Healthcare Improvement Scotland | Evidence
Advice, guidance and intelligence

Rapid Response

Evidence synthesis: Dose-dense adjuvant chemotherapy for patients with high-risk early breast cancer

June 2023

HIS evidence conclusions

For women undergoing chemotherapy for early breast cancer, systematic reviews consistently found that dose-dense schedules improved recurrence rates and survival when compared with standard schedules. Combining the seven trials most relevant to this rapid response, dose-dense schedules reduced 10-year risk of recurrence by around 15%, representing an absolute risk reduction in the region of 4%.

Based on incomplete data, the reductions in recurrence and breast cancer mortality appeared to apply regardless of tumour and disease characteristics such as nodal status, tumour grade and hormone receptor status.

Dose-dense chemotherapy had similar profiles of serious adverse events and treatment adherence to standard chemotherapy schedules.

Patient-reported quality of life was reduced when dose intensity was increased compared with standard chemotherapy during the treatment period, but was similar in the two groups after treatment was completed.

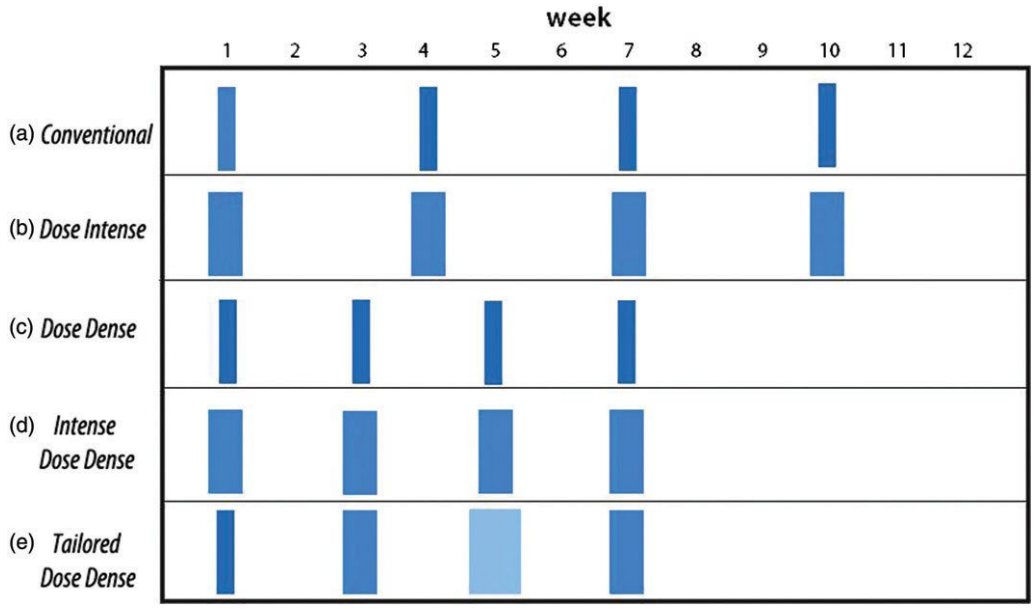
Applicability of the findings of the secondary evidence to current practice is limited in that studies were conducted before the routine use of targeted therapies and contemporary radiotherapy protocols.

What were we asked to look at?

As part of a process of developing recommendations, we were asked by the Scottish Cancer Network to examine the evidence on dose-dense chemotherapy for patients with high-risk early breast cancer. The parameters of the research question as developed by the topic referrers are set out in *Appendix 1*.

Dose-dense chemotherapy is among a range of methods of increasing chemotherapy dose intensity, some of which are illustrated in *Figure 1* (reproduced from an editorial review by Matikas et al, 2017).[1]

Figure 1: Chemotherapy dose intensities



Evolving strategies for adjuvant chemotherapy in breast cancer. In the conventional schedule (a) chemotherapy is administered every 21 days. In the dose-intense schedule (b) escalated doses are administered every 21 days. In the dose-dense schedule (c) conventional doses are administered every 14 days. In the intense dose-dense schedule (d) escalated doses are administered every 14 days. Finally, in the tailored-dose schedule (e) chemotherapy doses are determined by the haematologic nadirs and are administered every 14 days.

Overview of the evidence

Systematic reviews

Six relevant systematic reviews with meta-analyses were identified (see *Appendix 2* for literature search strategies). These were assessed for methodological quality using a SIGN checklist and the overall findings extracted. *Appendix 3* illustrates the overlap of the trials that were included in each of the analyses. In general, the findings of each analysis were similar regardless of methodological quality and the manner in which dose-dense chemotherapy was defined. Three analyses were of low methodological quality and are not considered in this rapid response. The two analyses that were of acceptable methodological quality had different approaches. The Zhou (2018) meta-analysis focused on 'pure' dose-dense chemotherapy where the only difference between trial arms was in the interval

between administration of medications, and where doses and number of cycles remained the same as with conventional chemotherapy.[2] The Lambertini (2017) analysis used individual participant data (IPD) from two Italian trials to examine the effect of dose-dense chemotherapy in pre-menopausal women.[3] Only one analysis was of high methodological quality and this IPD meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was selected as the main secondary data source for this rapid response.[4]

EBCTCG meta-analysis

Effectiveness

The EBCTCG meta-analysis compared the benefits and risks of increased dose-intensity and standard-schedule chemotherapy in patients receiving chemotherapy for early breast cancer.[4] Most of the trials were conducted in the adjuvant context but trials in the neo-adjuvant setting were also included. Trials in the analysis were grouped according to how dose intensification was achieved. Trials of dose fractionation, for example giving drugs once weekly at approximately a third of the dose used in a 3-weekly regimen, were excluded (see *Appendix 4* for this aspect of the research question). One grouping of trials (grouping A) examined the impact of reducing dose interval to increase dose density. There were three subsets within grouping A:

- A1 – shorter interval between cycles with the same drugs, doses and number of cycles in each arm
- A2 – shorter interval between cycles plus additional drugs in the control arm
- A3 – shorter interval between cycles plus additional treatment in the dose-dense arm

In group A1, the average weekly dose in the dose-dense arm was 1.5 times that in the standard-schedule arm (two-weekly versus three-weekly chemotherapy cycles). To indicate the level of risk of the trial populations *Table 1* sets out the characteristics of patients in group A1.

Table 1: Characteristics of trial participants in analysis A1 (shorter interval between cycles with the same drugs, doses and number of cycles in each arm)

	Number of study participants with data	Proportion with status categorised
All A1 trial participants	10,004	NA
Age (years)		100%
<45	2,534 (25.3%)	
45-54	3,615 (36.1%)	
55-69	3,715 (37.1%)	
70+	137 (1.4%)	
HER2 status		70%
HER2 positive	1,452 (20.8%)	
HER2 negative	5,528 (79.2%)	
Tumour grade		75%
Well differentiated	369 (4.9%)	
Moderately differentiated	3,254 (43.1%)	
Poorly differentiated	3,926 (52.0%)	
Nodal status		97%
N0	2,517 (26.0%)	
N1-3	4,686 (48.5%)	
N4+	2,465 (25.5%)	
ER/PR status		100%
ER- PR any	2,881 (28.8%)	
ER? PR any	566 (5.7%)	
ER+ PR+	4,582 (45.8%)	
ER+ PR-	1,022 (10.2%)	
ER+ PR?	953 (9.5%)	

ER oestrogen receptor status
PR progesterone receptor status
HER2 human epidermal growth factor receptor 2

Dose-dense chemotherapy consistently reduced the rate ratio of recurrence and breast cancer mortality by approximately 15% compared with standard schedules, with no statistically significant impact on death without recurrence (*see Table 2*). The absolute reduction in recurrence at 10 years was 4.3% and the absolute reduction in breast cancer mortality at 10 years was 2.8%. There was significant statistical heterogeneity across the trials that likely reflects the different treatments and schedules.

In exploratory subgroup analyses (on group A1 trials) of relevance to the current research question, the meta-analysis authors note that the following categorisations did not statistically significantly affect the proportional reductions in recurrence:

- tumour grade (few patients had low grade cancers)
- nodal status (where known, 75% were N+)
- hormone receptor status (where known)
    - The five year risk of recurrence for women with oestrogen receptor negative (ER-) status (n=2,881) was 23.4% in the dose-dense group compared with 27.0% in the standard chemotherapy group (RR=0.82, 95% CI 0.71 to 0.95, p=0.008). The corresponding data for women with oestrogen receptor positive (ER+) status (n=6,557) was 13.1% compared with 16% (RR 0.83, 95% CI 0.75 to 0.93, p=0.001). Relative effects were similar across the two risk groups.

Across all 15 dose-dense chemotherapy trials included in the meta-analysis (groups A1–A3), six involved combinations of anthracycline and taxane, and incorporating six or more dose-dense cycles. Patient data was available from five of the six trials. (One of the trials examined tailored dose-dense chemotherapy.) No significant statistical heterogeneity in intervention effects was reported across the five studies. The pooled RR for 10-year recurrence was 0.78 (95% CI 0.71 to 0.87), p=0.00001. The pooled RR for 10-year breast cancer mortality was 0.76 (95% CI 0.67 to 0.86), p=0.00002. As this is a subgroup analysis findings should be viewed with caution.

Adverse events and toxicity

Toxicity data (grade 3 or above) at trial level for the meta-analysis group A1 is displayed in *Table 3*. Few trials reported statistical significance of toxicity differences between groups. No data was provided on hospitalisations for adverse events.

There were only minor differences in toxicities between dose-dense and standard chemotherapies. In four trials there were higher rates of anaemia and stomatitis in the dose-dense chemotherapy arm compared with control. Diarrhoea and vomiting symptoms at grade 3 or above (variously categorised across trials) were also experienced by a higher proportion of study participants receiving dose-dense chemotherapy in two and four trials respectively. The meta-analysis authors note that the use of colony-stimulating growth factors (G-CSF) to reduce the risk of neutropenic events in the dose-dense chemotherapy arm complicates comparisons of haematological toxicity between treatments, with leukopenia recorded statistically significantly less frequently with dose-dense chemotherapy treatment in two trials.

Table 2: Parameters and findings of the three dose-dense meta-analyses (RR=rate ratio, first event)

Trial grouping	Number of trials / number of trials contributing data (number of trials with neo-adjuvant context)	Number of patients with data obtained / number missing (%)	Recurrence (95% CI)	Breast cancer mortality (95% CI)	All-cause mortality (95% CI)	Death without recurrence (95% CI)
A1 – shorter intervals between cycles and same chemotherapy drugs, same doses and same number of cycles in both arms	8/7 (2)	10,004/128 (1.3%)	RR=0.83 (0.76 to 0.91) p<0.0001	RR=0.86 (0.77 to 0.96) p=0.005	RR=0.88 (0.80 to 0.96) p=0.007	RR=0.96 (0.76 to 1.20) p>0.1 NS
			10 year risk of recurrence 24.0% vs 28.3%	10 year risk of breast cancer mortality 16.8% vs 19.6%	10 year risk of all-cause mortality 21.1% vs 23.3%	10 year risk of death without recurrence 4.8% vs 5.4%
A2 – shorter intervals between cycles and additional drugs (eg fluorouracil) in the control arm	5/3 (2)	3,372/1,067 (24.0%)	RR=0.89 (0.76 to 1.03) p=0.13 NS	RR=0.95 (0.79 to 1.15) p>0.1 NS	RR=0.92 (0.77 to 1.10) p>0.1 NS	RR=0.73 (0.45 to 1.18) p>0.1 NS
A3 – shorter intervals between cycles and additional treatment in the dose-dense arm	2/2 (1)	2,136/0 (0%)	RR= 0.79 (0.67 to 0.92) p=0.004	RR=0.76 (0.62 to 0.93) p=0.007	RR=0.80 (0.66 to 0.97) p=0.02	RR 1.39 (0.73 to 2.63) p>0.1 NS
Groups A1–A3 combined	15/12 (5)	15,512/1,195 (7.2%)	RR=0.84 (0.78 to 0.90) p<0.0001	RR=0.86 (0.79 to 0.93) p=0.0004		

Table 3: Toxicity data for trials in group A1 – data is percentage of participants unless otherwise stated

Trials	Venturini 2005 GONO MIG1		Baldini 2003 Pisa / Genoa		Citron 2003 CALGB 9741		Wulfing 2004 Bayreuth		Jones 2009		Del Mastro 2015 GIM2α		Wu 2008 CAMsα		Cameron 2017 TACT2	
	DD	C	DD	C	DD	C	DD	C	DD	C	DD	C	DD	C	DD	C
Death from toxicity	NR	NR	NR	NR	0.20	0.62	0	0	0	0	0	0	0	0	NR	NR
Anaemia	3	<2	4.4	0	<1	<1	NR	NR	0	0	1*	0*	0	0	2.3≠	1.2≠
Leukopenia	3	9	5.4	5.4	<1	1	NR	NR	0	5	15*	44*	16*	55*	10.5≠	10.9≠
Thrombocytopenia	1	<1	<1	<1	<1	<1	NR	NR	0	0	1≠	<1≠	0	0	0.9≠	1.1≠
Febrile neutropenia	<1	<1	NR	NR	2	3	NR	NR	NR	NR	NR	NR	NR	NR	8.6≠	7.7≠
Stomatitis	3	1	1.4	0	1	1	NR	NR	0	0	1≠	<1≠	0	0	4.1≠	3.6≠
Diarrhoea	<1	<1	NR	NR	3	1	NR	NR	0	5	<1≠	<1≠	0	0	7.1≠	5.8≠
Vomiting	12	11	7.4	10.8	4	3	NR	NR	0	0	3≠	2≠	16≠	9.8≠	3.5≠	4.2≠
Asthenia	1	<1	NR	NR	NR	NR	NR	NR	9	0	3≠	2≠	NR	NR	11.1≠	11.1≠
Transaminase	1	<1	NR	NR	NR	NR	NR	NR	NR	NR	2*	<1*	4≠	0≠	0.3≠	0.6≠
Sensory neuropathy	NR	NR	NR	NR	4	4	NR	NR	NR	NR	3≠	2≠	0	0	0.3≠	0.5≠

Grey highlighting indicates where the proportion of participants in the dose-dense arm reporting the adverse event was greater than in the control group.
DD = dose-dense arm, C = control arm
NR = not reported
* reported as statistically significant difference
≠ reported as not statistically significant difference
α For GIM2 Italy and CAMS values were for neutropenia as leukopenia not reported separately

Cardiac complications

The meta-analysis authors report no consistent difference in cardiotoxicity between dose-dense and standard-schedule chemotherapy across all trials in the meta-analysis.

Adherence

Across group A1 trials, in five trials where data were available, there was no statistically significant difference in the proportion of patients not completing all cycles of chemotherapy: 12.3% vs 12.8%, RR=0.96, 95% CI 0.84 to 1.09, p>0.1.

Quality of life

The meta-analysis authors note that, from five trials of dose intensification, two of which were from group A1 and thus relevant to this rapid response, quality of life was worse during treatment with dose-intense therapy but was similar in both treatment arms when measured after the end of the treatment phase.

Treatment-induced amenorrhoea

The EBCTCG meta-analysis did not report this outcome. Another IPD meta-analysis of two trials examined the impact of dose-dense chemotherapy on treatment-induced amenorrhoea in premenopausal women with breast cancer at high risk of recurrence (n=1,549).[3] There was no evidence that dose-dense chemotherapy resulted in an increased risk of treatment-induced amenorrhoea (odds ratio (OR) 1.00, 95% CI 0.80 to 1.25, p=0.989). The two trials had different definitions of treatment-induced amenorrhoea, one requiring an absence of menses for at least 3 months during or after chemotherapy and one measuring absence of menses for at least 12 months after treatment, so the analysis findings should be viewed with caution.

Applicability of the EBCTCG meta-analysis

There are several limitations around applicability of the EBCTCG meta-analysis to current practice in Scotland:

- trial participants were treated between 1985 and 2011 so, in the majority of trials, targeted therapies, eg for HER2 positive or ER+ patients, were not routinely used
- few women (<2%) included in the relevant trials were aged over 70
- the use of postoperative radiotherapy may now be more frequent than in older trials, and
- patient assessment in the included studies would not have included tumour profiling tests used in early breast cancer, such as Endopredict®, Mammaprint®, Oncotype DX® and Prosigna®. The effectiveness of these tests is currently being evaluated by the Scottish Health Technologies Group (SHTG).

Randomised controlled trials

A supplementary literature search was conducted to identify any randomised controlled trials (RCTs) that have been published since March 2018, which was the cut-off date in the EBCTCG meta-analysis (see *Appendix 5* for a summary of the trials found in the search).

Two studies provided follow up data from trials within the EBCTCG meta-analysis,[5, 6] one provided additional data on quality of life[7] and one reported on neutropenic complications.[8]

Two exploratory analyses, with statistically inconclusive findings, examined the effect of dose-dense chemotherapy in trial sub-populations of patients with HER2+ tumours receiving trastuzumab.[9, 10]

No RCTs were identified which were likely to change the conclusions of the meta-analysis.

References

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Appendix 1: Research question

For patients with high risk early breast cancer is dose-dense chemotherapy superior to standard chemotherapy regimens in the adjuvant setting?

Patient group	Patients with high risk early breast cancer requiring adjuvant chemotherapy. Risk level denoted by where chemotherapy provides >5% additional 10 year survival benefit according to PREDICT or using similar criteria. High risk may be defined in trials as: • Nottingham prognostic index (NPI) – combines tumour size, grade and nodal status • node positive, or • node negative AND grade 3 tumour or T3/4 size.
Intervention **(treatment more frequent than every three weeks)**	Dose-dense chemotherapy (reducing dose intervals and/or increasing number of cycles)* anthracycline (epirubicin or doxorubicin) + cyclophosphamide (EC) 3 x 14 day cycles followed by taxane (docetaxel or paclitaxel) 3 x 14 day cycles (total 6 cycles) or anthracycline (epirubicin or doxorubicin) + cyclophosphamide (EC) 4 x 14 day cycles followed by taxane (docetaxel or paclitaxel) 4 x 14 day cycles (total 8 cycles) or paclitaxel 12 x 1 week cycles
Comparison **(treatment every three weeks)**	Standard dose intervals eg anthracycline (epirubicin or doxorubicin) + cyclophosphamide (EC) 3 or 4 x 21 day cycles followed by taxane (docetaxel or paclitaxel) 3 or 4 x 21 day cycle.
Outcomes	Overall survival Recurrence-free survival Invasive breast cancer-free survival Time to recurrence Non-breast-cancer mortality Total dose received (incorporating dose reductions/stopping early) Adverse events Early acute adverse events (G3/4 toxicities) Hospital admission and length of stay Quality of life

*UK practice is to use sequential anthracycline/taxane therefore the impact of dose intensification gained through moving from concurrent to sequential therapies is not relevant to the NHSS context

Appendix 2: Literature search strategies

Database: Ovid MEDLINE(R) ALL <1946 to March 30, 2023>
Search Strategy:
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1 exp breast neoplasms/ (338472)
2 (breast$ adj5 (neoplas$ or carcinom$ or cancer$ or tumor$ or tumour$)).tw. (395465)
3 1 or 2 (465151)
4 epirubicin.tw. (6060)
5 ellence.tw. (19)
6 Anthracyclines/ (4732)
7 doxorubicin.tw. (52414)
8 adriamycin.tw. (16425)
9 docetaxel.tw. (17660)
10 taxotere.tw. (1216)
11 paclitaxel.tw. (35066)
12 taxol.tw. (7936)
13 Taxoids/ (13745)
14 cyclophosphamide.tw. (53252)
15 cytoxan.tw. (749)
16 fluorouracil.tw. (40995)
17 adrucil.tw. (8)
18 or/4-17 (200453)
19 (dose adj3 (intens$ or dens$ or frequenc$ or concurrent or sequential)).tw. (15431)
20 (cycle adj2 (frequenc$ or number$ or interval$)).tw. (2642)
21 or/19-20 (18058)
22 3 and 18 and 21 (1016)
23 limit 22 to (english language and yr="1995 -Current") (854)

Embase
Database: Embase <1974 to 2023 March 30>
Search Strategy:
---
1 breast tumor/ (93777)
2 (breast$ adj5 (neoplas$ or carcinom$ or cancer$ or tumor$ or tumour$)).tw. (574862)
3 or/1-2 (603519)
4 epirubicin/ (32350)
5 epirubicin.tw. (9102)
6 ellence.tw. (158)
7 doxorubicin/ (217587)
8 doxorubicin.tw. (73243)
9 adriamycin.tw. (28185)
10 anthracycline/ (26827)
11 taxoid/ (2712)
12 docetaxel/ (71562)
13 docetaxel.tw. (32715)
14 taxotere.tw. (4626)

15 paclitaxel/ (130590)
16 taxol.tw. (15124)
17 paclitaxel.tw. (58775)
18 cyclophosphamide/ (244444)
19 cyclophosphamide.tw. (87079)
20 cytoxan.tw. (4845)
21 fluorouracil/ (156234)
22 fluorouracil.tw. (53211)
23 adrucil.tw. (158)
24 or/4-23 (645802)
25 (dose adj3 (intens$ or dens$ or frequenc$ or concurrent or sequential)).tw. (27008)
26 (cycle adj2 (frequenc$ or number$ or interval$)).tw. (3671)
27 or/25-26 (30634)
28 3 and 24 and 27 (2103)
29 limit 28 to (english language and yr="1995 -Current") (1856)

Cochrane

#1 MeSH descriptor: [Breast Neoplasms] explode all trees (17634)
#2 breast? near/5 (neoplas? or carcinom? or cancer? or tumor? or tumour?) (43526)
#3 #1 or #2 (44463)
#4 epirubicin (3464)
#5 ellence (10)
#6 doxorubicin (8632)
#7 adriamycin (1943)
#8 docetaxel (8208)
#9 paclitaxel (12173)
#10 taxotere (533)
#11 taxol (570)
#12 cyclophosphamide (13457)
#13 cytoxan (206)
#14 fluorouracil (11600)
#15 adrucil (5)
#16 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 (42524)
#17 dose near/3 (intens? or dens? or frequenc? or concurrent or sequential) (4379)
#18 cycle near/2 (frequenc? or number? or interval?) (490)
#19 #17 or #18 (4844)
#20 #3 and #16 and #19 (412)

Appendix 3: Systematic reviews and meta-analyses

Included trials (grey=studies included in each review)	Yoshinami (2020)[11]	EBCTCG (2019)[4] IPD (comparison A1)	Goldvaser (2018)[12]	Zhou (2018)[2]	Lambertini (2017)[3] IPD (pre-menopausal)	Petrelli (2015)[13]
Systematic review quality	**Low**	**High**	**Low**	**Acceptable**	**Acceptable**	**Low**
Del Mastro (2015) *GIM2 Italy*						
Venturini(2005)/Giraudi (2006) *GONO MIG1 Italy*						
Citron (2003)/Hudis (2005) *CALGB 9741*						
Baldini (2003) *Pisa/Genoa**						
Cameron (2017) *TACT2*						
Wulfing (2004) *Bayreuth**						
Wu (2008) *CAMs Beijing*						
Linden (2007)						
Burnell (2010)						
Moebus (2010)						
Gogas (2012)						
Swain (2013)						
Results from the meta-analyses (95% CI)						
Overall survival	RR=0.76 (0.64 to 0.90)		HR=0.86 (0.77 to 0.96)	HR=0.86 (0.73 to 1.02)	HR=0.71 (0.54 to 0.95)	HR=0.86 (0.79 to 0.93)

	p=0.001		p=0.008	p=0.08 (NS)	p=0.021	p=0.0001
Disease-free survival	RR=0.83 (0.75 to 0.92) p=0.0003		HR=0.85 (0.77 to 0.93) p<0.001	HR=0.83 (0.75 to 0.91) p=0.0001		HR=0.84 (0.77 to 0.91) p<0.0001
10 year risk of recurrence		RR=0.83 (0.76 to 0.91) p<0.0001				
Breast cancer mortality		RR=0.86 (0.77 to 0.96) p=0.0054				
All-cause mortality		RR=0.88 (0.80 to 0.97) p=0.007				

* = includes neo-adjuvant setting
IPD = individual participant data meta-analysis; NS = not statistically significant; RR = relative risk; HR = hazard ratio; CI = confidence interval
A1 = trials with shorter interval between cycles (same drugs, doses and number of cycles in each arm)

Appendix 4: Paclitaxel dose fractionation

The 2019 EBCTCG analysis on increasing dose intensity excluded trials classified as dose fractionation. A 2023 IPD meta-analysis from the same group examined anthracycline-containing and taxane-containing chemotherapy.[14]

In an analysis of data from patients in four out of five identified trials (n=6,745) comparing paclitaxel chemotherapy delivered in smaller compared with larger fractions (similar cumulative dose) there were fewer breast cancer recurrences (ratio of annual recurrence rates=0.86, 95% CI, 0.78 to 0.96; p=0.0064), but not breast cancer deaths (ratio of annual death rates=0.90, 95% CI 0.79 to 1.02; p=0.10), with paclitaxel administered once a week compared with less frequent paclitaxel treatment.

The authors noted that 'The greatest difference was seen in the ECOG EST1199 comparison of paclitaxel 80 mg/m² administered once a week versus the less dose-intense 175 mg/m² administered once every 3 weeks. In the SWOG S0221 trial little difference was seen when the same paclitaxel 80 mg/m² once a week was compared with paclitaxel 175 mg/m² administered once every 2 weeks; the groups had similar dose intensities.'

Appendix 5: Randomised controlled trials

Citation	Description of trial	Comment
Blondeaux E, Lambertini M, Michelotti A, Conte B, Benasso M, Dellepiane C, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: 15-year results of the Phase 3 Mammella InterGruppo (MIG)-1 study. Br J Cancer. 2020;122(11):1611-7.	Long term follow up of trial included in the meta-analysis: Venturini M, Del Mastro L, Aitini E, Baldini E, Caroti C, Contu A, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: results from a randomized trial. J Natl Cancer Inst. 2005;97(23):1724-33.	Unlikely to change conclusions of EBCTCG meta-analysis.
Brandberg Y, Johansson H, Hellstrom M, Gnant M, Mobus V, Greil R, et al. Long-term (up to 16 months) health-related quality of life after adjuvant tailored dose-dense chemotherapy vs. standard three-weekly chemotherapy in women with high-risk early breast cancer. Breast Cancer Res Treat. 2020;181(1):87-96.	Quality of life information from the PANTHER trial included in the meta-analysis: Foukakis T, Von Minckwitz G, Bengtsson NO, Brandberg Y, Wallberg B, Fornander T, et al. Effect of tailored dose-dense chemotherapy vs standard 3-weekly adjuvant chemotherapy on recurrence-free survival among women with high-risk early breast cancer: a randomized clinical trial. JAMA. 2016;316(18):1888-96.	Unlikely to change conclusions of EBCTCG meta-analysis.
Del Mastro L, Poggio F, Blondeaux E, De Placido S, Giuliano M, Forestieri V, et al. Fluorouracil and dose-dense adjuvant chemotherapy in patients with early-stage breast cancer (GIM2): end-of-study results from a randomised, phase 3 trial. Lancet Oncol. 2022;23(12):1571-82.	Long term follow up of GIM2 trial included in the meta-analysis: Del Mastro L, De Placido S, Bruzzi P, De Laurentiis M, Boni C, Cavazzini G, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment	Unlikely to change conclusions of EBCTCG meta-analysis.

	of patients with early-stage breast cancer: an open-label, 2× 2 factorial, randomised phase 3 trial. Lancet. 2015;385(9980):1863-72.	
Lambertini M, Poggio F, Bruzzone M, Conte B, Bighin C, de Azambuja E, et al. Dose-dense adjuvant chemotherapy in HER2-positive early breast cancer patients before and after the introduction of trastuzumab: exploratory analysis of the GIM2 trial. Int J Cancer. 2020;147(1):160-9.	Exploratory subgroup analysis in HER2+ patients receiving trastuzumab.	Exploratory subgroup analysis. Concluded that "…no apparent absolute and relative differences in DFS and OS could be observed between the dose-dense and standard-interval schedules among patients with HER2-positive patients who received trastuzumab." This is an exploratory post hoc analysis – findings did not reach statistical significance – small patient numbers. (DFS: HR, 0.99; 95% CI 0.52–1.89; OS: HR, 0.95; 95% CI 0.37–2.41). No exploration of potential differences in treatment effect between HER2-positive patients with hormone receptor-positive or negative disease.
Papakonstantinou A, Matikas A, Bengtsson NO, Malmström P, Hedayati E, Steger G, et al. Efficacy and safety of tailored and dose-dense adjuvant chemotherapy and trastuzumab for resected HER2-positive breast cancer: results from the phase 3 PANTHER trial. Cancer. 2020;126(6):1175-82.	Pre-specified subgroup analysis of trial included in the meta-analysis: Foukakis T, von Minckwitz G, Bengtsson NO, Brandberg Y, Wallberg B, Fornander T, et al. Effect of tailored dose-dense chemotherapy vs standard 3-weekly adjuvant chemotherapy on recurrence-	Exploratory subgroup analysis. Concluded that "The combination of DD chemotherapy and trastuzumab decreased the relative risk for relapse by 32% in comparison with standard treatment, a statistically nonsignificant difference. Its

	free survival among women with high-risk early breast cancer: a randomized clinical trial. JAMA. 2016;316(18):1888-96.	efficacy and safety merit further evaluation as part of both escalation and de-escalation strategies." In the intention-to-treat population, there were 16 BC relapse events among patients treated with tDD EC/D and trastuzumab and 26 events among patients treated with FEC/D and trastuzumab (HR, 0.68; 95% CI, 0.37-1.27; p=0 .231)
Papakonstantinou A, Hedayati E, Hellstrom M, Johansson H, Gnant M, Steger G, et al. Neutropenic complications in the PANTHER phase III study of adjuvant tailored dose-dense chemotherapy in early breast cancer. Acta Oncol. 2020;59(1):75-81.	Additional adverse events information from the PANTHER trial: Foukakis T, von Minckwitz G, Bengtsson NO, Brandberg Y, Wallberg B, Fornander T, et al. Effect of tailored dose-dense chemotherapy vs standard 3-weekly adjuvant chemotherapy on recurrence-free survival among women with high-risk early breast cancer: a randomized clinical trial. JAMA. 2016;316(18):1888-96.	Unlikely to change conclusions of EBCTCG meta-analysis.

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