2015 San Antonio Breast Cancer Symposium Review

Survivorship, chemo prevention, bio markers

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Abstracts

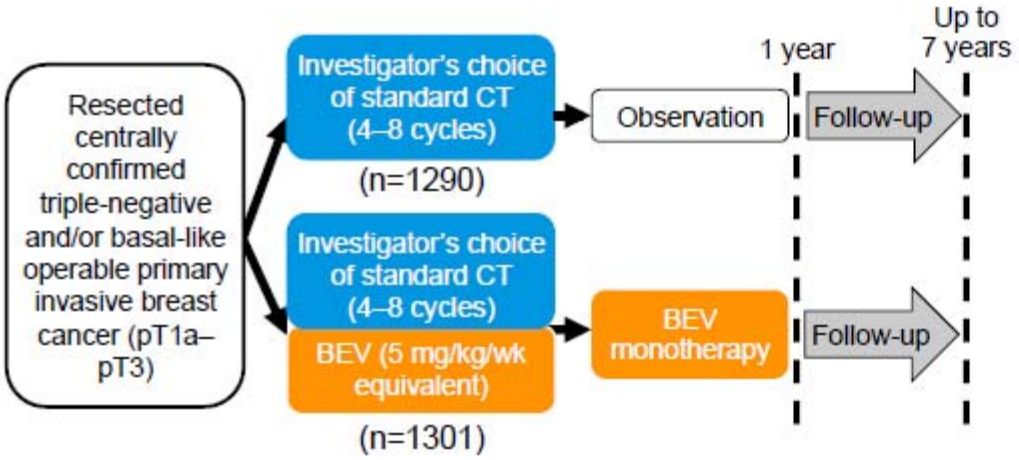
- Molecular prognostic factors in BEATRICE (S01-01)
- TILs in lobular cancer (S01-02)
- Stromal tumor infiltrating lymphocytes in primary triple negative breast cancer (S01-03)
- Early versus late drivers (S04-01)
- Anastrozole versus tamoxifen in DCIS (S6-03, S05-04)

Analysis of molecular prognostic factors associated with tumor immune and stromal microenvironment in BEATRICE, an open-label phase 3 trial in early triple-negative breast cancer (eTNBC)

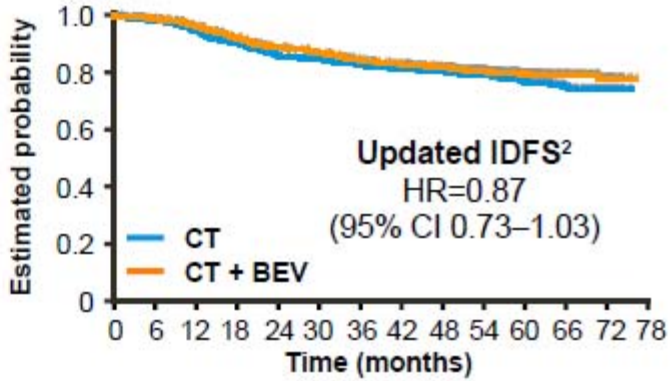
Molinero et al SABCS 2015

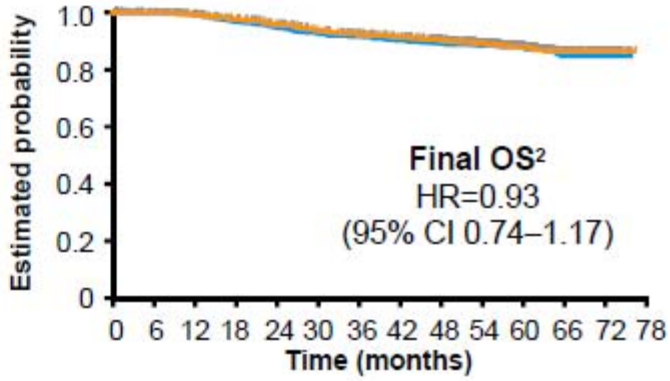
S1-01 Beatrice

BEATRICE: Open-label phase III adjuvant trial in TNBC[1,2]



- Data cutoff for final OS analysis: June 30, 2014
- Median follow-up: 56 months





BEV = bevacizumab; CI = confidence interval; CT = chemotherapy; HR = hazard ratio;
IDFS = invasive disease-free survival; OS = overall survival; TNBC = triple-negative breast cancer

[1]Cameron et al. Lancet Oncol 2013
[2]Bell et al. SABCS 2014

Molinero et al SABCS 2015

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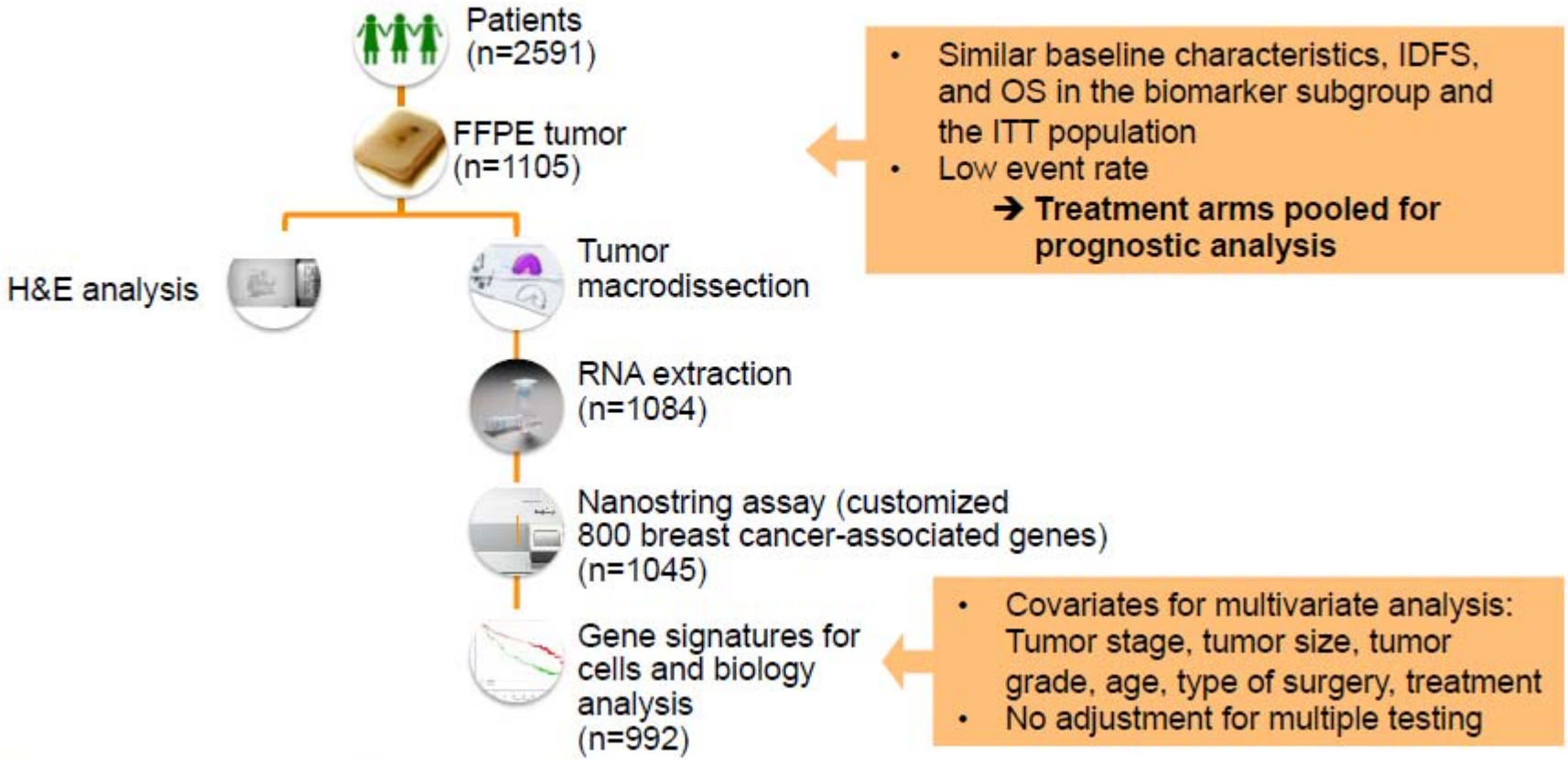
Methodology for exploratory retrospective prognostic biomarker analyses



FFPE = formalin-fixed paraffin-embedded; H&E = hematoxylin and eosin stain; ITT = intent-to-treat

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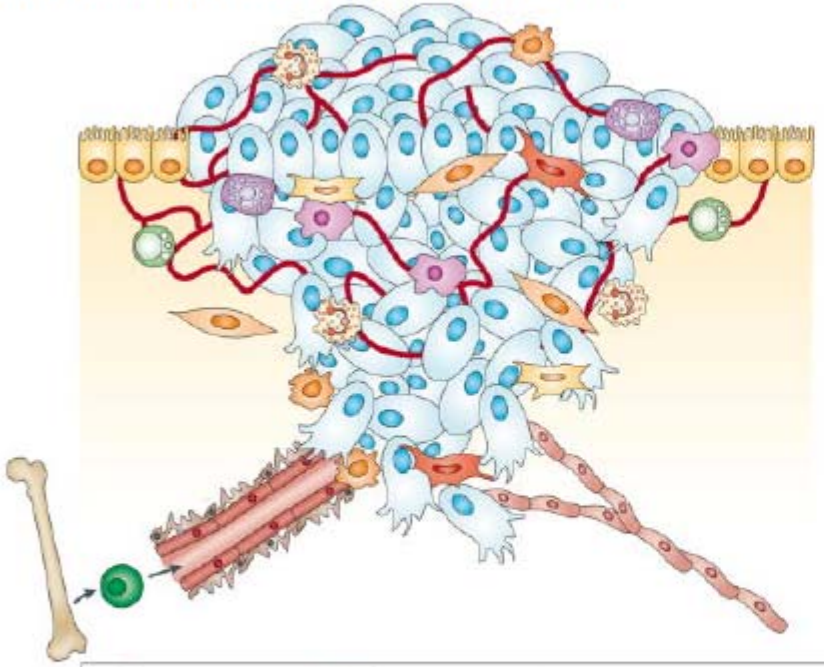
Tumor microenvironment

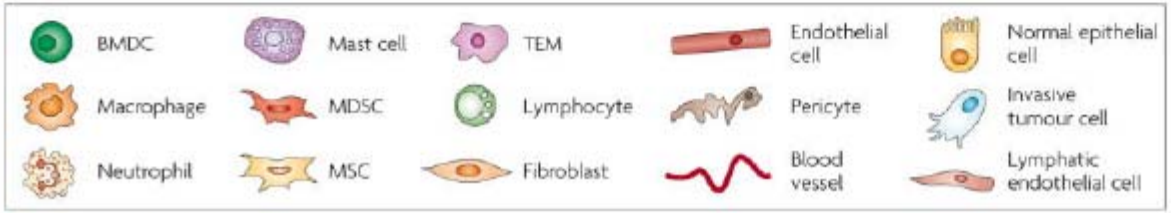


- Tumor cells
- Cancer-associated fibroblasts
- Microvasculature: endothelial cells, pericytes

Poor outcome

- Immune cells (TILs)[1,2]: macrophages, T cells[3], B cells, natural killer cells, dendritic cells

Good outcome



TIL = tumor-infiltrating lymphocyte

Joyce & Pollard. Nat Rev Cancer 2009 (adapted)
[1]Denkert et al. JCO 2010
[2]Loi et al. Ann Oncol 2014
[3]Ali et al. Ann Oncol 2014

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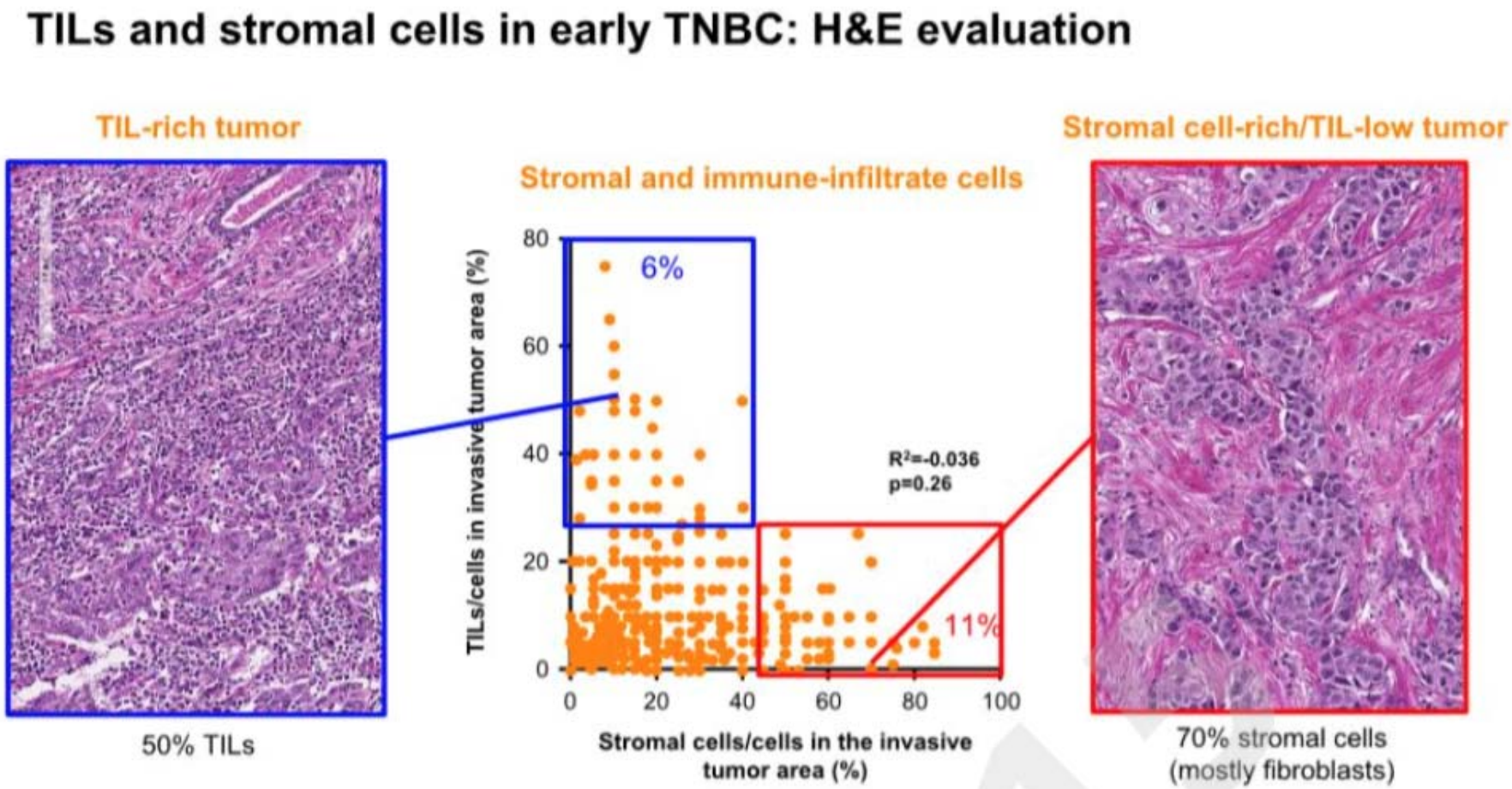

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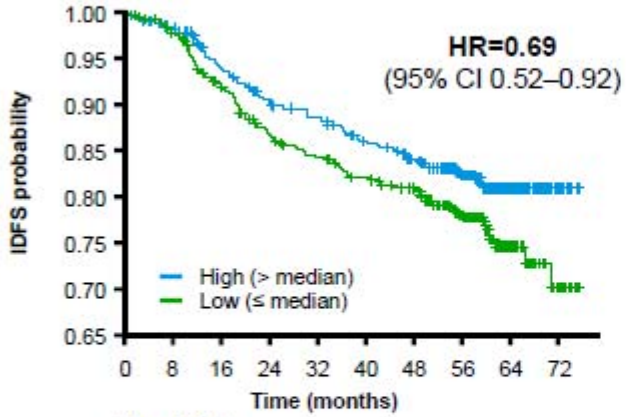
TILs linked to better prognosis, while higher levels of stromal cells associated with worse prognosis (IDFS[a])

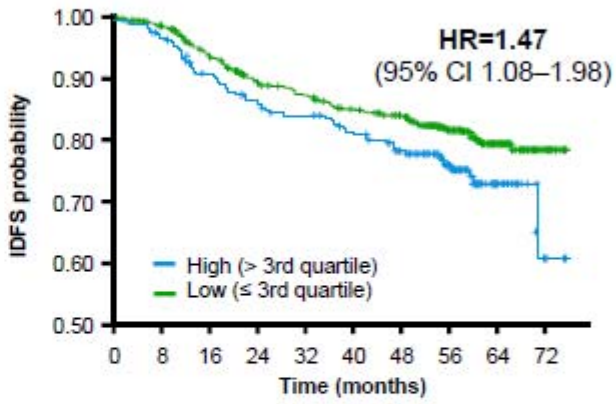
TILs



Quartile cutoff	No. of IDFS events/patients Low	High	IDFS HR	High better	Low better	p-value
1	42/193	154/797	0.89			0.49
2	109/486	87/504	0.69			0.013
3	129/541	67/449	0.54			<0.001

0.2 0.5 1 2
HR (95% CI)

Stromal cells



Quartile cutoff	No. of IDFS events/patients Low	High	IDFS HR	High better	Low better	p-value
1	33/186	163/804	1.16			0.44
2	71/400	125/590	1.20			0.23
3	126/686	70/304	1.47			0.013

0.5 1 2 5
HR (95% CI)

Median TILs = 7%; 3rd quartile stromal cells = 25%

[a]OS results showed a similar pattern to IDFS

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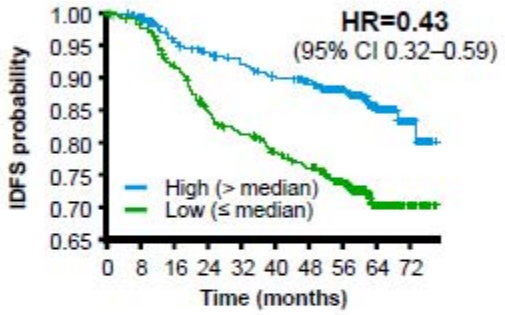
CD8 effector T-cell and immune checkpoint signatures associated with improved prognosis (IDFS[a])

CD8 effector T-cell signature[b]

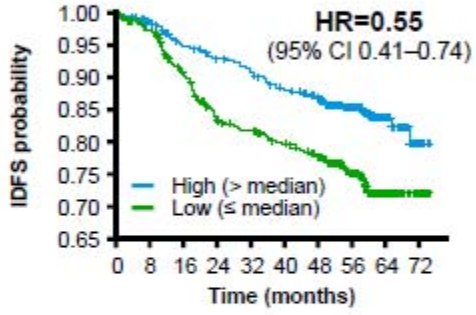


Quartile cutoff	No. of IDFS events/patients Low	High	IDFS HR	p-value
1	72/248	124/744	0.46	<0.001
2	131/496	65/496	0.43	<0.001
3	168/744	28/248	0.49	<0.001

High better | Low better

0.2 0.5 1 2
HR (95% CI)

Immune checkpoint signature[c]



Quartile cutoff	No. of IDFS events/patients Low	High	IDFS HR	p-value
1	63/248	133/744	0.63	0.0031
2	122/496	74/496	0.55	<0.001
3	167/744	29/248	0.51	0.0012

High better | Low better

0.2 0.5 1 2
HR (95% CI)

[b]CD8A, GZMA, GZMB, IFNG, EOMES, PRF1
[c]PD-L1, PD-L2, IDO1

[a]OS results showed a similar pattern to IDFS

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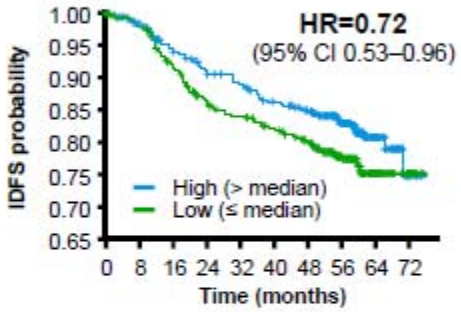
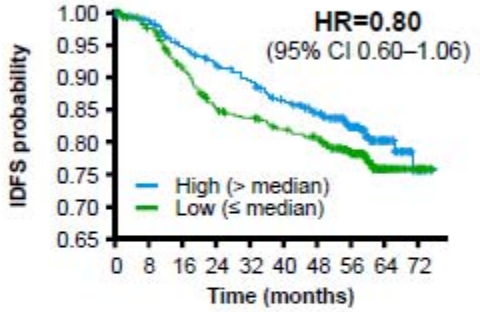
B cells and macrophages: Association with good prognosis less pronounced than for CD8 effector T cells (IDFS[a])

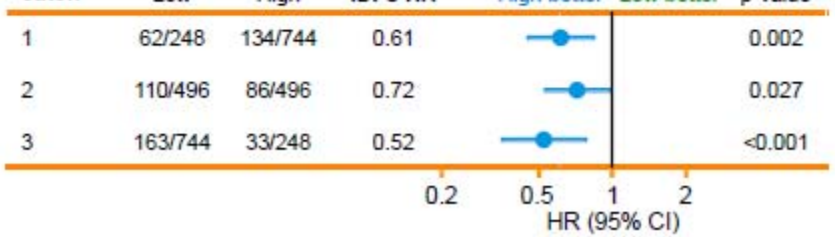
B-cell signature[b]



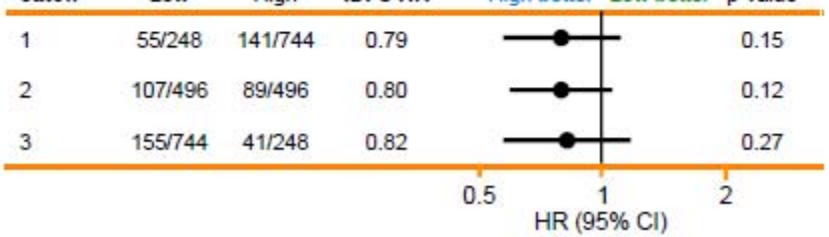
Macrophage signature[c]



Quartile cutoff	No. of IDFS events/patients: Low	High	IDFS HR	p-value
1	62/248	134/744	0.61	0.002
2	110/496	86/496	0.72	0.027
3	163/744	33/248	0.52	<0.001



Quartile cutoff	No. of IDFS events/patients: Low	High	IDFS HR	p-value
1	55/248	141/744	0.79	0.15
2	107/496	89/496	0.80	0.12
3	155/744	41/248	0.82	0.27



[b]CD22, CD79b
[c]CD68, ITGAM, ITGAX

[a]OS results showed a similar pattern to IDFS

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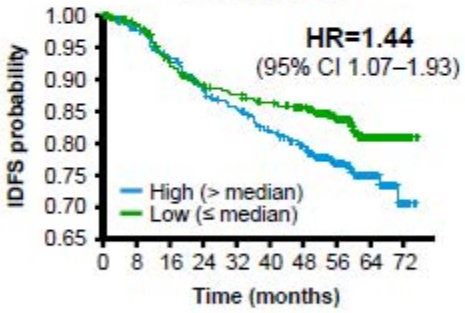
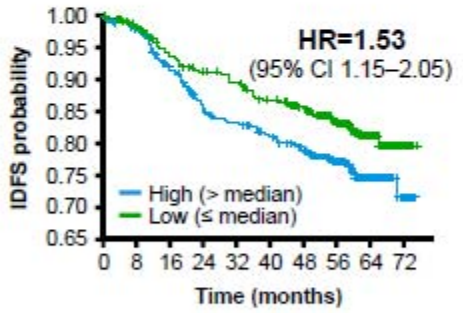
Stroma signatures associated with worse outcome in BEATRICE (IDFS)

- Cancer-associated fibroblasts are linked to worse prognosis in colorectal carcinoma[1]
- Microvasculature and angiogenesis supports tumor growth and early metastases. ESM1, a transcriptional target of VEGF-A,[2] is a biomarker of tip cells during tumor neoangiogenesis[3]
- Notch signaling influences neoangiogenesis and pericyte formation[4]

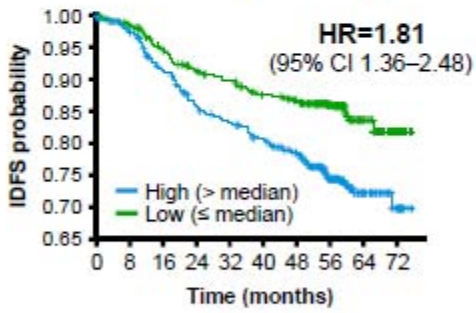
Cancer-associated fibroblast[a]



ESM-1



Notch pathway[c]



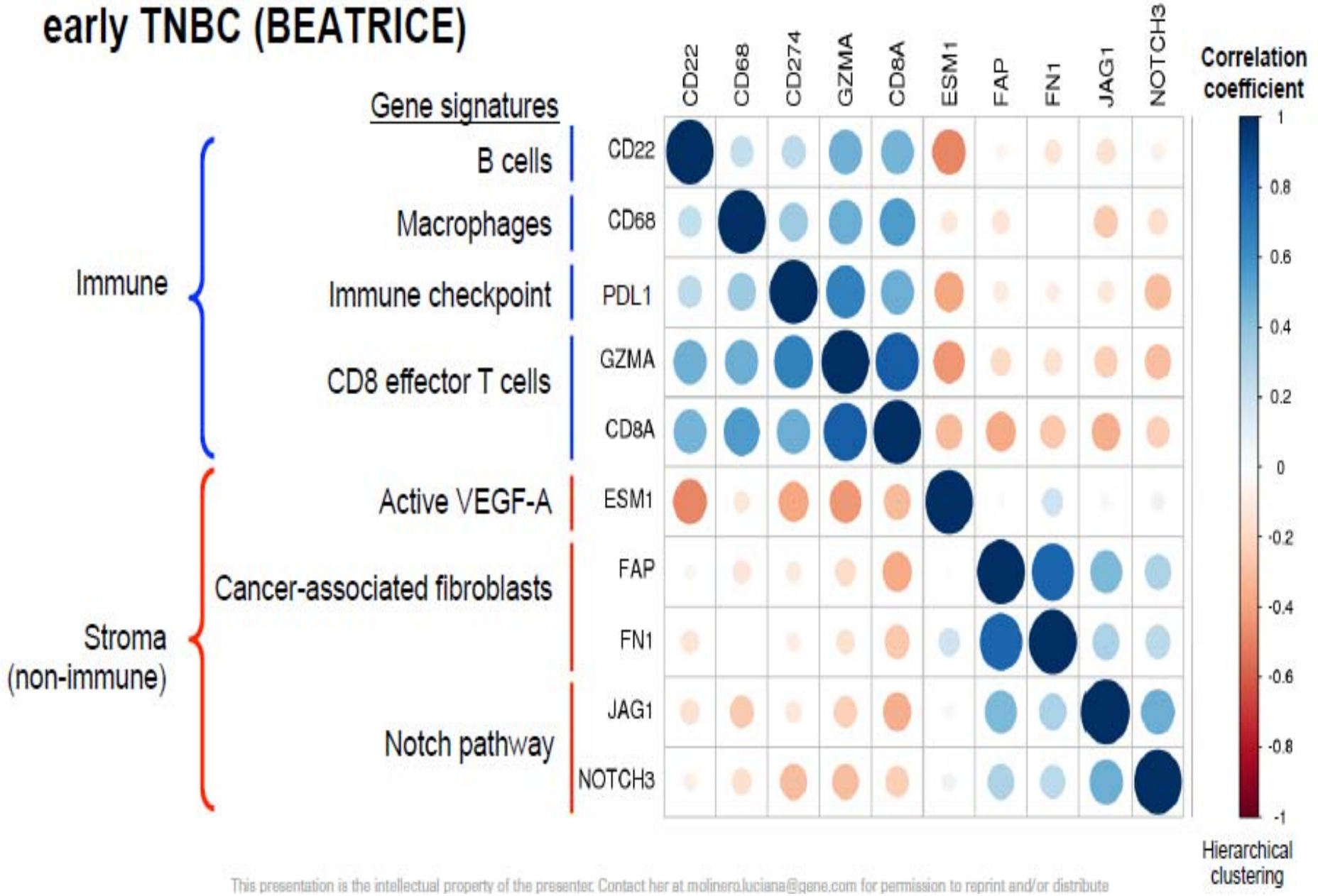
No prognostic or predictive effect of VEGF-A, VEGF-C RNAs, and microvasculature signature[b]

[a]FAP, FN1, MMP2, MMP11, PDGFRB
[b]LAMA4, NID2, CDH5, FLT1, CD34, KCNE3, PRND
[c]NOTCH1, NOTCH2, NOTCH3, JAG1, DLL1, DLL4
VEGF = vascular endothelial growth factor

[1]Calon et al. Nat Genet 2015
[2]Brauer et al. Clin Cancer Res 2013
[3]Roudnicky et al. Cancer Res 2013
[4]Stewart et al. Blood 2011

Molinero et al SABCS 2015

Immune and stromal gene signatures are non-overlapping in early TNBC (BEATRICE)



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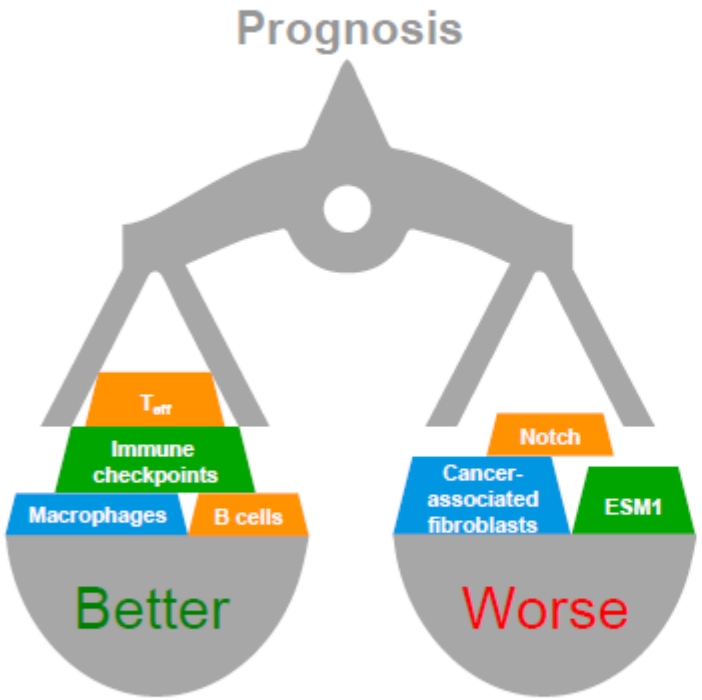
Summary from the BEATRICE dataset



- Immune cells improve prognosis in early TNBC, albeit with differing magnitude of effect:
  - Cytotoxic CD8 effector T-cell and immune checkpoint signatures are highly prognostic
  - B-cell signature is weakly prognostic
  - Macrophages are not prognostic
- Stromal cells/function in invasive tumors drive poor prognosis in early TNBC
  - Stromal factors affecting prognosis include cancer-associated fibroblasts, ESM1, and Notch pathway

Signals derived from the stroma and immune system may influence prognosis in early TNBC

- Results of these exploratory analyses require validation in other annotated tissue sets

T_{eff} = CD8 effector T cell

Molinero et al SABCS 2015

Lymphocytic infiltration in invasive lobular breast cancer

- Desmedt et al

S01-2 TILs in lobular cancer

- Tumor infiltrating lymphocytes (TILs) are increased in TNBC and HER2 + breast cancer
- Associated with higher pCR rates after neo-adjuvant chemo
- Associated with improved outcomes
- Invasive lobular breast cancer accounts for 5-15% of breast cancer and is mostly ER + and HER2 – characterized by late relapses
- The objective of this study was to evaluate TILs in ILBC

Desmedt et al SABCS 2015

Patients and samples (n=614)

Age (years)	%
<50	201 (33)
≥50	413 (67)

Tumor size (cm)	%
<2	248 (40)
≥2	366 (60)

Nodal status	%
Negative	296 (48)
Positive	296 (48)
Unknown	22 (4)

Histological subtype	%
Classic	301 (49)
Alveolar	100 (16)
Solid	89 (15)
Mixed, non classic	91 (15)
Trabecular	33 (5)

Receptor status	%
ER-	37 (6)
ER+ PgR-	115 (19)
ER+ PgR+	461 (75)
Unknown	1 (0)

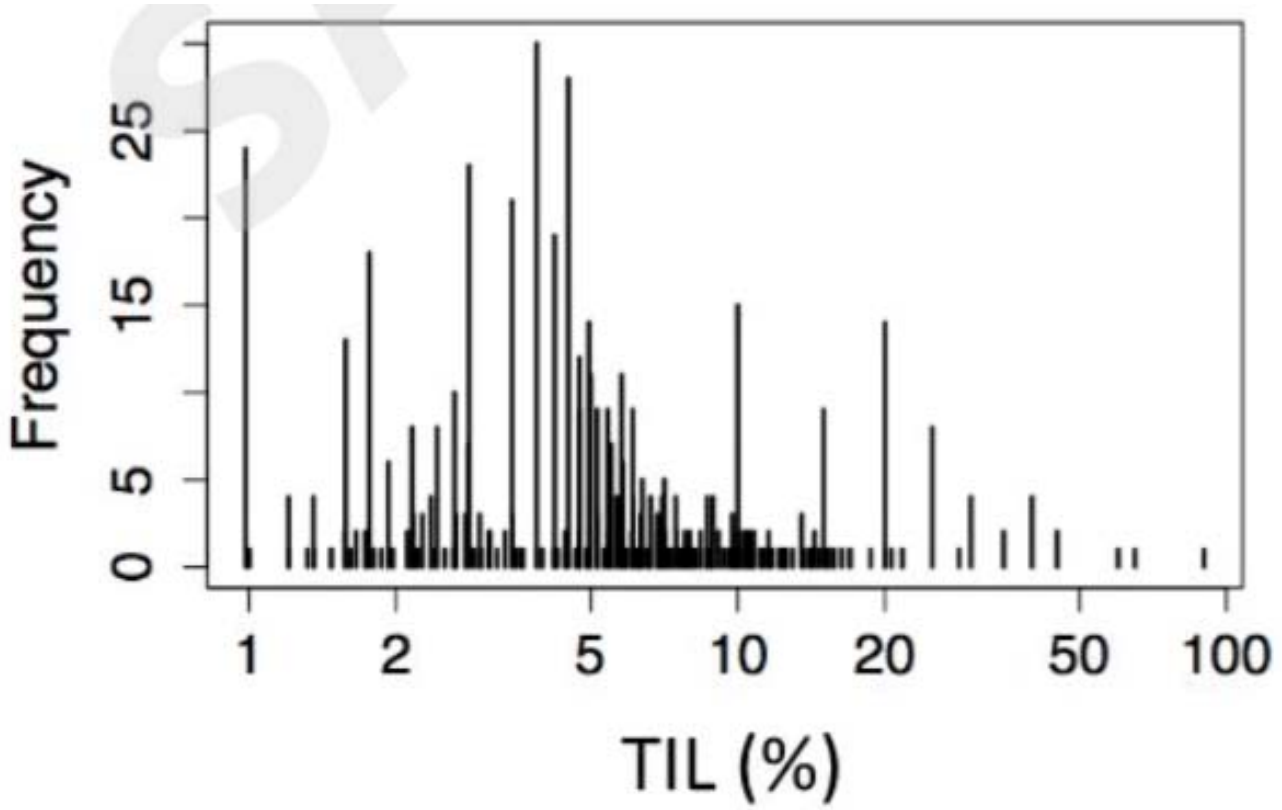
Ki67	%
<10	161 (26)
10-19	255 (42)
20 or >	190 (31)
Unknown	8 (1)

Her-2	%
Negative	586 (95)
Positive	27 (5)
Unknown	2 (0)

Tumor grade	%
G1	76 (12)
G2	438 (71)
G3	95 (16)
Unknown	5 (1)

Desmedt et al SABCS 2015

Distribution of TIL in ILBC



Median= 5%

IQR= 3-7%

Only 15% of samples have >10% TIL

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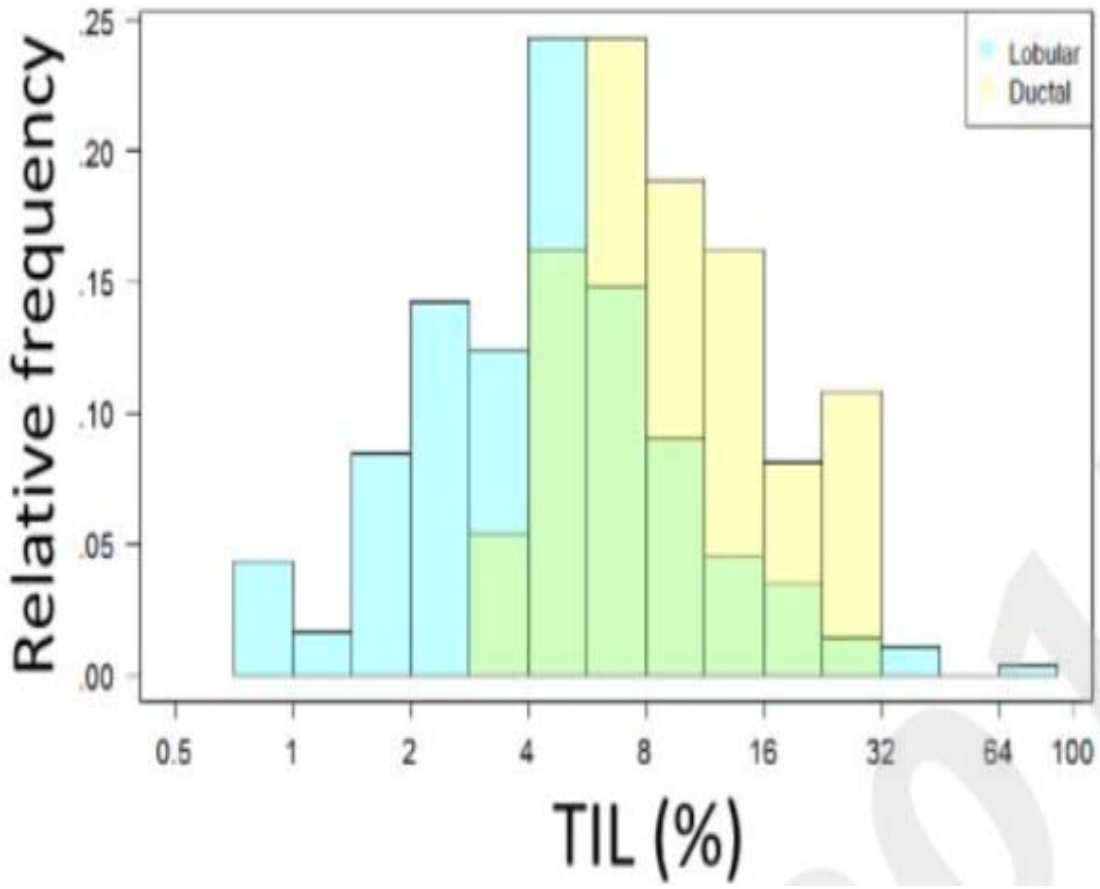
Distribution of TIL: ILBC vs IDBC



ER+/HER2-
IDBC (n=37)
vs
ER+/HER2-
ILBC (n=555)

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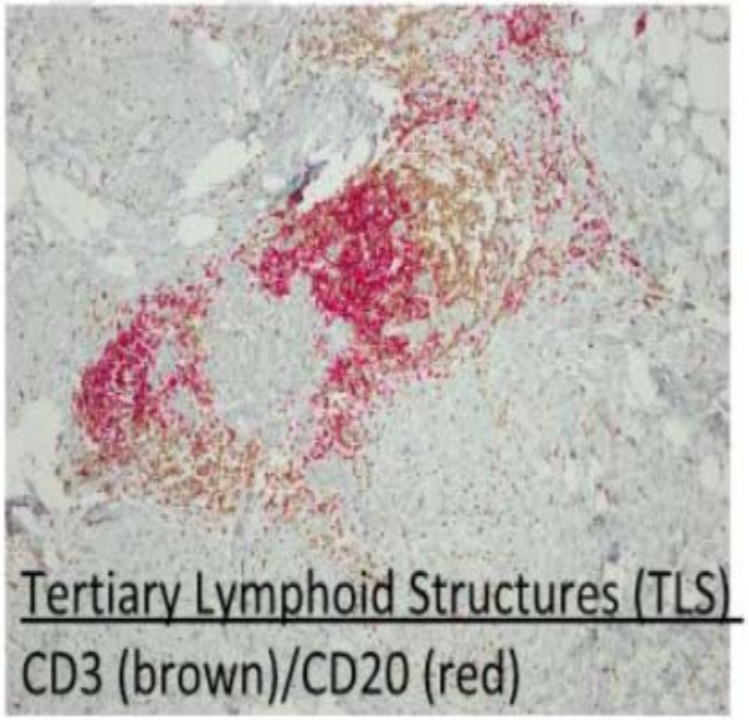
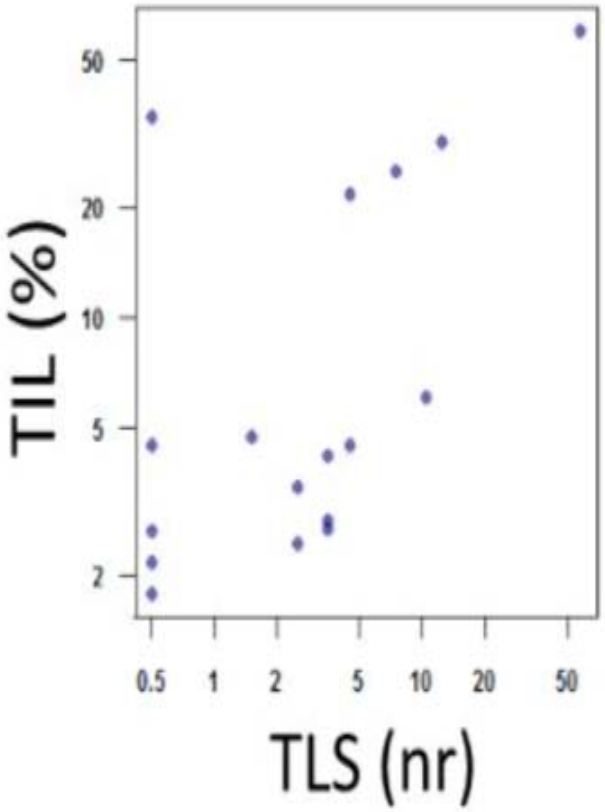
Lymphocytic organization





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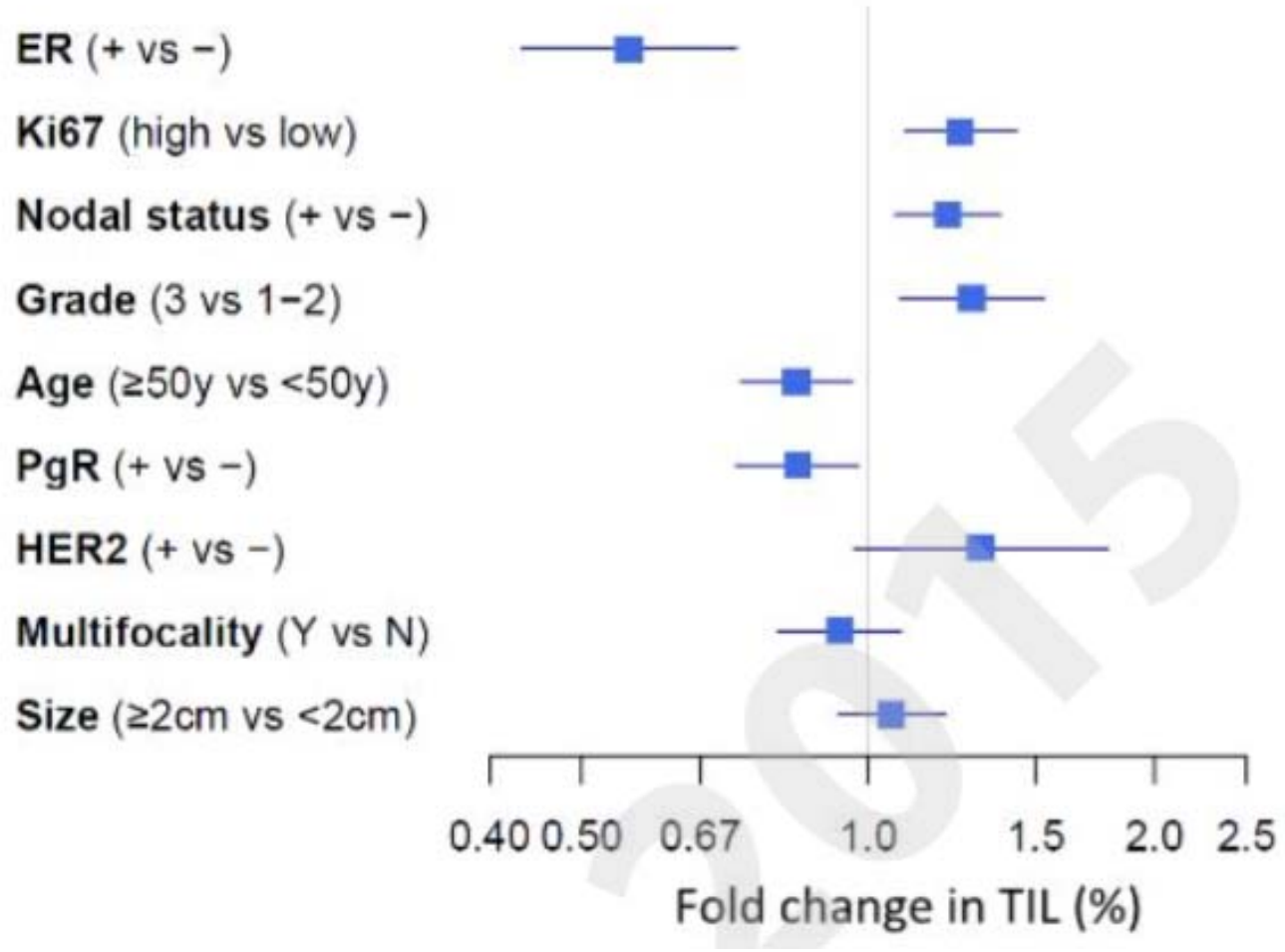
TIL and clinicopathological variables



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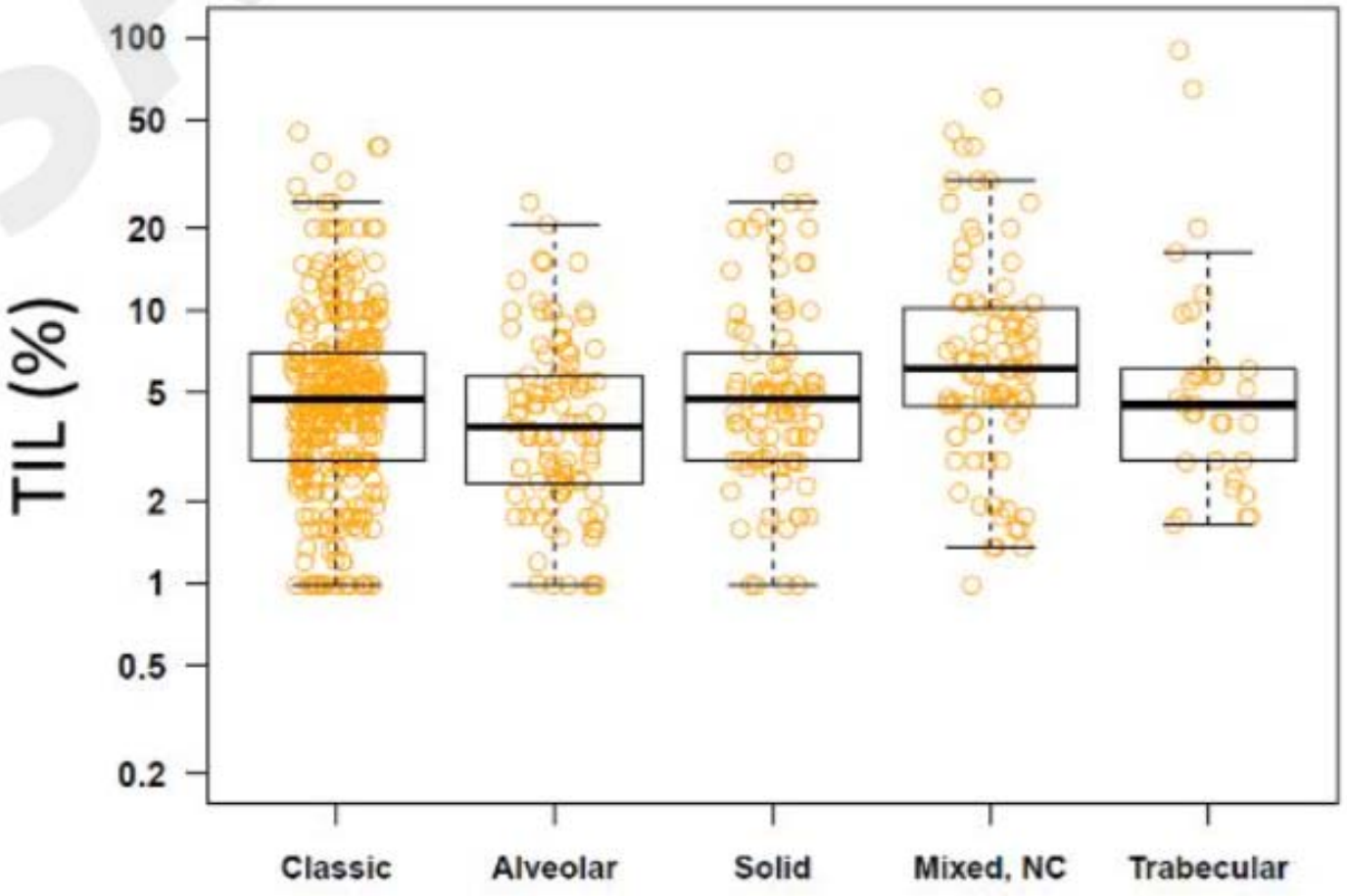
TIL and clinicopathological variables



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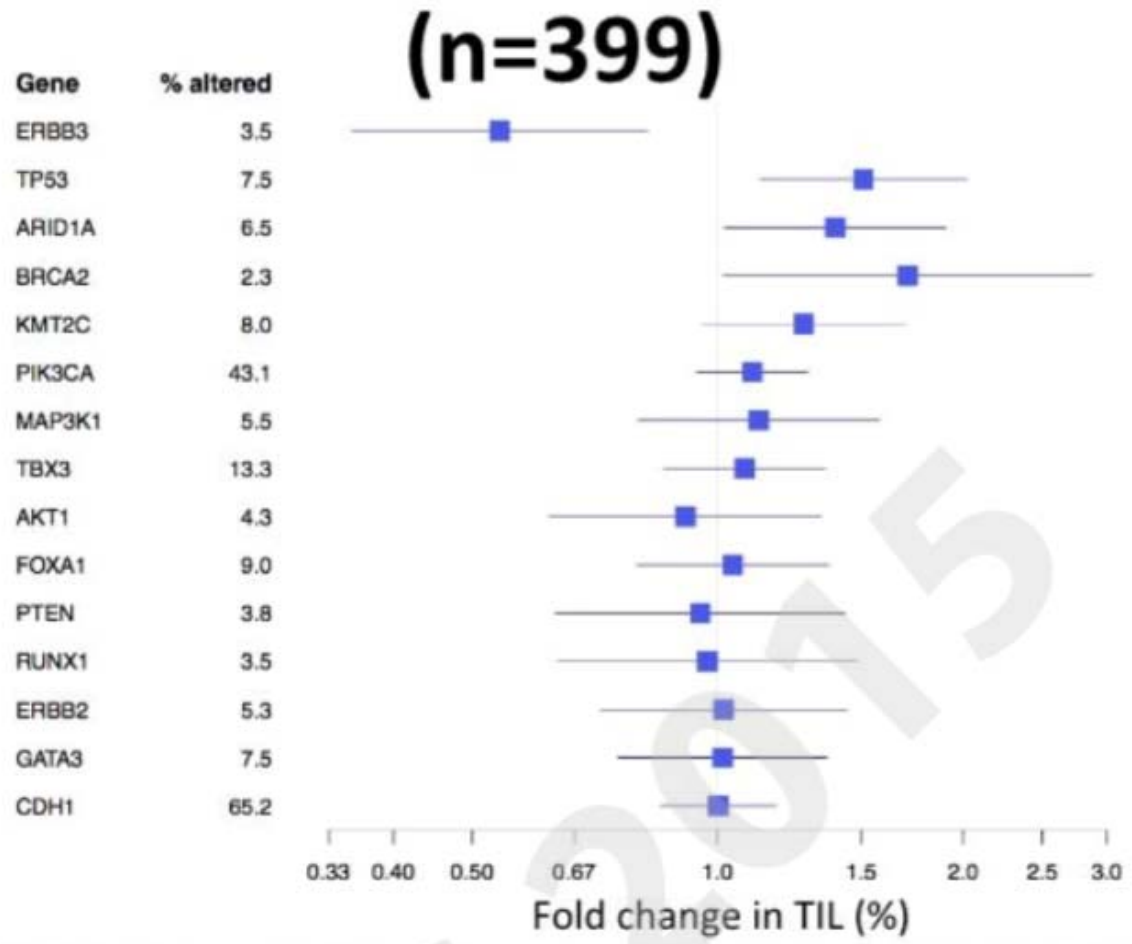
Association of TIL and mutations



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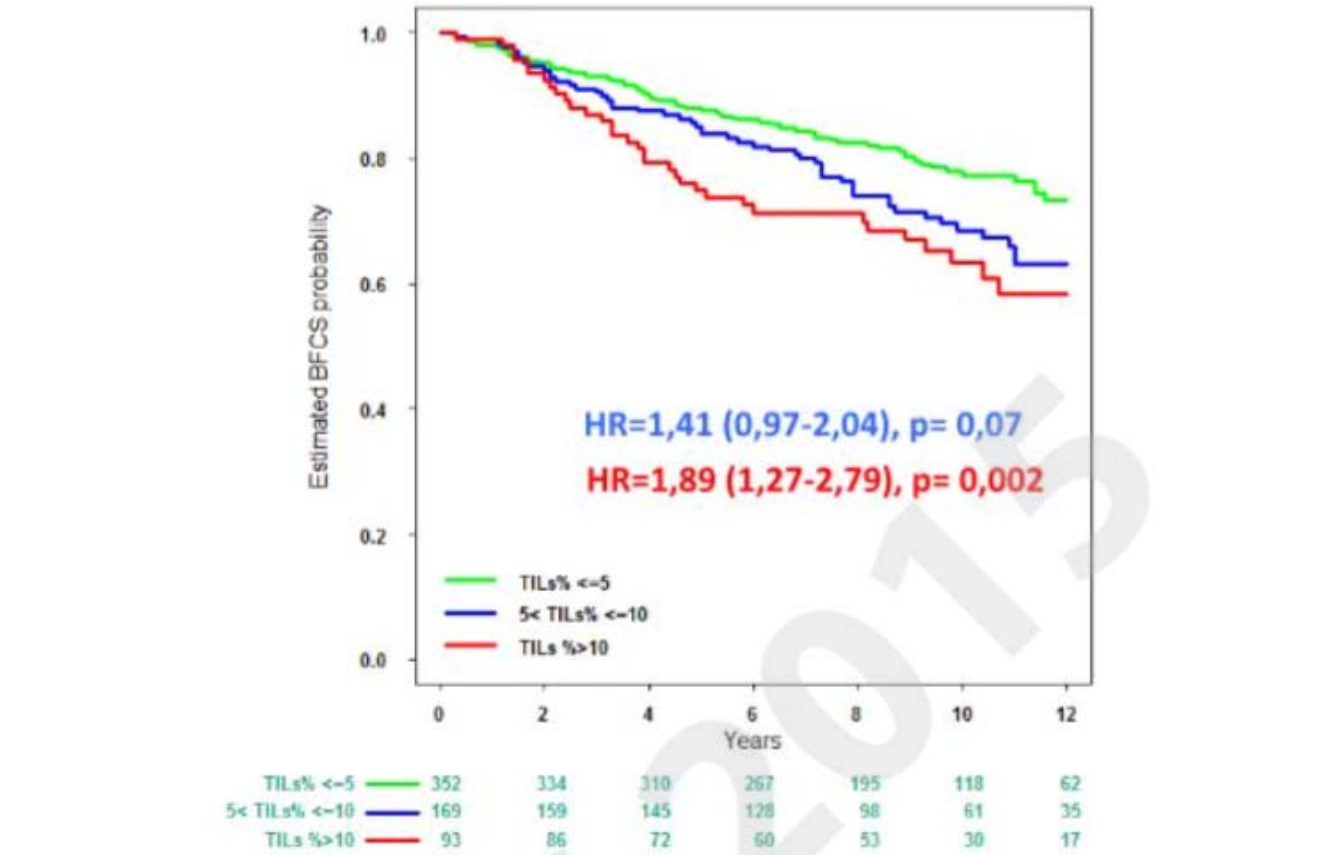
Survival analysis: univariate



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Survival analysis: multivariate

Variable	HR	95%CI	p-value
TIL (6-10 vs ≤5%)	1.6	1.1 – 2.3	0.02
TIL (>10 vs ≤5%)	1.3	0.8- 2.0	0.24
Age (≥50y vs <50y)	1.5	1.1 – 2.2	0.02
Size (≥2 vs <2cm)	1.7	1.2 – 2.5	0.007
Nodal status (+ vs -)	2.8	1.9 – 4.1	<0.0001
ER (+ vs -)	0.6	0.4 – 1.1	0.09
Ki67 (high vs low)	1.7	1.2 – 2.5	0.003
HER2 (+ vs -)	1.5	0.8 – 2.8	0.19
Grade (3 vs 1-2)	1.4	0.9 – 2.2	0.13

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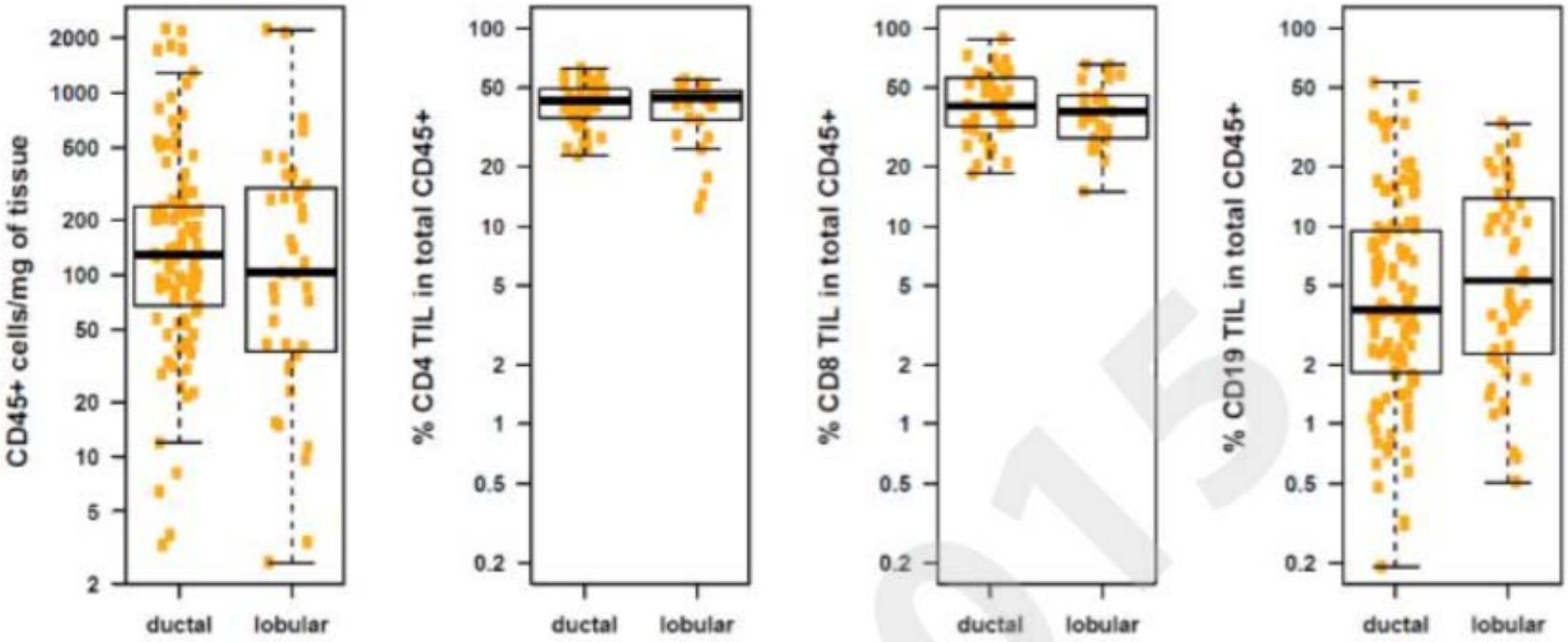
Lymphocyte density & composition: ER + HER2 – ILBC vs IDBC



Desmedt et al SABCS 2015

Conclusions

1. ILBC is characterized by low lymphocytic infiltration
2. TLS are present in ILBC
3. Higher TIL associated with ER/PR – tumors, high grade, high proliferative tumors, younger age at diagnosis, + LNs
4. TILs are associated with specific mutations
5. High TILs >10% was associated with worse outcomes in the univariate analysis but not the multivariate analysis
6. ER + HER2 – IDBC and ILBC is similar

Desmedt et al SABCS 2015

Pooled individual patient data analysis of stromal tumor infiltrating lymphocytes in primary triple negative breast cancer treated with anthracycline-based chemotherapy

Loi et al SABCS 2015

S1-03 Stromal TILs in TNBC

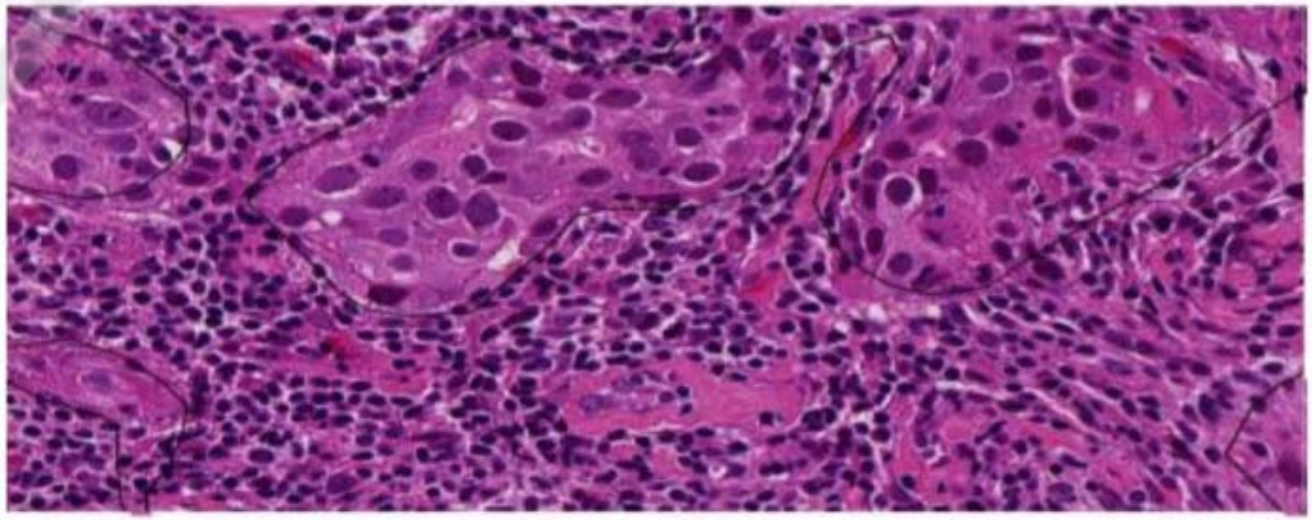
- TILs are a surrogate for the presence of adaptive immune response and have prognostic significance in early-stage TNBC
- Primary objective was to achieve a better understanding of the prognostic value of TILs in early-stage TNBC treated with anthracycline based adjuvant chemotherapy by performing a pooled analysis of individual studies

Loi et al SABCS 2015

Predefined parameters of TILs in BC

intratumoral TILs =
direct contact to tumor cells

stromal TILs =
between the tumor cells but within tumor stroma



Loi et al SABCS 2015

Clinical trials pooled

Study	Original Trial Reference	Number of TNBC pts	Treatment	Definition TNBC
BIG 2-98	Francis *et al*, JNCI 2008	269	A-T- CMF vs A-CMF AT- CMF vs AC-CMF	ER<1%
ECOG 1199	Sparano *et al*, NEJM 2008	291	AC-q3w taxol/docetaxel AC-q1w taxol/docetaxel	ER<10%
ECOG 2197	Goldstein *et al*, JCO 2008	190	AC vs AT	ER<1%
FinHER	Joensuu *et al*, NEJM 2006	134	FEC-V vs FEC-Docetaxel	ER<10%
Gustave Roussy	Arriagada *et al*, Acta Oncologica 2005	107	FEC*6	ER<10%
total		991		

Loi et al SABCS 2015

Patient characteristics

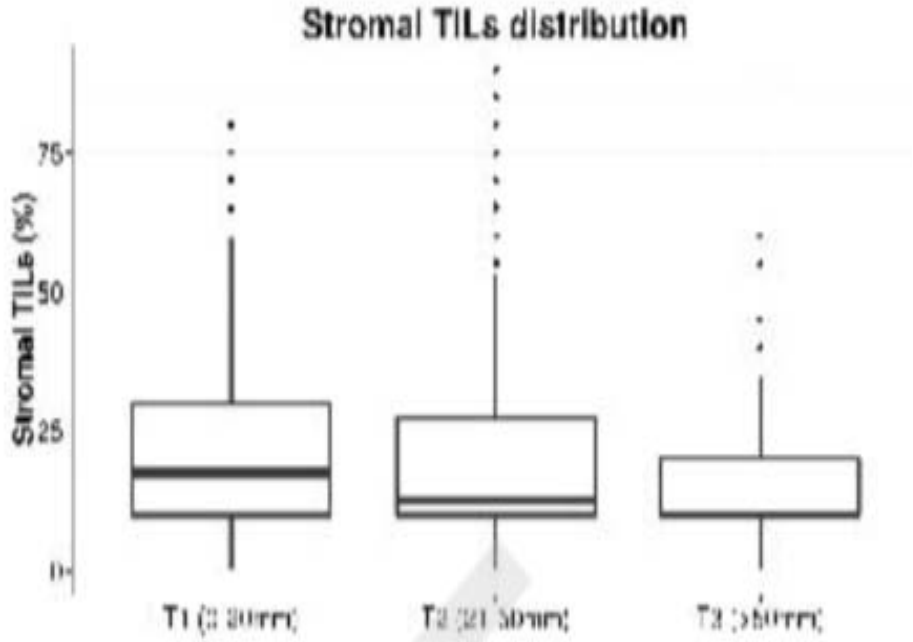
n=991	
Age (years)	Mean 49.5 (range 22.6-85); Median 49.4
Tumor size (cm)	Mean 2.86 (range 0-16); Median 2.50
Nodal status	Negative n=318 (32%)
	1-3 n=421 (42.5%)
	>3 n=252 (25.4%)
Chemo Treatment	Anthracycline (A) n=376 (37.9%)
	Anthracycline & taxane (A+T) n=615 (62.1%)
Median Follow-up	6.6 yrs for iDFS; 7.55 yrs for D-DFS, 7.3 yrs for OS
Stromal TILs (%)	Mean 19.6% (0-90%); Median 12.5%
Intratumoral TILs (%)	Mean 6.12% (0-90%); Median 1%

Loi et al SABCS 2015

TIL association with clinicopathological factors

- ***Larger*** **tumor size was significantly *associated* with lower Stromal* (p=0.001) & inTu TILs* (0.04)**

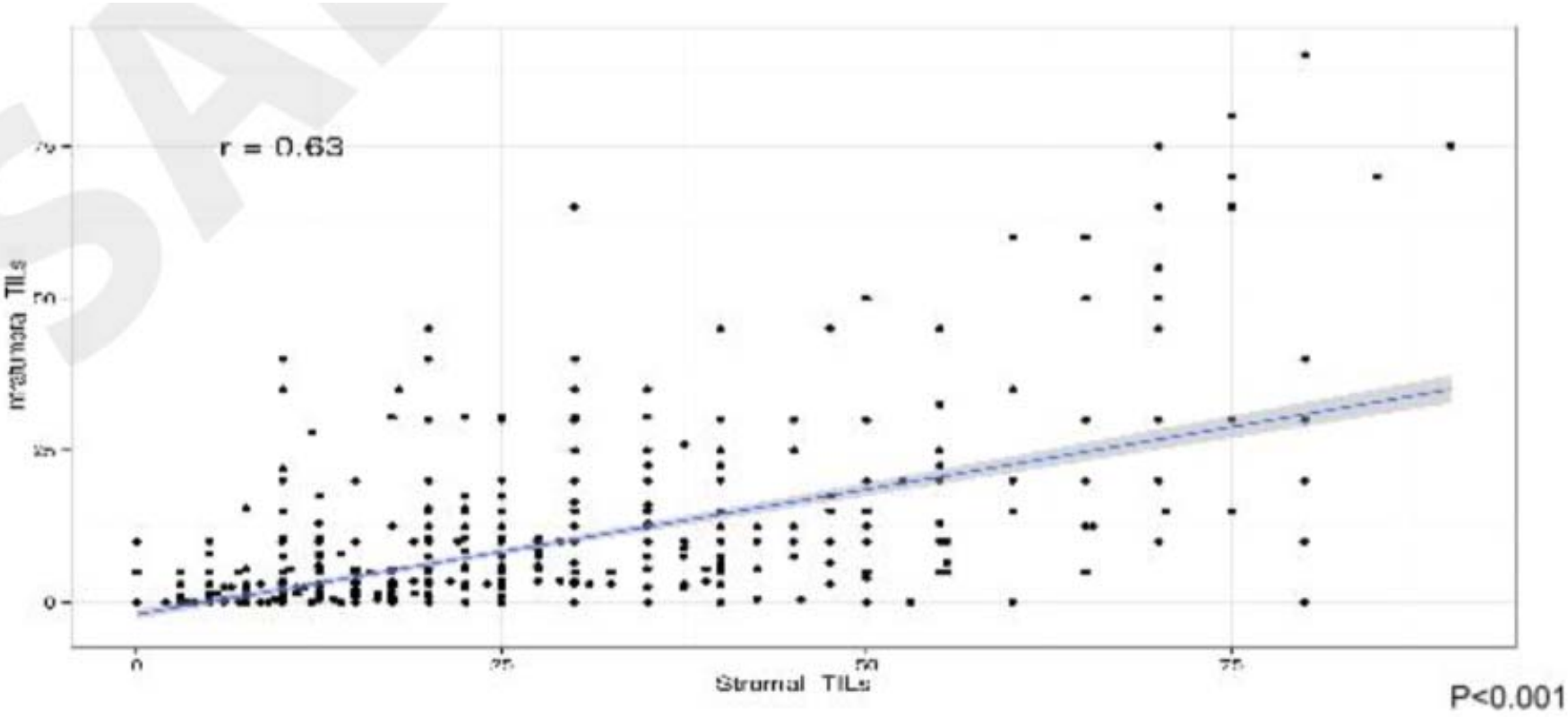
- **Age and nodal status was not significantly associated with TIL values**



P values obtained using linear regression

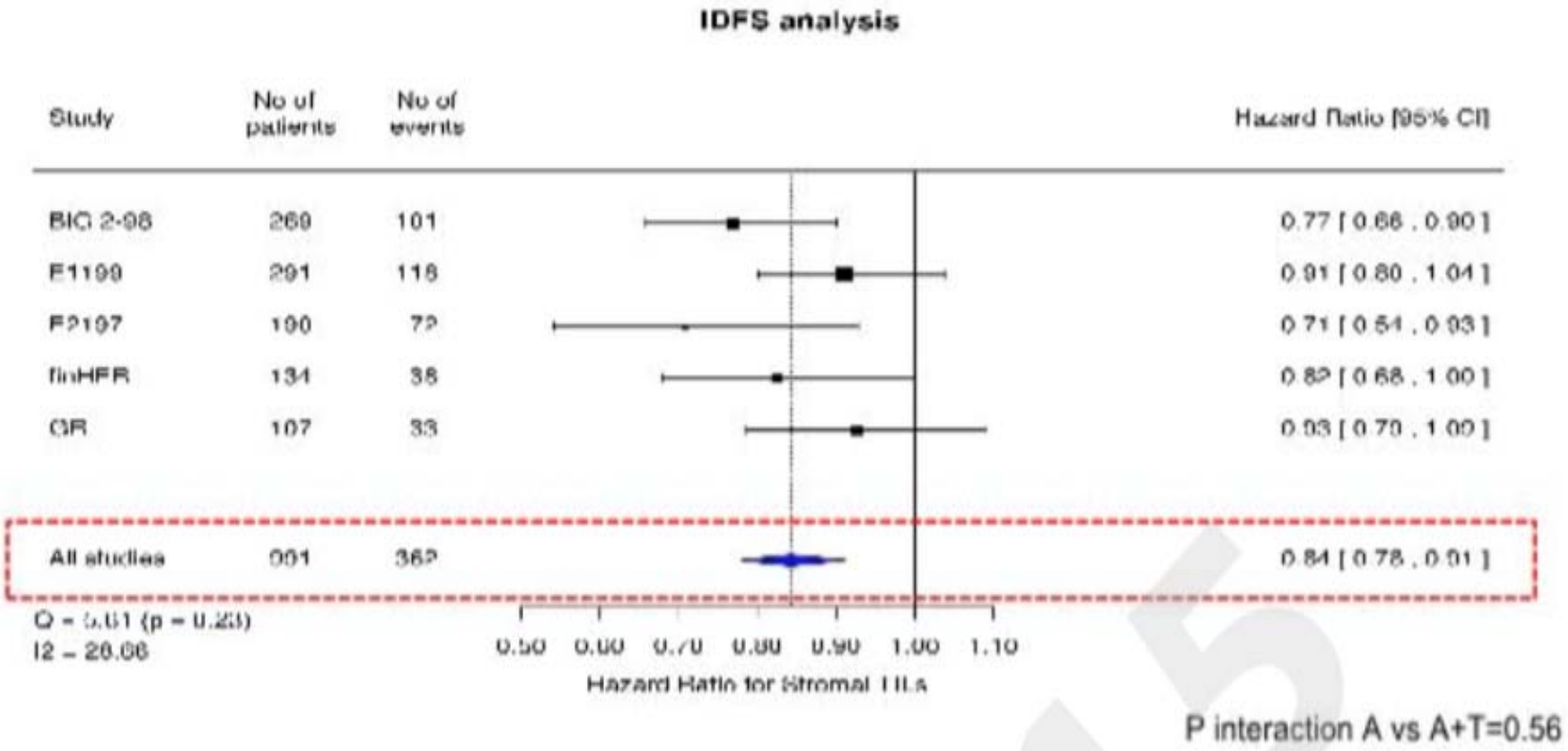
Loi et al SABCS 2015

Significant correlation between stromal and intratumoral TILs



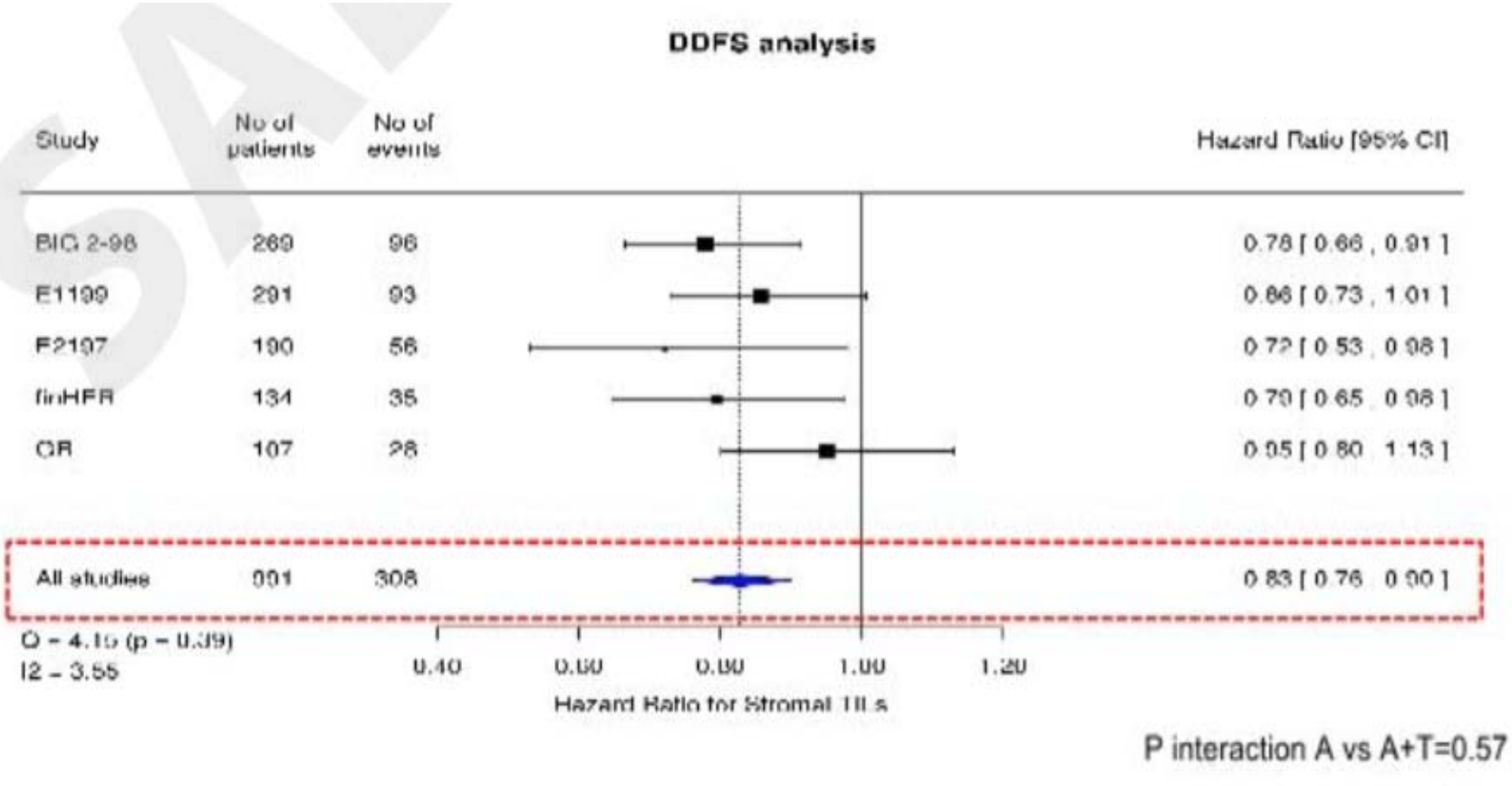
Loi et al SABCS 2015

Stromal TILs & iDFS



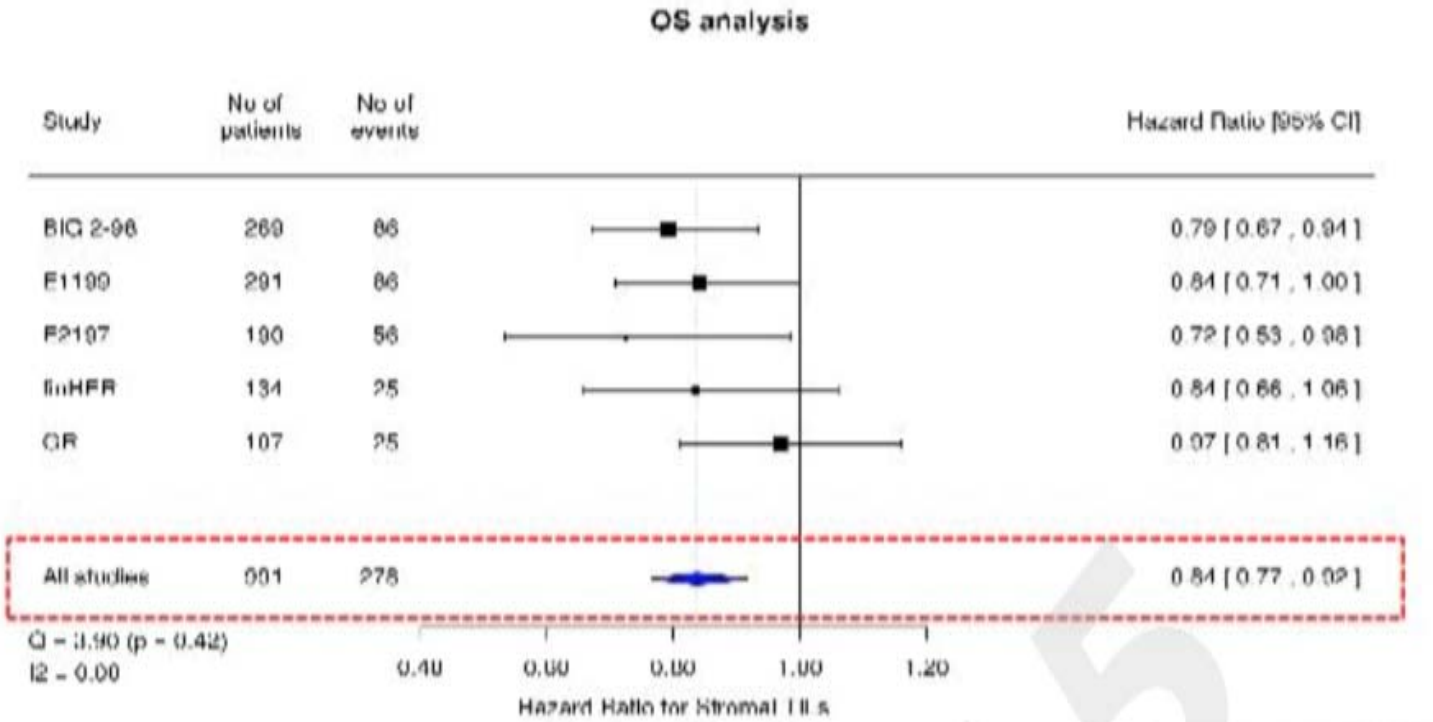
Loi et al SABCS 2015

Stromal TILs & D-DFS



Loi et al SABCS 2015

Stromal TILs & OS



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Intratumoral TILs

Intratumoral TILs	Hazard ratio (HR, 95%CI) all patients pooled
iDFS (number of events:362)	HR 0.74 (0.64-0.86), p<0.001
D-DFS (number of events:308)	HR 0.72 (0.61-0.85), p<0.001
OS (number of events:278)	HR 0.73 (0.62-0.88), p<0.001

Univariate analyses
TILs treated as a continuous variable
Tests for heterogeneity suggested little evidence for heterogeneity between studies
Overall HR is obtained using individual patient data, stratified by study

Loi et al SABCS 2015

Multivariate Cox analysis

	iDFS (events 362)	D-DFS (events 308)	OS (events 278)
Stromal TILs (per 10%)	0.88 (0.79-0.97) p=0.01	0.87 (0.79-0.97) p=0.01	0.88 (0.79-0.99) p=0.03
InTu TILs (per 10%)	0.86 (0.72-1.02) p=0.08	0.85 (0.70-1.03) p=0.09	0.86 (0.71-1.05) p=0.13
Age* (yrs)	1.01 (1.001-1.02) p=0.04	1.01 (1.002-1.03) p=0.02	1.02 (1.005-1.03) p=0.006
Tumor size* (cm)	1.08 (1.03-1.14) p=0.004	1.08 (1.03-1.15) p=0.003	1.09 (1.03-1.16) p=0.003
Positive nodes			
1-3	1.70 (1.27-2.33) p<0.001	2.01 (1.42-2.84) p<0.001	1.95 (1.36-2.81) p<0.001
>3	3.42 (2.40-4.87) p<0.001	4.04 (2.72-5.99) p<0.001	4.19 (2.76-6.35) p<0.001

* *TILs, tumor size and age treated as continuous variables*

Using Wald tests

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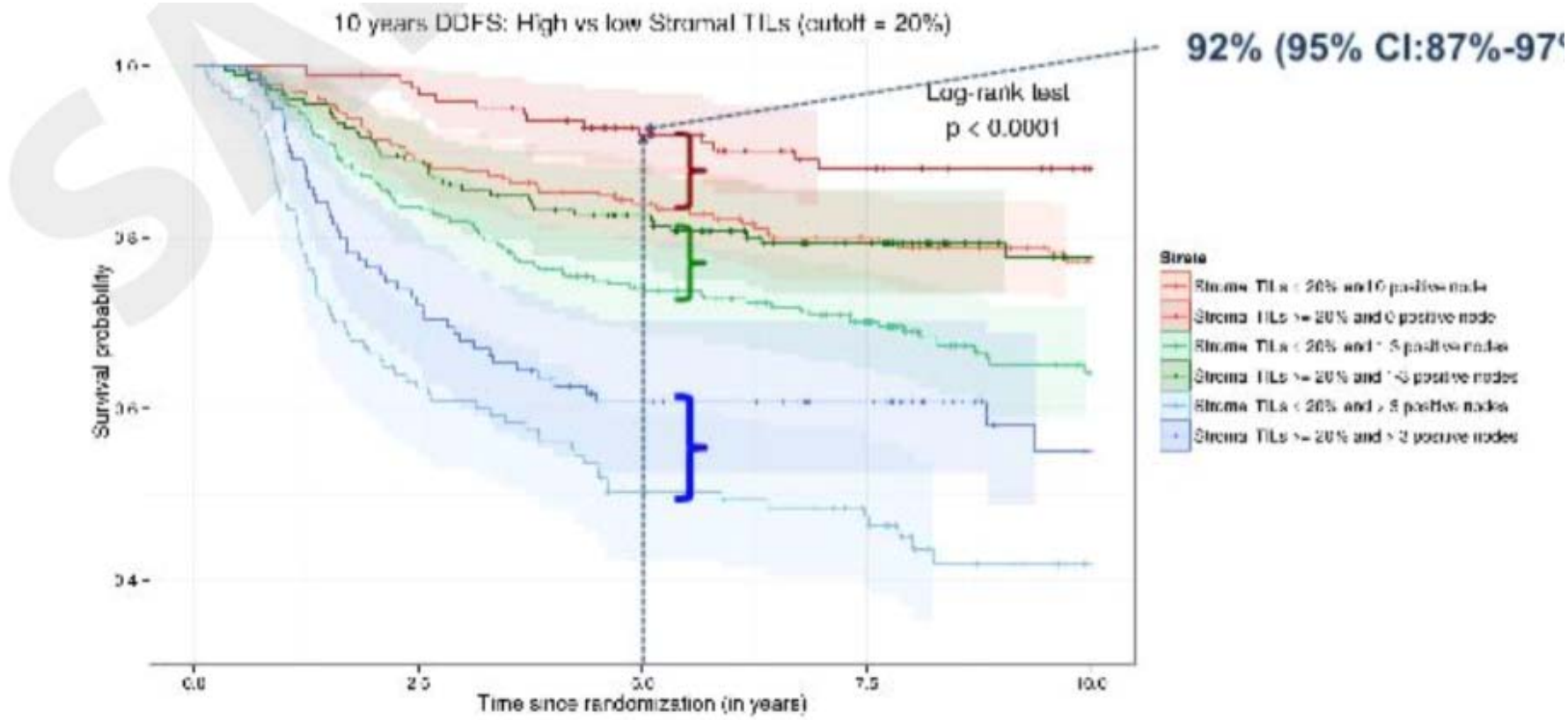
Multivariate model for estimating *added effect* of TILs to clinical pathological (CP) factors

	iDFS (events 362) $\Delta\chi^2$	*p value*	D-DFS (events 308) $\Delta\chi^2$	*p value*	OS (events 278) $\Delta\chi^2$	*p value*
CP vs none	70.17	p<0.0001	76.77	p<0.0001	75.93	p<0.0001
CP+ Str vs CP	21.31	p<0.0001	20.9	p<0.0001	16.48	p<0.0001
CP + inTu vs CP	18.28	p<0.0001	17.4	p<0.0001	14.01	p=0.001
CP+ Str+ InTu vs CP	24.90	p<0.0001	24.09	p<0.0001	19.07	p<0.0001
CP+ Str + inTU vs CP+ Str	3.56	p=0.06	3.19	p=0.07	2.60	p=0.11
CP+Str+ inTU vs CP+ inTu	6.62	p=0.01	6.69	p=0.01	5.06	p=0.02

Likelihood ratio test for Stromal and intratumoral TILs with or without adjustment for CP factors (age, tumor size, nodes and treatment)

Loi et al SABCS 2015

Stromal TILs >20% have excellent D-DFS



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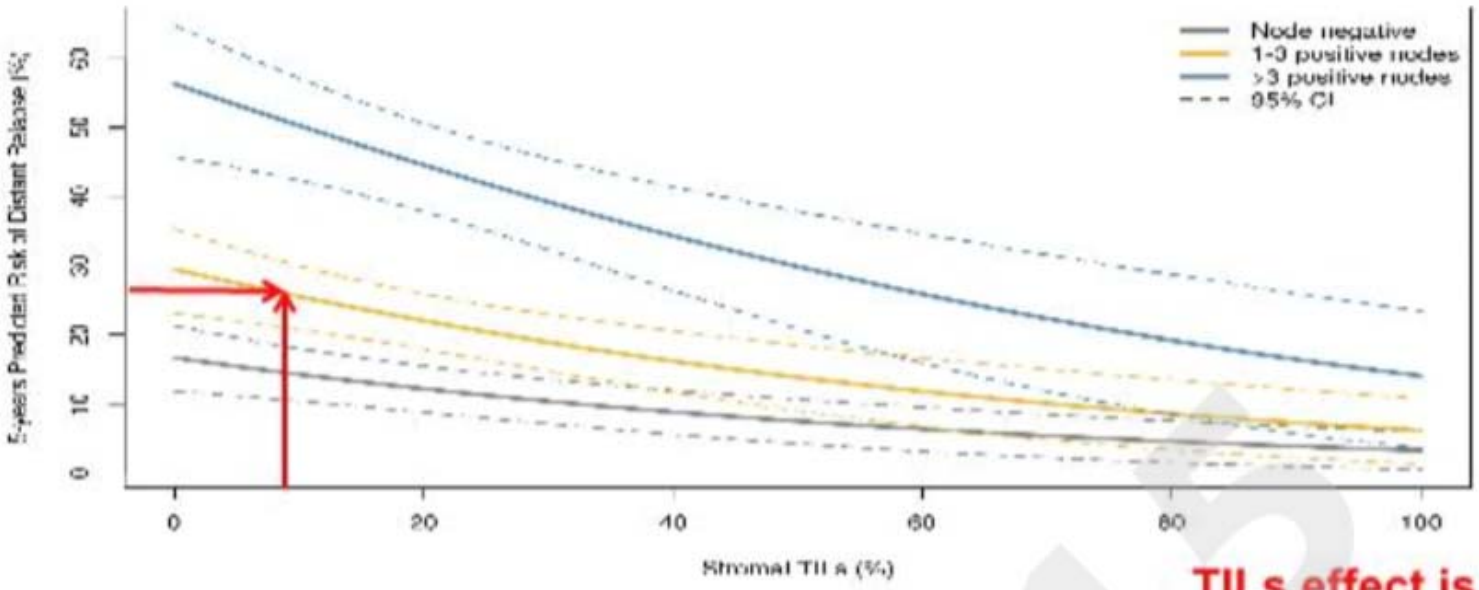
Model to predict risk of distant recurrence at 5 years (%) by TILs & nodal status by tumor size and age

Mean age 49.5yrs and mean tumor size=2cm



TILs effect is linear

Loi et al SABCS 2015

Conclusions

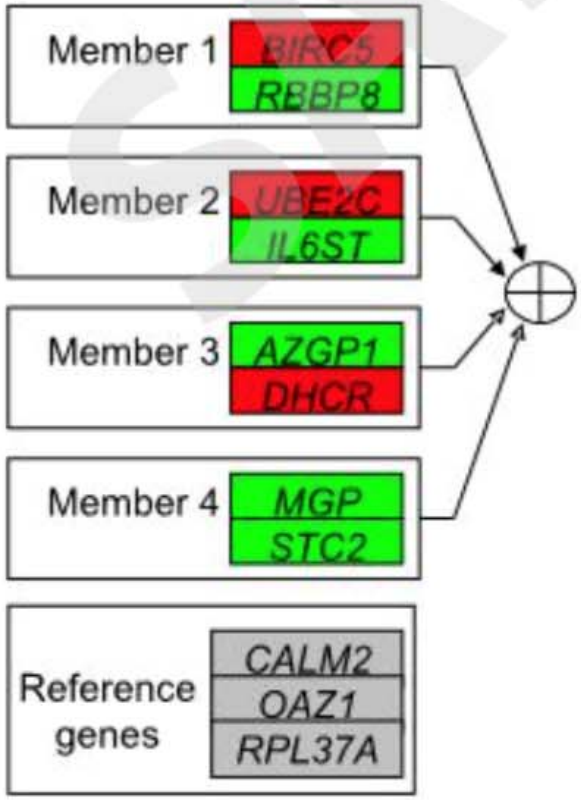
- TILs represent a strong prognostic factor with every 10% increment =12% adjusted relative risk reduction
- TILs add significant prognostic information to standard measures of nodal status, age and tumor size in TNBC
- Stromal TILs value >20% in node negative early stage TNBC could identify a good prognostic group
- Intratumoral TILs have significant prognostic but did not seem to add prognostic information to stromal TILs in current dataset

Loi et al SABCS 2015

EndoPredict (EPclin) score for estimating residual distant recurrence (DR) risk in ER+/HER2- breast cancer (br ca) patients treated with 5 years adjuvant endocrine therapy alone: Validation and comparison with the oncotype DX recurrence score (RS)

Dowsett et al SABCS 2015

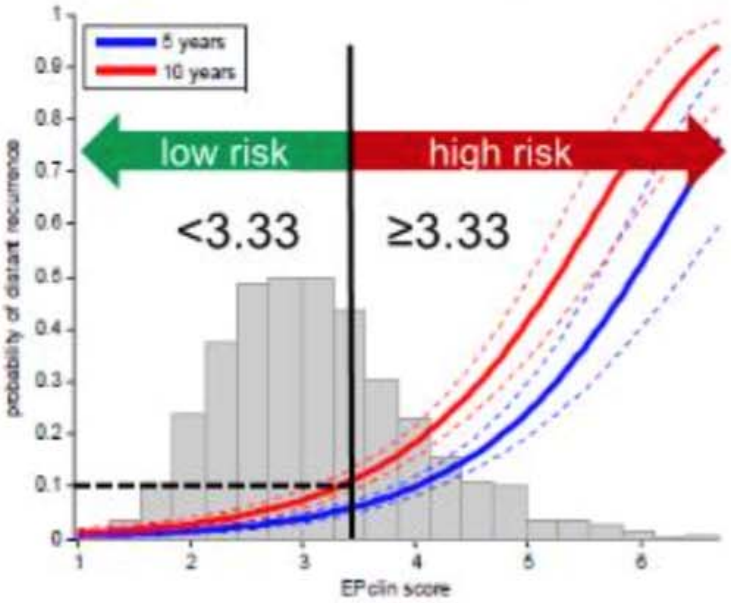
Components of the EPclin and definition of risk categories



RT-PCR

ER+, HER2-ve, 5-year tamoxifen

EP Score → **Nodal status + tumour size** → **EPclin** Score Risk class: low vs. high



EPclin 3.33 = 10% 10-year DR

Filipits et al, Clin Cancer Res 2011, 17:6012

Patient characteristics

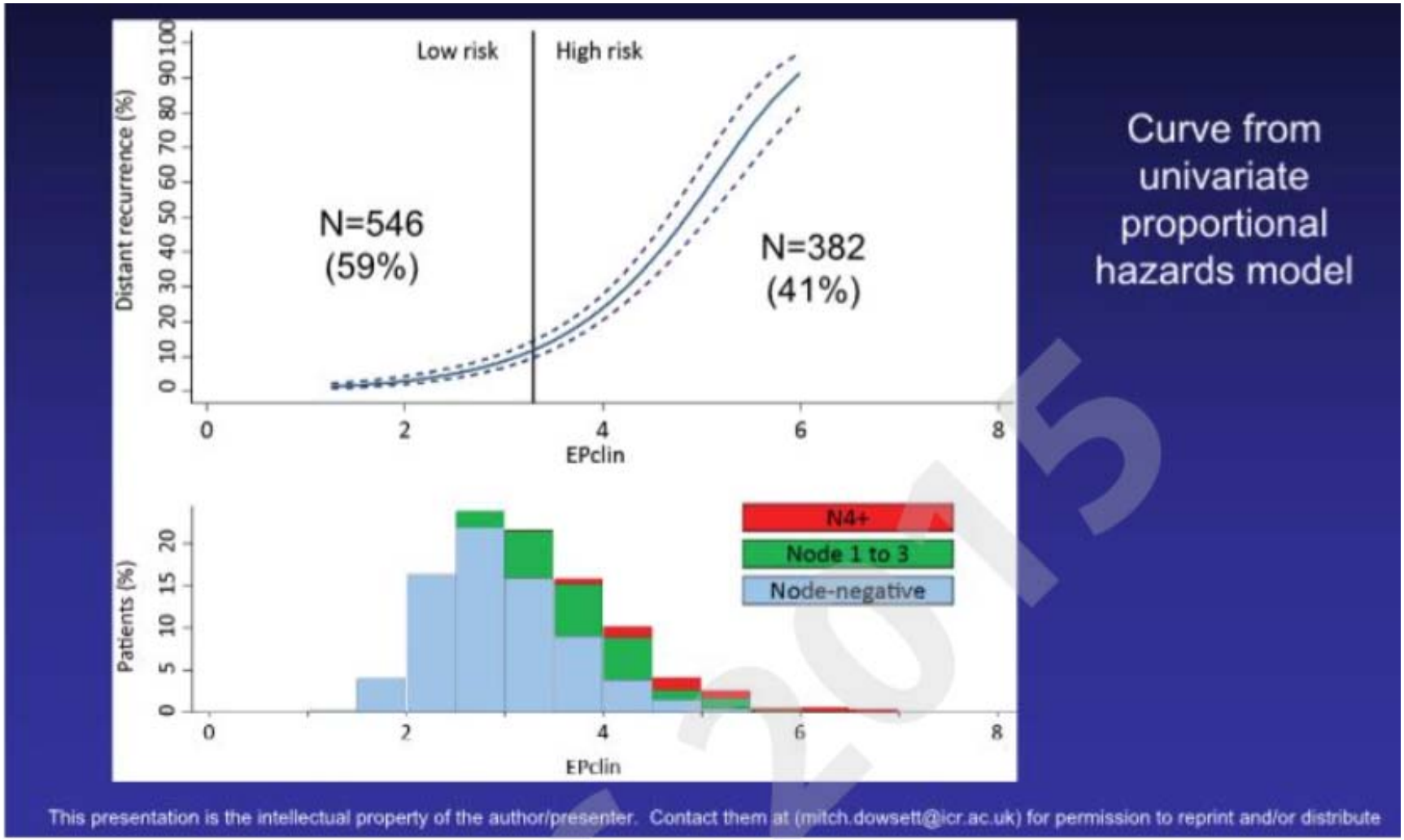
All patients ER-positive, HER2-negative	Analysis (N=928)
Age (years), mean (SD)	64.7 (8.3)
Nodal status	
Negative	680 (73.3%)
1-3 positive nodes	198 (21.3%)
4 or more positive nodes	50 (5.4%)
Tumour size	
<1cm	130 (14.0%)
1-2cm	489 (52.7%)
2-5cm	290 (31.3%)
>5cm	19 (2.1%)
Grade (40 missing values)	
Well	244 (26.3%)
Moderate	497 (53.6%)
Poor	147 (15.8%)
Treatment	
Radiotherapy	649 (69.9%)
Mastectomy	363 (39.1%)
Chemotherapy	0 (0%)

	Pats	DR
N-neg	680	59
N-pos	248	69

RNA extracted by GHI
57 sample cross validation

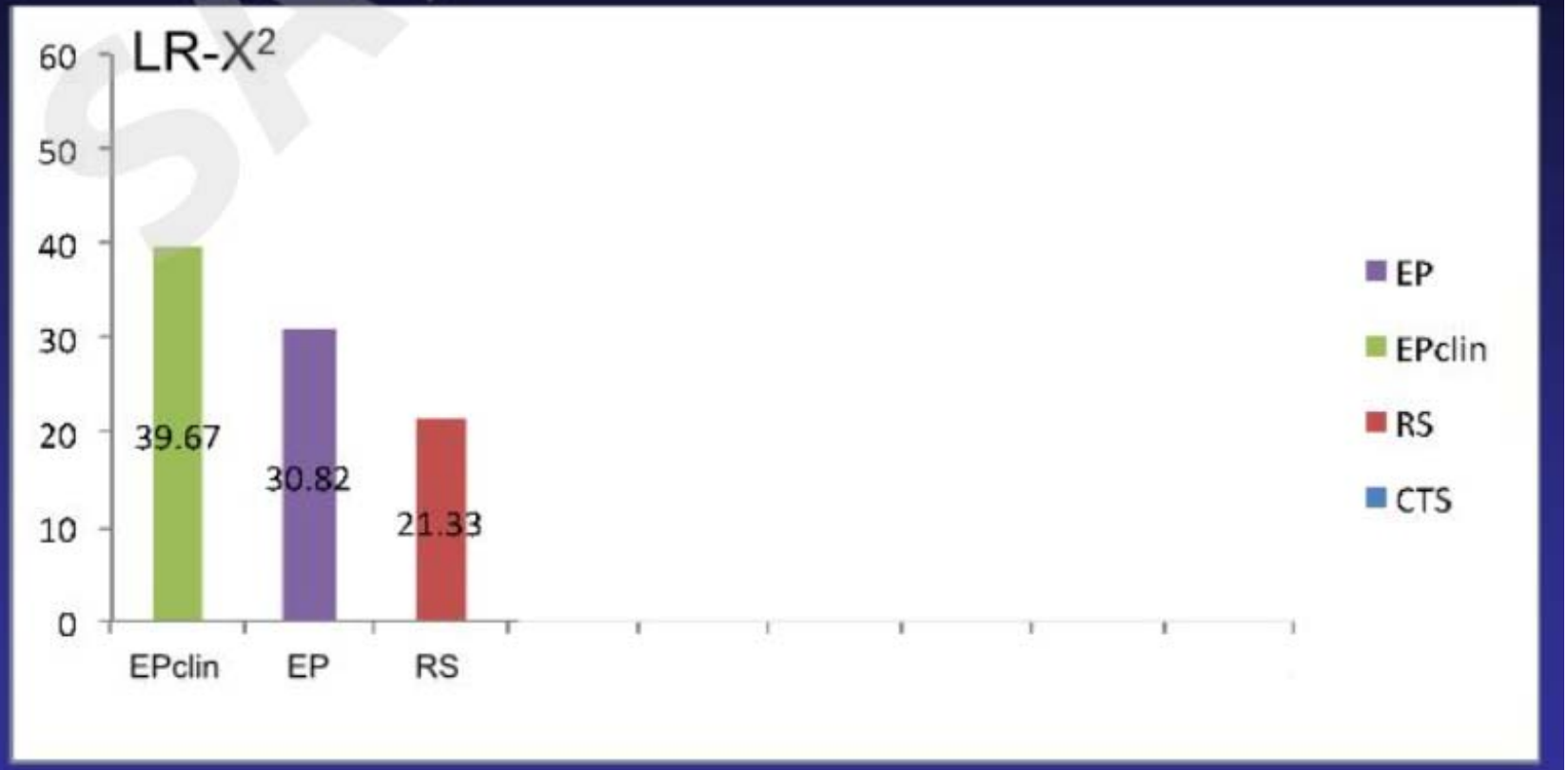
Dowsett et al SABCS 2015

EndoPrectict score and fitted 10-year risk of distant recurrence



Dowsett et al SABCS 2015

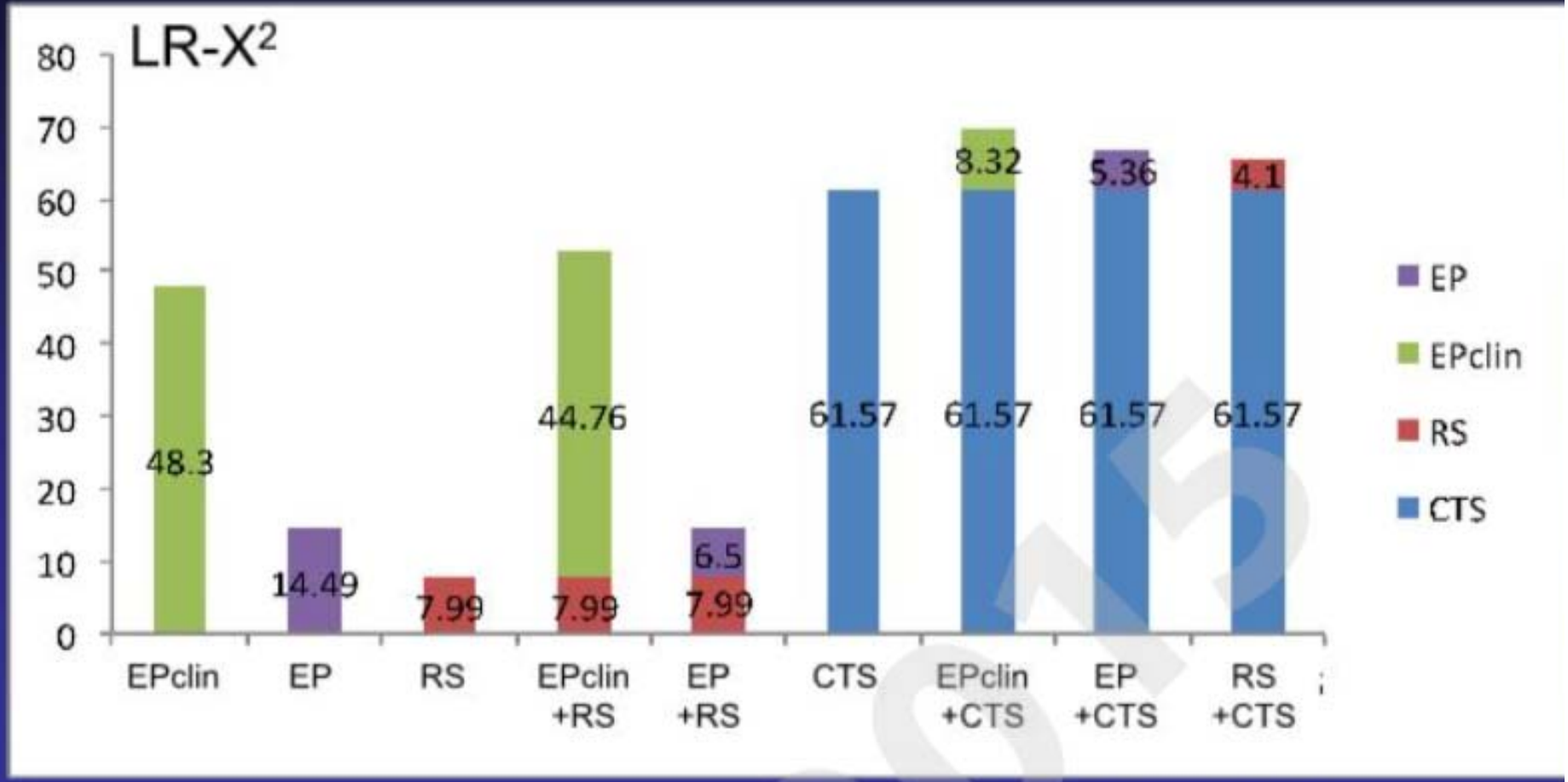
Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node negative



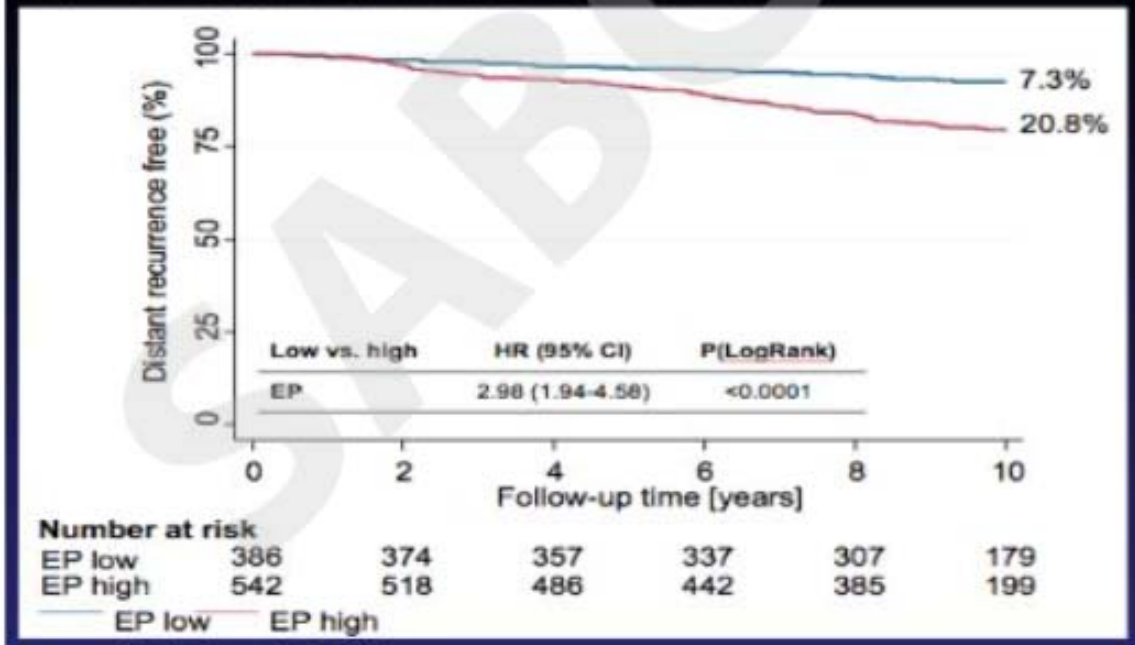
Based on 10-year risk of distant recurrence

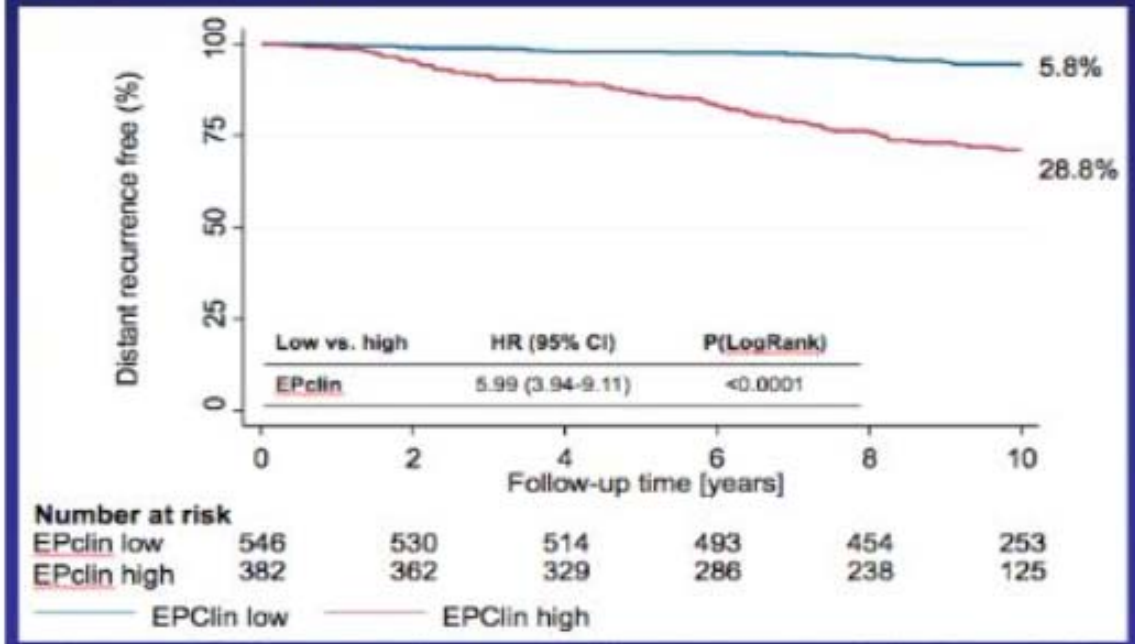
Dowsett et al SABCS 2015

Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node positive



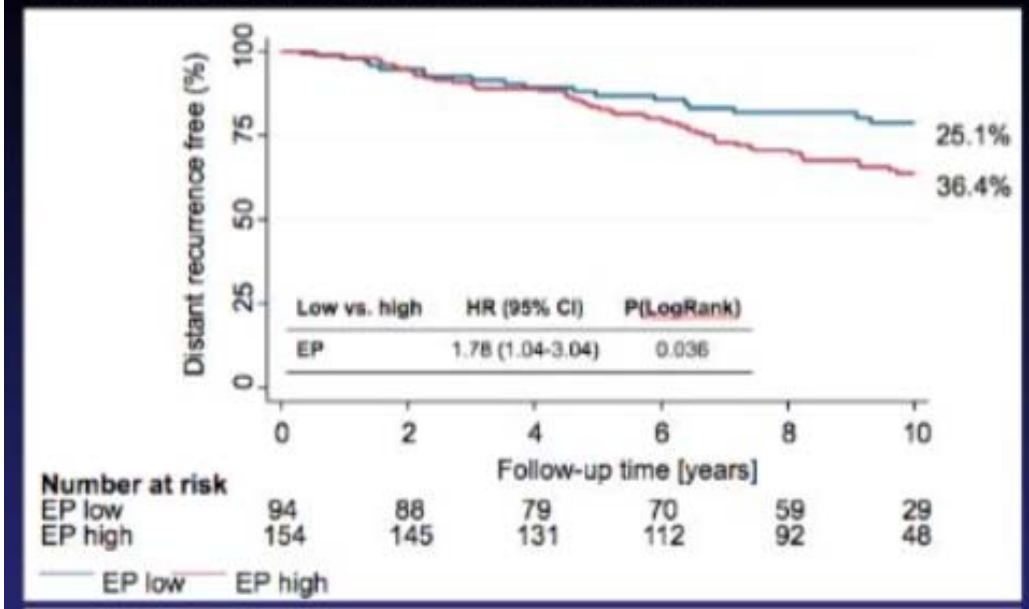
Dowsett et al SABCS 2015

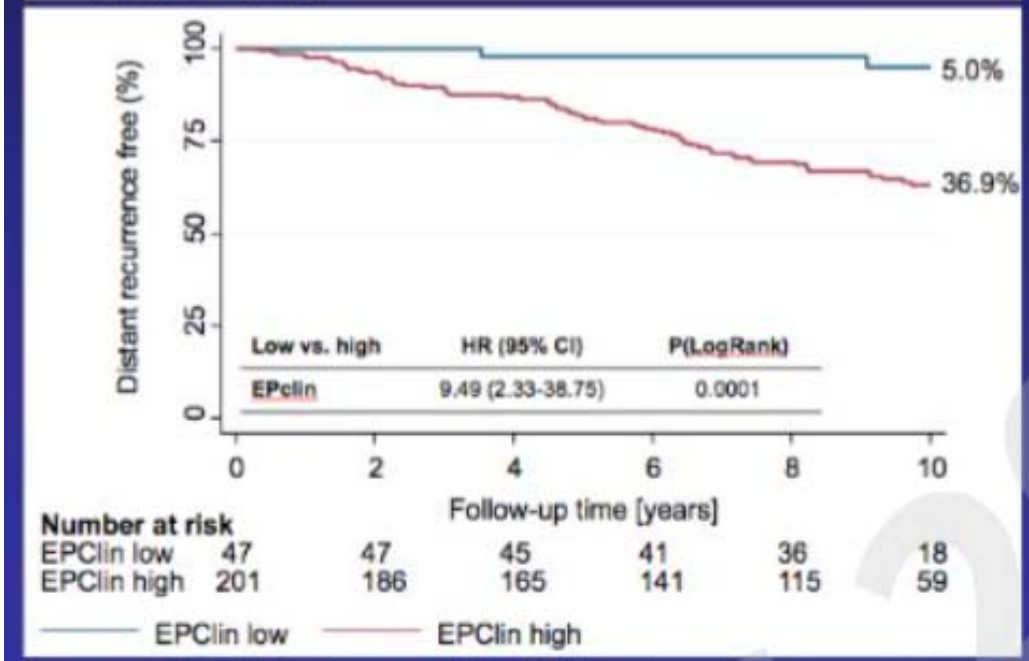




Distant recurrence rate according to pre-specified risk stratification in TransATAC:
EP vs EPclin: all patients

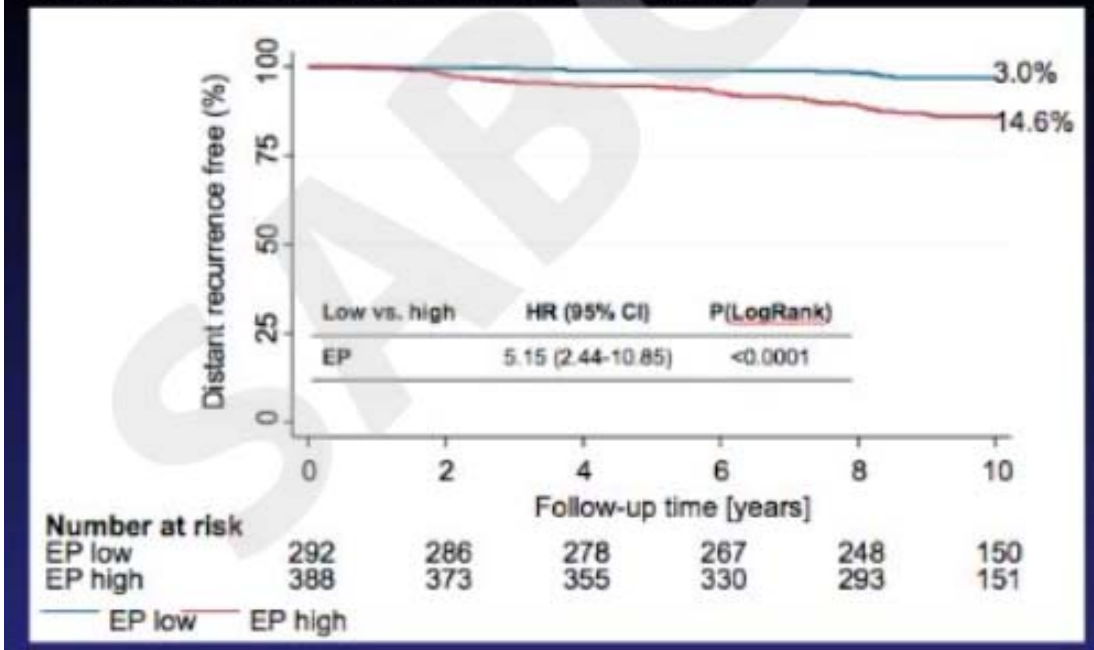
Dowsett et al SABCS 2015

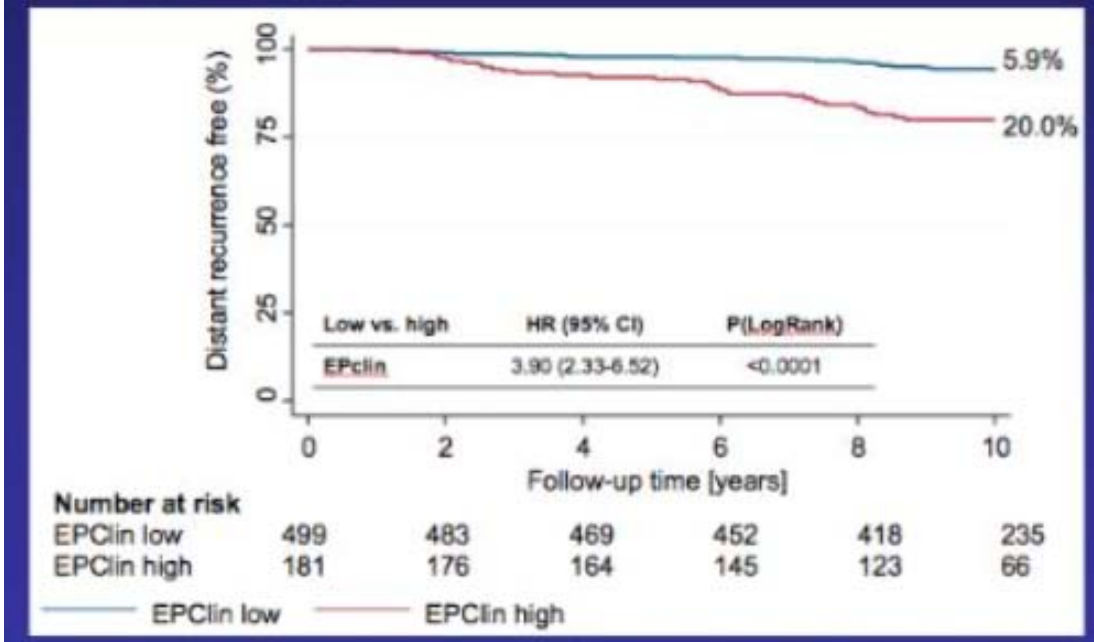




Distant recurrence rate according to pre-specified risk stratification in TransATAC:
EP vs EPclin:
node positive

Dowsett et al SABCS 2015





Distant recurrence rate according to pre-specified risk stratification in TransATAC:
EP vs EPclin:
node negative

Dowsett et al SABCS 2015

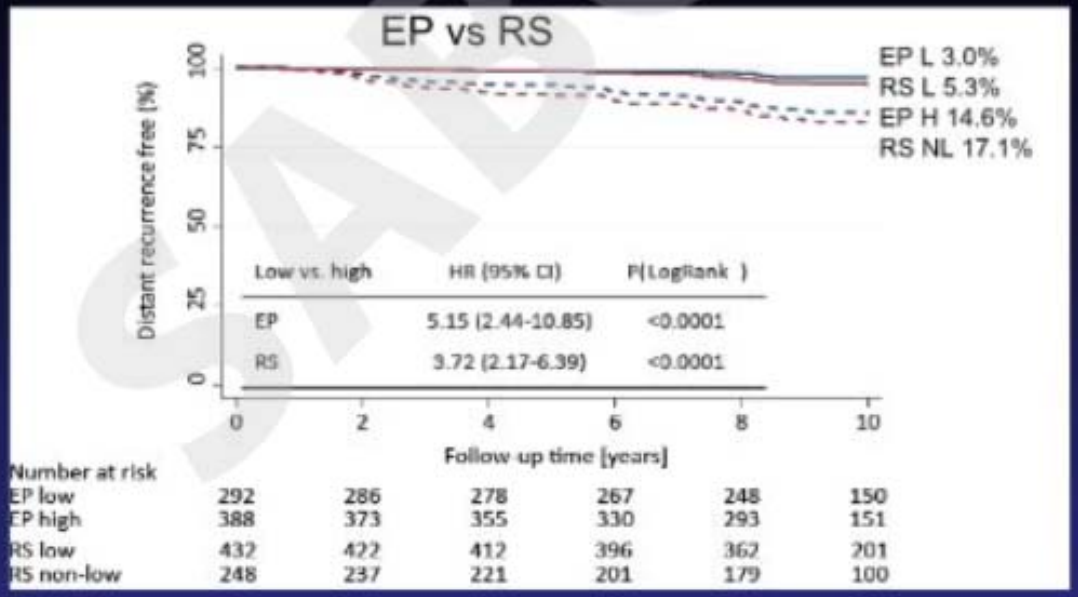
Risk stratification using prespecified cut-offs for 10-year risk of distant recurrence

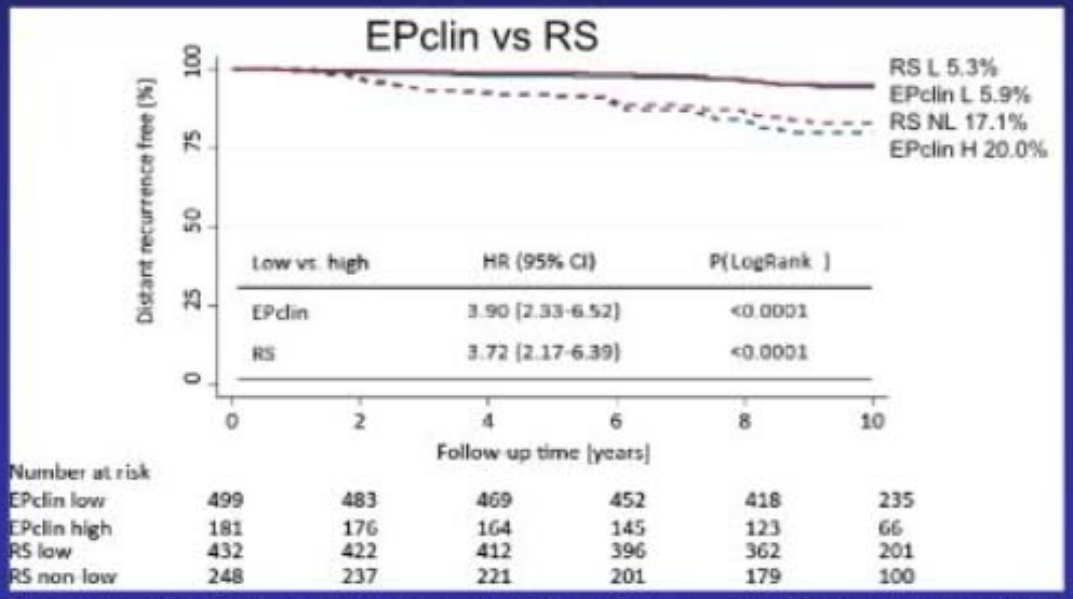
EPclin: low risk <10%
high risk ≥10%

RS: low risk <10%
intermediate risk 10-20%
high risk >20%

non-low risk ≥10%

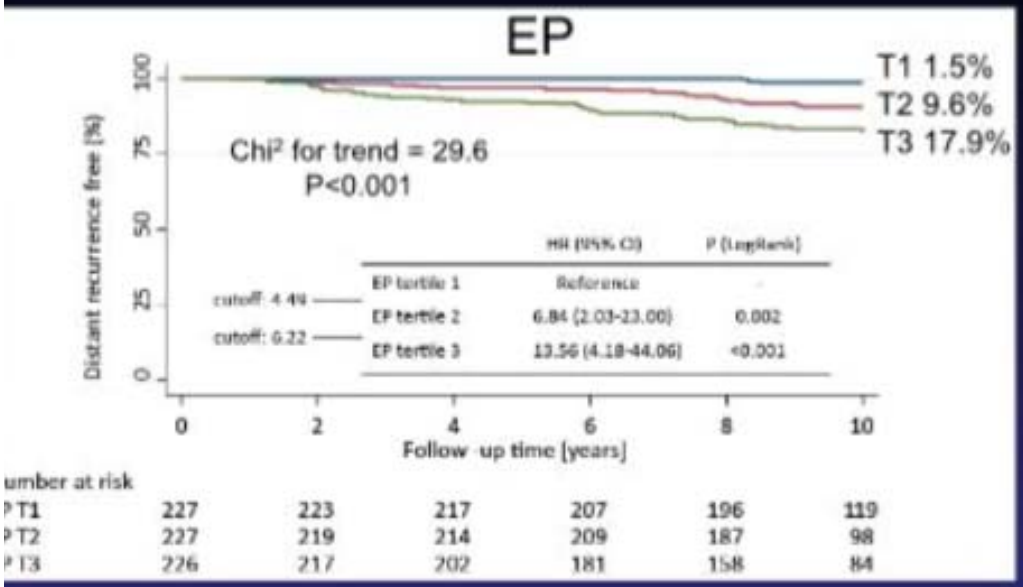
calibrated for node negative

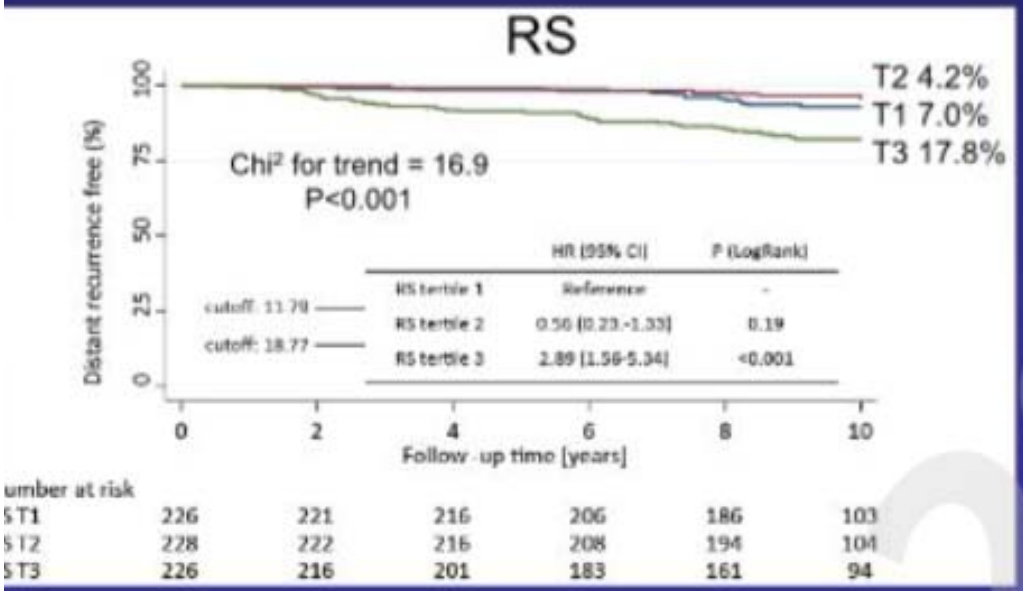




Distant recurrence rate according to pre-specified risk stratification in TransATAC: EP vs RS and EPclin vs RS in Node negative

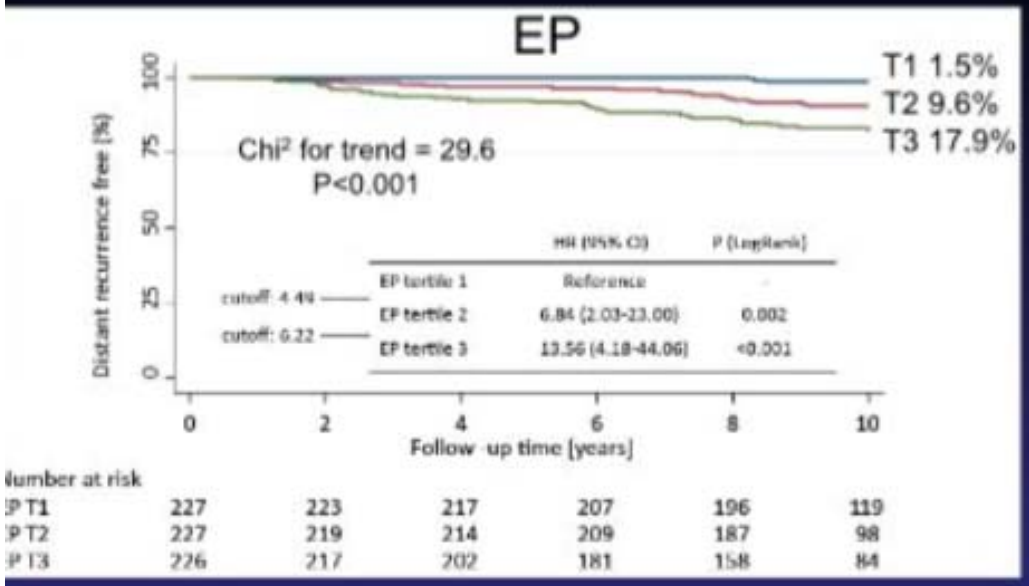
Dowsett et al SABCS 2015

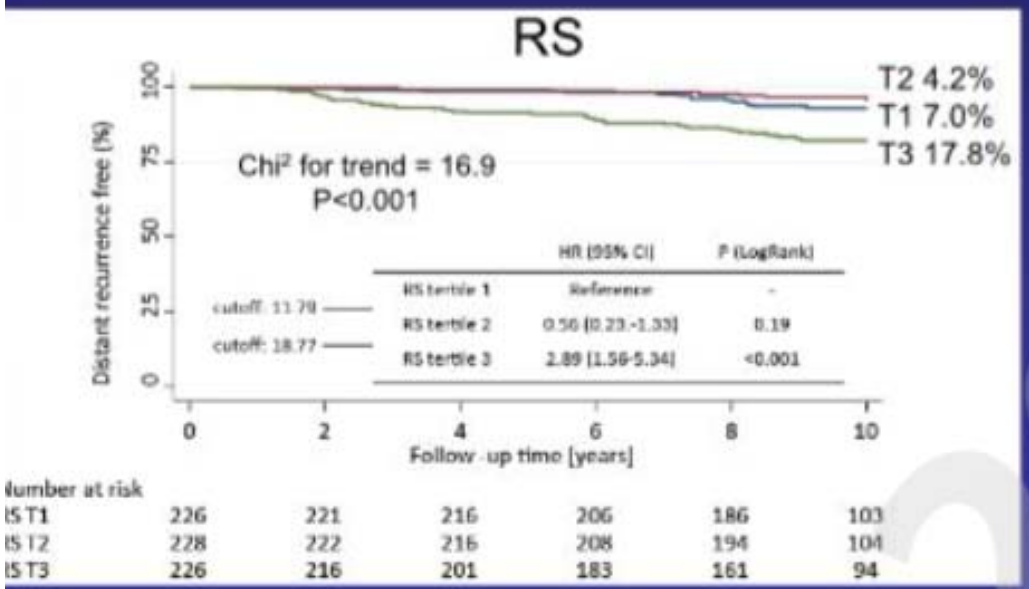




Distant recurrence rate according to tertiles of EP vs RS in TransATAC: Node negative

Dowsett et al SABCS 2015

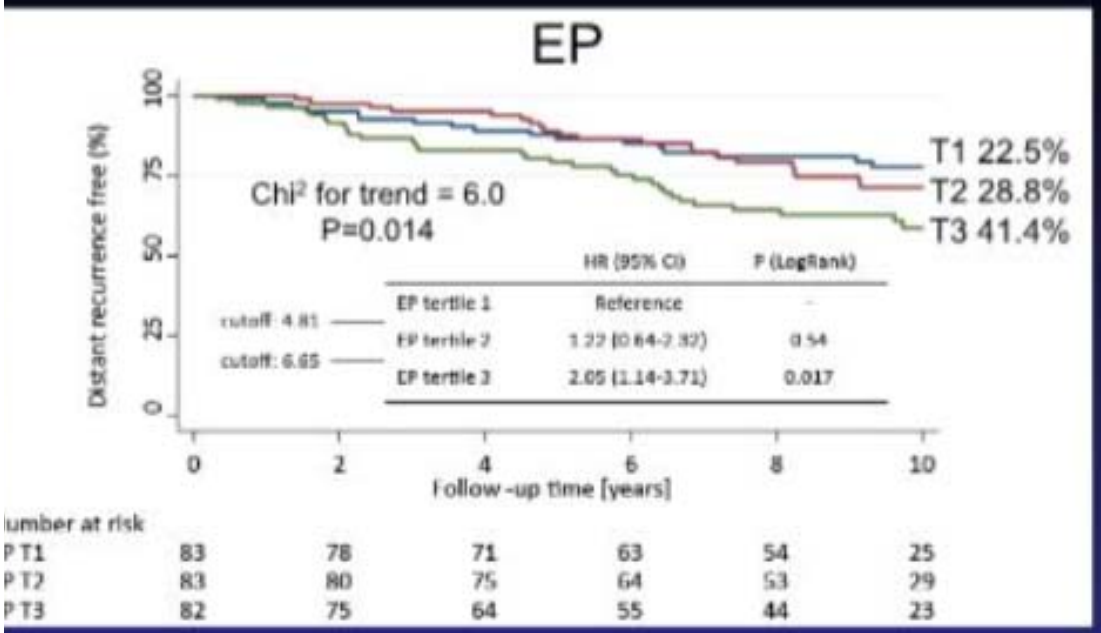


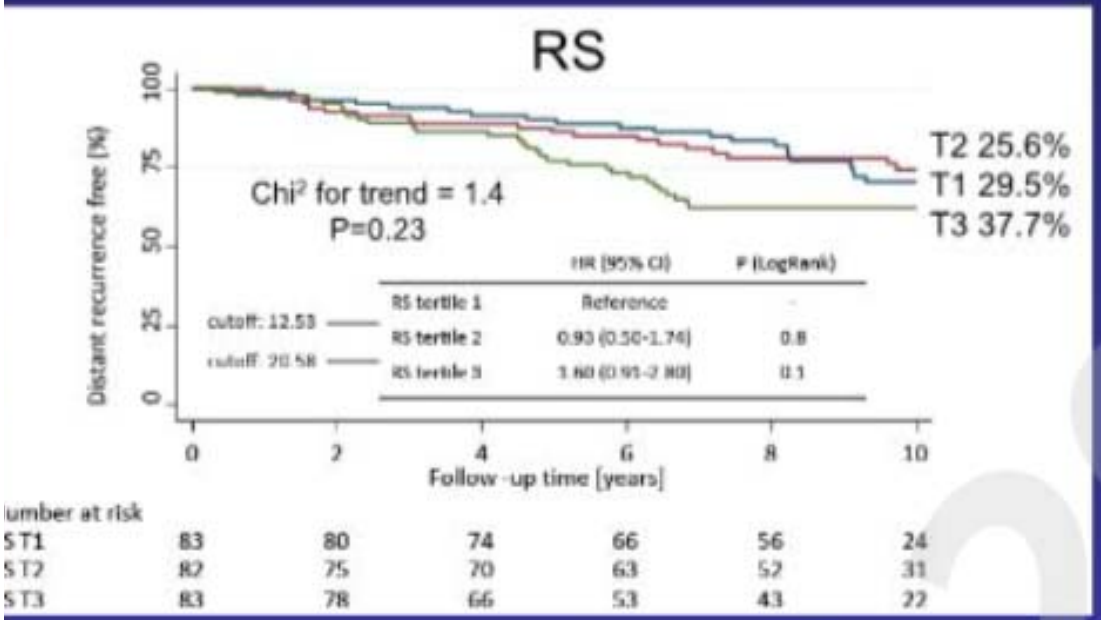


Distant recurrence rate according to tertiles of EP vs RS in TransATAC: Node negative

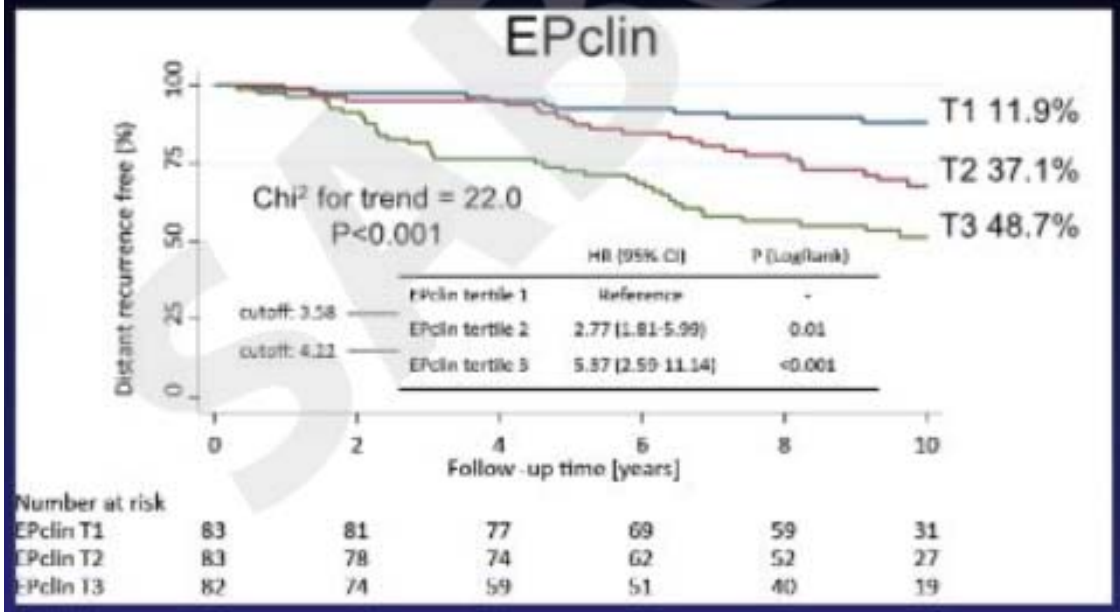
Dowsett et al SABCS 2015

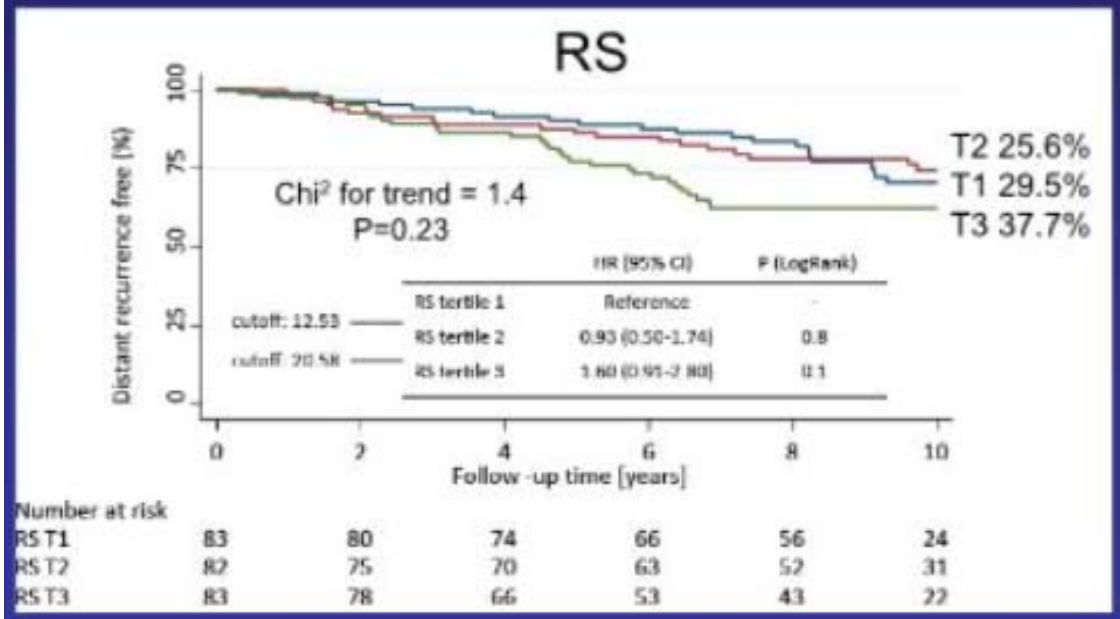
Distant recurrence rate according to tertiles of EP vs RS in TransATAC: Node positive





Dowsett et al SABCS 2015





Distant recurrence rate according to tertiles of EPclin vs RS in TransATAC: Node positive

Dowsett et al SABCS 2015

S3-01 EndoPrectict score

- EPclin identified a low risk group that might be spared chemotherapy
- EPclin provided more accurate prognostic information than the RS
- Difference between the Epclin and RS were greatest in the node + patients
- The bottom tertile in node negative patients identified a group with extremely poor prognosis
- The data highlight the importance of the inclusion of clinicopathologic factors for estimates of residual risk of distant recurrence

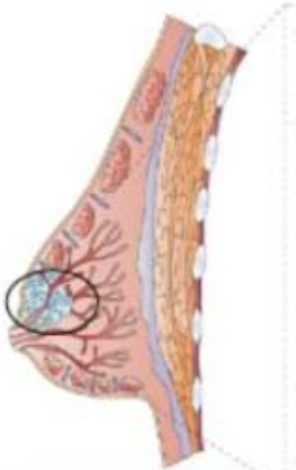
Dowsett et al SABCS 2015

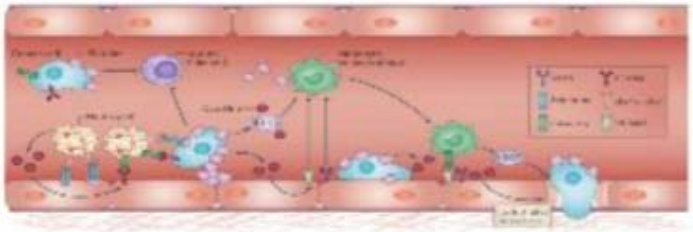
Identification of early versus late drivers of breast tumors and metastasis

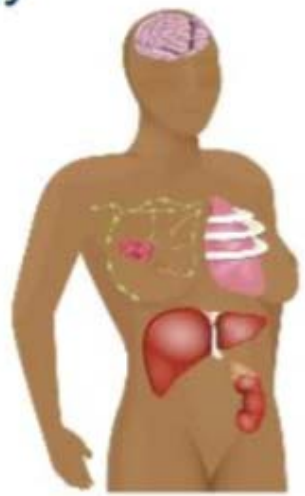
Siegel et al SABCS 2015

San Antonio Breast Cancer Symposium, December 8-12, 2015

Critical Questions in Metastasis Biology







1. Are there features in the primary that destine cells for metastasis?

2. Is breast cancer metastasis a monoclonal or multiclonal process?

3. Are most genetic drivers found in metastases established early or late?

Smith SC, Theodorescu D. 2009. *Nat Rev Cancer*. PMID: 19242414.
Reymond N, d'Agua BB, Ridley AJ. 2013. *Nat. Rev. Cancer*. PMID: 24263189.

UNC

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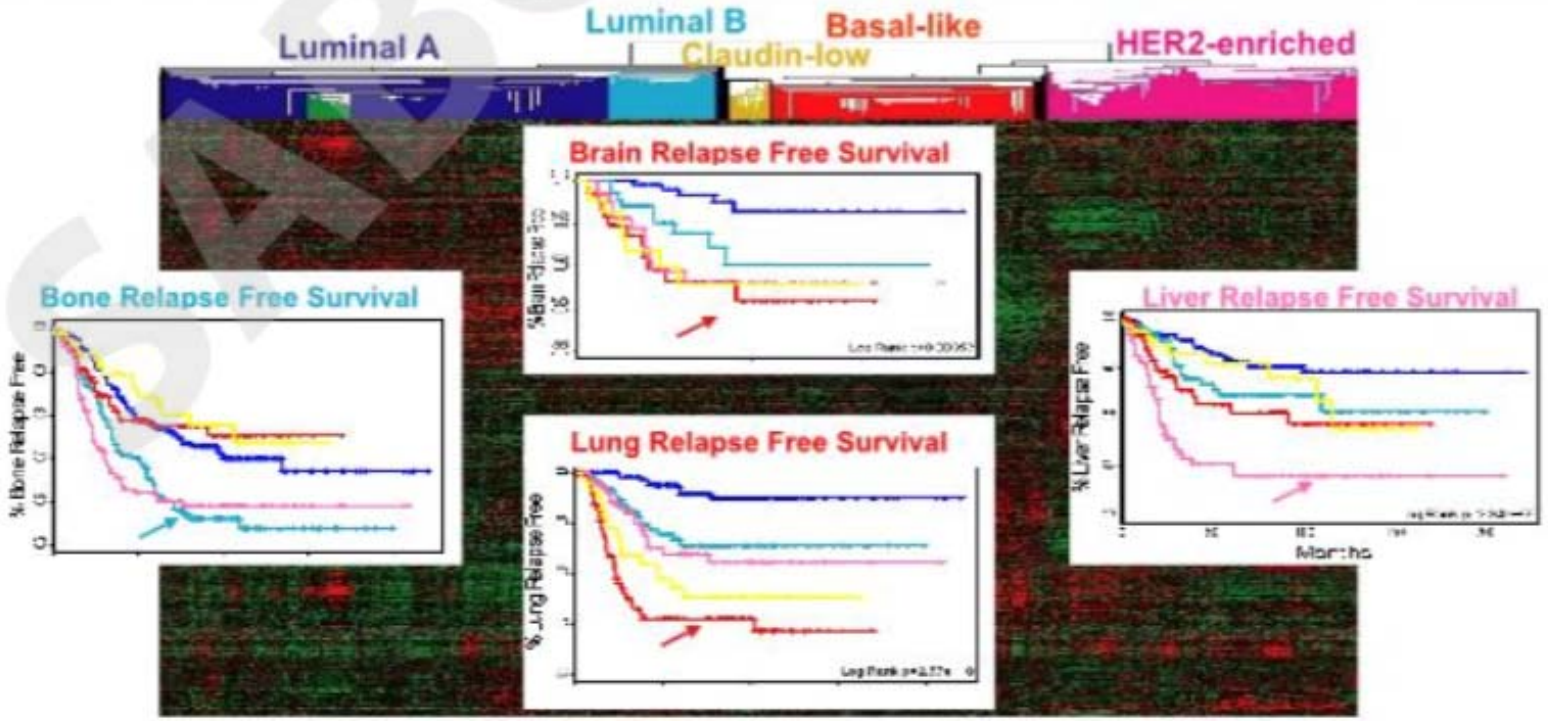
Breast cancer subtypes predict future site of metastasis



Harrell JC, Prat A, Parker JS, Fan C, He X, Carey LA, Anders CK, Ewend M, Perou CM. 2012. *BCRT*. PMID: 21671017

Siegel et al SABCS 2015

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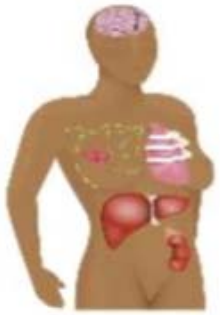
Methods



14 patients with matched primary + ≥ 2 metastases from 44 participants in rapid autopsy program* (63 total specimens)

- **DNAseq**: Agilent SureSelect XT DNA Exome capture followed by Illumina HiSeq 2x100 bp paired end reads
  - Mapped with BWA to matched normal, adjusted with ABRA, and variants called with STRELKA.
  - Copy Number Variants (CNV) called using SYNTHEX
- **RNAseq:** Illumina TruSeq mRNA library prep followed by Illumina HiSeq 2x50 bp paired end reads
  - Mapped using MAPSPLICE
  - Quantitated using RSEM with upper quantile normalization

*program designed to collect tissues within 6 hours of death

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Siegel et al SABCS 2015

Clinical characteristics of 14 metastatic patients

Age at Diagnosis (years old)	60 yo (53 – 66 yo)
ER/PR/HER2 status at dx	# (PAM50)
TNBC	9 (All Basal-like)
HER2+ (Any ER/PR)	2 (1 HER2-enriched, 1 Basal)
ER+/PR+/HER2-	3 (All Luminal A)
Time to Relapse	17 months (range: 0 – 8 years)
Total Lines of Therapy after Relapse	
Chemotherapy	4 (range: 1 - 15)
Endocrine Therapy	2.5 (range: 0 - 5)
HER2 Therapy	1
Overall Survival from Relapse	18 months (range: 2 months - 13 years)
Number of Metastases per Patient	
Known Prior to Autopsy	6 (range: 2 - 16)
Collected at Autopsy	9 (range: 2 - 27)
Sequenced per Patient (RNA and DNA)	5 (range: 2-7)

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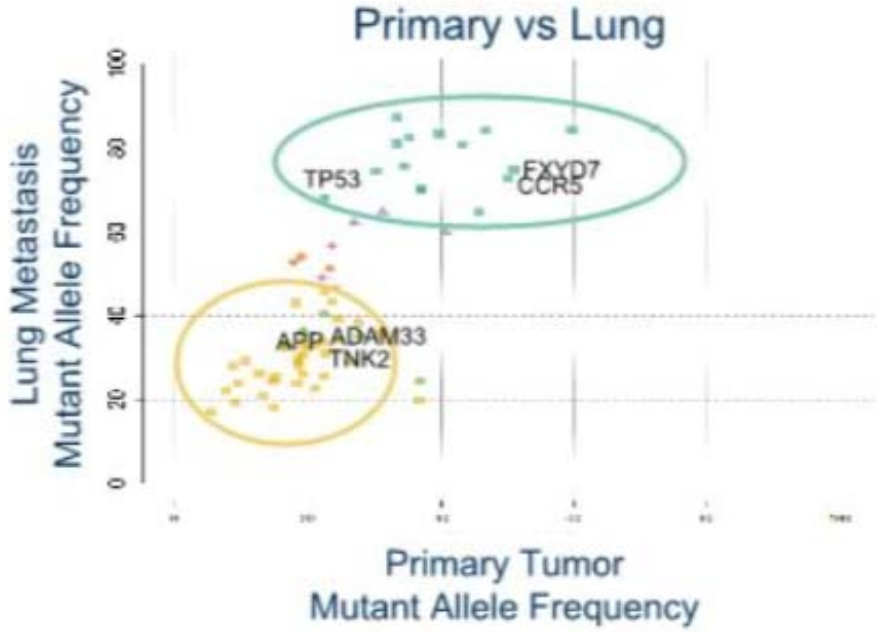
Clonality Analysis of Matched Primaries and Metastases Using DNA Mutant Allele Frequency

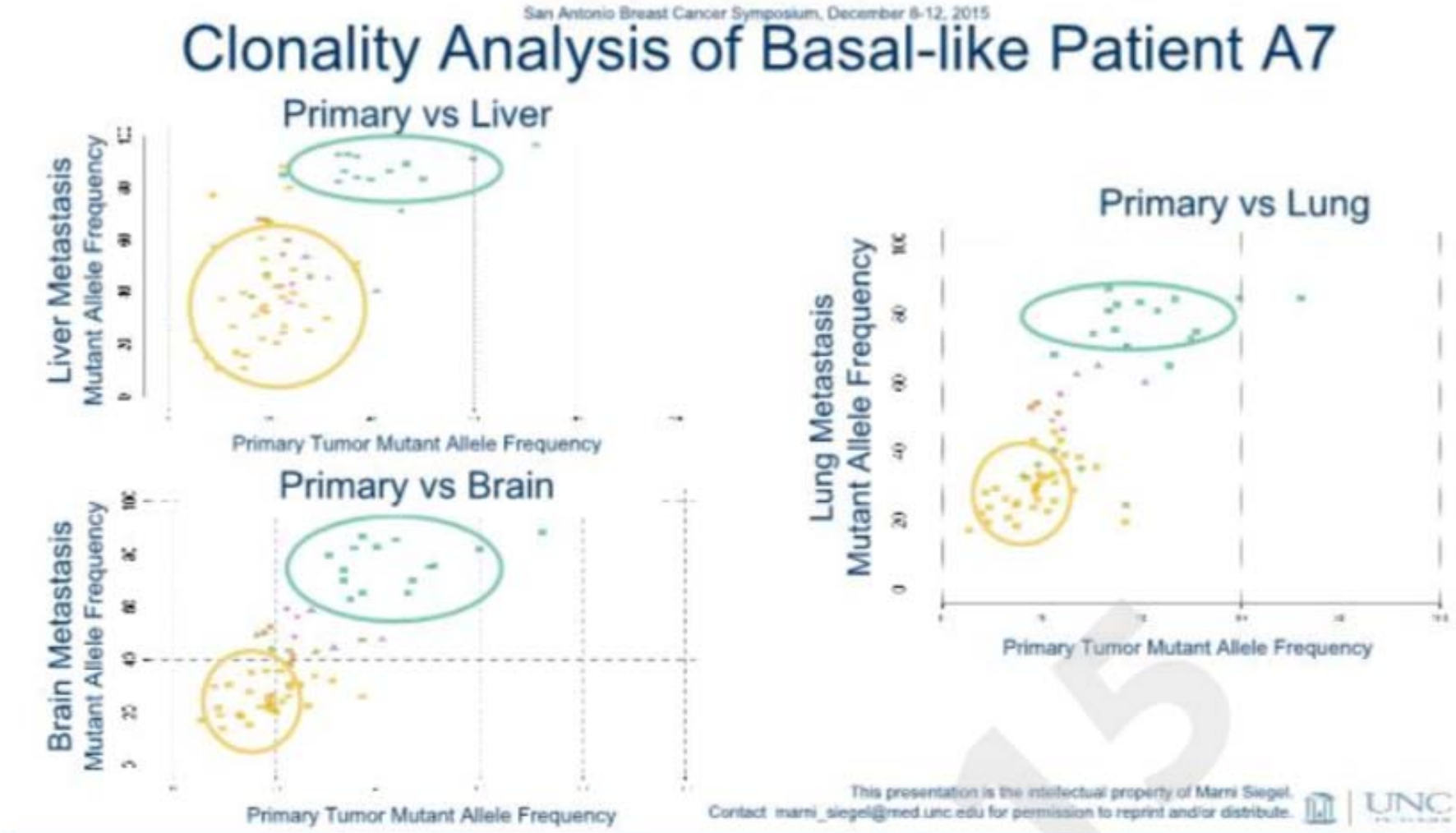
	Primary	Brain	Lung	Liver
CCR5	50.00	75.00	72.73	83.33
ZDK1B	37.04	86.67	70.59	83.87
CXXC11	33.33	69.84	87.34	92.86
DDRGK1	45.69	65.12	64.89	71.11
FXYD7	51.00	75.47	74.85	75.00
YRPH	22.58	38.10	68.18	85.00
RAPGEF4	34.62	62.50	75.56	86.36
HIM52	72.22	88.06	84.75	96.55
RUNK1T1	59.79	81.59	84.43	91.28
TMEM132C	35.19	82.26	82.50	92.54
TP53	30.30	79.63	74.29	96.55
LTN	36.99	65.38	69.81	91.94
ZC3H7A	33.33	73.91	81.05	82.26
ADAM33	32.73	30.67	31.00	27.18
APP	24.58	38.23	34.43	39.58
BAI2	18.18	35.59	43.08	66.47
CERKL	22.58	38.24	45.83	88.24
ELASP2	9.52	13.93	24.09	16.61
COL26A1	24.49	38.51	39.13	48.61
DHRS9	15.07	25.11	25.35	15.85
IPP7	31.01	21.88	35.68	38.00
FSD1	19.44	26.67	30.77	45.71
HUWE1	23.64	71.82	43.48	80.00
EGL1	22.48	29.68	25.42	24.57
RNF157	12.96	19.05	26.39	26.92
RSBN1	22.17	26.19	33.78	38.36
SEMG1	19.27	22.67	26.09	32.74
EC2N	16.64	36.43	29.27	37.50
FJP3	19.44	28.51	33.33	66.67
TNK2	21.13	35.59	32.93	42.16
TUBB4A	16.83	21.98	32.47	39.68
XRN1	18.71	23.68	29.05	34.93



Miller CA *et al.* 2014. *PLoS Comput Biol.* PMID: 25102416.

UNC

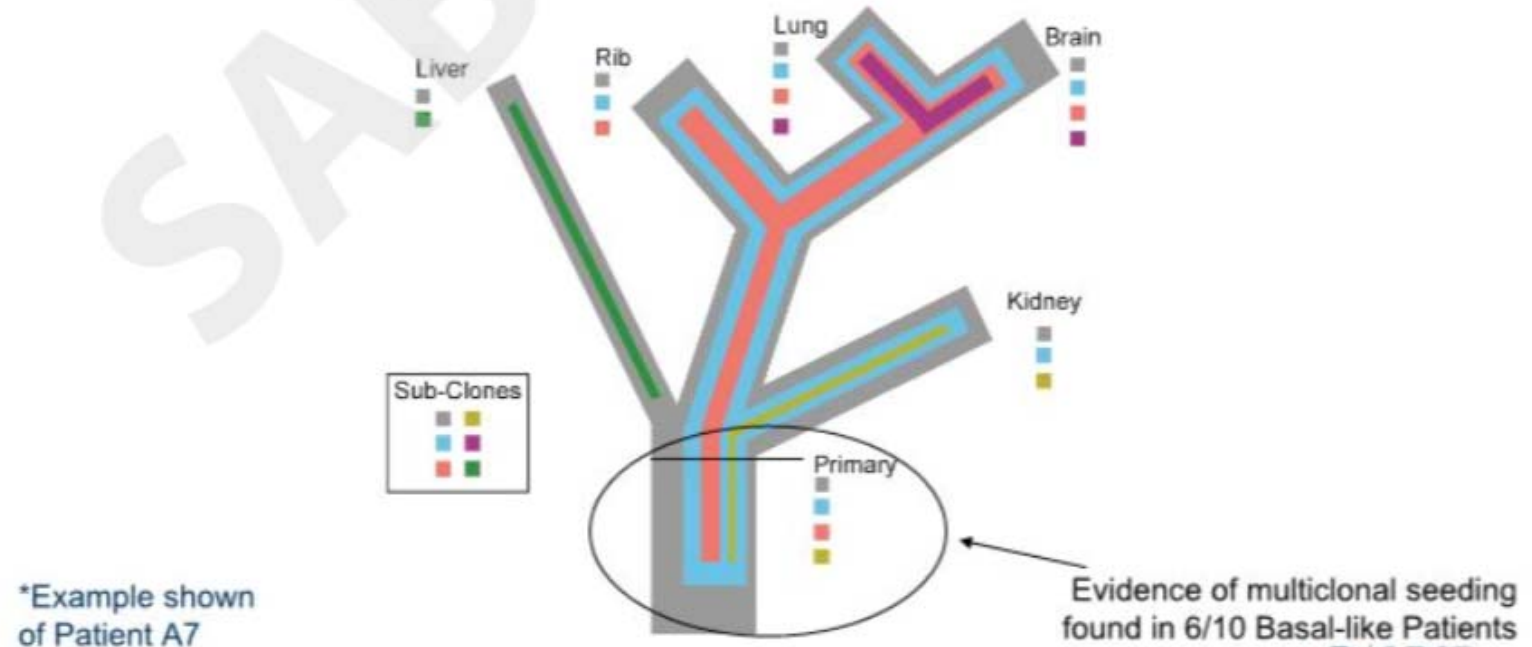
Siegel et al SABCS 2015



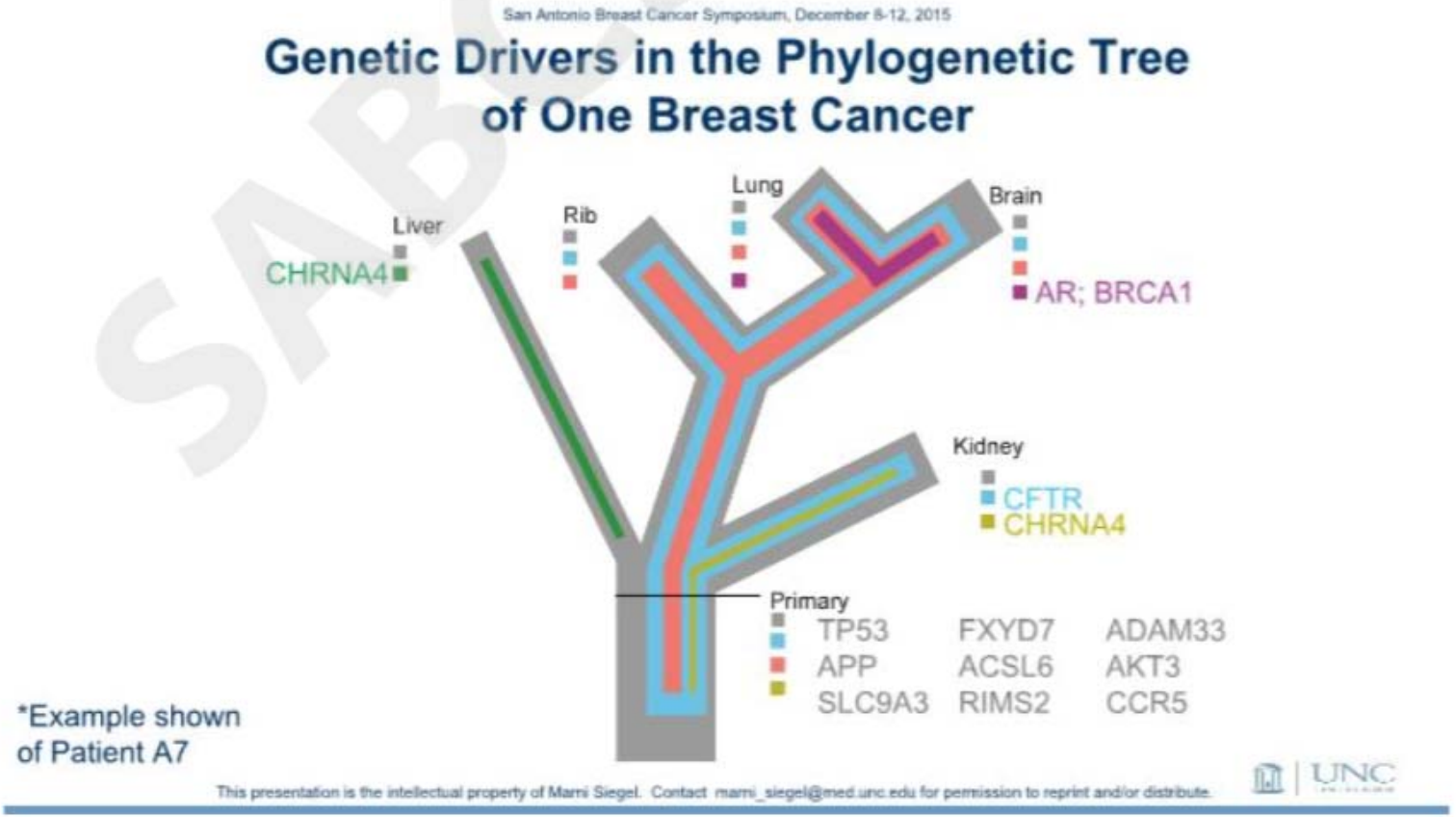
Siegel et al SABCS 2015

San Antonio Breast Cancer Symposium, December 8-12, 2015

Phylogenetic Tree Analysis of Basal-like A7



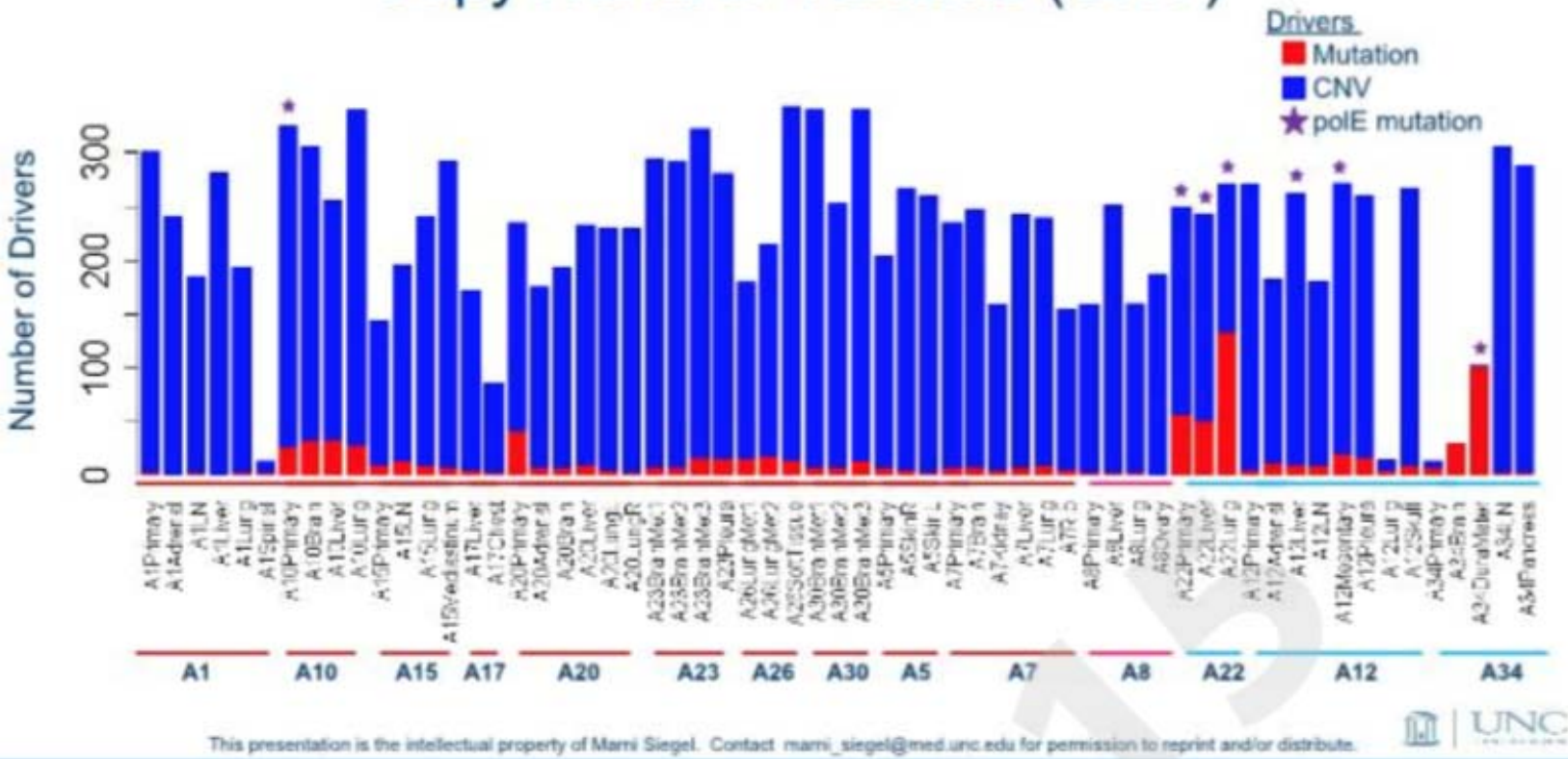
Siegel et al SABCS 2015



Siegel et al SABCS 2015

San Antonio Breast Cancer Symposium, December 8-12, 2015

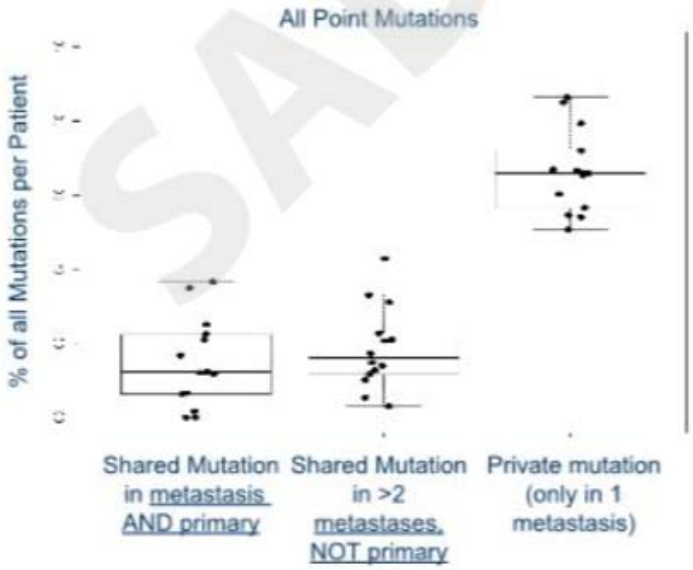
Proportion of Drivers from Point Mutations and Copy Number Variants (CNV)

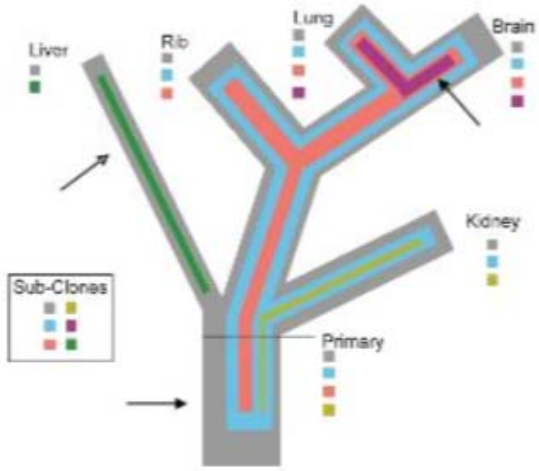


Siegel et al SABCS 2015

San Antonio Breast Cancer Symposium, December 8-12, 2015

DNA Alterations in the Development of Metastases (**all** alterations)

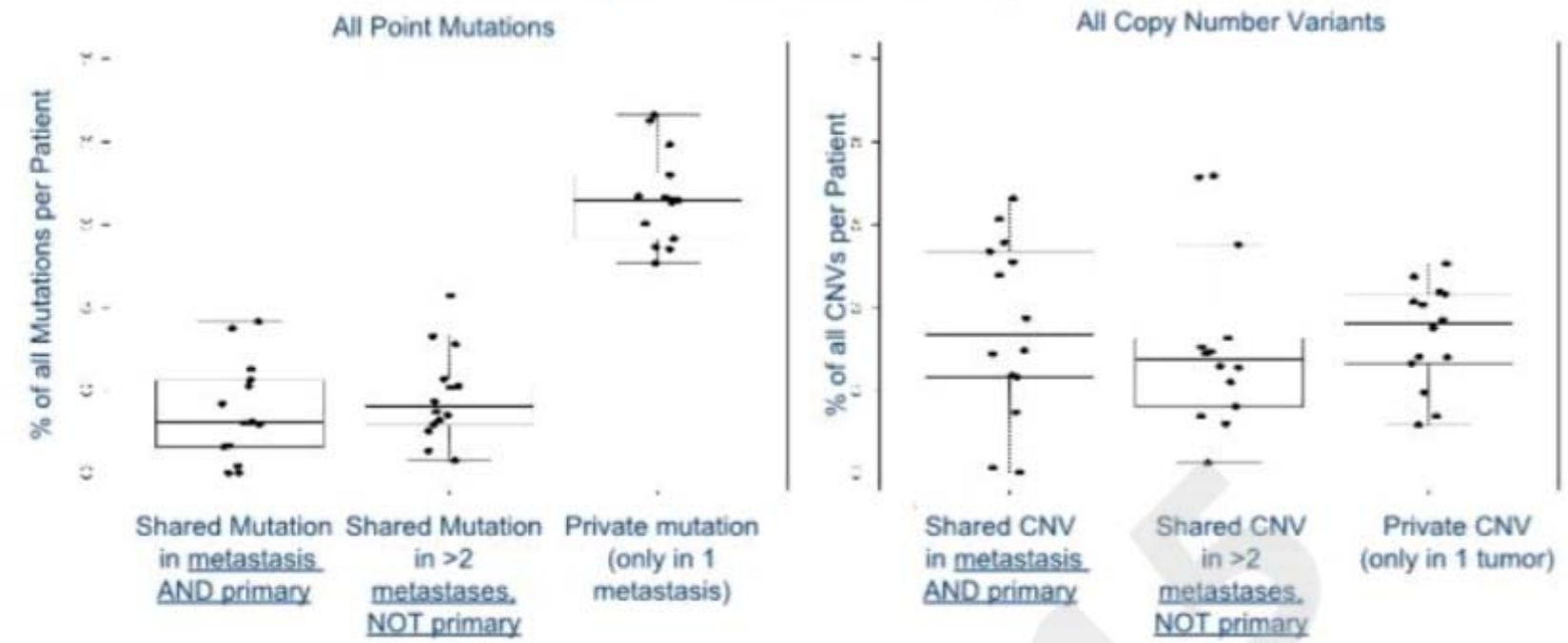




Siegel et al SABCS 2015

San Antonio Breast Cancer Symposium, December 8-12, 2015

DNA Alterations in the Development of Metastases (**all** alterations)

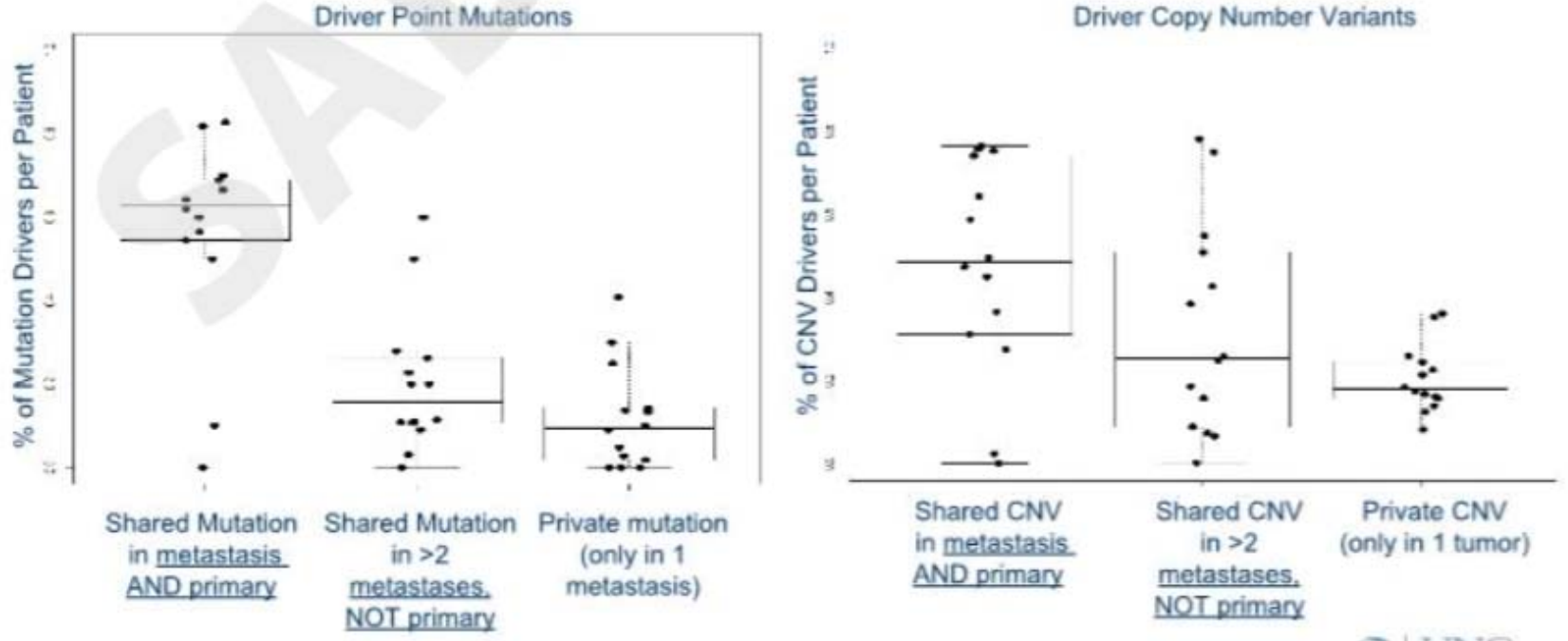


UNC

Siegel et al SABCS 2015

San Antonio Breast Cancer Symposium, December 8-12, 2015

DNA Alterations in the Development of Metastases (**only** DawnRank drivers)



Siegel et al SABCS 2015

Conclusions

- Metastasis can be the result of multi-clonal seeding from primary
- Functional drivers using the integration of DNA alterations and RNA gene expression for individual tumors provide evidence that:
- DNA copy number Variants (CNV) accounts for the large majority of individual tumor drivers in both primaries and metastases
- Most genetic drivers, whether from CNV or point mutations, are established in the primary breast cancer

Siegel et al SABCS 2015

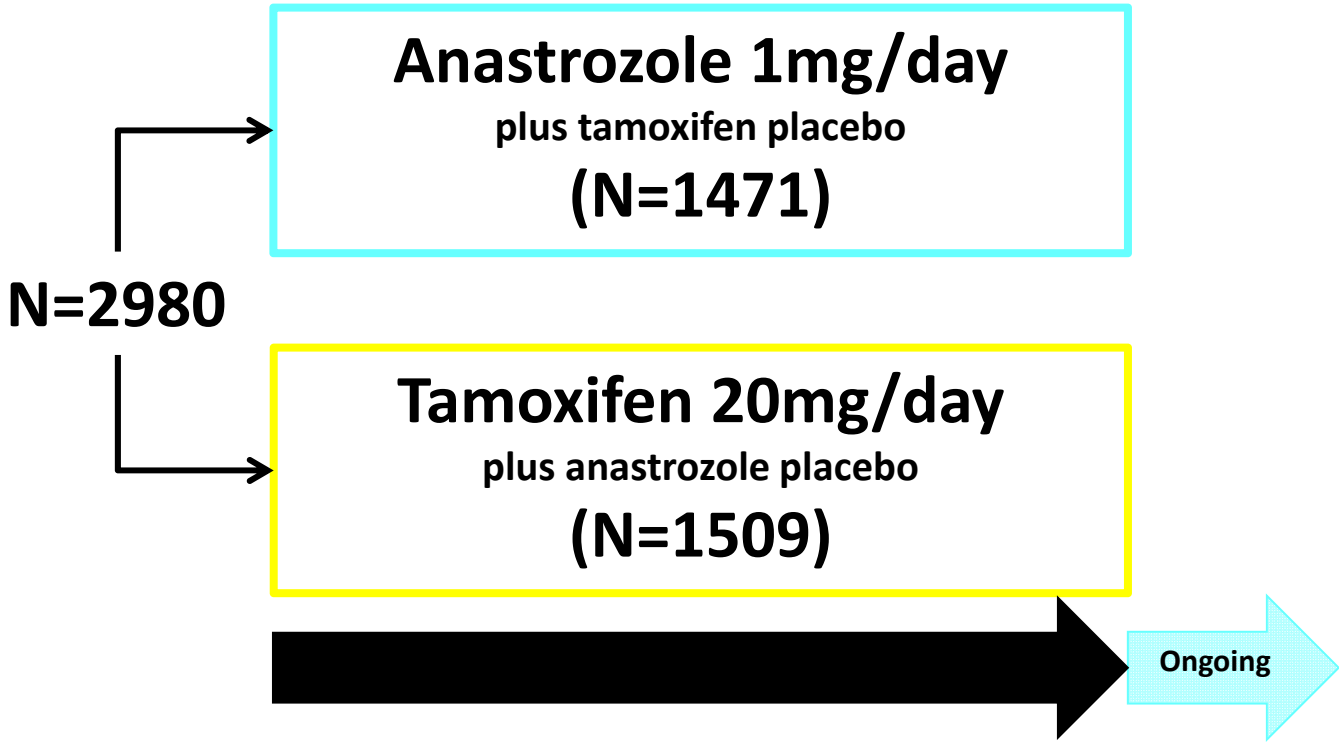
Anastrozole versus tamoxifen for the prevention of loco-regional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in-situ (IBIS-II DCIS)

Cuzick et al SABCS 2015

Trial Schema

Postmenopausal women:

- Aged 40-70 years
- Locally excised ER+ DCIS within last 6 months
- Atypical hyperplasia/LCIS



Primary analysis: **1449 anastrozole - 1489 tamoxifen**
(excluding those who withdrew consent for data use)

Primary endpoint: All breast cancer recurrence (incl. DCIS)

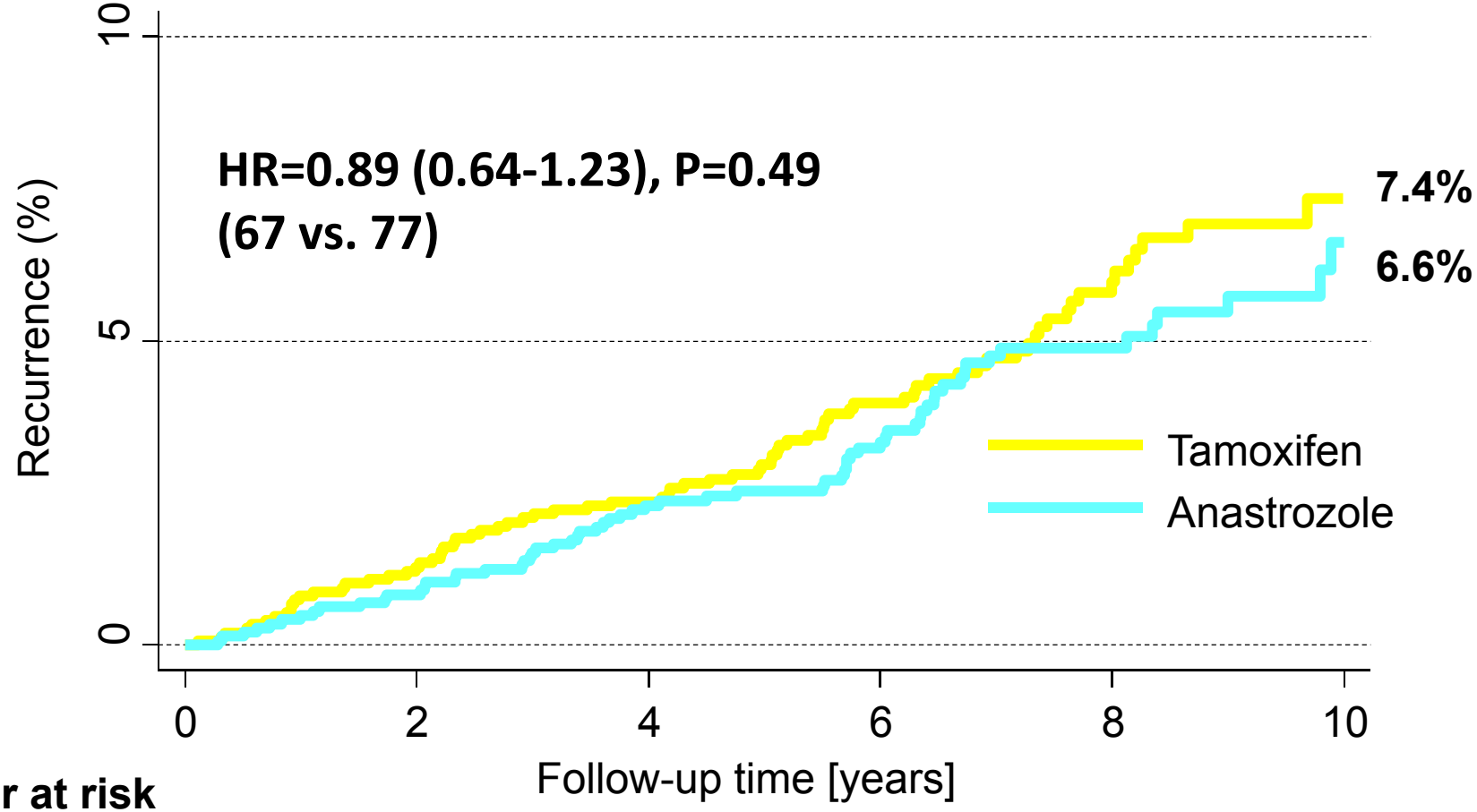
Median follow-up: 7.2 years (IQR 5.6-8.9)

Baseline demographics

	Anastrozole (N=1449)	**Tamoxifen (N=1489)**
Age (years), median (IQR)	60.4 (56.4-64.5)	60.3 (55.8-64.5)
BMI (kg/m^2), median (IQR)	26.7 (23.5-30.4)	26.6 (23.7-30.2)
Ever users of HRT	46.8%	44.2%
Hysterectomy	28.0%	27.4%
Radiotherapy	70.9%	71.5%
Tumour size (mm), median (IQR) (560 missing)	13 (7-22)	13 (7-22)
Margins, (mm), median (IQR) (56 missing)	5 (2-10)	5 (2-10)
Grade (local)		
Low	20.2%	18.7%
Intermediate	41.8%	41.5%
High	37.4%	39.4%

Breast cancer recurrence

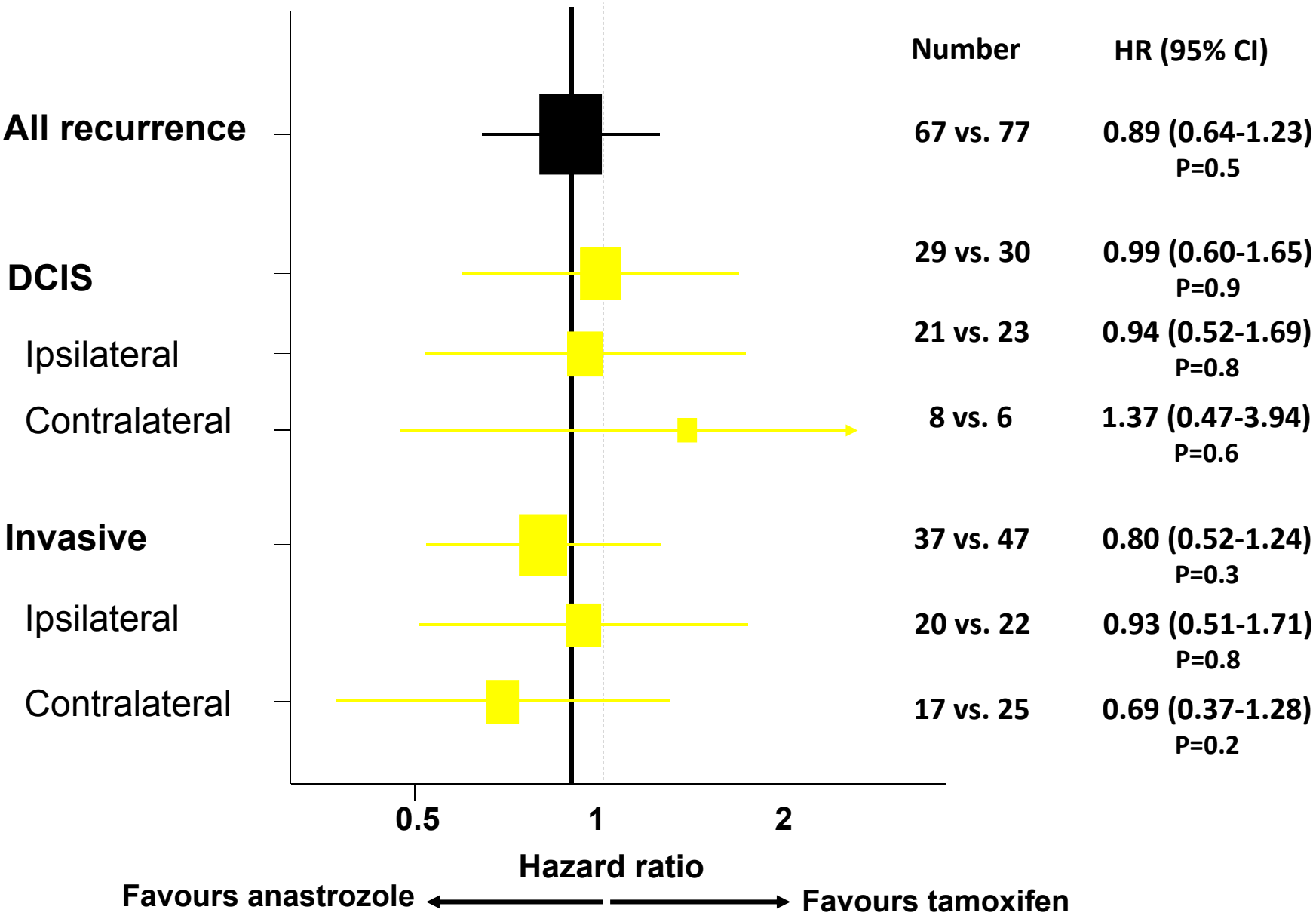
(invasive and DCIS)



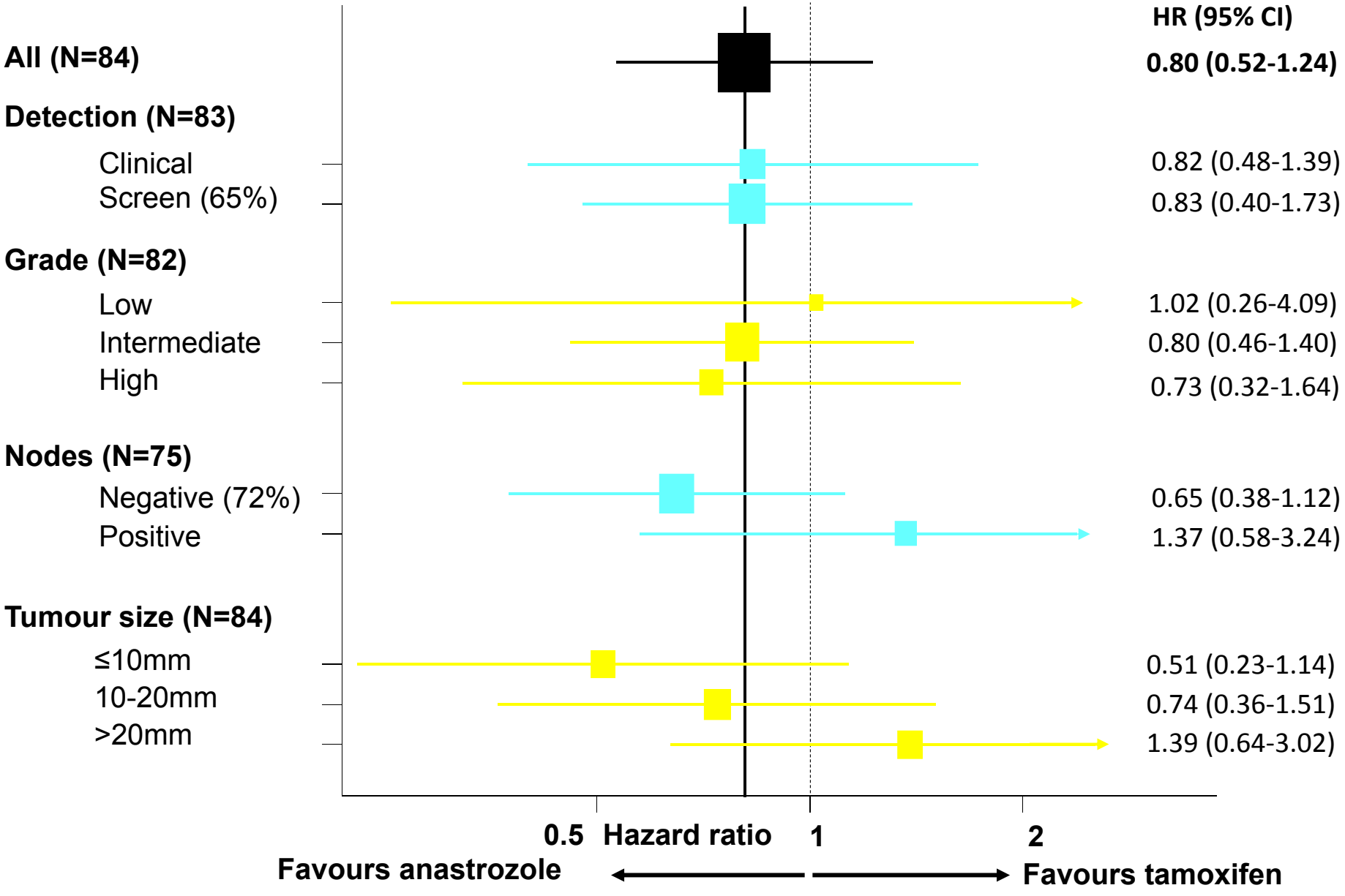
Number at risk

Tamoxifen	1489	1465	1372	1032	553	177
Anastrozole	1449	1434	1345	1006	541	185

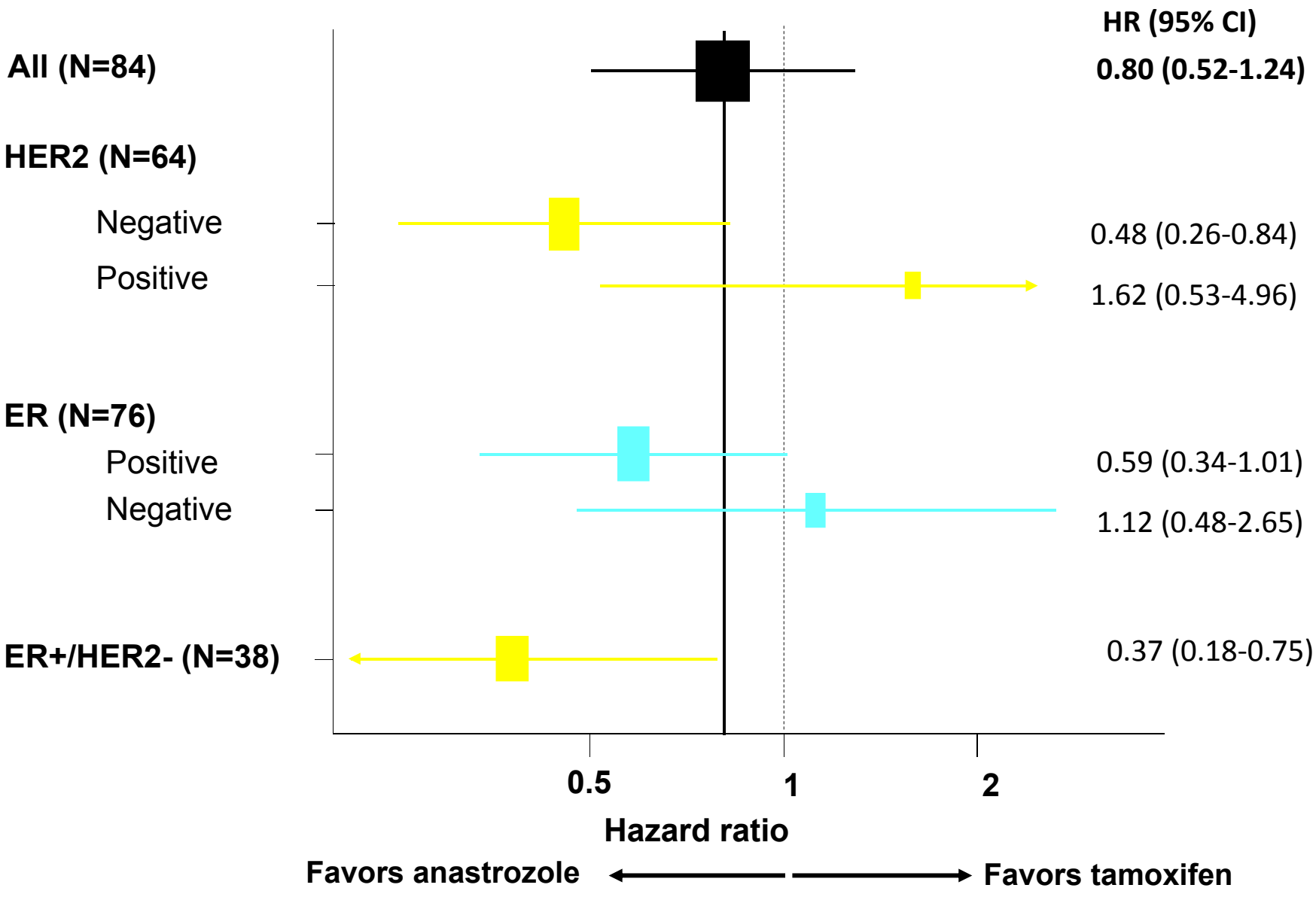
Breast cancer recurrence



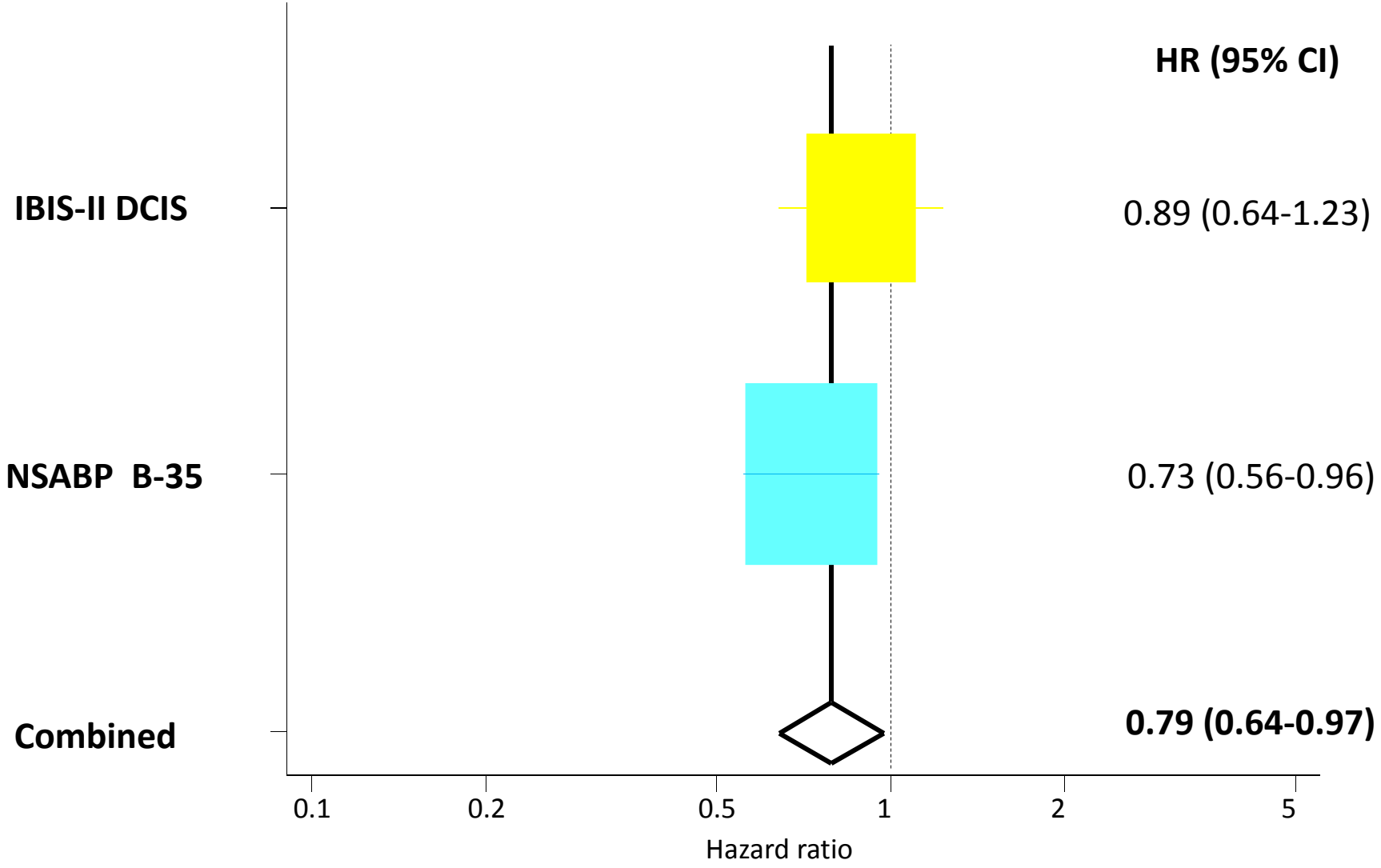
Invasive recurrence: subgroup analysis



Invasive recurrence: subgroup analysis cont.



Meta-analysis



Deaths

	Anastrozole (N=1449)	Tamoxifen (N=1489)	HR (95% CI)
All	**33 (2.3%)**	**36 (2.4%)**	**0.93 (0.58-1.50)**
Breast cancer	**1**	**3**	
Other cancer	15	12	
Colorectal cancer	2	2	
Lung cancer	6	2	
Endometrial cancer	0	1	
Pancreas cancer	1	3	
CVA/Stroke/Thromboembolic	5	7	
Myocardial infarction	2	2	
Other	4	5	
Unknown	6	7	

Other cancer

	Anastrozole (N=1449)	Tamoxifen (N=1489)	OR (95% CI)	P-value
Total	**61**	**71**	**0.88 (0.61-1.26)**	**0.5**
Gynaecological	1	17	0.06 (0.001-0.38)	0.0002
Endometrial	1	11	0.09 (0.002-0.64)	0.004
Ovarian	0	5	0.00 (0.00-0.79)	0.03
Skin	12	23	0.53 (0.24-1.12)	0.07
Melanoma	4	4	1.03 (0.19-5.53)	0.9
Non-melanoma	8	19	0.43 (0.16-1.03)	0.04
Gastrointestinal	16	10	1.65 (0.70-4.08)	0.2
Colorectal	10	5	2.06 (0.64-7.71)	0.2
Lung	11	7	1.62 (0.57-4.94)	0.3
Lymphoma/Leukaemia	8	5	1.65 (0.47-6.42)	0.4
Other	13	9	1.49 (0.59-3.96)	0.4

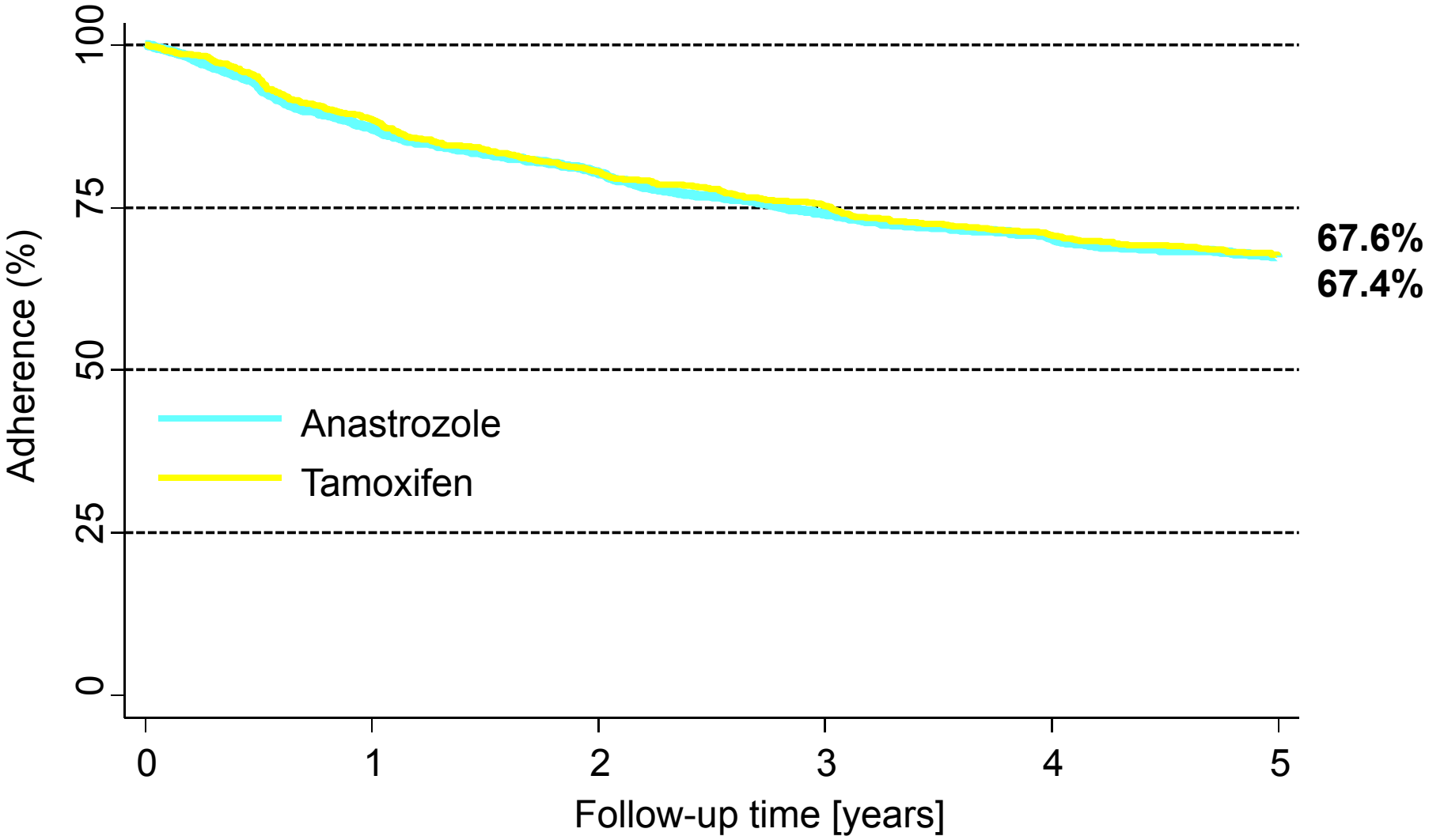
Adverse events

	Anastrozole (N=1449)	Tamoxifen (N=1489)	OR (95% CI)	P-value
Fractures	**129**	**100**	**1.36 (1.03-1.80)**	**0.03**
Pelvic, hip	11	4	2.84 (0.84-12.25)	0.06
Spine	6	6	1.03 (0.27-3.85)	0.9
Major thromboembolic	**7**	**24**	**0.30 (0.11-0.71)**	**0.003**
Pulmonary embolism (PE)	5	8	0.64 (0.16-2.23)	0.4
Deep vein thrombosis (without PE)	2	16	0.13 (0.01-0.54)	0.001
Any cardiovascular	**93**	**84**	**1.15 (0.84-1.57)**	**0.4**
Myocardial infarction	6	6	1.03 (0.27-3.85)	0.9
Cerebrovascular accident	13	4	3.36 (1.04-14.18)	0.025
Transient ischaemic attack	13	5	2.69 (0.90-9.65)	0.05
Hypertension	82	73	1.16 (0.83-1.63)	0.4

Side effects

	Anastrozole (N=1449)	Tamoxifen (N=1489)	OR (95% CI)	P-value
Any Musculoskeletal	**929 (64.1%)**	**811 (54.5%)**	**1.49 (1.28-1.74)**	**<0.001**
Arthralgia	832	729	1.41 (1.21-1.63)	<0.001
Joint stiffness	74	35	2.24 (1.46-3.47)	<0.001
Paraesthesia	42	23	1.90 (1.11-3.33)	0.01
Carpal tunnel syndrome	35	11	3.33 (1.64-7.29)	<0.001
Osteoporosis	97	54	1.91 (1.34-2.73)	<0.001
Muscle spasm	25	106	0.23 (0.14-0.36)	<0.001
Any Vasomotor/Gynaecological	**879 (60.7%)**	**1031 (69.2%)**	**0.69 (0.59-0.80)**	**<0.001**
Hot flushes	818	899	0.85 (0.73-0.99)	0.03
Vaginal bleeding	35	80	0.44 (0.28-0.66)	<0.001
Vaginal discharge	30	136	0.21 (0.14-0.32)	<0.001
Vulvovaginal candidiasis	8	42	0.19 (0.08-0.41)	<0.001
Vaginal dryness	189	159	1.25 (1.00-1.58)	0.047
Other				
Headache	82	61	1.40 (0.99-2.00)	0.049
Hypercholesterolemia	43	11	4.11 (2.07-8.86)	<0.001

Adherence


Adherence (%)
100
75
50
25
0
Anastrozole
Tamoxifen
67.6%
67.4%
0
1
2
3
4
5
Follow-up time [years]

Summary & Conclusions

- No significant difference in recurrence between anastrozole and tamoxifen
  - Trend for lower invasive recurrence with anastrozole (not significant)
    - Non-inferiority established (Upper CI for HR <1.25)
  - Data from all sources (B-35, ATAC, IBIS-II) support lower recurrences with anastrozole
- No overall effect on other cancers
  - Large decrease in endometrial, ovarian and skin cancer with anastrozole
  - Increase in gastrointestinal, lung, and lymphatic cancer with anastrozole (not significant)
- No effect on death (data not mature)

Summary & Conclusions (cont)

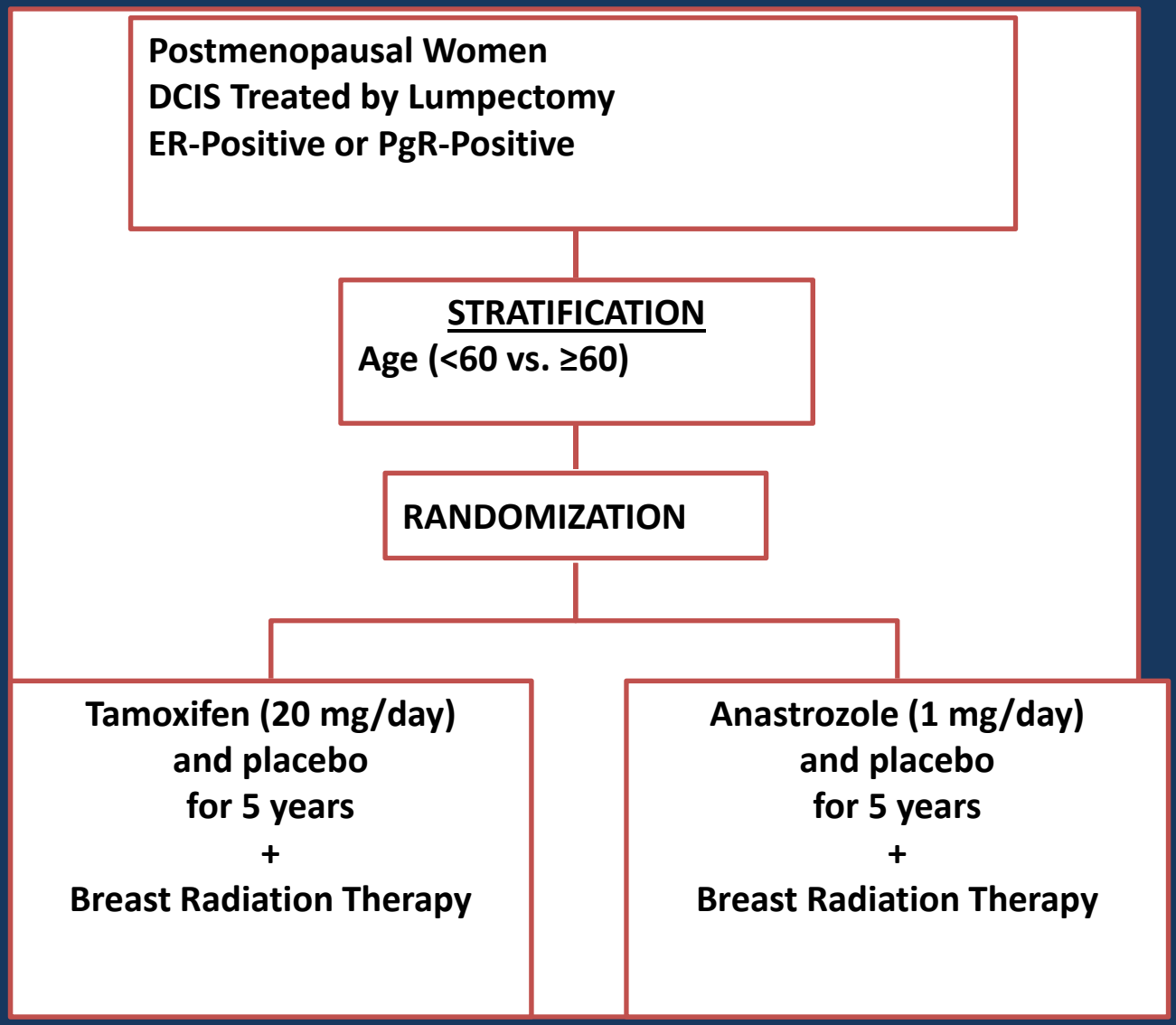
- Expected difference in side effect profiles
  - Increase in fractures and joint related symptoms with anastrozole
  - Decrease in vasomotor and gynaecological symptoms (except vaginal dryness), and muscle spasms with anastrozole
- Unexpected increase in CVA with anastrozole
  - Not seen in ATAC (62 anastrozole vs. 80 tamoxifen)

    or IBIS-II prevention (3 anastrozole vs. 6 placebo)
- No clear difference in effectiveness but significant differences in toxicity profiles

Patient-reported outcome (PRO) results, NRG Oncology/NSABP B-35: A clinical trial of anastrozole (A) vs tamoxifen (tam) in postmenopausal patients with DCIS undergoing lumpectomy plus radiotherapy

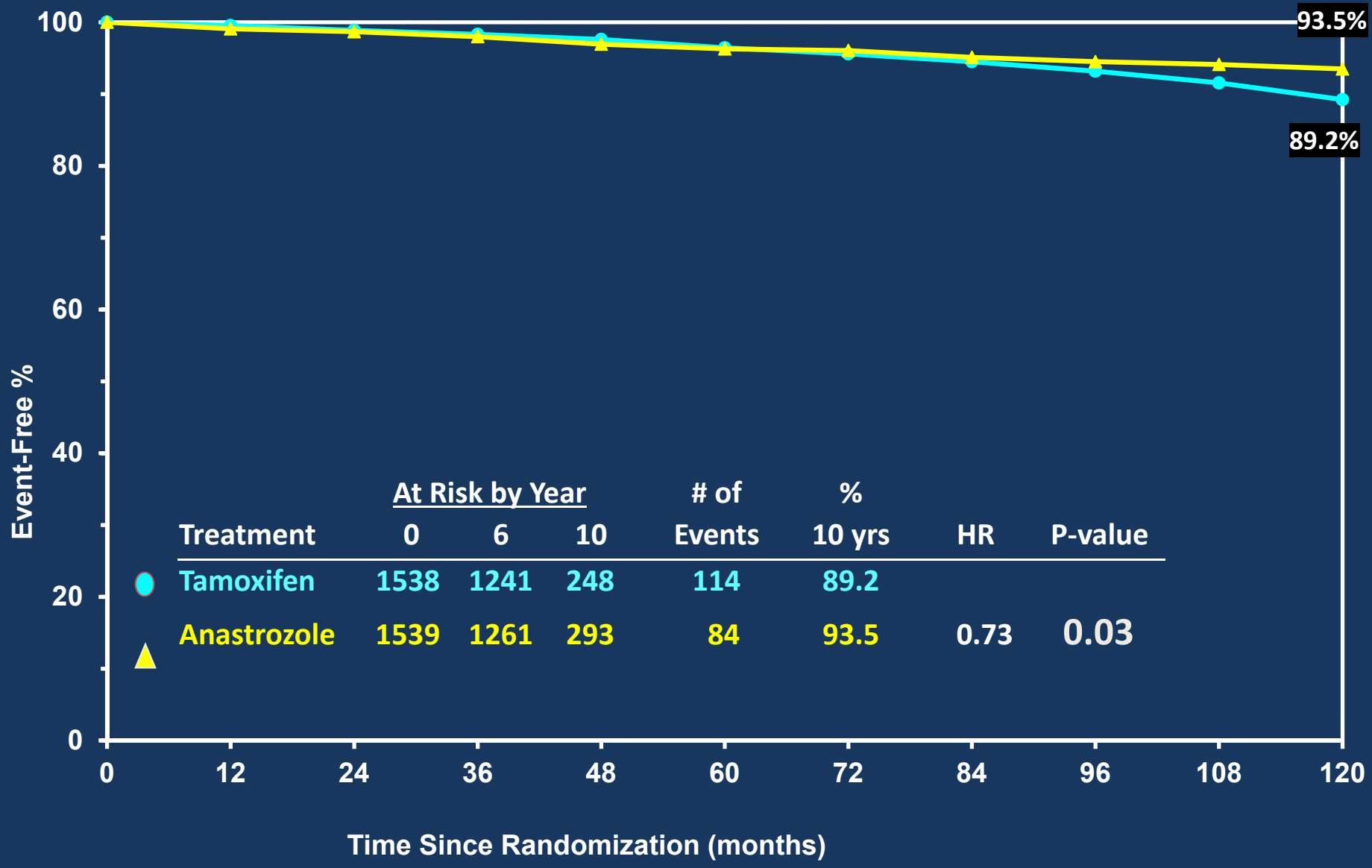
Ganz et al SABCS 2015

NRG Oncology/NSABP B-35 Schema



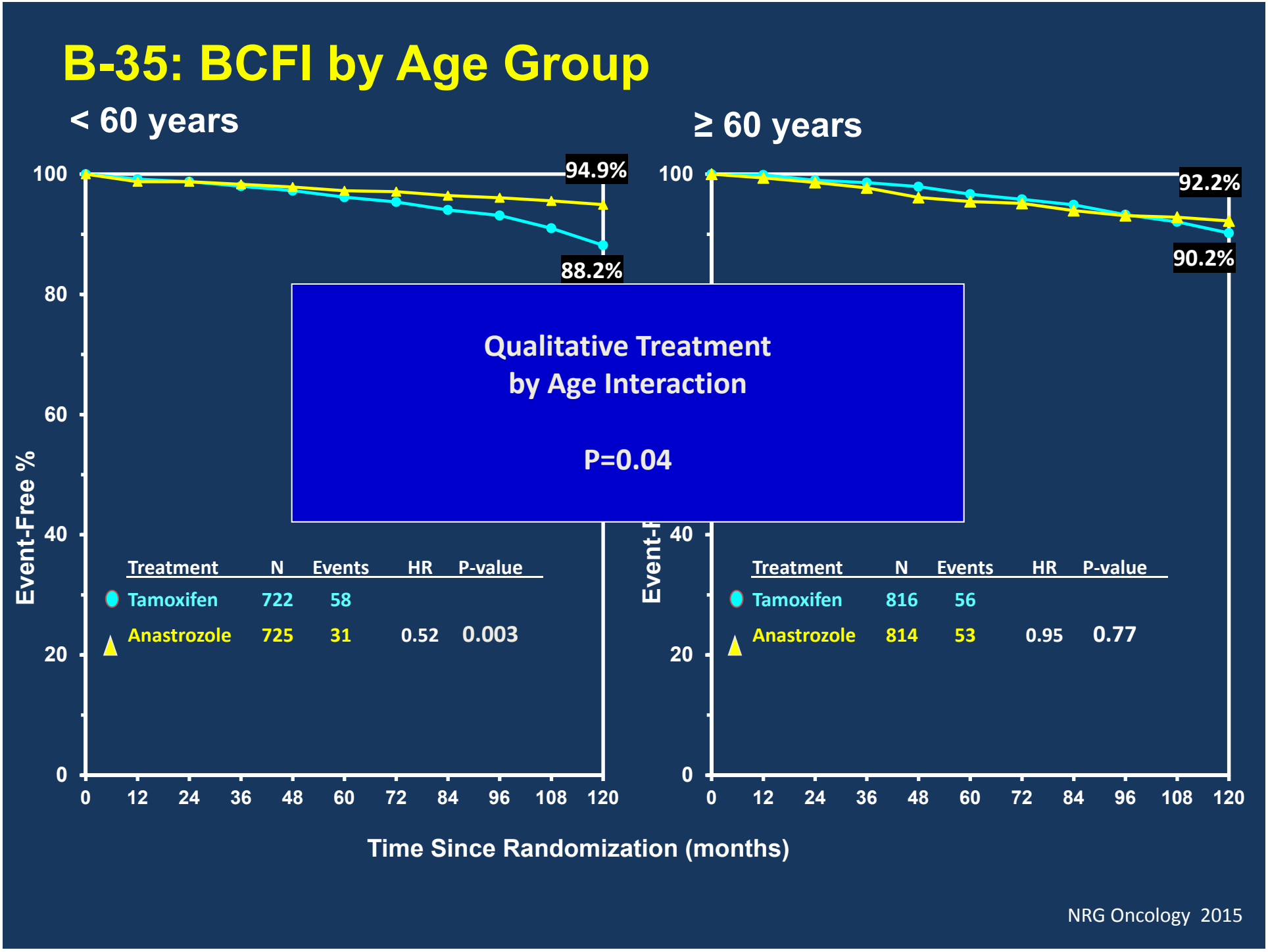
NRG Oncology 2015

B-35: Breast Cancer-Free Interval



Treatment	At Risk by Year 0	6	10	# of Events	% 10 yrs	HR	P-value
Tamoxifen	1538	1241	248	114	89.2		
Anastrozole	1539	1261	293	84	93.5	0.73	0.03

B-35: BCFI by Age Group

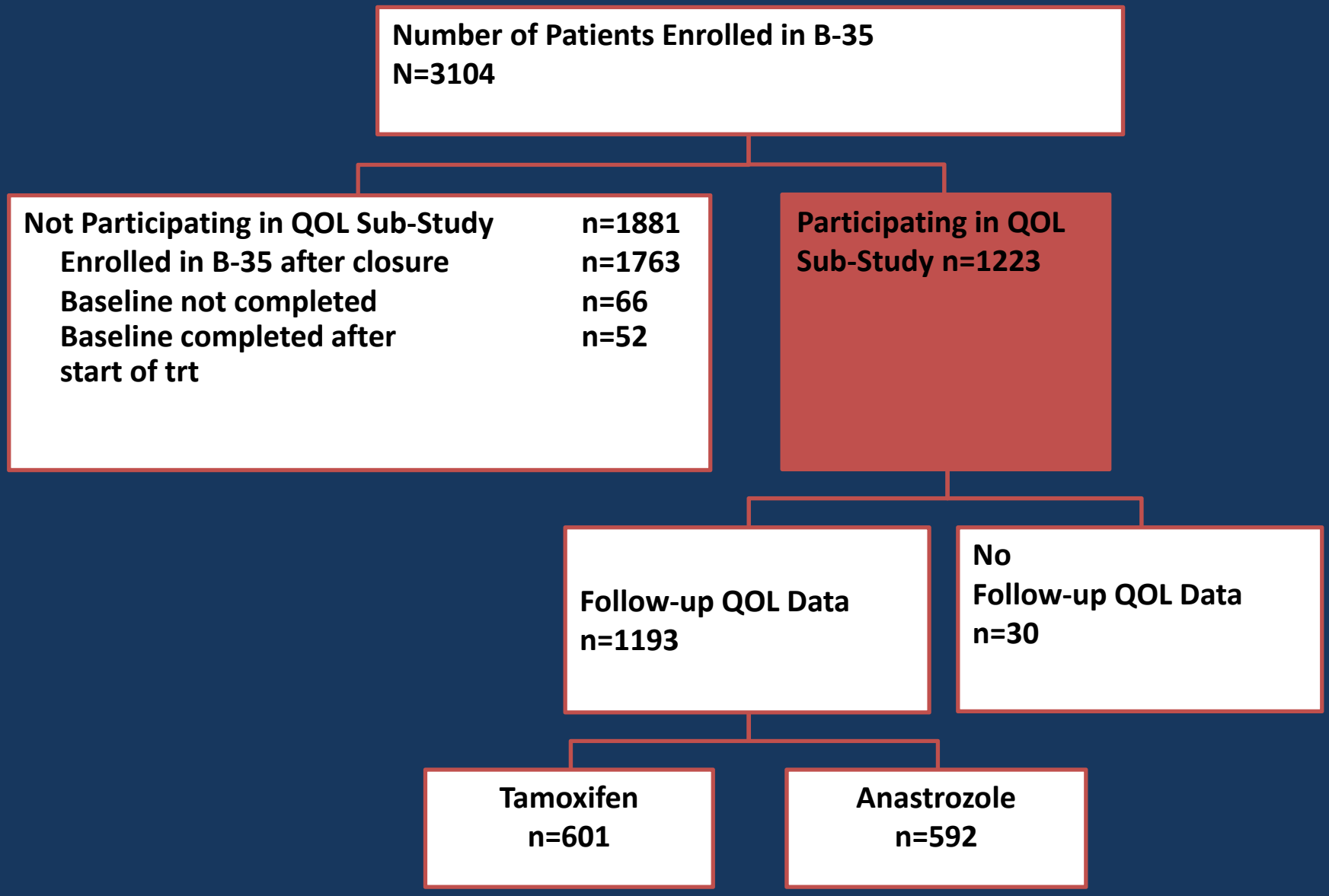


NRG Oncology 2015

PRO Instruments for QOL

- SF-12 Mental and Physical Component Scales
- SF-36 Vitality Scale
- BCPT symptom checklist scales
- CES-D short form for depressive symptoms
- MOS Sexual Problems Scale

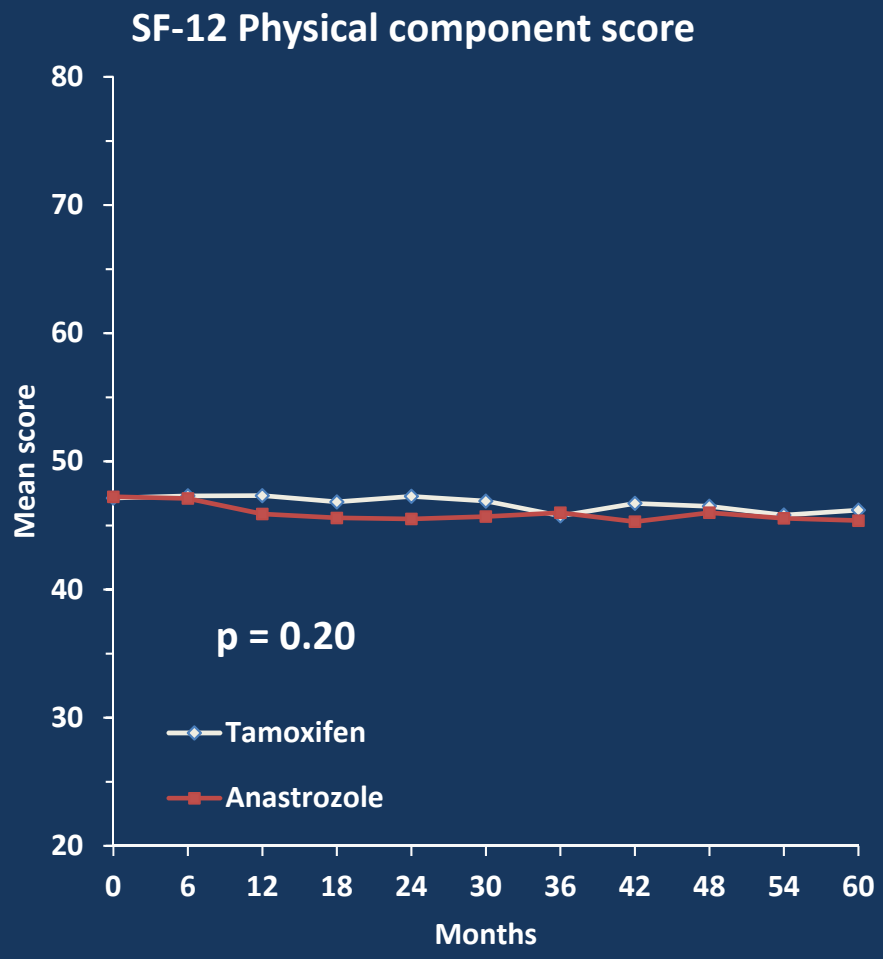
NRG Oncology/NSABP B-35 Consort

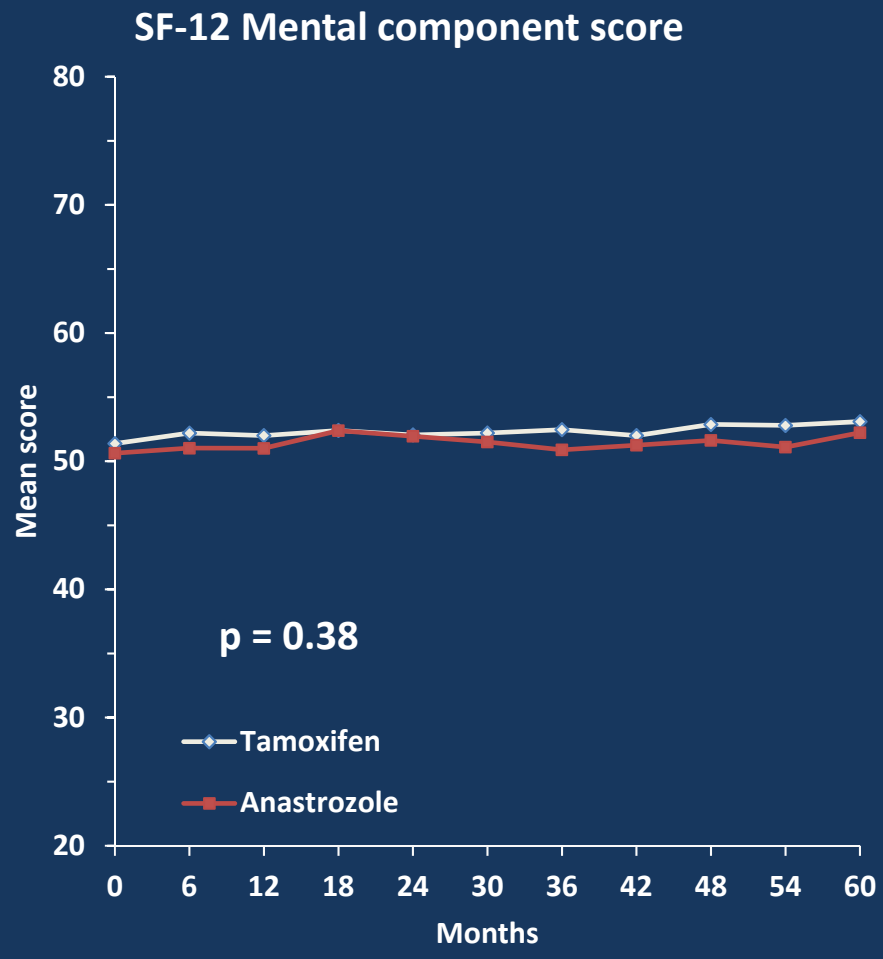


Patient Characteristics

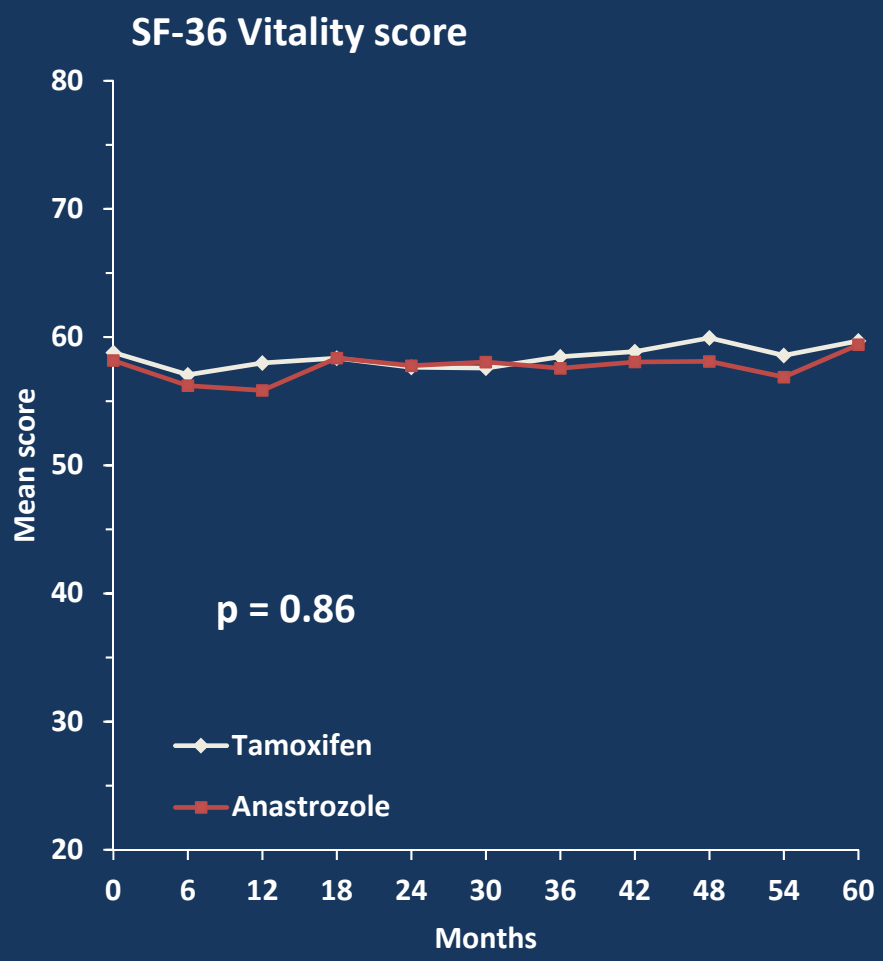
Characteristic	Tamoxifen		Anastrozole		TOTAL	
	n	%	n	%	n	%
Age						
<60	278	46.3	282	47.6	560	46.9
60+	323	53.7	310	52.4	633	53.1
Race						
White	529	88.0	516	87.2	1045	87.6
Black	47	7.8	55	9.3	102	8.5
Pacific Islander	2	0.3	2	0.3	4	0.3
Asian	16	2.7	12	2.0	28	2.3
Native American/Alaskan	0	0	1	0.2	1	0.1
Multi-racial	4	0.7	1	0.2	5	0.4
Unknown	3	0.5	5	0.8	8	0.7

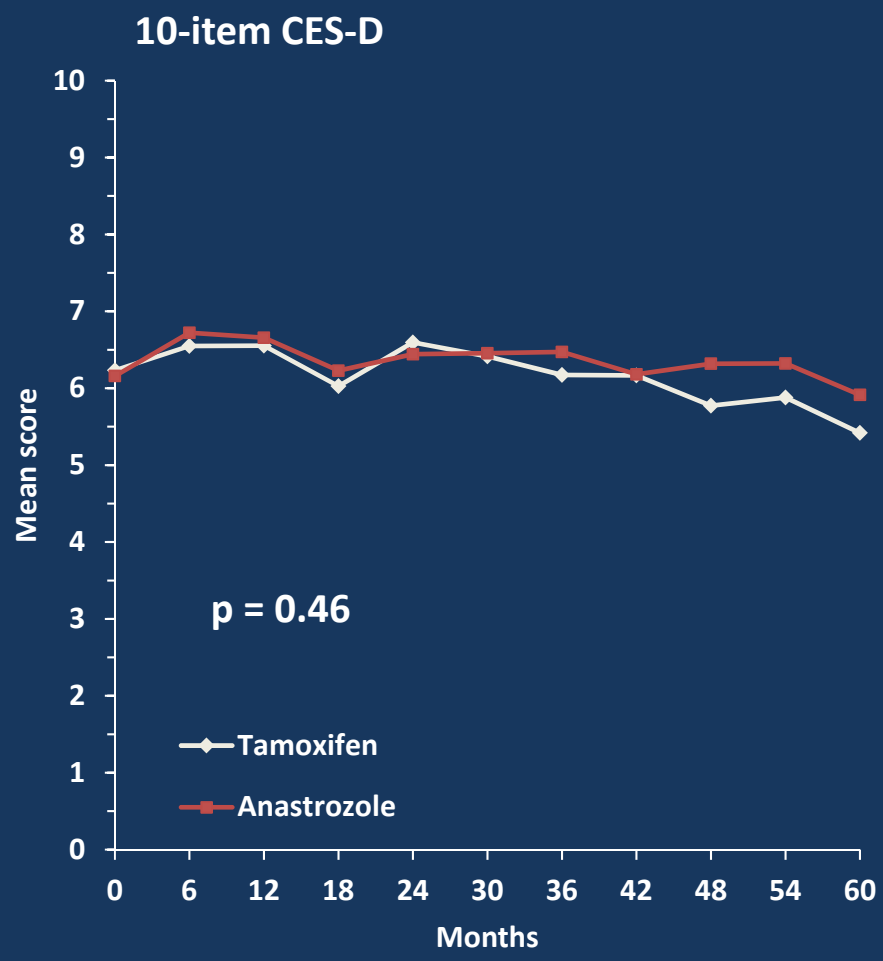
SF-12 Component Scores

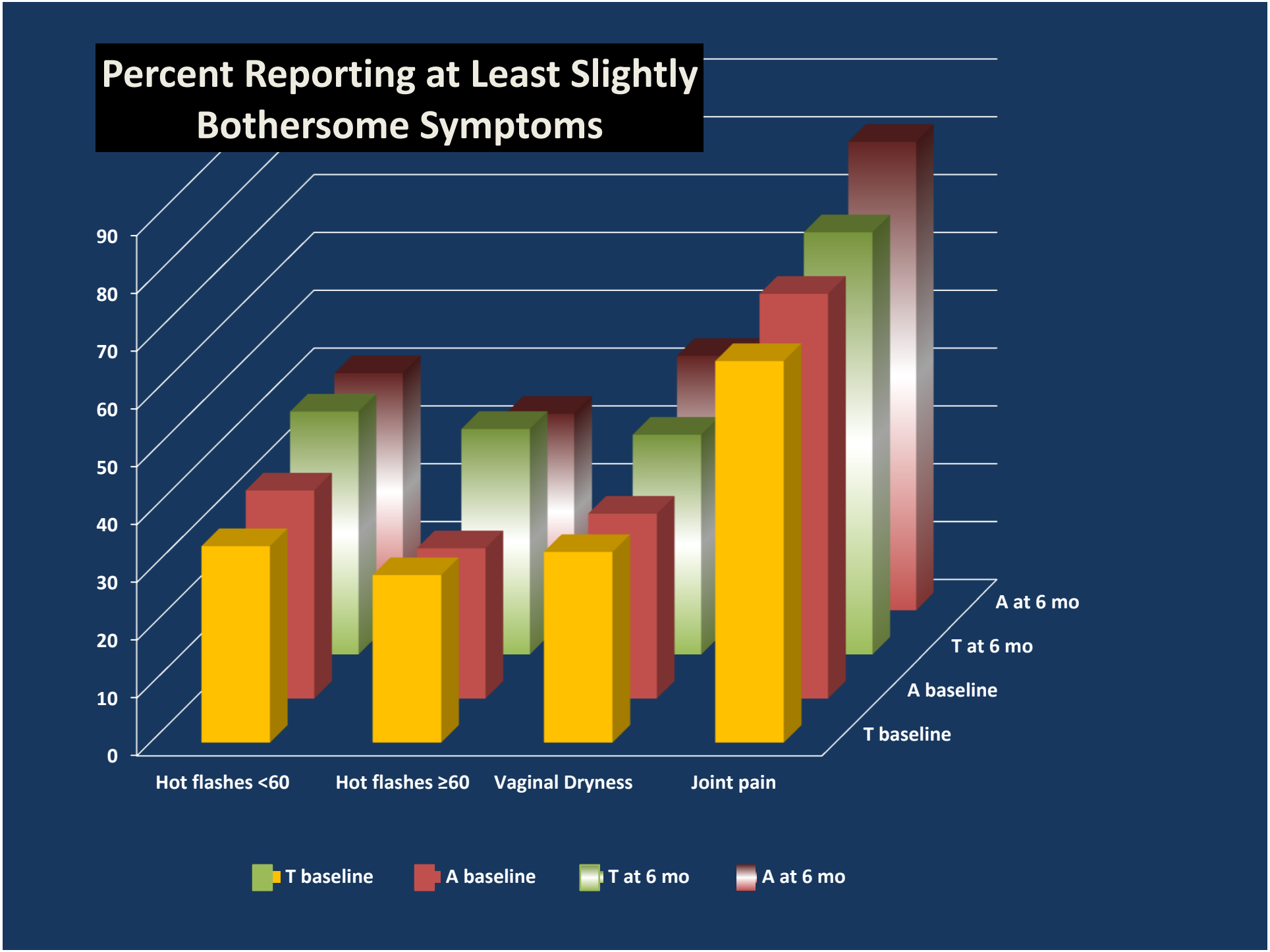




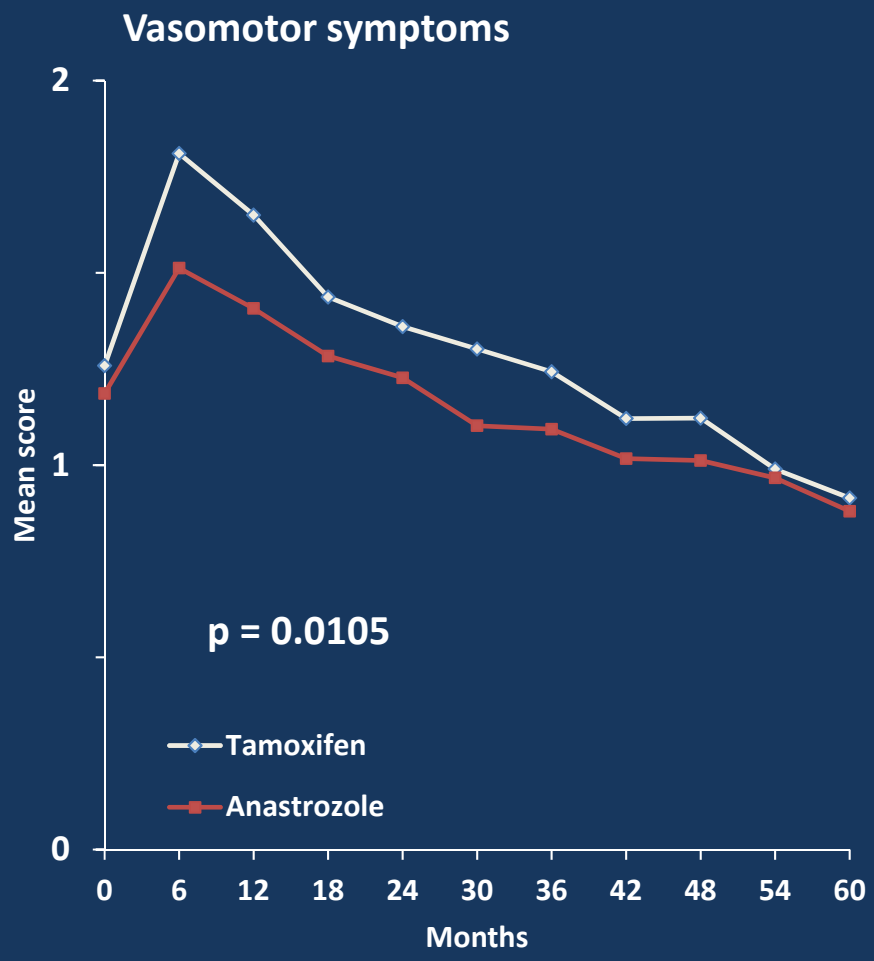
Vitality and Depressive Symptoms

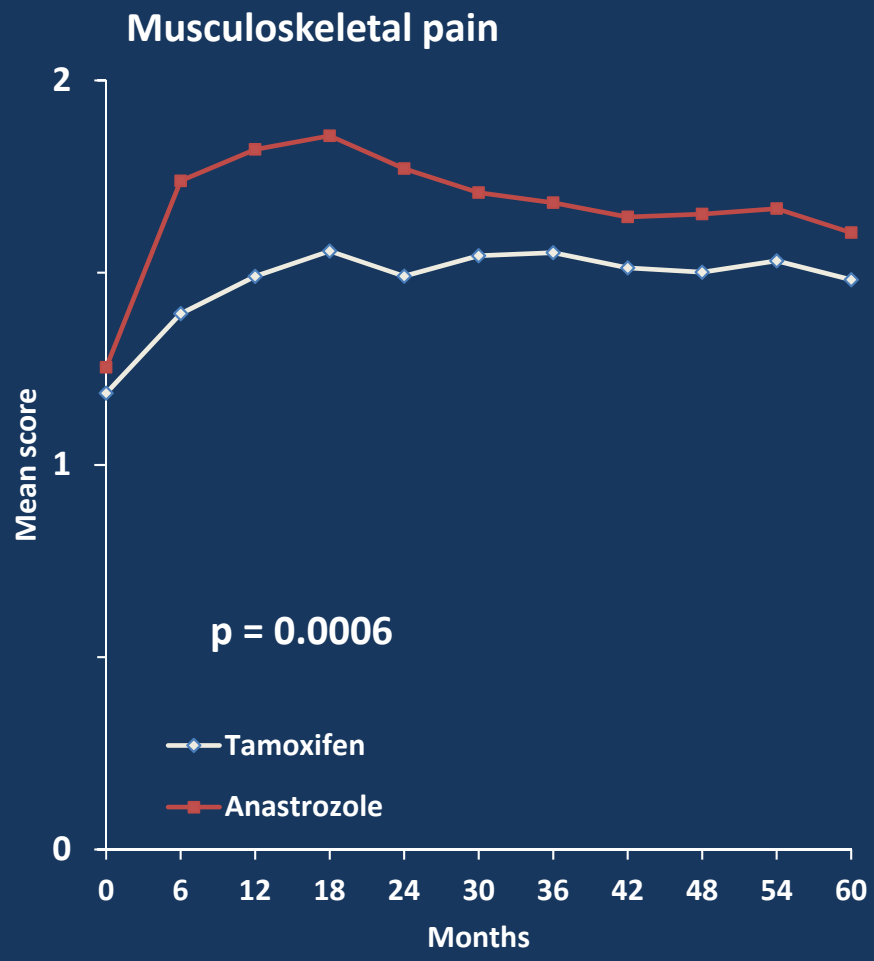




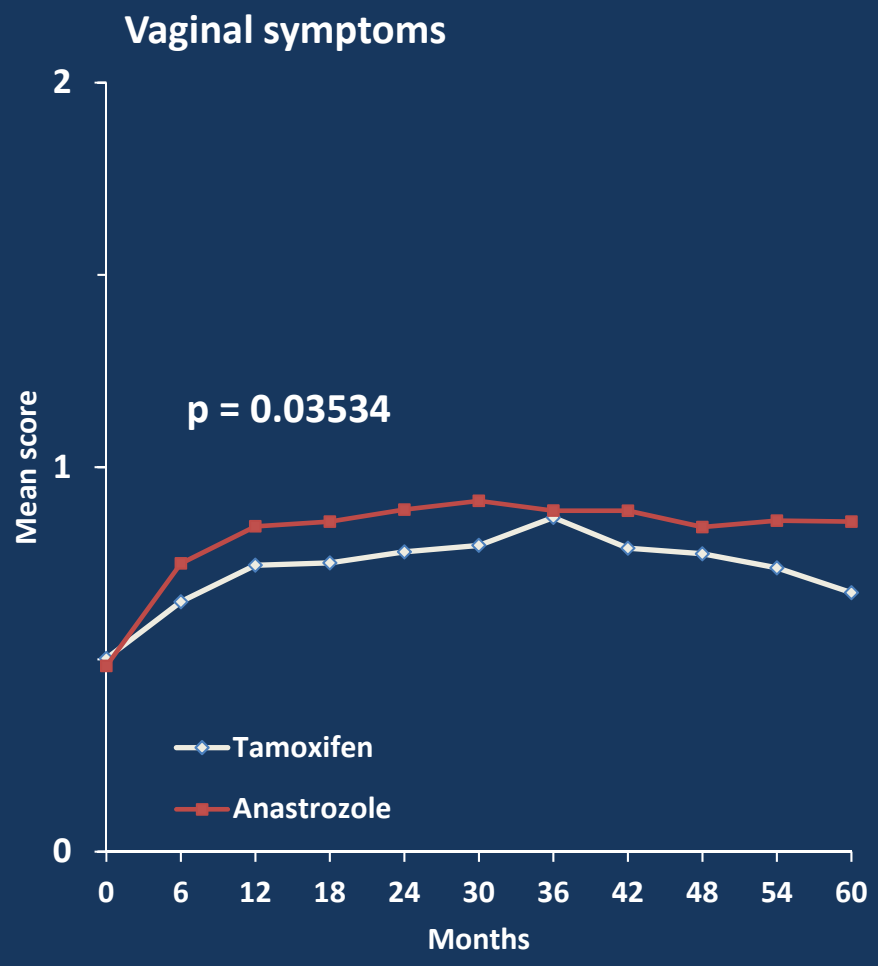

Percent Reporting at Least Slightly Bothersome Symptoms
90
80
70
60
50
40
30
20
10
0
Hot flashes <60
Hot flashes ≥60
Vaginal Dryness
Joint pain
T baseline
A baseline
T at 6 mo
A at 6 mo
T baseline
A baseline
T at 6 mo
A at 6 mo

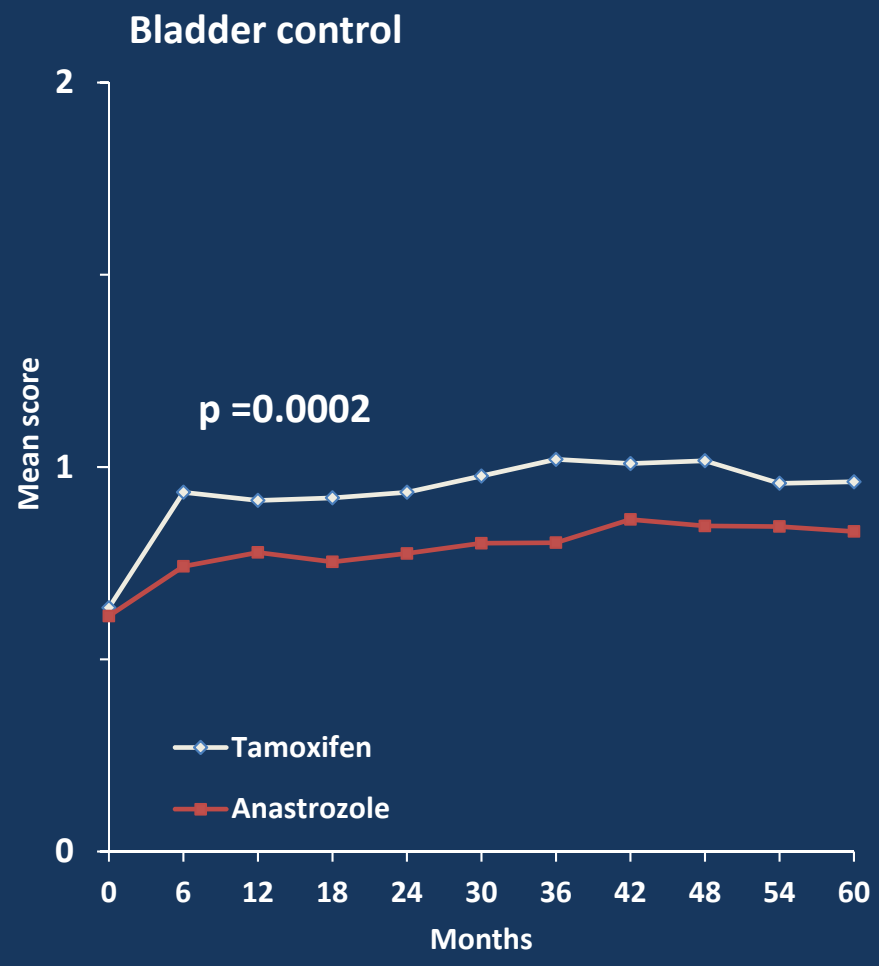
Severity of Vasomotor Symptoms and Musculoskeletal Pain



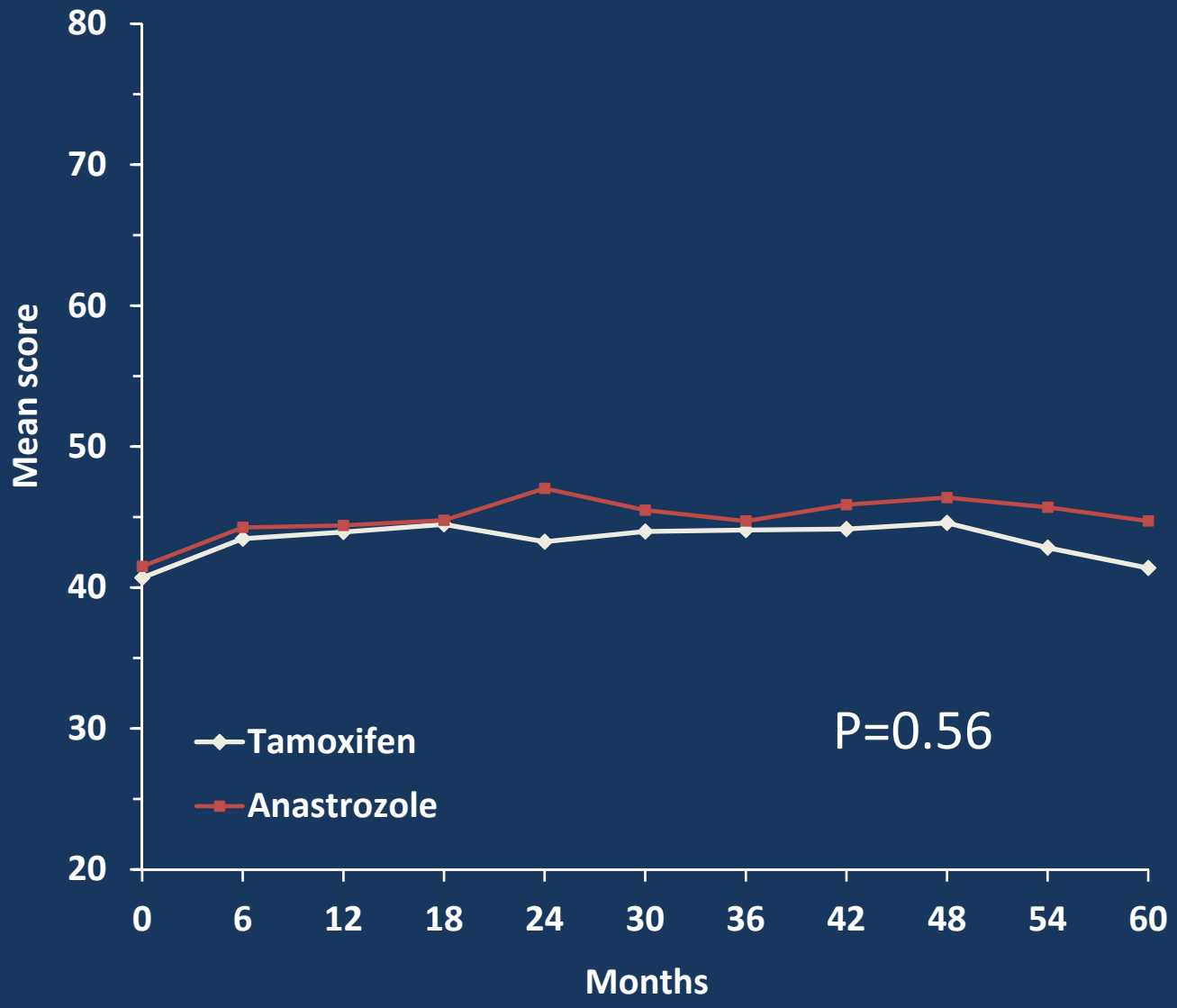


Severity of Vaginal and Bladder Control Problems

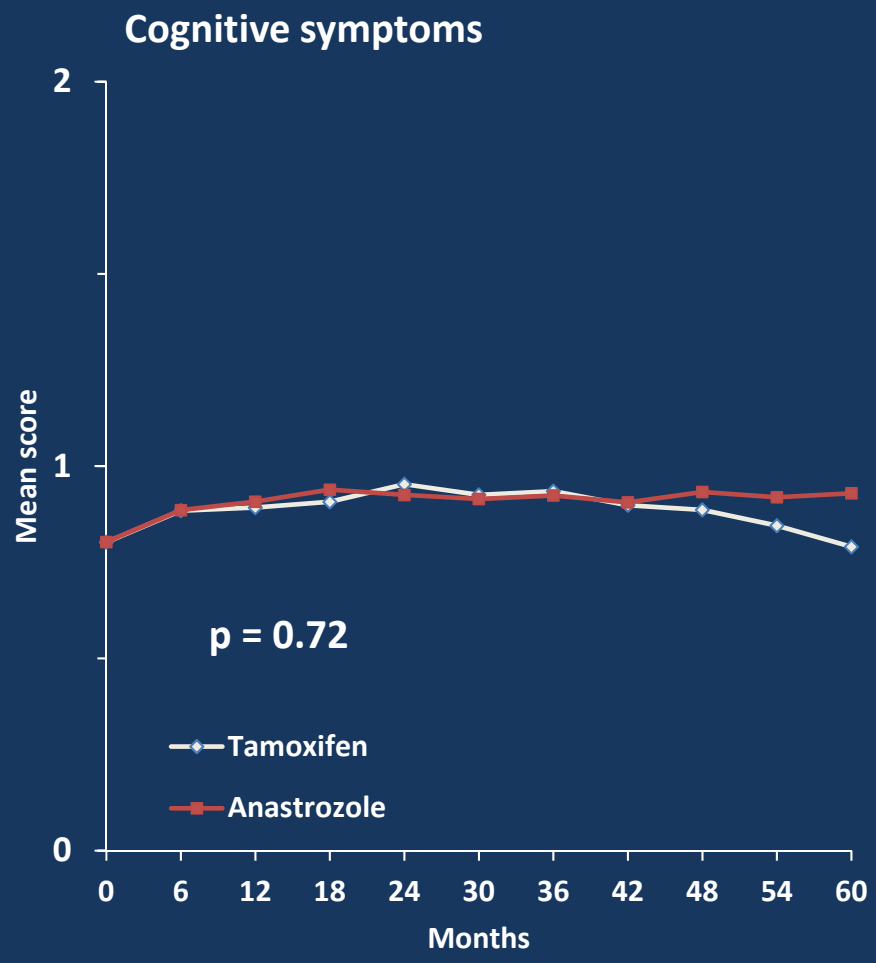


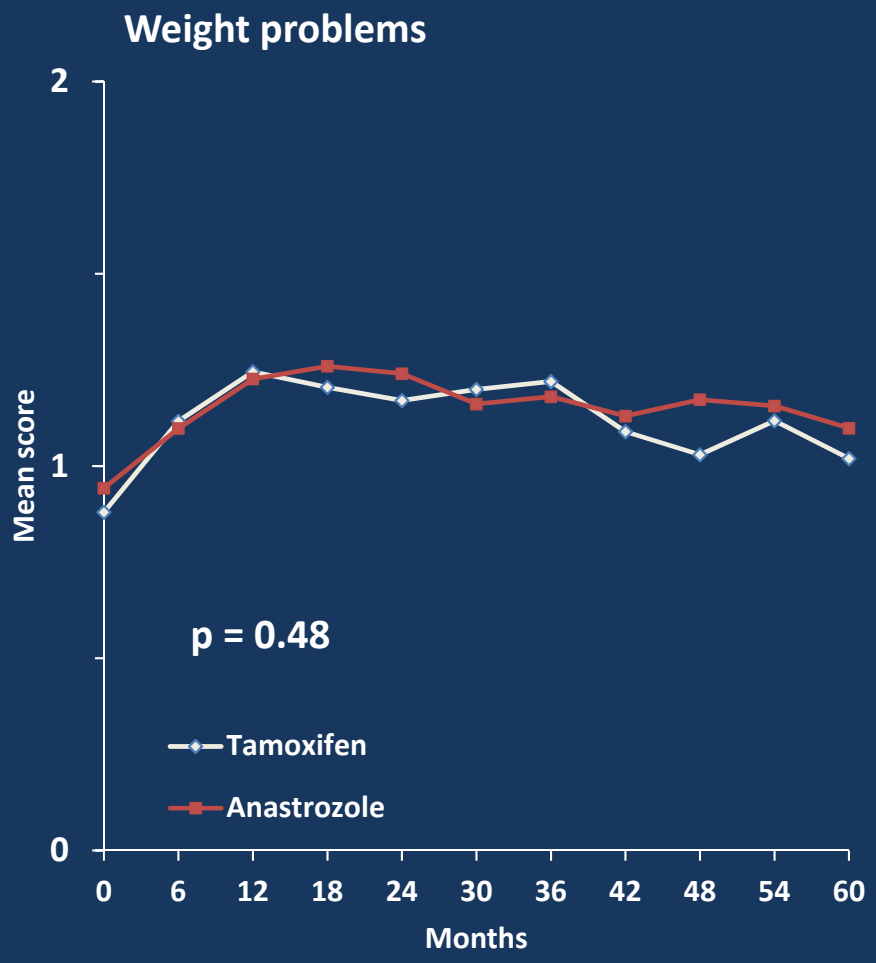


Mean Sexual Functioning Score by Treatment Group and Time Point

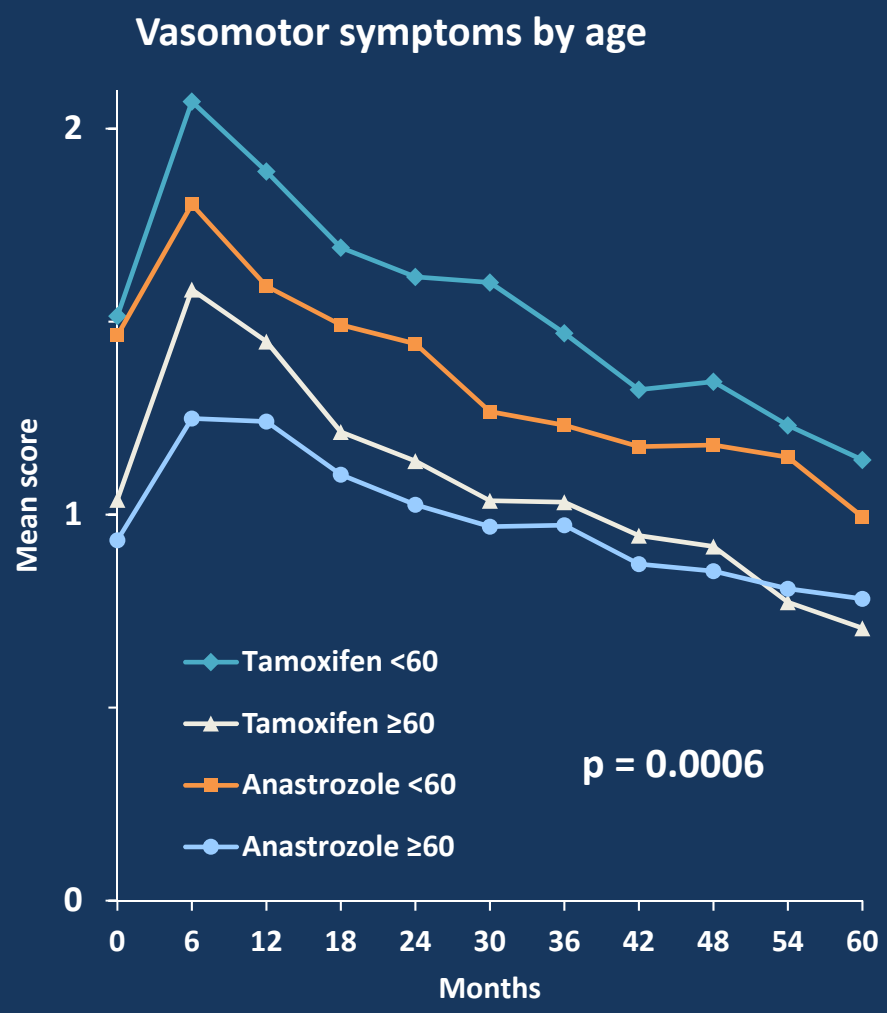


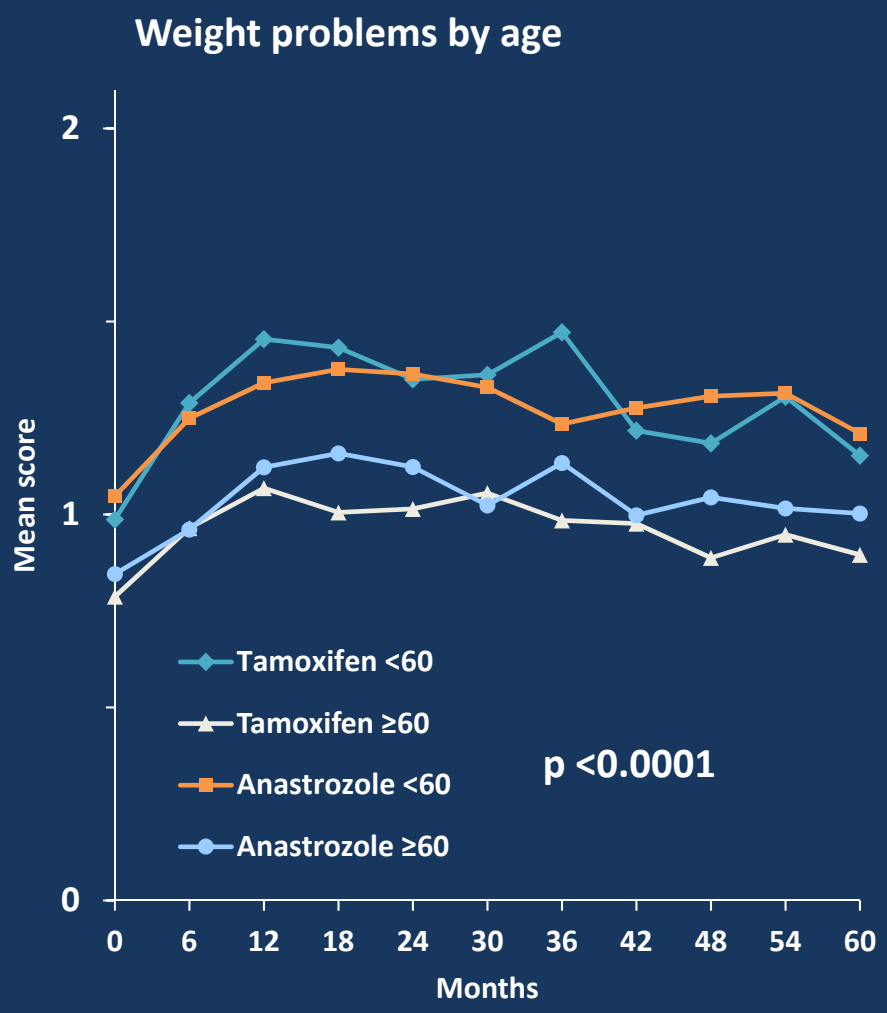
Severity of Cognitive and Weight Control Problems



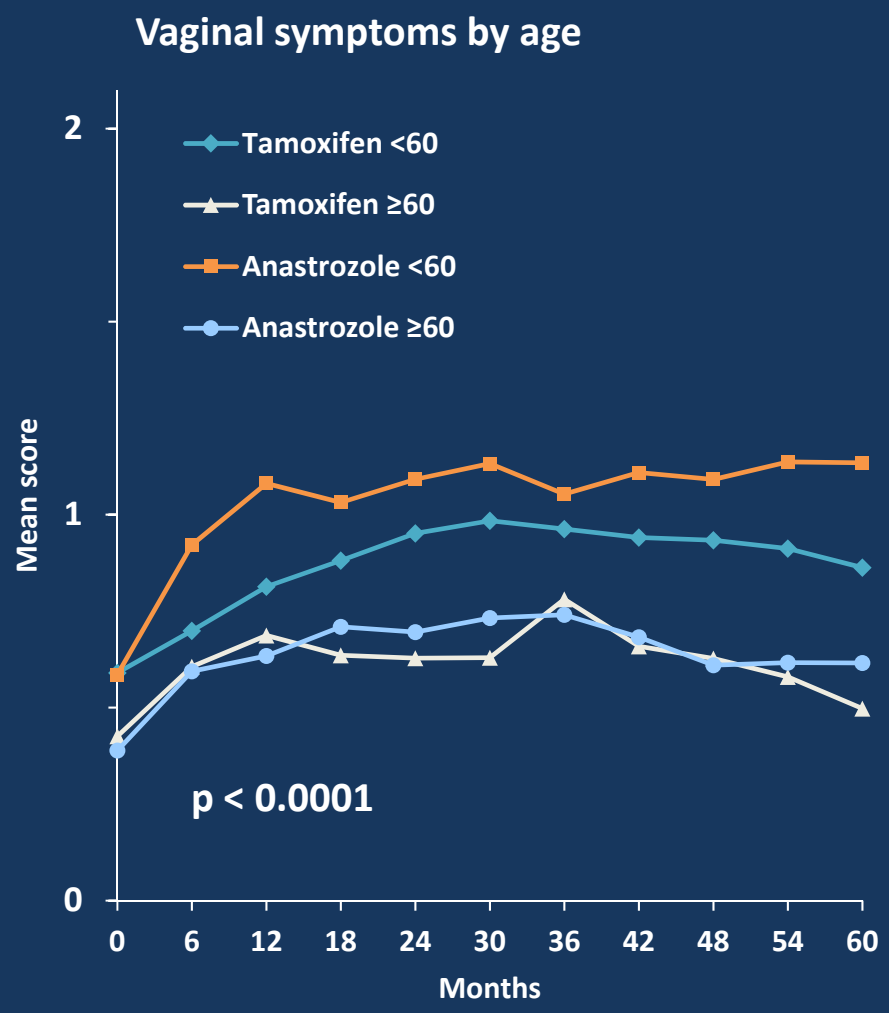


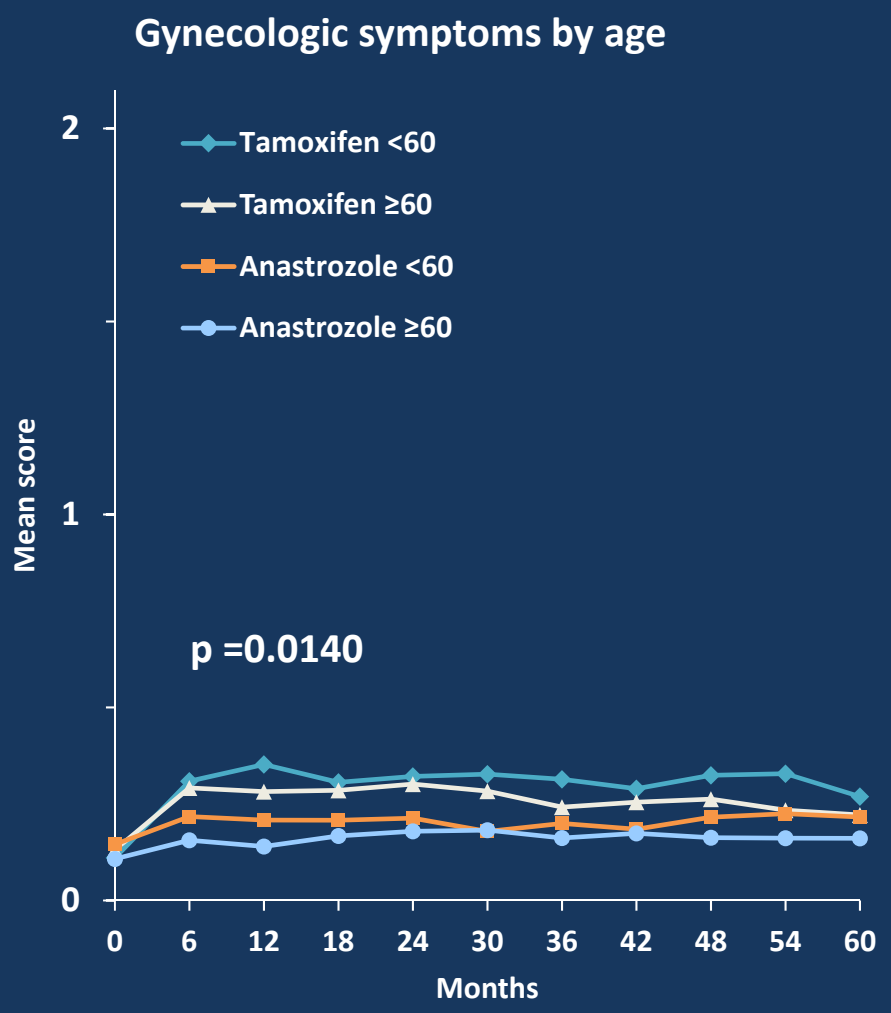
Vasomotor Symptoms and Weight Problems by Age





Vaginal Symptoms and Gynecologic Symptoms by Age





Summary

- Both Anastrozole and Tamoxifen were well-tolerated with no significant differences in physical or mental health-related QOL
- There was no increase in severity of fatigue, depressive symptoms, cognitive problems, or weight gain with either therapy
- Tamoxifen increased the severity of vasomotor symptoms, bladder control and gynecological symptoms compared to Anastrozole
- Anastrozole increased the severity of musculoskeletal and vaginal symptoms compared to Tamoxifen
- Patients <60 yrs had significantly worse vasomotor and vaginal symptoms, as well as weight gain and gynecological symptoms

Conclusions

- Both A and T are well-tolerated in patients with DCIS, with greater severity of some symptoms in women <60 years
- Symptom profiles differ in the expected directions
- With information on PROs as well as BCFI, *patients and their physicians can now make personalized decisions* about which of these two effective agents to select

In conclusion, take home message

- TILs play significant prognostic role
- ILBC is characterized by low lymphocytic infiltration but ER+ Her2 – ILBC is similar to IDBC
- EPclin identified a low risk group that might be spared chemotherapy and it provided more accurate prognostic information than the RS
- Anastrozole is an alternative to tamoxifen for DCIS with a different side profile
- Practice changing? Not so much

THANK YOU