WELCOME

OFFICIAL best of SABCS

INSTITUT JULES BORDET H.U.B

BSMO

LICENSED BY ENCORE MEDICAL EDUCATION

FACULTY OF MEDICINE AND HEALTH SCIENCES

ANTRACYCLINES STILL NEEDED IN LUMINAL EARLY DISEASE?

YES

Hannelore Denys 27/1/2023

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HISTORY OF SOC CHEMOTHERAPY

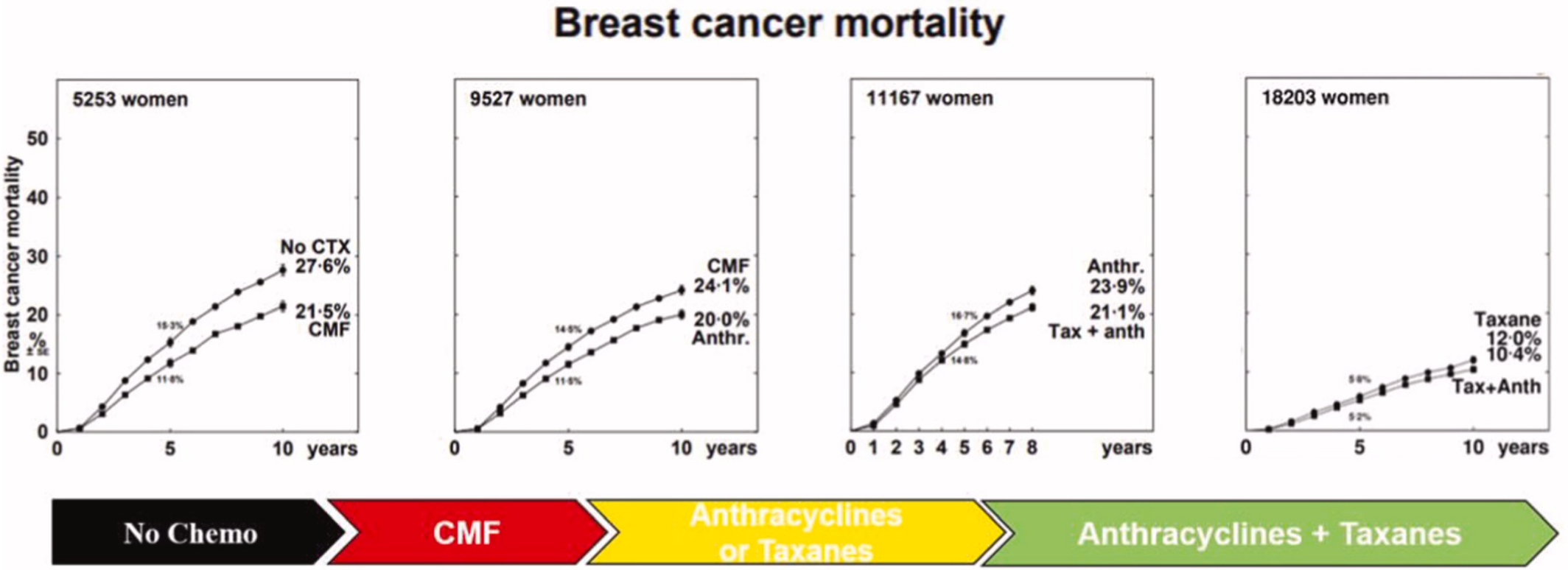

Fig. 1. Breast cancer mortality data adapted from EBCTCG meta-analysis.

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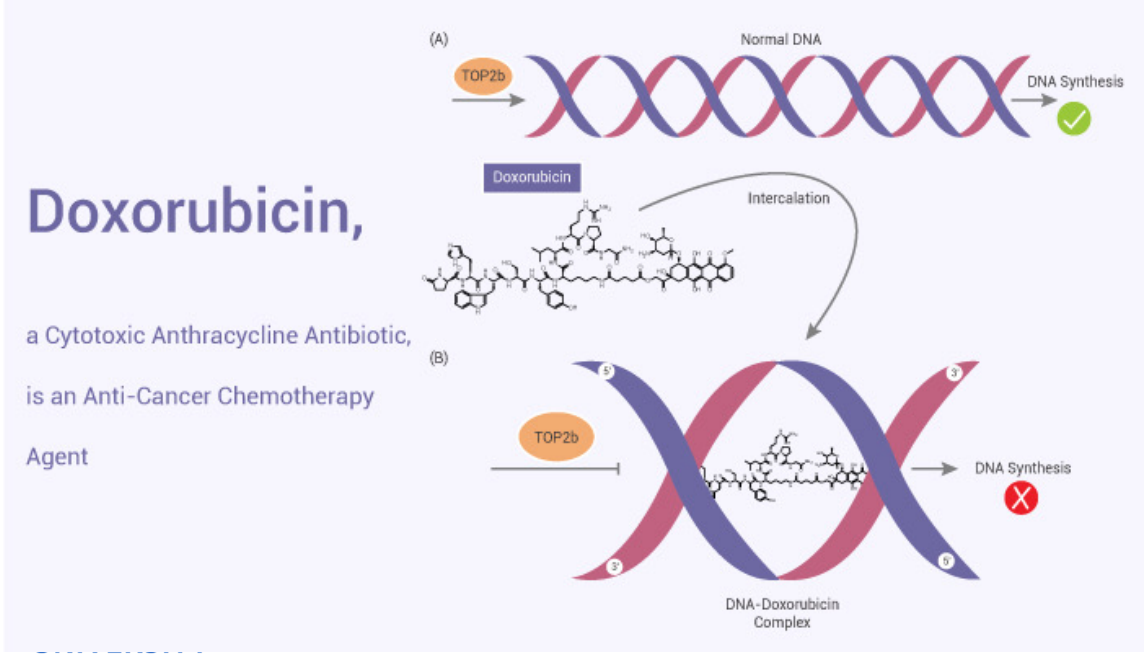
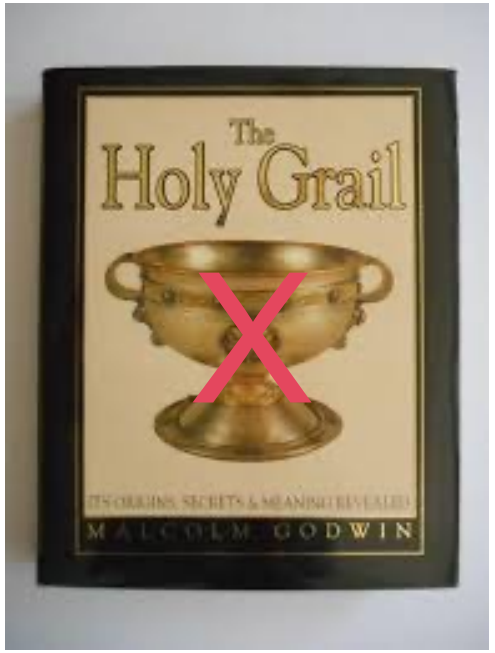
Vuger AT et al, The breast 2022

HISTORY: BIOMARKER FOR ANTYRACYCLINES?

Best known attempts were studies of anthracyclines in patients with HER2 overexpression, amplification and possible deletion of the TOP2A gene, and chromosome 17 centromeric duplication

→ results were **not conclusive**





2023: ANTRACYCLINE-TAXANE SOC

- Antracyclines and taxane based chemotherapy for early-stage breast cancer reduces the risk of breast cancer mortality by about one third, when compared to no chemotherapy

- Concerns about toxicity:
  - antracyclines: cardiovascular, leukemia
  - taxanes: neuropathy

- Increasing use of non antracycline based chemotherapy

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EBCTCG, SABCS 2021

WHAT IS THE EVIDENCE OF USING NON ANTRACYCLINE BASED CHEMOTHERAPY AS A NEW SOC?

Multiple trials

-> Heterogeneity in trial design, dosing, number of cycles, …

-> Regimens used as controls are not up to date

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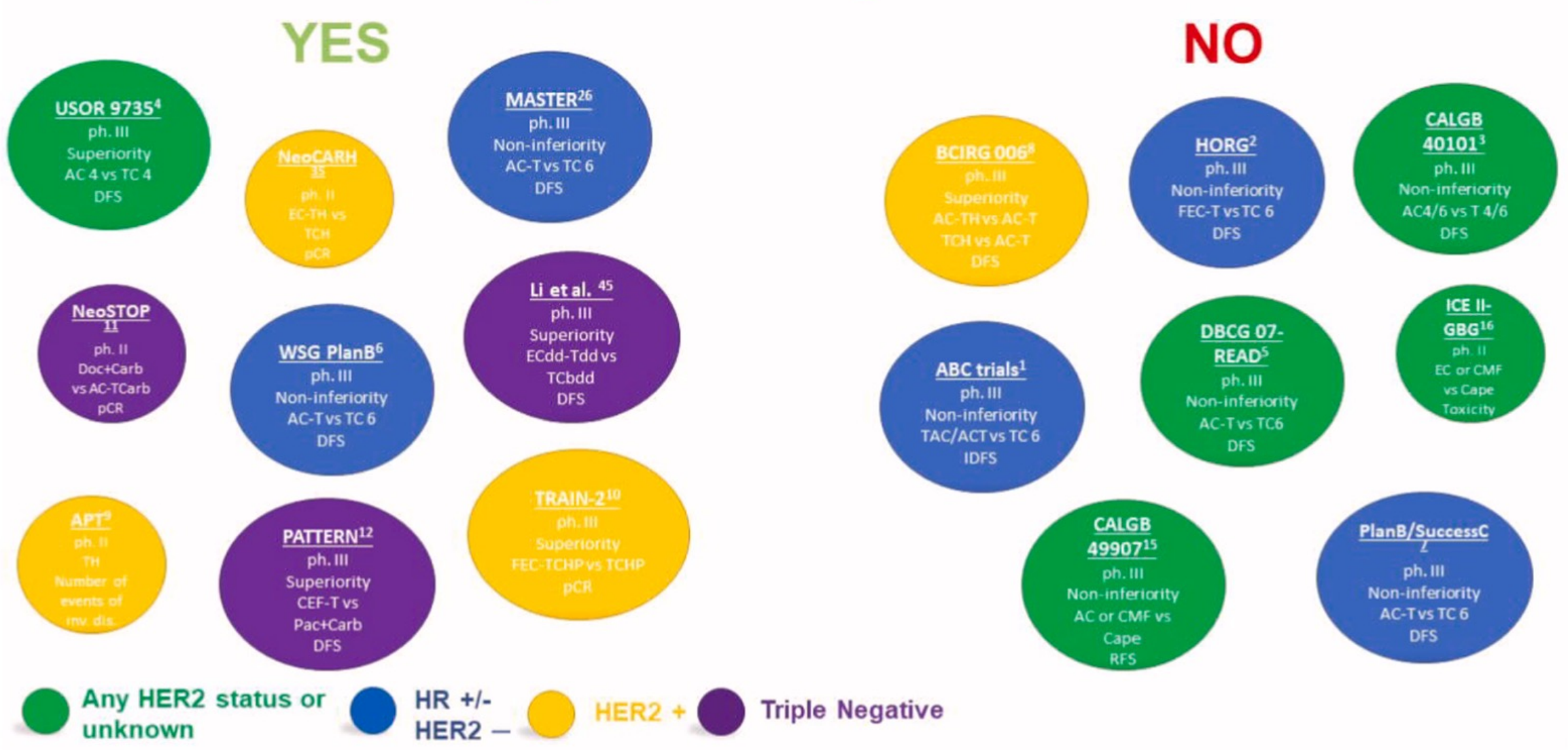
Can we spare antracyclines in EBC?



Vuger AT et al, The Breast 2022

ABC TRIALS

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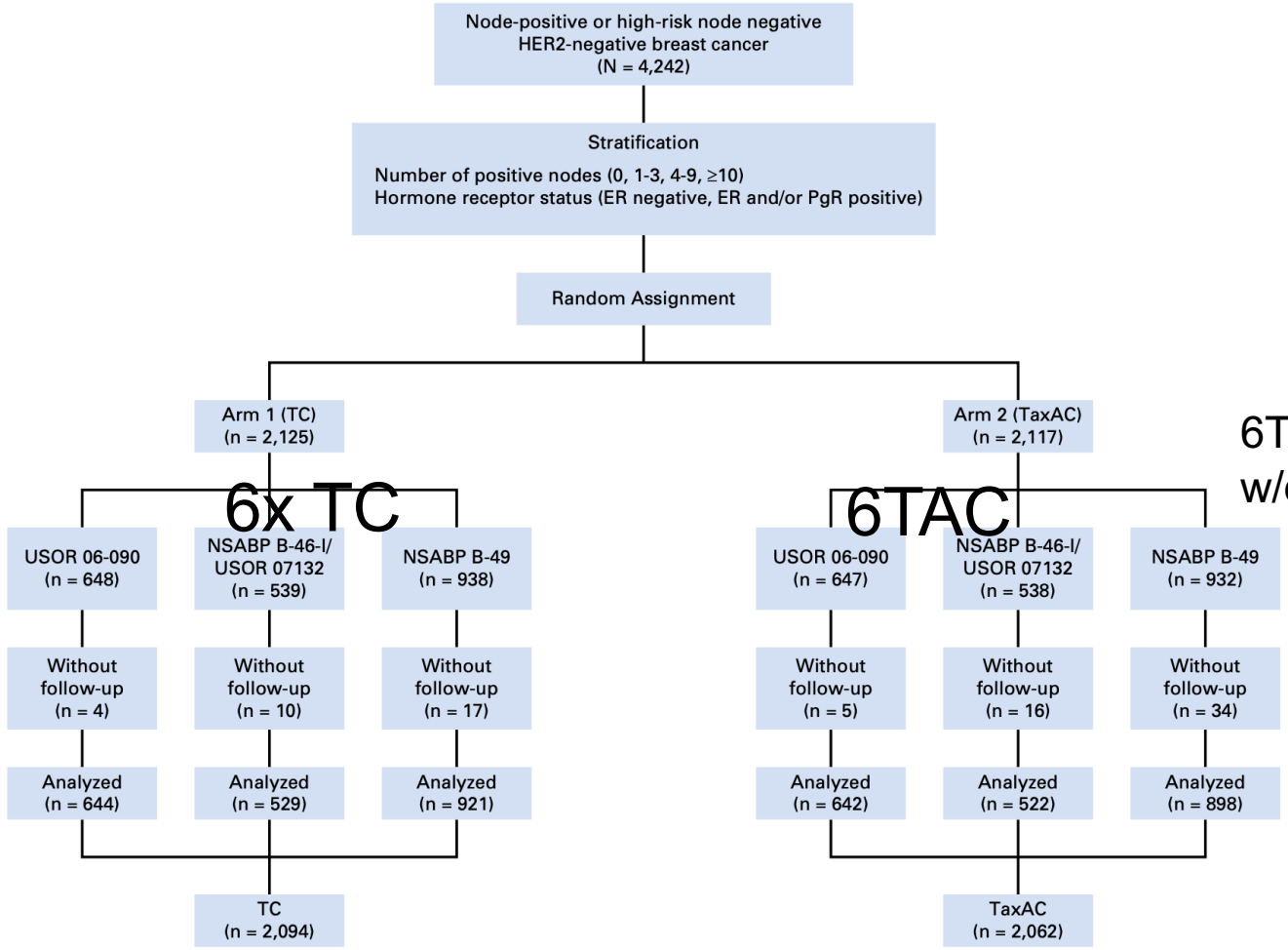
ABC TRIALS

- 4242 patients from 3 trials: USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49
- Non-inferiority trial
- 70% HR+
- 35-46% pN0



6TAC/AC3wPacl12
w/ddAC+Pacl3W

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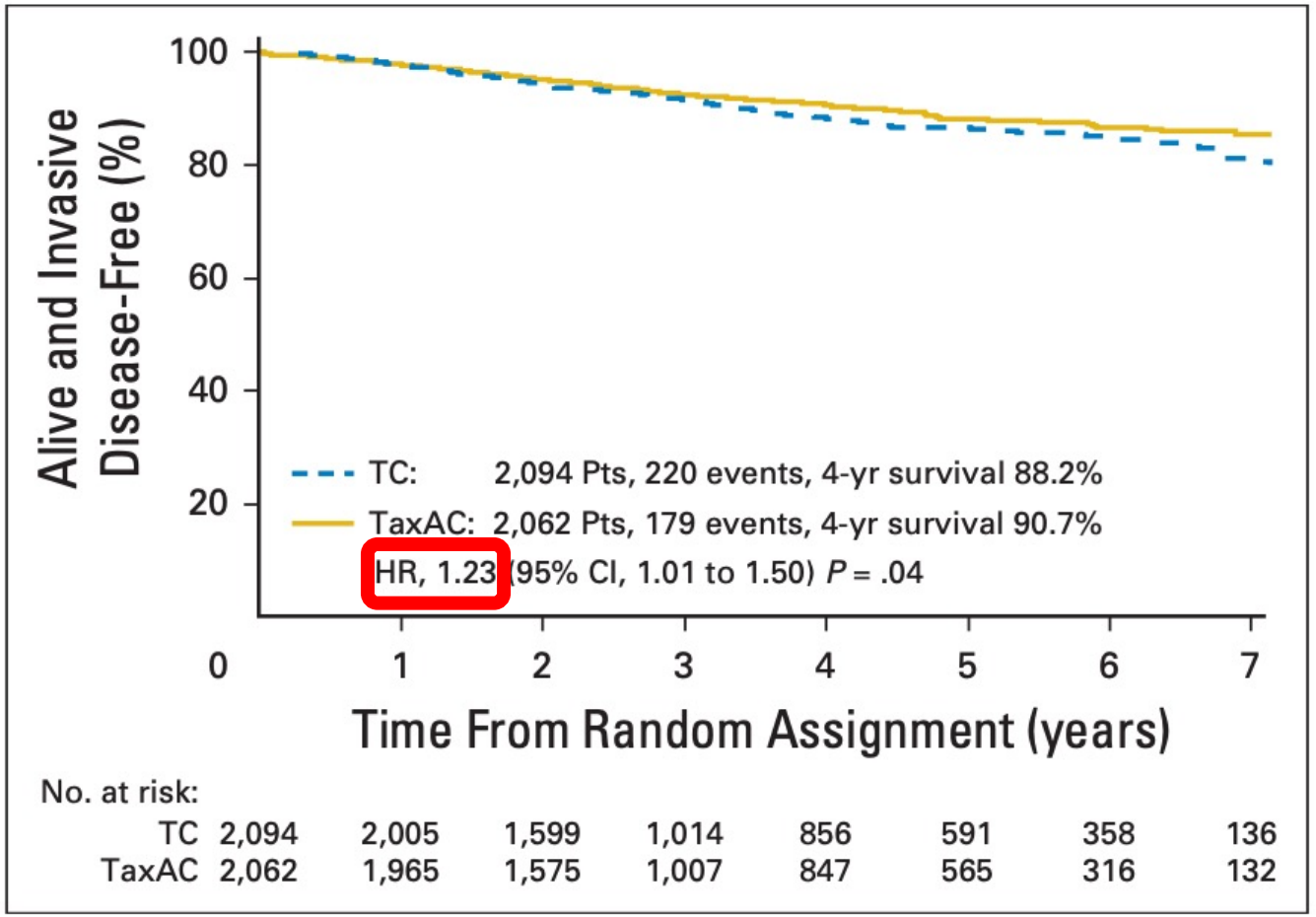
Blum J et al, JCO 2017

ABC TRIALS ITT IDFS

The observed HR for IDFS on basis of the ITT analysis was 1.23, which exceeded the 1.18 non-inferiority threshold



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ABC TRIALS: LUMINAL HR+

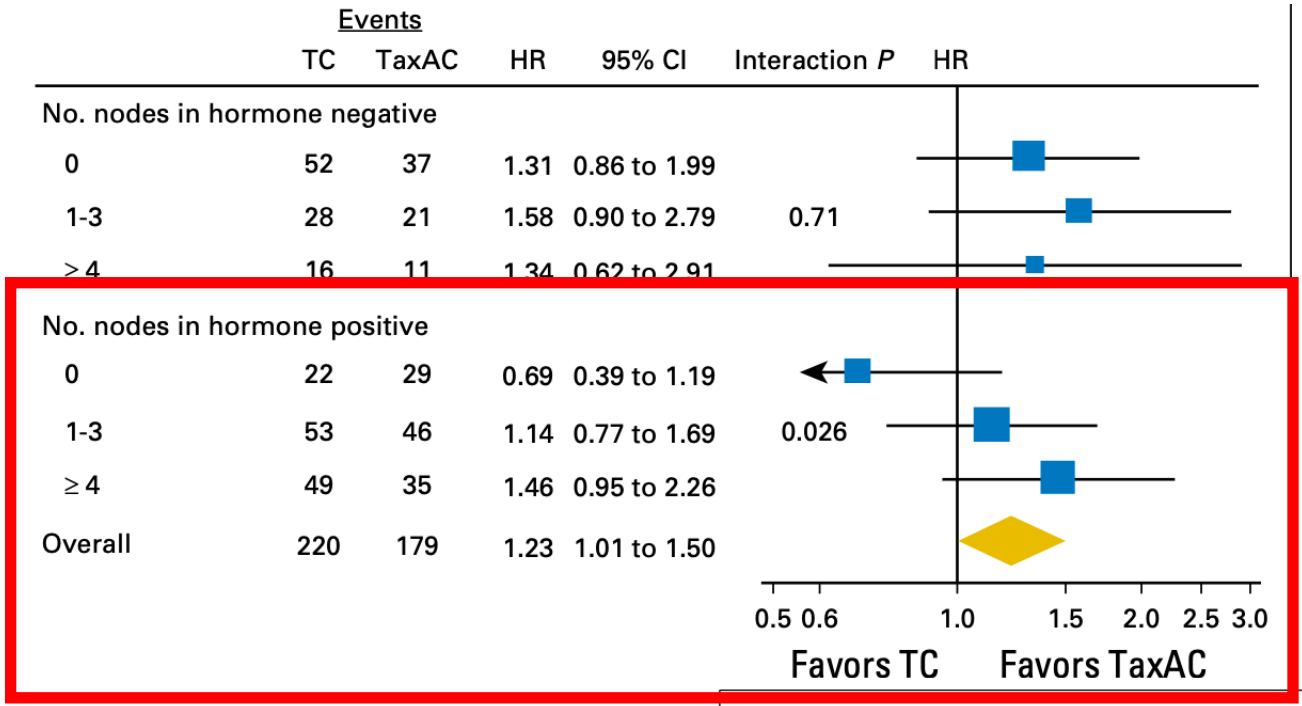

Table 3. IDFS by Hormone and Nodal Status

Status	No. of Patients		No. of Events		4-Year IDFS (%)		4-Year IDFS Δ (%)	HR (95% CI)
	TaxAC	TC	TaxAC	TC	TaxAC	TC		
HR negative								
Node negative	459	488	37	52	89.5	87.0	2.5	1.31 (0.86 to 1.99)
1-3 positive nodes	153	119	21	28	85.5	74.6	10.9	1.58 (0.90 to 2.79)
≥ 4 positive nodes	42	40	11	16	71.8	60.8	11.0	1.34 (0.62 to 2.91)
HR positive								
Node negative	358	378	29	22	91.5	94.2	−2.7	0.69 (0.39 to 1.19)
1-3 positive nodes	771	789	46	53	94.3	92.3	2.0	1.14 (0.77 to 1.69)
≥ 4 positive nodes	279	280	35	49	87.2	81.4	5.8	1.46 (0.95 to 2.26)

Abbreviations: HR, hormone receptor; IDFS, invasive disease-free survival; TaxAC, doxorubicin and cyclophosphamide regimens with a taxane; TC, docetaxel and cyclophosphamide.

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Blum J et al, JCO 2017

ABC TRIALS TOXICITY

Table 4. Distribution of Selected Adverse Events by Treatment on NSABP B-49

Adverse Event	Percentage of Events by Grade					
	TaxAC (n = 913)			TC (n = 919)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Overall toxicity	38	4	0	37	3	0
Blood and lymphatic system disorders						
Anemia	2	0	0	< 1	0	0
Febrile neutropenia	3	< 1	0	7	1	0
Cardiac disorders						
Acute coronary syndrome	0	0	0	0	0	0
Heart failure	0	0	0	0	0	0
Left ventricular systolic dysfunction	< 1	0	0	< 1	0	0
Myocardial infarction	0	0	0	0	0	0

Table 2. First Invasive Disease-Free–Survival Event by Treatment

Type of event	No. of Patients		
	TC (n = 2,094)	TaxAC (n = 2,062)	Total (N = 4,156)
Recurrence			
Locoregional	46	34	80
Distant	111	75	186
Site unknown	18	12	30
Contralateral breast cancer	3	3	6
Leukemia	0	5	5
Other second primary	20	22	42
Death	22	28	50
Total	220	179	399

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Blum J et al, JCO 2017

ABC TRIALS CONCLUSION

- The TaxAC regimens improved IDFS in patients with high-risk HER 2–negative breast cancer compared with the TC6 regimen.
- Exploratory analysis suggests benefit in patients with HR+ tumors with positive axillary nodes (high risk luminal)

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Blum J et al, JCO 2017

PLANB AND SUCCESS C

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PLANB AND SUCCESS C POOLED ANALYSIS

- 5924 Patients recruited between 2008-2011
- 78% HR
- pN0 48%

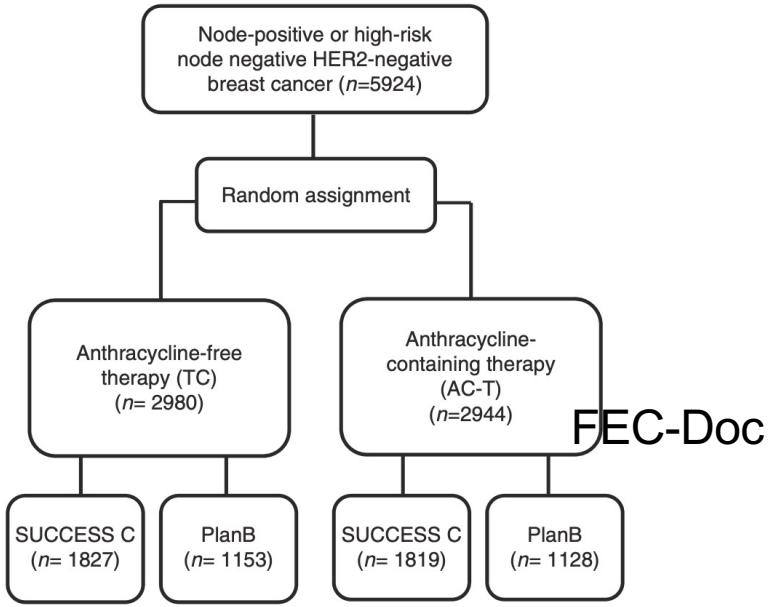
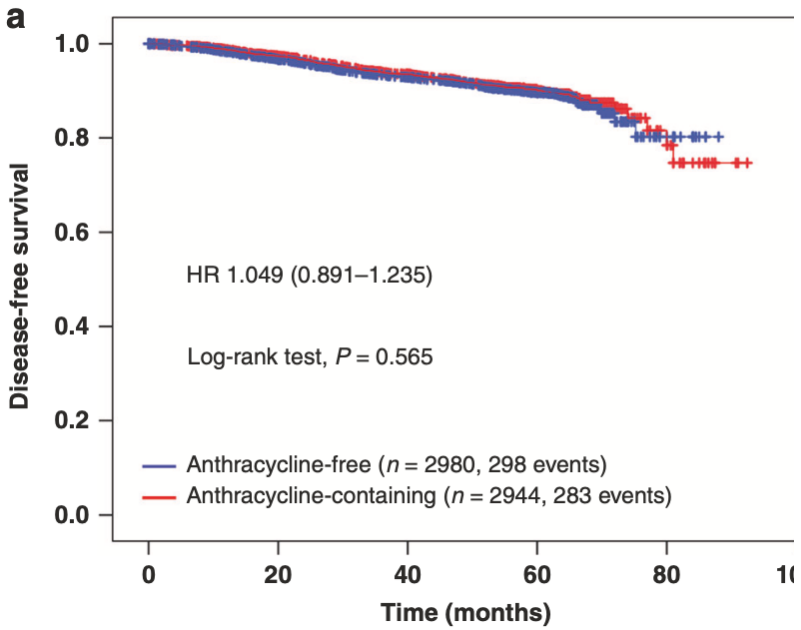
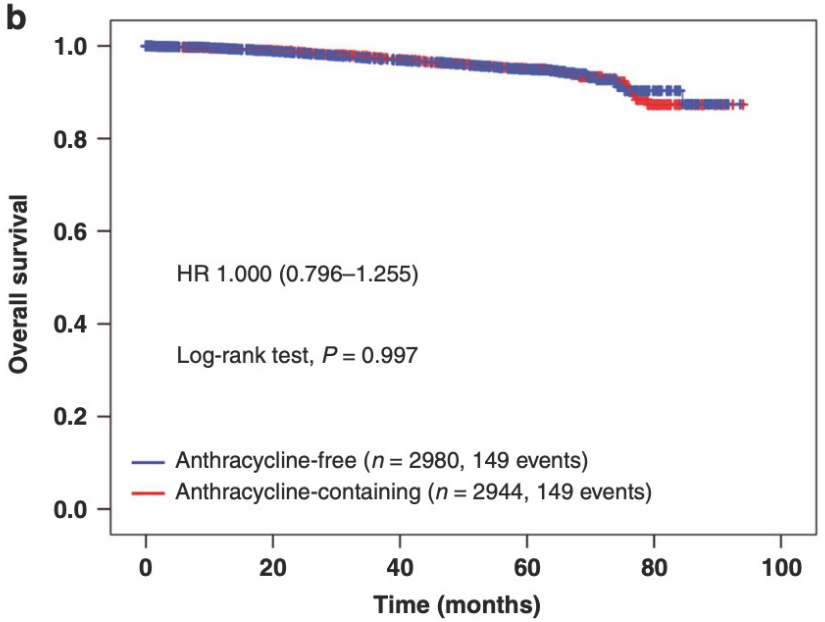


Fig. 1 Consort Diagram. CONSORT patient flow diagram of the PlanB and Success C pooled analysis.

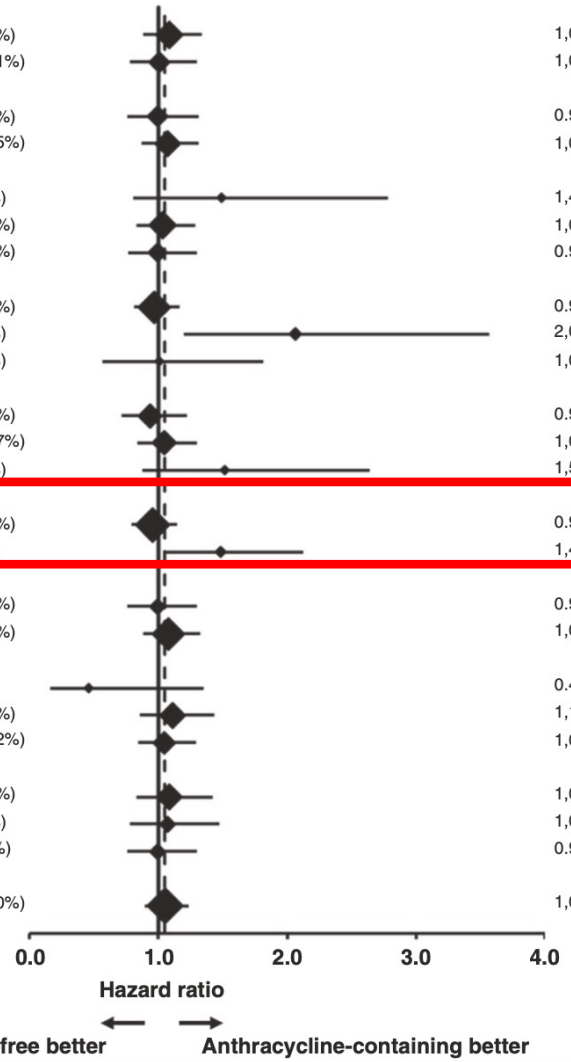




De Gregorio A et al, British Journal of Cancer 2022

PLANB AND SUCCESS C POOLED ANALYSIS

	DFS events/women		Hazard ratio	95% CI		*P* value
	Anthracyline-containing	Anthracycline-free		Lower limit	Upper limit	Interaction
Study						0.657
Success C	168/1816 (9.3%)	181/1827 (9.9%)	1,086	0.879	1,341	
PlanB	115/1128 (10.2%)	117/1153 (10.1%)	1,004	0.776	1,299	
Menopausal status						0.701
Premenopausal	103/1115 (9.2%)	104/1134 (9.2%)	0.996	0.758	1,310	
Postmenopausal	175/1749 (10.0%)	185/1754 (10.5%)	1,070	0.870	1,315	
Age (years)						0.481
≤ 40	17/205 (8.3%)	24/194 (12.4%)	1,493	0.802	2,780	
41–60	157/1795 (8.7%)	162/1799 (9.0%)	1,035	0.831	1,290	
> 60	109/944 (11.5%)	112/987 (11.3%)	0.995	0.764	1,297	
Histological type						0.041
Ductal	240/2393 (10.0%)	236/2415 (9.8%)	0.971	0.811	1,162	
Lobular	20/350 (5.7%)	40/376 (10.6%)	2,065	1,196	3,566	
Other	23/201 (11.4%)	22/189 (11.6%)	1,010	0.563	1,813	
Tumour size						0.314
pT1	113/1456 (7.8%)	101/1401 (7.2%)	0.935	0.715	1,224	
pT2	149/1330 (11.2%)	166/1423 (11.7%)	1,044	0.836	1,303	
pT3/pT4	21/158 (13.3%)	31/156 (19.9%)	1,519	0.873	2,643	
Nodal status						0.033
pN0/pN1	232/2660 (8.7%)	223/2684 (8.3%)	0.953	0.793	1,146	
pN2/pN3	51/284 (18.0%)	74/295 (8.2%)	1,483	1,035	2,125	
Hormone receptor status						0.639
Negative	107/633 (16.9%)	108/646 (16.7%)	0.992	0.759	1,297	
Positive	176/2311 (7.6%)	190/2334 (8.1%)	1,080	0.879	1,327	
Histological grade						0.331
G1	10/184 (5.4%)	5/185 (2.7%)	0.462	0.157	1,353	
G2	109/1567 (7.0%)	122/1600 (7.6%)	1,109	0.856	1,437	
G3	164/1191 (13.8%)	170/1193 (14.2%)	1,045	0.843	1,296	
Biological subtype						0.896
Luminal A like	103/1656 (6.2%)	112/1667 (6.7%)	1,086	0.831	1,421	
Luminal B like	73/653 (11.2%)	78/666 (11.7%)	1,070	0.776	1,475	
Triple negative	107/633 (16.9%)	108/646(16.7%)	0.992	0.759	1,297	
Total	283/2944 (9.6%)	298/2980 (10.0%)	1,049	0.891	1,235	



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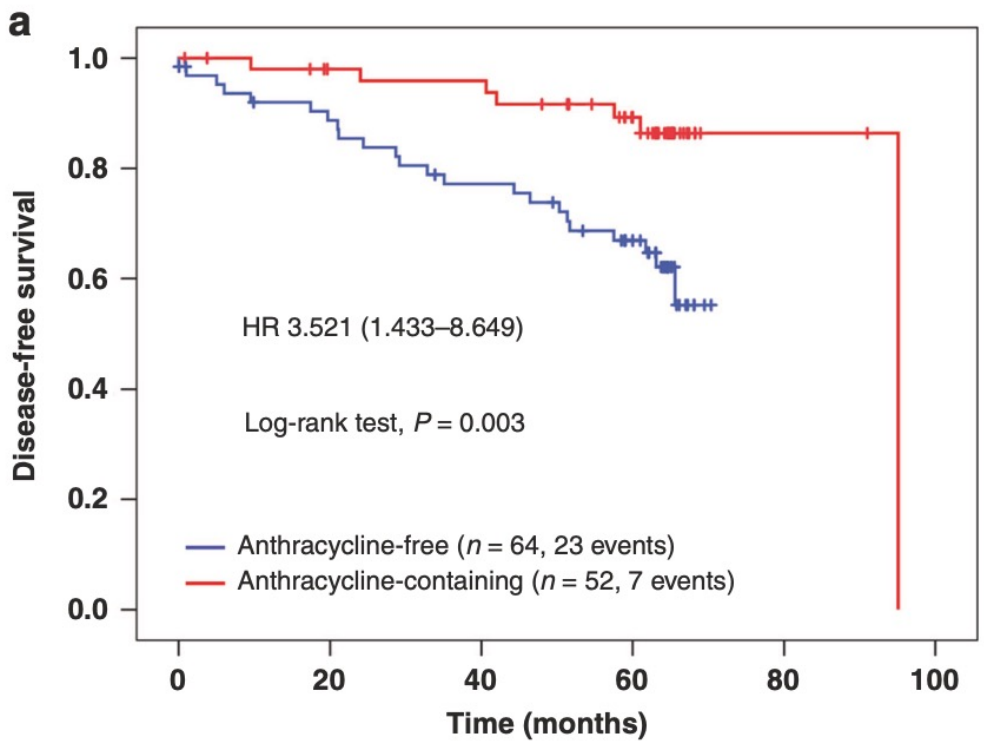
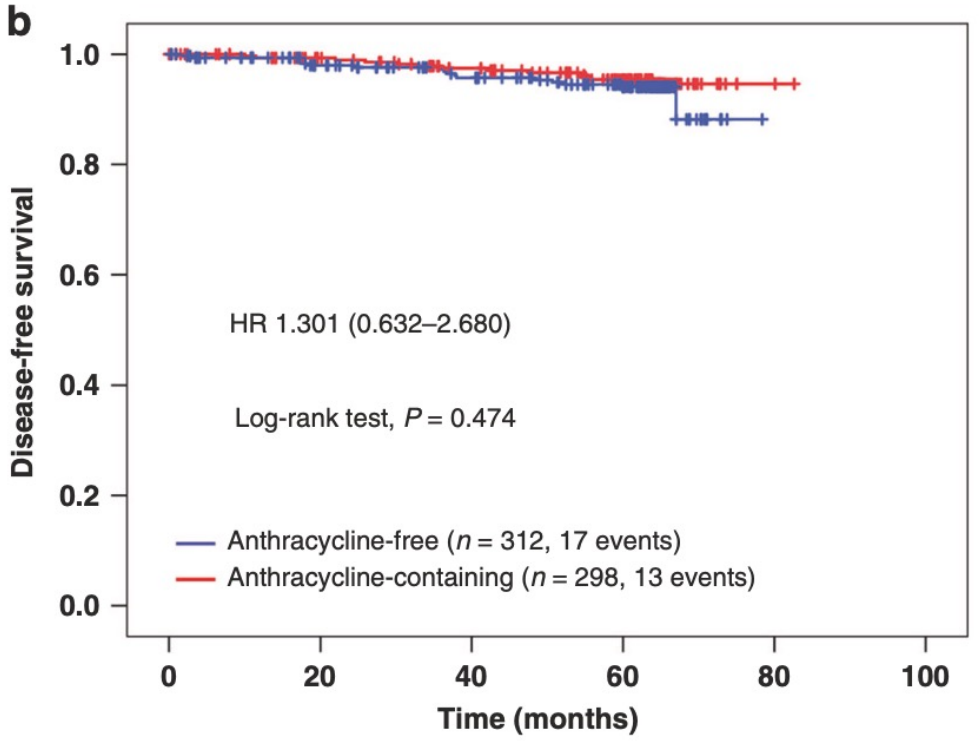
PLANB AND SUCCESS C POOLED ANALYSIS: LOBULAR CARCINOMAS

pN2/pN3 lobular tumours



pN0/pN1 lobular tumours



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PLANB AND SUCCESS C POOLED ANALYSIS

Variable	Anthracycline-containing chemotherapy (FEC-Doc[a]/EC-Doc[b]; $N = 2944$)	Anthracycline-free chemotherapy (Doc-C[c]; $N = 2980$)	P value[d]
(A)			
Any adverse event	2245 (76.3%)	2089 (70.1%)	<0.001*
Anaemia	20 (0.7%)	21 (0.7%)	0.91
Leukopenia	1509 (51.3%)	1358 (45.6%)	<0.001*
Neutropenia	1187 (40.3%)	1101 (36.9%)	0.008
Nausea	88 (3.0%)	40 (1.3%)	<0.001*
Fatigue	131 (4.4%)	83 (2.8%)	0.001*
Vomitting	53 (1.8%)	18 (0.6%)	<0.001*
Stomatitis	57 (1.9%)	26 (0.9%)	<0.001*
Constipation	21 (0.7%)	12 (0.4%)	0.11
Diarrhoea	55 (1.9%)	63 (2.1%)	0.50
SGPT elevation	46 (1.6%)	39 (1.3%)	0.41
SGOT elevation	10 (0.3%)	6 (0.2%)	0.31
Pain	68 (2.3%)	45 (1.5%)	0.024
Infection	59 (2.0%)	78 (2.6%)	0.12
Neuropathy	45 (1.5%)	23 (0.8%)	0.006
Arthralgia	45 (1.5%)	29 (1.0%)	0.054
Febrile neutropenia	114 (3.9%)	145 (4.9%)	0.062

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PLANB AND SUCCESS C POOLED ANALYSIS:

For most patients with HER2-negative EBC, AC-T is not associated with a survival benefit compared to 6xTC. However, patients with pN2/pN3 and lobular tumours seem to benefit from anthracycline-containing chemotherapy.

No dose dense chemotherapy

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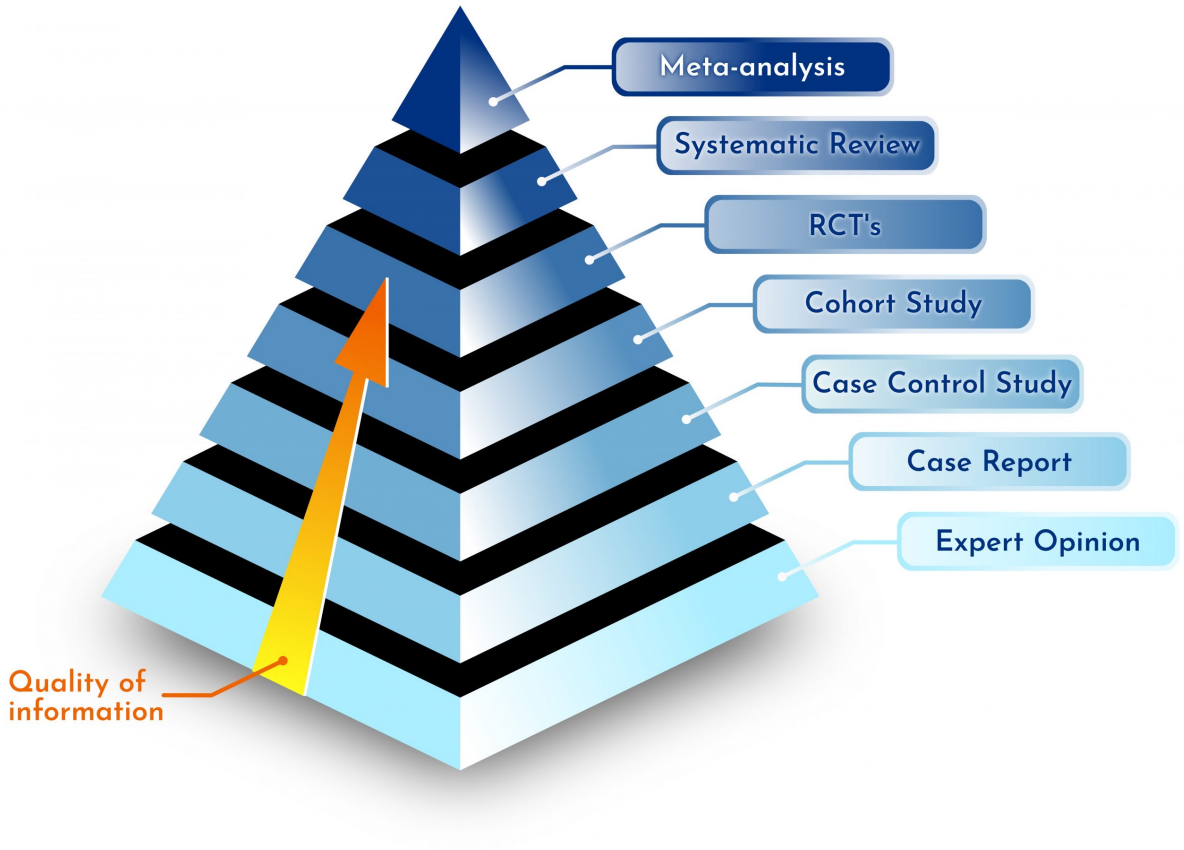
De Gregorio A et al, British Journal of Cancer 2022

META-ANALYSIS



The Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

EBCTCG 2021

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SABCS 2021: TAXANE WITH ANTRACYCLINE VERSUS TAXANE WITHOUT ANTRACYLINE

A patient level meta-analysis

Randomised trials that started before 2012

All trials included at least 6 cycles of chemotherapy

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Braybrooke J, EBCTCG SABCS 2021

EBCTCG TRIAL COMPARISONS

	Comparisons	No. people	No. Trials with data
(A)	6 x concurrent anth + docetaxel + cyclophosph. vs 6 x **SAME** dose docetaxel plus cyclophosph.	**2,469**	**3**
(B)	Sequential anthracycline / taxane vs **HIGHER** cumulative dose docetaxel plus cyclophosph.	**11,386**	**8**
(C)	Taxane plus anthracycline versus **HIGHER** cumulative dose taxane +/- capecitabine	**1,552**	**3**
(D)	Taxane plus anthracycline versus **HIGHER** cumulative dose taxane plus carboplatin	**2,796**	**2**
	Total	**18,203**	**16**

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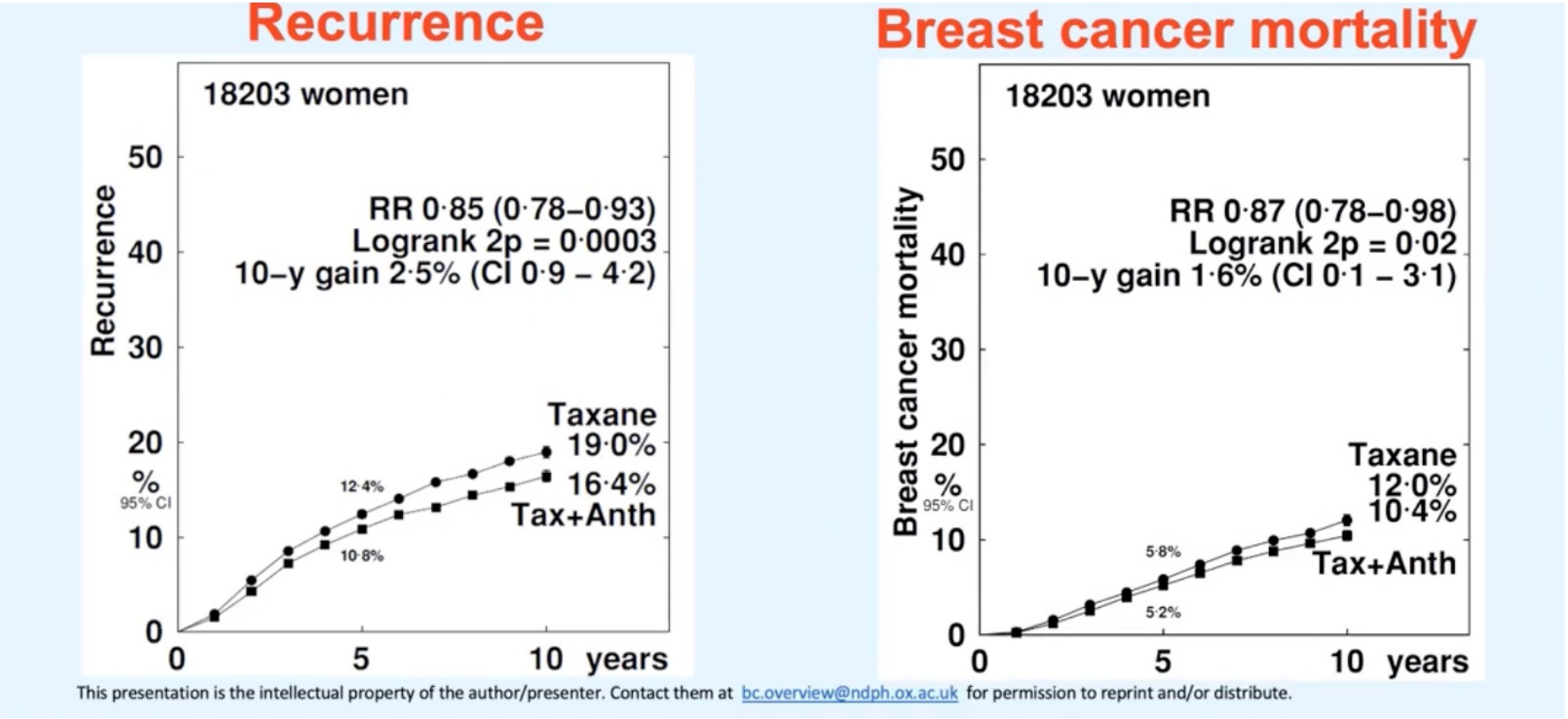
COMBINED ANALYSIS OF ALL 16 TRIALS (A-D)



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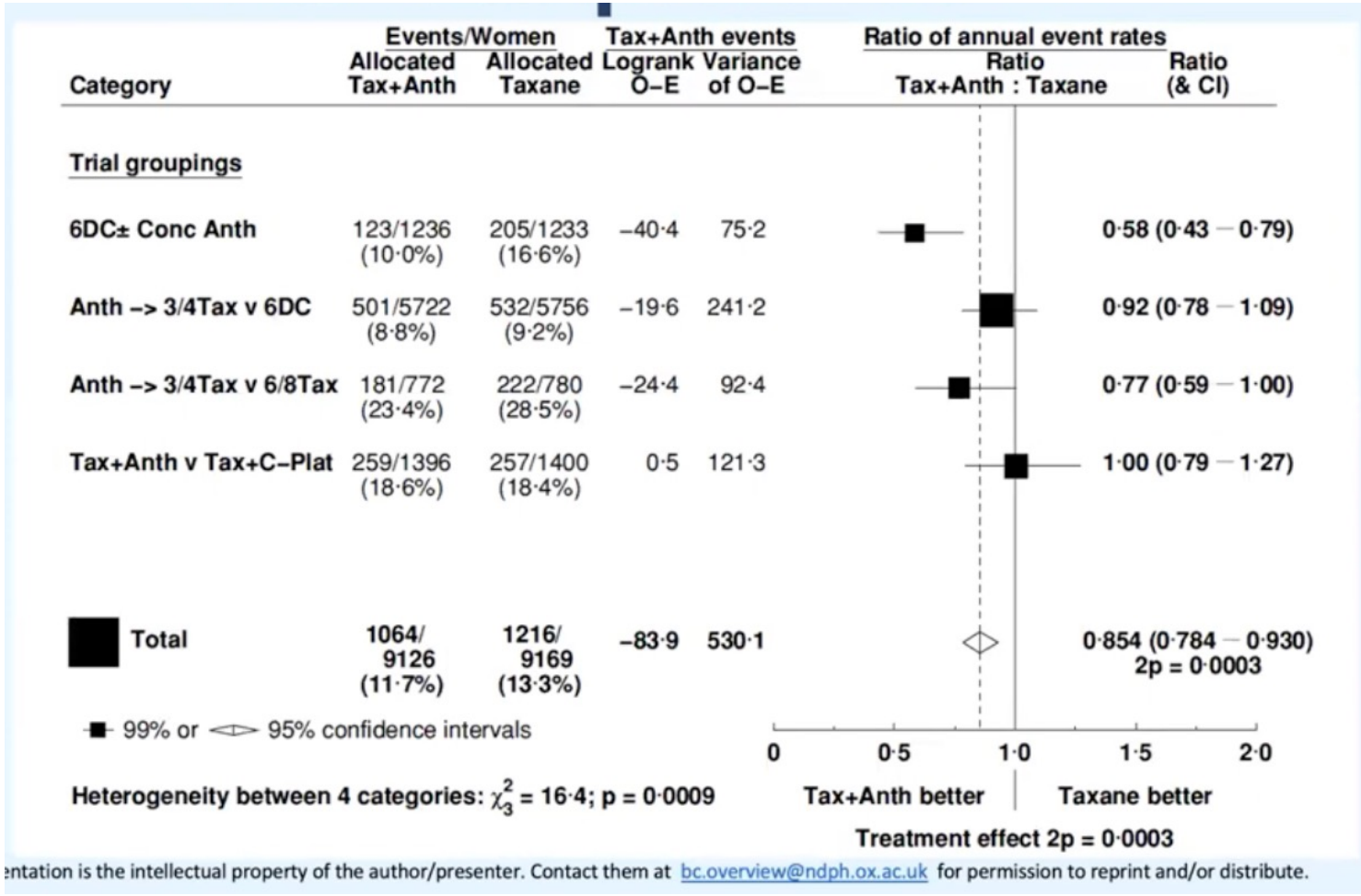
TRIAL COMPARISONS A-D



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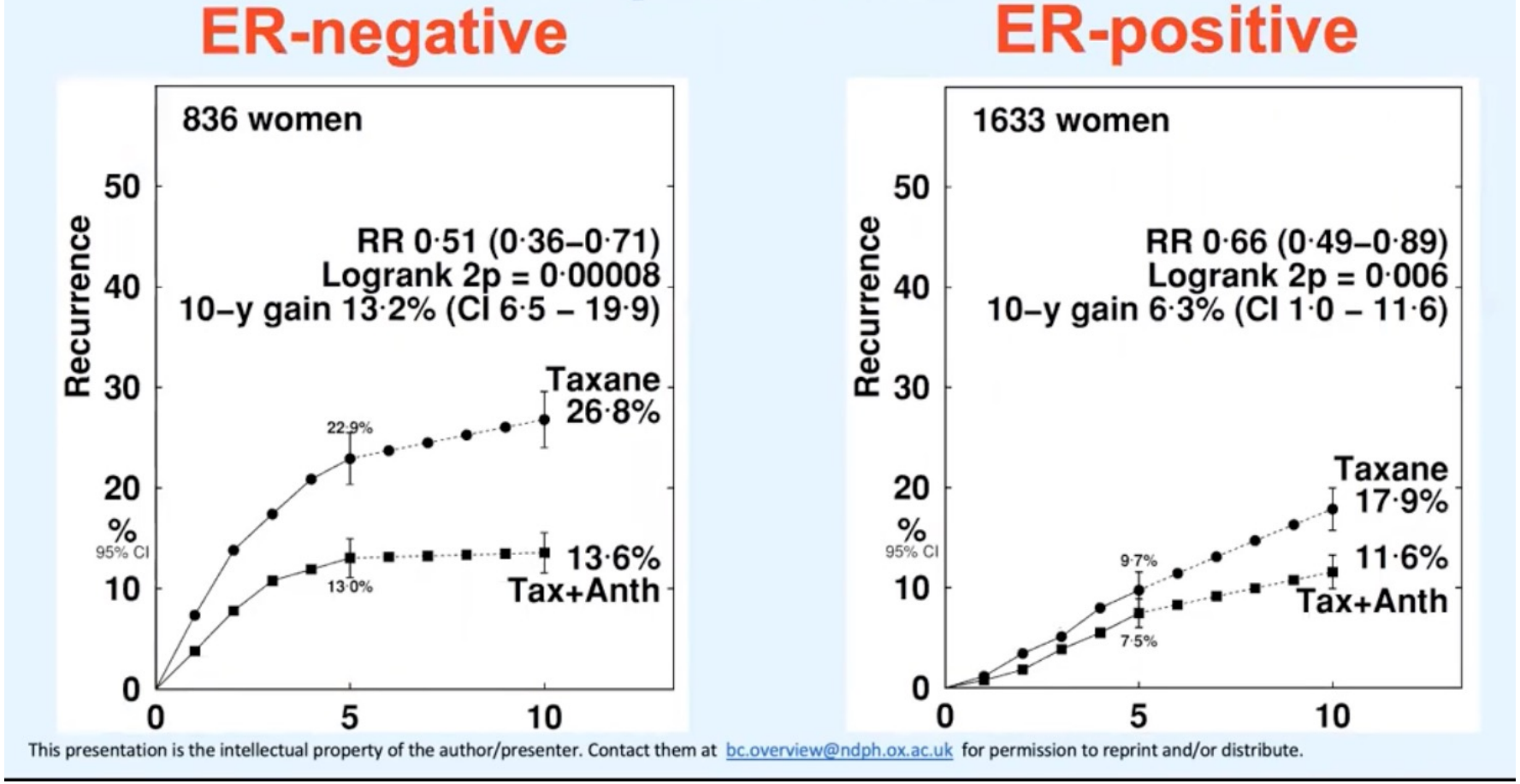
COMPARISON A VS B



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TOXICITY AND QOL

- Combined analysis - no statistically significant difference in death without recurrence (RR 1.06 95%CI 0.83-1.37, p=0.63)
- No difference in deaths from cardio-vascular disease or leukaemia **but longer term follow up needed**
- Individual patient level data on quality of life and toxicity not available

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CONCLUSION EBCTCG 2021

- All trials: 15% proportional reduction and 2.5 % absolute reduction at 10 years in the risk of invasive recurrence for antracyclines + taxane vs taxane chemotherapy

- Proportional reduction in recurrence dit not differ by ER status or nodal status

These are trials started before 2012, no dose dense chemotherapy

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DO WE NEED DOSE DENSE CHEMOTHERAPY? YES

134O GIM2: FACTORIAL Study design

ARM A EC x 4 cycles -> T x 4 cycles q3 wks	ARM C EC x 4 cycles -> T x 4 cycles q2 wks + Pegfilgrastim
ARM B FEC x 4 cycles -> T x 4 cycles q3 wks	ARM D FEC x 4 cycles -> T x cycles 4 q2 wks + Pegfilgrastim

EC vs FEC

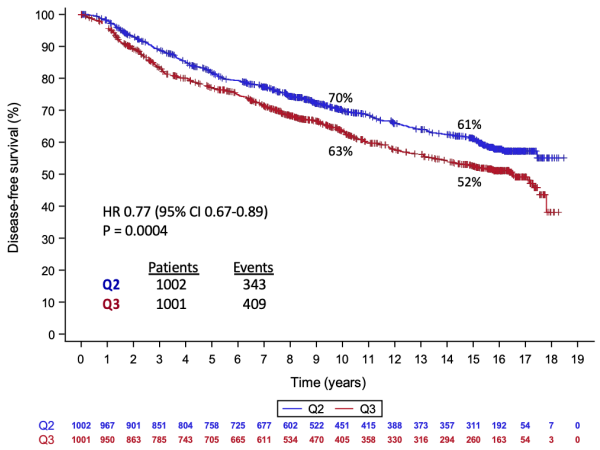
q3 wks vs q2 wks

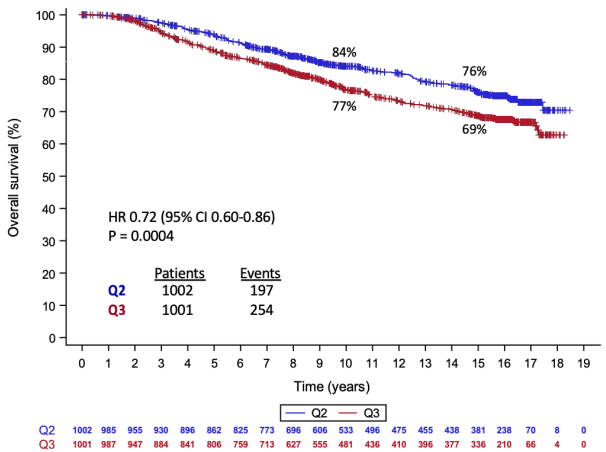
I will not go ever these data but in case you hae doubts, using 5-Fu is not necessary and the GIM 2 trial confirms it once and for all.

N+ early breast cancer patients = **2091**
HR+ or HR- tumors
HER2+ or HER2 - tumors

Primary end point: **DFS**
Secondary end points: **OS and safety**

15 year follow-up comparison for Q2 vs Q3 chemotherapy regimes





Dose-dense chemotherapy improves outcomes in terms of DFS and OS (absolute benefit 9% for DFS and 7% for OS)

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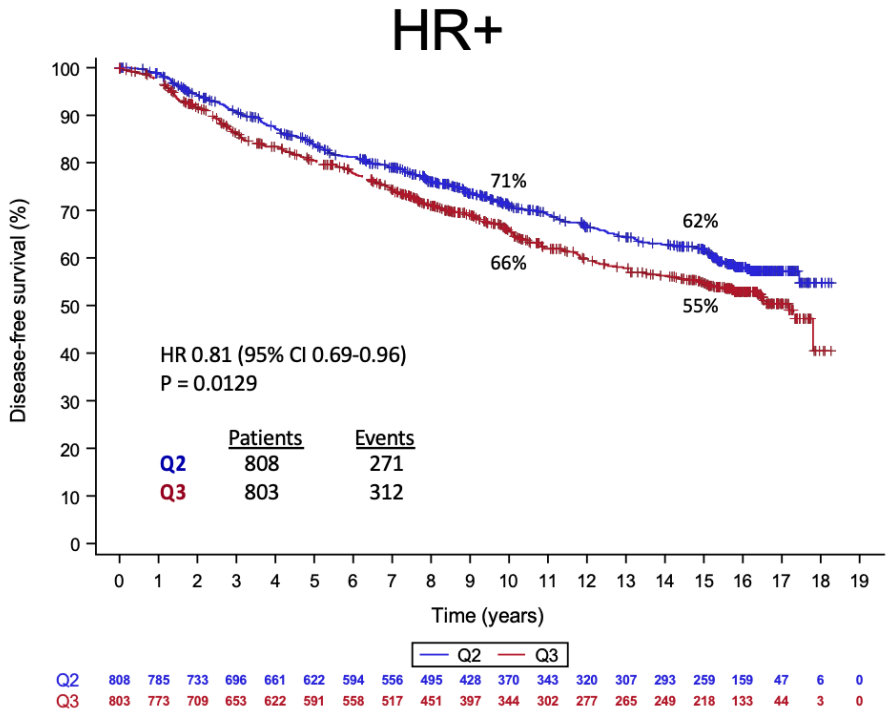
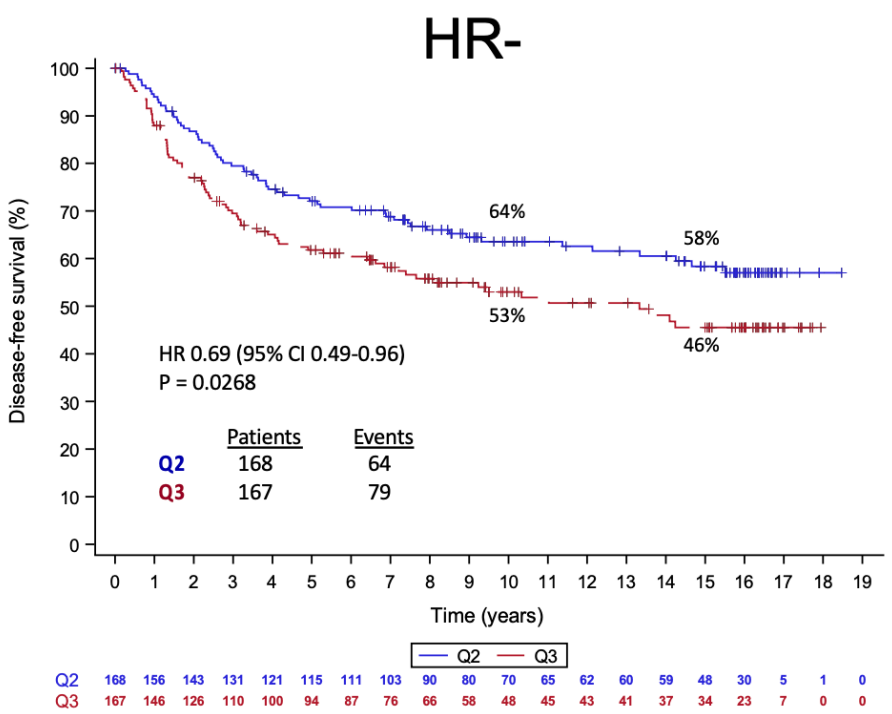
DO WE NEED DOSE DENSE CHEMOTHERAPY? YES

Analysis in terms of subgroups HR+ vs HR- disease





Dose-dense chemotherapy should be considered the optimal regimen to propose to N+ breast cancer patients candidates for adjuvant chemotherapy, irrespective of the hormone receptor status of the disease

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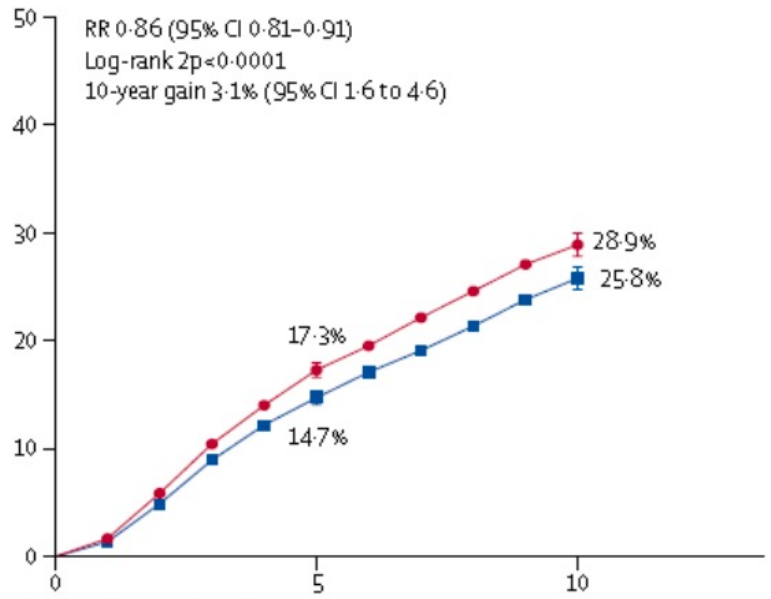
DO WE NEED DOSE DENSE CHEMOTHERAPY? YES

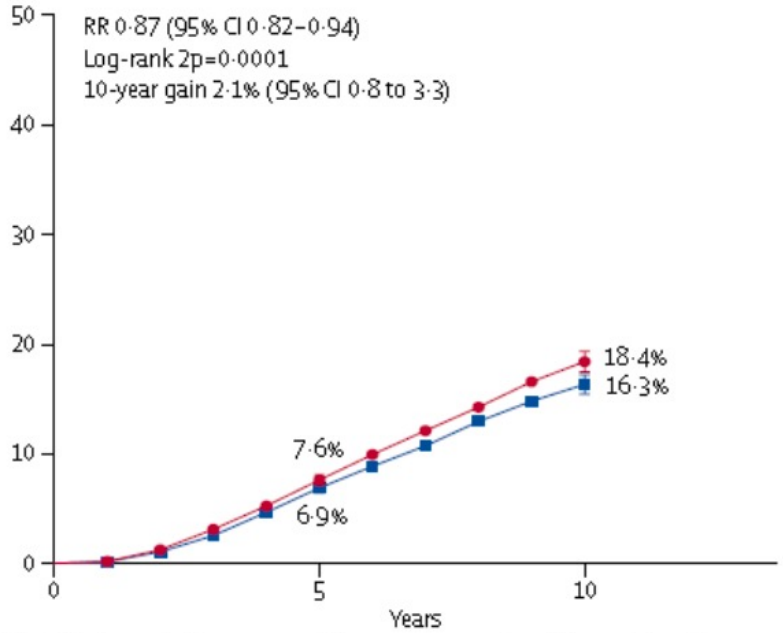
Any recurrence, ER-positive (25 029 women)



Recurrence rate per year (%) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Dose-intense	3·18 (1775/55 830)	2·77 (699/25 218)	1·92 (119/6192)
Standard schedule	3·74 (2055/54 904)	3·02 (724/23 971)	2·12 (122/5746)
Rate ratio (95% CI) from	0·84 (0·78–0·90)	0·91 (0·81–1·01)	0·89 (0·65–1·13)
(O–E)/V	−160·9/910·9	−33·9/342·5	−6·7/58·6

Breast cancer mortality, ER-positive (25 029 women)



Death rate per year (%) (total rate – rate in women without recurrence) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Dose-intense (95% CI)	1·41 (1·31–1·50)	2·18 (2·01–2·35)	1·50 (1·24–1·77)
Standard schedule (95% CI)	1·53 (1·43–1·63)	2·46 (2·28–2·65)	2·04 (1·71–2·36)
Rate ratio (95% CI) from	0·90 (0·81–0·99)	0·86 (0·76–0·97)	0·77 (0·56–0·98)
(O–E)/V	−45·2/420·7	−46·5/317·8	−17·1/66·1

Of the 25 029 women who are ER-positive, 84% are N+

CONCLUSIONS

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CONCLUSION (1) EFFICACY

- No trial has unequivocally demonstrated superiority of a non- anthracycline regimen in any breast cancer subtype

- The recent data from the EBCTCG meta-analysis show that regimens with anthracyclines and taxanes are superior to regimens with taxanes alone, in terms of recurrence and mortality. Proportional reduction in recurrence did not differ by ER or nodal status

- For high risk luminal disease: best results obtained with an antracycline/taxane regimen

CONCLUSION (2) TOXICITY

- Sequential use of anthracycline and taxane allows a lower total dose of anthracyclines.

- Upfront patient selection, cardiac monitoring and preventive measures protect against chemotherapy–related LVEF decline and heart remodeling.

- Moreover, the last EBCTCG meta-analysis showed no significant difference in death without recurrence and no difference in deaths from cardiovascular disease or leukemia was observed

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CONCLUSION (3) A CHANGED REALITY

- Furthermore, data discussed tonight are derived from trials treating patients **BEFORE the era of GEP and dose dense chemotherapy schemes**

- Anno 2023: we have better selection of high risk patients, GEP reduces overtreatment, so high risk patients are better selected (luminal pN0 are rarely treated with chemotherapy)

- “Antracyline yes or no” is an obsolete question. Focus on new agents which are emerging in (neo)adjuvant setting

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TRIO-US B-12 (TALENT): Study Design

Study Population:
- Hormone Receptor +
- HER2-low (by local and/or central review)
- Stage II-III operable
- Men or Pre-/Post-menopausal women

stratified by HER2 expression level (1+ or 2+ by IHC) and menopausal status (pre or post)

Arm A (N=29): T-DXd 5.4mg/kg

Arm B (N=29): T-DXd 5.4mg/kg + anastrozole (+GnRH analog for men/premenopausal women)

Treatment: 6 or 8 cycles* + EOT

Surgery**

**After surgery, adjuvant therapy as per discretion of treating provider.

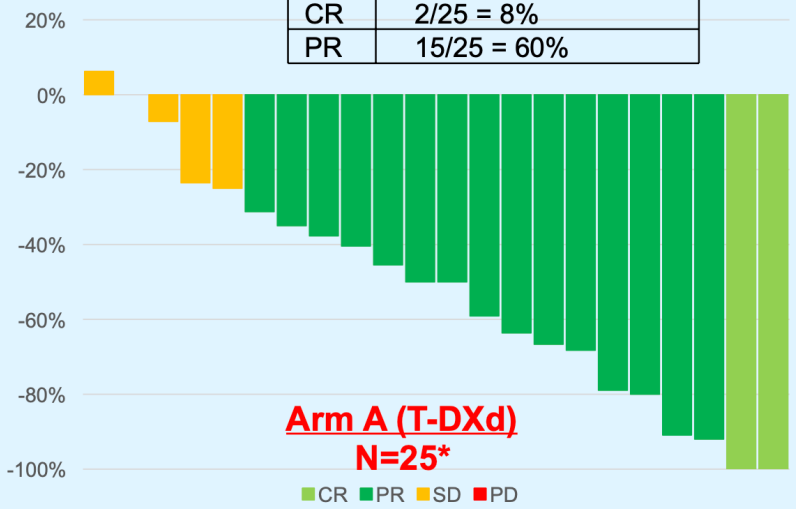
Tissue acquisition from archival tissue or biopsy at baseline and biopsy between C1D17-C1D21, and tissue at time of surgical resection

All tissue collected for study: pathology centrally reviewed

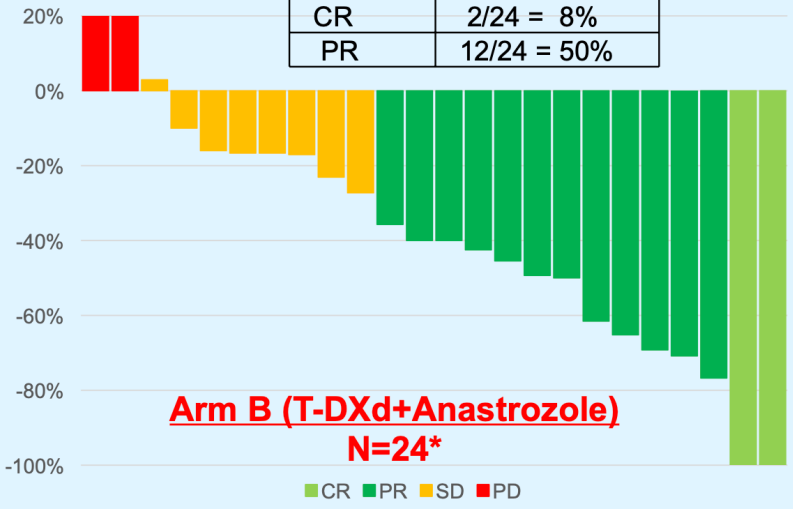
* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatmer

Objective Response Rate with T-DXd (based on imaging)

Arm A	
ORR	17/25 = 68%
CR	2/25 = 8%
PR	15/25 = 60%



Arm B	
ORR	14/24 = 58%
CR	2/24 = 8%
PR	12/24 = 50%



Waterfall plot with bars representing change in tumor size after treatment with T-DXd, compared to baseline, as per RECIST v1.1. Intention to treat population for ORR includes all who received at least 1 cycle of protocol therapy, data cutoff 11/25/2022.

- 4 patients still on treatment; 3 patients did have imaging (treatment discontinued prematurely), but included in intention to treat (ITT) denominator for ORR analysis per protocol

* 5 patients still on treatment

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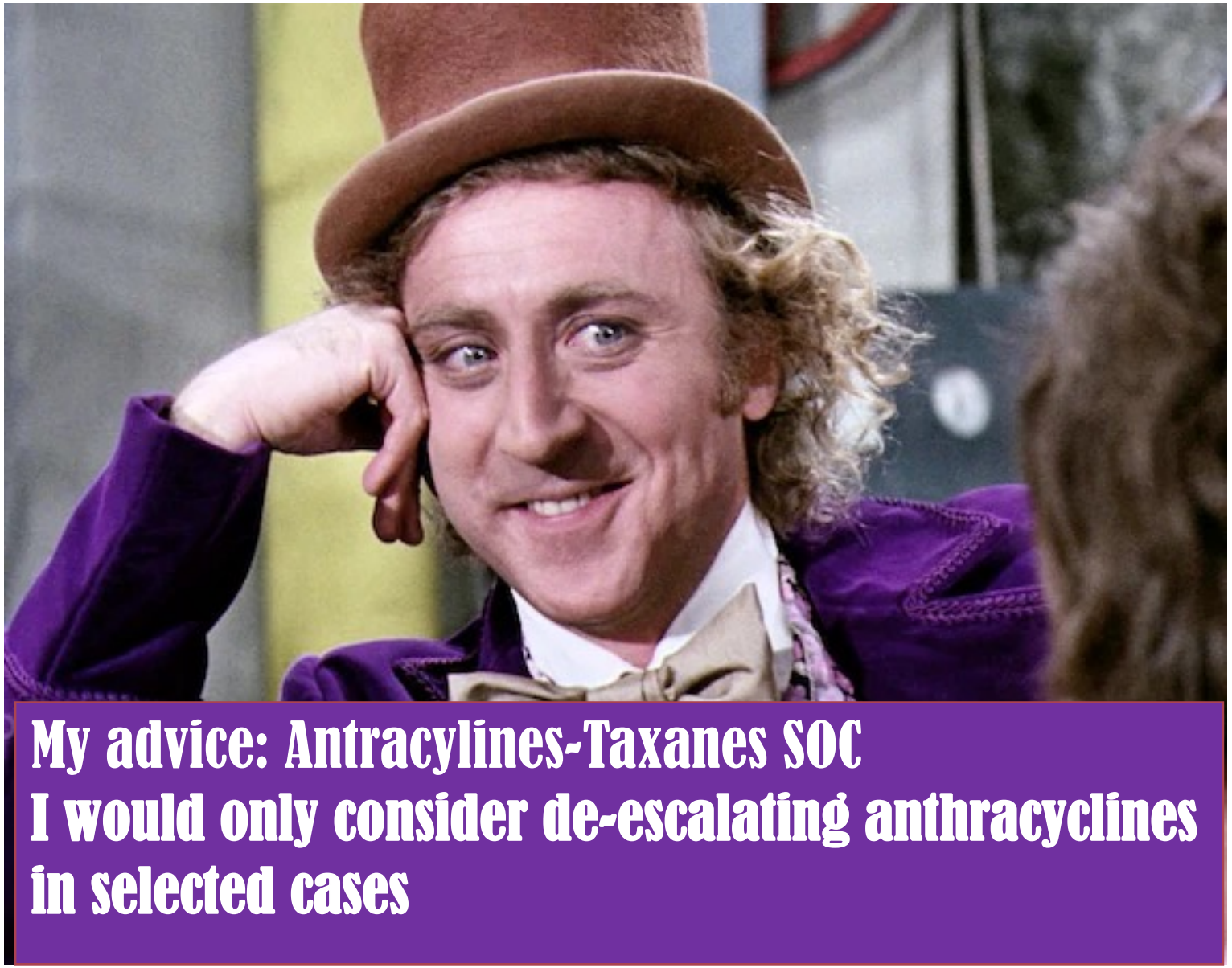

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ANTRACYCLINES STILL NEEDED IN LUMINAL EARLY DISEASE?
YES

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THANK YOU

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Breast Cancer Debate of the Year

OFFICIAL best of SABCS

INSTITUT JULES BORDET

H.U.B HÔPITAL UNIVERSITAIRE DE BRUXELLES ACADEMISCHE ZIEKENHUIS BRUSSEL

BSMO

LICENSED BY ENCORE MEDICAL EDUCATION

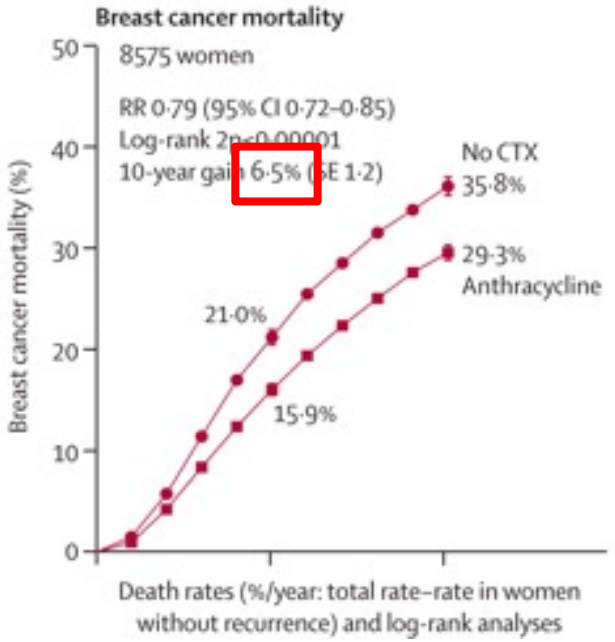
Anthracyclines still needed in luminal early disease?
NOT IN FAVOUR!

Hans Wildiers
Medical Oncologist
Multidisciplinary Breast Centre
Leuven

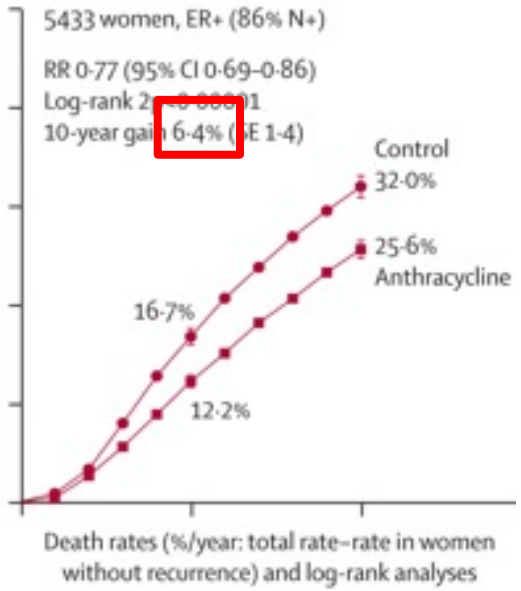
Anthracyclines improve outcome

Breast cancer mortality ↓

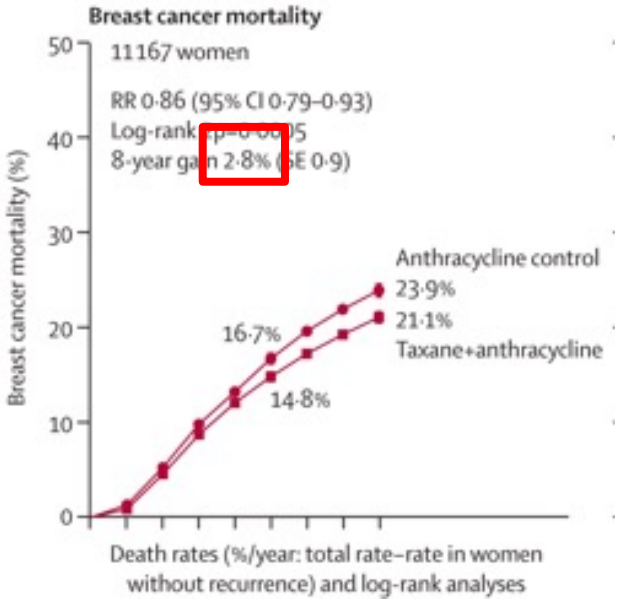
Anthracycline vs
no chemo



Anthracycline vs
no chemo in ER+

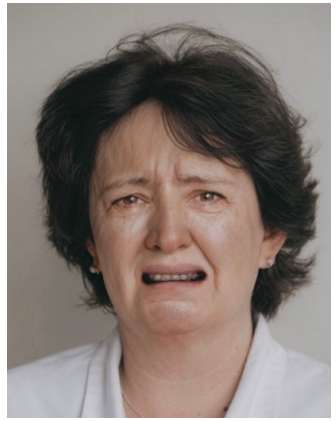


Anthracycline+Taxane
vs Anthracycline



Lancet 2011 EBCTCG

Anthracyclines are potentially toxic



Acute side effects

- Anemia
- Trombocytopenia
- Nausea and vomiting
- Mucositis
- Alopecia
- …

Long term side effects

- **Heart failure**: 0,5 – 1% (RR 1,5-2x), 10% LVEF decline

- **Myelodysplasie / leukemia**: 0,5% (RR 3-5x)

The oncologist 2018 Shah ; BCRT Shah 2018

4 x TC adjuvant (docetaxel cyclophosphamide) US Oncol 9735

Studie	Studie armen	N	Outcome	Toxicity
ER+ 70% N0 49% **≥65y** 16% FUP 7y	**4TC**	506	DFS 81%* OS 87%*	more febrile neutropenia (8% vs 4%) more gr III-IV anemia (5 vs <1%) and asthenia (9 vs 4%)
	4AC	510	DFS 75% OS 82% *No influence of age and ER status*	

- Subsequent elderly specific trials with **TC**:
  - 110 women ≥70y EBC **TC ± G-CSF** (49%) (retrospective)
    - 5% febrile neutropeniea, alle other gr II-IV toxicities ≤5%
    - 91% could receive 4 cycles
  - 57 women ≥70y EBC with **TC + G-CSF** (prospective)
    - 13% febrile neutropenia, all other gr III toxicities ≤2%
    - 93% could receive 4 cycles. Clinical frailty and QoL ↓ but recovered

⇒ 4 x TC is an interesting and accepted 'elderly' chemoregimen.

DFS = Disease Free Survival ; OS = Overall Survival ;
EBC = early breast cancer

JCO 2009 Jones ; JCO 2014 Shulman ; CROH 2011 Freyer ; Oncotarget 2016 Brouwers

6 x TC adjuvant (docetaxel cyclophosphamide): studies in HER2-

	ABC trials
Regimens	6xTC vs 6xTaxAC
Study characteristics	N=4156 59% N pos 69% ER+
Primary endpoint	4y-IDFS 88,2% vs 90,7% (p 0,04)
Subgroup analysis	Anthracycline benefit mainly in ER neg/N pos
OS data	4y-OS 94,7% vs 95% (ns)

J Clin Oncol 2017
Blum et al

6 x TC adjuvant (docetaxel cyclophosphamide): studies in HER2-

	ABC trials	Hellenic Oncology Research Group
Regimens	6xTC vs 6xTaxAC	6xTC vs 4xddFEC -> 4xddDoc
Study characteristics	N=4156 59% N pos 69% ER+	N=650 100% N pos 89% ER+
Primary endpoint	4y-IDFS 88,2% vs 90,7% (p 0,04)	3y-DFS 91,1% vs 89.5% (ns)
Subgroup analysis	Anthracycline benefit mainly in ER neg/N pos	No difference
OS data	4y-OS 94,7% vs 95% (ns)	No difference

J Clin Oncol 2017
Blum et al

Ann Oncol 2016
Mavroudis et al

6 x TC adjuvant (docetaxel cyclophosphamide): studies in HER2-

	ABC trials	Hellenic Oncology Research Group	DBCG
Regimens	6xTC vs 6xTaxAC	6xTC vs 4xddFEC -> 4xddDoc	6xTC vs 3xEC -> 3xDoc
Study characteristics	N=4156 59% N pos 69% ER+	N=650 100% N pos 89% ER+	N=2102 (TOP2A normaal) 53% N pos 71% ER+
Primary endpoint	4y-IDFS 88,2% vs 90,7% (p 0,04)	3y-DFS 91,1% vs 89.5% (ns)	5y-DFS 88,3% vs 87,9% (ns)
Subgroup analysis	Anthracycline benefit mainly in ER neg/N pos	No difference	Grade 3 tumors more benefit from TC
OS data	4y-OS 94,7% vs 95% (ns)	No difference	No difference

J Clin Oncol 2017
Blum et al

Ann Oncol 2016
Mavroudis et al

JCO 2017
Ejlertsen et al

6 x TC adjuvant (docetaxel cyclophosphamide): studies in HER2-

	ABC trials	Hellenic Oncology Research Group	DBCG	Plan B
Regimens	6xTC vs 6xTaxAC	6xTC vs 4xddFEC -> 4xddDoc	6xTC vs 3xEC -> 3xDoc	6xTC vs 4xEC -> 4xDoc
Study characteristics	N=4156 59% N pos 69% ER+	N=650 100% N pos 89% ER+	N=2102 (TOP2A normaal) 53% N pos 71% ER+	N=2449 (genomic intermediate or high risk) 41% N pos, RS>25 26% 82% ER+
Primary endpoint	4y-IDFS 88,2% vs 90,7% (p 0,04)	3y-DFS 91,1% vs 89.5% (ns)	5y-DFS 88,3% vs 87,9% (ns)	5y-DFS 89.6% vs 89,8% (ns)
Subgroup analysis	Anthracycline benefit mainly in ER neg/N pos	No difference	Grade 3 tumors more benefit from TC	No impact of age, pN, ER status, LumA/B TC 5 R/deaths, EC 1
OS data	4y-OS 94,7% vs 95% (ns)	No difference	No difference	5y-OS 94.7% vs 94.5% (ns)

J Clin Oncol 2017
Blum et al

Ann Oncol 2016
Mavroudis et al

JCO 2017
Ejlertsen et al

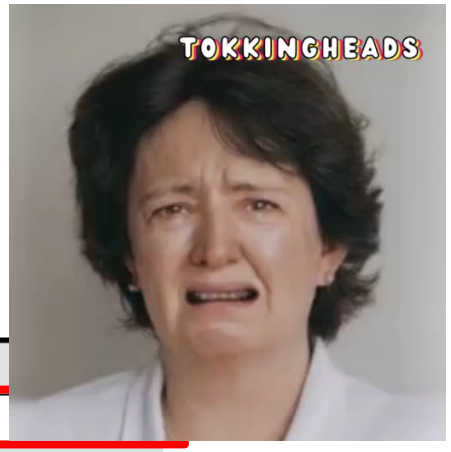
JCO 2021
Nitz et al

6 x TC adjuvant: PLAN B safety

Grade 3-5 side effects

	TC		EC-T		
Adverse Event	**No.**	**%**	**No.**	**%**	***P***
Leukopenia	598	50.8	671	57.5	.001
Neutropenia	598	50.8	676	57.9	.001
Anemia	4	0.3	9	0.8	.18
Febrile neutropenia	63	5.3	45	3.9	.09
Infection	82	7.0	62	5.3	.1
Nausea	20	1.7	44	3.8	.002
Vomiting	5	0.4	23	2.0	< .001
(Peripheral) polyneuropathy	10	0.8	26	2.2	.007
Hand-foot syndrome/palmar syndrome	9	0.8	33	2.8	< .001
Diarrhea	37	3.1	39	3.3	.8
Mucositis/stomatitis	20	1.7	43	3.7	.003
Arthralgia/myalgia	18	1.5	35	3.0	.02
Pain	37	3.1	61	5.2	.01
Cardiac failure	3	0.3	3	0.3	> .999
Fatigue	35	3.0	68	5.8	.001
Thrombosis	19	1.6	24	2.1	.48
Therapy-related death	5	0.4	1	0.08	.2
Cardiac-related death*	2	0.1	2	0.1	>.999
Acute myeloid leukemia*	0	0	1	0.08	.3

6 x TC adjuvant: PLAN B safety



Grade 3-5 side effects

	TC		EC-T		
Adverse Event	No.	%	No.	%	
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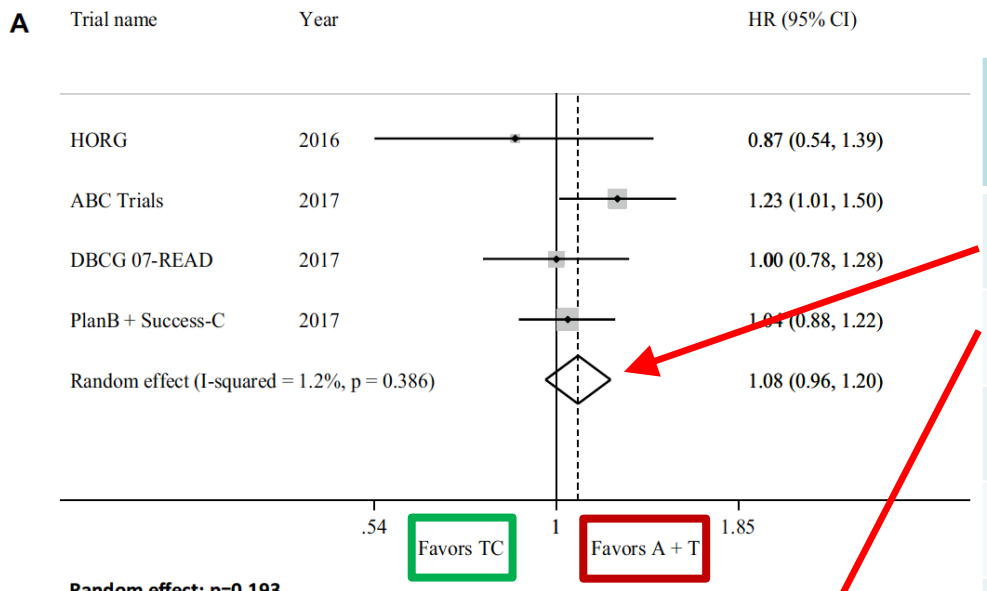
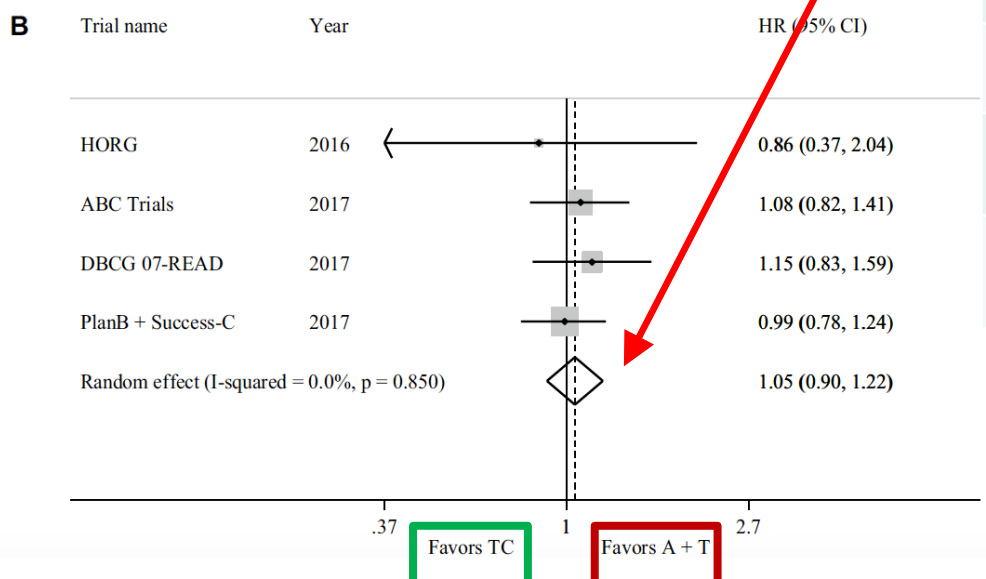
Acute myeloid leukemia*	0	0	1	0.08	.3

6 x TC adjuvant (docetaxel cyclophosphamide): meta-analysis

2018 ; N = 12741

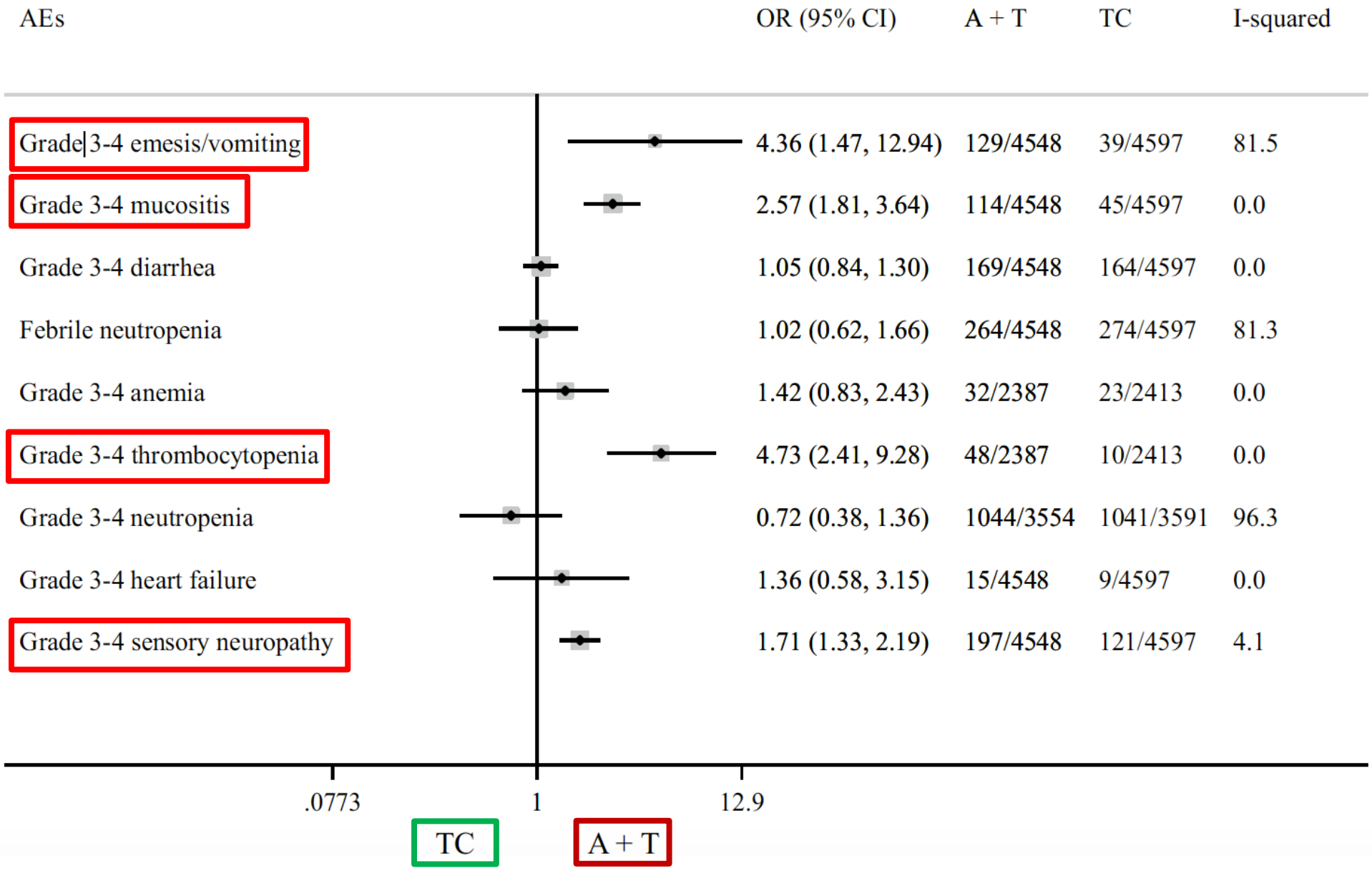




Population	Hazard Ratio TC versus A+T
DFS whole population	1,08 (0,96 – 1,20)
OS whole population	1,05 (0,90 – 1,22)
DFS ER positive	1,05 (0,86 – 1,27)
DFS ER negative	1,12 (0,93 – 1,34)
DFS pN1	1,06 (0,65 – 1,73)
DFS pN2	1,25 (0,82 – 1,90)
DFS premenopausal	0,78 (0,56 – 1,09)
DFS postmenopausal	1,16 (0,83 – 1,61)

BCRT 2018 Caparica et al

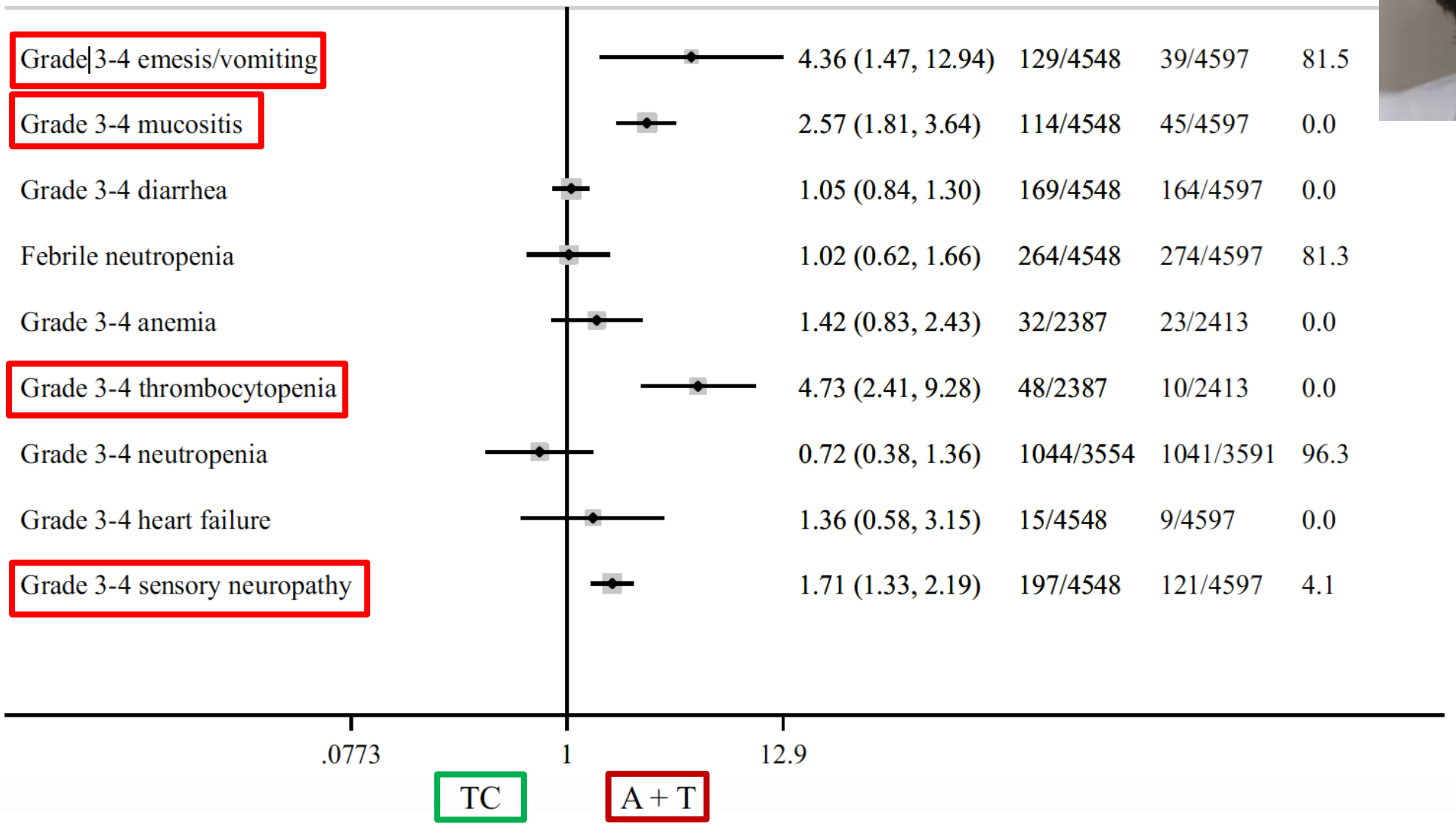
Toxicity of 6 x TC adjuvant versus Anthracycline + taxane



BCRT 2018 Caparica et al

Toxicity of 6 x TC adjuvant versus Anthracycline + taxane

AEs	OR (95% CI)	A + T	TC	I-squar
Grade 3-4 emesis/vomiting	4.36 (1.47, 12.94)	129/4548	39/4597	81.5
Grade 3-4 mucositis	2.57 (1.81, 3.64)	114/4548	45/4597	0.0
Grade 3-4 diarrhea	1.05 (0.84, 1.30)	169/4548	164/4597	0.0
Febrile neutropenia	1.02 (0.62, 1.66)	264/4548	274/4597	81.3
Grade 3-4 anemia	1.42 (0.83, 2.43)	32/2387	23/2413	0.0
Grade 3-4 thrombocytopenia	4.73 (2.41, 9.28)	48/2387	10/2413	0.0
Grade 3-4 neutropenia	0.72 (0.38, 1.36)	1044/3554	1041/3591	96.3
Grade 3-4 heart failure	1.36 (0.58, 3.15)	15/4548	9/4597	0.0
Grade 3-4 sensory neuropathy	1.71 (1.33, 2.19)	197/4548	121/4597	4.1



BCRT 2018 Caparica et al

Anthracyclines still needed in luminal early disease?

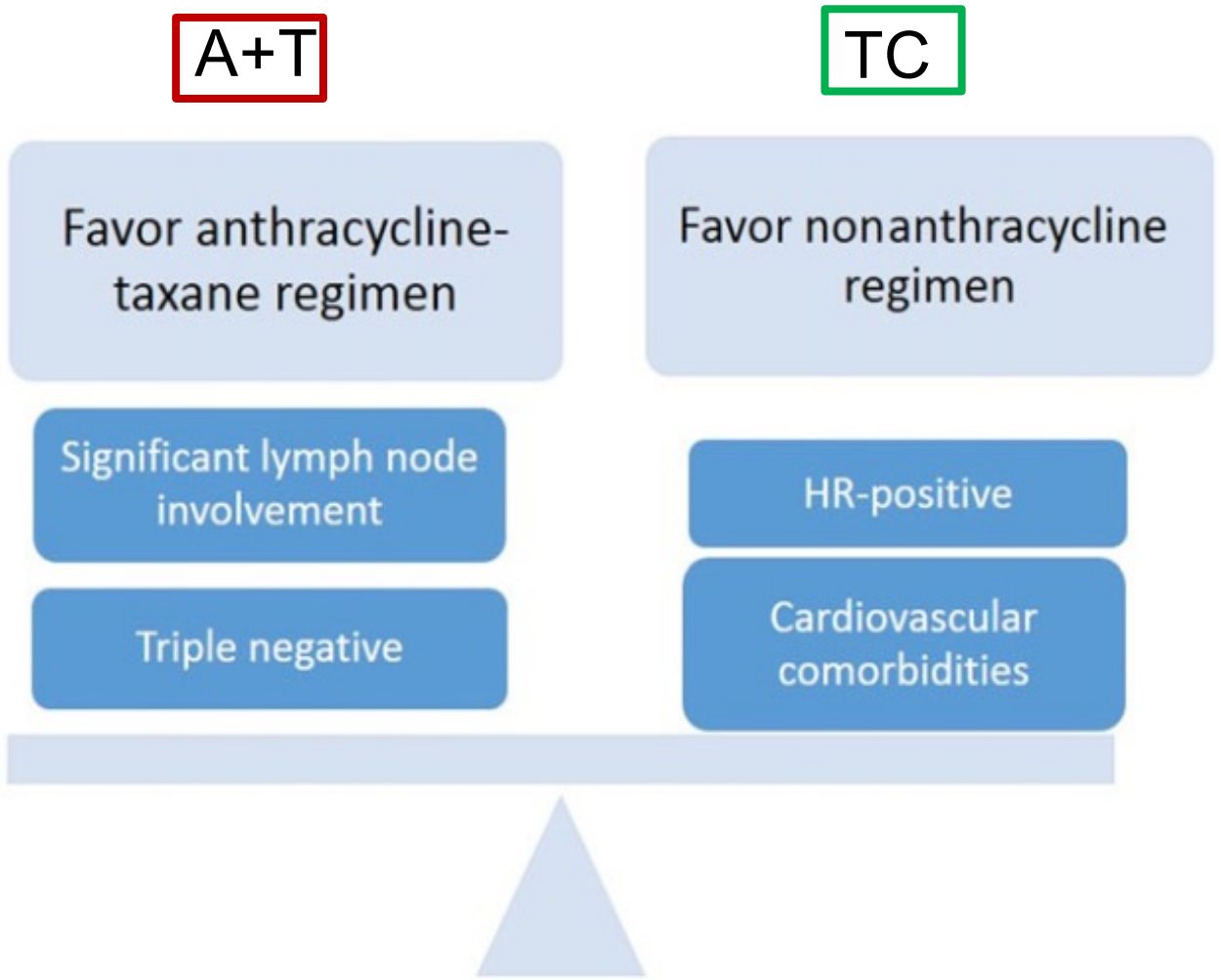


Figure 1. Factors influencing decisions regarding anthracycline use for adjuvant breast cancer therapy.
Abbreviation: HR, hormone receptor.

The oncologist 2018 Shah

6 x TC adjuvant: MASTER study 2021

HER2-

Upfront surgery

pT1-3N+ or pT2-3N0 high risk

- 6 x TC (docetaxel cyclophosphamide)
- 3 CEF -> 3 Docetaxel
- 4 EC_{q3w} -> 12 paclitaxel

Stratification for age, pT, pN, ER status

Outcome similar

No impact of ER status, pT, pN, …

TC vs EC-paclitaxel

* More rash and neuropathy
* Less diarrhea, nausea/vomiting, mucositis, cardiac gr III-IV (0,2% vs 1,1%), AML (0 vs 1)

ER+ 92%

Median 5,5y FUP

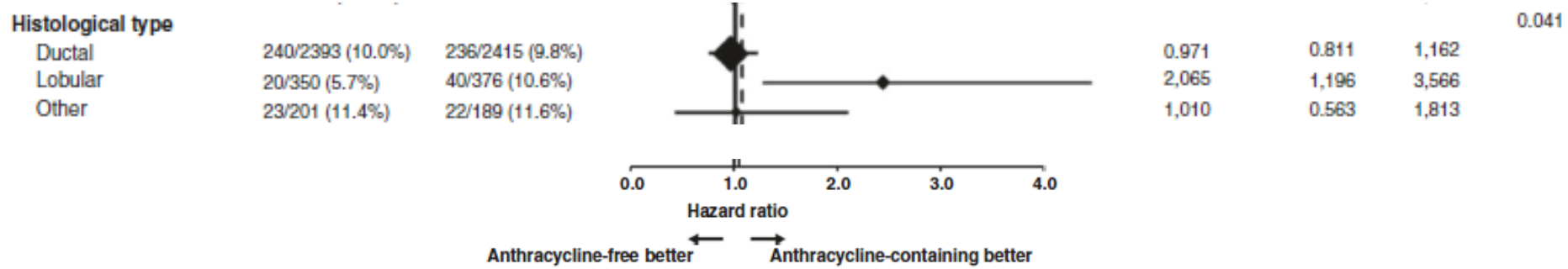
	Arms	Events	Cases	5-yr rate (%)	HR# (90% CI)	Log-rank P*
DFS	TC	72	524	85.0	1.05 (0.79–1.39)	0.771
	CEF-T	73	523	85.1	0.99 (0.75–1.30)	0.946
	EC-P	70	524	85.9	–	–
DDFS	TC	38	524	91.6	0.88 (0.61–1.28)	0.572
	CEF-T	39	523	92.4	0.83 (0.57–1.19)	0.391
	EC-P	43	524	91.4	–	–
OS	TC	21	524	96.5	0.96 (0.58–1.59)	0.893
	CEF-T	24	523	94.9	0.84 (0.51–1.37)	0.549
	EC-P	23	524	95.4	–	–

Lancet Regional Health 2021 Yu

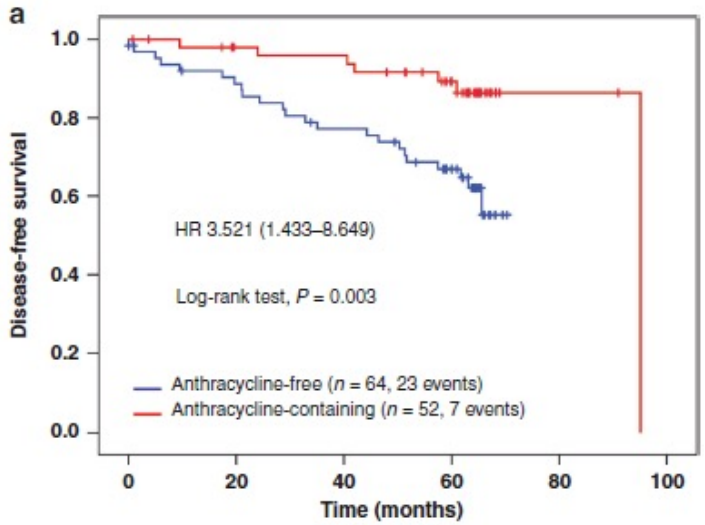
6 x TC adjuvant: Plan-B + SUCCESS C

5924 pts
ER+ 78%
5y FUP

Plan B:	**4 EC -> 4 Docetaxel**	**vs**	**6 TC**	
SUCCESS C:	**3 FEC -> 3 Docetaxel**	**vs**	**6 TC**	
5y-DFS	**90,0%**	**vs**	**89,3%**	(p 0,57)
5y-OS	**95,0%**	**vs**	**94,9%**	(p0,79)



DFS in **Lobular** pN2/3



BJC 2022 Di Gregorio

6 x TC adjuvant: Plan-B + SUCCESS C

Variable	Anthracycline-containing chemotherapy (FEC-Doc[a]/EC-Doc[b]; N = 2944)	Anthracycline-free chemotherapy (Doc-C[c]; N = 2980)	P value[d]
(A)			
Any adverse event	2245 (76.3%)	2089 (70.1%)	<0.001*
Anaemia	20 (0.7%)	21 (0.7%)	0.91
Leukopenia	1509 (51.3%)	1358 (45.6%)	<0.001*
Neutropenia	1187 (40.3%)	1101 (36.9%)	0.008
Nausea	88 (3.0%)	40 (1.3%)	<0.001*
Fatigue	131 (4.4%)	83 (2.8%)	0.001*
Vomitting	53 (1.8%)	18 (0.6%)	<0.001*
Stomatitis	57 (1.9%)	26 (0.9%)	<0.001*
Constipation	21 (0.7%)	12 (0.4%)	0.11
Diarrhoea	55 (1.9%)	63 (2.1%)	0.50
SGPT elevation	46 (1.6%)	39 (1.3%)	0.41
SGOT elevation	10 (0.3%)	6 (0.2%)	0.31
Pain	68 (2.3%)	45 (1.5%)	0.024
Infection	59 (2.0%)	78 (2.6%)	0.12
Neuropathy	45 (1.5%)	23 (0.8%)	0.006
Arthralgia	45 (1.5%)	29 (1.0%)	0.054
Febrile neutropenia	114 (3.9%)	145 (4.9%)	0.062

Toxicity Gr III-IV

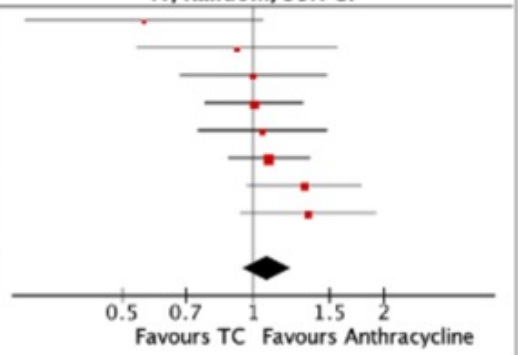
6 x TC adjuvant (docetaxel cyclophosphamide): meta-analysis

2022 ; N = 11902

Disease Free Survival (**DFS**)

Study or Subgroup	log[Hazard Ratio]	SE	TC Total	Anthracycline Total	Weight	Hazard Ratio IV, Random, 95% CI
Jones, 2009	-0.5798	0.3185	55	69	3.8%	0.56 [0.30, 1.05]
Mavroudis, 2016 (HORG)	-0.0844	0.2685	324	326	5.3%	0.92 [0.54, 1.56]
Blum, 2017 (NSABP B-49)	0	0.1968	921	898	9.4%	1.00 [0.68, 1.47]
Nitz, 2019 (PLAN B)	0.004	0.1314	1153	1128	18.7%	1.00 [0.78, 1.30]
Yu, 2021 (MASTER)	0.0488	0.173	524	524	11.8%	1.05 [0.75, 1.47]
de Gregorio, 2022 (SUCCESS C)	0.0825	0.1079	1827	1816	25.3%	1.09 [0.88, 1.34]
Blum, 2017 (USOR 06-090)	0.27	0.1533	644	642	14.6%	1.31 [0.97, 1.77]
Blum, 2017 (NSABP B-46-I/USOR 07132)	0.2927	0.1809	529	522	11.0%	1.34 [0.94, 1.91]
Total (95% CI)			5977	5925	100.0%	**1.07 [0.95, 1.22]**

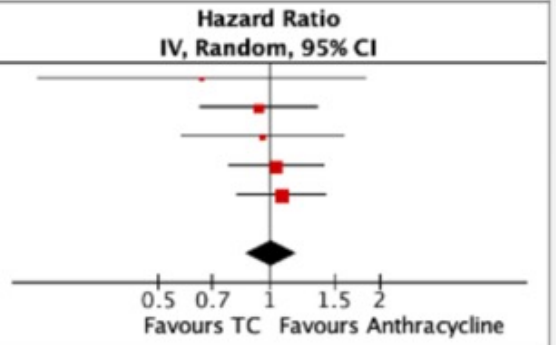
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.11$, df = 7 (P = 0.32); $I^2 = 14\%$
Test for overall effect: Z = 1.13 (P = 0.26)



Overal Survival (**OS**)

Study or Subgroup	log[Hazard Ratio]	SE	TC Total	Anthracycline Total	Weight	Hazard Ratio IV, Random, 95% CI
Mavroudis, 2016 (HORG)	-0.4227	0.5232	324	326	2.6%	0.66 [0.24, 1.83]
Nitz, 2019 (PLAN B)	-0.0651	0.1866	1153	1128	20.1%	0.94 [0.65, 1.35]
Yu, 2021 (MASTER)	-0.0408	0.2571	524	524	10.6%	0.96 [0.58, 1.59]
de Gregorio, 2022 (SUCCESS C)	0.044	0.1499	1827	1816	31.2%	1.04 [0.78, 1.40]
Blum, 2017 (ABC)	0.077	0.1405	2094	2062	35.5%	1.08 [0.82, 1.42]
Total (95% CI)			5922	5856	100.0%	**1.01 [0.86, 1.19]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.16$, df = 4 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 0.15 (P = 0.88)



No information on impact of ER status of N status

Neoadjuvant TC? (docetaxel cyclophosphamide)

- **Neoadjuvant** chemotherapy not so often used in luminal breast cancer

- Sometimes in **locally advanced** luminal breast cancer (stage III)

- Single arm trials with 6 TC in HER2- BC suggest relatively **low pCR rates** (7-17%), but majority were luminal BC, known to have a lower likelihood of achieving pCR.

2013 BCRT, Chen ; 2017 Breast cancer, Nakatsukasa

Anthracyclines still needed in luminal early disease?

A+T

TC

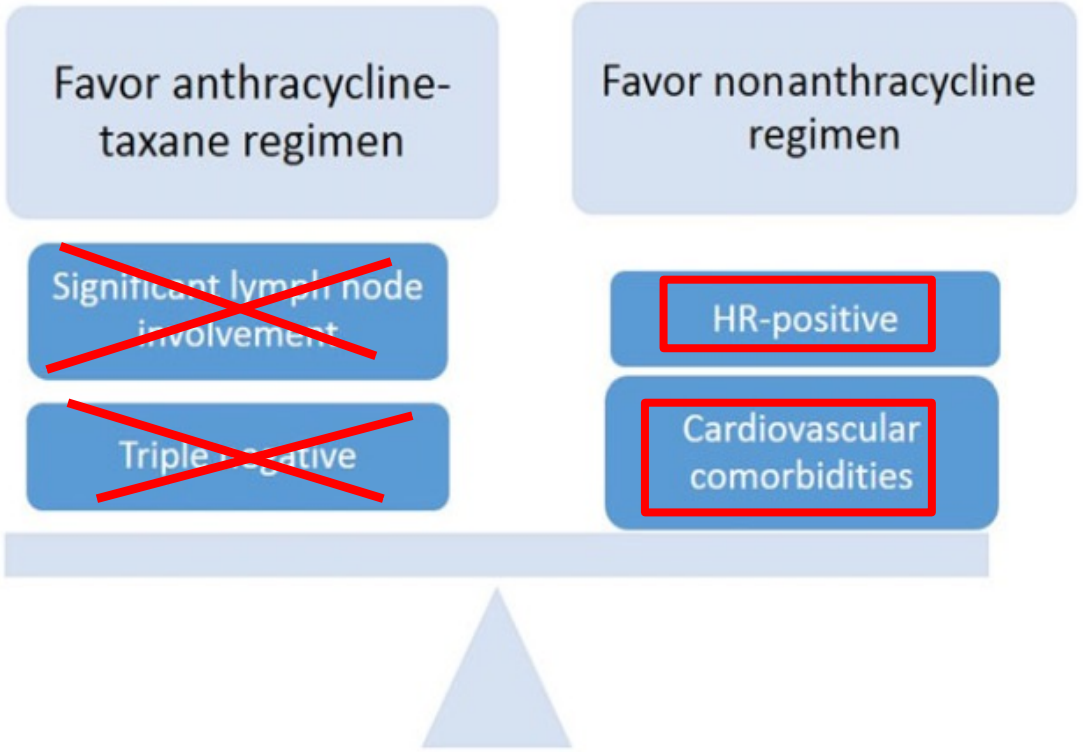


Figure 1. Factors influencing decisions regarding anthracycline use for adjuvant breast cancer therapy.
Abbreviation: HR, hormone receptor.

Controversies?

~~Neoadjuvant chemo?~~

~~Lobular and pN2-3?~~

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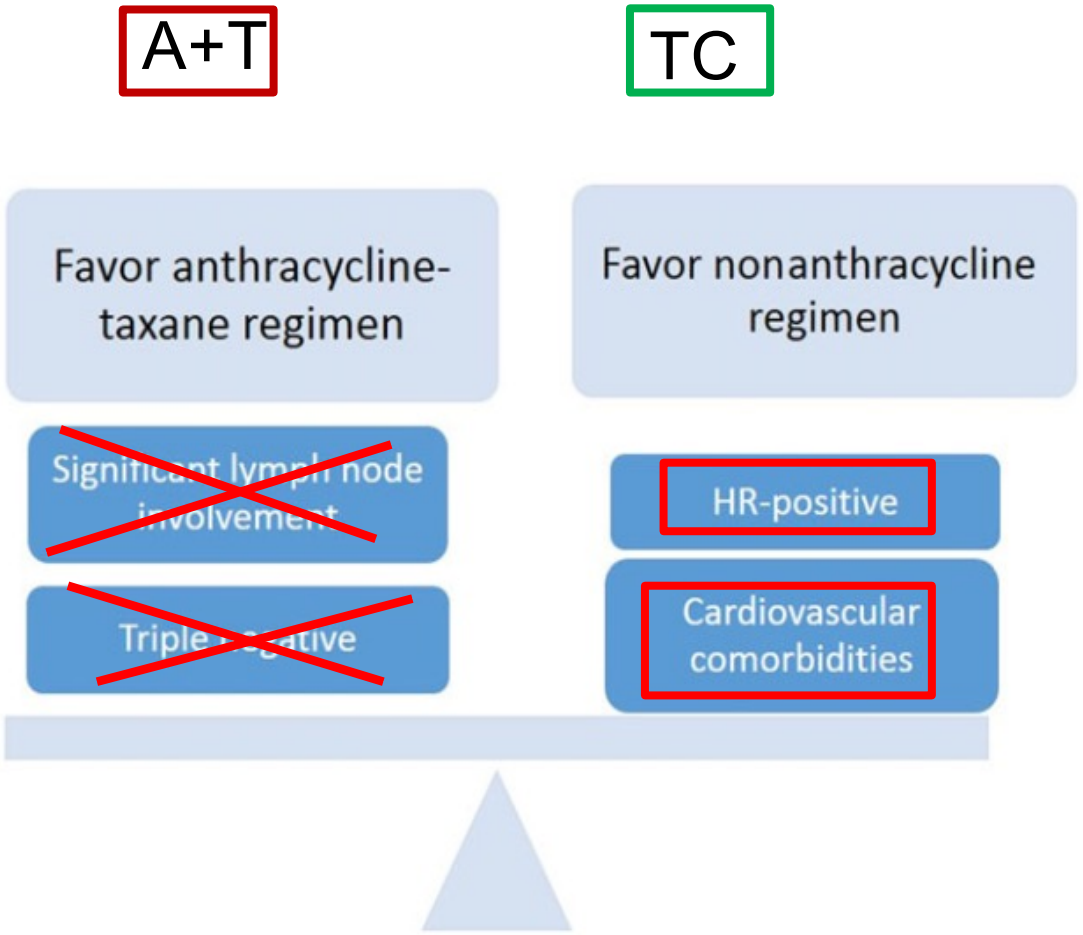
Anthracyclines still needed in luminal early disease?



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