

Important data
from BCIRG 006

Taxotere^{®*} and carboplatin plus Herceptin (TCH): the first approved non-anthracycline Herceptin-containing regimen¹

in the adjuvant treatment
of HER2+ breast cancer

*Taxotere (docetaxel) is a registered trademark of sanofi-aventis U.S. LLC.

Adjuvant indications

Herceptin is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature) breast cancer:

- As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- With docetaxel and carboplatin
- As a single agent following multi-modality anthracycline-based therapy

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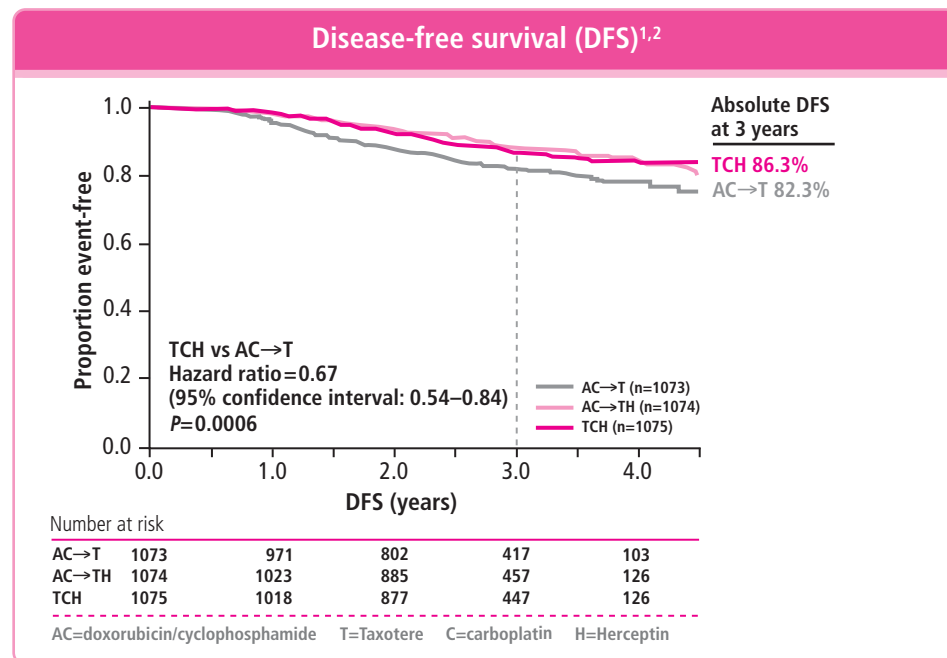


Efficacy of TCH regimen demonstrated in BCIRG 006

BCIRG 006 confirmed the benefit of Herceptin¹

- The efficacy and safety of 12 months of Herceptin therapy have been demonstrated in 4 adjuvant trials of more than 10,000 patients

TCH regimen increased benefit compared with AC→T¹



BCIRG 006 study design: Conducted by the Breast Cancer International Research Group (BCIRG), this clinical trial evaluated the efficacy and cardiac safety of 2 regimens vs control in a 1:1:1 randomization. The TCH arm consisted of concurrent docetaxel, carboplatin, and Herceptin and the AC→TH arm consisted of AC (doxorubicin and cyclophosphamide), followed by docetaxel and Herceptin. Control did not include Herceptin. Hormonal and/or radiotherapy were given as appropriate.

- At 3 years, there was an absolute reduction in the risk of disease recurrence of 4.0% in the TCH arm (95% confidence interval: 0.6%–7.4%) compared with AC→T²

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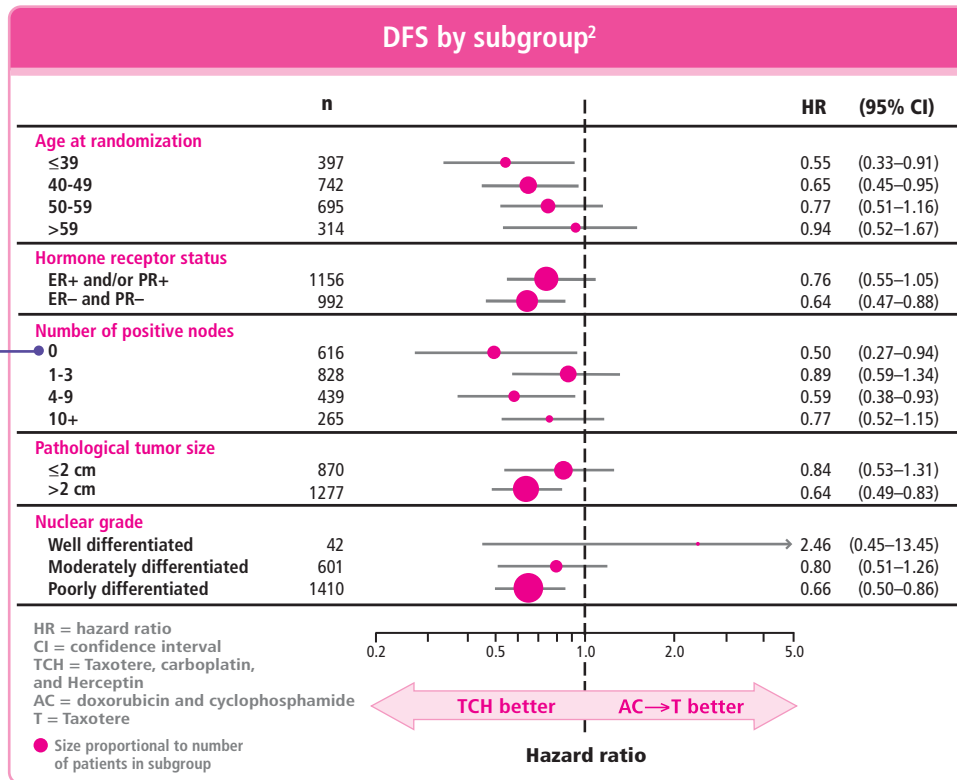
Herceptin administration can result in sub-clinical and clinical cardiac failure manifesting as congestive heart failure and decreased left ventricular ejection fraction. Serious infusion reactions and pulmonary toxicity have occurred; fatal infusion reactions have been reported. Exacerbation of chemotherapy-induced neutropenia has also occurred. The most common adverse reactions associated with Herceptin use were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia.

- 2** Please see page 13 and enclosed full Prescribing Information for **Boxed WARNINGS** and additional important safety information.

For the adjuvant treatment of HER2+ breast cancer, the TCH regimen provides¹:

- Similar efficacy to AC→TH
- Shorter duration of IV therapy than AC→TH
- Lower cardiac risk than AC→TH
- Higher completion rate of adjuvant therapy than AC→TH

TCH regimen improved DFS across diverse subgroups²



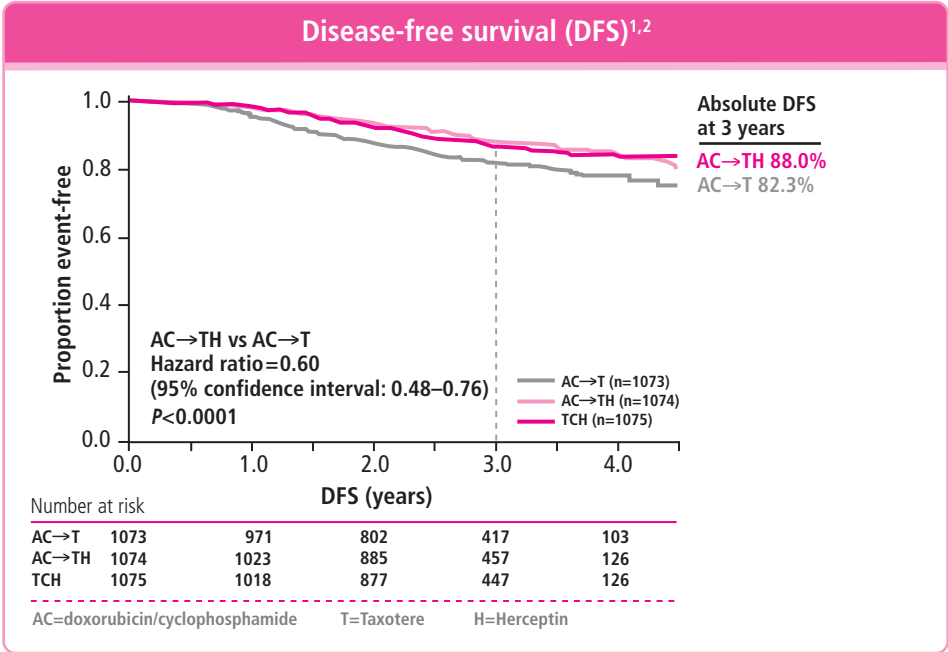
29% of patients enrolled had high-risk* node-negative disease

- Results within patient subgroups were generally consistent with the overall treatment effects
 - Exploratory analyses for the risk of recurrence, contralateral breast cancer, or death within patient subgroups were generally consistent with the overall treatment effects
- There were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect for them was different from that for the overall patient population¹
 - Patients with low tumor grade
 - Patients within specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander)
 - Patients >65 years of age

*High-risk features were defined as: tumor that was ER-negative and PR-negative, tumor size >2 cm, histologic and/or nuclear grade 2/3, and age <35 years.

Efficacy of AC→TH* demonstrated in BCIRG 006

AC→TH increased benefit compared with AC→T¹



- At 3 years, there was an absolute reduction in the risk of disease recurrence of 5.7% in the AC→TH arm (95% confidence interval: 2.4%–9.0%) compared with AC→T²

*In the BCIRG 006 trial, the "T" in AC→TH refers to Taxotere.

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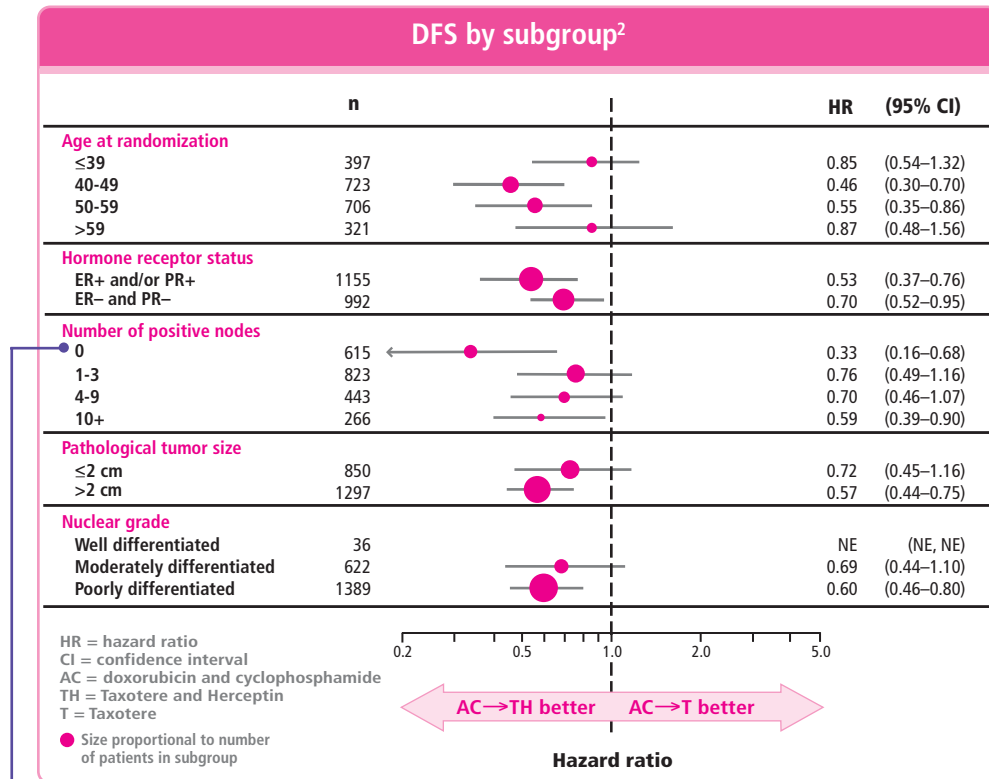
Herceptin administration can result in sub-clinical and clinical cardiac failure manifesting as congestive heart failure (CHF) and decreased left ventricular ejection fraction (LVEF). The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens. Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin in patients with metastatic breast cancer who develop a clinically significant decrease in left ventricular function. In one adjuvant clinical trial, cardiac ischemia or infarction occurred in the Herceptin-containing regimens.

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- Higher completion rate of adjuvant therapy than AC→TH

AC→TH regimen improved DFS across diverse subgroups²



• 29% of patients enrolled had high-risk[†] node-negative disease

- Results within patient subgroups were generally consistent with the overall treatment effects
 - Exploratory analyses for the risk of recurrence, contralateral breast cancer, or death within patient subgroups were generally consistent with the overall treatment effects
- There were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect for them was different from that for the overall patient population¹
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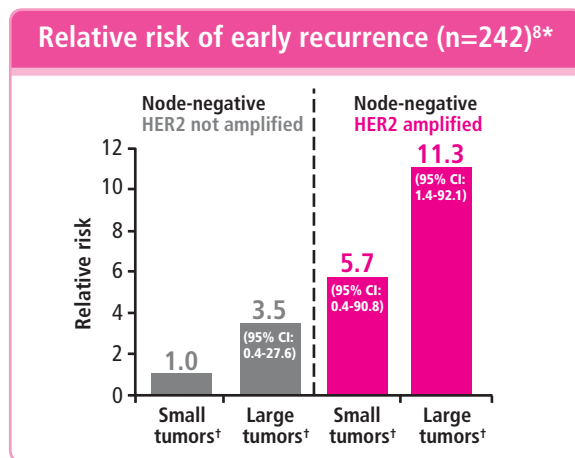
Targeting aggressive HER2+ breast cancer

HER2+ breast cancer is an aggressive form of the disease³⁻⁵

- HER2 overexpression has been associated with increased metastasis and angiogenesis⁶
- Patients with HER2+ disease experience increased risk of disease recurrence and inferior survival^{3,7}

HER2 amplification increases risk in node-negative tumors⁸

- In a retrospective study of node-negative invasive breast cancer, HER2 gene amplification strongly impacted the risk for both early recurrence and disease-related death



*Based on a sample of 324 node-negative archival breast cancer specimens. Patients were treated by surgery only. Early recurrent disease (n=242 cases) was defined as occurring within 24 months of diagnosis. Evaluation of disease-related death was restricted to 232 patients known to have died of disease, or who had at least 36 months of follow-up.

†Small tumors defined as ≤ 1.0 cm in diameter; large tumors defined as >1.0 cm in diameter.

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Serious infusion reactions and pulmonary toxicity have occurred; fatal infusion reactions have been reported. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

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The first Herceptin non-anthracycline regimen for the adjuvant setting[‡]

Targeting HER2 with the TCH regimen

The TCH regimen **enables immediate initiation of Herceptin** with chemotherapy¹

The TCH regimen **reduces the overall duration** of infused therapy to 12 months total (vs 15 months with AC→TH)¹

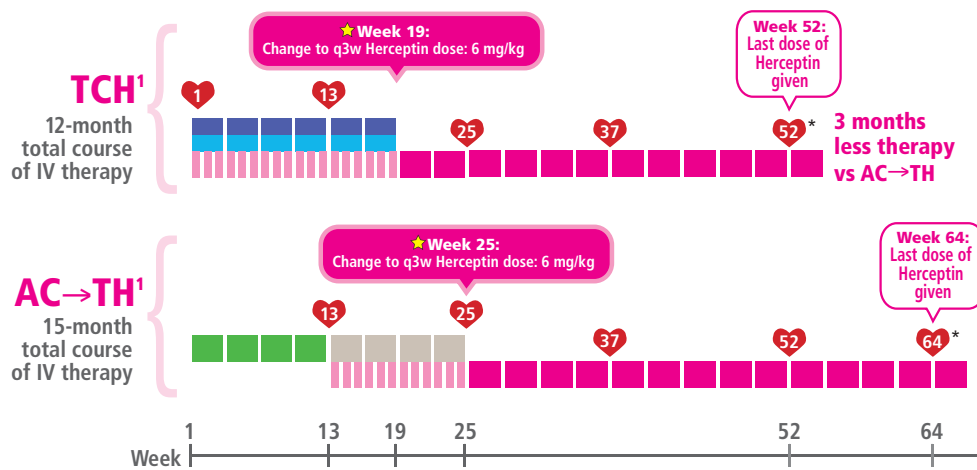
Herceptin dosing and administration throughout TCH and AC→TH regimens

Herceptin dosing and administration guidelines ¹		
	Dosage	Infusion time
Loading dose <ul style="list-style-type: none"> • For TCH regimen: week 1 • For AC→TH regimen: week 13 of total regimen 	4 mg/kg	90 minutes
Subsequent doses during weekly administration <ul style="list-style-type: none"> • For TCH regimen: through week 18 • For AC→TH regimen: from week 14 through week 24 of total regimen 	2 mg/kg	30 minutes
Subsequent doses during q3w administration <ul style="list-style-type: none"> • For TCH regimen: from week 19 through end of Herceptin therapy • For AC→TH regimen: from week 25 through week 64 of total regimen 	6 mg/kg	30–90 minutes

[‡]Taxotere and carboplatin plus Herceptin (TCH) is the first approved non-anthracycline Herceptin-containing regimen.



Herceptin dosing, administration, and



In the clinical trial, for the TCH regimen²:

- For the first cycle, Herceptin was given on day 1 and Taxotere and carboplatin were given on day 2
- For all subsequent cycles (2–6), Taxotere, carboplatin, and Herceptin were all given on the same day (in that order)

cardiac monitoring in the adjuvant setting

Total Herceptin doses

	q1w	q3w
TCH	18	12
AC→TH	12	14

- **TCH (weeks 1–18):** 4 mg/kg loading dose, as a 90-minute infusion, at week 1; 2 mg/kg at weeks 2–18, as a 30-minute infusion, weekly for 17 weeks
- **TCH (weeks 19–52):** 6 mg/kg, as a 30–90-minute infusion, every 3 weeks for 12 cycles
- **AC→TH (weeks 13–24):** 4 mg/kg loading dose, as a 90-minute infusion, at week 13; 2 mg/kg at weeks 14–24, as a 30-minute infusion, weekly for 11 weeks
- **AC→TH (weeks 25–64):** 6 mg/kg, as a 30–90-minute infusion, every 3 weeks for 14 cycles
- **Taxotere®† (docetaxel):** 75 mg/m² every 3 weeks for 6 cycles
- **Carboplatin:** at a target AUC of 6 mg/mL•min, as a 30- to 60-minute infusion, every 3 weeks for 6 cycles
- **AC:** doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for 4 cycles
- **T:** Taxane, either:
 - Taxotere 100 mg/m², every 3 weeks for 4 cycles, or
 - paclitaxel 175 mg/m², every 3 weeks for 4 cycles, or 80 mg/m² weekly for 12 weeks

- ★ **q3w Herceptin dose begins the week immediately following chemotherapy cycle.**
- ♥ **Week of cardiac assessment**

Radiation therapy and/or hormonal therapy may be given after completion of chemotherapy if indicated.

*Left ventricular ejection fraction (LVEF) should be measured at baseline immediately prior to initiation of Herceptin, every 3 months during and upon completion of Herceptin, and every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.¹

†Taxotere is a registered trademark of sanofi-aventis U.S. LLC.

In the clinical trial, for the AC→TH regimen²:

- For the first cycle of TH, Herceptin was given on day 1 and Taxotere was given on day 2
- For cycles 2–4 of TH, Taxotere and Herceptin were given on the same day (in that order)

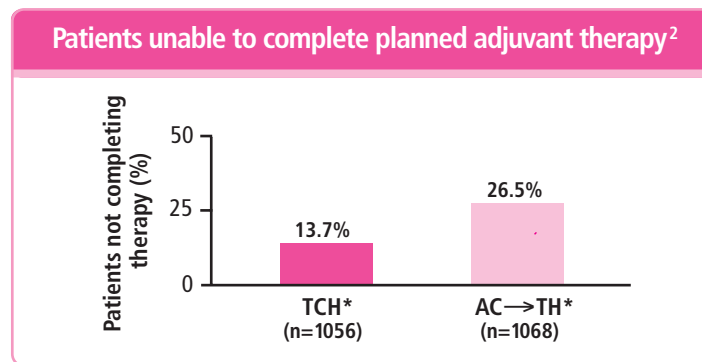
Improving completion rates of planned Herceptin treatment

Lower risk of cardiac-related discontinuation

- The TCH regimen eliminates the potential for anthracycline-related cardiotoxicity that may prevent Herceptin initiation
- 2.9% of patients in the TCH arm discontinued Herceptin due to a cardiac event compared with 5.7% of patients in the AC→TH arm¹

Higher completion rates²

- On average, for every 100 patients receiving each regimen in BCIRG 006, 13 more were able to complete therapy with TCH



- In the AC→TH arm, 2.3% of patients in the safety population* discontinued therapy prior to receiving any Herceptin
 - Herceptin was initiated in 100% of patients in the safety population for the TCH arm
- 91.3% of patients in the AC→TH arm and 95.5% of patients in the TCH arm started Herceptin monotherapy after completion of chemotherapy
 - Herceptin was discontinued during monotherapy in 10% of patients in the AC→TH arm and 5.4% of patients in the TCH arm

*Includes all patients who received at least 1 dose of study treatments.

Important Safety Information

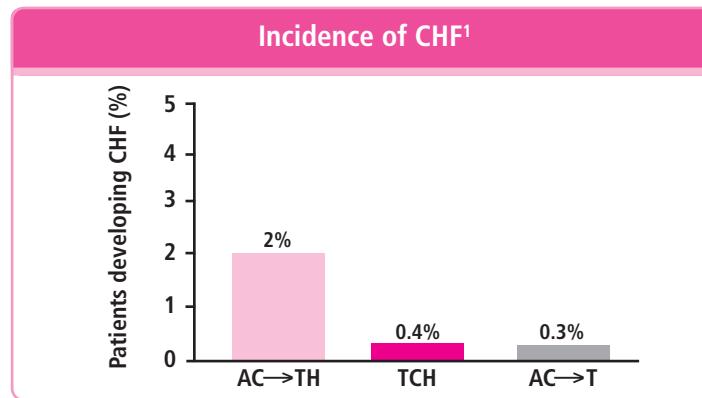
Candidates for treatment with Herceptin should undergo a thorough baseline cardiac assessment, including history, physical examination, and an assessment of LVEF by echocardiogram or MUGA scan. Patients should undergo frequent monitoring for decreased left ventricular function during and after Herceptin treatment. More frequent monitoring should be employed if Herceptin is withheld in patients who develop significant left ventricular cardiac dysfunction.

For the adjuvant treatment of HER2+ breast cancer, the TCH regimen provides¹:

- Similar efficacy to AC→TH
- Shorter duration of IV therapy than AC→TH
- Lower cardiac risk than AC→TH
- Higher completion rate of adjuvant therapy than AC→TH

Reduced risk of CHF in non-anthracycline regimen¹

- In BCIRG 006, a lower rate of congestive heart failure (CHF) was seen with the TCH regimen vs the AC→TH regimen



- Patients were ineligible if they had 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
- The incidence of NCI-CTC grade 3/4 cardiac ischemia/infarction was higher in the Herceptin-containing regimens as compared with AC→T
 - 0.3% (3/1068) with AC→TH; 0.2% (2/1056) with TCH; and 0% with AC→T

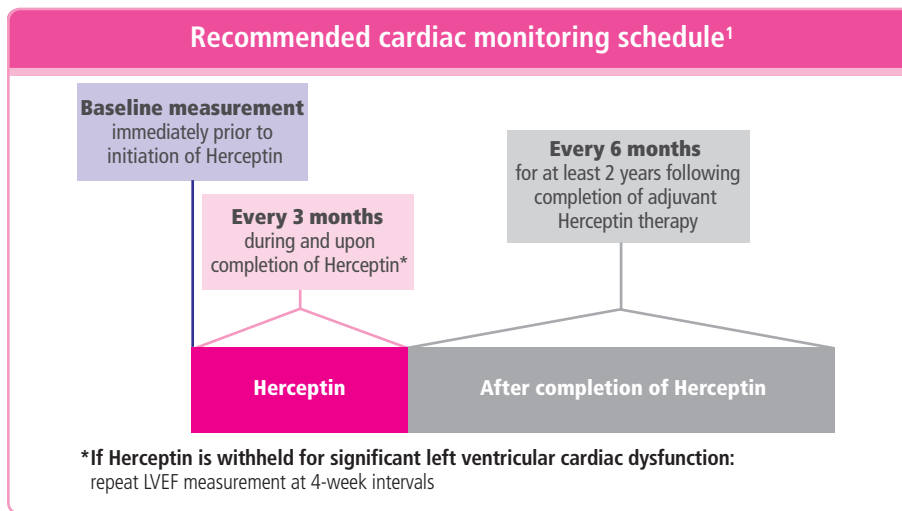
Reduced risk of asymptomatic LVEF drops in non-anthracycline regimen¹

Per-patient incidence of new-onset cardiac dysfunction (by LVEF) ¹					
	LVEF <50% and absolute decrease from baseline			Absolute LVEF decrease	
	LVEF <50%	≥ 10% decrease	≥ 16% decrease	<20% and ≥ 10%	≥ 20%
AC→T (n=1050)	9.5%	6.6%	3.3%	34.0%	5.5%
TCH (n=1056)	8.5%	5.9%	3.3%	34.5%	6.3%
AC→TH (n=1068)	17.0%	13.3%	9.8%	44.3%	13.2%

Cardiac monitoring and important safety information

Cardiac monitoring¹

- Conduct a thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan
- Patients should undergo monitoring for deteriorating left ventricular function prior to Herceptin treatment, and frequently during and after Herceptin treatment



Treatment modifications for cardiac issues¹

- Discontinue Herceptin for CHF or clinically significant asymptomatic decreases in left ventricular function
- In patients with asymptomatic declines in LVEF, Herceptin may be held and resumed **up to 3 times**, using the management protocol below

Herceptin administration for asymptomatic decreases in LVEF¹

Relationship of LVEF to LLN [†]	Absolute decrease from baseline (percentage points)		
	<10	10–15	≥16
Within normal limits	CONTINUE	CONTINUE	HOLD for ≥ 4 weeks
Below LLN	CONTINUE	HOLD for ≥ 4 weeks	HOLD for ≥ 4 weeks

[†]Lower limit of normal.

- When Herceptin is held, it may be resumed if, within 4–8 weeks:
 - The LVEF returns to normal limits, **and**
 - The absolute decrease from baseline is ≤15 percentage points
- Herceptin should be permanently discontinued if:
 - Persistent (>8 weeks) LVEF decline is observed, **or**
 - Herceptin dosing is held on more than 3 occasions for cardiomyopathy

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Cardiotoxicity and cardiac monitoring

- **Herceptin administration can result in sub-clinical and clinical cardiac failure manifesting as congestive heart failure (CHF) and decreased left ventricular ejection fraction (LVEF)**
 - The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens
 - Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin in patients with metastatic breast cancer who develop a clinically significant decrease in left ventricular function
- Patients should undergo monitoring for decreased left ventricular function before Herceptin treatment, and frequently during and after Herceptin treatment
 - More frequent monitoring should be employed if Herceptin is withheld in patients who develop significant left ventricular cardiac dysfunction
- In one adjuvant clinical trial, cardiac ischemia or infarction occurred in the Herceptin-containing regimens

Infusion reactions, pulmonary toxicity, and neutropenia

- **Serious infusion reactions and pulmonary toxicity have occurred; fatal infusion reactions have been reported**
 - In most cases, symptoms occurred during or within 24 hours of administration of Herceptin
 - Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension
 - Patients should be monitored until signs and symptoms completely resolve
 - Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome
- Exacerbation of chemotherapy-induced neutropenia has also occurred

Pregnancy category D

- Herceptin can cause oligohydramnios and fetal harm when administered to a pregnant woman

Most common adverse events

- The most common adverse reactions associated with Herceptin use were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia

In the adjuvant treatment of HER2+ breast cancer,

The evolution of Herceptin-containing regimens

TCH regimen proven effective in BCIRG 006

- Proven clinical benefit for TCH across diverse patient subgroups^{1,2}
 - Including ≤39 years, hormone-receptor–negative, 4–9 positive nodes, and tumor size >2 cm
- Lower cardiac risk than AC→TH (CHF rate of 0.4% vs 2.0% with AC→TH)¹
 - Eliminates the potential for anthracycline-related cardiotoxicity
- Shorter duration of IV therapy (12 months vs 15 months with AC→TH)¹
 - Enables immediate initiation of Herceptin with chemotherapy
- Higher completion rate of adjuvant therapy²

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References: **1.** Herceptin Prescribing Information. Genentech, Inc. March 2009. **2.** Data on file. Genentech, Inc. **3.** Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235:177-182. **4.** Paik S, Hazan R, Fisher ER, et al. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: prognostic significance of erbB-2 protein overexpression in primary breast cancer. *J Clin Oncol*. 1990;8:103-112. **5.** Ross JS, Fletcher JA. HER-2/neu (c-erb-B2) gene and protein in breast cancer. *Am J Clin Pathol*. 1999;112(suppl 1):S53-S67. **6.** Niu G, Carter WB. Human epidermal growth factor receptor 2 regulates angiopoietin-2 expression in breast cancer via AKT and mitogen-activated protein kinase pathways. *Cancer Res*. 2007;67:1487-1493. **7.** Witton CJ, Reeves JR, Going JJ, et al. Expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. *J Pathol*. 2003;200:290-297. **8.** Press MF, Bernstein L, Thomas PA, et al. HER-2/neu gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. *J Clin Oncol*. 1997;15:2894-2904.

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