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NEOADJUVANT CHEMOTHERAPY FOR EARLY BREAST CA

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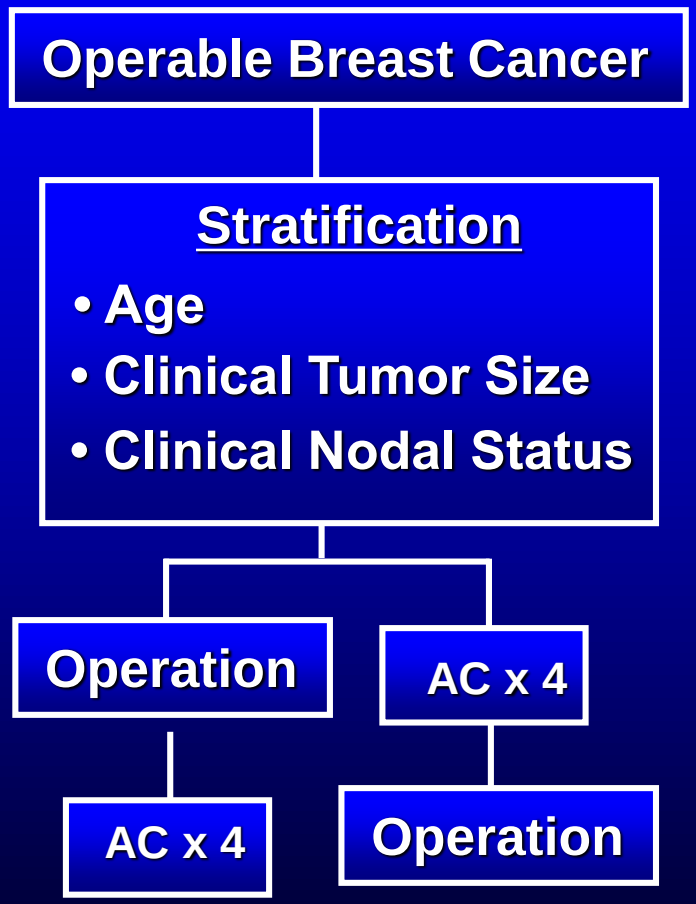
Goals of Neoadjuvant Therapy in Breast Cancer

- Treatment of non-operable tumors
- Downstaging to increase breast conserving surgeries
- Reduce the extent of surgery required in breast and axilla
- In vivo response assessment
- Tailor adjuvant therapies (i.e. CREATE-X, NSABP B50))
- Improve prognosis of certain disease subtypes (i.e. HER2+)
- Assessment of molecular, pharmacodynamic and intratumoral pharmacokinetic measures

NSABP B-18
Neoadjuvant vs. Adjuvant AC

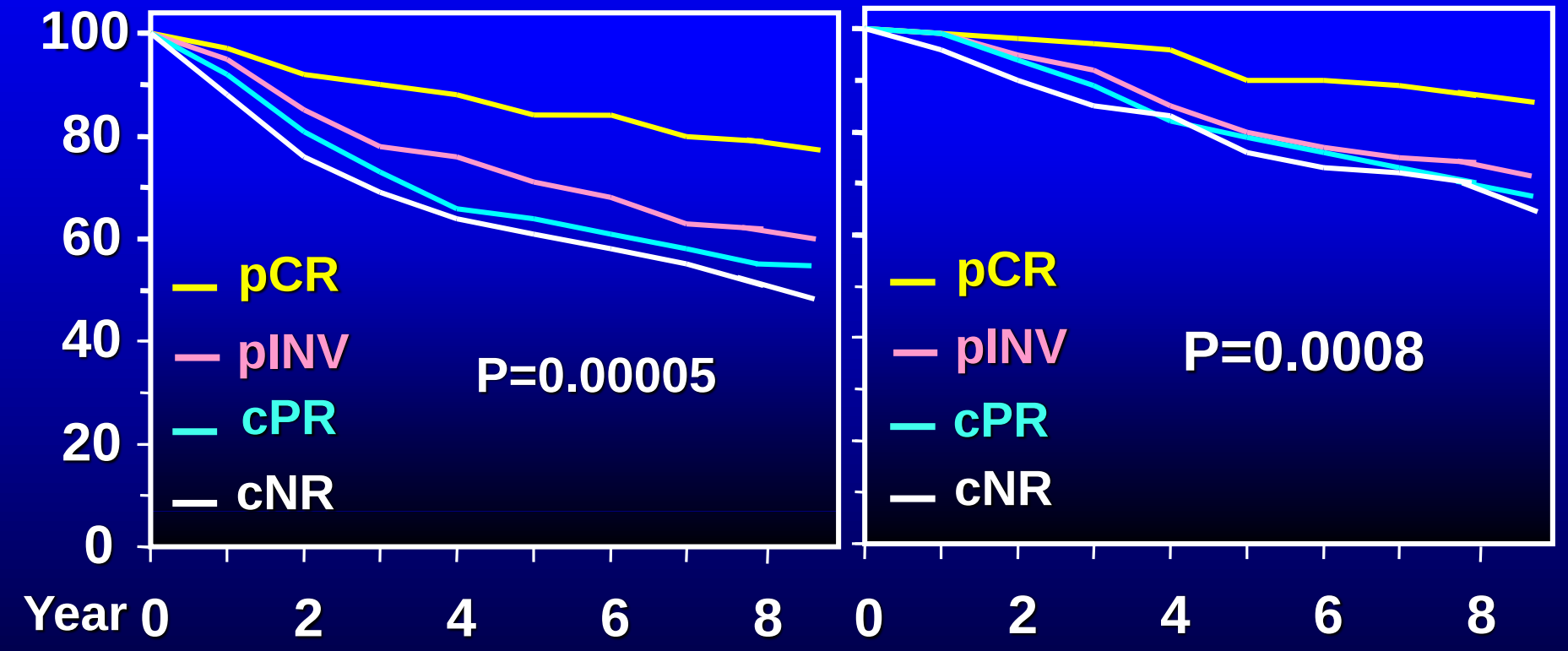


Key Principles from B-18

- N = 1,493
- High Clinical Response Rate: 79%
- cCR: 36% cPR: 43%
- pCR: 13%
- Increase in lumpectomy rate: 68% vs. 60%
- Downstaging of (+) axillary nodes: 58% vs. 40%
- No difference in DFS and OS
- Significant correlation between pCR and outcome

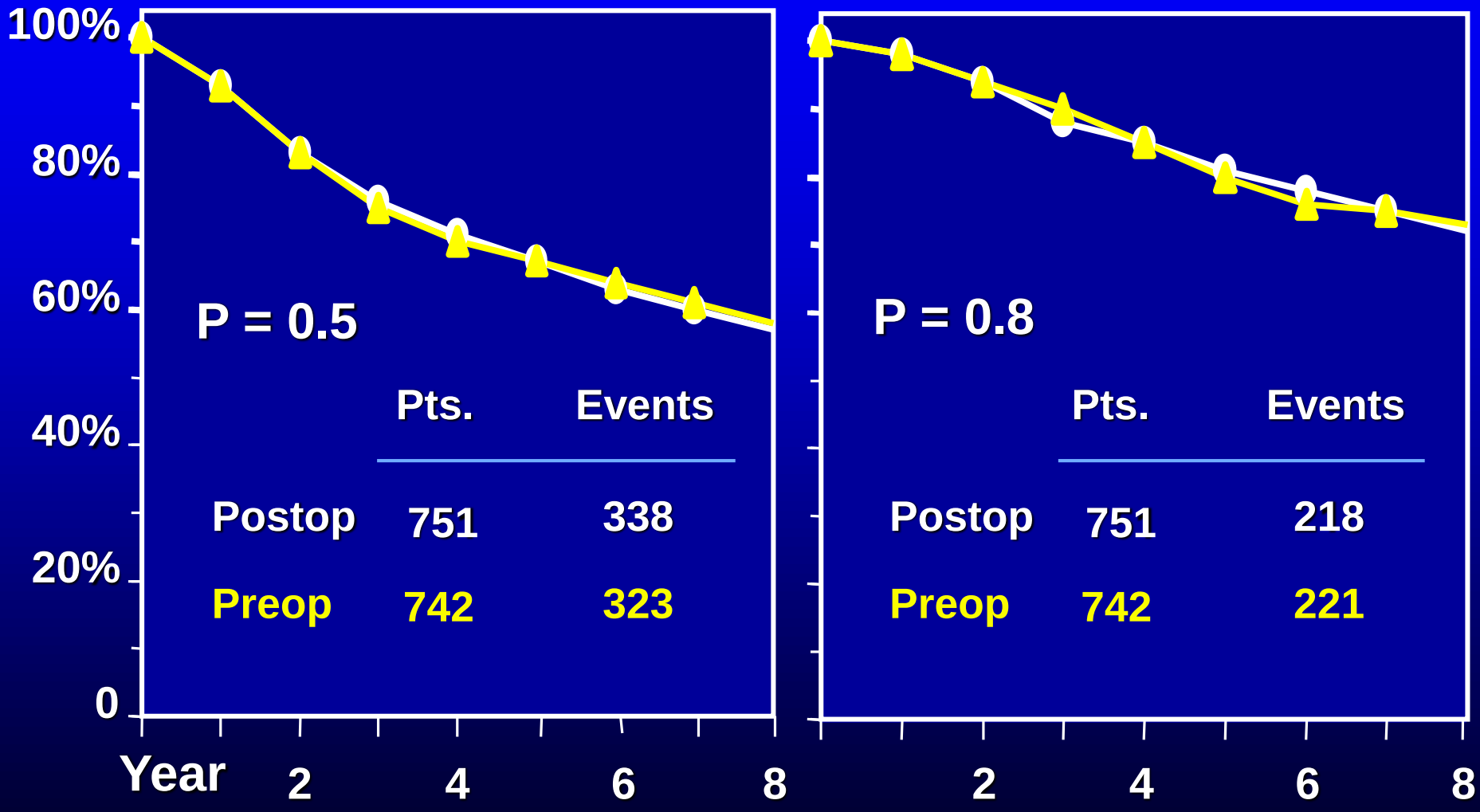
Wolmark et al: JNCI Monographs 2001

B-18
Disease-Free and Overall Survival According to Response



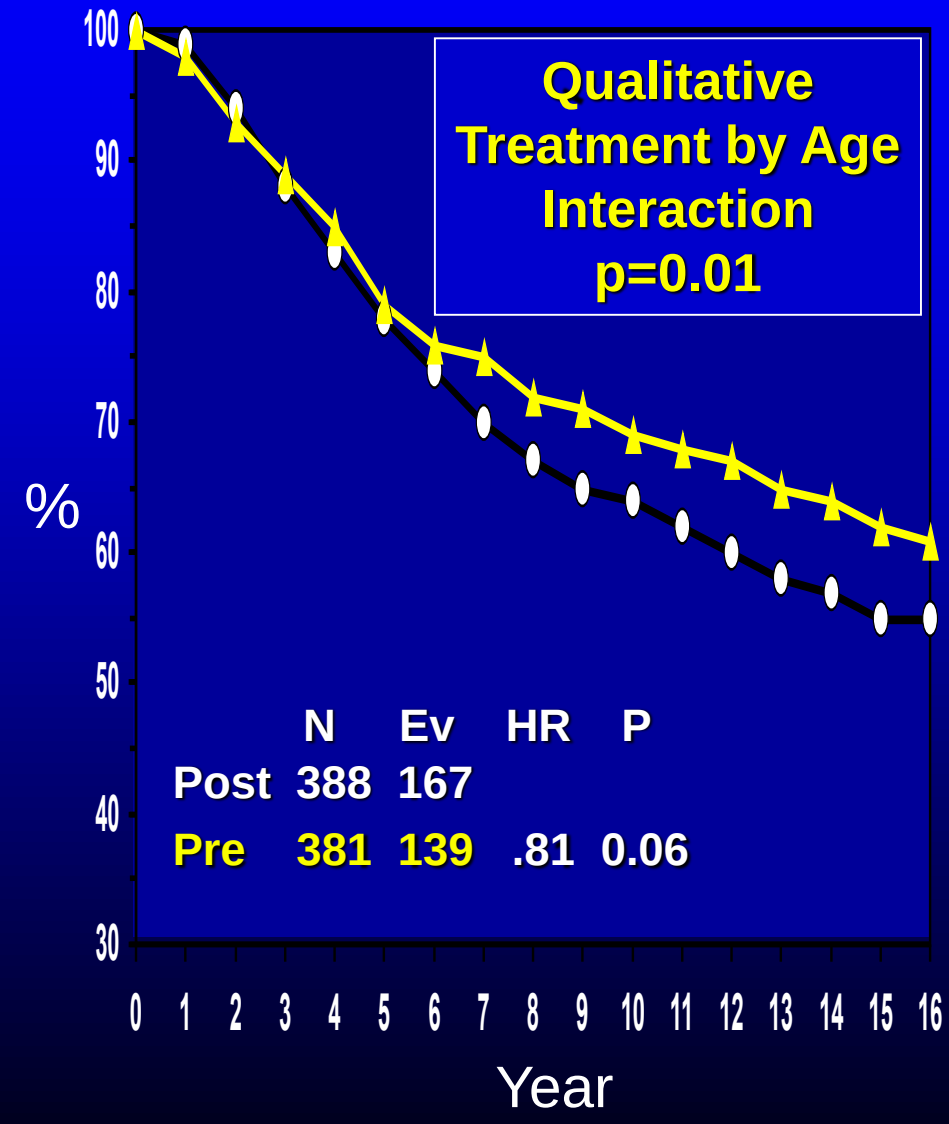
Wolmark N: JNCI Monogr, 2001

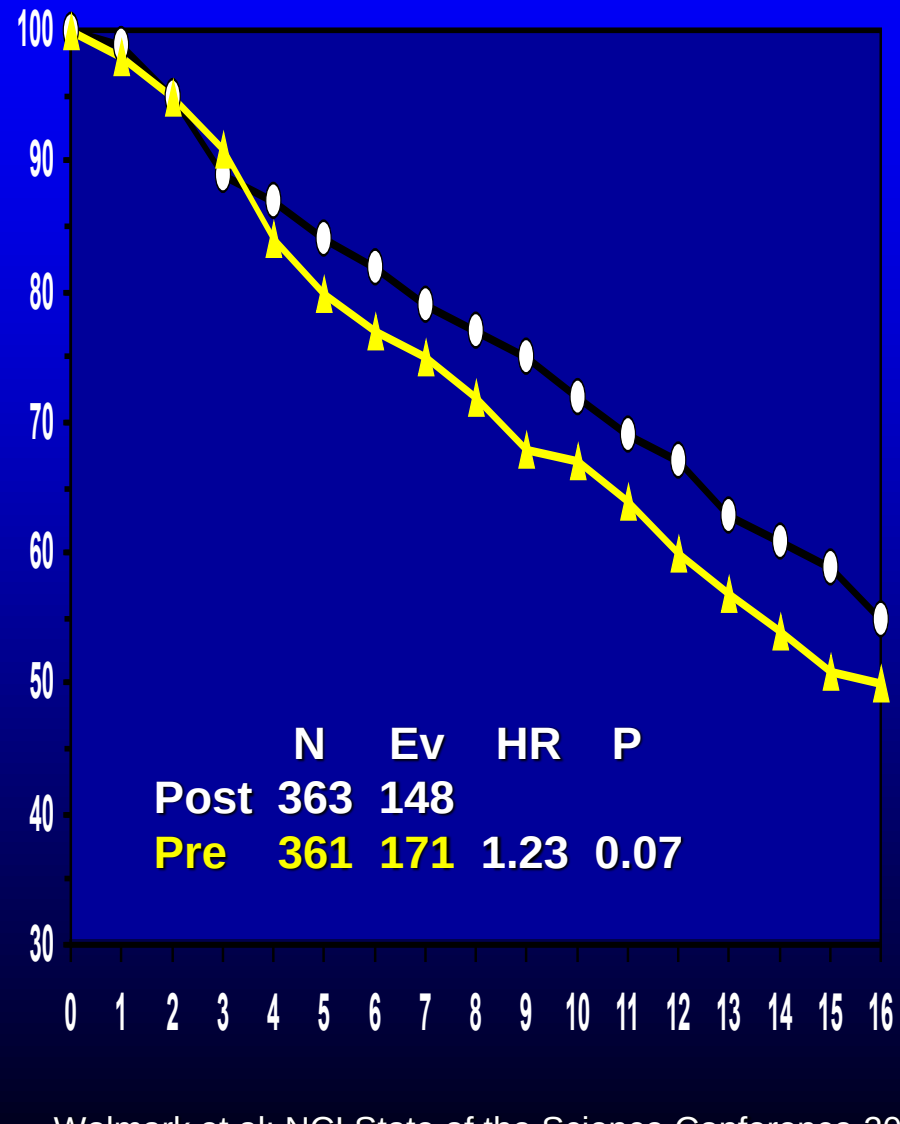
B-18
Disease-Free Survival and Overall Survival



Wolmark et al: JNCI Monographs 2001

B-18 Udate: Overall Survival by Age





Wolmark et al: NCI State of the Science Conference 2007

NEOADJUVANT CHEMOTHERAPY FOR EARLY BREAST CANCER
Early Breast Cancer Trialists' Collaborative Group Meta-analysis

THE LANCET
Oncology

Articles

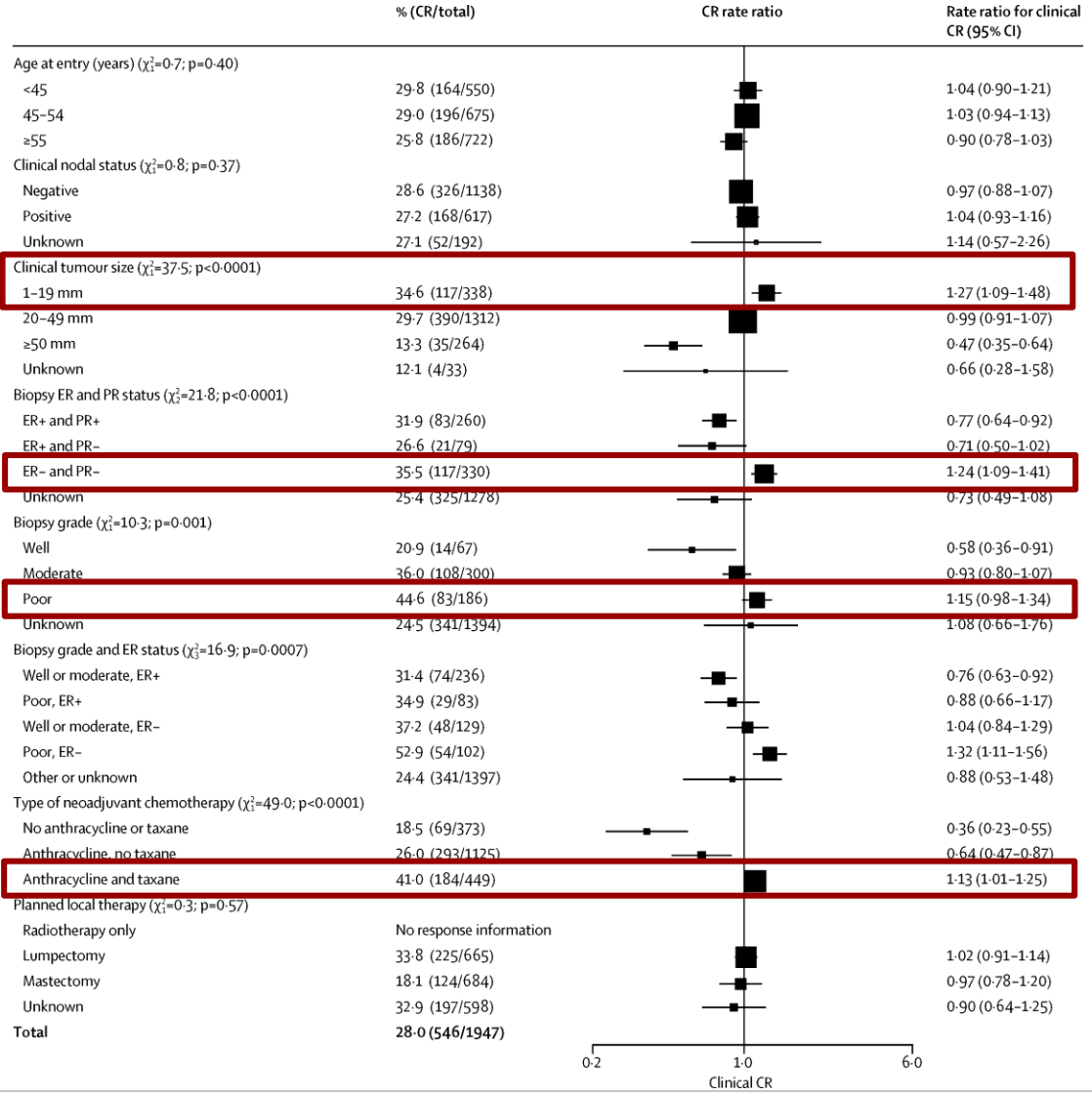
Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials

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

- **N = 4,756 from 10 randomized trials**
- **Median follow-up = 9 years**
- **81% anthracycline-based chemo**
- **69% overall clinical response rate**
- **Breast-conserving surgery = 65% (versus 49% for adjuvant chemo)**

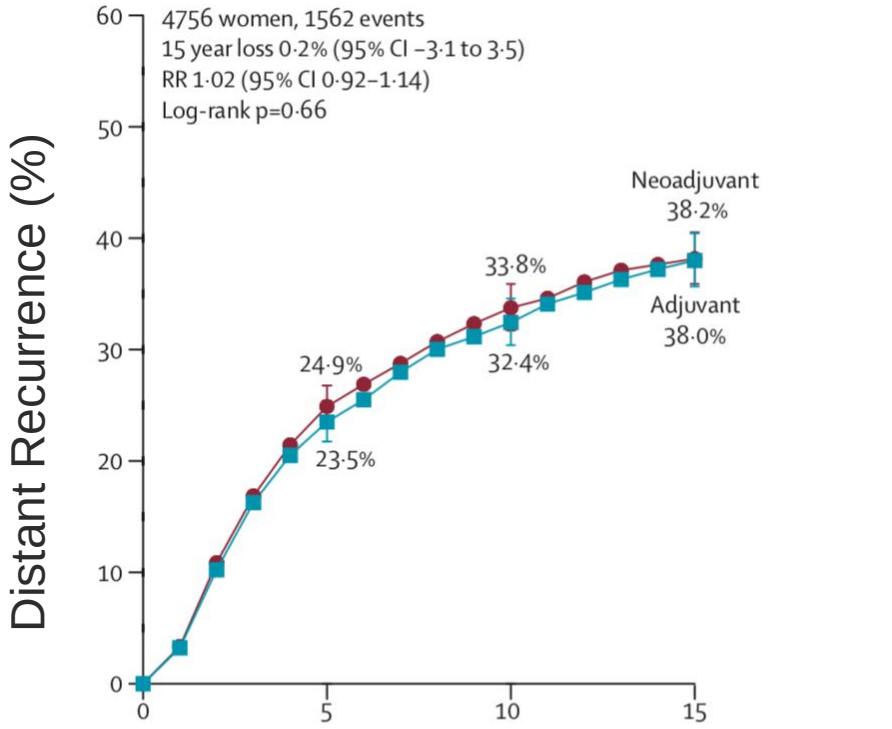
***Asselain B, et al., Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The Lancet Oncology* 2018, 19: 27-39.**

Early Breast Cancer Trialists' Collaborative Group – Meta-analysis: Clinical complete response rate ratios



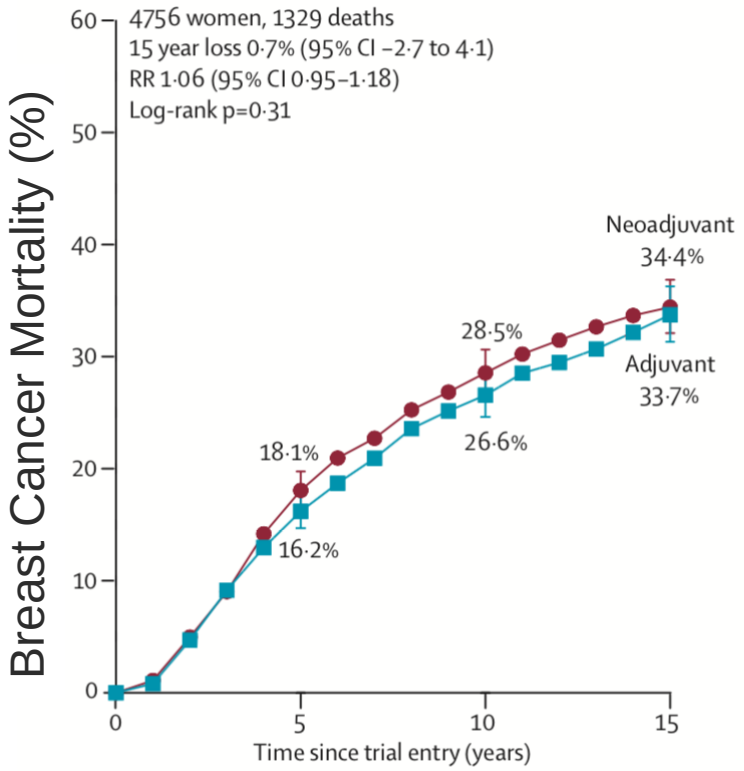
Asselain B, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The Lancet Oncology 2018, 19: 27-39.

Early Breast Cancer Trialists' Collaborative Group – Meta-analysis: Effect of neoadjuvant versus adjuvant chemotherapy on distant recurrence and mortality



Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
5·69 (568/9983)	2·58 (162/6291)	1·49 (50/3351)	1·44 (14/974)
5·44 (535/9840)	2·54 (157/6187)	1·84 (60/3270)	1·74 (16/919)
1·07 (0·94–1·21)	0·99 (0·79–1·24)	0·80 (0·55–1·18)	0·75 (0·35–1·61)
16·5/251·5	−0·6/75·5	−5·7/25·8	−1·9/6·7



Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	3·90 (412/10 567)	2·82 (191/6785)	1·93 (69/3570)	1·24 (13/1050)
Adjuvant	3·49 (364/10 432)	2·81 (190/6771)	2·19 (78/3559)	1·18 (12/1014)
Rate ratio (95% CI)	1·12 (0·97–1·30)	1·03 (0·84–1·27)	0·88 (0·63–1·21)	0·90 (0·41–1·97)
from (O–E)/V	20·5/179·6	2·8/91·6	−4·8/36·6	−0·7/6·2

Asselain B, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The Lancet Oncology 2018, 19: 27-39.

Early Breast Cancer Trialists' Collaborative Group – Meta-analysis: Local Therapy by Clinical Response

	Clinical response				
	Complete*	Partial†	Stable or progressive disease‡	Unknown	Total
Planned breast-conserving therapy					
Breast-conserving	215 (96%)	256 (90%)	119 (77%)	211 (81%)	801 (87%)
Mastectomy	10 (4%)	30 (10%)	35 (23%)	48 (19%)	123 (13%)
Unknown	0	0	0	2 (NA)	2 (NA)
Total response§	225/665 (34%)	286/665 (43%)	154/665 (23%)	261 (NA)	926 (100%)
Planned mastectomy					
Breast-conserving	75 (60%)	121 (41%)	30 (12%)	26 (36%)	252 (33%)
Mastectomy	49 (40%)	175 (59%)	231 (88%)	47 (64%)	502 (67%)
Unknown	0	1 (NA)	2 (NA)	11 (NA)	14 (NA)
Total response§	124/684 (18%)	297/684 (43%)	263/684 (38%)	84 (NA)	768 (100%)
Unknown planned therapy					
Breast-conserving	162 (83%)	164 (76%)	97 (56%)	28 (49%)	451 (70%)
Mastectomy	33 (17%)	53 (24%)	76 (44%)	29 (51%)	191 (30%)
Unknown	2 (NA)	3 (NA)	8 (NA)	38 (NA)	51 (NA)
Total response§	197/598 (33%)	220/598 (37%)	181/598 (30%)	95 (NA)	693 (100%)
All women					
Breast-conserving	452 (83%)	541 (68%)	246 (42%)	265 (68%)	1504 (65%)
Mastectomy	92 (17%)	258 (32%)	342 (58%)	124 (32%)	816 (35%)
Unknown	2 (NA)	4 (NA)	10 (NA)	51 (NA)	67 (NA)
Total response§	546/1947 (28%)	803/1947 (41%)	598/1947 (31%)	440 (NA)	2387 (100%)

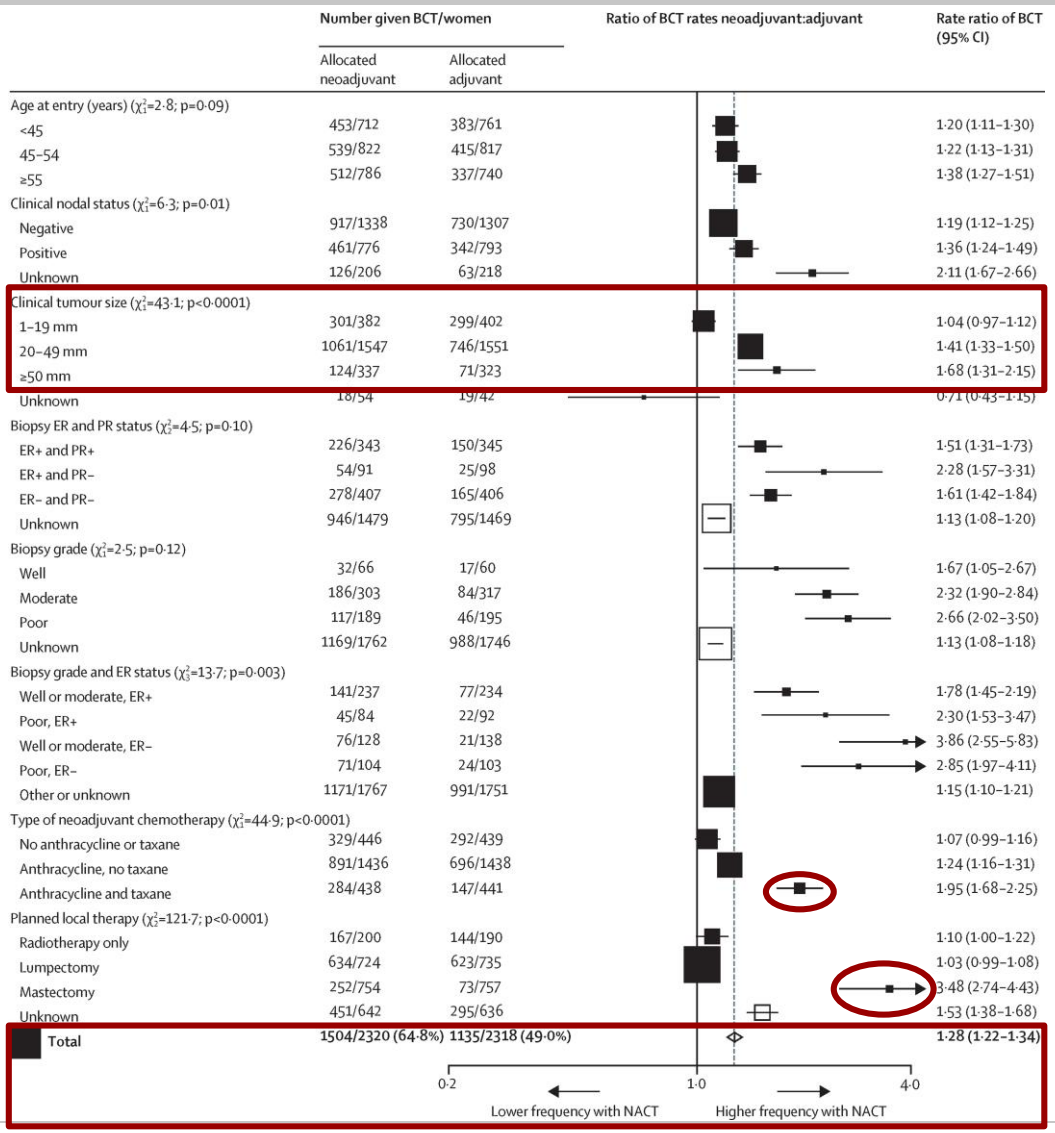
Data are n (%) or n/N (%). NA=not applicable. *No clinical evidence of disease. †≥50% reduction in tumour size. ‡<50% reduction or increase in tumour size. §Percentages are of those with a known response.

Table 2: **Local therapy, planned versus done, in women allocated to neoadjuvant chemotherapy, by clinical response**

Asselain B, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The Lancet Oncology 2018, 19: 27-39.

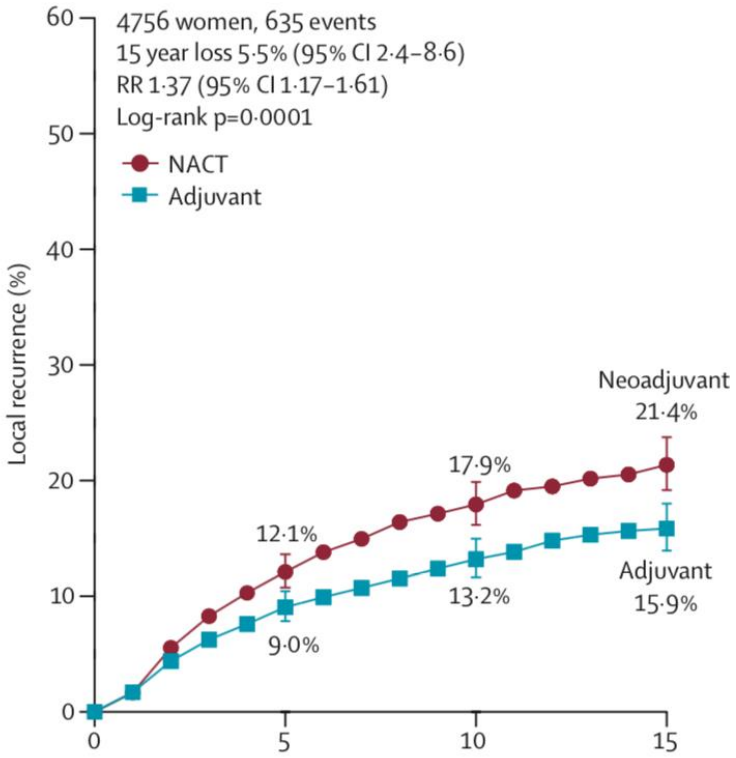
Ratios of Breast Conservation Therapy (BCT) rates

Age, clinical LN status, ER/PR, and grade did not impact BCT



Asselain B, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The Lancet Oncology 2018, 19: 27-39.

Early Breast Cancer Trialists' Collaborative Group – Meta-analysis: Effect of neoadjuvant versus adjuvant chemotherapy on local recurrence

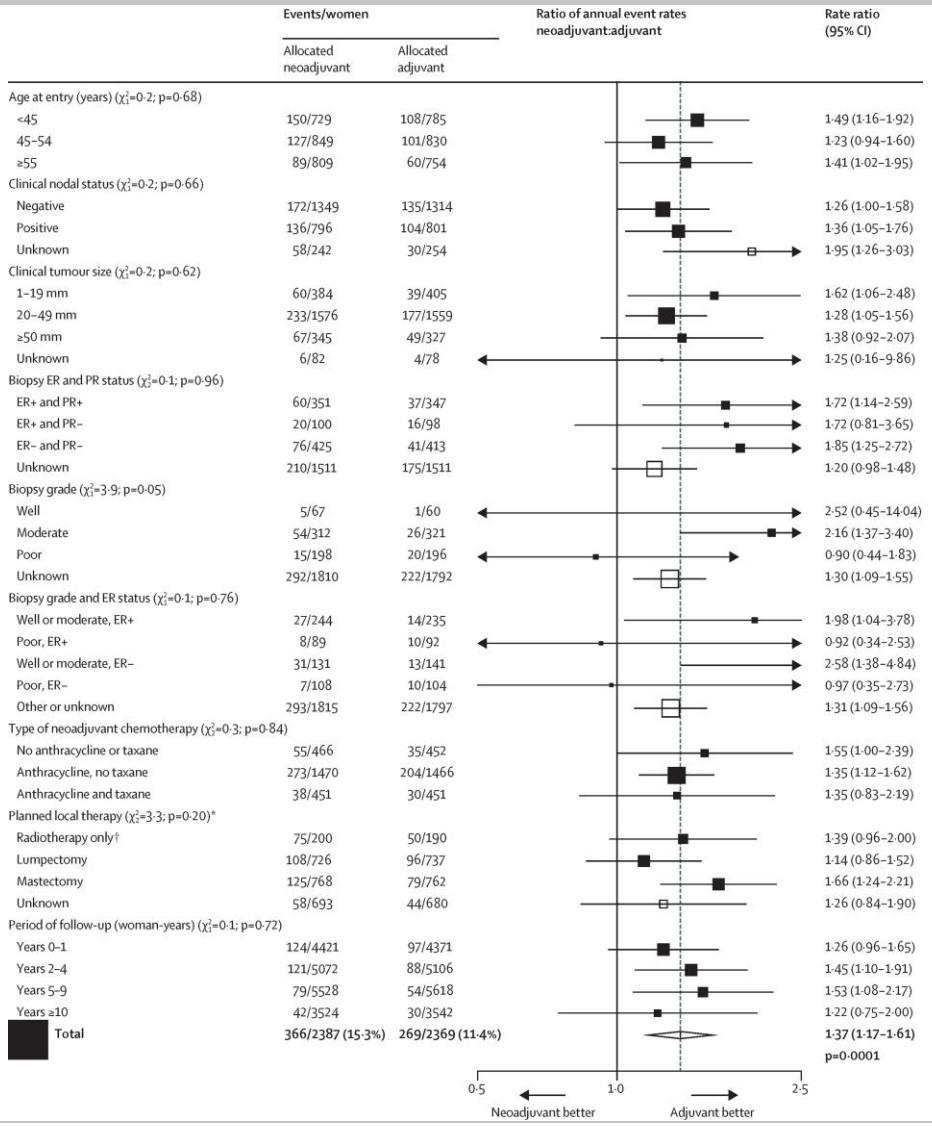


Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	2·58 (245/9493)	1·43 (79/5528)	0·93 (26/2784)	2·16 (16/740)
Adjuvant	1·95 (185/9477)	0·96 (54/5618)	0·69 (19/2769)	1·42 (11/772)
Rate ratio	1·35 (1·11–1·64)	1·53 (1·08–2·17)	1·29 (0·70–2·38)	1·11 (0·48–2·57)
(95% CI) from (O–E)/V	30·4/102·0	13·6/31·8	2·7/10·3	0·6/5·4

Asselain B, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The Lancet Oncology 2018, 19: 27-39.

Early Breast Cancer Trialists' Collaborative Group – Meta-analysis: Local recurrence rate ratios



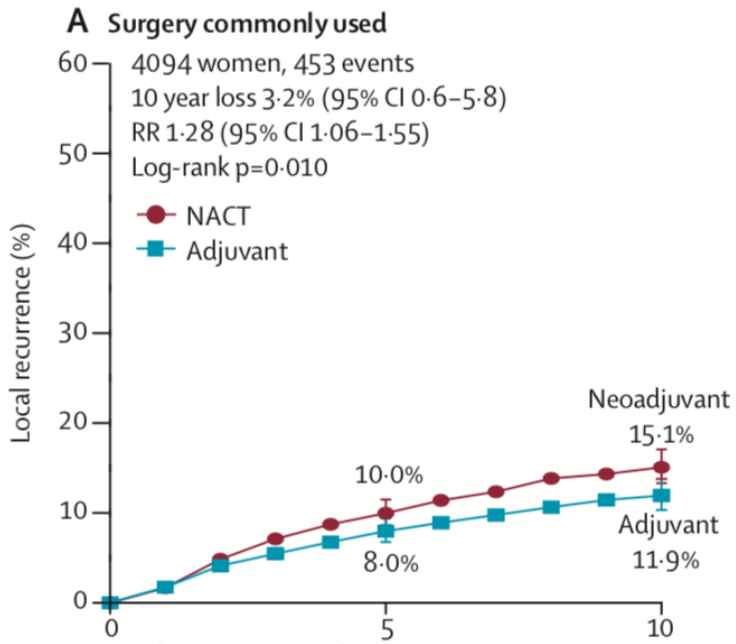
	Events/women		Ratio of annual event rates neoadjuvant:adjuvant	Rate ratio (95% CI)
	Allocated neoadjuvant	Allocated adjuvant		
Age at entry (years) (χ^2_1=0·2; p=0·68)				
<45	150/729	108/785		1·49 (1·16–1·92)
45–54	127/849	101/830		1·23 (0·94–1·60)
≥55	89/809	60/754		1·41 (1·02–1·95)
Clinical nodal status (χ^2_1=0·2; p=0·66)				
Negative	172/1349	135/1314		1·26 (1·00–1·58)
Positive	136/796	104/801		1·36 (1·05–1·76)
Unknown	58/242	30/254		1·95 (1·26–3·03)
Clinical tumour size (χ^2_1=0·2; p=0·62)				
1–19 mm	60/384	39/405		1·62 (1·06–2·48)
20–49 mm	233/1576	177/1559		1·28 (1·05–1·56)
≥50 mm	67/345	49/327		1·38 (0·92–2·07)
Unknown	6/82	4/78		1·25 (0·16–9·86)
Biopsy ER and PR status (χ^2_3=0·1; p=0·96)				
ER+ and PR+	60/351	37/347		1·72 (1·14–2·59)
ER+ and PR–	20/100	16/98		1·72 (0·81–3·65)
ER– and PR–	76/425	41/413		1·85 (1·25–2·72)
Unknown	210/1511	175/1511		1·20 (0·98–1·48)
Biopsy grade (χ^2_3=3·9; p=0·05)				
Well	5/67	1/60		2·52 (0·45–14·04)
Moderate	54/312	26/321		2·16 (1·37–3·40)
Poor	15/198	20/196		0·90 (0·44–1·83)
Unknown	292/1810	222/1792		1·30 (1·09–1·55)
Biopsy grade and ER status (χ^2_1=0·1; p=0·76)				
Well or moderate, ER+	27/244	14/235		1·98 (1·04–3·78)
Poor, ER+	8/89	10/92		0·92 (0·34–2·53)
Well or moderate, ER–	31/131	13/141		2·58 (1·38–4·84)
Poor, ER–	7/108	10/104		0·97 (0·35–2·73)
Other or unknown	293/1815	222/1797		1·31 (1·09–1·56)
Type of neoadjuvant chemotherapy (χ^2_3=0·3; p=0·84)				
No anthracycline or taxane	55/466	35/452		1·55 (1·00–2·39)
Anthracycline, no taxane	273/1470	204/1466		1·35 (1·12–1·62)
Anthracycline and taxane	38/451	30/451		1·35 (0·83–2·19)
Planned local therapy (χ^2_3=3·3; p=0·20)*				
Radiotherapy only†	75/200	50/190		1·39 (0·96–2·00)
Lumpectomy	108/726	96/737		1·14 (0·86–1·52)
Mastectomy	125/768	79/762		1·66 (1·24–2·21)
Unknown	58/693	44/680		1·26 (0·84–1·90)
Period of follow-up (woman-years) (χ^2_1=0·1; p=0·72)				
Years 0–1	124/4421	97/4371		1·26 (0·96–1·65)
Years 2–4	121/5072	88/5106		1·45 (1·10–1·91)
Years 5–9	79/5528	54/5618		1·53 (1·08–2·17)
Years ≥10	42/3524	30/3542		1·22 (0·75–2·00)
Total	366/2387 (15·3%)	269/2369 (11·4%)		1·37 (1·17–1·61) p=0·0001

0·5 1·0 2·5

Neoadjuvant better Adjuvant better

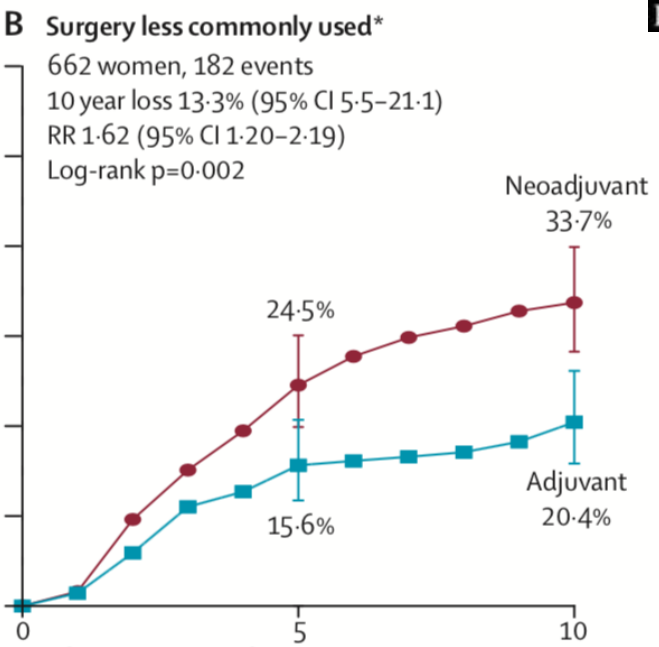
Asselain B, et al., Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The Lancet Oncology 2018, 19: 27-39.

Early Breast Cancer Trialists' Collaborative Group – Meta-analysis: Critique



Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Neoadjuvant	2·12 (173/8164)	1·21 (57/4721)	0·85 (22/2577)
Adjuvant	1·73 (142/8200)	0·94 (45/4778)	0·55 (14/2547)
Rate ratio (95% CI)	1·26 (1·00–1·58)	1·35 (0·91–2·01)	1·32 (0·65–2·69)
from (O–E)/V	17·3/75·2	7·3/24·3	2·1/7·5



Local recurrence crude rates (events per woman-years) and log-rank analyses

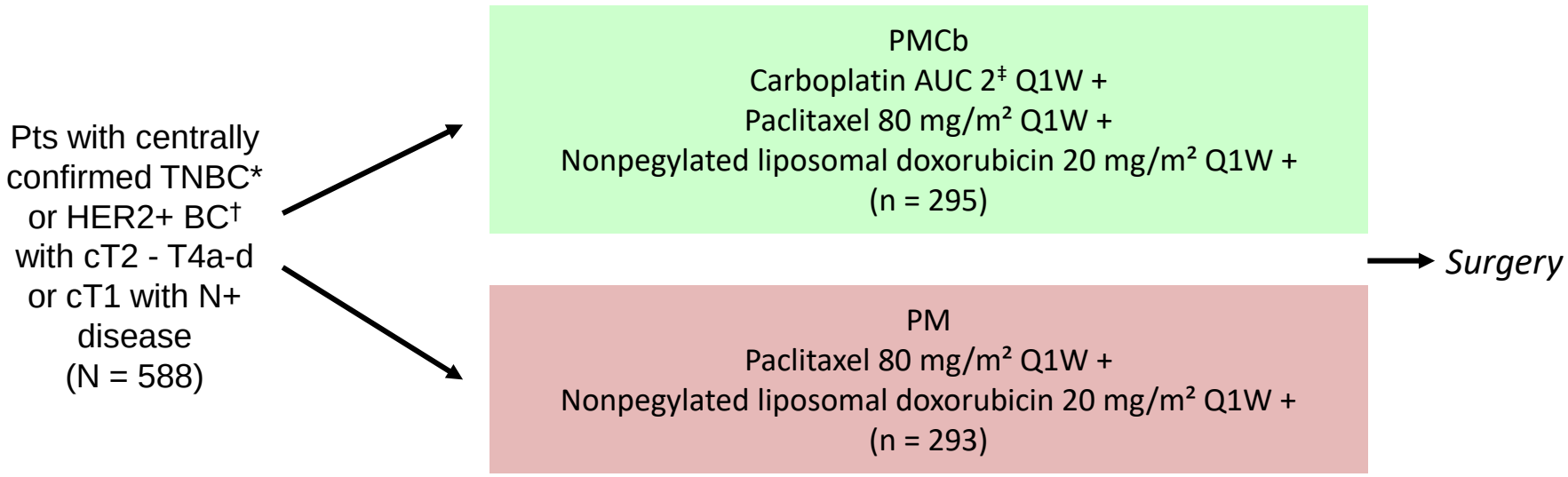
	Years 0–4	Years 5–9	Years ≥10
	5·42 (72/1329)	2·73 (22/806)	2·11 (20/947)
	3·37 (43/1277)	1·07 (9/840)	1·61 (16/994)
	1·63 (1·12–2·39)	2·30 (1·13–4·70)	1·15 (0·58–2·27)
	13·2/26·8	6·3/7·5	1·1/8·2

Asselain B, et al., Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The Lancet Oncology 2018, 19: 27-39.

Early Breast Cancer Trialists' Collaborative Group – Meta-analysis: Critique

- Patient-level data for radiotherapy were unavailable.
- Only 2 trials provided pathologic response data.
- Only 902 of 4,756 (19%) received a taxane.
- All patients were enrolled prior to 2005, so no adjuvant trastuzumab given.
- This study is not able to assess reliably whether presurgical systemic therapy is more effective at eradicating micrometastatic disease than the same chemotherapy administered after surgery (due to confounding effects of different types surgery between the two groups).

Neoadjuvant Therapy for TNBC: GeparSixto -- Study Design



*TNBC pts also received bevacizumab 15 mg/kg IV Q3W.
†HER2+ BC pts also received trastuzumab 8 mg/kg IV (initial dose), then 6 mg/kg IV Q3D (subsequent doses) and lapatinib 750 mg QD.
‡Dose reduced to AUC 1.5 after 330 pts enrolled.

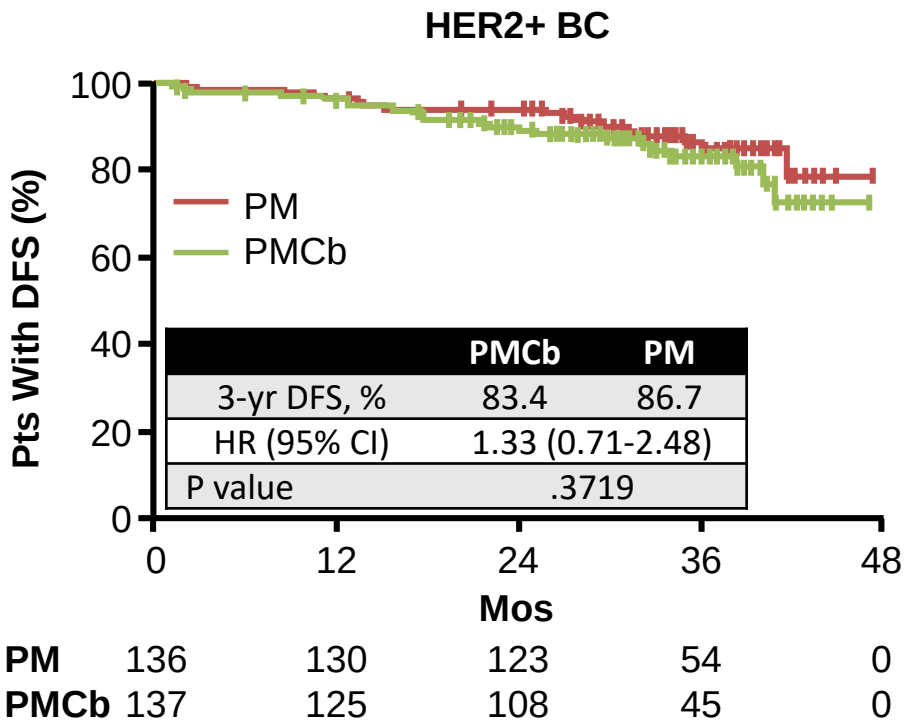
- Primary endpoint: pCR
- Secondary endpoints: RFS, DFS, OS

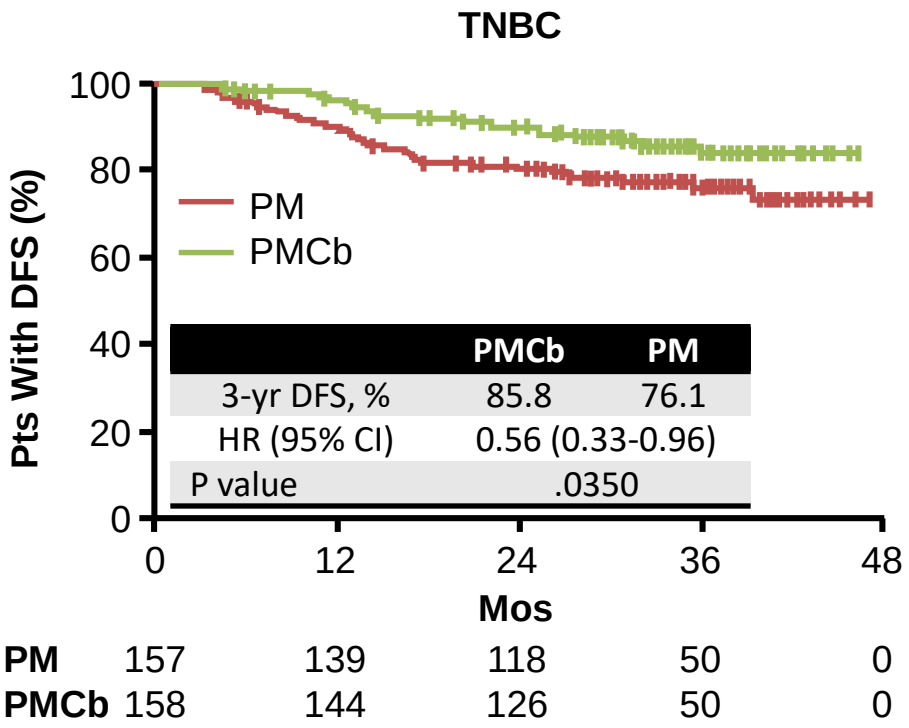
- **Recent renewed interest in investigating the role of platinum chemotherapy in breast cancer**
- **Hypothesis of greater susceptibility of TN and BRCA mutant BC to DNA damaging chemotherapeutic agents**

von Minckwitz G, et al. SABCS 2015. Abstract S2-04.

GeparSixto: DFS by Breast Cancer Subtype

- Test for Interaction: Treatment HER2+/TNBC: *P* = .046





- **Achieving pCR led to favorable outcomes irrespective of BRCA mutation status**
- **Authors conclude the trial supports addition of carboplatin in TNBC**
- **Addition of carboplatin adds toxicity**

von Minckwitz G, et al. SABCS 2015. Abstract S2-04.

The relative efficacy of neoadjuvant endocrine therapy versus chemotherapy in postmenopausal women with ER positive breast cancer

V. F. Semiglazov, V. Semiglazov, V. Ivanov, A. Bozhok, E. Ziltsova, R. Paltuev, G. Dashian, A. Kletzel, E. Topuzov and L. Berstein

- **Methods:** 121 postmenopausal women with ER(+) and/or PgR(+) breast cancer T2N1–2, T3N0–1, T4N0M0 assigned to NAT with either CT Dox 60 mg/m2 + Pac 200 mg/m2, every 3 weeks, 4 cycles, n=62 patients (pts), or HT with aromatase inhibitors, anastrazole 1 mg, n = 30 pts, 3 months).

Neoadjuvant therapy	Clinical OR %	Mammography OR %	BCS %
CT (dox + pac)	75.8	62,9	20.9
Anastrazole	89.8	69,4	37,2
p - value	>0.05	> 0.5	0.054

In CT arm the most frequent grade III/IV toxicity was alopecia (79.3 %), neutropenia (43.1 %), cardiotoxicity (6.8 %), diarrhea (1.7%). HT was well tolerated. The most commonly adverse events were hot flushes (23.3%), vaginal discharge (6.6%), musculoskeletal disorders (1.7%).

Journal of Clinical Oncology, Vol 22, No 14S 2004: 519

CREATE-X: Results

Figure 1: DFS from the CREATE-X Trial

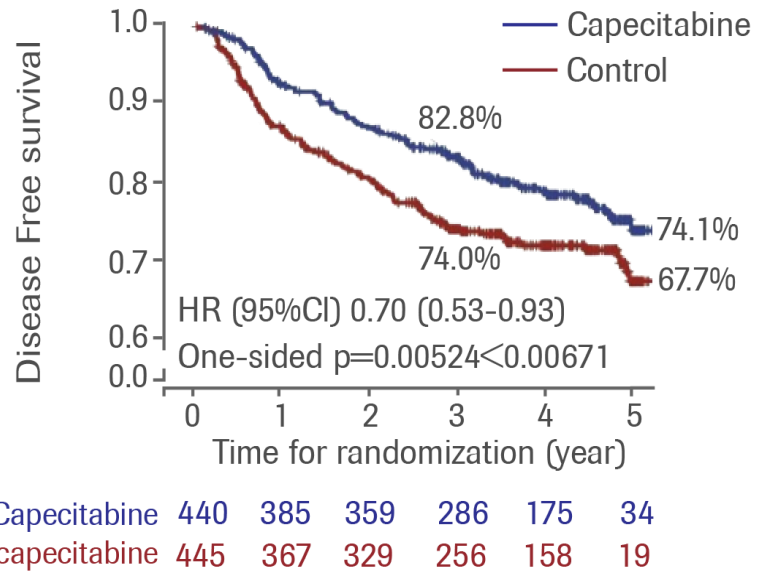
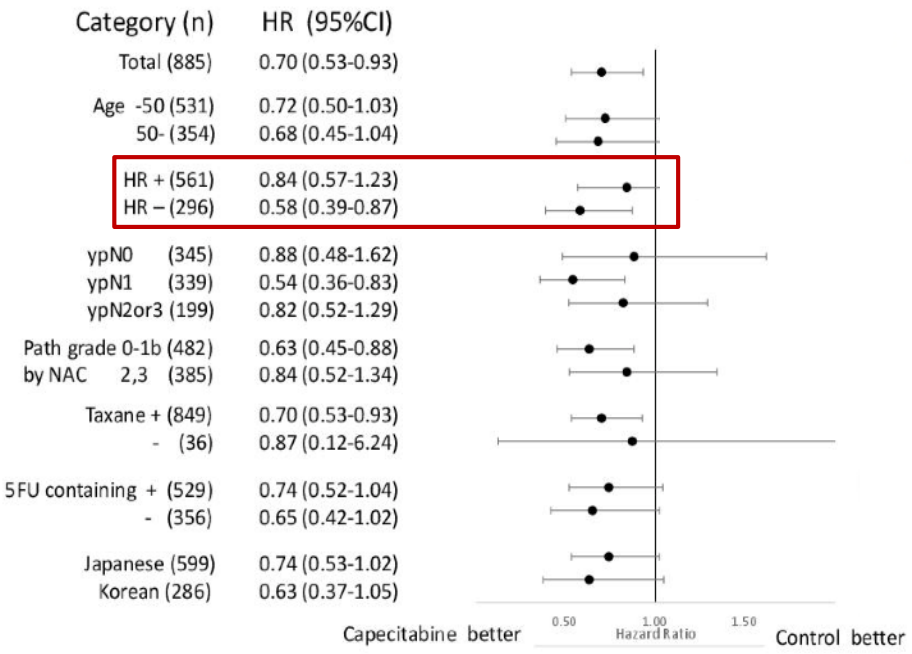


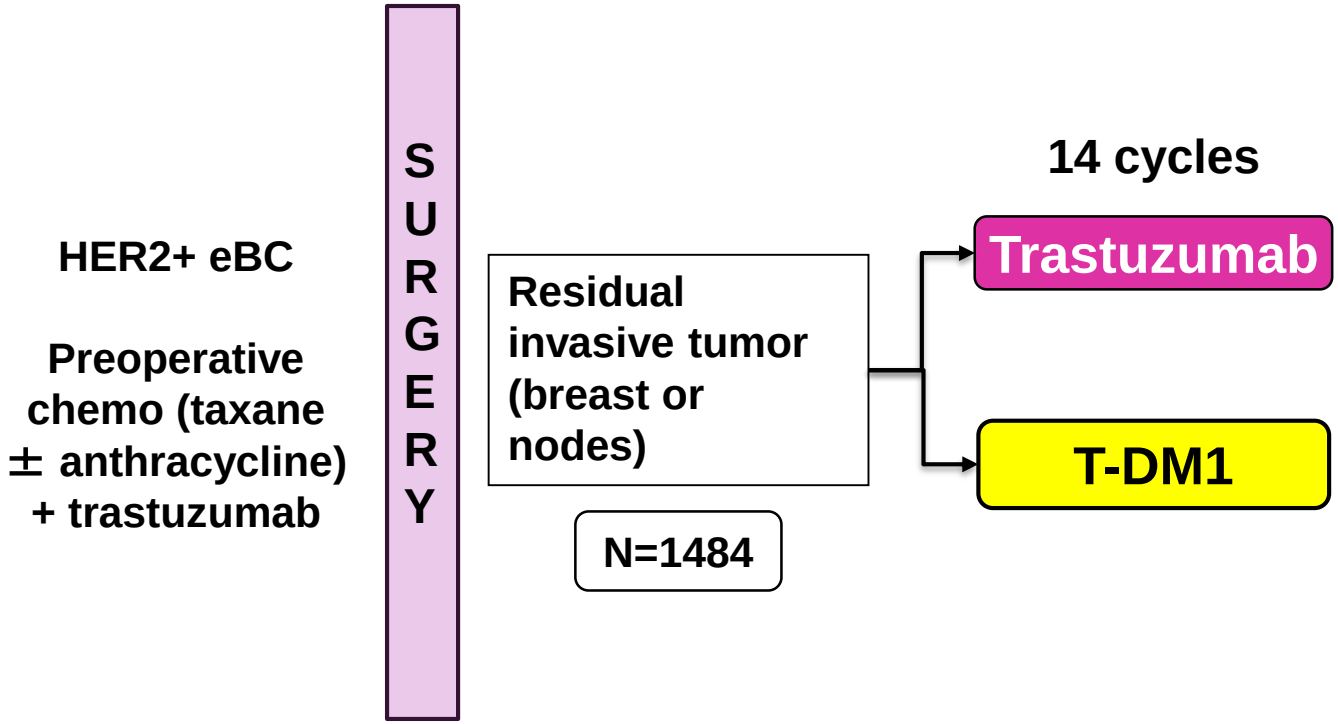
Figure 2: Subgroup analysis for DFS



	Cap (n = 440)	No Cap (n = 445)	HR (95% CI)	*P* Value
5-yr OS	89.2 %	83.9 %	0.60 (0.40-0.92)	< .01

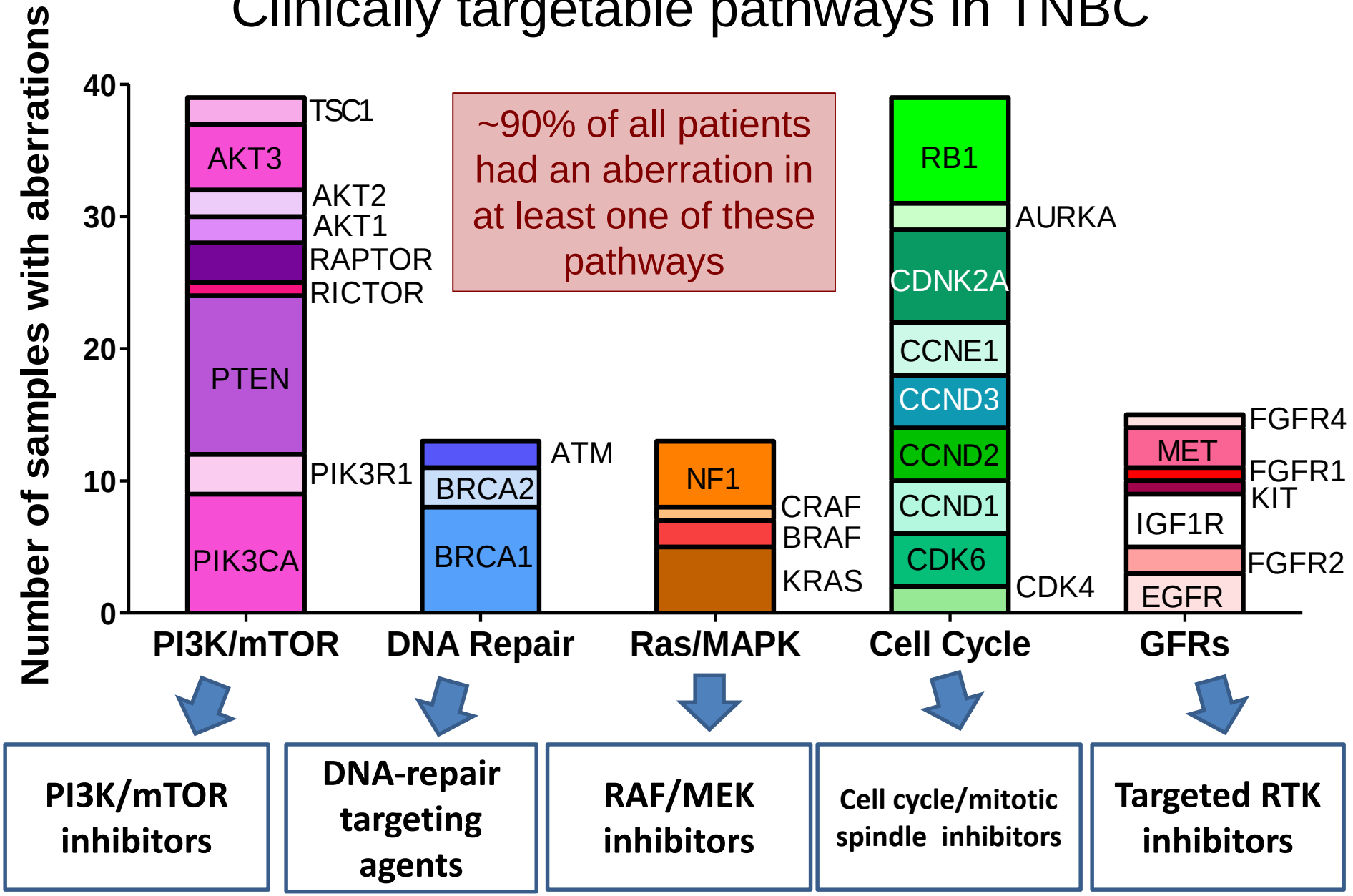
Toi M, et al. SABCS 2015. Abstract S1-07.

Post Neo-adjuvant T-DM1: NSABP B-50 Trial Schema



Primary Endpoint: DFS
Secondary Endpoints: OS, Safety

Clinically targetable pathways in TNBC



Balko J M et al. Cancer Discovery 2014;4:232-245

Neoadjuvant Therapy in Primary Breast Cancer: MESSAGES

- High clinical response rates
- Increased opportunity for breast-conserving surgery
- Pathologic CR rates vary by treatment and tumor subtype
  - <10% with endocrine therapy for ER+ disease
  - 10 – 15% with anthracylines
  - 25 – 30% with anthracycline/taxanes; higher with platinums
  - 40 – 50% with chemotherapy + trastuzumab in HER2+ disease
  - 50 – 60% with chemotherapy + trastuzumab + pertuzumab
- Decrease rates of positive axillary lymph nodes
  - ~40% with anthracycline/taxanes
  - Likely even higher with HER2 antibody combinations
- Molecular profiles of tumors may provide leads for additional (targeted) adjuvant therapy

Stanford Breast Oncology Program

Name	Department	Academic Rank	Program Role (Basic or Clinical Research)	Current Program Affiliation
George Sledge, MD	Medicine – Oncology	Professor	Clinical	Translational Onc
Michael Clarke, MD	Medicine – Oncology	Professor	Basic & Clinical	Cancer Stem Cells
Frederick Dirbas, MD	Surgery	Associate Professor	Clinical	Cancer Stem Cells
Bruce Daniel, MD	Radiology	Professor	Clinical	Cancer Imaging
James Ford, MD	Medicine	Professor	Basic & Clinical	Cancer Prevention
Debra Ikeda, MD	Radiology	Associate Professor	Clinical	Cancer Imaging
Stefanie Jeffrey, MD	Surgery	Professor	Clinical	Cancer Imaging
Kimberly Allison, MD	Pathology	Associate Professor	Clinical	Translational Onc
Kristin Jensen, MD	Pathology	Assistant Professor	Clinical	Associate Member
Allison W. Kurian, MD, MSci	Medicine	Associate Professor	Clinical	Cancer Epidemiology
Jafi Lipson, MD	Radiology	Associate Professor	Clinical	Cancer Imaging
Amanda Wheeler, MD	Surgery	Assistant Professor	Clinical	Associate Member
Mark Pegram, MD	Medicine – Oncology	Professor	Basic & Clinical	Translational Onc
Douglas Blayney, MD	Medicine – Oncology	Professor	Clinical	Translational Onc
Melinda Telli, MD	Medicine – Oncology	Assistant Professor	Clinical	Associate Member
Irene Wapnir, MD	Surgery	Associate Professor	Clinical	Associate Member
Christina Curtis, PhD	Oncology – Genetics	Associate Professor	Basic	Translational Oncology
Suleiman Massarweh, MD	Medicine – Oncology	Associate Professor	Clinical	Associate Member
Wendy DeMartini, MD	Radiology	Professor	Clinical	Cancer Imaging
Haruka Itakura, MD, PhD	Medicine— Oncology	Assistant Professor	Basic	Translational Onc

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