Dose-dense sequential adjuvant chemotherapy with epirubicin, paclitaxel and CMF versus epirubicin, CMF and weekly docetaxel or paclitaxel followed by trastuzumab for one year in patients with early breast cancer

HE 10/05

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Disclosures

Positions

•Chairman of the Hellenic Cooperative Oncology Group (HeCOG)

•Chairman of the Hellenic Foundation for Cancer Research (HeFCR)

Consultant or advisory role: None

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Honoraria: None

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Patents

•On behalf of the HeFCR, I have pending patent applications with Siemens Healthcare Diagnostics, Tarrytown, NY, USA

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Background - 1

- Adjuvant systemic therapy has significantly reduced death rates in early breast cancer (EBC)[1,2]
- Clinical research on adjuvant chemotherapy (CT) of EBC is based on two principles;
  - Dose density (DD) and sequential administration
  - Incorporation of taxanes
- Two meta-analyses have shown that DD adjuvant CT improves DFS but not OS[3] and that sequential CT prolongs both DFS and OS[4]

[1]EBCTCG, Lancet, 2005; [2] EBCTCG, Lancet, 2012; [3]Lemos Duarte L, Breast, 2012; [4]Shao N, Breast, 2012

Background - 2

- Taxanes when incorporated in anthracycline-based adjuvant CT slightly but significantly improve DFS and OS in EBC[2]
- The most effective taxane and optimal schedules of administration are under intensive investigation[5-7]

[2] EBCTCG, Lancet, 2012; [5]Martin N, NEJM, 2005; [6]Sparano JA, NEJM, 2008; [7]Loesch D, JCO, 2010

Background - 3

- Randomized trials[8-10] have shown that patients with HER2-positive tumors derive significant benefit in DFS, OS, LRR and DR from the addition of trastuzumab to adjuvant CT
- Our Group has conducted two randomized trials[11,12] exploring the role of DD CT and the incorporation of paclitaxel
- We have also conducted two feasibility studies evaluating weekly docetaxel[13] or paclitaxel[14] following DD chemotherapy with epirubicin and CMF

[8]Romond EH, NEJM, 2005; [9]Piccart-Gebhart MJ, NEJM, 2005; [10]Joensuu H, NEJM, 2006;
[11]Fountzilas G, Ann Oncol, 2005; [12]Gogas H, Br Cancer Res Treat, 2012;
[13]Papadimitriou C, Cancer Invest 2008; [14]Fountzilas G, Med Oncol, 2006

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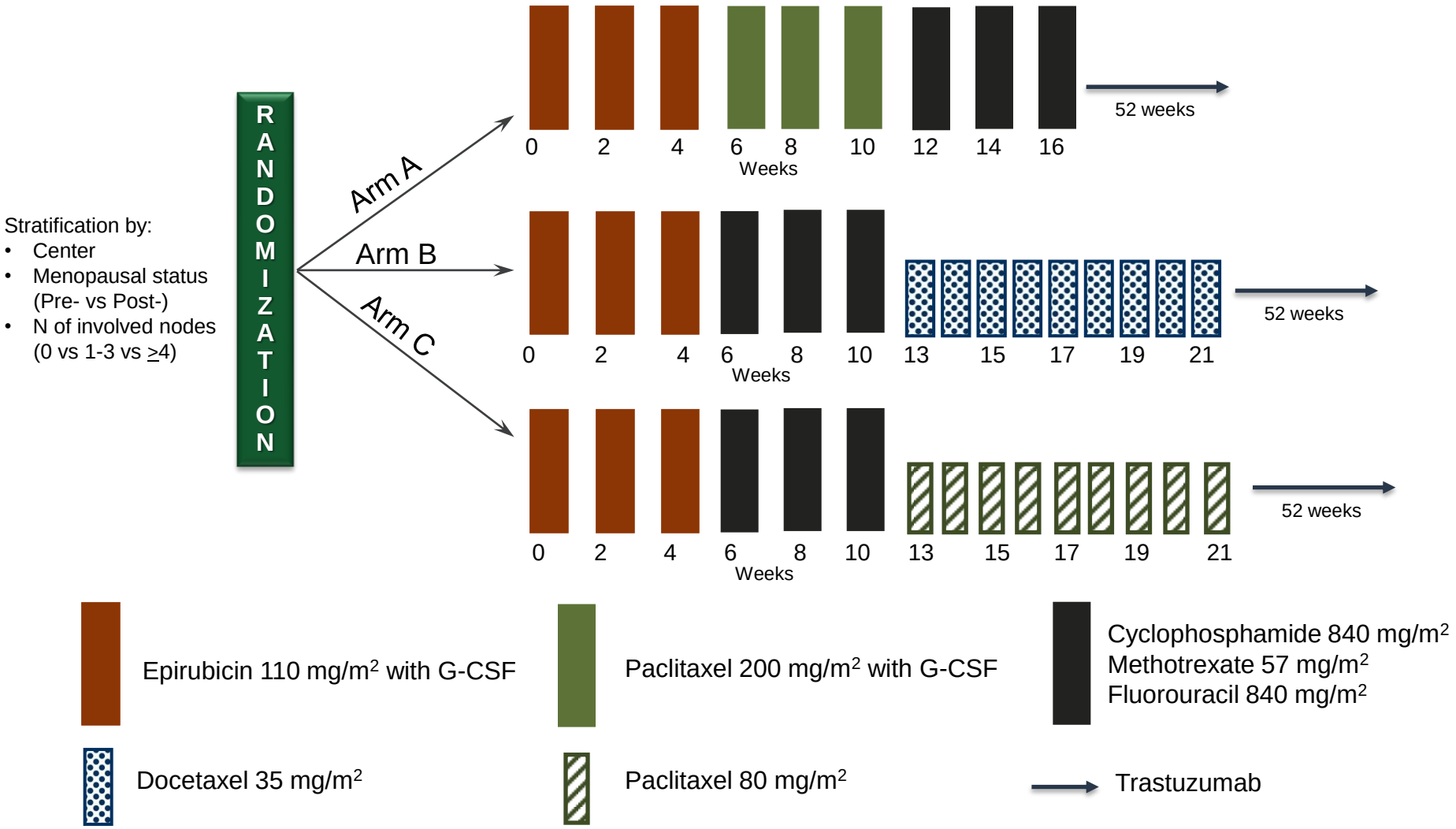
(ACTRN 12610000151033)



Post-CT treatment

- RT was given to all patients with PM or to those with tumor size ≥5 cm and/or ≥4 infiltrated nodes
- Premenopausal HR-positive patients received TAM for 5 years and an LH-RH agonist for 2 years
- Postmenopausal HR-positive patients received anastrazole for 5 years
- Trastuzumab 8 mg/kg, as l.d., followed by 6 mg/kg every 3 weeks for 1 year
- Hormonal therapy and trastuzumab were administered after the completion of chemotherapy and RT

Inclusion criteria

- Histologically confirmed invasive breast cancer following MRM or PM
- N1 or “high risk” N0 disease (St. Gallen criteria, 2005)
- Age ≥18 years
- Adequate hepatic, renal or bone marrow function
- PS 0-1 ECOG scale
- Baseline ejection fraction >55%
- Informed consent

Statistical Design

- Intent to treat analysis
- Primary endpoint: DFS

E – CMF – Dw or Tw® (Arms B & C)

vs

E – T® – CMF arm (Arm A)

- Two-sided test, 0.05 level of significance
- Power 80%, to detect a 5% difference in 3-yr DFS to a rate of 80% for arm A
- N= 1,000 patients, 330 DFS events
- Maximum study duration: 8.1 years
- Accrual rate: 332 patients per year
- Interim analysis at half of the 330 events

T®= Taxol (BMS, Princeton, NJ)

Current analysis

- 5-year median follow-up
- Approximately 50% of total information

  (half of the 330 events)
- *Interim analysis*

Observed event rate approximately half of expected

→

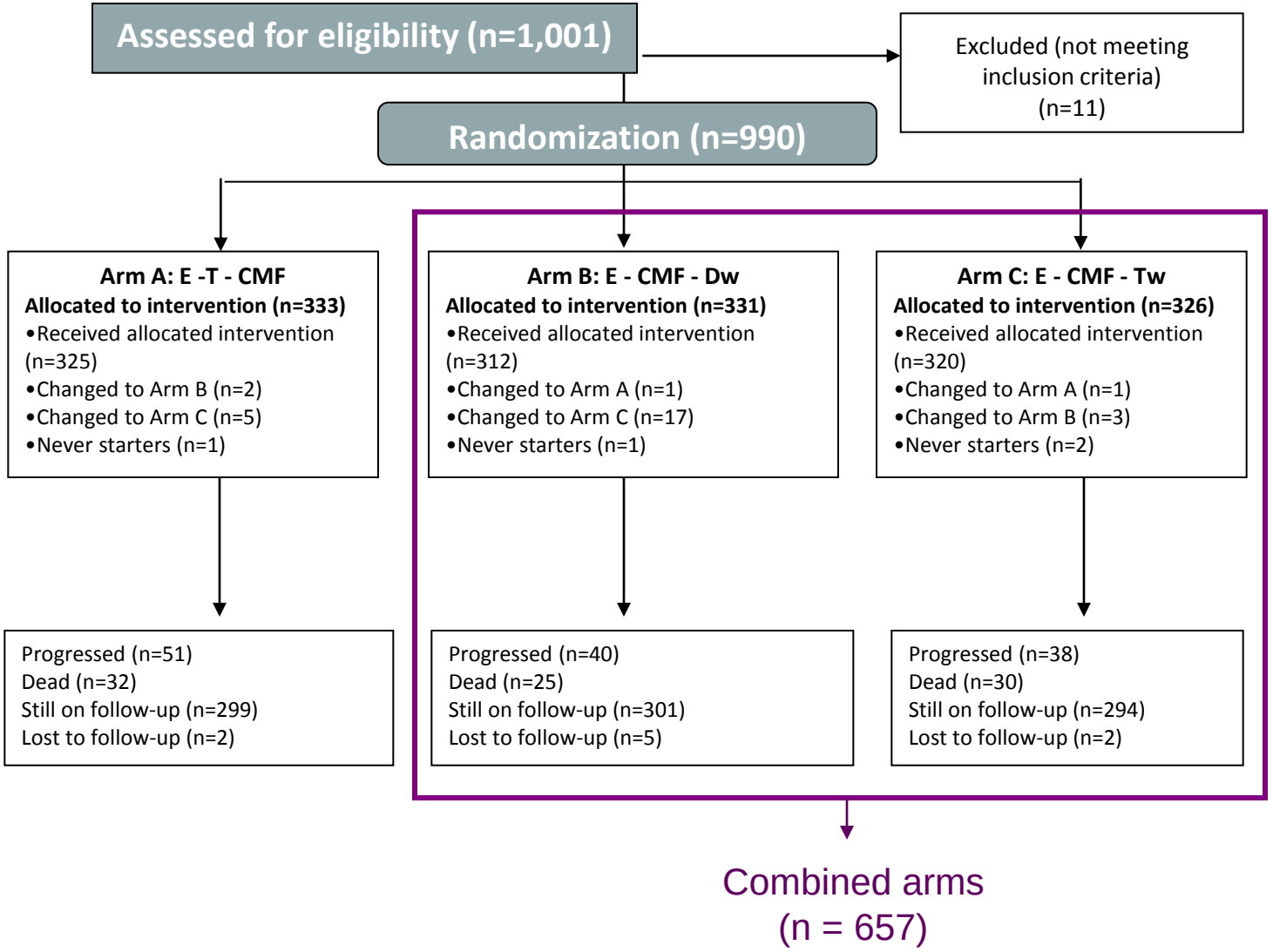
Much longer than anticipated study duration
to observe the 330 DFS events

Results

Accrual time	:	July 2005 to November 2008
Assessed for eligibility	:	1,001
Eligible	:	990
Reasons for ineligibility[a]		
M1 disease	:	4
Bilateral breast cancer	:	1
Protocol violation	:	5
Second neoplasm	:	1
Survival cut-off date	:	July 31, 2012
Median follow-up	:	60.4 months

[a]at study entry

CONSORT flow chart



Patient characteristics - 1

	Arm A: E - T - CMF N=333	Arm B: E - CMF - Dw N=331	Arm C: E - CMF - Tw N=326
Age			
Median (range)	53 (28-79)	53 (21-78)	54 (23-78)
	(%)	**(%)**	**(%)**
Menopausal status			
Premenopausal	46.5	47.4	45.7
Postmenopausal	53.5	52.6	54.3
Surgery			
MRM	49.8	49.2	53.4
Partial/Simple mastectomy	50.2	50.8	46.6
Tumor size			
≤2	47.7	42.0	36.5
2.1-5	46.5	51.1	56.1
>5	5.7	6.9	7.4
Positive nodes			
0	24.9	24.2	25.5
1-3	40.8	41.1	41.7
≥4	34.2	34.4	32.8
Missing data	-	0.3	-

Patient characteristics - 2

	Arm A: E - T - CMF N=333	Arm B: E - CMF - Dw N=331	Arm C: E - CMF - Tw N=326
Tumor grade	**(%)**	**(%)**	**(%)**
1	7.5	4.8	6.1
2	46.2	42.6	46.6
3	45.6	52.6	47.2
Missing data	0.6	-	-
Histology type			
Ductal	85.0	86.1	89.6
Medullary	2.1	2.1	1.4
Mucinous	0.7	0.4	0.7
Papillary	0.4	1.1	1.0
Tubular	-	-	0.3
Apocrine	-	0.4	0.3
Metaplastic	-	0.4	-
Neuroendocrine	-	-	0.3
Myeloepithelioma	-	-	0.4
Lobular	9.3	8.5	6.7
Mixed	5.4	5.4	3.4
Other	0.3	-	0.3

Patient characteristics - 3

	Arm A: E - T - CMF N=333	Arm B: E - CMF - Dw N=331	Arm C: E - CMF - Tw N=326
ER status[a]	**(%)**	**(%)**	**(%)**
Negative	25.8	26.3	26.1
Positive	74.2	73.4	73.9
PgR status[a]			
Negative	34.5	32.3	32.5
Positive	65.5	67.7	67.5
HER2 overexpression[a]			
No	71.8	71.9	73.3
Yes	28.2	28.1	26.7

[a]assesed locally

Treatment characteristics

	Arm A: E - T - CMF N=328	Arm B: E - CMF - Dw N=318	Arm C: E - CMF - Tw N=344
	N (%)	**N (%)**	**N (%)**
Completed treatment	308 (93.9)	275 (86.2)	291 (84.8)
Never starters	1 (0.3)	1 (0.3)	2 (0.6)
Discontinued treatment	19 (5.8)	42 (13.2)	51 (14.9)
During Epirubicin	2	5	5
During CMF	8	5	9
During Paclitaxel	9		37
During Docetaxel		32	
Total cycles given	2,878	4,561	4,894
Median (range)	9 (2-10)	15 (1-15)	15 (1-15)
Median RDI			
Epirubicin	0.98 (0.47-1.05)	0.99 (0.48-1.17)	0.99 (0.55-1.17)
Paclitaxel	1.00 (0.57-1.05)	-	0.96 (0.25-1.52)
Cyclophsphamide	0.98 (0.48-1.55)	0.98 (0.46-1.17)	0.98 (0.41-1.16)
Methotrexate	0.96 (0.47-1.53)	0.97 (0.46-1.93)	0.97 (0.40-1.52)
Fluorouracil	0.97 (0.48-1.55)	0.99 (0.46-1.17)	0.98 (0.41-1.16)
Docetaxel	-	0.95 (0.45-2.29)	-

RDI: Relative dose intensity

Treatment with trastuzumab

	Arm A: E-T-CMF N=333	Arm B: E-CMF-Dw N=331	Arm C: E-CMF-Tw N=326	Total study population N=990
	N (%)	**N (%)**	**N (%)**	**N (%)**
Received trastuzumab				
No	242 (72.7)	247 (74.6)	245 (75.2)	734 (74.1)
Yes	91 (27.3)	84 (25.4)	81 (24.8)	256 (25.9)
Completed 1 year	65 (71.4)	58 (69.0)	61 (75.3)	184 (71.9)
Missing Data	3 (3.3)	-	-	3 (1.2)
Discontinued				
Temporarily	15 (16.5)	16 (19.0)	13 (16.0)	44 (17.1)
Permanently[a]	8 (8.8)	10 (11.9)	7 (8.6)	25 (9.8)

[a]CHF (n=3), asymptomatic reduction of EF (n=4), PD (n=7), withdrawal consent (n=9), other (n=2)

Most frequent[a] severe adverse events (%)

	Arm A: E-T-CMF			Arm B: E-CMF-Dw			Arm C: E-CMF-Tw	
	N=326			N=316			N=333	
	Grade III	Grade IV	Grade V	Grade III	Grade IV	Grade V	Grade III	Grade IV
Leucocytes	8.6	3.4		11.4	1.6		9.3	2.1
Neutrophils	16.9	13.5		19.3	7.6		14.7	10.8
Febrile neutropenia	5.2	0.6	0.3	3.8	0.3	0.3	3.9	1.2
Mucositis	1.8	0.3		5.4			3.0	
Pain[1]	5.2			0.9			1.5	
Neurology[2]	4.9			1.3			0.9	
Metabolic	3.7			2.2	0.3		4.8	1.5
Infection	2.1		0.3	4.7			2.1	

[a]in >4% of patients; [1]p=0.002; [2]p=0.001

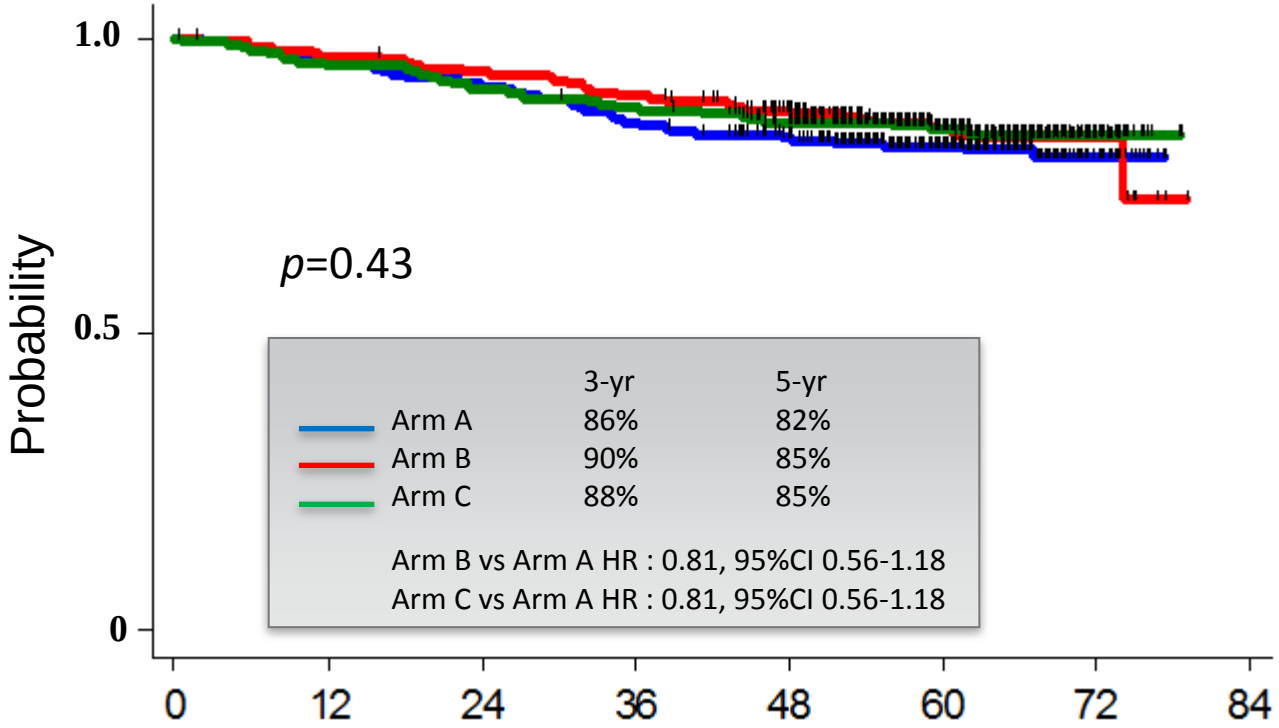
National Cancer Institute Common Terminology Criteria, version 3.0

Cause of death during CT

	N	Treatment arm	Time from initiation of CT until death (weeks)
Febrile neutropenia	1	A	19
Febrile neutropenia	1	B	9
Infection (Hepatitis B reactivation)	1	A	10
Pulmonary embolism	1	C	13
Acute myocardial infarction	1	C	3
Acute respiratory failure	1	B	15
Unknown	1	C	18

DFS

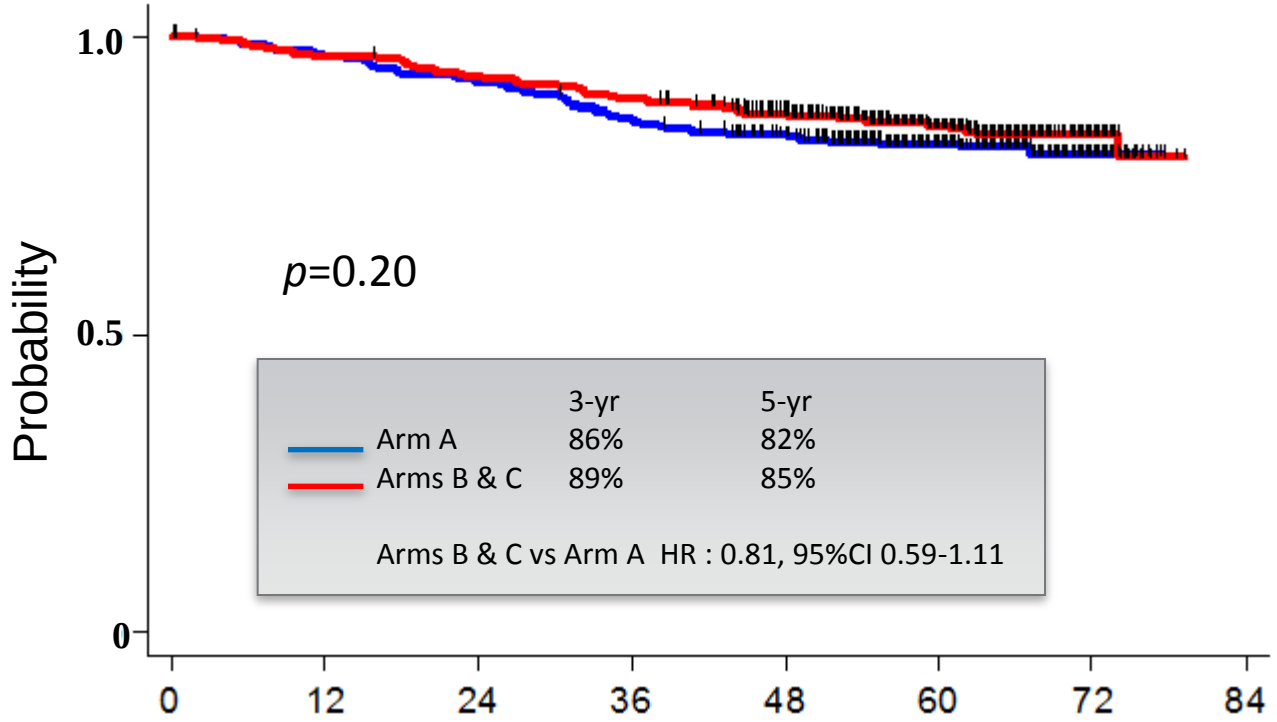
All patients (n=990)



Patients at risk								
Arm A	333	322	306	285	253	148	22	0
Arm B	331	320	310	296	260	144	26	0
Arm C	326	311	297	287	265	143	27	0

DFS

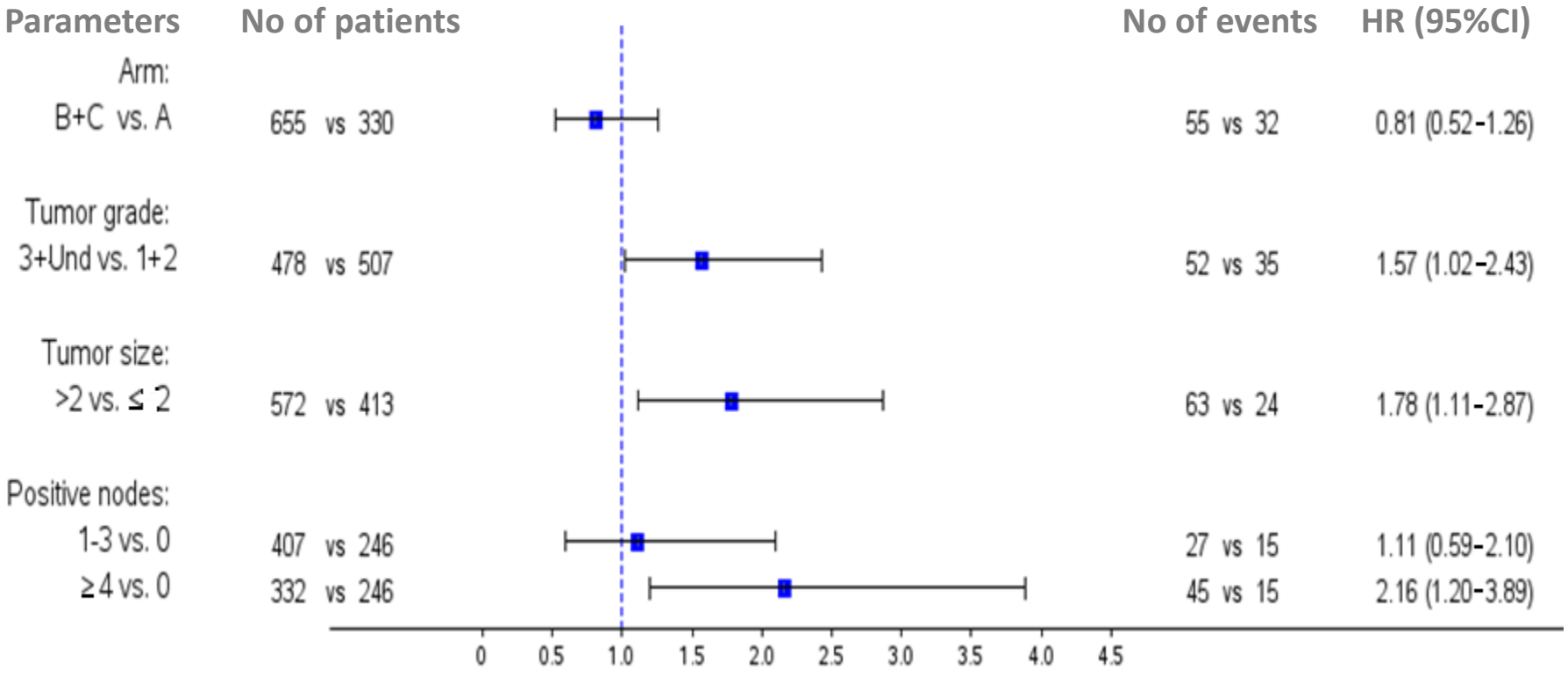
All patients (n=990)
Combined B & C arms



Patients at risk

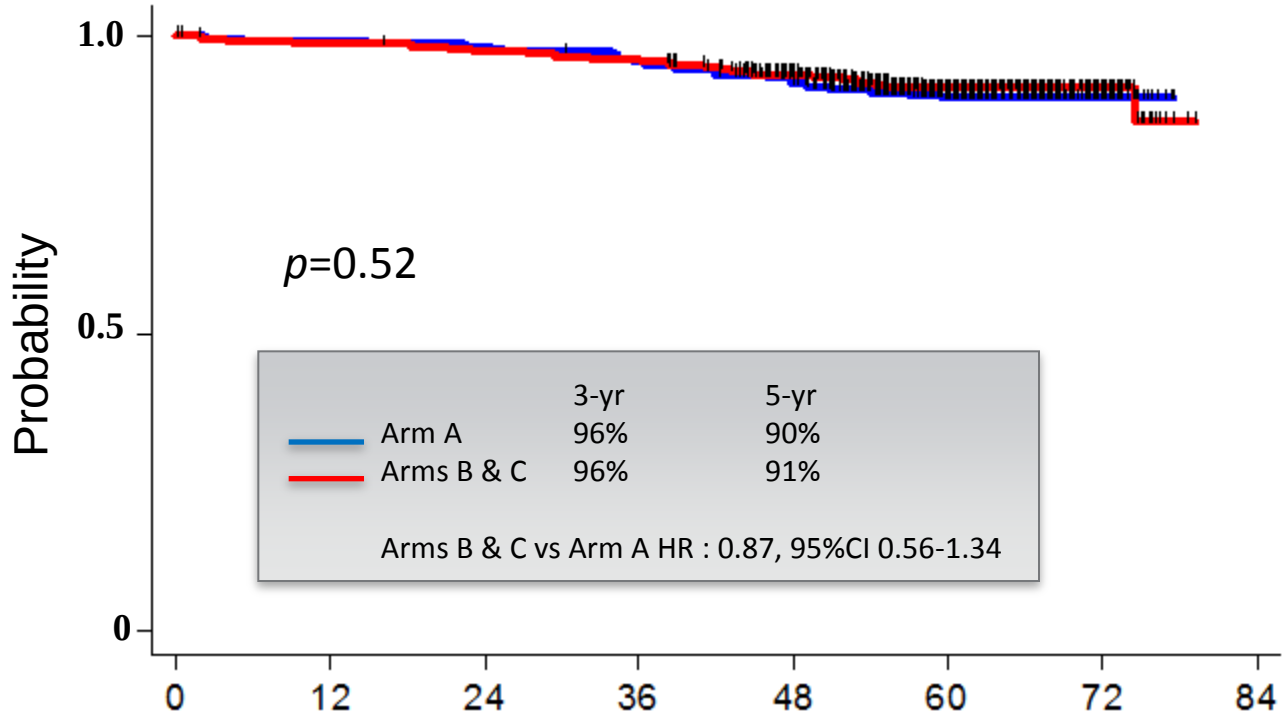
Arm A	333	322	306	285	253	148	22	0
Arms B & C	657	631	607	583	525	288	51	0

Multivariate analysis for DFS



OS

All patients (n=990)
Combined B & C arms

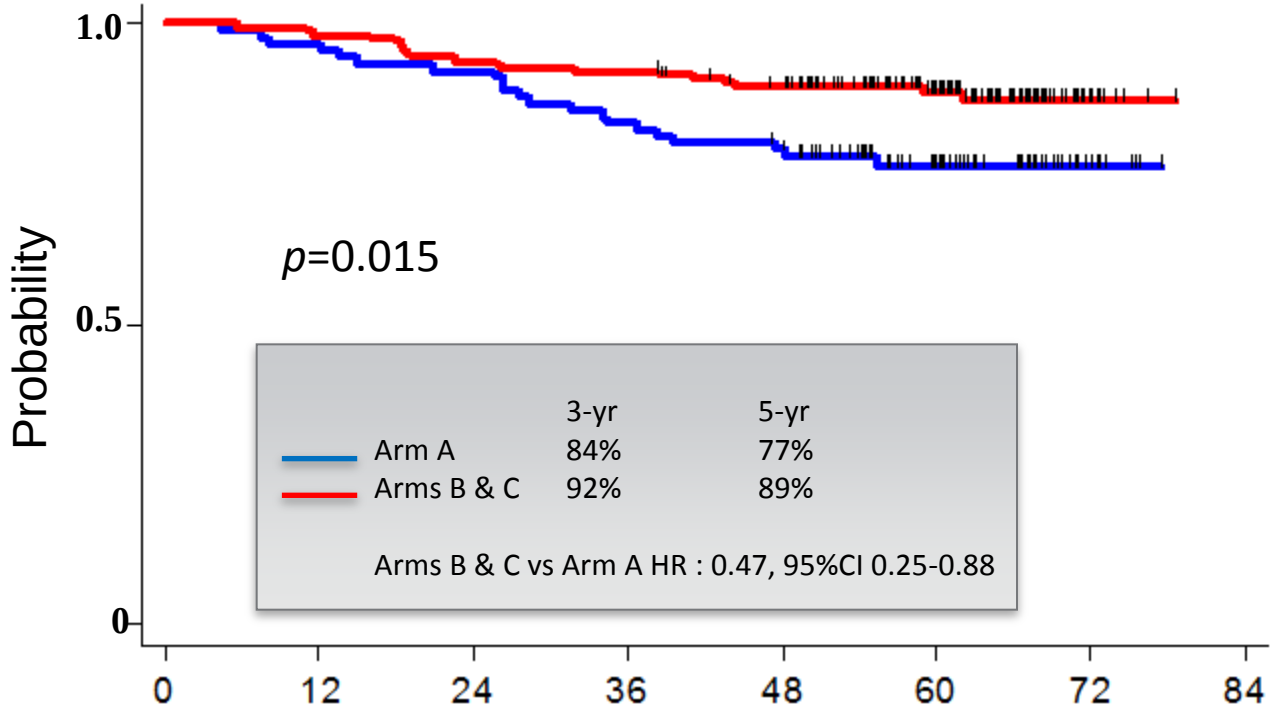


Patients at risk

Arm A	333	329	326	317	279	157	25	0
Arms B & C	657	645	638	627	566	312	58	0

DFS

Only trastuzumab-treated patients (n=256)
Combined B & C arms

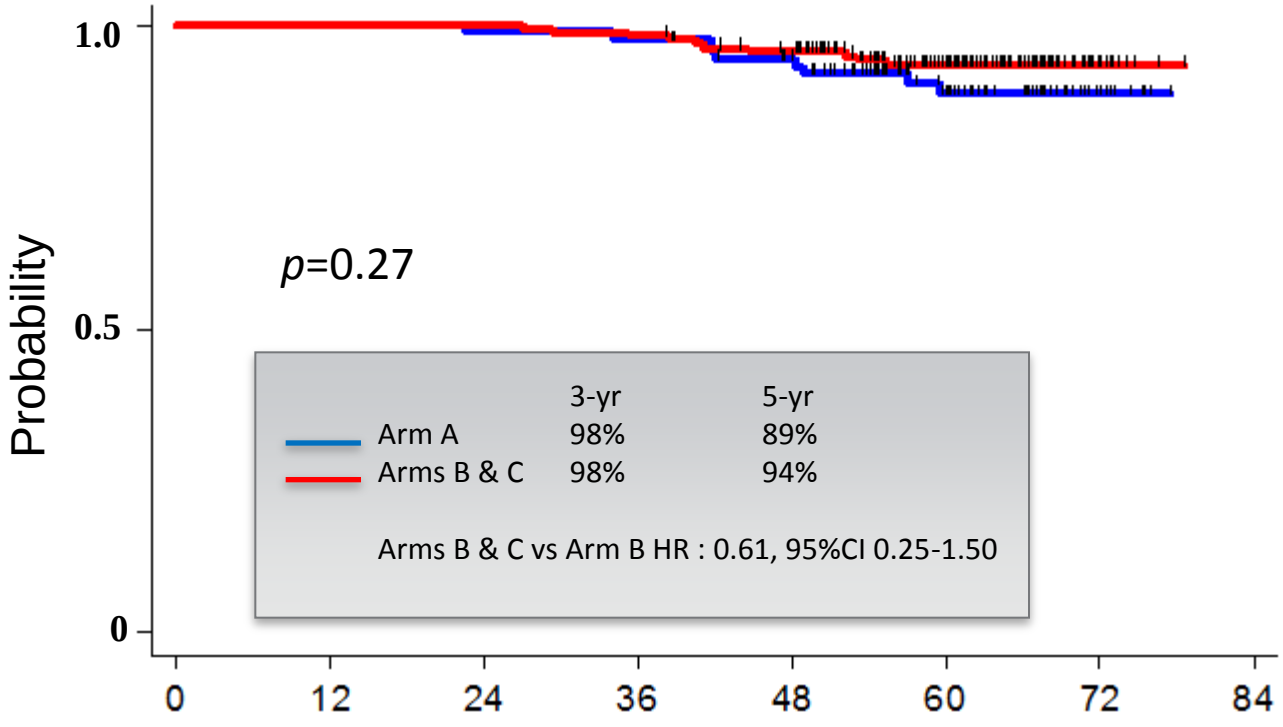


Patients at risk

Arm A	91	88	84	76	71	43	8	0
Arms B & C	165	162	155	152	142	85	10	0

OS

Only trastuzumab-treated patients (n=256)
Combined B & C arms



Patients at risk

Arm A	91	91	90	89	83	47	9	0
Arms B & C	165	165	165	162	152	90	11	0

Conclusions - 1

- In this report, at 5-year follow-up, a significant difference in DFS was not demonstrated between the control arm and the combined sequential weekly schedules of the two taxanes
- The study follow-up continues up to the time 330 events will be observed (conditional power 0.44)
- The incidence of severe adverse events differed significantly among the three regimens

Conclusions - 2

- 3-yr DFS and OS rates of patients treated with TR were similar to those reported in pivotal randomized trials
- In a subgroup analysis of TR-treated patients, DFS was significantly longer in the patients receiving the weekly taxane regimen
- The present randomized trial is the first showing that 3-weekly TR for one year following DD CT is feasible and safe

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