

# Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year With Concomitant Chemotherapy for Early Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: The SOLD Randomized Clinical Trial

Heikki Joensuu, MD; Judith Fraser, MD; Hans Wildiers, MD; Riikka Huovinen, MD; Päivi Auvinen, MD; Meri Utriainen, MD; Paul Nyandoto, MD; Kenneth K. Villman, MD; Päivi Halonen, MD; Helena Granstam-Björneklett, MD; Lotta Lundgren, MD; Liisa Sailas, MD; Taina Turpeenniemi-Hujanen, MD; Minna Tanner, MD; Jeffrey Yachnin, MD; Diana Ritchie, MD; Oskar Johansson, MD; Teppo Huttunen, MSc; Patrick Neven, MD; Peter Canney, MD; Vernon J. Harvey, MD; Pirkko-Liisa Kellokumpu-Lehtinen, MD; Henrik Lindman, MD

## Supplemental content

**IMPORTANCE** Trastuzumab plus chemotherapy is the standard adjuvant treatment for patients with human epidermal growth factor receptor 2 (*HER2*)-positive early breast cancer. While the standard duration of trastuzumab treatment is 12 months, the benefits and harms of trastuzumab continued beyond the chemotherapy are unclear.

**OBJECTIVE** To evaluate the efficacy and safety of adjuvant trastuzumab continued beyond chemotherapy in women treated with up-front chemotherapy containing a taxane and trastuzumab.

**DESIGN, SETTING, AND PARTICIPANTS** Open-label, randomized (1:1) clinical trial including women with *HER2*-positive breast cancer. Chemotherapy was identical in the 2 groups, consisting of 3 cycles of 3-weekly docetaxel (either 80 or 100 mg/m<sup>2</sup>) plus trastuzumab for 9 weeks, followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide. Thereafter, no trastuzumab was administered in the 9-week group, whereas controls received trastuzumab to complete 1 year of administration. Disease-free survival (DFS) was compared between the groups using a Cox model and the noninferiority approach. The estimated sample size was 2168 patients (1-sided testing, with a relative noninferiority margin of 1.3). From January 3, 2008, to December 16, 2014, 2176 patients were accrued from 7 countries.

**INTERVENTION** Docetaxel plus trastuzumab for 9 weeks, followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide in both groups. Controls continued trastuzumab to 1 year.

**MAIN OUTCOMES AND MEASURES** The primary objective was DFS; secondary objectives included distant disease-free survival, overall survival, cardiac DFS, and safety.

**RESULTS** In the 2174 women analyzed, median age was 56 (interquartile range [IQR], 48-64) years. The median follow-up was 5.2 (IQR, 3.8-6.7) years. Noninferiority of the 9-week treatment could not be demonstrated for DFS (hazard ratio, 1.39; 2-sided 90% CI, 1.12-1.72). Distant disease-free survival and overall survival did not differ substantially between the groups. Thirty-six (3%) and 21 (2%) patients in the 1-year and the 9-week groups, respectively, had cardiac failure; the left ventricle ejection fraction was better maintained in the 9-week group. An interaction was detected between the docetaxel dose and DFS; patients in the 9-week group treated with 80 mg/m<sup>2</sup> had inferior and those treated with 100 mg/m<sup>2</sup> had similar DFS as patients in the 1-year group.

**CONCLUSIONS AND RELEVANCE** Nine weeks of trastuzumab was not noninferior to 1 year of trastuzumab when given with similar chemotherapy. Cardiac safety was better in the 9-week group. The docetaxel dosing with trastuzumab requires further study.

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**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Heikki Joensuu, MD, Department of Oncology, Helsinki University Hospital and University of Helsinki, Haartmaninkatu 4, PO Box 180, FIN-00029 Helsinki, Finland ([heikki.joensuu@hus.fi](mailto:heikki.joensuu@hus.fi)).

Patients with breast cancer treated with adjuvant trastuzumab, an antibody targeting human epidermal growth factor receptor 2 (*HER2*), and chemotherapy after surgery for localized cancer have fewer recurrences and live longer compared with patients treated with chemotherapy alone.<sup>1,2</sup> The most notable adverse effect of trastuzumab therapy is congestive heart failure (CHF), which occurs in 1% to 3% of the patients treated in clinical trials,<sup>1,3</sup> but the proportion is higher in elderly populations with risk factors for CHF.<sup>4</sup> Trastuzumab-related decrease in the cardiac left ventricular ejection fraction (LVEF) usually resolves after drug discontinuation and initiation of therapy for CHF.<sup>5-7</sup>

Adjuvant trastuzumab is recommended to be administered for 1 year and in part concomitantly with chemotherapy.<sup>8,9</sup> The choice of this duration was arbitrary<sup>10</sup> in the trials that established the current standard 12-month duration.<sup>11-13</sup> While the optimal duration remains unknown, 6 months of adjuvant trastuzumab did not lead to noninferior survival outcomes compared with 1-year administration in randomized trials, although the results tended to favor the longer duration,<sup>14,15</sup> and 2-year administration was not superior to 1 year of administration.<sup>16</sup>

Observations from in vitro studies,<sup>17,18</sup> randomized trials in the treatment of advanced breast cancer,<sup>19,20</sup> and data from 1 adjuvant trial<sup>21</sup> suggest that concomitant administration of a taxane with trastuzumab improves efficacy, and may be synergistic. In 2 randomized trials<sup>22,23</sup> the experimental group patients were treated with trastuzumab and a concomitant taxane and received no trastuzumab after chemotherapy, whereas the standard group patients were treated with trastuzumab both during chemotherapy and after chemotherapy for a total duration of 1 year. Neither trial found the standard group to have superior disease-free survival (DFS) or overall survival (OS), but these trials had relatively limited power. We studied in the present Synergism or Long Duration (SOLD) trial the benefits and harms of adjuvant single-agent trastuzumab continued beyond chemotherapy in a patient population treated with upfront chemotherapy containing docetaxel and trastuzumab. The study hypothesis was that a brief course of trastuzumab, administered concomitantly with potentially synergistic chemotherapy, leads to similar efficacy as chemotherapy plus trastuzumab administered for 1 year, and to fewer cardiac toxic effects.

## Methods

### Patients

Patients who had histologically confirmed *HER2*-positive breast cancer with either regional node-positive or node-negative disease and with cancer size 5 mm or greater were eligible (when size was 6-10 mm, histological grade was required to be 2 or 3). Cancer *HER2* positivity was verified by demonstrating either the presence of *ERBB2/HER2* amplification using in situ hybridization or strong *HER2* protein expression by immunohistochemical analysis (a score of 3+ on a scale from negative to 3+) according to the institutional guidelines. Other eligibility criteria included age 18 years or older; World Health Organi-

### Key Points

**Question** Does administration of trastuzumab concomitantly with a taxane for a brief period (9 weeks) lead to similar survival outcomes as chemotherapy and 1 year of trastuzumab in women with early human epidermal growth factor receptor 2–positive breast cancer?

**Findings** In this randomized clinical trial including 2174 women, both treatments were associated with high 5-year distant disease-free survival and overall survival rates, but the 9-week trastuzumab regimen resulted in a shorter disease-free survival than the 1-year regimen. The shorter treatment was associated with fewer cardiac adverse effects and better maintained cardiac function.

**Meaning** Trastuzumab continued beyond chemotherapy increases efficacy but may lead to more cardiac adverse effects.

zation performance score 0 or 1 (on a scale of 0-5); and adequate renal, hepatic, and bone marrow function. An LVEF of at least 50% was required (or within the institutional reference range). Patients with clinically significant cardiac disease were excluded. Other exclusion criteria included presence of distant metastases, neoadjuvant systemic therapy, and history of another malignant neoplasm within the past 5 years. Independent ethics committees of the participating hospitals and the relevant medical authorities of the participating countries approved the study. All patients provided written informed consent prior to study inclusion.

### Study Procedures

The primary objective in this open-label phase 3 trial was DFS, defined as the interval between the date of randomization and date of diagnosis of invasive cancer recurrence (distant recurrence, locoregional recurrence, contralateral breast cancer, or any invasive second cancer) or death if the patient died prior to recurrence. The secondary objectives included distant disease-free survival (DDFS, the time from randomization to the date of first diagnosis of distant recurrence of breast cancer, or to death), cardiac DFS (the period from randomization to the date of a cardiac event, cancer recurrence, or death; a cardiac event was defined as CHF necessitating medication or medical intervention, myocardial infarction, cardiac or coronary artery surgery, or stenting), OS (the period from randomization to the date of death), and treatment safety.

Patients were randomized centrally with blinded computer-assisted allocation to the study groups. Randomization (1:1) was performed using dynamic minimization, with a 90% chance of allocation to the group with the lowest count. Patients were stratified at randomization between the groups by axillary nodal status, *HER2* analysis method (in situ hybridization or immunohistochemical analysis), cancer estrogen receptor expression (positive vs negative), and study center.

Chemotherapy was identical in the groups. It consisted of 3 cycles of 3-weekly docetaxel given concomitantly with trastuzumab, followed by 3 cycles of 3-weekly fluorouracil, epirubicin hydrochloride, and cyclophosphamide (FEC). The only

difference in the treatment between the groups was that in the experimental group (the 9-week group) no further trastuzumab was given after completion of chemotherapy, whereas in the standard treatment group (1-year group) trastuzumab was given to complete 1 year of administration (for a total of 51 weeks).

The docetaxel dose was prespecified for each center, either 80 or 100 mg/m<sup>2</sup> intravenously, based on center preference. Use of the starting dose of 100 mg/m<sup>2</sup> in patients younger than 60 years and 80 mg/m<sup>2</sup> among those 60 years or older was allowed, provided that this practice was followed throughout the study. FEC consisted of intravenous fluorouracil (600 mg/m<sup>2</sup>), epirubicin hydrochloride (75 mg/m<sup>2</sup>), and cyclophosphamide (600 mg/m<sup>2</sup>), each given on day 1 of the 3-week cycle. Intravenous trastuzumab was administered with docetaxel either weekly or 3-weekly, or subcutaneously 3-weekly (weekly: first dose 4 mg/kg, subsequently 2 mg/kg; 3-weekly: first dose 8 mg/kg, subsequently 6 mg/kg; 3-weekly subcutaneously: each dose 600 mg regardless of body weight). When trastuzumab was administered after chemotherapy (standard group only), it was given 3-weekly 14 times (either intravenously or subcutaneously; intravenously: first dose 8 mg/kg, subsequently 6 mg/kg; subcutaneously: 600 mg regardless of body weight).

Hematopoietic growth factor support was permitted at the discretion of the investigator. Patients with estrogen receptor-positive and/or progesterone receptor-positive cancer received adjuvant endocrine therapy for a minimum of 5 years on completion of chemotherapy. The choice of endocrine therapy was at the treating physician's discretion. The institutional criteria for hormone receptor-positive cancer were followed when the decision about adjuvant endocrine treatment was made, but tumors with at least 10% positive cancer cells by immunohistochemical analysis were considered receptor positive for the stratification. Locoregional radiotherapy was given according to institutional practice. In the 1-year group, single-agent trastuzumab was started 3 weeks ( $\pm$ 1 week) after the last FEC cycle.

Adverse effects were graded according to the Common Terminology Criteria for Adverse Events, version 3.0. Docetaxel and FEC doses were reduced 20% in case of febrile neutropenia, neutropenic infection, grade 4 neutropenia lasting longer than 7 days, any grade 3 or 4 nonhematological toxic effect, or any treatment-related toxic effect that resulted in hospitalization. Trastuzumab doses were not reduced despite docetaxel dose reduction. When docetaxel administration was deferred, trastuzumab administration was also deferred. In the 1-year group no trastuzumab dose reductions were performed, but trastuzumab was discontinued when grade 3 or 4 nonhematological toxic effects considered trastuzumab related occurred, or when a grade 3 or 4 cardiac event, symptomatic cardiac failure, or cardiac failure necessitating medical management took place, or when the LVEF decreased more than 10 percentage points from the baseline value to a value less than 50%, or to less than 45% from any baseline value.

Staging examinations were done according to the institutional practice. However, computed tomography or radiography of the chest; isotope bone scan or skeletal radiography;

and computed tomography, magnetic resonance imaging, or ultrasound of the liver were mandatory at screening for patients with at least 4 positive axillary nodes, metastases in the internal mammary, infraclavicular, or supraclavicular nodes, or when the primary tumor was larger than 5 cm, or classified as pT4. The LVEF was measured at baseline, at study weeks 18, 31, 43, and 61, and 36 months after study entry with either echocardiography (1295 patients [60%]) or isotope cardiography (876 patients [40%]), using the same method throughout the study. The patients were scheduled for a minimum of 8 years of follow-up after randomization.

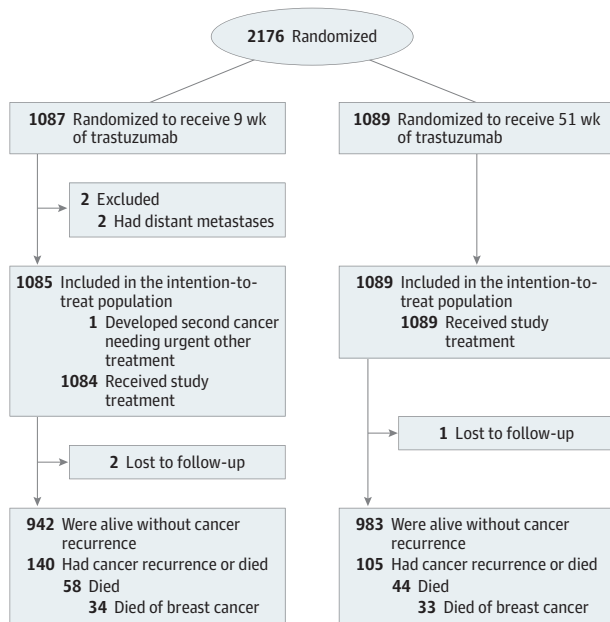
### Statistical Analysis

The study was designed as a superiority trial with an estimated recruitment period of 4 years. The sample calculation was carried out considering a 4% difference in DFS between the groups, 80% vs 84% after 5 years of follow-up, a power of 0.80, a 2-sided significance level of .05, a hazard ratio (HR) of 0.781, and 3% of the patients estimated to be lost to follow-up or to discontinue the study. With these assumptions, 516 events and a sample size of 3000 patients (1500 per group) were estimated to be needed.

These power calculations were revised and the study protocol (Supplement 1) was amended on February 21, 2014, because new data<sup>2,24</sup> suggested that the assumptions made for DFS were too low, and it seemed unreasonable to assume that DFS in the experimental group could be superior to the standard arm because trastuzumab-related cardiac toxic effects were reported relatively rarely. Therefore, a noninferiority design seemed a more reasonable approach. Coincidentally, patient accrual was slower than anticipated, and the longer-than-expected accrual period affected the power calculations. A 5-year DFS of 85.0% was estimated in the 1-year group,<sup>2</sup> and absolute 5-year DFS differences of less than 4% were not considered clinically significant, leading to a relative noninferiority margin of 1.3. The noninferiority margin corresponding to the true (observed) 5-year DFS rate of 88.7% is 1.385 (Statistical Analysis Plan in Supplement 1). Based on an estimated accrual duration of 7.5 years, 1-sided testing,<sup>25,26</sup> a relative noninferiority margin of 1.3, and a 3% dropout rate, the final sample size was 2168 patients (1084 patients per group). The primary analysis was planned for when approximately 366 DFS events were reached or when the last patient entered was followed up for 2.0 years after randomization, whichever occurred first. The sample size was calculated using nQuery Advisor, version 6.0 (Statistical Solutions Ltd).

Efficacy analyses were based on the intention-to-treat principle. Exploratory subgroup analyses were defined in the Statistical Analysis Plan approved prior to the study analysis on February 28, 2017, but not in the original study protocol. The safety population included patients who received at least 1 dose of the study drugs. Frequency tables were analyzed using the  $\chi^2$  test. The LVEF between the groups with time was compared with repeated-measures analysis of variance. Survival between groups was compared using the Kaplan-Meier life-table method and with a Cox proportional hazards model adjusted with the stratification factors. The subgroup analyses were done by including the treatment group, the subgroup

Figure 1. CONSORT Diagram



The numbers of individuals screened for eligibility and the reasons for exclusion were not captured.

variable, and their interaction in the Cox model. Survival analysis results are provided with a 90% 2-sided confidence interval (corresponding to the 1-sided 95% upper limit used in the evaluation of noninferiority). The *P* values are 2 sided and not adjusted for multiple testing. Statistical analyses were performed with SAS, version 9.3 for Windows (SAS Institute, Inc).

## Results

Between January 3, 2008, and December 16, 2014, 2176 patients were accrued from 65 centers (9-week group, 1087; 1-year group, 1089). On December 16, 2016, when the last patient accrued had been followed up for 2 years after randomization, fewer than the anticipated number of DFS events were reported, and therefore the study was analyzed as per the protocol based on the landmark follow-up time. December 31, 2016, was set as the data collection cutoff date.

Two patients with overt metastases at the time of study entry were excluded from the intention-to-treat analysis (Figure 1). Two patients in the 9-week group and 1 in the 1-year group were lost to follow-up. The patient and breast cancer characteristics were similar in the groups; most had axillary node-negative cancer (Table 1). Adjuvant endocrine therapy was administered to 714 (66%) and 727 (67%) participants after chemotherapy in the 9-week and 1-year groups, respectively, and locoregional radiotherapy to 824 (76%) and 811 (74%).

### Survival

During a median follow-up time of 5.2 years (interquartile range [IQR], 3.8-6.7 years), 140 and 105 DFS events were recorded

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	No. (%) <sup>a</sup>	
	Trastuzumab for 9 wk (n = 1085)	Trastuzumab for 51 wk (n = 1089)
Age, median (IQR), y	56 (49-64)	56 (48-63)
Weight, median (IQR), kg	70 (62-80)	70 (61-79)
Race		
White	1061 (98)	1066 (98)
Other	24 (2)	23 (2)
Menopausal status		
Premenopausal	353 (33)	364 (33)
Postmenopausal	731 (67)	724 (66)
Not available	1 (<1)	1 (<1)
World Health Organization performance status		
0	975 (90)	963 (88)
1	102 (9)	112 (10)
Not available	8 (1)	14 (1)
Breast tumor diameter, mm		
≤10	129 (12)	155 (14)
11-20	473 (44)	453 (42)
21-50	447 (41)	452 (42)
>50	36 (3)	29 (3)
No. of axillary lymph nodes with cancer		
0	647 (60)	649 (60)
1-3	322 (30)	320 (29)
>3	116 (11)	120 (11)
Stage		
I	427 (39)	430 (39)
II	529 (49)	528 (48)
III	129 (12)	131 (12)
Histological grade		
1	26 (2)	27 (2)
2	340 (31)	327 (30)
3	714 (66)	731 (67)
Not available	5 (<1)	4 (<1)
Histological type		
Ductal	1000 (92)	1000 (92)
Lobular	44 (4)	49 (4)
Other	39 (4)	39 (4)
Not available	2 (<1)	1 (<1)
Estrogen receptor status		
Positive	711 (66)	723 (66)
Negative	374 (34)	366 (34)
Progesterone receptor status		
Positive	504 (46)	517 (47)
Negative	576 (53)	565 (52)
Not available	5 (<1)	7 (1)
HER2 status		
Positive	1078 (99)	1084 (100)
Negative	0	1 (<1)
Unconfirmed, IHC++	7 (1)	4 (1)

Abbreviations: HER2, human epidermal growth factor-2; IHC, immunohistochemistry; IQR, interquartile range.

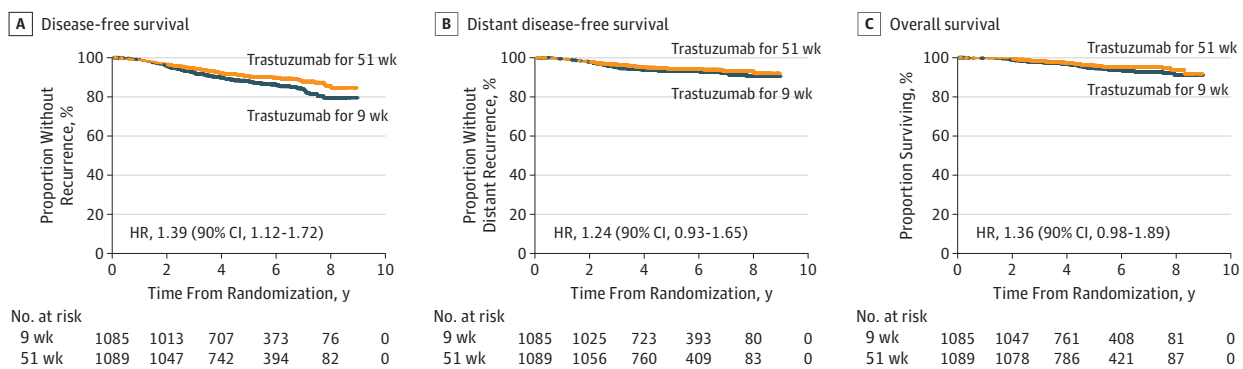
<sup>a</sup> Percentages may not total 100 because of rounding.

**Table 2. Cancer Recurrence and Survival**

Variable	No. (%)		Hazard Ratio <sup>a</sup> (90% CI)
	Trastuzumab for 9 wk (n = 1085)	Trastuzumab for 51 wk (n = 1089)	
Any recurrence or death <sup>b</sup>	140 (13)	105 (10)	1.39 (1.12-1.72)
Distant recurrence	73 (7)	61 (6)	1.24 (0.93-1.65)
Locoregional recurrence	17 (2)	13 (1)	1.35 (0.74-2.48)
Contralateral breast cancer	15 (1)	7 (1)	2.24 (1.05-4.75)
Second cancer	27 (3)	24 (2)	1.16 (0.73-1.84)
Death without cancer	14 (1) <sup>c</sup>	5 (0)	2.88 (1.22-6.78)
Death from any cause	58 (5)	44 (4)	1.36 (0.98-1.89)
Death from breast cancer	34 (3)	33 (3)	1.06 (0.71-1.59)
Death from other cause <sup>d</sup>	24 (2)	11 (1)	2.24 (1.23-4.08)

<sup>a</sup> Calculated with an unadjusted Cox proportional hazards model.  
<sup>b</sup> Six patients in the 9-week group and 5 patients in the 1-y group had 2 disease-free survival events.  
<sup>c</sup> The cause of death was unknown in 3 cases.  
<sup>d</sup> Eleven patients died of second cancer, 5 of infection, 2 of a cardiac cause, 3 of other causes, and 3 of an unknown cause in the 9-week group; in the 1-year group, 6 died of second cancer, 2 of infection, 1 of a cardiac cause, and 2 of other causes.

**Figure 2. Kaplan-Meier Estimates of Survival Outcomes**



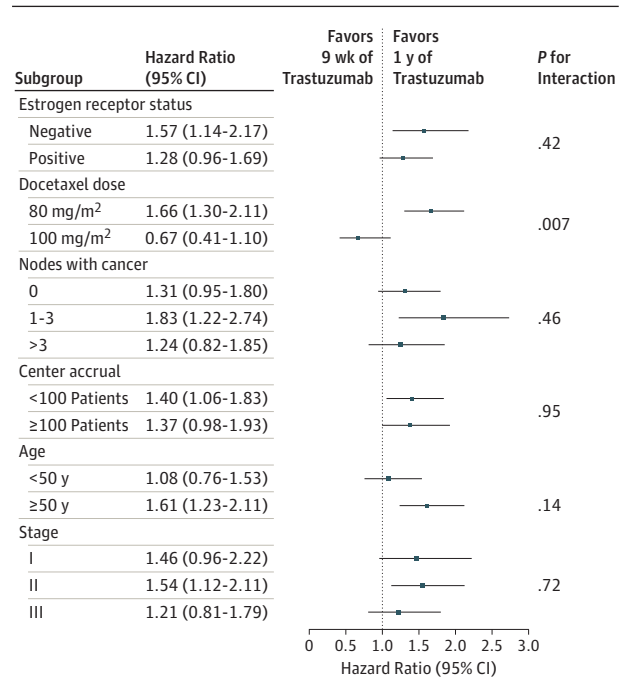
in the 9-week and 1-year groups, respectively (Table 2). Non-inferiority of the 9-week treatment as compared with the 1-year treatment was not demonstrated (5-year DFS, 88.0% vs 90.5%, respectively; HR, 1.39; 2-sided 90% CI, 1.12-1.72) (Figure 2). When the analysis was adjusted for axillary nodal status and cancer estrogen receptor content using a Cox model, the HR was 1.42 (90% CI, 1.15-1.76). The DDFS and OS did not differ substantially between groups (5-year DDFS, 93.2% vs 94.2%; HR, 1.24; 90% CI, 0.93-1.65; 5-year OS, 94.7% vs 95.9%; HR, 1.36; 90% CI, 0.98-1.89). Five-year cardiac DFS was 86.6% and 87.5%, respectively (HR, 1.16; 90% CI, 0.96-1.40) (eFigure 1 in Supplement 2).

The subgroup analyses on DFS generally favored the 1-year treatment duration (Figure 3). The subgroups were formed with a stratification factor (cancer estrogen receptor content) or factors predefined in the study Statistical Analysis Plan (docetaxel dosing, the number of axillary nodes with cancer, center accrual, patient age at study entry, and cancer stage) (Supplement 1). A significant interaction ( $P = .007$ ) was found between docetaxel dosing and DFS; the 1678 patients who received docetaxel, 80 mg/m<sup>2</sup>, had inferior and the 480 who received 100 mg/m<sup>2</sup> had similar DFS to patients in the 1-year group treated with the same docetaxel dosing (eFigure 2 in Supplement 2).

**Treatment Tolerance**

Twenty-two (2%) of the 1085 patients in the 9-week group and 42 (4%) of the 1089 patients in the 1-year group had a protocol-

**Figure 3. Disease-Free Survival in Prespecified Subgroups**



defined cardiac adverse event ( $P = .01$ ). Most were CHF (21 and 36, respectively). The LVEF was better maintained in the 9-week group, with less decrease in LVEF during follow-up

(mean LVEF was 63% in the 9-week group and 61% in the 1-year group 61 weeks after study entry;  $P < .001$ ) (eFigure 3 in Supplement 2). As expected, chemotherapy-related adverse effects were similar in both groups (eTables 1 and 2 in Supplement 2). A total of 185 (17%) and 203 (19%) patients in the 9-week and 1-year groups had the docetaxel dose reduced on 1 or more occasion, respectively, and 128 (12%) and 120 (11%) had FEC administered at a reduced dose.

Ninety-six (9%) patients in the 9-week group and 217 (20%) in the 1-year group discontinued scheduled trastuzumab administration, usually due to adverse effects. Most patients completed all 6 chemotherapy cycles (9-week group, 1041; 1-year group, 1038).

## Discussion

Women with HER2-positive breast cancer treated with adjuvant chemotherapy and trastuzumab for 1 year had higher DFS compared with patients who received trastuzumab during chemotherapy only. Because the only difference between the regimens was administration of trastuzumab after chemotherapy in the 1-year group, postchemotherapy trastuzumab improved DFS despite prior trastuzumab plus docetaxel. The HR for OS was in agreement with that for DFS, although this analysis was based on a relatively small number of events. The numbers of deaths considered to have resulted from breast cancer were similar in the groups. The 9-week regimen was associated with fewer cardiac adverse effects and a smaller decline in the LVEF.

The numerical difference in the DFS events recorded between the groups was 35 (140 [13%] vs 105 [10%]). The number of distant recurrences was numerically higher in the 9-week group (73 [7%] vs 61 [6%] events). The numbers of death from a cause other than breast cancer (24 [2%] vs 11 [1%]) and the numbers of contralateral breast cancers (15 [1%] vs 7 [1%]) were also higher in the 9-week group, which may have been due to chance because there are no biological explanations for a higher incidence of these events with less trastuzumab. There was only approximately 1% absolute difference between the groups in the 5-year DDFS and OS rates, which are clinically relevant survival end points. Considering this, patients who are unable to complete the longer duration of trastuzumab therapy due to treatment toxic effects or other reasons usually still have a favorable outcome.

We found an interaction between docetaxel dosing and DFS. A subgroup of the patients were treated in centers where the 100 mg/m<sup>2</sup> docetaxel dose was preferred, and in this patient population the 1-year duration of trastuzumab did not yield better DFS than the 9-week duration. This observation needs to be viewed with caution because this is a subgroup analysis and site-related confounding factors cannot be excluded. Other trials have suggested that docetaxel and trastuzumab have additive or synergistic effects for breast cancer.<sup>17-21</sup> In the Short-HER trial, which compared a regimen of trastuzumab given for 9 weeks con-

comitantly with 100 mg/m<sup>2</sup> of docetaxel<sup>27</sup> vs a modified standard chemotherapy regimen including 1 year of trastuzumab administration,<sup>2</sup> patients assigned to 9 weeks of trastuzumab did not have inferior DFS or OS compared with those treated with the 1-year trastuzumab regimen despite larger cumulative doses of epirubicin and docetaxel administered in the 1-year trastuzumab group.<sup>23</sup> Similarly, in the small randomized E2198 trial, in which the patients first received 12 weeks of a full dose of 3-weekly paclitaxel (175 mg/m<sup>2</sup>) and concomitant trastuzumab, followed by 4 cycles of doxorubicin and cyclophosphamide, or the aforementioned treatment followed by 1 year of trastuzumab, trastuzumab continued beyond chemotherapy did not improve DFS or OS.<sup>22</sup>

Collectively, these results from SOLD, E2198, and Short-HER suggest that a relatively high dose of the coadministered taxane should be given with trastuzumab when a brief course of trastuzumab will be evaluated in further clinical trials. The biological explanation for the interaction between taxane dosing and trastuzumab remains speculative. Trastuzumab action likely involves the host immune system and activation of antibody-dependent cellular cytotoxicity.<sup>28,29</sup> Hypothetically, a large enough dose of a taxane might reduce the numbers of immunosuppressive lymphocytes and other cells in the cancer microenvironment to a level that allows immune system activation for a period long enough to enhance trastuzumab efficacy.

## Limitations

The study has some limitations. Many patients had node-negative cancer. Some investigators may have preferred not to enroll patients with a high risk of cancer recurrence, and some study centers participated in a concurrent trial.<sup>30</sup> The likely too low estimation for DFS and the longer-than-planned accrual time led to a revision of the study design and the power calculations during the study. The protocol-defined median follow-up time, rather than the number of events, triggered the analysis because it seemed not possible to reach the planned number of events within a reasonable time frame, leading to a lower-than-planned study power. Yet, the present analysis seems to be adequately powered for the primary objective of evaluating noninferiority.

## Conclusions

Noninferiority of 9-week administration of adjuvant trastuzumab, when given with docetaxel, could not be demonstrated compared with chemotherapy and 1-year duration of trastuzumab therapy. Although the shorter regimen was associated with fewer cardiac toxic effects and there was little absolute difference in clinically important survival outcomes, DDFS and OS, in the overall assessment chemotherapy plus 1 year of anti-HER2 therapy should remain the standard treatment. Adequate dosing of the partner chemotherapy agents is likely important and requires further evaluation.

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**Author Affiliations:** Department of Oncology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland (Joensuu, Utriainen, Halonen); Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom (Fraser, Ritchie, Canney); University Hospitals Leuven, Leuven, Belgium (Wildiers, Neven); Department of Oncology, Turku University Central Hospital, Turku, Finland (Huovinen); Department of Oncology, Kuopio University Hospital, Kuopio, Finland (Auvinen); Päijät-Häme Central Hospital, Lahti, Finland (Nyandoto); Örebro University Hospital, Örebro, Sweden (Villman); Västerås Central Hospital, Västerås, Sweden (Granstam-Björneklett); Skåne University Hospital, Lund, Sweden (Lundgren); Vaasa Central Hospital, Vaasa, Finland (Sailas); North Carelia Central Hospital, Joensuu, Finland (Sailas); Department of Oncology and Radiotherapy, Oulu University Hospital, Oulu, Finland (Turpeenniemi-Hujanen); Department of Oncology, Tampere University Hospital, Tampere, Finland (Tanner, Kellokumpu-Lehtinen); Eskilstuna Hospital, Eskilstuna, Sweden (Yachnin); Landspítali University Hospital, Reykjavik, Iceland (Johansson); 4Pharma, Turku, Finland (Huttunen); Auckland City Hospital, Auckland, New Zealand (Harvey); Uppsala University Hospital, Uppsala, Sweden (Lindman).

**Author Contributions:** Dr Joensuu and Mr Huttunen had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Joensuu, Auvinen, Sailas, Tanner, Johansson, Huttunen, Canney, Kellokumpu-Lehtinen, Lindman.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Joensuu, Auvinen, Halonen, Tanner, Johansson, Lindman.

**Critical revision of the manuscript for important intellectual content:** Joensuu, Fraser, Wildiers, Huovinen, Auvinen, Utriainen, Nyandoto, Villman, Granstam-Björneklett, Lundgren, Sailas, Turpeenniemi-Hujanen, Tanner, Yachnin, Ritchie, Huttunen, Neven, Canney, Harvey, Kellokumpu-Lehtinen.

**Statistical analysis:** Joensuu, Huttunen.

**Obtained funding:** Joensuu, Johansson, Lindman.

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**Study supervision:** Joensuu, Fraser, Johansson, Neven, Canney, Lindman.

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