HER2陰性乳癌
（Luminal A, triple negative）
に対する
術後化学療法レジメン

相良病院

＜背景＞

- 医師の化学療法レジメンに関する見解に、若干の相違がある
- 朝のカンファで毎回、ディスカッションが白熱してしまい、外来診療の開始に支障を来している

＜目的＞

- 現在までのエビデンスをもとに、化学療法レジメンに関する、基本的な院内コンセンサス作り

症例1　60歳　女性

- Breast (Rt):invasive ductal carcinoma, a3
- f, pT2, ly+, v−, pn−, wide excision
- Lymph node: no metasitasis, 2/12, リンパ節転移巣5mm
  sentinel with axillary dissection
- ER: 90%以上, PgR: 50−90%, Hercep test: スコア1+
- 核異型度：Grade 2
- 組織学的腫瘍の広がり　50x35mm、浸潤径　25x15mm

Luminal A, node positive, リスク因子 3個

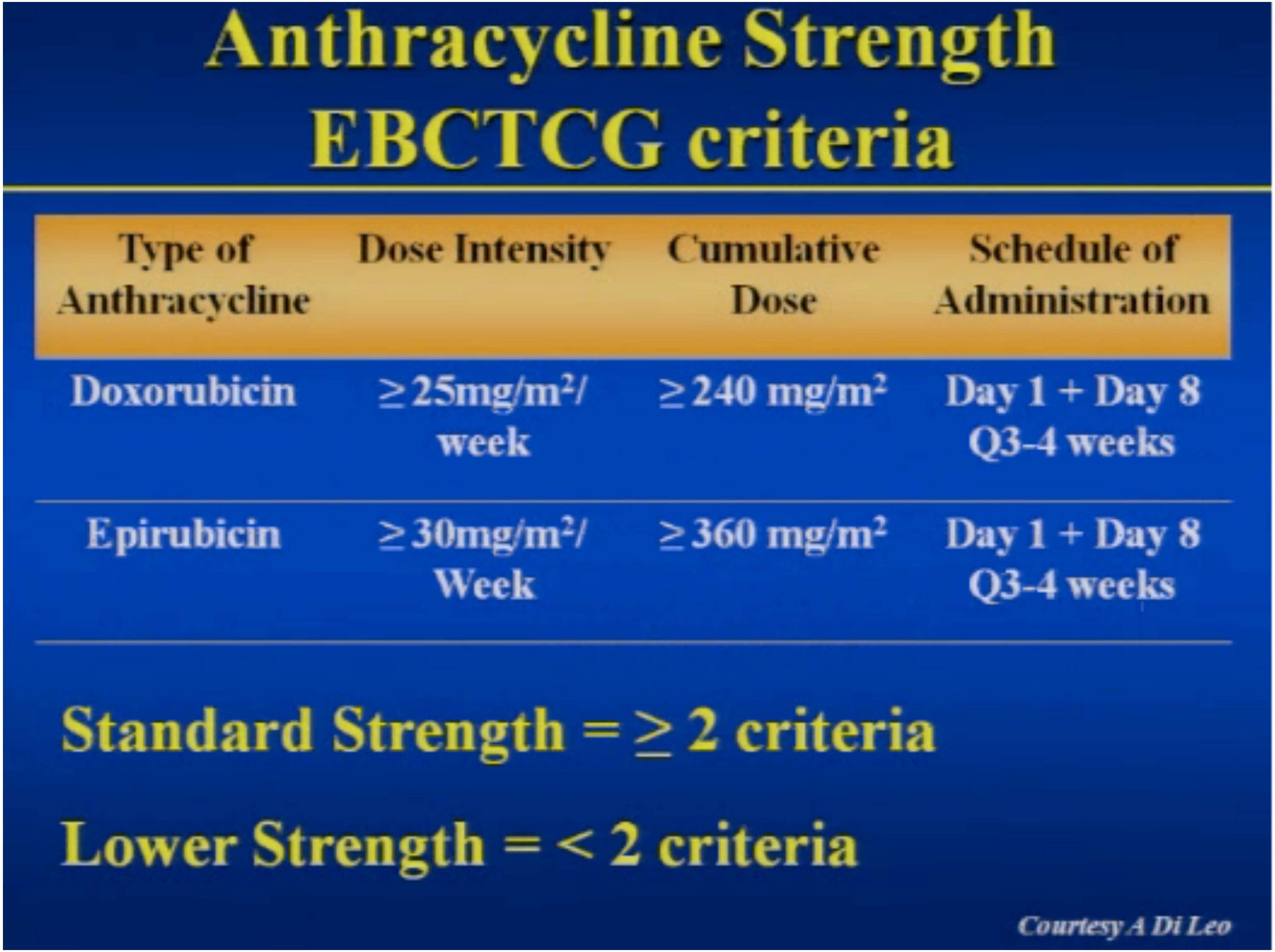
症例2　39歳　女性

- Breast (Rt):invasive ductal carcinoma, a2
- g, pT1c, ly−, v−, pn−, wide excision
- Lymph node: no metasitasis, 0/3, sentinel sampling
- ER: 1−10%, PgR: <1%, Hercep test: スコア1+
- 核異型度：Grade 3
- 組織学的腫瘍の広がり　26x10mm、浸潤径　25x10mm

Triple negative, node negative, リスク因子 3個

- AC4 ?
- FEC 6 ?
- AC → Taxane ?
- FEC→Taxane?

AC or FEC ?



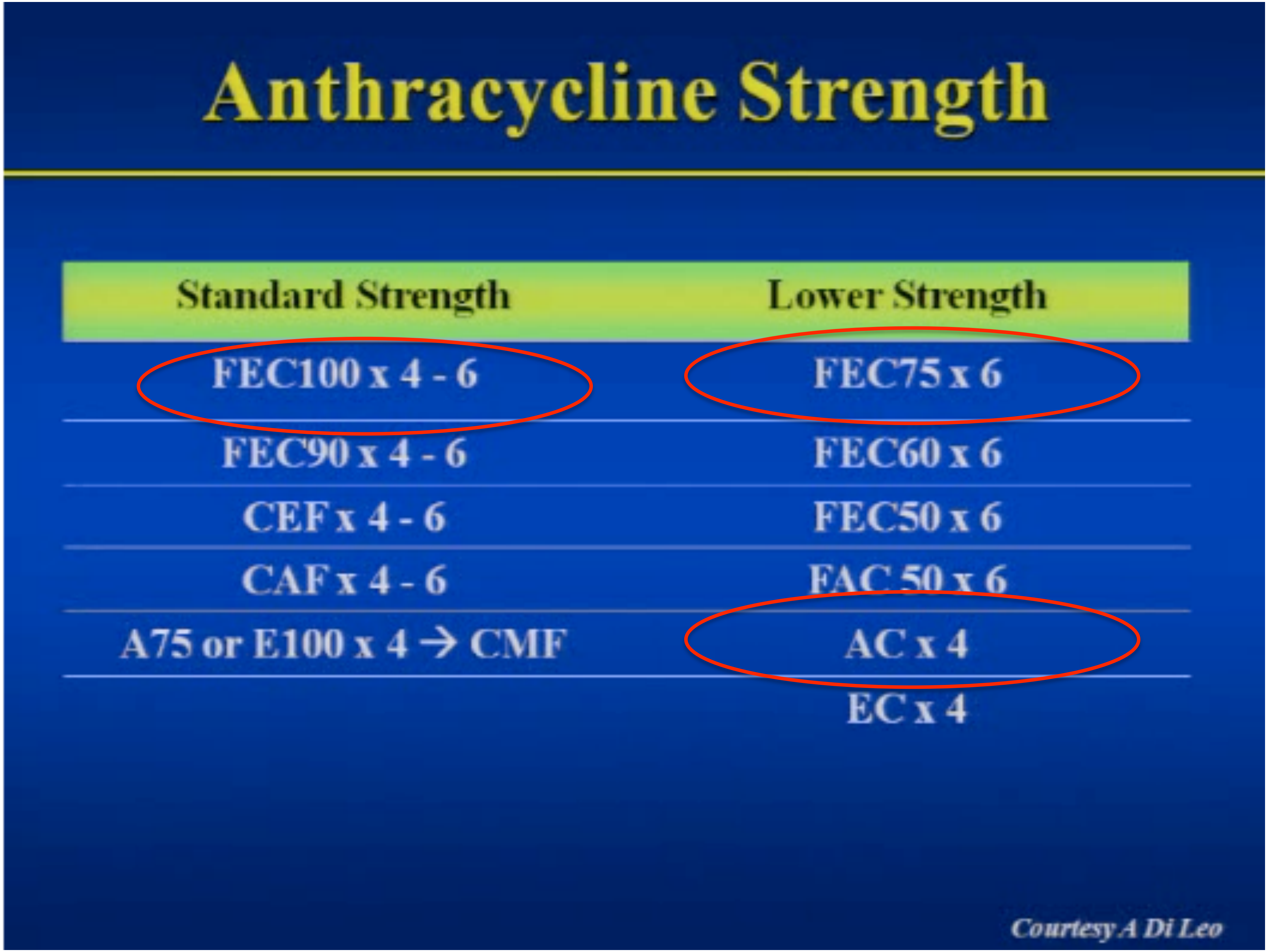
Anthracycline Strength EBCTCG criteria

Type of Anthracycline	Dose Intensity	Cumulative Dose	Schedule of Administration
Doxorubicin	$\geq$25mg/m^2/ week	$\geq$240 mg/m^2	Day 1 + Day 8 Q3-4 weeks
Epirubicin	$\geq$30mg/m^2/ Week	$\geq$360 mg/m^2	Day 1 + Day 8 Q3-4 weeks

Standard Strength = $\geq$ 2 criteria

Lower Strength = < 2 criteria

Courtesy A Di Leo



Anthracycline Strength

Standard Strength	Lower Strength
FEC100 x 4 - 6	FEC75 x 6
FEC90 x 4 - 6	FEC60 x 6
CEF x 4 - 6	FEC50 x 6
CAF x 4 - 6	FAC 50 x 6
A75 or E100 x 4 → CMF	AC x 4
	EC x 4

Courtesy A Di Leo

Relapse free survival
MA5

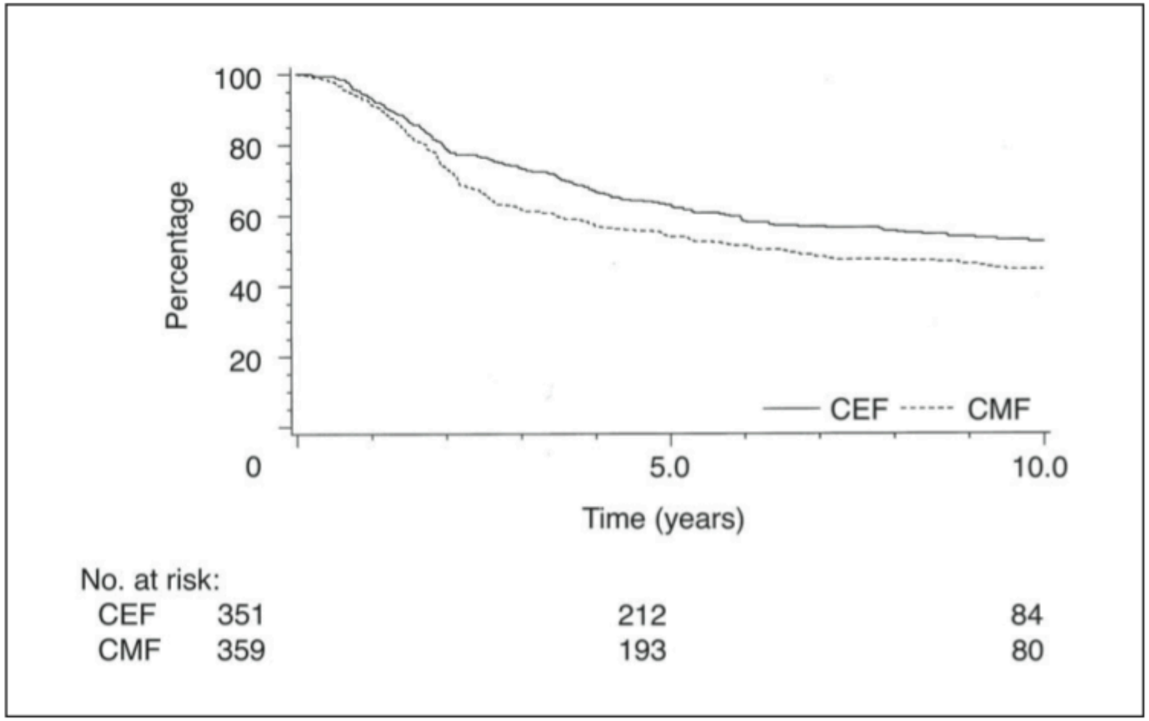


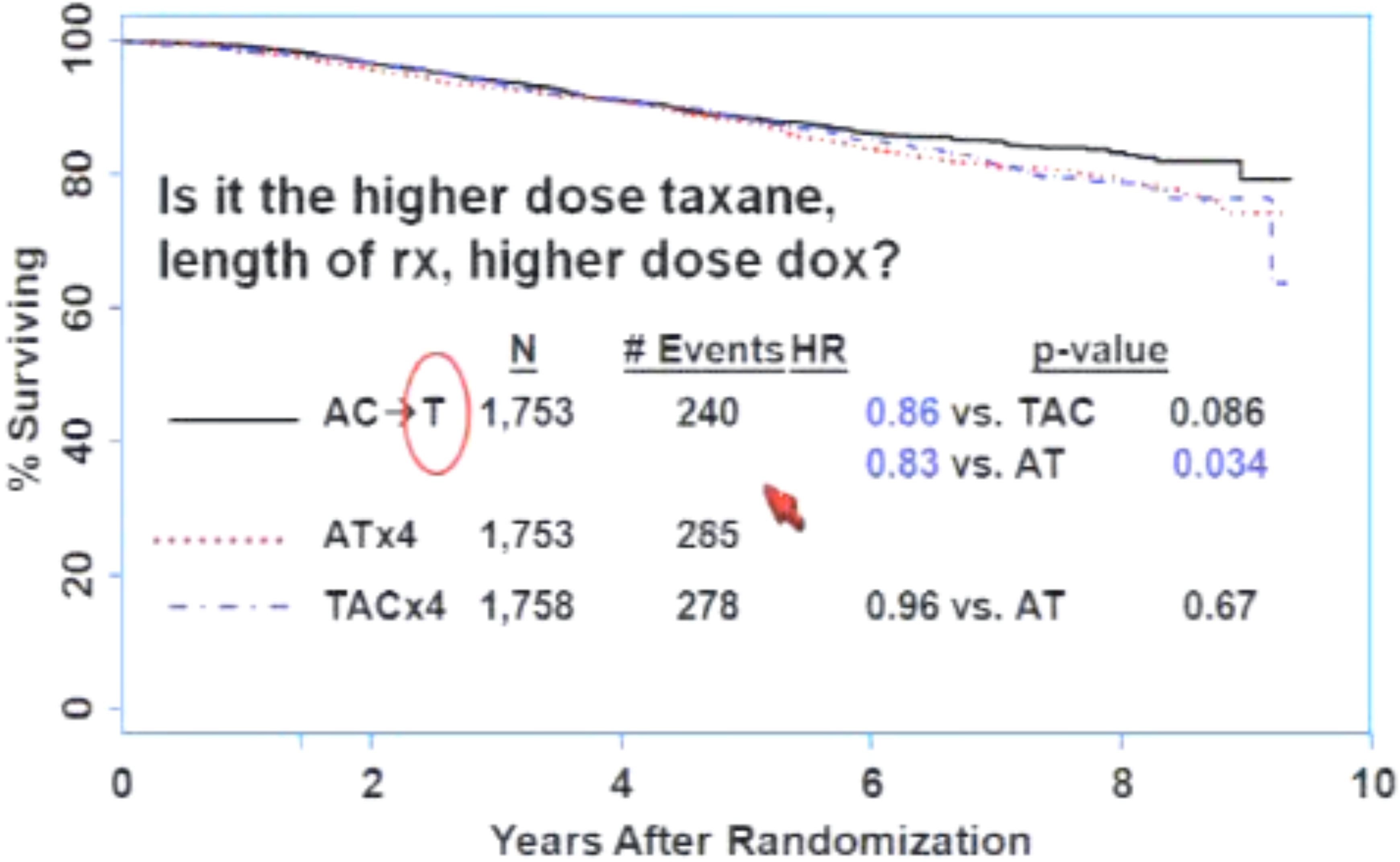
Fig 1. Ten-year relapse-free survival of cyclophosphamide, methotrexate, and fluorouracil (CMF) versus cyclophosphamide, epirubicin, and fluorouracil (CEF).

CEF 6cycle
C: 75 mg/m2 days 1 〜 14,
E: 60 mg/m2 **days 1 and 8**
F: 500 mg/m2 days 1 and 8

CMF 6cycle
C: 100 mg/m2 days 1 〜 14
M: 40 mg/m2 days 1 and 8
F: 600 mg/m2 days 1 and 8

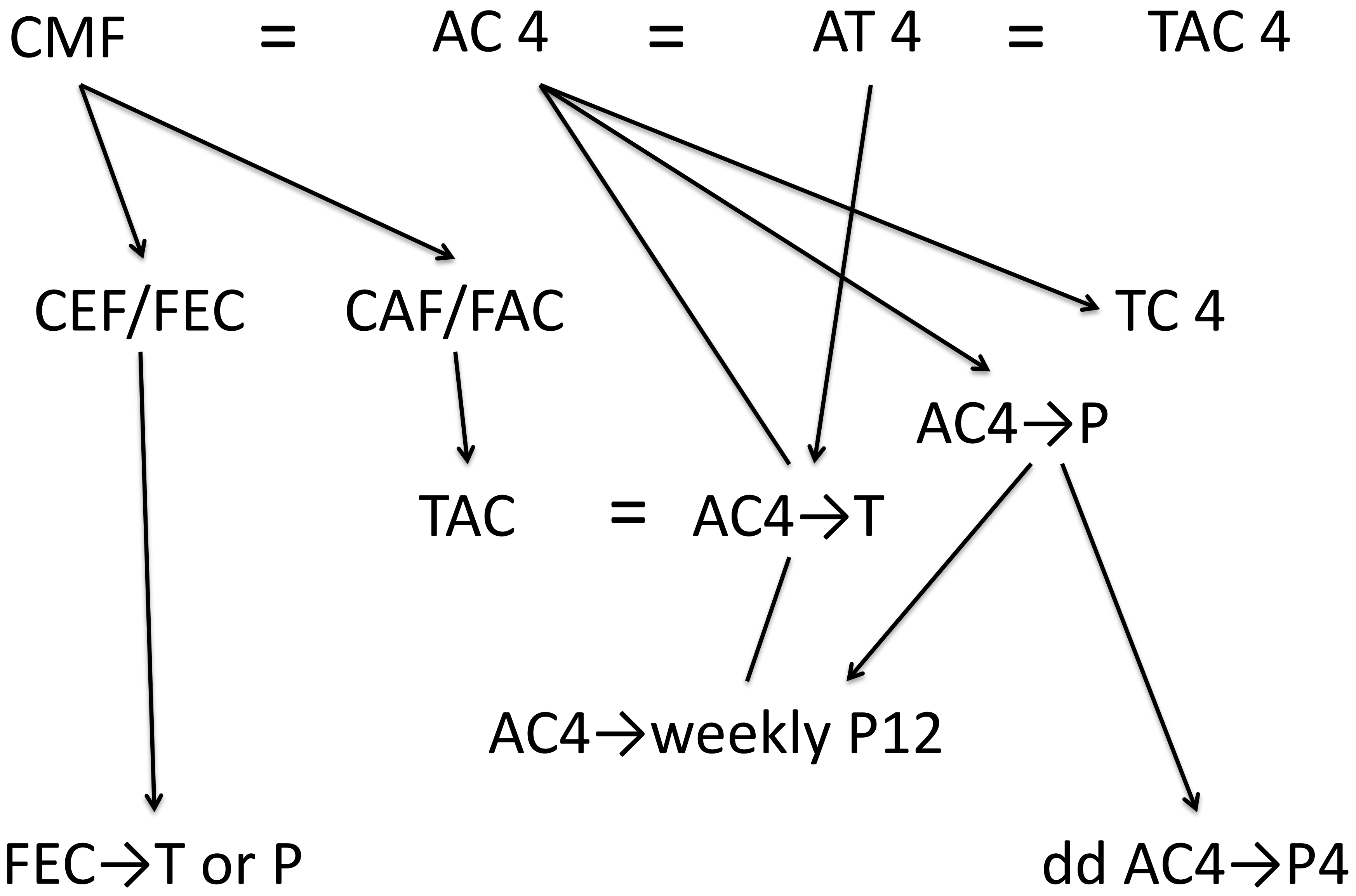
J Clin Oncol 23:5166-5170

NSABP B-30
Overall Survival (Intention-To-Treat)



Is it the higher dose taxane, length of rx, higher dose dox?

		N	# Events	HR	p-value
—	AC → T	1,753	240	0.86 vs. TAC	0.086
				0.83 vs. AT	0.034
⋯	ATx4	1,753	285		
-·-	TACx4	1,758	278	0.96 vs. AT	0.67



CMF = AC 4 = AT 4 = TAC 4

CEF/FEC

CAF/FAC

TC 4

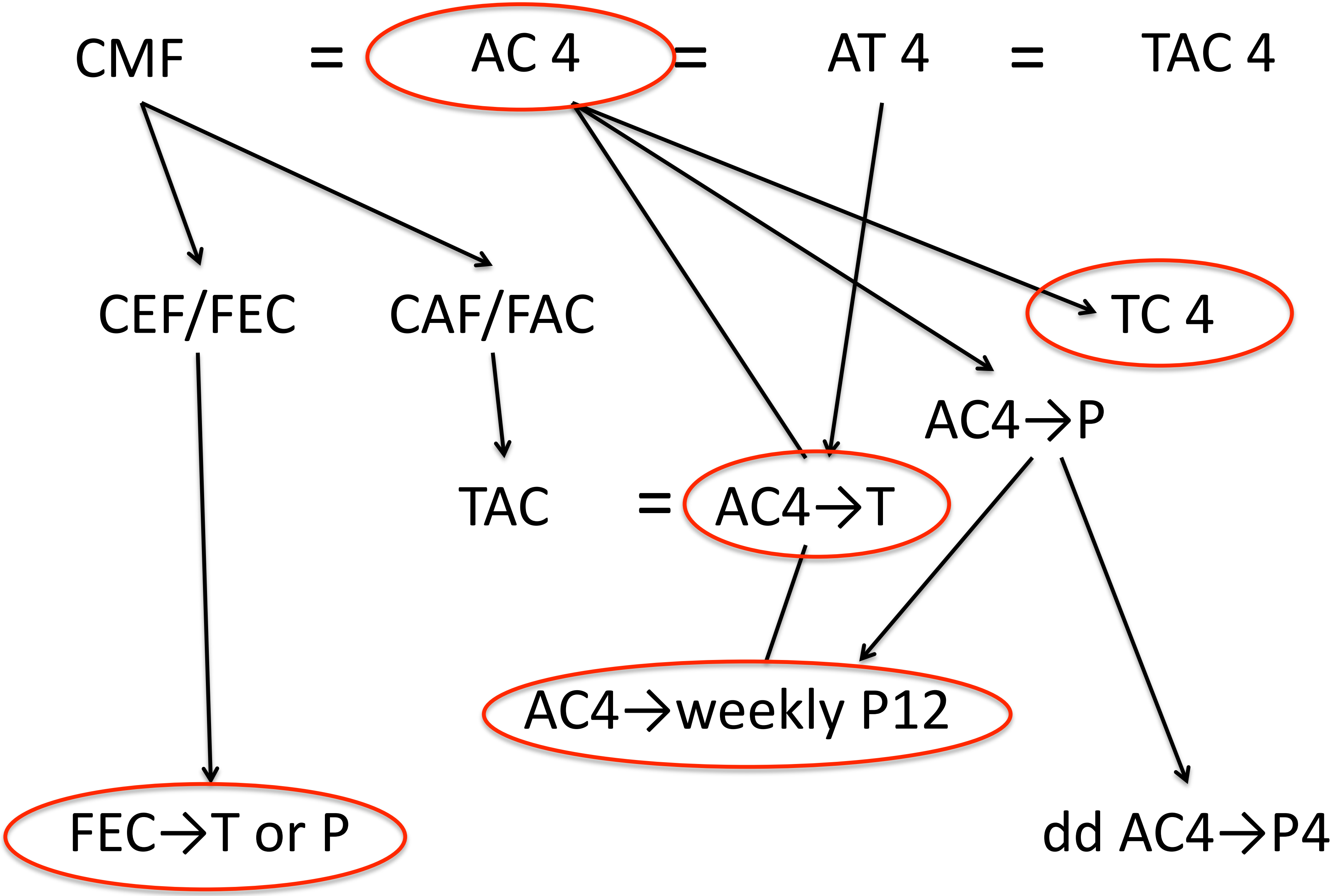
AC4→P

TAC = AC4→T

AC4→weekly P12

FEC→T or P

dd AC4→P4



CMF = AC 4 = AT 4 = TAC 4

CEF/FEC CAF/FAC TC 4

AC4→P

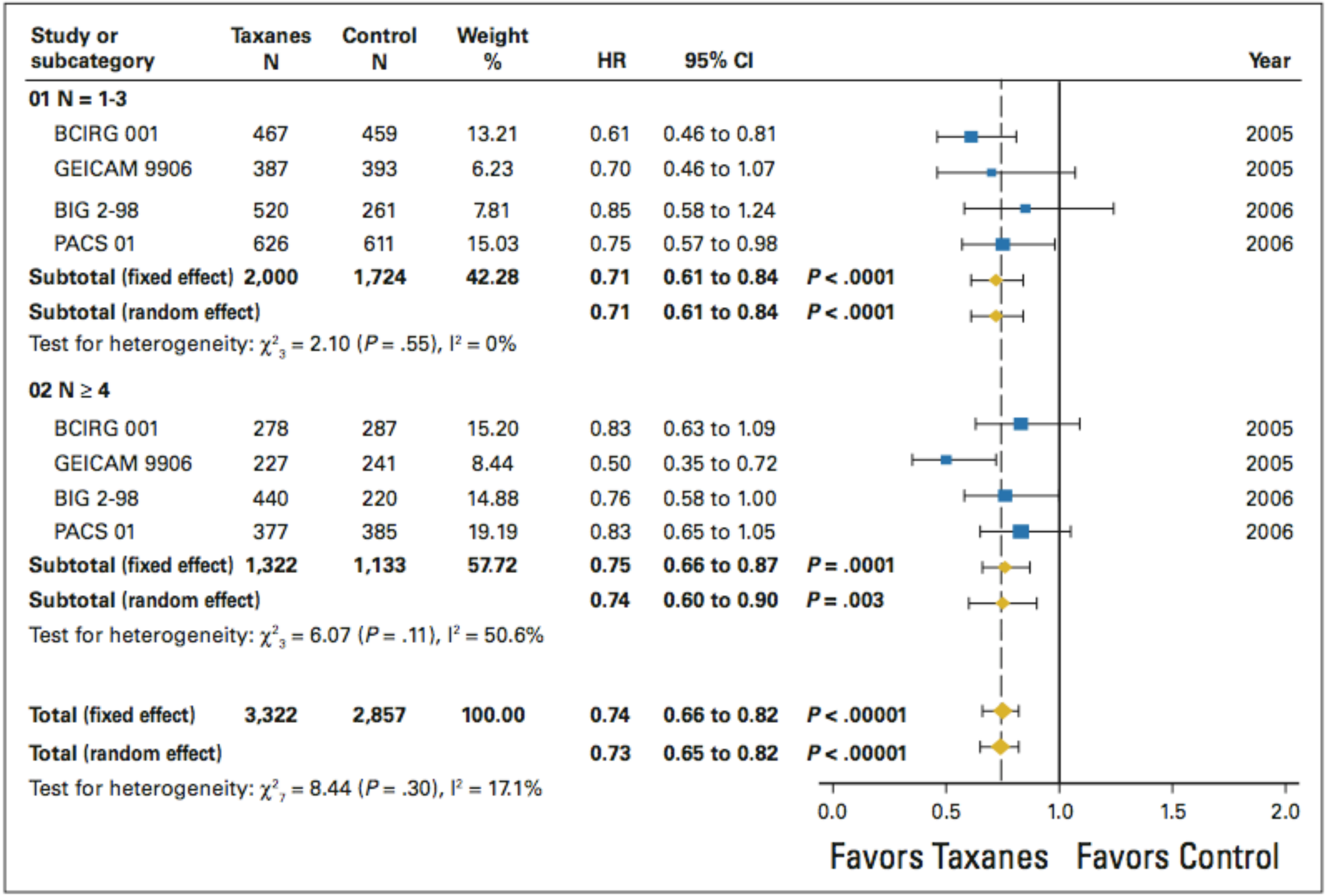
TAC = AC4→T

AC4→weekly P12

FEC→T or P dd AC4→P4

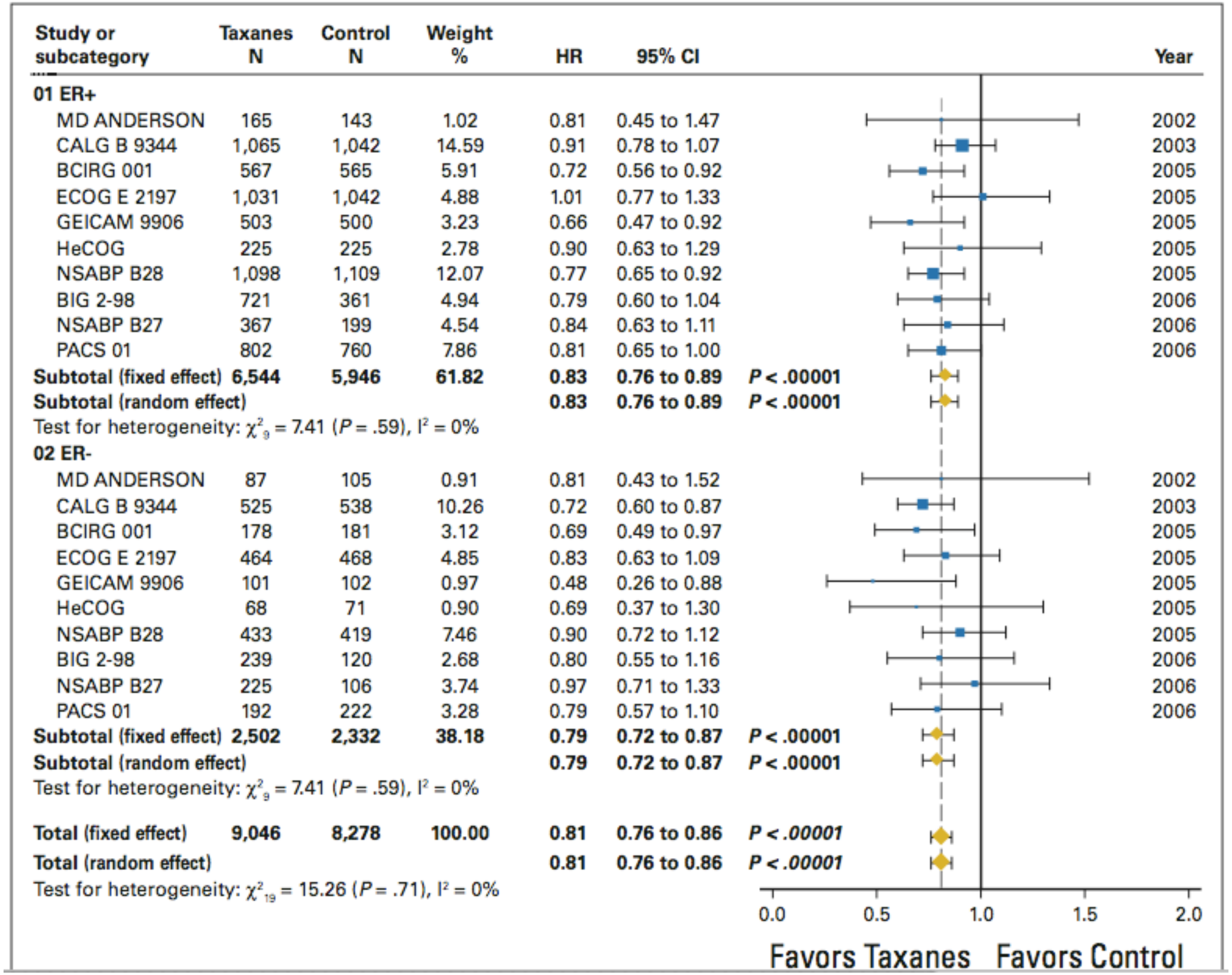
どのような症例に
Taxaneの追加を行うか？

リンパ節転移個数とタキサン追加効果

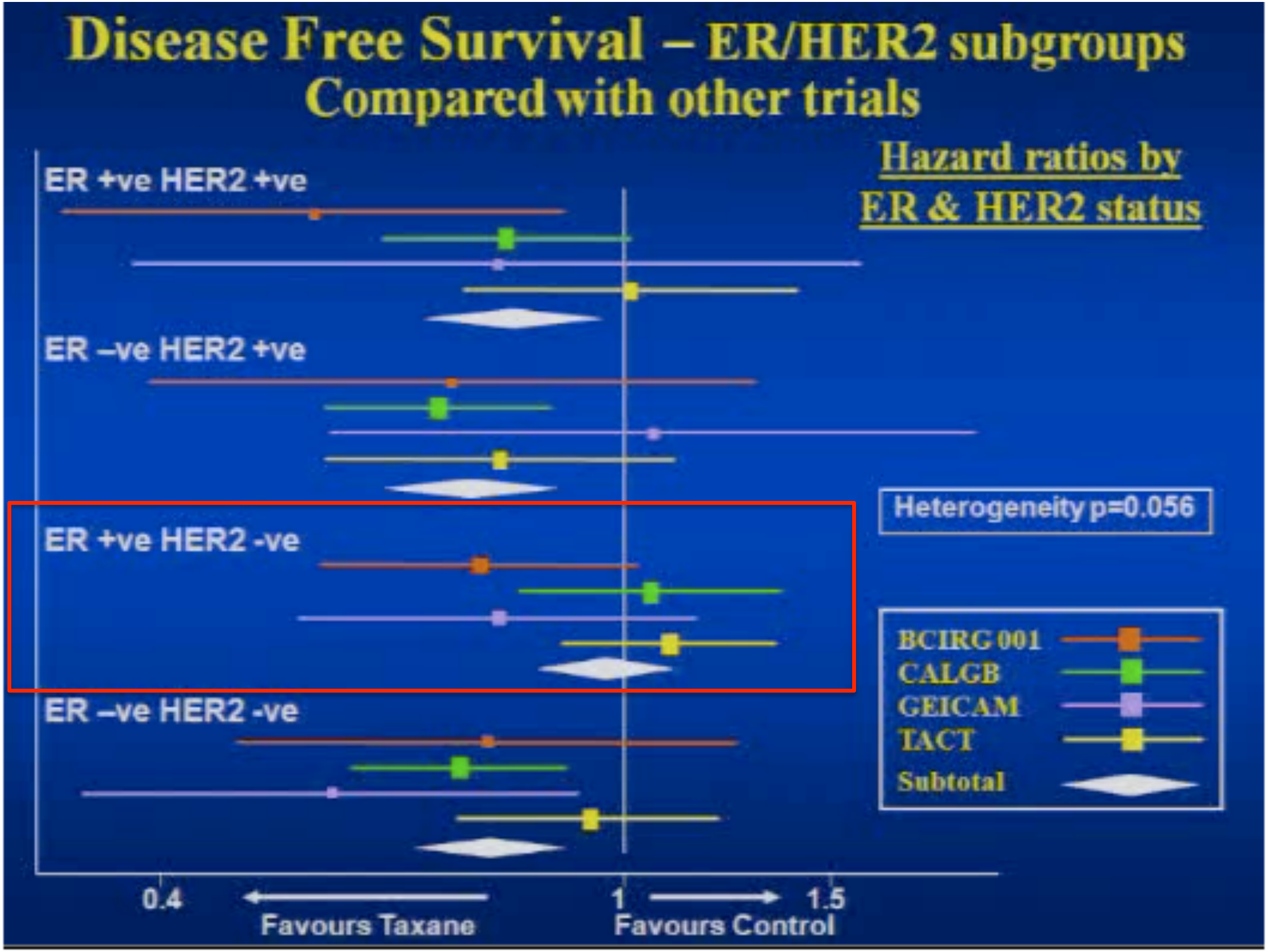


Study or subcategory	Taxanes N	Control N	Weight %	HR	95% CI		Year
01 N = 1-3							
BCIRG 001	467	459	13.21	0.61	0.46 to 0.81		2005
GEICAM 9906	387	393	6.23	0.70	0.46 to 1.07		2005
BIG 2-98	520	261	7.81	0.85	0.58 to 1.24		2006
PACS 01	626	611	15.03	0.75	0.57 to 0.98		2006
Subtotal (fixed effect)	**2,000**	**1,724**	**42.28**	**0.71**	**0.61 to 0.84**	**$P < .0001$**	
Subtotal (random effect)				**0.71**	**0.61 to 0.84**	**$P < .0001$**	
Test for heterogeneity: $\chi^2_3 = 2.10$ ($P = .55$), $I^2 = 0\%$							
02 N ≥ 4							
BCIRG 001	278	287	15.20	0.83	0.63 to 1.09		2005
GEICAM 9906	227	241	8.44	0.50	0.35 to 0.72		2005
BIG 2-98	440	220	14.88	0.76	0.58 to 1.00		2006
PACS 01	377	385	19.19	0.83	0.65 to 1.05		2006
Subtotal (fixed effect)	**1,322**	**1,133**	**57.72**	**0.75**	**0.66 to 0.87**	**$P = .0001$**	
Subtotal (random effect)				**0.74**	**0.60 to 0.90**	**$P = .003$**	
Test for heterogeneity: $\chi^2_3 = 6.07$ ($P = .11$), $I^2 = 50.6\%$							
Total (fixed effect)	**3,322**	**2,857**	**100.00**	**0.74**	**0.66 to 0.82**	**$P < .00001$**	
Total (random effect)				**0.73**	**0.65 to 0.82**	**$P < .00001$**	
Test for heterogeneity: $\chi^2_7 = 8.44$ ($P = .30$), $I^2 = 17.1\%$							

ホルモン受容体とタキサン追加効果



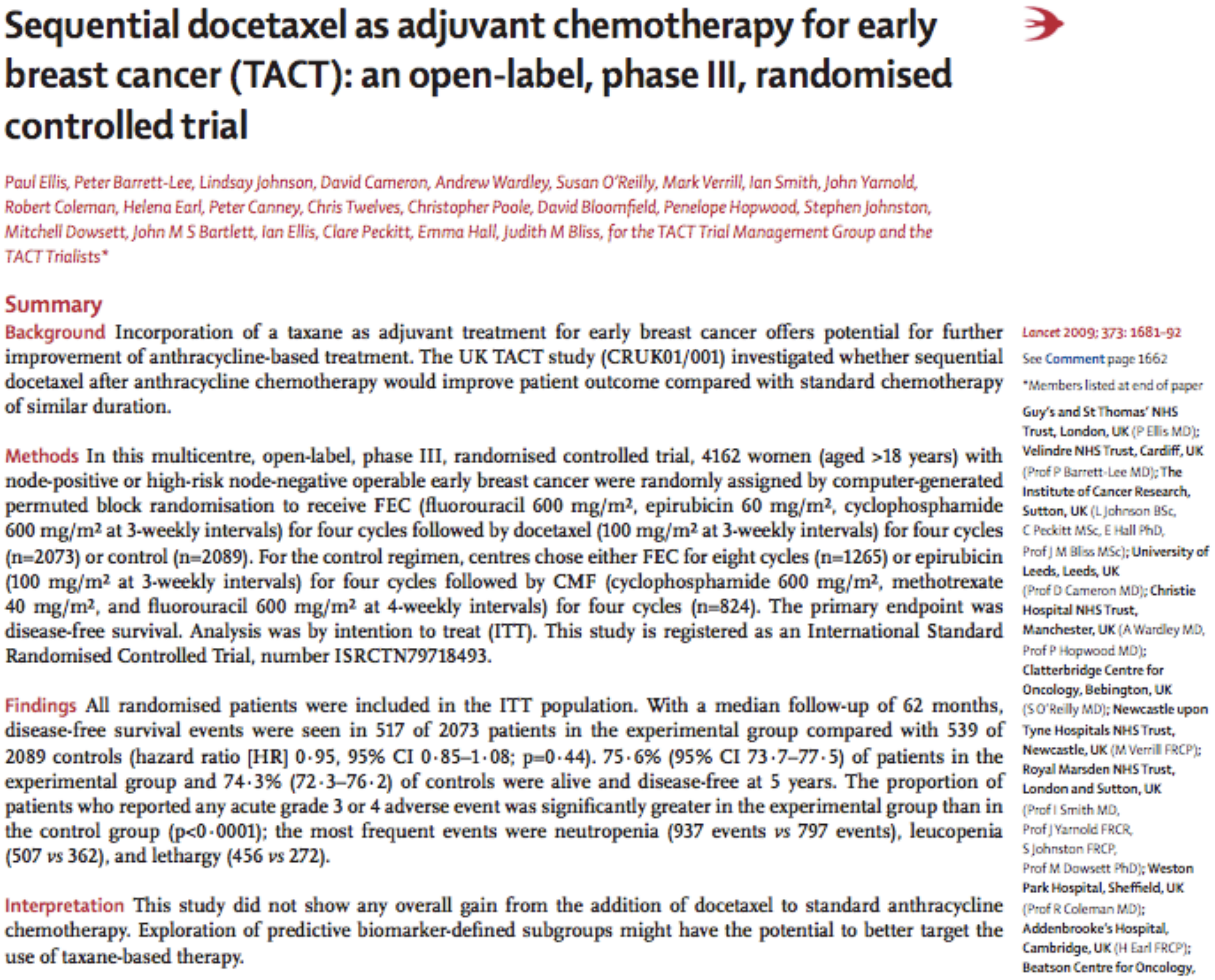
Study or subcategory	Taxanes N	Control N	Weight %	HR	95% CI		Year
01 ER+							
MD ANDERSON	165	143	1.02	0.81	0.45 to 1.47		2002
CALG B 9344	1,065	1,042	14.59	0.91	0.78 to 1.07		2003
BCIRG 001	567	565	5.91	0.72	0.56 to 0.92		2005
ECOG E 2197	1,031	1,042	4.88	1.01	0.77 to 1.33		2005
GEICAM 9906	503	500	3.23	0.66	0.47 to 0.92		2005
HeCOG	225	225	2.78	0.90	0.63 to 1.29		2005
NSABP B28	1,098	1,109	12.07	0.77	0.65 to 0.92		2005
BIG 2-98	721	361	4.94	0.79	0.60 to 1.04		2006
NSABP B27	367	199	4.54	0.84	0.63 to 1.11		2006
PACS 01	802	760	7.86	0.81	0.65 to 1.00		2006
Subtotal (fixed effect)	**6,544**	**5,946**	**61.82**	**0.83**	**0.76 to 0.89**	***P* < .00001**	
Subtotal (random effect)				**0.83**	**0.76 to 0.89**	***P* < .00001**	
Test for heterogeneity: $\chi^2_9 = 7.41$ (*P* = .59), $I^2 = 0\%$							
02 ER-							
MD ANDERSON	87	105	0.91	0.81	0.43 to 1.52		2002
CALG B 9344	525	538	10.26	0.72	0.60 to 0.87		2003
BCIRG 001	178	181	3.12	0.69	0.49 to 0.97		2005
ECOG E 2197	464	468	4.85	0.83	0.63 to 1.09		2005
GEICAM 9906	101	102	0.97	0.48	0.26 to 0.88		2005
HeCOG	68	71	0.90	0.69	0.37 to 1.30		2005
NSABP B28	433	419	7.46	0.90	0.72 to 1.12		2005
BIG 2-98	239	120	2.68	0.80	0.55 to 1.16		2006
NSABP B27	225	106	3.74	0.97	0.71 to 1.33		2006
PACS 01	192	222	3.28	0.79	0.57 to 1.10		2006
Subtotal (fixed effect)	**2,502**	**2,332**	**38.18**	**0.79**	**0.72 to 0.87**	***P* < .00001**	
Subtotal (random effect)				**0.79**	**0.72 to 0.87**	***P* < .00001**	
Test for heterogeneity: $\chi^2_9 = 7.41$ (*P* = .59), $I^2 = 0\%$							
Total (fixed effect)	**9,046**	**8,278**	**100.00**	**0.81**	**0.76 to 0.86**	***P* < .00001**	
Total (random effect)				**0.81**	**0.76 to 0.86**	***P* < .00001**	
Test for heterogeneity: $\chi^2_{19} = 15.26$ (*P* = .71), $I^2 = 0\%$							



Disease Free Survival – ER/HER2 subgroups
Compared with other trials

Hazard ratios by ER & HER2 status

Heterogeneity p=0.056



Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial

*Paul Ellis, Peter Barrett-Lee, Lindsay Johnson, David Cameron, Andrew Wardley, Susan O'Reilly, Mark Verrill, Ian Smith, John Yarnold, Robert Coleman, Helena Earl, Peter Canney, Chris Twelves, Christopher Poole, David Bloomfield, Penelope Hopwood, Stephen Johnston, Mitchell Dowsett, John M S Bartlett, Ian Ellis, Clare Peckitt, Emma Hall, Judith M Bliss, for the TACT Trial Management Group and the TACT Trialists**

Summary

Background Incorporation of a taxane as adjuvant treatment for early breast cancer offers potential for further improvement of anthracycline-based treatment. The UK TACT study (CRUK01/001) investigated whether sequential docetaxel after anthracycline chemotherapy would improve patient outcome compared with standard chemotherapy of similar duration.

Methods In this multicentre, open-label, phase III, randomised controlled trial, 4162 women (aged >18 years) with node-positive or high-risk node-negative operable early breast cancer were randomly assigned by computer-generated permuted block randomisation to receive FEC (fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 at 3-weekly intervals) for four cycles followed by docetaxel (100 mg/m^2 at 3-weekly intervals) for four cycles (n=2073) or control (n=2089). For the control regimen, centres chose either FEC for eight cycles (n=1265) or epirubicin (100 mg/m^2 at 3-weekly intervals) for four cycles followed by CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and fluorouracil 600 mg/m^2 at 4-weekly intervals) for four cycles (n=824). The primary endpoint was disease-free survival. Analysis was by intention to treat (ITT). This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN79718493.

Findings All randomised patients were included in the ITT population. With a median follow-up of 62 months, disease-free survival events were seen in 517 of 2073 patients in the experimental group compared with 539 of 2089 controls (hazard ratio [HR] 0·95, 95% CI 0·85–1·08; p=0·44). 75·6% (95% CI 73·7–77·5) of patients in the experimental group and 74·3% (72·3–76·2) of controls were alive and disease-free at 5 years. The proportion of patients who reported any acute grade 3 or 4 adverse event was significantly greater in the experimental group than in the control group (p<0·0001); the most frequent events were neutropenia (937 events *vs* 797 events), leucopenia (507 *vs* 362), and lethargy (456 *vs* 272).

Interpretation This study did not show any overall gain from the addition of docetaxel to standard anthracycline chemotherapy. Exploration of predictive biomarker-defined subgroups might have the potential to better target the use of taxane-based therapy.

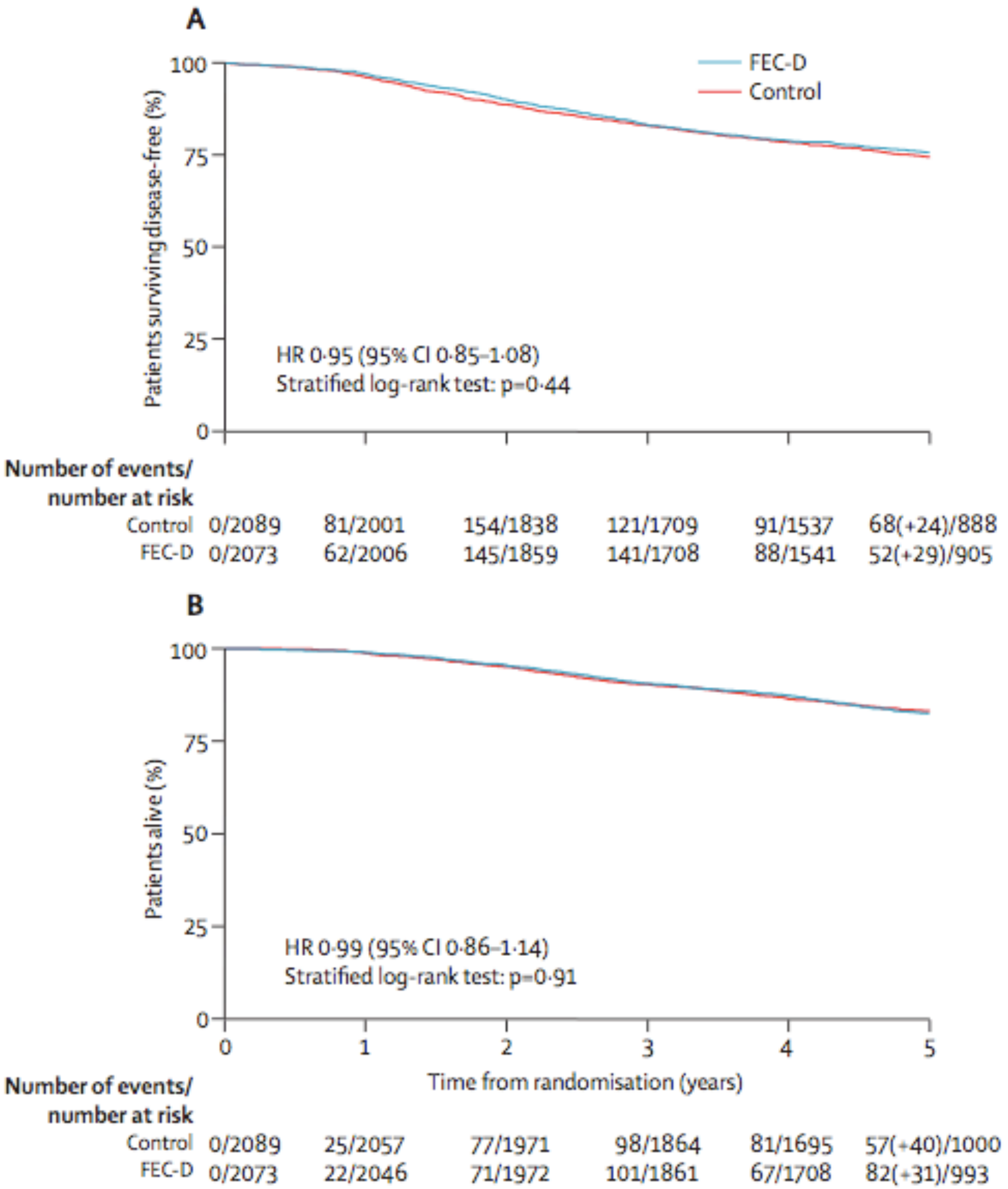
Lancet 2009; 373: 1681–92

See Comment page 1662

*Members listed at end of paper

Guy's and St Thomas' NHS Trust, London, UK (P Ellis MD); **Velindre NHS Trust, Cardiff, UK** (Prof P Barrett-Lee MD); **The Institute of Cancer Research, Sutton, UK** (L Johnson BSc, C Peckitt MSc, E Hall PhD, Prof J M Bliss MSc); **University of Leeds, Leeds, UK** (Prof D Cameron MD); **Christie Hospital NHS Trust, Manchester, UK** (A Wardley MD, Prof P Hopwood MD); **Clatterbridge Centre for Oncology, Bebington, UK** (S O'Reilly MD); **Newcastle upon Tyne Hospitals NHS Trust, Newcastle, UK** (M Verrill FRCP); **Royal Marsden NHS Trust, London and Sutton, UK** (Prof I Smith MD, Prof J Yarnold FRCR, S Johnston FRCP, Prof M Dowsett PhD); **Weston Park Hospital, Sheffield, UK** (Prof R Coleman MD); **Addenbrooke's Hospital, Cambridge, UK** (H Earl FRCP); **Beatson Centre for Oncology,**

Lancet 2009; 373: 1681–92



Number of events/ number at risk						
Control	0/2089	81/2001	154/1838	121/1709	91/1537	68(+24)/888
FEC-D	0/2073	62/2006	145/1859	141/1708	88/1541	52(+29)/905

Number of events/ number at risk						
Control	0/2089	25/2057	77/1971	98/1864	81/1695	57(+40)/1000
FEC-D	0/2073	22/2046	71/1972	101/1861	67/1708	82(+31)/993

FEC4-D4 (n=2073)
F:600 mg/m^2
E:60 mg/m^2,
C: 600 mg/m^2
at 3-weekly intervals
D: 100 mg/m^2
at 3-weekly intervals

Control
FEC8 (n=1265)
F:600 mg/m^2
E:60 mg/m^2,
C: 600 mg/m^2
at 3-weekly intervals

FEC4-CMF4 (n=824)
E: 100 mg/m^2
at 3-weekly intervals

エンドキサンによる
Ovarian suppression効果？
E:100の効果？

Lancet 2009; 373: 1681–92

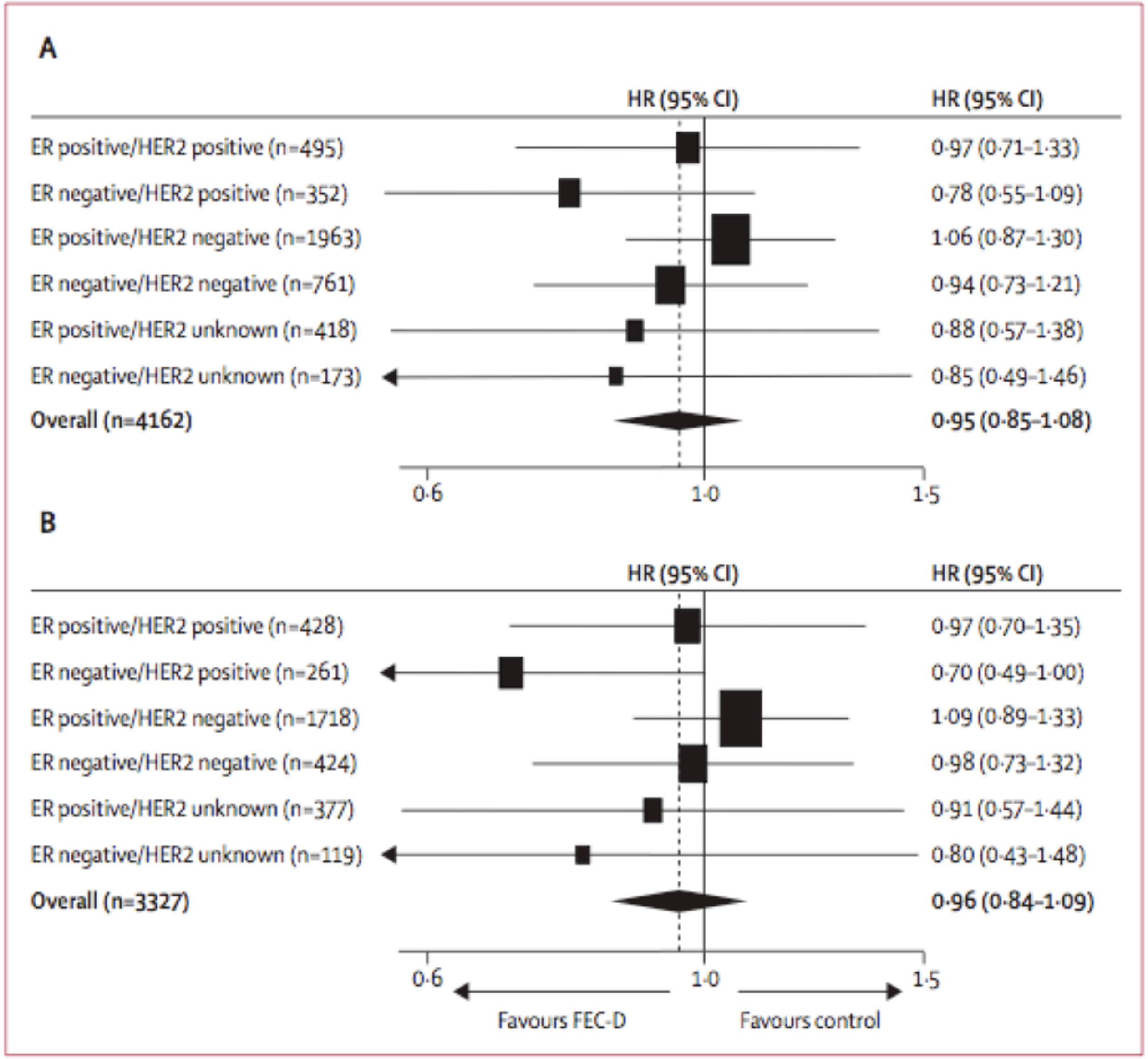
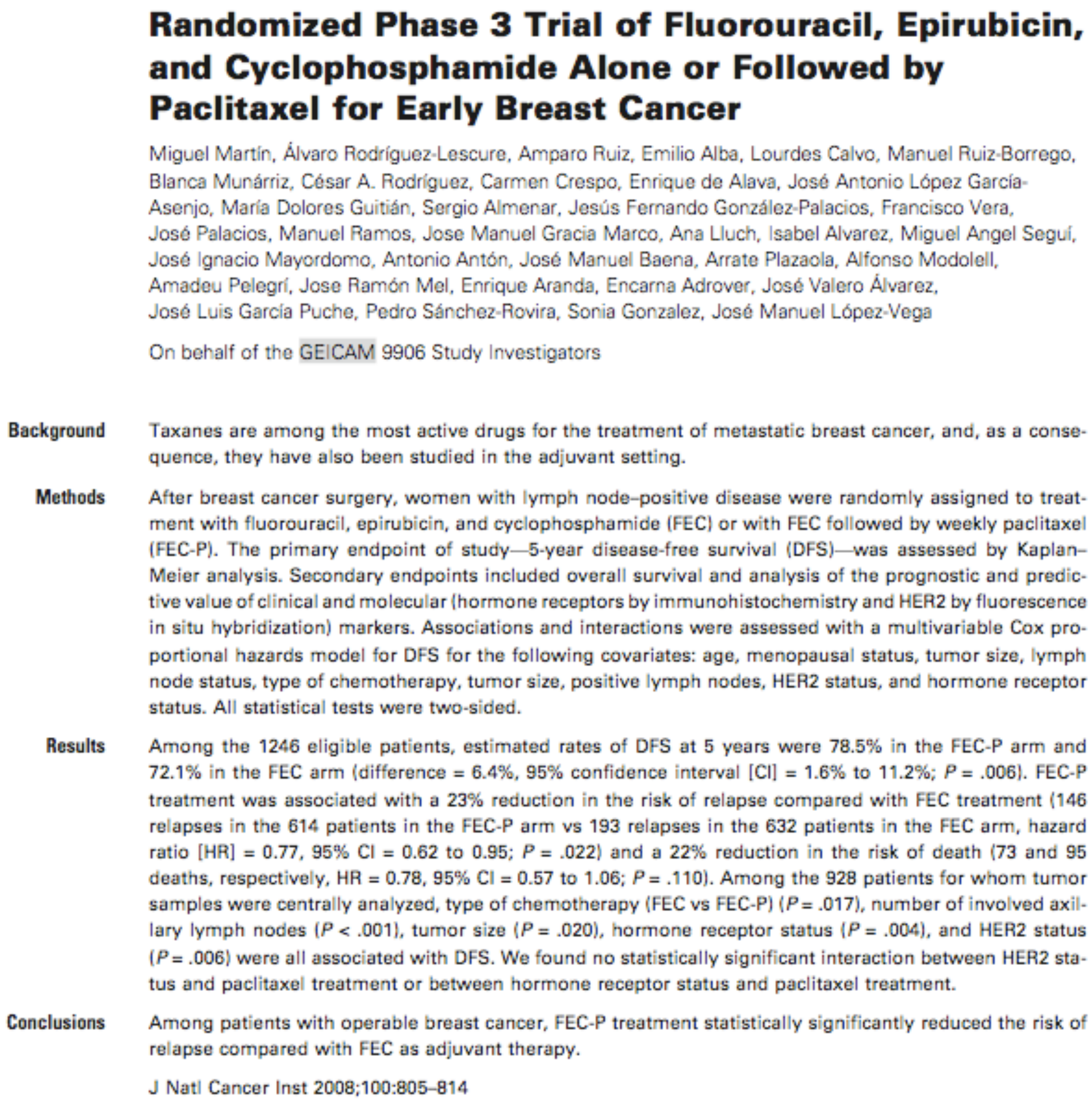


***Figure 5*: Hazard ratios for disease-free survival by combined ER and HER2 status in (A) all patients and (B) node-positive patients**

ER=oestrogen receptor. FEC-D=fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel. HER2=human epidermal growth factor receptor 2. HR=hazard ratio.

Lancet 2009; 373: 1681–92



Randomized Phase 3 Trial of Fluorouracil, Epirubicin, and Cyclophosphamide Alone or Followed by Paclitaxel for Early Breast Cancer

Miguel Martín, Álvaro Rodríguez-Lescure, Amparo Ruiz, Emilio Alba, Lourdes Calvo, Manuel Ruiz-Borrego, Blanca Munárriz, César A. Rodríguez, Carmen Crespo, Enrique de Alava, José Antonio López García-Asenjo, María Dolores Guitián, Sergio Almenar, Jesús Fernando González-Palacios, Francisco Vera, José Palacios, Manuel Ramos, Jose Manuel Gracia Marco, Ana Lluch, Isabel Alvarez, Miguel Angel Seguí, José Ignacio Mayordomo, Antonio Antón, José Manuel Baena, Arrate Plazaola, Alfonso Modolell, Amadeu Pelegrí, Jose Ramón Mel, Enrique Aranda, Encarna Adrover, José Valero Álvarez, José Luis García Puche, Pedro Sánchez-Rovira, Sonia Gonzalez, José Manuel López-Vega

On behalf of the GEICAM 9906 Study Investigators

Background Taxanes are among the most active drugs for the treatment of metastatic breast cancer, and, as a consequence, they have also been studied in the adjuvant setting.

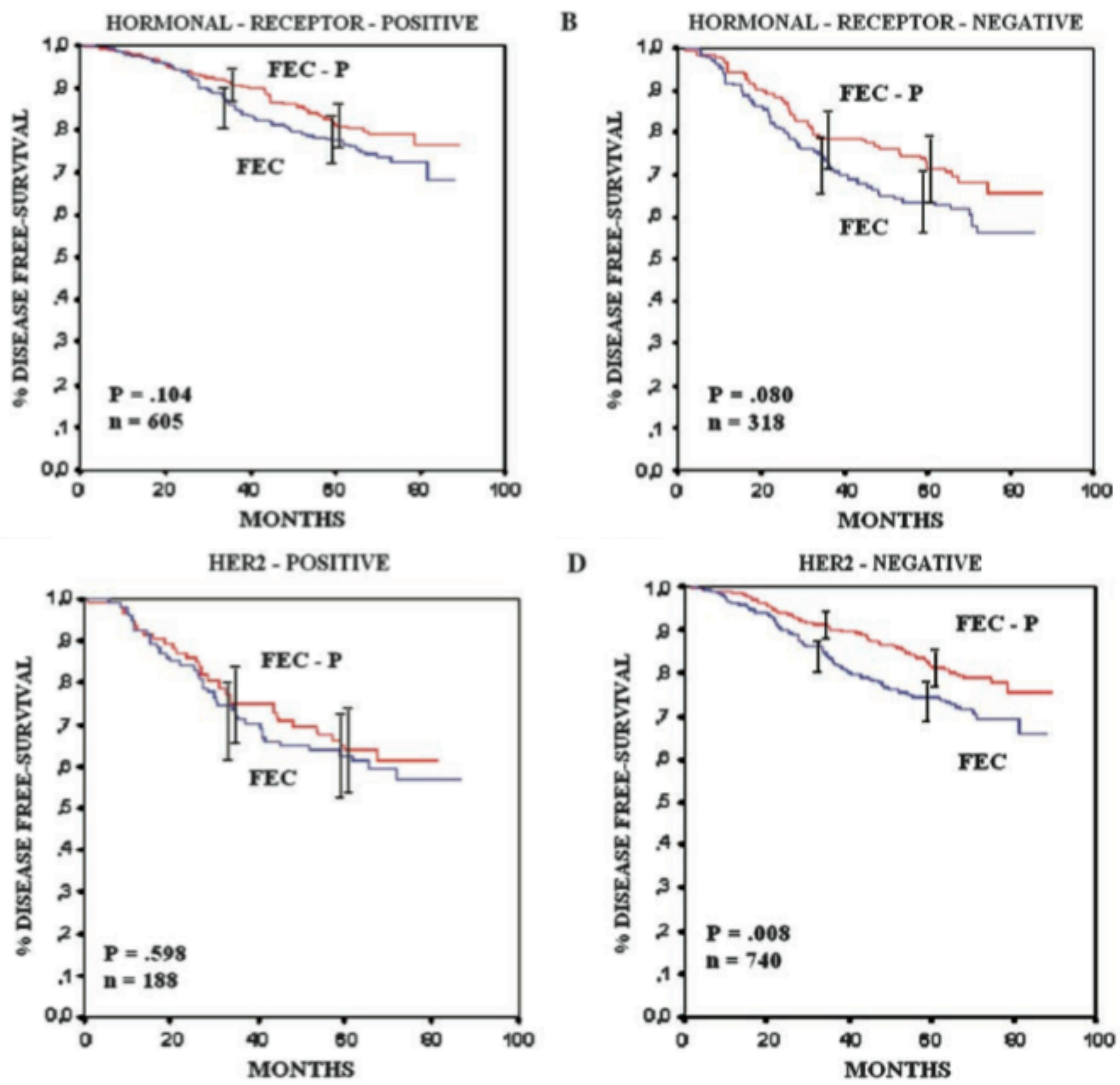
Methods After breast cancer surgery, women with lymph node–positive disease were randomly assigned to treatment with fluorouracil, epirubicin, and cyclophosphamide (FEC) or with FEC followed by weekly paclitaxel (FEC-P). The primary endpoint of study—5-year disease-free survival (DFS)—was assessed by Kaplan–Meier analysis. Secondary endpoints included overall survival and analysis of the prognostic and predictive value of clinical and molecular (hormone receptors by immunohistochemistry and HER2 by fluorescence in situ hybridization) markers. Associations and interactions were assessed with a multivariable Cox proportional hazards model for DFS for the following covariates: age, menopausal status, tumor size, lymph node status, type of chemotherapy, tumor size, positive lymph nodes, HER2 status, and hormone receptor status. All statistical tests were two-sided.

Results Among the 1246 eligible patients, estimated rates of DFS at 5 years were 78.5% in the FEC-P arm and 72.1% in the FEC arm (difference = 6.4%, 95% confidence interval [CI] = 1.6% to 11.2%; $P = .006$). FEC-P treatment was associated with a 23% reduction in the risk of relapse compared with FEC treatment (146 relapses in the 614 patients in the FEC-P arm vs 193 relapses in the 632 patients in the FEC arm, hazard ratio [HR] = 0.77, 95% CI = 0.62 to 0.95; $P = .022$) and a 22% reduction in the risk of death (73 and 95 deaths, respectively, HR = 0.78, 95% CI = 0.57 to 1.06; $P = .110$). Among the 928 patients for whom tumor samples were centrally analyzed, type of chemotherapy (FEC vs FEC-P) ($P = .017$), number of involved axillary lymph nodes ($P < .001$), tumor size ($P = .020$), hormone receptor status ($P = .004$), and HER2 status ($P = .006$) were all associated with DFS. We found no statistically significant interaction between HER2 status and paclitaxel treatment or between hormone receptor status and paclitaxel treatment.

Conclusions Among patients with operable breast cancer, FEC-P treatment statistically significantly reduced the risk of relapse compared with FEC as adjuvant therapy.

J Natl Cancer Inst 2008;100:805–814

J Natl Cancer Inst 2008;100: 805 – 814



FEC-P arm (n=632)

•FEC
at 3weekly, **4**cycle

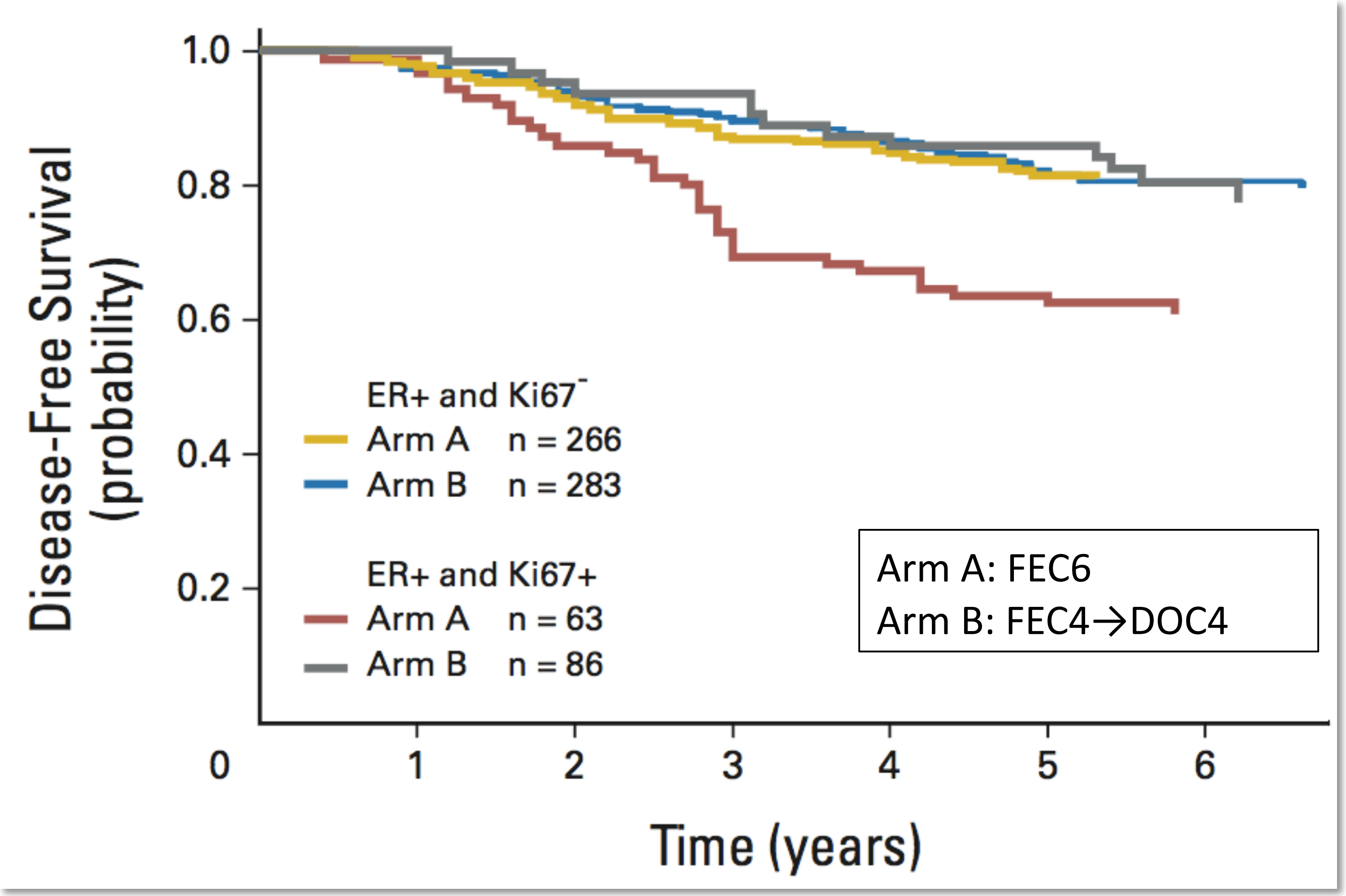
•Paclitaxe
P:100mg/m2
at weekly, **8**cycle

FEC arm (n=614)

F: 600mg/m2
E: 90mg/m2
C: 600mg/m2
at 3weekly, **6** cycle

J Natl Cancer Inst 2008;100: 805 – 814

Ki 67とdocetaxelの追加効果との関係
PACS 01



Arm A: FEC6
Arm B: FEC4→DOC4

J Clin Oncol. 2009 Apr 20.

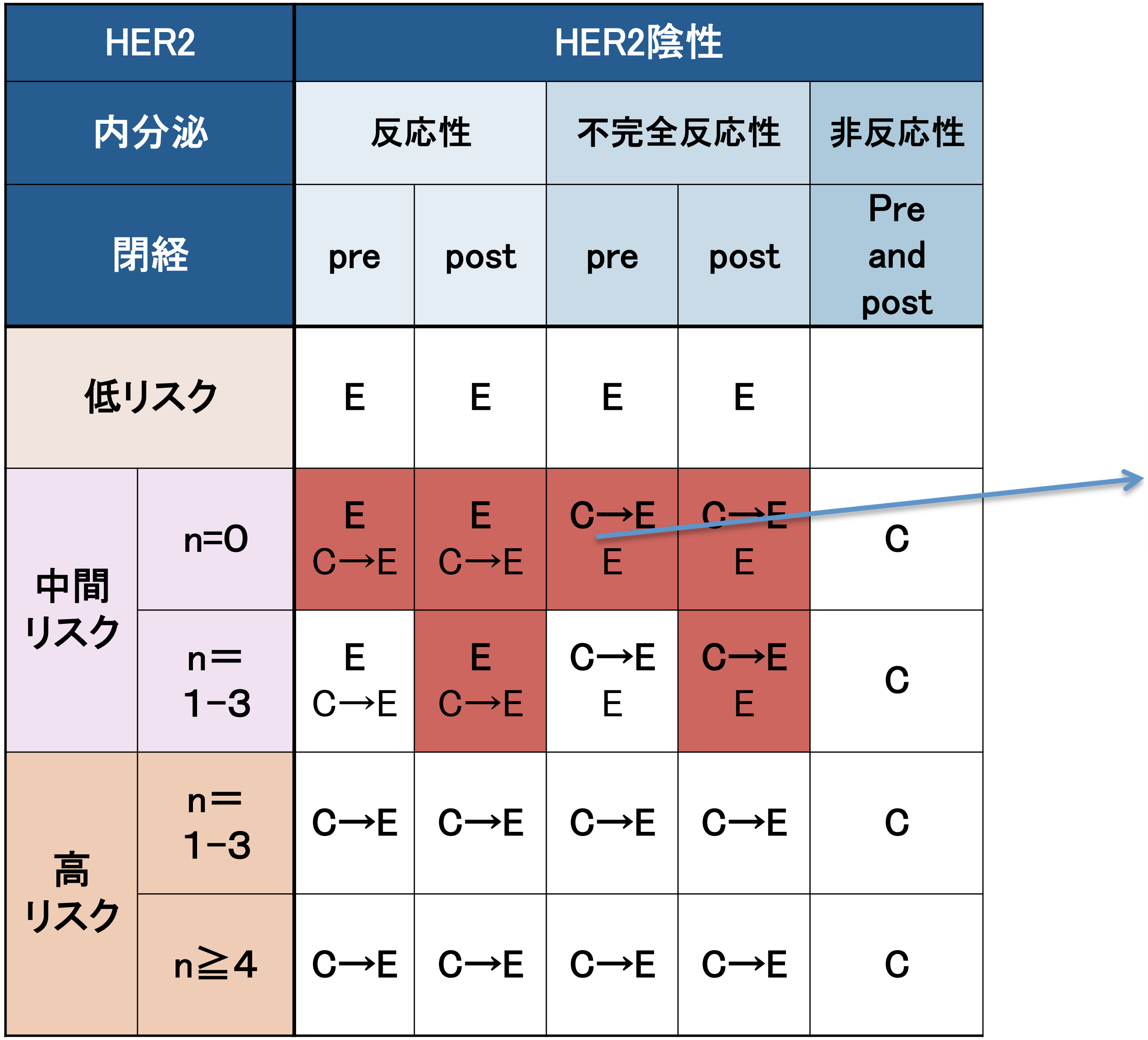
化学療法の適応は？

HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0	E C→E	E C→E	C→E E	C→E E	C
	n＝1−3	E C→E	E C→E	C→E E	C→E E	C
高リスク	n＝1−3	C→E	C→E	C→E	C→E	C
	n≧4	C→E	C→E	C→E	C→E	C

化学療法の
メリットが少ない

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

化学療法の適応は？



HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0	E C→E	E C→E	C→E E	C→E E	C
	n＝1−3	E C→E	E C→E	C→E E	C→E E	C
高リスク	n＝1−3	C→E	C→E	C→E	C→E	C
	n≧4	C→E	C→E	C→E	C→E	C

oncotype DX® Breast Cancer Assay

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

化学療法の適応は？

HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0	E C→E	E C→E	C→E E	C→E E	C
	n＝1−3	E C→E	E C→E	C→E E	C→E E	C
高リスク	n＝1−3	C→E	C→E	C→E	C→E	C
	n≧4	C→E	C→E	C→E	C→E	C

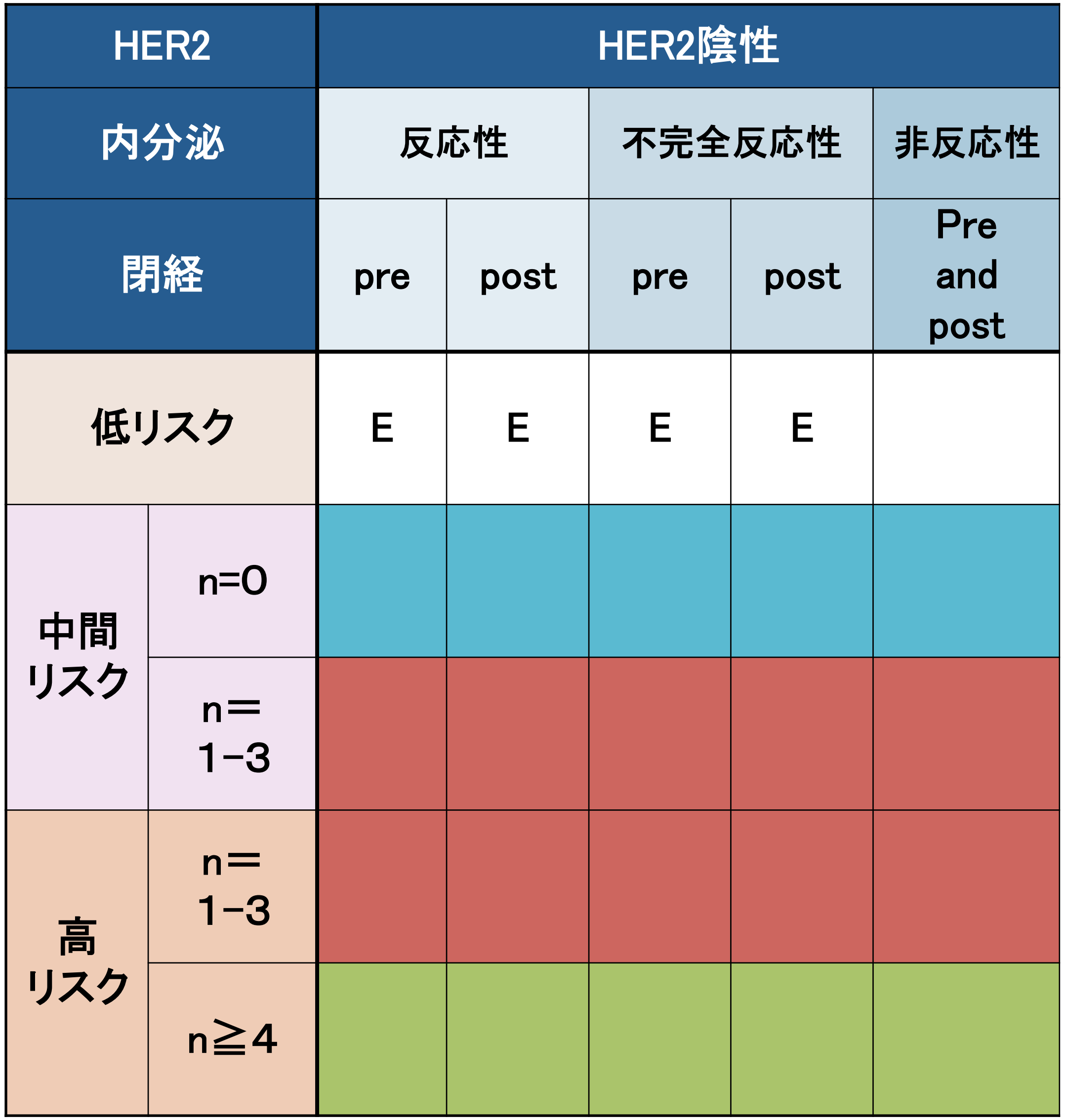
C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

mammaprint™

化学療法のレジメンは？

HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0	E C→E	E C→E	C→E E	C→E E	C
	n＝1−3	E C→E	E C→E	C→E E	C→E E	C
高リスク	n＝1−3	C→E	C→E	C→E	C→E	C
	n≧4	C→E	C→E	C→E	C→E	C

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab



HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0	🟦	🟦	🟦	🟦	🟦
	n＝1−3	🟥	🟥	🟥	🟥	🟥
高リスク	n＝1−3	🟥	🟥	🟥	🟥	🟥
	n≧4	🟩	🟩	🟩	🟩	🟩

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

化学療法のレジメンは？
リンパ節転移個数を重視すると‥

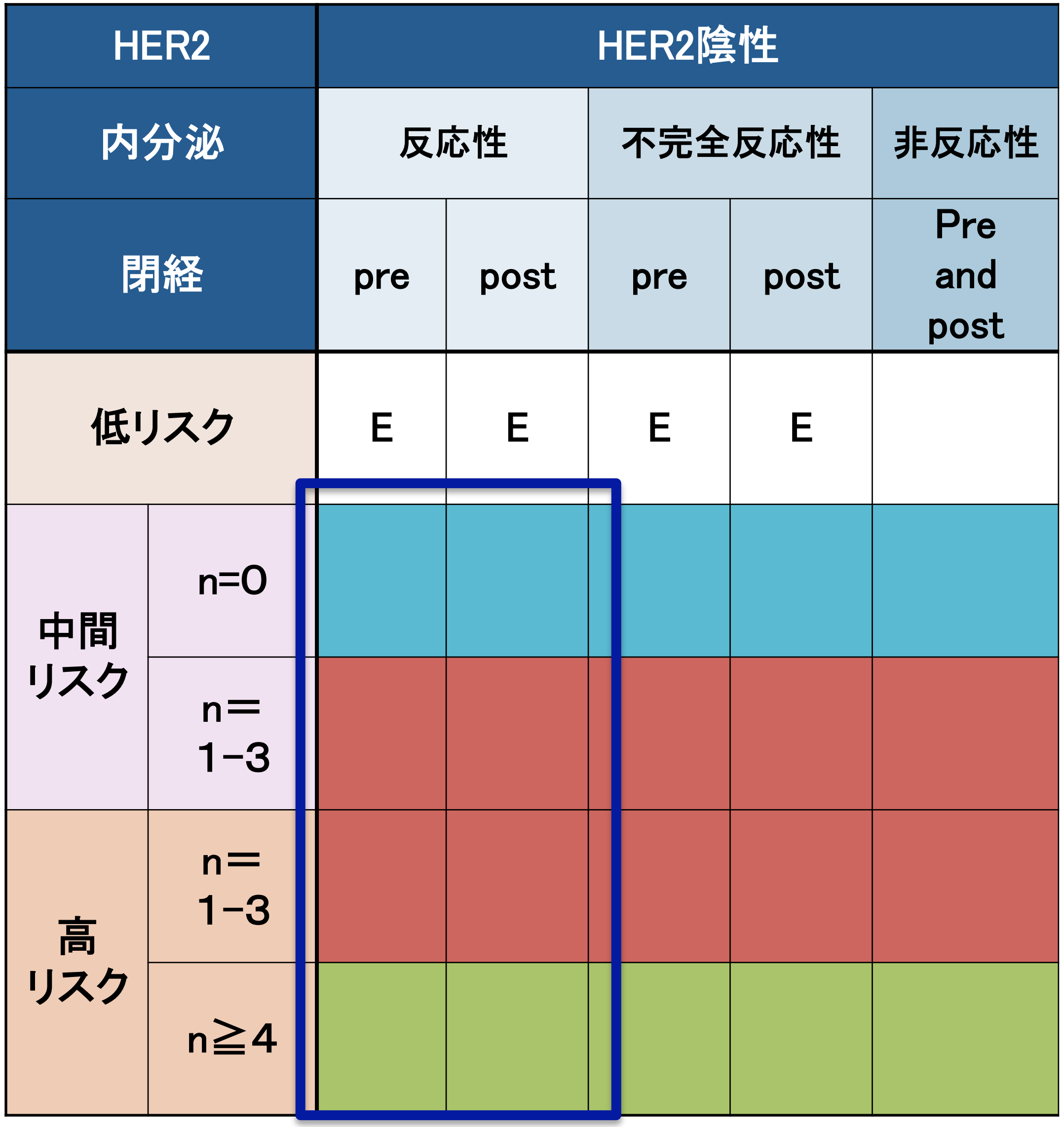
化学療法レジメン

🟦 AC4 or TC4

🟥 AC4 → T

🟩 FEC → T

化学療法のレジメンは？
Risk とresponseを重視すると‥



HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0	🟦	🟦	🟦	🟦	🟦
	n＝1-3	🟥	🟥	🟥	🟥	🟥
高リスク	n＝1-3	🟥	🟥	🟥	🟥	🟥
	n≧4	🟩	🟩	🟩	🟩	🟩

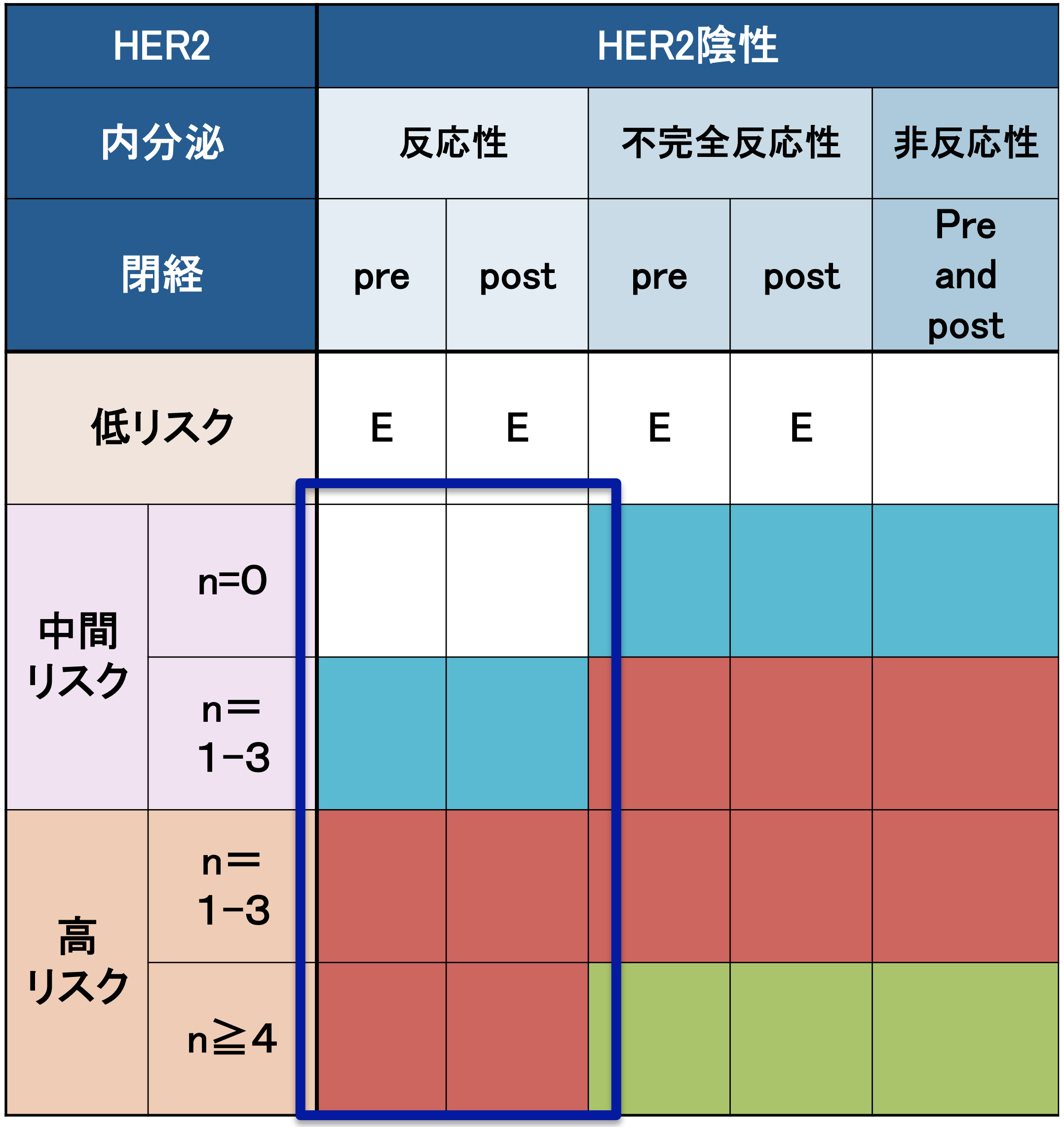
C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

化学療法レジメン

🟦 AC4 or TC4

🟥 AC4 → T

🟩 FEC → T



HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0			🟦	🟦	🟦
	n＝1−3	🟦	🟦	🟥	🟥	🟥
高リスク	n＝1−3	🟥	🟥	🟥	🟥	🟥
	n≧4	🟥	🟥	🟩	🟩	🟩

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

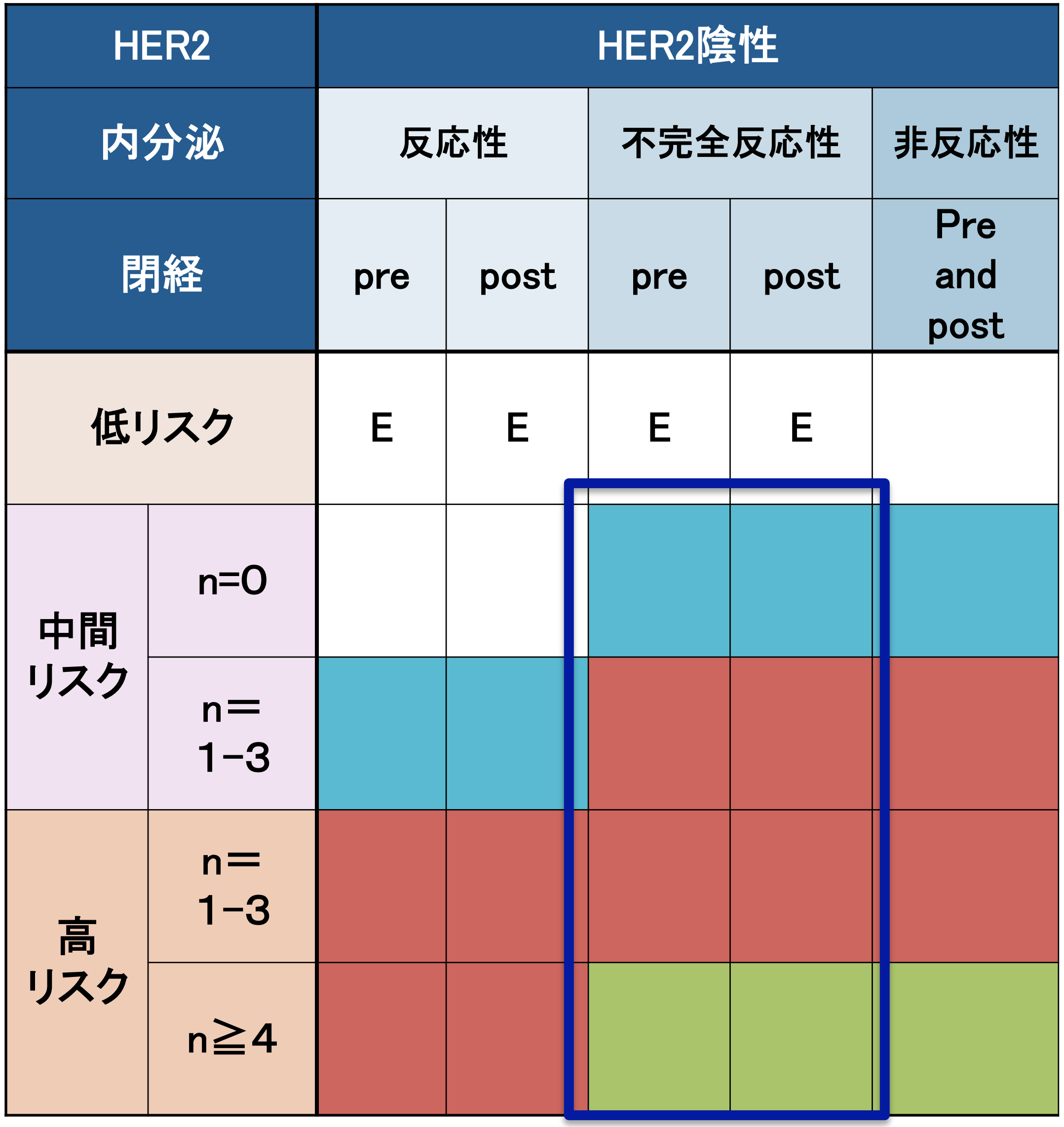
化学療法のレジメンは？
Risk とresponseを重視すると･･

化学療法レジメン

🟦 AC4 or TC4

🟥 AC4 → T

🟩 FEC → T



HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0			🟦	🟦	🟦
	n＝1−3	🟦	🟦	🟥	🟥	🟥
高リスク	n＝1−3	🟥	🟥	🟥	🟥	🟥
	n≧4	🟥	🟥	🟩	🟩	🟩

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

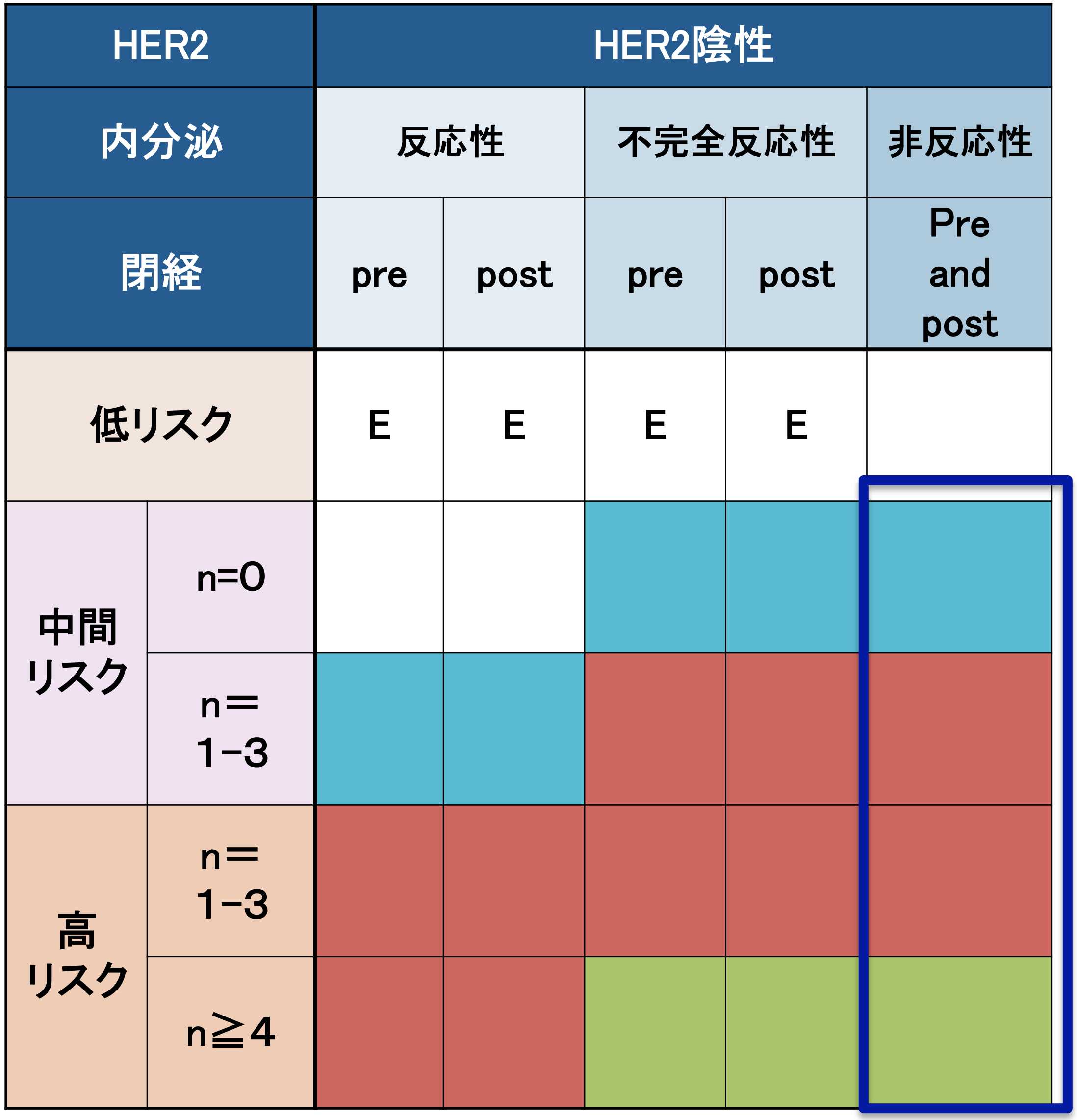
化学療法のレジメンは？
Risk とresponseを重視すると‥

化学療法レジメン

🟦 AC4 or TC4

🟥 AC4 → T

🟩 FEC → T



HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0			🟦	🟦	🟦
	n＝1−3	🟦	🟦	🟥	🟥	🟥
高リスク	n＝1−3	🟥	🟥	🟥	🟥	🟥
	n≧4	🟥	🟥	🟩	🟩	🟩

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

化学療法のレジメンは？
Risk とresponseを重視すると・・

化学療法レジメン

🟦 AC4 or TC4

🟥 AC4 → T

🟩 FEC → T

HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0			🟦	🟦	🟥
	n＝1−3	🟦	🟦	🟥	🟥	🟥
高リスク	n＝1−3	🟥	🟥	🟥	🟥	🟩
	n≧4	🟥	🟥	🟩	🟩	🟩

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

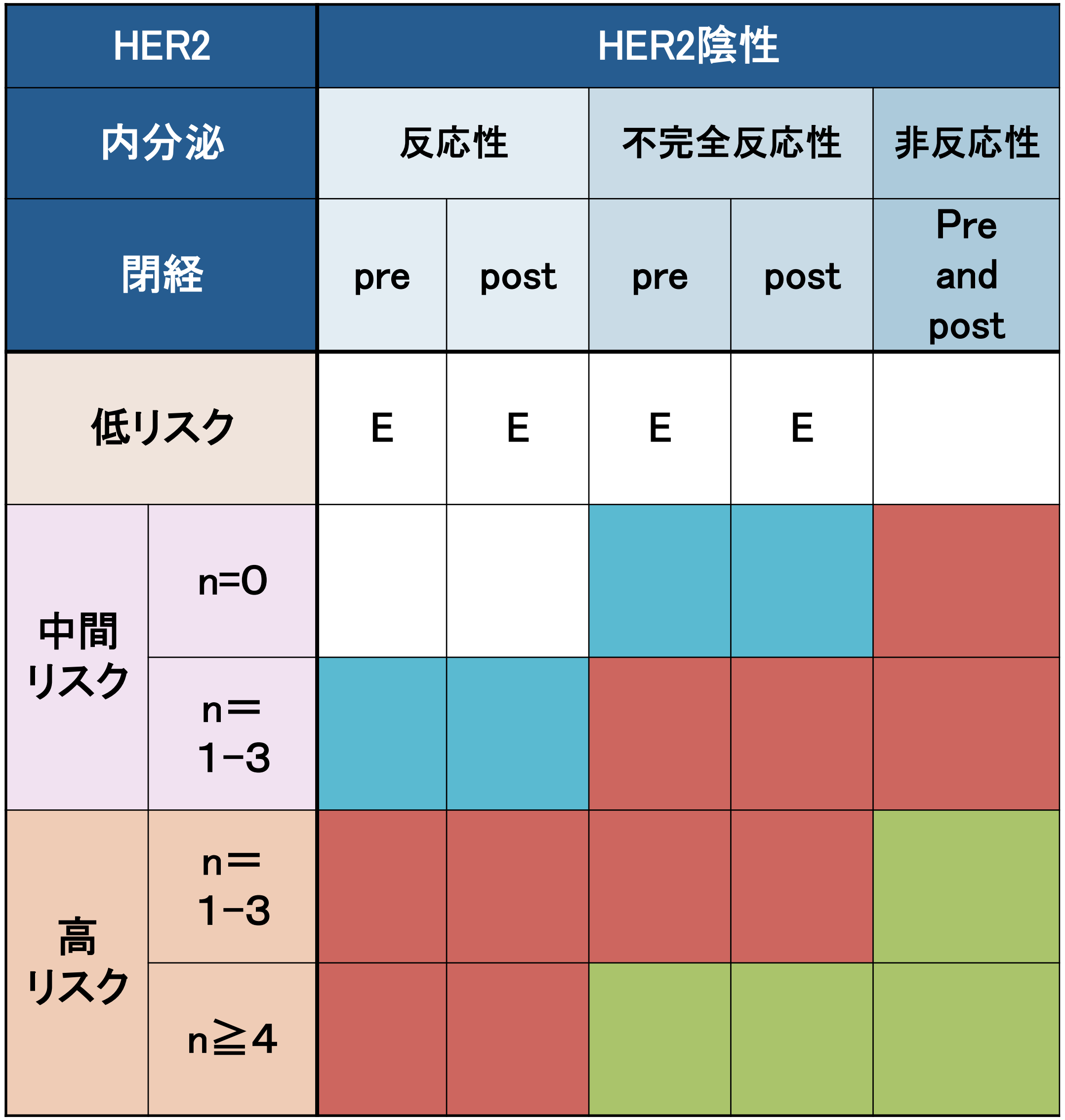
化学療法のレジメンは？
Risk とresponseを重視すると‥

化学療法レジメン

🟦 AC4 or TC4

🟥 AC4 → T

🟩 FEC → T



HER2		HER2陰性				
内分泌		反応性		不完全反応性		非反応性
閉経		pre	post	pre	post	Pre and post
低リスク		E	E	E	E	
中間リスク	n=0			🟦	🟦	🟥
	n＝1−3	🟦	🟦	🟥	🟥	🟥
高リスク	n＝1−3	🟥	🟥	🟥	🟥	🟩
	n≧4	🟥	🟥	🟩	🟩	🟩

C: chemotherapy, E: endcrine therapy, Tr: Trastzumab

化学療法のレジメンは？
Risk とresponseを重視すると･･

化学療法レジメン

🟦 AC4 or TC4

🟥 AC4 → T

🟩 FEC → T