

TAILORED ADJUVANT SYSTEMIC THERAPY FOR BREAST CANCER: MYTH OR REALITY?

Presented by

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NCIC-MA5

Pre-menopausal
node positive
(n=710)



CMF 6 cycles every 4 weeks

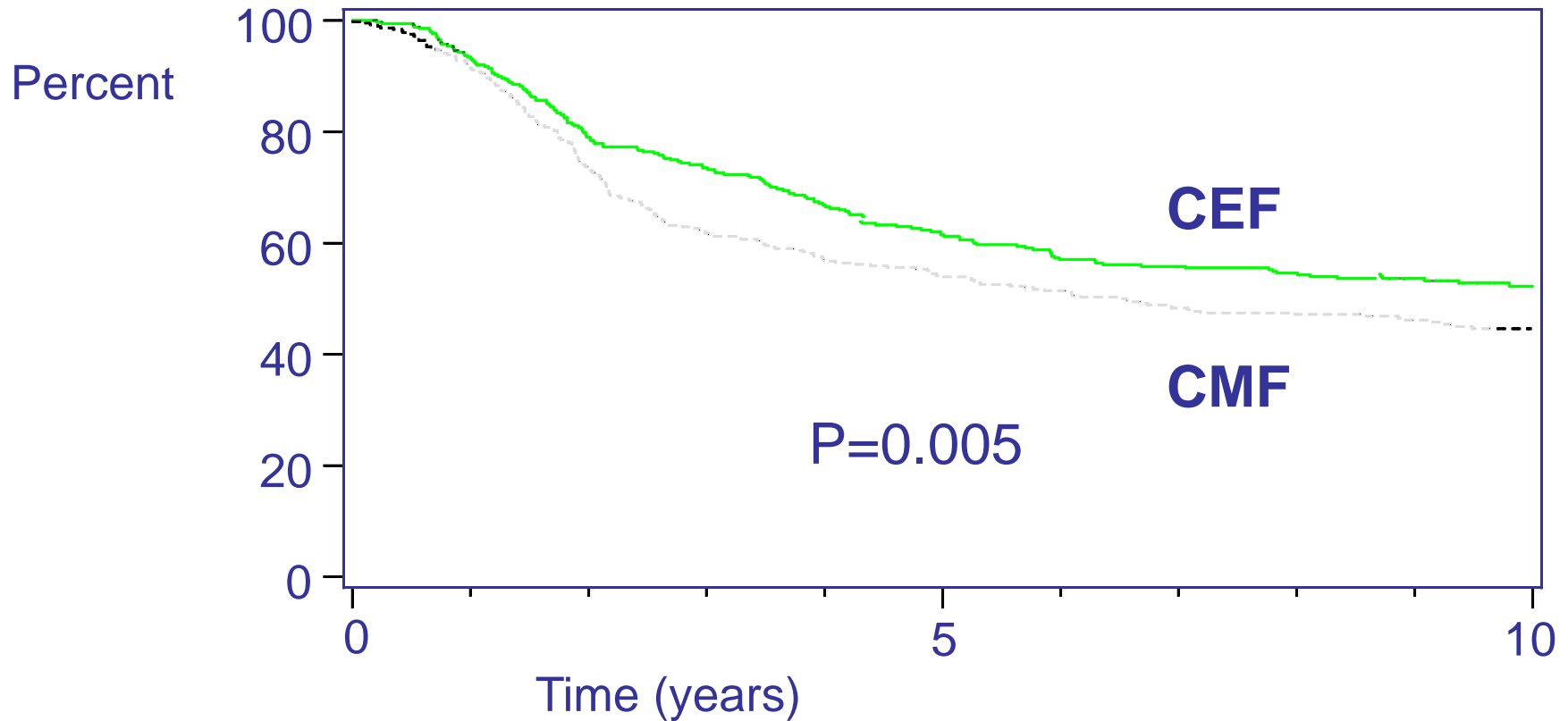
- Cyclophosphamide 100 mg/m² po x 14 d
- Methotrexate 40 mg/m² iv d 1 & 8
- 5FU 600 mg/m² iv d 1 & 8

CEF 6 cycles every 4 weeks

- Cyclophosphamide 75 mg/m² po x 14d
- Epirubicin 60 mg/m² iv d 1 & 8
- 5FU 500 mg/m² iv d 1 & 8

Cotrimoxazole or
norfloxacin/ciprofloxacin

MA.5 Disease-Free Survival



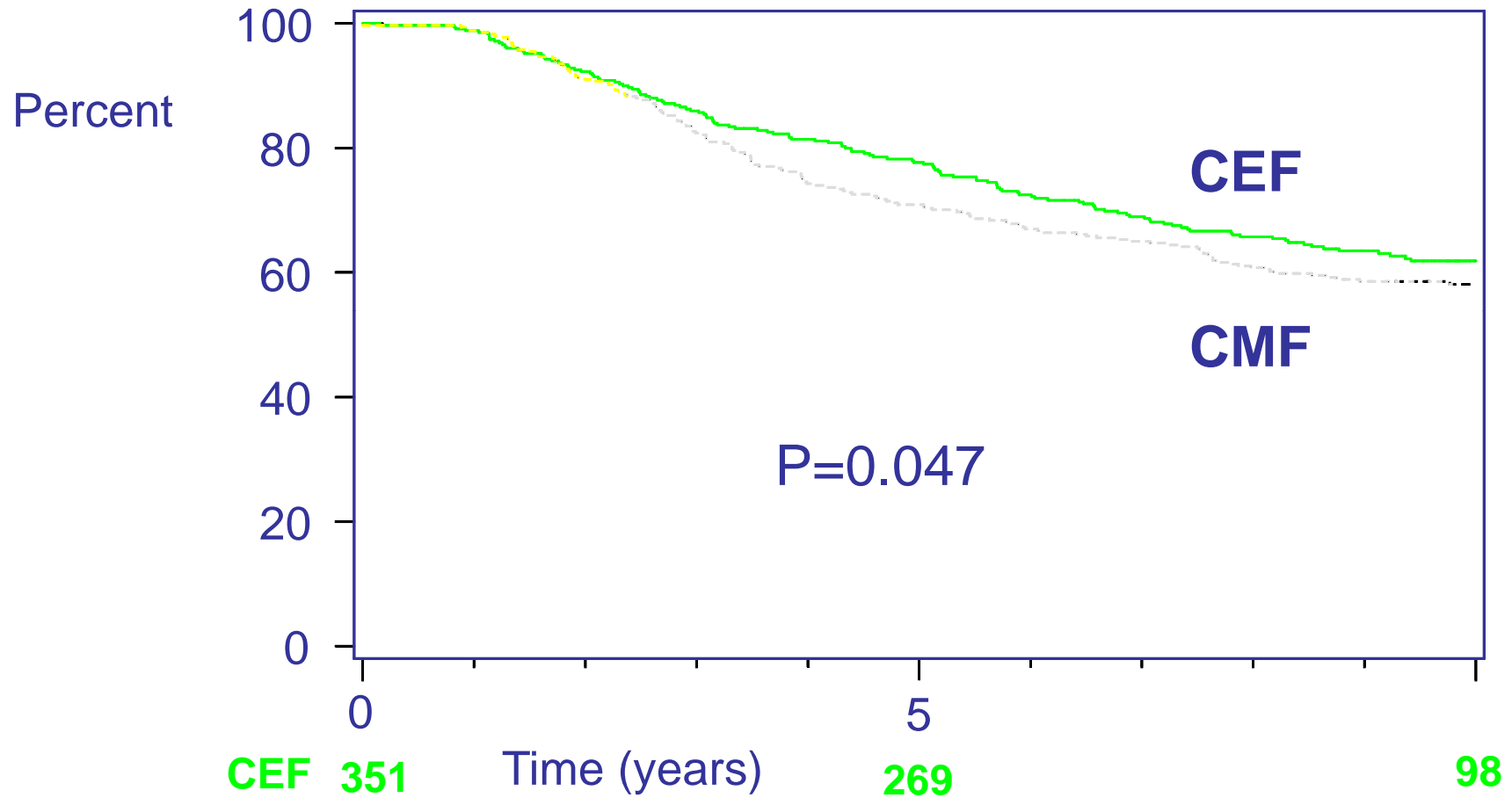
CEF 351

212

84

At
Risk:

MA.5 Overall Survival

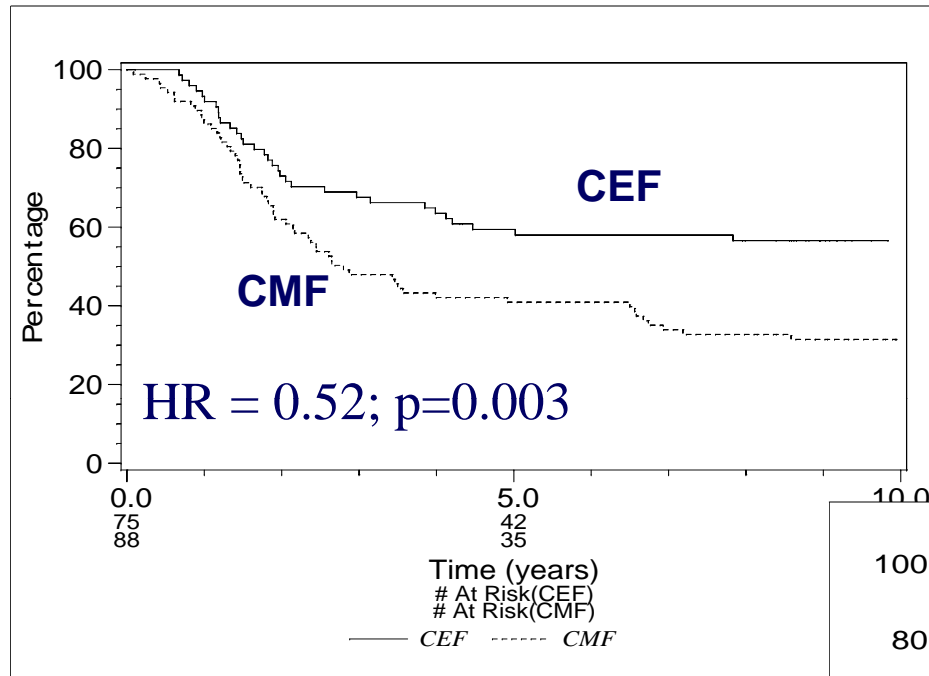


At
Risk:

Adverse Events

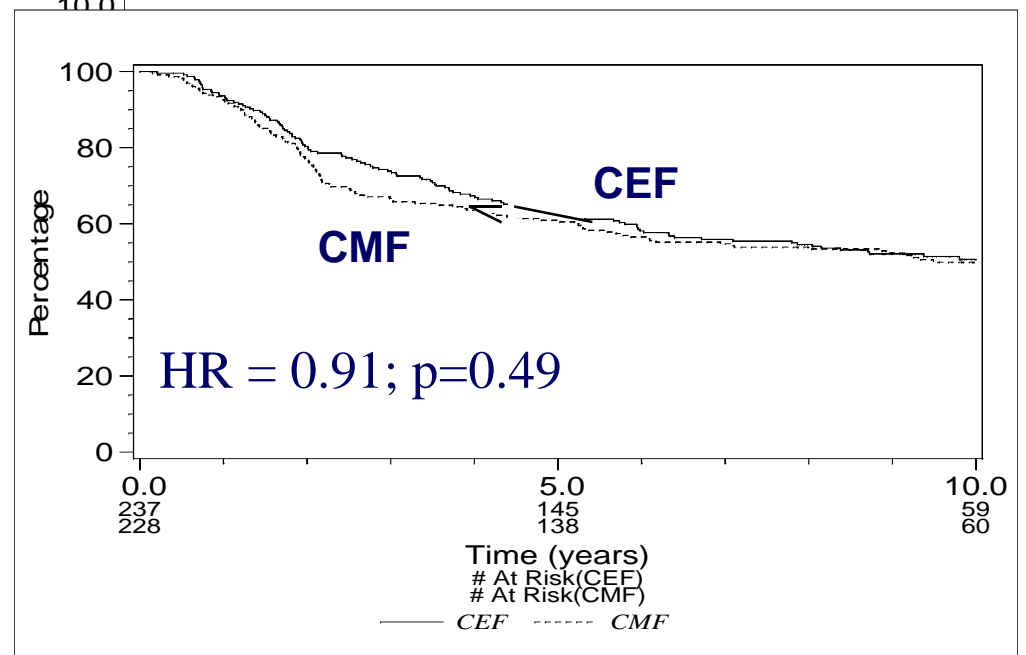
- **4 cases of CHF in the CEF group compared to 1 in the CMF group**
- **5 patients in the CEF group experience acute leukemia (4 myeloid and 1 lymphoid) vs 1 in the CMF group**

DFS by treatment for those with HER2 amplification

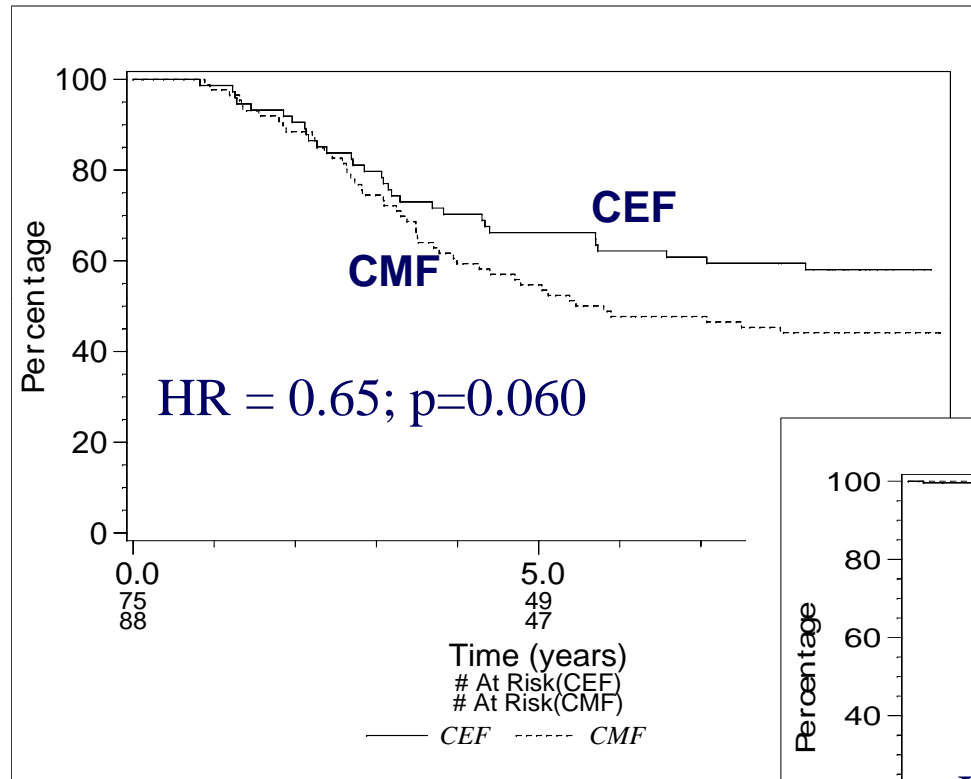


HER2 as a predictive factor

DFS by treatment for those with no HER2 amplification

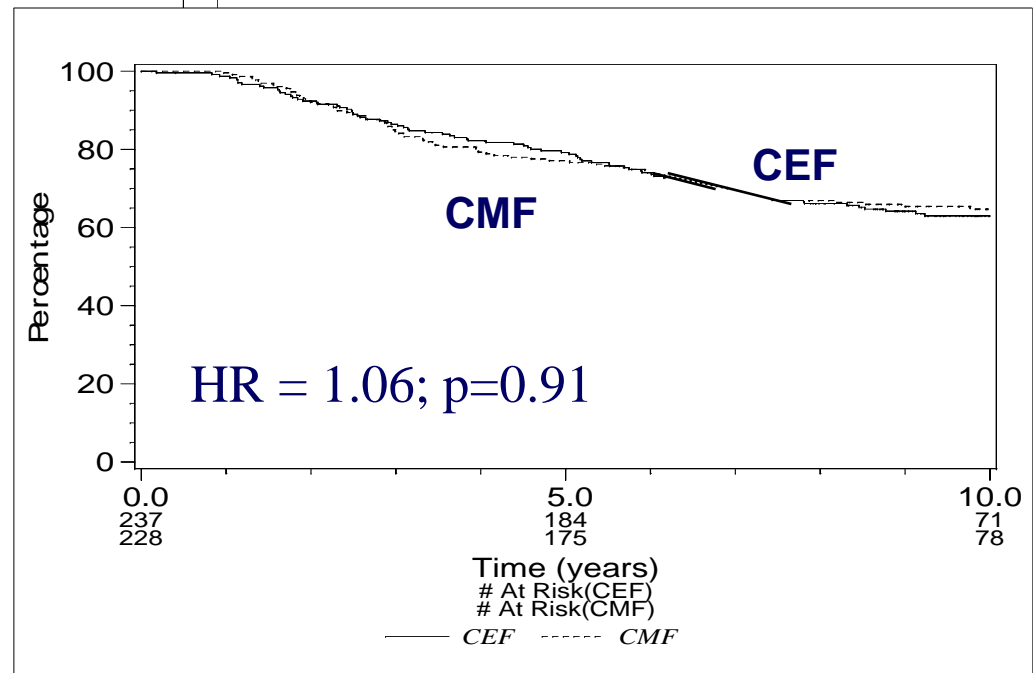


OS by treatment for those with HER2 amplification



HER2 as a predictive factor

OS by treatment for those not HER2 amp



Adjusted* Hazard Ratios by HER2 Status (CEF vs. CMF)

Disease Free Survival

Overall Survival

HER2	HR	95% CI	p-value	HR	95% CI	p-value
Amplified	0.52	0.34 - 0.80	0.003	0.65	0.42 – 1.02	0.06
Not Amplified	0.91	0.71 - 1.18	0.49	1.06	0.83 - 1.44	0.68

* adjusted for age, nodal status, grade, ER status, surgical procedure, tumor size

Test for interaction: $p=0.02$ for DFS; $p=0.01$ for OS

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HER2 and Responsiveness of Breast Cancer
to Adjuvant Chemotherapy

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Her 2-neu amplification/overexpression is predictive of chemotherapy response

ANTHRACYCLINE vs NON-ANTHRACYCLINE CONTAINING TRIALS: HER 2-NEU

- **10 large studies**
- **Each suggests that HER 2-NEU overexpression is a positive factor for response to anthracycline**
- **Each underpowered to test the question**

Her 2-neu amplification/overexpression is predictive of chemotherapy response

- **All from published data**

- **DeLaurentis et al**
- **Gennari et al**
- **Dhesy-Thind et al**

All support interaction between +Her2/neu status and advantage of anthracycline vs non-anthracycline containing regimen

Her 2-neu amplification/overexpression is predictive of chemotherapy response

Topoisomerase 2 A gene (TOP 2A)

- **Located close to Her 2/neu on the 17q chromosome**
- **Integrally involved in the antitumor action of anthracyclines**
- **Topoisomerase II α is essential for DNA replication and recombination**
- **Anthracyclines target topoisomerase II α enzyme**

TOPO IIa (not HER2) Amplification as a Predictor of Anthracycline Response in Breast Cancer

Study	Yr	N
Park et al.	2006	284
Tanner et al.	2006	525
Knoop at al.	2005	805
Park et al.	2003	188
Coon et al.	2002	35
Di Leo et al.	2002	354

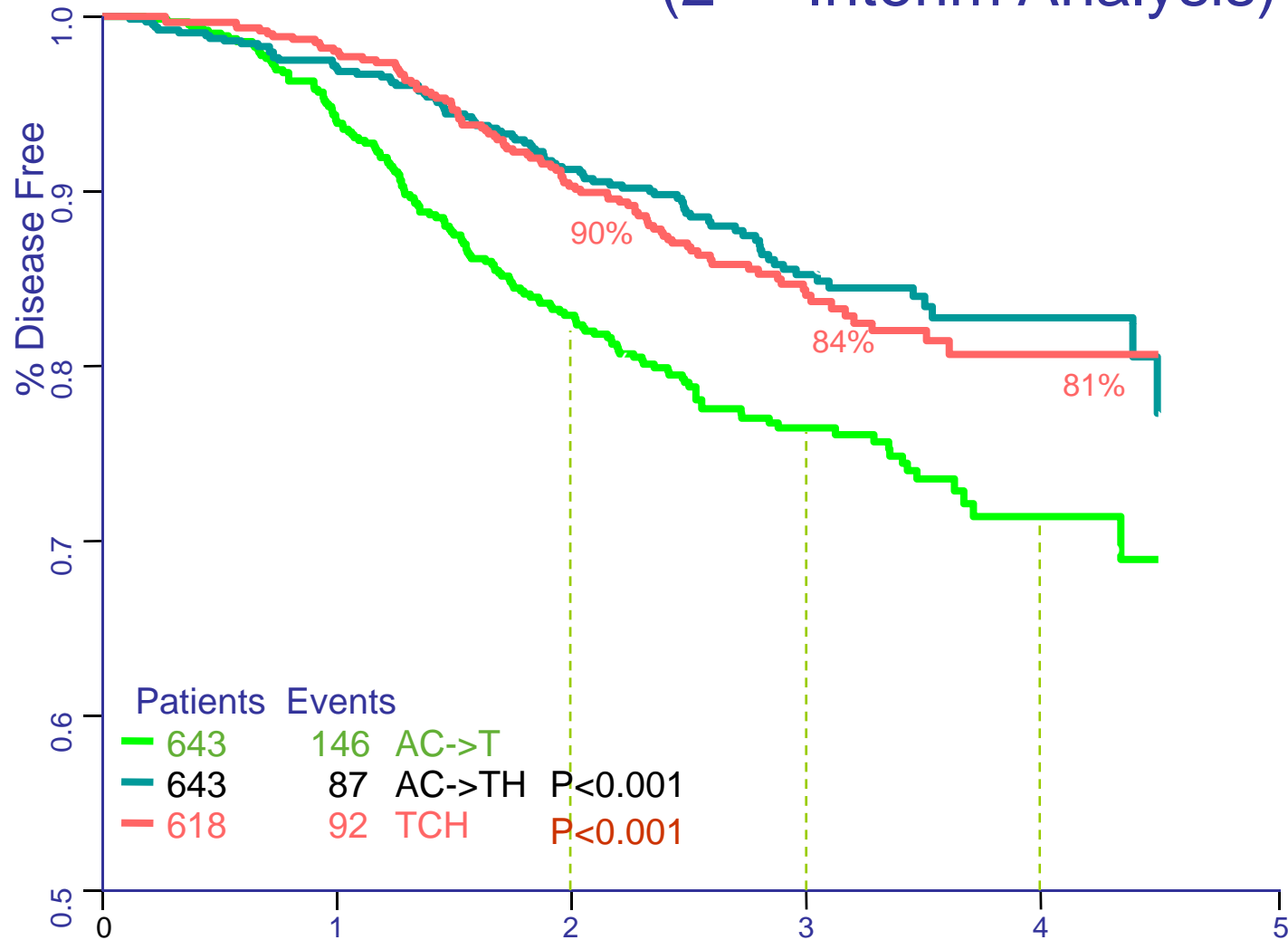
TOP2A as a Predictive Factor

Knoop et al

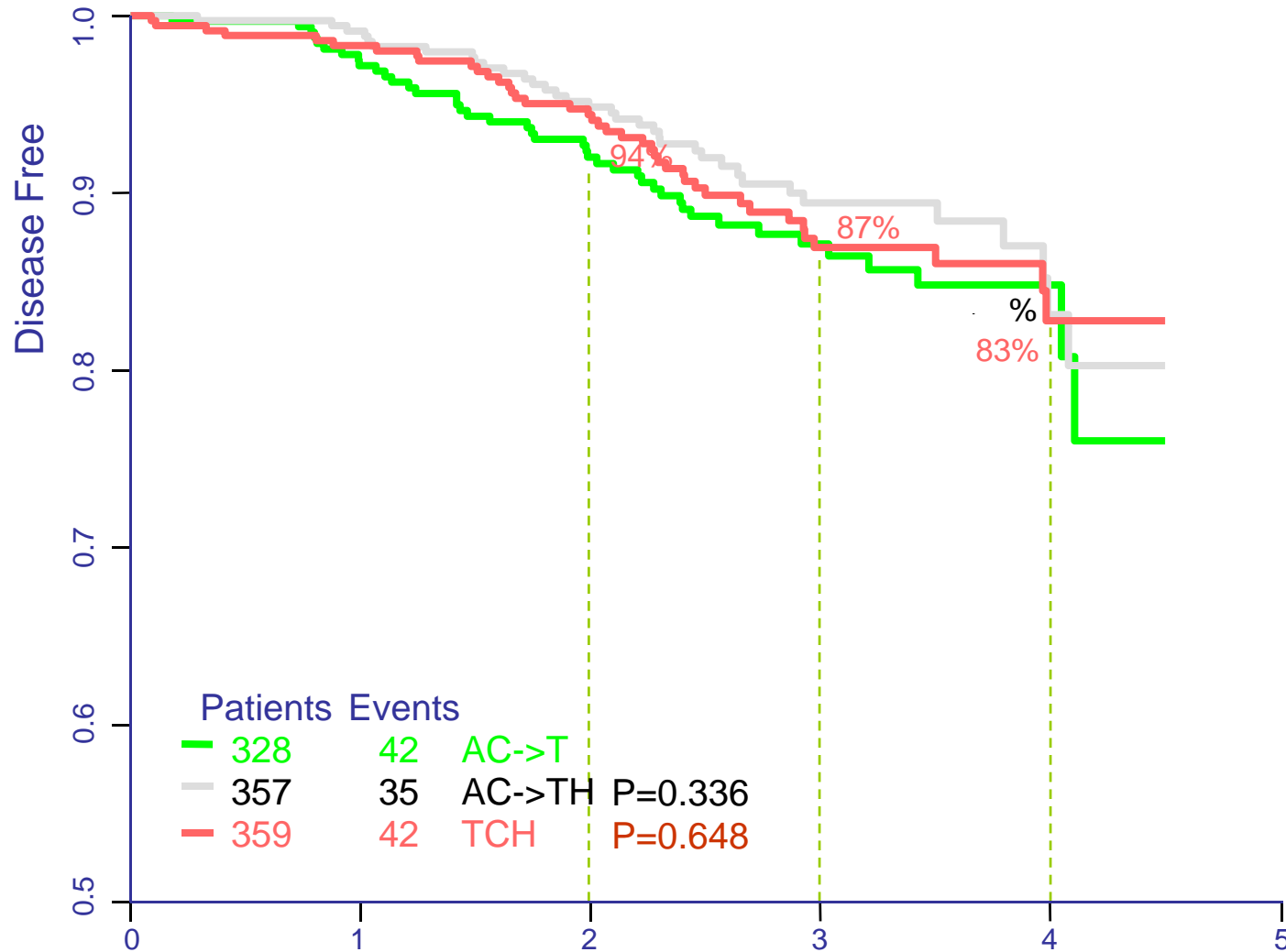
CEF vs CMF

- **patients with TOP 2A amplification or deletion had increased RFS (HR = 0.43; 0.63) and OS (HR = 0.57; HR = 0.56) if treated with CEF vs CMF**
- **TOP 2A vs treatment interaction was negative**

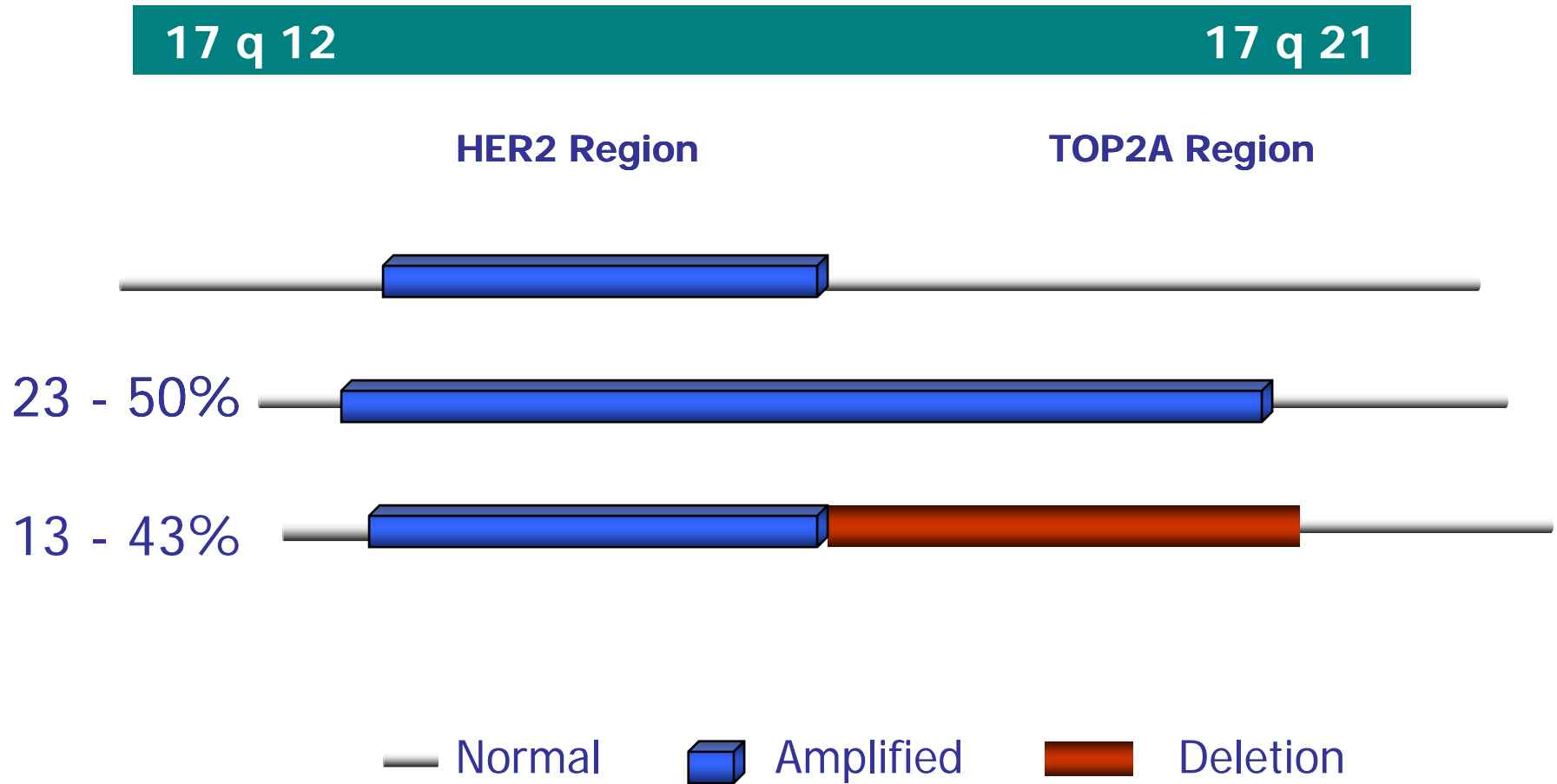
DFS Non Co-Amplified Topo II by Arm (2nd Interim Analysis)



DFS Co-Amplified Topo II by Arm (2nd Interim Analysis)



HER2 and TOPO II



MA5 Clinical Trial

- **TMAAs constructed**
 - **480 patients (67% entire cohort)**
- **TOP2A gene alterations (FISH)**
 - **FISH results available on 443/480 (92%)**

TOP2A FISH Results

- **Amplified:** 48 (10.8%)
- **Deleted:** 27 (6.1%)
- **Normal:** 368 (83.2%)

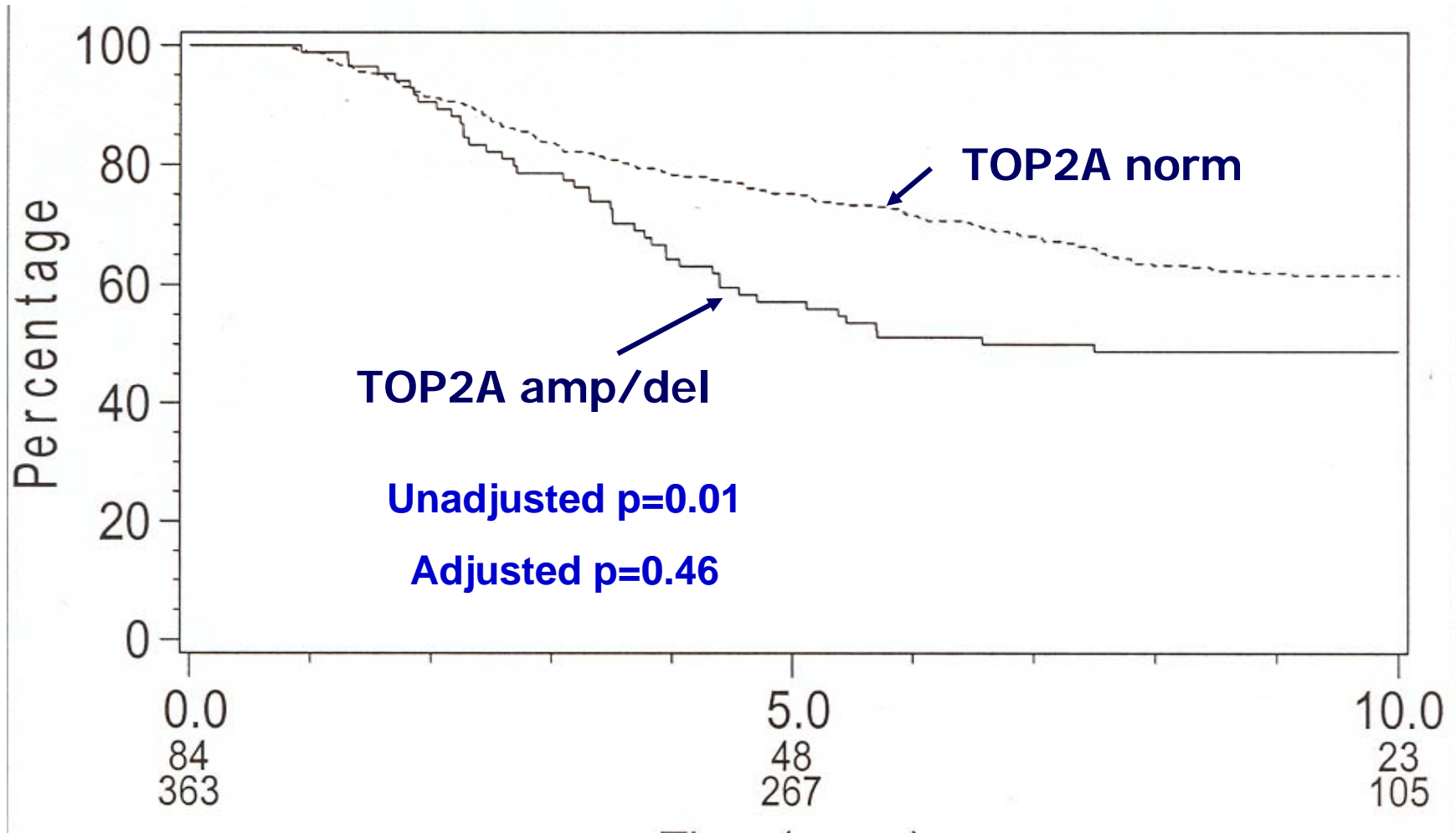
Baseline Characteristics for Patients with TOP2A FISH Measurements

TOP2A gene status

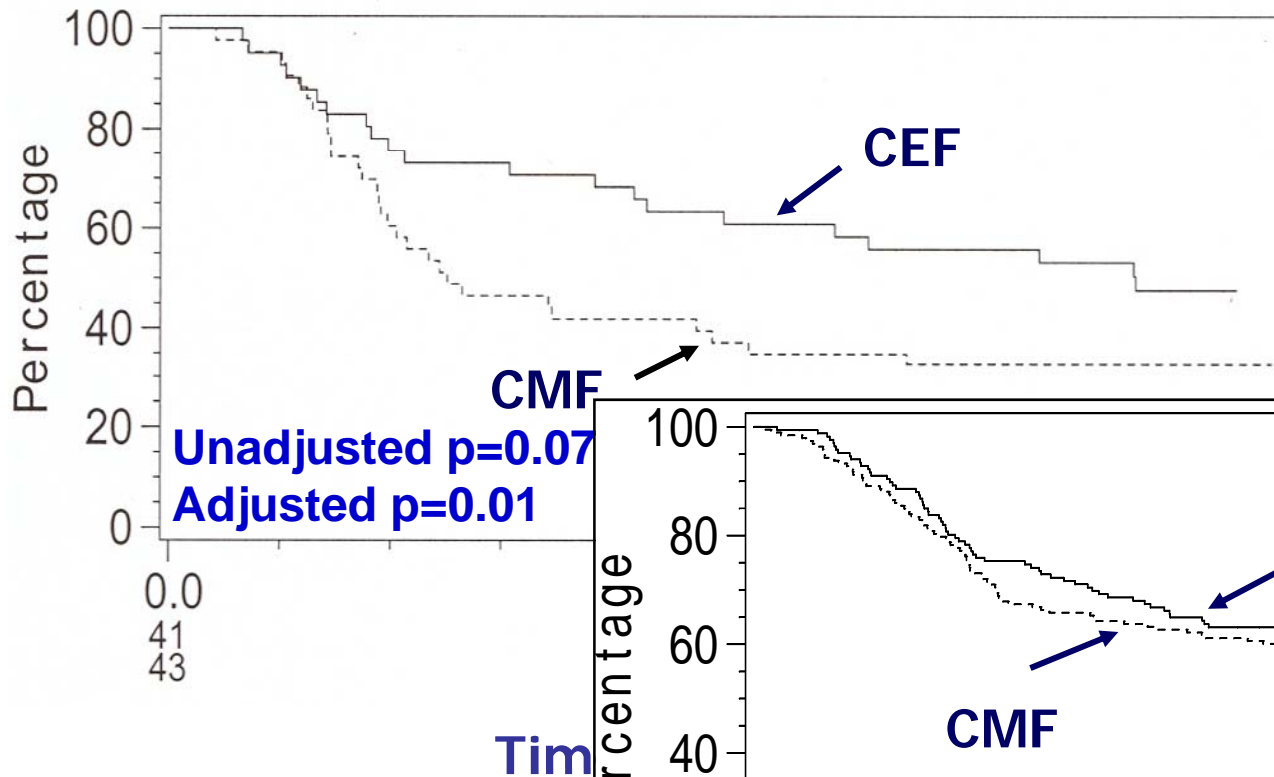
<i>Characteristic</i>	<i>Amplified</i> (n=48)	<i>Deletion</i> (n=27)	<i>Normal</i> (n=368)	<i>p</i> *
HER2/neu				
Amplified	28 (60%)	18 (67%)	73 (20%)	<0.0001
Not amplified	19 (40%)	9 (33%)	288 (80%)	

OS by TOP2A Status

TOP2A as a prognostic factor

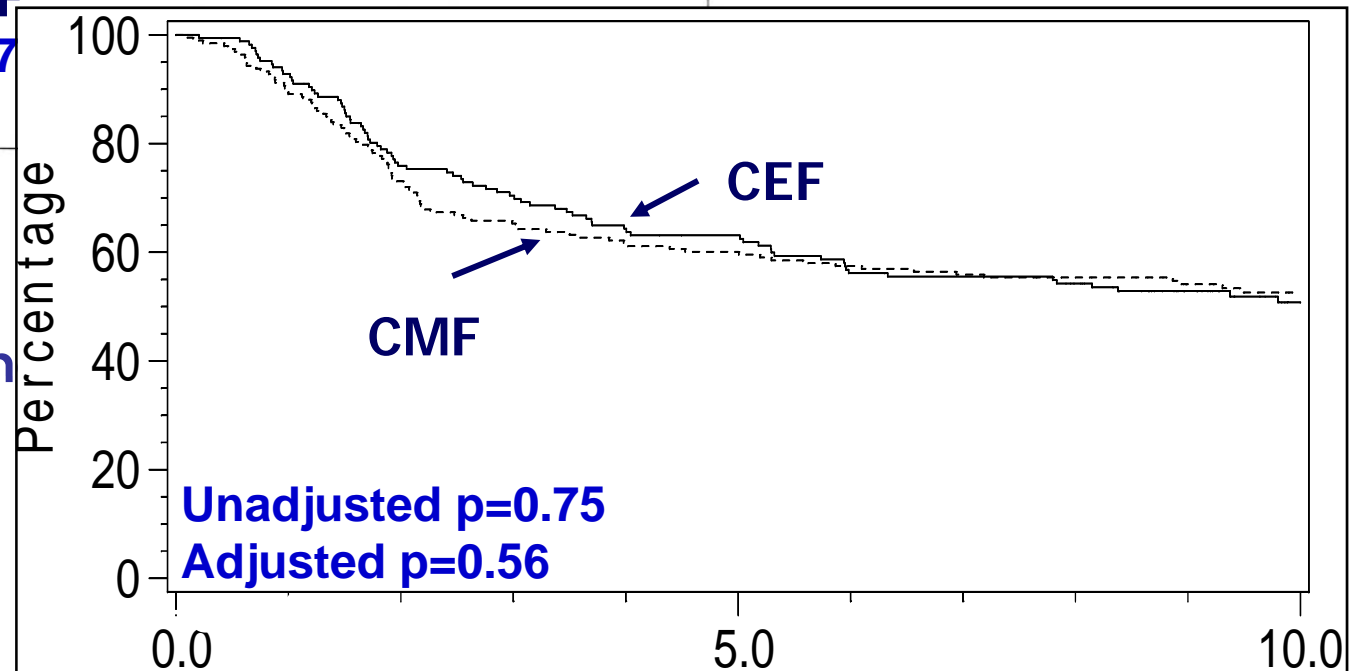


DFS by Treatment for patients with TOP2A amplified or deleted tumors

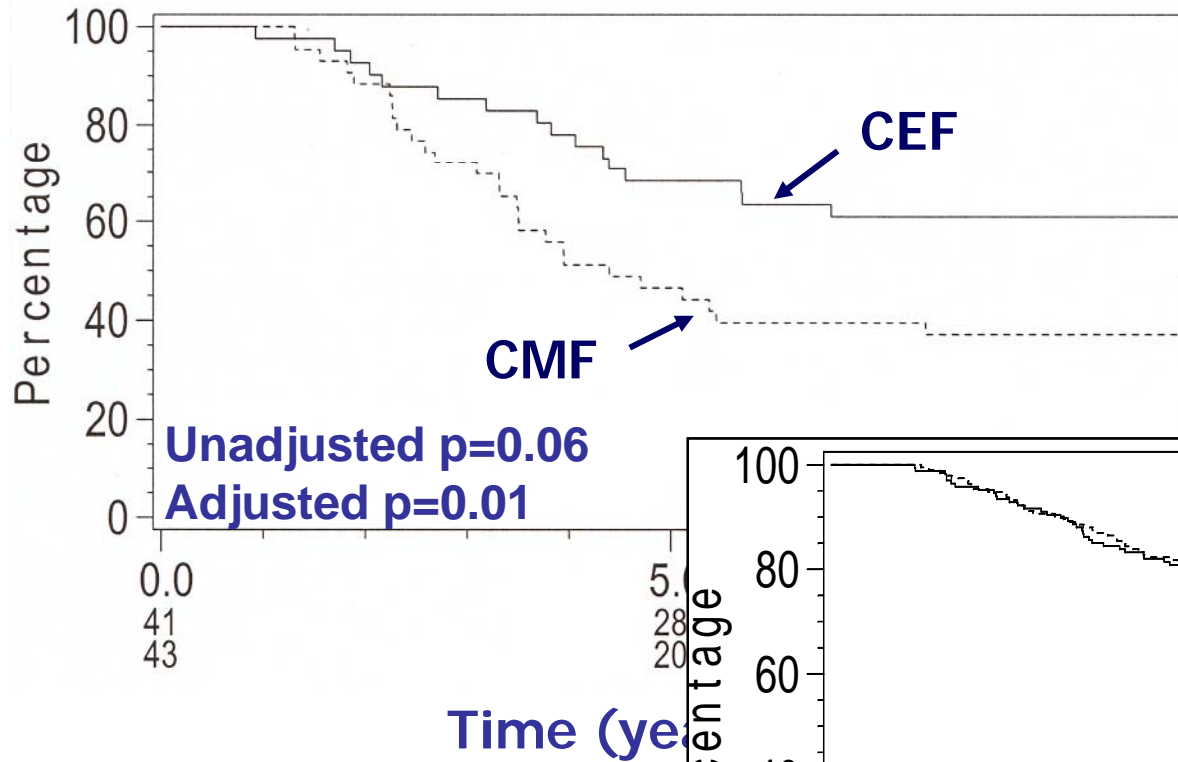


DFS by Treatment for patients with normal TOP2A

TOP2A as a Predictive Factor

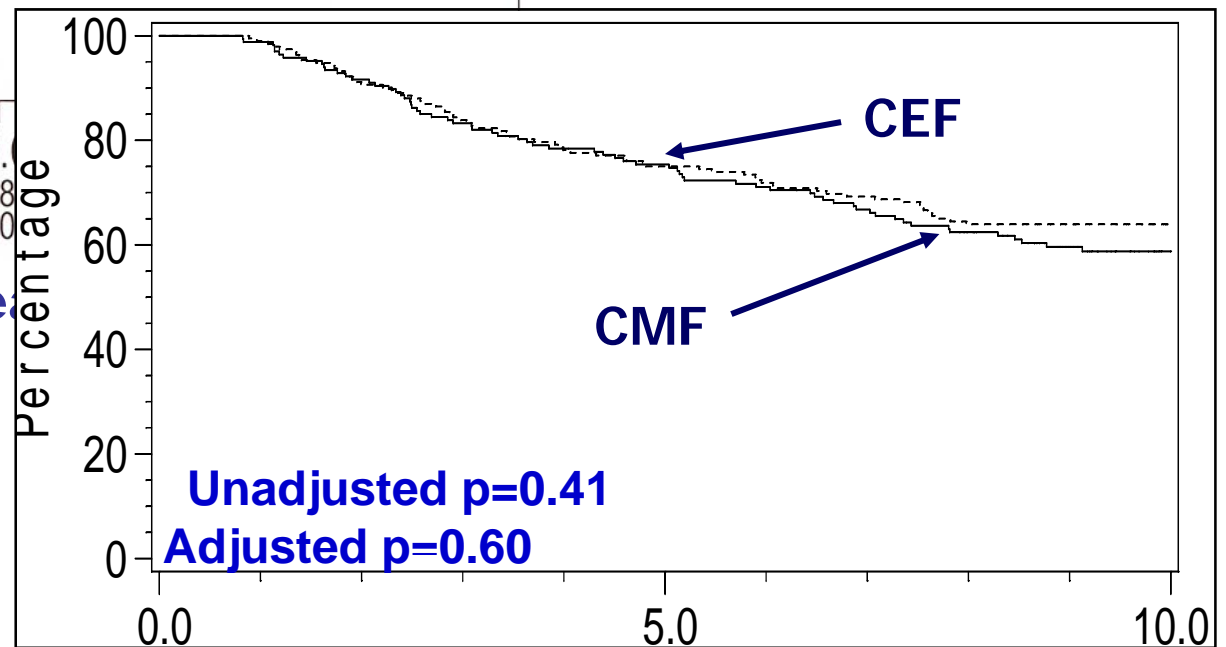


OS by Treatment for patients with TOP2A amplified or deleted tumors



OS by Treatment for patients with normal TOP2A

TOP2A as a predictive factor



Hazard Ratios* by Treatment (CEF vs. CMF) and TOP2A Status

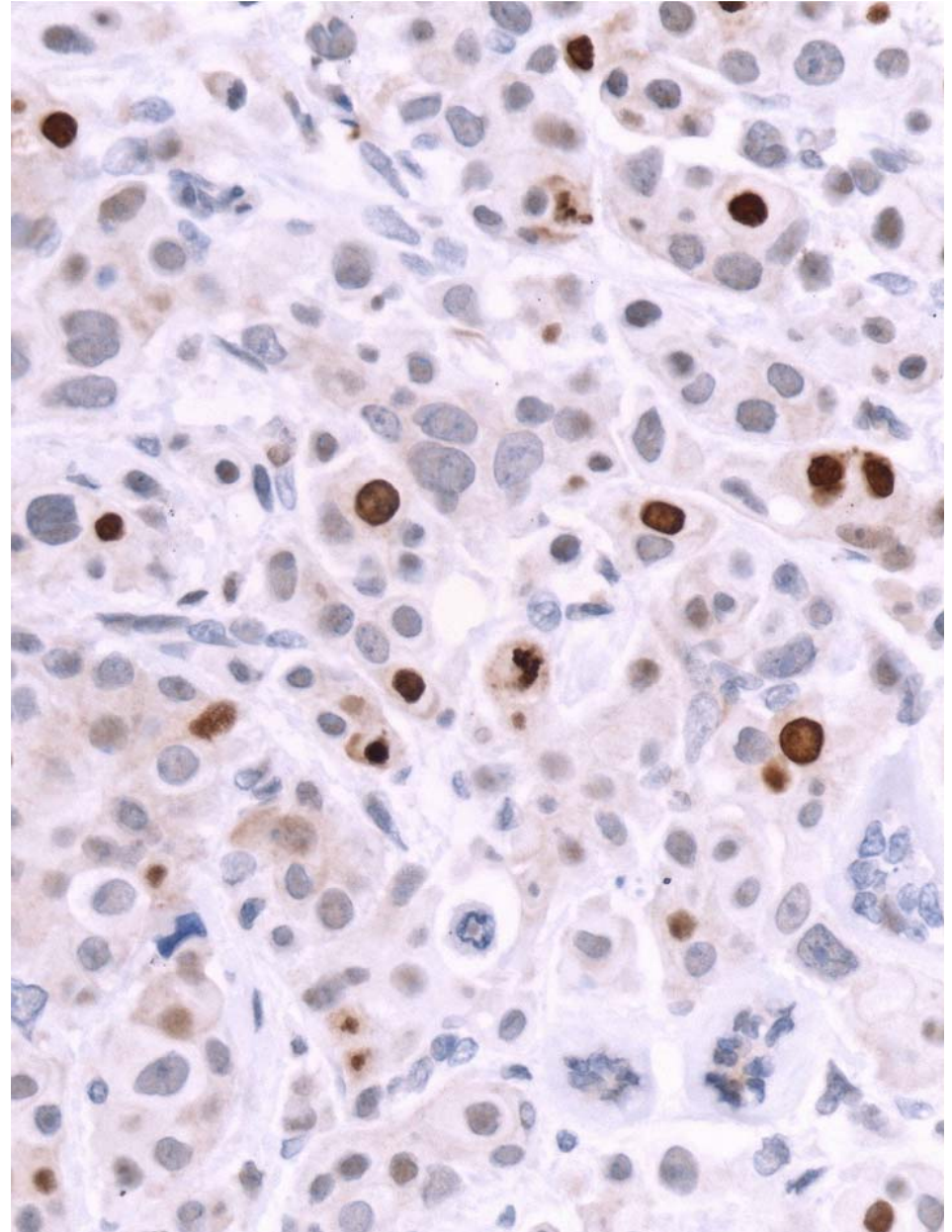
DFS			OS		
HR	95%CI	P	HR	95%CI	P
Amp/del	0.42	0.21-0.83	0.38	0.18-0.80	0.01
Norm	0.93	0.68-1.25	1.10	0.77-1.56	0.60

*Adjusting for age, nodal status, grade, ER status, surgical procedure, tumor size, HER2 status

Test for interaction: (adjusted) $p=0.09$ for DFS; $p=0.04$ for OS

Topo protein IHC:

- 1. No. positive cells/500;
expressed as a
percentage**
- 2. Initial analysis used
topo protein as a
continuous variable**
- 3. Final analysis used
13% as a cut-off**



TOPO II Status by FISH and IHC

		FISH <i>TOP2A</i> gene status			
IHC <i>Topo</i> protein status	Amplified (n=44)	Deleted (n=23)	Normal (n=351)	p-value*	
Over-expression	13 (30%)	7 (30%)	97 (28%)	0.93	
Normal	31 (71%)	16 (70%)	254 (72%)		

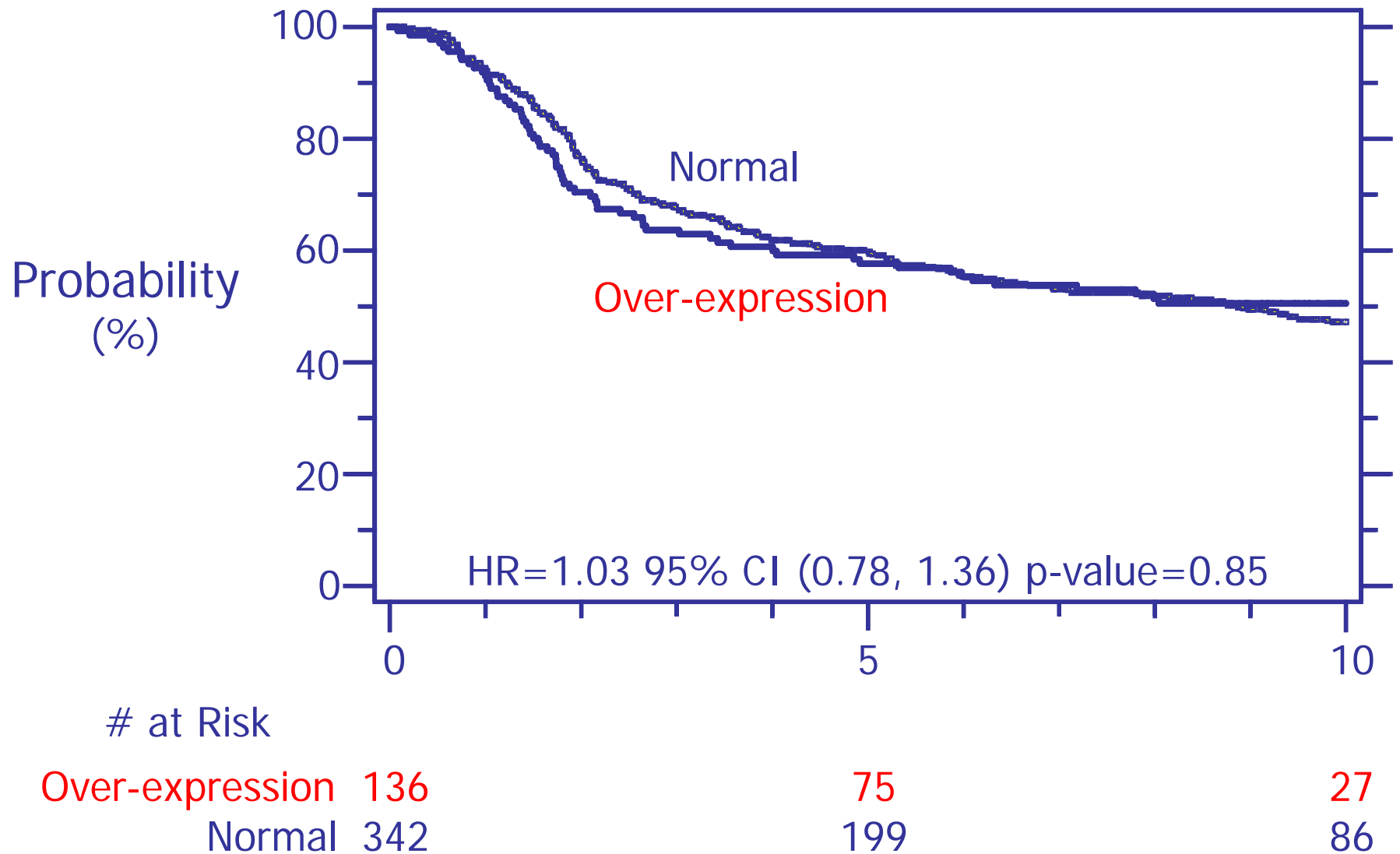
CHI-Square

**Earlier work has also shown that
topo protein expression and
TOP2A gene amplification status
are not correlated**

Mueller, Parkes, Andrulis, O'Malley
Genes, Chromosomes & Cancer, 2004

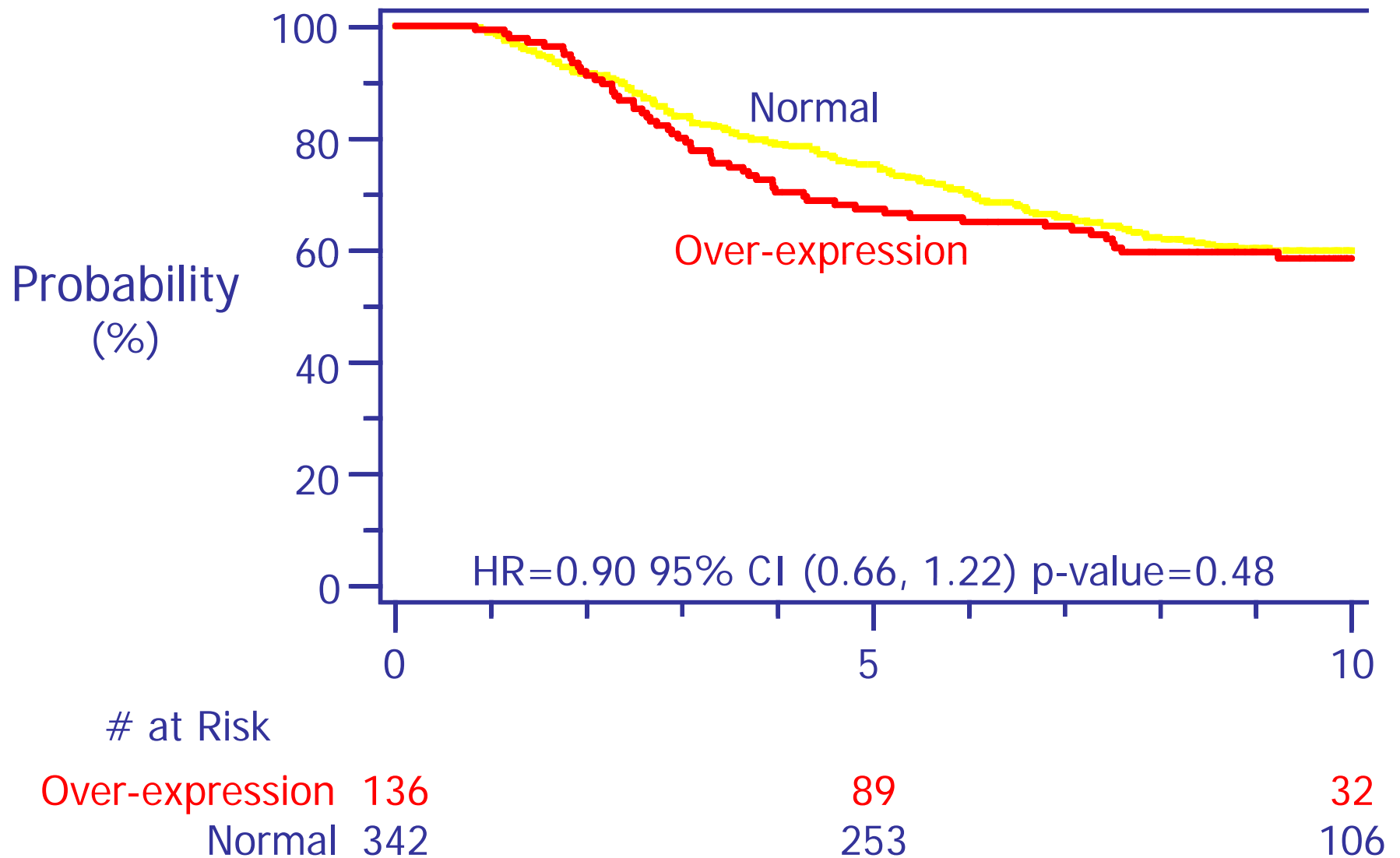
PROGNOSIS

Disease Free Survival by *topo* protein expression

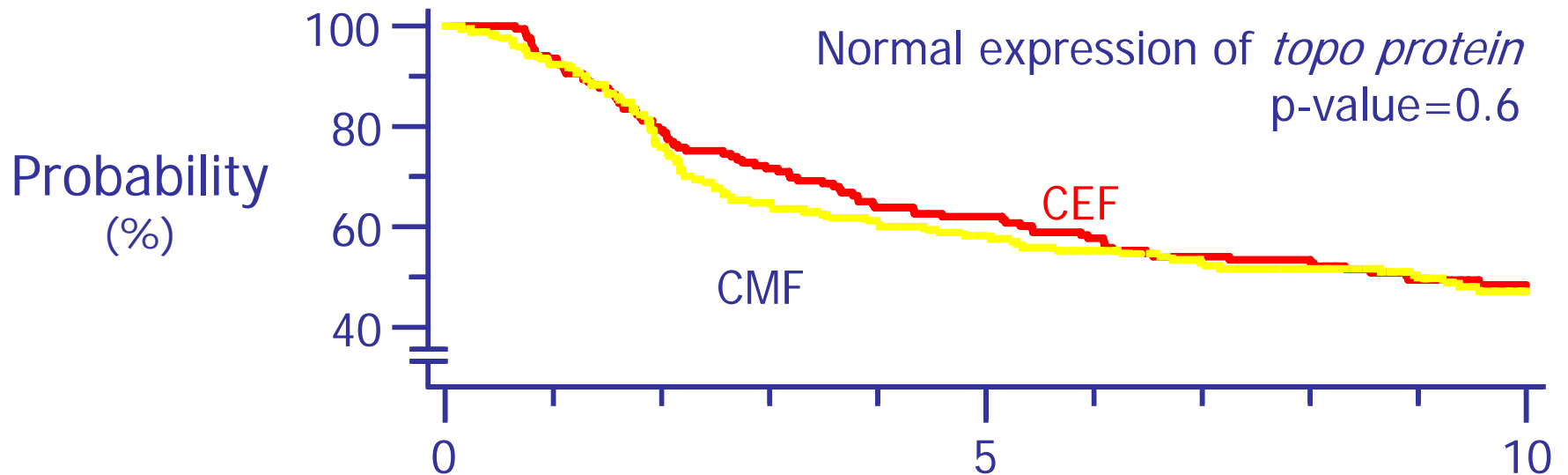
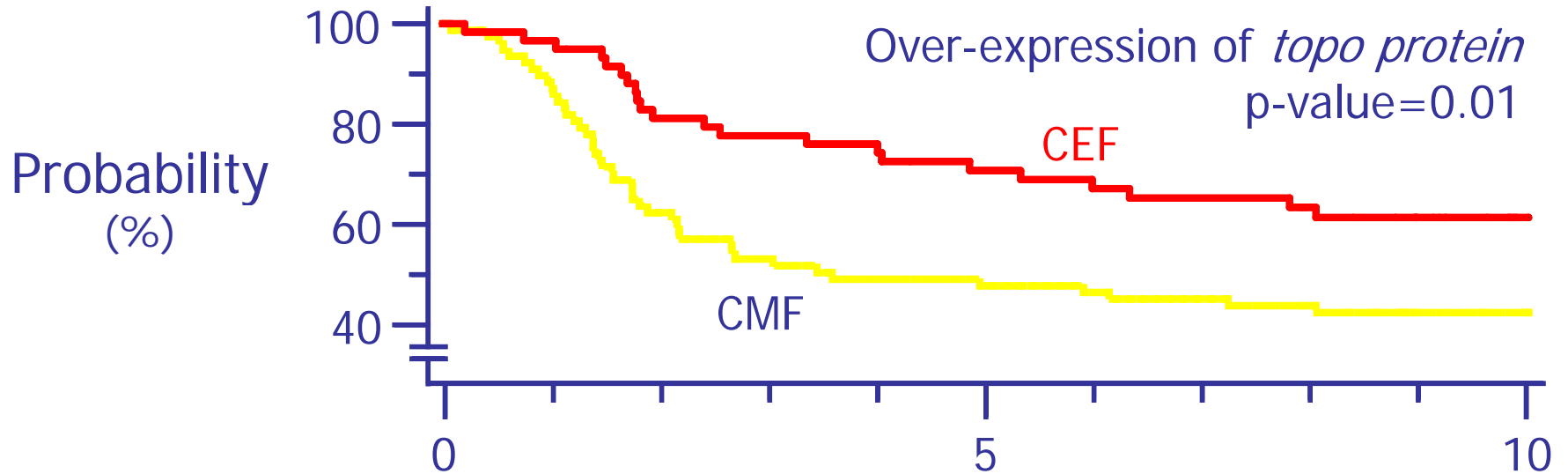


PROGNOSIS

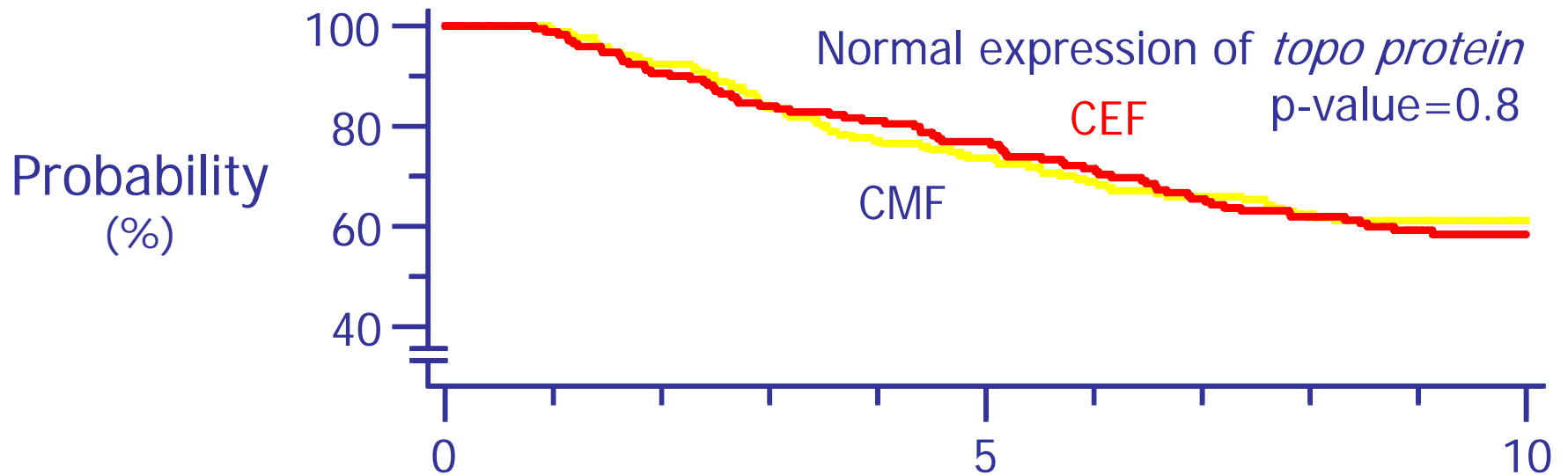
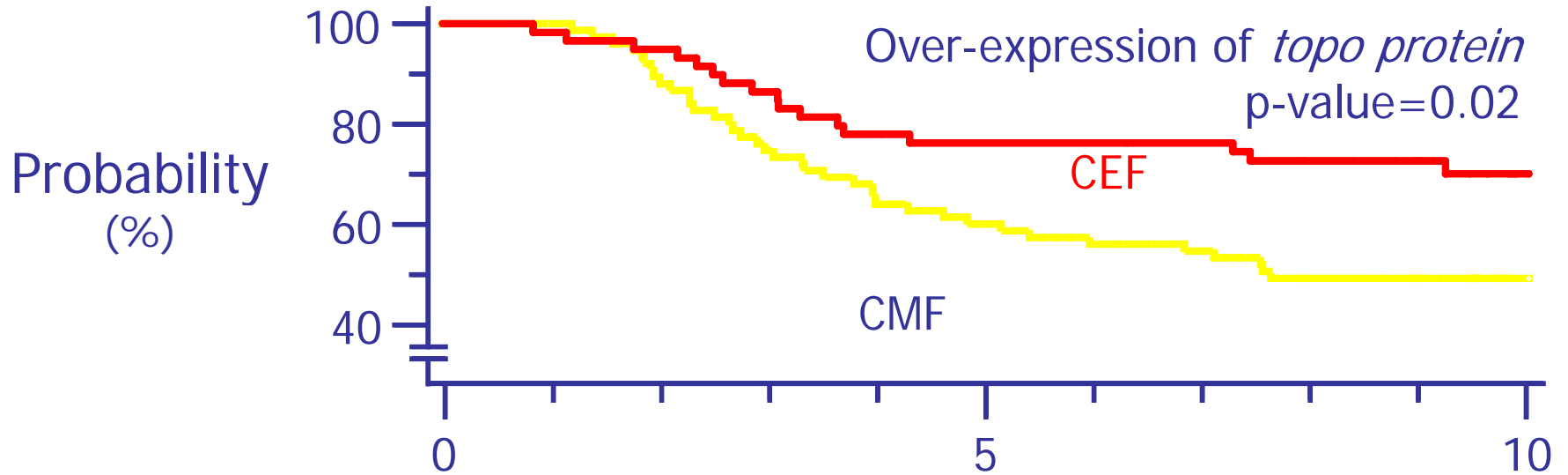
Overall Survival by *topo protein* expression



Disease Free Survival by Treatment



Overall Survival by Treatment



Adjusted* Hazard Ratios by *Topo* protein over-expression (CEF vs. CMF)

Disease Free Survival

Overall Survival

<i>Topo</i> protein	HR	95% CI	p-value	HR	95% CI	p-value
Over-expression	0.49	0.28 - 0.85	0.01	0.51	0.28 - 0.93	0.03
Normal	0.90	0.66 - 1.23	0.50	0.98	0.68 - 1.41	0.91

* adjusted for age, nodal status, grade, ER status, surgical procedure, tumor size, HER2 status

Test for interaction: p=0.04 for DFS; p=0.03 for OS

SABCS 2006

WHICH IS THE BEST PREDICTIVE FACTOR FOR CEF vs CMF IN MA.5 ?

- **Regression adjustment is not an appropriate technique (R. Simon, JNCI 2006)**
- **Needs new statistical methodology**
- **Can use “ranked” p value as a rough estimate**

WHICH IS THE BEST PREDICTIVE FACTOR FOR CEF vs CMF IN MA.5 ?

	DFS p value	OS p value
Her2 neu	0.01	0.02
Topo protein *	0.04	0.03
Topo gene	0.09	0.04

* Exploratory analysis

CONCLUSIONS (I)

- **Strong theoretical underpinning for TOP 2A gene and TOPO 2 α protein and anthracycline efficacy**
- **More robust data supporting role of Her 2/neu and anthracycline efficacy**
- **TOP 2A and TOPO 2 α not routinely available**
- **HER 2/neu available in most centres, quality assured**

CONCLUSIONS (II)

- **Individual trials and three meta-analyses support HER 2/neu amplification as a predictor of response to anthracycline vs non-anthracycline chemotherapy**
- **Her 2/neu amplified or overexpressed: candidates for anthracycline**
- **Her 2/neu non-amplified or non-overexpressed may do equally well with non-anthracycline combinations such as CMF**

CONCLUSIONS (III)

- **TOP 2A or TOPO 2 α may be better predictors but more data and more robust and widely used testing is required before this can be concluded or operationalized**

