What chemotherapy regimen do I use for high risk ER+/HER2- breast cancer?

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Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials

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

Summary

Background Anthracycline–taxane chemotherapy for early-stage breast cancer substantially improves survival compared with no chemotherapy. However, concerns about short-term and long-term side-effects of anthracyclines

Lancet 2023; 401: 1277–92

See Comment page 1243

***Lancet* 2023; 401: 1277-92**

Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials

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

Lancet 2019; 393: 1440–52

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Summary

Background Increasing the dose intensity of cytotoxic therapy by shortening the intervals between cycles, or by giving individual drugs sequentially at full dose rather than in lower-dose concurrent treatment schedules, might enhance efficacy.

***Lancet* 2019; 393: 1440-52**

2023: Taxane ± anthracycline

- **<u>Eligibility</u>: Any randomised trial that included comparisons of taxane ± anthracycline**

- **Trial designs varied:** concurrent/sequential, number of cycles, dose (per cycle and cumulative), doxorubicin/epirubicin, docetaxel/paclitaxel, other drugs in comparator arms eg carboplatin, capecitabine

- Median age 53 years (IQR 46 – 60)
- **53% node positive disease, 67% ER positive**
- Median follow up 5.4 years

Taxane + anthracycline vs docetaxel + cyclophosphamide

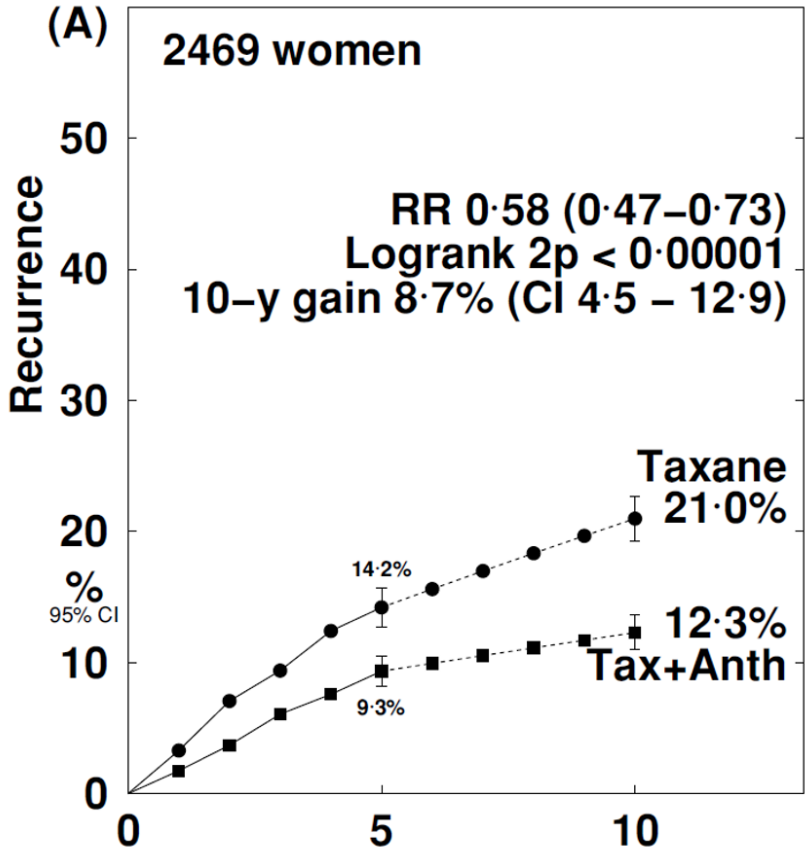
11/15 trials same comparator 6 x Docetaxel 75mg/m^2 + Cyclo 600mg/m^2 q3

(a) <u>Unconfounded</u> concurrent regimens: N = 2,469 in 3 trials	6 x Doxorubicin 50mg/m^2 + Docetaxel 75mg/m^2 + Cyclo 500mg/m^2 **<u>ONLY</u> difference:** addition of anthracycline in one arm (mostly doxorubicin 300mg/m^2 cumulative dose)
(b) <u>Confounded</u> sequential regimens: N = 11,386 in 8 trials	Usually 3-4 x epirubicin 90-100mg/m^2 and 3-4 docetaxel 75-100 mg/m^2 ,mostly q3 **<u>Differences</u>**: Anthracycline <u>substituted</u> for docetaxel Cumulative docetaxel ~ one third lower (300mg/m^2)

Taxane + anthracycline vs docetaxel + cyclophosphamide

Recurrence

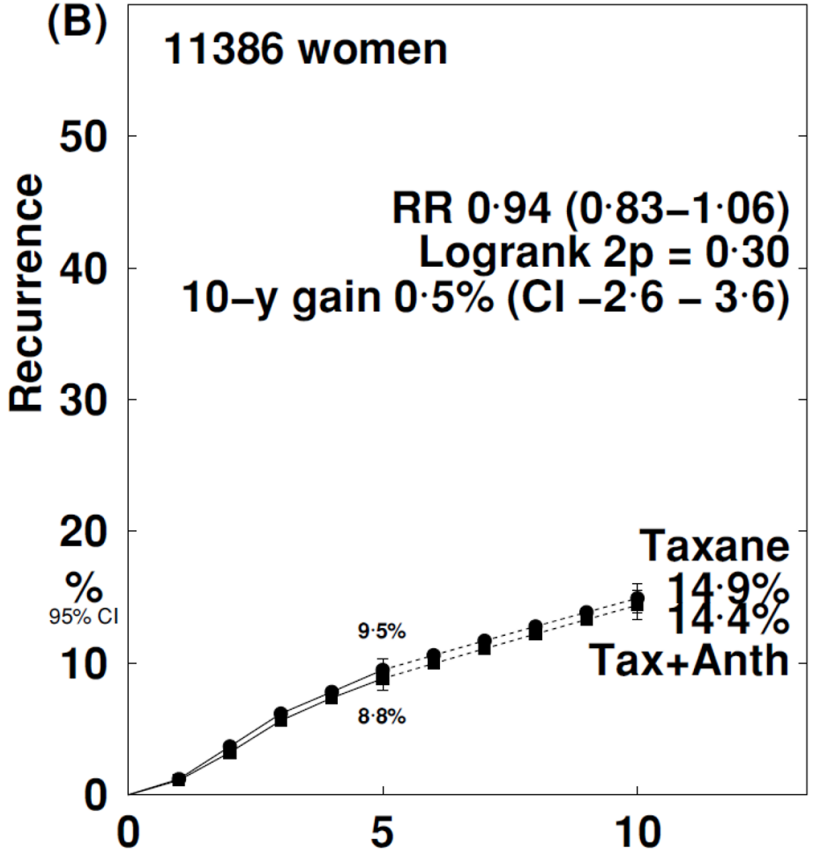
(A) Unconfounded (concurrent)



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tax+Anth	2·02 (106 / 5251)	0·66 (17 / 2580)	0·0(0/16)
Taxane	3·04 (161 / 5302)	1·63 (43 / 2633)	3·85 (1 / 26)
Rate ratio, from (O–E) / V	0·64 CI 0·49 – 0·82 −27·4 / 60·3	0·42 CI 0·25 – 0·71 −12·6 / 14·7	0·19 CI 0·00 – 10·32 −0·4 / 0·2

(B) Confounded (sequential)



Recurrence rates (% / year) and logrank analyses

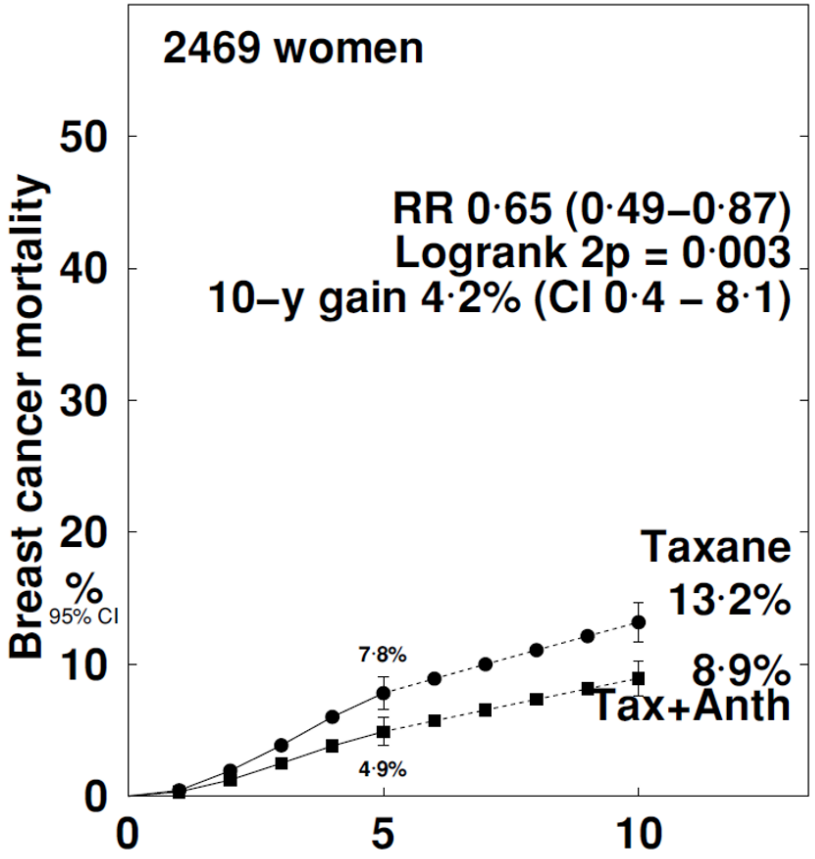
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tax+Anth	1·88 (455 / 24172)	1·28 (55 / 4285)	0·0(0/20)
Taxane	1·96 (473 / 24103)	1·21 (51 / 4198)	0·0(0/18)
Rate ratio, from (O–E) / V	0·93 CI 0·81 – 1·06 −16·8 / 219·1	1·02 CI 0·69 – 1·50 0·4 / 25·2	

Plots smoothed after year 5

Taxane + anthracycline vs docetaxel + cyclophosphamide

Breast Cancer Mortality

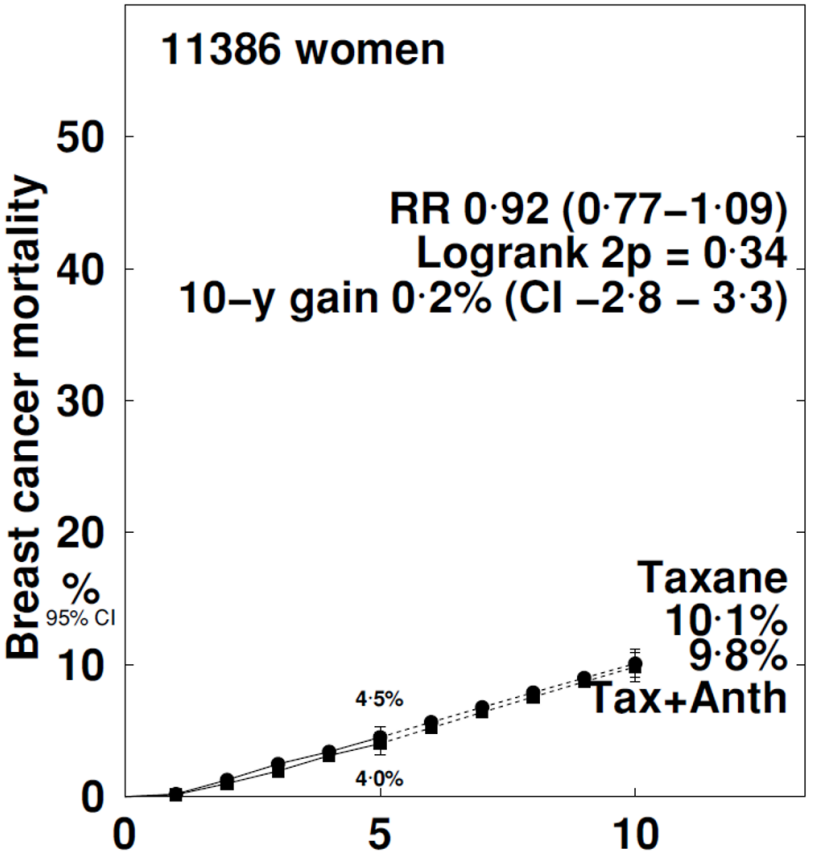
(A) Unconfounded (concurrent)



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tax+Anth	1·02 CI 0·75 – 1·29	0·86 CI 0·51 – 1·21	0·0
Taxane	1·55 CI 1·22 – 1·88	1·21 CI 0·80 – 1·61	0·0
Rate ratio, from (O–E) / V	0·62 CI 0·44 – 0·88 –15·6 / 32·9	0·72 CI 0·42 – 1·23 –4·4 / 13·6	

(B) Confounded (sequential)



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tax+Anth	0·82 CI 0·71 – 0·94	1·30 CI 0·97 – 1·63	0·0
Taxane	0·88 CI 0·76 – 1·00	1·15 CI 0·84 – 1·47	0·0
Rate ratio, from (O–E) / V	0·89 CI 0·73 – 1·08 –11·8 / 100·7	1·04 CI 0·71 – 1·53 1·0 / 25·9	

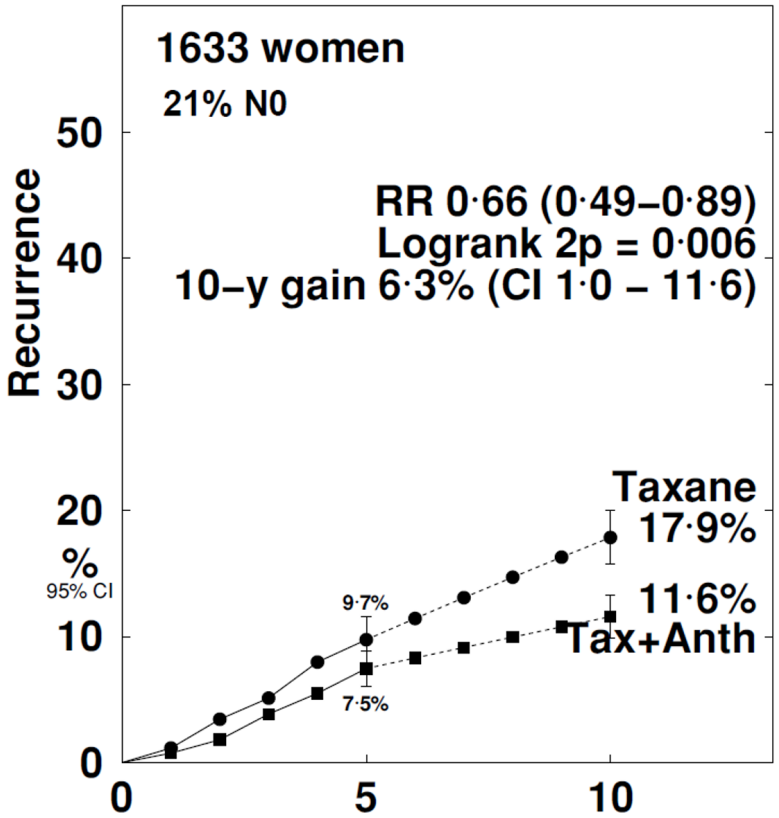
Plots smoothed after year 5

Taxane ± anthracycline

Sub-group analysis for Group (a)- Unconfounded (Concurrent)

Recurrence

ER-positive

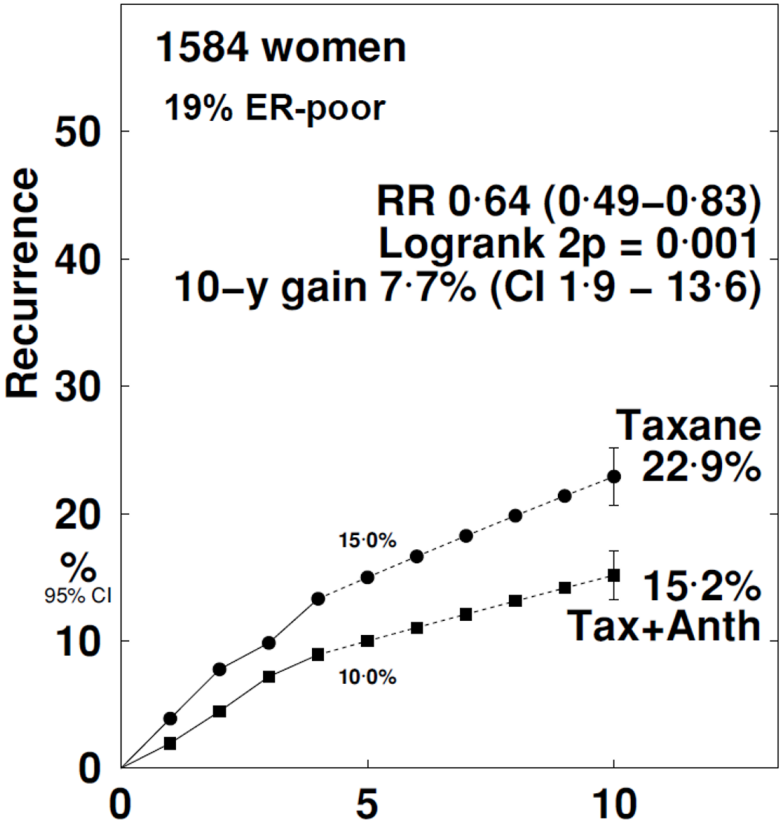


Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tax+Anth	1·51 (54 / 3587)	0·89 (16 / 1796)	0·0(0/10)
Taxane	2·04 (74 / 3626)	1·88 (35 / 1859)	6·25 (1 / 16)
Rate ratio, from (O–E) / V	0·75 CI 0·53 – 1·06 –9·0 / 31·0	0·50 CI 0·28 – 0·86 –8·8 / 12·5	0·14 CI 0·00 – 7·01 –0·5 / 0·2

Plots smoothed after year 5

Node positive



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tax+Anth	2·34 (80 / 3426)	0·85 (14 / 1652)	0·0(0/10)
Taxane	3·40 (113 / 3325)	1·71 (28 / 1639)	7·69 (1 / 13)
Rate ratio, from (O–E) / V	0·67 CI 0·50 – 0·91 –17·0 / 43·1	0·53 CI 0·28 – 0·97 –6·6 / 10·3	0·19 CI 0·00 – 10·32 –0·4 / 0·2

Choice of Taxane?

- Three weekly Docetaxel (75-100mg/m^2) superior to three weekly paclitaxel (175mg/m^2)
- Weekly paclitaxel (80mg/m^2) superior to three weekly paclitaxel (175mg/m^2)
- No large randomised trials comparing 12 weeks weekly paclitaxel versus 4 cycles of 2-weekly paclitaxel
- No large trials comparing 6 cycles docetaxel/cyclophosphamide with 4 cycles docetaxel/cyclophosphamide

Toxicity / QOL

- Limited data available for meta-analysis, better evaluated from well conducted randomized trials

In this meta-analysis (note short median follow up):

- No significant difference in deaths from cardiovascular disease or other primary cancers

- Similar incidence of new, non-breast primary cancers

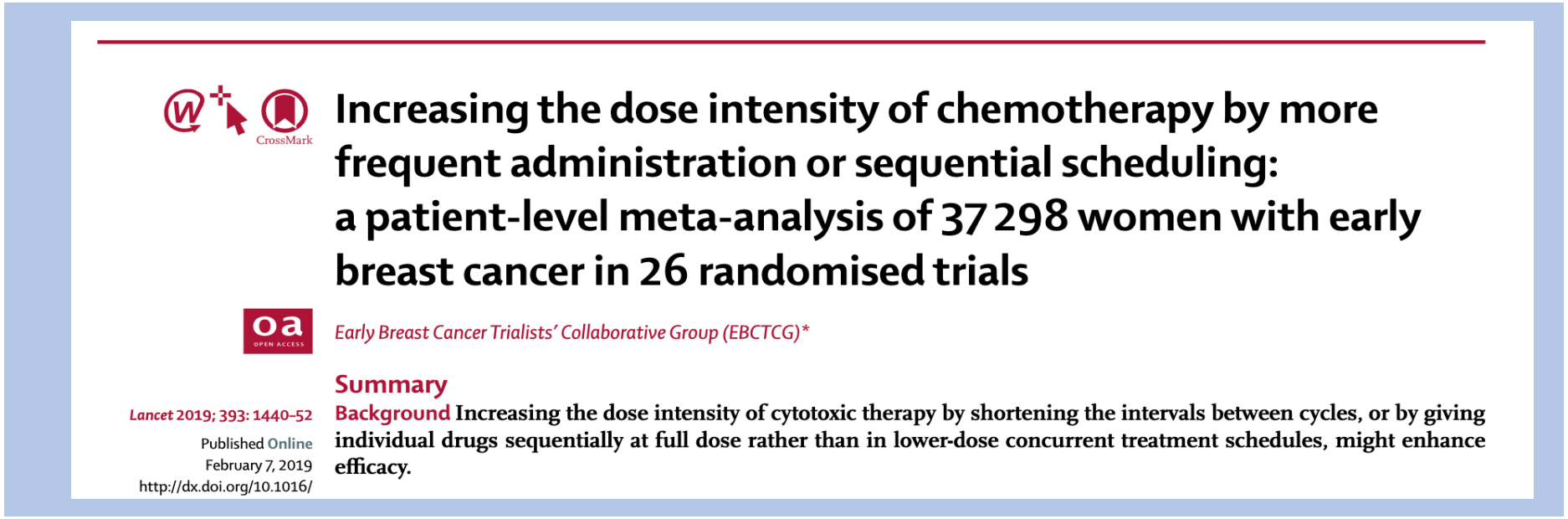
- **Incidence of AML: 12 (0.18%) vs 2 (0.03%) ie ~ one extra per 700 women treated with anthracycline**

2023 meta-analysis

- Anthracycline + taxane better than taxane without anthracycline but only in concurrent schedule i.e. when anthracycline added to taxane rather than substituted for taxane

- Cumulative dose of chemotherapy important

- Meta-analysis did not include comparisons of anthracycline and taxane regimens



Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials

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Summary

Background Increasing the dose intensity of cytotoxic therapy by shortening the intervals between cycles, or by giving individual drugs sequentially at full dose rather than in lower-dose concurrent treatment schedules, might enhance efficacy.

Three ways to increase dose intensity*

1. Use higher doses of drugs in each cycle
2. Give drugs sequentially rather than concurrently
3. Reduce the interval between treatment cycles

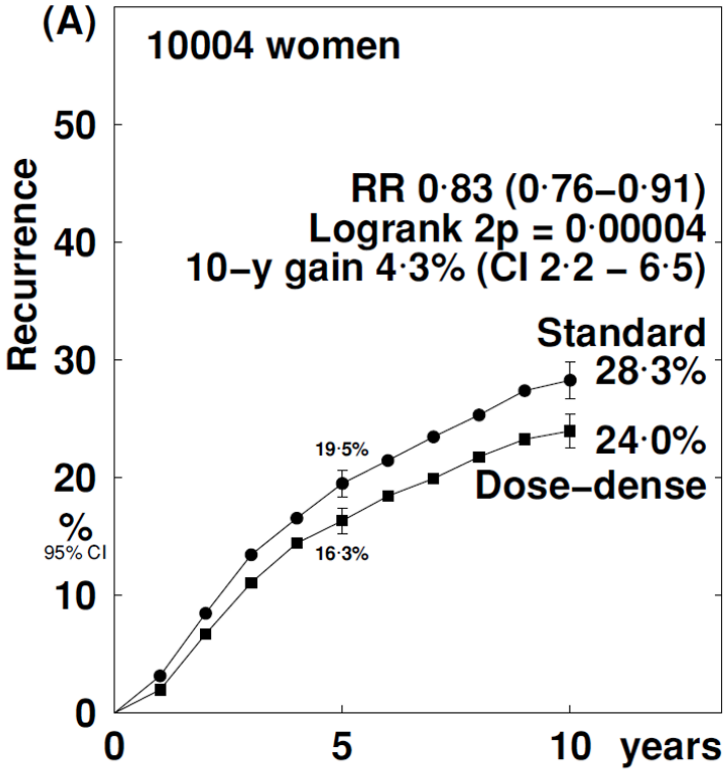
* Norton L. Sem Oncol 1997

Comparing taxane + anthracycline regimens

Dose Density – SAME drugs and doses in each arm i.e. unconfounded

Comparison: 2 weekly versus 3 weekly

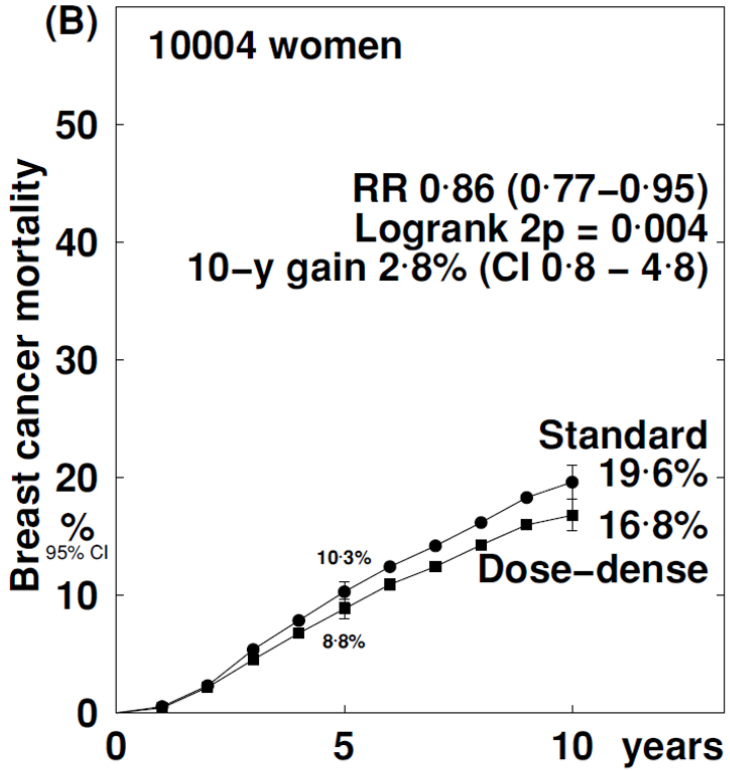
Recurrence



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Dose–dense	3·57 (780 / 21834)	2·14 (228 / 10630)	0·92 (22 / 2403)
Standard	4·36 (940 / 21578)	2·41 (249 / 10343)	0·92 (22 / 2396)
Rate ratio, from	0·82 CI 0·73 – 0·91	0·87 CI 0·69 – 1·04	1·10 CI 0·44 – 1·76
(O–E) / V	–77·8 / 385·6	–15·6 / 109·8	0·9 / 9·7

Breast Cancer Mortality

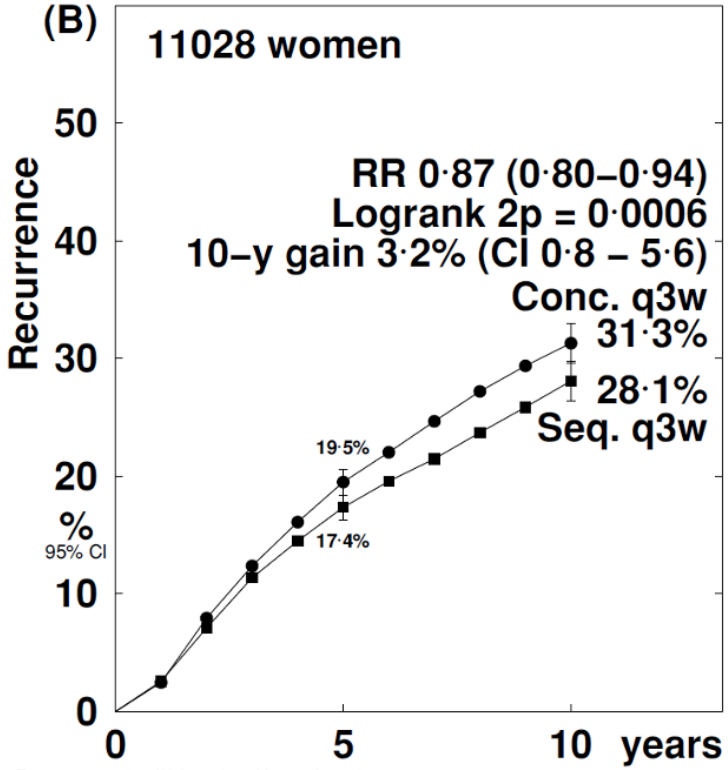


Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Dose–dense	1·80 CI 1·63 – 1·98	2·00 CI 1·75 – 2·26	1·25 CI 0·82 – 1·67
Standard	2·15 CI 1·96 – 2·34	2·21 CI 1·94 – 2·48	1·57 CI 1·09 – 2·04
Rate ratio, from	0·85 CI 0·73 – 0·98	0·87 CI 0·70 – 1·05	0·80 CI 0·38 – 1·22
(O–E) / V	–33·5 / 208·4	–15·2 / 113·8	–3·9 / 17·5

Tax + Anth: sequential versus concurrent
3 weekly regimens (both arms)

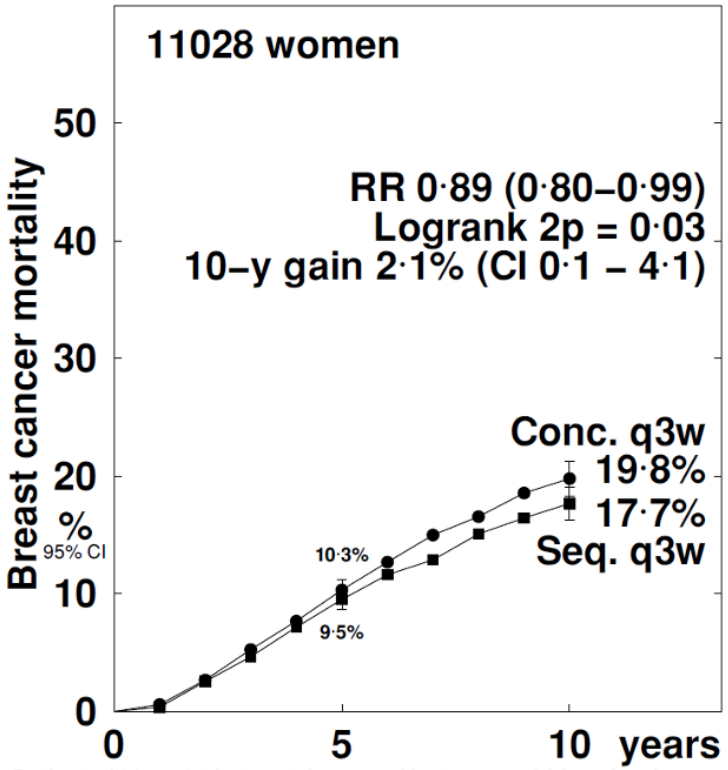
Recurrence



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Seq. q3w	3·83 (917 / 23937)	2·72 (244 / 8956)	2·58 (16 / 621)
Conc. q3w	4·30 (1025 / 23819)	3·24 (281 / 8684)	3·75 (22 / 587)
Rate ratio, from (O–E) / V	0·88 CI 0·79 – 0·97 −57·7 / 451·5	0·84 CI 0·68 – 1·00 −21·4 / 125·6	0·62 CI 0·10 – 1·14 −4·3 / 9·0

Breast Cancer Mortality

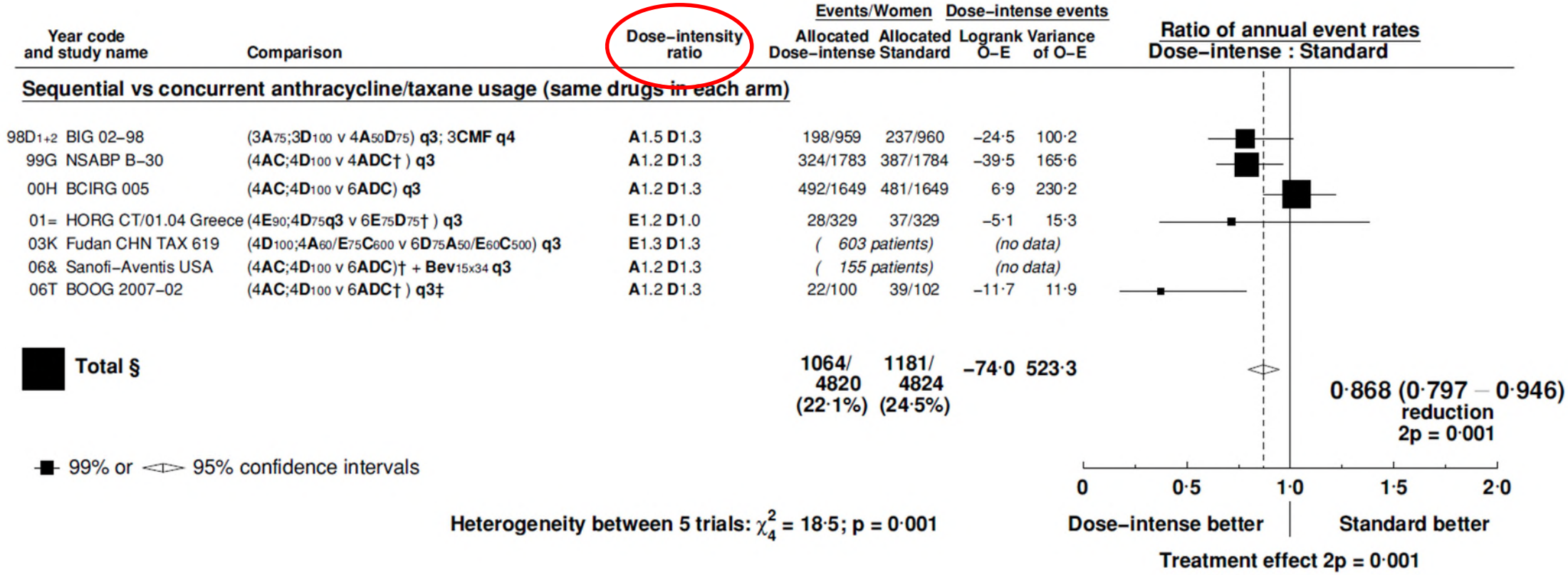


Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Seq. q3w	1·98 CI 1·80 – 2·15	1·96 CI 1·69 – 2·24	2·21 CI 1·13 – 3·29
Conc. q3w	2·12 CI 1·94 – 2·30	2·37 CI 2·07 – 2·67	2·37 CI 1·25 – 3·50
Rate ratio, from (O–E) / V	0·92 CI 0·80 – 1·04 −21·5 / 243·9	0·83 CI 0·66 – 1·01 −18·8 / 103·6	0·91 CI 0·25 – 1·58 −0·7 / 7·9

Tax + Anth: sequential versus concurrent
3 weekly regimens (both arms)

Recurrence



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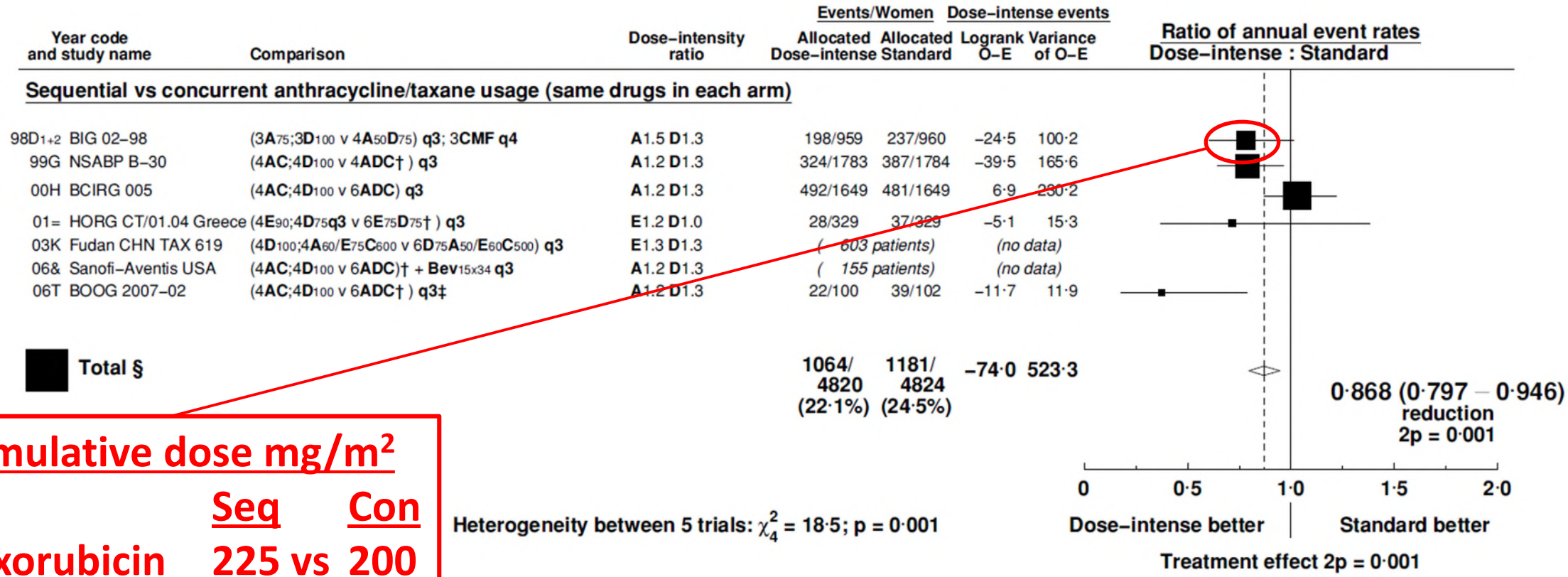
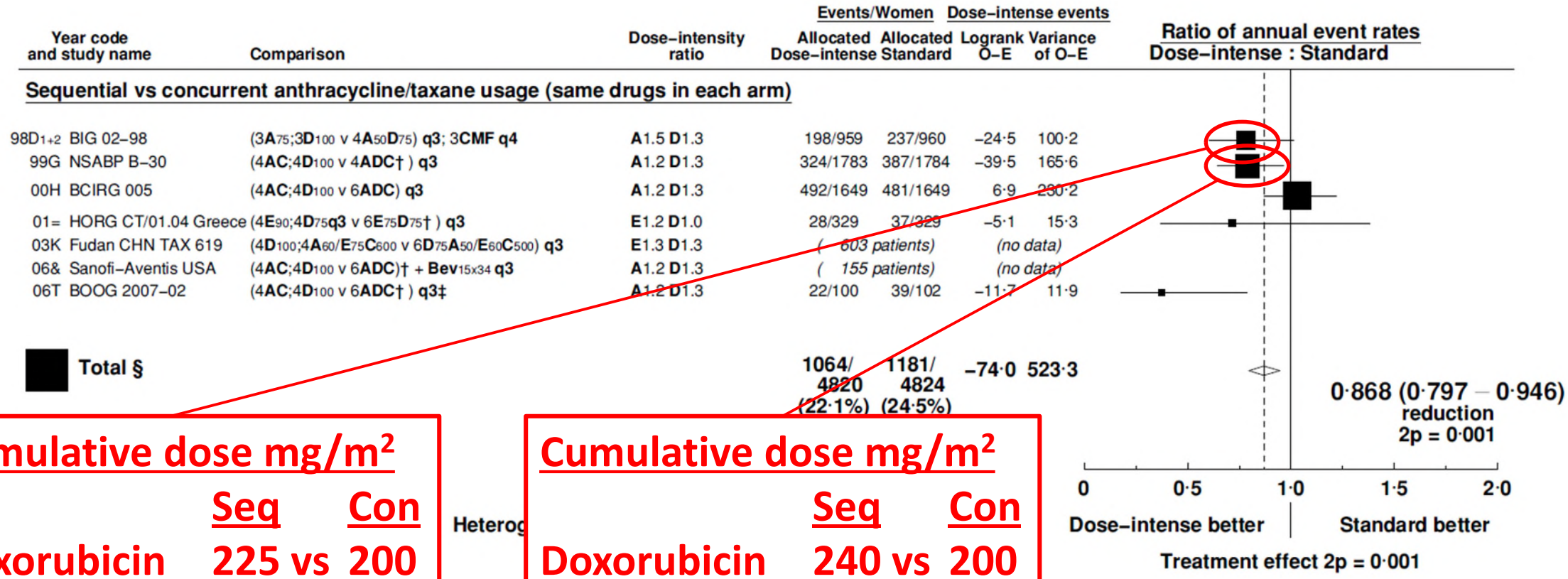


Cumulative dose mg/m²

	Seq	Con
Doxorubicin	225 vs	200
Docetaxel	300 vs	300

Tax + Anth: sequential versus concurrent
3 weekly regimens (both arms)

Recurrence



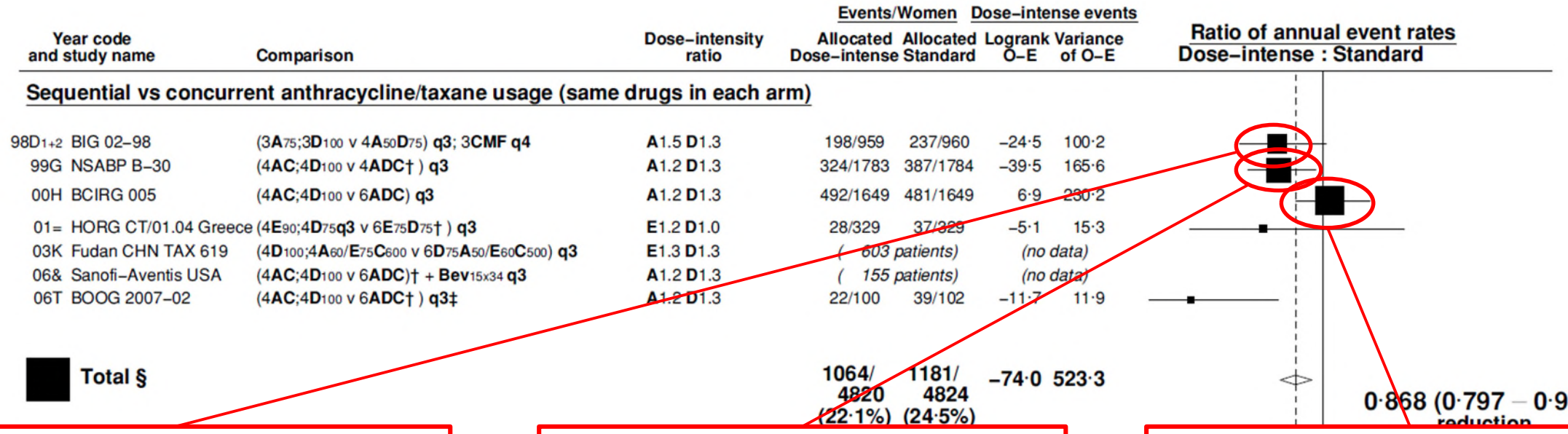
Cumulative dose mg/m²	Seq	Con
Doxorubicin	225 vs	200
Docetaxel	300 vs	300

Heterog

Cumulative dose mg/m²	Seq	Con
Doxorubicin	240 vs	200
Docetaxel	400 vs	300

Tax + Anth: sequential versus concurrent
3 weekly regimens (both arms)

Recurrence



Cumulative dose mg/m²

	Seq	Con
Doxorubicin	225 vs	200
Docetaxel	300 vs	300

Cumulative dose mg/m²

	Seq	Con
Doxorubicin	240 vs	200
Docetaxel	400 vs	300

Cumulative dose mg/m²

	Seq	Con
Doxorubicin	240 vs	300
Docetaxel	400 vs	450

What chemotherapy regimen do I use for high risk ER+/HER2- breast cancer?

- **If no significant contra-indications:**
    - Dose Dense 2-weekly EC90 x 4 cycles

  Then
    - Dose Dense Paclitaxel (80mg/m^2) weekly x 12 weeks (*or* 2-weekly x 4 cycles?)
- ***Consider side effects – cardiac, AML, neuropathy***
- ***BUT:***
    - Individual considerations, day unit capacity
    - Substantial proportional benefit from chemotherapy versus no chemotherapy
    - Moderate additional benefits with more dose intense regimens
    - **Consider alongside benefits from endocrine therapy, CDK4/6 inhibitors**
    - **Will better molecular markers improve our recommendations?**

Acknowledgements

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Trialists who shared their data

Secretariat who processed and analysed data

>100,000 participants in >100 trials