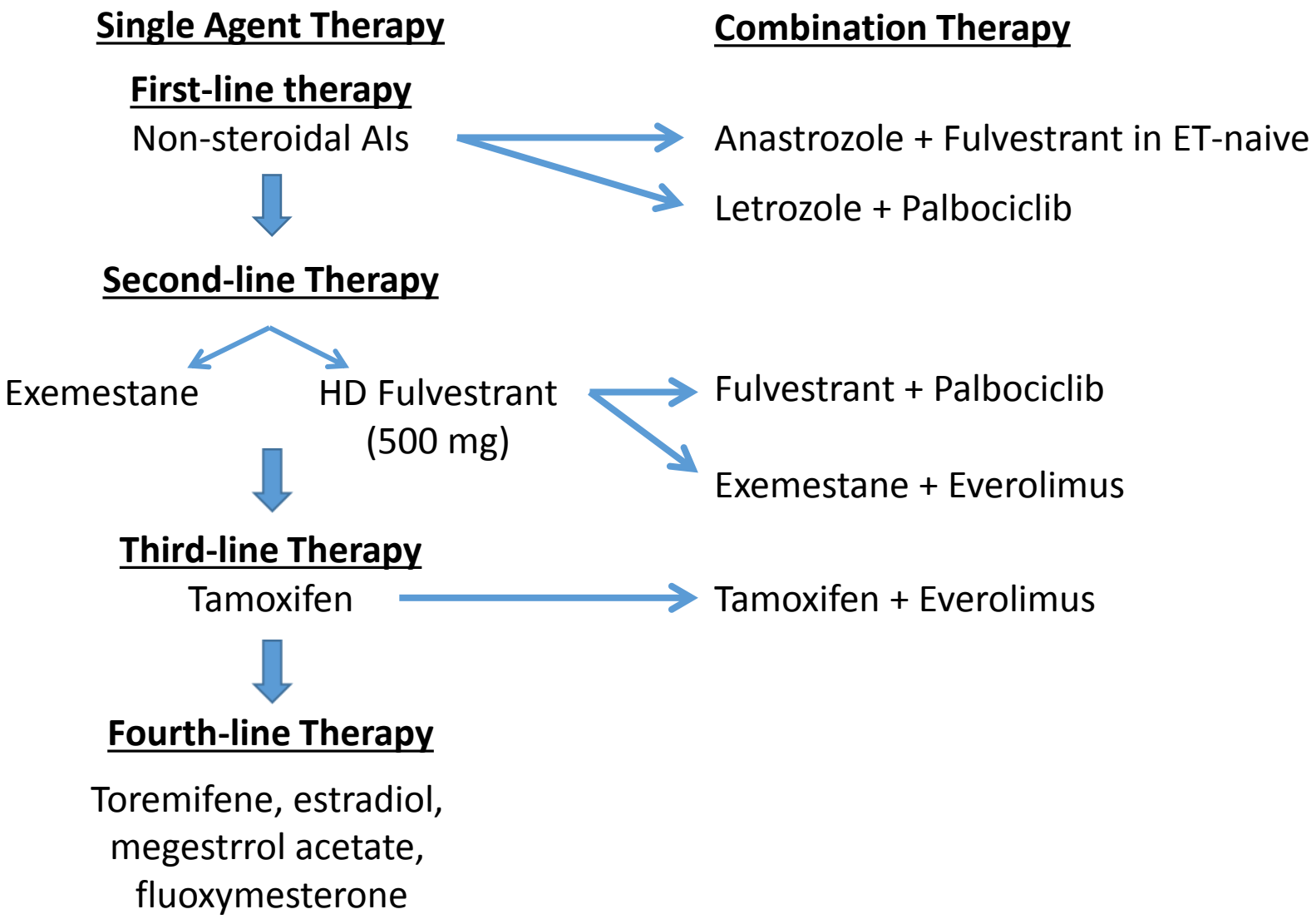
Table 1 | Criteria to support first-line choices in ER+, HER2– advanced disease[13,44]

Criteria	In favour of chemotherapy	Uncertain*	In favour of endocrine therapy
DFI‡	<1 year	1–2 years	>2 years
Visceral metastases	High burden, impending organ dysfunction (visceral crisis)	Moderate burden	Minimal burden or absent
Symptoms	Prominent	Moderate	Minimal or asymptomatic

* The 'uncertain' column represents a grey area where either treatment might be justifiable, and tailoring to patient expectations would be of particular benefit. ‡DFI accounts for disease tempo (rapidity of progression), as well as type of resistance; visceral metastases and symptoms relate to disease tempo and the rapidity of the response required. Abbreviations: DFI, disease-free interval; ER+, oestrogen receptor positive; HER2–, HER2 negative.

Sequencing of endocrine therapy for 2016

(Courtesy of Dr. Maura Dickler, MSKCC)



Prospective evaluation of the conversion rate in the receptor status between primary breast cancer and metastasis: results from the GEICAM 2009-03 ConvertHER study

Eduardo Martínez de Dueñas · Ana Lluch Hernández · Ángel Guerrero Zotano · Ramón María Pérez Carrión · José Ignacio Chacón López-Muñiz · Silvia Antolín Novoa · Ángela López Rodríguez · José Alejandro Pérez Fidalgo · Jaime Ferrer Lozano · Octavio Burgués Gasión · Eva Carrasco Carrascal · Andrés Hernando Capilla · Isabel Blancas López-Barajas · Montserrat Muñoz Mateu · María Helena López de Ceballos Reyna · Amparo Oltra Ferrando · Noelia Martínez Jañez · Vicente Carañana Ballerini · Antonio Antón Torres · Gustavo Catalán · José Ángel García Sáenz · Salomón Menjón · Ana María González-Angulo

Breast Cancer Res Treat 143:507-515, 2014

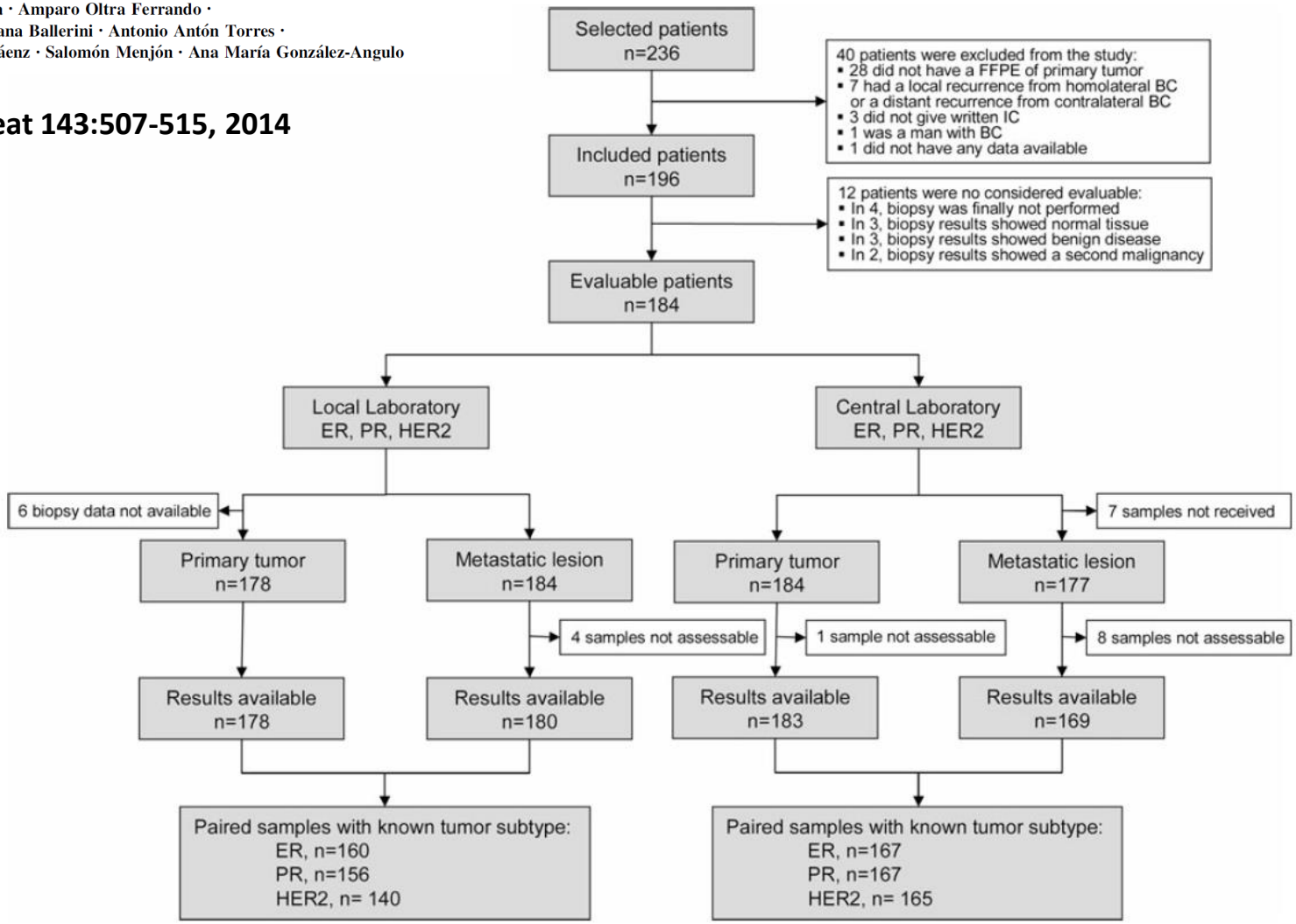


Fig. 1 CONSORT diagram of the ConvertHER study

Prospective evaluation of the conversion rate in the receptor status between primary breast cancer and metastasis: results from the GEICAM 2009-03 ConvertHER study

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Primary tumor	Metastatic lesion					
	HR positive/HER2 negative $n = 69$		HER2 amplified $n = 43$		Triple negative $n = 27$	
	n	%	*n*	%	*n*	%
At local laboratory, $n = 139$						
HR positive/HER2 negative, $n = 74$	55	74	12	16	7	10
HER2 amplified, $n = 38$	8	21	29	76	1	3
Triple negative, $n = 27$	6	22	2	7	19	71
	HR positive/HER2 negative $n = 108$		HER2 amplified $n = 36$		Triple negative $n = 21$	
At central laboratory, $n = 165$						
HR positive/HER2 negative, $n = 117$	105	90	4	3	8	7
HER2 amplified, $n = 31$	0	0	31	100	0	0
Triple negative, 17	3	18	1	6	13	76

Of 54 pts with discordance, treatment was modified in 24 (46%)

Intrinsic subtype and gene expression changes between primary and metastatic breast cancer

Aleix Prat[1,2], Eduardo Martínez de Dueñas[3], Patricia Galván[1], Susana Garcia[2], Octavio Burgués[4], Laia Paré[2], Silvia Antolín[2], Rossella Martinello[3], Isabel Blancas[5], Barbara Adamo[2], Ángel Guerrero[7], Montserrat Muñoz[2], Paolo Nuciforo[1], Maria Vidal[1], Ramón M Pérez[8], José I Chacón[9], Rosalía Caballero[10], Pere Gascón[2], Eva Carrasco[10], Federico Rojo[11], Charles M Perou[12], Javier Cortés[1], Vincenzo Adamo[13], Joan Albanell[14] and Ana Lluch[4]

1 Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Barcelona, Spain, 08035; 2 Hospital Clínic IDIBAPS, Barcelona, Barcelona, Spain, 08036; 3 Hospital Provincial de Castellón, Castellón, Spain, 12002; 4 Hospital Clínico Universitario de Valencia, Valencia, Spain, 46010; 5 Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, 15006; 6 Hospital Clínico San Cecilio de Granada, Granada, Spain, 18012; 7 Instituto Valenciano de Oncología, Valencia, Spain, 46009; 8 Hospital Universitario Quirón de Madrid, Madrid, Spain, 28223; 9 Hospital Virgen de la Salud, Toledo, Spain, 45004; 10 GEICAM, Spanish Breast Cancer Group, Madrid, Spain, 28703; 11 Fundación Jiménez Díaz, Madrid, Spain, 28040; 12 University of North Carolina, Chapel Hill, NC, United States, 27519; 13 University of Messina, Messina, Italy and 14 Hospital del Mar, Barcelona, Spain, 08003

Prat et al, SABCS 2015

	Metastasis				
Primary	Basal	HER2E	LumA	LumB	Genes diff expressed
Basal	12 (100%)	0	0	0	0
HER2E	2 (15.4%)	10 (76.9%)	1 (7.7%)	0	7
LumA	0	7 (14.9%)	21 (44.7%)	19 (40.4%)	24
LumB	0	4 (13.3%)	5 (16.7%)	21 (70%)	8

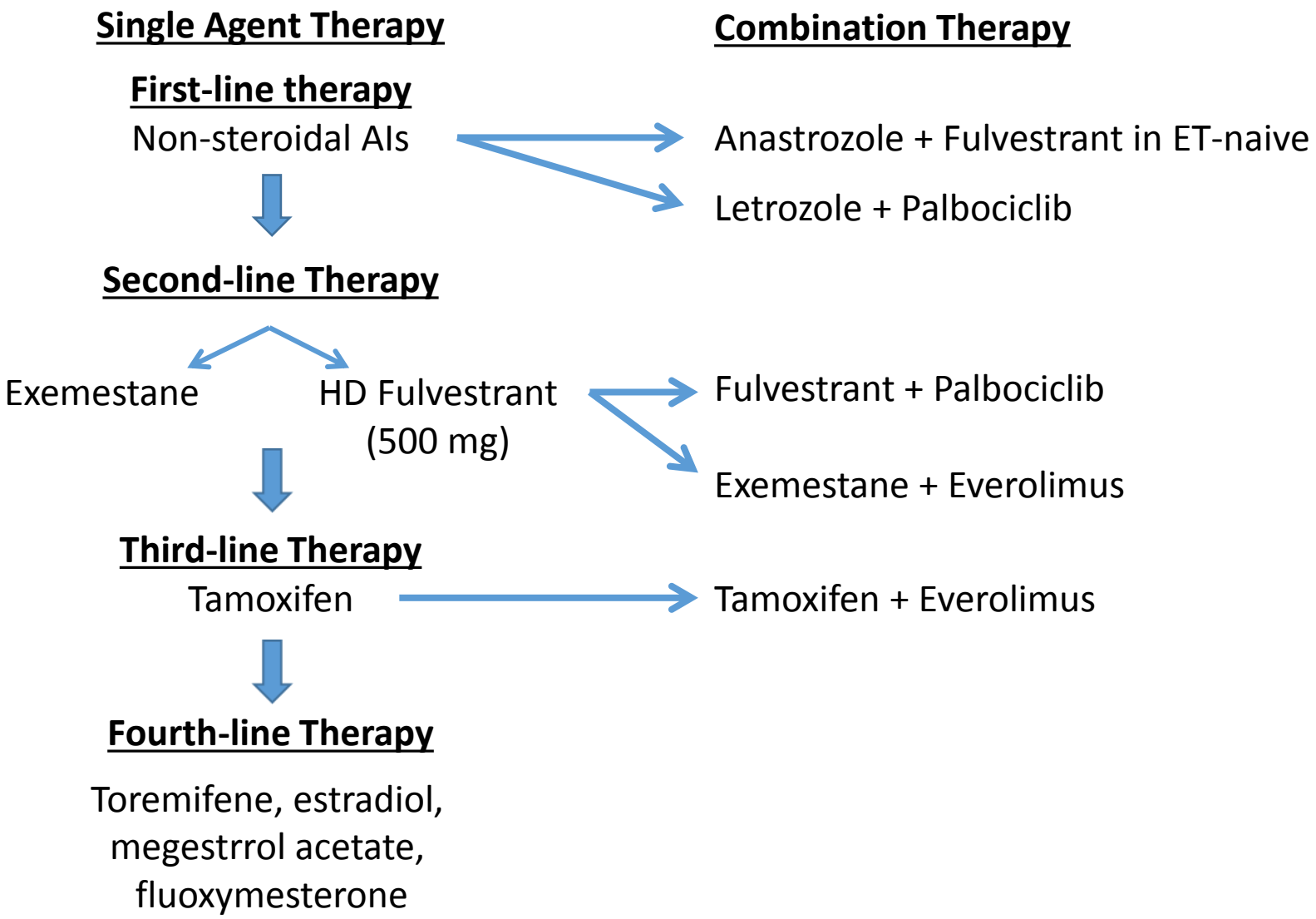
Clinical implication of subtype switching?

- The ESMO ABC2 consensus guidelines recommend using targeted therapy if there has ever been receptor positivity
- No evidence yet for better OS when Rx changed by metastatic biopsy
  - But if we use intrinsic subtype for adjuvant chemo decision, why not in metastatic setting to decide chemo?
- Biopsy of originally TNBC is justified

Can we use genome sequencing of metastatic ER+ BC to guide endocrine (+ targeted) therapy?

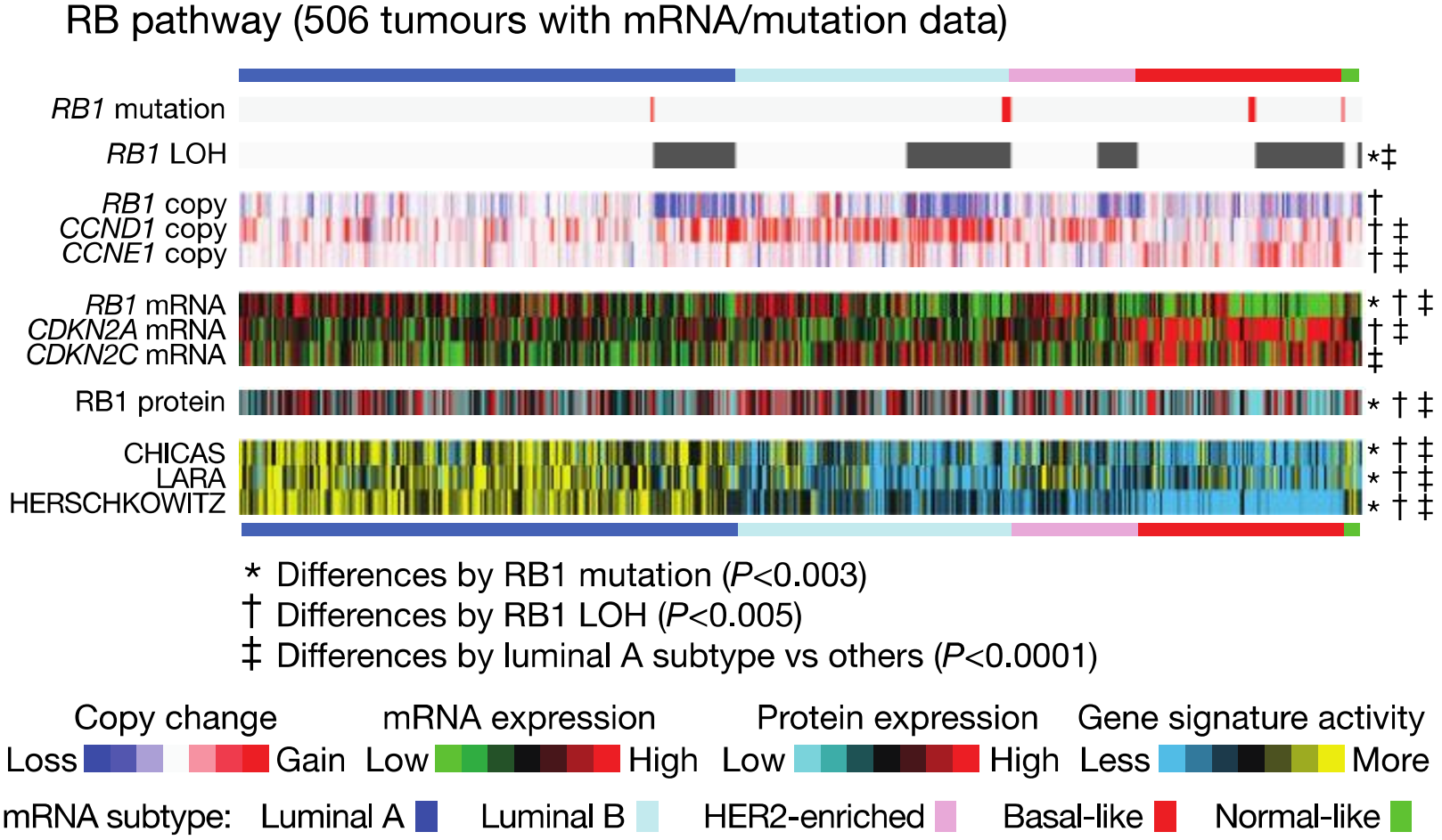
Sequencing of endocrine therapy for 2016

(Courtesy of Dr. Maura Dickler, MSKCC)



RB is intact in most of ER+ tumors

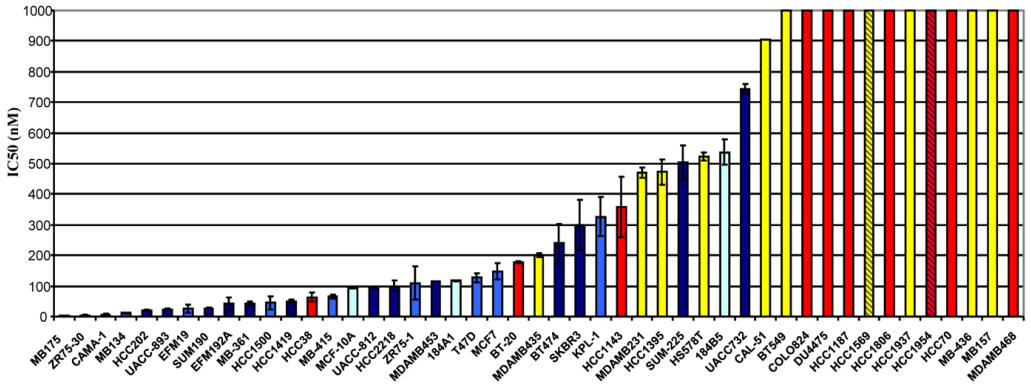
(TCGA, Nature 2012)



Palbociclib (CDK4/6 inhibitor) inhibits growth of ER+ breast cancer

(Fin RS et al, Breast Cancer Res, 2009 and SABCS abstract, 2012)

Figure 1

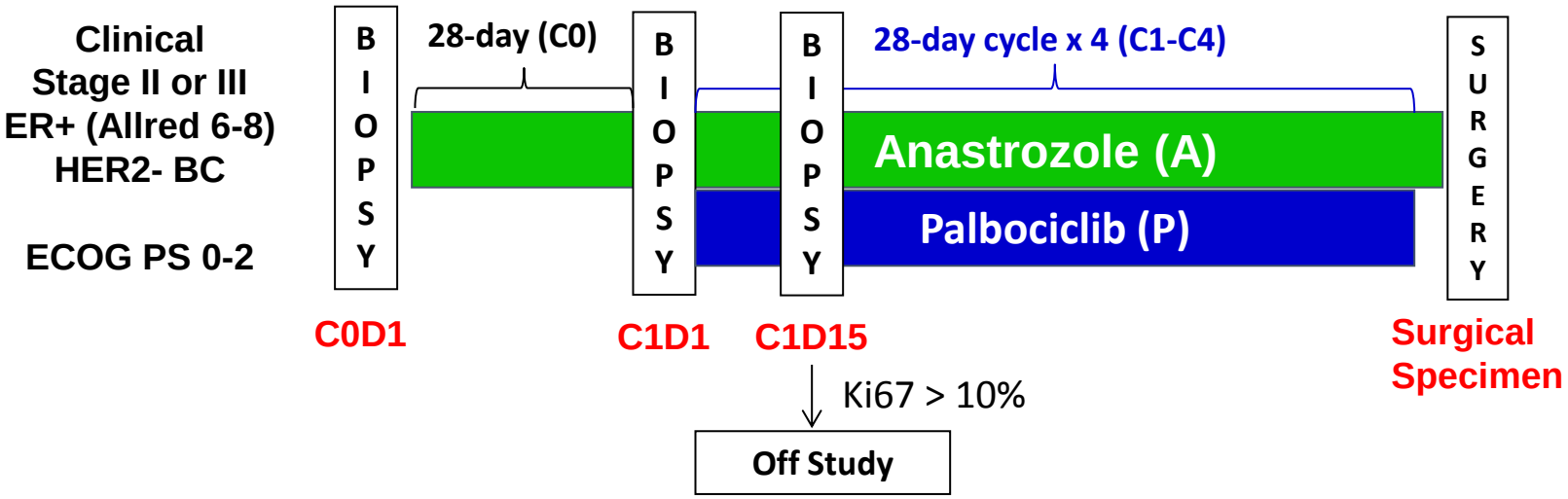


Intrinsic subtypes as a predictor of response to Palbociclib?

- Phase 2 neoadjuvant trial - Cynthia Ma et al, SABCS 2015)

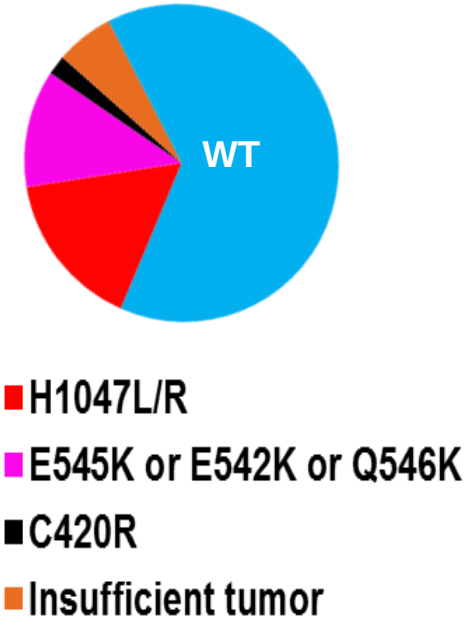
Single Arm Phase II

Schema

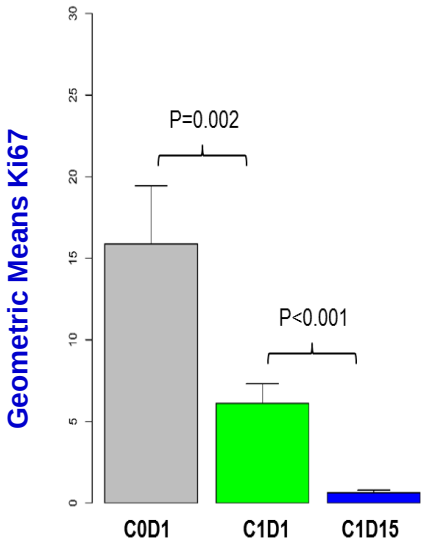


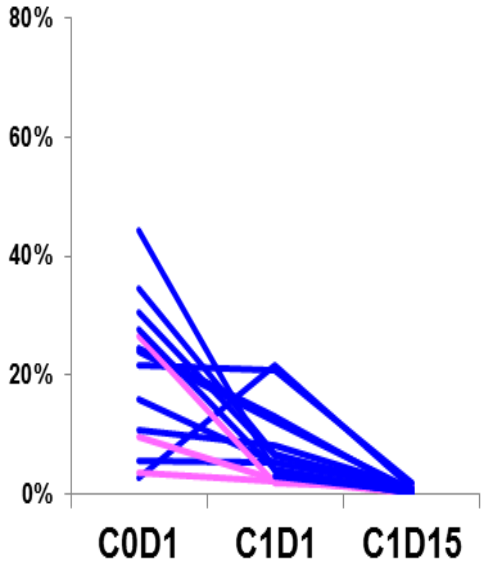
courtesy of Cynthia Ma, WashU

Ki67 Response by *PIK3CA* Status

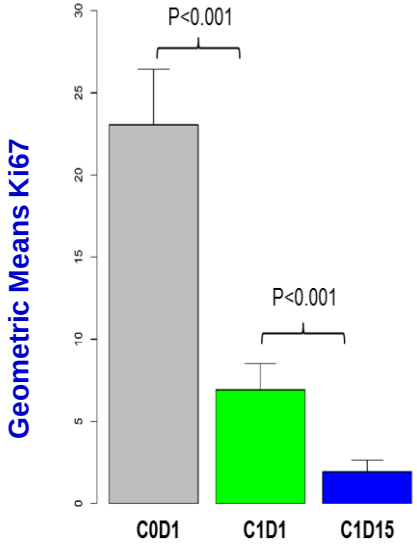


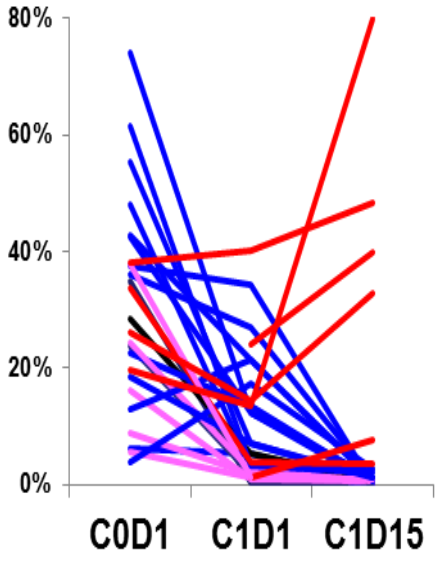
PIK3CA Mut. (n=15)



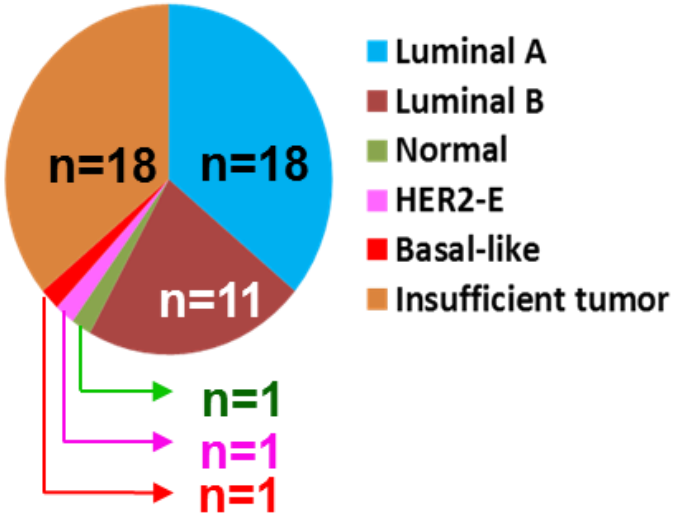


PIK3CA WT (n=28)



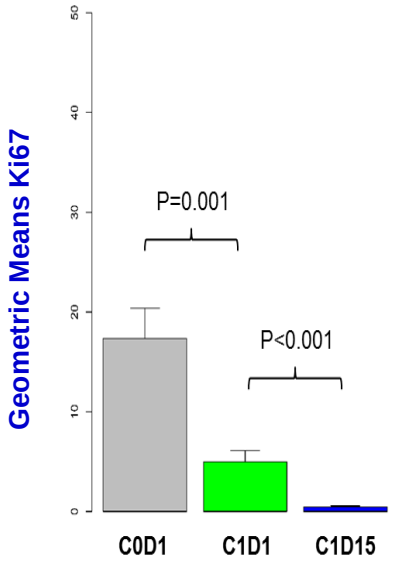


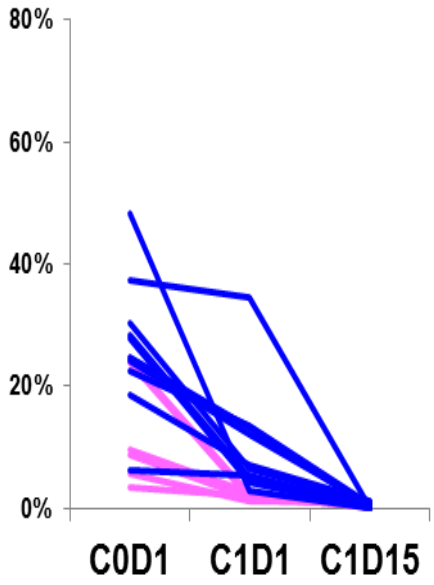
Ki67 Response by Intrinsic Subtype



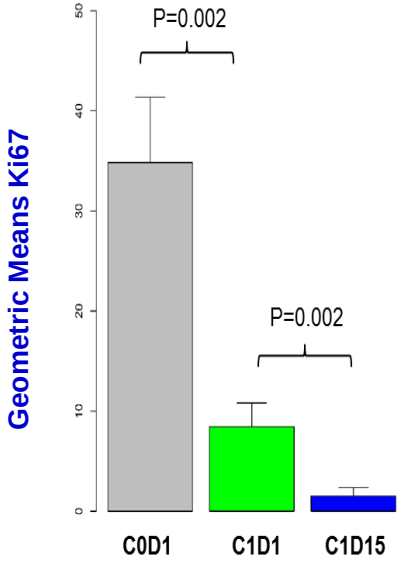
Agilent 4x44K array platform and Research Use Only PAM50 algorithm

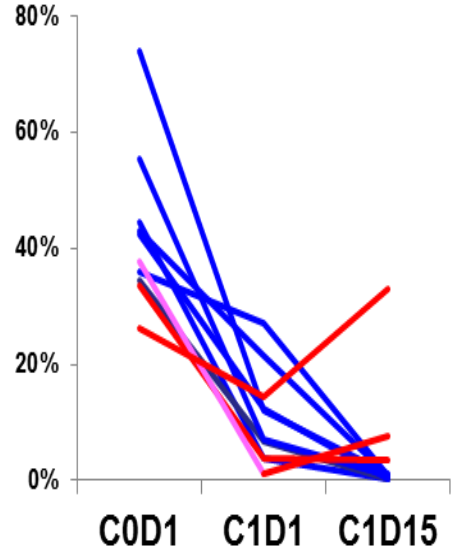
Luminal A (n=18)



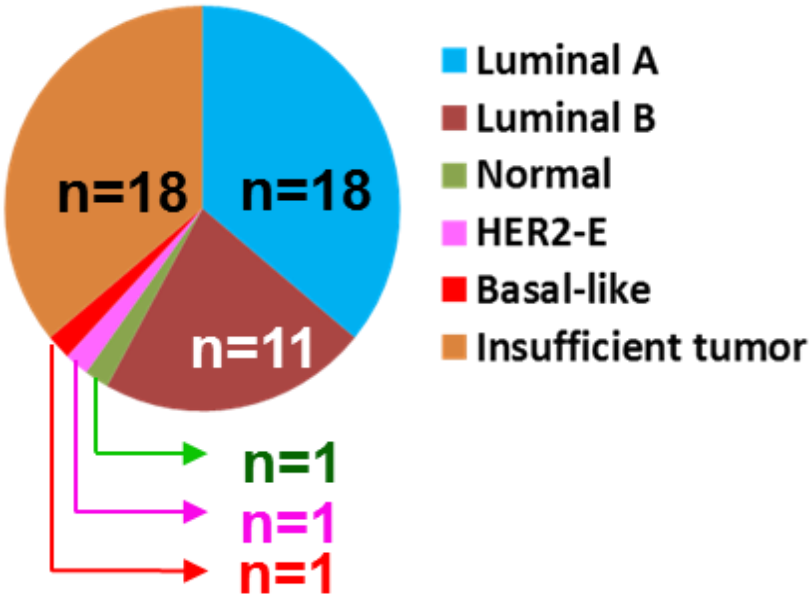


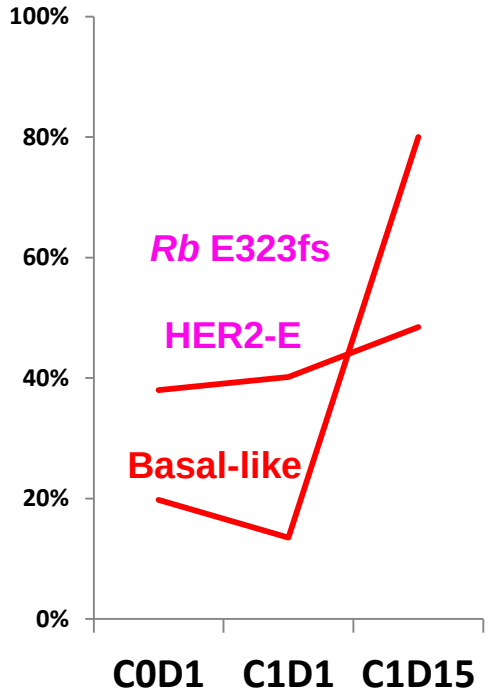
Luminal B (n=11)





Ki67 Response in Non-luminal BC

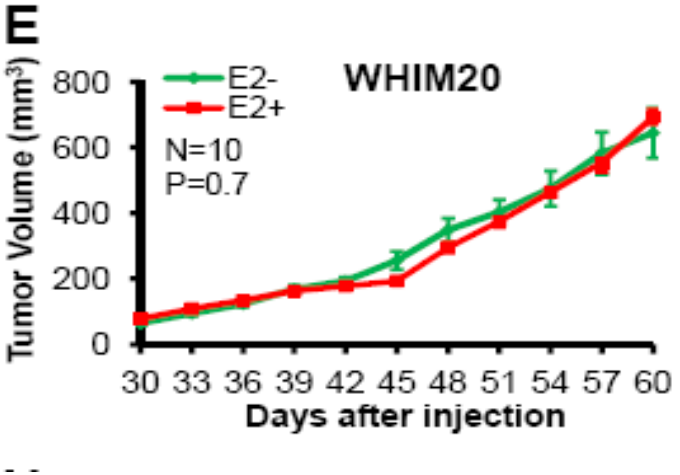


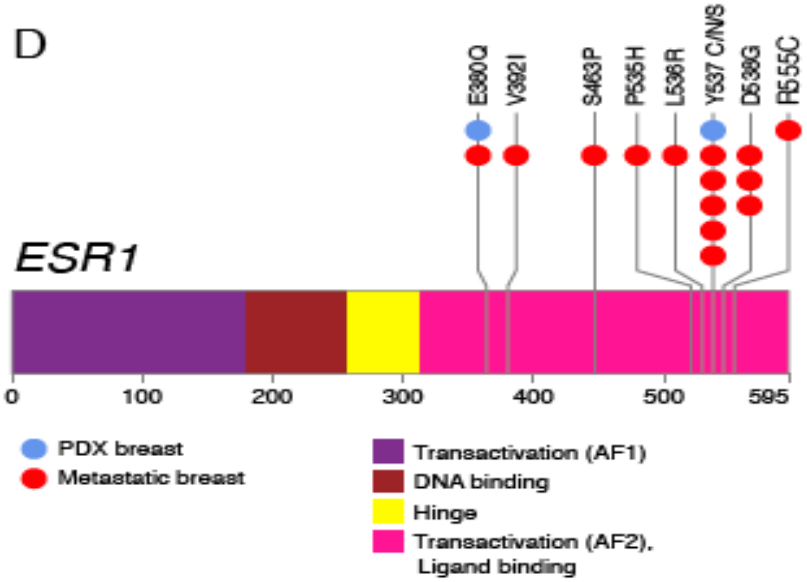


ESR1 mutation as a mechanism of acquired resistance of ER positive tumors to estrogen deprivation therapy

- Li et al, Cell Reports 2013
- Toy et al, Nature Genetics 2013
- Robinson et al, Nature Genetics 2013

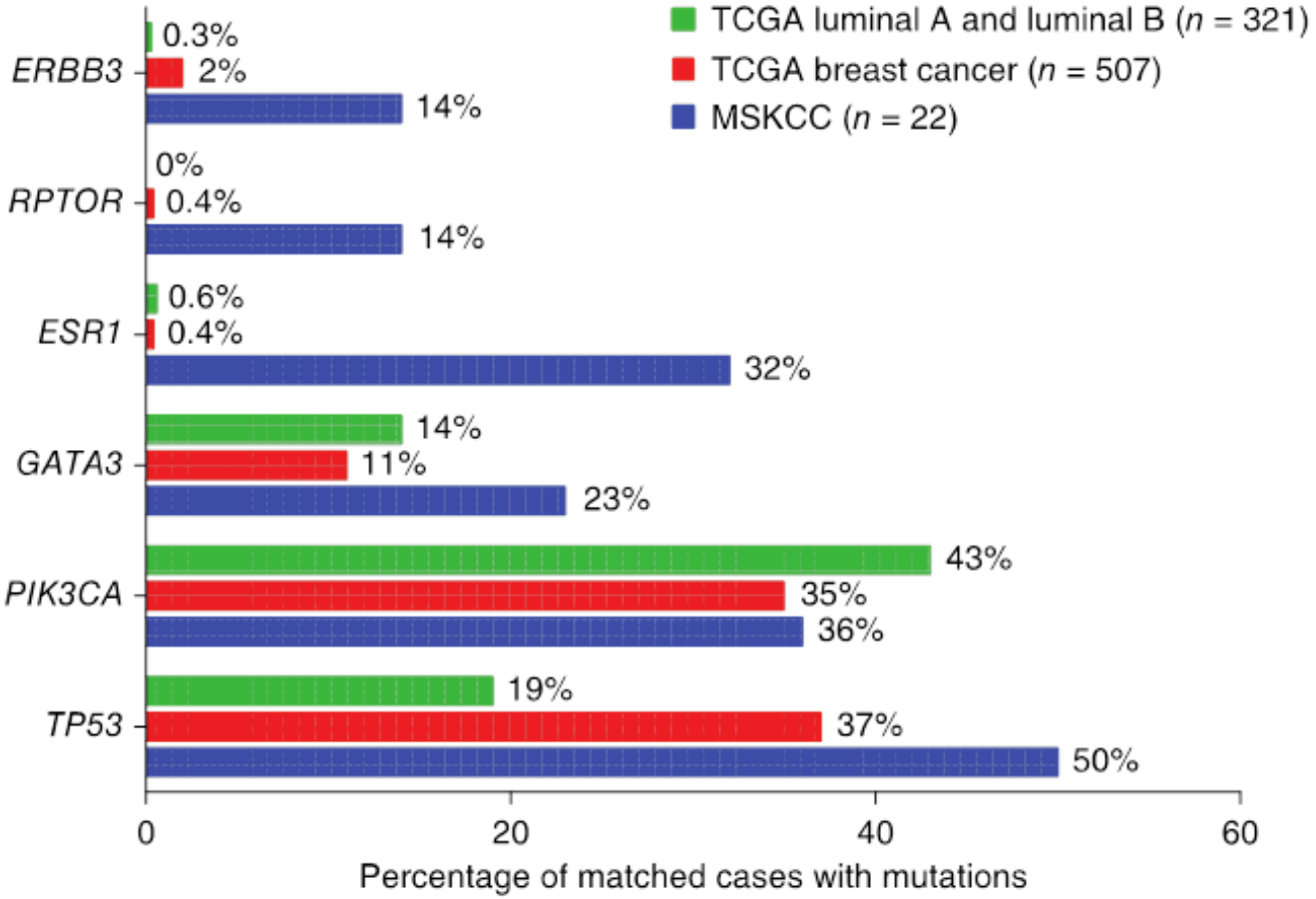
Mutations in the ligand binding domain of ESR1 are an under-recognized cause of endocrine therapy resistance





Li et al. Cell Reports (2013), http://dx.doi.org/10.1016/j.celrep.2013.08.022

ESR1 mutation is rare in primary breast cancer but frequently found in metastatic breast cancer



Toy et al and Robinson et al, Nature Genetics 2013

Emergence of Constitutively Active Estrogen Receptor-alpha Mutations in Pretreated Advanced Estrogen Receptor Positive Breast Cancer

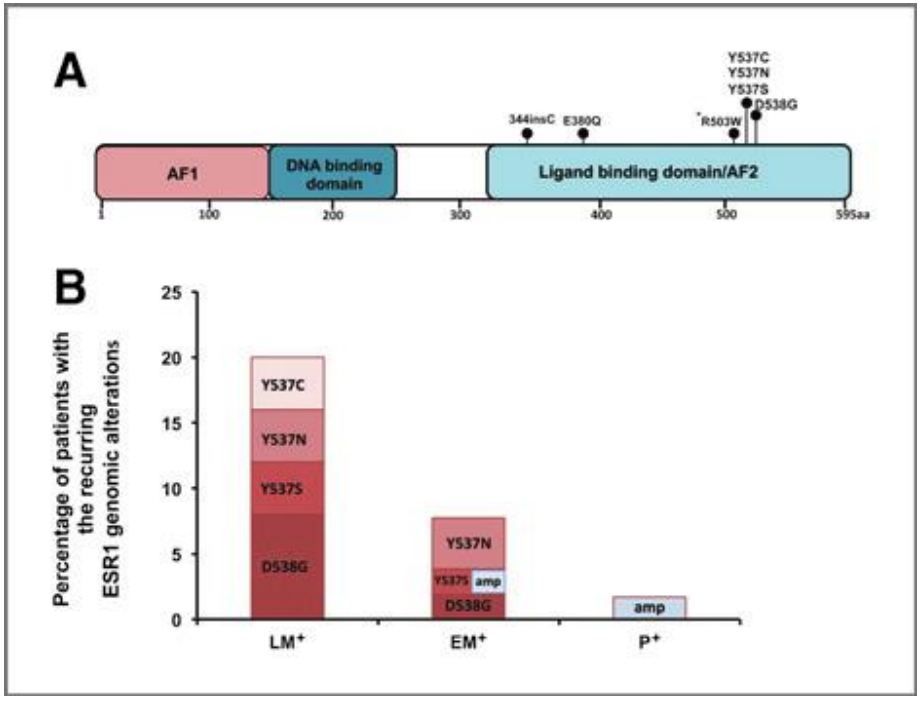
Jeselsohn et al, Clin Cancer Res 20(7):1757-67, 2014

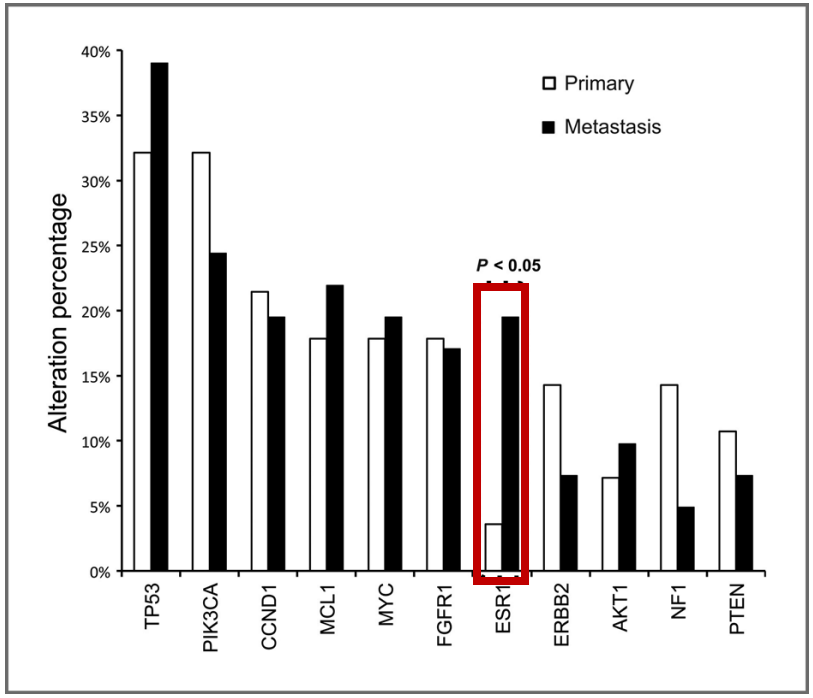
Table 1. Patient cohorts

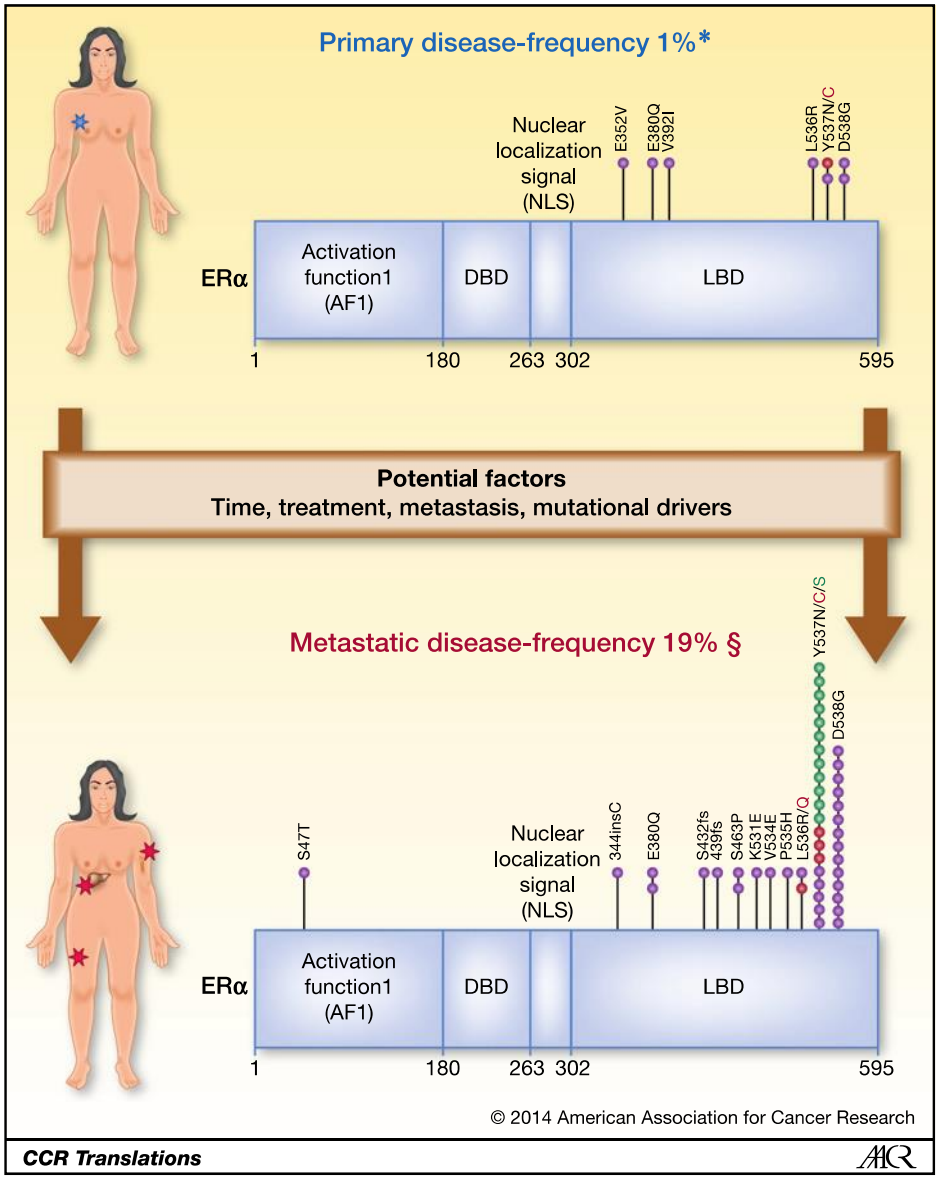
	Patient cohort	No. of specimens	Average number of treatments[a] before biopsy
LM^+	Metastases from patients with advanced ER^+ disease that were heavily pretreated before biopsy (participants in "Personalized Treatment Selection for Metastatic Breast Cancer" trial NCT00780676)	25	7
EM^+	Metastases from patients with early metastatic ER^+ disease	51	1–2
P^+	Primary ER^+ tumors	58	NA
M^-	Metastases from patients with ER^- disease	11	NA
P^-	Primary ER^- primary breast cancer disease	104	NA

Abbreviations: EM^+, early metastatic ER^+ disease; LM^+, late metastatic ER^+ breast cancer; M^-, ER^- metastatic disease; P^+, ER^+ primary breast cancer; and P^-, ER^- primary breast cancer.

[a]Including endocrine treatments and chemotherapy regimens.







Segal and Dowsett, CCR 2014

If ESR1 sequencing, what to sequence and with which method?

- Primary index tumor
- Biopsy of metastatic site
- Liquid biopsy

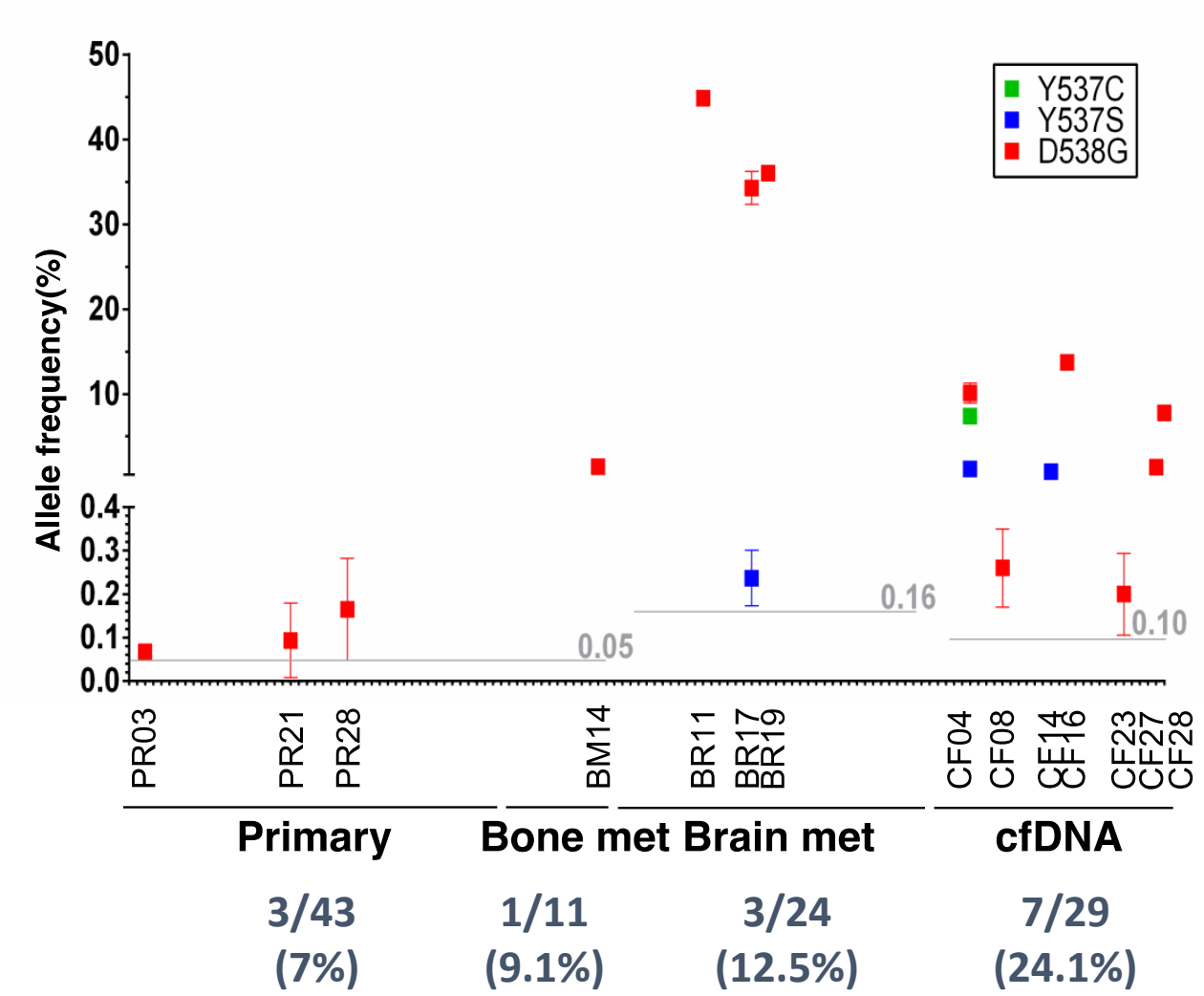
ESR1 allele frequency is usually below the detection limit of usual NGS

Austin et al, SABCS poster

patient	cf DNA date	mutations: gene	mutation (AA)	percent mutant allele	lines of therapy	lines of ET	bone vs visceral metastases	ET duration
1	2/10/2015	ESR1	L536R	17.24%	5	3	both	7
		ESR1	D538G	7.74%				
	3/31/2015	NF1	D1237V	0.16%				
	6/2/2015	AR	E323K	0.10%				
		NF1	D1237V	0.10%				
	7/20/2015	ND						
	9/29/2015	ND						
2	9/9/2014	ND			3	2	bone	3
	11/4/2014	ND						
	2/10/2015	ESR1	D538G	0.28%				
3	2/4/2015	ESR1	D538G	0.44%	6	3	both	6
		ESR1	Y537N	4.52%				
		ESR1	C530Y	0.83%				
		ESR1	Y537S	23.76%				
4	2/4/2015	ESR1	Y537N	12.53%	9	3	both	5.5
		ESR1	D538G	3.76%				
5	2/11/2015	ESR1	Y537S	0.94%	6	4	bone	4
		ESR1	D538G	0.40%				
6	2/24/2015	ESR1	Y537S	2.73%	6	2	both	2
7	5/22/2015	ESR1	D538G	0.72%	10	4	both	3
	3/9/2015	ESR1	D538G	1.13%				
8	3/13/2015	ESR1	Y537C	0.38%	3	3	both	3.5
9	3/27/2015	ESR1	Y537S	1.06%	5	4	bone	4.5

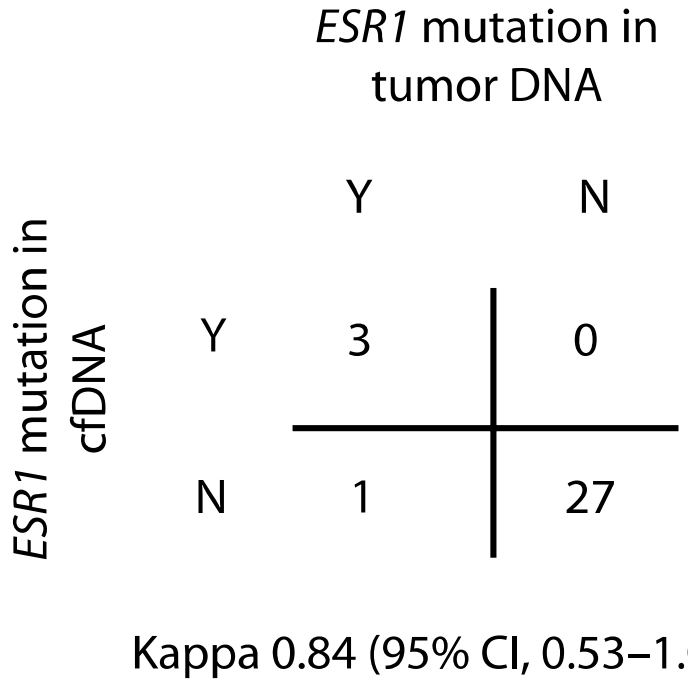
In brain mets, ESR1 mutant clones are dominant

Wang P et al, CCR 2015

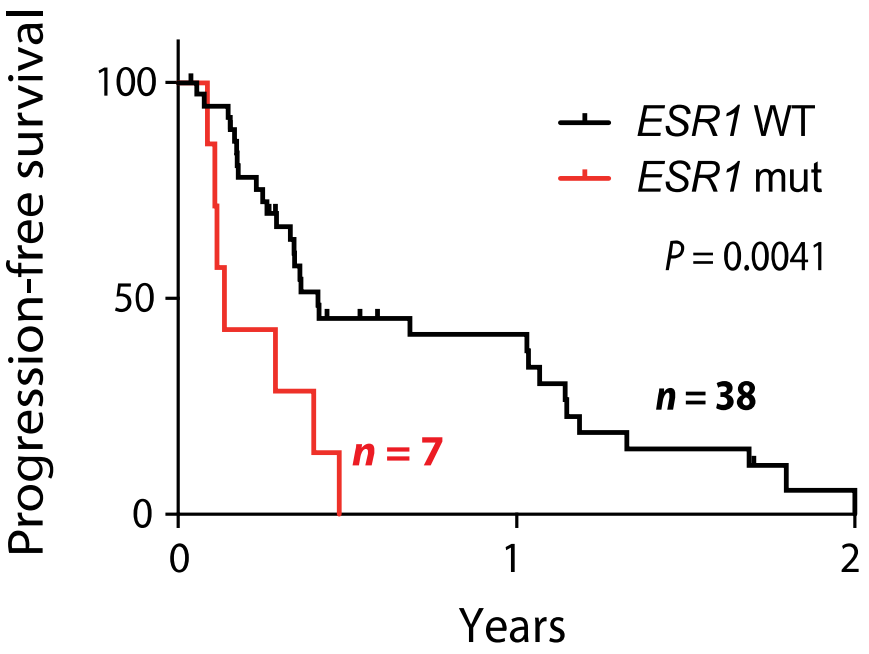


Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer

Schiavon et al, Science Trans Med 2015

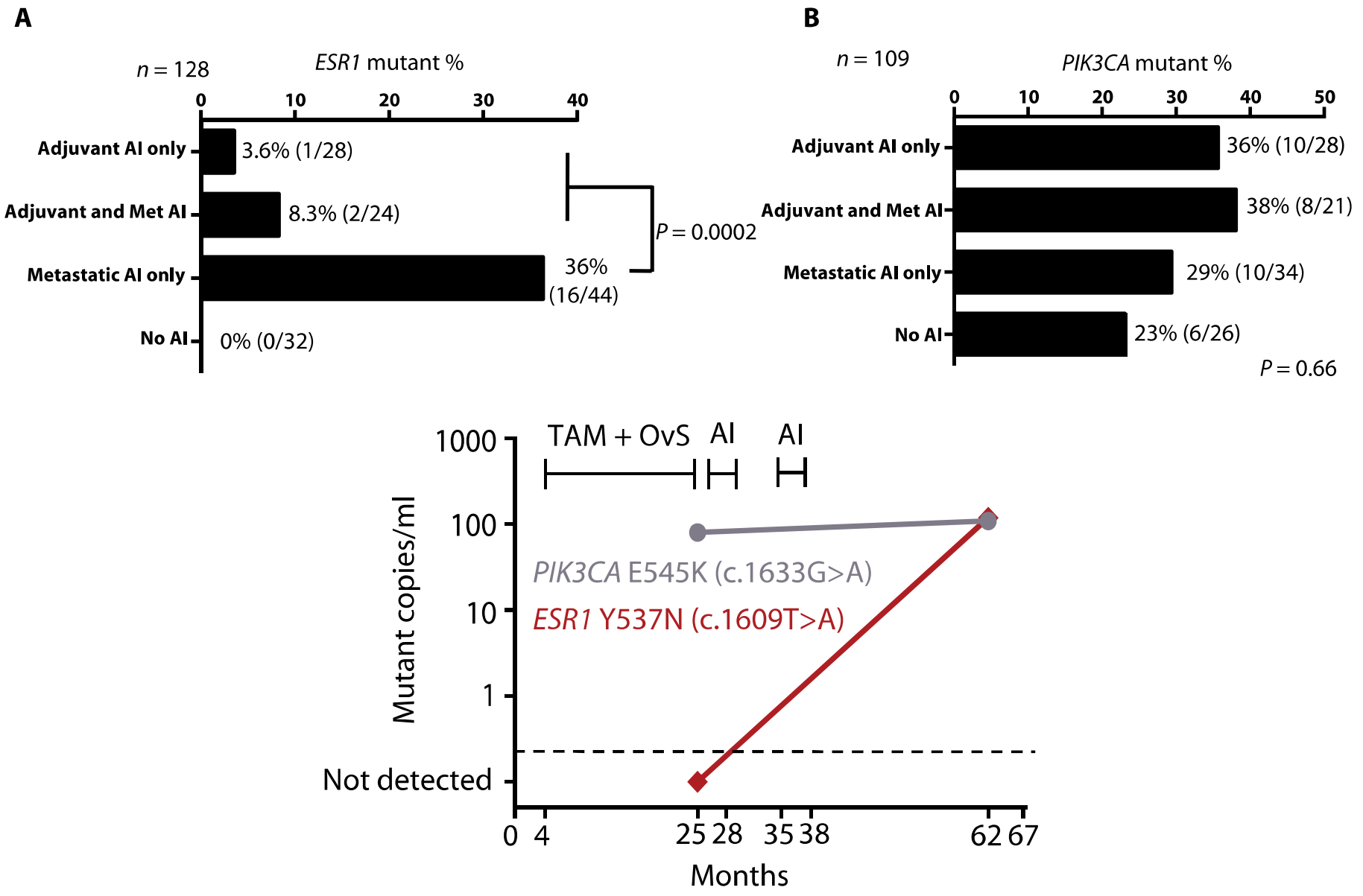


Kappa 0.84 (95% CI, 0.53–1.00)



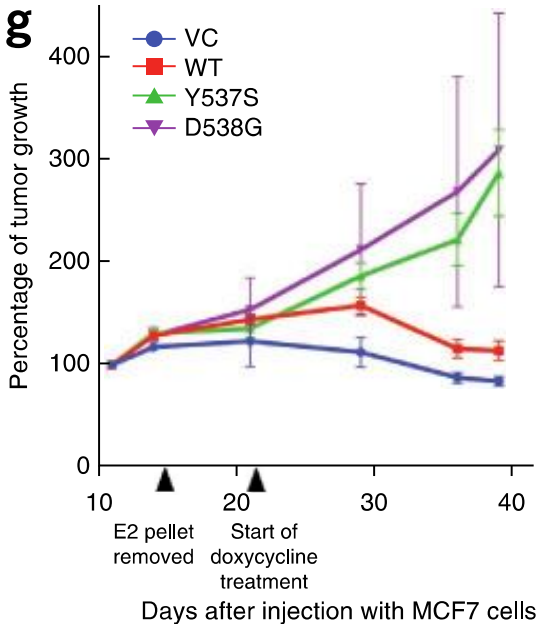
ESR1 mutation emerged when metastatic disease is treated with AI

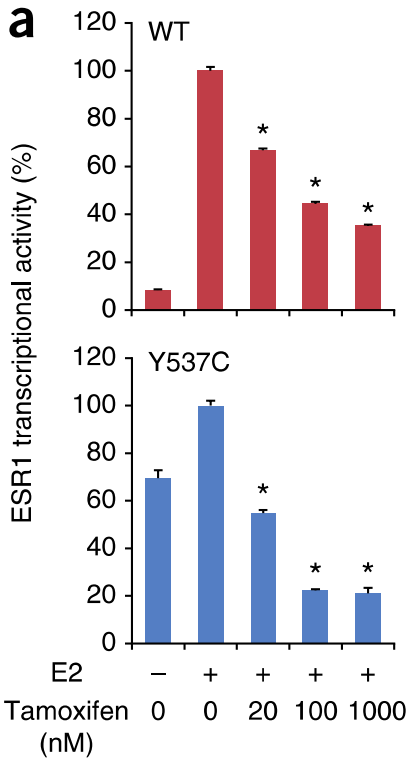
Schiavon et al, Science Trans Med 2015

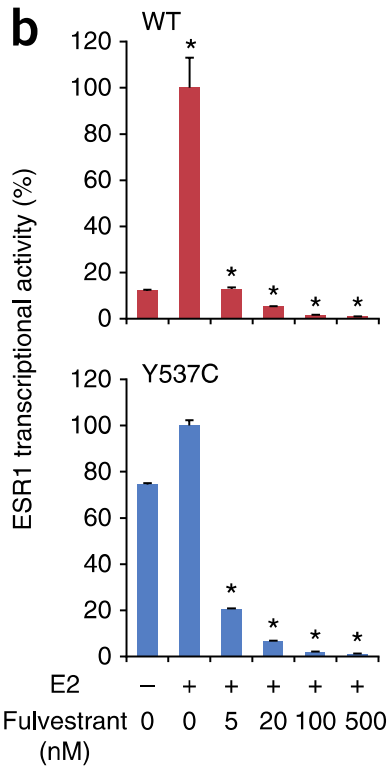


Therapeutic implication of ESR1 mutation

ESR1 mutants are resistant to estrogen deprivation but may be sensitive to high dose fulvestrant







Toy et al and Robinson et al, Nature Genetics 2013

BOLERO-2 ctDNA analysis

Chandarlapaty et al, SABCS S2-07

- 541 of 724 pts analyzed
- Found ESR1 hotspot mutations in 156 (28.8%)
- ESR1 mutation associated with shorter OS (20.7 m vs 32.1 m)

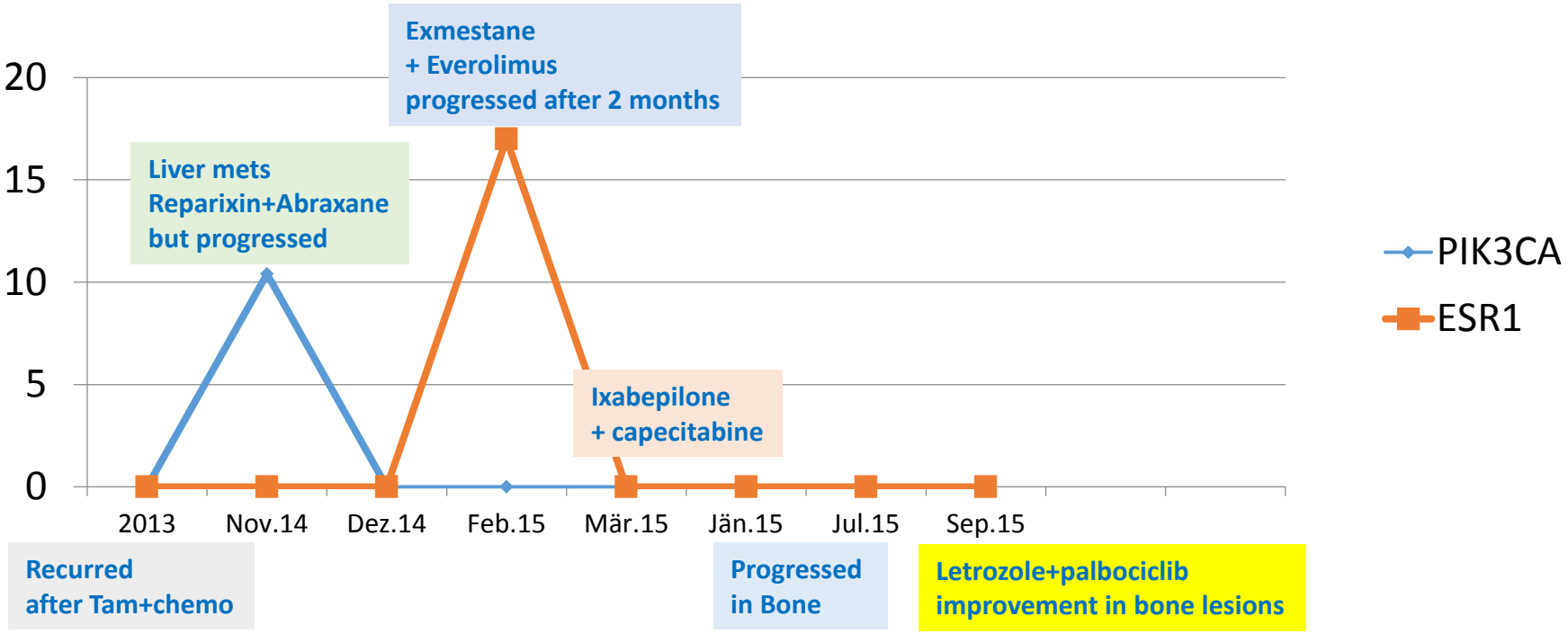
DFS according to mutation and treatment regimen

	frequency	exemestane	everolimus plus exemestane
D538G	83 (15.3%)	2.7m	5.8m
Y537S	42 (7.8%)	4.1m	4.2m
D538G + Y537S	30 (5.5%)	2.78m	5.42m
All pts	541	3.2m	7.8m

Serial monitoring of ESR1 mutation in cfDNA

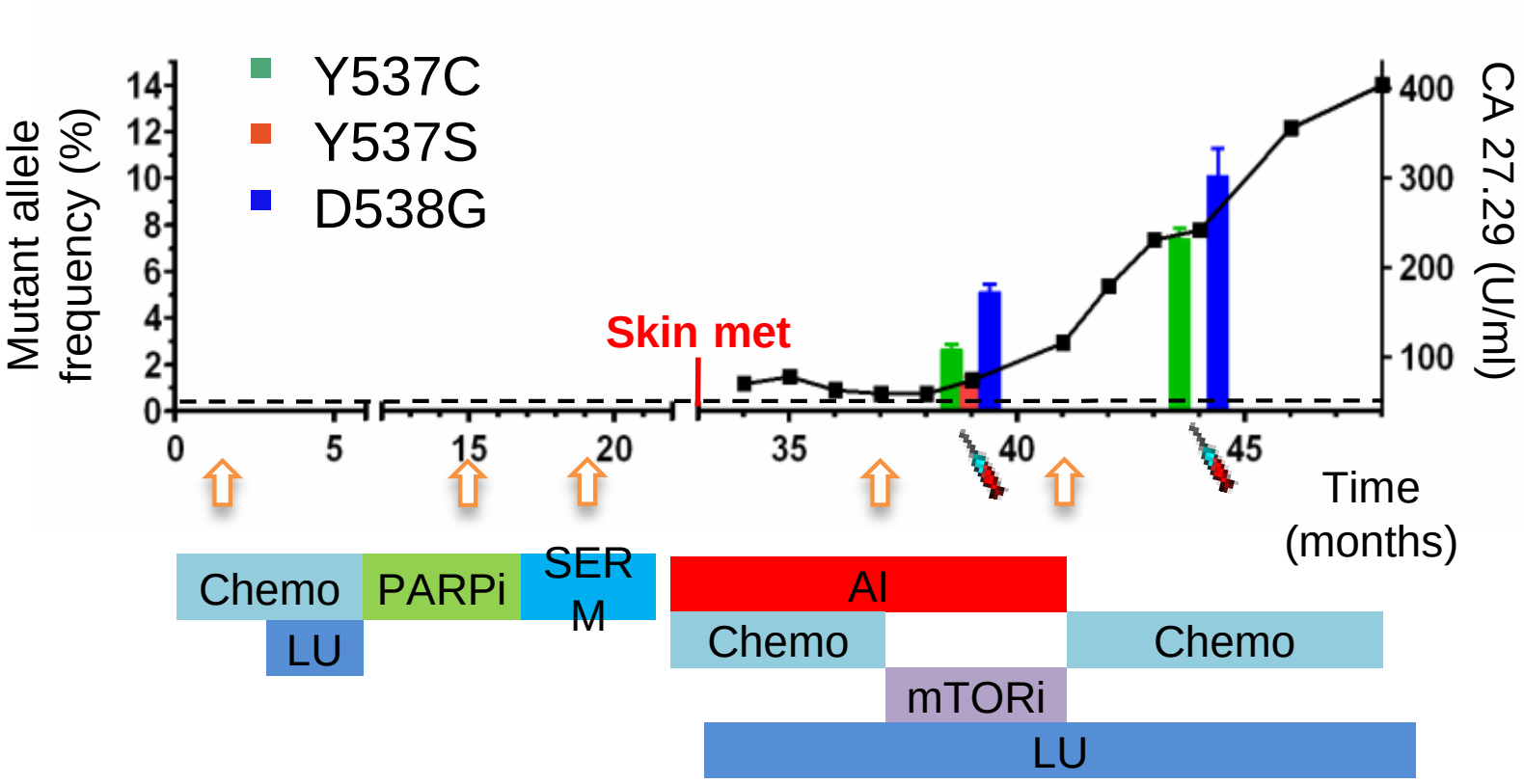
ctDNA mutatiuon profiling (using Guardant360 Panel)

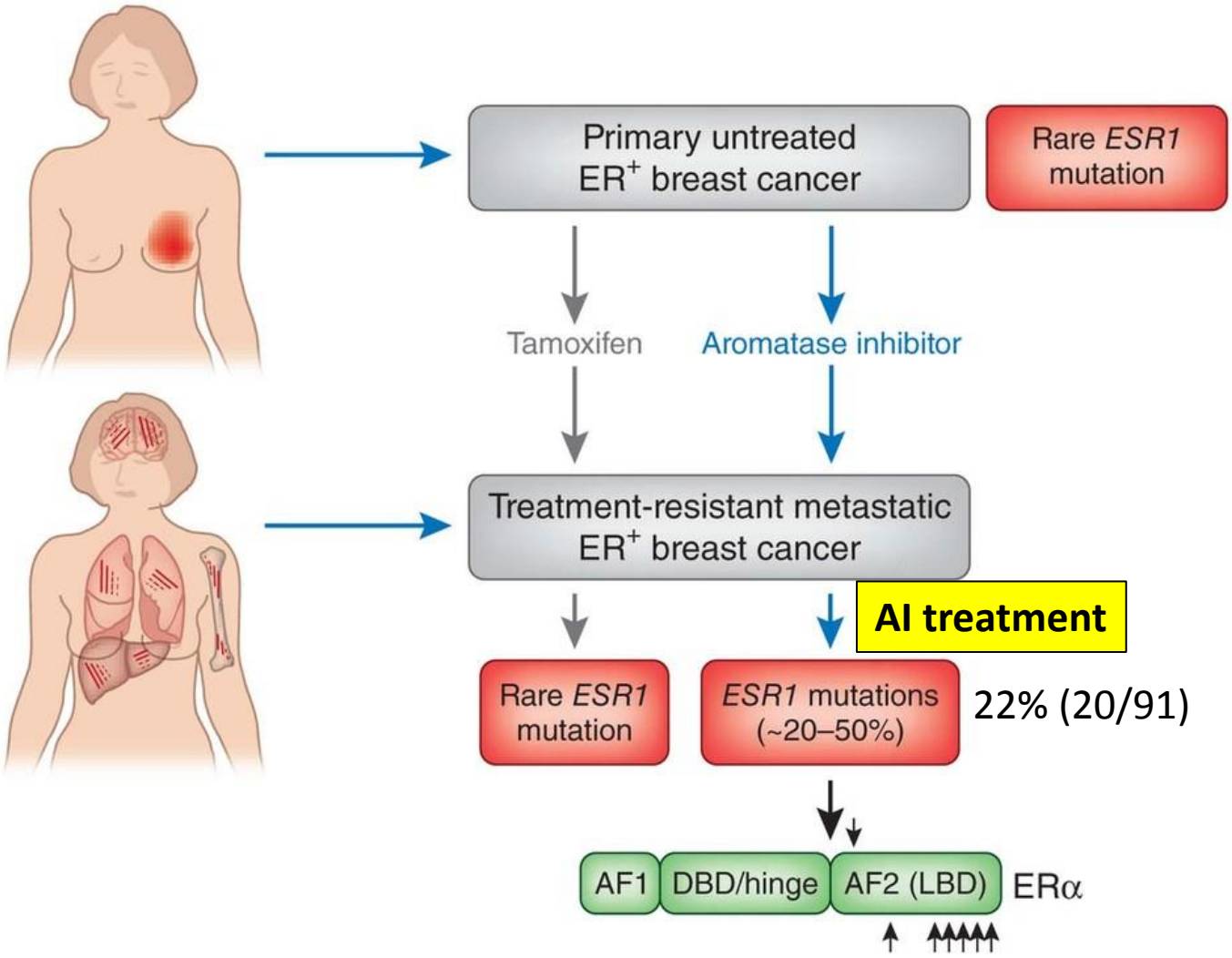
Austin et al, SABCS poster



Rising ESR1 mutant allele frequency is associated with rise in CA27.29

Wang P et al, CCR 2015





Oesterreich and Davidson, Nature Genetics 2013

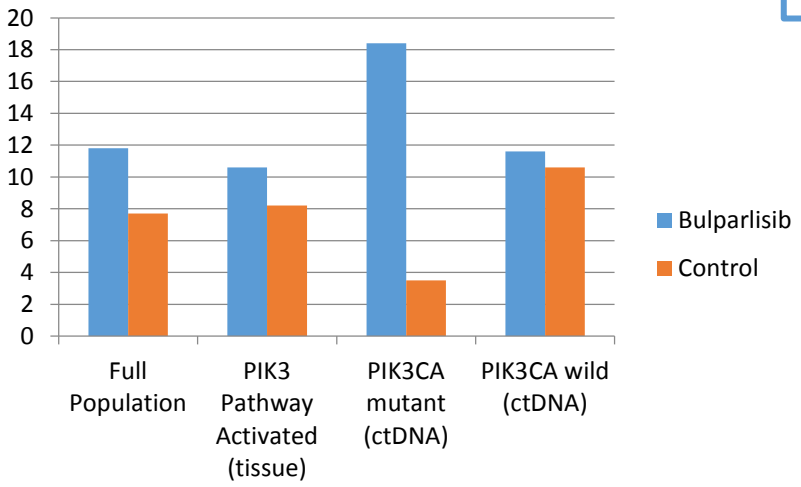
PIK3CA mutation as a predictive marker for PIK3CA inhibitors

PIK3CA inhibitor (Bulparlisib)

BELLE-2

AI failure (N=1147)

- Fulvestrant 500mg + placebo
- Fulvestrant 500mg + bulparlisib

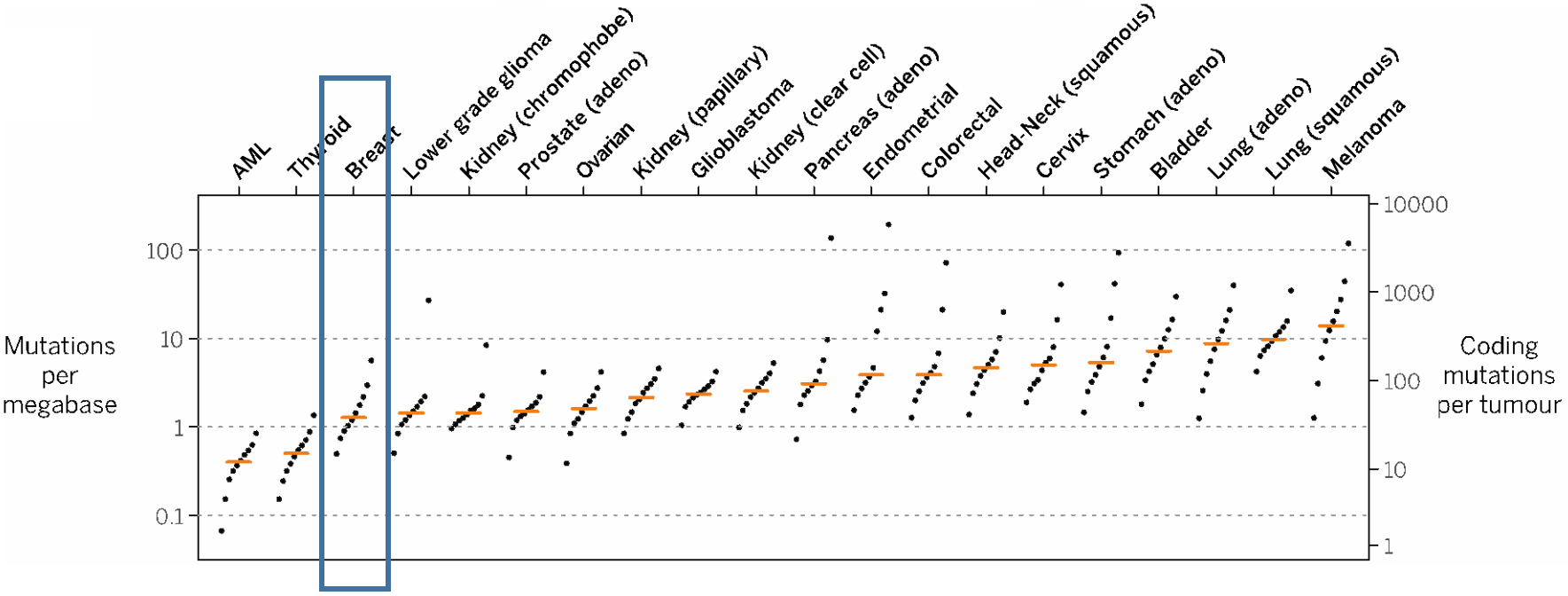


Median PFS, Mos (95% CI)	Buparlisib + Fulvestrant	Placebo + Fulvestrant	HR (95% CI)	*P* Value
Overall population (n=1147)	6.9 (6.8-7.8)	5.0 (4.0-5.2)	0.78 (0.67-0.89)	< .001
PI3K-activated pts (n=372)	6.8 (4.9-7.1)	4.0 (3.1-5.2)	0.76 (0.60-0.97)	.014†
ctDNA *PIK3CA* mutant (n = 200)	7.0 (5.0-10.0)	3.2 (2.0-5.1)	0.56 (0.39-0.80)	< .001
ctDNA *PIK3CA* non mutant (n = 387)	6.8 (4.7-8.5)	6.8 (4.7-8.6)	1.05 (0.82-1.34)	.642

From Baselga et al, SABCS 2015, S6-01

Is there a role for immune check point therapy for ER+ metastatic BC?

Overall mutation burden (TCGA)



But a subset of ER+ mets have higher mutation burden similar to TNBC

Genome sequencing for ER+ metastatic BC

- Most of the KOL surveyed do not order sequencing for ER+ metastatic breast cancer in clinical practice
  - The ESMO ABC2 consensus guidelines recommend using targeted therapy if there has ever been receptor positivity
  - Sequencing based targeted approaches low yield
    - SAFIR01 – 43/423 pts received targeted Tx – 4 objective response

- Focused assays for ctDNA - potential utility as a predictive markers for
  - CDK4/6 inhibitors (Palbociclib)
  - SERDs
  - PIK3CA inhibitors

- Exome/RNAseq - potential utility as a predictive marker for
  - Immune Checkpoint therapy