70mm

50mm

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Trastuzumab for Injection (r-DNA origin)

150 mg/440 mg

For I.V. Infusion, single & multiple use vial (Lyophilized powder)

Ogivri™ 150/440

COMPOSITION

Ogivri™ (Trastuzumab for injection) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture.

Each multiple-dose vial of Ogivri™ delivers 440 mg trastuzumab, 337.9 mg D-sorbitol, 6.3 mg L-Histidine, 9.9 mg L-Histidine hydrochloride monohydrate and 98.6 mg Polyethylene glycol 3350/Macrogol 3350. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/mL trastuzumab that delivers 20 mL (440 mg trastuzumab), at a pH of approximately 6. If Ogivri™ is reconstituted with SWFI without preservative, the reconstituted solution is considered single-dose.

Each single-dose vial of Ogivri™ delivers 150 mg trastuzumab, 115.2 mg D-sorbitol, 2.16 mg L-Histidine, 3.36 mg L-Histidine hydrochloride monohydrate and 33.6 mg Polyethylene glycol 3350/Macrogol 3350. Reconstitution with 7.2 mL of sterile water for injection (SWFI) yields a solution containing 21 mg/mL trastuzumab that delivers 150 mg trastuzumab, at a pH of approximately 6.

PHARMACEUTICAL FORM

Ogivri™ is a sterile, off-white to pale yellow, preservative-free lyophilized powder for injection, for intravenous administration.

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning

Cardiomyopathy: Trastuzumab products can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Ogivri™ for cardiomyopathy.

Infusion Reactions, Pulmonary Toxicity: Discontinue Ogivri™ for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Embryo-Fetal Toxicity: Exposure to Ogivri™ during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

Mechanism of action

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Trastuzumab products have been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Trastuzumab products are mediators of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, trastuzumab product-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Pharmacodynamics

Cardiac Electrophysiology:

The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors.
In a method comparison study a high degree of concordance (>95%) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

Pharmacokinetics

The pharmacokinetics of trastuzumab were evaluated in a pooled population pharmacokinetic (PK) model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC) receiving intravenous trastuzumab. Total trastuzumab clearance increases with decreasing concentrations due to parallel linear and non-linear elimination pathways.

Although the average trastuzumab exposure was higher following the first cycle in breast cancer patients receiving the three-weekly schedule compared to the weekly schedule of trastuzumab, the average steady-state exposure was essentially the same at both dosages. The average trastuzumab exposure following the first cycle and at steady state as well as the time to steady state was higher in breast cancer patients compared to MGC patients at the same dosage; however, the reason for this exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters following the first trastuzumab cycle and at steady state exposure are described in Tables 1 and 2, respectively.

Population PK based simulations indicate that following discontinuation of trastuzumab, concentrations in at least 95% of breast cancer patients and MGC patients will decrease to approximately 3% of the population predicted steady-state trough serum concentration (approximately 97% washout) by 7 months [*see Warnings and Precautions and Use in Specific Populations*]

Table 1: Population Predicted Cycle 1 PK Exposures (Median with 5th to 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	Cmin (µg/mL)	Cmax (µg/mL)	$AUC_{0-21days}$ (µg.day/mL)
8mg/kg + 6mg/kg q3w	Breast Cancer	1195	29.4 (5.8 to 59.5)	178 (117 to 291)	1373 (736 to 2245)
	MGC	274	23.1 (6.1 to 50.3)	132 (84.2 to 225)	1109 (588 – 1938)
4mg/kg + 2mg/kg qw	Breast Cancer	1195	37.7 (12.3 to 70.9)	88.3 (58 to 144)	1066 (586 to 1754)

Table 2: Population Predicted Steady State PK Exposures (Median with 5th to 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	Cmin,ss (µg/mL)[a]	Cmax,ss (µg/mL)[b]	$AUC_{0-21days}$ (µg.day/mL)	Time to Steady state (week)	Total CL range at steady- state (L/day)
8mg/kg + 6mg/kg q3w	MBC	1195	47.4 (5 - 115)	179 (107 - 309)	1794 (673 -3618)	12	0.173 – 0.283
	AGC	274	32.9 (6.1 – 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 – 0.337
4mg/kg + 2mg/kg qw	MBC	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 – 0.244

[a] Steady-state trough serum concentration of trastuzumab

[b] Maximum steady-state serum concentration of trastuzumab

Specific Populations: Based on a population pharmacokinetic analysis, no clinically significant differences were observed in the pharmacokinetics of trastuzumab based on age (<65 (n = 1294); ≥65 (n = 288)), race (Asian (n = 264); non-Asian (n = 1324)) and renal impairment (mild (creatinine clearance [CLcr] 60 to 90 mL/min) (n = 636) or moderate (CLcr 30 to 60 mL/min) (n = 133)). The pharmacokinetics of trastuzumab products in patients with severe renal impairment, end-stage renal disease with or without hemodialysis, or hepatic impairment is unknown.

Drug Interaction Studies: There have been no formal drug interaction studies performed with trastuzumab products in humans. Clinically significant interactions between trastuzumab and concomitant medications used in clinical trials have not been observed.

Paclitaxel and doxorubicin: Concentrations of paclitaxel and doxorubicin and their major metabolites (i.e., 6-α hydroxyl-paclitaxel [POH], and doxorubicinol [DOL], respectively) were not altered in the presence of trastuzumab when used as combination therapy in clinical trials. Trastuzumab concentrations were not altered as part of this combination therapy.

Docetaxel and carboplatin: When trastuzumab was administered in combination with docetaxel or carboplatin, neither the plasma concentrations of docetaxel or carboplatin nor the plasma concentrations of trastuzumab were altered.

Cisplatin and capecitabine: In a drug interaction substudy conducted in patients in Study 7, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with trastuzumab.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Trastuzumab products have not been tested for carcinogenic potential.

No evidence of mutagenic activity was observed when trastuzumab was tested in the standard Ames bacterial and human peripheral blood lymphocyte mutagenicity assays, at concentrations of up to 5000 mcg/mL. In an in vivo micronucleus assay, no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg of trastuzumab.

A fertility study was conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg of trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.

CLINICAL STUDIES

Study MYL-Her-1001:

A randomized, double-blind, Phase I study to assess the bioequivalence of Ogivri vs Herceptin® administered as a single intravenous infusion to healthy male volunteers

Objectives:

Primary objective: to ascertain pharmacokinetic (PK) bioequivalence of Ogivri and Herceptin® after 8 mg/kg as a single intravenous (i.v.) dose infused over 90 min in healthy male subjects. Bioequivalence is established if the 90% confidence interval of the mean ratio of Ogivri to Herceptin meets the standard bioequivalence criteria of 80-125% for the area under the serum concentration curve from 0 to infinity (AUC0-inf) and maximum observed serum concentration (Cmax). Secondary objectives: to assess comparative systemic safety and tolerability including local tolerance, and to evaluate immunogenicity with anti-drug antibody (ADA) formation.

Exploratory objectives: to investigate pharmacodynamic (PD) parameters such as ex vivo immunomodulation in stimulated peripheral blood mononuclear cells (PBMCs) and serum for cytokine production, to compare anti-proliferative activity of serum samples on SKBR3, a cell line with overexpressed HER2 receptors, to assess markers of apoptosis (caspase-3 activation, deoxyribonucleic acid [DNA] fragmentation) and akt phosphorylation, to perform non-compartmental PK analysis, and finally to assess PK/PD correlations.

PK results:

The time course of serum concentrations for comparing Ogivri and Herceptin® were essentially superimposable. All parameters assayed by ANOVA applying the PE approach (equivalent to 2-one-sided test approach) as ratio of geometric means for Ogivri vs. Herceptin® confirmed that the 90% CIs around normalized Cmax and normalized AUC0-∞ as well as all secondary parameters were well within the target bioequivalence range of 80.0 to 125.0%

Safety results:

A total of 120 treatment-emergent adverse events (TEAEs) were reported in 22 subjects during the study, including 47 AEs in 16 subjects after administration with Ogivri (N=19) and 73 AEs in 21 subjects after administration with Herceptin® (N=22). There were no deaths and no serious AEs. The vast majority of the TEAEs were rated as mild (92%), some as moderate (7.5%), and only 1 (0.5%) as severe (streptococcal pharyngitis after Ogivri). The most frequently reported AE preferred terms for Ogivri were: headache (47%), followed by nasopharyngitis (26%) and CRP increased (21%), while for Herceptin® were: nasopharyngitis (55%), followed by headache (46%), rhinitis (36%), and CRP increase (32%).

Study MYL-Her-1002:

A Single-Center, Randomized, Double-Blind, Three-Arm, Parallel-Group Phase I Study to Compare the Pharmacokinetic Profiles of Ogivri, EU-approved Herceptin® and US-Licensed Herceptin® Administered as a Single Intravenous Infusion to Healthy Male Volunteers.

Objectives:

The primary objective of this study was to demonstrate pharmacokinetic similarity of Mylan trastuzumab (Ogivri) versus EU-approved Herceptin® and US-licensed Herceptin® and pharmacokinetic similarity of EU-approved Herceptin® versus US-licensed Herceptin® after 8 mg/kg as single dose administered as intravenous infusion over 90 minutes in healthy male subjects based on the equivalence criterion that AUC0-∞, AUC0-last, and Cmax least square mean ratios are bounded within the 90% confidence intervals, 80.00% - 125.00%. Three similarity assessments were performed, 1) Ogivri vs. EU-approved Herceptin®, 2) Ogivri vs. US-licensed Herceptin® and 3) EU-approved Herceptin® vs. US-licensed Herceptin®. Secondary objectives included further pharmacokinetic assessment of similarity of Ogivri, EU-approved Herceptin® and US-licensed Herceptin® λz, tmax and t1/2 along with assessment of safety (including immunogenicity) and local tolerance.

Results:

Mylan's trastuzumab (Ogivri), EU-approved Herceptin® and US-licensed Herceptin® were well tolerated after 8 mg/kg as single dose administered to healthy male volunteers as intravenous infusion over 90 minutes. Eighty-three (83) subjects experienced a total of two hundred twenty-seven (227) treatment-emergent adverse events (TEAEs) over the course of the study. The TEAEs were mild to moderate in severity. No SAEs were reported. No subjects were withdrawn from the study due to TEAEs. All TEAEs were considered resolved by the principal investigator at the end of the study. Local infusions were well tolerated and reactions observed were minimal with all three treatments. There were no instances of either treatment-induced or treatment-boosted ADA-positive subjects in the study.

All statistical analyses of these data reveal that the 90% confidence intervals fall within 80%-125% for the test to reference ratio for the natural log transformed parameters, LNAUC0-last, LNAUC0-∞ and LNCmax, for trastuzumab. This study demonstrates that Mylan trastuzumab (Ogivri) is bioequivalent to both EU-approved Herceptin® and US-licensed Herceptin® after 8 mg/kg as single dose administered as intravenous infusion over 90 minutes in healthy male subjects. In addition, EU-approved Herceptin® is bioequivalent to US-licensed Herceptin® after 8 mg/kg as single dose administered as intravenous infusion over 90 minutes in healthy male subjects.

Study MYL-Her-3001:

A multicenter, double-blind, randomized, parallel-group, phase III study to compare the efficacy and safety of Mylan's trastuzumab versus Herceptin® in patients with HER2+ metastatic breast cancer

This was a multicenter, double-blind, randomized, parallel-group, study to compare the efficacy and safety of Mylan's Trastuzumab plus docetaxel or paclitaxel (i.e., taxane) versus Herceptin® plus a taxane in patients with HER2+ MBC with continuation of single-agent MYL-1401O versus Herceptin® for patients who had at least stable disease (SD) in order to evaluate continued safety and immunogenicity.

In Part 1 of the study, Mylan's Trastuzumab plus a taxane or Herceptin® plus a taxane was administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration) unless the patient experienced unacceptable side effects, disease progression, or was prematurely withdrawn from treatment. The choice of taxane (docetaxel or paclitaxel) was made by the Investigator at each study site and applied to all patients enrolled by that site. Tumor assessments were conducted every 6 weeks (±3 days).

In Part 2 of the study, after completing a minimum of 8 cycles of treatment in Part 1 of the study, all patients with at least SD continued with the trastuzumab product that they were originally allocated to as a single agent until disease progression, unacceptable toxicity, or death, whichever occurred first. Tumor assessments were conducted every 12 weeks (±3 days).

The endpoints for the primary and secondary objectives were to be analyzed at Week 24 in Part 1 and at Week 48 in Part 2. This report summarizes the results from both Part 1 and Part 2 of the study, including the pharmacokinetic (PK) analysis and immunogenicity results through 48 weeks.

Study population: 500 Mylan's trastuzumab (n = 250) EU-approved Herceptin®(n=250)

The efficacy of Mylan's Trastuzumab was confirmed in the pivotal confirmatory, study (MYL-Her-3001) which compared the efficacy and safety between Mylan's Trastuzumab and the EU reference product, Herceptin®, when used as primary treatment in patients with newly diagnosed HER2+ MBC. The first part of the study evaluated both treatments in combination with a taxane (docetaxel or paclitaxel), and the second part of the study evaluated continued treatment with Mylan's Trastuzumab or Herceptin® alone in those patients who had at least stable disease (SD) at 24 week in the first part. The therapeutic equivalence was confirmed by the primary efficacy evaluation of best ORR (according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) at Week 24. All secondary efficacy analyses (TTP, PFS, and OS evaluated at Week 24 and 48) also supported the conclusion of therapeutic equivalence.

Time to Tumor Progression:

In the Mylan's Trastuzumab arm at week 24, 35 patients (15.2%) had tumor progression compared to 44 patients (19.3%) in the Herceptin® arm. According to the log-rank test, the time-to-event curves for both treatment arms were not statistically significantly different (p = 0.192). Until Week 48, 95 patients (41.3%) in the Mylan's Trastuzumab group had tumor progression compared with 98 patients (43.0%) in the Herceptin® group. According to the logrank test, the time-to-event curves for both treatment groups were not statistically significantly different (p = 0.684). Median time to tumor progression (Kaplan-Meier estimate) was 11.1 months in both treatment arms.

Progression-Free Survival

In the Mylan's Trastuzumab arm, 189 patients (82.2%) had PFS until Week 24 compared with 180 patients (78.9%) in the Herceptin® arm. According to the log-rank test, the time-to-event curves for both treatment groups were not statistically significantly different (p = 0.303).

Until Week 48, 128 patients (55.7%) in the Mylan's Trastuzumab group and 126 patients (55.3%) in the Herceptin® group still did not have progression of the disease. According to the log-rank test, the time-to-event curves for both treatment groups were also not statistically significantly different (p = 0.842).

The median PFS (Kaplan-Meier estimate) was 11.1 months in both arms.

Overall Survival

In the Mylan's Trastuzumab arm, 223 patients (97.0%) survived until Week 24 compared to 218 patients (95.6%) in the Herceptin® arm According to the log-rank test, this difference was not statistically signficant (p=0.439).

Until 48 week 205 patients (89.1.0%) survived in the Mylan's Trastuzumab group compared with 194 patients (85.1%) in the Herceptin® group. According to the log-rank test, this difference was not statistically significant (p=0.131). The median OS was not reached at 48 weeks.

Primary Efficacy Analysis

The primary efficacy endpoint was the best ORR according to RECIST 1.1 criteria based on central tumor evaluation at Week 24.

- At Week 24, the ORR in the Mylan's Trastuzumab group was 69.6% and 64.0% in the Herceptin® group. The ratio of the ORRs of Mylan's Trastuzumab: Herceptin® was 1.09 with a 90% CI of (0.974, 1.211). As this CI is entirely within the pre-defined equivalence boundaries of 0.81 and 1.24, therapeutic equivalence of Mylan's Trastuzumab and Herceptin® was statistically confirmed per FDA's recommendation in this study.
- For the primary endpoint per EMA's recommendation, the difference in best ORRs between treatment groups (MYL-1401O minus Herceptin) was 5.5% with a 95% CI of (-3.08%, 14.04%). As this CI is entirely within the pre-defined equivalence boundaries of -15% and 15%, therapeutic equivalence of MYL-1401O and Herceptin was statistically confirmed per EMA's recommendation in this study.

Adjuvant Breast Cancer

The safety and efficacy of trastuzumab in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year trastuzumab treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

Studies 1 and 2:

In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1). Patients with a history of active cardiac disease based on symptoms, abnormal electrocardiographic, radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension (diastolic > 100 mm Hg or systolic > 200 mm Hg) were not eligible.

Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC → paclitaxel) alone or paclitaxel plus trastuzumab (AC → paclitaxel + trastuzumab).
In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m². Paclitaxel was administered either weekly (80 mg/m²) or every 3 weeks (175 mg/m²) for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in Study 2. Trastuzumab was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a dose of 2 mg/kg weekly for a total of 52 weeks. Trastuzumab treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/ recurrent LVEF decline *[see Dosage and Administration*]. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. The primary endpoint of the combined efficacy analysis was Disease-Free Survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death. The secondary endpoint was overall survival (OS).

A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of DFS following a median follow-up of 2.0 years in the AC → paclitaxel + trastuzumab arm. The pre-planned final OS analysis from the joint analysis included 4063 patients and was performed when 707 deaths had occurred after a median follow-up of 8.3 years in the AC → paclitaxel + trastuzumab arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of 49 years (range, 22 to 80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4% Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1, 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy evaluable population, after 8.3 years of median follow-up in the AC → paclitaxel + trastuzumab arm.

Study 3:

In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative disease were required to have ≥ T1c primary tumor. Patients with a history of congestive heart failure or LVEF < 55%, uncontrolled arrhythmias, angina requiring medication, clinically significant valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension (systolic > 180 mm Hg or diastolic > 100 mm Hg) were not eligible.

Study 3 was designed to compare one and two years of three-weekly trastuzumab treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). Patients were randomized (1:1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy to receive no additional treatment, or one year of trastuzumab treatment or two years of trastuzumab treatment. Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Trastuzumab was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks. The main outcome measure was Disease-Free Survival (DFS), defined as in Studies 1 and 2.

A protocol specified interim efficacy analysis comparing one-year trastuzumab treatment to observation was performed at a median follow-up duration of 12.6 months in the trastuzumab arm and formed the basis for the definitive DFS results from this study. Among the 3386 patients randomized to the observation (n = 1693) and trastuzumab one-year (n = 1693) treatment arms, the median age was 49 years (range 21 to 80), 83% were Caucasian, and 13% were Asian. Disease characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32% node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant chemotherapy. Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk features: among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and 47% (512) were ER and/or PgR + and had at least one of the following high-risk features: pathological tumor size greater than 2 cm, Grade 2 to 3, or age <35 years. Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens.

After the definitive DFS results comparing observation to one-year trastuzumab treatment were disclosed, a prospectively planned analysis that included comparison of one year versus two years of trastuzumab treatment at a median follow-up duration of 8 years was performed. Based on this analysis, extending trastuzumab treatment for a duration of two years did not show additional benefit over treatment for one year [Hazard Ratios of two-years trastuzumab versus one-year trastuzumab treatment in the intent to treat (ITT) population for Disease-Free Survival (DFS) = 0.99 (95% CI: 0.87, 1.13), p-value = 0.90 and Overall Survival (OS) = 0.98 (0.83, 1.15); p-value = 0.78].

Study 4:

In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. Patients were required to have either node-positive disease, or node-negative disease with at least one of the following high-risk features: ER/PR negative, tumor size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mm Hg), any T4 or N2 or known N3 or M1 breast cancer were not eligible.

Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab (AC-TH), or docetaxel and carboplatin plus trastuzumab (TCH). In both the AC-T and AC-TH arms, doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² were administered every 3 weeks for four cycles; docetaxel 100 mg/m² was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m² and carboplatin (at a target AUC of 6 mg/mL/min as a 30-to 60-minute infusion) were administered every 3 weeks for six cycles. Trastuzumab was administered weekly (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-Free Survival (DFS) was the main outcome measure.

Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6% ≥ 65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to randomization, all patients underwent primary surgery for breast cancer.

The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 and OS results for the integrated analysis of Studies 1 and 2, and Study 3 are presented in Table 3. For Studies 1 and 2, the duration of DFS following a median follow-up of 2.0 years in the AC → TH arm is presented in Figure 1, and the duration of OS after a median follow-up of 8.3 years in the AC → TH arm is presented in Figure 2. The duration of DFS for Study 4 is presented in Figure 3. Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall patient population: patients with low tumor grade, patients within specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients > 65 years of age. For Studies 1 and 2, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median follow-up [AC → TH], the survival rate was estimated to be 86.9% in the AC → TH arm and 79.4% in the AC → T arm. The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery/radiation therapy was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n = 1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n = 2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and PR-negative) (n = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

Table 3: Efficacy Results from Adjuvant Treatment of Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value
Studies 1 + 2[a]				
AC → TH (n = 1872)[b] (n = 2031)[c]	133[b]	0.48[b,d] (0.39, 0.59) p < 0.0001[e]	289[c]	0.64[c,d] (0.55, 0.74) p < 0.0001[e]
AC → T (n = 1880)[b] (n = 2032)[c]	261[b]		418[c]	
Study 3[f]				
Chemo → Trastuzumab (n = 1693)	127	0.54 (0.44, 0.67) p < 0.0001[g]	31	0.75 p = NS[h]
Chemo → Observation (n = 1693)	219		40	
Study 4[i]				
TCH (n = 1075)	134	0.67 (0.54 to 0.84) p = 0.0006[e,j]	56	
AC → TH (n = 1074)	121	0.60 (0.48 to 0.76) p < 0.0001[e,j]	49	
AC T (n = 1073)	180		80	

CI = confidence interval.

[a]Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC → T) or paclitaxel plus trastuzumab (AC → TH).

[b]Efficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC → TH arm.

[c]Efficacy evaluable population, for the final OS analysis, following 707 deaths (8.3 years of median follow-up in the AC → TH arm).

[d]Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

[e]stratified log-rank test.

[f]At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year trastuzumab treatment arm.

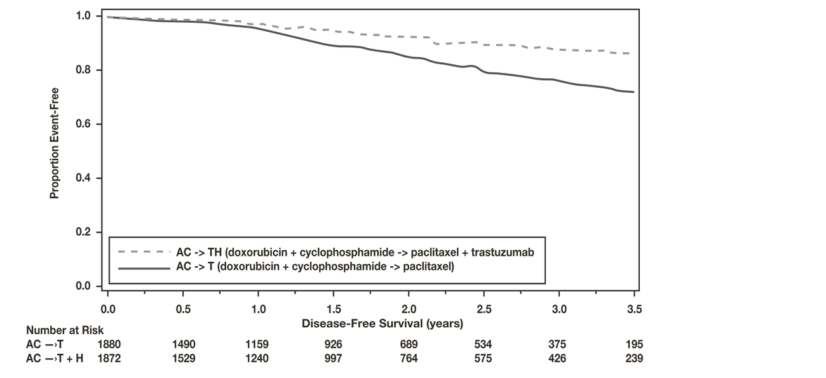
[g]log-rank test.

[h]NS = non-significant.

[i]Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC → T) or docetaxel plus

[j]two-sided alpha level of 0.025 for each comparison.

Figure 1: Duration of Disease-Free Survival in Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



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