

TRAZIMERA®
Trastuzumab

1. NAME OF THE MEDICINAL PRODUCT

TRAZIMERA Powder for Concentrate for Solution for Infusion 440 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 440 mg multidose vial containing powder for concentrate for solution for infusion and one vial of diluent, which is a clear, colorless solution containing 20 mL bacteriostatic water for injection (BWFI) with 1.1% benzyl alcohol as preservative.

Reconstituted TRAZIMERA concentrate contains 21 mg/mL of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by chromatography including specific viral inactivation and removal procedures.

Excipients: see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White lyophilized powder or cake.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Metastatic breast cancer (MBC)

TRAZIMERA is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress human epidermal growth factor receptor 2 (HER2):

- as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease.
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab. This indication is based on data from one Phase III trial which studied the use of trastuzumab in combination with anastrozole (see section 5.1). Experience with other aromatase inhibitors is limited.

Early breast cancer (EBC)

TRAZIMERA is indicated for the treatment of patients with HER2 positive early breast cancer.

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant TRAZIMERA therapy, for locally advanced (including inflammatory) disease or tumours >2 cm in diameter (see sections 4.4 and 5.1).

TRAZIMERA should only be used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

Metastatic gastric cancer (MGC)

TRAZIMERA in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

TRAZIMERA should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC 3+, as determined by an accurate and validated assay (see sections 4.4 and 5.1).

4.2. Posology and method of administration

General

HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1).

TRAZIMERA treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4), and should be administered by a healthcare professional only.

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

The safety and efficacy of alternating or switching between TRAZIMERA and products that are biosimilar but not deemed interchangeable to TRAZIMERA has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

TRAZIMERA intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

Do not administer as an intravenous push or bolus.

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is TRAZIMERA (trastuzumab) and not Kadcyła (trastuzumab emtansine).

Metastatic breast cancer

Weekly schedule

Loading dose: The recommended initial loading dose is 4 mg/kg body weight TRAZIMERA administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses: The recommended weekly dose of TRAZIMERA is 2 mg/kg body weight. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8).

Administration in combination with an aromatase inhibitor

In the pivotal trial (BO16216) trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration (for dose, see the Product Information for anastrozole or other aromatase inhibitors).

3-weekly schedule

Alternatively the following loading and subsequent doses are recommended for monotherapy and in combination with paclitaxel or an aromatase inhibitor.

Initial TRAZIMERA loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

Early breast cancer

3-weekly schedule

As a three-weekly regimen the recommended initial loading dose of TRAZIMERA is 8 mg/kg body weight. The recommended maintenance dose of TRAZIMERA at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Alternative weekly schedule

As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

See section 5.1 for chemotherapy combination dosing.

Metastatic gastric cancer

3-weekly schedule

TRAZIMERA is administered at an initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose is well tolerated, the subsequent doses can be administered as a 30-minute infusion (see section 5.1 for chemotherapy combination dosing).

Duration of treatment

In clinical studies, patients with metastatic breast cancer or metastatic gastric cancer were treated with trastuzumab until progression of disease or unmanageable toxicity. Patients with early breast cancer should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first. Extending treatment in EBC beyond one year is not recommended (see section 5.1).

For instructions for use and handling refer to section 6.6.

Dose modification

If the patient develops an infusion-related reaction (IRR), the infusion rate of TRAZIMERA may be slowed or interrupted (see section 4.4).

No reductions in the dose of trastuzumab were made during clinical trials. Patients may continue trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression, but they should be monitored carefully for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Missed doses

If the patient has missed a dose of TRAZIMERA by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent TRAZIMERA maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of TRAZIMERA by more than one week, a re-loading dose of TRAZIMERA should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent TRAZIMERA maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

Special dosage instructions

Geriatric use

Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine. In clinical trials, patients ≥ 65 years of age did not receive reduced doses of trastuzumab. Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. However in a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric use

The safety and efficacy of TRAZIMERA in paediatric patients <18 years of age have not been established.

4.3. Contraindications

- Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients.
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.4. Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see section 5.1).

Currently no data from clinical trials are available on re-treatment of patients with previous exposure to TRAZIMERA in the adjuvant setting.

Cardiac dysfunction

General considerations

Patients treated with trastuzumab products are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab product therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death (see section 4.8). In addition, caution should be exercised in treating patients with increased cardiac risk, e.g., hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.

All candidates for treatment with TRAZIMERA, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help

to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. A careful risk-benefit assessment should be made before deciding to treat with TRAZIMERA.

Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment based on population pharmacokinetic analysis of all available data (see section 5.2). Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients cardiac function should be monitored during treatment (e.g., every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g., every 6 - 8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of TRAZIMERA therapy has been seen.

The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. If LVEF percentage drops ≥ 10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of TRAZIMERA should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

If symptomatic cardiac failure develops during TRAZIMERA therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on therapy without additional clinical cardiac events.

Metastatic breast cancer

Trastuzumab and anthracyclines should not be given concurrently in combination in the MBC setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

Early breast cancer

For patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment

until 24 months from the last administration of trastuzumab. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of trastuzumab, or longer if a continuous decrease of LVEF is observed.

Patients with history of myocardial infarction (MI), angina pectoris requiring medical treatment, history of or existing CHF (NYHA Class II –IV), LVEF of <55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with trastuzumab and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

Trastuzumab products and anthracyclines should not be given concurrently in combination in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when trastuzumab was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered trastuzumab concurrently with a taxane following anthracycline therapy up to 2.37% compared to approximately 1% in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and trastuzumab).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (>50 years), low LVEF (<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products. In patients receiving trastuzumab after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of trastuzumab and a body mass index (BMI) >25 kg/m².

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, TRAZIMERA should be used concurrently with anthracyclines only in chemotherapy-naïve patients and only with low-dose anthracycline regimens i.e., maximum cumulative doses of doxorubicin 180 mg/m² or epirubicin 360 mg/m².

If patients have been treated concurrently with a full course of low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials (MO16432 and BO22227).

In the pivotal trial MO16432, trastuzumab was administered intravenously concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m²).

The incidence of symptomatic cardiac dysfunction was low in the trastuzumab arms (up to 1.7%).

In the pivotal trial BO22227, trastuzumab was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m²); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the trastuzumab intravenous arm.

Clinical experience is limited in patients above 65 years of age.

Infusion-related reactions (IRRs) and hypersensitivity

Serious IRRs to trastuzumab infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported (see section 4.8). Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). These symptoms can be treated with an analgesic/antipyretic such as pethidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with TRAZIMERA (see section 4.3).

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Pulmonary events

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting (see section 4.8). These events have occasionally been fatal. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with

interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with TRAZIMERA (see section 4.3). Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

4.5. Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. Clinically significant interactions between trastuzumab and the concomitant medicinal products used in clinical trials have not been observed.

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Pharmacokinetic data from studies BO15935 and M77004 in women with HER2 positive MBC suggested that exposure to paclitaxel and doxorubicin (and their major metabolites 6- α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV, respectively). However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite was unclear.

Data from study JP16003, a single-arm study of trastuzumab (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m² IV) in Japanese women with HER2 positive MBC, suggested that concomitant administration of trastuzumab had no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer to study the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab. The results of this substudy suggested that the exposure to the bioactive metabolites (e.g., 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 in patients with metastatic or locally advanced inoperable HER2 positive cancer suggested that trastuzumab had no impact on the PK of carboplatin.

Effect of antineoplastic agents on trastuzumab pharmacokinetics

By comparison of simulated serum trastuzumab concentrations after trastuzumab monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2 positive MBC (study JP16003) no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found.

Comparison of PK results from two Phase II studies (BO15935 and M77004) and one Phase III study (H0648g) in which patients were treated concomitantly with trastuzumab and paclitaxel and two Phase II studies in which trastuzumab was administered as monotherapy (W016229 and MO16982), in women with HER2 positive MBC indicates that individual and

mean trastuzumab trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab. Comparison of trastuzumab PK data from Study M77004 in which women with HER2 positive MBC were treated concomitantly with trastuzumab, paclitaxel and doxorubicin to trastuzumab PK data in studies where trastuzumab was administered as monotherapy (H0649g) or in combination with anthracycline plus cyclophosphamide or paclitaxel (Study H0648g), suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab.

Pharmacokinetic data from Study H4613g/G001305 suggested that carboplatin had no impact on the PK of trastuzumab.

The administration of concomitant anastrozole did not appear to influence the pharmacokinetics of trastuzumab.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with TRAZIMERA and for 7 months after treatment has concluded (see section 5.2).

Pregnancy

Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab intravenous formulation and have revealed no evidence of impaired fertility or harm to the foetus. Placental transfer of trastuzumab during the early (days 20–50 of gestation) and late (days 120–150 of gestation) foetal development period was observed. It is not known whether trastuzumab can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with TRAZIMERA, or if a patient becomes pregnant while receiving TRAZIMERA or within 7 months following the last dose of TRAZIMERA, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

A study conducted in lactating Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab intravenous formulation demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during TRAZIMERA therapy and for 7 months after the last dose.

Fertility

There is no fertility data available.

4.7. Effects on ability to drive and use machines

Trastuzumab may have a minor influence on the ability to drive or use machines (see section 4.8). Patients experiencing infusion-related symptoms (see section 4.4) should be advised not to drive and use machines until symptoms abate.

4.8. Undesirable effects

Summary of the safety profile

Amongst the most serious and/or common adverse reactions reported in trastuzumab usage to date are cardiac dysfunction, infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

Tabulated list of adverse reactions

In this section, the following categories of frequency have been used: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Presented in Table 1 are adverse reactions that have been reported in association with the use of intravenous trastuzumab alone or in combination with chemotherapy in pivotal clinical trials. All the terms included are based on the highest percentage seen in pivotal clinical trials.

Table 1: Summary of Adverse Drug Reactions Occurring in Patients Treated with Trastuzumab in Clinical Trials

System organ class	Adverse reaction	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Infection	Very common
	Influenza	Common
	Neutropenic sepsis	Common
	Pharyngitis	Common
	Sinusitis	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	⁺ Pneumonia	Common (<1%)
	Cystitis	Common
	Herpes zoster	Common
	Skin infection	Common
	Erysipelas	Common
	Cellulitis	Common
	Sepsis	Uncommon
Blood and lymphatic	Anaemia	Very common

system disorders	Thrombocytopenia	Very common
	Febrile neutropenia	Very common
	White blood cell count decreased/leukopenia	Very common
	Neutropenia	Very common
	Hypoprothrombinemia	Not known
	Immune thrombocytopenia	Not known
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Immune system disorders	Hypersensitivity	Common
	⁺ Anaphylactic reaction	Not known
	⁺ Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight increased	Very common
	Weight decreased/weight loss	Very common
	Decreased appetite	Very common
	Anorexia	Common
	Hyperkalaemia	Not known
Psychiatric disorders	Anxiety	Common
	Depression	Common
	Insomnia	Very common
	Thinking abnormal	Common
Nervous system disorders	¹ Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Peripheral neuropathy	Common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Hypertonia	Very common
	Somnolence	Common
	Dysgeusia	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	¹ Blood pressure decreased	Very common
	¹ Blood pressure increased	Very common
	¹ Heart beat irregular	Very common
	¹ Palpitation	Common
	¹ Cardiac flutter	Very common
	⁺ ¹ Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Ejection fraction decreased*	Very common

	⁺ Cardiac failure (congestive)	Common (2%)
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known
	Bradycardia	Not known
	Gallop rhythm present	Not known
Vascular disorders	Lymphoedema	Very common
	Hot flush	Very common
	⁺¹ Hypotension	Common
	Hypertension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	⁺¹ Wheezing	Very common
	⁺ Dyspnoea	Very common (14%)
	Cough	Very common
	Epistaxis	Very common
	Oropharyngeal pain	Very common
	Rhinorrhoea	Very common
	Asthma	Common
	Lung disorder	Common
	Pneumonia	Common
	⁺ Pleural effusion	Common
	Pneumonitis	Uncommon
	⁺ Pulmonary fibrosis	Not known
	⁺ Respiratory distress	Not known
	⁺ Respiratory failure	Not known
	⁺ Lung infiltration	Not known
	⁺ Acute pulmonary oedema	Not known
	⁺ Acute respiratory distress syndrome	Not known
	⁺ Bronchospasm	Not known
	⁺ Hypoxia	Not known
	⁺ Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	¹ Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Haemorrhoids	Common
	Constipation	Very common
	Stomatitis	Very common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular injury	Common
	Hepatitis	Common
	Liver tenderness	Common
	Jaundice	Rare

	Hepatic failure	Not known
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	¹ Swelling face	Very common
	Nail disorder	Very common
	Acne	Common
	Alopecia	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasia	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	¹ Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Pain in extremity	Common
	Neck pain	Common
Renal and urinary conditions	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal disorders	Oligohydramnios	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like illness	Very common
	Infusion/Administration related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Mucosal inflammation	Very common
	Oedema	Common

	Injection site pain**	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common
	Contusion	Common

⁺ Denotes adverse reactions that have been reported in association with a fatal outcome.

¹ Denotes adverse reactions that are reported largely in association with infusion-related reactions. Specific percentages for these are not available.

* Observed with combination therapy following anthracyclines and combined with taxanes.

** Injection site pain was identified as an ADR in the SC arm in the BO22227 study. ADRs were added to the appropriate system organ class (SOC) category and are presented in a single table according to the highest incidence seen in any of the major clinical trials.

Note: Specific percentage frequencies have been provided in brackets for terms that have been reported in association with a fatal outcome with the frequency designation ‘common’ or ‘very common’. The specific percentage frequencies relate to total number of these events, both fatal and non-fatal.

The following adverse drug reactions have been identified from post-marketing experience with trastuzumab (Table 2).

Table 2: Adverse Reactions Reported in the Post-marketing Setting

System organ class	Adverse reaction
Blood and lymphatic system disorders	Hypoprothrombinaemia
	Immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction
	Anaphylactic reaction
Metabolism and nutrition disorders	Tumour lysis syndrome
Eye disorders	Madarosis
Cardiac disorders	Cardiogenic shock
	Tachycardia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Oxygen saturation decreased
	Respiratory failure
	Interstitial lung disease
	Lung infiltration
	Acute respiratory distress syndrome
	Respiratory distress
	Pulmonary fibrosis
	Hypoxia
	Laryngeal oedema
Renal and urinary disorders	Glomerulonephropathy
	Renal failure
Pregnancy, puerperium and perinatal conditions	Pulmonary hypoplasia
	Renal hypoplasia
	Oligohydramnios

Description of selected adverse reactions

Cardiac dysfunction

Congestive heart failure (NYHA Class II - IV) is a common adverse reaction associated with the use of trastuzumab and has been associated with a fatal outcome (see section 4.4). Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough,

pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with trastuzumab (see section 4.4).

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (i.e., did not receive trastuzumab) and in patients who were administered trastuzumab sequentially after a taxane (0.3-0.4%). The rate was highest in patients who were administered trastuzumab concurrently with a taxane (2.0%). In the neoadjuvant setting, the experience of concurrent administration of trastuzumab and low dose anthracycline regimen is limited (see section 4.4).

When trastuzumab was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the one-year arm after a median follow-up of 12 months. In study BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III & IV) in the trastuzumab 1 year treatment arm was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values $\geq 50\%$ after the event) was evident for 71.4% of trastuzumab-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of patients. Approximately 17% of cardiac dysfunction related events occurred after completion of trastuzumab.

In the pivotal metastatic trials of intravenous trastuzumab, the incidence of cardiac dysfunction varied between 9% and 12% when it was combined with paclitaxel compared with 1%–4% for paclitaxel alone. For monotherapy, the rate was 6%–9%. The highest rate of cardiac dysfunction was seen in patients receiving trastuzumab concurrently with anthracycline/cyclophosphamide (27%), and was significantly higher than for anthracycline/cyclophosphamide alone (7%–10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2% in patients receiving trastuzumab and docetaxel, compared with 0% in patients receiving docetaxel alone. Most of the patients (79%) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Infusion reactions, allergic-like reactions and hypersensitivity

It is estimated that approximately 40% of patients who are treated with trastuzumab will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (National Cancer Institute [NCI]-Common Toxicity Criteria [CTC] grading system) and tend to occur earlier in treatment, i.e., during infusions one, two and three and lessen in frequency in subsequent infusions. Reactions include chills, fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache (see section 4.4). The rate of infusion-related reactions of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of trastuzumab (see section 4.4) and have been associated with a fatal outcome.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity

Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Pulmonary events

Severe pulmonary adverse reactions occur in association with the use of trastuzumab and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see section 4.4).

Immunogenicity

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1% (30/296) of patients treated with intravenous trastuzumab developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the trastuzumab intravenous arm.

The clinical relevance of these antibodies is not known. The presence of anti-trastuzumab antibodies had no impact on the pharmacokinetics, efficacy (determined by pathological Complete Response [pCR] and event free survival [EFS]) and safety determined by occurrence of administration related reactions (ARRs) of intravenous trastuzumab.

There are no immunogenicity data available for trastuzumab in gastric cancer.

TRAZIMERA Comparative Clinical Studies

The results of the TRAZIMERA clinical trial program support comparable safety profiles for TRAZIMERA and Herceptin. (See section 5.1 TRAZIMERA Clinical Studies.)

4.9. Overdose

There is no experience with overdose in human clinical trials. Single doses of trastuzumab alone greater than 10 mg/kg have not been administered in the clinical trials; a maintenance dose of 10 mg/kg q3w following a loading dose of 8 mg/kg has been studied in a clinical trial with metastatic gastric cancer patients. Doses up to this level were well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20% -

30% of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8% - 34.0% for IHC and 7.1% - 42.6% for FISH. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

Mechanism of action

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Detection of HER2 overexpression or HER2 gene amplification

Detection of HER2 overexpression or HER2 gene amplification in breast cancer

Trastuzumab should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks (see section 4.4). HER2 gene amplification should be detected using fluorescence *in situ* hybridisation (FISH) or chromogenic *in situ* hybridisation (CISH) of fixed tumour blocks. Patients are eligible for trastuzumab treatment if they show strong HER2 overexpression as described by a 3+ score by IHC or a positive FISH or CISH result.

To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 3:

Table 3: Recommended Scoring System to Evaluate the IHC Staining Patterns in Breast Cancer

Score	Staining pattern	HER2 overexpression assessment
0	No staining is observed or membrane staining is observed in <10% of the tumour cells	Negative
1+	A faint/barely perceptible membrane staining is detected in >10% of the tumour cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in >10% of the tumour cells.	Equivocal
3+	Strong complete membrane staining is detected in >10% of the tumour cells.	Positive

In general, FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2, or if there are more than 4 copies of the HER2 gene per tumour cell if no chromosome 17 control is used.

In general, CISH is considered positive if there are more than 5 copies of the HER2 gene per nucleus in greater than 50% of tumour cells.

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH and CISH assays. Official recommendations on HER2 testing may also apply.

For any other method that may be used for the assessment of HER2 protein or gene expression, the analyses should only be performed by laboratories that provide adequate state-of-the-art performance of validated methods. Such methods must clearly be precise and accurate enough to demonstrate overexpression of HER2 and must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) overexpression of HER2.

Detection of HER2 over expression or HER2 gene amplification in gastric cancer

Only an accurate and validated assay should be used to detect HER2 over expression or HER2 gene amplification. IHC is recommended as the first testing modality and in cases where HER2 gene amplification status is also required, either a silver-enhanced *in situ* hybridization (SISH) or a FISH technique must be applied. SISH technology is however, recommended to allow for the parallel evaluation of tumour histology and morphology. To ensure validation of testing procedures and the generation of accurate and reproducible results, HER2 testing must be performed in a laboratory staffed by trained personnel. Full instructions on assay performance and results interpretation should be taken from the product information leaflet provided with the HER2 testing assays used.

In the ToGA (BO18255) trial, patients whose tumours were either IHC3+ or FISH positive were defined as HER2 positive and thus included in the trial. Based on the clinical trial results, the beneficial effects were limited to patients with the highest level of HER2 protein overexpression, defined by a 3+ score by IHC, or a 2+ score by IHC and a positive FISH result.

In a method comparison study (study D008548) a high degree of concordance (>95%) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

HER2 over expression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks; HER2 gene amplification should be detected using *in situ* hybridisation using either SISH or FISH on fixed tumour blocks.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 4:

Table 4: Recommended Scoring System to Evaluate the IHC Staining Patterns in Gastric Cancer

Score	Surgical specimen - staining pattern	Biopsy specimen - staining pattern	HER2 overexpression assessment
0	No reactivity or membranous reactivity in <10% of tumour cells	No reactivity or membranous reactivity in any tumour cell	Negative
1+	Faint/barely perceptible membranous reactivity in $\geq 10\%$ of tumour cells; cells are reactive only in part of their membrane	Tumour cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumour cells stained	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in $\geq 10\%$ of tumour cells	Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in $\geq 10\%$ of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive

In general, SISH or FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2.

Clinical efficacy and safety

Metastatic breast cancer

Trastuzumab has been used in clinical trials as monotherapy for patients with MBC who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease (trastuzumab alone).

Trastuzumab has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC) as first line therapy for patients with metastatic breast cancer who have tumours that overexpress HER2.

Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m² infused over 3 hours) with or without trastuzumab. Patients were treated with trastuzumab until progression of disease.

Trastuzumab monotherapy, when used as second or third line treatment of women with metastatic breast cancer which overexpresses HER2, results in an overall tumour response rate of 15% and a median survival of 13 months.

The use of trastuzumab in combination with paclitaxel as first line treatment of women with metastatic breast cancer that overexpresses HER2 significantly prolongs the median time to

disease progression, compared with patients treated with paclitaxel alone. The increase in median time to disease progression for patients treated with trastuzumab and paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumour response and one year survival rate are also increased for trastuzumab in combination with paclitaxel versus paclitaxel alone.

Combination treatment with trastuzumab and anastrozole

Trastuzumab has been studied in combination with anastrozole for first line treatment of MBC in HER2 overexpressing, hormone-receptor (i.e., estrogen-receptor [ER] and/or progesterone-receptor [PR]) positive postmenopausal patients. Progression free survival was doubled in the trastuzumab plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters the improvements seen for the combination were for overall response (16.5% versus 6.7%); clinical benefit rate (42.7% versus 27.9%); time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be recorded between the arms. The median overall survival was extended by 4.6 months for patients in the combination arm. The difference was not statistically significant, however more than half of the patients in the anastrozole alone arm crossed over to a trastuzumab containing regimen after progression of disease.

Three-weekly dosing in metastatic breast cancer

The efficacy results from the non-comparative monotherapy and combination therapy studies are summarized in Table 5:

Table 5: Efficacy Results from the Non-Comparative Monotherapy and Combination Therapy Studies

Parameter	Monotherapy		Combination Therapy
	Trastuzumab ¹ N=105	Trastuzumab ² N=72	Trastuzumab plus paclitaxel ³ N=32
Response rate (95% CI)	24% (15 - 35)	27% (14 - 43)	59% (41 - 76)
Median duration of response (months) (range)	10.1 (2.8 - 35.6)	7.9 (2.1 - 18.8)	10.5 (1.8 - 21)
Median TTP (months) (95% CI)	3.4 (2.8 - 4.1)	7.7 (4.2 - 8.3)	12.2 (6.2 - ne)
Median Survival (months) (95% CI)	ne	ne	ne

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

¹ Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule.

² Study MO16982: loading dose 6 mg/kg weekly x 3; followed by 6 mg/kg 3-weekly schedule.

³ Study BO15935.

Early breast cancer (adjuvant setting)

Early breast cancer is defined as non-metastatic primary invasive carcinoma of the breast.

In the adjuvant treatment setting, trastuzumab was investigated in 4 large multicentre, randomised, Phase III trials.

- Study BO16348 was designed to compare one and two years of three-weekly trastuzumab treatment versus observation in patients with HER2 positive EBC following

surgery, established chemotherapy and radiotherapy (if applicable). In addition, comparison of two years of trastuzumab treatment versus one year of trastuzumab treatment was performed. Patients assigned to receive trastuzumab were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.

- The NSABP B-31 and NCCTG N9831 studies that comprise the joint analysis were designed to investigate the clinical utility of combining trastuzumab treatment with paclitaxel following AC chemotherapy, additionally the NCCTG N9831 study also investigated adding trastuzumab sequentially to AC→P chemotherapy in patients with HER2 positive EBC following surgery.
- The BCIRG 006 study was designed to investigate combining trastuzumab treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive EBC following surgery.

Early breast cancer in the study BO16348 was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative tumours of at least 1 cm in diameter.

In the joint analysis of the NSABP B-31 and NCCTG N9831 studies, EBC was limited to women with operable breast cancer at high risk, defined as HER2 positive and axillary lymph node positive or HER2 positive and lymph node negative with high risk features (tumour size >1 cm and ER negative or tumour size >2 cm, regardless of hormonal status).

In the BCIRG 006 study HER2 positive, EBC was defined as either lymph node positive or high risk node negative patients with no (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histological and/or nuclear grade 2-3, or age <35 years).

The efficacy results from the BO16348 trial following 12 months* and 8 years** median follow-up are summarized in Table 6:

Table 6: Efficacy Results from Study BO16348

	Median follow-up 12 months*		Median follow-up 8 years**	
Parameter	Observation N=1693	Trastuzumab 1 Year N=1693	Observation N=1697***	Trastuzumab 1 Year N=1702***
<i>Disease-free survival</i>				
- No. patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
- No. patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
<i>Recurrence-free survival</i>				
- No. patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
- No. patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
P-value versus Observation	<0.0001		<0.0001	
Hazard Ratio versus Observation	0.51		0.73	

Table 6: Efficacy Results from Study BO16348

	Median follow-up 12 months*		Median follow-up 8 years**	
<i>Distant disease-free survival</i>				
- No. patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
- No. patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
P-value versus Observation	<0.0001		<0.0001	
Hazard Ratio versus Observation	0.50		0.76	
<i>Overall survival (death)</i>				
- No. patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
- No. patients without event	1653 (97.6%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

* Co-primary endpoint of disease-free survival (DFS) of 1 year versus observation met the pre-defined statistical boundary.

** Final analysis (including crossover of 52% of patients from the observation arm to trastuzumab).

*** There is a discrepancy in the overall sample size due to a small number of patients who were randomized after the cut-off date for the 12-month median follow-up analysis.

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of trastuzumab versus observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease-free survival (DFS) was 0.54 (95% CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8% versus 78.2%) in favour of the trastuzumab arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year trastuzumab treatment is associated with a 24% risk reduction compared to observation only (HR=0.76, 95% CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8 year disease-free survival rate of 6.4 percentage points in favour of 1 year trastuzumab treatment.

In this final analysis, extending trastuzumab treatment for a duration of two years did not show additional benefit over treatment for 1 year (DFS HR in the intent to treat [ITT] population of 2 years versus 1 year=0.99 [95% CI: 0.87, 1.13], p-value=0.90 and overall survival [OS] HR=0.98 [0.83, 1.15]; p-value=0.78).

The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1% versus 4.6% in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4%) compared with the 1-year treatment arm (16.3%).

In the NSABP B-31 and NCCTG N9831 studies trastuzumab was administered in combination with paclitaxel, following AC chemotherapy.

Paclitaxel, in combination with trastuzumab, was administered as follows:

- intravenous paclitaxel - 80 mg/m² as a continuous intravenous infusion, given every week for 12 weeks.

or

- intravenous paclitaxel - 175 mg/m² as a continuous intravenous infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

The efficacy results from the joint analysis of the NSABP B-31 and NCCTG 9831 trials at the time of the definitive analysis of DFS* are summarized in Table 7. The median duration of follow up was 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

Table 7: Summary of Efficacy Results from the Joint Analysis of the NSABP B-31 and NCCTG N9831 Trials at the Time of the Definitive DFS Analysis*

Parameter	AC→P (n=1679)	AC→PH (n=1672)	Hazard Ratio versus AC→P (95% CI) p-value
Disease-free survival			
No. patients with event (%)	261 (15.5)	133 (8.0)	0.48 (0.39, 0.59) p<0.0001
Distant recurrence			
No. patients with event (%)	193 (11.5)	96 (5.7)	0.47 (0.37, 0.60) p<0.0001
Death (OS event):			
No. patients with event (%)	92 (5.5)	62 (3.7)	0.67 (0.48, 0.92) p=0.014**

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

* At median duration of follow up of 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

** p value for OS did not cross the pre-specified statistical boundary for comparison of AC→PH versus AC→P.

For the primary endpoint, DFS, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 11.8 percentage points (87.2% versus 75.4%) in favour of the AC→PH (trastuzumab) arm.

At the time of a safety update after a median of 3.5 - 3.8 years follow up, an analysis of DFS reconfirms the magnitude of the benefit shown in the definitive analysis of DFS. Despite the cross-over to trastuzumab in the control arm, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence. The addition of trastuzumab to paclitaxel chemotherapy also resulted in a 37% decrease in the risk of death.

The pre-planned final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→PH group). Treatment with AC→PH resulted in a statistically significant improvement in OS compared with AC→P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p-value < 0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC→PH arm and 79.4% in the AC→P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).

The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in Table 8 below:

Table 8: Final Overall Survival Analysis from the Joint Analysis of Trials NSABP B-31 and NCCTG N9831

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	<0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

DFS analysis was also performed at the final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831. The updated DFS analysis results (stratified HR=0.61; 95% CI [0.54, 0.69]) showed a similar DFS benefit compared to the definitive primary DFS analysis, despite 24.8% patients in the AC→P arm who crossed over to receive trastuzumab. At 8 years, the disease-free survival rate was estimated to be 77.2% (95% CI: 75.4, 79.1) in the AC→PH arm, an absolute benefit of 11.8% compared with the AC→P arm.

In the BCIRG 006 study trastuzumab was administered either in combination with docetaxel, following AC chemotherapy (AC→DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenous docetaxel - 100 mg/m² as an intravenous infusion over 1 hour, given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle).
- or
- intravenous docetaxel - 75 mg/m² as an intravenous infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each subsequent cycle).

which was followed by:

- carboplatin - at target AUC = 6 mg/mL/min administered by intravenous infusion over 30 - 60 minutes repeated every 3 weeks for a total of six cycles.

Trastuzumab was administered weekly with chemotherapy and 3 weekly thereafter for a total of 52 weeks.

The efficacy results from the BCIRG 006 are summarized in Tables 9 and 10. The median duration of follow up was 2.9 years in the AC→D arm and 3.0 years in each of the AC→DH and DCarbH arms.

Table 9: Overview of Efficacy Analyses BCIRG 006 AC→D versus AC→DH

Parameter	AC→D (n=1073)	AC→DH (n=1074)	Hazard Ratio versus AC→D (95% CI) p-value
Disease-free survival No. patients with event	195	134	0.61 (0.49, 0.77) p<0.0001
Distant recurrence No. patients with event	144	95	0.59 (0.46, 0.77) p<0.0001

Parameter	AC→D (n=1073)	AC→DH (n=1074)	Hazard Ratio versus AC→D (95% CI) p-value
Death (OS event) No. patients with event	80	49	0.58 (0.40, 0.83) p=0.0024

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→DH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CI = confidence interval

Table 10: Overview of Efficacy Analyses BCIRG 006 AC→D versus DCarbH

Parameter	AC→D (n=1073)	DCarbH (n=1074)	Hazard Ratio versus AC→D (95% CI) p-value
Disease-free survival No. patients with event	195	145	0.67 (0.54, 0.83) p=0.0003
Distant recurrence No. patients with event	144	103	0.65 (0.50, 0.84) p=0.0008
Death (OS event) No. patients with event	80	56	0.66 (0.47, 0.93) p=0.0182

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; DCarbH = docetaxel, carboplatin and trastuzumab; CI = confidence interval

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 5.8 percentage points (86.7% versus 80.9%) in favour of the AC→DH (trastuzumab) arm and 4.6 percentage points (85.5% versus 80.9%) in favour of the DCarbH (trastuzumab) arm compared to AC→D.

For the secondary endpoint overall survival, treatment with AC→DH reduced the risk of death by 42% when compared to AC→D (hazard ratio 0.58 [95% CI: 0.40, 0.83] p=0.0024, log-rank test) and the risk of death was reduced by 34% for patients treated with DCarbH compared to patients treated with AC→D (hazard ratio 0.66 [95% CI: 0.47, 0.93], p=0.0182). In the BCIRG 006 study at the second interim analysis, 185 randomized patients had died: 80 patients (7.5%) in the AC→D arm, 49 patients (4.6%) in the AC→DH arm, and 56 patients (5.2%) in the DCarbH arm.

In study BCIRG 006, 213/1075 patients in the DCarbH (TCH) arm, 221/1074 patients in the AC→DH (AC→TH) arm, and 217/1073 in the AC→D (AC→T) arm had a Karnofsky performance status ≤90 (either 80 or 90). No disease-free survival (DFS) benefit was noticed in this subgroup of patients (hazard ratio = 1.16, 95% CI [0.73, 1.83] for DCarbH (TCH) versus AC→D (AC→T); hazard ratio 0.97, 95% CI [0.60, 1.55] for AC→DH (AC→TH) versus AC→D).

In addition a post-hoc exploratory analysis was performed on the data sets from the joint analysis (JA) NSABP B-31/NCCTG N9831* and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events and summarized in Table 11:

Table 11: Post-Hoc Exploratory Analysis Results from the Joint Analysis NSABP B-31/NCCTG N9831* and BCIRG006 Clinical Studies Combining DFS Events and Symptomatic Cardiac Events

	AC→PH (versus AC→P) (NSABP B-31 and NCCTG N9831)*	AC→DH (versus AC→D) (BCIRG 006)	DCarbH (versus AC→D) (BCIRG 006)
Primary efficacy analysis DFS Hazard ratios (95% CI) p-value	0.48 (0.39, 0.59) p<0.0001	0.61 (0.49, 0.77) p<0.0001	0.67 (0.54, 0.83) p=0.0003
Long-term follow-up efficacy analysis** DFS Hazard ratios (95% CI) p-value	0.61 (0.54, 0.69) p<0.0001	0.72 (0.61, 0.85) p<0.0001	0.77 (0.65, 0.90) p=0.0011
Post-hoc exploratory analysis with DFS and symptomatic cardiac events Long-term follow-up** Hazard ratios (95% CI)	0.67 (0.60, 0.75)	0.77 (0.66, 0.90)	0.77 (0.66, 0.90)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: trastuzumab

CI = confidence interval

* At the time of the definitive analysis of DFS. Median duration of follow up was 1.8 years in the AC→P arm and 2.0 years in the AC→PH arm.

** Median duration of long-term follow-up for the Joint Analysis clinical studies was 8.3 years (range: 0.1 to 12.1) for the AC→PH arm and 7.9 years (range: 0.0 to 12.2) for the AC→P arm; Median duration of long-term follow-up for the BCIRG 006 study was 10.3 years in both the AC→D arm (range: 0.0 to 12.6) arm and the DCarbH arm (range: 0.0 to 13.1), and was 10.4 years (range: 0.0 to 12.7) in the AC→DH arm.

Early breast cancer (neoadjuvant-adjuvant setting)

So far, no results are available which compare the efficacy of trastuzumab administered with chemotherapy in the adjuvant setting with that obtained in the neo-adjuvant/adjuvant setting.

In the neoadjuvant-adjuvant treatment setting, study MO16432, a multicentre randomised trial, was designed to investigate the clinical efficacy of concurrent administration of trastuzumab with neoadjuvant chemotherapy including both an anthracycline and a taxane, followed by adjuvant trastuzumab, up to a total treatment duration of 1 year. The study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory EBC. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone.

In study MO16432, trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance every 3 weeks) was administered concurrently with 10 cycles of neoadjuvant chemotherapy

as follows:

- Doxorubicin 60 mg/m² and paclitaxel 150 mg/m², administered 3-weekly for 3 cycles,

which was followed by

- Paclitaxel 175 mg/m² administered 3-weekly for 4 cycles,

which was followed by

- CMF on day 1 and 8 every 4 weeks for 3 cycles,

which was followed after surgery by

- additional cycles of adjuvant trastuzumab (to complete 1 year of treatment).

The efficacy results from Study MO16432 are summarized in Table 12. The median duration of follow-up in the trastuzumab arm was 3.8 years.

Table 12: Efficacy Results from MO16432

Parameter	Chemo + trastuzumab (n=115)	Chemo only (n=116)	
Event-free survival			Hazard Ratio (95% CI)
No. patients with event	46	59	0.65 (0.44, 0.96) p=0.0275
Total pathological complete response* (95% CI)	40% (31.0, 49.6)	20.7% (13.7, 29.2)	p=0.0014
Overall survival			Hazard Ratio (95% CI)
No. patients with event	22	33	0.59 (0.35, 1.02) p=0.0555

* Defined as absence of any invasive cancer both in the breast and axillary nodes.

An absolute benefit of 13 percentage points in favour of the trastuzumab arm was estimated in terms of 3-year event-free survival rate (65% versus 52%).

Metastatic gastric cancer

Trastuzumab has been investigated in one randomised, open-label Phase III trial ToGA (BO18255) in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m² orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or

- intravenous 5-fluorouracil - 800 mg/m²/day as a continuous intravenous infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:

- cisplatin - 80 mg/m² every 3 weeks for 6 cycles on day 1 of each cycle.

The efficacy results from study BO18225 are summarized in Table 13:

Table 13: Efficacy Results from BO18225

Parameter	FP N=290	FP +H N=294	HR (95% CI)	p-value
Overall Survival, Median months	11.1	13.8	0.74 (0.60 - 0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59 - 0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58 - 0.85)	0.0003
Overall Response Rate, %	34.5%	47.3%	1.70 ^a (1.22 - 2.38)	0.0017
Duration of Response, Median months	4.8	6.9	0.54 (0.40 - 0.73)	<0.0001

FP + H: Fluoropyrimidine/cisplatin + trastuzumab

FP: Fluoropyrimidine/cisplatin

^a Odds ratio

Patients were recruited to the trial who were previously untreated for HER2 positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182 patients (62.8%) in the control arm and 167 patients (56.8%) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

Post-hoc subgroup analyses indicate that positive treatment effects are limited to targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ or IHC 3+). The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95% CI 0.51 - 0.83) and the median progression free survival was 5.5 months versus 7.6 months, HR 0.64 (95% CI 0.51 - 0.79) for FP versus FP + H, respectively. For overall survival, the HR was 0.75 (95% CI 0.51 - 1.11) in the IHC 2+/FISH+ group and the HR was 0.58 (95% CI 0.41 - 0.81) in the IHC 3+/FISH+ group.

In an exploratory subgroup analysis performed in the TOGA (BO18255) trial there was no apparent benefit on overall survival with the addition of trastuzumab in patients with ECOG PS 2 at baseline (HR 0.96 [95% CI 0.51 - 1.79]), non measurable (HR 1.78 [95% CI 0.87 - 3.66]) and locally advanced disease (HR 1.20 [95% CI 0.29 - 4.97]).

TRAZIMERA Clinical Studies

The biosimilar clinical development program for TRAZIMERA included a total of two randomized, multicenter, double-blinded, active-controlled trials were conducted in adult patients (n=933) with the use of intravenous trastuzumab in combination with chemotherapy.

Study B3271002 was a trial comparing TRAZIMERA to Herceptin-EU when administered in combination with paclitaxel in patients with HER2 positive metastatic breast cancer. The primary endpoint for this study was objective response rate (ORR) achieved by Week 25 in accordance with RECIST 1.1 based on the assessments of a central radiology review. The analysis of the primary endpoint met the pre-specified equivalence criterion.

Study B3271004 was a trial comparing TRAZIMERA to Herceptin-EU when administered in combination with Taxotere and carboplatin in patients with operable HER2 positive breast cancer in the neoadjuvant setting. Secondary endpoints of the study included pathologic complete response (pCR) rate defined as the absence of invasive neoplastic cells in the breast and lymph nodes, safety and immunogenicity. The percentage of patients achieving pCR, based on a qualified local pathologist, was comparable in the 2 treatment groups.

In both studies, the safety and immunogenicity results support comparable safety profiles for TRAZIMERA and Herceptin-EU. There is no clinically meaningful difference in efficacy or safety between TRAZIMERA and Herceptin-EU reference product when administered intravenously in subjects with HER2 positive breast cancer.

5.2. Pharmacokinetic properties

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects, including patients with HER2 positive MBC, EBC, AGC or other tumour types, and healthy volunteers, in 18 Phase I, II and III trials receiving trastuzumab IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to non-linear elimination, total clearance increased with decreasing concentration. Therefore, no constant value for half-life of trastuzumab can be deduced. The $t_{1/2}$ decreases with decreasing concentrations within a dosing interval (see Table 16). MBC and EBC patients had similar PK parameters (e.g., clearance [CL], the central compartment volume [V_c]) and population-predicted steady-state exposures (C_{min} , C_{max} and AUC). Linear clearance was 0.136 L/day for MBC, 0.112 L/day for EBC and 0.176 L/day for AGC. The non-linear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92 $\mu\text{g/mL}$ for the Michaelis-Menten constant (K_m) for the MBC, EBC, and AGC patients. The central compartment volume was 2.62 L for patients with MBC and EBC and 3.63 L for patients with AGC.

In the final population PK model, in addition to primary tumour type, body-weight, serum aspartate aminotransferase and albumin were identified as a statistically significant covariates affecting the exposure of trastuzumab. However, the magnitude of effect of these covariates on trastuzumab exposure suggests that these covariates are unlikely to have a clinically meaningful effect on trastuzumab concentrations.

The population predicted PK exposure values (median with 5th - 95th Percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for MBC, EBC and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 14 (Cycle 1), Table 15 (steady-state), and Table 16 (PK parameters).

Table 14: Population Predicted Cycle 1 PK Exposure Values (median with 5th - 95th Percentiles) for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumour type	N	C _{min} (µg/mL)	C _{max} (µg/mL)	AUC _{0-21 days} (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	MBC	805	28.7 (2.9 - 46.3)	182 (134 - 280)	1376 (728 - 1998)
	EBC	390	30.9 (18.7 - 45.5)	176 (127 - 227)	1390 (1039 - 1895)
	AGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4 mg/kg + 2 mg/kg qw	MBC	805	37.4 (8.7 - 58.9)	76.5 (49.4 - 114)	1073 (597 - 1584)
	EBC	390	38.9 (25.3 - 58.8)	76.0 (54.7 - 104)	1074 (783 - 1502)

Table 15: Population Predicted Steady State PK Exposure Values (median with 5th - 95th Percentiles) for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumour type	N	C _{min,ss} * (µg/mL)	C _{max,ss} ** (µg/mL)	AUC _{ss, 0-21days} (µg.day/mL)	Time to steady-state*** (week)
8 mg/kg + 6 mg/kg q3w	MBC	805	44.2 (1.8 - 85.4)	179 (123 - 266)	1736 (618 - 2756)	12
	EBC	390	53.8 (28.7 - 85.8)	184 (134 - 247)	1927 (1332 - 2771)	15
	AGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9
4 mg/kg + 2 mg/kg qw	MBC	805	63.1 (11.7 - 107)	107 (54.2 - 164)	1710 (581 - 2715)	12
	EBC	390	72.6 (46 - 109)	115 (82.6 - 160)	1893 (1309 - 2734)	14

* C_{min,ss} = C_{min} at steady state

** C_{max,ss} = C_{max} at steady state

*** Time to 90% of steady-state

Table 16: Population Predicted PK Parameter Values at Steady State for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumour type	N	Total CL range from C _{max,ss} to C _{min,ss} (L/day)	t _{1/2} range from C _{max,ss} to C _{min,ss} (day)
8 mg/kg + 6 mg/kg q3w	MBC	805	0.183 - 0.302	15.1 - 23.3
	EBC	390	0.158 - 0.253	17.5 - 26.6
	AGC	274	0.189 - 0.337	12.6 - 20.6
4 mg/kg + 2 mg/kg qw	MBC	805	0.213 - 0.259	17.2 - 20.4
	EBC	390	0.184 - 0.221	19.7 - 23.2

Trastuzumab washout

Trastuzumab washout period was assessed following q1w or q3w intravenous administration using the population PK model. The results of these simulations indicate that at least 95% of

patients will reach concentrations that are $<1 \mu\text{g/mL}$ (approximately 3% of the population predicted $C_{\text{min,ss}}$, or about 97% washout) by 7 months.

Circulating shed HER2 ECD

The exploratory analyses of covariates with information in only a subset of patients suggested that patients with greater shed HER2-ECD level had faster nonlinear clearance (lower K_m) ($P < 0.001$). There was a correlation between shed antigen and SGOT/AST levels; part of the impact of shed antigen on clearance may have been explained by SGOT/AST levels.

Baseline levels of the shed HER2-ECD observed in MGC patients were comparable to those in MBC and EBC patients and no apparent impact on trastuzumab clearance was observed.

TRAZIMERA Comparative Pharmacokinetic Studies

Pharmacokinetic comparability of TRAZIMERA and Herceptin was evaluated in Study B3271001 in 105 healthy adult subjects in a three arm, double-blind, randomized, (1:1:1) parallel group, single dose study comparing TRAZIMERA, Herceptin-EU and Herceptin-US administered intravenously.

The 90% CIs for test-to-reference ratios of C_{max} , AUC_t , and AUC_{inf} were contained within the pre-specified acceptance boundaries of 80% to 125% for the comparisons of TRAZIMERA to Herceptin-US and TRAZIMERA to Herceptin-EU. The test-to-reference ratios (90% CIs of the ratios) of adjusted geometric means of C_{max} , AUC_t , and AUC_{inf} were 97.41% (90.71%, 104.62%), 99.94% (93.08%, 107.31%), and 99.83% (93.06%, 107.09%), respectively, for the TRAZIMERA to Herceptin-US comparison; and 91.49% (85.32%, 98.09%), 92.66% (86.44%, 99.34%), and 92.15% (86.03%, 98.69%), respectively, for the TRAZIMERA to Herceptin-EU comparison.

In Study B3271004 in patients with early breast cancer treated with TRAZIMERA or Herceptin-EU in combination with Taxotere and carboplatin, the primary endpoint of the study was the percent of patients with Cycle 5 C_{trough} (Cycle 6 predose trastuzumab concentration) $>20 \mu\text{g/mL}$. The analysis of the primary endpoint met the non-inferiority criterion. The study demonstrated a comparable percentage of patients with steady state (Cycle 5) $C_{\text{trough}} >20 \mu\text{g/mL}$ of TRAZIMERA and Herceptin-EU.

5.3. Preclinical safety data

There was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies with trastuzumab. Trastuzumab is not genotoxic.

No long-term animal studies have been performed to establish the carcinogenic potential of trastuzumab, or to determine its effects on fertility in males.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder

L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 20
Sucrose

Diluent

Water for injection
Benzyl alcohol

6.2. Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned under section 6.6.

Do not dilute with dextrose or glucose solutions.

6.3. Shelf life

Refer to outer carton for expiration date.

6.4. Special precautions for storage

TRAZIMERA should be stored in the original package in order to protect from light.

Unopened vials of TRAZIMERA should be stored under refrigeration (2°C - 8°C) until expiry shown on the vial.

Unopened vials of TRAZIMERA may be removed from refrigeration and stored up to 30°C for a single period of up to 3 months. Once removed from refrigeration and stored under these conditions, discard after 3 months. A date field is provided on the carton to record the discard date.

For storage conditions of the opened medicinal product, see section 6.6.

6.5. Nature and contents of container

Each carton contains 1 glass vial with 440 mg trastuzumab + 1 glass vial with 20 mL bacteriostatic water for injection containing benzyl alcohol as preservative.

6.6. Special precautions for disposal and other handling

Appropriate aseptic technique should be used. Each 440 mg vial of TRAZIMERA is reconstituted with 20 mL of bacteriostatic water for injection (BWFI), containing 1.1%

benzyl alcohol as a preservative (supplied). This yields a multi-dose solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.0.

In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative (not supplied) to yield a single use solution.

TRAZIMERA should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of TRAZIMERA that can be withdrawn from the vial.

The reconstituted solution should not be frozen.

Instructions for reconstitution:

- 1) Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized TRAZIMERA.
- 2) Swirl the vial gently to aid reconstitution. **DO NOT SHAKE!**

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted trastuzumab results in a clear to slightly opalescent and colourless to pale yellow-brown solution and should be essentially free of visible particulates.

Store reconstituted TRAZIMERA at 2°C - 8°C.

- If TRAZIMERA is reconstituted with BWFI, discard unused TRAZIMERA after 28 days.
- If TRAZIMERA is reconstituted with SWFI without preservative, the reconstituted solution is physicochemically stable for 48 hours at 2°C - 8°C. However, from a microbiological point of view, the product should be used immediately. Any remaining reconstituted solution should be discarded.

Determine the volume of the solution required:

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (4 mg/kg for loading or 2 mg/kg for maintenance)}}{21 \text{ (mg/mL, concentration of reconstituted solution)}}$$

- based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (8 mg/kg for loading or 6 mg/kg for maintenance)}}{21 \text{ (mg/mL, concentration of reconstituted solution)}}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with dextrose- or glucose-containing solutions (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming.

No incompatibilities between TRAZIMERA and polyvinylchloride, polyethylene, polypropylene, or ethylene vinyl acetate bags or glass IV bottles have been observed.

Solutions for intravenous infusion are physicochemically stable in polyvinylchloride, polyethylene, polypropylene, or ethylene vinyl acetate bags or glass IV bottles containing sodium chloride 9 mg/mL (0.9%) solution for injection for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and infusion solution should be used immediately. The product is not intended to be stored after dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

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TRA-SIN-0919/2
Date of last revision: October 2020