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A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer

The Synergism Or Long Duration (SOLD) trial

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Author disclosures

HJ is an advisor of Neutron Therapeutics, has received consultation fees from Orion Pharma, has Orion Pharma, Faron Pharmaceuticals, and Sartar Therapeutics stock ownership interest, and has a co-appointment for Orion Pharma. HW has received honoraria from Amgen and Novartis, has a consulting role with Roche, Amgen, Novartis, Celldex, Pfizer, and PUMA, has received research funding from Roche, and compensation for travelling from Roche, Pfizer, and PUMA. RH has acted as an advisor with Teva Pharmaceuticals, Amgen, AstraZeneca, and Roche. MU has a consulting role with Roche, Pfizer, AstraZeneca, Teva Pharmaceuticals, and Amgen. HGB and DR have a consulting role with Pfizer. TH is an employee of 4Pharma Ltd. PKL has a consulting role with Sanofi, Pfizer, Roche, and Bristol-Myers Squibb, and has received compensation for travelling from Roche, Astellas Pharma, Sanofi, and Bayer. HL has acted as an advisor for AstraZeneca, Novartis, Pfizer, Amgen, and Daiichi Sankyo, and is in the speakers' bureau of Servier, Amgen, Celgene, AstraZeneca, and Roche.

Background

- The standard duration of adjuvant trastuzumab is 12 months in the treatment of early HER2-positive BC
- This duration was selected arbitrarily,[1,2] but is now supported by a few studies[3-5]

[1]Pinto AC et al. Breast 2013; 22(Suppl) 2:S:152-5
[2]Mathew A et al. Curr Probl Cancer 2016; 40:106-11
[3]Pivot X et al. Lancet Oncol 2013; 14:741-48
[4]Mavroudis D et al. Ann Oncol 2015; 26:1333-40
[5]Cameron D et al. Lancet 2017; 389:1195-1205

Background

- Administration of trastuzumab concomitantly with a taxane improves trastuzumab efficacy, and might be synergistic
  - Evidence from in vitro studies[1,2]
  - Randomized trials carried out in advanced BC[3,4]
  - Data from one randomized trial in the adjuvant setting[5]
- Continuing of trastuzumab after trastuzumab plus concomitant taxane might not markedly add to efficacy[6,7]

[1]Pegram MD et al. Semin Oncol 2000; 27 (6 Suppl 11):21-5; [2]Pegram MD et al. JNCI 2004; 96:739-49; [3]Inoue K et al. Breast Cancer Res Treat 2010; 119:127-36; [4]Hamberg P et al. Clin Breast Cancer 2011; 11:103-13; [5]Perez EA et al. JCO 2011; 29:4491-7; [6]Schneider BP et al. Br J Cancer 2015; 113:1651-7; [7]Conte PF et al. JCO 2017; 35 (Suppl): abstr 501

SOLD hypothesis

- Administration of trastuzumab concomitantly with a taxane for a brief time period is not inferior in terms of DFS as compared with the standard treatment*, and may be less cardiotoxic

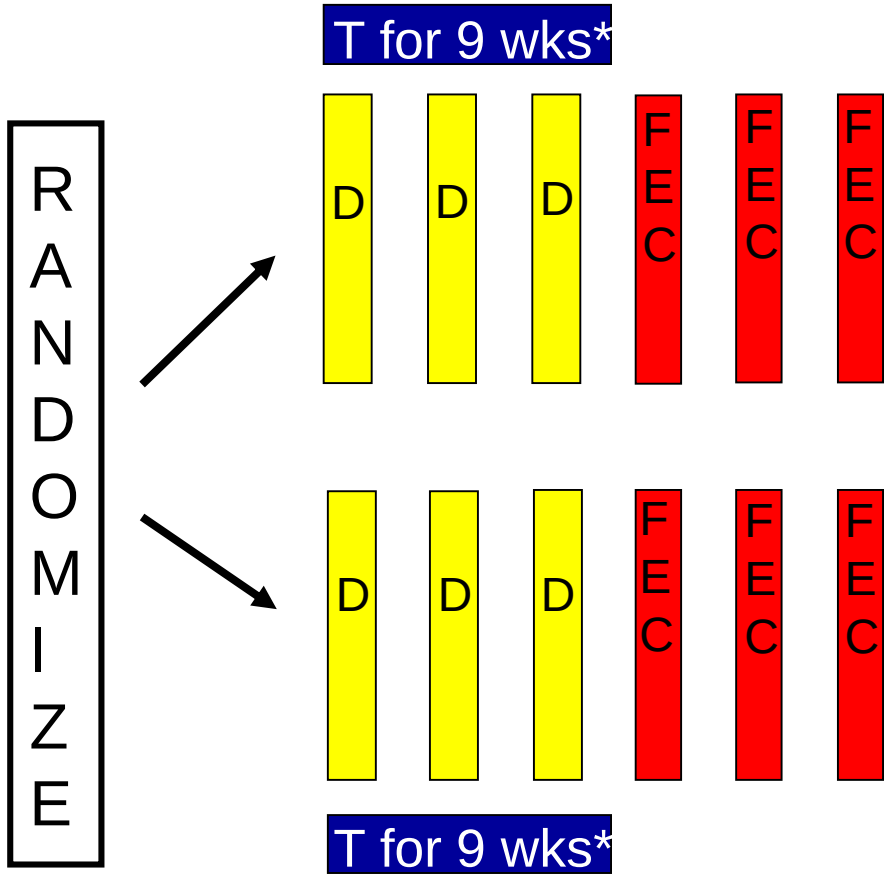
*Standard:
Chemotherapy plus 12 months of anti-HER2-directed treatment ± endocrine therapy

SOLD design

Docetaxel (D)
80/100 mg/m^2
iv 3-wkly

$F_{600}E_{75}C_{600}$
iv 3-wkly

Trastuzumab
(T)



*Wkly iv,
or 3-wkly either iv or sc

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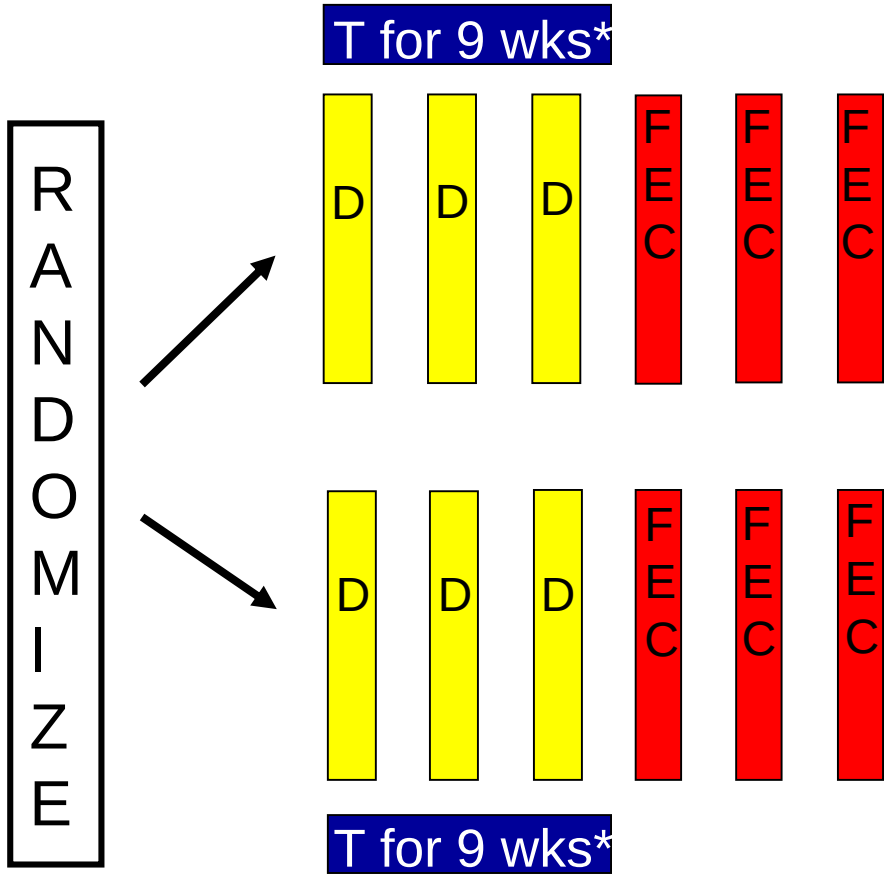

T to complete 1 year of administration**

*Wkly iv,
or 3-wkly either iv or sc

**14 times 3-weekly, either iv or sc

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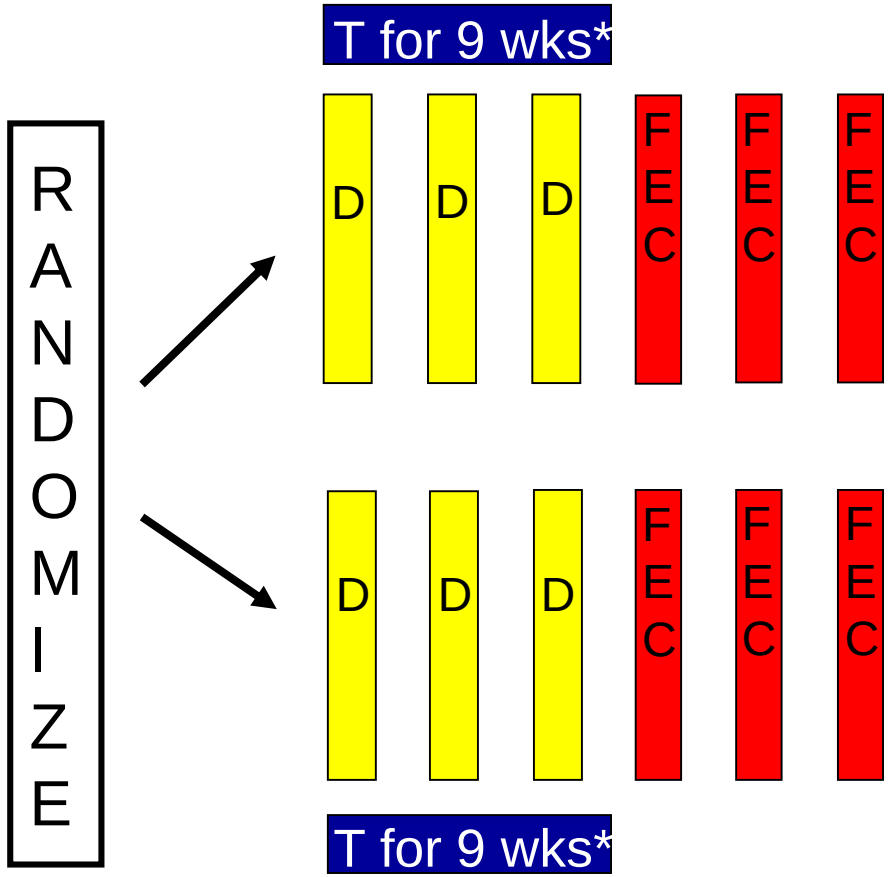


*Wkly iv,
or 3-wkly either iv or sc

In both groups:

- Locoregional RT given according to the institutional practice
- Endocrine therapy for a minimum of 5 yrs when cancer ER/PR +ve

T to complete 1 year of administration**

**14 times 3-weekly, either iv or sc

Study objectives

Primary objective

- Disease-free survival (DFS)*

Secondary objectives included

- Distant disease-free survival (DDFS)
- Overall survival
- Treatment safety

*Endpoints: distant recurrence, locoregional recurrence, contralateral breast cancer, invasive second cancer, death

Key inclusion criteria

- WHO performance status 0 or 1
- Histologically confirmed HER2-positive BC
  -Either in situ hybridization +, or IHC +++
- Node-positive cancer, or node-negative with size >5 mm (if 6-10 mm, histological grade 2 or 3)
- LVEF ≥50%

WHO = World Health Organization
IHC = immunohistochemistry
LVEF = left ventricular ejection fraction

Key exclusion criteria

- Presence of distant metastases
- Neoadjuvant systemic therapy for breast cancer
- Clinically significant cardiac disease

Study procedures

- Central randomization using dynamic minimization
  -Stratification factors: the axillary nodal status, the HER2 analysis method (in situ hybridization or IHC +++), cancer ER expression (positive vs. negative), the study center
- Side effects were graded according to the CTCAE v.3.0
- The LVEF was measured at baseline, on study weeks 18, 31, 43, and 61, and 36 months after study entry with either echocardiography or isotope cardiography

LVEF = Left ventricular ejection fraction
CTCAE = Common Terminology Criteria for Adverse Events

Estimation of the sample size

- Original design: A superiority trial, a sample size of 3,000 pts needed to achieve 516 events, based on
  - -a 4% difference in 5-yr DFS between the groups (80% vs. 84%)
  - -a power of 0.80, 2-sided significance level of .05, a HR of 0.781

Revised sample size

- Study design was revised (amendment on Feb 21, 2014)
  - -The assumptions made for 5-yr DFS were likely too low[1,2]
  - -A non-inferiority design seemed more reasonable
  - -Longer than expected accrual affected the power calculations
- 5-yr DFS of 85.0% was estimated in the 1-yr group, and absolute 5-yr DFS differences <4% were not considered clinically significant, leading to a relative non-inferiority margin of 1.3, and a sample size of 2168 patients (366 events using 1-sided .05 significance level)

[1]Perez EA et al. JCO 2014; 32:3744-52; [2]Perez EA et al. JCO 2011; 29:3366-73

Accrual and follow-up

- 2,176 patients accrued between Jan 3, 2008, and Dec 16, 2014
  - -From 65 centers located in 7 countries*
- The study was analyzed based on the landmark follow-up time (as per protocol)
  - -In Dec. 2016, when the last patient accrued had been followed up for 2 yrs, fewer than 366 events had occurred
- The data collection cut-off date was set as Dec. 31, 2016
- Median follow-up time was 5.2 years

*Finland, Sweden, the United Kingdom, Belgium, New Zealand, Iceland, Serbia

Patient disposition

Category	9 weeks	1 year
	no. (%)	no. (%)
Randomized (Jan 2008 to Dec 2014)	1,087	1,089
Included in ITT Population*	1,085	1,089
- Withdrew consent	0 (0)	0 (0)
- Had distant metastases at study entry	2 (0)	0 (0)
Received study treatment (Safety Population)	1,084	1,089

ITT = Intention to treat

Key baseline characteristics

Characteristic	9-week group (n=1,085)	1-year group (n=1,089)
Median age (range) – years (range)	56 (23-82)	56 (27-79)
Premenopausal	33 %	33 %
Breast tumor diameter		
≤10 mm	12 %	14 %
11-21 mm	44 %	42 %
21-50 mm	41 %	42 %
>50 mm	3 %	3 %
Axillary lymph nodes with cancer		
0	60 %	60 %
1-3	30 %	29 %
>3	11 %	11 %
Ductal histological type	92 %	92 %
Estrogen receptor-positive	66 %	66 %
Progesterone receptor-positive	46 %	47 %

DFS events (ITT)

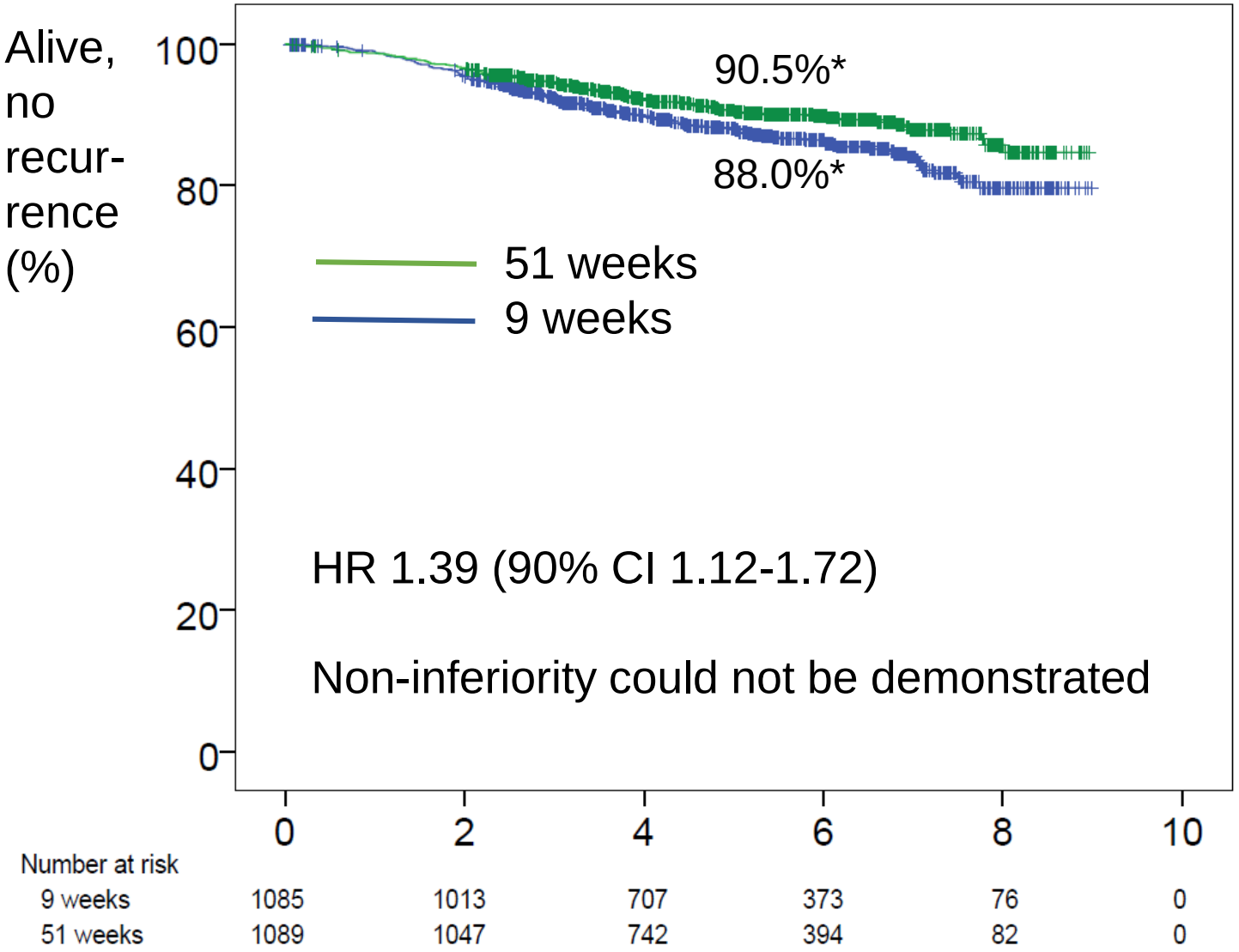
Event	9-wk group (n=1,085) n (%)	1-yr group (n=1,089) n (%)
Any recurrence or death	140 (13)	105 (10)
Distant recurrence	73 (7)	61 (6)
Locoregional recurrence	17 (2)	13 (1)
Contralateral BC	15 (1)	7 (1)
Second cancer	27 (3)	24 (2)
Death without cancer	14 (1)	5 (0)

DFS = Disease-free survival
ITT = Intention-to-treat

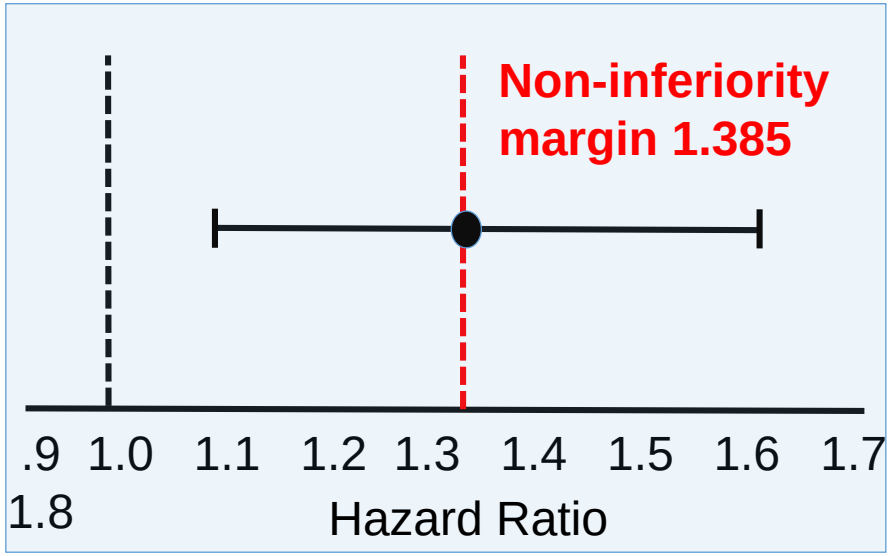
DFS events and deaths (ITT)

Event	9-wk group (n=1,085) n (%)	1-yr group (n=1,089) n (%)
Any recurrence or death	140 (13)	105 (10)
Distant recurrence	73 (7)	61 (6)
Locoregional recurrence	17 (2)	13 (1)
Contralateral BC	15 (1)	7 (1)
Second cancer	27 (3)	24 (2)
Death without cancer	14 (1)	5 (0)
Death from any cause	58 (5)	44 (4)
Death from BC	34 (3)	33 (3)
Death from another cause	24 (2)	11 (1)

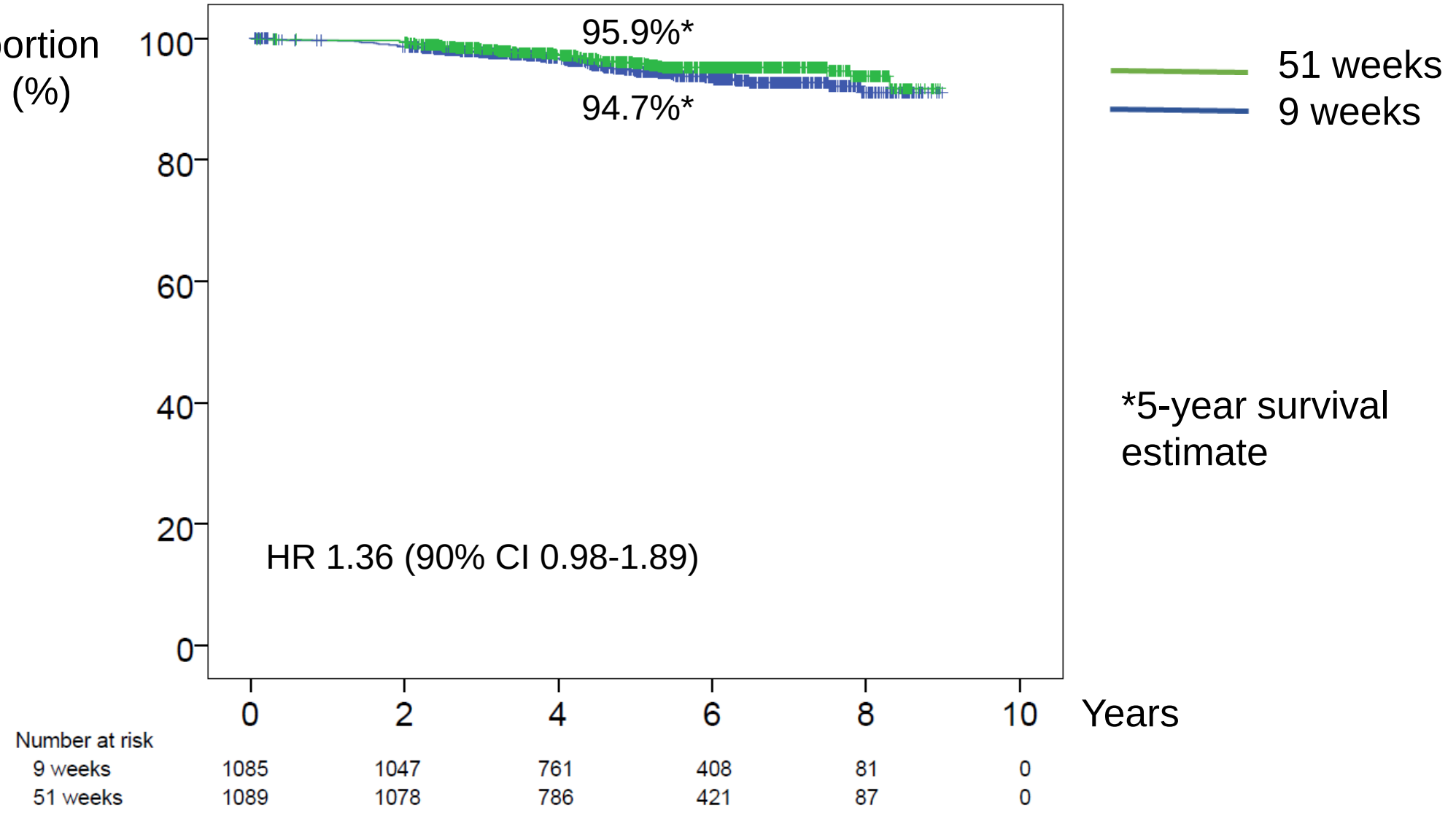
Disease-free survival



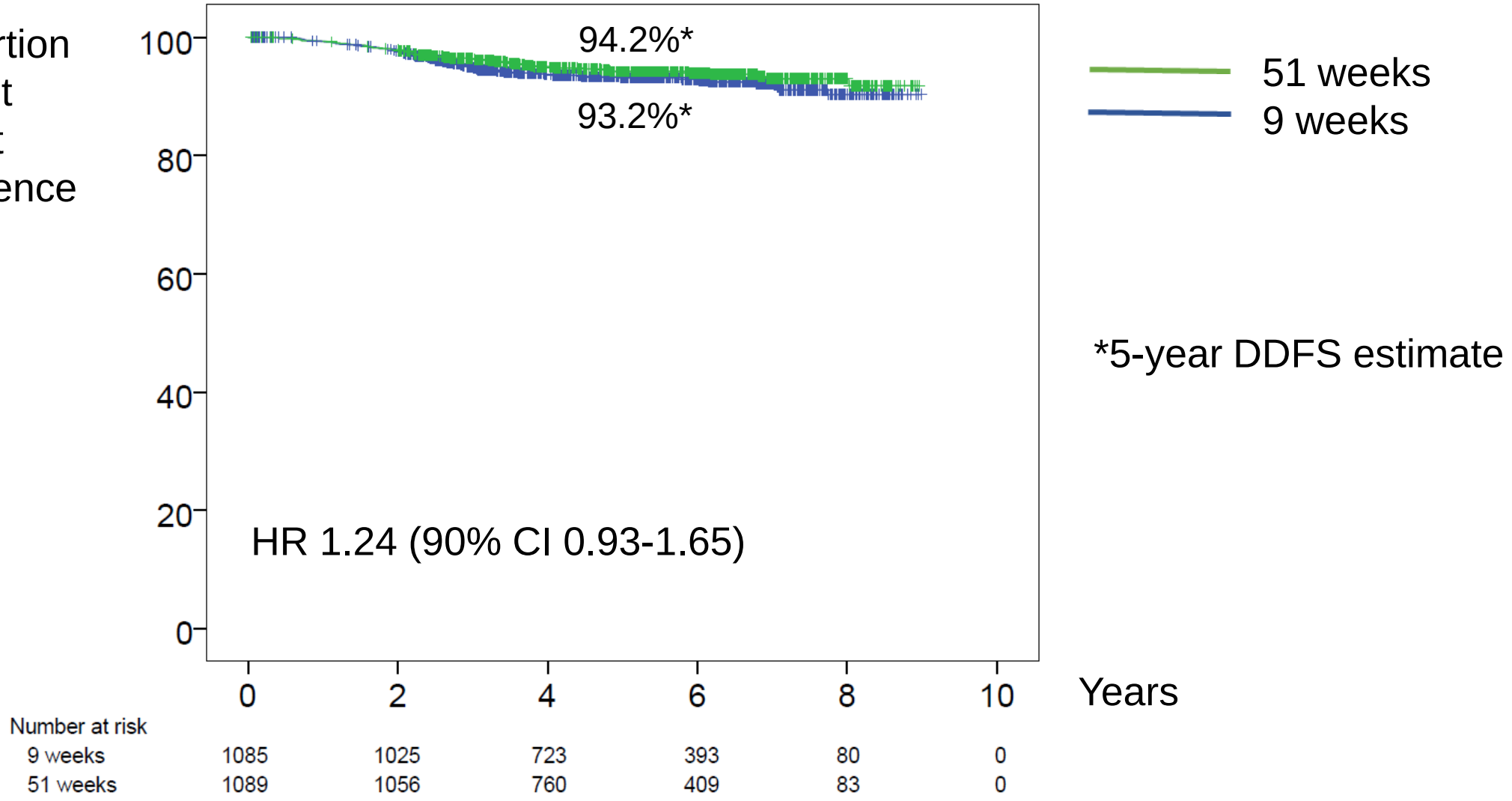
*5-year DFS estimate



Overall survival

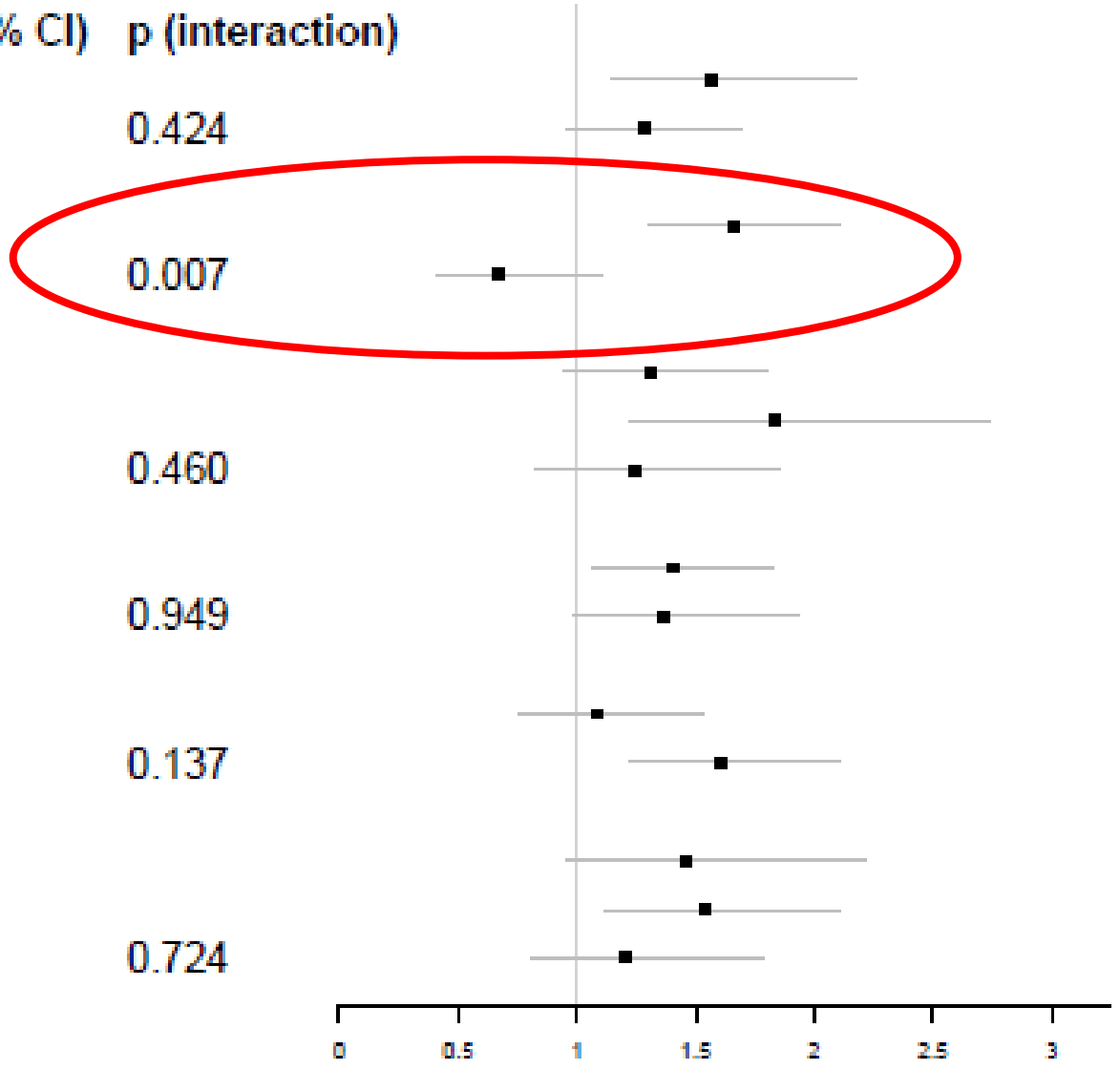


Distant disease-free survival



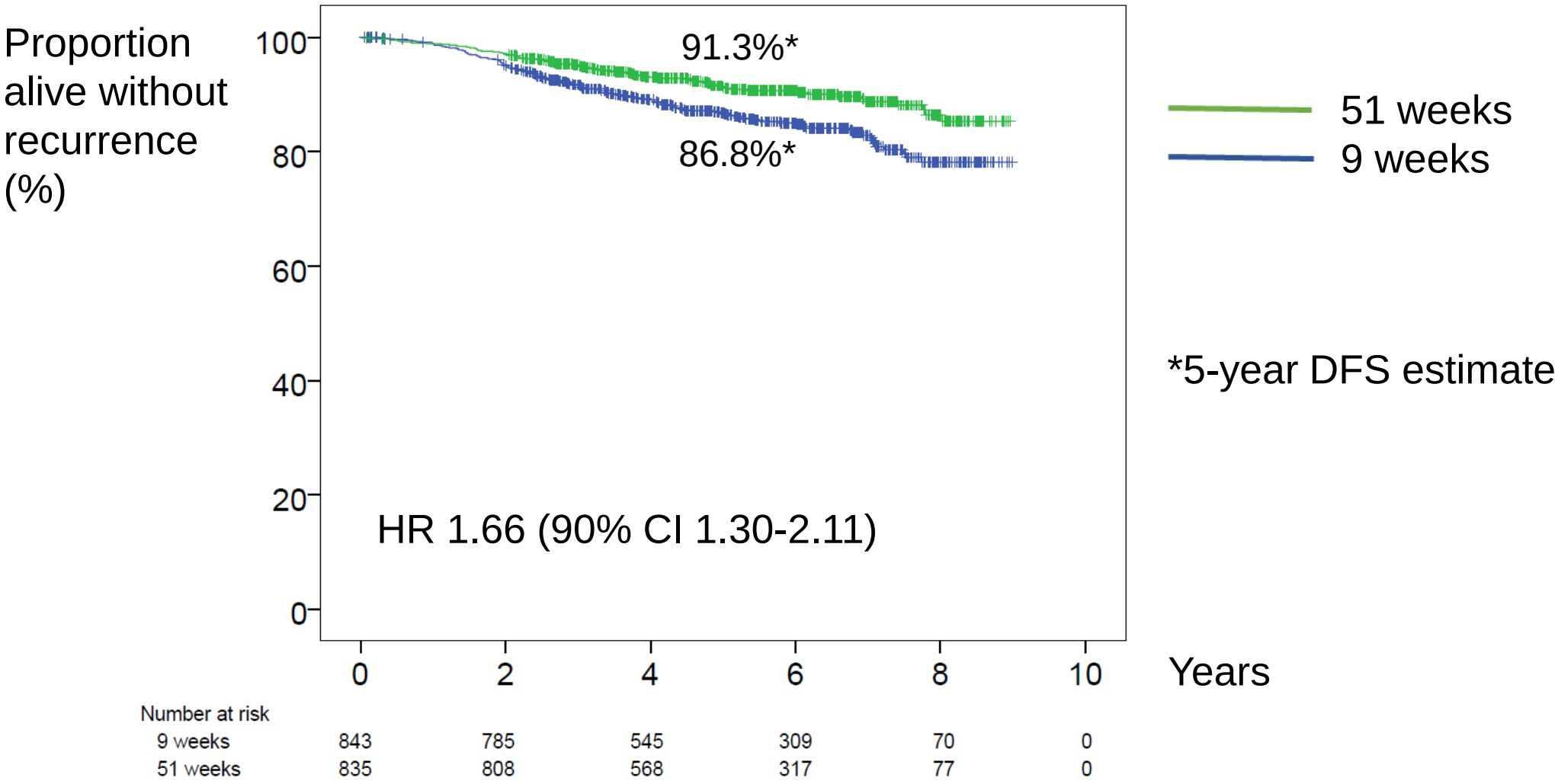
Predefined subgroup analyses for DFS

Subgroup		Hazard Ratio (90−% CI)	p (interaction)
ER status	Negative	1.57 (1.14−2.17)	
	Positive	1.28 (0.96−1.69)	0.424
Docetaxel dose	80 mg/m2	1.66 (1.30−2.11)	
	100 mg/m2	0.67 (0.41−1.10)	0.007
Nodes with cancer	0	1.31 (0.95−1.80)	
	1−3	1.83 (1.22−2.74)	
	3+	1.24 (0.82−1.85)	0.460
Centre accrual	< 100 patients	1.40 (1.06−1.83)	
	=> 100 patients	1.37 (0.98−1.93)	0.949
Age	< 50 yrs	1.08 (0.76−1.53)	
	>= 50 yrs	1.61 (1.23−2.11)	0.137
Stage	I	1.46 (0.96−2.22)	
	II	1.54 (1.12−2.11)	
	III	1.21 (0.81−1.79)	0.724

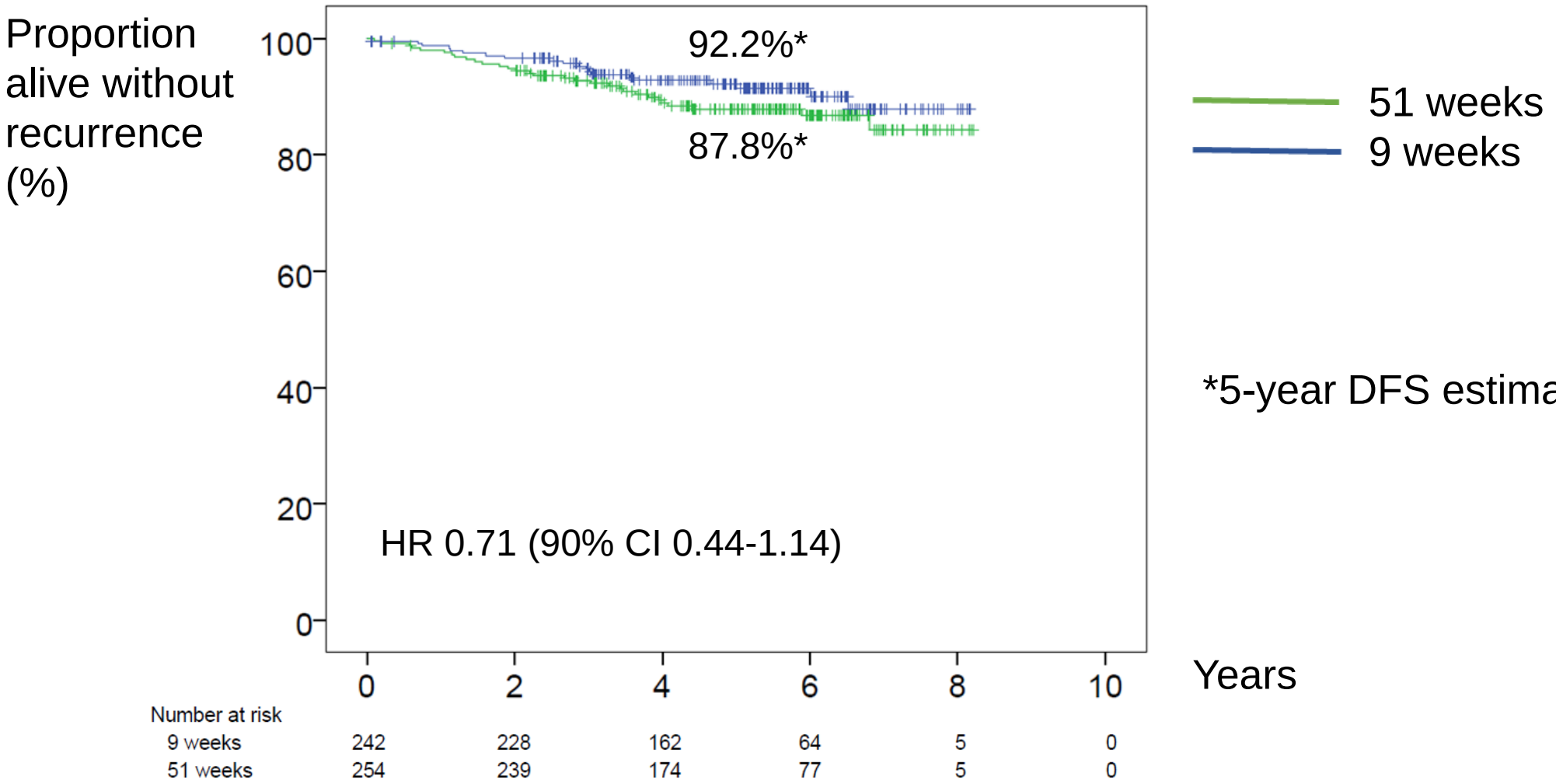


Favors 9 weeks Favors 1-year

DFS: Docetaxel dose 80 mg/m²



DFS: Docetaxel dose 100 mg/m²



Treatment safety

- Chemotherapy-related toxicity generally similar and expected in the 2 groups

	9-week group n (%)	1-year group n (%)
Discontinued chemotherapy	44 (4.1)	51 (4.7)
Discontinued trastuzumab	96 (8.9) -53% for toxicity	217 (19.9) -66% for toxicity
Died from a treatment-related cause	2 (0.2)	2 (0.2)

Cardiac safety

- Less cardiac toxicity was observed in the 9-week group

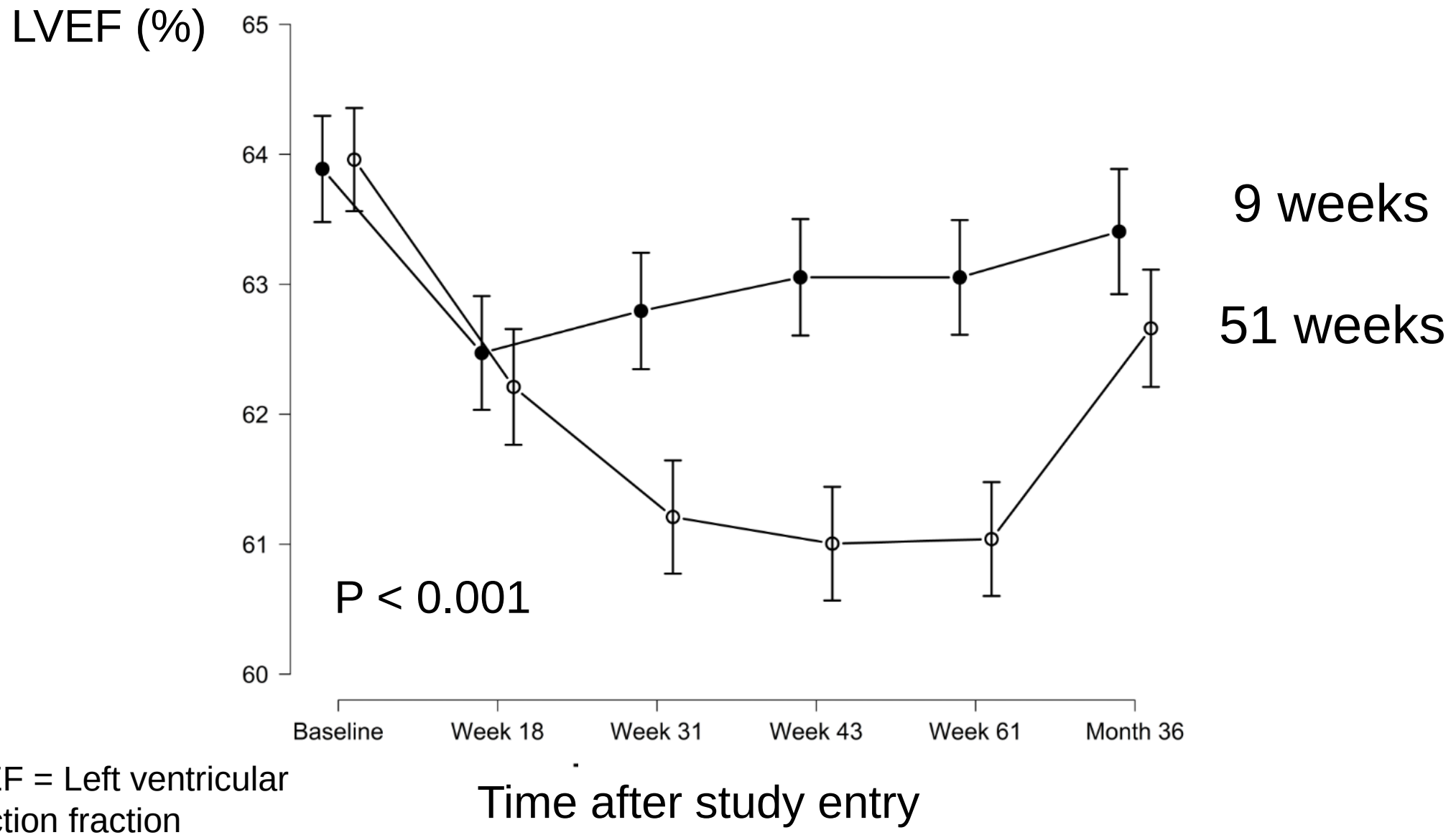
Event	9-week group n (%)	1-year group n (%)
Any protocol-defined cardiac adverse event*	22 (2.0)	42 (3.9)*
Congestive heart failure	21 (1.9)	36 (3.3)**

*P = 0.012

**P = 0.046

*Any Gr. 3 or 4 cardiac event; symptomatic cardiac failure; cardiac failure requiring medical management; LVEF decrease >10 percentage points and to a value <50%; LVEF decrease to <45% from any baseline value

Mean LVEF stratified by the treatment group



LVEF = Left ventricular ejection fraction

Conclusions

- Non-inferiority of 9-weeks of adjuvant trastuzumab plus chemotherapy could not be demonstrated as compared to 1-year of trastuzumab plus chemotherapy in terms of DFS
- Patients treated with the 9-week duration had fewer cardiac events and had the LVEF better maintained
- Docetaxel dosing with trastuzumab requires further study
- Chemotherapy plus 1-year of anti-HER2 therapy should remain the standard

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SOLD investigators:

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