La chemioterapia dose-dense: quale ruolo nella pratica clinica?

Lucia Del Mastro

SS Sviluppo Terapie Innovative

Verona 21 marzo 2014

IRCCS Azienda Ospedaliera Universitaria San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

Dose-Dense Chemotherapy in Nonmetastatic Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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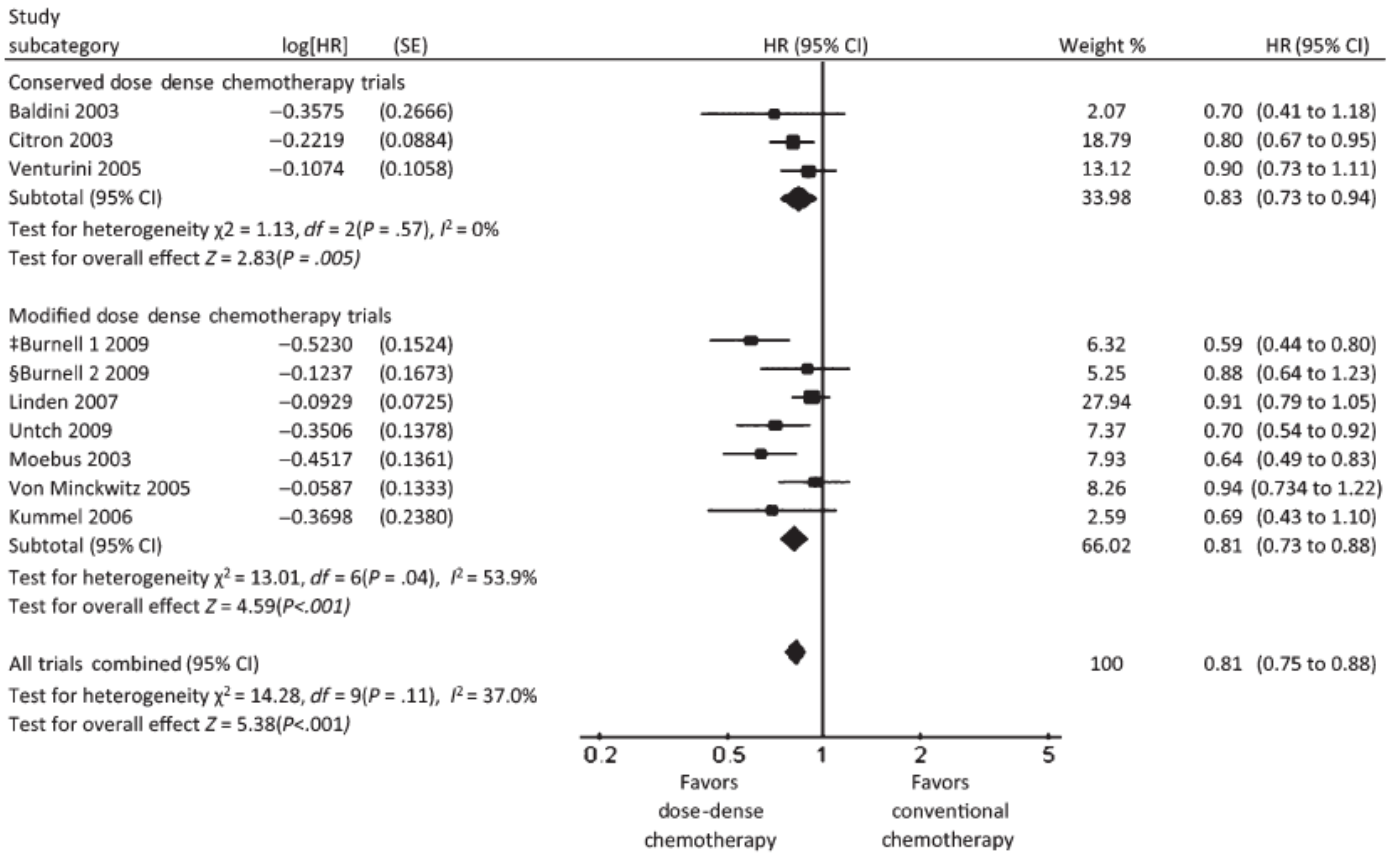
DFS



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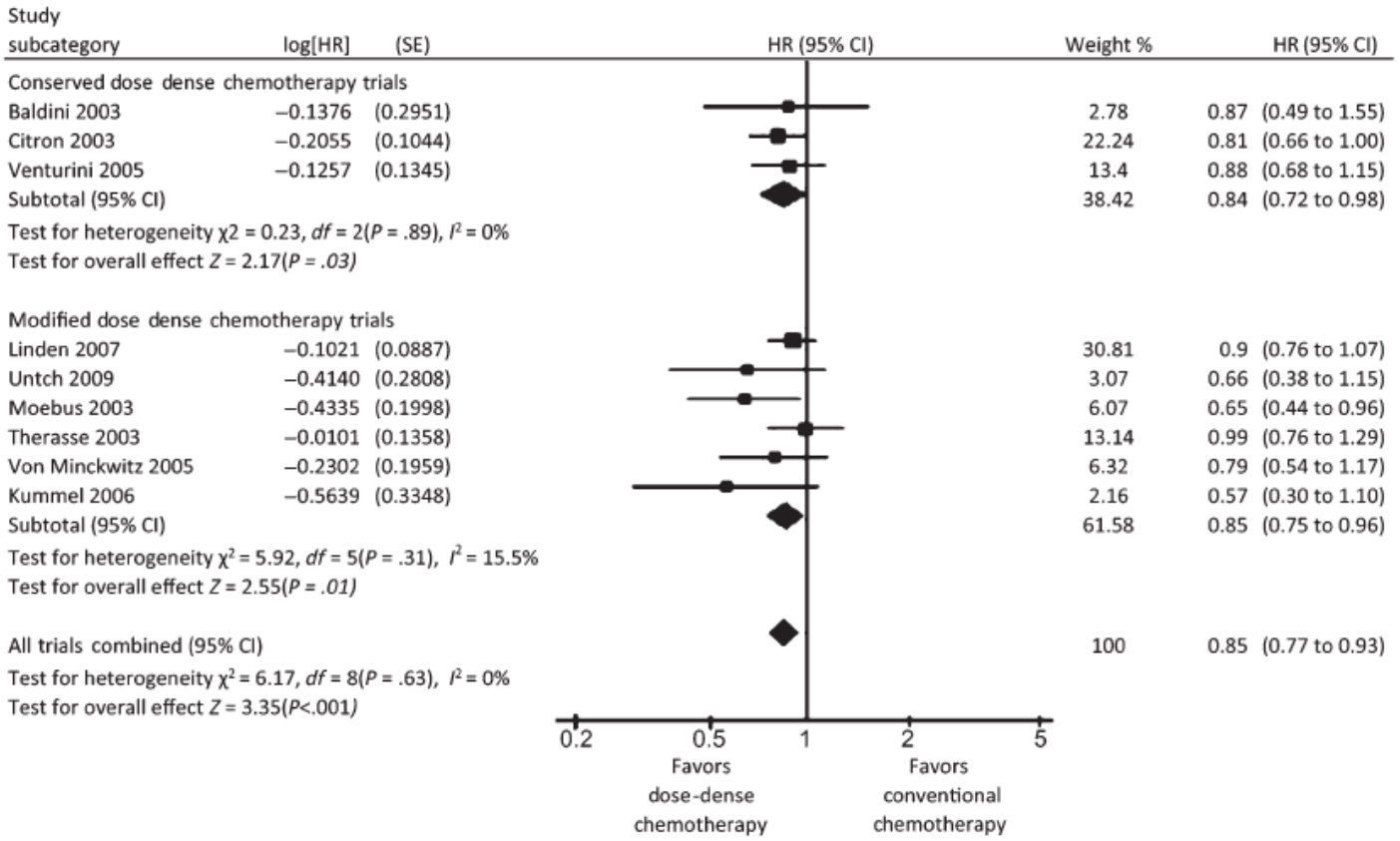

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VOLUME 30 · NUMBER 8 · MARCH 10 2012

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Uptake and Economic Impact of First-Cycle Colony-Stimulating Factor Use During Adjuvant Treatment of Breast Cancer

Dawn L. Hershman, Elizabeth T. Wilde, Jason D. Wright, Donna L. Buono, Kevin Kalinsky, Jennifer L. Malin, and Alfred I. Neugut

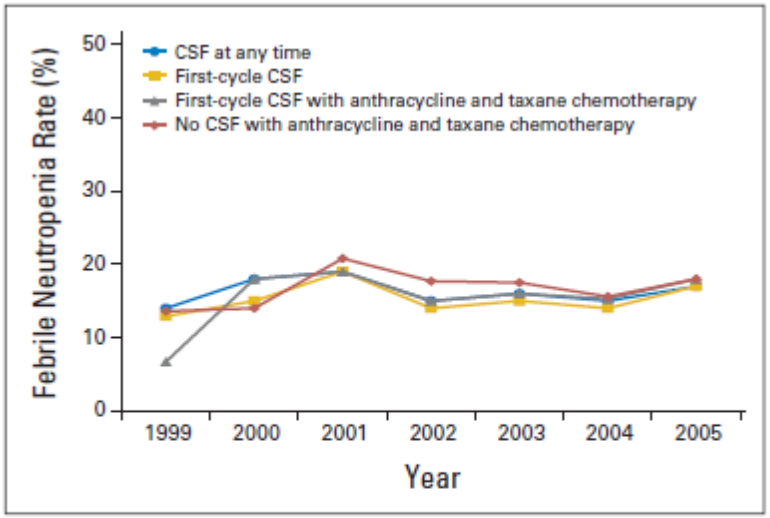
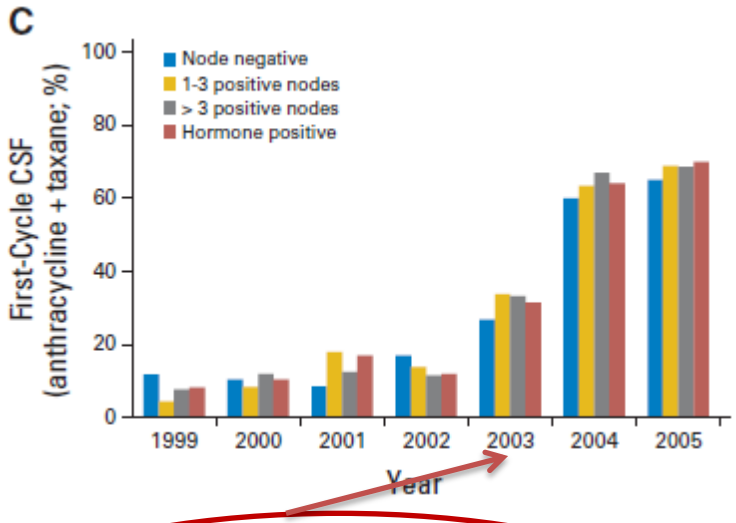


Fig 4. Febrile neutropenia rates over time with colony-stimulating factor (CSF) use at any time during adjuvant chemotherapy, with the first cycle of any adjuvant chemotherapy, with the first cycle of combination anthracycline and taxane chemotherapy, and without CSF.



2002 ASCO meeting presentation and 2003 publication of INT9741 trial , showing a benefit of dose-dense CT at 2-year follow up

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

NEOADJUVANT/ADJUVANT CHEMOTHERAPY[1,2,3,4]

Regimens for HER2-negative disease (all category 1[5])

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- FEC/CEF followed by T
  (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or
  (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)
- FAC followed by T
  (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab[9]
  (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab[9]
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- Pertuzumab + trastuzumab + docetaxel followed by FEC[9]
- Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]

Adjuvant dose-dense chemotherapy

	Indicazioni
ESMO[1]	La CT dose-dense deve essere considerata nei tumori ad alta attività proliferativa
AIOM[2]	La CT dose-dense non trova indicazione al di fuori di studi clinici

1 2012 ESMO GUIDELINES

2 AIOM

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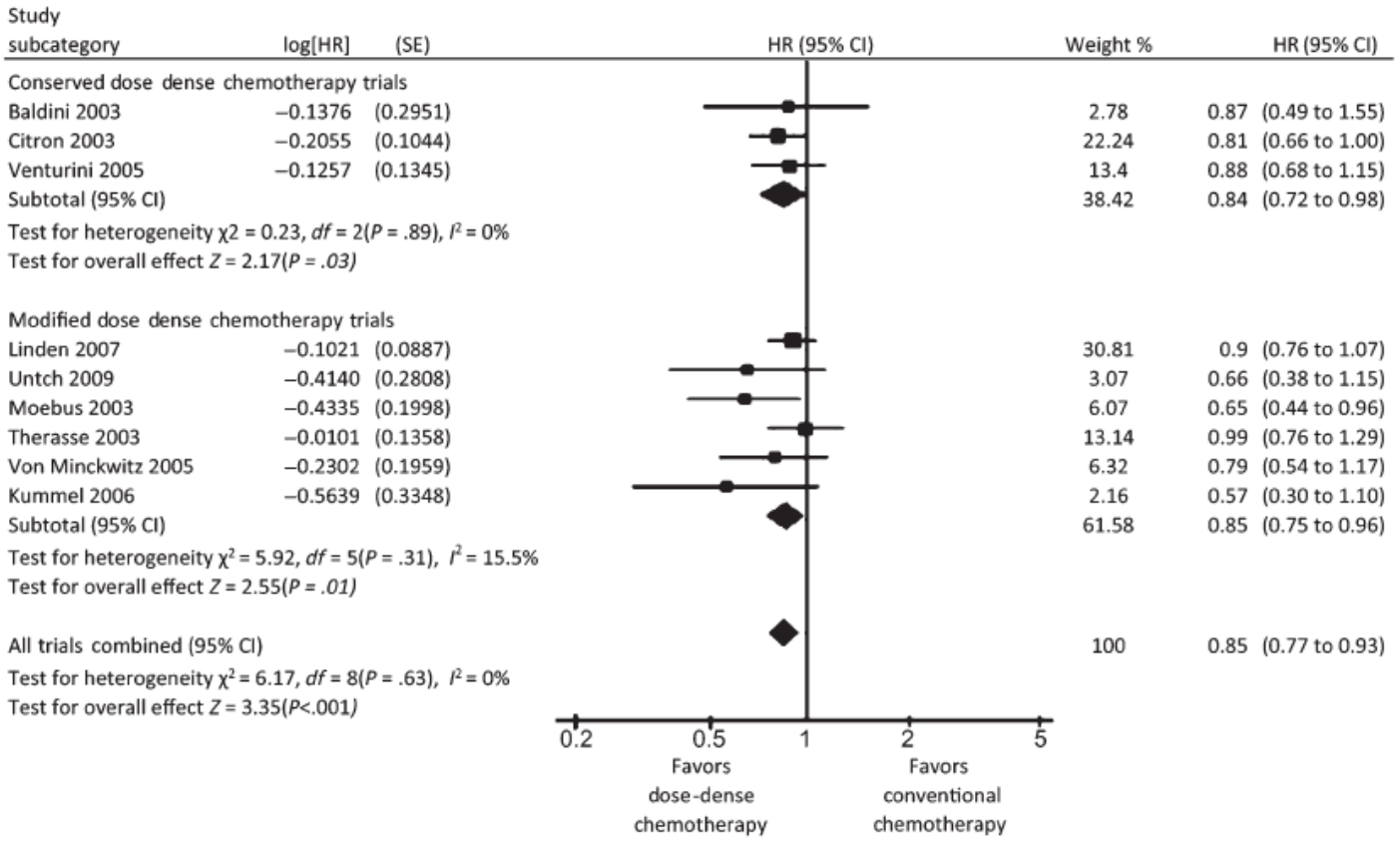
Overall survival



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VOLUME 31 · NUMBER 26 · SEPTEMBER 10 2013

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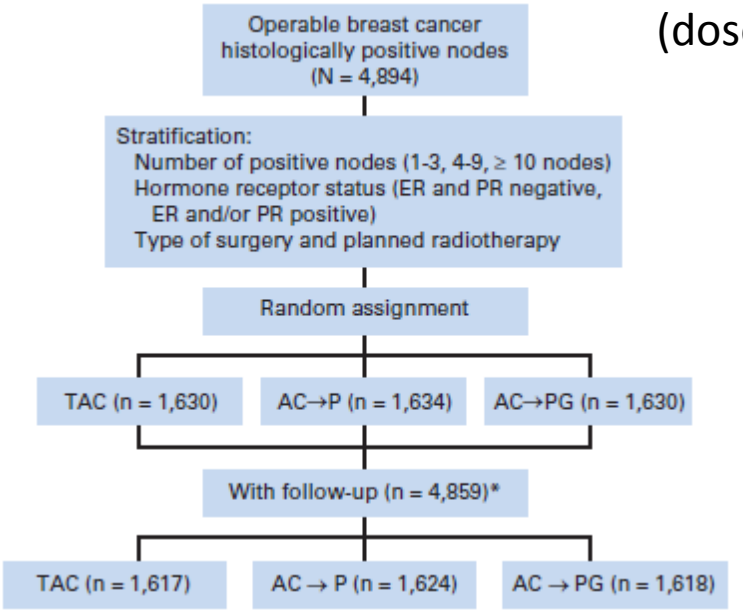
ORIGINAL REPORT

Definitive Results of a Phase III Adjuvant Trial Comparing Three Chemotherapy Regimens in Women With Operable, Node-Positive Breast Cancer: The NSABP B-38 Trial

AC->P and AC->PG every 2 wks (dose-dense)



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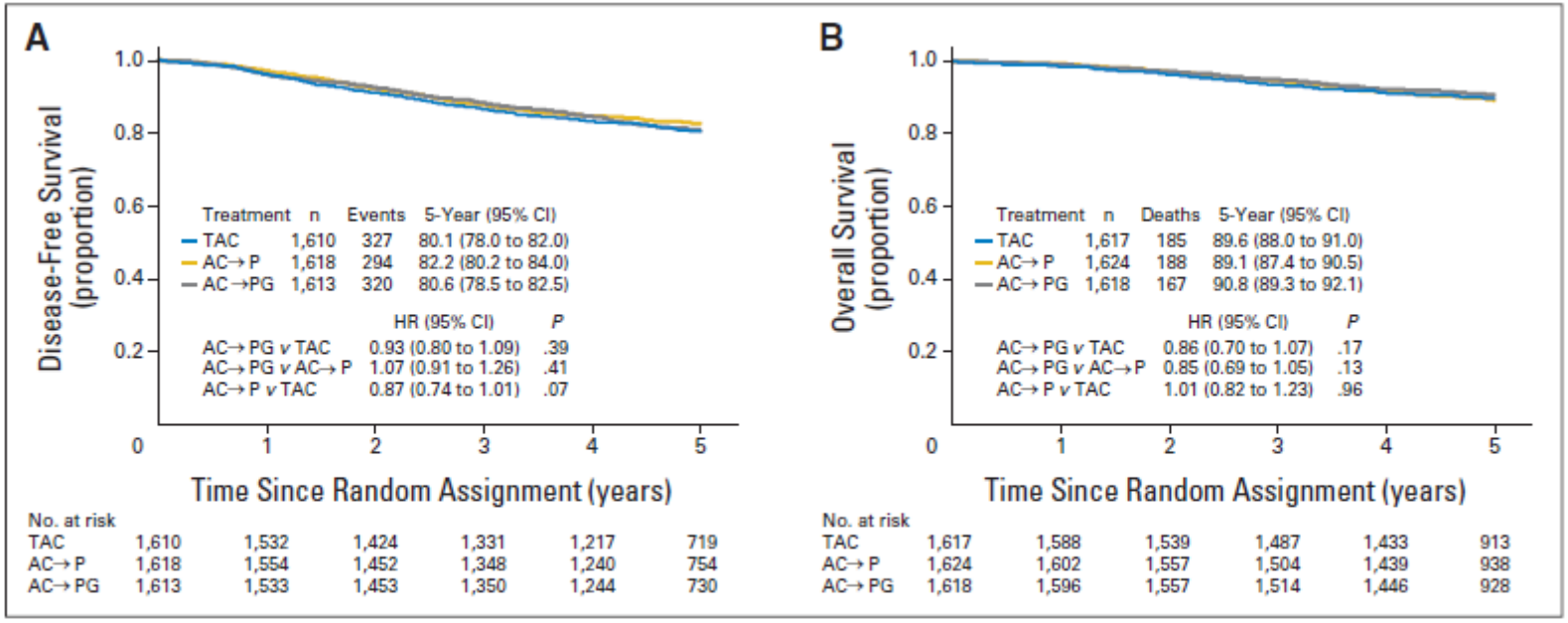

Fig 2. Disease-free survival and overall survival in National Surgical Adjuvant Breast and Bowel Project B-38 trial. Results of Kaplan-Meier analyses for (A) disease-free survival and for (B) overall survival across all three treatment arms. AC→P, doxorubicin and cyclophosphamide followed by paclitaxel; AC→PG, doxorubicin and cyclophosphamide followed by paclitaxel and gemcitabine; HR, hazard ratio; TAC, docetaxel, doxorubicin, and cyclophosphamide.

VOLUME 28 · NUMBER 17 · JUNE 10 2010

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Acute Myeloid Leukemia or Myelodysplastic Syndrome in Randomized Controlled Clinical Trials of Cancer Chemotherapy With Granulocyte Colony-Stimulating Factor: A Systematic Review

Gary H. Lyman, David C. Dale, Debra A. Wolff, Eva Culakova, Marek S. Poniewierski, Nicole M. Kuderer, and Jeffrey Crawford

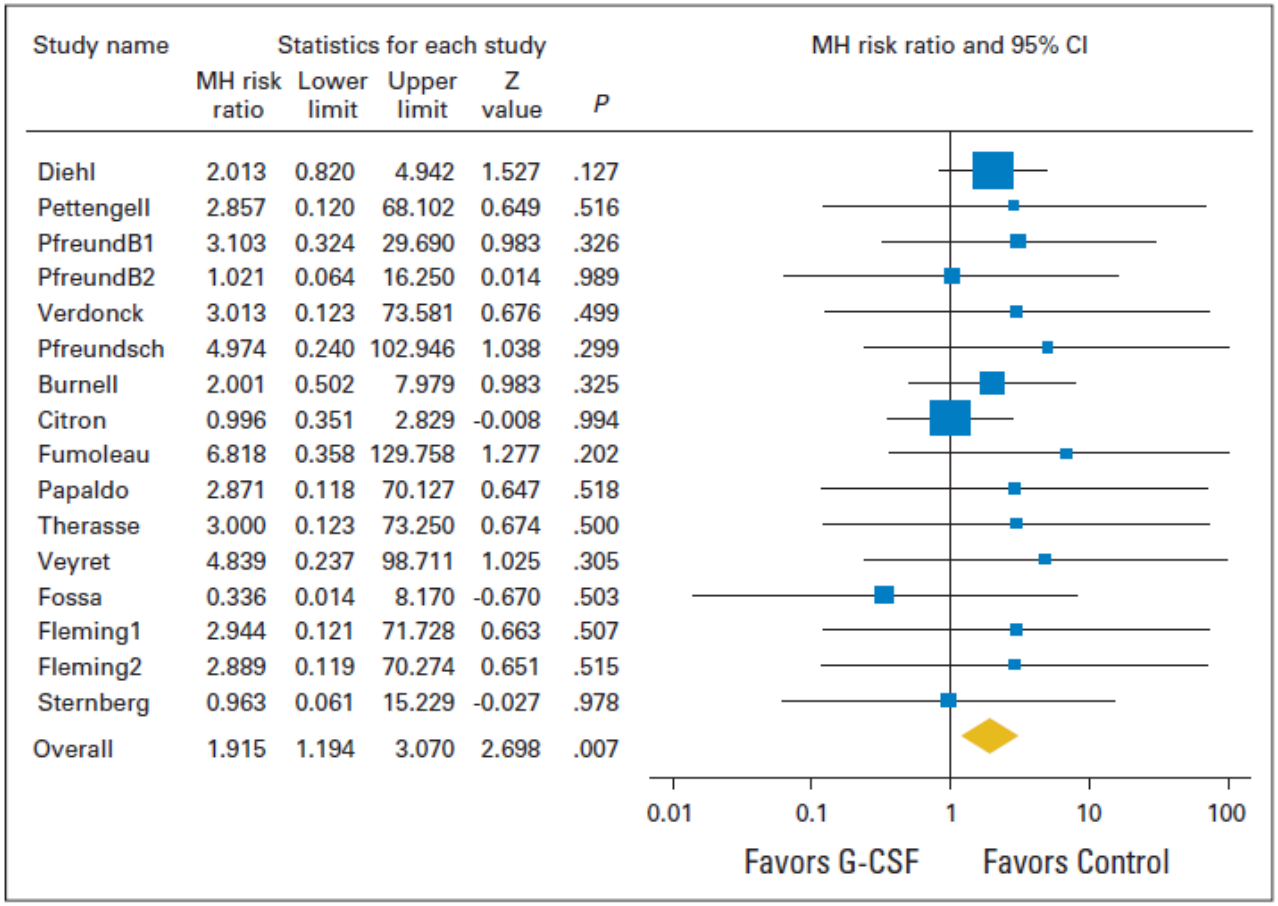

Fig 2. Forest plot of the estimated relative risks (RRs) and 95% CIs for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) comparing granulocyte colony-stimulating factor (G-CSF) –supported chemotherapy with control for each study (squares), with weighted summary RR (diamond) based on the Mantel-Haenszel (MH) method. Studies with no AML/MDS in either study arm are not shown.

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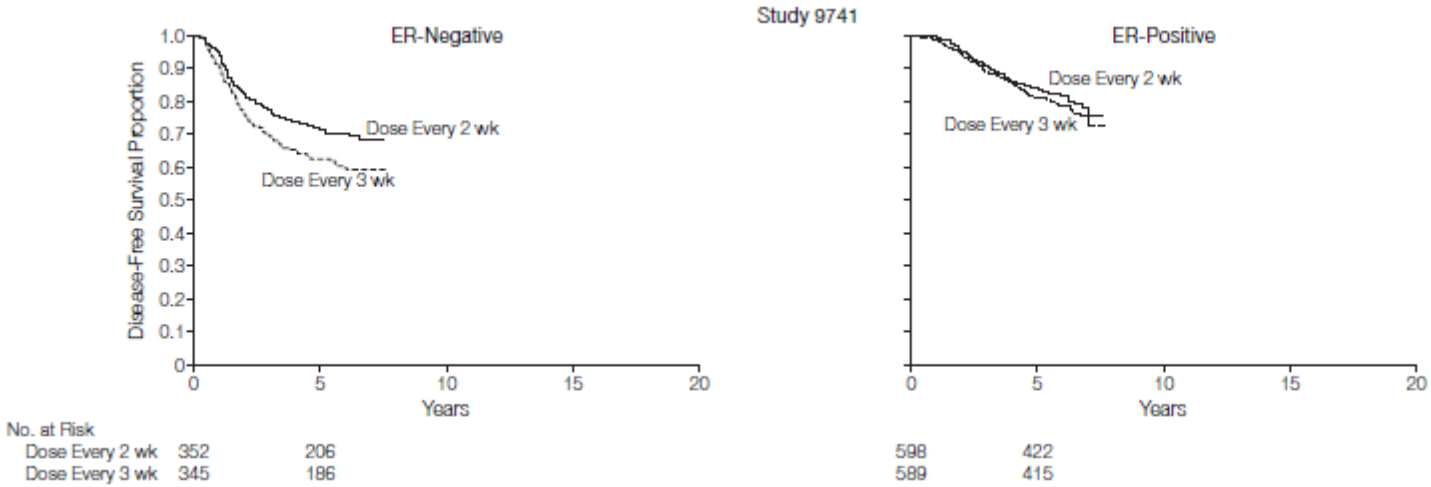
Table 2. Absolute and Relative Risk for AML/MDS and All-Cause Mortality With G-CSF Versus No G-CSF by Cancer Type and Regimen Category

Cancer Type and Regimen	AML/MDS					All-Cause Mortality				
	No. of Trials	Relative Risk	95% CL	Absolute Risk Difference (%)	95% CI	No. of Trials	Relative Risk	95% CL	Absolute Risk Difference (%)	95% CI
Overall	23	1.915*	1.195 to 3.070	0.41*	0.11 to 0.73	25	0.897†	0.857 to 0.938	−3.40†	−4.80 to −2.01
Cancer type										
Breast	7	1.811	0.897 to 3.656	0.30	−0.06 to 0.67	7	0.902‡	0.815 to 0.998	−1.89‡	−3.72 to −0.06
Endometrial	2	2.916	0.305 to 27.872	0.68	−0.66 to 2.02	2	0.945	0.874 to 1.021	−4.64	−10.89 to 1.61
Germ cell	1	0.336	0.014 to 8.170	−0.77	−2.90 to 1.36	1	0.849	0.568 to 1.269	−4.42	−15.23 to 6.38
Hodgkin's	1	2.013	0.820 to 4.942	1.51	−0.39 to 3.41	1	0.660‡	0.452 to 0.963	−4.42‡	−8.39 to −0.46
Non-Hodgkin's	8	2.732	0.804 to 9.280	0.45	−0.13 to 1.03	10	0.895*	0.832 to 0.963	−4.66*	−7.57 to −1.75
Lung	3	0.956	0.101 to 9.072	0.00	−1.66 to 1.66	3	0.945	0.875 to 1.021	−4.88	−11.46 to 1.71
Urothelial	1	0.963	0.061 to 15.229	−0.03	−2.13 to 2.07	1	0.868‡	0.772 to 0.977	−11.45‡	−20.79 to −2.11
Regimen category										
Same drugs, dose, and schedule	9	1.947	0.487 to 7.779	0.35	−0.51 to 1.21	11	0.942	0.881 to 1.009	−2.90	−6.22 to 0.42
Dose-dense schedule	6	1.288	0.577 to 2.875	0.11	−0.25 to 0.48	6	0.841†	0.776 to 0.912	−4.79†	−7.01 to −2.57
Dose escalation	3	2.211	0.940 to 5.203	1.34	−0.09 to 2.78	3	0.785	0.589 to 1.045	−2.97	−6.46 to 0.52
Added or substituted agent	5	2.827‡	1.013 to 7.885	0.56‡	0.01 to 1.12	5	0.945	0.868 to 1.029	−1.65	−4.08 to 0.78

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; G-CSF, granulocyte colony-stimulating factor.
*$P < .01$.
†$P < .001$.
‡$P < .05$.

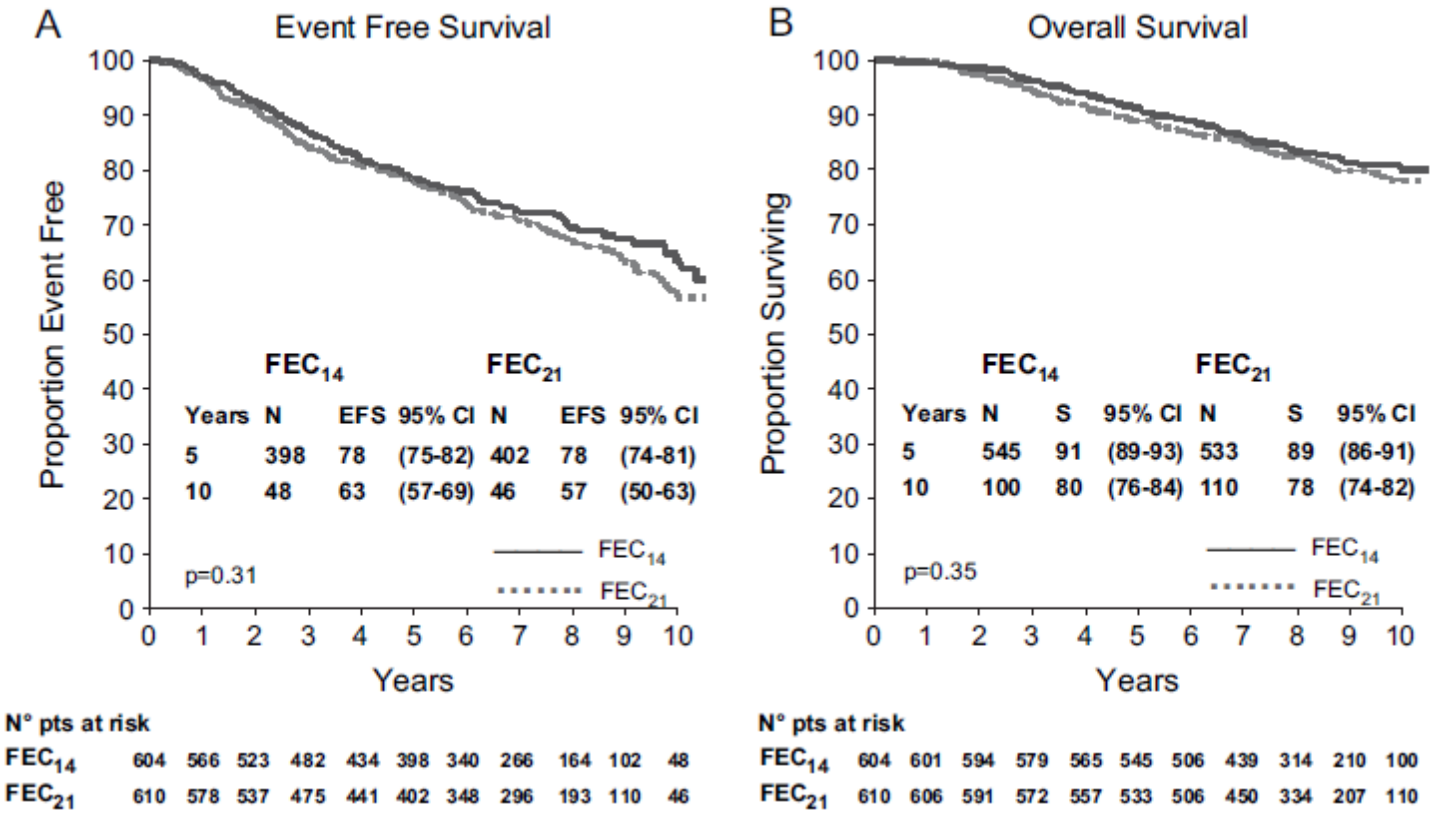
Estrogen-Receptor Status and Outcomes of Modern Chemotherapy for Patients With Node-Positive Breast Cancer



JAMA. 2006;295:1658-1667

Dose-Dense Adjuvant Chemotherapy in Early Breast Cancer Patients: Results From a Randomized Trial

Marco Venturini, Lucia Del Mastro, Enrico Aitini, Editta Baldini, Cinzia Caroti, Antonio Contu, Franco Testore, Fulvio Brema, Paolo Pronzato, Giovanna Cavazzini, Mario Roberto Sertoli, Giuseppe Canavese, Riccardo Rosso, Paolo Bruzzi



[J Natl Cancer Inst 2005;97:1724–33]

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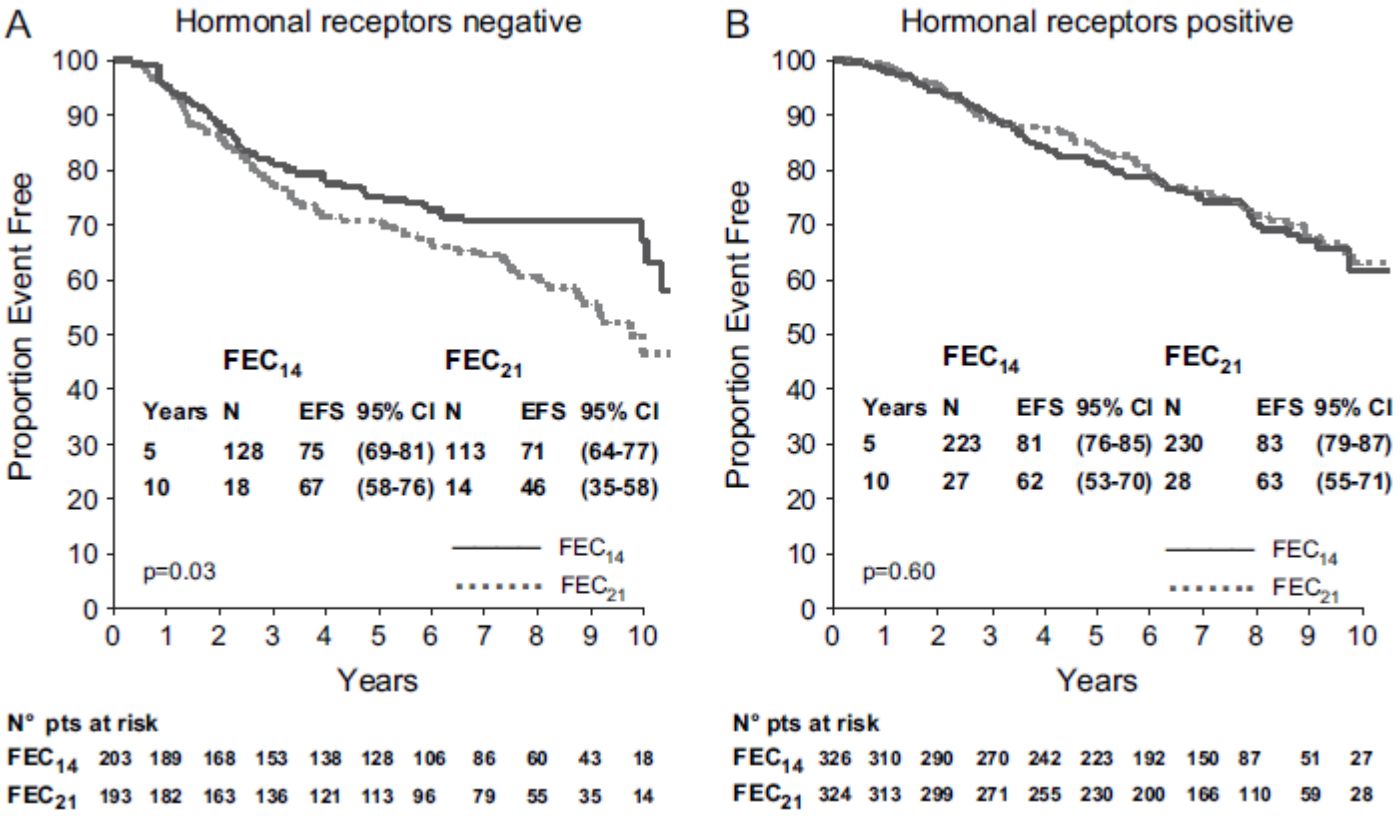

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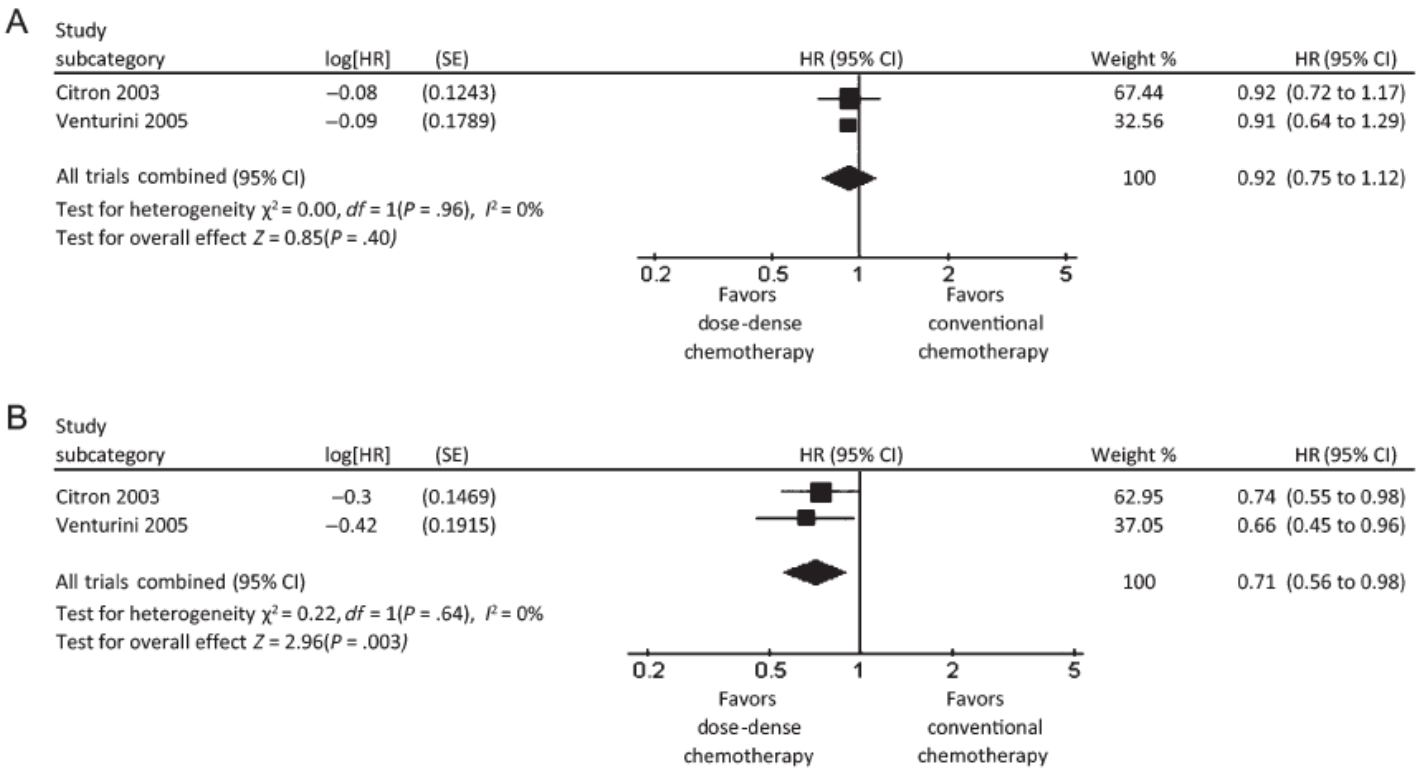

Figure 4. Forest plot of hazard ratios (HRs) comparing disease-free survival for estrogen receptor–positive and estrogen receptor–negative patients who received dose-dense chemotherapy vs those who received conventional chemotherapy in the conserved dose-dense chemotherapy trials. **A)** Estrogen receptor–positive patients. **B)** Estrogen receptor–negative patients. Hazard ratios for each trial are represented by the **squares**, the size of the square represents the weight of the trial in the meta-analysis, and the **horizontal line** crossing the square represents the 95% confidence interval (CI). The **diamonds** represents the estimated overall effect based on the meta-analysis fixed effect of all trials.

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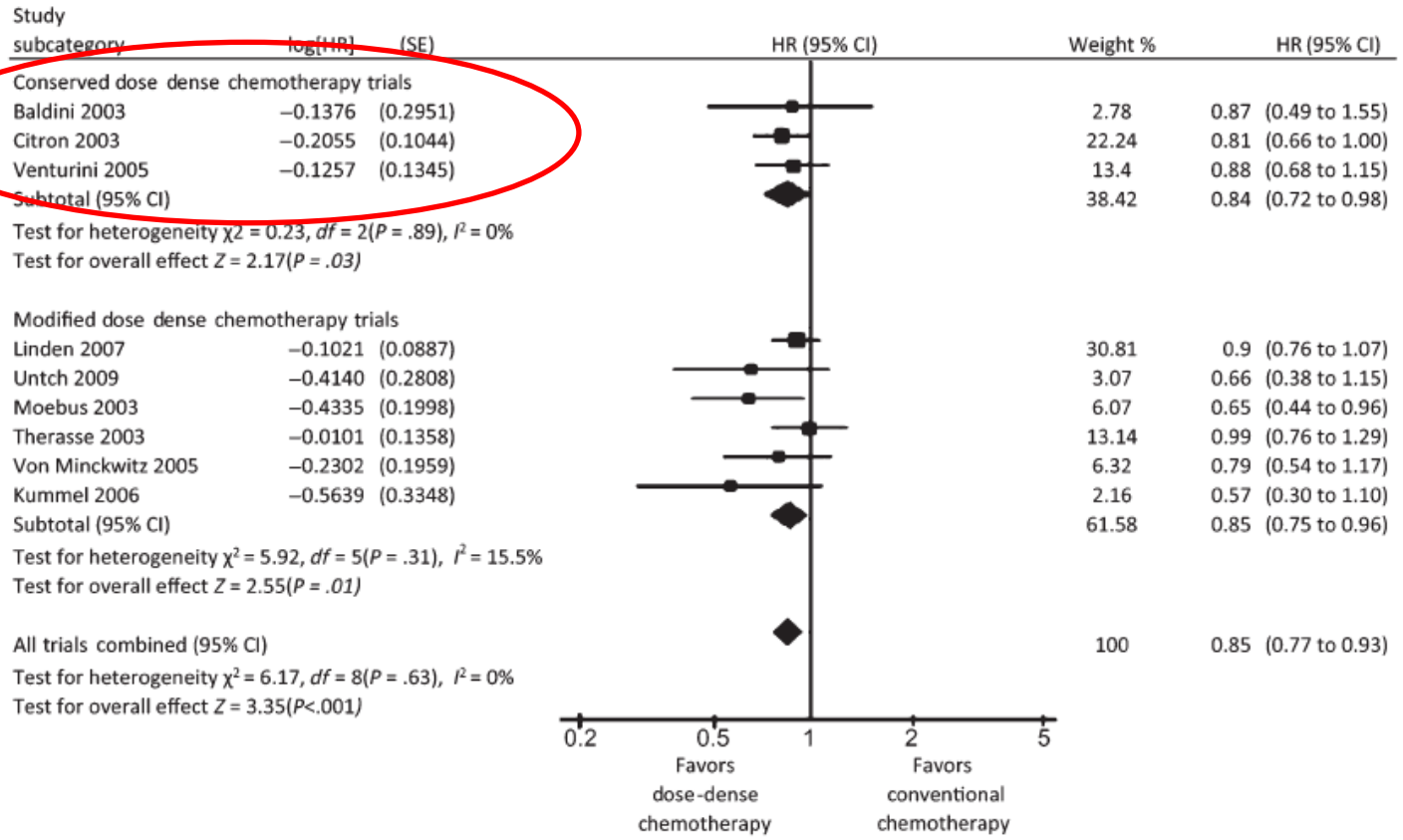

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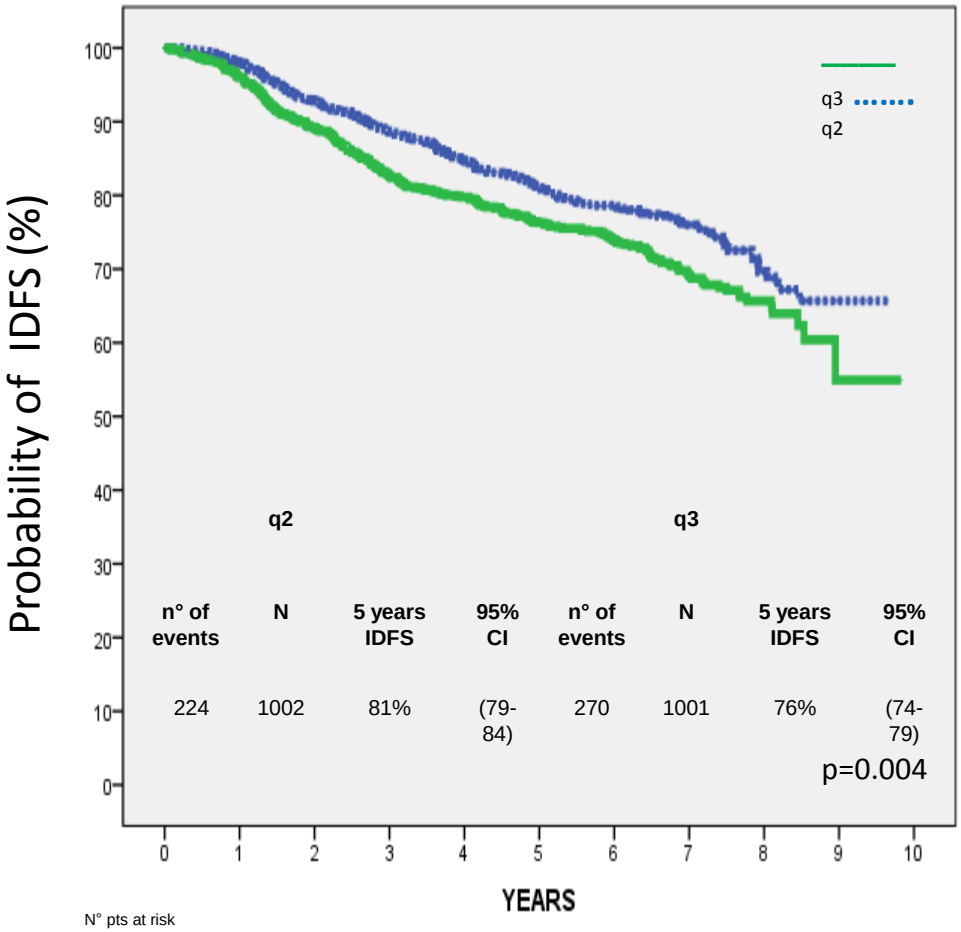
GIM2 study



	q2				q3			
	n° of events	N	5 years IDFS	95% CI	n° of events	N	5 years IDFS	95% CI
	224	1002	81%	(79-84)	270	1001	76%	(74-79)

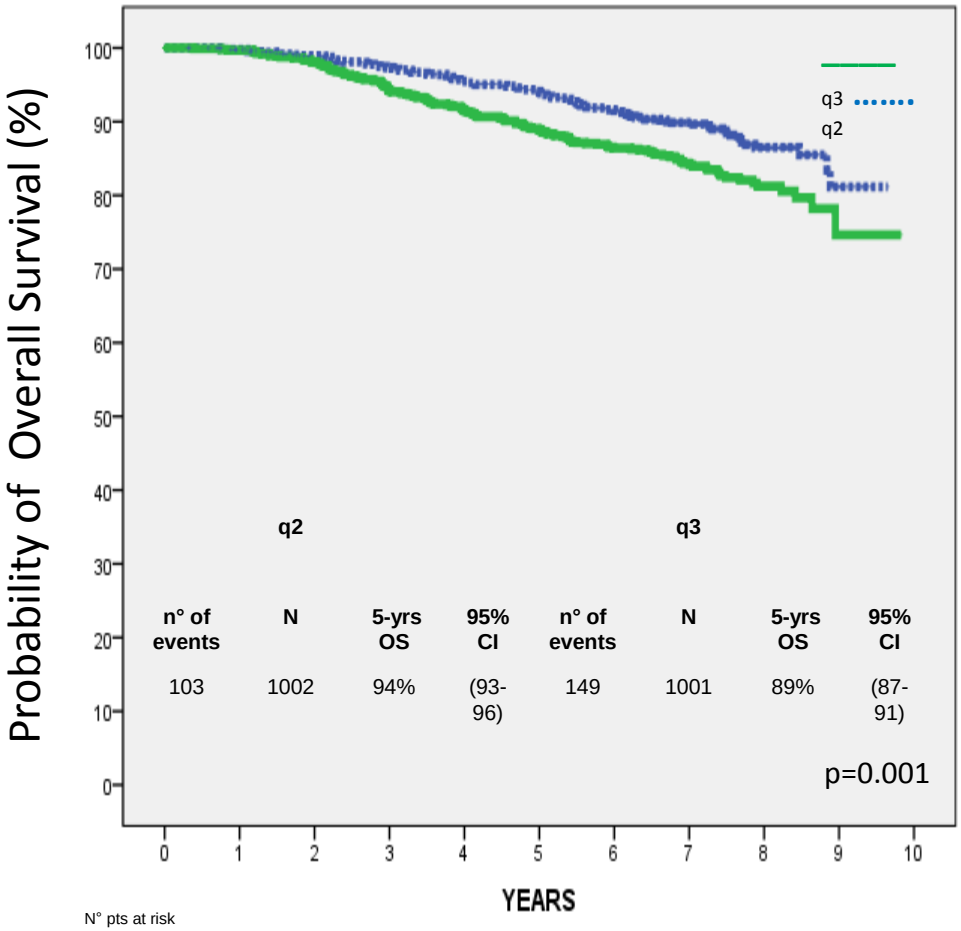
p=0.004

N° pts at risk

		1	2	3	4	5	6	7	8	9	10
q2 wks	1002	935	857	795	725	646	554	343	101	13	-
q3 wks	1001	907	810	724	662	599	492	294	92	9	-

*STRATIFIED FOR EC/FEC

GIM2 study



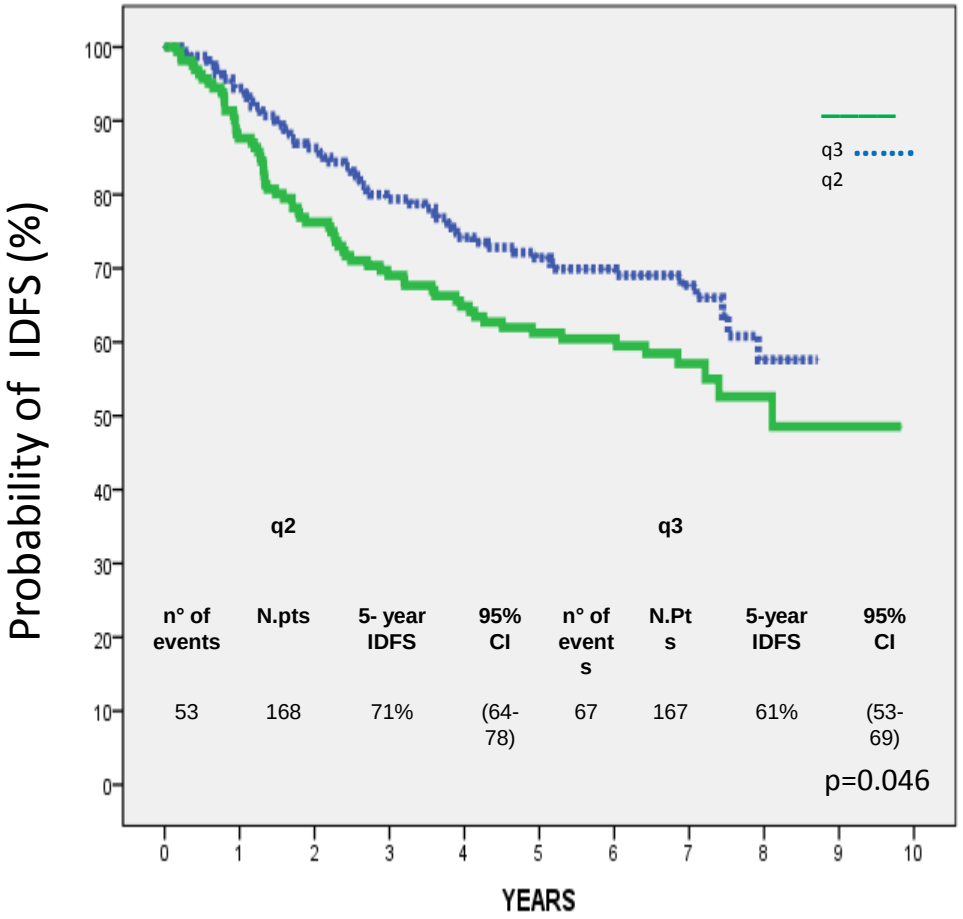
N° pts at risk

		1	2	3	4	5	6	7	8	9	10
q2	1002	970	930	900	855	810	737	479	186	24	-
q3	1001	956	914	849	802	758	675	427	166	19	-

*STRATIFIED FOR EC/FEC

GIM2 study

Hormonal receptor negative patients



	n° of events	N.pts	5- year IDFS	95% CI	n° of events	N.Pts	5-year IDFS	95% CI
	q2				q3			
	53	168	71%	(64-78)	67	167	61%	(53-69)

p=0.046

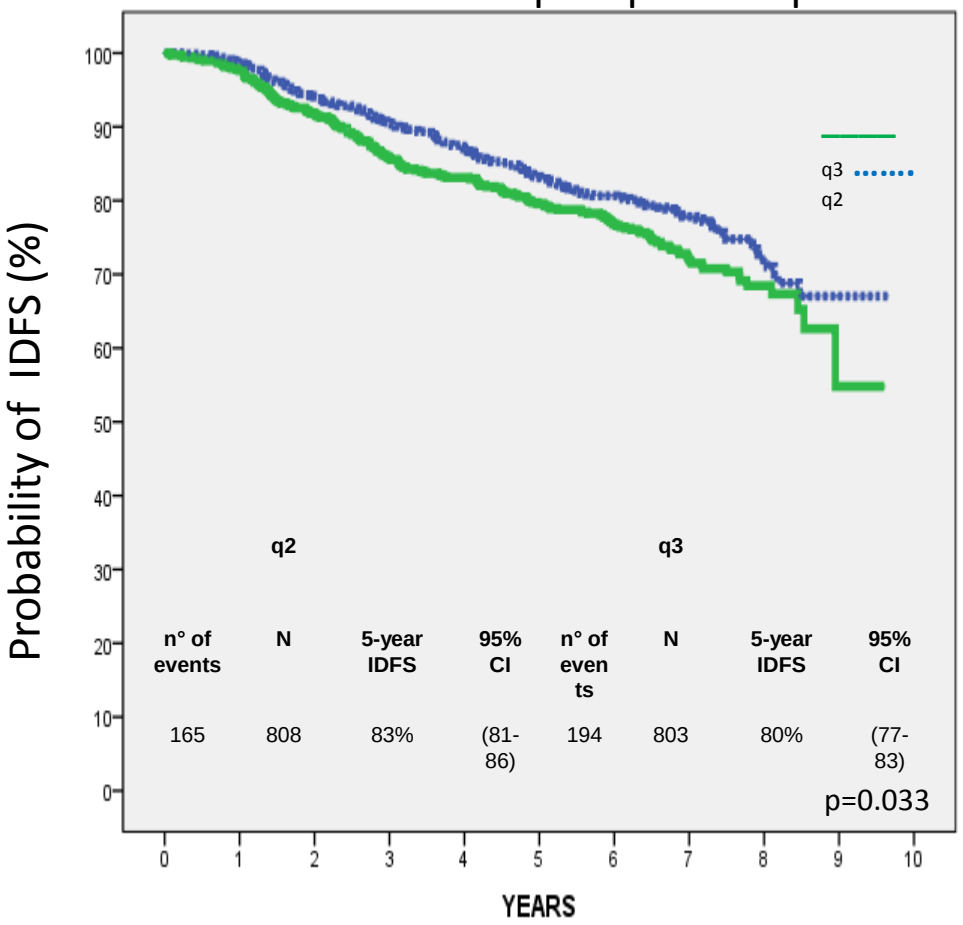
No. at risk

		1	2	3	4	5	6	7	8	9	10
q2	168	152	137	126	112	101	81	45	16	-	-
q3	167	141	118	102	91	81	66	35	16	2	-

*STRATIFIED FOR EC/FEC

GIM2 study

Hormonal receptor positive patients



	q2				q3			
n° of events	N	5-year IDFS	95% CI	n° of events	N	5-year IDFS	95% CI
165	808	83%	(81-86)	194	803	80%	(77-83)

p=0.033

No. at Risk

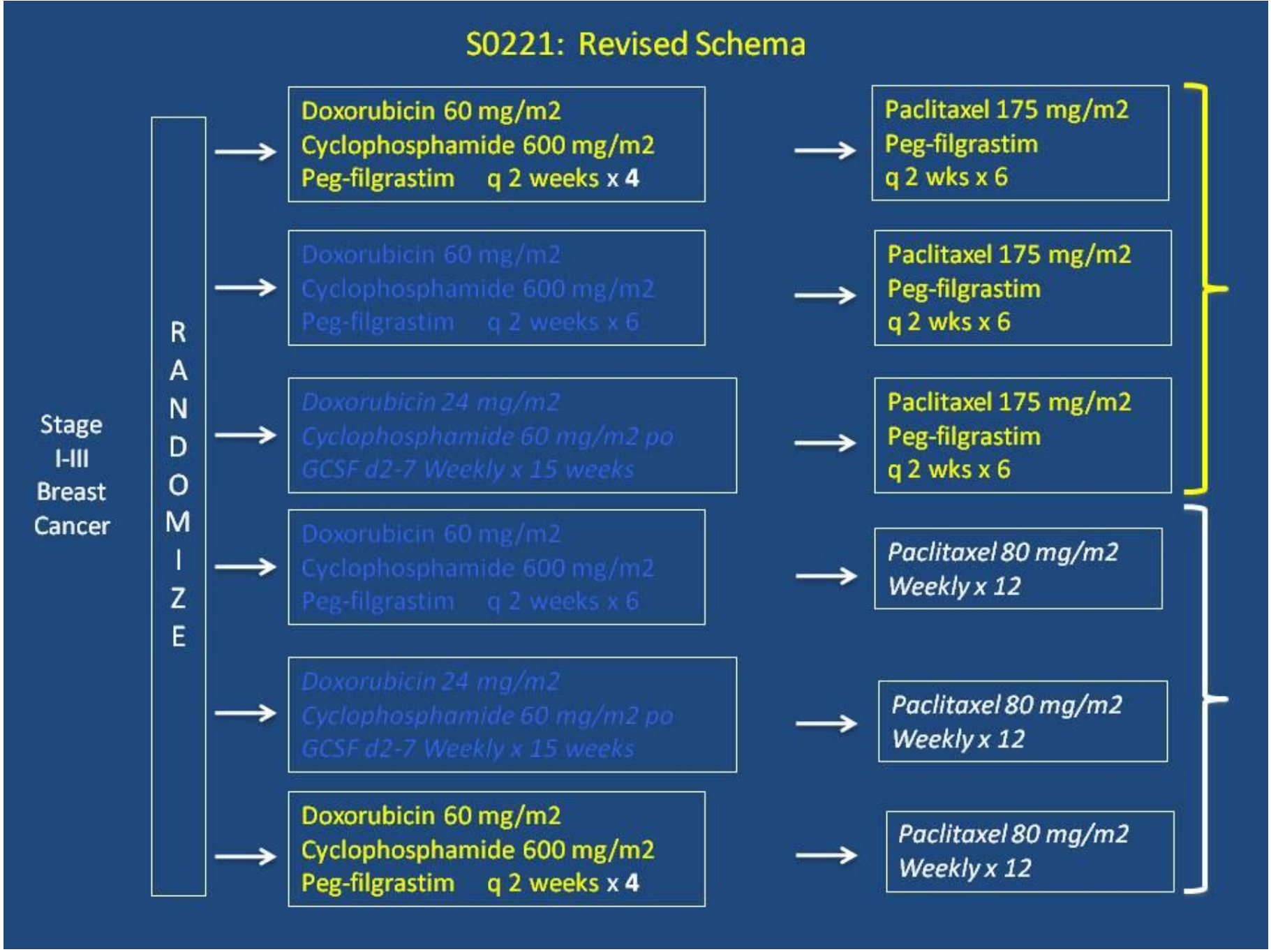
		1	2	3	4	5	6	7	8	9	10
q2 wks	808	758	697	647	594	527	459	267	82	13	-
q3 wks	803	737	666	603	553	501	415	225	71	6	-

*STRATIFIED FOR EC/FEC

Dose dense CT
OXFORD meta-analysis 2013

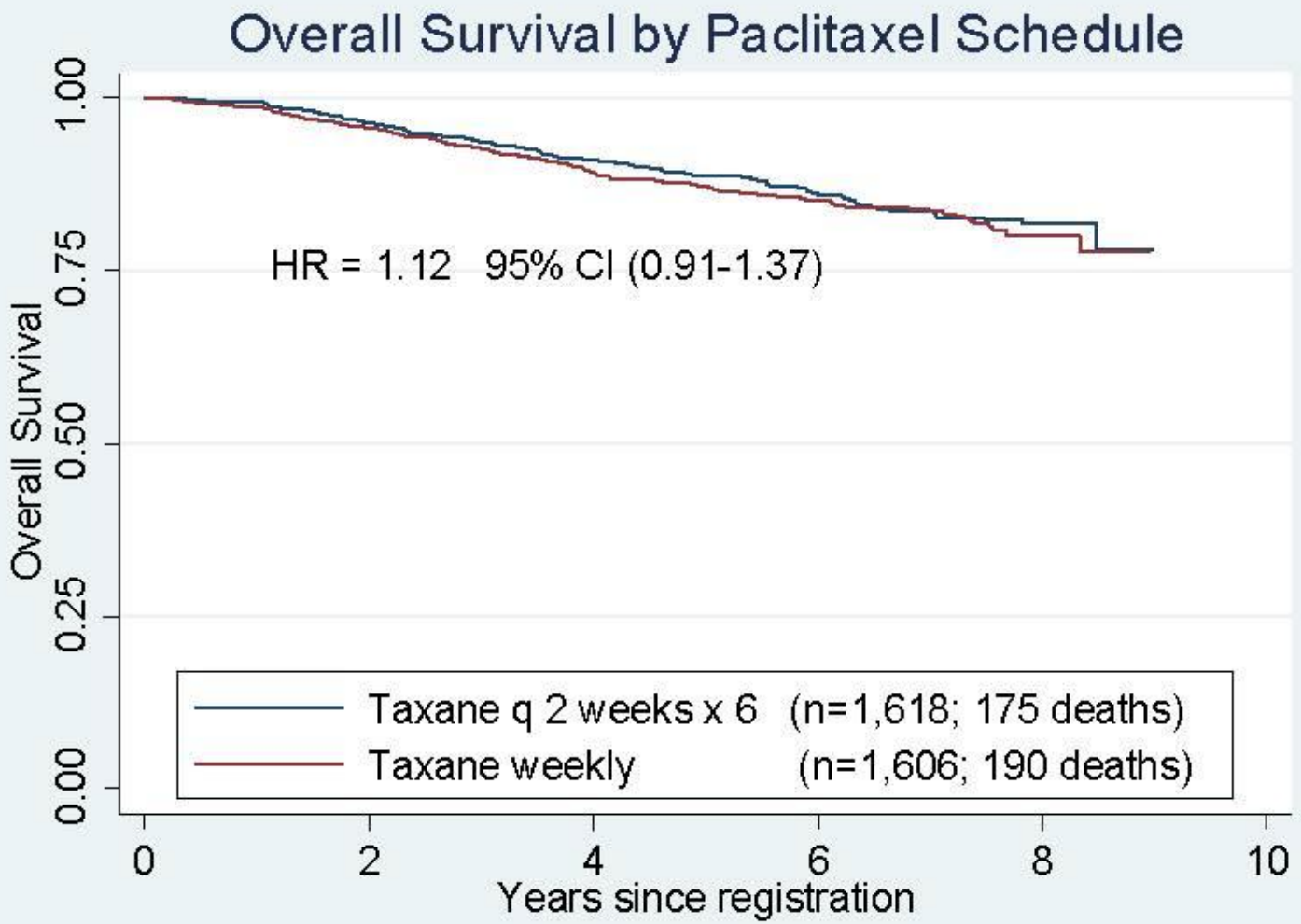
- 10261 Pts 10 Years

	DFS	OS
ALL	4,8% (2p: 0,0004)	2,4% sig
ER-	10,6% (2p<0,0001)	5,6% (2p 0,03)
ER+	4,4% (2p :0,01%)	0,8% non sig



Presented By G. Thomas Budd, MD at 2013 ASCO Annual Meeting

April 2013 Updated Analysis



Number at risk

q2 wk	1618	1246	955	515	111	0
weekly	1606	1232	925	484	90	0

Presented By G. Thomas Budd, MD at 2013 ASCO Annual Meeting

Summary

- DFS and OS produced by 6 cycles of q 2 week paclitaxel and 12 weeks of weekly paclitaxel was similar
- Leukopenia was observed more commonly with weekly paclitaxel, but these patients had CBC's performed weekly and did not receive CSF's routinely
- Allergic-type reactions, musculoskeletal pain, and neuropathy were more common in patients treated q 2 weeks for 12 weeks

La chemioterapia dose-dense: quale ruolo nella pratica clinica?

- Vantaggio in DFS e OS (livello di evidenza 1++, grado raccomandazione A, positiva forte)
  - Vantaggio clinicamente maggiore nelle pazienti con RO negativi, ma presente anche nelle pazienti con RO positivi