

PERSONALIZED MEDICINE:  
Identifying the Appropriate  
Patient Through Biomarkers  
in Oncology

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# PERSONALIZED MEDICINE: Identifying the Appropriate Patient Through Biomarkers in Oncology

For decades, Americans have displayed great optimism in the face of cancer — the cure always seemed to be somewhere in the near future. In 1924, Charles H. Mayo, MD, cofounder of the Mayo Clinic in Minnesota, opined that cancer soon would be considered a contagious disease and, with the germs discovered, “doctors may be able to prevent infection and bring about a cure” (NYT 1924a). That same year, a prominent Johns Hopkins surgeon, Joseph Colt Bloodgood, MD, claimed that “deaths from cancer would be practically eliminated and cures accomplished if persons afflicted sought medical aid immediately upon the discovery of a foreign growth in any part of the body” (NYT 1924b).

The salient question today is “What is the best method to discover those foreign growths?” The answer may lie in the development of biomarkers that can complement or replace existing screening tools. Furthermore, in addition to improving methods to detect cancer at an early stage, biomarkers are being developed to guide treatment.

With continuing encouragement from advocacy groups, celebrities, and politicians, Americans today enthusiastically embrace the belief that early detection of cancer is the key to an early cure. They participate in large numbers in screening programs (i.e., programs aimed at broad populations of apparently healthy, asymptomatic people) intended to reduce mortality from cervical cancer (Pap smear), colon cancer (colonoscopy), breast cancer (mammography), and prostate cancer (prostate-specific antigen [PSA] assay), among others.

The value of these screening programs, however, is being questioned. An article in the *New York Times* (Singer 2009) noted that “Nearly every body part susceptible to cancer now has an advocacy group, politician or athlete with a public awareness campaign to promote routine

testing — even though it is well established that many of these exams offer little benefit for the general public.” One study (Domenighetti 2003) captured the extent to which women in the United States overvalue the benefits of cancer screening: Women overestimate the effect of mammography screening on mortality by a factor of about 10, and 75 percent believe that regular mammography screening prevents or reduces the risk of cancer.

Although Pap smears and colonoscopy have succeeded in identifying premalignant lesions, thereby decreasing the incidence and the rate of death from these cancers, mammography and PSA testing have been less successful (Esserman 2009), and the evidence supporting a mortality benefit from colonoscopy isn’t very strong (Bretthauer 2009). In addition to generating a high rate of false-positive test results in low-risk populations, mammography and PSA tests appear to identify small, nonaggressive tumors that ultimately would not harm a person if undetected. At the same time, these tests often fail to identify aggressive tumors at an early stage sufficient to reduce mortality. For the same reasons, existing screening methods for lung cancer, ovarian cancer, and many other cancers are inadequate. With the four cancers that have been the target of early-detection programs, over the course of 30 years there has been a sharp increase in their incidence rates but not a corresponding decline in mortality rates.

A recent study (Kramer 2009) shows that the true value of cancer screening tests is clouded by four kinds of bias (Table 1). For example, with some periodic tests, length-biased sampling has a tendency to detect more slowly progressive tumors than rapidly progressive tumors. To overcome these biases, the study authors state that randomized controlled clinical trials are needed to determine the true value of screening programs.

**TABLE 1**  
**Biases affecting cancer screening programs**

<b>Lead-time bias</b>	Moves the time of diagnosis to an earlier point in the course of a disease but does not necessarily improve outcome
<b>Healthy-volunteer bias</b>	People who participate in screening programs tend to behave differently in ways that affect their health than people who do not participate
<b>Length-biased sampling</b>	Tendency of screening tools to detect slow-growing tumors more often than rapidly progressive tumors
<b>Overdiagnosis</b>	Histological diagnosis of cancer in a lesion lacking true malignant potential or that is so slow growing that the patient will die from some other cause

Source: Kramer 2009

Please see safety information on page 6.

The Herceptin Prescribing Information is provided in the supplement to this publication.

## Biomarkers — a new tool to address cancer

The inadequacy of contemporary screening programs to address the deadliest cancers makes it clear that new tools are needed to improve the screening, diagnosis, and treatment of cancer patients. One such tool is biomarkers. For example, susceptibility biomarkers could determine which, if any, screening modalities should be utilized to determine the level of risk. For highly targeted therapies, predictive biomarkers can be used to prospectively identify appropriate patients for treatment and prognosis biomarkers can be used to monitor treatment response. The use of biomarkers will be essential for success both in clinical development and in the marketplace.

Biomarkers have been defined as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention that can be objectively measured (BDWG 2001). They can take many forms — genes, proteins, carbohydrates, radioactively labeled molecules, cells, or physiologic measurements. In clinical trials conducted for regulatory purposes, biomarkers sometimes are used as surrogates for “hard” clinical endpoints that reflect how a patient feels, functions, and survives. For example, numerous antihypertensive medications have been approved on the basis of a reduction in systolic blood pressure and several statins have been approved based on their ability to reduce concentrations of LDL-cholesterol. Today, most cancer drugs are approved on the basis of surrogate endpoints such as objective response rate, progression-free survival, and time to progression, all of which are regarded as biomarkers (Fleming 2009).

Biomarkers also can be used in drug development, especially in preclinical studies and early-phase clinical trials. The U.S. Food and Drug Administration (FDA) recommends that diagnostics be developed in tandem with new drugs (Figure 1) and suggests that the clinical utility of a diagnostic could be established at the end of a phase 1 trial so that it could be used for patient stratification in the phase 2 and phase 3 trials. Although this goal may seem overly ambitious, clinical utility could be realistically established by the end of a phase 2 trial.

As the second leading cause of death in the United States, cancer imposes a substantial disease burden on an aging population. About 1.5 million new cases of cancer were expected to be diagnosed in the United States in 2010, accounting for about 569,000 deaths, and 11 million people were estimated to be living with cancer\* (ACS

2010). Biomarkers are successfully used for the estimated 80 million Americans living with one or more types of cardiovascular disease (AHA 2010), the leading cause of death in the United States. However, identifying and developing cancer biomarkers may present a greater research challenge because of the biological complexity of cancer.

The diverse settings in which biomarkers can be useful in the screening, diagnosis, and treatment of cancer include the identification of patients who are predisposed to cancerous disease; conclusive identification of disease and differentiation of disease subtypes and prognoses; selection of the most appropriate therapy for an individual patient, including dosage titration and minimization of adverse events; and monitoring of therapy. The requirements of biomarkers employed in early cancer detection are different from those used in disease staging and treatment decisions. For example, a screening assay for cancer should be able to identify a unique biomarker in plasma or serum that distinguishes patients with neoplasms from healthy people and it should do so with high sensitivity and specificity. The assay also should be quick, easy, and inexpensive.

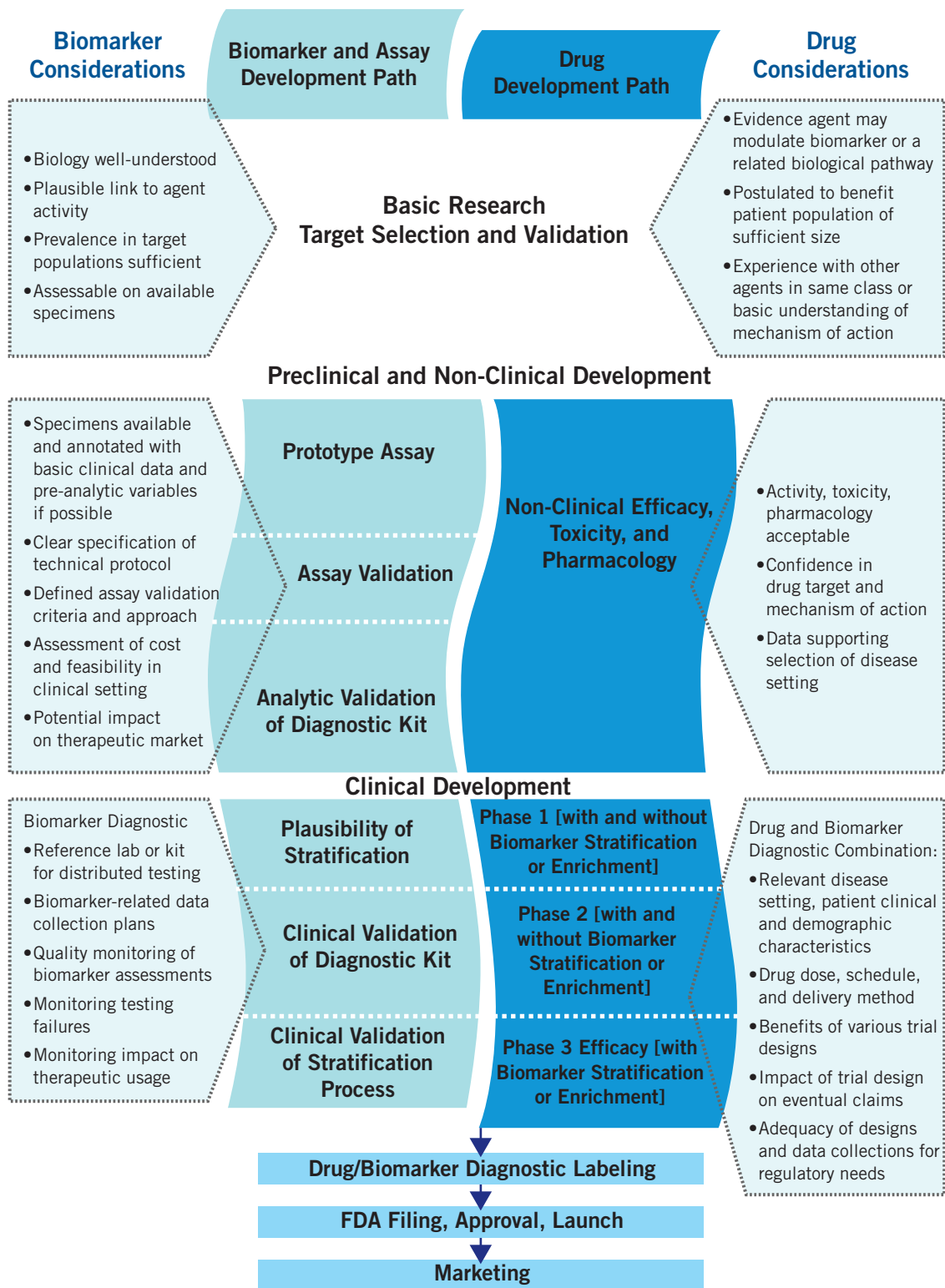
## A brief history of biomarkers

In the past, physicians used rather crude instruments to diagnosis and treat disease. The chief diagnostic tool was the patient’s account of the illness, occasionally supplemented by the doctor’s hands, eyes, nose, and ears. The invention of the stethoscope in the early 19th century allowed physicians to listen to chest sounds without coming into direct contact with the patient — an important consideration in an age of lice and ticks. When a correct diagnosis was made, treatment options were limited. As recently as the 1930s, few specific medical therapies were available to physicians. Commonly used were digitalis for heart failure, liver extract for anemia, insulin for diabetes, quinine for malaria, and arsenicals and heavy metals for syphilis.

Researchers are now developing increasingly sophisticated imaging technologies that will allow physicians to peer noninvasively inside the body and track physiologic processes in real time. We also have a growing number of therapies that are exquisitely engineered to target a single molecule involved in a disease process to better understand that process. The number of medical therapies also has increased, especially with the development of the biologic drugs and targeted therapies. Unfortunately, the rate at which patients respond to drugs, targeted or otherwise, is considerably less than 100 percent, and we generally lack the knowledge to determine which patients will

\* Excluding basal and squamous cell skin cancer and in situ carcinomas except urinary bladder.

**FIGURE 1**  
**FDA-recommended drug and diagnostic development pathways**



Source: Taube 2009

benefit from which drugs.

If the physician's black bag in the 1930s contained only a handful of disease-specific drugs, the modern physician is similarly constrained by the limited number of biomarkers available to diagnose disease and guide therapy. An early biomarker (broadly defined) was the Pap smear to detect in women premalignant processes in the cervix. This biomarker entered wide use during the 1940s and became regarded as the most effective cancer screening method in medical history. Although the Pap smear is being supplanted in the United States by automated liquid-based cytology, that technology has now been found to be no better than a well-performed Pap smear for the detection of cervical precancer (Siebers 2009).

The history of biomarkers (Table 2) is relatively young. In 1847, the English physician and chemist Henry Bence Jones described a protein found in the urine of a patient with multiple myeloma, establishing the concept of cancer markers. In 1938, prostatic acid phosphatase was identified as a biomarker for diagnosing prostate cancer, and in 1940, a test for rheumatoid factor, an antibody, was developed. The middle decades of the 20th century were a time of momentous discoveries — the structure of DNA and proteins and the genetic code, for example — that spurred an explosion in biomedical research. The discovery of monoclonal antibodies in 1975 paved the way for

the discovery of CA-125, a biomarker for ovarian cancer, and the breast cancer biomarkers CA 15-3 and CA 27-29. Routine PSA testing was introduced in 1987, and in 1994, PSA became the first biomarker to gain FDA approval for use in the early detection of cancer. The first protein molecule to be targeted by a cancer therapy was the estrogen receptor. Tamoxifen was FDA-approved in 1977, and toremifene and fulvestrant were approved in 1997 and 2002, respectively. In 1998, the FDA approved the targeted therapy trastuzumab (Herceptin) for the treatment of patients whose breast cancer tumors overexpress human epidermal growth factor receptor 2 (HER2), which promotes the growth of cancer cells.

### Current picture

PSA remains the only tumor biomarker that is FDA-approved for widespread cancer screening. The FDA has compiled a table of genomic biomarkers that is included in the prescribing information of approved cancer drugs. In this table, the biomarkers speak to clinical response and differentiation (often just for informational purposes); risk identification; guidance with dose selection; susceptibility, resistance, and differential disease diagnosis; and polymorphic drug targets (FDA 2011). This table includes about 70 drugs, of which more than half are affected by gene variants for the various cytochrome P450 enzymes

#### Herceptin® (Trastuzumab)

##### Boxed WARNINGS and Additional Important Safety Information

- **Herceptin administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline-containing chemotherapy regimens. In a pivotal adjuvant trial, one patient who developed CHF died of cardiomyopathy.**
- **Evaluate cardiac function prior to and during treatment. For adjuvant therapy, also evaluate cardiac function after completion of Herceptin. Discontinue Herceptin for cardiomyopathy.**
- **Herceptin can result in serious and fatal infusion reactions and pulmonary toxicity. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.**
- **Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.**
- Exacerbation of chemotherapy-induced neutropenia has also occurred.
- Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy.
- 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.

Please see the Herceptin full prescribing information including **Boxed WARNINGS** and additional important safety information.

that control drug metabolism. Although tests for these genomic biomarkers are available, clinicians often employ therapeutic drug monitoring instead of genotype testing when relatively low-cost drugs, such as fluoxetine or celecoxib, are under consideration.

Pharmacogenomic markers are more commonly used to guide the selection of cancer drugs, owing to their high cost and low efficacy rates. If tumor genetics are used to

stratify patients, the response rates for targeted therapies such as trastuzumab, imatinib, gefitinib, erlotinib, and panitumumab can be increased.

From the perspectives of patients, physicians, and payers, it would be advantageous to know prior to the prescribing of a drug whether or not it is likely to work. Pharmaceutical companies historically have taken a different approach — they want a product to be used by as broad

**TABLE 2**  
**Notable events in the history of biomarkers**

DATE	EVENT	DATE	EVENT
1847	English physician and chemist Henry Bence Jones describes a protein found in the urine of a patient with multiple myeloma	1987	Introduction of routine PSA testing
1928	George Papanicolaou invents his simple and inexpensive method of screening for cervical cancer that became known as the Pap smear test	1987	First report of the Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) recommends the use of total cholesterol levels for identifying cases and LDL-C levels for making treatment decisions
1938	Prostatic acid phosphatase (PAP) is identified as a biomarker for diagnosing prostate cancer	1990s	Research begins in the United States on developing automated liquid-based cytology (LBC) for screening of cervical precancer
1940	Test for rheumatoid factor is developed	1994	PSA becomes the first biomarker to gain FDA approval for use in early detection of cancer
1940s	Pap smear test wins acceptance and becomes a routine screening technique	1994	Breast cancer susceptibility gene BRCA1 is identified
1953	James Watson and Francis Crick describe the structure of DNA	1995	Breast cancer susceptibility gene BRCA2 is identified
1954	A crude assay becomes available for C-reactive protein (CRP), a serum marker of inflammation	1996	American Society of Clinical Oncology publishes its first evidence-based clinical practice guidelines for the use of tumor markers in breast cancer
1955	Frederick Sanger determines the first protein sequence of insulin	1998	Modernization of tissue microarrays (TMAs) allows simultaneous IHC analysis of up to 1,000 samples on a single slide
1958	Crick sets forth the sequence hypothesis for the structure of proteins from nucleic acid coding	1998	Trastuzumab (Herceptin) is approved for treatment of patients with breast cancer overexpressing HER2. FDA approval is facilitated by the availability of assays for HER2.
1965	Carcinoembryonic antigen (CEA) is identified as a serum biomarker for colon cancer	2000	Measurement of high-sensitivity CRP (hs-CRP) is suggested as a means for identifying persons at risk for cardiovascular events
1974	Estrogen receptor (ER) assay is established as a predictive test for endocrine treatment of advanced breast cancer	2000	European Society of Cardiology and American Heart Association deem biomarker elevations the cornerstone of acute myocardial infarction (AMI) diagnosis
1975	Publication of the discovery of monoclonal antibodies, paving the way for discovery of CA-125, CA 15-3, and CA 27-29	2000	National Institutes of Health launches the Pharmacogenetics Research Network to study the relationship between genetic variation and drug response
1979	Identification of p53, a tumor suppressor protein (its gene, TP53, was cloned in 1983). Elevated expression of p53 may be an indicator of tumor recurrence and poor prognosis, especially when used in combination with other biomarkers.	2006	National Cancer Institute and National Human Genome Research Institute launch The Cancer Genome Atlas (TCGA), a pilot project to explore the genomic changes involved in all types of human cancer
1980	Prostate-specific antigen (PSA) in serum is found to be similar to PSA in the prostate, paving the way for development of a PSA screening test	2009	TCGA is expanded to include more than 20 types of human cancer
1981	CA-125 is identified as a biomarker for ovarian cancer. Its use as a screening test is limited by its lack of sensitivity and inability to detect early-stage cancers.		
1981	CA 19-9 is identified as a biomarker for colon cancer and pancreatic cancer. Its use today is limited to monitoring recurrence of pancreatic cancer after treatment.		

Source: Genentech DOF

a population as possible. In this model, the effectiveness of a drug is determined by having the patient take the drug on trial, so to speak, to determine whether or not the patient is a non or low responder or is subject to adverse events. At first glance, this approach might appear to be good from a business standpoint but not good for the patient.

Developing a biomarker in tandem with a new therapeutic could be a positive financial move on the part of a drug manufacturer, because the availability of a biomarker that separates responders from nonresponders would make it easier to recruit subjects for clinical trials and would speed the drug approval process to facilitate early market entry. Such an enlightened approach could lead to more patients using more effective drugs as well as enhanced patient compliance.

As an example, without the support of biomarkers, the targeted metastatic breast cancer drug trastuzumab might not have made it to market or at least would have been postponed. Trastuzumab is a monoclonal antibody against HER2, which is overexpressed in about 25 percent of breast cancer cases. HER2 overexpression is associated with a poor prognosis and an increased response to anthracycline-based chemotherapy but a poor response to hormonal therapy. When the clinical trials leading to the approval of trastuzumab were conducted, only patients who tested positive for the presence of the biomarker HER2 were enrolled. In this population, a survival benefit of 5 months was observed — an improvement of 22.7 percent. The trial enrolled 1,250 patients and lasted 52 months. Had the study enrolled patients with metastatic breast cancer without regard to their HER2 status, in which case no more than 25 percent of the study population would have been expected to overexpress HER2, a sample size of 11,000 patients would have been required and the study would have had to last 349 months to demonstrate a survival benefit of 1.25 months, an improvement of only 5.7 percent.

FDA approval of a biomarker is not necessarily proof of its clinical value. For example, in 2004, cetuximab, along with an immunohistochemistry (IHC) test for epidermal growth factor receptor (EGFR), was approved for metastatic colon cancer. It was thought that patients who were EGFR-positive on this test were suitable candidates for cetuximab therapy. It soon became apparent, however, that the test was inadequate for that purpose. A study by Chung (2007) showed that cetuximab produced a robust response in 4 EGFR-negative patients in a group of 16 such patients. The investigators concluded that the IHC test for EGFR lacked predictive value and was not suited for select-

ing or excluding patients from cetuximab therapy. The National Comprehensive Cancer Network has since updated its guidelines to state that the diagnostic test fails to demonstrate improved value and should not be used (NCCN 2011).

Although scientists may identify a biomarker, developing a clinically useful assay can be difficult. There are only two validated methods for determining HER2 status in routine clinical practice: IHC and fluorescence in situ hybridization (FISH). IHC uses staining to detect HER2 proteins on the cell surface whereas FISH measures HER2 gene amplification. Neither method appears superior as a predictor of benefit from HER2 therapy and about 20 percent of HER2 testing using these methods may be inaccurate (Wolff 2007). Widely used, IHC is relatively quick, easy, and inexpensive and is performed in most pathology laboratories with a conventional bright-field microscope, but it uses a semiquantitative and somewhat subjective scoring system. FISH generates a more objective and quantitative score and is less susceptible than IHC to variations in testing protocol (owing to the greater stability of DNA compared with protein). FISH is more expensive because it requires the use of a fluorescent microscope. Newer methods of HER2 detection are chromogenic in situ hybridization (CISH) and silver-enhanced in situ hybridization (SISH), both of which require only a standard light microscope and, thus, are less expensive than FISH (Penault-Llorca 2009).

### Future of biomarkers in oncology

It is likely that in the near future, physicians will begin to use molecular biomarkers to guide all aspects of care for patients with cancer or at risk of developing cancer. Research aimed at developing new biomarkers is occurring in interconnected disciplines such as pharmacogenomics, transcriptomics, proteomics, metabolomics, and glycomics. Each of these disciplines examines how cancerous or precancerous cells and tissues differ from their healthy counterparts at the molecular level. Eventually, the most sophisticated tools are likely to be integrated sets of biomarkers forming biomarker “signatures” that draw on all these disciplines.

**Pharmacogenomics.** Pharmacogenomics involves the study of changes in DNA sequence, chromosomal aberrations, and epigenetic alterations of the chromatin and DNA (i.e., changes that don't affect DNA sequence). A new program, the Cancer Genome Atlas, launched by the National Cancer Institute and the National Human Genome Research Institute, is generating data sets to help the cancer research community better understand the

changes found in the DNA of cancer cells. In 2009, the program was expanded to include the compilation of genomic catalogs for more than 20 types of cancer. The related field of pharmacogenomics is concerned with variations in large sets of genes as they relate to drug response, whereas pharmacogenetics is a subset of pharmacogenomics that deals with the relationship between single-gene variants and drug response (Roden 2006), which is important for patient selection in cancer pharmacotherapy. Polymerase chain reaction (PCR) gene amplification is a common technology for detecting cancer-related genes.

**Transcriptomics.** Transcriptomics is the study of the messenger RNA (mRNA) molecules transcribed from DNA (so that the message encoded in DNA and carried by the mRNA can be translated into the amino acids from which polypeptides are formed). At one time, it was believed that each human gene expressed a single protein, but it has been discovered that the number of proteins vastly exceeds the number of genes in the human genome. The diversity of proteins stems from the mechanism of alternative splicing in which segments of gene transcripts are spliced into different arrangements, resulting in structurally and functionally different proteins and mRNA. A better understanding of the alternative splicing variants particular to cancer can result in the identification of new diagnostic and prognostic biomarkers along with new therapeutic strategies (He 2009).

**Proteomics.** Proteomics is the comparative study of the production, structure, and function of proteins in normal and pathological samples, complementing genomic information (Kruse 2008, Latterich 2008). Proteins expressed in the cancer phenotype can distinguish a cancer patient from a healthy person. The technical challenge is to identify minute amounts of these potential biomarkers within the proteome where a mere 22 proteins account for 99 percent of the protein mass. The proteome is far more complex than the genome. Whereas the genome of an organism is essentially stable, proteins are more numerous than genes and the kinds of proteins expressed vary from cell to cell and even from day to day. Also, posttranslational modifications that affect protein function cannot be captured in genomic studies. Proteins, though, are a more suitable therapeutic target than DNA or RNA.

In oncology, tissue microarrays (TMAs) are commonly used to study proteins in tissue samples. TMAs can now allow simultaneous IHC analysis of up to 1,000 samples on a single slide. Various mass spectrometric technologies are also used to study proteins.

Carefully designed nanoparticles also are being developed as a tool for isolating potential protein biomarkers from the common serum proteins with which they are often associated. About 700 nanometers in diameter, they consist of a core containing a “bait” designed to attract the proteins of interest and a porous shell that excludes larger proteins that might compete for the bait and also protects the harvested proteins. Nanoparticles, thus, address three formidable barriers to the identification of proteins that could serve as biomarkers for the early detection of cancer: The very low concentration of candidate proteins in blood; the association of the proteins with vastly more abundant carrier proteins such as albumin; and the tendency of the proteins to be rapidly degraded by proteases immediately after blood is drawn (Longo 2009). Nanoparticle technology can be used to harvest other kinds of potential biomarkers, such as lipids and fatty acids, metabolites, nucleic acids, and posttranslationally modified peptides such as glycosylated and phosphorylated proteins. A mixture of nanoparticles baited to target these separate classes of analytes could be applied to a single fluid sample (blood, urine, cerebrospinal fluid, amniotic fluid) to facilitate multiplex analysis.

**Glycomics.** Glycomics analyzes glycans — free oligosaccharides and glycoconjugates such as glycoproteins and glycolipids — throughout biologic systems (An 2009). As many as 70 percent of human proteins are glycosylated and these glycoproteins perform numerous functions, which may be altered in the disease state. Glycans are found mostly in bodily fluids. As disease markers, glycans are more reflective of a disease state than are proteins. With current technologies, it is easier to quantify oligosaccharide expression than protein expression (Lebrilla 2009).

Although the structure of a protein can be predicted by genomic information, the same is not true of glycans — they form branched structures instead of linear structures and a single glycan site on a protein may be associated with more than 100 different structures. For a glycan to function as a biomarker, however, it may be sufficient simply to determine its composition using mass spectrometry. The glycan array is an emerging technology for identifying novel glycomics-based biomarkers. The glycan groups from which cancer biomarkers are most likely to emerge are believed to be N-linked glycans, O-linked glycans, and glycosaminoglycans (GAGs), each of which must be studied separately because of the differences among glycan groups (Lebrilla 2009).

**Metabolomics.** Metabolomics is the study of small molecules that are the intermediate or end products of

metabolism, reflecting the response of biological systems to genetic and environmental changes. In cancer cells, numerous metabolic pathways behave differently than they do in normal cells, including virtually all the pathways involved in cellular growth and proliferation (Van 2009). The challenge in identifying metabolite biomarkers is to define “normal” because intraindividual and interindividual metabolic variation is considerable owing to numerous factors affecting a person’s metabolic phenotype at any given time. Mass spectrometry and nuclear magnetic resonance (NMR) spectrometry are the chief technologies used in metabolic profiling. Metabolomics holds the potential for classifying tumor types and comparing malignancies with normal tissue, developing new predictors of therapeutic response, and identifying new prognostic markers (Denkert 2006).

## Conclusion

Current cancer screening methods are inadequate for the early identification of patients so that they can reap optimal benefit from treatment. For highly targeted therapies, diagnostic tests integrating biomarker technology to identify prospectively the appropriate patients for treatment will be essential for success in clinical development and in the marketplace.

The future of drug development relies on identifying those patients most likely to benefit from a particular medical therapy. Although some pharmaceutical companies may believe biomarkers will limit markets, getting the right drug to the right patient at the right time is the right thing to do for patients. Targeted therapies such as trastuzumab already have demonstrated that commercial success can be achieved with this approach.

## References

- ACS (American Cancer Society). Cancer Facts & Figures 2010. <http://www.cancer.org/Research/CancerFactsFigures/CancerFacts-Figures/cancer-facts-and-figures-2010>. Accessed June 16, 2011.
- AHA (American Heart Association). Heart Disease and Stroke Statistics – 2010 Update. <http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192667> Accessed June 16, 2011.
- An HJ, Kronewitter SR, de Leoz ML, Lebrilla CB. Glycomics and disease markers. *Curr Opin Chem Biol*. 2009; Sep 21. [Epub ahead of print]
- Brethauer M. The capsule and colorectal-cancer screening—the crux of the matter. *N Engl J Med*. 2009;361:300–301.
- BDWG (Biomarkers Definitions Working Group). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69:89–95.
- Chung CH, Chan E, Berlin J et al. Cetuximab-related hypersensitivity reactions associated with pre-existing cetuximab-specific IgE antibody. *J Clin Oncol*. 2007; ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supp); 2007:9097.
- Denkert C, Budzies J, Kind T, et al. Mass spectrometry-based metabolic profiling reveals different metabolite patterns in invasive ovarian carcinomas and ovarian borderline tumors. *Cancer Res*. 2006;66:10795–10804.
- Domenighetti G, D’Avanzo B, Egger M. Women’s perception of the benefits of mammography screening: population-based survey in four countries. *Int J Epidemiol*. 2003;32:816–821.
- Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009;302:1685–1692.
- FDA (U. S. Food and Drug Administration). List of valid genomic biomarkers in the context of approved drug labels. <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>. Accessed June 16, 2011.
- Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when evaluating oncology products. *J Clin Oncol*. 2009;27:2874–2880.
- He C, Zhou F, Zuo Z, Cheng H, Zhou R. A global view of cancer-specific transcript variants by subtractive transcriptome-wide analysis. *PLoS One*. 2009;4:e4732. Epub 2009 Mar 6.
- Kramer BS, Crosswell JM. Cancer screening: the clash of science and intuition. *Ann Rev Med*. 2009;60:125–137.
- Kruse U, Bantscheff M, Drewes G, Hopf C. Chemical and pathway proteomics: powerful tools for oncology drug discovery and personalized health care. *Mol Cell Proteomics*. 2008 Oct;7:1887–1901.
- Latterich M, Abramovitz M, Leyland-Jones B. Proteomics: new technologies and clinical applications. *Eur J Cancer*. 2008;44:2737–2741.
- Lebrilla CB, An HJ. The prospects of glycan biomarkers for the diagnosis of diseases. *Mol Biosyst*. 2009;5:17–20.
- Longo C, Patanarut A, George T, et al. Core-shell hydrogel particles harvest, concentrate and preserve labile low abundance biomarkers. *PLoS One*. 2009;4:e4763.
- NCCN (National Comprehensive Cancer Network). Clinical Practice Guidelines in Oncology: Colon Cancer. V3.2011. [http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf)
- NYT (New York Times). Mayo predicts cancer cure by discovery of its germ. May 24, 1924a. <http://select.nytimes.com/gst/abstract.html?res=F1061EF8345812738DDDA10994DD405B848EF1D3&scp=1&sq=charles+mayo&st=p> <<http://select.nytimes.com/gst/abstract.html?res=F1061EF8345812738DDDA10994DD405B848EF1D3&amp;scp=1&sq=charles+mayo&st=p>. Accessed June 16, 2011.
- NYT (New York Times). Cure for cancer in prompt action; Dr. Bloodgood of Johns Hopkins declares elimination almost sure in early stage. June 8, 1924b. <http://select.nytimes.com/gst/abstract.html?res=F70816FF3D5B12738DDDA10894DE405B848EF1D3&amp;scp=4&sq=bloodgood&st=p>. Accessed June 16, 2011.
- Penault-Llorca F, Bilous M, Dowsett M, et al. Emerging technologies for assessing HER2 amplification. *Am J Clin Pathol*. 2009;132:539–548.
- Roden DM, Altman RB, Benowitz NL, et al; Pharmacogenetics Research Network. Pharmacogenomics: challenges and opportunities. *Ann Intern Med*. 2006;145:749–757.
- Siebers AG, Klinkhamer PJ, Grefte JM, et al. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. *JAMA*. 2009;302:1757–1764.
- Singer N. In push for cancer screening, limited benefits. *New York Times*. July 17, 2009. <http://www.nytimes.com/2009/07/17/health/17screening.html>. Accessed June 16, 2011.
- Taube SE, Clark GM, Dancy JE, et al. A perspective on challenges and issues in biomarker development and drug and biomarker codevelopment. *J Natl Cancer Inst*. 2009;101:1453–1463.
- Van QN, Veenstra TD. How close is the bench to the bedside? Metabolic profiling in cancer research. *Genome Med*. 2009;1:5.
- Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2007;25:118–145.





# Full Prescribing Information for HERCEPTIN<sup>®</sup> (trastuzumab)

*Supplement to*

**M A N A G E D**  
**Care**

*Volume 20, No. 7  
Supplement 3  
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### 1.14.1.3 Final Labeling Text

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Herceptin safely and effectively. See full prescribing information for Herceptin.

**HERCEPTIN® (trastuzumab)**  
Intravenous Infusion  
Initial U.S. Approval: 1998

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

See full prescribing information for complete boxed warning  
**Cardiomyopathy:** Herceptin can result in sub-clinical 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 Herceptin for cardiomyopathy. (5.1, 2.2)

**Infusion reactions, Pulmonary toxicity:** Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

**Embryo-Fetal Toxicity:** Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.

#### RECENT MAJOR CHANGES

Indications and Usage, Metastatic Gastric Cancer (1.3)	10/2010
Dosage and Administration (2.1)	10/2010
Warnings and Precautions, Embryo-Fetal Toxicity (5.3)	10/2010
Warnings and Precautions, HER2 Testing (5.6)	10/2010

#### INDICATIONS AND USAGE

Herceptin is a HER2/neu receptor antagonist indicated for:

- the treatment of HER2 overexpressing breast cancer (1.1, 1.2).
- the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma (1.3)

#### DOSAGE AND ADMINISTRATION

For intravenous (IV) infusion only. Do not administer as an IV push or bolus (5.2).

#### Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.1)

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks, or

- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.

#### Metastatic HER2-Overexpressing Breast Cancer (2.1)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

#### Metastatic HER2-overexpressing Gastric Cancer (2.1)

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

#### DOSAGE FORMS AND STRENGTHS

- Multidose vial nominally containing 440 mg Herceptin as a lyophilized, sterile powder. (3)

#### CONTRAINDICATIONS

- None. (4)

#### WARNINGS AND PRECAUTIONS

- Cardiomyopathy (5.1, 6.1)
- Infusion Reactions (5.2, 6.1)
- Embryo-fetal Toxicity. Pregnancy registry available (1-800-690-6720) (5.3, 8.1)
- Pulmonary Toxicity (5.4, 6.1)
- Exacerbation of Chemotherapy-Induced Neutropenia (5.5, 6.1)
- HER2 testing should be performed using FDA-approved tests by laboratories with demonstrated proficiency. (5.6)

#### ADVERSE REACTIONS

##### Adjuvant Breast Cancer

- Most common adverse reactions (≥5%) are headache, diarrhea, nausea, and chills. (6.1)

##### Metastatic Breast Cancer

- Most common adverse reactions (≥10%) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. (6.1)

##### Metastatic Gastric Cancer

- Most common adverse reactions (≥10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (6.1)

#### USE IN SPECIFIC POPULATIONS

Nursing Mothers: Discontinue nursing or discontinue Herceptin. (8.3)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2010

#### FULL PRESCRIBING INFORMATION: CONTENTS\*

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## **FULL PRESCRIBING INFORMATION**

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

#### **Cardiomyopathy**

Herceptin administration can result in sub clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function. *[see Warnings and Precautions (5.1) and Dosage and Administration (2.2)]*

#### **Infusion Reactions; Pulmonary Toxicity**

Herceptin administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration. Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. *[see Warnings and Precautions (5.2, 5.4)]*

#### **Embryo-Fetal Toxicity**

Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*

## **1 INDICATIONS AND USAGE**

### **1.1 Adjuvant Breast Cancer**

Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature *[see Clinical Studies (14.1)]*) 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.

### **1.2 Metastatic Breast Cancer**

Herceptin is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

### **1.3 Metastatic Gastric Cancer**

Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Recommended Doses and Schedules**

**Do not administer as an intravenous push or bolus. Do not mix Herceptin with other drugs.**

*Adjuvant Treatment, Breast Cancer:*

Administer according to one of the following doses and schedules for a total of 52 weeks of Herceptin therapy:

During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:

- Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

[see *Dose Modifications (2.2)*]

*Metastatic Treatment, Breast Cancer:*

- Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30 minute intravenous infusions until disease progression.

*Metastatic Gastric Cancer*

- Administer Herceptin at an initial dose of 8 mg/kg as a 90 minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30-90 minutes every three weeks until disease progression [see *Dose Modifications (2.2)*].

## **2.2 Dose Modifications**

*Infusion Reactions*

[see *Boxed Warning, Warnings and Precautions (5.2)*]

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue Herceptin for severe or life-threatening infusion reactions.

*Cardiomyopathy*

[see *Boxed Warning, Warnings and Precautions (5.1)*]

Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

- $\geq 16\%$  absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and  $\geq 10\%$  absolute decrease in LVEF from pretreatment values.

Herceptin may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is  $\leq 15\%$ .

Permanently discontinue Herceptin for a persistent ( $> 8$  weeks) LVEF decline or for suspension of Herceptin dosing on more than 3 occasions for cardiomyopathy.

## **2.3 Preparation for Administration**

*Reconstitution*

Reconstitute each 440 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection (BWI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/mL trastuzumab. In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Herceptin. The stream of diluent should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Store reconstituted Herceptin at 2–8°C; discard unused Herceptin after 28 days. If Herceptin is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

#### *Dilution*

- Determine the dose (mg) of Herceptin [*see Dosage and Administration (2.1)*]. Calculate the volume of the 21 mg/mL reconstituted Herceptin solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.

### **3 DOSAGE FORMS AND STRENGTHS**

440 mg lyophilized powder per multi-use vial.

### **4 CONTRAINDICATIONS**

None.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Cardiomyopathy**

Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [*see Boxed Warning: [Cardiomyopathy](#)*].

Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline.

Withhold Herceptin for  $\geq 16\%$  absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and  $\geq 10\%$  absolute decrease in LVEF from pretreatment values [*see Dosage and Administration (2.2)*]. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

#### *Cardiac Monitoring*

Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- Baseline LVEF measurement immediately prior to initiation of Herceptin
- LVEF measurements every 3 months during and upon completion of Herceptin

- Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction [see *Dosage and Administration (2.2)*]
- LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.

In Study 1, 16% (136/844) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF. In Study 3, the number of patients who discontinued Herceptin due to cardiac toxicity was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) patients in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued Herceptin due to cardiac toxicity.

Among 32 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy and all other patients were receiving cardiac medication at last follow-up. Approximately half of the surviving patients had recovery to a normal LVEF (defined as  $\geq 50\%$ ) on continuing medical management at the time of last follow-up. Incidence of congestive heart failure is presented in Table 1. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

**Table 1**  
Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

Study	Regimen	Incidence of CHF	
		Herceptin	Control
1 & 2 <sup>a</sup>	AC <sup>b</sup> →Paclitaxel+Herceptin	2% (32/1677)	0.4% (7/1600)
3	Chemo → Herceptin	2% (30/1678)	0.3% (5/1708)
4	AC <sup>b</sup> →Docetaxel+Herceptin	2% (20/1068)	0.3% (3/1050)
4	Docetaxel+Carbo+Herceptin	0.4% (4/1056)	0.3% (3/1050)

<sup>a</sup> Includes 1 patient with fatal cardiomyopathy.

<sup>b</sup> Anthracycline (doxorubicin) and cyclophosphamide

**Table 2**  
Incidence of Cardiac Dysfunction<sup>a</sup> in Metastatic Breast Cancer Studies

Study	Event	Incidence			
		NYHA I–IV		NYHA III–IV	
		Herceptin	Control	Herceptin	Control
5 (AC) <sup>b</sup>	Cardiac Dysfunction	28%	7%	19%	3%
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
6	Cardiac Dysfunction <sup>c</sup>	7%	N/A	5%	N/A

<sup>a</sup> Congestive heart failure or significant asymptomatic decrease in LVEF.

<sup>b</sup> Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

<sup>c</sup> Includes 1 patient with fatal cardiomyopathy.

In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the Herceptin containing regimens: (AC-TH: 0.3% (3/1068) and TCH 0.2% (2/1056)) as compared to none in AC-T.

## 5.2 Infusion Reactions

Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. [see *Adverse Reactions (6.1)*]

In postmarketing reports, serious and fatal infusion reactions have been reported. Severe reactions which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered, which may include: epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin infusions, others had recurrent severe infusion reactions despite pre-medications.

## 5.3 Embryo-Fetal Toxicity

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise women of the potential hazard to the fetus resulting from Herceptin exposure during pregnancy and provide contraception counseling to women of childbearing potential. [see *Use in Specific Populations (8.1)*, *Patient Counseling Information (17)* ].

## 5.4 Pulmonary Toxicity

Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [see *Warnings and Precautions (5.2)*]. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

## 5.5 Exacerbation of Chemotherapy-Induced Neutropenia

In randomized, controlled clinical trials the per-patient incidences of NCI CTC Grade 3–4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received Herceptin and those who did not. [see *Adverse Reactions (6.1)*]

## 5.6 HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown. Due to differences in tumor histopathology, use FDA-approved tests for the specific tumor type (breast or gastric/gastroesophageal adenocarcinoma) to assess HER2 protein overexpression and HER2 gene amplification. Tests should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay

instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

Several FDA-approved commercial assays are available to aid in the selection of breast cancer and metastatic gastric cancer patients for Herceptin therapy. Users should refer to the package inserts of specific assay kits for information on the Intended Use, and the validation and performance of each assay. Limitations in assay precision make it inadvisable to rely on a single method to rule out potential Herceptin benefit.

Treatment outcomes for adjuvant breast cancer (Studies 2 and 3) and for metastatic breast cancer (Study 5) as a function of IHC and FISH testing are provided in [Tables 8 and 10](#).

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers. Study 7 demonstrated that gene amplification and protein overexpression were not as well correlated as with breast cancer. Treatment outcomes for metastatic gastric cancer (Study 7), based on HER2 gene amplification (FISH) and HER2 protein overexpression (IHC) test results are provided in [Table 12](#).

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiomyopathy [*see Warnings and Precautions (5.1)*]
- Infusion reactions [*see Warnings and Precautions (5.2)*]
- Embryo-fetal Toxicity [*see Warnings and Precautions (5.3)*]
- Pulmonary toxicity [*see Warnings and Precautions (5.4)*]
- Exacerbation of chemotherapy-induced neutropenia [*see Warnings and Precautions (5.5)*]

The most common adverse reactions in patients receiving Herceptin in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [*see Dosage and Administration (2.2)*].

In the metastatic gastric cancer setting, the most common adverse reactions ( $\geq 10\%$ ) that were increased ( $\geq 5\%$  difference) in the Herceptin arm as compared to the chemotherapy alone arm were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of treatment on the Herceptin-containing arm in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### *Adjuvant Breast Cancer Studies*

The data below reflect exposure to Herceptin across three randomized, open-label studies, Studies 1, 2, and 3, with (n= 3355) or without (n= 3308) trastuzumab in the adjuvant treatment of breast cancer.

The data summarized in [Table 3](#) below, from Study 3, reflect exposure to Herceptin in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18.

Among the 3386 patients enrolled in Study 3, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

**Table 3**  
Adverse Reactions for Study 3, All Grades<sup>a</sup>:

Adverse Reaction	1 Year Herceptin (n= 1678)	Observation (n=1708)
<u>Cardiac</u>		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias <sup>b</sup>	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
<u>Respiratory Thoracic Mediastinal Disorders</u>		
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
<u>Gastrointestinal Disorders</u>		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
<u>Musculoskeletal &amp; Connective Tissue Disorders</u>		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
<u>Nervous System Disorders</u>		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
<u>Skin &amp; Subcutaneous Tissue Disorders</u>		
Rash	70 (4%)	10 (0.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritis	40 (2%)	10 (0.6%)

**Table 3 (cont'd)**  
Adverse Reactions for Study 3, All Grades<sup>a</sup>:

Adverse Reaction	1 Year Herceptin (n= 1678)	Observation (n=1708)
<u>General Disorders</u>		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (.06%)	0 (0%)
<u>Infections</u>		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
<u>Immune System Disorders</u>		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

<sup>a</sup> The incidence of Grade 3/4 adverse reactions was <1% in both arms for each listed term.

<sup>b</sup> Higher level grouping term.

The data from Studies 1 and 2 were obtained from 3206 patients, of whom 1635 received Herceptin; the median treatment duration was 50 weeks. The median age was 49 years (range: 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 4% Asian.

In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (31% vs. 28%), fatigue (28% vs. 22%), infection (22% vs. 14%), hot flashes (17% vs. 15%), anemia (13% vs. 7%), dyspnea (12% vs. 4%), rash/desquamation (11% vs. 7%), neutropenia (7% vs. 5%), headache (6% vs. 4%), and insomnia (3.7% vs. 1.5%). The majority of these events were Grade 2 in severity.

In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (11% vs. 8.4%), myalgia (10% vs. 8%), nail changes (9% vs. 7%), and dyspnea (2.5% vs. 0.1%). The majority of these events were Grade 2 in severity.

Safety data from Study 4 reflect exposure to Herceptin as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n=1056]. The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms. The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low incidence of CHF in the TCH arm.

### Metastatic Breast Cancer Studies

The data below reflect exposure to Herceptin in one randomized, open-label study, Study 5, of chemotherapy with (n=235) or without (n=234) trastuzumab in patients with metastatic breast cancer, and one single-arm study (Study 6; n=222) in patients with metastatic breast cancer. Data in Table 4 are based on Studies 5 and 6.

Among the 464 patients treated in Study 5, the median age was 52 years (range: 25–77 years). Eighty-nine percent were White, 5% Black, 1% Asian and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for  $\geq 6$  months and  $\geq 12$  months were 58% and 9%, respectively.

Among the 352 patients treated in single agent studies (213 patients from Study 6), the median age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for  $\geq 6$  months and  $\geq 12$  months were 31% and 16%, respectively.

**Table 4**  
Per-Patient Incidence of Adverse Reactions Occurring in  $\geq 5\%$  of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent <sup>a</sup> n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC <sup>b</sup> n = 143	AC <sup>b</sup> Alone n = 135
<u>Body as a Whole</u>					
Pain	47%	61%	62%	57%	42%
Asthenia	42%	62%	57%	54%	55%
Fever	36%	49%	23%	56%	34%
Chills	32%	41%	4%	35%	11%
Headache	26%	36%	28%	44%	31%
Abdominal pain	22%	34%	22%	23%	18%
Back pain	22%	34%	30%	27%	15%
Infection	20%	47%	27%	47%	31%
Flu syndrome	10%	12%	5%	12%	6%
Accidental injury	6%	13%	3%	9%	4%
Allergic reaction	3%	8%	2%	4%	2%
<u>Cardiovascular</u>					
Tachycardia	5%	12%	4%	10%	5%
Congestive heart failure	7%	11%	1%	28%	7%

**Table 4 (cont'd)**

Per-Patient Incidence of Adverse Reactions Occurring in  $\geq 5\%$  of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent <sup>a</sup> n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC <sup>b</sup> n = 143	AC <sup>b</sup> Alone n = 135
<u>Digestive</u>					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
<u>Heme &amp; Lymphatic</u>					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
<u>Metabolic</u>					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
<u>Musculoskeletal</u>					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
<u>Nervous</u>					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
<u>Respiratory</u>					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
<u>Skin</u>					
Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	< 1%
<u>Urogenital</u>					
Urinary tract infection	5%	18%	14%	13%	7%

<sup>a</sup> Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6.

<sup>b</sup> Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

### *Metastatic Gastric Cancer*

The data below are based on the exposure of 294 patients to Herceptin in combination with a fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the Herceptin plus chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to

chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m<sup>2</sup> on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m<sup>2</sup> orally twice a day on Days 1-14 or 5-fluorouracil 800 mg/m<sup>2</sup>/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin infusions administered was eight.

**Table 5**  
**Study 7: Per Patient Incidence of Adverse Reactions of All Grades**  
**(Incidence ≥5% between Arms) or Grade 3 /4 (Incidence >1% between Arms)**  
**and Higher Incidence in Herceptin Arm**

Body System/Adverse Event	Herceptin +FC (N = 294) N (%)		FC (N = 290) N (%)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
<u>Investigations</u>				
Neutropenia	230 (78)	101 (34)	212 (73)	83 (29)
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (6)
Anemia	81 (28)	36 (12)	61 (21)	30 (10)
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (3)
<u>Blood And Lymphatic System Disorders</u>				
Febrile Neutropenia	—	15 (5)	—	8 (3)
<u>Gastrointestinal Disorders</u>				
Diarrhea	109 (37)	27 (9)	80 (28)	11 (4)
Stomatitis	72 (24)	2 (1)	43 (15)	6 (2)
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤1)
<u>Body as a Whole</u>				
Fatigue	102 (35)	12 (4)	82 (28)	7 (2)
Fever	54 (18)	3 (1)	36 (12)	0 (0)
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (1)
Chills	23 (8)	1 (≤1)	0 (0)	0 (0)
<u>Metabolism And Nutrition Disorders</u>				
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2)
<u>Infections And Infestations</u>				
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (0)
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0)
<u>Renal And Urinary Disorders</u>				
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (2)
<u>Nervous System Disorders</u>				
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0)

The following subsections provide additional detail regarding adverse reactions observed in clinical trials of adjuvant breast, metastatic breast cancer, metastatic gastric cancer, or post-marketing experience.

### Cardiomyopathy

Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and 2, 23 months in the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF < 50% or  $\geq 15$  point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving Herceptin monotherapy compared to observation in Study 3 (see Table 6, [Figures 1 and 2](#)).

**Table 6<sup>a</sup>**  
Per-patient Incidence of New Onset  
Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

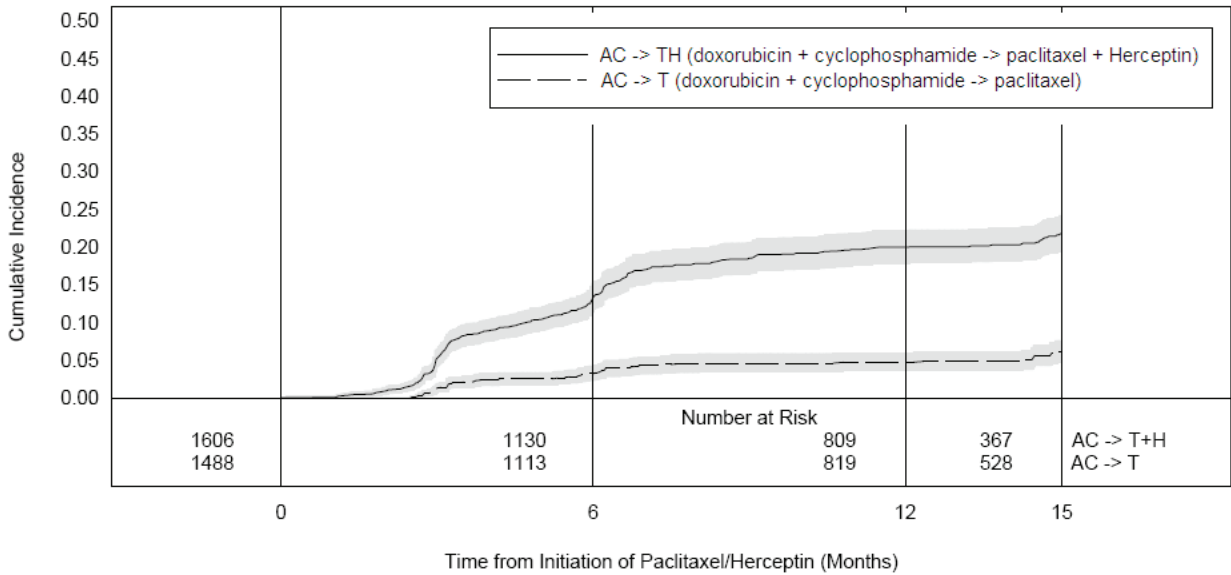
	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	$\geq 10\%$ decrease	$\geq 16\%$ decrease	<20% and $\geq 10\%$	$\geq 20\%$
<b>Studies 1 &amp; 2<sup>b</sup></b>					
AC→TH (n=1606)	22.8% (366)	18.3% (294)	11.7% (188)	33.4% (536)	9.2% (148)
AC→T (n=1488)	9.1% (136)	5.4% (81)	2.2% (33)	18.3% (272)	2.4% (36)
<b>Study 3</b>					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
<b>Study 4<sup>c</sup></b>					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

<sup>a</sup> For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization.

<sup>b</sup> Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

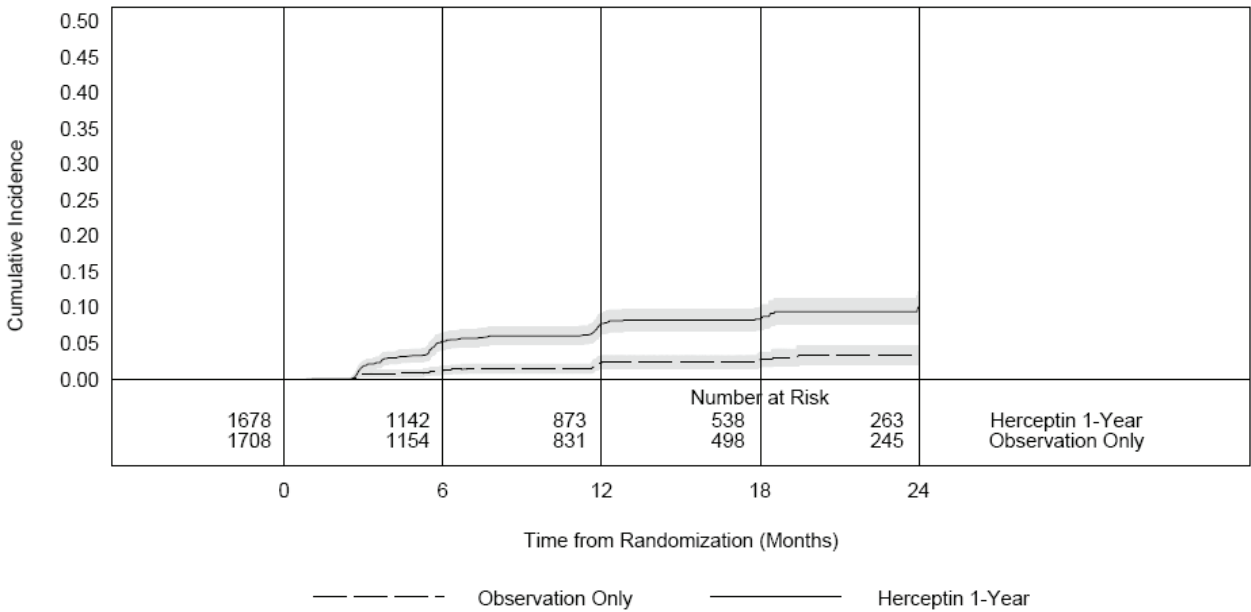
<sup>c</sup> Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

**Figure 1**  
 Studies 1 and 2: Cumulative Incidence of Time to First LVEF  
 Decline of  $\geq 10$  Percentage Points from Baseline and to  
 Below 50% with Death as a Competing Risk Event



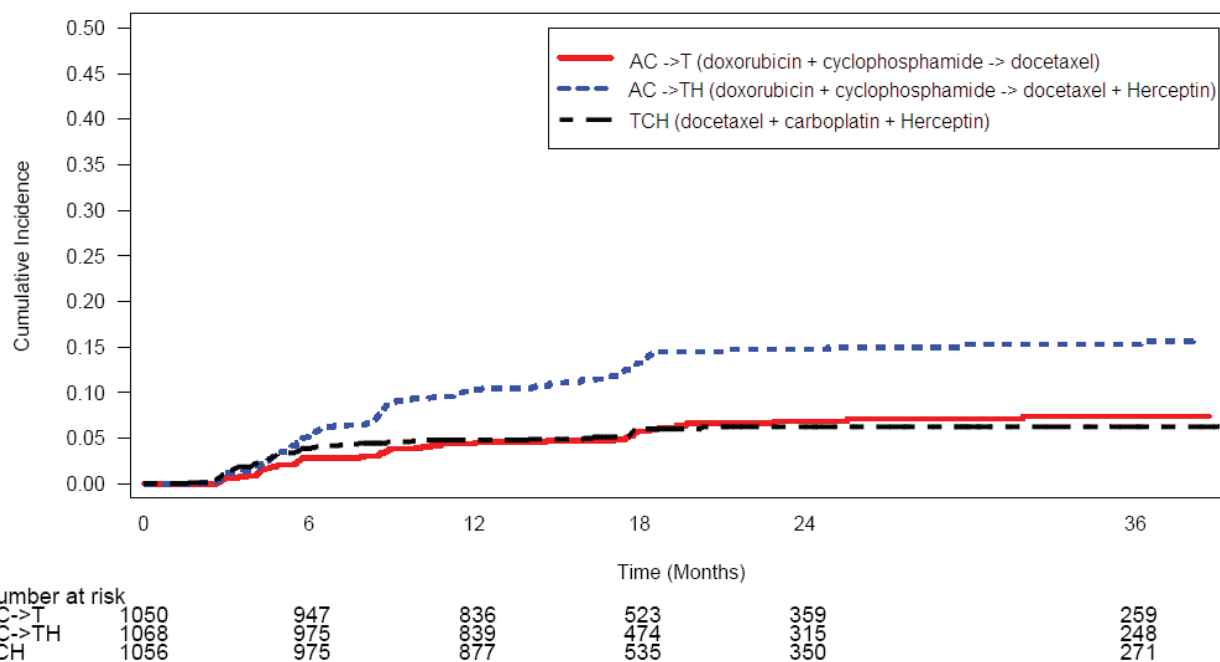
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

**Figure 2**  
 Study 3: Cumulative Incidence of Time to First LVEF  
 Decline of  $\geq 10$  Percentage Points from Baseline and to  
 Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

**Figure 3**  
 Study 4: Cumulative Incidence of Time to First LVEF  
 Decline of  $\geq 10$  Percentage Points from Baseline and to  
 Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic breast cancer trials the probability of cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracyclines.

In Study 7, 5.0% of patients in the Herceptin plus chemotherapy arm compared to 1.1% of patients in the chemotherapy alone arm had LVEF value below 50% with a  $\geq 10\%$  absolute decrease in LVEF from pretreatment values.

### Infusion Reactions

During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in  $<1\%$  of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9% of patients, on second or subsequent Herceptin infusions administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting, severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

### Anemia

In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2-5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of

Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%. In Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone arm the overall incidence of anemia was 28% compared 21% and of NCI CTC Grade 3/4 anemia was 12.2% compared to 10.3%.

### *Neutropenia*

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia (7.1% vs. 4.5% [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone arm, the incidence of NCI CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia 5.1% compared to 2.8%.

### *Infection*

The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2–5 infection/febrile neutropenia (22% vs. 14% [Study 1]) and of selected Grade 3–5 infection/febrile neutropenia (3.3% vs. 1.4%) [Study 2]), were higher in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract.

In Study 4, the overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC Grade 3–4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms.

In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

### *Pulmonary Toxicity*

#### *Adjuvant Breast Cancer*

Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14% vs. 5% [Study 1]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4 % vs. 1% [Study 2]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 12% vs. 4% [Study 1]; NCI-CTC Grade 2–5: 2.5% vs. 0.1% [Study 2]).

Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone.

In Study 3, there were 4 cases of interstitial pneumonitis in Herceptin-treated patients compared to none in the control arm.

#### *Metastatic Breast Cancer*

Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings and Precautions* (5.4).

### *Thrombosis/Embolism*

In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies (3.0% vs. 1.3% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

### *Diarrhea*

Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2–5 diarrhea (6.2% vs. 4.8% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (1.6% vs. 0% [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3]) were higher in patients receiving Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer.

### *Renal Toxicity*

In Study 7 (metastatic gastric cancer) on the Herceptin-containing arm as compared to the chemotherapy alone arm the incidence of renal impairment was 18% compared to 14.5%. Severe (Grade 3/4) renal failure was 2.7% on the Herceptin-containing arm compared to 1.7% on the chemotherapy only arm. Treatment discontinuation for renal insufficiency/failure was 2% on the Herceptin-containing arm and 0.3% on the chemotherapy only arm.

In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Herceptin therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

## **6.2 Immunogenicity**

As with all therapeutic proteins, there is a potential for immunogenicity. Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to Herceptin was detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer.

The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to other products may be misleading.

## **6.3 Post-Marketing Experience**

The following adverse reactions have been identified during post approval use of Herceptin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Infusion reaction [*see Warnings and Precautions (5.2)*]
- Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death [*see Warnings and Precautions (5.3)*]
- Glomerulopathy [*see Adverse Reactions (6.1)*]

## 7 DRUG INTERACTIONS

In Study 5, the mean serum trough concentration of trastuzumab was consistently elevated approximately 1.5-fold, when administered in combination with paclitaxel as compared to trough concentrations of trastuzumab when administered in combination with an anthracycline and cyclophosphamide.

In other pharmacokinetic studies, where Herceptin was administered in combination with paclitaxel, docetaxel or doxorubicin, Herceptin did not alter the plasma concentrations of these chemotherapeutic agents, or the metabolites that were analyzed. 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 Herceptin.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy: Category D [see *Warnings and Precautions (5.3)*, *Nonclinical Toxicology (13.2)*]

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy resumed after the amniotic fluid index improved, and oligohydramnios recurred.

Monitor women exposed to Herceptin during pregnancy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of IV hydration in management of oligohydramnios due to Herceptin exposure is not known.

Advise women of the potential hazard to the fetus resulting from Herceptin exposure during pregnancy. Encourage pregnant women with breast cancer who are using Herceptin to enroll in MoHER-the Herceptin Pregnancy Registry: phone 1-800-690-6720. [see *Patient Counseling Information (17)*].

No teratogenic effects were observed in offspring from reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab. In mutant mice lacking HER2, embryos died in early gestation. Trastuzumab exposure was reported at delivery in offspring of cynomolgus monkeys treated during the early (Days 20-50 of gestation) or late (Days 120-150 of gestation) fetal development periods, at levels of 15 to 28% of the maternal blood levels.

### 8.3 Nursing Mothers

It is not known whether Herceptin is excreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts.

Trastuzumab was present in the breast milk of lactating cynomolgus monkeys given 12.5 times the recommended weekly human dose of 2 mg/kg of Herceptin. Infant monkeys with detectable serum levels of trastuzumab did not have any adverse effects on growth or development from birth to 3 months of age; however, trastuzumab levels in animal breast milk may not accurately reflect human breast milk levels.

Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from Herceptin, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of trastuzumab and the importance of the drug to the mother.

## 8.4 Pediatric Use

The safety and effectiveness of Herceptin in pediatric patients has not been established.

## 8.5 Geriatric Use

Herceptin has been administered to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease in Studies 5 and 6, or adjuvant therapy in Studies 1 and 2. Limitations in data collection and differences in study design of the 4 studies of Herceptin in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of Herceptin in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin treatment in older patients is different from that observed in patients <65 years of age for metastatic disease and adjuvant treatment.

In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin 108 (37%) were 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or effectiveness were observed.

## 10 OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg have not been tested.

## 11 DESCRIPTION

Herceptin (trastuzumab) 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 containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous administration. Each multi-use vial of Herceptin contains 440 mg trastuzumab, 400 mg  $\alpha,\alpha$ -trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.

## 12 CLINICAL PHARMACOLOGY

### 12.1 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. Herceptin has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Herceptin is a mediator of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, Herceptin-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

### 12.2 Pharmacokinetics

The pharmacokinetics of trastuzumab were studied in women with metastatic breast cancer. Short duration intravenous infusions of 10 to 500 mg Herceptin once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 2 and 12 days at the 10 and 500 mg dose levels, respectively. The volume of

distribution of trastuzumab was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 mcg/mL.

In studies using an initial dose of 4 mg/kg followed by a weekly dose of 2 mg/kg, a mean half-life of 6 days (range 1–32 days) was observed. Between weeks 16 and 32, trastuzumab serum concentrations reached a steady state with mean trough and peak concentrations of approximately 79 mcg/mL and 123 mcg/mL, respectively.

In a study of women receiving adjuvant therapy for breast cancer, a mean half-life of trastuzumab of 16 days (range: 11–23 days) was observed after an initial dose of 8 mg/kg followed by a dose of 6 mg/kg every three weeks. Between weeks 6 and 37, trastuzumab serum concentrations reached a steady-state with mean trough and peak concentrations of 63 mcg/mL and 216 mcg/mL, respectively.

In patients with metastatic gastric cancer (Study 7), mean serum trastuzumab trough concentrations at steady state were 24 to 63% lower as compared to the concentrations observed in patients with breast cancer receiving treatment for metastatic disease in combination with paclitaxel, as monotherapy for metastatic disease, or as adjuvant monotherapy.

Sixty-four percent (286/447) of women with metastatic breast cancer had detectable circulating extracellular domain of the HER2 receptor (shed antigen), which ranged as high as 1880 ng/mL (median 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations.

Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine ( $\leq 2.0$  mg creatinine/dL).

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Herceptin has 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 Herceptin.

A fertility study conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels. Studies to evaluate the effects of trastuzumab on male fertility have not been conducted.

### 13.2 Animal Toxicology and/or Pharmacology

#### *Reproductive Toxicology Studies*

Reproductive toxicology studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg Herceptin and have revealed no evidence of impaired fertility or harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation. Placental transfer of trastuzumab was detected at Caesarean section in offspring from pregnant cynomolgus monkeys dosed during the early (Days 20–50 of gestation) or late (Days 120–150 of gestation) fetal development periods.

## 14 CLINICAL STUDIES

### 14.1 Adjuvant Breast Cancer

The safety and efficacy of Herceptin 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 3752 women, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women, 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 mmHg or systolic > 200 mmHg) were not eligible.

Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin). In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup>. Paclitaxel was administered either weekly (80 mg/m<sup>2</sup>) or every 3 weeks (175 mg/m<sup>2</sup>) for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in Study 2. Herceptin 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. Herceptin treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/recurrent LVEF decline [*see Dosage and Administration (2.2)*]. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-free survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death, was the main outcome measure of the combined efficacy analysis.

A total of 3752 patients were included in the efficacy analyses. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. Of these patients, the median age was 49 years (range, 22–80 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. At the time of randomization 53% of the population were to receive paclitaxel on a weekly regimen, and the remainder were to receive a q3 week schedule of paclitaxel.

### *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.

Patients were randomized (1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy to receive no additional treatment (n = 1693) or 1 year of Herceptin treatment (n = 1693). Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Herceptin was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks for a total of 52 weeks. The main outcome measure was disease-free survival (DFS), defined as in Studies 1 and 2.

Among the 3386 patients randomized to the two treatment arms, the median age was 49 years (range 21–80), 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 2-3, or age < 35 years. Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens.

#### *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 mmHg), 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 Herceptin (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms, doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup> were administered every 3 weeks for four cycles; docetaxel 100 mg/m<sup>2</sup> was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m<sup>2</sup> 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. Herceptin 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.

**Table 7**  
Efficacy Results from Adjuvant Treatment of  
Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	Hazard ratio (95% CI) p value	Deaths	Hazard ratio p value
<u>Studies 1 + 2<sup>c</sup></u>				
AC→TH (n = 1872)	133	0.48 <sup>a</sup> (0.39, 0.59) p=< 0.0001 <sup>b</sup>	62	0.67 p=NS <sup>d</sup>
AC→T (n = 1880)	261		92	
<u>Study 3</u>				
Chemo→ Herceptin (n = 1693)	127	0.54 (0.44, 0.67) p=< 0.0001 <sup>c</sup>	31	0.75 p=NS <sup>d</sup>
Chemo→ Observation (n = 1693)	219		40	
<u>Study 4<sup>f</sup></u>				
TCH (n=1075)	134	0.67 (0.54 – 0.84) p=0.0006 <sup>b,g</sup>	56	
AC→TH (n=1074)	121	0.60 (0.48 – 0.76) p=< 0.0001 <sup>b,g</sup>	49	
AC→T (n=1073)	180		80	

CI = confidence interval.

<sup>a</sup> Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

<sup>b</sup> stratified log-rank test.

<sup>c</sup> log-rank test.

<sup>d</sup> NS= non-significant.

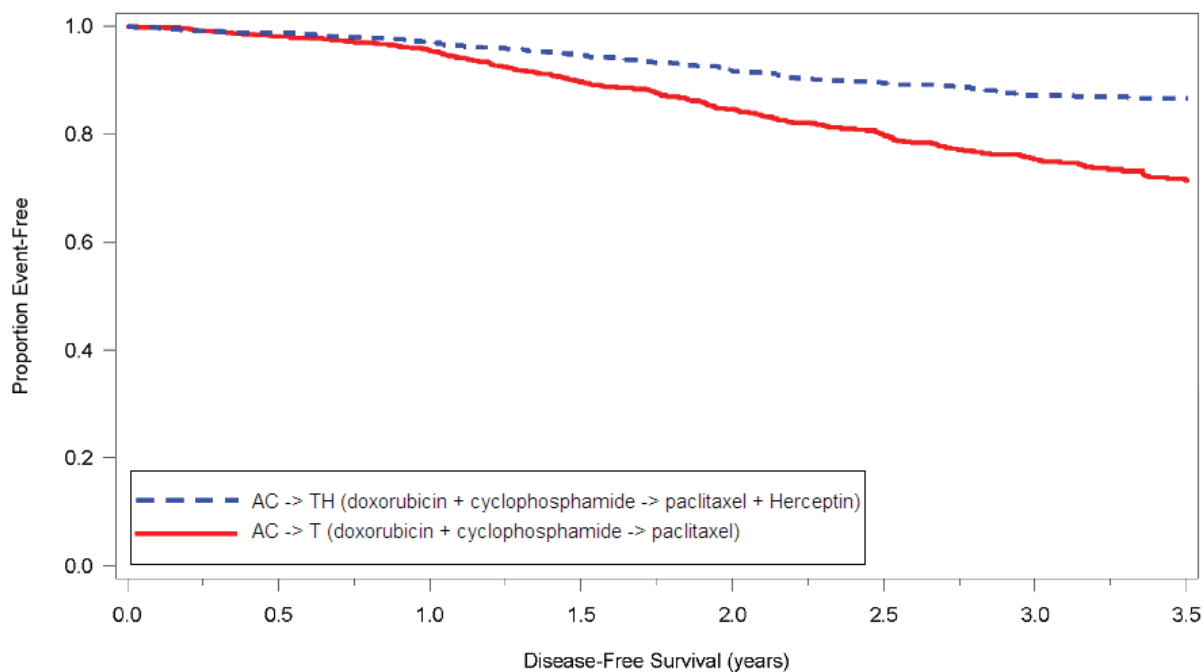
<sup>e</sup> Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

<sup>f</sup> Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

<sup>g</sup> A two-sided alpha level of 0.025 for each comparison.

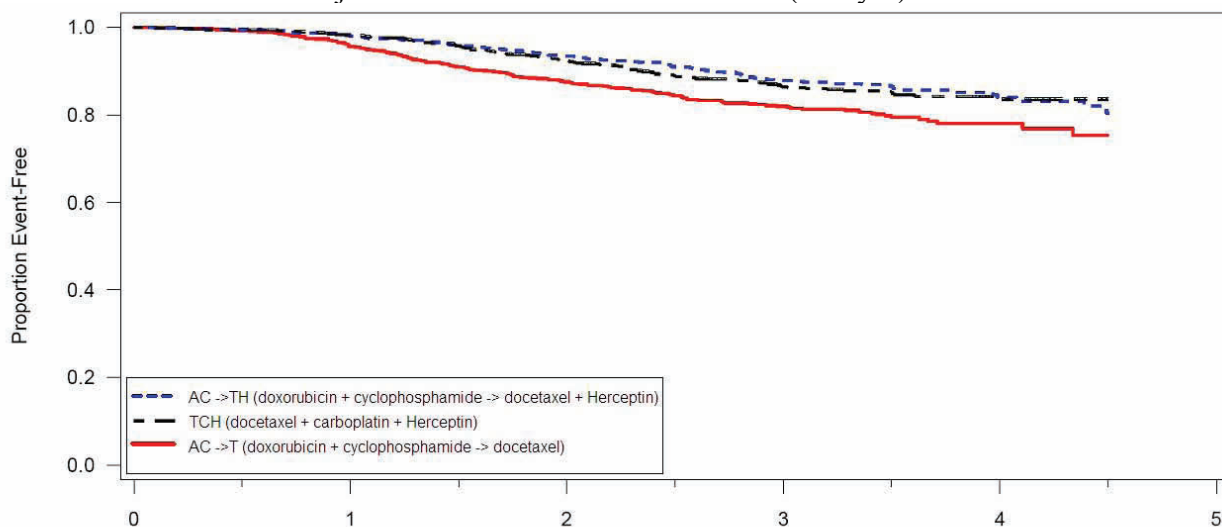
The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 are presented in [Table 7](#). The duration of DFS for Studies 1 and 2 is presented in [Figure 4](#), and the duration of DFS for Study 4 is presented in [Figure 5](#). Across all four studies, there were insufficient 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.

**Figure 4**  
Duration of Disease-Free Survival in  
Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



Number at risk		0.5	1.0	1.5	2.0	2.5	3.0	3.5
AC→ T	1880	1490	1159	926	689	534	375	195
AC→ T + H	1872	1529	1240	997	764	575	426	239

**Figure 5**  
Duration of Disease-Free Survival in Patients with  
Adjuvant Treatment of Breast Cancer (Study 4)



Number at risk		1	2	3	4
AC->T	1073	971	802	417	103
AC->TH	1074	1023	885	457	126
TCH	1075	1018	877	447	126

AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.  
Kaplan-Meier estimates are shown.

Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. The results are shown in Table 8. The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.

**Table 8**  
Treatment Outcomes in Studies 2 and 3 as a Function of  
HER2 Overexpression or Amplification

HER2 Assay Result <sup>a</sup>	Study 2		Study 3	
	Number of Patients	Hazard Ratio DFS (95% CI)	Number of Patients	Hazard Ratio DFS (95% CI)
<b>IHC 3+</b>				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (-)	51	0.71 (0.04, 11.79)	8	—
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)
IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299 <sup>b</sup>	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	—	—	724	0.59 (0.38, 0.93)

<sup>a</sup> IHC by HercepTest, FISH by PathVysion (HER2/CEP17 ratio  $\geq 2.0$ ) as performed at a central laboratory.

<sup>b</sup> All cases in this category in Study 3 were IHC 2+.

## 14.2 Metastatic Breast Cancer

The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n=469 patients) and an open-label single agent clinical trial (Study 6, n=222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

### *Previously Untreated Metastatic Breast Cancer (Study 5)*

Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m<sup>2</sup> over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m<sup>2</sup> or epirubicin 75 mg/m<sup>2</sup> plus 600 mg/m<sup>2</sup> cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to

receive chemotherapy alone in this study received Herceptin at the time of disease progression as part of a separate extension study.

Based upon the determination by an independent response evaluation committee the patients randomized to Herceptin and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), and a longer median duration of response, as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin and chemotherapy also had a longer median survival (see [Table 9](#)). These treatment effects were observed both in patients who received Herceptin plus paclitaxel and in those who received Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.

**Table 9**  
Study 5: Efficacy Results in  
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo- therapy (n = 235)	All Chemo- therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC <sup>a</sup> (n = 143)	AC (n = 138)
<b>Primary Endpoint</b>						
<u>Median</u> <u>TTP(mos)</u> <sup>b,c</sup>	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value <sup>d</sup>	< 0.0001		< 0.0001		0.002	
<b>Secondary Endpoints</b>						
<u>Overall</u> <u>Response</u> <u>Rate</u> <sup>b</sup>	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value <sup>e</sup>	< 0.001		< 0.001		0.10	
<u>Median Resp</u> <u>Duration</u> <u>(mos)</u> <sup>b,c</sup>	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% Quartile	6, 15	4, 8	5, 11	4, 7	6, 15	4, 8
<u>Med Survival</u> <u>(mos)</u> <sup>c</sup>	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value <sup>d</sup>	0.05		0.17		0.16	

<sup>a</sup> AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

<sup>b</sup> Assessed by an independent Response Evaluation Committee.

<sup>c</sup> Kaplan-Meier Estimate.

<sup>d</sup> log-rank test.

<sup>e</sup>  $\chi^2$ -test.

Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see [Table 10](#)).

**Table 10**  
Treatment Effects in Study 5 as a  
Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk <sup>b</sup> for Time to Disease Progression (95% CI)	Relative Risk <sup>b</sup> for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+) <sup>a</sup>	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (-) <sup>a</sup>	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)
FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)
FISH (-)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (-)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

<sup>a</sup> FISH testing results were available for 451 of the 469 patients enrolled on study.

<sup>b</sup> The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

### *Previously Treated Metastatic Breast Cancer (Study 6)*

Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at 2 mg/kg IV.

The ORR (complete response+partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes. The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

### **14.3 Metastatic Gastric Cancer**

The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%).

On the Herceptin-containing arm, Herceptin was administered as an IV infusion at an initial dose of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms cisplatin was administered at a dose of 80 mg/m<sup>2</sup> Day 1 every 3 weeks for 6 cycles as a 2 hour IV

infusion. On both study arms capecitabine was administered at 1000 mg/m<sup>2</sup> dose orally twice daily (total daily dose 2000 mg/m<sup>2</sup>) for 14 days of each 21 day cycle for 6 cycles. Alternatively continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m<sup>2</sup>/day from Day 1 through Day 5 every three weeks for 6 cycles.

The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1; 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant therapy, and 2% had received prior radiotherapy.

The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log-rank test. The final OS analysis based on 351 deaths was statistically significant (nominal significance level of 0.0193). An updated OS analysis was conducted at one year after the final analysis. The efficacy results of both the final and the updated analyses are summarized in Table 11 and Figure 6.

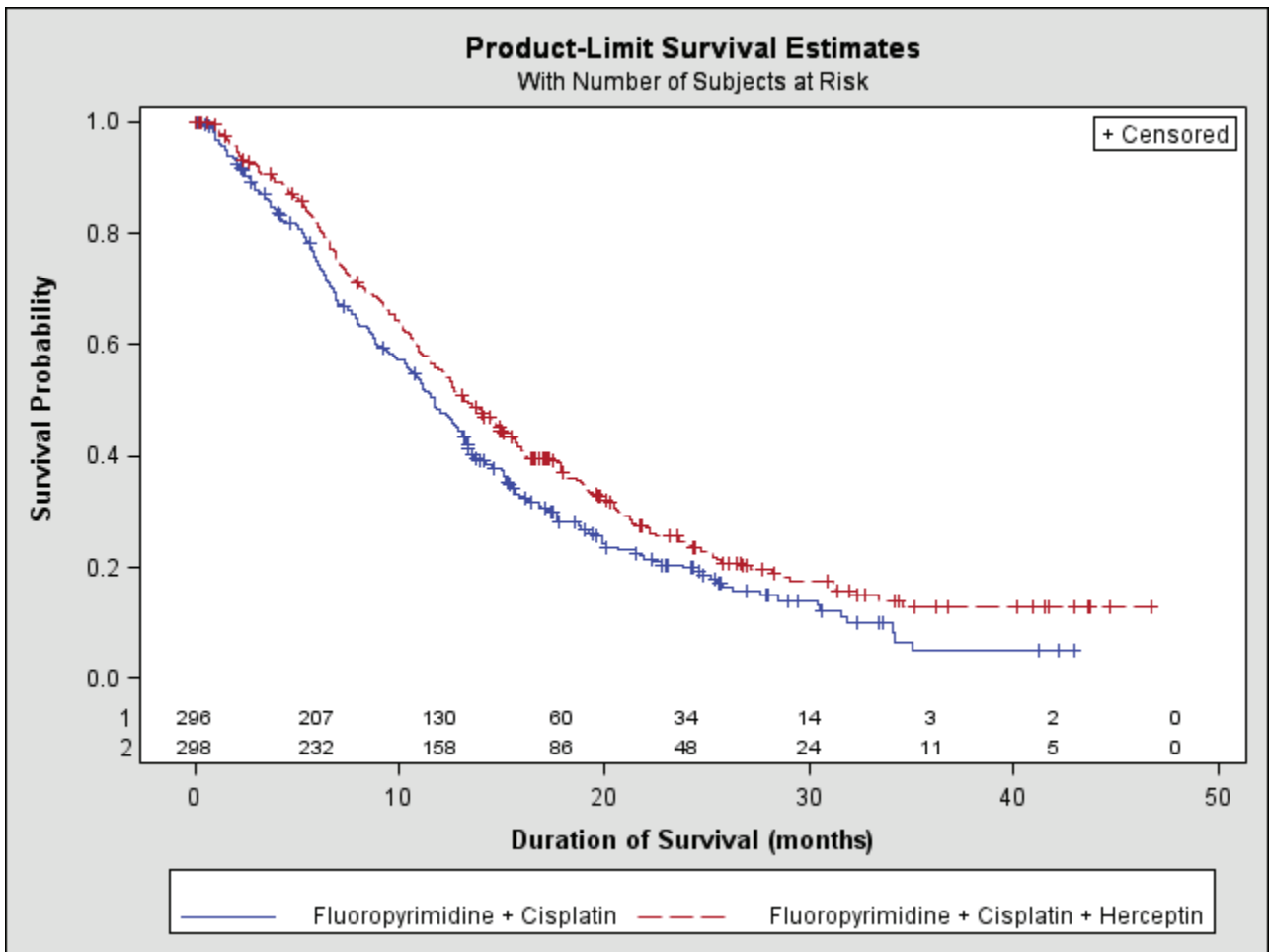
**Table 11**  
Study 7: Overall Survival in ITT Population

	FC Arm N=296	FC + H Arm N=298
<u>Definitive (Second Interim) Overall Survival</u>		
No. Deaths (%)	184 (62.2%)	167 (56.0%)
Median	11.0	13.5
95% CI (mos.)	(9.4, 12.5)	(11.7, 15.7)
Hazard Ratio		0.73
95% CI		(0.60, 0.91)
p-value*, two-sided		0.0038
<u>Updated Overall Survival</u>		
No. Deaths (%)	227 (76.7%)	221 (74.2%)
Median	11.7	13.1
95% CI (mos.)	(10.3, 13.0)	(11.9, 15.1)
Hazard Ratio		0.80
95% CI		(0.67, 0.97)

\* Comparing with the nominal significance level of 0.0193.

**Figure 6**

Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 12.

**Table 12**  
Exploratory Analyses by HER2 Status using Updated Overall Survival Results

	FC (N= 296) <sup>a</sup>	FC+H (N=298) <sup>b</sup>
<u>FISH+ / IHC 0, 1+ subgroup (N=133)</u>		
No. Deaths / n (%)	57/71 (80%)	56/62 (90%)
Median OS Duration (mos.)	8.8	8.3
95% CI (mos.)	(6.4, 11.7)	(6.2, 10.7)
Hazard ratio (95% CI)	1.33 (0.92, 1.92)	
<u>FISH+ / IHC2+ subgroup (N=160)</u>		
No. Deaths / n (%)	65/80 (81%)	64/80 (80%)
Median OS Duration (mos.)	10.8	12.3
95% CI (mos.)	(6.8, 12.8)	(9.5, 15.7)
Hazard ratio (95% CI)	0.78 (0.55, 1.10)	
<u>FISH+ or FISH-/IHC3+<sup>c</sup> subgroup (N=294)</u>		
No. Deaths / n (%)	104/143 (73%)	96/151 (64%)
Median OS Duration (mos.)	13.2	18.0
95% CI (mos.)	(11.5, 15.2)	(15.5, 21.2)
Hazard ratio (95% CI)	0.66 (0.50, 0.87)	

<sup>a</sup> Two patients on the FC arm who were FISH+ but IHC status unknown were excluded from the exploratory subgroup analyses.

<sup>b</sup> Five patients on the Herceptin-containing arm who were FISH+, but IHC status unknown were excluded from the exploratory subgroup analyses.

<sup>c</sup> Includes 6 patients on chemotherapy arm, 10 patients on Herceptin arm with FISH-, IHC3+ and 8 patients on chemotherapy arm, 8 patients on Herceptin arm with FISH status unknown, IHC 3+.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Herceptin is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial Herceptin<sup>®</sup> and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative. NDC 50242-134-68.

### 16.2 Stability and Storage

Vials of Herceptin are stable at 2–8°C (36–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of Herceptin reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2–8°C (36–46°F). Discard any remaining multi-dose reconstituted solution after 28 days. A vial of Herceptin reconstituted with unpreserved SWFI (not supplied) should be used immediately and any unused portion discarded.

**Do Not Freeze** Herceptin following reconstitution or dilution.

The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2–8°C (36–46°F) for no more than 24 hours prior to use.

## 17 PATIENT COUNSELING INFORMATION

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Boxed Warning Cardiomyopathy*].
- Advise pregnant women and women of childbearing potential that Herceptin exposure can result in fetal harm [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)*].
- Advise women of childbearing potential to use effective contraceptive methods during treatment and for a minimum of six months following Herceptin [*see Warnings and Precautions (5.3)*].
- Advise nursing mothers treated with Herceptin to discontinue nursing or discontinue Herceptin, taking into account the importance of the drug to the mother [*see Use in Specific Populations (8.3)*].
- Encourage women who are exposed to Herceptin during pregnancy to enroll in MoTHER- the Herceptin Pregnancy Registry (1-800-690-6720) [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)*].

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### HERCEPTIN<sup>®</sup> [trastuzumab]

Manufactured by:

Genentech, Inc.

**A Member of the Roche Group**

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South San Francisco, CA 94080-4990

4851301

Initial US Approval: September 1998

Revision Date: October 2010

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